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UMI
Mathieu Lemay  
AUTEUR DE LA THÈSE / AUTHOR OF THESIS  

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TITRE DE LA THÈSE / TITLE OF THESIS  

William Ogilvie  
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR  

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR  

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS  

Robert Ben  
Michael Kerr  

Tony Durst  
Jeffrey Manthorpe  

Gary W. Slater  
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies
Design, Development and Mechanistic Studies of Hydrazide-Catalyzed Enantioselective Cycloaddition Reactions

Thesis by
Mathieu Lemay

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Candidate
Mathieu Lemay

Supervisor
William W. Ogilvie

Ottawa-Carleton Chemistry Institute
Faculty of Science
University of Ottawa

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Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.
À mes parents, Carole et Jerry
To all of you seeking a PhD, remember that it's all about the journey, not the actual destination.

"Many of life's failures are people who did not realize how close they were to success when they gave up."

- Thomas Edison
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Abstract

Novel cyclic hydrazides were designed and found to function as asymmetric organocatalysts in aqueous Diels-Alder reactions. The LUMO-lowering activation of α,β-unsaturated aldehydes by the reversible formation of iminium ions from hydrazides was used as an efficient platform to achieve highly enantioselective Diels-Alder cycloadditions. The implementation of the hydrazide functionality promoted faster iminium formation relative to secondary amine catalysts via the α-heteroatom effect.

The mechanism of the enantioselective hydrazide catalyzed Diels-Alder cycloaddition was investigated in detail. Both the formation of the reactive iminium species and the hydrolysis of the product iminium intermediates were found to be extremely rapid, leaving the cycloaddition as the kinetically significant step. Mechanistic studies using NMR showed that a retro Diels-Alder reaction occurred during the catalytic cycle suggesting a thermodynamic component to the reaction. Conformational control was utilized to design an improved hydrazide organocatalyst for asymmetric Diels-Alder reactions, thus introducing a new aspect to organocatalysis. Enhanced diastereoselectivities and enantioselectivities of up to 96% were achieved by the application of the rigidified catalyst. The first crystal structure of a key iminium intermediate in an organocatalyzed process was also achieved.

The hydrazide-catalyzed protocol was expanded to the enantioselective [3+2] cycloadditions of nitrones with α,β-unsaturated aldehydes to provide isoxazolidines in excellent optical purity.

A synthetic approach to the α-oximation of carbonyls was investigated. 1-chloro-1-nitroso cyclohexane can be used in conjunction with cyclohexanone with catalytic L-proline to provide α-oximated product in 98% enantiomeric excess, in modest yield.

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Å: Ångström
Ac: Acetyl
Ar: Aryl
BHT: 2,6-Di-tert-butyl-4-methylphenol
Bmim: 1-butyl-3-methylimidazolium
Boc: tert-butylloxy carbonyl
Bn: Benzyl
br: broad
calcd: calculated
Cbz: Benzyloxycarbonyl
Cl: Chemical ionization
COSY: Correlation spectroscopy
Cy: Cyclohexyl
ΔE: Energy Difference
°C: Degree Celcius
d: doublet
DABCO: 1,4-Diazabicyclo[2.2.2]octane
DCC: N,N'-Dicyclohexylcarbodiimide
dd: doublet of doublet
ddd: doublet of doublet of doublet
DHQD: dihydroquinidyl
DIPEA: N,N-Diisopropylethylamine
DPEN: R,R-1,2-diamino-1,2-diphenylethane
dq: doublet of quartet
dt: doublet of triplet
DMF: Dimethyl formamide
DMSO: Dimethyl sulfoxide
EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide
EDG: Electron-donating group
ee: enantiomeric excess
EI: Electron Impact
eq./equiv.: Equivalent
Et: Ethyl
ev: Electron-volt
EWG: Electron-withdrawing group
FAB: Fast atom bombardment ionization
FMO: Frontier molecular orbital
g: gram
GLC: Gas liquid chromatography
HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HMDS: Hexamethyl disilazide
HOAc: Acetic acid
HOBT: 1-Hydroxybenzotriazole
HOMO: Highest occupied molecular orbital
HPLC: High Pressure Liquid Chromatography
hr: hour
HRMS: High resolution mass spectrometry
Hz: Hertz
IMDA: Intramolecular Diels-Alder
IR: Infrared
kCal: Kilocalorie
LA: Lewis acid
LUMO: Lowest unoccupied molecular orbital
m: multiplet
M: Molar
mCPBA: 3-Chloroperbenzoic acid
Me: Methyl
mg: milligram
MHz: Megahertz
min: minute
mL millimeter
mmol: millimole
mp: Melting point
MS: Mass spectrometry
MTO: Methyltrioxorhenium
N: Normal
n/d: Not determined
NHC: N-heterocyclic carbene
NMR: Nuclear magnetic resonance spectroscopy
NOESY: Nuclear Overhauser Enhancement Spectroscopy
p: para
PEG: Poly ethleneglycol
Ph: Phenyl
PHANOL: 4,12-Dihydroxy[2.2]paracyclophane
pKa: Acid dissociation constant
ppm: Parts per million
p-TSA: para-Toluene sulfonic acid
s: singlet
SAMP: (S)-(−)-1-Amino-2-(methoxymethyl)pyrrolidine
SM: Starting material
TADDOL: (4R,5R)-2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
TMS: Trimethylsilyl
TFA: Trifluoroacetic acid
TfOH: Trifluoromethane sulfonic acid
THF: Tetrahydrofuran
TLC: Thin layer chromatography
TOCSY: Total correlated spectroscopy
t_r: Retention time
Ts: Tosyl
μL: microliter
USD: United-States dollars
Xc: Chiral auxiliary
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1

Organocatalysis

1.1 Introduction

In order to induce asymmetry to a molecule, chemists have developed a plethora of tools. In the last three decades, the achievements in catalytic asymmetric synthesis consist of some of the most remarkable developments in synthetic chemistry. Nowadays, asymmetric catalysis has become of paramount importance to the development of new chemical processes. The value of catalysis to the chemical community is clearly illustrated by the fact that the Nobel Prize in chemistry has been awarded on three occasions, including twice in the past six years, to chemists for their work in catalysis.

Transition metal complexes have been utilized to catalyze a broad range synthetic transformations such as asymmetric epoxidations, dihydroxylations, hydrogenations and olefin metathesis with much success. Metal-catalyzed processes have however been somewhat blemished by their high price, toxicity, pollution, and product contamination, making their use less appealing.


Chemists have formulated alternatives to the use of metals in catalysis in order to address these issues. Biocatalysis is one of these solutions, in which enzymes are employed to carry out chemical reactions. More recently, chemists have explored a number of catalytic processes facilitated by small, purely organic molecules. The development of these so called "organocatalysts" is becoming one of the most effervescent fields in organic chemistry today.

1.2 Catalysis by Organic Molecules

The term organocatalysis is defined as "the acceleration of chemical reactions with a sub-stoichiometric amount of organic compound which does not contain a metal ion."\(^9\)\(^10\) The idea that small organic molecules can be used to mimic the outcome of enzyme-mediated reactions is stunning. Analogous to enzymes, these small molecules take advantage of the reversible formation of an activated intermediate bearing a chiral moiety to enhance the rate and selectivity of a given reaction. Organocatalysts are particularly attractive for their straightforward operation, ease of recovery, air and water tolerance and lack of product/substrate inhibition. Moreover, these small organic catalysts can be easily synthesized using enantiopure organic materials found in nature such as carbohydrates, amino and nucleic acids and small peptides.

The earliest report of an asymmetric organocatalyzed reaction dates back to 1912, when Fiske and Bredig used alkaloids to catalyze the synthesis of cyanohydrins.\(^11\) But perhaps the most significant organocatalyzed reaction was achieved in the mid-seventies, when the Weichert and Parrish groups reported that sub-stoichiometric amounts of \(L\)-proline could catalyze a highly enantioselective Robinson annulations to afford ketone 1.2.\(^12\)

---


\(^11\) Bredig, G.; Fiske, P. S. \textit{Bichem. Z.} 1912, 46, 7.

It would be another quarter century from the discovery of the Hajos-Parrish-Eder-Sauer-Wiechert reaction until the door to organocatalysis would be reopened. This time however, the full potential catalysis using small organic molecules would be realized. Since the year 2000, the field of enantioselective organic catalysis, although still in its infancy, has impressed the scientific community with its potential and broad applicability to organic synthesis. With such interest invested toward organocatalysis, several modes of activation have been surveyed to offer alternatives to conventional catalysis. Catalysis by organic molecules can be classified into five types of activation: (i) enamine; (ii) iminium; (iii) phase-transfer; (iv) nucleophilic and (v) hydrogen-bonding. It is certainly not possible to survey all transformations catalyzed by these small catalysts, but before examining reactions specific to the work in this thesis, the following section will highlight selected transformations made possible by use of organic molecules within the five modes of activation.

Many organocatalytic reactions proceed through the enamine-iminium cycle (Scheme 1.2). With the loss of water, a secondary amine along with an acid co-catalyst can react with a carbonyl moiety to form an iminium ion 1.4. The iminium ion can either undergo a chemical transformation or, if an enolizable proton is present, the reversible formation of enamine 1.5 can occur. The formation of an enamine leads to an increase in electron density at the α-carbon, thereby acting as a nucleophile, whereas, iminium ions lead to a decrease in electron density making the species electrophillic. These two types of activation modes are complementary and can be used simultaneously in the same reaction sequence.13

---

Proline 1.6 is without a doubt the most commonly used catalyst to generate enamine intermediates. This simple secondary amine catalyst became of recent synthetic interest when List, Barbas and Lerner\(^\text{14}\) applied it toward intramolecular enantioselective aldol reactions in 2000 (Scheme 1.3). In the catalytic sequence, this amino acid functions as a bifunctional catalyst in which the nucleophilic nitrogen atom reacts with the carbonyl of the nucleophilic component to form reactive enamine 1.9. During this process, the carboxylic acid moiety serves as a Brønsted acid, and creates a hydrogen bonding network with explicit groups on the electrophillic partner, in this case aldehyde 1.10, thus facilitating highly organized transition states. Many research groups have proposed transition state models to explain the remarkably high catalytic activity of proline.\(^\text{14,15}\) The transition state provided by Houk and co-workers\(^\text{16}\) 1.11, in which a proline molecule features O-H---O and NCH---O hydrogen bonds, is the generally accepted model. Upon formation of the new carbon-carbon bond, the residual iminium ion adduct 1.12 is then hydrolyzed by the water present in the medium to afford the enantioenriched β-keto alcohol product 1.13 and L-proline.
Since this initial report, the scope of reactions catalyzed by proline has been extended to include transformations such as the Mannich reaction to form β-amino aldehydes and ketones 1.18 (Figure 1.1). The intermolecular cross-aldol between two different aldehydes 1.14 can also be achieved if only one of the aldehyde partners can form an enamine intermediate with proline. As an alternative to the Sharpless dihydroxylation, the reaction of hydroxy ketones with an electrophillic aldehyde affords enantiomerically pure anti-diols 1.15. In addition to the formation of carbon-carbon bonds, the concept of enamine catalysis has been extended to

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enantioselective α-heteroatom functionalization of aldehydes and ketones. When the enamine intermediate is trapped with an alkyl diazodicarboxylate, a nitrogen group is installed in the α-position of the carbonyl allowing access to amino acid derivatives 1.17.20 Alternatively, when nitrosobenzene is used in conjunction with a proline catalyzed enamine intermediate, α-oxygenated compounds are obtained which can be easily transformed into useful chiral building blocks.21

Figure 1.1 Selected scope of reactions catalyzed by proline

- Mannich reaction
- α-amination
- α-aminoxylation
- Dihydroxylation
- Aldehyde cross-aldol

Although proline can catalyze numerous transformations in excellent yield and optical purity, it does have its shortcomings. For example, the proline-catalyzed addition of ketones to nitroalkenes results in poor yields and low selectivities. To overcome such difficulties, researchers have designed a range of proline-derived catalysts in attempts to expand the scope of enamine catalyzed protocols (Figure 1.2). Although few catalysts have been able to mimic the success achieved with proline, diphenyl prolinol and its derivatives 1.19, have been effectively applied toward several asymmetric transformations including conjugate additions between enals and nitro olefins 1.24 and α,β-unsaturated ketones 1.25 as shown in Figure 1.2.²²

**Figure 1.2 Proline alternatives and the applications of diphenyl prolinol and its derivatives to conjugate additions**

---

Enamine catalysis has covered significant ground in the last seven years but its supremacy is concurrently being challenged by new alternate modes of activation such as catalysis via iminium ions.

### 1.2.2 Iminium Catalysis

In this mode of activation the active species is an iminium ion formed reversibly by the reaction of a carbonyl group and a secondary amine (see Scheme 1.2). As a result, the LUMO orbital of the iminium intermediate is lowered in energy permitting interaction with various coupling partners. Iminium catalysis provides a metal-free alternative to Lewis acid activation of α,β-unsaturated compounds. This area of iminium catalysis remained largely unexplored until MacMillan and co-workers showed that imidazolidinone catalyst 1.30 could facilitate the Diels-Alder cycloaddition in high optical purity (Scheme 1.4).\(^\text{24}\)

**Scheme 1.4 The first iminium-catalyzed enantioselective Diels-Alder cycloaddition**

These catalysts provide rigid iminium ion geometry, generally directed by the geminal substitution, whereas the benzylic side-chain induces facial discriminations, leading to attack at only one face of the activated conjugated system. The catalyst can be easily tailored in order to increase the reactivity and selectivity of the imidazolidinone toward specific transformations.

Iminium catalysis can promote an array of cycloaddition reactions including the [4+2] Diels-Alder, 24 [3+2] 1,3-dipolar nitrone cycloaddition 25 and [4+3] processes 26 in excellent yields and enantiomeric excesses (Figure 1.3). Iminium ion catalysis also offers an attractive alternative to the Friedel-Crafts alkylation of heteroaromatics. By means of conjugate addition, aromatic nucleophiles such as pyrroles, 27 indoles 28 and anilines 29 can be added in high selectivity to \( \alpha,\beta \) unsaturated compounds and produce pharmaceutically valuable building blocks. Iminium catalysis can also promote the enantioselective conjugate reductions of terminally substituted enals using Hantzch esters as a hydride source to afford optically pure \( \beta \)-substituted aldehydes 1.38. 30

Iminium and enamine catalysis can also be used in tandem. Upon the conjugate addition of a nucleophile to an iminium-activated enal, an enamine is generated which can be trapped by an appropriate electrophile. MacMillan has shown that a cascade reaction involving Hantzsch esters 1.43 together with electrophillic sources of chloride 1.40 or fluoride 1.44 can add HCl or HF asymmetrically across trisubstituted olefins 1.39.31

---

1.2.3 Phase-Transfer Catalysis

Phase transfer catalysts are typically quaternary ammonium salts, which facilitate the migration of a molecule from one phase to another in a heterogeneous solvent system. The first step typically involves formation of a metal enolate with a base, followed by ion-exchange of the anion with the catalyst. This results in a lipophilic chiral onium enolate which brings the reagent into the organic phase for the reaction with an electrophile. If the salt is chiral and sufficiently fast ion-exchange occurs, effective shielding of one of reactive faces will produce optically pure product. Modified cinchona alkaloid salts 1.47 have been successfully used for enantioselective alkylation reactions of glycine imines 1.46 in the synthesis of unnatural amino acid derivatives 1.48.\(^\text{32}\) More recently, this class of phase transfer catalyst has promoted the α-arylation of β-ketoesters 1.49, via an SNAr mechanism in excellent enantiomeric excess (Scheme 6).\(^\text{33}\)


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Scheme 1.6 Cinchona alkaloids used as phase transfer catalysts in the synthesis of unnatural amino acids derivatives and \( \alpha \)-arylation of \( \beta \)-ketoesters

\[
\begin{align*}
\text{Ph} & - \text{N} - \text{O} & \text{Ot-Bu} \\
\text{Ph} & & 1.46
\end{align*}
\]

\[
\begin{align*}
\text{10\% mol} & \ 1.47 \\
\text{BnBr} & \\
\text{KOH or CsOH} & \ \\
\text{-78°C - r.t.} & \\
\rightarrow & \\
\text{Ph} & - \text{N} - \text{O} & \text{Ot-Bu} \\
\text{Bn} & & 1.48
\end{align*}
\]

68-95\% yield

ee 60-94\%

\[
\begin{align*}
\text{R} & \text{O} & \text{Ot-Bu} & \text{O} \\
\text{Et} & & 1.49
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{N} & \text{F} & \text{NO} & \text{2} \\
\text{NO} & & 1.50
\end{align*}
\]

\[
\begin{align*}
\text{CsOH, -40°C} & \ \\
\text{PhMe-CHCl}_3 & \\
\rightarrow & \\
\text{O}_2\text{N} & \text{NO} & \text{2} \\
\text{CO}_2\text{Et} & & 1.51
\end{align*}
\]

65-96\% yield
up to 92\% ee

The range of reactions catalyzed by phase transfer catalysts has been extended with the introduction ammonium salts 1.53 encompassed within a binaphthyl framework. These \( N \)-spiro \( C_2 \)-symmetric salts effect the conjugate addition of nitroalkanes 1.54 to various alkylidenemalonates 1.55, furnishing products that can be converted to the corresponding \( \gamma \)-amino acids without loss of optical purity.\(^{34}\) Alternatively, when a diarylmethanol functionality is incorporated into the framework of the catalyst as a substrate-recognition site, enone epoxidations can be achieved with rigorous stereocontrol under mild conditions (Scheme 1.7).\(^{35}\)


Scheme 1.7 $N$-spiro $C_2$-symmetric onium salts for the conjugate addition of nitroalkanes and enone epoxidation

$R_3 = \text{alkyl}$  
$R_4 = \text{aryl}$

$R_5 = \text{aryl, f-Bu}$

\[ R_3\text{-NO}_2 + R_4\text{-CO}_2\text{-Pr} \xrightarrow{1\% \text{ mol cat. 1.52}} R_3\text{-CO}_2\text{-Pr} \]

$\text{Cs}_2\text{CO}_3, \text{PhMe, } 0^\circ\text{C}$

$>97\% \text{ yield}$  
$\text{dr}>8:2$  
$\text{ee} \geq 95-99\%$

\[ R_5\text{-CO}_2\text{-Pr} \xrightarrow{3\% \text{ mol cat. 1.53}} R_5\text{-CO}_2\text{-Pr} \]

$\text{NaOCl, PhMe, } 0^\circ\text{C}$

$80-99\% \text{ yield}$  
$\text{ee}>92\%$

1.2.4 Nucleophilic Catalysis

Cinchona alkaloids can also be used as bases to deprotonate moderately acidic protons such as those found in malonates or thiols. This forms a contact ion complex between the anion and the protonated amine, resulting in a chiral environment around the anion that permits enantioselective reactions to occur with electrophilic partners.\textsuperscript{36} Catalysts in which two cinchona alkaloids are attached together, such as the bis(dihydroquinidyl)pyrimidine derivative

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(DHQD)$_2$PYR can be more effective than cinchona alkaloids themselves. These commercially available ethers of bis-cinchona alkaloids have been used to catalyze several Brønsted base-mediated transformations including the conjugate addition of thiols 1.59 to a variety cyclic enones 1.60 forming β-mercaptoketones 1.61 in excellent enantioselectivity (Scheme 1.8).\(^{37}\) Similar catalysts also accelerate the allylic amination of diimides 1.63 to provide γ-aminated compounds 1.64 in reliable yields and excellent selectivities.\(^{38}\)

Scheme 1.8 Transformations promoted by asymmetric nucleophilic catalysts Bis(dihydroquinidyl)pyrimidine

\[ \text{Scheme 1.8 Transformations promoted by asymmetric nucleophilic catalysts Bis(dihydroquinidyl)pyrimidine} \]

\[ \text{MeO}_2\text{C} - \text{H} - \text{R}^1 + \text{Boc} - \text{N} - \text{N} - \text{Boc} \stackrel{(\text{DHQD})_2\text{PYR}}{\xrightarrow{\text{CH}_2\text{Cl}_2, -24^\circ\text{C}}} \text{MeO}_2\text{C} - \text{H} - \text{R}^1 \]

\[ \text{R}^1 = \text{alkyl, Bn} \]

\[ \text{77-91\% yield} \]

\[ \text{ee > 94\%} \]

\[ \text{Scheme 1.8 Transformations promoted by asymmetric nucleophilic catalysts Bis(dihydroquinidyl)pyrimidine} \]

\[ \text{MeO}_2\text{C} - \text{H} - \text{R}^1 + \text{Boc} - \text{N} - \text{N} - \text{Boc} \stackrel{(\text{DHQD})_2\text{PYR}}{\xrightarrow{\text{CH}_2\text{Cl}_2, -24^\circ\text{C}}} \text{MeO}_2\text{C} - \text{H} - \text{R}^1 \]

\[ \text{R}^1 = \text{alkyl, Bn} \]

\[ \text{65-90\% yield} \]

\[ \text{ee 86-99\%} \]

\[ \text{Scheme 1.8 Transformations promoted by asymmetric nucleophilic catalysts Bis(dihydroquinidyl)pyrimidine} \]


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Inspired by the coenzyme thiamine, nucleophilic carbenes are emerging as excellent tools for the generation of reactive acyl ion equivalents from aldehydes. Through this *Umpolung* process, carbonyls can react as nucleophilic species that can undergo reactions with various electrophilic partners. As depicted in Scheme 1.9, several N-heterocyclic carbene catalysts have been designed and successfully applied to the asymmetric benzoin\(^{39}\) and Stetter\(^{40}\) reactions to afford \(\alpha\)-keto alcohols 1.67 and heterocyclic chromanone analogues 1.70, respectively.

Scheme 1.9 Chiral N-heterocyclic carbenes in the asymmetric benzoin and Stetter reactions

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1.2.5 Hydrogen-Bonding Catalysis

Hydrogen-bonding catalysts activate the electrophilic partner in a similar fashion to that of Lewis acids by producing a weak hydrogen bond that coordinates to the lone pairs of a carbonyl moiety.\(^{41}\) This lowers the electron density at the oxygen of the carbonyl, resulting in a lower energy LUMO, thus activating the group toward nucleophilic attack. When an asymmetric catalyst is used, this type of activation generates a chiral environment around the electrophile to provide optically enriched products.

Chiral oligopeptide thioureas \(1.71\) are very powerful catalysts capable promoting a range of chemical transformations between imines and an assortment of nucleophiles in processes such as the Strecker,\(^{42}\) Mannich,\(^{43}\) nitro-Mannich\(^ {44}\) and hydrophosphorylation reactions\(^ {45}\) in excellent optical purity (Figure 1.4). These catalysts function by creating a hydrogen bond between the nitrogen of the imine substrate and the acidic hydrogens of the thioureas moiety of the catalyst, providing products in excellent selectivity.

Analogously, binol-derived phosphoric acid catalysts 1.76 can also be applied successfully to reactions involving imines. These catalysts can effect the Mannich reaction in the presence of several nucleophiles, including electron rich furans,$^{46}$ β-diketones$^{47}$ and silyl enolethers (Figure 1.5).$^{48}$ Conveniently, when silylated derivatives of the phosphoric acid catalyst are used, one-pot enantioselective reductive aminations can be achieved using a Hantzch ester as the hydride source.$^{49}$

---

This chapter is merely a brief summary of selected undertakings toward organocatalysis in the last seven years. Manifestly, small organic molecules are setting the pace for new and exciting discoveries in the field of synthetic organic chemistry. The work in this thesis was initiated in 2002, at a time when there were still few catalyst architectures established for organic transformations, particularly within iminium catalysis. Accordingly, the results described in the following chapters focus primarily on the development of novel iminium modes of activation toward cycloaddition processes.
Diels-Alder Catalysis

2.1 The Diels-Alder Cycloaddition

Early examples of the [4+2] cycloaddition dates back to the end of the 19th century, but it wasn't until 1928 that the product from the outcome of a thermal reaction between cyclopentadiene 2.1 and \( \beta \)-benzoquinone 2.2 was elucidated. Otto Diels and Kurt Alder were awarded the Nobel Prize in Chemistry for this discovery, which was to become one of the most powerful reactions known today.

Scheme 2.1 Thermal Diels-Alder reaction between cyclopentadiene and \( \beta \)-benzoquinone

The Diels-Alder reaction involves a [4+2] cycloaddition between a 2 \( \pi \)-electron dienophile and a conjugated 4 \( \pi \)-electron diene that affords regio- and diastereoselective six-membered and polycyclic ring systems. In one single step, up to four stereogenic centers can be created.

---

Frontier Molecular Orbital (FMO) theory dictates that the Diels-Alder reaction occurs as the result of an overlap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). In bond formation, a filled molecular orbital of one reagent overlaps with an unfilled molecular orbital of a second reactive species. The process can only occur if the overlapping orbitals have complementing symmetries and if they have similar energies. In order to bring their orbitals closer in energy, the electronic properties of the reactants can be altered. As such, the energy gap between the HOMO and LUMO can be minimized by the addition of appropriate substituents to the reacting substrates, resulting in a better orbital overlap, and enhanced reactivity. Consequently, the Diels-Alder reaction can be classified as normal or inverse electron demand, based on the energy of the frontier molecular orbitals involved (Figure 2.1). In a normal electron demand Diels-Alder the reaction is controlled by the interaction between the HOMO of a diene and the LUMO of a dienophile, whereas an inverse electron demand Diels-Alder shows the opposite trend. Generally, most Diels-Alder reactions are normal electron demand and involve the reaction of an electron donating (EDG) diene with an electron withdrawing (EWG) dienophile.

---

The electronic properties of the reactants in the Diels-Alder reaction also dictate the nature of stereocontrol in the reaction. Regeoselectivity and diastereoselectivity are governed by orbital coefficients and secondary orbital interactions respectively.

When both reactants are unsymmetrical, regiochemistry can be predicted by consideration of orbital coefficients. The size of the coefficients and the relative energies of the diene and dienophile molecular orbitals will foretell the regiochemistry of the reaction. The atoms with the larger terminal orbital coefficients on each reactant will preferentially bond in the transition state as shown in Figure 2.2. In a normal Diels-Alder reaction, the resulting cyclohexene can exhibit a 1,2 or 1,4-relationship, depending on the substitution pattern of the reactants.

---

Two diastereomeric products, referred to as endo and exo, can arise from the Diels-Alder cycloaddition depending on the spacial arrangement between the diene and the dienophile. The exo adduct is thermodynamically favored due to minimized steric repulsions in the product. The endo product is less stable than the exo product yet is preferred in irreversible Diels-Alder cycloadditions as it is the kinetic product of the reaction.

Diels-Alder Cycloadditions

The \textit{endo} adduct is thought to arise from due to stabilizing secondary orbital interactions in the \textit{endo} transition state which are not present in the \textit{exo} transition state (Figure 2.4). This favorable interaction is a result of a bonding interaction between the electron-withdrawing group of the dienophile and the developing $\pi$-bond at the back of the diene. Unless steric demands override the secondary orbital interaction, the Diels-Alder reaction typically forms \textit{endo} cycloadducts.\textsuperscript{57}

Figure 2.4 Primary and secondary Orbital interactions in the Diels-Alder cycloaddition

While certain Diels-Alder reactions occur with facility, most require activation, either by means of physical or chemical methods, enabling cycloadditions to be carried out under mild conditions.\textsuperscript{52b} High pressure-induced Diels-Alder cycloadditions have been developed in order to improve the rate and selectivity of the transformation.\textsuperscript{58} These conditions allow reactions with heat sensitive functionalities to be carried out efficiently. Ultrasonic radiation, which produces sound waves in solution, is known to induce cavitation.\textsuperscript{59} In this process the rapid growth and sudden collapse of bubbles within the liquid causes an increase in temperature, high pressure and electrostatic potential differentials to accelerate a variety of cycloadditions. The nature of the solvent can also provide dramatic rate acceleration of the Diels-Alder reaction. Although most

\textsuperscript{57} There is a debate as to whether secondary orbital actually exist. Certain research groups argue that there is no clear evidence to support its existence. Analysis of the \textit{endo/exo} selectivity in several Diels-Alder reactions of relatively simple reactants have demonstrated that the assumed effects of secondary orbital interactions can instead be attributed to common interactions such as solvent effects, steric repulsion, hydrogen bonds, and electrostatic forces. For in an in depth discussion see: García, J. I; Mayoral, J. A.; Salvatella, L. \textit{Acc. Chem. Res.} \textbf{2000}, 33, 658-664 and references therein.


Diels-Alder Cycloadditions

solvents are only moderately sensitive to cycloadditions, Breslow and co-workers demonstrated a dramatic acceleration of the Diels-Alder reaction in aqueous media.\(^{60}\) Both inter- and intramolecular reactions are characterized by large rate accelerations and diastereoselectivity improvements when changing from an organic solvent to water as the reaction medium. Explanations for this effect have been based on high internal pressure of water, packing of the diene and dienophile, and entropy-driven aggregation processes. Moreover, the influence of LiClO\(_4\)/diethyl ether results in dramatic rate accelerations in polar transition states of the Diels-Alder reaction.\(^{61}\) When the concentration of the lithium salt was increased, the formation of the endo product was enhanced. The accelerating effect of LiClO\(_4\) on the Diels-Alder reaction has been rationalized in analogy to reactions in aqueous media, in which an inner pressure created by a change in the solvent structure compresses the reagents. Alternatively, another model was suggested in which the rate acceleration is a result of the lithium cation acting as Lewis acid catalyst.\(^{61}\)

Of the many approaches developed to overcome the sluggish nature of Diels-Alder reactions, Lewis acid catalysis has been the instrument of choice to increase both the rate of the reaction and the selectivity of the process. In analogy to electron-withdrawing groups, Lewis acids such as SnCl\(_4\), AlCl\(_3\), and BF\(_3\)OEt\(_2\) lower the dienophile LUMO energy by complexing to the oxygen of a carbonyl group on the dienophile (Figure 2.5). The energy change of the LUMO that ensues, allows for better mixing with the HOMO of the diene. This results in a smaller energy difference (\(\Delta E\)) between the relevant frontier molecular orbitals of the two reacting species.


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Figure 2.5 Effect of dienophile activation on the relative energy gap between the LUMO of a dienophile and the HOMO of a diene

The differences between the uncatalyzed and Lewis acid activated cycloadditions are exemplified in the reaction between cyclopentadiene and methyl acrylate. When AlCl₃·Et₂O was employed as a catalyst, the rate of the reaction was dramatically increased and the endo:exo ratio was improved from 82:18 to 99:1, clearly revealing the advantages of Lewis acid catalysis. 62

2.2 Enantioselective Catalysis of the Diels-Alder Reaction

2.2.1 Lewis Acid activation

Due to the success achieved in promoting Diels-Alder reactions with the aid of Lewis acids, much attention has been devoted to the development enantioselective catalytic systems. 62,63 One

---

of the first reported asymmetric Lewis acid catalysts was based on an aluminum-menthol complex 2.5 that promoted the reaction between methacrolein 2.4 and cyclopentadiene 2.1 in a modest ee of 64%.\(^\text{64}\)

Scheme 2.2 Diels-Alder cycloaddition promoted by an aluminium menthol complex

Shortly after, other aluminum-based catalysts were synthesized as monoethers of unsymmetrical or chiral \(C_2\) symmetric diols (Scheme 2.2). These were found to be slightly more selective toward the Diels-Alder (up to 73\% ee), partly due to an extra oxygen that induced better organization of the metal complex.\(^\text{65}\) The highest levels of enantioselectivity were obtained by Chapuis et. al. using \textit{in situ} complexation of chiral diols 2.9 and 2.10 and sulfonamides 2.11 with EtAlCl\(_2\).\(^\text{66}\) Using these conditions, oxazolidinone 2.13 was employed as a bidentate dienophile in conjunction with cyclopentadiene to yield cycloadducts 2.8 in 98\% ee. However, the reaction required a stoichiometric amount of aluminum complex and the system was restricted to the use of the bidentate crotonate dienophiles 2.7. Corey was able to overcome this restriction using a catalytic amount of aluminum complexes of bis-\(C_2\)-symmetric sulfonamides 2.15 to promote


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cycloadditions between a bidentate crotonate 2.13 and cyclopentadienes in high enantiomeric excess.\(^67\)

Scheme 2.3 Aluminium Lewis acid complexes for the asymmetric Diels-Alder cycloaddition between bidentate dienophiles and cyclopentadienes

Chiral alkoxytitanium complexes prepared from chiral diols have been used as Lewis acids in the Diels-Alder cycloaddition. Initially, an excess of the titanium complex had to be used in

cyclizations between cyclopentadiene and acryl- or crotonamides 2.16 to reach enantiomeric excesses in the range of 90-95%. It wasn’t until Nagasaka and co-workers discovered that when 4 Å molecular sieves were added, in part to remove water from the reaction mixture, that the reaction could be performed catalytically while maintaining excellent enantioselectivities.\(^6\) In the transition state model, the dialkoxydichlorotitane forms a planar six-membered chelate with the acyloxazolidinone that imparts facial selectivity by an attractive $\pi-\pi$ interaction between one of the phenyl rings and the olefin of the dienophile.

Scheme 2.4 Chiral alkoxytitaium diol complexes as Lewis acids in Diels-Alder cycloaddition

\[
\begin{align*}
\text{2.1} + \text{2.16} & \quad \rightarrow \text{2.17} \\
\text{R} &= \text{H, Me, Ph, niPr} \\
100 \text{ mol\% 2.18} & \quad \text{or} \\
10 \text{ mol\% 2.18 with 4A MS} & \quad \text{CH}_2\text{Cl}_2, -15^\circ\text{C} \\
\end{align*}
\]

The bis-(oxazoline) family of ligands, when combined with a copper metallic center, is known for its ability to provide cyclopropanes from olefins in high yields and stereoselectivities.\(^6\) Conversely, when the corresponding iron complex 2.21 is formed, the resulting catalyst provided enantioselective Diels-Alder cycloadducts in good yields and enantioselectivities, demonstrating the use of transition metals in promoting cyclizations (Scheme 2.5).\(^7\)

---


Another attractive approach has been developed by Yamamoto, who found that the reaction of diborane and the carboxylic acid moiety of an acetylated tartaric acid derivative led to boron intermediate 2.22 that behaved as a Lewis acid catalyst.\(^\text{71}\) Dienophiles such as acrylic acid 2.24 and methacrolein were reacted with cyclopentadiene in enantioselectivities of 78 and 96%, respectively whereas \(\alpha,\beta\)-enals devoid of an \(\alpha\)-substituent did not provide satisfying asymmetric induction. The unusual tolerance of acrylic acid 2.24 as a dienophile is worth mentioning as few Lewis acids are compatible with the carboxylic acid moiety in catalysis.

Scheme 2.6 Boron-mediated Diels-Alder catalysis between cyclopentadiene and various dienophiles

While these examples paint a brief portrait of the achievements in terms of Lewis Acid catalysis, the Diels-Alder reaction need not be activated by a catalyst bearing a metal centre.

2.2.2 Chiral Amine Organocatalysis in Diels-Alder

Chiral amines such as cinchona alkaloids have been known to catalyze Diels-Alder reactions since the late 1980’s\textsuperscript{72}, but it wasn’t until the pioneering work of Macmillan that the reaction reached the echelon of synthetic utility.

In 1985, Grieco demonstrated that Diels-Alder reactions can be enhanced when the carbonyl group of an unsaturated aldehyde is converted to iminium ion 2.27.\textsuperscript{73} These iminium salts,

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generated in situ under Mannich-like conditions, reacted with dienes in an exceptionally mild and convenient aqueous aza Diels-Alder reaction, as depicted in Scheme 2.7.\textsuperscript{74}

Scheme 2.7 First report of iminium ion Diels-Alder cycloaddition

\[
\text{Ph}^+\text{NH}_3^+ \quad \text{Ph}^+\text{N}^+ \quad \text{N}^+\text{Ph}
\]

Inspired by this concept, Macmillan discovered that the equilibrium between the aldehyde and a secondary amine could serve as grounds for iminium-based catalysis.\textsuperscript{24} When an iminium ion is created from an \(\alpha,\beta\)-unsaturated aldehyde, the obtained effect is akin to that observed from Lewis acid catalysis. That is, the orbital overlap between the LUMO of the \(\alpha,\beta\)-unsaturated iminium ion and the HOMO of the diene will be superior, thereby resulting in a stabilizing effect which facilitates the reaction.

Figure 2.6 Alternative modes of LUMO-activation

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>LUMO-activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{O})</td>
<td>Lewis acid (LA)</td>
<td>(\text{O}^{\text{LA}})</td>
</tr>
<tr>
<td>(\text{O})</td>
<td>(\text{R}^+\text{N}^+\text{R}^+) HCl</td>
<td>(\text{N}^+\text{R}^+\text{R}^+)</td>
</tr>
</tbody>
</table>

The catalyst designed by the Macmillan research group (shown in Scheme 2.8) is based on a chiral imidazolidinone framework that incorporates a secondary amine within a five-membered ring containing an electron-withdrawing carbonyl moiety. These compounds have found a range of applications, in particular as chiral auxiliaries\textsuperscript{75} and as chiral templates for the synthesis of \(\alpha\)-

substituted amino acids.\textsuperscript{76} Imidazolidinones can be easily assembled by the reaction of chiral amino esters \textit{2.29} with a mono-substituted amine, followed by cyclization with acetone and precipitation with hydrochloric acid.

\textbf{Scheme 2.8 Synthesis of the MacMillan imidazolidinone}

When tested in the Diels-Alder cycloaddition between \textit{E}-cinnamaldehyde and cyclopentadiene, catalyst \textit{2.33} possessing a geminal methyl substituent and benzyl side-chain displayed the best results, providing a 1:1.3 mixture of \textit{endo} and \textit{exo} isomers of the cycloadduct in 99% yield and 93% \textit{ee}. Without a catalyst, the reaction between an $\alpha$,$\beta$-unsaturated aldehyde, such as \textit{E}-cinnamaldehyde \textit{2.32}, with cyclopentadiene did not occur to an appreciable extent. The catalyst was found to be tolerant of a variety of dienophiles and was general with respect to the diene, as highlighted in Scheme 2.9.

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**Scheme 2.9** Imidazolidinone catalyzed Diels-Alder cycloaddition between α,β-unsaturated aldehydes and dienes

The imidazolidinone-catalyzed Diels-Alder cycloaddition is believed to proceed via the catalytic cycle shown in Scheme 2.10. Production of iminium 2.41 by condensation with imidazolidinone 2.33 (and a Brønsted acid co-catalyst) with an α,β-unsaturated aldehyde 2.40 is driven by the loss of water. The activated dienophile can then undergo a [4+2] cycloaddition with the corresponding diene to generate iminium cycloadduct 2.42. This is followed by hydrolysis to afford the enantioenriched cycloadduct 2.43 and regenerate imidazolidinone salt 2.33.
In order to achieve enantiocontrol, the catalyst must be able to control the iminium geometry. Macmillan provided semi-empirical molecular calculations that established that the gem-dimethyl groups on the catalyst create a steric environment favoring formation of the $E$-iminium isomer 2.45 to avoid non-bonding interactions between the $\alpha$-proton of the iminium and the geminal group. The benzyl group of the catalyst provides facial discrimination for the conjugated $\pi$-system by shielding the top face from the dienophile, consequently leaving the bottom face exposed for cycloaddition.
Two computational chemistry groups have investigated the transition state of the imidazolidinone-catalyzed Diels-Alder reaction between an α,β-unsaturated aldehyde and cyclopentadiene at higher levels of theory. Their results support the use of the iminium ground-state geometry to predict the lowest energy transition state. Houk presented a study to elucidate the observed enantioselectivities in the organocatalytic Diels-Alder reaction. These calculations revealed that the s-trans and E-iminium geometries produced the lowest energy conformation. However, divergent to the Macmillan model, the benzyl group was not positioned over the conjugated iminium system but rather over the imidazolidinone ring. This model was based on a more stable conformation resulting from a C-H⋯π interaction between a geminal methyl group on the catalyst and the phenyl ring of the benzyl moiety. However, the iminium conformation presented by Houk is a mere 0.5 kcal/mol lower in energy relative to the conformation proposed

77 Although the used of the ground state of the iminium geometry to predict the geometry of the transition state is a violation of the Curtin-Hammett principle, it is widely used in the literature due to its accuracy in predicting the stereochemical outcome.

by MacMillan. Accordingly, in another report, Kozlowski and Panda\textsuperscript{79} found that the iminium most likely existed in a conformation similar to that predicted by Macmillan, in which the $\pi$-$\pi$ interaction between the phenyl ring and the olefin of the iminium provided a more favorable interaction.

An enantioselective organocatalytic intramolecular version of the Diels-Alder was formulated using imidazolidinone based catalysts and applied to the total synthesis of marine metabolite Solanapyrone D.\textsuperscript{80} In this report, a second generation imidazolidinone catalyst 2.46 was utilized in place of catalyst 2.33 as it afforded superior yields and enantioselectivities. This second generation catalyst was discovered when the Macmillan group attempted to expand the organocatalyzed Friedel-Crafts alkylation from pyrroles to indoles, but found limited success.\textsuperscript{81}

To overcome the poor reactivity of the indoles, a new imidazolidinone was designed to increase the amine reactivity in an effort to promote iminium formation, hypothesized to be the rate-limiting step. Structural constraints in proximity of the nucleophilic amine were relieved to better expose the reactive nitrogen lone pair (Figure 2.8). This was accomplished by replacing the gem-dimethyl group found in catalyst 2.33 with a \textit{tert}-butyl group. Eclipsing of the nitrogen lone pair of the amine and the neighboring methyl group was now minimized and the reaction was found to proceed at an elevated reaction rate.

Incorporation of a tert-butyl group in place of the geminal substitution on the imidazolidinone ring would not only favor better exposure of the nucleophilic amine, but also create a larger cavity on the bottom face of the conjugated iminium system (Figure 2.9). The alterations brought to the imidazolidinone core delivered shortened reaction times and produced higher levels of selectivity in contrast to what had been observed with catalyst 2.33.

In the intramolecular Diels-Alder reaction, several intramolecular substrates underwent facile cycloaddition to provide the corresponding [4.3.0] bicyclic systems in good yield and excellent diastereo- and enantioselectivity. The trans-fused decalin ring systems such as 2.50 obtained by
this IMDA methodology were used to construct Solanapyrone D in nine steps from commercial starting materials, a significant improvement to Higawara’s synthesis\(^\text{82}\) which required a total of 19 steps. The reaction of trienal 2.49 in the presence of catalyst 2.46 provided the core of Solanapyrone D in 71% yield and 90% ee setting all four stereocenters in a single catalytic operation.

Scheme 2.11 Total synthesis of Solanapyrone D imidazolidinone-catalyzed intramolecular Diels-Alder cycloaddition

![Scheme 2.11 Total synthesis of Solanapyrone D imidazolidinone-catalyzed intramolecular Diels-Alder cycloaddition](image)

Other groups have demonstrated the applicability of organocatalyzed Diels-Alder cycloadditions to the synthesis of natural products. The Kerr group achieved a concise total synthesis of (+) Hapalindole Q by the means of imidazolidinium catalysis.\(^\text{83}\) The cycloaddition proceeded in somewhat low yield but afforded modest diastereoelectivity and excellent enantiomeric excess of 93%. Nine subsequent steps were necessary to convert the obtained cycloadduct to the desired synthetic target in what would be the first example of an organic catalyzed Diels-Alder reaction used in total synthesis.

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Efforts to recycle the catalyst were undertaken by the groups of Cozzi\textsuperscript{84} and Pihko,\textsuperscript{85} independently, in which chiral imidazolidinone catalysts were attached to solid supports. The Cozzi group showed that a modified poly(ethylene glycol) could be a convenient support for an imidazolidinone catalyst in the enantioselective Diels-Alder cycloaddition of acrolein 2.58 and cyclohexadiene 2.57. The solid-phase catalyst 2.62 displayed good yields, outstanding endo:exo ratios and stereoselectivity levels very similar to those observed with a related, non-immobilized catalyst. Catalyst recovery and recycling was efficient, but only for a limited number of cycles, partly due to the requirement to dry the hygroscopic PEG at 90 °C under high vacuum to eliminate traces of water absorbed from the solvent. Pihko et al. synthesized both JandaJel polymer- 2.56 and silica-supported 2.61 chiral imidazolidinone catalysts and applied them to several dienes and α,β-unsaturated aldehydes. The solid-supported organocatalysts were easily recovered by filtration and the catalysts could be directly reused. They noted that the reactivity of these organocatalysts was surprisingly sensitive to the nature of the solid support, thus allowing them to tailor the reactivity of the catalysts by simply changing the support medium. Endo:exo ratios, enantioselectivities, yields and reaction rates similar to those obtained by Macmillan.
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Scheme 2.13 Solid support chiral imidazolidinone catalysis of the Diels-Alder reaction

Alternatively, Kim et al. envisioned that the catalyst could be contained in a polar medium such as an ionic liquid, based on the ionic nature of the imidazolidinone derivatives.\textsuperscript{86} Yields of up to 85% and enantioselectivities of 93%, similar to those achieved by the Macmillan group, were obtained from reactions in [Bmim]PF\textsubscript{6} and [Bmim]SbF\textsubscript{6}. Products were isolated by simple extraction using diethyl ether, which allowed recycling of the ionic liquid containing the immobilized catalyst without significant losses of yield or enantioselectivities.

A novel catalyst architecture based on (R,R)-1,2-diamino-1,2-diphenylethane (DPEN) and its derivatives 2.64 was investigated in the Diels-Alder cycloadditions of crotonaldehyde 2.63 and cyclopentadiene.\textsuperscript{87} Catalyst 2.64 generated an iminium intermediate which was activated by

internal hydrogen bonding with an ammonium proton. Structural modifications to the diamine backbone by attachment of an alkyl substituent to one of the nitrogens, provided an increase in yield and selectivity. Interestingly, two equivalents of Brønsted acid relative to the diamine were required in order to maintain good selectivity. This effect was attributed to the unwanted formation of a tight internal hydrogen-bonding interaction in the mono-protonated diamine, which consequently retarded formation and hydrolysis of the imine. The reactive intermediate 2.67 was thought to adopt an E-imine geometry to minimize steric interactions with the neighboring phenyl group. Moreover, the alkyl substituent on the ammonium nitrogen was forced to occupy the bottom face of the hydrogen-bonded five-membered ring, leaving the top face open for diene attack, resulting in the observed cycloadducts 2.65 and 2.66 (Scheme 2.14).

Scheme 2.14 Asymmetric Diels-Alder cycloadditions of crotonaldehyde and cyclopentadiene promoted by (R,R)-1,2-diamino-1,2-diphenylethane

Recently, the Maruoka group designed binaphthyl-based diamine catalyst 2.68 for the organocatalyzed stereoselective Diels-Alder reaction. These new axially chiral catalysts exhibited unprecedented levels of exo selectivity, a challenge that remains significant in these transformations. Sterically demanding aryl groups at the 3,3'-positions of the octahydrobinaphthyl moiety were installed to produce good yields and selectivities in the reaction of various α,β-enals and cyclopentadiene. Of particular interest was the use of α,α,α-trifluorotoluene as a solvent in place of dichloromethane to procure higher levels of selectivity.

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and reactivity. The reaction was believed to proceed via the transition state 2.69 shown in Scheme 2.15, in which the endo approach of the dienophile is disfavored because of steric hindrance created by the binaphthyl moiety. These researchers also proposed that the lone pair interaction between the methylamino group and the iminium carbon might decrease the effect of secondary orbital interactions between cyclopentadiene and the iminium, which is postulated to be the origin of the endo selectivity on Diels-Alder reaction.

Scheme 2.15 Binaphthyl-based diamine catalysts for the stereoselective Diels-Alder reaction of various α,β-enals and cyclopentadiene

![Scheme 2.15](image)

A chiral triamine organic catalyst 2.72 bearing a primary amine was used in the first example of an enantioselective Diels-Alder cycloaddition with α-acyloxyacrolens.89 The α-substituted enals 2.71 are particularly poor substrates in organocatalytic cycloadditions, particularly when used in conjunction with secondary amine catalysts because sterically demanding α-substituents inhibit the generation of iminium ions. To overcome this deficiency, Ishihara developed a catalyst based on L-phenylalanine and L-leucine derivatives. Using catalyst 2.72 the Diels-Alder reaction was effected between α-acyloxyacrolens and a variety of dienes such as cyclopentadiene, 2,3-dimethylbutadiene 2.70 and isoprene in high yields and selectivities. These results can be

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interpreted by the mechanistic model 2.74 proposed in Scheme 2.16, in which favorable \( \pi-\pi \) interactions exist between the aromatic ring and the conjugated system of the diene and steric hindrance between the counterion (\( X^- \)) and the \( \alpha \)-iminium hydrogen is at a minimum.

Scheme 2.16 Chiral triamine catalyst for the enantioselective Diels-Alder cycloadditions with \( \alpha \)-acyloxyacroliens

MacMillan later introduced an imidazolidinone-catalyzed enantioselective Diels-Alder reaction of \( \alpha,\beta \)-unsaturated ketones.\(^{90}\) The reaction is of particular interest due to the poor stereocontrol resulting from Lewis acid activation in this type of transformation. With simple ketones, the environment near the carbonyl is sterically and electronically similar, as opposed to the environment procured by aldehydes, esters or imides. This challenge can be overcome by the use of iminium geometry control, which involves selective \( \pi \)-bond formation to generate the iminium, rather than lone pair coordination.

Surprisingly, when imidazolidinone catalysts 2.33 and 2.46 were tested in Diels-Alder cycloadditions between α,β-unsaturated ketones and cyclopentadiene, the cycloadducts displayed no enantiomeric excess and were obtained in low yield. In contrast, when a new catalyst bearing a methylfuryl substituent 3.76 was tested, the reaction proceeded in 83% yield as a 92% ee mixture of 22:1 endo:exo cycloadducts (Scheme 2.17).
Scheme 2.17 The imidazolidinone-catalyzed Diels-Alder cycloaddition between enones and various dienes

Based on computational work, MacMillan proposed that a non-bonding interaction between the benzyl ring of 2.76 and the R\textsuperscript{1} group of 2.82 resulted in an energetically disfavored isomer. This negative interaction directs the orientation of the R\textsuperscript{1} substituent to the bottom face of the catalyst, causing both faces of the E-iminium 2.83 to be shielded from attack of the diene. This interaction is not present in the Z-isomer 2.84 which is exposed on the bottom face for cycloaddition and accounts for the observed stereochemistry of the major product.
Houk and coworkers performed further calculations to establish the minimum energy conformations of the \(E\)- and \(Z\)-iminium in this reaction.\(^9\) Their findings were in agreement with Macmillan’s proposed transition state, in which the \(Z\)-iminium \(2.84\) is 0.4 kcal/mol lower in energy than that of the \(E\)-iminium \(2.83\). The molecular modeling results also suggested that the benzyl side chain was positioned over the conjugated system rather than over the imidazolidinone catalyst in order to minimize the repulsive interactions between the lone pair of the furan ring and the benzene ring.

### 2.2.3 Other Organocatalytic Diels-Alder Reactions

Although secondary amine catalysts have been the most successful in providing enantioselective Diels-Alder cycloadducts via non-metallic pathways, certain works displaying alternative modes of activation are worth mentioning.

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The enantioselective Diels–Alder reaction catalyzed by Cinchona alkaloids was originally reported by Kagan in 1989. A catalytic amount of quinidine was utilized to catalyze the reaction between N-methylmaleimide and anthrone at -50°C to afford cycloadduct in excellent yield and 61% ee. Similarly, Natakani used cinchonine to promote the Diels-Alder cycloaddition between 3-hydroxy-2-pyrones and N-substituted maleimides to give the expected endo cycloadducts in 95% yield and 71% ee. The asymmetric induction in these transformations is believed to involve complexation of the diene enolate with the protonated alkaloid as well as a hydrogen-bonding interaction between hydroxy group of the catalyst and N-methylmaleimide. When the hydroxyl group was derivatized to a chlorobenzoate, the catalyst gave a racemic product, showing the significance of alcohol moiety towards effective catalysis. C₂-Chiral pyrolidines were also used to promote base-catalyzed asymmetric [4+2] cycloadditions between anthrone and N-substituted maleimides in 88% yield and 61% ee.

---

Scheme 2.18 Early examples of the enantioselective Diels-Alder reaction catalyzed by Cinchona alkaloids and C$_1$-chiral pyrolidines

Hydrogen bonds can also be used to activate carbonyl dienophiles in lieu of Lewis acids. Thioureas$^{94}$ and amidinium ions$^{95}$ have been used to activate oxazolidinone and 1,2-diketones toward Diels-Alder reactions, respectively. These examples rely on multiple hydrogen-bonds between donors and acceptors and are often not suitable for substrates bearing multiple functional groups. Alternatively, carbonyl groups can be specifically activated by the formation of hydrogen bonds with a carbonyl group, as was demonstrated by Braddock.$^{96}$ PHANOLs 2.94 can promote asymmetric Diels-Alder cycloadditions between $\alpha,\beta$-unsaturated aldehydes or ketones with various dienes by double hydrogen-bond activation with the lone pairs of the carbonyl group dienophile. Unfortunately, the enantioselectivities were found to be minimal.

$^{96}$ Braddock, D. C; MacGilp, I. D.; Perry, B. G. Synlett, 2003, 1121.
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(<5%), presumably because of the insufficient planar chirality associated with the paracyclophane backbone around the conjugated dienophile.

Scheme 2.19 PHANOL hydrogen-bonding catalysis of Diels-Alder cycloadditions between α,β-unsaturated aldehydes or ketones with various dienes

Barbas presented a strategy in which an (S)-1-(2-pyrrolidinylmethyl)pyrrolidine catalyst 2.99 provided both iminium activation of the dienophile as well as in situ generation of a 2-amino-1,3-butadiene 2.100. The reaction takes advantage of the equilibrium between iminium ions and enamines to generate prochiral cyclohexanones in good yields and modest diastereoselectivities. Although, this reaction is synthetically useful and can be amenable to large scale, the cycloadducts 2.102 and 2.103 are only enantioselective with respect to the minor endo diastereomer, and selectivities were at best 23% ee. In another report, this strategy was applied toward the direct asymmetric Diels–Alder reactions of α,β-unsaturated ketones with nitro olefins. The requisite enamine was generated in situ and reacted with nitro olefin dienophiles under secondary amine catalysis to provide the cycloadducts in good yield and with enantioselectivities of up to 38% ee.

Recently, Bode et al. developed a powerful approach for the generation of reactive dienophiles that provided highly enantioselective dihydropyridinone products by an inverse-electron demand azadiene Diels-Alder reaction (Scheme 2.21).\(^\text{98}\) Using chiral N-heterocyclic carbenes as nucleophilic catalysts, activated dienophiles participated in a diene-LUMO controlled cycloaddition with α,β-unsaturated imines 2.105 under unprecedented facile conditions. In the course of this work a new NHC catalyst 2.110 was developed that provided diastereomeric ratios superior to 50:1 and enantiomeric excesses ranging from 97-99% in over 10 different examples. The reaction was thought to proceed via the formation of a homoenolate 2.111 followed by a proton transfer to give reactive intermediate 2.112. This chiral enolate equivalent could then undergo carbon-carbon bond formation and catalyst turnover to afford the desired dihydropyridinones 2.106. Using the same catalytic system, Bode described NHC-catalyzed enantioselective 1-oxodiene Diels-Alder reactions from several different enones as dienes.\(^\text{99}\) Due to the tendency of enals to undergo polymerization, they resorted to using racemic α-chloroaldehyde 2.107 as dienophile precursors to afford a broad range of nonracemic 3,4,6-


trisubstituted dihydropyran-2-ones 2.109. The reactions were promoted with as little as 0.5% mol NHC catalyst, setting an unparalleled example in the field of organocatalysis.

Scheme 2.21 N-heterocyclic carbenes as catalysts for the Diels-Alder cycloaddition

The application of small organic molecules toward enantioselective Diels-Alder catalysis represents a powerful and complementary paradigm to metal catalyzed asymmetric variants. With such promising outcome, the exploration of new means of activation is an inviting challenge that prompts further investigation.
Results and Discussion: 
Hydrazide Catalysis

3.1 Initial catalyst Screen

With the exception of MacMillan’s imidazolidinones, no other catalyst architecture has achieved high optical purity in an extensive collection of iminium-activated chemical transformations. As a result, we set out to design and develop an alternative organocatalytic system that could potentially expand the scope and further enhance selectivities of reactions promoted by small organic entities. In order to compete with existing catalysts, the design of our catalyst manifold should require swift assembly from easily accessible chiral building blocks.

In order to develop a cost-effective catalyst, we initially focused our studies on bicyclic compound 3.3, featuring a benzyl ester adjacent to a secondary amine. This compound is a non-recyclable enantiomerically pure industrial waste material obtained in the synthesis of the ACE-inhibitor ramipril 3.4 by Hoechst AG. In the synthesis of this drug, the racemic derivative 3.1 is submitted to an optical resolution by crystallization of the diastereomeric salts with benzylcarbonyl-L-phenylalanine. Once separated and converted to a stable hydrochloride salt, S,S,S-benzyl ester hydrochloride 3.2 is subsequently used in the synthesis of ramipril, which leaves the all-R derivative 3.3 as an unwanted by-product.

Figure 3.1 Chemical step in the synthesis of ACE-inhibitor ramipril in which 3.3 is formed

Samples of by-product hydrochloride salt of 3.3 were readily available and shipped at no cost from Germany in a generous contribution from the Martens laboratory. The recycling of this waste product and its use as a catalyst paves the way for a truly environmentally friendly organic scaffold. In addition, compound 3.3 would be the first bicyclic catalyst tested in organocatalytic transformations, further validating its investigation as a reactive species.

We hypothesized that the extended benzyl ester moiety would provide more efficient shielding of the reactive iminium dienophile compared to the benzylic side chain found in imidazolidinone-type catalysts 3.18. This extended chain would create an enhanced facial bias in favor of a top-face attack of the olefin, resulting in higher selectivities. In addition, the cis-ring fusion of the adjacent cyclopentane ring could create a steric bias through non-bonding interactions between the folded cyclopentane and the iminium ion. This is analogy to the geminal substitution found in the imidazolidinone catalysts and would consequently set the iminium geometry toward the benzyl ester moiety. A simple computational model for the iminium of 3.3, generated using MM-2, confirms that the extended benzyl ester group would provide excellent shielding of the reactive olefin (Figure 3.2).

101 Prof. Jurgen Martens, Fachbereich Chemie, Universität Oldenburg, D-2611 Oldenburg, Germany. Martens@Uni-Oldenburg.de
To verify the catalytic potential of bicyclic catalyst 3.3, we focused our efforts toward the Diels-Alder cycloaddition between cyclopentadiene and E-cinnamaldehyde using similar conditions to the model study described in MacMillan's initial work. The hydrochloride salt of 3.3 was dissolved in a mixture of 95:5 methanol-water followed by the addition of E-cinnamaldehyde. The reaction was stirred for a few minutes at room temperature after which time freshly distilled cyclopentadiene was added. Upon completion of the reaction as judged by TLC, hydrolysis of the dimethyl acetal product was accomplished by stirring the crude mixture in TFA:H2O:CHCl3 (1:1:2) for 2 hours at room temperature. A $^1$H NMR spectrum of the crude product was obtained to determine the diastereoselectivity. The peaks corresponding to the aldehyde proton of the endo product ($\delta$ 9.60 ppm) and of the exo product ($\delta$ 9.93 ppm) corresponded with the literature values. The optical purity of the compound was determined by 500 MHz $^1$H NMR in deuterated benzene following the conversion aldehydes 3.9 and 3.10 to the corresponding (+)-(R,R)-hydrobenzoin acetals. Acetal peaks in the $^1$H NMR were assigned from racemic samples.
Hydrazide-Catalyzed Diels-Alder Cycloadditions

prepared by the Lewis acid BF$_3$-Et$_2$O catalyzed reaction between cyclopentadiene and $E$-cinnamaldehyde after derivatization to the hydrobenzoin acetals

![Chemical structure](image)

Table 3.1 Diels-Alder reaction between cyclopentadiene and aldehydes catalyzed by ramipril waste product 3.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (hr)</th>
<th>Mol% catalyst</th>
<th>% conversion$^a$</th>
<th>$endo$:exo$^b$</th>
<th>$endo$ ee (%)$^{c,d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>24</td>
<td>20</td>
<td>47</td>
<td>2.4:1</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>40</td>
<td>20</td>
<td>56</td>
<td>2.1:1</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>40</td>
<td>50</td>
<td>65</td>
<td>2.4:1</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>24</td>
<td>20</td>
<td>61</td>
<td>2.3:1</td>
<td>15</td>
</tr>
</tbody>
</table>

(a) Conversion based on limiting reagent. (b) Product ratios were determined by $^1$H NMR. (c) Enantioselectivity determined by $^1$H NMR after conversion to acetal with (R,R)-(+)-hydrobenzoin. (d) Absolute stereochemistry not determined.

