ACYL IMIDAZOLE: A PROMISING TEMPLATE FOR ASYMMETRIC LEWIS AND BRØNSTED ACID MEDIATED 1,3-DIPOLAR CYCLOADDITIONS

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Construction of chiral complex molecules continues to be a challenge for organic chemists all over the world and to address this challenge numerous methodologies have been developed. 1,3-Dipolar cycloaddition reactions is one such simple and elegant method, which can be employed towards the construction of chiral heterocycles. The ability to construct multiple stereocenters in one operation is one of the salient features of dipolar cycloaddition reaction. Asymmetric dipolar cycloaddition via chiral Lewis or Brønsted acid catalyzed processes is aided by the development of various templates, which provide points of attachment for these catalyst. Application of acyl imidazoles as multifunctional templates has been investigated for Lewis and Brønsted acid catalyzed 1,3-dipolar cycloaddition of azomethine imines and nitrones.

Chapter 1. A review of 1,3-dipolar cycloaddition towards the construction of chiral nitrogen containing heterocycles is discussed in this chapter. This chapter intends to provide the reader a current state of asymmetric 1,3-dipolar cycloaddition.

Chapter 2. Development of *exo* and enantioselective Cu(II) catalyzed azomethine imine cycloaddition to pyrazolidinone acrylates is discussed in this chapter. The key issues approached in this chapter includes impact of metal geometry on diastereoselectivity as well as effect of *N*-1 and C-5 substitution on enantioselectivity of cycloadducts. Investigation into the scope and limitation of azomethine imines and dipolarophiles has also been discussed.
Chapter 3. This chapter introduces acyl imidazoles as multifunctional template for asymmetric azomethine imine cycloaddition. Limitation of substrate scope for azomethine imine cycloaddition encountered in the previous chapter has been resolved by the use of acyl imidazoles as templates. Synthesis of complementary diastereomers of azomethine imine cycloadducts via Lewis acid and Brønsted acid catalyzed reactions has been discussed in this chapter.

Chapter 4. This chapter highlights the application of acyl imidazoles as template for first Bronsted acid catalyzed exo and enantioselective nitrone cycloaddition to electron deficient olefins. Study of appropriate chiral Brønsted acid and investigation of breadth and scope of nitrones and dipolarophiles has also been discussed here.

Chapter 5. This chapter address one of the most challenging aspect of synthetic organic chemistry namely the construction of chiral quaternary stereocenters. This study highlights chiral Brønsted catalyzed nitro cycloaddition to β,β-disubstituted-α,β-unsaturated acyl imidazole leading to the formation of isoxazolidines with chiral quaternary stereocenter. This methodology is useful for the construction of chiral fluorinated heterocycles.
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LIST OF ABBREVIATIONS

Å...........................................Angstrom

[α]...........................................Specific rotation (° mL/g dm)

Ac.........................................Acetyl

Aq.........................................Aqueous

Ar...........................................Aryl

BA..........................................Brønsted acid

BINOL.....................................1,1′-Bi-2-naphthol

BOX........................................Bis(oxazoline)

Bn............................................Benzyl

t-Bu...........................................tert-Butyl

Calcd......................................Calculated

CBA........................................Chiral Brønsted acid

CLA........................................Chiral Lewis acid

δ.............................................Chemical shift in parts per million

DBFOX....................................4,6-Dibenzofurandiyl-2,2′-bis(oxazoline)

DCM........................................Dichloromethane

Dil...........................................Dilute

dr............................................Diastereomeric ratio

ee............................................Enantiomeric excess

ent..........................................Enantiomer
Equiv..........................Equivalent
ESI..............................Electrospray ionization
Et.................................Ethyl
EWG...............................Electron-withdrawing group
FMO...............................Frontier Molecular Orbital
GC.................................Gas chromatography
h.................................Hours
HCl...............................Hydrochloric acid
HOMO..............................Highest occupied molecular orbital
HPLC..............................High pressure liquid chromatography
HRMS..............................High resolution mass spectroscopy
Hz.................................Hertz
IR.................................Infrared
J.................................Coupling constants (in NMR)
L.................................Ligand
L*.................................Chiral ligand
LA.................................Lewis acid
lit.................................Literature
LUMO..............................Lowest unoccupied molecular orbital
m.................................meta
M.................................Molar (concentration unit)
Me.................................Methyl
MeO...............................Methoxy
min.................................Minute(s)

mL......................................milliliter

mol.................................Moles

Mol. Wt.................................Molecular weight

mp......................................Melting point

MS........................................Molecular Sieves

Naph.....................................Naphthyl

NMR......................................Nuclear magnetic resonance

nOe......................................Nuclear Overhauser effect

Nu.........................................Nucleophile

NHTf.....................................Trifluoromethane sulfonimide

NTf$_2$....................................Bis(trifluoromethane) sulfonimide

o...........................................ortho

OBn......................................Benzyloxy

OiPr......................................Isopropoxide

OTf........................................Triflate

p...........................................para

Ph.........................................Phenyl

ppm......................................Parts per million

$i$-Pr....................................Isopropyl

Pybox....................................Pyridine-2,6-bis(oxazoline)

R*.................................Chiral directing group

rt.........................................Room temperature

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TBDMS.........................................tert-Butyldimethylsilyl
TBDPS.........................................tert-Butyldiphenylsilyl
TIPS...........................................Triisopropylsilyl
Temp.........................................Temperature
Tert...........................................Tertiary
TFA...........................................Trifluoroacetic acid
THF...........................................Tertahydrofuran
TLC...........................................Thin layer chromatography
Tol...........................................Tolyl
$t_R$............................................Retention time
UV...........................................Ultraviolet
X..............................................Halogen Ligand or Achiral auxiliary
Z...............................................Achiral auxiliary
CHAPTER 1.

ENANTIOSELECTIVE 1,3-DIPOLAR CYCLOADDITIONS FOR THE SYNTHESIS OF NITROGEN CONTAINING HETEROCYCLES

1.1. Introduction

Development of new methodologies for the synthesis of molecules with complex architecture is at the forefront of synthetic organic chemistry. Dipolar cycloadditions involving reaction of a dipole and a dipolarophile represents a powerful and elegant method for the construction of heterocycles (Scheme 1.1). One of the important features of dipolar cycloaddition is its ability for the installation of multiple stereocenters and in the simplest form one can introduce from one to four stereocenters in a single step. Also unique is the range of substituents one can introduce in a single operation, which in turn yields highly substituted heterocycles. Dipolar cycloaddition can be considered to be atom economical and is routinely employed in the synthesis of macromolecules. Chiral heterocycles are important as they serve as important synthetic building blocks. For example, nitrogen-containing heterocycles such as isoxazolines, isoxazolidine, and pyrrolidines can be prepared easily via dipolar cycloaddition.

The development of 1,3-dipolar cycloadditions was abetted by the discovery of the first 1,3-dipole in the form of diazoacetic ester by Curtius in 1883. Five years later, Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters which was the first 1,3-dipolar cycloaddition reaction reported. Over the next few decades several new 1,3-dipoles were discovered, however few general applications were investigated. This trend continued for the next 70 years since the discovery of the first 1,3-dipole. In 1960,
pioneering work by Prof. Huisgen towards the application of 1,3-dipoles in synthetic organic chemistry contributed towards the rapid development of the field. Further notable contributions towards the understanding of relative reactivity and regioselectivity of 1,3-dipolar cycloaddition came from the studies carried out by Houk and co-workers.\textsuperscript{2}

General Representation of 1,3-Dipolar Cycloaddition

Scheme 1.1. Application of 1,3-Dipolar Cycloadditions for the Synthesis of Heterocycles
Before investigating dipolar cycloaddition it would be useful to understand the nature, reactivity, and geometry of the two reactants involved in this reaction. The dipole represented by a-b-c structure is further classified into two types: allyl anion type dipoles have 4π electrons distributed in three parallel p-orbitals, which are perpendicular to the plane of the dipole and the dipole has a bent structure; the allenyl anion type dipole has 6π electrons of which 4π electrons are distributed in three parallel p-orbitals perpendicular to the plane of dipole and 2π electrons in two p-orbitals which are in the plane of the dipole (Figure 1.1). The dipolarophile is usually a substituted alkene or an alkyne but any molecule containing unsaturation can be employed.

Figure 1.1. General Representation of 1,3-Dipoles

1,3-Dipolar cycloaddition reactions can be classified based on the frontier molecular orbital (FMO) interactions and are classified into three types (Figure 1.2). Type I reactions involves a dominant interaction between the HOMO of the dipole and the LUMO of the alkene. In type II reactions, the energy level of the two reacting species are similar and hence depending on reaction conditions the dominant interaction can be between
HOMO of the dipole and LUMO of the alkene or vice versa. Type III reactions involve a dominant interaction of the HOMO of the alkene with LUMO of the dipole. These classifications are for reactions in the absence of Lewis acids or other promoters.

Lewis acids can interact with either the dipole or the alkene and thus affect the course of the reaction (Figure 1.3). Coordination of the Lewis acid with the alkene results in stabilization of its HOMO energy level (lower energy). This coordination also leads to lowering of the LUMO level of the alkene. Thus the energy gap between the HOMO (dipole) and the LUMO (dipolarophile) is smaller when the dipolarophile is coordinated with Lewis acid as compared to that of the free alkene. The smaller energy gap results in faster reactions.

Figure 1.2. Classification of 1,3-Dipolar Cycloaddition Reactions Based on FMO
Key issues involved in 1,3-dipolar cycloaddition to olefins are the control of regio-, diastereo- and enantioselectivity. Uncatalyzed reactions may proceed to give either a single compound or a statistical mixture of regioisomers and/or diastereomers. In an uncatalyzed reaction, the orbital coefficients of the dipole and the dipolarophile will dictate the regioselectivity of the reaction. Additionally, diastereoselectivity may be influenced by steric and electronic interactions between the substituents present in the dipole and the dipolarophile. In the presence of an activator, such as a Lewis acid, two scenarios are possible. The activator can coordinate either the dipole or the dipolarophile resulting in lowering of their HOMO energy levels. This stabilization leads to higher reactivity between activated dipolarophile (LUMO) and dipole (HOMO) (Type I reaction) or activated dipole (LUMO) and electron rich dipolarophiles (HOMO) (Type III reaction).

Figure 1.3. Effect of Lewis Acid Interaction with Alkene on FMO of Type I 1,3-Dipolar Cycloaddition Reaction
Irrespective of where the activator coordinates, its interaction with the dipole or the dipolarophile will influence the electronic properties at the respective centers leading to changes in either regioselectivity or diastereoselectivity of the reaction compared to the uncatalyzed one (Scheme 1.2). Enantioselectivity can be introduced in dipolar cycloaddition by utilizing chiral activators. Steric hindrance around the reaction center caused by the bulky catalyst may also inadvertently impact both regio- and diastereoselectivity.

Scheme 1.2. Diastereoselectivity in 1,3-Dipolar Cycloaddition Reactions

In the past two decades rapid advancement in the field of catalysis has allowed for the development of new methods for the construction of chiral heterocycles using dipolar cycloadditions. The period of 1990-2000 saw tremendous development of the field of chiral Lewis acid catalysis and in many ways was the golden era in the field of catalysis. The past decade saw the emergence of organocatalysis as a focused area of investigation and it has rapidly grown to a point that it can compete with traditional transition metal catalysis. Dipolar cycloaddition has truly gained from the development of both the fields of catalysis. Several reviews have been published which highlight different aspects of dipolar
cycloadditions with the most recent review from our laboratory focusing on the use of Cu(II)-mediated dipolar cycloadditions. This review will discuss enantioselective methods developed for the construction of nitrogen containing heterocycles using 1,3-dipolar cycloaddition reactions. We have restricted ourselves to enantioselective intermolecular cycloadditions only. The discussion is organized based on the dipole and within each section on the nature of the chiral activator.

1.2. Nitrone Cycloaddition

Nitrone cycloaddition to alkenes represents one of the most widely investigated 1,3-dipolar cycloaddition reactions. Isoxazolidines, the products from these reactions, are an important class of heterocycles since they often exhibit biological activity and serve as precursors for the preparation of important molecules such as chiral 1,3-amino alcohols etc. This section will discuss the development of various asymmetric strategies towards enantioselective nitrone cycloadditions.

1.2.1. Nitrone Cycloadditions to α,β-Unsaturated Imides

Jorgensen et al. reported one of the earliest asymmetric nitrone cycloaddition to electron deficient alkenes using a chiral titanium Lewis acid. In this pioneering example, oxazolidinone crotonate 1.1 reacted with nitrone 1.2a to yield a mixture of exo and endo cycloadducts (Table 1.1). In the absence of any Lewis acid, the reaction proceeded at elevated temperature to yield a 91:09 mixture of exo and endo diastereomers (entry 1). Initial screening with 1 equivalent of chiral catalyst in either dichloromethane or toluene as the solvent suggested that the chiral Lewis acid could catalyze the reaction efficiently at
room temperature giving predominantly the exo cycloadduct. Solvent had a minor impact on selectivity. TADDOL ligands having different aromatic substituents R were also investigated. The highest enantioselectivity for the exo product was obtained when R= Ph (entry 7). The strong Lewis acid coordination with the dipolarophile 1.1 rather than the nitrone 1.2a accounts for a favorable HOMO(dipole)-LUMO(dipolarophile) interactions making the cycloaddition efficient.

Table 1.1. Asymmetric Nitrone Cycloaddition Catalyzed by Ti-TADDOLate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol %</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Conv. (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>-</td>
<td>CHCl₃</td>
<td>50</td>
<td>38</td>
<td>91:09</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.3a</td>
<td>100</td>
<td>Toluene</td>
<td>rt</td>
<td>91</td>
<td>94:06</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>1.3b</td>
<td>100</td>
<td>Toluene</td>
<td>rt</td>
<td>85</td>
<td>95:05</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>1.3c</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>90</td>
<td>89:11</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>1.3c</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>85</td>
<td>89:11</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>1.3c</td>
<td>10</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>83</td>
<td>89:11</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>1.3c</td>
<td>10</td>
<td>Toluene</td>
<td>0</td>
<td>94</td>
<td>90:10</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>1.3d</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>81</td>
<td>77:23</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>1.3e</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>78</td>
<td>57:43</td>
<td>27</td>
</tr>
</tbody>
</table>

Jorgensen et al.⁶ further studied the effect of group X of the Ti-TADDOL complex on enantio- and diastereoselectivity of nitrone cycloaddition with oxazolidinone crotonate 1.1 (Table 1.2). A complete reversal of diastereoselectivity was observed when the group X
was changed from chloro 1.3c to OTs 1.3j. Thus nitrone cycloaddition of 1.1 using 10 mol% of 1.3c gave a 90:10 mixture of exo and endo cycloadducts where as the same reaction using 25 mol% of 1.3j gave >95:05 mixture of endo and exo cycloadducts. This unexpected reversal in diastereoselectivity was due to the steric hindrance of the -OTs group on the Lewis acid. In the absence of this group, the calculated energy for the exo approach of the nitrone was 25 kcal lower than the endo approach. Remarkably high level of enantioselectivity for the endo isomer was observed with 50 mol% catalyst loading.

Jørgensen et al. also reported the use of succinimide as a template for chiral Lewis acid mediated nitrone cycloadditions (Table 1.3). Thus reaction of N-crotonoyl succinimide 1.5 with nitrone in the presence of chiral Ti(IV) Lewis acid yielded the cycloadduct as
>95:05 mixture of exo and endo diastereomers. Furthermore, even with 5 mol% of catalyst loading, the reaction proceeded with modest yield and gave up to 72% enantiomeric excess for the exo cycloadduct. Treatment of the cycloadducts with hydrazine resulted in cleavage of the succinimide template to yield carboxamides. One of the issues arising from the use of Ti(IV) as a Lewis acid is their relative sensitivity to air and moisture.

Table 1.3. Asymmetric Nitrone Cycloaddition using Succinimides Template

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrone</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2a</td>
<td>Ph</td>
<td>Ph</td>
<td>1.4a</td>
<td>76</td>
<td>&gt;95:05</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>1.2b</td>
<td>Bn</td>
<td>Ph</td>
<td>1.4b</td>
<td>38</td>
<td>64:36</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>1.2c</td>
<td>Ph</td>
<td>p-CH₃C₆H₄</td>
<td>1.4c</td>
<td>64</td>
<td>&gt;95:05</td>
<td>65</td>
</tr>
</tbody>
</table>

Jørgensen et al. have also reported nitrone cycloadditions to oxazolidinone imide 1.1 using chiral Lewis acids 1.6 and 1.7. The reactions catalyzed with 10 mol% of Mg(II)/bisoxazoline complex 1.6 yielded a 92:08 mixture of endo and exo cycloadducts with 79% enantiomeric excess for the endo cycloadducts (Scheme 1.3). Similarly, reactions catalyzed with 20 mol% of Yb(III)/bisoxazoline complex 1.7 yielded a 94:06 mixture of endo and exo cycloadducts with similar enantiomeric excess for the endo cycloadduct. Jørgensen et al. also studied the effect of molecular sieves on enantio- and
diastereoselectivity of nitrone cycloadditions. It was found that in the absence of molecular
sieves, the opposite endo enantiomer (ent-1.4’a) was obtained in most cases.\(^8\)

Kobayashi et al\(^9\) have described a very versatile chiral Yb(III) catalyst for
enantioselective nitrone cycloadditions (Scheme 1.4). The significance of this report is the
use of a nitrogen base in combination with transition metal salts.

\[\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{A} & \quad \text{N} \\
\text{A}^+ & \quad \text{Me}^- \\
\end{align*}\]

\[\xrightarrow{\text{Chiral Lewis Acid}}\]

\[\begin{align*}
\text{Ph} \quad \text{Ph} \\
\text{1.1} & \quad \text{1.2a} \\
\end{align*}\]

\[
\begin{array}{c}
\text{1.4 a (exo)} \\
\text{1.4'a (endo)}
\end{array}\]

Scheme 1.3. Nitrone Cycloaddition using Metal-Bisoxazoline Ligand

Typically nitrogen bases with metal salts are avoided as they can coordinate with
the metal thus rendering them ineffective. The chiral Lewis acid complex 1.10 was
generated from Yb(OTf)\(_3\)/\((S)\)-BINOL and a base such as (R)-1-(1-naphthyl)ethylamine
1.11 which was effective for cycloaddition of oxazolidinone imide 1.1 with nitrone 1.8.
The reactions gave exclusively the endo diastereomer in up to 96% enantiomeric excess.

A notable feature of this report is the chiral Lewis acid complex was one of the
most selective chiral catalysts to be reported for endo selective nitrone cycloaddition. A
variety of nitrones derived from aromatic and heteroaromatic aldehydes were successfully
used in the cycloaddition. Kobayashi et al\(^{10}\) also studied the effect of additives such as
molecular sieves on enantio- and diastereoselectivity of nitrone cycloadditions. Thus cycloaddition of oxazolidinone imide 1.1 with nitrone 1.8 in the absence of molecular sieves gave enantiomeric endo cycloadducts as compared to those obtained in the presence of molecular sieves. Earlier reports on nitrone cycloaddition from Jørgensen et al. used chiral Ti(IV) as Lewis acid which is difficult to handle due to its moisture and air sensitivity. Kobayashi et al. reported the use of chiral lanthanide salts as Lewis acids, which are fairly easy to handle. However, enantioselectivities with these lanthanide salts were often a factor of the amount of moisture present in them and results would vary based on moisture content. The use of molecular sieves can negate the effect of moisture. However, reactions catalyzed in the presence of molecular sieves would proceed by a slightly different chiral complex as those without them, which impacts the sense as well as levels of stereoinduction.

Scheme 1.4. Yb-BINOL Catalyzed Nitrone Cycloadditions
Furukawa et al. were the first to report the use of relatively robust Lewis acids, which could be utilized for nitrone cycloaddition to electron deficient olefins (Scheme 1.5). They reported the use of late transition metals such as Pd to catalyze nitrone cycloadditions.\textsuperscript{11} The reaction of oxazolidinone imide 1.1 with nitrone 1.8 catalyzed by 10 mol\% of 1.20a gave a 1:1 mixture of \textit{endo} and \textit{exo} cycloadducts in modest yield (59\%). The enantiomeric excess of the \textit{endo} cycloadduct was 89\% whereas the enantiomeric excess of the \textit{exo} cycloadduct was 60\%. Catalyst 1.20b was prepared from 1.20a in acetonitrile as solvent and it catalyzed the increase the rate of the reaction and gave higher yield (89\%) of cycloadduct with similar enantioselectivity for the \textit{endo} adduct.

Scheme 1.5. Pd-BINAP Catalyzed Nitrone Cycloadditions

With the development of chiral Lewis acid chemistry and aided by the rapid development in the field of ligand synthesis, numerous new ligands with different shielding environments were available for use (Figure 1.4). Many groups have employed these unique ligands to access their impact on asymmetric nitrone cycloadditions. Kanemasa et al. have demonstrated the application of a new chiral Lewis acid complex of ligand
DBFOX 1.22 with Ni(ClO₄)₂·6H₂O for asymmetric nitrone cycloaddition of oxazolidinone imide 1.1. A significant feature of this report is that the reaction is highly endo selective and yields cycloadduct with very high levels of enantioselectivity (>95%). Typical catalyst loading was 10 mol% but the amount of chiral Lewis acid can be reduced to up to 1 mol% without appreciable loss of both enantio- and diastereoselectivity. Molecular sieves were essential for this catalyst system to be effective.

Figure 1.4. Ligands for Nitrone Cycloadditions

Based on the success of BINOL ligands in conjunction with lanthanide Lewis acids for asymmetric nitrone cycloadditions reported by Kobayashi, Ohta et al. developed a novel BINOL-BOX ligand 1.23 which would have features of both BINOL ligands and bisoxazoline ligands. Chiral Lewis acid complex prepared from Sc(OTf)₃ with ligand
1.24 performed well in cycloaddition of oxazolidinone imide 1.1 with various N-benzyl nitrone to give predominantly the *endo* cycloadduct with high enantioselectivity.

Similarly, Iwasa et al. developed a chiral ligand 1.24 based on the PyBOX scaffold with silyl protecting group, which provide the steric shielding for asymmetric nitrone cycloaddition of oxazolidinone imide 1.1. A significant advantage of this ligand design was that several ligands with different steric volume could be synthesized with relative ease starting from the same primary alcohol precursor. Reaction of oxazolidinone imide 1.1 with nitrones were catalyzed with 10mol% of Ni(ClO₄)₂/1.24 complex in isopropanol and gave predominantly the *endo* cycloadduct with high levels of enantioselectivity.

Iwasa et al. also reported the synthesis and application of a new series of tridentate ligands XaBOX 1.25 which is similar to DBFOX 1.22 developed by Kanemasa. They have reported a highly *endo* and enantioselective nitrone cycloaddition of oxazolidinone imide 1.1 using Mn(ClO₄)₂/1.25 as catalyst. Saito et al. have reported the use of a chiral bisimine 1.26/ Cu(II) based catalyst system for *endo* and enantioselective nitrone cycloaddition to 1.1. An elegant feature of this catalyst design is the ease of its synthesis, ready availability of the starting material and also the easy tunability of group R for steric or electronic properties.

Recently Evans et al. have reported the development of a new template for *endo* and enantioselective nitrone cycloaddition catalyzed by Ce(IV)/1.29 complex as catalyst (Scheme 1.6). High levels of diastereoselectivity and enantioselectivity for the cycloadducts were obtained when 5 mol% of the catalyst was employed. The cycloadducts were further converted into β-lactams using relatively simple procedures.
Numerous examples of asymmetric nitrone cycloadditions have been reported for the selective formation of the *endo* diastereomer. However, there is no general method for the construction of the *exo* diastereomer. An *exo* selective nitrone cycloaddition has been reported by Jørgensen using a TiCl<sub>2</sub>/TADDOL catalyst. Sibi et al. reported the first general method for highly enantio- and *exo* selective nitrone cycloaddition to electron deficient olefins. The reactions of β-substituted α,β-unsaturated pyrazolidinone 1.31 were catalyzed with Cu(OTf)<sub>2</sub>/1.32 catalyst to give the *exo* cycloadducts 1.32 (Table 1.4).

![Scheme 1.6. N-Methyl Imidazoles as Template for Nitrone Cycloaddition](image)

Another significance of this report is the scope of the β-substituent (R= alkyl and aromatic) of the olefin, which was much improved than any other previous report. The *exo* selectivity of this reaction was attributed to the square planar organization of the chiral Cu(II)-substrate complex. Other Lewis acid complexes with Mg(II) and Fe(II) with 1.32 which do not possess square planar organization gave 1:1 mixture of *exo* and *endo* cycloadducts. Where as reactions with Sc(OTf)<sub>3</sub>/1.29 which have octahedral organization gave *endo* cycloadducts. Ligand 1.32 gave the best enantioselectivity while other bidentate bisoxazoline ligands were tried and fared poorly.

The impact of molecular sieves was also investigated and reversal of *exo*/*endo* selectivity was observed when reactions were carried out in the absence of molecular...
sieves. Thus, reaction of Cu(ClO₄)₂/1.32 gave a 32:68 mixture of exo and endo diastereomers with 67% ee for the exo isomer in the absence of molecular sieves. The same reaction gave 83:17 mixture of exo and endo diastereomers with similar enantiomeric excess for the exo isomer in the presence of molecular sieves. Jørgensen et al. and Kanemasa et al. have also reported similar effect of molecular sieves. The scope of nitrones was also investigated and with the exception of 1.28c which gave a 1:1 mixture of exo and endo diastereomers, most other nitrones gave predominantly the exo diastereomer in excellent enantiomeric excess.

Table 1.4. Example of Exo-Selective Asymmetric Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Nitrone</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃ (1.31a)</td>
<td>1.28a</td>
<td>CH₃</td>
<td>Ph</td>
<td>94</td>
<td>96:04</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Et (1.31b)</td>
<td>1.28a</td>
<td>CH₃</td>
<td>Ph</td>
<td>88</td>
<td>94:06</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Ph (1.31c)</td>
<td>1.28a</td>
<td>CH₃</td>
<td>Ph</td>
<td>23</td>
<td>84:16</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Et (1.31d)</td>
<td>1.28a</td>
<td>CH₃</td>
<td>Ph</td>
<td>44</td>
<td>67:33</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>CH₃ (1.31a)</td>
<td>1.28b</td>
<td>Bn</td>
<td>4-ClPh</td>
<td>52</td>
<td>85:15</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>CH₃ (1.31a)</td>
<td>1.28c</td>
<td>Ph</td>
<td>Ph</td>
<td>85</td>
<td>52:48</td>
<td>99</td>
</tr>
</tbody>
</table>

Examples of nitrone cycloaddition to α,β-disubstituted α,β-unsaturated electron deficient olefins are scarce due to the low reactivity of these substrates. Sibi et al. reported enantioselective nitrone cycloaddition of α,β-disubstituted acroloyl imides 1.34 with
nitrone 1.8 catalyzed by a Mg(NTf2)2/1.32 chiral Lewis acid complex (Table 1.5). These reactions were also highly *exo* selective and in most cases >98:02 mixture of *exo* and *endo* diastereomers were isolated. Better reactivity of this imide template as compared to oxazolidinone or pyrazolidinone templates, which were previously tried, was due to efficient control of rotamer geometry. Thus, reactions were postulated to be proceeding through an s-cis rotamer of 1.34, which leads to greater polarization of the double bond. This methodology is also a good example for the construction of chiral quaternary center, which is very difficult to achieve and is highly sought after.

Table 1.5. Nitrone Cycloaddition for the Construction of Quaternary Stereo Centers

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>R¹, R²</th>
<th>Yield (%)</th>
<th><em>exo/endo</em></th>
<th><em>exo ee</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.34a</td>
<td>Me, Me</td>
<td>60</td>
<td>99:01</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1.34b</td>
<td>Me, H</td>
<td>57</td>
<td>81:19</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>1.34c</td>
<td>Me, Et</td>
<td>63</td>
<td>99:01</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1.34d</td>
<td>(CH₂)₃</td>
<td>82</td>
<td>99:01</td>
<td>92</td>
</tr>
</tbody>
</table>

Suga et al. reported *exo* and enantioselective nitrone cycloaddition of 3-(2-alkenoyl)-2-thiazolidinethiones using Ni(ClO₄)₂/1.37 as chiral Lewis acid (Scheme 1.7). Similar to previous report from Sibi et al. this protocol also has a wide scope of β-substituents on the dipolarophile and substituents on dipole.
Scheme 1.7. Thiazolidinethiones as Template for Nitrone Cycloaddition

Desimoni et al. reported enantio- and diastereoselective nitrone cycloaddition to 2-acrolyl-oxazolidinone 1.39 catalyzed by BOX ligand-metal complexes (Scheme 1.8).\textsuperscript{23} Mg(II)/1.42 complex containing cis diphenyl groups gave predominantly the exo diastereomer in excellent enantioselectivity.

Scheme 1.8. Impact of Ligands on Diastereoselectivity of Nitrone Cycloaddition
Complex 1.41 prepared from Mg(ClO$_4$)$_2$/Ph-BOX ligand gave the opposite diastereomer. A similar trend in diastereo- and enantioselectivity was observed when other Lewis acids such as Ni(ClO$_4$)$_2$ which can form tetrahedral complexes similar to Mg(II) were employed.

Kim et al. have recently reported endo selective nitrone cycloaddition to $\alpha'$-phosphoric enones as templates using 1.44/Cu(OTf)$_2$ as a chiral Lewis acid (Scheme 1.9).$^{24}$ An advantage of using this template over traditional oxazolidinone or pyrazolidinone templates is that products can be readily converted to ketones using Horner-Wadsworth-Emmons (HWE) reaction.

![Scheme 1.9. Example of $\alpha'$-Phosphoric Enones as Template for Nitrone Cycloaddition](image)

At the same time, the 1,3-dicarbonyl motif allows binding of traditional chiral Lewis acids via a 6-membered chelate. A combination of Cu(OTf)$_2$ with cis-diphenyl BOX ligand 1.44 previously developed by Desimoni gave very high enantio- and diastereoselectivity for the endo diastereomer. The authors demonstrated the scope of $\beta$-substituents on the dipolarophiles. However, the catalyst was ineffective for catalyzing
reaction involving cinnamoyl substrates (R=Ph). High levels of enantioselectivities were attributed to the shielding of the re-face of the dipolarophile by the Ph substituent on the ligands thereby allowing the dipole to approach from the si-face.

1.2.2. Nitrone Cycloadditions to α,β-Unsaturated Aldehydes

Early reports on asymmetric nitrone cycloaddition by Jørgensen et al. were based on electron deficient olefins tethered to an oxazolidinone template. The 1,3-dicarbonyl unit of these dipolarophiles help form tight chelates with chiral Lewis acids (Figure 1.5). Many other groups have successfully applied similar templates, which are capable of forming chelates with chiral Lewis acids. In Lewis acid-mediated nitrone cycloaddition to electron deficient olefins, there is always a possibility Lewis acid coordination of the nitrone leading to its deactivation. Formation of a stronger chelate of the Lewis acid with dipolarophile has always helped in avoiding or reversing this equilibrium binding.

![Figure 1.5. Binding Mode of Metals to Bidentate and Monodentate Substrates and Nitrones](image)

The use of α,β-unsaturated aldehydes as dipolarophiles for asymmetric nitrone cycloaddition was initially limited as it was always presumed that the Lewis acid would form a tighter complex with nitrones compared to the carbonyl carbon of the dipolarophile. However, aldehydes are an interesting class of substrates and are relatively simple. Many
groups have therefore attempted development of nitrone cycloaddition to $\alpha,\beta$-unsaturated aldehydes using single point binding chiral Lewis acids.

Kündig et al. reported the first asymmetric nitrone cycloaddition to $\alpha,\beta$-unsaturated aldehydes using a chiral ruthenium catalyst (Scheme 1.10). The authors postulated that a highly tuned aldehyde selective chiral Lewis acid would be able to discriminate between aldehyde and nitrone or would favor coordination of the aldehyde or bind with the nitrone in a readily reversible fashion. Catalyst 1.51 was prepared and initial NMR studies indicated that in solution a 7:3 ratio of chiral Lewis acid/aldehyde complex and chiral Lewis acid/nitrone complex was formed. Encouraged by these studies they tried reaction of various $\alpha,\beta$-unsaturated aldehydes with nitrones. Cycloaddition of methacrolein 1.49 with N-phenyl nitrone 1.50 gave a $\geq60:40$ ratio of endo isomer 1.52 and endo isomer 1.53 in good enantioselectivity. In the same report the authors have also described a chiral Lewis acid similar to 1.51 by replacing Fe(II) in place of Ru(II) which was investigated for cycloaddition of enals with cyclic nitrone with great success.

![Scheme 1.10. Early Example of Nitrone Cycloaddition to Enals](image)
After the initial report on nitrone cycloaddition to $\alpha,\beta$-unsaturated aldehydes using single point binding Lewis acids by Kündig et al., several groups have reported the design of catalysts, which would catalyze similar transformations. Carmona et al. have reported an extensive study on the development of an Ir(II) based catalyst 1.54 for asymmetric nitrone cycloaddition to methacrolein (Figure 1.6). Reactions with this catalyst occur with perfect \textit{endo} selectivity and yields cycloadducts in excellent enantiomeric excess.

![Figure 1.6. Chiral Metal Complexes for Nitrone Cycloaddition to Enals](image)

This paper also reported the development a Rh(II) catalyst instead of Ir(II) for the same transformation. Carmona et al. have recently reported the use of catalyst 1.54 derived from Ir(II) or Rh(II) for \textit{endo} and enantioselective nitrone cycloaddition to $\beta$-substituted-$\alpha,\beta$-disubstituted enals. Kanemasa et al. reported the development of a unique catalyst for nitrone cycloaddition to enals. Previous reports by Kündig et al. and by Carmona et al.
have relied on preferential binding of dipolarophiles to Lewis acids based on electronic properties, Kanemasa however developed aluminum phenoxide based Lewis acid 1.55 which prevents binding of the dipole to Lewis acid by utilizing steric hindrance of the phenyl ring around the Lewis acid. Bulky group on the nitrogen atom of the nitrone was essential for the success of this catalyst.

Maruoka et al. developed a bis-Ti(IV) oxide based Lewis acid 1.56 for highly endo and enantioselective nitrone cycloaddition to enals. They also studied the effect of bulky substituents on the nitrogen atom of the dipole on yield and enantioselectivity and observed that bulky substituent on nitrogen atom of the nitrone resulted in higher enantioselectivity and yield of the products (Table 1.6). It was postulated that one of the reaction intermediate was a complex in which the metal coordinated with both nitrone and enal (Lewis acid-substrate-dipole complex). Elimination of nitrone from this complex gave rise to the active substrate-Lewis acid complex through which the reaction proceeded. Thus increasing the bulk at nitrogen of the dipole would facilitate quick elimination of the dipole for the Lewis acid-substrate-dipole complex thus gives higher yields for the product. Thus changing the nitrogen substituent from benzyl to diphenyl methyl increased the yield and enantioselectivities of the cycloadducts. Maruoka et al. have also studied the impact of substituent at 6,6'-position on catalyst 1.56 on enantioselectivity of cycloaddition of methacrolein and various N-diphenyl methyl nitrones. Yamada et al. have reported highly endo and enantioselective nitrone cycloaddition to cyclic enals using β-ketoiminato cationic cobalt(III) complexes 1.57.
Table 1.6. An Example of Ti(IV) Catalyzed Nitrone Cycloaddition to Enals

\[
\begin{align*}
\text{H} & \text{Me} \\
\text{R} & \text{N} & \text{O} \\
1.58 & 1.59a-b & 1.60a-b
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH(_2) (1.59a)</td>
<td>1.60a</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Ph(_2)CH (1.59b)</td>
<td>1.60b</td>
<td>58</td>
<td>90</td>
</tr>
</tbody>
</table>

Several reports on asymmetric nitrone cycloaddition to \(\alpha,\beta\)-unsaturated aldehydes utilized the concept of single point binding chiral Lewis acids. Kanemasa et al. reported the use of bidentate bisoxazolines in conjunction with Lewis acids such as Ni(II) and Zn(II) to catalyze the same process.\(^{33}\) Interestingly, dramatic change in regioselectivity was observed depending on the nature of the Lewis acid employed. Thus, Ni(ClO\(_4\))\(_2/1.22\) chiral Lewis acid gave steric controlled *endo* product 1.62 in high enantioselectivity while Zn(ClO\(_4\))\(_2/1.22\) chiral Lewis acid gave electronically controlled *endo* product 1.63 in 97% enantiomeric excess (Scheme 1.11).

\[
\begin{align*}
\text{Ph} & \text{O} & \text{1.22/Lewis acid} & \text{Ph} \\
\text{R} & \text{N} & \text{O} \\
1.61 & 1.2a & \text{1.62/1.63}
\end{align*}
\]

Scheme 1.11. An Example of Nitrone Cycloaddition to Enals Catalyzed by Metal-Bis(oxazoline) Complex
Tang et al. have reported asymmetric nitrone cycloaddition to alkylidene malonate catalyzed by a BOX ligand 1.65/Co(ClO₄)₂. Dramatic effect of temperature on *endo/exo* selectivity of cycloadducts was observed (Scheme 1.12). Reaction of 1.64 with diphenyl nitrone 1.2a was when carried out at 0 °C, gave a >90:10 mixture of *endo/exo* diastereomers 1.66 (endo) and 1.67 (exo) and the endo adduct was obtained in 98% enantiomeric excess. Whereas, the same reaction when carried out at -40 °C, a >14:86 mixture of *endo/exo* diastereomers 1.66 (endo) and 1.67 (exo) were obtained. The exo adduct was formed in 94% enantiomeric excess.

![Scheme 1.12. Nitrone Cycloaddition to Alkylidene Malonate](image)

Scheme 1.12. Nitrone Cycloaddition to Alkylidene Malonate

Carmona et al. have recently reported asymmetric cycloaddition of cyclic nitrones with α,β-unsaturated nitriles using chiral rhodium catalyst similar to 1.54. Typical Lewis acid catalyzed reactions of nitrones with electron deficient olefins utilize α,β-unsaturated carbonyl compounds as acceptors in which there is competitive binding of the single point
binding Lewis acid with either the oxygen atom of carbonyl carbon of the acceptor or the oxygen of the nitrone. However with the use of α,β-unsaturated nitriles as acceptors due to the strong donor ability of cyano groups this equilibrium binding can be pushed in favor of the acceptor.

1.2.3. Lewis Acid Catalyzed Nitrone Cycloaddition to Electron Rich Olefins

1,3-Dipolar cycloaddition of nitrones to electron deficient olefins involves the interaction of HOMO (nitrone) with the LUMO (olefin) has been investigated in details. In this mode, coordination of the chiral Lewis acid to the olefin confers reactivity to the substrate. In contrast, reports of inverse electron demand nitrone cycloadditions are scarce. Inverse electron demand nitrone cycloaddition requires interaction of HOMO (olefin) with LUMO (nitrone).

Scheeren et al. reported one of the earliest chiral nitrone cycloaddition to ketene acetal 1.68 using chiral oxazaborolidine 1.69 (Scheme 1.13). These reactions were highly exo selective and gave cycloadduct 1.70 in 62% enantiomeric excess at -78 °C in dichloromethane.

Scheme 1.13. Oxazaborolidine Catalyzed Nitrone Cycloaddition
Jørgensen et al. reported the very first highly enantio- and diastereoselective nitrone
cycloaddition to ethyl vinyl ether \textbf{1.71} catalyzed by aluminum-BINOL complex \textbf{1.73} (Table 1.7).\textsuperscript{37} Aluminum-BINOL catalyst was prepared by mixing corresponding 3,3'-substituted BINOL with methyl aluminum chloride. \textit{Exo} selectivity of >95:05 was observed for reaction of ethyl vinyl ether \textbf{1.71} with various \textit{N}-phenyl nitrones \textbf{1.71a-d}.

The enantioselectivities for the \textit{exo} adducts ranged from 88 to 94%. However, when \textit{t}-butyl vinyl ether was used as the dipolarophiles, some deterioration in \textit{exo/endo} selectivity was observed and the enantioselectivity of the cycloadducts was lower than those obtained with ethyl vinyl ether. Jørgensen et al. have extended the application of catalyst \textbf{1.73} for cycloaddition of cyclic nitrones to vinyl ethers.\textsuperscript{38} A polymeric-catalyst based on aluminum-BINOL scaffold for inverse electron demand dipolar cycloadditions has also been reported.\textsuperscript{39}

Table 1.7. Example of Inverse Electron Demand Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>\textit{exo/endo}</th>
<th>\textit{exo ee} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (1.71a)</td>
<td>\textbf{1.74a}</td>
<td>79</td>
<td>&gt;95:05</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>\textit{p}-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4} (1.71b)</td>
<td>\textbf{1.74b}</td>
<td>70</td>
<td>&gt;95:05</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>\textit{p}-ClC\textsubscript{6}H\textsubscript{4} (1.71c)</td>
<td>\textbf{1.74c}</td>
<td>78</td>
<td>&gt;95:05</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>\textit{p}-MeOC\textsubscript{6}H\textsubscript{4} (1.71d)</td>
<td>\textbf{1.74d}</td>
<td>50</td>
<td>&gt;95:05</td>
<td>88</td>
</tr>
</tbody>
</table>
An asymmetric nitrone cycloaddition to vinyl ether catalyzed by Cu(OTf)2/1.79 has been reported (Scheme 1.14). The significance of this work is the use of bidentate Lewis acid for catalysis. All previous reports of similar nitrone additions utilized single point binding Lewis acids such as aluminum. Nitrone 1.76 was prepared by condensation of aromatic N-hydroxylamines with corresponding glyoxylates and presented sites for chelation of the chiral Lewis acid. Most reactions gave modest to good diastereoselectivity and yield. The cycloadducts were formed with high enantioselectivity.

Scheme 1.14. Nitrone Cycloaddition to Vinyl Ethers Catalyzed by Cu(II)/bis(oxazoline)

1.2.4. Organocatalyzed Nitrone Cycloadditions

The development of small organic molecules to catalyze enantioselective transformations has emerged as a major frontier for research in the field of asymmetric catalysis. Organocatalyzed asymmetric reactions also provide an environmentally benign approach for the construction of optically active compounds. Furthermore, organocatalysis also addresses the issues of catalyst interaction with dipole rather than dipolarophile in case of cycloaddition to electron deficient acceptors, which has been plaguing the field of Lewis acid catalysis. Also, organocatalysts are relatively inert to other issues related to loss of catalysis due to catalyst degradation or deactivation, which are common in Lewis acid...
catalysis. Lewis acid catalysis often requires stringent reaction conditions and moisture can deactivate the catalyst. Many organocatalysts are tolerant to moisture and hence are user-friendly. During the initial development of organocatalysis, only a limited number of chiral scaffolds were available but with the recent development in this field many newer structures are available to the synthetic chemist.

MacMillan et al. reported the very first example of enantioselective organocatalyzed nitrone cycloaddition (Table 1.8). In this pioneering example, cycloaddition of acyclic nitrones 1.28a-f with crotonaldehyde was catalyzed by chiral imidazolidinone salt 1.82. Early studies from this group on catalyst development concluded that the benzylic substituent at C3 position on the catalyst was essential for obtaining best enantioselectivity. The nature of the imidazolidinone salt also had an appreciable impact on diastereoselectivity and catalyst activity.

Table 1.8. First Example of Organocatalyzed Nitrone Cycloaddition to Enals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrone</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>endo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.28a</td>
<td>Bn</td>
<td>Ph</td>
<td>1.81a</td>
<td>98</td>
<td>94:06</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1.28b</td>
<td>Bn</td>
<td>p-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1.81b</td>
<td>78</td>
<td>92:08</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>1.28c</td>
<td>Bn</td>
<td>p-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1.81c</td>
<td>93</td>
<td>98:02</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1.28d</td>
<td>Bn</td>
<td>2-Naphthyl</td>
<td>1.81d</td>
<td>98</td>
<td>95:05</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>1.28e</td>
<td>Bn</td>
<td>c-hex</td>
<td>1.81e</td>
<td>70</td>
<td>99:01</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>1.28f</td>
<td>Allyl</td>
<td>Ph</td>
<td>1.81f</td>
<td>73</td>
<td>94:06</td>
<td>98</td>
</tr>
</tbody>
</table>
Co-catalyst HClO₄ was the best amongst other protic acid co-catalyst screened. Nitrones prepared by condensation of N-substituted hydroxy amine with aromatic and aliphatic aldehydes were reacted with crotonaldehyde using 20 mol% of catalyst 1.82. The reactions were highly endo selective and typical enantioselectivities were >90%. Following this discovery, several groups have reported different catalysts for enantioselective nitrone cycloaddition to α,β-unsaturated aldehydes. Karlsson et al. reported enantioselective 1,3-dipolar cycloaddition of acyclic nitrones to cyclic α,β-unsaturated aldehydes (Figure 1.7). Catalysts 1.83a-b, 1.84a-c were used for cycloaddition of cyclopent-1-enecarbaldehyde with N-methylphenyl nitrone 1.8. The reactions yield exo cycloadduct (exo/endo = 72:28 to 97:03) in good to excellent enantioselectivity, however the catalytic activity was low and only 70% yield was obtained with 10 mol% of 1.84c.

![Diagram](image)

Figure 1.7. Organocatalyst for Nitrone Cycloadditions

Nevalainen et al. reported nitrone cycloaddition to α,β-unsaturated aldehydes catalyzed by a diphenyl prolinol catalyst 1.84d. Excellent enantioselectivity (up to 95%) for endo cycloadducts (endo/exo = >92:08) were obtained using 5-20 mol% of the catalyst
system. Ogilvie et al. have developed a camphor-derived hydrazide catalyst for \( \text{exo} \) selective nitrone cycloaddition to \( \alpha,\beta \)-unsaturated aldehydes. This catalyst system gave modest diastereoselectivity and moderate to good enantioselectivity for \( \text{exo} \) cycloadducts.

The earliest example of organocatalyzed nitrone cycloaddition to \( \alpha,\beta \)-unsaturated aldehydes utilized iminium type activation of \( \alpha,\beta \)-unsaturated aldehydes using imidazolidinone derived catalysts. Other proline-derived catalysts, which are also able to form iminium intermediates with \( \alpha,\beta \)-unsaturated aldehydes, have also been thoroughly investigated (Figure 1.7). These reactions represent normal electron demand nitrone cycloadditions. In contrast, there are very few examples of organocatalyzed inverse electron demand nitrone cycloadditions reported in literature.

Phosphoric acids have recently gained tremendous attention as organocatalysts. Typical phosphoric acid catalyzed reactions have been limited to 1,2-addition to imines. However, Yamamoto et al. recently reported activation of nitrones using chiral phosphoric acids (Scheme 1.15). 3,3'-BINOL derived phosphoramidate was found to be an efficient catalyst for nitrone cycloaddition to ethyl vinyl ether. This report is significant since the \( \text{endo} \) cycloadduct are formed in excellent enantioselectivities. The cycloadducts formed are complementary to those earlier reported by Jørgensen, who have reported \( \text{exo} \) selective nitrone cycloadditions to ethyl vinyl ether catalyzed by BINOL-aluminum as chiral Lewis acids. The authors postulated that secondary interaction between the Bronsted-dipole complex and oxygen atom on the substrate is responsible for proper organization giving the \( \text{endo} \) cycloadduct. Reactions of \( N \)-aryl nitrones with ethyl vinyl ether furnishes \( \text{endo} \) cycloadduct in >88:12 diastereoselectivity with excellent enantioselectivity.
Scheme 1.15. Organocatalyzed Inverse Electron Demand Nitrone Cycloaddition

Thioureas represent one of the most successful organocatalysts relying on hydrogen bonding for substrate activation. Chen et al. have recently reported the first chiral thiourea catalyzed nitrone cycloaddition to nitro olefins (Scheme 1.16). Thus nitrone cycloaddition to nitroolefins 1.88a was catalyzed by 10 mol% of chiral thiourea 1.85b to give cycloadduct 1.90a as a single diastereomer. High yield and high enantioselectivity was reported for this reaction. It has been previously reported by Takemoto that this catalyst can act in a bifunctional manner coordinating both the dipole and the dipolarophile.

Scheme 1.16. Thiourea Catalyzed Nitrone Cycloaddition
1.2.5. Nitrone Cycloaddition to Alkynes

Cycloaddition of nitrone to alkynes is significant since it would lead to the formation of 4-isoxazoline. Compounds bearing this 4-isoxazoline moiety serve as potential intermediates for the synthesis of other important nitrogen containing compounds. Therefore, these compounds are highly sought after for their chemical and medicinal values. Nitrone cycloaddition to alkynes are usually non-selective and yield a mixture of regioisomers. Obtaining enantioselectivity in cycloaddition to alkynes is also difficult due to the linear geometry of the dipolarophile. Inomata et al. have developed a strategy for the construction of chiral 4-isoxazoline by the addition of alkynyl zinc reagents to nitrones followed by cyclization (Scheme 1.17).47

Ishihara et al. have recently reported the first chiral Lewis acid catalyzed enantio- and regioselective nitrone cycloaddition to alkynones.48 In this example the \( \pi \)-cation interaction of the pendant aromatic group on the ligand with the Lewis acid is essential for imparting enantioselectivity.

![Scheme 1.17. Nitrone Cycloadditions to Alkynones](image)
Excellent yield and enantioselectivity for the cycloadduct was obtained when 
Cu(NTf₂)₂/ 1.89 was employed as the chiral Lewis acid. The scope of the nitrone as well as 
the dipolarophiles was investigated. The products were easily converted to β-lactams using 
standard transformations without loss in enantioselectivity.

1.3. Enantioselective Nitrile Oxide Cycloaddition

1,3-Dipolar cycloaddition of nitrile oxides to alkenes lead to the formation of 4,5-
dihydroisoxazoles. 4,5-Dihydroisoxazoles are an importance class of molecules as they are 
frequently found in many compounds that show significant biological activity. These 
molecules also serve as important building blocks for the synthesis of β-amino alcohols 
and β-amino ketones. Despite their significance, there have been a limited number of 
strategies for their construction via 1,3-dipolar cycloaddition. One of the key issues 
concerning nitrile oxide cycloaddition is the control of regiochemistry. Also, generation of 
nitrile oxide requires the presence of a base, which can potentially coordinate the Lewis 
acid thereby inhibiting catalysis. Furthermore, nitrile oxides undergo dimerization slowly 
and thus effectively reducing the concentration of the dipole in solution. Very few groups 
have been successful in addressing these issues and hence examples of enantioselective 
nitrile oxide cycloadditions are scarce.

1.3.1. Nitrile Oxide Cycloaddition to Allylic and Homoallylic Alcohols

Kanemasa et al. reported the first example of metal-mediated nitrile oxide 
cycloaddition to allylic and homoallylic alcohols.49 In this report the effect of magnesium 
ions on the rate and regioselectivity of nitrile oxide cycloaddition to chiral and achiral
allylic and homoallylic alcohols was investigated. The authors found that presence of magnesium ion dramatically improved the rate of the reaction and also had pronounced effect on regioselectivity. The reason for this impact of magnesium ions was attributed to the formation of a reactive intermediate between the allylic alcohol and the nitrile oxide. Other metal ions such as lithium, zinc and aluminum were less effective compared to magnesium. Kanemasa et al. have also reported a similar protocol for nitrile oxide cycloaddition to optically active α-silyl allyl alcohols.\textsuperscript{50} Inomata et al. reported the first enantioselective nitrile oxide cycloaddition to allylic alcohols.\textsuperscript{51} Nitrile oxides generated in-situ from corresponding hydroximoyl chlorides 1.92 reacted with allyl alcohol 1.91 in the presence of diethyl zinc, 1,4-dioxane as additive, and diisopropyl tartrate as chiral auxiliary to give corresponding 4,5-dihydroisoxazole in high enantio- and regioselectivity (Table 1.9). The reaction is proposed to proceed through a bimetallic zinc-DIPT complex, which helps orienting the dipole and dipolarophile giving single regiomeric product and also accelerating the rate of the cycloaddition.

