Bifunctional Organocatalysts Containing Primary Amines for Asymmetric Michael Additions

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Dedication

This dissertation is dedicated to my Father, Abdul Wahid, without his moral support and encouragement this would not have been possible for me to come so far to do my highest degree in academic career.
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My eternal thanks go to my parents, wife, and my cute little daughter who can bless me with happiness on every second of my life.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet ((^1)H NMR)</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl group</td>
</tr>
<tr>
<td>Boc</td>
<td>Tertiary-butyl carbamates</td>
</tr>
<tr>
<td>iBu</td>
<td>iso-Butyl</td>
</tr>
<tr>
<td>nBu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>conv</td>
<td>Conversion</td>
</tr>
<tr>
<td>CDCl(_3)</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>d</td>
<td>Doublet ((^1)H NMR)</td>
</tr>
<tr>
<td>DBSAS</td>
<td>Dodecylbenzenesulfonic acid sodium salt</td>
</tr>
<tr>
<td>DNBSA</td>
<td>Dinitrobenzene sulfonic acid</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet ((^1)H NMR)</td>
</tr>
<tr>
<td>dq</td>
<td>Doublet of quartet ((^1)H NMR)</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift ((^1)H NMR)</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization (Mass spectroscopy)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
</tbody>
</table>
EtOAc  Ethylacetate
GC    Gas chromatography
h     Hours
HPLC  High performance liquid chromatography
HRMS  High resolution mass spectrometry
Hz    Hertz
IR    Infrared spectroscopy
J     Coupling constant (\(^1\)H NMR)
m     Multiplate (\(^1\)H NMR)
M     Molar
Me    Methyl
min   Minutes
MS    Mass spectroscopy
MTBE  Methyl tertiary butyl ether
MW    Molecular weight
m/z   Mass/charge
m     Meta
NMR   Nuclear Magnetic Resonance
o     Ortho
p     Para
Pd/C  Palladium on carbon
Ph    Phenyl
iPr   iso-Propyl
nPr   n-Propyl
Pt/C  Platinum on carbon
Pyr   Pyridine
q     Quartet (\(^1\)H NMR)
R     Alkyl group
Ref   Reference
rt    Room Temperature
s Singlet ($^1$H NMR)
sep Septet ($^1$H NMR)
t Triplet ($^1$H NMR)
tBu Tertiary butyl
tert Tertiary
temp Temperature
TFA Trifluoroacetic acid
THF Tetrahydrofuran
TLC Thin layer chromatography
TMS Trimethylsilane
Ts Tosyl
TsOH $p$-Toluenesulfonic acid
Ti(OiPr)$_4$ Titanium(IV) isopropoxide
Abstract

The asymmetric Michael addition of nucleophilic carbonyls (via enamine) to a diverse number of Michael acceptors produces an important carbon-carbon bond, producing a truly large number of products. Over the past decade an enormous number of organocatalysts have been developed for the asymmetric Michael addition. Challenging nucleophilic carbonyl additions, e.g. α-substituted carbonyls and some cyclic carbonyls, e.g. cyclopentanone, remain and require attention in terms of stereoselectivity, catalyst loading reaction time and yield.

Here we have focused on designing new organocatalysts with primary amines to overcome the above outlined challenges. We have developed two types of organocatalysts: 1) primary-tertiary diamine organocatalysts and 2) non-covalent bifunctional organocatalysts. Diamines were found to be better organocatalysts for the asymmetric Michael addition of cyclopentanone to various nitroolefins. While the assembled catalysts were found to be superior for the asymmetric Michael addition of α-substituted aldehydes addition to maleimides.
Table of Contents

Chapter 1. Introduction ........................................................................................................ 1

1.1 Organocatalysis ........................................................................................................... 2
1.2 Enamine catalysis ......................................................................................................... 4
1.3 First asymmetric examples of various enamine based reactions ................................... 6
  1.3.1 Enamine promoted asymmetric Aldol reaction .................................................... 6
  1.3.2 Enamine promoted asymmetric Michael reaction ................................................ 7
  1.3.3 Enamine promoted asymmetric Mannich reaction .............................................. 8
  1.3.4 Enamine promoted asymmetric α-amination ....................................................... 9
  1.3.5 Enamine promoted asymmetric α-alkylation ....................................................... 9
1.4 Asymmetric Michael addition ...................................................................................... 10
  1.4.1 Generic mechanism of bifunctional catalysts ....................................................... 11
  1.4.2 Classification of organocatalysts .......................................................................... 13
    1.4.2.1 Steric based catalysts ...................................................................................... 15
    1.4.2.2 Thiourea based bifunctional catalysts ............................................................. 17
    1.4.2.3 Amino-sulfonamides, Amino-thiophosphoramides and Amino-amides ......... 19
    1.4.2.4 Proline based diamine catalysts ...................................................................... 21
    1.4.2.5 Cinchona based bifunctional catalysts ............................................................ 23
    1.4.2.6 Miscellaneous bifunctional catalysts ............................................................... 23
    1.4.2.7 Proline based electrostatic catalysts ............................................................... 24
  1.4.3 Asymmetric Michael addition to nitroolefins ....................................................... 25
  1.4.4 Asymmetric Michael addition to maleimides ....................................................... 30
Chapter 2. Results and discussion: Diamine catalysts ................................................................. 40

2.1 Introduction .......................................................................................................................... 41
2.2 Synthesis of chiral primary-tertiary diamines ................................................................. 42
2.3 Model reaction: cyclopentanone addition to trans-β-nitrostyrene .................................. 44
2.3.1 Diamine catalyst screening .......................................................................................... 44
2.3.2 Solvent screening ......................................................................................................... 45
2.3.3 Acid and additive screening .......................................................................................... 46
2.4 Asymmetric Michael addition of cyclopentanone to various nitroolefins ...................... 48
2.5 Asymmetric Michael addition of isobutyraldehyde to various nitroolefins .............. 49
2.6 Mechanism ....................................................................................................................... 51
2.7 Absolute and relative stereochemistry .......................................................................... 54
2.8 Conclusion .......................................................................................................................... 55
References .................................................................................................................................. 56

Chapter 3. Results and discussion: Assembled bifunctional catalysts ................................. 57

3.1 Introduction .......................................................................................................................... 58
3.2 Non-covalent bifunctional catalyst for asymmetric Michael additions .......................... 59
3.3 Model reaction: isobutyraldehyde addition to N-phenylmaleimide ............................. 62
3.3.1 Solvent screening ....................................................................................................... 63
Chapter 1

INTRODUCTION
1.1 Organocatalysis

In parallel to metal complexes and enzymes, small organic molecules may promote chemical reactions. Organocatalysis, using small organic molecules as non-metal catalysts, provides a means for accelerating chemical reactions using substoichiometric amounts of the catalyst. The concept of organocatalysis was reported about a century ago and is now a well established research area. If we study the current reviews on organocatalysis, one finds a well defined history for the discovery and development of organocatalysis. Here I will describe a short history of organocatalysis based on these selected reviews.

In 1894, Knoevenagel reported for the first time an amine promoted Aldol type condensation. Two decades later Bredig and Fiske, in 1912, reported for the first time a chiral molecule catalyzing an organic reaction (Scheme 1.1). They described cinchonidine catalyzed additions of hydrogen cyanide to benzaldehyde (1) followed by hydrolysis. The resulting mandelic acid (3) was of very low enantioselectivity (3-8%) but this was the first demonstration of a chiral molecule catalyzing an enantioselective reaction.

Scheme 1.1. First demonstration of asymmetric organocatalytic concept.

In the early 1970s, two industrial groups used (S)-proline for enantioselective aldol reactions. In this reaction an achiral triketone was fully converted to an optically active bicyclic ketol by the use of (S)-proline (3 mol%) (Scheme 1.2). The product was obtained in high yield (100%) and enantioselectivity (93% ee).
**Scheme 1.2.** First proline catalyzed asymmetric aldol reaction.

Despite the publications of these early examples of organocatalysis, the concept was not further explored. At that time, the mechanisms were not clear and the applications were limited. After 30 years of essentially dormant existence, the field was brought to life with the discovery of proline-catalyzed asymmetric intermolecular aldol reactions. In the same year MacMillan reported the first enantioselective organocatalytic Diels-Alder reaction (Scheme 1.3).  

**Scheme 1.3.** First enantioselective organocatalytic Diel-Alder reaction.

In the past, metal complexes provided flexible bases for most new reactions and has been developed to a high level as compared to organocatalysis. Currently the picture of asymmetric catalysis is changing and organocatalysis is becoming an increasingly important complementary topic which can be at times a competitive alternative to metal based catalysis. This increasing tendency for asymmetric organocatalysis happens because of the benefits that they can sometimes provide:

- High catalytic activity
- Easily available
• Easy and promising preparation
• Low price
• Low molecular weight
• Easily separable from reaction mixture
• Recycling after workup
• Non toxic
• Stable

Today, reactions can be performed under an aerobic atmosphere, with wet solvents; sometimes, the presence of water is beneficial to the rate and selectivity of the reaction. The operational simplicity and availability of these inexpensive bench-stable catalysts makes organocatalysis, in general, an attractive method for the synthesis of complex structures. Furthermore, unlike earlier developed organic fields, organocatalysis provides a rich platform for multistep or tandem reactions, allowing easy to important building blocks for drug or natural product synthesis.

1.2 Enamine catalysis

An enamine is an unsaturated compound formed by the nucleophilic attack of a secondary amine on an aldehyde or ketone followed by the loss of H₂O. Earlier literature reveals that enamines can be used as enolate equivalents, therefore enamines can be used to attack the electrophiles. This nucleophilic character of enamines makes them useful intermediates in a variety of organocatalytic reactions.

In 2000, List and Barbas demonstrated for the first time intermolecular aldol reactions between acetone and a variety of aldehydes (Scheme 1.4). They use a high loading of (S)-proline (30 mol%) to catalyze their reactions. The authors mentioned that proline most likely functions as a micro-aldolase, the aldolase antibodies they had created and natural aldolase enzyme aldolase A. So they strongly believed that (S)-proline was also working through an enamine intermediate. Afterwards, List went on to expand the application of this reaction for the synthesis of chiral 1,2-diols by reacting hydroxy acetones with aldehydes.
Scheme 1.4. First example of a (S)-proline catalyzed asymmetric intermolecular aldol reaction.

Scheme 1.5. Proposed enamine mechanism for intermolecular aldol reaction.
Scheme 1.5 shows a possible mechanism for the intermolecular reaction of acetone with an aldehyde catalyzed by (S)-proline. This enamine mechanism was first proposed by the Barbas group in 2000 and later on supported by the kinetic studies of Houk and List.\textsuperscript{14a} This initially proposed mechanism was further supported by List using labeled water (H\textsubscript{2}\textsuperscript{18}O), the oxygen isotope finding its way to the reaction product.\textsuperscript{14b} This proposed mechanism was also acceptable for asymmetric Michael reactions proved by List in 2001.\textsuperscript{15}

In the first step, the (S)-proline A attacks on acetone, forming intermediate B, which by loss of water molecule converts into the iminium ion C. The iminium ion C readily tautomerizes to an enamine D which is an active nucleophile. The enamine attacks on the carbonyl carbon of the aldehyde making the iminium-aldol intermediate F, which by hydrolysis provides the aldol product freeing the catalyst for recycle.

### 1.3 First asymmetric examples of various enamine based reactions

The enamine mechanism proposed by List et. al. (Section 1.2) has been widely accepted. In addition to the aldol reaction, other reactions can also proceed through enamine activation such as Michael reactions, Mannich reactions, \(\alpha\)-aminations, and \(\alpha\)-alkylations. Here I will provide a short introduction for each category.

#### 1.3.1 Enamine promoted asymmetric Aldol reaction

Aldol reaction was discovered in 1872 by Adolphe Wurtz. The catalytic asymmetric aldol reaction is a very important carbon-carbon bond forming reaction in chemical and biological sciences. In 2000,\textsuperscript{6a} List discovered the asymmetric intermolecular aldol reaction catalyzed by natural amino acids (Scheme 1.6).
Scheme 1.6. First example of asymmetric intermolecular Aldol reaction via enamine.

### 1.3.2 Enamine promoted asymmetric Michael reaction

Asymmetric Michael additions of various enolizable carbonyls to Michael acceptors provide a convenient access to versatile synthetic intermediates e.g. Michael reaction of enamine with a nitroalkene is a useful synthetic method for preparation of nitroalkanes. List reported the first example of an intermolecular enamine-based catalytic asymmetric Michael addition (Scheme 1.7).\(^\text{15}\)

Scheme 1.7. First example of asymmetric Michael addition to nitroolefins via enamine.

Asymmetric Michael additions of enolizable carbonyls to maleimides give chiral succinimides. The first \((S)\)-proline catalyzed Michael addition of acetone to maleimide was reported by Barbas (Scheme 1.8).\(^\text{16}\) The main aim of the reported article was fluorescent detection of carbon-carbon bond formation, therefore they did not mention enantioselectivity.
Scheme 1.8. First example of Michael addition to maleimides via enamine.

1.3.3 Enamine promoted asymmetric Mannich reaction

The Mannich reaction is a well-known reaction for the construction of nitrogen containing compounds. The reaction is catching attraction because most of the drug molecules or natural products also consist of nitrogenous building blocks. Generally the three reacting parts of a Mannich reaction are: carbonyl with an acidic proton at α-position, an aldehyde and an amine which attacks on aldehyde making the electrophilic imine. The final product is a β-amino carbonyl. List in 2000, has shown the first example of proline-catalyzed asymmetric three-component Mannich reaction (Scheme 1.9).

Scheme 1.9. First example of organocatalytic asymmetric three-component Mannich reaction via enamine.
1.3.4 Enamine promoted asymmetric $\alpha$-amination

In asymmetric $\alpha$-amination, a carbonyl with an acidic $\alpha$-hydrogen is attacked by an amine converting a carbonyl to an enamine. The enamine in situ attacks the electrophile, making the new bond. The presented example (Scheme 1.10) is the first direct catalytic asymmetric $\alpha$-amination of aldehydes.\(^{18}\)

Scheme 1.10. First example of catalytic asymmetric direct $\alpha$-amination aldehydes via enamine.

1.3.5 Enamine promoted asymmetric $\alpha$-alkylation

In $\alpha$-alkylation, the enamine from a carbonyl can attack the electrophilic carbon of an alkyl halide. After pioneering many other asymmetric reactions, List (2004) reported the first catalytic asymmetric $\alpha$-alkylation of aldehydes (Scheme 1.11).\(^{19}\)

Scheme 1.11. First example of asymmetric $\alpha$-alkylation of aldehydes via enamine.
1.4 Asymmetric Michael additions

Michael additions are an important carbon-carbon and carbon-heteroatom bond forming reaction in organic synthesis. The asymmetric versions offer a powerful tool for the synthesis of a variety of useful chiral functionalized organic molecules in an atom-economical manner. Over the past few years, a variety of classes of organocatalysts have been developed for enamine catalyzed asymmetric Michael additions of aldehydes or ketones to different Michael acceptors. Herein, I will focus on two different types of organocatalytic asymmetric Michael reactions, specifically the historical literature pertaining to:

- Ketone (cyclohexanone and cyclopentanone) additions to nitroolefins;
- \(\alpha\)-substituted aldehyde additions to maleimides.

Before going into details for the above two sections, I will present an overview of the organocatalysts examined in the field of asymmetric Michael additions. The next section contains a generic mechanism of bifunctional catalysis (section 1.4.1), followed by an overview of the commonly used catalyst templates (section 1.4.2, Table 1.1) used for asymmetric Michael additions. Based on the published literature, examples of catalysts are provided for each template category in section 1.4.2. For more details about catalyst loadings, starting material steechiometries, reaction times, yields, \(d\)\(r\)s and \(e\)\(e\)s, the readers will have to wait until section 1.4.3 and 1.4.4 (Table 1.2, 1.3, 1.4).
1.4.1 Generic mechanism of bifunctional catalysts

Bifunctional organocatalysts bear two main parts: a nucleophilic nitrogen and a second part which attracts the electrophile. For aminocatalysts and specifically for diamines, a primary or secondary amine serves to form an enamine nucleophilic, while a protonated tertiary amine acts as the H-bonding site for the electrophile. To explain the mechanism of bifunctional catalysis, let us consider the general example of ketone addition to an unsaturated nitro compound (Scheme 1.12).

\[
\begin{align*}
\text{R} & - \text{C} = \text{O} - \text{R}' + \text{Ar} = \text{CH} - \text{NO}_2 & \text{R}_1 \text{H} - \text{N} - \text{NR}_2 & \rightarrow \text{R} - \text{C} = \text{O} - \text{Ar} - \text{CH} - \text{NO}_2
\end{align*}
\]

**Scheme 1.12.** General example of organocatalytic Michael addition.

The nucleophilic nitrogen (primary or secondary) on a bifunctional organocatalyst attacks the carbonyl (aldehyde or ketone) forming an iminium ion. The iminium ion can readily rearrange to an enamine. Meanwhile, the protonated tertiary nitrogen (on the catalyst) serves as a hydrogen bonding site to activate the electrophile (nitroalkenes, maleimides, etc.) and to simultaneously bring it close to the enamine. This spacial arrangement of the enamine and the electrophile allows practical reaction rates that are less often achievable with purely steric based catalysts (Scheme 1.13).
Scheme 1.13. Catalytic cycle of bifunctional catalyst.
1.4.2 Classification of organocatalysts

Over the past decade, a variety of classes of organocatalysts have been developed for asymmetric Michael additions. Among them, aminocatalysis is broadly established. In aminocatalysis, chiral secondary amines are by far the most intensively studied to date. Chiral secondary amine catalysts are widely studied because of their known propensity to form enamines. By contrast, primary amine catalysts were ignored. Despite the reasons, primary amine organocatalysis recently emerged as a new and powerful class of organocatalysts for enantioselective reactions. Regarding asymmetric Michael additions, much attention has been paid to the design and application of bifunctional organocatalyst.

Design with intent, coupled with excellent product profiles is an increasing challenge for organocatalyst researchers. Interestingly, only a small number of successful organocatalyst templates have been identified in the asymmetric Michael addition literature. Classification of organocatalysts used for the asymmetric Michael additions is shown in Table 1.1.

Table 1.1: Classification of organocatalysts

<table>
<thead>
<tr>
<th>Catalyst type</th>
<th>Non-covalent participant</th>
<th>Catalyst template</th>
<th>Generic structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>steric based catalysts</td>
<td>-</td>
<td>proline derivatives</td>
<td><img src="https://example.com/proline.png" alt="" /></td>
</tr>
<tr>
<td>sterically based catalysts</td>
<td>-</td>
<td>non-proline based</td>
<td><img src="https://example.com/non-proline.png" alt="" /></td>
</tr>
<tr>
<td>bifunctional catalysts</td>
<td>static H-bond</td>
<td>amino-thioureas</td>
<td><img src="https://example.com/thiourea.png" alt="" /></td>
</tr>
<tr>
<td>Bifunctional Catalysts</td>
<td>H-Bond Type</td>
<td>Functional Group</td>
<td>Structures</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>------------</td>
</tr>
</tbody>
</table>
| **Static H-bond**      |             | **Amino-sulfonamides** | R= alkyl  
R’= H or alkyl |
| **Static H-bond**      |             | **Amino-thiophosphoramides** | |
| **Static H-bond**      |             | **Amino-amides** | |
| **In situ H-bond**     |             | **Proline based diamines** | R = H or alkyl, R’ = alkyl |
| **In situ H-bond**     |             | **Amino-cinchona** | |
| **In situ H-bond**     |             | **Miscellaneous** | R= N, S, O  
R= H or alkyl  
R’= alkyl |
| **Permanent Dipole**   |             | **Amino-phosphine oxides** | |

A brief description of each is now provided.
1.4.2.1 Steric based catalysts

Unlike all other bifunctional catalysts, steric based catalysts lack the presence of a tertiary or secondary nitrogen as the site for *in situ* hydrogen bond formation. In steric catalysts, a nucleophilic nitrogen makes the enamine and the bulky group on the catalyst block one face of the enamine and the electrophile approach from the least hindered side of enamine to promote the reaction. These types of catalysts are common in asymmetric Michael additions and the most examined ones are proline derivatives and some of them are non-proline based (Figure 1.1, 7). Figure 1.1 represents a few examples of these alternative types of proline-based catalysts. Herein, I will discuss a few of the catalysts from Figure 1.1.

Hayashi in 2005,\(^{21}\) showed that silylation of prolinol can dramatically improve its catalytic activity (Figure 1.1, 4). They acquire excellent results with unsubstituted aldehyde additions to nitroolefins (e.g. 10 mol% 4, offers 85% yield, 96:4 *dr* and 99% *ee* in a 5h reaction). However, their catalysts reveal comparatively poor results when using α-substituted aldehydes (e.g. for isobutyraldehyde addition, 10 mol% 4, 85% yield, 68% *ee* in 96h).

In 2007, Córdova and coworkers used the same catalyst (Figure 1.1, 4) for asymmetric Michael addition of aldehydes to maleimides.\(^{22}\) They also had promising results when using unsubstituted aldehydes additions to maleimides (e.g. 10 mol% 4, offers upto 91% yield, 15:1 *dr* and >99% *ee*). However, their catalyst did not show a productive result when using α-substituted aldehydes (e.g. for isobutyraldehyde addition, 10 mol% 4, offers only 40% yield with 51% *ee*).

Jørgensen and coworkers\(^{23}\) used chiral amines (Figure 1.1, 6) as organocatalysts for the asymmetric Michael addition. They investigated two possible structures for the enamine intermediate (8 and 9, Figure 1.2). After calculating the energy for structures 8 and 9, they found structure a to be the most stable. Further investigations proved that one of the 3,5-dimethylphenyl groups on the catalyst shields the *Re*-face and thus the *Si*-face is available for approach.

