STUDIES ON ORGANOCATALYTIC ASYMMETRIC MICHAEL ADDITION REACTIONS

KEYUR M. PANDYA
STUDIES ON
ORGANOCATALYTIC ASYMMETRIC
MICHAEL ADDITION REACTIONS

By

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In partial fulfillment of the requirements for the degree of
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Department of Chemistry
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Abstract

The development of organocatalysts for asymmetric synthesis continues to be actively investigated in recent years due to the advantages over conventional metal-based catalysts. Research in our laboratory has focused on the development of organocatalysts for fundamental carbon-carbon bond forming reactions, such as the Michael addition reaction.

The organocatalytic Michael addition of ketones to nitroalkenes is of special interest since the reaction generates two contiguous stereocenters and the products (γ-nitro ketones) are useful synthetic intermediates. We have observed that this reaction is efficiently catalyzed by pyrrolidine-based chiral, secondary diamines as well as triamines. The use of a protic acid in conjunction with the amine catalyst is beneficial and the Michael addition products (syn diastereomers) are obtained with excellent enantioselectivities (up to 99% ee) and diastereoselectivity (up to 50:1 dr) for cyclic ketones and nitroalkenes derived from aromatic aldehydes. Details regarding the effect of changes in the catalyst and protic acid structure, variation of catalyst/protic acid combinations and the scope of the reaction with respect to structural changes in the ketone and nitroalkenes will be discussed.

In addition, the application of the chiral triamines in Michael reactions involving iminium ion intermediates has been examined. Preliminary results from these studies will be presented. The attempted synthesis of pyrrolidine-based organocatalysts with guanidine-containing side chains as well as catalysts based on the camphor scaffold will also be presented.
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<table>
<thead>
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<th>Abbreviation</th>
<th>Meaning</th>
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<tr>
<td>Boc</td>
<td>t-Butyloxy carbonyl</td>
</tr>
<tr>
<td>Cbz / Z</td>
<td>Benzyloxy carbonyl</td>
</tr>
<tr>
<td>C-C</td>
<td>Carbon-carbon</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionization</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-Dicyclohexyl-Carbodiimide</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>dr.</td>
<td>Diastereomer ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electronspray Ionization</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HOBT</td>
<td>Hydroxybenzotriazole</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
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<td>meta</td>
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mg: milligram
mL: milliliter
mmol: millimole
NMR: Nuclear Magnetic Resonance Spectroscopy
o: ortho
p: para
ppm: parts per million
pTsOH: para-toluene sulfonic acid
THF: tetrahydrofuran
TMS: trimethylsilyl
TFA: trifluoroacetic acid
TLC: thin layer chromatography
Chapter 1

Enantioselective Organocatalysis

I. Introduction

For the last four decades, the need for single-enantiomer molecules in biomedical research has driven great advances in asymmetric synthetic methodology. The importance of marketing only single-enantiomer drugs has further amplified the need for the development of general procedures for enantiocontrolled synthesis. Out of several procedures, the use of asymmetric catalysis has been well recognized for asymmetric induction. It offers the best “atom economy” as the stoichiometric addition and removal of chiral auxiliaries can be avoided or minimized. The role of the catalyst is to transfer chirality information through a well-defined transition state, to achiral substrates.

I.A Asymmetric catalysis (organocatalysts vs metal-containing catalysts):

For several years, it was believed that transition metal complexes and enzymes were the two main classes of asymmetric catalysts. The importance of enantioselective metal catalysis has been recognized by the award of the 2001 Nobel Prize in Chemistry to Knowles, Noyori, and Sharpless for their pioneering work in this field. The advantages of metal-based catalysts are due to the properties of the metal. Since metals can act as either Lewis acids or Lewis bases, the reactivity of these catalysts can be fine-tuned by varying the ligands surrounding the metal atom. The disadvantages of these catalysts, such as high price, toxicity, pollution, and product contamination has turned the scientific
community towards an in-depth exploration of Nature's way of asymmetric induction (biocatalysis). The last few years have witnessed the emergence of enzymatic catalysis in current industrial production of enantiomerically pure fine chemicals. However, the enzymatic catalysts can be of very complex structure, unstable and handling of these catalysts can be tedious.

Between the two extremes of transition metal catalysis and biocatalysis, a third general approach (organocatalysis) to the catalytic production of enantiomerically pure compounds has emerged as a rapidly growing part of metal-free homogenous catalysis. Organocatalysts are purely "organic" molecules. These small, stable, metal-free molecules are often derived from natural chiral pool sources such as α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates. Organocatalyzed reactions mechanistically resemble the enzyme-catalyzed reactions with respect to the formation of reversible complexes with substrates. They also mimic the role of a metal as a Lewis acid or Lewis base. The acidity or basicity arises from the type of heteroatom (mainly N, O, P, and S) present in the organocatalyst.

I.B Asymmetric organocatalytic reactions:

Stereoselective reactions promoted by organic molecules of low molecular weight are at the forefront because organocatalysts can be as efficient as other catalysts with the bonus of being robust, inexpensive and readily available. Their inertness toward moisture and oxygen avoids the need for expensive and time-consuming reaction conditions (for example inert atmosphere, low temperatures, anhydrous solvents etc.) used in transition metal catalysis. Unlike enzymes or other bioorganic catalysts, they are more stable at
ambient temperatures. They can be easily separated and reused from the products without racemization or loss of catalytic activity. The possibility of anchoring small molecules to solid support and simple work-up procedures without involving any metallic waste as well as the biodegradability of these catalysts makes them extremely attractive, timely and well suited for “green chemistry”. The scope of organocatalytic reactions has been extended to such an extent that typical transition metal-mediated coupling reactions, such as the Suzuki, Sonogashira, Heck-type coupling reactions, Ullmann and Tsuji-Trost reactions, can now be carried out under metal-free conditions. Thus, organocatalysis is complementary with the metal complex-mediated, and also with biocatalytic transformations.

Interestingly, the concept of “Organic Catalysts” (coined by German chemist Wolfgang Langenbeck in 1932) was established almost 100 years ago. Bredig and Fiske reported the first example of an asymmetric organocatalytic reaction in 1912. Much later in 1960, Pracejus reported the development of an organocatalyzed asymmetric ketene methanolysis reaction. As shown in Scheme 1, the methanolysis of ketene 1 was catalyzed by 1 mol% of catalyst 3 to yield the methyl ester 2 in 40%ee.
One of the best known early asymmetric organocatalytic reactions is the proline-catalyzed intramolecular aldol reaction, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, (Scheme 2).\textsuperscript{20} The proline (6)-catalyzed Robinson annulation of symmetrical triketone 4, to provide the bicycle 5 with high enantioselectivity, though widely used for natural product synthesis,\textsuperscript{21} remained relatively under-studied until List and co-workers reported the first proline-catalyzed intermolecular aldol reaction in 2000 (Scheme 3).\textsuperscript{22}

![Scheme 2](image)

![Scheme 3](image)

This milestone study where proline mimics a type I aldolase has stimulated intensive research activities in the proline-catalyzed aldol, Mannich, Michael, and related reactions. In the same year, MacMillan reported the phenylalanine-derived imidazolinone 13 catalyzed Diels-Alder reaction of $\alpha,\beta$-unsaturated aldehydes with enantioselectivities up to 94% ee (Scheme 4).\textsuperscript{23}
Other examples of highly enantioselective organocatalysis include the enantioselective hydrocyanation catalyst developed by Corey (Scheme 5)\(^\text{24}\) and Jacobsen,\(^\text{25}\) the highly enantioselective epoxidation catalysts developed by the groups of Shi (scheme 6),\(^\text{26}\) Yang\(^\text{27}\) and Denmark\(^\text{28}\) and the chiral quaternary ammonium salts developed by Corey,\(^\text{29}\) O’Donnell,\(^\text{30}\) and Maruoka (Scheme 7)\(^\text{31}\) for phase-transfer catalysis.
These organocatalysts should not only function like an enzyme, but should also possess typical characteristics with respect to technical applications: (i) easy availability, (ii) accessibility of both the enantiomers with comparable price, (iii) low molecular weight, (iv) easy separation from the product, and (v) easy recovery after work-up, without racemization.¹⁰

I.C Classification of organocatalysts:

Recently, organocatalysts have been broadly classified as Lewis acids, Lewis bases, (covalent catalysis)⁹⁸ and Brønsted acids, Brønsted bases (noncovalent catalysis).³² The majority of organocatalytic reactions are amine-based reactions³³ and in this asymmetric amino-catalysis, amino acids, peptides, alkaloids and synthetic nitrogen-containing molecules are used as chiral catalysts.

I.D Proline- an effective enantioselective organocatalyst:

Interestingly, proline has proven to be the model-compound in all the catalytic strategies listed above, including asymmetric aminocatalysis. Proline can serve as a ligand in asymmetric transition-metal catalysis; a chiral modifier in heterogeneously-catalyzed hydrogenation and most importantly, proline itself can be an effective
organocatalyst as it is inexpensive and is available in both enantiomeric forms.\textsuperscript{34} Similar to enzymatic catalysis, all amino acids can act as bifunctional catalysts, with a carboxylic acid and an amine portion, but it is the pyrrolidine portion of proline which has unique nucleophilic reactivity. Modes of action in proline-catalysis, is shown in Figure 1.\textsuperscript{9a}

**Figure 1:** Modes of action in proline-catalysis

Proline based organocatalytic transformations cover a wide range of reactions\textsuperscript{9i} including the Diels-Alder, aldol, Mannich, 1,3-dipolar cycloaddition, \( \alpha \)-amination, Friedel-Craft alkylation, Robinson annulation and Michael reactions. Organocatalytic Michael reactions, have attracted us (along with many other researchers\textsuperscript{35}) because the proline-mediated conjugate addition of various enolizable carbonyl compounds to activated olefins proceeds with only moderate enantioselectivity (Scheme 8).\textsuperscript{35b,c}

**Scheme 8**
II. Outline of the research described in the thesis

The efforts toward general organocatalytic methodology that utilizes chiral enamine and iminium ion formation for enantioselective Michael addition reactions are discussed in the following chapters. The organocatalytic asymmetric Michael addition reactions of ketones to nitroalkenes by the enamine pathway are reported in chapter 2. The synthesis of selected organocatalysts as well as the results obtained by employing them for enamine catalysis has been discussed. In Chapter 3 the application of these catalysts in the construction of carbon-carbon bonds by iminium ion pathways and attempts towards the synthesis of new, proline-derived chiral catalysts with basic side chains are described. In addition, the progress towards the synthesis of some camphor-based organocatalysts for selected Michael reactions will also be discussed.
III. References


15 Ma, D; Cai, Q. Synthesis 2004, 128.


17 Langenbeck, W., Angew. Chem. 1932, 45, 97.

18 Bredig, G.; Friske, P. S. Bichem. Z. 1912, 46, 7.


Chapter 2

Enantioselective Organocatalytic Michael Additions of Ketones to Nitroalkenes by Enamine Catalysis

I. Introduction

Since its discovery in the 1880s, the Michael reaction is generally regarded as one of the most efficient methods for carbon-carbon bond formation. Its atom economy, wide substrate scope, and easily accessible starting materials render it one of the best methods for enantioselective C-C bond formation. Wynberg reported the first example of a catalytic enantioselective Michael addition reaction in 1975 using quinine, a cinchona alkaloid, as the catalyst. Among the different ways to generate chiral Michael adducts, the catalytic asymmetric approach (with achiral Michael donors and acceptors) has become popular in recent times because it is the most efficient way to construct as many as three stereocenters (Scheme 1) in a single step.

Catalytic enantioselective Michael additions normally proceed by activation of either the Michael donor or acceptor with a chiral catalyst. Simultaneous activation approach of both reaction partners by bifunctional catalysts has also been investigated.
The mechanistic approach for activation of the electrophile or the nucleophile is summarized in Figure 1.

The majority of organocatalytic reactions are amine-based reactions, which proceed through either an iminium ion intermediate or an enamine. The work described in this chapter focuses on activation of the nucleophile by enamine formation, while in Chapter 3 our studies on activation of the electrophile by iminium ion formation are described.

II. Enamine catalysis (Nucleophilic catalysis - activation of donor)

The first example of asymmetric enamine catalysis was the Hajos-Parrish-Eder-Sauer-Wiechert reaction, an intramolecular aldol reaction catalyzed by proline. Blarer and Seebach employed chiral enamines derived from (S)-2-methoxymethylpyrrolidinone.
and cyclohexanones in Michael additions to alkylidenemalonates and nitroalkenes. Surprisingly, the catalytic version of this reaction was not explored until recently, when List, Barbas and Enders independently reported that the ketone-nitroalkene Michael addition could be carried out using catalytic quantities of chiral secondary amines. Catalytic asymmetric aldol reactions and Mannich reactions were also reported. This concept of enamine catalysis has also been extended to highly enantioselective α-functionalization reactions of aldehydes and ketones, such as aminations, hydroxylations, alkylations, chlorinations and an intramolecular Michael reaction.

The potential limitation of this enamine catalysis would be irreversible deactivation of the amine catalyst if the electrophile is a carbonyl compound, unless the catalyst reacts reversibly with the electrophile. Some electrophiles may not even react with the amine catalyst but only with the enamine (e.g. nitroalkenes), while electrophiles such as aldehydes, enones and imines can react reversibly with the amine. These side reactions are coined as “parasitic equilibria” as they can limit reaction rates but still allow for the formation of the desired product.

III. Design of chiral organocatalysts for Michael reactions

Since the first chiral amine (proline) catalyzed asymmetric Michael additions of carbonyl compounds to nitroalkenes offered only modest enantioselectivity, identification of more efficient chiral catalysts has been actively investigated. Recent investigations have examined the catalysis of the enolizable carbonyl-nitroalkene conjugate addition reaction with derivatives of amine-thiourea catalysts, amino acids and ionic liquids but a significant amount of effort has been devoted to the development
of proline-based chiral diamine derivatives.\textsuperscript{21-29} Chiral pyrrolidines in which a tertiary aminomethyl, \textsuperscript{21} tertiary aminomethyl \textsuperscript{22} 2-morpholinomethyl, \textsuperscript{23} tetrazole \textsuperscript{24} tetrazolylmethyl, \textsuperscript{25} pyrrolidinyl, \textsuperscript{26} trifluoromethylsulfonamido, \textsuperscript{27} methylpyridyl, \textsuperscript{28} and \textsuperscript{1-((pyrrolidin-2-yl) methyl) pyrrolidine, \textsuperscript{29}} (fluorous)diphenyl-methanol silyl-ether, \textsuperscript{30} or carboxymethyl \textsuperscript{31} functionality replaces the carboxyl function in proline have been investigated. Selected proline-based catalysts used for asymmetric conjugate additions of aldehydes and ketones to nitroalkenes are shown in Figure 2.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Selected proline-based organocatalysts}
\end{figure}
It should be noted that the synthesis of several of these chiral pyrrolidine catalysts is quite complicated. In addition, these pyrrolidine catalysts normally require long reaction times, low temperature and a large excess of ketone for good-to-excellent enantioselection for a narrow range of substrates. Hence, the identification of new, structurally simple catalysts that overcome these limitations is an ongoing challenge.

IV. Objective

The main objective of this project was to identify a simple, bifunctional catalyst system, which would facilitate Michael reactions by enamine or iminium ion pathways depending on the substrates used for the reaction. The catalyst was also expected to have the capacity to activate both reactants (Michael donor and acceptor) simultaneously.

We chose to investigate proline-derived triamines 4 and 5 as organocatalysts (Figure 3). The rationale for this choice is discussed below:

![Figure 3: Chiral pyrrolidine based triamines](image)

For *iminium ion catalysis* (Scheme 2) the activation of the enone is anticipated, through iminium ion 6 formation, by the pyrrolidine part (secondary amine) of catalyst. Furthermore, the neighbouring amine may participate in reversible formation of the aminal 7 from the iminium ion 6 to offer a more organized transition state assembly. The
pendant tertiary amine was anticipated to assist with the deprotonation and/or delivery of the nucleophile.

**Scheme 2**

The new triamine 5 was prepared to examine the role of the internal tertiary amine in catalyst 4. A potential limitation of catalyst 5 would be irreversible formation of an aminal by deprotonation of the ammonium species 7.

It seemed possible that triamines 4 and 5 could be also utilized for enamine catalysis of the ketone/nitroalkene conjugate addition reactions (Scheme 3).
In this case, the pendant tertiary amine could enhance the rate of formation of enamine 10 by assisting in the deprotonation of the iminium ion 8. Unlike catalyst 4, the secondary amine in the side chain of 5 may function as a H-bond donor to activate the nitroalkene. These design elements are summarized in Figure 4.

![Figure 4](image_url) Design elements for chiral pyrrolidine based triamine catalysts.

The role of the terminal tertiary amine in the catalyst 5 can be examined by preparing the diamine catalyst 11 as an analogue of 5 lacking the tertiary amine (Figure 5). In addition, another diamine catalyst 12, in which a phenyl group replaces the tertiary amine, can be utilized to prove the importance of π-stacking between catalyst and nitroalkene substrates (Figure 5).

![Figure 5](image_url) Design elements for chiral pyrrolidine based diamine catalysts.
V. Synthesis of organocatalysts

The proline-derived triamines 4 and 5 were readily prepared by adaptation of a literature procedure as shown in Scheme 4.

\[ \text{Boc} \quad 13 \]

\[ \text{DCC, HOBT, CH}_2\text{Cl}_2 \]

\[ \text{RHN} \quad \text{NMe}_2 \quad \text{CH}_2\text{Cl}_2 \]

\[ \text{LiAlH}_4 \quad \text{THF, reflux} \]

\[ \text{TFA, CH}_2\text{Cl}_2 \]

This convenient synthesis of triamines begins with the condensation of \( N \)-Boc-proline 13 with appropriate diamines in the presence of stoichiometric amounts of DCC and HOBt to offer the amides 14 and 15 in good-to-excellent yields. Removal of the Boc protecting group was effected by TFA in dichloromethane to provide the amides 16 and 17. The amides were reduced to the desired triamines 4 and 5 with LiAlH\(_4\).

Dimaines 11 and 12 were also prepared in a similar manner as shown in Scheme 5.
With the triamines 4, 5 and the diamines 11, 12 in hand we proceeded to examine their efficacy in asymmetric Michael reactions. Investigations on enamine catalysis are described in this chapter. In Chapter 3 our preliminary studies on iminium ion catalysis with the triamines 4 and 5 are detailed.