Table 1.9. Diethyl Zinc Catalyzed Nitrile Oxide Cycloaddition to Allyl Alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p-\text{ClC}_6\text{H}_4) (1.92a)</td>
<td>1.93a</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>Ph (1.92b)</td>
<td>1.93b</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>(t-\text{Bu}) (1.92c)</td>
<td>1.93c</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CH}_3(\text{CH}_2)_6) (1.92d)</td>
<td>1.93d</td>
<td>62</td>
<td>92</td>
</tr>
</tbody>
</table>
After formation of the product, the oxygen atom of the cycloadduct is less Lewis basic than that of the nitrile oxide and hence dissociates thereby promoting catalyst turnover. The addition of additives helps dissociate aggregates of zinc with DIPT and thus improves enantioselectivity. Inomata et al. have recently reported the development of N-sulfonylated (S,S)-diaminosuccinate type chiral auxiliary for enantioselective nitrile oxide cycloaddition to allyl alcohol. Golebiewski et al. have recently reported enantioselective nitrile oxide cycloaddition to \( \text{z-pentenol 1.94} \) catalyzed by \( \text{Yb(OTf)}_3/(\text{-})\text{-sparteine as a chiral Lewis acid (Scheme 1.18).} \) Various mixtures of cycloadducts 1.96 and 1.97 were obtained in modest enantioselectivity. The same authors reported similar reaction catalyzed by \( \text{Yb(OTf)}_3/R-(\text{+})\text{-BINOL giving rise to a 1:1 mixture of 1.96 and 1.97. The enantioselectivity of 1.97 was reported to be up to 86% (Scheme 1.19).} \)

Scheme 1.18. Chiral Lewis Acid Catalyzed Nitrile Oxide Cycloaddition to Allyl Alcohol

Scheme 1.19. Example of Nitrile Oxide Cycloaddition to Allyl Alcohol
1.3.2. Nitrile Oxide Cycloaddition to Electron Deficient Alkenes

This section describes recent developments in 1,3-dipolar cycloaddition of nitrile oxides to α,β-unsaturated carbonyl compounds such as enones, enals, α,β-unsaturated esters, imides, sultams, etc. Both diastereo- and enantioselective nitrile oxide cycloadditions to α,β-unsaturated carbonyl compounds have been reported in the literature. The diastereoselective methods have relied on the use of well-established chiral auxiliaries in the literature. These reactions benefit from the use of Lewis acid for rate enhancement as well as rotamer control. Enantioselective nitrile oxide cycloadditions to α,β-unsaturated carbonyl compounds are difficult due to the inherent problems of regio and stereoselectivity. Furthermore, the potential interaction of the Lewis acid with the base required for the preparation of the dipole also complicates the issues. Hence prior to 2000 there were no reports of Lewis acid mediated asymmetric nitrile oxide cycloaddition to α,β-unsaturated carbonyl compounds.

Table 1.10. Nitrile Oxide Cycloaddition to Polymer Bound Acceptors

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mg(ClO₄)₂ (equiv.)</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>1.100:1.101</th>
<th>1.100 ee (%)</th>
<th>1.101 ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>4</td>
<td>54</td>
<td>67:33</td>
<td>60</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>7</td>
<td>48</td>
<td>70:30</td>
<td>56</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>7</td>
<td>53</td>
<td>59:41</td>
<td>38</td>
<td>07</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>7</td>
<td>49</td>
<td>36:64</td>
<td>-41</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>7</td>
<td>47</td>
<td>26:74</td>
<td>-55</td>
<td>20</td>
</tr>
</tbody>
</table>
Faita et al. demonstrated the use of chiral auxiliaries on solid support in 1,3-dipolar cycloaddition of nitrile oxide mediated by a Lewis acid (Table 1.10).\textsuperscript{55} Chiral oxazolidinone crotonate 1.98 underwent cycloaddition with mesityl nitrile oxide to give a mixture of regioisomers 1.100 and 1.101. The reaction was equally efficient in the presence or absence of a Lewis acid additive. The enantioselectivities for the products were modest, and the amount of Lewis acid additive impacted the regioselectivity.

An inversion in regio- and stereoselectivity was observed in reactions using the Lewis acid. The inversion of stereochemistry in the product was explained by reactions from different rotamers (Figure 1.8). The coordination of the Lewis acid to the two carbonyl oxygens forces the carbonyls of the substrate to adopt a *syn* *s*-cis conformation 1.102b. The nitrile oxide approaches the *si*-face of the olefin, which is less hindered, to give one enantiomer 1.100.

---

![Figure 1.8. Explanation for Regio- and Enantioselectivity of Nitrile Oxide Cycloaddition to Polymer Bound Oxazolidinone Crotonate.](image)

In the absence of the coordinating Lewis acid, the two carbonyls must reside in an *anti* *s*-cis conformation 1.102a so that the nitrile oxide approaches the *re*-face of the olefin.
This gives the opposite enantiomer, 1.101. The erosion of regiochemistry is also attributed to the coordination of the dipole oxygen to the Lewis acid complex 1.103.

Sibi et al. reported a substantial improvement in regio- and stereochemical control in nitrile oxide cycloaddition using chiral Lewis acids (Table 1.11). Thus enantioselective nitrile oxide cycloaddition with crotonates 1.31 bound to an achiral template using chiral magnesium Lewis acids proceeded with nearly 99:1 regioselectivity and 99% enantioselectivity for 1.105a-d. After a careful screening of different achiral templates, the authors concluded that the pyrazolidinone template was optimal for obtaining excellent regio- and enantioselectivity. The reaction has broad scope, since a variety of substituents on the dipolarophile such as alkyl, aryl and carboethoxy were tolerated without appreciable compromise in regio- and enantioselectivities. Aromatic as well as aliphatic nitrile oxides could be used, but aliphatic nitrile oxides gave lower yields.

Table 1.11. First Example of Highly Enantio- and Regioselective Nitrile Oxide Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (1.31e)</td>
<td>1.105a</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Et (1.31f)</td>
<td>1.105b</td>
<td>86</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Ph (1.31g)</td>
<td>1.105c</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Et (1.31h)</td>
<td>1.105d</td>
<td>75</td>
<td>99</td>
</tr>
</tbody>
</table>
Sibi et al. also reported enantioselective nitrile oxide cycloaddition to \(\alpha,\beta\)-disubstituted acryloyl imide 1.34 using Mg(NTf\(_2\))\(_2\)/1.32 as a chiral Lewis acid for the construction of sterically congested isoxazolines. Other groups have reported the use of chiral transition metals to catalyzed nitrile oxide cycloadditions. Yamamoto et al. have studied nitrile oxide cycloaddition to acrylamides tethered to auxiliaries such as oxazolidinones and imidazolidinones under chiral Lewis acid catalysis.\(^{57}\) Investigation of different metal with BOX ligands lead to the conclusion that reactions catalyzed by Mg(II) and Yb(III) complexes with Ph-PyBOX ligands gave highest enantioselectivity for the cycloadducts.

Suga et al. have reported an extensive study of nitrile oxide cycloaddition to dipolarophiles tethered to templates such as oxazolidinone and pyrazolidinone in the presence of chiral binaphthyldiimine-Ni(II) catalyst (Scheme 1.20).\(^{58}\) In a representative scheme shown, nitrile oxide cycloaddition to oxazolidinone crotonate 1.107 with a variety of nitrile oxides was efficiently catalyzed by a Ni(ClO\(_4\))\(_2\)/1.109 catalyst. Regioselectivity of 99:01 was reported for most of the cycloadducts 1.110 and in most cases the enantiomeric excess of cycloadducts was >90%.

![Scheme 1.20. Ni-BINIM Catalyzed Nitrile Oxide Cycloaddition](image-url)
Nitrile oxide cycloaddition to α,β-unsaturated aldehydes using single point binding Lewis acids is challenging since the Lewis acid must be finely tuned to differentiate between the carbonyl oxygen of the dipolarophile and the strongly Lewis basic oxygen of the dipole. There are only a couple of examples utilizing single point binding Lewis acids for nitrile oxide cycloadditions. Nitrile oxide cycloaddition to methacrolein has been carried out using a ruthenium catalyst. Kündig et al. showed that regioselective addition of nitrile oxide to methacrolein 1.58 resulted in the formation of isoxazolines 1.111 with a quaternary carbon center (Table 1.12).59 The reactions proceeded smoothly at -5 °C using 5 mol% of the chiral ruthenium catalyst in dichloromethane. Slow addition of the dipole was essential for obtaining higher enantioselectivities. Enantiomeric excess of up to 93% was achieved when 4-trifluoromethyl benzonitrile oxide was used as the dipole at -20 °C (entry 2).

Table 1.12. Nitrile Oxide Cycloaddition to Enals

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>T</th>
<th>Time</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mesityl (1.108a)</td>
<td>-15</td>
<td>72</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>4-CF₃C₆H₄ (1.108b)</td>
<td>-20</td>
<td>16</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>4-FC₆H₄ (1.108c)</td>
<td>-20</td>
<td>24</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>3,5-(CF₃)₂C₆H₃ (1.108d)</td>
<td>-20</td>
<td>16</td>
<td>40</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC₆H₄ (1.108e)</td>
<td>-05</td>
<td>39</td>
<td>57</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>4-iPrC₆H₄ (1.108f)</td>
<td>-05</td>
<td>38</td>
<td>65</td>
<td>63</td>
</tr>
</tbody>
</table>
1.4. Dipolar Cycloaddition to Nitrile Imines

1,3-Dipolar cycloaddition of nitrile imines to olefinic acceptors is one of the least studied reactions in this class. Nitrile imine cycloaddition to olefins lead to the formation of dihydropyrazoles, which has been shown to have some medicinal applications. However, till now only a couple of reports of enantioselective nitrile imine cycloaddition have been reported. Molteni et al have reported some of the earliest attempts towards diastereoselective nitrile imine cycloaddition starting from chiral acceptors. Sibi et al. reported the first enantio- and regioselective nitrile imine cycloaddition to electron deficient olefins (Table 1.13). The reaction of 1.112 with nitrile imine generated from its precursor 1.114 catalyzed by Mg(NTf₂)₂/1.32 as achiral Lewis acid gave exclusively the cycloadduct 1.113 in very high yield and excellent enantioselectivity.

Table 1.13. Lewis Acid Catalyzed Highly Enantioselective Nitrile Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (1.112a)</td>
<td>1.113a</td>
<td>91</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Et (1.112b)</td>
<td>1.113b</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>Ph (1.112c)</td>
<td>1.113c</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>2-furyl (1.112d)</td>
<td>1.113d</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>OBz (1.112e)</td>
<td>1.113e</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>CO₂-t-Bu (1.112f)</td>
<td>1.113f</td>
<td>92</td>
<td>91</td>
</tr>
</tbody>
</table>
The reaction is proposed to proceed through a concerted pathway since only the anti
diastereomer was detected in $^1$H NMR. Other Lewis acid such as Cu(OTf)$_2$, Ni(ClO$_4$)$_2$ and
Zn(NTf$_2$)$_2$ were also tried and gave low enantioselectivity and poor yields for the
cycloadducts.

Sibi et al. have also reported enantioselective nitrile imine cycloaddition to $\alpha,\beta$-
disubstituted-$\alpha,\beta$-unsaturated pyrazolidinone imides 1.115 catalyzed by a chiral Lewis acid
derived from MgI$_2$/1.32 for the construction of highly substituted 4,5-dihydropyrazoles
1.117 (Scheme 1.21).

![Scheme 1.21. Nitrile Imine Cycloaddition for the Synthesis of Highly Substituted
Dihydropyrazoles](image)

1.5. Diazoalkanes, Diazoacetates and Acylhydrazone

Dipolar cycloaddition of diazoalkanes, diazoacetates, and acylhydrazones have not
been extensively studied. Cycloaddition of these dipoles to olefins lead to the formation of
pyrazolidines. Diazoalkanes are typically used for the preparation of cyclopropanes rather
than for the construction of 5-membered heterocycles. This is one of the most reactive
dipole, however, Lewis basicity of the nitrogen atom of this dipole can lead to strong
coordination with Lewis acid employed for these reactions and result in catalyst inhibition. Thus, fine-tuning of the catalyst is essential to exploit the reactivity of these dipoles.

Carriera et al. have demonstrated the application of 1,3-dipolar cycloaddition of (trimethylsilyl)diazomethane to α,β-unsaturated compounds for the synthesis of azaprolines, ent-stelletamide A, and highly functionalized pyrazolidines.63 Kanemasa et al. reported the first enantioselective diazoalkane cycloaddition to electron deficient olefins catalyzed by a chiral Lewis acid. Trimethylsilyl diazomethane 1.118 reacted with α,β-unsaturated oxazolidinone imide 1.112 to yield 4,5-dihydropyrazoles 1.119 in excellent enantioselectivity and good yields (Table 1.14).64 Mg(ClO₄)₂/DBOX 1.22 was the best chiral Lewis acid to catalyze this reaction and other chiral Lewis acids prepared from Ni(II) and Zn(II) metal salts and 1.22 and were also tried successfully.

Table 1.14. Lewis Acid Catalyzed Asymmetric Diazomethane Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Product</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (1.112a)</td>
<td>1.119a</td>
<td>-78</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Et (1.112b)</td>
<td>1.119b</td>
<td>-60</td>
<td>62</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr (1.112g)</td>
<td>1.119c</td>
<td>-60</td>
<td>93</td>
<td>98</td>
</tr>
</tbody>
</table>

Sibi et al. have demonstrated the application of enantioselective diazoacetate cycloaddition to substituted α,β-unsaturated pyrazolidinone imides for the construction of highly substituted chiral pyrazolines (Scheme 1.22).65
Scheme 1.22. Asymmetric Lewis Acid Catalyzed Diazoacetate Cycloaddition

The significance of this report is the wide substrate scope for dipolarophiles, which includes α-substituted, β-substituted and α,β-disubstituted α,β-unsaturated pyrazolidinone imides. Typical enantioselectivities for cycloadducts were >95%. One of the cycloadducts was used for the synthesis of (-)-manzacidin A.

Maruoka et al. have recently reported the first highly enantioselective 1,3-dipolar cycloaddition between diazoacetate and α-substituted acroleins (Table 1.15). In this report selective activation of the enals was accomplished using Ti(IV)-BINOL catalysts 1.56a-b. For cycloaddition of various α-substituted acroleins with diazoacetate 1.120, catalyst 1.56a performed similar to catalyst 1.56b to give pyrazolines in high enantioselectivity. Slightly better yields were obtained with 1.56a and a catalyst loading of 10 mol%. Reactions could also be catalyzed with 5 mol% catalyst loading. The chiral pyrazolines synthesized were used for the synthesis of (-)-manzacidin A. Ryu et al. have reported dipolar cycloaddition between substituted acroleins and diazoacetate using chiral oxazaborolidinium salt for the synthesis of substituted pyrazolines.
1.6. Dipolar Cycloaddition of Azomethine Ylide

Cycloaddition of azomethine ylides to olefins is perhaps one of the most studied dipolar cycloadditions.\textsuperscript{70} The importance of the study lies in the utility of the cycloadducts generated. Azomethine imine cycloaddition to olefins lead to the formation of substituted pyrrolidines, which are very important targets for the pharmaceutical industry. Pyrrolidine nucleus is found in many naturally occurring alkaloids, serve as organocatalysts, and function as building blocks in organic synthesis. Asymmetric azomethine ylide cycloaddition can lead to the construction of up to four contiguous chiral centers in a single step. Various strategies have been employed towards asymmetric azomethine ylide cycloaddition. Earlier asymmetric methods utilized chiral dipoles or chiral dipolarophiles.\textsuperscript{71} One disadvantage of this approach is the need for a stoichiometric amount of the chiral source. With the development of asymmetric catalysis one can use sub-stoichiometric amount of the chiral mediator for dipolar cycloaddition of azomethine ylides. The chiral information can be in the form of a Lewis acid coordinated to a chiral ligand or an organocatalyst, which can suitably interact with the substrate. Also the chiral catalyst can interact with the dipole or the dipolarophile. One of the important issues concerning catalysis is the coordination of the dipole to the catalyst as in case of chiral Lewis acid mediated reactions. If the Lewis acid serves to activate the dipolarophile then the interaction of the Lewis acid with the dipolarophile must be strong compared to that with the dipole. Also, the Lewis acid should not bind with product strongly otherwise catalyst turn over would be difficult. Similar argument holds true if the Lewis acid activates the dipole.
1.6.1. Azomethine Ylide Cycloaddition to Acrylates

Grigg et al. reported the first enantioselective chiral Lewis acid-mediated azomethine ylide cycloaddition to acrylates (Scheme 1.23). The reaction of azomethine ylide 1.123 with various acrylates 1.124 was catalyzed by a chiral Mn(II) or Co(II) Lewis acid using chiral ephedrine ligands 1.125 to yield substituted pyrrolidines 1.126. The enantioselectivity of the cycloadduct reached a maximum of 96% when chiral Co(II) was used as a Lewis acid. A significant disadvantage of this method was the use of one equivalent of the chiral catalyst.

Table 1.15. Asymmetric Diazoacetate Cycloaddition to Enals

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>Product</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (1.58a)</td>
<td>1.121a</td>
<td>1.56a (10)</td>
<td>1</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Me (1.58a)</td>
<td>1.121a</td>
<td>1.56b (5)</td>
<td>1</td>
<td>43</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>Et (1.58b)</td>
<td>1.121b</td>
<td>1.56a (10)</td>
<td>3</td>
<td>63</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Et (1.58b)</td>
<td>1.121b</td>
<td>1.56b (5)</td>
<td>3</td>
<td>48</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>BnOCH(_2)CH(_2) (1.58c)</td>
<td>1.121c</td>
<td>1.56a (10)</td>
<td>1</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>PhCH(_2)CH(_2) (1.58d)</td>
<td>1.121d</td>
<td>1.56a (10)</td>
<td>4</td>
<td>63</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>( i-Pr ) (1.58e)</td>
<td>1.121e</td>
<td>1.56a (10)</td>
<td>3</td>
<td>82</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>Cy (1.58f)</td>
<td>1.121f</td>
<td>1.56a (10)</td>
<td>5</td>
<td>77</td>
<td>94</td>
</tr>
</tbody>
</table>
After the initial report on asymmetric azomethine ylide cycloaddition, several other groups have reported synthesis of chiral pyrrolidines using silver, copper or zinc salts. Many of these reports were prompted by the development of newer chiral ligands. Jørgensen et al. reported one of the first catalytic azomethine ylide cycloaddition with acrylates using Zn(OTf)$_2$ and t-Bu-PyBOX ligand 1.79 (Scheme 1.24). Coordination of the chiral Lewis acid occurs between the nitrogen and oxygen atom of the azomethine ylide. The reaction is proposed to proceed through a bipyramidal intermediate of Lewis acid-ligand and the dipole. There is also coordination of the dipolarophile with the metal as reaction with acrylonitrile does not proceed. Catalyst loading of 10 mol% was sufficient to catalyze the reaction giving high yield of the cycloadduct with excellent enantioselectivity. Other Lewis acid such as Cu(OTf)$_2$ were also tried in which led to the formation of racemic products. Many groups have had considerable success with chiral silver(I) as a Lewis acid for enantioselective azomethine ylide cycloaddition. Schreiber et al. have developed a methodology for asymmetric azomethine ylide cycloaddition using silver(I)-QUINAP 1.129 ligand. This catalyst system is very efficient and only 3 mol% of catalyst is sufficient for catalyzing reactions of various azomethine ylides with acrylates. Typical enantioselectivity of >95% was obtained for most cycloadducts.

\[
\begin{align*}
\text{Ar} & \equiv \text{N} \equiv \text{Me} \\
\text{CO}_2 \text{R}^1 & \equiv \text{Me} \\
\text{H} & \equiv \text{O} \\
\text{N} & \equiv \text{R} \equiv \text{R}'
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \equiv \text{N} \equiv \text{Me} \\
\text{CO}_2 \text{R}^2 & \equiv \text{R}^2 \equiv \text{C}_2 \equiv \text{Ar}
\end{align*}
\]

Scheme 1.23. Early Example of Azomethine Ylide Cycloaddition
Scheme 1.24. Various Ligands for Asymmetric Azomethine Ylide Cycloaddition to Acrylates

Azomethine ylide cycloaddition requires the use of a catalytic amount of base for the generation of the ylide from the corresponding imines. While most reports utilize the base only for the generation of dipole, Jørgensen et al. developed a methodology, which uses a chiral base. Chiral dipole-base ion pair is generated between hydrocinchonine 1.130 and imine 1.127 which reacted with various acrylates to give pyrrolidines in excellent yield.\(^{80}\) However enantioselectivity of the cycloadducts were modest. Silver(I) was
essential for promoting the reaction as other Lewis acids such as LiBr and ZnCl₂ failed to yield cycloadducts in good yield.

The nature of the silver salt was important as reactions with AgF yielded >95% of cycloadducts where as reactions catalyzed with AgCl failed to give any reaction. Nájera et al. have reported BINOL phosphoramidite 1.131-Ag(I) based chiral catalyst for enantioselective azomethine ylide cycloaddition. After screening various silver salts it was observed that best enantioselectivity was obtained when AgClO₄ was used in combination with phosphoramidite 1.131. This catalyst was particularly useful for the reaction of azomethine ylide derived from α-substituted amino esters and enantioselectivity of >95% were obtained for pyrrolidinones. Oh et al. investigated Cu(I) and Ag(I) catalyzed azomethine ylide cycloaddition using brucine derived ligand 1.132. Catalytic system using 1.132/Cu(I) and 1.132/Ag(I) gave enantiomerically opposite pyrrolidines in high enantiomeric excess. The formation of enantiomeric pyrrolidines was attributed to the different coordination of the Lewis acid with 1.132 based on ionic radius of the Lewis acid. The use of ferrocene-derived ligand 1.133/AgOAc was reported by Fukuzawa et al. and was found to be an effective catalyst for azomethine ylide cycloaddition to α-enones. The same authors also reported similar ferrocene based ligand with CuOAc, which was efficient for catalyzing azomethine ylide cycloaddition to acrylates.

1.6.2. Azomethine Ylide Cycloaddition to Maleates, Maleimides, Sulfones, and Other Dipolarophiles

Various groups have employed different catalysts for azomethine ylide cycloaddition to N-substituted maleimides 1.140 (Scheme 1.25). Komatsu et al. reported
exo selective azomethine ylide cycloaddition to N-phenyl maleimide by employing SEGPHOS 1.134/Cu(OTf)₂ as a catalyst.⁸⁶ Endo selective azomethine ylide cycloaddition to N-Aryl maleimide using Fesulphos 1.135/Cu(I) and 1.137/Cu(I) by Carretero⁸⁷ and Shi⁸⁸ respectively.

Scheme 1.25. Ligand Scope for Asymmetric Azomethine Ylide Cycloaddition to Maleimides

Silver(I) catalyzed endo selective azomethine ylide cycloaddition have also been reported by Sansano et al. using (S)-BINAP 1.136.⁸⁹ (S)-BINAP 1.136/AuTFA was found to be effective catalyst for endo selective azomethine ylide cycloaddition to N-methyl
maleimide.\textsuperscript{90} Silver(I)/TF-biphamphos 1.139 have also been found to catalyze \textit{endo} selective azomethine ylide cycloaddition to \textit{N}-substituted maleimide.\textsuperscript{91} Shi et al. have reported \textit{endo} selective azomethine ylide cycloaddition to \textit{N}-aryl maleimides catalyzed by Ni(II)/BINIM 1.138 catalyst.\textsuperscript{92} Wang et al. have also reported \textit{endo} selective azomethine ylide cycloaddition to dimethyl maleate using a CuBF\textsubscript{4}/1.139 catalyst system.\textsuperscript{93}

Zhang et al. reported one of the first azomethine ylide cycloaddition catalyzed by a chiral silver(I) Lewis acid.\textsuperscript{94} In this pioneering example, reactions of various azomethine ylides were tried in the presence of a catalytic amount of silver acetate and chiral phosphine ligands (Table 1.16).

Table 1.16. Lewis Acid Catalyzed Azomethine Imine Cycloaddition to Dimethyl Maleate

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (1.142a)</td>
<td>1.145a</td>
<td>7</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>\textit{p}-MeOC\textsubscript{6}H\textsubscript{4} (1.142b)</td>
<td>1.145b</td>
<td>7</td>
<td>98</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>\textit{p}-CNC\textsubscript{6}H\textsubscript{4} (1.142c)</td>
<td>1.145c</td>
<td>7</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>\textit{m}-pyridyl (1.142d)</td>
<td>1.145d</td>
<td>7</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>\textit{i}-Pr (1.142e)</td>
<td>1.145e</td>
<td>48</td>
<td>82</td>
<td>70</td>
</tr>
</tbody>
</table>

The screening of different phosphine ligands identified ferrocene derived phosphine ligand 1.144 as the best ligand. This catalyst system was very efficient and azomethine
ylides derived from electron rich, electron deficient, and as well as those derived from heteroaromatic and aliphatic aldehydes reacted with just 3 mol% catalyst to yield endo cycloadducts in good yield and excellent enantioselectivity. The enantioselectivity was lower when R was alkyl or heteroaromatic as compared to cases when R was aromatic.

α,β-Unsaturated sulfones are another important class of reactive dipolarophiles that many groups have used to study asymmetric azomethine ylide cycloadditions. Carretero et al. have developed a Cu(I)/1.134 catalyst system for highly endo and enantioselective azomethine cycloaddition to trans-1,2-bisphenylsulfonylethylenes as an acceptor (Scheme 1.26). The advantage of using this acceptor is that the sulfonyl groups can be eliminated to form alkenes. The authors have used this strategy for the synthesis of chiral 3-pyrrolines 1.149, hydroxymethyl pyrrolidines 1.148, and C-azonucleoside 1.150.

Scheme 1.26. Azomethine Ylide Cycloaddition to Bis-sulfonyl Ethylene

Carretero et al. have also reported azomethine ylide cycloaddition to aryl vinyl sulfones catalyzed by Cu(I)/1.151. The significance of this report is that it is the first exo selective azomethine ylide cycloaddition (Scheme 1.27). Cu(MeCN)₄ClO₄ was the best catalyst for obtaining exo adduct selectively with high enantioselectivity. Other Lewis acids
such as AgOAc which has also been widely used was also tried and gave the \textit{exo} product but with lower enantioselectivity. Complementary \textit{endo} pyrrolidines were obtained when 1.154/AgOAc was employed as the chiral Lewis acid. In a report by Wang et al. 5 mol\% of the chiral catalyst was sufficient to effect azomethine ylide cycloaddition to vinyl sulfones 1.152.\textsuperscript{97}

![Scheme 1.27. Ligand Dependant Diastereoselectivity of Azomethine Ylide Cycloaddition](image)

Azomethine ylide cycloaddition of \(\beta\)-phenylsulfonyl enones has been shown to proceed with high \textit{endo} selectivity using 1.134/Cu(MeCN)\textsubscript{4}PF\textsubscript{6} as a chiral Lewis acid (Scheme 1.28).\textsuperscript{98} Hou et al. have reported a Cu(I)/P,N-ferrocene 1.157 catalyzed asymmetric azomethine ylide cycloaddition to nitro styrene to yield diastereomeric pyrrolidines.\textsuperscript{99} The diastereoselectivity of the products could be changed by modifying the aromatic substituent on the phosphorous atom of the ligand. Thus, \textit{exo} cycloadduct 1.156 was obtained in >90\% enantiomeric excess when ligand 1.157\textsubscript{a} was employed where as \textit{endo} cycloadduct 1.156' was obtained in similar enantiomeric excess when ligand 1.157\textsubscript{b} was employed.
1.6.3. Organocatalyzed Azomethine Ylide Cycloaddition

There are only few examples of organocatalyzed azomethine ylide cycloadditions. Vicario et al. have reported the first example of azomethine ylide cycloaddition to enals catalyzed by prolinol 1.159 by iminium ion activation of the substrate (Scheme 1.29). High endo selectivity and enantioselectivity for the cycloadducts was observed with catalyst 1.159. The hydroxy group on the catalyst was essential for high enantioselectivity and diastereoselectivity as other catalyst which lack the hydroxy group or in which the hydroxy group was masked fared poorly.

Scheme 1.29. Organocatalyzed Azomethine Ylide Cycloaddition
The use of an organic base in azomethine ylide cycloaddition is to promote the formation of the dipole by deprotonation of the imine precursor and most literature examples have utilized either Et<sub>3</sub>N or i-Pr<sub>3</sub>N as a base.

Hence the use of acid or reagents with relatively more acidic protons than that of the ylide precursor is avoided. Gong et al. reported an elegant three-component azomethine ylide cycloaddition to form chiral pyrrolidines catalyzed by a chiral phosphoric acid (Scheme 1.30).<sup>101</sup> The ylide precursor was generated in-situ by condensing aromatic aldehydes 1.161 and diethyl amino malonate 1.1612. The cycloaddition between dimethyl maleate 1.143 and in-situ generated ylide catalyzed with chiral phosphoric acid 1.164 proceeded satisfactorily to yield endo cycloadducts in good yield and excellent enantioselectivity. The authors proposed a 7-membered chelate complex between the dipole and the chiral Brønsted acid and reaction proceeding with this activated dipole and dipolarophile. The same authors also utilized this multicomponent methodology for intramolecular enantioselective 1,3-dipolar cycloaddition of azomethine ylides to form chiral hexahydrochromeno[4,3-b]pyrrolidine derivatives.<sup>102</sup>

![Scheme 1.30. Three-Component Azomethine Ylide Cycloaddition Catalyzed by Chiral Phosphoric Acid](image-url)
Chiral thioureas represent a very important class of organocatalysts, which activate substrates by hydrogen bonding. Various groups have reported activation of carbonyl groups by thiourea. The Takemoto group has carried out pioneering work in this area. They have recently reported the utility of chiral thioureas as hydrogen bonding catalyst for formal [3+2] cycloaddition of azomethine ylide to nitroolefins (Scheme 1.31).\textsuperscript{103}

The reaction presumably involves an initial Michael addition to the catalyst bound nitroolefin followed by an intramolecular aza-Henry reaction. The initial Michael addition reaction is catalyzed by thiourea as in the absence of the catalyst the reaction did not proceed.

![Scheme 1.31. Thiourea Catalyzed Formal [3+2] Azomethine Ylide Cycloaddition](image)

Gong et al. have recently reported azomethine ylide cycloaddition to nitro olefins catalyzed by chinchona alkaloid derived chiral thiourea \textbf{1.192} (Scheme 1.32).\textsuperscript{104}
This bifunctional catalyst circumvents the need for an external base, which is required to generate the azomethine ylide from its precursors. Typical reactions were catalyzed by 10 mol% of the catalyst \textbf{1.192} and yielded highly functionalized pyrrolidines in modest yield and enantioselectivity.

\textbf{1.7. Azomethine Imine Cycloaddition}

Cycloadditions of azomethine imines are important since the product cycloadducts have been shown to exhibit biological activity (Figure 1.9). Molecules containing N,N-bicyclic pyrazolidin-3-ones such as \textbf{1.165} have been developed and investigated as antibiotics. Similarly, \textbf{1.166} has been investigated for the treatment of Alzheimer’s disease. Other molecules containing the pyrazolidin-3-one nucleus have been found useful in the field of medicine as antitumor agents and in the field of agriculture as pesticides and herbicides. Despite these potential utilities, the development of asymmetric azomethine imine cycloaddition has been slow. Until now only a handful of examples of enantioselective azomethine imine cycloadditions have been reported in the literature.
1.7.1. Examples of Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition

Suga and co-workers reported 1,3-dipolar cycloaddition of azomethine imine to 3-acryloyl-2-oxazolidinone 1.39 using binaphthyldiimine-Ni(II) complex as the chiral Lewis acid (Scheme 1.33). This particular combination of Lewis acid chiral ligand combination gave predominantly endo cycloadducts in high enantiomeric. This was one of the very first reports of chiral Lewis acid mediated azomethine imine cycloaddition, which involves a dipole-HOMO/dipolarophile-LUMO type interaction.

Scheme 1.33. Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition

A notable feature of this report was the wide variety of groups R that can be incorporated on the azomethine imine and a low catalyst loading of 10 mol% which is very
much desired. However, yield and enantiomeric excess of the cycloadduct obtained was less when R was alkyl as compared to when R was aromatic.

Sibi et al. have reported *exo* selective azomethine imine cycloaddition to acryloyl pyrazolidinone 1.167 catalyzed by Cu(OTf)$_2$/1.32 (Scheme 1.34).$^{106}$ The significance of this report is that it is the first *exo* and enantioselective dipolar cycloaddition of azomethine imines. Square planar organization of the chiral Lewis acid-substrate complex is essential for diastereoselectivity as reactions with other Lewis acids such as Zn(II) and Ni(II) which form tetrahedral and octahedral complexes gave *endo* diastereomers.

Scheme 1.34. *Exo* Selective Lewis Acid Catalyzed Azomethine Imine Cycloaddition

A majority of enantioselective dipolar cycloaddition reported previously utilized N,N-cyclic azomethine imines such as 1.167 as dipoles.$^{107}$ The synthetic utility of C,N-cyclic azomethine imines such as 1.172 has not been explored extensively. Maruoka et al. have reported the first enantioselective azomethine imine cycloaddition to enals utilizing azomethine imine 1.172 (Scheme 1.35). Reactions were catalyzed by a Ti-BINOL catalyst and gave *exo* cycloadducts in excellent enantioselectivity and diastereoselectivity.
Inomata and co-workers have recently reported 1,3-dipolar cycloaddition reaction of azomethine imine 1.167 to allyl alcohol 1.91 using a chiral Lewis acid generated by the reaction of butyl magnesium bromide with \( R,R \)-diisopropyl tartrate.

\[
\begin{align*}
&\text{HCO}_2R^1 + \text{R}^2\text{N}^+\text{NBz}^- \quad \text{Ti(O'Pr)}_4 (10 \text{ mol\%}) \\
&\quad \text{(S)-BINOL (20 \text{ mol\%})} \\
&\text{Toluene} \\
\end{align*}
\]

\[
\text{1.171} \quad \text{1.172} \quad \text{1.173}
\]

\( \text{endo: exo} \text{ up to } 95:05 \)

\( \text{ee \% up to } 99\%
\)

Scheme 1.35. Asymmetric Cycloaddition of C,N-cyclic Azomethine Imines to Enal

The proposed structure of the reactive complex is depicted in Scheme 1.36 and involves a 2:1 complex of metal and diisopropyl tartrate. A number of azomethine imines
prepared by condensation of pyrazolidinone with aromatic and aliphatic aldehydes have been tried with good success.

1.7.2. Azomethine Imine Cycloaddition to Alkynes

Alkynes represent another important class of dipolarophiles for azomethine imine cycloaddition. The cycloadducts from this reaction are similar to 1.165, which have been found to be analogs of β-lactams. There are only few reports asymmetric azomethine cycloaddition to alkynes.

Fu et al. have reported the first enantioselective azomethine imine cycloaddition to terminal alkynes 1.175 (Scheme 1.37). These reactions were catalyzed by 5.5 mol% of Cul2/phosphoferrocene ligand 1.177 furnishing the cycloadducts 1.178 in high yields and excellent enantioselectivity. The reaction proceeds via a transient chiral Cu-acetylide complex. P,N-ligands were essential for catalysis as P,P-ligands such as BINAP essentially shuts off the reaction. A variety of substituents on the pyrazolidinone ring of the dipole were tolerated and also the reaction was amenable to different substituents on the alkynes. The same authors also reported kinetic resolution of 5-substituted azomethine imines by azomethine imine cycloaddition to terminal alkynes using a catalyst system similar to 1.77.

Scheme 1.37. Azomethine Imine Cycloaddition to Terminal Alkynes
1.7.3. Examples of Organocatalyzed Enantioselective Azomethine Imine Cycloaddition

In recent years there has been considerable interest in the use of small molecules for enantioselective transformations. In particular, asymmetric imine catalysis using proline derivatives has been extensively studied. Chen et al. have developed an elegant method for the construction of three contiguous stereocenters by azomethine imine cycloaddition of pyrazolidin-3-one derived azomethine imine 1.176 with α,β-unsaturated aldehydes 1.179 catalyzed by prolinol derived catalyst 1.180 (Scheme 1.38).

Prolinol derived catalyst 1.180 furnished the desired cycloadducts in high exo selectivity and in high enantiomeric excess.

\[
\text{N}^0 - \text{N}^\circ - \text{R}^H \quad 1.176
\]
\[
\text{CHO} \quad 1.180 / \text{TFA} (10\text{mol}) \quad \text{THF-H}_2\text{O, rt}
\]
\[
\text{exo} \quad 1.181 \quad \text{Up to 95% yield}
\]
\[
\text{endo} \quad 1.182 \quad \text{Up to 98:2 (exo:endo)}
\]
\[
\text{Up to 96% ee}
\]

Scheme 1.38. Prolinol Catalyzed Azomethine Cycloaddition to α,β- Unsaturated Aldehydes

Typical reactions were carried out in polar aprotic solvents such as THF or nitromethane in the presence of a small amount of water as an additive, which aided the catalytic process. A variety of azomethine imines prepared by reacting pyrazolidin-3-one with electron rich and electron poor aromatic aldehydes were used with good success. However, azomethine imines prepared from aliphatic aldehydes (R=alkyl) fared poor as
compared to those prepared from aromatic aldehydes in furnishing the exo cycloadducts. Finally α,β-unsaturated aldehydes containing β-aromatic substituents were non-reactive under optimized reaction condition, which represents a severe shortcoming of the method.

Suga and co-workers who have recently reported the 1,3-dipolar cycloaddition of azomethine imine $1.176$ and acrolein using proline as an organocatalyst (Scheme 1.39). These reactions yielded the endo cycloadducts in very good enantiomeric excess. However, reactions were limited to β-unsubstituted α,β-unsaturated aldehydes. On a positive note, proline is cheap, commercially available, and thus avoids the multiple step synthesis and purification processes typically employed for catalyst preparation.

Scheme 1.39. Proline Catalyzed Azomethine Imine Cycloadditions to α,β-Unsaturated Aldehydes

Chen$^{113}$ and co-workers have also reported 1,3-dipolar cycloaddition of azomethine imine to cyclic enones $1.187$ using organocatalysts derived from cinchona alkaloids $1.188$ (Scheme 1.40). This report represents one of the few, which use primary amine as catalysts for dipolar cycloaddition reactions. Some of the key highlights of this catalyst design are:

(1) the tertiary amine group forms a salt by reacting with the achiral additive 2,4,6-triisopropyl benzoic acid (TIPBA) and enhances steric shielding at the reaction center and
(2) the hydroxy group on the naphthyl ring helps in directing the dipole towards the reaction center.

![Scheme 1.40. Organocatalyzed Azomethine Imine Cycloaddition to α,β-Unsaturated Ketones](image)

The use of cyclic enones as acceptors which has a fixed alkene geometry helps addressing the issues that arise from change in rotamer geometry in asymmetric catalysis. Typical reactions were carried out using 10 mol% of the catalyst 1.188 along with TIPBA as an additive yielding the cycloadducts in high yield and with high enantiomeric excess.

1.8. Conclusions

In conclusion, 1,3-dipolar cycloaddition reactions continues to be an important tool for the construction of chiral heterocycles. These heterocycles are important for their biological significance or as precursors for the construction of other important chiral molecules. Dipolar cycloaddition is particularly important for the construction of nitrogen containing heterocycles such as oxazolines, isoxazolines, pyrrolidine and pyrazolidines, etc. These can be easily converted into 1,3-amino alcohols, and diamines, etc, important building blocks in synthetic chemistry.
With the continuing demand for these chiral heterocycles, numerous group have developed methodologies for asymmetric 1,3-dipolar cycloaddition. These included chiral Lewis acid catalyzed dipolar cycloaddition to electron rich and electron deficient olefins. At the same time organocatalyzed 1,3-dipolar cycloaddition provides a mild method for the construction of the same heterocycles.

1.9. References

(1) For a comprehensive review of 1,3-dipolar cycloadditions, see Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003.


(15) (a) Synthesis of Novel Chiral Bis(2-oxazolinyl)xanthene (XaBox) Ligands and their Evaluation in Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with 3-Crotonyl-2-oxazolidinone. Iwasa, S.; Ishima, Y.; Widago, H. S.; Aoki, K.; Nishiyama, H. *Tetrahedron Lett.* 2004, 45, 2121-2124. (b) Chiral Bis(2-oxazolinyl)xanthene (XaBox)/Transition-Metal Complexes Catalyzed 1,3-Dipolar Cycloaddition Reactions and Diels-Alder Reactions. *Tetrahedron* 2008, 64, 1813-1822.


(26) Enantioselective 1,3-Dipolar Cycloaddition of Nitrone to Methacrolein Catalyzed by (η⁵-C₅Me₅)M{(R)-Prophos} Containing Complexes (M= Rh, Ir; (R)-Prophos = 1,2-Bis(diphenylphosphino)propane): On the Origin of the Enantioselectivity. Carmona,


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(71) (a) 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides on Enantiomerically Pure (E)-γ-Alkoxo-*α*,*β*-unsaturated Esters. Annunziata, R.; Cinquini, M.; Cozzi, F.;


(84) Highly Endo-Selective and Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylide with α-Enones Catalyzed by a Silver(I)/Thioclickferrophos Complex. Oura, I.; Shimizu, K.; Ogata, K.; Fukuzawa, S-I. Org. Lett. 2010, 12, 1752-1755.
(85) Highly Enantioselective Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylide Catalyzed by a Copper(I)/Clickferrophos cCmplex. Fukuzawa, S-I.; Oki, H. *Org. Lett.* **2003**, *10*, 1747-1750.


(90) Binap-Gold(I) Trifluoroacetate as a Bifunctional Catalyst for the Synthesis of Chiral Prolines through 1,3-Dipolar Cycloaddition of Azomethine Ylides. Martín-


(104) The First Organocatalytic Enantio- and Diastereoselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with Nitroalkenes. Xue, M-X.; Zhang, X-M.; Gong, L-Z. Synlett 2008, 691-694.


CHAPTER 2.

COPPER(II) CATALYZED EXO AND ENANTIOSELECTIVE AZOMETHINE IMINE CYCLOADDITION

2.1. Introduction

The construction of complex chiral organic molecules continues to be an ongoing challenge for the organic chemist world over. In the past several decades aided by numerous advances in the field of asymmetric catalysis it is now possible to construct chiral molecules in an enantioselective fashion relatively efficiently. These chiral molecules are highly sought after as their targeted end use may aid in improving the quality of human life. In particular, optically pure molecules, which exhibit bioactivity, have been significant for the pharmaceutical industry.

Optically pure molecules can be obtained in a number of different ways. Isolation from natural sources is one of the most straightforward methods however it may involve complicated process of extraction and require an extraordinary amount of feedstock to obtain reasonable amount of the target. Also this method suffers from the fact that it may not be utilized as isolated and some form of chemical modification may be required. Other physical methods involve synthesis of racemic material and separation of the enantiomers. This can be achieved by fractional crystallization of diastereomers or by utilizing chromatographic methods for separation. Though this may be tedious but it is still practical and with the advances made in the field of chromatography it is possible to separate large quantities to make the process economical. Asymmetric synthesis however offers the
luxury of synthesizing the desired enantiomers and could be a more practical method for the construction of enantiopure/enantioenriched materials in a relatively short time.

In the preceding chapter we had extensively reviewed available literature on asymmetric 1,3-dipolar cycloaddition reactions. Despite all the progress there are many questions that still remain unanswered. Dipolar cycloadditions of mono substituted electron deficient olefins, which represents the most reactive dipolarophiles, is abundant in literature. Similarly, there are sufficient examples to 1,2-disubstituted olefins though the scope of \( \beta \)-substituents is rather limited. Whereas cycloadditions with 1,2,2-trisubstituted olefins, which are sterically congested and also less reactive, remains a challenge for organic chemists.

My thesis work focuses on the development of dipolar cycloadditions with less studied dipoles as well as reactions of highly substituted olefins as dipolarophiles. Reactions with trisubstituted olefins provide an opportunity to install chiral quaternary centers, one of the most demanding tasks in synthetic chemistry for which there are very few solutions. Furthermore, I have also investigated chiral Brønsted acids as activators in dipolar cycloadditions. This has allowed us to answer questions as to the complementary nature of Lewis and Brønsted acid activation of substrates as well their unique characteristics. My work also focuses on the identification of achiral templates that are essential to the development of enantioselective transformations. My thesis work is divided into four chapters. Chapter 2 details the development of exo selective dipolar cycloadditions with azomethine imines and acryloyl imides. In chapter 3, the development of Lewis and Brønsted acid mediated azomethine imine additions to 2-acyl imidazole substrates are detailed. In chapter 4, Brønsted acid mediated nitrone cycloadditions to 2-
Acylimidazoles are discussed. In the final chapter, chapter 5, nitrone cycloadditions to $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated carbonyl compounds leading to heterocycles with chiral quaternary centers are described.

A brief introduction to the fundamental aspects of dipolar cycloadditions relating to reactivity and selectivity of electron deficient olefins are discussed first. This is followed by a brief discussion of the role of achiral templates in asymmetric synthesis. The discussion of my work on exo selective Lewis acid catalyzed azomethine imine cycloadditions are detailed next.

2.2. Asymmetric Reactions: Chiral Auxiliaries, Chiral Lewis Acids, and Achiral Templates

Development of chiral auxiliaries for conducting a variety of asymmetric transformations is one of the most notable achievements in synthetic organic chemistry.\(^1\) Auxiliaries provide a point of attachment for the substrate as well as provide coordination sites for the Lewis acid. Scheme 2.1 outlines a schematic for a chiral auxiliary-mediated asymmetric transformation using a carboxylic acid as a substrate. It is important to note that one needs a stoichiometric amount of the chiral information. Since the chiral auxiliary containing products are diastereomers, the target can be purified readily by a variety of techniques to obtain enantiopure material. After completion of the reaction, the auxiliary can be cleaved readily to obtain the target enantioenriched material and the chiral auxiliary can be recovered. A list of commonly used chiral auxiliaries is included in Scheme 2.1.

Development of asymmetric transformations which utilize substoichiometric amounts of the chiral information have been sought after for a long time. This field known
as 'asymmetric catalysis' or 'chiral catalysis' is at the forefront of synthetic organic chemistry as practiced today (Scheme 2.2). Much of the early development in the field relied on a combination of a Lewis acid and a chiral ligand (chiral Lewis acid).\(^2\) In the past decade asymmetric transformations using organic catalysts have received significant attention from synthetic chemists.

A number of reliable synthetic methods have allowed chemists to generate a library of chiral ligands in a relatively short amount of time. These ligands can be easily manipulated for their steric and electronic properties to suit a particular application. The user thus has the ability to influence the reaction center by varying Lewis acidities as well as vary ligand combination. A net outcome of these processes is the better understanding of the reaction conditions necessary for obtaining high selectivity. The use of achiral templates and chiral Lewis acid is thus well suited for the modern synthetic chemist and gradually the use of chiral auxiliaries in asymmetric synthesis has declined over the past
several years. Another key component of chiral Lewis acid mediated transformations is a template that contains all the features of a chiral auxiliary but is achiral. For example, 2-oxazolidinone is an achiral template that has all the features of the chiral oxazolidinone 2.9.

![Scheme 2.2. Chiral Lewis Acid Mediated Asymmetric Transformations](image)

Over the years a large number of achiral templates have been devised for asymmetric transformations including work from our laboratory.\(^3\) A recent and interesting addition to the family of achiral templates is based on a concept termed 'chiral relay'. These templates incorporate fluxional chirality that can effectively shield distant reaction centers using relatively less bulky ligands as a static source of chirality.

Dellaria and co-workers reported one of the earliest examples on the use of fluxional chirality embedded in the substrate to affect a proximal reaction center (Scheme 2.3).\(^4\) Alkylation of enolate generated from 2.11 gave product 2.12, whereas 2.13 under similar condition gave 2.14 in high diastereomeric excess. The relative stereochemistry of the product depended on the hybridization of the nitrogen atom next to the reaction center. In 2.13 the substituent on the sp\(^3\) hybridized nitrogen orients away from the fixed chirality and hence allows bond construction from the same side as the fixed chiral group. As this
process involves relay of the stereochemical information from the static chirality to a fluxional center in the substrate, which in turn will influence the reaction center, the concept was coined as chiral relay. This concept was studied and further extended by Davis, Clayden, and Hitchcock.

Scheme 2.3. Preliminary Evidence for Chiral Relay

We have been able to successfully utilize the concept of chiral relay through the development of \( N1 \)-substituted pyrazolidinones as achiral auxiliaries. The example described above and others in the literature require a stoichiometric amount of the chiral source (diastereoselective methodology). The pyrazolidinones were designed with the goal of being able to conduct asymmetric reactions using catalytic amounts of the chiral source. In reactions with pyrazolidinones, the static chirality would originate from chiral ligands with the fluxional chirality present at \( N1 \)-position. This development was significant since now it was possible to use substochiometric amount of chiral Lewis acids during asymmetric transformations. Another important design element was that the substitution at \( N1 \)-position in 2.15 could be varied easily and do not require special reaction conditions.
Thus, the $N_1$- group can be modulated from a simple alkyl group such as ethyl to a bulky group such as mesitylmethyl or naphthylmethyl to suit one's need. The present understanding on the mode of action of the relay template is that the overall process is a double diastereoselection experiment with reactions occurring only from the matched conformation as shown in 2.16 (Figure 2.1).

2.15 Stereogenic nitrogen center

2.16 Ligand and fluxional center shield the same face

2.17 Ligand and fluxional center shield opposite faces

Figure 2.1. Development of Pyrazolidinones as Relay Templates

2.3. 1,3-Dipolar Cycloaddition Reactions of Azomethine Imines

We focused our attention towards azomethine imines as potential dipoles for cycloadditions. Cycloadditions of azomethine imines are important since the cycloadducts have been shown to exhibit biological activity. Molecules containing N,N-bicyclic
pyrazolidin-3-ones such as 2.18 has been developed and investigated as analogs of antibiotics such as penicillin and cephalosporin (Figure 2.2). Similarly compound 2.19 has been investigated for the treatment of Alzheimer’s disease. Molecules containing the pyrazolidin-3-one nucleus have found utility in medicine as antitumor agents and in the field of agriculture as pesticides and herbicides. Despite these potential applications, the development in the field of asymmetric azomethine imine cycloaddition has been slow. Until now only a handful of examples of enantioselective azomethine imine cycloadditions have been reported in literature.