Barros and coworkers\(^{24a}\) used chiral piperazine derivatives as organocatalysts (Figure 1.1, 7). They used their catalyst for asymmetric Michael addition of aldehydes to nitroolefins. Their catalyst showed comparatively low activity for α-substituted aldehydes, e.g. isobutyraldehyde addition to *trans*-β-nitrostyrene which gave 75% *ee* and only 36% yield in 11 days reaction. They
proposed that the secondary amine forms an enamine and the electrophile approaches from the less hindered site. The electrostatic attraction between the partial positively charged enamine nitrogen and the partial negatively charged nitro-group help define the stereochemistry of the product.

![Figure 1.1. Reported steric based catalysts for the asymmetric Michael additions to nitroolefins and maleimides.](image)

**Figure 1.1.** Reported steric based catalysts for the asymmetric Michael additions to nitroolefins and maleimides.

![Figure 1.2. Enamine intermediate proposed by Jørgensen for catalyst 6 (Figure 1.1).](image)

**Figure 1.2.** Enamine intermediate proposed by Jørgensen for catalyst 6 (Figure 1.1).
1.4.2.2 Thiourea based bifunctional catalysts

Thiourea is an important building block in the design of bifunctional organocatalysts. The presence of static-double hydrogen bonding site on thiourea moiety makes it useful in the design of thiourea based bifunctional organocatalysts. Figure 1.3 shows some examples of thiourea-based catalysts used for asymmetric Michael additions. All these thiourea based catalysts are acting on the same principle of a bifunctional catalyst. A primary or secondary nitrogen on the catalyst attacks on the carbonyl carbon, converting them into chiral enamines. Meanwhile, the thiourea unit attracts the electrophile (nitroolefin or maleimide) through a hydrogen bond interaction. Here, I will explain shortly the catalytic activities of two catalysts from Figure 1.3. Tang and coworkers used a thiourea-based organocatalyst for the addition of ketones (cyclic and acyclic) and isobutyraldehyde to nitroolefins. They combined two well-known moieties, pyrrole and thiourea in close proximity to make an efficient organocatalyst (Figure 1.3, 11). With this specially designed catalyst they obtained up to 99% yield, 99:1 dr and 98% ee when using cyclohexanone as Michael donor. However, their catalyst showed only a mediocre result when using cyclopentanone as Michael donor. With cyclopentanone, 20 mol% loading of catalyst 11 reached only to 27% yield, 75:25 dr and 71% ee in a reaction of 60h. They also got a mediocre result with isobutyraldehyde addition to trans-β-nitrostyrene (20 mol% loading of catalyst 11, 61% yield and 82% ee).

Wang and coworkers, in 2010, reported asymmetric Michael addition of aldehydes (unsubstituted and α-substituted) to maleimides using a thiourea-based catalyst (Figure 1.3, 14). Their catalyst showed brilliant results with unsubstituted aldehydes or less sterically hindered α-substituted aldehydes (e.g isobutyraldehyde). For cyclopentanecarboxyaldehyde and cyclohexancarboxyaldehyde addition to maleimides, they increased their catalyst loading from 1 mol% to 15 mol% and obtained only 69% and 72% yields, with 96% ee and 95% ee, respectively.

All the remaining catalysts in Figure 1.3 work on the same common principle of a bifunctional catalyst.
**Figure 1.3.** Reported examples of thiourea based bifunctional catalysts for asymmetric Michael additions to nitroolefins and maleimides.
1.4.2.3 Amino-sulfonamides, amino-thiophosphoramide and amino-amides

Unlike thiourea-based catalysts, these catalysts contain only one hydrogen bond donor site, whereas like thiourea-based catalysts contain a static hydrogen bond donor. In the mechanism for these types of bifunctional catalysts, the acidic N-H group is used for electrophile attraction. Examples are shown in Figure 1.4. Here, I will discuss several examples of this category.

Wang and coworkers\textsuperscript{26} used catalyst \textbf{21} (Figure 1.4) for asymmetric Michael addition of aldehydes (unbranched and \(\alpha\)-branched) and ketones (cyclic and acyclic) to various nitroalkenes. Overall, they had excellent product profiles but their catalyst fails to show reaction progress when using cyclopentanone as a Michael donor. Under the same reaction conditions, they obtained only 11\% yield without any chiral induction.

Headley (2009)\textsuperscript{27} used catalyst \textbf{22} (Figure 1.4) for asymmetric Michael additions to nitroolefins. They demonstrated examples of ketone additions to nitroolefins and got up to 97\% isolated yield with 99\% \textit{ee} and 99:1 \textit{dr}. Using cyclopentanone as Michael donor, they obtained a negligible results, in 36 h only 10\% conversion without chiral induction.

Recently, Wang and Zhou\textsuperscript{24c} reported a new primary amine-thiophosphoramide bifunctional catalyst (Figure 1.4, \textbf{24}) for the asymmetric Michael addition. They had better results with their catalyst (97 to >99\% \textit{ee} and upto >99\% yield) for the asymmetric Michael addition of acetone to nitroolefins. Their main disadvantage was that they used only acetone as Michael donor in their reactions.

Córdova\textsuperscript{24b} was the first to demonstrate enantioselective Michael additions catalyzed by simple amino amide derivatives. He screened 15 different derivatives and found that only one of them showed prominent results for the addition of various cyclic and acyclic ketones to nitroolefins (Figure 1.4, \textbf{25}).
Figure 1.4. Amino-sulfonamides, thiophosphoramides, and amino-amides
1.4.2.4 Proline based diamine catalysts

Proline derivatives are very common in organocatalysis and an enormous number of variations have been synthesized. One of the reasons for their successful use is the less hindered nucleophilic secondary nitrogen on the pyrrolidine ring. By converting the carboxylic acid group of proline, one can easily reach secondary-tertiary diamine organocatalysts (Figure 1.5). These types of bifunctional catalysts are very common for asymmetric Michael additions. Examples of proline based bifunctional catalysts, used in asymmetric Michael additions are shown in Figure 1.5. All these diamines work on the same mechanism as shown in Scheme 1.13. Herein, I will shortly discuss some of the best examples.

Barbas and coworkers\textsuperscript{28} reported direct catalytic asymmetric Michael addition in brine. They used a pyrrolidine based bifunctional catalyst (Figure 1.5, 27) for the addition of various ketones and aldehydes to nitroolefins. Using cyclohexanone (2.0 equiv) as Michael donor, they obtained upto 99% yield, 98:1 \textit{dr} and upto 97% \textit{ee} with 10 mol% loading of the diamine, in 48h. On the other hand, the same reaction conditions did not show the same level of catalytic activity when using cyclopentanone as Michael donor (96h reaction, 75% yield, 77:23 \textit{dr} and 80% \textit{ee}).

Kotsuki and coworker\textsuperscript{29} designed chiral pyrrolidine catalysts with a pyridine base moiety adjacent to a stereogenic carbon (Figure 1.5, 28). The author mentioned that the pyridine base will facilitate enamine formation from ketone precursors by abstracting the $\alpha$-hydrogen. They used their catalyst for asymmetric Michael addition of ketones and aldehydes to nitroolefins and obtained up to 100% yield, 99:1 \textit{dr} and 98% \textit{ee}. They account that the resulting pyridinium ring shields one side of the enamine double bond within the transition state, and the nitroolefins approach from the non-shielded side to give the desired Michael product in high enantio- and diastereoselectivity.

Singh in 2007\textsuperscript{30} reported a pyrrolidine based bifunctional catalyst for the asymmetric Michael addition of ketones to aryl and alkyl nitroolefins (Figure 1.5, 29). Mostly, they obtained brilliant results with their catalyst i.e. up to 98% yield, 99:1 \textit{dr} and 99% \textit{ee}. Out of 26 examples studied, they obtained mediocre results not only with acetone but also with challenging cyclopentanone as compared to compared to other ketones. The same catalyst system provided an 89% yield for
acetone with only 16% ee. Cyclopentanone also showed a mediocre result (78% yield, 77:23 $dr$ and 75% ee).

**Excellent proline based diamines**

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28

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**Common examples of proline based diamines**

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**Figure 1.5.** Reported examples of proline based diamine organocatalysts for asymmetric Michael additions.
1.4.2.5 Cinchona based bifunctional catalysts

Cinchona alkaloid derivatives are another important class of organocatalysts used for asymmetric reactions from the early stage of organocatalysis.\textsuperscript{3,31} Though this is a natural class of organocatalysts, they are less common for catalyzing the asymmetric Michael addition. Connon and co-workers\textsuperscript{32} used a cinchona based primary-tertiary diamine catalyst (Figure 1.6, 44) for asymmetric Michael additions. They applied their catalyst for the addition of ketones (cyclic and acyclic) and aldehydes (unbranched and $\alpha$-substituted) to nitroolefins. In comparison with the reported literature they had superior results i.e. 10 mol\% of catalyst 44 achieved up to 98 % yield, 99 \% ee and 99/1 dr. These results show that not only secondary amines, but also primary amines have the ability to convert a carbonyl to an enamine.

![Figure 1.6. Reported examples of cinchona based bifunctional catalysts.](image)

1.4.2.6 Miscellaneous bifunctional catalysts

Applying the same principle of a bifunctional organocatalyst, some research groups have designed new organocatalysts which are different from the pre-existing templates (proline, thiourea, cinchona, etc.) as shown in figure 1.7. All of these catalysts hold the two important parts of a bifunctional catalyst in common: primary or secondary amines for the formation of a chiral enamine and another part which attracts the electrophile and bring it into close proximity.
1.4.2.7 Proline based electrostatic catalysts

These types of catalysts have nucleophilic nitrogen in combination with permanent dipole. The nitrogen attacks the carbonyl carbon converting it to a nucleophilic enamine, while the second part of the catalyst attracts the electrophile by electrostatic attraction. Figure 1.8 shows an example of this category of catalysts.

Recently, Zhong and coworkers\textsuperscript{33} used a proline based catalyst which has a secondary amine in combination with a polar group (Figure 1.8, \textsuperscript{49}). They explained that the secondary amine of the catalyst attacks on the carbonyl, converting it into a chiral enamine. Meanwhile the polar group (P=O) attract the nitro group (NO\textsubscript{2}) of the electrophile via electrostatic attraction, favoring higher selectivities and increased reaction rate. They used their catalyst for the asymmetric Michael addition of various cyclohexanones to nitroolefins and obtained excellent yields upto 99\%, upto 99:1 \textit{drs} and \textit{ees} upto 99\%.

\begin{center}
\includegraphics[width=0.8\textwidth]{Fig1_8.png}
\end{center}

\textbf{Figure 1.8.} Reported example of proline based electrostatic catalyst.
1.4.3 Asymmetric Michael addition to nitroolefins

List in 2001\textsuperscript{15} demonstrated for the first time the asymmetric Michael additions of different unmodified ketones to nitroolefins (Scheme 1.7). He got high yields (up to 94\%) and diastereoselectivities (>20:1) but the ee was very poor (maximum 23\%).

Aldehydes as Michael donors in catalytic asymmetric Michael additions were pioneered by Barbas group (Scheme 1.14).\textsuperscript{34} They used catalyst 33 (Figure 1.5) for this study and had up to 96\% yield with 98:2 dr and 78\% ee.

\[
\begin{align*}
\text{H} & \text{O} \\
\text{R} & \text{H} \\
\text{R'} & \text{NO}_2 \\
\text{THF, rt} & \text{33 (20 mol\%)} \\
\text{Yields} & \text{42 to 96\%} \\
\text{drs} & \text{85:15 to 98:2} \\
\text{ees} & \text{56 to 78\%}
\end{align*}
\]

\textbf{Scheme 1.14.} First example of catalytic asymmetric Michael addition of aldehydes to nitroolefins.

After these two reports, organocatalytic asymmetric Michael addition of aldehydes and ketones to nitroolefins is presently further developed. Figure 1.9 represents ketones that have been examined in asymmetric Michael additions. A commonly used electrophile is \textit{trans}-\textit{β}-nitrostyrene (Figure 1.10), however a variety of electrophiles can be used. Among the examined ketones (Figure 1.9), cyclohexanone (Figure 1.9, 50) is the most common nucleophile and excellent results in terms of ee, dr, yield, reaction time, temperature and catalyst loading are possible (as shown in Table 1.2). Despite the fact that ketones are common in asymmetric Michael additions, some of these are still challenging for the reported catalysts (e.g cyclopentanone 51, Figure 1.9). For a complete comparison of the product profile given by cyclohexanone and cyclopentanone, see Table 1.2 and Table 1.3.
Figure 1.9. Ketones commonly used for catalytic asymmetric Michael addition.

Figure 1.10. Commonly used electrophile in asymmetric Michael additions.

**Summary for the asymmetric Michael addition of cyclohexanone to nitroolefins**

In Table 1.2, I summarize the top 10 results on the basis of product product profile regarding asymmetric Michael addition of cyclohexanone to nitroolefins. Cyclohexanone is a standard substrate and shows excellent results in terms of ee and de >99% at room temperature (Entries 1
and 2 in Table 1.2). The enamine formed from is a good nucleophile and readily allows the reaction to proceed even by using low stoichiometry of cyclohexanone (Entries 3 and 4 in Table 1.2). All the catalysts used in Table 1.1 are proline based except for one (catalyst 26, Figure 1.4) which is a chiral bispidine-based catalyst. This organocatalyst contains a primary-secondary diamine template. The primary amine of the catalyst (26, Figure 1.4) attacks the carbonyl to make an enamine in the presence of 3,3,5,5-tetramethylbiphenol (additive). In the transition state, one of the hydrogen atoms of the hydroxyl group of TBBP participates in intramolecular H-bonding and another is free to protonate the secondary amine of 26 and to activate the nitroalkenes by H-bonding. All the results in Table 1.2 show that cyclohexanone is no longer a challenging ketone, but can be used as a model substrate for Michael addition to nitroolefins.

Table 1.2: Top 10 references about Michael addition of cyclohexanone to nitroolefins.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Loading (mol %)</th>
<th>Equiv ratio[a]</th>
<th>Time (h)</th>
<th>Temp [°C]</th>
<th>Yield (%)</th>
<th>dr (syn/anti)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
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<td>49 / 15</td>
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<td>16</td>
<td>rt</td>
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<td>29 / 10</td>
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<td>24</td>
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<td>99</td>
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<td>3</td>
<td>37 / 20</td>
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<td>99</td>
<td>98 : 2</td>
<td>97</td>
</tr>
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<td>0°C</td>
<td>96</td>
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<td>99 : 1</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>28 / 10</td>
<td>20</td>
<td>8</td>
<td>0°C</td>
<td>99</td>
<td>98 : 2</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>43 / 10</td>
<td>5</td>
<td>16</td>
<td>rt</td>
<td>100</td>
<td>96 : 4</td>
<td>91</td>
</tr>
</tbody>
</table>

[a] Equivalent ratio of cyclohexanone to nitroolefins.
Summary for the asymmetric Michael addition of cyclopentanone to nitrostyrene (a challenging Michael donor)

It is clear from the above table (Table 1.2) that cyclohexanone is a common substrate, and it is used as a standard or model substrate in asymmetric Michael addition to nitroolefins. Cyclopentanone on the other hand, unlike cyclohexanone, is a challenging carbonyl and often shows a much poorer product profile than cyclohexanone.\(^{25a, 28, 30, 35-37}\)

Under the same reaction conditions, cyclopentanone always showed poor results as compared to cyclohexanone, which reveals that probably the enamine of cyclopentanone is less nucleophilic as compared to cyclohexanone (For comparison see the activities of catalysts \(^{27, 31, 37, 29, 11, 26}\) in Table 1.2 and 1.3).

Based on the product profile in asymmetric Michael addition to \textit{trans-\(\beta\)}-nitrostyrene, I summarized 12 best results in Table 1.3. In 75\% (Table 1.3, 9 entries out of 12) of the cases, proline-based chiral secondary amines have been used to catalyze the Michael addition of cyclopentanone to \textit{trans-\(\beta\)}-nitrostyrene.\(^{25a, 28, 30, 36, 37, 39-42}\) The remaining 25\% (Table 1.3, 3 entries out of 12) use the salt of an amino acid,\(^{43}\) a chiral bispidine-based organocatalyst,\(^{35}\) and a thiourea assembled with an amino acid.\(^{25b}\) An explanation of these three types of organocatalyst is:

Feng and coworkers\(^{43}\) used chiral functionalized salt catalysts (35, Figure 1.5) for asymmetric Michael addition of ketones (cyclic and acyclic) to nitroolefins. They classified their catalysts into three different types: Type 1 has an achiral cation part and a chiral anion part, Type 2 with a chiral cation part and an achiral anion part, and Type 3 has both parts chiral. They investigated that all the three types can effectively promote the addition of various ketones to nitroolefins but Type 1 was superior as compared to the other two types. By using Type 1 (35, Figure 1.5), they obtained up to 99\% yield, 95\% \textit{ee} and 96:4 \textit{dr} with cyclohexanone, but with the cyclopentanone as a Michael donor they observed a mediocre result (Table 1.3, entry 5, 52\% yield, 83\% \textit{ee} and 83:17 \textit{dr}).

Zhao and coworkers\(^{25b}\) used a catalyst assembly (13, Figure 1.3) for Michael addition of ketones (cyclic and acyclic) to nitroolefins. They concluded that when a carboxylic acid and a tertiary
amine carrying a thiourea moiety are mixed, acid-base reaction occurs to form an ammonium salt. The ionic interaction between the ammonium cation and the carboxylate causes these two modules to self-assemble, forming a catalyst system. They used different modules and found that quinidine-thiourea matched with L-phenylglycine and formed a model organocatalyst. They catalyzed the Michael addition of different cyclic and acyclic ketones to nitroolefins and obtained up to 92% yield, 96:4 \textit{dr} and 99% \textit{ee} but under the same set of conditions cyclopentanone gave poor diastereoselectivity and yield (Table 1.3, entry 4).

Feng and coworkers\textsuperscript{35} used a chiral bispidine-based catalyst (26, Figure 1.4) for asymmetric Michael additions. They suggested that a primary-secondary diamine template on bispidine could serve through an enamine activation and H-bonding interaction. With the addition, of, acyclic ketones to nitroalkenes they achieve up to 99% yield and 99% \textit{ee}. In the addition of cyclohexanone to various nitroalkenes they obtained up to 99% yield, 98:2 \textit{dr} and 99% \textit{ee}. Under their optimized conditions, cyclopentanone showed a poor result (Table 1.3, entry 12, 85% yield, 48:52 \textit{dr}; 26% \textit{ee}), which was an indication of the limits of their catalyst’s activity.

In conclusion, results in Table 1.3 show that cyclopentanone is still difficult and overcoming this challenge may be possible by designing a proper catalyst. Even recent attempts to solve this problem are not successful in a practical reaction.\textsuperscript{44}

\textbf{Table 1.3:} Top 12 references about Michael addition of cyclopentanone to \textit{trans-β}-nitrostyrene.

\begin{center}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
\textbf{Entry} & \textbf{Catalyst/Loading (mol %)} & \textbf{Equiv. ratio$^{[a]}$} & \textbf{Time (h)} & \textbf{Temp ($^\circ$C)} & \textbf{Yield (\%)} & \textbf{\textit{dr} (syn/anti)} & \textbf{\textit{ee} (\%)} \\
\hline
1$^{[39]}$ & 5 / 10 & 3 & 26 & rt & 80 & 90 : 10 & 98$^{[38]}$ \\
2$^{[35]}$ & 37 / 20 & 2 & 156 & rt & 88 & 83 : 17 & 95$^{[3]}$ \\
3$^{[40]}$ & 32 / 10 & 8 & 30 & rt & 85 & 80 : 2 & 83$^{[4]}$ \\
\hline
\end{tabular}
\end{center}
### Table 1.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopentanone / trans-β-nitrostyrene</th>
<th>Temperature</th>
<th>ee of syn diastereomer</th>
<th>ee of anti diastereomer</th>
</tr>
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<tbody>
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<td>13 / 5</td>
<td>7</td>
<td>63</td>
<td>77 : 23</td>
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<tr>
<td>6[^a]</td>
<td>27 / 10</td>
<td>2</td>
<td>25 °C</td>
<td>75</td>
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<tr>
<td>7[^a]</td>
<td>31 / 10</td>
<td>20</td>
<td>rt</td>
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</tr>
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</tr>
<tr>
<td>12[^a]</td>
<td>26 / 10</td>
<td>20</td>
<td>-</td>
<td>85</td>
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</table>

[^a] Equivalent ratio of cyclopentanone to trans-β-nitrostyrene.  
[^b] ee of syn diastereomer.  
[^c] ee of anti diastereomer.

#### 1.4.4 Asymmetric Michael addition to maleimides

The addition of *in situ* generated chiral enamine (from an aldehyde or a ketone) to maleimide Michael acceptors access to chiral pyrrolidinediones (succinimides). These products can be further reduced to pyrrolidines and pyrrolidinone (δ-lactams),[^45] which are important structural units in natural products and some clinical drug candidates.[^46] The addition of *in situ* generated enamine to maleimides (Michael acceptors) was demonstrated for the first time by Barbas in 2003.[^16] He did not report any stereoselectivity for the products. Since then, the use of maleimides as Michael acceptors remains unexplored for a few years. Currently, asymmetric Michael addition to maleimides is catching attraction, and additions of unmodified ketones[^47] and aldehydes[^22] to maleimides are reported. The molecular complexity of the resulting chiral succinimides increased when the generated chiral enamine is from an α-substituted aldehyde. Cordóva and coworkers[^22] for the first time explored this possibility by the addition of isobutyraldehyde to N-phenylmaleimide. They used a silyl protected diphenyl (S)-prolinol as catalyst (Figure 1.1, 4) and obtained very poor yield and ee as shown in Scheme 1.15.
Scheme 1.15. Example of asymmetric Michael addition of α-substituted aldehydes to maleimides.

After this first demonstration, four more attempts are reported\textsuperscript{25c,48} for the synthesis of similar Michael products, to achieve excellent products profile, but unfortunately they didn't achieve this goal. Interestingly, all four reports used a monothiourea of trans-1,2-diaminocyclohexane as catalyst (Figure 1.3, 14, 15 and 16). A product summary of those reports is shown in Table 1.4. Figure 1.11 shows α-substituted aldehydes examined in asymmetric Michael additions to maleimides.

