This thesis is made of two parts: Part one includes an introduction to asymmetric catalysis, an important strategy to create enantiopure compounds. The introduction explores two main subsets of asymmetric catalysis: organocatalysis and organometallic catalysis. The investigation performed has studied asymmetric reactions combining organocatalysis, by using arylamines for enamine catalysis, with metal Lewis acid catalysis, by using Lewis-acid assisted Lewis acid (LLA) catalysis, leading to products that cannot be created by using either type of catalyst alone. Part two includes an introduction of signal transducer and activator of transcription 3 (STAT3) and its activation in cancerous cells. Different inhibitors have been studied to reduce STAT3 activity, which can lead to cancer fighting drugs. Design and synthesis of small molecular inhibitors and results of inhibition of STAT3 will be summarized. These inhibitors are derived from amino acids, which are readily available and non-toxic, therefore perfect building blocks for anti-cancer pharmaceuticals.
ASYMMETRIC MULTICOMPONENT AZA-DIELS-ALDER REACTION FOR CONSTRUCTION OF MULTICYCLIC HETEROCYCLES AND DEVELOPMENT OF XZH-5 DERIVATIVES AS INHIBITORS OF SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3)

A Thesis

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<thead>
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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADA</td>
<td>aza-Diels-Alder</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>Bzl (Bn)</td>
<td>benzyl</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>chloroform</td>
</tr>
<tr>
<td>D$_2$O</td>
<td>deuterium oxide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>HDA</td>
<td>hetero-Diels-Alder</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-Layer Chromatography</td>
</tr>
<tr>
<td>Yb(OTf)$_3$</td>
<td>ytterbium (III) trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Y(OTf)$_3$</td>
<td>yttrium (III) trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Y[P]$_3$</td>
<td>yttrium (III) phosphate</td>
</tr>
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Part I - Asymmetric Catalysis

Chapter 1: Introduction and Background

1.1 Chirality and Enantiopurity Importance

Stereoisomers are molecules in which the atoms have the same connectivities but have different three-dimensional shapes. In organic chemistry, it is common for molecules to have asymmetric carbon atoms, known as chiral centers, which are carbon atoms with four different substituents attached. These molecules exist as stereoisomers because the four different substituents lead to different spatial arrangements of the molecule. When a molecule has one chiral center, there are two arrangements of the substituents, which make two enantiomers, or compounds that are nonsuperimposable mirror images. These are examples of chiral compounds. If molecules have more than one chiral center, there can be numerous three-dimensional arrangements of the molecule, which may or may not be enantiomers. Diastereomers are stereoisomers that are not enantiomers. Enantiomers have the same physical and chemical properties, but diastereomers differ in properties.¹

Chiral molecules are common in biology, including sugars, genetic materials, and amino acids. Different enantiomers react differently in biological systems, showing the importance of chirality.² Regarding pharmaceuticals, one enantiomer may be a helpful drug, while the other enantiomer may be inactive or even toxic to the body. A famous example is the drug thalidomide (Figure 1.1). It was prescribed as a racemic mixture, a mixture of equal amounts of both enantiomers, and used to treat morning sickness in pregnant women. However, it caused birth defects because one enantiomer is a helpful drug and the other is a harmful toxin.² Another example of the importance of enantiopurity is the artificial sweetener aspartame. The molecule has two chiral centers, which leads to four chiral stereoisomers. Only one of the four provides a sweet taste, while the other three have no taste or are bitter (Figure 1.1).³ It is important to be able to create compounds of high enantiopurity, resulting in a product of one enantiomer, in order to get desired effects.
1.2 Obtaining Improved Enantiopurity

There are several ways to obtain improved enantiopurity. Some methods include: resolution of racemates, using the chiral pool (enantiopure starting materials), and performing stereoselective reactions (involving enantiopure reagents). The choice depends on the properties of the product, the ease and efficiency of the method, and how enantiopure the compound needs to be.

1.2.1 Resolution of Racemates

With this method, a mixture of enantiomers is separated. The ways to achieve resolution include: crystallization\(^5\), conversion into diastereomers\(^6\), biochemical resolution\(^7\), and kinetic resolution.\(^8\) Crystallization can be used when both enantiomers make different types of crystals that can be separated. However, most organic compounds do not separate into different crystals.\(^5\) Enantiomers can be converted into diastereomers when reacted with an enantiopure compound, known as the resolving agent. This is often a chiral acid or base, making a salt, but other chiral reagents can be used. Since diastereomers differ in chemical and physical properties, they can be separated more easily. Similarly, separation can be completed by chiral chromatography. This method uses a chiral stationary phase through which the enantiomers are eluted. They elute at different times, leading to separation, since one enantiomer may form a more stable complex with the stationary phase than the other enantiomer.\(^6\) Biochemical resolution uses enzymes to selectively react with one enantiomer over the other. It is ideal to find an enzyme that reacts with the undesired enantiomer, leaving the desired enantiomer behind, which can then be separated by common techniques.\(^7\) Kinetic resolution is based on the premise of one enantiomer reacting much quicker with a chiral resolving agent than the other enantiomer. If the difference in reaction rates is large enough, this method can be used to obtain one enantiomer. This also works
best if there is interconversion between the two starting enantiomers because a total conversion could occur. A downfall to this method is that resolution may be difficult since enantiomers have the same physical properties. Additionally, with racemates half of the product is undesirable. These reasons show a need for reactions that selectively create one stereoisomer over the other.

1.2.2 Using the Chiral Pool

The chiral pool is a group of enantiopure starting reagents that can be used in reactions and keep their chirality in the structure of the final product. It is useful when the structure of the final product is similar to the structure of the chiral reagent. Many reagents in the chiral pool are natural products, such as carbohydrates, amino acids, and hydroxy acids. The main disadvantage is the restriction of the structures of molecules that can be found in the chiral pool.

1.2.3 Performing Stereoselective Reactions

The method of performing stereoselective reactions leads to the greatest variety of enantiopure compounds. These reactions introduce chirality to non-chiral starting materials and lead to a non-racemic product. To induce the chirality, an auxiliary or a catalyst is used.

A chiral auxiliary is an enantiomerically pure molecule that can attach to an achiral molecule so the next reaction will be stereoselective. The downfall is that two extra steps are needed, one step to add the auxiliary and one step to remove it. Another downfall is that the auxiliary must be added in stoichiometric quantities.

Using a chiral catalyst is known as asymmetric (or enantioselective) catalysis, which is the area of focus for this investigation. An advantage is that the molecules of the chiral catalyst are regenerated, and therefore are needed in sub-stoichiometric amounts, leading to reactions with good atom economy. Additionally, asymmetric catalysis allows for a broad variety of stereoselective reactions.

1.3 Asymmetric Catalysis

The focus of this study is asymmetric catalysis, or using chiral catalysts to run stereoselective reactions that favor one spatial configuration of the product, creating a non-racemic product. Advantages to this method are that it can be economically and environmentally
favorable since the chiral catalysts are reused throughout the reaction and stoichiometric amounts of the catalysts are not needed. Also, due to the variety of catalysts that are available and can be created, a broad variety of stereoselective reactions can be conducted. However, the downsides can be the cost, toxicity, and scarcity of the catalysts.\textsuperscript{12}

There are three types of asymmetric catalysis: biocatalysis, metal catalysis, and organocatalysis.\textsuperscript{4}

1.3.1 Biocatalysis

This method uses enzymes as the catalysts. Some of the downfalls are insufficient stereoselectivity in the products, limited substrate scopes, and inefficacy under certain conditions since enzymes can be pH and temperature sensitive. However, due to chiral active sites of enzymes, they can lead to high stereoselectivities.\textsuperscript{13}

1.3.2 Organometallic Catalysis

This type is catalysis by metal complexes (usually transition metals, which can form many different complexes) where organometallic intermediates occur.\textsuperscript{14} Typically, the metal atom is the reaction center and ligands are coordinated to the metal, which are varied to change electronic and steric effects. Asymmetric induction comes from the metal-ligand complex, from where the chirality can be generated from the metal, the ligands, or both. An active catalyst should not be too stable and should have exchangeable ligands, which allow the reactants to enter the coordination sphere and bind to the metal, where they are activated and influenced by the chiral environment.\textsuperscript{15}

This area of chemistry has been studied more recently, leading to recognition in the field. A breakthrough contribution occurred when Knowles made a rhodium and phosphine ligand complex that catalyzes asymmetric hydrogenation with high enantioselectivity (Scheme 1.3.2). This reaction was used in the commercial preparation of L-DOPA, which is used to treat Parkinson’s disease.\textsuperscript{16} Showing the importance and growth of the field, a Noble prize has been awarded to Noyori, Sharpless, and Knowles in 2001 for this asymmetric hydrogenation.\textsuperscript{17}
Common rigid, chiral ligands are known as the privileged ligands, which have high levels of enantiocontrol in many different metal-catalyzed reactions. Many of them have C₂-symmetry, including BINOL, BINAP, DuPhos, BOX, PyBOX, TADDOL, and SALEN (Figure 1.3.2). This type of symmetry can have advantages such that it can reduce the number of isomeric metal complexes as well as the number of substrate-catalyst configurations and reaction pathways. Additionally, it may help enantioselectivity by eliminating other, less selective pathways. However, not all privileged ligands have these properties and molecules that do have this symmetry do not necessarily function as effective ligands. Therefore, to discover new ligands can be difficult and often requires luck.

Organometallic catalysts have an extensive number of uses, including: oxidations, reductions, pi-bond activations, hydrogenations, and alkylations. However, the catalysts can be expensive and toxic.

1.3.3 Organocatalysis

This method uses small organic molecules, which do not contain metals, as the catalysts. Organocatalysis is gaining importance and has recently become a main focus of research. It has
advantages in that the catalysts are typically inexpensive, readily available, non-toxic, inert towards moisture and oxygen, and do not contaminate the products with metals. The catalysts can be covalent or non-covalent. The former forms a covalent bond with a substrate or transition state while the latter takes part in non-covalent interaction such as hydrogen bonding.\(^{20}\)

Most organocatalysts can be classified as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids (Figure 1.3.3). Lewis base catalysts start the catalytic cycle by nucleophilic addition to a substrate. The complex undergoes a reaction and releases the product and the catalyst. Lewis acid catalysts activate nucleophilic substrates similarly. Brønsted base catalysts start the catalytic cycle with a deprotonation step and Brønsted acid catalysts start with a protonation step.\(^{21}\)

![Organocatalytic cycles](image)

**Figure 1.3.3**: Organocatalytic cycles.

1.3.3.1 **Lewis Base Catalysis**

Equilibrium exists between the electron-rich and electron-deficient states (the acidic and basic forms) of organocatalysts. As a result of this equilibrium, the same center can act as a Lewis acid or as a Lewis base, depending on the reaction conditions. The catalysts will be discussed based on their usual use.\(^ {22}\) Before looking at enamine and iminium ion catalysis, a few types of Lewis base organocatalysis will be examined.
Acyl-ammonium ions are used to allow for nucleophilic attack. This type of catalysis is usually used for acyl-transfer reactions and is often done with DMAP (4-dimethylaminopyridine) and its analogues (Scheme 1.3.3.1A).\textsuperscript{21}

![Scheme 1.3.3.1A: Acyl-ammonium catalysis.]

Carbene catalysts react with aldehydes, making a nucleophilic Breslow intermediate, facilitating addition to an electrophile (Scheme 1.3.3.1B).\textsuperscript{21}

![Scheme 1.3.3.1B: Carbene catalysis.]

Ammonium enolate intermediates are formed by reaction of a carbonyl substrate with a nucleophilic amine catalyst. These intermediates can attack electrophiles (Scheme 1.3.3.1C).\textsuperscript{21}

![Scheme 1.3.3.1C: 1-, 2-, and 3-ammonium enolate catalysis.]

Sulfonium ylides are known for use in the Corey-Chaykovsky reaction, where addition of a nucleophilic sulfur ylide to a ketone, aldehyde, imine, or enone produces the corresponding 3-membered ring (Scheme 1.3.3.1D).\textsuperscript{23}

![Scheme 1.3.3.1D: Creation of sulfur ylide catalyst for Corey-Chaykovsky reactions.]

These are just a few examples of Lewis base organocatalysis. Now enamine and iminium ion catalysis will be discussed in detail.

1.3.3.1.1 Enamine/Iminium Ion Formation

Commonly used in Lewis base catalysis is the enamine/iminium ion formation (Scheme 1.3.3.1.1A). The two types of activation are complimentary. A donor molecular can be activated
with enamine formation, which increases electron density at the reactive center, while an acceptor molecule can be activated with iminium ion formation, which decreases the electron density at the reactive center. Reactions using this type of catalysis can be stereoselective by using chiral amine catalysts, which affect the chirality by hydrogen bonding or steric hindrance.

\[
\begin{align*}
R^1N^+R^2 & \xrightleftharpoons{+H^+} R^1NHR^2 \xrightarrow{-H^+} R^1\text{enamine} \\
\text{R-Iminium ion} & \xrightarrow{-H_2O} \text{R-Enamine}
\end{align*}
\]

**Scheme 1.3.3.1.1A:** The activation of a carbonyl group by a secondary amine.

The iminium ion and the enamine can both be used in catalysis. A condensation occurs between a primary or secondary amine and a carbonyl compound to create an iminium ion. If using a primary amine, a loss of hydrogen can lead to an imine from the iminium salt. However, typically secondary amines are used for this type of catalysis. If the carbonyl compound has an enolizable α-proton the enamine can be formed by deprotonation of the iminium ion.

Using enamine catalysis became more well-known in the 1970s with the Hajos-Parrish-Eder-Sauer-Wiechert reaction, which is an asymmetric proline-catalyzed intramolecular aldol reaction (Scheme 1.3.3.1.1B).

**Scheme 1.3.3.1.1B:** The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

However, it was not until 2000 that the field of organocatalysis gained popularity with a publication of enamine catalysis by Barbas, Lerner, and List with a proline-catalyzed asymmetric aldol reaction (Scheme 1.3.3.1.1C).

**Scheme 1.3.3.1.1C:** Asymmetric aldol reaction using proline for enamine catalysis.

This publication showed that the underlying mechanism of the Hajos-Parrish-Eder-Sauer-Wiechert reaction had a broader application. Additionally, it showed that small organic molecules, like proline, could catalyze the same reactions as large organic molecules, such as
enzymes, with similar mechanisms.\textsuperscript{27} For example, the mechanism is essentially the same mechanism of class I aldolases (Scheme 1.3.3.1D).\textsuperscript{28}

![Scheme 1.3.3.1D](image)

**Scheme 1.3.3.1D:** Mechanism of aldol reaction utilizing enamine catalysis.

In the mechanism, the proline acts as a bifunctional catalyst, a catalyst with two catalytic sites, which will be discussed in more detail later. As shown in the transition state, the carboxylic acid acts as a Brønsted acid co-catalyst by protonating the acceptor carbonyl group and the enamine acts as a Lewis base by reacting with the carbonyl carbon.\textsuperscript{28} This hydrogen bonded framework with the catalyst provides for enantiofacial selectivity, since the carboxylic acid is anti to the \((E)\)-enamine double bond.\textsuperscript{25}

Another important enamine-catalyzed reaction, developed by Juhl and Jorgensen, is the asymmetric inverse-electron-demand hetero-Diels-Alder (HDA) reaction, a carbon-carbon bond-creating cycloaddition yielding a heterocycle (Scheme 1.3.3.1E).\textsuperscript{29}

![Scheme 1.3.3.1E](image)

**Scheme 1.3.3.1E:** Organocatalytic asymmetric inverse-electron-demand HDA reaction.
The transition state was proposed to justify the stereoselectivity of the reaction. The
diarylmethyl substituent of the catalyst shields the \textit{si}-face of the enamine, leading to the
approach of the enone possible only from the \textit{re}-face in an \textit{endo}-selective fashion.\textsuperscript{29}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (catalyst) {\textbf{Scheme 1.3.3.1.1F:} Plausible catalytic cycle for enamine-catalyzed HDA reaction.}
  \node at (1.5,0) {The plausible catalytic cycle (Scheme 1.3.3.1.1F) involves an enamine, formed from the
amine catalyst and aldehyde substrate, which acts as an electron-rich dienophile that reacts with
the electron-poor diene, the enone, to produce the hemiaminal ether. Hydrolysis, facilitated by
silica, gives the hemiacetal and regenerates the catalyst.\textsuperscript{29}}
\end{tikzpicture}
\end{center}

Moreover, the aza-Diels-Alder (ADA) reaction is a specific type of HDA reaction that
leads to nitrogen-containing cycles. The first direct catalytic enantioselective ADA reaction was
performed by Cordova and co-workers and used proline as the catalyst (Scheme 1.3.3.1.1G).\textsuperscript{30}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (catalyst) {\textbf{Scheme 1.3.3.1.1G:} Proline-catalyzed three-component enantioselective ADA reaction.}
  \node at (1.5,0) {X-ray structure analysis of the product was studied, and based on the absolute
configuration, a reaction mechanism was determined (Scheme 1.3.3.1.1H).}
\end{tikzpicture}
\end{center}
Scheme 1.3.3.1.1H: Proposed mechanism for ADA reaction.

First, the proline catalyst forms an enamine with the α-β unsaturated ketone. The generated imine, from the amine and the aldehyde substrates, attacks the *si* face of the diene via a transition state and an activated iminium salt is formed. The secondary amine of the chiral iminium salt performs a 6-*endo-trig* cyclization to create an azabicycle. The amino acid catalyst is then released and the ADA product is obtained by hydrolysis.\(^{30}\)

Looking at iminium catalysis, it brought notice to organocatalysis in 2000 when MacMillan performed the first asymmetric iminium-catalyzed cycloaddition reaction with an asymmetric Diels-Alder reaction (Scheme 1.3.3.1.1I).\(^{31}\)

Scheme 1.3.3.1.1I: Asymmetric Diels-Alder reaction using iminium catalysis.

The condensation of the α-β unsaturated aldehyde with the chiral amine forms an iminium ion, which reacts with the diene to perform a Diels-Alder reaction.\(^{21}\) The diene approaches the iminium ion from the *si* face, allowing the diene to avoid the large benzyl substituent stacked on top of the double bond.\(^{32}\)
This publication showed that organocatalysts could provide economic and environmental benefits. Additionally, it described a general activation approach using chiral amines for reactions that traditionally used metal catalysts.  

Looking more in detail at the enamine and iminium ion formation, the basis to this type of catalysis is the reversible condensation of an amine and carbonyl compound. This condensation leads to an iminium ion, which increases the \( \alpha \)-proton acidity and electrophilicity of the substrate. This is because it lowers the energy of the lowest unoccupied molecular orbital (LUMO), which in turn decreases the energy gap between the LUMO of the electrophile and the highest occupied molecular orbital (HOMO) of the nucleophile, facilitating the reaction. A deprotonation of the iminium ion leads to the enamine, which is the nucleophilic equivalent. Creation of the enamine increases the energy of the HOMO, again decreasing the energy gap between the LUMO and the HOMO of the two species, catalyzing a reaction. Additionally, these catalysts are useful because the amine can be easily hydrolyzed to obtain the desired products. The two catalytic intermediates are opposites, yet interdependent.  

There are two modes of enamine catalysis depending on the electrophile used. Double bond-containing electrophiles are inserted via nucleophilic addition, while single bond-containing electrophiles react by nucleophilic substitution (Scheme 1.3.3.1.1J).  

\[ \text{Nucleophilic Addition} \quad \text{Nucleophilic Substitution} \]

**Scheme 1.3.3.1.1J:** Two modes of enamine catalysis.  

Iminium catalysis is used for nucleophilic additions (Scheme 1.3.3.1.1K). It is initiated via iminium ion formation from the \( \alpha \)-\( \beta \)-unsaturated aldehyde and the catalyst. Conjugate addition of a nucleophile gives an enamine intermediate, which yields the product upon
hydrolysis. Additionally, a combination of the two catalytic principles in tandem sequence has recently been studied (Scheme 1.3.3.1K).\textsuperscript{33}

\textbf{Scheme 1.3.3.1K:} Iminium and tandem iminium-enamine catalytic cycles.

MacMillan and coworkers studied enamine singly occupied molecular orbital (SOMO) catalysis, which is a type of middle ground between iminium ion and enamine catalysis. This expands chiral amine catalysis by applying a single-electron oxidant, creating a radical species. SOMO activation was tested with a $\alpha$-allylation of aldehydes, using an imidazolidinone catalyst, ceric ammonium nitrate (CAN) as the oxidant, and allyltrimethylsilane as the nucleophile (Scheme 1.3.3.1L).\textsuperscript{34}

\textbf{Scheme 1.3.3.1L:} Allylation of aldehydes using SOMO catalysis.

A mechanistic study was completed (Scheme 1.3.3.1M). Two key points are that enamine oxidation is rapid and preferred over catalyst oxidation and that water concentration is crucial for efficiency. The aldehyde reacts with the catalyst, forming an enamine and water. The enamine is oxidized by Ce$^{IV}$ to give the radical cation electrophile. Coupling occurs between this radical and the nucleophilic allyl silane. A second equivalent of Ce$^{IV}$ is used to oxidize this intermediate. The silyl cation is eliminated through reaction with a nucleophile. Adding water
yields the product and the catalyst, as well as a proton that is absorbed by a base to prevent protonation of the catalyst.\(^{35}\)

Scheme 1.3.3.1.1M: Proposed mechanism of SOMO activated catalyst.

1.3.3.2 Lewis Acid Catalysis

Typically, Lewis acid catalysis involves metal salt catalysts, such as aluminum chloride, titanium chloride, and zinc chloride. They are applied in asymmetric catalysis by adding enantiopure ligands to these salts. However, organocatalysts can also function as Lewis acids, including compounds containing carbenium, silyl, or phosphonium cations. Additionally, hypervalent compounds based on phosphorous or silicon, as well as ionic liquids, which are organic salts with a melting point below 100°C, exhibit Lewis acid activity.\(^{36}\)

Carbocations are still rarely represented in organocatalysis.\(^{36}\) The first reported application of a carbenium salt as a catalyst used trityl perchlorate and was used in Mukaiyama aldol-type reactions (combining silyl enol ether and aldehyde) (Scheme 1.3.3.2A) and Michael transformations.\(^{37-42}\)

Scheme 1.3.3.2A: General Mukaiyama aldol-type reaction.
Scheme 1.3.3.2B: Proposed mechanism for Mukaiyama reaction.

The mechanism (Scheme 1.3.3.2B) was proved to go through catalytic activation of the aldehyde, its interaction with the silyl enol ether, and the formation of an intermediate. After, there are two possible pathways. One is the release of the salt and its electrophilic attack on the trityl group. The other is the intramolecular transfer of the silyl group, both creating the product and regenerating the catalyst.43-45

Silyl cations are Lewis acid organocatalysts. The most common silyl cation compounds used for catalysis are: Me₃SiOTf, Me₃SiNTf₂, and Me₃SiClO₄.36 In 1998, the groups of Jorgensen and Helmchen reported the preparation of a chiral silyl cationic salt, which was the first chiral silyl cation catalyst used in an enantioselective reaction. To ensure high reactivity, chemically inert and non-coordinating anions were used as the counter anions (Figure 1.3.3.2).46

Figure 1.3.3.2: Chiral silyl cationic salt with coordinating anion TPFPB.

