2014-07-29

Asymmetric Catalysis of Pericyclic Reactions via Chiral Hydrogen-Bond Donors

Maurice J. Narcis
University of Miami, mauricenarcis@gmail.com

UNIVERSITY OF MIAMI

ASYMMETRIC CATALYSIS OF PERICYCLIC REACTIONS VIA CHIRAL HYDROGEN-BOND DONORS

By

Maurice Narcis

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

A dissertation submitted in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy

ASYMMETRIC CATALYSIS OF PERICYCLIC REACTIONS VIA CHIRAL HYDROGEN-BOND DONORS

Maurice Narcis

Approved:

_____ Norito Takenaka, Ph.D. Professor of Chemistry	_____ Angel Kaifer, Ph.D. Professor of Chemistry
_____ James Wilson, Ph.D. Professor of Chemistry	_____ M. Brian Blake, Ph.D. Dean of the Graduate School

_____
Konstantinos Kavallieratos, Ph.D.
Professor of Chemistry
Florida International University

NARCIS, MAURICE (Ph.D., Chemistry)

Asymmetric Catalysis of Pericyclic Reactions via Chiral Hydrogen-Bond Donors. (August 2014)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Norito Takenaka.
No. of pages in text. (103)

The Diels – Alder reaction and the Claisen rearrangement are pericyclic reactions involving a cyclic transition state. In the nitroalkene Diels – Alder reaction, efforts of LUMO-lowering catalysis through activation of nitroalkenes by metal-based Lewis acids have proven unsuccessful. Conversely, studies have shown that double hydrogen bond donors possess symmetrical coordination sufficient for activation of nitroalkenes. In the Claisen rearrangement, while there have been rare reports of enantioselective catalysis via Lewis acids, studies have shown that in rearrangement of chorismate, the enzyme chorismate mutase stabilizes the chair-like transition state through hydrogen-bonding interactions. In light of this, highly enantioselective Claisen rearrangements through the use of guanidinium ions have been achieved. This highlights the potential for hydrogen bond donors as potential catalysts for these pericyclic reactions.

The development of helical chiral double hydrogen bond donor catalysts for the enantioselective nitroalkene Diels – Alder reaction of 5-substituted pentamethylcyclopentadiene substrates and nitroethylene is described in chapter two. The use of 11,12-benzo-1-aza[6]helicene based hydrogen-bond donor catalysts effectively activates nitroalkenes through LUMO-lowering catalysis to provide desired Diels – Alder products in up to 40% ee. Catalyst evaluation and expansion of the substrate scope are discussed. A synthetic route was designed and performed to access 1,4,5,5-

tetrasubstituted cyclopentadienes and the evaluation of these new diene substrates are discussed.

The catalysis of an *O*-allylated β-ketoester model substrate by helical chiral hydrogen bond donor catalysts is described in the third chapter. Initial evaluations of existing helical hydrogen bond donor catalysts and the development of new helical chiral dimers are discussed. These helical dimers are then synthesized and are observed to provide yields of up to 96% in the Claisen rearrangement of the model substrate.

The final chapter describes the efforts to develop a third generation synthesis of 1-azahelicenes to provide them in an enantiopure form. Studies of the initial step, asymmetric formation of a biaryl intermediate utilizing existing coupling methods are discussed and a highly aymmetric intramolecular coupling of an intermediate providing enantioenriched 1-aza[6]helicene are discussed.

ACKNOWLEDGEMENTS

I would first like to acknowledge my advisor Norito Takenaka, who has provided me with the encouragement over the last five years needed to get to this point. Your vast knowledge of organic chemistry propelled me to want to know more about my field as I began working in the group. Not only our lessons having the right attitude towards chemistry research but those of dedication, diligence and open-minded curiosity are invaluable. They will stay with me always. Thank you.

I am grateful to my lab mates, past and present. To Dr. Chen, our post-doc when I joined the group. You thought me skills and techniques that I would need use in lab. Sometimes when I observed while you set up reactions, it seemed as if you had four hands! I was always amazed at how much you got done in a day and even when you looked tired, you had a smile and a joke. Thank you Andreina for being a friend, at times you were like my big sister. We were always laughing and that got us through the difficult times. Hey, we even got some work done too. To Zhili, whom I started with and we've been through it all for the past five years. We got along great and supported each other when we had to. I'm happy that I had such a great person as my lab mate. Glad we made it out alive.

To my family I am forever thankful. My sisters, Fern and Gisele, and my brother Andrade, your words of encouragement always came at the right times. I hope you know it is to your achievements that I looked to, for the inspiration to forge my own. Mom and dad, you've always been there for me through the most difficult times. Your everlasting support has been paramount and without it I'm sure I would not be where I am today.

Even at my lowest times, when I considered quitting, you urged me to keep fighting through and it is to you both that I owe this and every success. I hope I have made you proud. I dedicate this to you.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

CHAPTER 1

Introduction

Pericyclic reactions can be defined as those having a cyclic transition state in which all bond forming and bond breaking takes place in concert, without the formation of an intermediate. The Diels – Alder reaction and Claisen rearrangement are examples of such. The Diels – Alder reaction, a [4+2] cycloaddition, can be considered to be the most powerful carbon-carbon (C – C) bond forming reaction to be discovered.[1] The ability to form up to four new stereogenic centers in one transformation underscores its utility for chemists as it finds a wide range of use in the natural product total synthesis. The nitroalkene Diels – Alder reaction, one of the many variants, holds additional synthetic utility as the nitro group can undergo various transformations leading to a variety of products.[2] The Claisen rearrangement – [3,3] sigmatropic rearrangement of allyl vinyl ethers – is another powerful (C – C) bond forming transformation and finds utility through the highly predictable stereochemistry.[3] As such, it is also used in the synthesis of complex organic molecules.

Longstanding efforts in asymmetric catalysis of these pericylic reactions have predominantly featured the use of metal-based Lewis acids. However, over the last decade the expansion of hydrogen bonding asymmetric catalysis have been significant. Studies have shown that small molecule hydrogen bond (H-bond) donors hold promise as chiral catalysts. Our laboratory became interested in the use of 1-azahelicenes as potential asymmetric catalysts due to the inherent chirality of these molecules derived from its naturally twisted state. Although a known limitation is the ready access to significant quantities of azahelicenes, we were surprised that they had not been previously

investigated as catalysts. As a result, we designed a synthetic route to 1-azahelicenes and successfully demonstrated their first use as asymmetric catalysts.[4] This section takes a brief review of advancements made in the development of asymmetric nitroalkene Diels – Alder and Claisen rearrangement reactions are along with the development of our helical chiral H-bond donor catalysts.

1.1 Enantio-enriched nitroalkene Diels – Alder products via activation of dienes

In 1960 Yates and Eaton first reported the acceleration of the Diels – Alder reaction by a metal-based Lewis acid.[5] Since then many enantioselective variants of the parent transformation catalyzed by chiral metal complexes have emerged.[6,7] However, extensive studies of the Diels-Alder reaction utilized carbonyl-based dienophiles. In light of this, it was apparent that catalytic activation of nitroalkenes for the asymmetric Diels – Alder reactions remained elusive. With Lewis acids the reaction preferentially undergoes the inverse electron-demand hetero Diels – Alder pathway providing nitronate products (Figure 1.1).[8,9]

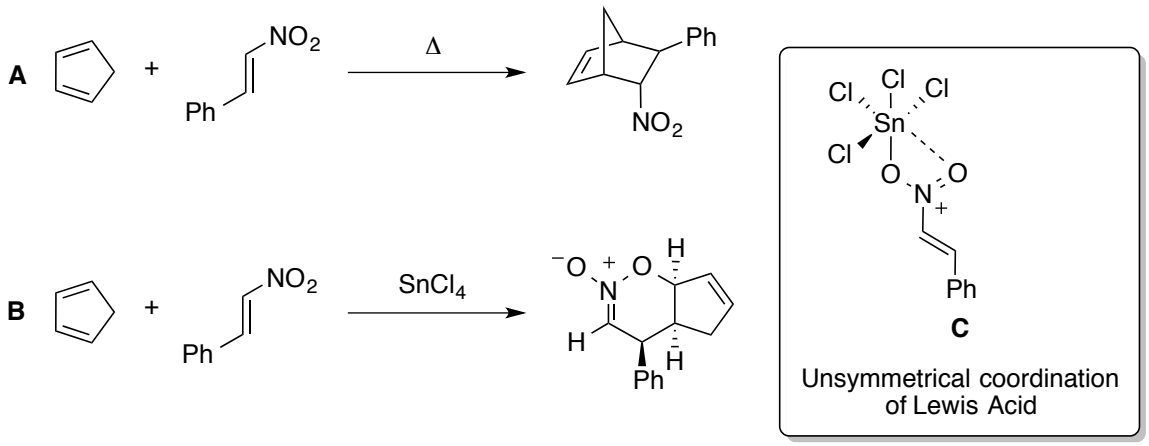
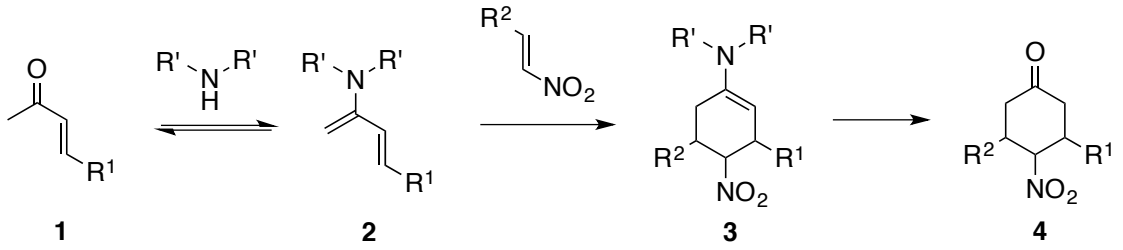


Figure 1.1 Reversed periselectivity of nitroalkene Diels-Alder reaction by Lewis acids. Reported by Denmark (Reference 8).

