DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALDOL, MANNICH, FRIEDLAENDER REACTIONS

by

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ABSTRACT OF THE DISSERTATION

DEVELOPMENT OF CATALYTIC ENANTIOSELECTIVE ALDOL, MANNICH, FRIEDLÄNDER REACTIONS

By LE LI

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Professor Daniel Seidel

In Chapter I, I introduce the explosive development of enantioselective organocatalysis. Selected significant landmarks in this area are reviewed and highlighted in this chapter.

Chapter II focuses on the development of catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes and α-ketoesters.

Chapter III outlines the development of enantioselective Mannich reactions of α-isothiocyanato imides with activated imines and the asymmetric synthesis of α, β-diamino acid derivatives.

In Chapter IV, the first catalytic enantioselective Friedländer condensation is described which provides access to quinolines and tacrines with remote stereogenic centers.
ACKNOWLEDGEMENTS

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I dedicate this thesis to my beloved grandmother, parents and wife. Their love and continuous support always encourage me to move forward.
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Chapter I

Enantioselective Organocatalysis as an Emerging Synthetic Toolbox

Introduction

1.1 Background

The use of small organic molecules as catalysts for organic reactions in the absence of metallic elements has been known for more than one century. However, different from transition-metal catalysis, which took up the central stage of homogeneous catalysis over the past fifty years, organocatalysis did not experience dramatic progress until the last two decades. Today, it has been widely accepted that organocatalysis is one of the most competitive branches of asymmetric catalysis. However, why had people overlooked this area for such a long time? To find out the answer to this question, we have to look back and track the history of organocatalysis.

1.1.1 History

The first report of organocatalysis by Justus von Liebig appeared in 1860. Almost sixty years later, Langenbeck coined the term “organocatalyst” and published a series of papers using small organic molecules as mimics of enzyme catalysts. In 1931, Fischer and Marschall reported amino acid catalyzed aldol reactions. Although these early
reports had initiated two main categories in organocatalysis, “covalent catalysis” and “non-covalent catalysis”, they were not examples of asymmetric catalysis.

The first asymmetric organocatalyzed reaction was reported by Bredig and Fiske in 1912. In their report, the natural alkaloid quinine catalyzed the reaction of HCN and benzaldehyde, although the optical yield was low. In 1960, Pracejus et al. found that O-acetylquinine catalyzed the addition of methanol to phenylmethylketene. Remarkably, 74% ee was obtained with 1 mol% catalyst loading. In the early 1970s, the discovery of the proline-catalyzed intramolecular aldol reaction, namely, the Hajos-Parrish-Eder-Sauer-Wiechert reaction, showcased the tremendous potentials of enamine catalysis. Unfortunately, this type of catalysis was not further explored until 2000 when it was revisited by List, Lerner and Barbas. In the 1980s, some other branches of organocatalysis started to sprout up. Inoue et al. reported that a cyclic peptide catalyzes the addition of HCN to benzaldehyde and high ee’s (up to 90%) were obtained. This remarkable result is considered as one of the pioneering works of peptide catalysis. Later, Juliá and Colona et al. discovered poly-amino acid catalyzed epoxidations of chalcones using alkaline hydrogen peroxide as an oxidant. In this case as well, more than 90% ee was achieved. Almost at the same time, Hiemstra and Wynberg exploited cinchona alkaloid catalyzed Michael additions of thiol to cyclohexenone (up to 75% ee). Meanwhile, asymmetric phase transfer catalytic alkylation of protected glycine was systematically investigated by O’Donnell et al.
1.1.2 Renaissance and Explosive Development

As mentioned above, although a number of reactions can be catalyzed by small organic molecules, most of them were not efficient and economical enough for preparing enantiopure materials in large scale. In sharp contrast, transition metal catalysis and enzymatic catalysis supplied most of the chiral materials in industry at that time and thus the area of organocatalysis before 1990 stagnated in the initial phase. However, this situation started to change at the end of the 20th century. Firstly, the pharmaceutical industry started looking for “greener” processes to avoid the contamination and the toxicity of transition metal. On the other hand, although enzymatic catalysis is very powerful and highly effective in some industrial processes, its highly specific character is not ideal for a wide range of substrates. In addition, for some reactions, no enzymatic approaches were available. As a result, chemists had to look for a third approach to address these issues.

Under these circumstances, organocatalysis launched its renaissance in the 1990s. In 1994, Denmark et al. reported that chiral Lewis bases catalyzed the asymmetric allylation of aldehydes in modest ee. This concept was later expanded to other reactions. Subsequently, Iseki et al. and others realized the same reaction using different organo-catalytic systems. In 1996, Shi and Yang independently utilized chiral ketones to catalyze the enantioselective epoxidations of olefins. In 1997, Corey et al. and Lygo et al. discovered a novel cinchona alkaloid derived phase transfer catalyst, which enabled alkylations of protected glycine with excellent enantioselectivity. Concurrently, Fu’s planar-chiral DMAP derivatives catalyzed the kinetic resolution of
secondary alcohols in a highly selective fashion. In 1998, Jacobsen et al. introduced (thio)urea catalysts to catalyze the enantioselective additions of HCN and imines. In the same year, Miller et al. developed synthetic oligo-peptide catalyzed kinetic resolution of alcohols. In 1999, Maruoka et al. developed a new generation of asymmetric phase transfer catalysts based on the binaphthalene backbone and excellent enantioselectivities were achieved in a number of reactions. Also, Corey et al. utilized a chiral guanidine catalyst to catalyze the hydrocyanation of benzaldehydes. In 2000, List et al. revisited enamine catalysis and developed the proline catalyzed intermolecular aldol reactions of ketones and aldehydes. In the same year, MacMillan designed the oxazolidinone catalyst family to enable the enantioselective Diels-Alder reactions of α, β-unsaturated aldehydes, which is regarded as the milestone work of iminium catalysis.

Since 2000, the field of organocatalysis stepped into the age of explosive development, which was also described as a “gold rush” by some chemists. Thousands of publications and more than one hundred types of reactions were discovered by chemists from all over the world. The major branches of organocatalysis will be summarized in the following part of this chapter.

1.2 Major Branches of Organocatalysis

1.2.1 Enamine Catalysis

Since List, Lerner and Barbas’ pioneering work on the proline–catalyzed aldol reactions of acetone with aldehydes, enamine catalysis has developed into a powerful synthetic tool in organic synthesis. This activation mode has been widely applied to various substrates and different types of reactions.
For aldol reactions, the scope of nucleophiles has been greatly extended including cyclic ketones, \( \alpha \)-keto acids, \( \alpha \)-keto esters, \( \alpha \)-keto phosphonates, hydroxyacetone, chloroacetone, ynone, \( \alpha \), \( \alpha \)-disubstituted aldehydes and even highly reactive acetaldehyde. For electrophiles, in addition to aliphatic aldehydes and aromatic aldehydes, phenylglyoxalates, \( \alpha \)-keto acids, \( \alpha \)-keto esters, \( \alpha \)-keto phosphonates, protected \( \alpha \)-amino aldehydes and isatins are also viable substrates. In addition, Maruoka et al. reported the syn-selective aldol reactions\(^{29}\) of aliphatic aldehydes with aromatic and activated aliphatic aldehydes using an axially chiral enamine catalyst \(^1.5\), while anti-selective products are typically obtained in the proline catalyzed reactions.

Extensive studies showed that enamine catalysis has much more applications than aldol reactions. Until now, a number of reaction types have been covered by using enamine catalysis including Mannich reactions, conjugate addition reactions, \( \alpha \)-halogenations, \( \alpha \)-oxygenations, \( \alpha \)-aminations and other \( \alpha \)-functionalization processes. Moreover, enamine catalysis has shown impressive potential to catalyze domino reactions and has been greatly developed for the construction of the skeleton of complex molecules.

In addition, a large amount of new catalysts were discovered in the past decade. There are two major categories in these enamine catalysts. The main difference in these two types of catalysts is whether an internal acid or a hydrogen bond donor exists. In other words, type I utilize an acid or a HB donor as a directing group which activates electrophiles while type II usually have a bulky group which only allows the eletrophile to attack from one side. For example, diarylprolinol trimethylsilyl ethers \(^1.6\), introduced
independently by Jørgensen et al. and Hayashi et al. in 2005, are a class of privileged catalysts of type II. Some representative catalysts are shown in Figure 1.1.

**Figure 1.1 Selected Examples of Enamine Catalysts**

1.1 1.2 1.3

1.4 1.5

1.6 1.7 1.8

1.9 1.10

1.2.2 Iminium Catalysis

Similar to enamine catalysis, iminium catalysis was not revived until recently, although early examples of iminium catalysis apparently date back to the early 20th century. In 2000, MacMillan et al. reported the first enantioselective Diels-Alder reactions of α,β-unsaturated aldehydes using an oxazolidinone catalyst 1.9, which is one of the significant landmarks in iminium catalysis. Subsequently, MacMillan et al. and others discovered a number of applications including [4+2], [3+2], [4+3] cycloadditions, ene reactions, conjugate additions, Friedel-Crafts type alkylations and hydrogenations.

During the past decade, a series of new iminium catalysts were discovered, although MacMillan’s oxazolidinone catalyst family continues to play an important role in this type of catalysis. Strikingly, chiral anion mediated iminium catalysis has become
a promising strategy in transfer hydrogenation. Some of these representative catalysts are shown in Figure 1.2.

**Figure 1.2 Selected Examples of Iminium Catalysts**

**Representative Iminium Catalysts**

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst Structure</th>
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<tr>
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</tr>
<tr>
<td>1.10</td>
<td><img src="image1.10" alt="Catalyst 1.10" /></td>
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<tr>
<td>1.11</td>
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<tr>
<td>1.6</td>
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**Chiral Anion Mediated Iminium Catalysts**

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<th>No.</th>
<th>Catalyst Structure</th>
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<tr>
<td>1.14</td>
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</table>

Recently, combining iminium catalysis with enamine catalysis has become a powerful strategy in the design of new cascade reactions. Several elegant total syntheses utilized this strategy to set up multiple chiral centers in one single step, significantly cutting down steps as compared to previous syntheses.

**1.2.3 Hydrogen Bond Catalysis**

Activation of substrates by hydrogen bond donors in enzymatic catalysis has been recognized for a long time. The extensive investigations of solid-state or solution-state in
molecular recognition and crystallography also showed that hydrogen bond donors could form complexes with themselves or with other molecules containing hydrogen bond acceptors. These facts suggested that hydrogen bonds could be a promising activation force for catalysis. However, hydrogen bond catalysis has not been extensively investigated until recently. This apparent contradiction can be explained by the nature of the hydrogen bond which is a much weaker interaction than covalent bonds.

Hydrogen bond catalysis had not been widely recognized as a key activation mode until the late 20th century. In the early 1980s, the reports from Wynberg et al.,11 Inoue et al.9 and Dolling et al.35 on cinchona alkaloid and oligo-peptide catalyzed reactions disclosed that hydrogen bonding has a beneficial effect on enantioselectivity. In 1998, Sigman and Jacobsen reported that a (thio)urea 1.15 catalyzed Strecker reactions.20 Later, in proline catalyzed aldol reactions, List and Houk proved that the carboxylic acid of proline activates the incoming aldehyde and accelerates the reaction.36 In addition to Jacobsen’s catalyst family, many other successful catalytic systems were developed in the last decade. Some representative examples are shown in Figure 1.3. In 2003, Takemoto et al. introduced a tertiary amine-(thio)urea type catalyst 1.22 using trans-cyclohexanediamine as backbone.37 In the same year, the discovery of TADDOL derivatives by Rawal indicated that the chiral diol 1.20 could be a good catalyst for hetero-Diels-Alder reactions.38 In 1999 and 2004, Hatakeyama et al.39 and Deng et al.40 individually discovered their own catalyst family (1.16 and 1.19), both of which are derived from cupreine and cupreidine. These systems have been finely tuned and extensively investigated by other researchers.34 In addition, Miller’s intensive research
on synthetic peptide catalysis can be regarded as an extension of hydrogen bond catalysis.\textsuperscript{41}

**Figure 1.3 Selected Hydrogen Bond Catalysts**

In 2007, Jacobsen’s mechanistic studies\textsuperscript{42} on thiourea 1.17-catalyzed Pictet-Spengler reactions exhibited binding between thiourea and anions, which opened the door to another new branch of hydrogen bond catalysis, anion binding catalysis. Meanwhile, some unprecedented reaction modes were introduced that combine hydrogen bond catalysis with other types of catalysis.\textsuperscript{8,43} In Figure 1.3, some of the classical hydrogen bond catalysts are summarized.
The last decade witnessed the exponential development of hydrogen bond catalysis. It has been expanded into a number of reactions including aldol reactions, Mannich reactions, conjugate additions, Diels-Alder cycloadditions, Baylis-Hillman reactions, aza-Baylis-Hillman reactions, Henry reactions, aza-Henry reactions, Friedel-Crafts additions, Strecker reactions, epoxidations, kinetic resolutions and desymmetrizations, radical cyclizations, photocyclizations, α-hydrazinations, hydrophosphonylation, Claisen rearrangements, Povarov reactions, Pictet-Spengler reactions, alkylations and allylations.

1.2.4 Stronger Brønsted Acid Catalysis

Different from conventional Lewis acid catalysis, Brønsted acid catalysis utilizes protons to catalyze organic transformations. In theory, all hydrogen bond donors, such as (thio)ureas, alcohols, phenols, carboxylic acids and phosphoric acids, can be regarded as Brønsted acids. Also, there is no strict distinction between hydrogen bond catalysis and other Brønsted acid catalysis. The term “stronger Brønsted acid catalysis” introduced by Akiyama was used to describe Brønsted acid catalysis that involves ion pair interactions, not hydrogen bonding interactions.

In 2004, Akiyama et al. and Terada et al. independently reported that axially chiral phosphoric acids catalyze Mannich reactions in highly enantioselective fashion, a milestone achievement in this area. Afterwards, the concept of chiral stronger Brønsted acid catalysis has been extended into many types of reactions including Mannich reactions, aza-Henry reactions, aza-ene type reactions, hydrophosphonylations of imines, Pictet-Spengler reactions, Friedel-Crafts reactions, alkylations, Strecker reactions, aza-Diels-Alder reactions, 1, 3-dipolar cycloadditions, Biginelli reactions, Nazarov reactions,
transfer hydrogenations, reductive aminations and other types of additions of nucleophiles to imines.

In the last five years, various chiral “stronger Brønsted acid” catalysts were discovered successively (Figure 1.4). Other chiral phosphoric acids were prepared from other chiral scaffolds. In 2005, the Akiyama group reported TADDOL derived phosphoric acids \(1.28\). In the same year, Antilla et al. utilized VAPPOL derived phosphoric acids \(1.27\) to catalyze enantioselective imine amidations.\(^47\) In 2006, BINAM variants \(1.26\) were developed in the Terada group.\(^48\) In 2008, Gong et al. discovered bisphosphoric acids \(1.30\) derived from BINOL that successfully catalyze asymmetric 1,3-dipolar cycloadditions.\(^49\) Also, bis-BINOL phosphoric acids \(1.31\) were used to catalyze the transfer hydrogenation of quinolines by Du et al.\(^50\)

Although chiral phosphoric acids are still the major player in stronger Brønsted acid catalysis, other chiral Brønsted acids have been used as a valuable supplement (Figure 1.4). For instance, more acidic chiral N-triflyl phosphoramides \(1.29\) provide stronger activation than the corresponding phosphoric acids and are thus good candidates for the activation of less reactive substrates. In 2006, Yamamoto et al. designed this type of catalysts and successfully applied them to asymmetric Diels-Alder reactions of \(\alpha, \beta\)-unsaturated ketones with silyloxydienes.\(^51\) Later, following this line, Yamamoto et al. prepared more acidic chiral N-triflyl thiophosphoramides and their seleno counterparts in 2008. These compounds catalyze the asymmetric protonation of cyclic silyl enol ethers.\(^52\) In addition, chiral carboxylic acids, chiral sulfonic acids and chiral protonated salts were discovered to catalyze asymmetric transformations.\(^44\)
Figure 1.4 Selected “Strong Brønsted Acid” Catalysts

1.2.5 Phase Transfer Catalysis\textsuperscript{23,53}

Since O’Donnell’s seminal investigations\textsuperscript{12} on alkylation of benzophenone imines of glycine derivatives, this reaction has become one of the most important methods to prepare optically active natural or unnatural α-amino acids. In 1997, Corey and Lygo independently discovered that bulky cinchona alkaloid derived ammonium salts \textsuperscript{1.37} catalyze the alkylation of protected glycines with excellent enantioselectivity.\textsuperscript{18} In 1999, Maruoka designed a new generation of chiral phase transfer catalysts \textsuperscript{1.36} using binaphthaleine as chiral backbone.\textsuperscript{22} Compared to cinchona alkaloid derived PTC, the
Maruoka catalyst family has several extraordinary advantages such as higher stability (less labile in basic conditions), better modularity and broader reaction scopes, although multi-step synthesis are often required for the preparation of catalysts. These two types of phase transfer catalysts are predominant in this area and most new applications involve them, although other research groups have been trying to design new privileged PTCs based on readily available chiral starting materials\textsuperscript{54} (Figure 1.5).

\textit{Figure 1.5 “Privileged” Phase Transfer Catalysts}

After almost 30 years of development, a wide range of reactions are available for asymmetric phase transfer catalysis such as alkylations, fluorinations, aldol reactions, Mannich reactions, Michael additions, Darzens reactions, epoxidations, Neber rearrangements, aziridinations, Strecker reactions and dihydroxylations.

1.2.6 \textit{N-heterocyclic Carbenes as Organocatalysts}\textsuperscript{55}

Carbene catalysts take a significant position in modern synthetic chemistry because of their unique properties. They constitute highly reactive intermediates and facilitate new synthetic pathways. Compared to other carbenes, N-heterocyclic carbenes are more stable and easier to handle.\textsuperscript{56} An early example of N-heterocyclic carbenes as organocatalysts was Sheehan and Hunneman’s research on asymmetric benzoin
condensations in the 1960s, although the enantioselectivity was low.\textsuperscript{57} The breakthrough in this area was achieved by Enders’ group in 2002.\textsuperscript{58} A chiral bicyclic triazolium salt \textbf{1.39} derived from (S)-\textit{tert}-leucine functioned as a carbene precursor to catalyze asymmetric benzoin condensations with good enantioselectivity. This bicyclic structure, first introduced by Leeper and Rawal,\textsuperscript{59} was shown to be crucial and many successful applications were discovered using this structure or other variants with similar topology (Figure 1.6). Another interesting application in this area is the asymmetric Stetter reaction. In 2002, Rovis et al. developed another series of triazolium pre-catalysts \textbf{1.40} that catalyze intramolecular Stetter reactions with good enantioselectivity.\textsuperscript{60}

N-heterocyclic carbenes were also disclosed to catalyze a number of asymmetric redox processes. In 2005, Rovis et al. reported the synthesis of chiral \(\alpha\)-chloroesters from \(\alpha\), \(\alpha\)-dichloroaldehydes.\textsuperscript{61} In 2006, Bode et al. demonstrated that N-heterocyclic carbenes \textbf{1.40} catalyze azadiene Diels-Alder reactions with excellent enantioselectivity.\textsuperscript{62} The corresponding oxadiene Diels-Alder reactions were also reported by the same group.\textsuperscript{63} In 2007, two complementary methods for the synthesis of chiral substituted cyclopentenes were reported by Bode et al.\textsuperscript{64} and Scheidt et al.\textsuperscript{65} Additionally, N-heterocyclic carbene catalyzed reactions have been applied into the synthesis of FD-838.\textsuperscript{66}
Lewis base catalysis has two major categories: amine catalysis (Figure 1.7) and phosphine catalysis (Figure 1.8). In addition, chiral alcohols, chiral phosphoramides and chiral amine oxides have been also investigated as Lewis base catalysts.

Historically, cinchona alkaloid catalysis \(^6^8\) played the central role in this area. In 1960, Pracejus et al. first reported the alcoholysis of disubstituted ketenes,\(^6\) which opened up the area of chiral amine nucleophilic catalysis. Recently, Lectka et al. utilized modified cinchona alkaloids 1.45 to catalyze a number of asymmetric reactions involving ketenes.\(^6^9\) Moreover, cinchona alkaloid derivatives 1.16 and 1.45 were confirmed to be good catalysts for Baylis-Hillman reactions by Hatakeyama et al.\(^3^9\) and for desymmetrizations of cyclic anhydrides by Deng et al. and others.\(^4^0, 7^0\)
Although there were sporadic reports in the last fifty years, other classes of Lewis base catalysis were not widespread until recently. For example, the common Lewis base catalysts such as imidazole, pyridine and guanidine have been incorporated into chiral scaffolds. In 1996, Fu et al. reported planar-chiral DMAP variants 1.46 catalyzed kinetic resolution of secondary alcohols. In 1998, Oriyama et al. successfully catalyzed the desymmetrizations of meso-diols using a new diamine catalyst 1.47 derived from proline. Concurrently, Spivey et al. and Fuji et al. developed two different chiral PPY catalysts 1.49 and 1.50 to catalyze the same reaction. Also, as mentioned in the previous sections, Miller et al. reported imidazole-containing synthetic peptides and used
them to catalyze a series of reactions.\textsuperscript{21, 41} In 1999, Corey et al. utilized a chiral guanidine \textbf{1.48} to catalyze the hydrocyanation of benzaldehydes.\textsuperscript{24} In 2004, Birman et al. developed a new set of nucleophilic catalysts \textbf{1.52} and \textbf{1.53} based on dihydroimidazole backbones.\textsuperscript{73} Later, these catalysts were applied to a number of kinetic resolution processes and excellent selectivities were obtained. In 2005, Sammakia et al. discovered a new chiral DMAP derivative \textbf{1.54} by which the kinetic resolutions of protected \(\alpha\)-hydroxyl acid derivatives\textsuperscript{74} were achieved.

\textit{Figure 1.8 Selected Examples of Chiral Phosphines as Lewis Base Catalysts}

![Chemical Structures]

Chiral phosphines constitute another important class of asymmetric Lewis base catalysts. In 1996, Vedejs et al. developed the first generation of phosphine \textbf{1.55} catalyzed kinetic resolutions of secondary alcohols.\textsuperscript{75} In 2002, Shi et al. discovered that axially chiral monophosphine \textbf{1.56} catalyzed aza-Baylis-Hillman reactions with excellent enantioselectivity.\textsuperscript{76} In 2007, Miller et al. reported that an \(\alpha\)-amino acid derived chiral monophosphine \textbf{1.61} catalyzes a [3+2] cycloadditions of allenic esters and \(\alpha\), \(\beta\)-unsaturated ketones.\textsuperscript{77} In 2008, Jacobsen developed a series of bifunctional phosphine-thiourea catalysts \textbf{1.57} to catalyze an asymmetric imine-allene [3+2] cycloaddition.\textsuperscript{78}
Recently, Fu et al. disclosed that some well-known chiral phosphine ligands (1.58, 1.59 and 1.62) can function as organocatalysts to catalyze a set of reactions which have never been achieved before.79

Until now, a number of reactions have been covered by Lewis base catalysis including aldol reactions, Mannich reactions, Michael additions, Strecker reactions, kinetic resolutions of alcohols and amines, asymmetric protonations of ketenes, cycloadditions of ketenes, halogenations, Baylis-Hillman reactions, desymmetrizations of cyclic anhydrides, Steglich rearrangements, dynamic kinetic resolutions of azlactones, [3+2] annulations, acylations of silyl ketene acetaLs and silyl ketene imines, allylic substitutions and [3+2] cycloadditions of allenic esters.

1.2.8 Miscellaneous Types

As the result of the exploration during the last two decades, organocatalysis has been developed into a highly diversified area. Continuous and intensive investigation in this area has generated some new activation modes.

Besides those organocatalysts mentioned previously, chiral organosulfides,80 chiral ketones and chiral iminiums81 have been discovered to accelerate asymmetric reactions. Although the scope of their applications is relatively narrow, some of them are quite useful. For instance, chiral ketone and iminium ion–catalyzed epoxidations are now one of the most significant methods to prepare chiral epoxides from olefins. In addition, chiral organosulfides provide a convenient catalytic approach to access chiral epoxides, aziridines and cyclopropanes.
New activation modes are always of significant interest to chemists. In contrast to organometallic chemistry, most organocatalytic reactions do not involve redox processes except some N-heterocyclic carbene catalyzed reactions, which greatly limited the development of this area. In 2007, MacMillan et al. presented a creative solution to this problem. The new type of catalysis, SOMO activation, involves a reactive cation radical species which inverts the original reactivity of the enamine intermediate. This concept was further used to develop a series of asymmetric reactions, which were unattainable by previous catalytic methods. In 2008, MacMillan et al. reported the direct asymmetric alkylation of aldehydes by merging photoredox catalysis with organocatalysis. This visible light mediated catalysis provides a “green” way to activate substrates by reduction as well as by oxidation, which shows great potential to perform asymmetric catalysis in an environmentally friendly manner.

1.3 Objectives

As mentioned in the last section, enantioselective organocatalysis has emerged as a powerful synthetic tool in organic synthesis, providing a robust platform to construct diversified molecular architectures with chiral centers. During the period of 2000-2010, hundreds of processes have been discovered and some of them have already become classics in modern synthetic chemistry. However, many challenges still remain in this area. For instance, in most of the organo-catalyzed reactions, 5-10 mol% or even higher catalyst loadings are still required. Secondly, the activation provided by organocatalysis is still hard to compare with metal catalyzed reactions, although some breakthroughs addressing this issue were achieved recently. In addition, further understanding and
elucidation of mechanisms and topology of privileged structures will be beneficial to the design of “minimized enzymes”.

The main objective of this dissertation was to develop new organocatalyzed methodologies addressing the issues mentioned above. Another target was to establish some practical routes to access various chiral building blocks. I hope that these discoveries and achievements will shed some light on further developments in this area. Chapter II focuses on the development of catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes and α-ketoesters.\textsuperscript{85, 86} Chapter III outlines the development of enantioselective Mannich reactions of α-isothiocyanato imides with activated imines and the asymmetric synthesis of α, β-diamino acid derivatives.\textsuperscript{87} Lastly, in Chapter IV, the first catalytic enantioselective Friedländer condensation is described which provides access to quinolines and tacrines with remote stereogenic centers.
References


Chapter II

Catalytic Enantioselective Synthesis of β-Hydroxy-α-Amino Acid Derivatives

2.1 Background

2.1.1 Significance of β-Hydroxy-α-Amino Acid Derivatives

Many biologically active natural products such as biphenomycin A, cyclomarins, exochelins, polyoxins, ustiloxins and vancomycin contain β-hydroxy-α-amino acids within their structural frameworks (Scheme 2.1).

Scheme 2.1 Selected Natural Products Containing β-Hydroxy-α-Amino Acid Moiety

The majority of methods currently available to synthesize β-hydroxy-α-amino acids rely on diastereoselective approaches, e.g. the use of chiral auxiliaries (Scheme 2.2).
The development of highly efficient catalytic enantioselective variants remains challenging\textsuperscript{10–15} with some methods requiring the use of preformed enolate equivalents.\textsuperscript{16}

**Scheme 2.2 Diastereoselective Method Using Evans Auxiliary**

\[
\begin{align*}
\text{SCN} & \quad \text{Br} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{R} \\
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{S} & \quad \text{NH} \\
\text{O} & \quad \text{O} \\
\text{Bn} & \quad \text{Bn}
\end{align*}
\]

\[\text{Sn(OTf)}_2 (1.2 \text{ eq}), \quad \text{NEP (1.5 eq)} \]

\[\text{THF, -78 } ^\circ \text{C, 4 h} \]

\[\text{6 examples, 71–93% yields,} \quad \text{dr 10:1 to 99:1} \]

Among the methods available to access this building block, direct aldol reactions of glycine equivalents with aldehydes represent a convenient method to obtain β-hydroxy-α-amino acids (Scheme 2.3). In 1986, Ito and Hayashi et al. reported a gold complex-catalyzed asymmetric aldol reaction of α-isocyano acetates 2.7 with aldehydes.\textsuperscript{14a} Although excellent ee’s were obtained in this elegant example, the use of the costly chiral ferrocene ligand 2.9 and the precious metal limited the application of this methodology. In 1999 and 2001, Suga and Ibata et al. and Evans et al. discovered the enantioselective aldol reactions of 5-alkoxyoxazoles 2.10 with aldehydes.\textsuperscript{14b, 14c} Interestingly, anti products 2.11 were obtained in this case. In 2002, Maruoka et al. utilized their chiral phase transfer catalysts 2.15 to catalyze the asymmetric aldol reactions of benzophenone imine protected glycine esters 2.13 with aldehydes.\textsuperscript{15a} However, the reaction scope was relatively limited. In 2005, Willis et al. developed the asymmetric aldol reaction of α-isothiocyanato imide 2.16 with aldehydes,\textsuperscript{10} which is regarded as a catalytic version of the corresponding Evans aldol reaction.\textsuperscript{9a}
Scheme 2.3 Direct Aldol Reactions of Glycine Equivalents with Aldehydes

Ito & Hayashi et al. (1986)

\[
\text{CNCH}_2\text{COOMe} + \text{RCHO} \xrightarrow{\text{[Au(c-HexNC)_2]}^+\text{BF}_4^- / ligand (1 mol\%)} \text{EtO}_2\text{C} \xrightarrow{\text{Me}_2\text{Cl}_2, 25 \degree\text{C}, 20 \text{h}} \\text{2.8}
\]

7 examples
83%-100% yield
81:19 to 100:0 dr
81%-97% ee

Evans et al. (2001)

\[
\text{2.10} + \text{ArCHO} \xrightarrow{\text{Me}_2\text{AlSbF}_6 / ligand (5-10 mol\%)} \text{2.11}
\]

25 examples
58%-100% yield
73:27 to 99:1 dr
91%-99% ee

Maruoka et al. (2002)

\[
\text{2.13} + \text{RCHO} \xrightarrow{1. \text{catalyst} (2 \text{ mol\%}), \text{PhMe/aq NaOH (1\%), 0 \degree\text{C}, 2 \text{h}}) \xrightarrow{2. \text{HCl (1 N), THF}} \text{2.14}
\]

9 examples
40-78% yields
dr 1.2:1 to 20:1
ee 80 to 98%

catalyst 2.15

Willis et al. (2005)

\[
\text{2.16} + \text{ArCHO} \xrightarrow{1. \text{Mg(ClO}_4)_2 (10 \text{ mol\%), ligand (11 \text{ mol\%})}, \text{iPr}_2\text{EtN (20 mol\%), 4 \AA \text{ MS, DCM, -78 \degree\text{C}, 24 h}}) \xrightarrow{2. \text{MeMgBr, EtOH}} \text{2.17}
\]

11 examples
64-95% yields
dr 50:50 to 93:7
ee 86 to 95%

ligand 2.18
2.2 Proposal and Objective

The last two decades witnessed the explosive development of organocatalyzed enantioselective processes. Compared to metal-catalyzed reactions, organocatalysis provides some unique advantages including relatively mild reaction conditions and less expensive catalysts. Therefore, it is reasonable to hypothesize that the organocatalytic aldol reactions of glycine equivalents and aldehydes may provide a convenient method to access chiral β-hydroxy-α-amino acids. In the following part of this chapter, I will report our efforts towards the asymmetric synthesis of β-hydroxy-α-amino acids.

2.3 Results and Discussions

2.3.1 General Considerations

With the goal of developing an organocatalytic approach to β-hydroxy-α-amino acids, we thought that some known glycine equivalents could be the ideal reaction partner including α-isocyano acetates 2.7, 5-alkoxyoxazoles 2.10, benzophenone imines of glycine esters 2.13 and α-isothiocyanato esters 2.19. Finally, commercially available ethyl α-isocyano acetate 2.20 and ethyl α-isothiocyanato ester 2.21 were selected for the evaluation of catalysts. In addition, the corresponding imides were also considered as suitable candidates since they provide different modes of coordination and further modulate the pKa of the substrates.

2.3.2 Preliminary Investigation on Aldol Reactions of α-Isocyano Acetates with Benzaldehydes
Scheme 2.4 Aldol Reactions of Ethyl $\alpha$-Isocyano Acetates with Benzaldehydes

We initiated our studies by evaluating the reaction between commercially available ethyl $\alpha$-isocyano acetate and benzaldehyde using readily available organocatalysts. Only modest ee’s and yields were obtained with a series of bifunctional organocatalysts under a variety of conditions. Experiments revealed that the bulkier tert-butyl ester gave better selectivity than the ethyl ester. However, the reactivity of this substrate is low and long reaction times are required for the completion of reactions. Nevertheless, these
experimental results indicated that bifunctional catalysts derived from trans-cyclohexanediamine have a great potential in this type of reaction since they can be modulated in both parts (tertiary amine and thiourea).

Scheme 2.5 Aldol Reactions of t-Butyl α-Isocyano Acetates with Benzaldehydes

![Scheme 2.5 Aldol Reactions of t-Butyl α-Isocyano Acetates with Benzaldehydes](image)

2.3.3 Development of Organocatalyzed Aldol Reactions of α-Isothiocyanato Imides and Esters with Aldehydes

2.3.3.1 Reaction Development

Encouraged with the investigation on aldol reactions of α-isocyano acetates with benzaldehydes, we turned to evaluate more active substrates. α-Isothiocyanato acetate has a lower pKa value and thus could have higher reactivity than the corresponding
isocyano acetate. The reaction between ethyl α-isothiocyanato acetate \(2.21\) and benzaldehyde was tested with quinidine \(2.29\) as the catalyst. In addition to the desired product \(2.35\), (obtained in low diastereo- and enantioselectivity), compound \(2.36\) was obtained as the major product resulting from the addition of primary product \(2.35\) to

**Scheme 2.6 Aldol Reactions of Ethyl α-Isothiocyanato Acetates with Benzaldehydes**
another equivalent of 2.21. Other readily available organocatalysts were subsequently evaluated (Scheme 2.6). Stereoselectivities were promising in some cases but 2.36 was consistently obtained as the major product. Control experiments revealed that the presence of catalyst is required for the formation of 2.36 from 2.35 and 2.21. We speculated that the reverse reaction may also be catalyzed by 2.40. Longer reaction times increase the yield of 2.35 at the expense of 2.36, but this process was found to be too slow to be practical. When other α-isothiocyanato esters (Me, i-Pr, t-Bu and Bn) were used, 2.36 was again obtained as the major product.