The silyl salt was tested in a Diels-Alder reaction (Scheme 1.3.3.2C). TPFPB, tetrakis (pentafluorophenyl) borate, was used as the weakly coordinating anion. Good reactivity occurred with a high yield, but with low enantioselectivity (10% ee).46
Scheme 1.3.3.2C: Diels-Alder reaction catalyzed with silyl salt.

Hypervalent compounds are also used as Lewis acid organocatalysts. These are molecules in which one or more main group elements holds more than eight electrons in its valence shell, known as having an expanded octet. Typically, these hypervalent compounds are based on phosphorous and silicon. Often, this type of catalysis is considered Lewis base catalysis because a Lewis base is needed to create the hypervalent compounds, which are usually created in situ. Phosphorous and silicon have the capability to expand their valence shells, and due to this Lewis bases can interact with vacant orbitals. The interaction increases the electron density on the most labile ligand and when ionized, a positively charged complex forms, which acts as a Lewis acid due to free 3d-orbitals.47-52

1.3.3.3 Brønsted Base Catalysis

An example of a Brønsted base organocatalytic reaction is a hydrocyanation reaction.21 This reaction is performed between an aldehyde or ketone and a cyanide anion to make a cyanohydrin. Inoue and coworkers performed an addition of HCN to aldehydes with good enantioselectivity (Scheme 1.3.3.3A).53

Scheme 1.3.3.3A: Asymmetric cyanohydrin reaction by Inoue and coworkers.

Hydrogen cyanide interacts with the catalytic base by hydrogen bonding, creating a cyanide ion, which can then add to the carbonyl compound (Scheme 1.3.3.3B).
1.3.3.3B: Proposed bonding with the catalyst for cyanohydrin reaction.

1.3.3.4 Brønsted Acid Catalysis

Recently, Brønsted acid activation of carbonyl compounds and imines has been gaining attention in chiral catalysis. These catalysts can activate by either hydrogen bonding, which is general acid catalysis, or protonation, which is Brønsted acid catalysis or specific acid catalysis. The specific acid catalysis is the stronger of the two. There is no clear line between hydrogen bonding activation and protonation activation so both will be included here (Figure 1.3.3.4A).

**Figure 1.3.3.4A:** Types of Brønsted acid activation.

Types of hydrogen bonding catalysts are: thiourea catalysts, TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol) derivatives, and BINOL (1,1′-Bi-2-naphthol) derivatives. These are neutral Brønsted acids. Types of Brønsted acid catalysts are: ammonium salts and phosphoric acids. These are the stronger Brønsted acids.

Jacobsen and coworkers discovered thiourea catalysts for the asymmetric hydrocyanation of imines (the Strecker reaction). Rawal and coworkers reported an asymmetric hetero-Diels-Alder reaction of non-activated aldehydes and aminodiene using the diol TADDOL as a hydrogen bonding catalyst (Scheme 1.3.3.4A). TADDOL and its derivatives have been used to catalyze numerous Diels-Alder reactions as well as aldol reactions.

**Scheme 1.3.3.4A:** Asymmetric HDA reaction catalyzed with TADDOL.
Yamamoto and Rawal have found that BAMOL, a TADDOL derivative with an axially chiral 1,1'-biaryl-2,2'-dimethanol scaffold, is as good a catalyst for this HDA reaction. They obtained an X-ray structure of a BAMOL catalyst/benzaldehyde complex. The structure shows a 1:1 ratio of BAMOL to benzaldehyde and shows intramolecular hydrogen bonding between the two hydroxyl groups as well as intermolecular hydrogen bonding to the carbonyl oxygen.\(^{60}\)

BINOL, as a chiral hydrogen-bond donor, was discovered by Schaus and coworkers with enantioselective Morita-Baylis-Hillman reactions, which are carbon-carbon bond-forming reactions between the \(\alpha\)-position of an activated alkene and an electrophile, typically an aldehyde or imine.\(^{61\text{-}62}\) They proposed the enolate of cyclohexanone is stabilized with a hydrogen bond to the BINOL derived catalyst.

Johnston and coworkers reported use of an ammonium salt as a catalyst in an aza-Henry reaction, also called a nitro-Mannich reaction, which is a nucleophilic addition of nitroalkanes to imines. The ligand, referred to as H-Quin-BAM-H-OTf, was synthesized using (+)-trans-cyclohexane diamine and 2-chloroquinoline with palladium catalysis. The making of the salt was complete by the reaction of the compound with trifluoromethane sulfonic acid.\(^{63}\)

Akiyama and coworkers created chiral cyclic phosphoric acid diester derivatives from \((R)\)-BINOL. They showed its activity with a Mannich-type reaction between ketene silyl acetal and aldime, obtaining up to 96\% ee (Scheme 1.3.4B). Substituting various aryl groups onto the Brønsted acid is needed for good enantioselectivity. Using 4-nitrophenyl groups led to the highest enantioselectivity and the quickest reaction rate. The reaction was considered to proceed through an iminium salt, created from the aldime and the Brønsted acid. The 3,3'-diaryl substituents are not coplanar with the naphthyl groups, and therefore shield the phosphate part of the molecule, leading to high enantioselectivities.\(^{64}\)

\[\text{Scheme 1.3.3.4B: Mannich reaction using phosphoric acid catalyst.}\]
Furthermore, Akiyama and coworkers completed a hydrophosphonylation of aldimines with dialkyl phosphite that was catalyzed by another derivative of the (R)-BINOL-based phosphoric acid, achieving up to 90% ee (Scheme 1.3.3.4C). A nine-membered transition state is proposed, where the phosphate plays two roles: the phosphoric acid hydrogen activates the imine as a Brønsted acid catalyst and the phosphoryl oxygen activates the nucleophile by coordinating with the hydrogen of the phosphite as a Brønsted base catalyst. Due to these two roles, one face is attacked over the other, leading to increased enantioselectivity.\textsuperscript{65}

\[ \text{Scheme 1.3.3.4C: Aldimine hydrophosphonylation with nine-membered transition state.} \]

Also performed by Akiyama and coworkers, was an aza-Diels-Alder reaction of aldimines and Danishefsky’s diene catalyzed by another derivative of (R)-BINOL-based phosphoric acid, which achieved up to 91% ee (Scheme 1.3.3.4D). Again, they proposed a nine-membered transition state. The phosphate hydrogen activates the imine and the phosphoryl oxygen interacts with the hydrogen of the aldimine hydroxyl group by hydrogen bonding, allowing the nucleophile to attack one face over the other.\textsuperscript{66}

\[ \text{Scheme 1.3.3.4D: ADA reaction of aldimines and Danishefsky’s diene.} \]

There are many different chiral Brønsted acid catalysts, with structures allowing for various derivatives (Figure 1.3.3.4B).
1.4 Bifunctional Catalysis

1.4.1 Introduction

As already touched upon, bifunctional catalysts contain two catalytic sites, usually an acidic site and a basic site. Enzymes are good examples of bifunctional (often times, polyfunctional) catalysts because they tend to have an arrangement of functional groups in an active site that act together on a substrate. Specifically, metalloenzymes use metal ions as Lewis acids and/or redox centers together with organic functional groups. Another common type of bifunctional catalysts are amino acids, which combine Lewis base and Brønsted acid catalysis. Proline (discussed earlier) is a good example of a bifunctional secondary amine catalyst.

In recent years, synthetic chemists have created bifunctional catalysts and applied them to asymmetric catalysis. Many of these systems combine a metal ion, typically part of a chiral Lewis acid complex, with a Lewis base, typically an organic functional group. The mechanism of synthetic bifunctional catalysts is usually unknown because of the intrinsic complexity.

Theoretically, combining an acid and a base can lead to self-quenching. If the acid and base catalysts can create a stable, inactive adduct, the chance for catalysis is gone. It is possible to find good combinations of acids and bases with minimal interaction that can be used to effectively catalyze reactions. Additionally, if the acidic and basic sites are within the same
molecule, they are constrained with fixed orientations. Therefore, double activation can be reached more easily.68

There are different categories of bifunctional catalysts. For example, they can be categorized as two-component systems, in which acids and bases work as a pair, or homogeneous systems, in which one molecule has both acidic and basic parts.67

Additionally, bifunctional catalysis can be categorized by how the acid and base react with the substrate, either simultaneously or successively. When both acid and base react simultaneously, it may be a concerted mechanism, meaning they react with the same substrate molecule, or it may be a go-together mechanism, meaning they interact independently with different molecules. In the concerted mechanism, the acid and base interact in a way that the base pushes the electron pair to one part of the substrate molecule and the acid pulls the electron pair from another part of the substrate. They share one catalytic function. With the go-together mechanism, they interact with different molecules, and these intermediates can react together to get the final product. The sites work separately, but make up one catalytic function.69

Bifunctional catalysis has led to chemical transformations that are impossible without cooperation between multiple groups. However, there is room for improvement, especially regarding high catalytic loading, limited substrate scope, long reaction times, and inability to catalyze more complex reactions.

1.4.2 Multiple Organocatalytic Sites

Discussed first will be bifunctional catalysts that combine multiple organocatalytic sites and do not use metals.

One example is combining BINOL catalysis and amine catalysis. Sasai and coworkers developed such a catalyst, a combination of a basic tertiary amine and an acidic BINOL group. It was tested on an aza-Morita-Baylis-Hillman reaction of α,β-unsaturated carbonyls and N-tosylimines, creating allylic amines and obtaining up to 96% yield and 95% ee. The Brønsted acid can activate the carbonyl group and the Lewis base can react with the β-position of the substrate to facilitate addition of the base (Scheme 1.4.2A).70
**Scheme 1.4.2A:** Aza-Morita-Baylis-Hillman reaction using BINOL-based catalysis.

Wang and coworkers also developed a BINOL-based bifunctional catalyst. It was tested on a Morita-Baylis-Hillman reaction between $\alpha,\beta$-unsaturated carbonyls and aldehydes (Scheme 1.4.2B). The same catalyst was also tested on a Michael addition between 2,4-pentandiones and nitroolefins with as little as 1 mol% catalyst loading (Scheme 1.4.2C). Both reactions gave good yields and enantioselectivities.

**Scheme 1.4.2B:** Morita-Baylis-Hillman reaction with bifunctional catalyst mechanism.

The proposed mechanism has the thiourea of the catalyst acting as an acid and activating the ketone by double hydrogen-bonding activation, therefore facilitating addition of the tertiary amine to the substrate (Scheme 1.4.2C).

**Scheme 1.4.2C:** Michael addition reaction and proposed transition state.
The catalyst is proposed to activate both substrates, in that the acidic thiourea double hydrogen bonds to the nitroolefin, while the amine hydrogen bonds to the dione.\textsuperscript{72}

With a similar catalyst, Takemoto and coworkers performed enantioselective Michael additions of malonate and nitroalkenes with a 1,2-\textit{trans}-cyclo-hexyldiamine-derived thiourea catalyst (Scheme 1.4.2D).\textsuperscript{73-74}

\textbf{Scheme 1.4.2D:} Michael addition combining thiourea and amino catalysis.

The proposed mechanism has the basic amino group of the catalyst deprotonating an acidic proton of malonate. The acidic thiourea group activates the nitroalkene with hydrogen bonding. The complex leads to a nitronate that takes the proton from the amino group to afford the final product (Scheme 1.4.2E).\textsuperscript{73-74}

\textbf{Scheme 1.4.2E:} Transition states of Michael reaction with bifunctional catalyst.

The same group also performed an asymmetric Michael addition of malononitrile to acyclic $\alpha,\beta$-unsaturated imides using the same bifunctional organocatalyst (Scheme 1.4.2F).\textsuperscript{75}
**Scheme 1.4.2F:** Michael addition with cyclo-hexyldiamine-derived thiourea catalyst.

A substrate catalyst complex is formed based on NMR data. A transition state is proposed in which the imide and the anion of the malononitrile coordinate to the thiourea group and the tertiary amine group of the catalyst, respectively, through hydrogen bonding.\(^{75}\)

### 1.4.3 Combining Organometallic Catalysis and Organocatalysis

Shibasaki and coworkers investigated uses of bifunctional catalysts combining Lewis acidic metal sites and Lewis basic functional groups, specifically phosphine oxide moieties, using BINOL as a scaffold. The addition of TMSCN to aldehydes was performed, achieving high yields and stereoselectivity (Scheme 1.4.3A).\(^{76-77}\)

Catalysts with differing linker lengths between the metal center and the phosphine oxides were compared and showed the importance of the position of the catalytic groups in space. The positions can be modified to increase stereoselectivity as well as decrease catalytic inactivation between the acidic and basic groups. When the linker increased in size, the yield decreased, implying self-quenching between the metal and base.\(^{76-77}\)

The reaction was also completed using a catalyst without the basic phosphine oxides and instead only with bulky groups. The opposite configuration for the product was favored, as compared to when the Lewis base was used. This suggests when there is no Lewis base, the TMSCN attacks from the less hindered side, and when the Lewis base is there, the TMSCN coordinates to the base, and therefore attacks from the opposite, more hindered side.\(^{76-77}\)
Scheme 1.4.3A: Addition of TMSCN to aldehydes with hydrolysis.

The mechanism suggests the aluminum atom coordinates to the oxygen of the aldehyde, while the phosphine oxide binds the TMSCN. A transition state to rationalize the asymmetric induction was proposed (Scheme 1.4.3B).\(^{76-77}\)

Theoretically, there is competition between two pathways. The desired pathway uses both the acidic and basic groups of the catalyst, while the undesired pathway uses only the acidic part (leading to lower and opposite stereoselectivity). The desired pathway could be favored by decreasing the acidity of the metal, increasing the chance of the acidic and basic parts working together. Additives were tested, which would coordinate with the metal and decrease acidity, as well as change the geometry of the metal, from tetrahedral to trigonal bipyramidal (a pentacoordinated intermediate), which could allow for more favorable positioning of the substrates. The additives did increase ee values significantly. The best additive was \(n\text{Bu}_3\text{PO}\).\(^{76-77}\)

Scheme 1.4.3B: Proposed transition states for addition of TMSCN to aldehydes.

Another bifunctional catalyst combining fluoride ions with traditional chiral Lewis acid catalysts, has been used in a variety of reactions, the most studied being silver(I) fluoride and copper(I) fluoride catalyzed aldol reactions.\(^{68}\)
Yamamoto and coworkers used a $p$-Tol-BINAP-AgF complex to catalyze an asymmetric aldol addition of trialkoxysilyl enol ethers to aldehydes when the reaction was performed in a protic solvent, like methanol (Scheme 1.4.3C). The reactions showed the syn form of the product was favored.\textsuperscript{78-79}

![Scheme 1.4.3C: Aldol addition using bifunctional catalysis.](image)

They propose a closed, six-membered-ring transition structure with an intramolecular silicon-fluoride interaction (Scheme 1.4.3D). A flip between a boat and a chair transition structure is thought to explain the observed stereochemistry. The BINAP-AgF complex coordinates as a Lewis acid to both the aldehyde and the silyl enol ether. This creates a six-membered cycle, further stabilized by the adjacent four-membered ring formed by AgF and the trimethoxysiloxy group. They propose that from the $E$-enol ether, the syn product is created from a boat-like transition structure, while from the $Z$-enol ether, the syn product is created from a chair-like transition structure.\textsuperscript{78-79}

![Scheme 1.4.3D: Six-membered transition state in aldol reaction, creating syn products.](image)

However, additional studies suggest an alternate mechanism, one that involves an open transition structure (Scheme 1.4.3E). Yamagishi and coworkers mechanistically studied aldol reactions catalyzed by a silver-diphosphane complex. They found that mixing BINAP-AgOAc
with a silyl ketene acetal does not create a silver enolate, but a proton NMR shift of the silyl enol ether does occur. They propose a hypervalent silicate, which may or may not stay connected to the silver complex. They show the type of anionic ligand of the silver complex does impact the reaction. Coordinating anions, like acetate and chloride, reacted similarly, while weakly coordinating anions, like tetrafluoroborate, react differently. They predict fluoride as an anionic ligand will react similarly to acetate.\textsuperscript{80}

\textbf{Scheme 1.4.3E}: Alternate open transition structure mechanism for aldol reaction.

Another example of combining organometallic catalysis and organocatalysis is combining a gold catalyst with chiral Brønsted acid counter anions that control the stereoselectivity. In 2007, Toste and coworkers studied asymmetric counteranion-directed catalysis (ACDC). Gold complexes have had success as catalysts, but stereoinduction has been a challenge. This is likely due to the linear coordination geometry of gold, placing the chiral components far and at 180° from the substrates. An asymmetric hydroalkoxylation of allenes using a BINOL-based phosphoric acid, (R)-TRIP (3,3’-Bis(2,4,5-trisopropylphenyl)-1,1’-binaphthyl-2,2’-diyl hydrogen phosphate), as a counter anion was completed (Scheme 1.4.3F).\textsuperscript{81}

\textbf{Scheme 1.4.3F}: Asymmetric counteranion-directed catalysis (ACDC) using gold.
1.4.4 Using Cinchona Alkaloid-Derived Catalysts

Cinchona alkaloids are from the bark of cinchona trees. These compounds, specifically quinine, have played an important medicinal role, and in the early 1980s they gained popularity as asymmetric catalysts (Figure 1.4.4A).\(^2\)

![Figure 1.4.4A: Examples of commonly used cinchona alkaloids.](image)

These compounds have diverse chiral skeletons and the ability to be tuned to various reactions. The 1,2-aminoalcohol subunit, made of the basic and bulky quinuclidine and the proximal Lewis acidic hydroxyl group, is mostly responsible for catalytic function.\(^2\)

The quinuclidine is a good ligand for metal-catalyzed processes. The nitrogen can be used as a chiral base or chiral nucleophilic catalyst. The quaternary ammonium salts can be used for catalysis, inducing stereoselectivity as a chiral phase transfer catalyst, through a chiral ion pairing mechanism between the positive ammonium species and an anionic nucleophile.\(^2\)

The hydroxyl group serves as an acidic site or a hydrogen bond donor. The hydroxyl group can be changed into other moieties (ureas, amides, etc.) to create a more powerful acid or hydrogen bond donor. Substituting the hydroxyl group for an amino group can allow for stereoselective aminocatalysis using enamine catalysis and/or iminium intermediates. Additionally, the methoxy group of quinine and quinidine can be changed into a hydroxyl group or a thiourea group, serving as an additional hydrogen bond donor site. The active sites of cinchona alkaloids act simultaneously together to catalyze reactions (Figure 1.4.4B).\(^2\)
Figure 1.4.4B: The active sites of cinchona alkaloids and their uses.

Sharpless and coworkers studied the osmium-catalyzed asymmetric dihydroxylation (AD) of olefins (Scheme 1.4.4A). This reaction has greatly impacted organic synthetic chemistry and as a result, Sharpless was awarded the Noble Prize in chemistry in 2001. Osmium tetroxide is combined with alkenes, a stoichiometric oxidant, and a chiral cinchona alkaloid-derived ligand for stereoselectivity, creating vicinal diols (Figure 1.4.4C).83-85 Chiral 1,2-diols are important as intermediates for pharmaceuticals and agrochemicals.84

Scheme 1.4.4A: Asymmetric dihydroxylation using cinchona alkaloid-derived ligands.

Figure 1.4.4C: Cinchona alkaloid-based catalysts for asymmetric dihydroxylation.
The mechanism includes creation of an osmium tetroxide-ligand complex (Scheme 1.4.4B). A [3+2] cycloaddition with the alkene creates a cyclic intermediate. Hydrolysis releases the diol, the ligand, and the reduced osmate. The stoichiometric oxidant regenerates osmium tetroxide.86

**Scheme 1.4.4B:** Proposed mechanism for asymmetric dihydroxylation.

Another reaction combining a cinchona alkaloid-derived catalyst with a metal was used to create β-lactams from ketenes and imines (Scheme 1.4.4C).87-88

**Scheme 1.4.4C:** Synthesis of β-lactams with benzoylquinine (BQ) catalyst.

First, the BQ cinchona alkaloid catalyst undergoes a dehydrohalogenation reaction with the acid chloride, yielding a ketene. Using a strategy known as “shuttle deprotonation”, the proton is transferred from the BQ to a proton sponge, which is a base that is thermodynamically active, but kinetically restricted, meaning non-nucleophilic. The BQ is then regenerated and is used to activate the ketene, making it nucleophilic. Simultaneously, the acidic metal salt activates the imine, making it more electrophilic. The two substrates can then react to create an asymmetric β-lactam product (Scheme 1.4.4D).87-88
In 1981, Wynberg and Hiemstra used cinchona alkaloids to catalyze the enantioselective addition of thiophenols to cyclic enones (Scheme 1.4.4E). The catalysts act bifunctionally because activity and selectivity were dependent on the presence of both a basic tertiary amine (deprotonates the thiol) and a hydrogen-bond donating hydroxyl group (activates the enone electrophile). This work led to rapid growth in the field.89

The addition of thiols to enones is a 1,4-addition reaction. The mechanism involves a base-catalyzed formation of a more nucleophilic thiol complex, a thiophenoxide anion, leaving a protonated base at the quinuclidine nitrogen. The ketone oxygen from the enone undergoes hydrogen bonding to the hydroxyl group of the catalyst, making it more electrophilic. This hydrogen bonding spreads the negative charge, lowering the free energy of the transition state. The reaction is finished with a proton transfer and a release of the product (Scheme 1.4.4F).89
Scheme 1.4.4F: Mechanism of addition reaction catalyzed with cinchona alkaloids.

More recently, based on thiourea bifunctional catalysts, cinchona alkaloid derivatives have been modified to include a urea or thiourea component to effectively catalyze various reactions. Connon and coworkers \(^90\) and Dixon and coworkers \(^92\) both independently reported the design of similar catalyst systems to catalyze the asymmetric Michael addition of malonates to nitroalkenes (Scheme 1.4.4G).

Connon and coworkers found that the urea-substituted analogues of cinchona alkaloids were more selective, but less active catalysts than their precursors. However, the diastereomers of the cinchona alkaloid derivatives showed better activity and enantioselectivity with low catalytic loading. A bifunctional catalyst is proposed, involving deprotonation of the malonate by the nitrogen and hydrogen bonding to the nitroalkene by the urea or thiourea. \(^91\)

Scheme 1.4.4G: Cinchona alkaloid derivative-catalyzed asymmetric Michael additions.

Dixon and coworkers had very similar research, also performing a Michael addition between malonates and nitroalkenes, with a similar catalyst (Scheme 1.4.4H). \(^92\)
Scheme 1.4.4H: Michael addition catalyzed with cinchona alkaloid urea-derivative.