The initial results are shown in Table 3.1. Using 20 mol% of catalyst, the product was obtained in 47% conversion after 24 hours as a 2.4:1 mixture of $endo$ and $exo$ diastereoisomers. The enantiomeric excess of the $endo$ isomer was however only 26%. In hopes of increasing the percent conversion and selectivity, the reaction was performed over a longer time (Table 3.1, entry 2), but did not provide a noticeable advantage. When the catalyst loading was increased to 50 mol%, the conversion to product increased but the diastereo- and enantiomeric excesses slightly eroded. Changing the dienophile to $E$-crotonaldehyde resulted in shortened reaction times but lower enantioselectivities.

When compared to the commercially available salt of $L$-proline methyl ester hydrochloride, the ramipril benzyl ester catalyst 3.3 did not offer any advantages in terms of yield or selectivities.$^{24}$
To test whether alteration of the side chain of \( \text{3.3} \) resulted in a more potent catalyst in the Diels-Alder cycloaddition between \( \text{E-cinnamaldehyde} \) and cyclopentadiene, analogues of the ramipril product were synthesized using known procedures.\(^{102}\) Two different catalysts featuring a tertiary alcohol were synthesized via a Grignard protocol. The synthesis of diphenyl derivative \( \text{3.14} \) was accomplished by the addition of an excess of phenyl magnesium bromide in small portions at \(-15 \text{ °C}\) followed by reflux for 5 hours. Following an acidic workup with 2N HCl and recrystallization from methanol/ether, the desired compound \( \text{3.14} \) was obtained as a hydrochloride salt in 52% yield. This procedure was however not suited for the synthesis of \( \text{bis-ethyl derivative 3.16} \). Therefore, the secondary amine was protected using Boc anhydride in the presence of triethyl amine to afford crude \( \text{N-protected intermediate} \). The latter was found to be sufficiently pure to be used directly in a Grignard reaction with ethyl magnesium bromide to afford compound \( \text{3.15} \) in an overall yield of 61%. The Boc protecting group was easily removed by refluxing in a 3N solution of HCl in acetic acid to furnish the desired hydrochloride salt of \( \text{3.16} \) in 72% yield. Amino acid derivative \( \text{3.13} \) was obtained by debenzylation of compound \( \text{3.3} \) using catalytic hydrogenation over palladium on charcoal in 90% yield.\(^{103}\)


\(^{103}\) Catalyst \( \text{3.13} \) which presents a striking resemblance to \( \text{L-proline} \) was tested as a free base in inter- and intramolecular versions of the aldol reaction but was found to be unreactive in all cases.
Scheme 3.2 Synthesis of ramipril analogues

Catalysts 3.13, 3.14 and 3.16 were tested under the similar conditions described above for the reaction promoted by 3.3. The reactions were carried out by the addition of E-cinnamaldehyde to a solution of 20 mol% catalyst in a 95:5 methanol:water mixture. Freshly distilled cyclopentadiene was then added, and the reaction was allowed to stir at room temperature for 40 hours. Zwitterionic species 3.13 was not effective in the Diels-Alder cycloaddition, providing the cycloadducts in poor yield (Table 3.2, entry 1). Tertiary alcohol derivatives 3.14 and 3.16 were found to provide a mixture of diastereoisomers with a slight preference for the endo isomers in a higher percent conversion albeit with unsatisfactory enantiomeric excess.
Table 3.2 Diels-Alder reaction between cyclopentadiene and \( E \)-cinnamaldehyde catalyzed by ramipril analogues

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>% conversion(^a)</th>
<th>( \text{endo:exo}^{b} )</th>
<th>( \text{endo ee} (%)^{c,d} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.13</td>
<td>10</td>
<td>1:1</td>
<td>n/d</td>
</tr>
<tr>
<td>2</td>
<td>3.14</td>
<td>25</td>
<td>1.8:1</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>3.16</td>
<td>40</td>
<td>1.7:1</td>
<td>18</td>
</tr>
</tbody>
</table>

(a) Conversion based on limiting reagent. (b) Product ratios were determined by \(^1\)H NMR. (c) Enantioselectivity determined by \(^1\)H NMR after conversion to acetal with (R,R)-(+)hydrobenzoin. (d) Absolute stereochemistry not determined.

In view of the lack of benefits provided by ramipril-derived catalysts, we directed our attention to an alternative scaffold for the catalysis of Diels-Alder cycloadditions.

We next sought to investigate whether an extended benzyl ester side-chain would have beneficial effects on an alternative scaffold. To do so we envisaged the synthesis target molecule 3.17 based on the established 2,2,3-trimethylimidazolidin-4-one framework 3.18 employed by the MacMillan research group in their Diels-Alder reactions.\(^{24}\) The incorporation of an extra methylene unit also allowed for potential functionalization of the side-chain, and thus opportunity for additional improvements in selectivity. To ensure the optical purity and convenient preparation of the catalyst, we devised a synthesis starting from readily available amino acid derivatives.
Formation of a peptide bond between commercially available Boc-L-aspartic acid-β-benzyl ester 3.19 and methylamine hydrochloride was carried out using DCC and HOBT in the presence of DIPEA to afford 3.20 in 62% yield. The Boc group was easily removed using trifluoroacetic acid in dichloromethane to give the primary amine 3.21 in 97% yield. With amine 3.21 in hand, formation of the imidazolidinone ring by condensation with an excess of acetone in methanol with catalytic p-toluenesulfonic acid afforded the desired acetonide 3.17 in 24% yield. We decided at this point that no attempt would be made to optimize the yield of this reaction unless warranted by the activity of the resulting catalyst 3.17.

Catalyst 3.17 was tested under similar conditions as those described above for ramipril analogues. The reactions were carried out by addition of the α,β-unsaturated aldehyde to a
solution of 10 mol% catalyst in 95:5 methanol:water. Freshly distilled cyclopentadiene was then added, and the reaction was allowed to stir at room temperature for 48 hours.

Scheme 3.4 Examination of catalyst 3.17 in the Diels-Alder cycloaddition between E-cinnamaldehyde and cyclopentadiene

Catalyst 3.17 procured a slight enhancement in terms of diastereoselectivity relative to imidazolidinone catalyst 3.18 (1.9:1 vs. 1.3:1 exo:endo, respectively). However, the observed yield of 64% and optical purity of 41% faired poorly in comparison with MacMillan’s imidazolidinone 3.18 which provided the Diels-Alder cycloadducts in 95% yield and 93% ee (exo isomer).

Although the catalyst presented in the initial research above afforded modest yields and acceptable optical purities, they did not show significant improvements over the previously existing systems used to mediate the Diels-Alder process. These catalysts relied on already known catalyst frameworks derived from either proline or imidazolidinones. Although more catalyst analogues could have been synthesized and tested, we felt that the similarity to the systems already in use did not warrant further investigation.

These preliminary investigations in the field of organocatalysis led us to believe that the design of new and unexplored catalyst architectures would be the key to enabling more successful transformations. This prompted us to revisit the iminium catalytic cycle in order to gain a better understanding of the overall reaction sequence.
3.2 The α-heteroatom effect

We noticed that the existing catalytic systems developed for the Diels-Alder cycloaddition often displayed limited substrate scopes and lengthy reaction times, as exemplified by the enone Diels-Alder cycloaddition, which requires up to 4.5 days. A potential solution to ameliorate the sluggish nature of these reactions would be to accelerate the rate limiting step of the transformation and as a result, enhance the turn-over of the catalytic sequence. At the time, minimal reports of kinetic studies had been published on iminium catalysis. It was however, suggested that the rate-limiting step in iminium-catalyzed protocols may be the initial formation of the iminium ion. This could imply that the nucleophilicity of the reactive secondary amine in the catalyst would be directly proportional to the rate of iminium ion formation and consequently, of the overall catalytic cycle. To enhance iminium formation, we hypothesized that the introduction of a heteroatom adjacent to the reactive nitrogen would increase the nucleophilicity of the catalyst toward carbonyl compounds (Figure 3.4). Flanking the nucleophilic atom with a heteroatom possessing an electron lone pair is termed the α-effect.

104 MacMillan observed that an imidazolidinone catalyst with a more accessible lone pair on the nucleophilic secondary amine resulted in rate increases and better selectivities. See ref. 81.

The unusual reactivity of nucleophiles that possess an unshared electron pair in the position alpha to the nucleophilic atom was established Edwards and Pearson in 1962.\textsuperscript{106} These non-bonding electrons can form a resonance structure which increases the electron availability of the nucleophile. Although these compounds do not gain basicity from this effect, they display a greater nucleophillicity than expected based on their $pK_a$ value. Hydrazines, for instance, exhibit an unusual increase in nucleophilicity that is attributed to the $\alpha$-effect. A better understanding of this trend and its application to iminium catalysis can be thoroughly understood by examining the FMO interactions.

Given that the orbital bearing the nucleophilic lone pair now overlaps with the lone pair of the adjoining heteroatom, a new molecular orbital is generated. This results in a HOMO that is higher in energy relative to the nucleophile which does not feature an adjacent heteroatom, as described in Figure 3.5A. When applied to the formation of an iminium ion the new HOMO, which is higher in energy, enjoys a smaller energy gap to the electrophile LUMO relative to that of a secondary amine. The outcome of this modification ultimately facilitates the formation of the iminium ion (Figure 3.5B).

To verify this hypothesis, commercially available hydrochloride salts of hydrazines and hydroxylamines were employed as to Diels-Alder catalysts. We were pleased to observe modest conversion to the desired cycloadducts after 24 hours. When N,O-dimethylhydroxylamine hydrochloride 3.24 was subjected to the Diels-Alder reaction between E-cinnamaldehyde and cyclopentadiene, in a 95:5 mixture of methanol-water at room temperature, a mixture of diastereoisomers was obtained in 45% conversion. Similarly, N,N-dimethyl hydrazine dihydrochloride 3.25 provided the desired products in 51% conversion.
Encouraged by these results we wished to further explore the activity of hydrazines as organic catalysts. We sought to incorporate the hydrazine moiety within a framework that could potentially lead to enantiocontrolled transformations. We initially targeted the synthesis of hydrazines derived from commercially available (S)-(−)-1-amino-2-methoxymethylpyrrolidine (SAMP) chiral auxiliaries. The chiral methoxy side chain could potentially create a facial bias in analogy to the methoxy-substituted proline analogues. In order to promote iminium formation, the mono-substituted nitrogen of SAMP had to be derivatized in order to promote the reversible formation of iminium ions. Consequently, SAMP was protected using methyl chloroformate to afford carbamate 3.26 in 83% yield. Attempts to reduce the carbamate with lithium aluminium hydride in refluxing THF unfortunately afforded air sensitive, dark purple mixtures of products that were indiscernible by NMR analysis. Alternatively, the simpler hydrazine 3.28 was exposed to Boc anhydride in basic conditions to afford mono-protected intermediate 3.29 in 76% yield. Methylation of the Boc-protected nitrogen was achieved using methyl iodide, albeit in low yield. All attempts to remove the Boc-protecting group using either HCl or TFA resulted in dark tinted products that did not exhibit the expected spectral properties of the desired mono-methylated pyrrolidine-1-amine 3.31 (Scheme 3.6).
Scheme 3.6 Attempted synthesis of various hydrazine catalysts

a) 
\[
\begin{align*}
\text{SAMP} & \quad \overset{\text{MeOCl}}{\xrightarrow{\text{NaHCO}_3/\text{Et}_2\text{O}}} \quad \overset{\text{LAH, THF reflux}}{\xrightarrow{\text{MeNOMe}}} \\
\text{3.27} & \quad \text{decomposition}
\end{align*}
\]

b) 
\[
\begin{align*}
\text{3.28} & \quad \overset{(\text{Boc})_2\text{O, DIPEA}}{\xrightarrow{\text{CH}_2\text{Cl}_2}} \quad \overset{\text{NaH, MeI}}{\xrightarrow{\text{THF}}} \quad \overset{\text{HCl, EtOAc}}{\xrightarrow{\text{TPA, CH}_2\text{Cl}_2}} \\
\text{3.31} & \quad \text{decomposition}
\end{align*}
\]

These results suggested that hydrazines might not be suitable templates for the activation of \(\alpha,\beta\)-unsaturated aldehydes in protocols such as the Diels-Alder cycloaddition due to their arduous manipulation and sensitivity. Thus, we wished to augment the stability of hydrazines by the incorporation of an electron withdrawing group. We envisioned that this could be achieved by the addition of a carbonyl next to the hydrazine moiety. The resulting hydrazides, which commonly exist as air-stable white solids, would provide the extra stability.

In addition, hydrazides would provide a balance between the increase in the nucleophilicity of the reactive nitrogen and the reactivity of the resulting iminium ion with a diene in Diels-Alder catalysis. A closer look at the FMO diagram for the reaction between a diene and the reactive iminium reveals that at the cost of a more rapid iminium formation, the newly formed hydrazine iminium ion would be higher in energy than the iminium ion formed from a secondary amine (Figure 3.6). This would increase the energy gap between the LUMO dienophile and the HOMO of the diene, thus resulting in a more sluggish reaction. As a result, altering the properties of the hydrazine by the addition of a carbonyl group would potentially attenuate this effect, while still promoting enhanced iminium formation.
Tomkinson and co-workers were also exploring the use of hydrazides toward iminium activation. In 2003 they reported the synthesis of a linear hydrazide catalyst that was successfully applied toward the Diels-Alder reaction.\textsuperscript{107} Using benzoic hydrazide catalyst 3.32, they were able to promote the [4+2] cycloaddition between cyclopentadiene and $E$-cinnamaldehyde in 67:33 \textit{exo:endo} and 93 \% yield.

Scheme 3.7 Diels-Alder reaction between cyclopentadiene and $E$-cinnamaldehyde using a benzoic hydrazide catalyst 3.32

This initial report confirmed our hypothesis that hydrazides could be used efficient catalysts in the Diels-Alder cycloaddition. However, their work was very brief and nominal studies were done to verify the overall efficiency of hydrazides as organic catalysts. As a result, we felt it necessary to gain a better perspective of the use of hydrazides such as 3.32 as organocatalysts. The information obtained in these studies would help us in the future design of novel hydrazide catalysts.

The Tomkinson catalyst was synthesized using a known procedure. Benzoic hydrazide 3.33 was stirred in acetone with a catalytic amount of acetic acid for 48 hours to give the benzoic acid isopropylidene hydrazide 3.34 in 85% yield. The latter was then reduced to the desired hydrazide 3.32 using platinum oxide in a 2:1 mixture of ethanol-acetic acid in 91% yield.

Scheme 3.8 Synthesis of benzoic hydrazide catalyst 3.32

In our initial study we wished to establish control reactions in order to verify the extent in which the hydrazide promoted catalysis between $E$-cinnamaldehyde and cyclopentadiene relative to the background reaction obtained from Brønsted acid catalysis.
Table 3.3 Variation of catalyst 3.32 and Brønsted acid on the Diels-Alder reaction of E-cinnamaldehyde and cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst equiv.</th>
<th>HCl equiv.</th>
<th>% Conversion*</th>
<th>exo:endob</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.2</td>
<td>6</td>
<td>1:2.6</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0</td>
<td>5</td>
<td>1:1.1</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.2</td>
<td>74</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.1</td>
<td>57</td>
<td>1:2</td>
</tr>
</tbody>
</table>

(a) Conversion based on limiting reagent. (b) Product ratios were determined by $^1$H NMR.

The hydrazide was dissolved in a of 9:1 methanol-water mixture followed by the addition the corresponding amount of E-cinnamaldehyde. The reaction was stirred for a few minutes at room temperature after which time freshly distilled cyclopentadiene was added. After 24 hours, hydrolysis of the dimethyl acetal product was accomplished by stirring the crude mixture in TFA:H$_2$O:CHCl$_3$ (1:1:2) to afford the corresponding aldehyde. A $^1$H NMR of the crude product was obtained to determine the conversion and diastereoselectivity.

The uncatalyzed reaction between cyclopentadiene and E-cinnamaldehyde did not occur over the course of 24 hours. However, when 20 mol% of hydrochloric acid was added to the reaction mixture, the cycloadducts were obtained in 6% and favor the endo diastereoisomer (Table 3.3, entry 2). This entry confirms that over time, a background reaction can occur if a Brønsted acid is present in the reaction mixture. Alternatively, when the reaction was performed with 0.2 equivalents of benzoic hydrazide 3.32 only, the products were obtained in 5% conversion, indicating that the Brensted acid was essential for catalysis. When equal amounts of catalyst and Brønsted acid were used, the cycloadducts were obtained in 74% conversion and a 2:1 ratio.
favoring the exo isomer. The reversal of diastereoselectivity relative to the general acid-catalyzed reaction (Table 3.3, entries 2 and 4), provided additional proof that the hydrazide salt was actually the active catalytic species. In an attempt to minimize the unwanted background reaction caused by Brønsted acid catalysis, the amount of hydrochloric acid was reduced by half compared to the hydrazide. Lowering the amount of Brønsted acid also lowered the reaction rate and the overall conversion, suggesting that an equimolar amount of acid to catalyst was ideal (entry 5).

Table 3.4 Brønsted acid effect on the conversion and diastereoselectivity of the Diels-Alder reaction between E-cinnamaldehyde and cyclopentadiene using achiral hydrazide catalyst 3.32

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst equiv.</th>
<th>Acid</th>
<th>Acid equiv.</th>
<th>% Conversiona</th>
<th>exo:endo b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>HCl</td>
<td>0.2</td>
<td>6</td>
<td>1:2.6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>HClO₄</td>
<td>0.2</td>
<td>7</td>
<td>1:1.3</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>HCl</td>
<td>0.2</td>
<td>74</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>HClO₄</td>
<td>0.2</td>
<td>84</td>
<td>1.9:1</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>HClO₄</td>
<td>0.4</td>
<td>88</td>
<td>1.8:1</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
<td>HClO₄</td>
<td>0.4</td>
<td>95</td>
<td>1.8:1</td>
</tr>
</tbody>
</table>

(a) Conversion based on limiting reagent. (b) Product ratios were determined by 1H NMR.

Next we investigated the use of perchloric acid, a stronger Brønsted acid co-catalyst, shown to be successful in other organocatalytic transformations. Compared to hydrochloric acid, perchloric acid provided a similar background reaction (Table 3.4, entries 1 and 2). However, the reaction using HClO₄ as a Brønsted acid instead of HCl accelerated the catalyzed reaction and gave a higher conversion (84 vs 74%, entries 3 and 4), while maintaining similar diastereoselectivities in favor of the exo isomer. Increasing the Brønsted acid to catalyst ratio to 2:1 amplified the
conversion, most likely due to enhanced general acid catalysis (entry 5). Increasing the catalyst and acid loading to 0.4 instead of 0.2 equivalents, results in a 95% vs 84% conversion to the products. The results shown above suggest that Brønsted acid catalysis does not significantly account for the generation of cycloadducts.

These preliminary results confirm that linear achiral hydrazides such as 3.32 can be used as efficient catalysts to promote Diels-Alder cycloadditions. Our next goal was to investigate the incorporation of the reactive hydrazide moiety within a ring system, based on the observation that most organic catalysts are embedded within a “privileged” five-membered ring. Such a design would shape ideal candidates for asymmetric hydrazide catalysis, a feat yet to be achieved. The first catalyst design that we envisaged relied on bicyclic hydrazide framework 3.35. Substitution α to the hydrazine could create a steric environment capable of controlling the formation of the iminum ion. If a racemic version of the catalyst showed promising catalytic activity toward the Diels-Alder cycloaddition, an asymmetric version of the catalyst could be put together where the cis-folded bicyclic ring junction could dictate the approach of the diene.

Figure 3.7 Proposed design of bicyclic hydrazide catalyst

The synthesis of catalysts of this structural design was envisioned in a protocol established by Oppolzer in 1972. In this article, it was suggested that hydrazide 3.38, when treated with an aldehyde in the presence of a dehydrating agent would form an intermediate dipole 3.39 that would spontaneously rearrange to afford 3.40. Removal of the benzyl protecting group under mild conditions would afford the potential catalyst 3.41. We began our synthesis with 2-formyl

\[ \text{Oppolzer, W. *Tetrahedron Lett.* 1972, 17, 1710.} \]
benzoic acid 3.36 which was submitted to Wittig conditions to give the resulting 2-vinylbenzoic acid 3.37 in 80% yield. Next, benzyl hydrazine was coupled to the carboxylic acid using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) in the presence of triethylamine in 60% yield. Efforts to cyclize intermediate 3.38 were unfortunately to no avail. Several reaction parameters were examined including variation of the solvent and drying agent while refluxing or under microwave conditions but only complex mixture were observed by NMR spectroscopy and mass spectrometry.\textsuperscript{109}

Scheme 3.9 Attempted synthesis of bicyclic hydrazide catalyst 3.41

As a consequence, we turned our attention to an alternative synthesis of this bicyclic hydrazide scaffold. Johnson and co-workers had reported the synthesis of related compounds starting from phtalides.\textsuperscript{110} Treatment of 4-methoxy acetophenone 3.42 in an ethanolic solution of KOH with 2-formyl benzoic acid 3.36 gave an aldol intermediate which cyclised to give derivative 3.43 after acidic treatment. Treatment of 3.43 with hydrazine hydrate in refluxing methanol afforded the

\textsuperscript{109} Attempts to synthesize non aromatic analogues were also briefly investigated but were not successful due to the specifically poor stability of the small molecular weight hydrazide intermediates.

bicyclic hydrazono derivative 3.44. Unfortunately, reduction of the unsaturated carbon-nitrogen bond proved to be more difficult than anticipated.

Scheme 3.10 Attempted synthesis of hydrazide catalyst 3.45

A variety of reducing conditions were applied to 3.44 in attempts to obtain hydrazide catalyst 3.45. Reductions using sodium borohydride or sodium cyanoborohydride, returned only starting material (Table 3.5, entry 1). Hydrogenation over palladium on carbon resulted in recovery of starting material, whereas the use of platinum oxide gave complex mixtures, unidentifiable by NMR analysis. This phenomenon was thought to be the result of compound 3.45's strong sp2 character, which most likely facilitated the air oxidation of the reduced compound back to the starting material.
Table 3.5 Reduction conditions for the reduction of hydrazide imine 3.44 to proposed catalyst 3.45

<table>
<thead>
<tr>
<th>Reducing agent</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH₄</td>
<td>MeOH/EtOAc</td>
<td>25 to reflux</td>
<td>SM</td>
</tr>
<tr>
<td>NaBH₃CN/HOAc</td>
<td>MeOH or EtOH</td>
<td>25</td>
<td>SM</td>
</tr>
<tr>
<td>H₂/Pd-C</td>
<td>MeOH or EtOAc</td>
<td>25</td>
<td>SM</td>
</tr>
<tr>
<td>H₂/PtO₂·H₂O</td>
<td>MeOH</td>
<td>25</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Due to the lack of success in the synthesis the latter catalysts, we decided to revise the design of our potential catalytic system by altering the arrangement of the hydrazide within the bicyclic system.

Figure 3.8 Comparison between unsuccessful and alternative hydrazide architecture

A simpler hydrazide model was devised that could be easily synthesized and readily altered. Of particular interest, the nitrogen providing the heteroatom effect was moved away from the ring junction in hopes to provide a more stable hydrazide arrangement, as seen in Figure 3.8. This nitrogen could be easily derivatized and provide access to a wealth of catalyst analogues. A
chiral center would also be introduced α to the nucleophilic nitrogen, whose configuration would determine the sense of selectivity.

Figure 3.9 Design of potential hydrazide catalyst 3.47

![Diagram of hydrazide catalyst 3.47]

We were pleased to find that the synthesis of racemic 3.51 was achieved in a two-step sequence starting from phenyl acetaldehyde 3.48. Using the Horner-Wadsworth-Emmonds protocol, the reaction of triethyphosphonoacetate 3.49 and phenyl acetaldehyde gave α-β-unsaturated ester 3.50 in 87% yield. The ester was then refluxed with hydrazine monohydrate in methanol to afford racemic hydrazide 3.51 in excellent yield.

Scheme 3.11 Racemic synthesis of hydrazide catalyst 3.51

![Scheme 3.11](image)

The efficiency of 3.51 as a catalyst was tested in the Diels-Alder cycloaddition between cyclopentadiene and E-cinnamaldehyde. Compound 3.51 was treated with perchloric acid to formulate a hydrazide salt which was a dissolved in 9:1 methanol-water solution together with 3.11 and 3.8. The reaction was stirred for 24 hours at room temperature, after which time the conversion and diastereoselectivity were measured by $^1$H NMR. The reaction with equimolar

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111 Obtained from a collaboration with Livia Aumand
amounts of hydrazide and perchloric acid afforded cycloadducts 3.9 and 3.10 in a very modest 5% conversion (Table 3.6, entry 3). When twice the amount of hydrazide per acid co-catalyst was used the conversion further diminished to 2%. Additionally, when 20 mol% of hydrazide 3.51 was used without any Brønsted acid, only negligible cycloaddition product was observed, as expected because perchloric acid facilitates the formation of the iminium ion (Table 3.6, entry 1). However, the reaction in which only perchloric acid was present, the cycloadduct was obtained in 7% conversion in a 1.1:1 endo:exo ratio. This entry confirmed that although perchloric acid itself is not an effective catalyst for the Diels-Alder cycloaddition, it catalyzes the reaction more efficiently than when hydrazide 3.51 is present. These observations suggest that the hydrazide in this study did not play a significant role in providing the desired Diels-Alder cycloadducts.

Table 3.6 Evaluation of catalyst 3.51 in the Diels-Alder cycloaddition between E-cinnamaldehyde and cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol% 3.51</th>
<th>mol% HClO₄</th>
<th>% conversion</th>
<th>endo:exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.2</td>
<td>7</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
<td>5</td>
<td>1.3:1</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>2</td>
<td>1:1</td>
</tr>
</tbody>
</table>

(a) Results obtained in conjunction with Livia Aumand (b) Conversion based on limiting reagent. (c) Product ratios were determined by ¹H NMR.

As a consequence of these poor preliminary results, we speculated that the free amide nitrogen might interfere with the iminium formation process. Since the MacMillan group has had significant success using a benzyl side chain next to the nucleophile, we anticipated that our catalysts should have this feature as well. Thus, the amide nitrogen in hydrazide 3.51 was
protected using a benzyl moiety as shown in Scheme 3.12. The more nucleophilic nitrogen in 3.51 was first derivatized as a tert-butyl carbamate using Boc-anhydride to afford monoprotected hydrazide 3.52 in 97% yield. The amide nitrogen was then benzylated using benzyl bromide in the presence of sodium hydride to give 3.53, followed by treatment with trifluoroacetic acid to unveil the reactive nitrogen in compound 3.54.

Scheme 3.12 Racemic synthesis of N-benzyl substituted catalyst 3.54

This catalyst was tested in Diels-Alder cycloadditions between cyclopentadiene and E-cinnamaldehyde in similar conditions employed for hydrazide 3.51. Although the combination of hydrazide and acid co-catalyst resulted in a higher percent conversion than the Brønsted acid alone (12 vs. 7% conversion, Table 3.7, entries 2 and 3), the low product conversions obtained entailed that catalyst 3.54 was not synthetically useful. Consequently, an asymmetric version of this catalyst was abandoned and our efforts were directed toward the design and synthesis of alternative cyclic hydrazide catalysts.
Table 3.7 Evaluation of catalyst 3.54 in the Diels-Alder cycloaddition between $E$-cinnamaldehyde and cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>mol% 3.54</th>
<th>mol% HClO₄</th>
<th>% conversion</th>
<th>endo:exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>0</td>
<td>6</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20</td>
<td>7</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>18</td>
<td>12</td>
<td>1:1:1</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>1:1:1</td>
</tr>
</tbody>
</table>

(a) Results obtained in conjunction with Livia Aumand (b) Conversion based on limiting reagent. (c) Product ratios were determined by $^1$H NMR.

Our efforts were next directed toward the design of bicyclic hydrazide catalysts. We speculated that encompassing the hydrazide within a bicyclic structure could impose ring strain and enhance exposure of the nucleophilic nitrogen lone pair. This change in the catalyst architecture should allow iminium formation with greater ease, as similarly observed with MacMillan's imidazolidinone catalyst 3.18.

Figure 3.10 Design of potential bicyclic hydrazide catalysts 3.56
A scaffold based on a cyclopentane pyrazolone was first envisaged. To prevent epimerization and potential β-eliminations, substitution was introduced at the ring junction next to the carbonyl group of the hydrazide. This group could also potentially serve as a handle to create a steric environment allowing for facial discrimination of the α,β-unsaturated iminium. A racemic model bearing a methyl substituent at the ring junction was synthesized starting with commercially available ketoester 3.57 (Scheme 3.13). Alkylation at the most acidic position afforded compound 3.58 in 80% yield. Next, a one-pot imine formation followed by cyclization onto the ester moiety was achieved by refluxing 3.58 with benzyl hydrazine in acetic acid. Reduction of the corresponding cyclized imine 3.59 with Adams' catalyst under a hydrogen atmosphere provided the desired catalyst 3.60 in 69% yield over three steps.

Scheme 3.13 Racemic synthesis of cyclopentane pyrazolone catalyst 3.60

Bicyclic hydrazide 3.60 was evaluated as a catalyst in the Diels-Alder reaction between E-cinnamaldehyde and cyclopentadiene at room temperature for 48 hours. The hydrazide catalyst itself did not catalyze the cycloaddition (Table 3.8, entry 2). A control experiment using Brønsted acid only, furnished a diastereomeric mixture of cycloadducts in 7% conversion with a 

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slight preference for the endo isomer (entry 1). In order to minimize the background acid-catalyzed reaction, the Brønsted acid co-catalyst was used in substoichiometric amounts relative to the hydrazide catalyst. A catalyst loading of 20 mol% together with 0.1 and 0.18 equivalents of perchloric acid as a co-catalyst furnished the products in 9 and 13% respectively with diastereoselectivity favoring the exo isomer (entry 3 and 4). Although the use of hydrazide catalyst 3.60 provided a slight improvement over the acid catalyzed reaction, the conversion to cycloadducts 3.9 and 3.10 was unacceptable.

Table 3.8 Evaluation of catalyst 3.60 in the Diels-Alder cycloaddition between E-cinnamaldehyde and cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst 3.60 (equiv.)</th>
<th>HClO₄ (equiv.)</th>
<th>% conversionᵇ</th>
<th>endo:exoᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.18</td>
<td>7</td>
<td>1.3:1</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0</td>
<td>1</td>
<td>1.7:1</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.1</td>
<td>9</td>
<td>1:3.1</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.18</td>
<td>13</td>
<td>1:1.9</td>
</tr>
</tbody>
</table>

(a) Results obtained in conjunction with Ami Chin (b) Conversion based on limiting reagent. (c) Product ratios were determined by ¹H NMR.

We hypothesized that the cis-fused [5.5.0] ring system of the cyclopentane pyrazolone 3.60 might create a congested environment in proximity to the nucleophilic amine, thus hampering the reactivity of the catalyst. This lead us to reconsider our catalyst design such that it would incorporate a 6-membered ring rather than a cyclopentane. The trans ring fusion in catalyst 3.64 would not exhibit steric shielding of the nucleophilic nitrogen.
The change from a five-membered to a six-membered ring catalytic scaffold was achieved in a similar sequence to Scheme 3.13. Starting from cyclohexane keto-ester 3.61, a selective methylation was accomplished in 96% yield followed by refluxing of the alkylated product with benzyl hydrazine to afford bicyclic imine 3.63 in excellent yield. Reduction of the imine using platinum oxide did not furnish the desired hydrazide imine in satisfying yield. However, reduction of the imine 3.63 using sodium cyanoborohydride in a 1:2 mixture of acetic acid and methanol afforded catalyst 3.64 in a 77% yield, as depicted in Scheme 3.14.

Scheme 3.14 Racemic synthesis of cyclohexane pyrazolone catalyst 3.64

Catalyst 3.64 was tested in our targeted Diels-Alder cycloaddition. The trends observed were similar to those obtained using catalyst 3.60. When 20 mol% catalyst was used in conjunction with 0.1 or 0.18 equivalents of perchloric acid, the yields slightly increased and the endo:exo selectivity was reversed relative to the Brønsted acid-catalyzed process. Once again, the hydrazide did not seem to significantly partake in the cycloaddition process as the conversion was largely accounted for by the competing acid-catalyzed process in the control experiment (Table 3.9, entry 1).
Table 3.9 Evaluation of catalyst 3.64 in the Diels-Alder cycloaddition between \( E \)-cinnamaldehyde and cyclopentadiene

\[
\text{PhCH}:\text{CHO} + \text{cyclopentadiene} \rightarrow \text{3.9} + \text{3.10}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst 3.64 (equiv.)</th>
<th>HClO(_4) (equiv.)</th>
<th>% conversion(^b)</th>
<th>endo:exo(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.18</td>
<td>7</td>
<td>1.3:1</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0</td>
<td>3</td>
<td>1:1:2</td>
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<tr>
<td>3</td>
<td>0.2</td>
<td>0.1</td>
<td>12</td>
<td>1:2:1</td>
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<tr>
<td>4</td>
<td>0.2</td>
<td>0.18</td>
<td>10</td>
<td>1:2:1</td>
</tr>
</tbody>
</table>

(a) Results obtained in conjunction with Ami Chin (b) Conversion based on limiting reagent. (c) Product ratios were determined by \(^1\)H NMR.

### 3.3 Novel Catalyst Design

Although the linear achiral catalyst developed by Tomkinson group confirmed that hydrazide catalysis can be a viable mode of activation in iminium induced processes, our efforts toward incorporating the hydrazide moiety within a cyclic framework remained unsuccessful. To overcome this setback, we next invested our efforts toward an intense literature search in order to adopt an alternative and unique chiral scaffold that could contain a hydrazide moiety. Particularly, we sought compounds that had been successfully utilized in asymmetric protocols, based on the fact that the imidazolidinone catalysts designed by the MacMillan research group had been previously used as chiral auxiliaries to induce optical purity in a broad range of transformations.\(^7\) We became interested in the camphor-derived family of chiral auxiliaries,
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designed by Oppolzer et al. in the late 1980’s. Oppolzer’s auxiliary was designed to include a sultam moiety within the camphor backbone that served as an anchor to attach achiral substrates via an amide bond (Scheme 3.15). The rigid tricyclic structure of camphor provided bulky groups in proximity to the asymmetric induction site in 3.66 resulting in highly diastereoselective transformations. The cleavage of the sultam auxiliary can be easily achieved in the presence of lithium hydroxide and hydrogen peroxide to afford products 3.67 in high optical purity. The Oppolzer sultam has been successfully applied to a range of synthetic transformations including 1,4-additions and Diels-Alder cycloaddition.

Scheme 3.15 Camphor sultam chiral auxiliary used in the asymmetric Diels-Alder reaction

Recently, a novel chiral auxiliary based on the Oppolzer template was designed to include a hydrazide functionality. Chen and co-workers employed these chiral auxiliaries in several reactions including the diastereoselective Baylis-Hillman protocol.

115 Various salts of camphor sultam were tested in the Diels-Alder cycloadditions but were not suitable organocatalysts for this process.
Scheme 3.16 Diastereoselective Bayliss-Hillman promoted by a chiral hydrazide auxiliary

\[ \text{Scheme 3.16} \]

A camphor-derived organocatalyst inspired from these chiral hydrazide auxiliaries would offer several advantages (Figure 3.11). Catalyst 3.70 would be based on commercially available and inexpensive camphorsulfonic acid which is available in both antipodal forms, thus allowing access to both enantiomeric forms of products.\(^{117}\) It would feature enhanced nucleophilicity supplied by the hydrazide moiety and the strained tricyclic framework. Geminal substitution next to the carbonyl would prevent \(\beta\)-elimination and reinforce the catalyst's stability. The R substituent on the catalyst could potentially be easily altered allowing access to a range of catalyst analogues. Most importantly, the camphor backbone could be used to incorporate a sense of stereochemistry in the rate-enhanced transformations.

Figure 3.11 Advantages provided by camphor-based hydrazide catalysts

The Chen group achieved the synthesis of camphor-based hydrazide 3.75 in a short four-step sequence starting from commercially available \((+)-\)camphorsulfonic acid 3.71. Using the Bartlett

\(^{117}\) 500g \((1S)-(-)-10\)-camphorsulfonic acid sells for $243 USD at Sigma-Aldrich.
and Knox procedure,\textsuperscript{118} (+)-ketopinic acid 7.72 was made by first converting 3.71 to the sulfonyl chloride, followed by its oxidation by potassium permanganate in aqueous basic media. Treatment of (+)-ketopinic acid with phenyl hydrazine under acid conditions provided 3.73 in 95\% yield (Scheme 3.17). The cyclization was accomplished by treatment of 3.73 with thionyl chloride in the presence of triethyl amine. Reduction of the imine bond with sodium borohydride provided hydrazide 3.75 as the sole product in 94\% yield. The structure of 3.75 was unambiguously characterized after derivatization with acryloyl chloride to afford 3.76 which was analyzed by spectroscopic analyses and further confirmed by X-ray analysis.

Scheme 3.17 Synthesis of the hydrazide chiral auxiliary 3.75 developed by Chen et al

This synthetic protocol was repeated in order to gain access to hydrazide 3.75. Although compound 3.75 was obtained in considerably lower chemical yield than previously reported, sufficient quantities were synthesized to verify its efficiency as a potential catalyst for the Diels-Alder cycloaddition. We were pleased to find that 20 mol\% of the perchloric salt of hydrazide 3.75 was capable of promoting the cycloaddition between \(E\)-cinamaldehyde and cyclopentadiene in 25\% conversion with 60\% optical purity for the \textit{endo} adduct.

Scheme 3.18 Initial reaction between \(E\)-cinnamaldehyde and cyclopentadiene catalyzed by hydrazide salt 3.75

\[
\begin{align*}
\text{Ph} &\text{CHO} \quad + \quad \text{3.8} \\
&\xrightarrow{20 \text{ mol%} \quad 3.75 \quad \text{Ph} \quad \text{HClO}_4} \\
&\quad 9:1 \text{MeOH-H}_2\text{O} \\
&\quad 23^\circ\text{C}, 24\text{h} \\
\text{3.11} &\quad \text{3.8} &\quad \text{3.9} \\
\quad &\quad \text{exo} &\quad \text{endo} \\
\end{align*}
\]

25\% conversion \\
1.1:1 exo:end o \\
60\% endo ee

This exceptionally encouraging result suggested that this catalyst architecture may be capable of achieving the hydrazide-catalyzed Diels-Alder cycloaddition in the high optical purities we initially set out to obtain. However, in this initial experiment, the percent conversion was significantly low. We hypothesized that the phenyl ring of 3.75, in close proximity to the nucleophilic nitrogen, limited the catalyst turnover due to steric hindrance. As a result, we wished to synthesize analogues of hydrazide 3.75 incorporating smaller alkyl groups and benzyl moieties. To our dismay, the procedure developed by Chen et al, particularly the cyclization and reduction steps, were found to be unsuitable for the synthesis of catalyst analogues. Hence, a set of alternative conditions had to be established in order to render the synthesis of hydrazide analogues viable.

Unearthing synthetically practical conditions for these two steps was however, not trivial. Cyclization of the methyl-derived hydrazoic acid 3.77 to the pyrazolone ring was particularly challenging in part due to the highly strained nature of the camphor backbone. Table 3.10 below, shows the conditions explored for this synthetic transformation.
Table 3.10 Exploration of various conditions for the cyclization of hydrazoic acid 3.77 to 3.78

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp. °C</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOCl₂/Et₃N</td>
<td>EtOAc</td>
<td>-</td>
<td>Reflux</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>SOCl₂/Et₃N</td>
<td>Toluene</td>
<td>-</td>
<td>Reflux</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>SOCl₂/DIPEA</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>Reflux</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Oxalyl chloride/Et₃N</td>
<td>CH₂Cl₂</td>
<td>DMF</td>
<td>0-23</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>EDC/HOBT/DIPEA</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>23</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>EDC/HOBT/DIPEA</td>
<td>DMF</td>
<td>-</td>
<td>23</td>
<td>72</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>HATU/HOBT/DIPEA</td>
<td>DMF</td>
<td>-</td>
<td>23</td>
<td>48</td>
<td>0</td>
</tr>
</tbody>
</table>

The conditions established for the cyclization by the Chen group involved the formation of an intermediate acid chloride. Their conditions, using 1.3 equivalents of thionyl chloride and one equivalent of triethylamine as an acid scavenger in refluxing ethyl acetate, gave only 10% yield of 3.78 after 24 hours (Table 3.10, entry 1). Longer reaction times resulted in disappearance of the product and formation of tar-like substances. Changing to a higher boiling solvent such as toluene did not result in a significant yield improvement. Oxalyl chloride in the presence of catalytic dimethyl formamide was also explored for the formation of a reactive intermediate but did not afford any observable product. Because the reaction is intramolecular, a potential predicament to this approach is the reaction of the amine with the electrophillic chloride source that could cause unwanted side-reactions. Consequently, peptide coupling conditions were also explored. Various coupling agents such as EDC or HATU in either dichloromethane of DMF were tested but only afforded traces of the desired cyclized product after 72 hours. A one-pot
sequence in which ketopinic acid methyl ester and methylhydrazine were refluxed in acetic acid provided the cyclized product 3.78 in only 22% yield after 72 hours.

An alternative protocol that utilized inexpensive and environmentally benign boric acid to promote the formation of amide bonds between carboxylic acids and amines was investigated.\(^{119}\)

It is proposed that the boric acid reacts with the carboxylic acid to form a mixed anhydride as the acylating agent. Upon reaction with an amine, this intermediate forms the desired amide and regenerates the catalytically active boric acid. When 3.77 was refluxed in toluene using a Dean-Stark trap in the presence of 25 mol% of boric acid, the desired cyclized product 3.78 was obtained in an improved 23% yield (Table 3.11, entry 1). It had been reported that although the reaction is catalytic, increasing the amount of boric acid further facilitated the reaction. Thus, when one equivalent of boric acid was used, the yield of 3.78 was increased to 36% after 72 hours. We then turned our attention to higher boiling solvents such as xylenes and mesitylene. Using 5 equivalents of boric acid, various desiccating agents were used to remove the water produced in the reaction sequence (entries 3, 4 and 5). Both molecular sieves and the use of a Dean-Stark apparatus proved to be efficient at promoting the cyclization. Changing the solvent to mesitylene was found to afford the desired product 3.78 in an optimal yield of 62% and in a shortened reaction time of 16 hours. Surprisingly, in a reaction in which the boric acid was accidentally omitted, we found that the cyclized hydrazoic imine 3.78 was obtained in 74% after 18 hours. Hence, boric acid was found to be a spectator in the reaction and the cyclization could be achieved using only a high boiling solvent under water-removing conditions. No product decomposition was observed in this very atom-efficient process. Furthermore, post-reaction manipulations were simplified since no work-up was needed and the high boiling mesitylene could be removed by flash-chromatography using hexanes.\(^{120}\)


\(^{120}\) Simple removal of the hexanes in vacuo allowed for recycling of the mesitylene.
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Table 3.11 The boric acid promoted cyclization of hydrazoic acid 3.77 to 3.78

![Catalyzed Diels-Alder Cycloadditions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Additive</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25 eq. B(OH)₃</td>
<td>toluene</td>
<td>Dean-Stark</td>
<td>72</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>1 eq. B(OH)₃</td>
<td>toluene</td>
<td>Dean-Stark</td>
<td>72</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>5 eq. B(OH)₃</td>
<td>xylenes</td>
<td>Dean-Stark</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>5 eq. B(OH)₃</td>
<td>xylenes</td>
<td>CaH</td>
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<td>xylenes</td>
<td>Mol sieves³</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>5 eq. B(OH)₃</td>
<td>mesitylene</td>
<td>Dean-Stark</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>mesitylene</td>
<td>Dean-Stark</td>
<td>18</td>
<td>74</td>
</tr>
</tbody>
</table>

(a) Molecular sieves were activated under vacuum before use.

With the cyclized intermediate in hand, we next focused our efforts toward the reduction of imine 3.78. The imine hydrazide, encompassed in the strained camphor ring system, was particularly robust and proved difficult to reduce. The use of borane or triethylsilane in the presence of TFA or boron trifluoroetherate provided complex mixtures of products in which 3.79 could not be identified (Table 3.12, entries 1, 2 and 3). Chen and co-workers had reported the use of an excess of sodium borohydride to induce the reduction of 3.78 (see Scheme 3.17).¹¹⁶ However, we found that when applied to 3.77 the desired compound could only be obtained in 50% yield as the reaction seemed to stall after a number of hours (entry 4). Decreasing the amount of equivalents of borohydride or adding the reagent in portions over time did not provide any advantage. Changing the solvent to ethanol and submitting the reaction to a reflux did not increase the yield. Sodium triacetyborohydride was found to be less efficient but sodium cyanoborohydride in a 2:1 mixture of methanol and acetic acid proved to be an effective system for the reduction of 3.77 (entries 6 and 7). Stronger reducing agents such as lithium aluminum
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Hydride afforded many by-products in a very short time frame and most likely reduced the amide functionality of the hydrazide (entries 8 and 9). Hydrogenating conditions were also examined toward the reduction of imine hydrazide 3.77. Both palladium on carbon and palladium hydroxide in hydrogen atmosphere provided traces of the desired reduced product. Platinum hydroxide did promote the reduction of 3.77 in excellent yield and in reasonable reaction time. Unfortunately, when catalyst analogues such as those bearing a benzyl side chain 3.86 rather than the methyl group found in 3.79 were submitted to these hydrogenating conditions, longer reaction times and higher catalyst loading were necessary to assure reaction completion. This resulted in reduction of the phenyl ring of the benzyl substituent to a cyclohexane ring. This impurity could not be removed by flash chromatography or recrystallization as the two compounds had very similar properties which rendered this approach futile. Consequently, sodium cyanoborohydride was chosen as the optimal reducing agent for the preparation of hydrazides.
Table 3.12 Conditions explored for the reduction of 3.78 to hydrazide 3.79

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp. °C</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>THF</td>
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<td>20</td>
<td>0</td>
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<tr>
<td>2</td>
<td>1</td>
<td>Et$_3$SiH</td>
<td>TFA</td>
<td>0-23</td>
<td>6</td>
<td>0$^a$</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Et$_3$SiH/BF$_3$ • OEt</td>
<td>CH$_2$Cl$_2$</td>
<td>0-23</td>
<td>6</td>
<td>0$^a$</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>NaBH$_4$</td>
<td>MeOH</td>
<td>23</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>NaBH$_4$</td>
<td>EtOH</td>
<td>reflux</td>
<td>120</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>NaB(OAc)$_3$</td>
<td>MeOH</td>
<td>23</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>NaBH$_3$CN</td>
<td>MeOH/HOAc</td>
<td>23</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>LiAlH$_4$</td>
<td>Et$_2$O</td>
<td>0-23</td>
<td>1</td>
<td>0$^b$</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>LiAlH$_4$</td>
<td>THF</td>
<td>0-23</td>
<td>1</td>
<td>0$^b$</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>Pd-C/H$_2$</td>
<td>MeOH</td>
<td>23</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>Pd(OH)$_2$/H$_2$</td>
<td>MeOH</td>
<td>23</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
<td>PdO$_2$ • H$_2$O/H$_2$</td>
<td>MeOH</td>
<td>23</td>
<td>24</td>
<td>92$^c$</td>
</tr>
</tbody>
</table>

(a) Many side-products were formed during these reactions making identification of the product impossible (b) Reduction of amide as well as many undesired spots were observed on TLC. (c) When this reaction was applied to catalyst bearing a benzyl side chain, significant reduction of the aromatic group to the cyclohexyl group occurred.

Following these optimizations, a general procedure was established for the synthesis of a variety of hydrazide catalysts (Scheme 3.19). Ketopinic acid was synthesized from commercially available camphorsulfonic acid using the method developed by Bartlett and Knox discussed above$^{118}$ (see Scheme 3.17). The product can either be purified by flash chromatography or used
directly to form the hydrazoic acid 3.80. If the desired mono-substituted hydrazines are not commercially available, they can be easily prepared by the reaction of an alkyl chloride or bromide in a tenfold excess of hydrazine in a methanol solution at 0 °C. Only minimal amounts of disubstituted hydrazines are formed using this method. The excess hydrazine can be easily removed in vacuo and the resulting oil can be used directly for condensation onto the ketone of ketopinic acid in presence of a catalytic amount of acetic acid in dichloromethane in 86-100% yield. Cyclization was achieved by heating the hydrazoic acid 3.80 in mesitylene using a Dean-Stark trap to obtain the cyclic imine 3.81 in 72-80% yield. Reduction of the imine using an excess of sodium cyanoborohydride in a 2:1 methanol-acetic acid mixture afforded the desired hydrazide catalysts 3.82 in 89-95% yield.

121 The disubstituted hydrazine will not form a product with ketopinic acid as the hydrazonium generated will be hydrolyzed on workup.

122 It is worth mentioning that an alternative assembly of the catalyst was explored in which a common unsubstituted hydrazide imine such as 3.83 could be treated with an appropriate base and alkylated to quickly gain access to a variety of intermediates. This sequence would avoid the cyclization step and improve the synthesis of hydrazide catalysts. Unfortunately, several bases were tested and all attempts to provide 3.85 resulted in only traces of product.
While manipulating hydrazide catalysts, it was found that the molecule could re-oxidize over time to the imine, especially in a solvent or at ambient temperature. This observation could, to a degree, explain the difficulty we had encountered, and the excess hydride reagent necessary to assure complete formation of the reduced hydrazide. However, if the catalysts were stored in a flask under nitrogen in a -20 °C freezer, the catalyst could be kept for over a year, without any signs of re-oxidation.

### 3.4 Optimization of Catalyst and Reaction parameters

With an efficient protocol to access a library of catalyst analogues, we first compared hydrazides with phenyl and benzyl side chains in hope of making the nucleophilic nitrogen more accessible. The reactions between $E$-cinnamaldehyde and an excess of cyclopentadiene were performed in a 9:1 mixture of methanol-water at 23 °C with varying amounts of hydrazide and acid co-catalyst. Upon completion of the reaction, hydrolysis of the dimethyl acetal product (obtained from the methanol-water solvent combination) was accomplished by stirring the crude mixture in TFA:H$_2$O:CHCl$_3$ (1:1:2) for 2 hours at room temperature. A $^1$H NMR of the crude product was obtained to determine percent conversion and the diastereoselectivity. The enantiomeric excess of the compound was determined by 500 MHz $^1$H NMR following the conversion of aldehydes.
Hydrazide-Catalyzed Diels-Alder Cycloadditions

3.9 and 3.10 to the corresponding (+)-(R,R)-hydrobenzoin acetals and comparison to known samples.

Table 3.13 Effect of catalyst structure and reaction time on the Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst equiv.</th>
<th>Acid equiv.</th>
<th>Time (hr)</th>
<th>% conversion</th>
<th>exo:endo</th>
<th>endo ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0</td>
<td>0.2</td>
<td>24</td>
<td>7</td>
<td>1:1.3</td>
<td>n/d</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>0.2</td>
<td>0</td>
<td>24</td>
<td>5</td>
<td>1:1.6</td>
<td>n/d</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>0.2</td>
<td>0.2</td>
<td>24</td>
<td>25</td>
<td>1.1:1</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>0.2</td>
<td>0.2</td>
<td>24</td>
<td>60</td>
<td>2.1:1</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>0.2</td>
<td>0.2</td>
<td>48</td>
<td>92</td>
<td>2.1:1</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>0.2</td>
<td>0.18</td>
<td>48</td>
<td>81</td>
<td>2.1:1</td>
<td>75</td>
</tr>
</tbody>
</table>

(a) Product is isolated as the aldehyde after treatment of the crude mixture with TFA:H₂O:CHCl₃ (1:1:2) for 2 hours at room temperature. (b) Conversion based on limiting reagent. (c) Product ratios were determined by ¹H NMR. (d) Enantioselectivity determined by ¹H NMR after conversion to acetal with (R,R)-(+)-hydrobenzoin.

As observed with Tomkinson's linear hydrazide catalyst 3.32, if only Brønsted acid is added to the reaction mixture, the reaction occurs in only 7% conversion whereas 20 mol% of the phenyl hydrazide itself provides the Diels-Alder adduct in a mere 5% conversion (Table 3.13, entries 1 and 2). This observation confirms that a reasonable rate increase will only be observed if the hydrazide is used as a Brønsted acid salt and that the background reaction induced by general acid catalysis is minimal. As expected, reducing the steric demands near the nucleophilic nitrogen of the hydrazide catalyst by replacing the phenyl side-chain with a benzyl group (entries 3 and 4) dramatically increased the percent conversion from 25 to 60%. When the R moiety was
changed to a benzyl group, the reaction displayed selectivity for the exo isomer and the enantiomeric excess also substantially improved from 60 to 77%. Cases in which the reaction was allowed to stir for 48 hours, the conversion was increased to 92% and the optical purity to 82% (entry 5). In an effort to reduce the background reaction, reducing the acid to catalyst ratio considerably reduced the conversion and the enantiomeric excess (entry 6). This observation suggests that the Brønsted acid should be used in an equimolar ratio with the catalyst.

Table 3.14 Survey of a variety of camphor-based hydrazides for enantioselective catalysis of the Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>% conversion</th>
<th>yield</th>
<th>exo:endo</th>
<th>endo ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>31</td>
<td>25</td>
<td>0.9:1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>22</td>
<td>18</td>
<td>1.2:1</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>25</td>
<td>25</td>
<td>1.1:1</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>92</td>
<td>90</td>
<td>2:1:1</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$-p-OMePh</td>
<td>94</td>
<td>89</td>
<td>2.2:1</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$-p-CF$_3$Ph</td>
<td>80</td>
<td>74</td>
<td>2.1:1</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>CH$_2$-1-naphthyl</td>
<td>86</td>
<td>82</td>
<td>1.7:1</td>
<td>74</td>
</tr>
</tbody>
</table>

*a* All reactions were done using 0.2 equiv. of catalyst and 0.2 equiv. of HClO$_4$. *Conversion based on limiting reagent. *Product ratios were determined by $^1$H NMR. *Enantioselectivity determined by $^1$H NMR after conversion to acetal with (R,R)-(++)-hydrobenzoin. *Reaction time 24 hours

123 Only the *endo* enantioselectivities are reported and show the trend in a column. In all cases, the *endo* and *exo* selectivities obtained were very similar but the resolution of the peaks for the *endo* hydrobenzoin acetals was significantly better.
Next we investigated changes to the indicated side chain which proved crucial to the reactivity and enantioselectivity of the Diels-Alder cycloaddition. Removal of the side chain was deleterious to catalyst activity and resulted in almost no enantioselectivity (Table 3.14, entry 1). This is divergent from Tomkinson's acyclic hydrazide 3.32 which lack substitution at this position but provide the cycloadducts in excellent yields. Small aliphatic groups such as a methyl gave yields and facial selectivity similar to that of catalyst bearing a phenyl substituent (entries 2 and 3). Changing the electronic properties on the aromatic ring of the benzyl side-chain was also investigated. Addition of an electron withdrawing such as p-CF₃ group decreases the reactivity as well as the enantiomeric excess (entry 6). When an electron donating group such as p-methoxy was inserted the reaction rate increased relative to entry 4 but a decrease the enantioselectivity was observed. Consequently, varying the electronics on the benzylic ring did not supply any advantages to the catalyst. Increasing the size of the aromatic function relative to a benzyl group to a CH₂-1-naphthyl moiety did not improve the enantioselectivity (entry 7). These results suggest that the optimal hydrazide catalyst should contain a benzyl moiety. Furthermore, in all cases the isolated yield corresponded to the percent conversion within a reasonable margin indicating that the aldehyde cycloadducts are stable for flash chromatography and post-reaction handling.

The use of benzyl catalyst 3.86 in a variety of aqueous solvent mixtures (9:1 solvent:water) was explored as shown in Table 3.15 below. The solvent water combination is necessary to assure proper hydrolysis of iminium and catalyst turnover.
Table 3.15 Effect of Solvent on the hydrazide-catalyzed Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde. a

\[
\text{Ph-} \equiv \text{CHO} + \text{C_5H_5} \rightarrow \text{Ph-} \equiv \text{CHO} + \text{C_5H_5} \\
3.11 + 3.8 \rightarrow 3.9 + 3.10
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Dielectric constant</th>
<th>Yield</th>
<th>exo:endo (^b)</th>
<th>ee endo (%) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene</td>
<td>2.3</td>
<td>8</td>
<td>1.6:1</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>7.6</td>
<td>23</td>
<td>1.6:1</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl(_2)</td>
<td>9.1</td>
<td>64</td>
<td>2.3:1</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>IPrOH</td>
<td>18.3</td>
<td>48</td>
<td>1.8:1</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>CF(_3)CH(_2)OH</td>
<td>26.5</td>
<td>96(^a)</td>
<td>2.1:1</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>32.6</td>
<td>88</td>
<td>2.1:1</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>CH(_3)NO(_2)</td>
<td>36.0</td>
<td>92(^d)</td>
<td>2.1:1</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>CH(_3)CN</td>
<td>37.5</td>
<td>49</td>
<td>2:1</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>38.3</td>
<td>16</td>
<td>1.8:1</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>47.0</td>
<td>35</td>
<td>1.9:1</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>H(_2)O</td>
<td>60.4</td>
<td></td>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were done using 0.2 equiv. of catalyst and 0.2 equiv. of HClO\(_4\). \(^b\) Product ratios were determined by \(^1\)H NMR. \(^c\) Enantioselectivity determined by \(^1\)H NMR after conversion to acetal with (R,R)-(\(+\))-hydrobenzoin. \(^d\) Almost done after 24h \(^e\) % conversion (product not isolated)

Aqueous mixtures of methanol (88% yield, 76% endo ee) and nitromethane (92% yield, 75% endo ee) gave efficient conversion to products in good enantiomeric purity (Table 3.15, entries 6 and 7). The reaction preformed in nitromethane was more rapid as the formation of the cycloadducts was nearly complete after 24 hours. Conversely, the use of acetonitrile (49% yield, 73% endo ee) or THF (23% yield, 83% endo ee) resulted in only moderate yields (entries 2 and 8). Trifluoroethanol afforded good conversion but also generated several by-products during the
reaction which were found to be inseparable by flash chromatography. Generally, solvents with low dielectric constants such as THF and benzene provided the products in low yield whereas solvents with mid-range or high dielectric constants (MeOH, CH₃NO₂, H₂O) afforded the best yields and ratios. In all cases the enantioselectivity was less sensitive to the nature of the solvent. Optimal catalyst performance was noted in water, in which an optical purity of 85% and chemical yield of 82% was achieved. Reactions performed in distilled water were biphasic and required vigorous stirring to assure adequate mixing. The favorable reaction in aqueous media could be caused by the high internal pressure of water which is known to pack the diene and dienophile in an entropy-driven aggregation process.

Table 3.16 Effect of Bronsted acid co-catalyst on the Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>pKa</th>
<th>Yield</th>
<th>exo:endo</th>
<th>ee endo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF₃SO₂H</td>
<td>-14</td>
<td>89</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>HClO₄</td>
<td>-10</td>
<td>82d</td>
<td>1.7:1</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>CSA</td>
<td>-3</td>
<td>17</td>
<td>1.6:1</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>CH₃SO₂H</td>
<td>-2.6</td>
<td>8</td>
<td>1.2:1</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>CF₃CO₂H</td>
<td>-0.3</td>
<td>13</td>
<td>1.7:1</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CO₂H</td>
<td>4.8</td>
<td>7</td>
<td>1:1</td>
<td>2</td>
</tr>
</tbody>
</table>

Reactions run with 0.2 equiv. catalyst and 0.2 equiv. TfOH. b Product ratios were determined by ¹H NMR. c Enantioselectivity determined by ¹H NMR after conversion to acetal with (R,R)-(+) hydrobenzoin. d Reaction complete after 24h.

