2014-07-15

Development of Helical Chiral Catalysts and Their Applications in Asymmetric Catalysis

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DEVELOPMENT OF HELICAL CHIRAL CATALYSTS AND THEIR APPLICATIONS IN ASYMMETRIC CATALYSIS

By

Zhili Peng

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2014

UNIVERSITY OF MIAMI

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DEVELOPMENT OF HELICAL CHIRAL CATALYSTS AND THEIR APPLICATIONS IN ASYMMETRIC CATALYSIS

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PENG, ZHILI (Ph.D., Chemistry)
Development of Helical Chiral Catalysts and Their Applications in Asymmetric Catalysis (August 2014)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Norito Takenaka.
No. of pages in text. (157)

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

ACKNOWLEDGEMENTS

This work was carried out from August 2009 to May 2014 under the guidance of Professor Norito Takenaka at Department of Chemistry, the University of Miami. I deeply thank everyone who has contributed to this work. Without you, I will not be able to come this far.

Foremost, I would like to express my gratitude to my advisor Professor Norito Takenaka for giving me the chance to study with him. Thank him for all the constructive discussions and critical comments about my research projects. His wide knowledge, creativity, kindness, guidance and encouragement benefice my whole Ph. D. training. It is a lot of fun to learn and explore chemistry under his direction and what I learned from him is what made me a true chemist.

It is my great luck to have worked with some fantastic people during my stay in Professor Norito Takenaka's lab. I wish to thank Dr. Chen for leading me into this field, helping me set up the very first experiment and being a great friend. I also want to thank Dr. Jimenez and Dr. Narcis; you are such great friends and lab mates. I could not imagine a life in the lab without you around! I also wish to express my appreciation to all the current and ex-members in this group.

I am also very grateful for having Professor Angel Kaifer, Professor James N. Wilson and Professor Kathleen Rein (Florida International University) in my doctoral committee and wish to thank them for their precious time and continual support.

I also offer thanks to Professor Captain for solving crystal structures for my research, to Dr. Hudson for help with NMR spectra, to Edward Torres for help with mass spectra, and to Jim Metcalf for help with the instruments. I also want to express my appreciation to Sara Sucklal, Lydia Gonzalez, Susana Gadanyi, Raul Hernandez as well as the entire chemistry department people for your kindness and help.

Thanks to you, my friends, Lihua Bai, Shangming Deng, Shanghao Li, Jiajia Lei, Yao Luo, Yanhua Qiu, Zhenghua Tang, Tingting Zhang, Ning Zhao and so many others. It is you that made the years so memorable.

Most importantly I would like to thank my parents for their support, help and sacrifice during my life. They have no idea about chemistry, but their words are the reason that keeps me moving forward. I also want to thank my brother for his support, how I miss the old days when we were both young! My deepest appreciation goes to my grandparents, without their care, that little boy would not be what he is right now!

The last and special thanks go to my wife for your love, support and company in these times. Twelve years ago, we were still high school kids, but now we are going to be parents, how exciting this is! I can't wait to say "Hi" to our first child! Love you!

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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
*m*CPBA	*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

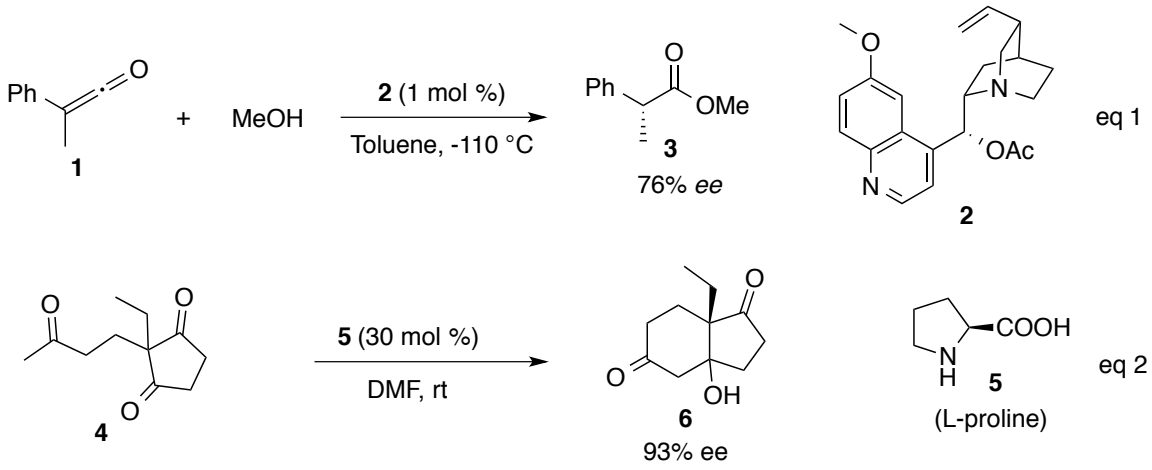
1.1. Organocatalysis

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

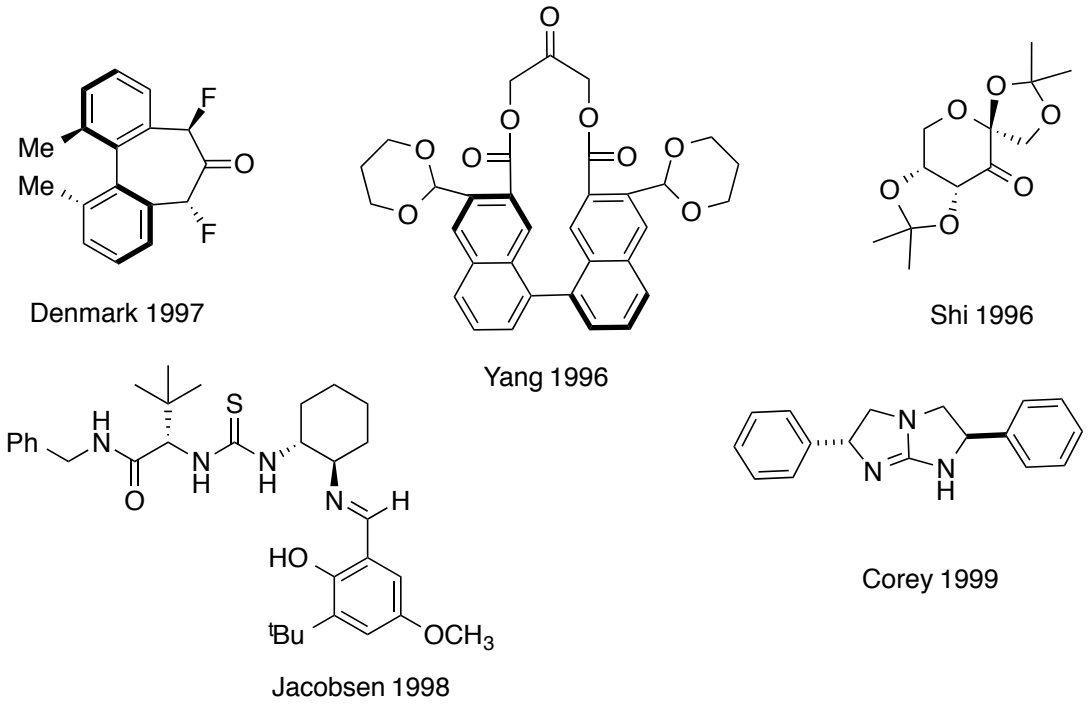
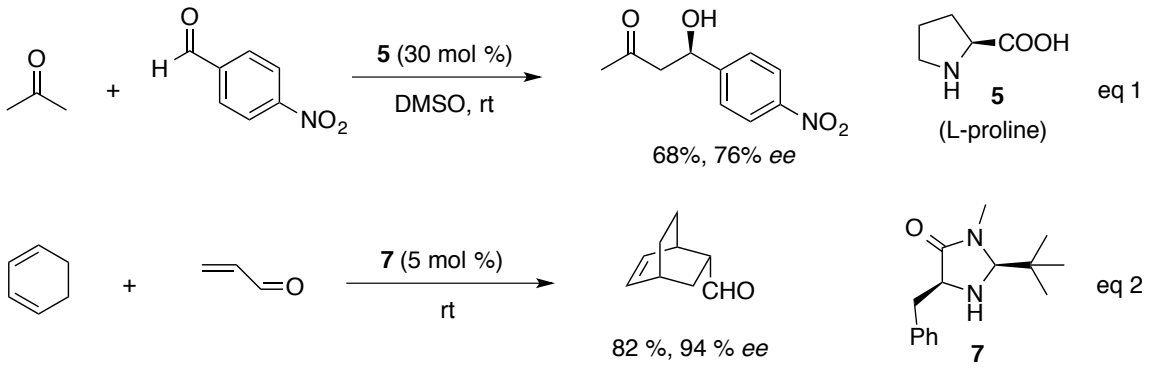


Figure 1.1. Selected examples of organocatalysts developed in 1990s

However, with the successful development of some small organic molecule catalyzed reactions, such as enantioselective epoxidation of simple alkenes[6] and asymmetric Strecker reactions[7] 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[8] (eq 1, Scheme 1.2); and the other is the development of iminium catalysis of asymmetric Diels-Alder reactions by MacMillan and coworkers[1] (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]

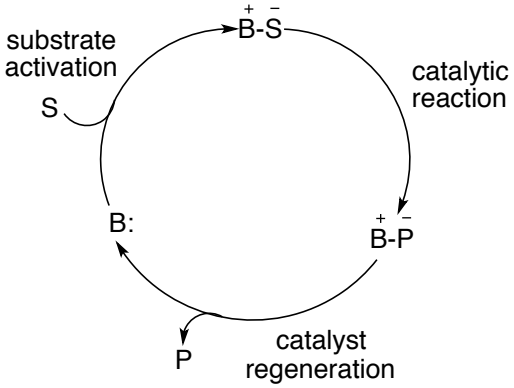
1.1.2. The Classifications of Organocatalysis

1.1.2.1. Classification Based on Reaction Mechanism

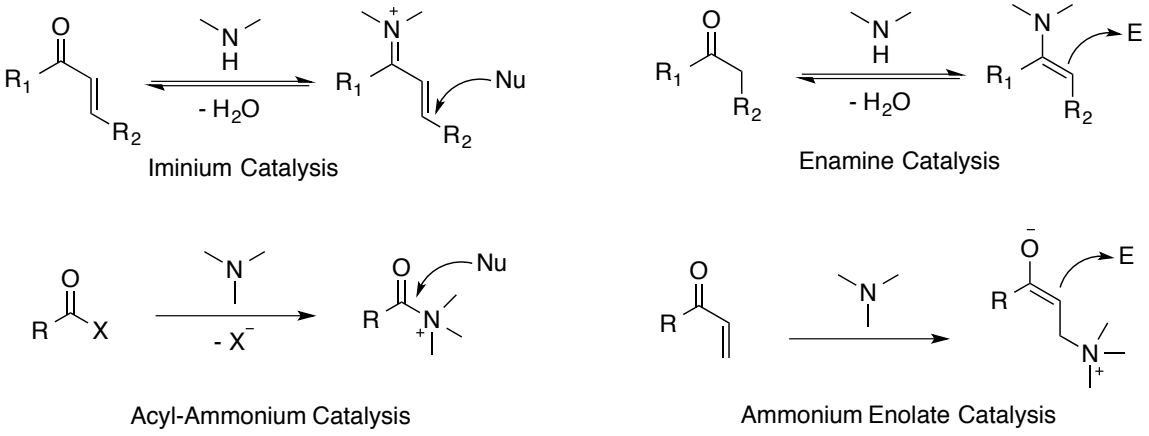
Research groups from all over the world have developed a vast number of organocatalysts in the short amount of time since 2000.[9] In order to better study these catalysts for the future design and development of new organocatalysts, the great number of organocatalytic reactions have been categorized 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:).



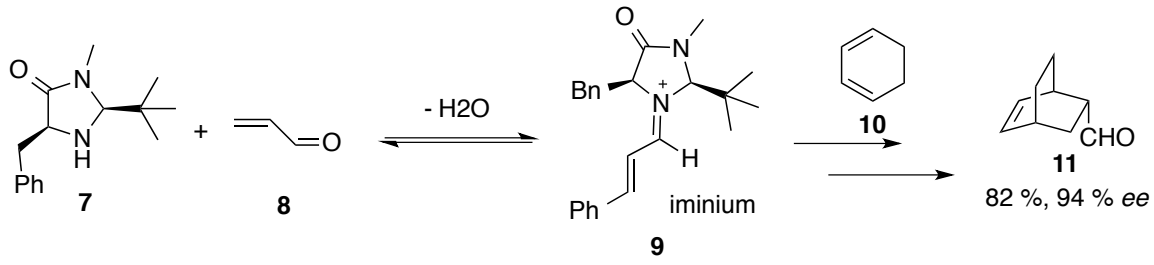
Scheme 1.3. Simplified Lewis base catalysis cycle



Scheme 1.4. Selected examples of Lewis base catalysis

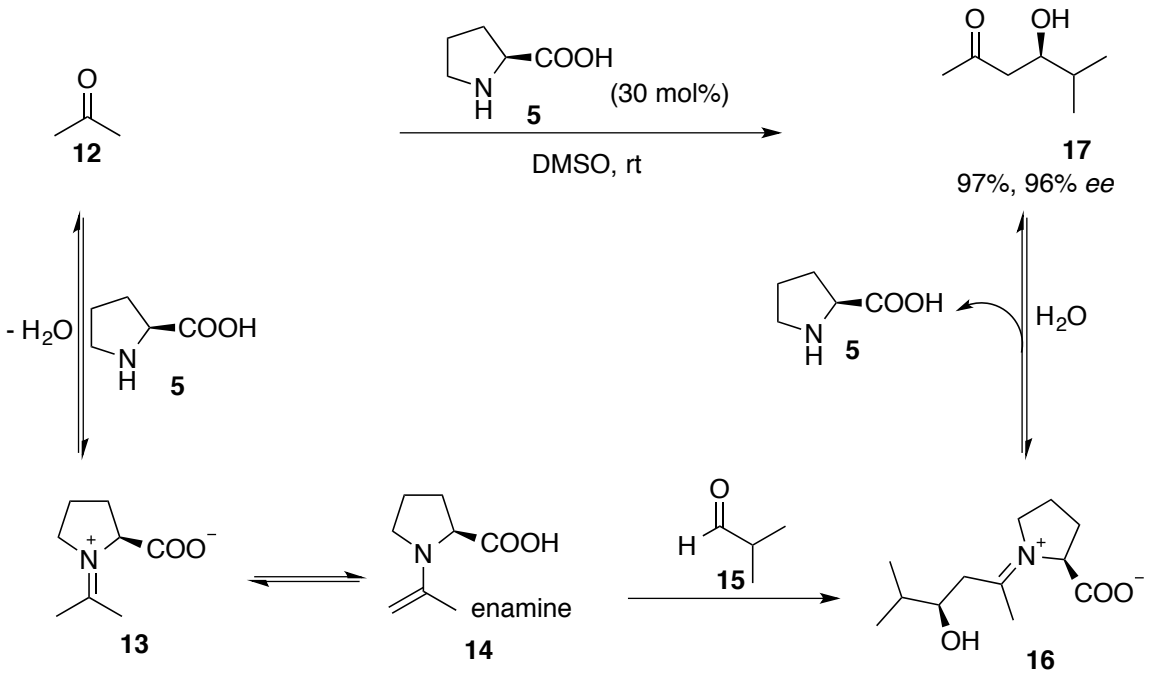
Most of the Lewis base organocatalysts, which mainly utilize N, O, P, S and C as their activation center, can activate substrates by converting them into activated intermediates such as iminium ions, enamines, acyl ammonium ions, and ammonium enolates (Scheme 1.4).[10]

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 α, β-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.*

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,[11] Friedel-Crafts reaction,[12] Mukaiyama-Michael reactions, Michael addition reactions, transfer hydrogenation reactions, epoxidation reactions, and *etc.*

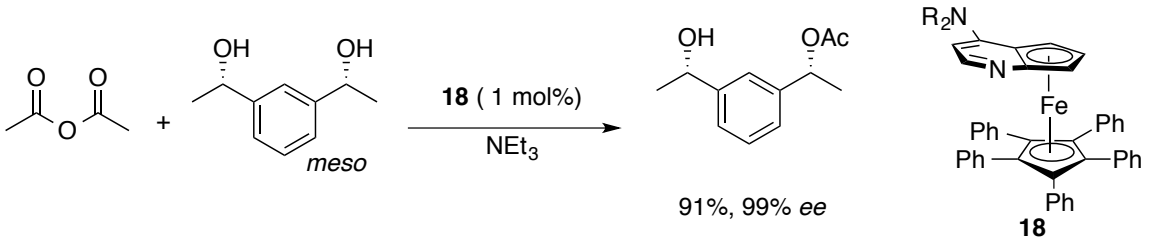


Scheme 1.6. Enantioselective enamine catalysis reported by List *et al.*

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,[5] 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.[8] 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.



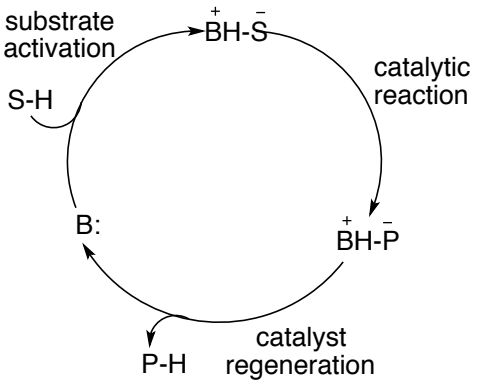
Scheme 1.7. DMAP-based organocatalysis developed by Fu *et al.*

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

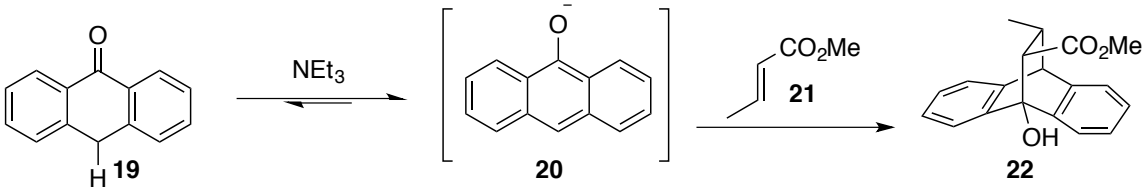
reaction[18] is such a reaction that undergoes ammonium enolate catalysis. Besides the above-mentioned four types of catalysis, there are also some other types of reactions falling into the category of Lewis base catalysis. Such catalysis includes carbene catalysis,[19] ylide catalysis, and *etc*.

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).



Scheme 1.8. Simplified Brønsted base catalysis cycle

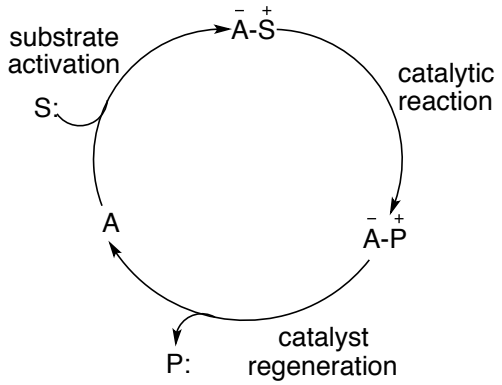


Scheme 1.9. Brønsted base catalysis in Diels-Alder reaction

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[20] (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:) 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:) and release of catalyst (A) (Scheme 1.10).



Scheme 1.10. Simplified Lewis acid catalysis cycle

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.[22] Five years later, O'Donnell

and coworkers[23] developed a comprehensive reaction based on the same chiral scaffold with a different counter ion. Lygo[24] and Corey[25] independently developed the second generation of organo phase transfer catalysts with much higher efficiency. Maruoka and coworkers[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 alkylaton reactions, Michael addition reactions, aldol reactions, Mannich reactions and epoxidation reactions.[27]

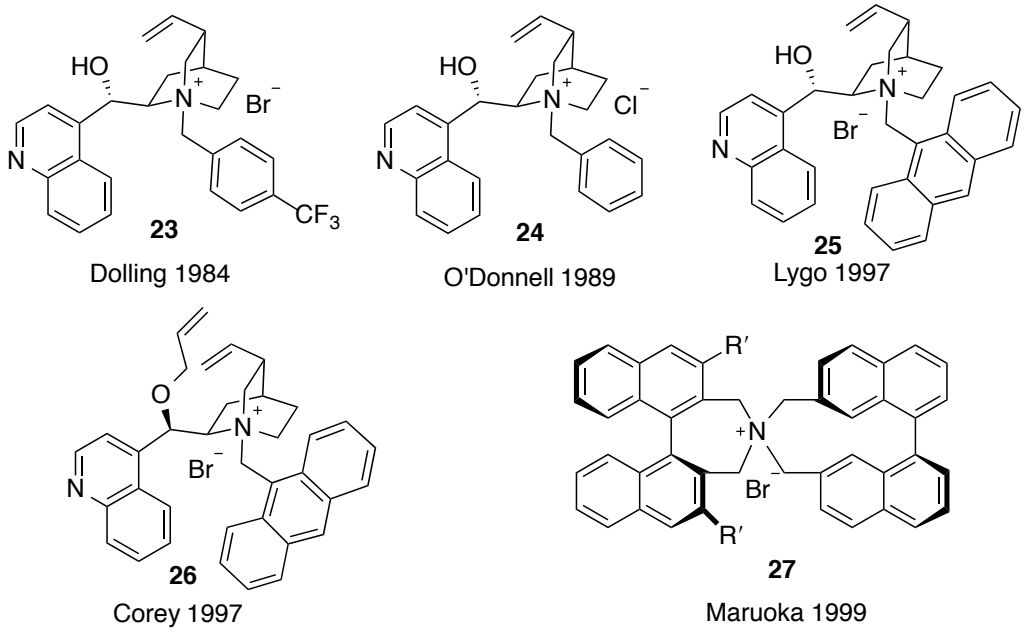
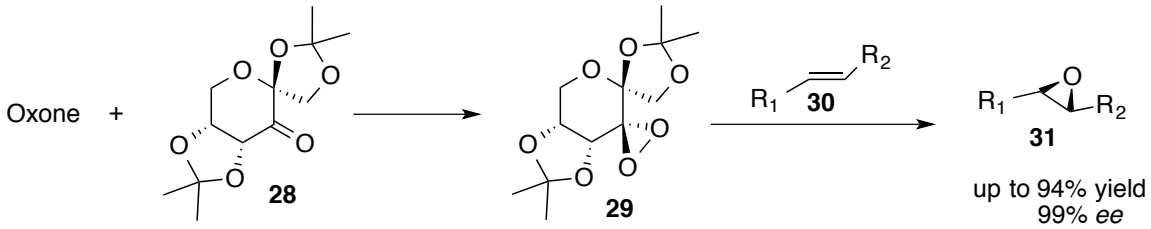


Figure 1.2. Selected phase transfer organocatalysts

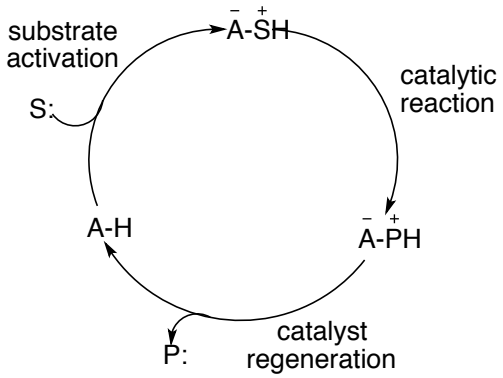


Scheme 1.11. Epoxidation catalyzed by chiral dioxirane

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

1.1.2.1.4. Brønsted Acid Catalysis

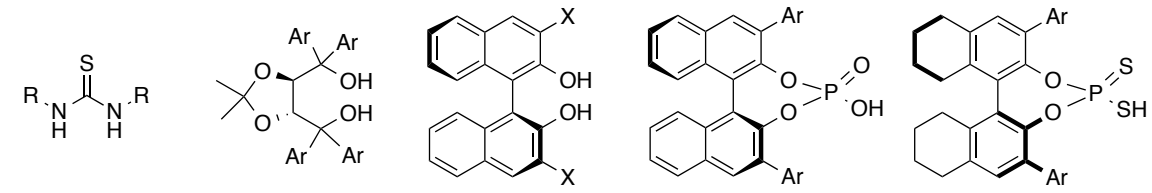
In general, Brønsted acid catalysis shares the same mechanism as Lewis acid catalysis does, except in the first step it involves a (partial) protonation of the substrate (S:) by the Brønsted acid catalyst (Scheme 1.12).