Hatayekama and coworkers found that a better hydrogen bond donor is formed by demethylation of the 6′-methoxy group in quinine derivatives, leading to a phenolic hydroxyl group that plays a crucial role on enantioselectivity. The group performed the first practical asymmetric Baylis-Hillman reaction, a carbon-carbon bond forming reaction of aldehydes and activated alkenes. An ester was the major product and a dioxanone was the minor product (Scheme 1.4.4I).

Scheme 1.4.4I: Cinchona alkaloid derivative-catalyzed Baylis-Hillman reaction.

The proposed mechanism involves a Michael addition of the catalyst to the acrylate, creating an enolate, which undergoes an aldol reaction with an aldehyde. This leads to two diastereomeric intermediates, stabilized by intramolecular hydrogen bonding between the oxide anion and the phenolic hydroxyl group. Intermediate B has steric hindrance between the side chain of the aldehyde and the ester and quinuclidine groups. Therefore, it undergoes a reaction with a second aldehyde molecule instead of elimination, creating the dioxanone. In contrast, intermediate A undergoes easier elimination due to less steric hindrance, creating the ester with regeneration of the catalyst (Scheme 1.4.4J).
Scheme 1.4.4J: Proposed mechanism for Baylis-Hillman reaction.

Furthermore, Deng and coworkers completed asymmetric Diels-Alder reactions between 2-pyrones and dienophiles using cinchona alkaloid derivatives (Scheme 1.4.4K). 2-pyrones are electron-deficient dienes of aromatic character and thus are difficult to use as diene partners in the Diels-Alder reaction.94

Scheme 1.4.4K: Cinchona alkaloid derivative-catalyzed Diels-Alder reaction.

The demethylated cinchona alkaloid derivative made a good bifunctional catalyst for the Diels-Alder reaction. The hydrogen bond donor, the hydroxyl group, and the hydrogen bond acceptor, the nitrogen, activate the nucleophile and electrophile, respectively, through hydrogen bonding interactions.94
The group also completed a Diels-Alder reaction using thiourea-derivatives of cinchona alkaloids (Scheme 1.4.4L). The proposed interactions are that of the quinuclidine nitrogen atom and the hydroxyl group of the diene in addition to hydrogen bonding between the thiourea and the nitrile lone pairs of the dienophile.\(^94\)

![Scheme 1.4.4L](image.png)

**Scheme 1.4.4L:** Cinchona alkaloid thiourea-catalyzed asymmetric Diels-Alder reaction.

### 1.4.5 Using Self-Assembled Metal Complexes

Another bifunctional catalyst encompasses using Lewis acid-Brønsted base catalysis from self-assembled metal complexes. Shibasaki and coworkers created REMB (Rare Earth-alkali Metal-BINOL) catalysts, which have been used in many organic syntheses. The catalyst has a center of asymmetry at the central metal and a configuration defined by the BINOL ligands. It has a Lewis acidic lanthanide rare earth metal center and basic BINOL oxygen atoms that are coordinated to alkali metals. This type of catalyst can be tuned by using various alkali metal and lanthanide combinations (Figure 1.4.5).\(^95\)-\(^97\)

![Figure 1.4.5](image.png)

**Figure 1.4.5:** REMB catalyst.
Shibasaki and coworkers tested the catalyst with an asymmetric nitroaldol reaction, also known as a Henry reaction, between an aldehyde and nitromethane (Scheme 1.4.5A). The lanthanum metal acts as a Lewis acid to activate the aldehyde and the lithium binaphthoxide acts as a Brønsted base to deprotonate the nitromethane (Scheme 1.4.5B).

\[
\text{RCHO} + \text{CH}_3\text{NO}_2 \xrightarrow{\text{THF, -40°C, catalyst (10 mol%)}} \text{RONO}_2 \quad \text{up to 91% yield}
\]

\text{up to 90% ee}

**Scheme 1.4.5A:** Asymmetric nitroaldol reaction using REMB catalyst.

The catalyst was also tested with an asymmetric Michael reaction of enones with malonates (Scheme 1.4.5C). The best catalyst for this reaction used sodium as the alkali metal. The reaction led to excellent yields and ee up to 92%.\(^{95-97}\)

**Scheme 1.4.5B:** Proposed mechanism of nitroaldol reaction using REMB catalyst.

**Scheme 1.4.5C:** Asymmetric Michael reaction between enones and malonates.
Furthermore, the group ran an asymmetric aldol reaction (Scheme 1.4.5D). Adding a catalytic amount of base to the reaction enhances the catalytic activity. A mechanism is proposed in which the ketone is deprotonated by the catalytic Brønsted base, KOH, and the aldehyde is activated and fixed in position by the Lewis acidic lanthanum ion (Scheme 1.4.5E).\(^{95-97}\)

![Asymmetric aldol reaction using REMB catalyst.](image)

**Scheme 1.4.5D:** Asymmetric aldol reaction using REMB catalyst.

![Proposed mechanism of asymmetric aldol reaction with REMB catalyst.](image)

**Scheme 1.4.5E:** Proposed mechanism of asymmetric aldol reaction with REMB catalyst.

The group also tested an asymmetric hydrophosphonylation (Scheme 1.4.5F) of imines using a catalyst with potassium as the alkali metal, creating an alpha-amino phosphonic acid.\(^{95-97}\)

![Asymmetric hydrophosphonylation reaction using REMB catalyst.](image)

**Scheme 1.4.5F:** Asymmetric hydrophosphonylation reaction using REMB catalyst.

The proposed mechanism suggests activation of the phosphonate by coordination of the carbonyl oxygen to the central rare earth metal and a deprotonation by an oxygen atom from the BINOL moiety of the catalyst. The imine can then bind to the phosphonate while also coordinated to the central rare earth metal (Scheme 1.4.5G).\(^{95-97}\)
Scheme 1.4.5G: Proposed mechanism for hydrophosphonylation with REMB catalyst.

An aluminum-alkali metal-BINOL complex was created, which is slightly different since a rare earth metal is replaced with aluminum. This catalyst was successful in catalyzing Michael reactions of cyclohexenone with malonates (Scheme 1.4.5H).

Scheme 1.4.5H: Aluminum-alkali metal-BINOL complex-catalyzed Michael reaction.

Shibasaki and coworkers created a bimetallic Schiff base catalyst that was used for a syn-selective asymmetric nitro-Mannich reaction. In the catalyst the transition metal is incorporated into the N₂O₂ inner cavity and the oxophilic rare earth metal, having a large ionic radius, is incorporated into the O₂O₂ outer cavity (Scheme 1.4.5I).

Scheme 1.4.5I: Asymmetric nitro-Mannich reaction catalyzed with bimetallic base.
The proposed catalytic cycle has the Sm-OAr group acting as a Brønsted base to generate samarium-nitronate by deprotonation. The copper acts as a Lewis acid to activate the imine. The copper and samarium metal centers act together to fix the imine and the nitronate in close proximity, resulting in high syn-selectivity from TS-1 after addition-protonation (Scheme 1.4.5J).

Scheme 1.4.5J: Proposed mechanism using bimetallic Schiff base catalyst.

1.5 Combined Acid Catalysis

1.5.1 Introduction

Combined acid systems lead to higher reactivity, selectivity, and versatility than the individual acids, and therefore create better tools for chemical reactions. Combined acids can be grouped as Brønsted acid-assisted Lewis acid (BLA), Lewis acid-assisted Lewis acid (LLA), Lewis acid-assisted Brønsted acid (LBA), and Brønsted acid-assisted Brønsted acid (BBA) (Table 1.5.1). These are useful tools for asymmetric catalysis because by tuning reactivity by associative interactions and by providing more organized structures, these catalysts allow for better asymmetric environments. An intramolecular assembly of combined systems is suggested, rather than an intermolecular assembly. Therefore, in order for success, a correct design of catalytic structure is required.
Table 1.5.1: Classification types of combined acid catalysts.

<table>
<thead>
<tr>
<th>Catalyst system</th>
<th>General</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brønsted acid-assisted Lewis acid catalyst (BLA) (Enhancement of Lewis acidity by combination with Brønsted acid)</td>
<td>![BLA structure]</td>
<td>![BLA example]</td>
</tr>
<tr>
<td>Lewis acid-assisted Lewis acid catalyst (LLA) (Enhancement of Lewis acidity by combination with Lewis acid)</td>
<td>![LLA structure]</td>
<td>![LLA example]</td>
</tr>
<tr>
<td>Lewis acid-assisted Brønsted acid catalyst (LBA) (Enhancement of Brønsted acidity by combination with Lewis acid)</td>
<td>![LBA structure]</td>
<td>![LBA example]</td>
</tr>
<tr>
<td>Brønsted acid-assisted Brønsted acid catalyst (BBA) (Enhancement of Brønsted acidity by combination with Brønsted acid)</td>
<td>![BBA structure]</td>
<td>![BBA example]</td>
</tr>
</tbody>
</table>

A more simple and studied example of combined acid catalysis is coordination of a ketone or aldehyde to a Lewis acid, which promotes enolization due to enhanced acidity of the α-hydrogen atoms. This is Lewis acid-activation of a weak Brønsted acid. The increase in acidity was examined by combining aldehydes and ketones with the Lewis acid BF$_3$ (Figure 1.5.1).$^{101}$

\[
pK_a = 17 \text{ (in } \text{H}_2\text{O)} \quad pK_a = -7 \text{ (in } \text{H}_2\text{O)}
\]

Figure 1.5.1: Lewis acid-activation of a weak Brønsted acid.

1.5.2 Brønsted Acid-Assisted Lewis Acid (BLA) Catalysis

Chiral Lewis acid catalysis can improve by attachment of a Brønsted acid.$^{100}$ In 1986, Yamamoto and coworkers completed an asymmetric Diels-Alder reaction of naphthoquinone derivatives and dienes with a chiral boron catalyst made from B(OMe)$_3$ and $(R,R)$-$(+)$-tartaric acid diamide (Scheme 1.5.2A). The rate enhancement and high enantioselectivity are due to intramolecular hydrogen bonding between the hydrogen of the amide and the oxygen attached to the boron atom.$^{102}$
In 1988, Yamamoto and coworkers reported a chiral boron catalyst based on a tartaric acid ligand. These chiral (acyloxy)borane (CAB) catalysts have high reactivity due to intramolecular hydrogen bonding between the terminal carboxylic acid and the alkoxy oxygen atom. The catalysts have been successful in aldol, Diels-Alder, and allylation reactions (Scheme 1.5.2B)\textsuperscript{100}. Based on NOE experiments, the shielding of the CAB-coordinated aldehydes arises from π-stacking of the 2,6-diisopropoxybenzaldehyde ring and the coordinated aldehyde.\textsuperscript{100}

\[ \text{CAB:} \]  

\[ \text{CAB (10 mol\%)} \]  

\[ \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \]  

\[ \text{85\% yield} \]  

\[ \text{exo/endo} = 89/11 \]  

\[ \text{96\% ee} \]  

\[ \text{CAB (20 mol\%)} \]  

\[ \text{EtCN, -78^\circ\text{C}} \]  

\[ \text{96\% yield} \]  

\[ \text{syn/anti} = 94/6 \]  

\[ \text{96\% ee} \]  

\[ (E/Z) = 4/1 \]

\textbf{Scheme 1.5.2A:} Asymmetric Diels-Alder reaction catalyzed with BLA catalysis.

\textbf{Scheme 1.5.2B:} Asymmetric reactions using CAB catalyst.

\section*{1.5.3 Lewis Acid-Assisted Lewis Acid (LLA) Catalysis}

Reactive LLA catalysts are fairly well-known. Electron-deficient metal compounds can be made more electrophilic with homodimeric and heterodimeric associations. These associative reactions are needed for higher reactivity as well as for an organized chiral environment leading to stereoselective reactions.\textsuperscript{100} Chiral heterobimetallic LLA catalysts, such as the REMB catalysts discussed earlier, have been studied extensively.\textsuperscript{95-97}
Shibasaki and coworkers created an enantioselective catalyst for the addition of Me$_2$Zn to $\alpha$-ketoesters (Scheme 1.5.3A). Adding a cis-hydroxyl group onto the ligand can lead to more organized aggregation of the zinc species, increasing activity and enantioselectivity. The alkyl zinc species increases in nucleophilicity by coordinating to the additional Lewis base. An alcohol additive, creating zinc isopropoxide, is proposed to promote the monomeric, more active form of the catalyst by mixed aggregate formation.\textsuperscript{103}

![Scheme 1.5.3A: Asymmetric addition of Me$_2$Zn to $\alpha$-ketoesters.](image)

Trost and coworkers reported using dinuclear zinc complexes as effective catalysts for asymmetric direct aldol reactions (Scheme 1.5.3B).\textsuperscript{104-105}

![Scheme 1.5.3B: Asymmetric aldol reaction catalyzed with dinuclear zinc complex.](image)

The active catalyst is prepared \textit{in situ} by reaction of the starting ligand with two equivalents of diethylzinc, releasing three equivalents of ethane. The catalyst reacts with the active methylene substrate, releasing another equivalent of ethane. The two zinCs act together to activate each of the two substrates. The intramolecular interaction of the Lewis acids through the attached heteroatom enhances the Lewis acidity in the chiral environment (Scheme 1.5.3C).\textsuperscript{104-105}
Scheme 1.5.3C: Proposed catalytic cycle for aldol reaction catalyzed by zinc complex.

Itsuno and coworkers led to the discovery of oxazaborolidines as chiral catalysts for the borane-mediated enantioselective reduction of achiral ketones (Scheme 1.5.3D). The coordination of the electrophilic BH$_3$ to the nitrogen atom of the catalyst serves to activate BH$_3$ as a hydride donor and to increase the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex readily binds to the ketone at the more sterically accessible electron lone pair and cis to the vicinal BH$_3$ group$^{106-107}$

Scheme 1.5.3D: Oxazaborolidines as chiral catalysts for reduction of ketones.
1.5.4 Lewis Acid-Assisted Brønsted Acid (LBA) Catalysis

LBA catalysis allows for design of a unique proton, formed when the coordination of a Lewis acid to a heteroatom of the Brønsted acid increases the acidity of the Brønsted acid.\textsuperscript{100}

Yamamoto and coworkers reported an LBA catalyst created \textit{in situ} from BINOL and SnCl\textsubscript{4} (Scheme 1.5.4). With a stoichiometric amount of catalyst, a silyl enol ether was protonated, resulting in the (S)-isomer. The proposed transition state suggests that the trialkylsiloxy group is directed opposite to the binaphthyl group to avoid steric interaction and that the aryl group is stacked on the naphthyl group.\textsuperscript{108-109}

\textbf{Scheme 1.5.4:} LBA catalyst for asymmetric protonation of silyl enol ethers.

1.5.5 Brønsted Acid-Assisted Brønsted Acid (BBA) Catalysis

Intramolecular hydrogen bonding occurs in the small molecule TADDOL (discussed earlier). One of the hydrogen atoms of the hydroxyl group participates in an intramolecular hydrogen bond, while the other hydrogen atom is free to react. Internal hydrogen bonding can organize the asymmetric environment of the catalyst. Also, an increase in Brønsted acidity of the other hydroxyl proton occurs, which coordinates to a carbonyl oxygen atom.\textsuperscript{56-57}

1.6 Combining Enamine Catalysis and Transition Metal Catalysis

1.6.1 Introduction

This is a specific subset of bifunctional catalysis, combining enamine catalysis and transition metal Lewis acid catalysis. Both of these areas have undergone much research, and combining them can increase activity and catalyze reactions that cannot occur with each type of catalysis individually.

Each type of catalysis provides specific benefits. Enamine chemistry helps to avoid the pre-formation of enols providing the opportunity of being atom-economical for carbon-carbon
bond-forming reactions. Transition metal Lewis acid chemistry offers structural advantages and allows for higher activation of electrophiles.

Enamine catalysis can be combined with metal catalysis in different ways: cooperative catalysis, synergistic catalysis, and sequential/relay catalysis. In cooperative catalysis, the catalysts activate the substrates independently, but in the same catalytic cycle, working together to create a new bond. In synergistic catalysis, there is simultaneous activation of both the nucleophile and the electrophile distinctively by the two catalysts in two directly coupled catalytic cycles to create a new bond. In sequential/relay catalysis, one catalyst activates the substrate, creating an intermediate, which is then activated by the other catalyst.\(^{110}\)

The main focus here will be cooperative catalysis and synergistic catalysis. There are five types of activation modes with these methods. Type I is enamine addition to a transition metal-\(\pi\)-allyl complex. Type II is enamine addition to a \(\sigma\)-electrophilic metal-activated substrate. Type III is enamine addition to a \(\sigma\)-electrophilic metal-formed cation. Type IV is enamine addition to a reactive Cu(III)-C(sp\(^2\)) species. Type V is enamine addition to a \(\pi\)-electrophilic metal-activated alkyne (Scheme 1.6.1).\(^{111}\)

![Scheme 1.6.1: The activation modes combining enamine and transition metal catalysis.](image)

The main strategy for these reactions is using HSAB (hard and soft acids and bases) theory to avoid self-quenching between the metal Lewis acid and amine Lewis base catalysts. Finding hard and soft combinations that work to catalyze reactions can be difficult. In addition to finding ideal combinations, chelating ligands can be used to avoid interaction between the acid and base catalysts.\(^{111}\)
1.6.2 Using Chelating Ligands

The Wang group designed and created a group of bifunctional amine/metal Lewis acid catalysts (Figure 1.6.2A). These catalysts have a basic amine tethered to a chelating ligand, which traps the acidic metal. This allows the basic amine and metal Lewis acid to be close, without interacting with one another, thus avoiding acid-base quenching. Two types of catalysts were created: one based on a bidentate ligand and one based on a tridentate ligand.\textsuperscript{111}

![Figure 1.6.2A: Chelating ligands used to combine enamine and metal Lewis acid catalysis.]

These catalysts, which combine the ligands with metal salts, were successfully used in asymmetric aldol reactions (Scheme 1.6.2A). The stereoselectivities are comparable to those from organocatalysts and the activities are higher than those from organocatalysts.\textsuperscript{112-114}

**Scheme 1.6.2A:** Asymmetric aldol reactions using various bifunctional catalysts.

The configurations of the products, mostly ($R$)-configuration, match predictions from the proposed transition state. The Cu$^{II}$ metal serves as a Lewis acid, activating the aldehyde, and the pyrrolidine ring serves as a Lewis base, forming an enamine with the ketone (Figure 1.6.2B).\textsuperscript{112}
Figure 1.6.2B: Transition state of bifunctional catalyst of asymmetric aldol reaction.

These catalysts were also used in an asymmetric inverse-electron-demand hetero-Diels-Alder reaction of cyclic ketones and β,γ-unsaturated-α-ketoesters, creating bicyclic dihydropyrans (Scheme 1.6.2B). This type of reaction, combining electron-rich alkenes with electron-deficient enones, creates dihydropyran and tetrahydropyran derivatives, which are important motifs in natural products and biologically important compounds.115-116

Scheme 1.6.2B: Using bifunctional catalyst in HDA reaction.

The ketone forms an enamine with the ligand amine, while the diene is activated by the metal Lewis acid coordinated to the ligand (Scheme 1.6.2C). The enamine and diene are brought into close proximity by the ligand, allowing for attack of the enamine onto the diene.115-116
Scheme 1.6.2C: Proposed catalytic cycle of bifunctionally catalyzed HDA reaction.

Additionally, a difficult asymmetric Michael addition of ketones to malonates was developed with the enamine-metal Lewis acid catalysis (Scheme 1.6.2D).\textsuperscript{117}

Scheme 1.6.2D: Asymmetric Michael addition of ketones to malonates.

Another reaction with a similar catalyst, using a bidentate ligand, is an asymmetric oxo-Diels-Alder reaction of isatins and enones, creating spirooxindole tetrahydropyranones (Scheme 1.6.2E). The metal, which is chelated to the ligand, coordinates to and activates the isatin. The chiral amine group, which is tethered to the ligand, activates the enone as dienamine. The catalyst brings the dienamine and isatin in close proximity, allowing the reaction to occur.\textsuperscript{118}

Scheme 1.6.2E: Oxa-Diels-Alder reaction of isatins and enones.
1.6.3 Combining Aliphatic Amines with Soft Metals

Aliphatic amines are hard Lewis bases and therefore combine better with soft metals, such as: Ag(I), Au(I), Ir(I), Cu(I), and Pd(0 or II).\textsuperscript{111}

In 2005, Cordova and coworkers performed the first example of successfully combining enamine catalysis with transition metal catalysis, specifically Pd(0) catalysis, exhibited with a $\alpha$-alkylation reaction between allyl acetate and aldehydes (Scheme 1.6.3A).\textsuperscript{119}

\begin{center}
\textbf{Scheme 1.6.3A:} Alkylation reaction using combined enamine-transition metal catalysis.
\end{center}

The proposed mechanism involves catalytic enamine intermediates generated \textit{in situ} to attack generated electrophilic palladium $\pi$-allyl complexes. Reductive elimination and hydrolysis of the iminium intermediate regenerate the palladium and amine catalysts, respectively, and release the product (Scheme 1.6.3B).\textsuperscript{119}

\begin{center}
\textbf{Scheme 1.6.3B:} Mechanism of alkylation using transition metal and enamine catalysis.
\end{center}

Breit and coworkers reported a Pd/proline-catalyzed $\alpha$-allylation reaction of aldehydes and ketones using allylic alcohols directly, as opposed to molecules with a good leaving group (Scheme 1.6.3C). An asymmetric version was attempted, but either no product was formed or the product was racemic.\textsuperscript{120}
Scheme 1.6.3C: Allylation reaction using allylic alcohols directly.

The high catalytic activity is likely due to the large bite angle of the diphosphine Xantphos ligand. Additionally, the carboxylic acid of the proline forms an ion pair intermediate through hydrogen bonding and protonation of the hydroxyl group (Scheme 1.6.3D).\textsuperscript{120}

Scheme 1.6.3D: Catalytic cycle of Pd/proline-catalyzed allylation.

Furthermore, List and coworkers used ACDC, discussed earlier, to create a quaternary chiral carbon center with an \(\alpha\)-allylation of aldehydes with an allylamine (Scheme 1.6.3E). A Pd(0) catalyst is combined with a chiral phosphoric acid.\textsuperscript{121}

Scheme 1.6.3E: Using ACDC to catalyze an allylation reaction.

An initial condensation of a secondary allylamine and an aldehyde, using the chiral phosphoric acid catalyst, leads to a phosphate salt. This reacts with Pd(0), creating a cationic allyl-Pd-complex, an enamine, and a phosphate counteranion. Next, the \(\alpha\)-allylated iminium ion

\[
\begin{align*}
\text{R}^1 \text{CHO} + \text{PhN} &\rightarrow \text{PhN}^* \\
&\rightarrow \text{PhN}^* \text{CHO}
\end{align*}
\]
is formed via nucleophilic attack of the enamine on the allyl-Pd-complex in the coordination sphere of the phosphate anion. After hydrolysis, the final product is formed (Scheme 1.6.3F).