Nitroalkenes react with dienes in a [4 + 2] cycloaddition fashion to provide nitro-cyclohexene products under thermal conditions (Figure 1.1 A). Conversely, in the

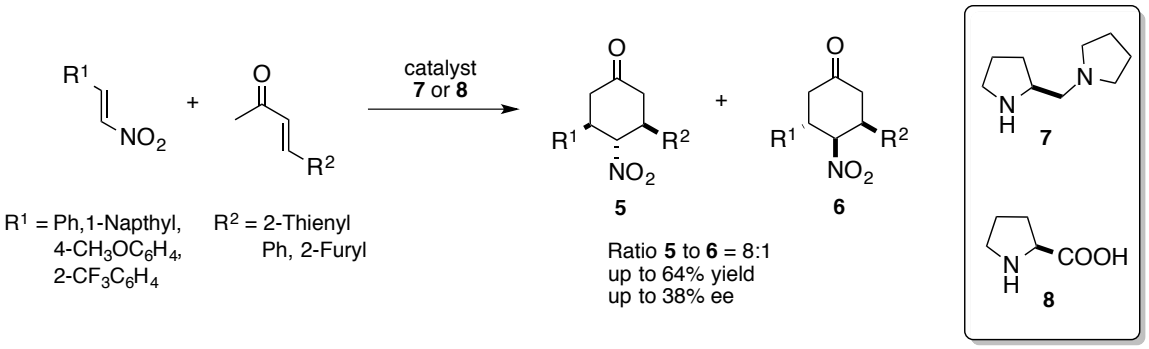
presence of $SnCl_4$, Denmark reported that a predominant nitronate species is formed due to the unsymmetrical coordination of the Lewis acid with one of the oxygen atoms of the nitroalkene (Figure 1.1 C). This serves to localize the double-bond character (O=N), enabling the nitroalkene to act as a 4π component rather than the expected 2π component, resulting in a reversal of periselectivity. Consequently, activation of nitroalkenes in the asymmetric Diels-Alder reaction via Lewis acid catalysis has proven ineffective.

As a result, different strategies and methods have been developed to activate the dienes for the nitroalkene Diels – Alder reaction. In 2002 Barbas first demonstrated an amine catalyzed Diels – Alder reaction of acyclic α,β-unsaturated ketones (enones) and nitroalkenes.[10] Diels – Alder products were obtained through in situ generation of dienes from α,β-unsaturated ketones by way of enamine catalysis (Scheme 1.1).



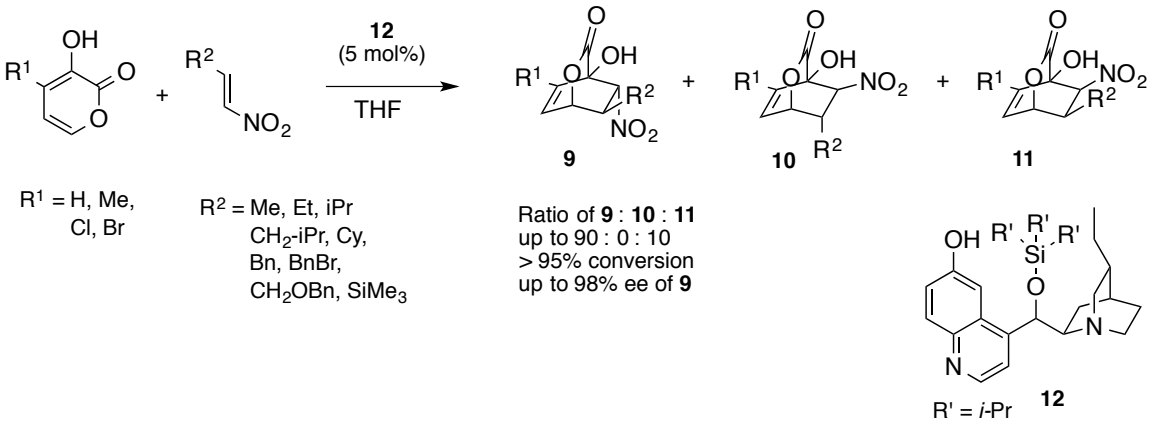
Scheme 1.1 Amine catalyzed Diels - Alder reactions of α,β-unsaturated ketones and nitroalkenes.

Using chiral amines Barbas was able to achieve yields of 32-75% and modest selectivities of up to 38% (Scheme 1.2).



Scheme 1.2 Diels - Alder reactions of α,β-unsaturated ketones and nitroalkenes via amine catalysis. Reported by Barbas (Referance 10).

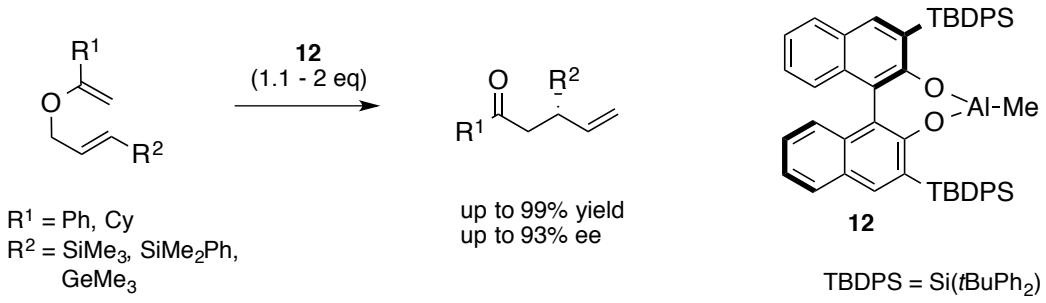
Subsequently, Cordova and coworkers utilized this method with cyclic enone substrates in the formation of bicyclic Diels – Alder products with various proline-derived catalysts.[11] Xu and coworkers demonstrated the use of a secondary amine chiral catalyst for the reaction achieving excellent selectivities (>25 : 1 *dr*, 83-96% ee).[12] Melchiorre then reported the use of chiral primary amine derived from natural cinchona alkaloids as a catalyst to obtain high selectivities with acyclic enones (2 : 1 to >19 : 1 *dr* and 88-99% ee).[13] Deng demonstrated different strategy by using 3-hydroxy-2-pyrones to and aliphatic nitroalkenes to access Diels – Alder products via a cinchona alkaloid derived bifunctional catalyst.[14]



Scheme 1.3 Asymmetric [4 + 2] cylcoadditions of 2-pyrones and aliphatic nitroalkenes. Reported by Deng (Reference 14).

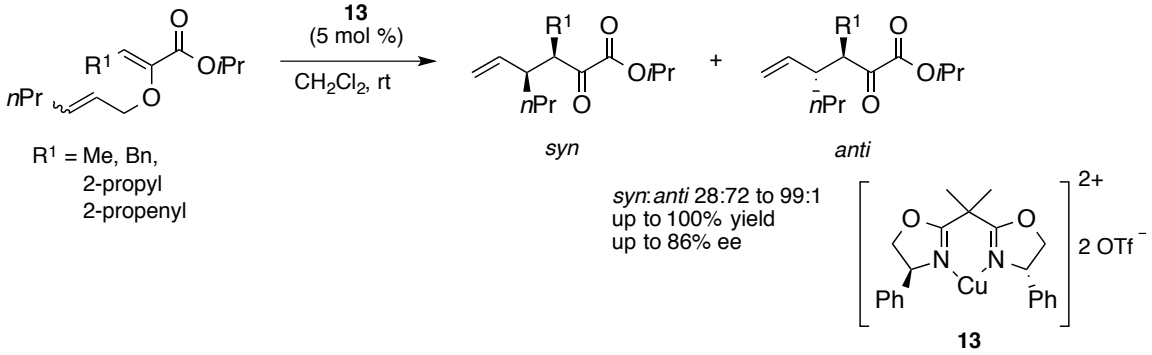
1.2 Enantioselective Claisen rearrangement reactions

In 1990 Yamamoto reported the first enantioselective Claisen rearrangement of silyl-substituted substrates via a chiral Lewis acid. The BINOL-derived organo-aluminum complex provided rearrangement products in up to 93% ee.[15] Stoichiometric catalyst loadings (up to 2 equivalents) were required due to the increased Lewis basicity of the carbonyl containing products.