VI. Asymmetric organocatalytic Michael addition of cyclic ketones to nitroalkenes

Enantioselective conjugate additions of unmodified carbonyl compounds to a few Michael acceptors, such as nitroalkenes,\textsuperscript{18-31} chalcones\textsuperscript{33} and vinyl ketones\textsuperscript{34} has been extensively investigated in recent years. Our study is mainly confined to the use of moderately-sized symmetrical aliphatic cyclic ketones as Michael donors and nitroalkenes as Michael acceptors. Nitroalkenes have remained of special interest as excellent Michael acceptors due to the strong electron-withdrawing effect of the nitro group. In addition, conjugate addition of carbonyl compounds to the nitroalkene offers synthetically useful γ-nitrocarbonyl derivatives for the preparation of complex synthetic targets.\textsuperscript{35} In addition, the nitro group itself is particularly versatile as it may be transformed into diverse functionalities.\textsuperscript{35c}
Preliminary results on the highly enantioselective (up to 99% ee) and diastereoselective (up to 50:1) conjugate addition of cyclic ketones to nitroalkenes catalyzed at ambient temperature by structurally simple, pyrrolidine-based amine catalysts in conjunction with a protonic acid are described below.¹

VI.A Results and Discussion:

The Michael reaction of cyclohexanone and nitrostyrene was selected for orienting experiments using the pyrrolidine-based triamines 4, 5 and the diaminos 11 and 12. The results of solvent screening are summarized in Table 1. Initial reactions were performed by using 20 mol% of the triamine 4 at room temperature in non-polar, as well as in polar solvents. The necessity of having a diamine within the side chain was also evaluated by using the amides 16 and 17 in the initial screening test. Interestingly, the asymmetric induction observed with 17 is opposite to that of 16, which demonstrates better enantioselection, lower yield and requires a shorter reaction time (Table 1; entries 2 and 4). The reaction employing triamine 4 seemed to be sluggish and low yields of the conjugate addition product 24 were obtained after 4 to 5 days at ambient temperature (Table 1; entries 5 to 7). For the triamine 4 the reaction yields and rates varied significantly in the range of solvents tested, but surprisingly a substantial change in the nature of solvent did not affect the enantioselectivity of the product. The highest enantioselectivity was obtained in DMF (Table 1; entries 5 to 7). This stereochemical outcome (2S, 1’R) was in accordance with that reported in the literature but was opposite to that obtained with amide 16. The reasons for this behavior are not clear at present.
Table 1: Catalyst and solvent screening for the asymmetric nitro-Michael reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Reaction Time (days)</th>
<th>Yield$^a$ (%)</th>
<th>dr$^b$ (syn/anti)</th>
<th>ee$^c$ (%) (syn)</th>
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<tr>
<td>1</td>
<td>16</td>
<td>toluene</td>
<td>5</td>
<td>60</td>
<td>5/1</td>
<td>24$^d$</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>DMF</td>
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<td>47</td>
<td>4/1</td>
<td>1$^d$</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>ethanol</td>
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<td>14</td>
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<td>5/1</td>
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$^a$Isolated yields. $^b$Determined by $^1$H NMR of crude product. $^c$Chiral HPLC analysis. $^d$Enantiomeric product.

An improved reaction rate with better enantio- as well as diastereoselectivity was observed when the catalysts 5 and 11 were employed in the same reaction in a variety of solvents (Table 1; entries 8 to 13). On the other hand catalyst 12 offered moderate...
enantioselectivity but excellent diastereoselectivity when used with toluene (Table 1; entry 14). Thus, it appeared that a subtle change in catalyst structure improved the catalytic activity remarkably (catalyst 5 vs. catalyst 4). The presence of the terminal tertiary amine moiety in catalyst 5 did not seem to have a significant effect since the catalyst 11 worked equally well in the initial screening test. It was found that toluene and DMF could be the solvents of choice for further optimization studies with diamines 5 and 11. Although high enantioselectivity was observed for the reaction in dichloromethane, the reaction was very slow.

The observation that the secondary amine moiety in catalyst 5 and 11, vicinal to the pyrrolidine, worked better than the tertiary amine moiety in catalyst 4 may be explained by the availability of an N-H bond in 5 and 11, which can participate in hydrogen bonding with nitroalkene 23. This is not possible for catalyst 4. The increased rate of reaction for catalyst 5 and 11 could be attributed to their ability to activate the Michael donor (ketone) by enamine catalysis as well as the Michael acceptor (nitroalkene) by single H-bond formation simultaneously. Catalyst 4 can activate only the Michael donor (ketone) by enamine formation and hence the reduced reaction rate (Table 1, entries 5, 7, 8 and 11) as compared to 5 and 11.

In the pioneering studies carried out by Hine, it was shown that protonated amines formed imines from the corresponding carbonyl compounds at a rate that was 15 times faster than that achieved by amines alone. Inspired by this report, further optimization studies were carried out to investigate the effect of an acid additive, change in catalyst loading and with the number of equivalents of ketone used (Table 2).
Table 2: Further optimization of studies for asymmetric conjugate addition of cyclohexanone to \(\beta\)-nitrostyrene.

![Diagram](image)

<table>
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<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Mol% Ketone equiv.</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yielda (%)</th>
<th>drb (syn/anti)</th>
<th>ee(^c) %</th>
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\(^a\)Isolated yields. \(^b\)Determined by \(^1\)H NMR of crude product. \(^c\)Chiral HPLC analysis. \(^d\)15 mol%. \(^e\)10 mol%. \(^f\)2, 4-dinitrobenzenesulfonic acid. \(^g\)Catalyst

To our delight, the use of an acid (pTsOH) in conjunction with diamine 11 and triamine 5 had a dramatic effect on the yield, diastereoselectivity and enantioselectivity of this reaction. Although catalyst 5 provided Michael adduct 24 with 90\% ee in toluene without any added acid, no product was obtained when pTsOH was added to this
reaction. This is probably due to the poor solubility of 5/pTsOH salt in toluene (Table 2, entry 1). Consequently, further studies in toluene could not be undertaken. Hence, DMF was used as the solvent for further optimization as it offered excellent enantioselectivity (95% ee) and moderate diastereoselectivity (Table 2, entry 3), while dichloromethane offered only good enantioselectivity (87% ee) and diastereoselectivity (Table 2, entry 2).

Interestingly, reducing the amount of catalysts led to lower enantioselectivity (Table 2, entries 3, 4 and 5) and 20 mol% catalyst loading was found to be optimum. The amount of ketone also influenced the reaction outcome and excellent enantioselectivity was obtained with either a slight excess (1.1 eq.) (Table 2, entry 3) or a large excess of the ketone (5 eq.) (Table 2, entry 11). Surprisingly, the use of 1.5 and 2.0 eq. of ketone in conjunction with 5pTsOH in DMF reduced the enantioselectivity (Table 2, entries 6 and 8). The use of 2,4-dinitrobenzenesulfonic acid (Table 2, entry 7 and 9) led to a similar observation while trifluoroacetic acid deactivated the catalyst and no product was obtained (Table 2, entry 10). Thus, 5 eq. ketone with 20 mol% catalyst 5 in DMF was chosen as the optimal system as it offered excellent enantioselectivity (>99% ee) (Table 2, entry 12) and much better diastereoselectivity (19/1) than that obtained with 1.1 eq. ketone. The same reaction was also carried out under the optimized conditions with amines 11 and 12. The stereochemical outcome was similar for catalyst 11, but slightly lower enantioselectivity was obtained for catalyst 12.

As anticipated, the enantioselectivity with the 4/pTsOH combination was much lower (83% ee) (Table 2, entry 14) than with the 5/pTsOH (>99% ee). The observation that 5 and 11 are much better catalysts than 4 highlights the importance of the secondary-
secondary diamine motif, which was examined by Yamamoto in asymmetric aldol reactions.\textsuperscript{37} However, this class of diamines has been mostly overlooked in organocatalytic conjugate addition studies and, in one earlier investigation, generated aminals of the carbonyl substrates.\textsuperscript{38} Diamine 5 or 11 with $p$TsOH in DMF was therefore the catalyst system of choice.

One possible reason that the secondary-secondary diamine 5 performs better than the secondary-tertiary diamine 4 in conjunction with a protonic acid, could be the ability of 5/$p$TsOH to form two hydrogen bonds with the nitroalkene (and hence a rigid transition state)\textsuperscript{36d} as compared to catalyst 4/$p$TsOH, where only one hydrogen bond is feasible.

![Figure 6: H-bonding of nitroalkene with catalyst 5 and catalyst 4](image)

Having established the optimized set of conditions for the conjugate addition reactions, the utility of secondary-secondary diamine catalysts 5, 11 and 12 was examined for Michael reactions of a variety of cyclic (6-membered) ketones to selected β-nitroalkenes. These reactions proceeded efficiently (up to 99% yield) with high-to-excellent enantioselectivity (up to >99% ee, (2$S$, 1'R)) and diastereoselectivity (up to 50:1 dr, favoring the syn diastereomer in all cases) as shown in Table 3.
Table 3: Results of organocatalyst 5-and 11-promoted Michael addition of cyclic ketones to less-hindered trans β-nitro-olefins.
(All reactions are done with 5 eq. of ketone, DMF solvent, 24 h, room temp., except as noted)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Cat/Additive</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt; (syn/anti)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%) (syn)</th>
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<td>92</td>
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<td>19/1</td>
<td>&gt;99</td>
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<sup>a</sup>Isolated yields.<sup>b</sup>Determined by <sup>1</sup>H NMR of crude product.<sup>c</sup>Chiral HPLC analysis.<sup>d</sup>Toluene/DMF: 3/1-ratio solvent.<sup>e</sup>11 h reaction.
Table 3 shows that a range of six-membered cyclic ketones, having various functionalities (Table 3, entries 1 to 7) could react with unsubstituted or para substituted phenylnitroalkenes to afford excellent enantioselectivity (86-99% ee) and diastereoselectivity ($\geq 19/1$ dr). The only exception is the $p$-nitro-substituted nitroalkene, which provided adduct 29 (Table 3, entry 8 and 9) with poor diastereoselectivity (3/1 dr). Use of MeSO$_3$H, instead of $p$TsOH offered better enatioselection for tetrahydropyran-4-one as the ketone substrate, to yield 26, but the reaction was too slow to be useful (Table 3, entry 4). The use of DMF/toluene as the solvent reduced the enantioselectivity (Table 3, entry 5). This may be due to lower solubility of the catalyst system.

The mild reaction conditions needed for these reactions allowed a substrate bearing an acid-sensitive group (ketal 27, Table 3, entry 6 and 7) to undergo the Michael addition with high ee and dr. Overall, enantioselectivities obtained for nitroalkenes with substitution at the 4-position in the phenyl ring were very high, irrespective of the electronic nature of substituents on the nitroalkenes (Table 3, entries 8 to 14).

Thus, the nature of ketone or substituent on the nitro-olefin has no significant effect on the outcome of the process, and in all cases Michael adducts formed with excellent stereocontrol and $2S, 1'R$ configuration. These results can be interpreted by assuming a synclinal transition state assembly$^{39}$ in which the nitroalkene is double-hydrogen bonded to the protonated catalyst side chain. The proposed catalytic cycle is shown in Figure 7.
Figure 7: Rationalization of the stereochemical outcome for asymmetric Michael reactions

In the first step of this catalytic cycle, the catalyst and ketone react to form enamine intermediates (A/A') (via iminium ion intermediates). The stereochemistry is decided by the second step of the reaction i.e. the addition of trans-β-nitroalkenes to these enamine intermediates. As shown in Figure 7, the enamine intermediate can adopt the anti (A') as well as the syn (A) conformation. Theoretical calculations suggest that (A') is more favored than (A). The nitroalkene can approach the anti enamine in two possible ways: from the re face of the enamine or from the si face of the enamine. These two possible approaches should result in formation of (2S, 1'R) and (2R, 1'S) products respectively. Relative and absolute configurations of all products were determined by comparing known 1H NMR data, chiral HPLC retention times and optical rotation values.
with those reported in the literature. The product obtained was found to have \((2S, 1'R)\) configuration.

The high enantio- and diastereoselectivity of this process can be attributed to the formation of a six-membered transition state assembly \(B\) (involving the nitro group in the nitroalkenes and the protonated side chain of catalyst) by double hydrogen bonding (Figure 7). This \(\text{re}\) face addition of enamine to the nitroalkene generates the iminium ion \(C\), which after hydrolysis yields the Michael adducts \((2S,1'R)\) and the regenerated catalyst.

Table 4 shows that although the nature of the substituent (electron-donating or withdrawing) on the nitroalkene has no significant effect on the enantioselection, the substitution pattern does influence the stereochemical outcome. Enantioselectivities for nitroalkenes with substitution at the \(\text{ortho}\) or \(\text{meta}\) position (Table 4) in the phenyl ring were lower than the cases with substitution at the \(\text{para}\) position in the nitroalkenes (Table 3, entries 8 to 14). In case of the \(m\)-nitro substituted Michael adduct 32 (Table 4, entries 1 and 2), the catalyst 11 gave the best result (90% \(\text{ee}\)) but the \(\text{ee}\) is lower than that obtained with the \(p\)-nitro substituted Michel adduct 28 (>99% \(\text{ee}\)) (Table 4, entries 8 and 9). Only \(p\)TsOH proved be a better acid additive than any other acid additives for this substrate (Table 4, entries 1, 4 and 5), while in a mixed solvent there was loss of \(\text{ee}\) (Table 4, entry 3).
Table 4: Organocatalysts 5-and 11-promoted Michael addition of cyclic ketones to sterically hindered trans β-nitro-olefins, and effect of size of acid additive on enantioselectivity.
(All reactions are done with 5 eq. of ketone, DMF solvent, 24 h, room temp., except as noted)

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<tr>
<th>Entry</th>
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<th>Cat/Additive</th>
<th>Yield(^a) (%)</th>
<th>dr(^b) (syn/anti)</th>
<th>ee(^c) (%)</th>
<th>syn</th>
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<td>21</td>
<td><img src="image21" alt="Product 21" /></td>
<td>5/pTsOH</td>
<td>79</td>
<td>10/1</td>
<td>70(^d)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated Yields. \(^b\) Determined by \(^1\)H NMR of crude products. \(^c\) Chiral HPLC analysis.
\(^d\) Toluene/DMF: 3/1-ratio solvent. \(^e\) 11 h reaction. \(^f\) Reaction at 0 °C for 45 h. \(^g\) 2 equiv. of acid additive.
Lower enantioselectivity (without affecting diastereoselectivity and yields) was observed for the Michael adducts 33, 34 and 35 derived from ortho substituted nitroalkenes (Table 4, entries 6, 10, 11 and 14) as compared to Michael adducts 29, 30 and 31 based on para substituted nitroalkenes (Table 3, entries 10, 11, 12 and 16).

The loading of acid additive also influences the reaction outcome by affecting the reaction rate, as can be seen for product 34. When a 2:1 ratio of acid:catalyst was used instead of 1:1 ratio of acid:catalyst, the reaction became very sluggish. However, there was a slight improvement in the enantio- and diastereoselectivity (Table 4, entries 12 and 13).

Interestingly, it was observed that apart from the substitution pattern in the nitroalkene, the size of the acid additive also influenced the enantioselectivity. In one case, decreasing the size of acid additive (use of MeSO₃H instead of pTsOH) significantly increased the enantio- and diastereoselection for 33 (Table 4, entries 6 and 7). On the other hand, increasing the size of acid additive significantly decreased the enantioselection for the 1-naphthyl substrate 35 (Table 4, entries 16, 17 and 18). These results suggest that the conjugate base of the protonic acid influences the enantioselection. Presumably, a large counter-ion causes crowding in the transition state assembly and this affects the hydrogen-bonding between the catalysts and sterically-demanding substrates, as shown in Figure 8.
As shown earlier, the stereochemical outcome of the Michael addition may be explained by a synclinal transition state assembly (A, Figure 8) in which, a protonated secondary amine delivers the nitroalkene by hydrogen bonding to provide the major product in all cases. This model can rationalize the excellent stereoselection for all of the unhindered nitroalkenes. For hindered nitroalkenes the enantioselectivity is lower, possibly due to a competing non-hydrogen bonded assembly such as (B, Figure 8) in order to avoid steric interactions (R′-R") caused by a large acid counter-ion. This would expose the si face of the enamine to react with the re face of the nitroalkene leading to the minor enantiomer (2R,1'S) thereby lowering the enantioselection for the desired syn product (2S, 1'R). The results obtained with the o-methoxy nitrostyrene (Table 4, entries 6 to 9) and the 1-naphthyl nitrostyrene (Table 4, entries 16 to 18) support this proposal.

In a related study, heteroaryl nitroalkenes were also examined as Michael acceptors. As shown in Table 5, enantioselection for these substrates was better with methanesulfonic acid as an additive in DMF at 0 °C.
Table 5: Organocatalyst 5-and 11-promoted Michael addition of cyclic ketones to trans β-heteroaryl nitro-olefins, and effect of size of acid additive on enantioselectivity.

(All reactions are done with 5 eq. of ketone, DMF solvent, 24 h, room temp., except as noted)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Cat/Additive</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt; (syn/anti)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%)&lt;sup&gt;syn&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
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<td>5/ HCl</td>
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<td>18/1</td>
<td>81</td>
</tr>
<tr>
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<td>5/ MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>82</td>
<td>15/1</td>
<td>88&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>11/ MeSO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>97</td>
<td>14/1</td>
<td>84&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
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<td><img src="image5" alt="Structure" /></td>
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<td>50/1</td>
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<td>87</td>
<td>8/1</td>
<td>78</td>
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<td>80</td>
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<td>5/ 2,4,6-tri-iPr-PhSO&lt;sub&gt;3&lt;/sub&gt;H</td>
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<td>19/1</td>
<td>82</td>
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<td>78</td>
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<td>19/1</td>
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<td>10/1</td>
<td>86&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>84&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>5/ HCl</td>
<td>75</td>
<td>12/1</td>
<td>83</td>
</tr>
<tr>
<td>19</td>
<td><img src="image19" alt="Structure" /></td>
<td>11/ HCl</td>
<td>99</td>
<td>19/1</td>
<td>84</td>
</tr>
<tr>
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<td><img src="image20" alt="Structure" /></td>
<td>5/ HCl</td>
<td>70</td>
<td>8/1</td>
<td>79&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>11/ HCl</td>
<td>75</td>
<td>10/1</td>
<td>72&lt;sup&gt;f&lt;/sup&gt;</td>
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</table>

<sup>a</sup>Isolated yields after 24 h. <sup>b</sup>Determined by <sup>1</sup>H NMR of crude products. <sup>c</sup>Chiral HPLC analysis. <sup>d</sup>Reaction at 0 °C for 45 h. <sup>e</sup>Toluene/DMF: 3/1-ratio solvent. <sup>f</sup>Dichloromethane solvent. <sup>g</sup>11 h reaction. <sup>h</sup>Reaction at −10 °C for 5 d.
For the furanyl substrate 36, the 5/MeSO₃H (Table 5, entry 3) combination performed better than 11/MeSO₃H (Table 5, entry 4) in DMF and yielded 88% ee. For thiophenyl substrate 37, the 11/MeSO₃H combination in DMF provided the best result (85% ee) (Table 5, entry 13).