Tuning the acid co-catalyst led to a further performance enhancement for catalyst 3.86. A striking correlation was apparent between the strength of the acid used and the efficiency of the
Hydrazide-Catalyzed Diels-Alder Cycloadditions

reaction (Figure 3.12). To our knowledge, such correlation had not been previously observed in organically catalyzed asymmetric reactions. Steady erosion in both yield and enantioselectivity was observed as the pKa of the Brønsted acid increased. Higher yields, diastereomeric and enantiomeric excesses were obtained using a stronger Brønsted acid such as triflic and perchloric acids (Table 3.16, entries 1 and 2). These two acids not only gave the best yield and selectivity but also the cleanest and fastest reactions. Although the reactions using perchloric and triflic acid were run on a 48 hour time frame for comparison with other acids, the product conversion was complete after 24 hours as judged by TLC.

Figure 3.12 $^1$H NMR of the hydrobenzoin acetal proton shift for the endo cycloadduct showing the relationship between acid strength and enantiomeric excess.

With two potential acid co-catalysts in hand we decided to revisit the combination of organic solvents and water to probe the potential effects on the selectivity of the transformation.
Particularly, we wished to alter the ratios of water with solvents such as methanol and nitromethane, in which the reactions occurred fastest and THF, in which high enantiomeric purity was obtained.

Table 3.17 Effect of mixed solvents on the hydrazide-catalyzed Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde.\textsuperscript{a}

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
<th>exo:endo\textsuperscript{b}</th>
<th>ee endo (%\textsuperscript{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9:1 CH\textsubscript{3}NO\textsubscript{2}:H\textsubscript{2}O</td>
<td>92\textsuperscript{d}</td>
<td>2.1:1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1:9 CH\textsubscript{3}NO\textsubscript{2}:H\textsubscript{2}O</td>
<td>90\textsuperscript{d}</td>
<td>1.9:1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>1:19 CH\textsubscript{3}NO\textsubscript{2}:H\textsubscript{2}O</td>
<td>88\textsuperscript{d}</td>
<td>1.8:1</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>9:1 THF:H\textsubscript{2}O</td>
<td>23</td>
<td>1.6:1</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1:9 THF:H\textsubscript{2}O</td>
<td>92\textsuperscript{e}</td>
<td>1.7:1</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>9:1 MeOH:H\textsubscript{2}O</td>
<td>88</td>
<td>2.1:1</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>19:1 MeOH:H\textsubscript{2}O</td>
<td>83</td>
<td>2.1:1</td>
<td>74</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were done using 0.2 equiv. of catalyst and 0.2 equiv. of HClO\textsubscript{4}.\textsuperscript{b}Product ratios were determined by \textsuperscript{1}H NMR.\textsuperscript{c}Enantioselectivity determined by \textsuperscript{1}H NMR after conversion to acetal with (R,R)-(\textsuperscript{+})-hydrobenzoin.\textsuperscript{d}Almost done after 24h.

First we investigated various solvent combinations using the perchloric acid salt of hydrazide catalyst 3.86. We found that in certain cases the addition of an organic co-solvent to water modestly increased the reactivity which in turn afforded higher conversions and yields. During the initial solvent scan, the fastest reaction was observed in a 9:1 mixture of nitromethane and water (Table 3.17, entry 1). When water was used as the main solvent and lesser amounts of nitromethane were added, this trend was maintained and the enantiomeric excesses were increased from 75 to 81% (entries 1, 2 and 3). The two solvents which afforded highest optical
purities, THF and water were combined in various ratios. Although THF as the principal solvent gave a low conversion of the cycloadducts, when combined with water in a 1:9 ratio, the product was obtained in excellent yield and 89% endo ee (entries 4 and 5). When methanol was used as the major solvent, a decrease in the water level from 9:1 to 19:1 was found to lower the yield and enantiomeric excess (entries 6 and 7) confirming that a minimum of water is necessary for turnover in hydrazide catalyzed Diels-Alder reaction.

Table 3.18 Combining the mixed solvent effect with the optimal Brønsted acid in the hydrazide-catalyzed Diels-Alder reaction between cyclopentadiene and E-cinnamaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst equiv.</th>
<th>Acid equiv.</th>
<th>Yield (%)</th>
<th>exo:endoa</th>
<th>ee endo (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9:1 H2O:THF</td>
<td>0.2</td>
<td>0.2</td>
<td>84</td>
<td>1.9:1</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>9:1 H2O:CH3NO2</td>
<td>0.2</td>
<td>0.2</td>
<td>89</td>
<td>2.1:1</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>H2O</td>
<td>0.2</td>
<td>0.2</td>
<td>89c</td>
<td>1.9:1</td>
<td>88</td>
</tr>
</tbody>
</table>

Product ratios were determined by 1H NMR. a Enantioselectivity determined by 1H NMR after conversion to acetal with (R,R)-(+)-hydrobenzoin. b Isolated yield after 24 hours.

Triflic acid was found to be the best acid co-catalyst in aqueous reactions delivering the product in 89% yield and 88% endo ee (Table 3.18, entry 3). Consequently, the effect of solvent mixing was also investigated using a triflate salt of hydrazide catalyst 3.86. Combining small amounts of either THF or nitromethane with water in a 1:9 ratio did not provide any advantages in terms of yield and diminished the optical purity relative to the reaction performed in water only (entries 2 and 3). This suggested that the mixed solvent effect with trifloromethane sulfonic acid did not provide a faster reaction. The yield and the enantiomeric excess were also lower than when the reaction was performed in water only. Fully aqueous reactions also provided the advantage of
Hydrazide-Catalyzed Diels-Alder Cycloadditions

reducing the reaction time of the cycloaddition to 24 hours, making the organocatalytic process altogether more attractive.

The results in tables 3.17 and 3.18 suggest that a co-solvent is not necessary and that optimal conditions can be achieved using triflic acid as the Brønsted acid catalyst in an aqueous solution.

Table 3.19 Variation of the equivalents of Brønsted acid in the hydrazide-catalyzed Diels-Alder reaction of cyclopentadiene and E-cinnamaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst equiv.</th>
<th>Acid equiv.</th>
<th>Yield</th>
<th>exo:endo</th>
<th>ee endo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
<td>71</td>
<td>1.8:1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.2</td>
<td>89</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>0.3</td>
<td>86</td>
<td>1.9:1</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.3</td>
<td>91</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.4</td>
<td>94</td>
<td>1.9:1</td>
<td>89</td>
</tr>
</tbody>
</table>

*a* Product ratios were determined by $^1$H NMR. *b* Enantioselectivity determined by $^1$H NMR after conversion to acetal with (R,R)-(+)-hydrobenzoin.

The optimal amount of the hydrazide triflic acid salt required for efficient and selective Diels-Alder cycloaddition was examined. When the catalyst was used in 10 mol%, the yield and selectivity obtained was less than when 0.2 equivalents of catalyst and Brønsted acid were used. (Table 3.19, entries 1 and 2). Increasing the catalyst loading to 30 mol% was also detrimental to the catalytic activity and facial selectivity of the reaction.

Triflic acid is a very strong acid. We had established earlier that the Brønsted acid itself can catalyze the reaction showing an inverse diastereoselectivity in favor of the *endo* cycloadducts.
Hydrazide-Catalyzed Diels-Alder Cycloadditions

Lowering the amount of Brønsted acid relative to the catalyst resulted in lower yields and selectivities. We wished to further investigate if such strong acids are capable of catalyzing the Diels-Alder process through a competing achiral process, thus lowering the enantioselectivity. The potential impact of this background reaction was tested using 0.2 equivalents of catalyst 3.86 with increased amounts of triflic acid. In cases where 0.3 and 0.4 equivalents of acid were used, the yield slightly increased and enantioselectivities were identical indicating that strong acid was not detrimental to selectivity (Table 3.19, entries 2, 4 and 5).

Table 3.20 Effect of the solvent molarity in the hydrazide-catalyzed Diels-Alder reaction of cyclopentadiene and cinnamaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent concentration M</th>
<th>Yield</th>
<th>exo:endo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>e.e. endo (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>41</td>
<td>1.9:1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>0.13</td>
<td>89</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>97</td>
<td>1.9:1</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>96</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>93</td>
<td>1.9:1</td>
<td>87</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions run with 0.2 equiv. catalyst and 0.2 equiv. TfOH. <sup>b</sup> Product ratios were determined by <sup>1</sup>H NMR. <sup>c</sup> Enantioselectivity determined by <sup>1</sup>H NMR after conversion to acetal with (R,R)-(+-)-hydrobenzoin.

The Diels-Alder reaction between E-cinnamaldehyde and cyclopentadiene was performed at different solvent concentrations. When the reaction was more dilute, the yield and enantioselectivity drastically decreased (Table 3.20, entry 1). Generally, the reactions appeared faster and gave higher product conversion as the solvent molarity increased. However, the yield began to diminish at 2.0M solvent concentration because of the appearance of a larger
amount of side products (visible by TLC). The diastereomeric ratio was maintained constant throughout the concentration study. The reaction at one molar was chosen as the optimal solvent concentration both in terms of yield and practicality. Diels-Alder cycloadditions performed in a minimal aqueous medium and in an aerobic environment create a truly benign process potentially applicable to large scale synthesis with minimal solvent waste.

The reaction was performed at lower temperature in hope of increasing the facial selectivity of the process. When the reaction was carried out +4 °C the cycloaddition was considerably slower and required 48 hours to achieve completion. As a result, the yield was lowered from 96 to 80% yield whereas the enantioselectivity was unchanged. Consequently all subsequent reactions were performed at room temperature.

3.5 Scope of Hydrazide Catalyzed Diels-Alder cycloaddition

Having identified the ideal catalyst and optimized reaction conditions for the model cycloaddition reaction, experiments that outline the scope of the present process are given in the tables below. All reactions were performed in distilled water in aerobic atmosphere and carried out at room temperature. The α,β-unsaturated aldehydes and dienes were freshly distilled under a nitrogen atmosphere prior to use. For all entries, a racemic version of the product was synthesized using linear hydrazide catalyst 3.32 to identify the enantiomers of endo and exo diastereoisomers. The enantiomeric excess was determined either by 1H NMR after conversion to an acetal with (R,R)-(+)hydrobenzoin or by chiral GLC. The absolute configuration of the products were established by correlation of the chemical shifts of the (+)-(R,R)-hydrobenzoin acetics with those of the corresponding acetics or by GLC comparison to authentic samples.

Experiments were performed to determine the span of the dienophile component with cyclopentadiene. Substituted cinnamaldehyde dienophiles produced excellent selectivity and yields (Table 3.21, entries 1 to 6). A variety of substitutions of the aryl ring, including electron-withdrawing and -donating groups were tested and gave excellent enantioselectivities. Ortho and meta and para substitution was tolerated and gave high facial selectivity in all cases. Aliphatic
substitution was also possible with increased bulk of the substituent producing slight advantages in terms of optical purity (entries 7 to 10). The diastereoselectivities were modest in all cases with a slight preference for the exo cycloadduct.

Table 3.21 Variation of the dienophile component in the hydrazide-catalyzed Diels-Alder cycloaddition with cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>exo:endo</th>
<th>exo ee</th>
<th>endo ee</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>24</td>
<td>96</td>
<td>1.9:1</td>
<td>90</td>
<td>88</td>
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<tr>
<td>2</td>
<td></td>
<td>24</td>
<td>93</td>
<td>2.2:1</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>36</td>
<td>88</td>
<td>2.1:1</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>24</td>
<td>90</td>
<td>1.2:1</td>
<td>87</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>48</td>
<td>84</td>
<td>1.7:1</td>
<td></td>
<td>90</td>
</tr>
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*Note: TTfH is trifluoromethanesulfonic acid.*
Hydrazide-Catalyzed Diels-Alder Cycloadditions

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<tr>
<td>6</td>
<td>48</td>
<td>92</td>
<td>2:1</td>
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<tr>
<td>7</td>
<td>Me</td>
<td>16</td>
<td>74</td>
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<td>68</td>
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<td>8</td>
<td>n-Pr</td>
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<td>84</td>
<td>2.6:1</td>
<td>85</td>
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<tr>
<td>9</td>
<td>i-Pr</td>
<td>16</td>
<td>84</td>
<td>2.6:1</td>
<td>85</td>
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<td>87</td>
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<td>50</td>
<td>51</td>
<td>52</td>
</tr>
</tbody>
</table>

* Reactions run with 0.2 equiv. catalyst and 0.2 equiv. TIOH in 1M solution of water at 23°C. *Product ratios were determined by $^1$H NMR. *Enantioselectivity determined by $^1$H NMR after conversion to acetal with (R,R)-(++)-hydrobenzoin or chiral GLC using cycloSil-B column. *exo ee could not be determined.

The hydrazide-catalyzed Diels-Alder cycloaddition was also general with respect to the diene. When reacted with $p$-nitrocinnamaldehyde, substituted dienes such as 2-phenylbutadiene gave high enantioselectivities as did the use of doubly substituted dienes such as 2-methyl-1,3-pentadiene (Table 3.22, entries 1 and 3). When less reactive dienes were submitted to smaller and more reactive dienophiles, the cycloadducts were obtained in good yield but with modest selectivities (entries 2 and 4). Generally, larger dienophiles afford higher enantioselectivities, perhaps due to the extra steric bulk which creates a better facial bias.
Table 3.22 Variation of the diene component in the hydrazide-catalyzed Diels-Alder cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Diene</th>
<th>Product</th>
<th>Yield (%)</th>
<th>exo:endo</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O₂N</td>
<td>Ph</td>
<td>Ph</td>
<td>86</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td></td>
<td>Ph</td>
<td>67</td>
<td>-</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>O₂N</td>
<td></td>
<td>Ph</td>
<td>71</td>
<td>1.9:1</td>
<td>69d</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td></td>
<td>Ph</td>
<td>81</td>
<td>1:23</td>
<td>16d</td>
</tr>
</tbody>
</table>

*Reactions run with 0.2 equiv. catalyst and 0.2 equiv. TfOH in 1M solution of water at 23°C. *Product ratios were determined by ¹H NMR. ¹Enantioselectivity determined by ¹H NMR after conversion to acetal with (R,R)-(+)hydrobenzoin or chiral GLC using cycloSil-B column. ²endo isomer

3.5.1 Limitations

Not all substrates were compatible with the hydrazide-catalyzed Diels-Alder protocol. α,β-unsaturated aldehydes bearing a substituent in the α position such as methacrolien 3.92 reacted with cyclopentadiene to afford the cycloadducts in very poor enantioselectivities. We hypothesized that these dienophiles are poor substrates due to a possible A¹³-interaction which
could limit the selective formation of the reactive iminium ion. Likewise, the less reactive \( \alpha,\beta \)-unsaturated ketones such as 3.93 were inefficient in the organocatalytic Diels-Alder reaction as only traces of product were observed after increased reaction times.

**Figure 3.13 Incompatible substrates in the hydrazide-catalyzed Diels-Alder cycloaddition**

Dienophiles possessing an electron-donating moiety such as a methoxy or a \( N,N \)-dimethyl group were completely unreactive compared to their electron deficient counterparts. Heteroaromatic \( \alpha,\beta \)-unsaturated aldehydes such as furyl or thiophenyl derivatives 3.96 were found to be poorly reactive over extended reaction periods. Similarly, certain dienes did not participate in the hydrazide-catalyzed Diels-Alder reaction. Danishefsky’s diene 3.98 was sensitive to the acid medium of the reaction and underwent decomposition during the reaction. The diphenyl isobenzofuran 3.97 did provide the Diels-Alder adduct when treated with crotonaldehyde but in minimal enantiomeric purity.

### 3.5.2 Stereochemical Rationale

At this point it was essential to understand the sense of selectivity achieved with our newly developed hydrazide catalyst. The role of the benzylic side-chain and that of the camphor bridgehead must be assessed in order to propose an accurate mechanism for this transformation.
Upon reaction of a carbonyl with the hydrazide salt, four possible iminium geometries can arise. The iminium can orient itself on either side of the camphor backbone to yield either the \textit{E}-iminium or the \textit{Z}-iminium. Additionally, the olefin of the \textit{\alpha,\beta}-unsaturated moiety can adopt an \textit{s-cis} or \textit{s-trans} conformation.

Figure 3.14 Possible iminium geometries arising from \textit{E}-cinnamaldehyde and hydrazide 3.86

We examined the structures of the iminiums formed in our reactions using semiempirical calculations (PM3 in Spartan Pro). These calculations indicated that the \textit{Z-s-trans} iminium 3.99 was the lowest energy conformer (Figure 3.14). This preferred geometry is in accordance with the iminiums generated from imidazolidinone catalyst architectures.\textsuperscript{24}
Figure 3.15 Stereochemical model for the attack of cyclopentadiene onto hydrazide iminium 3.99

This model reveals that there are two vital stereocontrol elements involved in the reaction of the hydrazide catalyst and E-cinnamaldehyde. The benzylic side-chain serves as a directing group to selectivity form the Z-iminium in order to minimize non-bonding interactions between the aromatic group and the olefin. The role of the benzyl groups in the hydrazide catalysts differs from that observed in imidazolidinone catalysts in which this group serves as a shield to discriminate both faces of the dienophiles. The benzyl side chain is used to mimic the gem dimethyl or tert-butyl functionality in the MacMillan imidazolidinones. The facial selectivity in iminium intermediate 3.99 arises from the camphor geminal bridgehead which favors approach of the diene from the bottom face. This iminium model explains the sense of selectivity observed and leads to the major stereoisomers in all cases.

Although we proposed a model which implies that hydrazide 3.86 enhances reaction rates via iminium catalysis, other means of activation of the α,β-unsaturated aldehyde, such as hydrogen bond complexation, could not be ruled out. As a result, the formation of the iminium ion was confirmed via spectral analysis. Attempts to isolate the iminium ion were unsuccessful but electrospray mass spectrometry obtained from the mixture of iminium, catalyst and cinnamaldehyde in CH₃NO₂ confirmed the presence of the iminium ion. A major peak was
observed with a mass of 385.5 corresponding to the iminium ion and a minor peak at 920.0 corresponding to two iminium ions and a triflate were observed.

Additional evidence for the iminium ion was obtained by $^1$H NMR analysis to support the calculated iminium ion model. In order to ascertain that the iminium ion was formed, an equimolar solution of $E$-cinnamaldehyde and catalyst were mixed in an NMR tube in CD$_3$NO$_2$ at room temperature. The reaction was monitored by $^1$H NMR and indeed, a new peak at 8.22 ppm corresponding to the iminium ion appeared over time. The structure of the hydrazide iminium ion 3.99 was fully assigned based on COSY experiments and is described in detail in the experimental section. Furthermore, a NOESY experiment confirmed the $Z$ configuration about the C-N bond, obtained from the calculated model in Figure 3.15. Specifically, interactions were observed between the iminium proton $H^3$ (8.22 ppm) and the doublet of the benzylic protons $H^4$ (5.27 and 5.31). Furthermore, the olefinic $H^1$ (7.12 ppm) showed interactions with the indicated protons on the camphor backbone (2.66 ppm and 2.73-2.84 ppm). The $s$-trans arrangement was confirmed by the contacts between $H^2$ (7.81 ppm) and $H^3$ (8.22 ppm). The results of these experiments are consistent with our hypothesis for iminium ion LUMO lowering substrate activation.

$^{124}$ Although the reactions were performed in distilled water, the use of deuterium oxide afforded inconsistent spectra that could not be used for mechanistic analysis because of the heterogeneous mixture formed. CD$_3$NO$_2$ was chosen for the NMR experiments as it replicated the aqueous conditions most accurately in terms of yield and selectivity.
Figure 3.16 NOESY spectrum of hydrazide iminium 3.99
We believe that the modest diastereoselectivity in the organocatalytic Diels-Alder cycloadditions was partly accounted for by the lack of steric effects in the small dienes used. The formation of the hydrazide iminium ion is reversible and the cycloadditions were not controlled by secondary orbital interactions such as those exhibited in Lewis acid-catalyzed Diels-Alder cycloadditions. This implies that a diene such as cyclopentadiene can approach the reactive olefin from either side (Figure 3.17). The small preference for the exo adduct can be attributed to the minimized steric repulsions in the product.

Figure 3.17 exo and endo approach of cyclopentadiene to iminium 3.99 explaining the diastereoselective outcome

3.5.3 Preliminary Mechanistic Investigations

With a working model that explained the stereochemical outcome of the Diels-Alder catalyzed cycloadditions, we wished to verify the efficacy of the hydrazides towards forming iminium ions. We initially hypothesized that the \(\alpha\)-heteroatom effect would enhance the rate of the iminium formation relative to secondary amine catalysts such as imidazolidinones. To verify this, equimolar amounts of \(E\)-cinnamaldehyde and the corresponding catalyst salts were dissolved in a deuterated solvent\(^{125}\) at room temperature in an NMR tube. Using \(^1\)H NMR we monitored the rate of iminium formation over time using 2, 5 and 10 minute intervals until near-equilibrium conditions were reached. The results are depicted in the Figure 3.18 below.

\(^{125}\) The reactions were performed in solvents in which the catalysts provided the most efficient iminium formation. The reaction with hydrazide 3.86 was performed in \(\text{CD}_3\text{NO}_2\) whereas the reaction with imidazolidinone 3.18 was examined in \(\text{CD}_3\text{OD}\).
Indeed the process catalyzed by hydrazide catalyst 3.86 was extremely rapid, in agreement with our hypothesis. The catalyst and \(\alpha,\beta\)-unsaturated aldehyde formed the iminium ion 3.99 in high conversion during the initial minutes of the reaction and produced high levels (94\% conversion) of iminium over 180 minutes. This is in contrast to the case of imidazolidinone catalyst 3.18, which forms an iminium species considerably more slowly and is not fully implicated as the reactive form, even after several hours. These observations suggest that the rate-limiting step of the present reaction is not the iminium formation but could be another transformation in the overall process.
3.6 Conclusions

We were pleased to find that the implementation of the hydrazide functionality did in fact, promote faster iminium formation via the α-heteroatom effect. This work represents the first successful asymmetric organocatalytic Diels-Alder promoted by a class of catalysts other than secondary amine salts. The hydrazide iminium ions behaved as Lewis acid mimics that promoted cycloadditions via LUMO-lowering activation. The catalysts functioned in water, providing an environmentally benign reaction that provides the cycloadducts in excellent yields and selectivities with a slight preference for the exo isomer. Although our initial hypothesis was confirmed, the limited mechanistic studies performed to date in organocatalysis and the unique catalyst architecture of the catalysts developed in our laboratories warranted further investigation of the reaction mechanism. Consequently, kinetic studies of the hydrazide Diels-Alder cycloaddition and further model studies were undertaken to shed light on catalysis promoted by hydrazides.
Mechanistic Investigations of Hydrazide Catalysis

4.1 Revisiting the Catalytic Cycle

Following the design and development of new hydrazide-based organic catalysts capable of catalyzing [4+2] cycloadditions, we realized that very few reports addressed the mechanistic aspects of organocatalytic transformations, particularly with respect to iminium catalysis. Mechanistic investigations primarily focused on computational and theoretical methods rather than synthetic experimentation. Thus, we set out to establish experiments that could elucidate in detail the mechanism of the hydrazide-catalyzed process. The resulting analysis could shed light on the differences between traditional secondary amine catalysis and activation prompted by α-heteroatom catalysts.

The proposed catalytic cycle for the process is depicted in Figure 4.1. The cycle is initiated by the condensation of catalyst 4.1 with aldehyde 4.2 to produce the reactive iminium intermediate 4.3. The electron withdrawing ability of this charged iminium lowers the LUMO energy of 4.3.
thus accelerating the addition to diene 4.4. This process produces two cycloadduct iminiums 4.6 and 4.5 corresponding to the *exo* and *endo* products respectively.\(^{127}\) After the cycloaddition has taken place, hydrolysis by water (present in the solvent or supplied by the formation of 4.3) releases products 4.7 and 4.8 and regenerates the catalyst for the next cycle. To better understand the overall process, each step of the catalytic cycle was studied separately using NMR methods.

**Figure 4.1 Iminium Catalysis of Diels-Alder Cycloadditions by hydrazides**

\(^{127}\) Only the major enantiomers are shown for clarity
In our Diels-Alder studies, water was chosen as the optimum solvent for the reaction and gave a yield of 89% and an endo enantiomeric excess of 88% for the condensation of E-cinnamaldehyde and cyclopentadiene. This presented technical difficulties for NMR work as the reaction was heterogeneous and the corresponding spectra of poor quality. Since CH$_3$NO$_2$ produced comparable yields (92%) and enantioselectivity (75% endo ee) to the fully aqueous process, our mechanistic investigations were carried out in that solvent.

As shown in Figure 4.2, the formation of 4.3 was rapid and essentially complete after 2 hours at room temperature. The progress of the iminium formation could be monitored by $^1$H NMR with the disappearance of the aldehyde peak of E-cinnamaldehyde (9.70 ppm) and the appearance of the iminium peak (8.22 ppm) over time. As mentioned earlier, this experiment confirms that the iminium formation with hydrazide catalyst 4.1 is faster and more complete than when using a secondary amine catalyst 3.18 (see Figure 3.18 of Chapter 3).
Given that our catalyst performed well in water, and that many organocatalyzed reactions function best in wet solvents, we investigated the effect of water on iminium generation. As shown in Figure 4.3, the addition of D$_2$O to the sample dramatically increased the rate of iminium formation. Impressively, in the presence of 5% D$_2$O, equilibrium was reached in less than 6 minutes. Presumably this effect was due to an increase in H$^+$ supply allowing for faster proton transfers. The addition of 10% D$_2$O was also investigated. These experiments gave essentially the same results, however spectral resolution was better with 5% D$_2$O. Performing the reaction at 0.01 M gave low conversion to 4.3 (65%) but the equilibration to the iminium was still rapid. Increasing the concentration to 1.0 M also resulted in rapid and complete conversion to 4.3. These results suggested that iminium formation was not rate limiting for the aqueous process.
After observing the formation of 4.3, our attention was directed toward the second step of the catalytic cycle: The formation of intermediate cycloadducts 4.5 and 4.6 from iminium 4.3 in the presence of cyclopentadiene. Due to the implication of several intermediates, peaks corresponding to all intermediates in the catalytic cycle were thoroughly identified by $^1$H NMR control experiments prior to doing kinetic studies. Control spectra for 4.1, 4.2, 4.3, 4.4 and 4.5-4.8 were independently collected in 1.0 M CD$_3$NO$_2$:D$_2$O (19:1).

We found that cycloadditions performed in 1.0 M CD$_3$NO$_2$:D$_2$O (19:1) were very well-behaved and resulted in smooth conversion to cycloadducts that could be monitored by $^1$H NMR. Water played a key role in this transformation, limiting polymerization and degradation of the sample. It is believed that water helped to dissociate the strongly acidic triflic acid and thus limited the formation of a dark brown precipitate following the addition of cyclopentadiene. Reactions involving stoichiometric amounts of catalyst 4.1, triflic acid and aldehyde 4.2 at 1.0 M resulted in an overly concentrated solution. Many side products, perhaps resulting from polymerization of
the reactants at high concentration, were identified by \(^1\)H NMR. Attempts to perform the equimolar reaction at lower concentrations (0.1 or 0.5 M in 19:1 CD\(_3\)NO\(_2\):D\(_2\)O) were very sluggish. This may be a consequence of the lack of mechanical stirring in reactions performed in NMR tubes. Optimal conditions were attained using 20 mol% catalyst in a 1.0 M solution of CD\(_3\)NO\(_2\):D\(_2\)O, which agreeably mirror the aqueous protocol used for the generation of cycloadducts.

Consequently, the kinetic experiments were conducted by the addition of 0.2 equivalents of catalyst 4.1 and triflic acid in a suspension of E-cinnamaldehyde in 5% D\(_2\)O/CD\(_3\)NO\(_2\). After stirring for 1-2 min, 3 equivalents of cyclopentadiene were added, and the resulting mixture was transferred to an NMR tube and monitored at 23 °C by \(^1\)H NMR using an automated experiment that acquired spectra at 40 min intervals for 48 h.\(^{128}\) The amounts of the various species were determined as the reaction proceeded. Distinct resonances were apparent for all species present.\(^{129}\) At the conclusion of the reaction, to ensure the reproducibility of this experiment, the products were isolated in 88% yield and 83% ee (exo) and 81% ee (endo).

\(^{128}\) It is very important to stir the reaction efficiently to prevent polymerization upon addition of cyclopentadiene. 
\(^{129}\) Spectral overlap precluded the direct measurement of the concentration of 4.5 in the mixture. The amounts of this compound were obtained by subtraction and used to normalize the values in Figure 4.4.
The formation of 4.3 was essentially complete as limited by the amount of original catalyst 4.1 (0.2 equivalents). This species displayed steady state behavior throughout the reaction until the amount of residual aldehyde 4.2 fell below 20% (crossover point, arrow on graph in Figure 4.4), as there was no longer sufficient 4.2 available to maintain a full concentration of 4.3. The concentration of 4.3 then fell smoothly as the amount of aldehyde 4.2 declined. This result could only be possible if the equilibrium between 4.1 and 4.3 was extremely rapid relative to the overall process. Concurrently, the concentration of product iminiums 4.5 and 4.6 began to increase as the supply of 4.2 fell below that of 4.1. This implied that the hydrolysis of iminiums 4.5 and 4.6, to products 4.6 and 4.8, was extremely rapid. Had this not been the case, the concentrations of these intermediates (4.5 and 4.6) would have been higher throughout the
reaction. The fact that the amounts of these iminiums were negligible initially and became significant only after the supply of 4.2 was exhausted is consistent with this hypothesis. This observation also implied that the catalyst preferentially binds with aldehyde 4.2 rather than cycloadducts 4.5 and 4.6, to form a consistent quantity of 4.3. This experiment clearly showed that the cycloaddition was kinetically significant as both the processes involving iminium formation were extremely rapid relative to the cycloaddition event.\(^\text{130}\)

**4.1.3 Hydrolysis**

In the Figure 4.4 above, we established that low concentration of 4.5 and 4.6 were a result of rapid hydrolysis to cycloadducts 4.7 and 4.8. If this had not been the case, the concentration of 4.5 and 4.6 would have been more significant throughout the reaction. The hydrolysis phase of the reaction was further studied by a series of experiments which examined the formation of 4.5 and 4.6, from 4.7 and 4.8, respectively. This was done to alleviate technical difficulties, such as the presence of numerous intermediates, associated with observing the forward process. Investigating the hydrolysis from products 4.7 and 4.8 to 4.5 and 4.6 invokes the principle of microscopic reversibility. Microscopic reversibility is a concept applied to reversible reactions in which the mechanism in one direction is exactly the reverse of the mechanism in the other direction. As result, the transition states and intermediates of the forward reaction are mirrored in opposite order in the reverse reaction.

Mixing products 4.7 and 4.8 with 0.2 equivalents of catalyst 4.1 immediately produced \(~-20\) mol\% of iminiums 4.5 and 4.6 before our first time point could be taken (Figure 4.5), and this concentration remained constant through duration of the experiment.\(^\text{131}\) These results corroborated our earlier hypothesis regarding the hydrolysis of iminiums 4.5 and 4.6 to products that suggested the rate of the final hydrolysis phase was extremely rapid relative to the overall process.

\(^{130}\) We attempted to extrapolate the rate constants for this reaction but due to several varying parameters, the resulting equation was too complex to be adequately derivatized. This is in part due to the fact that water behaves not only as a solvent but also as a reagent.

\(^{131}\) After 16 hours the amounts of all species were unchanged.
Careful examination of the spectra obtained in the hydrolysis experiment (Figure 4.5) showed trace quantities of an unexpected species that was produced initially and remained at a concentration ~2% throughout the experiment. An expansion of a typical spectrum from this experiment is shown in Figure 4.6a. All of the resonances could be accounted for by comparisons with sample spectra of the various species present (4.5 - 4.8) with the exception of a
small resonance at 8.25 ppm. The chemical shift of this signal was consistent with a resonance of iminium 4.3. Comparison with spectra of 4.3, prepared separately in the same solvent, showed excellent overlap (Figure 4.6b). In order to isolate the spin system of 4.3 from the reaction spectrum, a 1D-TOCSY experiment was performed (Figure 4.6c). A TOCSY experiment or Total Correlation Spectroscopy uses homonuclear Hartman-Hahn to transfer magnetization between protons. In a 1D-TOCSY, a specific peak is irradiated and the signal is transferred to all J-coupled protons in a stepwise process. The extent of correlation depends mainly on the length of the mixing period. Typically, as the mixing period gets longer, correlation with more distant protons can be observed. An experiment was performed in which 20 mol% of catalyst 4.1 and triflic acid were dissolved in 19:1 CD$_3$NO$_2$·D$_2$O. To this solution was then added racemic 4.7 and 4.8 and the reaction was monitored at 23°C by $^1$H NMR recording spectra at 5 min intervals for 80 min. At this time, a TOCSY experiment was performed by irradiation of the doublet at 8.25 ppm at 60, 120, 150, and 200 ms mixing times. Resonances at 7.79 and 7.11 ppm were most significant at 60 ms and were consistent with the resonances of spin system 4.3 (figure 4.6b).
Compound 4.3 could arise only through a catalyzed retro-Diels-Alder process. To test this, a racemic sample of 4.7 and 4.8 (1.7:1 exo:endo), obtained from linear achiral catalyst 3.32, was subjected to the standard reaction conditions (0.2 % 4.1 in 19:1 CH$_3$NO$_2$:H$_2$O) to verify the presence of the reverse process. To simulate the normal forward process, two equivalents of cyclopentadiene were added as the reaction typically requires an excess of 3 equivalents of cyclopentadiene. After 48 hours at room temperature, a small increase in enantiomeric excess was observed for both 4.7 and 4.8 confirming that retro-Diels-Alder reactions had in fact taken place (Table 4.1, entry 1). In water the effect was less dramatic as enantiomeric excesses of 8 and 3 % (endo/exo) were observed using 20 mol % catalyst. Attempts to improve the selectivity by performing the reaction at +4 °C were unsuccessful (entry 5). However, by using equimolar amounts of catalyst and acid relative to the cycloadducts we found that the extent of
deracemization increased slightly to 32 and 16% exo/endo ee (entry 2). When a stoichiometric amount of catalyst was used, changes in the ratio of diastereomers were also more pronounced (from 1.7:1 to 1:1 endo:exo, Table 4.1, entries 1 vs. 2). These observations prompted us to investigate the effects of varying the ratios of acid and hydrazide on the extent of chiral amplification. Using a slight excess of catalyst relative to acid resulted in a smaller enantioselectivity change (entry 3) whereas the presence of excess acid produced a modest enantioselectivity increase (entry 4). This result suggested that the incidence of retro Diels-Alder was dependant on the Brønsted acid. To verify this, when 20 mol% of TfOH was added to a mixture of 4.7 and 4.8 in 19:1 CD$_3$NO$_2$:D$_2$O, the $^1$H NMR spectra of this mixture clearly showed the presence of small amounts of cinnamaldehyde arising from a retro Diels-Alder process. Conversely, triflic acid alone was a poor catalyst of the forward reaction giving only 7% yield of 4.7 and 4.8 after a 48 h reaction with 4.2 and 4.4.

Table 4.1 Deracemization of cycloadducts 4.7 and 4.8 in 19:1 CH$_3$NO$_2$:H$_2$O$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. 4.1</th>
<th>Equiv. TfOH</th>
<th>exo ee$^c$ (%)</th>
<th>endo ee$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.2</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.18</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>1.0</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>5$^b$</td>
<td>0.2</td>
<td>1.0</td>
<td>18</td>
<td>26</td>
</tr>
</tbody>
</table>

$^a$Reactions performed at 1.0 M and 23 °C for 24-48 hrs. $^b$Reaction performed at +4 °C. $^c$Enantiomeric excess determined by chiral GLC.
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Taken together, these results imply that triflic acid can catalyze a small amount of retro Diels-Alder directly from 4.7 and 4.8, but the cinnamaldehyde produced would then afford iminium 4.3 that reacts in a kinetically controlled process to give non-racemic adducts (Scheme 4.1).  

Scheme 4.1 Retro-Diels-Alder in hydrazide catalysis

\[
\begin{align*}
4.1 & \quad \text{TfOH} \\
4.7 & \quad \text{Ph} \\
4.8 & \quad \text{CHO} \\
4.6 & \quad \text{TfO}^- \\
4.5 & \quad \text{Ph} \\
4.3 & \quad \text{R} \\
\end{align*}
\]

Similar contributions could be occurring in other organocatalyzed cycloadditions. However, only small amounts of retro-cycloaddition were observed when racemic 4.7 and 4.8 were mixed with MacMillan’s imidazolidinone catalyst in 9:1 MeOH:H\textsubscript{2}O for 24 hours. This process was apparently unique to hydrazide catalysis and could be attributed to the enhanced iminium formation provided by the \(\alpha\)-heteroatom effect.

The results discussed above clearly illustrate the presence of a thermodynamic component to the hydrazide Diels-Alder cycloaddition. The key cycloaddition step was in fact a reversible process. Although the extent of the reverse reaction was slight, and did not significantly impact the enantioselectivity of the overall reaction, this retrocyclization component could potentially be used to amplify the enantiomeric ratio of racemic Diels-Alder products by carefully limiting the amount of acid co-catalyst present. As such it has significant implications for the design of

\[132\] This is supported by the observation that the enantioselectivities for the entire process were not dependant on the relative amounts of catalyst and acid See table 3.19 of chapter 3.
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subsequent catalysts and can potentially be exploited to design deracimization reactions. There are currently very few methods available to perform this type of chiral amplification and such a process would have practical significance. Other members of the Ogilvie laboratory could potentially investigate this possibility with catalysts related to 4.1.

4.2 **Design of a Conformationally Rigid Hydrazide Organic Catalyst**

Proteins and peptides adopt conformations which allow them to mediate biological processes with a high degree of selectivity. Lacking the long range interactions found in macromolecules, smaller molecules rely more heavily on local conformations to achieve selectively in synthetic transformations. This has been successfully demonstrated through the synthesis of non-natural peptides, in which a change in conformational behavior can alter the catalytic activity.\(^\text{133}\) Small-molecule catalysts have the potential to bridge the link between synthetic and natural catalysts through the incorporation of elements such as conformational restraints.\(^\text{134}\) A better understanding of such interactions within a catalytic entity could facilitate the design of small organic catalysts. In a continuation to our mechanistic analysis, we wished to investigate structural modifications that could produce a conformationally rigid hydrazide-based catalyst. The desire to incorporate such modifications to our hydrazide catalyst was by prompted the ability of the benzylic side-chain to freely rotate about the C-N bond.

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Condensation of catalyst 4.1 with aldehyde 4.2 results in the formation of iminium ions that can adopt one of two key geometries (4.9 and 4.10), as established by $^1$H NMR. The structures of these reactive iminiums can account for the enantioselectivity observed in the asymmetric Diels-Alder reaction. As shown in Figure 4.7, Z-iminium 4.9 leads to the major enantiomers 4.7 and 4.8 through bottom-face approach of the diene. Stereochemical bias is provided in this structure by the steric bulk of the camphor bridgehead methyl groups that impair top-face approach of the diene. E-iminium 4.10 leads to the minor enantiomers 4.11 and 4.12 through a process that also invokes bottom-face approach of the diene. This analysis suggests that enantioselectivity is a consequence of the position of the benzyl side-chain of the catalyst that dictates the energy of transition states arising from E-iminium 4.10. One could therefore postulate that structural changes that favor Z-iminiums such as 4.9 would lead to a corresponding increase in the amounts of 4.7 and 4.8 resulting in higher enantioselectivities. This could be most easily accomplished through destabilization of E-iminium 4.10 and, consequently, the transition states involved in
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forming 4.11 and 4.12. The structure of 4.10 suggested that simply increasing the size of the benzyl group would destabilize this iminium relative to 4.9.

Table 4.2 Effect of substituents on the side chain of hydrazide catalysts in asymmetric Diels-Alder reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>exo:endo</th>
<th>ee (exo/endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Ph</td>
<td>96</td>
<td>1.9:1</td>
<td>90/88</td>
</tr>
<tr>
<td>2</td>
<td>CH₂(3,5-dimethylphenyl)</td>
<td>91</td>
<td>1.8:1</td>
<td>89/87</td>
</tr>
<tr>
<td>3</td>
<td>CH₂-1-naphthyl</td>
<td>82e</td>
<td>1.7:1</td>
<td>77/74</td>
</tr>
<tr>
<td>4</td>
<td>CHPh₂f</td>
<td>32</td>
<td>1.6:1</td>
<td>75/58</td>
</tr>
<tr>
<td>5</td>
<td>C(CH₃)₃</td>
<td>10</td>
<td>1.1:1</td>
<td>6/7</td>
</tr>
</tbody>
</table>

*Reactions performed at 1M in water using 20 mol % of catalyst and TfOH. bProduct ratios determined by ¹H NMR. cCombined isolated yield. eEnantiomeric excess determined by chiral GLC. fHClO₄ was used in place of TfOH. gCatalyst provided by Livia Aumand

Armed with this hypothesis, we tested several catalysts with large side chains (Table 4.2). These were synthesized in an analogous fashion to hydrazide 4.1 using the protocol established in Scheme 3.19 of Chapter 3. The introduction of methyl groups onto the phenyl ring of the benzyl group or the use of a large planar naphthyl unit at this position did not increase selectivity relative to the benchmark benzyl side-chain when catalyzing the cycloaddition of cinnamaldehyde and cyclopentadiene (Table 4.2, entries 1-3). Bulkier substituents such as a diphenylmethyl or tert-butyl group led to reduced selectivity and reactivity presumably due to increased sterics during iminium formation (entries 4 and 5).

Since simple steric modifications to the benzyl side chain did not improve the facial selectivity of the process, a more detailed understanding of the catalyst behavior was sought. NOESY
analysis of the major iminium 4.9 showed a strong correlation between the iminium proton and the neighboring benzylic hydrogens, thus confirming the Z-iminium geometry (Figure 4.8).

**Figure 4.8** NOESY interactions and possible iminium conformation that could lead to unwanted cycloadducts 4.11 and 4.12

The interaction between the iminium and aromatic protons was considerably weaker relative to that of the iminium and benzylic protons suggesting that the methylene unit of the benzyl side-chain was closer to the iminium moiety than was the phenyl ring. Given that the benzyl group could freely rotate about the C-N bond, it was apparent that alternate, undesired catalyst conformations were being accessed. The benzyl group of the catalyst could be directed away from the iminium moiety in these conformers allowing space for the undesired $E$-iminium 4.10 to form, resulting in lower enantioselectivities.

To investigate this effect, a dihedral driver study on iminium 4.9 was conducted using PM3 semi-empirical methods. The dihedral angle between the hydrazide nitrogen and benzyl side-chain (C-C-N-CO) was altered systematically in 30° increments and at each fixed dihedral angle, the energy of the conformer was minimized and the energy plotted as a function of the dihedral angle. To account for possible hysteresis in the dihedral driver experiment, the rotations about

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the C-N bond were performed from 0° to 360° and then back to 0°. The values were averaged and converted to relative kCal/mol.

Figure 4.9 Plot of the energy surface of iminium 4.9 generated from catalyst 4.1 as a function of the C-C-N-CO dihedral angle.

This analysis revealed the presence of two energy minima at dihedral angles of approximately 150° and 270° as depicted in Figure 4.9. The energy barrier between these conformers was in the order of ~2 kcal/mol, in principle permitting rotation about the C-N bond. The 150° conformer (4.9-150°) positioned the phenyl ring in close proximity to the iminium moiety thus inhibiting the formation of undesired E-iminium 4.10. This conformer would be expected to show selectivity for the major enantiomers 4.7 and 4.8 during the Diels-Alder process. In contrast, the 270° (4.9-270°) conformer could create a void in proximity to the iminium moiety. This structural gap could in principle accommodate E-iminium structures similar to 4.10 resulting in stereochemical erosion. This study suggested that conformational restraints on the catalyst side-
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chain to disallow conformers similar to $4.9-270^\circ$ would produce an increase in enantioselectivity by raising the energy required to access transition states and iminiums related to $4.10$.

This could be accomplished through the introduction of a conformational control element that would ensure exclusive access to desired conformers. To accomplish this restriction, the delocalized nature of the hydrazide linkage could be exploited to provide 1,3-allylic strain by the incorporation of a stereogenic centre, such as a methyl group on the benzylic side-chain, to act as a conformational lock. With the introduction of this new chiral centre, two possible diastereomeric catalysts $4.14$ and $4.15$ could be envisaged (figure 4.10a). The three different conformations arising from the $A_{1,3}$ strain in catalyst $4.14$ are depicted in Figure 4.10b. We anticipated that conformer $4.16$ should minimize the allylic-type strain via a syn-periplanar arrangement of the benzylic hydrogen with the C-O bond. Conversely, conformer $4.18$ may be disfavored due to the increased steric between the delocalized carbonyl and the phenyl ring.

Figure 4.10 (a) Proposed diastereomeric catalysts $4.14$ and $4.15$ for conformational control. (b) Conformations arising from $A_{1,3}$ strain in catalyst $4.14$. 
Dihedral driver investigations were done on the iminiums that would be formed from both diastereomers 4.14 and 4.15 to clarify the conformational profile of each. We were pleased to find that the iminium derived from 4.14 experienced one large energy minimum near the dihedral angle of 150° suggesting that a significant part of the population would exist as 4.19-150° (Figure 4.11). At 150° the benzylic hydrogen was approximately syn-periplanar to the hydrazide carbonyl as anticipated by allylic-type strain, and the phenyl moiety was properly positioned to interfere with the formation of undesired E-iminiums such as 4.10. Thus, 4.14 would be expected to be a more selective catalyst than 4.1. Allylic-type strain is also possible between the benzyl side-chain and the iminium moiety but was apparently less significant in these structures.

An analysis of the iminium derived from 4.15 produced significantly different results as three conformers were sampled at 60°, 210° and 270° suggesting that minimal conformational selection would occur. The lowest energy conformer was found to occur at 270°, providing considerable space to accommodate an E-iminium moiety and suggesting that 4.15 would yield lower enantioselectivities in the Diels-Alder cycloaddition relative to catalyst 4.1.
Figure 4.11 Plots of the energy surfaces of iminiums generated from catalysts 4.14 and 4.15 respectively, as a function of the C-C-N-CO dihedral angle

Encouraged by the anticipated selectivity enhancement procured by the conformational control element, compounds 4.14 and 4.15 were synthesized to verify the outcome predicted by computational methods. Their synthesis was inspired from the protocol established for the assembly of all other hydrazide catalysts (Scheme 3.19 of Chapter 3). The synthesis was carried out as a mixture of diastereoisomers until the final reduction step when diastereoisomers 4.14 and 4.15 were separated by silica gel chromatography. The effects of conformationally rigid catalysts 4.14 and 4.15 were measured in the asymmetric Diels-Alder cycloaddition between E-cinnamaldehyde and cyclopentadiene (Table 4.3).
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Table 4.3 Effect of conformationally rigid substituents in the hydrazide catalyzed asymmetric Diels-Alder

![Diels-Alder Reaction Diagram](image)

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Catalyst</th>
<th>R</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>exo:endo&lt;sup&gt;c&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;d&lt;/sup&gt; exo/endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.1</td>
<td>Ph</td>
<td>96</td>
<td>1.9:1</td>
<td>90/88</td>
</tr>
<tr>
<td>2</td>
<td>4.14</td>
<td>Ph</td>
<td>94</td>
<td>2.8:1</td>
<td>95/93</td>
</tr>
<tr>
<td>3</td>
<td>4.15</td>
<td>Ph</td>
<td>55</td>
<td>1.9:1</td>
<td>74/60</td>
</tr>
<tr>
<td>4</td>
<td>4.1</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>93</td>
<td>2.2:1</td>
<td>92/87</td>
</tr>
<tr>
<td>5</td>
<td>4.14</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>90</td>
<td>4:1</td>
<td>96/93</td>
</tr>
<tr>
<td>6</td>
<td>4.1</td>
<td>2-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>90</td>
<td>1.2:1</td>
<td>87/86</td>
</tr>
<tr>
<td>7</td>
<td>4.14</td>
<td>2-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>89</td>
<td>3.3:1</td>
<td>94/92</td>
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<tr>
<td>8</td>
<td>4.1</td>
<td>Me</td>
<td>74</td>
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<td>68/72</td>
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<td>4.14</td>
<td>Me</td>
<td>78</td>
<td>1.8:1</td>
<td>82/80</td>
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</tbody>
</table>

<sup>a</sup>Reactions performed at 1M in water using 20 mol % of catalyst and TFOH. <sup>b</sup>Isolated yield. <sup>c</sup>Product ratios determined by <sup>1</sup>H NMR. <sup>d</sup>Enantiomeric excess determined by chiral GLC.

The use of catalyst 4.14 maintained excellent yields while providing superior diastereoselectivities and enantioselectivities relative to catalyst 4.1 (Table 4.3, entries 1 and 2). As anticipated the mismatched catalyst 4.15 proved to be inferior to the original catalyst in this cycloaddition process (entry 3). The improvements in both exo/endo ratio and enantioselectivity gained from using conformationally rigid catalyst 4.14 were consistent for other substrates. Using 4-nitrocinnamaldehyde as the dienophile resulted in enantioselectivity increases when using catalyst 4.14, giving an enantiomeric excess of 96% for the exo isomer (entries 4 and 5). The corresponding 2-substituted dienophile enjoyed similar improvements producing an ee of 94% for the exo isomer (entries 6 and 7). Catalyst 4.14 produced a more dramatic improvement when used together with crotonaldehyde as the ee increased by as much as 14% over the results obtained with 4.1 (entries 8 and 9).
The enhanced selectivity observed in the transformations above can be attributed to the conformational "lock" that limits rotation about the double bond. The allylic control provided by the delocalization of the C-N bond bond arranges the catalyst side-chain so that the hydrogen and oxygen of the hydrazide are syn-periplanar. In the preferred conformer of iminium 4.19, the phenyl group is appropriately located to efficiently prevent the formation of unwanted $E$-iminium 4.10. This additional control element also ensues that the methyl group is oriented upwards which reinforces the top face shielding provided by the geminal groups of the camphor bridgehead. Consequently, attack of the diene occurs from the bottom of the reactive olefin resulting in the observed increased product selectivity.

Figure 4.12 Features promoting enhanced selectivity in conformationally controlled iminium 4.19

In hopes to further enhance in selectivity attributed to conformational control in hydrazide catalysts, diastereomeric catalysts bearing an ethyl rather than a methyl moiety at the benzylic position were also synthesized. Unfortunately, hydrazides 4.21 and 4.22 did not provided the selectivity enhancement observed with catalyst 4.14.
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The steric repulsion between the ethyl moiety and the gem-dimethyl groups on the camphor bridgehead could force the catalyst to adopt alternative conformations. This could also be a consequence of the alternative allylic strain between the benzyl side-chain and the iminium moiety becoming more significant. This observation suggests that the choice of groups on the chiral side-chain of hydrazide catalysts has a significant impact in providing successful conformational control. Further investigations in the developments of additional catalysts displaying a conformational control mechanism could potentially be investigated by another group member in the Ogilvie lab.

Figure 4.13 Effect of hydrazide catalyst 4.21 and 4.22 on the asymmetric Diels-Alder between E-cinnamaldehyde and cyclopentadiene

4.3 Crystallographic Evidence of Iminium Ion

We were able to successfully crystallize catalyst 4.14 whose x-ray structure gave information about the electronic properties of the hydrazide ring. One striking factor was the hybridization of the N4 which was trigonal planar. This could be rationalized by resonance into the carbonyl group in addition to delocalization arising from alignment of the N-N lone pairs, consistent with
an alpha-effect. This was corroborated with our previous observations that hydrazide catalyst 4.1 was much more reactive toward iminium formation than other catalytic amine systems.\(^1\)

Figure 4.14 x-ray structures of hydrazide catalyst 4.14 and of intermediate iminium 4.19 (triflate anion omitted for clarity)

The ability of hydrazide catalysts to rapidly and completely generate iminium ions prompted us to try to isolate the reactive species. The iminium ion 4.19, derived from 4.14 and 4.2, was prepared in 5% H\(_2\)O/CH\(_3\)NO\(_2\) and crystallized from THF to provide material for x-ray analysis. To our knowledge this is the first reported example of the crystallographic structure of an iminium intermediate in an organocatalyzed cycle.\(^{138}\) Attempts to crystallize MacMillan’s imidazolidinone catalyst 3.18 failed, possibly due to the lower conversion of activated iminium formed in solution.

Figure 4.14 shows that the hydrazide-iminium \(\pi\) system was completely conjugated in this structure, from the hydrazide carbonyl to the aromatic ring of the dienophile, as indicated by the complete planarity of the system. The N1-C10 bond was slightly elongated, relative to N3-C27 in 4.14, from 1.36 Å to 1.39 Å, and the N-N bond was slightly shortened from 1.43 Å to 1.41 Å.

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The small reduction in delocalization this implied could be explained by the fact that the "amide" nitrogen must donate more of its electron density, relative to 4.14, to compensate for the newly generated positive charge at the iminium nitrogen.

The x-ray structure of 4.19 was compared to our calculated structure 4.19-150°. The average bond length error between the crystal structure 4.19 and 4.19-150° was 0.021 Å and the average dihedral angle error was 1.45°, indicating a good correlation between the calculated structures and the actual iminium intermediate. One significant deviation was noted between these structures that involved the planarity of the "amide" nitrogen (N1 in Figure 4.14). In the calculated structure 4.19-150° the improper torsion along C10-N1-N2-C11 was 136.1° whereas the same angle in the x-ray structure of 4.19 was almost 180°. This discrepancy could be accounted for by the well known propensity of the PM3 basis set to pyramidalize amide nitrogens.

Within the crystal lattice, the iminium molecule 4.19 showed close contacts to the triflate counter-ions within a distance allowable for C-H O hydrogen-bonding (Figure 4.15). Although C-H contacts are much weaker than the typically observed hydrogen bonds with X-H, where X is a heteroatom, these contributions can potentially increase the stability of an intermediate. Moderately acidic C-H groups can create significant hydrogen-bonding sites with anion receptors. However, the triflate anion is a poorly coordinating ion and the likelihood of such hydrogen bonding occurring in aqueous solution with this ion was expected to be negligible. Yet, due of the significant effect of the counter-ion observed in our early Diels-Alder studies (Table 3.16 of Chapter 3), we wished to perform various experiments in an attempt to shed light on the implications of counter-ions in the hydrazide-catalyzed Diels-Alder cycloaddition.

As mentioned above, we noted that the nature of the co-catalyst counter ion had a significant effect on the outcome of the reaction both in terms of yield and enantioselectivity. Initially this appeared to be correlated with the acid strength of the co-catalyst used. To better understand this effect, we carried out an expanded study of acids looking for patterns that could suggest improved reaction conditions.

Strong acids such as HClO₄ and CF₃SO₃H (Table 4.4, entries 3 and 4) were extremely efficient in the process whereas weaker acids such as CH₃SO₃H, CF₃CO₂H or CH₃CO₂H were much less efficient (entries 9, 12 and 13). Several other acids were investigated in order to gain insight into this counter ion effect, and it was quickly apparent that catalytic efficiency did not strictly correlate with acid strength. HClO₄, H₂SO₄, HI and HBr are of comparable acidity, yet produced dramatically different turnovers and inductions (entries 4-6, 14). All of the halogen acids in fact were rather inefficient co-catalysts (entries 5-7). The use of sulfonic acids also did not show any clear trends. Changing the steric bulk of the counter ion (entries 3, 8, 9, 10) did not produce any discernable pattern other than acid strength. Acid strength did not correlate when steric bulk was controlled as exemplified by the results in the phenylsulfonyl series (entries 10-11). Interestingly
two very strong acids, HBF$_4$ and HSbF$_4$ proved to be very effective, but did not offer any advantages in terms of efficiency, selectivity or practicality (entries 1-2) over CF$_3$SO$_3$H. Furthermore, the addition of sodium triflate to the reaction mixture did not provide any beneficial effects.

Table 4.4 Effect of acid co-catalyst on the enantioselective Diels-Alder reactions of cyclopentadiene and E-cinnamaldehyde catalyzed by 4.1*

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>pKa</th>
<th>Yield (%)$^b$</th>
<th>exo:endo$^c$</th>
<th>endo ee (%)$^{d,e}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HSbF$_6$</td>
<td>-</td>
<td>59</td>
<td>1.8:1</td>
<td>81</td>
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<tr>
<td>2</td>
<td>HBF$_4$</td>
<td>-</td>
<td>98</td>
<td>1.7:1</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>CF$_3$SO$_3$H</td>
<td>-14</td>
<td>89</td>
<td>1.9:1</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>HClO$_4$</td>
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<td>82</td>
<td>1.7:1</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>HI</td>
<td>-10</td>
<td>13</td>
<td>1.2:1</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>HBr</td>
<td>-9</td>
<td>40</td>
<td>1.7:1</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>HCl</td>
<td>-8</td>
<td>11</td>
<td>1.3:1</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>CSA</td>
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<td>17</td>
<td>1.6:1</td>
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<tr>
<td>9</td>
<td>CH$_3$SO$_3$H</td>
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<td>8</td>
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<tr>
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<td>1.2:1</td>
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<tr>
<td>11</td>
<td>4-CH$_3$-C$_6$H$_4$SO$_3$H</td>
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<td>15</td>
<td>1.5:1</td>
<td>41</td>
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<tr>
<td>12</td>
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<td>13</td>
<td>1.7:1</td>
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<tr>
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<td>7</td>
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<table>
<thead>
<tr>
<th>14</th>
<th>H₂SO₄</th>
<th>-10</th>
<th>11</th>
<th>1.1:1</th>
<th>17</th>
</tr>
</thead>
</table>

a1M in water using 20 mol % of 4.1 and indicated acid. bCombined isolated yield. cProduct ratios determined by ¹H NMR. dEnantiomeric excess determined by chiral GLC. eOnly endo isomers are reported to show trend across column. Both endo and exo isomers were found to be very similar.

Further evidence for a counter-ion effect was obtained using ¹H NMR experiments. Various iminium ion complexes were formed by mixing equimolar quantities of hydrazide catalyst 4.1 and E-cinnamaldehyde together with a range of Brønsted acids in 19:1 CD₃NO₂:D₂O. The spectra of the perchlorate and triflate iminiums were very similar (Figure 4.16a and 4.16b). However, considerable differences were observed when comparing the typically non-coordinating triflate anion to iodide, an excellent hydrogen acceptor. If hydrogen bonding was present between the counter-ion and a C-H bond of the iminium, a downfield chemical shift should have been observed. The chemical shift of the iminium proton was altered from 8.28 to 8.57 ppm and the proton resonance corresponding to H6A of Figure 4.15, changed from 5.05 to 5.29 ppm in the triflate and iodide spectra respectively (Figure 4.16b and 4.16c). The AB spin system of the benzylic protons was also significantly altered by changing the counter-ion. With the triflate counter-ion, the benzylic system showed the characteristics of an AB system (typically Δδ < J) in which Δδ = 34.2 Hz and J = 17.1 Hz. Conversely, the benzyl proton of the iodide anion of iminium 4.3 displayed chemical shifts that resemble more of an AX system in which Δδ 80.9 and J = 17.0 Hz.
These interesting results prompted us to perform variable temperature $^1$H NMR experiments using the triflic hydrazide 4.3 in an attempt to verify the possibility of coordination between the counter-ion and the hydrazide moiety. The temperature study was executed at temperatures ranging from 0 to 80 °C in 20 °C increments. Analysis of the spectra showed no significant change in chemical shifts, consistent with inoperative C-H hydrogen bonding in this system. The resolution in the spectrum run at 0 °C was very poor but this could be attributed to freezing of the 5% water present in the deuterated nitromethane solution.

Variable concentration $^1$H NMR experiments were also examined. The concentration study was executed in 19:1 CD$_3$NO$_2$:D$_2$O using solvent molarities ranging from 0.01, 0.05, 0.1, 0.5 and 1.0 M. The insignificant change in chemical shifts relative to concentration observed in these experiments was also consistent with the idea that the triflate ion acted as a non-coordinating counter-ion.
Furthermore, the nucleophilic ability of certain conjugate bases could possibly deter overall reaction conversion and selectivity through the formation of hemiaminals with the counterion rather than iminium intermediates. However, no signs of such a species could be detected by $^1\text{H}$ or $^{13}\text{C}$ NMR using CF$_3$SO$_3$H, CH$_3$SO$_3$H or HI.

