Development of Helical Chiral Catalysts and Their Applications in Asymmetric Catalysis

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UNIVERSITY OF MIAMI

DEVELOPMENT OF HELICAL CHIRAL CATALYSTS AND THEIR APPLICATIONS IN ASYMMETRIC CATALYSIS

By

Zhili Peng

A DISSERTATION

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DEVELOPMENT OF HELICAL CHIRAL CATALYSTS AND THEIR
APPLICATIONS IN ASYMMETRIC CATALYSIS

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The design and development of novel chiral catalysts for efficient construction of carbon-carbon bonds, especially in an enantioselective manner, stays as a major goal for organic chemists. In the last two decades, various organocatalysts have been developed to solve important problems in asymmetric organic synthesis. Novel chiral catalysts based on previously unexplored 1-azahelicenes have been developed by our group and found great applications in mechanistically unrelated reactions. As part of Ph.D. research projects, the design and development of new helical chiral catalysts based on 11, 12-benzo-1-aza[6]helicene N-oxide and their applications in asymmetric synthesis are presented in this thesis.

First, the development of a diastereomeric salt-mediated optical resolution of 11,12-benzo-1-aza[6]helicene will be discussed. This process performed best when (-)-dibenzoyl-L-tartaric acid monohydrate was used as resolving agent and acetonitrile was used as solvent.
Second, substrate scope of the helical chiral hydrogen-bond donor catalyzed nitroalkene Diels-Alder reaction has been extensively studied. An efficient, synthetically versatile synthesis to access a new class of dienes has been designed and developed. The activity profiles of these new dienes have also been tested in the context of nitroalkene Diels-Alder reactions.

Third, a series of novel helical chiral catalysts has been designed and synthesized via simple reactions. These catalysts include both Lewis base catalysts and Brønsted acid catalysts. Structures of some of the catalysts have been elucidated unambiguously by X-ray crystallography.

Last, the asymmetric allylation of ketoimines by helical chiral pyridine N-oxides have been developed to access enantiomerically pure α-trisubstituted homoallylic amines. Study revealed that a product inhibition probably occurred in this reaction, and extensive efforts have been devoted to solve this problem. Good yield and high level of selectivity has been realized with this allyltrichlorosilane-mediated reaction by utilizing a Lewis basic solvent.
For My Family
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LIST OF ABBREVIATIONS

BINOL  1, 1′-bi-2-naphthol
DDQ   2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone
DMAP  4-dimethylaminopyridine
DMF   N, N′-dimethylformamide
DMPU  1, 3-dimethyl-3, 4, 5, 6-tetrahydro-2(1H)-pyrimidinone
DMSO  dimethyl sulfoxide
ee    enantiomeric excess
equiv. equivalent
HMPA  hexamethylphosphoramide
HPLC  high performance liquid chromatography
HRMS  high-resolution mass spectra
LDA   lithium diisopropylamide
LUMO  lowest unoccupied molecular orbital
mCPBA meta-chloroperoxybenzoic acid
NaBArF$_{24}$ sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate
NMR   nuclear magnetic resonance
TADDOL α, α, α′, α′-tetraaryl-1, 3-dioxolan-4, 5-dimethanol
3c-4e  three-center four-electron bonding
THF   tetrahydrofuran
TLC   thin-layer chromatography
VAPOl 2, 2′-diphenyl-(4-biphenanthrol)
CHAPTER 1. INTRODUCTION

1.1. Organocatalysis

1.1.1. The History of Organocatalysis

Organocatalysis, also known as metal-free catalysis, was coined by MacMillan in 2000.\(^1\) It is referred to a research area where chemical transformations are catalyzed by small organic molecules.\(^2\) Although only in the last two decades has the organic synthetic community witnessed the vast development of organocatalysis, it has a long history in asymmetric synthesis.

Bredig and Fiske\(^3\) documented the first report of organocatalysis in 1912, where a cinchona alkaloids catalyst promoted the addition of HCN to benzaldehyde with modest enantioselectivities. Much after this, in 1960, Pracejus and coworkers\(^4\) reported the development of an asymmetric ketene methanolysis reaction, where the addition of methanol to ketene \(1\) was catalyzed by the quinine derivative catalyst \(2\) (eq 1, Scheme 1.1). Moderate enantioselectivities were achieved in these reactions. The Hajos-Parrish-Eder-Sauer-Wiechert reaction,\(^5\) discovered in 1971, was considered to be a milestone for small organic molecule catalyzed asymmetric synthesis. This L-proline (5) catalyzed Robinson annulation of triketone \(4\) furnished the bicycle aldol product \(6\) with a high level of enantioselectivity (eq 2, Scheme 1.1). In these early studies, however, the focus was mostly put on the individual chemical reactions that had been achieved; the potential
benefits of applying organocatalysts or the demonstration of new organocatalysis concepts were not emphasized.

Scheme 1.1. Early developments of organocatalysis

Figure 1.1. Selected examples of organocatalysts developed in 1990s
However, with the successful development of some small organic molecule catalyzed reactions, such as enantioselective epoxidation of simple alkenes and asymmetric Strecker reactions in the late 1990s (Figure 1.1), the synthetic community began to realize, for the first time, that small organocatalysts could be of great help in solving important problems in asymmetric chemical synthesis.

Scheme 1.2. Reactions that launched organocatalysis

The awareness paved the way for the effective launch of organocatalysis by two discoveries in 2000: one is the development of enamine catalysis of intermolecular aldol reaction by List and coworkers (eq 1, Scheme 1.2); and the other is the development of iminium catalysis of asymmetric Diels-Alder reactions by MacMillan and coworkers (eq 2, Scheme 1.2). These studies demonstrated the broad applicability of organocatalysts as well as the potential advantages of organocatalysis over its counterpart organometallic catalysis. 1) Generally, most of the organocatalysts are either directly available from naturally occurring “chiral pool” as single enantiomer (i.e. alkaloids), or could be synthesized from simple chemical transformations, making organocatalysts relatively inexpensive. 2) Due to their inherent property, organic molecules are generally
Insensitive to oxygen and moisture, making organocatalysts are easy to synthesize, store and use. There is no necessary to use inert gas atmosphere, special reaction vessels, or anhydrous solvents and reagents. 3) Unlike most of transition metal complexes, small organic molecules used as organocatalysts are relatively non-toxic and safe to both researcher themselves and the environment. The combination of these factors, and more importantly, the disclosure of the underlying concepts of organocatalysis by the aforementioned publications are the main reason that the field of organocatalysis has thrived quickly in the last two decades.²

1.1.2. The Classifications of Organocatalysis

1.1.2.1. Classification Based on Reaction Mechanism

Research groups from all over the world have developed a vast number of organocatalysts in the short amount of time since 2000.⁹ In order to better study these catalysts for the future design and development of new organocatalysts, the great number of organocatalytic reactions have been categorized into different families. One of the most popular classifications was suggested by List in 2005, which classifies most of the organocatalysts as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids based on the functionalities of the organocatalysts and their catalytic mechanism.¹⁰
1.1.2.1.1. Lewis Base Catalysis

A typical Lewis base catalysis cycle (Scheme 1.3) starts with the nucleophilic attacking to the substrate (S) by a Lewis base catalyst (B:\). The resulted complex (B\(^+\)S\(^-\)) then undergoes reaction and forms an intermediate complex (B\(^+\)P\(^-\)), which is followed by the generation of product (P) and release of catalyst (B:\).

Scheme 1.3. Simplified Lewis base catalysis cycle

Scheme 1.4. Selected examples of Lewis base catalysis
Most of the Lewis base organocatalysts, which mainly utilize N, O, P, S and C as their activation center, can activate substrates by converting them into activated intermediates such as iminium ions, enamines, acyl ammonium ions, and ammonium enolates (Scheme 1.4).\(^{10}\)

In *iminium catalysis*, catalysts are often primary or secondary amines; they activate the acceptor molecule by decreasing the electron density at the reactive center through the formation of iminium intermediate. In the pioneering work of the enantioselective Diels-Alder reaction of \(\alpha, \beta\)-unsaturated aldehydes and ketones with diene, MacMillan and coworkers described the concept of iminium catalysis for the first time.\(^1\) In their reaction, a less reactive conjugated aldehyde 8 was activated by forming an iminium intermediate (9) with catalyst 7. Then the reaction proceeded smoothly between the intermediate 9 (with a lower LUMO energy) and the diene 10 to furnish the product 11 with good enantioselectivity (Scheme 1.5).

![Scheme 1.5. Enantioselective iminium catalysis reported by MacMillan et al.](image-url)
Thereafter, the concept of activating unsaturated carbonyl compounds into more reactive iminium ions have been utilized in many other transformations, including [3+2]-cycloaddition reactions, Friedel-Crafts reaction, Mukaiyama-Michael reactions, Michael addition reactions, transfer hydrogenation reactions, epoxidation reactions, and etc.

**Scheme 1.6.** Enantioselective enamine catalysis reported by List *et al.*

In *enamine catalysis*, an enamine intermediate is formed *via* the deprotonation of an iminium ion. The activated enamine intermediate then can react with different kinds of electrophiles. The Hajos-Parrish-Eder-Sauer-Wiechert reaction, an intramolecular aldol reaction catalyzed by proline, is probably the very first example of asymmetric enamine catalyzed reaction. However, its counterpart, the intermolecular aldol reaction was only developed after almost 30 years later. The less reactive ketone 12 was activated by
forming an enamine intermediate (14) via iminium ion 13 with catalyst 5. Then the reaction proceeded smoothly between enamine 14 (with a higher HOMO energy) and electrophile 15 to form intermediate 16 that eventually released catalyst 5 and produced final product 17 (Scheme 1.6). After this, a series of enamine-catalyzed reactions has been developed. These reactions include Mannich reaction,13 Michael reaction,14 a-functionalization of aldehydes and ketones,15 and etc.

In acyl-ammonium catalysis, the acyl-ammonium ion intermediate is formed by the addition of a Lewis base catalyst to the acyl substrate. One of such examples is the acylation of alcohols catalyzed by 4-dimethylaminopyridine (DMAP) and DMAP-based catalysts (Scheme 1.7).16 A lot of transformations have been carried out based on this catalysis,17 such as the kinetic resolution of secondary alcohols, protonation of ketenes, and halogenation reactions.

**Scheme 1.7.** DMAP-based organocatalysis developed by Fu et al.

In ammonium enolate catalysis, the active intermediate – ammonium enolate is formed via addition of Lewis base catalysts to electrophilic substrates. Then the activated intermediate could further react with various electrophiles. Morita-Baylis-Hillman
reaction\textsuperscript{18} is such a reaction that undergoes ammonium enolate catalysis. Besides the above-mentioned four types of catalysis, there are also some other types of reactions falling into the category of Lewis base catalysis. Such catalysis includes carbene catalysis,\textsuperscript{19} ylide catalysis, and \textit{etc.}

\subsection{1.1.2.1.2. Brønsted Base Catalysis}

In general, Brønsted base catalysis shares the same mechanism as Lewis base catalysis does, except in the first step it involves a (partial) deprotonation of the substrate (SH) (Scheme 1.8).

\begin{center}
\textbf{Scheme 1.8. Simplified Brønsted base catalysis cycle}
\end{center}

\begin{center}
\textbf{Scheme 1.9. Brønsted base catalysis in Diels-Alder reaction}
\end{center}
The Diels-Alder reaction of anthrone (19) with various dienophiles (e.g. 21) catalyzed by Brønsted bases is one of the most common Brønsted base catalyzed reactions\(^2\) (Scheme 1.9). Asymmetric hydrocyanation reactions\(^7b, 21\) could be also considered as Brønsted base catalyzed reactions, since the deprotonation of hydrogen cyanide by the catalysts are most likely involved in the reactions.

1.1.2.1.3. Lewis Acid Catalysis

Generally speaking, Lewis acid catalysis shares a quite similar mechanism as Lewis base catalysis: the catalytic cycle starts with the activation of the substrate (S\(_i\)) by forming the intermediate A\(^+\)S\(^-\), the activated complex (A\(^-\)S\(^+\)) then undergoes a reaction and forms complex (A\(^-\)P\(^+\)), followed by the generation of product (P\(_i\)) and release of catalyst (A) (Scheme 1.10).

![Scheme 1.10. Simplified Lewis acid catalysis cycle](image)

In the field of organocatalysis, phase transfer catalysis is an important class that falls into the category of Lewis acid catalysis. The first efficient chiral phase transfer catalyst (23) was developed by a group of scientists at Merck in 1984.\(^2\) Five years later, O'Donnell
and coworkers\textsuperscript{23} developed a comprehensive reaction based on the same chiral scaffold with a different counter ion. Lygo\textsuperscript{24} and Corey\textsuperscript{25} independently developed the second generation of organo phase transfer catalysts with much higher efficiency. Maruoka and coworkers\textsuperscript{26} developed highly efficient and enantioselective catalysts (27) based on a different chiral scaffold (Figure 1.2). After this, many other phase transfer catalysts have been developed and tested in reactions such as alkylation reactions, Michael addition reactions, aldol reactions, Mannich reactions and epoxidation reactions.\textsuperscript{27}

![Figure 1.2. Selected phase transfer organocatalysts](image)

**Figure 1.2.** Selected phase transfer organocatalysts

![Scheme 1.11. Epoxidation catalyzed by chiral dioxirane](image)

**Scheme 1.11.** Epoxidation catalyzed by chiral dioxirane
Shi and co-workers\textsuperscript{28} developed another important class of Lewis acid catalysis. The epoxidation of olefins \textsuperscript{30} were carried out with high efficiency by chiral dioxiranes \textsuperscript{29} generated in \textit{situ} from the chiral ketone \textsuperscript{28} and Oxone (Scheme 1.11).\textsuperscript{6a}

\subsection*{1.1.2.1.4. Brønsted Acid Catalysis}

In general, Brønsted acid catalysis shares the same mechanism as Lewis acid catalysis does, except in the first step it involves a (partial) protonation of the substrate (S:) by the Brønsted acid catalyst (Scheme 1.12).

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme12.png}
\end{center}

\textbf{Scheme 1.12.} Simplified Brønsted acid catalysis cycle

Based on their acidity\textsuperscript{29} (Figure 1.3), most of the Brønsted acid catalysts could be classified into three groups: the first one is catalysts derived from (thio) urea\textsuperscript{7a,30} (32), TADDOL\textsuperscript{31} (33) and BINOL\textsuperscript{32} (34); the second group is strong Brønsted acids, such as chiral phosphoric acids and their derivatives\textsuperscript{33} (35); and the last type is recently developed chiral dithiophosphoric acids\textsuperscript{34} (36), which are much stronger acids than chiral...
phosphoric acids. Due to the difference in their acidity, these chiral acid organocatalysts have quite different mechanism activating substrates (Scheme 1.13).

![Diagram of catalysts](image)

**Figure 1.3.** Selected examples of chiral Brønsted acid organocatalysts

![Diagram of activation modes](image)

**Scheme 1.13.** Simplified activation modes of Brønsted acid catalysts

Catalysts belonging to the first group are normally weakly acidic and thus considered to interact with substrates only through hydrogen-bonding interactions (type I, Scheme 1.13). Jacobsen’s thiourea derived catalyst system is such an example. These Schiff base catalysts (Figure 1.4) were initially identified and optimized for asymmetric Strecker reactions from parallel synthetic libraries. Later it was found that they were also excellent catalysts for asymmetric Mannich and hydrophosphonylation reactions. It’s generally believed that they activate the substrates through the hydrogen bonds donated from the acidic (thio) urea hydrogens.
Figure 1.4. Selected examples of Jacobsen's (thio) urea catalysts

Scheme 1.14. Chiral diols catalyzed (hetero) Diels-Alder reactions

Rawal and co-workers\textsuperscript{31a, 31b} have found that the Diels-Alder and hetero Diels-Alder reactions of a very reactive amino-siloxy dienes can be accelerated by the TADDOL derived chiral alcohol, rendering good to excellent enantioselectivity (Scheme 1.14). It's
proposed that the single hydrogen bonding interaction with a hydroxyl group of the chiral catalyst activates the dienophiles, which is supported by an x-ray crystallography study in a similar reaction.\textsuperscript{35}

Due to the nature of higher acidity of phosphoric acids, it’s generally believed that in some reactions this type of catalysts can (partially) protonate substrates (e.g. an imine or carbonyl), generating a species that can hydrogen-bond with the conjugate base of the chiral Brønsted acid\textsuperscript{33} (type II, Scheme 1.13). This hydrogen bond then serves as an anchor to keep a chiral environment close to the reaction center and also contributes to the favorable molecular organization in the transition state.

![Scheme 1.15](image.png)

**Scheme 1.15.** First generation of chiral phosphoric acid catalysis

Akiyama \textit{et al.}\textsuperscript{36} (eq 1, Scheme 1.15) and Terada \textit{et al.}\textsuperscript{37} (eq 2, Scheme 1.15) developed the first generation of chiral phosphoric acid catalysts almost at the same time. Soon after their developments, more chemists devoted into this area of research and a series of such strong Brønsted acid catalysts has been developed and used in various transformations
such as Friedel-Crafts alkylation,\textsuperscript{38} transfer hydrogenation,\textsuperscript{39} Diels-Alder reaction,\textsuperscript{40} Nazarov cyclization\textsuperscript{41} and \textit{etc}.

The last type of chiral Brønsted acid was recently developed by Toste and coworkers.\textsuperscript{34b} This type of catalysts has been used to catalyze highly enantioselective transformations of unactivated alkenes (Scheme 1.16). The protonation of alkene \textit{39} by dithiophosphoric acid \textit{40} results in carbocation \textit{41} which does not form a hydrogen bond, but still holds the conjugate base \textit{42} in proximity through electro-static interaction. This interaction then facilitates the formation of intermediate \textit{43}. In the following step, the nucleophilic amine group displaces the chiral leaving group in a SN\textsubscript{2}' fashion, rendering product \textit{44} in high enantioselectivity and efficiency.

\begin{center}
\textbf{Scheme 1.16.} Chiral dithiophosphoric acid catalyzed hydroamination reaction
\end{center}
1.1.2.1.5. Bifunctional Catalysis

Inspired by enzyme’s cooperative catalysis, Shibasaki and coworkers\(^\text{42}\) developed the concept of bifunctional (multifunctional) catalysis, where both partners (i.e. nucleophile and electrophile) of a bimolecular reaction are simultaneously activated by the same catalyst. A typical bi/multifunctional catalyst\(^\text{43}\) (Figure 1.5) should contain two or more of active sites (functionalities), and each of them activates a substrate separately. With this unique activation mechanism, the bi/multifunctional catalysts can enable some transformations that are generally hard to achieve by single functional catalysts.

![Selected examples of multifunctional organocatalysts](image-url)

**Figure 1.5.** Selected examples of multifunctional organocatalysts
One of such example is Takemoto’s bifunctional thiourea catalyst\textsuperscript{43d} (\textbf{45}, Figure 1.5). The thiourea catalyst (\textbf{45}) catalyzed the Michael addition of malonate to nitroalkene with great efficiency and enantioselectivities (Scheme 1.17). It’s believed that the thiourea moiety of the catalyst presumably interacts with the nitro group of Michael acceptor \textbf{50} via hydrogen bonding, while the tertiary amine group helps to activate the Michael donor \textbf{51}.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {$\text{Ph} \equiv \text{NO}_2$};
\node at (1.5,0) {+ \text{EtO}_2\text{C} \equiv \text{CO}_2\text{Et}};
\node at (3,0) {$\xrightarrow{45 \ (10 \ \text{mol\%})}$};
\node at (4.5,0) {$\text{Ph} \equiv \text{NO}_2$};
\node at (5,0) {$\text{EtO}_2\text{C} \equiv \text{CO}_2\text{Et}$};
\node at (6,0) {$86\%, \ 93\% \ \text{ee}$};
\node at (6,1) {$\text{toluene}$};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.17}. Enantioselective reaction catalyzed by a bifunctional catalyst

The other bifunctional catalysts share similar activation manner with Takemoto’s catalyst. Bifunctional catalysis has been successfully applied to many reactions including Michael addition,\textsuperscript{43d} Henry reaction,\textsuperscript{44} Strecker reaction,\textsuperscript{45} Morita-Baylis-Hillman reaction,\textsuperscript{18b} kinetic resolution of alcohols and a wide range of carbonyl $\alpha$-functionalization reactions.

\textbf{1.1.2.2. Classification Based on Bonding Interactions}

Another way of classifying the organocatalysis is more focusing on the bonding formation between catalyst and substrate within the catalytic cycle, dividing most of the organocatalysis as “covalent catalysis” and “non-covalent catalysis”\textsuperscript{9}. 
1.1.2.2.1. Covalent Catalysis

Covalent catalysis, as indicated by the name, refers to reactions involve organocatalysts that catalyze reactions through the formation of covalent adducts between catalyst and substrate(s) within the catalytic cycle. Because of the fact that covalent catalyst promotes reactions by forming strong covalent bonding with substrates, covalent catalysts are usually considered to be more “stronger” catalysts than their counterparts, non-covalent ones.

![Selected examples of nucleophilic organocatalysts](image)

**Figure 1.6.** Selected examples of nucleophilic organocatalysts
The aforementioned enamine and iminium catalysis are both considered to be covalent catalysis since the amine catalysts form covalent bonding with the carbonyl substrates in the catalytic cycle. Most of the nucleophilic organocatalysts are also considered to be covalent organocatalysts since they promote reactions through nucleophilic attacking to substrate and thus leading to the formation of covalent adducts between catalyst and substrate. Some of the most studied nucleophilic organocatalysts in the field of acylation chemistry are listed $^{46}$ (Figure 1.6).

1.1.2.2. Non-Covalent Catalysis

Non-Covalent catalysis, refers to reactions involve organocatalysts that catalyze reactions without the formation of covalent adducts between catalyst and substrate(s) within the catalytic cycle. In general, the catalysis of this type depends on the hydrogen bonding between substrate and catalyst or on protonation/deprotonation processes. $^{47}$ Because of the fact that non-covalent catalyst promotes reactions by these types of weak interactions with substrates, non-covalent catalysts are usually considered to be “weaker” catalysts. Phase transfer catalysis, in which no covalent bonding is formed in a catalytic cycle, may also be considered as non-covalent catalysis.
1.1.2.3. Classification Based on Chirality Types

A molecule that is not superimposable on its mirror image is a chiral molecule, and we say it has the property of “chirality”. There are four types of chirality in nature: central chirality, axial chirality, planar chirality and helical chirality (Figure 1.7). The numerous organocatalysts developed so far could be categorized into four families based on their molecular chirality types, namely central chiral organocatalysts, axial chiral organocatalysts, planar chiral organocatalysts and helical chiral organocatalysts.

Figure 1.7. Selected examples of chiral molecules
1.1.2.3.1. Central Chirality Type Catalysis

Central chirality, also known as point chirality, refers to chirality that arises from the existence of chiral center(s) in the molecular (a, Figure 1.7). Most of the chiral centers are generated from sp$^3$ carbons with four different groups attached to them. However, in some circumstances, chiral center could also be some other atoms like nitrogen, phosphorous, sulfur and etc. As the most abundant chirality type, a lot of central chiral organocatalysts have been developed (Figure 1.8). These catalysts have been useful for quite a range of applications. It is quite surprising, providing the highly specificity of enzymes towards their substrates, that certain classes of those synthetic catalysts are enantioselective over a wide range of mechanistically unrelated reactions. Due to their broad applicability in asymmetric synthesis, this type of organocatalysts has been recognized as “privileged catalysts” (33, 53, and 54 in Figure 1.8).

![Chemical structures of central chirality based organocatalysts]

Figure 1.8. Selected examples of central chirality based organocatalysts
1.1.2.3.2. Axial Chirality Type Catalysis

Axial chirality is a special case of chirality in which a molecule does not have a chiral center but a chiral axis. The chirality arises from the non-planar arrangement of four groups (a, b and c, d) in pairs about a chiral axis (Figure 1.9). The groups don’t have to be all-different as long as each pair consists of two different substituents (that is, a is unequal b and c is unequal d). This type of chirality is most commonly observed in atropisomeric biaryl compounds wherein the aryl-aryl bond rotation is restricted due to the steric between ortho-substituents, for example, biphenyl, binaphthyl and etc. Certain types of allenes, alkylidenecycloalkanes, spiranes and adamantanes also display axial chirality (b, Figure 1.7)

![Figure 1.9. Chiral axis connecting four groups a, b, c and d](image)

A great number of axial chirality based organocatalysts, most of which derived from atropisomeric biaryl compounds, have been developed so far (Figure 1.10). A bifunctional spiro-type organocatalyst (55) have been reported to catalyze aza-Morita-Baylis-Hillman reaction with high enantio control. Lewis base N-oxides 56 and 57 have been found to be highly efficient and selective for the allylation of aldehydes with allyltrichlorosilane while catalyst 58 is an excellent catalyst for Diels-Alder reaction. BINOL and chiral phosphoric acid derived catalysts (59 and 60) are highly effective over
a wide range of mechanistically unrelated reactions, and thus they are recognized as “privileged catalysts”.