The use of any of the catalysts 5, 11 or 12 in conjunction with pTsOH showed almost equal enantioselectivity (Table 5, entries 5, 6 and 7), yet different diastereoselectivity. Interestingly, increasing the size of acid additive in conjunction with catalyst 5 increased the enantioselection for the thiophenyl substrate (product 37, Table 5, entries 7, 8 and 9). This trend is opposite to that seen for the 1-naphthyl-based substrate (product 35, Table 4, entries 15, 16 and 17).

The 5/MeSO₃H combination at room temperature gave 82% ee (Table 5, entry 10), when the reaction was performed at 0 °C, the enantioselection improved marginally (Table 5, entry 12). Lowering the temperature to −10 °C had no beneficial effect (Table 5, entries 14/15, 13/17 and 16/19). It is noteworthy that the 11/HCl combination at room temperature, is as efficient as the 5/MeSO₃H, 11/MeSO₃H or 12/MeSO₃H combinations at 0 °C, which is similar to 11/HCl at −10 °C!

In DMF, the 5/HCl or 11/HCl combination worked equally well with respect to enantioselectivity (Table 5, entries 18 and 19) but in dichloromethane, 5/HCl was superior (79% ee) to 11/HCl (72% ee) (Table 5, entries 20 and 21). It is plausible that, in dichloromethane, the diamine pendant in catalyst 5 has increased steric requirements. This may be due to internal hydrogen bonding in the ethylenediamine unit of catalyst 5 in a noncoordinating solvent like dichloromethane. The selectivity of the chain-extended
conformer of 5 is reflected by 11 which is incapable of internal hydrogen bonding in the side chain (Figure 9).

![Chemical structures and reactions](image)

**Figure 9**: Internal H-bonding in triamine 5 and its effect on stereoselection

At this point, it becomes important to note that the published literature shows some variation in the proposed transition-state models to explain the observed outcome of the Michael reactions of carbonyls to nitroalkenes. Enders and Wang propose an **anti-enamine** formation, while Barbas III, Alexakis, and Kotsuki propose a **syn-enamine**. In addition, Barbas III and Alexakis propose an **anti-enamine**, while Wang proposes a **syn-enamine** for the aldehyde Michael addition. This shows that the detailed understanding of the stereochemical outcome of this process is not well understood and is an ongoing question for organic chemists.
The effect of cyclic ketone ring size on the stereochemical outcome of the Michael reaction under our optimized reaction condition with catalyst 5, 11 and 12 was also investigated. It was known that the ring size of cyclic ketones affects the reaction rate by controlling the rate of iminium ion formation\(^4\) and the results obtained in this study has been shown in Table 6.

**Table 6: Organocatalyst 5-, 11-and 12- promoted Michael addition of various sized cyclic ketones to trans β- nitro-styrene.**

(All reactions are done with 5 eq. of ketone, DMF solvent, 24 h, *room temp.*, except as noted)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (d)</th>
<th>Cat/Additive</th>
<th>Yield(^a) (%)</th>
<th>dr(^b) (syn/anti)</th>
<th>ee(^c) (%) (syn)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Ketone 38" /></td>
<td>1.8</td>
<td>5/pTsOH</td>
<td>51</td>
<td>7/1</td>
<td>29 (37)(^d)</td>
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<td><img src="image" alt="Ketone 38" /></td>
<td>1.8</td>
<td>11/pTsOH</td>
<td>33</td>
<td>2/1</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ketone 38" /></td>
<td>1.8</td>
<td>12/pTsOH</td>
<td>37</td>
<td>3/1</td>
<td>62 (77)(^d)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ketone 38" /></td>
<td>1.8</td>
<td>11/HCl</td>
<td>35</td>
<td>5/1</td>
<td>25(^e)</td>
</tr>
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<td><img src="image" alt="Ketone 38" /></td>
<td>1.8</td>
<td>12(^f)</td>
<td>40</td>
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<td>5/pTsOH</td>
<td>90</td>
<td>19/1</td>
<td>&gt;99</td>
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<tr>
<td>7</td>
<td><img src="image" alt="Ketone 24" /></td>
<td>1</td>
<td>11/pTsOH</td>
<td>86</td>
<td>19/1</td>
<td>&gt;99</td>
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<td>12/pTsOH</td>
<td>90</td>
<td>45/1</td>
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<td>2</td>
<td>12/pTsOH</td>
<td>84</td>
<td>15/1</td>
<td>62</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields. \(^b\)Determined by \(^1\)H NMR of crude products. \(^c\)Chiral HPLC analysis. \(^d\)ee of anti-diastereoisomer. \(^e\)Enantiometric product. \(^f\)Toluene solvent.

As seen from the data in Table 6, the ring size of the cyclic ketone does affect the yield, reaction rate, diastereoselectivity as well as enantioselectivity of the Michael reaction. The combination of 12/pTsOH proved to be better for ring sizes other than six-
membered (Table 6; entries 3, 8 and 10). It may be interesting to see the effect of more bulky group (i.e. naphthyl instead of phenyl) at the terminal position of the catalyst side chain. For cyclopentanone, the 12/pTsOH combination proved to be significantly better than 11/pTsOH, which in turn was better than 5/pTsOH, by providing 62% ee of the syn (major) diastereomer and 77% ee of the anti (minor) diastereomer (Table 6; entries 1, 2 and 3) of 38. Interestingly, the combination of 11/HCl provided the enantiomeric product with 25% ee (Table 6; entry 4). For reactions with cycloheptanone, the diastereoselectivities and yields were better than those obtained with cyclopentanone. The best enantioselectivity was achieved with cyclohexanone.

It is noteworthy that the reaction rates for cyclopentanone and cycloheptanone are lower than those obtained with cyclohexanone. Nonetheless, the overall efficacy of catalysts 5, 11 and 12 appears to be better than some of the other reported catalysts.21,27c

In addition to Michael reactions of cyclic ketones, we have also examined the utility of catalyst 5, 11 and 12 for acyclic ketones and aldehydes with nitroalkenes. The unoptimized results of this study are summarized in Table 7.
Table 7: Organocatalyst 5-, 11- and 12-promoted Michael addition of acyclic ketones and aldehydes to trans β-nitro-styrene.
(Reactions are done with 5 eq. of ketone/aldehyde, DMF solvent, 24 h, room temp., except as noted)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Cat/Additive</th>
<th>Yield(^a) (%</th>
<th>dr(^b) (syn/anti)</th>
<th>ee(^c) (%)</th>
<th>syn</th>
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<td><img src="image1" alt="Structure" /></td>
<td>5/pTsOH</td>
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<td>14</td>
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<tr>
<td>2</td>
<td><img src="image2" alt="Structure" /></td>
<td>12</td>
<td>94</td>
<td>-</td>
<td>34</td>
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<td>5/pTsOH</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>11/pTsOH</td>
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<td>-</td>
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<td>1</td>
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<td>12(^d)</td>
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<td>11/HCl</td>
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<td>2/1</td>
<td>29</td>
<td></td>
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</tbody>
</table>

\(^a\) Isolated yields after 24 h. \(^b\) Determined by \(^1\)H NMR of crude products. \(^c\) Chiral HPLC analysis. \(^d\) 1.1 eq. aldehyde. \(^e\) iPrOH solvent. \(^f\) Toluene solvent.

In general, the optimized reaction conditions for the Michael addition of cyclic ketones do not appear to work well for aldehydes and acyclic ketones. With the exception of acetone, practically no reaction was observed with these Michael donors and starting materials were recovered. Clearly, further studies are required for this class of carbonyl compounds.
VII. Synthetic utility of the ketone/nitroalkene Michael addition: Synthesis of nitrone 44

The ketone-nitroalkene Michael reaction is potentially useful in organic synthesis. As shown in Scheme 6, partial reduction of the Michael adduct 24, provided the cyclic nitrone 44\(^{42}\) by cyclization of the intermediate hydroxylamine (Reissig nitrone synthesis).\(^{43}\)

![Scheme 6](image)

Cyclic nitrones can be used in stereoselective 1, 3-dipolar cycloaddition reactions with electron-rich olefins to generate fused isoxazolidines.\(^{44}\) These isoxazolidines, in turn, are versatile intermediates for the stereoselective preparation of substituted \(\alpha\)-amino acids. In addition, the Michael adduct 24 can also be readily converted into 3-phenyloctahydroindole.\(^{55}\)
VIII. Conclusion

In summary, we have developed simple protonated triamine and diamine catalysts for the highly enantioselective conjugate addition of cyclic, six-membered ketones to nitroalkenes. To the best of our knowledge, this is the first study in which pyrrolidine-based, monoprotonated secondary-secondary diamines have been used to activate nitroalkenes by a proposed double hydrogen bonding mechanism. The main advantages of these catalysts are the ease of synthesis and very good enantioselection at ambient temperature. For unhindered nitroalkenes, the enantioselection with these simple catalysts at ambient temperature is better than the enantioselection with structurally more complex pyrrolidine catalysts at subambient temperatures. However, further optimization is needed for enantioselective conjugate addition reactions with acyclic ketones and aldehydes.
IX. Experimental Section

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C). All organic layers obtained from extractions were dried over anhydrous sodium sulfate. THF was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride prior to use. Chromatographic purification of products was done using flash column chromatography on Merck 60F 230-400 mesh silica gel according to the standard procedure. Reactions were monitored by TLC on commercial precoated silica (Merck 60F-254) by staining with iodine. All melting points are uncorrected.

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AVANCE 500 at 500 MHz and 125.8 MHz respectively at room temperature. The chemical shifts are reported in ppm downfield to TMS (δ = 0) for $^1$H NMR and relative to the central CDCl$_3$ resonance (δ = 77.23). Data for $^1$H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for $^{13}$C NMR are reported in terms of chemical shift. IR spectra were recorded on a Bruker TENSOR 27 spectrometer and are reported in wavenumbers (cm$^{-1}$). Mass spectra (APCI or ESI) were obtained on an Atmospheric Pressure Ionization-Mass Spectrometer (API-MS, Agilent 1100 series LC/MSD chromatographic system) at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were obtained on a Waters/Micromass GCT Time of Flight Mass Spectrometer, (CI gas ammonia), at the McMaster Regional Centre for Mass Spectrometry. Optical rotations were measured at the sodium D line on a JASCO DIP-
370 polarimeter at ambient temperature. Enantiomeric excess (ee) was determined by high performance liquid chromatography (HPLC) on an Agilent 1100 series chromatograph using either a Chiralpak AD-H column (1.6 x 25 cm) or Chiralpak AS-H (1.6 x 25cm) column. All Michael addition reactions were carried out in a closed vial without the exclusion of air or moisture.

**Materials**

All solvents and commercially available chemicals were used as received. Organic substrates cyclohexanone, cyclopentanone tetrahydrothiopyran-4-one tetrahydropyran-4-one 4-(1,3-dioxolane)-cyclohexanone cycloheptanone, acetone, 3-pentanone, isobutyraldehyde, isovaleraldehyde, L-proline, N1,N1,N2-trimethylethane-1,2-diamine, N,N-dimethylethane-1,2-diamine, 3-methylbutan-1-amine, 2-phenylethane-1-amine, 1-nitro-4-((E)-2-nitrovinyl)benzene, 1-methoxy-2-((E)-2-nitrovinyl)benzene, 1-(trifluoromethyl)-2-((E)-2-nitrovinyl)benzene, 2-((E)-2-nitrovinyl)furan, 2-((E)-2-nitrovinyl)thiophene were obtained from commercial sources and were used without any purification. Michael acceptors, such as 1-((E)-2-nitrovinyl)benzene, 1-methoxy-4-((E)-2-nitrovinyl)benzene, 1-(trifluoromethyl)-4-((E)-2-nitrovinyl)benzene, 2-((E)-2-nitrovinyl)naphthalene, 1-nitro-3-((E)-2-nitrovinyl)benzene, 1-((E)-2-nitrovinyl)naphthalene were prepared according to the literature procedure.46
Procedures

\[ N^1,N^1\text{-Dimethyl-}N^2\text{-((S)-pyrrolidin-2-yl)methyl} \text{ethane-1,2-diamine (5):} \]

To a solution of Boc-L-proline 13 (5.4 g, 25 mmol) in 50 mL dry CH\(_2\)Cl\(_2\) were added 1-hydroxybenzotriazole (3.45 g, 25.5 mmol) and DCC (5.3 g, 25.5 mmol). The resulting suspension was stirred at room temperature for 30 minutes and a solution of the amine (2.7 mL, 25 mmol) in CH\(_2\)Cl\(_2\) (25 mL) was added. The resulting mixture was stirred at ambient temperature for 24 h and filtered twice to remove precipitated solids. The filtrate was extracted once with saturated aqueous NaHCO\(_3\) (25 mL) followed by back extraction of the aqueous phase with CH\(_2\)Cl\(_2\) (2 x 25 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was dissolved in a minimum volume of CH\(_2\)Cl\(_2\) and the suspension was filtered. The process was repeated thrice to provide 6.8 g (96%) of the the \(N\)-Boc amide 15 as a clear, pale yellow oil that was pure by \(^1\)H NMR and was used further without purification. The material gradually solidifies at room temperature.

The crude \(N\)-Boc-amide 15 (6.56 g, 23 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (100 mL), trifluoroacetic acid (64 mL, 0.83 mol) was added, the solution was stirred at room temperature for 3 h and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue was dissolved in CH\(_2\)Cl\(_2\) (75 mL) and the solution was extracted with water (3 x 25 mL). The aqueous phase was cooled (5 °C), basified with NaOH pellets and extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The combined organic layers were
dried \((K_2CO_3)\) and concentrated under reduced pressure to provide 3.6 g (86\%) of the amino amide 17 as a clear, colorless oil that was pure by \(^1H\) NMR and was used further without purification.

To a suspension of LiAlH\(_4\) (0.61 g, 16.4 mmol) in dry THF (35 mL) at 0 °C was slowly added a solution of the above amide (2.02 g, 11 mmol) in THF (10 mL). After stirring for an hour at 0 °C the mixture was heated to reflux for 15 h and then cooled to 0 °C. Water (0.3 mL, 16.4 mmol), aqueous 1M NaOH (16.4 mL, 16.4 mmol) and water (0.9 mL, 49.2 mmol), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered, washed with THF and the filtrate was dried \((K_2CO_3)\) and concentrated under reduced pressure to give a pale yellow liquid. Acid-base purification of the crude product followed by kugelrohr distillation provided 0.88 g (47\%) of triamine 5 as a colorless liquid.

**Bp:** 120 °C (air bath)/0.5 torr.

\(^1H\) NMR (500MHz, CDCl\(_3\)):

\[
\begin{align*}
\delta & \text{ 3.32-3.29 (m, 1H, NCH)} , 2.92-2.89 (m, 2H, NCH}_2\text{ (ring))}, 2.71 (t, 2H, J = 6.2, NCH}_2\text{CH}_2\text{N}), 2.61 (dd, 1H, J = 12, 4.5, CHCH}_2\text{N}), 2.55 (dd, 1H, J = 12, 8.3, CHCH}_2\text{N}), 2.40 (t, 2H, J= 6.2, NCH}_2\text{CH}_2\text{N}), 2.22 (s, 6H, N(CH}_3)_2\text{), 1.96-1.92 (br m, 3H, 2 x NH, CH}_2\text{CH}_2\text{), 1.80-1.72 (m, 1H, CH}_2\text{CH}_2\text{), 1.72-1.65 (m, 1H, CH}_2\text{CH}_2\text{), 1.35-1.33 (m, 1H, CH}_2\text{CH}_2\text{).}
\end{align*}
\]

\(^{13}C\) NMR (125.8 MHz, CDCl\(_3\)):

\[
\begin{align*}
\delta & \text{ 59.1 (NCH), 58.3 (NCH}_2\text{), 55.3 (NCH}_2\text{), 47.6 (NCH}_2\text{), 46.4 (NCH}_2\text{), 45.5 (N(CH}_3)_2\text{), 29.7 (CH}_2\text{CH}_2\text{), 25.6 (CH}_2\text{CH}_2\text{).}
\end{align*}
\]
IR (neat):

3294, 2944, 2816, 2767, 1457 cm\(^{-1}\).

**MS** (APCI, positive):

\[\text{m/z} \quad 172.3 \ (\text{M+1, 100}), \ 184.2 \ (45), \ 186.2 \ (20), \ 212.4 \ (30), \ 242.4 \ (40)\]

**HRMS** (CI):

\[\text{m/z} \quad 172.1807 \ (172.1814 \ \text{calc. for C}_9\text{H}_{22}\text{N}_3 \ (\text{M+H}))\].

\([\alpha]^{23}_D: \ +13.0 \ (c \ 1, \ \text{CHCl}_3)\).

\(N^1,N^4,N^2\)-Trimethyl-N^2-(((S)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine (4):\(^{32}\)

\[\begin{align*}
\text{Reaction of Boc-S-proline 13 (4.84 g, 22.5 mmol), DCC (4.73 g, 22.9 mmol),} \\
\text{HOBT (3.1 g, 22.9 mmol) and } N^1,N^4,N^2\text{-trimethylthene-1,2-diamine (3.0 mL, 30 mmol)}
\end{align*}\]

in dichloromethane (100 mL), according to the procedure described for 5, gave 5.0 g (75%) of the N-Boc amide 14. Deprotection with trifluoroacetic acid (47 mL, 0.61 mol) in dichloromethane (150 mL), as described for 5, provided 2.68 g (80%) of the amino amide 16. Reduction of the amino amide (1.15 g, 5.8 mmol) with LAH (340 mg, 8.7 mmol) in THF (30 mL), as described for 5, followed by kugelrohr distillation under reduced pressure gave 0.45 g (45%) of 4. Spectroscopic data for 4 was in agreement with that reported in the literature.\(^{32}\)
3-Methyl-N-(((S)-pyrrolidin-2-yl)methyl)butan-1-amine (11):

Reaction of Boc-S-proline 13 (5.4 g, 25 mmol), DCC (5.169 g, 25.1 mmol), HOBt (5.067 g, 37.5 mmol) and 3-methylbutan-1-amine (2.4 mL, 25 mmol) in dichloromethane (80 mL), according to the procedure described for 5, provided 4.74 g (67%) of the N-Boc amide 18. Deprotection with trifluoroacetic acid (11.6 mL, 0.15 mol) in dichloromethane (25 mL), as described for 5, provided 2.54 g (83%) of the amino amide 20. Reduction of the amino amide (2.48 g, 13.5 mmol) with LAH (760 mg, 20.2 mmol) in THF (35 mL), as described for 5, followed by kugelrohr distillation under reduced pressure gave 1.55 g (65%) of 11.