**Scheme 1.6.3F:** Proposed mechanism of allylation reaction by List and coworkers.

In addition to activating allyl groups, metals can also activate alkynes. Wu and coworkers combined enamine with transition metal catalysis for condensation of ketones, amines, and 2-alkyne aldehydes to create 1,2-dihydroisoquinoline derivatives (Scheme 1.6.3G).

**Scheme 1.6.3G:** Condensation reaction combining enamine with metal catalysis.

The enamine is generated from the ketone with proline as a catalyst. It attacks the imine formed from the aldehyde and the amine substrate. Intramolecular attack occurs at the metal-activated alkyne, forming the final product (Scheme 1.6.3H).

**Scheme 1.6.3H:** Mechanism combining enamine catalysis and metal-activated alkyne.
Dixon and coworkers combined catalytic iminium activation of $\alpha,\beta$-unsaturated ketones, enamine activation of ketones, and metal ion activation of alkynes to react $\alpha,\beta$-unsaturated ketones and propargylated carbon acids to create cyclopentenes (Scheme 1.6.3I).\textsuperscript{123}

**Scheme 1.6.3I:** Combinational catalysis by Dixon and coworkers creating cyclopentenes.

The enone is condensed with the amine catalyst, leading to iminium ion activation. Michael addition can now occur with the alkyne-tethered malonate via its conjugate base, creating an enamine. This allows for nucleophilic attack on the alkynyl electrophile activated by the metal, a Cu(I) species generated from reduction of a Cu(II) complex by PPh$_3$. Intramolecular carbon-carbon bond formation occurs and hydrolysis releases the catalysts and product (Scheme 1.6.3J). To quench residual protic acids from the commercial metal salts, ps-BEMP is used.\textsuperscript{123}

![Catalytic cycle of combinational catalysis creating cyclopentenes.](image)

**Scheme 1.6.3J:** Catalytic cycle of combinational catalysis creating cyclopentenes.

### 1.6.4 Combining Amines with Hard Metals

Aliphatic amine catalysts have been successfully combined with hard metal Lewis acid catalysts, creating carbocation intermediates. Nishibayashi and coworkers reported an asymmetric propargylation of aldehydes with propargylic alcohols, based on similar $\alpha$-
alkylations of aldehydes with alcohols by the Cozzi group (Scheme 1.6.4A). The alkylation products are formed in high enantioselectivities, but poor diastereoselectivities.\textsuperscript{124}

\[ \text{Ar} = \text{R}^1 + \text{R}^2 \rightarrow \text{OH} \quad \text{InBr}_3 \text{ or FeCl}_3 (20 \text{ mol\%}) \rightarrow \text{CH}_2\text{Cl}_2, 0^\circ\text{C} \rightarrow \text{NaBH}_4 \rightarrow \text{EtOH} \rightarrow \text{syn/anti: 1.2-0.6/1} \]

\[ 81-97\% \text{ ee} \]

\textbf{Scheme 1.6.4A: Asymmetric propargylation of aldehydes with propargylic alcohols.}

The MacMillan chiral amine catalyst is used to activate the aldehyde, creating an enamine. The InBr\textsubscript{3} is used to activate the propargylic alcohol, creating a carbocation, after the InBr\textsubscript{3} is weakly coordinated to the hydroxyl oxygen atom. It is required that a stable carbocation intermediate can be formed, so in this case a strong electron donating group is used. Subsequent attack of the enamine on the propargylic cation forms an intermediate, leading to the product when catalysts are released (Scheme 1.6.4B). It is interesting that acid-base quenching does not occur, however, the Lewis acid was added slowly after the amine was added.\textsuperscript{124}

\textbf{Scheme 1.6.4B: Catalytic scheme for propargylation of aldehydes with alcohols.}

Additionally, soft base arylamines have been combined with hard Lewis acid metals. The Wang group performed a Sc(OTf\textsubscript{3})-catalyzed three-component cyclization reaction of
arylamines, β,γ-unsaturated α-ketoesters and 1,3-dicarbonyl compounds, creating highly substituted 1,4-dihydropyridines and fused bicyclic tetrahydropyridines (Scheme 1.6.4C).  

Scheme 1.6.4C: Sc(OTf)₃-catalyzed ADA reaction.

The aza-Diels-Alder reaction occurs between an in situ formed 1-azadiene intermediate, created from an enone and an arylamine, and a dicarbonyl compound, which reacts as either an enol or enamine intermediate. The addition of a pyridine-based ligand improves the yield, likely because it enhances the stability of possible metal complex intermediates.  

Preliminary asymmetric results were obtained, using a chiral ligand based on PyBOX. This resulted in a low enantioselectivity of 27% ee and a moderate yield of 44%.  

Combining arylamines with hard metals will be discussed more in the next chapter.
Chapter 2: Asymmetric Multicomponent ADAR Constructing Multicyclic Heterocycles

2.1 Introduction

Multicomponent reactions are an efficient and atom-economical way to create structural complexity and diversity. Furthermore, six-membered nitrogen-containing heterocyclic compounds, like dihydropyridines and tetrahydropyridines, are important molecular skeletons. They are abundant in natural products, pharmaceuticals, agrochemicals, and functional materials, and are intermediates in the preparation of nitrogen-containing alkaloids. The asymmetric aza-Diels-Alder reaction (ADAR) is an important and powerful method to create these types of nitrogen-containing heterocycles.¹²⁶

In the Diels-Alder reaction, an electron-rich diene is combined with an electron-deficient dienophile. In an inverse-electron-demand Diels-Alder reaction, an electron-deficient diene is combined with an electron-rich dienophile. Regarding aza-Diels-Alder reactions, normal-electron-demand reactions, which use dienamine and imine dienophiles, have been studied more than inverse-electron-demand reactions, which use enamine dienophiles.¹²⁶

The Wang group studies asymmetric multicomponent inverse-electron-demand aza-Diels-Alder reactions constructing multicyclic heterocycles. These reactions use arylamines for enamine catalysis. Arylamines (pK_a of conjugate acid 4-6) are softer than aliphatic amines (pK_a of conjugate acid 9-11) due to the delocalization of the lone pair to the aromatic π-system leading to higher polarizability. The nucleophilicity of arylamines can be tuned by various groups at the aromatic rings. The lower nucleophilicity of the amines is compensated by the metal Lewis acids catalyzing enamine formation and activating the electrophiles. These factors allow for successful combination of arylamines with hard metal Lewis acids, avoiding acid-base quenching.¹¹¹

2.1.1 Lewis Acid-Catalyzed Aza-Diels-Alder Reaction

The Wang group reported the first application of arylamines in enamine catalysis in 2013.¹²⁶ A chemoselective and enantioselective three-component inverse-electron-demand aza-Diels-Alder reaction of β,γ-unsaturated α-ketoesters, cyclic ketones, and aromatic amines was completed by combining enamine catalysis with metal Lewis acid catalysis. Using a three-component reaction avoids preparation of the enamine dienophiles and the unstable 1-azadiene intermediates. Arylamines can form enamines with cyclic ketones, serving as the enamine
catalyst, and can also form 1-azadienes with enones in the presence of a metal Lewis acid catalyst. The \textit{in situ} formed 1-azadiene, activated by the metal Lewis acid, reacts with the enamine, generating an aza-Diels-Alder reaction yielding dihydropyridines after hydrolysis and dehydroxylation (Scheme 2.1.1A).\textsuperscript{126}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_2.1.1A}
\end{center}

\textbf{Scheme 2.1.1A:} Inverse-electron-demand aza-Diels-Alder reaction.

This reaction has various challenges to overcome. First off, there are a number of side reactions that can occur, including the aza-Michael addition, aldol reaction, Mannich reaction, and hetero-Diels-Alder reaction (Figure 2.1.1). Also, both the ketone and 1-azadiene intermediate are difficult substrates. Ketones are less reactive than aldehydes due to steric and electronic effects. The 1-azadiene intermediate is less reactive than the more commonly used 2-azadienes.\textsuperscript{126}

\begin{center}
\includegraphics[width=\textwidth]{Figure_2.1.1}
\end{center}

\textbf{Figure 2.1.1:} Possible products from side reactions of ADAR.

Various metal salts were screened. They catalyzed the reaction toward the dihydropyridine, as no tetrahydropyridine was isolated. Y(OTf)\textsubscript{3}, Yb(OTf)\textsubscript{3}, La(OTf)\textsubscript{3}, and Zn(OTf)\textsubscript{2} showed high activity for the reaction regarding reaction time (less than 4 hours) and yield (61-91\%).\textsuperscript{126}
An asymmetric version of the reaction was studied. Since the arylamines act as reactants in the reaction, the asymmetry has to be induced through the metal species, which can be done through chiral ligands. Ligands including BOX, PyBOX, naphthol, and SALEN were tested in combination with the metal salts previously listed. However, only low enantioselectivities were obtained due to decreased catalytic activity and/or increased rates of side reactions.126

Since using chiral ligands was not successful, using a chiral anion was tested with the counter anion approach by the Toste group.81 The study was started by combining a $\text{M}^{\text{III}}\text{Cl}_3$ with a chiral silver phosphate. After solvent and metal screening, the best combination was $\text{YCl}_3$ (10 mol %) and silver phosphate (5 mol %) in toluene (Scheme 2.1.1B).126

![Scheme 2.1.1B: Three-component inverse-electron-demand ADAR.](attachment:image)

After finding optimized conditions, substrate scope was tested (Table 2.1.1). Enones with both electron-donating and electron-withdrawing aromatic substituents reacted well with cyclohexanone and the electron-rich $p$-methoxyaniline. More electron-deficient arylamines were tested and successful, such as aniline, $p$-chloroaniline, and $p$-bromoaniline. Similar to cyclohexanone, heteroatom-containing dihydrothiopyran-4-one was used successfully.

Cyclopentanone and cycloheptanone created the ADAR products in good yields when $\text{Y(OTf)}_3$ was used as the catalyst. However, when the asymmetric chiral anion approach was used, only modest results were obtained, with 45% ee and 35% yield for cyclopentanone and 27% ee and 30% yield for cycloheptanone. X-ray crystallography was used to determine the absolute configuration ($R$) of the product (Entry 4, Table 2.1.1) and other products were assumed to have similar configurations.126
Table 2.1.1: Substrate scope performed for ADAR.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Z</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<td>Ph</td>
<td>12</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
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<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>12</td>
<td>80</td>
<td>92</td>
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<td>Me</td>
<td>Ph</td>
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<td>70</td>
<td>86</td>
</tr>
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<td>93</td>
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<td>Cl</td>
<td>H</td>
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<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>H</td>
<td>p-NO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
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<td>Cl</td>
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<td>H</td>
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<td>OMe</td>
<td>H</td>
<td>Ph</td>
<td>36</td>
<td>30</td>
<td>27</td>
</tr>
</tbody>
</table>

The arylamine was replaced with an aliphatic amine, showing that arylamines are more compatible with Lewis acids. The reaction was messy, the enone was not fully consumed, and no ADA product was detected. Additionally, when the Lewis acid was replaced with a Brønsted acid, the results were similar, indicating that an arylamine and a Lewis acid are both needed.\textsuperscript{126}

To examine the catalytic role of the amine, the reaction was carried out with 1-azadiene and cyclohexanone using Y(OTf)<sub>3</sub> as the only catalytic species. The ADAR product was formed in very low yield and a large amount of starting material was left, as well as the enone that results from decomposition of the 1-azadiene. When aniline was added, the reaction went to completion. Without a metal Lewis acid, no reaction occurred. Whether or not Y(OTf)<sub>3</sub> was used, when an aliphatic primary amine was used, no product was formed and starting material was recovered. These results suggest the reaction needs an enamine catalyst, requiring both a metal Lewis acid and an arylamine for success.\textsuperscript{126}

2.1.2 LLA-Catalyzed Aza-Diels-Alder Reaction

Expanding on this previous work, similar reactions were completed with a new type of chiral Lewis acid-assisted Lewis acid (LLA) catalyst derived from metal Lewis acids and chiral metal phosphates (Scheme 2.1.2A). By combining LLA catalysis with enamine catalysis, asymmetric three-component inverse-electron-demand aza-Diels-Alder reactions of cyclic
ketones, unsaturated ketoesters, and arylamines created fused bicyclic dihydropyridines in high yields and enantioselectivities.\textsuperscript{127} 

\[
\begin{align*}
\text{Scheme 2.1.2A: ADAR of cyclic ketones using LLA catalyst.}
\end{align*}
\]

Creating new chiral LLA catalysts leads to reactions that previously could not be achieved. This type of bimetallic LLA catalyst takes advantage of the strong Lewis acidity of a hard metal Lewis acid and the chirality of a chiral metal phosphate. Chiral phosphate anions have multiple coordinating atoms allowing for binding multiple metals in one structural entity, serving as a platform for the development of new LLA catalysts. Better asymmetric environments can be prepared by combined acid catalysis, which was discussed earlier. The LLA catalysts are easily accessible and structurally flexible, given the varieties of metal Lewis acids and chiral metal phosphates available, leading to either homobimetallic or heterobimetallic systems. Also, the catalysts are neither water-sensitive nor air-sensitive. However, the complex nature of combined catalysts makes it hard to show the true nature of the reaction mechanism.\textsuperscript{127} 

In the research previously discussed, the yttrium (III) phosphate (Y[P]_{3}) (Figure 2.1.2A) was prepared \textit{in situ} from the treatment of YCl_{3} (10 mol\%) with chiral silver phosphate (Ag[P]) (5 mol\%). Theoretically, three equivalents of Ag[P] are needed to react with one equivalent of YCl_{3} to create Y[P]_{3}. Using excess YCl_{3} resulted in higher enantioselectivity and activity of the reaction. Also, both YCl_{3} and Ag[P] did not dissolve well in the solvent. These outcomes suggest formation of a more complicated metal-complex catalyst rather than a simple chiral Y[P]_{3}.\textsuperscript{127} 

To better understand this complex, the Y[P]_{3} was prepared differently, from the reaction of yttrium(III) tris(isopropoxide) (Y(Oi-Pr)_{3}) and chiral phosphoric acid. Both Y[P]_{3} and YCl_{3}, when used alone, did not catalyze the reaction. Combination of Y[P]_{3} and YCl_{3} in 1:1 molar ratio, as 5 mol\% of \textit{in situ} YCl_{3}/Y[P]_{3}-LLA complex, led to a successful reaction. (Scheme 2.1.2B) Compared to YCl_{3}/Ag[P] the reaction time was shortened from 12 hours to 4 hours,
suggesting the LLA catalyst was formed more efficiently. Similar results were obtained when Y[P]$_3$ was prepared in other ways as well, confirming the necessity of a combined catalyst, which offers stronger Lewis acidity and stereoselectivity than individual metal complexes.$^{127}$

![Diagram of Y[P]$_3$ chiral metal phosphate catalyst.](image)

**Figure 2.1.2A**: Y[P]$_3$ chiral metal phosphate catalyst.

The ratio was tested of YCl$_3$ to Y[P]$_3$. With Y[P]$_3$ at 5 mol%, when YCl$_3$ was reduced to 3 mol%, the reaction time increased and the yield decreased. When YCl$_3$ was increased to 10 or 15 mol%, the reactions ran similarly to ones using 5 mol%, showing the most efficient LLA catalyst is formed at 1:1 molar ratio. Since YCl$_3$ does not catalyze the reaction when used alone, excess YCl$_3$ does not affect the outcome.$^{127}$

![Diagram of LLA-catalyzed ADAR of cyclohexanone.](image)

**Scheme 2.1.2B**: LLA-catalyzed ADAR of cyclohexanone.

Other metal chlorides were tested with Y[P]$_3$. YbCl$_3$ reacted similarly to YCl$_3$. InCl$_3$, LaCl$_3$, and NaCl showed good activity and enantioselectivity, but did not work as well as YCl$_3$. CuCl$_2$ showed poor activity, but yielded the opposite enantiomer, showing possible formation of the LLA catalyst. Solvent screening was conducted to obtain optimal conditions. More polar solvents, like THF or methanol, resulted in lower enantioselectivities, and less polar solvents, like toluene and xylene, resulted in higher enantioselectivities.$^{127}$

Substrate scope of the ADARs of cyclohexanone was conducted (Table 2.1.2A). Using the optimized conditions of 5 mol% YCl$_3$ and 5 mol% Y[P]$_3$ in toluene, the reaction was
successful with a range of enones and arylamines, yielding dihydropyridines with high enantioselectivities and yields. This combined catalyst yielded better results than the previous YCl\textsubscript{3}/Ag[P] system.\textsuperscript{127}

**Table 2.1.2A**: Substrate scope performed for ADAR of cyclohexanone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Z</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>t (h)</th>
<th>yield (%)\textsuperscript{(a)}</th>
<th>ee (%)\textsuperscript{(b)}</th>
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<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>Cl</td>
<td>CH\textsubscript{2}Ph</td>
<td>4</td>
<td>92</td>
<td>93</td>
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<td>Cl</td>
<td>H</td>
<td>4</td>
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</table>

Reactions completed with 0.2mmol scale. \textsuperscript{(a)}Isolated yields. \textsuperscript{(b)}Values determined by chiral HPLC analysis. \textsuperscript{(c)}Substitute dihydrothiopyran-4-one for cyclohexanone.

The asymmetric three-component ADARs of cyclopentanone and cycloheptanone were tested using the YCl\textsubscript{3}/YP\textsubscript{3}-LLA catalyst, which would create enantiomerically pure dihydropyridines containing 5/6 and 7/6 fused bicyclic rings, respectively. However, with cyclopentanone, this catalytic system provided moderate activity (37% yield and 45% ee) only slightly better than the data obtained with YCl\textsubscript{3}/Ag[P] previously. These results are not surprising because cyclic ketones with differing ring sizes can vary in reactivity due to distinct electronic and steric properties.\textsuperscript{127}

When YCl\textsubscript{3} was replaced with Y(OTf)\textsubscript{3}, the reactions of cyclopentanone and cycloheptanone were successful (Scheme 2.1.2C, Scheme 2.1.2D). Y(OTf)\textsubscript{3}, which is a stronger metal Lewis acid thus enhancing the Lewis acidity of the LLA catalyst, does catalyze the reaction alone with 42% yield, unlike YCl\textsubscript{3}. Therefore, to achieve high stereoselectivity, Y(OTf)\textsubscript{3}/YP\textsubscript{3}-LLA must be a more efficient catalyst than Y(OTf)\textsubscript{3} alone and/or Y(OTf)\textsubscript{3} must form a tight complex with YP\textsubscript{3} so no free Y(OTf)\textsubscript{3} is available. A 1:1 molar ratio of Y(OTf)\textsubscript{3} to YP\textsubscript{3} was found to be the most effective. Using less Y(OTf)\textsubscript{3} led to similar results and using more Y(OTf)\textsubscript{3} led to reduced enantioselectivity, likely due to present free Y(OTf)\textsubscript{3}.\textsuperscript{127}

**Scheme 2.1.2C**: LLA-catalyzed ADAR of cyclopentanone.
Table 2.1.2B: Substrate scope performed for ADAR of cyclopentanone.

<table>
<thead>
<tr>
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<th>R²</th>
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<th>ee (%) (b)</th>
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<td>78</td>
<td>88</td>
</tr>
<tr>
<td>8(²)</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>18</td>
<td>69</td>
<td>83</td>
</tr>
<tr>
<td>9(²)</td>
<td>Cl</td>
<td>OMe</td>
<td>Ph</td>
<td>18</td>
<td>66</td>
<td>63</td>
</tr>
</tbody>
</table>

Reactions completed with 0.2mmol scale. (a) Isolated yields. (b) Values determined by chiral HPLC analysis. (²) Reactions were performed at room temperature.

Since YbCl₃ led to similar results as YCl₃ in ADARs of cyclohexanone, Yb(OTf)₃/Y[P]₃-LLA was created. This heterobimetallic catalyst effectively catalyzed the ADARs of cyclopentanone and cycloheptanone, giving slightly higher enantioselectivity than Y(OTf)₃. The enantioselectivity was further improved by using lower temperature. The reactions were successful using enones with both electron-donating and electron-withdrawing aromatic substituents. Electron-rich p-methoxyaniline was the amine most often used. Aniline gave similar results, while more electron-deficient p-chloroaniline provided slightly lower enantioselectivities and yields (Table 2.1.2B, Table 2.1.2C).

Scheme 2.1.2D: LLA-catalyzed ADAR of cycloheptanone.

The more powerful Yb(OTf)₃/Y[P]₃-LLA catalyst was used to retest the reaction of cyclohexanone, affording the dihydropyridine with similar yield and enantioselectivity as the YCl₃/Y[P]₃ catalyst, but the reaction was shortened from 4 hours to 2 hours. Additionally, using oxygen-containing tetrahydro-4H-pyran-4-one, Yb(OTf)₃/Y[P]₃ gave the product with 70% ee and 80% yield, while YCl₃/Y[P]₃ resulted in only 21% ee and 18% yield.
Table 2.1.2C: Substrate scope performed for ADAR of cycloheptanone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Z</th>
<th>R¹</th>
<th>R²</th>
<th>t (h)</th>
<th>yield (%)&lt;sup&gt;(a)&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;(b)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>CH₃</td>
<td>H</td>
<td>16</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>16</td>
<td>74</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>OMe</td>
<td>Ph</td>
<td>16</td>
<td>71</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>Cl</td>
<td>H</td>
<td>16</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>F</td>
<td>H</td>
<td>16</td>
<td>79</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>Br</td>
<td>H</td>
<td>16</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>7&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>18</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>8&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>Cl</td>
<td>OMe</td>
<td>Ph</td>
<td>18</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>9&lt;sup&gt;(d)&lt;/sup&gt;</td>
<td>OMe</td>
<td>Cl</td>
<td>Ph</td>
<td>2</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>10&lt;sup&gt;(e)&lt;/sup&gt;</td>
<td>OMe</td>
<td>Cl</td>
<td>H</td>
<td>4</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

Reactions completed with 0.2mmol scale.<sup>(a)</sup> Isolated yields. <sup>(b)</sup> Values determined by chiral HPLC analysis. <sup>(c)</sup> Reactions were performed at room temperature. <sup>(d)</sup> Substitute cyclohexanone for cycloheptanone. <sup>(e)</sup> Substitute tetrahydro-4H-pyran-4-one for cycloheptanone.