**Figure 1.10.** Selected examples of axial chirality based organocatalysts

1.1.2.3.3. Planar Chirality Type Catalysis

Planar chirality is also a special type of chirality in which a molecule does not posses a chiral center but a chiral plane. The chirality arises from the arrangement of non-planar groups with respect to a plane. This type of chirality is observed in some di or poly substituted metalloccenes (e.g. ferrocenes), (E)-cyclooctene, and certain mono substituted paracyclopahnes and bridged aromatics (c, Figure 1.7).
A great number of planar chiral organocatalysts, most of which are ferrocene-based compounds, have been developed so far (Figure 1.11). An aza-paracyclophane-oxazoline-N-oxide catalyst (61) has been reported to be highly efficient and selective for the allylation of aldehydes with allyltribromosilane.\textsuperscript{54} Catalyst 62 have been found to be an excellent catalyst for the asymmetric, catalytic phenyl transfer to imines.\textsuperscript{55} Chiral DMAP analogue 63 catalyzed the dynamic kinetic resolution and rearrangement reaction of azlactones with good yield and moderate selectivities.\textsuperscript{56} Fu and coworkers developed a series of ferrocene-based catalysts, these catalysts are highly effective over a wide range of mechanistically unrelated reactions, and thus they are also recognized as “privileged catalysts” (64 in Figure 1.11).

![Figure 1.11. Selected examples of planar chirality based organocatalysts](image)

**Figure 1.11.** Selected examples of planar chirality based organocatalysts

### 1.1.2.3.4. Helical Chirality Type Catalysis

Helical chirality is another case of special chirality wherein a molecule does not possess a chiral center but a helix. The chirality arises from the twisting nature of the structure around a fixed line called the helical axis. Helical chirality can also be referred to as helicity; it is best described by a smooth space curve (Figure 1.12).
This type of chirality is observed in special twisted molecules like molecular propeller and bulky substituted heptalenes. The best known small molecules possess helical chirality are helicenes (orthofused aromatic rings) and their derivatives (d, Figure 1.7). With four or more rings, steric hindrance at both ends of these molecules prevents the formation of planar conformations, and helicenes rather adopt the non-planar, helical chiral structures. Despite helicity has been of great importance in nature and other scientific fields, their application in asymmetric synthesis has been far less explored compared to the other tree types of chirality. Only a few examples of asymmetric catalysis utilizing helical chirality exist before our contribution into this field (discussed below).
1.2. Helical Chiral Small Molecules in Asymmetric Synthesis

1.2.1. Helical Chiral Small Molecules in Organometallic Catalysis

In 1997, Reetz and coworkers\textsuperscript{58} developed a new optically pure [6]helicene derived diphosphane ligand and named it “PHelix” (\textbf{65}, Figure 1.13). This ligand was subsequently tested in a rhodium-catalyzed asymmetric hydrogenation reaction of itaconic acid ester with moderate selectivity, proving the effectiveness of helical chiral ligand in asymmetric synthesis. Later on, the same ligand was used in the palladium-catalyzed kinetic resolution of allylic substrates with very high selectivities.\textsuperscript{59}

In 1998, Yamaguchi and coworkers\textsuperscript{60} reported an asymmetric addition reaction of diethylzinc to aromatic aldehydes with good yield and moderate selectivity, this reaction was catalyzed by a macrocyclic catalyst consisting of optically active helical element (\textbf{66}, Figure 1.13). Encouraged by the results of this study, they developed a new class of phosphate ligands possessing both helical and axial chirality (\textbf{67}, Figure 1.13). A careful study about the rhodium-catalyzed hydrogenation reaction of dimethyl itaconate revealed that there exited a significant effect of matched/mismatched helical and axial chirality on the selectivity.\textsuperscript{61} Very recently, Starý \textit{et al.} developed a novel helical phosphite based on [6]helicene-related compounds\textsuperscript{62} (\textbf{68}, Figure 1.13). This type of ligands was not effective for the rhodium-catalyzed hydroformylation of alkenes, but they were found to be very selective for Ir-catalyzed allylic amination of allyl carbonates.
In 2001, Soai and coworkers reported a remarkable asymmetric synthesis induced by unfunctionalized helicenes.\(^{63}\) In this study, the enantioselective addition of iPr\(_2\)Zn to 69, which was triggered with chiral helicene 70, generated product 71 in high yield and enantioselectivity through asymmetric autocatalysis (eq 1, Scheme 1.18). Later an even higher enantioselectivity for the same transformation catalyzed by a tetraphia-[7]-helicene was reported by the same group and collaborators\(^{64}\) (eq 2, Scheme 1.18).
Scheme 1.18. Helicenes as chiral introducer developed by Soai and coworkers

1.2.3. Helical Chiral Small Molecules in Organocatalysis

In 2000, Katz and coworkers\(^6\) developed a chiral bis-helicene diphenolic ligand (75), believing it should possess a larger chiral pocket around the reaction center than BINOL and VAPOL, thus make it a better catalyst for transformations which are steric demanding. Indeed, this catalyst was found quite effective in the asymmetric addition of diethylzinc to several aldehydes with a general better performance over BINOL (Scheme 1.19).

Starý \textit{et al.}\(^6\) reported a study on the kinetic resolution of secondary alcohol with azahelicenes 77 and 78. They found the two catalysts have dramatically different catalytic activity despite their similarity in the structures (Scheme 1.20). While 1-aza-[6]helicene (77) was found ineffective towards the resolution of racemic alcohol 76, 2-
aza-[6]helicene (78) was quite powerful towards this reaction, rendering enantio-enriched alcohol 79 with 99% ee at 72% conversion. It was believed that the inefficiency of 77 was due to the limited accessibility of the nitrogen atom arising from the steric hindrance of position 1.

**Scheme 1.19.** Alkylation of aldehydes catalyzed by [5]HELOL

**(P)-** 77  

76  

conversion < 5%  

**Scheme 1.20.** aza-[6]helicenes catalyzed kinetic resolution of alcohol
In 2011, Carbery et al. developed a novel helical DMAP analogue and applied it in the kinetic resolution of racemic alcohols.\textsuperscript{67} This catalyst displayed good to excellent selectivity towards a range of secondary aromatic alcohols with only 0.5 mol\% loading (Scheme 1.21). A new synthetic route for an analogue of 81 was also developed by the same group which doesn’t require resolution during the process.\textsuperscript{68}

\begin{center}
\textbf{Scheme 1.21.} Helical DMAP catalyzed kinetic resolution of alcohols
\end{center}

### 1.3. Development of Helical Chiral Pyridines as Asymmetric Catalysts

Despite the fact that helical chirality in asymmetric synthesis has been far less explored, the limited studies available have demonstrated the great potential of helicenes and their derivatives as chiral catalysts in organic synthesis. These studies also revealed the potential advantage of helical molecules in developing catalytic asymmetric systems over other three types of chirality. Due to their unique structures, helical chiral molecules, especially helicenes and their derivatives possess continuously chiral frameworks that would in principle create continuously chiral space around the catalyst – an idea case for asymmetric induction.\textsuperscript{69}
In light of these studies, our group became interested in pursuing the possibility of the design and development of a new class of chiral catalysts based on helical chiral pyridines. A first-order analysis of the crystal structure of 1,16-diaza[6]helicene (Figure 1.14) suggests that the space around the nitrogen atom is effectively surrounded by the chiral helical framework (83, Figure 1.14), well desymmetrizing the reactive center - pyridine ring, in terms of both left-to-right and top-to-bottom differentiations (84, Figure 1.14). In addition, helicene 82 also has the trend as the other privileged catalysts do: a rigid structure with a nitrogen-containing functional group (which can be easily transformed to oxygen-containing functional groups by simple oxidation of the nitrogen atom) that allows the effective binding and activation of substrates.
1.3.1. Desymmetrization of meso-epoxides with a Chloride Nucleophile\textsuperscript{72}

In 2008, our group developed the first generation of a gram-scale modular synthesis of 1-azahelicenes that allows variations at the bottom part of these structures (Figure 1.15). The feature allowed our direct study of the relationship between the structures of these catalysts and their reactivity and selectivity in the asymmetric synthesis of chlorohydrins by desymmetrization of meso-epoxides with chlorosilanes. Catalyst 87, which has the largest bottom screen part, was found to be optimum catalyzing the reactions with up to 94\% ee (Scheme 1.22). In this study, a clear trend about these catalysts has been established: the larger the bottom part of the catalyst is, the better selectivity the catalyst will achieve.

Figure 1.15. 1-azahelicenes developed by our group

Scheme 1.22. Desymmetrization of meso-epoxides with SiCl\textsubscript{4}
1.3.2. Propargylation of Aldehydes with Allenyltrichlorosilane

The same catalyst (87) was tested in the propargylation of benzaldehyde with allenyltrichlorosilane, rendering the product with excellent yield and moderate ee at -20 °C (eq 1, Scheme 1.23).

\[
\text{PhCHO} + \text{SiCl}_3 \xrightarrow{87 \text{ (10\% mol)}} \text{PhOH} + \text{PhCH=CH}_2, \text{ee} = 90\%, 34\%
\]

\[
\text{ArCHO} + \text{SiCl}_3 \xrightarrow{88 \text{ (10\% mol)}} \text{ArOH} + \text{ArCH=CH}_2, \text{ee} = \text{up to 96\%}, \text{yield} = \text{up to 99\%}
\]

\[
\text{NHCOAr}^{\text{N}} \xrightarrow{88 \text{ (10\% mol)}} \text{NHCOAr}^{\text{N}}, \text{ee} = 53\%, 78\%
\]

Scheme 1.23. Asymmetric propargylation of aldehydes developed by Takenaka et al.

A new catalyst (88) that was readily derived from 87 by simple pyridination was synthesized to utilize the potential beneficial effects of bidentate catalyst in this reaction. Surprisingly, the bidentate catalyst 88 turned out to be much more reactive than the monodentate counterpart 87, leading to the completion of reactions after only three hours with excellent yields and selectivities (eq 2, Scheme 1.23). Without optimizing the reaction, it was demonstrated that the same catalyst (88) could also achieve the propargylation of aldimine 89 with good yield and selectivity (eq 3, Scheme 1.23).
1.3.3. **Friedel-Crafts Alkylation of 4,7-Dihydroindoles with Nitroalkenes**\(^\text{74}\)

Besides the Lewis base catalysts developed above, our group also developed a class of helical chiral Brønsted acid catalysts as part of our broad interests in hydrogen bonding catalysis. \(92\), an excellent double hydrogen-bond donor, was readily synthesized by amination at the 2-position of \(87\), and followed by protonation and counterion exchange. Catalyst \(92\) was found to be excellent for the asymmetric addition of dihydroindoles to nitroalkenes, achieving excellent yields and selectivities with only 2 mol\% catalyst loading (Scheme 1.24). Stereochemical models based on the crystal structure of HCl salt of \(92\) and the observed sense of enantioselection of the product \(93\) were proposed.

![Scheme 1.24. Asymmetric addition of dihydroindoles to nitroalkenes](image)

\begin{equation}
\text{Scheme 1.24. Asymmetric addition of dihydroindoles to nitroalkenes}
\end{equation}
1.4. Objectives

Based on 11,12-benzo-1-aza[6]helicene-N-oxide\(^{72}\) (87), my previous colleagues developed easy accesses to bidentate Lewis base catalyst 88\(^{73}\) and double hydrogen-bond donor catalyst 92,\(^{74}\) highlighting the versatility of 87 as a chiral scaffold. Catalysts derived from this chiral scaffold (87) were highly effective towards a range of mechanistically unrelated reactions, which highlights its potential general applicability in asymmetric catalysis. As such, I present here my continue effort of the past five years towards the development of chiral organocatalysts based on 11,12-benzo-1-aza[6]helicene-N-oxide (87) and their applications in asymmetric synthesis. Specifically, the thesis will cover the following topics:


4) The development of asymmetric allylation of ketoimines catalyzed by helical chiral N-oxides.
CHAPTER 2. DIASTEREOMERIC SALT-MEDIATED OPTICAL RESOLUTION OF 11,12-BENZO-1-aza[6]HELICENE

2.1. Background

As discussed in chapter 1, our group has previously developed a gram-scale modular synthesis of 1-aza[6]helicenes-N-oxides (Figure 1.15, Chapter 1) that allows systematic structural variations. This first generation synthesis method allowed us the quick access to this novel chiral scaffold and build new effective catalysts based on it. However, this first generation method is still a racemic synthesis, and thus, for the most demanded 11,12-benzo-1-aza-[6]helicene-N-oxide (87), it requires a chiral HPLC resolution in the synthesis which is non-trivial. As our research progresses, the time-consuming and costly resolution has become the “bottleneck” for our research; therefore, the development of a new method that could allow us to avoid the chiral HPLC optical resolution is needed. With this purpose in mind, the diastereomeric salt-mediated optical resolution of 11,12-benzo-1-aza-[6]helicene was developed.
2.2. Results and Discussion

To achieve the goal of obtaining optically pure 11,12-benzo-1-aza[6]helicene (94) without the chiral HPLC resolution, a diastereomeric salt-mediated resolution method was proposed (Scheme 2.1). In this procedure, the racemic 11,12-benzo-1-aza[6] helicene (rac-94) is treated with chiral resolving acids. Both enantiomers of rac-94 (P and M) are then protonated by the chiral acid introduced, forming two diastereoisomers (95). Since diastereoisomers P-95 and M-95 are different in energy, their difference in solubility would, in principle, allow their separation by simply isolating the insoluble salt from the mother solution. Simple treatment with base will deliver the optically enriched 94, which would be eventually obtained as optically pure by recrystallization.

Scheme 2.1. Proposed method for the resolution of racemic helicene

The first thing we need to consider for this procedure is to identify a suitable chiral acid which would allow the preferential precipitation of one of the diastereoisomers over the other one. In order to identify the ideal chiral acid for this purpose, a series of commonly used chiral acids was tested. Racemic 94 was treated with each chiral acid in EtOAc; the resulting clear solution was stored in refrigerator overnight. The crystals (or precipitate)
formed from the above solution were separated from the mother solution, treated with base, and analyzed with chiral HPLC; the results are presented (Table 2.1).

Table 2.1. Screen of chiral acids for resolution of racemic helicene

<table>
<thead>
<tr>
<th>Chiral Acid</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) camphorsulfonic acid (96)</td>
<td>0% ee</td>
</tr>
<tr>
<td>100</td>
<td>7% ee</td>
</tr>
<tr>
<td>Benzoinic acid (97)</td>
<td>0% ee</td>
</tr>
<tr>
<td>Malic acid (98)</td>
<td>0% ee</td>
</tr>
<tr>
<td>Lactic acid (99)</td>
<td>0% ee</td>
</tr>
<tr>
<td>Tartaric acid (100)</td>
<td>15.3% ee</td>
</tr>
<tr>
<td>(R) BINOL (101)</td>
<td>15% ee</td>
</tr>
<tr>
<td>102</td>
<td>0% ee</td>
</tr>
<tr>
<td>103</td>
<td>5% ee</td>
</tr>
</tbody>
</table>

Treatments with 10-camphorsulfonic acid (96), mandelic acid (97), malic acid (98) and lactic acid (99) resulted in no selectivity, only racemic helicene (94) were acquired. Tartaric acid (100), to our surprise, gave some definite selectivity. Encouraged by this result, a similar chiral acid\(^\text{75}\) (101) that has been used to resolve 1-aza[6]helicene was tested next. To our delight, 101 was found to be much more effective under the same condition, resulting in 15% ee favoring P enantiomer. The treatment with chiral BINOL
(102) did not form any precipitate, presumably because it’s too weak for this purpose. A chiral phosphoric acid (103) was able to give 5% ee. Based on the results, (-)-dibenzoyl-L-tartaric acid monohydrate (101) was chosen as our chiral resolving acid for the following development.

Table 2.2. Optimization of chiral acid ratios

<table>
<thead>
<tr>
<th>entry</th>
<th>101 (equiv)</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>13.0</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>10.0</td>
<td>15.3</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>17.8</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>15.0</td>
<td>25.0</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>17.0</td>
<td>16.0</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>19.0</td>
<td>9.0</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>25.0</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

*a Yield was calculated against only one enantiomer of the helicene used*

Next, the effects of the amount of chiral acid 101 used were carefully investigated. A series of resolution experiments was set up where the only variation was the ratio between racemic helicene 94 and the chiral acid 101 (Table 2.2). When only 1 equivalent
of 101 was used, no salt (95) formed (entry 1, Table 2.2). As we gradually increased the ratio of chiral acid 101, the corresponding positive results were observed (entries 2-5, Table 2.2). When chiral acid 101 was applied in 15 equivalents, we were able to get the highest selectivity (entry 5, Table 2.2). Further increasing in the ratio of chiral acid 101 led to a decrease in the selectivity, and when 25.0 equivalents of acid were applied, no desired salt precipitate was obtained from the solution (entry 8, Table 2.2).

Solvent effects were then taken into consideration for the further optimization of this procedure. Commonly used solvents were screened under the identical condition (Table 2.3). All of the chlorinated solvents such as CH₂Cl₂, CH₃Cl and CH₂ClCH₂Cl failed to produce any sort of precipitate or crystal after 14 h at -20 °C (entries 2-4, Table 2.3). Acetone as well as methyl tert-butyl ether behaved the same as chlorinated solvents (entries 5 and 12, Table 2.3). We were able to collect some precipitated salt when isopropyl alcohol was used, which turned out to be only racemic samples (entry 6, Table 2.3). Due to the poor solubility, we were not able to effectively test aromatic solvents benzene and toluene (entries 7 and 8, Table 2.3). Unlike tert-butyl ether, we observed some marginal selectivity when diethyl ether was used (entry 9 vs. 12, Table 2.3). The best result was achieved when using polar solvent CH₃CN, which provided enantio enriched helicene 94 in 35% ee favoring P as the major enantiomer. Some efforts to use mixture of solvents did not succeed with all attempts providing less than 15% ee (entry 11, Table 2.3). Based on these results we embarked on using CH₃CN as our resolving solvent.
Table 2.3. Screen of solvents for resolution of racemic helicene

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>ee (%)</th>
<th>entry</th>
<th>solvent</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc</td>
<td>25.0</td>
<td>8</td>
<td>toluene</td>
<td>N/A²</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>N/A⁷</td>
<td>9</td>
<td>Et₂O</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>CH₃Cl</td>
<td>N/A⁷</td>
<td>10</td>
<td>CH₃CN</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>(CH₂Cl)₂</td>
<td>N/A⁷</td>
<td>11</td>
<td>solvent mixtures</td>
<td>&lt;15</td>
</tr>
<tr>
<td>5</td>
<td>acetone</td>
<td>N/A⁷</td>
<td>12</td>
<td>benzene</td>
<td>N/A¹</td>
</tr>
<tr>
<td>6</td>
<td>iPrOH</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>benzene</td>
<td>N/A⁷</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No desired precipitate attained

Unsuccessful because of low solubility

Since the diastereomeric salt-mediated resolution of a chiral compound involves the preferential precipitation of one salt (one diastereoisomer) over the other (the other diastereoisomer) that is highly empirical, we began to test various methods such as slow cooling, vapor diffusion and slow evaporation to induce the precipitation besides refrigerator cooling.

In *slow cooling*, a typical procedure went as follow (Scheme 2.2): A clear saturated solution was prepared by refluxing racemic 94 and chiral acid 101 in CH₃CN, then the clear solution was slowly cooled down by turning off the power. Precipitate was collected
after the solution cooled down to ambient temperature, worked up and analyzed. The best result obtained from five identical trials was 27.5% ee (entry 3, Scheme 2.2), which was less efficient than refrigerator cooling.

**Scheme 2.2. Resolution of racemic helicene by slow cooling**

Next we tried to induce precipitation by vapor diffusion, a very common method for introducing crystal or precipitate. A saturated solution of racemic 94 and chiral acid 101 in CH$_3$CN was prepared in a small vial, and this vial was placed inside a larger sealed vial that contained a small volume of a less efficient solvent system. Vapor from the associate solvent of the outer vial then diffused into the CH$_3$CN solution in the inner vial, causing the desired precipitation of the diastereomeric salt after overnight. The precipitate was then collected, worked up and analyzed (Table 2.4).
Table 2.4. Resolution of racemic helicene by vapor diffusion

Commonly used solvents that have a low solubility for 94 and 101 were screened as associate solvents under the identical condition. More than one trial was performed for each associate solvent, and the best result was presented here (Table 2.4). Unfortunately, when THF, Et₂O and benzene were used as the associated solvents, no desired precipitate was obtained even after overnight diffusion (entries 1-3, Table 2.4). We were able to collected enough precipitate when hexane was used, however there was only 11.0% ee (entry 4, Table 2.4). Nice clear crystals formed after overnight with MeOH as associate solvent, however, those crystals turned out to be pure racemic helicene 94 (entry 5, Table 2.4). None of these vapor diffusion experiments we tested resulted in a comparable result to direct refrigerator cooling precipitation.
Without any success from the above methods, slow solvent evaporation was tested next. A saturated solution was prepared in a suitable sample vial and was allowed to slowly evaporate. As solvent evaporated, the solution became concentrated and some yellow, shining particles formed at the bottom of the sample vial. Different results were obtained by varying the evaporation speed. When a saturated solution of helicene in acetonitrile was quickly evaporated, a lot of yellow precipitate formed which gave 110% of helicene with 7% ee (entry 1, Table 2.5).

**Table 2.5. Resolution of racemic helicene by slow evaporation**

<table>
<thead>
<tr>
<th>entry</th>
<th>helicene (mg)</th>
<th>time</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60</td>
<td>3h</td>
<td>110</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>1d</td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>2d</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>3d</td>
<td>32</td>
<td>94</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60</td>
<td>4d</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>481</td>
<td>2d</td>
<td>52</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield was calculated against only one enantiomer of the helicene used  
<sup>b</sup> Over precipitation  
<sup>c</sup> No desired precipitation was obtained

When the evaporation was slowed down, the resulted precipitate gave a better selectivity with 16% ee (entry 2, Table 2.5). We were able to get much better results by gradually
slowing down the evaporation speeds, highly enantio enriched helicene was obtained after days of evaporation (entries 3 and 4, Table 2.5). The effort to further slow down the precipitation by increasing the volume of solvent did not work at all; no desired precipitate was formed even after four days of evaporation (entry 5, Table 2.5). After optimization, we were able to get reasonable enantio enriched helicene in large scale by two days of evaporation (entry 6, Table 2.5).

The next step for the process was straightforward, we were able to obtain optically pure (P)-11,12-benzo-1-aza-[6]helicene (P-94) from the above optically enriched helicene (85% ee) through simple recrystallization from a mixture of CH$_2$Cl$_2$/hexanes by slow evaporation at ambient temperature overnight. In summary, optically pure helicene can now be obtained by optical resolution of racemic helicene with (-)-dibenzoyl-L-tartaric acid monohydrate (101) in CH$_3$CN followed by a single recrystallization in CH$_2$Cl$_2$ and hexane solvent mixture (Scheme 2.3).

![Scheme 2.3. Diastereomeric salt-mediated resolution of helicene](image-url)
2.3. Summary

In order to quickly access enantiomerically pure 11,12-benzo-1-aza-[6]helicene (94) and avoid the time and cost demanding chiral HPLC separation, a diastereomeric salt-mediated optical resolution of 11,12-benzo-1-aza-[6]helicene (94) was developed. Based on this study, (-)-dibenzoyl-L-tartaric acid monohydrate (101) was found to be the most successful resolving agent for the purpose and it gave the optimum performance when 15 equivalents of this acid were used. A solvent screening revealed that EtOAc and CH$_3$CN were the two most effective solvents for the resolution. Slow evaporation of the saturated solution of helicene and chiral resolving acid gave the most promising result. After optimization, enantiomerically pure 11,12-benzo-1-aza-[6]helicene (94) was obtained by optical resolution of racemic 94 with (-)-dibenzoyl-L- tartaric acid monohydrate (101) in CH$_3$CN followed by a single recrystallization from CH$_2$Cl$_2$ and hexane solvent mixture.

2.4. Experimental Section

2.4.1. General Information

All resolution reactions were carried out in the oven- or flame-dried glassware without further protection unless otherwise noted. Except as otherwise indicated, all reactions were monitored by analytical thin-layer chromatography using Silicycle pre-coated silica gel plates with F$_{254}$ indicator. Visualization was accomplished by UV light (256 nm), with combination of potassium permanganate and/or vanillin solution as an indicator. Flash column chromatography was performed according to the method of Still$^{76}$ using
silica gel 60 (mesh 230-400) supplied by Silicycle. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH₂Cl₂) was freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. THF was freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use.

¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 300 (300 MHz ¹H) and a Bruker Avance 400 (400 MHz ¹H, 100 MHz ¹³C). Chemical shift values (δ) are reported in ppm relative to Me₄Si (δ 0.0 ppm) unless otherwise noted. The proton spectra are reported as follows δ (multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL® III automatic polarimeter. Infrared spectra were recorded using PerkinElmer™ SPECTRUM ONE with Universal ATR Sampling Accessory (Composite Zinc Selenide and Diamond crystals). High-resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, the University of Miami.

The HPLC analyses of chiral azahelicenes 94 were performed by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (10 % iPrOH in hexanes, flow rate = 0.50 mL/min.) with simultaneous UV detection at 254 nm (Varian).
2.4.2. General Procedures for Refrigerator Cooling

A saturated solution of racemic azahelicene 97 (58 mg, 0.153 mmol) in CH$_3$CN was mixed with a saturated solution of (-)-dibenzoyl-L-tartaric acid monohydrate 101 (863 mg, 2.29 mmol) in CH$_3$CN and the solution was sealed and transferred to a refrigerator at -20 °C. After 14 hours cooling, the yellow solid formed was carefully separated from the clear solution, washed with a small amount of cold CH$_3$CN, dissolved back into solution by dichloromethane and basified by 1M NaOH solution. The resulting organic layer was separated, washed with saturated NaHCO$_3$ solution, water and brine sequentially, and then dried over NaSO$_4$, filtered, and concentrated in vacuo to yield a yellow solid material. The crude material was then purified by a short flash chromatography on silica gel (8% EtOAc in hexanes) to afford the enantio-enriched azahelicene 97 (31 mg, 54%). All the spectra are in agreement with the literature value$^{72}$. The resulted material was then analyzed by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (10 % iPrOH in hexanes, flow rate = 0.50 mL/min), $t_r$ (minor) = 21.81 min, $t_r$ (major) = 67.18 min. to give an ee of 35%, favoring $P$ enantiomer.

The above general procedure was followed for the identification of chiral resolving acid, optimization of stoichiometry of chiral acid and solvent screening.
2.4.3. General Procedure for Slow Cooling Resolution Method

A flame-dried 25 ml round bottom flask was charged with azahelicene 97 (58 mg, 0.153 mmol), (-)-dibenzoyl-L-tartaric acid monohydrate 101 (863 mg, 2.29 mmol) and a stir bar. The mixture was then added with minimum amount of CH$_3$CN and stirred at 80°C using an oil bath. Small amount of CH$_3$CN was slowly added until the entire solid went into the solution and became a nice clear yellow solution. And then the solution was slowly cooled down to ambient temperature by turning off the power of the oil bath. After cooling down to room temperature, the yellow solid formed was carefully separated from the solution, washed with a small amount of cold ethyl acetate, dissolved back into solution by dichloromethane and basified by 1M NaOH solution. The resulting organic layer was separated, washed with saturated NaHCO$_3$ solution, water and brine sequentially, and then dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to yield a yellow solid material. The crude material was then purified by a short flash chromatography on silica gel (8% EtOAc in hexanes) to afford the enantio-enriched azahelicene 97 (24 mg, 42%). All the spectra are in agreement with the literature value$^{72}$. The resulted material was then analyzed by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (10% iPrOH in hexanes, flow rate = 0.50 mL/min), $t_R$ (minor) = 21.81 min, $t_R$ (major) = 67.18 min. to give an ee of 27.5%, favoring $P$ enantiomer.
2.4.4. General Procedures for Vapor Diffusion Method

A saturated solution of racemic azahelicene 97 (58.0 mg, 0.153 mmol) in CH$_3$CN was mixed with a saturated solution of (-)-dibenzoyl-L-tartaric acid monohydrate 101 (863 mg, 2.29 mmol) in the same solvent in a small vial. This inner vial was then placed inside a larger sealed vial that contained a small volume of hexanes and stored over night. The yellow solid formed was carefully separated from the solution, washed with a small amount of cold ethyl actate, dissolved back into solution by dichloromethane and basified by 1.0 M NaOH solutions. The resulting organic layer was separated, washed with saturated NaHCO$_3$ solution, water and brine sequentially, and then dried over NaSO$_4$, filtered, and concentrated in vacuo to yield a yellow solid material. The crude material was then purified by a short flash chromatography on silica gel (8% EtOAc in hexanes) to afford the enantio-enriched azahelicene 97 (10.4 mg, 18%). All the spectra are in agreement with the literature value$^{72}$. The resulted material was then analyzed by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (10 % iPrOH in hexanes, flow rate = 0.50 mL/min), $t_f$ (minor) = 21.81 min, $t_f$ (major) = 67.18 min. to give an $ee$ of 11%, favoring $P$ enantiomer.
2.4.5. General Procedure for Slow Evaporation Method

A saturated solution of racemic azahelicene 97 (481 mg, 1.27 mmol) and (-)-dibenzoyl-L-tartaric acid monohydrate 101 (7.16 g, 19.0 mmol) in CH$_3$CN (40 ml) was prepared in a round bottom flask. The flask was then sealed with aluminum foil, and several small holes were made. After two days evaporation at ambient temperature, the formed yellow solid and white particles were carefully separated from the solution, washed with a small amount of cold ethyl acetate, dissolved back into solution by dichloromethane and basified by 1M NaOH solution. The resulting organic layer was separated, washed with saturated NaHCO$_3$ solution, water and brine sequentially, and then dried over NaSO$_4$, filtered, and concentrated in vacuo to yield a yellow solid material. The crude material was then purified by a short flash chromatography on silica gel (8% EtOAc in hexanes) to afford the enantio-enriched azahelicene 97 (125 mg, 26%). All the spectra are in agreement with the literature value$^{72}$. The resulted material was then analyzed by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (10 % iPrOH in hexanes, flow rate = 0.50 mL/min), $t_R$ (minor) = 21.64 min, $t_R$ (major) = 63.04 min. to give an $ee$ of 85%, favoring $P$ enantiomer.
CHAPTER 3. NITROALKENE DIELS-ALDER REACTION CATALYZED BY HELICAL CHIRAL HYDROGEN-BOND DONOR CATALYSTS

3.1. Background

Asymmetric catalysis of Diels-Alder reaction through LUMO-lowering is one of the most extensively studied areas, and its current state is certainly impressive.\(^77\) However, carbonyl compounds are the only dienophiles that have been utilized in this field, leaving a tremendous gap in an otherwise robust field of chemistry. The catalytic activation of nitroalkene (ketene equivalent) for the asymmetric Diels-Alder reaction has remained nonexistent presumably because of its inherent nature to form nitronate products \textit{via} an inverse electron-demand hetero Diels-Alder reaction with Lewis acids\(^78\) (eq 1, Scheme 3.1). In 2007, our group reported that the nitroalkene Diels-Alder reaction could be catalyzed periselectively by double hydrogen-bond donors, making the realization of its enantioselective catalysis feasible\(^79\) (eq 2, Scheme 3.1).

\[
\text{eq 1}
\]

\[
\text{eq 2}
\]

\textbf{Scheme 3.1.} Activation of nitroalkene by different catalysts
It should be mentioned that two different strategies for the asymmetric catalysis of nitroalkene Diels-Alder reaction via dienes activation (instead of nitroalkene activation) have been reported. Barbas and some other groups exploited the activated dienes generated in situ from enones via enamine catalysis (eq 1, Scheme 3.2). On the other hand, Deng and co-workers successfully developed another strategy, which is the activation of 3-hydroxy-2-pyrone (dienes) via general base catalysis (eq 2, Scheme 3.2).

Scheme 3.2. Asymmetric nitroalkene Diels-Alder reaction via dienes activation

Catalytic asymmetric nitroalkene Diels-Alder reactions are of great interest to synthetic chemists since they can open ready access to cyclopentenes with multiple contiguous quaternary stereocenters, a motif often found in medicinally relevant complex natural products (Figure 3.1). The Diels-Alder reaction between cyclopentadienes and nitroethylene followed by ring opening reaction has been proved to be very effective for the synthesis of highly substituted cyclopentenes (Scheme 3.3). It’s worth mentioning that some research groups have reported notable advancements in the asymmetric [3+2]
However, neither of these [3+2] reactions nor the aforementioned nitroalkene Diels-Alder reactions activated by dienes can provide cyclopentenes with three or more contiguous quaternary stereocenters.

![Figure 3.1](image)

**Figure 3.1.** Selected examples of natural products with a cyclopentane core

![Scheme 3.3](image)

**Scheme 3.3.** A proven strategy for the synthesis of cyclopentenes

Most of the known hydrogen-bond donor catalysts are associated with additional complementary functionalities that activate and constrain an incoming nucleophile to an orientation necessary for asymmetric induction\textsuperscript{32,85} (such bifunctional catalysts typically have the additional hydrogen bond donor or acceptor unit for these purposes). Obviously, this bifunctional strategy is not applicable for cyclopentadienes (type I, Scheme 3.4), and thus the development of catalysts that do not rely on the additional complementary
functionalities is required. We previously designed and developed such catalyst (92, Scheme 3.4) using the addition reaction of pyrroles to nitroalkenes as a platform.\(^{70,74}\)

![Scheme 3.4. Activation of nitroalkene by different types of H-bond donor catalysts](image)

In 2012, my colleagues\(^ {86}\) demonstrated that helical-chiral double hydrogen-bond donor catalysts (i.e. 92) could promote the nitroalkene Diels-Alder reaction in an enantio- and periselective manner, which represents the first asymmetric catalytic nitroalkene Diels-Alder reaction by LUMO-lowering catalysis. In order to gain more understanding about this new process, the substrate scope of this reaction was investigated by exploiting readily available 5-substituted pentamethylcyclopentadienes.\(^ {87}\) Since the synthetic utility of 5-substituted pentamethylcyclopentadienes is rather limited, a three-step route to 1,4,5,5-tetrasubstituted cyclopentadienes from commercially available ketones was also developed during this course. Preliminary results indicated the reactivity of these newly synthesized 1,4,5,5-tetrasubstituted cyclopentadienes in terms of nitroalkene Diels-Alder reaction was rather low.
3.2. Results and Discussion

3.2.1. Evaluation of Catalysts

As part of our broad interest in hydrogen-bond donor catalysis, our group\textsuperscript{74} has previously developed double hydrogen-bond donor catalysts based on 11,12-benzo-1-aza[6]helicene-N-oxide (87), which do not require additional complementary functionalities for asymmetric induction. In the pursuit of possible catalysis of the nitroalkene Diels-Alder reaction by this type of catalysts, my colleagues\textsuperscript{86} chose cyclopentadiene 106 as a model substrate because 5-substituted pentamethylcyclopentadienes are readily available and have similar structures to the desired 1,4,5,5-tetrasubstituted cyclopentadienes (105, Scheme 3.3). Based on their study, catalysts derived from 11, 12-benzo-1-aza[6]helicene-N-oxide indeed catalyzed the nitroalkene Diels-Alder reaction, providing only the desired product (no inverse electron-demand hetero Diels-Alder product) with only one diastereomer and definite enantioselectivity (entries 1-5, Table 3.1). Based on their initial investigation, catalyst 111 seemed optimum. So we selected this catalyst for our further substrate scope study of this reaction.\textsuperscript{88}
Table 3.1. Nitroalkene Diels-Alder reaction developed by Takenaka

\[
\begin{align*}
\text{Ph} \quad \text{106} \quad \text{+} \quad \begin{aligned}
\text{NO}_2 \quad \text{107}
\end{aligned} \quad \text{Cat. (10 mol %)} \quad \text{CH}_2\text{Cl}_2, -78 \degree \text{C, 20 h} \quad \text{Ph} \quad \text{112}
\end{align*}
\]

\[
\text{(M) 92,109-111}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Cat.</th>
<th>Yield(^b) (%)</th>
<th>er(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>92</td>
<td>70</td>
<td>64:36</td>
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<tr>
<td>2</td>
<td></td>
<td>(P)-108</td>
<td>84</td>
<td>62:38</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>109</td>
<td>70</td>
<td>59.5:40.5</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>110</td>
<td>70</td>
<td>67:33</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>111</td>
<td>77</td>
<td>70:30</td>
</tr>
</tbody>
</table>

\(^a\)Reaction condition: diene (0.4 mmol) and nitroethylene (0.2 mmol) in the presence of 10 mol% of catalyst in CH\(_2\)Cl\(_2\) (0.7 ml). \(^b\)Yield of isolated products. \(^c\)Determined by HPLC analysis. 

\(^{\ddagger}\)BARF\(_{24}\) = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.
3.2.2. Evaluation of Dienes

Starting with catalyst 111, we systematically investigated various 5-substituted pentamethylcyclopentadienes. We were glad to find that most of the dienes were tolerated by our catalysts (Table 3.2). The 4-F-substituted diene gave comparable results to a model diene 106. However, we observed a significantly low yield with the 4-Cl-substituted diene (entry 3, Table 3.2). The reason was not immediately clear to us since all of those dienes are equally reactive under the thermal reaction condition (*i.e.*, without a catalyst). We hypothesized that there might be steric repulsion between 4-Cl-substitution and the catalyst (111) in the transition state, and thus we tested the sterically less demanding catalyst 92. We were pleased to find that 92 restored the yield (entry 4, Table 3.2). Consequently, catalyst 92 was used for evaluation of the remaining entries. 3- and 2-Cl-substituted dienes were also tolerated although yields were somewhat lower than that of 4-Cl-substituted counterpart (entries 4-6, Table 3.2).

While an iodo-substituent did not adversely affect the reaction yield, bromo-substituted diene 113f afforded much lower yield than other halogenated dienes did (entries 4-7 vs. entry 8, Table 3.2). This suppressed reactivity of 4-Br-substituted diene was puzzling since we did not observe any other products that could possibly arise from the diene, and unreacted 113f was fully recovered from the reaction mixture. This observation led us to investigate how the nature (*e.g.*, the size) of the 4-substituent would affect the overall reactivity and selectivity of the dienes.
Table 3.2. Nitroalkene Diels-Alder reaction with different dienes

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Diene</th>
<th>Ar</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
<th>er&lt;sup&gt;d&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>1&lt;sup&gt;e&lt;/sup&gt;</td>
<td>106</td>
<td>Ph</td>
<td>77</td>
<td>30:70</td>
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<td>80</td>
<td>35:65</td>
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<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>4-Cl-Ph</td>
<td>38</td>
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<td>80</td>
<td>36:64</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>113c</td>
<td>3-Cl-Ph</td>
<td>67</td>
<td>31:69</td>
</tr>
<tr>
<td>6</td>
<td>113d</td>
<td>2-Cl-Ph</td>
<td>55</td>
<td>68:32</td>
</tr>
<tr>
<td>7</td>
<td>113e</td>
<td>2-I-Ph</td>
<td>65</td>
<td>60:40</td>
</tr>
<tr>
<td>8&lt;sup&gt;g&lt;/sup&gt;</td>
<td>113f</td>
<td>4-Br-Ph</td>
<td>35</td>
<td>68:32</td>
</tr>
<tr>
<td>9</td>
<td>113g</td>
<td>4-Me-Ph</td>
<td>85</td>
<td>65:35</td>
</tr>
<tr>
<td>10</td>
<td>113h</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;-Ph</td>
<td>75</td>
<td>64:36</td>
</tr>
<tr>
<td>11</td>
<td>113i</td>
<td>4-tert-Butyl-Ph</td>
<td>80</td>
<td>70:30</td>
</tr>
<tr>
<td>12</td>
<td>113j</td>
<td>2-naphthyl</td>
<td>83</td>
<td>69:31</td>
</tr>
<tr>
<td>13</td>
<td>113k</td>
<td>3-OMe-Ph</td>
<td>80</td>
<td>66:34</td>
</tr>
<tr>
<td>14</td>
<td>113l</td>
<td>4-SMe-Ph</td>
<td>89</td>
<td>67:33</td>
</tr>
<tr>
<td>15&lt;sup&gt;h&lt;/sup&gt;</td>
<td>113m</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>0</td>
<td>_</td>
</tr>
<tr>
<td>16</td>
<td>113n</td>
<td></td>
<td>79</td>
<td>63:37</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction condition: diene (0.4 mmol) and nitroethylene (0.2 mmol) in the presence of 10 mol % of catalyst in CH<sub>2</sub>Cl<sub>2</sub> (0.7 ml).  
<sup>b</sup>Entries 1-5 were previously developed by my colleagues.  
<sup>c</sup>Yield of isolated products.  
<sup>d</sup>Determined by HPLC analysis.  
<sup>e</sup>(M)-111 was used.  
<sup>f</sup>(M)-92 was used.  
<sup>g</sup>Unreacted diene 113f was recovered in 60%.  
<sup>h</sup>Unreacted diene 113m was recovered in 90%. 
The 4-Me-substituted diene gave a good yield and moderate selectivity (entry 9, Table 3.2). The sterically demanding 4-CF₃- and 4-tBu-substituted dienes and the 2-naphthylated diene were all as reactive as a model diene 106 (A values of CF₃, tBu and Br are 2.5 kcal mol⁻¹, 4.9 kcal mol⁻¹ and 0.67 kcal mol⁻¹, respectively) (entries 10-12, Table 3.2), and so were other 4-substituted dienes (entries 2, 4 and 9). Therefore, at least, the low reactivity of bromo-substituted diene 113f does not appear to be the steric origin.

We were also interested in testing dienes bearing heteroatoms that can function as a hydrogen bond acceptor because such dienes can potentially compete with a dienophile (nitroethylene) for the catalyst’s binding site. We were gratified that the dienes substituted with either oxygen or sulfur atoms were well tolerated by catalyst 92 (entries 13 and 14, Table 3.2). Conversely, the diene bearing a nitro group gave no product, an outcome of which might be attributable to the expected similar binding ability of its nitro group to the hydrogen bonding site of the catalyst (entry 15, Table 3.2). We were pleased to see the π-facial selectivity of the styrene-substituted diene was also excellent in this reaction albeit the decreased steric bias (entry 16, Table 3.2). Only one diastereomer was detected by ¹H NMR analysis of the crude reaction mixture.

3.2.3. Stereochemical Models

Based on the sense of enantioselection observed in the above reactions and the X-ray structure of the HCl salt of catalyst (P)-92, we were able to propose the stereochemical models for the nitroalkene Diels-Alder reaction (Figure 3.2). The nitroalkene is activated
by the double hydrogen-bond donor catalyst and its backside is completely screened by
the bottom half of the helicene framework. Owing to this screen effect, dienes could only
approach to and react with nitroalkene from the top face. In the disfavored transition
state, the adamantyl group, which is designed to extend the top half of the helical
framework, effectively hinders the approach of an incoming diene.

Figure 3.2. Stereochemical models for P-92 catalyzed nitroalkene DA reaction

3.2.4. Synthesis of New Dienes

We established that the nitroalkene Diels-Alder reaction could be catalyzed in an enantio-
and periselective manner by hydrogen-bond donor catalysts. However, synthetic utility of
5-substituted pentamethyl-cyclopentadienes is rather limited. As such, the 1,4,5,5-
tetrasubstituted cyclopentadienes (105) in Scheme 3.3 would be desired although a
general route to this class of dienes has not been reported. To the best of our knowledge,
the Diels-Alder reaction of such dienes has never been reported.
We envisioned that dienes 105 should be accessed by a classical acid catalyzed alkene isomerization from diolefins 115, which in turn would be obtained by the alkenation of diketones 116 (Scheme 3.5). The synthesis of various diketones 116 from commercially available materials 117 and 118 should be easily achieved by following the procedures reported by Burnell and co workers.

Scheme 3.5. Retrosynthetic design for a new class of dienes

Table 3.3. The methylenation of diketone by different methods

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protocol</th>
<th>Reagents</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wittig</td>
<td>MeP&lt;sup&gt;•&lt;/sup&gt;Ph&lt;sub&gt;3&lt;/sub&gt;J&lt;sup&gt;−&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Lombardo</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;-Zn-TiCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>Curran</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;-Zn-TiCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Takai</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;J&lt;sub&gt;2&lt;/sub&gt;-Zn-TiCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>trace</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yan</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;-Mg-TiCl&lt;sub&gt;4&lt;/sub&gt;-THF</td>
<td>50%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated product. <sup>b</sup> The reaction was not fully optimized.
There are various alkenation methods in literature. Considering the ease operation, we tested the Wittig reaction first. Unfortunately, the methylenation of diketone 116 by this protocol resulted in no desired product (entry 1, Table 3.3), presumably because it is sterically congested.\textsuperscript{93} We then directed our search to titanium-based alkenating reagents, being non-basic; they have found broad utility for various ketones.\textsuperscript{94} Lombardo’s reagent,\textsuperscript{95} generated by aging the reaction mixture of CH$_2$Br$_2$, Zn and TiCl$_4$ at 5 °C for 3 days, has been successfully employed for enolizable ketones.\textsuperscript{96} However, only 7% desired product was formed by this protocol (entry 2, Table 3.3). Some useful modifications\textsuperscript{91,97} of this method (e.g., reagent ratio, reaction time, temperature) reported in the literature were examined, but the difference was marginal (entry 3, Table 3.3). Takai and co-workers\textsuperscript{98} have reported a CH$_2$I$_2$-Zn-TiCl$_4$ system that is more reactive than Lombardo’s system in some cases. Unfortunately, only trace amount of product was observed by TLC analysis (entry 4, Table 3.3). A breakthrough was made by applying a CH$_2$Cl$_2$-Mg-TiCl$_4$-THF system that was recently developed by Yan and co-workers.\textsuperscript{99} We were able to obtain the product in a satisfactory yield without any optimization to this protocol (entry 5, Table 3.3).

\textbf{Scheme 3.6.} A three-step synthesis of new dienes
The following step was straightforward. The diolefin 119 was cleanly isomerized to 120 by HI, which could also be done on the crude diolefins with similar efficiency. Thus, we developed an efficient, synthetically versatile preparation of a new class of dienes 120 in three steps (Scheme 3.6), starting from commercially available ketones (117) and 1,2-bis(trimethylsilyloxy)cyclobutene (118).

3.2.5. Evaluation of New Dienes

With the new dienes at hand, we began to investigate their reactivity profiles in nitroalkene Diels-Alder reaction. Oddly enough, the dienes turned out to be quite unreactive toward nitroethylene (entries 1, 2 and 4, Table 3.4) while analogous 5-substituted pentamethylcyclopentadienes (106 and 113) rapidly reacted with nitroethylene under identical conditions. Giving the structural similarity between them, such a striking difference in their reactivity is very surprising although extra alkyl substituents are expected to raise HOMO of dienes. Therefore, it was not surprising that the hydrogen-bond donor catalyst 92, weakly activating by its very nature, did not promote the reaction (entry 5, Table 3.4).

As mentioned in the introduction, there are no obvious ways to activate nitroalkene for the Diels-Alder reaction other than the hydrogen-bond donors that are typically weakly activating. Considering the low reactivity of 1,4,5,5-tetrasubstituted cyclopentadienes (120) toward nitroethylene under thermal conditions, typical hydrogen-bond donors do not seem promising. However, our group previously found that the intramolecular
nitroalkene Diels-Alder reaction can be catalyzed more efficiently by NaBArF$_{24}$·2.5H$_2$O than the typical hydrogen-bonding catalysts.$^{100}$

**Table 3.4.** The reactivity of new dienes in nitroalkene Diels-Alder reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>dienes</th>
<th>Ar</th>
<th>catalyst</th>
<th>yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120a</td>
<td>Ph</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>120b</td>
<td>Bn</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>120b</td>
<td>Bn</td>
<td>121</td>
<td>67$^b$</td>
</tr>
<tr>
<td>4</td>
<td>120c</td>
<td>PhCH$_2$CH$_2^-$</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>120c</td>
<td>PhCH$_2$CH$_2^-$</td>
<td>(P)-92</td>
<td>14$^c$</td>
</tr>
<tr>
<td>6</td>
<td>120c</td>
<td>PhCH$_2$CH$_2^-$</td>
<td>121</td>
<td>42$^b$</td>
</tr>
</tbody>
</table>

$^a$ Yield of isolated product. $^b$ Reactions were not fully optimized. $^c$ 0% ee.