Scheme 2.7 Aldol Reactions of α-Isothiocyanato Imides with Benzaldehydes
The experimental results shown in Scheme 2.6 indicated that the pyrrolidine ring on the catalysts is crucial for both reactivity and selectivity. Therefore, these catalysts were further tested in the reactions of imide 2.16 with benzaldehyde (Scheme 2.7). The yield of products could be dramatically increased with imide 2.16, the substrate previously used by Willis and coworkers in their enantioselective metal catalyzed approach. Formation of undesired product was almost completely suppressed but the expected product (2.41 and 2.42) was obtained in low diastereoselectivity slightly favoring the cis isomer 2.42. A poorly defined enolate geometry might be responsible for the low levels of diastereoselectivity. Greatly enhanced diastereomeric ratios were observed with the dimethyl analogue 2.46. Evaluation of different catalysts revealed that 2.39 provides product 2.47 in excellent yield and with high levels of selectivity in a relatively short reaction time (Scheme 2.8).

*Scheme 2.8 Aldol Reactions of α-Isothiocyanato Dimethyl Imides with Benzaldehydes*
Further optimization allowed for reducing the catalyst loading to 5 mol% and the
equivalents of aldehyde to 1.2. Virtually no difference was seen between reactions
performed under anhydrous conditions and reactions run simply in capped flasks with
HPLC grade toluene and without rigorous exclusion of air or moisture.

2.3.3.2 Scope of the Reaction

The substrate scope was evaluated using these operationally convenient conditions
(Table 2.1). Several electron-rich and electron-poor aromatic aldehydes with different
substitution patterns gave rise to products that were generally obtained in good yields and
with high levels of diastereo- and enantioselectivity. Heteroaromatic systems were also
viable substrates as were α,β-unsaturated aldehydes. Aliphatic aldehydes were found to
be less reactive and gave rise to products in lower yields and selectivities.

We observed that reaction times are significantly reduced in instances where
products (partially) precipitate in the course of the reaction. The minimization of
nonproductive product-catalyst interactions could account for this finding which provides
an opportunity for practical product recovery. A reaction between benzaldehyde and 2.46
gave rise to analytically pure product 2.47 in 67% yield (dr > 99:01, 98% ee) when
worked up through a simple filtration rather than by the usual chromatographic
purification. Additional product 2.47 was isolated from the filtrate in 27% yield (dr =
78:22, 77% ee).
### Table 2.1 Scope of the Reaction

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<th>Product</th>
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<th>Yield [%]</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee [%]</th>
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<td>93</td>
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<td>91</td>
<td>95:05</td>
<td>94</td>
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<td>94</td>
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<td>72</td>
<td>55</td>
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</table>

[a] Reactions were run on a 1 mmol scale using 1.2 equiv of aldehyde. The enantiomeric excess was determined by HPLC analysis. ppt: product partially precipitated in course of the reaction. [b] combined yield of both diastereomers. [c] trans:cis, determined by <sup>1</sup>H-NMR. [d] reaction was performed at 0 °C. [e] performed at 0.1 M concentration.
2.3.3.3 Scale-up Synthesis of Protected β-Hydroxy-α-Amino Acid

To evaluate the applicability of our method, compound 2.51 was prepared on a larger scale (Scheme 2.9). Using only 1 mol% of catalyst 2.39, product 2.51 was obtained in good yield and with excellent levels of diastereo- and enantioselectivity without the need for chromatographic purification. The protected β-hydroxy-α-amino acid 2.51 is related to intermediates previously used in the synthesis of vancomycin\textsuperscript{20} and ristocetin.\textsuperscript{21}

Scheme 2.9 Gram-scale Synthesis of Protected β-Hydroxy-α-Amino Acid

\[
\begin{align*}
\text{SCN} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

2.46 (20 mmol)

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CHO} \\
\text{Me} & \quad \text{F} \\
\text{F} & \quad \text{N}^{+}
\end{align*}
\]

2.50 (20.4 mmol)

(i) catalyst 2.39 (1 mol%), PhMe (0.1 M), rt, 21 h, filtration

(ii) recrystallization

2.51 (5.35 g, 70% yield), >99.5% ee (dr > 99:01)

2.3.3.4 Summary

In summary, we have introduced a mild and facile method for catalytic enantioselective aldol additions of α-isothiocyanato imides to aldehydes. Low catalyst loadings and operationally convenient conditions make this method attractive for the synthesis of various protected syn β-hydroxy-α-amino acids.

2.3.4 Development of Organocatalyzed Aldol Reactions of α-Isothiocyanato Imides and Esters with α-Ketoesters

2.3.4.1 Reaction Development
Encouraged with our success on catalytic enantioselective aldol reactions between α-isothiocyanato imide 2.46 and aldehydes, we decided to expand this methodology to other substrates. The asymmetric aldol reaction of glycine equivalents and ketones is of significant value since the reaction yields protected β-hydroxy-α-amino acids with a tetra-substituted carbon center. Although a number of catalytic enantioselective methods for the addition of glycine equivalents to aldehydes have been reported, the corresponding reaction with ketones as electrophiles has seen much less development. Recently, Shibasaki et al. reported catalytic enantioselective additions of α-isothiocyanato esters 2.52 to aryl alkyl ketones, employing chiral magnesium Schiff base catalysts 2.54.

Scheme 2.10 Aldol Reactions of α-Isothiocyanato Esters with Ketones

The bifunctional thiourea compound 2.39 proved to be an excellent catalyst for the reaction of imide and aldehydes, providing products 2.49 with high levels of stereoselectivity. However, our attempts using this catalyst for the reaction of imide with simple ketone substrates (acetone, acetophenone and trifluoroacetophenone) were unsuccessful. The lack of reactivity seen for these substrates suggested that more reactive substrates are required. Therefore, we turned to evaluate the reactions between α-isothiocyanato imides 2.16 and 2.46 and highly activated α-ketoesters.
2.55. A series of organocatalysts were investigated and the results are summarized in Table 2.2. Different catalysts readily promoted reactions between imides 2.16 and 2.46 and α-ketoesters (ethyl pyruvate 2.55o or ethyl 2-oxo-2-phenylacetate 2.55a) in toluene at room temperature. The more sterically encumbered imide 2.46 gave rise to the formation of products with higher levels of diastereo- and enantioselectivity. Amine-thiourea 2.39 was identified as the most efficient and selective catalyst. An evaluation of different solvents revealed methyl tert-butyl ether (MTBE) to be superior to toluene with regard to overall efficiency. The best result for the reaction of imide 2.46 and ethyl 2-oxo-2-phenylacetate 2.55a was obtained in MTBE at 0.15 M concentration, using 5 mol% of catalyst 2.39 (entry 21). In this instance, the reaction went to completion within 3 hours and product 2.56a was obtained in 93% yield (dr = 80:20; 95% ee). Reactions conducted at lower (entry 22) or higher concentration (entry 23) gave rise to poorer results. Moreover, the use of methyl or tert-butyl α-ketoesters yielded inferior results.

Table 2.2 Optimization of Reaction Parameters

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<th>Catalyst</th>
<th>Solvent, rt</th>
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<tr>
<td>2.39</td>
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<td>R = Me</td>
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2.56: R = Me

2.61: R = H
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<th>Entry</th>
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<th>Sm</th>
<th>R'</th>
<th>Solvent</th>
<th>Time [h]</th>
<th>Yield [%]b</th>
<th>dr [%]c</th>
<th>ee [%]d</th>
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<td>PhMe</td>
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<td>2.16</td>
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<td>67:33</td>
<td>77</td>
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*a* Reactions were performed at rt on a 0.17 mmol scale in solvent (0.15 M) using 1.1 equiv of ketoester. Reactions were run to full conversion as judged by TLC analysis. The ee’s were determined by HPLC analysis. *b* Combined yield of both diastereomers. *c* Determined by ¹H-NMR. *d* ee of major diastereomer shown. *e* Run at 0.1 M concentration. *f* Run at 0.25 M concentration; CPME = cyclopentyl methyl ether; MTBE = methyl tert-butyl ether.
2.3.4.2 Substrate Scope

*Table 2.3 Scope of the Reaction* 

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>time [h]</th>
<th>yield [%]</th>
<th>dr</th>
<th>ee [%]</th>
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<tr>
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<td>2</td>
<td>4-OMe-C₆H₄</td>
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<td>75:25</td>
<td>87</td>
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<td>95</td>
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<td>2.56o</td>
<td>4</td>
<td>99</td>
<td>83:17</td>
<td>79</td>
</tr>
</tbody>
</table>

ᵃ Reactions were run at rt on a 0.5 mmol scale using 1.1 equiv of the ketoester. The ee’s were determined by HPLC analysis. ᵇ Combined yield of both diastereomers. ᶜ Determined by ¹H-NMR. ᵈ Reaction was performed in PhMe.

With the optimized reaction conditions in hand, a series of different α-ketoesters was evaluated (Table 2.3). Electron rich and electron poor aromatic substituents with
different substitution patterns provided products in generally good yields and with high 
enantioselectivities and moderate diastereoselectivities (entries 1–13). Heteroaromatic \( \alpha \)-ketoesters were also viable substrates (entry 14).

As is customary, for all examples reported in Table 2.3, the yields and 
stereoselectivities correspond to all of the obtained product (solution and solid phase 
combined). Gratifyingly, in some instances, product precipitation offers the opportunity 
to directly obtain highly diastereomerically and enantiomerically enriched products by 
simple filtration. For instance, when a reaction leading to product 2.56e was worked up 
by filtration, followed by washing with a small amount of MTBE, this product was 
obtained in 66% yield as diastereomerically and enantiomerically pure material (within 
the limits of HPLC detection).

2.3.4.3 Summary

In summary, we have introduced a mild and facile method for catalytic 
enantioselective aldol additions of \( \alpha \)-isothiocyanato imides to \( \alpha \)-ketoesters using a readily 
available bifunctional thiourea catalyst that operates under mild reaction conditions.

2.3.5 Latest Progress in this Area

Recently, Wang and co-workers have reported catalytic enantioselective additions 
of \( \alpha \)-isothiocyanato imides to \( \alpha \)-ketoesters, using a rosin-derived amine-thiourea 
catalyst.\(^{25}\) Most recently, Feng and co-workers reported catalytic enantioselective 
additions of \( \alpha \)-isothiocyanato imides to aldehydes,\(^{26}\) using a nickel complex.
Scheme 2.11 Recent Catalytic Methods for Chiral β-Hydroxy-α-Amino Acids

Wang et al. (2010)

\[
\text{SCN-CONO}_2^\text{MeMe} + \text{R'CONO}_2^\text{Et} \rightarrow \text{NHCONO}_2^\text{MeMe} \quad \text{catalyst (1 mol%) PhMe, rt, 5 h}
\]

14 examples
68-98% yields
dr 70:30 to 97:3
ee 78 to 99%

Feng et al. (2010)

\[
\text{SCN-CONO}_2^\text{MeMe} + \text{ArH} \rightarrow \text{NHCONO}_2^\text{MeMe} \quad \text{catalyst 2.62}
\]

1. Ni(acac)$_2$ (2.5 mol%),
2. MeMgBr, EtOH
31 examples
68-98% yields
dr 85:15 to 99:1
ee 80 to 99%

2.4 Experimental Section

2.4.1 Preparation of Substrates and Precursors

Substrate 2.46 was prepared based on the procedures below. Substrate 2.16 was prepared in a similar manner as 2.46.

The α-ketoesters 2.55 were prepared according to literatures procedures.$^{27}$
3-(2-bromoacetyl)-4,4-dimethyloxazolidin-2-one (2.64)

4,4-Dimethyloxazolidin-2-one (1.15 g, 10 mmol) was added to a suspension of sodium hydride (0.24 g, 10 mmol) in THF (100 mL) and the mixture was stirred at room temperature for 8 h. After cooling to 0 °C, bromoacetyl bromide (0.965 mL, 11 mmol) was added to the mixture and the stirring was continued for 1.5 h at the same temperature. The mixture was diluted with saturated aqueous potassium dihydrogen phosphate solution and extracted with EtOAc. The combined extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (Hexane/EtOAc 4:1 to 2:1 v:v) to give as a pale yellow solid 2.64 (1.77 g, 75% yield). mp 55-57 °C (EtOAc/Hexane); Rf 0.70 (Hexane/EtOAc 1:1 v:v); IR (KBr) 3007, 2977, 1772, 1718, 1489, 1459, 1397, 1320, 1101, 964, 891, 763, 669 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.49 (s, 2H), 4.08 (s, 2H), 1.58 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 166.8, 153.8, 75.8, 61.0, 30.4, 24.7; m/z (CI-MS) 236(⁷⁹Br), 238(⁸¹Br) [MH]+.

3-(2-azidoacetyl)-4,4-dimethyloxazolidin-2-one (2.65)

Sodium azide (15.60 g, 0.24 mol) was added to a solution of the bromoimide 2.64 (14.16 g, 0.06 mol) in DMSO (100 mL) at room temperature. The reaction mixture was stirred for 1 h and diluted with 250 mL water. The resulting mixture was extracted with
EtOAc (4 x 200 mL). The organic layer was combined, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. Colorless crystals 2.65 (10.94 g, 92% yield) were obtained by flash chromatography (Hexane/EtOAc 4:1 to 2:1 v:v). mp 34-35 °C (EtOAc/Hexane); Rf 0.64 (Hexane/EtOAc 1:1 v:v); IR (KBr) 3008, 2980, 2947, 2114, 1781, 1709, 1383, 1368, 1312, 1291, 1243, 1179, 1103, 1035, 910, 766, 708 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.35 (s, 2H), 4.03 (s, 2H), 1.54 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 168.6, 153.8, 75.9, 60.7, 53.4, 24.6; m/z (CI-MS) 199 [MH]$^+$.  

3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one (2.46)$^{9a,10}$

\[
\begin{align*}
2.65 & \xrightarrow{\text{PPh}_3, \text{CS}_2, \text{THF}} \text{SCN} \\
2.46 & \end{align*}
\]

Triphenylphosphine (18.37 g, 70.0 mmol) was added to a solution of the azidoimide 2.65 (12.62 g, 63.7 mmol) in THF (80 mL) and CS$_2$ (80 mL) in a 1000 mL round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After concentration under reduced pressure, the residue was purified by flash chromatography (CH$_2$Cl$_2$/Hexane 1:1 v:v to CH$_2$Cl$_2$) to yield 2.46 as a white solid (10.23 g, 75% yield). mp 106-108 °C (CH$_2$Cl$_2$/Hexane); Rf 0.57 (Hexane/EtOAc 1:1 v:v); IR (KBr) 2978, 2256, 2048, 1776, 1720, 1397, 1378, 1363, 1311, 1249, 1187, 1091, 1024, 930, 767, 699 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.78 (s, 2H), 4.12 (s, 2H), 1.63 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.3, 153.9, 139.5, 76.4, 61.2, 50.5, 25.0; m/z (ESI-MS) 215.0 [M+H]$^+$, 237.1 [MNa]$^+$.  

The title compound was further characterized by X-ray crystallography.
2.4.2 Preparation of Catalysts

The catalysts 2.23-2.31, 2.34, 2.37, 2.57 and 2.58 were prepared according to literature methods.¹⁸a, ¹⁸b, ¹⁸f, ¹⁸g, ²⁹

1-(4-nitrophenyl)-3-((1R,2R)-2-(pyrrolidin-1-yl)cyclohexyl)thiourea (2.39)

1-Isothiocyanato-4-nitrobenzene (1.13 g, 6.24 mmol, 1.0 equiv) was added to a solution of (1R,2R)-2-(pyrrolidin-1-yl)cyclohexanamine³⁰ (1.05 g, 6.24 mmol, 1.0 equiv) in dichloromethane (25 mL) at room temperature. The resulting solution was stirred overnight, then concentrated to ~4 mL in vacuo and loaded onto a silica gel column directly and chromatographed (EtOAc:MeOH:NH₄OH=100:15:1 to 100:20:1) to afford 1-(4-nitrophenyl)-3-((1R,2R)-2-(pyrrolidin-1-yl)cyclohexyl)thiourea (1.84 g, 85% yield) as
an orange solid. mp 80-82 °C (EtOAc/Hexane); Rf 0.15 (MeOH/EtOAc 1:1 v/v); $[\alpha]_D^{20} = 12.0^\circ$ (c 1.0, CH$_2$Cl$_2$); IR (KBr) 3221, 2931, 2856, 1596, 1507, 1330, 1252, 1176, 1110, 850, 748 cm$^{-1}$; $^1$H NMR (500 MHz, (CD$_3$)SO) δ 10.07 (s, 1H), 8.38 (d, $J = 7.5$ Hz, 1H), 8.14 (d, $J = 9.2$ Hz, 2H), 7.82 (d, $J = 9.2$ Hz, 2H), 4.18(br, 1H), 2.53-2.86 (comp, 5H), 2.15 (app d, $J = 8.9$ Hz, 1H), 1.81 (app d, $J = 11.5$ Hz, 1H), 1.65-1.78 (comp, 5H), 1.56-1.65 (m, 1H), 1.15-1.46 (comp, 4H); $^{13}$C NMR (125 MHz, (CD$_3$)$_2$SO) δ 178.5, 146.6, 141.3, 124.6, 119.4, 60.5, 55.8, 47.2, 30.4, 23.9, 23.7, 23.5, 22.4; m/z (ESI-MS) 349.2 [MH]$^+$. 

The catalysts 2.38, 2.40, 2.43-2.45 and 2.59-2.60 were prepared in a similar manner as 2.39.

### 2.4.3 General Procedure for the Catalytic Aldol Reaction Between 2.46 and Aldehyde

Catalyst 2.39 (17.5 mg, 0.05 mmol), 3-(2-isothiocyanatoacetyl)-4,4-dimethylloxazolidin-2-one 2.46 (214 mg, 1.00 mmol) and the corresponding aldehyde (1.20 mmol) were dissolved in toluene (6.67 mL) at room temperature. The reaction progress was monitored by TLC analysis. Upon consumption of 2.46, the crude reaction mixture was applied to silica gel and the mixture of diastereomers were obtained by flash chromatography (CH$_2$Cl$_2$/EtOAc 100:2 v/v).

The mixture of diastereomers was dissolved in dry THF (20 mL) and cooled to 0 °C. A solution of methyl magnesium chloride (1.2 eq., 3M in THF) in ethanol (8 mL) at 0 °C was added via syringe. After 3 min the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (8 mL). The mixture was concentrated in vacuo, taken up in
aqueous HCl (1M, 16 mL) and CH₂Cl₂ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The organic portions were combined, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH₂Cl₂/EtOAc 100:2 v/v) to obtain the corresponding ethyl ester as a solid or an oil.

The absolute configuration of the 3-methoxy benzaldehyde adduct 2.66h was established by X-ray crystallography; the remaining adducts are assigned by analogy or compared with the optical rotations in the literature.¹⁰

2.4.4 General Procedure for Catalytic Aldol reaction between isothiocyanates and α-ketoesters

α-Keto esters and catalyst were dissolved in anhydrous methyl t-butyl ether. The reaction progress was monitored by TLC analysis. Upon consumption of the α-ketoesters the solvent was removed in vacuo and applied to silica gel to separate the diastereomers.

The absolute configuration of 2.56e was established by X-Ray Crystallography; the remaining adducts were assigned by analogy.

2.4.5 Preparation Procedures for Racemic Samples

Racemic compounds were prepared either by using DABCO/toluene or the literature method.³¹

2.4.6 Product Characterization Data
4,4-dimethyl-3-((4R,5S)-5-phenyl-2-thioxooxazolidine-4-carbonyl)oxazolidin-2-one

(2.47): Following the general procedure, compound 2.47 was obtained as white crystals in 99% yield (318 mg). mp 154-156 °C (EtOAc/Hexane); Rf 0.32 (CH₂Cl₂/EtOAc 50:1 v/v); [α]D²⁰ = -77.2° (c 1.0, CH₂Cl₂); IR (KBr) 3374, 3017, 2978, 2934, 1779, 1686, 1487, 1376, 1339, 1250, 1178, 1099, 1026, 951 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78 (br, s, 1H), 7.45-7.35 (comp, 5H), 6.31 (d, J = 5.0 Hz, 1H), 5.10 (d, J = 5.0 Hz, 1H), 4.17 (d, J = 8.5 Hz, 1H), 4.12 (d, J = 8.5 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.1, 167.2, 154.5, 137.0, 129.8, 129.3, 126.3, 84.6, 76.4, 66.4, 61.7, 24.8, 24.5; m/z (ESI-MS) 321.1 [MH⁺].

(4R,5S)-ethyl 5-phenyl-2-thioxooxazolidine-4-carboxylate (2.35): Following the general procedure, compound 2.35 was obtained as a colorless oil in 89% yield (224 mg). Rf 0.33 (CH₂Cl₂/EtOAc 100:2 v/v); (R,S) [α]D²⁰ = -43.5° (c 1.0, CH₂Cl₂, 93% ee); (4S,5R) Lit.³ [α]D²¹ = +44° (c 1.0, CH₂Cl₂, 90% ee); IR (neat) 3318, 2982, 2359, 1741, 1497, 1370, 1236, 1172, 1096 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (br, s, 1H), 7.46-7.33 (comp, 5H), 5.96 (d, J = 6.0 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 4.32 (comp, 2H), 1.34 (app t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.2, 168.2, 137.0, 129.7, 129.4, 125.8, 85.8, 64.8, 63.2, 14.3.; m/z (ESI-MS)
(4R,5S)-ethyl 5-(4-nitrophenyl)-2-thioxooxazolidine-4-carboxylate (2.66a): Following the general procedure, the title compound was obtained as a pale yellow solid in 80% yield (237 mg). mp 129-130 °C (EtOAc/Hexane); Rf 0.19 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D₂⁰⁺6.5⁰ (c 1.0, CH₂Cl₂, 93% ee); IR (KBr) 3320, 3183, 2984, 1750, 1724, 1602, 1506, 1525, 1352, 1321, 1241, 1186, 1171, 1104, 1026, 983, 853, 843 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, J = 8.7 Hz, 2H), 8.13 (br, s, 1H), 7.63 (d, J = 8.7 Hz, 2H), 6.08 (d, J = 6.2 Hz, 1H), 4.47 (d, J = 6.2 Hz, 1H), 4.43-4.29 (comp, 2H), 1.37 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.7, 167.7, 148.7, 143.8, 126.7, 124.6, 84.1, 64.6, 63.6, 14.3; m/z (ESI-MS) 297.1 [MH]⁺, 319.1 [MNa]⁺; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=13.4 min and t_R=21.6 min (major).

(4R,5S)-ethyl 5-(4-bromophenyl)-2-thioxooxazolidine-4-carboxylate (2.66b): Following the general procedure, the title compound was obtained as a colorless oil in 74% yield (240 mg). Rf 0.29 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D₂⁰⁻22.5⁰ (c 1.0, CH₂Cl₂, 94% ee); IR (neat) 3180, 2982, 1736, 1594, 1491, 1370, 1236, 1072, 1011, 923, 823, 736, 576, 512 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br, s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.92 (d, J = 6.2 Hz, 1H), 4.44 (d, J = 6.2 Hz, 1H), 4.40-4.23 (comp, 2H), 1.34 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.9, 167.9, 136.0, 132.6, 127.5, 124.0, 85.0, 64.7, 63.3, 14.3; m/z (ESI-MS) 329.9(⁷⁹Br), 332.0(⁸¹Br) [MH]⁺; HPLC: Daicel Chiralpak AS-H, n-
hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=27.1 min and $t_R$=45.2 min (major).

(4R,5S)-ethyl 5-(4-fluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66c):

Following the general procedure, the title compound was obtained as a colorless oil in 82% yield (221 mg). Rf 0.36 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –21.0° (c 1.0, CH$_2$Cl$_2$, 94% ee); IR (neat) 3187, 2984, 1743, 1607, 1512, 1370, 1228, 1157, 1100, 1014, 955, 921, 837, 587, 534 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.04 (br, s, 1H), 7.40 (dd, $J$ = 5.1, 8.7 Hz, 2H), 7.12 (app t, $J$ = 8.7 Hz, 2H), 5.94 (d, $J$ = 6.2 Hz, 1H), 4.46 (d, $J$ = 6.2 Hz, 1H), 4.41-4.24 (comp, 2H), 1.34 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.0, 168.0, 163.5 (d, $J_{C-F}$ = 249.3 Hz), 132.8 (d, $J_{C-F}$ = 3.3 Hz), 128.0 (d, $J_{C-F}$ = 8.5 Hz), 116.4 (d, $J_{C-F}$ = 21.9 Hz), 85.2, 64.8, 63.3, 14.3; m/z (ESI-MS) 270.0 [MH]$^+$, 292.0 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=19.2 min and $t_R$=31.6 min (major).

(4R,5S)-ethyl 5-(4-methoxyphenyl)-2-thioxooxazolidine-4-carboxylate (2.66d):

Following the general procedure, the title compound was obtained as a pale yellow oil in 60% yield (168 mg). Rf 0.18 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –57.0° (c 1.0, CH$_2$Cl$_2$, 96% ee); (4S,5R) Lit.$^3$ $[\alpha]_D^{21}$ +49° (c 1.0, CH$_2$Cl$_2$, 86% ee); IR (neat) 3188, 2981, 1743, 1613, 1516, 1370, 1233, 1168, 1115, 1028, 949, 918, 832, 591 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (br, s, 1H), 7.33 (d, $J$ = 8.7 Hz, 2H), 6.94 (d, $J$ = 8.7 Hz, 2H), 5.90 (d, $J$ = 6.3 Hz, 1H), 4.48 (d, $J$ = 6.3 Hz, 1H), 4.39-4.15 (comp, 2H), 3.82 (s, 3H), 1.33 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.2, 168.2, 160.8, 128.8, 127.7, 114.7, 86.0, 64.7, 63.1, 55.6, 14.3; m/z
(ESI-MS) 282.1 [MH]$^+$, 304.1 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, $n$-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=28.7 min and $t_R$=51.3 min (major).

(4R,5S)-ethyl 5-(4-methylphenyl)-2-thioxooxazolidine-4-carboxylate (2.66e):

Following the general procedure, the title compound was obtained as a colorless oil in 80% yield (212mg). Rf 0.32 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –38.0° (c 1.0, CH$_2$Cl$_2$, 94% ee); (4S,5R) Lit.$^3$ $[\alpha]_D^{21}$ +32° (c 1.0, CH$_2$Cl$_2$, 92% ee); IR (neat) 3310, 2982, 1742, 1674, 1504, 1371, 1170, 1097, 1020, 956, 816, 590, 513 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.23 (br, s, 1H), 7.29 (d, $J$ = 8.1 Hz, 2H), 7.22 (d, $J$ = 8.1 Hz, 2H), 5.91 (d, $J$ = 6.2 Hz, 1H), 4.48 (d, $J$ = 6.2 Hz, 1H), 4.37-4.23 (comp, 2H), 2.36 (s, 3H), 1.33 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.2, 168.2, 139.8, 134.0, 130.0, 126.0, 86.0, 64.8, 63.1, 21.4, 14.3; m/z (ESI-MS) 266.0 [MH]$^+$, 288.0 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, $n$-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=17.1 min and $t_R$=29.0 min (major).

(4R,5S)-ethyl 5-(3-bromophenyl)-2-thioxooxazolidine-4-carboxylate (2.66f):

Following the general procedure, the title compound was obtained as a colorless oil in 70% yield (231mg). Rf 0.31 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –9.5° (c 1.0, CH$_2$Cl$_2$, 92% ee); IR (neat) 3180, 2982, 1743, 1598, 1573, 1502, 1370, 1235, 1095, 1017, 918, 878, 787, 694, 573 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (br, s, 1H), 7.62-7.50 (comp, 2H), 7.38-7.28 (comp, 2H), 5.93 (d, $J$ = 6.2 Hz, 1H), 4.46 (d, $J$ = 6.2 Hz, 1H), 4.40-4.27 (comp, 2H), 1.36 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.9, 167.8, 139.2, 132.9, 131.0, 128.9, 124.4, 123.4, 84.7, 64.7, 63.4, 14.3; m/z (ESI-MS) 330.0($^{79}$Br), 331.9($^{81}$Br) [MH]$^+$; HPLC:
Daicel Chiralpak AS-H, n-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, 
$\text{t}_R=23.9$ min and $\text{t}_R=40.7$ min (major).

**5-(3-methylphenyl)-2-thioxooxazolidine-4-carboxylate (2.66g):**

Following the general procedure, the title compound was obtained as a colorless oil in 74% yield (196 mg). Rf 0.38 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); (R,S) $[\alpha]_D^{20}$ –25.5° (c 1.0, CH$_2$Cl$_2$, 93% ee); (4S,5R) Lit.\(^3\) $[\alpha]_D^{21}$ +25° (c 1.0, CH$_2$Cl$_2$, 86% ee); IR (neat) 3319, 2982, 2838, 1743, 1603, 1494, 1370, 130.5, 129.2, 126.4, 122.9, 85.9, 64.8, 63.2, 21.6, 14.3; $m/z$ (ESI-MS) 266.1 [MH]$^+$, 288.1 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $\text{t}_R=13.7$ min and $\text{t}_R=23.8$ min (major).

**5-(3-methoxyphenyl)-2-thioxooxazolidine-4-carboxylate (2.66h):**

Following the general procedure, the title compound was obtained as colorless crystals in 70% yield (196 mg). mp 78-79 °C (EtOAc:Hexane); Rf 0.25 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –33.0° (c 1.0, CH$_2$Cl$_2$, 92% ee); IR (KBr) 3300, 2981, 2838, 1743, 1603, 1494, 1370, 1233, 1096, 1038, 923, 859, 787, 734, 696, 559 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.07 (br, s, 1H), 7.33 (app t, $J=7.8$ Hz, 1H), 6.98 (app d, $J=7.8$ Hz, 1H), 6.95-6.90 (comp, 2H), 5.93 (d, $J=6.0$ Hz, 1H), 4.48 (d, $J=6.0$ Hz, 1H), 4.39-4.26 (comp, 2H), 3.82 (s, 3H), 1.35 (app t, $J=7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 189.1, 168.1, 160.3, 138.5, 130.5, 117.9,
115.2, 111.3, 85.6, 64.8, 63.2, 55.6, 14.3; m/z (ESI-MS) 282.1 [MH]+, 304.1 [MNa]⁺; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, tᵣ=20.3 min and tᵣ=38.4 min (major).

The title compound was further characterized by X-ray crystallography.

**Figure 2.2 Crystal Structure of Compound 2.66h**

(4R,5S)-ethyl 5-(2-nitrophenyl)-2-thioxooxazolidine-4-carboxylate (2.66i): Following the general procedure, the title compound was obtained as a colorless oil in 81% yield (241 mg). Rf 0.27 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D ²⁰ - 50.1° (c 1.0, CHCl₃, 90% ee); IR (neat) 3372, 1744, 1612, 1527, 1500, 1347, 1244, 1195, 1169, 1072, 1029, 973, 856 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.58 (br, s, 1H), 8.19 (app d, J = 7.7 Hz, 1H), 7.76 (app t, J = 7.7 Hz, 1H), 7.67 (app d, J = 7.7 Hz, 1H), 7.60 (app t, J = 7.7 Hz, 1H), 6.63 (d, J = 4.0 Hz, 1H), 4.43 (d, J = 4.0 Hz, 1H), 4.34 (comp, 2H), 1.33 (app t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.1, 167.9, 136.0, 135.2, 129.2, 128.9, 127.2, 123.0, 85.7, 63.1, 62.9, 14.3; m/z (ESI-MS) 319.1 [MNa]⁺; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH=95/5, Flow rate = 1 mL/min, UV = 254 nm, tᵣ=48.4 min and tᵣ=51.8 min (major).
(4R,5S)-ethyl 5-(2-chlorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66j):

Following the general procedure, the title compound was obtained as a colorless oil in 68% yield (194 mg). Rf 0.35 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20} +17.0^\circ$ (c 1.0, CH$_2$Cl$_2$, 93% ee); IR (neat) 3182, 2982, 1746, 1504, 1445, 1371, 1204, 1172, 1036, 973, 758, 613, 572 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.92 (br, s, 1H), 7.50-7.40 (comp, 2H), 7.40-7.32 (comp, 2H), 6.36 (d, $J$ = 4.6 Hz, 1H), 4.47 (d, $J$ = 4.6 Hz, 1H), 4.40-4.25 (comp, 2H), 1.34 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 189.4, 167.9, 134.4, 131.9, 130.9, 130.4, 127.8, 127.7, 83.2, 64.0, 63.2, 14.3; m/z (ESI-MS) 286.0$^{(35\text{Cl})}$, 288.0$^{(37\text{Cl})}$ [MH]$^{+}$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=16.3 min and $t_R$=28.2 min (major).