Metal phosphates were tested and were inactive when used alone. When combined with Yb(OTf)₃, which alone catalyzed the ADAR of cyclopentanone, they all had similar activity with variable enantioselectivity, with ee values of 70% for Yb[P]₃, 54% for La[P]₃, 27% for Sm[P]₃, 3% for Sc[P]₃, and 62% for Zn[P]₂. These results suggest association with Yb(OTf)₃.<sup>127</sup>

BINOL is the most commonly used chiral ligand in LLA catalysis, sharing a similar chiral binaphthyl backbone with Y[P]₃. A Y(III)-BINOL complex, bis-Y(III) tris(binaphthoxide) (Y₂BINOL₃), was tested to see if it could replace the chiral phosphate (Figure 2.1.2B). However, chiral metal phosphates have higher Lewis acidity than the corresponding metal alkoxides derived from BINOL, due to the lower pKa values of chiral phosphoric acids (2-4) than BINOL (9-11). Additionally, the coordination chemistry of the two is expected to be very different. Neither Y₂BINOL₃ nor its combination with YCl₃ catalyzed the reaction. When combined with Y(OTf)₃, the ADAR product was formed with almost no enantioselectivity (4% ee and 74% yield), similar to using Y(OTf)₃ alone (78% yield). This suggests there are no strong associations between Y(OTf)₃ and Y₂BINOL₃ and supports the necessity of the chiral phosphate ligand.<sup>127</sup>

![Figure 2.1.2B](image-url)

**Figure 2.1.2B:** Comparing structures of Y[P]₃ and Y₂BINOL₃.
Previously, different molar ratios to create the LLA catalyst were tested. However, the catalysts do not dissolve well in toluene. To gain more information, 1,4-dioxane was used as a solvent because it dissolves all of the catalysts and complexes, yet still leads to good activity and enantioselectivity of the ADAR. The results are consistent with the results in toluene. The 1:1 molar ratio gave the best results, while a higher ratio of Y[P]₃ gave a similar enantioselectivity and a lower yield. With a higher ratio of Y(OTf)₃, enantioselectivity dramatically decreased while activity increased, indicating presence of free Y(OTf)₃.¹²⁷

¹H and ³¹P NMR spectroscopy were used to examine the Y(OTf)₃/Y[P]₃-LLA catalyst in 1,4-dioxane-d₈. Both NMR spectra of Y[P]₃ showed broad peaks, suggesting an oligomeric structure. Regarding ¹H NMR data (Figure 2.1.2C), when Y(OTf)₃ was added in increasing amounts with in situ stirring for 30 minutes, new sharper peaks appeared, suggesting association of Y(OTf)₃ with Y[P]₃. With a 1:2 molar ratio of Y(OTf)₃: Y[P]₃, two sets of shifts were seen, the sharp peaks from formation of a new species and the broad peaks from un-reacted Y[P]₃. When the ratio is 1:1, the broad peaks disappear and the sharper peaks are more defined, suggesting all Y[P]₃ was converted to LLA catalyst. When more Y(OTf)₃ is added, the spectrum stays the same, indicating the formation of a stable species is complete.¹²⁷

![Figure 2.1.2C: ¹H NMR spectra of HCPA, Y[P]₃, and Y(OTf)₃/Y[P]₃-LLA catalyst.](image-url)
The proton shifts of the chiral phosphoric acid (HCPA) and the LLA catalyst (Figure 2.1.2D) are assigned based on proton NMR spectra and COSY spectra. Comparing the proton shifts of both suggests all the binaphthyl phosphate ligands in the LLA catalyst are identical with only one set of proton shifts. All of the proton shifts of the LLA catalyst are downfield relative to those of HCPA, consistent with $\text{Y(OTf)}_3$ binding to the binaphthyl phosphate scaffold.$^{127}$

![HCPA and LLA catalyst structures](image)

**Figure 2.1.2D:** Comparison of HCPA and LLA catalyst for assignment of proton shifts.

Also, $^{31}$P NMR spectroscopic studies were conducted (Figure 2.1.2E). The spectra show one triplet resonance for the LLA catalyst, a singlet for HCPA, and two broad peaks with different intensities for $\text{Y[P]}_3$. The more complicated spectra of $\text{Y[P]}_3$ again show its oligomeric nature. The triplet shift for the LLA catalyst is from nuclear spin coupling, which has been reported between $^{89}\text{Y}$ and phosphorous atoms, based on the coupling constant. It suggests one phosphorous atom is associated with two identical yttrium atoms. Based on the NMR data, the LLA catalyst adopts a symmetrical structure containing two identical yttrium atoms.$^{127}$

![31P NMR spectra](image)

**Figure 2.1.2E:** $^{31}$P NMR spectra of HCPA, $\text{Y[P]}_3$, and $\text{Y(OTf)}_3/\text{Y[P]}_3$-LLA catalyst.
Additionally, electron paramagnetic resonance (EPR) spectroscopy was completed to learn more about the metal centers. Since in these studies, ytterbium has been reacting similarly to yttrium in the catalytic systems, it is assumed that the active catalyst has a similar structure using either metal. However, Y(III) is diamagnetic while Yb(III) is paramagnetic and EPR is sensitive to the crystal field of the paramagnet, meaning changes that occur should be easily detected. The configuration of Yb(III) leaves a single unpaired electron that could localize on either the phosphate catalyst or the Lewis acid co-catalyst. YbCl$_3$/Y[PH]$_3$, YbCl$_3$/Yb[PH]$_3$, YbCl$_3$/Ag[PH], and Yb(OTf)$_3$/Y[PH]$_3$ were examined to see the level of interaction between the phosphate catalyst and the paramagnetic Yb(III) co-catalyst.$^{127}$

YbCl$_3$ gives an axial spectrum consistent with the spin-orbit ground state expected from Yb(III) in a symmetric environment (Figure 2.1.2F). This is in contrast to the Yb[PH]$_3$ catalyst, which gives a broad spectrum with a feature of minimal g-anisotropy at $g = 2.0$. The suspension of the two components in toluene eliminates the axial YbCl$_3$ spectrum, as well as the feature at $g = 2.0$, suggesting intimate interaction. The spectrum of YbCl$_3$ in suspension with Ag[PH] or Y[PH]$_3$ is similar in shape to the one with Yb[PH]$_3$, suggesting trans-metallation in situ. These two spectra are sharper than the one from YbCl$_3$/Yb[PH]$_3$, supporting intimate contact between the two metals, leading to dipolar broadening. The YbCl$_3$/Y[PH]$_3$ spectrum supports the catalyst and co-catalyst forming an inner-sphere complex, based on poorly resolved hyperfine coupling, likely due to coupling of the unpaired electron on Yb(III) to the diamagnetic $^{89}$Y nucleus.$^{127}$

![Figure 2.1.2F: EPR spectra of YbCl$_3$, Yb[PH]$_3$, and YbCl$_3$/phosphate catalyst suspensions.](image)
The YbCl$_3$/Ag[P] suspension is examined with substrates (Figure 2.1.2G). After 10 minutes, the spectrum shows sharpening of low-field features and appearance of the feature at $g=2.0$. The feature shows hyperfine structure that cannot be assigned, but the splitting is large enough to rule out coupling to any nuclei other than $^{107/109}$Ag. After two hours, the hyperfine structure is lost and the spectrum becomes closer to that of Yb[P], suggesting trans-metallation. Replacing YbCl$_3$ with Yb(OTf)$_3$ leads to similar results, indicating a similar mechanism.$^{127}$

![Figure 2.1.2G: EPR spectra of Ag[P]/YbCl$_3$ suspension with substrates.](image)

Single crystals formed by slow vapor diffusion of hexane into the 1,4-dioxane/metal complex solution. The crystal structure was resolved with diffraction data. The structure of the Y(OTf)$_3$/Y[P]$_3$ complex shows pseudo-C$_4$-symmetrical distribution of four bridging phosphate ligands centered at a bi-yttrium core, leading to a molecular formula of Y$_2$[P]$_4$(OTf)$_2$·6H$_2$O (Figure 2.1.2H). It supports the data obtained from NMR and EPR spectroscopy. MALDI-TOF mass spectrometry shows multiple peaks corresponding to Y$_2$[P]$_3$·2H$_2$O, Y$_2$[P]$_4$·H$_2$O and Y$_2$[P]$_5$, again supporting a bimetallic structure of the metal complex.$^{127}$

![Figure 2.1.2H: X-ray crystallography-obtained LLA catalyst of Y$_2$[P]$_4$(OTf)$_2$·6H$_2$O.](image)
The proposed transition state has the arylamine activating the cyclic ketone, forming an enamine. The enone and arylamine form a 1-azadiene, which is activated by the LLA catalyst. The enamine approaches the 1-azadiene via an endo-selective mode. The binaphthyl skeleton shields the Si face of the 1-azadiene, allowing enamine attack from the Re face. The absolute configuration of the product derived from the model matches the X-ray crystal structure.  

### 2.2 LLA-Catalyzed Asymmetric ADAR Constructing Multicyclic Heterocycles

This work is based on the previous work, again combining LLA catalysis with enamine catalysis to complete an asymmetric three-component inverse-electron-demand ADAR of cyclic ketones, unsaturated ketoesters, and arylamines, creating dihydropyridines (Scheme 2.2A). This work uses different substrates, leading to more complicated final products. It expands the scope of the reaction and opens up more possibilities for use of the combined catalytic system.

The ADAR was conducted with a bifunctional amine substrate. Based on the $^1$H NMR spectroscopic data, the main byproducts were the partially-reacted ADA product (only one side of the diamine reacted), the aldol product, and the Diels-Alder product. $Y$(OTf)$_3$ catalyzed the racemic reactions and $Y$(OTf)$_3$/Y[P]$_3$-LLA catalyst catalyzed the asymmetric reactions. $Yb$(OTf)$_3$ catalyzed the reaction similarly to $Y$(OTf)$_3$, according to TLC.

Substrate scope was completed with different enones (Table 2.2A). The reaction times were longer than the previous work, likely because two cyclic reactions occur per molecule when using a diamine substrate. NMR confirmed the ADA products were formed (Figure 2.2). Regarding stereoselectivity, the molecule has two chiral centers, but also has symmetry. Therefore, the HPLC data shows only three peaks with ratios of 1:1:2, since two of the stereoisomers are meso compounds (same molecules due to symmetry). The $dr$ values were varied, with some correlation with the $R^1$ groups on the enone, since products with the same $R^1$ group tended to have similar $dr$ values. The $ee$ values were high and the yields were good.

![Scheme 2.2A](image)

**Scheme 2.2A**: ADAR of cyclohexanone with bifunctional amine substrate.
Table 2.2A: Substrate scope performed for ADAR using bifunctional amine substrate.

<table>
<thead>
<tr>
<th>Product</th>
<th>R₁</th>
<th>R₂</th>
<th>t (h)</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>61</td>
<td>6.4:1</td>
<td>97</td>
</tr>
<tr>
<td>1b</td>
<td>CH₃</td>
<td>H</td>
<td>48</td>
<td>68</td>
<td>20.6:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>1c</td>
<td>OMe</td>
<td>H</td>
<td>48</td>
<td>56</td>
<td>26.5:1</td>
<td>99</td>
</tr>
<tr>
<td>1d</td>
<td>F</td>
<td>H</td>
<td>48</td>
<td>71</td>
<td>16.4:1</td>
<td>98</td>
</tr>
<tr>
<td>1e</td>
<td>H</td>
<td>Ph</td>
<td>48</td>
<td>73</td>
<td>5.8:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>1f</td>
<td>CH₃</td>
<td>Ph</td>
<td>24</td>
<td>71</td>
<td>17.1:1</td>
<td>88</td>
</tr>
<tr>
<td>1g</td>
<td>OMe</td>
<td>Ph</td>
<td>48</td>
<td>66</td>
<td>24.5:1</td>
<td>99</td>
</tr>
<tr>
<td>1h</td>
<td>F</td>
<td>Ph</td>
<td>24</td>
<td>65</td>
<td>11.3:1</td>
<td>&gt;99</td>
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<tr>
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<td>Cl</td>
<td>Ph</td>
<td>24</td>
<td>70</td>
<td>7.8:1</td>
<td>99</td>
</tr>
</tbody>
</table>

(a) Isolated yields. (b) Values determined by chiral HPLC analysis.

Figure 2.2: ¹H NMR proton shift assignments of product 1a.

Reduction was completed on a diamine product, yielding 69% after 48 hours (Scheme 2.2B). When the racemic product was reduced, the reduced product had a dr of 1.2:1. When the asymmetric product was reduced, the reduced product had a dr of 22.3:1 and an ee of 95%.
Scheme 2.2B: Reduction of diamine product.

Obtaining a crystal structure was attempted with this reduced product, in effort to solve the absolute product configuration. However, several solvents and solvent combinations were tried, the most promising of which was vapor diffusion of methanol into 1,4-dioxane. A white solid was collected, but testing showed unsuccessful attempts at a grown crystal.

Scheme 2.2C: ADAR creating symmetrical molecules with bicyclohexanone substrate.

The ADAR was also completed with a bicyclohexanone substrate. There were two different variations of the reaction. In one, the bicyclohexanone was reacted with excess enone and amine, creating a symmetrical product (Scheme 2.2C, Table 2.2B). In the other, the enone and amine were reacted with excess bicyclohexanone, creating a half-reacted ADA product with only one side of the bicyclohexanone used in the reaction. This product was then reacted with the amine and a different enone, creating an unsymmetrical molecule (Scheme 2.2D, Table 2.2C).

Table 2.2B: Substrate scope performed for symmetrical ADAR with bicyclohexanone.

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>t (h)</th>
<th>yield (%) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>F</td>
<td>CH₂Ph</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>2c</td>
<td>CH₃</td>
<td>CH₂Ph</td>
<td>48</td>
<td>71</td>
</tr>
<tr>
<td>2d</td>
<td>H</td>
<td>CH₃</td>
<td>48</td>
<td>57</td>
</tr>
</tbody>
</table>

(a) Isolated yields.
Scheme 2.2D: ADAR creating unsymmetrical molecules with bicyclohexanone.

When the half-reacted intermediate is created first when making the unsymmetrical product, this intermediate only has two chiral centers. Therefore, with HPLC data it has four peaks, allowing for calculation of a $dr$ and $ee$. The calculated $dr$ is 1.5:1 and the $ee$ is 94% for the major product and 87% for the minor product.

Table 2.2C: Substrate scope performed for unsymmetrical ADAR with bicyclohexanone.

<table>
<thead>
<tr>
<th>Product</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>t (h)</th>
<th>yield (%)(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>2e</td>
<td>H</td>
<td>CH$_3$</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td>2f</td>
<td>CH$_3$</td>
<td>CH$_2$Ph</td>
<td>48</td>
<td>51</td>
</tr>
</tbody>
</table>

(a) Isolated yields.

These final products have four chiral centers, and therefore can have up to 16 stereoisomers as 8 pairs of enantiomers. When a symmetric molecule is made, some of the stereoisomers are actually the same molecule, therefore decreasing the amount of different stereoisomers. With a racemic reaction, there should be no enantioselectivity, meaning there should be the same amount of each enantiomer in each enantiomeric pair.

The table below looks at the 16 stereoisomers using R-/S-notation for each of the four chiral centers (Table 2.2D). The 8 enantiomeric pairs are shown in each vertical column. The boxes are around identical species (when the molecule is symmetric). As shown, there are 10 boxes, meaning 10 peaks would show up in ideal HPLC conditions. Theoretically, with no stereoselectivity in the reaction, each of the 16 stereoisomers would make up 6.25% of the total mixture, although typically even racemic reactions favor certain diastereomers over the others.
Table 2.2D: Theoretical HPLC results for symmetrical bicyclohexanone-based molecules.

<table>
<thead>
<tr>
<th></th>
<th>SSSS</th>
<th>RSSS</th>
<th>SSSR</th>
<th>SRSS</th>
<th>SSRS</th>
<th>RRSS</th>
<th>RSRS</th>
<th>RSSR</th>
<th>RRRR</th>
<th>SRRR</th>
<th>RRRL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 equal peaks (6.25% each)</td>
<td>2 equal peaks (12.5% each)</td>
<td>2 equal peaks (12.5% each)</td>
<td>1 peak (12.5%)</td>
<td>1 peak (12.5%)</td>
<td>2 equal peaks (6.25% each)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The HPLC data from the racemic versions of both 2c and 2d show fewer peaks than the expected 10 peaks, with 7 and 8 peaks, respectively. Also, HPLC data was collected for 2f, an unsymmetrical product. Therefore, 16 peaks would be expected, but only 14 appeared. Since fewer peaks resolved than expected, it is probable that incomplete separation occurred. Due to the varying areas of each peak and the incorrect number of peaks, it is not possible to assign enantiomeric pairs. Asymmetric versions of these reactions were also tested. This led to major and minor products, suggesting that stereoselectivity and enantioselectivity does occur with the LLA-catalyst. The asymmetric version of the reaction of 2c was completed with both the R- and S-forms of the catalyst (Y[P]₃). When using different forms, the HPLC spectra show different major and minor peaks, again suggesting stereoselectivity due to the LLA-catalyst.

There are also attempted reactions that were unsuccessful. A diketone reaction was tried (Scheme 2.2E). The racemic reaction combined enone, p-anisidine, and 1,4-cyclohexanedione in a ratio of 2:2:1, respectively, with 10 mol% Y(OTf)₃ catalyst in THF. However, the TLC showed many spots, including a major spot on the base line and starting enone. The reaction was repeated, mixing everything except dione together for an hour and then adding 10 equivalents dione. Column chromatography was performed, but NMR data and mass spectrometry data were unclear. Mass spectrometry revealed peaks at 496.2, 601.3, and 901.4. The mass of the fully-reacted ADA product is 887.8 and the mass of the half-reacted ADA product (only one side of the dione reacted) is 499.9. An asymmetric version of the reaction was conducted with Y(OTf)₃ and Y[P]₃ in toluene, but NMR data was not clean and product seemed unstable.

The reaction was performed with 100 equivalents of dione to obtain the partially-reacted ADA product. The TLC was cleaner and after separation, NMR was better, but not pure. Also, mass spectrometry data revealed peaks of 496.2 and 601.3. When attempting to purify further, the sample seemed to decompose. No product eluted from the column, including attempts of a
neutral aluminum oxide column, as opposed to an acidic silicon dioxide column. Additionally, impurities showed up on the base line of TLC plates, indicating decomposition.

Scheme 2.2E: Attempted reaction using diketone substrate.

Reactions were attempted using cyclopentanone and cycloheptanone in combination with enone, diamine, and Y(OTf)$_3$ catalyst in THF. After five days, the reactions were stopped and underwent column chromatography. With cycloheptanone, NMR showed no ADA product. With cyclopentanone, NMR showed ADA product with an estimated yield of 23%.

The product seemed unstable, so to obtain stability, the reduction was tried with a procedure similar to the reduction described previously. The product was mixed with DCM, glacial acetic acid, and 12 equivalents of sodium triacetoxyborohydride added slowly. After 24 hours, 6 more equivalents of reducing agent were added. TLC data did not change, so the reaction was stopped. According to NMR data, the product was not reduced, but rather starting material. Reduction was tried on crude product, but via TLC the product seemingly decomposed.

Additionally, different types of 1,3-diamines were tested. The racemic reactions were completed with $m$-phenylenediamine (Scheme 2.2F), 2,6-diaminotoluene, and 2,4-diaminotoluene. The reaction with 2,6-diaminotoluene formed a precipitate and crude NMR data showed no product and the reaction with 2,4-diaminotoluene showed little product via TLC.

With the racemic reaction of $m$-phenylenediamine, a small amount of ADA product was collected and HPLC data was acquired. The asymmetric reaction was performed and NMR data showed ADA product. However, the racemic version seemed to produce mainly the half-reacted ADA product and very little of the fully-reacted ADA product in comparison with the asymmetric version. The racemic reaction was performed again, this time combining Y(OTf)$_3$ with equal amounts of the $R$- and $S$- forms of the Y[P]$_3$ complex. However, it still resulted in very little ADA product.
The reaction was also tried with a different enone, replacing the fluorine with hydrogen. Racemic and asymmetric versions were tried, but TLC was messy and NMR data was unclear. The reaction was attempted with a higher temperature, but again was unsuccessful.

Scheme 2.2F: ADAR attempted using m-phenylenediamine.

2.3 Experimental Data for LLA-Catalyzed Asymmetric ADAR

2.3.1 General Information

Unless noted, commercial materials were used without further purification. Small-scale reactions were conducted in one-dram vials fitted with a threaded cap and equipped with a magnetic stir bar. NMR spectra were collected with Bruker-500 MHz spectrometer. Optical rotation was measured on Rudolph Research Autopol III and was reported as follows: \([\alpha]_D^T\) (c: g/100 mL in solvent). Diastereomeric ratios and enantiomeric excesses were determined by chiral HPLC analysis using Hitachi L-2000 series organizer box on Daicel Chiralpak AD-H in comparison to racemates. Monitoring of the reactions was performed on Silicycle silica gel 60 F254 silica gel plates (TLC). Flash column chromatography was carried out on Silicycle 60 silica gel (40-63 \(\mu\)m). Cyclohexanone was ACS reagent pure and dried with molecular sieves. Toluene was dried on Innovative Technology solvent purification system. Other reagents were purchased from Acros or Aldrich and used directly.

\(^1\)H NMR chemical shifts are referenced to residual solvent peak of CDCl\(_3\) at 7.26 ppm. \(^{13}\)C NMR spectra were run with broadband decoupling and chemical shifts are referenced to residual solvent peak of CDCl\(_3\) at 77.1 ppm. NMR chemical shifts are reported in ppm downfield.
of tetramethylsilane. NMR peak descriptors are abbreviated as such: br= broad, s=singlet, d=doublet, t= triplet, q= quartet, quin= quintet, m= multiplet.

2.3.2 General Reaction Procedures

Enones were prepared according to known procedures. One equivalent of substituted benzaldehyde was added to one equivalent of pyruvic acid in MeOH at 0°C (Scheme 2.3.2A). Two equivalents of potassium hydroxide were dissolved in MeOH and added dropwise while the mixture was kept at 0°C and stirred. Yellow precipitate was formed. Reaction temperature was brought to room temperature for one hour and kept at 0°C overnight. Yellow crystals were filtered, washed with cold MeOH and/or ether, and dried under reduced pressure. 128-129

Scheme 2.3.2A: Creating potassium salt for enone synthesis.

This potassium salt is used to create the starting material enones (Scheme 2.3.2B). To create enones with a methyl ester, 3.5 equivalents of acetyl chloride were added to MeOH at 0°C, making hydrochloric acid. The potassium salt was added and the solution was stirred for thirty minutes. The reaction was brought to room temperature, and after two hours refluxed overnight. Potassium chloride and solvent were removed and enone was recrystallized in MeOH. To create enones with a benzyl ester, the potassium salt was dissolved in acetonitrile and 0.95 equivalents of benzyl bromide were added. The solution refluxed overnight. Potassium bromide and solvent were removed and enone was recrystallized with MeOH. 128-129

Scheme 2.3.2B: Synthesis of enones from potassium salt.
To make the Y[P]₃ complex, 3 equivalents (0.3mmol, 104.4mg) of (R)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate were dissolved in 2mL of DCM and 4mL of MeOH (Scheme 2.3.2C). 1 equivalent (0.1mmol, 26.6mg) of yttrium(III) i-propoxide was added and the mixture was stirred for three hours at room temperature. Solvent was evaporated under reduced pressure to afford the product as a white solid.