Figure 2.2. Biologically Significant N,N-Bicyclic Pyrazolidin-3-one Derivatives

Huisgen reported one of the earliest examples of azomethine imine cycloadditions. Azomethine imine 2.20 was reacted with a variety of substituted olefins 2.21 to yield substituted pyrazolidines 2.22 as a mixture of regioisomers (Scheme 2.4). Much of the early reports on azomethine imine cycloaddition were achiral and many of these reactions were carried out under thermal conditions. Development in this era was particularly limited due to the lack of protocols for the preparation of stable azomethine imines as many of the azomethine imines were prepared in situ by thermolysis. Control of regiochemistry of the cycloadducts was also complicated under thermal conditions. Stable azomethine imines
were later prepared by condensation of aldehydes or ketones to pyrazolidinones. These azomethine imines could be purified and stored over a period of time and thus allowed development of asymmetric azomethine imine cycloadditions.

\[ \text{R}^1 = p-\text{ClC}_6\text{H}_4 \]

Scheme 2.4. Earlier Example of Azomethine Imine Cycloaddition

### 2.3.1. Azomethine Imine Cycloaddition Using Chiral Azomethine Imines

Several groups have reported the use of chiral azomethine imines as dipoles for cycloadditions. Husson\(^{10}\) reported azomethine imine cycloadditions using chiral azomethine imine 2.24 derived by the condensation of corresponding carbazate with aromatic aldehydes (Scheme 2.5). The utility of the azomethine imine thus generated was demonstrated by reacting with either dimethyl fumarate or dimethyl maleate. The reaction of azomethine imine 2.24 (R = Ph) with dimethyl fumarate in chloroform gave cycloadduct 2.23 in good yield (82%) whereas the same azomethine imine reacted with dimethyl maleate under similar condition gave cycloadduct 2.25 in modest yields (62%). It should be noted that the stereochemistry of the starting alkene is conserved in the product indicating that the reaction should be occurring by a concerted pathway. Also the cycloaddition gave the endo adducts exclusively. Svete\(^{11}\) reported cycloaddition of chiral azomethine imines 2.26 obtained by the condensation of corresponding pyrazolidin-3-one and benzaldehyde with electron deficient olefins in anisole. The reaction of azomethine imine 2.26 with
dimethyl maleate gave the corresponding *endo* cycloadduct 2.27 in good yields of up to 88%. Similarly, reaction of 2.26 with methyl acrylate gave *endo* adduct 2.28 in yield up to 81%. Cycloadduct 2.27 and 2.28 are particularly important as they can serve as building blocks for the synthesis of analogs of 2.18 that are important for its biological properties.

Scheme 2.5. Examples of Application of Chiral Azomethine Imines

### 2.3.2. Examples of Organocatalyzed Enantioselective Azomethine Imine Cycloaddition

In recent years there has been considerable interest in the use of small organic molecules for enantioselective transformation. In particular asymmetric imine catalysis using proline derivatives has been extensively studied. Chen\(^\text{12}\) and co-workers have developed an elegant method for the construction of three contiguous stereocenters by
azomethine imine cycloaddition of pyrazolidin-3-one derived azomethine imine 2.29 with α,β-unsaturated aldehydes (Scheme 2.6). Prolinol derived catalyst 2.31 furnished the desired cycloadduct in high exo selectivity and in high enantiomeric excess. Typical reactions were carried out in polar aprotic solvents such as THF or nitromethane in the presence of a small amount of water as an additive that aided the catalytic process. A variety of azomethine imines prepared by reacting pyrazolidin-3-one with electron rich and electron poor aromatic aldehydes were used with good success. However, azomethine imines prepared from aliphatic aldehydes (R=alkyl) fared poorly as compared to those prepared from aromatic aldehydes in furnishing the exo cycloadducts. Finally α,β-unsaturated aldehydes containing β-aromatic substituents were non-reactive under the optimized reaction condition, which represents a severe shortcoming of the method.

Scheme 2.6. Prolinol Catalyzed Azomethine Imine Cycloaddition to α,β-Unsaturated Aldehydes

Suga and co-workers have recently reported the 1,3-dipolar cycloaddition of azomethine imine 2.29 and acrolein (Scheme 2.7) to demonstrate the application of small molecules as organocatalysts. These reactions yielded the endo cycloadducts in very good enantiomeric excess. Reactions were limited to β-unsubstituted α,β-unsaturated aldehydes.
On a positive note, proline is cheap, commercially available, and thus avoids the multiple stage synthesis and purification processes typically employed for catalyst preparation.

Scheme 2.7. Proline Catalyzed Azomethine Imine Cycloadditions to \(\alpha,\beta\)-Unsaturated Aldehydes

Chen\(^{13}\) and co-workers have also reported 1,3-dipolar cycloaddition of azomethine imine to cyclic enones using organocatalysts derived from cinchona alkaloids 2.33 (Scheme 2.8). This report represents one of the few that use primary amines as catalysts for dipolar cycloaddition reactions. Some of the key highlights of this catalyst design are; the tertiary amine group which forms a salt by reacting with the achiral additive and enhances steric shielding at the reaction center and the hydroxy group on the naphthyl ring which helps in directing the dipole towards the reaction center. The use of cyclic enones as acceptors which has a fixed alkene geometry helps address issues that arise from change in rotamer geometry in asymmetric catalysis. Typical reactions were carried out using 10 mol\% of the catalyst 2.33 along with 2,4,6-trisopropyl benzoic acid (TIPBA) as additive yielding the cycloadducts in high yield and with high enantiomeric excess.
Scheme 2.8. Organocatalyzed Azomethine Imine Cycloaddition to α,β-Unsaturated Ketones

2.3.3. Examples of Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition

The use of chiral Lewis acids to control absolute stereochemistry in an organic transformation has been one of the most successful strategies for the construction of chiral molecules. Inomata and co-workers have recently reported 1,3-dipolar cycloaddition reaction of azomethine imine 2.29 to allyl alcohol 2.39 using a chiral Lewis acid generated by reaction of butyl magnesium bromide with R,R-diisopropyl tartrate (Scheme 2.9). The proposed structure of the reactive complex involves a 2:1 complex of metal and diisopropyl tartrate. A number of azomethine imines prepared by condensation of pyrazolidinone with aromatic and aliphatic aldehydes have been tried with good success.

Scheme 2.9. Azomethine Imine Cycloaddition to Allyl Alcohol
Suga and co-workers reported 1,3-dipolar cycloaddition of azomethine imine to 3-acryloyl-2-oxazolidinone $2.42$ using binaphthyldiimine-Ni(II) complex as the chiral Lewis acid (Scheme 2.10). This particular combination of Lewis acid and chiral ligand gave endo cycloadducts in high enantiomeric excess. This was one of the very first reports of chiral Lewis acid mediated azomethine imine cycloaddition that involves a dipole-HOMO/dipolarophile-LUMO type interaction. A notable feature of this report was the wide variety of R groups that can be incorporated on the azomethine imine and a low catalyst loading of 10 mol%. However, yield and enantiomeric excess of the cycloadducts was lower when R is alkyl as compared to when R is aromatic.

![Scheme 2.10. Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition](image)

**2.4. Results and Discussions**

The Sibi group has previously reported the utility of $\alpha,\beta$-unsaturated pyrazolidinone imide $2.15$ in a wide variety of transformations. Especially these $\alpha,\beta$-unsaturated pyrazolidinone imides have been shown to be excellent substrates for Diels Alder cycloaddition as well as 1,3-dipolar cycloaddition of nitrones,$^{14}$ nitrile oxides,$^{15}$ nitrile imines,$^{16}$ and diazoacetates.$^{17}$ In particular, it was shown that for Diels Alder
cycloadditions there was a significant impact of the \( N_1 \)- fluxional group on enantioselectivity as well as on diastereoselectivity. For chiral Lewis acid complexes with less bulky ligands this influence was more pronounced. Ligands with larger steric volume had major contribution towards enantioselectivity, thus overriding the influence of fluxional chirality. Another important aspect was the effect of metal geometry, which was studied in detail. A square planar organization of chiral Lewis acid-substrate complex was essential for amplifying the effect of the fluxional group. Thus metals such as Cu(II) and Pd(II) were found to be ideal for obtaining higher levels of enantioselectivities as compared to metals such as Mg(II) and Zn(II). After demonstrating the utility of \( \alpha,\beta \)-unsaturated pyrazolidinone amide as substrate for a variety of 1,3-dipolar cycloadditions we wanted to extend the scope of our study.

At the beginning of my thesis work there were few reports on chiral Lewis acid catalyzed azomethine imine cycloadditions to electron deficient olefins as acceptors leading to the formation of \textit{endo} cycloadducts. However, there was no general method for the construction of \textit{exo} cycloadducts. Our previous experience with nitrone cycloaddition using \( \alpha,\beta \)-unsaturated pyrazolidinone amide 2.45 as substrates indicated that Cu(II)/bis(oxazoline) catalyzed reactions yielded predominantly \textit{exo} cycloadducts 2.47 (Scheme 2.11). Hence we wanted to investigate the possibility of an \textit{exo} selective azomethine imine using a similar catalyst ligand combination. We also wanted to investigate if there was an influence of the fluxional group on the enantioselectivity and/or diastereoselectivity of the cycloadducts. The effect of C5- substituent on the pyrazolidinone ring 2.48 on enantio- and diastereoselectivity of the cycloadduct was also to be evaluated. Finally we also wanted to
extend the scope of the reaction by utilizing $\beta$-substituted $\alpha,\beta$-unsaturated pyrazolidinone amide with the hope to construct three contiguous stereo centers.

Scheme 2.11. *Exo* Selective Azomethine Imine Cycloaddition

**2.4.1. Optimization of Chiral Lewis Acids**

Our initial studies were oriented towards finding an optimal Lewis acid and chiral ligand combination for azomethine cycloadditions to $\alpha,\beta$-unsaturated pyrazolidinone amide. The substrates were synthesized by procedures developed in our laboratory whereas a variety of $C_2$-symmetric bis(oxazoline) ligands were synthesized using procedures reported in the literature.\(^{18}\)

We began by optimizing reaction conditions for the 1,3-dipolar cycloaddition of azomethine imines with pyrazolidinone acrylate 2.48. Initial reactions were carried out at room temperature using 30 mol% of a chiral Lewis acid. As with our previous study of *exo* selective nitrone cycloadditions, Cu(OTf)$_2$/2.52 was found to be an effective catalyst for *exo* selective azomethine imine cycloadditions. Thus azomethine imine cycloaddition of
pyrazolidinone acrylate with azomethine imine gave the desired exo cycloadduct in 81% yield as a 90:10 mixture of exo and endo diastereomers (entry 1, Table 2.1). Furthermore the exo cycloadduct was formed in 98% enantiomeric excess. Chiral Lewis acids prepared from additional bis(oxazoline) ligands and Cu(OTf)₂ were also tried in an attempt to increase enantio- and diastereoselectivity. When Cu(OTf)₂/t-Bu-BOX 2.53 (entry 2) was used as the chiral Lewis acid, the cycloadduct was formed in 98% enantiomeric excess, however the diastereoselectivity of the exo adduct decreased (83:17 versus 90:10). The Ph-BOX ligand 2.54 with flat Ph ring gave cycloadducts with lower enantiomeric excess (82%) as compared to Cu(OTf)₂/t-Bu-BOX combination (compare entries 2 and 3). Similarly when Cu(OTf)₂/Bn-BOX 2.55 was used, the cycloadducts were formed with high exo selectivity but lower yields (entry 4). We have also investigated the impact of metal atom geometry on the cycloaddition reaction of pyrazolidinone acrylate with azomethine imines. In our previous reports we had shown metals that have tetrahedral, octahedral and higher coordination geometries were not suited for use with the pyrazolidinone template. Reactions with metals such as Mg(II) and Zn(II) which have been proposed to have tetrahedral or octahedral geometries were tried and preferentially gave the endo cycloadduct over exo with lower enantiomeric excess. Thus Mg(OTf)₂/2.52 gave an exo:endo mixture of 4:96 in poor yield of 38% (entry 5). The exo cycloadduct was formed in 46% enantiomeric excess while the endo cycloadduct was formed in 47% enantiomeric excess. This result shows the ineffectiveness of the ligand in shielding the reaction center when the geometry of the central metal deviated from a preferred square planar arrangement. A similar trend was observed when Zn(OTf)₂/2.52 was used for the same
reaction. A 33:67 ratio of exo and endo isomers were formed and an enantiomeric excess of 60% and 59% was obtained for the exo and endo isomers respectively (entry 6).

Table 2.1. Optimization of Chiral Lewis Acids for Azomethine Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Chiral Ligand</th>
<th>mol%</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>2.52</td>
<td>30</td>
<td>81</td>
<td>90:10</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>2.53</td>
<td>30</td>
<td>85</td>
<td>83:17</td>
<td>-98</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)₂</td>
<td>2.54</td>
<td>30</td>
<td>88</td>
<td>84:16</td>
<td>-82</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)₂</td>
<td>2.55</td>
<td>30</td>
<td>75</td>
<td>84:16</td>
<td>-84</td>
</tr>
<tr>
<td>5</td>
<td>Mg(OTf)₂</td>
<td>2.52</td>
<td>30</td>
<td>38</td>
<td>4:96</td>
<td>46(47)</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)₂</td>
<td>2.52</td>
<td>30</td>
<td>84</td>
<td>33:67</td>
<td>60(-59)</td>
</tr>
<tr>
<td>7</td>
<td>Ni(ClO₄)₂</td>
<td>2.52</td>
<td>30</td>
<td>80</td>
<td>7:93</td>
<td>55(85)</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>2.52</td>
<td>20</td>
<td>83</td>
<td>89:11</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)₂</td>
<td>2.52</td>
<td>10</td>
<td>90</td>
<td>88:12</td>
<td>94</td>
</tr>
</tbody>
</table>

*a* Isolated yield after column chromatography. *b* Exo/endo determined by ¹H NMR. *c* Enantiomeric excess of products determined by chiral HPLC.

Ni(II) on the other hand has been proposed to exist in either octahedral or square planar geometry. Thus when Ni(ClO₄)₂/2.52 was used as the chiral Lewis acid, cycloadducts were formed in 80% yield with a 7:93 mixture of exo and endo isomers (entry 7). Notably even though the exo isomer was formed in modest enantioselectivity of 55%, the endo adduct was formed in good enantioselectivity of 85%.
This initial screening of chiral Lewis acid provided us with a good picture regarding the optimal Lewis acid and bis(oxazoline) ligand combination required to synthesize the exo cycloadduct in high enantiomeric excess. One of the important aspects of catalysis is the amount of chiral activator utilized for the reaction or catalytic loading. This parameter indicates the efficiency of the catalytic process and is a critical factor if the Lewis acid or ligands are scarce and/or expensive. We therefore diverted our attention towards lowering chiral Lewis acid loading. Cu(OTf)$_2$/2.52 which was the best combination of Lewis acid and ligand was used for this study. Decreasing the amount of chiral Lewis acid from 30 to 20 mol% did not affect the enantioselectivity or diastereoselectivity of the cycloadducts (compare entries 1 and 8, Table 2.1). Catalyst loading could be further reduced to 10 mol% furnishing the cycloadducts as a 88:12 mixture of exo and endo isomer with slight erosion in enantioselectivity of the exo isomer (entry 9). The catalyst loading could have been reduced further to 5 mol% but was never pursued. Thus, subsequent reactions were optimized using 10 mol% of Cu(OTf)$_2$/2.52 as the chiral Lewis acid.

2.4.2. Effect of N-1 Substituent

The primary role of the N-1 substituent on pyrazolidinone is to relay and amplify the stereochemical information from the ligand to the reaction center. Previous studies on Cu(II) catalyzed cycloaddition carried out in our group has shown significant impact of the relay group on the enantio- and diastereoselectivity of cycloadducts. In particular for Diels-Alder cycloaddition it was shown that a good correlation between the size of relay group and selectivity of the products exists when ligands with relatively smaller steric volume were used.
To investigate the effect of $N$-1 substituent in azomethine imine cycloaddition we prepared a series of $\alpha,\beta$-unsaturated pyrazolidinone imides 2.48a-c. Reactions of pyrazolidinone imide 2.48b where $N$-1 substituent was ethyl with azomethine imine gave a 92:08 mixture of exo and endo cycloadducts with 98% enantiomeric excess for the exo adduct (entry 2, Table 2.2). Though the reaction was done at an elevated temperature, it was interesting that we could still obtain the cycloadducts with no erosion of stereochemistry. Increasing the bulk at $N$-1 position by incorporating a phenyl ring did not have any effect on either diastereoselectivity or enantioselectivity of the cycloadducts (entry 1, Table 2.2). Similarly when the $N$-1 substituent was changed to 1-naphthylmethyl there was no significant impact on diastereoselectivity or enantioselectivity ($exo/endo=95:05$ and ee 98% for exo isomer, entry 3).

Table 2.2. Effect of Pyrazolidinone $N$-1 Substitution

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>$exo/endo$</th>
<th>$exo$ ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.48a</td>
<td>rt</td>
<td>90</td>
<td>88:12</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>2.48b</td>
<td>40</td>
<td>86</td>
<td>92:08</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>2.48c</td>
<td>rt</td>
<td>79</td>
<td>95:05</td>
<td>98</td>
</tr>
</tbody>
</table>

* Isolated yield after column chromatography.  
* Exo/endo determined by $^1$H NMR.  
* Enantiomeric excess of products determined by chiral HPLC.
Thus, it can be concluded that in the presence of bulky amino indanol derived bis(oxazoline) ligand 2.52, the contribution towards enantio- and diastereoselectivity comes predominantly from the ligand and the relay group has little involvement.

2.4.3. Effect of C-5 Substitution on Azomethine Imines

One of the goals of this study was to investigate the impact of the C-5 substitution of the pyrazolidinone ring of azomethine imine on the enantio- and diastereoselectivity of the cycloadducts. The C-5 substituent on the pyrazolidinone ring of the dipolarophiles is believed to be important for pushing the N-1 substituent closer to the reaction center. In our previous report on Diels-Alder cycloaddition a trend was observed which suggested, an increase in steric volume of the C-5 substituent resulted in increased enantioselectivity of the cycloadducts.\textsuperscript{19} We wanted to study the effect of varying the steric bulk at C-5 position of the azomethine imine on the enantio- and diastereoselectivity of the cycloadducts.

To investigate the effect of the C-5 substituent, a series of azomethine imines with different alkyl substituents at the C-5 position were synthesized and reacted under optimized conditions with pyrazolidinone imide 2.48a. We also did a limited study on the effect of molecular sieves on the reaction outcome. The results of these studies are summarized in Table 2.3.

The reaction of pyrazolidinone imide 2.48a with azomethine imine 2.50a where R = Me furnishes the cycloadducts in 90% yield in a 88:12 mixture of the exo and endo diastereomers with 94% enantiomeric excess for the desired exo adduct (entry 1, Table 2.3). Decreasing the steric bulk at C-5 position on the azomethine imine had a positive effect on both enantio- and diastereoselectivity of the exo adduct. Thus reaction of 2.48a
with azomethine imine 2.50d (where, \( R = H \)) gave a >96:04 mixture of \textit{exo} and \textit{endo} cycloadducts with the \textit{exo} cycloadduct formed in 95% enantiomeric excess (entry 2). Increasing the steric bulk at C-5 position leads to further erosion in \textit{exo}/\textit{endo} selectivity. Thus azomethine imine 2.50e (\( R = \text{Et} \)) and 2.50f (\( R = -(\text{CH}_2)_5^- \)) which have C-5 substituents bulkier than 2.50d gave 72:28 (entry 3) and 73:27 (entry 6) mixture of the \textit{exo} and \textit{endo} adducts respectively.

Table 2.3. Effect of C-Substitution on Azomethine Imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipole</th>
<th>Product</th>
<th>4Å MS</th>
<th>Yield (%)</th>
<th>\textit{exo}/\textit{endo}</th>
<th>ee (%)</th>
</tr>
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<tr>
<td>1</td>
<td>2.51a</td>
<td>2.50a</td>
<td>yes</td>
<td>90</td>
<td>88:12</td>
<td>94</td>
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<tr>
<td>2</td>
<td>2.51b</td>
<td>2.50d</td>
<td>yes</td>
<td>79</td>
<td>&gt;96:04</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>2.51c</td>
<td>2.50e</td>
<td>yes</td>
<td>69</td>
<td>72:28</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>2.51c</td>
<td>2.50e</td>
<td>no</td>
<td>33</td>
<td>88:12</td>
<td>94</td>
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<tr>
<td>5(^d)</td>
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<td>2.50e</td>
<td>no</td>
<td>75</td>
<td>81:19</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>2.51d</td>
<td>2.50f</td>
<td>yes</td>
<td>77</td>
<td>73:27</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>2.51d</td>
<td>2.50f</td>
<td>no</td>
<td>65</td>
<td>86:14</td>
<td>95</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of products after column chromatography. \(^b\) \textit{Exo}/\textit{endo} ratios were determined by \(^1\)H NMR. \(^c\) Enantiomeric excess of products were determined by chiral HPLC. \(^d\) Reaction performed in a sealed heavy walled pressure vessel at 40 °C.

The effect of molecular sieves on the reaction was also investigated. Molecular sieves help to trap moisture in the reaction medium thus providing anhydrous conditions, which are vital to keep the Lewis acid active in many cases and also to prevent side reactions, which may arise due to the decomposition of the starting materials or products.
In many cases it has also been observed that substantial changes in metal geometry occurs when the reactions are carried out with/without molecular sieves. These changes will impact both the yield and the enantio-/diastereoselectivity of the products. In our studies we have observed that reactions without any molecular sieves were sluggish and furnished the cycloadduct in much lower yields than reaction performed in the presence of molecular sieves (entry 4 and 7, Table 2.3). The diastereoselectivity of the cycloadduct in fact improved in the absence of molecular sieves (compare entry 3 with 4 and entry 6 with 7). Enantioselectivity of the cycloadduct however remained unchanged. One reason for the lower yields of the isolated products may be due to Lewis acid decomposition as the starting materials and products were found to be stable under the reaction conditions. Higher yields were obtained when the reactions were carried out at 40 °C in a sealed tube (entry 5), the enantioselectivity and diastereoselectivity was however unchanged.

### 2.4.4. Scope of Azomethine Imines for Cu(II)/2.52 Catalyzed 1,3-Dipolar Cycloaddition

After optimizing the reaction condition for the best chiral Lewis acid and varying N-1 substitution and C-5 substitution on the pyrazolidinone ring of the dipolarophile and dipole respectively, we decided to extend the scope of the reaction. For this study various azomethine imines were prepared by the condensation of 3,3-dimethyl pyrazolidin-3-one with a variety of aldehydes.

1,3-Dipolar cycloaddition reaction of electron rich azomethine imine 2.51e derived from p-methoxy benzaldehyde gives the desired exo cycloadduct in high enantiomeric excess (entry 2, Table 2.4). Similar result was obtained with another electron rich
azomethine imine 2.51f, which gave the cycloadduct as a 91:09 mixture of exo and endo diastereomers in high enantiomeric excess (entry 3). Azomethine imine prepared from p-halogenated benzaldehydes were also tried as dipoles and reacted to furnish the desired exo cycloadduct in 98% enantiomeric excess and ≥92:08 exo:endo ratio (entry 4 and 5).

Azomethine imine derived from aromatic aldehydes bearing strong electron withdrawing group in the para position was also tested. Thus reaction of azomethine imine 2.51i bearing p-cyano group gave a 82:18 exo and endo diastereomeric mixture in 80% yield with 93% enantiomeric excess for the exo adduct (entry 6).

Table 2.4. Survey of Azomethine Imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>4Å MS</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>exo/endo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>exo ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
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<td>90</td>
<td>88:12</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>pMeOC₆H₄ (2.51e)</td>
<td>2.50g</td>
<td>yes</td>
<td>81</td>
<td>96:04</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>pMeC₆H₄ (2.51f)</td>
<td>2.50h</td>
<td>yes</td>
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<td>91:09</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>pBrC₆H₄ (2.51g)</td>
<td>2.50i</td>
<td>yes</td>
<td>83</td>
<td>93:07</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>pClC₆H₄ (2.51h)</td>
<td>2.50j</td>
<td>yes</td>
<td>82</td>
<td>92:08</td>
<td>98</td>
</tr>
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<td>pCNC₆H₄ (2.51i)</td>
<td>2.50k</td>
<td>yes</td>
<td>80</td>
<td>82:18</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>pCNC₆H₄ (2.51i)</td>
<td>2.50k</td>
<td>no</td>
<td>81</td>
<td>87:13</td>
<td>96</td>
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<tr>
<td>8</td>
<td>oClC₆H₄ (2.51j)</td>
<td>2.50l</td>
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<tr>
<td>11&lt;sup&gt;d&lt;/sup&gt;</td>
<td>iPr (2.51l)</td>
<td>2.50n</td>
<td>yes</td>
<td>72</td>
<td>88:12</td>
<td>78</td>
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</table>

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> Exo/endo determined by <sup>1</sup>H NMR. <sup>c</sup> Enantiomeric excess of products determined by chiral HPLC. <sup>e</sup> 20 mol% of Cu(OTf)<sub>2</sub> and 22 mol% of 2.52 was used to prepare the catalyst.
Reactions of the same azomethine imine performed in the absence of molecular sieves gave better exo/endo mixture and also furnished the exo cycloadduct in much higher enantiomeric excess (compare entry 6 and 7, Table 2.4). Azomethine imines derived from o-halogenated benzaldehydes were also tried with good success. Thus reaction of pyrazolidinone imide 2.48a with azomethine imine 2.51j bearing a ortho chloro group gave a 94:06 exo and endo diastereomers in 89% yield and a 98% enantiomeric excess for the exo isomer (entry 8). Similarly, azomethine imine 2.51k bearing an ortho fluoro group furnished the cycloadducts with lower diastereo- and enantioselectivity compared to azomethine imine 2.51j (compare entries 8 and 9). However the same reaction when performed in the absence of molecular sieves gave much better exo/endo ratio and higher enantiomeric excess for the exo adduct (compare entries 9 and 10). Finally, azomethine imine 2.51l derived from aliphatic aldehydes can also be employed under the designed protocol but with a slightly higher catalyst loading and yielded predominantly the exo cycloadduct (exo:endo= 88:12) with slightly less enantioselectivity (entry 11).

We have also made attempts to expand the scope of dipolarophiles in exo and enantioselective cycloaddition of azomethine imine. Specifically, we sought to apply this methodology to β-substituted α,β-unsaturated pyrazolidinone imides (Scheme 2.12). 1,3-dipolar cycloaddition of azomethine imine 2.51a with pyrazolidinone imide 2.56 was tried with 10 mol% of Cu(OTf)₂/2.52 and did not yield cycloadduct 2.57a after several days of reaction time. Eventually the catalyst loading was increased to 100 mol%. However it was disappointing to see that even with such high catalyst loading the reaction did not proceed. Changing the azomethine imine from 2.51a to 2.51b did promote the reaction though the catalyst loading could not be reduced and a stoichiometric amount of the Cu(OTf)₂/2.52
was required. This was considered a serious limitation to the current methodology as it substantially reduces the scope of dipolarophiles, which we will address in the next chapter.

\[
\begin{align*}
\text{Scheme 2.12. Further Expansion of Cu(II)/2.52 Catalyzed Exo Selective Azomethine Imine Cycloadditions}
\end{align*}
\]

2.4.5. Explanation of Diastereoselectivity and Enantioselectivity

In the previous sections we have discussed \textit{exo} and enantioselective azomethine imine cycloaddition to acryloyl pyrazolidinone catalyzed by Cu(OTf)\(_2\)/2.52. A square planar or a distorted square planar complex of Cu(II) has been previously postulated by our group in explaining selectivity in nitrone cycloadditions to \(\alpha,\beta\)-unsaturated pyrazolidinone imides.\(^{21}\) Based on crystal structure of Cu(OTf)\(_2\)/2.52 we have confirmed the formation of this square planar complex (Figure 2.3).

Based on this Cu(OTf)\(_2\)/2.52 crystal structure we were able to construct a model to understand the formation of \textit{exo} cycloadducts in azomethine cycloadditions (Figure 2.4). From these models we can see that the \textit{si}-face of the dipolarophile is shielded by the indanol moiety of the chiral ligand 2.52. Thus the approach of the dipole can only be possible from the \textit{re}-face. Furthermore, the \(N\)-1 group of the pyrazolidinone ring of the
substrate additionally shields the si-face of the dipolarophile. The endo approach of the dipole is sterically encumbered due to repulsion between the 5,5-dimethyl groups on the dipole and hydrogen atoms on the ligand. These repulsive forces are minimal when the dipole approaches in an exo fashion. This may be a reason why the exo cycloadducts are formed preferentially over the endo.

Figure 2.3. Crystal Structure of Cu(OTf)$_2$/2.52. 2H$_2$O Complex

2.5. Conclusion

We have developed the first strategy for exo and enantioselective azomethine imine cycloaddition using 2-acryloyl pyrazolidinone imide 2.48a as dipolarophile. This methodology is complementary to other strategies reported for endo selective azomethine imine cycloaddition. Investigation of the geometry of metal complex proved that metals with square planar geometries such as copper(II) are ideal and supports conclusions from previous studies on exo selective nitrone cycloaddition reported by our group.
The combination of Cu(OTf)$_2$/2.52 was found to be the best for high exo and enantioselectivities and a catalyst loading of as low as 10 mol% can be accommodated. These reactions are performed at room temperature, which add to the ease of operation, but we can also do reactions at elevated temperature with no loss in enantio- and diastereoselectivity. We have also tested the effect of the N-1 substituent on the pyrazolidinone ring of the dipolarophile and the C-5 substituents on the azomethine imine for their effect on reaction outcome. Interesting effect of molecular sieves on exo/endo selectivity and enantioselectivity was observed with reactions performed in the absence of molecular sieves gave better diastereoselectivity with slightly lower yields that those performed in the presence of molecular sieves. To demonstrate the scope of our methodology we have also tried azomethine imines prepared from a variety of aldehydes.
In general most of these reactions were high yielding and gave the exo diastereomer in
excellent enantiomeric excess. To extend the scope of dipolarophiles we have initiated
some studies with β-substituted α,β-unsaturated pyrazolidinone imides.

2.6. Experimental

Dichloromethane was distilled from calcium hydride under nitrogen prior to use.
Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or
on an ISCO CombiFlash Companion with Analogix RS-4 columns. All glassware was oven
dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air
sensitive materials were carried out by standard syringe technique. Molecular sieves were
dried by heating under vacuum prior to use.

Melting points were measured with a Fisher-Johns melting point apparatus and are
uncorrected. $^1$H NMR was recorded on a Varian Mercury-300 (300 MHz), Varian Unity/
Inova-400 NB (400 MHz), or Varian Unity/Inova-500NB (500 MHz) spectrometer.
Chemical shifts are reported in parts per million (ppm) downfield from TMS, using
residual CDCl$_3$ (7.27 ppm) as an internal standard. Data are reported as follows: chemical
shifts, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet),
integration and coupling constants. $^{13}$C NMR was recorded on a Varain Unity/Inova-500
NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300
(75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported
in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl$_3$
(77.23) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC
pump and a 2487 dual λ absorbance detector connected to a PC with Empower
workstation. Optical rotations were measured on a JASCO-DIP-370 polarimeter. High-resolution mass spectra (HRMS) (ESI+) were obtained from the Mass Spectrometry Laboratory, North Dakota State, Fargo, North Dakota.

2.6.1. Materials and Methods

Copper triflate was purchased from Aldrich. Cyclopropyl bisoxazoline ligand {3aR-[2(3'a'S, 8'a'R), 3aa, 8aa]}-2,2'-(cyclopropylidene)-bis{3a,8a-dihydro-8H-indeno[1,2d]-oxazole} was prepared according to literature procedure.22 3-Pyrazolidinone hydrochloride was purchased from Acros. 5,5-Dimethylpyrazolidin-3-one, 5,5-diethylpyrazolidin-3-one, 5-spiro cyclohexylpyrazolidin-3-one, 1-ethyl-5,5-dimethylpyrazolidin-3-one, 1-benzyl-5,5-dimethylpyrazolidin-3-one, 1-(1-naphthylmethyl)-pyrazolidin-3-one, 2-acryloyl-1-benzyl-5,5-dimethylpyrazolidin-3-one (2.48a), and 2-acryloyl-1-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (2.48c) were prepared according to literature procedures.23

2.6.2. Synthesis of 2-Acryloyl-1-ethyl-5,5-dimethylpyrazolidin-3-one (2.48b)

2-Acryloyl-1-ethyl-5,5-dimethylpyrazolidin-3-one (2.48b) was prepared by a modified literature procedure.24 To a solution of acrylic acid (1.3 equiv) and triethylamine (2.5 equiv) in THF (0.2 M) was added acryloyl chloride (1.2 equiv) at -20 °C. An off white solid was formed instantaneously. The mixture was stirred at -20 °C for 1 hour. Lithium chloride (1.1 equiv) was then added, followed by the addition of 1-ethyl-5,5-dimethylpyrazolidin-3-one (1 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 0.2 N HCl (2 equiv) and the THF was removed under reduced pressure. The residue was taken up in
EtOAC, washed with 0.2 N HCl then brine, and dried over MgSO₄. The organic solution was filtered and solvent removed in vacuo. 2-Acryloyl-1-ethyl-5,5-dimethylpyrazolidin-3-one was purified by flash column chromatography to give 2.48b in 70% yield as a low melting white solid. ¹H NMR (CDCl₃, 400 MHz); δ 1.01 (t, 3H, J = 7.2 Hz), 1.25 (s, 6H), 2.52 (s, 2H), 2.94 (q, 2H, J = 7.2 Hz), 5.78 (dd, 1H, J = 1.8, 10.5 Hz), 6.47 (dd, 1H, J = 1.8, 17.1 Hz), 7.20 (dd, 1H, J = 10.5, 17.1 Hz); ¹³C NMR (CDCl₃, 100 MHz); δ 13.0, 25.9, 44.0, 47.5, 60.9, 128.7, 131.5, 164.0, 175.3. IR (KBr) 3090, 2982, 2843, 1750, 1690, 1651, 1431, 1357, 1309, 1227, 1010, 990, 792 cm⁻¹. HRMS calcd. for C₁₀H₁₆N₂NaO₂⁺: 219.1104; Found: 219.1100.

Scheme 2.13. Synthesis of 2-Acryloyl-1-ethyl-5,5-dimethyl Pyrazolidin-3-one

2.6.3. General Procedure for Synthesis of Azomethine Imines:

Azomethine imines (2.51a-l) were prepared according to a modified literature procedure (Scheme 2.14). The appropriate pyrazolidin-3-one (1.0 equiv) was dissolved in EtOH (10 mL) at room temperature. To this solution was added the appropriate aldehyde (1.05 equiv) and the resulting solution was stirred overnight at room temperature. The following morning the solvent was evaporated, and the products were purified by flash chromatography (EtOAc/MeOH) to obtain pure azomethine imines. The average yields were 60-70%.
Scheme 2.14. General Procedure for Synthesis of Azomethine Imines

**1-Benzylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51a):**

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and benzaldehyde. This compound has been previously prepared and characterized. (off-white solid, mp = 142-144 °C); $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.76 (s, 6H), 2.79 (s, 2H), 7.04 (s, 1H), 7.49-7.51 (m, 3H), 8.35-8.38 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz); δ 29.1, 44.6, 74.0, 129.0, 129.7, 129.9, 131.9, 132.0, 181.9.

**1-Benzylidene-3-oxopyrazolidin-1-ium-2-ide (2.51b):**

Prepared according to the general procedure from pyrazolidin-3-one and benzaldehyde. This compound has been previously prepared and characterized. (off-white solid, mp = 192-194 °C); $^1$H NMR (CDCl$_3$, 100 MHz) δ 2.73-2.78 (m, 2H), 4.49-4.54 (m, 2H), 7.17 (s, 1H), 7.41-7.44 (m, 3H), 8.24-8.27 (m, 2H). $^{13}$C NMR (DMSO, 100 MHz); δ 29.9, 58.1, 129.4, 130.6, 131.6, 131.7, 132.5, 185.1. HRMS calcd. for C$_{10}$H$_{10}$N$_2$NaO$^+$: 197.0685; Found: 197.0684.
1-Benzylidene-5,5-diethyl-3-oxopyrazolidin-1-ium-2-ide (2.51c):
Prepared according to the general procedure from 5,5-diethylpyrazolidin-3-one and benzaldehyde. (off-white solid, mp = 184-186 °C); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 0.92 (t, 6H, \(J = 7.4\) Hz), 1.82-2.01 (m, 4H), 2.64 (s, 2H), 6.8 (s, 1H), 7.45-7.46 (m, 3H), 8.32-8.35 (m, 2H); \(^1\)C NMR (CDCl\(_3\), 100 MHz); \(\delta\) 7.9, 33.1, 37.6, 81.0, 128.9, 129.6, 130.3, 131.9, 132.0, 182.7. IR (KBr) 3045, 2970, 1659, 1586, 1564, 1447, 1332, 1306, 1090, 957, 674 cm\(^{-1}\). HRMS calcd. for C\(_{14}\)H\(_{19}\)N\(_2\)O\(^+\): 231.1492; Found: 231.1491.

1-Benzylidene-5-spirocyclohexane-3-oxopyrazolidin-1-ium-2-ide (2.51d):
Prepared according to the general procedure from 5-spirocyclohexylpyrazolidin-3-one and benzaldehyde. (off-white solid, mp = 201-203 °C); \(^1\)H NMR (CDCl\(_3\), 400MHz); \(\delta\) 1.23-1.52 (m, 3H), 1.80-2.04 (m, 7H), 2.72 (s, 2H), 7.07 (s, 1H), 7.45-7.46 (m, 3H), 8.32-8.35 (m, 2H); \(^1\)C NMR (CDCl\(_3\), 100MHz); \(\delta\) 24.1, 24.9, 38.0, 41.1, 78.8, 129.0, 129.7, 130.8, 132.0, 132.1, 182.4. IR (KBr) 3050, 2936, 2856, 1661, 1586, 1566, 1448, 1300, 1086, 1036, 755, 693, 655 cm\(^{-1}\). HRMS calcd. for C\(_{15}\)H\(_{19}\)N\(_2\)O\(^+\): 243.1492; Found: 243.1499.

1-[(4-Methoxyphenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51e):
Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 4-methoxybenzaldehyde. (off-white solid, mp = 194-196
°C); $^1$H NMR (CDCl$_3$, 400 MHz); δ 1.68 (s, 6H), 2.74 (s, 2H), 3.85 (s, 3H), 6.94 (d, 2H, $J$ = 8.7 Hz), 7.08 (s, 1H), 8.33 (d, 2H, $J$ = 8.7); $^{13}$C NMR (CDCl$_3$, 100 MHz); δ 29.1, 44.9, 55.7, 73.1, 114.4, 122.7, 129.8, 134.0, 162.6, 181.5. HRMS calcd. for C$_{13}$H$_{17}$N$_2$O$_2^+$: 233.1285; Found: 233.1285.

1-[(4-Methylphenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51f):
Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and p-tolualdehyde. (off-white solid, mp = 203-205 °C); $^1$H NMR (CDCl$_3$, 400 MHz); δ 1.68 (s, 6H), 2.38 (s, 2H), 2.70 (s, 3H), 6.98 (s, 1H), 7.23 (d, 2H, $J$ = 8.3 Hz), 8.21 (d, 2H, $J$ = 8.5 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz); δ 22.0, 29.1, 44.7, 73.6, 127.1, 129.8, 130.1, 132.0, 143.1, 181.7. HRMS calcd. for C$_{13}$H$_{17}$N$_2$O$: 217.1335; Found: 217.1333.

1-[(4-Bromophenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51g):
Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 4-bromobenzaldehyde. (off-white solid, mp = 197-199 °C); $^1$H NMR (CDCl$_3$, 400 MHz); δ 1.70 (s, 6H), 2.75 (s, 2H), 7.02 (s, 1H), 7.57-7.60 (dt, 2H, $J$ = 8.8, 2.5 Hz), 8.20-8.23 (dt, 2H, $J$ = 8.8, 2.5 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz); δ 29.0, 44.5, 74.3, 126.5, 128.0, 128.7, 132.2, 133.0, 181.7. HRMS calcd. for C$_{12}$H$_{13}$BrN$_2$NaO$: 303.0103; Found: 303.0096.
1-[(4-Chlorophenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51h):

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 4-chlorobenzaldehyde. (off-white solid, mp = 199-201 °C);

$^1$H NMR (CDCl$_3$, 400 MHz); δ 1.70 (s, 6H), 2.72 (s, 2H), 6.97 (s, 1H), 7.40-7.43 (dt, 2H, $J$ = 8.8, 2.5 Hz), 8.27-8.31 (dt, 2H, $J$ = 8.8, 2.5 Hz);

$^{13}$C NMR (CDCl$_3$, 100 MHz); δ 29.1, 44.5, 74.3, 127.7, 128.2, 129.2, 132.8, 137.9, 181.9. HRMS calcd. for C$_{12}$H$_{14}$ClN$_2$O$: 237.0789; Found: 237.0784.

1-[(4-Cyanophenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51i):

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 4-cyanobenzaldehyde. (off-white solid, mp = 278-280 °C);

$^1$H NMR (CDCl$_3$, 400 MHz); δ 1.73 (s, 6H), 2.74 (s, 2H), 6.99 (s, 1H), 7.71 (d, 2H, $J$ = 8.6 Hz), 8.42 (d, 2H, $J$ = 8.4 Hz);

$^{13}$C NMR (CDCl$_3$, 100 MHz); δ 29.1, 44.2, 75.3, 114.4, 118.1, 126.0, 131.6, 132.4, 133.5, 182.3. HRMS calcd. for C$_{13}$H$_{14}$N$_3$O$: 228.1131; Found: 228.1130.

1-[(2-Chlorophenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51j):

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 2-chlorobenzaldehyde. (off-white solid, mp = 174-176 °C);

$^1$H NMR (CDCl$_3$, 400MHz); δ 1.73 (s, 6H), 2.73 (s, 2H), 7.35-7.38 (m, 2H), 7.43-7.45 (m,
1H), 7.56 (s, 1H), 9.28-9.31 (m, 1H); 13C NMR (CDCl₃, 100 MHz); 29.4, 44.3, 75.0, 124.8, 127.3, 127.5, 129.7, 132.4, 133.0, 135.01, 182.0. HRMS calcd. For C₁₂H₁₄ClN₂O⁺: 237.0789; Found 237.0806

1-[(2-Fluorophenyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51k):

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and 2-fluorobenzaldehyde. (off-white solid, mp = 194-196 °C); 'H NMR (CDCl₃, 400 MHz); δ 1.68 (s, 6H), 2.69 (s, 2H), 7.04-7.09 (m, 1H), 7.21 (t, 1H, J = 7.6 Hz), 7.37-7.43 (m, 1H), 9.17-9.22 (dt, 1H, J = 1.7, 7.8 Hz); ¹³C NMR (CDCl₃, 100 MHz); δ 29.1, 44.5, 74.7, 114.9 (d, ²JCF = 21.6 Hz), 118.3 (d, ²JCF = 8.07 Hz), 121.1 (d, ³JCF = 8.25 Hz), 124.9 (d, ⁴JCF = 3.8 Hz), 132.6, 133.4 (d, ³JCF = 8.6 Hz), 161.3 (d, ¹JCF = 255.6 Hz), 182.2. HRMS calcd. for C₁₂H₁₄FN₂O⁺: 221.1085; Found: 221.1081.

I-[(Isopropyl)methylene]-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (2.51l):

Prepared according to the general procedure from 5,5-dimethylpyrazolidin-3-one and isovaleraldehyde. (off-white solid, mp = 92-94 °C); 'H NMR (CDCl₃, 400 MHz); δ 1.12 (d, 6H, J = 6.9), 1.53 (s, 6H), 2.63 (s, 2H), 3.23-3.31 (dq, 1H, J = 7.5, 6.9 Hz), 6.28 (d, 1H, J = 7.5 Hz); ¹³C NMR (CDCl₃, 100 MHz); δ 18.8, 28.9, 29.3, 45.5, 72.0, 141.9, 180.5. HRMS calcd. for C₆H₁₇N₂O⁺: 169.1335; Found: 169.1327.
2.6.4. Procedures for Cu(II)-Catalyzed Exo and Enantioselective Cycloadditions of Azomethine Imines

2.6.4.1. Representative Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imines 2.51a-l with α,β- Unsaturated Pyrazolidinone Imides 2.48a and 2.48c

To a 6-dram vial containing 4Å molecular sieves (100 mg), Cu(OTf)₂ (0.010-0.030 mmol), and ligand 5 (0.011-0.033 mmol) was added CH₂Cl₂ (1 mL). The contents were stirred for 1 hour. The α,β-unsaturated pyrazolidinone imide (0.1 mmol) was then added and the reaction mixture was stirred for 30 minutes. A solution of azomethine imine (0.1 mmol) in CH₂Cl₂ (1 mL) was finally added. The reaction was stirred at room temperature for 24-48 h until the dipolarophile was consumed (TLC). The reaction mixture was then filtered through a pad of celite and rinsed with CH₂Cl₂ (2 x 10 mL). The organic layer was washed with 15% aq. NH₃ solution (2 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL). The organic layer was finally dried over anhydrous magnesium sulfate. Silica gel (2 g) was added to the organic layer and the solvent was removed in vacuo. The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogix RS-4 columns. The cycloaddition products were isolated as inseparable mixtures of exo and endo adducts. exo/endo ratios were determined by ¹H NMR spectroscopy prior to chromatography or by HPLC analysis after chromatography.

2.6.4.2. Representative Procedure for High Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imine 2.51a with α,β- Unsaturated Pyrazolidinone Imide 2.48b
In a 15 mL heavy wall pressure vessel with a threaded Teflon bushing was added 4 Å molecular sieves (100 mg), Cu(OTf)$_2$ (0.010-0.030 mmol), ligand 5 (0.011-0.033 mmol), and CH$_2$Cl$_2$ (1 mL). The vessel was then stirred for 1 hour at room temperature. The α,β-unsaturated pyrazolidinone imide (0.1 mmol) was then added and the reaction mixture was stirred for an additional 30 min. A solution of azomethine imine (0.1 mmol) in CH$_2$Cl$_2$ (1 mL) was finally added. The vessel was sealed and heated to the 40 °C for 24-48 h until the dipolarophile was consumed (TLC). The reaction mixture was then cooled to room temperature, filtered through a pad of celite and rinsed with CH$_2$Cl$_2$ (2 x 10 mL). The organic layer was washed with 15% aq. NH$_3$ solution (2 x 10), water (1 x 10 mL) and brine (1 x 10 mL). The organic layer was finally dried over anhydrous magnesium sulfate. Silica gel (2g) was added to the organic layer and the solvent was removed in vacuo. The cycloaddition products were purified by flash column silica gel chromatography on a ISCO CombiFlash Companion with AnaLogix RS-4 columns. The cycloaddition products were isolated as inseparable mixtures of exo and endo adducts. Exo/endo ratios were determined by $^1$H NMR spectroscopy prior to chromatography or by HPLC analysis after chromatography.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50a):

Colorless prisms, mp 76-80°C [α]$_D^{25}$ 59.3 (c 1.0, CHCl$_3$), (exo:endo = 88:12); $^1$H NMR (CDCl$_3$, 400 MHz); δ 0.55 (3H, s), 0.95 (3H, s), 1.11 (3H, s), 1.18 (3H, s), 2.30 (1H, d, $J = 17.0$ Hz), 2.38 (1H, d, $J = 17.0$ Hz), 2.46 (1H, d, $J = 17.2$ Hz), 2.51 (1H,
d, J = 17.2 Hz), 3.20 (1H, d, J = 14.2 Hz), 3.33 (1H, d, J = 14.2 Hz), 3.70 (1H, t, J = 11.0 Hz), 3.90-3.99 (1H, m), 4.42 (1H, d, J = 10.2 Hz), 4.62-4.72 (1H, m), 7.15-7.35 (10H, m, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta\) 23.5, 25.5, 26.5, 29.8, 42.7, 43.7, 45.7, 51.2, 55.9, 59.3, 60.1, 64.9, 127.5, 128.3, 128.4, 128.5, 128.8, 129.7, 138.0, 138.2, 166.5, 173.4, 174.3; IR (KBr) 3460, 3057, 3025, 2971, 2928, 1738, 1697, 1455, 1238, 777 cm\(^{-1}\). HRMS calcd. for C\(_{27}\)H\(_{33}\)N\(_4\)O\(_3^+\): 461.2547; Found: 461.2542.

**Entry 1, Table 2.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_R\) 13.7 min (exo major), \(t_R\) 14.8 min (endo major), \(t_R\) 21.8 min (endo minor), \(t_R\) 32.9 min (exo minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 94% ee for the exo cycloadduct.

\[
\text{(5R,6S)-6-(1-ethyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50b):}
\]

Colorless viscous liquid, \([\alpha]_D^{25}\) 75.3 (c 1.0, CHCl\(_3\)), (exo/endo = 92:08); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 0.62 (3H, s), 0.71 (3H, t, J = 7.1 Hz), 0.96 (3H, s), 1.12 (3H, s), 1.17 (3H, s), 2.20 (1H, d, J = 17.2 Hz), 2.41 (1H, d, J = 17.2 Hz), 2.48 (2H, s), 2.50-2.61 (2H, m), 3.85-3.90 (1H, dd, J = 11.4, 8.0 Hz), 4.03-4.08 (1H, dd, J = 11.4, 8.7 Hz), 4.45 (1H, d, J = 10.2 Hz), 4.60-4.67 (1H, dt, J = 10.1, 8.2 Hz), 7.1-7.2 (3H, m, Ar-H), 7.3 (2H, m, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 125MHz); \(\delta\) 13.0, 23.3, 25.6, 25.7, 29.7, 43.0, 44.5, 45.8, 46.5, 51.2, 59.5, 59.6, 64.9, 128.3, 128.4, 129.7, 138.2, 167.0, 173.3, 175.0; IR (KBr) 3465, 3031, 2973, 2933, 1741, 1700, 1456, 1373, 1305, 1238, 1126, 700 cm\(^{-1}\). HRMS calcd. for C\(_{22}\)H\(_{36}\)N\(_4\)NaO\(_3^+\): 421.2210; Found: 421.2171.
Entry 2, Table 2.2: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \( t_R \) 13.7 min (endo major), \( t_R \) 16.1 min (exo major), \( t_R \) 20.3 min (endo minor), \( t_R \) 26.3 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 98% ee for the \( \text{exo} \) cycloadduct.

(\(5R,6S\))-6-(1-(1-naphthylmethyl)-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50c):

Colorless solid, mp = 115-120 °C, [\(\alpha\)]\(D\)\(25\) 39.3 (c 1.0, CHCl\(_3\)), (exo/endo = 95:05); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 0.59 (3H, s), 0.98 (3H, s), 1.18 (3H, s), 1.24 (3H, s), 2.46-2.54 (4H, m), 3.50-3.60 (2H, bs), 3.79-3.82 (1H, t, \(J = 10.0\) Hz), 3.89 (1H, d, \(J = 14.4\) Hz), 4.45 (1H, d, \(J = 10.0\) Hz), 4.59-4.64 (1H, dd, \(J = 17.2, 8.6\) Hz), 7.20-7.25 (3H, m, Ar-H), 7.33-7.36 (2H, m, Ar-H), 7.41-7.44 (1H, t, \(J = 7.5\) Hz), 7.49-7.56 (2H, m, Ar-H), 7.72-7.73 (1H, d, \(J = 6.5\) Hz), 7.75-7.76 (1H, d, \(J = 8.1\) Hz), 7.86-7.88 (1H, d, \(J = 7.8\) Hz), 7.97-7.99 (1H, d, \(J = 8.2\) Hz); \(^1\)C NMR (CDCl\(_3\), 125 MHz); \(\delta\) 23.4, 24.9, 26.6, 29.8, 42.4, 43.6, 45.6, 51.1, 52.8, 59.1, 60.1, 64.9, 123.2, 125.6, 125.7, 126.1, 127.2, 128.0, 128.3, 128.4, 129.0, 129.7, 131.2, 133.5, 133.8, 138.3, 166.4, 173.4, 174.2; IR (KBr) 3446, 2972, 2931, 1743, 1700, 1387, 1373, 1238, 1121, 1048, 799, 778 cm\(^{-1}\). HRMS calcd. for C\(_{31}\)H\(_{34}\)N\(_4\)NaO\(_3\): 533.2523; Found: 533.2534.