To our delight, NaBArF$_{24}$·2.5H$_2$O (121) did catalyze the reaction, and provided the desired products in satisfactory yields (entries 3 and 6, Table 3.4), which might be attributed to metal cation assisted hydrogen-bond donor activation (A, Figure 3.3). It was previously reported by our group that NaBArF$_{24}$·(H$_2$O)$_x$(PhOH)$_y$, a derivative of NaBArF$_{24}$·2.5H$_2$O by replacing some of the water molecules with more acidic phenol molecules, provided better yield and selectivity in an intramolecular nitroalkene Diels-
Alder reaction.\textsuperscript{100} It was attributed to the higher acidity of the complex. In light of these findings, it might be interesting to develop new hydrogen-bond donor catalysts by introducing chiral acids (e.g., BINOLs, TADDOLs and chiral phosphoric acids) into NaBArF$_{24}$·2.5H$_2$O (121) (B, Figure 3.3).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Metal cation assisted H-bond donor catalysis}
\end{figure}

### 3.3. Summary and Outlook

In summary, we successfully demonstrated that the nitroalkene Diels-Alder reaction could be catalyzed by helical-chiral double-hydrogen-bond donor catalysts in an enantio- and periselective manner. This represents, to the best of our knowledge, the first asymmetric catalytic nitroalkene Diels-Alder reaction by LUMO-lowering catalysis. A broad range of 5-substituted pentamethycyclopentadienes (113) has been catalyzed in nitroalkene Diels-Alder reaction achieving good yields and enantioselectivities by catalyst 92. An efficient, synthetically versatile synthesis to access a new class of dienes (120) has been designed and developed. Based on this preparation, various new dienes
which are synthetically useful have been synthesized from commercially available ketones and 1,2-bis(trimethylsilyloxy)cyclobutene. The activity profiles of these new dienes were explored in the context of nitroalkene Diels-Alder reaction. It was found that these dienes were surprisingly unreactive, which is hard to rationalize. To our delight, salt complex NaBArF$_{24}$·2.5H$_2$O (121) was found to be able to catalyze the nitroalkene Diels-Alder reaction of these new dienes with moderate yield, the result of which provides potential applications in the new asymmetric catalysts development.

3.4. Experimental Section

3.4.1. General Information

All reactions were carried out in the oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Silicycle pre-coated silica gel plates with F$_{254}$ indicator. Visualization was accomplished by UV light (256 nm), with combination of potassium permanganate and/or vanillin solution as an indicator. Flash column chromatography was performed according to the method of Still$^{76}$ using silica gel 60 (mesh 230-400) supplied by Silicycle. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH$_2$Cl$_2$) was freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. THF was freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. Nitroethylene was prepared according to the literature.$^{101}$
$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 300 (300 MHz $^1$H) and a Bruker Avance 400 (400 MHz $^1$H, 100 MHz $^{13}$C). Chemical shift values (δ) are reported in ppm relative to Me$_4$Si (δ 0.0 ppm) unless otherwise noted. The proton spectra are reported as follows δ (multiplicity, coupling constant $J$, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL® III automatic polarimeter. Infrared spectra were recorded using PerkinElmer™ SPECTRUM ONE with Universal ATR Sampling Accessory (Composite Zinc Selenide and Diamond crystals). High-resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, the University of Miami.

3.4.2. General Procedures for Preparation of 113

All the 5-substituted pentamethylcyclopentadienes (113) were synthesized according to a previously reported procedures; Substrates 106 and 113a-c were previously synthesized and tested in nitroalkene Diels-Alder reaction by my colleagues$^{86}$. The reactions were not optimized.
1-chloro-2-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene \( (113d) \):

Obtained as a colorless oil with 72% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.25 (dd, \( J = 1.7, 7.7 \) Hz, 1H), 6.95-7.04 (m, 2H), 6.78 (dd, \( J = 1.7, 7.6 \) Hz, 1H), 2.92 (s, 2H), 1.73 (s, 12H), 1.05 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 140.5, 137.0, 134.5, 134.0, 129.6, 128.9, 126.9, 126.1, 56.3, 36.2, 23.4, 11.2, 10.3; FTIR (neat) \( \nu_{\text{max}} \) 2963, 2915, 2859, 1472, 1442, 1379, 1050, 1037, 748 cm\(^{-1}\); GCMS: 260[M]\(^+\)

1-iodo-2-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene \( (113e) \): Obtained as a white solid with 61% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.76 (dd, \( J = 1.2, 7.9 \) Hz, 1H), 7.04-7.08 (m, 1H), 6.72-6.80 (m, 2H), 2.88 (s, 2H), 1.76 (s, 6H), 1.70 (s, 6H), 1.06 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 142.0, 140.6, 139.0, 134.5, 128.4, 127.9, 127.6, 102.5, 56.5, 44.6, 24.1, 11.2, 10.4; FTIR (neat) \( \nu_{\text{max}} \) 2961, 2912, 2858, 1561, 1442, 1378, 1087, 1009, 908, 742 cm\(^{-1}\); GCMS: 352[M]\(^+\)

1-bromo-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene \( (113f) \):

Obtained as a white solid with 61% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.18 (d, \( J = 8.4 \) Hz, 2H), 6.70 (d, \( J = 8.4 \) Hz, 2H), 2.64 (s, 2H), 1.76 (s, 6H), 1.59 (s, 6H), 0.99 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 139.0, 137.7, 135.1, 130.3, 130.2, 119.4, 56.7, 40.9, 21.8, 10.9, 10.5; FTIR (neat) \( \nu_{\text{max}} \) 2964, 2916, 2852, 1657, 1588, 1487, 1440, 1377, 1071, 1009, 830, 777, 711 cm\(^{-1}\); GCMS: 304 [M]\(^+\)

1-methyl-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene \( (113g) \):

Obtained as a white solid with 86% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.88 (d, \( J = 7.9 \) Hz, 2H), 6.73-6.77 (m, 2H), 2.88 (s, 2H), 1.72 (s, 6H), 1.03 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 139.1, 137.8, 135.2, 130.4, 130.3, 119.5, 57.0, 40.9, 21.8, 0.98 (s, 3H); FTIR (neat) \( \nu_{\text{max}} \) 2963, 2915, 2853, 1561, 1442, 1379, 1050, 1037, 748 cm\(^{-1}\); GCMS: 256[M]\(^+\)
Hz, 2H), 6.74 (d, J = 7.9 Hz, 2H), 2.66 (s, 2H), 2.23 (s, 3H), 1.76 (s, 6H), 1.60 (s, 6H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.6, 135.8, 134.9, 134.5, 128.6, 128.0, 56.9, 41.3, 22.0, 21.1, 11.0, 10.5; FTIR (neat) $\nu_{\text{max}}$ 2968, 2914, 2857, 1657, 1515, 1442, 1378, 1110, 820, 782, 757 cm$^{-1}$; GCMS: 240 [M]$^+$

$I$-$(1,2,3,4,5$-pentamethylcyclopenta$-2,4$-dienyl)methyl$-4$-(trifluoromethyl)benzene

(113h): Obtained as a white solid with 73% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 2.74 (s, 2H), 1.78 (s, 6H), 1.57 (s, 6H), 1.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.9, 138.9, 135.2, 128.8, 124.0 (2x), 56.8, 41.3, 21.9, 10.9, 10.4; FTIR (neat) $\nu_{\text{max}}$ 2968, 2919, 2860, 1618, 1417, 1323, 1162, 1120, 1067, 1019, 847 cm$^{-1}$; GCMS: 294 [M]$^+$

$I$-tert-butyl$-4$-$(1,2,3,4,5$-pentamethylcyclopenta$-2,4$-dienyl)methyl$benzene

(113i): Obtained as a light yellow oil with 88% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.08 (d, J = 8.1 Hz, 2H), 6.78 (d, J = 8.1 Hz, 2H), 2.66 (s, 2H), 1.76 (s, 6H), 1.59 (s, 6H), 1.25 (s, 9H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.2, 139.6, 135.7, 134.4, 128.2, 123.9, 56.7, 41.1, 34.3, 31.4, 21.8, 10.9, 10.4; FTIR (neat) $\nu_{\text{max}}$ 2960, 2913, 2863, 1516, 1448, 1378, 1363, 1269, 1105, 1020, 834, 785 cm$^{-1}$; GCMS: 282 [M]$^+$

$2$-$(1,2,3,4,5$-pentamethylcyclopenta$-2,4$-dienyl)methyl)naphthalene

(113j): Obtained as a white solid with 81% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70-7.77 (m, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.38-7.42 (m, 2H), 7.36 (s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 2.91 (s, 2H), 1.86 (s, 6H), 1.60 (s, 6H), 1.10 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.5, 136.7,
134.8, 133.3, 132.1, 127.8, 127.7, 127.5, 126.9, 126.4, 125.4, 124.9, 57.0, 41.7, 22.1, 11.0, 10.6; FTIR (neat) $\nu_{\text{max}}$ 3061, 2965, 2914, 2857, 1601, 1509, 1445, 1378, 1095, 852, 815, 788, 748 cm$^{-1}$; GCMS: 276$[\text{M}]^+$

1-methoxy-3-((1,2,3,4,5-pentamethycyclopenta-2,4-dienyl)methyl)benzene  (113k):
Obtained as a white solid with 84% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.02 (t, $J = 7.8$ Hz, 1H), 6.65 (dd, $J = 2.4$, 8.2 Hz, 1H), 6.52 (d, $J = 7.6$ Hz, 1H), 6.45 (s, 1H), 3.72 (s, 3H), 2.72 (s, 2H), 1.80 (s, 6H), 1.65 (s, 6H), 1.02 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.8, 140.5, 139.6, 134.6, 128.1, 121.4, 113.8, 111.5, 56.8, 55.1, 41.4, 22.2, 11.0, 10.5; FTIR (neat) $\nu_{\text{max}}$ 2959, 2915, 2858, 1600, 1584, 1490, 1447, 1378, 1291, 1261, 1153, 1048, 910, 776 cm$^{-1}$; GCMS: 256 [M]$^+$

methyl(4-((1,2,3,4,5-pentamethycyclopenta-2,4-dienyl)methyl)phenyl)sulfane  (113l):
Obtained as a light yellow solid with 87% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.99 (d, $J = 8.3$ Hz, 2H), 6.77 (d, $J = 8.3$ Hz, 2H), 2.65 (s, 2H), 2.41 (s, 3H), 1.76 (s, 6H), 1.59 (s, 6H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.3, 136.0, 134.8, 134.7, 129.2, 126.0, 56.8, 41.1, 21.9, 16.4, 11.0, 10.5; FTIR (neat) $\nu_{\text{max}}$ 2967, 2916, 2857, 1494, 1441, 1378, 1093, 1017, 835, 810, 781 cm$^{-1}$; GCMS: 272 [M]$^+$

1-Nitro-4-((1,2,3,4,5-pentamethycyclopenta-2,4-dienyl)methyl)benzene  (113m):
Obtained as a bright yellow solid with 10% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.6$ Hz, 2H), 2.79 (s, 2H), 1.80 (s, 6H), 1.56 (s, 6H), 1.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.7, 146.3, 138.5, 135.6, 129.2, 122.4, 56.9, 41.3,
21.8, 10.9, 10.5; FTIR (neat) $\nu_{\text{max}}$ 2918, 2859, 1601, 1447, 1342, 851, 806, 746, 702 cm$^{-1}$; GCMS: 271 [M]$^+$

\textbf{(E)-(3-(1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)prop-1-enyl)benzene} \quad \text{(113n)}:

Obtained as a colorless oil with 80% yield; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.14-7.28 (m, 5H), 6.30 (d, $J$ = 15.8 Hz, 1H), 5.40-5.47 (m, 1H), 2.34 (dd, $J$ = 1.4, 7.0 Hz, 2H), 1.79 (s, 6H), 1.76 (s, 6H), 0.97 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 140.1, 138.4, 134.2, 129.9, 128.5, 128.1, 126.7, 126.0, 55.9, 38.5, 21.4, 11.2, 10.0; FTIR (neat) $\nu_{\text{max}}$ 3026, 2962, 2913, 2861, 1600, 1496, 1444, 1378, 960, 738 cm$^{-1}$; GCMS: 252[M]$^+$

\textbf{3.4.3. General Procedure for Asymmetric Nitroalkene Diels-Alder Reaction}

A flame-dried test tube was charged with catalyst 92 (28 mg, 0.02 mmol). To this were added CH$_2$Cl$_2$ (0.3 mL) and a solution of nitroethylene (15 mg, 0.2 mmol) in CH$_2$Cl$_2$ (0.1 mL). The resulting mixture was cooled to -78 °C, slowly treated with a solution of diene (0.4 mmol) in CH$_2$Cl$_2$ (0.3 mL), stirred at -78 °C for 20 h, and then quenched with a solution of hydrazine hydrate (0.1 mL) in MeOH (0.1 mL). The resulting mixture was washed with H$_2$O (3 x 1 mL) and brine (1 x 1 mL), dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The crude material was purified by flash chromatography on silica gel (2% EtOAc in hexanes). The catalyst ligand was recovered by eluting the column with 100% EtOAc and reused without loss in activity and selectivity.
(-)-7-(2-Chlorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene \( \text{(114d)} \):

Obtained as a colorless oil in 55% yield with e.r. of 68:32. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), \( t_r \) (major) = 54.04 min., \( t_r \) (minor) = 60.32 min. \([a]^{20}_D = -12, c = 0.0005\), CH\(_2\)Cl\(_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.29 – 7.31 (m, 1H), 7.09 – 7.20 (m, 3H), 4.69 – 4.72 (m, 1H), 2.80 (d, \( J = 14.0 \) Hz, 1H), 2.67 (d, \( J = 14.0 \) Hz, 1H), 1.88 – 1.91 (m, 2H), 1.73 (s, 3H), 1.56 (s, 3H), 1.25 (s, 3H), 0.93 (s, 3H), 0.84 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( d \) 139.3, 137.8, 135.3, 133.0, 131.3, 129.9, 127.6, 126.2, 91.8, 64.6, 63.9, 56.7, 37.5, 34.9, 15.4, 12.6, 11.5, 11.1, 10.4; FTIR (neat) \( \nu_{\text{max}} \) 2943, 1541, 1444, 1382, 1361, 1058, 753, 682 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{19}\)H\(_{24}\)ClNNaO\(_2\) [M + Na]\(^+\), expected: 356.1393, found: 356.1387.

(-)-7-(2-Iodobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene \( \text{(114e)} \):

Obtained as a colorless oil in 65% yield with e.r. of 60:40. Enantiomeric ratio was determined by HPLC from corresponding compound 3, in which the iodo-substituent has been replaced with H, with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), \( t_r \) (major) = 40.71 min., \( t_r \) (minor) = 45.09 min. \([a]^{20}_D = -16, c = 0.0005\), CH\(_2\)Cl\(_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.79 (d, \( J = 8.0 \) Hz, 1H), 7.19 – 7.24 (m, 2H), 6.83 – 6.85 (m, 1H), 4.68 – 4.70 (m, 1H), 2.85 (d, \( J = 14.4 \) Hz, 1H), 2.72 (d, \( J = 14.4 \) Hz, 1H), 1.88 – 1.90 (m, 2H), 1.73 (s, 3H), 1.50 (s, 3H), 1.26 (s, 3H), 0.93 (s, 3H), 0.86 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( d \) 143.2, 140.6, 139.6, 131.9, 131.8, 128.3, 127.9, 103.6, 92.0, 65.0, 64.7, 57.1, 42.3, 37.7, 16.4, 13.5, 12.1, 12.0, 11.0; FTIR (neat) \( \nu_{\text{max}} \) 2943, 1540, 1449, 1382, 1361, 1009, 733, 753 cm\(^{-1}\);

(-)-7-(4-Bromobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene  **(114f)**:

Obtained as a colorless oil in 35% yield with e.r. of 68:32. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), tₑ (major) = 46.93 min., tₑ (minor) = 59.41 min. [α]20D = - 44, c = 0.0005, CH₂Cl₂. 

1H NMR (400 MHz, CDCl₃) δ 7.34 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 4.69 – 4.71 (m, 1H), 2.54 (d, J = 13.6 Hz, 1H), 2.43 (d, J = 13.6 Hz, 1H), 1.87 – 1.89 (m, 2H), 1.69 (s, 3H), 1.46 (s, 3H), 1.12 (s, 3H), 0.86 (s, 3H), 0.78 (s, 3H); 

13C NMR (100 MHz, CDCl₃) δ 139.2, 138.5, 132.4, 131.5, 131.1, 120.0, 95.5, 91.6, 64.2, 63.4, 56.2, 38.7, 37.6, 15.5, 12.7, 11.4, 11.0, 10.3; FTIR (neat) νmax 2940, 1540, 1487, 1446, 1361, 1072, 1011, 808, 733 cm⁻¹; HRMS (ESI-TOF): Exact mass calcd for C₁₉H₂₄BrINaO₂ [M + Na]⁺, expected: 400.0888, found: 400.0880.

(-)-1,2,3,4,7-Pentamethyl-7-(4-methylbenzyl)-5-nitrobicyclo[2.2.1]hept-2-ene  **(114g)**:

Obtained as a colorless oil in 85% yield with e.r. of 65:35. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), tₑ (major) = 29.73 min., tₑ (minor) = 33.85 min. [α]20D = - 52, c = 0.0005, CH₂Cl₂. 

1H NMR (400 MHz, CDCl₃) δ 7.03 (d, J = 7.6 Hz, 2H), 6.94 (d, J = 7.6 Hz, 2H), 4.69 – 4.71 (m, 1H), 2.55 (d, J = 13.6 Hz, 1H), 2.45 (d, J = 13.6 Hz, 1H), 2.31 (s, 3H), 1.87 – 1.89 (m, 2H), 1.70 (s, 3H), 1.49 (s, 3H), 1.12 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H); 

13C NMR (100 MHz, CDCl₃) δ 139.3, 136.3,
135.6, 131.3, 130.7, 128.7, 96.7, 91.8, 64.3, 63.8, 56.2, 21.1, 15.5, 12.6, 11.4, 11.0, 10.3;
FTIR (neat) $\nu_{\text{max}}$ 2936, 1542, 1447, 1362, 1109, 813, 774 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for $\text{C}_{20}\text{H}_{27}\text{NNaO}_2$ [M + Na]$^+$, expected: 336.1939, found: 336.1947.

(-)-1,2,3,4,7-Pentamethyl-5-nitro-7-(4-(trifluoromethyl)benzyl)bicyclo[2.2.1]hept-2-ene (114h): Obtained as a colorless oil in 75% yield with e.r. of 64:36. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), $t_r$ (major) = 31.85 min., $t_r$ (minor) = 38.25 min. $\left[a\right]^{20}_D = -22$, c = 0.0005, CH$_2$Cl$_2$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 4.69 – 4.72 (m, 1H), 2.65 (d, $J = 13.6$ Hz, 1H), 2.54 (d, $J = 13.6$ Hz, 1H), 1.87 – 1.91 (m, 2H), 1.70 (s, 3H), 1.48 (s, 3H), 1.14 (s, 3H), 0.89 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.9 (d, $J = 1.4$ Hz), 131.5, 131.0, 128.4 (t, $J = 320.0$ Hz), 125.8, 124.9 (dd, $J = 3.6$ Hz, $J = 72.0$ Hz), 91.5, 64.2, 63.9, 56.2, 39.2, 37.6, 15.6, 12.6, 11.4, 11.0, 10.3; FTIR (neat) $\nu_{\text{max}}$ 2945, 1543, 1323, 1162, 1067, 1018, 842, 746 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for $\text{C}_{20}\text{H}_{24}\text{F}_3\text{NNaO}_2$ [M + Na]$^+$, expected: 390.1657, found: 390.1654.

(-)-7-(4-tert-Butylbenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (114i): Obtained as a colorless oil in 80% yield with e.r. of 70:30. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.4mL/min), $t_r$ (major) = 26.76 min., $t_r$ (minor) = 29.51 min. $\left[a\right]^{20}_D = -54$, c = 0.0005, CH$_2$Cl$_2$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.23 (d, $J = 8.4$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 2H), 4.69 – 4.72 (m, 1H), 2.55 (d, $J = 13.6$ Hz, 1H),
2.45 (d, \( J = 13.6 \) Hz, 1H), 1.85 – 1.89 (m, 2H), 1.70 (s, 3H), 1.48 (s, 3H), 1.3 (s, 9H), 1.12 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 149.0, 139.2, 136.3, 131.3, 130.4, 124.8, 91.8, 64.3, 63.8, 56.2, 38.7, 37.7, 34.5, 31.5, 15.6, 12.6, 11.4, 10.9, 10.3; FTIR (neat) \( \nu_{\text{max}} \) 2952, 1542, 1362, 1269, 1110, 908, 835, 731 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{23}\)H\(_{33}\)NNaO\(_2\) [M + Na]\(^+\), expected: 378.2409, found: 378.2408.

\((-\)-2-\((1,2,3,4,7\text{-Pentamethyl-5-nitro}\text{bicyclo[2.2.1]hept}\text{-2-en-7-yl})\text{methyl}naphthalene (114j): Obtained as a colorless oil in 83% yield with e.r. of 69:31. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (100% Hexanes, flow rate = 0.5mL/min), \( t_r \) (minor) = 52.69 min., \( t_r \) (major) = 69.35 min. \([\alpha]^D_{20} = -48, c = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.73 – 7.81 (m, 3H), 7.51 (br s, 1H), 7.41 – 7.48 (m, 2H), 7.21 (dd, \( J = 2.0, 8.4 \) Hz, 1H), 4.71 – 4.74 (m, 1H), 2.77 (d, \( J = 13.6 \) Hz, 1H), 2.61 (d, \( J = 13.6 \) Hz, 1H), 1.90 – 1.91 (m, 2H), 1.74 (s, 3H), 1.53 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H), 0.79 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 139.3, 137.1, 133.4, 132.1, 131.4, 129.6, 129.0, 127.7, 127.6, 127.3, 126.1, 125.4, 91.7, 64.3 64.1, 56.3, 39.5, 37.7, 15.7, 12.7, 11.5, 11.0, 10.4; FTIR (neat) \( \nu_{\text{max}} \) 2943, 1540, 1382, 1362, 1084, 821, 748 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{23}\)H\(_{28}\)NO\(_2\) [M + 1]\(^+\), expected: 350.2120, found: 350.2116.

\((-\)7-\((3\text{-Methoxybenzyl})\text{-1,2,3,4,7-pentamethyl-5-nitro}\text{bicyclo[2.2.1]hept}\text{-2-ene (114k): Obtained as a colorless oil in 80% yield with e.r. of 66:34. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard}}\)
column (1% iPrOH in Hexanes, flow rate = 0.3mL/min), $t_r$ (minor) = 22.48 min., $t_r$ (major) = 25.07 min. $[\alpha]^{20}_D = -30$, $c = 0.0005$, CH$_2$Cl$_2$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.12 – 7.16 (m, 1H), 6.61 – 6.73 (m, 2H), 4.68 – 4.71 (m, 1H), 3.78 (s, 3H), 2.55 (d, $J = 13.6$ Hz, 1H), 2.45 (d, $J = 13.6$ Hz, 1H), 1.88 – 1.89 (m, 2H), 1.70 (s, 3H), 1.48 (s, 3H), 1.13 (s, 3H), 0.89 (s, 3H), 0.79 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 141.1, 139.2, 131.3, 128.9, 123.3, 116.8, 111.1, 102.7, 91.7, 64.3, 63.8, 56.2, 55.2, 39.4, 37.7, 15.7, 12.6, 11.5, 10.9, 10.3; FTIR (neat) $\nu_{\text{max}}$ 2939, 1599, 1583, 1541, 1488, 1362, 1264, 1154, 1045, 768, 699 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{20}$H$_{27}$NNaO$_3$ [M + Na]$^+$, expected: 352.1889, found: 352.1898.

$(-)$-Methyl(4-((1,2,3,4,7-pentamethyl-5-nitro bicyclo[2.2.1]hept-2-en-7-yl)methyl)phenyl)sulfane (114l): Obtained as a colorless oil in 89% yield with e.r. of 67:33. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (1% iPrOH in Hexanes, flow rate = 0.3mL/min), $t_r$ (minor) = 25.25 min., $t_r$ (major) = 28.71 min. $[\alpha]^{20}_D = -60$, $c = 0.0005$, CH$_2$Cl$_2$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (d, $J = 8.4$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 4.68 – 4.71 (m, 1H), 2.42 – 2.56 (m, 5H), 1.87 – 1.89 (m, 2H), 1.69 (s, 3H), 1.47 (s, 3H), 1.12 (s, 3H), 0.86 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.5, 136.7, 136.1, 131.7, 131.6, 126.7, 92.0, 64.5, 64.1, 56.5, 39.1, 38.0, 16.5, 15.9, 13.0, 11.8, 11.3, 10.6; FTIR (neat) $\nu_{\text{max}}$ 2939, 1540, 1439, 1362, 1090, 810, 755 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{20}$H$_{28}$NO$_2$S [M + 1]$^+$, expected: 346.1841, found: 346.1845.
(-)-7-Cinnamyl-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (114n): Obtained as a colorless oil in 79% yield with e.r. of 63:37. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (100% Hexanes, flow rate = 0.5mL/min), \( t_r \) (minor) = 19.25 min., \( t_r \) (major) = 24.89 min. \([\alpha]^{20}_D = -54, c = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.25 – 7.33 (m, 4H), 7.17 – 7.23 (m, 1H), 6.03 – 6.22 (m, 2H), 4.72 – 4.75 (m, 1H), 2.07 – 2.19 (m, 2H), 1.89 – 1.98 (m, 2H), 1.65 (s, 3H), 1.42 (s, 3H), 1.29 (s, 3H), 1.06 (s, 3H), 0.81 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 139.3, 137.9, 131.3, 130.3, 128.7, 128.67, 127.0, 126.0, 91.7, 63.9, 63.5, 55.7, 37.4, 36.9, 15.7, 12.7, 11.2, 11.1, 10.2; FTIR (neat) \( \nu_{\text{max}} \) 2939, 1540, 1446, 1362, 1077, 966, 745, 693 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{21}\)H\(_{27}\)NNaO\(_2\) [M + Na]\(^+\), expected: 348.1939, found: 348.1931.