**Scheme 2.3.2C:** Preparation of Y[P]₃ complex.

For the ADAR using the diamine substrate, both racemic and asymmetric versions of the reaction were performed in a one dram vial equipped with a magnetic stir bar (Scheme 2.3.2D). The racemic version combined enone substrate (0.2mmol, 2 equivalents), p-phenylenediamine (0.1mmol, 1 equivalent), 0.1mL of cyclohexanone, 1mL THF, and Y(OTf)₃ catalyst (10.7mg, 0.02mmol, 10 mol%). The asymmetric version combined Y[P]₃ (11.4mg, 0.01mmol, 5 mol%), Y(OTf)₃ (5.4mg, 0.01mmol, 5 mol%), and 0.1mL of cyclohexanone in 1mL toluene to generate the catalyst first. After three hours, enone substrate (0.2mmol, 2 equivalents) and p-phenylenediamine (0.1mmol, 1 equivalent) were added. Solutions were stirred at room temperature for 24 to 48 hours until reactions were complete (TLC monitored). Products were purified using column chromatography or preparative TLC on silica gel with an eluent mixture of hexanes and ethyl acetate.

**Scheme 2.3.2D:** ADA reactions of cyclohexanone, enone, and p-phenylenediamine.

To form the reduced product, the ADA product using the diamine substrate was collected (Scheme 2.3.2E). This product was dissolved in 2mL DCM. 1mL glacial acetic acid was added and reaction was stirred for 15 minutes at room temperature. 48 equivalents of sodium borohydride were added to 2mL DCM and added slowly to the reaction. Reaction was monitored
by TLC and stirred for 48 hours. Saturated aqueous sodium bicarbonate was added and product was extracted with DCM. The organic layer was dried over magnesium sulfate. Solvent was removed and product was purified through column chromatography, affording a light yellow solid. Reduction was attempted first with sodium triacetoxyborohydride, but with no success.

**Scheme 2.3.2E**: Reduction of ADA diamine product.

Similarly, the ADAR using the bicyclohexanone substrate was conducted with both a racemic and asymmetric version (Scheme 2.3.2F). As discussed above, this reaction was used to create symmetrical and unsymmetrical molecules. To create the symmetrical molecules a dimer was made. Reactions were performed in a one dram vial with a magnetic stir bar. To obtain the racemic dimer, enone substrate (0.2mmol, 3 equivalents) was combined with p-anisidine (0.2mmol, 3 equivalents), 4,4'-bicyclohexanone (0.0667mmol, 1 equivalent), and Y(OTf)$_3$ catalyst (0.02mmol, 10 mol%) in 1mL THF. To obtain the asymmetric dimer, Y(OTf)$_3$ (0.01mmol, 5 mol%) and Y[P]$_3$ (0.01mmol, 5 mol%) were stirred in 1mL toluene to create the catalyst. After three hours, enone substrate (0.2mmol, 3 equivalents), p-anisidine (0.2mmol, 3 equivalents), and 4,4'-bicyclohexanone (0.0667mmol, 1 equivalent) were added. The resulting solutions were stirred at room temperature until reactions were complete (monitored by TLC) in about 48 hours. Products were purified using column chromatography or preparative TLC on silica gel with an eluent mixture of hexanes and ethyl acetate.

**Scheme 2.3.2F**: ADARs of bicyclohexanone, enone, and p-anisidine, obtaining dimer.
To obtain the unsymmetrical molecule, a half-reacted product is made first, and this product is reacted with a different enone to cause the asymmetry (Scheme 2.3.2G). Reactions were performed in a one dram vial with a magnetic stir bar. To obtain the racemic half-reacted intermediate, enone substrate (0.2mmol, 1 equivalent) was combined with p-anisidine (0.2mmol, 1 equivalent), 4,4′-bicyclohexanone (0.6mmol, 6 equivalents), and Y(OTf)$_3$ catalyst (0.02mmol, 10 mol%) in 1mL THF. To obtain the asymmetric half-reacted intermediate, Y(OTf)$_3$ (0.01mmol, 5 mol%) and Y[P]$_3$ (0.01mmol, 5 mol%) were combined in 1mL toluene to create the catalyst. Three hours later, enone substrate (0.2mmol, 1 equivalent), p-anisidine (0.2mmol, 1 equivalent), and 4,4′-bicyclohexanone (0.6mmol, 6 equivalents) were added. The resulting solutions were stirred at room temperature until reactions were complete (monitored by TLC) in 24 hours. Products were purified using preparative TLC on silica gel with an eluent mixture of hexanes and ethyl acetate. This purified partially-reacted product was then mixed with 2 equivalents of p-anisidine and 2 equivalents of a different enone substrate along with the catalyst respective of the racemic or asymmetric version to obtain the unsymmetrical product.

Scheme 2.3.2G: ADARs of bicyclohexanone to obtain unsymmetrical product.
2.3.3 Product Characterization Data and Spectra

**1a:** Prepared according to the general procedure. Chromatography on SiO₂ (4:1, hexanes: EtOAc) afforded the product as brown oil (61.0% yield, dr = 6.40:1, ee = 96.7%). \([\alpha]_D^{25} = 57.4\) (c = 0.33, CHCl₃); Reaction time 24 hours. MS (ESI) (M-H)⁺ 611.4; MS calculated for \(\text{(C}_{40}\text{H}_{40}\text{N}_{2}\text{O}_{4}-\text{H})^+\) 611.3.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, \(t_r\) (minor) = 16.6 min., \(t_r\) (major) = 26.1 min., \(t_r\) (minor) = 38.6 min.

**Racemic 1a HPLC spectroscopy**
Asymmetric 1a HPLC spectroscopy

$^1$H NMR (500MHz, CDCl$_3$): $\delta = 7.39 - 7.34$ (m, 8H), 7.25 (s, 6H), 5.86 (dd, $J = 2.1, 5.3$ Hz, 2H), 4.10 (s, 2H), 3.43 (d, $J = 1.6$ Hz, 6H), 2.01 - 1.91 (m, 2H), 1.88 - 1.74 (m, 6H), 1.68 - 1.62 (m, 2H), 1.55 - 1.48 (m, 6H)
13C NMR (125MHz, CDCl3) δ = 165.1, 145.2, 143.1, 143.1, 134.4, 134.4, 133.7, 133.7, 129.6, 129.5, 128.7, 128.1, 126.7, 116.4, 116.4, 110.2, 51.6, 51.6, 45.8, 28.4, 28.4, 27.3, 23.1, 22.5

1b: Prepared according to the general procedure. Chromatography on SiO2 (6:1, hexanes:EtOAc) afforded the product as brown oil (68.1%, dr = 20.56:1, ee = 99.8%). [α]D 25 = 43.3 (c = 0.16, CHCl3); Reaction time 48 hours. MS (ESI) (M-H)+ 639.4; MS calculated for (C42H44N2O4-H)+ 639.3.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, \( t_r \) (minor) = 12.2 min., \( t_r \) (major) = 16.0 min., \( t_r \) (minor) = 23.8 min.

**Racemic 1b HPLC spectroscopy**

**Asymmetric 1b HPLC spectroscopy**
$^1$H NMR (500MHz, CDCl$_3$) δ = 7.28 (br. s, 5H), 7.26 (s, 3H), 7.20 (d, $J = 7.6$ Hz, 4H), 5.86 (d, $J = 4.8$ Hz, 2H), 4.08 (br. s, 2H), 3.44 (s, 6H), 2.38 (s, 6H), 1.95 (br. s, 2H), 1.92 - 1.78 (m, 6H), 1.77 (br. s, 2H), 1.74 (br. s, 2H), 1.69 - 1.60 (m, 4H)

1b $^1$H NMR spectroscopy

$^{13}$C NMR (125 MHz, CDCl$_3$) δ = 165.2, 143.2, 143.1, 142.3, 136.3, 134.3, 134.3, 133.6, 133.6, 129.6, 129.5, 129.4, 128.0, 116.7, 116.7, 110.3, 51.5, 45.3, 28.4, 27.3, 23.1, 22.5, 21.2

1b $^{13}$C NMR spectroscopy
1c: Prepared according to the general procedure. Chromatography on SiO$_2$ (5:1, hexanes: EtOAc) afforded the product as brown oil (55.5% yield, dr = 26.46:1, ee = 99.2%). $[\alpha]_{D}^{25} = 30.2$ (c = 0.16, CHCl$_3$); Reaction time 48 hours. MS (ESI) (M-H)$^+$ 671.4; MS calculated for (C$_{42}$H$_{44}$N$_2$O$_6$-H)$^+$ 671.3.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, $t_r$ (minor) = 49.6 min., $t_r$ (major) = 58.4 min., $t_r$ (minor) = 92.7 min.

Racemic 1c HPLC spectroscopy
Asymmetric 1c HPLC spectroscopy

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.27 - 7.31$ (m, 7H), 6.93 (d, $J = 7.79$ Hz, 5H), 5.86 (dd, $J = 1.15$, 5.04 Hz, 2H), 4.04 - 4.09 (m, 2H), 3.84 (d, $J = 1.37$ Hz, 6H), 3.45 (d, $J = 1.37$ Hz, 6H), 1.94 - 1.99 (m, 2H), 1.83 (d, $J = 9.16$ Hz, 2H), 1.73 - 1.77 (m, 2H), 1.65 - 1.68 (m, 2H), 1.44 - 1.57 (m, 8H)

1c $^1$H NMR spectroscopy
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 165.2, 158.5, 143.2, 143.1, 137.5, 134.3, 134.2, 133.5, 133.4, 129.5, 129.5, 129.0, 116.7, 114.1, 110.5, 55.4, 51.5, 44.9, 28.3, 27.3, 23.1, 22.5

$^{13}$C NMR spectroscopy

1c: Prepared according to the general procedure. Chromatography on SiO$_2$ (5:1, hexanes: EtOAc) afforded the product as brown oil (70.9% yield, dr = 16.42:1, $ee$ = 98.0%). [$\alpha$]$_D^{25}$ = 64.0 ($c$ = 0.55, CHCl$_3$); Reaction time 48 hours. MS (ESI) (M-H)$^+$ 647.3; MS calculated for (C$_{40}$H$_{38}$F$_2$N$_2$O$_4$-H)$^+$ 647.3.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, \( t_r \) (minor) = 15.4 min., \( t_r \) (major) = 25.1 min., \( t_r \) (minor) = 83.7 min.

Racemic 1d HPLC spectroscopy

Asymmetric 1d HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.33$ (dd, $J = 5.38$, 8.13 Hz, 7H), 7.08 (t, $J = 8.48$ Hz, 5H), 5.83 (d, $J = 5.04$ Hz, 2H), 4.13 (d, $J = 4.35$ Hz, 2H), 3.46 (s, 6H), 1.94 - 2.00 (m, 2H), 1.88 (s, 2H), 1.76 - 1.81 (m, 4H), 1.67 - 1.71 (m, 2H), 1.50 - 1.56 (m, 6H)

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 165.0$, 162.8, 160.8, 143.0, 141.0, 141.0, 134.5, 133.7, 129.6, 129.5, 129.4, 115.8, 115.5, 115.4, 110.0, 51.6, 45.0, 28.3, 27.3, 23.1, 22.4

$^{1d}$ $^1$H NMR spectroscopy

$^{1d}$ $^{13}$C NMR spectroscopy
1e: Prepared according to the general procedure. Chromatography on SiO₂ (8:1, hexanes: EtOAc) afforded the product as brown oil (72.8% yield, dr = 5.82:1, ee = 99.8%). [α]D²⁵ = 41.8 (c = 0.11, CHCl₃); Reaction time 48 hours. MS (ESI) (M-H)⁺ 763.4; MS calculated for (C₅₂H₄₈N₂O₄-H)⁺ 763.4.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, tᵣ (minor) = 38.4 min., tᵣ (major) = 57.1 min., tᵣ (minor) = 116.1 min.

Racemic 1e HPLC spectroscopy
Asymmetric 1e HPLC spectroscopy

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.41$ (s, 10H), 7.27 - 7.34 (m, 10H), 7.18 (s, 4H), 5.98 (dd, $J = 3.44, 5.04$ Hz, 2H), 4.87 - 4.94 (m, 4H), 4.14 (s, 2H), 1.95 - 2.04 (m, 2H), 1.77 - 1.88 (m, 6H), 1.67 (s, 2H), 1.46 - 1.56 (m, 6H)
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 164.5, 145.1, 143.0, 135.6, 134.5, 134.4, 133.8, 133.8, 129.7, 129.7, 128.7, 128.5, 128.3, 128.3, 128.2, 126.7, 117.0, 116.9, 110.3, 66.6, 45.9, 45.8, 28.4, 28.4, 27.3, 23.1, 22.4

$^{13}$C NMR spectroscopy

1f: Prepared according to the general procedure. Chromatography on SiO$_2$ (6:1, hexanes:EtOAc) afforded the product as brown oil (70.6% yield, dr = 17.05:1, $ee = 87.8$%). [$\alpha$]$_{D}^{25} = 46.2$ ($c = 0.22$, CHCl$_3$); Reaction time 24 hours. MS (ESI) (M-H)$^+$ 791.6; MS calculated for (C$_{54}$H$_{52}$N$_2$O$_4$-H)$^+$ 791.4.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 4: 96, 0.5 mL/min, 214 nm, $t_r$ (minor) = 30.0 min., $t_r$ (minor) = 35.7 min., $t_r$ (major) = 43.7 min.

Racemic 1f HPLC spectroscopy

Asymmetric 1f HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) δ = 7.27 - 7.34 (m, 12H), 7.21 - 7.25 (m, 5H), 7.15 - 7.20 (m, 5H), 5.95 - 6.00 (m, 2H), 4.86 - 4.95 (m, 4H), 4.12 (d, $J = 4.58$ Hz, 2H), 2.42 (s, 6H), 1.94 - 2.01 (m, 2H), 1.78 - 1.90 (m, 6H), 1.64 - 1.68 (m, 2H), 1.48 - 1.56 (m, 6H)

$^{13}$C NMR (125MHz, CDCl$_3$) δ = 164.5, 143.1, 142.2, 136.3, 135.6, 134.4, 133.7, 129.7, 129.4, 128.7, 128.3, 128.2, 128.1, 117.3, 110.5, 66.5, 45.4, 28.4, 27.4, 23.1, 22.5, 21.2

If $^1$H NMR spectroscopy

If $^{13}$C NMR spectroscopy
1g: Prepared according to the general procedure. Chromatography on SiO₂ (6:1, hexanes: EtOAc) afforded the product as brown oil (65.9% yield, dr = 24.52:1, ee = 99.3%). \([\alpha]_{D}^{25} = 37.0 \ (c = 0.10, \text{CHCl}_3)\); Reaction time 48 hours. MS (ESI) (M-H)⁺ 823.5; MS calculated for (C₅₄H₄₂N₂O₆-H)⁺ 823.4.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 6: 94, 0.5 mL/min, 214 nm, \(t_r\) (minor) = 101.4 min., \(t_r\) (minor) = 166.7 min., \(t_r\) (major) = 187.1 min.

Racemic 1g HPLC spectroscopy
Asymmetric 1g HPLC spectroscopy

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.28 (s, 10H), 7.19 - 7.23 (m, 4H), 7.12 - 7.15 (m, 4H), 6.91 (d, $J$ = 7.56 Hz, 4H), 5.92 (dd, $J$ = 2.29, 5.04 Hz, 2H), 4.80 - 4.92 (m, 4H), 4.04 (s, 2H), 3.81 - 3.83 (m, 6H), 1.84 - 1.93 (m, 4H), 1.77 - 1.83 (m, 4H), 1.70 - 1.75 (m, 4H), 1.59 - 1.65 (m, 4H)

1g $^1$H NMR spectroscopy
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 164.5, 158.5, 143.1, 143.0, 137.4, 135.6, 134.3, 134.2, 133.6, 133.5, 129.6, 129.6, 129.1, 128.4, 128.3, 128.3, 128.2, 117.3, 117.3, 114.1, 110.6, 66.5, 55.4, 44.9, 29.8, 28.4, 27.3, 23.1, 22.5

\(1g\) \(^{13}\)C NMR spectroscopy

\(1h\): Prepared according to the general procedure. Chromatography on SiO\(_2\) (5:1, hexanes: EtOAc) afforded the product as brown oil (64.6% yield, dr = 11.30:1, \(ee = 99.7\%\)). \([\alpha]_D^{25} = 55.6\) (c = 0.23, CHCl\(_3\)); Reaction time 24 hours. MS (ESI) (M-H)\(^+\) 799.4; MS calculated for (C\(_{52}\)H\(_{46}\)F\(_2\)N\(_2\)O\(_4\)-H)\(^+\) 799.3.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5:95, 0.5 mL/min, 214 nm, $t_r$ (minor) = 39.7 min., $t_r$ (major) = 55.5 min., $t_r$ (minor) = 82.0 min.

Racemic 1h HPLC spectroscopy

Asymmetric 1h HPLC spectroscopy
$^{1}$H NMR (500 MHz, CDCl$_3$) δ = 7.32 - 7.39 (m, 10H), 7.26 (s, 4H), 7.21 (s, 4H), 7.12 (t, $J = 8.02$ Hz, 4H), 5.95 (t, $J = 4.81$ Hz, 2H), 4.87 - 4.98 (m, 4H), 4.16 (s, 2H), 1.93 - 2.02 (m, 2H), 1.87 (s, 2H), 1.82 (d, $J = 7.10$ Hz, 4H), 1.69 (s, 2H), 1.48 - 1.59 (m, 6H)

$^{1}$h $^{1}$H NMR spectroscopy
\(^{13}\text{C} \text{NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta = 164.4, 162.8, 160.9, 142.9, 142.9, 140.9, 135.6, 134.5, 134.4, 133.8, 133.8, 129.7, 129.6, 129.5, 129.5, 128.5, 128.3, 128.3, 116.5, 116.4, 115.6, 115.4, 110.1, 66.6, 45.1, 29.8, 28.4, 28.4, 27.3, 23.1, 22.4

\[ \text{1h} \ ^{13}\text{C} \text{NMR spectroscopy} \]

\[ \text{1i: Prepared according to the general procedure. Chromatography on SiO}_2 \ (6:1, \text{hexanes:EtoAc}) \text{ afforded the product as brown oil (70.3\% yield, dr = 7.78:1, } ee = 99.3\%). \ [\alpha]_D^{25} = 31.7 \ (c = 0.18, \text{CHCl}_3); \text{ Reaction time 24 hours. MS (ESI) (M-H)}^+ 831.4; \text{ MS calculated for } (\text{C}_{52}\text{H}_{40}\text{Cl}_2\text{N}_2\text{O}_4-\text{H})^+ 831.3. \]
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, $t_r$ (minor) = 48.5 min., $t_r$ (major) = 55.5 min., $t_r$ (minor) = 82.6 min.

Racemic 1i HPLC spectroscopy

Asymmetric 1i HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.36 - 7.43 (m, 5H), 7.27 - 7.36 (m, 12H), 7.18 - 7.22 (m, 5H), 5.93 (d, $J$ = 5.27 Hz, 2H), 4.87 - 4.98 (m, 5H), 4.15 (d, $J$ = 4.81 Hz, 2H), 1.95 - 2.02 (m, 2H), 1.79 - 1.90 (m, 6H), 1.67 - 1.73 (m, 2H), 1.49 - 1.58 (m, 6H)

\[ \text{1i } ^1\text{H NMR spectroscopy} \]
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 164.3, 143.6, 142.8, 135.5, 134.6, 134.0, 132.4, 129.6, 129.4, 128.8, 128.4, 128.3, 128.2, 116.0, 109.8, 66.6, 45.2, 28.3, 27.3, 23.0, 22.4\)

2a: Prepared according to the general procedure. Chromatography on SiO\(_2\) via preparative TLC (2:1, hexanes: EtOAc) afforded the product as brown oil (73.5% yield, \(dr = 1.47:1\), \(ee\) (major) = 94.1%, \(ee\) (minor) = 87.1%). \([\alpha]_D^{25} = 63.4\) (\(c = 2.38\), CHCl\(_3\)); Reaction time 24 hours. MS (ESI) (M-H\(^+\)) = 564.4; MS calculated for (C\(_{36}\)H\(_{38}\)FNO\(_4\)-H\(^+\)) = 564.3.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 9: 91, 0.6 mL/min, 214 nm, \( t_r \) (major) = 39.4 min., \( t_r \) (minor) = 43.0 min., \( t_r \) (major) = 47.3 min., \( t_r \) (minor) = 61.2 min.

**Racemic 2a HPLC spectroscopy**

Asymmetric 2a HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) δ = 7.32 (t, $J$ = 5.84 Hz, 2H), 7.26 (s, 3H) 7.14 - 7.21 (m, 2H), 7.03 - 7.11 (m, 4H), 6.81 (d, $J$ = 7.10 Hz, 2H), 5.79 - 5.84 (m, 1H), 4.99 (t, $J$ = 12.72 Hz, 1H), 4.84 - 4.90 (m, 1H), 4.08 - 4.15 (m, 1H), 3.79 (s, 3H), 2.21 - 2.36 (m, 4H), 1.88 - 2.10 (m, 4H), 1.61 – 1.81 (m, 4H), 1.28 - 1.46 (m, 4H)

2a $^1$H NMR spectroscopy
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 211.9, 211.8, 211.4, 164.4, 164.3, 162.6, 162.6, 160.7, 160.6, 158.2, 158.1, 140.9, 140.8, 140.8, 136.7, 136.6, 135.4, 135.4, 134.6, 134.5, 134.4, 134.4, 134.1, 130.1, 129.4, 129.3, 129.3, 129.2, 128.2, 128.0, 115.5, 115.4, 115.4, 115.3, 115.2, 114.9, 113.7, 113.6, 108.8, 108.2, 66.4, 66.4, 55.2, 45.3, 44.3, 40.8, 40.7, 40.7, 40.7, 40.3, 40.1, 39.9, 37.9, 37.3, 32.9, 31.4, 29.8, 29.8, 29.7, 29.4, 27.4, 26.4, 26.2
2b: Prepared according to the general procedure. Chromatography on SiO$_2$ via preparative TLC (2:1, hexanes: EtOAc) afforded the product as brown oil (65% yield). Reaction time 48 hours. MS (ESI) (M-H)$^+$ 935.5; MS calculated for (C$_{60}$H$_{54}$F$_2$N$_2$O$_6$-H)$^+$ 935.4.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.20$ - 7.26 (m, 9H), 6.95 - 7.13 (m, 13H), 6.73 - 6.78 (m, 4H), 5.71 - 5.80 (m, 2H), 4.92 - 4.99 (m, 2H), 4.81 - 4.88 (m, 2H), 3.95 - 4.06 (m, 2H), 3.76 - 3.80 (m, 6H), 1.75 - 1.97 (m, 3H), 1.51 - 1.72 (m, 6H), 1.34 - 1.49 (m, 3H), 1.16 (br. s, 2H)
\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta = 164.6, 164.6, 162.7, 160.8, 158.2, 141.1, 141.0, 137.0, 136.9, 135.6, 134.8, 134.8, 134.6, 134.6, 134.5, 134.5, 134.2, 134.1, 130.3, 129.6, 129.5, 129.5, 129.4, 129.4, 129.3, 128.6, 128.4, 128.3, 128.1, 115.6, 115.6, 115.5, 115.4, 115.3, 115.3, 115.2, 115.2, 113.8, 109.2, 109.1, 108.9, 108.8, 108.7, 108.6, 108.5, 108.4, 66.6, 66.5, 55.4, 45.4, 45.3, 44.5, 44.4, 37.8, 37.6, 37.6, 37.5, 37.4, 36.9, 33.1, 32.8, 31.7, 31.4, 31.3, 31.0, 29.8, 27.6, 27.5, 27.3, 27.2, 27.2, 26.6, 26.4, 26.3, 26.1, 25.9, 25.8

\textbf{2b} \textsuperscript{13}C NMR spectroscopy
2c: Prepared according to the general procedure. Asymmetric version completed twice, once using usual $R$-form of catalyst, another using alternate $S$-form of catalyst. Chromatography on SiO$_2$ (5:1, hexanes: EtOAc) afforded the product as brown oil (71% yield). Reaction time 48 hours. MS (ESI) (M-H)$^+$ 927.4; MS calculated for (C$_{62}$H$_{60}$N$_2$O$_6$-H)$^+$ 927.4.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 12: 88, 0.6 mL/min, 214 nm, $t_r$ values = 22.0 min., 28.7 min., 32.4 min., 37.8 min., 44.8 min., 49.7 min., 59.8 min.