Entry 3, Table 2.2: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \( t_R \) 12.8 min (exo major), \( t_R \) 13.6 min (endo major), \( t_R \) 22.6 min (endo minor), \( t_R \) 33.6 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 98% ee for the \(\text{exo}\) cycloadduct.
(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dihydro-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50d):

Colorless solid, mp = 72-76 °C, [α]_D^{25} -31.6 (c 1.0, CHCl₃), (exo/endo = >96:04); ^1H NMR (CDCl₃, 400 MHz); δ 1.09 (3H, s), 1.12 (3H, s), 2.49 (1H, d, J = 17.2 Hz), 2.41 (1H, d, J = 17.2 Hz) 2.57-2.65 (1H, m), 2.69-2.78 (1H, m), 2.94 (1H, d, J = 9.0 Hz), 4.24 (1H, dd, J = 16.0, 7.6 Hz), 7.22-7.29 (9H, m, Ar-H), 7.37-7.39 (2H, m, Ar-H); ^13C NMR (CDCl₃, 125 MHz); δ 26.2, 29.0, 31.5, 43.6, 44.8, 46.3, 55.4, 56.8, 61.1, 114.0, 121.5, 127.9, 128.2, 128.6, 128.8, 128.9, 129.3, 137.1, 167.8, 173.7, 174.6; IR (KBr) 3446, 2972, 1747, 1699, 1495, 1455, 1375, 1235, 1124, 1085, 1029, 700 cm⁻¹. HRMS calcd for C₂₅H₂₉N₄O₃⁺: 455.2054; Found: 455.2057.

Entry 2, Table 2.3: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 13.9 min (exo minor) t_R 16.0 min (exo major) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/ min] as 95% ee for the exo cycloaduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-diethyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50e):

Colorless solid, mp = 72-76 °C, [α]_D^{25} 42.4 (c 1.0, CHCl₃), (exo/endo = 72:28); ^1H NMR (CDCl₃, 400 MHz); δ 0.55 (s, 3H), 0.66 (t, 3H, J =7.4 Hz), 0.76 (t, 3H, J =7.3 Hz), 1.21 (s, 3H), 1.3-1.4 (m, 2H), 1.65-1.75 (m, 2H), 2.29-2.35 (m, 3H), 2.56 (d, 1H, J = 17.2 Hz), 3.11 (d, 1H, J = 14.0 Hz), 3.29 (d, 1H, J =14.0 Hz), 3.70 (dd, 1H, J =
11.1, 8.4 Hz), 3.93-4.01 (m, 1H), 4.48-4.59 (m, 1H), 7.15-7.31 (m, 10H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta\) 8.3, 9.5, 25.4, 26.3, 26.6, 30.1, 42.2, 42.6, 43.7, 51.2, 55.8, 60.1, 64.5, 64.9, 127.4, 128.1, 128.2, 128.4, 128.7, 129.8, 138.1, 138.5, 166.3, 174.2, 175.9; IR (KBr) 3446, 3030, 2970, 2937, 1745, 1700, 1653, 1456, 1375, 1303, 1235, 1029, 700 cm\(^{-1}\).

HRMS calcd for C\(_{29}\)H\(_{36}\)N\(_4\)NaO\(_3\): 511.2680; Found: 511.2663

**Entry 4, Table 2.3:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t\(_R\) 10.8 min (exo major), t\(_R\) 11.5 min (endo major), t\(_R\) 13.8 min (endo minor), t\(_R\) 21.1 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 91% ee for the exo cycloadduct.

\((5R,6S)-6-(1\text{-benzyl}-5,5\text{-dimethyl}-3\text{-oxopyrazolidine-2-carbonyl})-3\text{-spirocyclohexyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)}\text{-one (3e): Cycloadduct 2.50f:}\)

Colorless solid, mp = 85-90°C, \([\alpha]_D^{25}\) 43.9 (c 1.0, CHCl\(_3\)), (endo/exo = 73:27); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 0.54 (s, 3H), 0.91-1.09 (m, 4H), 1.04 (s, 3H), 1.20-1.24 (m, 1H), 1.30-1.36 (m, 1H), 1.38-1.44 (m, 2H), 1.48-1.57 (m, 2H), 1.80-1.83 (m, 1H), 2.31 (d, 1H, \(J = 17.0\) Hz), 2.37 (d, 1H, \(J = 17.0\) Hz), 2.49 (d, 1H, \(J = 17.0\) Hz), 2.55 (d, 1H, \(J = 17.0\) Hz), 3.12 (d, 1H, \(J = 14.0\) Hz), 3.29 (d, 1H, \(J = 14.0\) Hz), 3.66-3.71 (m, 1H), 3.94-3.99 (m, 1H), 4.48-4.59 (m, 2H), 7.16-7.31 (m, 10H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz); \(\delta\) 23.2, 23.5, 25.5, 26.5, 33.3, 38.1, 41.0, 42.8, 43.6, 51.0, 55.8, 60.1, 62.4, 64.3, 127.4, 128.1, 128.3, 128.4, 128.7, 129.7, 138.1, 138.6, 166.3, 174.2, 175.7; IR (KBr) 3446, 3029, 2934, 2857, 1744, 1700, 1653, 1455, 1374, 1304, 1235, 1030, 773, 700 cm\(^{-1}\). HRMS calcd for C\(_{33}\)H\(_{35}\)N\(_4\)NaO\(_3\): 523.2680; Found: 523.2659.
Entry 6, Table 2.3: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 12.1 min (exo major), t_R 13.4 min (endo major), t_R 17.9 min (endo minor), t_R 24.9 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/ min] as 95% ee for the exo cycloaduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(4-methoxy-phenyl)-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50g):
Colorless solid, mp = 168-172°C, [α]_D^25 57.3 (c 1.0, CHCl₃), (exo/endo = 96:04); ^1H NMR (CDCl₃, 400 MHz); δ 0.55 (3H, s), 0.96 (3H, s), 1.11 (3H, s), 1.17 (3H, s), 2.31 (1H, d, J = 17.0 Hz), 2.39 (1H, d, J = 17.0 Hz), 2.47 (2H, d, J = 5.5 Hz), 3.24 (1H, d, J = 13.8 Hz), 3.36 (1H, d, J = 13.8 Hz), 3.65-3.70 (4H, m), 3.89-3.99 (1H, m), 4.50 (1H, d, J = 10.1 Hz), 4.61-4.68 (m, 1H), 6.71-6.83 (2H, m, Ar-H), 7.21-7.27 (7H, m, Ar-H); ^13C NMR (CDCl₃, 125 MHz); δ 23.5, 25.5, 26.4, 29.9, 42.5, 43.7, 45.7, 51.1, 55.4, 56.0, 59.1, 60.1, 64.4, 113.7, 127.5, 128.5, 128.7, 130.0, 130.7, 138.0, 159.7, 166.7, 173.3, 174.2; IR (KBr) 3461, 3062, 3023, 2972, 2932, 1742, 1696, 1512, 1374, 1239, 1032, 728 cm⁻¹. HRMS calcd. for C_{29}H_{35}N_{4}O_{4}⁺: 491.2653; Found: 491.2674.

Entry 2, Table 2.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 14.4 min (exo major), t_R 18.3 min (endo major), t_R 26.8 min (endo minor), t_R 35.9 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/ min] as 98% ee for the exo cycloaduct.
(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(4-
methyl-phenyl)-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50h):

Colorless solid, mp = 169-172 °C, [α]D25 67.6 (c 1.0, CHCl3),
(exo/endo = 91:09); 1H NMR (CDCl3, 400 MHz); δ 0.55 (3H, s),
0.96 (3H, s), 1.11 (3H, s), 1.17 (3H, s), 2.2 (3H, s), 2.30 (1H, d, J
= 17.0 Hz), 2.38 (1H, d, J = 17.0 Hz), 2.44 (1H, d, J = 16.8 Hz),
2.50 (1H, d, J = 16.8 Hz), 3.18 (1H, d, J = 13.8 Hz), 3.32 (1H, d, J = 13.8 Hz), 3.66-3.71
(1H, m), 3.92-3.97 (1H, m), 4.39 (1H, d, J = 10.2 Hz), 4.6- 4.7 (1H, m), 6.98 (2H, d, J =
7.8 Hz), 7.17-7.24 (7H, m, Ar-H); 13C NMR (CDCl3, 125 MHz); δ 21.2, 23.4, 25.3, 26.4,
29.8, 42.5, 43.7, 45.7, 51.1, 55.9, 59.2, 60.0, 64.6, 127.5, 127.9, 128.5, 128.7, 129.0, 129.4,
135.1, 138.0, 166.5, 173.4, 174.2; IR (KBr) 3461, 3023, 2969, 2922, 1743, 1695, 1455,
1237, 1037, 776 cm⁻¹. HRMS calcd for C29H34N4NaO3+ : 497.2523; Found: 497.2531.

Entry 3, Table 2.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR
16.7 min (exo major), tR 20.7 min (endo major), tR 29.6 min (endo minor), tR 41.9 min (exo
minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5
mL/ min] as 98 % ee for the exo cycloadduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-
carbonyl)-3,3-dimethyl-5-(4-bromo-phenyl)-
tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50i):

Colorless solid, mp = 179-183°C, [α]D25 40.5 (c 1.0, CHCl3),
(exo/endo = 93:07); 1H NMR (CDCl3, 400 MHz); δ 0.58 (3H, s), 0.95 (3H, s), 1.15 (3H, s),
1.19 (3H, s), 2.30 (1H, d, J = 17.1 Hz), 2.44 (2H, d, J = 16.9 Hz), 2.51 (1H, d, J = 16.9
Hz), 3.30 (1H, d, J = 13.9 Hz), 3.39 (1H, d, J = 13.9 Hz), 3.60- 3.65 (1H, m), 3.87- 4.0 (1H, m), 4.35 (1H, d, J = 10.3 Hz), 4.62 (1H, dd, J = 18.4, 8.5 Hz), 7.2-7.3 (8H, m, Ar-H), 7.35 (2H, d, Ar-H); $^{13}$C NMR (CDCl$_3$, 125 MHz); δ 23.7, 25.5, 26.2, 30.0, 42.8, 43.6, 45.2, 51.2, 56.0, 59.1, 60.1, 64.5, 122.4, 127.6, 128.5, 128.8, 131.4, 131.5, 137.3, 137.7, 166.3, 174.0, 174.4; IR (KBr) 3446, 2970, 2931, 1741, 1695, 1373, 1237, 1211, 1010, 776 cm$^{-1}$.

HRMS calcd. for C$_{27}$H$_{32}$BrN$_4$O$_3^+$: 539.1652; Found: 539.1658.

**Entry 4, Table 2.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t$_R$ 6.8 min (exo minor), t$_R$ 7.7 min (endo major), t$_R$ 9.4 min (exo major), t$_R$ 14.9 min (endo minor) [Chiralpak IC (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/ min] as 98% ee for the exo cycloaduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(4-chloro-phenyl)-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50j):

Colorless solid, mp = 186-190 °C, [α]$_D^{25}$ 53.7 (c 1.0, CHCl$_3$), (exo/endo = 92:08); $^1$H NMR (CDCl$_3$, 400 MHz); δ 0.58 (3H, s), 0.95 (3H, s), 1.14 (3H, s), 1.19 (3H, s), 2.3 (1H, d, J = 17.1 Hz), 2.44 (2H, d, J = 16.9 Hz), 2.51 (1H, d, J = 16.9 Hz), 3.31 (1H, d, J = 13.7 Hz), 3.39 (1H, d, J = 13.7 Hz), 3.62 (1H, dd, J = 11.1, 8.1 Hz), 3.94 (1H, t, J = 10.9 Hz), 4.35 (1H, d, J = 10.2 Hz), 4.62 (1H, dd, J = 18.3, 8.4 Hz), 7.15-7.3 (10H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 125 MHz); δ 23.6, 25.5, 26.2, 29.9, 42.8, 43.7, 45.4, 51.3, 56.0, 59.1, 60.1, 64.3, 127.5, 128.5, 128.7, 129.0, 131.0, 134.2, 136.9, 137.8, 166.2, 173.7, 174.3; IR (KBr) 3446, 2970, 2921, 1742, 1695, 1493, 1373, 1238, 1088, 1038, 777 cm$^{-1}$. HRMS calcd. for C$_{27}$H$_{32}$ClN$_4$O$_3^+$: 495.2157; Found: 495.2155.
Entry 5, Table 2.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR 6.7 min (exo minor), tR 7.7 min (endo major), tR 9.5 (exo major), tR 14.9 min (endo minor) [Chiralpak IC (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) 50:50 Ethyl Acetate:Hexane, 1.0 mL/ min] as 98% ee for the exo cycloadduct.

$\text{(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(4-cyano-phenyl)-}$
$tetrahydropyrazolo[1,2-a]pyrazol-1(5H)$-$\text{one (2.50k):}$

Colorless solid, mp = 174-178, $[\alpha]_D^{25}$ 33.5 (c 1.0, CHCl$_3$), (exo/endo = 82:18); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 0.55 (3H, s), 0.9 (3H, s), 1.15 (3H, s), 1.2 (3H, s), 2.26 (1H, d, $J = 17.1$ Hz), 2.45-2.55 (3H, m), 3.40 (2H, s), 3.56 (1H, dd, $J = 11.3$, 7.9 Hz), 3.91-3.99 (1H, m), 4.43 (1H, d, $J = 10.3$ Hz), 4.58 (1H, app dt, $J = 8.4$, 9.7 Hz), 7.2-7.3 (6H, m, Ar-H), 7.45-7.6 (4H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 125 MHz); $\delta$ 23.8, 24.1, 25.8, 29.9, 43.2, 43.6, 45.0, 51.5, 56.2, 59.3, 60.3, 64.6, 112.1, 118.5, 127.8, 128.6, 129.0, 130.6, 132.1, 137.2, 144.0, 166.1, 174.3, 174.6; IR (KBr) 3469, 3062, 3026, 2972, 2931, 2227, 1746, 1697, 1607, 1456, 1372, 1305, 1236, 1041, 776 cm$^{-1}$. HRMS calcd. for C$_{29}$H$_{31}$N$_5$NaO$_3$ : 508.2319; Found: 508.2309.

Entry 6, Table 2.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR 13.5 min (endo major), tR 14.9 min (exo major), tR 19.9 min (endo minor), tR 35.1 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/ min] as 93% ee for the exo cycloadduct.
(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(2-chloro-phenyl)-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.501):

Colorless solid, mp = 78-82 °C, $[\alpha]_D^{25}$ 24.5 (c 1.0, CHCl$_3$), (exo/endo = 94:06); $^1$H NMR (CDCl$_3$, 400 MHz); δ 0.65 (3H, s), 0.99 (3H, s), 1.12 (3H, s), 1.16 (3H, s), 2.41-2.57 (4H, m), 3.38 (1H, d, $J$ = 13.7 Hz), 3.56 (2H, d, $J$ = 13.7 Hz), 3.95-4.10 (1H, m). 4.85-4.95 (2H, m), 7.05-7.15 (2H, m, Ar-H), 7.15- 7.3 (7H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 125 MHz); δ 22.6, 25.8, 26.2, 29.1, 43.5, 43.6, 46.3, 49.6, 56.2, 60.1, 60.4, 60.5, 127.1, 127.6, 128.5, 128.9, 129.2, 129.3, 132.4, 133.7, 135.6, 137.9, 166.6, 172.1, 173.9; IR (KBr) 3461, 2973, 2931, 1747, 1698, 1456, 1373, 1233, 1037, 771 cm$^{-1}$. HRMS calcd. for C$_{27}$H$_{33}$ClN$_4$NaO$_3$$: 517.1977; Found: 517.1990.

**Entry 8, Table 2.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t$_R$ 53.8 min (endo minor) t$_R$ 15.5 min (exo minor) t$_R$ 11.1 min (endo major) t$_R$ 17.4 min (exo major) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 98% ee for the exo cycloadduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-(2-fluoro-phenyl)-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50m):

Colorless solid, mp = 76-80 °C, $[\alpha]_D^{25}$ 31.2 (c 1.0, CHCl$_3$), (exo/endo = 79:21); $^1$H NMR (CDCl$_3$, 400 MHz); δ 0.65 (3H, s), 1.03 (3H, s), 1.14 (3H, s), 1.16 (3H, s), 2.40-2.48 (4H, m), 3.48 (1H, d, $J$ = 13.8 Hz), 3.54 (1H, d, $J$ = 13.8 Hz), 3.56-3.64 (m, 1H), 3.97 (1H, d, $J$ = 4.8 Hz), 4.62 (1H, dd, $J$ = 16.8, 8.2 Hz), 4.84 (1H, d, $J$ =
Entry 9, Table 2.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR 12.2 min (endo major), tR 14.0 min (exo major), tR 16.5 min (endo minor), tR 41.2 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 93% ee for the exo cycloadduct.

(5R,6S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-3,3-dimethyl-5-isopropyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.50n):
Viscous Liquid, [α]D 25 7.1 (c 1.0, CHCl₃), (exo/endo = 88:12); ¹H NMR (CDCl₃, 400 MHz); δ 0.84 (3H, d, J = 3.2 Hz), 0.86 (3H, d, J = 3.2 Hz) 1.08 (3H, s), 1.19 (3H, s), 1.25 (6H, s), 1.35-1.43 (1H, m), 2.09 (1H, d, J = 14.7 Hz), 2.56 (1H, d, J = 17.1 Hz), 2.63 (1H, d, J = 17.5 Hz), 2.73 (1H, d, J = 14.7 Hz), 3.50-3.65 (2H, m), 3.99-4.09 (3H, m), 7.2-7.3 (3H, m, Ar-H), 7.4 (2H, d, Ar-H); ¹³C NMR (CDCl₃, 125 MHz); δ 14.3, 17.3, 19.2, 22.9, 26.3, 26.9, 31.2, 43.8, 44.2, 48.4, 49.0, 56.8, 60.9, 61.7, 66.2, 127.8, 128.6, 129.1, 137.5, 169.4, 171.2, 174.5. IR (KBr) 2973, 1741, 1686, 1415, 1374, 1307, 1237, 1045, 1026, 756 cm⁻¹. HRMS calcd. for C₂₄H₃₄N₄NaO₃⁺: 449.2523; Found: 449.2519.
**Entry 11, Table 2.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t\textsubscript{R} 16.4 min (exo major), t\textsubscript{R} 18.3 min (endo minor), t\textsubscript{R} 21.0 min (endo major), t\textsubscript{R} 82.7 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate, 0.5 mL/min] as 78 % ee for the exo cycloadduct.

2.6.4.3. **Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imine 2.51b with Pyrazolidinone Crotonate 2.56**

To a 6-dram vial containing 4Å molecular sieves (100 mg), Cu(OTf)\textsubscript{2} (0.1 mmol), and ligand 5 (0.11 mmol) was added CH\textsubscript{2}Cl\textsubscript{2} (1 mL). The vial was stirred for 1 hour. Then pyrazolidinone crotonate 2.56 (0.1 mmol) was added and the reaction mixture was stirred for 30 minutes. A solution of azomethine imine 2.51b (0.1 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was finally added. The reaction was stirred at room temperature for 24-48 h until the dipolarophile was consumed (TLC). The reaction mixture was then filtered through a pad of celite and rinsed with CH\textsubscript{2}Cl\textsubscript{2} (2 x 10 mL). The organic layer was washed with 15% aq. NH\textsubscript{3} solution (2 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL). The organic layer was finally dried over anhydrous magnesium sulfate. Silica gel (2g) was added to the organic layer and the solvent was removed in vacuo. The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogix RS-4 columns. The cycloaddition products were isolated as an inseparable mixture of exo and endo adducts. The exo/endo ratio was determined by ¹H NMR spectroscopy prior to chromatography or by HPLC analysis.
(5R,6S,7S)-6-(1-benzyl-5,5-dimethyl-3-oxopyrazolidine-2-carbonyl)-7-methyl-5-phenyl-tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (2.57b):

Colorless oil, $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.93 (s, 3H), 1.15 (s, 3H), 1.48 (3H, d, $J = 6.5$ Hz), 2.22 (1H, d, $J = 17.2$ Hz), 2.48 (2H, d, $J = 17.2$ Hz), 2.63-2.77 (m, 2H), 2.88-2.95 (m, 1H), 3.37-3.43 (m, 1H), 3.81 (1H, d, $J = 14.1$ Hz), 3.98 (1H, d, $J = 3.6$Hz), 4.01 (s, 1H), 4.10-4.16 (m, 1H), 4.54 (1H, t, $J = 7.2$Hz), 7.22-7.27 (m, 8H), 7.32-7.34 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 20.7, 25.5, 26.5, 32.6, 43.7, 47.3, 55.1, 56.8, 60.6, 61.3, 74.4, 127.9, 128.0, 128.6, 128.8, 128.9, 129.3, 136.2, 137.1, 168.2, 171.5, 174.7. HRMS calcd. for C$_{26}$H$_{30}$N$_4$NaO$_3^+$: 469.2216; Found: 469.2227.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 12.8 min (exo major) $t_R$ 16.2 min (exo minor) [Chiralpak IA (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) 50:50 Ethyl Acetate:Hexane, 1.0 mL/min] as 67% ee (exo).

2.6.5. Determination of Relative Stereochemistry

The relative stereochemistry was established by nOe experiments (Figure 2.5). Irradiation of the proton labeled H$_a$ led to an 8.1% nOe enhancement for the proton labeled H$_c$, establishing the exo cycloadduct as the major product.
Suga and co-workers have recently described an *endo* and enantioselective 1,3-dipolar cycloaddition reaction between azomethine imines and 3-acryloyl-2-oxazolidinone catalyzed by binaphthylidimine-Ni(II) complexes.\textsuperscript{26} A reaction of 3-acryloyl-2-oxazolidinone with azomethine imine 2a gave the corresponding cycloadduct in 93% yield (\textit{endo}/\textit{exo} = 89:11 and 97% ee (\textit{endo})) (Scheme 2.15). HPLC conditions: Chirapak IA (254 nm, 35 °C) ethyl acetate, 0.5 mL/min \( t_R = 13.6 \text{ min (\textit{endo} minor)} \) \( t_R = 16.7 \text{ min (\textit{exo} minor)} \) \( t_R = 22.1 \text{ min (\textit{endo} major)} \) \( t_R = 30.9 \text{ min (\textit{exo} major)} \).

Additional evidence for \textit{exo} selectivity was provided by a Cu(OTf)\textsubscript{2}/bisoxazoline 5-catalyzed cycloaddition of azomethine imine 2a with 3-acryloyl-2-oxazolidinone.

\begin{align*}
\text{Scheme 2.15. Enantioselective Azomethine Imine Cycloaddition to Acryloyl Oxazolidinone}
\end{align*}

White foamy solid, \(^1\text{H} \text{NMR (CDCl}_3, 400 MHz) \delta 0.99 (s, 3H), 1.19 (s, 3H), 2.51 (2H, d, \( J = 2.9 \text{ Hz} \)), 3.03-3.09 (m, 1H), 3.55-3.67 (m, 2H), 3.85-3.90 (m, 1H), 3.90-4.10 (m, 3H), 4.37 (d, 1H, \( J = 9.8 \text{ Hz} \)), 4.95-5.01 (m, 1H), 7.23-7.27 (m, 3H), 7.32-7.34 (m, 2H); \( ^{13}\text{C} \text{NMR (CDCl}_3, 100 MHz) \delta 23.4, 29.7, 41.3, 42.6, 46.0, 50.1, 59.3, 62.0, 64.9, 128.2, 128.3, 128.6, 137.7, 152.9, 170.3, 172.4. \text{HRMS calcd. for C}\text{}_{19}\text{H}_{21}\text{N}_3\text{NaO}_4^+: 366.1430; \text{Found: 366.1442}\)
The enantiomeric excess was determined by HPLC analysis (Diacel Chiralpak IA, ethyl acetate, detector UV 254 nm, Flow rate = 0.5 mL/min, 25°C) $t_R = 14.5$ min (endo minor) $t_R = 18.4$ min (exo minor) $t_R = 25.6$ min (endo major) $t_R = 38.0$ min (exo major).

2.6.6. Tentative Assignment of Absolute Stereochemistry

The absolute stereochemistry has been assigned as $5R,6S$ for cycloadducts 2.50i based on single crystal analysis (Figure 2.6). Absolute stereochemistry of all other cycloadducts was tentatively assigned $5R,6S$ and $5R,6S,7S$ for cycloadduct 2.57b based on the absolute stereochemistry of cycloadduct 2.50i.

![Figure 2.6. Single Crystal Structure of Cycloadduct 2.50i](image)

2.7. References


(c) Chiral Relay Effects Influence the Facial Selectivity of N-Alkylated 5-
Phenylmorpholin-2-one Enolates. Bull, S. D.; Davies, S. G.; Fox, D. J.; Sellers, T.
for the Synthesis of Homochiral α-Amino Acids. Bull, Steven D.; Davies, Stephen

(6) (a) Conformationally Interlocked Amides: Remote Asymmetric Induction by
Mechanical Transfer of Stereochemical Information. Clayden, J.; Pink, J. H.;
in Aromatic Amides Bearing Chiral ortho Substituents: Its Origin and Application
Synthesis of Atropisomers Containing Two Non-biaryl Stereogenic Axes:
Stereochemical Relay Though Stereogenic Centres in Dihydrostilbene-2,2'-

(7) For use of the relay concept in chiral auxiliary development, see (a) Conformational
Studies of N3-Substituted [1,3,4]-Oxadiazinan-2-ones. Casper, D. M.; Blackburn,
of a Structurally Novel Class of Chiral Auxiliaries: Diastereoselective Aldol


3.1. Introduction

Chiral heterocycles are important targets for synthetic organic chemists all over the world. The significance of these heterocycles is due to the fact that they are present in many naturally occurring molecules, which are of importance in the pharmaceutical industry. Also, many of these heterocycles have nitrogen or oxygen as a key heteroatom and thus incorporation of one or more such heteroatoms in a cyclic ring is important. The heterocycles find utility as chiral ligands and auxiliaries in asymmetric transformations. 1,3-Dipolar cycloaddition is a viable route for the construction of 5-membered heterocyclic ring in a simple and an elegant fashion. The rapid development in the field of 1,3-dipolar cycloadditions has led to the discovery of several stable 1,3-dipoles, which can be synthesized and stored. Also, development in the field of catalysis has allowed the modern organic chemist to employ much milder reaction conditions for these cycloadditions. Extensive studies on the mechanistic aspects have provided a better understanding of these important reactions.

Our group has extensively investigated chiral Lewis acid catalyzed asymmetric 1,3-dipolar cycloadditions. In the past we have reported examples for the construction of chiral isoxazolines and isoxazolidines via chiral Lewis acid mediated 1,3-dipolar cycloaddition of nitrones and nitrile oxides to pyrazolidinone imide 3.1 (Scheme 3.1. eqs.1 and 2).
pyrazolidinone template has been one of the very successful templates to be developed in our laboratory.

Scheme 3.1. Examples of Enantioselective Dipolar Cycloadditions from Sibi Group
We have also investigated nitrile imine and nitrile ylide as dipoles for the construction of dihydropyrazoles. One of the dipole that we did not investigate was azomethine imine and in fact there are only a few examples on enantioselective azomethine imine cycloadditions. This lack of literature on azomethine imine prompted us to develop the first *exo* selective chiral Lewis acid catalyzed azomethine imine cycloaddition to electron deficient olefins which was discussed in the previous chapter (Scheme 3.1. eq. 3).

However, the shortcoming of this protocol with respect to the dipolarophile was that the reactions proceeded only with the parent acrylate using a catalytic amount of chiral Lewis acids. This limitation is general to all azomethine imine cycloadditions reported in the literature. The review of literature on asymmetric azomethine imine cycloaddition has been previously discussed in chapters 1 and 2. In this chapter we have attempted to solve the problem of low reactivity of β-substituted dipolarophiles towards azomethine imine cycloaddition by switching from pyrazolidinone imide to acyl imidazole as a template. We found this template to be excellent not only for Lewis acid catalyzed reactions but also for organocatalysis.

### 3.2. Search of Templates

Pyrazolidinone imide 3.1 has been an excellent template for a wide number of Lewis acid catalyzed transformations reported in our laboratory. However in terms of reactivity it is not the most reactive one. For 1,3-dipolar cycloadditions, regiochemistry and diastereoselectivity are other issues that can be addressed by template modification. The Sibi group has reported Lewis acid catalyzed nitrile oxide cycloaddition to β-substituted α,β-unsaturated imides 3.14, which leads to the formation of two regioisomeric
cycloadducts 3.6 and 3.6'. It was observed that the nature of the template played a pivotal role in the regiochemistry of cycloadducts isolated (Scheme 3.2).

Scheme 3.2. Effect of Template on Enantioselectivity and Diastereoselectivity

Cycloaddition with pyrazolidinone 3.15 gave exclusively cycloadduct 3.6 whereas cycloaddition with 3,5-dimethyl pyrazole 3.16 gave a mixture of cycloadducts 3.6 and 3.6' in a 1:5 ratio. We have also reported cycloaddition reaction of tiglate 3.17 with nitrile oxide.
This report presented the importance of rotamer control in reactions involving \( \alpha,\beta \)-unsaturated carbonyl compounds as acceptors. Substrate where \( Z=3.19 \) provided superior rotamer control which translated to high reactivity and good yield for cycloadduct 3.18. However, when \( Z=3.15 \) was used, lower yield of the desired cycloadduct was obtained which translated to poor control of rotamer geometry.

Reactions involving substrates with \( \alpha,\beta \)-unsaturated carbonyl compounds typically have a 1,3-dicarbonyl moiety and have been used for Lewis acid catalyzed reactions since they provide site for Lewis acid chelation. This motif has been extensively used for conjugate and cycloaddition reactions and represents a great majority of chiral Lewis acid mediated reactions.

As seen from Scheme 3.2, many of these make use of the imide moiety. During the course of our search for a reactive template we started investigating \( \alpha,\beta \)-unsaturated ketones as potential substrates. There are not too many reports on the utilization of ketones as chelating substrates for Lewis acid catalyzed reactions. The use of \( \alpha \)-hydroxy ketones as templates was first introduced by Masamune et al.\(^7\) and their application for Diels-Alder reaction was reported by Palomo et al. (Figure 3.1).\(^8\) Similarly, Evans et al. have recently reported the use of acyl imidazoles as templates for chiral Lewis acid catalyzed 1,4-conjugate addition reactions.\(^9\) The Sibi group has also investigated use of acyl pyridines as templates for chiral Lewis acid catalyzed radical additions. With the success of ketone-derived templates for 1,4-conjugate reactions, we decided to investigate their applicability for cycloadditions.

The use of acyl imidazoles as templates was prompted due to the fact that these templates can also be utilized as multifunctional templates. The nitrogen atom on the
Imidazole ring can serve as a donor for chelation with an appropriate Lewis acid but also possesses sufficient basicity to be protonated with a Brønsted acid. Thus acyl imidazoles can be utilized for reactions catalyzed by both Lewis and Brønsted acids which is a feature that not many templates posses.

Acyl imidazoles are also known to be latent acyl transfer reagents and can be conveniently converted to esters, amides, β-diketones, β-ketoesters and aldehydes.\(^\text{10}\) α,β-Unsaturated-2-acyl imidazoles are also more reactive as compared to α,β-unsaturated amides, imides or esters. This increase in reactivity is due to the decreased electron donation into the carbonyl group of the enone in α,β-unsaturated-2-acyl imidazoles as compared to the α,β-unsaturated amides, imides or esters.

![Imide Templates](image)

![Ketone Templates](image)

Figure 3.1. Various Important Scaffolds Employed as Templates
3.3. Chiral BINOL Derived Phosphoric Acid Catalyzed Reactions

Organocatalysis in asymmetric organic synthesis is a relatively new branch of chemistry. The development of imidazolidinone-derived catalysts by MacMillan et al. as well as the development of chiral thiourea catalyzed reactions by Jacobsen et al. marked the entry of organocatalysis as a major force in asymmetric catalysis. Relatively new to this arena are chiral BINOL derived phosphoric acids. Pioneering work from Akiyama, Terada, and Yamamoto have established these Bronsted acids as potential catalysts for many organic transformations (Figure 3.2). Compared to thiourea these form much strong hydrogen bonds with heteroatoms such as oxygen and hence can be utilized for activating less reactive substrates. Similar to Lewis acids the reactions involving chiral Bronsted acids are based on activation of the LUMO of the acceptor.

Figure 3.2. Examples of Important Organocatalysts Developed in Recent Years for Asymmetric Synthesis

Chiral Bronsted acids were initially employed for Mannich type 1,2-addition reactions to imines. This reaction utilized the acid base interaction between the imine nitrogen and the chiral Bronsted acid (Figure 3.3). The reaction proceeds via formation of a chiral counter ion or a chelated ion pair complex. Akiyama, Terada, Rueping and others
have reported several elegant chiral Brønsted acid catalyzed transformations utilizing imines as substrates.\textsuperscript{13}

Activation of carbonyl group by hydrogen bonding towards nucleophilic additions is another important application of Brønsted acids and has been typically utilized for 1,2-addition and 1,4-addition type reactions (Scheme 3.3). Examples of this type of reactions are few as compared to reactions with imines primarily due to the better recognition of the imine substrate by the Brønsted acid compared to the carbonyl ones.

![Figure 3.3. Brønsted Acid Catalyzed Transformations to Imines](image)

3.4. Results and Discussions

We intended to utilize \(\alpha,\beta\)-unsaturated acyl imidazoles as substrates for azomethine imine cycloaddition by two-separate modes of activation. The traditional Lewis acid model would utilize the bidentate nature of these \(\alpha,\beta\)-unsaturated acyl imidazoles. The activation of the \(\beta\)-carbon of the substrate of chiral Lewis acid-substrate complex would depend on the strength of the Lewis acid. This mode of activation has been thoroughly studied before.
Scheme 3.3. Activation of Enones by Brønsted Acid for Nucleophilic Addition

Due to the basicity of the nitrogen atom of the imidazole ring, an acid-base interaction with a Brønsted acid is possible which would lead to the activation of β-carbon of the substrate towards nucleophiles (Scheme 3.4). This mode of activation has not been previously reported in the literature. The formation of an ion pair complex of the Brønsted acid with the substrate via protonation of the imidazole nitrogen would be the first step of this catalytic cycle. Subsequently, reaction of this activated complex with the dipole or other reactants would lead to the formation of the desired products. Dissociation of the Brønsted acid from the product can be a result of slightly enhanced basicity of the starting materials compared to the product and also due to the increased steric bulk around the imidazole ring of the product compared to the starting material. Nevertheless, this is the most important step as it would determine catalyst turnover numbers. Finally, the Brønsted acid will re-enter the catalytic cycle and form activated substrate complex. One of the many challenges with dipolar cycloaddition arises from the Lewis basicity of the dipole. The dipole should not coordinate with the Brønsted acid since this would inhibit catalysis.
3.4.1. Continuation of Azomethine Imine Cycloaddition to Pyrazolidinone Imides

We had previously reported azomethine imine cycloaddition to acroloyl pyrazolidinone imides 3.8 (Scheme 3.1 equation 3) catalyzed by Cu(OTf)$_2$/ 3.3a. During the course of this study we wanted to expand the scope of the dipolarophile, which was limited to acrylates only. Cycloadditions of crotonoyl pyrazolidinone imide 3.41a with azomethine imine 3.42a did not proceed using 30 mol% of the same chiral Lewis acid (Table 3.1 entry 1). Even when 100 mol% of Cu(OTf)$_2$ was employed as the Lewis acid for the same reaction no product was obtained (Table 3.1 entry 2). Interestingly when the 5,5-dimethyl group on the azomethine imine was replaced with hydrogen, the same reaction with 100 mol% of Cu(OTf)$_2$ proceeded to yield cycloadduct 3.43a in modest yield (Table 3.1 entry 3).
Table 3.1. Cu(II) Catalyzed Azomethine Imine Cycloaddition to Crotonoyl Pyrazolidinone Imides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipole</th>
<th>Product</th>
<th>mol% LA</th>
<th>mol% 3.3a</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.42a</td>
<td>3.43a</td>
<td>10</td>
<td>10</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>3.42a</td>
<td>3.43a</td>
<td>100</td>
<td>-</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>3.42b</td>
<td>3.43b</td>
<td>100</td>
<td>-</td>
<td>67</td>
<td>&gt;96:4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3.42b</td>
<td>3.43b</td>
<td>100</td>
<td>100</td>
<td>77</td>
<td>&gt;96:4</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>3.42b</td>
<td>3.43b</td>
<td>30</td>
<td>30</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Isolated yield after column chromatography. NR = no reaction; ND = not determined
* Determined by $^1$H NMR.
* Determined by chiral HPLC.

Improvement in reactivity of azomethine imine 3.42b over 3.42a could be attributed to decrease of steric interaction between the chiral Lewis acid-substrate complex and the azomethine imine 3.42b. We decided to pursue reactions using azomethine imine 3.42b. The cycloadduct was formed in high diastereoselectivity (>96:04) and was determined as exo by nOe analysis. Furthermore reactions catalyzed with 100 mol% chiral Lewis acid yielded exo cycloadduct 3.43b in good yield, excellent diastereoselectivity and high enantiomeric excess (Table 3.1, entry 4). However it was very disappointing to find that reactions with 30 mol% of chiral Lewis acid did not proceed (entry 5). We tried to explore effect of other β-substituents on the reaction of azomethine imine 3.42b.

It was very discouraging to find that no matter the nature of the β-substituent on the pyrazolidinone, the cycloaddition of azomethine imine 3.42b catalyzed with 30 mol% Cu(OTf)$_2$/3.3a did not proceed (Table 3.2, entries 2, 3, 4, and 5). Similar reactions were
also performed with other Lewis acids such as Sc(OTf)₃ and yielded similar result. This failure was attributed to the low reactivity of the template and hence we decided to investigate other templates such as acyl imidazoles.

3.4.2. Azomethine Imine Cycloaddition to Acyl Imidazoles

The first successful application of acyl imidazoles in asymmetric 1,4-addition was reported by Evans. The required acyl imidazoles were synthesized convenient by 1,2-addition of lithiated 1-methyl imidazole to corresponding Weinreb amides which furnished the desired substrates in good yields. During our initial screening we found out that this template was much more reactive than pyrazolidinone imide templates as azomethine imine cycloaddition of β-substituted α,β-unsaturated carbonyl compounds proceeded much faster and yielded the cycloadducts in good yield. Thus it was decided that a systematic study of various chiral Lewis acids was to be pursued.

Table 3.2. Azomethine Imine Cycloaddition to β-Substituted Pyrazolidinone Imides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)ᵃ</th>
<th>exo/endoᵇ</th>
<th>exo ee (%)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (3.41a)</td>
<td>3.43b</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>Ph (3.41b)</td>
<td>3.43c</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>Cl (3.41c)</td>
<td>3.43d</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Et (3.41d)</td>
<td>3.43e</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>-OCOPh (3.41e)</td>
<td>3.43f</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield after column chromatography. NR = No reaction; ND = Not determined
ᵇ Determined by ¹H NMR. ᶜ Determined by chiral HPLC.
We started optimizing chiral Lewis acids for azomethine imine cycloaddition to crotonyl-1-methyl imidazole 3.40a. Initial studies were carried out using 30 mol% chiral Lewis acid at room temperature. Reaction of acyl imidazole 3.40a and azomethine imine 3.42b catalyzed with Sc(OTf)3 and 2-butyl PyBOX ligand 3.45a yielded cycloadduct 3.44a as a single diastereomer which was later confirmed by single crystal X-ray as endo in high yield (85%, Table 3.3, entry 1.) The enantiomeric excess of the cycloadduct was found to be low. Reaction catalyzed by Sc(OTf)3/3.45b whose i-Pr group provide spherical shielding environment similar to t-Bu group in 3.45a were found the ineffective in conferring enantioselectivities to the cycloadduct (Table 3.3, entry 2). Ligand 3.45c with flat Ph ring did not fare better and reaction of 3.40a with azomethine imine 3.42b catalyzed by Sc(OTf)3/3.45c yielded endo cycloadduct in modest yield and poor enantioselectivity (Table 3.3, entry 3). Azomethine imine cycloadditions catalyzed by Sc(OTf)3 and amino indanol derived ligand 3.45d followed similar trend and poor yield and enantioselectivity for the endo cycloadduct was obtained (Table 3.3, entry 4). Similar low yield and enantioselectivity for cycloadduct 3.44a was obtained when Sc(OTf)3/3.45e was employed as chiral Lewis acid (Table 3.3. entry 5). Chiral Lewis acid obtained from additional bis(oxazoline) ligand and Sc(OTf)3 were also tried in an attempt to increase enantioselectivity. PyBOX ligands 3.45f-i whose trialkyl silyl group provide shielding are interesting since the steric shielding provided by these ligands can be easily modulated by changing the silyl protecting group. Thus Sc(OTf)3 reactions catalyzed using ligand 3.45f and 3.45g gave similar yield and enantioselectivities for endo cycloadduct (compare Table 3.3, entries 6 and 7).
Table 3.3. Azomethine Imine Cycloaddition Catalyzed by Chiral Lanthanum Lewis Acids

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>LA</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>endo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)₃</td>
<td>3.45a</td>
<td>85</td>
<td>&gt;98:02</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)₃</td>
<td>3.45b</td>
<td>64</td>
<td>&gt;98:02</td>
<td>06</td>
</tr>
<tr>
<td>3</td>
<td>Sc(OTf)₃</td>
<td>3.45c</td>
<td>43</td>
<td>&gt;98:02</td>
<td>04</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)₃</td>
<td>3.45d</td>
<td>36</td>
<td>&gt;98:02</td>
<td>02</td>
</tr>
<tr>
<td>5</td>
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<td>63</td>
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<td>02</td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)₃</td>
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<td>&gt;98:02</td>
<td>02</td>
</tr>
<tr>
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<td>Sc(OTf)₃</td>
<td>3.45g</td>
<td>56</td>
<td>&gt;98:02</td>
<td>04</td>
</tr>
<tr>
<td>8</td>
<td>Sc(OTf)₃</td>
<td>3.45h</td>
<td>46</td>
<td>&gt;98:02</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>Sc(OTf)₃</td>
<td>3.45i</td>
<td>41</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
<td>10</td>
<td>Nd(OTf)₃</td>
<td>3.45a</td>
<td>90</td>
<td>&gt;98:02</td>
<td>44</td>
</tr>
<tr>
<td>11</td>
<td>Nd(OTf)₃</td>
<td>3.45a</td>
<td>NR</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>Nd(OTf)₃</td>
<td>3.45b</td>
<td>43</td>
<td>&gt;98:02</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>Nd(OTf)₃</td>
<td>3.45c</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>Nd(OTf)₃</td>
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<td>59</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
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<td>3.45e</td>
<td>90</td>
<td>&gt;98:02</td>
<td>23</td>
</tr>
<tr>
<td>16</td>
<td>Yb(OTf)₃</td>
<td>3.45a</td>
<td>65</td>
<td>&gt;98:02</td>
<td>23</td>
</tr>
<tr>
<td>17</td>
<td>Pr(OTf)₃</td>
<td>3.45a</td>
<td>85</td>
<td>&gt;98:02</td>
<td>44</td>
</tr>
<tr>
<td>18</td>
<td>Dy(OTf)₃</td>
<td>3.45a</td>
<td>79</td>
<td>&gt;98:02</td>
<td>06</td>
</tr>
<tr>
<td>19</td>
<td>Sm(OTf)₃</td>
<td>3.45a</td>
<td>84</td>
<td>&gt;98:02</td>
<td>51</td>
</tr>
<tr>
<td>20</td>
<td>Gd(OTf)₃</td>
<td>3.45a</td>
<td>98</td>
<td>&gt;98:02</td>
<td>50</td>
</tr>
</tbody>
</table>

*a* Isolated yield after column chromatography. *b* Determined by ¹H NMR. *c* Determined by chiral HPLC. *d* Reaction done at -78 °C. NR = No Reaction, ND = Not Determined
Lower yield and poor enantioselectivity were also observed when ligands 3.45h and 3.45i were employed along with Sc(OTf)₃ (Table 3.3, compare entries 8 and 9).

We decided to investigate other lanthanum Lewis acids for azomethine imine cycloaddition. Thus reaction of Nd(OTf)₃/ 3.45a gave endo cycloadduct 3.44a in 44% enantiomeric excess and excellent yield (Table 3.3, entry 10). This was the best chiral Lewis acid combination in terms of the enantioselectivity of the cycloadducts. Cooling the reaction lead to better organization of substrate-chiral Lewis acid complex and often times helps in improving enantioselectivities. However, reaction of Nd(OTf)₃/ 3.45a at -78 °C were very slow and did not give cycloadducts in appreciable yield (Table 3.3, entry 11). Azomethine imine cycloaddition catalyzed by Nd(OTf)₃ and i-Pr PyBOX ligand 3.45b gave cycloadduct 3.44a in 35% enantiomeric excess (Table 3.3, entry 12). This result may indicate that ligands which, provide spherical shielding may be better since the same reaction with Ph-PyBOX ligand 3.45c provided lower numbers for enantioselectivity compared to 3.45b (Table 3.3, compare entry 12 with 13). Reactions of Nd(OTf)₃ with other ligand combinations also did not fare well (Table 3.3, entry 14 and 15).

Since i-Bu PyBOX 3.45a gave better enantioselectivity for cycloadducts compared to other ligands screened, we decided to examine some more Lewis acids with this ligand. Reactions catalyzed with Yb(OTf)₃ and 3.45a gave cycloadduct in 44% enantiomeric excess and in good yield (Table 3.3, entry 16). Reactions catalyzed by Dy(OTf)₃/3.45a were completely non-selective (Table 3.3, entry 18). Furthermore, similar selectivity for the cycloadduct was observed when chiral Lewis acid complexes of 3.45a with Pr(OTf)₃, Sm(OTf)₃ and Gd(OTf)₃ were employed for azomethine imine cycloaddition of 3.40a with 3.42b (Table 3.3, entries 17, 19 and 20).
After a comprehensive screening of chiral lanthanoid metals for azomethine imine cycloaddition, we decided to screen chiral Lewis acid complexes of Ce(IV) as catalyst for the same reaction.

Table 3.4. Chiral Ce(IV) Mediated Azomethine Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>endo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.45a</td>
<td>90</td>
<td>&gt;98:02</td>
<td>25</td>
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<tr>
<td>2</td>
<td>3.45b</td>
<td>57</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
<td>3</td>
<td>3.45c</td>
<td>62</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
<td>4</td>
<td>3.45d</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>3.45e</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>07</td>
</tr>
</tbody>
</table>

*a* Isolated yield after column chromatography. *b* Determined by $^1$H NMR. *c* Determined by chiral HPLC.

The geometry of Ce(IV) complexes may be different than other lanthanoids which would perhaps provide shielding and hence better enantioselectivities which had evaded us in the previous screens. Thus, chiral complexes of Ce(IV) with various PyBOX ligands were prepared and tested for azomethine imine cycloaddition of 3.40a with 3.42b at room temperature. Reactions catalyzed with Ce(OTf)$_4$/ 3.45 yielded the endo cycloadduct 3.44a in good yield but with poor enantioselectivity (Table 3.4, entry 1). Similarly, other chiral
Lewis acid complexes of Ce(OTf)₄ with ligands 3.45b-e consistently gave good yield of the endo cycloadduct 3.44a, however, in all cases poor enantioselectivity for the cycloadduct was observed (Table 3.4, entries 2-5). Thus, even though we were able to obtain high yields and excellent diastereoselectivities for these cycloadducts, we were unable to attain the high levels of enantioselectivities typically desired.

All the screening till now indicated that t-Bu PyBOX ligand 3.45a consistently performed much better for all the Lewis acids than all other PyBOX ligands screened. We therefore decided to investigate the impact of temperature on the enantioselectivity of the cycloadduct. Chiral Lewis acid complexes of 3.45a with various Lewis acids were tested for their catalytic activity at 0 °C using 30 mol% catalyst loading for azomethine imine cycloaddition reaction of 3.40a with 3.42b. Typical reaction time of 2 days was required for most of these reactions. Reactions catalyzed by Nd(OTf)₃/3.45a as a chiral Lewis acid gave cycloadduct 3.44a in 75% yield and 44% enantioselectivity (Table 3.5, entry 1) which, was similar to the reaction carried out at room temperature. Similarly, Pr(OTf)₃/3.45a catalyzed reactions at 0 °C gave similar yields and enantioselectivity for the endo cycloadduct 3.44a (Table 3.5, entry 2) compared to reaction performed at room temperature. A similar trend was observed when other lanthanoid Lewis acids such as Sm(OTf)₃, Gd(OTf)₃ and Ce(OTf)₄ complexes with 3.45a were employed to catalyze cycloaddition of 3.40a with 3.42b (Table 3.5, entries 3, 4, and 5). The conclusion drawn from this set of experiments was that lower temperature slowed the reaction rates, however, no impact on enantioselectivities of the cycloadducts was observed. Having failed to achieve any improvement in enantioselectivity by varying ligand size and reaction
temperature, we decided to evaluate the impact of solvent on yield and selectivities of dipolar cycloaddition of 3.40a with azomethine imine 3.42b.

Table 3.5. Low Temperature Study for Azomethine Imine Cycloaddition Catalyzed by Lewis Acid/3.45a Complexes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>endo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nd(OTf)₃</td>
<td>75</td>
<td>&gt;98:02</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>Pr(OTf)₃</td>
<td>85</td>
<td>&gt;98:02</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>Sm(OTf)₃</td>
<td>81</td>
<td>&gt;98:02</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Ce(OTf)₄</td>
<td>80</td>
<td>&gt;98:02</td>
<td>08</td>
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<tr>
<td>5</td>
<td>Gd(OTf)₃</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>50</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography. b Determined by ¹H NMR. c Determined by chiral HPLC.

The reactions were performed at room temperature using 30 mol% Nd(OTf)₃/3.45a which was one of the better Lewis acid ligand combination in terms of enantioselectivity of the cycloadduct. Halogenated solvents such as dichloromethane was tested and performed well to yield endo cycloadduct 3.44a in high yield and moderate enantioselectivity (Table 3.6, entry 1). Non-polar aromatic solvents such as toluene performed poorly and gave cycloadduct 3.44a in low yield and enantioselectivity (Table 3.6, entry 2). A variety of polar aprotic solvents were also tested. Thus reactions carried out in ethyl acetate gave good yield for the desired endo cycloadduct in 28% enantiomeric excess (Table 3.6, entry 3). Modest to poor yields were also obtained when diethyl ether, tetrahydrofuran, and
acetonitrile were employed as solvent. The reactions performed in these three solvents were nonselective and racemic mixture of cycloadduct 3.44a was obtained (Table 3.6, entries 4, 5 and 6).

Table 3.6. Effect of Solvent on Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>endo/exo (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>endo ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>75</td>
<td>&gt;98:02</td>
<td>44</td>
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</tr>
<tr>
<td>3</td>
<td>EtOAc</td>
<td>70</td>
<td>&gt;98:02</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Et₂O</td>
<td>37</td>
<td>&gt;98:02</td>
<td>05</td>
</tr>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>CH₃CN</td>
<td>49</td>
<td>&gt;98:02</td>
<td>07</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography.  
<sup>b</sup> Determined by <sup>1</sup>H NMR.  
<sup>c</sup> Determined by chiral HPLC.