Figure 1.11. α-substituted aldehydes used in asymmetric Michael additions to maleimides.
Table 1.4: Summary for the asymmetric Michael addition of reported α-substituted aldehydes addition to maleimides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product structure</th>
<th>Catalyst/Loading (mol %)</th>
<th>Equiv ratio$^a$</th>
<th>Temp [$^\circ$C]</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>$dr$</th>
<th>ee (%)</th>
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<td>97</td>
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<td>2</td>
<td>25</td>
<td>1</td>
<td>96</td>
<td>-</td>
<td>99</td>
</tr>
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<td>2</td>
<td>25</td>
<td>6</td>
<td>98</td>
<td>-</td>
<td>99</td>
</tr>
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<td><img src="image4" alt="Product structure" /></td>
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<td>2</td>
<td>25</td>
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<td>85</td>
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<td>25</td>
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<td>95</td>
<td>-</td>
<td>98</td>
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<tr>
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<td><img src="image7" alt="Product structure" /></td>
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<td>25</td>
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<td>Isolation</td>
<td>Diastereoisomer Ratio</td>
<td>Ref.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>----------</td>
<td>-------</td>
<td>-----------</td>
<td>----------------------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15&lt;sup&gt;2Xc&lt;/sup&gt;</td>
<td><img src="image1" alt="Structure" /></td>
<td>14/5</td>
<td>2</td>
<td>25</td>
<td>70</td>
<td>79</td>
<td>2.3:1</td>
<td>98&lt;sup&gt;hj&lt;/sup&gt; / 96&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>16&lt;sup&gt;4Xb&lt;/sup&gt;</td>
<td><img src="image2" alt="Structure" /></td>
<td>15/5</td>
<td>2</td>
<td>25</td>
<td>6</td>
<td>85</td>
<td>1:1</td>
<td>93&lt;sup&gt;hj&lt;/sup&gt; / 94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>17&lt;sup&gt;2Xc&lt;/sup&gt;</td>
<td><img src="image3" alt="Structure" /></td>
<td>14/5</td>
<td>2</td>
<td>25</td>
<td>84</td>
<td>81</td>
<td>11:2</td>
<td>99&lt;sup&gt;hj&lt;/sup&gt; / 96&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>18&lt;sup&gt;4Xa&lt;/sup&gt;</td>
<td><img src="image4" alt="Structure" /></td>
<td>15/10</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>96</td>
<td>2:1</td>
<td>99&lt;sup&gt;hj&lt;/sup&gt; / 96&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>19&lt;sup&gt;4Xa&lt;/sup&gt;</td>
<td><img src="image5" alt="Structure" /></td>
<td>15/10</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>98</td>
<td>2:1</td>
<td>99&lt;sup&gt;hj&lt;/sup&gt; / 99&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Wang and coworkers\textsuperscript{25c} presented a primary amine thiourea catalyst (Figure 1.3, \textbf{14}) for direct asymmetric Michael addition of aldehydes (unsubstituted and $\alpha$-substituted) to maleimides. Their catalyst showed brilliant activity with unsubstituted aldehydes and the only $\alpha$-substituted aldehyde was isobutyraldehyde (Table 1.4, entry 1). For aldehydes like cyclopentanecarboxyaldehyde and cyclohexanecarboxyaldehyde they increased their catalyst loading from 1 mol\% to 15 mol\% and up to 10 equivalents of aldehyde but still they did not achieve a high isolated yield (Table 1.4, entries 7 and 10). They also tried $\alpha,\alpha'$-substituted aldehyes to get contiguous quaternary-tertiary stereogenic carbons (Table 1.4, entries 15 and 17). The observed enantioselectivities were comparable to their previous examples but the reaction times were 70h and 84h with poor $dr$s of 2.3:1 and 11:2 respectively.

Similarly, the reports\textsuperscript{48} show that symmetrical $\alpha$-substituted aldehydes can give a similar product profile (Table 1.4, entries 2-6, 8, 9, 11, and 12) when using the same type of catalyst (Figure 1.3, \textbf{15} and \textbf{16}).

Liang and Ye\textsuperscript{48a} performed additions of asymmetrical $\alpha$-substituted aldehydes to maleimides (Table 1.4, entries 13, 14, 18 and 20). They were unable to report the absolute stereochemistry for their products. Their catalyst loading used to synthesize these products was always high (10-20 mol\%) and the diastereoselectivity was again a remaining challenge.
Chapter 1

1.5 Research Goals: bifunctional based asymmetric Michael additions

1.5.1 Primary-tertiary diamine for addition of cyclopentanone to nitroolefins

Over the past few years, a variety of classes of organocatalysts has been developed for different asymmetric reactions. Aminocatalysis represents a prevailing class of these catalysts. Chiral secondary amines are by far the most intensively studied. By contrast, primary amine catalysts were ignored. Despite the reasons, primary amine catalysts recently emerged as a new tool for asymmetric reactions. On the other hand, some substrates (e.g. cyclopentanone, α-substituted aldehydes) in asymmetric Michael addition are still an open challenge for new researchers. My goal was the synthesis of bifunctional organocatalysts containing primary amine and to explore their applications in asymmetric Michael addition of ketones (cyclopentanone) and aldehydes to nitroolefins.

1.5.2 Non-covalent catalysts for addition of α-substituted aldehydes to maleimides

Asymmetric Michael addition to maleimides leads to the products, called succinimides. These products and their reduced forms (chiral pyrrolidines and δ-lactams) are important building blocks for drugs and natural products. Additions of α-branched aldehydes to maleimides give more complex succinimides products with contiguous quaternary-tertiary stereogenic carbons. These types of Michael additions are uncommon and not fully explored. My goal was to design bifunctional catalysts which would overcome the reported limitations to access these tough α-succinimide products.
References


Chapter 2

RESULTS AND DISCUSSION:
DIAMINE CATALYSTS
2.1 Introduction

Based on the existing literature on organocatalysis, diamines are considered to be useful bifunctional catalysts. Of the diamines, primary-tertiary diamines will be of high value in asymmetric organocatalysis. So my prime research goal was to synthesize primary-tertiary diamines and apply it for asymmetric reactions, specifically asymmetric Michael addition of challenging carbonyls to nitroolefins. This new designed diamine template contains a tertiary amine in a pyridine ring and a primary amine (Figure 2.1). Catalysts based on this template can be synthesized in a short number of steps and allows a high degree of modularity.

Figure 2.1. Primary-tertiary diamines.

Based on the principles of organocatalysis and the literature results from a primary-tertiary diamine catalyst,\(^1\) I believe that my primary-tertiary diamine template (Figure 2.1) will hold the potential to induce enantioselective Michael addition. Like most of the diamines, my template holds the two important parts which represent an ideal organocatalyst: a nucleophilic heteroatom and a tertiary amine which upon protonation acts as a hydrogen bond donor. My diamine template has a nucleophilic primary amine and tertiary nitrogen for hydrogen bonding. The primary amine of the diamine should attack the carbonyl, converting it into a nucleophilic
enamine. Meanwhile, the protonated nitrogen on the pyridine ring of the bifunctional catalyst serves as a site which activates the electrophile and simultaneously brings it close to the enamine through H-bonding. This special arrangement of the enamine and electrophile allows practical reaction rates that were not achievable without such a bifunctional catalyst.

2.2 Synthesis of chiral primary-tertiary diamines

The catalyst 86 (Scheme 2.1) has been synthesized according to the reported method.\(^2\) The corresponding ketone (Scheme 2.1, structure 83) for catalyst 78 is commercially available. For catalyst 79, the corresponding ketone was synthesized by treating the commercially available acetylpyridine (Scheme 2.1, structure 82) with NaH in the presence of a phase transfer catalyst (18-C-6) in toluene followed by slow addition of \(\alpha,\alpha\)-dibromoxylene. Then the corresponding ketone (83) was treated with commercially available \((S\)-\(p\)-methoxyethylbenzylamine in the presence of Ti(OiPr)\(_4\) at 60 °C to afford the imine (84) followed by hydrogenation with Pt/C using 10 bars of hydrogen pressure to obtain the corresponding secondary amine (85). The secondary amine had mediocre diastereoselectivity (63:37), which was enriched to >99% \(dr\) by flash chromatography (85a). The single diastereomer (85a) was treated with BCl\(_3\) and NaI to afford enantiopure primary amine (86).
Scheme 2.1. Synthesis of chiral pyridyl-primary diamines.
2.3 Model reaction: cyclopentanone addition to \textit{trans}-\(\beta\)-nitrostyrene

To test the efficiency of our designed catalyst template for asymmetric Michael addition, I selected the addition of cyclopentanone to \textit{trans}-\(\beta\)-nitrostyrene as a model reaction.

2.3.1 Diamine catalysts screening

Based on the optimized conditions of reported literature\(^3\) about diamine promoted asymmetric Michael addition of ketones to nitroolefins, I considered the same reaction conditions as an ideal starting point for screening our catalysts. Using 10 mol\% loading of catalyst with 10 mol\% of 2,4-dinitrobenzenesulfonic acid in chloroform, I performed the reaction of cyclopentanone to \textit{trans}-\(\beta\)-nitrostyrene \((87)\) using different pyridyl-primary amine catalysts (Scheme 2.2).

Catalyst \((S)-79\) showed poor performance in terms of reaction rate and stereoselectivity for asymmetric Michael addition of cyclopentanone to \textit{trans}-\(\beta\)-nitrostyrene under the reported reaction conditions.\(^3\)

Next, I used \((S)-78\) as catalyst for the same reaction under the same reaction conditions as shown in Scheme 2.3. After 24h, the product formation was good (65% HPLC conversion) with encouraging diastereoselectivity (82:18 \(dr\)) and enantioselectivity (83\% \(ee\)).
Scheme 2.3. Asymmetric Michael addition of cyclopentanone to \textit{trans}-\(\beta\)-nitrostyrene catalyzed by (S)-78.

Finally I used another pyridyl-primary amine ((S)-80) for the same reaction of cyclopentanone with \textit{trans}-\(\beta\)-nitrostyrene under the same reaction conditions. After 48h there were only traces of product as shown in Scheme 2.4.

Scheme 2.4. Asymmetric Michael addition of cyclopentanone to \textit{trans}-\(\beta\)-nitrostyrene catalyzed by (S)-80.

2.3.2 Solvent screening

Catalyst (S)-78 is doubly benzylic, which most likely enhances its nucleophilicity and perhaps it is the reason for its greater reactivity (Scheme 2.3). Afterwards, I screened a few solvents for catalyst (S)-78.

Protic solvents like methanol, water or a 1:1 mixture of the two provided either lower \(ee\) or lower \(dr\)s than chloroform (Table 2.1, entries 2, 6, and 7). A brine medium provided a quantitative yield, but the \(ee\) (74\%) was significantly lower as compared to the reaction in chloroform (Table
2.1, entry 3). THF and a mixture of chloroform and water (1:1) were also poor in terms of stereoinduction and reaction rate (Table 2.1, entries 4 and 5).

As my main focus was to get Michael products with higher diastereoselectivity and enantioselectivity, chloroform appeared to be the ideal solvent for further optimizations.

**Table 2.1:** Solvent screening for asymmetric Michael addition of cyclopentanone to trans-β-nitrostyrene catalyzed by (S)-78.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>syn/anti[^a]</th>
<th>Yield (%)[^b]</th>
<th>ee (%)[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>24</td>
<td>82:18</td>
<td>65</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>24</td>
<td>60:40</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>Brine</td>
<td>24</td>
<td>77:23</td>
<td>95</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>CHCl₃+H₂O</td>
<td>14</td>
<td>70:30</td>
<td>50</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>24</td>
<td>70:30</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>24</td>
<td>60:40</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>MeOH+H₂O</td>
<td>14</td>
<td>70:30</td>
<td>60</td>
<td>67</td>
</tr>
</tbody>
</table>

[^a]: Determined by chiral HPLC analysis from crude reaction mixture. 
[^b]: Estimated conversion by TLC.

### 2.3.3 Acids and additive screening

Taking chloroform as solvent, I screened different acids and additives for the asymmetric Michael addition of cyclopentanone to trans-β-nitrostyrene catalyzed by (S)-78 as shown in Table 2.2.

Before going to the acids screening, I set up a reaction without any acid and confirmed that the reaction is not productive without the presence of an acid (Table 2.2, compare entries 1 and 2). I tested some other sulfonic acids such as p-toluene sulfonic acid and camphor sulfonic acid but they were not as good as 2,4-dinitrobenzene sulfonic acid (Table 2.2, compare entries 3 and 5.
with 1). Carboxylic acids were found to be poor in combination with our diamine catalyst (Table 2.2, entries 4 and 6). Finally, dodecylbenzene sulfonic acid sodium salt (as additive) in combination with 2,4-dinitrobenzene sulfonic acid improved the selectivity (Table 2.2, entries 7-9). Using different ratios of 2,4-DNBSA and DBSAS, it was found that a ratio of 1:4 of 2,4-DNBSA and DBSAS gave an improved result i.e. after 24h the product formed was up to 80% with 83:17 \textit{dr} and 90% \textit{ee}.

**Table 2.2:** Acids and additive screening for the asymmetric Michael addition of cyclopentanone to \textit{trans}-β-nitrostyrene catalyzed by \((S)-78\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acids and additive</th>
<th>Time (h)</th>
<th>syn/anti([a])</th>
<th>Yield (%)([b])</th>
<th>ee (%)([a])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2,4-DNBSA</td>
<td>14</td>
<td>82:18</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>No acid</td>
<td>24</td>
<td>60:40</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>(p)-toluene SA</td>
<td>14</td>
<td>75:25</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>(p)-nitro BA</td>
<td>14</td>
<td>60:40</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Camphor SA</td>
<td>14</td>
<td>75:25</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>TFA</td>
<td>24</td>
<td>90:10</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>2,4-DNBSA+DBSAS (1:1)</td>
<td>14</td>
<td>81:19</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>2,4-DNBSA+DBSAS (1:2)</td>
<td>14</td>
<td>82:18</td>
<td>55</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>2,4-DNBSA+DBSAS (1:4)</td>
<td>24</td>
<td>83:17</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

\([a]\) Determined by chiral HPLC analysis from crude reaction mixture.  
\([b]\) Estimated conversion by TLC.
2.4 Asymmetric Michael addition of cyclopentanone to various nitroolefins

It was clear from the reported literature\(^5\) that cyclopentanone is a difficult Michael donor and that it is rarely used in asymmetric Michael addition. As a first example, I added cyclopentanone (6) to trans-β-nitrostyrene (7) under the optimized reaction conditions (Table 2.3, entry 1). In a 24h reaction, a 76% isolated yield with 81:19 \(dr\) and 87% \(ee\) of 88 was encouraging for further studies.

**Table 2.3:** Asymmetric Michael addition of cyclopentanone (86) to nitroolefins catalyzed by (S)-78.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)(^{[b]})</th>
<th>syn/anti(^{[c]})</th>
<th>ee (%)(^{[d]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>24</td>
<td>76</td>
<td>81:19</td>
</tr>
<tr>
<td>2</td>
<td>[(\text{S})-78 (10 mol%), 2,4-DNBSA (2.5 mol%), DBSAS (10 mol%), CHCl(_3) (2.0 M), rt]</td>
<td></td>
<td>33</td>
<td>98</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>[(\text{S})-78 (4 mol%), DBSAS (4 mol%), 2,4-DNBSA (1 mol%), Brine (1.0 M), room temperature]</td>
<td></td>
<td>21</td>
<td>92</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>24</td>
<td>85</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>30</td>
<td>89</td>
<td>57:43</td>
</tr>
</tbody>
</table>

---

\(^{[a]}\)General reaction conditions: Nitroolefins (1.0 equiv), cyclopentanone (5.0 equiv), (S)-78 (10 mol %), DBSAS (10 mol %), 2,4-DNBSA(2.5 mol%), CHCl\(_3\) (2.0 M), room temperature. \(^{[b]}\)Isolated yield data after column chromatography on silica gel. \(^{[c]}\)Determined by \(^1\)H NMR and chiral HPLC of the crude reaction. \(^{[d]}\)Determined by chiral HPLC of the pure product. \(^{[e]}\)Reaction condition: trans-β-nitrostyrene (1.0 equiv), cyclopentanone (5.0 equiv), (S)-78 (4 mol %), DBSAS (4 mol %), 2,4-DNBSA (1 mol %), Brine (1.0 M), room temperature. \(^{[f]}\)\(ee\) of the anti product.
To our knowledge the best result regarding selectivity for the product 88 (Table 2.3) is 98 % ee, 90 : 10 dr and 80 % yield in 26 h with 10 mol % of catalyst loading. Our result to get product 88 was parallel to the reported result in terms of catalyst loading, reaction time and yield at room temperature, but the selectivity was slightly lower (Table 2.3, entry 1). The lowest catalyst loading reported to date for obtaining product 88 is 5 mol % with only 63 % yield in a 5 days reaction. Loading 4 mol % of (S)-78 offer 98 % isolated yield in relatively shorter reaction time with mediocre selectivity (Table 2.3, entry 2). Continuing our research for cyclopentanone, several substituted β-nitrostyrenes were evaluated under the optimized conditions (Table 2.3, entries 3, 4 and 5). A facile reaction as can be depicted by the reaction time and yield was found with trans-4-Methyl-β-nitrostyrene offering product 89 in optimum selectivity (Table 2.3, entry 3). To date, products 89 and 90 are only reported in racemic form while product 91 is a new substrate. Product 90 also appeared with higher diastereoselectivity and yield (Table 2.3, entry 4).

2.5 Asymmetric Michael addition of isobutyraldehyde to various nitroolefins

Next, I studied the catalytic asymmetric Michael addition of isobutyraldehyde to different nitroolefins (Table 2.4): α-substituted aldehydes are also challenging in asymmetric Michael additions.

I found that under my optimized conditions, isobutyraldehyde can be added to different nitroolefins with mediocre to good yields (53-70%) and good to high enantioselectivities (78-90%). A higher enantioselectivity (90%) with good yield (70%) was observed when using 2-(2-Nitrovinyl)furan as Michael acceptor (Table 2.4, entry 3).
Table 2.4: Asymmetric Michael addition of isobutyraldehyde (90) to nitroolefins catalyzed by (S)-78.\textsuperscript{[a]}

\[
\begin{align*}
\text{H} & \quad \text{CHCl}_3 (2.0 \text{ M}), \text{rt} \\
\text{O} \quad \text{Ar} & \quad \text{NO}_2 \\
\text{N} & \quad \text{NH}_2 \\
\text{O} & \quad \text{Ar} \\
\text{N} & \quad \text{NO}_2
\end{align*}
\]

\[\text{(S)-78} \quad \text{(10 mol\%)} \]

\[\text{2,4-DNBSA} \quad \text{(2.5 mol\%)} \]

\[\text{DBSAS} \quad \text{(10 mol\%)} \]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Entry} & \text{Product} & \text{Time (h)} & \text{Yield (%)}\textsuperscript{[b]} & \text{ee (%)}\textsuperscript{[c]} \\
\hline
1 & \begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{NO}_2
\end{array} & 36 & 58 & 78 \\
\hline
2 & \begin{array}{c}
\text{O} \\
p\text{-MePh} \\
\text{NO}_2
\end{array} & 40 & 53 & 80 \\
\hline
3 & \begin{array}{c}
\text{O} \\
2\text{-furyl} \\
\text{NO}_2
\end{array} & 45 & 70 & 90 \\
\hline
4 & \begin{array}{c}
\text{O} \\
p\text{-OMePh} \\
\text{NO}_2
\end{array} & 52 & 59 & 90 \\
\hline
\end{array}
\]

\textbf{Note:} General reaction conditions: Nitroolefins (1.0 equiv), isobutyraldehyde (5.0 equiv), (S)-78 (10 mol \%), DBSAS (10 mol \%), 2,4-DNBSA (2.5 mol \%), CHCl\textsubscript{3} (2.0 M), room temperature.\textsuperscript{[b]} Isolated yield data after column chromatography on silica gel.\textsuperscript{[c]} Determined by chiral HPLC analysis of the pure product.
2.6 Mechanism

For reasons shortly discussed, it is assumed that the primary amine of \((S)-78\) attacks on the carbonyl carbon of cyclopentanone forming the nucleophilic enamine. Two possible rotamers of this enamine are shown in Scheme 2.5 (97 and 98). A total of eight facial approaches of the electrophile are possible for 97 and 98, but the \(Re_{\text{enamine}}, Re_{\text{nitroolefin}}\) approach provides the correct stereochemical product, \((S,R)-88\).\(^{10}\) In a co-operative bifunctional catalysis model, it is envisioned that the protonated pyridine ring attracts the electrophile (\(\text{trans-}\beta\)-nitrostyrene) as depicted in transition state 99 (Scheme 2.5). Another possibility is a transition state based on steric consideration, as depicted in 100 (Scheme 2.5), providing the same \((S,R)-88\) product. Based on literature precedent,\(^1,9,11\) and the expected steric repulsion, as noted in 100, between the phenyl group and the methylene unit of \(\text{trans-}\beta\)-nitrostyrene, I currently believe the bifunctional catalysis model is operative for my catalyst.
Scheme 2.5. Proposed transition state: cyclopentanone addition to \textit{trans}-\(\beta\)-nitrostyrene with catalyst \((S)-78\).
Further support of this catalysis model comes from observing the reactivity of isobutyraldehyde and cyclohexanecarboxyaldehyde. For example, in the steric based model, **101** (Scheme 2.6), one additionally noted a further steric hinderance from the methyl group with the phenyl and pyridyl groups of the catalyst. It consequently seems more likely that transition state **102** represents a lower energy pathway to the major product (S)-93. Nonetheless, it is perhaps unsurprising that this reaction is slower than that of cyclopentanone because the phenyl moiety of the trans-β-nitrostyrene is gauche to the two methyl groups.