Racemic 2c HPLC spectroscopy
Asymmetric (R) 2c HPLC spectroscopy

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Asymmetric (S) 2c HPLC spectroscopy

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$^{1}H$ NMR (500 MHz, CDCl$_3$) $\delta =$ 7.27 (br. s, 6H), 7.16 - 7.18 (m, 6H), 7.14 (d, $J$ = 8.02 Hz, 4H), 7.11 (br. s, 2H), 7.09 (br. s, 4H), 6.75 - 6.79 (m, 4H), 5.80 - 5.85 (m, 2H), 4.94 - 5.01 (m, 2H), 4.82 - 4.87 (m, 2H), 3.95 - 4.04 (m, 2H), 3.80 (s, 6H), 2.32 - 2.37 (m, 6H), 1.94 (t, $J$ = 15.12 Hz, 2H), 1.74 – 1.95 (m, 6H), 1.51 – 1.62 (m, 6H)

$2c$ $^{1}H$ NMR spectroscopy
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 164.6, 158.2, 142.3, 137.2, 136.1, 135.7, 134.5, 134.5, 134.3, 134.0, 130.4, 129.4, 129.3, 128.3, 128.1, 128.1, 128.0, 127.9, 116.6, 116.2, 113.7, 109.7, 109.4, 108.9, 66.5, 66.4, 55.4, 45.7, 45.6, 44.8, 44.7, 37.7, 37.6, 37.5, 37.2, 36.9, 32.9, 32.9, 32.0, 31.9, 31.4, 29.8, 27.6, 27.4, 27.2, 26.8, 26.1, 25.6, 22.8, 21.1, 21.1, 14.2

$2c$ $^{13}$C NMR spectroscopy

$2d$: Prepared according to the general procedure. Chromatography on SiO$_2$ via preparative TLC (2:1, hexanes: EtOAc) afforded the product as brown oil (57% yield). Reaction time 48 hours. MS (ESI) (M-H)$^+$ 747.4; MS calculated for (C$_{48}$H$_{48}$N$_2$O$_6$-H)$^+$ 747.3.
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 8: 92, 0.7 mL/min, 214 nm, $t_r$ values = 31.8 min., 33.4 min., 47.7 min., 50.9 min., 58.3 min., 63.1 min., 74.9 min., 79.6 min.

Racemic 2d HPLC spectroscopy

Asymmetric 2d HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.28 - 7.35$ (m, 8H), 7.13 - 7.20 (m, 5H), 6.79 - 6.86 (m, 5H), 5.77 (t, $J = 4.35$ Hz, 2H), 3.98 - 4.09 (m, 2H), 3.79 (s, 6H), 3.46 (br. s, 6H), 1.79 - 1.98 (m, 4H), 1.70 - 1.79 (m, 2H), 1.60 - 1.69 (m, 3H), 1.39 - 1.58 (m, 5H)

2d $^1$H NMR spectroscopy
$^{13}$C NMR (125 MHz, CDCl$_3$) δ = 165.2, 165.1, 158.2, 145.3, 145.2, 137.2, 134.6, 134.5, 134.2, 130.4, 130.4, 130.4, 129.0, 128.7, 128.7, 128.6, 128.2, 128.1, 128.0, 127.7, 127.0, 126.6, 123.8, 118.5, 116.0, 115.6, 114.8, 114.2, 114.1, 113.7, 109.4, 109.1, 108.6, 106.3, 55.7, 55.4, 51.7, 46.1, 45.2, 45.2, 45.1, 37.7, 37.6, 37.2, 37.0, 32.9, 31.9, 31.4, 29.8, 27.5, 27.4, 27.4, 27.3, 26.8, 26.4, 26.1, 25.7, 25.4

$^{13}$C NMR spectroscopy
2e: Prepared according to the general procedure. Chromatography on SiO$_2$ via preparative TLC (2:1, hexanes: EtOAc) afforded the product as brown oil (45% yield). Reaction time 48 hours. MS (ESI) (M-H)$^+$ 841.6; MS calculated for (C$_{54}$H$_{51}$FN$_2$O$_6$-H)$^+$ 841.4.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 7.28 - 7.37 (m, 4H), 7.17 - 7.25 (m, 6H), 7.05 - 7.17 (m, 6H), 6.97 - 7.04 (m, 2H), 6.82 (d, $J$ = 8.48 Hz, 2H), 6.74 - 6.78 (m, 2H), 5.73 - 5.80 (m, 2H), 4.93 - 5.00 (m, 1H), 4.82 - 4.88 (m, 1H), 3.96 - 4.07 (m, 2H), 3.77 - 3.80 (m, 6H), 3.45 - 3.48 (m, 3H), 1.82 - 1.98 (m, 3H), 1.70 - 1.80 (m, 2H), 1.58 - 1.69 (m, 3H), 1.55 (d, $J$ = 13.52 Hz, 2H), 1.28 - 1.50 (m, 4H)
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 165.1, 165.1, 164.7, 164.6, 162.7, 160.8, 158.2, 145.3, 145.2, 141.1, 141.0, 137.2, 137.2, 137.0, 136.9, 135.6, 135.6, 134.8, 134.7, 134.6, 134.5, 134.5, 134.4, 134.3, 134.2, 130.4, 130.4, 130.3, 130.3, 129.7, 129.6, 129.5, 129.4, 129.4, 129.3, 129.0, 128.7, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 128.0, 128.0, 126.6, 116.0, 115.9, 115.7, 115.6, 115.6, 115.5, 115.4, 115.3, 115.3, 115.3, 115.2, 114.2, 113.7, 109.3, 109.3, 109.1, 109.0, 108.7, 108.6, 108.5, 66.6, 66.5, 55.4, 53.5, 51.7, 46.1, 46.0, 45.4, 45.2, 45.1, 44.5, 44.4, 37.9, 37.8, 37.7, 37.6, 37.6, 37.5, 37.5, 37.1, 37.1, 37.0, 36.9, 33.1, 32.8, 32.8, 32.7, 31.8, 31.7, 31.4, 31.3, 31.1, 29.8, 27.7, 27.5, 27.5, 27.4, 27.3, 27.2, 26.7, 26.4, 26.4, 26.1, 26.0, 25.8, 22.7, 14.2

$2e$ $^{13}$C NMR spectroscopy
**2f**: Prepared according to the general procedure. Chromatography on SiO₂ via preparative TLC (2:1, hexanes: EtOAc) afforded the product as brown oil (51% yield). Reaction time 48 hours. MS (ESI) (M-H)⁺ 931.4; MS calculated for (C₆₁H₅₇FN₂O₆-H)⁺ 931.4.

HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 10: 90, 0.6 mL/min, 214 nm, tᵣ values = 18.8 min., 20.3 min., 25.0 min., 28.3 min., 32.0 min., 37.2 min., 41.2 min., 46.7 min., 56.8 min., 62.0 min., 74.2 min., 80.4 min., 100.5 min., 107.3 min.

**Racemic 2f HPLC spectroscopy**
Asymmetric 2f HPLC spectroscopy
$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.22 - 7.26$ (m, 6H), 7.06 - 7.19 (m, 14H), 6.99 - 7.05 (m, 2H), 6.77 (d, $J = 8.48$ Hz, 4H), 5.72 - 5.86 (m, 2H), 4.97 (t, $J = 12.83$ Hz, 2H), 4.85 (m, 2H), 3.95 - 4.07 (m, 2H), 3.79 (s, 6H), 2.32 - 2.37 (m, 3H), 1.34 - 1.91 (m, 14H)
\[^{13}\text{C}\] NMR (125 MHz, CDCl\(_3\)) \(\delta = 164.7, 164.6, 162.7, 160.8, 158.2, 158.2, 142.3, 142.2, 141.1, 141.0, 137.3, 137.0, 136.9, 136.1, 135.7, 135.6, 134.8, 134.7, 134.6, 134.6, 134.5, 134.4, 134.2, 133.9, 130.3, 129.7, 129.5, 129.5, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 116.6, 116.5, 116.3, 116.2, 116.1, 115.6, 115.5, 115.4, 115.3, 115.3, 114.0, 113.8, 113.7, 109.6, 109.3, 109.3, 108.9, 108.8, 108.5, 66.5, 66.5, 66.3, 55.4, 55.3, 53.5, 45.7, 45.6, 45.4, 44.8, 44.7, 44.5, 44.4, 37.7, 37.6, 37.5, 36.9, 32.8, 32.8, 31.7, 31.3, 29.8, 27.5, 27.4, 27.3, 26.7, 26.6, 26.0, 25.7, 22.7, 21.1, 21.1, 14.2

\[2^f \] \[^{13}\text{C}\] NMR spectroscopy

\[3\]

3: Prepared according to the general procedure. Chromatography on SiO\(_2\) (8:1, hexanes: EtOAc) afforded the product as yellow/brown solid (69% yield, dr (racemic) = 1.19:1, dr (asymmetric) = 22.28:1, \(ee = 95.0\%\)). \([\alpha]_D^{25} = -27.1 \ (c = 0.23, \text{CHCl}_3)\); Reaction time 48 hours. MS (ESI) (M-Na\(^+\) 863.4; MS calculated for (C\(_{52}\)H\(_{54}\)Cl\(_2\)N\(_2\)O\(_4\)+Na\(^+\) 863.3.

120
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 3: 97, 0.5 mL/min, 214 nm, $t_r$ (major) = 32.6 min., $t_r$ (minor) = 45.6 min., $t_r$ (minor) = 80.2 min.

### Racemic 3 HPLC spectroscopy

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### Asymmetric 3 HPLC spectroscopy

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$^1$H NMR (500 MHz, CDCl$_3$) $\delta = 7.26 - 7.39$ (m, 14H), 7.18 (d, $J = 6.41$ Hz, 4H), 7.12 (d, $J = 7.79$ Hz, 4H), 4.87 (d, $J = 12.60$ Hz, 2H), 4.63 (d, $J = 12.60$ Hz, 2H), 3.80 (d, $J = 10.54$ Hz, 2H), 3.18 (br. s, 2H), 3.06 (d, $J = 12.83$ Hz, 2H), 2.47 (q, $J = 12.37$ Hz, 2H), 1.83 - 1.96 (m, 6H), 1.57 - 1.75 (m, 6H), 1.26 - 1.33 (m, 2H), 1.14 (d, $J = 12.37$ Hz, 4H), 0.93 (d, $J = 10.31$ Hz, 2H)

3 $^1$H NMR spectroscopy
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta = 172.5, 147.4, 141.9, 135.7, 131.9, 128.8, 128.5, 128.4,
128.2, 128.2, 128.1, 69.6, 66.2, 61.7, 45.0, 43.6, 30.1, 28.9, 26.4, 20.3

$^{13}$C NMR spectroscopy

3 $^{13}$C NMR spectroscopy
HPLC analysis chiralpak AD-H, i-PrOH: hexanes = 5: 95, 0.5 mL/min, 214 nm, \( t_r = 35.4 \) min., 52.1 min., 58.4 min., 90.6 min.

Racemic 4 HPLC spectroscopy

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta = 7.33 \) (s, 4H), 7.32 (s, 4H), 7.23 - 7.21 (m, 2H), 7.18 (d, \( J = 2.1 \text{ Hz} \), 1H), 7.16 (d, \( J = 1.8 \text{ Hz} \), 1H), 5.89 (d, \( J = 5.0 \text{ Hz} \), 2H), 4.09 (d, \( J = 4.8 \text{ Hz} \), 2H), 3.46 (s, 6H), 1.88 - 1.86 (m, 4H), 1.86 (d, \( J = 6.9 \text{ Hz} \), 4H), 1.79 - 1.74 (m, 4H), 1.74 - 1.71 (m, 4H)

\(^4\)H NMR spectroscopy
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Asymmetric Catalysis: A Tandem Nucleophile/Lewis Acid Promoted Synthesis of β-
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Catalyzed by Chiral β-Hydroxy Amines: A Mechanistic Study on Homogeneous
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Derivatives as Highly Efficient Bifunctional Organocatalysts for the Asymmetric


Part II- STAT3 Inhibitors

Chapter 3: Introduction and Background

3.1 STAT3 and its Relationship to Cancer

The group of signal transducer and activator of transcription (STAT) proteins are key factors in whether or not immune responses promote or inhibit cancer in tumor microenvironments. Inflammatory conditions start and promote oncogenic (tumor developing) transformations. Genetic and epigenetic changes in malignant cells can create an inflammatory microenvironment, further supporting tumor progression. STAT3 is linked to inflammation-associated tumorigenesis, initiated by changes in malignant cells and environmental factors.\(^1\)

The STAT proteins transduce signals through the cytoplasm and act as transcription factors, activating certain genes, in the nucleus. Overexpression and high levels of STAT3 are often detected in cancer patients and in cancer cell lines\(^1\) and the protein may induce tumor formation in nude mice. For example, hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. The median survival time for patients is less than one year and a mere 9% of patients survive five years. Evidence shows STAT3 plays an important role in HCC, promoting invasion and migration of HCC cells.\(^2\)

3.2 Process of STAT3 Activation and Inflammation

Inflammation and cancer are linked by oncogenic (intrinsic), as well as environmental (extrinsic) pathways (Figure 3.2A). The intrinsic pathway is activated by genetic or epigenetic changes in transformed cells. This includes changes that cause the overexpression or persistent activation of growth factor receptors that have intrinsic tyrosine kinase activity and cytokine receptors that activate Janus kinase (JAK)-family tyrosine kinases. Many receptors, as well as non-receptor tyrosine kinases can be activated by extrinsic pathways, environmental factors that are associated with cancer inflammation, such as ultraviolet radiation, chemical carcinogens, infection, stress, and cigarette smoke.\(^1\)

These activated tyrosine kinases phosphorylate STAT3, therefore activating the protein. Active STAT3 forms dimers that translocate to the nucleus, where they upregulate gene expression in genes involved in proliferation, survival, invasion, and metastasis. It also induces
expression of cytokines, chemokines, and other mediators that are associated with cancer-promoting inflammation. Receptors for these mediators can further activate STAT3, creating autocrine (same cell) and paracrine (nearby cell) feedforward loops, resulting in change to the genetic program and promotion of cancer inflammation from tumor cells to non-transformed stromal (connective tissue) cells.¹

One specific cytokine is interleukin-6 (IL-6). IL-6 is activated by a cytokine receptor, and through signal receptor proteins, leads to activation of Janus kinases, which activates STAT3.¹ People with HCC have higher levels of IL-6 than healthy controls and the IL-6 levels are higher in HCC stage III patients than patients with lower stages. STAT3 is the major transducer to relay the IL-6 signal to the nucleus and it is significantly correlated with the presence of HCC.²

![Figure 3.2A: Active STAT3. (Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer. 2009, 9, 802, Copyright 2009.)(Image)](image)

Among anti-tumor cells, are myeloid cells, including dendritic cells (DCs) and macrophages (Figure 3.2B). These stimulate T helper-1 (T_H1) adaptive immunity and can cause direct tumor cell death, associated with production of T_H1 cytokines (cell signalers), including interleukin-12 (IL-12) and interferon-γ (IFNγ). Activation of STAT1 and STAT4 is important for the T_H1 responses.¹
However, among pro-cancer cells are tumor-associated macrophages (TAMs), which no longer show anti-tumor effects when STAT3 is activated, and myeloid-derived suppressor cells (MDSCs), which are activated by STAT3. The STAT3 activity contributes to the expression of pro-cancer inflammatory mediators, including angiogenic factors, which influence blood vessel formation, and growth factors, which increase cell growth and proliferation. These STAT3-dependent factors are produced by tumor cells and endothelial cells, forming a network among cells, important for tumor angiogenesis and metastasis. 

Figure 3.2B: Cellular effects of STAT proteins. (Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cancer. 2009, 9, 804, Copyright 2009.)

The STAT3 protein is made of four domains: a coil (alpha-helix) domain, a SH2-dimerization domain, a DNA-binding domain, and a transactivation domain. The direct activation of STAT3 starts with phosphorylation of tyrosine705, followed by dimerization, nuclear translocation, and DNA binding. The binding cleft of the STAT3 SH2 domain is made of 3 pockets: pTyr705 (polar and basic), Leu706 (hydrophobic), and a side pocket of Ile597, Leu607, Thr622, Ile634 (hydrophobic).

3.3 Inhibition of STAT3

STAT3 inhibition is being studied with hopes to create a cancer therapy. Targeting STAT3 with small molecules can decrease proliferation of cancer cells and increase sensitivity to anticancer drugs. Different molecules have been created and tested to inhibit STAT3 through different mechanisms. The inhibitors can either directly inhibit STAT3 by targeting STAT3 or they can indirectly inhibit STAT3 by targeting associated proteins.
Some examples of indirect inhibitors include: small molecule pyridone-6, which inhibits JAK proteins\textsuperscript{5}, natural product-based resveratrol, which inhibits SRC-tyrosine kinase\textsuperscript{6}, and cucurbitacin analogues, which inhibit JAK proteins and others (Figure 3.3A).\textsuperscript{7,8}

![Chemical structures of pyridone-6, resveratrol, and cucurbitacin Q](image1)

**Figure 3.3A:** Indirect inhibitors of STAT3.

However, indirect inhibition has limitations due to targeting of upstream proteins, not STAT3 directly, leading to the inhibitors affecting other pathways. Additionally, this method affects STAT3 activation from one pathway, leaving STAT3 to be activated by other methods.

Direct inhibition of STAT3 focuses on stopping dimerization of STAT3, since this is the necessary step for STAT3 activation. Therefore, the main target is the phospho-tyrosine-SH2 domain. Methods to test for inhibition and create inhibitors include structure-based design of inhibitors and compound screening. There are inhibitors designed based on peptides, called peptidomimetics (Figure 3.3B)\textsuperscript{9-11}, and inhibitors not based on peptides (Figure 3.3C).\textsuperscript{12-15}

![Chemical structures of peptidomimetics](image2)

**Figure 3.3B:** Examples of peptidomimetics inhibiting STAT3.
Peptide-based inhibitors can strongly bind to STAT3, resulting in high affinities for the protein. However, they tend to have lower cellular permeability and quicker clearance from the bloodstream. Non-peptide-based inhibitors tend to have better cellular permeability and extended bioavailability, but lower affinity for STAT3.\(^{16}\)

Looking closely at specific inhibitors, examples of direct inhibitors are the FLLL series, which are analogues of curcumin (Figure 3.3D). The modifications to curcumin include eliminating the ability to enolize by replacing the hydrogen atoms with various groups and adding 3,4-dimethoxy substituents. These modifications were made to increase stability and efficacy, therefore interacting better with binding sites. The inhibitors did inhibit cancer cell colony growth and showed synergy with anticancer drugs. These analogues inhibited JAK2 and STAT3 phosphorylation by binding to the SH2 domain of STAT3.\(^{17,18}\)
Another inhibitor example used multiple ligand simultaneous docking (MLSD) to create inhibitors. MLSD virtually looks at common drug building blocks binding to the three main binding sites of the SH2 domain. The small molecular building blocks could then be linked and tested for inhibition. A variety of polar and nonpolar small molecules were studied. T2 and T3 were physically created and the predicted binding energies were consistent to results from a cell based assay. T2 and T3 showed good inhibitory activity against STAT3 and were better inhibitors than the drug Celecoxib, due to better binding affinity (Figure 3.3E).4

![Chemical structures of T2, T3, and Celecoxib](image_url)

**Figure 3.3E:** Using MLSD to create STAT3 inhibitors, compared to drug Celecoxib.

Although there has been much study done on STAT3 inhibitors, very few of the current inhibitors have been developed enough to be tested in clinical trials.12
Chapter 4: Synthesis and Design of STAT3 Inhibitors

4.1 XZH-5 Inhibitor

The Wang group has developed an inhibitor of STAT3, known as XZH-5 (Figure 4.1A). It was originally made to be a catalyst for asymmetric catalysis studies, but it was only a mediocre catalyst, and was instead found to have inhibitory activity of STAT3 phosphorylation.

XZH-5 was tested on rhabdomyosarcoma cells (cells that develop into skeletal muscle)\(^\text{19}\), HCC cells\(^\text{20}\), and breast and pancreatic cancer cells.\(^\text{21}\) XZH-5 had success in downregulating STAT3 phosphorylation. It inhibited STAT3 DNA-binding ability, downregulated STAT3 downstream genes, and blocked IL-6-induced STAT3 phosphorylation. It led to apoptosis and inhibited colony formation in cancerous cells. It selectively inhibited STAT3 over STAT1 in human rhabdomyosarcoma cells and enhanced the cytotoxicity of chemotherapeutic drugs in human breast and pancreatic cancer cell lines.\(^\text{19-21}\) The group has a patent on XZH-5, and therefore compounds with its general formula, based on its inhibition of STAT3 phosphorylation in HCC cell lines.\(^\text{2}\)

![Figure 4.1A: XZH-5, STAT3 inhibitor.](image)

Design of inhibitors is based on XZH-5 and is structure-based, assisted by computational modeling (Figure 4.1B). The design components are: an amino acid (proline or histidine), which binds to the polar and basic pTyr\(^705\) site, and an aromatic group (a substituted benzene ring), which binds to the hydrophobic side-pocket of isoleucine and leucine. Computational modeling has shown that XZH-5 binds to STAT3 through these two pockets in the SH2 domain.

The carboxylate ester mimics the phosphate binding to pTyr\(^705\), the aromatic group has decent hydrophobic side-pocket interaction, and a combination of urea and peptidyl linkers offers the right distance and hydrogen bonding to acceptors and donors in between the two sites.\(^\text{19}\) To achieve more effective binding, the next step is to attach a group that can bind to the hydrophobic Leu\(^706\) site.
Figure 4.1B: XZH-5 docked to the STAT3 SH2 domain binding sites.