After a comprehensive and exhaustive screen of various metals in 3+ oxidation state, we decided to examine metals such as Cu, Mg, Zn, Ni and Co which exist in 2+ oxidation state. Complexes of Mg(II), Zn(II) have been known to exist in tetrahedral or octahedral coordination geometries. Also, Ni(II) and Co(II) have been proposed to exist in octahedral and higher coordination geometries where as Cu(II) from our previous experience has been proposed to exist in a distorted square planar coordination geometry. With this screen of metal complexes we would be able to investigate the impact of metal
geometries on enantioselectivity and reactivity of azomethine imine cycloaddition of acyl imidazole 3.40a with azomethine imine 3.42b. We were very excited to see that 30 mol% chiral Lewis acid complex of Mg(ClO₄)₂/3.3a not only gave the cycloadduct 3.44a in excellent diastereoselectivity but also in good enantioselectivity (67% ee, Table 3.7, entry 1). However the isolated yield of the cycloadduct was low. Azomethine imine cycloaddition catalyzed by 30 mol% of Zn(ClO₄)₂/3.3a gave cycloadduct in 43% yield and 23% enantiomeric excess (Table 3.7, entry 2). Similarly reactions catalyzed by 30 mol% of Cu(ClO₄)₂/3.3a gave poor yield and enantioselectivity for the endo adduct 3.44a. Changing the counter ion on Cu(II) from perchlorate to triflate did not have any significant impact on enantioselectivity as reactions catalyzed by Cu(OTf)₂/3.3a gave the cycloadduct in 13% enantiomeric excess.

An interesting fact to note is that the reaction did not proceed when the same chiral Lewis acid was employed for azomethine imine cycloaddition of crotonoyl pyrazolidinone imide 3.41a with 3.42b (compare Table 3.1 entry 5 and Table 3.7 entry 4). These results highlight the superior reactivity of the acyl imidazole template compared to pyrazolidinone imides. Modest yield (65%) and enantioselectivity (50%) for the cycloadducts were obtained when Ni(ClO₄)₂/3.3a was employed as the chiral Lewis acid. However, the best enantioselectivity for azomethine imine cycloaddition was obtained when Ni(ClO₄)₂/ (S,S)-DBFOX 3.45j was employed as the chiral Lewis acid (Table 3.7, entry 6). This combination of Lewis acid-ligand was previously reported by Kanemasa and Curran for various cycloaddition and conjugate addition reactions. Chiral Lewis acid complex of Co(ClO₄)₂/3.45j also catalyzed cycloaddition 3.40a with azomethine imine 3.42b at -10 °C to give endo cycloadduct 3.44a in good yield and enantioselectivity (Table 3.7, entry 7).
Table 3.7. Survey of Additional Chiral Lewis Acids for Azomethine Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>endo/exo</th>
<th>endo ee (%)</th>
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</tr>
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<td>3.3a</td>
<td>43</td>
<td>&gt;98:02</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Cu(ClO₄)₂</td>
<td>3.3a</td>
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<td>90</td>
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<td>Cu(OTf)₂</td>
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<td>&gt;98:02</td>
<td>13</td>
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<tr>
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<td>&gt;98:02</td>
<td>50</td>
</tr>
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<td>3.45j</td>
<td>80</td>
<td>&gt;98:02</td>
<td>80</td>
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<tr>
<td>7</td>
<td>Co(ClO₄)₂</td>
<td>3.45j</td>
<td>73</td>
<td>&gt;98:02</td>
<td>84</td>
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</tbody>
</table>

*a* Isolated yield after column chromatography. *b* Determined by ¹H NMR. *c* Determined by chiral HPLC. *d* Reaction done at -10 °C.

3.4.3. Catalyst Loading and Temperature Studies

After this initial chiral Lewis acid screening we concluded that Ni(ClO₄)₂/3.45j as the best Lewis acid-ligand combination for catalyzing azomethine imine cycloaddition of 3.40a with 3.42b. The next step was to optimize the catalyst loading and reaction condition for the same reaction using this chiral Lewis acid. Lowering of chiral Lewis acid loading is essential in one has to conserve the amount of ligand utilized per reaction as this ligand synthesis is fairly challenging. Also a lower catalyst loading indicated the efficiency of the catalytic cycle. The reactions catalyzed by 30 mol% Ni(ClO₄)₂/3.45j gave 80% for the endo cycloadduct 3.44a in 80% enantiomeric excess at room temperature (Table 3.8, entry...
Usage of 20 mol% of catalyst loading gave similar yield and enantioselectivity for the cycloadduct (Table 3.8, entry 2). Further lowering of the catalyst loading was not pursued at this temperature and we set our goals towards examining catalyst loading at -10 °C. Low temperature assists in improving enantioselectivities by a two fold action: first, at lower temperature the rate of uncatalyzed background reaction would be much lower than the rate of catalyzed reaction which means that more of the enantioenriched product is generated compared to the racemic one, and second, lower temperature helps in better organization of the chiral Lewis acid substrate complex which would lead to better shielding and hence enhanced enantioselectivities for the products. Reactions catalyzed by 30 mol% Ni(ClO₄)₂/3.45j at -10 °C gave superior enantioselectivity for the cycloadduct 3.44a as compared to the same at room temperature (Table 3.8, compare entry 1 with entry 3).

Higher yields were attributed to the fact that these reactions would require more time than those at room temperature. We then lowered the catalyst loading to 20 mol% and did not find any change in enantioselectivity and isolated yield of the cycloadduct. At 15 mol% catalyst loading, both the enantioselectivity and the yield of the cycloadduct dropped compared to those at 20 and 30 mol% (Table 3.8, entry 4). Finally at 10 mol% catalyst loading, substantial lowering of yield and enantioselectivity for the cycloadduct was observed (Table 3.8, entry 5). This was the lowest limit for catalyst loading that we studied and no further studies towards lowering catalyst loading were pursued. We thus concluded that the optimal catalyst loading of 20 mol% would be required for reaction carried out at -10 °C. For reactions with challenging substrates however the same reaction needed to be carried out at room temperature using similar chiral Lewis acid loading.
Table 3.8. Effect of Catalyst Loading and Temperature on Chiral Lewis Acid Catalyzed Azomethine Imine Cycloaddition

![Chemical structure image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol % CLA</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>endo ee (%)</th>
</tr>
</thead>
<tbody>
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<tr>
<td>6</td>
<td>10</td>
<td>-10</td>
<td>69</td>
<td>73</td>
</tr>
</tbody>
</table>

*a* Isolated yield after column chromatography. *b* Determined by $^1$H NMR. *c* Determined by chiral HPLC.

3.4.4. Scope of β-Substituent on α,β-Unsaturated-2-acyl-1-methyl Imidazole

The scope of the β-substituent on the dipolarophile was investigated using 20 mol% Ni(ClO$_4$)$_2$/3.45j as the Lewis acid at room temperature. The significance of this study is because all previous reports on azomethine imine cycloaddition to α,β-unsaturated dipolarophiles suffered from a poor scope of the β-substituent on the dipolarophile. Reactions of these substrates are also attractive since it would lead to the construction of three contiguous stereocenters. Azomethine imine cycloaddition of 3.40a to 3.42b catalyzed by Ni(ClO$_4$)$_2$/3.45j yielded exclusively the endo cycloadduct 3.44a in good yield and excellent enantioselectivity (Table 3.9, entry 1). Similarly, reaction of acyl imidazole 3.40b where R = Et with azomethine imine 2.42b gave 90% yield for the endo cycloadduct 3.44b in 81% enantiomeric excess (Table 3.9, entry 2). Increasing the steric bulk at the β-substituent of the dipolarophile led to decrease in enantioselectivity and also reduced the
substrate reactivity. Thus, reaction of acyl imidazole 2.40c where R = i-Pr with azomethine imine 2.42b required 3 days of reaction time to yield the endo cycloadduct 3.44c in 67% yield and modest enantiomeric excess (Table 3.9, entry 3). Similarly, when sterically encumbered β-substituent such as dihydrocinnamyl was present on the dipolarophile, the reaction with azomethine imine 3.42b was slow and gave cycloadduct 3.44d in 58% yield. The enantioselectivity for this cycloadduct was found to be 81% (Table 3.9, entry 4). Cycloadditions with β-alkoxy substituent (R = -CH₂OBn) proceeded relatively smoothly and gave much higher yield and enantioselectivity for the desired cycloadduct (Table 3.9, entry 5). Dipolarophiles containing aromatic or heteroaromatic β-substituents were the least reactive of all the β-substituent examined for this study. Thus reaction of 3.40f where R = 2-furanyl with azomethine imine 3.42b unexpectedly gave the exo cycloadduct 3.44'f in 21% yield and 30% enantiomeric excess (Table 3.9, entry 6). Substrates with β-Ph substituent 3.40g which is electronically and sterically challenging for azomethine imine cycloaddition did not react at all and no significant generation of cycloadduct was observed even after one week of stirring with the chiral Lewis acid.

In spite of this limitation the general scope of the β-substituent on the dipolarophile was satisfactory and in general good yields and excellent enantioselectivities were obtained for most of the cycloadducts. The salient feature of this study is not only the ability to obtain high enantiomeric excess for the cycloadducts but also the cycloadducts were obtained as a single endo diastereomer. This methodology remains to date the first endo and enantioselective azomethine imine cycloaddition to β-substituted α,β-unsaturated dipolarophiles.
Table 3.9. Evaluation of Substrate Scope for Azomethine Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (d)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>endo ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (3.40a)</td>
<td>3.44a</td>
<td>1</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Et (3.40b)</td>
<td>3.44b</td>
<td>1</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr (3.40c)</td>
<td>3.44c</td>
<td>3</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>-CH₂CH₂PH (3.40d)</td>
<td>3.44d</td>
<td>3</td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>-CH₂OBn (3.40e)</td>
<td>3.44e</td>
<td>2</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2-Furanyl (3.40f)</td>
<td>3.44f</td>
<td>4</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Ph (3.40g)</td>
<td>3.44g</td>
<td>7</td>
<td>NR</td>
<td>ND</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography. NR = No reaction; ND = Not determined.
<sup>b</sup> Determined by chiral HPLC. <sup>c</sup> Exo isomer was formed than the expected endo

3.4.5. Study of Scope of Azomethine Imines

After studying the scope of β-substituent on the dipolarophile we wanted to extend the scope of this reaction with respective to the dipolarophiles. For this study various azomethine imine were prepared by condensation of aromatic aldehydes with pyrazolidin-3-one. Dipolar cycloaddition of azomethine imines with acyl imidazole 3.40a were reactive enough that they can be studied at -10 °C. Dipolar cycloaddition of azomethine imine 3.42c prepared from p-halogenated benzaldehyde catalyzed by 20 mol% Ni(ClO₄)₂/3.45j gave the endo cycloadduct 3.44i in 82% yield and excellent enantioselectivity (96% ee, Table 3.10, entry 2). Similarly electron rich azomethine imines prepared from p-methoxy benzaldehyde also reacted equally well and gave cycloadduct 3.44j in 78% yield and 94% enantiomeric excess (Table 3.10, entry 3). Electron deficient azomethine imine prepared from p-cyano benzaldehyde were relatively slow to react but still yielded the cycloadduct
3.44k in good yield with 86% enantiomeric excess (Table 3.10, entry 4). Azomethine imines prepared from o-halogenated benzaldehydes were also tried as dipoles. Thus, reaction of acyl imidazole 2.40a with 3.42f catalyzed by 20 mol% of Ni(ClO₄)₂/ 3.45j gave the endo cycloadduct 3.44h in modest yield (50%) and poor enantioselectivity (Table 3.10, entry 5). The reason for this loss of reactivity and selectivity may be attributed to the steric hindrance of the o-substituent on the phenyl ring of the azomethine imine. The same reaction when performed in the absence of molecular sieves gave similar yield for the endo cycloadduct.

Table 3.10. Evaluation of Scope of Azomethine Imine

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (d)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>endo ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>Ph (3.42b)</td>
<td>3.44a</td>
<td>1</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>p-BrC₆H₄ (3.42c)</td>
<td>3.44i</td>
<td>3</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOC₆H₄ (3.42d)</td>
<td>3.44j</td>
<td>3</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>p-CNC₆H₄ (3.42e)</td>
<td>3.44k</td>
<td>7</td>
<td>81</td>
<td>86</td>
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<tr>
<td>5</td>
<td>o-FC₆H₄ (3.42f)</td>
<td>3.44h</td>
<td>4</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>o-FC₆H₄ (3.42f)</td>
<td>3.44h</td>
<td>4</td>
<td>49</td>
<td>66</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography  <sup>b</sup> Determined by chiral HPLC  
<sup>d</sup> Reactions done in the absence of MS 4Å

However, the enantioselectivity of the cycloadduct was much improved as compared to the reaction in the presence molecular sieves (compare entry 5 and entry 6). Kanemasa et al. have already studied the effect of moisture on geometry of Ni(ClO₄)₂/
It was observed that the Ni(II)-DBFOX complex adopts a square bipyramidal arrangement in the presence of molecular sieves where as the same complex adopts an octahedral arrangement in the absence of molecular sieves. Different selectivity were observed for reactions carried with or without molecular sieves which may be due to the different metal geometry operating in these two cases. At this point of time we are not sure that a similar argument can be applied to our study.

3.4.6. Chiral Brønsted Acid Catalyzed Azomethine Imine Cycloadditions

After successful completion of chiral Lewis acid catalyzed endo and enantioselective azomethine imine cycloaddition we turned our attention towards Brønsted acid mediated variant of the same reaction. As we had proposed earlier, the Brønsted acid could serve to catalyze reactions of β-substituted α,β-unsaturated acyl imidazole by protonation of the imidazole ring and thus activate the β-carbon of the substrate towards cycloaddition. Two factors are essential for the successful execution of this reaction; first the Brønsted acid should be sufficiently acidic so as to protonate the imidazole nitrogen and second a tight ion-pair formation of the Brønsted acid with the substrate would be essential for achieving high levels of enantioselectivity. Both these factors if they work in concert should theoretically provide high enantioselectivity for the product.

We started optimizing reaction conditions for Brønsted acid catalyzed azomethine imine reactions by using acyl imidazole 3.40a as the dipolarophile and 3.42b as azomethine imine as the combination of these two would constitute the least challenging donor-acceptor combination. All reactions were performed at room temperature in dichloromethane as the solvent. Reactions in the absence of any catalyst failed to provide any product (Table 3.11, entry 1), which was encouraging, as any uncatalyzed reaction
would reduce the efficiency of the chiral activator. In the presence of acetic acid as an
activator, a small amount of product was obtained (Table 3.11, entry 2). This result
indicated that there was certain interaction between the Brønsted acid and the substrate.
When the same reaction was carried out in the presence of 30 mol% of trifluoroacetic acid,
the cycloadduct was obtained in 83% yield (Table 3.11, entry 3). This result was of very
much significance due to several reasons. This result supports our hypothesis of Brønsted
acid activation of the dipolarophile.

Since the product was isolated in such high yield with 30 mol% of the activator, a
catalytic cycle must be in progress which, also indicated that the basicity of the product
was slightly lower than that of the starting material 3.40a. It also emphasizes the
importance of the strength of the Brønsted acid, reactions with a weak acid such as acetic
acid were much slower than the same reaction with trifluoroacetic acid which is several
orders of magnitude stronger than acetic acid. One of the most unique aspects of this
reaction is in the stereochemistry of the cycloadducts. The cycloadduct formed in this
reaction was deemed exo by single crystal X-ray studies which is exactly opposite to what
we obtained for the same reaction catalyzed by Ni(ClO₄)₂/ DBFOX 3.45j. This type of
complementary process has been very rarely seen before. Achiral phosphoric acids such as
diphenyl phosphate can also catalyze the above transformation giving selectively the exo
cycloadduct in good yield (Table 3.11, entry 4). After a brief but satisfactory screening of
achiral Brønsted acids, we decided to investigate different chiral BINOL derived
phosphoric acids for the same reactions. These chiral Brønsted acids were synthesized in
our laboratory and a detailed description of their preparation is provided in the
experimental section. Cycloaddition of azomethine imine 3.42b with acyl imidazole 3.40a
when catalyzed by 30 mol% of chiral BINOL phosphoric acid \textbf{3.46a} containing 9-
anthracene as the substituent at the 3,3’-positions of BINOL, gave exclusively the \textit{exo}
cycloadduct \textbf{3.44’a} in 50% yield and -23% enantiomeric excess (Table 3.11, entry 5). The
sign indicates formation of the enantiomeric product than from the other Brønsted acids
tested. Similarly, reactions catalyzed by phosphoric acid \textbf{3.46b} gave the racemic
cycloadduct \textbf{3.44’a} in 36% yield (Table 3.11, entry 6). We were surprised that the reactions
of these two phosphoric acid were much slower than that catalyzed by same amount of
trifluoroacetic acid or diphenyl phosphate. One possible explanation for this low reactivity
is the increase in steric bulk around the protonated substrate, which hinders the approach of
the dipole. This may be especially true for Brønsted acid \textbf{3.46b} whose triisopropyl groups
would fan out like a tree branch and can potentially hinder the approach of both the
substrate as well as the dipole. Thus reactions with \textbf{3.46b} (R= 2,4,6-(iPr)\textsubscript{3}-C\textsubscript{6}H\textsubscript{2}) were
much slower than that with \textbf{3.46a} (R= 9-anthracenyl). BINOL derived phosphoramides
developed by Yamamoto\textsuperscript{17} are much more acidic than the corresponding phosphoric acid
and hence can be employed for activation of challenging substrates. We decided to
investigate application of these phosphoramides towards catalyzing reaction of acyl
imidazole \textbf{3.40a} with azomethine imine \textbf{3.42b}.

Thus reactions catalyzed by chiral Brønsted acid \textbf{3.46c} furnished the cycloadduct
\textbf{3.44’a} in 31% yield and 14% enantiomeric excess. Low yield can again be attributed to the
steric hindrance of the 2,4,6-triisopropyl phenyl substituent at the 3,3’-position of the
BINOL ring. Best enantioselectivity and yield was obtained when catalyst \textbf{3.46d} with
anthracene groups as the substituent on the catalyst. Thus reactions catalyzed by 30 mol%
of $3.46d$ gave cycloadduct $3.44'a$ in 93% yield and 93% enantiomeric excess (Table 3.11, entry 8).

Table 3.11. Optimization of Reaction Conditions for Chiral Brønsted Acid Mediated Azomethine Imine Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Brønsted Acid</th>
<th>mol (%)</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>$exo/endo$</th>
<th>$exo$ ee (%)</th>
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<td>none</td>
<td>-</td>
<td>1</td>
<td>Trace</td>
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</tr>
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<td>83</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
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<td>(PhO)$_2$POOH</td>
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<td>1</td>
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<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
<td>5</td>
<td>$3.46a$</td>
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<td>1</td>
<td>50</td>
<td>&gt;98:02</td>
<td>-23</td>
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<td>&gt;98:02</td>
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<td>93</td>
</tr>
<tr>
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<td>2</td>
<td>90</td>
<td>&gt;98:02</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>$3.46c$</td>
<td>10</td>
<td>2</td>
<td>93</td>
<td>&gt;98:02</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after column chromatography $^b$ Determined by $^1$H NMR of crude reaction mixture $^c$ Determined by chiral HPLC analysis

We believe that this is the best chiral Brønsted acid and further variations of R groups on the Brønsted acid were not pursued. With this optimal catalyst we proceeded to study the effect of catalyst loading on enantioselectivity of the cycloadduct $3.44'a$. Reactions of acyl imidazole $3.40a$ with azomethine imine $3.42b$ with 20 mol% $3.46d$ gave good yield of the cycloadduct $3.44'a$ in 90% enantiomeric excess (Table 3.11, entry 9).
With 10 mol% of 3.46d, the cycloadduct 3.44'a was obtained in 92% yield and 93% enantiomeric excess (Table 3.11, entry 10). Catalyst loading could be further reduced but was not pursued. Also we did not pursue lowering reaction temperature, as it is convenient to perform reactions at room temperature. Thus a catalyst loading of 10 mol% was determined to be optimal for this reaction and further reactions were performed at this catalyst loading.

3.4.7. Scope of β-Substituent on Acyl Imidazole

After optimizing the reaction condition for catalyst and catalyst loading we decided to explore the scope of the β-substituent on the dipolarophile. These reactions were performed at room temperature using 10 mol% of 2.46d in dichloromethane as solvent. Azomethine imine cycloaddition to acyl imidazole 2.40b where R = Et gave exclusively the exo cycloadduct in 92% yield and 96% enantiomeric excess (Table 3.12, entry 2). Similarly, when bulky isopropyl group was present at the β-substituent of the dipolarophile the exo cycloadduct 3.44'c was generated in 92% yield and nearly perfect enantioselectivity (Table 3.12, entry 3). Reaction with a β-dihydrocinnamoyl substituent gave the exo cycloadduct 3.44'd in 89% yield and 93% enantiomeric excess (Table 3.12, entry 4).

The reaction also proceeded smoothly when a β-alkoxymethyl substituent was present at the β-position of the dipolarophile. Thus cycloadduct 3.44'e was formed in 88% enantiomeric excess and in good yield where R = -CH2OBn (Table 3.12, entry 5). The superior activity of these chiral Brønsted acids over Lewis acids was highlighted in reactions with β aromatic or heteroaromatic substituents were employed as dipolarophiles.
Thus reaction with acyl imidazole 3.40f where R = 2-furanyl gave 63% yield for cycloadduct 3.44'f. The enantioselectivity for this reaction was 86%. It should be recalled that the same reaction with Ni(ClO₄)₂/3.45j gave the endo cycloadduct in poor yield and enantioselectivity.

Table 3.12. Evaluation of Different β-Substituents on the Dipolarophile

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (3.40a)</td>
<td>3.44'a</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Et (3.40b)</td>
<td>3.44'b</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr (3.40c)</td>
<td>3.44'c</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>-CH₂CH₂Ph</td>
<td>3.44'd</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>-CH₂OBn</td>
<td>3.44'e</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>2-Furanyl</td>
<td>3.44'f</td>
<td>63</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>Ph (3.40g)</td>
<td>3.44'g</td>
<td>93</td>
<td>97</td>
</tr>
</tbody>
</table>

* Isolated yield after column chromatography  † Determined by chiral HPLC analysis

Similarly, when acyl imidazole where R = Ph was employed, cycloadduct 3.44'g was obtained in 93% yield and 97% enantiomeric excess (Table 3.12, entry 7). This is a significant improvement in terms of azomethine imine cycloaddition reactions as no previous report has described cycloaddition to this sterically and electronically challenging substrate. This entry also highlights the considerable superiority of Bronsted acid over traditional Lewis acids as catalysts. The same reaction with optimized Lewis acid did not
proceed at all (see Table 3.9, entry 7). We are very confident that any other substituted phenyl group as β-substituent on acyl imidazole would work equally well.

3.4.8. Scope of Azomethine Imine

After exploring the scope of the β-substituent on the dipolarophile, we wanted to explore the scope of azomethine imine for 3.46d catalyzed cycloaddition to 3.40a. For this study various azomethine imines were prepared by condensation of substituted benzaldehydes with pyrazolidin-3-one. We have already discussed that cycloaddition of azomethine imine 3.42b catalyzed by 10 mol% 3.46d gave cycloadduct 3.44’a as a single exo diastereomer in 93% yield and 92% enantioselectivity (Table 3.13, entry 1). Azomethine imines prepared from p-halogenated benzaldehydes were also tried as dipoles.

Table 3.13. Evaluation of the Scope of Azomethine Imine for Brönsted Acid Catalyzed Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (3.42b)</td>
<td>3.44’a</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>p-BrC₆H₄ (3.42c)</td>
<td>3.44’i</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>p-MeOC₆H₄ (3.42d)</td>
<td>3.44’j</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>o-FC₆H₄ (3.42f)</td>
<td>3.44’h</td>
<td>85</td>
<td>80</td>
</tr>
</tbody>
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<table>
<thead>
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<th>Note</th>
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<tbody>
<tr>
<td>a Isolated yield after column chromatography</td>
</tr>
<tr>
<td>b Determined by chiral HPLC</td>
</tr>
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</table>

Thus cycloaddition of azomethine imine 3.42c with 3.40a catalyzed by 10 mol% chiral Brönsted acid 3.46d gave cycloadduct 3.44’i in 84% enantiomeric excess and 92%
yield (Table 3.13, entry 2). Electron rich azomethine imine 3.42d prepared from p-anisaldehyde also performed admirably well and furnished cycloadduct 3.44j in near quantitative yields and 93% enantiomeric excess (Table 3.13, entry 3). Azomethine imine 3.42f prepared from o-fluorobenzaldehyde which failed to provide good enantioselectivity for Lewis acid catalyzed reactions performed very well in the presence of chiral Brønsted acid and gave the cycloadduct 3.44h in good yield and enantioselectivity (Table 3.13, entry 4).

3.4.9. Origin of Diastereoselectivity in Chiral Lewis Acid and Chiral Brønsted Acid Catalyzed Azomethine Imine Cycloaddition

To understand the origin of diastereoselectivity in Lewis and Brønsted acid catalyzed 1,3-dipolar cycloaddition of azomethine imines to α,β-unsaturated-2-acyl imidazole we must look at the various rotamers of the dipolarophile that exist in the reaction medium. There are four rotamers possible and two of these arise due to single bond rotation between the carbonyl carbon and the imidazole ring of the substrate and the other two are due to single bond rotation between the carbonyl carbon and olefin. Rotamer 3.50 and 3.52 could be ruled out as less possible due to the steric interaction between β-H atom of the olefin and methyl group at N-1 position on the imidazole ring in case of 3.50. Similarly, in case of rotamer 3.52, steric repulsion between β-H atom of the olefin and lone pair on N-3 position of the imidazole ring would be severe. Hence the two most probable rotamers in solution would be 3.49 and 3.51 and are the most stable amongst the four drawn in Figure 3.4.
Chelation of Lewis acid with the nitrogen atom of the imidazole ring and carbonyl carbon of the enone would force the equilibrium towards 3.49 which, would be the preferred geometry of the dipolarophile in case of Lewis acid mediated reactions. However, in case of Brønsted acid catalyzed reaction the exact rotamer geometry could be either 3.49 or 3.51.

A crystal structure of chiral Brønsted acid coordinated with substrate provided evidence to understand the rotamer geometry in case of Brønsted acid catalyzed reactions with azomethine imine. As seen from the crystal structure the protonated imidazole is hydrogen bonded with the phosphorus bound oxygen atom of the chiral Brønsted acid 3.49d (Figure 3.5). The substrate is seen to adopt an s-cis (anti) geometry as depicted in 3.51. There is a possibility of π-stacking interaction between the imidazole ring and the 9-anthracenyl group of the BINOL which could potentially provide additional stabilization to the substrate-catalyst complex.

Kanemasa et al. had previously proposed the formation of an octahedral complex of Ni(ClO₄)₂/DBFOX with oxazolidinone crotonates. Based on this data and the data obtained from the crystal structure of the Brønsted acid with substrate we can construct models to explain the approach of the dipole to the substrate complex giving rise to exo or endo cycloadducts.
In the case of Lewis acid catalyzed reactions two transition state models (3.53 and 3.57) can be constructed to explain the formation of exo and endo diastereomers (Figure 3.6). In these models, the substrate is chelated to the chiral Lewis acid and adopts an s-cis (syn) conformation. During the formation of the exo diastereomer there exists severe steric interaction between the group R on the dipole and the N-methyl group on the imidazole ring of the substrate 3.57. We believe that this interaction would be general for all azomethine imine cycloadditions to α,β-unsaturated-2-acyl imidazole catalyzed by Lewis acids. Our results from the Lewis acid screen supports this theory since we have isolated exclusively the endo diastereomer in all the reactions. The steric repulsion to the incoming dipole is minimum when the dipole approaches the substrate-chiral Lewis acid complex in an endo fashion 3.53. Our results from the Lewis acid catalyzed reactions further reinforce this assumption. The enantioselectivity of the endo cycloadduct is dependant on the ability of the chiral ligand to shield one face of the acceptor over the other.
In the case of Brønsted acid catalyzed reactions, data from crystal structure of the chiral Brønsted acid 3.49d with acyl imidazole 3.40g suggests that the rotamer geometry of the substrate is s-cis (anti) 3.51. In this arrangement the incoming dipole experiences unfavorable steric interaction of the R group on the dipole with the N-methyl group on the imidazole nitrogen, which potentially retards the endo approach to the dipolarophile. Additional steric interaction may also exist between the trifluoromethyl sulfonyle group of the Brønsted acid and the group R of the dipole. The exo approach (3.59) of the dipole to the dipolarophile does not encounter the same steric interaction as the endo approach due to the relatively smaller hydrogen of the dipole being pointed towards the catalyst-substrate complex. Hence the endo transition state would be higher in energy than the exo transition state. For this reason the exo diastereomer would be formed preferentially over the endo.

The results obtained from Brønsted acid catalyzed reactions agree with this analysis and all the Brønsted acid catalyzed azomethine imine cycloadditions yield exclusively the exo cycloadduct. The Brønsted acid creates a well-defined chiral pocket and the 9-anthracenyl group on the BINOL provides efficient face shielding to provide high levels of enantioselectivity. Additional π-stacking interactions between the imidazole ring and the 9-anthracenyl group on the BINOL may help stabilize the exo transition state. These interactions may also be responsible for the increased reactivity of the β-aromatic substituted dipolarophiles towards the incoming dipole.
3.5. Conclusions

In conclusion, we have developed a novel method for the synthesis of both *endo* and *exo* azomethine imine cycloadducts utilizing acyl imidazoles as templates. The key feature of this transformation is the wide variation of β-substitutents that can be accommodated on the dipolarophile. As mentioned in the discussion in the previous chapter, azomethine imine cycloaddition to electron deficient olefins were limited with respect to the β-substituent on the dipolarophile due to the low reactivity of the azomethine imines. We have demonstrated that chiral Ni(ClO₄)₂ catalyzed azomethine imine cycloaddition to acyl imidazoles yield exclusively the *endo* diastereomer in high yield and excellent enantioselectivity. The substrate scope of this reaction is fairly broad. During the course of this investigation we had also proposed a novel Brønsted acid
catalyzed activation of the dipolarophile by the formation of a chiral counter ion with the acyl imidazole. This activation is remarkably efficient for β-aromatic substituents on the dipolarophile, which have been known to be non-reactive by any other modes of activation. It is notable that these less reactive substrates undergo cycloadditions with azomethine imines using catalytic amounts of Brønsted acids. The catalytic cycles for this Brønsted acid mediated reaction surpasses that for the corresponding Lewis acid mediated reactions. We are currently exploring other reactions that can be catalyzed both by Lewis and Brønsted acids using acyl imidazoles as substrates.

3.6. Experimental

Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Metal salts used as Lewis acids were purchased from Aldrich. Pyridine bis(oxazoline) ligands 3.45a-e, amino indanol derived bis(oxazoline) ligand 3.3a and DBFOX ligand 3.45j were synthesized by known methods.20 Azomethine imine 3.42a-e have been prepared by known procedures. Acyl imidazoles 3.40a-g have been synthesized by known literature procedures. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO™ CombiFlash Companion with AnaLogix™ RS-4 columns. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected.1H-NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz). Chemical shifts are
reported in parts per million (ppm) downfield from TMS, using residual CDCl₃ (7.26 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ¹³C-NMR was recorded on Varian Unity/Inova-500 NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300 (75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl₃ (77.0) as an internal standard. ¹⁹F-NMR was recorded on Varian Mercury-300 (282 MHz) spectrometers with trifluorotoluene (-64 ppm) CDCl₃ as an external standard. ³¹P-NMR was recorded on Varian Mercury-300 (121 MHz) spectrometers with H₃PO₄ (0 ppm) in CDCl₃ as an external standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower workstation. Rotations were recorded on a JASCO-DIP-370 instrument. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High Resolution Mass Spectra (HRMS) (ESI) were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

3.6.1. Synthesis and Characterization of Chiral Brønsted Acid

3.6.1.1. General Procedure for the Synthesis of Chiral Brønsted Acid 3.46d

POCl₃ (2 mmol) was added dropwise at room temperature to a stirred solution of BINOL derivative (3.47, 1 mmol) in pyridine (3 mL) (Scheme 3.5). The reaction mixture was then heated to 95 °C for 4 hours and monitored by thin layer chromatography (TLC) (20% EtOAC in Hexane). After the starting material was completely consumed the reaction mixture was cooled to room temperature and quenched with 6N HCl (pH=2-3). After
extraction with DCM (100 mL), the combined organics were dried over Na₂SO₄ and the solvent removed. After a short column chromatography (silica gel, using DCM as an eluant), the corresponding chlorophosphate 3.48 can be obtained as a yellow solid.

3.48: [α]D²⁵ 30.0 (c 0.5, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.25-7.29 (m, 1H), 7.32-7.46 (m, 7H), 7.55-7.59 (m, 2H), 7.62-7.76 (m, 6H), 7.82-7.87 (m, 2H), 8.01-8.08 (m, 6H), 8.14 (s, 1H), 8.21 (s, 1H), 8.55 (2, H); ¹³C NMR (125 MHz, CDCl₃) δ 122.6, 122.62, 124.8, 124.9, 125.3, 125.36, 125.4, 125.5, 125.7, 125.9, 126.0, 126.5, 126.77, 126.8, 126.9, 127.3, 127.5, 127.53, 128.0, 128.1, 128.2, 128.6, 128.66, 128.7, 129.9, 129.92, 130.0, 130.1, 130.2, 130.5, 130.7, 130.9, 131.1, 131.2, 131.5, 131.6, 131.7, 132.0, 132.6, 134.9, 135.0, 145.7, 145.8, 146.0, 146.1; ³¹P NMR (121 MHz, CDCl₃) δ 8.09; IR (KBr) 1101, 1206, 1225, 1316, 1403, 1446 cm⁻¹; HRMS calcd. for C₄₈H₂₉ClNaO₃P⁺: 741.1357; found: 741.1391.

To the suspension of chlorophosphate 3.48 in 25 mL DCM/EtCN (1/5), TfNH₂ (2 mmol) and DMAP (6 mmol) were sequentially added. The reaction mixture was refluxed at 100 °C under argon for 15 hours. The reaction was monitored by TLC and was judged complete when all the chlorophosphate 3.48 was consumed. The reaction mixture was then cooled to room temperature and quenched with H₂O (50 mL), extracted with DCM (100 mL x 2). After column chromatography (silica gel, ether/DCM= 20-50%), the DMAP salt of 3 can be obtained as a white solid. The salt was then suspended in THF (40 mL) and hydrolyzed by refluxing with 4N HCl (40 mL) for 10 hours. The reaction mixture was then concentrated under reduced pressure and cooled to 0 °C to obtain an off-white solid which was filtered and washed with water. The solids were redissolved in DCM (50 mL) and dried with Na₂SO₄. One more column chromatography (silica gel, ether/DCM= 50%)
yielded a yellow solid. These solids were then dissolved in excess amount of ether and washed with 4N HCl to yield the product 3.46d as a light yellow solid in 90% yield.

3.46d: Yellow solid, 250 °C decompose; [α]D 41.4 (c 1.0, CH2Cl2). 1H NMR (CDCl3, 500 MHz) δ 5.52 (bro, 1H), 7.15 (bro, 2H), 7.32-7.49 (m, 6H), 7.55-7.59 (m, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.64-7.75 (m, 7H), 7.85 (s, 1H), 8.01-8.09 (m, 5 H), 8.19 (s, 2H), 8.47 (s, 1H), 8.57 (s, 1H); 13C NMR (125 MHz, CDCl3) δ 118.0 (q, J_C,F = 320.6 Hz, 1C), 121.9, 122.2, 124.3, 124.8, 125.1, 125.3, 125.35, 125.4, 125.6, 125.9, 125.95, 126.6, 126.8, 126.82, 127.0, 127.3, 127.4, 127.5, 127.6, 127.8, 128.0, 128.4, 128.5, 128.6, 128.7, 129.4, 129.5, 129.6, 130.2, 130.3, 130.7, 130.8, 131.2, 131.4, 131.7, 132.0, 132.5, 132.7, 134.4, 134.7, 144.9, 145.0, 145.9, 146.0; 31P NMR (121 MHz, CDCl3) δ -5.69; 19F NMR (282 MHz, CDCl3) δ -79.09; IR (KBr) 957, 1101, 1199, 3438 cm⁻¹; HRMS calcd. for C49H28F3NO5PS⁻: 830.1378; found: 830.1338.

![Scheme 3.5. Synthesis of Chiral Brønsted Acid 3.46d](image)

3.46a: This is a known compound; [α]D 60.7 (c 1.0, EtOH). 1H NMR (CDCl3, 500 MHz) δ 6.88 (bro, 1H), 7.02-7.08 (m, 4H), 7.26-7.29 (m, 2H), 7.42-7.45 (m, 2H), 7.51-7.55 (m, 8H), 7.61-7.64 (m, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 7.97 (s, 2H),
7.99 (d, J = 9.0 Hz, 2H), 8.11 (s, 2H); \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) 0.59. HRMS calcd. for C\(_{48}\)H\(_{28}\)O\(_4\)P-H\(^-\): 699.1725; found: 699.1749.

**3.46b:** This is a known compound;\(^{22}\) \([\alpha]\)\(_D\)\(^{25}\) = 22.0 (c 1.0, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.70 (d, J = 6.6 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H), 0.96 (d, J = 6.6 Hz, 6H), 1.02 (d, J = 6.6 Hz, 6H), 1.20 (d, J = 6.6 Hz, 6H), 1.22 (d, J = 6.6 Hz, 6H), 2.45-2.61 (m, 4H), 2.78-2.87 (m, 2H), 5.87 (bro, IH), 6.92 (dd, J = 1.2 Hz, J = 6.6 Hz, 4H), 7.26-7.35 (m, 4H), 7.47-7.53 (m, 2H), 7.80 (s, 2H), 7.88 (d, J = 8.1 Hz, 2H); \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) 2.83. HRMS calcd. for C\(_{50}\)H\(_{56}\)O\(_4\)P\(^-\): 751.3916; found: 751.3939.

**3.46e:** This is a known compound;\(^{23}\) \([\alpha]\)\(_D\)\(^{25}\) 28.6 (c 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.94 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.17-1.30 (m, 24H), 2.51-2.60 (m, 2H), 2.72-2.80 (m, 2H), 2.91-3.00 (m, 2H), 3.30 (bro, 1H), 7.04 (d, J = 6.9 Hz, 1H), 7.13-7.16 (m, 3H), 7.29 (s, 1H), 7.33-7.40 (m, 3H), 7.54-7.59 (m, 2H), 7.95-7.99 (m, 4H); \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) -3.71; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -78.6. HRMS calcd. for C\(_{51}\)H\(_{56}\)F\(_3\)NO\(_5\)PS\(^-\): 882.3569; found: 882.3545.
3.6.2. Representative Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imines with α,β-Unsaturated-2-acyl Imidazoles Catalyzed by Ni(ClO₄)₂/ (S,S)-DBFOX

To a 6 dram vial containing 4 Å molecular sieves (150 mg), Ni(ClO₄)₂·6H₂O (0.02 mmol), and ligand (0.022 mmol) was added in CH₂Cl₂ (1 mL). The vial was stirred for 3 h. The α,β-unsaturated 2-acyl imidazole (0.1 mmol) was then added and the reaction mixture was stirred for 45 minutes. A solution of azomethine imine (0.1 mmol) in CHCl₃ (1 mL) was finally added. The reaction was stirred at room temperature until the dipolarophile was consumed (TLC). The reaction mixture was filtered through a pad of celite and rinsed with EtOAc (2 X 10 mL). The organic layer was washed with saturated Na₂CO₃ solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate. Silica gel (2 g) was added to the organic layer and the solvent was removed in vacuo. The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogiX RS-4 columns. The Exo/Endo ratios were determined by 1H NMR spectroscopy prior to chromatography and enantioselectivities were measure by HPLC analysis after chromatography.

3.6.3. Representative Procedure for Low Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imines with α,β-Unsaturated 2-acyl Imidazoles Catalyzed by Ni(ClO₄)₂/ (S,S)-DBFOX

To a 6 dram vial containing 4 Å molecular sieves (150 mg), Ni(ClO₄)₂·6H₂O (0.02 mmol), and ligand (0.022 mmol) was added in CH₂Cl₂ (1 mL). The vial was stirred for 3 hrs. The α,β-unsaturated 2-acyl imidazole (0.1 mmol) was then added and the reaction mixture was
stirred for 45 minutes. The vial was then transferred to a low temperature bath and stirred for 30 min. A solution of azomethine imine (0.1 mmol) in CHCl₃ (1 mL) was finally added. The reaction was stirred at -10 °C until the dipolarophile was consumed (TLC). The reaction mixture was worked up according to the procedure are mentioned above. The Exo/Endo ratios were determined by ¹H NMR spectroscopy prior to chromatography and enantioselectivities were measure by HPLC analysis after chromatography.

3.6.4. Representative Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Imines with α,β-Unsaturated 2-acyl Imidazoles Catalyzed by Chiral Brønsted Acid

To a 6 dram vial containing α,β-unsaturated 2-acyl imidazole (0.1 mmol) and Chiral Brønsted acid, CH₂Cl₂ (1 mL) was added. The vial was stirred for 1 hrs. A solution of azomethine imine (0.1 mmol) in CHCl₃ (1 mL) was finally added. The reaction was stirred at room temperature until the dipolarophile was consumed (TLC). The reaction mixture was worked up according to the procedure are mentioned above. The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogiX RS-4 columns. The exo/endo ratios were determined by ¹H NMR spectroscopy prior to chromatography and enantioselectivities were measure by HPLC analysis after chromatography.

(5RS,6RS,7RS)-7-Methyl-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44a) :
Viscous oil, $[\alpha]_D^{25} -121.5$ (c 1.0, CHCl$_3$), ($\text{endo:exo} = >99:01$); $^1$H NMR (CDCl$_3$, 100 MHz); $\delta$ 1.63 (d, $J = 6.3$ Hz, 3H), 2.63 (ddd, $J = 16.3, 9.5, 6.0$ Hz, 1H), 2.80 (ddd, $J = 16.3, 9.5, 7.7$ Hz, 1H), 2.99 (ddd, $J = 11.6, 9.5, 6.0$ Hz, 1H), 3.44 (ddd, $J = 11.6, 9.5, 7.8$ Hz, 1H), 3.92 (s, 3H), 4.17 (d, $J = 3.4$ Hz, 1H), 4.18 (dd, $J = 18.5, 6.3$ Hz, 1H), 4.38 (dd, $J = 9.1, 3.4$ Hz, 1H), 6.98 (s, 1H), 7.02 (s, 1H), 7.23 (m, 3H), 7.38 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 21.0, 31.6, 36.1, 46.3, 54.6, 65.5, 71.6, 127.8, 128.0, 128.3, 128.8, 129.8, 137.7, 142.9, 173.0, 189.1 IR (KBr) 3065, 2970, 2885, 2849, 1673, 1456, 1287, 1150, 1045; 920, 759, 687 cm$^{-1}$; HRMS calcd. for C$_{18}$H$_{20}$N$_4$O$_2$Na$: 347.1484$; Found: 347.1466.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_r$ 21.3 min (major), $t_r$ 24.3 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane: Ethyl Acetate = 1:1, 1mL/min] as 93% ee for the $\text{endo}$ cycloadduct.

(5RS,6RS,7RS)-7-Ethyl-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44b):

Viscous oil, $[\alpha]_D^{25} -93.1$ (c 1.0, CHCl$_3$), ($\text{endo:exo} = >99:01$); $^1$H NMR (CDCl$_3$, 100 MHz); $\delta$ 1.04 (t, $J = 7.3$ Hz, 3H), 1.92-2.02 (m, 1H), 2.12-2.20 (m, 1H), 2.66 (ddd, $J = 17.8, 9.4, 4.7$ Hz, 1H), 2.86-2.93 (m, 1H), 3.08 (ddd, $J = 12.0, 9.4, 4.7$ Hz, 1H), 3.51 (dt, $J = 17.8, 9.4$ Hz, 1H), 3.97 (s, 3H), 4.04-4.08 (m, 1H), 4.21 (d, $J = 9.0$ Hz, 1H), 4.48 (dd, $J = 9.0, 5.4$ Hz, 1H), 7.02 (s, 1H), 7.06 (s, 1H), 7.25-7.32 (m, 3H), 7.40-7.42 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 19.1, 19.6, 30.8, 32.6, 36.3, 45.2, 61.5, 65.4, 73.9, 127.9, 128.4, 128.5, 128.8, 129.8, 137.5, 142.8, 175.7, 190.5; IR (KBr) 3055, 2960, 2853,
1675, 1460, 1365, 1289, 1040, 920, 685 cm\(^{-1}\); HRMS calcd. for C\(_{19}\)H\(_{22}\)N\(_4\)O\(_2\)Na\(^+\): 361.1640; Found: 361.1618.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_r\) 11.1 min (major), \(t_r\) 13.4 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate 0.5 mL/min] as 80% ee for the endo cycloadduct.

\[\text{(SRS,6RS,7RS)-7-Isopropyl-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44c):}\]

Viscous oil, \([\alpha]_D^{25}\) -64.4 (c 1.0, CHCl\(_3\)), (endo:exo = >99:01); \(^1\)H NMR (CDCl\(_3\), 100 MHz) \(\delta\) 0.96 (d, \(J = 6.7\) Hz, 3H), 1.04 (d, \(J = 6.7\) Hz, 3H), 2.19 (sept., \(J = 6.7\) Hz, 1H), 2.60 (m, 1H), 2.83 (m, 1H), 3.45 (m, 1H), 3.92 (s, 3H), 3.9 (m, 2H), 4.66 (dd, \(J = 9.2, 6.0\) Hz, 1H), 6.94 (s, 1H), 6.95 (s, 1H), 7.20-7.26 (m, 3H), 7.30-7.32 (m, 2H); \(^1^\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 19.1, 19.5, 30.7, 32.5, 36.2, 45.2, 61.5, 65.3, 73.8, 127.8, 127.9, 128.3, 128.7, 129.8, 137.5, 142.8, 175.6, 190.5; IR (KBr) 3110, 2880, 2835, 1687, 1597, 1410, 1155, 1065, 1045, 935, 850, 703 cm\(^{-1}\); HRMS calcd. for C\(_{20}\)H\(_{24}\)N\(_4\)O\(_2\)Na\(^+\): 375.1797; Found: 375.1787.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_r\) 11.0 min (major), \(t_r\) 22.7 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:Ethyl Acetate =1:1 1 mL/min] as 67% ee for the endo cycloadduct.
(5RS,6RS,7RS)-6-(1-Methyl-1H-imidazole-2-carbonyl)-7-phenethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44d):

White foam, $[\alpha]_D^{25} -28.3$ (c 1.0, CHCl$_3$), (endo:exo = >99:01); $^1$H NMR (CDCl$_3$, 100 MHz); $\delta$ 2.22-2.32 (m, 1H), 2.42-2.51 (m, 1H), 2.59-2.75 (m, 2H), 2.79-2.93 (m, 2H), 3.04-3.10 (m, 1H), 3.50 (dt, $J$= 12.1, 9.4 Hz, 1H), 3.92 (s, 3H), 4.12 (ddd, $J$ = 9.4, 5.2, 4.0 Hz, 1H), 4.20 (d, $J$ = 8.9 Hz, 1H), 4.45 (dd, $J$ = 8.9, 5.3 Hz, 1H), 6.97 (s, 1H), 7.19-7.30 (m, 8H), 7.38-7.40 (m, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 30.9, 33.2, 36.2, 36.6, 45.4, 59.4, 64.1, 71.3, 125.8, 127.8, 128.1, 128.3, 128.7, 128.8, 129.9, 137.9, 141.9, 142.8, 175.5, 189.3; IR (KBr) 3115, 2985, 1679, 1546, 1420, 1160, 1040, 793, 710 cm$^{-1}$; HRMS calcd. for C$_{25}$H$_{26}$N$_4$O$_2$Na$: 437.1953; Found: 437.1962.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_r$ 4.7 min (major), $t_r$ 6.2 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 1 mL/min] as 81% ee for the endo cycloaduct.

(5RS,6SR,7SR)-7-(Benzyloxymethyl)-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44e):

White foam, $[\alpha]_D^{25} -63.4$ (c 1.0, CHCl$_3$), (endo:exo = >99:01); $^1$H NMR (CDCl$_3$, 100 MHz); $\delta$ 2.64 (ddd, $J$ = 14.2, 9.5, 4.9 Hz, 1H), 2.80-2.89 (m, 1H), 3.04 (ddd, $J$ = 11.9, 9.5, 4.9 Hz, 1H), 3.5 (dt, $J$ = 11.9, 9.5 Hz, 1H), 3.9 (s, 3H), 3.96 (dd, $J$ = 10.3, 7.4 Hz, 1H), 4.05 (dd, $J$ = 10.3, 4.3 Hz, 1H), 4.17 (d, $J$ = 8.9 Hz, 1H), 4.36-4.64 (m,
2H), 4.62 (dd, J = 12.0, 19.0 Hz, 2H), 6.95 (s, 1H), 6.96 (s, 1H), 7.22-7.32 (m, 8H), 7.37-7.39 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 31.0, 36.0, 45.7, 58.6, 60.7, 70.9, 71.1, 73.1, 127.5, 127.7, 127.9, 128.1, 128.3, 128.4, 128.7, 129.7, 137.6, 138.5, 142.7, 175.1, 188.8; IR (KBr) 2950, 2910, 2849, 2805, 1669, 1570, 1449, 1425, 1118, 1076, 970, 886, 755, 699 cm\(^{-1}\); HRMS calcd. for C\(_{25}\)H\(_{26}\)N\(_4\)O\(_3\)Na\(^{+}\): 453.1897; Found: 453.1915.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_r\) 4.9 min (major), \(t_r\) 7.7 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 mL/min] as 88% ee for the endo cycloadduct.