From the NMR data obtained, it was clear that the counter-ion played a significant role in the outcome of the reaction.\textsuperscript{140} An acid scan revealed that hydrazide-catalyzed cycloadditions in which weakly coordinating counter-ions such as triflate, perchlorate and tetrafuloroborate are used gave the highest yields and selectivities. The use of an iodide counter-ion gave poor results (13% yield, 31% endo ee) relative to the triflate counter-ion which afforded the cycloadducts in 89% yield and 88% endo ee (Table 4.4, entries 5 and 3 respectively). This was supported by the $^1\text{H}$ NMR study in Figure 4.16, which showed that the iminium/iodide ion pair afforded more deshielded peaks, consistent with hydrogen bonding. Further studies could be done in the future to investigate whether this trend translates to other organocatalytic systems.

\textsuperscript{140} Significant counter-ion effects have been noted in other organocatalytic cycloadditions. See ref 107 and Cavill, J.L.; Elliot, R.L.; Evans, G.; Jones, I.L.; Platts, J.A.; Ruda, A.M.; Tomkinson, N.C.O. Tetrahedron \textit{2006}, \textit{62}, 410.
4.4 Conclusions

The mechanism of the enantioselective hydrazide catalyzed Diels-Alder cycloaddition was investigated in detail. Our investigations showed that the cycloaddition step was rate limiting in the hydrazide catalyzed Diels-Alder reaction. The equilibrium between iminium 4.3 and free catalyst 4.1 was extremely rapid and heavily favored iminium 4.3 thus maximizing the effective concentration of the reactive dienophile. Final hydrolysis of intermediate iminiums 4.5 and 4.6 to products was very rapid and so this step did not significantly affect the rate of the overall process. Mechanistic studies using NMR showed that a retro Diels-Alder reaction occurred during the catalytic cycle suggesting a thermodynamic component to the reaction. These thermodynamic contributions to enantioselectivity suggest the potential development of desymmetrization catalysts.

Manipulating the conformational space available to molecules can result in superior asymmetric organic catalysts. This was exemplified by catalyst 4.14, designed with careful consideration given to the reactive conformations available that gave higher exo/endo ratios and enantioselectivities in the hydrazide-catalyzed Diels-Alder cycloadditions than our original catalyst 4.1. This introduces a new aspect to organocatalysis with the introduction of a rotational barrier on the facial directing side chain of our catalyst which could result in the development of novel organocatalysts. The first crystal structure of a key iminium intermediate has also been obtained. This provided absolute proof of the structure of the reactive iminium intermediate and provided valuable information on the key enantiodetermining step.

With the discovery of an efficient catalytic scaffold, our efforts were next directed toward the application of hydrazide catalysts to other cycloaddition processes.
General Information. All solvents were used as obtained from commercial suppliers unless otherwise indicated. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. All starting materials were purchased and were used without purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F₂₅₄. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. Room temperature corresponds to 22 °C. Excess solvents were removed in vacuo at pressures obtained by water or air aspirators connected to a rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with Silica Gel 60 (230-400 mesh). Infrared (IR) spectra were obtained as neat films on a sodium chloride cell. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. Mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a mass spectrometer with an electron beam energy of 70 eV (for EI). Electrospray analyses were run on a triple quad mass spectrometer VG QUATTRO. High resolution mass spectroscopy (HRMS) was performed on a mass spectrometer with an electron beam of 70 eV, or a double focusing magnetic sector mass spectrometer. Melting points were measured using a Melt Temp apparatus and are uncorrected. Diastereomeric ratios were determined by ¹H NMR. Absolute configuration determined by analogy with products provided using Macmillan’s catalyst 3.18. Non-commercial mono-substituted hydrazines were prepared by syringe pump addition of a methanolic solution of benzyl,
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aryl or aliphatic halides to an excess of hydrazine monohydrate (10 eq) at 0 °C.\textsuperscript{141} For kinetic studies \textsuperscript{1}H and \textsuperscript{13}C NMR were recorded at 500 and 125 MHz, respectively, in CD\textsubscript{3}NO\textsubscript{2} or in a mixture of CD\textsubscript{3}NO\textsubscript{2}/D\textsubscript{2}O. Chemical shifts are reported in ppm relative to CH\textsubscript{3}NO\textsubscript{2} (δ = 4.33 ppm) for \textsuperscript{1}H NMR and relative to the central CD\textsubscript{3}NO\textsubscript{2} resonance at 62.8 ppm for \textsuperscript{13}C NMR. Cyclopentadiene and \textit{E}-cinnamaldehyde were freshly distilled before use.

(2\textit{R},3\textit{aR},6\textit{aR})-octahydrocyclopenta[b]pyrrole-2-carboxylic acid hydrochloride (3.13). (\textit{R},3\textit{aR},6\textit{aR})-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride 3.3 (100 mg, 0.355 mmol) was dissolved in MeOH (4 mL). Palladium on charcoal 10% (15 mg) was added and the flask was evacuated/purged with nitrogen three times then filled with hydrogen. The reaction was stirred at 22 °C until deemed complete by TLC analysis (5 hours). The mixture was filtered over celite and washed with warm THF. The solution was concentrated \textit{in vacuo} to give a white solid in 90% yield (89.7 mg). \textsuperscript{1}H NMR (CD\textsubscript{3}OD, 300 MHz) δ 4.12-4.00 (m, 2H), 2.97-2.83 (m, 1H), 2.45 (ddd, J = 13.6, 7.9, 2.5 Hz, 1H), 2.11-1.45 (m, 7H). \textsuperscript{1}H NMR, \textsuperscript{13}C NMR and IR data were identical to those previously reported.\textsuperscript{142}

((2\textit{R},3\textit{aR},6\textit{aR})-octahydrocyclopenta[b]pyrrol-2-yl)diphenylmethanol hydrochloride (3.14). (2\textit{R},3\textit{aR},6\textit{aR})-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride 3.3 (100 mg, 0.355

mmol) was added in portions to a solution of 1.0 M PhMgBr in THF (3.00 mL, 2.84 mmol) at -15°C. The reaction was then refluxed for 5 hours, cooled and poured into a minimum solution of 2N HCl. The solution was cooled for several hours and the precipitate formed was filtered. The crude solid was recrystallized using a methanol/ether solution to provide the title compound as a white hydrochloride salt in 52% yield (62 mg). ^1H NMR (MeOD, 300 MHz) δ 7.68-7.63 (m, 2H), 7.57-7.50 (m, 2H), 7.39-7.20 (m, 6H), 4.12-4.09 (m, 1H), 2.96-2.90 (m, 1H), 2.29-2.18 (m, 1H), 2.12-2.01 (m, 1H), 1.85-1.55 (m, 7H). ^1H NMR, ^13C NMR and IR data were identical to those previously reported.\(^{143}\)

(2R,3aR,6aR)-diethyl-(octahydrocyclopenta[b]pyrrole-2-yl)methanol hydrochloride (3.16). (2R,3aR,6aR)-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride 3.3 (100 mg, 0.355 mmol) was dissolved in 5 mL of 2:1 dioxane:water solution. NaHCO₃ (89 mg, 1.07 mmol) was added and the mixture was stirred for 5 minutes at 0 ºC. Boc anhydride (122 mg, 0.561 mmol), dissolved in 2 mL of 2:1 dioxane-water solution, was syringed into the mixture. The solution was warmed to room temperature and stirred for an additional hour after which time the dioxane was removed in vacuo. The solution was diluted with EtOAc and extracted with sat. NaHCO₃, distilled water and brine. The solution was dried with Na₂SO₄, filtered and concentrated in vacuo to afford a clear oil that was sufficiently pure for the next step. The benzyl ester of the N-Boc-protected amino acid was added over 30 minutes to a solution of 3.0 M ethylmagnesium bromide/diethyl ether (1.2 mL) in 10 mL of diethyl ether at 0 ºC. After the addition, the solution was warmed to 22 ºC and stirred for 24 hours. The mixture was stirred for 30 mins. with a saturated solution of sat. NH₄Cl. The organic layer was separated and the aqueous layer was extracted several times with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by silica gel chromatography (10% EtOAc in hexanes) provided the (2R,3aR,6aR)-(1-tert-butoxycarbonyl-octahydrocyclopenta[b]pyrrole-2-yl)-1'-1'-diethyl-methanol 3.15 as a colorless oil in 61% yield (64 mg). ^1H NMR (CDCl₃, 300 MHz) δ 6.70 (br, 1H), 4.25-4.10 (m, 1H), 3.99-3.88

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(m, 1H), 2.57-2.44 (m, 1H), 2.27-2.01 (m, 1H), 1.42 (s, 9H), 1.95-1.01 (m, 11H), 0.99-0.88 (q, J = 9.4 Hz, 6H). The protected amino alcohol was then treated with 10 mL of a 1:1 solution of 3N HCl/HOAc for 3 hours to remove the Boc protecting group. Once complete as judged by TLC, the mixture was concentrated under reduced pressure and the residue was washed twice with diethyl ether. The aqueous layer was basified with a 20% aqueous NaOH solution and extracted with dichloromethane several times. The combined organic layers were dried using Na2SO4, filtered and concentrated in vacuo to afford the amino alcohol 3.16 in 71% yield (30 mg). 1H NMR (CDCl3, 300 MHz) δ 3.79-3.64 (m, 1H), 3.15-3.00 (m, 1H), 2.65-2.25 (m, 1H), 1.94-1.76 (m, 1H), 1.68-1.30 (m, 12H), 0.93-0.77 (m, 6H). 1H NMR, 13C NMR and IR data were identical to those previously reported.144 The hydrochloride salt of the title compound was obtained by bubbling of HCl gas into a solution of 3.16 in dry diethyl ether.

**General procedure for catalysis with ramipril analogues.** To a solution of (2R,3aR,6aR)-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate hydrochloride 3.3 (42.6 mg, 0.151 mmol) in methanol/water (95/5 v/v, 0.75 mL) was added E-cinnamaldehyde (0.100 g, 0.756 mmol). The solution was stirred for 1-2 minutes before addition of freshly distilled cyclopentadiene (150 mg, 2.26 mmol). Upon consumption of the cinnamaldehyde as by TLC (40 hours), the reaction mixture was diluted with ether and washed successively with distilled water and brine. The organic layer was dried with magnesium sulfate, filtered, and solvent was removed in vacuo. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA:H2O:CHCl3 (1:1:2, 8 mL) for 2 hours at room temperature, followed by neutralization with a saturated solution of sodium bicarbonate and extraction with ether. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1:2.1 mixture of exo and endo isomers (colourless oil, 56 % conversion). endo ee 29%. Enantiomeric ratios were obtained by acetalization with (+)-(R,R)-hydrobenzoin and 1H NMR analysis:145 (500 MHz, C6D6) exo isomers δ 5.57 (d, J = 4.8 Hz, CHO2, major isomer), endo isomers δ 5.21 (d, J = 8.1 Hz, CHO2, major isomer), 5.56 (d, J = 4.8 Hz, CHO2,

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minor isomer), 5.17 (d, J = 8.2 Hz, CHO₂, minor isomer). Percent conversion was determined by $^1$H NMR. $^1$H NMR, $^{13}$C NMR and IR data were identical to those previously reported.¹⁴⁶

Procedure for synthesis of Diels-Alder cycloadducts racemates.¹⁴⁷ To a solution of boron trifluoride etherate (0.18 mL, 1.4 mmol) in dry tetrahydrofuran (2 mL) at 0° C was added E-cinnamaldehyde (185 mg, 1.40 mmol). After stirring for one minute, freshly distilled cyclopentadiene (463 mg, 7.00 mmol) was added. After 2 hours, the reaction was quenched with dilute sodium bicarbonate, and extracted with chloroform. The organic layer was dried with magnesium sulfate, filtered, and the solvent was removed in vacuo. Flash chromatography using 1:9 EtOAc:hexanes yielded the racemic mixture of cycloadducts (95 mg g, 34%) as a colourless oil. exo:endo ratio was determined to be 1:16.

(S)-benzyl 3-(tert-butoxycarbonyl)-4-(methylamino)-4-oxobutanoate (3.20). Performed using a variation of a patented procedure.¹⁴⁸ Boc-Asp(OBzl) 3.19 (6.4 g, 19.8 mmol), hydroxybenzotriazole (3.0 g, 21.8 mmol) and methylamine hydrochloride (2.0 g, 29.6 mmol) were charged in a round bottom flask. These were dissolved in THF (30 mL) and N,N-diisopropylethylamine (10.3 mL, 3.9 g, 59.4 mmol) was added via syringe. Dicyclohexylcarbodiimide (4.1 g, 21.8 mmol) was then added under ice cooling and the mixture was stirred for 3 hours at 0 °C. The ice bath was then removed and the mixture was allowed to stir for a further 15 hours. Insolubles were removed from the mixture by filtration and rinsed with THF and the filtrate was concentrated in vacuo. The residue was dissolved

¹⁴⁷ De la Torre, M. F.; Caballero, M. C; Whiting, A. Tetrahedron, 1999, 55, 8547-8554.
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in ethyl acetate and the organic layer was washed with a 10% aqueous solution of citric acid. A small amount of crystalline material precipitated in the organic layer. The organic layer was filtered, then washed with a saturated aqueous solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo gave a yellow viscous oil which was purified by flash chromatography using 1:19 methanol:chloroform to afford the title compound (4.14 g, 62%) as a pale-yellow powder. m.p. = 221 (dec.)°C; IR (neat) 3332, 2979, 1732, 1675, 1660 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.38 (m, 5H), 6.51 (br s, 1H), 5.78 (d, J = 7.8 Hz, 1H), 5.12 (s, 2H), 4.50 (br s, 1H), 3.00 (dd, J = 18.2, 7.9 Hz, 1H), 2.78 (m, 4H), 1.43 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.3 (C), 170.7 (C), 156.4 (C), 134.8 (C), 128.1 (CH), 127.8 (CH), 79.5 (C), 66.3 (CH₂), 50.1 (CH), 35.7 (CH₂), 27.9 (CH₃), 25.9 (CH₃). MS (CI) m/z 337 (M+1), 281 (M-C₄H₇).

\[ \text{(S)-benzyl 3-amino-4-(methylamino)-4-oxobutanoate (3.21).} \]

(S)-benzyl 3-(tert-butoxycarbonyl)-4-(methylamino)-4-oxobutanoate 3.20 (3.75 g, 11.1 mmol) was dissolved in a 50 mL solution of 1:4 trifluoroacetic acid : methylene chloride. The mixture was stirred for 1 hour at ambient temperature until the reaction was deemed to be complete by TLC. The mixture was then stripped of solvent in vacuo to obtain the crude trifluoroacetate salt of the primary amine. Chloroform (40 mL) was added to the flask, and the resulting mixture was washed with a saturated solution of sodium bicarbonate (50 mL) and distilled water (50 mL) and then dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave the title compound (2.55 g, 97%) as a viscous colourless oil. To obtain samples for characterization purposes, a small amount was purified by flash chromatography using 1:9 methanol:chloroform. IR (neat) 3066, 2944, 1963, 1731, 1656 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.26 (m, 5H), 5.10 (s, 2H), 3.65 (dd, J = 3.8 Hz, 8.2 Hz, 1H), 2.94 (dd, J = 19.7, 3.8 Hz, 1H), 2.77 (d, J = 5.0 Hz, 3H), 2.65 (dd, J = 19.8, 8.2 Hz, 1H), 1.64 (br s, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 173.6 (C), 171.5 (C), 135.5 (C), 128.5 (CH), 128.1 (CH), 66.4 (CH₂), 51.8 (CH), 39.4 (CH₂), 25.9 (CH₃). MS (CI) m/z 237 (M+1), 218 (M-H₂O), 147 (M-Bz).
(S)-benzyl 2-(1,2,2-trimethyl-5-oxoimidazolidin-4-yl)acetate (3.17). To (S)-benzyl 3-amino-4-(methylamino)-4-oxobutanoate 3.21 (0.411 g, 1.74 mmol) was added acetone (1.9 mL, 26.1 mmol) via syringe. These were dissolved in 8 mL methanol, followed by addition of a catalytic amount of para-toluene sulfonic acid (20 mg, 0.11 mmol). The mixture was refluxed for 24 h until the reaction was deemed complete by TLC. The mixture was cooled to ambient temperature, and the solvent was removed in vacuo. The reaction mixture was taken up in ether and filtered to remove insolubles. The mother liquor was concentrated in vacuo and the compound was purified by flash chromatography using 1:19 methanol:chloroform to afford the title compound (117 mg, 24%), as a colorless oil. The hydrochloride salt was produced by bubbling hydrogen chloride gas into a solution of the compound in 10 mL of freshly distilled ether. The ether was removed in vacuo and trace amounts of water were removed by azeotropic distillation with benzene (3 x 10 mL) to give the hydrochloride salt of the title compound quantitatively. IR (neat) 3328, 3065, 2977, 1962, 1733, 1684 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.20 (m, 5H), 5.03 (s, 2H), 3.81 (dd, J = 8.4, 3.4 Hz, 1H), 2.83 (dd, J = 17.2, 3.5Hz, 1H), 2.66 (s, 3H), 2.53 (dd, J = 17.2, 8.4Hz, 1H), 2.38 (br s, 1H), 1.25 (s, 3H), 1.23 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.6 (C), 170.8 (C), 140.9 (C), 128.0 (CH), 126.4 (CH), 126.8 (CH), 66.1 (CH₂), 64.2 (C), 54.4 (CH), 36.1 (CH₂), 27.0 (CH₃), 24.6 (CH₃), 24.4 (CH₃). MS (Cl) m/z 277 (M+1).

General procedure for catalysis with (S)-benzyl 2-(1,2,2-trimethyl-5-oxoimidazolidin-4-yl)acetate hydrochloride (3.17). To a solution of (S)-benzyl 2-(1,2,2-trimethyl-5-oxoimidazolidin-4-yl)acetate hydrochloride 3.17 (23.8 g, 0.076 mmol) in methanol/water (95/5 v/v, 0.75 mL) was added E-cinnamaldehyde (0.100 g, 0.76 mmol). The solution was stirred for 1-2 minutes before addition of freshly distilled cyclopentadiene (0.151 g, 2.3 mmol). Upon consumption of the cinnamaldehyde as by TLC (24 hours), the reaction mixture was diluted with ether and washed successively with distilled water and brine. The organic layer was dried with magnesium sulfate, filtered, and solvent was removed in vacuo. Hydrolysis of the product dimethyl acetal was performed
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by stirring the crude product mixture in TFA:H₂O:CHCl₃ (1:1:2, 8 mL) for 2 hours at room temperature, followed by neutralization with a saturated solution of sodium bicarbonate and extraction with ether. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1.9:1 mixture of \textit{exo} and \textit{endo} isomers (colourless oil, 95.5 mg, 64%). \textit{endo} ee 41%. Enantiomeric ratios were obtained by acetalization with \(+\)-(\textit{R},\textit{R})-hydrobenzoin and \(^1\text{H} \text{NMR analysis: (}500 \text{ MHz, C}_6\text{D}_6\text{)} \textit{exo} \text{ isomers } \delta 5.57 (d, J = 4.8 Hz, \text{CHO}_2, \text{major isomer}), \textit{endo} \text{ isomers } \delta 5.21 (d, J = 8.1 Hz, \text{CHO}_2, \text{major isomer}), 5.56 (d, J = 4.8 Hz, \text{CHO}_2, \text{minor isomer}), 5.17 (d, J = 8.2 Hz, \text{CHO}_2, \text{minor isomer}). \textsuperscript{1}H \text{NMR, }\textsuperscript{13}C \text{NMR and IR data were identical to those previously reported.}\textsuperscript{146}

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{N} \\
\text{O} & \quad \text{H} \quad \text{N}
\end{align*}
\]

\textbf{N'}-(\textit{propan-2-ylidene})benzohydrazide (3.34). Prepared according to procedure described by Tomkinson \textit{et al.}\textsuperscript{107} Benzoic hydrazide \textbf{3.33} (5.00 g, 36.7 mmol) was dissolved in a mixture of 22 mL of acetone and acetic acid (40 \textmu L, 0.69 mmol). The reaction mixture was stirred at room temperature for 48 hours after which time the solution was dissolved in water and extracted with diethyl ether. The combined extracts were washed with brine, dried with MgSO₄ and concentrated to yield 5.44 g 84% of the title compound as a white solid. \textsuperscript{1}H \text{NMR (300 MHz, CDCl₃)} \delta 8.63 (s, 1H), 7.78 (d, J = 6.7 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.44 (dd, J = 7.7, 7.3 Hz, 2H), 2.15 (s, 3H), 1.97 (s, 3H). \textsuperscript{1}H \text{NMR, }\textsuperscript{13}C \text{NMR and IR data were identical to those previously reported.}\textsuperscript{107}

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{N} \\
\text{O} & \quad \text{H} \quad \text{N}
\end{align*}
\]

\textbf{N'}-(\textit{isopropyl})benzohydrazide (3.32). Prepared according to procedure described by Tomkinson \textit{et al.}\textsuperscript{107} Platinum oxide (78.0 mg, 0.345 mmol) was dissolved in 15 mL of ethanol and 7 mL of acetic acid under nitrogen atmosphere. \textbf{N'}-(\textit{propan-2-ylidene})benzohydrazide \textbf{3.34} (3.00 g, 17.0 mmol) was added and the flask was purged with hydrogen using a balloon. The reaction mixture was stirred for
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48 hours and then filtered with celite. The filtrate was slowly treated with sat. bicarbonate solution until the solution was basic. The solution was extracted with EtOAC, washed with brine, dried with MgSO₄ and concentrated to yield 2.89g (95%) of the title compound as a pure white powder. ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.51 (m, 3H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (dd, J = 7.9, 7.1 Hz, 2H), 4.81 (br s, 1H), 3.16 (hept, J = 6.4 Hz, 1H), 1.04 (d, J = 6.4 Hz, 6H). ¹H NMR, ¹³C NMR and IR data were identical to those previously reported.

**General procedure for catalysis using acyclic N'-isopropylbenzohydrazide catalyst 3.32.** To a solution of N'-isopropylbenzohydrazide 3.32 (26.9 mg, 0.151 mmol) and perchloric acid (9.1 µL, 0.151 mmol) in methanol/water (90/10 v/v, 0.75 mL) was added £-cinnamaldehyde (0.100 g, 0.757 mmol). The solution was stirred for 1-2 minutes before addition of freshly distilled cyclopentadiene (29.9 mg, 0.453 mmol). Upon consumption of the cinnamaldehyde as by TLC (24 hours), the reaction mixture was diluted with ether and washed successively with distilled water and brine. The organic layer was dried with magnesium sulfate, filtered, and solvent was removed *in vacuo*. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA:H₂O:CHCl₃ (1:1:2, 8 mL) for 2 hours at room temperature, followed by neutralization with a saturated solution of sodium bicarbonate and extraction with ether. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1:9.1 mixture of *exo* and *endo* isomers (colourless oil, 84% conversion). ¹H NMR, ¹³C NMR and IR data were identical to those previously reported.

2-vinylbenzoic acid (3.37). 60% NaH (4.36 g, 109 mmol) was dissolved in 150 mL dry THF and cooled to 0°C with an ice bath. Ph₃P'MeI (29.4 g, 72.7 mmol) was slowly added and the reaction was allowed to warm to room temperature over 1 hour. 2-carboxybenzaldehyde 3.36 (10.0g, 66.6 mmol) was then added in one portion and the reaction was stirred at 40°C for 3 hours. The reaction was quenched with distilled water and washed with EtOAc. The aqueous layer was acidified with 1N
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HCl to pH 2 and extracted once more with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The crude mixture was purified by silica gel chromatography using 15% EtOAc/hexanes to afford the title compound in 80% yield (7.90 g). ¹H NMR (300 MHz, CDCl₃) δ 8.05 (dd, J = 7.9, 1.1 Hz, 1H), 7.60-7.54 (m, 3H), 7.38 (dt, J = 7.6, 1.4 Hz, 1H), 5.68 (dd, J = 17.3, 1.2 Hz, 1H), 5.37 (dd, J = 11.2, 1.3 Hz, 1H). ¹H NMR, ¹³C NMR and IR data were identical to those previously reported.¹⁴⁹

![Structure of N'-benzyl-2-vinylbenzohydrazide](image)

N¹-benzyl-2-vinylbenzohydrazide (3.38). Benzyl hydrazine dihydrochloride (680 mg, 3.48 mmol) and triethyl amine (696 mg, 6.88 mmol) were dissolved in 60 mL of dry CH₂Cl₂. A solution of 2-vinylbenzoic acid 3.37 (500 mg, 3.42 mmol) in 30 mL dry CH₂Cl₂ was then added via syringe. 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide (675 mg, 3.52 mmol) was added and the solution was stirred for 26 hours. The reaction mixture was washed with sat. NaHCO₃, brine and dried with Na₂SO₄ before being concentrated. The crude mixture was then purified by silica gel chromatography using 30% EtOAc/hexanes to afford the title compound in 60% yield (518 mg) as a clear oil. All spectral properties corresponded with literature values.¹⁵⁰

![Structure of 3-(2-(4-methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3H)-one](image)

3-(2-(4-methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3H)-one (3.43). Prepared following based on a protocol from Johnson et al.¹⁵¹ Phtalaldehydic acid 3.36 (5.00g, 33.3 mmol) and 4-

¹⁴⁹ Matos, M.-C.; Murphy, P. V. J. Org. Chem. 2007, 72, 1803.
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methoxylacetophenone 3.42 (5.00g, 33.3 mmol) were dissolved in 20 mL of 99% ethanol. Using a syringe pump, 13.5 mL of 85% KOH solution in 1:1 EtOH/H₂O was added over the course of 1 hour. The mixture solidified after 75% of the KOH solution had been added, and it was necessary to add another 40 mL of EtOH. The reaction was stirred for another 30 mins after which time the potassium salt was filtered, rinsed with EtOH and dried in vacuo. The crude salt was dissolved in 30 mL of distilled H₂O and acidified with concentrated HCl, cooled and filtered to give the title compound in 78% yield (7.43 g). The material was sufficiently pure for condensation with hydrazine. ¹H NMR (300 MHz, CDCl₃) δ (7.97-7.86 (m, 3H), 7.65-7.51 (m, 3H), 6.95 (d, J = 6.1 Hz, 2H), 6.19 (t, J = 5.5 Hz, 1H), 3.83 (s, 3H), 3.77 (dd, J = 17.5, 5.6 Hz, 1H), 3.34 (dd, J = 17.6, 7.7 Hz, 1H). ¹H NMR, ¹³C NMR and IR data were identical to those reported by Johnson.¹⁵¹

![Structure of 2-(4-methoxyphenyl)-3H-pyrazolo[5,1-a]isoindol-8(3aH)-one](image_url)

2-(4-methoxyphenyl)-3H-pyrazolo[5,1-a]isoindol-8(3aH)-one (3.44). Prepared following based on a protocol from Johnson et al.¹⁵¹ 3-(2-(4-methoxyphenyl)-2-oxoethyl)isobenzofuran-1(3H)-one 3.43 (1.00g, 3.54 mmol) was dissolved in 30 mL EtOH and heated to reflux. Hydrazine (0.35 mL, 7.08 mmol) was slowly added via syringe from the top of the condenser and the solution was stirred for another 3 hours. The reaction mixture was cooled and acidified to pH 4 with concentrated HCl. The solution was concentrated to one third its volume, diluted with distilled water and allowed to stand until pale yellow crystals were produced. The crystals were filtered and recrystallized from methanol to afford the title compound as white crystals (867 mg, 88%). ¹H NMR (200 MHz, CDCl₃) δ 7.94-7.87 (m, 1H), 7.82-7.71 (m, 2H), 7.68-7.43 (m, 3H), 6.96-6.84 (m, 2H), 5.46 (dd, J = 11.2, 11.3 Hz, 1H), 3.83 (s, 3H), 3.52 (dd, 16.9, 11.2 Hz, 1H), 3.04 (dd, J = 16.8, 11.0 Hz, 1H). ¹H NMR, ¹³C NMR and IR data were identical to those reported by Johnson.¹⁵¹
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**Ethyl-E-4-phenylbut-2-enoate (3.50).** Triethylphosphonoacetate 3.49 (9.80 g, 43.7 mmol) was added dropwise to a dispersion of sodium hydride (1.10 g, 45.8 mmol) in 150 mL of THF. After stirring for 15 minutes, phenyl acetaldehyde 3.48 (5.00 g, 41.6 mmol) was added by syringe. The reaction mixture was stirred at 22 °C until judged complete by TLC (20 hours). The reaction mixture was concentrated and EtOAc was added to the resulting viscous liquid. The solution was washed sequentially with saturated sodium bicarbonate solution, water and brine. After drying over anhydrous MgSO₄ and filtering, the solvent was removed in vacuo and the crude product was purified via silica gel chromatography (5% EtOAc in hexanes) to give the title compound (6.88 g, 87%) of which the spectral properties correspond with literature values.¹⁵² ¹H NMR (200 MHz, CDCl₃) δ 7.38-7.02 (m, 6H), 5.80 (dt, J = 15.5, 1.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.50 (d, J = 6.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).

**5-benzylpyrazolidin-3-one (3.51).** To a flask containing ethyl-E-4-phenylbut-2-enoate 3.50 (10.0 g, 53.6 mmol), was added 200 mL of MeOH. Hydrazine monohydrate (3.95g, 78.9 mmol) was then added and the mixture was brought to reflux for 17 hours. The reaction mixture was concentrated and subsequently diluted with Et₂O (200 mL). After washing brine, the solvent was removed in vacuo. Purification via silica gel chromatography (5% MeOH in CHCl₃) afforded the title compound as a pale yellow oil (7.60 g, 82%). IR (neat) 3403, 3065, 3013, 2978, 1674, 1123 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.92 (br s, 1H), 7.28-7.13 (m, 5H), 4.15 (br s, 1H), 3.87-3.82 (m, 1H), 2.90 (dd, J = 13.8, 6.9 Hz, 1H), 2.75 (dd, J = 13.8, 7.1 Hz, 1H), 2.45 (dd, J = 16.3, 7.2 Hz, 1H), 2.24 (dd, J = 16.4, 7.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 176.8 (C), 137.2 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 59.6 (CH), 39.4 (CH₂), 37.3 (CH₂); MS (EI) m/z 176.2 (M⁺).

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5-Benzyl-1-(tert-butoxycarbonyl)pyrazolidin-3-one (3.52). To a flask containing 5-benzylpyrazolidin-3-one 3.51 (500 mg, 2.84 mmol) in 30 mL CH₂Cl₂ was added tert-butylpyrocarbonate (650 mg, 2.98 mmol). The reaction mixture was stirred at 22°C until judged complete by TLC (18 hours). The mixture was washed with saturated sodium bicarbonate solution, water and brine before being dried over Na₂SO₄. The solvent was removed in vacuo and the crude mixture was purified via silica gel chromatography (5% MeOH in CHCl₃) to yield the title compound (757 mg, 97%) as a pale yellow foam. IR (neat) 3216, 3032, 2979, 2928, 1699, 1478, 1455, 1368, 1342, 1250, 1165, 1121 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.15 (m, 5H), 4.58-4.49 (m, 1H), 3.05 (dd, J = 13.4, 6.4 Hz, 1H), 2.87-2.72 (m, 2H), 2.31 (dd, J = 17.2, 2.6 Hz, 1H), 1.39 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 170.7 (C), 153.2 (C), 136.5 (C), 129.4 (CH), 128.6 (CH), 126.8 (CH), 82.3 (C), 57.7 (CH), 40.5 (CH₂), 35.9 (CH₂), 28.5 (CH₃); MS (Cl/iso) 277.3 (MH⁺), 176.2 (MH⁺ - t-Boc).

2,5-Dibenzyl-1-(tert-butoxycarbonyl)pyrazolidin-3-one (3.53). To a 25 mL flask containing sodium hydride (28 mg, 1.2 mmol) in 5 mL DMF was added 5-Benzyl-1-(tert-butoxycarbonyl)pyrazolidin-3-one 3.52 (250 mg, 0.905 mmol), in 3 mL DMF via cannula. After stirring at 22 °C for 15 minutes, benzyl bromide (170 mg, 0.996 mmol) was added via syringe, followed by tetrabutylammonium iodide (33 mg, 0.09 mmol). The reaction mixture was stirred at 22 °C overnight and then poured into a separatory funnel containing 100 mL of water. The resulting suspension was extracted three times with EtOAc. The organic extracts were combined and washed with water and brine before being dried with Na₂SO₄. The crude product was purified by gradient silica gel chromatography (15 to 30% EtOAc in hexanes) to yield the title compound (242 mg, 73%) as a pale yellow oil. IR (neat) 3091, 2981, 1713, 1607, 1493, 1316 1156 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.37 (m, 5H), 7.12-7.09 (m, 3H), 6.50-6.47 (m, 2H), 5.40 (d, J = 14.1 Hz, 1H), 4.53
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\[(d, J = 14.1 \text{ Hz}, 1\text{H}), 4.49-4.41 (m, 1\text{H}), 2.93 (dd, J = 16.6, 8.6 \text{ Hz}, 1\text{H}), 2.34-2.07 (m, 3\text{H}), 1.30 (s, 9\text{H}); ^{13}\text{C} \text{NMR} (75 \text{ MHz, CDCl}_3) \delta 170.2 (C), 155.6 (C), 136.9 (C), 136.0 (C), 129.9 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 126.3 (CH), 82.2 (C), 59.1 (CH), 48.3 (CH\text{\textsubscript{2}}), 39.9 (CH\text{\textsubscript{2}}), 36.3 (CH\text{\textsubscript{2}}), 27.9 (CH\text{\textsubscript{3}}); \text{MS (Cl/iso)} 367.5 (M^+) , 266.3 (M^+ - t\text{-Boc}).\]

2,5-Dibenzylpyrazolidin-3-one (3.54). To a flask containing 2,5-Dibenzyl-1-(tert-butoxycarbonyl)pyrazolidin-3-one 3.53 (172 mg, 0.470 mmol) in 4 mL of CH\text{\textsubscript{2}}Cl\text{\textsubscript{2}} was added trifluoroacetic acid (1 mL). After stirring at 22 °C for 3 hours, the reaction mixture was concentrated and 20 mL of CH\text{\textsubscript{2}}Cl\text{\textsubscript{2}} was added. Saturated sodium bicarbonate was then carefully added to neutralize the remaining TFA. The organic phase was separated from the aqueous phase and was washed sequentially with water and brine. After treatment with Na\text{\textsubscript{2}}SO\text{\textsubscript{4}} the solvent was removed \textit{in vacuo} to yield the title compound (121 mg, 97%) as a yellow oil. IR (neat) 3482, 2919, 1678, 1554, 1357 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 7.38-7.18 (m, 8H), 7.05-7.02 (m, 2H), 4.63 (d, J = 14.6 Hz, 1H), 4.51 (d, J = 14.6 Hz, 1H), 3.95 (br s, 1H), 3.76-3.67 (m, 1H), 2.83 (dd, J = 13.7, 6.9 Hz, 1H), 2.68-2.60 (m, 2H), 2.35 (dd, J = 16.4, 6.4 Hz, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 171.5 (C), 137.2 (C), 135.9 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 126.7 (CH), 56.1 (CH), 48.8 (CH\textsubscript{2}), 39.7 (CH\textsubscript{2}), 38.0 (CH\textsubscript{3}); MS (EI) \textit{m/z} 266.2 (M\textsuperscript{+}).

1-Methyl-2-oxo-cyclopentanecarboxylic acid ethyl ester (3.58). Ethyl 2-oxocyclopentanecarboxylate 3.57 (5.00g, 32.0 mmol) and potassium carbonate (17.7 g, 0.128 mmol) were dissolved in acetone at 22 °C. Freshly distilled methyl iodide (4.0 mL, 64 mmol) was then added drop-wise to the reaction and the mixture was refluxed for 1.5 hours. Water was added to the reaction mixture
which was extracted three times with Et$_2$O. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. This provided 4.14 g (77%) of crude product which, by comparison of the literature $^1$H NMR$^{153}$, was deemed pure enough for the next step. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.07 (dq, J = 7.2, 1.5 Hz, 2H), 2.49-2.15 (m, 3H), 2.06-1.71 (m, 3H), 1.22 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H).

2-Benzyl-3a,4,5,6-tetrahydro-2H-cyclopentapyrazol-3-one (3.59). 1-Methyl-2-oxo-cyclopentanecarboxylic acid ethyl ester 3.58 (100 mg, 0.588 mmol), benzyl hydrazine dihydrochloride (138 mg, 0.705 mmol) and sodium acetate (212 mg, 2.59 mmol) were dissolved in 5 mL of acetic acid. The mixture was refluxed for 40 hours after which time saturated sodium bicarbonate solution was added to the flask. The reaction mixture was extracted with EtOAc and washed with brine before being dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (25% EtOAc in hexanes) provided 67 mg (50%) of the title compound as a white solid. IR (neat) 3440, 2976, 2365, 1692, 1455 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36-7.20 (m, 5H), 4.86 (d, J = 15.2 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 2.63-2.49 (m, 1H), 2.42-2.08 (m, 3H), 1.85-1.72 (m, 1H), 1.66-1.52 (m, 1H), 1.37 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.8 (C), 175.6 (C), 137.3 (C), 128.6 (CH), 127.9 (CH), 127.5 (CH), 55.2 (C), 47.8 (CH$_2$), 24.5 (CH$_2$), 22.6 (CH$_2$), 18.4 (CH$_3$); MS (EI) m/z 228.1 (M$^+$).

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2-Benzyl-3a-methyl-hexahydro-cyclopentapyrazol-3-one (3.60). 2-Benzyl-3a,4,5,6-tetrahydro-2H-cyclopentapyrazol-3-one 3.59 (168 mg, 0.738 mmol) was stirred in 6 mL of MeOH in a 25 mL flask to which a three way valve was attached. The solution was degassed twice and purged with N\textsubscript{2} before Adam’s catalyst was added (18 mg, 0.07 mmol) was added. The reaction was purged again with N\textsubscript{2} before switching to H\textsubscript{2} atmosphere. The reduction proceeded for 1 hour before being passed through a celite pad using CHCl\textsubscript{3} as the eluant. The organic solvent was then removed under reduced pressure and the crude product was subjected to silica gel chromatography (50% EtOAc in hexanes) which provided 166 mg (86%) of the title compound as a colourless oil. IR (neat) 3550, 3064, 2925, 2236, 1667, 1454 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDC\textsubscript{3}) \delta 7.42-7.03 (m, 5H), 4.62 (d, J = 14.5 Hz, 1H), 4.41 (d, J = 14.5 Hz, 1H), 4.10 (br, 1H), 3.39 (br d, J = 6.3 Hz, 1H), 2.32-2.02 (m, 1H), 2.01-1.74 (m, 1H), 1.76-1.35 (m, 4H), 1.24 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDC\textsubscript{3}) \delta 176.0 (C), 136.2 (C), 129.2 (CH), 128.6 (CH), 128.2 (CH), 66.6 (CH), 53.0 (C), 48.5 (CH\textsubscript{2}), 37.7 (CH\textsubscript{2}), 34.2 (CH\textsubscript{2}), 24.4 (CH\textsubscript{2}), 21.4 (CH\textsubscript{3}); MS (EI) m/z 230.1 (M\textsuperscript{+}).

1-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (3.62). Ethyl 2-cyclohexanone-carboxylate 3.61 (5.00g, 29.4 mmol) and potassium carbonate (16.2 g, 0.117 mmol) were dissolved in 50 mL of acetone at 22 °C. Freshly distilled methyl iodide (3.66 mL, 58.7 mmol) was then added drop-wise to the reaction and the mixture was reafluxed for 18.5 hours. Water was added to the reaction mixture which was extracted three times with Et\textsubscript{2}O. The combined organic extracts were dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. This provided 5.22 g (96%) of crude product which, by comparison of the literature \textsuperscript{1}H NMR,\textsuperscript{153} was deemed pure enough for the next step. \textsuperscript{1}H NMR (300 MHz, CDC\textsubscript{3}) \delta 4.13 (dq, J = 7.2, 2.0 Hz, 2H), 2.51-2.31 (m, 3H), 2.06-1.86 (m, 1H), 1.72-1.51 (m, 3H), 1.46-1.31 (m, 1H), 1.2 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H).
Experimental Section: Diels-Alder Catalysis

2-Benzyl-3a-methyl-2,3,4,5,6,7-hexahydro-indazol-3-one (3.63). Compound 1-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester 3.62 (1.00 g, 5.43 mmol), benzyl hydrazine dihydrochloride (1.27 g, 6.51 mmol) and sodium acetate (1.11 g, 13.6 mmol) were dissolved in 50 mL of acetic acid. The mixture was refluxed for 46 hours after which time the acetic acid was removed by azeotropic distillation with toluene. The remaining mixture was extracted with EtOAc and washed saturated sodium bicarbonate and brine before being dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (25% EtOAc in hexanes) provided 1.18 g (90%) of the title compound as an off-white solid, mp 81°C; IR (neat) 2952, 1702, 1450, 1404 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.16 (m, 5H), 4.89 (d, J = 15.2 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 2.51 (dd, J = 9.7, 3.8 Hz, 1H), 2.24 (dt, J = 13.3, 5.4 Hz, 1H), 2.11-1.95 (m, 2H), 1.78-1.53 (m, 2H), 1.45-1.30 (m, 2H), 1.37 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 179.1 (C), 167.9 (C), 137.3 (C), 128.6 (CH), 127.8 (CH), 127.5 (CH), 49.1 (C), 47.9 (CH₂), 35.5 (CH₂), 29.1 (CH₂), 27.2 (CH₂), 21.0 (CH₂), 18.0 (CH₃); MS (EI) m/z 242.1 (M⁺).

2-Benzyl-3a-methyl-octahydro-indazol-3-one (3.64). 2-Benzyl-3a-methyl-2,3a,4,5,6,7-hexahydro-indazol-3-one 3.63 (100 mg, 0.413 mmol) was stirred in a solvent mixture consisting of 3 mL MeOH and 1.5 mL of acetic acid. To this was added sodium cyanoborohydride (259 mg, 4.13 mmol) and the reaction was stirred for 39 hours. The mixture was poured into a beaker containing 50 mL of a 2N NaOH solution and was stirred for 15 minutes. The mixture was then extracted three times with EtOAc, washed with brine and dried over MgSO₄. After concentration under reduced pressure, the crude material was subjected to silica gel chromatography (50% EtOAc in hexanes) to afford 78 mg (77%) of the desired product as a colourless oil. IR (neat) 2959, 1702, 1446, 1400 cm⁻¹; ¹H NMR
Experimental Section: Diels-Alder Catalysis

(300 MHz, CDCl₃) δ 7.42-7.03 (m, 5H), 4.61 (d J = 14.9 Hz, 1H), 4.54 (d, J = 13.9 Hz, 1H), 3.17-2.93 (br, 1H), 3.06 (t, J = 5.6 Hz, 1H), 1.80-1.57 (m, 2H), 1.58-1.23 (m, 6H), 1.14 (s, 3H);¹³C NMR (75 MHz, CDCl₃) δ 177.2 (C), 136.5 (C), 129.2 (CH), 128.6 (CH), 128.1 (CH), 61.3 (CH), 48.6 (CH₂), 43.5 (C), 30.7 (CH₂), 25.7 (CH₂), 22.3 (CH₂), 21.7 (CH₂), 20.4 (CH₃); MS (EI) m/z 244.2 (M⁺).

General procedure for Diels-Alder Reaction using catalysts 3.51, 3.54, 3.60, 3.64. E-cinnamaldehyde (50 mg, 0.38 mmol) in 3.4 mL of MeOH and the respective pyrazolidinone (0.08 mmol). Perchloric acid (0.20 mL, 0.08 mmol) was added as a 0.3734 M aqueous solution, followed by distilled water (0.18 mL). Cyclopentadiene was then added and the reaction mixture was stirred at 22 °C and monitored by TLC. When ready for work-up the reaction mixture was diluted with water and extracted with Et₂O. The combined organic extracts were washed with saturated bicarbonate solution, water and brine before being dried over Na₂SO₄. After removing the solvent, CHCl₃ (4 mL), water (2 mL) and trifluoroacetic acid (2 mL) were added in succession and the resulting mixture was stirred for 24 hours. Saturated sodium bicarbonate solution (20 mL) was added carefully. Et₂O was added and the phases were separated. The combined organic phases were dried over Na₂SO₄ and the solvent was removed in vacuo to yield an oil. The percent conversion was determined by ¹H NMR. ¹H NMR, ¹³C NMR and IR data were identical to those previously reported.¹⁴⁶

(MOH) (S)-(+)–ketopinic acid (3.72).¹¹⁸ To a 500 mL flask fitted with a water-cooled condenser and a base trap (using a vacuum adapter and a nalgene tubing connected to an inverted funnel in a strongly basic NaOH solution) was added (1S)-(+)–10-camphorsulfonic acid 3.71 (100g, 430 mmol). Thionyl chloride (100 mL) was carefully added and the resulting solution was heated using a steam bath for 45 minutes until HCl gas production diminished. The reaction was then cooled to room temperature, poured onto ice (~100g) and stirred to ensure precipitation. The resulting white precipitate was filtered by suction and rinsed several times with cold water. The crude sulfonyl chloride was dried in vacuo before being used in the next step. To a 3 L flask equipped with a water-cooled condenser was
added anhydrous sodium carbonate (100g, 944 mmol) and distilled water 600 mL. The mixture was heated using a steam bath after which potassium permanganate (33.0 g, 208 mmol) and hot water (250 mL) were added. At this point, 1/3 of the crude sulfonyl chloride (careful the product is very acidic and corrosive) was added followed by 15 minutes of stirring. This process was repeated twice, so that a total of 100 g (633 mmol) of potassium permanganate and all the crude sulfonyl chloride were added. The reaction was allowed to stir for an addition 3 hours in the steam bath. After cooling to ambient temperature, the solution was made acidic by careful addition of four 100 mL portions of 20% aqueous sulfuric acid solution (add acid slowly, as considerable foaming occurs). The reaction mixture was replaced in the steam bath and sodium sulfite (80.0 g, 635 mmol) was added. After cooling, the resulting clear and colourless solution was extracted with Et₂O (3 x 500 mL). The combined organic extracts were dried over Na₂SO₄ and the solvent was removed in vacuo.

The crude product 3.72 (38 to 45 g) could be carried on to the next step or be purified via silica gel chromatography (50% EtOAc in hexanes). mp 197°C; IR (Nujol mull) 2964, 1750, 1690, 1465 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.49 (br, 1H), 2.55 (dt, J = 18.6, 3.9 Hz, 1H), 2.40-2.34 (m, 1H), 2.12 (t, J = 4.3 Hz, 1H), 2.10-2.02 (m, 1H), 1.98 (d, J = 18.6 Hz, 1H), 1.81-1.75 (m, 1H), 1.44-1.39 (m, 1H), 1.14 (s, 3H), 1.11 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.7 (C), 174.9 (C), 67.1 (C), 49.7 (C), 44.1 (CH), 43.6 (CH₂), 26.8 (CH₂), 26.6 (CH₂), 20.8 (CH₃), 19.8 (CH₃); MS (EI) m/z 182.2 (M⁺).

General procedure for the preparation of hydrazono-carboxylic acids. (S)-(+)−7,7-Dimethyl-2-(methyl-hydrazono)-bicyclo[2.2.1]heptane-1-carboxylic acid (3.77). Acetic acid (0.13 mL, 2.20 mmol) was added dropwise to a solution of (S)-(+)−ketopinic acid 3.72 (2.00 g, 11.0 mmol) and methylhydrazine (758 mg, 16.5 mmol) in anhydrous dichloromethane (100 ml) at room temperature. The reaction mixture was stirred at that temperature until judged complete by TLC analysis (15 hours). Removal of solvent in vacuo and purification by silica gel chromatography (5% MeOH in CHCl₃) provided the title compound as a white solid (2.17 g, 94 %). mp 106-110 °C; [α]D = +76.0 (c 1.02, CHCl₃); IR (neat) 3275, 1720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.80 (br, 1H), 2.91 (s, 3H), 2.42-2.33 (m, 2H) 2.1-1.9 (m, 3H), 1.82 (d, J = 17.2 Hz, 1H), 1.71 (ddd, J = 13.0, 9.3, 4.0 Hz, 1H).
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1.33-1.23 (m, 1H), 1.20 (s, 3H), 0.86 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 172.9 (C), 158.7 (C), 59.6 (C), 51.6 (C), 44.4 (CH), 38.0 (CH₃), 32.7 (CH₂), 32.3 (CH₂), 28.2 (CH₂), 20.1 (CH₃) 19.8 (CH₃); MS (EI) m/z 210.0 (M⁺); HRMS (EI) calcd. for C₁₁H₁₈N₂O₂ (M⁺) 210.1368; found 210.1369.

\[
\text{(S)-(+-)-7,7-Dimethyl-2-(2-phenylhydrazono)bicyclo[2.2.1]heptane-1-carboxylic acid (3.73).}
\]
Prepared by a procedure similar to that described above for 3.77 from (S)-(+)ketopinic acid 3.72 (3.36 g, 16.5 mmol) and phenylhydrazine (2.68 g, 24.8 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the desired compound as a pale yellow oil (4.18 g, 93%). \(^1\)H NMR (300 MHz, CDCl₃) δ 7.35-7.22 (m, 2H), 7.01-6.91 (m, 3H), 2.65-2.44 (m, 2H), 2.16-2.01 (m, 3H), 1.83 (ddd, J = 12.3, 9.2, 3.8 Hz, 1H), 1.44-1.29 (m, 1H), 1.27 (s, 3H), 0.90 (s, 3H). \(^1\)H NMR, \(^13\)C NMR and IR data were identical to those previously reported.

\[
\text{(S)-(+-)-2-(Benzyl-hydrazono)-7,7-dimethyl-bicyclo[2.2.1]heptane-1-carboxylic acid (3.80-1).}
\]
Prepared by a procedure similar to that described above for 3.77 from (S)-(+)ketopinic acid 3.72 (3.00 g, 18.4 mmol) and benzylhydrazine (3.38 g, 27.7 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the desired compound as a pale yellow oil (5.28 g, 100%). \([\alpha]_D = +53.7 \text{ (c 1.10, CHCl₃); IR (neat) 3282, 1742 cm}^{-1}; \) \(^1\)H NMR (500 MHz, CDCl₃) δ 7.34-7.24 (m, 5H), 4.31 (s, 2H), 2.39 (ddd, J = 12.3, 12.1, 4.2 Hz, 1H), 2.32 (ddd J = 17.1, 3.7, 3.7 Hz, 1H), 2.08-2.01 (m, 1H), 1.97 (t, J = 4.38 Hz, 1H) 1.78 (d, J = 17.1 Hz, 1H), 1.72-1.67 (m, 1H), 1.30-1.24 (m, 1H), 1.21 (s, 3H), 0.79 (s, 3H); \(^13\)C NMR (125 MHz, CDCl₃) δ 172.7 (C), 159.3 (C), 138.2 (C), 128.6 (CH), 128.2 (CH), 127.6 (CH), 59.3 (C), 55.0 (CH₂), 51.4 (C), 44.3 (CH), 32.6
Experimental Section: Diels-Alder Catalysis

(CH₂), 32.1 (CH₂), 28.1 (CH₂), 19.9 (CH₃), 19.6 (CH₃); MS (EI) m/z 268.2 (M⁺); HRMS (EI) calcd. for C₁₇H₂₂N₂O₂ (M⁺) 286.1681 found 286.1692.

\[(\text{S})-\text{(+)}-2-(2-(4\text{-methoxybenzyl})\text{hydrazono})-7,7\text{-dimethylbicyclo}[2.2.1]\text{heptane-1-carboxylic acid}\]
(3.80-2). Prepared by a procedure similar to that described above for 3.77 from (S)-(+)-ketopinic acid 3.72 (1.00 g, 5.48 mmol) and p-methoxybenzylhydrazine (1.00 g, 6.59 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the desired compound as a clear oil (1.23 g, 71%). IR (neat) 3241, 1730 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ ²H NMR (500 MHz, CDCl₃) δ 7.25-7.18 (m, 2H), 6.88-6.82 (m, 2H), 4.24 (s, 2H), 3.77 (s, 3H), 2.45-2.27 (m, 2H), 2.15-1.94 (m, 2H), 1.77 (d, J = 17.1 Hz, 1H), 1.74-1.65 (m, 1H), 1.32-1.21 (m, 1H), 1.21 (s, 3H), 0.80 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.9 (C), 159.4 (C), 130.3 (C), 129.6 (CH), 114.0 (CH), 59.6 (C), 55.3 (CH₃), 54.6 (CH₂), 51.5 (C), 44.4 (CH), 32.7 (CH₂), 32.2 (CH₂), 28.2 (CH₂), 20.0 (CH₃), 19.7 (CH₃); MS (EI) m/z 316.2 (M⁺); HRMS (EI) calcd. for C₁₈H₂₄N₂O₃ (M⁺) 316.1787 found 316.1802.

\[(\text{S})-\text{(+)}-7,7\text{-Dimethyl-2-(naphthalen-1-ylmethyl-hydrazono)-bicyclo[2.2.1]\text{heptane-1-carboxylic acid}}\]
(3.80-3). Prepared by a procedure similar to that described above for 3.77 from (S)-(+)ketopinic acid 3.72 (1.97 g, 10.8 mmol) and naphthyl(1-methylhydrazine) (2.25 g, 13.0 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the compound as a pale yellow oil (3.12 g, 86%); IR (neat) 3278, 1724 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, J = 8.4 Hz, 1H),
7.88-7.77 (m, 2H), 7.57-7.39 (m, 4H), 4.82 (d, J = 13.0 Hz, 1H), 4.76 (d, J = 13.0 Hz, 1H), 2.39 (ddd, J = 12.3, 12.3, 4.5 Hz, 1H), 2.25 (ddd, J = 17.1, 3.7, 3.7 Hz, 1H), 2.08-1.88 (m, 2H), 1.74-1.63 (m, 2H), 1.27-1.22 (m, 1H), 1.20 (s, 3H), 0.73 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 172.8 (C), 159.4 (C), 133.9 (C), 133.5 (C), 131.4 (C), 128.9 (CH), 128.6 (CH), 127.1 (CH), 126.4 (CH), 125.9 (CH), 125.4 (CH), 123.3 (CH), 59.6 (C), 52.9 (CH2), 51.5 (C), 44.3 (CH), 32.6 (CH2), 32.1 (CH2), 28.2 (CH2), 20.0 (CH3), 19.6 (CH3); MS (EI) m/z 336.2 (M+); HRMS (EI) calcd. for C21H24N2O2 (M+) 336.1838 found; 336.1822.

(S)-(+-3-Phenyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.01,5]dec-4-en-2-one (3.74). Prepared following the procedure described by Chen et al.116 (S)-(+-7,7-Dimethyl-2-(2-phenylhydrazono)bicyclo[2.2.1]heptane-1-carboxylic acid 3.73 (2.00 g, 7.34 mmol) and triethyl amine (817 mg, 8.07 mmol) were dissolved in 150 mL EtOAc. Thionyl chloride (1.31 g, 11.0 mmol) was added dropwise over the period of one hour. The reaction mixture was warmed to 60°C for 6 hours before the reaction was quenched with distilled water. The solution was diluted with EtOAc and the layers were separated. The organic layer was washed with distilled water and brine, dried over Na2SO4 and concentrated. Purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a white solid (765 mg, 41%). 1H NMR (300 MHz, CDCl3) δ 7.95-7.86 (m, 2H), 7.44-7.33 (m, 2H), 7.19-7.10 (m, 1H), 2.71 (dt, J = 17.9, 3.5 Hz, 1H), 2.45-2.38 (m, 2H), 2.32-2.15 (m, 2H), 1.82 (ddd, J = 12.1, 9.3, 3.5 Hz, 1H), 1.55 (ddd, J = 11.4, 9.3, 3.5 Hz, 1H), 1.25 (s, 3H), 1.01 (s, 3H). 1H NMR, 13C NMR and IR data were identical to those previously reported.116
Experimental Section: Diels-Alder Catalysis

(5)-(+-)10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]dec-4-en-2-one (3.81-4). A solution of (5)-(+-)-ketopinic acid 3.72 (2.00g, 11.0 mmol) in 85 % hydrazine hydrate (10 mL) was stirred at room temperature for 17 hours. Excess hydrazine and water were then removed from the white suspension by azeotropic distillation with toluene and the residue dried under vacuum for several hours. The white solid was suspended in mesitylene (60 mL) and the resulting mixture was refluxed while water was removed in dean-stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC. The cooled reaction mixture was directly loaded onto a silica column and was purified by flash chromatography (hexanes then with 50 % EtOAc in hexanes) to afford the title compound as a white solid (1.15 g, 59 %). mp 176-178 °C; [a]D = +119 (c 1.03, CHCl3); IR (neat) 3207, 1678 cm
-1; 1H NMR (300 MHz, CDCl3) δ 8.91 (br, 1H), 2.62-2.54 (m, 1H), 2.29-2.20 (m, 2H), 2.00-2.15 (m, 2H) 1.76-1.64 (m, 1H), 1.52-1.38 (m, 1H), 1.17 (s, 3H), 0.93 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 176.7 (C), 175.6 (C), 62.4 (C), 49.7 (C), 49.3 (CH), 32.0 (CH2), 27.0 (CH2), 25.3 (CH2), 19.0 (CH3), 18.5 (CH3); MS (EI) m/z 178.1 (M+); HRMS (CI) calcd. for C10H14N2O (M+) 178.1106; found 178.1095.

General procedure for the preparation of imino hydrazides. (5)-(+-)3,10,10-Trimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]dec-4-en-2-one (3.78). A solution of 7,7-Dimethyl-2-(methyl-hydrazono)-bicyclo[2.2.1]heptane-1-carboxylic acid 3.77 (800 mg, 3.80 mmol) in mesitylene (38 mL) was refluxed while water was removed in dean-stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC. The cooled reaction mixture was directly loaded onto a silica column and was purified by flash chromatography (hexanes followed by 30 % EtOAc in hexanes) to provide the desired compound as a white solid (540 mg, 74 %). mp 87-88 °C;
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\([\alpha]_D = +74.9\) (c 1.31, CHCl\(_3\)); IR (neat) 1690, 1633 cm\(^{-1}\); \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) 3.23 (s, 3H), 2.57-2.51 (m, 1H), 1.96-2.79 (m, 4H), 1.64-1.56 (m, 1H), 1.48-1.40 (m, 1H), 1.14 (s, 3H), 0.86 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 174.2 (C), 173.6 (C), 63.6 (C), 49.6 (C), 49.2 (CH), 31.8 (CH\(_2\)), 31.4 (CH\(_3\)), 26.9 (CH\(_2\)), 25.2 (CH\(_2\)), 19.1 (CH\(_3\)), 18.6 (CH\(_3\)); MS (EI) \(m/z\) 192.1 (M\(^+\)); HRMS (EI) calcd. for C\(_{11}\)H\(_{16}\)N\(_2\)O (M\(^+\)) 192.1263; found 192.1252.

(\(S\))-\(+\)-3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0\(^1\)5\]dec-4-en-2-one (3.81-1). Prepared by a procedure similar to that described above for 3.78 from 2-(Benzyl-hydrazono)-7,7-dimethyl bicyclo[2.2.1]heptane-1-carboxylic acid 3.80-1 (3.43 g, 11.9 mmol). Purification by silica gel chromatography (hexanes then 30% EtOAc in hexanes) provided the title compound as a white solid (2.56 g, 80%). mp 90-92°C; \([\alpha]_D = +28.0\) (c 1.04, CHCl\(_3\)); IR (film) 1690, 1630 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.20 (m, 5H), 4.79 (s, 2H), 2.53 (ddd, \(J = 17.5, 3.6, 3.6\) Hz, 1H), 2.26 (ddd, \(J = 12.0, 4.3, 4.3\) Hz, 1H), 2.21 (t, \(J = 4.32\) Hz, 1H), 2.13-2.06 (m, 2H), 1.64 (ddd, \(J = 13.4, 9.5, 4.5\) Hz, 1H), 1.45 (ddd, \(J = 13.3, 9.5, 4.3\) Hz, 1H), 1.19 (s, 3H), 0.87 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.4 (C), 173.5 (C), 137.1 (C), 128.4 (CH), 127.7 (CH), 127.3 (CH), 63.6 (C), 49.7 (C), 49.1 (CH), 47.8 (CH\(_2\)), 31.8 (CH\(_2\)), 26.9 (CH\(_2\)), 25.2 (CH\(_2\)), 19.1 (CH\(_3\)), 18.5 (CH\(_3\)); MS (EI) \(m/z\) 268.2 (M\(^+\)); HRMS (EI) calcd. for C\(_{17}\)H\(_{20}\)N\(_2\)O (M\(^+\)) 268.1576; found 268.1589.
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(5)-(+)-3-(4-methoxybenzyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.01,5]dec-4-en-2-one (3.81-2).
Prepared by a procedure similar to that described above for 3.78 from (S)-(+)-2-(2-(4-
methoxybenzyl)hydrazono)-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid 3.80-2 (1.06 g,
3.36 mmol). Purification by silica gel chromatography (hexanes then 30% EtOAc in hexanes)
provided the title compound as a clear oil (641 mg, 64%). IR (neat) 1692, 1513 cm⁻¹; ¹H NMR (300
MHz, CDCl₃) δ 7.25-7.18 (m, 2H), 6.86-6.80 (m, 2H), 4.73 (s, 2H), 3.76 (s, 3H), 2.59-2.49 (m, 1H),
2.32-2.02 (m, 4H), 1.69-1.59 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (s, 3H), 0.86 (s, 3H); ¹³C NMR (75
MHz, CDCl₃) δ 174.4 (C), 173.5 (C), 129.4 (C), 129.2 (C), 113.9 (CH), 63.7 (C), 55.2 (CH₃), 49.8
(C), 49.2 (CH), 47.4 (CH₂), 32.0 (CH₂), 27.0 (CH₂), 25.3 (CH₂), 19.1 (CH₃), 18.6 (CH₃); MS (EI) m/z
298.2 (M⁺); HRMS (EI) calcd. for C₁₈H₂₅N₂O₂ (M⁺) 298.1681 found 298.1695.