3.4.4. General Procedure for the Synthesis of Diones 116

All the diones were synthesized according to the reported procedures\(^92\).

2-methyl-2-phenylcyclopentane-1,3-dione (116a): Obtained as pale yellow oil with 68% yield, all the spectral were the same as reported in literature \(^{102}\).

2-methyl-2-phenemethylcyclopentane-1,3-dione (116b): Obtained as light orange solid with 72% yield, all the spectral were the same as reported in literature \(^{92b}\).

2-methyl-2-phenethylcyclopentane-1,3-dione (116c): Obtained as a brown solid with 84% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.27-7.07 (m, 5H), 2.58-2.81 (m, 4H), 2.46-2.50 (m,
2H), 1.95-1.99 (m, 2H), 1.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 216.7, 140.9, 128.9, 128.8, 126.7, 56.8, 37.3, 35.5, 31.2, 20.2; FTIR (neat) $\nu_{\text{max}}$ 3029, 2922, 1757, 1713, 1497, 1454, 1377, 1269, 1039, 1000, 922, 748, 700 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcld for C$_{14}$H$_{16}$NaO$_2$ [M + Na]$^+$, expected: 239.1043, found: 239.1043

3.4.5. General Procedure for the Synthesis of Dienes 120

The methylenation of diones 116$^{90}$ and the following isomerization of 119$^{91}$ were carried out with slightly modified procedures reported in literature, the reactions were not fully optimized, a typical procedure is as follows: to a 0 °C suspension of Mg (3.36 g, 140 mmol), TiCl$_4$ (7.65 ml, 70 mmol), and CH$_2$Cl$_2$ (70 mL) was added via cannula a solution of dione (7.0 mmol) in CH$_2$Cl$_2$ (26 mL) and THF (26 mL). After being stirred for 2 h at 0 °C, the resulting green-black mixture was stirred for another 2 h at room temperature. The reaction mixture was then quenched by slowly adding saturated potassium carbonate solution (150 mL) and diluted with ether (300 mL). The organic layer was then separated, dried, evaporated, and passed through a short plug of silica gel with pentane, and used as crude without further purification in the following step. The crude was then dissolved in PhH (14 ml), and 47% HI (0.7 ml) was added. The reaction mixture was then stirred vigorously for 20 h in the dark. The reaction was diluted with pentane (20 mL), washed with saturated aqueous NaHCO$_3$, (2 X 15 mL), aqueous Na$_2$S$_2$O$_3$, (2 X 15 mL), and brine (15 mL), and the organic phase was dried over a mixture of MgSO$_4$ and K$_2$CO$_3$. The product was purified by flash chromatography (100% hexane) to yield the desired products.
(1,2,5-trimethylcyclopenta-2,4-dienyl)benzene (120a): Obtained as a colorless oil with 25% yield based on dione 13a; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25-7.31 (m, 2H), 7.17-7.21 (m, 1H), 7.03-7.06 (m, 2H), 5.98 (s, 2H), 1.70 (s, 6H), 1.38 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.4 (2x), 128.7, 126.4, 126.3, 125.1, 18.8, 13.3 (2x); FTIR (neat) $\nu_{max}$ 3055, 2965, 2932, 2914, 2878, 1600, 1492, 1444, 1372, 1023, 819, 756 cm$^{-1}$; GCMS: 184[M]$^+$

(2-(1,2,5-trimethylcyclopenta-2,4-dienyl)methyl)benzene (120b): Obtained as a colorless oil with 28% yield based on dione 13b; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.96-7.13 (m, 5H), 5.76 (s, 2H), 2.78 (s, 2H), 1.92 (s, 6H), 1.07 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.4, 138.3, 128.7, 127.6, 126.1, 125.8, 57.2, 41.2, 22.5, 13.4; FTIR (neat) $\nu_{max}$ 3046, 2959, 2918, 1604, 1495, 1450, 1377, 1030, 821, 755 cm$^{-1}$; GCMS: 198[M]$^+$

(2-(1,2,5-trimethylcyclopenta-2,4-dienyl)ethyl)benzene (120c): Obtained as a colorless oil with 40% yield based on dione 13c; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24-7.28 (m, 2H), 7.15-7.19 (m, 1H), 7.11-7.13 (m, 2H), 5.99 (s, 2H), 1.95-1.99 (m, 2H), 1.88 (s, 6H), 1.74-1.78 (m, 2H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.9, 143.5, 128.6, 128.5, 125.9, 125.5, 56.6, 37.3, 30.5, 22.4, 13.1; FTIR (neat) $\nu_{max}$ 3061, 3028, 2965, 2931, 2863, 1604, 1496, 1450, 1376, 1030, 911, 821, 748 cm$^{-1}$; GCMS: 212[M]$^+$
3.4.6 General Procedure for NaBArF$_{24}$•2.5H$_2$O Catalyzed Nitroalkene Diels-Alder Reaction

A flame-dried test tube was charged with NaBArF$_{24}$•2.5H$_2$O (19 mg, 0.02 mmol). To this were added CH$_2$Cl$_2$ (0.3 mL) and a solution of nitroethylene (15 mg, 0.2 mmol) in CH$_2$Cl$_2$ (0.1 mL). The resulting mixture was cooled to -78 °C, slowly treated with a solution of diene (0.4 mmol) in CH$_2$Cl$_2$ (0.3 mL), then the mixture was warmed up to r.t and stirred for 20 h, and then quenched with a solution of hydrazine hydrate (0.1 mL) in MeOH (0.1 mL). The resulting mixture was washed with H$_2$O (3 x 1 mL) and brine (1 x 1 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (2% EtOAc in hexanes).

7-Benzyl-1,4,7-trimethyl-5-nitrobicyclo[2.2.1]hept-2-ene (122b): Obtained as a white solid with 67% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 – 7.26 (m, 5H), 6.20 (d, $J = 6.0$ Hz, 1H), 5.68 (d, $J = 6.0$ Hz, 1H), 4.72 – 4.75 (m, 1H), 2.80 (d, $J = 14.4$ Hz, 1H), 2.61 (d, $J = 13.6$ Hz, 1H), 2.04 – 2.10 (m, 1H), 1.92 – 1.97 (m, 1H), 1.21 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.1, 139.2, 133.4, 130.8, 128.0, 126.3, 90.3, 65.1, 62.1, 55.5, 39.2, 38.9, 15.1, 14.0, 12.6; FTIR (neat) $\nu_{\text{max}}$ 2955, 1541, 1452, 1366, 1091, 877, 748, 704 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{17}$H$_{22}$NO$_2$ [M + 1]$^+$, expected: 272.1651, found: 272.1643.

1,4,7-Trimethyl-5-nitro-7-phenethylbicyclo[2.2.1]hept-2-ene (122c): Obtained as colorless oil with 42% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26 – 7.29 (m, 2H), 7.12 –
7.20 (m, 3H), 6.11 (d, J = 6.0 Hz, 1H), 5.58 (d, J = 6.0 Hz, 1H), 4.78 – 4.81 (m, 1H), 2.51 – 2.57 (m, 2H), 2.13 – 2.18 (m, 1H), 1.96 – 2.00 (m, 1H), 1.56 – 1.75 (m, 2H), 1.38 (s, 3H), 1.21 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.3, 141.7, 133.1, 128.55, 128.2, 125.9, 90.3, 64.1, 61.9, 55.3, 39.0, 35.1, 32.5, 14.7, 14.3, 13.0; FTIR (neat) $\nu_{\text{max}}$ 2952, 1542, 1453, 1366, 1091, 752, 700 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for $\text{C}_{18}\text{H}_{23}\text{NNaO}_2 [\text{M} + \text{Na}]^+$, expected: 308.1626, found: 308.1628.

**Note to the Reader:**

This chapter (Pages 53-83) has been previously published and is utilized here with the permission of the publisher.
4.1. Background

The design, synthesis and disclosure of a new catalyst framework and its application in chemical synthesis have been of great importance to chemists, and continue to be a central interest especially in asymmetric synthesis. Chemists have witnessed the great impact a new catalyst system could bring to the field if carefully studied. The derivatization of an existing “privileged” chiral scaffold has been an important method to develop new catalyst systems. Our group previously introduced a new chiral scaffold-11, 12-benzo-1-aza[6]helicene-N-oxide, and demonstrated its versatility and great potential in asymmetric synthesis.\(^70,72-74\) Catalysts based on these helical chiral structures have been found to be effective in reactions with different mechanisms. To better study this chiral scaffold, elucidate their structure-reactivity-selectivity relationships and find further more important applications, it is important for us to develop more novel helical chiral catalysts based on the “mother” architecture. However, 11, 12-benzo-1-aza[6]helicene-N-oxide has been remained nonexistent in literature before our contribution\(^72\) to this field, not to mention developing new chiral catalysts based on it. It’s worth to mention that a few groups have reported elegant preparation and derivatization of helical chiral molecules recently, however none of these studies are closely related to our system. It became highly necessary for us to design and develop efficient methods to synthesize new helical chiral catalyst based on 11, 12-benzo-1-aza[6]helicene-N-oxide.
4.2. Results and Discussion

4.2.1. Synthesis of Helical Bis-N-oxides

Chiral pyridine-N-oxides have found great applications\textsuperscript{103} in the field of asymmetric organic synthesis because of their strong electron donating ability. Most of them were used as chiral ligands in the synthesis of metal complexes, and recently they have been utilized as nucleophilic catalysts in the field of organocatalysis. Previously we have synthesized catalyst \textbf{88}, and successfully catalyzed propargylation of aldehyde with this catalyst. In the course of developing a catalytic, enantioselective allylation of ketoimines, we became interested in bis-N-oxides catalyst \textbf{123} (Figure 4.1).

![Figure 4.1. Development of chiral pyridine N-oxide catalyst](image)

Based on our previous experience in the synthesis of helicene-N-oxides,\textsuperscript{72} we envisioned \textit{meta}-chloroperoxybenzoic acid (\textit{m}CPBA) should be a suitable oxidant for this purpose. However, due to the potentially lower accessibility of the pyridine ring of \textbf{88}, harsh conditions might be required. To get a general idea whether the pyridyl nitrogen atom of \textbf{88} is accessible and therefore be oxidized by \textit{m}CPBA, we first tested a harsh condition where \textbf{88} was refluxed with 3.0 equivalent of \textit{m}CPBA for 3 hours. To our delight, we
were able to identify, purify and obtain about 30% of the desired product 123, though no starting material 88 was recovered (entry 1, Table 4.1).

Table 4.1. The synthesis of bis-N-oxide by mCPBA oxidization

<table>
<thead>
<tr>
<th>entry</th>
<th>mCPBA (equiv)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>CHCl₃</td>
<td>61</td>
<td>3</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>CHCl₃</td>
<td>25</td>
<td>24</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
<td>CHCl₃</td>
<td>25</td>
<td>16</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>2.4</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>16</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>2.4</td>
<td>CH₂Cl₂/PhCF₃</td>
<td>25</td>
<td>16</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>CH₂Cl₂/PhCF₃</td>
<td>25</td>
<td>16</td>
<td>72</td>
<td>18</td>
</tr>
</tbody>
</table>

*a* Isolated yield

We speculated that refluxing might be too harsh and that we may have lost starting material due to a competitive oxidization of the helicene backbone. So the same reaction was run at ambient temperature for 24 hours, we were able to get a slightly higher yield and some starting material (88) was recovered (entry 2, Table 4.1). This confirmed our hypothesis, and a shorter reaction time further increased the yield, providing 50% of 123 and 20% of 88 was recovered (entry 3, Table 4.1). A solvent study revealed that CH₂Cl₂ was a slightly better solvent for this reaction (entry 4, Table 4.1). A mixture of CH₂Cl₂ and PhCF₃ in a ratio of 3/5 was found to be optimum; giving 60% of 123 and 18% of 88.
was recovered (entry 5, Table 4.1). We were able to get an overall 90% yield by slightly optimizing the ratio of mCPBA used (entry 6, Table 4.1).

4.2.2. Synthesis of 2-phenyl-substituted Helical Bipyridine Bis-N-oxides

Catalyst 123 was found to be quite effective in the enantioselective allylation of ketoimines. In a similar reaction, Hayashi et al. reported that an extra phenyl group was responsible for an unprecedented high reactivity of their catalyst.\textsuperscript{52} Inspired by the report, we became interested in catalyst 124 (Scheme 4.1).

\begin{center}
\textbf{Scheme 4.1.} Synthesis of helical catalysts by nucleophilic reactions
\end{center}

One can easily think of two ways to assemble the molecule based on the structure of 124. One way is to directly put a phenyl group to the bis-N-oxide 123, and the other one is to add 2-phenyl pyridine N-oxide to 11,12-benzo-1-aza[6]helicene N-oxide (87). Since we
already have 123 at hand, we started with the first method. Unfortunately, attempts to adding phenyllithium to 123 resulted no desired product, presumably because the outside pyridine N-oxide ring is not conjugated with the huge aromatic helicene rings (eq 1, Scheme 4.1). So we quickly shifted to the second method, attempts to lithiating 2-phenyl pyridine N-oxide by "BuLi and then directly add to 11,12-benzo-1-aza[6]helicene N-oxide (87) in one step resulted only trace amount of product (eq 2, Scheme 4.1). To our delight, reaction went smoothly when the lithium reagent was directly generated from 2-phenyl, 6-iodo pyridine N-oxide (125). We were able to get 60% desired product (124) from this reaction after slightly optimizing the reaction condition (eq 3, Scheme 4.1).

4.2.3. Synthesis of Halogen-substituted Helical Bipyridine mono-N-oxides

Previously we have synthesized mono-N-oxide 88, in the course of developing a catalytic, enantioselective allylation of ketoimines, we became interested in its halogen-substituted counterparts (126, Scheme 4.2). There are mainly two ways to synthesize this type of structures based on 11,12-benzo-1-aza[6]helicene N-oxide (87). The first one is the ionic reaction pathway, which has been used to synthesize 124; and the other method is through coupling reaction (Scheme 4.2). Since we already had experience synthesizing 88 and 124 through ionic reactions and the coupling partner 127 based on 11,12-benzo-1-aza[6]helicene N-oxide was not available yet, pathway 1 in Scheme 4.2 was chosen as the first option.
Scheme 4.2. Two pathways for the synthesis of helical chiral catalyst

Table 4.2. The synthesis of chloro-substituted catalyst

<table>
<thead>
<tr>
<th>entry</th>
<th>condition</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) nBuLi, THF, -78 °C 2) DDQ, THF, -78 °C</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1) tBuLi, THF, -78 °C 2) DDQ, THF, -78 °C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1) nBuLi, THF, DMPU, -78 °C 2) DDQ, THF, -78 °C</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>1) nBuLi, THF, DMPU, -78 °C 2) DDQ, THF, -78 °C to r.t, 72h</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

To our surprise, attempts to adding 2-lithium, 6-chloro-pyridine to 87 resulted no desired product (entry 1, Table 4.2) although 2-lithium pyridine was added to 87 smoothly in the synthesis of 88. tBuLi was used in hope of getting high concentration of 2-lithium, 6-chloro-pyridine in the reaction, which did not help at all (entry 2, Table 4.2). It has been well documented that some bases can change the ligation state of the lithium species, thus
increase their reactivity\textsuperscript{104}. In light of these studies, DMPU\textsuperscript{105} was added as an additive, however the reaction was just improved marginally (entry 3, Table 4.2). The attempt to elongate the reaction time and increase the reaction temperature did not help either (entry 4, Table 4.2).

\textbf{Scheme 4.3.} Synthesis of helical chiral catalysts by Negishi coupling reactions

Without any success in the ionic reaction pathway, we turned our direction to Negishi coupling reaction. Among the most versatile reactions, Negishi coupling reaction has found great applications in organic synthesis\textsuperscript{106}. To our delight, we were able to quickly access the coupling partner 2-I-11, 12-benzo-1-aza[6]helicene N-Oxide (127). Direct deprotonation by \textit{in situ} generated LDA followed by nucleophilic attack on I\textsubscript{2} provided
127 with 87% yield (eq 1, Scheme 4.3). The Negishi reaction between 127 and \textit{in situ} generated organozinc compound 128 in THF provided the desired product 126a in an 83% yield (eq 2, Scheme 4.3). To our delight, we were able to synthesize the other two catalysts (126b and 126c) with excellent yields by following the same procedures.

4.2.4. Dimerization of Helical Pyridine-N-Oxide

The bis-helicene structures (e.g. 129 and 130) have always been of great interest due to their unique structural properties, especially their ability to form a large chiral pocket that is important in chiral induction. We are especially interested in developing a chiral catalyst in asymmetric synthesis based on the dimer of 11, 12-benzo-1-aza[6]helicene N-oxide (129, Figure 4.2).

Considering the highly congested structure of 129, we envisioned it would be wise to design the synthesis using coupling reactions, which are not as sensitive to steric hindrance as ionic reactions are. Unfortunately, there was no desired product 129 obtained. However, we were able to isolate about 20% of product 132, which lost an oxygen atom compared to the desired dimer 129 (Scheme 4.4).
During our studies for the synthesis of 127 using LDA, we serendipitously found some interesting results. For the same reaction conditions, when the THF solution of 87 was added into a LDA solution slowly, only desired product 127 was formed (eq 1, Scheme 4.5). On the other hand, if the THF solution of 87 was quickly added into the LDA solution, a mixture of products were obtained, one was the desired product 127 and the other one, to our delight, turned out to be the dimerized product 129 (eq 2, Scheme 4.5).
Scheme 4.5. A serendipitous finding

Based on the observed products distribution and their reaction mechanism, we propose what might have happened as follows (Scheme 4.6): Once N-oxide 87 was transferred into LDA solution; it was quickly deprotonated by LDA to form lithiated species 133 (eq 2, Scheme 4.6). If 87 was transferred slowly (i.e. dropwise), then there would be enough time for LDA to deprotonate 87 and form exclusively 133. Once iodine (I₂) was added to the solution, a nucleophilic reaction occurred between 133 and I₂, rendering 127 exclusively (eq 1, Scheme 4.6). On the other hand, if 87 was quickly added to the LDA solution (i.e. transferred by a large size cannula), LDA would not be able to deprotonate all of 87 added in the short amount of time. As a result, there would be a coexistence of 87 and its lithiated species 133 in the reaction. The two reacted with each other, forming 134 that eventually turned into bis-N-oxide 129 (eq 3, Scheme 4.6). Due to the high steric hindrance, the reaction between 87 and 133 were very slow, so most of 87 would still be deprotonated by LDA and reacted with I₂ to generate 127. So in the end of the reaction
we got a mixture of products when transferring 87 quickly into LDA solution (eq 2, Scheme 4.5).

Scheme 4.6. Proposed reaction pathways for the observed product distribution

Encouraged by the fact 129 could be synthesized by simple ionic reaction from 87, we envisioned that if we could create conditions where 87 and the lithiated species 133 stay long time before any other reactions could occur, we would have a much higher distribution of the desired bis-N-oxide 129. With this in mind, it would be obvious for us
to add LDA into the solution of 87, not the other way round. Ideally, only half equivalent of LDA would be needed to bring the reaction to a completion. So 0.6 equivalent of freshly made LDA solution was transferred into a THF solution of 87, however, no reaction was observed even after overnight stirring at -78°C (entry 1, Table 4.3). When the ratio of LDA was increased to 1.2 equivalents, still no reaction was observed (entry 2, Table 4.3). When 1.8 equivalents of LDA were used, the reaction was still marginal (entry 3, Table 4.3). To our delight, the reaction went smoothly when 2.4 equivalents of LDA were applied, rendering 60% of desired product 129 with 28% of 87 recovered (entry 4, Table 4.3). Further increasing the ratio of LDA was found to adversely affect the reaction (entry 4 vs. 5, Table 4.3).

Table 4.3. The synthesis of bis-N-oxide

<table>
<thead>
<tr>
<th>entry</th>
<th>LDA (equiv)</th>
<th>yield (%)</th>
<th>recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>0</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>&lt;5</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2.4</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>49</td>
<td>22</td>
</tr>
</tbody>
</table>
4.2.5. Synthesis of New Helical Chiral Brønsted Acid Catalysts

Our group previously designed and developed a family of novel helical chiral Brønsted acid catalysts that were very effective for the asymmetric activation of nitroalkenes.\(^\text{74}\) With the newly synthesized bis-N-oxide \textbf{123} at hand, we became interested in developing the corresponding Brønsted acid catalyst based on this scaffold. To our delight, catalyst \textbf{123} was smoothly reduced to corresponding dipyridyl compound \textbf{135} by a classic zinc mediated reduction with excellent yield. The protonation of \textbf{135} by HCl (Et\(_2\)O solution), followed by a counterion exchange with NaBArF\(_{24}\) resulted the desired Brønsted acid catalyst \textbf{136} in excellent yield (Scheme 4.7).

\begin{center}
\textbf{Scheme 4.7.} Synthesis of new helical chiral Brønsted acids (1)
\end{center}

With the successful synthesis of \textbf{136}, we set our feet to the synthesis of new helical chiral acid catalysts based on \textbf{129}. We were able to reduce \textbf{129} into the corresponding dipyridyl \textbf{137} with excellent yield by a slightly modified protocol (eq 1, Scheme 4.8). Two new helical chiral Brønsted acid catalysts were synthesized by simply controlling the extent of protonation of \textbf{137} in the following step. When only one equivalent of proton was provided, the mono protonated catalyst (\textbf{138}) was obtained (eq 2, Scheme 4.8). We were able to grow a nice crystal of \textbf{138} and elucidated its structure unambiguously
with X-ray crystal structure analysis (Figure 4.3). With 2 equivalents of proton, we got the di-protonated catalyst 139 (eq 3, Scheme 4.8).

**Scheme 4.8.** Synthesis of new chiral Brønsted acids (2)

**Figure 4.3.** Solid-state structure of mono protonated catalyst

(Counter anion was omitted for clarity)
4.3. Summary

In summary, we have successfully demonstrated the versatility of 11, 12-benzo-1-aza[6]helicene-N-oxide (87) as a chiral scaffold for the design and development of new helical chiral catalysts. Among all the reactions tested, Negishi coupling and deprotonation followed by nucleophilic reaction were the most powerful ones for the development of new helical chiral catalysts.

Figure 4.4. Newly developed helical chiral catalysts
Based on these simple reactions, a series of unique helical chiral catalysts have been developed (Figure 4.4). These catalysts include both Lewis base (123, 124, 126a-c, 127, 129, 135 and 137) and Brønsted acid (137-139). Crystals of some of the catalysts have been obtained and their structures have been elucidated unambiguously by X-ray crystallography (Figure 4.5), the fact of which surely will increase our understanding towards the behaviors of helical chiral catalysts in asymmetric catalysis.

4.4. Experimental Section

4.4.1. General Information

All reactions were carried out in the oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Silicycle pre-coated silica gel plates with $F_{254}$ indicator. Visualization was accomplished by UV light (256 nm), with combination of potassium permanganate and/or vanillin solution as an indicator. Flash column chromatography was performed according to the
method of Still\textsuperscript{76} using silica gel 60 (mesh 230-400) supplied by Silicycle. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}) was freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. THF and diethyl ether were freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. Commercial mCPBA was recrystallized from CH\textsubscript{2}Cl\textsubscript{2}. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded on a Bruker Avance 300 (300 MHz \textsuperscript{1}H) and a Bruker Avance 400 (400 MHz \textsuperscript{1}H, 100 MHz \textsuperscript{13}C). Chemical shift values (\(\delta\)) are reported in ppm relative to Me\textsubscript{4}Si (\(\delta\) 0.0 ppm) unless otherwise noted. The proton spectra are reported as follows \(\delta\) (multiplicity, coupling constant \(J\), number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL\textsuperscript{®} III automatic polarimeter. Infrared spectra were recorded using PerkinElmer\textsuperscript{TM} SPECTRUM ONE with Universal ATR Sampling Accessory (Composite Zinc Selenide and Diamond crystals). High-resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, the University of Miami.