Scheme 1.12. Simplified Brønsted acid catalysis cycle

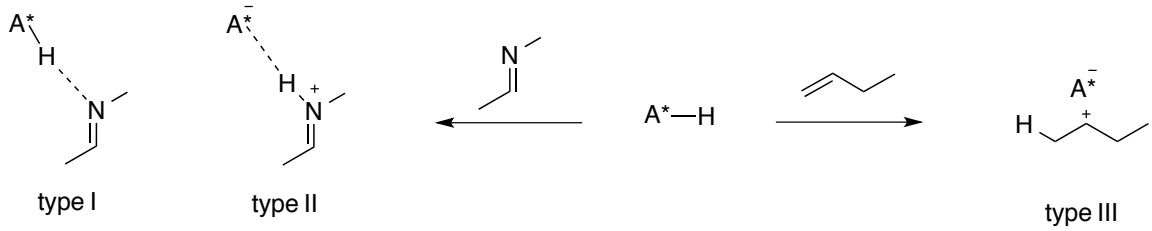
Based on their acidity[29] (Figure 1.3), most of the Brønsted acid catalysts could be classified into three groups: the first one is catalysts derived from (thio) urea[7a, 30] (**32**), TADDOL[31] (**33**) and BINOL[32] (**34**); the second group is strong Brønsted acids, such as chiral phosphoric acids and their derivatives[33] (**35**); and the last type is recently developed chiral dithiophosphoric acids[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).



32 **33** **34** **35** **36**

Figure 1.3. Selected examples of chiral Brønsted acid organocatalysts



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.[7a] Later it was found that they were also excellent catalysts for asymmetric Mannich[30c] and hydrophosphonylation[30b] reactions. It's generally believed that they activate the substrates through the hydrogen bonds donated from the acidic (thio) urea hydrogens.

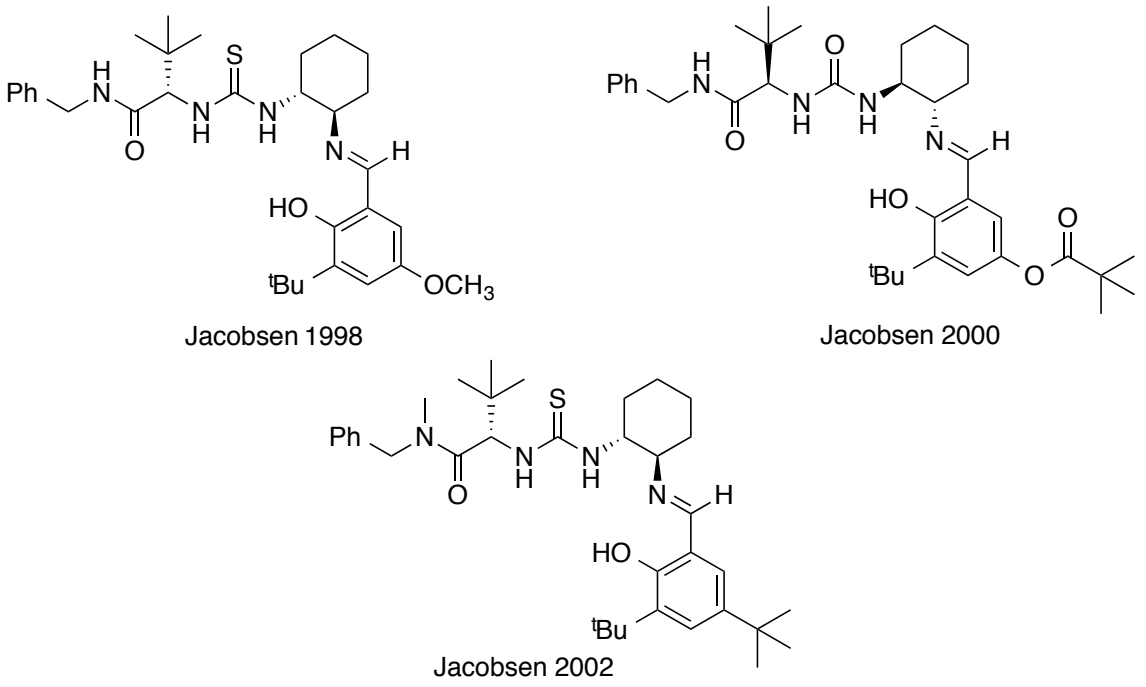
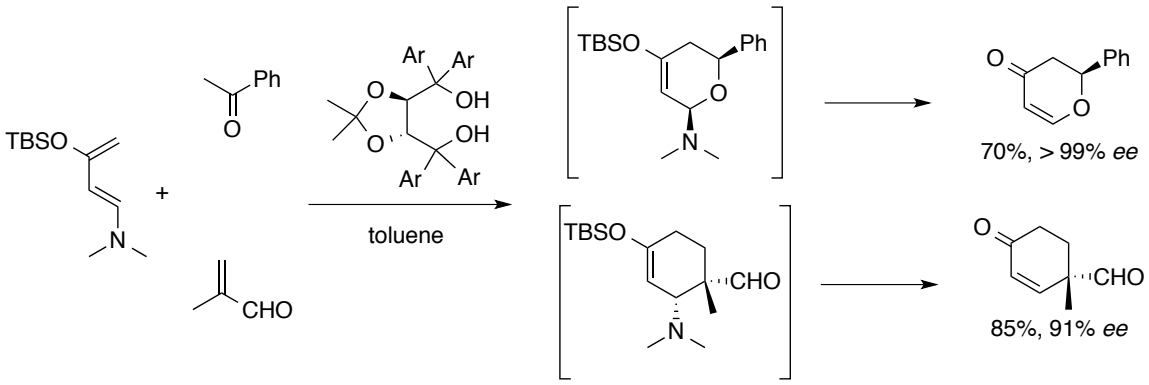


Figure 1.4. Selected examples of Jacobsen's (thio) urea catalysts

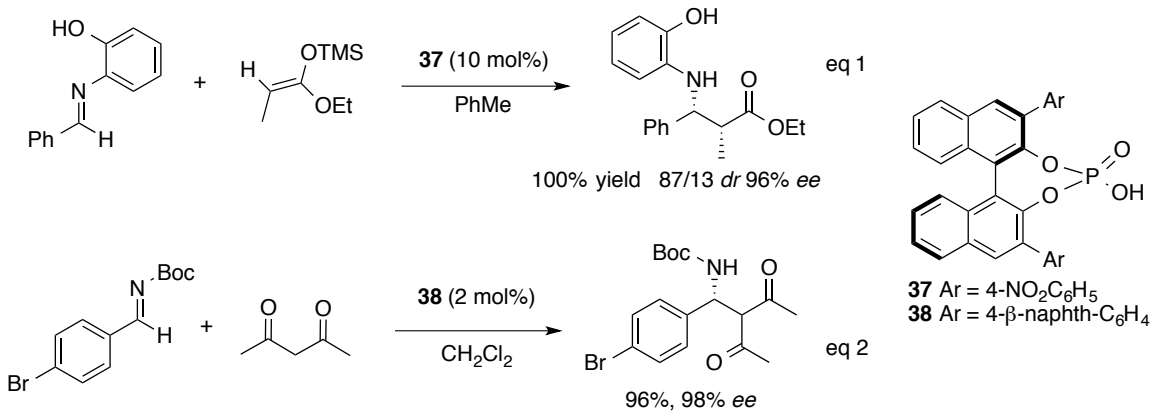


Scheme 1.14. Chiral diols catalyzed (hetero) Diels-Alder reactions

Rawal and co-workers[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.[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[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.

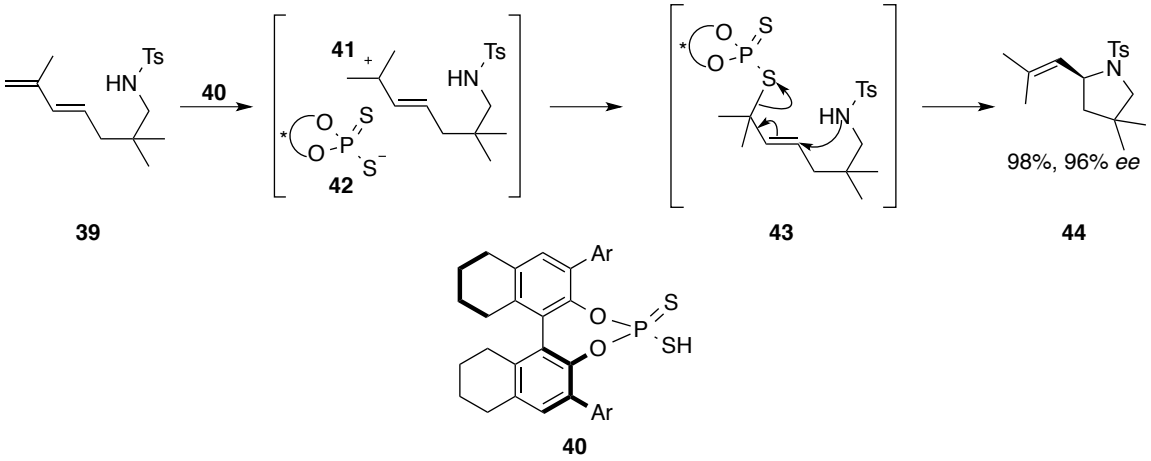


Scheme 1.15. First generation of chiral phosphoric acid catalysis

Akiyama *et al.* [36] (eq 1, Scheme 1.15) and Terada *et al.* [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,[38] transfer hydrogenation,[39] Diels-Alder reaction,[40] Nazarov cyclization[41] and *etc*.

The last type of chiral Brønsted acid was recently developed by Toste and coworkers.[34b] This type of catalysts has been used to catalyze highly enantioselective transformations of unactivated alkenes (Scheme 1.16). The protonation of alkene **39** by dithiophosphoric acid **40** results in carbocation **41** which does not form a hydrogen bond, but still holds the conjugate base (**42**) in proximity through electro-static interaction. This interaction then facilitates the formation of intermediate **43**. In the following step, the nucleophilic amine group displaces the chiral leaving group in a S_N2' fashion, rendering product **44** in high enantioselectivity and efficiency.



Scheme 1.16. Chiral dithiophosphoric acid catalyzed hydroamination reaction

1.1.2.1.5. Bifunctional Catalysis

Inspired by enzyme's cooperative catalysis, Shibasaki and coworkers[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[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.

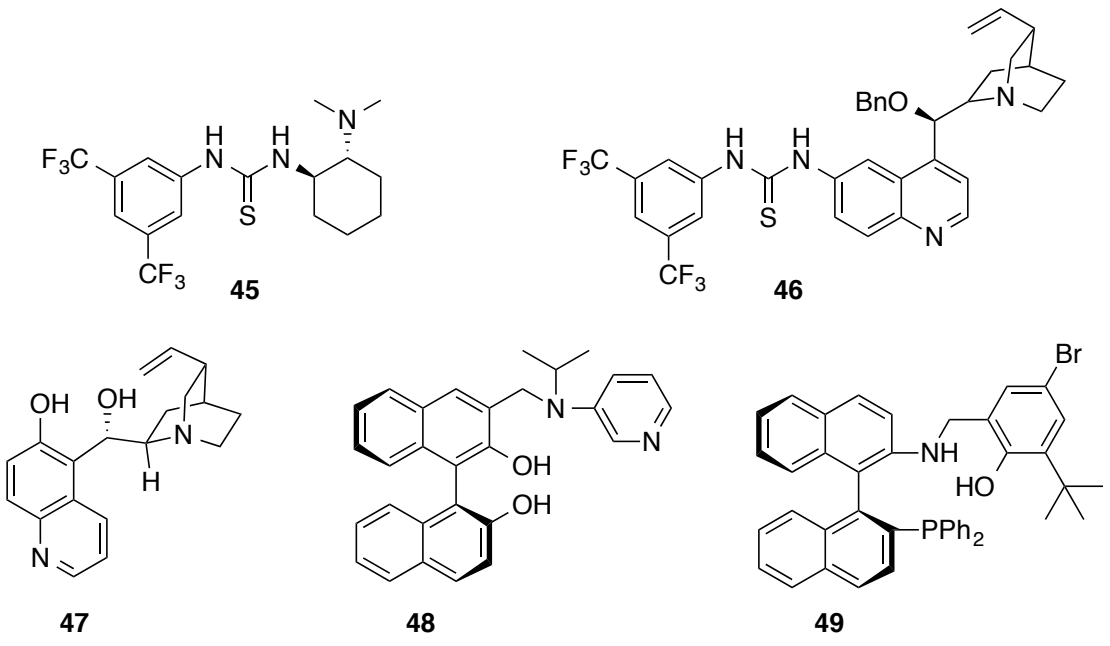
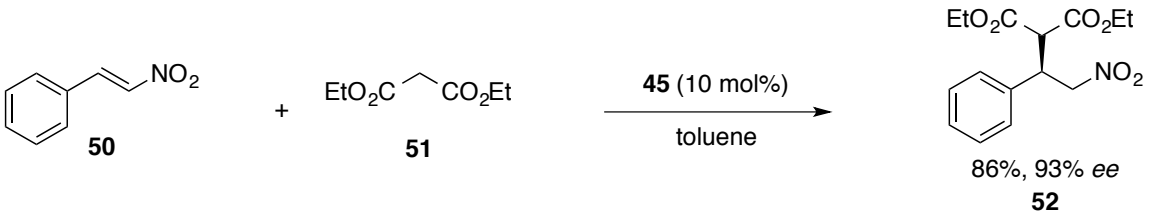


Figure 1.5. Selected examples of multifunctional organocatalysts

One of such example is Takemoto's bifunctional thiourea catalyst[43d] (**45**, Figure 1.5). The thiourea catalyst (**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 **50** *via* hydrogen bonding, while the tertiary amine group helps to activate the Michael donor **51**.



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,[43d] Henry reaction,[44] Strecker reaction,[45] Morita-Baylis-Hillman reaction,[18b] kinetic resolution of alcohols and a wide range of carbonyl α-functionalization reactions.

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".[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.

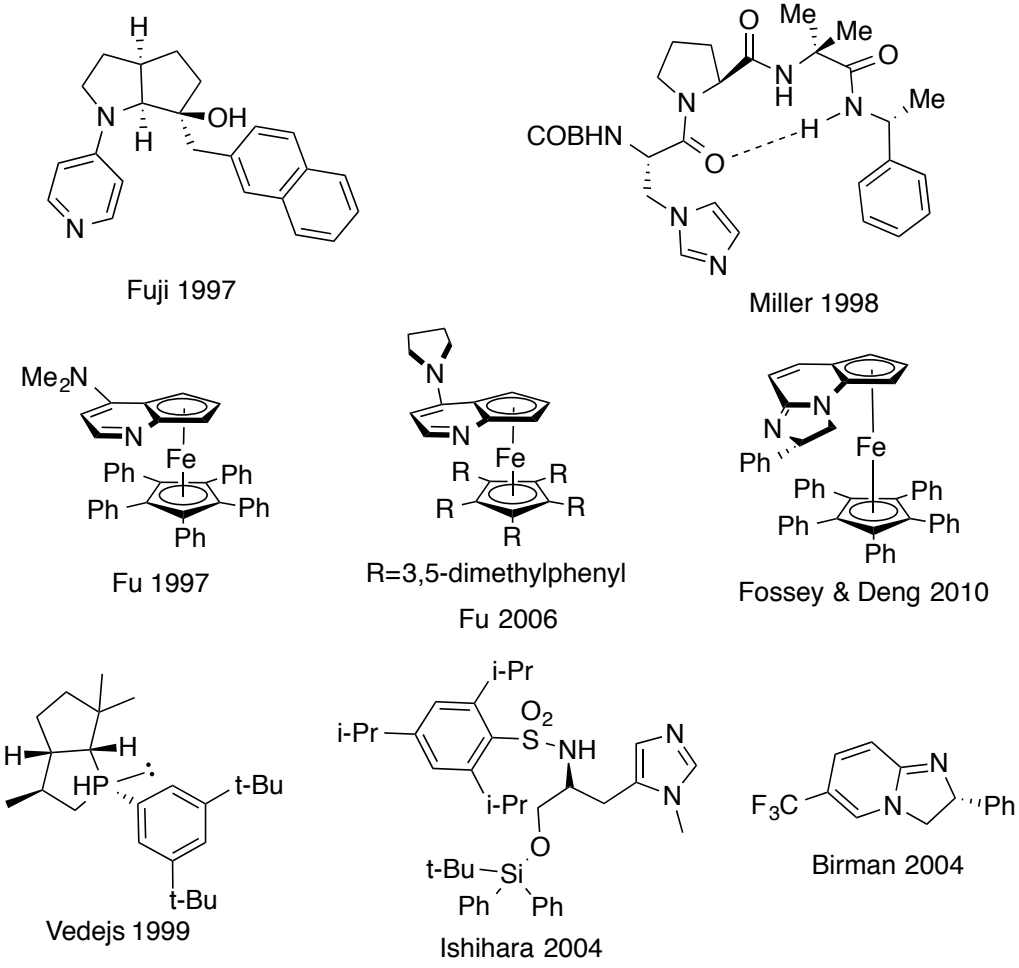


Figure 1.6. Selected examples of nucleophilic organocatalysts

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).

1.1.2.2.2. 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 week 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).[48] 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.

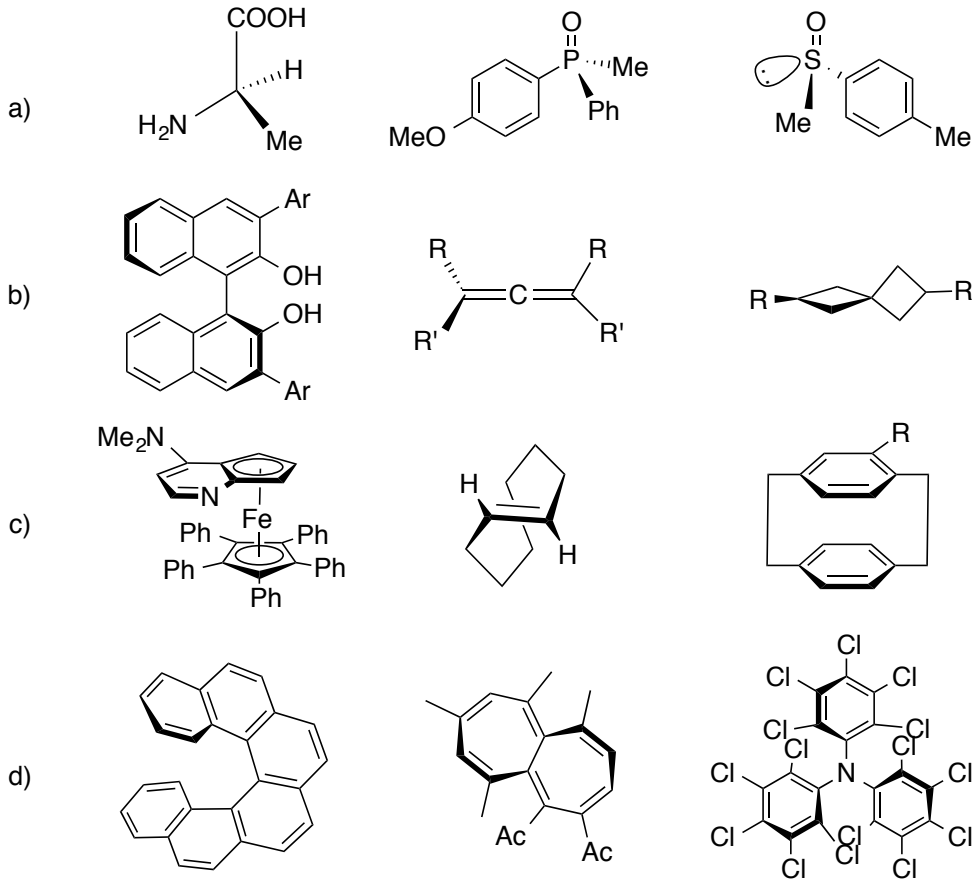


Figure 1.7. Selected examples of chiral molecules

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"[49] (**33**, **53**, and **54** in Figure 1.8).

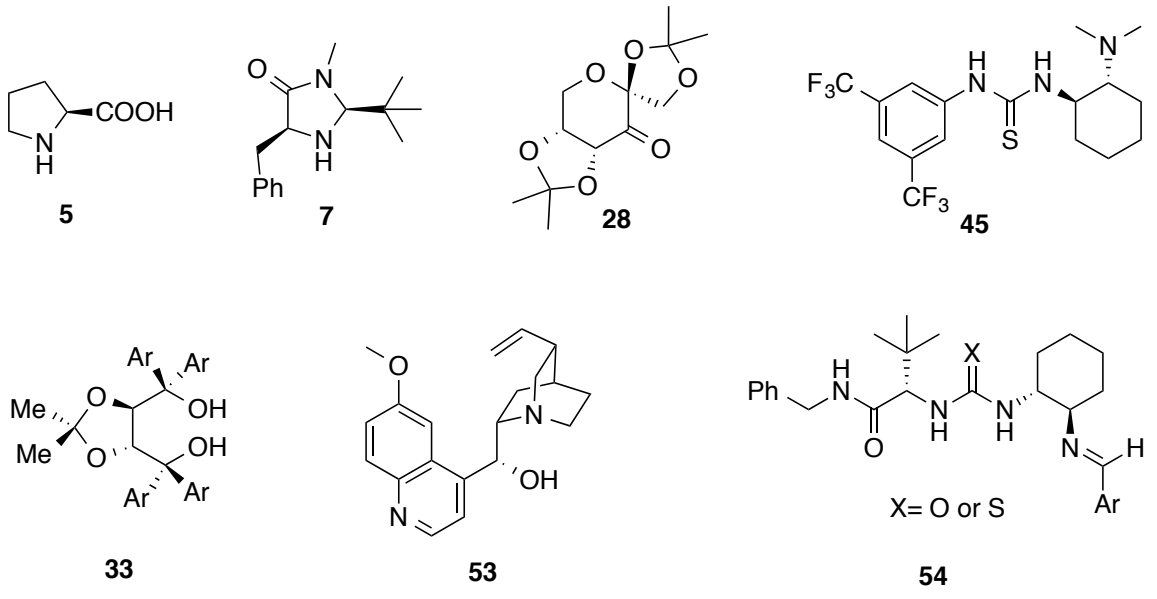


Figure 1.8. Selected examples of central chirality based organocatalysts

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)

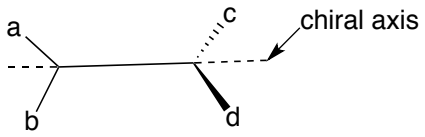


Figure 1.9. Chiral axis connecting four groups a, b, c and d

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.[50] Lewis base N-oxides **56**[51] and **57**[52] have been found to be highly efficient and selective for the allylation of aldehydes with allyltrichlorosilane while catalyst **58**[53] 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".