**Scheme 2.6.** Proposed transition state: Isobutyraldehyde addition to trans-β-nitrostyrene with catalyst (S)-78.
A final convincing argument for the bifunctional model over the steric catalysis model is that cyclohexanecarboxyaldehyde is essentially unreactive (~30% yield, 52 h). This makes sense only if a bifunctional catalysis model transition state is operative, because it would be sterically very challenging to place the phenyl moiety of \textit{trans}-\beta-nitrostyrene over the ring of cyclohexane (Figure 2.2, 103). But note that if the steric model was correct, no arguments for reduced rates of reaction can be made.

![Figure 2.2. Proposed transition state: cyclohexanecarboxylaldehyde addition to \textit{trans}-\beta-nitrostyrene with catalyst (S)-78.](image)

2.7 Absolute and relative stereochemistry

The optical rotation of diamine (S)-78 is reported. Based on my measurements I have determined the optical rotation of diamine (S)-78.

The reported $^1$H NMR of compound 88 (Table 2.3), reveals that in the case of the \textit{syn} product, the benzylic proton (–CHPh in 88) gives a splitting at 3.70 ppm while in the case of the \textit{anti} product the same proton appears at 3.83 ppm. Comparing the $^1$H NMR of my product with the reported data confirmed that I have the \textit{syn} product (\textit{syn}-88). Using a literature based HPLC method, I observed the same retention time for the major and minor enantiomers, confirming that I have (S, \textit{R})-88. Compounds 89, 90 and 91 (Table 2.3) showed a similar trend when using the same HPLC column. Using a chiral AS-H HPLC column, the minor enantiomer appeared before the major enantiomer, while a reverse trend of both enantiomers was observed when using chiral OD-H
HPLC column. Based on these stereochemical findings, compounds 89, 90 and 91 were also assigned the *syn* diastereomer configuration.

Compounds 93-96 (Table 2.4) were previously synthesized in our laboratory, using the same HPLC method I found the same retention times for major and minor enantiomers.\textsuperscript{13}

### 2.8 Conclusion

(S)-phenyl(pyridin-2-yl)methanamine [(S)-78] was used as an effective catalyst for asymmetric Michael addition of isobutyraldehyde and cyclopentanone to various nitroolefins. The overall performance of (S)-78 was good to excellent for the addition of cyclopentanone to nitroolefins in terms of yields (76-98%), diastereoselectivities (57:43-88:12) and enantioselectivities (77-88%). Isobutyraldehyde as Michael donor also gave decent yields (53-70%) and enantioselectivities (78-90%).
References

5. For literature details regarding asymmetric Michael addition of cyclopentanone to trans-β-nitrostyrene see chapter 1, section 1.4.3.
12. (S)-78 catalyzed asymmetric Michael addition of cyclohexanecarboxyaldehyde with trans-β-nitrostyrene was not preceded further, therefore no analytical data is provided for this product in my thesis.
Chapter 3

RESULTS AND DISCUSSION:
ASSEMBLED BIFUNCTIONAL CATALYSTS
3.1 Introduction

Asymmetric Michael addition to maleimides leads to the products, called succinimides. These products and their reduced forms (chiral pyrrolidines and δ-lactams)\(^1\) are important building blocks found in drugs and natural product synthesis\(^2,3\). Additions of α-branched aldehydes to maleimides give more complex α-succinimides products with contiguous quaternary-tertiary stereogenic carbons. The possibility for catalytic synthesis of these complex α-succinimides was pioneered by Córdova in 2007.\(^4\) Until today these types of Michael products are uncommon and not yet fully explored. This is not surprising that α-branched aldehyde additions versus unbranched aldehydes additions to maleimides is showing poor results.\(^4,5\) The challenge in the addition of these α-substituted aldehydes to maleimides is the lack of practical organocatalytic examples. In short, starting material stoichiometries, catalyst loading, reaction times and an excellent stereoselectivity is required. Here I have presented a new catalyst system to overcome the reported shortcomings for the asymmetric Michael addition of α-branched aldehydes to maleimides.

The encouraging factor to start this challenging project was the catalyst system discovered by our research group.\(^6\) A non-covalent bifunctional catalyst showed better performance for the asymmetric Michael addition of α-branched aldehydes to nitroalkenes (Scheme 3.1).

![Scheme 3.1. Asymmetric Michael addition of α,α-disubstituted aldehydes to nitroalkenes.\(^6\)](image-url)
Chapter 3

3.2 Non-covalent bifunctional catalyst for asymmetric Michael additions

Over the past decade, organocatalysis has been a well established field and a variety of classes of organocatalysts have been developed for asymmetric Michael additions. Amino acids, especially (S)-proline and its derivatives, have risen to prominence, and have been successfully applied to catalyze a wide range of asymmetric reactions. In proline derivatives, the carboxylic group has been used as a site of modifications. Typically, covalent bonds are used to connect the pyrrolidine backbone with stereocontrolling moieties. Therefore, to find an effective catalyst, one has to perform several synthetic steps for synthesizing a library of catalysts for screening.

Addition of an additive/ or co-catalyst (small, neutral, organic molecules capable of binding or activating either catalyst or substrates or both via noncovalent interactions, particularly H-bonding) can be crucial for enhancing the reactivity and/or stereoselectivity of the catalytic system. So an alternative and simple approach would be to use this additive/ or co-catalyst in combination with amino acids to find out the best catalyst system. This simple approach will have overall advantages over other synthetic methods. Clarke was the first who used a self-assembled catalyst system for the asymmetric Michael addition. Although his first attempt afforded mediocre results in terms of catalyst activity and stereoselectivity, it was an important and easy way to design suitable catalysts for such a reaction.

After this first report on a self-assembled catalyst, several attempts were reported to bring forward the best catalyst. Although the reported assembled catalysts showed some disadvantages (e.g. catalyst loading, starting material stochiometry or especially substrate scope when using α-substituted carbonyls). But the main advantage of this approach is obvious: mostly, there is no chemical synthesis, so the modification of the catalyst structure only needs a simple replacement of the catalyst components. Moreover, libraries of catalysts for screening and structure modification can be obtained easily and efficiently.

Keeping the main principle of a bifunctional catalyst, our group developed a new self-assembled catalyst for asymmetric Michael addition of α-substituted aldehydes to nitroalkenes. A three component catalyst system entailing an amino acid (O'Bu-L-threonine), a H-bond donor (sulfamide), and an amine base (DMAP) can make a bifunctional catalyst by non-covalent
interaction, as shown in Scheme 3.1. A 5 mol% loading of the catalyst with only 1.2–2.0 equiv of aldehyde starting material was the best product profile (upto 98% isolated yield, 78:22 \( dr \) and 99% \( ee \)).

To expand the reported catalyst system, I performed asymmetric Michael addition of isobutyaldehyde to trans-\( \beta \)-nitrostyrene catalyzed by non-covalent catalysts (Table 3.1).

**Table 3.1: Nitroalkene additions: expanded catalyst system investigation.\(^{[a]}\)**

The numbers, 107-119, in the table represent different hydrogen bond donors that were investigated, their structure can be found in Figure 3.1.

<table>
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<tr>
<th>S. No</th>
<th>Catalyst system (mol%)</th>
<th>Time (h)</th>
<th>HPLC conversion (%)</th>
<th>ee (%)(^{[b]})</th>
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<tbody>
<tr>
<td>1</td>
<td>O'Bu-L-Thr+DMAP+107 (5+5+5)</td>
<td>7</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>O'Bu-L-Thr+LiOH+107 (5+5+5)</td>
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<td>96</td>
</tr>
<tr>
<td>3</td>
<td>O'Bu-L-Thr+KOH+107 (5+5+5)</td>
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<td>100</td>
<td>94</td>
</tr>
<tr>
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<td>O'Bu-L-Thr+DMAP+108 (5+5+5)</td>
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<tr>
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<td>60</td>
<td>88</td>
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<tr>
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<td>O'Bu-L-Thr+DMAP+110 (5+5+5)</td>
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<td>100</td>
<td>94</td>
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<td>7</td>
<td>O'Bu-L-Thr+DMAP+111 (5+5+5)</td>
<td>7</td>
<td>44</td>
<td>80</td>
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<td>8</td>
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<td>O'Bu-L-Thr+DMAP+112 (5+5+5)</td>
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<td>Reaction Conditions</td>
<td>Yield</td>
<td>Isolated (%)</td>
<td>Selectivity (%)</td>
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<td>--------------</td>
<td>-----------------</td>
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<td>65</td>
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<tr>
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<td>7</td>
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<td>8</td>
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<tr>
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<td>nd</td>
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<tr>
<td>21</td>
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<td>8</td>
<td>86</td>
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<tr>
<td>22</td>
<td>O'Bu-L-Thr+LiOH (5+5)</td>
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<td>60</td>
<td>92</td>
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<tr>
<td>23</td>
<td>O'Bu-L-Thr+LiOH (5+10)</td>
<td>7</td>
<td>76</td>
<td>91</td>
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<tr>
<td>24</td>
<td>O'Bu-L-Thr+KOH (5+5)</td>
<td>7</td>
<td>67</td>
<td>91</td>
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</tbody>
</table>

[a] This is an expanded catalyst system investigation of the reported template. [b] Determined by chiral HPLC.
Based on the principles of organocatalysis and reactivity of the proposed catalyst (Table 3.1), I selected the asymmetric Michael addition of $\alpha$-substituted aldehydes to maleimides as a research goal. In this regard, I selected the asymmetric Michael addition of isobutyraldehyde to $N$-phenylmaleimide as a model reaction. To promote the project, I examined 5 mol% each of O'Bu-
L-threonine, DMAP and sulfamide for the asymmetric Michael addition of isobutyraldehyde to N-phenylmaleimide (Scheme 3.2).

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{tBu-L-Thr (5 mol\%)} \\
\text{1.2 equiv} & \quad \text{N-phenylmaleimide}
\end{align*}
\]

**Scheme 3.2.** Asymmetric Michael addition of isobutyraldehyde to N-phenylmaleimide catalyzed by O^tBu-L-threonine in the presence of DMAP and sulfamide.

### 3.3.1 Solvent screening

Encouraged by the initial overwhelming result (Scheme 3.2), I went on to optimize the reaction conditions. First, I screened different solvents to find out the optimal solvent for our model reaction (Table 3.2). Nonpolar solvents like \(n\)-hexane or cyclohexane were not good solvents for our reaction because of insolubility of catalyst components and maleimide (Table 3.2, entries 1 and 2). The polar protic solvents like methanol and water were also poor solvents in terms of reaction rate and enantioselectivity (Table 3.2, entries 7 and 8). All the remaining solvents or mixtures of solvents tested (Table 3.2, entries 3-6, and 9-15), provided excellent enantioselectivities (94-97%) and different conversions in less than 24h reactions. Among all solvents examined, dichloromethane was found to be superior solvent providing 100% conversion after 12h with 97% \(ee\) (Table 3.2, entry 15). A surprising effect on reaction rate was observed when using a higher concentration (dichloromethane, 2.0 M) i.e. 100% conversion was observed with 97% \(ee\) in only 7h (Table 3.2, entry 16).
Table 3.2: Solvent screening for the enantioselective Michael addition of isobutyraldehyde to \(N\)-phenylmaleimide.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>HPLC conversion (%)</th>
<th>ee (%)(^{[a]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(n)-hexane</td>
<td>-</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexane</td>
<td>-</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>5</td>
<td>22</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>tetrahydrofuran</td>
<td>5</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>ethyl acetate</td>
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<td>23</td>
<td>96</td>
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<td>97</td>
</tr>
<tr>
<td>7</td>
<td>methanol</td>
<td>3</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>water</td>
<td>5</td>
<td>5</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>benzene</td>
<td>12</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>1,2-dimethoxyethane</td>
<td>12</td>
<td>40</td>
<td>96</td>
</tr>
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<td>11</td>
<td>(\text{CHCl}_3)</td>
<td>24</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>(\text{CHCl}_3 + \text{H}_2\text{O} (15 mol%))</td>
<td>18</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>(\text{CHCl}_3 + \text{H}_2\text{O} (1 : 1))</td>
<td>3</td>
<td>18</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>1,2-dichloroethane</td>
<td>20</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>15</td>
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<td>97</td>
</tr>
<tr>
<td>16(^{[b]})</td>
<td>dichloromethane</td>
<td>7</td>
<td>100</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^{[a]}\)Determined by chiral HPLC. \(^{[b]}\)2.0 M dichloromethane was used.

3.3.2 Catalyst system investigations

Taking the advantage of the self-assembled catalyst system, I switched different catalyst components to find out the constructive effect on the product formation (Table 3.3). Replacing the sulfamide with thiourea produced almost comparable results with a lower isolated yield (Table 3.3, compare entry 1 and 2). Schreiner's thiourea as a hydrogen bond donor gave slightly lower \(ee\) and product formation, i.e. 98% conversion and 92% \(ee\) in 9 hrs (Table 3.3, entry 3).
Replacing the amine base (DMAP) with an alkali base (KOH) proved to be a positive change in the catalyst system (Table 3.3, compare entry 1 and 4). Surprisingly, the same result (full conversion in 4hrs, >99% ee) was obtained without the use of a hydrogen bond donor (Table 3.3, entry 5). However, DMAP was not effective without a hydrogen bond donor, and only 25% conversion was found after 4h (Table 3.3, entry 6). All other alkali bases tested were poorer as compared to KOH in terms of reaction rate and/or enantioselectivity (Table 3.3, entries 7-12).

Finally, an inexpensive amino acid (L-isoleucine) also gave an excellent result with 2.0 equiv of KOH (10 mol%), i.e. 93% isolated yield and 98% ee in 14h (Table 3.3, entry 14).

Table 3.3: Isobutyraldehyde addition to N-phenylmaleimide: catalyst system investigations.
(For structures of catalyst components used in this table see Figure 3.2)
### Table 3.3: Asymmetric Michael Addition of α-substituted Aldehydes to Maleimides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>O'Bu-L-threonine</td>
<td>-</td>
<td>Ca(OH)\textsubscript{2}</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>O'Bu-L-threonine</td>
<td>-</td>
<td>NaOH</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>12[c]</td>
<td>O'Bu-L-threonine</td>
<td>-</td>
<td>NaOH</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>L-\textit{iso}leucine</td>
<td>-</td>
<td>KOH</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>14[b]</td>
<td>L-\textit{iso}leucine</td>
<td>-</td>
<td>KOH[c]</td>
<td>14</td>
</tr>
</tbody>
</table>

* Determined by chiral HPLC. \[b\] Isolated yield data. \[c\] 10 mol% base was used.

---

**Figure 3.2.** Structures of catalyst components used in Table 3.3.

---

### 3.4 Asymmetric Michael addition of α-substituted aldehydes to maleimides

According to Table 3.3, not one but several reaction conditions allow excellent product profile for the asymmetric Michael addition of isobutyraldehyde to N-phenylmaleimide. Conclusively, the product formation was optimal when using one of the following catalyst systems: (i) O'Bu-L-
threonine (5 mol%), KOH (5 mol%) or (ii) O\textsuperscript{t}Bu-L-threonine (5 mol%), sulfamide (5 mol%), DMAP (5 mol%), see Table 3.4 (entries 1 and 2). A remarkable result can be found by replacing O\textsuperscript{t}Bu-L-threonine with L-isoleucine, albeit with a longer reaction time (Table 3.4, entry 4).

Table 3.4 represents a diverse set of symmetrical and asymmetrical \(\alpha\)-substituted aldehyde additions to \(N\)-phenyl (121) and \(N\)-bezylmaleimides (122). Compounds 127, 129, 131 and 132 are reported for the first time. Taken in total, the method is excellent for synthesizing of \(\alpha\)-substituted succinimides, because of an excellent product profile when using only 5 mol\% of the catalyst system, and 1.2 equiv of aldehyde. Different symmetrical \(\alpha\)-substituted aldehydes were tested (Table 3.4, entries 1-10), I obtained excellent yields and enantioselectivities regardless of the steric hindrance of the substitution. In particular, asymmetric aldehydes construct the Michael products with excellent diastereoselectivities (Table 3.4, entries 11-20), solving a known limitation of the reaction.\(^\text{10}\)

For the construction of two contiguous (quaternary-tertiary) stereogenic centers, we tested different asymmetric \(\alpha\)-substituted aldehydes. An \(\alpha\)-Methyl-\(\alpha\)-phenyl substituted aldehyde gave the \(\alpha\)-substituted succinimide 130 as single diastereomer (>99:1) in 86\% isolated yield with 94\% ee. Using two more of my optimized methods to make 130, I got a similar product profile after a slightly longer reaction time (Table 3.4, compare entries 12 and 13 with 11). None of the reported catalyst systems can achieve a similar product profile.\(^\text{11}\) Using a less hindered \(\alpha\)-substituted aldehyde (\(\alpha\)-benzyl analog vs \(\alpha\)-phenyl substitution), an 89\% isolated yield of 131 was achieved with a 96:4 \(dr\) and 99\% \(ee\) in 4h (Table 3.4, entry 14). Applying the tri-component method to get the same product (131) returned a parallel result after 20h (Table 3.4, entry 15). Examination of the same aldehyde with \(N\)-benzylmaleimide (122), instead of \(N\)-phenylmaleimide (121), resulted in 132 with a 97:3 \(dr\) and excellent yields and \(ees\) when using two different methods (Table 3.4, entries 16 and 17). Further reduction of the steric bulk of the larger \(\alpha\)-substituent on the aldehyde led to 133 (Table 3.4, entries 18 and 19) with very good \(dr\)s (92:8 and 90:10 exceeding the reported \(dr\) of 2:1\(^\text{10}\)) and excellent yields and \(ees\). Finally, examining an \(\alpha\)-Methyl-\(\alpha\)-propyl substituted aldehyde revealed a mediocre \(dr\) (74:26), with excellent yield and \(ee\) (Table 3.4, 134). However, this \(dr\) can be considered high when a methyl group has been differentiated from an \(n\)-propyl moiety, but still this \(dr\) is much better than the best reported \(dr\) of 1:1.\(^\text{10}\)
Table 3.4: Asymmetric Michael addition of α-substituted aldehydes to maleimides$^\text{[a]}$

\[
\begin{align*}
\text{H} - \text{C} - \text{R}'' & + \quad \text{O} - \text{N} - \text{R} & \xrightarrow{\text{Method A, B, C, or D}} \quad \text{O} - \text{N} - \text{R} \\
\text{(1.2 equiv)} & \quad \text{121, R} = \text{Ph} & \quad \text{122, R} = \text{Bn} \\
\end{align*}
\]

$^\text{[a]}$ R' and R'' = see the products structures in table

Method A: O$_\text{t}$Bu-L-Thr, KOH (each 5.0 mol%)  
Method B: O$_\text{t}$Bu-L-Thr, sulfamide, DMAP (each 5.0 mol%)  
Method C: O$_\text{t}$Bu-L-Thr, thiourea, DMAP (each 5.0 mol%)  
Method D: L-isoLeu (5.0 mol%), KOH (10.0 mol%)  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)$^\text{[b]}$</th>
<th>$dr^\text{[c]}$</th>
<th>ee (%)$^\text{[d]}$</th>
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<td>&gt;99</td>
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<td>2</td>
<td>B</td>
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</tr>
<tr>
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<td>10</td>
<td>86</td>
<td>&gt;99:1</td>
<td>94</td>
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</tr>
<tr>
<td>12</td>
<td>B</td>
<td>24</td>
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<td>&gt;99:1</td>
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<tr>
<td>13</td>
<td>C</td>
<td>24</td>
<td>81</td>
<td>&gt;99:1</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>A</td>
<td>4</td>
<td>89</td>
<td>96:4</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>B</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>20</td>
<td>84</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>A</td>
<td>4</td>
<td>87</td>
<td>97:3</td>
<td>98</td>
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<tr>
<td>17</td>
<td>B</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
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<td>89</td>
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<tr>
<td>18</td>
<td>A</td>
<td>4</td>
<td>94</td>
<td>92:8</td>
<td>&gt;99/&gt;99&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>B</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>5</td>
<td>98</td>
<td>90:10</td>
<td>&gt;99/&gt;99&lt;sup&gt;[c]&lt;/sup&gt;</td>
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</table>
It is clear from the above results that carbon substituted quaternary carbons can be formed with relative ease, and compounds 125 (entry 6) and 130 (entry 11) demonstrate that very congested quaternary carbons can be formed in high yields. However, to find the limitations of the developed method for quaternary carbon formation, I tested the addition of 2-ethylisovaleraldehyde to N-phenylmaleimide (Scheme 3.3). I discovered that under our optimal reaction conditions no product was formed.

**Scheme 3.3.** 2-ethylisovaleraldehyde addition to maleimide under normal reaction condition.

To make the above reaction possible I did some optimization study (Table 3.5). As the reaction was not possible under normal reaction conditions, I started with 20 mol% loading of catalyst at 40 °C, and found a slow product formation (Table 3.5, entry 1). The use of other chlorinated solvents at higher temperature (60 °C) gave a small improvement in product formation, but a direct effect on ee was found at higher temperatures (entries 2 and 3). I looked at a diverse array of solvents to solve the problem (entries 4-12), but the selectivity (especially diastereoselectivity)
and product formation was always sluggish. Finally, the use of 1,2-dimethoxyethane provided 88% conversion with very good \( dr \) and \( ee \) in 24hrs (Table 3.5, entry 13). Nevertheless, a promising effect on stereoselectivity was found with slightly lower conversion when decreasing the number of equiv of KOH as compared to O\(^t\)Bu-L-threonine (entry 14). A 5 mol% increase in catalyst loading was good to try for getting maximum conversion (>95%) at a comparable short reaction time (entry 15). Finally, a 10 °C decrease in reaction temperature lead me to the optimal reaction conditions (entry 16).