\textbf{4.4.2. General Procedure for the Synthesis of bis-N-oxides 123}

\textbf{Entry 1}: A chloroform solution (3.0 ml, 0.01M) of (\(M\))-2-pyridine 11, 12-benzo-1-aza[6]helicene N-oxide (88) (28.5 mg, 0.06 mmol) and mCPBA (31.0 mg, 0.18 mmol) was stirred under reflux for 3 hours. The reaction was then cooled down to ambient temperature, quenched with saturated aqueous K\textsubscript{2}CO\textsubscript{3} solution and extracted with
dichloromethane. The crude material was purified by flash chromatography on silica gel (first 30% EtOAc in hexanes, then 3% MeOH in dichloromethane) to afford the desired product as a bright yellow solid (9 mg, 30%). \([\alpha]_{D}^{20} = \text{2124}, c = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.90 (t, \(J = 8.6\) Hz, 2H), 8.82 (d, \(J = 7.6\) Hz, 1H), 8.75 (d, \(J = 8.1\) Hz, 1H), 8.37-8.42 (m, 2H), 8.22-8.29 (m, 3H), 8.13 (d, \(J = 8.3\) Hz, 1H), 8.02-8.04 (m, 1H), 7.74-7.80 (m, 2H), 7.55 (d, \(J = 8.3\) Hz, 1H), 7.41 (t, \(J = 7.3\) Hz, 1H), 7.30-7.31 (m, 2H), 6.79 (d, \(J = 8.1\) Hz, 1H), 6.67 (t, \(J = 7.2\) Hz, 1H), 6.38-6.40 (m, 1H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(d\) 143.2, 139.9 (x2), 139.5, 134.7, 132.0, 131.3, 131.1, 131.0, 130.7, 130.5, 130.4, 129.9, 129.5, 128.6, 128.5, 128.2 (x2), 127.5 (x2), 127.1, 126.8 (x2), 126.4, 125.2, 125.1, 124.9, 124.6, 124.5, 124.0 (x2), 123.7, 123.1, 120.4; FTIR (neat) \(\text{u}_{\text{max}}\) 2927, 1619, 1467, 1426, 1349, 1257, 1097, 848, 754, 728 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{34}\)H\(_{20}\)N\(_2\)O\(_2\) \([\text{M} + 1]^{+}\), expected: 489.1598, found: 489.1595.

**Entries 2-6:** Slightly modified procedures were applied.

### 4.4.3. General Procedure for the Synthesis of 2-phenyl, 6-iodo-pyridine-N-oxide 125

To a freshly generated LDA solution\(^{107}\) (0.68 mmol in 5.5 ml THF) was added a THF (1.7 ml) solution of 2-phenyl-pyridine-N-oxide (98 mg, 0.57 mmol) dropwise at -78 °C. The resulting mixture was stirred for two hours at the same temperature. Then a solution of I\(_2\) (218 mg, 0.86 mmol) in THF (1.7 mL) was transferred to the above solution dropwise at -78 °C. The reaction mixture was stirred for one hour at -78 °C, quenched with H\(_2\)O (7 mL), and then the excess iodine was removed by adding an aqueous
The resulting mixture was extracted with CH$_2$Cl$_2$, washed with aqueous NH$_4$Cl solution, H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (15% EtOAc in hexanes) to afford the title compound as a brown solid (70 mg, 41%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.77-7.79 (m, 2H), 7.44-7.48 (m, 3H), 7.41 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.98 (t, $J = 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.0, 136.4, 133.5, 130.1, 129.6, 128.5, 127.4, 125.7, 113.5; FTIR (neat) $\nu_{max}$ 1533, 1454, 1442, 1361, 1229, 1021, 1000, 836, 757, 692 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{11}$H$_8$INO [$M + 1]^+$, expected: 297.9723, found: 297.9739.

4.4.4. General Procedure for the Synthesis of 2-phenyl, bis-N-oxides 124

To the solution of 2-phenyl, 6-iodo pyridine N-oxide (125) (65 mg, 0.22 mmol) in THF (2.0 mL) was added a solution of n-BuLi (1.57 M, 147 µL) in hexane dropwise at -78 °C. The resulting mixture was stirred for one hour at the same temperature. Then a solution of (M)-11,12-benzo-1-aza[6]helicene N-oxide (87) (43.5 mg, 0.11 mmol) in THF (2.5 mL) was transferred to the above solution dropwise at -78 °C. The reaction mixture was stirred for two hours at -78 °C, slowly warmed up and stirred overnight until the reaction reached ambient temperature. The resulted solution was cooled back to -78 °C and treated with a solution of DDQ (50 mg, 0.22 mmol) in THF (2.5 mL). The resulting mixture was allowed to warm up to ambient temperature, treated with water (8 mL) then 50% NaOH solution (8 mL), and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were washed with water (10 mL) then brine (10 mL), dried over Na$_2$SO$_4$, filtered, and
concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (50% EtOAc in hexanes, and then 65% EtOAc in hexanes) to afford the title compound as a yellow solid (37 mg, 60%). $\alpha_{D}^{20} = -2536, c = 0.0005, \text{CH}_2\text{Cl}_2$. $^1\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 8.70-8.77 (m, 3H), 8.62 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.69-7.76 (m, 2H), 7.57-7.61 (m, 3H), 7.25-7.37 (m, 5H), 7.12 (t, $J = 8.0$ Hz, 1H), 7.02 (dd, $J = 8.4$, 0.8 Hz, 1H), 6.63-6.69 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) $d$ 149.6, 143.6, 140.7, 139.1, 134.4, 132.9, 132.1, 131.4, 130.8, 130.7 (x2), 130.4, 130.1, 130.0, 129.7 (x2), 129.6, 128.2, 128.0, 127.8, 127.5, 127.3, 126.6, 126.4, 126.2 (x2), 125.9, 125.8, 125.1, 124.5 (x2), 124.2, 123.9, 123.2, 123.0, 122.9, 122.7, 121.0; FTIR (neat) $\nu_{\text{max}}$ 2920, 1469, 1443, 1378, 1241, 845, 751, 726, 693 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{40}$H$_{24}$N$_2$O$_2$ [M + 1]$^+$, expected: 565.1911, found: 565.1907.


To a freshly generated LDA solution (1.16 mmol in 18 ml THF) was added a THF (6.5 ml) solution of ($M$)-87 (128 mg, 0.32 mmol) *dropwise* at $-78$ °C. The resulting mixture was stirred for two hours at the same temperature. Then a solution of I$_2$ (295 mg, 1.16 mmol) in THF (6.5 mL) was transferred to the above solution at $-78$ °C. The reaction mixture was stirred for 15 minutes at $-78$ °C, quenched with H$_2$O, and then the excess iodine was removed by adding an aqueous Na$_2$S$_2$O$_4$ solution. The resulting mixture was extracted with Et$_2$O, washed with aqueous NH$_4$Cl solution, H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash
chromatography on silica gel (20% EtOAc in hexanes) to afford the title compound as a yellow solid (144 mg, 87%). \([\alpha]^{20}_D = -3260, \text{c} = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.73-8.82\) (m, 3H), 8.55 (d, \(J = 8.2\) Hz, 1H), 8.21 (d, \(J = 8.2\) Hz, 1H), 8.04-8.11 (m, 2H), 7.98 (d, \(J = 8.2\) Hz, 1H), 7.83 (d, \(J = 8.4\) Hz, 1H), 7.70-7.78 (m, 2H), 7.63 (d, \(J = 8.4\) Hz, 1H), 7.40 (d, \(J = 8.4\) Hz, 1H), 7.26-7.30 (m, 1H), 6.80 (d, \(J = 8.1\) Hz, 1H), 6.46-6.50 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 140.1, 134.2, 131.8\) (x2), 131.2, 131.0, 130.4, 130.2, 130.1, 130.0, 129.8, 129.0, 127.4, 127.2, 126.8, 126.1, 125.8, 125.5, 125.3, 124.5 (x2), 123.6, 123.5, 123.4, 123.3, 123.1, 122.6, 120.8, 108.3; FTIR (neat) \(\nu_{\text{max}}\) 1701, 1554, 1468, 1319, 1239, 1097, 847, 755, 730 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{29}\)H\(_{16}\)INO [M + 1]\(^+\), expected: 522.0349, found: 522.0378.

**4.4.6 General Procedure for the Synthesis of Halogen-substituted bipyridine-mono-N-oxides 126**

Preparation of organozinc reagent: To the solution of 2-chloro, 6-bromo pyridine (127.5 mg, 0.66 mmol) in THF (6.6 mL) was added a solution of \(n\)-BuLi (1.10 M, 602 \(\mu\)L) in hexane dropwise at -78 °C. The resulting mixture was stirred for one hour at the same temperature. Then a solution of ZnCl\(_2\) (108 mg, 0.80 mmol) in THF (2.7 mL) was transferred to the above solution dropwise at -78 °C. The reaction mixture was stirred for 5 minutes at same temperature, and then slowly warmed up to ambient temperature.

A flame-dried round bottom flask was charged with a suspension of 127 (144 mg, 0.276 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (39 mg, 0.055 mmol) in THF (5.5 ml). To this were added the above freshly made organozinc reagent solution. The resulting mixture was heated to
reflux for 2.5 hours, and then quenched with a saturated aqueous solution of NH₄Cl (15 mL). The resulting mixture was extracted with Et₂O, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (10% EtOAc in hexanes).

**(P)-126a:** Obtained as a yellow solid in 83% yield. [α]$_{D}^{20}$ = + 2814, c = 0.0005, CH₂Cl₂. 
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.80 (t, $J$ = 7.2 Hz, 2H), 8.56 (d, $J$ = 8.0 Hz, 1H), 8.20 (t, $J$ = 6.4 Hz, 3H), 8.09 (t, $J$ = 9.2 Hz, 2H), 8.01 (d, $J$ = 8.0 Hz, 1H), 7.94 (d, $J$ = 7.6 Hz, 1H), 7.88 (d, $J$ = 8.0 Hz, 1H), 7.75-7.80 (m, 3H), 7.36 (t, $J$ = 8.0 Hz, 1H), 7.19 (d, $J$ = 8.0 Hz, 1H), 7.10 (t, $J$ = 7.6 Hz, 1H), 6.95 (d, $J$ = 8.4 Hz, 1H), 6.53 (t, $J$ = 7.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.4, 149.9, 142.5, 141.3, 138.8, 134.6, 132.0, 131.1, 130.8 (x2), 130.4, 130.2, 130.1, 130.0, 129.1, 127.8, 127.4, 126.7, 126.6, 126.2, 126.0, 125.9, 125.4, 124.5, 124.2, 123.8, 123.6, 123.1, 123.0, 122.9, 122.6, 121.0; FTIR (neat) $\nu_{max}$ 2922, 2853, 1559, 1429, 1416, 1363, 1347, 1134, 843, 749, 724 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{34}$H$_{19}$ClN$_2$O [M + 1]$^+$, expected: 507.1259, found: 507.1261.

**(M)-126b:** Obtained as a yellow solid in 90% yield. [α]$_{D}^{20}$ = - 2066, c = 0.0005, CH₂Cl₂. 
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.78-8.82 (m, 2H), 8.54-8.56 (m, 1H), 8.15-8.22 (m, 3H), 8.07-8.12 (m, 2H), 7.96-8.02 (m, 2H), 7.87 (d, $J$ = 8.4 Hz, 1H), 7.73-7.82 (m, 3H), 7.50 (q, $J$ = 8.0 Hz, 1H), 7.06-7.10 (m, 1H), 6.93-6.96 (m, 1H), 6.82-6.84 (m, 1H), 6.50-6.54 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 162.2 (d, $J$ = 236.0 Hz), 148.0 (d, $J$ = 13.0 Hz), 142.4, 141.4, 141.3 (x2), 134.5, 132.0, 131.1, 130.9, 130.8, 130.3, 130.2, 130.1, 130.0, 129.1, 127.7, 127.3, 126.7, 126.6, 126.1, 126.0 (d, $J$ = 4.0 Hz), 125.4, 124.9, 124.1, 123.8,
123.5, 123.3 (d, J = 3.0 Hz), 123.1, 122.9 (x2), 122.6, 121.0, 109.9 (d, J = 37.0 Hz); FTIR (neat) \( \text{v}_{\text{max}} \) 3056, 2922, 1710, 1597, 1573, 1439, 1421, 1356, 1309, 1231, 928, 845, 802, 750, 725 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{34}\)H\(_{19}\)F\(_3\)N\(_2\)O [M + 1]\(^{+}\), expected: 541.1554, found: 541.1552.

\((M)\)-126c: Obtained as a yellow solid in 87% yield. \([\alpha]^{20}_{D} = -1722, c = 0.0005, \text{CH}_2\text{Cl}_2\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.79-8.83 (m, 2H), 8.55-8.58 (m, 1H), 8.01-8.23 (m, 7H), 7.88 (d, J = 8.4 Hz, 1H), 7.74-7.90 (m, 3H), 7.52-7.58 (m, 2H), 7.06-7.10 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.51-6.55 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 150.5 (m), 147.2 (q, J = 35.0 Hz), 141.3, 141.2, 137.2, 134.6, 132.0, 131.1, 130.8 (x2), 130.4, 130.0, 129.1, 128.8, 128.6, 128.5, 127.8, 127.4, 126.8, 126.6, 126.5, 126.3, 126.1, 126.0, 125.4, 125.0, 124.2, 123.8, 123.1, 123.0, 122.9, 122.6, 120.9, 120.4, 120.2; FTIR (neat) \( \text{v}_{\text{max}} \) 3045, 2933, 2875, 1576, 1556, 1431, 1415, 1368, 1347, 1140, 863, 749, 715 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{34}\)H\(_{19}\)F\(_3\)N\(_2\)O [M + 1]\(^{+}\), expected: 541.1522, found: 541.1522.

4.4.7 General Procedure for the Synthesis of Dimer mono-N-oxide 132

To the solution of 127 (91 mg, 0.17 mmol) in THF (1.8 mL) was added a solution of \( n\)-BuLi (1.05 M, 166 \( \mu \)L) in hexane dropwise at -78 °C. The resulting mixture was stirred for half hour at the same temperature. Then a solution of ZnCl\(_2\) (71 mg, 0.52 mmol) in THF (2.0 mL) was transferred to the above solution dropwise at -78 °C. The reaction mixture was stirred for 5 minutes at same temperature, and then slowly warmed up to ambient temperature. This solution was then transferred to a flame-dried round bottom
flask that was charged with a suspension of PdCl\(_2\)(PPh\(_3\))\(_2\) (67 mg, 0.096 mmol) in THF (3.0 ml). The resulting mixture was stirred at ambient temperature for 7 hours, and then quenched with a saturated aqueous solution of NH\(_4\)Cl. The resulting mixture was extracted with CH\(_2\)Cl\(_2\), washed with H\(_2\)O and brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The crude material was purified by flash chromatography on silica gel (20\% EtOAc in hexanes) to afford the title compound as a yellow solid (14 mg, 21\%). 

\[\alpha\]\(_D\) = -3404, c = 0.0005, CH\(_2\)Cl\(_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.88 (d, \(J = 10.2\) Hz, 1H), 8.64-8.81 (m, 5H), 8.54 (d, \(J = 10.7\) Hz, 1H), 8.32 (d, \(J = 10.7\) Hz, 1H), 8.10 (d, \(J = 10.9\) Hz, 1H), 8.01-8.04 (m, 3H), 7.89-7.96 (m, 6H), 7.82-7.86 (m, 1H), 7.66-7.78 (m, 4H), 7.60 (d, \(J = 11.3\) Hz, 1H), 7.32-7.49 (m, 2H), 7.04-7.18 (m, 1H), 6.82-6.92 (m, 2H), 6.74 (d, \(J = 11.4\) Hz, 1H), 6.41-6.58 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 148.4, 145.3, 143.7, 141.0, 134.4, 134.3, 133.7, 133.2, 131.9, 131.4, 131.1, 131.0, 130.9, 130.6 (x2), 130.1, 130.0, 129.8, 129.7, 129.6, 129.5, 129.3, 129.0, 128.4, 128.2, 127.9, 127.7, 127.4, 127.3 (x2), 127.2, 127.1, 126.7, 126.6, 126.4 (x3), 126.3, 126.0, 125.9 (x2), 125.1, 125.0, 124.2, 124.0, 123.9 (x2), 123.3, 123.1 (x2), 122.9, 122.8, 122.4, 121.1; FTIR (neat) \(\nu_{\text{max}}\) 2922, 2852, 1589, 1436, 1296, 843, 750, 723 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{58}\)H\(_{32}\)N\(_2\)O [M + 1]\(^+\), expected: 773.2587, found: 773.2593.

4.4.8 General Procedure for the Synthesis of Dimer N-oxides 129

To the solution of \((M)\)-87 (60 mg, 0.15 mmol) in THF (3.0 mL) was added a freshly generated LDA solution (0.365 mmol in 3.5 ml THF) \textit{via} cannula at -78 °C. The resulting mixture was stirred for one hour at the same temperature. Then a solution of DDQ (69
mg, 0.30 mmol) in THF (3.0 mL) was transferred to the above solution dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C, quenched with water then 50% NaOH solution, and extracted with CH₂Cl₂. The combined organic layers were washed with water then brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 50% EtOAc in hexanes as eluent to recover \( (M) - 87 \) (17 mg, 28%) and then 3% MeOH in CH₂Cl₂ to afford the title compound as a yellow solid (36 mg, 60%). \([\alpha]^{20}_D = -6038, c = 0.0005, \text{CH}_2\text{Cl}_2\). ¹H NMR (400 MHz, CD₂Cl₂) \( \delta 8.78 \ (d, J = 7.8 \text{ Hz}, 1\text{H}), 8.57-8.63 \ (m, 3\text{H}), 8.03 \ (d, J = 8.2 \text{ Hz}, 1\text{H}), 7.93 \ (t, J = 7.9 \text{ Hz}, 2\text{H}), 7.86 \ (d, J = 8.1 \text{ Hz}, 1\text{H}), 7.68-7.78 \ (m, 3\text{H}), 7.44 \ (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.33 \ (t, J = 7.5 \text{ Hz}, 1\text{H}), 6.78 \ (d, J = 8.3 \text{ Hz}, 1\text{H}), 6.59 \ (t, J = 7.8 \text{ Hz}, 1\text{H}), 6.33 \ (d, J = 8.3 \text{ Hz}, 1\text{H}); ¹³C NMR (100 MHz, CD₂Cl₂) \( \delta 145.3, 140.2, 139.8, 134.3, 131.8, 130.7, 130.6, 130.5, 130.1, 129.9, 129.7, 129.5, 128.0, 127.7, 126.4 \ (x3), 126.2, 126.0, 125.5, 124.9, 124.8 \ (x2), 124.3, 123.9, 123.5, 123.1, 122.4 \ (x2); \text{FTIR (neat)} \ u_{\text{max}} 2925, 1633, 1441, 1372, 1314, 1238, 841, 750, 725 \text{ cm}^{-1}; \text{HRMS (ESI-TOF)}: \text{Exact mass calcd for } C_{58}H_{32}N_2O_2 [M + 1]^+, \text{expected: 789.2537, found: 789.2556.}

### 4.4.9 General Procedure for the Deoxygenation Reactions

\( (P) - 135 \): A round bottom flask was charged with \( (P) - 123 \) (12.2 mg, 0.025 mmol), zinc (26 mg, 0.4 mmol) and HCOONH₄ (38 mg, 0.6 mmol) in MeOH (4.0 mL). The resulted suspension was stirred at ambient temperature, monitored by TLC and stopped after 3 hours. The reaction mixture was then filtered through Celite, washed with small amount of MeOH and CH₂Cl₂. The filtrate was then combined and concentrated in vacuo. The
crude material was purified by flash chromatography on silica gel (8% EtOAc in hexanes) to afford the title compound as a light color solid (11 mg, 96%). \([\alpha]^{20}_D = +2950, c = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.73-8.77\) (m, 2H), 8.46-8.48 (m, 2H), 8.36 (d, \(J = 8.4\) Hz, 1H), 8.22 (d, \(J = 8.4\) Hz, 1H), 8.06-8.12 (m, 3H), 8.01 (d, \(J = 8.2\) Hz, 2H), 7.90 (d, \(J = 5.1\) Hz, 1H), 7.75-7.81 (m, 2H), 7.60 (dd, \(J = 8.3, 0.7\) Hz, 1H), 7.01-7.07 (m, 2H), 6.77-6.85 (m, 2H), 6.57-6.61 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 155.4, 153.2, 148.7, 145.2, 136.5, 136.2, 133.8, 133.7, 131.9, 131.3, 131.2, 130.4, 129.6, 129.3, 129.2, 128.7, 128.0, 127.5, 127.3 (x2), 127.2, 127.1 (x2), 126.7, 126.1, 125.5, 124.8, 124.6, 123.8 (x2), 122.8, 122.6, 122.5, 118.2; FTIR (neat) \(\nu_{\text{max}} 3039, 1567, 1464, 1125, 779, 756 \text{cm}^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{34}\)H\(_{20}\)N\(_2\) [M + 1]\(^+\), expected: 457.1699, found: 457.1703.

\((M)-137\): A round bottom flask was charged with \((M)-129\) (12 mg, 0.015 mmol), zinc (16 mg, 0.24 mmol) and HCOONH\(_4\) (23 mg, 0.365 mmol) in MeOH (4.0 mL). The resulted suspension was refluxed overnight. After cooled down, the reaction mixture was then filtered through Celite, washed with small amount of MeOH and CH\(_2\)Cl\(_2\). The filtrate was then combined and concentrated in vacuo. The resulted crude material was washed with small amount of CH\(_2\)Cl\(_2\) to afford the title compound as a light color solid (10.5 mg, 96%). \([\alpha]^{20}_D = -2816, c = 0.0005, \text{CH}_2\text{Cl}_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.75\) (d, \(J = 7.6\) Hz, 1H), 8.68-8.71 (m, 2H), 8.22 (d, \(J = 8.0\) Hz, 1H), 8.01-8.05 (m, 2H), 7.83-7.95 (m, 4H), 7.68 (d, \(J = 8.8\) Hz, 1H), 7.63 (dd, \(J = 8.4, 0.8\) Hz, 1H), 7.22-7.26 (m, 1H), 7.09 (d, \(J = 8.4\) Hz, 1H), 6.70-6.74 (m, 1H), 6.65 (d, \(J = 8.4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 152.7, 144.8, 135.0, 133.7, 133.6, 131.9, 131.4, 131.2, 130.4, 129.7, 129.2, 129.1, 128.4,
127.6, 127.5, 127.3, 127.2 (x2), 127.1, 127.0, 126.8, 126.7, 125.5, 124.8, 124.4, 123.9, 122.7, 122.6, 119.9; FTIR (neat) \( \nu_{\text{max}} \) 3042, 1580, 1481, 1439, 904, 849, 832, 751, 724 cm\(^{-1} \); HRMS (ESI-TOF): Exact mass calcd for \( \text{C}_{58}\text{H}_{32}\text{N}_2 [\text{M + 1}]^+ \), expected: 757.2638, found: 757.2680.

4.4.9 General Procedure for the Synthesis of Brønsted Acid Catalysts

136: To a solution of 135 (47 mg, 0.103 mmol) in \( \text{CH}_2\text{Cl}_2 \) (2.0 mL) was added \( \text{Et}_2\text{O} \) solution of HCl (1M, 0.25 mL) drop-wise at room temperature. The reaction mixture was stirred for 30 minutes and then concentrated \textit{in vacuo}. The resulting solid was dissolved back into \( \text{CH}_2\text{Cl}_2 \) (2.0 mL), and then concentrated \textit{in vacuo}, the process of which was repeated three times. To the resulting bright red solid were added \( \text{CH}_2\text{Cl}_2 \) (2.0 mL), MeOH (13.7 ml) and \( \text{NaBArF}_{24}\cdot2.6\text{H}_2\text{O} \) (192 mg, 0.206 mmol) at room temperature. The resulting mixture was stirred for 4 hours, filtered through a short pad of Celite, concentrated \textit{in vacuo} to result the title compound as a brownish solid (203 mg, 90%), and then used in reactions without further purification.