(5)-(+)-10,10-Dimethyl-3-naphthalen-1-ylmethyl-3,4-diaza-tricyclo[5.2.1.01,5]dec-4-en-2-one (3.81-3).
Prepared by a procedure similar to that described above for 3.78 from (S)-(+)-2-(2-(4-
methoxybenzyl)hydrazono)-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid 3.80-2 (1.06 g,
3.36 mmol). Purification by silica gel chromatography (hexanes then 30% EtOAc in hexanes)
provided the title compound as a clear oil (641 mg, 64%). IR (neat) 1692, 1513 cm⁻¹; ¹H NMR (300
MHz, CDCl₃) δ 7.25-7.18 (m, 2H), 6.86-6.80 (m, 2H), 4.73 (s, 2H), 3.76 (s, 3H), 2.59-2.49 (m, 1H),
2.32-2.02 (m, 4H), 1.69-1.59 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (s, 3H), 0.86 (s, 3H); ¹³C NMR (75
MHz, CDCl₃) δ 174.4 (C), 173.5 (C), 129.4 (C), 129.2 (C), 113.9 (CH), 63.7 (C), 55.2 (CH₃), 49.8
(C), 49.2 (CH), 47.4 (CH₂), 32.0 (CH₂), 27.0 (CH₂), 25.3 (CH₂), 19.1 (CH₃), 18.6 (CH₃); MS (EI) m/z
298.2 (M⁺); HRMS (EI) calcd. for C₁₈H₂₅N₂O₂ (M⁺) 298.1681 found 298.1695.
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(11H), 2.28 (ddd, J = 7.2, 7.2, 2.7 Hz, 1H), 2.19 (dd, J = 2.4, 2.4 Hz, 1H), 2.12-2.02 (m, 1H), 2.04
d, J = 10.5 Hz, 1H), 1.57 (ddd, J = 8.1, 5.7, 2.7 Hz, 1H), 1.41 (ddd, J = 7.8, 5.7, 2.7 Hz, 1H), 1.22 (s,
3H), 0.84 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 174.6 (C), 173.1 (C), 133.7 (C), 132.5 (C), 131.2 (C),
128.5 (CH), 128.4 (CH), 127.4 (CH), 126.2 (CH), 125.7 (CH), 125.2 (CH), 123.7 (CH), 63.7 (C), 49.7 (C),
49.1 (CH), 46.1 (CH2), 31.9 (CH2), 26.8 (CH2), 25.3 (CH2), 19.1 (CH3), 18.5 (CH3); MS (EI) m/z 318.2 (M+);
HRMS calcd. for C21H22N2O (M+) 318.1732; found 318.1737.

(S)-(−)-3-Phenyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.01^5]dec-2-one (3.75, Table 3.14,
entry 3). Prepared following the procedure described by Chen et al.116 (S)-(−)-3-Phenyl-10,10-
dimethyl-3,4-diaza-tricyclo[5.2.1.01^5]dec-4-en-2-one 3.74 (400 mg, 1.57 mmol) was dissolved in 10
mL of MeOH. NaBH4 (594 mg, 15.7 mmol) was added over the course of one hour and the mixture
was stirred at room temperature for 48 hours. The solvent was partially removed in vacuo and the
mixture was diluted with CH2Cl2, washed with distilled water and brine, dried over Na2SO4 and
concentrated. Purification by silica gel chromatography (15% EtOAc in hexanes) provided the title
compound as a white solid (129 mg, 32 %). 1H NMR (300 MHz, CDCl3) δ 7.82-7.77 (m, 2H), 7.36-
7.30 (m, 2H), 7.14-7.03 (m, 1H), 4.20 (br s, 1H), 3.73 (dd, J = 8.4, 4.5 Hz, 1H), 2.33-2.17 (m, 2H),
2.06-1.87 (m, 2H), 1.83 (dd, J = 13.1 Hz, 1H), 1.56-1.23 (m, 2H), 1.24 (s, 3H), 1.10 (s, 3H). 1H
NMR, 13C NMR and IR data were identical to those previously reported.116
General procedure for the preparation of catalysts. (S)-(+-)-10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]decan-2-one (3.83, Table 3.14, entry 1). To a solution of 10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]dec-4-en-2-one 3.80-4 (1.05 g, 5.89 mmol) in a 2:1 mixture of acetic acid and methanol (60 mL) was added sodium cyanoborohydride (3.70 g, 58.9 mmol) in small portions over 1 h. The reaction mixture was then stirred at room temperature until TLC indicated that the reaction was complete (16 hours). Excess borohydride was quenched by the addition of 10 % HCl. The products were extracted using CH2Cl2 and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH2Cl2. The organic extracts were combined, washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the product was purified by flash chromatography (10% MeOH in CHCl3) to afford the desired compound as a white solid (914 mg, 86 %). mp 206-209 °C; [α]D = +33.9 (c 1.04, CHCl3); IR (neat) 3427, 1659 cm−1; 1H NMR (300 MHz, CDCl3) δ 5.76 (br, 1H), 3.73 (dd, J = 8.4, 4.7 Hz, 1H) 2.17-2.05 (m, 2H) 1.98-1.84 (m, 2H) 1.72 (dd, J = 13.1, 8.4 Hz, 1H) 1.34-1.19 (m, 2H), 1.27 (s, 3H), 1.06 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 175.6 (C), 69.0 (CH), 57.6 (C), 50.6 (C), 46.9 (CH), 36.4 (CH2), 28.3 (CH2), 26.6 (CH2), 21.0 (CH3), 20.4 (CH3); MS (EI) m/z 180.1 (M+) HRMS (EI) calcd. for C10H16N2O (M+) 180.1263; found 180.1248.

(S)-(+-)-3,10,10-Trimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]decan-2-one (3.79, Table 3.14, entry 2). Prepared by a procedure similar to that described above for 3.83 from 3,10,10-Trimethyl-3,4-diaza-tricyclo[5.2.1.0
1,5]dec-4-en-2-one 3.78 (450 mg, 2.34 mmol). Purification by silica gel chromatography (50% EtOAc in hexanes) provided the title compound as a white solid (434 mg, 95 %). mp 101-104°C; [α]D = +33.3 (c 1.01, CHCl3); IR (neat) 3431, 1656 cm−1; 1H NMR (300 MHz, CDCl3) δ 4.10 (br, 1H), 3.57 (dd, J = 8.4, 4.7 Hz, 1H) 2.98 (s, 3H) 2.17-2.03 (m, 2H) 1.96–1.83 (m,
(S)-(+) -3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^1,5]decan-2-one (3.86, Table 3.14, entry 4). Prepared by a procedure similar to that described above for 3.83 from 3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^1,5]dec-4-en-2-one 3.81-1 (2.40 g, 8.94 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the desired compound as a white solid (2.28 g, 94%). mp 113-115°C; [α]_D = +12.6 (c 1.03, CHCl_3); IR (neat) 3210, 1656 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 7.30-7.22 (m, 5H), 4.68 (d, J = 14.3 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.48 (dd, J = 8.3, 4.7 Hz, 1H) 2.14 (dt, J = 11.6, 4.8 Hz, 1H), 1.97 (ddd, J = 12.9, 7.6, 3.4 Hz, 1H), 1.90-1.82 (m, 2H), 1.62 (dd, J = 13.1, 8.4 Hz, 1H), 1.27 (ddd, J = 11.9, 9.1, 2.7 Hz, 1H), 1.22-1.17 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H); ^13C NMR (125 MHz, CDCl_3) δ 170.6 (C), 135.9 (C), 128.6 (CH), 128.3 (CH), 127.7 (CH), 65.2 (CH), 58.3 (C), 51.1 (C), 47.9 (CH_2), 46.7 (CH), 36.3 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.2 (CH_3); MS (EI) m/z 270.2 (M^+); HRMS (EI) calcd. For C_{17}H_{22}N_2O (M^+) 270.1732; found 270.1723.

(S)-(+) -3-(4-methoxybenzyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^1,5]decan-2-one (Table 3.14, entry 5). Prepared by a procedure similar to that described above for 3.83 from 3-(4-methoxybenzyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^1,5]dec-4-en-2-one 3.81-2 (500 mg, 1.68
mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the desired compound as a clear oil (459 mg, 91%). IR (neat) 3231, 1655 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.21-7.16 (m, 2H), 6.83-6.78 (m, 2H), 4.59 (d, \(J = 14.4\) Hz, 1H), 4.37 (d, \(J = 14.3\) Hz, 1H), 3.74 (s, 3H), 3.47 (dd, \(J = 8.3, 4.7\) Hz, 1H), 2.17-1.09 (m, 1H), 2.00-1.93 (m, 1H), 1.90-1.80 (m, 2H), 1.61 (dd, \(J = 13.0, 8.4\) Hz, 1H), 1.29-1.12 (m, 2H), 1.06 (s, 3H), 1.04 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.4 (C), 159.2 (C), 129.7 (CH), 128.0 (C), 114.0 (CH), 65.2 (CH), 58.4 (C), 55.2 (CH\(_3\)), 51.1 (C), 47.2 (CH\(_2\)), 46.7 (CH), 36.3 (CH\(_2\)), 28.5 (CH\(_2\)), 26.6 (CH\(_2\)), 20.9 (CH\(_3\)), 20.2 (CH\(_3\)); MS (EI) \(m/z\) 300.2 (M\(^+\)); HRMS (EI) calcd. for C\(_{18}\)H\(_{24}\)N\(_2\)O\(_2\) (M\(^+\)) 300.1838 found 300.1843.

![Chemical structure](image)

(S)-(+-)10,10-Dimethyl-3-naphthalen-1-ylmethyl-3,4-diaza-tricyclo[5.2.1.0\(^1,5\)]decan-2-one (Table 3.14, entry 7). Prepared by a procedure similar to that described above for 3.83 from 10-Dimethyl-3-naphthalen-1-ylmethyl-3,4-diaza-tricyclo[5.2.1.0\(^1,5\)]dec-4-en-2-one 3.81-3 (1.60 g, 5.02 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes provided the title compound as a white solid (1.43 g, 89%). mp 144-145 °C; \([\alpha]_D^0 +39.5\) (c = 1.00, CHCl\(_3\)); IR (neat) 3245, 1667 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.27 (d, \(J = 4.8\) Hz, 1H), 7.81 (dd, \(J = 10.2, 4.8\) Hz, 2H), 7.56-7.37 (m, 4H), 5.26 (br, 1H), 4.78 (br, 1H), 3.88 (br, 1H), 3.43-3.40 (m, 1H), 2.17 (ddd, \(J = 7.2, 7.2, 3.0\) Hz, 1H), 1.97-1.81 (m, 3H), 1.58 (dd, \(J = 7.5, 4.8\) Hz, 1H), 1.28-1.15 (m, 2 H), 1.08 (s, 3H), 1.02 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.0 (C), 133.7 (C), 131.4 (C), 128.9 (CH), 128.4 (CH), 127.9 (CH), 126.6 (CH), 126.0 (CH), 125.0 (CH), 124.1 (CH), 64.9 (CH), 58.6 (C), 51.3 (C), 46.6 (CH), 46.2 (CH\(_2\)), 36.4 (CH\(_2\)), 28.5 (CH\(_2\)), 26.6 (CH\(_2\)), 20.8 (CH\(_3\)), 20.1 (CH\(_3\)); MS \(m/z\) 320.2 (M\(^+\)); HRMS calcd for C\(_{21}\)H\(_{24}\)N\(_2\)O 320.1889; found 320.1894.
General Procedure for Hydrazide-Catalyzed Diels-Alder Reactions. (1R, 2R, 3R,4S)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 1). To a suspension of E-cinnamaldehyde (500 mg, 3.78 mmol) in distilled water (3.8 ml) was added 3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0\(^1,5\)]decan-2-one (204 mg, 0.756 mmol) followed by CF\(_3\)SO\(_3\)H (67 \(\mu\)L, 0.76 mmol). After stirring for 1 to 2 minutes cyclopentadiene (749 mg, 11.3 mmol) was slowly added and the resulting mixture was stirred at room temperature until the reaction was judged to be complete by TLC analysis. The reaction mixture was extracted twice with ether and the combined organic extracts were washed successively with water and brine then dried over Na\(_2\)SO\(_4\). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1.9:1 mixture of exo and endo isomers (colourless oil, 721 mg, 96 %). exo ee 90%, endo ee 88%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 100°C hold 3 min then 2°C/min gradient, flow = 3.0 mL/min) exo isomers tr = 42.7 min, 43.8 min, endo isomers tr = 43.4 min, 44.3 min. The same enantiomeric ratios were obtained by acetalization with (+)-(R,R)-hydrobenzoin and \(^1\)H NMR analysis\(^\text{145}\) (500 MHz, C\(_6\)D\(_6\)) exo isomers \(\delta\) 5.57 (d, J = 4.8 Hz, CHO\(_2\), major isomer), endo isomers \(\delta\) 5.21 (d, J = 8.1 Hz, CHO\(_2\), major isomer), 5.56 (d, J = 4.8 Hz, CHO\(_2\), minor isomer), 5.17 (d, J = 8.2 Hz, CHO\(_2\), minor isomer). \(^1\)H NMR, \(^13\)C NMR and IR data were identical to those previously reported\(^\text{24,146}\).

(1R, 2R, 3R, 4S)-3-(4-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-(4-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 2). Prepared according to the general procedure described above from E-4-nitrocinamaldehyde (100}
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mg, 0.564 mmol) and cyclopentadiene (112 mg, 1.69 mmol). Purification by silica gel chromatography (15% EtOAc in hexanes) provided the desired material as a 2.2:1 mixture of exo and endo isomers (pale yellow oil, 128 mg, 93 %). exo ee 92 %, endo ee 87%. Enantiomeric ratios were determined by acetalization with (+)-(R,R)-hydrobenzoin and $^1$H NMR analysis: (500 MHz, C$_6$D$_6$) exo isomers δ 5.48 (d, J = 5.2 Hz, CHO$_2$, major isomer), 5.46 (d, J = 6.0 Hz, CHO$_2$, minor isomer), endo isomers δ 5.14 (d, J = 8.1 Hz, CHO$_2$, major isomer), 5.07 (d, J = 8.2 Hz, CHO$_2$, minor isomer). [$\alpha$]$_D$ -198 (c 1.11 CHCl$_3$); IR (neat) 1720, 1591, 1511, 1344 cm$^{-1}$; exo isomer $^1$H NMR (300 MHz, CDCl$_3$) δ 9.87 (d, J = 1.5 Hz, 1H), 8.06-8.01 (m, 2H), 7.25 (dd, J = 8.4, 0.6 Hz, 2H), 6.36 (dd, J = 5.7, 3.3 Hz, 1H), 6.00 (dd, J = 5.7, 2.7 Hz, 1H), 3.84 (dd, J = 4.5, 4.5 Hz, 1H), 3.26-3.13 (m, 2H), 2.59 (dd, J = 5.1, 0.6 Hz, 1H), 1.74-1.63 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.0 (CH), 151.0 (C), 146.8 (C), 137.4 (CH), 136.3 (CH), 129.1 (CH), 123.7 (CH), 59.9 (CH), 48.8 (CH), 48.0 (CH$_2$), 45.9 (CH), 45.5 (CH); endo isomer $^1$H NMR (300 MHz, CDCl$_3$) δ 9.60 (d, J = 1.5 Hz, 1H), 8.11-8.08 (m, 2H), 7.38 (dd, J = 8.4, 0.6 Hz, 2H), 6.39 (dd, J = 5.7, 3.3 Hz, 1H), 6.15 (dd, J = 5.7, 3.0 Hz, 1H), 3.39 (br, 1H), 3.26-3.13 (m, 2H), 2.94-2.90 (m, 1H), 1.74-1.63 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.6 (CH), 152.0 (C), 146.7 (C), 139.4 (CH), 134.3 (CH), 128.6 (CH), 124.1 (CH), 61.5 (CH), 48.3 (CH), 47.5 (CH$_2$), 45.9 (CH), 45.4 (CH). MS (ESI) m/z 244.1 (MH$^+$).

(1R, 2R, 3R, 4S)-3-(3-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-(3-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 3). Prepared according to the general procedure described above from E-3-nitrocinnamaldehyde (100 mg, 0.564 mmol) and cyclopentadiene (112 mg, 1.69 mmol) using CH$_2$Cl$_2$ in place of ether during the extraction. Purification by silica gel chromatography (15% EtOAc in hexanes) provided the desired material as a 2.1:1 mixture of exo and endo isomers (colourless oil, 121 mg, 88 %). exo ee 90%, endo ee 94%. Enantiomeric ratios were determined by acetalization with (+)-(R,R)-hydrobenzoin and $^1$H NMR analysis: (500 MHz, C$_6$D$_6$) exo isomers δ 5.46 (d, J = 4.5 Hz, CHO$_2$, major isomer), 5.38 (d, J = 5.1 Hz, CHO$_2$, minor isomer) endo isomers δ 5.09 (d, J = 7.6 Hz, CHO$_2$, major isomer), 5.05 (d, J = 7.5 Hz, CHO$_2$, minor isomer).
major isomer), 5.00 (d, J = 7.6 Hz, CHO₂, minor isomer). [α]D -149 (c 1.24 CHCl₃); IR (neat) 1713 cm⁻¹; **exo isomer** ¹H NMR (300 MHz, CDCl₃) δ 9.90 (d, J = 1.5 Hz, 1H), 8.11-7.95 (m, 2H), 7.59-7.37 (m, 2H), 6.43-6.40 (m, 1H), 6.03 (dd, J = 5.7, 3.0 Hz, 1H), 3.86 (dd, J = 4.5, 3.9 Hz, 1H), 3.28-3.15 (m, 2H), 2.62 (dd, J = 5.1, 0.6 Hz, 1H), 1.70-1.66 (m, 1H), 1.61-1.57 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 201.5 (CH), 148.1 (C), 144.8 (C), 137.1 (CH), 135.9 (CH), 134.3 (CH), 129.0 (CH), 122.5 (CH), 121.5 (CH), 59.6 (CH), 48.4 (CH), 47.5 (CH₂), 45.5 (CH), 44.7 (CH); **endo isomer** ¹H NMR (300 MHz, CDCl₃) δ 9.62 (d, J = 1.8 Hz, 1H), 8.11-7.95 (m, 2H), 7.59-7.37 (m, 2H), 6.43-6.40 (m, 1H), 6.17 (dd, J = 5.7, 2.7 Hz, 1H), 3.41 (br, 1H), 3.28-3.15 (m, 2H), 2.98-2.95 (m, 1H), 1.78-1.75 (m, 1H), 1.61-1.57 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 202.2 (CH), 148.1 (C), 145.9 (C), 139.1 (CH), 134.3 (CH), 133.9 (CH), 129.5 (CH), 122.5 (CH), 121.4 (CH), 61.0 (CH), 48.2 (CH), 47.1 (CH₂), 45.2 (CH), 45.0 (CH).

(1R, 2R, 3R, 4S)-3-(2-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-(2-Nitrophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 4). Prepared according to the general procedure described above from E-2-nitrocinnamaldehyde (100 mg 0.564 mmol) and cyclopentadiene (112 mg, 1.69 mmol). Purification by silica gel chromatography (15% EtOAc in hexanes) provided the desired material as a 1.2:1 mixture of exo and endo isomers (pale yellow oil, 123 mg, 90 %). **exo ee** 87%, **endo ee** 86%. Enantiomeric ratios were determined by acetalization with (+)-(R,R)-hydrobenzoin and ¹H NMR analysis: (500 MHz, C₆D₆) exo isomers δ 5.55 (d, J = 5.2 Hz, CHO₂, major isomer), 5.51 (d, J = 6.3 Hz, CHO₂, minor isomer), endo isomers δ 5.22 (d, J = 8.1 Hz, CHO₂, major isomer), 5.14 (d, J = 8.3 Hz, CHO₂, minor isomer). [α]D +1.86 (c 1.40 CHCl₃); IR (Neat) 1713 cm⁻¹; ¹³C NMR (125 MHz, CDCl₃) δ 203.5 (CH), 201.4 (CH), 151.0 (C), 150.2 (C), 139.1 (CH), 137.2 (C), 136.8 (CH), 136.2 (CH), 135.9 (C), 134.0 (CH), 132.8 (CH), 131.6 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 124.7 (CH), 123.8 (CH), 59.1 (CH), 58.9 (CH), 49.7 (CH), 49.1 (CH), 48.0 (CH₂), 47.1 (CH), 46.5 (CH), 46.1 (CH), 41.5 (CH), 39.9 (CH); **exo isomer** ¹H NMR (500 MHz, CDCl₃) δ 9.78 (d, J = 2.3 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.57-7.50 (m, 1H), 7.43-7.24 (m, 1H), 7.16-7.14 (d, J = 7.2 Hz, 1H), 6.48-6.44 (m, 1H), 5.99 (dd, J =
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5.4, 2.4 Hz, 1H), 4.07-4.06 (m, 1H), 3.54 (s, 1H), 3.26 (s, 1H), 2.59-2.58 (m, 1H), 1.65-1.63 (m, 1H),
1.55 (d, J = 9.2 Hz, 1H); **endo isomer** 1H NMR (500 MHz, CDCl3) δ 9.37 (d, J = 3.4 Hz, 1H), 7.79
d (J = 7.8 Hz, 1H), 7.57-7.50 (m, 1H), 7.43-7.24 (m, 2H), 6.48-6.44 (m, 1H), 6.19 (dd, J = 5.4, 2.9
Hz, 1H), 3.41 (d, J = 4.9 Hz, 1H), 3.30 (s, 1H), 3.10 (s, 1H), 2.93-2.91 (m, 1H), 1.81 (d, J = 9.1 Hz,
1H), 1.63 (d, J = 8.9 Hz, 1H). MS (ESI) m/z (MH+) 244.2.

(1R, 2R, 3R, 4S)-3-(4-isopropylphenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S,
3S, 4R)-3-(4-isopropylphenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 5).
Prepared according to the general procedure described above from £-4-isopropylcinnamaldehyde (75
mg, 0.43 mmol) and cyclopentadiene (85 mg, 1.3 mmol). Purification by silica gel chromatography
(5% EtOAc in hexanes) provided the desired material as a 1.7:1 mixture of **endo and exo isomers**
colourless oil, 87 mg, 84%). **endo** ee 90%. Enantiomeric ratios were determined by acetalization
with (+)-(R,R)-hydrobenzoin and 1H NMR analysis: (500 MHz, C6D6) **exo** isomers chemical shift
were identical, **endo** isomers δ 5.35 (d, J = 8.1 Hz, CHO2, major isomer), 5.31 (d, J = 8.2 Hz, CHO2,
minor isomer). [α]D -170.6 (c 1.09 CHCl3); IR (neat) 1713 cm⁻¹; **exo isomer** 1H NMR (500 MHz,
CDCl3) δ 9.91 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.32 (dd, J =
5.5, 3.0 Hz, 1H), 6.08 (dd, J = 5.5, 2.5 Hz, 1H), 3.67 (dd, J = 5.5, 4.0 Hz, 1H), 3.20 (br, 2H), 2.90-
2.83 (m, 1H), 2.58-2.56 (m, 1H), 1.61-1.59 (m, 1H), 1.55-1.53 (m, 1H), 1.21 (d, J = 7.0 Hz, 6H); 13C
NMR (125 MHz, CDCl3) δ 202.9 (CH), 146.8 (C), 139.8 (C), 139.1 (CH), 136.5 (CH), 127.7 (CH),
126.1 (CH), 59.5 (CH), 48.4 (CH), 47.5 (CH2), 45.4 (CH), 45.0 (CH), 33.5 (CH), 23.9 (CH3); **endo
isomer** 1H NMR (500 MHz, CDCl3) δ 9.58 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.16 (d, J =
8.5 Hz, 2H), 6.40 (dd, J = 5.5, 2.5 Hz, 1H), 6.15 (dd, J = 5.5, 2.5 Hz, 1H), 3.31 (br, 1H), 3.09 (br,
1H), 3.05-3.04 (m, 1H), 2.98-2.96 (m, 1H), 2.90-2.83 (m, 1H), 1.80 (d, J = 8.5 Hz, 1H), 1.61-1.60
(m, 1H), 1.23 (d, J = 8.0 Hz, 6H); 13C NMR (125 MHz, CDCl3) δ 203.6 (CH), 146.7 (C), 140.7 (C),
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136.1 (CH), 133.6 (CH), 127.2 (CH), 126.5 (CH), 60.6 (CH), 48.5 (CH), 47.0 (CH₂), 45.3 (CH), 45.0 (CH), 33.5, (CH), 23.9 (CH₃). MS m/z (FAB⁺) (MH⁺) 241.2.

(1R, 2R, 3R, 45)-3-(4-chlorophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-(4-Chlorophenyl)-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 6). Prepared according to the general procedure described above from E-4-chlorocinnamaldehyde (125 mg, 0.750 mmol) and cyclopentadiene (149 mg, 2.25 mmol). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 2:1 mixture of exo and endo isomers (colourless oil, 161 mg, 92 %). exo ee 87 %, endo ee 90 %. Enantiomeric ratios were determined by acetalization with (+)-(R,R)-hydrobenzoin and ¹H NMR analysis: (500 MHz, C₆D₆)

exo isomers δ 5.54 (d, J = 5.0 Hz, CHO₂, major isomer), 5.52 (d, J = 5.9 Hz, CHO₂, minor isomer),
endo isomers δ 5.19 (d, J = 8.2 Hz, CHO₂, major isomer), 5.13 (d, J = 8.3 Hz, CHO₂, minor isomer).

[α]D -181.0 (c 1.07 CHCl₃); IR (neat) 1713 cm⁻¹; exo isomer ¹H NMR (300 MHz, CDCl₃) δ 9.87 (d, J = 2.1 Hz, 1H), 7.23-7.15 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.32 (dd, J = 5.7, 3.0 Hz, 1H), 6.01 (dd, J = 5.7, 3.0 Hz, 1H), 3.68 (dd, J = 4.8, 3.6 Hz, 1H), 3.20-3.15 (m, 1H), 3.07-3.02 (m, 1H), 2.52-2.50 (m, 1H), 1.55-1.51 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 202.7 (CH), 141.5 (C), 136.9 (CH), 136.7 (CH), 132.4 (C), 129.6 (CH), 128.6 (CH), 60.0 (CH), 48.8 (CH), 47.9 (CH₂), 45.8 (CH), 45.1 (CH);
endo ¹H NMR (300 MHz, CDCl₃) δ 9.56 (d, J = 1.8 Hz, 1H), 7.26-7.15 (m, 4H), 6.38 (dd, J = 5.7, 3.3 Hz, 1H), 6.14 (dd, J = 5.7, 3.0 Hz, 1H), 3.32 (br, 1H), 3.20-3.15 (m, 2H), 2.90-2.87 (m, 1H), 1.62-1.58 (m, 1H), 1.55-1.51 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 203.4 (CH), 142.5 (C), 139.5 (CH), 134.2 (CH), 132.3 (C), 129.1 (CH), 129.0 (CH), 61.4 (CH), 48.6 (CH), 47.5 (CH₂), 45.5 (CH), 45.4 (CH). MS (CI) m/z 233 (MH⁺); HRMS (FAB⁺) calcd. for C₁₄H₁₄ClO (MH⁺) 233.0733; found 233.0816.
(1R, 2S, 3R, 4S)-3-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S, 2S, 3R, 4R)-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (Table 3.21, entry 7). Prepared according to the general procedure described above from E-crotonaldehyde (100 mg 1.42 mmol) and cyclopentadiene (282 mg, 4.28 mmol). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1.8:1 mixture of exo and endo isomers (clear oil, 151 mg, 78%). exo ee 82%, endo ee 80%. Enantiomeric ratios were determined by acetalization with (+)-(R,R)-hydrobenzoin and $^1$H NMR analysis: $^1$H NMR (500 MHz, CHCl$_3$) exo isomers δ 5.53 (d, J = 6.2 Hz, CHO$_2$, major isomer), 5.52 (d, J = 6.2 Hz, CHO$_2$, minor isomer), endo isomers δ 5.17 (d, J=8.2 Hz, CHO$_2$, major isomer), 5.12 (d, J=8.2 Hz, CHO$_2$, minor isomer). $^1$H NMR, $^{13}$C NMR and IR data were identical to those previously reported.$^{24,146}$

(1R, 2R, 3R, 4S)-3-propyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-propyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 8). Prepared according to the general procedure described above from E-2-hexenal (50 mg, 0.51 mmol) and cyclopentadiene (101 mg, 1.53 mmol). Purification by silica gel chromatography (5% EtOAc in hexanes) provided a colourless oil (69 mg, 83%); 1.6:1 exo:endo, exo ee 81% endo ee 75%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 100 °C hold 3 min then 1 °C/min gradient, flow = 3.0 mL/min) exo isomers tr = 26.2 min, 27.6 min, endo isomers tr = 26.9 min, 28.8 min. $^1$H NMR, $^{13}$C NMR and IR data were identical to those previously reported.$^{24,146}$
(1R, 2R, 3R, 4S)-3-isopropyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-isopropyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 9). Prepared according to the general procedure described above from E-4-methyl-2-pentenal (85 mg, 0.87 mmol) and cyclopentadiene (171 mg, 2.60 mmol). Purification by silica gel chromatography (5% EtOAc in hexanes) provided a colourless oil (120 mg, 84%). 2.6:1 exo:endo, exo ee 85%, endo ee 84%. Enantiomeric ratios were determined by reduction (4 eq. of NaBH₄ in MeOH) and subjection of to the corresponding alcohols to chiral GLC analysis (Agilent/J&W CycloSil-B, 100°C hold 3 min then 1°C/min gradient, flow = 3.0 mL/min) exo isomers tr = 39.6 min, 42.2 min, endo isomers tr = 38.9 min, 39.3 min. 'H NMR, ¹³C NMR and IR data were identical to those previously reported.¹⁴,¹⁶

(1R, 2R, 3R, 4S)-3-cyclohexyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1S, 2S, 3S, 4R)-3-cyclohexyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (Table 3.21, entry 10). Prepared according to the general procedure described above from E-cyclohexylcinnamaldehyde (50 mg 0.362 mmol) and cyclopentadiene (93 mg, 1.09 mmol). Purification by silica gel chromatography (15% EtOAc in hexanes) provided the desired material as a 3.3:1 mixture of exo and endo isomers (clear oil, 64 mg, 87 %). exo ee 83%, endo ee 84%. Enantiomeric ratios were determined by chiral GLC analysis (Agilent/J&W CycloSil-B, ramp from 100-200°C at 5°C/min. then hold at 200°C for 10 min., flow = 2.0 mL/min) exo isomers tr = 21.0 min, 21.4 min, endo isomers tr = 21.7 min, 22.0 min. 'H NMR, ¹³C NMR and IR data were identical to those previously reported.¹⁴,¹⁶
(1R, 6R)-6-(4-nitrophenyl)-4-phenylcyclohex-3-enecarboxaldehyde (Table 3.22, entry 1). Prepared according to the general procedure described above from E-4-nitrocinamaldehyde (50 mg, 0.28 mmol) and 1-(methylene-allyl)-benzene\textsuperscript{154} (146 mg, 1.12 mmol). Purification by silica gel chromatography (15% EtOAc in hexanes) provided the material as a pale yellow solid (74 mg, 86%). mp 159-161 °C; 85% ee. Enantiomeric ratio was determined by acetalization with (+)-(R,R)-hydrobenzoin and \textsuperscript{1}H NMR analysis: (500 MHz, C\textsubscript{6}D\textsubscript{6}) δ 5.29 (d, J = 3.1 Hz, CHO\textsubscript{2}, major isomer), 5.13 (d, J = 2.4 Hz, CHO\textsubscript{2}, minor isomer). [\textalpha]\textsubscript{D}\textsubscript{+}8.6 (c 0.88 CHCl\textsubscript{3}); IR (neat) 1724, 1597, 1519, 1350 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 9.57 (d, J = 2.2 Hz, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 9.3 Hz, 2H), 7.37-7.25 (m, 5H), 6.21 (br, 1H), 3.45 (ddd, J = 9.0, 9.0, 5.6 Hz, 1H), 2.96-2.91 (m, 1H), 2.84-2.80 (m, 1H), 2.66-2.43 (m, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 202.6 (CH), 151.0 (C), 146.8 (C), 140.4 (C), 136.1 (C), 128.7 (CH), 128.4 (CH), 127.4 (CH), 124.9 (CH), 124.0 (CH), 121.5 (CH), 50.6 (CH), 40.3 (CH), 33.9 (CH), 25.0 (CH); MS (EI) m/z 307.1 (M\textsuperscript{+}); HRMS calcd. for C\textsubscript{19}H\textsubscript{17}NO\textsubscript{3} (M\textsuperscript{+}) 307.1209; found 307.1191.


(1S)-4-methyl-3-cyclohexene-1-carboxaldehyde (Table 3.22, entry 2). Prepared according to the general procedure described above from acrolein (123 mg, 2.20 mmol) and isoprene (50 mg, 0.734 mmol). Purification by silica gel chromatography (10% EtOAc in hexanes) provided the material as a clear oil (61 mg, 67%). 37% ee. Enantiomeric ratios were determined by reduction (4 eq. of NaBH\textsubscript{4} in MeOH) and subjection of to the corresponding alcohols to chiral GLC analysis (Agilent/J&W CycloSil-B, hold 3min, ramp to 120°C at 1°/min. then hold at 120°C for 10 min., flow = 3.0 mL/min)
tr = 23.8 min, 24.6 min. \(^1\)H NMR, \(^{13}\)C NMR and IR data were identical to those previously reported.\(^{24}\)

\[(1R, \ 6R)\]-2,4-Dimethyl-6-(4-nitrophenyl)-cyclohex-3-ene-carboxaldehyde and \((1S, \ 6S)\)-2,4-Dimethyl-6-(4-nitrophenyl)-cyclohex-3-ene-carboxaldehyde (Table 3.22, entry 3). Prepared according to the general procedure described above from \(E\)-4-nitrocinamaldehyde (100 mg, 0.564 mmol) and \(trans\)-2-methyl-1,3-pentadiene (231 mg, 2.82 mmol) using \(CH_2Cl_2\) in place of ether during the extraction. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 1.9:1 mixture of \(exo\) and \(endo\) isomers (pale yellow solid, 102 mg, 71%). mp 92-97 °C; \(exo\) ee 24% \(endo\) ee 69%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 210°C isotherm, flow = 3.0 mL/min) \(exo\) isomers tr = 24.7 min, 28.6 min, \(endo\) isomers tr = 23.8 min, 27.3 min; [\(\alpha\)]\(D\) -38.7 (c 0.85 CHCl\(_3\)); IR (neat) 1720, 1595, 1515 cm\(^{-1}\). \(exo\) isomer \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.63 (d, \(J = 2.9\) Hz, 1H), 8.16-8.13 (m, 2H), 7.36-7.33 (m, 2H), 5.48-5.47 (br, 1H), 3.44-3.40 (m, 1H), 2.84 (ddd, \(J = 8.3,\ 5.4,\ 2.9\) Hz, 1H), 2.61 (br, 1H), 2.29 (dd, \(J = 18.1,\ 6.3\) Hz, 1H), 2.20-2.01 (m, 1H), 1.70 (s, 3H), 1.04 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 204.0 (CH), 152.1 (C), 146.5 (C), 132.16 (C), 128.2 (CH), 126.1 (CH), 123.7 (CH), 58.8 (CH), 37.0 (CH), 36.6 (CH\(_2\)), 29.5 (CH), 23.0 (CH\(_3\)), 17.1 (CH\(_3\)) \(endo\) isomer \(^1\)H NMR (125 MHz, CDCl\(_3\)) \(\delta\) 9.39 (d, \(J = 4.9\) Hz, 1H), 8.16-8.13 (m, 2H), 7.36-7.33 (m, 2H), 5.31 (br, 1H), 3.22 (ddd, \(J = 11.2,\ 11.2,\ 5.9\) Hz, 1H), 2.61 (br, 1H), 2.43 (ddd, \(J = 11.4,\ 10.2,\ 4.4\) Hz, 1H), 2.20-2.01 (m, 2H), 1.71 (s, 3H), 1.02 (d, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.7 (CH), 150.1 (C), 146.5 (C), 132.1 (C), 128.3 (CH), 125.6 (CH), 124.0 (CH), 54.8 (CH), 41.9 (CH), 38.2 (CH\(_2\)), 31.5 (CH), 22.9 (CH\(_3\)), 19.9 (CH\(_3\)). MS \(m/z\) 259.1 (M\(^+\)); HRMS calcd. for C\(_{15}\)H\(_{15}\)NO\(_3\) (M\(^+\)) 259.1208; found 259.1196.
(2S)-Bicyclo[2,2,2]oct-5-ene-2-carbaldehyde (Table 3.22, entry 4). Prepared according to the general procedure described above from acrolein (123 mg, 2.20 mmol) and 1,3-cyclohexadiene (50 mg, 0.734 mmol). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 23:1 mixture of endo and exo isomers (colourless oil, 81 mg, 81%). endo ee 16%. Enantiomeric ratios were determined by reduction (4 eq. of NaBH₄ in MeOH) and subjection of to the corresponding alcohols to chiral GLC analysis (Agilent/J&W CycloSil-B, hold 3min, ramp to 140°C at 10/min. then hold at 140°C for 5 min., flow = 3.0 mL/min) endo isomers tr = 37.8 min, 39.2 min. H NMR, C NMR and IR data were identical to those previously reported.²⁴

NMR study of the inimium ion formed from (S)-(+)3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo [5.2.1.0₁,₅]decan-2-one (3.86), E-cinnamaldehyde and triflic acid. To a solution of E-cinnamaldehyde (12.2 mg, 0.092 mmol) and (S)-(+)3-Benzyl-10,10-dimethyl-3,4-diaza-tricyclo [5.2.1.0₁,₅]decan-2-one 3.86 (25.0 mg, 0.092 mmol) in CD₃NO₂ (1.0 mL) was added CF₃SO₃H (8.2 μL, 0.09 mmol). The reaction was monitored at room temperature by H NMR using 2, 5 and 10 minute intervals until equilibrium was reached. H NMR (300 MHz, CD₃NO₂) δ 8.22 (dd, J = 10.2, 2.1 Hz, 1H), 7.81 (d, J = 15.3 Hz, 1H), 7.77-7.40 (m, 2H), 7.59-7.42 (m, 8H), 7.12 (dd, J = 15.3, 10.5 Hz, 1H), 5.31 (d, J = 17.0 Hz, 1H), 5.27 (d, J = 17.0 Hz, 1H), 5.04-4.99 (m, 1H), 2.84-2.73 (m, 1H), 2.66 (dd, J = 13.5, 8.4 Hz, 1H), 2.42 (ddd, J = 11.9, 11.9, 5.4 Hz, 1H), 2.23-2.19 (m, 2H), 1.84-1.76 (m, 1H), 1.66-1.57 (m, 1H), 1.22 (s, 3H), 1.06 (s, 3H).
NMR study of the iminium ion formed from (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride (3.18) and E-cinnamaldehyde. To a solution of E-cinnamaldehyde (13.0 mg, 0.098 mmol) in CD$_3$OD (1.0 mL) was added (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride 3.18 (25.0 mg, 0.098 mmol). The reaction was monitored at room temperature by $^1$H NMR using 2, 5 and 10 minute intervals until equilibrium was reached. Only peaks assigned to the iminium salt are reported. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 9.39 (d, $J = 10.6$ Hz, 1H), 8.39 (d, $J = 14.9$ Hz, 1H), 8.07-8.02 (d, 1H), 7.76-7.2 (m, 7H), 7.13- 7.07 (m, 2H), 5.57-5.50 (br, 1H), 3.67 (dd, $J = 14.8$, 5.6, 1H), 3.58-3.53 (m, 1H), 2.89 (s, 3H), 1.82 (s, 3H), 0.89 (s, 3H).
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![Structural Diagram](image)

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NMR Study of Iminium Ion 4.3 Formation (Figure 4.3). To a solution of E-cinnamaldehyde (12.2 mg, 0.092 mmol) and 4.1 (25.0 mg, 0.092 mmol) in 19:1 CD$_3$NO$_2$:D$_2$O (1.0 mL) was added trifluoromethanesulfonic acid (8.2 µL, 0.092 mmol). The reaction was monitored at 23 °C by $^1$H NMR using an automated experiment that acquired spectra at 4 min intervals until equilibrium was reached. $^1$H NMR (300 MHz, CD$_3$NO$_2$) δ 8.22 (dd, $J = 10.2, 2.1$ Hz, 1H), 7.81 (d, $J = 15.3$ Hz, 1H), 7.77-7.40 (m, 2H), 7.12 (dd, $J = 15.3, 10.5$ Hz, 1H), 5.31 (d, $J = 17.0$ Hz, 1H), 5.27 (d, $J = 17.0$ Hz, 1H), 5.04-4.99 (m, 1H), 2.84- 2.73 (m, 1H), 2.66 (dd, $J = 13.5, 8.4$ Hz, 1H), 2.42 (ddd, $J = 11.9, 11.9, 5.4$ Hz, 1H), 2.23-2.19 (m, 2H), 1.84-1.76 (m, 1H), 1.66-1.57 (m, 1H), 1.22 (s, 3H), 1.06 (s, 3H). $^{13}$C NMR (75 MHz, CD$_3$NO$_2$) δ 170.1, 158.6, 146.4, 135.3, 133.2, 131.1, 130.8, 130.7, 130.3, 129.0, 115.7, 74.2, 58.6, 55.1, 48.6, 47.8, 38.5, 27.8, 27.1, 20.6, 20.0.

NMR Study of Cycloaddition To Form 4.7 and 4.8 (Figure 4.4). To a suspension of E-cinnamaldehyde (12.2 mg, 0.092 mmol) in 19:1 CD$_3$NO$_2$:D$_2$O (1 mL) was added 4.1 (5 mg, 0.018 mmol) followed by trifluoromethanesulfonic acid (1.6 µL, 0.018 mmol). After stirring for 1-2 min, cyclopentadiene (18.3 mg, 0.277 mmol) was added, and the resulting mixture was monitored at 23 °C by $^1$H NMR using an automated experiment that acquired spectra at 40 min intervals for 48 h. The reaction mixture was then extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na$_2$SO$_4$. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 2.4:1 mixture of exo and endo isomers 4.7 and 4.8 (colorless oil, 16 mg, 88%), exo ee 83%, endo ee 81%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 100 °C hold 3 min then 2 °C/min gradient, flow = 3.0 mL/min), exo isomers $t_r = 42.7$ min, 43.8 min, endo isomers $t_r = 43.4$ min, 44.3 min.

TOCSY NMR Experiment on Racemic 3-Phenylbicyclo[2.2.1]-hept-5-ene-2-carboxaldehydes 4.7 and 4.8 (Figures 4.5 and 4.6). Compound 4.1 (22.6 mg, 0.083 mmol) was dissolved in 19:1 CD$_3$NO$_2$:D$_2$O (0.45 mL) followed by the addition of trifluoromethanesulfonic acid (7.4 µL, 0.083 mmol). To this solution was then added racemic 4.7 and 4.8 (83 mg, 0.419 mmol), and the reaction was monitored at 23°C by $^1$H NMR recording spectra at 5 min intervals for 80 min (Figure 4.5). At this time, a TOCSY experiment was performed by irradiation of the doublet at 8.25 ppm at 60, 120,
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150, and 200 ms mixing times. Resonances at 7.79 and 7.11 ppm were most significant at 60 ms and were consistent with the resonances of spin system 4.3.

General Procedure for Deracemization of Racemic Cycloadducts 4.7 and 4.8 (Table 4.1 entry 4). A solution of compound 4.1 (68.1 mg, 0.252 mmol) in 0.25 mL of 19:1 CH$_3$NO$_2$:H$_2$O was treated with trifluoromethanesulfonic acid (22.3 µL, 0.252 mmol). To this solution was added a 1.7:1 exo:endO racemic mixture of 4.7 and 4.8 (50 mg, 0.252 mmol). Freshly distilled cyclopentadiene (33 mg, 0.504 mmol) was slowly added, and the reaction stirred for 24 h at 23 °C. The reaction mixture was extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na$_2$SO$_4$. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the enantiomerically enriched 4.7 and 4.8 material as a 1:1 mixture of exo and endo isomers (colorless oil, 23.5 mg, 47%), exo ee 11%, endo ee 28%.

(5)-(+)-2-(tert-Butyl-hydrazono)-7,7-dimethyl-bicyclo[2.2.1]heptane-1-carboxylic acid (3.80-5). Acetic acid (0.16 mL, 3.29 mmol) was added drop wise to a solution of (S)-(+)-ketopinic acid 3.72 (3.00 g, 16.5 mmol), tert-butyl-hydrazine monohydrochloride (2.75 g, 16.5 mmol) and sodium acetate (1.35g, 16.5 mmol) in anhydrous dichloromethane (100 mL) at room temperature. The reaction mixture was stirred at that temperature until judged complete by TLC analysis (17 hours). Removal of solvent in vacuo and purification by silica gel chromatography (30% EtOAc in hexanes) provided the compound as a pale yellow oil in 79% yield (3.29 g, 13.0 mmol); mp 119-121°C; [α]$_D$ +67.9° (c 1.03, CHCl$_3$); IR (neat) 1689, 2969, 3237 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 2.42-2.32 (m, 2H), 2.09-1.97 (m, 2H), 1.80 (d, J = 17.1 Hz, 1H), 1.73 (ddd, J = 13.1, 9.4, 4.3 Hz, 1H), 1.34-1.27 (m, 3H), 1.21 (s, 3H), 1.16 (m, 9H), 0.84 (s, 3H); $^{13}$C NMR δ (125 MHz, CDCl$_3$) 173.1 (C), 158.3 (C), 59.4 (C), 53.7 (C), 51.3 (C), 44.4 (CH), 32.3 (CH$_2$), 32.2 (CH$_2$), 28.3 (CH$_3$), 28.2 (CH$_2$), 20.0 (CH$_3$), 19.7 (CH$_3$); MS (EI) $m/z$ 252.2 (M$^+$); HRMS calcd for C$_{14}$H$_{24}$N$_2$O$_2$ 252.1838; found 252.1839.
(S)-(+)-2-(Benzhydryl-hydrazono)-7,7-dimethyl-bicyclo[2.2.1]heptane-1-carboxylic acid (3.80-6). Prepared by a procedure similar to that described above for 3.77 from (S)-(+)-ketopinic acid 3.72 (2.78 g, 15.3 mmol) and benzhydrylhydrazine (3.64 g, 18.4 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the title compound as a pale yellow oil (4.16 g, 75 %); [α]_D +5.94° (c 1.00, CHCl₃); IR (neat) 3268, 2972, 1735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.31 (m, 8H), 7.29-7.24 (m, 2H), 5.53 (s, 1H), 2.46-2.36 (m, 2H), 2.11-2.03 (m, 1H), 2.01 (t, J = 4.3 Hz, 1H), 1.88 (d, J = 17.2 Hz, 1H), 1.71-1.66 (m, 1H), 1.33-1.27 (m, 1H), 1.22 (s, 3H), 0.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.6 (C), 141.4 (C), 141.1 (C), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 67.8 (CH), 59.6 (C), 51.5 (C), 44.4 (CH), 32.9 (CH₂), 28.2 (CH₂), 20.0 (CH₃), 19.6 (CH₃); MS (EI) m/z 362.2 (M⁺).

(5)-(+)-3-(3,5-Dimethylbenzyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0¹⁵]dec-4-en-2-one (3.81-7). Acetic acid (0.16 mL, 3.33 mmol) was added drop wise to a solution of (S)-(+)-ketopinic acid 3.72 (3.70 g, 16.5 mmol) and (3,5-Dimethyl-benzyl)-hydrazine (2.50 g, 16.5 mmol) in anhydrous dichloromethane (100 mL) at room temperature. The reaction mixture was stirred at that temperature until judged complete by TLC analysis (17 hours), then passed through a short silica plug and the solvent was removed in vacuo. The crude hydrazonocarboxylic acid was dissolved in mesitylene (90 mL) and was refluxed while water was removed in dean-stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC (36 hours). The cooled reaction mixture was directly loaded onto a silica column and was purified by flash chromatography (hexanes followed by 15 % EtOAc in hexanes) to provide the desired compound as a white solid (2.70 g, 55 %), mp 83.5-84.5°C; [α]_D +27.8° (c 1.08, CHCl₃); IR (neat) 2963, 1696, 1610 cm⁻¹; ¹H NMR (500
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MHz, CDCl$_3$ δ 6.89-6.86 (m, 3H), 4.73 (s, 2H), 2.59-2.52 (m, 1H), 2.32-2.21 (m, 8H), 2.16-2.08 (m, 2H), 1.66 (ddd, J = 13.5, 9.4, 4.4 Hz, 1H), 1.47 (ddd, J = 13.4, 9.4, 4.3 Hz, 1H), 1.21 (s, 3H), 0.90 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 174.5 (C), 173.6 (C), 138.1 (C), 137.0 (C), 129.1 (CH), 125.6 (CH), 63.7 (C), 49.9 (CH), 49.2 (CH2), 47.8 (C), 32.0 (CH2), 27.0 (CH2), 25.3 (CH2), 21.2 (CH3), 19.1 (CH3), 18.6 (CH3); MS (El) m/z 296.2 (M$^+$); HRMS calcd for C$_{19}$H$_{24}$N$_2$O 296.1889; found 296.1900.

(5)-(+)-3-Benzhydryl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]dec-4-en-2-one (3.81-6).

Prepared by a procedure similar to that described above for 3.78 from (5)-(+)-2-(Benzhydryl-hydrazono)-7,7-dimethyl-bicyclo[2.2.1]heptane-1-carboxylic acid 3.80-6 (502 mg, 1.39 mmol). Purification by silica gel chromatography (hexanes then 20% EtOAc in hexanes) provided the compound as a white solid (294 mg, 62 %). mp 156-158°C; [a]$_D$ +0.23$^\circ$ (c 1.00, CHCl$_3$); IR (neat) 1694 cm$^{-1}$; 1H NMR (500 MHz, CDCl$_3$) δ 7.37-7.26 (m, 10H), 6.64 (s, 1H), 2.59 (m, 1H), 2.35-2.09 (m, 4H), 1.72-1.64 (m, 1H), 1.53-1.45 (m, 1H), 1.22 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 174.2 (C), 173.6 (C), 140.0 (C), 139.5 (C), 128.5 (CH), 128.3 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.3 (CH), 63.5 (C), 59.8 (CH), 50.1 (C), 49.2 (CH), 32.2 (CH2), 27.0 (CH2), 25.3 (CH2), 19.1 (CH3), 18.6 (CH3); MS (El) m/z 344.2 (M$^+$); HRMS calcd. for C$_{23}$H$_{24}$N$_2$O 344.1890; found 344.1881.

(S)-(+)-3-tert-Butyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]dec-4-en-2-one (3.81-5).

(S)-(+)-2-(tert-Butyl-hydrazono)-7,7-dimethyl-bicyclo[2.2.1]heptane-1-carboxylic acid 3.80-5 (2.31 g, 9.15 mmol) and triethylamine (926 mg, 9.15 mmol) were dissolved in EtOAc (90 ml). SOCl$_2$ (0.86 ml, 11.9 mmol) was added drop wise and the reaction was brought to 60°C for 6 hours and quenched.
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with H₂O. The products were extracted with EtOAc, washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the product was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired compound as pale yellow crystals (1.01 g, 47 %). mp 45-46 °C; [α]D +38.3° (c 1.06, CHCl₃); IR (neat) 2965, 1637, 1694, 1290 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 2.56-2.50 (m, 1H), 2.21-2.15 (m, 2H), 2.11-2.03 (m, 2H), 1.66-1.59 (m, 1H), 1.47 (s, 9H), 1.46-1.41 (m, 1H), 1.15 (s, 3H), 0.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.5 (C), 172.2 (C), 64.6 (C), 57.6 (C), 49.6 (C), 49.1 (CH), 32.0 (CH₂), 28.4 (CH₃), 27.0 (CH₂), 25.1 (CH₂), 18.8 (CH₃), 18.4 (CH₃); MS (EI) m/z 234.2 (M⁺); HRMS calcd for C₁₄H₂₂N₂O 234.1732; found 234.1734.

(5)-(+)-10,10-Dimethyl-3-(1-phenylethyl)-3,4-diaza-tricyclo[5.2.1.0¹⁵]dec-4-en-2-one (3.80-8).

Prepared by a procedure similar to that described above for 3.78 from (5)-(+)-ketopinic acid 3.72 (7.14 g, 39.2 mmol) and (1-Phenylethyl)-hydrazine (6.4 g, 47.0 mmol). Purification by silica gel chromatography (hexanes then 20% EtOAc in hexanes) provided an inseparable mixture of diastereoisomers as a clear oil (6.97 g, 63 %). IR (neat) 2962, 1693, 1633 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.17 (m, 5H), 5.56-5.39 (m, 1H), 2.60-2.48 (m, 1H), 2.30-2.02 (m, 4H), 1.69-1.38 (m, 5H), 1.19 (s, 1.5H major isomer), 1.15 (s, 1.5H minor isomer), 0.91 (s, 1.5H major isomer), 0.72 (s, 1.5H minor isomer); ¹³C NMR (100 MHz, CDCl₃) δ major isomer: 174.0 (C), 173.1 (C), 141.3 (C), 128.3 (CH), 127.2 (CH), 126.8 (CH), 63.9 (CH), 51.6 (C), 49.7 (CH), 49.6 (CH), 32.0 (CH₂), 26.9 (CH₃), 24.9 (CH₂), 19.3 (CH₃), 18.8 (CH₃), 18.5 (CH₃); minor isomer: 174.0 (C), 173.2 (C), 141.8 (C), 128.2 (CH), 127.1 (CH), 126.6 (CH), 63.9 (CH), 51.7 (C), 49.9 (CH), 49.2 (CH), 31.9 (CH₂), 26.9 (CH₂), 25.1 (CH₂), 18.9 (CH₃), 18.8 (CH₃), 18.5 (CH₃); MS (EI) m/z 282.2 (M⁺); HRMS calcd for C₁₈H₂₂N₂O 282.1732; found 282.1718.
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\[(S)-(\pm)-3-(3,5\text{-Dimethyl-benzyl})-10,10\text{-dimethyl-3,4-diaza-tricyclo[5.2.1.0\text{1,5}]decan-2-one (Table 4.2, entry 2).}\n
A solution of 10,10-Dimethyl-3,4-diazatricyclo[5.2.1.0\text{1,5}]dec-4-en-2-one \(3.81-7\) (300 mg, 1.01 mmol) in a 2:1 mixture of acetic acid and methanol (20 mL) was added sodium cyanoborohydride (636 mg, 10.1 mmol) in small portions over 1 h. The reaction mixture was then stirred at room temperature until TLC indicated that the reaction was complete (21 hours). Excess borohydride was quenched by the addition of 10 % HCl. The products were extracted using CH\(_2\)Cl\(_2\) and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH\(_2\)Cl\(_2\). The organic extracts were combined, washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the product was purified by flash chromatography (30% EtOAc in hexanes) to afford the desired compound as a white solid (263 mg, 87 %). mp 84-85 °C; \([\alpha]_D +16.3^\circ\) (c 1.18, CHCl\(_3\)); IR (neat) 3241, 1665 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.89-6.86 (m, 3H), 4.65 (d, J = 13.4 Hz, 1H), 4.31 (d, J = 13.4 Hz, 1H), 3.49 (dd, J = 8.2, 4.8 Hz, 1H), 2.25 (s, 6H), 2.15 (dt, J = 11.5, 4.6 Hz, 1H), 2.03-1.96 (m, 1H), 1.92-1.82 (m, 2H), 1.62 (dd, J = 13.1, 8.4 Hz, 1H), 1.32-1.25 (m, 1H), 1.24-1.17 (m, 1H), 1.11 (s, 3H), 1.06 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.4 (C), 138.2 (C), 135.6 (C), 129.3 (CH), 126.1 (CH), 65.1 (CH), 58.4 (C), 51.2 (C), 47.7 (CH\(_2\)), 46.7 (CH), 36.3 (CH\(_2\)), 28.6 (CH\(_2\)), 26.6 (CH\(_2\)), 21.1 (CH\(_3\)), 20.9 (CH\(_3\)), 20.2 (CH\(_3\)); MS (EI) \(m/z\) 298.2 (M\(^+\)); HRMS calcd for C\(_{19}\)H\(_{26}\)N\(_2\)O 298.2045; found 298.2055.

\[(S)-(\pm)-3-Benzhydryl-10,10\text{-dimethyl-3,4-diaza-tricyclo[5.2.1.0\text{1,5}]decan-2-one (Table 4.2, entry 4).}\n
Prepared by a procedure similar to that described above for 3.83 from \((S)-(\pm)-3\text{-Benzhydryl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0\text{1,5}]decan-4-en-2-one}\) 3.81-6 (760 mg, 2.21 mmol).
Purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a white solid (698 mg, 91%). mp 178-179 °C; [α]D -71.1° (c 1.00, CHCl3); IR (neat) 1675, 3336 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.26 (m, 10H), 6.65 (s, 1H), 3.62 (dd, J = 4.7, 8.3 Hz, 1H), 2.24-2.15 (m, 1H), 2.00-1.87 (m, 3H), 1.71 (dd, J = 8.4, 13.1 Hz, 1H), 1.39-1.22 (m, 2H), 1.07 (s, 3H) 0.90 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.4 (C), 138.6 (C), 138.4 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 66.0 (CH), 59.3 (CH), 58.0 (C), 51.0 (C), 47.0 (CH), 35.6 (CH₂), 28.9 (CH₂), 26.6 (CH₂), 21.2 (CH₃), 20.2 (CH₃); MS (EI) m/z 346.2 (M⁺); HRMS calc'd for C₂₃H₂₆N₂O 346.2047; found 346.2056.

(S)-(+-)₃-tert-Butyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one (Table 4.2, entry 5). Prepared by a procedure similar to that described above for 3.83 from (S)-(+-)₃-tert-Butyl-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]dec-4-en-2-one 3.81-5 (200 mg, 0.854 mmol). Purification by silica gel chromatography (30% EtOAc in hexanes) provided the title compound as a white solid (190 mg, 94%). mp 103-106 °C; [α]D +26.1° (c 1.10, CHCl₃); IR (neat) 3263, 2961, 1647 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.38 (dd, J = 8.3 Hz, 1H), 2.03-1.93 (m, 2H), 1.82-1.74 (m, 2H), 1.59 (dd, J = 13.2, 8.4 Hz, 1H), 1.34 (s, 9H), 1.21-1.08 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.3 (C), 64.5 (CH), 59.3 (C), 55.9 (C), 50.5 (C), 46.8 (CH), 36.2 (CH₂), 28.9 (CH₂), 27.6 (CH₃), 26.4 (CH₂), 20.9 (CH₃), 20.5 (CH₃); MS (EI) m/z 236.2 (M⁺); HRMS calc'd for C₁₄H₂₄N₂O 236.1889; found 236.1864.