4.2 Structure Activity Relationship (SAR) Analysis

Many XZH-5 analogues were created to examine structure-activity relationships (SARs) (Table 4.2A). The structure of the inhibitor was broken up into three parts: the head imidazole, the core, and the arene group (Figure 4.2). Compounds were found with IC$_{50}$ values as low as 6.5µM in breast cancer cell lines and 7.6µM in pancreatic cancer cell lines.$^{22}$

![Chemical Structure](image)

Figure 4.2: XZH-5 inhibitor-based derivatives.
Table 4.2A: XZH-5 derivatives synthesized.

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>Me</td>
<td>CH(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>1b</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1c</td>
<td>Me</td>
<td>Me</td>
<td>CH₂CH(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>1d</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1e</td>
<td>OH</td>
<td>Me</td>
<td>CH(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>1f</td>
<td>OH</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1g</td>
<td>Me</td>
<td>Me</td>
<td>Bn</td>
<td>CF₃</td>
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<tr>
<td>1h</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1i</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1j</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>1k</td>
<td>Me</td>
<td>Et</td>
<td>CH(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>1l</td>
<td>Me</td>
<td>Me</td>
<td>C(CH₃)₃</td>
<td>CF₃</td>
</tr>
<tr>
<td>1m</td>
<td>Me</td>
<td>H</td>
<td>CH(CH₃)₂</td>
<td>CF₃</td>
</tr>
<tr>
<td>1n</td>
<td>Me</td>
<td>Me</td>
<td>CH(CH₃)₂</td>
<td>H</td>
</tr>
</tbody>
</table>

The cell lines tested were the pancreatic cancer cell lines of PANC-1, HPAC, and SW1990 and the breast cancer cell line of MDA-MB-231 (Table 4.2B).

Table 4.2B: Inhibitor IC₅₀ values (µM) on four different cell lines.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>PANC-1</th>
<th>HPAC</th>
<th>MDA-MB-231</th>
<th>SW1990</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>24.7</td>
<td>17.4</td>
<td>15.5</td>
<td>17.9</td>
<td>18.9</td>
</tr>
<tr>
<td>1b</td>
<td>50-100</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;50-100</td>
</tr>
<tr>
<td>1c</td>
<td>16.8</td>
<td>13.2</td>
<td>10.6</td>
<td>9.1</td>
<td>12.4</td>
</tr>
<tr>
<td>1d</td>
<td>10.1</td>
<td>7.6</td>
<td>6.5</td>
<td>8.3</td>
<td>8.1</td>
</tr>
<tr>
<td>1e</td>
<td>&gt;100</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;100</td>
</tr>
<tr>
<td>1f</td>
<td>&gt;100</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;100</td>
</tr>
<tr>
<td>1g</td>
<td>16.1</td>
<td>9.6</td>
<td>6.8</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>1h</td>
<td>31.4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;31.4</td>
</tr>
<tr>
<td>1i</td>
<td>68.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;68.6</td>
</tr>
<tr>
<td>1j</td>
<td>85.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;85.5</td>
</tr>
<tr>
<td>1k</td>
<td>11.1</td>
<td>9.5</td>
<td>7.6</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>1l</td>
<td>8.8</td>
<td>9.8</td>
<td>9.4</td>
<td>8.5</td>
<td>9.1</td>
</tr>
<tr>
<td>1m</td>
<td>98.4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;98.4</td>
</tr>
<tr>
<td>1n</td>
<td>61.9</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;61.9</td>
</tr>
</tbody>
</table>

ND= not determined
When R₁ was replaced with hydrogen (1n), leaving only one trifluoromethyl group, there was a decline in inhibition, suggesting both trifluoromethyl groups are needed.²²

Looking at the imidazole substituent, when the R₂ methyl group was removed (1m), the inhibitory activity worsened. Another inhibitor was made without an imidazole ring, and the IC₅₀ value went up to 29.6µM. Additionally, when the R₂ methyl group was replaced by an ethyl group (1k), a longer substituent, the inhibitory activity was enhanced by about two-fold in all cancer cell lines tested. These data suggest the substituted imidazole ring is important.²² In addition, hydrolysis of the R₁ esters to free carboxylic acids (1e, 1f) led to decreases in activity, likely due to a decrease in lipophilicity or unfavorable electrostatics.²²

Coupling with different amino acids led to inhibitors with a range of various R₃ groups. With a methyl group (1b), the inhibitory activity is barely detectable. Bulkier groups (1c, 1d, 1l) showed better inhibition with IC₅₀ values near 10µM across tested cell lines. An aromatic phenyl group (1g) increased inhibitory activity, but expanding the aromatic group with an indole ring (1h) reduced inhibition by two-fold. Using a benzyl ester (1i, 1j) led to decreased activity.²²

Computational docking studies were conducted against the STAT3 SH2 domain, of which a homology model was rebuilt with Rosetta side chain repacking, improving reliability of docking results. The model was paired with a molecular modeling protocol allowing for full flexibility, creating realistic representations of the molecules in solution, XZH-5 analogues, and STAT3 SH2 domain. The docking model shows the CF₃-substituted phenyl ring packing against the Lys₆₂₆ and Gln₆₃₃ side chains. Also, the R₁ and R₃ groups participate in hydrophobic packing, reinforcing a position that encloses the pTyr₇₀₅ binding site by binding in SH2 domain pockets.²²

1c, 1d, and 1k have very similar backbone positions, likely due to tertiary carbon centers in the R₃ group, allowing the hydrogen atom to pack against a cleft created by Ile₆₃₄ and Gln₆₃₅. In 1l, the backbone and methyl ester positions are changed due to a R₃ quaternary carbon center. Each inhibitor makes similar electrostatic contacts with STAT3 despite minor alterations in backbone positions. 1c, 1d, 1g, 1k, and 1l can be used as guides for future SAR studies since these inhibitors obtained the best results.²²

4.3 Synthesis of Inhibitors

In the inhibitor synthesis, there is a main intermediate created that can be coupled with different amino acids (Scheme 4.3A).
Scheme 4.3A: Creation of \(N\)-ethyl histidine methyl ester intermediate.

First, \(L\)-histidine undergoes esterification. Thionyl chloride converts the carboxylic acid into a more reactive acyl chloride. Then methanol attacks and expels the chlorine, creating an ester. The next step involves carbonyldiimidazole, which would react with carboxylic acid. This is unwanted so the ester is made.

Next, a carbamide ring is created. The nitrogen atoms from the histidine attack the central carbon of the carbonyldiimidazole, creating a carbamide ring. This reaction leaves one open nitrogen atom on which the ethyl group can be added in the next step. Then, an ethylation occurs when the ethyl iodide, an electrophilic alkylation agent, adds an ethyl group onto the nitrogen atom, creating a salt.

Next, hydrolysis of the ring occurs when hydrochloric acid protonates the carbonyl oxygen, allowing water to attack the carbonyl carbon, breaking it from the amino groups. This reaction also changes the wanted ester back into a carboxylic acid, which will be changed back in the next step. Finally, esterification occurs again, as in the first step.
Scheme 4.3B: Preparation of XZH-5 from the intermediate.

XZH-5 is the intermediate (with a methyl group, not an ethyl group) coupled with valine (Scheme 4.3B). DCC (dicyclohexylcarbodiimide) converts the carboxylic acid to an ester, making it more reactive towards nucleophilic attack by the amine. HOBt (hydroxybenzotriazole) serves to decrease racemization and to enhance the efficiency of amide-bond formation. Next, the Boc group is deprotected with TFA, allowing for the amino group to react in the next step. Finally, the molecule is coupled with the aromatic group (3,5-bis(trifluoromethyl)phenyl isocyanate).
Scheme 4.3C: Preparation of inhibitor E1-21 from the intermediate.

Inhibitor E1-21 was created, which was the intermediate coupled with lysine, followed by deprotection of the Boc groups, then coupling with the aromatic moiety (3,5-bis(trifluoromethyl)phenyl isocyanate) (Scheme 4.3C). The IC$_{50}$ value found for E1-21 on the HPAC cell line was 27.7µM, which is comparable to inhibition with XZH-5.
Scheme 4.3D: Incomplete synthesis of a new inhibitor.

Another inhibitor that was attempted, but never completed, was this inhibitor of the intermediate coupled with aspartic acid, which has two different protecting groups (Scheme 4.3D). This means two deprotection steps are needed and two different aromatic groups could be added. However, after the first aromatic group was added, the compound was difficult to separate and purify.

Complete inhibitors were sent to collaborators at National Children’s Hospital in Columbus where inhibitory activity was tested. Also, these inhibitors, as well as others made by the group, were sent to NIH for testing.

4.4 Experimental Data for STAT3 Inhibitors (Section 4.3)

4.4.1 General Information

All reagents were obtained from Sigma-Aldrich, Acros Organics, and appTec and were of analytical grade. Solvents were obtained from commercial sources and dried utilizing standard procedures. NMR spectra were collected with Bruker-300 and Bruker-500 MHz spectrometers.
$^1$H NMR chemical shifts are referenced to residual solvent peak of CDCl$_3$ at 7.26 ppm or D$_2$O at 4.79 ppm. $^{13}$C NMR spectra were run with broadband decoupling and chemical shifts are referenced to residual solvent peak of CDCl$_3$ at 77.1 ppm. NMR chemical shifts are reported in ppm downfield of tetramethylsilane. NMR peak descriptors are abbreviated as such: br= broad, s=singlet, d=doublet, t= triplet, q= quartet, quin= quintet, m= multiplet. Monitoring of the reactions was performed on Silicycle silica gel 60 F254 silica gel plates (TLC). Flash column chromatography was carried out on Silicycle 60 silica gel (40-63μm). Mass spectra were collected on Bruker ESQUIRE-LCMS.

4.4.2 General Reaction Procedures

Scheme 4.4.2A: Preparation of intermediate structure.

To create the main intermediate (Scheme 4.4.2A), L-histidine was dissolved in dry MeOH and solution was cooled to 0°C. 1.4 equivalents of thionyl chloride were added dropwise. Solution was heated back to room temperature and then refluxed overnight. Solvent was evaporated to obtain a white solid, completing esterification. To create the carbamide ring, this product was mixed with one equivalent of CDI (carbonyldiimidazole) in DMF and refluxed for 4-7 hours. The solvent was evaporated and solution was mixed with sodium bicarbonate. The product was extracted ten times with DCM, dried with magnesium sulfate, and recrystallized with acetonitrile. This product was then mixed with 3 equivalents of ethyl iodide in acetonitrile. Refluxing overnight, evaporation of solvent, and recrystallization with MeOH was complete to finish ethylation. Product was refluxed for 48 hours at 110-120°C with HCl to complete hydrolysis of carbamide ring. To finish the intermediate, the esterification was run again. Product
was dissolved in dry MeOH and cooled to 0°C. 1.4 equivalents of thionyl chloride were added dropwise while keeping the solution at 0°C. Temperature was brought up to room temperature and reflux was done overnight. Solvent was evaporated and main intermediate was obtained.

**Scheme 4.4.2B: Preparation of XZH-5.**

To create XZH-5 (Scheme 4.4.2B), the intermediate (methylated, not ethylated) was coupled with valine by combining intermediate with 1.2 equivalents each of Boc-HN-Val-COOH, HOBt, and DCC along with 2 equivalents of TEA in DCM. The solution was stirred at room temperature for 5 days. The mixture was filtered and washed with aqueous sodium bicarbonate twice. The organic phase was dried with magnesium sulfate and solvent was evaporated. Silica column chromatography was performed (eluent of 50:1 DCM: MeOH, to 30:1 DCM: MeOH when product started eluting) and monitored by silica TLC plates and potassium permanganate. Deprotection of the Boc group was complete when product was mixed with DCM: TFA (3:1 v:v) at room temperature overnight, yielding an oily yellow product after solvent removal.

To couple with the aromatic moiety, the deprotected product (molecular weight including two equivalents of TFA since that previously protonated product) was dissolved in DCM with 3 equivalents of TEA and 1.2 equivalents of 3,5-bis(trifluoromethyl) phenyl isocyanate. The reaction was stirred for 48 hours at room temperature. The mixture was washed with aqueous sodium bicarbonate three times. The organic phase was dried with magnesium sulfate and solvent was evaporated. Silica gel column chromatography was used for purification (eluent 50:1 DCM: MeOH, to 30:1 DCM: MeOH when product started eluting) and monitored by silica TLC plates and UV light, yielding a white solid product.
Scheme 4.4.2C: Preparation of E1-21.

To create E1-21 (Scheme 4.4.2C), the intermediate was coupled with lysine by combining intermediate with 1.2 equivalents each of Boc-protected lysine, HOBt, and DCC along with TEA and DCM. The solution was stirred at room temperature for 5 days. The mixture was filtered and washed with sodium bicarbonate twice. The organic phase was dried with magnesium sulfate and solvent was evaporated. Silica column chromatography was performed (eluent of 30:1 DCM: MeOH) and monitored by silica TLC plates and potassium permanganate. Deprotection of the Boc groups was complete when product was mixed with DCM: TFA (3:1 v:v) at room temperature overnight and the solvent was removed.

To couple with the aromatic moiety, the deprotected product (molecular weight including three equivalents of TFA since that previously protonated product) was dissolved in DCM with 6 equivalents of TEA and 2.5 equivalents of 3,5-bis(trifluoromethyl) phenyl isocyanate. Reaction was stirred for 48 hours at room temperature. The mixture was washed with aqueous sodium bicarbonate three times. The organic phase was dried with magnesium sulfate and solvent was evaporated. Silica gel column chromatography was used for purification (eluent 40:1 DCM: MeOH, to 25:1 DCM: MeOH when product started eluting) and monitored by silica TLC plates and UV light, yielding white solid product.
The attempted inhibitor (Scheme 4.4.2D) coupled the intermediate with aspartic acid by combining intermediate with 1.2 equivalents each of Boc-Asp(OBzl)-OH, HOBt, and DCC along with TEA and DCM. The solution was stirred at room temperature for 5 days. The mixture was filtered and washed with sodium bicarbonate twice. The organic phase was dried with magnesium sulfate and the solvent was evaporated. Silica column chromatography was performed (eluent of 30:1 DCM: MeOH) and monitored by silica TLC plates and potassium permanganate. NMR data and TLC seemed to show the product, but included impurities. The reaction was repeated, this time using 40:1 DCM: MeOH eluent for silica column, leading to cleaner data. Deprotection of the Boc group was complete when product was mixed with DCM: TFA (3:1 v:v) at room temperature for 45 minutes (lower time as not to deprotect OBzl group) and solvent was removed.

To couple with the aromatic moiety, the deprotected product (molecular weight including two equivalents of TFA since that previously protonated product) was dissolved in DCM with 6 equivalents of TEA and 2.5 equivalents of 3,5-bis(trifluoromethyl) phenyl isocyanate. The reaction was stirred for 48 hours at room temperature. Mixture was washed with aqueous sodium bicarbonate three times. Organic phase was dried with magnesium sulfate and solvent was evaporated. Silica gel column chromatography was used for purification (eluent 40:1 DCM:
MeOH) and monitored by silica TLC plates and UV light. TLC showed multiple tiny spots and after column, there was too little product for the next deprotection so the reaction was repeated. Again, the assumed product was isolated. $^1$H NMR data indicated the formation of the product, but also impurities. Two spots showed up on TLC plate. Another silica column was performed with 40:1 DCM: MeOH eluent. The darker (top) spot of the two was collected and $^1$H NMR looked similar to before. The bottom spot was not the desired product. Overall the reaction needs improvement. An idea is to repeat deprotection and decant with diethyl ether to remove all TFA. Also, in the coupling reaction 10 (instead of 6) equivalents of TEA could be used.

4.4.3 Product Characterization Data and Spectra

4.4.3.1 Spectra for Primary Intermediate

$^1$H NMR (300 MHz, D$_2$O): $\delta = 8.70$ (s, 1H), 7.44 (s, 1H), 4.50 (dt, $J = 2.74, 6.75$ Hz, 1H), 3.84 (s, 3H), 3.46 (t, $J = 7.27$ Hz, 2H)
\(^1\)H NMR (500 MHz, D\(_2\)O): \(\delta = 8.22\) (s, 1H), 6.89 (s, 1H), 4.59 (dd, \(J = 4.47, 5.84\) Hz, 1H), 3.75 (s, 3H), 3.36 - 3.41 (m, 2H)

\(^1\)B \(^1\)H NMR spectroscopy

\(^1\)H NMR (500 MHz, D\(_2\)O): \(\delta = 9.44\) (s, 1H), 7.51 (s, 1H), 4.74 - 4.76 (m, 1H), 4.32 (q, \(J = 7.33\) Hz, 2H), 3.80 (s, 3H), 3.51 (d, \(J = 5.50\) Hz, 2H), 1.55 (t, \(J = 7.45\) Hz, 3H)

\(^1\)C \(^1\)H NMR spectroscopy
$^1$H NMR (300 MHz, D$_2$O): $\delta = 8.71$ (s, 1H), 7.48 (s, 1H), 4.30 - 4.37 (m, 1H), 4.21 (q, $J = 7.24$ Hz, 2H), 3.40 (d, $J = 6.42$ Hz, 2H), 1.47 (dt, $J = 1.04, 7.32$ Hz, 3H)

$^1$D $^1$H NMR spectroscopy

$^1$H NMR (500 MHz, D$_2$O): $\delta = 8.74$ (s, 1H), 7.51 (s, 1H), 4.50 (t, $J = 6.87$ Hz, 1H), 4.24 (q, $J = 7.33$ Hz, 2H), 3.85 (s, 3H), 3.38 - 3.53 (m, 2H), 1.50 (t, $J = 7.33$ Hz, 3H)

$^{1E}$ $^1$H NMR spectroscopy
4.4.3.2 Spectra for XZH-5

\[ \text{H NMR (500 MHz, D}_2\text{O): } \delta = 8.56 \text{ (s, 1H), 7.27 (s, 1H), 4.82 - 4.85 (m, 1H), 3.82 (s, 3H), 3.81 (d, } J = 5.50 \text{ Hz, 1H), 3.74 (s, 3H), 3.32 (dd, } J = 5.84, 15.69 \text{ Hz, 1H), 3.18 (dd, } J = 8.48, 15.58 \text{ Hz, 1H), 2.15 - 2.27 (m, 1H), 0.99 (dd, } J = 6.87, 9.16 \text{ Hz, 6H)} \]

\[ \text{H NMR spectroscopy} \]
$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.58$ (s, 1H), 8.36 (d, $J = 6.87$ Hz, 1H), 7.79 (s, 2H), 7.32 (s, 2H), 6.81 (d, $J = 8.94$ Hz, 1H), 6.69 (s, 1H), 4.68 - 4.76 (m, 1H), 4.37 (dd, $J = 6.76$, 8.82 Hz, 1H), 3.64 (s, 3H), 3.56 (s, 3H), 3.08 (d, $J = 5.73$ Hz, 2H), 2.05 - 2.17 (m, 1H), 1.03 (d, $J = 6.87$ Hz, 3H), 0.96 (d, $J = 6.64$ Hz, 3H)

XZH-5 $^1$H NMR spectroscopy

4.4.3.3 Spectra for E1-21
$^1$H NMR (300 MHz, D$_2$O): δ = 8.63 (s, 1H), 7.35 (s, 1H), 4.11 - 4.21 (m, 2H), 4.01 (t, $J =$ 6.33 Hz, 1H), 3.70 - 3.77 (m, 3H), 3.31 (d, $J =$ 2.83 Hz, 2H), 3.13 - 3.23 (m, 1H), 2.97 (t, $J =$ 7.27 Hz, 2H), 1.86 - 1.94 (m, 2H), 1.63 - 1.72 (m, 2H), 1.39 - 1.48 (m, 5H)

3A $^1$H NMR spectroscopy
$^1$H NMR (500 MHz, CD$_3$OD): $\delta = 7.98$ (s, 2H), 7.97 (s, 2H), 7.51 (s, 1H), 7.48 (s, 1H), 7.45 (s, 1H), 6.97 (s, 1H), 4.66 (dd, $J = 4.81, 8.94$ Hz, 1H), 4.34 (dd, $J = 5.73, 7.79$ Hz, 1H), 3.92 (q, $J = 7.18$ Hz, 2H), 3.69 (s, 3H), 3.24 (t, $J = 6.76$ Hz, 2H), 3.09 (dd, $J = 4.81, 14.89$ Hz, 1H), 2.91 - 3.02 (m, 1H), 1.79 - 1.90 (m, 1H), 1.66 - 1.76 (m, 1H), 1.61 (quin, $J = 7.16$ Hz, 2H), 1.47 - 1.54 (m, 2H), 1.32 (t, $J = 7.33$ Hz, 3H)
$^{13}$C NMR (126 MHz, CD$_3$OD): $\delta$ = 174.9, 173.3, 157.5, 156.6, 143.5, 143.2, 137.9, 137.4, 133.6, 133.5, 133.3, 133.2, 133.0, 132.8, 132.7, 128.1, 125.9, 125.9, 123.7, 123.7, 121.6, 118.9, 118.2, 115.6, 115.4, 54.6, 54.0, 52.8, 49.5, 49.5, 49.3, 49.2, 48.8, 48.7, 48.5, 42.9, 40.6, 33.6, 30.9, 30.7, 23.8, 16.6

**E1-21 $^{13}$C NMR spectroscopy**

**E1-21 MS (ESI):** 836.4 [M+H]$^+$, calculated for (C$_{33}$H$_{33}$F$_{12}$N$_7$O$_5$+H)$^+$: 836.2.

4.4.3.4 Spectra for Attempted Inhibitor
$^1$H NMR (500 MHz, D$_2$O): $\delta = 8.60$ (s, 1H), 7.40 – 7.44 (m, 5H), 7.31 (s, 1H), 5.21 (s, 2H), 4.67 - 4.74 (m, 1H), 4.38 (t, $J = 5.84$ Hz, 1H), 4.15 (q, $J = 7.41$ Hz, 2H), 3.68 (s, 3H), 3.27 (dd, $J = 6.07$, 15.69 Hz, 1H), 3.16 - 3.19 (m, 1H), 3.12 (d, $J = 5.50$ Hz, 2H), 1.44 (t, $J = 7.45$ Hz, 3H)

4A $^1$H NMR spectroscopy
$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 10.87$ (br. s, 1H), 8.09 (s, 2H), 7.85 (s, 1H), 7.68 (s, 1H), 7.43 (s, 1H), 7.30 - 7.39 (m, 1H), 6.77 (s, 1H), 6.65 (s, 1H), 5.16 (s, 1H), 4.87 (d, $J = 3.97$ Hz, 2H), 4.58 - 4.77 (m, 1H), 4.16 - 4.28 (m, 1H), 3.94 (q, $J = 7.36$ Hz, 2H), 3.76 (s, 3H), 3.34 (dd, $J = 4.06$, 14.82 Hz, 2H), 2.92 - 3.12 (m, 2H), 2.37 - 2.52 (m, 1H), 1.43 (t, $J = 7.37$ Hz, 3H)

4B $^1$H NMR spectroscopy
Part II References