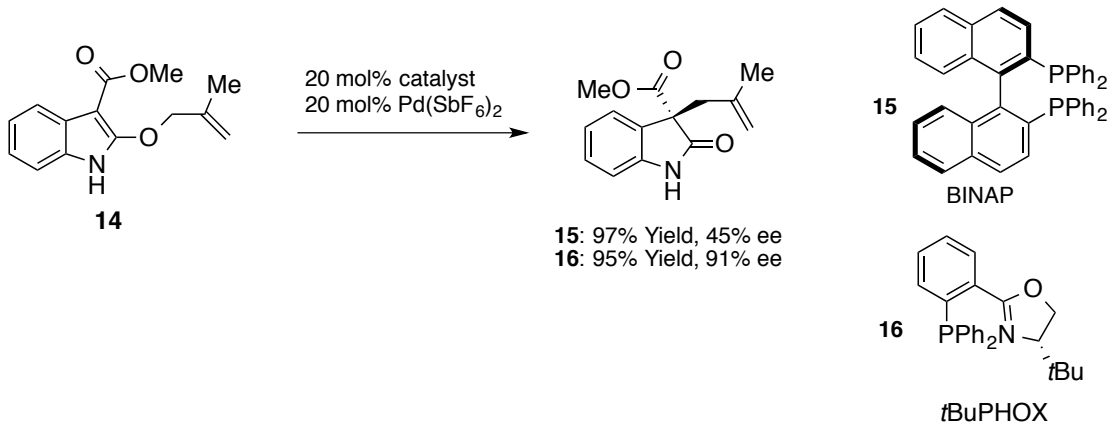
Scheme 1.4 Enantioselective rearrangements of silyl-substituted allyl vinyl ethers. Reported by Yamamoto (Reference 15).

In 2001 Hiersemann reported the first catalytic asymmetric Claisen rearrangement.[16] He demonstrated that copper (II) bisoxazoline complexes accelerated the rearrangements of ester substituted allyl vinyl ethers at sub-stoichiometric quantities.[17,18] The diastereoselectivities were generally predictable based on the configuration of the double bonds ad indicative of a chair-shaped transition state. The mode of catalysis proposed was the bidentate coordination of the ester carbonyl and the ether oxygen atoms which is in accord with other known enantioselective transformations utilizing copper (II) bisoxazoline catalysts.



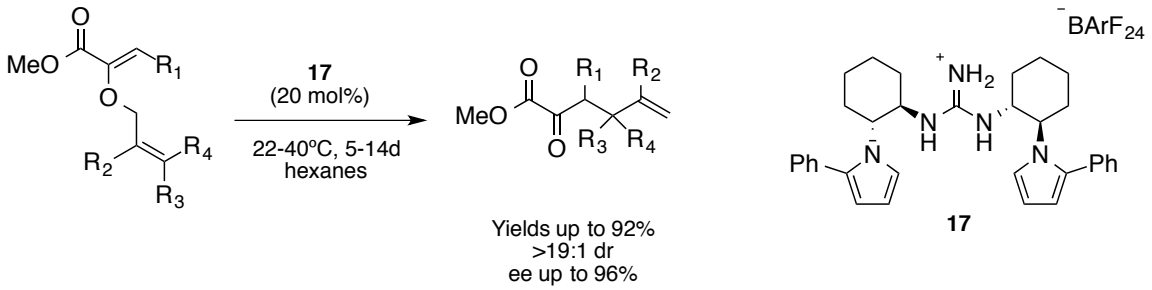
Scheme 1.5 Enantioselective rearrangements of *O*-allyl α-ketoesters. Reported by Hiersemann (Reference 16).

Kozlowski then demonstrated enantioselective rearrangements of 2-allyloxyindole-3-carboxylate substrates using multiple Lewis acid metal complexes.[19] Combinations of bisphosphines or phosphinooxazolines chiral ligands and palladium (II) SbF_6 salts were found to be optimal, providing oxindoles products in high yields and enantioselectivities. Kozlowski proposed a two-point coordination binding in the rearrangement between the Lewis acidic palladium complex and ether and ester oxygen atoms of the substrate in a chair-shaped transition state which was in accord for the stereochemical outcomes of both bisphosphine and phosphinooxazoline catalysts.



Scheme 1.6 Catalytic enantioselective rearrangements of 2-allyloxyindole-3-carboxylates. Reported by Kozlowski (Reference 19).

In 2008 Jacobsen demonstrated the first asymmetric catalysis of the Claisen rearrangement via small molecule H-Bond donor guanidinium ions.[20] Using ester substituted allyl vinyl ethers[16] they observed high enantio- and diastereoselectivities. Disubstituted compounds rearranged to form tertiary stereocenters in accord with the predicted six-membered chair-like transition state. However, the catalyst exhibited sluggish activity with reaction times ranging from 5 to 14 days.



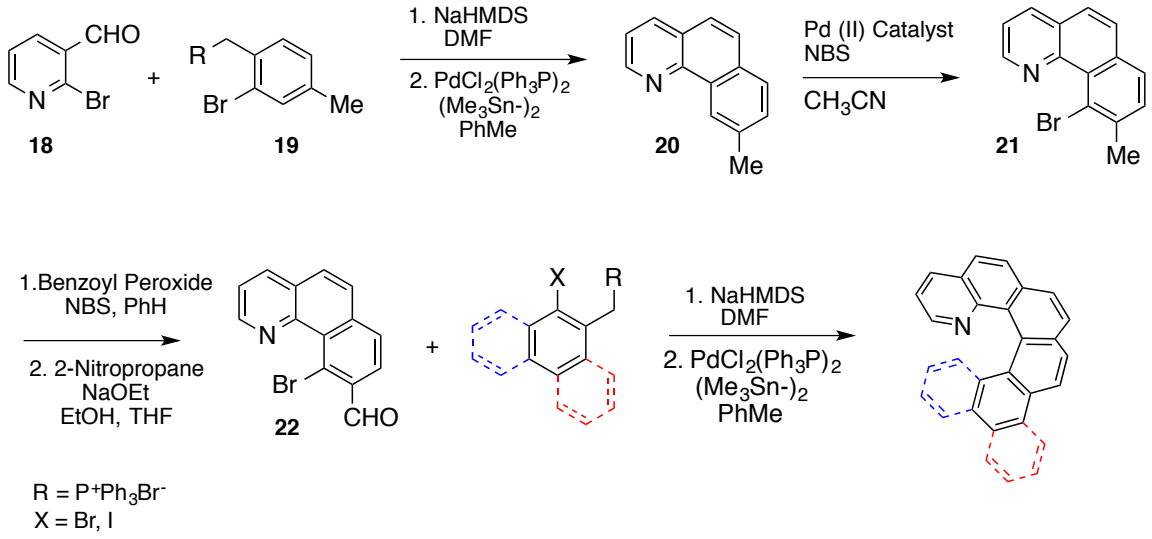
Scheme 1.7 Asymmetric Claisen rearrangement via guanidinium ions. Reported by Jacobsen (Reference 20).

Allyl vinyl ethers with electron-withdrawing substituents at the 2-position have a high degree of charge separation (highly dipolar) in transition state structures and are known to be stabilized by H-bond donors.[21,22,23] Computational studies provided support for transition state stabilization through H-bonding of both the ether and ester carbonyl-derived oxygen atoms.[24] Jacobsen then demonstrated asymmetric rearrangements with *O*-Allyl β-Ketoesters.[25] Again high yields and selectivities were observed with low catalytic activity as reaction times ranged from 2 – 6 days.

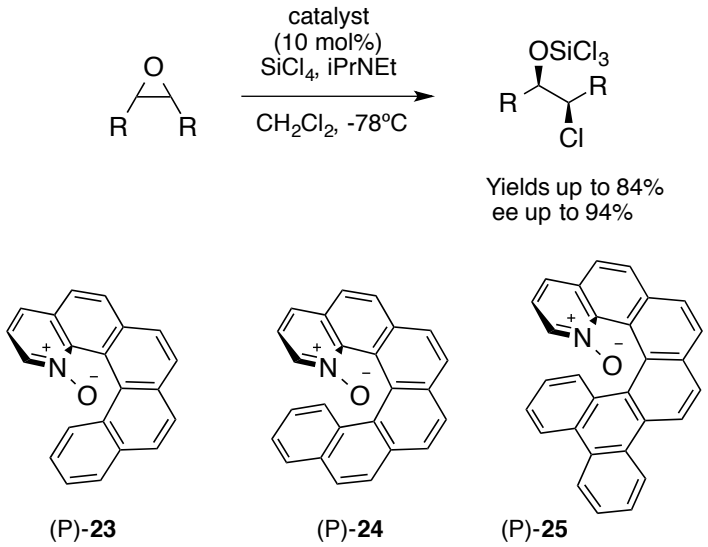
1.3 Helical chiral hydrogen-bond donors

Numerous pyridine-based catalysts possessing central,[26,27] axial,[28, 29] or planar,[30] chirality have been shown to be effective in asymmetric synthesis and catalysis. However, there were no instances in the literature of helical molecules as asymmetric catalysts prior to our initial report in 2008.[4] Helicenes are distinctly characterized by a

naturally twisted state, parallel to a curve through three-dimensional space. This unique topology is a source of inherent chirality thus making 1-azahelicenes a viable option for use as a catalytic scaffold. While there have been several methods and strategies to access helicenes since its first optically pure synthesis by Newman,[31] efficient synthetic routes allowing for structural variation remains a challenge. As such Takenaka and coworkers designed a modular synthetic route to access 1-azahelicenes and demonstrated the use of helical chiral pyridine *N*-oxides as asymmetric catalysts in the ring opening of *meso* epoxides.[4]