Bp: 115 °C (air bath)/0.5 torr.

$^1$H NMR (500MHz, CDCl$_3$):

$\delta$ 3.27-3.25 (m, 1H, NCH), 2.96-2.89 (m, 2H, NCH$_2$ (ring)), 2.65-2.60 (m, 4H, CHCH$_2$NH, NHCH$_2$, NH), 2.54 (dd, 1 H, $J = 11.8$, 8.7, CHCH$_2$NH), 1.93-1.87 (m, 1H, CH$_2$CH$_2$), 1.83-1.75 (m, 1H, CH$_2$CH$_2$), 1.75-1.68 (m, 1H, CH$_2$CH$_2$), 1.68-1.60 (m, 1H, CH$_2$CH$_2$), 1.43-1.34 (m, 3H, CH$_2$CH), 0.92 (d, 6H, $J = 7.3$, CH (CH$_3$)$_2$).

$^{13}$C NMR (125.8 MHz, CDCl$_3$):

$\delta$ 59.0 (NCH), 56.0 (NCH$_2$), 49.1 (NCH$_2$), 47.1 (NCH$_2$), 39.9 (CH), 30.5 (CH$_2$), 26.9 (CH$_2$), 26.4 (CH$_2$), 23.45 (CH$_3$), 23.4 (CH$_3$).
IR (neat):

3276, 2954, 2869, 2815, 1462 cm⁻¹.

MS (APCI, positive):

m/z 171.2 (M+1, 100).

HRMS (CI):

m/z 171.1861 (171.1861 calc. for C₁₀H₂₃N₂ (M+H)).

[a]₂³⁰ D: +20.6 (c 1, CHCl₃).

2-Phenyl-N-(((S)-pyrrolidin-2-yl)methyl)ethane-1-amine (12):

Reaction of Boc-S-proline 13 (5.4 g, 25 mmol), DCC (5.169 g, 25.1 mmol), HOBut (5.067 g, 37.5 mmol) and 2-phenylethane-1-amine (3.1 mL, 25 mmol) in dichloromethane (80 mL), according to the procedure described for 5, provided 7.1 g (90%) of the N-Boc amide 19. Deprotection with trifluoroacetic acid (17.4 mL, 0.22 mol) in dichloromethane (35 mL), as described for 5, provided 4.4 g (90%) of the amino amide 21. Reduction of the amino amide (2.9 g, 13.5 mmol) with LAH (760 mg, 20.2 mmol) in THF (35 mL), as described for 5, followed by kugelrohr distillation gave 2.2 g (84%) of 12.

Bp: 190 °C (air bath)/0.5 torr.

¹H NMR (500MHz, CDCl₃):
7.29-7.26 (m, 2H, ArH), 7.20-7.17 (m, 3H, ArH), 3.17-3.20 (m, 1H, NCH), 2.90-2.83 (m, 4H, NCH$_2$ (ring), CHCH$_2$NH), 2.80-2.77 (m, 2H, NHCH$_2$), 2.62 (dd, 1 H, $J = 11.6$, 5.0, ArCH$_2$CH$_2$), 2.53 (dd, 1 H, $J = 11.6$, 8.4, ArCH$_2$CH$_2$), 2.0 (br, 1H, NH), 1.86-1.82 (m, 1H, CH$_2$CH$_2$), 1.75-1.66 (m, 2H, CH$_2$CH$_2$), 1.31-1.27 (m, 1H, CH$_2$CH$_2$).

$^{13}$C NMR (125.8 MHz, CDCl$_3$):

$\delta$ 140.2 (para ArC), 128.7 (meta ArC), 128.4 (ortho ArC), 126.1 (ArC), 58.3 (NCH), 55.1 (NCH$_2$), 51.6 (NCH$_2$), 46.5 (NCH$_2$), 36.5 (CH), 29.7 (CH$_2$), 25.7 (CH$_2$)

IR (neat):

3294, 3026, 2940, 2869, 1453 cm$^{-1}$.

MS (APCI, positive):

m/z 205.2 (M+1, 100).

HRMS (CI):

m/z 205.1696 (205.1705 calc. for C$_{13}$H$_{21}$N$_2$ (M+H)).

$[^{23}\alpha]^p$: +15 (c 1, CHCl$_3$).
General experimental procedure for the Michael addition of ketones or aldehydes to nitroalkenes:

To a solution of the amine catalyst (0.1 mmol), *p*-toluene sulfonic acid monohydrate (0.1 mmol) and the nitroalkene (0.5 mmol) in DMF (1 mL) was added the ketone or aldehyde (2.5 mmol), and the solution was stirred at ambient temperature for 24 h except when noted otherwise. The solution was then concentrated at ambient temperature under reduced pressure and the residue was purified by flash column chromatography on silica gel. Alternatively, ethyl acetate (10 volumes) was added and the solution was washed with water, aqueous 1M HCl, dried (Na$_2$SO$_4$), filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel.

The relative configurations of the products (*syn* and *anti*) were determined by comparison of $^1$H NMR spectral data with those reported in the literature. The absolute configurations of each product were determined either by comparison of optical rotation values with those reported in the literature or by comparison of HPLC retention times. All the compounds reported here and in Tables 3, 4, 5, 6 and 7 have previously been reported by others.\textsuperscript{9c,19,21,24,27c,28a}
(S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (24):  

\[ \text{Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 117 mg (90\%) of 24 as a white solid.} \]

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl₃):} \]

\[ \delta 7.37-7.29 (m, 3H, Ar\text{II}), 7.19 (d, 2H, \text{J} = 7.7, \text{ortho ArH}), 4.96 (dd, 1H \text{J} = 12.4, 4.5, \text{CH}_{2}\text{NO}_2), 4.67 (dd, 1H \text{J} = 12.4, 10, \text{CH}_{2}\text{NO}_2), 3.79 (dt, 1H, \text{J} = 10, 4.5, \text{PhCH}), 2.75-2.69 (m, 1H, \text{CH(C)O}), 2.53-2.50 (m, 1H, \text{CH}_2\text{C(O)}), 2.50-2.39 (m, 1H, \text{CH}_2\text{C(O)}), 2.13-2.08 (m, 1H, \text{CH}_2), 1.84-1.57 (m, 4H, \text{CH}_2), 1.31-1.23 (m, 1H, \text{CH}_2). \]

\[ \text{HPLC (Chiralpak AD-H):} \]

\[ \text{(hexane/i-PrOH, 90/10, flow rate 1 mL min}^{-1}, \text{conc. 1mg/mL, } \lambda = 247 \text{ nm):} \]

\[ t_{\text{major}} = 11.1 \text{ min.} \]

\[ \text{[\alpha]^{23}_{D} : -21.0 (c 1, CHCl}_3), \]

\[ \text{ee : >99\%.} \]
(S)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)thiopyran-4-one (25): \(^{24}\)

![Chemical structure of compound 25]

Reaction of tetrahydrothiopyran-4-one (0.29 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl) benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 103 mg (78%) of 25 as a white solid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)):

\[\delta 7.36-7.33 \ (m, \ 2H, \text{ArH}), 7.33-7.29 \ (m, \ 1H, \text{ArH}), 7.19 \ (d, \ 2H, J = 6.5, \text{ortho ArH}),
4.73 \ (dd, \ 1H, J = 12.7, 4.5, \text{CH}_2\text{NO}_2),
4.63 \ (dd, \ 1H, J = 12.7, 10, \text{CH}_2\text{NO}_2),
3.98 \ (dt, \ 1H, J = 10, 4.5, \text{PhCH}),
3.07-3.00 \ (m, \ 1H, \text{CHC(O)}),
3.00-2.94 \ (m, \ 2H, \text{CH}_2\text{C(O)}),
2.88-2.84 \ (m, \ 1H, \text{SCH}_2),
2.84-2.77 \ (m, \ 1H, \text{SCH}_2),
2.64-2.60 \ (ddd, \ 1H, J = 13.8, 4, 2, \text{SCH}_2\text{CH}),
2.45 \ (dd, \ 1H, J = 13.8, 9.7, \text{SCH}_2\text{CH}).\]

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 50/50, flow rate 0.5 mL min\(^{-1}\), conc. 1 mg/mL, \(\lambda = 247 \text{ nm}\));

\(t_{\text{minor}} = 17 \text{ min}; \ t_{\text{major}} = 21 \text{ min}.\)

\([\alpha]_D^{23} : -16.0 \ (c1, \text{CHCl}_3).\]

\(\text{ee} : 99\%.\)
(R)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)pyran-4-one (26):\(^{27c}\)

![Chemical structure of (R)-Tetrahydro-3-((R)-2-nitro-1-phenylethyl)pyran-4-one (26)](image)

Reaction of tetrahydropyran-4-one (0.23 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl) benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 40/60), 91 mg (90%) of 26 as a white solid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)):

\(\delta\) 7.39-7.31 (m, 3H, ArH), 7.21 (d, 2H, J = 7.4, ortho ArH), 4.96 (dd, 1H, J = 12.5, 4.7, CH\(_2\)NO\(_2\)), 4.68 (dd, 1H, J = 12.5, 10, CH\(_2\)NO\(_2\)), 4.20-4.15 (m, 1H, PhCH), 3.89-3.79 (m, 2H, OCH\(_2\)), 3.73 (dd, 1H, J = 11, 5.3, OCH\(_2\)CH), 3.31 (dd, 1H, J = 11, 8.8, OCH\(_2\)CH), 2.94-2.89 (m, 1H, CHC(O)), 2.72-2.67 (m, 1H, CH\(_2\)C(O)), 2.62-2.58 (m, 1H, CH\(_2\)C(O)).

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 50/50, flow rate 0.5 mL min\(^{-1}\), conc. 1mg/mL, \(\lambda = 247\) nm);

\(t_{\text{minor}} = 18.4\) min; \(t_{\text{major}} = 22.4\) min.

ee : 92%.
(S)-2-[(R)-2-Nitro-1-phenylethyl]-4-[1,3-dioxolane)cyclohexanone (27): 27c

![Chemical structure of (S)-2-[(R)-2-Nitro-1-phenylethyl]-4-[1,3-dioxolane)cyclohexanone](image)

Reaction of 4-(1,3-dioxolane)-cyclohexanone (0.39 gm, 2.5 mmol) and 1-((E)-2-nitrovinyl) benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 40/60), 296 mg (97%) of 27 as a white solid.

$^1H$ NMR (500 MHz, CDCl$_3$):

$\delta$ 7.35-7.28 (m, 3H, ArH), 7.21 (d, 2H, $J=7.5$, orthoArH), 4.95 (dd, 1H, $J=12.5$, 4.5, $CH_2NO_2$), 4.63 (dd, 1H, $J=12.5$, 10, $CH_2NO_2$), 4.04-3.81 (m, 5H, PhCH, OCH$_2$CH$_2$O), 3.10-3.05 (m, 1H, CHC(O)), 2.71 (m, 1H, dt, 1H, $J=13.6$, 4.6, 1H, CH$_2$CH$_2$), 2.52 (dt, 1H, $J=13.6$, 4.5, 1H, CH$_2$CH$_2$), 2.04-2.01 (m, 1H, CH$_2$CH$_2$), 2.00-1.91 (m, 1H, CH$_2$CH$_2$), 1.72-1.66 (m, 1H, CH$_2$CH), 1.60-1.52 (m, 1H, CH$_2$CH).

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 40/60, flow rate 0.8 mL min$^{-1}$, conc.1mg/mL, $\lambda = 247$ nm);

$t_{\text{minor}} = 10.8$ min; $t_{\text{major}} = 16.3$ min.

$[\alpha]_{D}^{23}: -15.0$ (c1, CHCl$_3$).

ee : 88%. 

(S)-2-((R)-2-Nitro-1-(4-nitrophenyl)ethyl)cyclohexanone (28):

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-nitro-4-((E)-2-nitrovinyl)benzene (97.6 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 98 mg (88%) of 28 as a yellow solid.

$^1$H NMR (500 MHz, CDCl$_3$):

$\delta$ 8.19 (d, 2H, $J = 9$, ArH), 7.39 (d, 2H, $J = 9$, ArH), 4.98 (dd, 1H, $J = 13.1$, 4.5, CH$_2$NO$_2$), 4.71 (dd, $J = 13.1$, 4.4, CH$_2$NO$_2$), 3.92 (dt, 1H, $J = 12$, 4.5, ArCH), 2.74-2.69 (m, 1H, CHC(O)), 2.52-2.47 (m, 1H, CH$_2$C(O)), 2.45-2.34 (m, 1H, CH$_2$C(O)), 2.14-2.06 (m, 1H, CH$_2$), 1.85-1.82 (m, 1H, CH$_2$), 1.73-1.56 (m, 3H, CH$_2$), 1.33-1.20 (m, 1H, CH$_2$), in agreement with the ent-28 reported in literature.$^{19b}$

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 80/20, flow rate 1 mL min$^{-1}$, conc. 1 mg/mL, $\lambda = 247$ nm);

$t_{major} = 38.7$ min.

$[\alpha]_{D}^{23} : -18.0$ (c 1, CHCl$_3$).

ee : $>99$ %. 
(S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (29): 28a

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-methoxy-4-((E)-2-nitrovinyl)benzene (90 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 116 mg (83%) of 29 as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$):

δ 7.09 (d, 2H, $J = 8$, ArH), 6.86 (d, 2H, $J = 8$, ArH), 4.91 (dd, 1H, $J = 12$, 4.5, $CH_2$NO$_2$), 4.60 (dd, 1H, $J = 12$, 10, $CH_2$NO$_2$), 3.80 (s, 3H, OCH$_3$), 3.72 (dt, 1H, $J = 10.5$, 5, ArCH), 2.69-2.63 (m, 1H, $CH_2$C(O)), 2.50-2.46 (m, 1H, $CH_2$C(O)), 2.42-2.36 (m, 1H, $CH_2$), 2.10-2.06 (m, 1H, $CH_2$), 1.82-1.55 (m, 4H, $CH_2$), 1.28-1.21 (m, 1H, $CH_2$).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min$^{-1}$, conc. 1mg/mL, λ = 247 nm);

$t_{\text{minor}} = 15.5$ min; $t_{\text{major}} = 19.4$ min;

$[\alpha]_D^{23} = -26.0$ (c 1, CHCl$_3$),

ee : 99%
(S)-2-((R)-1-(4-Trifluoromethyl) phenyl)-2-nitroethyl)cyclohexanone (30): A reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-(trifluoromethyl)-4-((E)-2-nitrovinyl)benzene (109 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 116 mg (95%), of 30 as a white solid.

\(^1\text{H NMR}\) (500 MHz, CDCl\textsubscript{3}):

\(\delta\) 7.60 (d, 2H, \(J = 8\), ArH), 7.31 (d, 2H, \(J = 8\), ArH), 4.98 (dd, 1H, \(J = 12.8, 4.5\) CH\textsubscript{2}NO\textsubscript{2}), 4.67 (dd, 1H, \(J = 12.8, 10\) CH\textsubscript{2}NO\textsubscript{2}), 3.86 (dt, 1H, \(J = 10, 4.5\) ArCH), 2.74-2.67 (m, 1H, CHC(O)), 2.52-2.46 (m, 1H, CH\textsubscript{2}C(O)), 2.43-2.35 (m, 1H, CH\textsubscript{2}C(O)), 2.15-2.07 (m, 1H, CH\textsubscript{2}), 1.83-1.75 (m, 1H, CH\textsubscript{2}), 1.75-1.65 (m, 2H, CH\textsubscript{2}), 1.65-1.55 (m, 1H, CH\textsubscript{2}), 1.28-1.20 (m, 1H, CH\textsubscript{2}).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min\(^{-1}\), conc. 1mg/mL, \(\lambda = 247\) nm):

\(t_{\text{minor}} = 16.9; t_{\text{major}} = 26.6\) min;

\([\alpha]^{23}_D\) : -24.0 (c 1, CHCl\textsubscript{3}),

ee : 96%. 
(S)-2-((R)-1-(Naphthalen-2-yl)-2-nitroethyl)cyclohexanone (31).\textsuperscript{28a}

![Chemical Structure](image)

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 2-((E)-2-nitrovinyl)naphthalene (100 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 134 mg (90\%) of 31 as a white solid.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}):

\[
\begin{align*}
\delta & \quad 7.82-7.78 & (m, & \text{2H, ArH}), \quad 7.63 & (s, & \text{1H, ArH}), \quad 7.50-7.45 & (m, & \text{2H, ArH}), \quad 7.28 & (dd, \text{2H, } J = 8.5, & \text{2, ArH}), \quad 5.01 & (dd, \text{1H, } J = 12, & \text{4.7, CH}_2\text{NO}_2), \quad 4.74 & (dd, \text{1H, } J = 12, & \text{10, CH}_2\text{NO}_2), \quad 3.95 & (dt, \text{1H, } 10, & \text{4.7, ArCH}), \quad 2.81-2.75 & (m, \text{1H, CHC(O)}), \quad 2.52-2.48 & (m, \text{1H, CHC(O)}), \quad 2.44-2.37 & (m, \text{1H, CH}_2\text{C(O)}), \quad 2.10-2.04 & (m, \text{1H, CH}_2\text{C(O)}), \quad 1.78-1.65 & (m, \text{3H, CH}_2), \quad 1.61-1.53 & (m, \text{1H, CH}_2), \quad 1.31-1.23 & (m, \text{1H, CH}_2). \end{align*}
\]

HPLC (Chiralpak AS-H):

(hexamne/i-PrOH, 50/50, flow rate 0.7 mL min\textsuperscript{-1}, conc. 1 mg/mL, \(\lambda = 247\) nm):

\[ t_{\text{major}} = 18.2 \text{ min}; \]

\([\alpha]^{23}_{D} : -20.0 \text{ (c 1, CHCl}_3),\]

\(\text{ee} : >99\%).\]
(S)-2-((R)-2-Nitro-1-(3-nitrophenyl)ethyl)cyclohexanone (32): 24

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-nitro-3-((E)-2-nitrovinyl)benzene (97.6 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 100 mg (90%) of 32 as a yellow solid.