(5RS,6RS,7RS)-5-(2-Fluorophenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44h):

White foam \([\alpha]_D^{25}\) -57.5 (c 1.0, CHCl\(_3\)) (endo:exo = >99:01); \(^1\)H NMR (CDCl\(_3\), 100 MHz); \(\delta\) 1.57 (d, \(J = 7.0\) Hz, 3H), 2.63 (ddd, \(J = 13.5, 9.5, 6\) Hz, 1H), 2.84 (ddd, \(J = 18.0, 11.0, 9.0\) Hz, 1H), 3.05 (ddd, \(J = 13.5, 9.5, 6.0\) Hz, 1H), 3.51 (ddd, \(J = 18.0, 11.0, 9.0\) Hz, 1H), 3.94 (s, 3H), 4.28-4.35 (m, 1H), 4.42-4.50 (m, 2H), 6.87-6.92 (m, 1H), 6.99 (s, 1H), 7.01 (s, 1H), 7.11-7.22 (m, 2H), 7.65 (dt, \(J = 7.0, 1.8\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 21.0, 31.6, 36.3, 46.6, 54.7, 64.1, 64.7, 115.5 (d, \(J = 21.9\) Hz), 124.7 (d, \(J = 4.0\) Hz), 125.2 (d, \(J = 12.5\) Hz), 127.9, 129.0 (d, \(J = 3.6\) Hz), 129.6 (d, \(J = 8.4\) Hz), 129.8, 142.9, 160.3, 162.3, 173.5, 188.8; IR (KBr) 3125, 3095, 2987, 2840, 1667, 1567, 1440, 1239, 1155, 1075, 1040, 896 cm\(^{-1}\); HRMS calcd. for C\(_{18}\)H\(_{19}\)FN\(_4\)O\(_2\)Na\(^{+}\): 365.1390; Found: 365.1397.
The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_r 4.8 min (major), t_r 5.9 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 mL/min] as 37% ee for the endo cycloadduct.

\[(5RS,6RS,7RS)-5-(4-Bromophenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44i):\]

White foam, mp = 50-55 °C [\(\alpha\)]D\textsubscript{25} -87.7 (c 1.0, CHCl\textsubscript{3}), (endo:exo = >99:01); \(^1\)H NMR (CDCl\textsubscript{3}, 100 MHz); \(\delta\) 1.61 (d, \(J = 7.0\) Hz, 3H), 2.63 (m, 1H), 2.79 (ddd, \(J = 13.6, 9.3, 7.3\) Hz, 1H), 2.95 (ddd, \(J = 13.6, 9.3, 7.3\) Hz, 1H), 3.44 (ddd, \(J = 13.6, 9.3, 7.3\) Hz, 1H), 3.93 (s, 3H), 4.14 (d, \(J = 9.0\) Hz, 1H), 4.15-4.21 (m, 1H), 4.31 (dd, \(J = 9.0, 6.0\) Hz, 1H), 7.0 (s, 1H), 7.04 (s, 1H), 7.26 (td, \(J = 9.0, 2.0\) Hz, 2H), 7.39 (td, \(J = 9.0, 2.0\) Hz, 2H); \(^13\)C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 21.1, 31.6, 36.2, 46.3, 54.7, 65.6, 70.9, 122.3, 128.0, 129.7, 130.0, 132.0, 136.9, 142.8, 173.1, 188.8; IR (KBr) 3110, 2985, 2955, 1673, 1490, 1420, 1355, 1280, 1165, 1040, 885, 775 cm\(^{-1}\); HRMS calcd. for C\textsubscript{18}H\textsubscript{19}BrN\textsubscript{4}O\textsubscript{2}Na\textsuperscript{+}: 425.0589; Found: 425.0604

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_r 5.4 min (major), t_r 8.9 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 mL/min] as 95% ee for the endo cycloadduct.
(5RS,6RS,7RS)-5-(4-Methoxyphenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44j):

White foam $[\alpha]_D^{25}$ -110.0 (c 1.0, CHCl$_3$), (endo:exo = >99:01); $^1$H NMR (CDCl$_3$, 100 MHz); δ 1.62 (d, $J= 6.5$ Hz, 3H), 2.59-2.67 (m, 1H), 2.74-2.83 (m, 1H), 2.94-3.01 (m, 1H), 3.38-3.45 (m, 1H), 3.72 (s, 3H), 3.91 (m, 3H), 4.09 (d, $J = 9.2$ Hz, 1H), 4.14-4.20 (m, 1H), 4.37 (dd, $J = 9.2$, 5.6 Hz, 1H), 6.80 (td, $J = 8.6$, 2.9 Hz, 2H), 6.97 (s, 2H), 7.03 (s, 1H), 7.30 (td, $J = 8.6$, 2.9 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 21.1, 31.7, 36.2, 46.2, 54.6, 55.4, 65.4, 71.4, 114.3, 127.9, 129.2, 129.4, 129.9, 143.0, 159.8, 173.0, 189.3; IR (KBr) 3110, 3055, 2965, 2840, 1669, 1520, 1425, 1290, 1190, 1045, 910, 890 cm$^{-1}$; HRMS calcd. For C$_{19}$H$_{22}$N$_4$O$_3$Na$^+$: 377.1590; Found: 377.1612

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t$_r$ 5.6 min (major), t$_r$ 8.6 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 mL/min] as 95% ee for the endo cycloadduct.

4-(1RS,2RS,3RS)-3-Methyl-2-(1-methyl-1H-imidazole-2-carbonyl)-5-oxohexahydropyrazolo[1,2-a]pyrazol-1-yl)benzonitrile (3.44k):

Foamy solid, mp= 60-65 °C $[\alpha]_D^{25}$ -91.1 (c 1.0, CHCl$_3$), (endo:exo = >99:01); $^1$H NMR (CDCl$_3$, 100MHz); δ; 1.60 (d, $J = 6.4$ Hz, 3H), 2.60-2.68 (m, 1H), 2.75-2.83 (m, 1H), 2.92-2.99 (m, 1H), 3.45-3.52 (m, 1H), 3.93 (s, 3H), 4.17-4.29 (m, 3H), 7.01 (s, 1H), 7.08 (s, 1H), 7.49-7.51 (m, 2H), 7.55-7.57 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ; 21.1, 31.4, 36.3,
46.4, 54.7, 65.6, 70.5, 112.2, 118.7, 128.3, 128.7, 130.1, 132.7, 142.5, 143.6, 173.3, 188.3; IR (KBr) 3125, 3067, 2967, 2823, 1665, 1530, 1490, 1355, 1219, 1130, 1032, 915, 799 cm⁻¹; HRMS calcd. For C₁₉H₂₂N₄NaO₃⁺: 372.1431; Found: 372.1428

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_r 6.0 min (major), t_r 10.4 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Hexane:THF =1:1 1 mL/min] as 95% ee for the endo cycloadduct.

(5S,6RS,7RS)-7-Methyl-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'a):

White foam [α]_D²⁵ -81.7 (c 1.0, CHCl₃), (exo:endo = >99:01); ¹H NMR (CDCl₃, 100 MHz); δ 1.63 (d, J = 8.3 Hz, 3H), 2.58-2.81 (m, 3H), 3.22-3.26 (m, 1H), 3.51 (s, 3H), 4.27 (d, J = 8.3 Hz, 1H), 4.47-4.53 (m, 1H), 4.81 (dd, J = 8.3, 5.0 Hz, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.02-7.09 (m, 5H); ¹³C NMR (CDCl₃, 125 MHz); δ 18.8, 35.4, 36.3, 49.0, 50.0, 62.9, 71.0, 126.9, 128.0, 128.1, 128.4, 129.1, 134.6, 143.6, 165.5, 188.8; IR (KBr) 3132, 3110, 2967, 2845, 1679, 1427, 1355, 1289, 1156, 1040, 920, 790, 695 cm⁻¹; HRMS calcd. for C₁₈H₂₀N₄O₂Na⁺: 347.1478; Found: 347.1490.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_r 8.9 min (major), t_r 9.9 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) THF:Hexane = 1:1, 1 mL/min] as 92% ee for the exo cycloadduct.
(5SR,6R,7R)-7-Ethyl-6-(1-methyl-1H-imidazole-2-carbonyl)-5-
phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'b):

Colorless solid, mp 128-130 °C [α]D25 -93.6 (c 1.0, CHCl3), (exo:endo = >99:01); 
1H NMR (CDCl3, 100 MHz); δ 0.98 (t, J = 7.4 Hz, 3H),
1.78 (sept. J = 7.4 Hz, 1H), 2.20-2.30 (m, 1H), 2.51-2.55 (m, 1H), 2.82 (q, J = 9.9 Hz, 1H),
3.11-3.16 (m, 1H), 3.47 (s, 3H), 2.9 (d, J = 8.2 Hz, 1H), 4.40-4.45 (m, 1H), 4.87 (dd, J =
8.2, 5.4 Hz, 1H), 6.69 (s, 1H), 6.91 (s, 1H), 7.03-7.08 (m, 4H) ; 
13C NMR (CDCl3, 125 MHz); δ 10.4, 25.7, 29.8, 35.4, 35.5, 35.9, 47.7, 55.4, 60.7, 71.0, 126.8, 128.1, 128.5,
128.7, 129.1, 134.6, 143.3, 166.6, 188.9; 
IR (KBr) 3109, 3066, 2969, 2894, 2843, 1676,
1456, 1413, 1357, 1291, 1155, 1038, 913, 878, 798, 742, 699 cm-1; 

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t 10.0 min (major), t 11.5 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) THF:Hexane = 1:1, 1 mL/min] as 96% ee for the exo cycloadduct.

(5SR,6RS,7RS)-7-Isopropyl-6-(1-methyl-1H-imidazole-2-carbonyl)-
5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'c):

Colorless solid, mp 44-46 °C [α]D25 -32.2 (c 1.0, CHCl3), (exo:endo = >99:01); 
1H NMR (CDCl3, 100 MHz); δ 0.98 (d, J = 6.8, 3H), 1.03 (d, J = 6.8, 3H), 2.27-
2.36 (m, 1H), 2.43-2.50 (m, 2H), 2.92-3.09 (m, 2H), 3.45 (s, 1H), 4.40 (d, J = 8.0 Hz, 1H),
4.50 (t, J = 5.6 Hz, 1H), 4.93 (dd, J = 8.0, 5.6 Hz, 1H), 6.70 (s, 1H), 6.95 (s, 1H), 6.99-7.01
(m, 2H), 7.07-7.10 (m, 3H); 
13C NMR (CDCl3, 125 MHz); δ 17.6, 19.6, 30.0, 35.1, 35.3,
46.1, 57.6, 59.1, 71.1, 126.7, 128.2, 128.3, 129.1, 129.2, 134.7, 143.2, 168.2, 188.7; IR (KBr) 3106, 2960, 1683, 1558, 1456, 1408, 1289, 1156, 1072, 1034, 916, 849, 703, 667 cm⁻¹; HRMS calcd. for C₂₀H₂₄N₄O₂Na⁺: 375.1797; Found: 375.1790.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 14.4 min (major), tᵣ 17.1 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) Ethyl Acetate:Hexane = 1:1, 1 mL/min] as 99% ee for the exo cycloadduct.

(5SR,6SR,7SR)-6-(1-Methyl-1H-imidazole-2-carbonyl)-5,7-diphenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'g):

Colorless solid, mp 154-156 °C [α]D²⁵ +51.4 (c 1.0, CHCl₃), (exo:endo = >99:01); ¹H NMR (CDCl₃, 100 MHz); δ 2.24-2.33 (m, 1H), 2.53 (ddd, J = 14.5, 9.5, 4.8 Hz, 1H), 3.06 (dt, J = 10.4, 4.8 Hz, 1H), 3.19 (q, J = 9.6 Hz, 1H), 3.52 (s, 3H), 4.80 (d, J = 7.8 Hz, 1H), 5.02 (dd, J = 7.8, 6.4 Hz, 1H), 5.76 (d, J = 6.4 Hz, 1H), 6.70 (s, 1H), 6.91 (s, 1H), 7.02-7.05 (m, 2H), 7.12-7.16 (m, 3H), 7.20-7.23 (m, 1H), 7.28-7.32 (m, 2H), 7.43-7.45 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz); δ 34.7, 35.4, 45.5, 56.1, 66.0, 70.4, 126.6, 126.8, 127.8, 128.4, 128.5, 128.9, 129.3, 129.3, 134.5, 140.1, 143.0, 168.0, 187.5; IR (KBr) 3131, 3109, 3062, 3033, 2963, 1680, 1494, 1408, 1355, 1296, 1156, 1033, 857, 731, 704 cm⁻¹; HRMS calcd. for C₂₃H₂₂N₄O₂Na⁺: 409.1640; Found: 409.1641.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 16.0 min (minor), tᵣ 19.9 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate, 0.5 mL/min] as 97% ee for the exo cycloadduct.
(5SR,6SR,7SR)-7-(Furan-2-yl)-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'f):

Colorless solid, mp 65-67 °C [α]D25 -16.3 (c 1.0, CHCl3), (exo:endo >99:01); 1H NMR (CDCl3, 100 MHz); δ 2.52-2.56 (m, 2H), 3.0 (q, J = 10.0, 1H), 3.19-3.24 (m, 1H), 3.56 (s, 3H), 4.64 (d, J = 7.8 Hz, 1H), 5.31 (dd, J = 7.8, 5.0 Hz, 1H), 5.62 (d, J = 5.0 Hz, 1H), 6.30-6.31 (m, 1H), 6.42 (d, J = 3.2 Hz, 1H), 6.69 (s, 1H), 6.88 (s, 1H), 7.08-7.12 (m, 5H), 7.38-7.39 (m, 1H); 13C NMR (CDCl3, 125 MHz); δ14.3, 35.3, 35.6, 47.8, 50.5, 61.3, 71.0, 108.9, 110.6, 126.9, 128.3, 128.4, 128.8, 129.3, 134.3, 142.9, 143.1, 150.5, 166.9, 187.7; IR (KBr) 3110, 2951, 1683, 1409, 1291, 1155, 1035, 793, 702 cm⁻¹. HRMS calcd. for C21H20N4O3Na⁺: 399.1428; Found: 399.1420.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t₁ 14.2 min (minor), t₂ 20.9 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate 0.5 mL/min] as 86% ee for the exo cycloadduct.

(5S,6R,7R)-6-(1-Methyl-1H-imidazole-2-carbonyl)-7-phenethyl-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'd):

Colorless solid, mp 48-50 °C [α]D25 -24.3 (c 1.0, CHCl3), (exo:endo >99:01); 1H NMR (CDCl3, 100 MHz); δ 2.02-2.09 (m, 1H), 2.42-2.61 (m, 3H), 2.70-2.79 (m, 2H), 2.9 (q, J = 9.85 Hz, 1H), 3.16 (ddd, J = 13.7, 9.8, 4.08 Hz, 1H), 4.41 (d, J = 8.1 Hz, 1H), 4.60 (dd, J = 12.4, 5.6 Hz, 1H), 4.94 (dd, J = 8.2, 5.6 Hz,
1H), 6.71 (s, 1H), 6.94 (s, 1H), 7.04-7.11 (m, 6H), 7.20-7.21 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz); δ 32.7, 34.8, 35.4, 35.5, 47.0, 54.2, 61.2, 70.9, 126.0, 126.8, 128.2, 128.4, 128.6, 128.9, 129.1, 134.6, 141.4, 143.3, 167.6, 188.5; IR (KBr) 3104, 3059, 3026, 2925, 2853, 1682, 1455, 1410, 1288, 1156, 1035, 749, 700 cm⁻¹; HRMS calcd. for C₂₅H₂₆N₄O₂Na⁺: 437.1948; Found: 437.1966.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 12.1 min (minor), tᵣ 15.1 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate 0.5 mL/min] as 93% ee for the exo cycloadduct.

(5SR,6SR,7SR)-7-(Benzyloxymethyl)-6-(1-methyl-1H-imidazole-2-carbonyl)-5-phenyltetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'e):

Colorless solid, mp 124-126 °C [α]D²⁵ -49.0 (c 1.0, CHCl₃), (exo:endo = >99:01); ¹H NMR (CDCl₃, 100 MHz); δ 2.55-2.86 (m, 3H), 3.24 (ddd, J = 12.1, 9.3, 3.4 Hz, 1H), 3.54 (s, 3H), 3.87 (dd, J = 9.9, 3.4 Hz, 1H), 4.15 (dd, J = 9.9, 5.0 Hz, 1H), 4.39 (d, J = 8.1 Hz, 1H), 4.62 (dd, J = 15.6, 11.9 Hz, 3H), 5.23 (dd, J = 8.0, 4.3 Hz, 1H), 6.69 (s, 1H), 6.90 (s, 1H), 7.04-7.13 (m, 5H), 7.23-7.35 (m, 5H); ¹³C NMR (CDCl₃, 125 MHz); δ 35.5, 36.0, 48.9, 54.0, 58.7, 68.2, 71.1, 73.5, 126.7, 127.6, 127.7, 128.0, 128.2, 128.4, 128.5, 129.1, 134.6, 138.4, 143.4, 166.2, 188.9; IR (KBr) 2932, 2904, 2859, 2828, 2803, 1671, 1437, 1410, 1287, 1118, 1089, 1035, 877, 750, 701 cm⁻¹; HRMS calcd. for C₂₅H₂₆N₄O₂Na⁺: 453.1897; Found: 53.1904.
The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t, 17.0 min (minor), t, 21.3 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate 0.5 mL/min] as 88% ee for the exo cycloadduct.

\[(5S,6R,7S)-5-(2-Fluorophenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one\] (3.44':h): Colorless solid, mp 127-130 °C \[\alpha^2D^2_{25} -83.7 (c 1.0, CHCl_3)\], (exo:endo = >99:01); \(^1\)H NMR (CDCl\(_3\), 100 MHz); \(\delta\) 1.62 (d, \(J=6.5\) Hz, 3H), 2.55-2.79 (m, 3H), 3.23-3.30 (m, 1H), 3.57 (s, 3H), 4.41-4.47 (m, 1H), 4.54 (d, \(J=7.7\) Hz, 1H), 8.84 (dd, \(J=7.7, 4.2\) Hz, 1H), 6.70-6.77 (m, 2H), 6.89-6.92 (m, 2H), 6.99-7.04 (m, 1H), 7.20-7.24 (m, 1H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz); \(\delta\) 18.9, 35.5, 35.6, 36.4, 49.7, 50.3, 61.6, 63.6, 122.1 (d, \(J=13.0\) Hz), 123.7 (d, \(J=3.2\) Hz), 127.1, 128.3, 129.4, 129.6 (d, \(J=8.4\) Hz), 143.3, 160.2, 162.1, 165.2, 188.8; IR (KBr) 3132, 3100, 2982, 2931, 2829, 2931, 2829, 1673, 1141, 1170, 1090, 1036, 896, 762 cm\(^{-1}\); HRMS calcd. for C\(_{18}\)H\(_{19}\)FN\(_4\)O\(_2\)Na\(^+\): 365.1384; Found: 365.1386.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t, 16.5 min (minor), t, 17.1 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate 0.5 mL/min] as 80 % ee for the exo cycloadduct.
(5SR,6RS,7RS)-5-(4-Bromophenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'i):

Colorless solid, mp 58-60 °C [α]D25 -60.9 (c 1.0, CHCl₃), (exo:endo = >99:01); ¹H NMR (CDCl₃, 100 MHz); δ 1.67 (d, J = 6.5 Hz, 3H), 2.67-2.84 (m, 3H), 3.27-3.30 (m, 3H), 3.69 (s, 3H), 4.24 (d, J = 8.2 Hz, 1H), 4.48-4.53 (m, 1H), 4.86 (dd, J = 8.2, 4.7 Hz, 1H), 6.83 (s, 1H), 6.97 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz); δ 18.5, 35.6, 36.5, 49.9, 50.1, 62.7, 70.5, 122.2, 127.1, 129.2, 131.2, 137.1, 143.3, 165.0, 188.5; IR (KBr) 3106, 2974, 2930, 1675, 1410, 1347, 1289, 1160, 1036, 899, 785 cm⁻¹; HRMS calcd. For C₁₉H₁₉N₄NaO₂⁺: 425.0589; Found: 425.0589.

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 25.9 min (major), tᵣ 32.1 min (minor) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 1:1= Hexane: Ethyl Acetate 1 mL/min] as 83 % ee for the exo cycloadduct.

(5SR,6RS,7RS)-5-(4-Methoxyphenyl)-7-methyl-6-(1-methyl-1H-imidazole-2-carbonyl)tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one (3.44'j):

Colorless solid, mp 142-144 °C [α]D25 -56.3 (c 1.0, CHCl₃), (exo:endo = >99:01); ¹H NMR (CDCl₃, 100 MHz); δ 1.59 (d, J = 6.4 Hz, 3H), 2.58-2.64 (m, 2H), 2.74-2.81 (m, 1H), 3.14-3.19 (m, 1H), 3.55 (s, 3H), 3.66 (s, 3H), 4.27 (d, J = 8.2 Hz, 1H), 4.48-4.54 (m, 1H), 4.75 (dd, J = 8.2, 5.3 Hz, 1H), 6.60-6.62 (m, 2H), 6.73 (s, 1H), 6.97 (s, 1H), 6.97-6.99 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz); δ 18.9, 35.5, 36.0, 48.3, 49.8, 55.3,
55.4, 63.0, 70.4, 113.5, 126.4, 126.8, 126.9, 129.1, 129.7, 143.5, 159.5, 165.8; IR (KBr)
3105, 3047, 2973, 2843, 1672, 1516, 1418, 1242, 1160, 1031, 906, 885 cm\(^{-1}\); HRMS calcd.
for C\(_{19}\)H\(_{22}\)N\(_4\)NaO\(_3^+\): 377.1590; Found: 377.1587

The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_r\) 17.4 min (minor), \(t_r\) 20.1 min (major) [Chiralpak IA (0.46 x 25 cm) (from Diacel Chemical Ltd.) 100% Ethyl Acetate 0.5 mL/min] as 95 % ee for the \textit{exo} cycloadduct.

3.6.5. Determination of Relative Stereochemistry

Figure 3.7. Crystal Structure of Lewis Acid Cycloadduct 3.44\(i\) and Brønsted Acid Cycloadduct 3.44'\(i\)
Determination of relative stereochemistry of the product was done by single crystal X-ray analysis of the cycloadducts 3.44i and 3.44'i obtained by Lewis acid and Brønsted acid catalyzed reactions. From these analyses it was found that the Lewis acid cycloadduct 3.44i was endo and Brønsted acid cycloadduct 3.44'i was exo. The stereochemistry of all the other cycloadducts was tentatively assigned based on these two structures.

3.7. References


CHAPTER 4.

DEVELOPMENT OF CHIRAL BRØNSTED ACID CATALYZED EXO AND
ENANTIOSELECTIVE NITRONE CYCLOADDITIONS

4.1. Introduction

After our success with dipolar cycloaddition of azomethine imines to acyl
imidazoles catalyzed by chiral Brønsted acid, we decided to investigate other possible
dipoles as reactants. One of the issues with extending the scope of this Brønsted acid
chemistry to other cycloadditions is with respect to the stability of the dipole towards the
reaction conditions. Protonation of the dipole by the strong acid was also another concern,
which could limit the scope of this methodology. Dipoles such as azomethine imines are
one of the most stable dipoles that can be synthesized before hand and stored for long time
use. Other dipoles such as nitrones can be synthesized and stored but may not be stable to
acidic conditions. Similarly, a vast majority of dipoles are typically generated in situ and
usually under the action of a non-nucleophilic base. These include dipoles such as nitrile
imines, nitrile ylides, azomethine ylides and to some extent nitrile oxides. Similarly,
dipoles such as carbonyl ylides are generated by metal mediated decomposition of
corresponding precursors. Thus one of the initial challenges faced by us was to find a
compatibility match of the dipole with the chiral Brønsted acid. However, the absence of
any known examples of Brønsted acid catalyzed dipolar cycloaddition of these dipoles to
electron deficient olefins was a strong driving force for us to pursue this chemistry.

Dipolar cycloaddition reaction of nitrones is probably one of the most studied in
this category. The reason for this intense scrutiny on this particular dipole lies in the
synthetic utility of the cycloadducts generated from this reaction. Cycloaddition of nitrone to alkenes lead to the formation of substituted isoxazolines. Isoxazolines are highly sought after entities as they can be converted into biologically significant molecules such as β-amino alcohols and their derivatives by simple reductive ring opening. These β-amino alcohols have been utilized in the total synthesis of several optically active natural products.

4.2. Examples of Asymmetric 1,3-Dipolar Cycloaddition of Nitrones

4.2.1. Nitrone Cycloaddition to α,β-Unsaturated Carbonyl Compounds Catalyzed by Chiral Lewis Acids

Jørgensen et al. reported one of the earliest asymmetric nitrone cycloaddition to electron deficient alkenes using a chiral titanium Lewis acid. In this pioneering example, oxazolidinone crotonate reacted with nitrone to yield a mixture of exo and endo cycloadducts (Scheme 4.1). In the absence of any Lewis acid the reaction proceeded at an elevated temperature to yield a 91:09 mixture of exo and endo diastereomers. Activation of the dipolarophile through coordination of a Lewis acid resulted in an increase in rate of the cycloaddition. The coordination of a strong Lewis acid with the dipolarophile rather than the nitrone leads to favorable HOMO(dipole)-LUMO(dipolarophile) interactions enhancing reactivity.

With the development of chiral Lewis acid chemistry and aided by the rapid development in the field of ligand synthesis, numerous new ligands with different shielding environments were available for use. Many groups have employed these unique ligands to access their impact on asymmetric nitrone cycloadditions. Kanemasa et al. have
demonstrated the application of a new chiral Lewis acid complex of ligand DBFOX 4.5 with Ni(ClO₄)₂•6H₂O for asymmetric nitrone cycloaddition of oxazolidinone imide 4.1.⁴ A significant feature of this report is that the reaction is highly *endo* selective and yields isoxazolidines with very high levels of enantioselectivity (>95%). Typical catalyst loading was 10 mol% but the amount of chiral Lewis acid could be reduced to 1 mol% without appreciable loss of both enantio- and diastereoselectivity. Molecular sieves were essential for this catalyst system to be effective. Based on the success of BINOL ligands in conjunction with lanthanide Lewis acids for asymmetric nitrone cycloadditions reported by Kobayashi,⁵ Ohta et al. developed a novel BINOL-BOX ligand 4.6 which would have features of both BINOL ligands and bisoxazoline ligands (Figure 4.1).⁶ Similarly, Iwasa et al. developed a chiral ligand 4.7 based on the PyBOX scaffold with silyl protecting group, which provide the steric shielding for asymmetric nitrone cycloaddition of oxazolidinone imide 4.1.⁷

![Scheme 4.1. Asymmetric Nitrone Cycloaddition Reaction Catalyzed by Ti-TADDOLate](image)

A significant advantage of this ligand design was that several ligands with different steric volume could be synthesized with relative ease starting from the same primary
alcohol precursor. Reaction of oxazolidinone imide 4.1 with nitrones were catalyzed with 10 mol\% of Ni(ClO$_4$)$_2$/4.7 complex in isopropanol and gave predominantly the endo cycloadduct with high levels of enantioselectivity.

Iwasa et al.$^8$ also reported the synthesis and application of a new series of tridentate ligands XaBOX 4.8 which is similar to DBFOX 4.5 developed by Kanemasa. They have reported a highly endo and enantioselective nitrone cycloaddition of oxazolidinone imide 4.1 using Mn(ClO$_4$)$_2$/4.8 catalyst. Saito et al. have reported the use of a chiral bisimine 4.9/Cu(II) based catalyst system for endo and enantioselective nitrone cycloaddition to 4.1.$^9$ An elegant feature of this catalyst design is the ease of synthesis, ready availability of the starting material also the easy tunability of the R group for steric or electronic properties.

![Figure 4.1. Various Ligands Developed for Enantioselective Nitrone Cycloadditions](image)

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Recently Evans et al. have reported the development of a new template for *endo* and enantioselective nitrone cycloaddition catalyzed by Ce(IV)/4.12 complex as a catalyst (Scheme 4.2).\textsuperscript{10} This group had previously reported the application of 1-methyl imidazole as a template for asymmetric Friedel-Crafts reaction. High levels of diastereoselectivity and enantioselectivity for the cycloadducts were obtained when 5 mol\% of the catalyst was employed. The cycloadducts were further converted into β-lactams through relatively simple procedures.

Scheme 4.2. N-Methyl Imidazoles as Template for Enantioselective Nitrone Cycloaddition

Numerous examples of asymmetric nitrone cycloadditions have been reported for the selective formation of the *endo* diastereomer. However, there is no general method for the construction of the *exo* diastereomer. An *exo* selective nitrone cycloaddition has been reported by Jørgensen using a TiCl\textsubscript{4}/ TADDOL catalyst.\textsuperscript{11} However, enantioselectivity for the cycloadduct was modest and the substrate scope was limited. Sibi et al. reported the first general method for highly enantio- and *exo* selective nitrone cycloaddition to electron
deficient olefins. The reactions of β-substituted α,β-unsaturated pyrazolidinone 4.15 were catalyzed using Cu(OTf)₂/4.17 to give exo cycloadducts 4.18 (Scheme 4.3). Another significance of this report is the scope of the β-substituent (R = alkyl and aromatic) of the olefin, which was much improved than any other previous report. The exo selectivity of this reaction was attributed to the square planar organization of the chiral Cu(II)-substrate complex. Other Lewis acid complexes with Mg(II) and Fe(II) with 4.17 which do not possess square planar organization gave 1:1 mixture of exo and endo cycloadducts. Whereas reactions with Sc(OTf)₃/4.12 which have octahedral organization gave endo cycloadducts. Ligand 4.17 gave the best enantioselectivity while other bidentate bisoxazoline ligands were tried and fared poorly. The impact of molecular sieves was also investigated and reversal of exo/endo selectivity was observed when reactions were carried out in the absence of molecular sieves.

Example of Exo-Selective Asymmetric Nitrone Cycloaddition

Examples of nitrone cycloaddition to α,β-disubstituted α,β-unsaturated electron deficient olefins are scarce due to the low reactivity of these substrates. Sibi et al. reported enantioselective nitrone cycloaddition of α,β-disubstituted acroloyl imides 4.19 with nitrone 4.20 catalyzed by a Mg(NTf₂)₂/4.17 chiral Lewis acid complex (Scheme 4.4).
These reactions were also highly exo selective and in most cases >98:02 mixture of exo and endo diastereomers were isolated. Better reactivity of this imide template as compared to oxazolidinone or pyrazolidinone templates, which were previously tried, was due to efficient control of rotamer geometry. Thus, reactions were postulated to be proceeding through an s-cis rotamer of 4.17, which leads to greater polarization of the double bond. This methodology is also a good example for the construction of chiral quaternary center, which is very difficult to achieve and is highly sought after.

Scheme 4.4. Nitrone Cycloaddition for the Construction of Quaternary Stereo Centers

4.2.2. Nitrone Cycloadditions to α,β-Unsaturated Aldehydes

Early reports on asymmetric nitrone cycloaddition by Jørgensen et al. were based on electron deficient olefins tethered to an oxazolidinone template. The 1,3-dicarbonyl moiety of these dipolarophiles help form tight chelates with chiral Lewis acids. Many other groups have successfully applied similar templates, which are capable of forming chelates with chiral Lewis acid. Of note is the work of Sibi who developed pyrazolidinones, Evans who described imidazoles and much recently Kim who have reported α'-phosphoric enones as templates. In Lewis acid mediated nitrone cycloaddition to electron deficient olefins, there is always a possibility Lewis acid coordination of the nitrone
leading to its deactivation. Formation of a stronger chelate of the Lewis acid with dipolarophile has always helped in avoiding or reversing this equilibrium binding.

The use of α,β-unsaturated aldehydes as dipolarophiles for asymmetric nitrone cycloaddition was initially limited as it was always presumed that the Lewis acid would form a tighter complex with nitrones compared to the carbonyl carbon of the dipolarophile. However, aldehydes are an interesting class of substrates and are relatively simple. Many groups have therefore attempted development of chiral Lewis acid-mediated nitrone cycloaddition to α,β-unsaturated aldehydes using single point binding Lewis acids (Figure 4.2).

Figure 4.2. Binding Mode of Metals to Bidentate and Monodentate Substrates

Kündig et al. reported the first asymmetric nitrone cycloaddition to α,β-unsaturated aldehydes using a chiral ruthenium catalyst (Scheme 4.5).17 The authors postulated that a highly tuned aldehyde selective chiral Lewis acid would be able to discriminate between aldehydes and nitrone or would favor coordination of the aldehydes or bind with the nitrones in a readily reversible fashion. Catalyst 4.27 was prepared and initial NMR studies indicated that in solution a 7:3 ratio of chiral Lewis acid/aldehyde complex and chiral Lewis acid/nitrone complex was formed. Encouraged by these studies they tried reaction of various α,β-unsaturated aldehydes with nitrones. Cycloaddition of methacrolein 4.25 with
N-phenyl nitron 4.26 gave a >60:40 ratio of endo isomer 4.28 and endo isomer 4.29 in good enantioselectivity. In the same report the authors have also developed a chiral Lewis acid similar to 4.27 by replacing Fe(II) in place of Ru(II) which was investigated for nitrone cycloaddition of enals with cyclic nitrone with great success.

After the initial report on nitrone cycloaddition to α,β-unsaturated aldehydes using single point binding Lewis acids by Kündig, several groups have reported the design of catalysts, which would catalyze similar transformations.

Scheme 4.5. Early Example of Chiral Lewis Acid Catalyzed Nitrone Cycloaddition to Enals

Carmona et al. have reported an extensive study on the development of an Ir(II) based catalyst 4.30 for asymmetric nitrone cycloaddition to methacrolein.\textsuperscript{18} The reactions with this catalyst occur with perfect endo selectivity and yield cycloadducts in excellent enantiomeric excess. This paper also reported the development a Rh(II) catalyst instead Ir(II) for the same transformation. Carmona et al. have recently reported the use of catalyst 4.30 derived for Ir(II) or Rh(II) for endo and enantioselective nitrone cycloaddition to β-substituted, α,β-disubstituted enals.\textsuperscript{19} Kanemasa et al. reported a unique catalyst for nitrone cycloaddition to enals.\textsuperscript{20} Previous reports by Kündig et al. and by Carmona et al. have relied on preferential binding of dipolarophiles to Lewis acids based on electronic
properties, Kanemasa however developed aluminum phenoxide based Lewis acid 4.31 which prevents binding of the dipole to Lewis acid by utilizing steric hindrance of the phenyl ring around the Lewis acid (Figure 4.3). Bulky group on the nitrogen atom of the nitrone was essential for the success of this catalyst. Maruoka et al. developed a bis-Ti(IV) oxide based Lewis acid 4.32 for highly endo and enantioselective nitrone cycloaddition to enals.

Figure 4.3. Chiral Metal Complexes for Nitrone Cycloaddition to Enals

Maruoka et al. also studied the effect of bulky substituents on nitrogen atom of the dipole on yield and enantioselectivity of nitrone cycloaddition to methacrolein using catalyst 4.32 and observed that bulky substituent on nitrogen atom of the nitrone resulted in higher enantioselectivity and yield of the products. Maruoka et al. have also studied the impact of substituent at 6,6’-position on catalyst 4.32 on enantioselectivity of nitrone
cycloaddition of methacrolein to various N-diphenyl methyl nitrones.\textsuperscript{23} Yamada et al. have reported highly endo and enantioselective nitrone cycloaddition to cyclic enals using β-ketoiminato cationic Co(III) complexes \textsuperscript{4.33}.\textsuperscript{24}

Several reports on asymmetric nitrone cycloaddition to α,β-unsaturated aldehydes utilized the concept of single point binding chiral Lewis acids. Kanemasa et al. reported the use of bidentate bisoxazolines in conjunction with Lewis acids such as Ni(II) and Zn(II) to catalyze the same process (Scheme 4.6).\textsuperscript{25} Interestingly, dramatic change in regioselectivity was observed depending on the nature of the Lewis acid employed. Thus, Ni(ClO$_4$)$_2$/\textsuperscript{4.5} chiral Lewis acid gave steric controlled endo product \textsuperscript{4.36} in high enantioselectivity while Zn(ClO$_4$)$_2$/\textsuperscript{4.5} chiral Lewis acid gave electronically controlled endo product \textsuperscript{4.37} in 97% enantiomeric excess.

\begin{center}
\textbf{Scheme 4.6. An Example of Nitrone Cycloaddition to Enals Catalyzed by a Metal-Bis(oxazoline) Complex}
\end{center}

\textbf{4.2.3. Lewis Acid Catalyzed Nitrone Cycloaddition to Electron Rich Olefins}

1,3-Dipolar cycloaddition of nitrones to electron deficient olefins involves the interaction of HOMO (nitrone) with the LUMO (olefin). It is one of the most preferred methods for the construction of isoxazolidines and has been investigated in detail. In this mode, coordination of the chiral Lewis acid to the olefin confers reactivity to the substrate.
In contrast, there are not many reports on inverse electron demand nitrone cycloadditions. Inverse electron demand nitrone cycloaddition requires interaction of HOMO (olefin) with LUMO (nitrone).

Jørgensen et al. reported the very first highly enantio- and diastereoselective nitrone cycloaddition to ethyl vinyl ethers 4.38 catalyzed by aluminum-BINOL complex 4.40 (Scheme 4.7). Exo selectivity of >95:05 was observed for reaction of ethyl vinyl ether 4.38 with various N-phenyl nitrones 4.39 and the enantiomeric excess of the cycloadducts were >88%. However, when t-butyl vinyl ether was used as the dipolarophile, some deterioration in exo/endo selectivity was observed and the enantiomeric excess of the cycloadducts were lower than those obtained with ethyl vinyl ether.

![Scheme 4.7. Example of Inverse Electron Demand Nitrone Cycloaddition](image)

Jørgensen et al. also reported the application of catalyst 4.44 for cycloaddition of vinyl ethers to cyclic nitrones. Jørgensen et al. have also reported the development of a polymeric catalyst based on aluminum-BINOL scaffold for nitrone cycloaddition to vinyl ethers. Jørgensen et al. have further reported asymmetric nitrone cycloaddition to vinyl ether catalyzed by Cu(OTf)$_2$/4.44 (Scheme 4.8). The significance of this report is the use of a bidentate Lewis acid for catalysis. All previous reports of similar nitrone addition utilized single point binding Lewis acids such as aluminum. Nitrones 4.43 were prepared.
by condensation of aromatic $N$-hydroxyl amines with corresponding glyoxylates and presented sites for chelation of the chiral Lewis acid. Most reactions gave modest to good diastereoselectivity and yield. The enantioselectivity for both the exo or endo isomers was high.

Scheme 4.8. Nitrone Cycloaddition to Vinyl Ethers Catalyzed by Cu(II)/bis(oxazoline)

4.2.4. Organocatalyzed Nitrone Cycloadditions

The development of small organic molecules to catalyze enantioselective transformations has emerged as a major frontier for research in the field of asymmetric catalysis. Organocatalyzed asymmetric reactions also provide an environmentally benign approach for the construction of optically active compounds. Furthermore, organocatalysis also addresses the issues of catalyst interaction with dipole rather than dipolarophile in case of cycloaddition to electron deficient acceptors, which has been plaguing the field of Lewis acid catalysis. Also organocatalysts are relatively inert to other issues related to loss of catalysis due to catalyst degradation or deactivation, which are common in Lewis acid catalysis. Lewis acid catalysis often requires stringent reaction conditions and moisture can deactivate the catalyst. Many organocatalysts are tolerant to moisture and hence are user friendly. During the initial development of organocatalysis only a limited number of chiral
scaffolds were available but with the recent development in this field many newer structures are available for the synthetic chemist.

MacMillan et al. reported the very first example of enantioselective organocatalyzed nitrone cycloaddition. In this example, cycloaddition of acyclic nitrones 4.11 with crotonaldehyde was catalyzed by chiral imidazolidinone salt 4.48. Earlier studies from this group on catalyst development concluded that the benzylic substituent at C3 position on the catalyst was essential for obtaining best enantioselectivity (Scheme 4.9). The nature of the imidazolidinone salt also had an impact on diastereoselectivity and catalyst activity. Co-catalyst HClO4 was the best amongst other protic acid co-catalysts screened. Nitrones prepared by condensation of N-substituted hydroxyl amine with aromatic and aliphatic aldehydes were reacted with crotonaldehyde using 20 mol% of catalyst 4.48. The reactions were highly endo selective and typical enantioselectivities were >90%. Following this discovery, several groups have reported different catalysts for enantioselective nitrone cycloaddition to α,β-unsaturated aldehydes.

Scheme 4.9. First Example of Organocatalyzed Nitrone Cycloaddition to Enals

Yield up to 98%
endo/exo up to 99:01
endo ee up to 98%
Karlsson et al. reported enantioselective 1,3-dipolar cycloaddition of acyclic nitrones to cyclic \( \alpha,\beta \)-unsaturated aldehydes (Figure 4.4).\(^\text{31}\) Catalyst 4.50a-b, 4.51a-c were used for cycloaddition of cyclopent-1-enecarbaldehyde with N-methylphenyl nitrone 4.20. The reaction gave the \textit{exo} cycloadduct (\( \text{exo/endo} = 72:28 \) to \( 97:03 \)) in good to excellent enantioselectivity, however the catalytic activity was low and best yield of 70% was obtained with 10 mol\% of 4.51c.

Nevalainen et al. reported nitrone cycloaddition to \( \alpha,\beta \)-unsaturated aldehydes catalyzed by diphenyl prolinol 4.51d.\(^\text{32}\) Excellent enantioselectivity (up to 95\%) for the \textit{endo} cycloadducts (\( \text{endo/exo} = >92:08 \)) were obtained using 5-20 mol\% of the catalyst. Ogilvie et al. have developed a camphor-derived hydrazide 4.52 catalyst for \textit{exo} selective nitrone cycloaddition to \( \alpha,\beta \)-unsaturated aldehydes.\(^\text{33}\) This catalyst system gave modest diastereoselectivity and moderate to good enantioselectivity for \textit{exo} cycloadducts.

Organocatalyst for Enantioselective Nitrone Cycloadditions

Organocatalyzed nitrone cycloaddition to \( \alpha,\beta \)-unsaturated aldehydes previously reported utilize iminium type activation of \( \alpha,\beta \)-unsaturated aldehydes using
imidazolidinone-derived catalyst. Other proline-derived catalyst which are able to form similar iminium complexes with α,β-unsaturated aldehydes have also been thoroughly investigated. These reactions represent normal electron demand nitrone cycloadditions. However examples of organocatalyzed inverse electron demand nitrone cycloaddition are sparse. Organocatalysis using phosphoric acids have recently gained tremendous attention. Typical phosphoric acid catalyzed reactions have been limited to 1,2-addition to imines. However, Yamamoto et al. recently reported activation of nitrone using chiral phosphoric acid.\textsuperscript{34} 3,3'-BINOL derived phosphoramidite 4.53 was found to be an efficient catalyst for nitrone cycloaddition to ethyl vinyl ether 4.38 (Scheme 4.10). The cycloadducts formed are complementary to those reported by Jørgensen for exo selective nitrone cycloadditions to ethyl vinyl ether catalyzed by BINOL-aluminum as a chiral Lewis acid. The authors postulated that secondary interaction between the Brønsted-dipole complex and oxygen atom on the substrate is responsible for proper organization giving the endo cycloadduct. Reactions of N-aryl nitrones with ethyl vinyl ether furnishes endo cycloadduct in >88:12 diastereoselectivity with excellent enantioselectivity.

![Scheme 4.10. Organocatalyzed Inverse Electron Demand Nitrone Cycloaddition](image-url)
4.2.5. Nitrone Cycloaddition to Alkynes

Cycloaddition of nitrone to alkynes is significant since it would lead to the formation of 4-isoxazoline. Compounds bearing this 4-isoxazoline moiety serve as potential intermediates for the synthesis of other important nitrogen containing compounds. Therefore these compounds are highly sought after for their chemical and medicinal values. Nitrone cycloaddition to alkynes are usually non-selective and yield a mixture of regioisomers. Obtaining enantioselectivity in cycloaddition to alkynes is also difficult due to the linear geometry of the dipolarophile. Inomata et al. have developed a strategy for the construction of chiral 4-isoxazoline by addition of alkynyl zinc reagents to nitrones followed by cyclization.\(^{35}\)

Ishihara et al. have recently reported the first chiral Lewis acid catalyzed enantioselective and regioselective nitrone cycloaddition to alkynones (Scheme 4.11).\(^{36}\)

![Scheme 4.11. Lewis Acid Catalyzed Nitrone Cycloadditions to Alkynones](image)

In this example the \(\pi\)-cation interaction of the pendant aromatic group on the ligand with the Lewis acid is essential for imparting enantioselectivity. Excellent yield and enantioselectivity for the cycloadduct was obtained when \(\text{Cu(NTf}_2\text{)}_2/\text{4.57}\) was employed as
the chiral Lewis acid. The scope of nitrone as well as dipolarophiles was extensively investigated and the products were easily converted to β-lactams using standard transformations without loss of enantioselectivity.

4.3. Results and Discussions

In the previous sections we have seen that there has been tremendous development of Lewis acid catalyzed asymmetric nitrone cycloadditions to both electron rich as well as electron deficient olefins as acceptors. Yamamoto was the first to investigate nitrone cycloaddition to electron rich vinyl ethers catalyzed by chiral BINOL derived phosphoramides. However, there are no reports of Brønsted acid mediated 1,3-dipolar cycloaddition of nitrone to electron deficient olefins. First and foremost, dipolar cycloadditions catalyzed by Brønsted acid to electron deficient olefins are challenging since there is a possibility of a strong dipole-Brønsted acid interaction. Since these reactions involve interaction of the LUMO(dipolarophile)-HOMO(dipole), any coordination of the Brønsted acid with the dipole would fundamentally decrease electron density at the dipole. This would stabilize the HOMO(dipole) increasing the energy gap between LUMO (dipolarophile)-HOMO(dipole). Hence if this reaction has to proceed the interaction of the Brønsted acid with the substrate should be better than that with the dipole. The second challenging aspect would be the stability of the dipole to the reaction condition. At the beginning of this work we were not sure whether the nitrone would be stable in the presence of a strong Brønsted acid. Typically nitrones are prepared by the condensation of corresponding hydroxylamine with aromatic aldehydes by the elimination of one molecule of water. In the presence of moisture and an acid catalyst the reverse
reaction may be possible. Other issues of reactivity and control of stereochemical information also needed to be addressed.

In our previous study we had developed a chiral Brønsted acid catalyzed azomethine imine cycloaddition to α,β-unsaturated acyl imidazole. We had postulated that the basicity of the nitrogen atom of the imidazole ring would help preferential binding of the Brønsted acid with the substrate rather than the dipole. Also that a catalytic cycle would be operative provided the basicity of the cycloadduct was lower than the substrates. During the course of the study we were able to prove many of those postulates to be true. As an extension we wanted to investigate Brønsted acid catalyzed nitrone cycloaddition to α,β-unsaturated acyl imidazoles. The results of these studies are disclosed herein.

4.3.1. Optimization of Reaction Conditions

We began exploring the possibility of a Brønsted acid catalyzed nitrone cycloaddition to α,β-unsaturated acyl imidazole using 4.10a and N-phenyl nitrone 4.35a. This nitrone is known in the literature to be much more reactive than other N-alkyl substituted nitrones. In the absence of any catalyst the reaction of 4.10a with nitrone 4.35a did not proceed and no cycloadduct products were formed (Table 4.1, entry 1). This result was encouraging for us since a low or zero background reaction would suggest that generation of any product in the presence of a catalyst would be attributed to the action of the catalyst. Also if we were to provide appropriate shield of one face of the dipolarophile there was a possibility of obtaining enantioenriched products. It was further encouraging to see that in the presence of a Brønsted acid the same reaction gave very high yield of the cycloadduct 4.60a (Table 4.1, entry 2). This result would suggest that there was an
activation of the dipolarophile probably by the interaction of the Brønsted acid with the imidazole ring of the substrate. After analyzing the product we observed that the reaction gave only one diastereomer. Since both the endo and exo diastereomers have been previously reported in the literature, NMR studies led us to conclude that the diastereomer 4.60b was the exo isomer.

We have previously studied chiral BINOL-derived phosphoric acids for azomethine imine cycloaddition to α,β-unsaturated acyl imidazole. The considerable success that we achieved in that reaction helped us realize that the acidity of these phosphoric acids properly matched with the basicity of the imidazole ring. BINOL-derived phosphoric acids and phosphoramides 4.59a-e with various substituents at 3,3'-position on the BINOL ring were prepared by known methods and utilized in screening for reactivity as well as selectivity toward cycloaddition of nitrone 4.35a to acyl imidazole 4.10a. H8-BINOL derived phosphoric acid 4.59a (10 mol%) catalyzed dipolar cycloaddition of 4.10a with nitrone 4.11a gave the exo cycloadduct in 75% yield (Table 4.1, entry 3). This Brønsted acid was non-selective as the cycloadducts were obtained as a racemic mixture. Though the catalyst was non-selective however the fact that over 75% yield of the cycloadduct was obtained with 10 mol% catalyst loading suggested that catalysis was possible. Similarly, nitrone cycloaddition reactions catalyzed by 10 mol% of Brønsted acid 4.59b gave exclusively the exo cycloadduct in 67% yield while the enantiomeric excess was determined to be -33% (entry 4). The sign indicates that the opposite enantiomer to that obtained with other Brønsted acids used in this screen was obtained. Chiral Phosphoric acid 4.59c where R= 2,4,6-(iPr)3C6H2 also gave the same enantiomer of cycloadduct 4.60a in 42% enantiomeric excess and similar yield (entry 5). The best enantioselectivity of 80% for
cycloadduct 4.60a was obtained when chiral phosphoramidate 4.59d where R=9-anthracenyl was employed in 10 mol% loading (Table 4.1, entry 6).

Table 4.1. Optimization of Reaction Condition for Chiral Brønsted Acid Catalyzed Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bronsted acid</th>
<th>mol %</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>-</td>
<td>00</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>(PhO)2POOH</td>
<td>100</td>
<td>90</td>
<td>&gt;98:02</td>
<td>00</td>
</tr>
<tr>
<td>3</td>
<td>4.59a</td>
<td>10</td>
<td>75</td>
<td>&gt;98:02</td>
<td>-03</td>
</tr>
<tr>
<td>4</td>
<td>4.59b</td>
<td>10</td>
<td>67</td>
<td>&gt;98:02</td>
<td>-33</td>
</tr>
<tr>
<td>5</td>
<td>4.59c</td>
<td>10</td>
<td>63</td>
<td>&gt;98:02</td>
<td>-42</td>
</tr>
<tr>
<td>6</td>
<td>4.59d</td>
<td>10</td>
<td>95</td>
<td>&gt;98:02</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>4.59e</td>
<td>10</td>
<td>90</td>
<td>&gt;98:02</td>
<td>61</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.59d</td>
<td>10</td>
<td>54</td>
<td>&gt;98:02</td>
<td>79</td>
</tr>
<tr>
<td>9</td>
<td>4.59d</td>
<td>05</td>
<td>90</td>
<td>&gt;98:02</td>
<td>79</td>
</tr>
<tr>
<td>10</td>
<td>4.59d</td>
<td>15</td>
<td>97</td>
<td>&gt;98:02</td>
<td>78</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> Determine by <sup>1</sup>H NMR of crude reaction mixture. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> Reaction was done at -15 °C.

One important point of differentiation between the reactions catalyzed by chiral phosphoric acid and chiral phosphoramidate is that opposite enantiomers of the same cycloadduct are obtained when the two Brønsted acids are employed. Similar trend was also observed for Brønsted acid catalyzed azomethine imine cycloaddition to acyl amidazole 4.10a. At this point of time we do not have a reasonable explanation for the
change in face selectivity of the dipolarophile with different Brønsted acids. We further screened one more chiral Brønsted acid \textit{4.59e} for catalyzing nitro nitrone cycloaddition to acyl imidazole \textit{4.10a} (Table 4.1, entry 7). The reaction catalyzed by this Brønsted acid gave 90% yield of the \textit{exo} cycloadduct \textit{4.60a} with modest enantioselectivity (61%). Based on the enantioselectivity and yield for the cycloadduct \textit{4.60a} we believe that BINOL derived phosphoramid e \textit{4.59d} is the best catalyst for this transformation. We decided to evaluate the effect of temperature on yield and enantioselectivity of Brønsted acid catalyzed cycloaddition between \textit{4.10a} and nitrone \textit{4.35a}. Thus reactions carried out at -15 °C in the presence of 10 mol% chiral Brønsted acid \textit{4.59d} did not have any effect on enantioselectivity of the \textit{exo} cycloadduct (entry 8). However, the reactions were slow at lower temperature and cycloadduct \textit{4.60a} was obtained in 54% yield. Since, there was no further advantage in conducting the reactions at lower temperature we did not pursue more low temperature studies and most of the reactions were conducted at room temperature. We decided to study the effect of catalyst loading on reaction of \textit{4.10a} and \textit{4.35a}. Reducing the catalyst loading to 5 mol% did not have any appreciable impact and \textit{exo} cycloadduct \textit{4.60a} was obtained in 90% yield and 79% enantioselectivity (entry 9). In an attempt to improve enantioselectivity we decided to carry out reactions utilizing 15 mol% of chiral Brønsted acid. However this increase in catalyst loading did not produce any impact on enantioselectivity of the product as cycloadduct \textit{4.60a} was isolated in 97% yield and 78% enantiomeric excess (entry 10). After this initial screening of reaction conditions, we decided to use 10 mol% of catalyst \textit{4.59d} for further reactions at room temperature.
4.3.2. Effect of Solvent in Brønsted Acid-Mediated Nitrone Cycloaddition

After optimizing for chiral Brønsted acid, catalyst loading and reaction temperature in the cycloaddition of 4.10a with nitrone 4.35a, we decided to study the effect of solvent on reactivity and selectivity. Solvent may impact on the nature of the ion pair formed between the chiral Brønsted acid and the acyl imidazole substrate. A tighter ion pair formation could potentially translate to better shielding of the dipolarophile where as a loose ion pair could lead to erosion of stereochemistry by poor face shielding. The nature of ion pair may also have a profound impact on reactivity and hence on the chemical efficiency of the reaction.