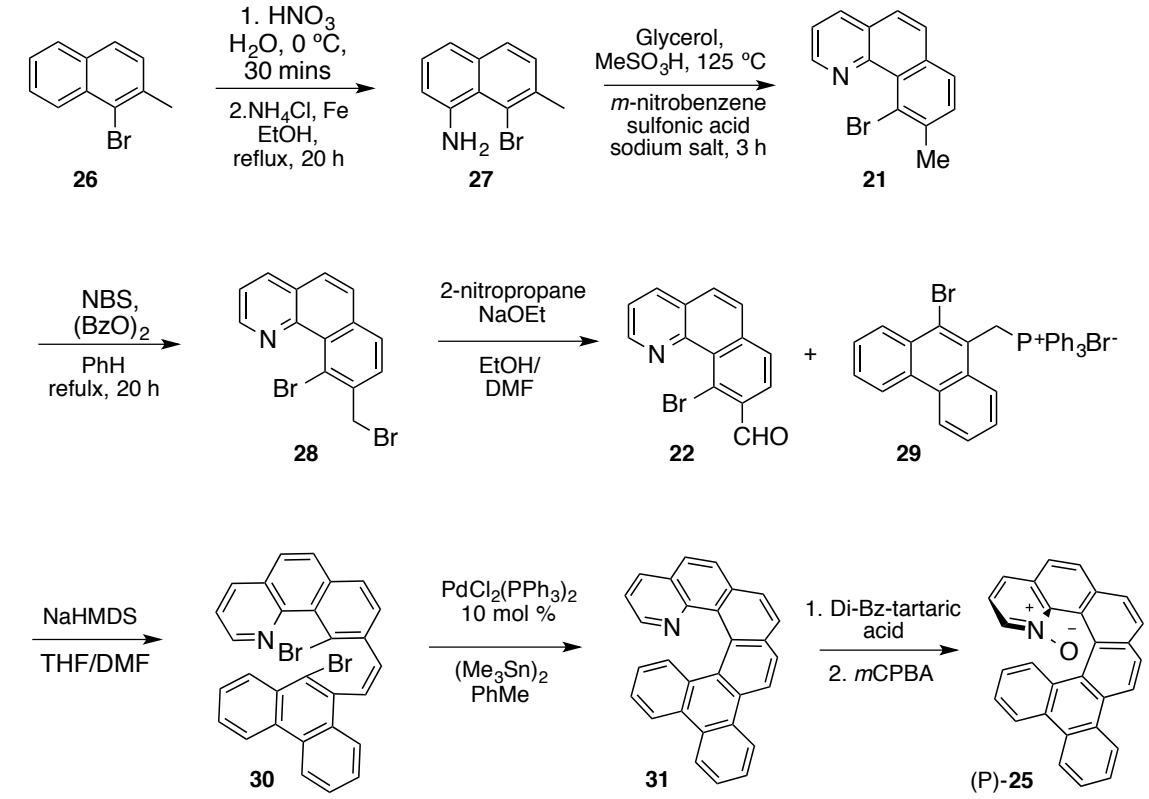


Scheme 1.8 First generation synthesis of 1-azahelicenes. Reported by Takenaka (Reference 4).



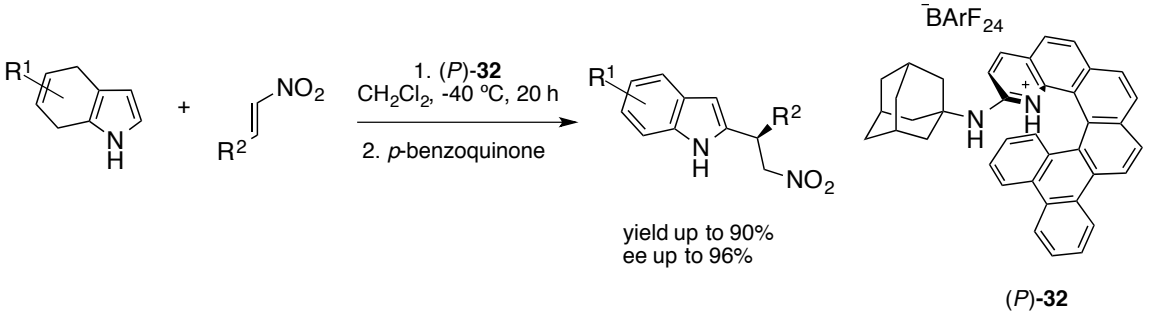
Scheme 1.9 Asymmetric ring opening of *meso* epoxides via helical chiral pyridine *N*-oxides. Reported by Takenaka (Reference 4).

We then modified our azahelicene preparation to address some limitations of the original synthesis. The benzoquinoline unit was prepared without the use of cross coupling reagents and can typically be synthesized in quantities of about five grams and stored without degradation. It can then be coupled with readily available screen units followed by tartaric acid resolution and oxidation to provide enantiopure *N*-oxides.



Scheme 1.10 Second generation synthesis of 1-azahelicenes. 11,12-Benzo-1-aza[6]helicene shown as a representative example. Reported by Takenaka (Reference 32).

In light of our interest in dual H-bond donors, we derived helicene-based catalysts with this bonding motif. We were able to synthesize helical chiral 2-aminopyridinium ions through amination of 1-azahelicene *N*-oxides. These double hydrogen-bond donors were demonstrated to be excellent catalysts in the addition of dihydroindoles to nitroalkenes.[32]



Scheme 1.11 Addition of dihydoindoles to nitroalkenes via helical chiral H-bond donors. Reported by Takenaka (Reference 32).

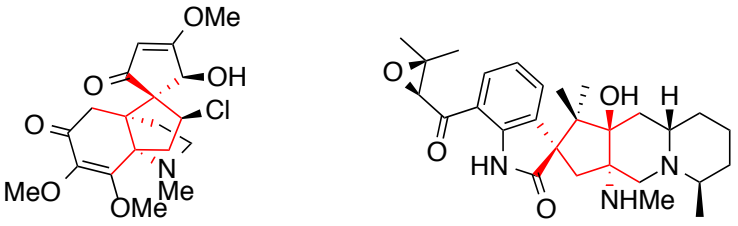
As a result, we recognized the potential for continued development of these 1-azahelicenes and there use as double H-bond donor catalysts in a variety of transformations.

CHAPTER 2

Enantio- and Periselective Catalysis of the Nitroalkene Diels – Alder Reaction

The Diels-Alder reaction is one of the most studied transformations in organic chemistry. First reported by Kurt Alder and Otto Diels in 1928, it enables the formation of carbon-carbon (C – C) bonds between a diene and dienophile making it a powerful and indispensable tool for chemists.[1] This [4 + 2] cycloaddition can provide access to functionalized cyclohexenes with up to four new stereogenic centers in a single step, making it a highly useful transformation in the synthesis of various natural products.[33,34] Efforts to carry out the Diels-Alder reaction in a catalytic and selective fashion have been extensively studied with early strategies focusing on metal-centered Lewis acids. Through asymmetric LUMO-lowering catalysis, via activation of the dienophile, Lewis acids have certainly proven to be powerful catalysts but the drawback is that the substrate scopes are generally limited to carbonyl-based dienophiles.[35,36,37] In addition, recent studies in organocatalysis have shown it to be a complimentary method to achieving acceleration of reaction rates with high levels of selectivity but with similar substrate scope limitations of Lewis acids. However, the asymmetric Diels – Alder reaction via catalytic activation of nitroalkenes had been nonexistent due to the reverse periselectivity observed with Lewis acids leading to undesired products.

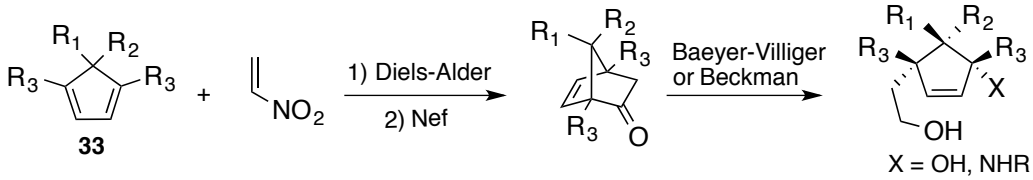
We became interested in the study of the nitroalkene Diels – Alder reaction due to the presence of highly functionalized cyclopentane core found in Acutumine and Citrinadin B, complex natural products with medicinal value.[38,39,40,41]



Acutumine Citrinadin B

Figure 2.1 Natural products containing cyclopentane core

An enantioselective nitroalkene Diels – Alder reaction would be the first step in our strategy to provide access to cyclopentenes with multiple contiguous quaternary stereocenters (Scheme 2.1). The Diels – Alder reaction of nitroethylene and cyclopentadienes followed by a ring opening has been demonstrated and thus is a proven strategy for the synthesis of highly substituted cyclopentenes.[42,43]