$^1$H NMR (500 MHz, CDCl$_3$):

$\delta$ 8.16 (m, 1H, ArH), 8.09 (m, 1H, ArH), 7.68-7.50 (m, 2H, ArH), 5.01 (dd, 1H, $J$ = 13.2, 4.5, CH$_2$NO$_2$), 4.71 (dd, $J$ = 13.2, 10, CH$_2$NO$_2$), 3.95 (dt, 1H, $J$ = 10, 4.5, ArCH), 2.77-2.72 (m, 1H, CHC(O)), 2.53-2.49 (m, 1H, CH$_2$C(O)), 2.45-2.37 (m, 1H, CH$_2$C(O)), 2.16-2.10 (m, 1H, CH$_2$), 1.86-1.82 (m, 1H, CH$_2$), 1.76-1.56 (m, 3H, CH$_2$), 1.33-1.25 (m,1H, CH$_2$).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 90/10, flow rate 1 mL min$^{-1}$, conc. 1 mg/mL, $\lambda$ = 247 nm);

$t_{\text{minor}}$ = 20 min; $t_{\text{major}}$ = 23.9 min.

$[\alpha]^23_D$ : -24.0 (c 1, CHCl$_3$).

ee : 90%.
(S)-2-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (33):^28a

![Chemical structure of (S)-2-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)cyclohexanone (33)]

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-methoxy-2-((E)-2-nitrovinyl) benzene (90 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and MeSO$_3$H (6 µL, 0.1 mmol) at room temperature for 11 h gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 132 mg (95%) of 33 as a colorless oil. A similar reaction for 45 h at 0 °C gave 129 mg (93%) of 33.

$^1$H NMR (500 MHz, CDCl$_3$)

$\delta$ 7.26 (dd, 1H, $J = 8, 1.6$, ArH), 7.1 (dd, 1H, $J = 7.6, 1.0$, ArH), 6.92-6.88 (m, 2H, ArH), 4.88-4.80 (m, 2H, CH$_2$NO$_2$), 3.98 (dt, 1H, $J = 10, 5$, ArCH), 3.85 (s, 3H, OCH$_3$), 3.02-2.96 (m, 1H, CHC(O)), 2.52-2.47 (m, 1H, CH$_2$C(O)), 2.43-2.36 (m, 1H, CH$_2$C(O)), 2.10-2.06 (m, 1H, CH$_2$), 1.81-1.77 (m, 1H, CH$_2$), 1.71-1.66 (m, 2H, CH$_2$), 1.66-1.55 (m, 1H, CH$_2$), 1.27-1.21 (m, 1H, CH$_2$).

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 90/10, flow rate 0.5 mL min$^{-1}$, conc. 1mg/mL, $\lambda = 254$ nm);

$t_{minor} = 24.1; t_{major} = 28.9$ min

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 90/10, flow rate 1.0 mL min$^{-1}$, conc. 1mg/mL, $\lambda = 254$ nm);

$t_{minor} = 8.1; t_{major} = 8.9$ min.
[α]$_D^{23}$ : -42.0 (c 1, CHCl$_3$),

ee : 94% (room temperature reaction) and 99% (0 °C reaction).

(S)-2-((R)-1-(2-Trifluoromethyl) phenyl)-2-nitroethyl)cyclohexanone (34):$^{21}$

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\text{NO}_2
\end{array}
\]

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-(trifluoromethyl)-2-((E)-
2-nitrovinyl) benzene (109 mg, 0.5 mmol) in the presence of catalyst 11 (17.0 mg, 0.1
mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure
gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane:
20/80), 143 mg (90%) of 34 as colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$):

\[\delta = 7.71 \text{ (d, 1H, } J = 7.5, \text{ ArH)}, \ 7.57 \text{ (t, 1H, } J = 7.5, \text{ ArH)}, \ 7.41 \text{ (t, 1H, } J = 7.5, \text{ ArH)}, \ 7.39 \text{ (d, 1H, } J = 7.5, \text{ ArH)}, \ 5.05 \text{ (dd, 1H, } J = 12, 7, \text{ CH}_2\text{NO}_2), \ 4.77 \text{ (dd, 1H, } J = 12, 3.7, \text{ CH}_2\text{NO}_2), \ 4.12-4.07 \text{ (m, 1H, ArCH)}, \ 3.05-3.0 \text{ (m, 1H, CHC(O))}, \ 2.53-2.41 \text{ (m, 2H, CH}_2\text{C(O))}, \ 2.17-2.11 \text{ (m, 1H, CH}_2\text{)}, \ 1.83-1.78 \text{ (m, 1H, CH}_2\text{)}, \ 1.76-1.64 \text{ (m, 2H, CH}_2\text{)}, 1.64-1.55 \text{ (m, 1H, CH}_2\text{)}, 1.38-1.28 \text{ (m, 1H, CH}_2\text{)).

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 90/10, flow rate 0.9 mL min$^{-1}$, conc. 1 mg/mL, λ = 254 nm):

$\tau_{\text{minor}} = 5.9$; $\tau_{\text{major}} = 6.6$ min.

[α]$_D^{23}$ : -38.0 (c 1, CHCl$_3$),

ee : 91%.
(S)-2-((R)-1-Naphthalen-1-yl-2-nitroethyl)cyclohexanone (35): 28a

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)naphthalene (100 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 20/80), 128 mg (86%) of 35 as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$):

$\delta$ 8.16 (brs, 1H, ArH), 7.85 (d, 1H, $J = 7.7$, ArH), 7.77 (d, 1H, $J = 8$, ArH), 7.56-7.43 (m, 3H, ArH), 7.37 (d, 1H, $J = 7$, ArH), 5.06 (dd, 1H, $J = 12.5$, 4.5, CH$_2$NO$_2$), 4.73 (brt, 1H, $J = 12.5$, CH$_2$NO$_2$), 4.75-4.71 (brm, 1H, ArCH), 2.86 (brs, 1H, CH$_2$), 2.52-2.48 (m, 1H, CH$_2$(O)), 2.44-2.37 (m, 1H, CH$_2$), 2.09-2.04 (m, 1H, CH$_2$), 1.76-1.60 (m, 3H, CH$_2$), 1.58-1.47 (m, 1H, CH$_2$), 1.29-1.21 (m, 1H, CH$_2$).

HPLC (Chiralpak AS-H):

(hexane/i-PrOH, 50/50, flow rate 0.7 mL min$^{-1}$, conc. 1mg/mL, $\lambda = 254$ nm);

$t_{\text{minor}} = 10.7$ min; $t_{\text{major}} = 15.8$ min.

$[\alpha]_D^{23} : -80.0$ (c 1, CHCl$_3$).

ee : 87%.
(S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (36):\(^{24}\)

![Chemical structure of (S)-2-((S)-1-(Furan-2-yl)-2-nitroethyl)cyclohexanone (36)](image)

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 2-((E)-2-nitrovinyl)furan (70 mg, 0.5 mmol), in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and MeSO\(_3\)H (6 μL, 0.1 mmol) at 0 °C. for 45 h gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 98 mg (82%) of 36 as a yellow solid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)):

δ 7.37 (d, 1H, J = 1, ArH), 6.29 (dd, 1H, J = 3, 2, ArH), 6.18 (dd, 1H, J = 8.3, 3, ArH), 4.80 (dd, 1H, J = 12, 5, CH\(_2\)NO\(_2\)), 4.68 (dd, 1H, J = 12, 9.0, CH\(_2\)NO\(_2\)), 4.00 (dt, 1H, J = 9.5, ArCH), 2.78-2.73 (m, 1H, CHC(O)), 2.48-2.50 (m, 1H, CH\(_2\)C(O)), 2.40-2.33 (m, 1H, CH\(_2\)C(O)), 2.18-2.09 (m, 1H, CH\(_2\)), 1.92-1.82 (m, 1H, CH\(_2\)), 1.82-1.75 (m, 1H, CH\(_2\)), 1.71-1.60 (m, 2H, CH\(_2\)), 1.35-1.26 (m, 1H, CH\(_2\)).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min\(^{-1}\), conc. 1mL/min., \(\lambda = 254\) nm):

\(t_{\text{major}} = 13.2\) min; \(t_{\text{minor}} = 15.8\) min.

ee : 88%. 


(S)-2-((S)-2-Nitro-1-(thiophen-2-yl)ethyl)cyclohexanone (37).  

Reaction of cyclohexanone (0.26 mL, 2.5 mmol) and 2-((E)-2-nitroviny]thiophene (77.6 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and MeSO\textsubscript{3}H (6 \mu L, 0.1 mmol) at 0 °C. for 45 h gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 93 mg (74%) of 37 as a white solid. A similar reaction employing 11 provided 37 in 88% yield.

\textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}): 

$\delta$ 7.23 (d, 1H, $J = 5.1$, ArH), 6.94 (dd, 1H, $J = 5.1$, 3.0, ArH), 6.88 (d, 1H, $J = 3.2$, ArH), 4.90 (dd, 1H, $J = 13$, 4, CH\textsubscript{2}NO\textsubscript{2}), 4.67 (dd, $J = 13$, 9, CH\textsubscript{2}NO\textsubscript{2}), 4.14 (dt, 1H, $J = 9$, 4, ArCH), 2.72-2.67 (m, 1H, CHC(O)), 2.50-2.46 (m, 1H, CH\textsubscript{2}C(O)), 2.42-2.36 (m, 1H, CH\textsubscript{2}C(O)), 2.13-2.10 (m, 1H, CH\textsubscript{2}), 1.96-1.90 (m, 1H, CH\textsubscript{2}), 1.88-1.85 (m, 1H, CH\textsubscript{2}), 1.73-1.56 (m, 2H, CH\textsubscript{2}), 1.38-1.24 (m, 1H, CH\textsubscript{2}).

\textbf{HPLC} (Chiralpak AD-H):

(hexane/i-PrOH, 95:5, flow rate 1 mL min\textsuperscript{-1}, $\lambda = 254$ nm):

$t_{\text{minor}} = 15.5$ min; $t_{\text{major}} = 17.9$ min.

$[\alpha]_{D}^{23} = -29.0$ (c 1, CHCl\textsubscript{3})

\textbf{ee} : 85%.  

\textbf{ee} : 85%.
(S)-2-((R)-2-Nitro-1-phenylethyl)cyclopentanone (38):²¹

![Chemical structure](image)

Reaction of cyclopentanone (0.22 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 12 (20.4 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 42 mg (37%) of 38 as a white solid.

**¹H NMR** (500 MHz, CDCl₃):

δ 7.34-7.26 (m, 3H, ArH), 7.17 (d, 2H, J = 7.7, ortho ArH), 5.33 (dd, 1H, J = 12.4, 7.5, CH₂NO₂), 4.72 (dd, 1H, J= 12.4, 10, CH₂NO₂), 3.71 (dt, 1H, J = 10, 4.5, PhCH), 2.43-2.34 (m, 2H, CHC(O)), 2.18-2.10 (m, 1H, CH₂C(O)), 1.96-1.87 (m, 2H, CH₂C(O)), 1.78-1.69(m, 1H, CH₂), 1.55-1.44 (m, 1H, CH₂).

**HPLC** (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min⁻¹, conc. 1mg/mL, λ= 247 nm):

$t_{\text{minor}} = 13.2$ min, $t_{\text{major}} = 18.1$ min.

$\text{ee} : 62\%$. 
(S)-2-((R)-2-Nitro-1-phenylethyl)cycloheptanone (39):\(^{21}\)

![](image)

Reaction of cycloheptanone (0.3 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 12 (20.4 mg, 0.1 mmol) and pTsOH monohydrate (19.0 mg, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 109 mg (84\%) of 39 as colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)):

\(\delta\): 7.36-7.32 (m, 2H, ArH), 7.30-7.27 (m, 1H, ArH), 7.19-7.18 (m, 2H, ArH), 4.70-4.63 (m, 2H, \(CH_2\)NO\(_2\)), 3.71-3.67 (m, 1H, PhCH), 3.04-2.99 (m, 1H, CHC(O)), 2.59-2.50 (m, 2H, \(CH_2\)C(O)), 1.95-1.88 (m, 2H, \(CH_2\)), 1.80-1.59 (m, 4H, \(CH_2\), \(CH_2\)), 1.28-1.14 (m, 2H, \(CH_2\)).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 98/2, flow rate 1 mL min\(^{-1}\), conc. 1mg/mL, \(\lambda=247\) nm):

\(t_{\text{minor}} = 11.4\) min, \(t_{\text{major}} = 15.6\) min.

ee : 62\%. 
(R)-5-Nitro-4-phenylpentan-2-one (40):

$$\text{O} \quad \text{Ph} \quad \text{NO}_2$$

Reaction of acetone (0.18 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 12 (20.4 mg, 0.1 mmol) and toluene according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 97 mg (94%) of 40 as a white solid.

$^1$H NMR (500 MHz, CDCl$_3$):

$\delta$ 7.34-7.20 (m, 5H, ArH), 4.68 (dd, 1H $J = 6.8, 12.4$, CH$_2$NO$_2$), 4.61 (dd, 1H $J = 12.4, 7.5$, CH$_2$NO$_2$), 4.00 (q, 1H, $J = 6.8$, PhCH), 2.91 (d, 2H, $J = 7.0$, CH$_2$C(O)), 2.12 (s, 3H, CH$_3$).

HPLC (Chiralpak AD-H):

(hexane/i-PrOH, 85/15, flow rate 1 mL min$^{-1}$, conc. 1mg/mL, $\lambda = 247$ nm):

$t_{\text{minor}} = 17.2$ min, $t_{\text{major}} = 23.1$ min.

ee : 34%.

(R)-2,2-Dimethyl-4-nitro-3-phenylbutanal (42):

$$\text{H} \quad \text{O} \quad \text{Ph} \quad \text{NO}_2$$

Reaction of isobutyraldehyde (0.05 mL, 0.55 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 5 (17.1 mg, 0.1 mmol) and iPrOH according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 6 mg (1%) of 42.
**1H NMR** (500 MHz, CDCl₃):

δ = 9.52 (s, 1H, CHO), 7.26-7.40 (m, 3H, ArH), 7.10-7.25 (m, 2H, ArH), 4.85 (dd, 1H, J = 8.4, 9.9, CH₂NO₂), 4.69 (dd, 1H, J = 3.1, 9.9, CH₂NO₂), 3.78 (dd, 1H, J = 3.1, 8.4 CHPh), 1.12 (s, 3H, CH₃), 0.99 (s, 3H, CH₃).

**HPLC** (Chiralpak AS-H):

(hexane/i-PrOH, 60/40, flow rate 0.8 mL min⁻¹, conc. 1mg/mL, λ = 254 nm):

\( t_{\text{minor}} = 10.8 \text{ min}, \ t_{\text{major}} = 11.3 \text{ min}. \)

ee = 25%.

(2R, 3S)-2-(Methylethyl)-4-nitro-3-phenylbutanal (43):²¹

![Chemical Structure]

Reaction of isovaleraldehyde (0.28 mL, 2.5 mmol) and 1-((E)-2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in the presence of catalyst 11 (17.1 mg, 0.1 mmol) and 1M methanolic HCl (0.8 mL, 0.1 mmol) according to the general procedure gave, after purification by flash chromatography on silica gel (ether/hexane: 20/80), 8 mg (1%) of 43.

**1H-NMR** (500 MHz, CDCl₃):

δ 9.93 (d, 1H, J = 2.6, CHO), 7.36-7.29 (m, 3H, ArH), 7.20-7.18 (m, 2H, ArH), 4.67 (dd, 1H, J = 12.5, 4.4, CH₂NO₂), 4.58 (dd, 1H, J = 12.5, 10.2, CH₂NO₂), 3.90 (dd, 1H, J = 10.2, 10.2, 4.4 Hz, CHPh), 2.79-2.75 (m, 1H, CHCHO), 1.76-1.69 (m, 1H, CH(CH₃)₂), 1.10 (d, 1H, J = 7.2, 3H, CH₃), 0.89 (d, 1H, J = 7.2, 3H, CH₃).
**HPLC** (Chiralpak AD-H):

(hexane/i-PrOH, 99.6/0.4, flow rate 0.5 mL min\(^{-1}\), conc. 1mg/mL, \(\lambda = 247\) nm):

\(t_{major} = 48.3\) min, \(t_{minor} = 67.6\) min.

ee : 29%.

(3R,3aS)-3-Phenyl-3,3a,4,5,6,7-hexahydro-2H-indole-1-oxide (44):

A suspension of Pd/C (4 mg) and 24 (25 mg) in MeOH (2 mL) was stirred at room temperature under 3 atm hydrogen atmosphere. After being stirred for 12 h, the mixture was filtrated through a pad of celite and the filtration was concentrated in vacuo, the residue was purified by column chromatography on silica gel to afford desired product 44 (23 mg, 95% yield).

\(^1\)H NMR (500MHz, CDCl\(_3\)):

\(\delta\) 7.38-7.34 (m, 2H, ArH), 7.30-7.20 (m, 3H, ArH), 4.30-4.26 (m, 1H, CHAr), 4.20-4.15 (m, 1H, CHCN), 3.25-3.19 (m, 2H, CH\(_2\)NO), 2.73 (m, 1H, CH\(_2\)CNO), 2.14-1.77 (m, 4H, CH\(_2\)CNO, CH\(_2\)CH\(_2\)), 1.45-1.21 (m, 3H, CH\(_2\)CH\(_2\), CH\(_2\)CH\(_2\)).

IR (KBr):

2934, 2857, 1639, 1448, 1248, 1224, 1180, 765, 702 cm\(^{-1}\)
**MS (APCI, positive):**

\[ m/z \ 198.1 \ (50), \ 216.1 \ (M+1, \ 100), \ 431.3 \ (90), \ 432.2 \ (30). \]

**HPLC (Chiralpak AD-H):**

(hexane/i-PrOH, 90/10, flow rate 0.6 mL min\(^{-1}\), conc. 1mg/mL, \( \lambda = 247 \) nm):

\[ t_{\text{major}} = 15.5 \ \text{min} \]

**ee** : >99%.

\[ \alpha \] : -36.3 (c 1.14, CHCl\(_3\)).
X. References

1 Part of the work described in this chapter has now been published: Pansare, S.V.; Pandya, K. J. Am. Chem. Soc. 2006, 128, 9624.