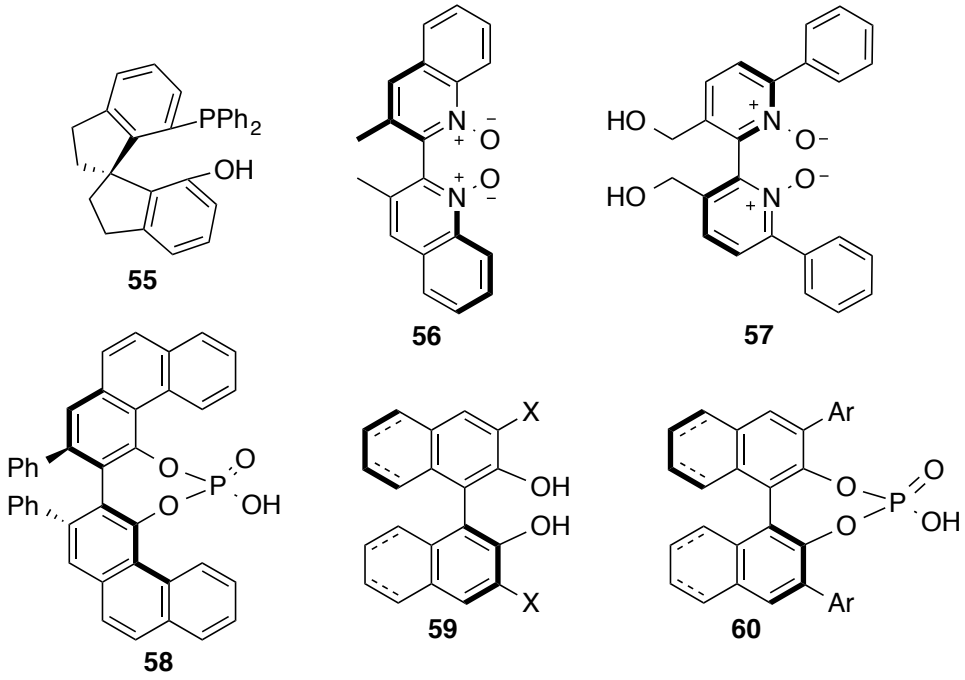
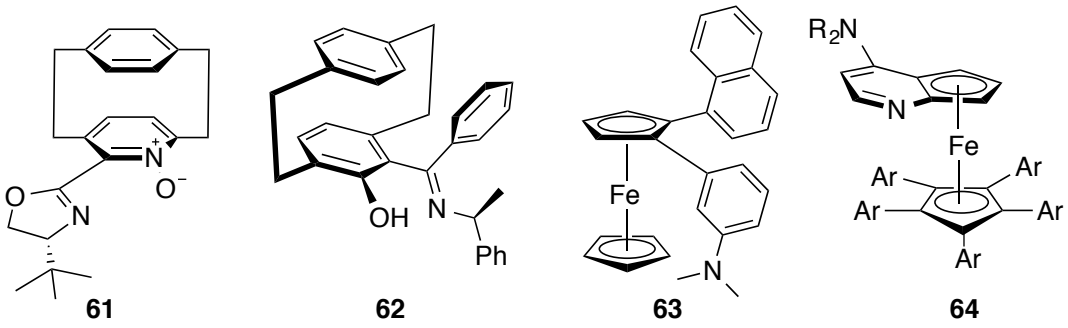


Figure 1.10. Selected examples of axial chirality based organocatalysts

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 metallocenes (e.g. ferrocenes), (E)-cyclooctene, and certain mono substituted paracyclophanes 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 allyltrichlorosilane.[54] Catalyst **62** have been found to be an excellent catalyst for the asymmetric, catalytic phenyl transfer to imines.[55] Chiral DMAP analogue **63** catalyzed the dynamic kinetic resolution and rearrangement reaction of azlactones with good yield and moderate selectivities.[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).



61 **62** **63** **64**

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 posses 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).

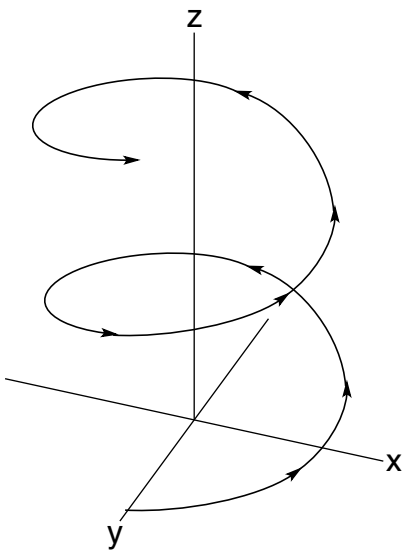


Figure 1.12. A helix represented by a three-dimensional curve

(Adopted from Narcis, M. J.; Takenaka, N., *Eur. J. Org. Chem.* **2014,** *2014*, 21.)

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[57] (*ortho*-fused 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[58] developed a new optically pure [6]helicene derived diphosphane ligand and named it "PHelix" (**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.[59]

In 1998, Yamaguchi and coworkers[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 (**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 (**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.[61] Very recently, Starý *et al.* developed a novel helical phosphite based on [6]helicene-related compounds[62] (**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.

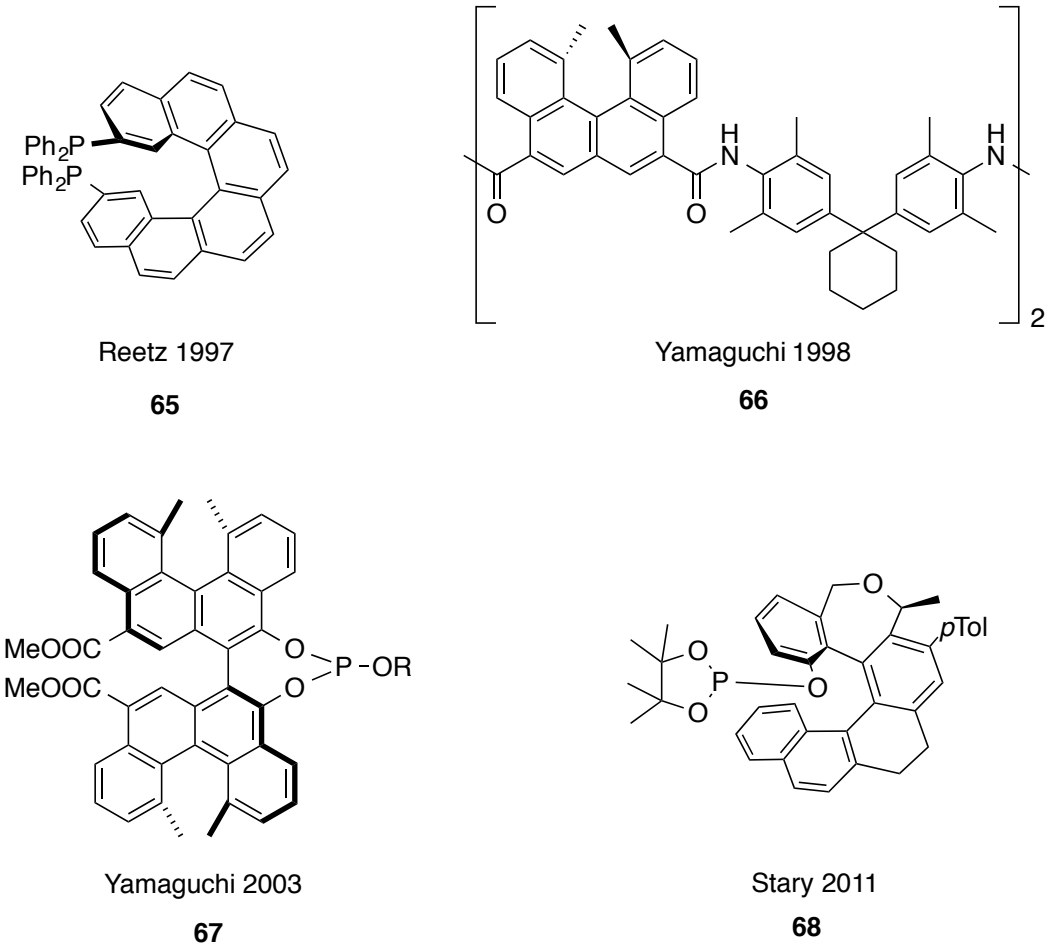
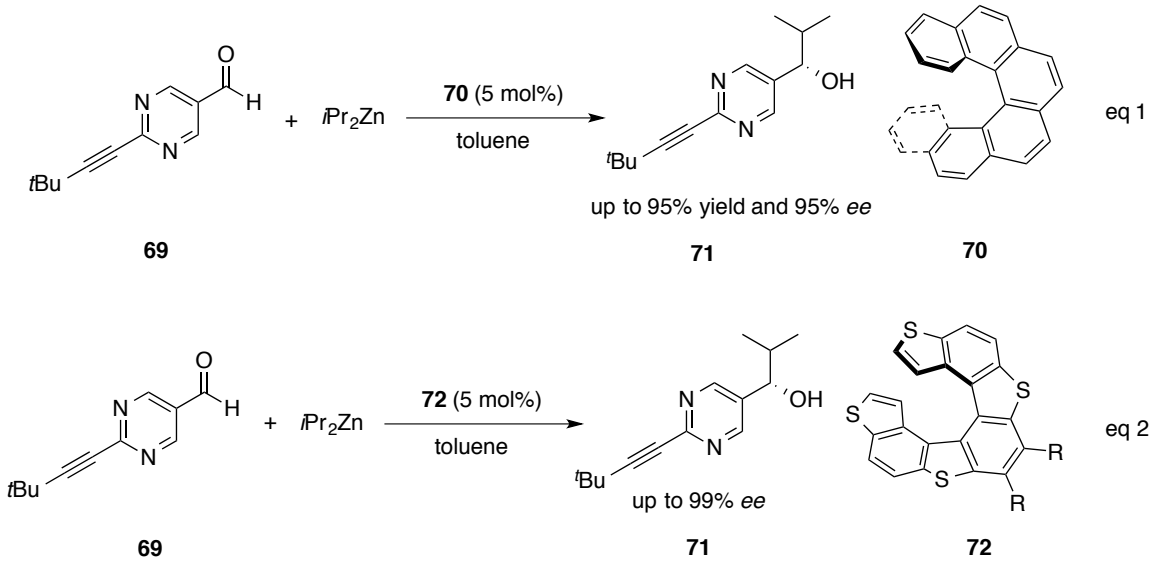


Figure 1.13. Helical chiral ligands in organometallic catalysis

1.2.2. Helical Chiral Small Molecules as Chiral Introducer

In 2001, Soai and coworkers reported a remarkable asymmetric synthesis induced by unfunctionalized helicenes.[63] In this study, the enantioselective addition of iPr_2Zn 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 tetrathia-[7]-helicene was reported by the same group and collaborators[64] (eq 2, Scheme 1.18).



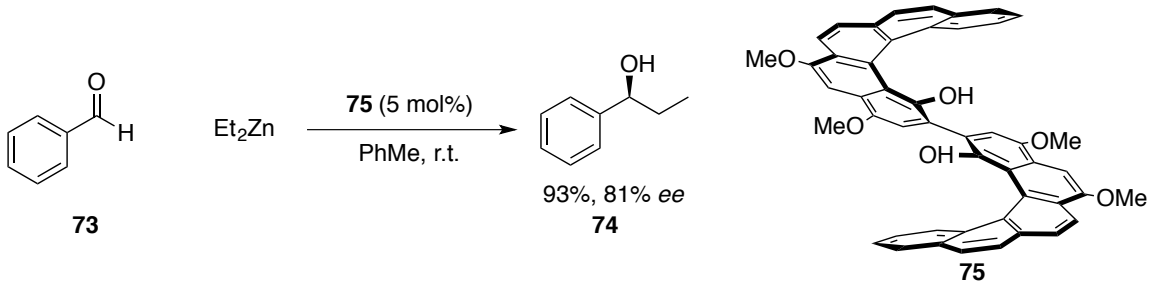
Scheme 1.18. Helicenes as chiral introducer developed by Soai and coworkers

1.2.3. Helical Chiral Small Molecules in Organocatalysis

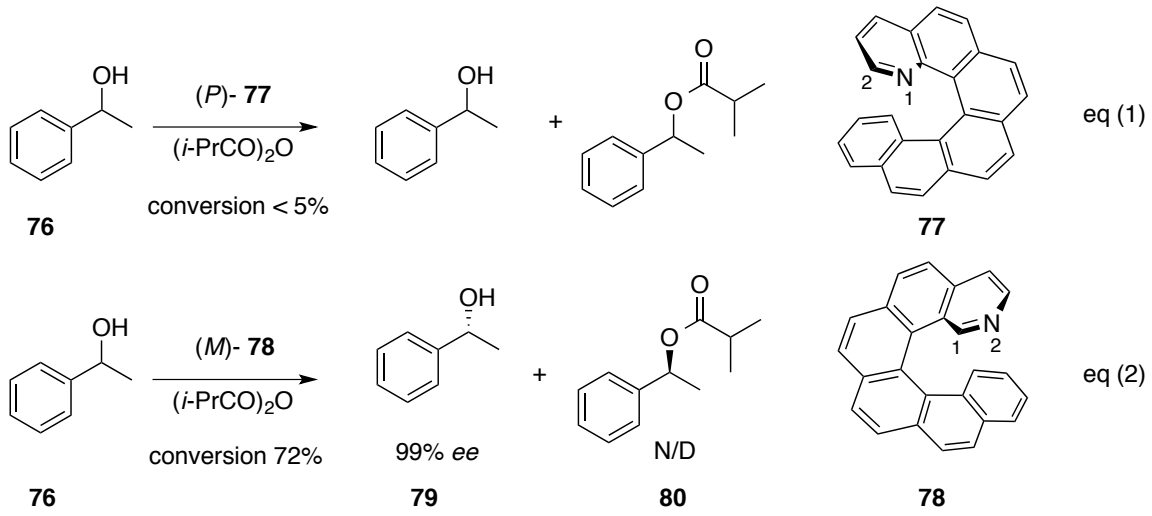
In 2000, Katz and coworkers[65] developed a chiral bis-helicene diphenolic ligand (**75**), believing it should possess a larger chiral pocket around the reaction center than BINOL and VAPOL, thus make it a better catalyst for transformations which are steric demanding. Indeed, this catalyst was found quite effective in the asymmetric addition of diethylzinc to several aldehydes with a general better performance over BINOL (Scheme 1.19).

Starý *et al.* [66] 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.

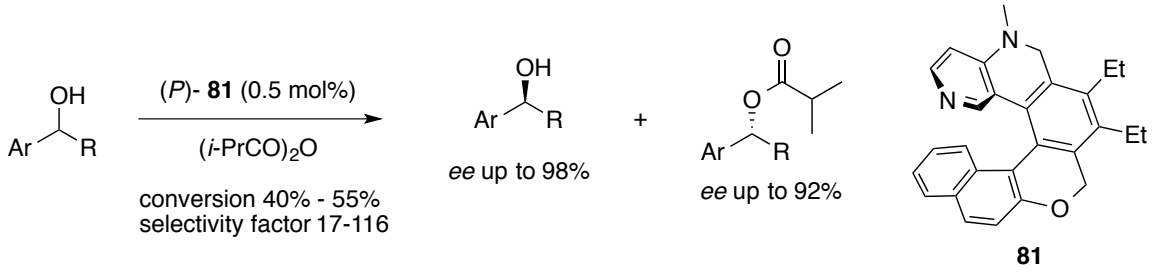


Scheme 1.19. Alkylation of aldehydes catalyzed by [5]HELOL



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.[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.[68]



Scheme 1.21. Helical DMAP catalyzed kinetic resolution of alcohols

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.[69]

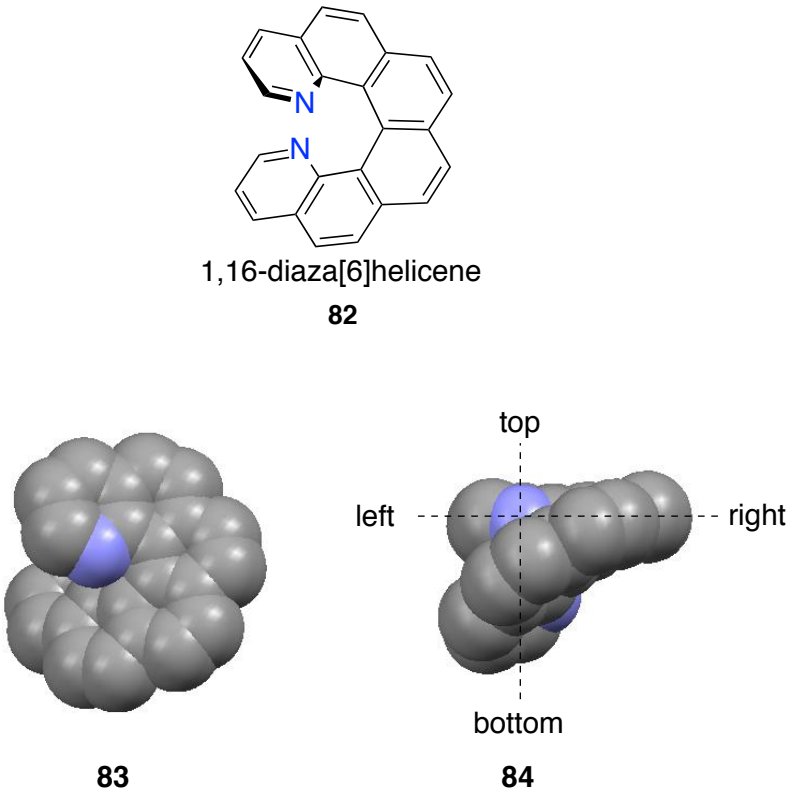


Figure 1.14. The crystal structure of 1, 16-diaza[6]helicene reported by Staab *et al.*

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.[70] A first-order analysis of the crystal structure of 1,16-diaza[6]helicene[71] (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[49] 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[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.

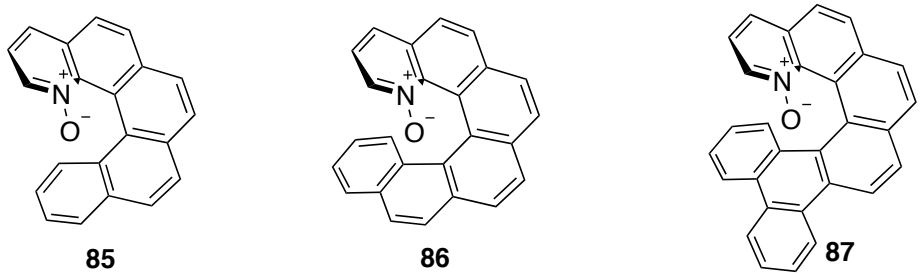
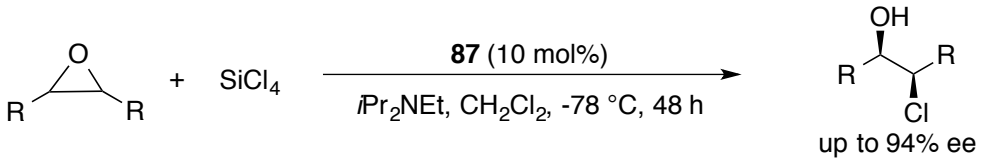


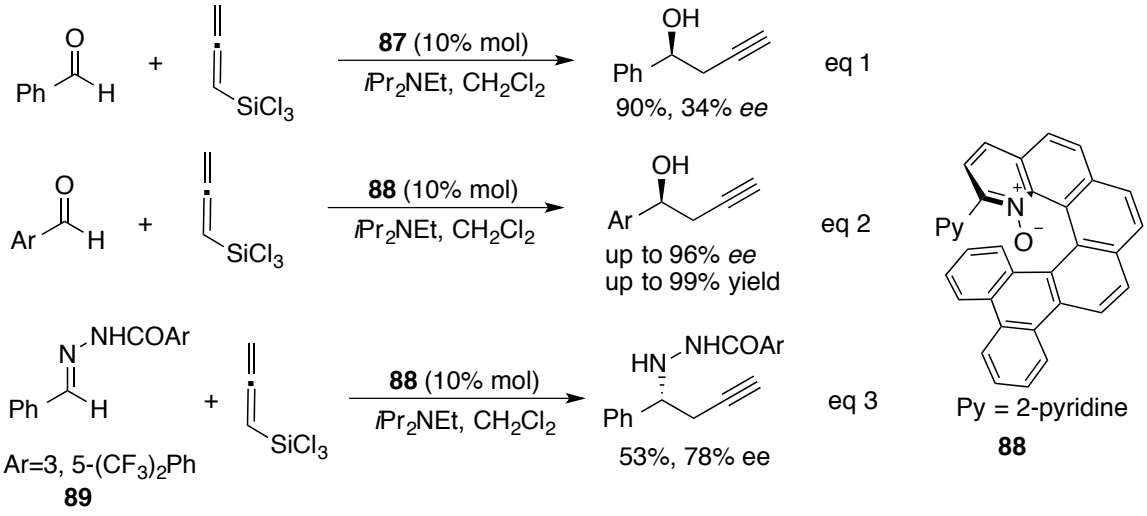
Figure 1.15. 1-azahelicenes developed by our group



Scheme 1.22. Desymmetrization of *meso*-epoxides with $SiCl_4$

1.3.2. Propargylation of Aldehydes with Allenyltrichlorosilane[73]

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).

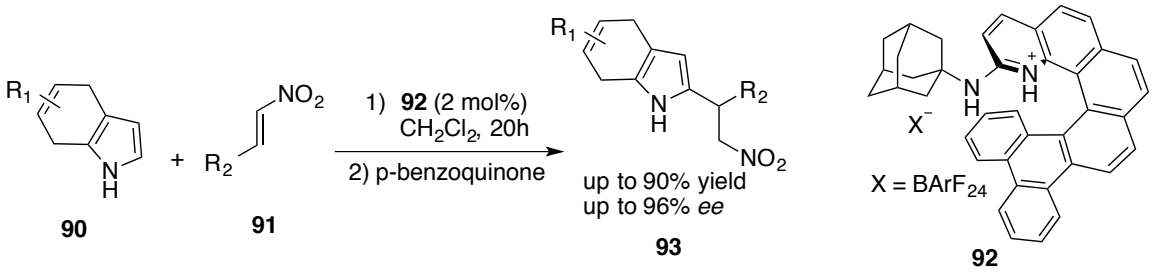


Scheme 1.23. Asymmetric propargylation of aldehydes developed by Takenaka *et al.*

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[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

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:

1) The development of a diastereomeric salt-mediated optical resolution of 11,12-benzo-1-aza[6]helicene.
2) The development of nitroalkene Diels-Alder reaction catalyzed by helical chiral hydrogen-bond donor catalysts.
3) The design and synthesis of new helical chiral catalysts based on 11,12-benzo-1-aza[6]helicene-N-oxide.
4) The development of asymmetric allylation of ketoimines catalyzed by helical chiral N-oxides

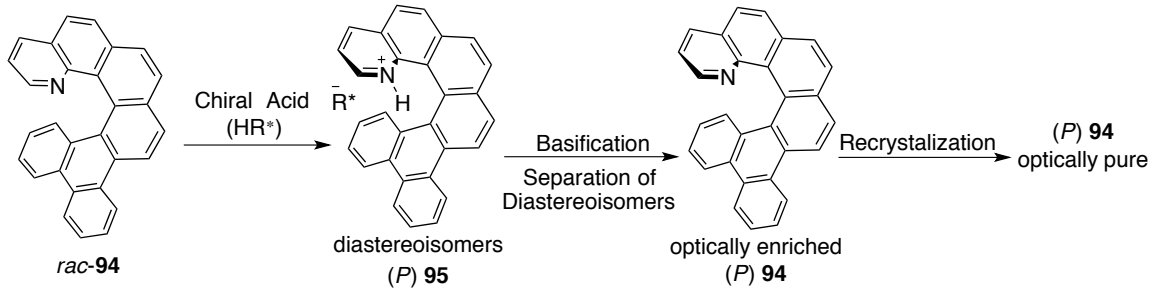
CHAPTER 2. DIASTEREOMERIC SALT-MEDIATED OPTICAL RESOLUTION OF 11,12-BENZO-1-AZA[6]HELICENE

2.1. Background

As discussed in **chapter 1**, our group has previously developed a gram-scale modular synthesis of 1-azahelicenes-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.