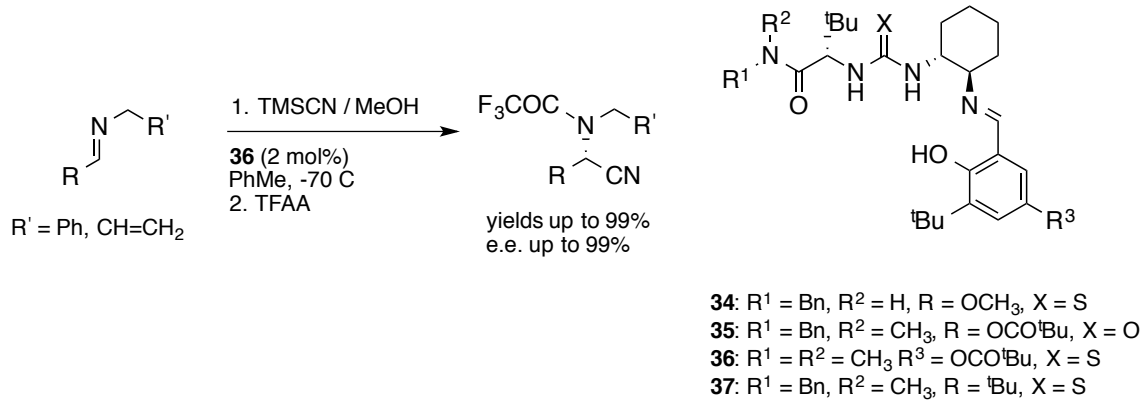
Scheme 2.1 Proven strategy for the synthesis of cyclopentenes

2.1 Background

2.1.1 Small molecule hydrogen-bond donors

Enantioselective synthesis via the use of small-molecule chiral hydrogen-bond (H-bond) donors has been a consistently developing area in the field of asymmetric catalysis.[44] Urea and Thiourea compounds containing chiral elements have emerged as prominent catalysts for a variety of synthetic transformations.[45] The key element is the ability of (Thio)ureas to act as a double H-bond donor.[46] The simultaneous donation of two hydrogen bonds results in increased strength and directionality in comparison to a single hydrogen bond, enhancing the effect of the catalyst.

Jacobsen demonstrated in 1998 that Schiff bases were effective catalysts in the asymmetric Strecker reaction for imine substrates.[47] This was the first instance where chiral ureas and thioureas illustrated the capability of facilitating highly enantioselective transformations (Scheme 2.2).

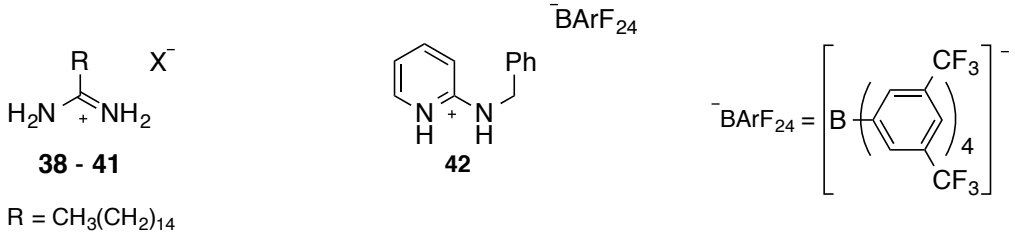


Scheme 2.2 Enantioselective Strecker reaction catalyzed by urea & thiourea Schiff bases. Reported by Jacobsen (Reference 47).

Studies of the mechanism for the activation of the imines and results were consistent with a double H-bond between the acidic NH protons of the catalyst and the imine lone pair, activating the electrophile towards attack by cyanide. Since then (thio)ureas have been utilized as catalysts inducing high levels of enantioselectivity for a variety of transformations.[48,49,50]

2.1.2 Amindinium ions as hydrogen-bond donor catalysts

In 2000 Göbel demonstrated the acceleration of the Diels – Alder reaction with amidinium ions.[51] His results revealed significant reaction rate enhancement with the use of double H-bond donor catalysts. These catalysts derived from palmitic acid (Figure 2.2, **28**) were observed to be up to 100 times faster that the background reaction i.e. without catalyst.

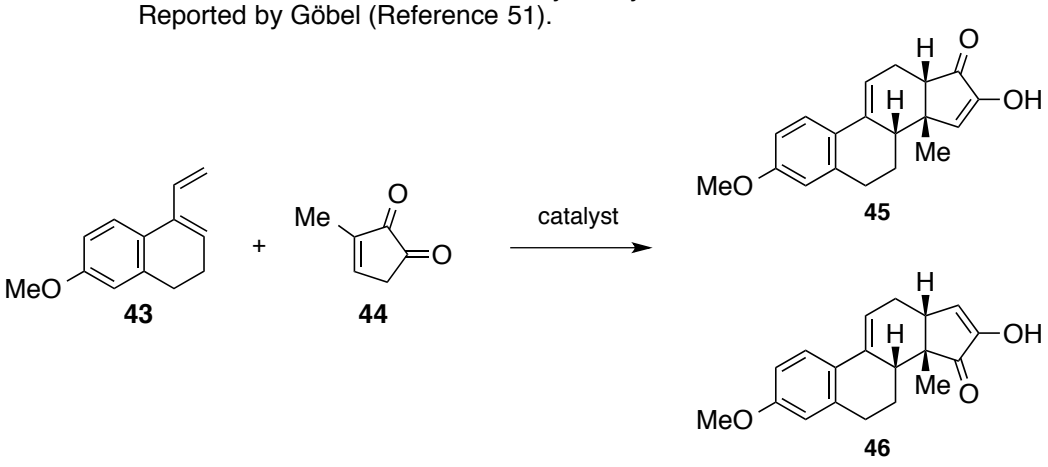


38: X^- = tetrafluoroborate
39: X^- = tetraphenylborate
40: X^- = tetrakis(4-chlorophenyl)borate
41: X^- = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($^-BArF_{24}$)

Figure 2.2 Amidinium ions. Reported by Göbel (Reference 51).

Interestingly, when they used 2-benzylaminopyridinium ions **42**, described by Göbel as a heterocyclic analogue, the reaction was up to 450 times faster than the background (Table 2.1). Also, different counter ions were tested and the non-coordinating tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($BArF_{24}^-$) anion proved essential for high catalytic activity. Other more coordinating counter ions showed poor solubility (**38**) or gave lower yields (**39** and **40**).

Table 2.1 Diels-Alder reaction catalyzed by amidinium ions. Reported by Göbel (Reference 51).



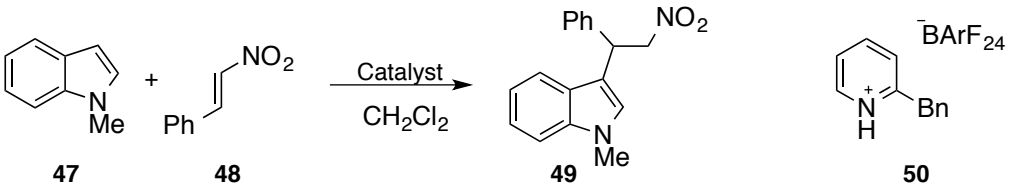
Catalyst (equiv)	Ratio *rac*-**45**:*rac*-**46**	Acceleration	Yield after 7d (%)
none	<0.1:1	1	<3
41(1)	2.6:1	100	82
42(0.25)	3.5:1	125	93
42(0.5)	3.3:1	300	~100
42(1)	3.3:1	450	~100

Subsequently, a chiral analogue of the amidinium catalyst was developed and modest levels of enantioselectivity were observed for the Diels – Alder reaction.[52,53]

2.1.3 2-Aminopyridinium ions activate nitroalkenes

In light of Göbel's studies, we became interested in the use of **42** as a H-bond donor catalyst.[54] In the conjugate addition of β-nitrostyrene to methylindole (Table 2.2), **42** was shown to have a higher reactivity than single H-bond donor 2-benzylpyridinium **50** even though it is less acidic. This indicated to us that the catalytic activity of 2-benzylaminopyridinium is not only reliant on its acidity but its ability to act as a double H-bond donor.

Table 2.2 Model reaction with different H-bond donors.
Reported by Takenaka (Reference 54).

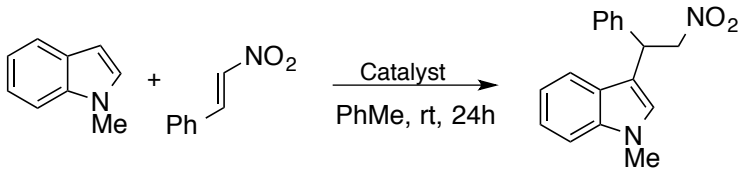


47 **48** **49** **50**

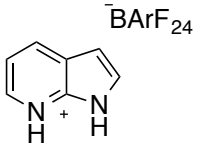
Entry	Cat (mol %)	temp (°C)	time (h)	yield w/ **42** (%)	yield w/ **50** (%)
1	1	0	24	99	75
2	1	-20	24	56	22
3	10	-50	72	51	trace

In turn, 7-azaindolium **51** was investigated as a catalyst to activate *β*-nitrostyrene in the Friedel-Crafts reaction. It was observed that the catalytic activity of 7-azaindolium surpassed that of 2-benzylaminopyridinium (Table 2.3) and we hypothesized that it could be due to a more favorable geometry of the double H-bonding and an increased acidity (pK_a 4.6).