(4R,5S)-ethyl 5-(2-fluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66k):

Following the general procedure, the title compound was obtained as a white solid in 62% yield (167 mg). mp 58-59 $^\circ$C (EtOAc/Hexane); Rf 0.28 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20} -41.0^\circ$ (c 1.0, CH$_2$Cl$_2$, 90% ee); IR (KBr) 3313, 2975, 1748, 1614, 1587, 1494, 1365, 1222, 1187, 1168, 1096, 1019, 982, 928, 863, 765, 575 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (br, s, 1H), 7.51-7.33 (comp, 2H), 7.25-7.19 (m, 1H), 7.17-7.09 (m, 1H), 6.19 (d, $J$ = 5.8 Hz, 1H), 4.55 (d, $J$ = 5.8 Hz, 1H), 4.41-4.18 (comp, 2H), 1.33 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 189.0, 167.9, 160.1 (d, $J_{C,F} = 249.2$ Hz), 131.8 (d, $J_{C,F} = 8.4$ Hz), 128.1 (d, $J_{C,F} = 3.0$ Hz), 125.1 (d, $J_{C,F} = 3.7$ Hz), 124.1 (d, $J_{C,F} = 12.4$ Hz), 116.3 (d, $J_{C,F} = 20.5$ Hz), 81.2 (d, $J_{C,F} = 3.0$ Hz), 63.9 (d, $J_{C,F} = 1.6$ Hz), 63.2, 14.2; m/z (ESI-MS) 270.0 [MH]$^+$, 292.1 [MNa]$^+$;
HPLC: Daicel Chiralpak AS-H, \textit{n}-hexane/\textit{i}-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \( t_R=16.7 \text{ min and } t_R=25.1 \text{ min (major).} \\

\textbf{(4R,5S)-ethyl 5-(2-methylphenyl)-2-thioxooxazolidine-4-carboxylate (2.66l):}\\

\begin{center}
\includegraphics[width=0.2\textwidth]{structure1}
\end{center}

Following the general procedure, the title compound was obtained as a colorless oil in 49% yield (130 mg). Rf 0.26 (CH\(_2\)Cl\(_2\)/EtOAc 100:2 v/v); \((R,S) [\alpha]_D^{20} = -24.0^\circ \text{ (c 1.0, CH}_2\text{Cl}_2, 90\% \text{ ee}); (4S,5R) \text{ Lit.}^3 [\alpha]_D^{21} \text{ +12.5}^\circ \text{ (c 1.0, CH}_2\text{Cl}_2, 89\% \text{ ee); IR (neat) 3310, 2981, 1743, 1495, 1369, 1217, 1181, 1171, 1092, 1023, 968, 760, 617, 576 cm}^{-1}; ^1\text{H} \text{ NMR (500 MHz, CDCl}_3) \delta 7.97 \text{ (br, s, 1H), 7.51-7.01 (comp, 4H), 6.22 (d, } J = 5.2 \text{ Hz, 1H), 4.44 (d, } J = 5.2 \text{ Hz, 1H), 4.39-4.25 \text{ (comp, 2H), 2.41 (s, 3H), 1.34 (app t, } J = 7.1 \text{ Hz, 3H); ^13\text{C} \text{ NMR (125 MHz, CDCl}_3) \delta 189.4, 168.3, 135.3, 134.9, 131.3, 129.7, 127.1, 125.9, 83.7, 64.2, 63.2, 19.3, 14.3; m/z (ESI-MS) 266.1, [MH]^+, 288.1 [MNa]^+; HPLC: Daicel Chiralpak AS-H, \textit{n}-hexane/\textit{i}-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \( t_R=16.9 \text{ min and } t_R=27.1 \text{ min (major).} \\

\textbf{(4R,5S)-ethyl 5-(naphthalen-1-yl)-2-thioxooxazolidine-4-carboxylate (2.66m):}\\

\begin{center}
\includegraphics[width=0.2\textwidth]{structure2}
\end{center}

Following the general procedure, the title compound was obtained as a yellow oil in 47% yield (141 mg). Rf 0.31 (CH\(_2\)Cl\(_2\)/EtOAc 100:2 v/v); \([\alpha]_D^{20} = -46.5^\circ \text{ (c 1.0, CH}_2\text{Cl}_2, 94\% \text{ ee); IR (neat) 3300, 2982, 1740, 1499, 1371, 1231, 1180, 1089, 1020, 965, 860, 776, 735 \text{ cm}^{-1}; ^1\text{H} \text{ NMR (500 MHz, CDCl}_3) \delta 8.06 \text{ (app d, } J = 8.3 \text{ Hz, 1H), 7.96-7.86 \text{ (comp, 2H), 7.76 \text{ (br, s, 1H), 7.65-7.45 \text{ (comp, 4H), 6.79 \text{ (d, } J = 4.1 \text{ Hz, 1H), 4.51 \text{ (d, } J = 4.1 \text{ Hz, 1H), 4.46-4.33 \text{ (comp, 2H), 1.40 \text{ (app t, } J = 7.1 \text{ Hz, 3H); ^13\text{C} \text{ NMR (125 MHz, CDCl}_3) \delta 189.6, 168.5, 134.1, 132.0, 130.2, 129.5, 129.4, 127.4, 126.5, 125.6, 123.6, 122.4, 83.9, 64.2, 63.4, 14.3; m/z (ESI-MS) 2661, [MH]^+, 2881 [MNa]^+; HPLC: Daicel Chiralpak AS-H, \textit{n}-hexane/\textit{i}-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \( t_R=16.9 \text{ min and } t_R=27.1 \text{ min (major).} \)
MS) 302.0 [MH]$^+$, 324.1 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, $n$-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=23.1 min and $t_R$=56.2 min (major).

(4R,5S)-ethyl 5-(naphthalen-2-yl)-2-thioxooxazolidine-4-carboxylate (2.66n):

Following the general procedure, the title compound was obtained as a yellow solid in 83% yield (250 mg). mp 104-106 °C (EtOAc:Hexane); Rf 0.28 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); (R,S) [α]$_D$+20 – 40.0° (c 1.0, CH$_2$Cl$_2$, 91% ee); (4S,5R) Lit. 3 [α]$_D$+46° (c 1.0, CH$_2$Cl$_2$, 87% ee); IR (KBr) 3299, 2989, 1746, 1602, 1500, 1340, 1228, 1178, 1194, 1019, 928, 859, 817, 751 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.97-7.81 (comp, 5H), 7.59-7.51 (comp, 2H), 7.47 (comp, 2H), 6.14 (d, $J$ = 6.0 Hz, 1H), 4.56 (d, $J$ = 6.0 Hz, 1H), 4.42-4.29 (comp, 2H), 1.37 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.2, 168.2, 134.1, 133.8, 133.2, 129.7, 128.5, 128.0, 127.3, 127.1, 125.6, 122.6, 86.1, 64.7, 63.3, 14.4; m/z (ESI-MS) 302.0 [MH]$^+$, 324.1 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, $n$-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=29.7 min and $t_R$=49.8 min (major).

(4R,5R)-ethyl 5-(thiophen-2-yl)-2-thioxooxazolidine-4-carboxylate (2.66o):

Following the general procedure, the title compound was obtained as a colorless oil in 65% yield (167 mg). Rf 0.32 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); [α]$_D$–102.0° (c 1.0, CH$_2$Cl$_2$, 91% ee); IR (neat) 3317, 2982, 1743, 1672, 1501, 1370, 1195, 1097, 1020, 919, 856, 712 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.20 (br, s, 1H), 7.41 (dd, $J$ = 1.2, 5.1 Hz, 1H), 7.22 (app d, $J$ = 3.5 Hz, 1H), 7.04 (dd, $J$ = 3.5, 5.1 Hz, 1H), 6.18 (d, $J$ = 6.2 Hz, 1H), 4.65 (d, $J$ = 6.2 Hz, 1H), 4.42-4.21 (comp, 2H), 1.32 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.4, 167.6, 138.5, 127.8, 127.6, 127.5, 81.9, 64.6, 63.3, 14.3; m/z (ESI-MS) 257.9 [MH]$^+$, 280.0 [MNa]$^+$; HPLC: Daicel Chiralpak AS-H, $n$-:
hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t<sub>R</sub>=27.8 min and t<sub>R</sub>=43.9 min (major).

(4R,5S)-ethyl 5-(perfluorophenyl)-2-thioxooxazolidine-4-carboxylate (2.66p):

Following the general procedure, the title compound was obtained as a yellow oil in 66% yield (225 mg). Rf 0.39 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 100:2 v/v); [α]_<sub>D</sub><sup>20</sup> = -41.8° (c 1.0, CHCl<sub>3</sub>, 90% ee); IR (neat) 3316, 2989, 1747, 1658, 1513, 1372, 1242, 1175, 1136, 946 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.72 (br, s, 1H), 6.23 (d, J = 7.7 Hz, 1H), 4.74 (d, J = 7.7 Hz, 1H), 4.37-4.22 (comp, 2H), 1.30 (app t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 188.1, 167.2, 146.9-144.5 (m), 144.0-141.6 (m), 139.2-136.7(m), 110.2-109.8 (m), 75.3, 63.5, 62.5, 14.0; m/z (ESI-MS) 342.1 [MH]<sup>+</sup>; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t<sub>R</sub>=15.6 min (major) and t<sub>R</sub>=25.0 min.

(4R,5S)-ethyl 5-styryl-2-thioxooxazolidine-4-carboxylate (2.66q): Following the general procedure, the title compound was obtained as a yellow solid in 73% yield (202 mg). mp 87-89 °C (EtOAc/Hexane); Rf 0.32 (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 100:2 v/v); [α]_<sub>D</sub><sup>20</sup> = -97.8° (c 1.0, CHCl<sub>3</sub>, 93% ee); IR (KBr) 3291, 2977, 1739, 1649, 1491, 1371, 1305, 1262, 1229, 1162, 1022, 983, 914, 749, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.14 (br, s, 1H), 7.43-7.27 (comp, 5H), 6.81 (d, J = 15.5 Hz, 1H), 6.28 (m, 1H), 5.55 (app t, J = 6.5, 1H) 4.42 (d, J = 6.5 Hz, 1H), 4.36-4.25 (comp, 2H), 1.33 (app t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 189.1, 168.0, 136.2, 135.1, 129.2, 128.9, 127.2, 123.0, 85.7, 63.1, 62.9, 14.3; m/z (ESI-MS) 299.9 [M+Na]<sup>+</sup>; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, t<sub>R</sub>=29.1 min and t<sub>R</sub>=48.2 min (major).
(4R,5S)-ethyl 5-phenethyl-2-thioxooxazolidine-4-carboxylate (2.66r): Following the general procedure, the title compound was obtained as a colorless oil in 54% yield (151 mg). Rf 0.30 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D₂⁰ = 100.5° (c 1.0, CHCl₃, 81% ee); IR (neat) 3316, 3026, 2981, 2934, 1742, 1602, 1499, 1455, 1370, 1216, 1097, 1019, 701, 665 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.92 (br, s, 1H), 7.33-7.27 (comp, 2H), 7.24-7.17 (comp, 3H), 4.93 (ddd, J = 11.5, 6.5, 5.0 Hz, 1H), 4.30-4.18 (comp, 3H), 2.94-2.76 (comp, 2H), 2.28-2.12 (comp, 2H), 1.28 (app t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.3, 168.2, 139.9, 128.8, 128.6, 126.6, 84.8, 63.0, 62.3, 36.7, 30.8, 14.2; m/z (ESI-MS) 280.1 [MH]+; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, tR=10.9 min and tR=17.9 min (major).

(4R,5S)-ethyl 5-butyl-2-thioxooxazolidine-4-carboxylate (2.66s): Following the general procedure, the title compound was obtained as a colorless oil in 44% yield (102 mg). Rf 0.31 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D₂⁰ = -38.8° (c 1.0, CH₂Cl₂, 82% ee); IR (neat) 3428, 3176, 3053, 2962, 2874, 2305, 1747, 1490, 1371, 1266, 1079, 1024, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.05 (br, s, 1H), 4.93 (m, 1H), 4.32-4.22 (comp, 2H), 4.21 (d, J = 6.5 Hz, 1H), 1.94-1.77 (comp, 2H), 1.57-1.34 (comp, 4H), 1.30 (app t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 189.3, 168.5, 85.7, 62.9, 62.3, 34.7, 26.5, 22.3, 14.2, 14.0; m/z (ESI-MS) 232.1 [MH]+; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH=85/15, Flow rate = 1 mL/min, UV = 254 nm, tR=16.1 min and tR=23.8 min (major).
**Rac-cis-ethyl 3-(2-ethoxy-2-oxoethylcarbamothioyl)-5-phenyl-2-thioxooxazolidine-4-carboxylate (cis-2.36):** The mixture of cis-2.36 and trans-2.36 was prepared from 1a and benzaldehyde using 10 mol% DABCO as catalyst in toluene (0.1 M). The mixture of diastereomers was obtained by flash chromatography (EtOAc/Heane 10:90 v:v). cis-2.36 was obtained as colorless crystals from recrystallization(CH₂Cl₂/Hexane). Rf 0.65 (CH₂Cl₂/EtOAc 100:2 v:v); mp 139-140°C (CH₂Cl₂/Hexane); IR (KBr) 3092, 2995, 2937, 1752, 1743, 1534, 1443, 1422, 1372, 1344, 1317, 1281, 1243, 1205, 1178, 1046, 1019, 933, 895, 753, 699, 677, 592 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 12.25 (s, 1H), 7.43-7.28 (m, 3H), 7.38-7.32 (m, 2H), 6.00 (d, J = 9.1 Hz, 1H), 5.91 (d, J = 9.1 Hz, 1H), 4.47 (dd, J = 4.5, 18.8 Hz, 1H), 4.37 (dd, J = 4.5, 18.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.81 (dq, J = 7.2, 10.7 Hz, 1H), 3.62 (dq, J = 7.2, 10.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 0.80 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 183.4, 178.0, 168.1, 166.0, 131.5, 130.0, 128.8, 126.8, 81.3, 69.3, 62.13, 62.12, 48.7, 14.4, 13.6; m/z (ESI-MS) 396.9 [MH]+, 419.0 [MNa]+.

* cis-2.36 was further characterized by X-ray crystallography.*
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-phenyl-2-thioxo-
oxazolidine-5-carboxylate (2.56a): mp : 172 –173 °C

(EtOAc/CH₂Cl₂); Rf 0.3 (EtOAc/CH₂Cl₂ 19:1 v/v); [α]D²⁰ -9.5 (c 1.0, CHCl₃, 95% ee); IR (KBr) 3334, 2970, 2932, 1814, 1783, 1740, 1681, 1506, 1473, 1451, 1387, 1339, 1300 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.67 – 7.69 (d, J = 8.1, 2H), 7.58 (br, s, 1H), 7.38 – 7.44 (comp, 3H), 5.93 (s, 1H), 4.20 – 4.26 (m, 1H), 4.10 – 4.17 (m, 1H), 4.15 (app s, 2H), 1.63 (s, 3H), 1.61 (s, 3H), 1.22 (t, J = 7.3 MHz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 188.6, 169.1, 167.5, 154.5, 136.1, 129.9, 129.2, 125.2, 92.6, 76.2, 66.0, 64.7, 63.1, 61.6, 25.5, 24.9, 24.0, 14.0; m/z (ESI-MS) 415.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, tᵣ = 16.48 min (major) and tᵣ = 22.54 min.
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(4-methoxyphenyl)-2-thioxooxazolidine-5-carboxylate (2.56b): Yellow oil; Rf = 0.25 (EtOAc/CH₂Cl₂ 3:97 v/v); [α]D²⁰⁻15.7 (c 1.0, CHCl₃, 94% ee). IR (KBr) 3426, 1775, 1736, 1704, 1646, 1610, 1513, 1381, 1306, 1257 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.67 (br, s, 1H), 7.58 – 7.60 (d, J = 8.9 Hz, 2H), 6.91 – 6.93 (d, J = 8.9 Hz, 2H), 5.91 (s, 1H), 4.19 – 4.25 (m, 1H), 4.14 (comp, 3H), 3.81 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.21 (app t, J = 5.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 188.7, 169.2, 167.7, 160.8, 154.6, 128.0, 126.7, 114.6, 92.6, 76.2, 66.0, 64.7, 63.0, 61.6, 55.6, 25.6, 25.0, 24.0, 14.0; m/z (ES-IMS) 445.0 [MNa]+; HPLC: Daicel (Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, tᵣ = 20.91 min (minor), tᵣ = 23.35 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxo-5-(p-tolyl)oxazolidine-5-carboxylate (2.56c): Yellow oil; Rf 0.25 (EtOAc/CH₂Cl₂ 3:97 v/v); [α]D²⁰⁻22.0 (c 1.0, CHCl₃, 92% ee); IR (KBr) 3441, 1775, 1703, 1646, 1495, 1381, 1303, 1275, 1238, 1201 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.56 (d, J = 4.1 Hz, 2H), 7.22 (d, J = 7.2 Hz, 2H), 5.9 (s, 1H), 4.19 – 4.26 (m, 1H), 4.10 – 4.17 (comp, 3H), 2.35 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 188.7, 169.2, 167.6, 154.5, 140, 133.2, 129.9, 125.1, 92.7, 76.2, 66.1, 64.7, 63.1, 61.6, 25.6, 25.0, 24.0, 21.3, 14.1; m/z (ES-IMS) 429.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, tᵣ = 13.70 min (minor), tᵣ = 18.31 min.
(4R,5S)-ethyl 5-(4-bromophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56d): mp : 165-166 °C (EtOAc/CH₂Cl₂); Rf = 0.25 (EtOAc/CH₂Cl₂ 3:97 v/v); [α]D₂⁰ -15.2 (c 1.0, CHCl₃, 97% ee); IR (KBr) 3334, 2977, 2932, 1777, 1705, 1490, 1490, 1382, 1304 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.56 (app t, J = 9.9Hz, 4H), 7.43 (br, s, 1H), 4.20 – 4.26 (m, 1H), 4.12 – 4.18 (comp, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 188.5, 168.9, 167.0, 154.6, 135.3, 132.4, 127.1, 124.4, 92.2, 76.2, 65.9, 63.4, 61.7, 25.6, 24.9, 24.1, 14.0; m/z (ESI-MS) 494.9 [MNa⁺]; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 12.60 min (minor), t_R = 18.23 min.

(4R,5S)-ethyl 5-(4-chlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56e): mp : 182 – 183 °C (EtOAc/CH₂Cl₂); Rf = 0.25 (EtOAc/CH₂Cl₂ 3:97 v/v); [α]D₂⁰ -7.0 (c 1.0, CHCl₃, 98% ee); IR (KBr) 3334, 2970, 2932, 1814, 1783, 1740, 1681, 1506, 1473, 1451, 1387, 1339, 1300 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.62 – 7.64 (d, J = 8.7 Hz, 2H), 7.47 (br, s, 1H), 7.38 – 7.40 (d, J = 8.7 Hz, 2H), 5.86, (s, 1H), 4.10 – 4.27 (comp, 4H), 1.62 (s, 3H), 1.60 (s, 3H), 1.22 (app t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 188.4, 168.9, 167.2, 154.6, 136.2, 134.7, 129.5, 126.8, 92.1, 76.2, 66.1, 63.4, 61.7, 25.0, 24.0, 14.0; m/z (ESI-MS) 494.9 [MNa⁺]; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 12.05 min (minor), t_R = 17.49 min.

The title compound was further characterized by X-ray crystallography.
Figure 2.4 Crystal Structure of Compound 2.56e

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxo-5-(4-(trifluoromethyl)phenyl)oxazolidine-5-carboxylate (2.56f): mp 157 – 158 °C (EtOAc/CH$_2$Cl$_2$); Rf 0.20 (EtOAc/CH$_2$Cl$_2$ 3:97 v/v); $[\alpha]_D^{20}$ -3.1 (c 1.0, CHCl$_3$, 97% ee); IR (KBr) 3231, 2974, 2942, 2915, 2360, 1771, 1753, 1706, 1683, 1618, 1500, 1413, 1382, 1328, 1308; $^1$H NMR (500 MHz, CDCl$_3$): 7.83 – 7.85 (d, J = 8.1 Hz, 2H), 7.68 – 7.72 (comp, 3H), 5.92 (s, 1H), 4.20 – 4.27 (m, 1H), 4.13 – 4.18 (comp, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.0, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 188.5, 168.8, 166.8, 154.6, 132.1 (q, $J_{C-F}$ = 32.5 Hz), 126.2 (q, $J_{C-F}$ = 3.7 Hz), 125.0, 122.8, 92.1, 77.5, 77.3, 77.0, 76.2, 66.0, 63.6 61.7, 24.8, 24.1, 14.0; m/z (ESI-MS) 483.2 [MNa]+; HPLC: Daicel
(Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 8.63 min (minor), t_R = 11.42 min.

(4R,5S)-ethyl 5-(4-(tert-butyl)phenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56g): mp 182 – 183 °C (EtOAc/CHCl_3); Rf 0.25 (EtOAc/CHCl_3 2:98 v/v); [α]_D^20 -17.7 (c 1.0, CHCl_3, 96% ee); IR (KBr) 3378, 2966, 2870, 1778, 1737, 1708, 1491, 1382, 1304, 1273, 1238, 1175, 1098, 1067, 1033, 927, 762, 711, 671, 564 cm⁻¹; ^1H NMR (500 MHz, CDCl_3) δ 7.74 (br, s, 1H), 7.58, (d, J = 4.1 Hz, 2H), 7.42, (d, J = 4.1 Hz, 2H), 5.93 (s, 1H), 4.20 – 4.28 (m, 1H), 4.08 – 4.18 (comp, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.30 (app s, 9H), 1.23 (app t, J = 7.1 Hz, 3H); ^13C NMR (125 MHz, CDCl_3) δ 188.7, 169.1, 167.6, 154.5, 153.0133.1, 126.3, 124.9, 92.6, 76.2, 66.1, 63.1, 61.6, 34.9, 31.4, 24.9, 24.1, 14.1; m/z (ESI-MS) 471.2 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 871 min (minor), t_R = 11.51 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(3-methoxyphenyl)-2-thioxooxazolidine-5-carboxylate (2.56h): Yellow oil; Rf 0.25 (EtOAc/CHCl_3 3:97 v/v); [α]_D^20 -22 (c 1.0 CHCl_3, 96% ee); IR (KBr) 3403, 1775, 1739, 1705, 1602, 1493, 1381, 1303, 1259 cm⁻¹; ^1H NMR (500 MHz, CDCl_3): δ 7.99 (br, s, 1H), 7.30 (app t, J = 7.3, 1H), 7.23 – 7.26 (comp, 2H), 6.90 – 6.92 (m, 1H), 4.19 – 4.26 (m, 1H), 4.09 – 4.15 (comp, 3H), 3.81 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.21 (app t, J = 7.0 Hz, 3H); ^13C-NMR(125 MHz, CDCl_3): δ 188.7, 169.1, 167.3, 160.2, 154.5, 137.7, 130.3, 117.2, 116.0, 110.5, 92.6, 76.1, 65.9, 63.2, 61.6, 24.9, 24.1, 14.1; m/z (ESI-MS) 445.2 [MNa]+; HPLC: Daicel Chiralpak AD-
H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t\textsubscript{R} = 18.78 min (major), t\textsubscript{R} = 27.54 min.

\((4R,5S)\)-ethyl 5-(3,4-dichlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56i): mp 161 – 162 °C; (EtOAc/CH\textsubscript{2}Cl\textsubscript{2}); Rf 0.25 (EtOAc/CH\textsubscript{2}Cl\textsubscript{2} 2:98 (v/v); [\alpha]\textsubscript{D}\textsuperscript{20} –9.2 (c, 1.0, CHCl\textsubscript{3}, 98% ee); IR (KBr) 3340, 2979, 2936, 1777, 1707, 1574, 1382, 1306, 1240, 1175, 1100, 1071, 1031, 925, 853, 823, 806, 763, 713, 683, 666, 635, 613, 572, 513, 441 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHZ, CDCl\textsubscript{3}) \delta 7.81 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 4.8 Hz, 1H), 7.51 (d, J = 21.5 Hz, 1H), 5.79 (s, 1H), 4.21 – 4.28 (m, 1H), 4.14 – 4.20 (comp, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 188.2, 168.6, 166.8, 154.6, 134.5, 133.7, 131.2, 127.6, 124.9, 76.3, 66.1, 63.6, 61.7, 24.8, 24.1, 14.0; m/z (ESI-MS) 483.1 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t\textsubscript{R} = 10.2 min (minor), t\textsubscript{R} = 14.3 min.

\((4R,5S)\)-ethyl 5-(3,5-difluorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56j): mp 155 – 156°C (EtOAc/CH\textsubscript{2}Cl\textsubscript{2}); Rf 0.2 (EtOAc/CH\textsubscript{2}Cl\textsubscript{2} 2:98 v/v); [\alpha]\textsubscript{D}\textsuperscript{20} –5.1 (c, 1.0, CHCl\textsubscript{3}, 97% ee); IR (KBr) 3332, 3103, 2972, 2937, 1770, 1729, 1707, 1627, 1601, 1513, 1477, 1443, 1397, 1382, 1354, 1309, 1274, 1251, 1189, 1158, 1122, 1105, 1079, 1050, 1026, 984, 942, 922, 861, 842, 761, 746, 713, 681, 668, 658, 638, 613, 599, 574, 532, 511 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHZ, CDCl\textsubscript{3}) \delta 7.8 (br, s, 1H), 7.26 (m, 1H), 6.84 (tt, J = 8.8 Hz, 1H), 5.85 (s, 1H), 4.21 – 4.28 (m, 1H), 4.10 – 4.20 (comp, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.24 (app t, J = 7.1 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 188.2,
168.5, 166.6, 164.4 (d, $J_{C-F} = 12.6$ Hz), 162.4 (d, $J_{C-F} = 12.5$ Hz) 154.6, 140.1 (t, $J_{C-F} = 9.0$ Hz), 109.1 (dd, $J_{C-F} = 7.3$ Hz), 105.5 (t, $J_{C-F} = 24.9$ Hz), 91.5, 76.3, 66.2, 63.6, 61.7, 24.9, 24.1, 14.0; m/z (ESI-MS) 451.2 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, $t_R = 10.5$ min (minor), $t_R = 12.5$ min.

(4R,5S)-ethyl 5-(2,4-dichlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56k): mp 186 – 187°C

(EtOAc/CH$_2$Cl$_2$); Rf 0.2 (EtOAc/CH$_2$Cl$_2$ 2:98 v/v); [$\alpha$]$^20_{D}$ 18.1 (c 1.0, CHCl$_3$, 93% ee); IR (KBr) 3338, 2980, 1778, 1711, 1587, 1475, 1381, 1308, 1242, 1176, 1099, 1057, 1031, 970, 924, 866, 815, 763, 710, 606, 574, 486 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62 (d, $J = 4.2$ Hz, 1H), 7.45 (d, $J = 7.4$ Hz, 1H), 7.41 (br, s, 1H), 7.34 (dd, $J = 4.2$ Hz, 1H), 6.24 (s, 1H), 4.18 – 4.26 (m, 1H), 4.10 – 4.16 (comp, 3H), 1.65 (app s, 3H), 1.60 (app s, 3H), 1.23 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.0, 167.9, 165.2, 154.3, 136.7, 132.5, 132.3, 131.6, 129.3, 128.0, 91.8, 76.1, 63.6, 63.6, 61.9, 25.0, 23.6, 14.0; m/z (ESI-MS) 483.1 [MNa]+; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, $t_R = 11.8$ min (minor), $t_R = 25.4$ min.
(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(naphthalen-2-yl)-2-oxooxazolidine-5-carboxylate (2.56l): Colorless oil; Rf 0.20 (EtOAc/CH₂Cl₂ 2:98 v/v); [α]⁺D 20 = -18.5 (c 1.0, CHCl₃, 97% ee); IR (KBr) 3332, 3103, 2972, 2937, 1770, 1729, 1707, 1627, 1601, 1513, 1477, 1443, 1397, 1382, 1354, 1309, 1274, 1251, 1189, 1158, 1122, 1105, 1079, 1050, 1026, 984, 942, 922, 861, 842, 761, 746, 713, 681, 668, 658, 638, 613m, 599, 574, 532, 511 cm⁻¹; ¹H NMR (500 MHZ, CDCl₃) δ 8.2 (br, s, 1H), 7.89 – 7.93 (comp, 2H), 7.84 – 7.85 (m, 1H), 7.76 (dd, 4.0 Hz, 1H), 7.21 (br, s, 1H), 6.0 (s, 1H), 4.22 – 4.28 (m, 1H), 4.12 – 4.20 (comp, 3H), 1.64 (s, 6H), 1.23 (app t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 188.8, 169.2, 167.4, 154.6, 133.8, 133.3, 133.0, 129.3, 129.0, 127.8, 127.4, 127.0, 125.1, 122.3, 92.8, 76.2, 65.8, 63.2, 61.7, 24.9, 24.2, 14.1; m/z (ESI-MS) 465.2 [MNa⁺]; Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/1min, UV = 254 nm, t_R = 20.0 min (minor), t_R = 26.1 min.

(4R,5S)-ethyl 5-(2-chlorophenyl)-4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-2-thioxooxazolidine-5-carboxylate (2.56m): Colorless oil, Rf 0.30 (EtOAc/CH₂Cl₂ 3:97 v/v); [α]⁺D 20 = 22.1 (c 1.0, CHCl₃, 87% ee); IR (KBr) 2980, 1774, 1710, 1506, 1382, 1309, 1248, 1176, 1097, 1030, 913, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.69 – 7.72 (m, 1H), 7.41 – 7.44 (m, 1H), 7.34 – 7.39 (comp, 2H), 6.27 (s, 1H), 4.19 – 4.27 (comp, 2H), 4.10 – 4.15 (comp, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.23 (app t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 188.2, 168.1, 165.5, 154.3, 133.7, 131.8, 131.6, 131.1, 128.2, 127.8, 76.2, 63.7, 63.4, 61.9, 25.0, 23.6, 14.0; m/z (ESI-MS) 449.3 [Mna⁺]; HPLC: Daicel Chiralpak AD-H, hexanes/i-
PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 22.91 min (minor), t_R = 31.25 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-(thiophen-2-yl)-2-thioxooxazolidine-5-carboxylate (2.56n): Pale Yellow oil; Rf 0.30 (EtOAc/CH_2Cl_2 1:19 v/v); [α]_D^{20} -44.5 (c 1.0, CHCl_3, 92% ee); IR (KBr) 3434, 1773, 1705, 1496, 1382, 1306, 1275, 1240 cm⁻¹; ¹H NMR (500 MHz, CDCl_3): 7.75 (br, s, 1H), 7.28 – 7.30 (comp, 2H), 7.2 (d, J = 1.2Hz, 1H), 5.80 (s, 1H), 4.12 – 4.25 (comp, 2H), 4.06 (app s, 2H), 1.55 (s, 3H), 1.57 (s, 3H), 1.21 (app t, J = 7.1 Hz, 3H); ¹³C-NMR (125 MHz, CDCl_3): δ 188.1, 168.1, 166.7, 154.6, 138.9, 127.6, 127.6, 126.8, 90.5, 76.3, 67.1, 63.4, 61.6, 24.9, 24.1, 14.1; m/z (ESI-MS) 420.9 [MNa]+; HPLC: (Chiracel AD-H, Hexane/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R = 28.07 min (major) and t_R = 31.19 min.

(4R,5S)-ethyl 4-(4,4-dimethyl-2-oxooxazolidine-3-carbonyl)-5-methyl-2-thioxooxazolidine-5-carboxylate (2.56o): Colorless oil; Rf 0.40 (3% EtOAc/DCM); [α]_D^{20} -17.1 (c 1.0, CHCl_3, 79% ee); IR (KBr) 3405, 2883, 1773, 1709, 1643, 1505, 1383, 1318, 1248, 1191, 1134, 1088, 1023, 942, 854, 764, 735, 711 cm⁻¹; ¹H NMR (500 MHz, CDCl_3) δ 7.61 (br, s, 1H), 5.23, (s, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.11 (app s, 2H), 1.87 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.30 (app t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl_3) δ 188.6, 168.3, 167.7, 154.8, 90.8, 76.4, 66.4, 63.0, 61.5, 24.9, 24.0, 17.1, 14.1; m/z (ESI-MS) 353.6 [MNa]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R= 8.54 min (minor) and t_R = 10.72 min.
2.4.7 Scale-up Preparation of 3-((4R,5S)-5-(4-fluoro-3-nitrophenyl)-2-thioxooxazolidine-4-carbonyl)-4,4-dimethyloxazolidin-2-one (2.51)

Catalyst 2.39 (70.0 mg, 0.20 mmol), 3-(2-isothiocyanatoacetyl)-4,4-dimethyloxazolidin-2-one 2.46 (4.28 g, 20.00 mmol) and 4-fluoro-3-nitrobenzaldehyde 2.50 (3.45 g, 20.40 mmol) were dissolved in HPLC grade toluene (200 mL) at room temperature. The mixture was stirred at the same temperature for 21 h. Pale yellow solid (7.09 g, 92% yield, 92% ee, d.r. ~17:1) was collected by simple filtration. Pure trans-product 2.51 (5.35 g, 70% overall yield, >99% ee) was obtained as white crystals by recrystallization (THF/Hexane). mp 199-200 °C (THF/Hexane); Rf 0.14 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); [α]$_D^{20}$ -32.0° (c 1.0, CH$_3$CN, 99% ee); IR (KBr) 3345, 2980, 1778, 1719, 1621, 1548, 1471, 1394, 1377, 1344, 1311, 1294, 1246, 1208, 1165, 1097, 1031, 844, 763, 598 cm$^{-1}$; $^1$H NMR (500 MHz, (CD$_3$)$_2$SO) δ 10.56(s, 1H), 8.20 (app dd, $J = 2.4, 7.1$ Hz, 1H), 7.80 (ddd, $J = 2.4, 4.1, 8.7$ Hz, 1H), 7.71(app dd, $J = 8.7, 11.2$ Hz, 1H), 6.25 (d, $J = 2.6$ Hz, 1H), 5.44 (d, $J = 2.6$ Hz, 1H), 4.28-4.12 (comp, 2H), 1.56 (s, 3H), 1.52 (s, 3H); $^{13}$C NMR (125 MHz, (CD$_3$)$_2$SO) δ 188.8, 168.5, 154.8 (d, $J_{C,F} = 263.1$ Hz), 153.8, 136.6 (d, $J_{C,F} = 7.8$ Hz), 135.4 (d, $J_{C,F} = 4.0$ Hz), 134.3 (d, $J_{C,F} = 9.5$ Hz), 124.6 (d, $J_{C,F} = 2.4$ Hz), 119.2 (d, $J_{C,F} = 21.3$ Hz), 82.3, 75.4, 64.2, 60.6, 24.0; m/z (ESI-MS) 384.1 [MH$^+$].
Following the general procedure, the title compound was obtained as a pale yellow oil. Rf 0.21 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D²⁰ +14.5° (c 1.0, CH₂Cl₂, 92% ee); IR (neat) 3304, 2986, 1747, 1623, 1596, 1540, 1527, 1351, 1235, 1172, 1087, 1014, 921, 837, 736, 547 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.23-8.10 (comp, 2H), 7.76 (ddd, J = 2.4, 4.0, 8.7 Hz, 1H), 7.40 (app dd, J = 8.7, 10.1 Hz, 1H), 6.02 (d, J = 6.6 Hz, 1H), 4.51 (d, J = 6.6 Hz, 1H), 4.45-4.28 (comp, 2H), 1.37 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 188.5, 167.5, 156.0 (d, J_C,F = 268.0 Hz), 137.8 (d, J_C,F = 8.4 Hz), 134.0 (d, J_C,F = 4.2 Hz), 133.0 (d, J_C,F = 9.0 Hz), 124.0 (d, J_C,F = 2.4 Hz), 119.8 (d, J_C,F = 21.4 Hz), 83.5, 64.6, 63.7, 14.3; m/z (ESI-MS) 315.0 [MH]+, 337.3 [MNa]+; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=12.5 min and t_R=14.2 min (major).
References


3.1 Background

3.1.1 Significance of Chiral \(\alpha,\beta\)-Diamino Acid Derivatives

*Scheme 3.1 Selected Natural Products Containing an \(\alpha,\beta\)-Diamino Acid Moiety*

Vicinal diamines are important structural motifs that have been incorporated into chiral auxiliaries, catalysts and ligands.\(^1\) \(\alpha,\beta\)-Diamino acids and their derivatives are part of many biologically active natural products (Scheme 3.1).\(^2\) For example, the polycondensation of Dab \(3.1\) and some other diamino acids are related to the prebiotic evolution of DNA and RNA genomes. In addition, capreomycins are a class of antibiotics, which have been used in the therapy of tuberculosis. Moreover, some synthetic materials derived from \(\alpha,\beta\)-diamino acids have been used in the treatment of diseases (Scheme 3.2).\(^2\) For instance, imidapril \(3.5\) is an ACE inhibitor and has been
used clinically for hypertension, chronic congestive heart failure, acute myocardial infarction and diabetic nephropathy. In addition, roxifiban 3.6, also known as DMP754, is a selective oral antagonist of the platelet glycoprotein IIb/IIIa receptor.