The reaction of acyl imidazole 4.10a with nitrone 4.35a catalyzed by 10 mol% of 4.59d in trifluorotoluene gave the exo cycloadduct 4.60a in 83% yield and 74% enantiomeric excess (Table 4.2, entry 1). In contrast, reaction carried out in toluene as solvent gave similar yield and enantioselectivity for the exo cycloadduct 4.60a (Table 4.2, entry 2). Polar aprotic solvents such as acetonitrile can also be utilized as solvent for the same reaction. However, this did not produce significant improvement in enantioselectivity, as the exo cycloadduct was isolated in 64% enantiomeric excess (Table 4.2, entry 3). Chlorinated solvents such as dichloromethane and 1,2-dichloroethane performed much better than most of the solvents screened so far and the exo cycloadduct 4.60a was obtained in good yield and good enantioselectivity (compare entries 4 and 5). Polar protic solvents such as methanol can also be used for the cycloaddition and unfortunately the cycloadduct was obtained with much lower enantioselectivity (Table 4.2, entry 6). Finally, we have also investigated the use of 1,4-dioxane as solvent and the
reaction yielded the cycloadduct 4.60a in 92% yield and 86% enantiomeric excess (Table 4.2, entry 7). After screening various solvents for the cycloaddition it was evident that reactions carried out in chlorinated solvents and 1,4-dioxane gave slightly better enantioselectivity than those done in aromatic solvents such as toluene or 1,1,1-trifluorotoluene. Similarly, reaction in polar aprotic solvent such as acetonitrile were similar to reactions done in polar protic solvents such as methanol but inferior to those carried out in chlorinated solvents. After this brief study on the effect of solvent on chiral Brønsted acid mediated nitrone cycloaddition we decided to use dichloromethane as the solvent system for further investigation.

Table 4.2. Survey of Solvents for Nitrone Cycloaddition Catalyzed by Chiral Brønsted Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>exo ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trifluorotoluene</td>
<td>83</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Acetonitrile</td>
<td>81</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>1,2-Dichloroethane</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>Dichloromethane</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Methanol</td>
<td>77</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>1,4-Dioxane</td>
<td>92</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> Determined by chiral HPLC.
4.3.3. Survey of Nitrones

After optimization of reaction conditions we wanted to explore the scope of this chiral Brønsted acid catalyzed nitrone cycloaddition. We investigated the scope of the dipole for this reaction. Various nitrones were prepared by condensation of $N$-substituted hydroxylamine with aromatic aldehydes. Chiral Brønsted acid 4.59d catalyzed reaction of nitrone 4.35b synthesized by condensation of $N$-methyl hydroxylamine and benzaldehyde with acyl imidazole 4.10a gave selectively the exo cycloadduct 4.60b in 89% yield and 79% enantiomeric excess (Table 4.3, entry 2). Nitrone 4.35c prepared from $p$-halogenated benzaldehyde also performed well and cycloadduct 4.60c was isolated as a 97:03 mixture of exo and endo cycloadducts in >98% yield. The enantiomeric excess of the exo cycloadduct was determined to be 72% (entry 3).

Table 4.3. Evaluation of Scope of Nitrone for Brønsted Acid Catalyzed 1,3-Dipolar Cycloaddition Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrone</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
<th>exo/endo$^b$</th>
<th>exo ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.35a</td>
<td>Ph</td>
<td>Ph</td>
<td>4.60a</td>
<td>95</td>
<td>&gt;98:02</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>4.35b</td>
<td>Me</td>
<td>Ph</td>
<td>4.60b</td>
<td>89</td>
<td>&gt;98:02</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>4.35c</td>
<td>Ph</td>
<td>$p$-BrC$_6$H$_4$</td>
<td>4.60c</td>
<td>&gt;98</td>
<td>97:03</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>4.35d</td>
<td>Ph</td>
<td>$p$-NO$_2$C$_6$H$_4$</td>
<td>4.60d</td>
<td>96</td>
<td>96:04</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>4.35e</td>
<td>Ph</td>
<td>$p$-CNC$_6$H$_4$</td>
<td>4.60e</td>
<td>92</td>
<td>&gt;98:02</td>
<td>80</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after column chromatography. $^b$ Determine by $^1$H NMR of crude reaction mixture. $^c$ Determined by chiral HPLC.
An Electron deficient nitrone prepared from \( p \)-nitro benzaldehyde also reacted under Brønsted acid condition to yield a 96:04 mixture of \textit{exo} and \textit{endo} cycloadducts in 96\% yield and 77\% enantiomeric excess for the \textit{exo} isomer (entry 4). Similarly, reaction of nitrone prepared from \( p \)-cyano benzaldehyde gave cycloadduct 4.60e in 92\% yield and 80\% enantioselectivity (entry 5).

### 4.3.4. Evaluation of Scope of \( \beta \)-Substituent on \( \alpha,\beta \)-Unsaturated Acyl Imidazole

After investigating the scope of nitrones for chiral Brønsted acid mediated cycloaddition to acyl imidazoles, we decided to study the scope of the \( \beta \)-substituent on \( \alpha,\beta \)-unsaturated acyl imidazole.

**Table 4.4. Evaluation of Scope of \( \beta \)-Substituent on \( \alpha,\beta \)-Unsaturated Acyl Imidazole**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>( \text{exo ee} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (4.10a)</td>
<td>4.60a</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Et (4.10b)</td>
<td>4.60g</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>( i-\text{Pr} ) (4.10c)</td>
<td>4.60h</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>-CH_2OBn (4.10d)</td>
<td>4.60i</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>-CH_2CH_2Ph (4.10e)</td>
<td>4.60j</td>
<td>&gt;98</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after column chromatography. \(^b\) Determined by chiral HPLC.
Nitrone cycloaddition reactions catalyzed by 10 mol% chiral BINOL phosphoramid e 4.59d with acyl imidazole 4.10b where R = Et, gave exclusively the exo cycloadduct 4.60g in 89% yield and 90% enantiomeric excess (Table 4.4, entry 2). Reaction with sterically hindered substrate such as 4.10c where R = tPr gave the exo cycloadduct 4.60h in good yield and excellent enantioselectivity (entry 3). Acyl imidazole containing alkoxy methyl substituent at the β-position was also prepared and utilized as a dipolarophile. Thus reaction of acyl imidazole 4.10d with nitrone 4.35a under chiral Bronsted acid catalysis gave selectively the exo cycloadduct 4.60i in 84% yield and 87% enantiomeric excess (entry 4). Finally, reaction of acyl imidazole 4.10e where R = -CH₂CH₂Ph was also reactive under chiral Bronsted acid catalysis and furnished the exo cycloadduct 4.60j in near quantitative yield and 81% enantiomeric excess (entry 5).

4.3.5. Origin of Diastereoselectivity
To explain the origin of diastereoselectivity in Bronsted acid catalyzed nitrone cycloaddition to β-substituted-α,β-unsaturated acyl imidazole we once again turn our attention to the rotamer geometry of the dipolarophile in solution, the nature of the chiral Bronsted complex with the dipolarophile and to approach of the dipole to this complex.

4.61 s-cis (syn)   4.62 s-cis (anti)
Figure 4.5. Rotamer Geometries of Acyl Imidazole
As discussed in chapter 3, there are various rotamers of the dipolarophile and due to various steric interactions we presume that only two would be more reasonable. Thus rotamers 4.61 with an s-cis (syn) configuration and 4.62 with an s-cis (anti) configuration would be the two most prevalent in the solution and following the protonation of the N-3 nitrogen of the imidazole would react with the dipole to give the desired cycloadducts (Figure 4.5).

Crystal structure of the chiral Brønsted acid with the substrate revealed that the substrate might exist as an s-cis (anti) rotamer (Figure 4.6). Crystal structure of this complex also reveals that the substrate fits tightly in the chiral pocket of the Brønsted acid and the reaction center is shielded by the flat 9-anthracenyl groups at 3,3'-position on the BINOL ring. The protonated imidazole is seen to be hydrogen bonded with the oxygen atom of the phosphoryl group.

Figure 4.6. Crystal Structure and Pictorial Representation of Chiral Brønsted Acid-Substrate Complex
Based on this crystal structure we were able to draw transition state model to explain the approach of the dipole to the catalyst substrate complex giving rise to either *exo* or *endo* cycloadducts (Figure 4.7).

![Transition State Models](image-url)

Figure 4.7. Transition State Models to Explain Diastereoselectivity

In case of the *endo* approach of the dipole to the dipolarophiles, steric interaction between the methyl group on the N-1 position of the imidazole and the group R on the dipole may exist. Due to these steric interactions the *endo* approach of the dipole is difficult and hence the *endo* diastereomer 4.65 is not formed. When the dipole approaches the substrate complex in an *exo* fashion, the formation of *exo* cycloadduct 4.66 will depend on
the nature of steric interaction between the \textit{N}-1 methyl group on the imidazole and the hydrogen atom of the dipole. This interaction is significantly less compared to that between the methyl group on the imidazole and the R group on the dipole for the \textit{endo} approach of the dipole. Hence we believe that the reduced steric interaction in the \textit{exo} transition state compared to \textit{endo} transition state is responsible for the high \textit{exo} selectivity observed in the product obtained in chiral Brønsted acid catalyzed nitroncycloaddition.

The enantioselectivity of the product is due to the excellent face shielding of the dipolarophile by the 9-anthracenyl groups of the catalyst. We have seen in chapter 3 that the same catalyst was most suited for highly enantioselective azomethine imine cycloaddition to acyl imidazole.

4.4. Conclusion

In conclusion we have developed chiral Brønsted acid catalyzed nitroncycloadditions to electron deficient olefins. We have previously reported similar azomethine imine cycloaddition to acyl imidazole catalyzed by chiral Brønsted acid. During which the ability of Brønsted acid to form ion pair with acyl imidazoles was first demonstrated. This example represents the first nitroncycloaddition using the same concept. The cycloadducts isoxazolines are of tremendous synthetic utility as they can be converted into amino acid derivatives.

Excellent enantioselectivities were obtained for reactions catalyzed by phosphoramid4.59d. At the same time the reactions were highly diastereoselective as the \textit{exo} adducts were exclusively isolated. Broad scope of substrate is another hallmark of this
reaction. Our future direction would be to explore this methodology for the construction of sterically hindered chiral heterocycles.

4.5. Experimental

**General:** Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Toluene was distilled from calcium hydride under nitrogen prior to use. Anhydrous 1,1,1-trifluorotoluene, 1,2-dichloroethane, methanol and 1,4-dioxane were purchased from Sigma Aldrich. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO™ CombiFlash Companion with AnaLogix™ RS-4 columns. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected. $^1$H-NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual CDCl$_3$ (7.26 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. $^{13}$C-NMR was recorded on Varian Unity/Inova-500 NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300 (75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl$_3$ (77.0) as an internal standard. $^{19}$F-NMR was recorded on Varian Varian Mercury-300 (282 MHz) spectrometers with trifluorotoluene (-64 ppm) CDCl$_3$ as an external standard. $^{31}$P-NMR was recorded on
Varian Varian Mercury-300 (121 MHz) spectrometers with H$_3$PO$_4$ (0 ppm) in CDCl$_3$ as an external standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower workstation. Rotations were recorded on a JASCO-DIP-370 instrument. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High Resolution Mass Spectra (HRMS) (ESI) were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

**Materials and Methods:** Diphenyl phosphate was purchased from Aldrich. N,α-Diphenyl nitrone 4.35a was purchased from Acros. β-Substituted α,β-acyl imidazoles 4.10a-e were prepared according to literature procedures.$^{37}$ Chiral Bronsted acid 4.59a, 4.59b, 4.59c and 4.59e were prepared from known literature procedures.$^{38}$ Chiral Brønsted acid 4.59d was prepared by a procedure previously reported in our laboratory.

4.5.1. Representative Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Nitrones with α,β-Unsaturated 2-acyl Imidazoles Catalyzed by Chiral Brønsted Acid

To a 6 dram vial containing α,β-unsaturated 2-acyl imidazole (0.1 mmol) and Chiral Brønsted acid, CH$_2$Cl$_2$ (2 mL) was added. The vial was stirred for 1 h. To this solution, nitro (0.15 mmol) was finally added. The reaction was stirred at room temperature until the dipolarophile was consumed (TLC). The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogiX RS-4 columns. The exo/endo ratios were determined by $^1$H NMR spectroscopy prior to
chromatography and enantioselectivities were measure by HPLC analysis after chromatography.

(1-Methyl-1H-imidazol-2-yl)((3RS,4RS,5SR)-5-methyl-2,3-diphenyloxazolidin-4-yl)methanone (4.60a):

Foamy Solid, $[\alpha]_D^{25}$ -55.8 (c 1.2, CHCl$_3$), (exo/endo= >98:02); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.45 (d, $J$ = 6.0 Hz, 3H), 3.35 (s, 3H), 4.65 (t, $J$ = 11.7 Hz, 1H), 4.99 (dt, $J$ = 11.7, 6.03 Hz, 1H), 5.09 (d, $J$ = 11.7 Hz, 1H), 6.82 (s, 1H), 6.83-6.94 (m, 3H), 7.08-7.17 (m, 8H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 17.8, 35.3, 62.0, 73.0, 74.2, 115.7, 122.0, 126.8, 127.7, 128.0, 128.7, 129.3, 138.8, 144.0, 150.5, 188.5; IR (KBr) 3109, 3038, 2966, 2931, 1673, 1490, 1417, 1269, 1157, 1039, 981, 849 cm$^{-1}$. HRMS calcd for C$_{21}$H$_{21}$N$_3$O$_2$Na$: 370.1526; Found: 370.1530.

Entry 1, Table 4.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 27.5 min (exo minor) $t_R$ 30.9 min (exo major) [Chiralpak AD-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 99:1, 1.0 mL/ min] as 80% ee for the exo cycloadduct

((3RS,4RS,5SR)-5-Ethyl-2,3-diphenyloxazolidin-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (4.60g)

Colorless solid, mp = 72-75 °C, $[\alpha]_D^{25}$ -81.1 (c 1.1, CHCl$_3$), (exo/endo$>$98:02); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.07 (t, $J$ = 7.4 Hz, 3H), 1.68-1.89 (m, 2H), 3.35 (s, 3H), 4.75 (t, $J$ = 10.0 Hz, 1H), 4.82-4.83 (m, 1H), 5.09 (d, $J$ = 10.0 Hz, 1H), 6.82 (s, 1H), 6.85-6.89 (m, 1H), 6.93-6.95 (m, 2H), 7.08-7.16 (m, 8H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 10.9, 26.5, 35.3, 60.4, 72.7, 79.4, 115.8, 122.0, 126.9, 127.7, 128.0, 128.1,
128.7, 129.3, 138.5, 144.0, 150.4, 188.6; IR (KBr) 3029, 2965, 2935, 2877, 1676, 1597, 1490, 1453, 1412, 1289, 1259, 1155, 1122, 1077, 1033, 984, 916, 849 cm\(^{-1}\). HRMS calcd for C\(_{22}\)H\(_{23}\)N\(_3\)O\(_2\)Na\(^{+}\): 384.1682; Found: 384.1660.

**Entry 2, Table 4.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_R\) 32.1 min (exo minor) \(t_R\) 50.7 min (exo major) [Chiralpak OJ-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Ethanol, 98:02, 0.5 mL/ min] as 90% ee for the exo cycloadduct.

\[
((3RS,4RS,5SR)-5-Isopropyl-2,3-diphenyloxazolidin-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (4.12h):
\]

Foamy solid, \([\alpha]_D^{25}\) -111.9 (c 0.75, CHCl\(_3\)), (exo/endo= >98:02); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 0.89 (d, \(J = 6.7\) Hz, 3H), 1.52, (d, \(J = 6.7\) Hz, 3H), 1.91-2.03 (m, 1H), 3.35 (s, 3H), 4.66 (t, \(J = 8.7\) Hz, 1H), 4.93 (t, \(J = 8.7\) Hz, 1H), 5.04 (d, \(J = 10.2\) Hz, 1H), 6.82 (s, 1H), 6.85-6.89 (m, 1H), 6.93-6.96 (m, 2H), 7.07-7.15 (m, 8H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \(\delta\) 19.3, 19.8, 32.2, 35.4, 58.8, 72.8, 83.3, 116.3, 122.1, 126.9, 127.6, 128.0, 128.2, 128.6, 129.2, 138.2, 143.9, 150.1, 188.7; IR (KBr) 2960, 2873, 1678, 1598, 1490, 1412, 1290, 1260, 1155, 1077, 1032, 915, 841, 776, 742, 700 cm\(^{-1}\). HRMS calcd for C\(_{23}\)H\(_{25}\)N\(_3\)O\(_2\)Na\(^{+}\): 398.1839; Found: 393.2103.

**Entry 3, Table 4.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_R\) 19.7 min (exo minor) \(t_R\) 27.8 min (exo major) [Chiralpak OJ-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Ethanol, 98:02, 0.5 mL/ min] as 96% ee for the exo cycloadduct.
(3RS,4RS,5RS)-5-(Benzyloxymethyl)-2,3-diphenylisoxazolidin-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (4.60i):

Foamy solid, $[\alpha]_{D}^{25} -34.4$ (c 1.0, CHCl$_3$), (exo/endo $>98:02$); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 2.02-2.17 (m, 2H), 2.79-2.85 (m, 1H), 2.94-3.00 (m, 1H), 3.41 (s, 3H), 4.83 (t, $J = 9.9$ Hz, 1H), 5.0 (m, 1H), 5.15 (d, $J = 9.9$ Hz, 1H), 6.86 (s, 1H), 6.90-6.93 (m, 1H), 6.97-6.99 (m, 2H), 7.12-7.30 (m, 8H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 33.0, 35.2, 35.3, 60.7, 72.6, 76.9, 115.8, 122.0, 126.1, 126.9, 127.7, 128.1, 128.2, 128.6, 128.7, 129.3, 138.4, 141.8, 143.9, 150.3, 188.4; IR (KBr) 3061, 3029, 2859, 1675, 1597, 1489, 1453, 1411, 1364, 1289, 1259, 1098, 1028, 916, 854, 777, 752, 739, 697 cm$^{-1}$. HRMS calcd for C$_{28}$H$_{27}$N$_3$O$_3$Na$: 476.1945; Found: 476.1943.

**Entry 4, Table 4.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 19.3 min (exo minor) $t_R$ 21.7 min (exo major) [Chiralpak IC (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Isopropanol, 90:10, 1.0 mL/ min] as 87% ee for the exo cycloadduct.

(1-Methyl-1H-imidazol-2-yl)(3RS,4RS,5SR)-5-phenethyl-2,3-diphenylisoxazolidin-4-yl)methanone (4.60j):

Foamy solid, $[\alpha]_{D}^{25} -38.5$ (c 1.0, CHCl$_3$), (exo/endo $>98:02$); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 3.43 (s, 3H), 3.74-3.80 (m, 1H), 4.64 (s, 2H), 4.95 (t, $J = 9.3$ Hz, 1H), 5.17-5.20 (m, 1H), 5.26 (d, $J = 9.3$ Hz, 1H), 6.87 (s, 1H), 6.91 (t, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 7.6$Hz, 2H), 7.12-7.19 (m, 7H), 7.30-7.35 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 33.0, 35.2, 35.3, 60.7, 72.6, 76.9, 115.8, 122.0, 126.1, 126.9, 127.7, 128.1, 128.2, 128.6, 128.7, 129.3, 138.4, 141.8, 143.9, 150.3, 188.4; IR (KBr) 3061, 3029, 2859, 1675, 1597, 1489, 1453, 1411, 1364, 1289, 1259, 1098, 1028, 916, 854, 777, 752, 739, 697 cm$^{-1}$. HRMS calcd for C$_{28}$H$_{27}$N$_3$O$_3$Na$: 476.1945; Found: 476.1943.
MHz); δ 35.4, 57.5, 70.3, 72.1, 73.5, 76.9, 115.8, 122.0, 126.9, 127.7, 127.9, 128.0, 128.1, 128.5, 128.7, 129.4, 138.1, 138.3, 143.7, 150.3, 187.6; IR (KBr) 3060, 3026, 2926, 1675, 1598, 1490, 1453, 1412, 1289, 1260, 1155, 1076, 1030, 959, 916, 856, 777, 739, 699 cm⁻¹. HRMS calcd for C₂₈H₂₇N₃O₂Na⁺: 460.1995; Found: 460.1994.

**Entry 5, Table 4.4:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 6.4 min (exo minor) tᵣ 7.3 min (exo major) [Chiralpak IC (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Isopropanol, 90:10, 1.0 mL/ min] as 81% ee for the exo cycloadduct.

((3RS,4RS,5SR)-2,5-Dimethyl-3-phenylisoxazolidin-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (4.60b):

Oil, [α]ᵢ deceased 116.5 (c 1.0, CHCl₃), (exo/endo= >98:02); ¹H NMR (CDCl₃, 400 MHz); δ 1.40 (d, J = 6.1 Hz, 3H), 2.66 (s, 3H), 3.42 (s, 3H), 4.13 (d, J = 11.1 Hz, 1H), 4.68 (dd, J = 11.1, 8.1 Hz, 1H), 4.85 (ddd, J = 11.1, 8.1, 6.1 Hz, 1H), 6.74 (s, 1H), 7.01 (s, 1H), 7.05-7.13 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz); δ 18.6, 35.4, 43.8, 62.2, 74.4, 76.7, 126.6, 127.6, 127.7, 128.6, 128.9, 136.9, 144.0, 189.9; IR (NaCl) 2952, 2919, 2868, 1670, 1492, 1415, 1379, 1288, 1119, 1075, 866 cm⁻¹. HRMS C₁₆H₁₉N₃O₂Na⁺: 308.1369; Found: 308.1379.

**Entry 2, Table 4.3:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tᵣ 19.8 min (exo minor) tᵣ 38.8 min (exo major) [Chiralpak AD-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Isopropanol, 98:02, 1.0 mL/ min] as 79% ee for the exo cycloadduct.
((3RS,4RS,5SR)-3-(4-Bromophenyl)-5-methyl-2-phenylisoxazolidin-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (4.60c):

Foamy solid, $[\alpha]_{D}^{25}$ -18.8 (c 1.0, CHCl$_3$), (exo/endo = 97:03); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.43 (d, $J$ = 6.0 Hz, 3H), 3.46 (s, 3H), 4.63 (t, $J$ = 9.9 Hz, 1H), 4.91-4.98 (m, 1H), 5.07 (d, $J$ = 9.9 Hz, 1H), 6.87-6.91 (m, 4H), 7.01-7.03 (m, 2H), 7.09 (s, 1H), 7.13-7.17 (m, 2H), 7.21-7.24 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz); 17.9, 35.4, 61.9, 72.4, 74.2, 115.8, 121.7, 122.2, 127.1, 128.8, 129.5, 129.8, 131.1, 137.9, 143.8, 150.2, 188.2; IR (KBr); 3107, 2974, 2929, 1673, 1596, 1506, 1488, 1455, 1412, 1270, 1071, 1010, 853, 751 cm$^{-1}$. HRMS; C$_{21}$H$_{20}$BrN$_3$O$_2$Na$^+$: 448.0631; Found: 448.0612.

Entry 3, Table 4.3: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 15.2 min (exo major) $t_R$ 19.4 min (exo minor) [Chiralpak OD-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.)] Hexane: Isopropanol, 96:04, 0.5 mL/min] as 72% ee for the exo cycloadduct.

(1-Methyl-1H-imidazol-2-yl)((3RS,4RS,5SR)-5-methyl-3-(4-nitrophenyl)-2-phenylisoxazolidin-4-yl)methanone (4.60d):

Oil, $[\alpha]_{D}^{25}$ 2.8 (c 1.0, CHCl$_3$), (exo/endo = 96:04); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.46 (d, $J$ = 6.0 Hz, 3H), 3.53 (s, 3H), 4.70 (t, $J$ = 9.9 Hz, 1H), 4.96, (ddd, $J$ = 15.0, 12.0, 6.0 Hz, 1H), 5.28 (d, $J$ = 9.9 Hz, 1H), 6.90-6.94 (m, 4H), 7.14-7.20 (m, 3H), 7.36-7.39 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz); 18.0, 35.7, 61.9, 72.4, 74.7, 115.8, 122.6, 123.2, 127.6, 128.9, 129.1, 129.2, 129.8, 143.4, 146.3, 147.4, 150.0, 187.4; IR (KBr); 3108, 2976,
2931, 1672, 1597, 1521, 1264, 1220, 1156, 1109, 1032, 890, 775, 694 cm$^{-1}$. HRMS; C$_{21}$H$_{20}$N$_4$O$_3$Na$^+$: 415.1377; Found: 415.1391.

**Entry 4, Table 4.3:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 18.0 min (exo major) $t_R$ 27.8 min (exo minor) [Chiralpak OD-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Isopropanol, 96:04, 1.0 mL/min] as 77% ee for the exo cycloadduct.

![4-((3RS,4RS,5SR)-5-Methyl-4-(1-methyl-1H-imidazole-2-carbonyl)-2-phenylisoxazolidin-3-yl)benzonitrile (4.60e)](image)

**4-((3RS,4RS,5SR)-5-Methyl-4-(1-methyl-1H-imidazole-2-carbonyl)-2-phenylisoxazolidin-3-yl)benzonitrile (4.60e)**

Colorless solid, mp = 160-165 °C, $[\alpha]_D^{25}$ -1.3 (c 1.15, CHCl$_3$), (exo/endo= >98:02); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.43 (d, $J$ = 6.0 Hz, 3H), 3.50 (s, 3H), 4.67 (t, $J$ = 9.7 Hz, 1H), 4.93 (ddd, $J$ = 15.5, 12.1, 6.0 Hz, 1H), 5.19 (d, $J$ = 9.7 Hz, 1H), 6.87-6.92 (m, 4H), 7.11 (s, 1H), 7.16 (t, $J$ = 7.6 Hz, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.39 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz); 18.0, 35.7, 61.9, 72.4, 74.7, 115.8, 122.6, 127.6, 128.9, 129.1, 129.2, 129.8, 143.4, 146.3, 147.4, 150.0, 187.4; IR (KBr); 2974, 2927, 2226, 1674, 1653, 1594, 1506, 1410, 1387, 1358, 1150, 1022, 833, 790, 765, 667 cm$^{-1}$. HRMS; C$_{22}$H$_{26}$N$_4$O$_3$Na$^+$: 395.1478; Found: 395.1476.

**Entry 5, Table 4.3:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 18.7 min (exo major) $t_R$ 28.2 min (exo minor) [Chiralpak OD-H (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane: Isopropanol, 96:04, 1.0 mL/min] as 80% ee for the exo cycloadduct.
4.6. References


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(22) Asymmetric 1,3-Dipolar Cycloadditions of Nitrone and Methacrolein Catalyzed by
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(23) 6,6'-Substituent Effect of BINOL in bis-Titanium Chiral Lewis Acid Catalyzed 1,3-Dipolar Cycloaddition of Nitrones. Hashimoto, T.; Omote, M.; Maruoka, K. *Org. Biomol. Chem.* **2008**, *6*, 2263-2265.


CHAPTER 5.

HIGHLY ENANTIO- AND DIASTEREOSELECTIVE NITRONE CYCLOADDITION FOR THE CONSTRUCTION OF CHIRAL QUATERNARY CENTERS

5.1. Introduction

The construction of chiral complex molecules continues to be a challenge for organic chemists all over the world. Numerous methods have been developed which aid the formation of these chiral molecules. 1,3-Dipolar cycloaddition is one such tool available to an organic chemist, which results in the construction of chiral five membered heterocycles. One of the key features of dipolar cycloaddition is the ability to install multiple stereocenters in a single operation. Also important is the range of substituents that can be incorporated which yields a highly functionalized heterocycles in a single operation. Thus the ability to construct highly functionalized chiral heterocycles makes dipolar cycloaddition reaction one of the premier methods in organic synthesis and there are very few reactions that can match its versatility. For these reasons there has been a tremendous interest in the development of various approaches towards asymmetric dipolar cycloaddition. Our laboratory has been over the years a key contributor towards the development of asymmetric dipolar cycloadditions. We have previously reported elegant examples of chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of nitrone, nitrile oxides, nitrile imines, and other such dipoles to electron deficient olefins for the construction of chiral nitrogen containing heterocycles. Despite these rapid advances in...
asymmetric nitrone cycloaddition to electron deficient olefins we believe that there are questions, which still remain unanswered.

Most of the available literature on asymmetric nitrone cycloaddition to electron deficient olefins deals with reactions to β-substituted olefins leading to the formation of three contiguous stereocenters. Nitrone cycloadditions to β,β-disubstituted olefins or α,α-disubstituted olefins which lead to the formation of a quaternary stereocenter is a relatively challenging reaction and there are only handful examples of such transformations in the literature. In this chapter we will provide a solution for the question of asymmetric construction of quaternary chiral centers during cycloaddition.

5.2. Examples of Construction of Quaternary Centers by Cycloaddition

In this section we will discuss some examples of asymmetric nitrone cycloaddition for the construction of chiral quaternary centers. Cycloadditions to α-substituted acroleins has been the method of choice for the construction of chiral quaternary centers. These reactions have been possible due to the development of new single point binding chiral Lewis acids for the activation of the carbonyl carbon of aldehydes. Kündig et al. reported the first asymmetric nitrone cycloaddition to α,β-unsaturated aldehydes using a chiral ruthenium catalyst (Scheme 5.1). The authors postulated that a highly tuned aldehyde selective chiral Lewis acid would be able to discriminate between an aldehyde and a nitrone or would favor coordination of the aldehydes or bind with the nitrones in a readily reversible fashion. Catalyst 5.3 was prepared and initial NMR studies indicated that in solution a 7:3 ratio of chiral Lewis acid/aldehyde complex and chiral Lewis acid/nitrone complex was formed. Encouraged by these studies they tried reaction of various α,β-
unsaturated aldehydes with nitrones. Cycloaddition of methacrolein 5.1 with N-phenyl nitrone 5.2 gave a >60:40 ratio of \textit{endo} isomer 5.4 and \textit{endo} isomer 5.5 in good enantioselectivity. Several groups have reported the design of catalysts, which would catalyze similar transformation for the construction of chiral quaternary center.

Carmona et al. have reported on the development of an Ir(II) based catalyst 5.6 for asymmetric nitrone cycloaddition to methacrolein.$^{5,6}$ The reactions with this catalyst occur with perfect \textit{endo} selectivity and yield cycloadducts in excellent enantiomeric excess.

![Scheme 5.1. Example of Nitrone Cycloaddition to Methacrolein](image)

Kanemasa et al. reported the development of a unique catalyst design 5.7 for nitrone cycloaddition to \(\alpha\)-substituted acroleins (Figure 5.1).$^{7}$ Kündig and Carmona’s strategies have relied on preferential binding of dipolarophiles to Lewis acids. Kanemasa has developed aluminum phenoxide based Lewis acid 5.7 which prevents binding of the dipole to the Lewis acid by utilizing steric hindrance of the phenyl ring around the Lewis acid. Bulky group on the nitrogen atom of the nitrone was essential for the success of this catalyst. Maruoka et al. developed a bis-Ti(IV) oxide based Lewis acid 5.8 for highly \textit{endo} and enantioselective nitrone cycloaddition to \(\alpha\)-substituted acroleins.$^{8}$ Yamada et al. have reported highly \textit{endo} and enantioselective nitrone cycloaddition to cyclic enals for the
construction of chiral quaternary centers using β-ketoiminato cationic cobalt(III) complexes 5.9.\(^9\)

The previous examples utilized α-substituted acroleins as acceptors for Lewis acid catalyzed nitrone cycloaddition for the construction of chiral quaternary stereocenters. There are no reports of nitrone cycloadditions to the more traditional imide type substrates toward the construction of quaternary stereocenters. We were the first to report nitrone cycloaddition to α,β-substituted acroloyl imides 5.10 catalyzed by chiral Mg(II) Lewis acid for the construction of chiral heterocycles containing a quaternary stereocenter.

![Figure 5.1. Design of Ligands for Enantioselective Nitrone Cycloaddition](image)

The reaction yielded exo cycloadduct in good yield and excellent enantioselectivity (Scheme 5.2).\(^{10}\) The substrate scope of this reaction for α-substituent is limited as in most cases R\(^1\) could only be methyl.
Scheme 5.2. Example of Chiral Mg(II) Catalyzed Nitrone Cycloaddition

As seen from the previous discussion most of the reported examples for the construction of chiral quaternary centers using nitrone cycloaddition utilized α-substituted acrolein or its derivatives as acceptors. One of the benefits of this substrate is that the β-carbon in most cases is unsubstituted and this translates to a decreased steric congestion around the dipolarophile and hence makes it more reactive. For the same reason nitrone cycloaddition to β,β-disubstituted α,β-unsaturated carbonyl compounds have not been reported due to the greater steric congestion around the β-carbon atom of the acceptor, which severely hampers the approach of the dipole towards the reaction center. We surmised that proper electronic activation of the β-carbon atom of a β,β-disubstituted α,β-unsaturated carbonyl compound may help override the steric congestion at this position and thus making the substrate amenable towards reaction with suitable dipoles. For this reason we set upon the synthesis of dipolarophiles containing β-trifluoromethyl group as the inductive effect of the three fluorine atoms of this group would sufficiently activate the β-carbon of the α,β-unsaturated carbonyl compound (Figure 5.2). And even though sterically trifluoromethyl group is slightly bigger than a methyl group, the improved electronic activation would impart higher reactivity for the substrate. The incorporation of fluorine atoms will also enable us in the synthesis chiral fluorinated heterocycles, which are of
biological significance. In the next section we will discuss the importance of fluorinated organic molecules.

![Chemical Structures](image)

**Figure 5.2. Rationale for Activation of Substrates due to the presence of CF$_3$ groups**

### 5.3. Significance of Fluorinated Organic Molecules

Fluoroorganic chemistry has generated considerable interest in recent years. This is due to the tremendous application of fluorinated organic molecules in organic, agricultural, medicinal, and material chemistry fields. Fluorine has an intermediate size between hydrogen and oxygen. The carbon-fluorine bond lengths are also slightly longer than carbon-hydrogen bond but smaller than carbon-oxygen bonds. However, the bond strength of carbon-fluorine bond is greater than that of carbon-hydrogen or carbon-oxygen bond. Thus, a replacement of a hydrogen atom with fluorine does not result in significant changes in size of the organic molecule. However, due to the electronegativity of the fluorine atom, fluorinated organic molecules may participate in hydrogen bonding analogous to those found between oxygen or nitrogen with hydrogen. This significantly alters the lipophilicity of fluorinated organic molecules compared to those devoid of fluorine. This feature of fluorinated organic molecules is particularly important in the field of biochemistry, which has furthered the application of fluorinated molecules tremendously (Figure 5.3).
Fluorinated organic molecules are found in relatively low abundance in natural products. Hence therapeutics containing fluorine atoms are processed as xenobiotics when they are encountered in the biological system.
5.4. Approaches Towards Synthesis of Fluorinated Organic Molecules

Fluorination of organic compounds is classified into those that involve electrophilic incorporation of fluorine or those that proceed by a nucleophilic attack of a fluoride anion. The use of fluorinated synthons is also an important strategy that is extensively used for the synthesis of fluorinated organic molecules. Electrophilic fluorinations typically involve the transfer of “F⁺” to a suitable acceptor and are widely used for the synthesis of α-fluoro carbonyl compounds. Reagents such as selectfluor, N-fluoropyridinium salts and N-fluorobenzene sulfonimide are commercially available, stable, convenient to handle, and are a good source of electrophilic fluorine (Figure 5.4).\(^{11}\)

---

**Examples of electrophilic fluorinating reagents**

- **Selectfluor**
- **N-fluoropyridinium salts**
- **N-fluorobenzene sulfonimide**

**Examples of nucleophilic fluorinating reagents**

- (Diethylamino)sulfur trifluoride
- Pyridinium poly(hydrogen fluoride)
- Tetrabutyl ammonium fluoride

Figure 5.4. Examples of Electrophilic and Nucleophilic Fluorinating Reagents

Nucleophilic fluorination utilizes addition of fluoride anion and is another way to incorporate fluorine into organic molecules. Reagents such as (diethylamino)sulfur trifluoride, pyridinium poly hydrogen fluoride, and tetrabutylammonium fluoride are
typically employed for nucleophilic fluorination. Several reviews highlighting application of electrophilic and nucleophilic fluorination of organic molecules have been reported and will not be discussed here.\textsuperscript{12}

The importance of fluorinated heterocycles in a variety of disciplines necessitates the development of novel and efficient strategies for the construction of chiral fluorinated heterocycles. Several groups have reported achiral nitrone cycloaddition to fluorinated dipolarophiles. Delpont et al have reported one of the earliest nitrone cycloaddition to a fluorinated dipolarophile.\textsuperscript{13} In this example $\alpha$-trifluoromethyl styrene $5.31$ reacted with $N$-methyl phenyl nitrone $5.30$ under microwave heating to yield mixtures of \textit{exo} and \textit{endo} cycloadducts ($5.32$ and $5.33$) in excellent yield (Scheme 5.3).

\begin{equation}
\begin{array}{c}
\text{Me}^+\text{Ph} \quad + \quad \text{PhCF}_3
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Nitrone} \quad \text{Dipolarophile}
\end{array}
\end{equation}

Scheme 5.3. Example of Nitrone Cycloaddition to a Fluorinated Dipolarophile

Makosza et al. have recently reported nitrone cycloaddition to fluorinated propenes towards the synthesis of fluorinated $\beta$-lactams.\textsuperscript{14} Cycloaddition of penta and hexafluorinated propenes $5.35$ to nitrones gave highly fluorinated isoxazolidines $5.36$ which were converted to $\beta$-lactams using reported protocols (Scheme 5.4).
Fluorinated nitro olefins represent a class of highly reactive dipolarophiles that can be utilized for the synthesis of highly functionalized chiral fluorinated heterocycles. Zanda et al. have reported the use of fluorinated nitro olefins for nitrone cycloadditions.\textsuperscript{15} β-trifluoromethyl nitro alkene reacted smoothly with a suitable nitrone to yield the \textit{exo} cycloadduct in good yield (Scheme 5.5).

5.5. Results and Discussions

The previous sections detailed the significance of fluorinated organic molecules in organic chemistry. At the present time there are no examples of the synthesis of chiral fluorinated heterocycles using fluorinated dipolarophiles via dipolar cycloaddition. This provided us a motivation for pursuing asymmetric nitrone cycloaddition to fluorinated dipolarophiles towards the construction of chiral fluorinated heterocycles. We also
envisioned that incorporation of fluorinated groups on the dipolarophile would make it more reactive than the corresponding non-fluorinated ones due to the activating effect of the fluorine atoms. This would imply that construction of more challenging stereocenters would be feasible. In chapter 3 we had shown that chiral BINOL derived phosphoramides fared much better than Lewis acids for the activation of α,β-unsaturated acyl imidazole towards azomethine imine cycloadditions. In chapter 4 we had shown that the same mode of activation could also be utilized for nitrone cycloaddition to the same acceptors for the construction of chiral isoxazolidines. We realized that we could construct chiral heterocycles bearing at least one quaternary stereocenter by utilizing the strong substrate activation using Brønsted acids and by additionally increasing the reactivity of the substrate by incorporating fluorinated groups at specific positions on the substrates. The results of this study are detailed in the subsequent discussion.

5.5.1. Synthesis of Substrates

The synthesis of fluorinated dipolarophiles for this study was carried out according to the scheme given below (Scheme 5.6). Phosphorus ylide 5.43 of the Weinreb amide is commercially available and was condensed with commercially available trifluoromethyl ketones 5.44 in benzene at room temperature to give the corresponding E-trifluoromethyl enamides 5.45 in good yields. The E:Z ratio in most cases was excellent and the E isomer could be isolated by a simple column chromatography (hexane: EtOAc). The synthesis of the corresponding β,β-disubstituted-α,β-unsaturated acyl imidazole 5.39 was accomplished by reacting the enamides with lithiated N-OBn-imidazole 5.46 followed by an acid workup. The synthesis of N-OBn-imidazole 5.46 has been reported in the literature.16
5.5.2. Optimization of Reaction Conditions

We began exploration of Brønsted acid catalyzed nitrone cycloaddition to β,β-disubstituted acyl imidazoles using 5.39a and N-phenyl nitrone 5.40a. In the absence of any activation, reactions carried out in benzene at room temperature did not proceed, which indicates zero or no background reaction (Table 5.1, entry 1). This feature is important for us since any product generated through this process would be achiral and would reduce the efficiency of the chiral Brønsted acid mediated reaction. We were discouraged by the fact that even in the presence of an activator such as trifluoroacetic acid the reaction failed to yield any product (entry 2). Similar outcome was observed when reactions were carried out in the presence of 20 mol% of diphenyl phosphate (entry 3). These two entries highlighted the difficulty of carrying out the desired transformation to sterically demanding substrates. To our amazement when the same transformation was carried out in the presence of 20 mol% of diphenyltrifluoromethylsulfonyl phosphoramid cycloadduct 5.42a and 5.42'a were formed in a 69:31 mixture in 68% yield (entry 4). This result highlights the
importance of the correct Brønsted acidity required to activate the substrate for the transformation. We have previously shown that BINOL derived phosphoramido 5.41a to be successful for catalyzing azomethine imine and nitrone cycloadditions to acyl imidazole and based on these results we used the same chiral Brønsted acid as a first choice for catalyzing nitrone cycloaddition to β,β-disubstituted acyl imidazole 5.39a. Thus reactions catalyzed with chiral Brønsted acid 5.41a gave cycloadduct 5.42a as a single diastereomer in good yield and excellent enantioselectivity (entry 5). This result shows the extraordinary ability of BINOL derived phosphoramides to catalyze seemingly difficult transformations. The diastereomer thus obtained was determined to be exo by single crystal X-ray analysis. Nitrone cycloaddition with acyl imidazole 5.39a catalyzed by 20 mol% chiral Brønsted acid 5.41a in dichloromethane as solvent gave the cycloadduct in good yield and selectivity. Similar diastereoselectivity was observed using benzene as a solvent which required more time for completion (entry 6). The enantioselectivity of the product was higher when benzene was used as a solvent in comparison to dichloromethane. We were encouraged to see that even at elevated temperature the chiral Brønsted acid could catalyze nitrone cycloaddition to acyl imidazole 5.39a. Higher temperature helped increase the rate of this reaction and reaction carried out at 55 °C were complete in one third of time required for the same at room temperature without any erosion of diastereoselectivity and enantioselectivity (entry 7). Though benzene was initially used as a solvent for Brønsted acid catalyzed nitrone cycloaddition to acyl imidazole 5.39a, due to inherent toxicity of benzene it would not be a proper choice as reaction medium if this methodology was to be applied for the synthesis of drug like molecules. Toluene due to its similarity to benzene was a viable option as reaction medium in place of benzene without the toxicity concerns.
Thus nitrone cycloaddition to acyl imidazole 5.39a catalyzed by 20 mol% chiral Brønsted acid 5.41a carried out in toluene gave cycloadduct 5.42a in identical yield, diastereoselectivity, and enantiomeric excess as that obtained when the same reaction was carried out in benzene (entry 8). The catalyst loading for this reaction could be reduced to 3 mol% of 5.41a and reactions typically required longer reaction times however. The yield and enantioselectivity for the exo cycloadduct 5.42a was similar with both 3 and 20 mol% of catalyst (entry 9). Lower catalyst loading help conserve the amount of precious chiral Brønsted acid used, as these catalysts are prepared through multi step synthesis. We decided to screen additional chiral Brønsted acids using 3 mol% catalyst loading for the cycloaddition of nitrone 5.40a to acyl imidazole 5.39a. When chiral BINOL derived phosphoramide 5.41b possessing a 9-phenanthryl group at 3,3'- position on the BINOL ring was employed as the chiral activator for nitrone cycloaddition to acyl imidazole 5.39a, the exo cycloadduct 5.42a was obtained in 97% yield and 67% enantiomeric excess (entry 10). This result when compared to that obtained with Brønsted acid 5.41a emphasizes that subtle variation in shielding groups on the Brønsted acid had a dramatic effect on enantiomeric excess of the product. We have also investigated chiral BINOL derived phosphoramide 5.41c having 2,4,6-(iPr)3-C6H2 as shielding groups at 3,3'-position on the BINOL ring for the same reaction. This chiral Brønsted acid has not been shown to be an effective catalyst for our previous studies due to the extreme steric hindrance caused by the 2,4,6-(iPr)3-C6H2 group towards the approach of the dipole. To our astonishment the same catalyst preformed relatively well for nitrone cycloaddition to acyl imidazole 5.39a yielding cycloadduct 5.42a in 71% yield and 75% enantiomeric excess (entry 11). Chiral BINOL derived phosphoric acid was however not particularly well suited for catalyzing
this reaction as Brønsted acids 5.41d and 5.41e failed to give any cycloadducts (entries 12 and 13). One of the reasons for the failure of these chiral Brønsted acids could be due to the lower acidity of the phosphoric acids compared to the phosphoramide.

Table 5.1. Optimization of Reaction Condition for Brønsted Acid Catalyzed Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Brønsted Acid</th>
<th>mol %</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%) (^a)</th>
<th>exo/endo (^b)</th>
<th>exo ee (%) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>-</td>
<td>Benzene</td>
<td>rt</td>
<td>24</td>
<td>00</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>20</td>
<td>Benzene</td>
<td>rt</td>
<td>24</td>
<td>&gt;5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>(PhO)₂POOH</td>
<td>20</td>
<td>Benzene</td>
<td>rt</td>
<td>24</td>
<td>&gt;5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>(PhO)₂PONHTf</td>
<td>20</td>
<td>Benzene</td>
<td>rt</td>
<td>24</td>
<td>68</td>
<td>69:31</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5.41a</td>
<td>20</td>
<td>Benzene</td>
<td>rt</td>
<td>6</td>
<td>80</td>
<td>&gt;98:02</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>5.41a</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>rt</td>
<td>&gt;16</td>
<td>&gt;98:02</td>
<td>&gt;98:02</td>
<td>98</td>
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<tr>
<td>7</td>
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<td>Benzene</td>
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<td>&gt;98:02</td>
<td>94</td>
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<tr>
<td>8</td>
<td>5.41a</td>
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<td>Toluene</td>
<td>55</td>
<td>4</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>5.41a</td>
<td>03</td>
<td>Toluene</td>
<td>55</td>
<td>12</td>
<td>94</td>
<td>&gt;98:02</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>5.41b</td>
<td>03</td>
<td>Toluene</td>
<td>55</td>
<td>12</td>
<td>97</td>
<td>&gt;98:02</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>5.41c</td>
<td>03</td>
<td>Toluene</td>
<td>55</td>
<td>24</td>
<td>71</td>
<td>95:05</td>
<td>ND</td>
</tr>
<tr>
<td>12</td>
<td>5.41d</td>
<td>03</td>
<td>Toluene</td>
<td>55</td>
<td>72</td>
<td>00</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>13</td>
<td>5.41e</td>
<td>03</td>
<td>Toluene</td>
<td>55</td>
<td>72</td>
<td>00</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>5.41a</td>
<td>01</td>
<td>Toluene</td>
<td>55</td>
<td>36</td>
<td>90</td>
<td>&gt;98:02</td>
<td>94</td>
</tr>
<tr>
<td>15</td>
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<td>Toluene</td>
<td>55</td>
<td>48</td>
<td>92</td>
<td>&gt;98:02</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after column chromatography. \(^b\) Determined by \(^1\)H NMR of crude reaction mixture. \(^c\) Determined by chiral HPLC.

We have seen in the early screening studies that the reaction could not be catalyzed by relatively strong Brønsted acid such as trifluoroacetic acid which achiral
phosphoramides could (compare entries 2 and 4). One of the notable features of this Brønsted acid catalyzed reaction is the efficiency of the catalytic cycle. Even when the catalyst loading was reduced to 1 mol%, the reaction still proceeded efficiently to yield exo cycloadduct 5.42a in 90% yield and 94% enantiomeric excess (entry 14). The catalyst turnover number for this entry was calculated to be 100, which is quite remarkable. We could further reduce the amount to chiral Brønsted acid to 0.5 mol% without appreciable impact on enantioselectivity of the cycloadduct. We believe that this is one of the lowest catalyst loading ever reported for an organocatalyzed process. Especially when this is viewed in context with the construction of highly complex heterocycles is even more astounding. For more practical purposes however, we decided to optimize the catalyst loading to 3 mol% of 5.41a which was by far the most superior chiral Brønsted acid.

5.5.3. Scope of Dipolarophiles for Brønsted Acid Catalyzed Nitrone Cycloaddition to β,β-Disubstituted α,β-Unsaturated Acyl Imidazole

After a comprehensive screening of reaction conditions for chiral Brønsted acid catalyzed nitrone cycloaddition to β,β-disubstituted α,β-unsaturated acyl imidazole, we decided to explore the scope of the dipolarophile for the same transformation. Various β,β-disubstituted α,β-unsaturated acyl imidazoles were synthesized according to procedures previously discussed. Chiral Brønsted acid 5.41a, which was found to be the optimal catalyst, was used in 3 mol% and typical reactions were carried out in toluene at 55 °C.

The reaction of nitrone 5.40a to β-trifluoromethyl cinnamate 5.39b proceeded smoothly to furnish exo cycloadduct 5.42b in good yield and excellent enantioselectivity.
(Table 5.2, entry 2). This particular entry highlights the impact of the β-trifluoromethyl group on the overall reactivity of the dipolarophile.

Table 5.2. Scope of Dipolarophile for Brønsted Acid Catalyzed Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>SM</th>
<th>R¹</th>
<th>R²</th>
<th>Product</th>
<th>Time (d)</th>
<th>Yield (%)a</th>
<th>exo ee (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.39a</td>
<td>CF₃</td>
<td>CH₃</td>
<td>5.42a</td>
<td>0.5</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>5.39b</td>
<td>CF₃</td>
<td>Ph</td>
<td>5.42b</td>
<td>3</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>5.39c</td>
<td>CF₃</td>
<td>p-FC₆H₄</td>
<td>5.42c</td>
<td>3</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>5.39d</td>
<td>CF₃</td>
<td>p-ClC₆H₄</td>
<td>5.42d</td>
<td>3</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>5.39e</td>
<td>CF₃</td>
<td>m-FC₆H₄</td>
<td>5.42e</td>
<td>3</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>5.39f</td>
<td>CF₃</td>
<td>m-CF₃C₆H₄</td>
<td>5.42f</td>
<td>3</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>5.39g</td>
<td>CH₃</td>
<td>CH₃</td>
<td>5.42g</td>
<td>6</td>
<td>92</td>
<td>94</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography. b Determined by chiral HPLC.
c Reaction was carried out using 20 mol% of 5.41a at room temperature.