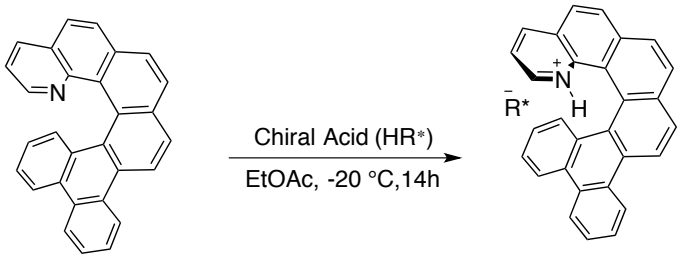


Scheme 2.1. Proposed method for the resolution of racemic helicene

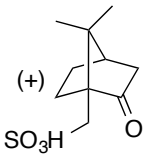
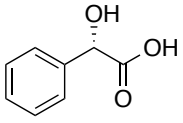
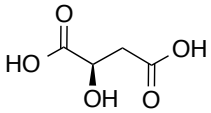
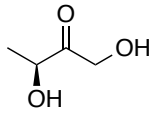
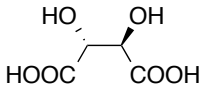
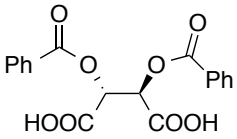
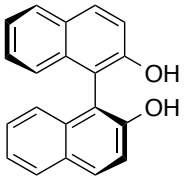
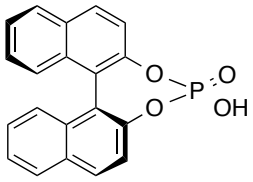
The first thing we need to consider for this procedure is to identify a suitable chiral acid which would allow the preferential precipitation of one of the diastereoisomers over the other one. In order to identify the ideal chiral acid for this purpose, a series of commonly used chiral acids was tested. 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



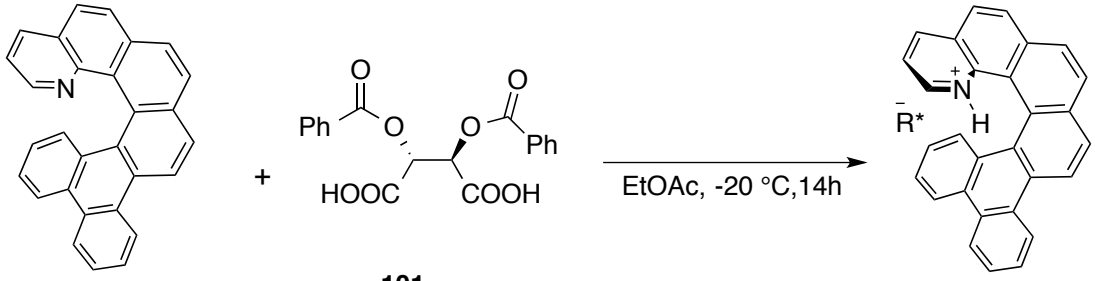
rac-**94** *P*-**95**

 0% *ee* **96**	 0% *ee* **97**	 0% *ee* **98**	 0% *ee* **99**
 7% *ee* **100**	 **15.3% *ee*** **101**	 0% *ee* **102**	 5% *ee* **103**

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[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



rac-**94**
1.0 equiv

101

P-**95**

entry	**101** (equiv)	*ee* (%)	*yield* [a] (%)
1	1.0	-	0
2	5.0	13.0	44
3	10.0	15.3	60
4	12.5	17.8	46
5	15.0	25.0	51
6	17.0	16.0	45
7	19.0	9.0	55
8	25.0	-	2

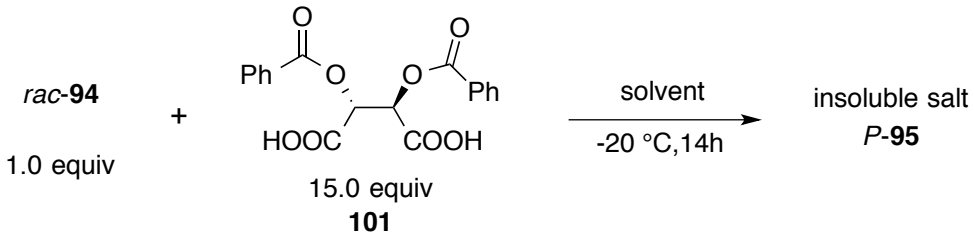
[a] Yield was calculated against only one enantiomer of the helicene used

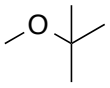
Next, the effects of the amount of chiral acid **101** used were carefully investigated. A series of resolution experiments was set up where the only variation was the ratio between racemic helicene **94** and the chiral acid **101** (Table 2.2). When only 1 equivalent

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 CH_2Cl_2, CH_3Cl and CH_2ClCH_2Cl 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 *t*-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 *t*-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 CH_3CN, 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 CH_3CN as our resolving solvent.

Table 2.3. Screen of solvents for resolution of racemic helicene



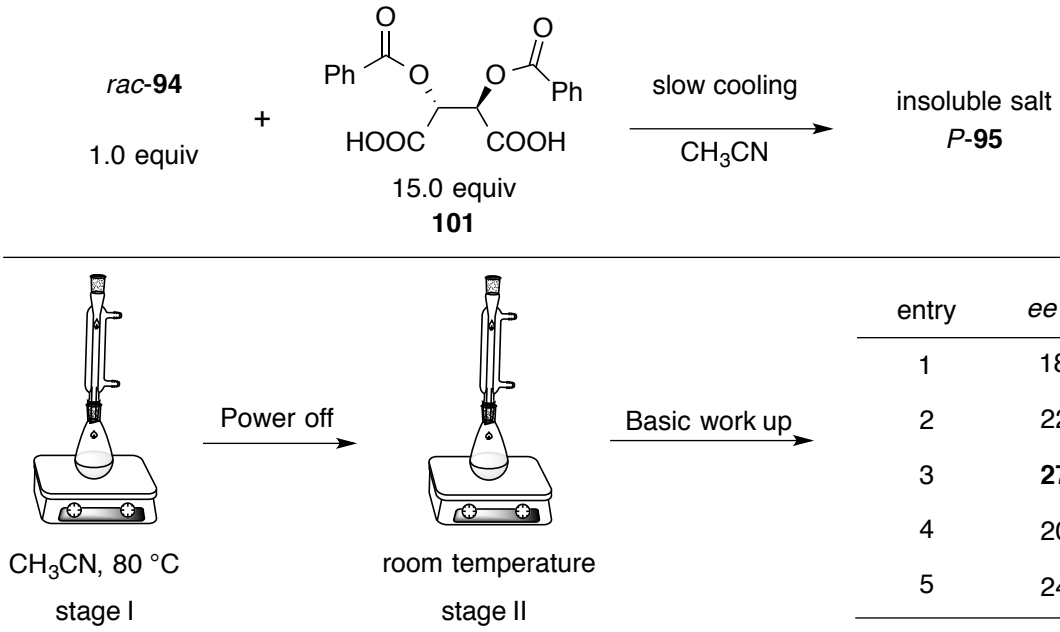
entry	solvent	*ee* (%)	entry	solvent	*ee* (%)
1	EtOAc	25.0	8	toluene	N/A[2]
2	CH_2Cl_2	N/A[a]	9	Et_2O	3
3	CH_3Cl	N/A[a]	10	CH_3CN	**35**
4	$(CH_2Cl)_2$	N/A[a]	11	solvent mixtures	< 15
5	acetone	N/A[a]			
6	*i*PrOH	0	12		N/A[1]
7	benzene	N/A[b]			

[a] No desired precipitate attained
[b] 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 CH_3CN, then the clear solution was slowly cooled down by turning off the power. Precipitate was collected

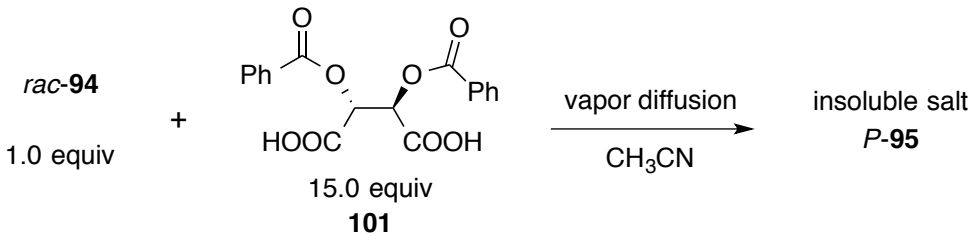
after the solution cooled down to ambient temperature, worked up and analyzed. The best result obtained from five identical trials was 27.5% *ee* (entry 3, Scheme 2.2), which was less efficient than refrigerator cooling.

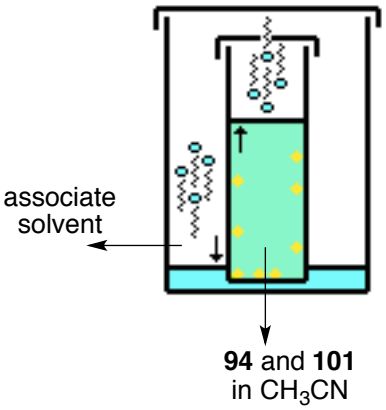


Scheme 2.2. Resolution of racemic helicene by slow cooling

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_3CN 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_3CN 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





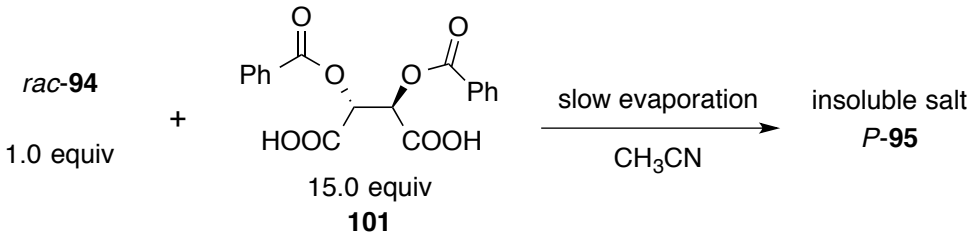
entry[a]	associate solvent	*ee* (%)
1	THF	-
2	Et_2O	-
3	benzene	-
4	hexane	11.0
5	MeOH	racemic

[a] Best result of multiple trials

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, Et_2O 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



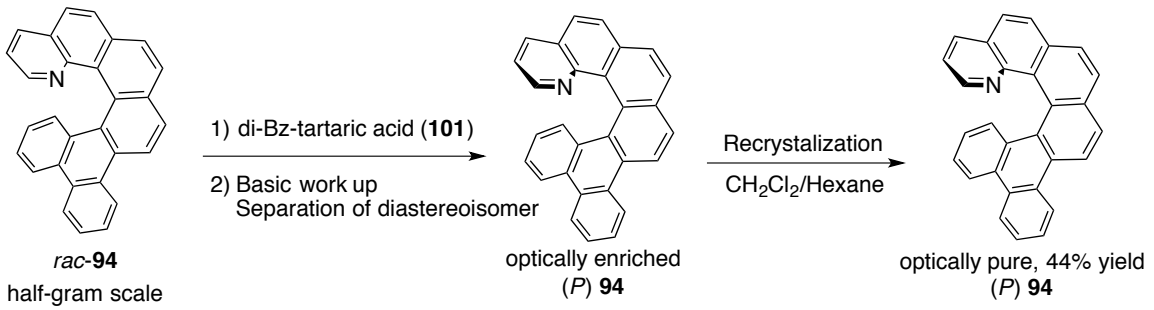
entry	helicene (mg)	time	yield[a](%)	*ee* (%)
1[b]	60	3h	110	7
2	60	1d	80	16
3	60	2d	40	90
4	60	3d	32	94
5[c]	60	4d	0	-
6	481	2d	52	85

[a] Yield was calculated against only one enantiomer of the helicene used
[b] Over precipitation [c] 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_2Cl_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_3CN followed by a single recrystallization in CH_2Cl_2 and hexane solvent mixture (Scheme 2.3).



Scheme 2.3. Diastereomeric salt-mediated resolution of helicene

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_3CN 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_3CN followed by a single recrystallization from CH_2Cl_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 (CH_2Cl_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.

^{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_4Si (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 % ^{i}PrOH 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_3CN was mixed with a saturated solution of (-)-dibenzoyl-L-tartaric acid monohydrate **101** (863 mg, 2.29 mmol) in CH_3CN 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_3CN, 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 % ^{i}PrOH 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_3CN and stirred at 80°C using an oil bath. Small amount of CH_3CN 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 actate, 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** (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% ^{i}PrOH 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_3CN 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 % ^{i}PrOH 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 11%, favoring *P* enantiomer.

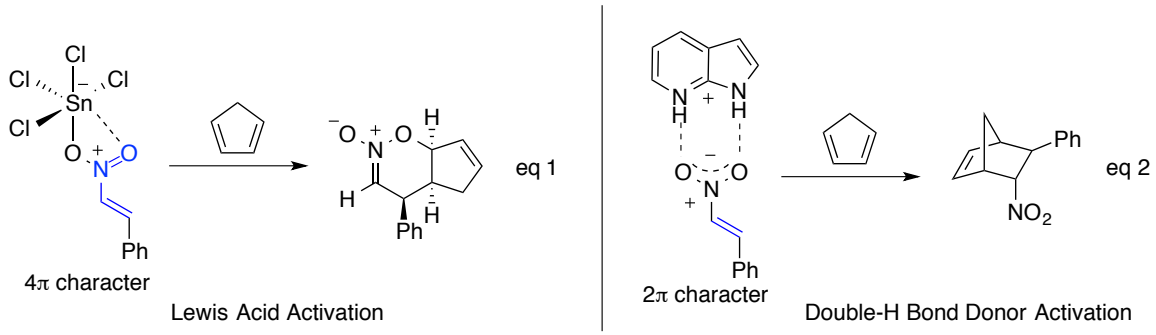
2.4.5. General Procedure for Slow Evaporation Method

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_3CN (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 actate, 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 % ^{i}PrOH 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

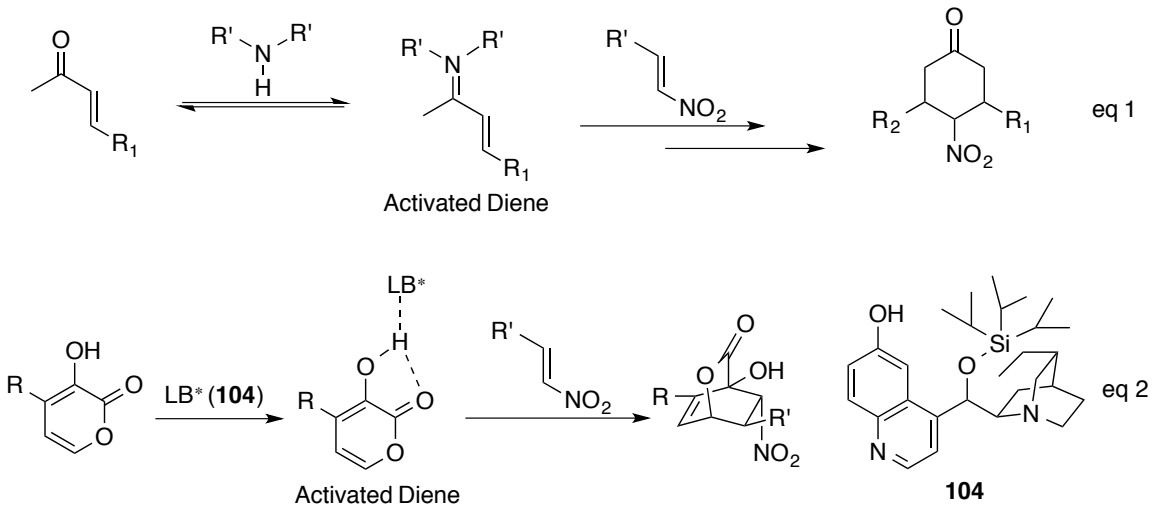
3.1. Background

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 *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).



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[80] (eq 1, Scheme 3.2). On the other hand, Deng and co-workers[81] successfully developed another strategy, which is the activation of 3-hydroxy-2-pyrones (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[82] (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[83] (Scheme 3.3). It's worth mentioning that some research groups have reported notable advancements in the asymmetric [3+2]

reactions.[84] 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.

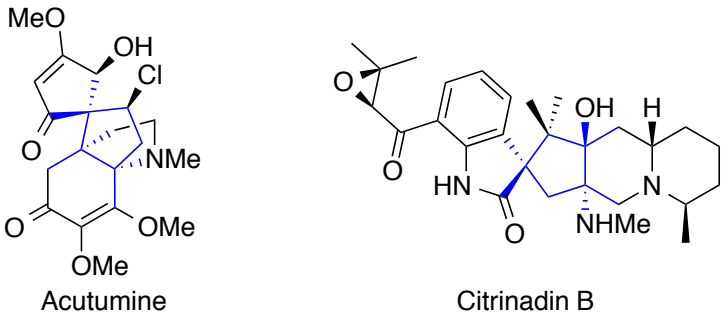
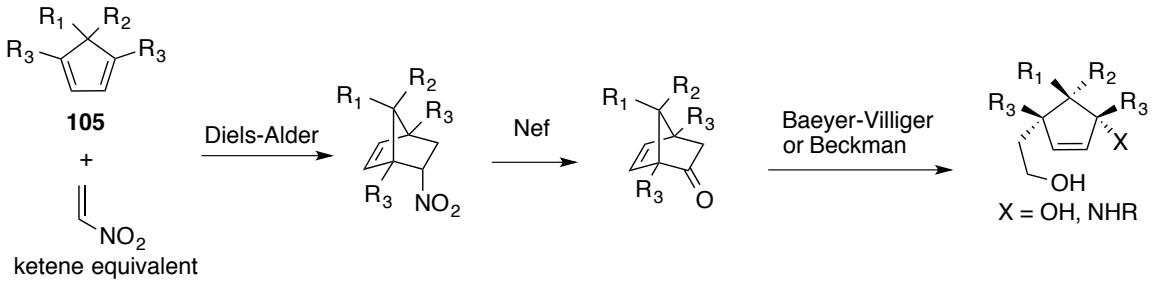


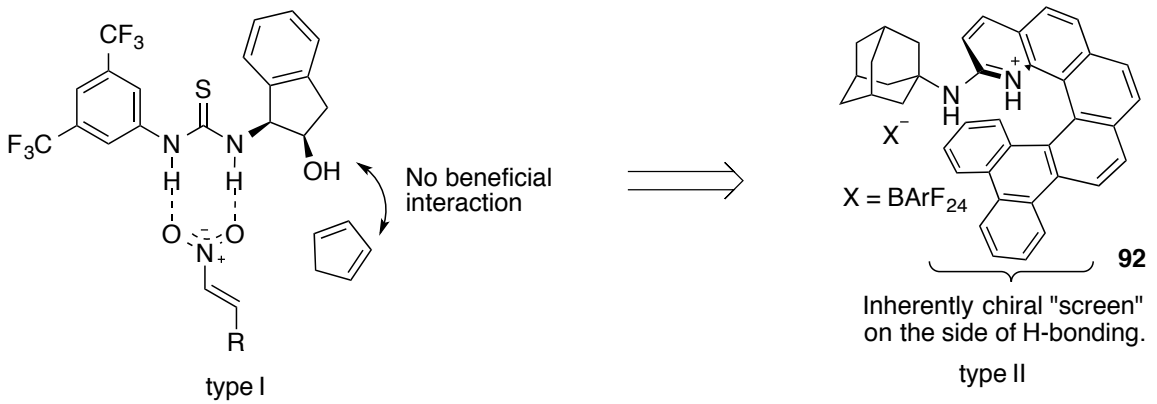
Figure 3.1. Selected examples of natural products with a cyclopentane core



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[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

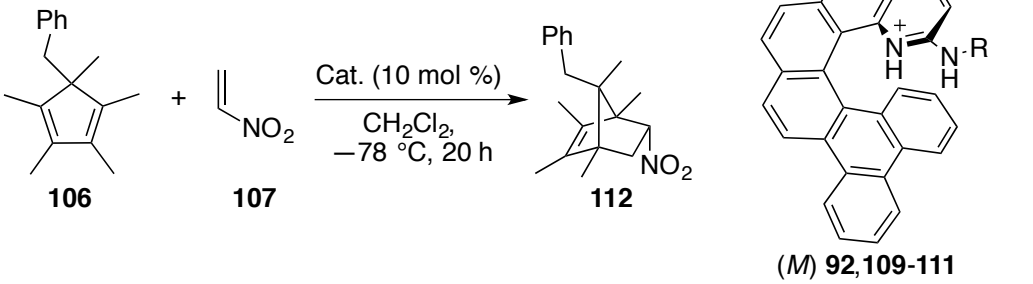
In 2012, my colleagues[86] demonstrated that helical-chiral double hydrogen-bond donor catalysts (i.e. **92**) could promote the nitroalkene Diels-Alder reaction in an enantio- and periselective manner, which represents the first asymmetric catalytic nitroalkene Diels-Alder reaction by LUMO-lowering 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

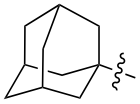
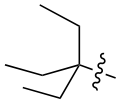
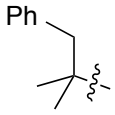
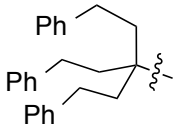
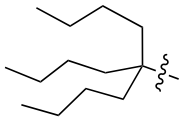
3.2.1. Evaluation of Catalysts

As part of our broad interest in hydrogen-bond donor catalysis, our group[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[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.[88]

Table 3.1. Nitroalkene Diels-Alder reaction developed by Takenaka



106 **107** **112** (*M*) **92**,**109**-**111**

Entry	R	Cat.	Yield[b] (%)	er[c]
1		**92**	70	64:36
2		(*P*)**-108**	84	62:38
3		**109**	70	59.5:40.5
4		**110**	70	67:33
5		**111**	77	70:30

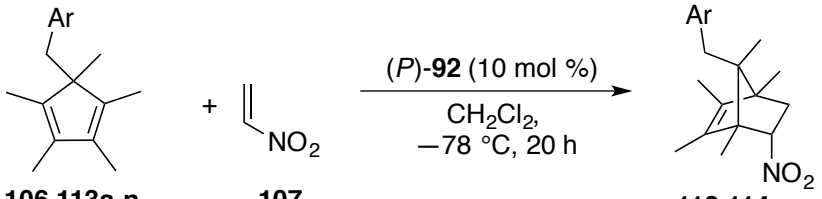
[a] Reaction condition: diene (0.4 mmol) and nitroethylene (0.2 mmol) in the presence of 10 mol% of catalyst in CH_2Cl_2 (0.7 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis. $^{-}BArF_{24}$ =tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

3.2.2. Evaluation of Dienes

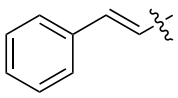
Starting with catalyst **111**, we systematically investigated various 5-substituted pentamethylcyclopentadienes. We were glad to find that most of the dienes were tolerated by our catalysts (Table 3.2). The 4-F-substituted diene gave comparable results to a model diene **106**. However, we observed 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-substittued 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



106,113a-n **107** **112,114a-n**

Entry[a,b]	Diene	Ar	Yield[c] (%)	er[d]
1[e]	**106**	Ph	77	30:70
2[e]	**113a**	4-F-Ph	80	35:65
3[e]	**113b**	4-Cl-Ph	38	34:66
4[f]	**113b**	4-Cl-Ph	80	36:64
5[e]	**113c**	3-Cl-Ph	67	31:69
6	**113d**	2-Cl-Ph	55	68:32
7	**113e**	2-I-Ph	65	60:40
8[g]	**113f**	4-Br-Ph	35	68:32
9	**113g**	4-Me-Ph	85	65:35
10	**113h**	4-CF_3-Ph	75	64:36
11	**113i**	4-*tert*-Butyl-Ph	80	70:30
12	**113j**	2-naphthyl	83	69:31
13	**113k**	3-OMe-Ph	80	66:34
14	**113l**	4-SMe-Ph	89	67:33
15[h]	**113m**	4-NO_2-Ph	0	–
16	**113n**		79	63:37

[a] Reaction condition: diene (0.4 mmol) and nitroethylene (0.2 mmol) in the presence of 10 mol % of catalyst in CH_2Cl_2 (0.7 ml). [b] Entries 1-5 were previously developed by my colleagues. [c] Yield of isolated products. [d] Determined by HPLC analysis. [e] (*M*)-**111** was used. [f] (*M*)-**92** was used. [g] Unreacted diene **113f** was recovered in 60%. [h] Unreacted diene **113m** was recovered in 90%.