16 This term has been coined by Professor J. P. Guthrie, *University of Western Ontario*, Canada.


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Chapter 3

Enantioselective Organocatalytic Michael Additions of Malonates to Enones by Iminium Ion Catalysis

I. Iminium catalysis (Electrophilic catalysis - activation of acceptor)

In 1991, Yamaguchi reported that the conjugate addition of nitroalkanes or malonates to \(\alpha,\beta\)-unsaturated ketones and aldehydes could be catalyzed by secondary amines like (S)-proline, specifically with the rubidium salt of proline (Scheme 1).\(^1\)

\[
\text{Scheme 1}
\]

It is proposed that these metal prolinate-catalyzed reactions are facilitated by the formation of an intermediate iminium ion, by condensation of the amine catalyst with the enone or enal starting material. The formation of the iminium ion decreases the electron density at the receiving center (acceptor). This activation effect is similar to that associated with reactions involving metal-derived Lewis acids. The activation of unsaturated aldehydes and ketones by chiral amines through reversible iminium ion formation was also reported as a highly generalized strategy by MacMillan (Scheme 2).\(^2\)
Iminium catalysis forms the basis for several conjugate addition reactions of a variety of Michael donors such as nitroalkanes, malonates (Scheme 3), thiols and thioacetic acid to enones as well as Mukaiyama-Michael reactions of silyloxyfurans with enals (Scheme 2).

It should be noted that the organocatalytic conjugate additions that proceed by iminium ion formation are not as extensively studied as the enamine catalysis of these reactions.

II Asymmetric organocatalytic Michael addition of malonates to enones

The catalytic asymmetric conjugate additions of stabilized carbanions to α,β-unsaturated enones is one of the fundamental C-C bond forming reactions in organic chemistry due to the easy availability of both substrates, usefulness of enantiomerically-enriched products, and high atom economy. Malonates are easily accessible donors as the two electron-withdrawing esters enable enolate formation under mild conditions. The
most general system reported for such reactions is the BINOL-heterobimetallic catalytic system developed by Shibasaki. In the organocatalytic version, Jørgensen’s imidazolidine organocatalyst (Scheme 3) has been observed to give good-to-excellent enantioselectivities for conjugate addition of malonates to acyclic enones (59-99% ee). However, the reaction times were typically between 5 to 12 days with the malonate as the reaction solvent, which creates problems for its eventual removal due to its high boiling point. Recently, Ley has used a tetrazole-containing analogue of proline for this transformation, but the enantioselection in this study varied from 0-92%. Therefore, there is a need for new and more efficient organocatalysts for this reaction.

II.A Results and Discussion:

Herein we disclose the preliminary, unoptimized results for the conjugate addition of dibenzyl malonates to acyclic and cyclic enones using the organocatalysts 13, 14, 15 and 16 (Figure 1) that are described in Chapter 2 of this thesis. The synthesis of and mechanistic rationale for these catalysts is already discussed in Chapter 2.

Figure 1: Organocatalysts for iminium ion catalysis

The results obtained by employing catalyst 13 and 15 in selected Michael reactions using acyclic enones and dibenzyl malonates are summarized in Table 1.
Table 1: Enantioselective conjugate addition of dibenzyl malonate to acyclic enones catalyzed by 13 and 15.
(Reactions are done with 0.55 mmol malonate and 0.5 mmol enone in anhydrous toluene (1mL), 20 mol% catalyst, room temp.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (d)</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BnO₂C</td>
<td>10</td>
<td>13</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>15</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>12</td>
<td>13</td>
<td>99</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>12</td>
<td>15</td>
<td>98</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>12</td>
<td>13</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>12</td>
<td>15</td>
<td>58</td>
<td>10</td>
</tr>
</tbody>
</table>

*Isolated yields.*  
*Chiral HPLC analysis*

The results show that only the amido amine 13 worked well for the adduct 18 and 19 (acyclic enones having a heterocyclic moiety) while the triamine 15 gave the best enantioselectivity for the adduct 17 (no heterocyclic moiety). The yields obtained with both catalysts range from poor-to-excellent with almost similar reaction rate (10-12 days). The absolute configuration of each of the Michael adducts 17, 18 and 19 was determined to be \( R \) by HPLC analysis, and by comparison of their optical rotations to those reported in the literature. To further explore the scope of this reaction and catalysts, studies with cyclic enones and malonates were undertaken. Cyclohexenone and dibenzyl
malonate were chosen as the model acceptor and donor respectively. The initial catalyst screening study is summarized in Table 2.

**Table 2: Catalyst and solvent screening for asymmetric Michael addition of dibenzyl malonate to cyclohexenone.**

(Reactions are done with 0.55 mmol malonate and 0.5 mmol enone in solvent (1mL), 20 mol% catalyst, room temp. except as noted)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Solvent</th>
<th>Reaction Time (d)</th>
<th>Yield* (%)</th>
<th>ee* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>-</td>
<td>toluene</td>
<td>9</td>
<td>99</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>-</td>
<td>toluene</td>
<td>4</td>
<td>73</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>-</td>
<td>DMF</td>
<td>3</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>-</td>
<td>ethanol</td>
<td>3.5</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>-</td>
<td>d</td>
<td>3</td>
<td>89</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>-</td>
<td>toluene</td>
<td>2</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>-</td>
<td>toluene</td>
<td>9</td>
<td>99</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>-</td>
<td>toluene</td>
<td>2</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>TEA</td>
<td>toluene</td>
<td>3</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>-</td>
<td>DMF</td>
<td>3</td>
<td>56</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>pTsOH</td>
<td>DMF</td>
<td>3</td>
<td>65</td>
<td>46</td>
</tr>
</tbody>
</table>


Initial experiments were carried out by employing amido amine 13 to yield Michael adduct 22. It was observed that a nonpolar solvent, such as toluene, offered better enantioselectivity than the polar solvents such as DMF and ethanol (Table 2, entries 2 to 4). Interestingly, the use of rigorously dried toluene raised the enantioselectivity considerably. The enantioselection was even better than the use of the
malonate itself as a solvent (Table 2, entries 1, 2 and 5). However the reaction in toluene was much slower. On the other hand, the use of catalyst 14, in dry toluene increased the reaction rate significantly but at the cost of enantioselectivity (Table 2, entries 1 and 6). Interestingly, it was observed that catalyst 16 worked better than the catalyst 15 by offering much better reaction rates and enantioselectivity albeit with moderate yield (Table 2, entries 7 and 8). This behaviour parallels that seen in the ketone / nitroalkene reactions (Chapter 2). This could be due to the ability of 16 to form a hydrogen-bonded complex with the malonate, which is not possible in the catalyst 15. The use of a base (triethylamine) in toluene significantly lowered the enantioselection (Table 2, entry 9).

Although the use of 16 in DMF provided 22 with only 5% ee, the addition of pTsOH significantly increased the enantioselection. (46% ee, Table 2, entries 10 and 11). A plausible reason would be the formation of a double hydrogen-bonded complex with malonate. Since non-coordinating solvents seem to provide better enantioselection (Table 2, entries 8 and 10), the use of catalyst 16 and pTsOH in chloroform would be an interesting study as a part of further optimization.

III. Other pyrrolidine- and camphor-based organocatalysts

As a part of the search for better organocatalysts for the enone/malonate conjugate addition reactions, we decided to examine the effect of introducing a strongly basic side-chain into the pyrrolidine ring. The pyrrolidines 23, 24 and 25 were identified as potential catalysts (Figure 2).
Besides these pyrrolidine-based organocatalysts, we also thought to explore camphor-derived organocatalysts for enone/malonate addition reactions. Several camphor derivatives have been used as chiral auxiliaries and ligands in asymmetric synthesis. However, to date, camphor-derived organocatalysts have not been reported. The camphor-based diamine 26 (Figure 3) was identified as a potential catalyst for iminium ion catalysis of the enone/malonate conjugate addition reaction.

The attempted synthesis of organocatalysts 23 – 26 is described below.

**IIIA Towards the synthesis of the pyrrolidine-based organocatalysts 23, 24 and 25:**

We reasoned that the easiest way to make catalyst 23 would be by reduction of an acyl guanidine 31 to the guanidine 23. This retrosynthetic analysis is shown in Scheme 4.
The approach seemed reasonable since the key chemical step (reduction of an acyl guanidine to an alkyl guanidine) has been shown to be feasible.\textsuperscript{10} The attempted synthesis of the proline-derived acyl guanidine is shown in scheme 5.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {27};
\node (b) at (1.5,-0.5) {28};
\node (c) at (3,0) {29};
\node (d) at (4.5,0) {30};
\node (e) at (6,0) {31};
\node (f) at (7.5,0) {Scheme 5};
\draw[->] (a) -- node[above] {1. DCC, HOBT, CH\textsubscript{2}Cl\textsubscript{2}} (b);
\draw[->] (b) -- node[above] {2. HN=N, CH\textsubscript{2}Cl\textsubscript{2}} (c);
\draw[->] (c) -- node[above] {TFA, CH\textsubscript{2}Cl\textsubscript{2} (95\%)} (d);
\draw[->] (d) -- node[above] {NaOH aq. work up} (e);
\end{tikzpicture}
\end{center}

Condensation of N-Boc-proline 27 with tetramethylguanidine (28) in the presence of stoichiometric amounts of DCC and HOBT provided the acyl guanidine 29 in 60\% yield. Unexpectedly, removal of the Boc protecting group in 29 to give 31 proved to be troublesome. Treatment of 29 with TFA in dichloromethane gave the triflate salt 30. Neutralization of 30 with aq. NaOH gave material that had lost a dimethylamino group (\textsuperscript{1}H NMR). We were unable to completely characterize the product obtained after basification, but it was clearly not the desired product 31. Since the stability of the free acyl guanidine 31 was in question, an alternative approach avoiding the acyl guanidine intermediate was investigated (Scheme 6).
Following the literature procedure, N-Boc proline 27 was reduced to N-Boc prololinol 32, which was then converted to the tosylate 33.\(^{11}\) Unfortunately, subsequent coupling of 33 with tetramethylguanidine 28 or trimethylthiourea 34\(^{12}\) failed to give 35 and 36 respectively. Compounds 35 and 36 are potential precursors to the targeted organocatalysts 23 and 24 respectively. Hence, a new synthetic route to the intermediate 35 has been developed (Scheme 7). In this route, tetramethylthiourea 39 was used as a guanylation agent\(^{13}\) to build the tetramethylguanidine side chain of 35.
The key intermediate in this route is the primary amine 38. Inspired by Brown and Curran's study\textsuperscript{14} on the use of borane-THF to reduce 1°, 2° and 3° amides to the corresponding amines, we envisioned that a one-step synthesis of the amine 38 would be possible, starting with (S)-2-carbamoyl-1-N-Boc-pyrrolidine (37). Gratifyingly, treatment of 37 with BH\textsubscript{3}-THF, after a modification of the Brown–Curran conditions, led to 38 (unoptimized yield of 50%).

It should be noted that the only reported method for the preparation of this amine 38 is lengthy (four steps), inefficient (offering 33% yield), and time consuming (approx. one week).\textsuperscript{15} Also, it is important to point out that potentially explosive NaN\textsubscript{3} is used in the conventional approach. Nevertheless, during the course of this work, a similar strategy involving selective amide reduction in the presence of a carbamate has appeared in the literature.\textsuperscript{16} With amine 38 in hand, efforts were directed towards the synthesis of
intermediate 35. To our delight, reaction of tetramethylthiourea 39 with oxalylchloride followed by treatment of the intermediate chloroamidinium chloride 40 with the chiral primary amine 38 afforded the desired intermediate 35. In principle, removal of the Boc protecting group from 35 should have given us the targeted catalyst 23. However, the treatment of 35 with TFA in dichloromethane followed by basification with NaOH failed to provide 23 and the bicyclic guanidine 41 was obtained instead. Similarly when the reaction scheme was repeated using the N-Cbz protected pyrrolidine amine 44 instead of N-Boc protected pyrrolidine amine 38, the final deprotection step generated 41 instead of 23 (scheme 8).

![Scheme 8](image)

To circumvent this problem of intramolecular cyclization, a new organocatalyst 25 having an extended side chain with the tetramethylguanidine moiety was considered.
as a target. The adopted synthetic strategy (similar to Schemes 7 and 8) is shown in Scheme 9. The Cbz-Proline 42 was converted to amide 47 by reacting with DCC / HOBT followed by the addition of mono Boc-protected ethylenediamine 46 in 50% yield. Removal of the Boc group by TFA in dichloromethane offered the Cbz-protected amido amine 48 in good yield. Following the same protocol as used in Schemes 7 and 8, the installation of tetramethylguanidine moiety to amido amine 48 was carried out to yield 49 in 52% yield.

Scheme 9
As anticipated, the removal of Cbz group was successfully carried out by hydrogenation in 9:1 acetic acid-water mixture. Subsequent basification offered the desired amido amine 50 with an intact tetramethylguanidine moiety. The final step of the synthesis, reduction of the amide to the amine 25, remains to be done.

### III.B Towards the synthesis of the camphor based organocatalyst 26:

The synthetic strategy to prepare catalyst 26 was based on the retrosynthetic analysis shown in Scheme 10. We envisioned that the easiest way to construct 26 would be a reduction of amido-ketimine 53, which should be readily available from the known keto-amide 52.\(^{19}\)

![Scheme 10](image)

Keto-amide 52 was readily prepared from (+)-ketopinic acid (51), which was in turn prepared from camphorsulfonyl chloride, in two steps according to the known procedure.\(^{20}\) Treatment of 51 with thionyl chloride, followed by amidation of the resulting acyl chloride with dimethyl amine led to the keto-amide 52\(^{19}\) in excellent yield as shown in Scheme 11.
Surprisingly, several attempts to condense keto-amide 52 with benzylamine were unsuccessful and did not provide the desired amido-ketimine 53. This is most likely due to steric congestion of the ketone by dimethylamide functionality. Hence, an alternate route to construct 26 via oxime 54 was investigated. The keto-amide 52 was converted to
amido-oxime 54 using standard procedures.\textsuperscript{21} Attempts to reduce 54 with LiAlH\textsubscript{4} or with a combination of NiCl\textsubscript{2}/NaBH\textsubscript{4} in equimolar ratio (1/1) did not give the desired diamine 55 or amido-amine 56, respectively. Nevertheless, the combination of NiCl\textsubscript{2}/NaBH\textsubscript{4} in a 1/5 molar ratio led to the desired amido-amine 56. Subsequent condensation of 56 with benzaldehyde followed by a treatment with NaBH\textsubscript{4} offered an amido-amine 57 in moderate yield. The final step of the synthesis, reduction of the amide 57 to the amine 26, remains to be done.

IV. Attempted Michael additions of malonates to enones by H-bonding activation of the enone

IV A. Introduction and design of camphor-based organocatalyst 64:

Organocatalysts capable of simultaneously donating two hydrogen bonds, for example ureas and thioureas\textsuperscript{22} and guanidinium and amidinium ions\textsuperscript{23} are proving to be “privileged”\textsuperscript{24} catalyst structures for several transformations such as carbonyl addition, acyl transfer, 1,4-addition and cycloaddition.

Recently Gong and Wu have shown that, L-prolinamide derivative 63\textsuperscript{25} and its analogue can be used for highly efficient organocatalytic direct Aldol reactions of ketone 61 with aldehydes 60 (scheme 13).

Scheme 13: L-Prolinamide with a terminal-hydroxyl group-catalyzed enantioselective Aldol reactions
It is proposed that the enantioselectivity is due to the formation of hydrogen bonds by amide N-H and the terminal hydroxyl group of catalyst with the aldehyde substrates. These hydrogen bonds are formed simultaneously (double hydrogen bonding) and are important for enantioselectivity.

Inspired by this study we decided to synthesize the camphor-based hydroxy amide 64 (Figure 4) to check its efficacy as a double hydrogen bond activator of an enone in enone / malonate addition reactions.

![Fig. 4 Camphor-based organocatalyst for noncovalent catalysis](image)

**IV.B Synthesis of organocatalyst 64:**

The synthesis of 64 involves a convenient three step route that starts with (+) ketopinic acid 51. Ketopinic acid was converted to the amide 65 (via the acid chloride) in 60% yield. Subsequent reduction of keto-amide 65 with NaBH₄ led to hydroxy-amide 64, which was examined as a catalyst in Michael addition reactions.
IV.C Results and discussion:

The efficacy of hydroxyl-amide 64 was examined by performing a few enone/malonate Michael addition reactions. The results are shown in Table 3.

Table 3: Organocatalyst 64 promoted Michael addition of malonates and nitromethane to cyclohexenone
(Reactions are done with 0.55 mmol malonate or nitromethane and 0.5 mmol cyclohexenone in solvent (1mL), 20 mol% catalyst for 12 d at room temperature.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<tr>
<td>3</td>
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<td></td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after 12 d. <sup>b</sup>Dry solvent. <sup>c</sup>20 mol% additive
Catalyst 64 did not initiate any of the reactions examined and Michael adducts 66, 67 or 68 could not be detected even after 12 days reaction at room temperature. Further optimization of these reactions and structural changes in the catalyst 64 are therefore required.

V. Conclusion

The efficacy of the pyrrolidine-based triamine catalysts, described in Chapter 2, has been examined for iminium ion catalysis of the enone/malonate conjugate addition reaction. The observed enantioselectivities are modest (maximum 46% ee) and further studies are necessary for the identification of a suitable catalyst for these reactions.
VI. Experimental Section

The general information can be found in Chapter 2, section VIII.

Materials

All solvents and commercially available chemicals were used as received. Organic substrates cyclohexenone, 5-methyl-3-hexene-2-one, trans-4-(2-thienyl)-3-butene-2-one, furfurylideneacetone, dibenzyl malonate, dimethyl malonate, nitromethane, L-Proline, \( N^1,N^1,N^2,N^2 \)-tetramethylguanidine, \( N^1,N^1,N^2,N^2 \)-tetramethylthiourea, camphor, camphor sulfonyl chloride and \( N,N \)-dimethyl ethylenediamine were obtained from commercial sources and were used without any purification. While, \( N^1,N^1,N^2 \)-trimethylthiourea\(^{12} \) and tert-butyl 3-aminopropylcarbamate\(^{18} \) were prepared according to published procedures.

General experimental procedure for the Michael addition of malonates to enones:

To a solution of the catalyst (0.1 mmol) and additive (0.1 mmol) in solvent (1 mL), the enone (0.5 mmol) and malonate (0.55 mmol), were added and the resulting solution was stirred at ambient temperature for the time indicated. The solution was then concentrated at ambient temperature under reduced pressure and the residue was purified by flash column chromatography on silica gel. Alternatively, ethyl acetate (10 volumes) was added and the solution was washed with water, aqueous 1M HCl, dried (Na\(_2\)SO\(_4\)), filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel.