(S)-(+-)₁₀,₁₀-Dimethyl-₃-(R-1-phenyl-ethyl)-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one (4.14) and (S)-(+-)₁₀,₁₀-Dimethyl-₃-(S-1-phenyl-ethyl)-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one  (4.15)
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(Table 4.3). Prepared by a procedure similar to that described above for 3.83 from (S)-(−)-10,10-Dimethyl-3-(1-phenylethyl)-3,4-diaza-tricyclo[5.2.1.01,5]dec-4-en-2-one 3.81-8 (300 mg, 1.06 mmol). The diastereoisomers were separated by silica gel chromatography (5% EtOAc in hexanes) to provide (S)-(−)-10,10-Dimethyl-3-(R-1-phenyl-ethyl)-3,4-diaza-tricyclo[5.2.1.01,5]decan-2-one 4.14 as a white solid (160 mg, 53%). Crystals of 4.14 suitable for X-ray crystallographic analysis were obtained by slow evaporation of the product from a minimum amount of THF at -20°C. Mp 79-81°C; [a]D +62.1° (c 1.44, CHCl3); IR (neat) 3249, 2958, 1662 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.35 (m, 4H), 7.26-7.22 (m, 1H), 5.50 (q, J = 7.0 Hz, 1H), 3.83 (br, 1H), 3.39 (dd, J = 8.3, 4.5 Hz, 1H), 2.19-2.11 (m, 1H), 2.07-2.01 (m, 1H), 1.90-1.81 (m, 2H), 1.58 (dd, J = 12.9, 8.3 Hz, 1H), 1.54 (d, J = 7.0 Hz, 3H), 1.28-1.23 (m, 2H), 1.22 (s, 3H), 1.07 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.2 (C), 139.6 (C), 128.5 (CH), 127.6 (CH), 127.0 (CH), 64.9 (CH), 58.7 (C), 51.0 (C), 50.7 (CH), 46.8 (CH), 36.6 (CH₂), 28.7 (CH₂), 26.6 (CH₂), 20.8 (CH₃), 20.5 (CH₃), 16.3 (CH₃); MS 284.2 (M⁺); HRMS calcd for C₁₈H₂₄N₂O 284.1889; found 284.1888 and (S)-(−)-10,10-Dimethyl-3-(S-1-phenyl-ethyl)-3,4-diaza-tricyclo[5.2.1.01,5]decan-2-one 4.15 as a clear oil (102 mg, 34%). [a]D -73.9° (c 1.03, CHCl₃); IR (neat) 3248, 2959, 1659 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.33 (m, 2H), 7.32-7.27 (m, 2H), 7.26-7.21 (m, 1H), 5.51 (q, J = 7.0 Hz, 1H), 3.45 (dd, J = 8.3, 4.5 Hz, 1H), 3.32 (br, 1H), 2.15-2.06 (m, 1H), 1.89-1.78 (m, 3H), 1.70-1.64 (m, 1H), 1.57 (d, J = 7.0 Hz, 3H), 1.28-1.17 (m, 2H), 1.02 (s, 3H), 0.82 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.9 (C), 139.7 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 66.5 (CH), 58.2 (C), 50.8 (C), 50.6 (CH), 46.9 (CH), 35.4 (CH₂), 28.6 (CH₂), 26.5 (CH₂), 21.3 (CH₃), 20.1 (CH₃), 16.3 (CH₃); MS (EI) m/z 284.2 (M⁺); HRMS calcd for C₁₈H₂₄N₂O 284.1889; found 284.1917.

General Procedure for the Bronsted acid scan Hydrazide-Catalyzed Diels-Alder Reactions (Table 4.4, Entry 2). To a suspension of E-cinnamaldehyde (100 mg, 0.756 mmol) in distilled water (0.75 mL) was added compound 4.1 (41 mg, 0.151 mmol) followed by 48% tetrafluoroboric acid (13.5 μL, 0.151 mmol). After the mixture stirred for 1-2 min, cyclopentadiene (150 mg, 2.27 mmol) was slowly added, and the resulting mixture was stirred at 23 °C until the reaction was judged complete by TLC analysis (24 h). The reaction mixture was extracted twice with ether, and the combined organic extracts were washed successively with water and brine and then dried over Na₂SO₄. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired
material 4.7 and 4.8 as a 1.7:1 mixture of exo and endo isomers (colorless oil, 147 mg, 98%), exo ee 89%, endo ee 85%.

**Iminium ion (4.19) from** (S)-(+-)10,10-Dimethyl-3-(R-1-phenyl-ethyl)-3,4-diazatricyclo[5.2.1.0\(^{1,5}\)]decan-2-one (4.14), E-cinnamaldehyde and triflic acid for X-ray Analysis. To a solution of E-cinnamaldehyde (46.0 mg, 0.352 mmol) and (S)-(+-)10,10-Dimethyl-3-(R-1-phenyl-ethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-one 4.14 (100 mg, 0.352 mmol) in 19:1 CH\(_3\)NO\(_2\):H\(_2\)O (0.5 ml) was added CF\(_3\)SO\(_3\)H (31 \(\mu\)l, 0.352 mmol). After 4 hours the solvent was removed in vacuo to afford a yellow oil which was dissolved in a minimum of THF. The solvent was then removed in vacuo and then the sample was redissolved in THF. This cycle was repeated several times until a pale yellow solid was obtained. This material was then dissolved in a minimum amount of THF and the mixture was allowed to stand at -20 °C to afford crystals of the iminium ion 4.19 that were of suitable quality for X-ray analysis.

**Computational Methods:** Calculations for the dihedral driver experiment were carried out at the PM3 semi empirical level of theory using the Gaussian 98 suite of programs. To account for possible hysteresis in the dihedral driver experiment, the rotations about the C-N bond were performed from 0° to 360° and then back to 0°. The values were averaged and converted to relative kCal/mol. The X-ray structure of 4.19 was compared to calculated structure 4.19-150°. The average bond length error between the crystal structure 4.19 and 4.19-150° was 0.021 Å and the average dihedral angle error was 1.45°, indicating a good correlation between the calculated structures and the actual iminium intermediate. One significant deviation was noted between these structures that involved the planarity of the “amide” nitrogen (N1 in Figure 4.14). In the calculated structure 4.19-150° the improper torsion along C10-N1-N2-C11 was 136.1° whereas the same angle in the X-ray structure of 4.19 was almost 180°. This discrepancy could be accounted for by the well known propensity of the PM3 basis set to pyramidalize amide nitrogens.
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Experimental Section: Diels-Alder Catalysis

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Experimental Section: Diels-Alder Catalysis

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6

Dipolar Cycloadditions

6.1 1,3 Dipolar Cycloaddition of Nitrones

Since the discovery of the first 1,3-dipolar cycloaddition over one hundred years ago, the reaction has gained synthetic utility as it is found in many chemical processes. The ozonolysis of olefins, the oxidation of olefins with osmium tetroxide and the cycloadditions of azides, nitrones and nitrile oxides are all examples of reactions that proceed via the [3+2] cycloaddition mechanism. Among the various cycloadditions studied the reaction of alkenes with nitrones to generate isoxazolidine ring systems has received the most interest.

Scheme 6.1 The [3+2] cycloaddition reaction between alkenes and nitrones

Isoxazolidines are particularly useful synthetic intermediates as the nitrogen-oxygen bond can be readily cleaved to form synthetically useful chiral 1,3-amino alcohols that can be converted into biologically relevant compounds such as alkaloids, β-amino acids, amino sugars and β-

\[ \text{R}^1 \text{N}^\bullet \text{R}^2 \xrightarrow{[3+2]} \text{R}^1 \text{N} \text{O} \text{R}^2 \xrightarrow{\text{reduction}} \text{R}^1 \text{N}^\text{OH} \text{R} \]

\[ \text{R}^1 \text{N} \text{O} \text{R}^2 \xrightarrow{\text{endo/exo}} \text{R}^1 \text{N} \text{O} \text{R}^2 \]

\[ \text{R}^1 \text{N} \text{O} \text{R}^2 \xrightarrow{\text{reduction}} \text{R}^1 \text{N}^\text{OH} \text{R} \]

\[ \text{R}^1 \text{N} \text{O} \text{R}^2 \xrightarrow{\text{endo/exo}} \text{R}^1 \text{N}^\text{OH} \text{R} \]

\[ \text{R}^1 \text{N} \text{O} \text{R}^2 \xrightarrow{\text{reduction}} \text{R}^1 \text{N}^\text{OH} \text{R} \]

155 (a) Gothelf, K. V.; Jorgensen, K. A. Chem. Rev. 1998, 98, 863. (b) Gothelf, K. V.; Jorgensen, K. A. In Synthetic Applications of 1,3 Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products; Padwa, A., Ed; Wiley: New York, 2002.
1,3-Dipolar Cycloadditions

Starting from relatively simple starting materials, this reaction provides a heterocyclic scaffold with up to three contiguous stereocenters. As in the Diels-Alder reaction, the dipolar cycloaddition can give rise to two pairs of regioisomers and diastereomers, depending on the approach of the nitrone to the alkene and the preference for the endo or exo transition states. Thus, this reaction requires the control of three different selectivity elements: regioselectivity, diastereoselectivity, and enantioselectivity.

The regioselectivity of the 1,3-dipolar cycloaddition is governed by electronic and steric factors. When electron rich or neutral alkenes undergo cycloaddition with nitrones, the process is controlled by the LUMO of the dipole and the HOMO of the dipolarophile. This arrangement provides the largest coefficients at the β-carbon of the alkene and the carbon of the nitrone resulting in 5-substituted isoxazolidines. (Figure 6.1). Sterically, the selectivity for 5-substituted products is further enhanced when terminal alkenes are used to avoid the non-bonding interactions between $R^3$ of the alkene and the $R^1$ substituent of the nitrone. Alternatively, the interaction between the HOMO of the dipole and the LUMO of an electron-withdrawing alkene provides 4-substituted isoxazolidines. This regiocontrol is the result of matching the largest coefficients, which are found at the oxygen of the HOMO of the dipole and at the β-carbon of the LUMO of the dipolarophile. When a Lewis acid is used to activate the $\alpha,\beta$-unsaturated alkene component, the coefficient value of the $\alpha$-carbon will decrease resulting in an enhanced electronic bias favoring 4-substituted isoxazolidines. However, when terminal electron-deficient alkenes are used, the steric and electronic factors will oppose each other, often resulting in mixtures of 4-and 5-substituted regioisomers. The use of a Lewis acid counters this effect, as the electronic properties become enhanced and overcome the steric. If 1,2-disubstituted alkenes, in which $R^3$ is larger than H, are used the steric bias will be negated, thus providing the desired 4-substituted isoxazolidine product.


In terms of diastereoselectivity, the dipolarophile may approach from either side of the nitrone to produce exo or endo diastereoisomers (Figure 6.2). In the 1,3-dipolar cycloaddition, diastereoselectivity is predominantly controlled by the structures of the catalyst and the substrate. The endo transition state tends to be more sterically hindered, unlike the Diels-Alder reaction in which there are favorable secondary orbital interactions to help stabilize the endo transition state. In general, there are no orbitals on the dipole for the electron withdrawing group of the dipolarophile to interact with favorably. Consequently, steric effects, such as the interaction between the carbonyl of the α,β-unsaturated dipolarophile and R\(^2\) of the nitrone dominate and typically favor the exo product.
For many years, research groups introduced asymmetry in 1,3-dipolar cycloadditions using chiral nitrones or dipolarophiles to relay the stereochemistry to the newly formed stereocenters on the isoxazolidine ring. In contrast, the development of catalytic asymmetric 1,3 dipolar cycloaddition reactions using racemic substrates, is still in its infancy. The earliest asymmetric catalytic studies of the 1,3-dipolar cycloaddition reaction were not reported until 1994, when Jorgensen investigated the interactions of the catalyst with the dipolarophile rather than with the dipole.\textsuperscript{158} Previous catalytic systems were found to interact with the dipole, which are good Lewis bases, resulting in an increase in energy of the transition state relative to the uncatalyzed reactions.\textsuperscript{159} Consequently, research efforts were centered on Lewis acid catalysts that interacted preferentially with the olefin.

\subsection*{6.1.1 Enantioselective Lewis Acid activation}

Favorable interactions with the olefin were first achieved using bidentate chelating oxazolidinone auxiliaries. These moieties shifted the equilibrium away from Lewis acid coordination of the nitrone toward the carbonyl, resulting in better structural rigidity and better

enantiocontrol compared to monodentate substrates. Jørgensen initially reported that titanium catalysts, generated \textit{in situ} from Ti(i-OPr)$_2$Cl$_2$ and chiral diols, could effectively mediate the reaction between 3-acyl-1,3-oxazolidinones 6.6 and nitrones 6.5.\textsuperscript{158} They observed that TiCl$_2$-TADDOLates 6.7 afforded the desired 4-isoxazolidinones in a regioselective manner, with a preference for the \textit{exo} diastereoisomer and optical purities that ranged from poor to fair (10-60% \textit{ee}). The same authors were able to improve these initial results by installing more sterically demanding ligands on the catalyst.\textsuperscript{160} When the chloride ligands were substituted for tosylato ligands, the reaction of N-aryl nitrones and alkenes proceeded to give isoxazolidines in good yield but with reversed diastereoselectivity (Scheme 6.2). Catalyst loadings of 50 mol\% were required in order to maintain high \textit{endo} diastereoselectivity and enantioselectivities.

Scheme 6.2 Titanium TADDOLate complexes applied toward the 1,3-dipolar cycloaddition of 3-acyl-1,3-oxazolidinones and nitrones

\begin{center}
\begin{tikzpicture}
\node[anchor=south east,inner sep=0] (image) at (0,0) {\includegraphics[width=\textwidth]{tikz62.png}};
\node at (image.north) {Scheme 6.2 Titanium TADDOLate complexes applied toward the 1,3-dipolar cycloaddition of 3-acyl-1,3-oxazolidinones and nitrones};
\end{tikzpicture}
\end{center}

Since Jørgensen et al. reported that Lewis acids catalyzed 1,3-dipolar cycloadditions, many varieties of metal based catalysts such as palladium,\textsuperscript{161} ytterbium,\textsuperscript{162} nickel\textsuperscript{163} and magnesium\textsuperscript{164}

\begin{thebibliography}{9}
\end{thebibliography}
1,3-Dipolar Cycloadditions

salts have been used to promote the [3+2] cycloaddition in high selectivities using auxiliaries such as N-alkenoyl-2-oxazolidinones 6.11 (Scheme 6.3). However, activation via these catalytic systems all necessitated the use of chiral auxiliaries which imposed post-reaction manipulations to unveil the free aldehyde.

Scheme 6.3 Various palladium, ytterbium, nickel and magnesium based catalysts promoting [3+2] cycloadditions between nitrones and various N-alkenoyl-2-oxazolidinones

Up until very recently, monodentate unsaturated carbonyl compounds such as aldehydes were poor substrates for metal catalyzed nitrone cycloadditions. Lewis acid-carbonyl adducts also displayed poor organizational control, as there is potential for free rotation around the Lewis acid-carbonyl bond which leads to poor enantiocontrol. This was overcome in 2002 when Kundig and co-workers developed highly tuned aldehyde-selective iron and ruthenium catalysts.

such as 6.23 that were able to discriminate between enals and nitrones. Structural and mechanistic studies provided evidence that the coordination to nitrones was reversible and that by adding excess enal, the equilibrium could be shifted toward carbonyl complexation. However, the scope of the reaction was limited to cyclic nitrone 6.20 and mostly methacrolein 6.21 as the enal as other substrates provided mixtures of regioisomers and diastereoisomers.

Shortly after, the Yamada group showed that β-ketoiminato cationic cobalt(III) complexes, originally developed for the Diels-Alder cycloaddition, could be also used in the 1,3-dipolar cycloaddition of 1-cyclopentene-1-carbaldehydes 6.26 with various nitrones. The enantioselective 1,3-dipolar cycloaddition of 6.26 catalyzed by the cationic cobalt (III) complex 6.27 proceeded with excellent endo selectivity and enantioselectivities of up to 91%, but only with nitrones derived from o-halo-substituted benzaldehydes such as 6.25. This was thought to be a result of a favorable coordination between the halogen atom on the ortho position of the donor molecule with the metal complex that improved the enantioselectivity.

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1,3-Dipolar Cycloadditions

Scheme 6.5 β-ketoiminato cationic cobalt(III) complexes as catalysts for 1,3-dipolar cycloaddition of 1-cyclopentene-1-carbaldehydes with various nitrones

Based on their previous work, Kanemasa et al. investigated the potential of chiral pinhole catalysts to effectively activate cycloadditions between nitrones and α,β-unsaturated aldehydes (Scheme 6.6). In these types of catalysts, the nitrones predominantly coordinate to the catalyst but the resulting Lewis acid/nitrone complex still has the catalytic capability to activate carbonyl compounds. The reaction of acyclic nitrones and various enals with the DBFOX/Ph complexes of several metal salts afforded the imidazolidine products in enantiomeric excesses of up to 99.5%, much higher than that of previously reported works. However, the catalysts were found to be very sensitive to the nature of the aldehyde used and thus required a specific metal center in each case to provide desirable enantioselectivities. DBFOX/Ph complexes of nickel(II) 6.30 and magnesium(II) 6.31 salts were used to provide sterically controlled 5-substituted cycloadducts 6.32 from α-alkyl and α-arylacroleins, whereas the reaction of α-bromoacrolein with zinc(II) complexes afforded electronically controlled 4-isoxazolidines 6.33 in good yields and selectivities.

Maruoka investigated the reaction of bis-titanium catalysts as Lewis acids for the asymmetric 1,3-dipolar cycloaddition between various aryl-substituted nitrones and acrolein. The isoxazolidines were obtained exclusively as endo diastereoisomers in high to excellent enantiomeric excesses ranging from 88-94% (Scheme 6.7). This study was the first to exhibit excellent selectivities with a broad range of acyclic nitrones bearing an easily removable N-benzyl moiety as opposed to the N-aryl substituent typically required to achieve high levels of enantioselectivity. Unfortunately, 6.35 was the only α,β-unsaturated aldehyde reported in this study. In a proposed mechanism, the nitrone was thought to coordinate to the acidic titanium center of 6.36 which caused an isopropyl group to shift to the other titanium atom. This created an open space on one of the metal centers permitting acrolein complexation. Steric repulsion by one of the ligands resulted in ejection of the nitrone and subsequent [3+2] cycloaddition.

---

Scheme 6.7 Bis-titanium catalysts as Lewis acids for the asymmetric 1,3-dipolar cycloaddition between various aryl-substituted nitrones and acrolein

\[ \text{Bn}_2\text{O} = \text{Ph} \quad 6.34 \quad + \quad \text{RC} = \text{O} \quad 6.35 \quad \xrightarrow{10 \text{ mol\% (S,S)-6.36}} \quad \text{Bn} = \text{N} - \text{Ph} \quad 6.37 \quad \text{OH} \quad \text{CH}_2\text{Cl}_2, -40^\circ\text{C} \quad 2. \text{NaBH}_4, \text{EtOH} \]

end only
93% ee
94% yield

6.1.2 Chiral Amine Organocatalysis in 1,3 Dipolar Cycloaddition

Organic catalysis was the first strategy developed to overcome the functional group compatibility issues associated with metal catalysis in the 1,3-dipolar cycloaddition involving nitrones and electron deficient alkenes. In 2000, MacMillan showed that his imidazolidinone catalysts were inert to nitrone association, thereby allowing unsaturated aldehydes to undergo iminium activation and subsequent [3+2] cycloadditions. Additionally, since the secondary amine catalyst is bound to the alkene substrate by a rigid double bond, the iminium intermediate is expected to possess structural integrity that can enforce organizational control and provide the cycloadducts in excellent enantioselectivities.
Scheme 6.8 Imidazolidinone-catalyzed [3+2] cycloadditions between various nitrones and α,β-unsaturated aldehydes

A survey of multiple catalysts revealed that imidazolidinone 6.39, used in the organocatalytic Diels-Alder cycloaddition between aldehydes and dienes was well suited for nitrone cycloadditions. Investigation of various reaction parameters revealed that the Brønsted acid HClO₄ and a solvent mixture of nitromethane and water at -20 °C provided optimal reaction efficiency and optical purity. The reaction was general with respect to the nitrone architecture, as variation of the N-alkyl group from Me, Bn to allyl is possible without significant loss of enantiomeric excess (91-99% ee, Scheme 6.8). Only two dipolarophiles were investigated in this study, crotonaldehyde and acrolein. Both provided the [3+2] cycloadducts in excellent enantiomeric excesses and yields with diastereomeric ratios ranging from 89:19 to 98:2 in favor of the endo isomer. The reaction did have some limitations in that it was limited to α,β-unsaturated aldehydes smaller than crotonaldehyde and less hindered or cyclic nitrones did not perform well in cycloadditions.
Scheme 6.9 Catalytic cycle of the [3+2] imidazolidinone-catalyzed nitrone cycloaddition

The imidazolidinone-catalyzed 1,3-dipolar cycloaddition is believed to proceed via the catalytic cycle shown in Scheme 6.9. Production of iminium 6.46 by condensation of imidazolidinone 6.39 and a Brønsted acid co-catalyst with an α,β-unsaturated aldehyde 6.45 is driven by the loss of water. The activated dienophile can then undergo a [3+2] cycloaddition with the corresponding nitrone to generate iminium cycloadduct 6.47, followed by hydrolysis to yield the enantioenriched cycloadduct 6.48 and regenerate imidazolidinone salt 6.39.

Enantiocontrol is achieved in a similar manner to that described for the Diels-Alder cycloaddition. Control of the iminium geometry was confirmed by semi-empirical calculations. The gem-dimethyl groups on the catalyst create a steric environment favoring formation of the E-iminium isomer in order to avoid non-bonding interactions between the α-proton of iminium 6.46, as depicted in Figure 6.3. Secondly, the benzyl group on the catalyst provides facial...
discrimination of the conjugated π-system by shielding the top face of the dipolarophile, consequently leaving the bottom face exposed approach of the nitrone. Moreover, the observed diastereoselectivity, favoring the *endo* adduct, is a consequence of non-bonding interactions between the gem-dimethyl groups of the catalyst and the phenyl substituent on the nitrone. These interactions are minimized in the transition state in which the phenyl group of the nitrone is oriented away from the geminal moiety of the catalyst.

Figure 6.3 Stereochemical rationale for the imidazolidinone-catalyzed 1,3-dipolar cycloaddition
1,3-Dipolar Cycloadditions

Karlsson and his group next investigated the use of small organic entities in the 1,3-dipolar cycloaddition of α,β-unsaturated aldehydes and nitrones. They found that the chiral diamonium salt 6.50 could promote 1,3-dipolar cycloadditions between 1-cycloalkene-1-carboxaldehyde 6.26 and a variety of nitrones to furnish fused exo-bicyclic isoxazolidines 6.51 and 6.52 in excellent diastereoselectivities and acceptable optical ratios ranging from 37 to 92% for the major exo cycloadducts (Scheme 6.10). In selected examples, they were able to increase the enantiomeric excess to 99% after recrystallization. In comparison with MacMillan's work, in which the major product from acyclic α,β-unsaturated aldehydes was endo selective, the products obtained by the reaction of cyclic olefins resulted in a high preference to the exo diastereomer. This was partly attributed to the fact that the cyclic olefins used in this study result in a sterically hindered endo transition state. The sense of stereo-selection observed in the formation of bicyclic isoxazolidines was attributed to an attack of the nitrone from the top face of a Z-iminium arranged in an s-cis conformation. This iminium ion intermediate should provide the best shielding of the conjugated π-system by the piperidinium side chain of the catalyst.

The Benaglia group successfully immobilized an imidazolidinone catalyst on a poly(ethylene glycol) support. The catalyst was synthesized using (S)-tyrosine rather than (S)-phenylalanine to provide a point of attachment on the aromatic ring to anchor the PEG support. The products were obtained in enantiomeric excesses similar to those observed with non-supported imidazolidinone catalysts but the chemical yields were somewhat lower than those obtained by MacMillan’s catalyst 6.39. Although the supported catalyst 6.57 could be recycled three times without significant loss of stereochemical efficiency the catalytic activity eroded...
considerably between each cycle. Experiments were done to determine whether the instability of the PEG-supported catalyst was induced by the presence of the polymer itself. The loss of activity was mainly attributed to the instability of the catalyst in the reaction conditions, indifferent of the supported or non-supported nature of the catalyst.

Scheme 6.11 Polymer supported imidazolidinone catalysts for the 1,3-dipolar nitrone cycloaddition

Very recently, Nevalainen presented a new organocatalyst capable of effecting 1,3-dipolar cycloadditions between simple $\alpha,\beta$-unsaturated aldehydes such as acrolein, crotonaldehyde and ethlyoxobutenoate with various nitrones, as an alternative to MacMillan's imidazolidinone catalyst (Scheme 6.12).\(^{172}\) Catalyst 6.58 has the advantage of being prepared in one synthetic step from reaction of commercially available diphenyl-S-prolinol and trimethylsilyl triflate. The cycloaddition was quite general in terms of the nitrone without significant change in yields and selectivities. Suprisingly, when acrolein was used as the dipolarophile, superior diastereoselectivities were obtained at 40 °C instead of room temperature ($\text{endo:exo} \ 97:3 \ vs \ 75:25$, respectively), whereas enantioselectivities remained intact. The reaction was thought to proceed via the formation of an E-iminium isomer 6.59, of which the top face was shielded by one of the phenyl groups and the silyl moiety, thus promoting approach of the nitrone from the bottom face.

Related to the nitrone cycloadditions discussed above, the Chen laboratory presented the first asymmetric 1,3-dipolar cycloaddition between azomethine imines 6.60 and α,β-unsaturated aldehydes. A readily available α,α-diarylprolinol 6.61 bearing strongly electron withdrawing trifluoromethyl substituents on the aromatic ring was found to provide the desired cycloadducts in short reaction times and excellent selectivities when used in conjunction with trifluoroacetic acid. Several bipyrazolidin-3-one derivatives, such as 6.62 and 6.63 were constructed under mild conditions in excellent diastereoselectivities ranging from 81:19 to 98:2 exo:endo and optical purity of 77-97% for the exo product. Reaction models were proposed to account for the selectivity observed in the cycloaddition reaction. Although an E-iminium s-trans or Z-iminium s-cis conformation could both provide the observed exo adduct 6.64 from an underside approach of the nitrone, Chen considered the latter to be the major reactive intermediate based on experimental results and the work previously established by Karlsson.

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Scheme 6.13 Asymmetric 1,3-dipolar cycloaddition between azomethine imines and α,β-unsaturated aldehydes

\[
\begin{align*}
\text{1,3-Dipolar Cycloadditions} \\
\text{Scheme 6.13 Asymmetric 1,3-dipolar cycloaddition between azomethine imines and } & \alpha,\beta\text{-unsaturated aldehydes} \\
\text{10 mol% } & \text{TFA} \\
\text{THF - H}_2\text{O } & \text{rt} \\
\text{exo:endo } & 84:16 \\
\text{96% exo ee} & 85\% \text{ yield}
\end{align*}
\]
Results and Discussion: Hydrazide-Catalyzed 1,3-Dipolar Nitrone Cycloadditions

7.1 Development of the Reaction

Based on our success achieved with the development of strategies for enantioselective catalysis using chiral hydrazides\(^1,2,3\) we directed our interest toward other chemical transformations. In the studies discussed in Chapters 3 and 4, we demonstrated that the LUMO-lowering activation of \(\alpha,\beta\)-unsaturated aldehydes by the reversible formation of iminium ions from hydrazides could be an efficient platform to achieve highly enantioselective Diels-Alder cycloadditions. We hypothesized that hydrazide-based catalysts could be applied in other processes such as the 1,3-dipolar cycloadditions between nitrones and \(\alpha,\beta\)-unsaturated aldehydes, to provide isoxazolidines with good selectivity (Figure 7.1). As discussed earlier, the metal-catalyzed asymmetric variations of these \([3+2]\) cycloadditions have enjoyed considerable success, but there have been few developments making use of chiral organocatalysts since the original report from MacMillan.\(^{25}\) Consequently, a complimentary mode of activation using the technology developed in our laboratory was envisioned.
The catalytic activity of hydrazide salts 7.10 in the [3+2] nitrone cycloaddition would initially involve reversible activation of an α,β-unsaturated aldehyde by iminium ion formation 7.11 (Scheme 7.2). The LUMO of the alkene moiety would consequently be lowered and its interaction with the nitrene should be enhanced which would afford iminium cycloaddition product 7.12. Finally, hydrolysis of 7.12 should release the cycloadduct 7.13 regenerate catalyst 7.10.
We sought to establish reaction conditions that would furnish the isoxazolidine products in good yield by the reaction with \(N\)-benzylidenebenzylamine-\(N\)-oxide 7.7 and a slight excess of \(E\)-crotonaldehyde 7.14 in the presence of 20 mol% of hydrazide salt 7.1. We were pleased to obtain the product in good conversion, as a mixture of \textit{endo}:\textit{exo} isomers generally favoring the \textit{exo} isomer, as determined by \(^1\)H NMR of the crude product. Enantiomeric excess was determined by HPLC on a chiral stationary phase after quantitative reduction of aldehyde 7.13 to the corresponding alcohol with NaBH\(_4\). In order to accurately identify the peaks corresponding to the enantiomers of the \textit{endo} and \textit{exo} cycloadducts, racemates of all dipolar products were synthesized as well. The achiral hydrazide catalyst 3.32 used to produce the racemic counterparts in the Diels-Alder cycloadditions gave only traces of the desired [3+2] products as detected by \(^1\)H NMR. Consequently, an alternative method was developed using the triflate salt of \(N,N\)-ethylbenzyl amine as an achiral catalyst to provide the necessary racemates.
The choice of solvent was found to have a significant impact on the outcome of the reaction, not only in terms of selectivity, but also with respect to the yield of the process. This was in part a consequence of the formation of undesired side-products 7.16 and 7.17 resulting from the hydrolysis of nitrone 7.7. During the reaction, the initial nitrone could react with water to release a hydroxylamine which could then condense with the \( \alpha,\beta \)-unsaturated aldehyde 7.14 to afford a new nitrone 7.15. This new species then underwent a \([3+2]\) cycloaddition to give the undesired products 7.16 and 7.17.

Scheme 7.3 Formation of by-products 7.16 and 7.17

This type of nitrone exchange is not unknown and has been observed in similar amine-catalyzed \([3+2]\) processes.\(^{170}\) We hypothesized that the initial nitrone hydrolysis was a Brønsted acid catalyzed process, but the cycloaddition itself could be promoted by either general acid or hydrazide catalysis. To verify this, by-products 7.16 and 7.17 were synthesized racemically using hydrochloric acid as catalyst from dipole 7.7 and crotonaldehyde 7.14. When compared to the products obtained from the reaction with hydrazide catalyst 7.1, the cycloadducts 7.16 and 7.17 displayed no enantiomeric excess.\(^{174}\) These observations suggested that catalyst 7.1 was not significantly implicated in this undesired transformation and as a result, our efforts were focused to minimize the production of 7.16 and 7.17.

The choice of solvent played a significant role in tuning the product distribution of the nitrone 1,3-dipolar cycloadditions. Most of the solvents investigated gave mixtures that contained

\(^{174}\) Compounds 7.16 and 7.17 were obtained as a mixture of isomers with a preference for the \textit{exo} isomer.
significant amounts of this byproduct (Table 7.1, entries 1, 4, 8, 9 and 10) making further optimizations in these media impractical. The use of benzene, CHCl₃ or CH₃CN resulted in the production of modest amounts of 7.20 (entries 2, 3 and 7) whereas reactions run in CH₂Cl₂ or CH₃NO₂ afforded only minor amounts of this material. In particular, the reaction run in CH₃NO₂ afforded a 68:32 mixture of exo and endo isomers (7.18 and 7.19) in 70% combined yield. The endo isomer was formed in 78% enantiomeric excess while the formation of 7.20 was minimized (entry 6).

Table 7.1 Effect of solvent on the hydrazide-catalyzed 1,3 dipolar cycloaddition reaction between E-crotonaldehyde and nitrone 7.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield %</th>
<th>exo:endo</th>
<th>ee exo</th>
<th>ee endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>14 (38)</td>
<td>58:42</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>67 (25)</td>
<td>48:52</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>CHCl₃</td>
<td>67 (12)</td>
<td>50:50</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>5 (48)</td>
<td>62:38</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>54 (6)</td>
<td>58:42</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>CH₃NO₂</td>
<td>70 (6)</td>
<td>68:32</td>
<td>53</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CN</td>
<td>46 (19)</td>
<td>33:67</td>
<td>29</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>17 (35)</td>
<td>38:62</td>
<td>33</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>14 (38)</td>
<td>28:72</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>H₂O</td>
<td>20 (56)</td>
<td>48:52</td>
<td>32</td>
<td>50</td>
</tr>
</tbody>
</table>
The effect of water on the outcome of the cycloaddition was then investigated. When the solvent was dried by the presence of molecular sieves, the yield decreased to 17%, consistent with the requirement of water for catalyst turnover (Table 7.2, entry 2). Unexpectedly, the anhydrous reaction also showed a propensity to generate the endo isomer. When a large excess of water was added, the hydrolyzed product 7.20 became more prevalent and the enantiomeric excess of the exo adduct was lowered (entry 3). Reducing the amount of available water to one equivalent gave not only improved product yields, but also increased the enantioselectivity of both the exo and endo isomers relative to that realized in entries 1 and 3. No by-product 7.20 was observed in this reaction, consistent with the observed requirement for excess water during the formation of 7.20 (entry 4). Further reducing the amount of water to 0.5 or 0.2 equivalents relative to the limiting reagent resulted in a slight improvement in enantioselectivity for the exo isomer while providing no clear advantage for the endo product (entries 5 and 6). The impact of the presence of water on the enantioselectivity is surprising, in that only the enantiomeric ratio of the exo isomer was strongly affected. The reasons for this are not clear, but a Brønsted acid-catalyzed background reaction may be implicated for this isomer.
Hydrazide-Catalyzed 1,3-Dipolar Cycloadditions

Table 7.2 Effect of water content on the hydrazide-catalyzed cycloaddition reaction between *E*-crotonaldehyde and nitrone 7.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of water</th>
<th>Yield %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>exo:endo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee exo&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee endo&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.5</td>
<td>70 (6)</td>
<td>68:32</td>
<td>53</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17 (0)</td>
<td>18:82</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>62 (12)</td>
<td>68:32</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>82 (0)</td>
<td>62:38</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>84 (0)</td>
<td>58:42</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>80 (0)</td>
<td>63:37</td>
<td>80</td>
<td>77</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated combined yield of 7.18 and 7.19. Value in parentheses refers to the yield of 7.20.<br><sup>b</sup>Determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup>Determined by HPLC after reduction to the corresponding alcohol. <sup>d</sup>4 Å molecular sieves were added.

Dipolar cycloadditions catalyzed by organic molecules typically require the presence of a large excess of α,β-unsaturated aldehyde (from 6 to 15 equivalents) to assure completion of the reaction. Hydrazide catalysts such as 7.1 rapidly and completely form iminium ions with the aldehyde components of these processes as demonstrated in Diels-Alder the kinetic studies.<sup>1,2</sup> Thus, consistent supplies of reactive iminium intermediate are available, enabling the reactions to be performed with as little as five equivalents of dipolarophile. Slow addition of the aldehyde component over 48 hours using a syringe-pump did not result in better selectivity but instead reduced the combined yield of the desired cycloadducts from 82 to 59 percent.

The reaction was also performed at lower temperature in an attempt to increase the selectivity. Although the diastereomeric ratios were found to be slightly higher at -20 °C than at +4 °C, there was no significant advantage in terms of enantioselectivity obtained (Table 7.3, entries 1 & 2).
Hydrazide-Catalyzed 1,3-Dipolar Cycloadditions

The main drawback of performing the reaction at -20 °C was the extensive time required for the reaction to achieve completion. When the reaction was performed at a higher concentration (1.0M) at -20 °C (entry 3), the reaction time was reduced to 72 hours and the diastereomeric ratio was increased to 79:21 favoring the exo isomer but the overall yield of the reaction was reduced together with the enantiomeric excess of the exo isomer. When a concentrated reaction was performed at +4 °C, the reaction time was shortened to 24 hours but decreases in both yields and enantioselectivities were noted. In addition, significant amounts of the unwanted by-product 7.20 were observed using these conditions (entry 4). When the reaction was attempted at room temperature, significant amounts of unwanted product 7.20 were observed together with several other uncharacterized impurities.

Table 7.3 Effect of temperature and concentration on the hydrazide-catalyzed dipolar cycloaddition reaction between E-crotonaldehyde and nitrene 7.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Yield %a</th>
<th>exo:endoa</th>
<th>ee exoa</th>
<th>ee endoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>+4</td>
<td>72</td>
<td>82 (0)</td>
<td>62:38</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>-20</td>
<td>280</td>
<td>81 (0)</td>
<td>74:26</td>
<td>63</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>-20</td>
<td>72</td>
<td>55 (4)</td>
<td>79:21</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>+4</td>
<td>24</td>
<td>55 (11)</td>
<td>72:28</td>
<td>26</td>
<td>71</td>
</tr>
</tbody>
</table>

aIsolated combined yield of 7.18 and 7.19. Value in parentheses refers to the yield of 7.20. b determined by 1H NMR of the crude product. c determined by HPLC after reduction to the corresponding alcohol.

In our studies related to the Diels-Alder cycloaddition, we had shown that counterion effects may have significant impacts on processes catalyzed by organic catalysts. The present reaction was also found to be sensitive to the nature of the Brønsted co-catalyst used. Both triflic and
perchloric acids were found to produce the best yields and enantioselectivities (Table 7.4, entries 1 and 2). Weaker acids provided significantly larger amounts of undesired product 7.20 (entries 3-5), together with reduced enantiomeric excesses, primarily in the *exo* adduct.

### Table 7.4 Effect of Bronsted acid co-catalyst on the 1,3 dipolar cycloaddition between *E*-crotonaldehyde and nitrore 7.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>*exo:*endo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee *exo&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee *endo&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>82 (0)</td>
<td>62:38</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>HClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>86 (0)</td>
<td>66:34</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>HCl</td>
<td>29 (31)</td>
<td>70:30</td>
<td>29</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;H</td>
<td>39 (24)</td>
<td>71:29</td>
<td>32</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>40 (14)</td>
<td>74:26</td>
<td>31</td>
<td>75</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated combined yield of 7.18 and 7.19. Value in parentheses refers to the yield of 7.20. <sup>b</sup>determined by <sup>1</sup>H NMR of the crude product. <sup>c</sup>determined by HPLC after reduction to the corresponding alcohol.

Variations in the side chain of the hydrazide catalyst had previously produced significant improvements in reactivity and enantioselectivity. Several hydrazides containing a variety of side chains were therefore prepared using the procedure described in Scheme 3.19 of Chapter 3 and were tested as catalysts in the [3+2] process. Incorporating a bulky tert-butyl group at this position dramatically reduced the yield of the process and produced no enantiomeric excess (Table 7.5, entry 2), suggesting that the aromatic residue found in catalyst 7.1 was essential at this position. We had previously observed that the incorporation of a conformational controlling element onto the benzylic position of the catalyst afforded superior selectivities in the Diels-
Alder cycloaddition.\(^3\) The use of this rigidified catalyst did increase the enantioselectivity of the \textit{endo} isomer but also resulted in a poor \textit{ee} for the \textit{exo} product (entry 3). The diastereoselectivity was reversed when this catalyst was used, now giving a slight preference for the \textit{endo} adduct. When an electron withdrawing \(p\)-CF\(_3\) group was incorporated on the phenyl ring no significant changes were observed suggesting that electronic effects did not offer any advantages relative to the unsubstituted benzyl catalyst. Replacement of the side-chain with a bulkier diphenylmethyl group did not improve the enantioselectivity as shown in entry 6. Interestingly, this modification was previously found to be highly deleterious in our studies of the Diels-Alder reaction.

Table 7.5 Effect of the side chain of the hydrazide catalyst on the dipolar cycloaddition reaction between \textit{E}-crotonaldehyde and nitrone 7.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Yield %(^a)</th>
<th>\textit{exo:endo}(^b)</th>
<th>\textit{ee exo}(^c)</th>
<th>\textit{ee endo}(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>72</td>
<td>80</td>
<td>63:37</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>96</td>
<td>24</td>
<td>67:33</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>120</td>
<td>72 (3)</td>
<td>34:66</td>
<td>37</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>72</td>
<td>83</td>
<td>68:32</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>72</td>
<td>81</td>
<td>64:36</td>
<td>73</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^a\) Yield expressed as a percentage of the isolated product.

\(^b\) Ratio of \textit{exo} to \textit{endo} isomers.\(^c\) Enantiomeric excess for the \textit{exo} and \textit{endo} isomers.
Hydrazide-Catalyzed 1,3-Dipolar Cycloadditions

We were pleased to find that a methyl-1-naphthyl moiety did offer a slight advantage relative to the benchmark catalyst 7.1, providing better diastereomeric ratios and improved enantioselectivities for both the exo and endo cycloadducts (entry 4). These improvements were however dependant on the nature of the dipole used, and did not translate to all substrates, as observed in investigations of the scope below.

### 7.2 Scope of the Reaction

Experiments that outline the scope of the present process are given in Table 7.6. All the nitrones used in this these transformations were synthesized starting from an aldehyde and hydroxylamine hydrochloride to afford the intermediate aldehyde oxime. These were reduced to the N-substituted hydroxylamines using a combination of sodium cyanoborohydride and hydrochloric acid. With this precursor in hand, simple treatment with the corresponding aldehyde in the presence of MgSO₄ gave the desired nitrones.

Scheme 7.4 Synthetic sequence for assembly of various nitrones

Generally, the hydrazide catalyst was dissolved in a 0.1 M solution of nitromethane and cooled to 0 °C. Half an equivalent of distilled water was added followed by 20 mol% of CF₃SO₃H to
minimize acid catalyzed polymerization. The corresponding nitrone was then added in one portion followed by 3 equivalents of freshly distilled E-crotonaldehyde. The reaction was stirred at +4 °C for 48 hours, after which time additional E-crotonaldehyde was added if necessary. Once complete, the reaction mixture was passed through a plug of silica with CH₂Cl₂, dried and analyzed by $^1$H NMR for determination of the diastereomeric ratio. The aldehyde was dissolved in ethanol and reduced to the primary alcohol using sodium borohydride at 0 °C. Purification by silica gel chromatography provided the cycloadducts for the determination of enantiomeric purity. The compounds were characterized as the more stable alcohols which also allowed for better separation of the diastereoisomers. The absolute stereochemistry was assigned by direct comparison with authentic samples.

\[175\] Water must be added before the triflic acid in order to minimize the formation of brown impurities upon addition of the aldehyde. It is thought that the water dissociates the acid and prevents polymerization of the aldehyde.
Table 7.6 Hydrazide-catalyzed 1,3 dipolar cycloaddition reactions between various aldehydes and nitrones

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Time</th>
<th>Yield %</th>
<th>exo:endo</th>
<th>ee exo</th>
<th>ee endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Bn</td>
<td>Ph</td>
<td>72</td>
<td>82</td>
<td>62:38</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Bn</td>
<td>2-ClPh</td>
<td>111</td>
<td>92</td>
<td>33:67</td>
<td>59</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Bn</td>
<td>4-OMePh</td>
<td>72</td>
<td>87</td>
<td>48:52</td>
<td>79</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Bn</td>
<td>4-MePh</td>
<td>72</td>
<td>88</td>
<td>57:43</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Bn</td>
<td>4-iPrPh</td>
<td>72</td>
<td>85</td>
<td>64:36</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Bn</td>
<td>4-CF₃Ph</td>
<td>72</td>
<td>67</td>
<td>55:45</td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>Bn</td>
<td>2-naphtyl</td>
<td>96</td>
<td>94</td>
<td>45:55</td>
<td>60</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>Me</td>
<td>4-MePh</td>
<td>72</td>
<td>71</td>
<td>52:48</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>95</td>
<td>61</td>
<td>57:43</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>Me</td>
<td>2-furyl</td>
<td>120</td>
<td>38</td>
<td>50:50</td>
<td>69</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>n-Pr</td>
<td>Bn</td>
<td>Ph</td>
<td>145</td>
<td>86</td>
<td>60:40</td>
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</tr>
<tr>
<td>12</td>
<td>i-Pr</td>
<td>Bn</td>
<td>Ph</td>
<td>145</td>
<td>68</td>
<td>57:43</td>
<td>66</td>
<td>77</td>
</tr>
</tbody>
</table>

*isolated combined yield of endo and exo products. b determined by ¹H NMR of the crude product. c determined by HPLC after reduction to the corresponding alcohol.

Ortho substituted aryl residues were tolerated on the nitrobenzene component, resulting in a 92% yield of products. In this case, the enantioselectivity of the endo product was found to be higher than the enantioselectivity observed in entry 1 however a slightly lower ee was noted for the corresponding exo material (entry 2). A variety of substituents were tolerated at the para position including electron donating and withdrawing substituents (entries 3, 4, 5 & 6). The nitrobenzene substituents (R₃) could also be varied to include smaller groups, giving high ee's for both the exo
and *endo* products (entries 8-10). When R₄ was changed to a 2-furyl group good selectivity was maintained but the yield for this reaction was considerably lower. Coincidentally, heteroaromatic substituents also gave poor chemical yields in the Diels-Alder cycloadditions. Larger α,β-unsaturated aldehydes such as those bearing $n$-propyl and *iso*-propyl substituents afforded good enantioselectivities and yields (entries 11 and 12). Larger α,β-unsaturated aldehydes such as these are seldom used in nitrode cycloadditions, particularly when catalyzed by Lewis acid.

A comparison was made between the benchmark benzyl catalyst 7.1 and the catalyst bearing a methyl-1-naphthyl side chain. The use of the latter hydrazide catalyst gave small improvements in the enantioselectivities of the *exo* isomers but no advantages in terms of yield or diastereoselectivities. (Table 7.7, entries 2, 4, 6, & 8). The increase in optical purity translated to only a selected number of nitrones relative to catalyst 7.1. However, this implies that simple tailoring of the catalyst can provide enhanced selectivities.
Table 7.7 Comparison between benchmark catalyst 7.1 and methyl-1-naphthyl catalyst in the Diels-Alder cycloaddition between various dipoles and E-crotonaldehyde

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (R₁)</th>
<th>R₃</th>
<th>R₄</th>
<th>Time</th>
<th>Yield %</th>
<th>exo:endo</th>
<th>ee exo</th>
<th>ee endo</th>
</tr>
</thead>
<tbody>
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<td>52:48</td>
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*a*isolated combined yield of *endo* and *exo* products. *b*determined by *¹*H NMR of the crude product. *c*determined by HPLC after reduction to the corresponding alcohol.

This observation prompted us to further expand the investigation of the effect of the hydrazide catalyst side chain to include sites for possible hydrogen-bonding. Of the many organic catalysts being used for asymmetric transformations, several incorporate pendant groups that bring the reaction components together in the transition state, often resulting in an increase in selectivity.
To investigate this possibility, catalysts bearing picolyl or picolyl-\(N\)-oxide side chains were synthesized (Scheme 7.5). Picolyl hydrazines were easily assembled from picolyl halides and hydrazine monohydrate. These were reacted directly in a slight excess with \(S\-\(+\)-ketopinic acid 7.29 in the presence of catalytic acetic acid. The unstable hydrazoic acid intermediates 7.30 were directly submitted to cyclization in mesitylene using a Dean-Stark apparatus to afford the cyclized products 7.31 in 53-71% for the two chemical transformations. This common intermediate could then be reduced using sodium cyanoborohydride to provide the picolyl hydrazide catalysts 7.32 in 78-87% yield. Alternatively, 7.31 could be treated under mild conditions with methyltrimethoxy rhenium in the presence of hydrogen peroxide to oxidize the pyridine ring to the picolyl \(N\)-oxide. Reduction of the latter with sodium cyanoborohydride gave the picolyl-\(N\)-oxide catalysts 7.34 in 54-76% for these two synthetic steps.
Table 7.8 Effect of pyridine and pyridine-N-oxide hydrazide catalysts on the dipolar cycloaddition reaction between E-crotonaldehyde and nitrone 7.7

<table>
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<th>Entry</th>
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<th>Time</th>
<th>Yield %</th>
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<td>72</td>
<td>72</td>
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*Isolated combined yield of 7.18 and 7.19. †Determined by 1H NMR of the crude product. ‡Determined by HPLC after reduction to the corresponding alcohol.

These new catalysts were tested in the [3+2] cycloaddition reaction between N-benzylidenebenzylamine-N-oxide and E-crotonaldehyde. Although all the picolyl-substituted catalysts (Table 7.8, entries 1-3) afforded slightly higher diastereoselectivities, in favor of the exo isomer, than the catalyst bearing a simple benzyl side chain, the enantiomeric excesses of the products were found to be low, particularly when the 4-picoly substituted catalyst was used. The
picoly-N-oxide substituted catalysts (entries 4-6) offered somewhat higher exo:endo ratios (83:17 for entry 10) but lower enantioselectivities than those of catalyst 7.1.

### 7.3 Limitations

Not all substrates were compatible with the hydrazide-catalyzed [3+2] protocol. When a nitrone bearing a cyclohexyl substituent 7.35 was reacted with E-crotonaldehyde, hydrolyzed product 7.20 was identified as the major product. When the same reaction was performed at -20 °C none of the desired cycloadduct was observed and the major by-product was crotyl nitrone 7.15. After 66 hours, tert-butyld derived nitrone 7.36 was completely hydrolyzed to crotyl nitrone 7.15 and the hydrolyzed cycloadducts 7.20 was obtained in 38% conversion. Electron-withdrawing 3-nitro derivative 7.37 afforded only traces of the product after 480 hours. Analogously to the Diels-Alder reaction, groups containing a thiophenyl moiety such as thiophenyl analogue 7.38 was also poorly reactive in the 1,3-dipolar cycloaddition reaction.

Figure 7.1 Unsuccessful substrates in the hydrazide-catalyzed 1,3-dipolar nitrone cycloadditions

Certain dipolarophiles were also found to be poorly reactive. E-cinnamaldehyde 7.39 provided only traces of the desired cycloadducts after 480 hours. We hypothesized that the phenyl group, in conjugation with the reactive olefin might limit the reactivity of the dienophile. Consequently, a substrate in which the phenyl group was extended by a two carbon 7.40 spacer was tested. The
Hydrazide-Catalyzed 1,3-Dipolar Cycloadditions

desired product of this reaction was obtained in a modest conversion but was hard to isolate from
the reaction mixture due to high boiling of the dipolarophile which also coincidentally co-spoted
with the desired product on TLC.

Since E-cinnamaldehyde was unreactive in hydrazide catalyzed [3+2] cycloadditions, p-
nitrocinnamaldehyde 7.41, a more reactive α,β-unsaturated aldehyde used in our previous Diels-
Alder experiments was tested. Unfortunately, none of the desired 1,3-dipolar cycloadducts was
observed but instead a polar product was identified on TLC. Isolation and characterization of the
bright yellow solid revealed that the new compound was formed from a nitrone exchange in 79% yield.

Scheme 7.6 Formation of nitrone by-product 7.42

On the other hand, when smaller substrates such as acrolein 7.44 were employed as the
dipolarophile, inseparable mixtures of regioisomers, together with endo and exo cycloadducts
were obtained. Attempts were made to isolate the mixture of regioisomers after conversion of the
cycloadducts to a primary alcohol. Unfortunately the mixture of regio and diastereoisomers was
extremely difficult to separate following multiple silica gel chromatographies.
7.4 Stereochemical rationale

Based on calculations and X-ray structures of iminium ions generated by hydrazide catalysts, a model for the facial selectivity observed in the dipolar cycloaddition can be proposed. The preferred Z-S-trans-iminium intermediate leads to the observed diastereoisomers 7.8 and 7.9 through bottom-face approach of the nitrone as shown below. Similarly to the Diels-Alder cycloadditions, stereochemical bias is provided in this structure by the steric bulk of the camphor bridgehead methyl groups that impair top-side approach of the nitrone.
The low diastereoselectivity observed, compared to other organocatalytic protocols, is suggestive of a limited ability of the catalyst to discriminate between \textit{exo} and \textit{endo} pathways. Larger and potential hydrogen-bonding substituents were introduced in place of the benzyl side-chain of the catalyst framework to test the effect of a potential increased steric requirement. Only small increases in diastereoselectivity were observed (Table 7.8) suggesting that other factors, perhaps not directly involved with the catalyst architecture, may be governing the diastereoisomer selection in this process.
Figure 7.3 Facial selectivity during the formation of \textit{exo} and \textit{endo} cycloadducts
7.5 Conclusions

We have developed a highly enantioselective organocatalyzed [3+2] cycloaddition reaction using a range of nitrones and \( \alpha,\beta \)-unsaturated aldehydes. This new system nicely complements other examples of organocatalyzed cycloadditions reactions reported to date. Although the diastereoselectivities observed were lower than some that have been previously observed, the use of hydrazide catalysts allows access to the \( \textit{exo} \) cycloadduct, which is otherwise difficult to obtain from acyclic dipolarophiles. Reaction optimization studies suggest that rigorous control of the water content is necessary for good yields in this process. Minimizing the amount of water available prevents the hydrolysis of the nitrone dipole, thus minimizing the amount of byproducts such as \( \texttt{7.20} \). We also found that the amount of water present also has an impact on the enantioselectivity of the major \( \textit{exo} \) isomer which could suggest that a non-asymmetric background reaction may be operative.

Camphor-based hydrazides have been effectively applied to 1,3-dipolar nitrone cycloadditions and Diels-Alder cycloaddition processes. The success obtained in these investigations suggests that other members of the Ogilvie groups could investigate the potential of this efficient catalytic scaffold toward other related chemical transformations in the near future.
**Experimental:**

**Hydrazide-Catalyzed 1,3-Dipolar Cycloadditions**

**General Information.** All solvents were used as obtained from commercial suppliers unless otherwise indicated. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. All starting materials were purchased and were used without purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F$_{254}$. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. Room temperature corresponds to 22 °C. Excess solvents were removed *in vacuo* at pressures obtained by water or air aspirators connected to a rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with Silica Gel 60 (230-400 mesh). Infrared (IR) spectra were obtained as neat films on a sodium chloride cell. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. Mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a mass spectrometer with an electron beam energy of 70 eV (for EI). Electrospray analyses were run on a triple quad mass spectrometer VG QUATTRO. High resolution mass spectroscopy (HRMS) was performed on a mass spectrometer with an electron beam of 70 eV, or a double focusing magnetic sector mass spectrometer. Melting points were measured using a Melt Temp apparatus and are uncorrected. Diastereomeric ratios were determined by 1H NMR. Absolute configuration determined by analogy with products provided using Macmillan’s catalyst.$^{25}$ Non-commercial mono-substituted
Experimental Section: 1,3-Dipolar Cycloadditions

Hydrazines were prepared by syringe pump addition of a methanolic solution of pyridyl halides to an excess of hydrazine monohydrate (10 eq) at 0 °C.\(^{141}\)

\[ (S)-(+)\text{-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0\_1\_5]dec-4-en-2-one (7.31-1).} \]

Acetic acid (0.19 mL, 3.38 mmol) was added dropwise to a solution of (S)-(+)ketopinic acid\(^{118}\) 7.29 (3.08 g, 16.9 mmol) and 2-picolylhydrazine (2.50 g, 20.3 mmol) in anhydrous dichloromethane (150 ml) at room temperature. The reaction mixture was stirred at that temperature until judged complete by TLC analysis (28 hours), then passed through a short silica plug and the solvent was removed \textit{in vacuo}. The crude hydrazonocarboxylic acid 7.30-1 was dissolved in mesitylene (120 mL) and was refluxed while water was removed using a dean-stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC (46 hours). The cooled reaction mixture was directly loaded onto a silica column and was purified by flash chromatography (hexanes followed by 40 % EtOAc in hexanes) to provide the desired compound as a white solid (3.10 g, 68 %). mp 131-133°C; [α]\(D\) +24.58° (c 1.11, CHCl\(_3\)); IR (neat) 2967, 1691, 1589 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.57-8.53 (m, 1H), 7.65-7.61 (m, 1H), 7.20-7.14 (m, 2H), 5.00 (d, J = 16.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 2.60 (ddd, J = 17.7, 3.4, 3.4 Hz, 1H), 2.32 (ddd, J = 12.2, 4.4, 4.4 Hz, 1H), 2.26 (t, J = 4.3 Hz, 1H), 2.19-2.10 (m, 2H), 1.73 (ddd, J = 13.3, 9.5, 4.4 Hz, 1H), 1.51 (ddd, J = 13.2, 9.5, 4.4 Hz, 1H), 1.23 (s, 3H), 0.96 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.7 (C), 173.9 (C), 156.7 (C), 149.4 (CH), 136.7 (CH), 122.3 (CH), 121.4 (CH), 63.6 (C), 49.9 (C), 49.7 (CH\(_2\)), 49.3 (CH), 32.0 (CH\(_2\)), 27.0 (CH\(_2\)), 25.5 (CH\(_2\)), 19.2 (CH\(_3\)), 18.6 (CH\(_3\)); MS (EI) 269.2 (M\(^+\)); HRMS calcd for C\(_{16}\)H\(_{19}\)N\(_3\)O 269.1528; found 269.1520.
Experimental Section: 1,3-Dipolar Cycloadditions

\[
(5)\, (+)-3-(3\text{-}picolyI\text{-}10,10\text{-}dimethyl\text{-}3,4\text{-}diaza\text{-}tricyclo[5.2.1.0^1,5]\text{-}dec-4\text{-}en-2\text{-}one} \quad (7.31\text{-}2).
\]
Prepared by a procedure similar to that described above for 7.31-1 from (5)-(+)\text{-}ketopinic acid 7.29 (3.08 g, 16.9 mmol) and 3\text{-}picolyIhydrazine (2.50 g, 20.3 mmol). Purification by silica gel chromatography (hexanes then 50% EtOAc in hexanes) provided the compound as a white solid (2.41 g, 53%). mp 124-126°C; \([\alpha]_D +27.5°\) (c 1.21, CHCl\textsubscript{3}); IR (neat) 2971, 1688, 1634 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.57-8.48 (m, 2H), 7.62-7.59 (m, 1H), 7.25-7.21 (m, 1H), 4.83 (d, J = 15.4 Hz, 1H), 4.79 (d, J = 15.4 Hz, 1H), 2.54 (ddd, J = 17.6, 3.5, 3.4 Hz, 1H), 2.30-2.21 (m, 2H), 2.15-2.07 (m, 2H), 1.64 (ddd, J = 13.3, 9.5, 4.3 Hz, 1H), 1.47 (ddd, J = 13.1, 9.4, 4.3 Hz, 1H), 1.19 (s, 3H), 0.86 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 174.9 (C), 173.7 (C), 149.3 (CH), 148.9 (CH), 135.6 (CH), 132.7 (C), 123.4 (CH), 63.7 (C), 50.0 (C), 49.2 (CH), 45.4 (CH\textsubscript{2}), 31.9 (CH\textsubscript{2}), 26.9 (CH\textsubscript{2}), 25.3 (CH\textsubscript{2}), 19.1 (CH\textsubscript{3}), 18.6 (CH\textsubscript{3}); MS (El) 269.2 (M\textsuperscript{+}); HRMS calcd. for C\textsubscript{16}H\textsubscript{19}N\textsubscript{3}O 269.1528; found 269.1529.

\[
(5)\, (+)-3-(4\text{-}picolyI\text{-}10,10\text{-}dimethyl\text{-}3,4\text{-}diaza\text{-}tricyclo[5.2.1.0^1,5]\text{-}dec-4\text{-}en-2\text{-}one} \quad (7.31\text{-}3).
\]
Prepared by a procedure similar to that described above for 7.31-1 from (5)-(+)\text{-}ketopinic acid 7.29 (2.47 g, 13.5 mmol) and 4\text{-}picolyIhydrazine (2.00 g, 16.2 mmol). Purification by silica gel chromatography (hexanes then 50% EtOAc in hexanes) provided the compound as a white solid (2.59 g, 71%). mp 140.5-142°C; \([\alpha]_D +25.6°\) (c 1.04, CHCl\textsubscript{3}); IR (neat) 2963, 1692, 1600 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.55-8.52 (m, 2H), 7.19-7.16 (m, 2H), 4.83 (d, J = 15.9 Hz, 1H), 4.79 (d, J = 15.9 Hz, 1H), 2.57 (ddd, J = 17.7, 3.4, 3.3 Hz, 1H), 2.33-2.24 (m, 2H), 2.17-2.09 (m, 2H), 1.68
Experimental Section: 1,3-Dipolar Cycloadditions

(ddd, J = 13.4, 9.5, 4.3 Hz, 1H), 1.50 (ddd, J = 13.1, 9.5, 4.3 Hz, 1H), 1.21 (s, 3H), 0.91 (s, 3H); $^1$C NMR (125 MHz, CDCl$_3$) δ 175.1 (C), 173.8 (C), 150.0 (CH), 146.0 (C), 122.5 (CH), 63.2 (C), 50.0 (C), 49.2 (CH), 46.9 (CH$_2$), 31.9 (CH$_2$), 27.0 (CH$_2$), 25.5 (CH$_2$), 19.1 (CH$_3$), 18.6 (CH$_3$); MS (EI) 269.2 (M$^+$); HRMS calcd. for C$_{16}$H$_{19}$N$_3$O 269.1528; found 269.1549.