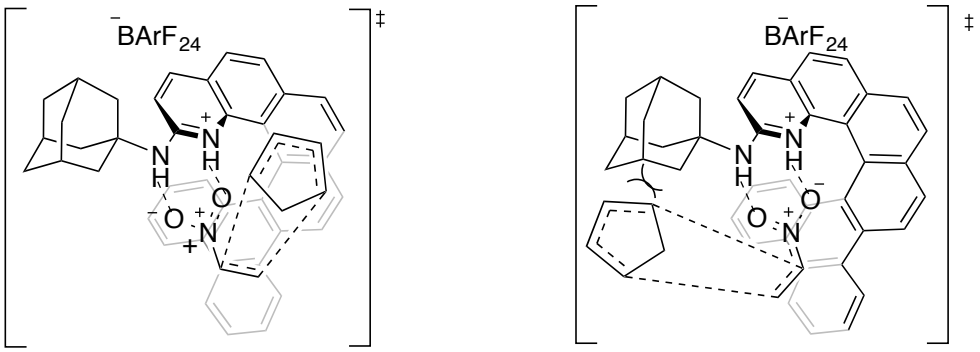
The 4-Me-substituted diene gave a good yield and moderate selectivity (entry 9, Table 3.2). The sterically demanding 4-CF_3- and 4-^{t}Bu-substituted dienes and the 2-naphthylated diene were all as reactive as a model diene **106** (A values of CF_3, ^{t}Bu and Br are 2.5 kcal mol^{-1}, 4.9 kcal mol^{-1} and 0.67 kcal mol^{-1}, respectively[89]) (entries 10-12, Table 3.2), and so were other 4-substitued 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 biding 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[90] 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 ^{1}H 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**,[74] 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.



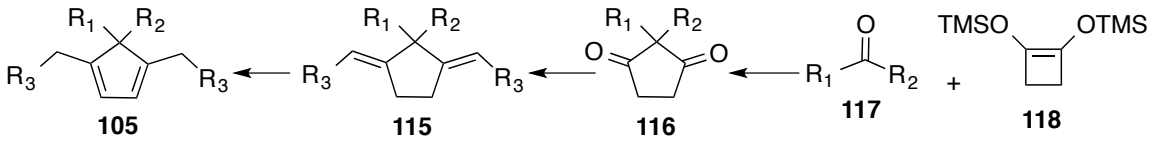
Favored endo TS Disfavored endo TS

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

3.2.4. Synthesis of New Dienes

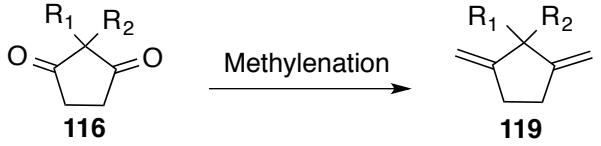
We established that the nitroalkene Diels-Alder reaction could be catalyzed in an enantio- and periselective manner by hydrogen-bond donor catalysts. However, synthetic utility of 5-substituted pentamethyl-cyclopentadienes is rather limited. As such, the 1,4,5,5-tetrasubstituted cyclopentadienes (**105**) 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).[91] 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.[92]



Scheme 3.5. Retrosynthetic design for a new class of dienes

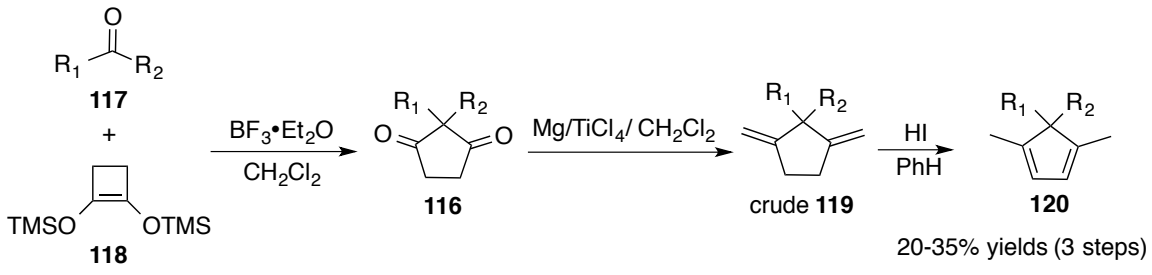
Table 3.3. The methylenation of diketone by different methods



Entry	Protocol	Reagents	Yield[a] (%)
1	Wittig	$MeP^{+}Ph_3I^{-}$	0
2	Lombardo	CH_2Br_2-Zn-$TiCl_4$	7
3	Curran	CH_2Br_2-Zn-$TiCl_4$	13
4	Takai	CH_2I_2-Zn-$TiCl_4$	trace
5[b]	Yan	CH_2Cl_2-Mg-$TiCl_4$-THF	50%

[a] Yield of isolated product. [b] 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.[93] We then directed our search to titanium-based alkenating reagents, being non-basic; they have found broad utility for various ketones.[94] Lombardo's reagent,[95] generated by aging the reaction mixture of CH_2Br_2, Zn and $TiCl_4$ at 5 °C for 3 days, has been successfully employed for enolizable ketones.[96] However, only 7% desired product was formed by this protocol (entry 2, Table 3.3). Some useful modifications[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[98] have reported a CH_2I_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_2Cl_2-Mg-$TiCl_4$-THF system that was recently developed by Yan and co-workers.[99] We were able to obtain the product in a satisfactory yield without any optimization to this protocol (entry 5, Table 3.3).



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**).

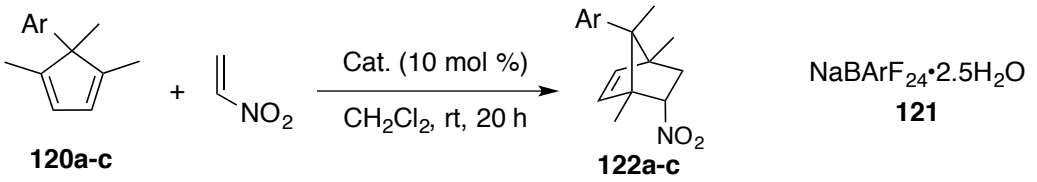
3.2.5. Evaluation of New Dienes

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.[78] 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 $NaBArF_{24}\cdot 2.5H_2O$ than the typical hydrogen-bonding catalysts.[100]

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



120a-c **122a-c**

entry	dienes	Ar	catalyst	yield[a] (%)
1	**120a**	Ph	—	0
2	**120b**	Bn	—	25
3	**120b**	Bn	**121**	67[b]
4	**120c**	$PhCH_2CH_2$-	—	11
5	**120c**	$PhCH_2CH_2$-	(*P*)-**92**	14[c]
6	**120c**	$PhCH_2CH_2$-	**121**	42[b]

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

To our delight, $NaBArF_{24}\cdot 2.5H_2O$ (**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 $NaBArF_{24}\cdot(H_2O)_x(PhOH)_y$, a derivative of $NaBArF_{24}\cdot 2.5H_2O$ by replacing some of the water molecules with more acidic phenol molecules, provided better yield and selectivity in an intramolecular nitroalkene Diels-

Alder reaction.[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 $NaBArF_{24}{\cdot}2.5H_2O$ (**121**) (B, Figure 3.3).

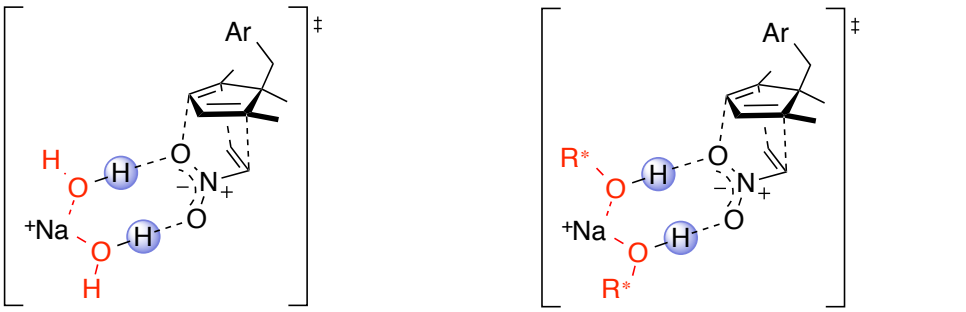


Figure 3.3. Metal cation assisted H-bond donor catalysis

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 pentamethylcyclopentadienes (**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 $NaBArF_{24}\cdot 2.5H_2O$ (**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_2Cl_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_4Si (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 139.0, 137.7, 135.1, 130.3, 130.2, 119.4, 56.7, 40.9, 21.8, 10.9, 10.5; FTIR (neat) υ_{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, $CDCl_3$) δ 6.88 (d, J = 7.9

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, $CDCl_3$) δ 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) υ_{max} 2968, 2914, 2857, 1657, 1515, 1442, 1378, 1110, 820, 782, 757 cm^{-1}; GCMS: 240 $[M]^+$

1-((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, $CDCl_3$) δ 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, $CDCl_3$) δ 142.9, 138.9, 135.2, 128.8, 124.0 (2x), 56.8, 41.3, 21.9, 10.9, 10.4; FTIR (neat) υ_{max} 2968, 2919, 2860, 1618, 1417, 1323, 1162, 1120, 1067, 1019, 847 cm^{-1}; GCMS: 294 $[M]^+$

1-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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{max} 3061, 2965, 2914, 2857, 1601, 1509, 1445, 1378, 1095, 852, 815, 788, 748 cm^{-1}; GCMS: 276$[M]^+$

1-methoxy-3-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (**113k**): Obtained as a white solid with 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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-pentamethylcyclopenta-2,4-dienyl)methyl)phenyl)sulfane (**113l**): Obtained as a light yellow solid with 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (**113m**): Obtained as a bright yellow solid with 10% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 146.7, 146.3, 138.5, 135.6, 129.2, 122.4, 56.9, 41.3,

21.8, 10.9, 10.5; FTIR (neat) υ_{max} 2918, 2859, 1601, 1516, 1447, 1342, 851, 806, 746,702 cm^{-1}; GCMS: 271 $[M]^+$

(E)-(3-(1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)prop-1-enyl)benzene (**113n**): Obtained as a colorless oil with 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{max} 3026, 2962, 2913, 2861, 1600, 1496, 1444, 1378, 960, 738 cm^{-1}; GCMS: 252$[M]^+$

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_2Cl_2 (0.3 mL) and a solution of nitroethylene (15 mg, 0.2 mmol) in CH_2Cl_2 (0.1 mL). The resulting mixture was cooled to -78 °C, slowly treated with a solution of diene (0.4 mmol) in CH_2Cl_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_2O (3 x 1 mL) and brine (1 x 1 mL), dried over Na_2SO_4, filtered, and concentrated *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 (**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_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}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) υ_{max} 2943, 1541, 1444, 1382, 1361, 1058, 877, 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 (**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_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}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) υ_{max} 2943, 1540, 1449, 1382, 1361, 1009, 733, 753 cm^1;

HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{24}INNaO_2$ $[M + Na]^+$, expected: 448.0749, found: 448.0760.

(-)-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), t_r (major) = 46.93 min., t_r (minor) = 59.41 min. $[a]^{20}_D$ = - 44, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) d 139.2, 138.5, 132.4, 131.4, 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) υ_{max} 2940, 1540, 1487, 1446, 1361, 1072, 1011, 808, 733 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{24}BrNNaO_2$ $[M + Na]^+$, 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), t_r (major) = 29.73 min., t_r (minor) = 33.85 min. $[a]^{20}_D$ = - 52, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) d 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) υ_{max} 2936, 1542, 1447, 1362, 1109, 813, 774 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{20}H_{27}NNaO_2$ $[M + Na]^+$, 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. $[a]^{20}_D$ = - 22, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 143.9 (d, J = 1.4 Hz), 139.3 (d, J = 1.5 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) υ_{max} 2945, 1543, 1323, 1162, 1118, 1067, 1018, 842, 746 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{20}H_{24}F_3NNaO_2$ $[M + Na]^+$, 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. $[a]^{20}_D$ = - 54, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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-Pentamethyl-5-nitrobicyclo[2.2.1]hept-2-en-7-yl)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. $[a]^{20}_D$ = - 48, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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-Methoxybenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-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. $[a]^{20}_D$ = - 30, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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-nitrobicyclo[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. $[a]^{20}_D$ = - 60, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{max} 2939, 1540, 1439, 1362, 1090, 810, 755 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{20}H_{28}NO_2S$ $[M + 1]^+$, 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. $[a]^{20}_D$ = - 54, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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, $CDCl_3$) δ 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) υ_{max} 3029, 2922, 1757, 1713, 1497, 1454, 1377, 1269, 1039, 1000, 922, 748, 700 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd 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**[99] 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_2Cl_2 (70 mL) was added via cannula a solution of dione (7.0 mmol) in CH_2Cl_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 $Na_2S_2O_2$, (2 X 15 mL), and brine **(**15 mL), and the organic phase was dried over a mixture of $MgSO_4$ and K_2CO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 154.4 (2x), 128.7, 126.4, 126.3, 125.1, 18.8, 13.3 (2x); FTIR (neat) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 149.4, 138.3, 128.7, 127.6, 126.1, 125.8, 57.2, 41.2, 22.5, 13.4; FTIR (neat) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 149.9, 143,5, 128.6, 128.5, 125.9, 125.5, 56.6, 37.3, 30.5, 22.4, 13.1; FTIR (neat) υ_{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 $NaBArF_{24}$•$2.5H_2O$ Catalyzed Nitroalkene Diels-Alder Reaction

A flame-dried test tube was charged with $NaBArF_{24}$•$2.5H_2O$ (19 mg, 0.02 mmol). To this were added CH_2Cl_2 (0.3 mL) and a solution of nitroethylene (15 mg, 0.2 mmol) in CH_2Cl_2 (0.1 mL). The resulting mixture was cooled to -78 °C, slowly treated with a solution of diene (0.4 mmol) in CH_2Cl_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_2O (3 x 1 mL) and brine (1 x 1 mL), dried over Na_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) υ_{max} 2952, 1542, 1453, 1366, 1091, 752, 700 cm^1; HRMS (ESI-TOF): Exact mass calcd for $C_{18}H_{23}NNaO_2$ $[M + Na]^+$, expected: 308.1626, found: 308.1628.

Note to the Reader:

CHAPTER 4. DESIGN AND DEVELOPMENT OF NEW HELICAL CHIRAL CATALYSTS BASED ON 11,12-BENZO-1-AZA[6]HELICENE-N-OXIDE

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[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 **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 **123** (Figure 4.1).

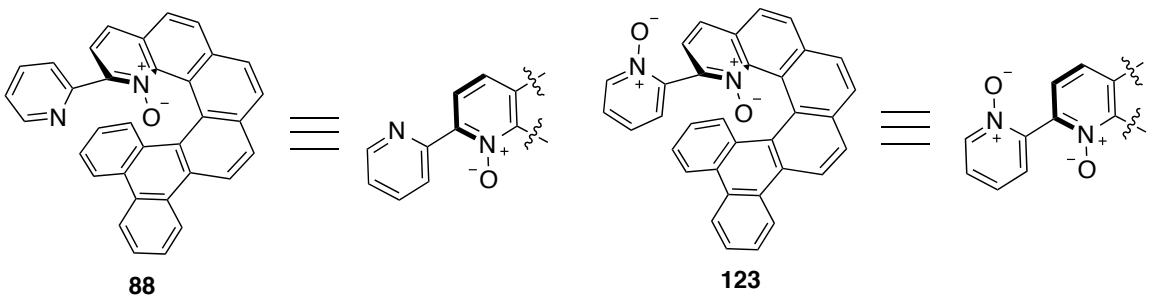
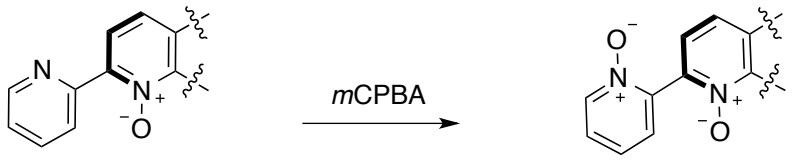


Figure 4.1. Development of chiral pyridine N-oxide catalyst

Based on our previous experience in the synthesis of helicene-N-oxides,[72] we envisioned *meta*-chloroperoxybenzoic acid (*m*CPBA) should be a suitable oxidant for this purpose. However, due to the potentially lower accessibility of the pyridine ring of **88**, harsh conditions might be required. To get a general idea whether the pyridyl nitrogen atom of **88** is accessible and therefor be oxidized by *m*CPBA, we first tested a harsh condition where **88** was refluxed with 3.0 equivalent of *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 *m*CPBA oxidization



88 **123**

entry	*m*CPBA (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)	**90** (%)
1	3.0	$CHCl_3$	61	3	30	0
2	3.0	$CHCl_3$	25	24	36	16
3	2.4	$CHCl_3$	25	16	50	20
4	2.4	CH_2Cl_2	25	16	54	23
5	2.4	$CH_2Cl_2/PhCF_3$	25	16	60	20
6	2.0	$CH_2Cl_2/PhCF_3$	25	16	72	18

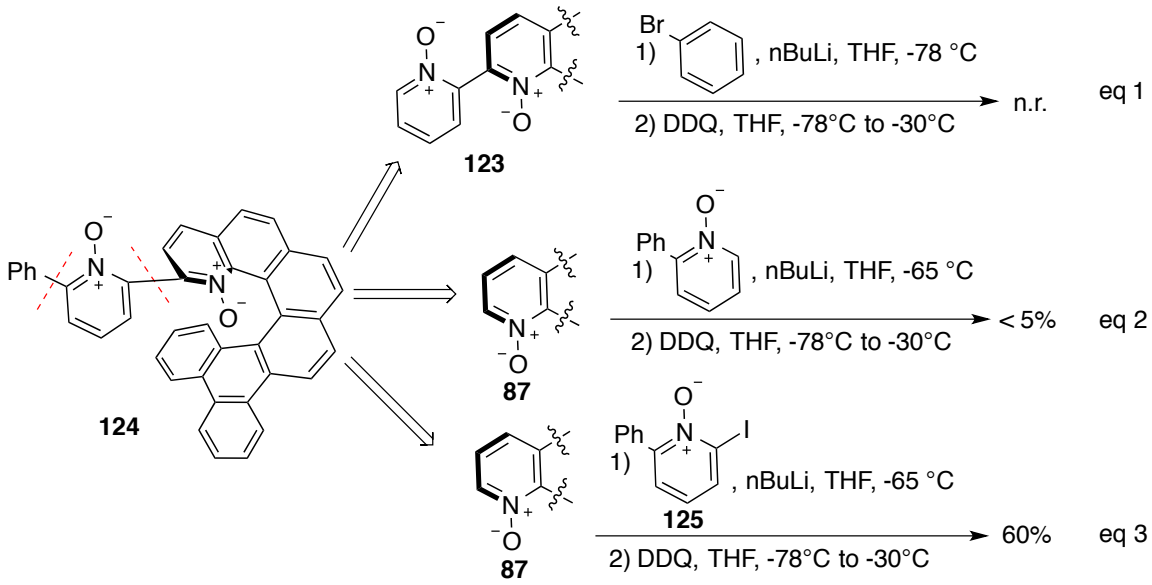
[a] Isolated yield

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 CH_2Cl_2 was a slightly better solvent for this reaction (entry 4, Table 4.1). A mixture of CH_2Cl_2 and $PhCF_3$ 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 *m*CPBA 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.[52] Inspired by the report, we became interested in catalyst **124** (Scheme 4.1).



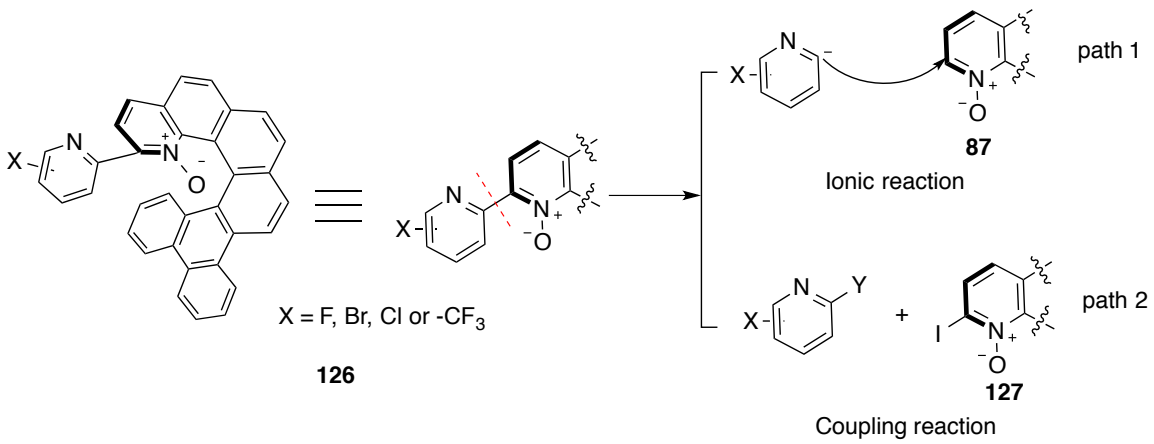
Scheme 4.1. Synthesis of helical catalysts by nucleophilic reactions

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 ^{n}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).