**Scheme 3.2 Selected Synthetic Materials Containing α,β-Diamino Acid Moiety**

3.5 imidapril

3.6 $R = \text{Me, roxifiban (DMP754)}$

3.7 $R = \text{H, XV459}$

### 3.1.2 Synthetic Methods for α,β-Diamino Acid Derivatives

Various diastereoselective methods for the synthesis of α,β-diamino acid derivatives have been reported. Catalytic enantioselective approaches have focused on Mannich reactions of glycine imines or nitro esters with various imines. In 2003 Jørgensen et al. reported chiral Copper(I)-3.13 complex-catalyzed the enantioselective Mannich reactions of imines of glycine alkyl esters with imines. Five years later, Kobayashi et al. reported the organocatalytic version of this reaction featured with the fluorenone imines of glycine esters as the substrate and a chiral guanidine catalyst. In 2007, Johnston et al. discovered enantioselective Mannich reactions of nitro esters with imines using a protonated catalyst 3.16. In 2008, Hou and Wu et al. realized the highly diastereoselective switchable enantioselective Mannich reaction. Both anti and syn products can be obtained in a highly enantioselective fashion. The key of this reaction is
Scheme 3.3 Direct Mannich Reactions for the Synthesis of Chiral α,β-Diamino Acids

Lin et al. (1999)

\[
\text{CNCH}_2\text{COOEt} + \text{NTs} + \text{Me}_2\text{SAuCl / ligand} \xrightarrow{0.5 \text{ mol%}} \text{CH}_2\text{Cl}_2, 20 \degree \text{C}, 20 \text{ h} \xrightarrow{\text{EtO}_2\text{C}} \text{3.9} \text{N}\text{Ts} \xrightarrow{\text{R}} \text{10 examples} \text{76%-91% yield}
\]

Jorgensen et al. (2003)

\[
\text{Ph}_2\text{C=N}\text{OMe} + \text{NTs} \xrightarrow{2.0 \text{ eq}} \text{CuClO}_4 \text{ (10 mol%), ligand (10 mol%), Et}_3\text{N (10 mol%), 4 Å MS} \xrightarrow{\text{THF, -20 \degree C, 24 h}} \text{3.12} \text{N}\text{CPH}_2 \xrightarrow{\text{R}} \text{10 examples} \text{61-99% yields}
\]

Johnston et al. (2007)

\[
\text{O}_2\text{N}\text{COt-Bu} + \text{NBoc} \xrightarrow{1.0 \text{ eq}} \text{1. catalyst (5 mol%), PhMe, -78 \degree C, 2 h} \xrightarrow{2. \text{ CoCl}_2, \text{NaBH}_4} \text{3.15} \text{CO}_2\text{t-Bu} \xrightarrow{\text{R}} \text{9 examples} \text{69-88% yields}
\]

Willis et al. (2007)

\[
\text{SCN}\text{N} + \text{NTs} \xrightarrow{2.0 \text{ eq}} \text{Mg(ClO}_4\text{)\text{2 (10 mol%), ligand (11 mol%), tPr}_2\text{EtN (20 mol%), 4 Å MS}} \xrightarrow{\text{DCM, -78 \degree C, 24 h}} \text{3.18} \text{N}\text{O}_2\text{S} \xrightarrow{\text{R}} \text{18 examples, 64-95% yields,}
\]

Ooi et al. (2008)

\[
\text{3.20} \xrightarrow{1.1 \text{ eq}} \text{catalyst (2 mol%), THF, -40 \degree C, 1 h} \xrightarrow{\text{R'}} \text{3.21} \text{10 examples}
\]
the use of a family of chiral ferrocene ligands. Later, another \textit{anti}-selective Mannich reaction has been reported by Carretero et al.\textsuperscript{4g} Furthermore, catalytic enantioselective Mannich reactions of nitroalkanes or silyl nitronates with $\alpha$-imino esters have also been reported.\textsuperscript{6} In addition, $\alpha$-isocyano esters\textsuperscript{7} and azlactones\textsuperscript{8} have been employed as glycine equivalents in Mannich reactions. Willis and coworkers have recently used the $\alpha$-isothiocyanato imide \textbf{3.17b} in highly enantioselective aldol and Mannich reactions.\textsuperscript{9,10} Using a chiral magnesium complex derived from DBFox \textbf{3.19}, products such as \textbf{3.18b} were obtained with high levels of enantioselectivity favoring the \textit{anti} product.\textsuperscript{9b}

\textbf{3.2 Proposal and Objective}

Although Willis’ report has shown that chiral $\alpha,\beta$-diamino acid derivatives can be obtained by the metal catalyzed Mannich reaction of $\alpha$-isothiocyanato imides with imines, no organocatalytic examples of this reaction have been developed. Based on our recent success in using $\alpha$-isothiocyanato imide \textbf{3.17a} in catalytic enantioselective aldol reactions employing catalyst \textbf{3.23},\textsuperscript{11} we sought to expand this methodology to the corresponding Mannich reaction (Scheme 3.4). Our approach relies on Mannich reactions between $\alpha$-isothiocyanato imides and sulfonyl imines (or other activated imines) using readily available organocatalysts.
Scheme 3.4 Organocatalytic Reactions Using α-Isothiocyanato Imides

The objective of this project was to develop a convenient method (relatively low catalyst loadings, ambient temperature, scaleable) to access chiral α,β-diamino acid derivatives since few methods currently available are economical for the scale-up synthesis of this building block. In the following part of this chapter, I will report the development of this catalytic enantioselective process.

3.3 Results and Discussions

3.3.1 General Considerations

Since N-alkyl and N-aryl imines are poorer electrophiles than aldehydes, some readily available activated imines could be good candidates for this reaction, such as N-
Boc, N-phosphoryl and N-sulfonyl imines. In addition, it is hard to predict whether the organocatalytic process will be *syn*-selective or *anti*-selective, although Willis’ protocol led to *anti* product. The interesting finding that product precipitation can accelerate reactions and lower catalyst loadings in our previously reported aldol reactions could be also applied to this reaction.

### 3.3.2 Reaction Development

With these considerations in mind, a reaction of \(3.17a\) with the tosyl imine derived from benzaldehyde was selected as a model reaction. The first trial was incomplete after 3 days when using 5 mol% of catalyst \(3.23\). Product \(3.18a\) was obtained in modest enantioselectivity and yield but with good diastereoselectivity favoring the *syn*-diastereomer (Table 3.1, entry 1). Subsequently, other readily available organocatalysts\(^{12-14}\) were evaluated. To our delight, the quinidine-derived bifunctional

**Scheme 3.5 Readily Available Organocatalysts for Evaluation**
### Table 3.1 Evaluation of Catalysts and Protecting Groups

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<th>Entry</th>
<th>Catalyst</th>
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<th>Pg</th>
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<th>Yield [%]</th>
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<td>3.17b</td>
<td>Ts</td>
<td>17</td>
<td>94</td>
<td>&gt;95:05</td>
<td>98</td>
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<tr>
<td>13</td>
<td>3.30d</td>
<td>3.17b</td>
<td>Bs</td>
<td>1.5</td>
<td>95</td>
<td>&gt;95:05</td>
<td>98</td>
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<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>3.17b</td>
<td>Ts</td>
<td>72</td>
<td>92</td>
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<td>3.17b</td>
<td>Bs</td>
<td>10</td>
<td>95</td>
<td>&gt;95:05</td>
<td>97</td>
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<tr>
<td>16</td>
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<td>3.17b</td>
<td>Ns</td>
<td>5.5</td>
<td>95</td>
<td>&gt;95:05</td>
<td>97</td>
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<td>3.17b</td>
<td>Ts</td>
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<td>80</td>
<td>92:08</td>
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<td>18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.29b</td>
<td>3.17b</td>
<td>Ts</td>
<td>72</td>
<td>62</td>
<td>93:07</td>
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<td>19&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.30a</td>
<td>3.17b</td>
<td>Ts</td>
<td>72</td>
<td>79</td>
<td>94:06</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed at rt on a 0.2 mmol scale in anhydrous toluene (0.1 M) using 1.5 equiv of imine. Reactions were run to full conversion as judged by TLC analysis. The ee’s were determined by HPLC analysis of the ester derivatives. <sup>b</sup> Combined yield of both diastereomers. <sup>c</sup> Determined by 1H-NMR. <sup>d</sup> Trans isomer. <sup>e</sup> The reaction is incomplete. <sup>f</sup> Run with 1 mol% catalyst loading.
catalyst 3.30d, pioneered by Deng,\textsuperscript{14b} provided product 3.18a in excellent enantio- and
diastereoselectivity (entry 6). However, a low reaction rate was observed. Interestingly,
significant rate acceleration was achieved by using the unsubstituted $\alpha$-isothiocyanato
imide 3.17b in place of 3.17a (entry 9). It was found that product 3.18b is less soluble in
toluene than 3.18a, limiting the possibility of product inhibition. This should serve at
least in part to explain the faster reaction rates observed with this substrate. The nature of
the acyl group on catalyst 3.30 was found to have little effect on the ee and dr of the
product, with more electron withdrawing groups resulting in lower reaction rates (entries
9–12).

We next focused on the use of other imine protecting groups.\textsuperscript{15} Remarkably,
replacement of the tosyl group for the simpler benzenesulfonyl (Bs) analogue resulted in
a ten-fold rate increase (compare entries 9 and 13). While subtle electronic effects can be
invoked to partially rationalize this dramatic rate acceleration, we noted a marked
solubility difference in the two products with 3.18c being less soluble than 3.18b. This
allowed for reduction of the catalyst loading to 1 mol\% while maintaining reasonable
reaction rates and without adverse effects on the stereoselectivity (entry 15).
Employment of the synthetically useful 4-nosyl (Ns) protecting group allowed for
complete conversion in only 5.5 hours with 1 mol\% of catalyst 3.30d (entry 16). Control
experiments with structurally related quinidine derivatives showed that a free hydroxyl
group on the quinoline ring is important for both reactivity and selectivity (entries 17–
19). In agreement with Deng’s findings,\textsuperscript{14b} this suggests a bifunctional role for catalyst
3.30d.

3.3.3 Substrate Scope
Table 3.2 Scope of the Reaction

With the optimized reaction conditions in hand, a series of different Bs protected imines was evaluated (Table 3.2). Electron-rich and electron-poor aromatic imines with
different substitution patterns provide products in generally good yields and with high levels of diastereo- and enantioselectivity (entries 1–13). Heteroaromatic and α,β-unsaturated imines are also viable substrates (entries 14–16).

*Scheme 3.6 Proposed Mechanism of Aminal Product Formation*

In addition, although aliphatic aldimines are typically less stable, these substrates are compatible with the current method. In the reaction yielding product 3.31q, an aminal byproduct 3.32 was isolated in 27% yield. This byproduct 3.32 results from 3.31q reacting with an additional equivalent of imine (Scheme 3.6).
Table 3.3 Reactions with Lower Catalyst Loading\(^a\)

\[
\begin{array}{cccccc}
\text{Entry} & \text{Ar} & \text{Product} & \text{Time [h]} & \text{Yield [%]}^b & \text{dr}^c & \text{Ee [%]} \\
1 & 4-\text{Me-C}_6\text{H}_4 & \text{3.33a} & 20 & 90 & 95:05 & 98 \\
2 & 3-\text{MeO-C}_6\text{H}_4 & \text{3.33b} & 24 & 92 & 91:09 & 97 \\
3 & 2-\text{naphthyl} & \text{3.33c} & 48 & 87 & 92:08 & 94 \\
\end{array}
\]

\(^a\) Reactions were run at rt on a 1 mmol scale using 1.5 equiv of imine. The ee's were determined by HPLC analysis of the ester derivatives. \(^b\) Combined yield of both diastereomers. \(^c\) trans:cis, determined by \(^1\text{H}-\text{NMR.}\)

It was generally observed that reactions yielding more soluble products (e.g., 3.31l) suffer from lower reaction rates. This is in agreement with our hypothesis that rapid catalyst turnover is linked to product precipitation. In an attempt to lower catalyst loadings further, we evaluated several more reactive and less soluble N-nosyl imines (Table 3.3). Gratifyingly, a catalyst loading of 0.25 mol% can routinely be applied to these substrates. High levels of stereoselectivity are preserved while reaction rates remain reasonable.

3.3.4 Synthesis of a Chiral $\alpha,\beta$-Diamino Acid

Starting with product 3.36a, a facile sequence was developed to access the corresponding $\alpha,\beta$-diamino acid. Following the straightforward sequence outlined in Scheme 3.7, the highly enantioenriched $\alpha,\beta$-diamino acid 3.39 was obtained in good yield and without loss of ee.
Scheme 3.7 Conversion of the Product 3.36a into Its Corresponding Diamino Acid

Reaction Conditions: a) Boc₂O/DMAP, CH₂Cl₂, rt, 4h, 99%; b) Hg(OAc)₂, CH₂Cl₂, rt, 24h, 96%; c) PhSH, K₂CO₃, DMF, rt, 3h, 74%; d) 2 M HCl aq., reflux, 5h, 100%.

3.3.5 Conclusion

In summary, we have reported catalytic enantioselective Mannich reactions of α-isothiocyanato imides with sulfonyl protected imines. Syn-α,β-diamino acid derivatives can be obtained in highly diastereo- and enantioselective fashion using substrate/catalyst ratios as high as 400:1. Product precipitation based approaches might offer a general solution to achieving lower catalyst loadings in a variety of different processes.

3.3.6 Latest Development in this Area

In 2009, Arrayás and Carretero reviewed the catalytic asymmetric direct Mannich reactions for the synthesis of chiral α,β-diamino acids. Recently, Zhong et al. reported an approach to syn-α,β-diamino acid derivatives that is similar to our methodology.
3.4 Experimental Section

3.4.1 Preparation Procedures for Substrates and Catalysts

The substrates \( \text{3.17a} \) and \( \text{3.17b} \) were prepared according to literature methods.\(^a,10^a,11^\) The imines were prepared according to literature methods.\(^19,20,21^\) The catalysts \( \text{3.23, 3.27–3.30} \) were prepared according to literature methods.\(^11,14^\)

3.4.2 General Procedure for the Catalytic Mannich Reaction Between Isothiocyanates and Imines

Catalyst \( \text{3.30d} \) (3.5 mg, 0.01 mmol), 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (\( \text{3.17b} \)) (186 mg, 1.00 mmol) and the corresponding imine (1.50 mmol) were dissolved in anhydrous toluene (10 mL) at room temperature. The reaction progress was monitored by TLC analysis. Upon consumption of \( \text{3.17b} \), the crude reaction mixture was applied to silica gel and the mixture of diastereomeric products was obtained by flash chromatography (\( \text{CH}_2\text{Cl}_2/\text{EtOAc/hexanes 1:1:1 or CH}_2\text{Cl}_2/\text{EtOAc 100:10 v/v)} \)).

3.4.3 General Procedure for the Conversion of Primary Products into Their Corresponding Ethyl Esters

The mixture of diastereomeric products \( \text{3.18, 3.31 or 3.33} \) was dissolved in dry THF (20 mL) and cooled to 0 °C. A solution of methyl magnesium iodide (1.2 eq., 3M in THF) in ethanol (8 mL) at 0 °C was added via syringe. After 2 min, the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (8 mL). The mixture was concentrated in vacuo, taken up in aqueous HCl (1 M, 16 mL) and \( \text{CH}_2\text{Cl}_2 \) (20 mL). The organic layer was separated and the aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 15
mL). The organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH$_2$Cl$_2$/EtOAc 100:1 or 100:2 v/v) to obtain the corresponding trans-ethyl esters as solids or colorless oils. Yields in this step are between 75%-85%.

3.4.4 Preparation Procedures for Racemic Samples

Racemic compounds were prepared from ethyl 2-thiocyanatoacetate by using DABCO/toluene or a literature method.\textsuperscript{22}

3.4.5 Product Characterization Data

4,4-dimethyl-3-((4R,5S)-5-phenyl-2-thioxo-1-tosylimidazolidine-4-carbonyl)oxazolidin-2-one (3.18a): Following the general procedure, the product (mixture of diastereomers) was obtained as white foam in 98% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. R$_f$ 0.52 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [\(\alpha\)]$_D$\textsuperscript{20} –14.0 (c 1.0, CHCl$_3$); IR (neat) 3380, 2976, 1777, 1707, 1596, 1470, 1397, 1361, 1310, 1244, 1168, 1094, 1061, 1032, 761, 701, 670, 597, 572, 544 cm\textsuperscript{-1}; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J$ = 8.2 Hz, 2H), 7.41–7.30 (comp, 5H), 7.17 (br s, 1H), 7.11 (d, $J$ = 8.2 Hz, 2H), 6.26 (d, $J$ = 2.1 Hz, 1H), 4.88 (app t, $J$ = 2.1 Hz, 1H), 4.18–4.08 (comp, 2H), 2.36 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.2, 167.4, 154.5, 145.0, 138.6, 135.1, 129.7, 129.4, 129.3, 128.9, 127.2, 76.4, 66.2, 64.9, 61.6, 24.9, 24.7, 21.9; m/z (ESI-MS) 474.1 [MH]$^+$, 496.2 [MNa]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 280 nm, t$_R$=16.9 min (major) and t$_R$=23.1 min.
3-((4R,5S)-5-phenyl-2-thioxo-1-tosylimidazolidine-4-carbonyl)oxazolidin-2-one

(3.18b): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 98% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp 228–229 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.24 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [α]$_D^{20}$ +18.5 (c 0.5, acetone); IR (KBr) 3365, 3066, 1799, 1778, 1702, 1494, 1396, 1366, 1267, 1216, 1166, 1116, 671 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.76 (s, 1H), 7.49 (d, $J$ = 8.2 Hz, 2H), 7.43–7.36 (comp, 3H), 7.36–7.30 (comp, 2H), 7.24 (d, $J$ = 8.2 Hz, 2H), 5.97 (d, $J$ = 1.5 Hz, 1H), 5.15 (d, $J$ = 1.5 Hz, 1H), 4.53–4.38 (comp, 2H), 4.02–3.85 (comp, 2H), 2.35 (s, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 179.7, 168.0, 153.7, 144.3, 139.4, 135.3, 128.8, 128.7, 128.5, 126.7, 66.7, 63.3, 61.8, 42.7, 21.0; m/z (ESI-MS) 446.1 [MH]$^+$, 468.2 [MNa]$^+$.

(4R,5S)-ethyl 5-phenyl-2-thioxo-1-tosylimidazolidine-4-carboxylate (3.34b):

Colorless oil; R$_f$ 0.42 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); [α]$_D^{20}$ –20.0 (c 1.0, CHCl$_3$, 98% ee); IR (neat) 3349, 2982, 1742, 1596, 1493, 1367, 1216, 1169, 1089, 1064, 1019, 756, 702, 671 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.52 (d, $J$ = 8.5 Hz, 2H), 7.42–7.32 (comp, 5H), 7.12 (d, $J$ = 8.5 Hz, 2H), 7.00 (br, s, 1H), 5.95 (d, $J$ = 2.6 Hz, 1H), 4.37–4.23 (comp, 2H), 4.18 (dd, $J$ = 2.6, 1.0 Hz, 1H), 2.37 (s, 3H), 1.33 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.8, 168.5, 145.2, 138.9, 135.0, 129.6, 129.4, 129.4, 129.0, 126.8, 67.7, 63.4, 63.1, 21.9, 14.3; m/z (ESI-MS) 405.3 [MH]$^+$, 427.2 [MNa]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t$_R$=15.3 min (major) and t$_R$=12.6 min.
**3-((4R,5S)-5-phenyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.18c):** Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 97% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp 225–226 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.21 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [α]$_D^{20}$ +22.5 (c 1.0, acetone); IR (KBr) 3363, 3069, 2996, 1778, 1702, 1495, 1396, 1365, 1268, 1214, 1167, 1114, 725, 692, 605, 570 cm$^{-1}$; $^1$H NMR (500 MHz, d$_6$-DMSO) δ 9.83 (s, 1H), 7.70–7.59 (comp, 3H), 7.51–7.43 (m, 2H), 7.43–7.28 (comp, 5H), 6.00 (d, $J = 1.4$ Hz, 1H), 5.17 (d, $J = 1.4$ Hz, 1H), 4.56–4.39 (comp, 2H), 4.05–3.85 (comp, 2H); $^{13}$C NMR (125 MHz, d$_6$-DMSO) δ 179.6, 168.0, 153.7, 139.3, 138.2, 133.7, 128.6, 128.6, 128.6, 128.6, 126.7, 66.7, 63.3, 62.0, 42.7; m/z (ESI-MS) 432.2 [MH]$^+$, 454.2 [MNa]$^+$.

**(4R,5S)-ethyl 5-phenyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.34c):** Colorless oil; R$_f$ 0.61 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); [α]$_D^{20}$ –10.5 (c 1.0, CHCl$_3$, 98% ee); IR (KBr) 3343, 3065, 2981, 1744, 1585, 1482, 1368, 1215, 1171, 1090, 1063, 1026, 857, 757, 726, 686, 600, 569 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.68–7.62 (m, 2H), 7.55–7.49 (m, 1H), 7.42–7.28 (comp, 7H), 7.08 (br, s, 1H), 5.96 (d, $J = 2.6$ Hz, 1H), 4.37–4.23 (comp, 2H), 4.19 (d, $J = 2.6$ Hz, 1H), 1.33 (app t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.7, 168.5, 138.7, 138.0, 134.0, 129.5, 129.5, 129.4, 128.4, 126.8, 67.7, 63.4, 63.1, 14.3; m/z (ESI-MS) 391.1 [MH]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=15.9 min (major) and $t_R$=11.6 min.
3-((4R,5S)-5-phenyl-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.18d): Following the general procedure, the product (mixture of diastereomers) was obtained as a pale yellow solid in 97% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp >250 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.24 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [$\alpha$]$_D$$^{20}$ +41.5 (c 0.5, acetone); IR (KBr) 3363, 3105, 2998, 1796, 1777, 1702, 1531, 1495, 1396, 1378, 1349, 1267, 1213, 1175, 1115, 854, 740, 608, 569 cm$^{-1}$; $^1$H NMR (500 MHz, d$_6$-DMSO) $\delta$ 10.02 (s, 1H), 8.28 (d, $J$ = 8.9 Hz, 2H), 7.92–8.32 (comp, 3H), 7.38–7.29 (comp, 2H), 6.07 (d, $J$ = 1.3 Hz, 1H), 5.20 (d, $J$ = 1.3 Hz, 1H), 4.54–4.39 (comp, 2H), 4.05–3.85 (comp, 2H); $^{13}$C NMR (125 MHz, d$_6$-DMSO) $\delta$ 179.4, 167.9, 153.5, 150.2, 143.2, 139.0, 130.3, 128.8, 128.7, 126.6, 123.5, 66.9, 63.1, 61.7, 42.3; m/z (ESI-MS) 477.4 [M+H]$^+$. 

(4R,5S)-ethyl 1-(4-nitrophenylsulfonyl)-5-phenyl-2-thioxoimidazolidine-4-carboxylate (3.34d): Pale yellow oil; R$_f$ 0.42 (CH$_2$Cl$_2$/EtOAc 100:2 v/v/v); [$\alpha$]$_D$$^{20}$ 47.0 (c 1.0, CHCl$_3$, 98% ee); IR (neat) 3385, 3107, 2983, 1743, 1532, 1493, 1371, 1350, 1240, 1214, 1173, 1088, 1065, 1013, 855, 740, 639 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16–8.08 (m, 2H), 7.79–7.71 (m, 2H), 7.49–7.42 (m, 1H), 7.36–7.30 (comp, 2H), 7.19 (br, s, 1H), 5.97 (d, $J$ = 2.4 Hz, 1H), 4.40–4.28 (comp, 2H), 4.26 (d, $J$ = 2.4 Hz, 1H), 1.36 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.2, 168.2, 150.7, 143.3, 138.2, 130.9, 130.0, 129.7, 127.1, 123.4, 67.7, 63.4, 63.3, 14.3; m/z (ESI-MS) 436.3 [M+H]$^+$, 458.1 [M+Na]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t$_R$=45.7 min (major) and t$_R$=26.7 min.
3-((4R,5S)-5-(4-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31a): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 96% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp 234–235 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.21 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [α]$_D^{20}$ +13.0 (c 0.5, acetone); IR (KBr) 3369, 3062, 2995, 2922, 1778, 1702, 1492, 1396, 1366, 1266, 1217, 1168, 1117, 1087, 726, 687, 597, 570 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 (app d, $J$ = 7.4 Hz, 2H), 7.53 (app t, $J$ = 7.4 Hz, 1H), 7.34 (app t, $J$ = 7.9 Hz, 2H), 7.24 (d, $J$ = 8.0 Hz, 2H), 7.16 (d, $J$ = 8.0 Hz, 2H), 7.13 (br, s, 1H), 6.32 (d, $J$ = 1.2 Hz, 1H), 4.85 (app t, $J$ = 1.9 Hz, 1H), 4.63–4.48 (comp, 2H), 4.17–4.04 (comp, 2H), 2.37 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.0, 166.6, 154.1, 139.5, 138.1, 133.9, 130.0, 129.7, 128.3, 127.0, 66.0, 63.9, 63.7, 42.9, 21.5; m/z (ESI-MS) 446.3 [MH]$^+$, 468.2 [MNa]$^+$.

(4R,5S)-ethyl 5-(4-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35a): Colorless oil; R$_f$ 0.63 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); [α]$_D^{20}$ −19.0 (c 1.0, CHCl$_3$, 99% ee); IR (KBr) 3341, 3064, 2985, 2928, 1753, 1496, 1449, 1365, 1216, 1170, 1090, 1066, 1025, 822, 756, 727, 686, 594, 570 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.69–7.62 (m, 2H), 7.55–7.48 (m, 1H), 7.36–7.28 (m, 2H), 7.25–7.09 (comp, 5H), 5.91 (d, $J$ = 2.6 Hz, 1H), 4.36–4.20 (comp, 2H), 4.16 (d, $J$ = 2.6 Hz, 1H), 2.37 (s, 3H), 1.31 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.7, 168.5, 139.5, 138.1, 135.8, 133.9, 130.0, 129.5, 128.3, 126.8, 67.6, 63.5, 63.1, 21.4, 14.3; m/z (ESI-MS) 405.1 [MH]$^+$; HPLC: Daicel Chiralpak AD-H,
hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R = 15.2 min (major) and t_R = 10.9 min.

3-((4R,5S)-5-(4-nitrophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31b): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 85% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 240–241 °C (CH_2Cl_2/hexanes); R_f 0.13 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); [α]_D^{20} +32.0 (c 1.0, acetone); IR (KBr) 3348, 3113, 3046, 1776, 1767, 1707, 1526, 1489, 1458, 1390, 1347, 1260, 1219, 1182, 1169, 1117, 1088, 1057, 621, 587, 567 cm\(^{-1}\); \(^1\)H NMR (500 MHz, d_6-DMSO) δ 9.94 (s, 1H), 8.32–8.27 (m, 2H), 7.77–7.71 (m, 2H), 7.70–7.63 (m, 1H), 7.63–7.56 (m, 2H), 7.54–7.46 (m, 2H), 6.21 (d, J = 1.6 Hz, 1H), 5.18 (d, J = 1.6 Hz, 1H), 4.55–4.39 (comp, 2H), 4.05–3.84 (comp, 2H); \(^{13}\)C NMR (125 MHz, d_6-DMSO) δ 179.5, 167.6, 153.8, 147.5, 146.4, 138.0, 134.0, 128.6, 128.5, 128.2, 123.9, 65.6, 63.4, 61.4, 42.6; m/z (ESI-MS) 477.2 [MH]^+, 499.1 [MNa]^+.

(4R,5S)-ethyl 5-(4-nitrophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35b): Colorless oil; R_f 0.52 (EtOAc/CH_2Cl_2 1:19 v/v); [α]_D^{20} +20.5 (c 1.0, CHCl_3, 93% ee); IR (KBr) 3418, 2981, 2918, 1746, 1627, 1605, 1525, 1483, 1350, 1216, 1174, 1090, 1065, 1024 cm\(^{-1}\); \(^1\)H NMR (500 MHz, d_6-DMSO) δ 10.30 (s, 1H), 8.34 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.76–7.49 (comp, 5H), 6.09 (d, J = 2.8 Hz, 1H), 4.36 (d, J = 2.8 Hz, 1H), 4.29–4.11 (comp, 2H), 1.21 (app t, J = 7.1 Hz, 3H); \(^{13}\)C NMR (125 MHz, d_6-DMSO) δ 178.3, 168.4, 147.6, 146.8, 137.8, 134.3, 128.7, 128.5, 127.5, 127.5, 124.3,
65.8, 62.3, 62.1, 13.9; m/z (ESI-MS) 436.1 [MH]⁺; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=41.6 min (major) and t_R=29.1 min.

3-((4R,5S)-5-(4-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31c): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 92% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH₂Cl₂. mp 240–242 °C (CH₂Cl₂); R_f 0.19 (hexanes/CH₂Cl₂/EtOAc 1:1:1 v/v/v); [α]D²⁰ +16.0 (c 1.0, acetone); IR (KBr) 3369, 3063, 2996, 1777, 1702, 1492, 1396, 1368, 1264, 1218, 1168, 1086, 1016, 725, 592, 570 cm⁻¹; ¹H NMR (500 MHz, d₆-DMSO) δ 9.87 (s, 1H), 7.74–7.69 (m, 2H), 7.69–7.62 (m, 1H), 7.54–7.44 (comp, 4H), 7.39–7.30 (m, 2H), 6.04 (d, J = 1.4 Hz, 1H), 5.15 (d, J = 1.4 Hz, 1H), 4.55–4.38 (comp, 2H), 4.04–3.84 (comp, 2H); ¹³C NMR (125 MHz, d₆-DMSO) δ 179.5, 167.8, 153.8, 138.4, 138.1, 133.9, 133.2, 128.6, 128.6, 128.6, 128.4, 66.0, 63.3, 61.7, 42.6; m/z (ESI-MS) 466.0 (³⁵Cl), 468.0 (³⁷Cl) [MH]⁺, 488.1 (³⁵Cl), 490.1 (³⁷Cl) [MNa]⁺.
(4R,5S)-ethyl 5-(4-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35c): Colorless oil; R$_f$ 0.62 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); $[\alpha]_D^{20} +19.0$ (c 1.0, CHCl$_3$, 98% ee); IR (KBr) 3319, 3067, 2982, 1745, 1701, 1594, 1493, 1448, 1371, 1212, 1172, 1089, 1064, 1014, 836, 755, 726, 685, 591, 569 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73–7.67 (m, 2H), 7.59–7.52 (m, 1H), 7.43–7.23 (comp, 7H), 5.91 (d, $J = 2.7$ Hz, 1H), 4.35–4.22 (comp, 2H), 4.14 (dd, $J = 2.7$, 1.0 Hz, 1H), 1.31 (app t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.6, 168.3, 137.9, 137.3, 135.5, 134.2, 129.6, 129.4, 128.5, 128.2, 67.0, 63.3, 63.3, 14.3; m/z (ESI-MS) 425.2 ($^{35}$Cl), 427.2 ($^{37}$Cl) [MH]$^+$, 447.1 ($^{35}$Cl), 449.1 ($^{37}$Cl) [MNa]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 280 nm, $t_R$=17.4 min (major) and $t_R$=10.5 min.

3-((4R,5S)-5-(4-fluorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31d): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 93% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp 244–245 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.19 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20} +37.0$ (c 1.0, acetone); IR (KBr) 3367, 2996, 1799, 1778, 1702, 1512, 1493, 1396, 1368, 1267, 1217, 1168, 1116, 1064, 725, 599, 570 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) $\delta$ 9.86 (s, 1H), 7.74–7.60 (comp, 3H), 7.48 (app t, $J = 7.9$ Hz, 2H), 7.43–7.32 (m, 2H), 7.25 (app t, $J = 8.8$ Hz, 2H), 6.03 (d, $J = 1.2$ Hz, 1H), 5.15 (d, $J = 1.2$ Hz, 1H), 4.56–4.36 (comp, 2H), 4.03–3.84 (comp, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) $\delta$ 179.5, 167.9, 162.0 (d, $^3$J$_{C-F} = 244.9$ Hz), 153.7, 138.2, 135.7 (d, $^4$J$_{C-F} = 3.0$ Hz), 133.8, 128.9 (d, $^3$J$_{C-F} = 8.5$ Hz), 128.6,
(4R,5S)-ethyl 5-(4-fluorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35d): Colorless oil; R<sub>f</sub> 0.60 (EtOAc/CH<sub>2</sub>Cl<sub>2</sub> 1:19 v/v); [α]<sub>D</sub><sup>20</sup> –3.0 (c 1.0, CHCl<sub>3</sub>, 97% ee); IR (KBr) 3348, 3067, 2984, 1745, 1606, 1511, 1369, 1227, 1172, 1091, 1064, 841, 756, 728, 686, 595, 570 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.73–7.66 (m, 2H), 7.59–7.50 (m, 1H), 7.41–7.30 (comp, 4H), 7.10 (br, s, 1H), 7.08–7.01 (comp, 2H), 5.95 (d, <i>J</i> = 2.6 Hz, 1H), 4.36–4.23 (comp, 2H), 4.15 (dd, <i>J</i> = 2.6, 0.9 Hz, 1H), 1.33 (app t, <i>J</i> = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 179.6, 168.4, 163.3 (d, <i>J</i><sub>C-F</sub> = 249.2 Hz), 138.0, 134.7 (d, <i>J</i><sub>C-F</sub> = 3.2 Hz), 134.2, 129.4, 128.8 (d, <i>J</i><sub>C-F</sub> = 8.4 Hz), 128.5, 116.4 (d, <i>J</i><sub>C-F</sub> = 21.8 Hz), 67.0, 63.4, 63.3, 14.3; m/z (ESI-MS) 409.0 [MH]<sup>+</sup>; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, <i>t</i><sub>R</sub>=17.1 min (major) and <i>t</i><sub>R</sub>=10.3 min.