Table 3.5: Optimization of reaction conditions for the Michael addition of 2-ethylisovaleraldehyde (ethylisovaleraldehyde) to \( N \)-phenylmaleimide.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp ( (^\circ\mathrm{C}) )</th>
<th>HPLC Conversion (%)</th>
<th>( dr ) (syn:anti)</th>
<th>( ee ) (%)</th>
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<tr>
<td>1</td>
<td>dichloromethane</td>
<td>40</td>
<td>26</td>
<td>63:37</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1,2-dichloroethane</td>
<td>60</td>
<td>31</td>
<td>67:33</td>
<td>84</td>
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<tr>
<td>3</td>
<td>chloroform</td>
<td>60</td>
<td>32</td>
<td>67:33</td>
<td>84</td>
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<tr>
<td>4</td>
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<td>5</td>
<td>acetonitrile</td>
<td>60</td>
<td>13</td>
<td>67:33</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>heptane</td>
<td>60</td>
<td>29</td>
<td>74:26</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>cyclohexane</td>
<td>60</td>
<td>30</td>
<td>79:21</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>toluene</td>
<td>60</td>
<td>62</td>
<td>67:33</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>( p)-xylene</td>
<td>60</td>
<td>25</td>
<td>73:27</td>
<td>78</td>
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<td>fluorobenzene</td>
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<td>34</td>
<td>68:32</td>
<td>80</td>
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<tr>
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<td>1,2-dimethoxyethane</td>
<td>60</td>
<td>88</td>
<td>76:24</td>
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<tr>
<td>14[^a]</td>
<td>1,2-dimethoxyethane</td>
<td>60</td>
<td>82</td>
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<td>90</td>
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<tr>
<td>15[^b],[^c]</td>
<td>1,2-dimethoxyethane</td>
<td>60</td>
<td>&gt;95</td>
<td>86:14</td>
<td>90</td>
</tr>
</tbody>
</table>
Under the optimized conditions, I performed the asymmetric Michael addition of 2-ethylisovaleraldehyde to N-phenylmaleimide (Scheme 3.4). A full conversion of starting material to product (135) with 83:17 $dr$ and 92% $ee$ was observed after 14h. Interestingly, both diastereomers were separable, so I obtain a combined isolated yield of 82% (74% major diastereomer and 8% minor diastereomer). This is a significant achievement because product 135 represents the most sterically congested succinimide formed to date.

Scheme 3.4. Asymmetric Michael addition of 2-ethylisovaleraldehyde to N-phenylmaleimide.
3.5 DFT supported mechanism

In collaboration with Professor Thomas Heine and coworkers we were able to use DFT studies to obtain greater insight into the complexes leading to product formation, and the unique role hydrogen bonding is likely playing in the tricomponent catalyst system (OtBu-L-threonine, sulfamide, DMAP) versus potassium activation in the bicomponent catalyst system (OtBu-L-threonine, KOH). Those findings, discussed shortly, support a synperiplaner approach of maleimide via two critical, bridging, hydrogen bonds: oxygen_{maleimide}····H-N_{sulfamide} and N-H_{sulfamide}····oxygen_{carboxylate} (Scheme 3.5, bottom). For the bicomponent system, OtBu-L-threonine, KOH, a synclinal approach was found to be optimal (Scheme 3.5, top). Importantly, these models (Scheme 3.5) support our conclusions regarding the diastereo- and enantiocontrol for the Michael products.

Scheme 3.5. DFT supported intermediates: correctly predict stereochemical outcome for hydratropaldehyde addition to maleimide.
To better appreciate the reaction pathways leading to the above noted products, we simulated the reaction of hydratropaldehyde with $N$-phenylmaleimide (Scheme 3.5). The succinimide product thereof, 130, was chosen for two major reasons: i) the product can be formed using three different catalyst systems (Table 3.4, entries 11-13), consequently insight into the nuances of each complex can be evaluated; and ii) the model would have to predict two levels of stereoselectivity, i.e. the diastereo- and enantiocontrol imposed during the carbon-carbon bond forming step.

The reaction can be thought of as working in two steps: first, van-der-Waals complexes (complexes), where reactants and catalyst are held together by temporary covalent bonds (aldehyde activation to an enamine) and hydrogen bond bridges (maleimide-to-hydrogen bond donor and hydrogen bond donor-to-carboxylate), are formed in the liquid phase. These complexes are local minima, relatively stable, and are the key to understanding the chemical reactions that take place. Consequently, they represent species in which the reacting centers are in close proximity for appreciable amounts of time and consequently govern the preferred stereochemical pathways. The second step of the reaction is a straightforward bond formation process, a chemical reaction transforming the complex into the product.

Our computational study concentrates on step one, to understand the structure and stability of the complexes of reactants and catalyst, while step two, responsible for the reaction rates, is the subject of a future study. Step one is focused on because the simulation of multi-component assemblies is not trivial, and this work represents the first attempt to model these intricate systems. As the quantitative description of hydrogen bonds is crucial for this study, we employed Density-Functional Theory with empirical corrections for London dispersion (BP86-D) together with the all electron TZP basis as implemented in the ADF code. Free enthalpies have been calculated using the harmonic approximation and solvent effects have been accounted for using COSMO.

Assembly of the tricomponent catalyst system, OrBu-L-threonine, sulfamide, DMAP, is assumed to be facial. Experimentally this is convincing because the catalyst components readily dissolve but only when all three are present in equamolar quantities in the presence of the starting materials. The tricomponent assembly itself is calculated to be robust by DFT. Accordingly, our study began by modeling trans enamine attack on maleimide with a $Re_{\text{enamine}}$, $Re_{\text{maleimide}}$ facial
approach (Scheme 3.5); and conversely with a $Si_{\text{enamine}}$, $Re_{\text{maleimide}}$ facial attack for the $cis$ enamine. This is a reasonable starting point because, if supported by DFT calculations, it would: i) explain the diastereo- and enantioselectivity for the major and minor products; ii) differentiate synclinal from synperiplanar approaches; iii) account for the fate of both the $cis$ and $trans$ enamines; and iv) support, or refute, the propensity of the maleimide electrophile to preorganize (hydrogen bond) at the assembled catalyst’s hydrogen bond donor site (sulfamide).

Four low energy $trans$ enamine complexes (136, 137, 138, 139) were identified, with relative energy differences ($\Delta G$) of 0, 0.56, 1.03, and 1.50 kcal/mol. All four complexes (Figure 3.3) reveal a $Re_{\text{enamine}}$, $Re_{\text{maleimide}}$ facial attack and are enabled by two critical, bridging, hydrogen bonds. For visualization purposes, the protonated DMAP counter ion is excluded from the drawn complexes in Figure 3.3, but all conclusions were reached after thorough examination of the three dimensional representations containing DMAP. Furthermore, all unmarked hydrogen bonds (Figures 3.3-3.5) were found to be $>2.90$ Å.

The lowest energy complex (136) displays a linear arrangement of threonine’s carboxylate, $\alpha$-carbon, and nitrogen, with the enamine (aldehyde) atoms (Figure 3.3, 136). This conformation, which is stabilized by a 2.15 Å intramolecular hydrogen-bond (not marked), $N-H_{\text{enamine}} \cdots OC(O)R_{\text{carboxylate}}$, jettisons the $\beta$-carbon of threonine to the $Si$ face of the enamine where the $-\text{O}t\text{Bu}$ group blocks this face.
Because the assembled sulfamide engages in hydrogen bonding with only one of the carboxylate oxygens,\textsuperscript{16} it has the rotational freedom to place its remaining –NH\textsubscript{2} hydrogen bonding unit in a plane parallel to the unoccupied Re face of the enamine (Figure 3.3, 136). Here, maleimide participates in hydrogen bond donor-acceptor pairing with the sulfamide –NH\textsubscript{2} group via a convincingly robust hydrogen bond (1.85 Å). This pairing has the consequence of placing the electrophilic carbon of maleimide within bonding distance proximity (3.20 Å) of the nucleophilic enamine carbon (Figure 3.3, complex A).

The three remaining, higher energy, complexes (137, 138, 139) share a common conformational feature, the enamine and threonine’s α- and β-carbons are in the same plane, but now the carboxylate moiety is approximately perpendicular to the Re face of the enamine. In response, the assembled sulfamide component rotates by an equal degree, again aligning maleimide in a plane.

**Figure 3.3.** Hydratropaldehyde addition to maleimide, complexes for 130 (Table 3.4, entry 12): OtBu-L-Threonine, sulfamide, DMAP catalyst system.
parallel to the \textit{Re} face of the enamine, albeit at an increased carbon-carbon pre-bond forming distance (3.42–3.51 Å) for complexes 137, 138, 139 as compared to complex 136 (3.20 Å). In two of the complexes, 137 and 138, the –OtBu group is essentially contiguous with the plane containing the enamine, \textit{i.e.}, no moiety blocks the \textit{Si} face of the enamine; while in complexes 136 and 139 the –OtBu group blocks the \textit{Si} face. As found for complex 136, complexes 137, 138, 139 have a \textit{Re}_\text{enamine}, \textit{Re}_\text{maleimide} facial approach, thus all four complexes (136, 137, 138, 139) lead to the same major product (\textit{S},\textit{R})-130 (Scheme 3.5).

It is noteworthy that these energy optimized complexes always choose to participate in hydrogen bonding, and when doing so, the catalyst’s sulfamide component becomes the preeminent handle regarding stereocontrol. In complexes 136-139 the carboxylate-sulfamide unit is always directed to the \textit{Re} face of the enamine, and there it directs the \textit{Re} face of maleimide within bonding distance proximity of the enamine (\textit{Re}_\text{enamine}, \textit{Re}_\text{maleimide} approach). A \textit{Si} face approach of maleimide, \textit{i.e.} \textit{Re}_\text{enamine}, \textit{Si}_\text{maleimide}, is unattainable under the organization of hydrogen bonding due to the overwhelming steric impediment imposed by the \textit{N}-phenyl moiety of \textit{N}-phenylmaleimide. These findings provide a conceptual basis for understanding the very high stereoselectivity (>99:1 \textit{dr}, 96:4 \textit{er}) noted for this reaction.

An open question is the viability of a purely steric based reaction pathway, \textit{i.e.}, the random approach of maleimide, without the aid of hydrogen bonding, onto the enamine. Entropically this reaction pathway is less competitive with product formation via preorganization with hydrogen bonding. Regardless, it is important to model this possibility. For this analysis, complexes 136-139 (Figure 3.3) are of little value, even though, \textit{e.g.}, complexes 137 and 138 have an accessible \textit{Si} enamine face, because they represent intermediates that already contain a highly integrated maleimide molecule.
Figure 3.4. Steric based model, low energy complex 140: hydratropaldehyde, OtBu-L-threonine, sulfamide, DMAP.

A more realistic approach is to consider the same complexes, albeit modeled without the presence of maleimide, and then consider the facial approach of maleimide on the enamine without the aid of hydrogen bonding. In the event, four energy optimized trans enamine complexes (hydratropaldehyde, OtBu-L-threonine, sulfamide, DMAP) were observed. Of those, the lowest energy complex (140), Figure 3.4, has a relative energy difference (ΔG) with the next lowest complex of 11.3 kcal. This extremely large energy difference focuses the analysis to complex 140 alone (Figure 3),\textsuperscript{17} who’s Re enamine face is completely blocked by the protonated DMAP counter ion, while the Si face (enamine) is exposed. This leaves the Si enamine face open to attack by maleimide, but the two possible approaches, $Si_{\text{enamine}}, Re_{\text{maleimide}}$ and $Si_{\text{enamine}}, Si_{\text{maleimide}}$, do not lead to the major product, $(S,R)$-130, which is formed in good yield (82%) and with high stereoselectivity (>99:1 $dr$, 92% $ee$).

Finally, it is possible that a steric based reaction pathway could occur via a complex without sulfamide, i.e., maleimide attack on a complex of only hydratropaldehyde, OtBu-L-threonine, DMAP (no bound sulfamide). This is less probable for two reasons: i) sulfamide is expected to have a high binding constant for the carboxylate,\textsuperscript{18} suggesting that sulfamide will more often be bound, e.g., as in complex 140 (Figure 3.4), than not, and ii) experimentally, there is little support for this hypothesis. Regarding the last point, performing the reaction, which normally takes 24 h
(Table 3.4, entry 12), without sulfamide provided 130 in 29 area % yield (HPLC), 4:1 \(dr\), and 92% ee, over 24 h.

The above findings can be summarized as follows. A \(Re_{enamine}, Re_{maleimide}\) reaction pathway, via a hydrogen bond donor-acceptor pair (maleimide····–sulfamide, Figure 3.3), overcomes the entropic disadvantage of maleimide’s random approach (steric model) onto the enamine, selectively forming \((S,R)-130\) (Scheme 3.5). The high propensity for the \(Re_{enamine}, Re_{maleimide}\) facial approach is in complete agreement, after the fact, with the reaction data. For example, experimentally hydratropaldehyde adds to maleimide providing only one diastereomer (>99:1 \(dr\)). This fact rules out the possibility of a \(Re_{enamine}, Si_{maleimide}\) or a \(Si_{enamine}, Re_{maleimide}\) facial approach, but the enantiomeric ratio, at 96:4, does suggest that the minor enantiomer, \((R,S)-130\), may be forming via complex 140 (Figure 3.4) using the non-competitive steric based approach (\(Si_{enamine}, Si_{maleimide}\)). In summary, the DFT calculations support hydrogen bond preorganization of maleimide at the assembled catalyst, and consequently the conceptual basis for the high stereoselectivity of \((S,R)-130\) can be better appreciated. Finally, four cis enamine complexes (analogous to complexes 136-139, Figure 3.3) were additionally identified for the \(O_{tBu}-L\)-threonine, sulfamide, DMAP catalyst system. Of those, the lowest energy cis complex was 4.34 kcal/mol greater in energy than \(trans\) enamine 136 (Figure 3.3), making their analysis inconsequential.

With a plausible reaction pathway clarified, it is important to note the mode of hydrogen bonding, catalyst to electrophile, departs from those depicted for non-assembled bifunctional catalysts. For example, the \(O_{tBu}-L\)-threonine, sulfamide, DMAP catalyst system used here employs one resilient hydrogen bond (Figure 3.3, complex 136, 1.85 Å) to preorganize the maleimide electrophile to the hydrogen bond donor catalyst site; while non-assembly based catalysts, to the best of our knowledge, are depicted as anchoring electrophiles via two critical, strong hydrogen bonds. These divergences are conceivable because sulfamide (Figure 3.5) is a new hydrogen bond donor motif, and its structure departs from the traditionally used hydrogen bond donors, \(e.g.,\) ureas and thioureas. For example, in thiourea all atoms are essentially coplanar, resulting in a hydrogen bond donor with both –NH\(_2\) units in the same plane (Figure 3.5). Sulfamide, by contrast, contains both –NH\(_2\) groups in parallel planes to one another. These geometric realities
permit fundamentally different transition states to exist for sulfamide versus thiourea. In Figure 3.3, the OtBu-L-threonine, sulfamide, DMAP catalyzed reaction is depicted in its four lowest energy complexes. Of note, the diagonal hydrogens of sulfamide always form the two critical (1.78-2.08 Å) hydrogen bonds required to bridge maleimide to the catalyst’s carboxylate moiety. When OtBu-L-threonine, thiourea, DMAP, is modeled a different pattern is observed, here the two critical, bridging, hydrogens of thiourea come from the same –NH₂ unit (Figure 3.5, compare thiourea 141 and sulfamide 136 complexes). A closer comparison of these two complexes additionally reveals a threonine conformational difference between the two minima. When sulfamide is present, a linear arrangement of the enamine and carboxylate is preferred, as discussed earlier. The hydrogen bridging required for this conformation of OtBu-L-threonine is not capable of being replicated by thiourea, based on its preferred hydrogen bonding motif in complex 141 (Figure 3.5). Finally, it should be noted that a third hydrogen bond is observed for all of the sulfamide and thiourea complexes (Figures 3.3 and 3.5), but at 2.31-2.46 Å are expected to play a supportive, but not ‘anchoring’, role.

It was demonstrated experimentally that OtBu-L-threonine, sulfamide, DMAP, was optimal for nitroalkene additions (Table 3.1). By contrast, additions to maleimide electrophiles were faster when using the bicomponent catalyst system of OtBu-L-threonine, KOH (Table 3.4, compare entries 11-13). A persuasive argument, for why this might be, is noted when comparing the low energy calculated complexes of Figure 3.5. For example, under potassium cation activation, complex 142, the synclinal complex is noteworthy for minimizing the steric repulsion between the maleimide N-phenyl and the hydrotropaldehyde phenyl moieties (Scheme 3.5, top complex). A likely consequence is the noted, and significantly shorter, carbon-carbon pre-bond forming distance of 2.77 Å under potassium activation (complex 142)¹⁹ versus sulfamide activation (3.20 Å, complex 136, Figure 3.5 and Scheme 3.5, bottom complex). The more compact potassium complex may be contributing to the increased rate of reaction (10 h versus 24 h, Table 3.4 entries 11 and 12). This line of reasoning is perhaps strengthened by the fact that formation of succinimide product 133 (Table 3.4) requires the same reaction time for both the bicomponent (entry 18, 4 h) and tricomponent (entry 19, 5 h) catalyst systems. In this instance, the above noted steric interaction (phenyl-on-phenyl for 130, Scheme 3.5, bottom complex) is reduced (phenyl-
on-linear alkyl) in 133. Sulfamide complex 133 (not shown) may consequently have shortened pre-bond forming distances that are similar to the corresponding K⁺ complex of 133. It should be noted that unlike the organic based tricomponent catalyst system calculations, the bicomponent system (potassium cation present) required inclusion of the solvent parameters, in particular, to differentiate the relative energy differences of the trans enamine complexes from the cis enamine complexes.

Figure 3.5. Hydratropaldehyde addition to N-phenylmaleimide: local minima for purely organic vs metal activated catalyst systems.
These combined results demonstrate the conformational relay effects imposed on the amino acid, of the assembled catalyst, in the presence of a thiourea based catalyst component (approximately two dimensional) versus a sulfamide catalyst component (three dimensional) versus a potassium cation (spherical), and the consequences on the trajectory of the approaching electrophile. When only considering the maleimide additions, all three catalyst systems enable similar product stereochemistry, albeit via clearly different complexes (Figure 3.5). In total, these experimental and computational studies have provided a foundation for how these newly identified catalyst systems might be activating and preorganizing the starting materials. The concept insights gained here can now be leveraged to exploit alternative catalyst components and different reaction types.
3.6 Absolute and relative stereochemistry

Here I will spectroscopically describe compounds 133, 134, and 135 in detail. I begin with the description of 133 whose relative and absolute stereochemistry I have been able to definitively confirm via X-ray crystallographic analysis as (S,S)-133 (Figure 3.6).

Figure 3.6. ORTEP diagram of (S,S)-133.


\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{)} \] of 133 (major product)

![Structure of compound 133](image)

**Figure 3.7.** Structure of compound 133 for \(^1H\) NMR.

<table>
<thead>
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<th>Entry</th>
<th>Assignment</th>
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Table 3.6: \(^1H\) NMR of compound 133 (major product).
Figure 3.8. $^1$H NMR spectrum of 133.

Please refer to the C2', C3, C4, C5, and C5' system of protons (Figure 3.7). $^1$H NMR (Figure 3.8) of compound 133 showed two singlets (each containing three protons) at 1.60 ppm and 1.68 ppm (Figure 3.9, right side). These two singlets confirm the presence of two methyl groups 5 and 5' which showed splitting slightly downfield, as compared to an aliphatic C–H, because of the electron withdrawing effect of alkene unit in 133 (Figure 3.7). Normally, the alkene protons can be seen at a chemical shift range of 4.5-6.5 ppm. In the $^1$H NMR spectrum of compound 133, a multiplet containing one proton ranging from 5.04-5.08 ppm (Figure 3.9, left side) confirmed the olefinic proton of C4. The two diastereotopic protons of C3 appeared as two multiplets (each containing a single proton) at chemical shift ranges of 1.89-1.99 ppm and 2.01-2.09 ppm (Figure 3.9, right side). The resonance patterns for the diastereotopic protons at C2' are found under the methyl protons of 5 or 5'. Complicating the further reading of the C2' methylene protons, the
methyl group of the minor diastereomer is also found here. However, the integration values for two protons has been confirmed which provides some level of confidence that they are present ranging from 1.64-1.72 ppm.