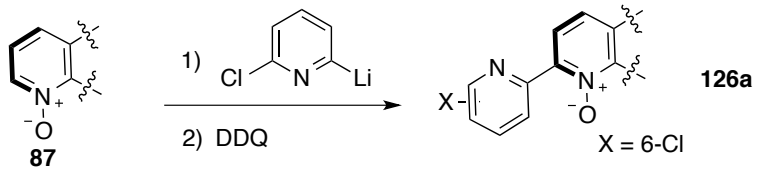
4.2.3. Synthesis of Halogen-substituted Helical Bipyridine mono-N-oxides

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

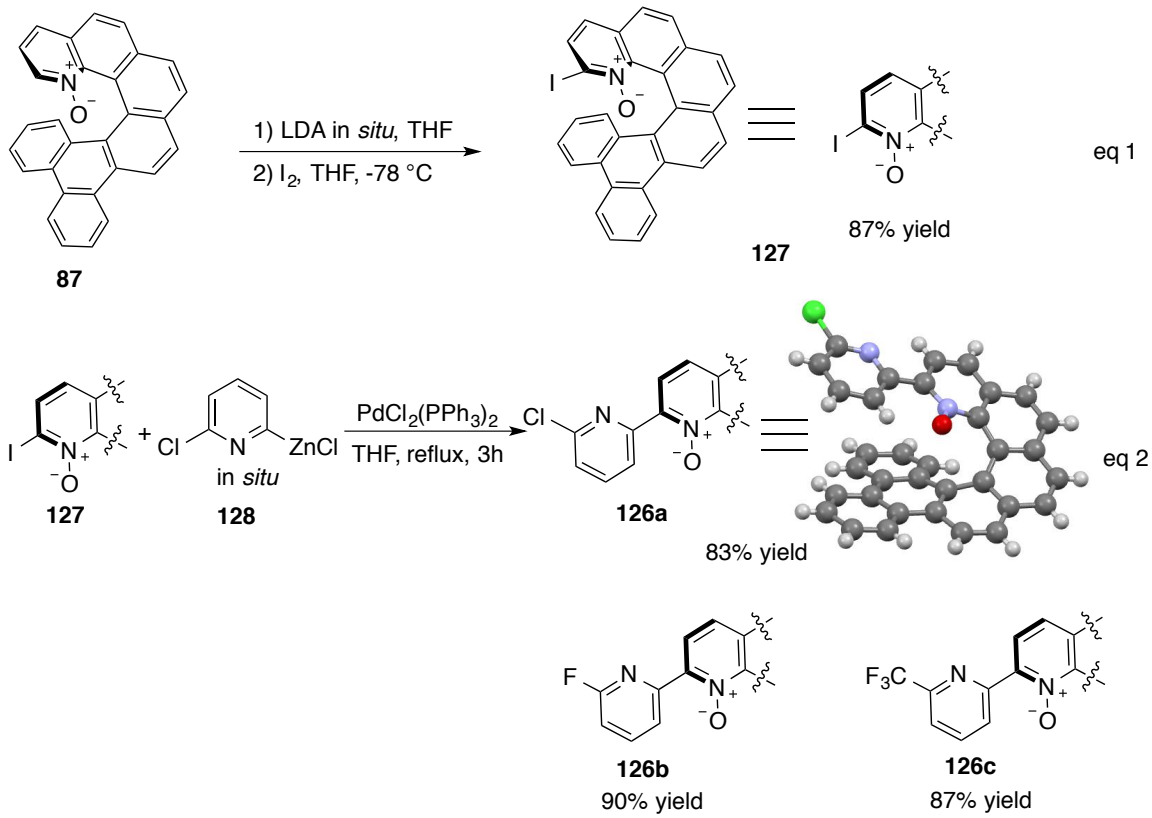
Table 4.2. The synthesis of chloro-substituted catalyst



entry	1	2	3	4
condition	1) nBuLi, THF, -78 °C 2) DDQ, THF, -78 °C	1) tBuLi, THF, -78 °C 2) DDQ, THF, -78 °C	1) nBuLi, THF, DMPU, -78 °C 2) DDQ, THF, -78 °C	1) nBuLi, THF, DMPU, -78 °C 2) DDQ, THF, -78°C to r.t, 72h
yield (%)	0	0	< 5	< 5

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**. ^{t}BuLi 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.[104] In light of these studies, DMPU[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).



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.[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 *in situ* generated LDA followed by nucleophilic attack on I_2 provided

127 with 87% yield (eq 1, Scheme 4.3). The Negishi reaction between **127** and *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)

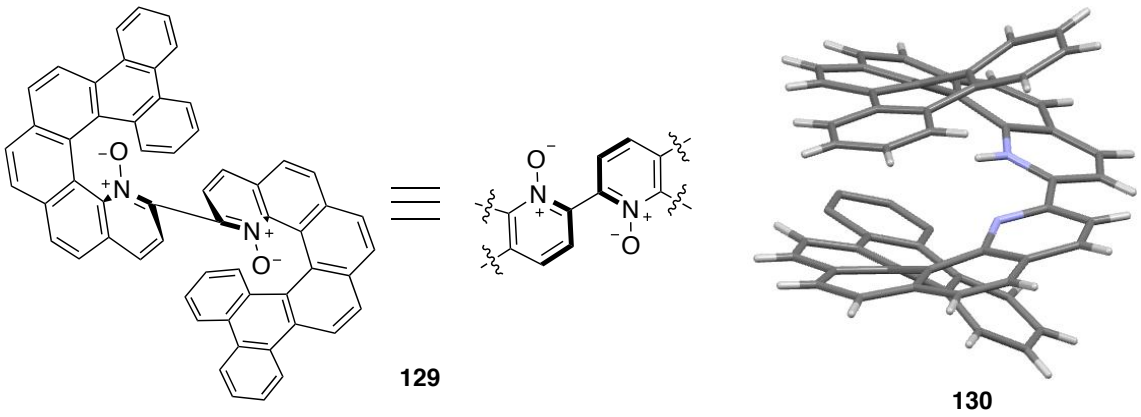
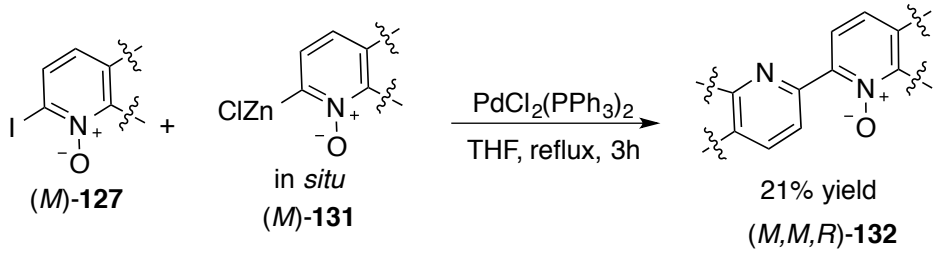
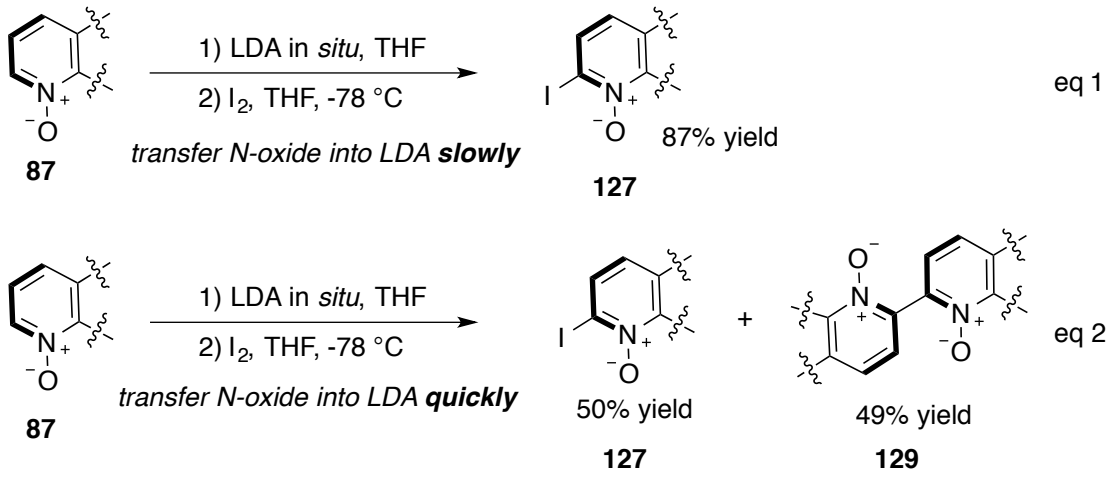


Figure 4.2. Dimerized helical structures



Scheme 4.4. Unexpected outcome of dimerization by Negishi coupling

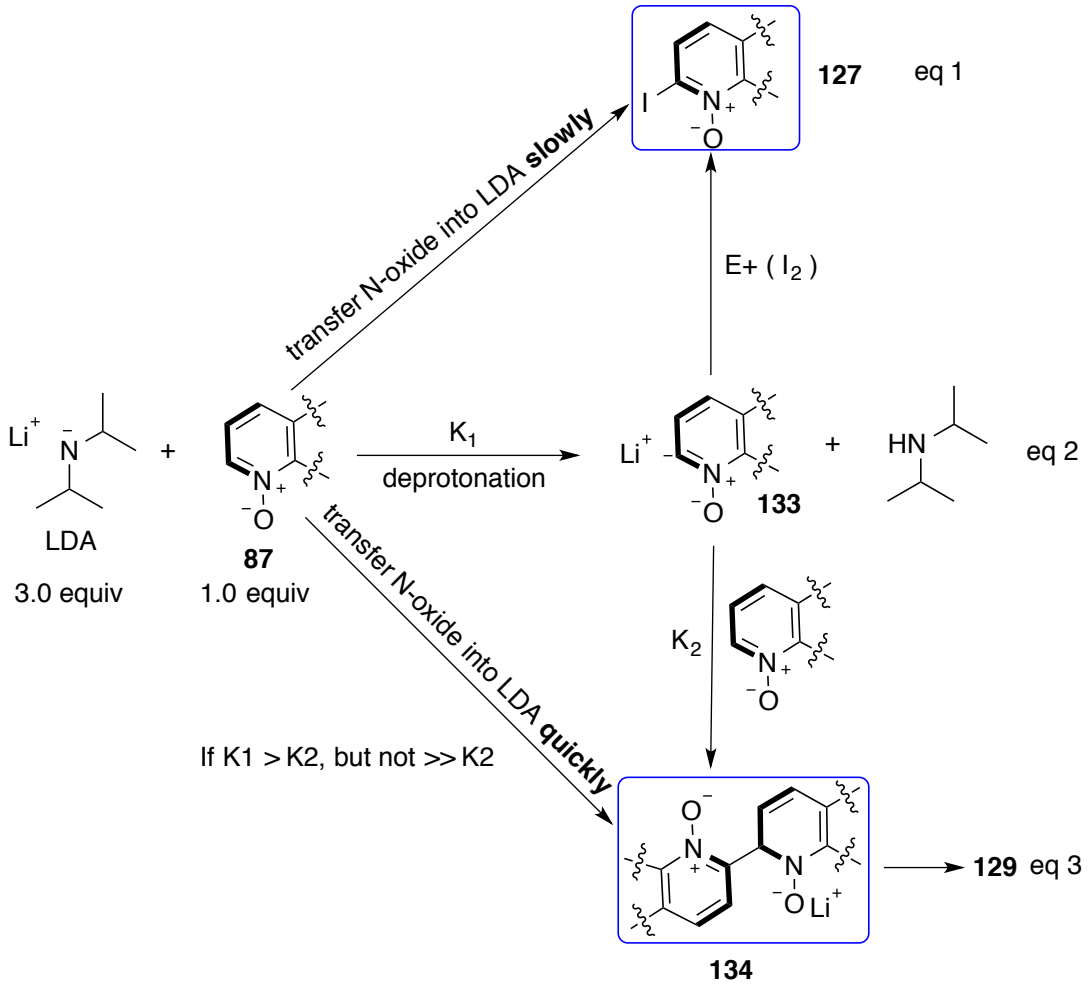
During our studies for the synthesis of **127** using LDA, we serendipitously found some interesting results. For the same reaction conditions, when the THF solution of **87** was added into a LDA solution slowly, only desired product **127** was formed (eq 1, Scheme 4.5). On the other hand, if the THF 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 (I_2) was added to the solution, a nucleophilic reaction occurred between **133** and I_2, 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 I_2 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).

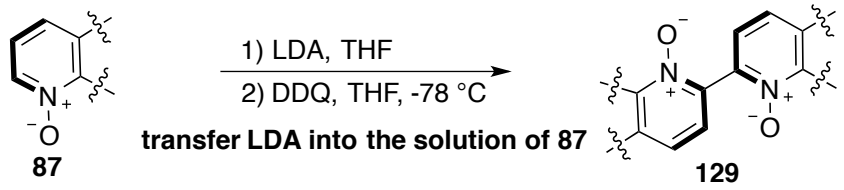


Scheme 4.6. Proposed reaction pathways for the observed product distribution

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).

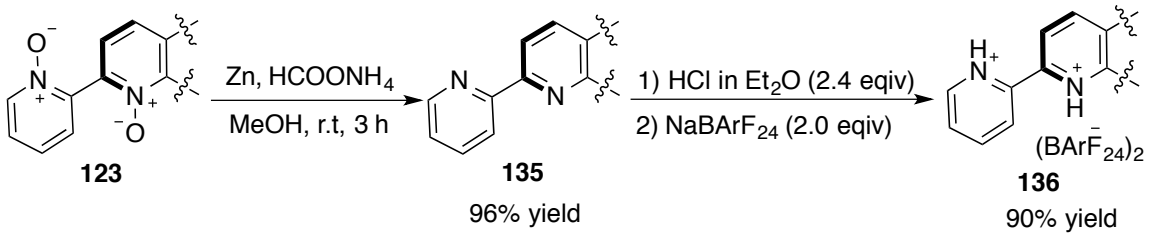
Table 4.3. The synthesis of bis-N-oxide



entry	LDA (equiv)	yield (%)	recovery (%)
1	0.6	0	92
2	1.2	0	83
3	1.8	<5	70
4	2.4	60	28
5	3.0	49	22

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.[74] With the newly synthesized bis-N-oxide **123** at hand, we became interested in developing the corresponding Brønsted acid catalyst based on this scaffold. To our delight, catalyst **123** was smoothly reduced to corresponding dipyridyl compound **135** by a classic zinc mediated reduction with excellent yield. The protonation of **135** by HCl (Et_2O solution), followed by a counterion exchange with $NaBArF_{24}$ resulted the desired Brønsted acid catalyst **136** in excellent yield (Scheme 4.7).

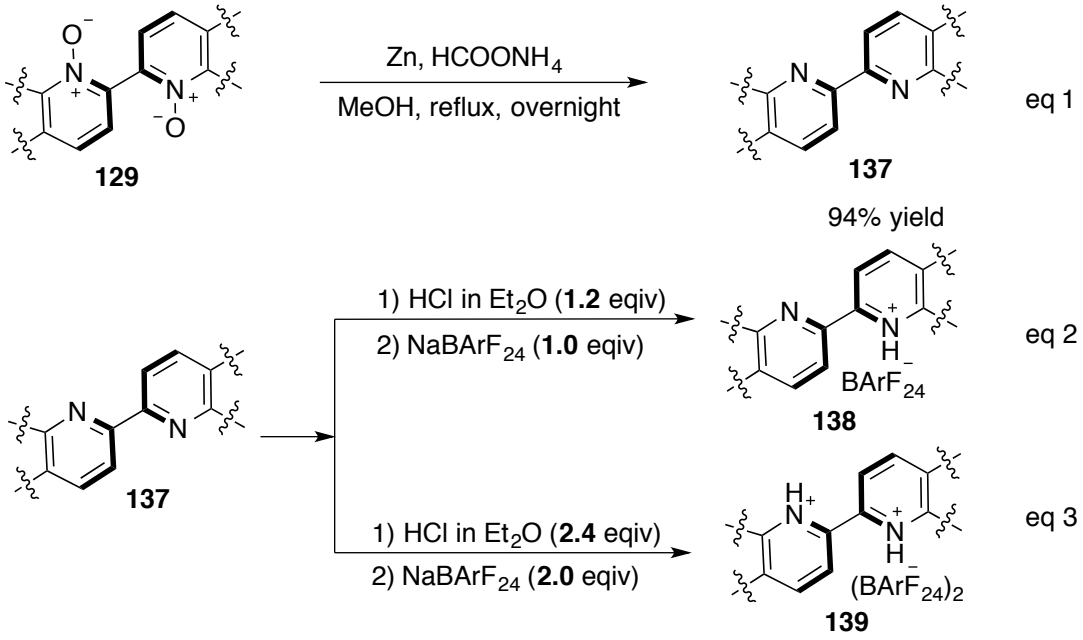


123 **135** 96% yield **136** 90% yield

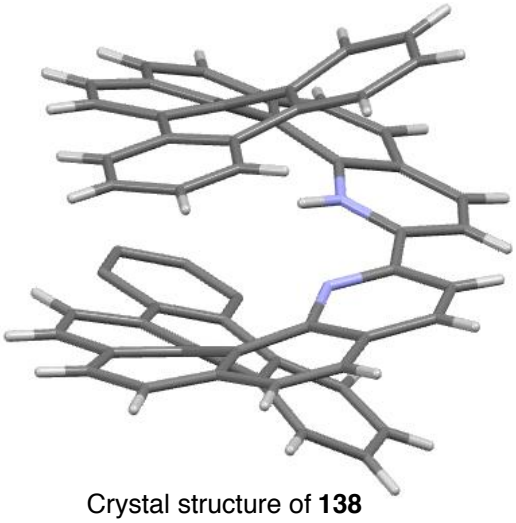
Scheme 4.7. Synthesis of new helical chiral Brønsted acids (1)

With the successful synthesis of **1136**, we set our feet to the synthesis of new helical chiral acid catalysts based on **129**. We were able to reduce **129** into the corresponding dipyridyl **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 **137** in the following step. When only one equivalent of proton was provided, the mono protonated catalyst (**138**) was obtained (eq 2, Scheme 4.8). We were able to grow a nice crystal of **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)



Crystal structure of **138**

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.

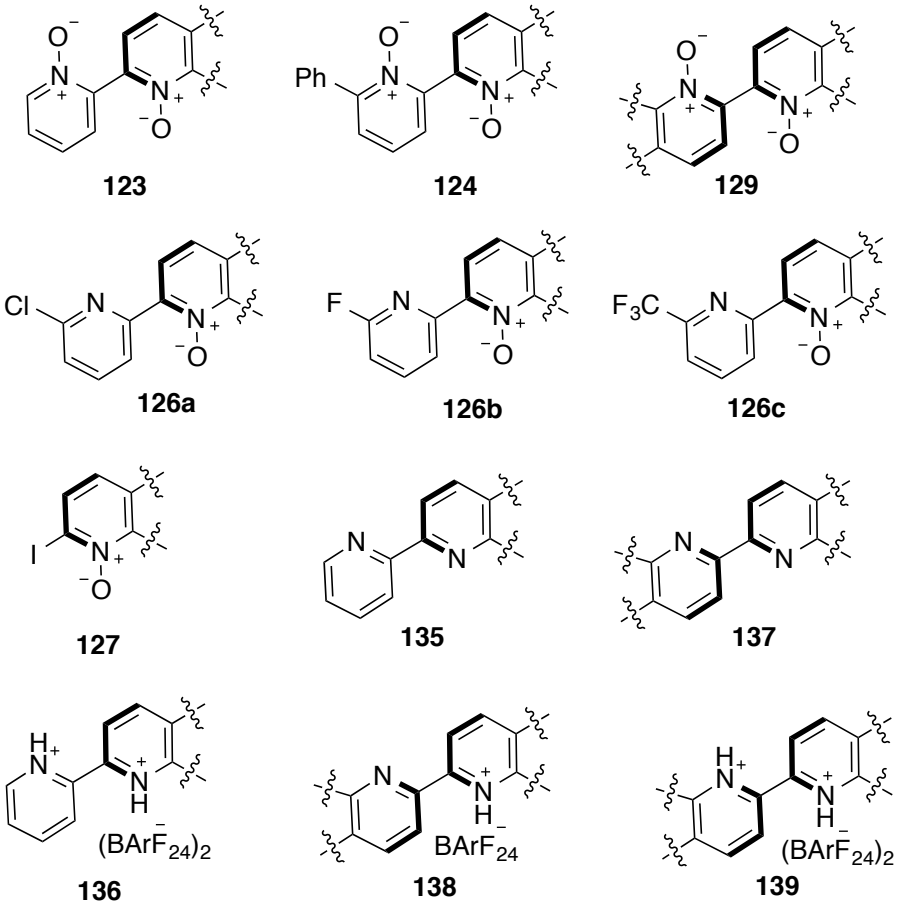


Figure 4.4. Newly developed helical chiral catalysts

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.

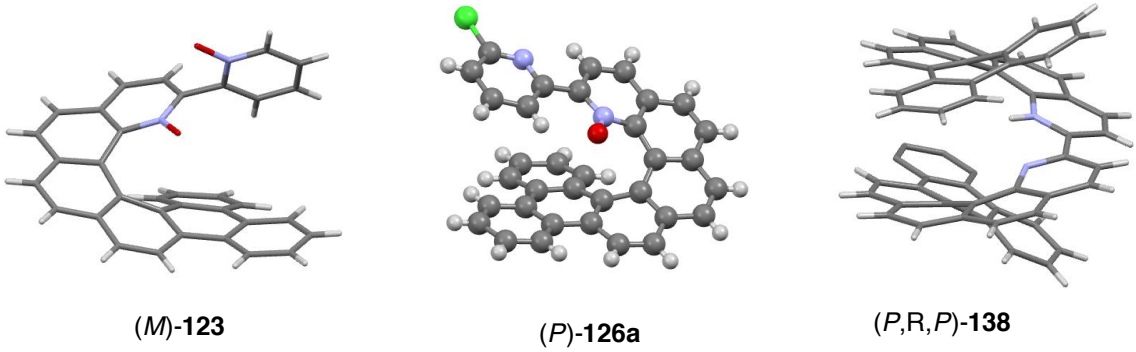


Figure 4.5. Solid-state structures of selected helical chiral catalysts

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[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_2Cl_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 *m*CPBA was recrystallized from CH_2Cl_2. ^{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_4Si (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.

4.4.2. General Procedure for the Synthesis of bis-N-oxides 123

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 *m*CPBA (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_2CO_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%). $[\alpha]^{20}_{D}$ = - 2124, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d6) δ 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-d6) *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) u_{max} 2927, 1619, 1467, 1426, 1349, 1257, 1097, 848, 754, 728 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{34}H_{20}N_2O_2$ $[M + 1]^+$, 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_2O (7 mL), and then the excess iodine was removed by adding an aqueous

$Na_2S_2O_4$ solution. The resulting mixture was extracted with CH_2Cl_2, washed with aqueous NH_4Cl solution, H_2O and brine, dried over Na_2SO_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, $CDCl_3$) δ 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, $CDCl_3$) δ 150.0, 136.4, 133.5, 130.1, 129.6, 128.5, 127.4, 125.7, 113.5; FTIR (neat) u_{max} 1533, 1454, 1442, 1361, 1229, 1021, 1000, 836, 757, 692 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{11}H_8INO$ $[M + 1]^+$, 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_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water (10 mL) then brine (10 mL), dried over Na_2SO_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%). $[\alpha]^{20}_{D}$ = - 2536, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}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) u_{max} 2920, 1469, 1443, 1378, 1241, 845, 751, 726, 693 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{40}H_{24}N_2O_2$ $[M + 1]^+$, expected: 565.1911, found: 565.1907.

4.4.5 Procedure for the Synthesis of 2-iodo-11, 12-1-aza[6]helicene N-oxide 127

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_2O, and then the excess iodine was removed by adding an aqueous $Na_2S_2O_4$ solution. The resulting mixture was extracted with Et_2O, washed with aqueous NH_4Cl solution, H_2O and brine, dried over Na_2SO_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, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{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 μL) 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 NH_4Cl (15 mL). The resulting mixture was extracted with Et_2O, washed with H_2O and brine, dried over Na_2SO_4, 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. $[\alpha]^{20}_D$ = + 2814, c = 0.0005, CH_2Cl_2. ^{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, $CDCl_3$) *d* 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) u_{max} 2922, 2853, 1559, 1429, 1416, 1363, 1347, 1134, 843, 749, 724 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{34}H_{19}ClN_2O$ $[M + 1]^+$, expected: 507.1259, found: 507.1261.

(*M*)-**126b**: Obtained as a yellow solid in 90% yield. $[\alpha]^{20}_D$ = - 2066, c = 0.0005, CH_2Cl_2. ^{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) u_{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 $C_{34}H_{19}FN_2O$ $[M + 1]^+$, expected: 491.1554, found: 491.1556.