Table 2.3 Friedel-Crafts reaction catalyzed by 2-aminopyridinium ions.
Reported by Takenaka (Reference 54)



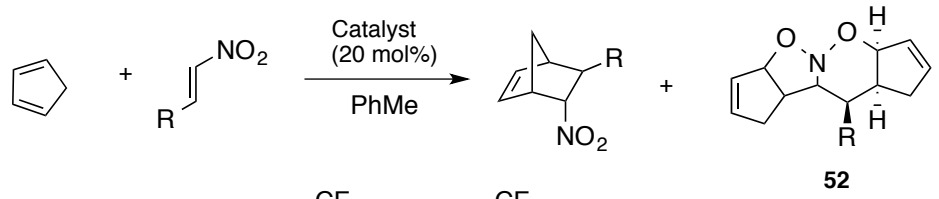
Entry	R	Catalyst	mol (%)	yield (%)
1	Ph	**42**	0.1	75
2	Ph	**42**	0.05	52
3	Ph	**51**	0.1	99
4	Ph	**51**	0.05	93
5	Me	**51**	0.5	97



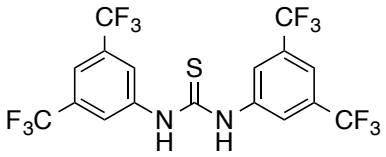
51

As a result, we investigated the use of achiral double H-bond donors as catalysts in the nitroalkene Diels – Alder reaction. Modest yields and high *endo:exo* ratios were observed with catalysts **42**, **51** and thiourea catalyst **53** (Table 2.4). While the product **52** was observed in trace amounts with **51** and less than 11% with **42**, the symmetric thiourea **53** only gave the desired cycloadduct.

Table 2.4 Nitroalkene Diels-Alder reaction catalyzed by double H-bond donors. Reported by Takenaka (Reference 54)



52



53

Entry	R	Catalyst	Temp (C)	time (h)	yield (%)	*endo*:*exo*	yield of **52** (%)
1	Ph	none	rt	8	9	7:1	0
2	Ph	**42**	rt	8	44	25:1	11
3	Ph	**53**	rt	8	42	25:1	0
4	Ph	**51**	rt	8	49	22:1	trace
5	Me	none	-10	36	7	25:1	0
6	Me	**42**	-10	36	30	> 30:1	2
7	Me	**53**	-10	36	24	> 30:1	0
8	Me	**51**	-10	36	37	> 30:1	trace

Based on the effects of Lewis acids, we believed that these double H-bond donors provide symmetrical bonding to both oxygen atoms of the nitroalkene (Figure 2.3) enabling it to act more as a 2π component of the Diels – Alder reaction and provides expected periselectivity.

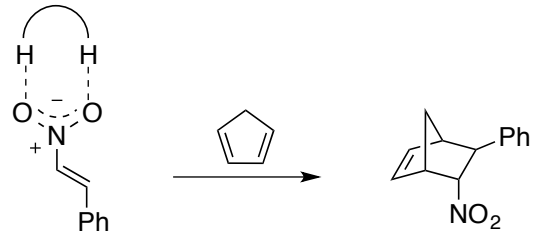


Figure 2.3 Symmetrical H-bonding provides desired cycloadduct

2.2 Development of helical double hydrogen-bond donors

Having demonstrated that 2-aminopyridinium ions can effectively activate nitroalkenes for different transformations, it seemed prudent to develop their chiral analogues. One of the challenges faced in designing these chiral variants is the difficulty in positioning the stereochemical elements (R*) near to the bonding site of the catalyst due to the directional nature of hydrogen bonds (Figure 2.4).

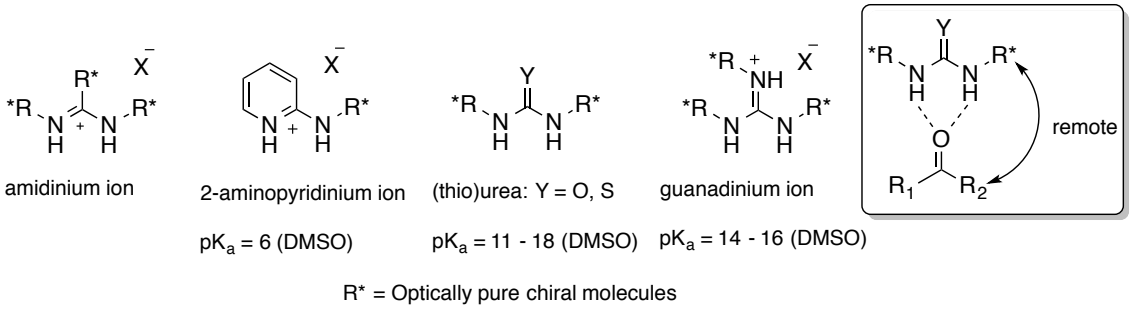


Figure 2.4 Dual hydrogen-bond donors

A common motif in most of the known double H-bond donor catalysts is the presence of additional complimentary functionalities constituting a bifunctional approach. These functionalities serve to activate and constrain the incoming nucleophile to an orientation necessary for asymmetric induction as demonstrated by Ricci in the enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes (Figure 2.5 A).[55] However, for the cyclopentadiene substrates of our interest, this additional functionality

would be ineffective (Figure 2.5 B). This underlines the need for H-bond donor catalysts that are not dependent on additional complimentary functionalities.

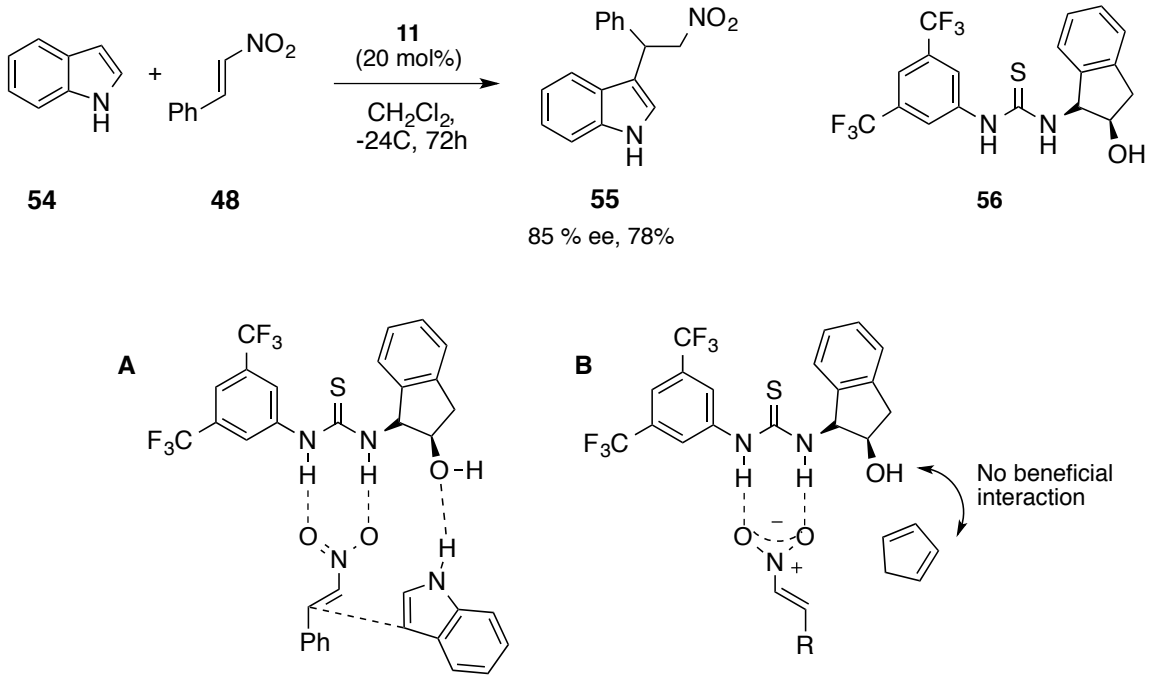


Figure 2.5 Complimentary functionality of bifunctional catalysts.
Reported by Ricci (Reference 55).

Our approach consisted of merging the 2-aminopyridinium core into the inherently chiral helicene framework (Figure 2.6). With this concept, our group successfully demonstrated the efficiency of these helical chiral double H-bond donor catalysts in the Friedel-Crafts reaction (Figure 2.7).[32]

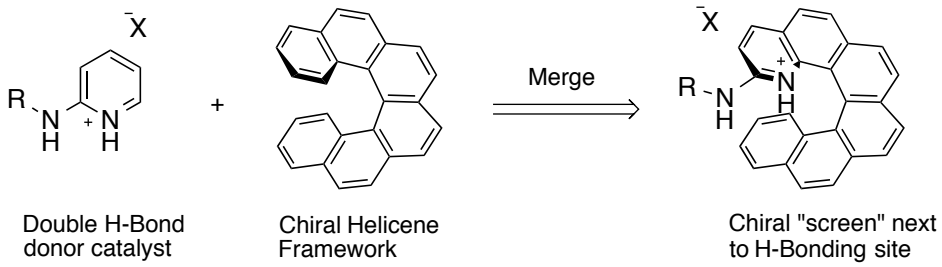


Figure 2.6 Approach for helical chiral double H-bond donors

On analysis of the crystal structure of the adamantyl catalyst **32**, two H-bonds to a chloride anion were observed. The space beneath these H-bonds are blocked or "screened" by the chiral helicene framework.