3-((4R,5S)-5-(4-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31e): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 87% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes. mp 239–240 °C (CH<sub>2</sub>Cl<sub>2</sub>/hexanes); R<sub>f</sub> 0.16 (hexanes/CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 1:1:1 v/v/v); [α]<sub>D</sub><sup>20</sup> –5.5 (c 0.5, acetone); IR (KBr) 3347, 1771, 1708, 1514, 1497, 1466, 1391, 1352, 1259, 1224, 1171, 1092, 1062, 1034, 593, 568 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, <i>d</i><sub>6</sub>-DMSO) δ 9.80 (s, 1H), 7.67–7.60 (comp, 3H), 7.49–7.39 (m, 2H), 7.25 (d, <i>J</i> = 8.7 Hz, 2H), 6.95 (d, <i>J</i> = 8.7 Hz, 2H), 5.93 (d, <i>J</i> = 1.3 Hz, 1H), 5.14 (d, <i>J</i> = 1.3 Hz, 1H), 4.53–4.40 (comp, 2H), 4.03–3.85
(comp, 2H), 3.78 (s, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 179.5, 168.0, 159.4, 153.7, 138.3, 133.7, 131.5, 128.6, 128.2, 128.0, 113.9, 66.5, 63.3, 62.0, 55.2, 42.6; m/z (ESI-MS) 462.2 [MH]$^+$, 484.2 [MNa]$^+$.

(4R,5S)-ethyl 5-(4-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35e): Pale yellow oil; R$_f$ 0.50 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); $[\alpha]_D^{20}$ –31.5 (c 1.0, CHCl$_3$, 99% ee); IR (KBr) 3463, 3166, 3062, 2964, 2845, 1739, 1612, 1504, 1358, 1253, 1176, 1095, 1054, 823, 726, 686 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67–7.62 (m, 2H), 7.55–7.48 (m, 1H), 7.36–7.30 (m, 2H), 7.28–7.23 (m, 2H), 7.20–7.12 (br, s, 1H), 6.89–6.82 (m, 2H), 5.90 (d, $J$ = 2.6 Hz, 1H), 4.36–4.22 (comp, 2H), 4.17 (d, $J$ = 2.6 Hz, 1H), 3.83 (s, 3H), 1.32 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.6, 168.6, 160.4, 138.1, 133.9, 130.8, 129.4, 128.3, 128.3, 114.6, 67.4, 63.5, 63.0, 55.6, 14.3; m/z (ESI-MS) 443.1 [MNa]$^+$;

HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=22.7 min (major) and $t_R$=15.3 min.

3-((4R,5S)-5-(3-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31f): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 95% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp 217–218 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.21 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +25.0 (c 0.5, CHCl$_3$); IR (KBr) 3353, 1780, 1706, 1494, 1393, 1365, 1268, 1228, 1206, 1168, 1111, 1089, 1065, 726, 688, 606, 571 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.77–7.70 (m, 2H), 7.53 (app t, $J$ = 7.5 Hz, 1H), 7.35 (app t, $J$ = 7.9 Hz, 2H), 7.25–7.12 (comp, 4H), 7.07 (br, s, 1H), 6.34 (d, $J$ = 1.9 Hz,
1H), 4.85 (app t, \( J = 1.9 \) Hz, 1H), 4.62–4.49 (comp, 2H), 4.18–4.04 (comp, 2H), 2.29 (s, 3H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \( \delta \) 178.9, 166.4, 154.1, 139.3, 138.2, 138.0, 134.0, 130.2, 129.7, 129.3, 128.3, 127.4, 124.2, 66.0, 63.9, 63.6, 42.9, 21.6; \( m/z \) (ESI-MS) 446.1 [MH]\(^+\), 468.1 [MNa]\(^+\).

\((4R,5S)\)-ethyl \( 5\)-(3-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35f): Colorless oil; \( R_f \) 0.64 (EtOAc/CH\(_2\)Cl\(_2\) 1:19 v/v); \([\alpha]_{D}^{20} +7.5\) (c 1.0, CHCl\(_3\), 99\% ee); IR (KBr) 3279, 3192, 2974, 1752, 1733, 1610, 1583, 1495, 1447, 1364, 1228, 1175, 1123, 791, 726, 572 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.71–7.62 (m, 2H), 7.58–7.48 (m, 1H), 7.38–7.29 (m, 2H), 7.26–7.04 (comp, 4H), 6.98–6.88 (br, s, 1H), 5.93 (d, \( J = 2.7 \) Hz, 1H), 4.38–4.23 (comp, 2H), 4.16 (d, \( J = 2.7 \) Hz, 1H), 2.29 (s, 3H), 1.33 (app t, \( J = 7.2 \) Hz, 3H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \( \delta \) 179.8, 168.5, 139.3, 138.5, 138.0, 134.0, 130.2, 129.5, 129.3, 128.3, 127.2, 124.0, 67.8, 63.4, 63.1, 21.5, 14.3; \( m/z \) (ESI-MS) 405.1 [MH]\(^+\); HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \( t_R \)=11.6 min (major) and \( t_R \)=10.1 min.

\(3\)-(\((4R,5S)\)-5-(3-bromophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31g): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 94\% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH\(_2\)Cl\(_2\)/hexanes. mp 247–249 \(^\circ\)C (CH\(_2\)Cl\(_2\)/hexanes); \( R_f \) 0.22 (hexanes/CH\(_2\)Cl\(_2\)/EtOAc 1:1:1 v/v/v); \([\alpha]_{D}^{20} +43.0\) (c 0.25, CHCl\(_3\)); IR (KBr) 3357, 3059, 2993, 1794, 1777, 1705, 1489, 1394, 1371, 1264, 1214, 1168, 1114, 1087, 755, 725, 688, 604, 571 cm\(^{-1}\); \(^1\)H NMR (500 MHz, \( d_6\)-DMSO) \( \delta \) 9.89 (s, 1H), 7.75–7.64 (comp, 3H),
7.63–7.57 (m, 1H), 7.55–7.44 (comp, 3H), 7.40 (app t,  $J = 7.8$ Hz, 1H), 7.37-7.32 (m, 1H), 6.04 (d,  $J = 1.4$ Hz, 1H), 5.17 (d,  $J = 1.4$ Hz, 1H), 4.55–4.39 (comp, 2H), 4.03–3.85 (comp, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) $\delta$ 179.5, 167.8, 153.8, 141.8, 138.0, 134.0, 131.5, 130.9, 129.5, 128.6, 128.4, 125.7, 121.6, 65.9, 63.3, 61.7, 42.6; $m/z$ (ESI-MS) 510.1 ($^{79}$Br), 512.0 ($^{81}$Br) [MH]$^+$, 532.1 ($^{79}$Br), 534.1 ($^{81}$Br) [MNa]$^+$.

(4R,5S)-ethyl 5-(3-bromophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35g): Colorless oil; R$_f$ 0.68 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); $[\alpha]_D^{20} +23.5$ (c 1.0, CHCl$_3$, 97% ee); IR (KBr) 3352, 2984, 2935, 1738, 1576, 1491, 1369, 1265, 1218, 1173, 1091, 1066, 1024, 910, 790, 729 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76–7.68 (m, 2H), 7.59–7.47 (comp, 2H), 7.43–7.33 (comp, 3H), 7.31–7.19 (comp, 2H), 5.89 (d,  $J = 2.8$ Hz, 1H), 4.35–4.20 (comp, 2H), 4.13 (dd,  $J = 2.8$, 0.9 Hz, 1H), 1.30 (app t,  $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.5, 168.2, 140.8, 137.8, 134.3, 132.6, 131.1, 129.6, 129.3, 128.5, 125.5, 123.4, 66.9, 63.3, 63.2, 14.3; $m/z$ (ESI-MS) 469.0 ($^{79}$Br), 471.0 ($^{81}$Br) [MH]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R=13.2$ min (major) and $t_R=11.9$ min.
3-((4R,5S)-5-(3-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31h): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 99% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH₂Cl₂/hexanes. mp 193–195 °C (CH₂Cl₂/hexanes); Rₚ 0.18 (hexanes/CH₂Cl₂/EtOAc 1:1:1 v/v/v); [α]D²⁰ +37.5 (c 1.0, acetone); IR (KBr) 3312, 3060, 2992, 2963, 2931, 2839, 1769, 1692, 1601, 1583, 1498, 1397, 1360, 1320, 1262, 1128, 1088, 1051, 798, 756, 727, 686, 632, 609, 575 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.72 (m, 2H), 7.56–7.49 (m, 1H), 7.38–7.32 (m, 2H), 7.29–7.24 (m, 1H), 7.20 (br, s, 1H), 6.94–6.87 (comp, 2H), 6.82–6.78 (m, 1H), 6.32 (d, J = 1.9 Hz, 1H), 4.86 (app t, J = 1.9 Hz, 1H), 4.63–4.49 (comp, 2H), 4.17–4.04 (comp, 2H), 3.72 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 178.9, 166.4, 160.3, 154.1, 139.6, 138.0, 134.0, 130.5, 129.7, 128.3, 119.1, 115.3, 112.0, 66.0, 63.8, 63.7, 55.5, 42.9; m/z (ESI-MS) 462.1 [MH]⁺, 484.1 [MNa]⁺.

The absolute configuration of the title compound was assigned by X-ray crystallography.
(4R,5S)-ethyl 5-(3-methoxyphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35h): Colorless oil; R<sub>f</sub> 0.52 (EtOAc/CH<sub>2</sub>Cl<sub>2</sub> 1:19 v/v); \([\alpha]_{D}^{20}+12.0\) (c 1.0, CHCl<sub>3</sub>, 97% ee); IR (KBr) 3329, 3063, 2983, 2938, 2838, 1745, 1603, 1367, 1265, 1213, 1172, 1090, 1064, 1026, 730 cm<sup>-1</sup>; \(^1\)H NMR (500 MHz, CDCl<sub>3</sub>) \(\delta\) 7.74 (br, s, 1H), 7.70–7.65 (m, 2H), 7.54–7.48 (m, 1H), 7.36–7.28 (m, 2H), 7.24 (app t, \(J=7.9\) Hz, 1H), 6.92–6.85 (comp, 2H), 6.80–6.76 (m, 1H), 5.88 (d, \(J=2.6\) Hz, 1H), 4.32–4.19 (comp, 2H), 4.15 (dd, \(J=2.6, 1.2\) Hz, 1H), 3.70 (s, 3H), 1.29 (app t, \(J=7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl<sub>3</sub>) \(\delta\) 179.6, 168.5, 160.2, 140.0, 138.0, 133.9, 130.5, 129.4, 128.2, 118.7, 115.0, 111.9, 67.6, 63.3, 63.0, 55.4, 14.2; \(m/z\) (ESI-MS) 421.0 [MH]<sup>+</sup>; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \(t_R=16.7\) min (major) and \(t_R=14.4\) min.
3-((4R,5S)-5-(2-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31i): Following the general procedure, the product (mixture of diastereomers) was obtained as white foam in 80% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. Rf 0.39 (hexanes/CH2Cl2/EtOAc 1:1:1 v/v/v); [α]D20 +106.0 (c 1.0, CHCl3); IR (KBr) 3427, 1780, 1707, 1476, 1449, 1395, 1366, 1265, 1223, 1172, 757, 598 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 8.02 (app d, J = 7.7 Hz, 2H), 7.63–7.55 (m, 1H), 7.50–7.38 (comp, 4H), 7.35–7.27 (comp, 2H), 7.24 (br, s, 1H), 6.94–6.87 (comp, 2H), 6.79 (app s, 1H), 4.80 (app s, 1H), 4.54–4.38 (comp, 2H), 4.13–3.94 (comp, 2H); ¹³C NMR (125 MHz, CDCl3) δ 178.3, 165.7, 154.1, 137.7, 136.0, 134.3, 131.5, 130.3, 130.2, 129.7, 128.6, 127.9, 127.8, 63.6, 63.3, 62.6, 42.7; m/z (ESI-MS) 466.1 (35Cl), 468.1 (37Cl) [MH]⁺, 488.1 (35Cl), 490.0 (37Cl) [MNa]⁺.

(4R,5S)-ethyl 5-(2-chlorophenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35i): Colorless oil; Rf 0.68 (EtOAc/CH2Cl2 1:19 v/v); [α]D20 +69.0 (c 1.0, CHCl3, 91% ee); IR (KBr) 3315, 3059, 2984, 1742, 1684, 1579, 1483, 1370, 1167, 1093, 1063, 911, 757, 728, 686, 600 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 7.90 (app d, J = 7.8 Hz, 2H), 7.62–7.50 (comp, 2H), 7.46–7.35 (comp, 4H), 7.34–7.28 (m, 1H), 7.28–7.23 (m, 1H), 6.37 (app s, 1H), 4.32–4.15 (comp, 2H), 4.09 (app s, 1H), 1.27 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl3) δ 179.7, 168.1, 137.8, 135.8, 134.2, 132.0, 130.4, 130.4, 129.4, 128.5, 127.8, 65.1, 63.0, 62.6, 14.2; m/z (ESI-MS) 425.2 (35Cl), 427.2 (37Cl) [MH]⁺, 447.1 (35Cl), 449.1 (37Cl) [MNa]⁺; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, tR=14.1 min (major) and tR=9.8 min.
3-((4R,5S)-5-(2-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31j): Following the general procedure, the product (mixture of diastereomers) was obtained as white foam in 90% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. Rf 0.31 (hexanes/CH2Cl2/EtOAc 1:1:1 v/v/v); [α]D²⁰ +19.5 (c 1.0, CHCl₃); IR (KBr) 3424, 1780, 1704, 1474, 1395, 1365, 1265, 1225, 1172, 1090, 1062, 757, 725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.70 (m, 2H), 7.57–7.49 (m, 1H), 7.38–7.30 (comp, 3H), 7.29–7.07 (comp, 4H), 6.69 (d, J = 2.2 Hz, 1H), 4.78 (app t, J = 2.2 Hz, 1H), 4.61–4.46 (comp, 2H), 4.15–4.04 (comp, 2H), 2.42 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 178.9, 166.4, 154.2, 138.0, 136.7, 135.3, 134.0, 131.3, 129.7, 129.2, 128.4, 127.2, 126.4, 63.7, 63.6, 62.4, 42.9, 19.5; m/z (ESI-MS) 446.2 [MH]⁺, 468.3 [MNa]⁺.

(4R,5S)-ethyl 5-(2-methylphenyl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35j): Colorless oil; Rf 0.68 (EtOAc/CH₂Cl₂ 1:19 v/v/v); [α]D²⁰ +15.0 (c 1.0, CHCl₃, 98% ee); IR (KBr) 3427, 3189, 3057, 2986, 1746, 1478, 1369, 1266, 1223, 1173, 1090, 1066, 1024, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70–7.64 (m, 2H), 7.56–7.49 (m, 1H), 7.37–7.30 (m, 2H), 7.26–7.22 (comp, 2H), 7.19 (br, s, 1H), 6.25 (d, J = 7.2 Hz, 1H), 4.38–4.22 (comp, 2H), 4.09 (d, J = 7.2 Hz, 1H), 2.52 (s, 3H), 1.33 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 179.8, 168.6, 138.0, 136.8, 135.5, 134.0, 131.2, 129.5, 129.1, 128.3, 127.1, 126.0, 64.1, 63.2, 63.1, 19.3, 14.2; m/z (ESI-MS) 405.1 [MH]⁺; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, tR=12.2 min (major) and tR=10.4 min.
3-((4R,5S)-5-(naphthalen-2-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31k): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH2Cl2. mp >250 °C (CH2Cl2); Rf 0.22 (hexanes/CH2Cl2/EtOAc 1:1:1 v/v/v); [α]D$^{20}$ –19.0 (c 0.5, acetone); IR (KBr) 3366, 3061, 1797, 1776, 1702, 1491, 1396, 1369, 1267, 1218, 1169, 1118, 1088, 726, 591, 570 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) δ 9.90 (s, 1H), 8.00–7.82 (comp, 4H), 7.71–7.63 (m, 2H), 7.63–7.52 (comp, 3H), 7.45 (app dd, $J = 8.6, 1.7$ Hz, 1H), 7.42–7.34 (m, 2H), 6.18 (d, $J = 1.5$ Hz, 1H), 5.29 (d, $J = 1.5$ Hz, 1H), 4.56–4.40 (comp, 2H), 4.07–3.87 (comp, 2H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 179.6, 168.0, 153.7, 138.1, 136.8, 133.7, 132.8, 132.4, 128.6, 128.5, 128.2, 128.0, 127.6, 126.6, 126.6, 126.1, 124.1, 66.9, 63.3, 61.7, 42.7; m/z (ESI-MS) 482.2 [MH]$^+$, 504.2 [MNa]$^+$.

(4R,5S)-ethyl 5-(naphthalen-2-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35k): Colorless oil; Rf 0.68 (EtOAc/CH2Cl2 1:19 v/v); [α]D$^{20}$ –45.5 (c 1.0, CHCl3, 99% ee); IR (KBr) 3307, 3298, 2981, 2935, 1752, 1732, 1601, 1492, 1367, 1219, 1170, 1092, 1069, 1017 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) δ 10.28 (s, 1H), 8.03–7.86 (comp, 4H), 7.79–7.72 (m, 2H), 7.70–7.63 (m, 1H), 7.61–7.55 (comp, 2H), 7.52–7.44 (m, 2H), 7.44–7.37 (m, 1H), 6.06 (d, $J = 2.7$ Hz, 1H), 4.41 (dd, $J = 2.7, 1.4$ Hz, 1H), 4.31–4.16 (comp, 2H), 1.25 (app t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) δ 178.5, 168.8, 138.0, 137.0, 134.0, 132.8, 132.5, 129.1, 128.5, 128.0, 127.7, 126.8, 126.7, 125.3, 123.3, 67.0, 62.8, 62.0, 13.9;
m/z (ESI-MS) 463.1 [MNa]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R$=20.0 min (major) and $t_R$=15.1 min.

3-((4R,5S)-5-(naphthalen-1-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31): Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 82% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. $R_f$ 0.34 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +179.0 (c 0.5, CHCl$_3$); IR (KBr) 3376, 3068, 2984, 2924, 1772, 1677, 1475, 1459, 1391, 1377, 1257, 1232, 1177, 1092, 1059, 728, 687, 595, 566 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) $\delta$ 9.91 (br, s, 1H), 8.17 (br, s, 1H), 8.06–7.96 (comp, 2H), 7.76–7.38 (comp, 9H), 6.84 (br, s, 1H), 5.28 (br, s, 1H), 4.54–4.36 (comp, 2H), 4.17–4.06 (m, 1H), 4.00–3.88 (m, 1H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) $\delta$ 179.1, 167.8, 153.3, 138.1, 135.8, 133.9, 133.4, 129.4, 129.1, 128.6, 128.4, 126.5, 126.1, 125.5, 123.6, 63.2, 62.3, 61.7, 42.7; m/z (ESI-MS) 482.2 [MH]$^+$, 504.1 [MNa]$^+$.

(4R,5S)-ethyl 5-(naphthalen-1-yl)-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35): Colorless oil; $R_f$ 0.70 (EtOAc/CH$_2$Cl$_2$ 1:19 v/v); $[\alpha]_D^{20}$ +137.0 (c 1.0, CHCl$_3$, 95% ee); IR (KBr) 3405, 3053, 2979, 1742, 1602, 1506, 1373, 1236, 1180, 1092, 1055, 1024, 858, 799, 728 cm$^{-1}$; $^1$H NMR (500 MHz, $d_6$-DMSO) $\delta$ 10.18 (s, 1H), 8.31 (br, s, 1H), 8.12–7.84 (comp, 4H), 7.80–7.50 (comp, 6H), 7.50–7.36 (m, 1H), 6.78 (br, s, 1H), 4.44–4.14 (comp, 3H), 1.28 (app t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $d_6$-DMSO) $\delta$ 178.6, 168.9, 138.0, 134.8, 134.1, 133.6, 129.1, 129.0, 128.9, 128.7, 128.6, 126.9, 126.3, 125.4, 122.8, 64.1, 62.7, 62.2, 13.9; m/z (ESIMS) 441.2 [MH]$^+$, 463.1 [MNa]$^+$; HPLC: Daicel Chiralpak AD-
H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=15.3 min (major) and t_R=13.7 min.

3-((4R,5R)-1-(phenylsulfonyl)-5-(thiophen-2-yl)-2-thioxoimidazolidine-4-carbonyl) oxazolidin-2-one (3.31m): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 95% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 215–216 °C (CH_2Cl_2/hexanes); R_f 0.24 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); [α]_D^{20} +5.0 (c 1.0, acetone); IR (KBr) 3374, 3069, 2987, 1775, 1705, 1484, 1396, 1364, 1261, 1217, 1168, 1119, 1087, 1057, 1034, 726, 757, 705, 604, 586, 570 cm⁻¹; ^1H NMR (500 MHz, d_6-DMSO) δ 9.91 (s, 1H), 7.70–7.61 (comp, 3H), 7.53 (dd, J = 5.1, 1.2 Hz, 1H), 7.49–7.43 (m, 1H), 7.50–7.42 (m, 2H), 7.17 (dd, J = 3.5, 1.2 Hz, 1H), 7.05 (dd, J = 5.1, 3.5 Hz, 1H), 6.30 (app s, 1H), 5.21 (d, J = 1.2 Hz, 1H), 4.53–4.40 (comp, 2H), 4.01–3.84 (comp, 2H); ^13C NMR (125 MHz, d_6-DMSO) δ 178.9, 167.4, 153.8, 141.4, 138.1, 133.8, 128.7, 128.3, 127.3, 126.5, 126.5, 63.3, 62.8, 62.4, 42.6; m/z (ESI-MS) 438.1 [MH]^+, 460.1 [MNa]^+.

(4R,5R)-ethyl 1-(phenylsulfonyl)-5-(thiophen-2-yl)-2-thioxoimidazolidine-4-carboxylate (3.35m): Yellow oil; R_f 0.65 (EtOAc/CH_2Cl_2 1:19 v/v); [α]_D^{20} –23.0 (c 1.0, CHCl_3, 97% ee); IR (KBr) 3447, 2978, 1750, 1636, 1485, 1371, 1206, 1173, 1088, 1059, 1021, 858, 727 cm⁻¹; ^1H NMR (500 MHz, CDCl_3) δ 7.69–7.63 (m, 2H), 7.56–7.49 (m, 1H), 7.38–7.31 (m, 2H), 7.30 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 3.5 Hz, 1H), 7.03–6.84 (comp, 2H), 6.30 (d, J = 2.0 Hz, 1H), 4.36–4.25 (comp, 3H), 1.33 (app t, J = 7.2 Hz, 3H); ^13C NMR (125 MHz, CDCl_3) δ 179.0, 168.0, 140.6, 137.9, 134.0, 129.4, 128.5, 128.4, 127.1, 127.1, 127.1, 63.5, 63.3, 63.3, 14.3; m/z
(ESI-MS) 397.0 [MH]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, $t_R=$18.3 min (major) and $t_R=$13.4 min.

3-((4R,5R)-1-(phenylsulfonyl)-5-(furan-2-yl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31n): Following the general procedure, the product (mixture of diasteromers) was obtained as white foam in 97% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. $R_f$ 0.19 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [$\alpha$]$_{D}^{20}$ +26.5 (c 1.0, CHCl$_3$); IR (KBr) 3410, 1779, 1708, 1478, 1392, 1365, 1266, 1230, 1171, 1090, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.73–7.67 (m, 2H), 7.57–7.50 (m, 1H), 7.42–7.34 (comp, 3H), 7.32 (d, $J$ = 1.2 Hz, 1H), 6.60 (d, $J$ = 3.2 Hz, 1H), 6.43–6.39 (comp, 2H), 5.11 (t, $J$ = 5.0 Hz, 1H), 4.64–4.49 (comp, 2H), 4.15–4.07 (comp, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.5, 166.2, 154.2, 149.7, 143.6, 137.9, 134.0, 129.4, 128.5, 111.1, 111.0, 63.8, 60.8, 59.4, 42.9; m/z (ESI-MS) 422.1 [MH]$^+$, 444.1 [MNa]$^+$.

(4R,5R)-ethyl 1-(phenylsulfonyl)-5-(furan-2-yl)-2-thioxoimidazolidine-4-carboxylate (3.35n): Pale yellow oil; $R_f$ 0.64 (EtOAc/CH$_2$Cl$_2$ 1:1 9/v/v); [$\alpha$]$_{D}^{20}$ +1.5 (c 1.0, CHCl$_3$, 92% ee); IR (KBr) 3344, 2983, 1745, 1605, 1484, 1366, 1172, 1090, 1018, 930, 727, 687, 622, 571 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.70–7.64 (m, 2H), 7.57–7.50 (m, 1H), 7.41–7.35 (m, 2H), 7.32 (d, $J$ = 1.8, 0.7 Hz, 1H), 7.15 (br, s, 1H), 6.64 (d, $J$ = 3.3, 0.7 Hz, 1H), 6.43 (d, $J$ = 3.3, 1.8 Hz, 1H), 6.09 (d, $J$ = 2.8 Hz, 1H), 4.39 (dd, $J$ = 2.8, 1.3 Hz, 1H), 4.36–4.22 (comp, 2H), 1.32 (app t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.0, 168.0, 149.7, 143.6, 137.9, 134.0, 129.3, 128.5, 111.3, 111.1, 63.3, 60.6, 60.0, 14.3; m/z (ESIMS) 380.1 [MH]$^+$; HPLC:
Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, 
t_R=16.7 min (major) and t_R=13.3 min.

3-((4R,5S)-1-(phenylsulfonyl)-5-styryl-2-thioxoimidazolidine-4-carbonyl)oxazolidin-

2-one (3.31o): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH_2Cl_2/hexanes. mp 225–226 °C (CH_2Cl_2/hexanes); R_f 0.17 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); [α]_D^{20} +12.5 (c 0.25, CHCl_3); IR (KBr) 3373, 3060, 3025, 3001, 1776, 1703, 1490, 1395, 1369, 1258, 1220, 1169, 1122, 1088, 1062, 1036, 753, 726, 687, 628, 603, 570 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl_3) δ 8.11–8.05 (m, 2H), 7.59–7.53 (m, 1H), 7.44–7.28 (comp, 7H), 7.19 (br, s, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.24 (dd, J = 15.7, 8.4 Hz, 1H), 5.93 (d, J = 8.4 Hz, 1H), 4.86 (t, J = 1.7 Hz, 1H), 4.63–4.51 (comp, 2H), 4.16–4.05 (comp, 2H); \(^13\)C NMR (125 MHz, CDCl_3) δ 178.9, 166.6, 154.2, 138.3, 135.9, 135.3, 134.1, 130.0, 129.0, 128.6, 127.2, 123.6, 65.7, 63.7, 61.9, 42.9; m/z (ESI-MS) 458.1 [MH]^+, 480.1 [MNa]^+.

The absolute configuration of the title compound was assigned by X-ray crystallography.
Figure 3.2 Crystal Structure of Compound 3.31o

(4R,5S)-ethyl 1-(phenylsulfonyl)-5-styryl-2-thioxoimidazolidine-4-carboxylate (3.35o): Pale yellow oil; Rf 0.66 (EtOAc/CH2Cl2 1:19 v/v); [α]D20 = 10.5 (c 1.0, CHCl3, 95% ee); IR (KBr) 3397, 3064, 2983, 2924, 1745, 1629, 1491, 1449, 1367, 1215, 1172, 1090, 1064, 1023, 753, 725, 687, 569 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 8.10–8.02 (m, 2H), 7.60–7.53 (m, 1H), 7.44–7.30 (comp, 7H), 7.15 (br, s, 1H), 6.90 (d, J = 15.7 Hz, 1H), 6.18 (dd, J = 15.7, 8.7 Hz, 1H), 5.63 (dd, J = 8.7, 1.9 Hz, 1H), 4.35–4.21 (comp, 2H), 4.08 (d, J = 1.9 Hz, 1H), 1.32 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl3) δ 179.4, 168.4, 138.4, 135.9, 135.2, 134.1, 129.8, 129.1, 129.0, 128.6, 127.2, 124.0, 67.1, 63.1, 61.3, 14.3; m/z (ESI-MS) 417.1 [MH]+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, tR=16.2 min (major) and tR=13.6 min.
3-((4R,5S)-5-phenethyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31p): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$. mp 208-210 °C (CH$_2$Cl$_2$); R$_f$ 0.18 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [α]$_D^{20}$ +19.0 (c 1.0, acetone); IR (KBr) 3365, 3064, 3027, 2993, 2956, 2928, 1769, 1708, 1485, 1391, 1357, 1260, 1211, 1165, 1124, 1085, 1065, 1037, 753, 727, 685, 603, 570 cm$^{-1}$; $^1$H NMR (400 MHz, d$_6$-DMSO) δ 9.74 (s, 1H), 8.04-7.96 (m, 2H), 7.76-7.68 (m, 1H), 7.63–7.54 (m, 2H), 7.35–7.27 (m, 2H), 7.25–7.14 (comp, 3H), 5.18–5.08 (comp, 2H), 4.55–4.39 (comp, 2H), 3.98–3.82 (comp, 2H), 2.77–2.64 (m, 1H), 2.64–2.52 (m, 1H), 2.32–2.18 (m, 1H); $^{13}$C NMR (100 MHz, d$_6$-DMSO) δ 179.3, 168.5, 154.0, 140.8, 138.4, 133.8, 128.6, 128.5, 128.1, 126.0, 64.6, 63.3, 59.0, 42.6, 36.7, 29.0; m/z (ESI-MS) 460.2 [MH]$^+$, 482.2 [MNa]$^+$.

(4R,5S)-ethyl 5-phenethyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.35p): Colorless oil; R$_f$ 0.28 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); [α]$_D^{20}$ +11.5 (c 1.0, CHCl$_3$, 89% ee); IR (KBr) 3424, 3173, 2927, 1744, 1496, 1370, 1218, 1171, 1089, 725, 570 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.06–8.00 (m, 2H), 7.66–7.58 (m, 1H), 7.55–7.47 (m, 2H), 7.36–7.27 (m, 2H), 7.26–7.18 (comp, 3H), 6.60 (br, s, 1H), 5.05–4.96 (m, 1H), 4.27–4.09 (comp, 2H), 3.98 (d, $J=2.0$ Hz, 1H), 2.86–2.70 (comp, 2H), 2.53–2.40 (m, 1H), 2.40–2.26 (m, 1H), 1.25 (app t, $J=7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.8, 168.9, 139.9, 138.3, 134.2, 129.2, 128.9, 128.8, 128.6, 126.7, 65.6, 62.9, 59.8, 36.8, 30.7, 14.3; m/z (ESI-MS) 419.2 [MH]$^+$,
441.2 [MNa]^+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=18.8 min (major) and t_R=10.5 min.

3-((4R,5S)-5-butyl-1-(phenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.31q): Following the general procedure, the product (mixtures of diastereomers) was obtained as white foam in 53% yield. An analytical sample of the pure trans-diastereomer was obtained by flash chromatography. R_f 0.28 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); [α]_D^{20} +39.0 (c 1.0, CHCl_3, 91% ee); IR (KBr) 3425, 2958, 2927, 2861, 1780, 1705, 1475, 1395, 1362, 1223, 1170, 1090, 1064, 1037, 727, 569 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 8.13–8.06 (m, 2H), 7.63–7.56 (m, 1H), 7.54–7.46 (m, 2H), 7.02 (br, s, 1H), 5.40–5.34 (m, 1H), 4.72 (app t, J = 1.9 Hz, 1H), 4.58–4.48 (comp, 2H), 4.15–3.94 (comp, 2H), 2.11–1.97 (comp, 2H), 1.46–1.21 (comp, 4H), 0.92 (app t, J = 7.1 Hz, 3H); ^13C NMR (125 MHz, CDCl_3) δ 178.7, 167.0, 154.1, 138.3, 134.1, 129.5, 128.6, 64.0, 63.6, 60.2, 42.8, 34.6, 26.2, 22.6, 14.1; m/z (ESI-MS) 412.2 [MH]^+, 434.2 [MNa]^+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, t_R=34.4 min (major) and t_R=30.2 min.

N-((R)-1-((4S,5R)-4-butyl-5-(2-oxooxazolidine-3-carbonyl)-3-(phenylsulfonyl)-2-thioxoimidazolidin-1-yl)pentyl)benzenesulfonamide (3.32): The title compound was obtained by flash chromatography. An analytical sample was obtained by recrystallization. mp 162–164 °C (CHCl_3); R_f 0.31 (hexanes/CH_2Cl_2/EtOAc 1:1:1 v/v/v); IR (KBr) 3293, 2960, 2932, 2871, 1788, 1706, 1448, 1414, 1397, 1363, 1337, 1231, 1174, 1091, 1060, 602, 562 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ 8.11–8.04 (m, 2H), 7.86–7.79 (m, 2H), 7.66–7.59 (m, 1H), 7.59–7.50 (comp, 3H), 7.50–7.43 (m, 2H), 5.94 (d, J = 8.6 Hz, 1H), 5.64 (d, J = 1.4
Hz, 1H), 5.48–5.35 (m, 1H), 4.64–4.46 (comp, 3H), 4.16–3.98 (comp, 2H), 2.06–1.78 (comp, 2H), 1.72–1.57 (m, 1H), 1.45–1.22 (comp, 5H), 1.13–0.86 (comp, 7H), 0.68 (app t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.2, 169.6, 154.3, 140.5, 138.6, 133.9, 133.2, 129.5, 129.4, 128.6, 127.3, 67.5, 65.2, 63.2, 60.1, 43.2, 34.8, 33.1, 27.6, 27.0, 22.5, 21.9, 14.1, 14.0; $m/z$ (ESI-MS) 658.9[MNa]$^+$. The absolute configuration of the title compound was assigned by X-ray crystallography.