Reactions with cinnamates are typically challenging due to the steric and electronic effect of the phenyl ring on the β-position and very few nitrone cycloadditions to cinnamates have been reported. However, due to the presence of the β-trifluoromethyl group on the substrate, the electronic activation of the β-carbon overrides the effect of steric repulsion. Equally important is the ability of the chiral Brønsted acid to activate such a challenging substrate with a significantly low catalyst loading. Para halogenated β-
trifluoromethyl cinnamates was also tried as a substrate for the same transformation. Thus reaction of acyl imidazole 5.39c to nitrone 5.40a catalyzed by 3 mol% of 5.41a gave cycloadduct 5.42c in 98% yield and 93% enantiomeric excess (entry 3). Also, the p-chloro phenyl substituted substrate reacted smoothly to yield the exo cycloadduct 5.42d in high yield and excellent enantioselectivity (entry 4). We have also evaluated meta halogenated β-trifluoromethyl cinnamate as a substrate and reaction of 5.39e with a m-fluoro substituent on the β-phenyl ring reacted smoothly to yield the cycloadduct 5.42e in 87% yield and 91% enantiomeric excess (entry 5). Dipolarophile with a m- trifluoromethyl substituent on the β-phenyl ring was also evaluated in the cycloaddition and the reaction proceeded satisfactorily (entry 6). Finally, non-fluorinated β,β-dialkyl substituted α,β-unsaturated acyl imidazole 5.39g was also tested as a potential dipolarophile. Reaction with substrate 5.39g was much slower and typically required a week to complete with 20 mol% catalyst loading. Though the enantiomeric excess of the cycloadduct 5.42g obtained was excellent (entry 7). The effect of β-trifluoromethyl substitutent on the reactivity of the substrate can be gauged by comparing entry 1 with entry 7 (Table 5.2). Reaction with 5.39g required 7 days to complete with 20 mol% of the catalyst when the β-substituent was a methyl group (entry 7) where as with β-trifluoromethyl substitutent this reaction took only 4 h to complete (entry 1).

5.5.4. Scope of Nitrone for Bronsted Acid Catalyzed Nitrone Cycloaddition to β,β-Disubstituted α,β-Unsaturated Acyl Imidazole

After exploring the range of dipolarophiles that could be used in the cycloaddition, we extended the scope of the reaction by screening various nitrones. Various N-phenyl-C-
aromatic nitrones were prepared by condensation of \( N \)-phenyl hydroxylamine with \( p \)-substituted benzaldehydes and reacted with acyl imidazole 5.39a in the presence of 3 mol% chiral Brønsted acid 5.41a at 55 °C in toluene as reaction medium.

Table 5.3. Scope of Nitrones for Chiral Brønsted Acid Catalyzed Nitrone Cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipole</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>Product</th>
<th>Yield (%)</th>
<th>exo/endo</th>
<th>exo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.40a</td>
<td>Ph</td>
<td>Ph</td>
<td>5.42a</td>
<td>&gt;98</td>
<td>&gt;98:02</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>5.40b</td>
<td>Ph</td>
<td>( p )-BrC(_6)H(_4)</td>
<td>5.42h</td>
<td>87</td>
<td>96:04</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>5.40c</td>
<td>Ph</td>
<td>( p )-MeOOC(_6)H(_4)</td>
<td>5.42i</td>
<td>89</td>
<td>88:12</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>5.40d</td>
<td>Ph</td>
<td>( p )-CNPh</td>
<td>5.42j</td>
<td>85</td>
<td>&gt;98:02</td>
<td>93</td>
</tr>
</tbody>
</table>

\( ^{a} \) Isolated yield after column chromatography. \( ^{b} \) Determined by \( ^1 \)H NMR of crude reaction mixture. \( ^{c} \) Determined by chiral HPLC

Reaction of \( N,\alpha \)-diphenyl nitrone 5.40a with acyl imidazole 5.39a has been discussed in earlier sections and gives exo cycloadduct 5.42a in quantitative yield and 96% enantiomeric excess (Table 5.3, entry 1). \( p \)-Halogenated nitrone 5.40b which was prepared by condensation of \( p \)-bromobenzaldehyde with \( N \)-phenyl hydroxyl amine also reacted smoothly under chiral Brønsted acid catalysis to give cycloadducts as 96:04 mixture of \( exo:endo \) isomers in excellent yield and enantioselectivity (entry 2). Electron rich nitrones prepared from \( p \)-methoxy benzaldehyde was also tested as a dipole and gave 88:12 mixture of \( exo:endo \) isomers in 87% yield and 93% enantiomeric excess for the exo adduct (entry
3). Similarly, an electron deficient nitrone prepared from p-cyano benzaldehyde also reacted satisfactorily to give exclusively the exo cycloadduct in 85% yield and 93% enantiomeric excess (entry 4).

With this brief screening of nitrone we have been able to show the broad applicability of this methodology. We have shown in this study that electron rich as well as electron deficient dipoles react equally well to furnish exo cycloadducts in excellent yield, diastereoselectivity and enantioselectivity. Similarly, halogenated nitrones could also be utilized in the cycloaddition. The products from this reaction are interesting since they provide sites for modification via organometallic coupling reactions.

5.5.5. Origin of Diastereoselectivity in Chiral Brønsted Acid Catalyzed Nitrone Cycloaddition

In chapter 3 we proposed that the different diastereoselectivity observed in Lewis acid and Brønsted acid catalyzed azomethine imine cycloaddition could be due the reaction of the dipole with different rotamers of the dipolarophile in the two cases. In Lewis acid catalyzed reactions, s-cis (syn) rotamer is predominant due to the bidentate binding of the metal with the substrate. However in case of Brønsted acid catalyzed reactions, the formation of the exo diastereomer can be best explained if the reaction proceeded via the s-cis (anti) rotamer. In chapter 4 the same rotamer geometry was used to explain the origin of exo diastereoselectivity in nitrone cycloaddition to β-substituted-α,β-unsaturated acyl imidazole. When we look at possible rotamers of β,β-disubstituted-α,β-unsaturated acyl imidazole there is no doubt that structures 5.43 and 5.45 are the most stable ones as they suffer least steric interactions (Figure 5.5).
Furthermore, based on the crystal structure of chiral Bronsted acid-substrate complex from our group we believe that the reaction occurs via s-cis (anti) rotamer 5.45 of the substrate. Models for endo and exo approach (5.47 and 5.48) of the dipole to this catalyst-substrate complex were drawn and analyzed for steric repulsion towards the incoming dipole (Figure 5.6). The endo approach of the dipole is sterically encumbered due to repulsion between the benzyloxy group (R2) of the imidazole and the aromatic groups R on the nitrones. We believe that due to these repulsive forces the endo approach of the dipole is unfavorable and hence the endo diastereomer is obtained as the minor isomer in most cases. In case of the exo approach of the dipole to this catalyst-substrate complex, the steric repulsion to the incoming dipoles is minimum. There can also be additional π-π stacking interaction between the aromatic rings at β-position on the dipolarophiles and the aromatic substituent on nitrogen atom of the dipole. These interactions may help stabilize the exo transition state and hence the exo diastereomer is preferentially formed over the endo diastereomer.

Previously we have seen that the catalyst 5.41a performed extremely well for nitrone and azomethine imine cycloaddition to α,β-saturated acyl imidazole. The chiral pocket of this catalyst is very well defined as provides excellent face selectivity. In case of
nitrone cycloaddition to β,β-disubstituted-α,β-unsaturated acyl imidazole the catalyst \( 5.41a \) provided similar face shielding and hence excellent enantioselectivity is observed in most reactions.

5.47

**Endo approach**

\[
\begin{align*}
\text{Endo adduct (5.49)}
\end{align*}
\]

5.48

**Exo approach**

\[
\begin{align*}
\text{Exo adduct (5.50)}
\end{align*}
\]

5.6. Transition State Model to Explain Diastereoselectivity

5.6. Conclusion

We have developed the first enantioselective nitrone cycloaddition to β,β-disubstituted α,β-unsaturated acyl imidazoles catalyzed by chiral Brønsted acids towards the construction of chiral quaternary centers. This reaction is also important since it leads to the construction of chiral fluorinated heterocycles that have tremendous importance in the field of medicinal chemistry. The catalyst loading for this reaction is 3 mol% which is quite remarkable for an organocatalyzed process. The catalyst loading can be reduced to 0.5 mol% which is one of the lowest catalyst loading reported in the literature. During the
course of this study we have been able to show that the incorporation of fluorinated groups on the β-carbon of α,β-unsaturated carbonyl compounds helps improve their reactivity toward nitrone cycloaddition. We are currently exploring the synthetic utility of the cycloadducts for the synthesis of fluorinated β-amino acids and other fluorinated derivatives.

5.7. Outlook

During the course of all of our studies we have demonstrated the utility of acyl imidazoles for chiral Brønsted acid catalyzed dipolar cycloadditions. This combination of template and activator was found to be very effective for performing reactions to sterically and electronically challenging substrates. We expect this combination to work well for other types of transformations that can provide access to functional group rich chiral molecules.

5.8. Experimental

**General:** Dichloromethane was distilled from calcium hydride under nitrogen prior to use. Toluene was distilled from calcium hydride under nitrogen prior to use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO™ CombiFlash Companion with AnaLogix™ RS-4 columns. All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were measured with a Fisher-Johns melting points apparatus and are uncorrected. $^1$H-NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian
Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual CDCl₃ (7.26 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ¹³C-NMR was recorded on Varian Unity/Inova-500 NB (125 MHz), Varian Unity/Inova-400 NB (100 MHz), and Varian Mercury-300 (75MHz) spectrometers, using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of CDCl₃ (77.0) as an internal standard. ¹⁹F-NMR was recorded on Varian Varian Mercury-300 (282 MHz) spectrometers with trifluorotoluene (-64 ppm) CDCl₃ as an external standard. ³¹P-NMR was recorded on Varian Varian Mercury-300 (121 MHz) spectrometers with H₃PO₄ (0 ppm) in CDCl₃ as an external standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower workstation. Rotations were recorded on a JASCO-DIP-370 instrument. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High Resolution Mass Spectra (HRMS) (ESI) were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

Materials and Methods: Diphenyl phosphate, trifluoroacetic acid and N-methoxy-N-methyl(triphenylphosphoranylidene) acetamide 5.5 was purchased from Aldrich. N,α-diphenyl nitrone 5.2a was purchased from Acros. Nitrone 5.2b-d were prepared according to known literature procedures. Chiral Brønsted acids 5.4b-e were prepared from known literature procedures.¹⁷ Chiral Brønsted acid 5.4a was prepared by procedure previously reported in our laboratory.

Trifluoromethyl ketones 5.6 were added to a suspension of N-methoxy-N-methyl(triphenylphosphoranylidene) acetamide 5.5 in benzene at room temperature (Scheme 5.7). The reaction progress was monitored by TLC, and after approximately stirring for 30 minutes no starting material was seen. The crude reaction mixture was purified by column chromatography over silica gel using hexane:ethyl acetate as eluant. Pure products were obtained as single isomers after concentration of various fractions.

\[ \text{Me} - \text{N} = \text{PPh}_3 + R - \text{CF}_3 \xrightarrow{\text{Benzene, rt}} \text{Me} - \text{N} = \text{CF}_3 \]

**Scheme 5.7. Preparation of β-Trifluoromethyl Enamides**

\[ (E)-4,4,4-	ext{Trifluoro-N-methoxy-N,3-dimethylbut-2-enamide (5.6a)}: \]

Oil, \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta \) 2.12 (s, 3H), 3.20 (s, 3H), 3.64 (s, 3H), 6.71 (s, 1H); \(^13\)C NMR (CDCl\(_3\), 100 MHz); \(\delta \) 12.1, 32.0, 61.7, 120.8, 123.5 (q, \(^1J_{CF} = 273.9\)), 138.7 (q, \(^2J_{CF} = 29.8\)), 165.5. \(^19\)F NMR (CDCl\(_3\), 282 MHz); \(\delta \) -71.0; IR (neat) 3329, 2943, 2824, 1772, 1655, 1445, 1381, 1345, 1286, 1180, 1017, 983, 934, 888, 834, 783, 613 cm\(^{-1}\). HRMS calcd for C\(_7\)H\(_{10}\)F\(_3\)NO\(_2\)Na\(^+\): 220.0561; Found: 220.0554.
\( (E) \)-4,4,4-Trifluoro-\( N \)-methoxy-\( N \)-methyl-3-phenylbut-2-enamide (5.6b):

Oil, \(^1\)H NMR (CDCl\(_3\), 400 MHz); \( \delta \) 3.08 (s, 3H), 3.64 (s, 3H), 6.94 (s, 1H), 7.33-7.35 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \( \delta \) 32.2, 61.9, 120.8, 123.0 (q, \(^1\)J\(_{CF} = 275.3\)), 125.6, 128.3, 128.9, 129.3, 131.4, 138.8 (q, \(^2\)J\(_{CF} = 33.9\)), 165.5; \(^{19}\)F NMR (CDCl\(_3\), 282 MHz); \( \delta \) -66.7. IR (neat) 3061, 2974, 2940, 1669, 1576, 1462, 1445, 1421, 1389, 1351, 1274, 1172, 1126, 1078, 1007, 975, 935, 878, 803, 776, 699, 627 cm\(^{-1}\). HRMS calcd for C\(_{12}\)H\(_{12}\)F\(_3\)NO\(_2\)Na\(^+\): 282.0712; Found: 282.0711.

\( (E) \)-3-(4-Chlorophenyl)-4,4,4-trifluoro-\( N \)-methoxy-\( N \)-methylbut-2-enamide (5.6c):

Oil, \(^1\)H NMR (CDCl\(_3\), 400 MHz); \( \delta \) 3.09 (s, 3H), 3.66 (s, 3H), 6.96 (s, 1H), 7.25 (d, \( J = 8.5\), 2H), 7.33 (d, \( J = 8.5\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \( \delta \) 32.2, 61.9, 122.0 (q, \(^1\)J\(_{CF} = 274.2\)), 125.9, 128.7, 129.7, 130.4, 135.6, 138.0 (q, \(^2\)J\(_{CF} = 30.0\)), 164.8; \(^{19}\)F NMR (CDCl\(_3\), 282 MHz); \( \delta \) -66.8; IR (neat) 2973, 2939, 1669, 1595, 1494, 1422, 1390, 1351, 1276, 1178, 1130, 1017, 977, 880, 729, 682 cm\(^{-1}\). HRMS calcd for C\(_{12}\)H\(_{11}\)ClF\(_3\)NO\(_2\)Na\(^+\): 316.0323; Found: 316.0327.

\( (E) \)-4,4,4-Trifluoro-3-(4-fluorophenyl)-\( N \)-methoxy-\( N \)-methylbut-2-enamide (5.6d):

Oil, \(^1\)H NMR (CDCl\(_3\), 400 MHz); \( \delta \) 3.09 (s, 3H), 3.65 (s, 3H), 6.95 (s, 1H), 7.04 (t, \( J = 8.5\), 2H), 7.30 (t, \( J = 8.5\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \( \delta \) 32.0, 61.7, 115.4 (d, \(^3\)J\(_{CF} = 21.8\) Hz), 122.9 (q, \(^1\)J\(_{CF} = 274.3\) Hz), 126.0, 127.2, 131.0 (d, \(^2\)J\(_{CF} = 8.4\) Hz),
137.7 (q, $^2J_{CF} = 27.6$ Hz), 163.3 (d, $^1J_{CF} = 248.8$), 164.9; $^{19}$F NMR (CDCl$_3$, 282 MHz); $\delta$ -67.0, -111.8; IR (neat) 3069, 2975, 2941, 1668, 1606, 1513, 1463, 1422, 1390, 1352, 1273, 1232, 1172, 1128, 1006, 977, 929, 880, 842, 800, 742, 709, 620 cm$^{-1}$. HRMS calcd for C$_{12}$H$_{11}$F$_4$NO$_2$Na$^+$: 300.0618; Found: 300.0612.

(E)-4,4,4-Trifluoro-3-(3-fluorophenyl)-N-methoxy-N-methylbut-2-enamide (5.6e):

Oil, $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 3.10 (s, 3H), 3.66 (s, 3H), 6.96 (s, 1H), 7.02-7.10 (m, 3H), 7.29-7.35 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 32.0, 61.8, 116.1 (d, $^2J_{CF} = 22.9$ Hz), 116.2 (d, $^2J_{CF} = 20.7$ Hz), 122.7 (q, $^1J_{CF} = 274.1$ Hz), 124.9 (d, $^4J_{CF} = 2.7$ Hz), 126.4, 130.0 (d, $^3J_{CF} = 8.0$), 133.3 (d, $^3J_{CF} = 6.7$ Hz), 137.4 (q, $^2J_{CF} = 30.5$ Hz), 162.4 (d, $^1J_{CF} = 246.1$ Hz), 164.7; $^{19}$F NMR (CDCl$_3$, 282 MHz); $\delta$ -67.0, -112.6; IR (neat) 3072, 2974, 2941, 1670, 1614, 1584, 1489, 1439, 1390, 1352, 1278, 1232, 1180, 1131, 1077, 1000, 940, 890, 868, 791, 753, 632 cm$^{-1}$. HRMS calcd for C$_{12}$H$_{11}$F$_4$NO$_2$Na$^+$: 300.0618; Found: 300.0594.

(E)-4,4,4-Trifluoro-N-methoxy-N-methyl-3-(3-(trifluoromethyl)phenyl)but-2-enamide (5.6f):

Oil, $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 3.09 (s, 3H), 3.68 (s, 3H), 7.03 (s, 1H), 7.47-7.55 (m, 3H), 7.62-7.64 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 31.9, 61.7, 122.7 (q, $^1J_{CF} = 274.0$ Hz), 124.0 (q, $^1J_{CF} = 272.4$ Hz), 125.8, 126.0, 126.7, 128.8, 130.8 (q, $^2J_{CF} = 32.5$ Hz), 132.5, 137.5 (q, $^2J_{CF} = 29.8$ Hz), 164.5; $^{19}$F NMR (CDCl$_3$, 282 MHz); $\delta$ -62.8, -66.8; IR (neat) 3073, 2975, 2943, 2825, 1671, 1490, 1441, 1391, 1357, 1324, 1275,
1127, 1097, 1076, 1006, 989, 938, 903, 840, 806, 743, 702, 657, 607 cm⁻¹. HRMS calcd for \( \text{C}_{13}\text{H}_{11}\text{F}_{6}\text{NO}_{2}\text{Na}^+ \): 350.0586; Found: 350.0604.

5.8.2. General Procedure for the Synthesis of \( \beta,\beta\)-Disubstituted-\( \alpha,\beta\)-Unsaturated Acyl Imidazole

\( N\)-Benzyloxy imidazole (1.5 equiv) was weighed into a flame dried flask flushed with argon. Dry THF (7 mL/mmol) was added to this flask and the solution was cooled to -78 °C using dry ice-acetone bath for 10 min (Scheme 5.8). To this solution 2.5 M \( n\)-butyl lithium solution (1.5 equiv.) was added dropwise. The contents of the flask was stirred at -78 °C for 15 min and then gradually warmed up to room temperature over 30 min. The solution was further stirred at room temperature for an additional 15 min and then cooled back to -78 °C. In another flask a solution of appropriate Weinreb amide 5.6 (1 equiv.) was prepared in dry THF (5 mL/mmol) and cooled to -78 °C. To this flask lithiated imidazole was cannulated and the reaction mixture was stirred for 1 h at -78 °C.

\[
\begin{align*}
\text{\textbf{N}^+} & \quad \text{O} \quad \text{OBn} \\
\text{5.8} & \quad \text{5.7a } R = \text{Me} \\
 & \quad \text{5.7b } R = \text{Ph} \\
 & \quad \text{5.7c } R = \text{p-ClC}_6\text{H}_4 \\
 & \quad \text{5.7d } R = \text{p-FC}_6\text{H}_4 \\
 & \quad \text{5.7e } R = \text{m-FC}_6\text{H}_4 \\
 & \quad \text{5.7f } R = \text{m-CF}_3\text{C}_6\text{H}_4 \\
\end{align*}
\]

\[
\begin{align*}
\text{\textbf{N}^+} & \quad \text{O} \quad \text{OBn} \\
\text{5.39a } R = \text{Me} & \quad \text{5.39b } R = \text{Ph} \\
 & \quad \text{5.39c } R = \text{p-ClC}_6\text{H}_4 \\
 & \quad \text{5.39d } R = \text{p-FC}_6\text{H}_4 \\
 & \quad \text{5.39e } R = \text{m-FC}_6\text{H}_4 \\
 & \quad \text{5.39f } R = \text{m-CF}_3\text{C}_6\text{H}_4 \\
\end{align*}
\]

Scheme 5.8. Preparation of \( \beta,\beta\)-Disubstituted-\( \alpha,\beta\)-unsaturated Acyl Imidazoles
Reaction progress was monitored by TLC and after completion the reaction was quenched by addition of sat. ammonium chloride solution. The crude product was extracted with ethyl acetate (2 X 50 mL) and purified by column chromatography. The average yield for pure products was 85%.

\( (E)-1-(1-(\text{Benzyloxy})-1H-\text{imidazol-2-yl})-4,4,4\text{-trifluoro-3-methylbut-2-en-1-one (5.39a)}: \)

Solid, \( ^1H \) NMR (CDCl\(_3\), 400 MHz); \( \delta \) 2.32 (s, 3H), 5.25 (s, 2H), 6.91 (s, 1H), 6.96 (s, 1H), 7.37-7.39 (m, 5H), 7.71 (s, 1H); \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz); \( \delta \) 12.9, 82.6, 122.8, 123.5 (q, \( J_{CF} = 273.9 \) Hz), 124.6 (q, \( J_{CF} = 5.4 \) Hz), 125.8, 128.9, 129.8, 130.2, 133.2, 141.6 (q, \( J_{CF} = 31.0 \) Hz), 178.7; \( ^{19}F \) NMR (CDCl\(_3\), 282 MHz); \( \delta \) -71.4; IR (KBr): 3093, 3013, 2967, 1676, 1643, 1473, 1417, 1354, 1287, 1159, 1035, 965, 918, 891, 846, 776, 697, 658, 621 cm\(^{-1}\). HRMS calcd. for C\(_{15}\)H\(_{13}\)F\(_3\)N\(_2\)O\(_2\)Na\(^{+}\): 333.0827; Found: 333.0835.

\( (E)-1-(1-(\text{Benzyloxy})-1H-\text{imidazol-2-yl})-4,4,4\text{-trifluoro-3-phenylbut-2-en-1-one (5.39b)}: \)

Solid, \( ^1H \) NMR (CDCl\(_3\), 400 MHz); \( \delta \) 5.06 (s, 2H), 6.78 (d, \( J = 1.0 \) Hz), 6.93 (d, \( J = 1.0 \) Hz), 7.21 (td, \( J = 8.1, 2.4 \) Hz, 2H), 7.29-7.38 (m, 8H), 7.8 (dd, \( J = 2.4, 1.4 \) Hz, 1H); \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz); \( \delta \) 82.4, 122.9 (q, \( J_{CF} = 274.1 \) Hz), 123.0, 126.0, 128.4, 128.6 (q, \( J_{CF} = 5.4 \) Hz), 128.9, 129.1, 129.8, 130.2, 131.4, 133.1, 138.7, 141.4 (q, \( J_{CF} = 31.1 \) Hz), 178.0; \( ^{19}F \) NMR (282 MHz); \( \delta \) -67.1; IR (KBr): 3141, 3070, 3033, 2886, 2886, 1670, 1656, 1498, 1410, 1363, 1279, 1202, 1177, 1165, 1130, 1022, 972, 952, 886.
(E)-1-(1-(Benzyloxy)-1H-imidazol-2-yl)-3-(4-chlorophenyl)-4,4,4-trifluorobut-2-en-1-one (5.39c):

`^1^H NMR (CDCl₃, 400 MHz); δ 5.06 (s, 2H), 6.82 (s, 1H), 6.93 (s, 1H), 7.20-7.34 (m, 9H), 7.86 (s, 1H); `^1^3^C NMR (CDCl₃, 100 MHz); δ 82.4, 122.8 (q, `^1^J_{CF} = 275.3 Hz), 123.2, 126.2, 128.8, 128.9, 129.0 (q, `^3^J_{CF} = 5.0 Hz), 129.8, 130.2, 130.6, 133.1, 135.6, 138.6, 140.6 (q, `^2^J_{CF} = 31.1 Hz), 177.4; `^1^9^F NMR (CDCl₃, 282 MHz); δ -67.9; IR (KBr): 3149, 3085, 3034, 2966, 1684, 1650, 1495, 1407, 1366, 1347, 1282, 1197, 1185, 1215, 1088, 1011, 973, 891, 833, 768, 758, 703 cm⁻¹. HRMS calcd. For C₂₀H₁₅F₃N₂O₂Na⁺: 429.0588; Found: 429.0577.

(E)-1-(1-(Benzyloxy)-1H-imidazol-2-yl)-4,4,4-trifluoro-3-(4-fluorophenyl)but-2-en-1-one (5.39d):

`^1^H NMR (CDCl₃, 400 MHz); δ 5.08 (s, 2H), 6.82 (s, 1H), 6.94 (s, 1H), 7.03-7.07 (m, 2H), 7.22-7.24 (m, 2H), 7.30-7.35 (m, 5H), 7.83 (s, 1H); `^1^3^C NMR (CDCl₃, 100 MHz); δ 82.4, 115.6 (d, `^2^J_{CF} = 21.7 Hz), 122.8 (q, `^1^J_{CF} = 274.8 Hz), 123.1, 126.2, 127.2, 128.8 (q, `^3^J_{CF} = 5.3 Hz), 128.9, 129.8, 130.2, 131.2 (q, `^3^J_{CF} = 8.9 Hz), 133.1, 138.6, 140.6 (q, `^2^J_{CF} = 30.8 Hz), 163.4 (d, `^1^J_{CF} = 249.4 Hz), 177.6; `^1^9^F NMR (CDCl₃, 282 MHz); δ -68.1, -112.5; IR (KBr): 3151, 3087, 2964, 1680, 1647, 1603, 1509, 1455, 1408, 1368, 1348, 1284, 1221, 1184, 1156, 1127, 1098, 1013, 974, 893, 847, 797, 758, 741, 701 cm⁻¹. HRMS calcd. for C₂₀H₁₄F₄N₂O₂Na⁺: 413.0884; Found: 413.0877.
\((E)-1-(1-(Benzyloxy)-1H-imidazol-2-yl)-4,4,4\text{-trifluoro-3-(3-fluorophenyl)but-2-en-1-one (5.39e):}\)

\(^1\text{H} \text{NMR (CDCl}_3, 400 \text{MHz); 5.06 (s, 2H), 6.83 (s, 1H), 6.95 (s, 1H), 7.05-7.11 (m, 3H), 7.21-7.23 (m, 2H), 7.28-7.36 (m, 4H), 7.84 (s, 1H);}^{13}\text{C} \text{NMR (CDCl}_3, 100 \text{MHz);} \delta 82.5, 116.3, 116.5 (d, {^4J}_{\text{CF}} = 2.3 \text{ Hz}), 122.7 (q, {^1J}_{\text{CF}} = 274.2 \text{ Hz}), 123.1, 125.0, 126.2, 128.9, 129.2 (q, {^3J}_{\text{CF}} = 4.5 \text{ Hz}), 129.8, 130.1, 130.2, 133.0, 133.3 (d, {^3J}_{\text{CF}} = 8.2 \text{ Hz}), 138.6, 139.4 (q, {^2J}_{\text{CF}} = 31.2 \text{ Hz}), 162.5 (d, {^1J}_{\text{CF}} = 246.8 \text{ Hz}), 177.4; {^19}\text{F} \text{NMR (CDCl}_3, 282 \text{ MHz);} \delta -68.0, -113.4; \text{IR (KBr):} 3148, 3117, 3069, 3033, 2998, 1678, 1638, 1583, 1496, 1487, 1456, 1438, 1402, 1364, 1353, 1279, 1230, 1194, 1176, 1152, 1123, 1009, 907, 894, 883, 873, 795, 771, 753, 729, 700 \text{ cm}^{-1}. \text{HRMS calcld. for C}_{20}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_2\text{Na}^+: 413.0884 \text{ Found: 413.0891.}

\((E)-1-(1-(Benzyloxy)-1H-imidazol-2-yl)-4,4,4\text{-trifluoro-3-(3-trifluoromethyl)phenyl)but-2-en-1-one (5.39f):}\)

\(^1\text{H} \text{NMR (CDCl}_3, 400 \text{ MHz); 5.06 (s, 2H), 6.83 (s, 1H), 6.95 (s, 1H), 7.05-7.11 (m, 3H), 7.21-7.23 (m, 2H), 7.28-7.36 (m, 4H), 7.84 (s, 1H);}^{13}\text{C} \text{NMR (CDCl}_3, 100 \text{ MHz);} \delta 82.5, 122.6 (q, {^1J}_{\text{CF}} = 274.6 \text{ Hz}), 123.2, 124.0 (q, {^1J}_{\text{CF}} = 272.5), 126.1 (2 \text{ carbons}), 126.3, 128.9, 129.2 (q, {^3J}_{\text{CF}} = 5.3 \text{ Hz}), 129.8, 130.2, 130.8 (q, {^2J}_{\text{CF}} = 32.7 \text{ Hz}), 132.2, 132.6, 133.0, 138.6, 140.0 (q, {^2J}_{\text{CF}} = 31.2 \text{ Hz}), 177.1; {^19}\text{F} \text{NMR (CDCl}_3, 282 \text{ MHz);} \delta -63.6, -68.1; \text{IR (KBr):} 3156, 3111, 3068, 3037, 2962, 1677, 1643, 1497, 1457, 1440, 1403, 1323, 1287, 1176, 1161, 1121, 1094, 1094, 1077, 1006, 986, 895, 880, 844, 805,
790, 777, 753, 700, 683 cm\(^{-1}\). HRMS calcd. for C\(_{21}H_{14}F_6N_2O_2Na^+\): 463.0852; Found: 463.0850.

1-(1-(Benzyloxy)-1H-imidazol-2-yl)-3-methylbut-2-en-1-one (5.39g):
Oil, \(^1\)H NMR (CDCl\(_3\), 500 MHz); \(\delta\) 2.04 (s, 3H), 2.33 (s, 3H), 5.31 (s, 2H), 6.84 (s, 1H), 6.91 (s, 1H), 7.20 (m, 1H), 7.38-7.44 (m, 5H); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz); \(\delta\) 21.3, 28.2, 82.3, 121.3, 121.6, 124.6, 128.8, 129.5, 130.1, 133.8, 139.9, 158.6, 179.6; IR (KBr): 3153, 3110, 3033, 2967, 1673, 1630, 1504, 1498, 1453, 1423, 1400, 1360, 1351, 1265, 1230, 1190, 1165, 1145, 1110, 990, 906, 895, 881, 753, 729, 700 cm\(^{-1}\). HRMS calcd. for C\(_{15}H_{16}N_2O_2Na^+\): 279.1104; Found: 279.1098.

5.8.3. Representative Procedure for Room Temperature Enantioselective 1,3-Dipolar Cycloadditions of Nitrone with \(\alpha,\beta\)-Unsaturated 2-Acyl Imidazoles Catalyzed by Chiral Brønsted Acid

To a 6 dram vial containing \(\alpha,\beta\)-unsaturated 2-acyl imidazole (0.1 mmol) and chiral Brønsted acid, solvent (2 mL) was added. The solution was stirred for 1 h. To this solution nitrone (0.15 mmol) was finally added. The reaction was stirred at room temperature until the dipolarophile was consumed (TLC). The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogiX RS-4 columns. The \textit{ex//endo} ratios were determined by \(^1\)H NMR spectroscopy prior to chromatography and enantioselectivities were measure by HPLC analysis after chromatography.
5.8.4. Representative Procedure for Enantioselective 1,3-Dipolar Cycloadditions of Nitrone with $\alpha,\beta$-Unsaturated 2-Acyl Imidazoles Catalyzed by Chiral Brønsted Acid at 55 °C

To a 6 dram vial containing $\alpha,\beta$-unsaturated 2-acyl imidazole (0.1 mmol) and Chiral Brønsted acid, solvent (2 mL) was added. The vial was stirred for 1 h. To the solution nitroene (0.15 mmol) was finally added. The reaction was stirred at 55 °C in a preheated oil bath until the dipolarophile was consumed (TLC). The cycloaddition products were purified by flash column silica gel chromatography on an ISCO CombiFlash Companion with AnaLogiX RS-4 columns. The exo/endo ratios were determined by $^1$H NMR spectroscopy prior to chromatography and enantioselectivities were measure by HPLC analysis after chromatography.

$\text{(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5R)-5-methyl-2,3-diphenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone (5.42a):}$

Foamy Solid, $[\alpha]_D^{25} -48.3$ (c 1.0, CHCl$_3$), (exo/endo= >98:02); $^1$H NMR (CDCl$_3$, 400 MHz); δ 1.66 (s, 3H), 4.48 (d, $J = 10.3$ Hz, 1H), 4.59 (d, $J = 10.3$ Hz, 1H), 5.33 (d, $J = 8.4$ Hz, 1H), 5.85 (d, $J = 8.4$ Hz, 1H), 6.76 (s, 1H), 6.91-6.93 (m, 4H), 7.15-7.20 (m, 6H), 7.30-7.42 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz); δ 16.5, 56.8, 71.7, 82.2, 83.7 (q, $^2J_{CF} = 29.8$ Hz), 115.6, 122.3, 123.1, 125.3 (q, $^1J_{CF} = 286.5$ Hz), 125.7, 127.9, 128.2, 128.4, 128.7, 128.8, 129.6, 130.1, 133.1, 136.8, 138.6, 150.2, 183.8; IR (KBr): 3128, 3065, 3038, 1688, 1597,1493, 1452, 1408, 1381, 1277, 1240, 1218, 1194, 1166, 1139, 1091, 981, 851, 769, 752, 739, 697, 692 cm$^{-1}$. $^{19}$F NMR (CDCl$_3$, 282 MHz) δ -78.7. HRMS calcd for $C_{28}H_{24}F_3N_5O_3Na^+$: 530.1662; Found: 530.1672.
Entry 1, Table 5.2: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 25.0 min (exo minor) t_R 31.1 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 99:01, 1.0 mL/ min] as 96% ee for the exo cycloadduct.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,SS)-2,3,5-triphenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methane (5.42b):
Foamy solid, [α]_D^25 -192.4 (c 1.0, CHCl_3), (exo/endo= >98:02); ^1H NMR (CDCl_3, 400 MHz); δ 4.24 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 5.46 (d, J = 7.6 Hz, 1H), 6.44 (d, J = 7.6 Hz, 1H), 6.58 (s, 1H), 6.88 (s, 1H), 6.96-6.99 (m, 3H), 7.03-7.08 (m, 3H), 7.11-7.15 (m, 2H), 7.20-7.30 (m, 9H), 7.47-7.49 (d, J = 7.4 Hz, 2H); ^13C NMR (CDCl_3, 100 MHz); δ 58.4, 71.7, 81.9, 86.9 (q, ^2J_{CF} = 28.6 Hz), 115.6, 122.3, 122.9, 124.6 (q, ^1J_{CF} = 284.4 Hz), 125.5, 127.0, 128.0, 128.3, 128.4, 128.6, 128.7, 128.8, 129.5, 130.1, 133.2, 134.0, 136.0, 139.0, 150.6, 183.2; ^19F NMR (CDCl_3, 282 MHz) δ -75.55; IR (KBr) 3063, 1692, 1490, 1454, 1409, 1259, 1165, 1127, 757, 700 cm^{-1}. HRMS calcd for C_{33}H_{26}F_{3}N_{3}O_{3}Na^{+}: 592.1818; Found: 592.1815.

Entry 2, Table 5.2: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 24.3 min (exo minor) t_R 27.7 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 98:02, 1.0 mL/ min] as 95% ee for the exo cycloadduct.
(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5S)-5-(4-chlorophenyl)-2,3-diphenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone (5.42c):

Foamy solid, \([\alpha]_D^{25} -196.9\) (c 1.0, CHCl₃), (exo/endo = >98:02); \(^1^H\) NMR (CDCl₃, 400 MHz); \(\delta\) 4.26 (d, \(J = 10.5\) Hz, 1H), 4.37 (d, \(J = 10.5\) Hz, 1H), 5.43 (d, \(J = 7.6\) Hz, 1H), 6.40 (d, \(J = 7.6\) Hz, 1H), 6.60 (s, 1H), 6.87 (s, 1H), 6.95-7.15 (m, 8H), 7.20-7.31 (m, 8H), 7.45-7.53 (m, 3H); \(^1^C\) NMR (CDCl₃, 100 MHz); \(\delta\) 58.4, 71.8, 82.0, 86.5 (q, \(^{19}J_{CF} = 28.5\) Hz), 115.9, 122.7, 123.1, 124.4 (q, \(^{19}J_{CF} = 287.5\) Hz), 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.5, 130.0, 132.6, 133.1, 135.1, 135.8, 139.0, 150.4, 183.1; \(^{19}F\) NMR (CDCl₃, 282 MHz) \(\delta\) -75.64; IR (KBr) 3063, 1733, 1694, 1652, 1599, 1540, 1490, 1455, 1407, 1257, 1166, 1126, 1095, 1040, 998, 954, 899, 854, 821, 757, 695 cm\(^{-1}\). HRMS calcd for C\(_{33}\)H\(_{25}\)ClF\(_3\)N\(_3\)O\(_3\)Na\(^+\): 626.1429; Found: 626.1442.

**Entry 3, Table 5.2:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_R\) 16.9 min (exo major) \(t_R\) 32.31 min (exo minor) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 99:01, 1.0 mL/ min] as 98% ee for the exo cycloadduct.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5S)-5-(4-fluorophenyl)-2,3-diphenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone (5.42d):

Foamy solid, \([\alpha]_D^{25} -171.6\) (c 1.0, CHCl₃), (exo/endo = >98:02); \(^1^H\) NMR (CDCl₃, 400 MHz); \(\delta\) 4.26 (d, \(J = 10.5\) Hz, 1H), 4.37 (d, \(J = 10.5\) Hz, 1H), 5.44 (d, \(J = 7.6\) Hz, 1H), 6.41 (d, \(J = 7.6\) Hz, 1H), 6.60 (s, 1H), 6.84 (s, 1H), 6.93-7.08 (m, 9H), 7.11-
7.15 (m, 2H), 7.20-7.31 (m, 5H) 7.46-7.47 (m, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \(\delta\) 58.4, 71.8, 81.9, 86.5 (q, \(^2J_{CF} = 29.1 \text{ Hz}\)), 115.3 (d, \(^2J_{CF} = 36.9 \text{ Hz}\)), 115.8, 122.6, 123.0, 125.6, 125.9, 128.0, 128.2, 128.4, 128.7, 128.8, 128.9 (d, \(^3J_{CF} = 7.7 \text{ Hz}\)), 129.1, 129.5, 129.8 (d, \(^4J_{CF} = 4.1 \text{ Hz}\)), 130.0, 133.1, 134.5, 135.8, 139.0, 150.4, 162.9 (d, \(^1J_{CF} = 248.9 \text{ Hz}\)), 183.1.

\(^{19}\)F NMR (CDCl\(_3\), 282 MHz) \(\delta\) -76.0, -112.9; IR (KBr) 3063, 3031, 1694, 1652, 1599, 1588, 1512, 1490, 1455, 1436, 1408, 1259, 1231, 1180, 1164, 1123, 1093, 1041, 999, 954, 898, 829, 757, 694, 667 cm\(^{-1}\). HRMS calcd for C\(_{33}\)H\(_{25}\)F\(_4\)N\(_3\)O\(_3\)Na\(^+\): 610.1724; Found: 610.1728.

**Entry 4, Table 5.2:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) \(t_R\) 17.4 min (exo major) \(t_R\) 27.5 min (exo minor) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 98:02, 1.0 mL/ min] as 93% ee for the exo cycloadduct.

(1-((Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5S)-5-(3-fluorophenyl)-2,3-diphenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone

(5.42e):

Foamy solid, [\(\alpha\)]\(_D\)\(^{25}\) -213.9 (c 1.0, CHCl\(_3\)), (exo/endo = >98:02); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \(\delta\) 4.29 (d, \(J = 10.5 \text{ Hz}, 1\)H), 4.38 (d, \(J = 10.5 \text{ Hz}, 1\)H), 5.44 (d, \(J = 7.6 \text{ Hz}, 1\)H), 6.41 (d, \(J = 7.6 \text{ Hz}, 1\)H), 6.58 (s, 1H), 6.87 (s, 1H), 6.97-6.99 (m, 4H), 7.03-7.08 (m, 3H), 7.09-7.14(m, 2H), 7.21-7.31 (m, 8H), 7.46 (d, \(J = 7.6\text{Hz}, 2\)H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz); \(\delta\) 58.4, 71.7, 82.0, 86.4 (q, \(^2J_{CF} = 30.2 \text{ Hz}\)), 114.7 (d, \(^2J_{CF} = 23.9 \text{ Hz}\)), 115.8, 116.0, 122.7 (2 carbons), 123.1, 124.5 (q, \(^1J_{CF} = 287.8 \text{ Hz}\)), 125.6, 128.1, 128.2, 128.4, 128.7 (d, \(^4J_{CF} = 5.4 \text{ Hz}\)), 129.5, 129.8 (d, \(^3J_{CF} = 8.6 \text{ Hz}\)), 130.1, 133.1, 134.5, 135.6, 138.5 (d, \(^3J_{CF} = 7.2 \text{ Hz}\),

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Entry 5, Table 5.2: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR 15.8 min (exo minor) tR 21.0 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 98:02, 1.0 mL/ min] as 91% ee for the exo cycloadduct.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5S)-2,3-diphenyl-5-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)isoxazolidin-4-yl)methanone (5.42f):

Foamy solid, [α]D 25 -155.1 (c 1.0, CHCl₃), (exo/endo = >98:02); ¹H NMR (CDCl₃, 400 MHz); δ 4.23 (d, J = 10.4 Hz, 1H), 4.35 (d, J = 10.4 Hz, 1H), 5.46 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 7.5 Hz, 1H), 6.61 (s, 1H), 6.90 (s, 1H), 6.90-6.95 (m, 3H), 7.01-7.05 (m, 4H), 7.12-7.16 (m, 2H), 7.22-7.29 (m, 6H), 7.37-7.41 (m, 1H), 7.46-7.51 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz); δ 58.5, 71.7, 82.0, 86.5 (q, ²JCFC = 29.6 Hz), 116.0, 122.8, 123.1, 123.8 (q, ²JCFC = 272.5 Hz), 124.4, 124.3 (q, ²JCFC = 287.7 Hz), 125.8, 128.1, 128.2, 128.4, 128.7, 128.8, 128.9 (2 carbons), 129.5, 130.0, 130.4, 130.8, 133.0, 135.2, 135.6, 138.9, 150.3, 183.0. ¹⁹F NMR (CDCl₃, 282 MHz) δ -62.77, -75.62; IR (KBr) 3145, 3129, 3066, 303, 2985, 1685, 1598, 1492, 1454, 1406, 1332, 1295, 1260, 1182, 1168, 1156, 1124, 108, 911, 857, 758, 737, 693 cm⁻¹. HRMS calcd for C₃₄H₂₅F₆N₃O₃Na⁺: 660.1692 Found: 660.1685.
Entry 6, Table 5.4: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) tR 18.2 min (exo major) tR 24.6 min (exo minor) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 99:01, 1.0 mL/ min] as 90% ee for the exo cycloadduct.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R)-5,5-dimethyl-2,3-diphenylisoxazolidin-4-yl)methanone (5.42g):
Oil, [α]D25 -43.3 (c 1.12, CHCl3), (exo/endo= >98:02); 1H NMR (CDCl3, 400 MHz); δ 1.36 (s, 3H), 1.46 (s, 3H), 4.52 (d, J = 10.8 Hz, 1H), 4.59 (d, J = 10.8 Hz, 1H), 5.30 (d, J = 8.0 Hz, 1H), 5.35 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 6.82-6.91 (m, 4H), 7.06-7.09 (m, 1H), 7.14-7.20 (m, 6H), 7.27-7.34 (m, 3H), 7.45-7.47 (m, 2H); 13C NMR (CDCl3, 100 MHz); δ 22.4, 28.0, 62.3, 72.4, 82.0, 84.7, 113.7, 120.6, 122.7, 125.2, 127.4, 127.5, 128.4, 128.7 (2 carbons), 129.6, 130.3, 133.2, 138.6, 139.1, 153.1, 186.5; IR (KBr) 3150, 3135, 3061, 2995, 1680, 1591, 1487, 1450, 1420, 1313, 1290, 1267, 1175, 1169, 1152, 1120, 1067, 923, 845, 765, 735, 692 cm⁻¹. HRMS calcd for C28H27N3O3Na+: 476.1945 Found: 476.1942.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5R)-3-(4-bromophenyl)-5-methyl-2-phenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone (5.42h):
Foamy solid, [α]D25 -24.9 (c 1.0, CHCl3), (exo/endo= >98:02); 1H NMR (CDCl3, 400 MHz); δ 1.64 (s, 3H), 4.62 (d, J = 10.5 Hz, 1H), 4.73 (d, J = 10.5 Hz, 1H), 5.26 (d, J = 8.4 Hz, 1H), 5.81 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 6.88-6.96 (m, 4H), 7.15-7.23 (m, 4H), 7.34-7.39 (m, 3H); 13C NMR (CDCl3, 100 MHz); δ 16.6, 56.7, 71.2, 82.2,
83.9 (q, $^2J_{CF} = 28.4$ Hz), 115.6, 122.6, 123.5, 125.2 (q, $^1J_{CF} = 287.5$ Hz), 125.9, 128.8, 128.9, 129.0, 129.7 130.0 (2 carbons), 131.5, 133.1, 135.9, 138.6, 149.9, 183.6; $^{19}$F NMR (CDCl$_3$, 282 MHz) δ -78.5; IR (KBr) 3091, 3065, 3036, 2924, 1684, 1595, 1486, 1455, 1408, 1384, 1290, 1280, 1241, 1213, 1163, 1135, 1092, 1009, 980, 856, 757, 693 cm$^{-1}$. 

HRMS calcd for C$_{28}$H$_{23}$BrF$_3$N$_3$O$_3$Na$: 608.0767; Found: 608.0775.

**Entry 2, Table 5.3:** The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 26.8 min (exo minor) $t_R$ 33.4 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:isopropanol, 98:02, 1.0 mL/min] as 94% ee for the exo cycloadduct.

(1-(Benzyloxy)-1H-imidazol-2-yl)((3R,4R,5R)-3-(4-methoxyphenyl)-5-methyl-2-phenyl-5-(trifluoromethyl)isoxazolidin-4-yl)methanone (5.42i):

Foamy solid, [α]$_D^{25}$ -40.3 (c 1.0, CHCl$_3$), (exo/endo= 88:12); $^1$H NMR (CDCl$_3$, 400 MHz); δ 1.67 (s, 3H), 3.57 (s, 3H), 4.55 (d, $J = 10.4$ Hz, 1H), 4.67 (d, $J = 10.4$ Hz, 1H), 5.27 (d, $J = 8.4$ Hz, 1H), 5.78 (d, $J = 8.4$ Hz, 1H), 6.67-6.69 (m, 2H), 6.74 (s, 1H), 6.89-6.93 (m, 4H), 7.14-7.19 (m, 4H), 7.31-7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz); 16.7, 55.2, 56.7, 71.4, 82.2, 83.5 (q, $^2J_{CF} = 29.8$ Hz), 113.8, 115.6, 122.3, 123.1, 125.3 (q, $^1J_{CF} = 287.5$ Hz), 125.7, 128.5, 128.6, 129.4, 129.6 130.1, 133.2, 138.6, 150.2, 159.4, 183.6; $^{19}$F NMR (CDCl$_3$, 282 MHz) δ -78.8; IR (KBr) 3127, 3038, 3002, 2924, 1684, 1597, 1512, 1489, 1456, 1408, 1248, 1169, 1135, 1094 cm$^{-1}$. HRMS calcd for C$_{29}$H$_{26}$F$_3$N$_3$O$_4$Na$: 560.1768; Found: 560.1768.
Entry 3, Table 5.3: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 36.0 min (exo minor) $t_R$ 41.5 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 98:02, 1.0 mL/ min] as 93% ee for the exo cycloadduct.

4-((3R,4R,5R)-4-(1-(Benzyloxy)-1H-imidazole-2-carbonyl)-5-methyl-2-phenyl-5-(trifluoromethyl)isoxazolidin-3-yl)benzonitrile (5.42j):

Foamy solid, $[\alpha]_D^{25} -72.2$ (c 1.0, CHCl$_3$), (exo/endo= >98:02); $^1$H NMR (CDCl$_3$, 400 MHz); $\delta$ 1.67 (s, 3H), 3.57 (s, 3H), 4.55 (d, $J = 10.4$ Hz, 1H), 4.67 (d, $J = 10.4$ Hz, 1H), 5.27 (d, $J = 8.4$ Hz, 1H), 5.78 (d, $J = 8.4$ Hz, 1H), 6.67-6.69 (m, 2H), 6.74 (s, 1H), 6.89-6.93 (m, 4H), 7.14-7.19 (m, 4H), 7.31-7.36 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz); $\delta$ 16.5, 56.8, 71.0, 82.3, 84.1 (q, $^2J_{CF} = 29.8$ Hz), 112.0, 115.4, 118.3, 122.8, 123.6, 126.1, 127.6 (q, $^1J_{CF} = 217.0$ Hz), 128.9 (2 carbons), 129.9, 130.0, 132.1, 138.7, 142.4, 149.6, 183.2; $^{19}$F NMR (CDCl$_3$, 282 MHz) $\delta$ -78.8; IR (KBr) 3127, 3038, 3002, 2962, 2840, 1685, 1597, 1512, 1489, 1456, 1408, 1248, 1169, 1135, 1094 cm$^{-1}$. HRMS calcd for C$_{29}$H$_{23}$F$_3$N$_4$O$_3$Na$: 555.1614; Found: 555.1599.

Entry 4, Table 5.3: The enantiomeric purity was determined by HPLC (254 nm, 25 °C) $t_R$ 36.0 min (exo minor) $t_R$ 41.5 min (exo major) [Chiralpak AD3 (0.46 cm x 25 cm) (from Diacel Chemical Ltd.) Hexane:Isopropanol, 98:02, 1.0 mL/ min] as 93% ee for the exo cycloadduct.
5.9. Determination of Relative Stereochemistry

Relative stereochemistry of products was determined as \textit{exo} by single X-ray crystal analysis of cycloadduct 5.42d (Figure 5.7). The relative stereochemistry of all other cycloadducts were tentatively assigned as \textit{exo} based on the stereochemistry of 5.42d.

![Crystal Structure of Exo Cycloadduct 5.42d]

Figure 5.7. Crystal Structure of \textit{Exo} Cycloadduct 5.42d

5.10. References