The synthesis of 138 and 139 followed same procedure as above and both were used in reactions without further purification.
CHAPTER 5. HELICAL CHIRAL PYRIDINE N-OXIDES CATALYZED KETOIMINE ALLYLATION

5.1. Background

5.1.1. Synthesis of α-Tertiary Amines

Due to their unique biological activities, the synthesis of α-trisubstituted amines has been of great interest for medicinal chemists. The aminosesquiterpene *Aminobisabololenol* (140), the alkaloid *Hemiargin D* (141), the NMDA receptor blocker *Dizocilpine* (142), homoallylic aminooxindole 143 and AG-041R (144) are such examples with their own unique biologic property\(^{108}\) (Figure 5.1).

![Chemical structures](image)

**Figure 5.1.** Biologically active α-trisubstituted amines
While a couple of methods have been developed to synthesize α-disubstituted amines by addition reactions to aldimines in a catalytic and asymmetric fashion,\textsuperscript{109} the catalytic and asymmetric synthesis of α-trisubstituted amines from ketoimines is not well established. The catalytic and asymmetric addition of nucleophiles to ketoimines is among the simplest routes for the preparation of enantiomerically enriched α-trisubstituted amines. Due to the low reactivity of ketoimines as well as their rapid isomerization to an unreactive enamine under basic conditions, most of the asymmetric nucleophilic addition reactions to ketoimines developed so far worked only for specially constructed substrates. These substrates not only have been activated by stronger electron withdrawing groups but also have been designed in such a way that isomerization to unreactive enamines could be avoided under basic conditions\textsuperscript{110} (Figure 5.2).

![Figure 5.2. Selected examples of specially designed ketoimines](image)

The asymmetric allylation of simple ketoimines is among the most useful transformations to afford enantiomerically enriched α-trisubstituted homoallylamines (a functionalized α-trisubstituted amines). There are mainly three methods reported so far for this type of reactions. Hua\textsuperscript{111} and Ellman\textsuperscript{112} developed the first method where an allyl Grignard reagent was added to chiral N-sulfinyl ketoimines. The second one was reported by Leighton and coworkers in which a chiral allylsilane was added to ketone-derived acyl...
hydrazones. Both of these two methods provide desired product with excellent stereoselectivity and substrate generality, however, stoichiometric amount of chiral reagents is required to carry out the reactions.

In 2006, Shibasaki and coworkers developed the first and the only catalytic asymmetric allylation of ketoimines to access \( \alpha \)-trisubstituted homoallylic amines based on their previously reported racemic catalytic allylation reactions (Scheme 5.1). In this study, the catalyst was generated in situ from CuF and a novel (R, R)-biscyclopentyl-DUPHOS ligand (145) in toluene at 0\(^\circ\)C, promoting the allylation of arylmethyl ketoimines with pinacolallylboration in good to excellent yield and selectivity. However, only one alkyl-alkyl ketoimine was studied with poor enantioselectivity (23% ee) in this report.

Indeed, there is no general method yet to access \( \alpha \)-tertiary amines in a catalytic and asymmetric fashion with a good substrate generality. Therefore, the development of general, catalytic and enantioselective methods for the synthesis of \( \alpha \)-tertiary amines remains an important goal and challenge for organic synthetic chemists.

Scheme 5.1. Catalytic asymmetric allylation of ketoimines developed by Shibasaki
5.1.2. Lewis Base Assisted Lewis Acid Catalysis

Meanwhile, chiral Lewis base catalyzed, polychlorosilane-mediated transformations have been successfully developed for the allylation\textsuperscript{51-52, 103, 115} and propargylation\textsuperscript{73, 116} of aldehydes. Such reactions were first pioneered by Hosomi and Sakurai,\textsuperscript{117} and later developed by Denmark and co-workers.\textsuperscript{115i, 116c, 118} Due to their environmentally benign properties (such as mildness, low toxicity) and regiospecificity, polychlorosilanes have been recognized as a useful class of nucleophiles to react with C=O and C=N for the enantioselective construction of new carbon-carbon bond. In these reactions, it is generally believed that hypervalent silicon intermediates are involved.

\textbf{Scheme 5.2. Hypervalent bonds in silicon bond formation}

It is now generally accepted that the 3d orbitals of silicon are too diffuse to engage in meaningful bonding.\textsuperscript{119} And the ability of silicon to expand its coordination sphere (to engage in hypervalent bonding) is due to the ability of the silicon 3p orbitals to engage in an electron-rich three-center four-electron (3c-4e) bonding.\textsuperscript{120} From the perspective of valence bond theory, a tetracoordinate silicon (146) possesses four sp3-hybridized
orbits. The expansion to a pentacoordinate silicon complex (SiL₅, 147) requires one of the p orbitals to form a hypervalent 3c-4e bonding with the ligands. For hexacoordinate silicon complex (SiL₆, 148), two p orbitals are involved in forming two hypervalent 3c-4e bonding (Scheme 5.2). ¹²¹

![Scheme 5.3. Generation of cationic silicate species by Lewis base](image)

Owing to the special nature of the 3c-4e bond, electron density from the ligands forming the hypervalent bonding could be easily communicated between each other through the center atom (i.e., silicon). If one of the ligands of the 3c-4e bond is strong Lewis base, the counterpart bonding acceptor becomes polarized in response to the electron density flow when the Lewis base binds to silicon. The extreme of the case leads to an ionization and generates a very acidic and highly reactive cationic silicate species¹²² (152, Scheme 5.3).

In order to generate a high concentration of 152, traditionally, strong Lewis bases (e.g., HMPA, DMSO) were used:

\[
2 \text{HMPA} + \text{SiCl}_4 \rightleftharpoons 2\text{HMPA} \cdot \text{SiCl}_3^+ \text{Cl}^-
\]

While weak Lewis bases (e.g., pyridine, pyridine N-oxide) were less utilized because of the weak donating ability to generate the cationic silicate species:

\[
2 \text{Py} + \text{SiCl}_4 \rightleftharpoons 2\text{Py} \cdot \text{SiCl}_3^+ \text{Cl}^-
\]
Not only does this limit the development of catalysts to strong Lewis bases, but also because of the strong electron donor ability of the Lewis bases used, the acidity of the cationic silicate species (152) generated is somewhat attenuated, which would decrease its activity in reaction.

Scheme 5.4. A highly reactive propargylation reaction by helical chiral catalyst

In a previous study on the propargylation of aldehydes, our group developed a catalyst (88) that is exceedingly more reactive than its analogous catalysts 153 and 154. The reaction catalyzed by 88 (10 mol%) went to completion with a 99% yield at -78 °C in only 3 hours while reaction catalyzed by 153 (20 mol%) at the same temperature only resulted 65% yield even after longer time (Scheme 5.4). Collectively consider the reaction mechanism and analyze the crystal structure of 88, it makes us believe that the extremely high reactivity of this reaction might be attributed to the cation-π interaction between the ionized Si atom and the aromatic rings of the helicene framework (Figure
5.3). Such interaction would increase the concentration of the reactive silicate species, leading to a more reactive reaction compared to ones catalyzed by 153 and 154 without such interaction.

![Diagram of Cation-π interaction, Crystal structure of (P)-88, Reaction intermediate]

**Figure 5.3.** An effective generation of reactive Lewis acid *via* cation-π interaction

In light of these findings, we became interested in the possibility to utilize hypervalent silicon chemistry to develop a catalytic and asymmetric allylation reaction of general ketoimines with our helical chiral pyridine derived catalysts.
5.2. Results and Discussions

5.2.1. Initial Reaction Development

Benzoylhydrazone 155 was chosen as the standard substrate for the initial reaction development, mainly because: 1), hydrazones are readily available, very easy to synthesize and stores very well\textsuperscript{123}; 2), benzyolhydrazones have been proved to be very good substrates for the synthesis of homoallylic amines\textsuperscript{124}; 3), compound 155 stands for the most challenge substrate for this type of reactions.\textsuperscript{114} Allyltrichlorosilane\textsuperscript{125} 149 was picked as the allylation reagent due to its mildness, low toxicity, regiospecificity and great responsiveness towards Lewis base activation. CH\textsubscript{2}Cl\textsubscript{2}, an ideal solvent for most allylation reaction of aldehydes,\textsuperscript{108f,108h} was therefore used as the solvent for our test\textsuperscript{115f,115h} (Table 5.1).

Reactions without catalysts were tested first to find out the best temperature for the development of a catalytic asymmetric version of this reaction (entries 1-4, Table 5.1). When 155 (1.0 equivalent) and 149 (1.5 equivalents) were stirred at r.t overnight, there was a significant reaction (entry 1, Table 5.1). A less but still significant background reaction was happening when temperature was decreased to 0 °C (entry 2, Table 5.1). No background reaction was observed when the temperature was down to -20 °C or lower (entries 3 and 4, Table 5.1). So -20 °C was chosen as the standard temperature for the development of the reaction.
Previously, our group reported that bidentate helical chiral pyridine N-oxide 88 efficiently activates allenyltrichlorosilane and is extremely reactive towards the propargylation of aldehydes. In light of this observation and the fact that reactions of propargylation of aldehydes and allylation of ketoimines should share similar mechanism, we became interested in exploring the reaction of ketoimine allylation with catalyst 88 since it represents a more challenging transformation as mentioned in the background. To our surprise, no reaction was observed when 10 mol% of 88 was used (entry 5, Table 5.1). The same result was obtained even when 30 mol% of 88 was used.
Unexpectedly, 10% of product with definite enantioselectivity (8% ee) was obtained with 10 mol% of 87, which is far less reactive in the propargylation of aldehydes (entry 7, Table 5.1). To our delight, we were able to get much promising results with 30 mol% of 87 in the reaction (entry 8, Table 5.1).

Collectively considering the information we gathered, we suspected the inactivity of catalyst 88 might be attributed to the adventitious HCl generated from the hydrolysis of allyltrichlorosilane 149, which cannot be avoided. Indeed, a quick NMR experiment revealed that at least one equivalent of HCl was generated in our standard operations. Catalyst 88 possesses a pyridine ring that is highly prone to be protonated by acid, and once protonated, 88 would lose its bidentate feature and only function as monodentate catalyst; even worse, the protonated pyridine ring would act as a space blocker and shield the N-oxide moiety (Figure 5.4). Catalyst 157 was previously synthesized in our group and presented absolute no reactivity towards the propargylation of aldehydes even after 24 hours at ambient temperature.73
Based on this hypothesis, some commonly used acid scavengers were tested to take care of the adventitious acid in the reaction. As an efficient additive for scavenging small amount of acid and water in many reactions, 4 Angstrom molecular sieves was tested first; some product formed as expected, however, it was racemic (entry 2, Table 5.2). Amylene (157) is a commonly used reagent for acid scavenging purpose in similar reactions, so it was tested next. The help was marginal, only trace product was observed based on TLC analysis (entry 3, Table 5.2). We then turned our search towards some commonly used nitrogen bases. A comparable result to entry 2 was obtained when 1.5 equivalents of triethylamine (158) was used (entry 4, Table 5.2). Much promising yield was acquired when a stronger Lewis base 159 was used, although still only racemic product observed (entry 5, Table 5.2). Unfortunately, with large access of 159, the reaction became very dirty and no desired product was formed presumably because of the isomerization under the strong basic condition (entry 6, Table 5.2). The use of 1.5 equivalents of 160 did not render any better results (entry 7, Table 5.2). To our delight, when 1.5 equivalents of proton sponge (161) were used, we got 28% product with a definite enantioselectivity (entry 8, Table 5.2). This is a good indication that catalyst 88 was involved in the reaction with the presence of acid scavengers.
Table 5.2. Acid scavenger study

\[
\begin{align*}
\text{entry} & \quad \text{1} & \quad \text{2} & \quad \text{3} & \quad \text{4} \\
\text{none} & \quad 4 \text{ AMS} & \quad \text{no rxn} & \quad 7\% \text{ yield, racemic} & \quad <5\% \text{ yield} \\
\text{7\% yield, racemic} & \quad (100 \text{ mg}) & \quad (1.5 \text{ equiv}) & \quad (1.5 \text{ equiv}) & \quad 9\% \text{ yield, racemic} \\
\text{157} & \quad \text{158} \\
\text{entry} & \quad \text{5} & \quad \text{6} & \quad \text{7} & \quad \text{8} \\
\text{23\% yield, racemic} & \quad (1.5 \text{ equiv}) & \quad \text{No desired product} & \quad (1.5 \text{ equiv}) & \quad 28\% \text{ yield, 4\% ee} \\
\text{159} & \quad \text{159} & \quad \text{160} & \quad \text{161} \\
\end{align*}
\]

\(^a\text{Reaction condition: hydrazone (0.25 mmol) and allylchlorosilane (0.375 mmol) in the presence of 30 mol \% of catalyst and acid scavengers in CH}_2\text{Cl}_2 (1.6 ml).} \\
\(^b\text{\% yield is the yield of isolated products.} \\
\(^c\text{ee was determined by HPLC analysis.} \)
5.2.2. Evaluation of New Catalysts

Without any substantial success with acid scavengers, we began to design and develop analogous catalysts of 88 that might function under acidic conditions owing to their decreased basicity (Figure 5.5).

Unfortunately, catalysts 126a-c were no better catalysts than 88, only trace product was observed by TLC analysis in these reactions (entries 2-4, Table 5.3). Surprisingly, a 30% yield and 82% ee (a value that is comparable to the best result available in the literature as far as we know\textsuperscript{113}) were achieved with the bis-N-oxides catalyst (123) (entry 5, Table 5.3). To our delight, the same efficiency was achieved for the large-scale reaction (1.0 mmol, entry 6, Table 5.3). However, it would be imprudent to solely attribute the increased reactivity and selectivity to the decreased basicity of catalyst 123. The change in the ligation numbers could dramatically change the reactivity have been reported.\textsuperscript{126}
a study of the allylation of aldehydes with allyltrichlorosilane, Hayashi et al. reported that a phenyl group was responsible for an unprecedented high reactivity they observed.\textsuperscript{52}

Inspired by the report, catalyst 124 was synthesized and tested. Unfortunately, only trace product was observed by TLC analysis (entry 7, Table 5.3). The dimerized N-oxide catalyst 129 was designed and synthesized to utilize the broad chiral space it creates, however, no reaction was observed in this case (entry 8, Table 5.3).

**Table 5.3.** Evaluation of new catalysts

<table>
<thead>
<tr>
<th>entry\textsuperscript{a}</th>
<th>Cat.</th>
<th>yield\textsuperscript{b}(%)</th>
<th>ee\textsuperscript{c}(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
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<tr>
<td>2</td>
<td>126a</td>
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<td>-</td>
</tr>
<tr>
<td>3</td>
<td>126b</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>126c</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>123</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>6\textsuperscript{d}</td>
<td>123</td>
<td>33.4</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>124</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>129</td>
<td>trace</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH\textsubscript{2}Cl\textsubscript{2} (1.6 ml).
\textsuperscript{b}Yield of isolated products. \textsuperscript{c}Determined by HPLC analysis. \textsuperscript{d}Reaction was run at 1.0 mmol scale.
5.2.3. Optimization of Reactions Catalyzed by bis-N-oxides Catalyst

A temperature effects study was conducted to better understand the behavior of bis-N-oxides 123 and to explore its full potential. Unexpectedly, the effort to obtain a higher enantioselectivity at a lower temperature did not succeed. The reaction run at -50 °C not only bared a lower yield but also was less selective (entry 1, Table 5.4). At higher temperatures, much better yields were obtained at the expense of selectivity (entries 4-6, Table 5.4), which could be attributed to the increased background reaction at the higher temperature (entry 7, Table 5.4).

Table 5.4. Evaluation of temperature effects

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>Cat.</th>
<th>temp (°C)</th>
<th>yield(^b) (%)</th>
<th>ee(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0</td>
<td>-</td>
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<td>3</td>
<td>123</td>
<td>-20</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>123</td>
<td>0</td>
<td>36</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>123</td>
<td>rt</td>
<td>41</td>
<td>64</td>
</tr>
<tr>
<td>6(^d)</td>
<td>123</td>
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<td>49</td>
<td>55</td>
</tr>
<tr>
<td>7(^d)</td>
<td>-</td>
<td>40</td>
<td>31</td>
<td>-</td>
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</tbody>
</table>

\(^a\)Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH\(_2\)Cl\(_2\) (1.6 ml).  
\(^b\)Yield of isolated products.  
\(^c\)Determined by HPLC analysis.  
\(^d\)CH\(_2\)ClCH\(_2\)Cl was used as solvent.
A detailed solvent effects study was also carried out. It has been proposed that in bipyridine \(N, N'-\)dioxides catalyzed alkylation of aldehydes; different types of intermediates could be formed. This is due to the possibility of monodentate or bidentate modes of ligation of bipyridine \(N, N'-\)dioxides to the silicon atom depends on the type of solvent used. The same study suggested that bipyridine \(N, N'-\)dioxides catalyze alkylation via a neutral six-coordinate silicon species in less electrophilic solvents such as PhCl, EtOAc, THF, etc. while the formation of a cationic six-coordinate silicon species as intermediate is possible if electrophilic solvents such as MeCN, CH\(_2\)Cl\(_2\), CHCl\(_3\), etc. are used.\(^{115h}\)

CH\(_2\)Cl\(_2\) has been proved to be a good solvent in our studies, so some other solvents that have a similar acceptor activity number\(^{127}\) (AN) were tested. Both CH\(_2\)ClCH\(_2\)Cl and CH\(_3\)CN gave comparable results, although with slightly lower selectivity (entries 2 and 4, Table 5.5). To our surprise, significant decrease in both yield and selectivity was observed when reaction was run in CH\(_3\)Cl (entry 3, Table 5.5). As expected, less electrophilic solvent Et\(_2\)O was not a good candidate, rendering only racemic product with a very low yield, and the same was true for toluene (entries 5 and 6, Table 5.5). To our surprise, \(\alpha,\alpha,\alpha\)-trifluorotoluene\(^{128}\) produced less product than toluene, although with slightly better selectivity (entry 7, Table 5.5). With iodobenzene, the selectivity was greatly diminished (entry 8, Table 5.5). THF was found to be quite useful, resulting the highest yield in all of the solvents tested (entry 9, Table 5.5). This might be attributed to its Lewis basic oxygen moiety, which can bind to silicon and accelerate the reaction (entry 10, Table 5.5).
Table 5.5. Evaluation of solvent effects

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>solvent</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt;(%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;(%)</th>
</tr>
</thead>
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<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30</td>
<td>82</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>7</td>
<td>α,α,α-trifluorotoluene</td>
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<tr>
<td>8</td>
<td>iodobenzene</td>
<td>32</td>
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<tr>
<td>9</td>
<td>THF</td>
<td>42</td>
<td>57</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>THF</td>
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<td>-</td>
</tr>
<tr>
<td>11</td>
<td>acetone</td>
<td>22</td>
<td>79</td>
</tr>
<tr>
<td>12</td>
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<td>27</td>
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<td>11</td>
<td>-</td>
</tr>
<tr>
<td>16&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>acetone</td>
<td>11</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH<sub>2</sub>Cl<sub>2</sub> (1.6 ml).  
<sup>b</sup> Yield of isolated products.  
<sup>c</sup> Determined by HPLC analysis.  
<sup>d</sup> No catalyst was used.  
<sup>e</sup> Reaction was run at 0 °C.  
<sup>f</sup> Reaction was run at ambient temperature.
To our surprise, we were able to get comparable results with acetone as solvent, and no sign of allylation of acetone was observed (entry 11, Table 5.5). A better yield and much higher selectivity (84% ee) was realized when a mixture of acetone and CH\(_2\)Cl\(_2\) were used (entry 12, Table 5.5). It appears that temperature was not a key factor when acetone was used as the solvent (entries 13-16, Table 5.5). Based on this study, CH\(_2\)Cl\(_2\) is still the solvent-of-choice for the reaction development.

The *additive effects* was carefully investigated next since additives play an important role in similar reactions.\(^{129}\) Some of the acid scavengers studied in Table 5.2 were tested to see whether it would be beneficial to remove the adventitious acid in the reaction with catalyst 123. When 100mg of 4-Angstrom molecular sieves were used, a slightly higher yield was observed (entry 1, Table 5.6). To our surprise, the use of nitrogen amines adversely affected the reaction (entries 2-5, Table 5.6). Iodobenzene was found useful when added as additive, improving both the yield and selectivity slightly (entry 6, Table 5.6). However, when used as a solvent, iodobenzene actually decreased the enantioselectivity quite a lot (entry 7, Table 5.6). It has been reported that thiourea could stabilize anions by donating double hydrogen bonding. We envisioned that a higher concentration of reactive silicate species might be generated if the chloride anion could be stabilized by such interaction. Thiourea 163 was chosen to test this hypothesis. Unfortunately, when 0.5 equivalent of 163 was used, no significant improvements were observed (entries 8 and 10-12, Table 5.6), although it was interesting that 163 seemed to be able to suppress the background reaction (entry 9, Table 5.6).
Inspired by the above study, it seemed to us that catalyst 123 is compatible with small amount of acid. To have an idea of the extent catalyst 123 still work in the acidic environment, an acid effects study was carefully carried out. Interestingly, when 0.5 equivalent of HCl was added to the reaction at 0 °C, the yield was only slightly dropped and almost no affection on the selectivity (entry 1, Table 5.7). To our surprise, a higher level of selectivity was observed when 0.5 equivalent of HCl was used at ambient
temperature (entry 3, Table 5.7), presumably due to the suppressed background reaction (entry 4, Table 5.7). While small amount of acid (i.e., 0.5 equivalent of HCl) did not seem to be harmful to the reaction, 1.5 equivalents of HCl completely stopped the reaction at -20 °C and reaction run at r.t was also greatly limited (entries 5 and 6, Table 5.7). As such, it appears that small amount of acid is compatible to the reaction while large amount does affect the reaction outcome.

**Table 5.7. Evaluation of acid effects**

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cat.</th>
<th>HCl (equiv)</th>
<th>temp (°C)</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt;(%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>0.5</td>
<td>-20</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>0.5</td>
<td>-20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>123</td>
<td>0.5</td>
<td>r.t</td>
<td>33</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>0.5</td>
<td>r.t</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>123</td>
<td>1.5</td>
<td>-20</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>123</td>
<td>1.5</td>
<td>r.t</td>
<td>14</td>
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<td>1.5</td>
<td>r.t</td>
<td>0</td>
<td>-</td>
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<sup>a</sup>Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH₂Cl₂ (1.6 ml). <sup>b</sup>Yield of isolated products. <sup>c</sup>Determined by HPLC analysis.
5.2.4. Product Inhibition

Considering all the results obtained with catalyst 123 so far, a clear trend could be revealed: in most of the reactions, a high level of enantioselectivity was achieved (up to 84% ee) while the yield was close to the mole percentage (30%) of catalyst used in those reactions. This is clearly an indication that product inhibition might have happened. To test whether this is the case, some experiments were carried out with 123. Indeed, a distinctive behavior between the yield and enantioselectivity of the product was observed. The sense of enantioselectivity was not affected by the mole percentage of 123 used; while the yield directly depended on the mole percentage of 123 used (Table 5.8). These observations clearly supported our hypothesis that a product inhibition might exist.

Table 5.8. Evaluation of catalyst loading effects

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>123 (mol%)</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt;(%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt;(%)</th>
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<tr>
<td>1</td>
<td>30</td>
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<tr>
<td>4</td>
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<td>92</td>
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<sup>a</sup>Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH<sub>2</sub>Cl<sub>2</sub> (1.6 ml).  
<sup>b</sup>Yield of isolated products.  
<sup>c</sup>Determined by HPLC analysis.
Collectively considering all the information available, a possible reaction mechanism was proposed to explain the observed phenomenon (Scheme 5.5). In an ideal catalytic cycle, catalyst 123 activates allyltrichlorosilane (149) and eventually leads to the ionization of chloride anion, generating a highly reactive Lewis acid intermediate (164). Substrate 165 is then activated through the intermediate 166, and the transfer of allyl group to ketoimine via an intramolecular reaction is followed. The release of catalyst (123) from 167 would finish the catalytic cycle and generate 168, which upon hydrolysis will become the final product.

**Scheme 5.5.** Proposed mechanism for observed product inhibition
As recently reported by Denmark and coworkers, however, five-coordinate silicon species is much more acidic than four-coordinate counterpart. Based on this study, 168 should be considerably more acidic than 149. Owing to the significant difference in acidity, free Lewis base catalyst (i.e. 123) preferentially binds to 168 instead of 149, which would theoretically cause the product inhibition we observed.

5.2.5. Efforts to Overcome Product Inhibition

One possible way to shift the balance is to increase the concentration of starting silicon reagent 149. It might be possible to change the equilibrium and shift the binding of 123 to 149 when 149 is used in excess.