**Figure 3.3 Crystal Structure of Compound 3.32**
3-((4R,5S)-1-(4-nitrophenylsulfonyl)-2-thioxo-5-p-tolylimidazolidine-4-carbonyl) oxazolidin-2-one (3.33a): Following the general procedure, the product (mixture of diasteromers) was obtained as a white solid in 90% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp >250 °C (CH$_2$Cl$_2$/hexanes); R$_f$ 0.25 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); [α]$_D^{20}$ +22.5 (c 1.0, acetone); IR (KBr) 3365, 3106, 2999, 1798, 1776, 1702, 1533, 1494, 1396, 1377, 1349, 1267, 1213, 1173, 1117, 1087, 740 cm$^{-1}$; $^1$H NMR (500 MHz, d$_6$-DMSO) δ 10.01 (s, 1H), 8.32–8.27 (m, 2H), 7.96–7.90 (m, 2H), 7.26–7.18 (comp, 4H), 6.02 (d, $J = 1.2$ Hz, 1H), 5.18 (d, $J = 1.2$ Hz, 1H), 4.55–4.40 (comp, 2H), 4.05–3.97 (m, 1H), 3.95–3.86 (m, 1H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, d$_6$-DMSO) δ 179.3, 168.0, 153.7, 150.2, 143.3, 136.1, 130.3, 129.2, 126.5, 66.7, 63.3, 62.1, 42.7, 20.7; m/z (ESI-MS) 491.2 [MH]$^+$, 513.1 [MNa]$^+$.

(4R,5S)-ethyl 1-(4-nitrophenylsulfonyl)-2-thioxo-5-p-tolylimidazolidine-4-carboxylate (3.36a): Pale yellow oil; R$_f$ 0.33 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); [α]$_D^{20}$ −59.0 (c 1.0, CHCl$_3$, 98% ee); IR (KBr) 3419, 1743, 1609, 1532, 1488, 1402, 1373, 1350, 1240, 1213, 1174, 1089, 741, 599 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.13 (d, $J = 8.8$ Hz, 2H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.22 (d, $J = 8.2$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 6.75 (br, s, 1H), 5.94 (d, $J = 2.5$ Hz, 1H), 4.40–4.28 (comp, 2H), 4.20 (d, $J = 2.5$ Hz, 1H), 2.41 (s, 3H), 1.36 (app t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 179.6, 168.2, 151.0, 143.8, 140.2, 135.6, 131.0, 130.3, 127.0, 123.4, 67.9, 63.6, 63.3, 21.4, 14.3; m/z (ESI-MS) 450.1 [MH]$^+$, 472.1 [MNa]$^+$; HPLC:
Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, 
$t_R$=41.0 min (major) and $t_R$=23.0 min.

3-((4R,5S)-5-(3-methoxyphenyl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.33b): Following the general procedure, the product (mixture of diasteromers) was obtained as a pale yellow solid in 92% yield. An analytical sample of the pure trans-diastereomer was obtained by recrystallization from CH$_2$Cl$_2$/hexanes. mp >250 °C (CH$_2$Cl$_2$); 
$R_f$ 0.20 (hexanes/CH$_2$Cl$_2$/EtOAc 1:1:1 v/v/v); $[\alpha]_D^{20}$ +49.0 (c 0.25, acetone); 
IR (KBr) 3364, 3104, 3000, 1797, 1777, 1703, 1526, 1494, 1397, 1375, 1351, 1265, 1210, 1175, 1114, 1085, 854, 740, 582 cm$^{-1}$; $^1$H NMR (400 MHz, $d_6$-DMSO) $\delta$ 10.02 (s, 1H), 8.34-8.28 (m, 2H), 8.01–7.93 (m, 2H), 7.35 (app t, $J = 8.0$ Hz, 1H), 6.99 (dd, $J = 8.0$, 2.3 Hz, 1H), 6.95–6.87 (comp, 2H), 6.06 (d, $J = 1.2$ Hz, 1H), 5.20 (d, $J = 1.2$ Hz, 1H), 4.56–4.40 (comp, 2H), 4.06–3.85 (comp, 2H), 3.73 (s, 3H); $^{13}$C NMR (100 MHz, $d_6$-DMSO) $\delta$ 179.4, 167.9, 159.2, 153.7, 150.2, 143.1, 140.3, 130.4, 129.9, 123.5, 118.4, 113.6, 113.0, 66.7, 63.3, 61.9, 55.1, 42.7; m/z (ESI-MS) 507.4 [MH]$^+$, 529.3 [MNa]$^+$.

(4R,5S)-ethyl 5-(3-methoxyphenyl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.36b): Pale yellow oil; 
$R_f$ 0.25 (CH$_2$Cl$_2$/EtOAc 100:2 v/v); $[\alpha]_D^{20}$ –31.5 (c 1.0, CHCl$_3$, 97% ee); 
IR (KBr) 3374, 3107, 2981, 1744, 1533, 1493, 1372, 1350, 1238, 1209, 1176, 1088, 1064, 855, 740 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.18–8.11 (m, 2H), 7.87–7.78 (m, 2H), 7.33–7.26 (m, 1H), 7.01 (br, s, 1H), 6.98–6.92 (m, 1H), 6.91–6.85 (m, 1H), 6.81–6.77 (m, 1H), 5.93 (d, $J = 2.5$ Hz, 1H), 4.41–4.27 (comp, 2H), 4.22 (d, $J = 2.5$ Hz, 1H), 3.77 (s, 3H), 1.35 (app t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.2, 168.1,
160.5, 150.7, 143.3, 139.5, 131.0, 130.9, 123.4, 118.9, 115.0, 112.9, 67.7, 63.4, 63.3, 55.6, 14.3; \textit{m/z} (ESI-MS) 466.2 [MH]^+; 488.2 [MNa]^+; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 254 nm, \( t_R = 20.9 \) min (major) and \( t_R = 15.2 \) min.

3-((4R,5S)-5-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.33c): Following the general procedure, the product (mixture of diastereomers) was obtained as a white solid in 87\% yield. The mixture of DCM/EtOAc/THF was used as eluent. An analytical sample of the pure \textit{trans}-diastereomer was obtained by recrystallization from CH\(_2\)Cl\(_2\). mp >250 °C (CH\(_2\)Cl\(_2\)); \( R_f = 0.21 \) (hexanes/CH\(_2\)Cl\(_2\)/EtOAc 1:1:1 v/v/v); \( [\alpha]_D^{20} = +65.0 \) (c 0.5, DMSO); \( \text{IR (KBr)} \) 3365, 3111, 1798, 1777, 1703, 1531, 1493, 1397, 1372, 1350, 1267, 1215, 1176, 1117, 1085, 740 cm\(^{-1}\); \( ^1\text{H NMR (500 MHz, } d_6\text{-DMSO)} \) δ 10.11 (s, 1H), 8.25–8.17 (m, 2H), 8.01–7.93 (comp, 4H), 7.92–7.81 (comp, 2H), 7.62–7.53 (comp, 2H), 7.50–7.44 (m, 1H), 6.26 (d, \( J = 1.5 \) Hz, 1H), 5.32 (d, \( J = 1.5 \) Hz, 1H), 4.57–4.42 (comp, 2H), 4.09–3.99 (m, 1H), 3.98–3.88 (m, 1H); \( ^{13}\text{C NMR (125 MHz, } d_6\text{-DMSO)} \) δ 179.4, 168.0, 153.7, 150.1, 143.2, 136.5, 132.8, 132.4, 130.2, 128.6, 128.0, 127.6, 126.7, 126.7, 126.0, 124.0, 123.5, 67.0, 63.4, 61.9, 42.7; \textit{m/z} (ESI-MS) 527.3 [MH]^+, 549.3 [MNa]^+.  

![Structural diagram of 3-((4R,5S)-5-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carbonyl)oxazolidin-2-one (3.33c)](attachment:structure.png)
(4R,5S)-ethyl 5-(naphthalen-2-yl)-1-(4-nitrophenylsulfonyl)-2-thioxoimidazolidine-4-carboxylate (3.36c): Pale yellow oil; Rf 0.33 (CH₂Cl₂/EtOAc 100:2 v/v); [α]D²⁰ –86.5 (c 1.0, CHCl₃, 94% ee); IR (KBr) 3396, 2982, 1743, 1532, 1487, 1372, 1350, 1215, 1177, 1088, 740 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.98–7.93 (m, 2H), 7.90–7.85 (m, 1H), 7.84–7.78 (comp, 3H), 7.76–7.70 (m, 2H), 7.63–7.52 (comp, 2H), 7.33–7.28 (m, 1H), 7.23 (br, s, 1H), 6.14 (d, J = 2.6 Hz, 1H), 4.43–4.29 (comp, 3H), 1.37 (app t, J = 7.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 179.3, 168.2, 150.6, 143.3, 135.0, 133.7, 133.1, 130.8, 129.9, 128.4, 128.0, 127.7, 127.5, 127.1, 123.3, 123.3, 68.0, 63.5, 63.2, 14.3; m/z (ESI-MS) 486.0 [MH]⁺, 508.1 [MNa]⁺; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=90/10, Flow rate = 1 mL/min, UV = 254 nm, tᵣ=66.1 min (major) and tᵣ=33.7 min.

3.4.6 Procedure for the Conversion of Products 3.36a Into Its Corresponding Diamino Acids

(4S,5R)-1-tert-butyl 5-ethyl 3-(4-nitrophenylsulfonyl)-2-oxo-4-p-tolylimidazolidine-1,5-dicarboxylate (3.37)

The mixtures of products 3.36a (763 mg, 1.697 mmol), DMAP (41.5 mg, 0.2 eq.) and Boc₂O (463 mg, 1.25 eq.) in 35 ml CH₂Cl₂ were stirred at rt until 3.36a was completely consumed (~4 h). The mixtures were loaded into the flash chromatography
(EtOAc: hexanes = 30:70) directly and the pale yellow foam was obtained in 920 mg (99% yield).

The product from the previous step was dissolved in 50 ml CH₂Cl₂ and then Hg(OAc)₂ (800 mg, 1.5 eq) were added in one portion. The reaction mixtures were stirred at rt for 24 h. The product 3.37 was obtained as white foam (856 mg, 96% yield) after the filtration with a short celite column. The product 3.37 is pure enough for the next step. Analytical samples were further purified by flash chromatography. Rₚ 0.68 (hexanes/EtOAc 60:40 v/v); [α]ᵢ²₀⁻2¹.0 (c 1.0, CHCl₃); IR (neat) 3107, 2982, 2931, 1805, 1778, 1752, 1731, 1533, 1370, 1350, 1324, 1256, 1204, 1179, 1096, 1023, 855, 741, 683, 661, 613 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.16 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 5.20 (d, J = 1.9 Hz, 1H), 4.46 (d, J = 1.9 Hz, 1H), 4.39–4.27 (comp, 2H), 2.38 (s, 3H), 1.48 (s, 9H), 1.34 (app t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.4, 150.8, 148.8, 148.3, 143.5, 140.2, 134.7, 130.2, 126.5, 123.9, 85.4, 63.0, 62.3, 59.6, 28.1, 21.4, 14.4; m/z (ESI-MS) 533.7 [MH]⁺, 556.0 [MNa]⁺.

(4S,5R)-1-tert-butyl 5-ethyl 2-oxo-4-p-tolylimidazolidine-1,5-dicarboxylate (3.38)

The mixtures of compound 3.37 (100 mg) and K₂CO₃ (78 mg, 3 eq) were dissolved in 5 ml dry DMF and then PhSH (26.8 mg, 1.3 eq) were added dropwise. The suspension was stirred at rt for 3 h. The solution was diluted with 10 ml water and extracted with CH₂Cl₂ (3 × 20 ml). The combined organic layer was dried with Na₂SO₄ and purified by
flash chromatography. The product 3.38 was obtained in 74% yield as white foam. R_f 0.24 (hexanes/EtOAc 60:40 v/v); [α]_D^{20} –36.0 (c 1.0, CHCl₃); IR (neat) 3294, 2979, 2930, 1784, 1709, 1369, 1331, 1233, 1197, 1160, 1116, 1023, 778 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 7.24 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.43 (br, s, 1H), 4.60 (d, J = 3.9 Hz, 1H), 4.41 (d, J = 3.9 Hz, 1H), 4.38–4.24 (comp, 2H), 2.36 (s, 3H), 1.44 (s, 9H), 1.36 (app t, J = 7.1 Hz, 3H); ^13C NMR (125 MHz, CDCl₃) δ 169.9, 155.5, 149.6, 139.0, 137.5, 130.1 , 125.8, 83.4, 65.0, 62.2, 55.4, 28.1, 21.4, 14.5; m/z (ESI-MS) 349.0 [MH]^+, 371.1 [MNa]^+.

(1R,2S)-1-carboxy-2-p-tolylethane-1,2-diaminium chloride (3.39)

![Chemical Structure]

Compound 3.38 (0.273 mmol, 95 mg) in 2 M HCl aqueous solution (12 ml) was heated at reflux for 5 h. The resulting solution was evaporated and the residue was further dried at 40 °C in vacuo overnight. A white solid 3.39 was obtained in quantitative yield. [α]_D^{20} +14.0 (c 0.49, H₂O); ^1H NMR (500 MHz, D₂O) δ 7.40–7.33 (comp, 4H), 4.84 (d, J = 4.8 Hz, 1H), 4.50 (d, J = 4.8 Hz, 1H), 2.38 (s, 3H); ^13C NMR (125 MHz, D₂O) δ 169.4, 141.8, 130.6, 128.0, 126.5, 53.8, 53.3, 20.5; m/z (ESI-MS) 195.1 [MH]^+. 
(4R,5S)-ethyl 2-oxo-5-p-tolylimidazolidine-4-carboxylate (3.40)

Compound **3.39** (73 mg, 0.273 mmol) was dissolved in EtOH (10 ml) and SOCl$_2$ (0.2 ml, 10 eq) was added dropwise at 0 °C. The solution was stirred at 40 °C for 2 h, and reflux for 5 h. The solvent was removed and the residue was extracted with 1 M HCl aq./DCM. Aqueous layer was basified (pH 8-9) with solid Na$_2$CO$_3$ and was extracted with 5% MeOH/DCM (3 × 20 ml). The combined organic layer was dried with Na$_2$SO$_4$. The solvent was removed after the filtration and the pale yellow oil was obtained in 91% yield without further purification.

The product from the previous step was dissolved in anhydrous CH$_2$Cl$_2$ (10 ml) and carbonyldiimidazole (60 mg, 1.5 eq) was added at rt. The solution was heated at reflux for 6 h. The resulting mixture was cooled down to rt and washed by 2 M HCl (5 ml) and water (5 ml). The organic layer was dried with Na$_2$SO$_4$. The compound **3.40** was obtained as white solid in 50% yield by flash chromatography. $R_f$ 0.36 (hexanes/EtOAc 20:80 v/v); $^1$H NMR (500 MHz, CD$_3$OD) δ 7.28 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.2$ Hz, 2H), 4.82 (d, $J = 4.8$ Hz, 1H), 4.33–4.19 (comp, 2H), 4.06 (d, $J = 4.8$ Hz, 1H), 2.34 (s, 3H), 1.31 (app t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 172.8, 165.0, 140.1, 139.3, 130.5, 127.0, 64.0, 62.8, 60.5, 21.1, 14.4; $m/z$ (ESI-MS) 249.2 [MH]$^+$; HPLC: Daicel Chiralpak AD-H, hexanes/i-PrOH=80/20, Flow rate = 1 mL/min, UV = 210 nm, $t_R$=15.5 min (major) and $t_R$=7.9 min.
C4 and C5 coupling constants (4.8 Hz) of compound 3.40 were consistent with data of syn-diastereomers of similar compounds. Also, ee (98%) of compound 3.40 was obtained from chiral HPLC analysis. They proved this reaction sequence did not change the stereo-chemistry of related compounds.
References

1. For a review, see: Lucet, D.; Le Gall, T.; Mioskowski, C. Angew. Chem., Int. Ed. 1998, 37, 2580.


15. Both N-Boc and N-phosphoryl imines gave inferior results.

16. See the experimental section for details.


Chapter IV

Facile Access to Tetrahydroacridine Derivatives with Remote Stereogenic Centers: Catalytic Enantioselective Friedländer Condensations

4.1 Background

4.1.1 Significance of Tetrahydroacridine Derivatives

Tetrahydroacridines, a class of tricyclic heterocycles, are of increasing interest in medicinal chemistry because of their uses as potent enzyme inhibitors. Without a doubt, tacrine is the most important member of this family since it has been marketed as a commercial drug for Alzheimer’s disease.

Scheme 4.1 Selected Examples of Biologically Active Tetrahydroacridines

- 4.1 tacrine
- 4.2 bis(7)-tacrine
- 4.3 EDT
Tacrine (4.1) and its derivatives show efficacy in the treatment of cognitive disorders such as Alzheimer’s disease. Tacrine’s mode of action is attributed to its potent acetylcholinesterase inhibitor activities,\textsuperscript{1b,1c} and compound 4.1 is also known to inhibit other enzymes including butylcholinesterase\textsuperscript{1e} and monoamine oxidase.\textsuperscript{1d} In addition, other pharmacological uses of tacrine, such as blockage of potassium channels and inhibition of neuronal monoamine uptake processes, have been reported.\textsuperscript{1g} Given their important functions in medicinal chemistry, the synthesis and evaluation of new tacrine analogs continues to be of significant interest. Furthermore, evaluation of tacrine analogs with stereogenic centers may constitute an attractive strategy considering the increasing demand for chiral drugs.\textsuperscript{2} Unfortunately, there are no reports focusing on the asymmetric synthesis of chiral non-racemic tacrine analogs.

4.1.2 Synthetic Methods for Tacrine and Tetrahydroacridine Derivatives

One of the most convenient methods for the synthesis of tacrine derivatives is the acid- or thermally-promoted condensation of substituted cyclohexanones and \textit{ortho}-amino benzonitriles.\textsuperscript{3} Another strategy involves the coupling of the corresponding chloro-tetrahydroacridine and amines. However, these methods usually require strong acidic or thermal conditions, which are typically detrimental to asymmetric catalysis.

For those tetrahydroacridine derivatives without amino group, the condensation of substituted cyclohexanones and \textit{ortho}-amino benzaldehydes, known as the Friedländer condensation,\textsuperscript{4} represents the most effective method to construct their tricyclic skeleton. However, relatively harsh reaction conditions are typically required in this type of reaction as well.\textsuperscript{5}
4.1.3 Enamine Catalysis as a Powerful Synthetic Tool

*Scheme 4.2 The Hajos-Parrish-Eder-Sauer-Wiechert Reaction*

Although the proline-catalyzed intramolecular aldol reaction, namely, the Hajos-Parrish-Eder-Sauer-Wiechert reaction,\(^\text{7c, 7d}\) was discovered in the early 1970s (Scheme 4.2), the renaissance of enamine catalysis started in the early 2000’s\(^\text{6-7}\) (Scheme 4.3). This organocatalytic mode of activation has been developed into a powerful synthetic tool for the preparation of valuable chiral building blocks. Enamine catalysis provides a mild and general solution for the in situ transformation of aldehydes and ketones into their corresponding enolate equivalents. In the past decade, a number of reactions were developed that employ this strategy, including aldol reactions\(^\text{8}\), Mannich reactions\(^\text{9}\), Michael additions\(^\text{10}\) and others.\(^\text{11}\) However, relatively few studies have focused on reactions that involve the desymmetrization of prochiral ketones\(^\text{12}\) (Scheme 4.4).
Scheme 4.3 Pioneering Works in Enamine Catalysis

List et al. (2000)

\[
\begin{align*}
&\text{O} + \text{OHC} + \text{(S)-proline (30 mol\%)} \\
&\text{DMSO, rt, 4 h} \quad 4.11 \quad 5 \text{ additional examples} \\
&68\% \text{ yield}, \quad 76\% \text{ ee}
\end{align*}
\]

Barbas et al. (2001)

\[
\begin{align*}
&\text{O} + \text{OHC} + \text{(S)-proline (35 mol\%)} \\
&\text{DMSO, rt, 12 h} \quad 4.11 \quad 5 \text{ additional examples} \\
&50\% \text{ yield}, \quad 94\% \text{ ee}
\end{align*}
\]

MacMillan et al. (2002)

\[
\begin{align*}
&\text{HOO} + \text{HOO} \quad \text{(S)-proline (10 mol\%)} \\
&\text{DMF, 4 °C, 11 h} \quad 4.16 \quad 7 \text{ additional examples} \\
&80\% \text{ yield}, \quad 4:1 \text{ dr}, \quad 99\% \text{ ee}
\end{align*}
\]

Gong et al. (2003)

\[
\begin{align*}
&\text{O} + \text{OHC} \quad \text{catalyst (20 mol\%)} \\
&\text{-25 °C, 24 h} \quad 4.11 \quad 15 \text{ additional examples} \\
&66\% \text{ yield}, \quad 93\% \text{ ee}
\end{align*}
\]
**Scheme 4.4 Desymmetrizations of Prochiral Ketones with Aldol Reactions**

**Gong et al. (2007)**

\[
\text{catalyst (5 mol\%)}
\]

10 equiv

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O}_2\text{N} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\hline
\text{4.10} & \quad \text{4.17 catalyst}
\end{align*}
\]

15 additional examples

90\% yield, 
<1\% other isomers, 
ee >99\%

**Moyano and Rios et al. (2009)**

\[
\begin{align*}
\text{proline (20 mol\%)} & \quad \text{co-cat (20 mol\%)} \\
\text{PhMe, rt, 120 h} & \quad \text{4.19 co-catalyst}
\end{align*}
\]

10 additional examples

85\% yield, 
10:1:0:0, 
ee 99\%

Whereas enamines are considered to be important intermediates in the classical Friedländer process, enamine catalysts such as proline had not been used to catalyze the Friedländer synthesis of achiral quinolines until recently.\textsuperscript{13} However, this reaction appears to be limited to the use of highly activated amino-trifluoromethylketones while simultaneously requiring mild heating.

**Scheme 4.5 Proline-Catalyzed Friedländer Condensations**

**Yu et al. (2008)**

\[
\begin{align*}
\text{proline (30 mol\%)} \\
\text{DMSO, rt or 50 °C}
\end{align*}
\]

11 examples

85-98\% yield
4.2 Proposal and Objective

Based on the discussions in section 4.1, tacrine derivatives share a common structural unit with tetrahydroacridine. The only difference between them is that tacrine derivatives have an additional amino group on the quinoline ring. Therefore, it is possible for us to envision that chiral nonracemic tacrine derivatives 4.22 may be derived from their corresponding tetrahydroacridines 4.25. Therefore, the question we raised here is how to develop a convenient method to access these chiral quinolines 4.25 (Scheme 4.6).

Scheme 4.6 Retrosynthesis of Chiral Tacrine Analogs

Friedländer condensations are one of the classic methods used to synthesize quinolines. However, no asymmetric version of this reaction had been reported. We proposed that chiral quinolines 4.25 could be prepared via an asymmetric Friedländer condensation of ortho-aminobenzaldehydes 4.24 and ketones 4.23. This catalytic enantioselective process could be realized by asymmetric enamine catalysis.

In addition, the elucidation of the mechanisms of proline-catalyzed desymmetrizations will be beneficial to the design of new small molecule catalysts. Although a number of catalytic systems have successfully catalyzed the desymmetrizations of prochiral cyclic ketones, the process of chirality transfer from
catalyst to products is not clear. This challenging problem is associated with several difficulties. Firstly, some known desymmetrizations including aldol reactions, Mannich reactions and Michael reactions generate multiple chiral centers in the products. It is challenging to analyze all of them experimentally. In other words, the isolations and the characterizations of all diastereomers, especially for those minor products, involve a highly complicated process. Another difficulty is that, compared to the corresponding aldol reactions, an increasing number of parameters should be considered when a theoretical model is established. Accordingly, no theoretical models have been reported to tackle this problem so far, although the models for aldol reactions are well established. The proposed asymmetric Friedländer condensations provide an ideal platform to investigate the origin of enantioselectivity in enamine catalyzed desymmetrization processes. In this reaction, only one chiral center exists in the final product and this simplifies the experimental analysis of products, which means that an experimental standard can be used to evaluate the theoretical model, which is a prerequisite for building up a theoretical model.

In the remaining part of this chapter, I will report the successful realization of this methodology, which was applied to the synthesis of a chiral tacrine analog. Furthermore, a theoretical model was established to explain the origin of enantioselectivity.

4.3 Results and Discussions

4.3.1 General Considerations

From the outset of our study, it was clear that several challenges would have to be addressed. First, compared to the relatively electron-poor benzaldehydes that have been
used predominantly in enamine catalyzed aldol reactions, the corresponding ortho-aminobenzaldehydes are appreciably more electron-rich and thus represent less reactive electrophiles. Secondly, it was not clear if it would be possible to conduct the necessary elimination step of the Friedländer sequence under mild enough conditions that would simultaneously allow for a highly enantioselective process. In addition, it is well known that ortho-aminobenzaldehydes tend to self-condense, even under mild conditions.\(^\text{14}\)

### 4.3.2 Evaluation of Catalysts

With these considerations in mind, we investigated the reaction of the commercially available and relatively electron poor 3,5-dibromo-aminobenzaldehyde (\(4.24a\)) with 4-phenyl-cyclohexanone (\(4.23a\)). Among the readily available organocatalysts tested, only amino acids gave acceptable rates and selectivities\(^\text{15}\) (Scheme 4.7 and Table 4.1)

**Scheme 4.7 Selected Chiral Amino Acid Catalysts**

\[
\begin{align*}
4.26a & \quad R = \text{Me} \\ 4.26b & \quad R = \text{t-Bu} \\ 4.26c & \quad R = \text{2-\text{n}Bu} \\ 4.26d & \quad R = \text{2-\text{i}Bu} \\ 4.26e & \quad R = \text{i-Pr} \\ 4.26f & \quad R = \text{Bn} \\ 4.26g & \quad R = \text{Ph} \\
4.26h & \\
4.26i & \\
4.27 & X = \text{CH}_2  \\
4.28a & \quad R = \text{H} \\ 4.28b & \quad R = \text{TBS} \\ 4.28c & \quad R = \text{TBDPS} \\
4.29 & \\
4.30 & \\
4.31 &
\end{align*}
\]
Table 4.1 Evaluation of Catalysts\textsuperscript{a}

\[
\begin{array}{cccccc}
\text{Entry} & \text{Catalyst} & \text{Time (d)} & \text{Yield (%)}\textsuperscript{b} & \text{ee (%)} \\
1 & 4.26\text{a} & 3 & 73 & 66 \\
2 & 4.26\text{b} & 3 & 75 & 72 \\
3 & 4.26\text{c} & 3 & 74 & 70 \\
4 & 4.26\text{d} & 3 & 75 & 66 \\
5 & 4.26\text{e} & 3 & 70 & 70 \\
6 & 4.26\text{f} & 3 & 70 & 47 \\
7 & 4.26\text{g} & 3\textsuperscript{c} & \text{ND} & 62 \\
8 & 4.26\text{h} & 3 & 65 & 50 \\
9 & 4.26\text{i} & 3 & 65 & 47 \\
10 & 4.9 & 1 & 83 & 74 \\
11 & 4.27 & 2 & 68 & 67 \\
12 & 4.28\text{a} & 1 & 78 & 79 \\
13 & 4.28\text{b} & 1 & 82 & 78 \\
14 & 4.28\text{c} & 1 & 83 & 76 \\
15 & 4.29 & 1 & 75 & -67 \\
16 & 4.30 & 1 & 80 & 66 \\
17 & 4.31 & 3\textsuperscript{c} & <5\% & \text{ND} \\
\end{array}
\]

\textsuperscript{a} Reactions were performed at rt on a 0.2 mmol scale in anhydrous DMSO (0.2 M) using 3.0 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee’s were determined by HPLC analysis. \textsuperscript{b} Isolated yields. \textsuperscript{c} The reaction was incomplete.

The catalytic results of the amino acid catalysts are summarized in Table 4.1. Proline derivatives provided the best results. \textit{Trans}-4-hydroxy proline (4.28\text{a}) gave rise
to a slightly higher ee compared to proline itself. Given the poor solubility of proline 4.9 and trans-4-hydroxy proline 4.28a in non-polar solvents, the more soluble silicon protected trans-4-hydroxy proline derivatives were prepared. Gratifyingly, the reactivity and selectivity of these catalysts proved to be very similar to that of unmodified trans-4-hydroxy proline 4.28a.

**Scheme 4.8 Evaluation of Non-Amino Acid Catalysts**

Other catalysts such as diarylprolinol 4.36, diarylprolinol silyl ether 4.35, diamine 4.33 and 4.37, diamine mono-thiourea 4.34 and proline amide 4.32 gave inferior results. Quite surprisingly, proline amides 4.32 incorporating a chiral amino alcohol moiety, which were reported to catalyze the desymmetrization of 4-substituted cyclohexanones with aldehydes, did not give satisfactory results.
Another interesting finding is the conformational effect on the proline ring. Proline molecules have two conformers, a 4-\textit{exo}-puckered one and a 4-\textit{endo}-puckered one.\textsuperscript{17} Although proline does not have an apparent bias (slightly 4-\textit{endo} favored) for each conformer, substituted prolines can strongly favor one of the conformers, which depends on the substituent itself, the substituted position and the stereochemistry of the compound.

In our experiments, the catalysts favoring 4-\textit{exo}-puckered conformation gave better results. Unfortunately, further attempts to increase ee’s were not successful. However, this conformational effect could have some valuable applications in other proline-catalyzed reactions. For example, List et al. recently reported catalytic, asymmetric transannular aldolizations for the total synthesis of (+)-hirsutene.\textsuperscript{18} In their report, the
enantioselectivity of the product is sensitive to the substitution on the proline ring. *Trans*-4-fluoro-proline 4.39 was found to be the best catalyst but no explanation was provided. We hypothesize that the better enantioselectivity is possibly related to the conformation of *trans*-4-fluoro-proline 4.39. Further research in this direction will bring new opportunities to proline-catalyzed reactions.

**Scheme 4.10 Substituted Proline-Catalyzed Asymmetric Transannular Aldolizations**

![Scheme 4.10 Substituted Proline-Catalyzed Asymmetric Transannular Aldolizations](image)

4.3.3 Evaluation of Solvents

In order to improve the rate and selectivity of the reaction, catalyst 4.28b was tested in a broad range of solvents (Table 4.2). Several interesting observations were made in the course of this study. Apolar solvents containing aromatic rings such as toluene and
### Table 4.2 Evaluation of solvents

Reactions were performed at rt on a 0.2 mmol scale in anhydrous solvent (0.2 M) using 3 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee’s were determined by HPLC analysis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>16</td>
<td>82</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>24</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>36</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>48</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>48</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane</td>
<td>36</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>CHCl(_3)</td>
<td>72(^c)</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>CH(_2)Cl(_2)</td>
<td>72(^c)</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>CCl(_4)</td>
<td>72(^c)</td>
<td>65</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>Cyclohexane</td>
<td>72(^c)</td>
<td>45</td>
<td>76</td>
</tr>
<tr>
<td>11</td>
<td>PhMe</td>
<td>72(^c)</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>Xylenes</td>
<td>72(^c)</td>
<td>65</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>PhCF(_3)</td>
<td>72(^c)</td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>14</td>
<td>Anisole</td>
<td>72(^c)</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>15</td>
<td>NMI</td>
<td>10</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>16</td>
<td>Pyridine</td>
<td>12</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>17(^d)</td>
<td>Pyridine</td>
<td>72</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>18(^e)</td>
<td>Pyridine</td>
<td>96(^c)</td>
<td>65</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed at rt on a 0.2 mmol scale in anhydrous solvent (0.2 M) using 3 equiv of cyclohexanone. Reactions were run to full conversion as judged by TLC analysis. The ee’s were determined by HPLC analysis.

\(^b\) Isolated yields.

\(^c\) The reaction was incomplete.

\(^d\) The reaction was run at –20 °C.

\(^e\) The reaction was run at –35 °C.
xylenes gave rise to high selectivities but reactions were very slow (incomplete after three days at rt). On the other hand, more polar solvents gave rise to faster reaction rates, albeit at the expense of selectivity. A closer inspection revealed that solvent polarity alone does not directly correlate with reaction rate. Rather, the presence of basic sites on the solvent appeared to be a factor that significantly impacts reaction rate. These collective observations led us to evaluate pyridine as a reaction medium since it combines apparently favorable attributes of other solvents. Indeed, a reaction conducted in pyridine went to completion in only 12 hours while giving rise to product 4.25a with 83% ee (Table 2, entry 16). This increase in reactivity allowed for the reaction to be performed at lower temperature. At –20 °C, product 4.25a was recovered with 90% ee (entry 17).

Ultimately, a toluene/pyridine solvent mixture was found to provide the best compromise between selectivity and yield. Further optimization also enabled the reduction of catalyst loading to 10 mol %.

4.3.4 Substrate Scope

To illustrate the scope of this methodology, different 4-substituted cyclohexanones were tested under the optimized conditions (Table 4.3). A number of aliphatic and aromatic functional groups with different electronic properties were readily accommodated. Generally, quinoline products were obtained in good yields and with excellent levels of selectivity.
Table 4.3 Scope of Cyclohexanones

\[
\text{R} + \begin{array}{l}
\text{NH}_2 \\
\text{CHO} \\
\text{Br} \\
\text{Br} \\
\text{Br} \\
\text{Br}
\end{array} \xrightarrow{\text{catalyst 4.28b (10 mol%)}} \begin{array}{l}
\text{Br} \\
\text{R}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Method</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4.25a</td>
<td>A</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-OH-Ph</td>
<td>4.25b</td>
<td>A</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-Ph</td>
<td>4.25c</td>
<td>A</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>3-MeO-Ph</td>
<td>4.25d</td>
<td>A</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>4-CF₃-Ph</td>
<td>4.25e</td>
<td>A</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>4.25f</td>
<td>B⁺</td>
<td>62</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>4.25g</td>
<td>B⁺</td>
<td>85</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>i-Pr</td>
<td>4.25h</td>
<td>B</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>n-Pr</td>
<td>4.25i</td>
<td>B</td>
<td>81</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>t-Bu</td>
<td>4.25j</td>
<td>B</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>n-Pentyl</td>
<td>4.25k</td>
<td>B</td>
<td>80</td>
<td>95</td>
</tr>
</tbody>
</table>

\footnotesize{a} Reactions were performed at –25°C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee’s were determined by HPLC analysis. \footnotesize{b} Isolated yields. \footnotesize{c} Method A: 2 equiv of cyclohexanone and solvent (0.5 M); Method B: 2 equiv of cyclohexanone and solvent (0.2 M). \footnotesize{d} 5 equiv of cyclohexanone were used.