(*M*)**-126c**: Obtained as a yellow solid in 87% yield. $[\alpha]^{20}_D$ = - 1722, c = 0.0005, CH_2Cl_2. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 3045, 2933, 2875, 1576, 1556, 1431, 1415, 1368, 1347, 1140, 863, 749, 715 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{34}H_{19}F_3N_2O$ $[M + 1]^+$, 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 μL) 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_4Cl. The resulting mixture was extracted with CH_2Cl_2, washed with H_2O and brine, dried over Na_2SO_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 (14 mg, 21%). $[\alpha]^{20}_D$ = - 3404, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 2922, 2852, 1589, 1436, 1296, 843, 750, 723 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{58}H_{32}N_2O$ $[M + 1]^+$, 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) *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 CH_2Cl_2. The combined organic layers were washed with water then brine, dried over Na_2SO_4, 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 CH_2Cl_2 to afford the title compound as a yellow solid (36 mg, 60%). $[\alpha]^{20}_D$ = - 6038, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.78 (d, *J* = 7.8 Hz, 1H), 8.57-8.63 (m, 3H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.93 (t, *J* = 7.9 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.68-7.78 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.59 (t, *J* = 7.8 Hz, 1H), 6.33 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 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); FTIR (neat) u_{max} 2925, 1633, 1441, 1372, 1314, 1238, 841, 750, 725 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{58}H_{32}N_2O_2$ $[M + 1]^+$, 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 $HCOONH_4$ (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 CH_2Cl_2. 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, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 3039, 1567, 1464, 1125, 852, 836, 779, 756703 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_2Cl_2. The filtrate was then combined and concentrated *in vacuo*. The resulted crude material was washed with small amount of CH_2Cl_2 to afford the title compound as a light color solid (10.5 mg, 96%). $[\alpha]^{20}_{D}$ = - 2816, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 3042, 1580, 1481, 1439, 904, 849, 832, 751, 724 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{58}H_{32}N_2$ $[M + 1]^+$, 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 CH_2Cl_2 (2.0 mL) was added Et_2O solution of HCl (1M, 0.25 mL) drop-wise at room temperature. The reaction mixture was stirred for 30 minutes and then concentrated *in vacuo*. The resulting solid was dissolved back into CH_2Cl_2 (2.0 mL), and then concentrated *in vacuo*, the process of which was repeated three times. To the resulting bright red solid were added CH_2Cl_2 (2.0 mL), MeOH (13.7 ml) and $NaBArF_{24}{\cdot}2.6H_2O$ (192 mg, 0.206 mmol) at room temperature. The resulting mixture was stirred for 4 hours, filtered through a short pad of Celite, concentrated *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 *Aminobisabolenol* (**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).

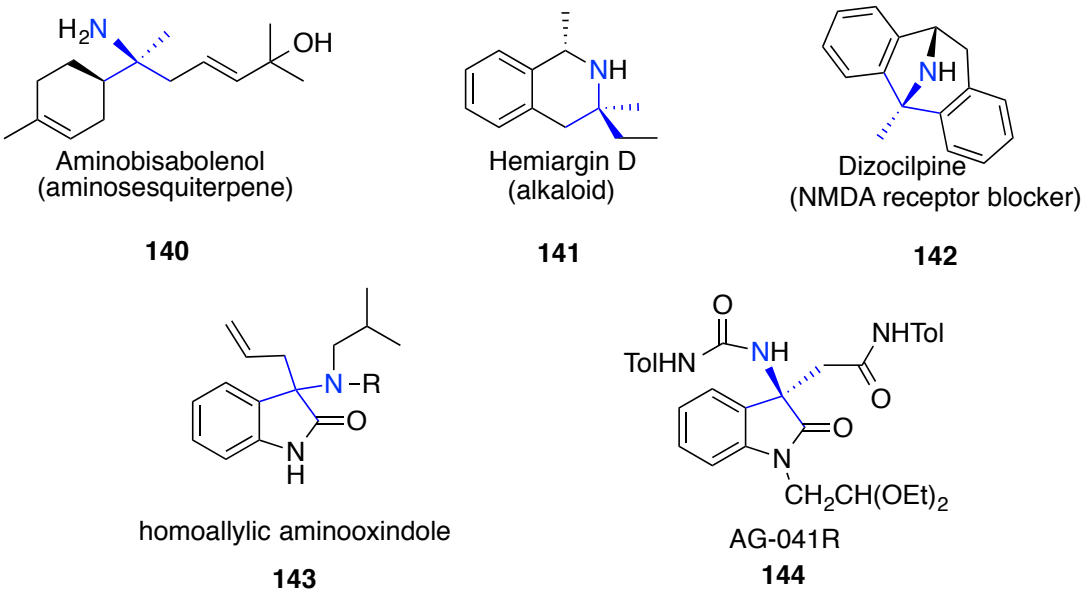


Figure 5.1. Biologically active α-trisubstituted amines

While a couple of methods have been developed to synthesize α-disubstituted amines by addition reactions to aldimines in a catalytic and asymmetric fashion,[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[110] (Figure 5.2).

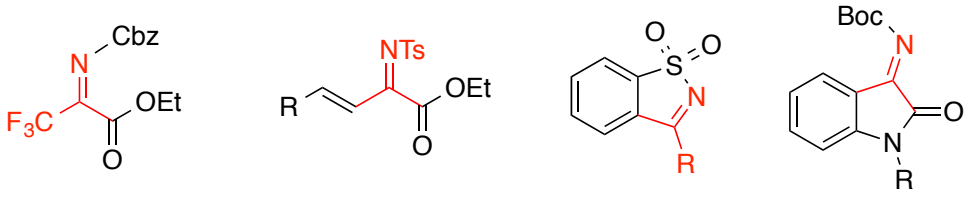


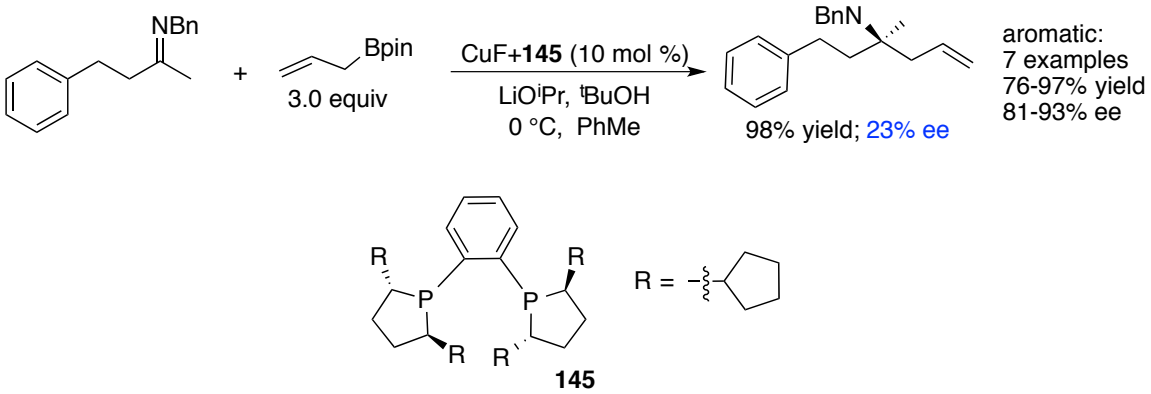
Figure 5.2. Selected examples of specially designed ketoimines

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[111] and Ellman[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.[113] 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[114] developed the first and the only catalytic asymmetric allylation of ketoimines to access α-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 0ºC, promoting the allylation of arylmethyl ketoimines with pinacolallylborane in good to excellent yield and selectivity. However, only one alkyl-alkyl ketoimine was studied with poor enantio selectivity (23% ee) in this report.

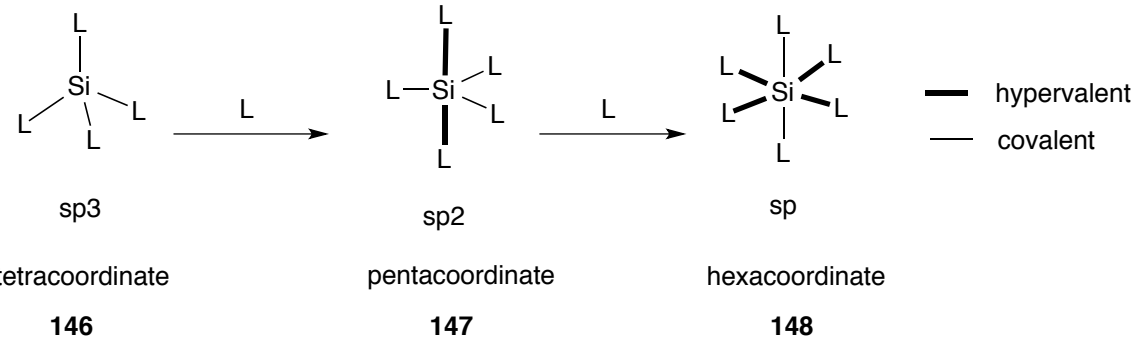
Indeed, there is no general method yet to access α-tertiary amines in a catalytic and asymmetric fashion with a good substrate generality. Therefore, the development of general, catalytic and enantioselective methods for the synthesis of α-tertiary amines remains an important goal and challenge for organic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



Scheme 5.1. Catalytic asymmetric allylation of ketoimines developed by Shibasaki

5.1.2. Lewis Base Assisted Lewis Acid Catalysis

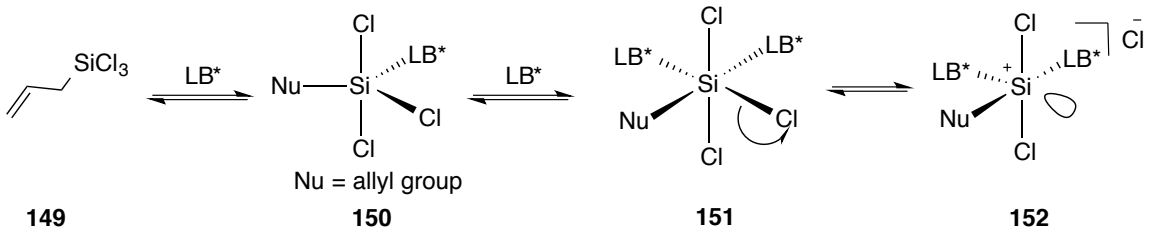
Meanwhile, chiral Lewis base catalyzed, polychlorosilane-mediated transformations have been successfully developed for the allylation[51-52, 103, 115] and propargylation[73, 116] of aldehydes. Such reactions were first pioneered by Hosomi and Sakurai,[117] and later developed by Denmark and co-workers.[115i, 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.



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.[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.[120] From the perspective of valence bond theory, a tetracoordinate silicon (**146**) possesses four sp3-hybridized

orbitals. The expansion to a pentacoordinate silicon complex (SiL_5, **147**) requires one of the p orbitals to form a hypervalent 3c-4e bonding with the ligands. For hexacoordinate silicon complex (SiL_6, **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

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 species[122] (**152**, Scheme 5.3).

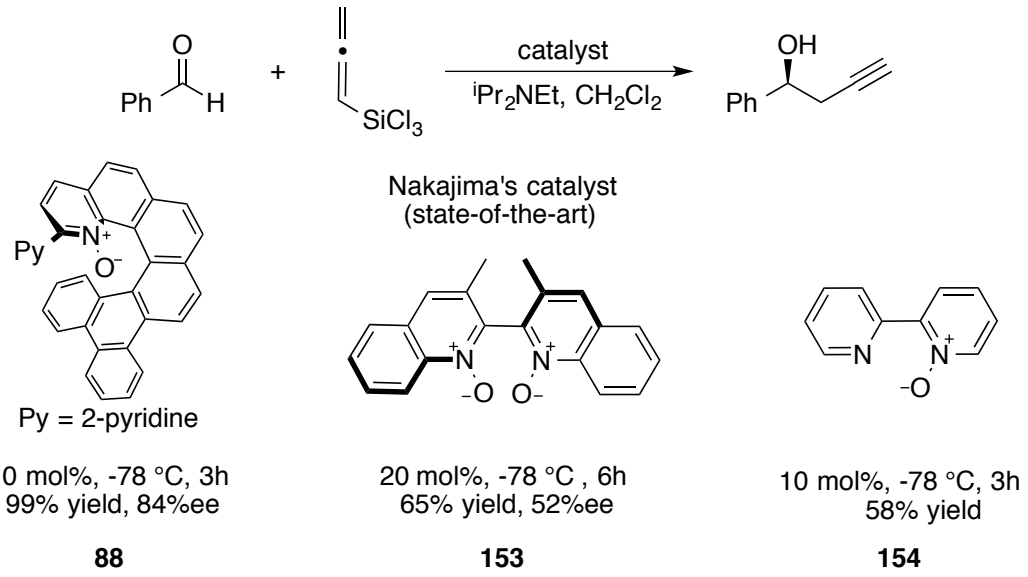
In order to generate a high concentration of **152**, traditionally, strong Lewis bases (e.g., HMPA, DMSO) were used:

$$2\,\text{HMPA} + SiCl_4 \rightleftharpoons 2\text{HMPA}\bullet SiCl_3^+Cl^-$$

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:

$$2\,\text{Py} + SiCl_4 \rightleftharpoons 2\text{Py}\bullet SiCl_3^+Cl^-$$

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,[73] our group developed a catalyst (**88**) that is exceedingly more reactive than its analogous catalysts **153**[51] 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.

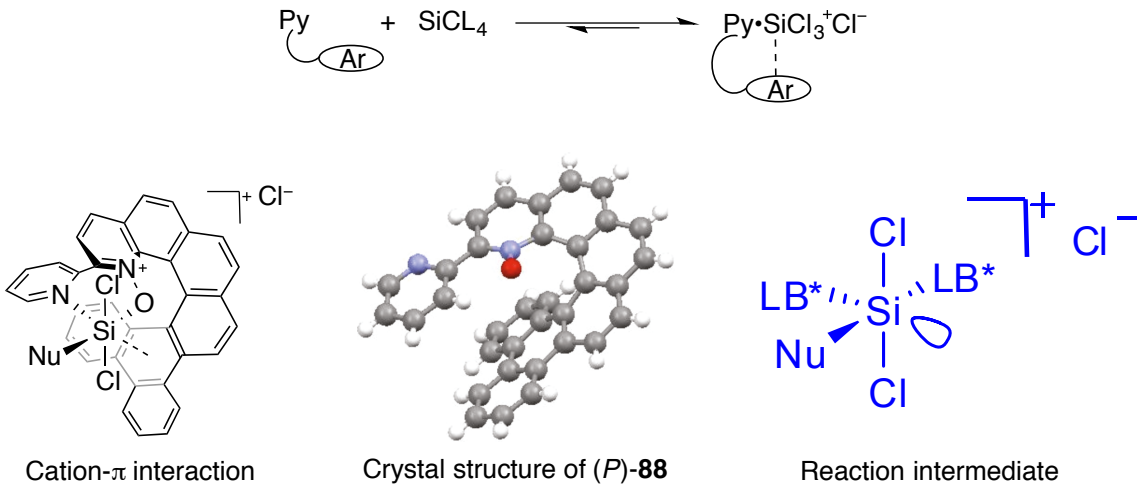


Figure 5.3. An effective generation of reactive Lewis acid *via* cation-π interaction

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.

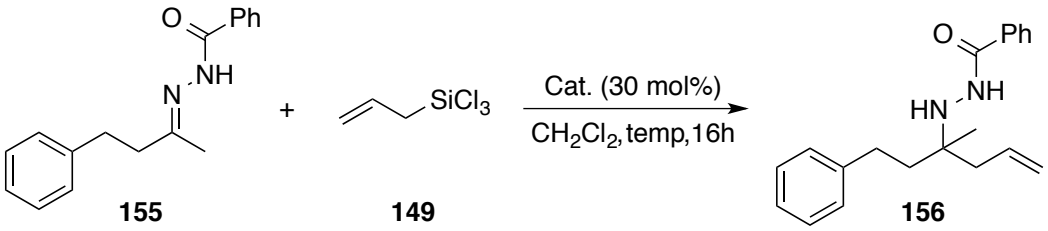
5.2. Results and Discussions

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[123]; 2), benzoylhydrazones have been proved to be very good substrates for the synthesis of homoallylic amines[124]; 3), compound **155** stands for the most challenge substrate for this type of reactions.[114] Allyltrichlorosilane[125] **149** was picked as the allylation reagent due to its mildness, low toxicity, regiospecificity and great responsiveness towards Lewis base activation. CH_2Cl_2, an ideal solvent for most allylation reaction of aldehydes,[108f, 108h] was therefore used as the solvent for our test[115f, 115h] (Table 5.1).

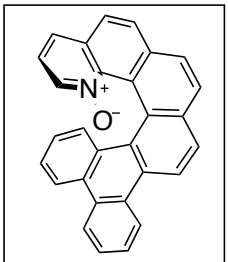
Reactions without catalysts were tested first to find out the best temperature for the development of a catalytic asymmetric version of this reaction (entries 1-4, Table 5.1). When **155** (1.0 equivalent) and **149** (1.5 equivalents) were stirred at r.t overnight, there was a significant reaction (entry 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.

Table 5.1. Evaluation of catalysts

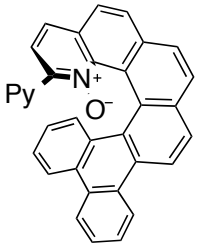


entry[a]	Cat.	temp (°C)	yield[b] (%)	ee[c] (%)
1	-	r.t	22	-
2	-	0	15	-
3	-	-20	0	-
4	-	-40	0	-
5[d]	**88**	-20	0	-
6	**88**	-20	0	-
7[d]	**87**	-20	10	8
8	**87**	-20	20	26

[a]Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b]Yield of isolated products. [c]Determined by HPLC analysis. [d]10 mol% catalyst was used



87



Py = 2-pyridine

88

Previously, our group reported that bidentate helical chiral pyridine N-oxide **88** efficiently activates allenyltrichlorosilane and is extremely reactive towards the propargylation of aldehydes.[73] 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

(entry 6, Table 5.1). 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).

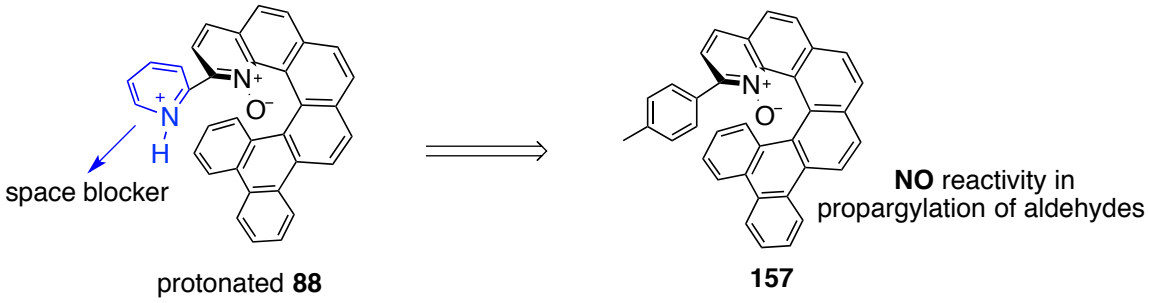
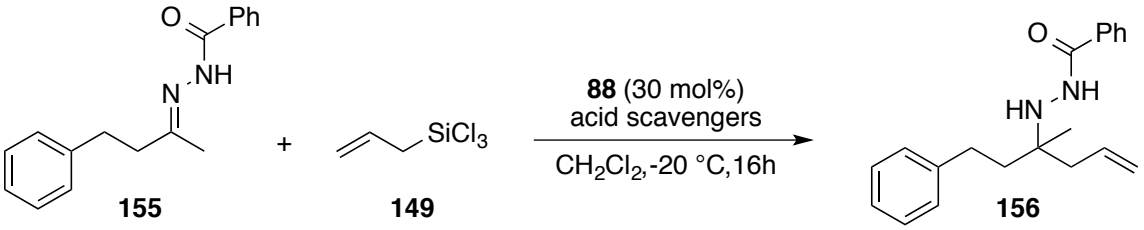


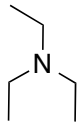
Figure 5.4. Protonated helical chiral catalyst

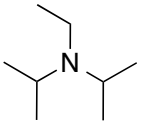
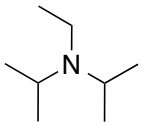
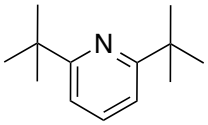
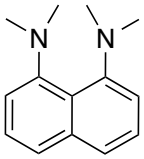
Collectively considering the information we gathered, we suspected the inactivity of catalyst **88** might be attributed to the adventitious HCl generated from the hydrolysis of allyltrichlorosilane **149**, which cannot be avoided. Indeed, a quick NMR experiment revealed that at least one equivalent 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



entry [a, b, c]	1	2	3	4
	none	4 A MS (100 mg)	 (1.5 equiv)	 (1.5 equiv)
	no rxn	7% yield, racemic	< 5% yield	9% yield, racemic
			157	**158**

entry [a, b, c]	5	6	7	8
	 (1.5 equiv)	 (5.0 equiv)	 (1.5 equiv)	 (1.5 equiv)
	23% yield, racemic	No desired product	15% yield, racemic	28% yield, 4% ee
	159	**159**	**160**	**161**

[a]Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst and acid scavengers in CH_2Cl_2 (1.6 ml). [b]% yield is the yield of isolated products. [c]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).

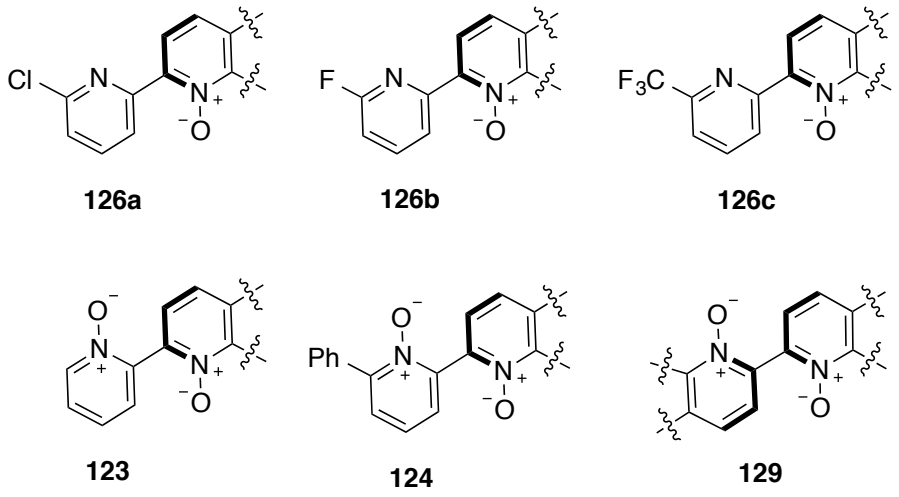
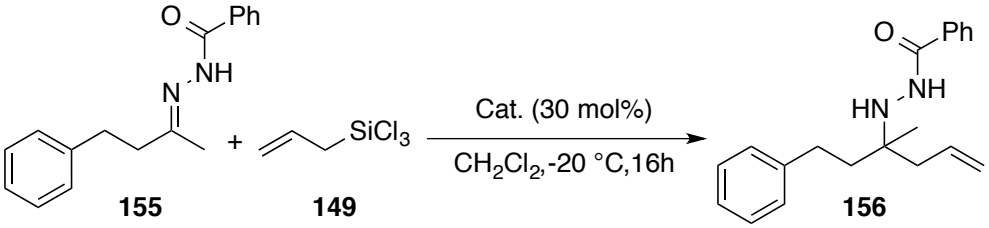


Figure 5.5. Lewis base catalysts

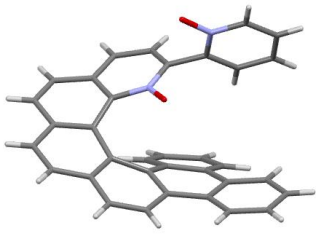
Unfortunately, catalysts **126a-c** were no better catalysts than **88**, only trace product was observed by TLC analysis in these reactions (entries 2-4, Table 5.3). Surprisingly, a 30% yield and 82% *ee* (a value that is comparable to the best result available in the literature as far as we know[113]) 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.[126] In

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.[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



entry[a]	Cat.	yield[b] (%)	ee[c] (%)
1	**88**	0	-
2	**126a**	trace	-
3	**126b**	trace	-
4	**126c**	trace	-
5	**123**	30	82
6[d]	**123**	33.4	82
7	**124**	trace	-
8	**129**	trace	-



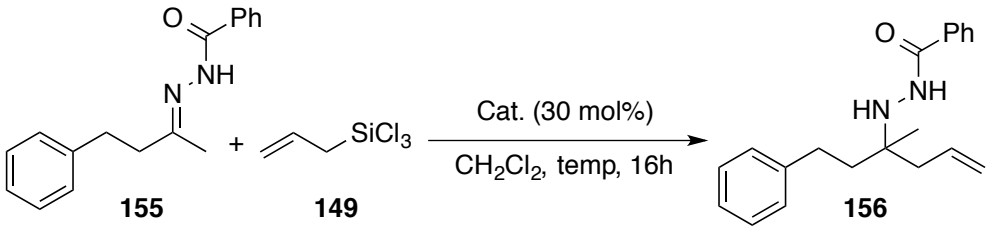
(*M*)-**123**

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis. [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



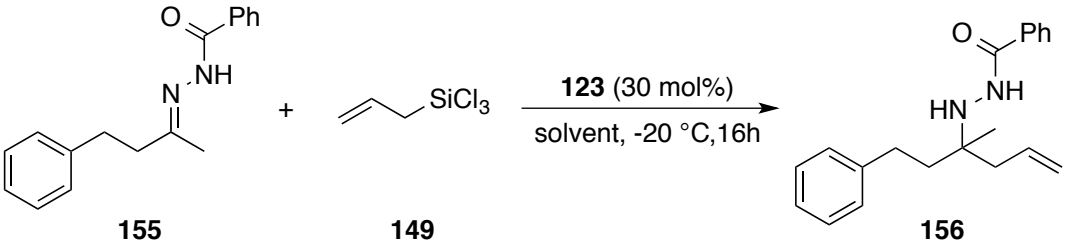
entry[a]	Cat.	temp (°C)	yield[b](%)	ee[c](%)
1	**123**	-50	11	63
2	-	-50	0	-
3	**123**	-20	30	82
4	**123**	0	36	73
5	**123**	rt	41	64
6[d]	**123**	40	49	55
7[d]	-	40	31	-

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis. [d] CH_2ClCH_2Cl was used as solvent.