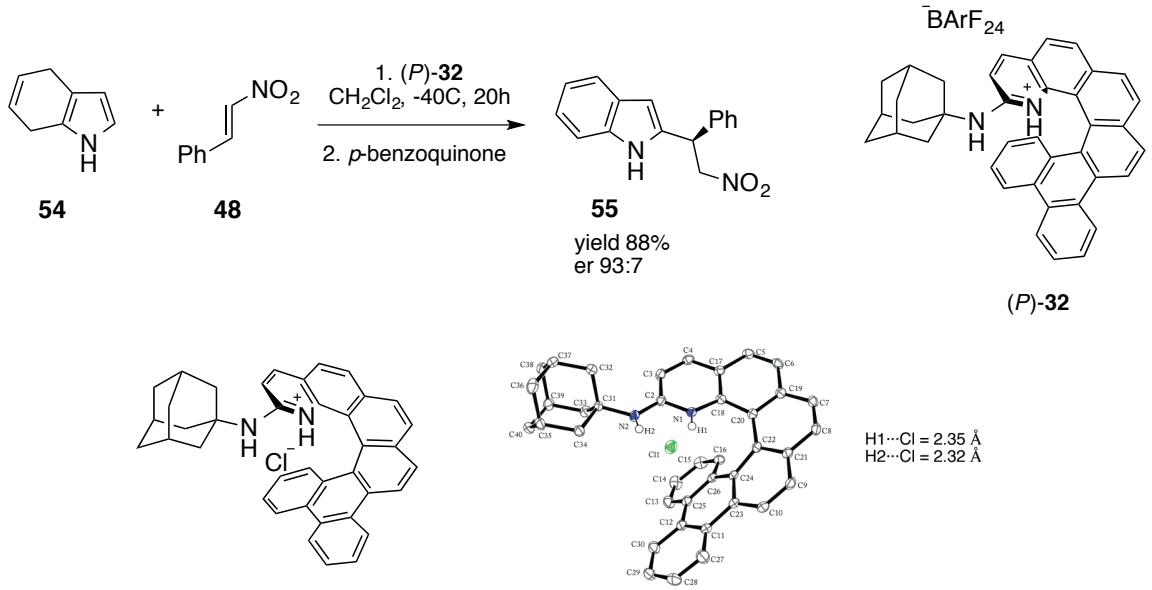


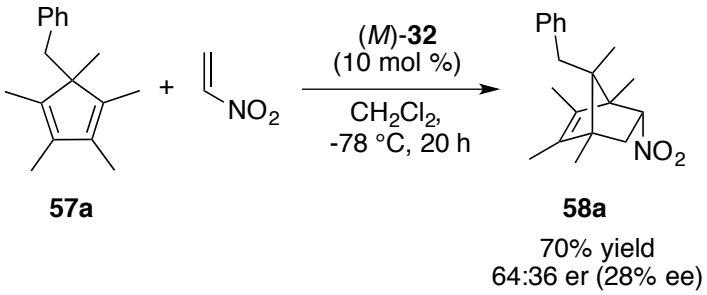
Figure 2.7 ORTEP of 2-(1-adamantylamino)-1-azahelicene·HCl. Reported by Takenaka (Reference 31)

Thus, a well-differentiated chiral environment is established and should be effective for transformations that require enantioselection.

2.3 Perspective

As previously mentioned, most known dual hydrogen bond donor catalysts are associated with additional complimentary functionalities that are a necessity for asymmetric induction. Our cyclopentadiene substrates of interest render this bifunctional approach inapplicable and so required the development of new catalyst systems. Consequently, in light of our interest in helicene-based catalysts, we developed double hydrogen donor catalysts based on the 1-azahelicene scaffold that are not reliant on complimentary functionalities. Based on our previous work of the addition reaction of pyrroles to nitroalkenes in which catalyst **32** was optimum, which led us to hypothesize

that **32** would be capable of asymmetric LUMO-lowering catalysis of the nitroalkene Diels-Alder reaction. We observed that the catalyst was indeed successful and provided on the desired cycloadduct with no hetero Diels – Alder product. In an ^{1}H NMR analysis of the crude reaction mixture, only the endo isomer was detected.[56]



Scheme 2.3 Enantioselective nitroalkene Diels-Alder reaction

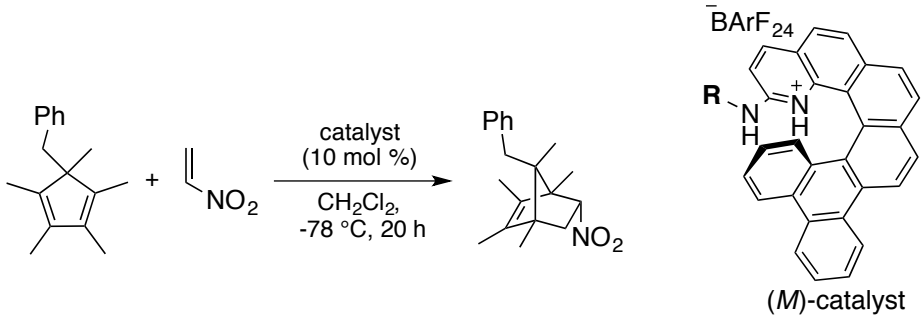
It was also observed in our previous study, that a change the size of the R group, which is designed to extend the catalysts' helical framework, can effectively tune the enantioselectivity of the catalyst.

In this chapter we describe the evaluation of several 1-azahelicene based catalysts containing a double hydrogen bonding motif, with different R substitutions and their effects on the enantioselectivity on the nitroalkene Diels – Alder reaction. A short screening of dienes was done to provide an idea of the scope of this protocol. Subsequently, a larger evaluation of the substrate scope was carried out to illustrate the effect of range of the dienes compatible with our catalyst system.

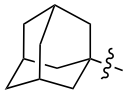
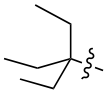
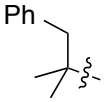
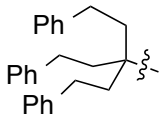
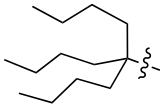
2.4 Results and discussion

2.4.1 Evaluation of catalysts

Table 2.5 Evaluation of catalysts for nitroalkene Diels-Alder reaction[a]



(*M*)-catalyst

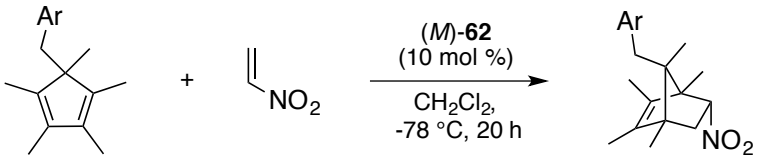
Entry	Catalyst	**R**	Yield[b] (%)	er[c]
1	—	—	< 5	—
2	**32**		70	64:36
3[d]	**59**		84	38:62
4	**60**		70	59.5:40.5
5	**61**		70	67:33
6	**62**		77	70:30

[a] Reaction conditions: 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 chiral HPLC analysis. [d] (*P*)-catalyst was used.

Several catalysts containing different R groups were evaluated with the model cyclopentadiene[57] substrate and it was found that the resulting enantioselectivity was also sensitive the structure of the R substitution. The catalysts **32**, **60 - 62** all show good yields

ranging from 70% – 77%, with catalyst **59** showing a slightly better yield of 84%. Interestingly, catalyst **60** in which its R group is not evenly substituted, gave distinctly lower enantioselectivity. Based on the results (Table 2.5) catalyst **62** seemed optimum and was chosen to fulfill a small screen of 5-substituted pentamethylcyclopentadienes (Table 2.6).

Table 2.6 Nitroalkene Diels-Alder reaction with halogenated dienes[a,b]



57a - d **58a - d**

Entry	Ar	Yield[c] (%)	er[d]
1[e]	Ph	77	30:70
2	4-F-Ph	80	65:35
3	4-Cl-Ph	38	66:34
4[f]	4-Cl-Ph	80	64:36
5	3-Cl-Ph	67	69:31

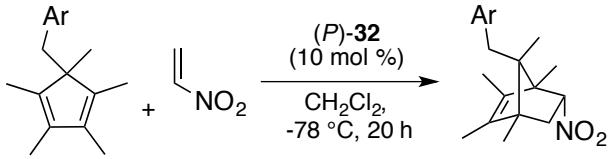
[a] Reaction conditions: diene (0.4mmol) and nitroethylene (0.2 mmol) in the presence of 10 mol% of catalyst in CH_2Cl_2 (0.7 mL). [b] The absolute stereochemistry of the 4-Cl sustituted product (entries 3 and 4) was established by X-ray analysis. The rest were assigned by analogy. [c] Yield of isolated products. [d] Determined by chiral HPLC analysis. [e] (*P*)-**62** catalyst was used. [f] (*M*)-**32** was used.

It was observed that these halogen-substituted dienes were tolerated well in comparison with the model substrate. However, the reason for the low yield of the 4-Cl-substituted diene **57c** (entry 3) was not immediately apparent to us. We hypothesized that there might be steric repulsion occurring between the 4-Cl-substitution and the catalyst in the transition state. Therefore, we tested a sterically less demanding catalyst **32** with this

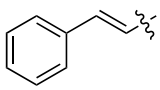
diene and were pleased to find that it gave the corresponding product in high yield and also gave comparative enantioselectivity to the other entries.