As summarized in Table 4.4, a number of ortho-amino benzaldehydes were evaluated in combination with 4-nPr- and 4-Ph-substituted cyclohexanones. Due to their attenuated reactivity, more electron-rich ortho-aminobenzaldehydes required slightly higher reaction temperatures. Satisfactory yields and ee’s were obtained for these substrates. Currently, ortho-aminobenzaldehydes with electron-withdrawing substituents do not work well for this protocol due to their low reactivity.
Table 4.4 Scope of Amino Benzaldehydes

![Diagram](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Product</th>
<th>Method</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>nPr</td>
<td>H</td>
<td>4.45a</td>
<td>A</td>
<td>62</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>4.45b</td>
<td>B</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>nPr</td>
<td>4-Cl</td>
<td>4.45c</td>
<td>A</td>
<td>73</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>4-Cl</td>
<td>4.45d</td>
<td>B</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>nPr</td>
<td>4-CF₃</td>
<td>4.45e</td>
<td>A</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>4-CF₃</td>
<td>4.45f</td>
<td>B</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>nPr</td>
<td>4-CO₂Me</td>
<td>4.45g</td>
<td>A</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>4-CO₂Me</td>
<td>4.45h</td>
<td>B</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>nPr</td>
<td>3,5-Cl₂</td>
<td>4.45i</td>
<td>A</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>3,5-Cl₂</td>
<td>4.45j</td>
<td>B</td>
<td>70</td>
<td>92</td>
</tr>
</tbody>
</table>

*Reactions were performed at –25 °C on a 0.5 mmol scale in anhydrous solvent for 72 h. The ee’s were determined by HPLC analysis. b Isolated yields. c Method A: 5 equiv of cyclohexanones and solvent (0.2 M); Method B: 2 equiv of cyclohexanones and solvent (0.5 M). d Reactions were performed at –5 °C.

4.3.5 Synthesis of a Chiral Non-Racemic Tacrine Analog

Starting from the chiral quinoline products, a facile sequence was developed to access the corresponding tacrine analogs. Quinoline oxide 4.46 was obtained through hydrogenation followed by m-CPBA oxidation. Initially, the nitration of quinoline oxide 4.46 with sulfuric acid and nitric acid gave irreproducible results. The combination of a weaker acid, trifluoroacetic acid, and potassium nitrate was selected based on some reported mechanistic considerations.²² Compound 4.47 was obtained with a satisfactory
**Scheme 4.11** Mechanistic Considerations of Nitration of Quinoline Oxide

![Mechanistic diagram]

yield (86%). Then, the reduction with iron power/acetic acid transformed 4.47 into the final product 4.48.

**Scheme 4.12** Synthesis of an Enantioenriched Tacrine Analog

![Synthesis diagram]

Reaction Conditions: a) 10% Pd/C, H₂, Et₃N, MeOH, rt, 8h, 99%; b) m-CPBA (2 equiv), CH₂Cl₂, rt, 1h, 82%; c) KNO₃, TFA, 60 °C, 1h, 86%; d) Fe, AcOH, 110 °C, 3h, 83%. 

Following the straightforward sequence outlined in Scheme 4.12, the highly enantioenriched tacrine derivative 4.48 was obtained in good yield and without loss of ee.

4.3.6 Computational Study

Given the remoteness of the stereogenic center in the products, the mode of chirality transfer from catalyst to product appeared non-obvious. We thus decided to conduct a computational study to explore the origin of the enantioselectivity for this desymmetrization reaction. As a starting point, we applied the theoretical model first developed by Houk and List.\textsuperscript{23} For aldol reactions of aldehydes with cyclohexanones, both experimental and theoretical results have previously indicated that the rate determining step of this reaction corresponds to the enamine attacking the aldehyde, rather than the preceding enamine formation step.\textsuperscript{19e, 19k} This trend appears to be reversed in reactions that involve very strong electrophiles.\textsuperscript{19j} Given the attenuated electrophilicity of ortho-aminobenzaldehydes, we hypothesized that the rate determining step would also be enamine attack. In other words, although the enamine formation step sets the stereogenic center, we assume that equilibration between different enamines is fast compared to the subsequent aldol addition.

DFT calculations\textsuperscript{24} were performed to locate 64 possible transition states (TS’s) for the C–C bond formation step. These calculations provided several important insights. Firstly, in TS’s with lower energy, the cyclohexane ring-substituent is placed in the pseudo equatorial position, rather than the pseudo axial position. Secondly, placement of the enamine double bond \textit{trans} to the proline carboxylic acid fragment is energetically favorable than the corresponding \textit{cis} arrangement. Another interesting feature is the
Scheme 4.13 Proposed Origin of Enantioselectivity

\[ \text{Scheme 4.13 Proposed Origin of Enantioselectivity} \]

\[ \begin{align*}
\text{TS-1 (endo-chair)} & \quad \Delta G_{\text{rel}} = 0.00 \text{ kcal/mol} \\
\text{TS-2 (exo-chair)} & \quad \Delta G_{\text{rel}} = 0.32 \text{ kcal/mol} \\
\text{TS-3 (endo-boat)} & \quad \Delta G_{\text{rel}} = 0.90 \text{ kcal/mol} \\
\text{TS-4 (exo-boat)} & \quad \Delta G_{\text{rel}} = 1.48 \text{ kcal/mol}
\end{align*} \]

DFT B3LYP/6-31 G (d, p)

exō or endo (conformation of proline ring)
chair or boat (conformation of cyclohexene ring)
presence of an intramolecular hydrogen bond in the ortho-aminobenzaldehyde. The four lowest energy TS’s are shown in Figure 1.\textsuperscript{25} TS 1 and TS 2 both give rise to the observed major enantiomer while TS 3 and TS 4 lead to the minor enantiomer. The calculated ee’s\textsuperscript{26} for gas phase and DMSO are both consistent with the experimental results.

4.3.7 Conclusion

In conclusion, we have reported the first catalytic enantioselective Friedländer reaction. Enamine catalysis allowed for the efficient desymmetrization of 4-substituted cyclohexanones in the reaction with ortho-aminobenzaldehydes. Quinolines with remote stereogenic centers were obtained in generally good yields and with good to excellent levels of enantioselectivity. Furthermore, a chiral quinoline was converted into a highly enantioenriched tacrine derivative. In addition, a theoretical model was established to explain the origin of product chirality. Our discovery of interesting solvent effects, in particular the rate acceleration observed with pyridine, may have implications for other enamine catalyzed reactions.

4.4 Experimental Section

4.4.1 Preparation Procedures for Catalysts, Cyclohexanones and Amino Aldehydes

Catalysts 4.9, 4.26a-l, 4.27, 4.28a and 4.29-4.31 were obtained from commercial suppliers and used directly without further purification. Catalysts 4.28b-c were prepared according to literature methods.\textsuperscript{27, 28} 4-Substituted cyclohexanones 4.23a, 4.23b and 4.23f-k were obtained from commercial suppliers and used directly without further purification. Cyclohexanones 4.23c-e were prepared according to literature methods.\textsuperscript{29, 30} Aminobenzaldehyde 4.24a was obtained from a commercial supplier and used directly.
without further purification. Aminobenzaldehydes 4.24b-f were prepared according to literature methods.\textsuperscript{32, 33, 34, 35}

### 4.4.2 General Procedure for Catalytic Enantioselective Friedländer Condensations

Catalyst 4.28b (12.0 mg, 0.05 mmol), 4-phenyl cyclohexanone (4.23a, 174 mg, 1.00 mmol) and 3,5-dibromo-2-amino-benzaldehyde (4.24a, 139 mg, 0.50 mmol) was dissolved in pyridine/toluene (7:3, v/v) (1 mL) at room temperature. The reaction mixture was placed immediately into a $-25 \, ^\circ C$ cooling bath. The reaction progress was monitored by TLC analysis. The crude reaction mixture was loaded directly onto a short silica gel column and eluted with EtOAc. The first 100 mL fraction was collected and dried in vacuo. The residue was purified by flash chromatography (eluent CH$_2$Cl$_2$/hexanes 1:3 to 1:1). The product was obtained as pale yellowish oil.

Reaction parameters for specific substrates:

- **A**: 0.5 M in aminobenzaldehyde
- **B**: 0.2 M in aminobenzaldehyde
- **C**: 2.0 equiv. of cyclohexanone
- **D**: 5.0 equiv. of cyclohexanone
- **E**: $-25 \, ^\circ C$
- **F**: $-5 \, ^\circ C$

\begin{align*}
4.25a-e, 4.45f, 4.45h, 4.45j : & \ A+C+E \\
4.25h-k : & \ B+C+E \\
4.45a, 4.45c : & \ B+D+F \\
4.45b, 4.45d : & \ A+C+F
\end{align*}

### 4.4.3 Product Characterization Data
(S)-5,7-dibromo-2-phenyl-1,2,3,4-tetrahydroacridine (4.25a): Following the general procedure, compound 4.25a was obtained as a pale yellowish oil (158 mg, 76% yield). Rf = 0.46 (Hexanes/EtOAc 9:1 v/v); [α]D20 = −37.0 (c 1.0, CHCl3, 92% ee); IR (KBr) 2922, 1586, 1462, 948, 746, 699 cm−1; 1H NMR (500 MHz, CDCl3) δ 8.06 (d, J = 2.1 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H), 7.40–7.34 (comp, 2H), 7.33–7.29 (comp, 2H), 7.29–7.24 (m, 1H), 3.46–3.37 (m, 1H), 3.33–3.21 (comp, 2H), 3.19–3.09 (comp, 2H), 2.39–2.31 (m, 1H), 2.21–2.10 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 160.7, 145.5, 142.8, 135.1, 134.6, 132.7, 129.1, 129.1, 128.9, 127.0, 126.9, 125.3, 118.8, 40.4, 37.3, 34.0, 30.5; m/z (ESI-MS) 416.2 ([79Br79Br]+), 418.2 ([79Br81Br]+), 420.2 ([81Br81Br]+); HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, tR = 41.8 min (major) and tR = 47.2 min.

(S)-4-(5,7-dibromo-1,2,3,4-tetrahydroacridin-2-yl)phenol (4.25b): Following the general procedure, compound 4.25b was obtained as a white solid (130 mg, 60% yield). mp = 238–240 °C (decomposition); Rf = 0.07 (Hexanes/EtOAc 9:1 v/v); [α]D20 = −25.0 (c 0.5, CHCl3, 92% ee); IR (KBr) 3367, 3067, 2937, 1585, 1515, 1464, 1242, 1205, 830 cm−1; 1H NMR (500 MHz, CDCl3) δ 8.06 (d, J = 2.1 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.73 (s, 1H), 7.19–7.13 (comp, 2H), 6.85–6.79 (comp, 2H), 4.95 (br s, 1H), 3.44–3.35 (m, 1H), 3.31–3.20 (comp, 2H), 3.14–3.03 (comp, 2H), 2.35–2.26 (m, 1H), 2.15–2.04 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 160.8, 154.4, 142.8, 137.7, 135.2, 134.7, 132.8, 129.1, 129.1, 128.1, 125.2, 118.8, 115.7, 39.5, 37.5, 33.9, 30.6; m/z (ESI-MS) 432.3 ([79Br79Br]+), 434.3 ([79Br81Br]+), 436.3 ([81Br81Br]+);
HPLC: Daicel Chiralpak AD-H, \(n\)-hexane/i-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, \(t_R = 31.0\) min (major) and \(t_R = 36.3\) min.

(S)-5,7-dibromo-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroacridine (4.25c): Following the general procedure, compound 4.25c was obtained as white foam (167 mg, 75% yield). \(R_f = 0.24\) (Hexanes/EtOAc 9:1 v/v); \([\alpha]_D^{20} –24.5\) (c 1.0, CHCl\(_3\), 93% ee); IR (KBr) 3062, 2918, 2834, 1608, 1584, 1511, 1460, 1243, 1174, 1030, 828 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.04\) (d, \(J = 2.1\) Hz, 1H), 7.82 (d, \(J = 2.1\) Hz, 1H), 7.70 (s, 1H), 7.25–7.19 (comp, 2H), 6.93–6.86 (comp, 2H), 3.82 (s, 3H), 3.45–3.35 (m, 1H), 3.31–3.19 (comp, 2H), 3.15–3.01 (comp, 2H), 2.36–2.26 (m, 1H), 2.17–2.03 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 160.8, 158.5, 142.8, 137.6, 135.1, 134.6, 132.7, 129.1, 129.1, 127.9, 125.3, 118.8, 114.3, 55.5, 39.5, 37.5, 34.1, 30.7; m/z (ESI-MS) 446.2 (\(^{79}\)Br\(^{79}\)Br) \([M+H]^{+}, 448.3 (\(^{79}\)Br\(^{81}\)Br) \([M+H]^{+}, 450.3 (\(^{81}\)Br\(^{81}\)Br) \([M+H]^{+}\); HPLC: Daicel Chiralpak OD-H, \(n\)-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \(t_R = 39.5\) min (major) and \(t_R = 46.3\) min.

(S)-5,7-dibromo-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroacridine (4.25d): Following the general procedure, compound 4.25d was obtained as a pale yellow solid (163 mg, 73% yield). \(\text{mp} = 132–134^\circ\) C; \(R_f = 0.27\) (Hexanes/EtOAc 9:1 v/v); \([\alpha]_D^{20} –19.5\) (c 1.0, CHCl\(_3\), 92% ee); IR (KBr) 2932, 1609, 1582, 1486, 1460, 1265, 1049, 925, 780, 695 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.04\) (d, \(J = 2.1\) Hz, 1H), 7.82 (d, \(J = 2.1\) Hz, 1H), 7.70 (s, 1H), 7.31–7.24 (m, 1H), 6.89 (app d, \(J = 7.7\) Hz, 1H), 6.87–6.83 (m, 1H), 6.83–6.78 (m, 1H), 3.82 (s, 3H), 3.46–3.34 (m, 1H), 3.33–3.18 (comp, 2H), 3.18–3.04 (comp, 2H), 3.04–2.94 (m, 1H), 2.90–2.76 (m, 1H), 2.76–2.65 (m, 1H), 2.65–2.54 (m, 1H), 2.54–2.43 (m, 1H), 2.43–2.34 (m, 1H), 2.34–2.26 (m, 1H), 2.26–2.16 (m, 1H), 2.16–2.03 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 161.9, 159.8, 143.9, 137.6, 135.1, 134.6, 132.7, 129.1, 129.1, 127.9, 125.3, 118.8, 114.3, 55.5, 39.5, 37.5, 34.1, 30.7; m/z (ESI-MS) 446.2 (\(^{79}\)Br\(^{79}\)Br) \([M+H]^{+}, 448.3 (\(^{79}\)Br\(^{81}\)Br) \([M+H]^{+}, 450.3 (\(^{81}\)Br\(^{81}\)Br) \([M+H]^{+}\); HPLC: Daicel Chiralpak OD-H, \(n\)-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \(t_R = 39.0\) min (major) and \(t_R = 46.3\) min.
2.38–2.28 (m, 1H), 2.20–2.05 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 160.7, 160.1, 147.2, 142.8, 135.1, 134.6, 132.6, 130.0, 129.1, 129.1, 125.3, 119.4, 118.8, 113.2, 111.7, 55.5, 40.4, 37.3, 34.0, 30.4; m/z (ESI-MS) 446.3 ($^{79}$Br$^{79}$Br) [M+H]$^+$, 448.3 ($^{79}$Br$^{81}$Br) [M+H]$^+$, 450.3 ($^{81}$Br$^{81}$Br) [M+H]$^+$; HPLC: Daicel Chiralpak AS-H, n-hexane/i-PrOH = 99/1, Flow rate = 0.5 mL/min, UV = 280 nm, $t_R = 24.1$ min and $t_R = 26.5$ min (major).

The absolute configuration of the title compound was assigned by X-ray crystallography.

Figure 4.1 Crystal Structure of Compound 4.25d

(S)-5,7-dibromo-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroacridine (4.25e):

Following the general procedure, compound 4.25e was obtained as pale yellowish foam (145 mg, 60% yield). Rf = 0.39 (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20}$ = -30.0 (c 1.0, CHCl$_3$, 90% ee); IR (KBr) 2927, 1619, 1586, 1463, 1326, 1164, 1124, 1069, 1017, 839, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.06 (d, $J = 2.0$ Hz, 1H), 7.84 (d, $J = 2.0$ Hz, 1H), 7.73 (s,
1H), 7.62 (d, \( J = 8.1 \) Hz, 1H), 7.42 (d, \( J = 8.1 \) Hz, 1H), 3.48–3.36 (m, 1H), 3.35–3.07 (comp, 4H), 2.42–2.30 (m, 1H), 2.24–2.09 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 160.2, 149.4 (app d, \( J_{C-F} = 1.3 \) Hz), 142.9, 135.3, 134.7, 132.0, 129.2 (q, \( J_{C-F} = 32.5 \) Hz), 129.1, 129.1, 127.4, 125.9 (q, \( J_{C-F} = 3.8 \) Hz), 125.3, 124.4 (q, \( J_{C-F} = 271.9 \) Hz), 119.0, 40.3, 37.0, 33.8, 30.2; \( m/z \) (ESI-MS) 484.2 (\(^{79}\)Br\(^{79}\)Br) [M+H]\(^+\), 486.2 (\(^{79}\)Br\(^{81}\)Br) [M+H]\(^+\), 488.3 (\(^{81}\)Br\(^{81}\)Br) [M+H]\(^+\); HPLC: Daicel Chiralpak OD-H, \( n \)-hexane/\( i \)-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, \( t_R = 23.2 \) min (major) and \( t_R = 29.9 \) min.

\((S)-5,7\text{-dibromo-2-methyl-1,2,3,4-tetrahydroacridine (4.25f):}\) Following the general procedure, compound \textbf{4.25f} was obtained as white foam (110 mg, 62\% yield). Rf = 0.52 (Hexanes/EtOAc 9:1 v/v); \([\alpha]_D^{20} = -46.0 \) (c 1.0, CHCl\(_3\), 91\% ee); IR (KBr) 2924, 1585, 1463, 1318, 924, 863, 736 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.02 (d, \( J = 2.1 \) Hz, 1H), 7.80 (d, \( J = 2.1 \) Hz, 1H), 7.65 (s, 1H), 3.29 (ddd, \( J = 18.1, 5.5, 3.5 \) Hz, 1H), 3.12 (ddd, \( J = 18.1, 11.4, 6.2 \) Hz, 1H), 3.04 (dd, \( J = 16.6, 3.8 \) Hz, 1H), 2.60 (dd, \( J = 16.6, 10.8 \) Hz, 1H), 2.14–1.92 (comp, 2H), 1.65–1.55 (m, 1H), 1.13 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 162.5, 143.8, 136.0, 135.6, 134.1, 130.3, 130.2, 126.4, 119.7, 38.9, 34.7, 32.5, 30.3, 23.0; \( m/z \) (ESI-MS) 354.3 (\(^{79}\)Br\(^{79}\)Br) [M+H]\(^+\), 356.3 (\(^{79}\)Br\(^{81}\)Br) [M+H]\(^+\), 358.3 (\(^{81}\)Br\(^{81}\)Br) [M+H]\(^+\); HPLC: Daicel Chiralpak OD-H, \( n \)-hexane/\( i \)-PrOH = 99/1, Flow rate = 1 mL/min, UV = 254 nm, \( t_R = 6.9 \) min (major) and \( t_R = 13.6 \) min.
**(S)-5,7-dibromo-2-ethyl-1,2,3,4-tetrahydroacridine (4.25g):** Following the general procedure, compound **4.25g** was obtained as a pale yellowish oil (157 mg, 85% yield). Rf = 0.51 (Hexanes/EtOAc 9:1 v/v); [α]$_D^{20}$ = 57.5 (c 1.0, CHCl$_3$, 94% ee); IR (KBr) 2958, 2922, 2873, 2854, 1586, 1462, 1425, 943, 734 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.67 (s, 1H), 4.25 (t, J = 6.4 Hz, 2H), 3.30 (ddd, J = 18.1, 5.4, 3.7 Hz, 1H), 3.15–3.04 (comp, 2H), 2.60 (dd, J = 16.7, 10.7 Hz, 1H), 2.19–2.09 (m, 1H), 1.81–1.70 (m, 1H), 1.64–1.52 (m, 1H), 1.50–1.42 (comp, 2 H), 1.02 (app t, J = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.6, 142.7, 134.8, 134.5, 133.0, 129.1, 129.0, 125.2, 118.6, 35.8, 35.6, 33.5, 29.0, 29.0, 11.7; m/z (ESI-MS) 368.4 ($^{79}$Br$^{79}$Br) [M+H]$^+$, 370.4 ($^{79}$Br$^{81}$Br) [M+H]$^+$, 372.4 ($^{81}$Br$^{81}$Br) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 254 nm, t$_R$ = 7.0 min (major) and t$_R$ = 12.7 min.

**(S)-5,7-dibromo-2-isopropyl-1,2,3,4-tetrahydroacridine (4.25h):** Following the general procedure, compound **4.25h** was obtained as a pale yellowish oil (153 mg, 80% yield). Rf = 0.51 (Hexanes/EtOAc 9:1 v/v); [α]$_D^{20}$ = –61.5 (c 1.0, CHCl$_3$, 93% ee); IR (KBr) 2956, 2870, 1586, 1463, 1425, 944, 862, 734 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.68 (s, 1H), 3.35–3.28 (m, 1H), 3.13–2.99 (comp, 2H), 2.71 (dd, J = 16.7, 9.7 Hz, 1H), 2.16–2.08 (m, 1H), 1.73–1.54 (comp, 3H), 1.01 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.7, 142.6, 134.8, 134.6, 133.0, 129.1, 129.0, 125.2, 118.5, 40.6, 34.0, 32.9, 32.3, 26.5, 20.0, 20.0; m/z (ESI-MS) 382.3 ($^{79}$Br$^{79}$Br) [M+H]$^+$, 384.3 ($^{79}$Br$^{81}$Br) [M+H]$^+$, 386.3 ($^{81}$Br$^{81}$Br) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t$_R$ = 7.4
min (major) and $t_R = 12.5$ min.

(S)-5,7-dibromo-2-propyl-1,2,3,4-tetrahydroacridine (4.25i): Following the general procedure, compound 4.25i was obtained as a pale yellowish oil (155 mg, 81% yield). $R_f = 0.54$ (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20} = -58.0$ (c 1.0, CHCl$_3$, 94% ee); IR (KBr) 2925, 1586, 1463, 1319, 945, 855, 779, 734 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.03 (d, $J = 2.1$ Hz, 1H), 7.81 (d, $J = 2.1$ Hz, 1H), 7.68 (s, 1H), 3.29 (ddd, $J = 18.1, 5.4, 3.9$ Hz, 1H), 3.16–3.03 (comp, 2H), 2.61 (dd, $J = 16.6, 10.6$ Hz, 1H), 2.17–2.08 (m, 1H), 1.92–1.80 (m, 1H), 1.64–1.54 (m, 1H), 1.51–1.36 (comp, 4H), 0.96 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.6, 142.7, 134.8, 134.5, 133.0, 129.2, 129.0, 125.2, 118.6, 38.5, 35.9, 33.8, 33.5, 29.3, 20.3, 14.5; $m/z$ (ESI-MS) 382.3 ($^{79}$Br$^{79}$Br) [M+H]$^+$, 384.3 ($^{79}$Br$^{81}$Br) [M+H]$^+$, 386.3 ($^{81}$Br$^{81}$Br) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, $t_R = 6.7$ min (major) and $t_R = 10.8$ min.

(S)-5,7-dibromo-2-tert-butyl-1,2,3,4-tetrahydroacridine (4.25j): Following the general procedure, compound 4.25j was obtained as a pale yellowish oil (163 mg, 82% yield). $R_f = 0.54$ (Hexanes/EtOAc 9:1 v/v); $[\alpha]_D^{20} = -56.5$ (c 1.0, CHCl$_3$, 91% ee); IR (KBr) 2959, 1586, 1463, 1394, 1365, 1318, 945, 868, 784, 752, 727 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J = 2.1$ Hz, 1H), 7.80 (d, $J = 2.1$ Hz, 1H), 7.69 (s, 1H), 3.33 (ddd, $J = 17.6, 4.7, 2.6$ Hz, 1H), 3.12–2.99 (comp, 2H), 2.72 (dd, $J = 16.4, 11.9$ Hz, 1H), 2.21–2.12 (m, 1H), 1.62–1.47 (comp, 2H), 1.00 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.7, 142.6, 134.8, 134.7, 133.7, 129.2, 129.0, 125.2, 118.5, 44.7, 34.8, 32.8, 30.9, 27.5, 24.6; $m/z$ (ESI-MS) 396.2 ($^{79}$Br$^{79}$Br) [M+H]$^+$, 398.2 ($^{79}$Br$^{81}$Br) [M+H]$^+$, 400.2 ($^{81}$Br$^{81}$Br) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-
hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \( t_R = 8.4 \) min (major) and \( t_R = 12.2 \) min.

(S)-5,7-dibromo-2-pentyl-1,2,3,4-tetrahydroacridine (4.25k): Following the general procedure, compound 4.25k was obtained as pale yellowish foam (165 mg, 80% yield). \( R_f = 0.53 \) (Hexanes/EtOAc 9:1 v/v); \([\alpha]_D^{20} = -54.5\) (c 1.0, CHCl\(_3\), 95% ee); IR (KBr) 2953, 2928, 2886, 2858, 1584, 1464, 1422, 1317, 924, 869, 851, 777, 734, 685 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 8.00\) (d, \( J = 2.1 \) Hz, 1H), 7.77 (d, \( J = 2.1 \) Hz, 1H), 7.64 (s, 1H), 3.27 (ddd, \( J = 18.1, 5.4, 3.8 \) Hz, 1H), 3.14–3.00 (comp, 2H), 2.58 (dd, \( J = 16.8, 10.6 \) Hz, 1H), 2.18–2.04 (m, 1H), 1.90–1.73 (m, 1H), 1.63–1.50 (m, 1H), 1.47–1.22 (comp, 8H), 0.91 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta 161.6, 142.6, 134.7, 134.5, 133.0, 129.1, 129.0, 125.2, 118.5, 36.3, 36.0, 34.0, 33.5, 32.3, 29.3, 26.9, 22.9, 14.3; m/z (ESI-MS) 410.4 (\(^{79}\)Br\(^{79}\)Br) [M+H]\(^+\), 412.4 (\(^{79}\)Br\(^{81}\)Br) [M+H]\(^+\), 414.4 (\(^{81}\)Br\(^{81}\)Br) [M+H]\(^+\); HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \( t_R = 6.5 \) min (major) and \( t_R = 11.2 \) min.

(S)-2-propyl-1,2,3,4-tetrahydroacridine (4.45a): Following the general procedure, compound 4.45a was obtained as white foam (70 mg, 62% yield). \( R_f = 0.15 \) (Hexanes/EtOAc 9 :1 v/v); \([\alpha]_D^{20} = -77.5\) (c 1.0, CHCl\(_3\), 87% ee); IR (KBr) 2955, 2926, 2870, 1492, 1456, 1415, 751 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 7.97\) (app d, \( J = 8.5 \) Hz, 1H), 7.78 (s, 1H), 7.68 (app d, \( J = 8.1 \) Hz, 1H), 7.63–7.55 (m, 1H), 7.46–7.38 (m, 1H), 3.22 (ddd, \( J = 17.6, 5.8, 3.8 \) Hz, 1H), 3.14–2.99 (comp, 2H), 2.58 (dd, \( J = 16.4, 10.6 \) Hz, 1H), 2.18–2.05 (m, 1H), 1.92–1.76 (m, 1H), 1.65–1.52 (m, 1H), 1.51–1.34 (comp, 4H), 0.95 (t, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \)
159.6, 146.9, 135.2, 130.9, 128.7, 128.5, 127.4, 127.1, 125.7, 38.6, 36.1, 33.9, 33.3, 29.6, 20.3, 14.6; m/z (ESI-MS) 226.4 [M+H]+; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, t_R = 8.2 min (major) and t_R = 9.5 min.

(S)-2-phenyl-1,2,3,4-tetrahydroacridine (4.45b): Following the general procedure, compound 4.45b was obtained as pale yellowish foam (78 mg, 60% yield). Rf = 0.17 (Hexanes/EtOAc 9:1 v/v); [α]_D^{20} –30.0 (c 1.0, CHCl₃, 87% ee); IR (KBr) 3027, 2929, 1601, 1492, 1415, 751, 700 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 8.02 (app d, J = 8.5 Hz, 1H), 7.84 (s, 1H), 7.72 (app d, J = 8.1 Hz, 1H), 7.67–7.58 (m, 1H), 7.50–7.42 (m, 1H), 7.41–7.32 (m, 1H), 7.37–7.23 (comp, 5H), 3.36 (ddd, J = 17.9, 5.6, 3.1 Hz, 1H), 3.31–3.20 (comp, 2H), 3.18–3.06 (comp, 2H), 2.39–2.28 (m, 1H), 2.23–2.11 (m, 1H); ^13C NMR (125 MHz, CDCl₃) δ 158.7, 147.0, 145.9, 135.3, 130.6, 129.0, 128.9, 128.6, 127.4, 127.2, 127.1, 126.7, 125.9, 40.7, 37.6, 33.9, 30.7; m/z (ESI-MS) 260.3 [M+H]+; HPLC: Daicel Chiralpak AD-H, n-hexane/i-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, t_R = 10.9 min and t_R = 11.9 min (major).

(S)-6-chloro-2-propyl-1,2,3,4-tetrahydroacridine (4.45c): Following the general procedure, compound 4.45c was obtained as a yellowish solid (75 mg, 73% yield). mp = 70–72 °C; Rf = 0.43 (Hexanes/EtOAc 9:1 v/v); [α]_D^{20} –58.5 (c 1.0, CHCl₃, 87% ee); IR (KBr) 2954, 2924, 1485, 1068, 921, 883, 797 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 7.95 (d, J = 1.9 Hz, 1H), 7.74 (s, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.36 (dd, J = 8.7, 1.9 Hz, 1H), 3.19 (dd, J = 18.0, 5.6, 3.8 Hz, 1H), 3.11–2.97 (comp, 2H), 2.56 (dd, J = 16.5, 10.7 Hz, 1H), 2.17–2.05 (m, 1H), 1.90–1.75 (m, 1H), 1.64–1.50 (m, 1H), 1.50–1.33 (comp, 4H), 0.95 (t, J = 7.0 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 160.8, 147.1, 135.0, 134.3, 131.2, 128.3, 127.5, 126.7, 125.7, 38.6, 36.1, 33.8,
33.3, 29.4, 20.3, 14.5; m/z (ESI-MS) 260.4 ($^{35}$Cl) [M+H]$^+$, 262.4 ($^{37}$Cl) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \( t_R = 6.8 \text{ min (major)} \) and \( t_R = 10.2 \text{ min} \).

**(S)-6-chloro-2-phenyl-1,2,3,4-tetrahydroacridine (4.45d):** Following the general procedure, compound 4.45d was obtained as a white solid (88 mg, 60% yield). mp = 90–92 °C; \( [\alpha]_D^{20} = -47.0 \) (c 1.0, CHCl$_3$, 87% ee); IR (KBr) 3028, 2929, 1615, 1484, 1413, 1068, 764, 699 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) \( \delta \) 8.01 (d, \( J = 1.9 \) Hz, 1H), 7.82 (s, 1H), 7.65 (d, \( J = 8.7 \) Hz, 1H), 7.41 (dd, \( J = 8.7, 1.9 \) Hz, 1H), 7.39–7.34 (comp, 2H), 7.34–7.30 (comp, 2H), 7.30–7.24 (m, 1H), 3.33 (ddd, \( J = 18.0, 5.6, 3.1 \) Hz, 1H), 3.30–3.18 (comp, 2H), 3.17–3.07 (comp, 2H), 2.39–2.29 (m, 1H), 2.23–2.10 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) \( \delta \) 159.9, 147.3, 145.7, 135.1, 134.6, 130.9, 128.9, 128.4, 127.6, 127.0, 126.8, 125.7, 113.5, 138.8, 138.4, 135.7, 33.8, 30.6; m/z (ESI-MS) 294.4 ($^{35}$Cl) [M+H]$^+$, 296.4 ($^{37}$Cl) [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 95/5, Flow rate = 1 mL/min, UV = 280 nm, \( t_R = 15.6 \text{ min (major)} \) and \( t_R = 18.1 \text{ min} \).

**(S)-2-propyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroacridine (4.45e):** Following the general procedure, compound 4.45e was obtained as a white solid (103 mg, 70% yield). mp = 48–49 °C; \( [\alpha]_D^{20} = -63.5 \) (c 1.0, CHCl$_3$, 90% ee); IR (KBr) 2958, 2929, 2874, 1443, 1418, 1325, 1291, 1222, 1159, 1126, 1058, 904, 688 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) \( \delta \) 8.29 (d, \( J = 1.1 \) Hz, 1H), 7.84 (s, 1H), 7.80 (d, \( J = 8.5 \) Hz, 1H), 7.60 (dd, \( J = 8.5, 1.1 \) Hz, 1H), 3.24 (ddd, \( J = 18.0, 5.6, 3.8 \) Hz, 1H), 3.15–3.04 (comp, 2H), 2.62 (dd, \( J = 16.6, 10.7 \) Hz, 1H), 2.18–2.10 (m, 1H), 1.93–1.80 (m, 1H), 1.67–1.55 (m, 1H),
1.50–1.37 (comp, 4H), 0.96 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.4, 145.7, 134.9, 133.2, 130.4 (q, J$_{C-F}$ = 32.4 Hz), 128.8 (app d, J$_{C-F}$ = 1.0 Hz), 128.2, 126.5 (q, J$_{C-F}$ = 4.4 Hz), 124.4 (q, J$_{C-F}$ = 272.3 Hz), 121.4 (q, J$_{C-F}$ = 3.2 Hz), 38.5, 36.2, 33.8, 33.3, 29.4, 20.3, 14.5; m/z (ESI-MS) 294.4 [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, $t_R$ = 4.6 min (major) and $t_R$ = 5.5 min.