![Figure 3.9. Expansion of $^1$H NMR splitting for C2', C3, C4, C5, and C5' system of protons.](image)

Now, please refer to the methine (C6) and methylene (C7) protons of the succinimide unit of compound 133 (Figure 3.7). The splitting pattern of these protons is shown in Figure 3.10. The two protons at position 7 (a & b) are diastereotopic and appear at different chemical shifts. Evidence for the presence of these two protons is the large coupling constant (18.3 Hz) which strongly indicates a geminal coupling. Proton at position 7a appeared at 2.68 ppm as doublet of doublet with coupling constants of 5.9 and 18.3 Hz. Similarly, the 7b proton appeared as a doublet of doublet at 2.97 ppm with coupling constants of 9.6 and 18.3 Hz. The proton at position 6 showed a splitting at 3.39 ppm. This proton is also a doublet of doublet ($J =5.9$ and 9.6 Hz) because the two diastereotopic protons 7a & 7b split it.
As aromatic protons can be seen in the range of 6.0-9.0 ppm, therefore three multiplets ranging from 7.24-7.48 ppm (Figure 3.8), with a total integration value of five protons, provide strong evidence for the presence of aromatic protons on 133 (Figure 3.7). The two ortho protons (8 & 8’ in 133, Figure 3.7) appeared as multiplet ranging from 7.24-7.27 ppm. A multiplet with an integration value of one proton ranging from 7.36-7.40 ppm (Figure 3.8), strongly represents the proton at para position (10 in 133, Figure 3.7). At 7.43-7.48 ppm an integration value of two protons is found and represents the meta protons (9 & 9’ in 133, Figure 3.7). The three protons of methyl group (C2, Figure 3.7) gave a singlet at 1.22 ppm. Finally, a singlet (containing one proton) appeared at 9.64 ppm, which is in the typical range of an aldehydic proton (range of aldehydic protons, is 9.0-10.0 ppm).
Chapter 3

\(^1\)H NMR (400 MHz, CDCl\(_3\)) of 134 (major product)

![Structure of compound 134 for \(^1\)H NMR.](Image)

**Figure 3.11.** Structure of compound 134 for \(^1\)H NMR.

**Table 3.7.** \(^1\)H NMR of compound 134 (major product)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Assignment</th>
<th>(\delta) (ppm)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Integration (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0.95</td>
<td>t</td>
<td>7.2</td>
<td>3</td>
</tr>
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<td>2</td>
<td>2</td>
<td>1.2</td>
<td>s</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>1.25-1.32</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3b</td>
<td>1.37-1.46</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2'</td>
<td>1.58-1.72</td>
<td>m</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>6a</td>
<td>2.67</td>
<td>dd</td>
<td>5.9, 18.3</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>6b</td>
<td>2.96</td>
<td>dd</td>
<td>9.6, 18.3</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>3.35</td>
<td>dd</td>
<td>5.9, 9.6</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>7, 7'</td>
<td>7.25-7.29</td>
<td>m</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>7.37-7.42</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>8, 8'</td>
<td>7.44-7.50</td>
<td>m</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>9.62</td>
<td>s</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

The compound 134 was synthesized in a 3:1 diastereomeric ratio, therefore for some of the protons a clear resonance pattern cannot be determined (Figure 3.12).
Please refer to the C2', C3, and C4 system of protons (Figure 3.11). All the splitting from the protons of the just noted system can be seen in Figure 3.13. A triplet of three protons at 0.95 ppm clearly represents the methyl group (C4) of compound 134. C3 is a methylene unit, containing two diastereotopic protons, giving two separate multiplets (each containing one proton) ranging from 1.25-1.32 ppm and 1.37-1.46 ppm. The two protons of C2' appeared as a multiplet ranging from 1.58-1.72 ppm.

The singlet (containing three protons) in Figure 3.13 at 1.20 ppm clearly represents the methyl group (C2). The singlet observed at 1.34 ppm can be attributed to the methyl group of the minor diastereomer and the triplet observed just under 1.0 ppm is also assigned to the minor diastereomer. I presume that the singlet at 1.58 ppm is due to the presence of water.
Figure 3.13. Expansion from $^1$H NMR of 134 (diastereomeric ratio = 3:1) showing protons of C2', C2, C3 and C4.

Now, please refer to the methine (C5) and methylene (C6) protons of the succinimide unit of compound 134 (Figure 3.11). The splitting pattern of these protons is shown in Figure 3.14. The two protons at position 6 (a & b) are diastereotopic and appear at different chemical shifts. Evidence for the presence of these two protons is the large coupling constant (18.3 Hz) which strongly indicates a geminal coupling. Proton at position 6a appeared at 2.67 ppm as a doublet of doublet with coupling constants of 5.9 and 18.3 Hz. Similarly, the 6b proton appeared as a doublet of doublet at 2.96 ppm with coupling constants of 9.6 and 18.3 Hz. The proton at position 5 showed a splitting at 3.35 ppm. This proton is also a doublet of doublet ($J = 5.9$ and 9.6 Hz) because the two diastereotopic protons 6a & 6b split it.
Figure 3.14. Expansion from $^1$H NMR of 134 showing splitting of protons at C5 and C6.

As aromatic protons can be seen in the range of 6.0-9.0 ppm, therefore three multiplets ranging from 7.25-7.50 ppm (Figure 3.12), with a total value of five protons, provide strong evidence for the presence of aromatic protons on 134 (Figure 3.11). The two ortho protons (7 & 7’ in 134, Figure 3.11) appeared as multiplet ranging from 7.25-7.29 ppm. A multiplet with an integration value of one proton ranging from 7.37-7.42 ppm (Figure 3.12), strongly represents the proton at para position (9 in 134, Figure 3.11). At 7.44-7.50 ppm an integration value of two protons is found and represents the meta protons (8 & 8’ in 134, Figure 3.11). Finally, a singlet (containing one proton) appeared at 9.62 ppm, which is in the typical range of an aldehydic proton (range of aldehydic protons, is 9.0-10.0 ppm).
$^1$H NMR (400 MHz, CDCl$_3$) of 135 (major product)

![Structure of compound 135](image)

**Figure 3.15.** Structure of compound 135 for $^1$H NMR.

**Table 3.8.** $^1$H NMR of compound 135 (major product)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Assignment</th>
<th>$\delta$ (ppm)</th>
<th>Multiplicity</th>
<th>J (Hz)</th>
<th>Integration (H)</th>
</tr>
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<tbody>
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<td>1</td>
<td>3</td>
<td>1.04</td>
<td>t</td>
<td>7.6</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1.09</td>
<td>d</td>
<td>7.2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4'</td>
<td>1.13</td>
<td>d</td>
<td>6.9</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>1.89-1.99</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>2.02-2.12</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>2'</td>
<td>2.55</td>
<td>sep</td>
<td>7.0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>6a</td>
<td>2.69</td>
<td>dd</td>
<td>5.6, 18.6</td>
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<td>8</td>
<td>6b</td>
<td>3.00</td>
<td>dd</td>
<td>9.7, 18.6</td>
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<tr>
<td>9</td>
<td>5</td>
<td>3.45</td>
<td>dd</td>
<td>5.6, 9.7</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>8, 8'</td>
<td>7.25-7.28</td>
<td>m</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>7.36-7.41</td>
<td>m</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>7, 7'</td>
<td>7.44-7.49</td>
<td>m</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>9.66</td>
<td>s</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>
Please refer to the isopropyl group of \textbf{135} (Figure 3.15), consisting of C4, C4', and C2'. Each of the two methyl groups (C4 and C4') are split into a doublet by the methine proton at position 2'. One can find these two doublets at 1.09 ppm and 1.13 ppm in Figure 3.17 (right side). A septet (1H) at 2.55 ppm represents the methine proton of position 2', which was split into a septet by the two neighbouring methyl groups, 4 & 4' (Figure 3.14, left side).
Please refer to α-ethyl group of 135 (Figure 3.15), consisting of C2 and C3. One would expect a doublet of doublet for the methyl group (C3), because of two neighbouring diastereotopic protons (2a & 2b). However, in the $^1$H NMR spectrum (Figure 3.16), this methyl group appears as a triplet which might be because of the fast rotation of the C–C single bond between C2 and C3. This would have the effect of providing an equivalent dihedral angle for each, allowing the C2 protons to appear to be equivalent and thus providing a triplet (Figure 3.18, right side). The two diastereotopic protons at position 2 appeared as two separate multiplets having chemical shifts ranges of 1.89-1.99 ppm and 2.02-2.12 ppm (Figure 3.18, left side).

![Figure 3.18. Expansion from $^1$H NMR of 135 showing splitting of protons from C2 & C3.](image)

The splittings for the methine (C5) and the methylene (C6) protons of the succinimide unit of compound 135 (Figure 3.15) are shown in Figure 3.19. The two methylene protons at position 6 (a & b) are diastereotopic and appear at different chemical shifts. An evidence for the presence of these two protons is the large coupling constant (18.6 Hz) which strongly indicates a geminal coupling. Proton at position 6a appeared at 2.69 ppm as a doublet of doublet with coupling constants of 5.6 and 18.6 Hz. Similarly, the 6b proton appeared as a doublet of doublet at 3.00 ppm with coupling constants of 9.7 and 18.6 Hz. The proton at position 5 showed a splitting at 3.45 ppm. This proton is also a doublet of doublet ($J = 5.9$ and 9.6 Hz) because the two diastereotopic protons 6a & 6b split it.
Figure 3.19. Expansion from $^1$H NMR of 135 showing splitting of protons at C5 and C6.

As aromatic protons can be seen in the range of 6.0-9.0 ppm, therefore three multiplets ranging from 7.25-7.49 ppm (Figure 3.16), with a total value of five protons, provide strong evidence for the presence of aromatic protons on 135 (Figure 3.15). The two ortho protons (7 & 7’ in 135, Figure 3.15) appeared as multiplet ranging from 7.25-7.28 ppm (Figure 3.16). A multiplet with an integration value of one proton ranging from 7.36-7.41 ppm strongly represents the proton at para position (9 in 135, Figure 3.15). At 7.44-7.49 ppm an integration value of two protons is found and represents the meta protons (8 & 8’ in 135, Figure 3.15). Finally, a singlet (containing one proton) appeared at 9.66 ppm (Figure 3.16), which is in the typical range of an aldehydic proton (range of aldehydic protons, is 9.0-10.0 ppm).
$^{13}$C NMR (100 MHz, CDCl$_3$) of 135 (major product)

![Diagram of compound 135](image)

**Figure 3.20.** Structure of compound 135 for $^{13}$C NMR.

**Table 3.9.** $^{13}$C NMR of compound 135 (major product)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Assignment</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
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<td>9.03</td>
</tr>
<tr>
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<td>5'</td>
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<td>5</td>
<td>3'</td>
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<td>40.46</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>56.80</td>
</tr>
<tr>
<td>9</td>
<td>10, 10'</td>
<td>126.51</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>128.67</td>
</tr>
<tr>
<td>11</td>
<td>11, 11'</td>
<td>129.19</td>
</tr>
<tr>
<td>12</td>
<td>9</td>
<td>131.93</td>
</tr>
<tr>
<td>13</td>
<td>8</td>
<td>175.10</td>
</tr>
<tr>
<td>14</td>
<td>8'</td>
<td>177.44</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>205.06</td>
</tr>
</tbody>
</table>
Figure 3.21. $^{13}$C NMR spectrum of 135.

Methyl groups, unaffected by electron withdrawing or donating groups are typically observed between 0-40 ppm in $^{13}$C NMR. The methyl group at position 4 appeared at 9.03 ppm (Figure 3.21). The carbons of position 5 and 5' appeared at different chemical shifts i.e. 18.02 and 18.69 ppm. This trend is also observed in the $^1$H NMR for 135 (Table 3.8 & Figure 3.16). As the secondary & tertiary carbons can be observed more downfield compared to the primary carbon, therefore 22.08 ppm can be assigned to C3 and 30.17 ppm to C3'. The $\alpha$-carbons, of a carbonyl compound will be expected to appear more downfield compared to the normal alkane carbons. Of C2, C6, & C7 (Figure 3.20), C2 would be expected to be the furthest downfield because its carbonyl carbon bears greater electropositive character and if found at 56.80 ppm (Figure 3.21). C6 & C7 can be seen at 32.64 & 40.46 ppm. The aromatic carbon of compound 135 (Figure 3.20) appear in a typical range (120-160 ppm) for aromatic carbons. The signals at 126.51, 128.67,
129.19, & 131.93 ppm represent the aromatic carbons (C9, C10, C10', C11, C11', and C12, Figure 3.20). The carbonyl carbons of pyrrolidine ring (8, and 8') appeared at 175.10, and 177.44 ppm, which is a typical range (160-180). As discussed earlier, that the carbonyl carbon of an aldehyde bears greater electropositive character as compared to the amide carbonyl, therefore C1 (Figure 3.20) would expect to be the furthest downfield. Finally, the presence of aldehydic carbon was confirmed by a signal at 205.06 ppm.

It is clear from the above discussion that compounds 133, 134, and 135 showed the same trend in the $^1$H NMR, therefore based on the absolute configuration of 133 (Figure 3.6), I assigned a syn diastereomeric configuration with the same enantiomeric form for 134 & 135.

The stereochemistry of products 123, 126, and 128 have been corroborated by comparison of the HPLC retention times from literature reports. The DFT studies also support the product stereochemistry (see Scheme 3.5), which fit the same trend as established by the X-ray structure (Figure 3.6).

For the following maleimide products, the HPLC data for the stereoisomer is either not available or we could not compare the HPLC data because of lack of access to the literature cited chiral HPLC column. Based on this larger body of stereochemical findings, I have therefore assigned the relative and absolute stereochemistries to products, 124, 125, 127, 129, 130, 131, and 132.
3.7 Conclusion

In summary, the examined and highlighted self-assembled catalysts are excellent for the asymmetric Michael addition of $\alpha$-substituted aldehydes to maleimides. Both the tricomponent and bicomponent catalyst systems were comparable in terms of enantioselectivities, diastereoselectivities, and yields, however the bicomponent system was superior in terms of reaction time. The obtained products represent the most diverse set of $\alpha$-branched aldehyde addition products known. All symmetrical $\alpha$-substituted aldehydes examined gave excellent yields (upto 96%) and enantioselectivities (upto >99%), regardless of the steric hindrance. The products of unsymmetrical $\alpha$-substituted aldehydes gave far reaching product profile in terms of catalyst loading, reaction time, yield, $dr$ and $ee$. Finally, the synthesis of 135 is the first example of the most sterically hindered $\alpha$-substituted succinimide known to date.
References

1. For the regioselective reduction of succinimides to lactams, see for example; (a) K.-J. Xiao, J.-M. Luo, K.-Y. Ye, Y. Wang, P.-Q. Huang, Angew. Chem. Int. Ed. 2010, 49, 3037-3040; (b) Y. Vo- Hoang, C. Gasse, M. Vidal, C. Garbay, H. Galon, Tetrahedron Lett. 2004, 45, 3603-3605.


3. For a recent pyrrolidine drug template, see: Hydroxylthienoquinolones and Related Compounds as Anti-Infective Agents; B. J. Bradbury; M. Deshpande; A. Hashimoto; H. Y. Kim; E. Lucien; G. Pais; M. Pucci; Q. Wang; J. A. Wiles; A. Phadke (Achillion Pharmaceuticals, Inc.), publication number: US 2010/0256112 A1, 07 October 2010.


11. The product profile for 122 in reference 10 is; 20 mol% catalyst loading, 2.0 equiv aldehyde, 90% yield, 8:1 \(dr\) and 91% \(ee\) at 35 \(^{\circ}\)C in 36hrs.


15. Three hydrogen bonds are always noted for each complex 136-139, Figure 3.3, but the third one appears to play an auxiliary role (second hydrogen bond to the carboxylate oxygen is weaker, ranging from 2.32-2.46 Å), perhaps fine tuning the rigidity of the complex initially provided via the two critical, anchoring, hydrogen bonds (1.78-2.08 Å).

16. When reactants are *not included*, hydrogen bond donors based on ureas are well known to form two hydrogen bonds, one to each of the carboxylate oxygens. Sulfamide appears to prefer one hydrogen bond, see Supp Info of attached paper (*Chem. Eur. J*. Nugent et. al.), Computational Section, compare snapshots in Figure S1 and S2 of Sections 1 and 2. When chemically reactive starting materials are added, *e.g.*, an aldehyde and maleimide, the resulting low energy reaction complexes, for both thiourea and sulfamide, show only one critical (1.78-1.86 Å) hydrogen bond to the carboxylate.

17. As an aside, complex 140 may be the overwhelmingly preferred low energy complex, in part, because of a secondary stabilizing effect marked by a dipole-dipole attractive force (3.3 Å distance between the \(\beta\)-carbon of the enamine and the indicated electron deficient carbon on the pyridium ring, Figure 3.4).

19. The potassium complex in Figure 3.5 is a low energy island unto itself, the next lowest \textit{trans} enamine potassium complex is 5.33 kcal/mol higher in energy, while the corresponding lowest energy \textit{cis} enamine potassium complex is 2.87 kcal/mol higher in energy. The Figure 3.5 potassium complex, alone, is consequently the only complex that needs to be considered here.
Chapter 4

EXPERIMENTAL:
DIAMINE CATALYSTS
4.1 General information

All reagents and solvents were received from Sigma-Aldrich. Routine monitoring of chemical reactions were performed by High Performance Liquid Chromatography (HPLC) and Thin-Layer Chromatography (TLC) using precoated plates of silica gel 60 F254 and visualized under ultraviolet irradiation (254 nm). Column chromatography separations were performed with silica gel 60 (0.040-0.063 mm). Petroleum ether used was of boiling range 60-80 °C. Organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents was performed at reduced pressure. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (TMS = 0) or relative to CHCl3 (7.26 ppm) for ¹H NMR. Multiplicities are abbreviated as; (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). Coupling constants are expressed in Hz. FT-IR spectra were obtained on Nicolet Avatar 370 thermonicolet spectrometer. MS was measured on Bruker Daltonics HCT Ultra while HRMS were recorded on Bruker microOTOF instrument with an ionization potential of 70 eV with ESI positive mode. The enantiomeric excess and diastereoselectivity ratio were determined by HPLC using a Chiralcel AS-H or OD-H column with n-heptane and i-propanol as eluents.

4.2 Procedure for the synthesis of diamine catalysts

1st step reaction
To a 100 mL round bottom flask was added NaH (3.00 equiv, 0.72 gm, 30 mmol) in anhydrous chloroform (30 mL), followed by addition of 18-C-6 (0.10 equiv, 0.264 gm, 1 mmol), acetyl pyridine (1.00 equiv, 1.12 gm, 10 mmol) and was stirred for 15 minutes. Then added slowly α,α-dibromoxylene (1.50 equiv, 3.96 gm, 15 mmol) over 5 minutes. The reaction mixture was stirred at room temperature. The progress of reaction was monitored by GC and TLC which show a complete conversion of starting material into new product at 12 h. The reaction mixture was quenched with H2O and extracted with EtOAc (3 x 20 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated under low vacuum gave yellow oil (crude product).
The crude product was submitted to flash chromatography eluting with 10% EtOAc/hexane to give the corresponding ketone (1.12 gm) with (51 %) yield as yellow oil.

2nd step reaction
To a small test tube was added the corresponding ketone (1.00 equiv, 1.12 gm, 5 mmol), MeO-α-MBA (1.2 equiv, 0.89 mL, 6 mmol) and Ti (OiPr)_4 (2.00 equiv, 2.98 mL, 10 mmol). The reaction mixture was stirred at 60 °C for 24 h. To this reaction mixture was added heterogeneous catalyst Pt/C (5 mol %) and isopropyl acetate (0.5 M), keep in hydrogenator at 60 °C with a hydrogen pressure of 10 bars (145 psi). Monitor the reaction by GC. A full conversion of starting material into new product was found at 36 h. Quenched the reaction mixture with NaOH (1.0 N), filter through a bed of celite and filtrate subsequently washed with EtOAc. The organic layer was concentrated under low vacuum to give crude secondary amine with low dr (63:37). The crude compound was submitted to slow chromatography eluting with 3 % EtOAc/petroleum ether gave pure secondary amine as single diastereomer.

3rd step reaction
To a small round bottom flask was added the pure secondary amine (1.00 equiv, 0.57 gm, 1.6 mmol) in anhydrous 1,2-dichloromethane (0.5 M), NaI (0.50 equiv, 0.12 gm, 0.8 mmol) and boron trichloride (2.50 equiv, 0.36 mL, 4 mmol). The reaction mixture was stirred at room temperature. The progress of reaction was monitored by GC and full conversion of starting material into new product was observed in 21hrs. Quenched the reaction mixture with NaOH solution (1.0 N) and extract with 1,2-dichloromethane (3 x 10 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated under low vacuum to get crude product. The crude product was submitted first to flash chromatography eluting with 30% EtOAc/petroleum ether and then eluting with 10% MeOH/DCM gave enantiopure diamine (0.35 g, 98% yield).
4.3 Racemate formation

4.3.1 General procedure for synthesis of racemic Michael adducts (ketones)

To a mixture of nitroolefin (1.00 equiv), 2-picolyamine (20 mol %) in the presence of 2,4-dinitrobenzene sulfonic acid hydrate (10 mol %) in chloroform (0.5 M) was added cyclopentanone (20.0 equiv). The reaction was stirred at room temperature and monitored by TLC. At maximum conversion the reaction was quenched with 1N HCl, extracted with dichloromethane and dried on reduced pressure. The crude product was purified by column chromatography on silica gel.

4.3.2 General procedure for synthesis of racemic Michael adducts (aldehydes)

To a mixture of nitro-olefin (1.00 equiv), aldehyde (20.0 equiv) in chloroform (0.5 M) was added glycine (15 mol %) and dimethyl amino pyridine (15 mol %). The reaction was stirred at room temperature and monitored by TLC. At maximum conversion the reaction mixture was filtered, dried on reduced pressure and purified by column chromatography on silica gel.

4.4 General procedure for enantioselective reactions

To a mixture of nitroolefin (1.00 equiv), \((S)-78\) (0.10 equiv) in the presence of dodecylbenzene sulfonic acid sodium salt (0.10 equiv) and 2,4-dinitrobenzene sulfonic acid hydrate (0.025 equiv) in chloroform (2.0 M) was added ketone or aldehyde (5.00 equiv). Stirred the reaction at room temperature and monitored by HPLC or TLC. At maximum conversion the reaction mixture was purified by column chromatography on silica gel to produce the Michael adduct. The reaction time for all products with their yields, \(drs\) and \(ees\) are given individually in the next section (4.5).
4.5 Analytical data (text)

(S)-phenyl(pyridin-2-yl)methanamine ((S)-78). The product was obtained as brown oil in enantiopure form with >99% ee. The ee was determined by Chiral HPLC (Chiralcel OD-H, i-propanol/heptane 2/98, flow rate = 0.5 mL/min, λ = 210 nm): $t_{\text{major}} = 55.6$ min, $t_{\text{minor}} = 60.9$ min; $[\alpha]_D^{20} +63.61^\circ$ (c 1.9, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) (ppm): 2.17 (bs, 2H), 5.20 (s, 1H), 7.07-7.11 (m, 1H), 7.19-7.31 (m, 4H), 7.39-7.41 (m, 2H), 7.53-7.58 (m, 1H), 8.55 (d, $J = 4.3$ Hz, 1H).

(S)-(2,3-dihydro-1H-inden-2-yl)(pyridin-2-yl)methanamine ((S)-79). The product was obtained as brown oil in enantiopure form with >99% ee. The ee was determined by Chiral HPLC (Chiralcel AS-H, i-propanol/heptane 5/95, flow rate = 0.4 mL/min, λ = 210 nm): $t_{\text{major}} = 24.5$ min, $t_{\text{minor}} = 27.5$ min.