The absolute configurations of the products were determined either by comparison of optical rotation values with those reported in the literature or by comparison of HPLC retention times. All the Michael adducts reported here and in Table
1 and Table 2 are known in the literature. In addition, the compounds 32, 33, 37, 38, 43, 44, 51, 52 and 52 are also known.

(R)-2-(1-Isopropyl-3-oxo-butyl)-malonic acid dibenzyl ester (17): 43

\[
\begin{align*}
\text{Reaction of 5-methyl-3-hexene-2-one (0.09 mL, 0.5 mmol) and dibenzyl malonate (0.14 mL, 0.55 mmol) in dry toluene (1 mL) in the presence of catalyst 15 (18.5 mg, 0.1 mmol), for 10 d according to the general procedure gave, after purification by flash chromatography on silica gel (dichloromethane), 108 mg (41%) of 17 as a colorless oil.}
\end{align*}
\]

\[\text{H NMR (500 MHz, CDCl}_3\text{):}\]

\[\delta 7.36-7.28 \text{ (m, 10H, ArH), 5.10 (d, 4H, } J = 3.6, 2(\text{OCH}_2\text{)), 3.63 (d, 1H, } J = 6.4, \text{CO}_2\text{CHCO}_2\text{), 2.73 (quintet, 1H, } J = 6.4, \text{C-H}, 2.65 (dd, 1H, } J = 5.6, 18.0, \text{COCH}_2\text{), 2.48 (dd, 1H, } J = 5.6, 18.0, \text{COCH}_2\text{), 2.07 (s, 3H, } \text{COCH}_3\text{), 1.68 (m, 1H, (CH}_3\text{)zCH), 0.87 (d, 3H, } J = 7.2, \text{CHzCH), 0.79 (d, } J = 7.2, 3H, \text{CHzCH).}\]

\[\text{HPLC (Chiralpak AD-H):}\]

\[\text{(hexane/i-PrOH, 98/2, flow rate 1 mL min}^{-1}, \text{conc. 1mg/mL, } \lambda = 230 \text{ nm):}\]

\[t_{\text{minor}} = 25.5 \text{ min, } t_{\text{major}} = 30.8 \text{ min}\]

\[\alpha^{23}_D = -2.1 (c 1, \text{CHCl}_3)\]

\[\text{ee} : 24\%\]
(R) -2-(3-Oxo-1-thiophen-2-yl-butyl)-malonic acid dibenzyl ester (18):\textsuperscript{4a}

![Chemical structure]

Reaction of trans-4-(2-thienyl)-3-butene-2-one (0.07 mL, 0.5 mmol) and dibenzyl malonate (0.14 mL, 0.55 mmol) in dry toluene (1 mL) in the presence of catalyst 13 (19.9 mg, 0.1 mmol) for 12 d according to the general procedure gave, after purification by flash chromatography on silica gel (ether/pentane: 15/85), 218 mg (99\%) of 17 as a colorless solid.

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}):\textsuperscript{5}

\begin{verbatim}
 δ 7.14-34 (m, 10H, ArH), 7.12 (t, 1H, J = 3.5, ArH), 6.84 (d, J = 3.5, 2H, ArH), 5.13 (d, 2H, J = 4.3, OCH\textsubscript{2}), 5.00 (s, 2H, OCH\textsubscript{2}), 4.31-4.37 (m, 1H, CH(CO\textsubscript{2}Bn)\textsubscript{2}), 3.87 (d, 1H, J = 8.6, CO\textsubscript{2}CHCO\textsubscript{2}), 2.90-2.96 (m, 2H, COCH\textsubscript{2}), 2.01 (s, 3H, CH\textsubscript{3}CO).
\end{verbatim}

\textbf{HPLC} (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min\textsuperscript{-1}, conc. 1mg/mL, \(\lambda = 230\) nm):

\(t_{\text{minor}} = 37.9\) min, \(t_{\text{major}} = 48.2\) min

\([\alpha]_{D}^{23} : -2.7\) (c 1, CHCl\textsubscript{3})

\textbf{ee} : 19\%.
(R)-2-(1-Furan-2-yl-3-oxo-butyl)-malonic acid dibenzyl ester (19):\(^{4a}\)

\[
\begin{align*}
\text{O} & \\
\text{CO}_2\text{Bn} & \text{CO}_2\text{Bn} \\
\end{align*}
\]

Reaction of furfurylideneacetone (0.07 gm, 0.5 mmol) and dibenzyl malonate (0.14 mL, 0.55 mmol) in dry toluene (1 mL) in the presence of catalyst 13 (19.9 mg, 0.1 mmol), for 12 d according to the general procedure gave, after purification by flash chromatography on silica gel (ether/pentane, 1/4), 129 mg (60\%) of 19 as a colorless oil.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)):

\[
\delta 7.21-7.34 (m, 11H, ArH), 6.20 (dd, 1H, J = 2.0, 3.1, ArH), 6.03 (d, 1H, J = 3.1, ArH), 5.13 (d, 2H, J = 1.6, OCH\(_2\)), 5.05 (s, 2H, OCH\(_2\)), 4.12-4.17 (m, 1H, CH(CO\(_2\)Bn)\(_2\)), 3.92 (d, 1H, J = 7.8 Hz, CO\(_2\)CHCO\(_2\)), 2.97 (dd, 1H, J = 9.0, 17.5, COCH\(_2\)), 2.85 (dd, 1H, J = 4.7, 17.5, COCH\(_2\)), 2.03 (s, 3H, CH\(_3\)CO).
\]

\text{HPLC} (Chiralpak AD-H):

(hexane/i-PrOH, 95/5, flow rate 1 mL min\(^{-1}\), conc. 1mg/mL, \(\lambda = 230\) nm):

\[
\begin{align*}
\text{t}_{\text{minor}} & = 34.3 \text{ min}, \text{t}_{\text{major}} = 42.5 \text{ min} \\
\end{align*}
\]

\([\alpha]^{23}_D\) : -2.3 (c 1, CHCl\(_3\))

\(\text{ee}\) : 17\%.
(R)-2-(3-Oxo-cyclohexyl)-malonic acid dibenzyl ester (22):[^4a]

![Chemical Structure](image)

Reaction of cyclohexenone (0.05 mL, 0.5 mmol) and dibenzyl malonate (0.14 mL, 0.55 mmol) in DMF (1 mL) in the presence of catalyst 16 (17.1 mg, 0.1 mmol) and pTsOH (19.1 mg, 0.1 mmol) for 3 days according to the general procedure gave, after purification by flash chromatography on silica gel (ethyl acetate/hexane: 25/75), 127 mg (65%) of 22 as a colorless solid.

**1H NMR (500 MHz, CDCl₃):**

δ 7.35-7.27 (m, 10H ArH), 5.16 (s, 2H, OCH₂), 5.12 (s, 2H, OCH₂), 3.42 (d, J = 8.6 Hz, 1H, CO₂CH₂CO₂), 2.60-2.54 (m, 1H, CH(CH₂Bn)₂), 2.47-2.37 (m, 2H, CH₂), 2.28-2.18 (m, 2H, CH₂), 2.06-2.01 (m, 1H, CH₂), 1.91-1.88 (br m, 1H, CH₂), 1.69-1.61 (m, 1H, CH₂), 1.52-1.45 (m, 1H, CH₂).

**HPLC (Chiralpak AS-H):**

(hexane/i-PrOH, 95/5, flow rate 1 mL min⁻¹, conc. 1 mg/mL, λ = 230 nm):

$t_{major} = 47.1$ min, $t_{minor} = 59.2$ min

$[\alpha]^{23}_{D} : +1.9$ (c 1, CHCl₃)

ee : 46%.
(2S)-N-[Bis(dimethylamino)methylene]-1-N-Boc-pyrrolidine-2-carboxamide (29):

To a solution of Boc-L-proline 27 (2.0 g, 9.3 mmol) in dry CH₂Cl₂ (25 mL) were added 1-hydroxybenzotriazole (1.28 g, 9.45 mmol) and DCC (1.95 g, 9.45 mmol). The resulting suspension was stirred at room temperature for 30 minutes and a solution of tetramethylguanidine 28 (1.17 mL, 9.3 mmol) in CH₂Cl₂ (25 mL) was added. The resulting mixture was stirred at ambient temperature for 24 h and filtered twice to remove precipitated solids. The filtrate was extracted once with saturated aqueous NaHCO₃ (25 mL) followed by back extraction of the aqueous phase with CH₂Cl₂ (2 x 25 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was dissolved in a minimum volume of CH₂Cl₂ and the suspension was filtered. The process was repeated thrice followed by further purification by flash column chromatography (CH₂Cl₂/MeOH: 9/1) to provide 1.7 g (60%) of the N-Boc amide 29 as a clear, gummy solid.

¹H NMR (500 MHz, CDCl₃):

δ 4.34 (dd, 1H, J = 9, 22, NCH), 3.62-3.55 (m, 1H, NCH₂), 3.50-3.35 (m, 1H, NCH₂), 2.91 (s, 12H, (C(N(CH₃)₂)₂), 2.24-2.16 (m, 1H, CH₂CH₂), 2.11-1.95 (m, 2H, CH₂CH₂), 1.85-1.82 (m, 1H, CH₂CH₂), 1.44 (br d, 9H, J = 14.2, (C(CH₃)₃).

IR (KBr):

2976, 2927, 1684, 1405, 1166 cm⁻¹.

MS (APCI, positive):

m/z 168.1 (20), 313.2 (M+1, 100).
HRMS (Cl): m/z 313.2233 (313.2240 calc. for C_{15}H_{29}N_{4}O_{3} (M+H)).

$[\alpha]^{23}_D : -70.0$ (c 1, CHCl₃).

(2S)-2-(((1E) (Dimethylamino) (dimethylammonio) methylene] amino) carbonyl) pyrrolidinium triflate (30):

The N-Boc-amide 29 (0.62 g, 2.0 mmol) was dissolved in dry CH₂Cl₂ (10 mL), trifluoroacetic acid (4.3 mL, 55 mmol) was added, the solution was stirred at room temperature for 3 h and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue was dissolved in dichloromethane and was subjected to flash column chromatography (CH₂Cl₂/MeOH: 85/15) to provide 0.83 g (95%) of the N-Boc amide triflate 30 as a clear gum.

$^1H$ NMR (500MHz, CDCl₃):

δ 9.54 (b, 1H, NH), 5.92 (b, 1H, NH), 4.27(t, 1H, J = 8.5, NCH), 3.57-3.52 (m, 1H, NCH₂), 3.48-3.45 (m, 1H, NCH₂) 3.24 (s, 6H, N(CH₃)₂), 2.7 (s, 6H, N(CH₃)₂), 2.27-2.12 (m, 3H, CH₂CH₂), 1.72-1.65 (m, 1H, CH₂CH₂), 1.35-1.33 (m, 1H, CH₂CH₂).

IR (KBr):

2910, 1684, 1471, 1205, 1134 cm⁻¹.

MS (APCI, positive):

m/z 168.1 (M+1, 100), 213.1 (47).
**HRMS (CI):**

m/z 168.1132 (168.1137 calc. for C₈H₁₄N₃O (M+H)).

[α]²³D: -62.0 (c 1, CHCl₃).

N¹,N¹,N²,N²-Tetramethyl-N³-(((2S)-l-N-Boc-pyrrolidin-2-yl) methyl)guanidine (35):

To a solution of N-Boc-L-proline 27 (1.00 g, 4.6 mmol) in THF (20mL) were added 1-hydroxybenzotriazole (0.94 g, 7.0 mmol) and DCC (0.98 g, 4.7 mmol). The resulting mixture was stirred at room temperature for 30 min and aqueous ammonia (4.5 mL) was added slowly by syringe. The resulting mixture was stirred at ambient temperature for 24 h and filtered twice to remove precipitated solids. After removing the THF from the filtrate, the obtained residues were dissolved in CH₂Cl₂ (25 mL). The solution was extracted once with aqueous saturated NaHCO₃ (25 mL) followed by back-extraction of the aqueous phase with CH₂Cl₂ (2 x 25 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was dissolved in a minimum volume of CH₂Cl₂ and the suspension was filtered. The process was repeated thrice to provide 980 mg (99%) of the N-Boc amide 37 as a colorless solid that was of sufficient purity to be used further without purification. The ¹H NMR was in accordance with that reported in the literature.

To a solution of N-Boc-amide 37 (1.0 g, 4.7 mmol) in THF (10 mL) was added borane (21 mL, 21 mmol, 1.0 M THF solution) slowly at 0 °C under N₂. The resulting solution was allowed to stir for 40 h at room temperature, then cooled to 0 °C, followed by slow addition of aqueous 1 M HCl to pH 4-5. The mixture was allowed to stir for 0.5
h at rt, and then was basified to pH 8 with aqueous 1M NaOH. After the THF and water were removed under reduced pressure, the crude product was purified by acid-base extraction to afford 0.47 g (50%) of (S)-2-aminomethyl-1-N-Boc-pyrrolidine (38) as a clear, pale yellow oil. The $^1$H NMR of 38 was in accordance with that reported in the literature.

A solution of tetramethylthiourea 39 (0.18 g, 1.3 mmol) and oxalyl chloride (0.24 mL, 2.7 mmol) in anhydrous toluene (4.0 mL) was stirred at 60 °C for 8 h. Evaporation of the solvent gave the crude chloroamidinium chloride 40, which was dissolved in CH$_2$Cl$_2$ (4.0 mL) and the solution was added to a solution of N-Boc-amine 38 (0.30 g, 1.5 mmol) and Et$_3$N (0.38 mL, 2.7 mmol) in CH$_2$Cl$_2$ (10 mL). The resulting mixture was stirred at room temperature for 2 h. It was transferred to a separating funnel and extracted with water twice. The aqueous phase was basified with NaOH pellets and then extracted with CH$_2$Cl$_2$. Concentration of the dried CH$_2$Cl$_2$ extract gave 0.32 g (72%) of 35 as a colorless oil.

$^1$H NMR (500MHz, CDCl$_3$):

\[
\begin{align*}
\delta & 3.93-3.74 \text{ (br m, 1H, NCH) }, 3.42-3.35 \text{ (br m, 4H, NCH$_2$(ring), NCH$_2$CH), 2.75 (s, 6H, CN(CH$_3$)$_2$) }, 2.67 \text{ (s, 6H, CN(CH$_3$)$_2$, 2.01-1.91 \text{ (m, 3H, CH$_2$CH, CH$_2$CH$_2$, 1.76-1.74 \text{ (m, 1H, CH$_2$CH$_2$, 1.47 (s, 9H, (C(CH$_3$)$_3$.}
\end{align*}
\]

$^{13}$C NMR (125.8 MHz, CDCl$_3$):

\[
\begin{align*}
\delta & 161.0 \text{ (NCOOC), 155.0 (NCN(CH$_3$)$_2$), 77.5 (OC(CH$_3$)$_3$), 59.2 (NCH), 52.3 (NCH$_2$), 46.7 (NCH$_2$), 39.6 (CN(CH$_3$)$_2$, 38.8 (CN(CH$_3$)$_2$, 28.6 (CH$_2$CH$_2$, 22.8 (CH$_2$CH$_2$).}
\end{align*}
\]
IR (neat):

2973, 2928, 2873, 1690, 1616, 1391, 1363 cm\(^{-1}\).

MS (APCI, positive):

m/z 299.3 (M+1, 100).

HRMS (CI):

m/z 299.2452 (299.2447 calc. for C\(_{13}\)H\(_{31}\)N\(_{4}\)O\(_{2}\) (M+H)).

\([\alpha]\)\(^{\text{D}}\): -101.0 (c 1, CHCl\(_{3}\)).

(7a S)-3-Isopropyl-5, 6, 7, 7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole (41):

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

Guanidine 35 (0.26 g, 0.89 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (5 mL), trifluoroacetic acid (2.5 mL, 32 mmol) was added, the solution was stirred at room temperature for 3 h and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue was dissolved in CH\(_2\)Cl\(_2\) (5 mL) and the solution was extracted with water (3 x 2 mL). The aqueous phase was cooled (5 °C), basified with NaOH pellets and extracted with CH\(_2\)Cl\(_2\) (3 x 2 mL). The combined organic layers were dried (K\(_2\)CO\(_3\)), filtered and concentrated under reduced pressure to provide 65 mg (36%) of 41 as a clear, colorless oil that was pure by \(^1\)H NMR.

\(^1\)H NMR (500MHz, CDCl\(_3\)):

\[
\begin{array}{c}
\delta 3.99-3.95 \text{ (m, 1H, NCH)}, 3.83 \text{ (dd, 1H, NCH}_2\text{ (ring))}, 3.42 \text{ (dd, 1H, NCH}_2\text{ (ring))}, 3.21-2.88 \text{ (m, 2H, NCH}_2\text{ (ring))}, 2.88 \text{ (s, 6H, CN(CH}_3\text{)}_2\text{)}, 1.98-1.92 \text{ (m, 1H, CH}_2\text{CH}_2\text{)}, 1.85-1.79 \text{ (m, 2H, CH}_2\text{CH}_2\text{)}, 1.55-1.47 \text{ (m, 1H, CH}_2\text{CH}_2\text{)}.\n\end{array}
\]
$^{13}$C NMR (125.8 MHz, CDCl$_3$):

\[ \delta 166.6 \text{ (NC(N(CH$_3$)$_2$)), 63.6 \text{ (NCH)}, 59.1 \text{ (NCH$_2$)}, 50.6 \text{ (CN(CH$_3$)$_2$), 44.8 \text{ (NCH$_2$)}, 39.1 \text{ (CN(CH$_3$)$_2$)}, 31.8 \text{ (CH$_2$CH$_2$), 25.8 \text{ (CH$_2$CH$_2$).}} } \]

IR (KBr):

2927, 1661 cm$^{-1}$.

MS (APCI, positive):

m/z 154.1 (M+1, 100).

HRMS (Cl):

m/z 154.1339 (154.1344 calc. for C$_8$H$_{16}$N$_3$ (M+H)).

$[\alpha]_{D}^{23}$: -129.0 (c 1, CHCl$_3$).