**(S)-2-phenyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroacridine (4.45f):** Following the general procedure, compound 4.45f was obtained as a white solid (98 mg, 60% yield). mp = 137–138 °C; Rf = 0.35 (Hexanes/EtOAc 9:1 v/v); [α]$_D^{20}$ -38.0 (c 1.0, CHCl$_3$, 92% ee); IR (KBr) 2922, 1606, 1440, 1417, 1333, 1152, 1119, 1058, 770 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.33 (app s, 1H), 7.89 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.63 (dd, $J = 8.5, 1.4$ Hz, 1H), 7.42–7.24 (comp, 5H), 3.38 (ddd, $J = 18.1, 5.6, 3.2$ Hz, 1H), 3.34–3.22 (comp, 2H), 3.22–3.10 (comp, 2H), 2.41–2.32 (m, 1H), 2.25–2.12 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.5, 145.9, 145.5, 135.0, 132.9, 130.7 (q, J$_{C-F}$ = 32.5 Hz), 128.9, 128.8 (app d, J$_{C-F}$ = 0.8 Hz), 128.3, 127.0, 126.9, 126.6 (q, J$_{C-F}$ = 4.4 Hz), 124.3 (q, J$_{C-F}$ = 272.3 Hz), 121.6 (q, J$_{C-F}$ = 3.1 Hz), 40.5, 37.6, 33.8, 30.5; m/z (ESI-MS) 328.4 [M+H]$^+$; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 98/2, Flow rate = 1 mL/min, UV = 254 nm, $t_R$ = 20.5 min (major) and $t_R$ = 23.1 min.

**(S)-methyl 7-propyl-5,6,7,8-tetrahydroacridine-3-carboxylate (4.45g):** Following the general procedure, compound 4.45g was obtained as an off-white solid (125 mg, 88% yield). mp = 117–118 °C; Rf = 0.10 (Hexanes/EtOAc 9:1 v/v); [α]$_D^{20}$ -70.0 (c 1.0, CHCl$_3$, 90% ee); IR (KBr) 2948, 2931,
2867, 1716, 1446, 1414, 1267, 1218, 1188, 1090, 764 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.71 (app s, 1H), 8.02 (d, \(J = 8.5\) Hz, 1H), 7.81 (s, 1H), 7.73 (app d, \(J = 8.5\) Hz, 1H), 3.97 (s, 3H), 3.29–3.19 (m, 1H), 3.15–3.02 (comp, 2H), 2.61 (dd, \(J = 16.6, 10.7\) Hz, 1H), 2.18–2.07 (m, 1H), 1.92–1.79 (m, 1H), 1.66–1.54 (m, 1H), 1.50–1.36 (comp, 4H), 0.96 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 167.3, 160.9, 146.1, 134.9, 133.2, 131.3, 130.2, 129.9, 127.3, 125.3, 52.5, 38.6, 36.3, 33.8, 33.3, 29.4, 20.3, 14.5; \(m/z\) (ESI-MS) 284.4 [M+H]\(^+\); HPLC: Daicel Chiralpak OD-H, \(n\)-hexane/i-PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, \(t_R = 12.7\) min (major) and \(t_R = 17.1\) min.

\((S)\)-methyl 7-phenyl-5,6,7,8-tetrahydroacridine-3-carboxylate (4.45h): Following the general procedure, compound 4.45h was obtained as an off-white solid (128 mg, 81% yield). mp = 143–145 °C; Rf = 0.05 (Hexanes/EtOAc 9:1 v/v); [\(\alpha\)]\(_D\)\(^{20}\) = –45.0 (c 1.0, CHCl\(_3\), 90% ee); IR (KBr) 2934, 1720, 1441, 1274, 1220, 1091, 759, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.74 (s, 1H), 8.05 (d, \(J = 8.5\) Hz, 1H), 7.84 (s, 1H), 7.75 (d, \(J = 8.5\) Hz, 1H), 7.42–7.22 (comp, 5H), 3.98 (s, 3H), 3.41–3.32 (m, 1H), 3.32–3.19 (comp, 2H), 3.19–3.07 (comp, 2H), 2.40–2.29 (m, 1H), 2.23–2.10 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 167.2, 160.0, 146.2, 145.6, 134.9, 132.8, 131.4, 130.4, 129.8, 128.9, 127.4, 127.0, 126.8, 125.4, 52.6, 40.5, 37.7, 33.8, 30.6; \(m/z\) (ESI-MS) 318.4 [M+H]\(^+\); HPLC: Daicel Chiralpak OD-H, \(n\)-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, \(t_R = 74.8\) min (major) and \(t_R = 90.1\) min.
(S)-5,7-dichloro-2-propyl-1,2,3,4-tetrahydroacridine (4.45i): Following the general procedure, compound 4.45i was obtained as a yellowish solid (113 mg, 77% yield). mp = 62–64 °C; Rf = 0.41 (Hexanes/EtOAc 9:1 v/v); [α]_D^20 −70.5 (c 1.0, CHCl₃, 93% ee); IR (KBr) 2955, 2926, 2870, 1593, 1464, 1425, 1321, 1237, 1089, 968, 928, 861, 781, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.70 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 2.2 Hz, 1H), 3.30 (ddd, J = 18.1, 5.4, 3.9 Hz, 1H), 3.17–3.02 (comp, 2H), 2.60 (dd, J = 16.6, 10.6 Hz, 1H), 2.17–2.08 (m, 1H), 1.91–1.80 (m, 1H), 1.62–1.53 (m, 1H), 1.50–1.36 (comp, 4H), 0.96 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 161.2, 141.7, 134.6, 133.8, 133.1, 130.5, 129.2, 128.7, 125.0, 38.5, 36.0, 33.7, 33.5, 29.3, 20.3, 14.5; m/z (ESI-MS) 294.4 (35Cl³⁵Cl) [M+H]^+, 296.3 (35Cl³⁷Cl) [M+H]^+, 298.3 (³⁷Cl³⁷Cl) [M+H]^⁺; HPLC: Daicel Chiralpak OD-H, n-hexane/i-PrOH = 99/1, Flow rate = 1 mL/min, UV = 280 nm, t_R = 6.3 min (major) and t_R = 10.7 min.

(S)-5,7-dichloro-2-phenyl-1,2,3,4-tetrahydroacridine (4.45j): Following the general procedure, compound 4.45j was obtained as a yellowish oil (115 mg, 70% yield). Rf = 0.31 (Hexanes/EtOAc 9:1 v/v); [α]_D^20 −51.0 (c 1.0, CHCl₃, 92% ee); IR (KBr) 2926, 1593, 1463, 1427, 1321, 1237, 1089, 971, 857, 780, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (s, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.40–7.24 (comp, 5H), 3.43 (ddd, J = 18.2, 5.4, 3.2 Hz, 1H), 3.34–3.22 (comp, 2H), 3.19–3.08 (comp, 2H), 2.40–2.31 (m, 1H), 2.22–2.09 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 160.3, 145.5, 141.8, 134.7, 134.0, 132.7, 130.8, 129.5, 128.9, 128.7, 127.0, 126.9, 125.1, 40.4, 37.4, 34.0, 30.5; m/z (ESI-MS) 328.4 (³⁵Cl³⁵Cl) [M+H]^⁺, 330.4 (³⁵Cl³⁷Cl) [M+H]^⁺, 332.4 (³⁷Cl³⁷Cl) [M+H]^⁺; HPLC: Daicel Chiralpak OD-H, n-
hexane/\text{-}i\text{-}PrOH = 98/2, Flow rate = 1 mL/min, UV = 280 nm, \( t_R = 34.4 \) min (major) and \( t_R = 38.6 \) min.

### 4.4.4 Synthesis of a Chiral Tacrine Analog

**Conversion of 4.25i into 4.45a**

\[
\begin{align*}
\text{4.25i} & \xrightarrow{\text{10\% Pd/C, H}_2, \text{Et}_3\text{N, MeOH, \text{rt}, 8 h}} \text{4.45a} \\
\text{766 mg, 2 mmol, triethylamine (0.85 mL, 3.0 equiv.) and Pd/C (10 wt\%, 77 mg) was mixed with 10 mL of methanol. The flask was sealed with a septum and charged with a hydrogen gas balloon. After 8 h, the mixture was filtered through a plug of celite and rinsed with EtOAc. The combined filtrate was dried with anhydrous Na}_2\text{CO}_3. The solvent was removed in vacuo after filtration and compound 4.45a was obtained (448 mg, 99\% yield) and used directly in the next step.}
\end{align*}
\]

**Conversion of 4.45a into (S)-2-propyl-1,2,3,4-tetrahydroacridine 10-oxide (4.46)**

\[
\begin{align*}
\text{4.45a} & \xrightarrow{\text{2.0 eq m-CPBA, CH}_2\text{Cl}_2, \text{rt, 1 h}} \text{4.46} \\
\text{245 mg, 1.087 mmol} & \text{ dissolved in 4 mL of CH}_2\text{Cl}_2 \text{ and cooled to 0 °C. Subsequently, a solution of m-CPBA (500 mg, 2.0 equiv.) in 6 mL of CH}_2\text{Cl}_2 \text{ was added slowly. The reaction was allowed to warm to rt. After completion of the reaction (1 h), the reaction mixture was quenched by dilution with water and extracted with CH}_2\text{Cl}_2. \text{ The organic layer was collected and washed with water. The}
\end{align*}
\]
solution was dried with anhydrous Na₂SO₄ and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 2:1 to 1:2). Compound 4.46 was obtained as an off-white solid (215 mg, 82% yield). mp = 92–94 °C; Rf = 0.35 (Hexanes/EtOAc 1:1 v/v); [α]D^20 = −76.5 (c 1.0, CH₂Cl₂, 94% ee); IR (KBr) 2954, 2926, 2869, 1569, 1502, 1325, 1234, 1093, 768, 749 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 8.69 (app d, J = 8.8 Hz, 1H), 7.72 (app d, J = 8.1 Hz, 1H), 7.68–7.61 (m, 1H), 7.56–7.48 (m, 1H), 7.43 (s, 1H), 3.41 (ddd, J = 20.0, 6.1, 3.3 Hz, 1H), 3.10–2.89 (comp, 2H), 2.57 (dd, J = 16.2, 10.5 Hz, 1H), 2.20–2.07 (m, 1H), 1.83–1.69 (m, 1H), 1.60–1.30 (comp, 5H), 0.94 (t, J = 7.1 Hz, 3H); ^13C NMR (125 MHz, CDCl₃) δ 147.1, 140.3, 132.2, 129.4, 128.5, 127.8, 127.5, 124.7, 119.6, 37.9, 35.9, 33.0, 28.2, 25.9, 20.3, 14.5; m/z (ESI-MS) 242.3 [M+H]^+.

Conversion of 4.46 into (S)-9-nitro-2-propyl-1,2,3,4-tetrahydroacridine 10-oxide (4.47)^22

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\[ \text{4.46} \xrightarrow{\text{KNO}_3/TFA, 60 °C, 1 h} \text{4.47} \]
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Compound 4.46 (46 mg, 0.191 mmol) was dissolved in trifluoroacetic acid (1.6 mL, 110 equiv.). The resulting solution was warmed to 60 °C and KNO₃ powder (58 mg, 3.0 equiv.) was added in one portion. After maintaining the temperature at 60 °C for one
hour, the reaction mixture was allowed to cool to rt and an excess of water was added. The mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL). The organic layers were combined, washed with 5% aqueous NaHCO$_3$ solution and dried with anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel (Hexanes/EtOAc = 4:1). Compound 4.47 was obtained as a yellowish solid (47 mg, 86% yield). mp = 118–120 °C; Rf = 0.34 (Hexanes/EtOAc 7:3 v/v); [α]$_D^{20}$ = -317.0 (c 1.0, CH$_2$Cl$_2$, 94% ee); IR (KBr) 2953, 1567, 1521, 1102, 764 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.73 (app d, $J$ = 8.7 Hz, 1H), 7.81–7.65 (comp, 3H), 3.41 (ddd, $J$ = 20.2, 5.3, 2.9 Hz, 1H), 3.05–2.88 (comp, 2H), 2.57 (dd, $J$ = 17.3, 10.6 Hz, 1H), 2.23–2.13 (m, 1H), 1.83–1.73 (m, 1H), 1.59–1.49 (m, 1H), 1.48–1.36 (comp, 4H), 0.94 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.0, 142.3, 140.8, 130.9, 130.0, 124.8, 122.3, 120.2, 120.0, 37.7, 32.3, 31.6, 27.3, 26.4, 20.1, 14.4; m/z (ESI-MS) 287.2 [M+H]+.

Conversion of 4.13 into (S)-2-propyl-1,2,3,4-tetrahydroacridin-9-amine (4.48)$^{38}$

![Conversion reaction](image)

Compound 4.47 (47 mg, 0.164 mmol) and iron powder (83 mg, 9.0 equiv.) was mixed with acetic acid (2 mL) at rt. The resulting mixture was heated at 110 °C for 3 h. Subsequently, the mixture was allowed to cool to rt and diluted with ethanol (15 mL). The crude mixture was filtered and the filtrate dried in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/MeOH/NH$_4$OH = 350:50:2 v/v). Compound 4.48 was obtained as a brownish solid (32.6 mg, 83% yield). mp = 153–155
°C; Rf = 0.11 (MeOH/EtOAc 1:1 v/v); [α]D\textsubscript{20} = -63.5 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}, 94% ee); IR (KBr) 3354, 3238, 2954, 2926, 2869, 1644, 1566, 1501, 1427, 1377, 1305, 758, 736 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD) δ 8.01 (dd, J = 8.4, 1.0 Hz, 1H), 7.72 (dd, J = 8.4, 1.0 Hz, 1H), 7.53 (ddd, J = 8.4, 6.8, 1.0 Hz, 1H), 7.33 (ddd, J = 8.4, 6.8, 1.0 Hz, 1H), 2.99 (ddd, J = 17.3, 5.1, 3.3 Hz, 1H), 2.90 (ddd, J = 17.3, 11.8, 5.5 Hz, 1H), 2.78 (dd, J = 16.1, 5.4 Hz, 1H), 2.15 (dd, J = 16.1, 10.5 Hz, 1H), 2.09–1.99 (m, 1H), 1.86–1.74 (m, 1H), 1.57–1.39 (comp, 5H), 0.98 (t, J = 7.1 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CD\textsubscript{3}OD) δ 158.7, 150.8, 147.0, 129.9, 127.4, 124.5, 122.4, 118.3, 110.4, 40.2, 35.1, 33.7, 31.5, 30.0, 21.2, 14.7; m/z (ESI-MS) 241.4 [M+H]+.

The product 4.48 was benzoylated with BzCl following a reported procedure.\textsuperscript{39} The ee of the benzoylated product 4.52 was found to be 94% as determined by HPLC analysis. HPLC conditions: Daicel Chiralpak AD-H, \textit{n}-hexane/i-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280 nm, \text{t}_R = 20.6 min (major) and \text{t}_R = 25.1 min.

4.4.5 Computational Studies

Stationary points of transition state geometries were optimized and characterized by frequency analysis using hybrid density functional theory (B3LYP)\textsuperscript{40} and the 6-31G (d, p) basis set as implemented in Gaussian 09.\textsuperscript{41} Enthalpies, Δ\textit{H}\textsubscript{298}, and free energies, Δ\textit{G}\textsubscript{298}, were computed for the gas phase. The solvation energies, Δ\textit{G}\textsubscript{298(ε=47)}, for transition states were computed using a polarizable continuum model\textsuperscript{42} with a permittivity of 47, the value for DMSO, the solvent used in the experiments. These calculations involve the solvation model CPCM as implemented in Gaussian 09. Enantiomeric excesses for the
predictions were determined by converting the differences in the calculated gas-phase free energies of activation, \( \Delta G_{298} \), to %ee using absolute rate theory: 
\[
\ln(k_1/k_2) = -e^{\Delta G/RT}.
\]

A theoretical model was established based on the Houk-List model\textsuperscript{23d} for proline catalyzed aldol reactions. The reaction of 4-phenyl cyclohexanone with ortho-amino benzaldehyde was selected for this computational study. Six independent parameters (exo or endo conformation of proline ring, cis or trans enamine, ax or eq disposition of the 4-substituent of the cyclohexene ring, pseudo-boat or pseudo-chair conformation of the cyclohexene ring, si or re approach of amino benzaldehyde and the conformations of amino benzaldehyde with or without intramolecular hydrogen bonding) were considered and 64 corresponding TS’s were calculated in the gas phase. The four TS’s with lowest energy were further calculated in DMSO using CPCM. The stationary point was located in each TS and only one negative frequency was found in each case. For comparison, four TS’s from the cis enamine were also provided.

**Coordinates of TS geometries for the reaction of proline enamine of 4-phenyl cyclohexanone with ortho-amino benzaldehyde.**

For trans-enamine TS’s:

**TS1 (endo-chair in gas phase)**

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TS1' (endo-chair in DMSO)

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Sum of electronic and thermal Free Energies= -1266.189093

TS7 (endo-boat in gas phase)
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21          6           0       1.066596   -1.062273   1.401720
22          1           0       -1.201921   -0.371080   -1.715294
23          1           0       -2.945611   -1.526245   -1.650685
24          1           0       -5.244107   -2.402385   1.793464
25          6           0       -4.735145   -1.659835   1.174257
26          1           0       -4.249250   -3.122004   2.349727
27          6           0       0.407274    2.275230   -0.260715
28          1           0       -0.782360   -0.426316    2.349727
29          1           0        0.915450   -1.264457   -2.033010
30          1           0       -1.310178    1.768976   -1.443356
31          1           0       1.032448    2.624761   -0.613699
32          1           0       1.557540    1.620131   2.205490
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34          6           0       1.475157   -1.621552   0.028093
35          6           0       2.867053    3.630598   -0.095807
36          6           0       1.134250   -2.613735  -1.412050
37          6           0       0.928311    2.644108   1.009378
38          6           0       2.164663    3.316890   1.061763
39          6           0       2.353174    3.287853  -1.349933
40          1           0       0.713228    2.364934   -2.381413
41          1           0       2.562522    3.600461   2.033262
42          1           0       2.887873    3.543313   -2.258513
43          1           0       3.813987    4.157287   -0.018278
44          6           0       2.978241   -1.777103  -0.129403
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46          6           0       3.843862   -0.678539   0.010505
47          6           0       4.914736   -3.196032   0.540622
48          1           0       2.880931   -3.896705  -0.493064
49          6           0       5.222037   -0.837141  -0.152579
50          1           0       3.442101    0.310073   0.193957
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Sum of electronic and thermal Free Energies= -1266.190560

TS8 (exo-boat in gas phase)

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</tbody>
</table>

HF = -1266.6118924
Sum of electronic and zero-point Energies= -1266.131631
Sum of electronic and thermal Energies= -1266.106905
Sum of electronic and thermal Enthalpies= -1266.105961
Sum of electronic and thermal Free Energies= -1266.186322
References


20. For instance, the reaction in dichloromethane (dielectric constant = 9.1) took substantially longer to go to completion as compared to the corresponding reaction in dioxane (dielectric constant = 2.2), while giving rise to a similar level of enantioselectivity.


24. Gaussian 09 (Revision A.02): Frisch, M. J. et al., Gaussian, Inc., Wallingford, CT, 2009 (For the full reference, see reference 39).

25. TS structures were generated using CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

26. The predicted enantiomeric excesses were determined by converting the differences in the calculated gas-phase free energies of activation, \( \Delta \Delta G_{298} \), to \% ee using absolute rate theory: \( \ln(k_1/k_2) = -e^{\Delta \Delta G/RT} \).


APPENDIX

Selected HPLC Profiles and NMR Spectra

General Information

Proton nuclear magnetic resonance spectra (¹H-NMR) were recorded on a Varian VNMRS-500 MHz instrument or a 400 MHz instrument and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm, CD₃OD at 3.31 ppm and d₆-DMSO at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex; br = broad; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (¹³C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument or a Varian VNMRS-400 MHz instrument and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.2 ppm, CD₃OD at 49.0 ppm and d₆-DMSO at 39.5 ppm). HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors.
HPLC profiles of 2.35

![HPLC profiles graph]

![HPLC profiles graph]
HPLC profiles of 2.66a
HPLC profiles of 2.66b
HPLC profiles of 2.66c

![HPLC profile diagram]
HPLC profiles of 2.66d
HPLC profiles of 2.66e
HPLC profiles of 2.66f
HPLC profiles of 2.66g
HPLC profiles of 2.66h
HPLC profiles of 2.66i
HPLC profiles of 2.66j

![HPLC profile diagram]
HPLC profiles of 2.66k

![Chemical Structure Image]

![Graph Image]

![Another Graph Image]
HPLC profiles of 2.66l

![HPLC profile graph]

![HPLC profile graph]
HPLC profiles of 2.66m

![HPLC Profile](image1)

![HPLC Profile](image2)
HPLC profiles of 2.66n

![HPLC Profiles](image-url)
HPLC profiles of 2.66o
HPLC profiles of 2.66p

![HPLC Profiles](image_url)
HPLC profiles of 2.66q
HPLC profiles of 2.66r

\[
\begin{align*}
&\text{HPLC profiles of 2.66r} \\
&\text{[Chemical structure image]}
\end{align*}
\]
HPLC profiles of 2.66s
HPLC profiles of 2.66t

\[
\begin{align*}
\text{O} & \quad \text{NH} \\
\text{S} & \quad \text{CO} \\
\text{O}_2\text{N} & \quad \text{CO}_2\text{Et} \\
\text{F} & \quad 
\end{align*}
\]
HPLC profiles of 3.18a

![HPLC profile diagram]
HPLC profiles of 3.34b

\[
\text{TsN} \quad \text{NH} \quad \text{CO}_2\text{Et}
\]

![HPLC profiles of 3.34b](image-url)
HPLC profiles of 3.34c

\[
\begin{align*}
\text{BsN} \quad &\text{NH} \\
&\text{CO}_2\text{Et}
\end{align*}
\]
HPLC profiles of 3.34d

trans+cis enantiomers
HPLC profiles of 3.35a

![HPLC profiles of 3.35a](image-url)
HPLC profiles of 3.35b
HPLC profiles of 3.35c

\[ \text{HPLC profiles of 3.35c} \]
HPLC profiles of 3.35d
HPLC profiles of 3.35e
HPLC profiles of 3.35f

\[
\text{BSN NH S}
\]
\[
\text{CO}_2\text{Et}
\]
HPLC profiles of 3.35g

\[
\text{BsN} \quad \text{NH} \\
\text{CO_2Et} \\
\text{Br}
\]
HPLC profiles of 3.35h

![HPLC profile image]
HPLC profiles of 3.35i

\[
\text{BSN NH Cl CO}_2\text{Et}
\]
HPLC profiles of 3.35j

\[
\text{BSN NH CO}_2\text{Et}
\]
HPLC profiles of 3.35k
HPLC profiles of 3.35l
HPLC profiles of 3.35m
HPLC profiles of 3.35n

\[
\begin{align*}
\text{S} & \\
\text{BsN} & \\
\text{NH} & \\
\text{CO}_2\text{Et} & \\
\text{O} & 
\end{align*}
\]
HPLC profiles of 3.35o

![HPLC profile diagram](image)
HPLC profiles of 3.35p

trans enantiomers

trans+cis enantiomers

cis cis
HPLC profiles of 3.31q
HPLC profiles of 3.36a
HPLC profiles of 3.36b

![HPLC profiles](image)

- [Image 1]: HPLC profile 1
- [Image 2]: HPLC profile 2
HPLC profiles of 3.36c

![Chemical structure of 3.36c](image)

![HPLC profile 1](image)

![HPLC profile 2](image)
HPLC profiles of 3.40

[Chemical structure image]

[Graphs showing HPLC profiles]
HPLC profile of 4.25a

![HPLC profile image](image-url)
HPLC profile of 4.25b
HPLC profile of 4.25c
HPLC profile of 4.25d
HPLC profile of 4.25e

\[
\text{Br} \quad \text{N} \quad \text{Br} \\
\text{Br} \quad \text{CF}_3
\]
HPLC profile of 4.25f

![HPLC profile diagram]

The diagram shows the HPLC profile of compound 4.25f, with peaks indicating the retention times and UV absorbance intensity. The structure of 4.25f is also shown, with molecular details such as the presence of bromine (Br) and methyl (Me) groups.
HPLC profile of 4.25g
HPLC profile of 4.25h

![HPLC Profile](image)

![HPLC Profile](image)
HPLC profile of 4.25i
HPLC profile of 4.25j

\[ \text{Br} \quad \text{N} \quad \text{t-Bu} \]

[Diagram of HPLC profile]

\[ mAU \]

[Graph showing HPLC peaks]
HPLC profile of 4.25k

Br
N
Br
Pent
HPLC profile of 4.45a
HPLC profile of 4.45b

\[
\begin{align*}
\text{Ph} & \\
\end{align*}
\]
HPLC profile of 4.45c

[Graph of HPLC profile]
HPLC profile of 4.45d
HPLC profile of 4.45e

\[ \text{Pr} \]

\[ \text{F}_3\text{C} \]
HPLC profile of 4.45f

\[
\text{F}_3\text{C}\begin{array}{c}
\text{N} \\
\text{Ph}
\end{array}
\]

[Graph of HPLC profile]
HPLC profile of 4.45g
HPLC profile of 4.45h

![HPLC profile image]

Chemical structure:

\[
\text{MeO}_2\text{C} \quad \text{Ph} \quad \text{N} \quad \text{MeO} \quad 2 \quad \text{C}
\]
HPLC profile of 4.45i
HPLC profile of 4.45j
HPLC profile of 4.52

NHBz

n-Pr
$^1$H NMR of 2.64 in CDCl$_3$
$^{13}$C NMR of 2.64 in CDCl$_3$
$^1$H NMR of 2.65 in CDCl$_3$
$^{13}$C NMR of 2.65 in CDCl$_3$
$^1\text{H NMR of 2.46 in CDCl}_3$
$^{13}$C NMR of 2.46 in CDCl$_3$
$^1$H NMR of 2.39 in $d_6$-DMSO
$^{13}$C NMR of 2.39 in $d_6$-DMSO
$^1$H NMR of 2.47 in CDCl$_3$
$^{13}$C NMR of 2.47 in CDCl$_3$
$^1$H NMR of 2.35 in CDCl$_3$
$^{13}$C NMR of 2.35 in CDCl$_3$
$^1$H NMR of 2.66a in CDCl$_3$
$^{13}$C NMR of 2.66a in CDCl$_3$
$^1$H NMR of 2.66b in CDCl$_3$
$^{13}$C NMR of 2.66b in CDCl$_3$
$^1$H NMR of 2.66c in CDCl$_3$
$^{13}$C NMR of 2.66c in CDCl$_3$
$^1$H NMR of 2.66d in CDCl$_3$
$^{13}$C NMR of 2.66d in CDCl₃
$^1\text{H NMR of 2.66e in CDCl}_3$

![NMR Spectrum Image]
$^{13}$C NMR of 2,66e in CDCl$_3$
$^1$H NMR of 2,66f in CDCl$_3$
$^{13}$C NMR of 2,5-difluorobenzaldehyde oxime in CDCl$_3$
\(^1\)H NMR of 2.66g in CDCl\(_3\)

\[
\begin{align*}
\text{O} & \text{S} \\
\text{O} & \text{N} \\
\text{Me} & \text{CO}_2\text{Et} \\
\end{align*}
\]
$^{13}$C NMR of 2.66g in CDCl$_3$
$^1$H NMR of 2,66h in CDCl$_3$
$^{13}$C NMR of 2.66h in CDCl$_3$
$^1$H NMR of 2,66i in CDCl$_3$
$^{13}\text{C NMR of 2.66i in CDCl}_3$
$^1$H NMR of 2.66j in CDCl$_3$
$^{13}$C NMR of 2,6-dimethyl-1,2-dihydroquinoline in CDCl$_3$
$^{1}H$ NMR of 2.66k in CDCl₃
$^1$C NMR of 2.66k in CDCl$_3$
$^1$H NMR of 2.66l in CDCl$_3$
$^{13}$C NMR of 2.661 in CDCl$_3$
$^1$H NMR of 2.66m in CDCl$_3$
$^{13}\text{C NMR of 2.66m in CDCl}_3$

![Chemical Structure](image)
$^1$H NMR of 2.66 in CDCl$_3$
$^{13}$C NMR of 2,66n in CDCl$_3$
$^{1}H$ NMR of 2,66o in CDCl$_3$
\( ^{13}\text{C NMR of 2.66o in CDCl}_3 \)
$^1$H NMR of 2.66p in CDCl$_3$
$^{13}$C NMR of 2.66p in CDCl$_3$
$^1$H NMR of 2.66g in CDCl₃
$^{13}$C NMR of 2.66q in CDCl$_3$
$^1$H NMR of 2.66r in CDCl$_3$
$^{13}$C NMR of 2,6-dimethyl in CDCl$_3$
$^1\text{H NMR of 2.66s in CDCl}_3$
$^{13}$C NMR of 2.66s in CDCl$_3$
$^1$H NMR of 2.51 in CDCl$_3$
\(^{13}\text{C} \text{NMR of 2.51 in CDCl}_3\)
$^1$H NMR of 2,6-difluoro-6-oxo-4-phenyl-4H-pyran-3-carboxylic acid ethyl ester in CDCl$_3$. 
$^{13}$C NMR of 2.66t in CDCl$_3$
$^1$H NMR of cis-2.36 in CDCl$_3$
$^{13}$C NMR of cis-2,36 in CDCl$_3$
D$_{2}$-NMR of 3.18s in CDCl$_{3}$
$^1$H NMR of 3.18c in $d_6$-DMSO
$^1$C NMR of 3,3-d in CDCl$_3$
$^1$H NMR of 3.18d in $d_6$-DMSO

![Chemical Structure](image)

| f (ppm) | 10.5 | 9.5 | 9.0 | 8.5 | 8.0 | 7.5 | 7.0 | 6.5 | 6.0 | 5.5 | 5.0 | 4.5 | 4.0 | 3.5 | 3.0 | 2.5 | 2.0 | 1.5 | 1.0 | 0.5 | 0.0 |
|---------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
$^1$H NMR $\delta$ (ppm) in CDCl$_3$
$^1$H NMR of 3.3.3 in CDCl$_3$
$^{31}$C NMR of 3.35c in CDCl$_3$
$^3$H NMR of 3.31d in d$_6$ DMSO

![NMR Spectrum](image)

fl (ppm): 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
$^{31}$C NMR of 3.3 ld in $d_6$-DMSO
$^3$H NMR of 3310 in $d_6$ DMSO
$^1$H NMR of 3,3'-diMe-CTC4
$^{1}{H}NMR$ of $33.5\text{mM CuCl}_2$
$^1$H NMR of 3.3S in CDCl$_3$
$^1$H NMR of 3.35 g in CDCl$_3$
$^1$H NMR of 3,35h in CDCl$_3$
$^{13}$C NMR of 3,3-dimethylcyclopentane in CDCl$_3$. The spectrum shows resonances at various ppm values, indicating the chemical shifts of different carbon atoms in the molecule.
^13C NMR of 3 SNs in CDCl₃
$^1$H NMR of 3.3lj in CDCl$_3$
$^1$H NMR of 3.35\% in CDCl$_3$
$^{13}$C NMR of 3.35K in $d_6$-DMSO

\[
\text{BSNII} \quad \text{NH} \\
\text{CO}_2\text{Et}
\]
$^{13}$C NMR of 3.38 ppm in $d_6$-DMSO

![Chemical Structure](image)

f (ppm)
$^{13}$C NMR of 3.31m in CDCl$_3$
$^{13}$C NMR of 3,35n in CDCl₃
$^1$H NMR of 3.35e in CDCl$_3$
$^{13}$C NMR of 3.35 ppm in CDCl$_3$
$^1$H NMR of 5.34q in CDCl$_3$
$^1$H NMR of 3.32 in CDCl$_3$
$\text{H}^1$ NMR of $\text{2oS}$ in $\text{d}_6$-DMSO
$^1$H NMR at 300 MHz in CDCl$_3$
$^1$H NMR of 5.336 in CDCl$_3$
$^1$H NMR of 3.55c in $d_6$-DMSO
$^1$H NMR of 3,55c in $d_6$-DMSO
$^1$H NMR of 3.66c in CDCl$_3$
$^1$H NMR of 37 in CDCl₃
$^1$H NMR of 3.38 in CDCl$_3$
$^{13}$C NMR of 3,38 in CDCl$_3$
$^{13}$C NMR of 3.39 in D$_2$O

![Chemical structure](image)
$^1$H NMR of 3.40 in CD$_3$OD
$^1$H NMR of 4.25a in CDCl$_3$
$\delta_C$ NMR of 4,25a in CDCl$_3$
$^1$H NMR of 4.25b in CDCl$_3$
$^1$H NMR of 4.25c in CDCl$_3$
$\delta_C$ NMR of 1,25-in CDCl$_3$
$^1$H NMR of 4.25e in CDCl$_3$
$^1\text{H NMR of 4.25f in CDCl}_3$
$^{13}$C NMR of 4.25h in CDCl$_3$
$^{13}C$ NMR of 4,25 in CDCl$_3$
$^1$H NMR of 4.25 in CDCl$_3$
$^1^3^C$ NMR of 4.25 in CDCl$_3$
$^1$H NMR of 445 in CDCl$_3$
$^1$H NMR of 45b in CDCl$_3$
$^1$C NMR of 445c in CDCl$_3$
$^1$H NMR of 4.45g in CDCl$_3$.

Diagram: Chemical structure and NMR spectrum with peaks labeled.
$^{13}\text{C} \text{ NMR of 445g in CDCl}_3$
^1H NMR of 4-45 in CDCl₃
$^{13}$C NMR of 4.45 in CDCl$_3$
$^1$H NMR of 4.45j in CDCl$_3$
$^{13}$C NMR of 445 in CDCl$_3$
$^1$H NMR of 4-46 in CDCl$_3$
$^{13}C$ NMR of 4.46 in CDCl$_3$
$^1$H NMR of 4.48 in CDCl$_3$
Curriculum Vitae

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Publications


Highlighted in “SYNFACT”, October 2009; also, highlighted in “JACS Select #7”, 2009.