$^1$H NMR (400 MHz, CDCl$_3$) (ppm): 2.11 (bs, 2H), 2.66-2.68 (m, 2H), 2.85-2.99 (m, 2H), 3.12-3.18 (m, 1H), 4.01 (d, $J = 7.6$ Hz, 1H), 7.09-7.14 (m, 3H), 7.19-7.22 (m, 2H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.65-7.70 (m, 1H), 8.59 (d, $J = 4.2$ Hz, 1H).

$^{13}$C NMR (100MHz. CDCl$_3$) (ppm): 36.3, 36.4, 46.6, 60.8, 124.3, 124.5, 126.2, 126.3, 136.8, 142.5, 142.6, 149.3, 161.9.

FT-IR: (KBr) $\nu_{\text{max}}$: 1168, 1542, 2851, 2859, 3356, 3382 cm$^{-1}$.

MS (EI), $m/z$ (relative intensity): 225 [M+H]$^+$;

HRMS (ESI-TOF) calculated for C$_{15}$H$_{17}$N$_2$ [M+H]$^+$ is 225.1386; found: 225.1392.
(S)-2-((R)-2-nitro-1-phenylethyl)cyclopentanone (88). White solid, 76 % isolated yield, syn/anti = 81/19, 87 % ee (syn).

The ee was determined by two different methods:
Method A: (Reported method) The ee was determined by chiral HPLC (Chiralcel AS-H, i-propanol/hexane 25/75, flow rate = 1.0 mL/min, λ = 210 nm): t\text{major} = 16.7 min, t\text{minor} = 10.7 min.

Method B: The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 5/95, flow rate = 1.0 mL/min, λ = 210 nm): t\text{major} = 24.1 min, t\text{minor} = 31.7 min.

R_f = 0.37 EtOAc/pet ether (1:4).

The HPLC spectra for 88, found later in chapter 6 is for method B.

^1H NMR (400 MHz, CDCl_3) (ppm) (major product): 1.43-1.54 (m, 1H), 1.61-1.76 (m, 1H), 1.82-1.96 (m, 2H), 2.06-2.18 (m, 1H), 2.31-2.43 (m, 2H), 3.66-3.73 (m, 1H), 4.73 (dd, \( J = 10.0, 12.9 \) Hz, 1H), 5.35 (dd, \( J = 5.6, 12.9 \) Hz, 1H), 7.15-7.20 (m, 2H), 7.24-7.34 (m, 3H).

(S)-2-((R)-2-nitro-1-p-tolylethyl)cyclopentanone (89). Yellow oil, 92 % isolated yield, syn/anti = 76/24, 88 % ee (syn), >99 % ee (anti). The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 15/85, flow rate = 1.0 mL/min, λ = 190 nm): t\text{minor} (anti) = 9.2 min, t\text{major} (syn) = 9.7 min, t\text{minor} (syn) = 11.4 min, t\text{major} (anti) = 15.4 min, R_f = 0.41 EtOAc/pet ether (1:4).

^1H NMR (400 MHz, CDCl_3) (ppm) (major product): 1.42-1.53 (m, 1H), 1.58-1.77 (m, 2H), 1.83-1.93 (m, 2H), 2.07-2.16 (m, 1H), 2.31 (s, 3H), 2.30-2.40 (m, 1H), 3.63-3.69 (m, 1H), 4.70 (dd, \( J = 10.0, 12.8 \) Hz, 1H), 5.31 (dd, \( J = 12.8, 5.6 \) Hz, 1H), 7.03-7.07 (m, 2H), 7.10-7.12 (m, 2H).
(S)-2-((R)-1-(4-methoxyphenyl)-2-nitroethyl)cyclopentanone (90). Yellowish solid, 85 % isolated yield, syn/anti = 88/12, 77 % ee (syn). The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1.0 mL/min, \( \lambda = 190 \) nm): \( t_{\text{major}} = 15.0 \) min, \( t_{\text{minor}} = 16.6 \) min, \( R_t = 0.29 \) EtOAc/pet ether (1:4).

\(^{1}\text{H} \) NMR (400 MHz, CDCl\(_3\)) (ppm) (major product): 1.44-1.54 (m, 1H), 1.64-1.76 (m, 1H), 1.85-1.96 (m, 2H), 2.07-2.16 (m, 1H), 2.31-2.39 (m, 2H), 3.63-3.69 (m, 1H), 3.78 (s, 3H), 4.68 (dd, \( J = 10.0, 12.6 \) Hz, 1H), 5.29 (dd, \( J = 5.6, 12.6, 1H \)), 6.84 (d, \( J = 8.7 \) Hz, 2H), 7.08 (d, \( J = 8.7 \) Hz, 2H).

\(^{13}\text{C} \) NMR (100MHz, CDCl\(_3\)) (ppm) (major product): 20.2, 27.0, 37.7, 38.3, 49.5, 75.9, 108.8, 110.4, 142.4, 150.6, 217.9.

FT-IR: (KBr) \( \nu_{\text{max}} \): 3122, 2968, 2882, 1729, 1378, 1150, 1013, 917, 817, 742, 599 cm\(^{-1}\).

(S)-2-((S)-1-(furan-2-yl)-2-nitroethyl)cyclopentanone (91). Dark yellow oil, 89 % yield, syn/anti = 57/43, 81 % ee (syn). The ee was determined by chiral HPLC (Chiralcel AS-H, i-propanol/heptane 10/90, flow rate = 0.5 mL/min, \( \lambda = 230 \) nm): \( t_{\text{minor}} = 37.6 \) min, \( t_{\text{major}} = 67.5 \) min, \( R_t = 0.30 \) EtOAc/pet ether (1:4).

\(^{1}\text{H} \) NMR (400 MHz, CDCl\(_3\)) (ppm) (major product): 1.51-1.61 (m, 1H), 1.67-1.78 (m, 1H), 1.89-1.95 (m, 1H), 2.00-2.14 (m, 2H), 2.29-2.43 (m, 2H), 3.95-4.02 (m, 1H), 4.78 (dd, \( J = 9.2, 12.9 \) Hz, 1H), 5.06 (dd, \( J = 6.2, 12.9 \) Hz, 1H), 6.13 (d, \( J = 3.24 \) Hz, 1H), 6.28-6.29 (m, 1H), 7.33 (s, 1H).

\(^{13}\text{C} \) NMR (100MHz, CDCl\(_3\)) (ppm) (major product): 20.2, 27.0, 37.7, 38.3, 49.5, 75.9, 108.8, 110.4, 142.4, 150.6, 217.9.

FT-IR: (KBr) \( \nu_{\text{max}} \): 3122, 2968, 2882, 1729, 1378, 1150, 1013, 917, 817, 742, 599 cm\(^{-1}\).
MS (EI), m/z (relative intensity): 246 [M+Na]+; HRMS (ESI-TOF) calculated for C_{11}H_{13}NO_4 [M+Na]^+ 246.0742; found: 246.0739.

\[
\begin{align*}
\text{NO}_2\text{H}_2\text{O} \quad \text{-2,2-dimethyl-4-nitro-3-phenylbutanal (93).} \quad \text{White oil, 58% isolated yield, 78% ee. The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 8/92, flow rate = 1 mL/min, } \lambda = 210 \text{ nm), } t_{\text{minor}} = 21.1 \text{ min, } t_{\text{major}} = 33.7 \text{ min, } R_f = 0.38 \text{ EtOAc/pet ether (1:4).} \\
\text{^1H NMR (400 MHz, CDCl}_3\text{) (ppm): 1.00 (s, 3H), 1.13 (s, 3H), 3.78 (dd, } J = 4.2, 11.3 \text{ Hz, 1H), 4.69 (dd, } J = 4.2, 13.1 \text{ Hz, 1H), 4.86 (dd, } J = 11.3, 13.1 \text{ Hz, 1H), 7.16-7.21 (m, 2H), 7.27-7.35 (m, 3H), 9.52 (s, 1H).}
\end{align*}
\]

\[
\begin{align*}
\text{(S)-2,2-dimethyl-4-nitro-3-phenylbutanal (93).} \\
\end{align*}
\]

\[
\begin{align*}
\text{NO}_2\text{H}_2\text{O} \quad \text{-2,2-dimethyl-4-nitro-3-p-tolylbutanal (94).} \quad \text{Yellow oil, 53% isolated yield, 80% ee. The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, } \lambda = 215 \text{ nm), } t_{\text{minor}} = 12.0 \text{ min, } t_{\text{major}} = 16.7 \text{ min, } R_f = 0.39 \text{ EtOAc/pet ether (1:4).} \\
\text{^1H NMR (400 MHz, CDCl}_3\text{) (ppm): 1.00 (s, 3H), 1.12 (s, 3H), 2.32 (s, 3H), 3.74 (dd, } J = 4.2, 11.3 \text{ Hz, 1H), 4.66 (dd, } J = 4.2, 13.3 \text{ Hz, 1H), 4.83 (dd, } J = 11.3, 13.3 \text{ Hz, 1H), 7.07, (d, } J = 8.1 \text{ Hz, 2H), 7.13 (d, } J = 8.0 \text{ Hz, 2H), 9.52 (s, 1H).}
\end{align*}
\]
(S)-3-(furan-2-yl)-2,2-dimethyl-4-nitrobutanal (95). Yellow oil, 70 % isolated yield, 90 % ee. The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 25/75, flow rate = 0.8 mL/min, λ = 190 nm), t_{minor} = 12.3 min, t_{major} = 18.1 min, R_f = 0.34 EtOAc/pet ether (1:4).

$^1$H NMR (400 MHz, CDCl$_3$) (ppm): 1.05 (s, 3H), 1.18 (s, 3H), 3.92 (dd, $J = 3.9$, 11.1 Hz, 1H), 4.59 (dd, $J = 4.0$, 12.9 Hz, 1H), 4.76 (dd, $J = 11.1$, 12.9 Hz, 1H), 6.22 (d, $J = 3.24$ Hz, 1H), 6.31-6.32 (m, 1H), 7.37 (d, $J = 1.75$ Hz, 1H), 9.52 (s, 1H).

(S)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (96). Colourless solid, 59 % isolated yield, 90 % ee. The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 10/90, flow rate = 1 mL/min, λ = 210 nm), t_{minor} = 13.3 min, t_{major} = 18.2 min, R_f = 0.33 EtOAc/pet ether (1:4).

$^1$H NMR (400 MHz, CDCl$_3$) (ppm): 0.99 (s, 3H), 1.11 (s, 3H), 3.78 (s, 3H), 3.73 (dd, $J = 4.2$, 11.5 Hz, 1H), 4.66 (dd, $J = 4.3$, 12.9 Hz, 1H), 4.80 (dd, $J = 11.5$, 12.8 Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.7$ Hz, 2H), 9.51 (s, 1H).
References

1. The two enantiomers of (S)-79 were not separable by our chiral HPLC, therefore a trifluoroacetamide derivative of the diamine is used to determine the ee.


Chapter 5

EXPERIMENTAL:
ASSEMBLED BIFUNCTIONAL CATALYSTS
5.1 General information

Reactions were performed in 2.0 mL screw cap vials. Liquid reagents were transferred with glass syringes. Routine monitoring of reactions were performed by thin-layer chromatography (TLC) using precoated plates of silica gel 60 F254 and visualized under ultraviolet irradiation (254 nm) or ceric ammonium molybdate stain. Column chromatography separations were performed with silica gel 60 (0.040-0.063 mm). Petroleum ether with a boiling point range of 60-80 °C was used. Organic extracts were dried over anhydrous sodium sulfate.

Instrumentation:
NMR spectra were recorded on a JEOL ECX 400 spectrometer, operating at 400 MHz (^1H) and 100 MHz (^13C) respectively. Chemical shifts (δ) were reported in parts per million (ppm) downfield from tetramethylsilane (TMS = 0) or relative to CHCl_3 (7.26 ppm) for ^1H NMR. Multiplicities are abbreviated as: (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet). Coupling constants are expressed in Hz. FT-IR spectra were obtained on Nicolet Avatar 370 thermonicolet spectrometer. MS data was measured on a Bruker Daltonics HCT Ultra. HRMS were recorded on a Brukar microTOF instrument with an ionization potential of 70 eV with ESI positive mode. All chiral HPLC analysis was performed on a CHIRALCEL OD-H and chiracel AS-H column with HPLC grade n-heptane and i-propanol as the eluents.

Materials:
Many aldehydes were examined and all were used without further purification. Because aldehydes are sold with different levels of purity and can suffer from short shelf life times, we have provided their catalog numbers here. The aldehydes were stored in a refrigerator and their purity was checked by ^13C NMR every three weeks.

Aldehydes:
Isobutyraldehyde (2-methylpropanal, Ald. Cat. No. 240788)
Cyclohexanecarbaldehyde (Ald. Cat. No. 108464)
Cyclopentanecarbaldehyde (Ald. Cat. No. 526037)
2-Ethylbutyraldehyde (Ald. Cat. No. 110094)
2,6-Dimethylhept-5-enal (Ald. Cat. No. W238902)
2-Phenylpropionaldehyde (hydratropaldehyde Ald. Cat. No. 241369)
2-Methyl-3-(3,4-methylenedioxyphenyl)-propanal (Ald. Cat. No. W523909).
2-Methylpentanal (Ald. Cat. No. 258563)
2-Ethylisovaleraldehyde (Ald. Cat. No. S416274)

**Maleimides:**
- N-Phenylmaleimide (Ald. Cat. No. P27100)
- N-Benzylmaleimide (Ald. Cat. No. 408018)

**Catalyst components:**
- O'Bu-L-threonine (Ald. Cat. No. 206444)
- L-iso-leucine (Ald. Cat. No. 151718)
- DMAP (Ald. Cat. No. 29224)
- sulfamide (Ald. Cat. No. 211370)
- thiourea (Ald. Cat. No. 88810)

**Commonly employed catalyst systems**

**Method A:**
- O'Bu-L-threonine (5.0 mol%), KOH (5.0 mol%)

**Method B:**
- O'Bu-L-threonine (5.0 mol%), sulfamide (5.0 mol%), DMAP (5.0 mol%)

**Method C:**
- O'Bu-L-threonine (5.0 mol%), Thiourea (5.0 mol%), DMAP (5.0 mol%)

**Method D:**
- L-iso-leucine (5.0 mol%), KOH (10.0 mol%)
5.2 Racemate formation

To a stirred solution of maleimide (1.0 mmol, 1.0 equiv) in chloroform (1.0 mL, 1.0 M) was added pyrrolidine (30 mol%) and the aldehyde (2.0 mmol, 2.0 equiv). The reaction mixture was stirred at 40 °C for 3-5 h. The reaction mixture was then cooled to room temperature and diluted with H₂O (15 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent removed (rotary evaporation). The crude reaction mixture was purified via column chromatography to afford the racemic Michael adduct. The product was confirmed by ¹H NMR and the enantiomers were separated using a chiral HPLC column at noted below.

5.3 General procedure for enantioselective reactions

To a screw cap vial was added O'Bu-L-threonine (8.75 mg, 5.0 mol%), sulfamide (4.80 mg, 5.0 mol%), and DMAP (6.10 mg, 5.0 mol%) [Method B]. To this mixture was added CH₂Cl₂ (2.0 M, 0.50 mL) and the aldehyde (1.20 equiv, 1.20 mmol). This mixture was stirred for 2 min at room temperature. N-phenylmaleimide or N-benzylmaleimide (1.00 equiv, 1.00 mmol), was then added and the reaction mixture became homogenous, regardless of the substrate examined. The specific reaction times can be found within the individual descriptions on the pages that follow. TLC and HPLC were used to monitor the reactions. At complete conversion, the reaction mixture was diluted with H₂O (15 mL) and extracted with dichloromethane (3×15 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and the solvent removed (rotary evaporator). The crude product was purified by column chromatography and the yield obtained.
5.4 Analytical data (text)

(S)-2-methyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal (123)

Method A was used: Reaction time = 4h, 96% isolated yield, >99% ee.
Method B was used: Reaction time = 6h, 91% isolated yield, 96% ee.
Method C was used: Reaction time = 5h, 81% isolated yield, 94% ee.
Method D was used: Reaction time = 14h, 93% isolated yield, 98% ee.

The ee was determined by two different methods:
Method A: Chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t_major = 21.1 min, t_minor = 27.2 min.
Method B: (Reported method) Chiral HPLC (Chiralcel OD-H, i-propanol/hexane 25/75, flow rate = 0.5 mL/min, λ = 210 nm): t_major = 38.6 min, t_minor = 49.4 min.
R_f = 0.29 (EtOAc/Pet ether 3:7).

The 1H NMR and HPLC spectra for 123, found later in next chapter is for Method A.

1H NMR (400 MHz, CDCl3) (ppm): 1.28 (s, 3H), 1.33 (s, 3H), 2.62 (dd, J = 5.5, 18.3 Hz, 1H), 2.98 (dd J = 9.6, 18.3 Hz, 1H), 3.14 (dd, J = 5.5, 9.6, Hz, 1H), 7.25-7.28 (m, 2H), 7.37-7.41 (m, 1H), 7.43-7.48 (m, 2H), 9.51 (s, 1H).

(S)-2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methyl propanal (124)

Method B was used: Reaction time = 5 h, 94% isolated yield, 97% ee.
The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): \( t_{\text{major}} = 15.8 \text{ min} \), \( t_{\text{minor}} = 17.2 \text{ min} \), \( R_f = 0.34 \) (EtOAc/Pet ether 3:7).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) (ppm): 1.15 (s, 3H), 1.16 (s, 3H), 2.45 (dd, \( J = 5.5, 18.3 \text{ Hz} \), 1H), 2.82 (dd \( J = 9.2, 18.3 \text{ Hz} \), 1H), 3.02 (dd, \( J = 5.5, 9.2 \text{ Hz} \), 1H), 4.64 (d, \( J = 6.8 \text{ Hz} \), 2H) 7.27-7.34 (m, 5H), 9.48 (s, 1H).

(S)-2-ethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)butanal (125)

Method A was used: Reaction time = 6h, 96% isolated yield, >99% ee.

The ee was determined by two different methods:

Method A: Chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): \( t_{\text{major}} = 17.7 \text{ min} \), \( t_{\text{minor}} = 31.2 \text{ min} \), \( R_f = 0.38 \) (EtOAc/Pet ether 3:7).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) (ppm): 0.99 (q, \( J = 7.36 \text{ Hz} \), 6H), 1.69-1.78 (m, 1H), 1.82-2.02 (m, 3H), 2.68 (dd, \( J = 5.5, 18.3 \text{ Hz} \), 1H), 2.96 (dd, \( J = 9.6, 18.3 \text{ Hz} \), 1H), 3.24 (dd, \( J = 5.6, 9.6 \text{ Hz} \), 1H), 7.26-7.28 (m, 2H), 7.37-7.41 (m, 1H), 7.45-7.49 (m, 2H), 9.63 (s, 1H).

1-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclopentanecarbaldehyde (126)

Method B was used: Reaction time = 16h, 93% isolated yield, 97% ee.

The ee was determined by two different methods:

Method A: Chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): \( t_{\text{major}} = 22.3 \text{ min} \), \( t_{\text{minor}} = 30.5 \text{ min} \).
Method B: (Reported method) Chiral HPLC (Chiralcel OD-H, i-propanol/hexane 25/75, flow rate = 0.5 mL/min, λ = 210 nm: t_major = 39.7 min, t_minor = 51.3 min
R_f = 0.30 (EtOAc/Pet ether 3:7).
The HPLC spectra used for 126, found later in chapter 6 is for method A.

\[1^H \text{NMR (400 MHz, CDCl}_3\text{)} (ppm): 1.71-1.84 (m, 5H), 2.04-2.09 (m, 2H), 2.28-2.33 (m, 1H), 2.58 (dd, } J = 5.1, 17.4 \text{ Hz, 1H}), 2.96 (dd, } J = 9.2, 17.4 \text{ Hz, 1H}), 3.02 (dd, } J = 5.1, 9.2 \text{ Hz, 1H}), 7.28-7.31 (m, 2H), 7.36-7.41 (m, 1H), 7.44-7.49 (m, 2H), 9.38 (s, 1H).

\[\text{1-((S)-1-benzyl-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde (127)}\]
Method B was used: Reaction time = 11h, 86% isolated yield, 99% ee.

The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t_major = 14.6 min, t_minor = 17.8 min, R_f = 0.44 (EtOAc/Pet ether 3:7)

\[1^H \text{NMR (400 MHz, CDCl}_3\text{)} (ppm): 1.62-1.73 (m, 1H), 1.73-1.79 (m, 4H), 1.96-2.08 (m, 3H), 2.43 (dd, } J = 5.6, 17.9 \text{ Hz, 1H}), 2.81 (dd, } J = 9.3, 17.9 \text{ Hz, 1H}), 2.94 (dd, } J = 5.6, 9.3 \text{ Hz, 1H}), 4.67 (d, } J = 14.7 \text{ Hz, 2H}), 7.25-7.32 (m, 3H), 7.36-7.38 (m, 2H), 9.34 (s, 1H).

\[1^3\text{C NMR (100MHz. CDCl}_3\text{)} (ppm): 25.6, 25.7, 31.6, 32.3, 32.8, 43.2, 45.7, 54.8, 127.8, 128.6, 128.7, 135.7, 175.6, 178.2, 201.7.

FT-IR: (KBr) v_max: 2950, 2868, 1769, 1699, 1344, 1164, 702 cm^{-1}.

MS (EI), m/z (relative intensity): 308 [M+Na]^+ (100%); HRMS (ESI-TOF) calculated for C_{17}H_{19}NO_{3} [M+Na]^+ 308.1265; found: 308.1263.
Method B was used: Reaction time = 20h, 77% isolated yield, 97% ee.