Table 5.9. Evaluation of silicon reagent effects

<table>
<thead>
<tr>
<th>entry</th>
<th>X (equiv)</th>
<th>yield (%)</th>
<th>ee (%)</th>
<th>background rxn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>30</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7.5</td>
<td>39</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>15.0</td>
<td>43</td>
<td>76</td>
<td>5</td>
</tr>
</tbody>
</table>

*a* Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane in the presence of 30 mol % of catalyst in \( \text{CH}_2\text{Cl}_2 \) (1.6 ml). *b* Yield of isolated products. *c* Determined by HPLC analysis.
Indeed, we observed some positive effects when increasing the equivalence of 149 used in the reaction. When 7.5 equivalents of 149 were used, a much better yield and selectivity were achieved (entry 1 vs. entry 2, Table 5.9). However, further increasing the equivalents of 149 did not improve the yield too much, and the selectivity was slightly dropped, presumably because the background reaction began to occur (entry 3, Table 5.9).

When carefully examined, there is a strong partial double bond that raises great steric strain between the “-Ar” group and the hydrogen atom in the structure of 168. We could increase the steric strain in 168 simply by increasing the size of the “-Ar” group of the substrates. Theoretically, the increased steric strain would weaken the Si-O bond, destabilize 168 and thus shift the equilibrium to the less acidic tetra-coordinate silicon species 169 (Scheme 5.6). The formation of a weak acidic species like 169 will be helpful for the turning over of catalyst 123 in the catalytic cycle since 169 is no better Lewis acid than allyltrichlorosilane (149).

Scheme 5.6. Potential solution for observed product inhibition (1)
Table 5.10. Evaluation of substrate effects (1)

Based on this assumption, a series of hydrazones that varies only at the “-Ar” group was synthesized and tested (Table 5.10). When hydrogen was installed as the “-Ar” group (substrate 170a), however, only trace product was observed by TLC analysis (entry 1, Table 5.10). No reaction was observed when substrate 170b was used, and to our surprise, the same result was observed at ambient temperature (entries 2 and 3, Table 5.10). Much better yields were obtained when substituted benzene rings were installed,
although selectivities were somewhat diminished (entries 5 and 6, Table 5.10). Unfortunately, no reaction happened at -20 °C or room temperature when substrate \textbf{170e} was tested (entries 7 and 8, Table 5.10), it was quite surprising because this structure should greatly raise the steric strain in \textbf{168}. No reaction was observed for a similar substrate \textbf{170f} even when the temperature was increased to 50 °C (entries 9-11, Table 5.10).

Another method to potentially shifting the equilibrium between \textbf{168} and \textbf{169} is to change the binding ability of the substrate to silicon. To test this idea, some specially designed hydrazones were synthesized (\textbf{170g-i}, Scheme 5.7).

\textbf{Scheme 5.7.} Potential solution for observed product inhibition (2)
Unfortunately, tosyl hydrazone 170g was found to be completely unreactive at both -20 °C and ambient temperature (entries 1 and 2, Table 5.11). To our surprise, only trace product was observed by TLC analysis at -20 °C when 170h was used (entry 3, Table 5.11). And only marginal reaction was observed when it was run at room temperature (entry 4, Table 5.11). Unexpectedly, there was no sign of reaction with 170i, even when the reaction was heated to 100 °C (entries 5-8, Table 5.11).

Table 5.11. Evaluation of substrate effects (2)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>temp (°C)</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>170g</td>
<td>-20</td>
<td>215</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>170g</td>
<td>r.t</td>
<td>215</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>170h</td>
<td>-20</td>
<td>216</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>170h</td>
<td>r.t</td>
<td>216</td>
<td>8</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>170i</td>
<td>-20</td>
<td>217</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>170i</td>
<td>r.t</td>
<td>217</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>170i</td>
<td>50</td>
<td>217</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>170i</td>
<td>100</td>
<td>217</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>155</td>
<td>-20</td>
<td>164</td>
<td>30</td>
<td>82</td>
</tr>
</tbody>
</table>

a Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH2Cl2 (1.6 ml). b Yield of isolated products. c Determined by HPLC analysis.
Mechanistically, the allylation of ketoimines by allyltrichlorosilane involves the Lewis base catalyst binding to and release from the silicon center. Unavoidably, the existence of other Lewis basic reagents would compete in such processes. Lewis basic solvent molecules, existing in abundant, might also participate in such processes and compete with the catalyst, instead of only serving as spectator molecules. Such competing process, when properly utilized, might be of great help to release the catalyst from the final product and to return into the catalytic cycle.

Table 5.12. Evaluation of Lewis basic solvent effects

<table>
<thead>
<tr>
<th>entry</th>
<th>basic solvent</th>
<th>volume (ml)</th>
<th>CH$_2$Cl$_2$ (ml)</th>
<th>yield$^b$(%)</th>
<th>ee$^c$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0</td>
<td>1.6</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>0.6</td>
<td>1.0</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0.8</td>
<td>0.8</td>
<td>58</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>1.0</td>
<td>0.6</td>
<td>46</td>
<td>64</td>
</tr>
<tr>
<td>5$^d$</td>
<td>THF</td>
<td>0.8</td>
<td>0</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>1,4-Dioxane</td>
<td>0.8</td>
<td>0.8</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>0.4</td>
<td>1.2</td>
<td>63</td>
<td>17</td>
</tr>
<tr>
<td>8$^e$</td>
<td>DMF</td>
<td>0.4</td>
<td>1.2</td>
<td>57</td>
<td>-</td>
</tr>
<tr>
<td>9$^f$</td>
<td>-</td>
<td>0</td>
<td>1.6</td>
<td>33</td>
<td>32</td>
</tr>
</tbody>
</table>

$^a$Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH$_2$Cl$_2$ (1.6 ml).

$^b$Yield of isolated products. $^c$Determined by HPLC analysis. $^d$0.8 ml of α,α,α-trifluorotoluene was used instead of CH$_2$Cl$_2$.

$^e$No catalyst was used. $^f$2,2'-bipyridine-N,N'-dioxide (0.25 mmol) was added as additive.
To test the feasibility of this hypothesis, a few commonly used Lewis basic solvents were added as a co-solvent in the reaction. Indeed, we were able to get much better results when Lewis basic solvents were used as co-solvents. When 0.6 ml THF was added as co-solvent, we got a slightly higher yield (entry 2, Table 5.12). To our delight, we were able to obtain a near 60% yield with a 71% ee when 0.8 ml of THF was added (entry 3, Table 5.12). While further increasing the amount of THF adversely affected the reaction (entry 4, Table 5.12), the attempt to replace CH$_2$Cl$_2$ with α,α,α-trifluorotoluene turned out to be un successful (entry 5, Table 5.12). Nevertheless, encouraged by the results above, 1,4-Dioxane was tested, and a near 40% yield and 80% ee were achieved (entry 6, Table 5.12). To our surprise, the use of 0.4 ml of DMF significantly increased the yield, although the selectivity was very poor (entry 7, Table 5.12), the reason may be attributed to the enhanced background reaction (entry 8, Table 5.12). An attempt to use 2,2′-bipyridine-N, N′-dioxide instead of basic solvents did not succeed, resulting poor selectivity (entry 9, Table 5.12).

### 5.3. Summary

In summary, the catalytic asymmetric allylation of ketoimines to access enantiomerically pure α-trisubstituted homoallylic amines is among the most important goals and challenges for organic synthetic chemists. A series of novel helical chiral catalysts was designed and synthesized to utilize hypervalent silicon chemistry to develop a catalytic asymmetric allylation reaction of general ketoimines. Among the catalysts developed, bis-N-oxides 123 was found to be very selective, rendering products with more than 80%
ee. A study demonstrated that the allylation of ketoimine-derived hydrazones catalyzed by catalyst 123 was compatible with small amount of acid. In order to improve the yield, a series of experiments was carefully carried out (e.g., solvent, temperature, and additive effects studies), although without too much success. A careful study indicated that the low yield might be due to a product inhibition. Based on a proposed mechanism, a series of reactions was carefully designed and carried out to overcome the product inhibition. We were able to solve this problem to some extent by applying Lewis basic solvent (i.e., THF) as co-solvent in the reaction.

5.4. Experimental Section

5.4.1. General Information

All reactions were carried out in the oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Silicycle pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (256 nm), with combination of potassium permanganate and/or vanillin solution as an indicator. Flash column chromatography was performed according to the method of Still76 using silica gel 60 (mesh 230-400) supplied by Silicycle.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH2Cl2) and toluene were freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. THF and diethyl ether
were freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. \((\text{iPr})_2\text{NEt}\) and \text{Et}_3\text{N}\) were distilled over calcium hydride, stored over Linde type 4Å molecular sieves in a Schlenk flask, and used from there. Amylene was distilled over sodium, stored over Linde type 4Å molecular sieves in a Schlenk flask, and used from there. Allyltrichlorosilane was purchased from Sigma-Aldrich and freshly distilled over \text{K}_2\text{CO}_3\) under reduced pressure prior to use.

\(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR spectra were recorded on a Bruker Avance 300 (300 MHz \(^1\text{H}\)) and a Bruker Avance 400 (400 MHz \(^1\text{H}\), 100 MHz \(^{13}\text{C}\)). Chemical shift values (\(\delta\)) are reported in ppm relative to \text{Me}_4\text{Si} (\(\delta\) 0.0 ppm) unless otherwise noted. The proton spectra are reported as follows \(\delta\) (multiplicity, coupling constant \(J\), number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). Optical rotations were measured on a Rudolph Research Analytical AUTOPOL® III automatic polarimeter. Infrared spectra were recorded using PerkinElmer™ SPECTRUM ONE with Universal ATR Sampling Accessory (Composite Zinc Selenide and Diamond crystals). High-resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, the University of Miami.
5.4.2. General procedure for the synthesis of hydrazones

(E)-N’-(4-phenylbutan-2-ylidene)benzohydrazide (155): A solution of the corresponding ketone (1482 mg, 10.0 mmol) and hydrazine (1360 mg, 10.0 mmol) in MeOH (12.0 ml) was refluxed for 1.0 hour. The reaction mixture was then filtered and washed with cold Et₂O to afford the title compound as a white solid (2.22 g, 84%). Small amount of the resulted product was taken for characterization. All spectral data were in agreement with literature value\textsuperscript{113}.

(E)-N’-(4-phenylbutan-2-ylidene)formohydrazide (170a): A solution of the corresponding ketone (740 mg, 5.0 mmol) and hydrazine (300 mg, 5.0 mmol) in EtOH (10.0 ml) was refluxed for 3.0 hours. The resulted crude material was purified by a quick flash chromatography on silica gel (first 15% EtOAc in hexanes, then 20% EtOAc in hexanes) to afford the title compound as a white solid (780 mg, 82%). \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 9.69 (s, 1H), 8.68 (s, 1H), 7.23-7.30 (m, 5H), 2.89 (t, \( J = 7.4 \) Hz, 2H), 2.60 (t, \( J = 7.6 \) Hz, 2H), 1.95 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 166.3, 154.6, 141.4, 128.8, 128.7, 126.5, 40.8, 32.7, 16.3; FTIR (neat) \( \nu_{\text{max}} \) 3174, 3026, 2888, 1673, 1635, 1542, 1381, 1292, 1194, 1028, 915, 732 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{11}\)H\(_{14}\)N\(_2\)O [M + 1]\(^+\), expected: 191.1184, found: 191.1188.

(E)-N’-(4-phenylbutan-2-ylidene)acetohydrazide (170b): A solution of the corresponding ketone (814 mg, 5.5 mmol) and hydrazine (370 mg, 5.0 mmol) in EtOH (6.0 ml) was refluxed for 4.0 hours. The resulted crude material was purified by a flash
chromatography on silica gel (30% EtOAc in hexanes) to afford the title compound as a white solid (337 mg, 33%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.54 (s, 1H), 7.21-7.32 (m, 5H), 2.90 (t, $J = 7.6$ Hz, 2H), 2.60 (t, $J = 7.6$ Hz, 2H), 2.25 (s, 3H), 1.84 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.7, 151.0, 141.5, 128.7, 128.6, 126.3, 40.6, 32.4, 20.7, 15.7; FTIR (neat) $u_{\text{max}}$ 3042, 1674, 1652, 1549, 1429, 1363, 1291, 1251, 1096, 1074, 1031, 741, 700 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{12}$H$_{16}$N$_2$O [M + 1]$^+$, expected: 205.1341, found: 205.1346.

(E)-4-nitro-N’-(4-phenylbutan-2-ylidene)benzohydrazide (170c): A solution of the corresponding ketone (222 mg, 1.5 mmol) and hydrazine (272 mg, 1.5 mmol) in EtOH (5.0 ml) was refluxed for 2.0 hours. The resulted crude material was purified by a quick flash chromatography on silica gel (first 8% EtOAc in hexanes, then 15% EtOAc in hexanes) to afford the title compound as a white solid (354 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.98 (s, 1H), 8.28 (d, $J = 8.8$ Hz, 2H), 7.85 (d, $J = 8.8$ Hz, 2H), 7.12-7.30 (m, 5H), 2.90 (t, $J = 7.5$ Hz, 2H), 2.64 (t, $J = 7.5$ Hz, 2H), 1.98 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.5, 141.3, 141.0, 131.4, 128.8, 128.7, 128.6, 126.6, 126.4, 123.0, 45.5, 30.4, 30.0; FTIR (neat) $u_{\text{max}}$ 3222, 3030, 1667, 1603, 1537, 1517, 1294, 1272, 1137, 856, 727, 696 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{17}$H$_{17}$N$_3$O$_3$ [M + 1]$^+$, expected: 312.1348, found: 312.1356.

(E)-3,5-bis(trifluoromethyl)-N’-(4-phenylbutan-2-ylidene)benzohydrazide (170d): A solution of the corresponding ketone (128 mg, 0.86 mmol) and hydrazine (234 mg, 0.86 mmol) in MeOH (3.0 ml) was refluxed for 1.5 hours. The resulted crude material was
purified by *a quick* flash chromatography on silica gel (first 5% EtOAc in hexanes, then 15% EtOAc in hexanes) to afford the title compound as a white solid (304 mg, 88%). All spectral data were identical to literature value.

*N'-(4-phenylbutan-2-ylidene)pivalohydrazide (170e)*: A solution of the corresponding ketone (778 mg, 5.25 mmol) and hydrazine (581 mg, 5.0 mmol) in EtOH (6.0 ml) was refluxed for 3.0 hours. The resulted crude material was purified by *a bulb-to-bulb* distillation to afford the title compound as a white solid (864 mg, 70%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.31 (s, 1H), 7.17-7.30 (m, 5H), 2.90 (t, $J$ = 7.6 Hz, 2H), 2.67 (t, $J$ = 7.6 Hz, 2H), 1.87 (s, 3H), 1.28 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.0, 157.7, 141.4, 128.7, 128.6, 126.3, 41.2, 33.0, 27.8, 27.6, 15.6; FTIR (neat) $\nu_{\text{max}}$ 3288, 2954, 1658, 1508, 1454, 1367, 1178, 749, 700 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{15}$H$_{22}$N$_2$O $[M + 1]^+$, expected: 247.1810, found: 247.1820.

**170f**: A solution of the corresponding ketone (1482 mg, 10.0 mmol) and hydrazine (1320 mg, 10.0 mmol) in MeOH (12.0 ml) refluxed for 3.0 hours. The reaction mixture was filtered and washed with cold Et$_2$O. Small amount of the resulted product was taken for characterization. All spectral data were in agreement with literature values$^{132}$.

*(E)-I-(4-phenylbutan-2-ylidene)-2-tosylhydrazine (170g)*: A solution of the corresponding ketone (1482 mg, 10.0 mmol) and hydrazine (1860 mg, 10.0 mmol) in MeOH (12.0 ml) was refluxed for 1.5 hours. The reaction mixture was filtered and washed with cold Et$_2$O. Small amount of the resulted product was taken for
characterization. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.98 (s, 1H), 7.84 (d, $J$ = 8.0 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.16-7.24 (m, 3H), 7.07-7.09 (m, 2H), 2.79 (t, $J$ = 7.6 Hz, 2H), 2.53 (t, $J$ = 7.6 Hz, 2H), 2.44 (s, 3H), 1.78 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.2, 144.3, 141.4, 135.7, 129.8, 128.7, 128.6, 128.4, 126.3, 40.6, 32.3, 22.0, 16.5; FTIR (neat) $u_{\text{max}}$ 3239, 1600, 1452, 1376, 1332, 1162, 914, 815, 736 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{17}$H$_{20}$N$_2$O$_2$S [M + Na]$^+$, expected: 339.1138, found: 339.1155.

(E)-I-(4-phenylbutan-2-ylidene)-2-(pyridin-2-yl)hydrazine (170h): A solution of the corresponding ketone (355 mg, 2.4 mmol) and hydrazine (262 mg, 2.4 mmol) in EtOH (12.0 ml) refluxed for 3.0 hours. The resulted crude material was purified by a quick flash chromatography on silica gel (first 10% EtOAc in hexanes, then 15% EtOAc in hexanes) to afford the title compound as yellow oil (490 mg, 85%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10-8.11 (m, 1H), 7.71 (s, 1H), 7.55-7.59 (m, 1H), 7.18-7.33 (m, 6H), 6.72-6.75 (m, 1H), 2.95 (t, $J$ = 7.6 Hz, 2H), 2.64 (t, $J$ = 7.6 Hz, 2H), 1.89 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.6, 147.7, 147.4, 141.8, 138.2, 128.5, 126.1, 115.5, 107.5, 40.7, 32.9, 15.2; FTIR (neat) $u_{\text{max}}$ 3029, 1596, 1574, 1500, 1443, 1122, 771, 698 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{17}$H$_{17}$N$_3$ [M + 1]$^+$, expected: 240.1495, found: 240.1508.

(E)-N'-(4-phenylbutan-2-ylidene)benzothiohydrazide (170i): A solution of the corresponding ketone (296 mg, 2.0 mmol) and hydrazine (304 mg, 2.0 mmol) in MeOH (3.0 ml) refluxed for 1.5 hours. The resulted crude material was purified by a flash chromatography on silica gel (5% EtOAc in hexanes) to afford the title compound as light yellow oil (530 mg, 94%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.65-7.67 (m, 2H), 7.19-
7.41 (m, 8H), 2.83-2.88 (m, 2H), 2.20-2.25 (m, 2H), 1.76 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.2, 141.5, 132.2, 130.0, 128.9, 128.8, 128.7, 127.2, 126.4, 84.2, 44.3, 32.6, 29.2; FTIR (neat) $\nu_{\text{max}}$ 3268, 3027, 2925, 1494, 1448, 1269, 975, 912, 757, 690 cm$^{-1}$; HRMS (ESI-TOF): Exact mass calcd for C$_{17}$H$_{18}$N$_2$S [M + 1]$^+$, expected: 283.1263, found: 283.1258.

5.4.3. General Procedure for Asymmetric Allylation of Ketoimines

156: To a solution of hydrazone 155 (67 mg, 0.25 mmol) and catalyst (M)-123 (36.6 mg, 0.075 mmol) in CH$_2$Cl$_2$ (1.6 mL) was added neat allyltrichlorosilane (66 mg, 0.375 mmol) dropwise at -30 °C. The resulting red solution was allowed to warm up to -20 °C and stirred for 16 h at the same temperature. The reaction was then quenched with a 1:1 mixture of saturated aqueous KF/1M KH$_2$PO$_4$ solutions, and extracted with CH$_2$Cl$_2$ three times. The combined organic layers were washed with water then brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (first 5%, then 15% EtOAc in hexanes) to afford the desired product as colorless oil (23 mg, 30%) and then the column was washed with 3% MeOH in CH$_2$Cl$_2$ to recover (P)-123 (34 mg, 94%), which was used in the allylation reaction without loss in activity and selectivity. All spectral data were in agreement with the literature values.$^{113}$ Enantiomeric ratio was determined by HPLC with a Chiralcel AD-H column equipped with an AD-H guard column (3% MeOH:EtOH (1:1) in hexane, flow rate = 1.0 mL/min), $t_r$ (minor) = 92.23 min, $t_r$ (major) = 102.34 min. The (S)-absolute configuration was assigned by comparing its chiral HPLC elution time to the literature.$^{113}$
(S)-N′-(3-methyl-1-phenylhex-5-en-3-yl)-4-nitrobenzohydrazide (171c): The general procedure was followed with the corresponding hydrazone 170c (78 mg, 0.25 mmol), and catalyst (M)-123 (36.6 mg, 0.075 mmol) to give the title compound as a yellow solid (38.4 mg, 44%) with 53 ee. Enantiomeric ratio was determined by HPLC with a Chiral Pack AD-H column equipped with an AD-H guard column (10% iPrOH in hexanes, flow rate = 0.45 mL/min), tR (major) = 36.72 min, tR (minor) = 39.16 min. The (S)-absolute configuration was assigned by analogy to 156. [a]D20 = +6, c = 0.0005, CH2Cl2. 1H NMR (400 MHz, CDCl3) δ 8.28 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.20-7.30 (m, 5H), 5.92-6.01 (m, 1H), 5.18-5.22 (m, 2H), 2.74 (t, J = 8.4 Hz, 2H), 2.33 (d, J = 7.2 Hz, 2H), 1.76-1.81 (m, 2H), 1.20 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 165.3, 150.1, 142.8, 138.6, 134.3, 128.9, 128.8, 128.4, 126.3, 124.3, 118.9, 60.4, 43.1, 39.9, 30.4, 23.3; FTIR (neat) νmax 3226, 3086, 2951, 1632, 1598, 1519, 1452, 1345, 916, 847, 739, 696 cm⁻¹; HRMS (ESI-TOF): Exact mass calcd for C20H23N3O3 [M + 1]+, expected: 354.1818, found: 354.1819.

(S)-3,5-bis(trifluoromethyl)-N′-(3-methyl-1-phenylhex-5-en-3-yl)benzohydrazide (171d): The general procedure was followed with the corresponding hydrazone 170d (100.6 mg, 0.25 mmol), and catalyst (M)-123 (36.6 mg, 0.075 mmol) to give the title compound as a white solid (48 mg, 43%) with 50 ee. Enantiomeric ratio was determined by HPLC with a Chiral Pack AD-H column equipped with an AD-H guard column (2 % iPrOH in hexanes, flow rate = 0.20 mL/min), tR (minor) = 45.17 min, tR (major) = 49.65 min. The (S)-absolute configuration was assigned by analogy to 156. [a]D20 = +6, c = 0.0005, CH2Cl2. 1H NMR (400 MHz, CDCl3) δ 8.09 (s, 2H), 8.01 (s, 1H), 7.18-7.32 (m, 5H),
5.92-6.03 (m, 1H), 5.18-5.22 (m, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.31-2.33 (m, 2H), 1.74-1.84 (m, 2H), 1.20 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.4, 143.0, 135.1, 134.4, 132.7 (q, \(J = 34.0\) Hz), 128.9, 128.8, 127.4 (d, \(J = 5.0\) Hz), 126.4, 125.6 (m), 123.2 (q, \(J = 272.0\) Hz), 118.8, 60.4, 43.2, 39.8, 30.4, 23.4; FTIR (neat) \(\nu_{\text{max}}\) 3272, 2944, 1642, 1451, 1376, 1276, 1132, 907, 698 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{22}\)H\(_{22}\)F\(_6\)N\(_2\)O \([\text{M + 1}]^+\), expected: 445.1709, found: 445.1738.

\((S)-1-(3\text{-methyl-1-phenylhex-5-en-3-yl})-2-(pyridin-2-yl)hydrazine (171h):\) The general procedure was followed with the corresponding hydrazone 170h (60 mg, 0.25 mmol), and catalyst (M)-123 (36.6 mg, 0.075 mmol) to give the title compound as light yellow oil (6 mg, 8%), enantioselectivity was not determined for this sample. The (S)-absolute configuration was assigned by analogy to 156. \([\alpha]\)\(^{20}\)\(_D\) = -118, c = 0.0005, CH\(_2\)Cl\(_2\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.68 (d, \(J = 3.6\) Hz, 1H), 7.82-7.86 (m, 1H), 7.46 (d, \(J = 8.0\) Hz, 1H), 7.36-7.39 (m, 1H), 7.14-7.28 (m, 5H), 5.76-5.87 (m, 1H), 5.09-5.16 (m, 2H), 2.65 (d, \(J = 7.6\) Hz, 2H), 2.53-2.63 (m, 2H), 2.10-2.29 (m, 2H), 1.40 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 165.7, 163.0, 149.5, 142.8, 138.7, 134.1, 128.7, 126.1, 125.2, 118.6, 113.8, 73.8, 43.4, 40.8, 30.5, 22.2; FTIR (neat) \(\nu_{\text{max}}\) 3060, 3031, 2979, 2932, 1584, 1460, 1426, 1380, 993, 917, 787, 742, 700 cm\(^{-1}\); HRMS (ESI-TOF): Exact mass calcd for C\(_{18}\)H\(_{23}\)N\(_3\) \([\text{M + 1}]^+\), expected: 282.1965, found: 282.1958.
REFERENCES