(S)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]decan-2-one (Table 7.8, entry 1). To a solution of (S)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]dec-4-en-2-one 7.31-1 (300 mg, 1.11 mmol) in a 1:2 mixture of acetic acid and methanol (20 mL) was added sodium cyanoborohydride (700 mg, 10.0 mmol) in small portions over 1 h. The reaction mixture was then stirred at room temperature until TLC indicated that the reaction was complete (29 hours). Excess borohydride was quenched by the addition of 10 % HCl. The products were extracted using CH$_2$Cl$_2$ and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH$_2$Cl$_2$. The organic extracts were combined, washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the product was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired compound as a white solid (248 mg, 82 %). mp 80.5-83 °C; [α]$_D$ -4.0° (c 1.04, CHCl$_3$); IR (neat) 3241, 2956, 1665 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.52-8.49 (m, 1H), 7.67-7.61 (m, 1H), 7.28-7.24 (m, 1H), 7.19-7.15 (m, 1H), 4.87 (d, J = 15.7 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 3.65-3.58 (m, 1H) 2.19-2.05 (m, 2H), 1.94-1.86 (m, 2H), 1.73-1.66 (m, 1H), 1.35-1.20 (m, 2H), 1.17 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.2 (C), 156.4 (C), 149.3 (CH), 136.8 (CH), 122.4 (CH), 122.1 (CH), 65.2 (CH), 58.4 (C), 51.2 (C), 49.1 (CH$_2$), 46.8 (CH), 36.4 (CH$_2$), 28.7 (CH$_2$), 26.7 (CH$_2$), 21.0 (CH$_3$), 20.4 (CH$_3$); MS (EI) 271.2 (M$^+$); HRMS calcd for C$_{16}$H$_{21}$N$_3$O 271.1685; found 271.1711.
(S)-(+)\-3-(3-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one (Table 7.8, entry 2). Prepared by a procedure similar to that described above for (S)-(+)\-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one from (S)-(+)\-3-(3-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one 7.31-2 (200 mg, 0.74 mmol). Purification by silica gel chromatography (EtOAc) provided the title compound as a white solid (175 mg, 87\%\). mp 76.5-78 °C; [α]_D\+9.0 (c 1.01, CHCl_3); IR (neat) 3229, 2957, 1660 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 8.57-8.51 (m, 2H), 7.67-7.63 (m, 1H), 7.28-7.23 (m, 1H), 4.67 (d, J = 14.5 Hz, 1H), 4.51 (d, J = 14.4 Hz, 1H), 3.57-3.50 (m, 1H) 2.21-2.13 (m, 1H), 2.04-1.97 (m, 1H), 1.94-1.86 (m, 2H), 1.71-1.64 (m, 1H), 1.33-1.16 (m, 2H), 1.07 (s, 3H), 1.06 (s, 3H); ^13C NMR (125 MHz, CDCl_3) δ 171.4 (C), 149.8 (CH), 149.2 (CH), 136.2 (CH), 131.8 (C), 123.6 (CH), 65.6 (CH), 58.3 (C), 51.3 (C), 46.8 (CH), 45.7 (CH_2), 36.3 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.3 (CH_3); MS (EI) 271.2 (M^+); HRMS calcd for C_{16}H_{21}N_3O 271.1685; found 271.1689.

(S)-(+)\-3-(4-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one (Table 7.8, entry 3). Prepared by a procedure similar to that described above for (S)-(+)\-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one from (S)-(+)\-3-(4-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one 7.31-3 (300 mg, 1.11 mmol). Purification by silica gel chromatography (EtOAc) provided the title compound as a white solid (236 mg, 78\%). mp 105-106.5 °C; [α]_D\+14.2° (c 1.07, CHCl_3); IR (neat) 3233, 2957, 1663 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 8.59-8.53 (m, 2H), 7.23-7.18 (m, 2H), 4.71 (d, J = 15.6 Hz, 1H), 4.44 (d, J = 15.6 Hz, 1H), 3.60-
Experimental Section: 1,3-Dipolar Cycloadditions

3.54 (m, 1H) 2.23-2.14 (m, 1H), 2.05-1.98 (m, 1H), 1.96-1.87 (m, 2H), 1.73-1.66 (m, 1H), 1.36-1.20 (m, 2H), 1.14 (s, 3H), 1.09 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.8 (C), 150.2 (CH), 145.2 (C), 123.0 (CH), 65.8 (CH), 58.2 (C), 51.3 (C), 47.3 (CH$_2$), 46.8 (CH), 36.2 (CH$_2$), 28.7 (CH$_2$), 26.7 (CH$_2$), 21.0 (CH$_3$), 20.4 (CH$_3$); MS (EI) 271.2 (M$^+$); HRMS calcd for C$_{16}$H$_{21}$N$_3$O 271.1685; found 271.1689.

(S)-(+-3-(2-picolyl-N-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]decan-2-one (Table 7.8, entry 4). A mixture of (S)-(+-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0$^{1,5}$]dec-4-en-2-one 7.31-1 (400 mg, 1.49 mmol) and methyltrioxorhenium (MTO) (1.9 mg, 0.01 mmol) in CH$_2$Cl$_2$ (8 mL) was cooled to 0 °C and treated with a 30% solution of aqueous hydrogen peroxide (0.17 mL, 1.78 mmol). The biphasic reaction mixture was stirred until judged complete by TLC (94 hours) and filtered over a small pad of celite with CH$_2$Cl$_2$. Removal of the solvent in vacuo afforded crude N-oxide-pyrazolone 7.33 which was dissolved in a 1:2 mixture of acetic acid and methanol (30 mL). Sodium cyanoborohydride (875 mg, 13.9 mmol) was added in small portions over 1 h and the reaction mixture was stirred at room temperature until TLC indicated that the reaction was complete (45 hours). Excess borohydride was quenched by the addition of 10 % HCl. The products were extracted using CH$_2$Cl$_2$ and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH$_2$Cl$_2$. The organic extracts were combined, washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the product was purified by flash chromatography (2% MeOH in CHCl$_3$) to afford the desired compound as a white solid (277 mg, 65 %). mp 144-145 °C; [$\alpha$]$_D$ +9.8° (c 1.00, CHCl$_3$); IR (neat) 3419, 2959, 1651 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, J = 6.2 Hz, 1H), 7.42 (dd, J = 7.6, 2.0 Hz, 1H), 7.25-7.15 (m, 2H), 4.81 (d, J = 15.2 Hz, 1H), 4.56 (d, J = 15.2 Hz, 1H), 3.57 (dd, J = 8.3, 4.6 Hz, 1H), 2.08-2.00 (m, 2H), 1.85-1.77 (m, 2H), 1.61 (dd, J = 12.9, 8.3 Hz, 1H), 1.24-1.13 (m, 2H), 1.10 (s, 3H), 0.96 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.9 (C), 146.6 (C), 139.3 (CH), 127.1 (CH), 126.4 (CH), 125.2 (CH), 64.9
Experimental Section: 1,3-Dipolar Cycloadditions

(CH), 58.1 (C), 51.1 (C), 46.6 (CH), 44.4 (CH₂), 36.3 (CH₂), 28.5 (CH₂), 26.6 (CH₂), 20.7 (CH₃), 20.1 (CH₃); MS (EI) 287.2 (M⁺); HRMS calcd for C₁₆H₂₁N₃O₂ 287.1634; found 287.1652.

(5)-(+)-3-(3-picolyl-N-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one (Table 7.8, entry 5). Prepared by a procedure similar to that described above for (S)-(+)-3-(2-picolyl-N-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one from (S)-(+)-3-(3-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-4-en-2-one 7.31-2 (300 mg, 1.11 mmol), MTO (1.4 mg, 0.01 mmol) 30% solution of aqueous hydrogen peroxide (0.13 mL, 1.34 mmol). After 26 hours, purification by silica gel chromatography (5% MeOH in CHCl₃) provided the title compound as a white solid (173 mg, 54%). mp 146-148 °C; [α]₀ +6.2° (c 1.01, CHCl₃); IR (neat) 3427, 2958, 1661 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.29-8.11 (m, 2H), 7.34-7.21 (m, 2H), 4.68 (d, J = 15.1 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H), 3.64-3.56 (m, 1H), 2.20-2.04 (m, 2H), 1.96-1.87 (m, 2H), 1.77-1.69 (m, 1H), 1.35-1.17 (m, 2H), 1.10 (s, 3H), 1.06 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8 (C), 138.9 (CH), 138.3 (CH), 136.1 (C), 126.2 (CH), 125.9 (CH), 65.6 (CH), 58.0 (C), 51.3 (C), 46.7 (CH), 45.0 (CH₂), 36.2 (CH₂), 28.5 (CH₂), 26.6 (CH₂), 20.9 (CH₃), 20.3 (CH₃); MS (EI) 287.2 (M⁺); HRMS calcd for C₁₆H₂₁N₃O₂ 287.1634; found 287.1620.

(5)-(+)-3-(4-picolyl-N-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one (Table 7.8, entry 6). Prepared by a procedure similar to that described above for (S)-(+)-3-(2-picolyl-N-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0₁₅]decan-2-one from (S)-(+)-3-(4-picolyl)-10,10-dimethyl-
Experimental Section: 1,3-Dipolar Cycloadditions

3,4-diaza-tricyclo[5.2.1.0^1,5]dec-4-en-2-one 7.31-3 (400 mg, 1.49 mmol), MTO (1.9 mg, 0.01 mmol) 30% solution of aqueous hydrogen peroxide (0.17 mL, 1.78 mmol). After 24 hours, purification by silica gel chromatography (5% MeOH in CHCl₃) provided the title compound as a white solid (324 mg, 76%). mp 186.5-188.5°C; [α]₀ +4.7° (c 1.01, CHCl₃); IR (neat) 3436, 2952, 1642 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09 (d, J = 6.9 Hz, 2H), 7.20 (d, J = 6.7 Hz, 2H), 4.59 (d, J = 15.4 Hz, 1H), 4.40 (d, J = 15.4 Hz, 1H), 3.54 (dd, J = 8.3, 4.6 Hz, 1H), 2.16-2.09 (m, 1H), 2.03-1.97 (m, 1H), 1.92-1.84 (m, 2H), 1.68 (dd, J = 13.1, 8.4, Hz, 1H), 1.30-1.13 (m, 2H), 1.07 (s, 3H), 1.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.9 (C), 139.1 (CH), 135.4 (C), 125.8 (CH), 64.8 (CH), 58.1 (C), 51.3 (C), 46.8 (CH), 46.4 (CH₂), 36.2 (CH₂), 28.6 (CH₂), 26.6 (CH₂), 20.9 (CH₃), 20.4 (CH₃); MS (EI) 287.2 (M⁺); HRMS caled for C₁₆H₂₁N₃O₂ 287.1634; found 287.1628.

Benzaldehyde oxime. To a solution of benzaldehyde (15.9 g, 0.15 mol) and hydroxylamine hydrochloride (32.3g, 0.50 mol) in 90% EtOH (500 mL) was added powdered NaOH (54g, 1.35 mol) in small portions. The mixture was stirred at 22°C for 1 hour and refluxed for another hour. After cooling, the mixture was poured into diluted HCl (60 mL HCl in 230 mL H₂O), and carefully concentrated to a third of the original volume (solution becomes cloudy) and finally extracted twice with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude oil was purified via micro distillation (lit.: bp. 71°C, 0.5 torr) to give 15.9 g (88 %) of benzaldehyde oxime as a semi-solid. Spectroscopic date is consistent with previously reported values.¹⁷⁶

Experimental Section: 1,3-Dipolar Cycloaditions

*N-benzylhydroxylamine.* Benzaldehyde oxime (10.7 g, 88.4 mmol) was dissolved in MeOH (120 mL) and cooled to 0°C. NaBH₃CN (9.5 g, 151 mmol) was then added followed by a dropwise addition of 12 N HCl (14.9 mL, 177 mmol). After addition, the reaction mixture was allowed to warm to 22°C and was stirred for 5 hours. The pH was adjusted to ~9 using 6 N NaOH, and the MeOH was removed *in vacuo.* The oily mixture was extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo.* The crude *N*-benzyl-hydroxylamine was recrystallized twice from a 1:6 benzene/hexanes mixture to afford 9.1 g (83 %) as colorless crystals. Spectroscopic data is consistent with previously reported values.¹⁷⁷

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\text{Ph} - \overset{+}{N} - \overset{-}{O} - \\
\text{H} - \text{Ph}
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*(Z)-*N-*benzylidene-benzylamine N-oxide.* *N*-benzylhydroxylamine (3.5 g, 28.5 mmol), benzaldehyde (3.02 g, 28.5 mmol) and MgSO₄ (3.43 g, 28.5 mmol) were stirred in Et₂O for 24 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography (EtOAc) afforded 6.5 g (86 %) of *(Z)-*N-*benzylidene-benzylamine-N-oxide* as a white solid. ¹H NMR (300 MHz, CDCl₃) 8.25-8.17 (m, 2H), 7.56-7.38 (m, 9H), 5.09 (m, 2H). ¹H NMR, ¹³C NMR and IR data are consistent with previously reported values.¹⁷⁸

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\text{Ph} - \overset{+}{N} - \overset{-}{O} - \text{Cl} \\
\text{H} - \text{Ph}
\]

*(Z)-N-*2-chlorobenzylidene-benzylamine N-oxide.* *N*-benzylhydroxylamine (750 mg, 6.09 mmol), 2-chlorobenzaldehyde (0.69 mL, 6.09 mmol) and MgSO₄ (733 mg, 6.09 mmol) were stirred in Et₂O for 121 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by

Experimental Section: 1,3-Dipolar Cycloadditions

Silica gel chromatography (30% EtOAc in hexanes) afforded the title compound as a clear crystals (1.41 g, 95%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.32-9.25 (m, 1H), 7.92 (s, 1H), 7.52-7.23 m, 8H), 5.08 (s, 2H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.$^{179}$

(Z)-N-4-methoxybenzylidene-benzylamine N-oxide. N-benzylhydroxylamine (750 mg, 6.09 mmol), p-anisaldehyde (829 mg, 6.09 mmol) and MgSO$_4$ (733 mg, 6.09 mmol) were stirred in 40 mL Et$_2$O for 70 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 50% EtOAc in hexanes afforded the title compound as a white solid (906 mg, 62%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.18 (d, J = 8.0 Hz, 2H), 7.48-7.25 (m, 6H), 6.89 (d, J = 8.1 Hz, 2H), 4.98 (s, 2H), 3.79 (s, 3H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.$^{180}$

(Z)-N-4-methylbenzylidene-benzylamine N-oxide. N-benzylhydroxylamine (500 mg, 4.06 mmol), p-tolualdehyde (488 mg, 4.06 mmol) and MgSO$_4$ (489 mg, 4.06 mmol) were stirred in 40 mL CH$_2$Cl$_2$ for 65 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 50% EtOAc in hexanes afforded the title compound as a white solid (839 mg, 92%). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.13 (d, J = 8.5 Hz, 2H), 7.53-7.39 (m, 5H), 7.37 (s, 1H), 7.23 (d, J = 8.2 Hz, 2H), 5.06 (s, 2H), 2.39 (s, 3H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.$^{180}$

(Z)-N-4-isopropylbenzylidene-benzylamine N-oxide. N-benzylhydroxylamine (500 mg, 4.06 mmol), 4-isopropylbenzaldehyde (602 mg, 4.06 mmol) and MgSO₄ (489 mg, 4.06 mmol) were stirred in 40 mL CH₂Cl₂ for 65 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 50% EtOAc in hexanes afforded the title compound as a white solid (1.03 g, 87%). IR (neat) 3413, 2960, 1605, 1457 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19-8.14 (m, 2H), 7.52-7.37 (m, 6H), 7.31-7.26 (m, 2H), 5.07 (s, 2H), 2.94 (sept, J = 7.0 Hz, 1H), 1.26 (d, J = 6.8 Hz, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 151.8 (C), 134.3 (CH), 133.4 (C), 129.1 (CH), 128.9 (CH), 128.9 (CH), 128.8 (CH), 128.1 (C), 126.5 (CH), 71.0 (CH₂), 34.2 (CH), 23.7 (CH₃); MS (EI) 253.1 (M⁺); HRMS calcd for C₁₇H₁₉NO 253.1467; found 253.1456.

(Z)-N-4-trifluoromethylbenzylidene-benzylamine N-oxide. N-benzylhydroxylamine (500 mg, 4.06 mmol), 4-trifluoromethylbenzaldehyde (707 mg, 4.06 mmol) and MgSO₄ (489 mg, 4.06 mmol) were stirred in 40 mL CH₂Cl₂ for 65 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 50% EtOAc in hexanes afforded the title compound as a white solid (1.08 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ 8.33 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.53-7.42 (m, 6H), 5.11 (s, 2H). ¹H NMR, ¹³C NMR and IR data are consistent with previously reported values.¹⁸¹

(Z)-N-2-naphtylidene-benzylamine N-oxide. N-benzylhydroxylamine (500 mg, 4.06 mmol), 2-naphtaldehyde (634 mg, 4.06 mmol) and MgSO$_4$ (489 mg, 4.06 mmol) were stirred in 40 mL CH$_2$Cl$_2$ for 65 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 50% EtOAc in hexanes afforded the title compound as a white solid (962 mg, 91%). $^1$H NMR (300 MHz, CDCl$_3$) δ 9.28 (s, 1H), 7.94-7.80 (m, 4H), 7.59-7.41 (m, 8H), 5.12 (s, 2H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.$^{182}$

(Z)-N-benzylidene-methylamine N-oxide. N-methyl-hydroxylamine hydrochloride (835 mg, 10.0 mmol), benzaldehyde (1.06 g, 10.0 mmol), NaHCO$_3$ (1.09 g, 13.0 mmol) and MgSO$_4$ (2.00 g, 17.0 mmol) were refluxed in 40 mL CH$_2$Cl$_2$ for 23 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with EtOAc afforded the title compound as a white solid (1.17 g, 87%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.21-8.15 (m, 2H), 7.41-7.37 (m, 3H), 7.34 (s, 1H), 3.85 (s, 3H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.$^{178}$

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Experimental Section: 1,3-Dipolar Cycloadditions

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\text{(Z)-}N\text{-4-methylbenzylidene-methylamine N-oxide.} \quad N\text{-methyl-hydroxylamine hydrochloride (835 mg, 10.0 mmol), p-tolualdehyde (1.20 mg, 10.0 mmol), NaHCO}_3 \ (1.1 \text{ g, 13.0 mmol) and MgSO}_4 \ (2.0 \text{ g, 17.0 mmol) were stirred in 40 mL CH}_2\text{Cl}_2 \text{ for 65 hours. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with EtOAc afforded the title compound as a white solid (976 mg, 66%).} \quad \text{\textsuperscript{1}H NMR (400 MHz, CDC}_1\text{3) } \delta 8.13 \text{ (d, } J = 8.4 \text{ Hz, 2H), 7.34 (s, 1H), 7.24 (d, } J = 8.2 \text{ Hz, 2H), 3.87 (s, 3H), 2.39 (s, 3H).} \quad \text{\textsuperscript{1}H NMR, \textsuperscript{13}C NMR and IR data are consistent with previously reported values.}\textsuperscript{178}
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\text{(Z)-}N\text{-fur-2-ylmethylidene-methylamine N-oxide.} \quad N\text{-methyl-hydroxylamine hydrochloride (835 mg, 10.0 mmol), furan-2-carbaldehyde (961 mg, 10.0 mmol), NaHCO}_3 \ (1.09 \text{ g, 13.0 mmol) and MgSO}_4 \ (2.00 \text{ g, 17.0 mmol) were refluxed in 40 mL CH}_2\text{Cl}_2 \text{ for 35 hours. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with EtOAc afforded the title compound as a pale yellow solid (1.06 g, 85%).} \quad \text{\textsuperscript{1}H NMR (400 MHz, CDC}_1\text{3) } \delta 7.73 \text{ (d, } J = 3.3 \text{ Hz, 1H), 7.52-7.50 (m, 1H), 7.46-7.44 (m, 1H), 6.54-6.52 (m, 1H), 3.81 (s, 3H).} \quad \text{\textsuperscript{1}H NMR, \textsuperscript{13}C NMR and IR data are consistent with previously reported values.}\textsuperscript{183}
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\textsuperscript{178} \text{DeShong, P.; Leginus J. M. J. Org. Chem., 1984, 49, 3421.}
\textsuperscript{183}
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(Z)-N-thiophen-2-ylmethylidene-methylamine N-oxide. N-methyl-hydroxylamine hydrochloride (835 mg, 10.0 mmol), 2-thiophene-carboxaldehyde (1.12 g, 10.0 mmol), NaHCO$_3$ (1.10 g, 13.0 mmol) and MgSO$_4$ (2.00 g, 17.0 mmol) were refluxed in 40 mL CH$_2$Cl$_2$ for 67 hours. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with EtOAc afforded the title compound as a pale pink solid (1.25 g, 89%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 7.43 (d, J = 3.9 Hz, 1H), 7.15 (dd, J = 5.1, 3.9 Hz, 1H), 3.87 (s, 3H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.\(^\text{184}\)

(Z)-N-neopentylidene-benzylamine N-oxide. N-benzylhydroxylamine (750 mg, 6.09 mmol), trimethyl acetaldehyde (0.66 mL, 6.09 mmol) and MgSO$_4$ (733 mg, 6.09 mmol) were stirred in 45 mL of Et$_2$O for 24 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 3:1 CH$_2$Cl$_2$/EtOAc afforded the title compound as a white solid (754 mg, 65%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38-7.33 (m, 5H), 6.48 (s, 1H), 8.20 (s, 2H), 1.23 (s, 9H). $^1$H NMR, $^{13}$C NMR and IR data are consistent with previously reported values.\(^\text{180}\)

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(Z)-N-cyclohexylmethylidene-benzylamine N-oxide. N-benzylhydroxylamine (504 mg, 4.1 mmol), cyclohexane carboxaldehyde (0.5 mL, 4.1 mmol) and MgSO₄ (497 mg, 4.1 mmol) were stirred in 35 mL Et₂O for 40 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with EtOAc afforded the title compound as a white solid (764 mg, 85%). ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.30 (m, 5H), 6.44 (d, J = 7.3 Hz, 1H), 4.83 (s, 2H), 3.02-2.90 (m, 1H), 1.89-1.78 (m, 2H), 1.71-1.56 (m, 3H), 1.41-1.26 (m, 2H), 1.25-1.03 (m, 3H). ¹H NMR, ¹³C NMR and IR data are consistent with previously reported values.

(Z)-N-3-nitrobenzylidene-benzylamine N-oxide. N-benzylhydroxylamine (500 mg, 4.06 mmol), 3-nitrobenzaldehyde (614 mg, 4.06 mmol) and MgSO₄ (489 mg, 4.06 mmol) were stirred in 40 mL CH₂Cl₂ for 65 hours at 22°C. The reaction mixture was filtered and concentrated in vacuo. Purification by silica gel chromatography with 70% EtOAc in hexanes afforded the title compound as a yellow solid (1.01 g, 97%). ¹H NMR (500 MHz, CDCl₃) δ 9.00 (s, 1H), 8.68-8.62 (m, 1H), 8.28-8.20 (m, 1H), 7.63-7.42 (m, 7H), 5.13 (s, 2H). ¹H NMR, ¹³C NMR and IR data are consistent with previously reported values.

General procedure for the synthesis of racemic dipolar cycloadducts. The following is an example of a procedure used to synthesize the racemates of all dipolar cycloadducts for the determination of enantiomeric excess. Ethyl benzyl amine (14 uL, 0.09 mmol) was dissolved in CH₃NO₂ (4.0 mL, 0.1 M), and cooled to 0°C. Distilled water (8.4 uL, 0.47 mmol) was added followed by CF₃SO₃H (8.4 uL, 0.09 mmol) and the solution was stirred for 5 mins. (Z)-N-benzylidenebenzylamine-N-oxide 7.7 (100 mg, 0.473 mmol) was then added in one portion followed
Experimental Section: 1,3-Dipolar Cycloadditions

by freshly distilled E-crotonaldehyde 7.14 (118 uL, 1.42 mmol). The reaction was stirred at +4°C for 48 hours, after which time additional E-crotonaldehyde (100 uL, 1.20 mmol) was added. After 72 hours, the reaction mixture was passed through a plug of silica with CH₂Cl₂. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a 3.8:1 mixture of exo and endo isomers (colourless oil, 117 mg, 88 %). The isoxazolidine aldehyde was dissolved in 99% EtOH (4 mL) and reduced to the primary alcohol using NaBH₄ at 0°C. After 2 hours, the reaction was quenched with sat. NH₄Cl and stirred for 15 minutes. The mixture was diluted with brine and extracted twice with CH₂Cl₂. The organic layer was dried with Na₂SO₄, filtered and concentrated. Purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity.

((3R,4S,5S)-2-benzyI-5-methyl-3-phenylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyI-5-methyl-3-phenylisoxazolidin-4-yl)methanol (Table 7.6, entry 1). (S)-(+-)10,10-Dimethyl-3-naphthalen-1-ylmethyl-3,4-diaza-tricyclo[5.2.1.0₁^5]decan-2-one (15 mg, 0.05 mmol) was dissolved in CH₃NO₂ (2.4 mL, 0.1 M), and cooled to 0°C. Distilled water (2.1 uL, 0.12 mmol) was added followed by CF₃SO₃H (4.2 uL, 0.05 mmol) and the solution was stirred for 5 mins. Z-N-benzyldenebenzylamine-N-oxide 7.7 (50 mg, 0.24 mmol) was then added in one portion followed by freshly distilled E-crotonaldehyde 7.14 (59 uL, 0.71 mmol). The reaction was stirred at +4°C for 48 hours, after which time additional (E)-crotonaldehyde (50 uL, 0.60 mmol) was added. After 72 hours, the reaction mixture was passed through a plug of silica with CH₂Cl₂. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a 68:32 mixture of exo and endo isomers (colourless oil, 55 mg, 83 %). The aldehyde was dissolved in 99% EtOH (2 mL) and reduced to the primary alcohol using NaBH₄ at 0°C. After 2 hours, the reaction was quenched with sat. NH₄Cl and stirred for 15 minutes. The mixture was diluted with brine and extracted twice with CH₂Cl₂. The organic layer was dried with Na₂SO₄, filtered and concentrated. Purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compounds as a clear oil in 80% overall yield for the determination of enantiomeric purity. endo 85%, exo 86%.
Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. \( \lambda = 220 \) nm (2% IPA/hexanes, 0.8 mL/min flow rate); endo isomers \( t_r = 34.6 \) min (major enantiomer) and 32.5 min (minor enantiomer); exo isomers \( t_r = 20.6 \) min (major enantiomer) and 22.8 min (minor enantiomer). exo isomer \( [\alpha]_D = -118^\circ \) (c 2.87, CHCl\(_3\)); IR (neat) 3408, 2925, 1602, 1495, 1453 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.45-7.41 \) (m, 2H), 7.38-7.32 (m, 4H), 7.32-7.27 (m, 3H), 7.25-7.21 (m, 1H), 4.04-3.97 (m, 3H), 3.69 (d, J = 13.9 Hz, 1H), 3.45-3.35 (m, 2H), 2.47-2.39 (m, 1H), 1.35 (d, J 5.3 Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 137.3 \) (C), 136.3 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 76.8 (CH), 72.1 (CH), 62.3 (CH\(_2\)), 59.9 (CH\(_2\)), 55.8 (CH), 19.9 (CH\(_3\)); MS (EI) 283.2 (M\(^+\)); HRMS calcd for C\(_{18}\)H\(_{21}\)NO\(_2\) 283.1572; found 283.1556. endo isomer \( [\alpha]_D = -64^\circ \) (c 1.29, CHCl\(_3\)); IR (neat) 3394, 2925, 1599, 1494, 1454 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 7.45-7.40 \) (m, 2H), 7.37-7.18 (m, 8H), 4.28-4.27 (m, 1H), 3.98 (d, J = 14.1 Hz, 1H), 3.83-3.63 (m, 4H), 2.43-2.33 (m, 1H), 1.43 (d, J = 6.1 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 139.3 \) (C), 137.5 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 76.3 (CH), 73.6 (CH), 62.3 (CH\(_2\)), 61.8 (CH), 59.7 (CH\(_2\)), 20.8 (CH\(_3\)); MS (EI) 283.2 (M\(^+\)); HRMS calcd for C\(_{18}\)H\(_{21}\)NO\(_2\) 283.1572; found 283.1575.

((3R,4S,5S)-2-benzyl-3-(2-chlorophenyl)-5-methylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyl-3-(2-chlorophenyl)-5-methylisoxazolidin-4-yl)methanol. (Table 7.6, entry 2). Prepared according to the general procedure from E-crotonaldehyde (51 uL, 0.61 mmol), Z-N-2-chlorobenzylidenebenzylamine-N-oxide (50 mg, 0.20 mmol), 7.1 (11 mg, 0.04 mmol), distilled water (3.7 uL, 0.20 mmol) and CF\(_3\)SO\(_3\)H (3.6 uL, 0.04 mmol) in CH\(_3\)NO\(_2\) (2.0 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 111 hours, purification by silica gel chromatography (5% ethyl acetate in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 92% yield (59 mg); 67:33 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compounds as a clear oil in 90% overall yield for the determination of enantiomeric purity. endo 94%, exo 59%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H
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column. \( \lambda = 220 \text{ nm} \) (2% IPA/hexanes, 0.8 mL/min flow rate); \textit{endo} isomers \( t_r = 26.8 \text{ min} \) (major enantiomer) and 23.5 min (minor enantiomer); \textit{exo} isomers \( t_r = 18.6 \text{ min} \) (major enantiomer) and 16.6 min (minor enantiomer). IR (neat) 3389, 2929, 1572, 1441 cm\(^{-1}\); \textit{exo} isomer \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.66 (d, \( J = 7.6 \text{ Hz} \), 1H), 7.42-7.13 (m, 8H), 4.34-4.28 (m, 2H), 4.13-4.07 (m, 1H), 4.01 (d, \( J = 13.3 \text{ Hz} \), 1H), 3.71 (d, \( J = 15.5 \text{ Hz} \), 1H), 3.35-3.26 (m, 2H), 2.69-2.60 (m, 1H), 1.37 (d, \( J = 6.0 \text{ Hz} \), 3H); \textit{endo} isomer \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.79 (d, \( J = 7.6 \text{ Hz} \), 1H), 7.41-7.11 (m, 8H), 4.36-4.33 (m, 1H), 3.98-3.91 (m, 2H), 3.85 (dd, \( J = 10.9, 4.4 \text{ Hz} \), 1H), 3.78 (dd, \( J = 10.9, 6.5 \text{ Hz} \), 1H), 2.32-2.25 (m, 1H), 2.31-2.25 (m, 1H), 1.40 (d, \( J = 6.2 \text{ Hz} \), 3H). MS (EI) 317.1 (M\(^+\)); HRMS calcd for C\(_{18}\)H\(_{20}\)NO\(_2\)Cl 317.1183; found 317.1168; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 137.7 (C), 137.2 (C), 135.0 (C), 134.6 (C), 133.7 (C), 133.0 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 77.4 (CH), 77.1 (CH), 68.7 (CH), 68.4 (CH), 62.6 (CH\(_2\)), 62.5 (CH), 61.7 (CH\(_2\)), 60.3 (CH\(_2\)), 60.1 (CH\(_2\)), 53.2 (CH), 20.3 (CH\(_3\)), 19.9 (CH\(_3\)).

\[
\begin{align*}
\text{Ph} & \quad \text{MeO} \\
\text{exo} & \quad \text{MeO} \\
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{OH} \\
\text{exo} & \quad \text{MeO} \\
\text{endo} & \quad \text{MeO} \\
\end{align*}
\]

\((3R,4S,5S)-2\text{-benzyl-3-(4-methoxyphenyl)-5-methylisoxazolidin-4-yl})\text{methanol and (3S,4S,5S)-2\text{-benzyl-3-(4-methoxyphenyl)-5-methylisoxazolidin-4-yl})methanol (Table 7.6, entry 3). Prepared according to the general procedure from \(E\)-crotonaldehyde (52 \( \mu \)L, 0.62 mmol), \(Z\)-N-4-methoxybenzylidenecarbonylbis-\(N\)-oxide (50 mg, 0.21 mmol), 7.1 (11 mg, 0.04 mmol), distilled water (3.7 \( \mu \)L, 0.21 mmol) and CF\(_3\)SO\(_3\)H (3.7 \( \mu \)L, 0.04 mmol) in CH\(_3\)NO\(_2\) (2.1 mL, 0.1 M) for 48 hours at +4°C, after which additional \(E\)-crotonaldehyde (50 \( \mu \)L, 0.60 mmol). After 72 hours, purification by silica gel chromatography (3% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 88% yield (57 mg); 52:48 \textit{endo}:\textit{exo}. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compound as a clear oil in 85% overall yield for the determination of enantiomeric purity. \textit{endo} 79%, \textit{exo} 87%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. \( \lambda = 210 \text{ nm} \) (2% IPA/hexanes, 0.8 mL/min flow rate); \textit{endo} isomers \( t_r = 43.7 \text{ min} \) (major enantiomer) and 70.3 min (minor enantiomer); \textit{exo} isomers \( t_r = 37.9 \text{ min} \) (major enantiomer) and
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48.9 min (minor enantiomer). *exo* isomer [α]D -127° (c 1.47, CHCl3); IR (neat) 3422, 2937, 1614, 1511, 1248 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.43-7.22 (m, 7H), 6.97-6.91 (m, 2H), 4.07-3.95 (m, 3H), 3.84 (s, 3H), 3.69 (d, J = 14.5 Hz, 1H), 3.54-3.37 (m, 2H), 2.48-2.36 (m, 1H), 1.37 (d, J = 6.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl3) δ 159.2 (C), 137.6 (C), 131.5 (C), 129.2 (CH), 128.7 (CH), 128.1 (CH), 127.1 (CH), 114.2 (CH), 76.7 (CH), 71.6 (CH), 62.4 (CH2), 59.8 (CH2), 55.8 (CH), 55.2 (CH3), 19.9 (CH3). MS (EI) 313.2 (M⁺); HRMS calcd for C₁₉H₂₃NO₃ 313.1678; found 313.1670. *endo* isomer [α]D -76.1° (c 1.30, CHCl3); IR (neat) 3423, 2928, 1611, 1512, 1248 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.42-7.20 (m, 7H), 6.93-6.88 (m, 2H), 4.20 (dq, J = 6.2, 6.1 Hz, 1H), 4.01-3.96 (d, J = 14.6 Hz, 1H), 3.83 (s, 3H), 3.80-3.68 (m, 3H), 3.60 (d, J = 8.5 Hz, 1H), 2.42-2.30 (m, 1H), 1.46 (d, J = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl3) δ 159.2 (C), 137.9 (C), 131.2 (C), 129.0 (CH), 128.4 (CH), 128.1 (CH), 126.8 (CH), 114.1 (CH), 76.1 (CH), 73.2 (CH), 62.5 (CH2), 61.7 (CH), 59.6 (CH2), 55.3 (CH3), 21.0 (CH3); MS (EI) 313.2 (M⁺); HRMS calcd for C₁₉H₂₃NO₃ 313.1678; found 313.1689.

((3R,4S,5S)-2-benzyl-5-methyl-3-p-tolylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyl-5-methyl-3-p-tolylisoxazolidin-4-yl)methanol (Table 7.6, entry 4). Prepared according to the general procedure from E-crotonaldehyde (56 uL, 0.67 mmol), Z-N-4-methylbenzylidenebenzylamine-N-oxide (50 mg, 0.22 mmol), 7.1 (12 mg, 0.04 mmol), distilled water (2.0 uL, 0.11 mmol) and CF₃SO₂H (3.9 uL, 0.04 mmol) in CH₃NO₂ (2.2 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 72 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 88% yield (58 mg); 43:57 *endo*:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil in 83% overall yield for the determination of enantiomeric purity. *endo* 80%, *exo* 84%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ = 210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers tᵣ = 37.6 min (major enantiomer) and 24.4 min (minor enantiomer); *exo* isomers tᵣ = 17.1 min (major enantiomer) and 18.4 min (minor enantiomer).
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exo isomer \([\alpha]_D^{-122}^o\) (c 2.07, CHCl\(_3\)); IR (neat) 3397, 2924, 1602, 1511, 1454 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.19 (m, 9H), 4.09-3.96 (m, 3H), 3.69 (d, J = 14.5 Hz, 1H), 3.55-3.36 (m, 2H), 2.50-2.39 (m, 1H), 2.38 (s, 3H), 1.37 (d, J = 6.1 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.7 (C), 137.7 (C), 133.3 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 76.6 (CH), 72.0 (CH), 62.4 (CH\(_2\)), 59.9 (CH\(_2\)), 55.9 (CH), 21.1 (CH\(_3\)), 19.9 (CH\(_3\)). MS (El) 297.2 (M\(^+\)); HRMS calcd for C\(_{19}\)H\(_{23}\)NO\(_2\) 297.1729; found 297.1712.

endo isomer \([\alpha]_D^{-127}^o\) (c 1.47, CHCl\(_3\)); IR (neat) 3422, 2937, 1614, 1511, 1248 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.38-7.15 (m, 9H), 4.21 (dq, J = 6.1, 6.1 Hz, 1H), 3.83-3.67 (m, 3H), 3.60 (d, J = 8.5 Hz, 1H), 2.42-2.32 (m, 1H), 2.37 (s, 3H), 1.46 (d, J = 6.2 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 137.9 (C), 137.5 (C), 136.3 (C), 129.4 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 76.1 (CH), 73.5 (CH), 62.5 (CH\(_2\)), 61.8 (CH), 59.6 (CH\(_2\)), 21.1 (CH\(_3\)), 21.0 (CH\(_3\)). MS (El) 297.2 (M\(^+\)); HRMS calcd for C\(_{19}\)H\(_{23}\)NO\(_2\) 297.1725.

\(((3R,4S,5S)-2\text{-benzyl-3-}-(4\text{-isopropylphenyl})-5\text{-methylisoxazolidin-4-yl})\text{methanol}\) and \(((3S,4S,5S)-2\text{-benzyl-3-}-(4\text{-isopropylphenyl})-5\text{-methylisoxazolidin-4-yl})\text{methanol}\) (Table 7.6, entry 5). Prepared according to the general procedure from E-crotonaldehyde (50 \(\mu\)L, 0.59 mmol), Z-N-4-isopropylbenzylidenebenzylamine-N-oxide (50 mg, 0.20 mmol), 7.1 (11 mg, 0.04 mmol), distilled water (1.8 \(\mu\)L, 0.10 mmol) and CF\(_3\)SO\(_3\)H (3.5 \(\mu\)L, 0.04 mmol) in nitromethane (2.0 mL, 0.1 M) at +4°C. After 48 hours, additional E-crotonaldehyde (50 \(\mu\)L, 0.60 mmol) was added. After 72 hours, purification by silica gel chromatography (2% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 85% yield (55 mg); 36:64 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compound as a clear oil in 81% overall yield for the determination of enantiomeric purity. endo 76%, exo 85%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. \(\lambda\) = 210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); endo isomers \(t_r = 19.2\) min (major enantiomer) and 27.3 min (minor enantiomer); exo isomers \(t_r = 14.3\) min (major enantiomer) and 16.6 min (minor enantiomer). exo isomer \([\alpha]_D^{-98.8}^o\) (c 1.92, CHCl\(_3\)); IR (neat) 3421, 2961, 1611,
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1454 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.32 (m, 4H), 7.31-7.26 (m, 2H), 7.25-7.19 (m, 3H), 4.05-3.94 (m, 3H), 3.66 (d, \(J = 14.5\) Hz, 1H), 3.50-3.36 (m, 2H), 2.89 (sept, \(J = 6.9\) Hz, 1H), 2.45-2.36 (m, 1H), 2.01 (d, \(J = 6.1\) Hz, 3H), 1.23 (d, \(J = 6.9\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.6 (C), 137.7 (C), 133.6 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.9 (CH), 76.6 (CH), 72.1 (CH), 62.4 (CH\(_2\)), 60.0 (CH\(_2\)), 56.0 (CH), 33.8 (CH), 23.9 (CH\(_3\)), 19.9 (CH\(_3\)). MS (EI) 325.2 (M\(^+\)); HRMS calcd for C\(_{21}\)H\(_{27}\)NO\(_2\) 325.2042; found 325.2034.

endo isomer [\(\alpha\)]\(_D\) -75.3\(^\circ\) (c 1.29, CHCl\(_3\)); IR (neat) 3416, 2925, 1602, 1455 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.29 (m, 4H), 7.28-7.23 (m, 2H), 7.25-7.22 (m, 3H), 4.17 (dq, \(J = 6.1, 6.1\) Hz, 1H), 3.96 (d, \(J = 14.6\) Hz, 1H), 3.79-3.65 (m, 3H), 3.56 (d, \(J = 8.4\) Hz, 1H), 2.88 (sept, \(J = 6.6\) Hz, 1H), 2.39-2.30 (m, 1H), 1.42 (d, \(J = 6.2\) Hz, 3H), 1.23 (d, \(J = 6.9\) Hz, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.4 (C), 138.0 (C), 136.7 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 126.7 (CH), 76.2 (CH), 73.6 (CH), 62.6 (CH\(_2\)), 61.8 (CH), 59.7 (CH\(_2\)), 33.8 (CH), 24.0 (CH\(_3\)), 21.0 (CH\(_3\)); MS (EI) 325.2 (M\(^+\)); HRMS calcd for

C\(_{21}\)H\(_{27}\)NO\(_2\) 325.2042; found 325.2044.

((3R,4S,5S)-2-benzyl-5-methyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyl-5-methyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-4-yl)methanol (Table 7.6, entry 6). Prepared according to the general procedure from E-crotonaldehyde (53 \(\mu\)L, 0.54 mmol), Z-N-4-trifluoromethylbenzylidenebenzylamine-N-oxide (50 mg, 0.18 mmol), 7.1 (9.7 mg, 0.04 mmol), distilled water (1.6 \(\mu\)L, 0.09 mmol) and CF\(_3\)SO\(_3\)H (3.2 \(\mu\)L, 0.04 mmol) in CH\(_3\)NO\(_2\) (1.8 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 \(\mu\)L, 0.60 mmol) as added. After 175 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 67% yield (42 mg); 45:55 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compounds as a clear in 64% overall yield oil for the determination of enantiomeric purity. endo 73%, exo 61%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. \(\lambda\) = 210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); endo isomers \(t_r \) = 19.4 min (major enantiomer) and 23.5 min (minor enantiomer); exo isomers \(t_r \) = 16.9 min.
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(major enantiomer) and 18.0 min (minor enantiomer). *exo* isomer $[\alpha]_D^{\text{neat}} -76.8^\circ$ (c 1.43, CHCl$_3$); IR (neat) 3422, 2926, 1619, 1455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.62-7.51 (m, 4H), 7.32-7.20 (m, 5H), 4.09-4.00 (m, 2H), 3.95 (d, $J = 14.3$ Hz, 1H), 3.75 (d, $J = 14.3$ Hz, 1H), 3.38 (dd, $J = 10.9$, 6.9 Hz, 1H), 3.30 (dd, $J = 10.9$, 6.4 Hz, 1H), 2.53-2.44 (m, 1H), 1.36 (d, $J = 6.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.1 (C), 137.0 (C), 129.8 (C), 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.2 (CH), 127.3 (CH), 125.5 (q, CF$_3$, $J_{CF} = 3.6$ Hz) 77.3 (CH), 71.7 (CH), 62.2 (CH$_2$), 60.3 (CH$_2$), 55.6 (CH), 19.9 (CH$_3$); MS (EI) 351.1 (M$^+$); HRMS calcd for C$_{19}$H$_{20}$NO$_2$F$_3$ 351.1446; found 351.1445. *endo* isomer $[\alpha]_D^{\text{neat}} -62.6^\circ$ (c 1.15, CHCl$_3$); IR (neat) 3446, 2925, 1621, 1325 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59-7.50 (m, 4H), 7.31-7.17 (m, 5H), 4.23 (dq, $J = 6.2$, 6.1 Hz, 1H), 3.95 (d, $J = 14.0$ Hz, 1H), 3.89 (d, $J = 14.0$ Hz, 1H), 3.81-3.69 (m, 3H), 3.34-3.26 (m, 1H), 1.41 (d, $J = 6.13$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.5 (C), 137.2 (C), 129.7 (C), 128.6 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 125.6 (q, CF$_3$, $J_{CF} = 3.8$ Hz), 76.0 (CH), 72.8 (CH), 62.2 (CH), 62.0 (CH$_2$), 60.3 (CH$_2$), 20.4 (CH$_3$); MS (EI) 351.1 (M$^+$); HRMS calcd for C$_{19}$H$_{20}$NO$_2$F$_3$ 351.1446; found 351.1436.

((3R,4S,5S)-2-benzyl-5-methyl-3-(naphthalen-2-yl)isoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyl-5-methyl-3-(naphthalen-2-yl)isoxazolidin-4-yl)methanol (Table 7.6, entry 7). Prepared according to the general procedure from E-crotonaldehyde (47 µL, 0.57 mmol), Z-N-2-naphtylbenzylidenebenzylamine-N-oxide (50 mg, 0.19 mmol), 7.1 (10 mg, 0.04 mmol), distilled water (1.7 µL, 0.10 mmol) and CF$_3$SO$_3$H (3.4 µL, 0.04 mmol) in CH$_3$NO$_2$ (1.9 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 µL, 0.60 mmol) was added. After 96 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 94% yield (59 mg); 55:45 *endo*:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil in 92% overall yield for the determination of enantiomeric purity. *endo* 81%, *exo* 60%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. $\lambda = 210$ nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers $t_r = 39.1$ min (major
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enantiomer) and 46.3 min (minor enantiomer); exo isomers $t = 33.4$ min (major enantiomer) and 42.9 min (minor enantiomer). **exo isomer** $[\alpha]_D -73.5^\circ$ (c 1.93, CHCl$_3$); IR (neat) 3408, 2925, 1599, 1447 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.91-7.80 (m, 4H), 7.57-7.52 (m, 1H), 7.52-7.45 (m, 2H), 7.37-7.33 (m, 2H), 7.32-7.26 (m, 2H), 7.25-7.20 (m, 1H), 4.17 (d, $J = 8.2$ Hz, 1H), 4.11-4.03 (m, 2H), 3.75 (d, $J = 14.5$ Hz, 1H), 3.43 (d, $J = 6.5$ Hz, 2H), 2.56-2.47 (m, 1H), 1.38 (d, $J = 6.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.5 (C), 134.1 (C), 133.2 (C), 133.0 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 77.1 (CH), 72.3 (CH), 62.4 (CH$_2$), 60.1 (CH$_2$), 56.0 (CH), 19.9 (CH$_3$). MS (EI) 333.2 (M$^+$); HRMS caledd for C$_{22}$H$_{23}$NO$_2$ 333.1729; found 333.1708. **endo isomer** $[\alpha]_D -47.4^\circ$ (c 2.57, CHCl$_3$); IR (neat) 3420, 2924, 1599, 1454 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86-7.78 (m, 4H), 7.63 (dd, $J = 8.4$ Hz, 1.7 Hz, 1H), 7.50-7.43 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.16 (m, 3H), 4.25 (dq, $J = 6.2$, 5.9 Hz, 1H), 4.00 (d, $J = 14.1$ Hz, 1H), 3.86-3.70 (m, 4H), 2.48-2.40 (m, 1H), 1.46 (d, $J = 5.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.8 (C), 137.1 (C), 133.3 (C), 133.1 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 76.1 (CH), 73.8 (CH), 62.3 (CH$_2$), 61.9 (CH), 60.0 (CH$_2$), 20.9 (CH$_3$); MS (EI) 333.2 (M$^+$); HRMS caledd for C$_{22}$H$_{23}$NO$_2$ 333.1729; found 333.1715.

$\text{H}_3\text{C}^\text{N}^\text{O}\text{H}$ + $\text{H}_3\text{C}^\text{N}^\text{O}\text{H}$

((3R,4S,5S)-2,5-dimethyl-3-phenylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2,5-dimethyl-3-phenylisoxazolidin-4-yl)methanol (Table 7.6, entry 9). Prepared according to the general procedure from E-crotonaldehyde (92 uL, 1.1 mmol), Z-N-benzylidenemethylamine-N-oxide (50 mg, 0.34 mmol), 7.1 (20 mg, 0.07 mmol), distilled water (3.3 uL, 0.18 mmol) and HClO$_4$ (6.2 uL, 0.07 mmol) in CH$_3$NO$_2$ (3.7 mL, 0.1 M) for 48 hours at $+4^\circ$C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 95 hours, purification by silica gel chromatography (10% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 61% yield (46 mg); 43:57 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a clear oil in 55%
overall yield for the determination of enantiomeric purity. \textit{endo} 89\%, \textit{exo} 80\%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. $\lambda = 210$ nm (2\% IPA/hexanes, 0.8 mL/min flow rate); \textit{endo} isomers $t_r = 33.6$ min (major enantiomer) and 27.0 min (minor enantiomer); \textit{exo} isomers $t_r = 18.7$ min (major enantiomer) and 20.3 min (minor enantiomer). \textit{exo} isomer $[^\alpha]_D-\text{203}^{\circ}$ (c 0.79, CHCl$_3$); IR (neat) 3385, 2925, 1558, 1456 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.32 (m, 4H), 7.31-7.26 (m, 1H), 4.01 (dq, J = 6.1, 6.0 Hz, 1H), 3.74 (d, J = 8.6 Hz, 1H), 3.42-3.32 (m, 2H), 2.61 (s, 3H), 3.47-3.40 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 136.2 (C), 128.8 (CH), 128.8 (CH), 127.9 (CH), 76.9 (CH), 74.9 (CH), 62.4 (CH$_2$), 55.4 (CH), 43.5 (CH$_3$), 19.8 (CH$_3$). MS (EI) 207.1 (M$^+$); HRMS calcd for C$_{12}$H$_{17}$NO$_2$ 207.1259; found 207.1234. \textit{endo} isomer $[^\alpha]_D-\text{100}^{\circ}$ (c 0.75, CHCl$_3$); IR (neat) 3420, 2921, 1652, 1455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.25 (m, 5H), 4.21 (dq, J = 18.4, 6.3 Hz, 1H), 3.78-3.65 (m, 2H), 3.40-3.25 (m, 1H), 2.56 (s, 3H), 2.22-2.32 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.8 (C), 127.8 (CH), 128.1 (CH), 127.9 (CH), 76.2 (CH), 74.9 (CH), 62.4 (CH), 62.2 (CH$_2$), 43.5 (CH$_3$), 21.4 (CH$_3$); MS (EI) 207.1 (M$^+$); HRMS calcd for C$_{12}$H$_{17}$NO$_2$ 207.1259; found 207.1238.

\begin{align*}
\text{exo} & \quad \text{endo} \\
\begin{array}{c}
\text{exo} \quad \text{(3R,4S,5S)-3-(furan-2-yl)-2,5-dimethylisoxazolidin-4-yl)methanol and (3S,4S,5S)-3-(furan-2-yl)-2,5-dimethylisoxazolidin-4-yl)methanol (Table 7.6, entry 10). Prepared according to the general procedure from E-crotonaldehyde (99 uL, 1.2 mmol), Z-N-fur-2-ylmethylidenemethylamine-N-oxide (50 mg, 0.40 mmol), 7.1 (22 mg, 0.08 mmol), distilled water (3.6 uL, 0.20 mmol) and HClO$_4$ (6.7 uL, 0.08 mmol) in CH$_3$NO$_2$ (4.0 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 120 hours, purification by silica gel chromatography (10\% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 38\% yield (29 mg); 50:50 \textit{endo}:\textit{exo}. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20\% EtOAc in hexanes) provided the title compounds in 32\% yield as a clear oil for the determination of enantiomeric purity. \textit{endo} 88\%, \textit{exo} 69\%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. $\lambda = 220$ nm (2\% IPC/Hexanes, 0.8 mL/min flow rate); \textit{endo} isomers $t_r = 33.6$ min (major enantiomer) and 27.0 min (minor enantiomer); \textit{exo} isomers $t_r = 18.7$ min (major enantiomer) and 20.3 min (minor enantiomer). \textit{exo} isomer $[^\alpha]_D-\text{203}^{\circ}$ (c 0.79, CHCl$_3$); IR (neat) 3385, 2925, 1558, 1456 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.32 (m, 4H), 7.31-7.26 (m, 1H), 4.01 (dq, J = 6.1, 6.0 Hz, 1H), 3.74 (d, J = 8.6 Hz, 1H), 3.42-3.32 (m, 2H), 2.61 (s, 3H), 3.47-3.40 (m, 1H), 1.38 (d, J = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 136.2 (C), 128.8 (CH), 128.8 (CH), 127.9 (CH), 76.9 (CH), 74.9 (CH), 62.4 (CH$_2$), 55.4 (CH), 43.5 (CH$_3$), 19.8 (CH$_3$). MS (EI) 207.1 (M$^+$); HRMS calcd for C$_{12}$H$_{17}$NO$_2$ 207.1259; found 207.1234. \textit{endo} isomer $[^\alpha]_D-\text{100}^{\circ}$ (c 0.75, CHCl$_3$); IR (neat) 3420, 2921, 1652, 1455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.25 (m, 5H), 4.21 (dq, J = 18.4, 6.3 Hz, 1H), 3.78-3.65 (m, 2H), 3.40-3.25 (m, 1H), 2.56 (s, 3H), 2.22-2.32 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.8 (C), 127.8 (CH), 128.1 (CH), 127.9 (CH), 76.2 (CH), 74.9 (CH), 62.4 (CH), 62.2 (CH$_2$), 43.5 (CH$_3$), 21.4 (CH$_3$); MS (EI) 207.1 (M$^+$); HRMS calcd for C$_{12}$H$_{17}$NO$_2$ 207.1259; found 207.1238. \end{align*}
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IPA/hexanes, 0.8 mL/min flow rate); endo isomers $t_r = 29.4$ min (major enantiomer) and 37.8 min (minor enantiomer); exo isomers $t_r = 27.9$ min (major enantiomer) and 33.8 min (minor enantiomer). IR (neat) 3392, 2933, 1656, 1500, 1458 cm$^{-1}$; exo isomer $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43-7.40 (m, 1H), 6.39-6.33 (m, 2H), 4.13-4.04 (m, 1H), 3.87-3.77 (m, 1H), 3.53 (d, $J = 6.0$ Hz, 2H), 2.63 (s, 3H), 2.48-2.38 (m, 1H), 1.36 (d, $J = 5.7$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 150.0 (C), 142.6 (CH), 110.4 (CH), 108.8 (CH), 77.1 (CH), 74.9 (CH), 62.2 (CH$_2$), 55.4 (CH), 43.7 (CH$_3$), 19.4 (CH$_3$); endo isomer $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43-7.35 (m, 1H), 6.36-6.26 (m, 2H), 4.19 (dq, $J = 18.1$, 5.9 Hz, 1H), 3.83-3.66 (m, 2H), 3.55-3.40 (m, 1H), 2.72-2.42 (m, 4H), 1.42 (d, $J = 5.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 151.0 (C), 142.7 (CH), 110.3 (CH), 108.1 (CH), 77.5 (CH), 74.9 (CH), 62.2 (CH), 61.9 (CH$_2$), 43.9 (CH$_3$), 20.7 (CH$_3$); MS (EI) 197.1 (M$^+$); HRMS calcd for C$_{16}$H$_{15}$NO$_3$ 197.1052; found 197.1047.

\[
\begin{align*}
\text{exo} & \quad \begin{array}{c}
\text{H}_3\text{C} \\
\text{N} \quad \text{O} \\
\text{OH} \quad \text{H}_3\text{C}
\end{array} \\
\text{endo} & \quad \begin{array}{c}
\text{H}_3\text{C} \\
\text{N} \quad \text{O} \\
\text{OH} \quad \text{H}_3\text{C}
\end{array}
\end{align*}
\]

((3R,4S,5S)-2,5-dimethyl-3-p-tolylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2,5-dimethyl-3-p-tolylisoxazolidin-4-yl)methanol (Table 7.6, entry 9). Prepared according to the general procedure from E-crotonaldehyde (84 uL, 1.0 mmol), Z-N-4-methylbenzylidenemethylamine-N-oxide (50 mg, 0.33 mmol), 7.1 (18 mg, 0.07 mmol), distilled water (3.0 uL, 0.17 mmol) and CF$_3$SO$_3$H (5.9 uL, 0.07 mmol) in CH$_3$NO$_2$ (3.4 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 72 hours, purification by silica gel chromatography (10% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 71% yield (53 mg); 48:52 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a clear oil in 66% overall yield for the determination of enantiomeric purity. endo 80%, exo 92%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. $\lambda = 210$ nm (2% IPA/hexanes, 0.8 mL/min flow rate); endo isomers $t_r = 14.9$ min (major enantiomer) and 16.3 min (minor enantiomer); exo isomers $t_r = 34.7$ min (major enantiomer) and 21.8 min (minor enantiomer). exo isomer $[^\alpha]_D - 192^\circ$ (c 1.42, CHCl$_3$); IR (neat) 3416, 2925, 1540, 1515 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.22 (d,
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\[^{13}\text{C}\] NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.6 (C), 133.1 (C), 129.5 (CH), 127.8 (CH), 76.7 (CH), 74.7 (CH), 62.4 (CH\(_2\)), 56.5 (CH), 43.4 (CH\(_3\)), 21.1 (CH\(_3\)), 19.8 (CH\(_3\)); MS (EI) 221.1 (M\(^+\)); HRMS calcd for C\(_{13}\)H\(_{19}\)NO\(_2\) 221.1416; found 221.1394.

endo isomer \(\left[\alpha\right]_D\) -98.9° (c 1.41, CHCl\(_3\)); IR (neat) 3397, 2925, 1653, 1515 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.19 (dq, J = 18.1, 6.0 Hz, 1H), 3.75-3.63 (m, 2H), 3.34-3.19 (m, 1H), 2.54 (s, 3H), 2.39-2.33 (m, 1H), 2.32 (s, 3H), 1.43 (d, J = 6.2 Hz, 3H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.8 (C), 135.5 (C), 129.4 (CH), 127.8 (CH), 76.1 (CH), 74.8 (CH), 62.4 (CH), 62.1 (CH\(_2\)), 43.5 (CH\(_3\)), 21.4 (CH\(_3\)), 21.1 (CH\(_3\)); MS (EI) 221.1 (M\(^+\)); HRMS calcd for C\(_{13}\)H\(_{19}\)NO\(_2\) 221.1416; found 221.1390.