The ee was determined by two different methods:
Method A: Chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t\text{major} = 22.4 min, t\text{minor} = 29.7 min.
Method B: (Reported method) Chiral HPLC (Chiralcel OD-H, i-propanol/hexane 25/75, flow rate = 1 mL/min, λ = 210 nm): t\text{major} = 50.2 min, t\text{minor} = 63.9 min
R_f = 0.33 (EtOAc/Pet ether 2:3).

The HPLC spectra used for 128, found later in chapter 6 is for method A.

\(^{1}\)H NMR (400 MHz, CDCl\textsubscript{3}) (ppm): 1.53-1.64 (m, 7H), 1.85-2.01 (m, 3H), 2.69 (dd, J = 5.6, 17.9 Hz, 1H), 2.87 (dd, J = 9.2, 17.9 Hz, 1H), 3.21 (dd, J = 5.6, 9.2 Hz, 1H), 7.25-7.48 (m, 5H), 9.54 (s, 1H).

Method B was used: Reaction time = 20h, 80% isolated yield, 96% ee.

The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t\text{major} = 14.3 min, t\text{minor} = 16.8 min, R_f = 0.43 (EtOAc/Pet ether 3:7).
\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) (ppm): 1.47-1.56 (m, 7H), 1.74-1.79 (m, 2H), 1.89-1.92 (m, 1H), 2.52 (dd, \(J = 5.6, 18.2\) Hz, 1H), 2.69 (dd, \(J = 9.2, 18.2\) Hz, 1H), 3.01 (dd, \(J = 5.6, 9.2\) Hz, 1H), 4.64 (d, \(J = 10.3\) Hz, 2H), 7.24-7.37 (m, 5H), 9.51 (s, 1H).

\(^{13}\)C NMR (100MHz, CDCl\(_3\)) (ppm): 21.4, 21.5, 25.1, 27.8, 28.7, 31.2, 42.4, 43.4, 51.5, 127.9, 128.6, 128.7, 135.7, 175.3, 177.5, 204.6.

FT-IR: (KBr) \(v_{\text{max}}\): 3033, 2933, 2868, 1774, 1701, 1344, 1170, 697 cm\(^{-1}\).

MS (EI), \(m/z\) (relative intensity): 300 \([M+H]^+\) (80%), 282 (100%), 222 (45%); HRMS (ESI-TOF) calculated for C\(_{18}\)H\(_{21}\)NO\(_3\) \([M+Na]^+\) 322.1419; found: 322.1418.

\((R)-2-((S)-2,5\text{-dioxo-1-phenylpyrrolidin-3-yl})\text{-2-phenylpropanal (130)}^2\)

Method A was used: Reaction time = 10 h, 86% isolated yield, >99:1 \(dr\), 94% \(ee\).
Method B was used: Reaction time = 24 h, 82% isolated yield, >99:1 \(dr\), 92% \(ee\).
Method C was used: Reaction time = 24 h, 81% isolated yield, >99:1 \(dr\), 92% \(ee\).
The \(ee\) was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, \(\lambda = 210\) nm): \(t_{\text{major1}} = 34.6\) min, \(t_{\text{minor1}} = 46.6\) min, \(t_{\text{major2+minor2}} = 19.6\) min, \(R_f = 0.45\) (EtOAc/Pet ether 1:2).
The \(^{1}\)H NMR and HPLC spectra for 130, found later in next chapter, is for Method A.

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) (ppm) (major product): 1.77 (s, 3H), 2.52 (dd, \(J = 4.6, 18.9\) Hz, 1H), 2.98 (dd, \(J = 9.4, 18.9\) Hz, 1H), 3.82 (dd, \(J = 4.6, 9.5\) Hz, 1H), 7.04-7.06 (m, 2H), 7.25-7.28 (m, 2H), 7.36-7.43 (m, 6H), 9.67 (s, 1H).
(S)-3-(benzo[d][1,3]dioxol-6-yl)-2-methyl-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal (131)

Method A was used: Reaction time = 4h, 89% isolated yield, 96:4 dr, >99% ee.

Method B was used: Reaction time = 20h, 84% isolated yield, 93:7 dr, 98% ee.

The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t\textsubscript{major1} = 52.2 min, t\textsubscript{minor1} = 75.1 min, t\textsubscript{major2} = 60.1 min, t\textsubscript{minor2} = 40.6 min, R\textsubscript{f} = 0.27 (EtOAc/Pet ether 3:7).

The \textsuperscript{1}H NMR and HPLC spectra for 131, found later in next chapter, is for Method A.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) (ppm) (major product): 1.21 (s, 3H), 2.63 (dd, \(J = 6.1, 18.2\) Hz, 1H), 3.00-3.08 (m, 2H), 3.14 (dd, \(J = 6.1, 9.5\) Hz, 1H), 3.28 (d, \(J = 13.6\) Hz, 1H), 5.95 (s, 2H), 6.70-6.77 (m, 3H), 7.30-7.32 (m, 2H), 7.38-7.42 (m, 1H), 7.46-7.50 (m, 2H), 9.56 (s, 1H).

\textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}) (ppm) (major product): 17.3, 31.9, 39.5, 42.4, 52.7, 101.1, 108.4, 110.9, 123.9, 126.6, 128.0, 128.7, 129.2, 131.8, 146.9, 147.8, 174.6, 177.5, 203.5.

FT-IR: (KBr) \(\nu_{\text{max}}\): 2918, 1778, 1709, 1597, 1190, 1037 cm\(^{-1}\).

MS (El), \(m/z\) (relative intensity): 388 [M+Na\(^{+}\)] (100%), 420 (7%); HRMS (ESI-TOF) calculated for C\textsubscript{21}H\textsubscript{16}NO\textsubscript{3} [M+Na\(^{+}\)]: 388.1161; found: 388.1162.
(S)-3-(benzo[d][1,3]dioxol-6-yl)-2-((S)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (132)

Method A was used: Reaction time = 4h, 87% isolated yield, 97:3 dr, 98% ee.
Method B was used: Reaction time = 16h, 89% isolated yield, 97:3 dr, 94% ee.

The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, λ = 210 nm): t_major1 = 39.0 min, t_minor1 = 42.3 min, t_major2+minor2 = 33.3 min R_f = 0.31 (EtOAc/Pet ether 3:7).

The 1H NMR and HPLC spectra for 132, found later in next chapter, is for Method A.

1H NMR (400 MHz, CDCl_3) (ppm) (major product): 1.06 (s, 3H), 2.49 (dd, J = 5.9, 18.1 Hz, 1H), 2.74 (dd, J = 9.4, 18.1 Hz, 1H), 2.82 (d, J = 13.7 Hz, 1H), 3.06-3.08 (m, 2H), 4.66 (d, J = 7.6 Hz, 2H), 5.92 (s, 2H), 6.58-6.71 (m, 3H), 7.25-7.38 (m, 5H), 9.54 (s, 1H).

13C NMR (100MHz, CDCl_3) (ppm) (major product): 16.7, 31.4, 40.3, 42.6, 43.1, 52.0, 101.2, 108.4, 110.8, 123.8, 128.0, 128.2, 128.7, 129.8, 135.7, 147.0, 147.8, 175.3, 178.0, 203.7.

FT-IR: (KBr) \( \nu_{\text{max}} \): 2922, 1774, 1699, 1608, 1246, 1170, 1037 cm\(^{-1}\).

MS (EI), m/z (relative intensity): 402 [M+Na\(^+\)] (100%), 314 (8%), 362 (5%); HRMS (ESI-TOF) calculated for C\(_{22}\)H\(_{21}\)NO\(_3\) [M+Na\(^+\)] = 402.1317; found: 402.1325.
(S)-2,6-dimethyl-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)hept-5-enal (133)

Method A was used: Reaction time = 4h, 94% isolated yield, 92:8 dr, >99% ee (major diastereomer), >99% ee (minor diastereomer).

Method B was used: Reaction time = 5h, 98% isolated yield, 90:10 dr, >99% ee (major diastereomer), >99% ee (minor diastereomer).

The ee was determined by chiral HPLC (Chiralcel OD-H, i-propanol/heptane 20/80, flow rate = 1 mL/min, \( \lambda = 210 \) nm): \( t_{\text{major1}} = 22.0 \) min, \( t_{\text{minor1}} = 24.4 \) min, \( t_{\text{major2}} = 16.1 \) min, \( t_{\text{minor2}} = 35.4 \) min \( R_f = 0.42 \) (EtOAc/Pet ether 3:7).

X-ray crystal formation: The dr for the title compound was enriched to >99:1 by crystallization from MeOH/pet ether (1:1). Again using MeOH/pet ether (1:1), 5 mL per gram of >99:1 diastereoenriched 133, 133 was dissolved at 50 \( ^{\circ} \)C and then allowed to slowly crystallized for 3 days providing the final crystal for the X-ray analysis.

The \( ^1 \)H NMR and HPLC spectra for 133, found later in next chapter, is for Method A.

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)) (ppm) (major product): 1.21 (s, 3H), 1.60 (s, 3H), 1.65-1.67 (m, 1H), 1.68 (s, 3H), 1.69-1.72 (m, 1H), 1.89-1.99 (m, 1H), 2.01-2.09 (m, 1H), 2.68 (dd, \( J = 5.9, 18.3 \) Hz, 1H), 2.97 (dd, \( J = 9.6, 18.3 \) Hz, 1H), 3.39 (dd, \( J = 5.9, 9.6 \) Hz, 1H), 5.04-5.08 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.40 (m, 1H), 7.43-7.48 (m, 2H), 9.64 (s, 1H).
(S)-2-methyl-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)pentanal (134)$^2$

Method B was used: Reaction time = 16 h, 88% isolated yield, 74:26 $dr$, 98% $ee$ (major diastereomer), 86% $ee$ (minor diastereomer).

The $ee$ was determined by chiral HPLC (Chiralcel OD-H, $i$-propanol/heptane 20/80, flow rate = 1 mL/min, $\lambda = 210$ nm): $t_{\text{major}} = 71.4$ min, $t_{\text{minor}} = 97.9$ min, $t_{\text{major}} = 42.3$ min, $t_{\text{minor}} = 64.2$ min $R_f = 0.34$ (EtOAc/Pet ether 3:7).

$^1$H NMR (400 MHz, CDCl$_3$) (ppm) (major product): 0.95 (t, $J = 7.2$ Hz, 3H), 1.20 (s, 3H), 1.25-1.32 (m, 1H), 1.37-1.46 (m, 1H), 1.58-1.72 (m, 2H), 2.68 (dd, $J = 5.9$, 18.3 Hz, 1H), 2.97 (dd, $J = 9.6$, 18.3 Hz, 1H), 3.36 (dd, $J = 5.9$, 9.6 Hz, 1H), 7.25-7.29 (m, 2H), 7.37-7.42 (m, 1H), 7.44-7.50 (m, 2H), 9.62 (s, 1H).

(S)-2-((S)-2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-2-ethyl-3-methyl-butyraldehyde (135)

Reaction conditions: N-phenylmaleimide (1.0 equiv), 2-ethylisovaleraldehyde (1.2 equiv), O$^\text{Bu}$L-threonine (25.0 mol%), KOH (23.0 mol%) in 1,2-dimethoxyethane (1.0 M) at 50 °C. Reaction time = 14 h, crude reaction $dr = 83:17$. After chromatography, a 74% isolated yield of the major diastereomer (135) and 8% isolated yield of the minor diastereomer were found. The major diastereomer was found in 92% $ee$, as measured after silica gel chromatographic purification.

The $ee$ was determined by chiral HPLC (Chiralcel OD-H, $i$-propanol/heptane 20/80, flow rate = 0.5 mL/min, $\lambda = 210$ nm): $t_{\text{major}} = 32.2$ min, $t_{\text{minor}} = 40.1$ min, $R_f(\text{major diastereomer}) = 0.38$ (EtOAc/Pet ether 3:7), $R_f(\text{minor diastereomer}) = 0.28$ (EtOAc/Pet ether 3:7).
\[ \text{H NMR (400 MHz, CDCl}_3\text{) (ppm) (major product): 1.04 (t, } J = 7.60 \text{ Hz, 3H), 1.09 (d, } J = 7.19 \text{ Hz, 3H), 1.13 (d, } J = 6.90 \text{ Hz, 3H), 1.89-1.99 (m, 1H), 2.02-2.12 (m, 1H), 2.55 (sep, } J = 7.02 \text{ Hz, 1H), 2.69 (dd, } J = 5.60, 18.60 \text{ Hz, 1H), 3.00 (dd, } J = 9.66, 18.60 \text{ Hz, 1H), 3.45 (dd, } J = 5.60, 9.66 \text{ Hz, 1H), 7.25-7.28 (m, 2H), 7.36-7.41 (m, 1H), 7.44-7.49 (m, 2H), 9.66 (s, 1H).} \]

\[ \text{C NMR (100MHz, CDCl}_3\text{) (ppm) (major product): 9.03, 18.02, 18.69, 22.08, 30.17, 32.64, 40.46, 56.80, 126.51, 128.67, 129.19, 131.93, 175.10, 177.44, 205.06.} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{) (ppm) (minor product): 0.95 (t, } J = 7.60 \text{ Hz, 3H), 1.04 (d, } J = 6.95 \text{ Hz, 3H), 1.08 (d, } J = 7.02 \text{ Hz, 3H), 1.80-1.90 (m, 1H), 1.93-2.02 (m, 1H), 2.15 (sep, } J = 7.03 \text{ Hz, 1H), 2.81 (dd, } J = 6.27, 18.56 \text{ Hz, 1H), 3.04 (dd, } J = 9.79, 18.56 \text{ Hz, 1H), 3.69 (dd, } J = 6.27, 9.79 \text{ Hz, 1H), 7.23-7.28 (m, 2H), 7.36-7.40 (m, 1H), 7.44-7.48 (m, 2H), 9.76 (s, 1H).} \]

\[ \text{C NMR (100MHz, CDCl}_3\text{) (ppm) (minor product): 9.37, 18.20, 18.23, 21.69, 31.50, 32.35, 41.72, 56.78, 126.33, 128.73, 129.21, 174.94, 177.64, 203.97.} \]

\[ \text{FT-IR: (KBr) } \nu_{\text{max}}: 2968, 1777, 1711, 1499, 1383, 1179 \text{ cm}^{-1}.} \]

\[ \text{MS (EI), } m/z \text{ (relative intensity): 288 [M+H]+ (12%), 270 (45%), 195 (100%); HRMS (ESI-TOF) calculated for C}_{17}\text{H}_{21}\text{NO}_3 [\text{M+H}]^+ \text{ is 288.1594; found: 288.1587.} \]
References


Chapter 6

SPECTRA
(HPLCs AND NMRs)
HPLC of phenyl(pyridin-2-yl)methanamine (rac-78)

HPLC of (S)-phenyl(pyridin-2-yl)methanamine ((S)-78)
HPLC of 2,2,2-trifluoro-N-((2,3-dihydro-1H-inden-2-yl)(pyridin-2-yl)methyl)acetamide

HPLC of 2,2,2-trifluoro-N-((S)-(2,3-dihydro-1H-inden-2-yl)(pyridin-2-yl)methyl)acetamide
HPLC of 2-(2-nitro-1-phenylethyl)cyclopentanone (rac-88)

HPLC of (S)-2-((R)-2-nitro-1-phenylethyl)cyclopentanone (88)
HPLC of 2-(2-nitro-1-p-tolylethyl)cyclopentanone (rac-89)

HPLC of (S)-2-((R)-2-nitro-1-p-tolylethyl)cyclopentanone (89)
Chapter 6

HPLC of 2-(1-(4-methoxyphenyl)-2-nitroethyl)cyclopentanone (rac-90)

HPLC of (S)-2-((R)-1-(4-methoxyphenyl)-2-nitroethyl)cyclopentanone (90)
Chapter 6

HPLC of 2-(1-(furan-2-yl)-2-nitroethyl)cyclopentanone (rac-91)

[Graphical representation of HPLC analysis]

HPLC of (S)-2-((S)-1-(furan-2-yl)-2-nitroethyl)cyclopentanone (91)

[Graphical representation of HPLC analysis]
HPLC of 2,2-dimethyl-4-nitro-3-phenylbutanal (rac-93)

![HPLC of rac-93](image)

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HPLC of (S)-2,2-dimethyl-4-nitro-3-phenylbutanal (93)

![HPLC of 93](image)

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HPLC of 2,2-dimethyl-4-nitro-3-p-tolylbutanal (rac-94)

HPLC of (S)-2,2-dimethyl-4-nitro-3-p-tolylbutanal (94)
Chapter 6

HPLC of 3-(furan-2-yl)-2,2-dimethyl-4-nitrobutanal (rac-95)

![HPLC chromatogram for rac-95](image)

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HPLC of (S)-3-(furan-2-yl)-2,2-dimethyl-4-nitrobutanal (95)

![HPLC chromatogram for 95](image)

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HPLC of 3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (rac-96)

HPLC of (S)-3-(4-methoxyphenyl)-2,2-dimethyl-4-nitrobutanal (96)
Chapter 6

HPLC of 2-methyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl) propanal (rac-123)

HPLC of (S)-2-methyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl) propanal (123)
HPLC of 2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methyl propanal (rac-124)

HPLC of (S)-2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methyl propanal (124)
HPLC of 2-ethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)butanal (rac-125)

HPLC of (S)-2-ethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)butanal (125)
HPLC of 1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclopentanecarbaldehyde (rac-126)

HPLC of 1-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclopentanecarbaldehyde (126)
HPLC of 1-(1-benzyl-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde (rac-127)

HPLC of 1-((S)-1-benzyl-2,5-dioxopyrrolidin-3-yl)cyclopentanecarbaldehyde (127)
HPLC of 1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclohexanecarbaldehyde (rac-128)

![HPLC chromatogram of rac-128](image)

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HPLC of (S)-1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclohexanecarbaldehyde (128)

![HPLC chromatogram of 128](image)

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156
HPLC of 1-(1-benzyl-2,5-dioxopyrrolidin-3-yl)cyclohexanecarbaldehyde (**rac-129**)

HPLC of (S)-1-(1-benzyl-2,5-dioxopyrrolidin-3-yl)cyclohexanecarbaldehyde (**129**)
HPLC of 2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenylpropanal (rac-130)

![HPLC graph of rac-130](image)

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HPLC of (R)-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-phenylpropanal (130)

![HPLC graph of 130](image)

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HPLC of 3-(benzo[d][1,3]dioxol-6-yl)-2-methyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal (rac-131)

HPLC of (S)-3-(benzo[d][1,3]dioxol-6-yl)-2-methyl-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal (131)
HPLC of 3-(benzo[d][1,3]dioxol-6-yl)-2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (rac-132)

HPLC of (S)-3-(benzo[d][1,3]dioxol-6-yl)-2-((S)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal (132)
HPLC of 2,6-dimethyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)hept-5-enal (rac-133)

HPLC of (S)-2,6-dimethyl-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)hept-5-enal (133)
Chapter 6

HPLC of 2-methyl-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)pentanal (rac-134)

HPLC of \((S\)-2-methyl-2-\((S\)-2,5-dioxo-1-phenylpyrrolidin-3-yl)pentanal (134)\)

HPLC of \((S\)-2-methyl-2-\((S\)-2,5-dioxo-1-phenylpyrrolidin-3-yl)pentanal (134)\)
HPLC of 2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-2-ethyl-3-methyl-butyraldehyde (rac-135)

HPLC of (S)-2-((S)-2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-2-ethyl-3-methyl-butyraldehyde (135)
Chapter 6
135 (major diastereomer)
135 (minor diastereomer)
Noncovalent Bifunctional Organocatalysts: Powerful Tools for Contiguous Quaternary-Tertiary Stereogenic Carbon Formation, Scope, and Origin of Enantioselectivity

Thomas C. Nugent,* Abdul Sadiq, Ahtaram Bibi, Thomas Heine, Lei Liu Zeonjuk, Nina Vankova, Bassem Bassil,


Abstract

Relying on the assembly of commercially available catalyst building blocks, highly stereocontrolled quaternary carbon (all carbon substituted) formation has been achieved with unmatched substrate diversity. For example, the in situ assembly of a tricomponent catalyst system allows α-branched aldehyde addition to nitroalkene or maleimide electrophiles (Michael products), while addition to an α-iminoester affords Mannich reaction products. Very good yields are observed and for fifteen of the eighteen examples 96-99% ee is observed. Using racemic α-branched aldehydes, two contiguous (quaternary-tertiary) stereogenic centers can be formed in high diastereo- and enantiomeric excess (eight examples) via an efficient in situ dynamic kinetic resolution, solving a known shortcoming for maleimide electrophiles in particular. The method is of practical value, requiring only 1.2 equiv of the aldehyde, a 5.0 mol% loading of each catalyst component, e.g. OtBu-threonine, sulfamide, DMAP or OtBu-threonine, KOH, and room temperature reactions. As a highlight, the first demonstration of ethylisovaleraldehyde (7) addition is disclosed, providing the most congested quaternary stereogenic carbon containing succinimide product (8) known to date (Scheme 2). Finally, mechanistic insight, via DFT calculations, support a noncovalent assembly of the catalyst components into a bifunctional catalyst, correctly predict two levels of product stereoselectivity, and suggest the origin of the tricomponent catalyst system’s exceptionality: an alternative hydrogen bond motif for the donor-acceptor pair than currently suggested for non-assembled catalysts.
Sequential Reductive Amination-Hydrogenolysis: A One-Pot Synthesis of Challenging Chiral Primary Amines

Thomas C. Nugent,* Daniela E. Negru, Mohamed El-Shazly, Dan Hu, Abdul Sadiq, Ahtaram Bibi, M. Naveed Umar


Abstract
Difficult-to-access chiral primary amines were formed in good to high yield and ee using a rare example of a one-pot synthesis from prochiral ketones (sequential reductive amination-hydrogenolysis). As a highlight we also demonstrate a one-pot reductive amination-hydrogenolysis-reductive amination (five reactions) of ortho-methoxyacetophenone resulting in the chiral diamine 1-(2-methoxy-phenyl)ethyl-(2-pyridylmethyl)-amine (4) (58% overall yield, >99% ee), a new organocatalyst for aqueous enantioselective aldol reactions.