A detailed *solvent effects* study was also carried out. It has been proposed that in bipyridine *N, N′*-dioxides catalyzed allylation 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 allylation *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_2Cl_2, $CHCl_3$, etc. are used.[115h]

CH_2Cl_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_2ClCH_2Cl and CH_3CN 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_3Cl (entry 3, Table 5.5). As expected, less electrophilic solvent Et_2O 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, α,α,α-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



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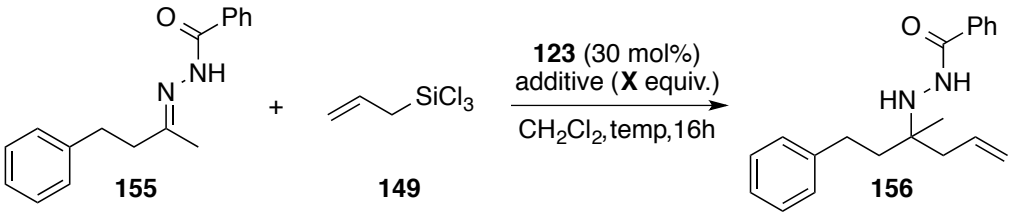
entry[a]	solvent	yield[b](%)	*ee*[c](%)
1	CH_2Cl_2	30	82
2	CH_2ClCH_2Cl	31	77
3	CH_3Cl	17	51
4	CH_3CN	31	72
5	Et_2O	18	racemic
6	toluene	24	4
7	α,α,α-trifluorotoluene	15	6
8	iodobenzene	32	40
9	THF	42	57
10[d]	THF	32	-
11	acetone	22	79
12	acetone/CH_2Cl_2=1/1	27	**84**
13[e]	acetone	30	79
14[f]	acetone	33	75
15[d,e]	acetone	11	-
16[d,f]	acetone	11	-

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis. [d] No catalyst was used. [e] reaction was run at 0 °C. [f] reaction was run at ambient temperature

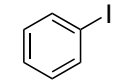
To our surprise, we were able to get comparable results with acetone as solvent, and no sign of allylation of acetone was observed (entry 11, Table 5.5). A better yield and much higher selectivity (84% *ee*) was realized when a mixture of acetone and CH_2Cl_2 were used (entry 12, Table 5.5). It appears 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_2Cl_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).

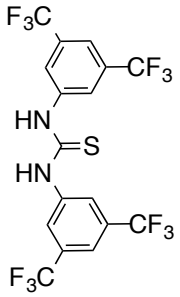
Table 5.6. Evaluation of additive effects



entry[a]	additive	X	temp (°C)	yield[b] (%)	ee[c] (%)
1	4 Å MS	100 mg	-20	35	79
2	**158**	1.5	-20	9	2
3	**159**	1.0	-20	25	29
4	**159**	5.0	-20	0	-
5	**160**	5.0	-20	30	6
6	**162**	1.0	-20	32	**83**
7[d]	**162**	1.6 ml	-20	32	40
8	**163**	0.5	25	43	66
9[e]	**163**	0.5	25	8	-
10	**163**	0.5	35	46	63
11	**163**	0.5	45	47	56
12	**163**	0.5	55	49	48



162



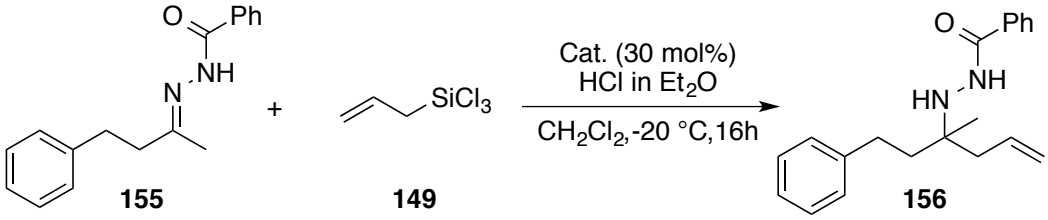
163

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis. [d] **162** was used as a slovent. [e] No catalyst was used.

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



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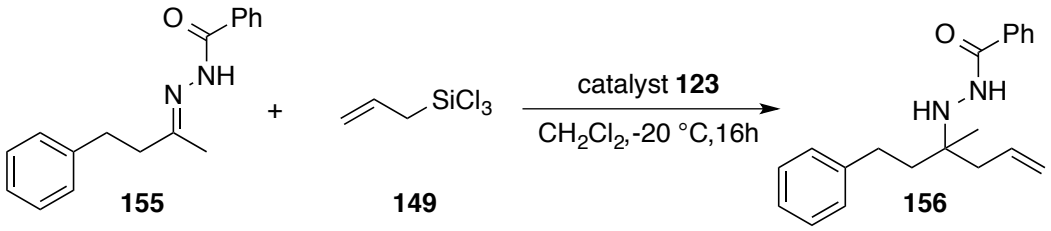
entry[a]	Cat.	HCl (equiv)	temp (°C)	yield[b](%)	ee[c](%)
1	**123**	0.5	-20	21	79
2	**-**	0.5	-20	0	-
3	**123**	0.5	r.t	33	76
4	**-**	0.5	r.t	13	-
5	**123**	1.5	-20	0	-
6	**123**	1.5	r.t	14	63
7	**-**	1.5	r.t	0	-

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] 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[130] 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

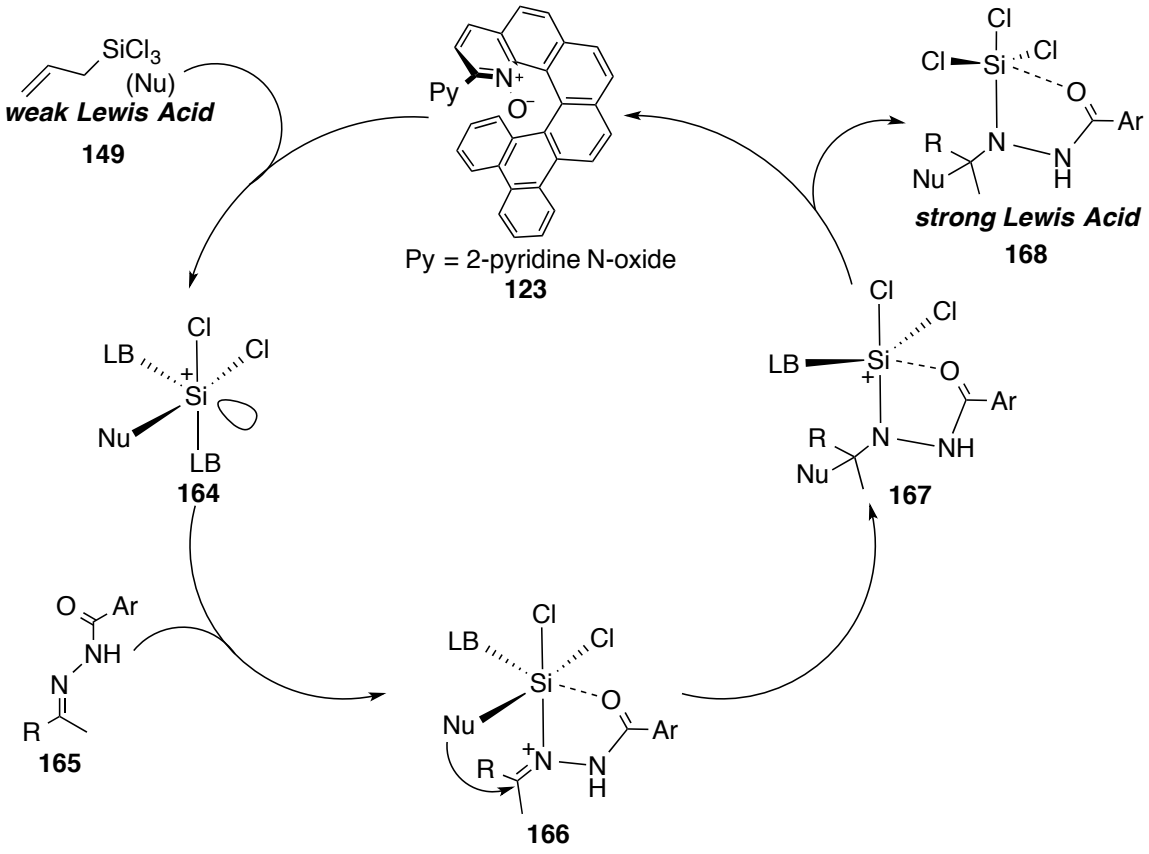


155 **149** **156**

entry[a]	**123** (mol%)	yield[b](%)	*ee*[c](%)
1	30	30	82
2	50	54	81
3	75	73	83
4	100	92	82

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] 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.



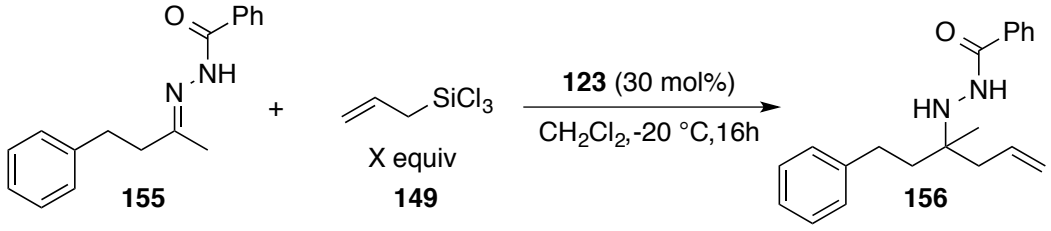
Scheme 5.5. Proposed mechanism for observed product inhibition

As recently reported by Denmark and coworkers,[131] 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

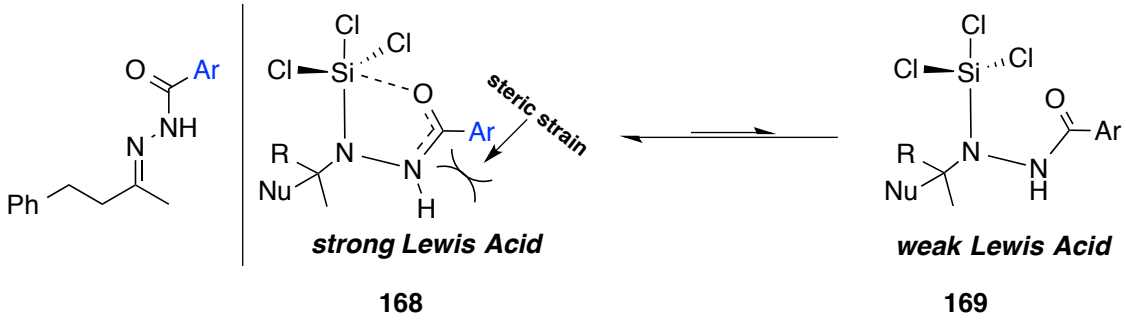


entry[a]	X (equiv)	yield[b](%)	ee[c](%)	background rxn (%)
1	1.5	30	82	0
2	7.5	39	84	0
3	15.0	43	76	5

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis.

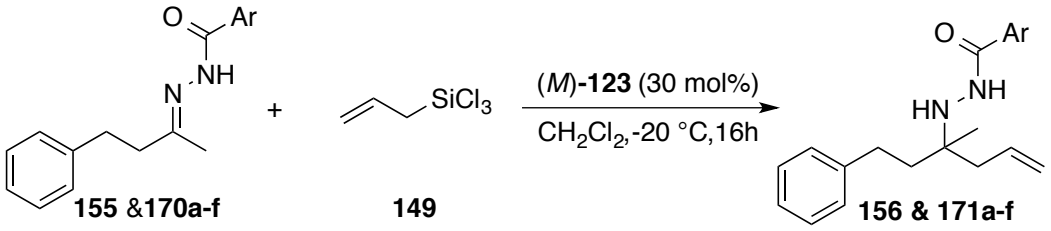
Indeed, we observed some positive effects when increasing the equivalence of **149** used in the reaction. When 7.5 equivalents of **149** were used, a much better yield and selectivity were achieved (entry 1 vs. entry 2, Table 5.9). However, further increasing the equivalents of **149** did not improve 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)



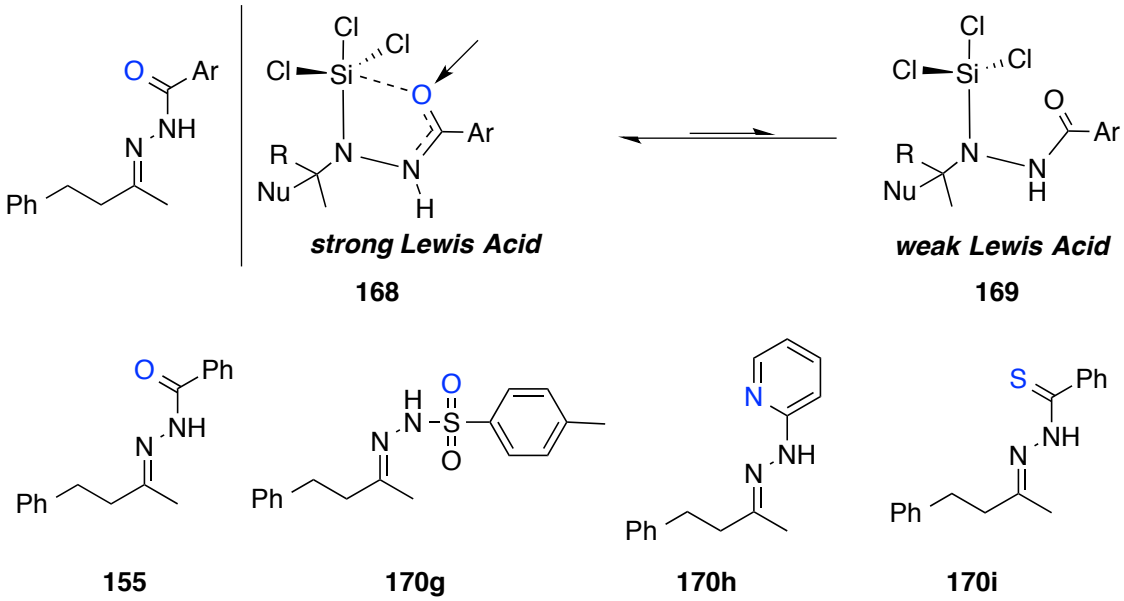
entry[a]	substrate	Ar	temp (°C)	product	yield[b] (%)	ee[c] (%)
1	**170a**	H	-20	**171a**	trace	-
2	**170b**	Me	-20	**171b**	0	-
3	**170b**	Me	r.t	**171b**	0	-
4	**155**	Ph	-20	**156**	30	82
5	**170c**	4-NO_2Ph	-20	**171c**	44	53
6	**170d**	3,5-$(CF_3)_2$Ph	-20	**171d**	43	50
7	**170e**	*t*Bu	-20	**171e**	0	-
8	**170e**	*t*Bu	r.t	**171e**	trace	-
9	**170f**	-*Ot*Bu	-20	**171f**	0	-
10	**170f**	-*Ot*Bu	r.t	**171f**	0	-
11	**170f**	-*Ot*Bu	50	**171f**	0	-

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (1.6 ml). [b] Yield of isolated products. [c] Determined by HPLC analysis.

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 **170e** was tested (entries 7 and 8, Table 5.10), it was quite surprising because this structure should greatly raise the steric strain in **168**. No reaction was observed for a similar substrate **170f** even when the temperature was increased to 50 °C (entries 9-11, Table 5.10).

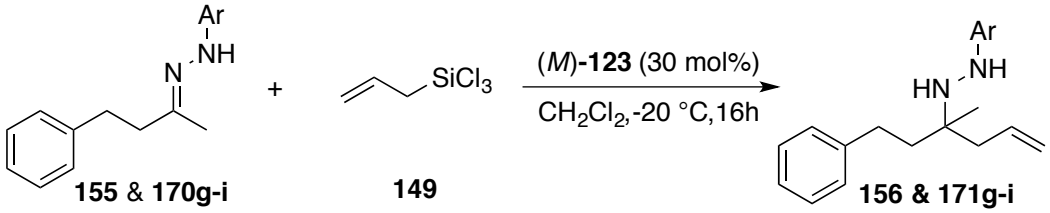
Another method to potentially shifting the equilibrium between **168** and **169** is to change the binding ability of the substrate to silicon. To test this idea, some specially designed hydrazones were synthesized (**170g-i**, Scheme 5.7).



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)

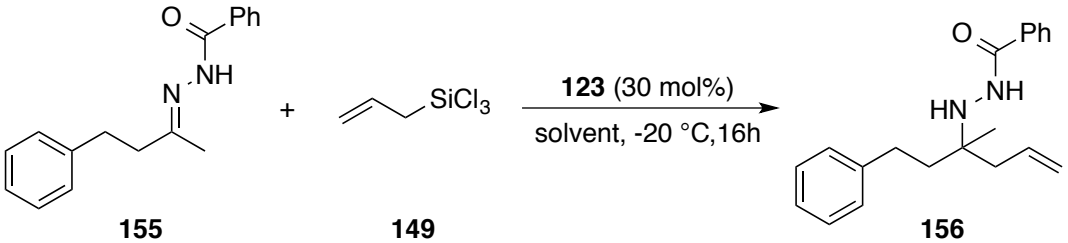


entry[a]	substrate	temp (°C)	product	yield[b](%)	ee[c](%)
1	**170g**	-20	**215**	0	-
2	**170g**	r.t	**215**	0	-
3	**170h**	-20	**216**	trace	-
4	**170h**	r.t	**216**	8	nd
5	**170i**	-20	**217**	0	-
6	**170i**	r.t	**217**	0	-
7	**170i**	50	**217**	0	-
8	**170i**	100	**217**	0	-
9	**155**	-20	**164**	30	82

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_2 (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



155 **149** **156**

entry	basic solvent	volume (ml)	CH_2Cl_2 (ml)	yield[b](%)	*ee*[c](%)
1	-	0	1.6	30	82
2	THF	0.6	1.0	35	75
3	THF	0.8	0.8	**58**	**71**
4	THF	1.0	0.6	46	64
5[d]	THF	0.8	0	26	14
6	1,4-Dioxane	0.8	0.8	39	79
7	DMF	0.4	1.2	63	17
8[e]	DMF	0.4	1.2	57	-
9[f]	-	0	1.6	33	32

[a] Reaction condition: hydrazone (0.25 mmol) and allyltrichlorosilane (0.375 mmol) in the presence of 30 mol % of catalyst in CH_2Cl_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_2Cl_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_2Cl_2 with α,α,α-trifluorotoluene turned out to be unsuccessful (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 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_2Cl_2) 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. (^{i}Pr)$_2$NEt and Et_3N 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 K_2CO_3 under reduced pressure prior to use.

^{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_4Si (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.

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 Et_2O 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[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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.6, 141.4, 128.8, 128.7, 126.5, 40.8, 32.7, 16.3; FTIR (neat) u_{max} 3174, 3026, 2888, 1673, 1635, 1542, 1381, 1229, 1194, 1028, 915, 732 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{11}H_{14}N_2O$ $[M + 1]^+$, 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_{max} 3042, 1674, 1652, 1549, 1429, 1363, 1291, 1251, 1096, 1074, 1031, 741, 700 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{12}H_{16}N_2O$ $[M + 1]^+$, 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 (272mg, 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_{max} 3222, 3030, 1667, 1603, 1537, 1517, 1294, 1272, 1137, 856, 727, 696 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{17}H_{17}N_3O_3$ $[M + 1]^+$, 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, $CDCl_3$) δ 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, $CDCl_3$) δ 174.0, 157.7, 141.4, 128.7, 128.6, 126.3, 41.2, 33.0, 27.8, 27.6, 15.6; FTIR (neat) u_{max} 3288, 2954, 1658, 1508, 1454, 1367, 1178, 749, 700 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{22}N_2O$ $[M + 1]^+$, 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_2O. Small amount of the resulted product was taken for characterization. All spectral data were in agreement with literature values[132].

(E)-1-(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_2O. Small amount of the resulted product was taken for

characterization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_{max} 3239, 1600, 1452, 1376, 1332, 1162, 914, 815, 736 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{17}H_{20}N_2O_2S$ $[M + Na]^+$, expected: 339.1138, found: 339.1155.

(E)-1-(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, $CDCl_3$) δ 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, $CDCl_3$) δ 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_{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, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 3268, 3027, 2925, 1494, 1448, 1269, 975, 912, 757, 690 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{17}H_{18}N_2S$ $[M + 1]^+$, 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_2Cl_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_2PO_4 solutions, and extracted with CH_2Cl_2 three times. The combined organic layers were washed with water then brine, dried over Na_2SO_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_2Cl_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% ^{i}PrOH in hexanes, flow rate = 0.45 mL/min), t_r (major) = 36.72 min, t_r (minor) = 39.16 min. The (*S*)-absolute configuration was assigned by analogy to **156**. $[a]^{20}_{D}$ = + 6, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) u_{max} 3226, 3086, 2951, 1632, 1598, 1519, 1452, 1345, 916, 847, 739, 696 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{20}H_{23}N_3O_3$ $[M + 1]^+$, 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 % ^{i}PrOH in hexanes, flow rate = 0.20 mL/min), t_r (minor) = 45.17 min, t_r (major) = 49.65 min. The (*S*)-absolute configuration was assigned by analogy to **156**. $[a]^{20}_{D}$ = + 6, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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) u_{max} 3272, 2944, 1642, 1451, 1376, 1276, 1132, 907, 698 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{22}H_{22}F_6N_2O$ $[M + 1]^+$, expected: 445.1709, found: 445.1738.

(S)-1-(3-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**. $[a]^{20}_D$ = - 118, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) u_{max} 3060, 3031, 2979, 2932, 1584, 1460, 1426, 1380, 993, 917, 787, 742, 700 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{18}H_{23}N_3$ $[M + 1]^+$, expected: 282.1965, found: 282.1958.

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