Ph Ph
\[\text{exo} \quad \text{endo}\]

\((3R,4S,5S)-2\text{-benzyl-3-phenyl-5-propylisoxazolidin-4-yl})\text{methanol and (3S,4S,5S)-2-benzyl-3-phenyl-5-propylisoxazolidin-4-yl})\text{methanol (Table 7.6, entry 11). Prepared according to the general procedure from E-hex-2-enal (93 mg, 0.95 mmol), Z-N-benzylidenebenzylamine-N-oxide (50 mg, 0.24 mmol), 7.1 (13 mg, 0.05 mmol), distilled water (1.4 uL, 0.11 mmol) and CF\(_3\)SO\(_3\)H (4.2 uL, 0.05 mmol) in CH\(_3\)NO\(_2\) (2.0 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 145 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 86% yield (63 mg); 40:60 \text{endo:exo}. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil in 85% overall yield for the determination of enantiomeric purity. \text{endo} 74%, \text{exo} 84%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. \(\lambda\) = 210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); \text{endo} isomers \(t_r\) = 26.1 min (major enantiomer) and 23.6 min (minor enantiomer); \text{exo} isomers \(t_r\) = 15.3 min (major enantiomer) and 17.4 min (minor enantiomer). \text{exo} isomer. \(\left[\alpha\right]_D\) -115° (c 2.40, CHCl\(_3\)); IR (neat) 3420, 2930, 1599, 1454 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.24 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.19 (dq, J = 18.1, 6.0 Hz, 1H), 3.75-3.63 (m, 2H), 3.34-3.19 (m, 1H), 2.54 (s, 3H), 2.39-2.33 (m, 1H), 2.32 (s, 3H), 1.43 (d, J = 6.2 Hz, 3H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.8 (C), 135.5 (C), 129.4 (CH), 127.8 (CH), 76.1 (CH), 74.8 (CH), 62.4 (CH), 62.1 (CH\(_2\)), 43.5 (CH\(_3\)), 21.4 (CH\(_3\)), 21.1 (CH\(_3\)); MS (EI) 221.1 (M\(^+\)); HRMS calcd for C\(_{13}\)H\(_{19}\)NO\(_2\) 221.1416; found 221.1390.
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CDCl$_3$ δ 7.44-7.20 (m, 10H), 4.02 (d, J = 14.4 Hz, 1H), 3.96 (d, J = 8.1 Hz, 1H), 3.89 (dd, J = 12.2, 5.7 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.47 (dd, J = 11.3 6.7 Hz, 1H), 3.38 (dd, J = 11.3, 5.3 Hz, 1H), 2.51-2.43 (m, 1H), 1.70-1.56 (m, 2H), 1.52-1.35 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.4 (C), 136.4 (C), 128.9 (CH), 128.8 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.1 (CH), 80.0 (CH), 72.0 (CH), 62.5 (CH$_2$), 59.9 (CH$_2$), 55.5 (CH), 37.1 (CH$_2$), 19.2 (CH$_2$), 14.2 (CH$_3$). MS (EI) 311.2 (M$^+$); HRMS calcd for C$_{20}$H$_{25}$NO$_2$ 311.1885; found 311.1873. endo isomer $[\alpha]_D$ -90.0° (c 1.38, CHCl$_3$); IR (neat) 3421, 2930, 1652, 1455 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44-7.39 (m, 2H), 7.36-7.29 (m, 4H), 7.29-7.23 (m, 3H), 7.22-7.16 (m, 1H), 4.01-3.90 (m, 2H), 3.79-3.67 (m, 2H), 3.56 (d, J = 7.2 Hz, 1H), 2.43-2.35 (m, 1H), 1.95-1.84 (m, 1H), 1.66-1.54 (m, 1H), 1.52-1.30 (m, 3H), 0.92 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.6 (C), 138.0 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 79.9 (CH), 73.8 (CH), 62.9 (CH$_2$), 60.7 (CH), 59.5 (CH$_2$), 37.7 (CH$_2$), 19.4 (CH$_2$), 14.1 (CH$_3$); MS (EI) 311.2 (M$^+$); HRMS calcd for C$_{20}$H$_{25}$NO$_2$ 311.1885; found 311.1858.

$^{((3R,4S,5S)-2-benzyl-5-isopropyl-3-phenylisoxazolidin-4-yl)methanol and ((3S,4S,5S)-2-benzyl-5-isopropyl-3-phenylisoxazolidin-4-yl)methanol (Table 7.6, entry 12). Prepared according to the general procedure from E-4-methylpent-2-enal (93 mg, 0.95 mmol), Z-N-benzylidenebenzylamine-N-oxide (50 mg, 0.24 mmol), 7.1 (13 mg, 0.05 mmol), distilled water (1.4 uL, 0.11 mmol) and CF$_3$SO$_3$H (4.2 uL, 0.05 mmol) in CH$_3$NO$_2$ (2.0 mL, 0.1 M) for 48 hours at +4°C, after which additional E-crotonaldehyde (50 uL, 0.60 mmol) was added. After 145 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided the isoxazolidine aldehyde as a colourless oil in 68% yield (50 mg); 43:57 endo:exo. Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compounds as a clear oil in 65% overall yield for the determination of enantiomeric purity. endo 77%, exo 66%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. $\lambda = 220$ nm (2%
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IPA/hexanes, 0.8 mL/min flow rate); endo isomers $t_r = 24.7$ min (major enantiomer) and 22.1 min (minor enantiomer); exo isomers $t_r = 13.0$ min (major enantiomer) and 15.0 min (minor enantiomer).

**exo isomer.** $[\alpha]_D - 134^\circ$ (c 1.40, CHCl$_3$); IR (neat) 3442, 2958, 1652, 1454 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.21 (m, 10H), 4.05 (d, $J = 14.4$ Hz, 1H), 3.87 (d, $J = 7.6$ Hz, 1H), 3.68-3.61 (m, 2H), 3.56 (dd, $J = 11.5$, 7.4 Hz, 1H), 3.36 (dd, $J = 11.5$, 4.1 Hz, 1H), 2.57-2.49 (m, 1H), 1.89-1.77 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.2 (C), 136.2 (C), 129.2 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.2 (CH), 84.4 (CH), 72.2 (CH), 62.8 (CH$_2$), 59.6 (CH$_2$), 52.1 (CH), 18.5 (CH$_3$), 18.4 (CH$_3$). MS (EI) 311.2 (M$^+$); HRMS calcd for C$_{20}$H$_{25}$NO$_2$ 311.1885; found 311.1867.

**endo isomer** $[\alpha]_D - 82.7^\circ$ (c 1.01, CHCl$_3$); IR (neat) 3461, 2921, 1652, 1454 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46-7.41 (m, 2H), 7.36-7.30 (m, 4H), 7.30-7.23 (m, 3H), 7.22-7.16 (m, 1H), 3.92 (d, $J = 14.7$ Hz, 1H), 3.80-3.70 (m, 2H), 3.65 (d, $J = 14.6$ Hz, 1H), 3.60-3.56 (m, 2H), 2.57-2.48 (m, 1H), 2.16-2.03 (m, 1H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 140.8 (C), 138.2 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 85.2 (CH), 74.6 (CH), 63.7 (CH$_2$), 59.4 (CH), 58.7 (CH$_2$), 32.7 (CH), 19.1 (CH$_3$), 18.5 (CH$_3$); MS (EI) 311.2 (M$^+$); HRMS calcd for C$_{20}$H$_{25}$NO$_2$ 311.1885; found 311.1888.

(2-benzyl-3-phenylisoxazolidin-4-yl)methanol and (2-benzyl-3-phenylisoxazolidin-5-yl)methanol (Scheme 7.7). Prepared according to the general procedure from acrolein (40 mg, 0.72 mmol), Z-N-benzylidenebenzylamine-N-oxide (85 mg, 0.24 mmol), 7.1 (13 mg, 0.05 mmol), distilled water (4.3 uL, 0.24 mmol) and CF$_3$SO$_3$H (4.2 uL, 0.05 mmol) in CH$_3$NO$_2$ (4.3 mL, 0.1 M) at +4°C. After 23 hours, purification by silica gel chromatography (15% EtOAc acetate in hexanes) provided a mixture of endo and exo regiosiomers of isoxazolidine aldehydes as a colourless oil in 88% yield (64 mg); Reduction of the aldehyde to the primary alcohols followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided an inseparable mixture of regio and diastereoisomers as a clear oil in 80% overall yield. Diastereoisomers of (2-benzyl-3-phenylisoxazolidin-4-yl)methanol were found to be the major products. IR (neat) 3403, 2873, 1602,
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1495, 1454 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.47-7.41 (m), 7.39-7.19 (m), 4.37-4.31 (m), 4.24 (dd, \(J = 8.3, 8.2\) Hz), 4.18 (dd, 8.3, 8.3 Hz), 4.05 (d, \(J = 14.8\) Hz), 4.00 (d, \(J = 8.3\) Hz), 3.93 (d, \(J = 14.2\) Hz), 3.89 (dd, \(J = 8.3, 4.5\) Hz), 3.81 (dd, \(J = 8.4, 5.5\) Hz), 3.79-3.64 (m), 3.56-3.51 (m), 3.50-3.43 (m), 3.38 (d, \(J = 6.6\) Hz), 3.00-2.92 (m), 2.79-2.70 (m), 2.57-2.50 (m), 2.40-2.32 (m), \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 139.0 (C), 137.2 (C), 136.2 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.2 (CH), 127.2 (CH), 127.1 (CH), 73.3 (CH), 71.5 (CH), 69.5 (CH\(_2\)), 69.1 (CH\(_2\)), 69.1 (CH\(_2\)), 63.1 (CH\(_2\)), 62.4 (CH\(_2\)), 60.1 (CH\(_2\)), 59.8 (CH\(_2\)), 54.7 (CH), 49.0 (CH); MS (EI) 269.1 (M\(^+\)); HRMS calcd for C\(_{17}\)H\(_{19}\)NO\(_2\) 269.1416; found 269.1418.

(2-benzyl-3-(2-chlorophenyl)isoxazolidin-4-yl)methanol and (2-benzyl-3-(2-chlorophenyl)isoxazolidin-5-yl)methanol (Scheme 7.7). Prepared according to the general procedure from acrolein (34.2 mg, 0.61 mmol), Z-N-2-chlorobenzylidenebenzylamine-\(N\)-oxide (50 mg, 0.20 mmol), 7.1 (11 mg, 0.04 mmol), distilled water (1.8 \(\mu\)L, 0.10 mmol) and CF\(_3\)SO\(_3\)H (3.6 \(\mu\)L, 0.04 mmol) in CH\(_3\)NO\(_2\) (2.0 mL, 1.0 M) at +4°C. After 26 hours, purification by silica gel chromatography (5% EtOAc in hexanes) provided a mixture of endo and exo regiosomers of isoxazolidine aldehydes as a colourless oil in 83% yield (61 mg); Reduction of the aldehydes to the primary alcohol followed by multiple purifications by silica gel chromatography (10-20% EtOAc gradient in hexanes) provided a difficult to separate mixture of regio and diastereoisomers. Purification via Biotage (5-20% EtOAc gradient in hexanes) afforded (2-benzyl-3-(2-chlorophenyl)isoxazolidin-5-yl)methanol IR (neat) 3456, 2923, 1487 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.77 (d, \(J = 7.0\) Hz, 1H), 7.37-7.16 (m, 8H), 4.42-4.28 (m, 2H), 4.02 (d, \(J = 14.4\) Hz, 1H), 3.87 (d, \(J = 14.3\) Hz, 1H), 3.80 (dd, \(J = 11.9, 2.7\) Hz, 1H), 3.58 (dd, \(J = 12.1, 4.3\) Hz, 1H), 2.74-2.65 (m, 1H), 2.25-2.15 (m, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 135.8 (C), 133.2 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.4 (CH), 127.2 (CH), 77.7 (CH), 65.9 (CH), 63.3 (CH\(_2\)), 60.1 (CH\(_2\)), 38.2 (CH\(_2\)); MS (EI) 303.1 (M\(^+\)); HRMS calcd for C\(_{17}\)H\(_{18}\)NO\(_2\)Cl 303.1026; found 269.
Experimental Section: 1,3-Dipolar Cycloadditions

303.1012 and the *endo* isomer of (2-benzyl-3-(2-chlorophenyl)isoxazolidin-4-yl)methanol as the major products. IR (neat) 3405, 2875, 1591, 1475, 1454 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.78 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.37-7.17 (m, 8H), 4.17 (dd, \(J = 8.1, 8.0\) Hz, 1H), 4.14 (d, \(J = 7.3\) Hz, 1H), 3.96 (dd, \(J = 8.4, 4.9\) Hz, 1H), 3.91-3.82 (m, 3H), 3.79-3.71 (m, 1H), 2.74-2.67 (m, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 137.3 (C), 133.5 (C), 129.4 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 127.2 (CH), 69.3 (CH\(_2\)), 68.3 (CH), 63.0 (CH\(_2\)), 60.3 (CH\(_2\)), 55.4 (CH\(_2\)); MS (El) 303.1 (M\(^+\)); HRMS calcd for C\(_{17}\)H\(_{18}\)NO\(_2\)Cl 303.1026; found 303.1030.

(Z)-N-(4-nitrophenyl)allylidenebenzylamine \(N\)-oxide (7.42). The following nitrone was isolated as the major product of the reaction between \(E\)-4-nitrocinnamaldehyde 7.41 (84 mg, 0.47 mmol), Z-N-benzylidenebenzylamine \(N\)-oxide 7.7 (50 mg, 0.24 mmol), 7.1 (13 mg, 0.05 mmol) and CF\(_3\)SO\(_3\)H (4.2 uL, 0.05 mmol) in nitromethane (2.0 ml, 0.1 M) at +4°C. After 32 hours, purification by silica gel chromatography (50% ethyl acetate in hexanes) provided the compound as a yellow solid in 79% yield (53 mg). mp 147.5°C; IR (neat) 3047, 2363, 1509, 1345 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.15 (d, 8.8 Hz, 2H), 7.57 (d, 8.8 Hz, 2H), 7.50 (dd, 16.3, 9.4 Hz, 1H), 7.44-7.37 (m, 5H), 7.28 (d, \(J = 9.4\) Hz, 1H), 7.00 (d, \(J = 16.3\) Hz, 1H), 4.97 (s, 2H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 147.5, 142.4, 135.6, 135.0, 132.5, 129.3, 129.2, 129.2, 127.6, 124.1, 122.2, 69.8; MS (El) 282.1 (M\(^+\)); HRMS calcd for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\) 282.1004; found 282.0993.

(E)-(2-benzyl-5-methyl-3-(prop-1-enyl)isoxazolidin-4-yl)methanol (7.20). Compound was obtained as a side product in dipolar cycloadditions and is formed by hydrolysis of Z-N-benzylidene-
Experimental Section: 1,3-Dipolar Cycloadditions

benzylamine N-oxide 7.7 and condensation of the resulting N-benzylhydroxylamine with crotonaldehyde. The following then undergoes a dipolar cycloaddition with crotonaldehyde to afford a mixture of exo and endo isomers of the title product as a clear oil. No enantiomeric excess was observed from the reaction. The exo isomer (diastereoselectivity assigned by NOESY analysis) was isolated from the mixture: IR (neat) 3052, 2354, 1511 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.20 (m, 5H), 5.80 (dq, \(J = 15.8, 6.6\) Hz, 1H), 5.55 (ddd, 15.7, 9.2, 1.5 Hz, 1H), 4.12-4.03 (m, 2H), 3.79-3.68 (m, 2H), 3.63 (d, 15.0 Hz, 1H), 3.42-3.35 (m, 1H), 2.26-2.16 (m, 1H), 1.74 (dd, \(J = 6.5, 1.59\) Hz, 3H), 1.26 (d, \(J = 5.8\) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 132.8 (CH), 128.9 (C), 128.8 (CH), 128.2 (CH), 127.2 (CH), 125.3 (CH), 76.4 (CH), 71.3 (CH), 61.9 (CH\(_2\)), 59.5 (CH), 54.9 (CH\(_2\)), 20.2 (CH\(_3\)), 18.2 (CH\(_3\)). MS (EI) 247.2 (M\(^+\)).
Progress Toward a Stereoselective Approach to α-Oximation of Carbonyls

9.1 Nitroso compounds: N- or O-nitroso aldol

Since the first preparation of nitrosobenzene by Baeyer at the end of nineteenth century,\textsuperscript{185} the nitroso function has become an attractive electrophile in carbon-nitrogen and/or carbon-oxygen bond forming reactions. The high reactivity of the nitroso electrophile is largely attributed to the polarizability of the nitrogen-oxygen bond. There exists an important equilibrium between the monomer 9.1 and azodioxy dimer 9.2 of nitroso compounds, as shown in Scheme 9.1. Careful control of this equilibrium is an essential prerequisite for the use of nitroso electrophiles in organic synthesis. Primary and secondary alkyl derivatives, prepared and stored as crystalline dimers, exist as monomers in solution that can undergo an irreversible tautomerization, via acid-base catalysis, to yield unreactive oximes 9.5. Consequently, electrophilic nitroso compounds are typically of aryl or tertiary nature, as these limit the undesired degradation pathways.\textsuperscript{186}

\textsuperscript{185} Bayer, A. Chem. Ber. 1874, 7, 1638.
The earliest example of the potential use of nitroso compounds for enantioselective processes was disclosed by Oppolzer.\textsuperscript{187} The success of the method relied on the clever use of $\alpha$-chloronitroso derivatives as a practical electrophilic [NH$_2$$^+$] equivalent to provide $\alpha$-amino compounds by reaction with an enolate. Using the camphor sultam chiral auxiliary 9.9 developed in their laboratories, the enolate generated from the resulting acylsultam 9.10 in the presence of sodium hexamethyldisilazide was then treated with the nitroschloride 9.7 and quenched with 1N aq. HCl to provide hydroxylamines 9.11 as a single diastereoisomer in yields ranging from 94-99%. Hydrogenolysis of the nitrogen-oxygen bond with zinc dust in aqueous hydrochloric acid provided the crude $N$-(\(\alpha\)-aminoacyl)sultam which was subsequently treated with lithium hydroxide to afford the enaniopure $\alpha$-amino acid 9.12 and return the sultam auxiliary 9.9.

Scheme 9.1 Preparation of optically pure amino acids by reaction of a chiral enolate with an α-chloronitroso derivative

This process was applied to the efficient preparation of a variety of pure (R) and (S)-α-amino acids. The selectivity observed in this transformation was provided by top face shielding created by the geminal methyl group on the sultam scaffold. Consequently, attack of the nitroso electrophile on the bottom face the kinetically controlled Z-enolate procured the desired product with an (R)-configuration. Evidence for the proposed intermediate nitrone 9.14 was obtained by trapping of the 1,3-dipole with phenyl isocyanate to afford 9.15.

Although the nitroso derivatives used by Oppolzer served as an electrophillic nitrogen source, one of the particular challenges in nitroso aldol reactions remains the control of chemo- and regioselectivity. The ambivalent nature of the nitroso functionality often results in mixtures of the O- or N-nitroso aldol products. Consequently, efforts were made to selectively control the attack onto electrophile depending on the reaction conditions employed. Yamamoto has shown
that reaction of various enolate anions 9.16 such as silyl, lithium or tin with nitrosobenzene 9.6 provided aminooxy ketone 9.17 selectively and in high yields.\(^{188}\) Surprisingly, when the reaction of nitrosobenzene with silyl enol ethers was performed in the presence of a Lewis acid catalyst, the sole product observed was the hydroxyamino ketone 9.18.\(^{189}\) These protocols, in which the regioselectivity of the nucleophilic attack on the nitroso species was adequately controlled by the choice of reagent, have paved the way for synthetically useful α-derivatization the carbonyl functionality (Scheme 9.2).

Scheme 9.2 Regioselectivity in the nitroso aldol reaction

![Scheme 9.2 Regioselectivity in the nitroso aldol reaction](image)

Subsequent efforts were directed toward the development of catalytic enantioselective process for the introduction of nitrogen or oxygen alpha to a carbonyl group. Yamamoto found that the reaction of tin enolates with nitrosobenzene conducted in the presence 10 mol% \((R)\)-BINAP/AgOTf complex could furnish the O-nitroso aldol 9.20 product in excellent regio- and enantioselectivity (Scheme 9.3).\(^{190}\) The reaction was tested with various tin enolates and in all cases, the O-regioselectivity and enantioselectivity was maintained. Conversely, the same research group has shown that nitrosobenzene can be used as an amination reagent in an enantioselective reaction by simply switching the structure of the silver/BINAP complex and the solvent.\(^{191}\)


Preformed enamines have also been used as enol synthons with nitroso derivatives. The reaction of nitrosobenzene with 1-morpholino-1-ylcyclohexene 9.23 followed by hydrolysis results in the α-hydroxyamino ketone 9.21 as the major product.\textsuperscript{192} Surprisingly, in a similar reaction in which nitrosobenzene is treated with a pyrrolidine enamine 9.24 followed by acidic workup, the α-oxaminated ketone 9.20 is obtained almost exclusively.\textsuperscript{193} This complete reversal in regiochemistry is thought to be a result of the structural differences of the enamines. Furthermore, it was found that these reactions could be significantly accelerated by the addition of Bronsted acids. The production of the N-nitroso aldol compound via the morpholine enamine could be achieved at -78 °C when methanol was added to the reaction mixture. In contrast, a significant acceleration for the O-nitroso aldol pathway took place in the presence of acetic acid. Therefore, by simply switching the acid catalyst and the structural motif of the amine moiety in the enamine, it is possible to obtain either N- or O-nitroso aldol product.\textsuperscript{194}

With this information in hand the Yamamoto group developed chiral Brønsted acid promoters for the regio- and enantioselective nitroso aldol reaction. They examined a variety of chiral carboxylic acids and found that 1-aryl glycolic acids 9.25 could promote the formation of O-nitroso aldol product 9.20 effectively in presence of the pyrrolidine or piperidine enamines in optical purities of up to 92% (Scheme 9.5). They also found that instead of methanol, (R,R)-TADDOL 9.27 derivatives could be used as chiral promoters for N-nitroso aldol reaction. When 30 mol% of 1-naphthyl TADDOL was added to the piperidine cyclohexene in toluene, the aminoketone 9.21 was obtained in excellent yields and enantiomeric purities of up to 83%.
The most attractive mode of activation toward enantioselective nitroso aldol reactions has been recently achieved using L-proline 9.29. The advantages of this organocatalyzed transformation include a metal-free environment as there is no requirement to preform the enolate prior to addition of the nitroso derivative. The use of catalytic L-proline enables the regio- and enantiomerically pure synthesis of O-alkylated products 9.30 from the parent carbonyl and nitrosobenzene. In 2003, the groups of MacMillan, Hayashi and Zhong simultaneously reported the first L-proline-catalyzed enantioselective O-nitroso aldol with aldehydes 9.28 with very high ee (97–99%). The reaction was general in terms of the aldehyde as aliphatic, aromatic, silyl-protected hydroxy groups and N-Boc amino groups do not affect the reaction in terms of reactivity and selectivity.

---

The proposed catalytic cycle for the proline-catalyzed α-oxamination of aldehydes and ketones 9.31 with nitrosobenzene is shown in Scheme 9.7. Condensation of proline with the carbonyl moiety initially results in an iminium ion which is subsequently tautomerized into the nucleophilic enamine 9.32. The reaction of 9.32 with nitrosobenzene results in a formal oxidation at the α-position of the carbonyl group. Hydrolysis of the intermediate O-alkylated iminium 9.35 regenerated the proline catalyst and frees the α-oxaminated product 9.36, thereby completing the catalytic cycle.
Scheme 9.7 Catalytic cycle of the L-proline-catalyzed α-oxamination of aldehydes and ketones

The preferred O-regioselectivity over the N-nitroso aldol product implies that directing features in proline are involved to ensure attack at the oxygen atom. It is believed that the appropriate Brønsted acidity found in the carboxylic acid may contribute to provide both high enantioselectivity and O-selectivity in the catalytic reaction. The most commonly accepted transition state 9.34, shown in Figure 9.7, suggests that the carboxyl group provides an intramolecular hydrogen bond stabilized by the enhanced Brønsted basicity of the nitrogen atom.

Additional studies regarding the transition states and selectivity in O-nitroso aldol reaction catalyzed by L-proline was provided in the computational studies of Houk and Cordova. The lowest-energy transition structure calculated involves an E-anti proline enamine intermediate 9.33 that preferably adopts the axial position of phenyl group in nitrosobenzene. Other groups have also postulated that the O-regioselectivity in the proline-catalyzed reaction may originate

The O-nitroso aldol reaction has also been extended to ketones. The groups of Cordova and Hayashi simultaneously reported the asymmetric α-oxamination of ketones 9.37 in excellent yields and selectivities. Several substrates including cyclic and aliphatic ketones also provided the O-substituted product. Although excellent enantioselectivities were obtained in all cases, lower chemical yields and considerable amounts of α,α-bis oxaminated product were observed in certain cases. Both groups also applied this concept toward the asymmetric desymmetrization of either 4- or 6- substituted cyclohexanones to afford diastereoisomers in good de and excellent ee.

Scheme 9.8 The L-proline-catalyzed α-oxamination of ketones

The α-oxaminated products can be converted into valuable synthetic intermediates. As such, the reduction of the carbonyl moiety in 9.36 with sodium borohydride followed by treatment with palladium on carbon in a hydrogen atmosphere provides an alternative procedure to the dihydroxylation of olefins. Treatment with copper sulfate allows for selective cleavage of the oxygen-nitrogen bond while keeping the carbonyl intact to afford α-hydroxy carbonyl compounds 9.40. Additionally, reductive amination of α-oxaminated intermediate 9.36 by treatment with sodium triacetoxy borohydride and benzylamine furnishes the synthetically useful amino alcohols 9.41 (Scheme 9.9).

Approach toward α-Oximation of Carbonyls

Scheme 9.9 Synthetic applications of the enantioselective L-proline-catalyzed α-oximation

\[ \text{R}^1\text{R}^2 + \text{PhNO} \rightarrow \text{L-proline} \]

\[ \text{R}^1\text{O}^\cdot\text{O}^\cdot\text{N}^\cdot\text{Ph} \]

\[ \text{9.36} \]

\[ \text{NaBH}_4, \text{H}_2, \text{Pd/C} \]

\[ \text{9.39} \]

\[ \text{9.31} \]

\[ \text{9.31} \]

\[ \text{CuSO}_4 \]

\[ \text{9.39} \]

\[ \text{NaBH}(\text{OAc})_3 \text{BnNH}_2 \]

\[ \text{9.41} \]

\[ \text{9.40} \]

\[ \text{9.40} \]

\[ \text{9.2 a-amination or α-oximation?} \]

It came to our attention that in the organocatalytic studies pertaining to the formation of α-oxamino derivatives, that nitrosobenzene was the only nitroso compound utilized. No research group had examined the use of α-chloronitroso cyclohexane 9.7, successfully used by Oppolzer in the formation of α-amino acids (Scheme 9.1), as an electrophillic reagent in reactions promoted by L-proline.

We hypothesized that the different electronic and structural properties of the α-chloronitroso cyclohexane 9.7 might afford an alternative organization in the transition state of proline-catalyzed reactions with nitroso derivatives. Such an outcome could potentially result in rate enhancements that would permit the synthesis of more complex substrates or effect a change in regioselectivity that would allow access to the N-nitroso aldol products. If this were the case, such a methodology would offer an elegant alternative to the current proline systems that make use of azodicarboxylates as electrophilic amination reagents to assemble α-amino derivatives.
Consequently, we wished to investigate the combination of enamine catalysis together with nitrosochloride 9.7 as an electrophile.

Scheme 9.10 Different nitroso aldol products that could arise in the L-proline catalyzed reaction between 9.42 and 9.7

1-chloro-1-nitrosocyclohexane 9.7 was synthesized by the addition of a carefully titrated solution of sodium hypochlorite (obtained from household bleach) to a two-phase benzene-water solution of cyclohexanone oxime or by bubbling Cl₂ gas into a cooled solution of cyclohexanone oxime in hexanes. The characteristically dark blue chloronitroso compound was then treated with ten equivalents of cyclohexanone in the presence of 10 mol% L-proline in DMSO at room temperature.

The major product, obtained in 10% isolated yield, did not display ¹H NMR resonances corresponding to that of the N-substituted product but rather featured an interesting doublet of doublet of doublets at 4.54 ppm. Furthermore, the ¹³C NMR revealed the presence of a carbonyl peak at 209.3 ppm, and resonances at 161.7 and 84.6 ppm. The compound had a mass of 209.1 as confirmed by HRMS, and a fragment at 114.1 m/e in the mass spectrum suggested the presence of 2-hydroxycyclohexanone. A detailed COSY analysis allowed us to elucidate the structure of the product which was obtained as a result of an electrophillic attack at the oxygen atom rather than at the nitrogen center.

---

Figure 9.2 Formation of α-oximated product 9.43 and COSY spectrum

\[
\text{9.42} + \text{9.7} \xrightarrow{10 \text{ mol\%}} \text{9.46} \quad \text{98% ee}
\]

\[
\text{DMSO, rt}
\]

\[
\begin{array}{c}
4.550 \quad 4.500 \\
\text{ppm (t1)}
\end{array}
\]

\[
\begin{array}{c}
4.50 \quad 4.00 \quad 3.50 \\
3.00 \quad 2.50 \\
2.00 \quad 1.50 \\
\text{ppm (t2)}
\end{array}
\]
Approach toward α-Oximation of Carbonyls

Thus, the observed product bearing an α-oxime ether was the result of an O-nitroso aldol reaction. The reaction was though to occur by the initial formation of a nucleophilic enamine 9.43 by the condensation of L-proline 9.29 with cyclohexanone 9.42, as depicted in Scheme 9.11. The reaction of 9.42 with 1-chloro-1-nitrosocyclohexane proceeded by attack at the oxygen, perhaps via a similar transition state to other enamine-catalyzed nitroso additions. The carboxyl group could potentially provide an intramolecular hydrogen bond with the nitrogen atom of the nitroso functionality that would render the oxygen more susceptible to attack. The chief distinction between the use of nitrosobenzene and 1-chloro-1-nitrosocyclohexane resides in the ability of 9.7 to displace a chloride ion which allows formation of the observed oxime. Hydrolysis of the intermediate O-alkylated iminium 9.45 releases the α-oximated product 9.46 and frees the proline catalyst, thereby completing the catalytic cycle.

Scheme 9.11 Proposed mechanism for the L-proline-catalyzed formation of α-oximated product 9.46 from cyclohexanone and 1-chloro-1-nitrosocyclohexane
Approach toward α-Oximation of Carbonyls

With α-oximation product 9.46 in hand, we set out to assess the extent of optical purity provided by L-proline catalysis. Compound 9.46 was synthesized racemically from cyclohexanone and 1-chloro-1-nitrosocyclohexane with DL-proline in DMSO at room temperature for comparison with the enantiomerically pure product. We were pleased to find that 9.46 was obtained in 98% optical purity as determined by chiral HPLC when L-proline was used as a catalyst.\(^{199}\) To the best of our knowledge the only other method to access compounds bearing an oxime ether α to a carbonyl group involves a complex rearrangement of alkynes with cationoid electrophiles in nitroalkane solutions that were obtained as a racemic mixture.\(^{200}\)

The assembly of these unique α-oximated derivatives could provide an excellent alternative for the α-oxygenation of carbonyl groups. The synthesis of 1-chloro-1-nitrosocyclohexane is simple and inexpensive and provides an excellent alternative to nitrosobenzene. Additionally, the synthesis of various chloronitroso analogues would allow access to a several alkyl α-oxaminated derivatives that cannot be accessed otherwise. The construction of N-O-C bonds from simple starting materials would allow access useful building blocks such as 9.49-9.51 for potentially important biologically active compounds (Scheme 9.12).

\(^{199}\) Absolute stereochemistry was not determined

Scheme 9.12 Potential C-O-N synthetic intermediates arising from the reaction of a carbonyl with chloronitroso derivatives

\[
\begin{align*}
R^1\text{C}=O + R^3\text{Cl}_N^+ \rightarrow L\text{-proline} & \rightarrow R^1\text{C}=O\text{N}R^3R^4 \\
9.48 & \\
\text{NaBH}_3\text{CN} \quad \text{not isolated} & \quad \text{NaBH(OAc)}_3 \quad R^5\text{NH}_2 \\
9.49 & \quad 9.50 \\
\text{H}_2\quad \text{Pd/C} \quad R^6\text{X} & \\
9.51
\end{align*}
\]

9.3 Optimization of the reaction

Although the use of chloronitroso cyclohexane as an electrophile provided access to the unforeseen product 9.46 bearing an oxime ether in excellent enantioselectivity, the product was obtained in a mere 14% conversion and 10% isolated yield. As a result, significant efforts were invested toward the yield optimization.\(^{201}\)

A solvent screen was performed in solvents known to be effective in proline-catalyzed reactions. Unfortunately DMSO was the only efficient solvent that promoted the formation of \(\alpha\)-oximated

\(^{201}\) The percent conversion was similar to that of the isolated yield confirming that the low yield is not a result of decomposition during isolation and purification of 9.46.
products as reactions performed in CHCl₃, CH₂NO₂, EtOAc, toluene, Et₂O, CH₃CN and DMF provided only traces of the desired product 9.46 after 24 hours. Longer reaction times resulted in decrease in yield of 9.46. A reaction without solvent was also performed at room temperature over the period of 30 hours to afford the product in 14% conversion but with several side-products.

The effect of temperature on the proline-catalyzed oxidation of cyclohexanone in DMSO was also examined. A reaction was performed at +4 °C in DMSO did not provide a significant advantage, affording the product in 12% yield.²⁰² Reduction of the temperature beyond this point could not be accomplished due to the high freezing point of DMSO. When the reaction was performed at 50 °C, formation of 9.46 was very rapid as observed by TLC, but degradation shortly ensued, resulting in traces of product after isolation. When the amount of L-proline was increased from 10 to 30 mol%, the yield of product 9.46 was changed to 12%. However, when proline was used in a stoichiometric amount relative to the chloronitroso reagent, the yield of 9.46 decreased to 7% and the formation of a significant amount of side-product was observed on TLC.

In our initial investigation, the chloronitroso derivative 9.7 was used as the limiting reagent and the cyclohexanone was used in a tenfold excess (Table 9.1, entry 1).²⁰³ When the ratio of reagents was varied so that the amount of nitroso derivative was increased relative to cyclohexanone (entries 2 and 3), we found that a lower yield of the desired product 9.46 was obtained. We hypothesized that this could be the result of dimerization of the chloronitroso cyclohexane 9.7. However, attempts to isolate or identify the nitroso dimer by ¹H NMR were unsuccessful. We did however observe a side-product which corresponded to cyclohexanone oxime 9.52 which was isolated in all instances from the reaction mixture.

²⁰² If the reaction in DMSO is performed at high enough concentration (2.0 M), and vigorous stirring is provided, reactions in DMSO can be performed at +4°C. The tenfold excess of cyclohexanone also helps in solubilizing the solution.

²⁰³ Although some of the double α-oxamination product had been observed with other systems, we did not observe any product corresponding to the double addition of 9.7 to cyclohexanone.
Table 9.1 Variation of the ratio of cyclohexanone to 1-chloro-1-nitro cyclohexanone toward the formation of \( \alpha \)-oximated product 9.46

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio 9.42:9.7</th>
<th>Yield 9.46 (%)(^b)</th>
<th>Yield 9.52 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10:1</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2:1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\) Reactions performed in 1.0 M DMSO. \(^b\) Absolute chemistry not determined.

It has been suggested that the formation of 9.52 from chloronitroso compound 9.7 can arise from either a light-involved or acid-catalyzed decomposition or a nucleophilic attack on the chloride. The formation of 1-chloro-1-nitroso cyclohexane from cyclohexanone oxime is reversible and continuous removal of HCl is necessary to drive the reaction to completion.\(^{204}\) Consequently, the hydrochloric acid released in the formation of 9.46 could induce the acid catalyzed formation of 9.52. An experiment in which the chloronitroso reagent 9.7 was added via syringe pump over 8 hours at room temperature was performed so that the concentration of 9.7 would remain low at all times during the reaction. These conditions were not satisfactory as the \( \alpha \)-oxaminated product 9.46 was obtained in a lower yield of 7% and generated side-product 9.52 in a more significant 19% yield.

Additionally, chloronitroso compounds are light sensitive as they can undergo radical reactions to produce the corresponding cyclohexanone oxime 9.52.\textsuperscript{205} In order to avoid the exposure of the chloronitroso cyclohexane to light, all reactions were performed in the dark. The addition of the radical inhibitor BHT in order to suppress the formation of 9.52 via a radical pathway did not display an improvement in the yield of the desired product. Control experiments were also performed to test whether 1-chloro-1-nitroso cyclohexane was stable in the reaction conditions. When 9.7 was dissolved in DMSO only or L-proline and DMSO for several hours, no decomposition was observed.

We hypothesized that the chloride anion released during the formation of 9.46 and the ensuing HCl produced in the reaction mixture could not only induce the formation of 9.52, but also inhibit the formation of the desired α-oximated product 9.46. To verify this, several bases were added in an equimolar amount to the chloronitroso reagent 9.7 in an attempt to neutralize the acid formed during the reaction.

\textsuperscript{205} Muller, E.; Metzger, H.; Fries, D. Chem. Ber. 1954, 87, 1449.
Table 9.2 Investigation of bases in the L-proline-catalyzed formation of α-oximated product 9.46

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield 9.46 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield 9.52 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
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<td>11</td>
<td>8</td>
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<tr>
<td>2</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;HPO&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>18</td>
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<tr>
<td>3</td>
<td>NaOAc</td>
<td>Trace</td>
<td>-</td>
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<tr>
<td>4</td>
<td>2,6-lutidine</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Pyridine</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
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<td>-</td>
</tr>
<tr>
<td>7</td>
<td>imidazole</td>
<td>10</td>
<td>18</td>
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<tr>
<td>8</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>20&lt;sup&gt;c&lt;/sup&gt;</td>
<td>18</td>
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<td>3</td>
</tr>
<tr>
<td>11</td>
<td>Amberlite</td>
<td>7</td>
<td>4</td>
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</table>

<sup>a</sup> Reactions performed in 1.0 M DMSO. <sup>b</sup> Absolute configuration not determined. <sup>c</sup> Enantiomeric excess for this reaction was 89% as determined by chiral HPLC.

When phosphate bases were added to the reaction mixture, the yield of α-oximated product 3 was constant but the formation of side product 9.52 was increased (Table 9.2, entries 1 and 2). When amine bases were introduced, we found that 2,6-lutidine provided product 9.56 in a moderate 13% isolated yield whereas the reaction in which triethylamine was added afforded only traces of the product (entries 4-7). The most dramatic effect was noticed upon addition of sodium bicarbonate to the reaction mixture. The production of both 9.46 and 9.52 were increased to 20 and 18%, respectively. However, when the enantiomeric excess for this reaction was measured, we observed a decrease in optical purity from 98 to 89% ee. The addition of DOWEX
and Amberlite resins, adjusted to a neutral pH, did not provide any considerable return toward the production of 9.46. Interestingly, when a catalytic amount of p-TSA was introduced to the reaction mixture, products 9.46 and 9.52 were not observed and the reaction was shut down. This result may be linked to the inhibition of the enamine formation in the acidic medium. The results discussed above suggest that the addition of a base or an acid to the reaction mixture is detrimental to both yield and optical purity.

Increasing the polarity of the reaction medium by the addition of water was investigated in hopes of enhancing the enamine formation and iminium hydrolysis. The addition of water could not only have a dramatic effect on the solution's polarity but also improve the solubility of the proline in this system.\textsuperscript{206}

\textsuperscript{206} Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* 2004, 1891.
When activated molecular sieves were added to mixture, the product was isolated in 3% yield together with 7% of 9.52 (Table 9.3, entry 1). The reaction had to be terminated earlier as the formation of dark tar-like substances on the sides of the flask was noted as the reaction progressed. The addition of 1 and 5 equivalents of water resulted in a lower yield of 9.46 and 9.52 and the reaction was completely shut-down when water and DMSO were used in a 1:1 ratio (entries 2-4). These results suggest that the presence of large amounts of water in the reaction mixture is unfavorable and inhibits the production of 9.46 and 9.52 at high concentrations.

Given that the production of α-oximated product 9.46 depended on the ejection of a chloride ion in order to form the corresponding oxime ether, the addition of silver salts to the reaction mixture was examined. The silver salts could potentially promote the loss of the chloride via an $S_N1$ pathway and consequently enhance the rate of the reaction.

---

Table 9.3 Effect of water on the $L$-proline-catalyzed α-oximation of cyclohexanone with 1-chloro-1-nitrosocloride $2^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield 9.46 (%)</th>
<th>Yield 9.52 (%)</th>
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<tr>
<td>1</td>
<td>Mol. Sieves</td>
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<tr>
<td>2</td>
<td>1 equiv. $H_2O$</td>
<td>26</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5 equiv. $H_2O$</td>
<td>29</td>
<td>5</td>
<td>2</td>
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<tr>
<td>4</td>
<td>1:1 $H_2O/\text{DMSO}$</td>
<td>72</td>
<td>0</td>
<td>0</td>
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<tr>
<td>5</td>
<td>DMSO only</td>
<td>25</td>
<td>12</td>
<td>3</td>
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</table>

$^a$ Reactions performed in 1.0 M DMSO.
Table 9.4 Effect of silver salts on the L-proline-catalyzed $\alpha$-oximation between cyclohexanone and nitrosochloride

<table>
<thead>
<tr>
<th>Entry</th>
<th>Silver salt</th>
<th>Yield 9.46 %</th>
<th>ee % $^{a,b}$</th>
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<td>-</td>
<td>12</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Ag$_2$O</td>
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<td>20</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>AgCO$_2$CH$_3$</td>
<td>16</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>AgNO$_3$</td>
<td>0$^c$</td>
<td>n/d</td>
</tr>
<tr>
<td>6</td>
<td>AgOTf</td>
<td>0</td>
<td>n/d</td>
</tr>
<tr>
<td>7</td>
<td>AgBF$_4$</td>
<td>0</td>
<td>n/d</td>
</tr>
</tbody>
</table>

$^a$ enantiomeric excess determined by chiral HPLC. $^b$ Absolute configuration not determined. $^c$ cyclohexanone oxime was the only product obtained.

The addition of salts such as silver oxide, silver carbonate and silver acetate all produced a rate enhancement and afforded $\alpha$-oximated product 9.46 in higher yield relative to the reaction conducted without a silver salt (Table 9.4, entries 1-4). Unfortunately, the enantiomeric excess obtained in the reactions performed with these silver salts was noticeably lower (82-91% ee) relative to the salt-free reaction (entry 1). The addition of silver nitrate resulted in exclusive formation of cyclohexanone oxime 9.52 (entry 5) whereas the AgOTf and AgBF$_4$ salts did not afford any of the desired $\alpha$-oximated product 9.46 (entries 6 and 7).

Other substrates were investigated toward the introduction of an oxime ether moiety $\alpha$ to a carbonyl compound. When the larger cyclohexanone derivative 9.54 was submitted to the $L$-proline-catalyzed reaction in the presence of 1-chloro-1-nitroso cyclohexane only traces of the desired $\alpha$-oximated product was observed. Similarly, the smaller methylethyl ketone 9.55 was
completely unreactive. Surprisingly, aldehydes such as 9.56 and 9.57, which provided the α-oxaminated products from nitrosobenzene in excellent yield,\textsuperscript{195} were also found to be poorly reactive upon reaction of the proline enamine with 1-chloro-1-nitroso cyclohexane. The structure of the chloronitro derivative was altered from a cyclohexane to a cyclopentane in an attempt to improve the formation of 9.46. Unfortunately, the reaction of 1-chloro-1-nitrosocyclopentane 9.58 with cyclohexanone was more sluggish than when the reaction was run with 9.7.

Blackmond and co-workers published a report in which they proposed an intriguing mechanism for the catalytic cycle of the proline-catalyzed O-nitroso aldol reaction.\textsuperscript{207} Based on calorimetry and kinetic experiments, they showed the possibility of an autoinductive process that would provide rate and selectivity enhancements. They observed that the rate of the reaction steadily increased as the reaction progressed, suggesting that the catalyst is improving over time. As a result, the α-oxaminated product was added to the crude reaction mixture containing the original proline catalyst and the reaction product in the first reaction. They observed a significant rate improvement which suggested that the product could be a catalyst or that the product promotes

the formation of a more effective catalyst. They also found that when non-enantiopure proline was used as a catalyst that the enantiomeric excess of the product was greater than what would be expected for a reaction following a linear relationship.

A mechanism was proposed in which L-proline 9.29 attacks the carbonyl group of the α-oxaminated product 9.30 to generate a new catalyst 9.59 (Scheme 9.14). The α-oxygen in this catalyst would increase the nucleophilicity of the reactive nitrogen by an α-heteroatom effect, providing a more reactive catalyst toward the condensation with a carbonyl moiety. The resulting enamine 9.61 would react with nitrosobenzene leading to the production of the observed O-nitroso aldol product and regeneration of more reactive and improved catalyst 9.59.

Scheme 9.14 The auto-inductive mechanism proposed by Blackmond

If the mechanism proposed by Blackmond and co-workers is correct, the lack of activity observed in the reaction performed with 1-chloro-1-nitroso cyclohexane could be rationalized by the inability of the α-oximated product (which has no available free amine) to undergo an autoinductive process. To verify this hypothesis nitroso analogue 9.66, in which the chloride was
replaced by a methyl group could be synthesized following known procedures, starting from 1-methylcyclohexanol.\textsuperscript{208} Alternatively the tert-butyl nitroso derivative 9.8 could be utilized.

Scheme 9.15 Synthesis of a 1-methyl-1-nitroso cyclohexane 9.66

![Scheme 9.15 Diagram]

The methyl group in 9.66 would disallow the formation of an oxime, which is permitted from the elimination of a chloride ion in 9.7. If significant rate and yield enhancements would be obtained using nitroso derivative 9.66 or 9.8, the Blackmond mechanism would therefore be confirmed and an explanation would be provided for the poor yields observed with 9.7.

9.4 Conclusions

We have demonstrated that 1-chloro-1-nitroso cyclohexane can be used in conjunction with cyclohexanone with catalytic $L$-proline to provide $\alpha$-oximated product 9.46 in 98\% enantiomeric excess. However, the efforts presented above to optimize the yield were to no avail. Consequently, our endeavors toward this project were brought to an end in order to focus our efforts on the successful application of hydrazide catalysts to cycloadditions, which was being concurrently investigated.

Although the project was suspended during its development stage, we believe that other members of the Ogilvie group could revisit this project and make the $\alpha$-oximation of carbonyl

compound a viable tool in organic synthesis. Such a study could include the investigation of catalysts bearing an alternate Bronsted acid group such as 9.67 and 9.68.

Figure 9.4 Potential alternative catalysts for the generation of α-oximated products

![Diagram of catalysts 9.67, 9.68, 9.69, 9.70, 9.71]

The groups of Yamamoto\textsuperscript{193} and Wang\textsuperscript{209} have developed these catalysts and demonstrated their efficiency toward the synthesis of α-oxaminated products. Their increased solubility compared to that of $L$-proline has allowed for enhanced reactivity, lower catalyst loading and more reproducible results. Additionally, alternative transition states 9.69-9.71 have been proposed for these pyrrolidine-based organic catalysts that could potentially enhance the compatibility of chloronitroso derivatives in these reactions. It is reasonable to hypothesize that altering the functional group on the pyrrolidine ring could provide the desired α-oximated product 9.46 in more satisfactory yields.

Experimental Section: 
α-Oximation of Carbonyls

**General experimental:** All solvents were used as obtained from commercial suppliers unless otherwise indicated. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. All starting materials were purchased and were used without purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F254. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. Excess solvents were removed *in vacuo* at pressures obtained by water or air aspirators connected to a rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with Silica Gel 60 (230-400 mesh). Infrared (IR) spectra were obtained as neat films on a sodium chloride cell. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. Mass spectroscopy (MS), using electron impact (EI). High resolution mass spectroscopy (HRMS) was performed on a mass spectrometer with an electron beam of 70 eV, or a double focusing magnetic sector mass spectrometer.

![1-chloro-1-nitrosocyclohexane](image)

**1-chloro-1-nitrosocyclohexane (9.7).** In a 2 neck 250 mL flask, cyclohehanone oxime (10.0 g, 88.4 mmol) was dissolved in 90 mL of cyclohexane. To vent the Cl₂ gas produced, the top neck of the flask was equipped with a septum pierced with glass pipette connected to a nalgene tube. The nalgene tube runs to an oil bubbler that will be used to monitor the flow of gas. The side neck was also equipped with a septum pierced with a glass pipette (that extends into the cyclohexane solution) connected to a nalgene tube. This nalgene tube was run to a smaller 2 neck flask. This flask was used to accumulate condensed gas or moisture coming from the Cl₂ lecture bottle. The flask was cooled to 0 °C, covered in aluminum foil and all light were shut off in the
fume hood. Cl₂ was bubbled into the flask while maintaining a constant flow for at least 1 hour, until the solution becomes bright blue and is completely miscible (the solution will be immiscible at first and vigorous stirring was required). The contents of the flask was transferred to a separatory funnel and extracted several times with distilled water followed by 10% NaHCO₃. The solution was treated with Na₂SO₄, filtered and concentrated in vacuo (be careful: some of the blue material will be trapped in the collecting flask of the rotovap). The excess cyclohexane was removed by distillation to obtain 74% (9.65 g) of the title compound as a dark blue liquid (bp: 75 °C, 41 mmHg.) CAUTION: the title compound has explosive properties and care must be taken during the distillation. IR (liquid film): 1571 cm⁻¹ (NO); ¹³C NMR (125 MHz, CDCl₃) δ 117.6 (C), 32.2 (CH₂), 24.6 (CH₂), 21.7 (CH₂). The title compound can be kept in the freezer in the dark for a maximum of 2 weeks without decomposition.

2-(cyclohexylideneaminoxy)cyclohexanone (9.46). To a solution of cyclohexanone 9.42 (665 mg, 6.78 mmol) in DMSO (1 mL) was added L-proline 9.29 (23.4 mg g, 0.203 mmol). The solution was stirred for 5 minutes under N₂ atmosphere before the addition of 1-chloro-1-nitrosocyclohexane 9.7 (100 mg, 0.678 mmol) via syringe. The reaction was covered from light and stirred overnight. The resulting brown-green solution was diluted with EtOAc and washed successively with distilled water and brine. The organic layer was dried with Na₂SO₄, filtered, and the solvent was removed in vacuo. Purification by silica gel chromatography (10% EtOAc in hexanes) provided the desired material as a colourless oil, 12% yield (17 mg). 98% ee. Enantiomeric ratio was determined by HPLC using a Chiralcel AS-H column. λ= 220 nm (2% IPA/hexanes, 0.8 mL/min flow rat) tᵣ = 9.92 min (major enantiomer) and 11.06 min (minor enantiomer). Absolute stereochemistry was not determined. [α]D -7.4° (c 1.55, CHCl₃); IR (neat) 3431, 2934, 1725, 1449 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.54 (ddd, J = 10.3, 5.4, 1.2 Hz, 1H), 3.57-2.47 (m, 3H), 2.36-2.29 (m, 1H), 2.28-2.21 (m, 1H), 2.17 (t, J = 6.31 Hz, 2H), 1.98-

Approach toward α-Oximation of Carbonyls

1.90 (m, 2H), 1.87-1.77 (m, 1H), 1.76-1.55 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.3 (C), 161.7 (C), 84.6 (CH), 40.6 (CH$_2$), 33.4 (CH$_2$), 32.0 (CH$_2$), 27.7 (CH$_2$), 26.9 (CH$_2$), 25.7 (CH$_2$), 25.6 (CH$_2$), 23.1 (CH$_2$); MS (EI) $m/z$ 209.1 (M$^+$); HRMS calcd for C$_{12}$H$_{19}$N$_1$O$_2$ 209.1416; found 209.1406.
Claims to Original Research

1. Discovery and design of a new hydrazide organic catalyst capable of promoting the LUMO-lowering activation of $\alpha,\beta$-unsaturated aldehydes by the reversible formation of iminium ions.

2. Application of hydrazide organocatalysts as an efficient platform to achieve highly enantioselective Diels-Alder cycloadditions in aqueous medium.

3. Investigation of the mechanism of the enantioselective hydrazide catalyzed Diels-Alder cycloaddition and identification of the kinetically significant step.

4. Discovery of a thermodynamic component to the hydrazide Diels-Alder reaction arising from a retro-cycloaddition process.

5. Design of an improved hydrazide catalyst, featuring conformational control, and its application to asymmetric Diels-Alder reactions.

6. Obtention if the first crystal structure of a key iminium intermediate in an organocatalyzed process.

7. Expansion of the hydrazide-catalyzed protocol to the enantioselective [3+2] cycloadditions of nitrones with $\alpha,\beta$-unsaturated aldehydes to provide isoxazolidines in excellent optical purity.

8. Development of a proline-catalyzed synthetic approach toward the $\alpha$-oximation of carbonyl compounds.
Publications from This Work


Presentations from This Work


Appendix
3.00
4.03
2.21
2.65
2.07
2.78
306
Table 3.14, entry 5
Table 3.14, entry 7
Table 3.21, entry 1
Table 3.21, entry 2
Table 3.21, entry 3

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[Chemical structures and spectra]
Table 3.21, entry 5
Table 3.21, entry 6

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Table 3.22, entry 1

[Chemical structure image]
Table 3.22, entry 3
Table 4.2, entry 2

ppm (1H)

i—i—i—|—r
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
9.0

Table 4.2, entry 2

HN

HN
Table 4.2, entry 4

Table 4.2, entry 4
Table 4.2, entry 5
Table 7.8, entry 1
Table 7.8, entry 2
Table 7.8, entry 3

NH

9.0 ppm (F1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Table 7.8, entry 4

[Chemical structure image]

ppm (H)
Table 7.8, entry 6
Table 7.6, entry 1
Table 7.6, entry 4

Chemical shifts (ppm)

- 3.09
- 3.87
- 1.97
- 1.00
- 2.93
- 8.84

Structure:

Ph

N

O

H

exo

H₃C
Table 7.6, entry 6

![Diagram of a chemical structure with chemical shifts]

ppm (f1)

- 3.79
- 1.03
- 2.91
- 2.00
- 1.02
- 5.32
- 3.86
Table 7.6, entry 6
Table 7.6, entry 7

![Chemical structure](image)

- Ph
- O
- N
- OH
- endo

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![Chemical Structure](image)

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Table 7.6, entry 9

[Chemical structure image]
Table 7.6, entry 10
Table 7.6, entry 9
Table 7.6, entry 12
Table 7.6, entry 12

Ph-exo

6.0 ppm (H1)

10.59

372
X-Ray data:

Crystal data and structure refinement for 4.14.

Identification code: wool1
Empirical formula: C18 H24 N2 O
Formula weight: 284.39
Temperature: 207(2) K
Wavelength: 0.71073 Å
Crystal system, space group: Triclinic, P1
Unit cell dimensions:
\[ a = 7.091(4) \text{ Å} \]
\[ b = 10.122(5) \text{ Å} \]
\[ c = 11.785(6) \text{ Å} \]
\[ \alpha = 76.267(8) \text{ deg.} \]
\[ \beta = 73.005(9) \text{ deg.} \]
\[ \gamma = 85.427(9) \text{ deg.} \]
Volume: 785.8(7) Å³
Z, Calculated density: 2, 1.202 Mg/m³

X-ray data:

Absorption coefficient: 0.076 mm⁻¹

F(000): 308

Crystal size: 0.25 x 0.15 x 0.10 mm

Theta range for data collection: 2.07 to 24.71 deg.

Limiting indices:
-8 <= h <= 8, -11 <= k <= 11, -13 <= l <= 13

Reflections collected / unique: 5559 / 4810 \( R(int) = 0.0631 \)
Completeness to theta = 24.71: 98.8 %
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.9926 and 0.9816
Refinement method: Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters: 4810 / 3 / 379
Goodness-of-fit on \( F^2 \): 1.078
Final R indices [I>2sigma(I)]: \( R_1 = 0.0774, \text{ wR}2 = 0.1062 \)
R indices (all data): \( R_1 = 0.2332, \text{ wR}2 = 0.1469 \)
Absolute structure parameter: 2(3)

Largest diff. peak and hole: 0.243 and -0.196 e.Å⁻³

Atomic coordinates ( x 10⁴) and equivalent isotropic displacement parameters (Å² x 10⁻³) for 4.14.

\[ \text{U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.} \]

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Anisotropic displacement parameters (Å$^2$ x 10$^2$) for 4.14.

The anisotropic displacement factor exponent takes the form:

-2 pi$^2$ [ h$^2$ a$^2$ U11 + ... + 2 h k a$^*$ b$^*$ U12 ]

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Symmetry transformations used to generate equivalent atoms:

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<td>H(2B)</td>
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<td>3739</td>
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Torsion angles [deg] for 4.1A.

| C(9) -H(1) -N(2) -C(15) | -11.1(8) |
| C(7) -H(1) -N(2) -C(15) | 158.8(6) |
| C(6) -C(1) -C(2) -C(3) | 0.6(14) |
| C(7) -C(1) -C(2) -C(3) | -175.6(8) |
| C(1) -C(2) -C(3) -C(4) | 0.1(15) |
| C(2) -C(3) -C(4) -C(5) | -6.3(14) |

N(2) -H(1) -C(9) -C(10) | -4.6(8) |
N(1) -C(9) -C(10) -C(11) | -174.0(7) |
O(1) -C(10) -C(11) -C(12) | -44.6(13) |
N(1) -C(10) -C(11) -C(12) | 135.6(8) |
O(1) -C(10) -C(11) -C(12) | -162.7(8) |
N(1) -C(9) -C(10) -C(11) | 17.6(8) |
N(1) -C(9) -C(10) -C(11) | -97.6(8) |
C(9) -C(10) -C(11) -C(12) | 174.7(7) |
C(15) -C(10) -C(11) -C(12) | -68.1(8) |
C(16) -C(10) -C(11) -C(12) | 41.6(8) |
C(16) -C(10) -C(11) -C(12) | 76.3(8) |
C(11) -C(12) -C(13) -C(14) | -33.7(8) |
C(16) -C(13) -C(14) -C(15) | 65.2(8) |
C(12) -C(13) -C(14) -C(15) | -65.1(8) |
H(1)-O(1) -C(15) -C(14) | 137.2(7) |
H(1)-O(1) -C(15) -C(14) | 23.5(8) |
C(12) -C(13) -C(14) -C(15) | -127.2(7) |
C(15) -C(10) -C(11) -C(12) | -10.3(8) |
C(9) -C(10) -C(11) -C(12) | -24.3(8) |
C(9) -C(10) -C(11) -C(12) | 15.8(8) |
C(16) -C(10) -C(11) -C(12) | 98.8(7) |
C(9) -C(10) -C(11) -C(12) | -150.3(6) |
C(11) -C(10) -C(11) -C(12) | -3.1(8) |
C(16) -C(10) -C(11) -C(12) | 72.7(8) |
C(14) -C(13) -C(14) -C(15) | 61.2(9) |
C(12) -C(13) -C(14) -C(15) | 175.9(7) |
C(14) -C(13) -C(14) -C(15) | -174.4(7) |
C(12) -C(13) -C(14) -C(15) | -60.0(8) |
C(12) -C(13) -C(14) -C(15) | 56.0(7) |
C(12) -C(13) -C(14) -C(15) | 45.4(10) |
C(9) -C(10) -C(11) -C(12) | 178.2(7) |
C(15) -C(10) -C(11) -C(12) | -68.7(8) |
C(9) -C(10) -C(11) -C(12) | -78.6(9) |
C(13) -C(10) -C(11) -C(12) | 58.0(9) |
C(15) -C(10) -C(11) -C(12) | 167.5(7) |
C(9) -C(10) -C(11) -C(12) | 164.9(7) |
C(13) -C(10) -C(11) -C(12) | -58.7(7) |
C(15) -C(10) -C(11) -C(12) | 50.8(7) |
C(27) -H(3) -N(4) -C(33) | -20.5(9) |
C(25) -H(3) -N(4) -C(33) | 175.5(7) |
Crystal data and structure refinement for 4.19.

Identification code: wo02
Empirical formula: C31 H37 F3 N2 O4.75 S
Formula weight: 602.69
Temperature: 213(2) K
Wavelength: 0.71073 Å
Crystal system, space group: Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions: a = 9.715(6) Å, alpha = 90 deg.
b = 11.386(7) Å, beta = 90 deg.
c = 28.978(17) Å, gamma = 90 deg.
Volume: 3205(3) Å³
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<th>Value</th>
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<td>Absorption coefficient</td>
<td>0.157 mm^-1</td>
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<td>F(000)</td>
<td>1272</td>
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<tr>
<td>Crystal size</td>
<td>0.45 x 0.20 x 0.20 mm</td>
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<tr>
<td>Theta range for data collection</td>
<td>1.92 to 23.26 deg</td>
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<tr>
<td>Limiting indices</td>
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</tr>
<tr>
<td>Reflections collected / unique</td>
<td>18961 / 4595 [R(int) = 0.0803]</td>
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<tr>
<td>Completeness to theta = 23.26 %</td>
<td>99.6 %</td>
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<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
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Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^-4) for 4.19.

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Bond lengths (A) and angles [deg] for 4.19.

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4.19 is a chemical compound, possibly a related to the structure of organic compounds.
Anisotropic displacement parameters (\(a^{2} \times 10^{3}\)) for 4.19.

The anisotropic displacement factor exponent takes the form:

\[-2p^2 \exp \left( -2 \pi h a_{h}^{2} + 2 \pi k a_{k} b_{k}^{2} + 2 \pi l a_{l}^{2} \right) \]

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Torsion angles [deg] for 4.19.

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