$N^1, N^1, N^2, N^2$-Tetramethyl-$N^3$-(((2S)-1-N-Cbz-pyrrolidin-2-yl) methyl)guanidine (45):

\[
\begin{align*}
\text{(S)-2-Aminomethyl-1-N-Cbz-pyrrolidine (44)}^{13} \text{ was prepared from Cbz-proline (42) by adaptation of the literature procedure. Following a similar method and identical molar quantities of reactants as those described for the preparation of compound 35 from N-Boc-amine 38, the compound 45 was obtained from 44 as a yellow oil. Yield: 0.27 g (82 %).} \\
\text{1H NMR (500MHz, CDCl$_3$):} \\
\delta 7.4-7.3 \text{ (m, 5H, ArH), 5.17-5.09 (m, 2H, CH$_2$Ar), 3.95 (br, 1H, NCH), 3.47-3.41 (br m, 3H, NCH$_2$ (ring), NCH$_2$CH), 2.81 (s, 6H, CN(CH$_3$)$_2$), 2.65 (s, 6H, CN(CH$_3$)$_2$), 1.99-1.90 (m, 4H, CH$_2$CH$_2$, CH$_2$CH$_2$), 1.79-1.69 (m, 1H, CH$_2$CH$_2$).}
\end{align*}
\]
**IR (neat):**

2942, 2881, 1684, 1594, 1411 cm\(^{-1}\).

**MS (APCI, positive):**

m/z 333.3 (M+1, 100).

**HRMS (CI):**

m/z 333.2305 (333.2291 calc. for C\(_{18}\)H\(_{29}\)N\(_4\)O\(_2\) (M+H)).

**{(2S)}-N-(2-Aminoethyl)1-N-Cbz-pyrrolidine-2-carboxamide (48):**

![Chemical Structure]

To a solution of Cbz-proline (39) (1.24 g, 5 mmol) in 20 mL dry CH\(_2\)Cl\(_2\) were added 1-hydroxybenzotriazole (0.69 g, 5.1 mmol) and DCC (1.05 g, 5.10 mmol). The resulting suspension was stirred at room temperature for 30 min. and a solution of the monoBoc-protected ethylenediamine (46) (0.8g, 5 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added. The resulting mixture was stirred at ambient temperature for 24 h and filtered twice to remove precipitated solids. The filtrate was extracted once with aqueous saturated NaHCO\(_3\) (20 mL) followed by back-extraction of the aqueous phase with CH\(_2\)Cl\(_2\) (2 x 25 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was dissolved in a minimum volume of CH\(_2\)Cl\(_2\) and the suspension was filtered. The process was repeated thrice to provide 0.97 g (50%) of the N-Boc amide 47 as a pale yellow liquid that was pure by \(^1\)H NMR and was used further without purification. The material gradually solidified at room temperature.

The crude N-Boc-amide 47 (0.85 g, 2.17 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (10 mL), trifluoroacetic acid (6.0 mL, 78.1 mmol) was added, the solution was stirred at
room temperature for 3 h and then concentrated under reduced pressure to remove excess trifluoroacetic acid. The residue was dissolved in CH$_2$Cl$_2$ (15 mL) and the solution was extracted with water (3 x 5 mL). The aqueous phase was cooled (5 °C), basified with NaOH pellets and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried (K$_2$CO$_3$) and concentrated under reduced pressure to provide 0.58 g (91%) the Cbz-protected amino amide 48 as a pale yellow solid that was pure by $^1$H NMR.

$^1$H NMR (500MHz, CDCl$_3$):

$\delta$7.38-7.31 (m, 5H, ArH), 6.93 (br s, 1H, NH$_2$), 6.39 (br s, 1H, NH$_2$), 5.29-5.08 (br m, 2H, ArCH$_2$), 4.33-4.31 (m, 1H, NCH), 3.58 (br s, 1H, NCH$_2$ (ring)), 3.50 (br s, 1H, NCH$_2$ (ring)), 3.32-3.22 (br s, 2H, NCH$_2$CH$_2$N), 2.82 (br s, 1H, NCH$_2$CH$_2$N), 2.68 (br s, 1H, NCH$_2$CH$_2$N), 2.25-1.90 (br m, 4H, CH$_2$CH$_2$).

IR (neat):

3294, 2953, 2880, 1663, 1542, 1419, 1356 cm$^{-1}$.

MS (APCI, positive):

m/z 274.1 (20), 292.1 (M+1, 100).

HRMS (CI):

m/z 292.1661 (292.1661 calc. for C$_{13}$H$_{22}$N$_3$O$_3$ (M+H)).

(2S)-N-(2-[[Bis(dimethylamino)methylene]amino]ethyl)pyrrolidine-2-carboxamide (50):

A solution of tetramethylthiourea 39 (0.21g, 1.61 mmol) and oxalyl chloride (0.28 mL, 3.21 mmol) in anhydrous toluene (5 mL) was stirred at 60 °C for 8 h followed by evaporation of the solvent to give the crude chloroamidinium chloride 40. This was
dissolved in CH$_2$Cl$_2$ (5 mL) and the solution was added to a solution of 48 (0.50 g, 1.77 mmol) and Et$_3$N (0.47 mL, 3.2 mmol), in CH$_2$Cl$_2$ (15 mL) and the resulting mixture was stirred at room temperature for 2 h. It was then transferred to a separating funnel and extracted twice with water. The aqueous phase was basified with NaOH pellets and then extracted with CH$_2$Cl$_2$, dried (Na$_2$SO$_4$), filtered and concentrated to give 0.36 g (52%) of 49 as a colorless oil.

A mixture of the N-Cbz-amide 49 (0.41 gm, 1.1 mmol) in acetic acid–water (9:1, 11 mL) and Pd/C (80 mg) was stirred under hydrogen (atmospheric pressure) at room temperature for 4 h. The mixture was then filtered through celite and the filtrate was concentrated. The residue was azeotroped with toluene to remove acetic acid. Acid-base extraction of the crude product followed by kugelrohr distillation provided 0.18 g (67%) 50 as a colorless liquid.

**Bp:** 240 °C (air bath)/0.5 torr.

**$^1$H NMR** (500MHz, CDCl$_3$):

$\delta$ 4.10-4.04 (dd, 1H, $J = 7.4, 8.0$, NCH), 3.71-3.61 (m, 3H, NCH$_2$ (ring), NCH$_2$CH$_2$N), 3.39-3.36 (m, 3H, NCH$_2$CH$_2$N, NCH$_2$CH$_2$N), 3.27-3.22 (m, 1H, NCH$_2$CH$_2$N), 2.75 (s, 6H, CN(CH$_3$)$_2$), 2.67 (s, 6H, CN(CH$_3$)$_2$), 2.25-2.20 (m, 1H, CH$_2$CH$_2$), 2.09-2.05 (m, 2H, CH$_2$CH$_2$, CH$_2$CH$_2$), 1.75-1.72 (m, 1H, CH$_2$CH$_2$).

**$^{13}$C NMR** (125.8 MHz, CDCl$_3$):

$\delta$ 174.1 (NCOCH), 161.2 (NC(N(CH$_3$)$_2$)$_2$), 63.3 (NCH), 53.4 (NCH$_2$), 45.5 (NCH$_2$), 41.1 (NCH$_2$), 39.6 (N(CH$_3$)$_2$), 38.7 (N(CH$_3$)$_2$), 27.4 (CH$_2$CH$_2$), 26.9 (CH$_2$CH$_2$).
IR (neat):

3360, 2957, 1616, 1582, 1539, 1404 cm\(^{-1}\).

MS (APCI, positive):

m/z 256.2 (M+1, 60).

\([\alpha]\)\(^{23}\)_D: -18.0 (c 1, CHCl\(_3\)).

(1S)-2-(Hydroxyimino)-N,N,7,7-tetramethylbicyclo[2.2.1]heptane-1-carboxamide (54):

(1S)-Dimethylketopinamide (52)\(^{19}\) (0.418 g, 2.0 mmol), prepared from (+)-ketopinic acid 51 (398 mg, 2.25 mmol) according to the reported method, was dissolved in 0.4 mL pyridine and 3 mL absolute anhydrous ethanol and to the solution were added hydroxylamine hydrochloride acid salt (0.27 g, 4.0 mmol) and sodium acetate (0.16 g, 2.0 mmol). The reaction mixture was heated to reflux for 3 h. After the solvents were removed in vacuo, 2 mL of water and 5 mL of ethyl acetate were added to the residue and the mixture was shaken vigorously. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over MgSO\(_4\) and filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/ethyl acetate 55/45) to afford 336 mg (75%) of 54 as a colorless solid.

Mp: 158 °C.
\( ^1\text{H NMR} \) (500MHz, CDCl\(_3\)):

\[ \delta 7.2 \text{ (br s, 1H, NOH), 3.06 (s, 3H, N(CH\(_3\))}, 2.96 \text{ (s, 3H, N(CH\(_3\))}, 2.75-2.70 \text{ (m, 1H, CH\(_2\)CNOH)}, 2.18-1.93 \text{ (m, 4H, CH\(_2\)CNOH, CHCH\(_2\), CH\(_2\)C)}, 1.79 \text{ (t, 1H, \( J = 4.5, CH\(_2\)CH)}, 1.36-1.31 \text{ (m, 1H, CH\(_2\)CH)}, 1.18 \text{ (s, 3H, C(CH\(_3\))}, 1.17 \text{ (s, 3H, C(CH\(_3\))}} \]

\( ^{13}\text{C NMR} \) (125.8 MHz, CDCl\(_3\)):

\[ \delta 170.4 \text{ (CON(CH\(_3\))}, 165.2 \text{ (CNOH), 60.6 ((N(CH\(_3\))}, 52.3 \text{ (C(CON(CH\(_3\))}, 43.9 \text{ (CCNOH), 33.4 (C(CH\(_3\))}, 29.0 \text{ (CCH), 27.4 (CCH\(_2\)}, 21.4 \text{ (CCH\(_2\)}, 20.3 \text{ (C(CH\(_3\))}} \]

Visible peaks for the minor isomer: \[ \delta 174.5, 165.9, 60.9, 51.6, 45.0, 38.8, 36.8, 30.6, 20.7, 19.7. \]

\( \text{IR (neat):} \)

\[ 3311, 2925, 1614, 1378, 924 \text{ cm}^{-1}. \]

\( \text{MS (APCI, positive):} \)

\[ m/z 225.1 \text{ (M+1, 100)}. \]

(1S)-2-(Benzylamino)-N,N,7,7-tetramethylbicyclo[2.2.1]heptane-1-carboxamide (57):

To a solution of oxime 54 (1.34 g, 6 mmol) and NiCl\(_2\) (1.56 g, 12 mmol) in methanol at –20 °C, was added NaBH\(_4\) (2.27 g, 60 mmol) in portions over the period of 1 h. The reaction mixture was further stirred for 1 h at –20 °C and 2 h at ambient temperature. After the removal of methanol, aqueous 3M NaOH (0.70 mL) was added to
the residue followed by ether (4.5 mL). The resulting suspension was filtered and the organic phase was separated, washed with brine (2 x 1mL) and dried over Na₂SO₄ and filtered. After removal of solvent under reduced pressure, the crude product was purified by acid-base extraction to afford 0.50 g (40%) of amido-amine 56 as a pale yellow liquid that was pure by ¹H NMR. The material gradually solidified at room temperature. This solid was used further without purification.

To a solution of 56 (0.21 g, 1.0 mmol) in methanol (2.0 mL), was added benzaldehyde (0.1 mL, 1 mmol). The reaction mixture was stirred for 3 h at ambient temperature. After cooling the mixture to 0 °C, NaBH₄ (0.11 g, 3.0 mmol) was slowly added and the mixture was further stirred for 15 h at ambient temperature. After removal of the methanol, the residues were dissolved in CH₂Cl₂ (4 mL). Acid-base extraction of the crude product followed by kugelrohr distillation under reduced pressure provided 0.18 g (58%) 57 as a colorless liquid, which gradually solidified at room temperature.

**Bp:** 200 °C (air bath)/0.5 torr.

¹H NMR (500MHz, CDCl₃):

δ 7.30-7.22 (m, 5H, ArH), 3.83 (d, 1H, J = 13.5 CH₂Ar), 3.59 (d, 1H, J = 13.5, CH₂Ar), 3.10-3.07 (m, 1H, CHNH), 2.91 (s, 6H, (N(CH₃)₂)), 1.96-1.87 (m, 3H, CH₂CH, CHCH₂), 1.82-1.77 (m, 1H, CH₂C), 1.68-1.53 (m, 4H, CH₂C, CH₂CH₂, NH), 1.31 (s, 3H, C(CH₃)₂), 1.16 (s, 3H, C(CH₃)₂).

¹³C NMR (125.8 MHz, CDCl₃):

δ 173.8 (CON(CH₃)₂), 140.8 (ArC), 128.5 (ArC), 128.4 (ArC), 127.0 (ArC), 64.2 (NHCH₂Ar), 60.0 ((N(CH₃)₂), 51.5 (CHNH), 50.8 (C(CON(CH₃)₂), 45.4
(CH₂CH), 39.3 (C(CH₃)₂), 37.1 (CHCH₂), 32.2 (CCH₂), 27.3 (CCH₂), 22.4 (C(CH₃)₂).

**IR (neat):**

2933, 1627, 1495, 1452, 1375, 740, 697 cm⁻¹.

**MS (APCI, positive):**

m/z 301.2 (M+1, 100).

**HRMS (CI):**

m/z 301.2266 (301.2280 calc. for C₁₉H₂₉N₂O (M+H)).

[α]ᵡ²³: -21.3 (c 1, CHCl₃).

(1S)-N-[2-(Dimethylamino)ethyl]-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxamide (65):

![Chemical Structure](attachment:image.png)

To a solution of the acid chloride prepared from (+) ketopinic acid 51 (2.00 g, 11 mmol) and SOCl₂ (4.1 mL, 55 mmol) according to the reported method, in dry CH₂Cl₂ (8 mL) was added Et₃N (1.5 mL, 11 mmol) and a solution of N,N-dimethylethlyenediamine (1.3 mL, 11 mmol) in anhydrous CH₂Cl₂ (8 mL) at 0 °C. The mixture was stirred for 6 h at ambient temperature and was diluted with CH₂Cl₂ (15 mL). The organic phase was washed with water and brine, and dried (Na₂SO₄). After removal of solvent under reduced pressure, the crude was purified by flash column chromatography (CH₂Cl₂/MeOH: 9/1) to give 1.73 g (63%) of keto-amide 65 as a colorless liquid.
$^1$H NMR (500MHz, CDCl$_3$):

$\delta$ 3.41- 3.36 (m, 2H, NHCH$_2$), 2.54 – 2.48 (m, 2H, CH$_2$N(CH$_3$)$_2$), 2.45 – 2.42 (m, 2H, CH$_2$CO), 2.26 (s, 6H, N(CH$_3$)$_2$), 2.15-2.12 (m, 1H, CHCH$_2$), 2.07 (t, 1H, J = 4.4, CH$_2$C), 1.98-1.94 (br m, 1H, CH$_2$C), 1.68 (br s, 1H, NH), 1.64 – 1.58 (m, 1H, CH$_2$CH), 1.45 – 1.41 (m, 1H, CH$_2$CH), 1.25 (s, 3H, (C(CH$_3$)$_2$)), 1.00 (s, 3H, (C(CH$_3$)).

$^{13}$C NMR (125.8 MHz, CDCl$_3$):

$\delta$ 216.6 (CONH), 168.9 (COCH$_2$), 64.7 (CCO), 58.1 (CH$_2$CO), 49.9 (NCH$_2$), 45.2 (NCH$_2$), 43.7 (N(CH$_3$)$_2$), 43.2 (C(CH$_3$)$_2$), 36.7 (CHCH$_2$), 28.0 (CH$_2$C), 27.5 (CH$_2$CH), 20.8 (C(CH$_3$)$_2$), 20.4 (C(CH$_3$)$_2$).

IR (neat):

3348, 2948, 2768, 1730, 1657, 1523, 1457 cm$^{-1}$.

MS (APCI, positive):

m/z 253.2 (M+1, 100)

$[\alpha]^2_D$: +69.0 (c 1, CHCl$_3$).

(1S)-N-[2-(Dimethylamino)ethyl]-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxamide (64):

![Structural formula](image)

To a solution of keto-amide 65 (1.00 g, 4 mmol) in methanol (15 mL) at 0 °C was added NaBH$_4$ (0.3 g, 8 mmol) was added in portions over a period of 20 min. The
reaction mixture was further stirred for 4 h at ambient temperature. After removal of the methanol, 3M NaOH (0.2 mL) was added to the residue followed by ethyl acetate (10 mL). The resulting suspension was filtered and the organic phase was separated, washed with brine (2 mL) and then dried over Na₂SO₄ and filtered. After removal of the solvent under reduced pressure, the crude product was purified by crystallization (EtoAc/hexane) to afford 0.87 g (65%) of the hydroxyl amide 64 as a colorless solid.

Mp: 63 °C.

¹H NMR (500MHz, CDCl₃):

δ 6.4 (br s, 1H, NH)), 3.99 (dd, 1H, J = 7.2, 2.6, CHOH), 3.55-3.48 (m, 1H, CH₂NH), 3.33- 3.27 (m, 1H, CH₂NH), 2.48- 2.39 (m, 2H, CH₂N(CH₃)₂), 2.24 (s, 6H, (N(CH₃)₂), 2.10-2.03 (m, 1H, (CH₂COH)), 1.92- 1.88 (m, 1H, (CH₂COH)), 1.83- 1.77 (m, 3H, CH₂C,CH₂CH), 1.30 (s, 3H, C(CH₃)), 1.15- 1.08 (m, 2H, CH₂CH), 1.04 (s, 3H, C(CH₃)).

¹³C NMR (125.8 MHz, CDCl₃):

δ 174.9 (CONH), 78.4 (COH), 58.3(CCO), 57.9 (CH₂CO), 48.9 (NCH₂), 46.2 (NCH₂), 45.1 (N(CH₃)₂), 40.7 (C(CH₃)₂), 36.8 (CHCH₂), 30.3 (CH₂C), 27.1 (CH₂CH), 21.7 (C(CH₃)₂), 21.1 (C(CH₃)₂).

IR (neat):

3408, 3267, 2937, 2825, 1650, 1551, 1060, 940 cm⁻¹.

MS (APCI, positive):

m/z 255.1 (M+1, 100).
HRMS (CI):

m/z 255.2064 (255.2073 calc. for C_{14}H_{27}N_{2}O_{2} (M+H)).

[^{23}\alpha]_{D}^{\text{a}}: +13.2 \ (c 1, \text{CHCl}_3).
VII. References


5 (a) Li, Bang - Jing; Jiang, Lin; Liu, Min; Chen, Ying-Chun; Ding, Li-Sheng; Wu, Yong. Synlett, 2005, 4, 603. (b) Mečiarová, M.; Toma, Š.; Kotrusz, P. Org. Biomol. Chem., 2006, 4, 1420.


9 Money, T. Natural Product Reports, 1985, 253.


Appendix

$^1$H and $^{13}$C Spectra
Boc 35