2.4.2 Expansion of diene substrate scope

Table 2.7 Nitroalkene Diels-Alder reaction with different dienes[a]



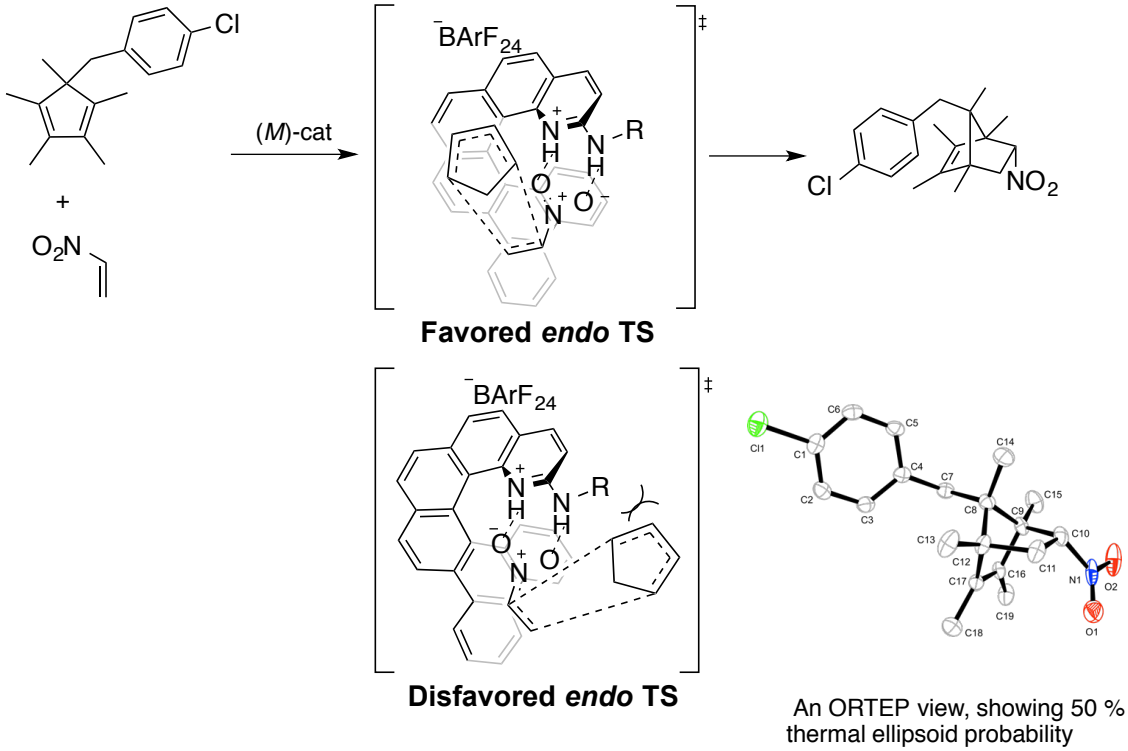
57e - n **58e - n**

Entry	Diene	Ar	Yield[b] (%)	er[c]
1	**57e**	2-Cl-Ph	55	32:68
2	**57f**	2-I-Ph	65	40:60
3	**57g**	4-Me-Ph	85	35:65
4	**57h**	4-CF_3-Ph	75	36:64
5	**57i**	4-*tert*-Butyl-Ph	80	30:70
6	**57j**	2-naphthyl	83	31:69
7	**57k**	3-OMe-Ph	80	34:66
8	**57l**	4-SMe-Ph	89	33:67
9[d]	**57m**	4-NO_2-Ph	0	–
10	**57n**		79	37:63

[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. [d] Unreacted diene **57m** was recovered (> 90%).

Subsequently, in our expansion of the substrate scope, we chose catalyst **32** based on its less sterically demanding nature as previously mentioned.[58] The 2-Cl-substituted diene and the 2-I-substituted counterpart were also tolerated well by catalyst **32** (Table 2.7, entries 1 and 2). Since we observed a beneficial effect of **32** with the 4-Cl-substituted diene (entries 3 and 4), we investigated how the size of a 4-substituent would affect its overall reactivity and selectivity. The 4-Me-substituted diene gave a good yield and

moderate selectivity (entry 3). Even the sterically demanding 4-CF_3-, 4-tBu-substituted and 2-naphthylated dienes were tolerated well by catalyst **32** (entries 4-6). We were also interested in testing dienes bearing heteroatoms that can function as a hydrogen bond acceptor because such dienes can potentially compete with a dienophile (nitroethylene) for the catalyst's binding site. We found that the dienes substituted with either O or S atoms were well tolerated by catalyst **32** (entries 7 and 8). 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 H-bonding site of the catalyst (entry 9). We were pleased to see the π-facial selectivity of the styrene-substituted diene was also excellent in this reaction albeit its decreased steric bias (entry 10). Only one diastereomer was detected by ^{1}H NMR analysis of the crude reaction mixture for all dienes.[59]

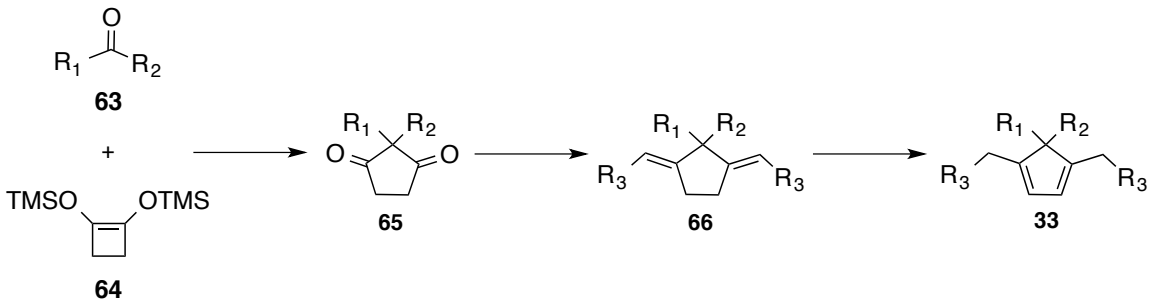


Scheme 2.4 Two endo TS models with (*M*)-catalyst. Non-substituted CP shown for clarity

Based on the sense of enantioselection observed in the above reactions and the X-ray structure of the HCl salt of catalyst **32**, we were able to propose the stereochemical models for the nitroalkene Diels-Alder reaction (Scheme 2.4). The backside of a bound nitroalkene is completely screened by the bottom half of the helicene framework. In the disfavored transition state (TS), the R group, which is designed to extend the top half of the helical framework, effectively hinders the approach of an incoming diene.

2.4.3 Synthesis of new dienes

Having established that the nitroalkene Diels – Alder reaction can be done both enantioselective and periselective via a double H-bond donor catalyst, we were aware that the synthetic utility of our diene substrates **57**, 5-substituted pentamethyl-cyclopentadienes, is limited. In keeping with our goal of accessing highly functionalized cyclopentenes, the use of our current dienes would be ineffectual. As such, the 1,4,5,5-tetrasubstituted cyclopentadienes **33** are required. To our knowledge, the Diels-Alder reaction of such dienes has never been reported.[60]

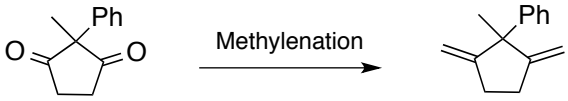


Scheme 2.5 A three step synthesis of 1,4,5,5-tetrasubstituted cyclopentadienes

Curran and coworkers have demonstrated the synthesis of 5,5-diallyl-1,4-dimethylcyclopenta-1,3-diene and we hypothesized that this protocol could be used to access our desired compounds (Scheme 2.5).[61] As such, my lab mate Zhili Peng carried out the synthesis of these 1,4,5,5-tetrasubstituted cyclopentadienes beginning with the

alkenation step (Table 2.8).[62,63] After no success in testing Wittig reaction to prepare the ylide, Zhili then followed the established literature procedures by Lombardo,[64,65] Curran[61] and Takai[66] with each giving poor results. However, he found success by using the procedure of Yan[67] and the product was obtained in adequate yield.

Table 2.8 Methylenation of diketones via different methods



65a **66a**

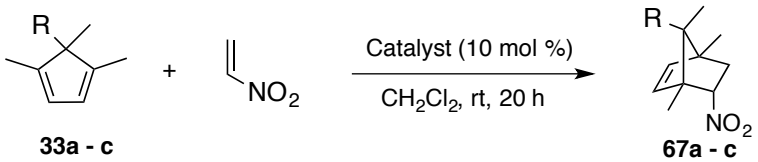
Entry	Protocols	Reagents	Yield[a] (%)
1	Wittig	$MeP^{+}Ph_3I^{-}$	0
2	Lombardo	CH_2Br_2-Zn-$TiCl_4$	7
3	Curran	CH_2Br_2-Zn-$TiCl_4$	13
4	Takai	CH_2I_2-Zn-$TiCl_4$	trace
5	Yan	CH_2Cl_2-Mg-$TiCl_4$-THF	50%[b]

[a] Yield of isolated product. [b] The reaction was not fully optimized.

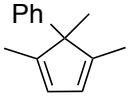
The diolefin **66a** was then isomerized to **33a** by HI in the following step. Resultantly, an efficient synthesis for the preparation of a new class of dienes **33** in three steps, starting from commercially available ketones and 1,2-bis(trimethylsilyloxy)cyclobutene **64** was developed.

2.4.4 Evaluation of new dienes

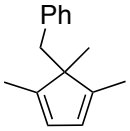
Table 2.9 Evaluation of new dienes



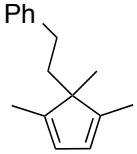
33a - c **67a - c**



33a



33b

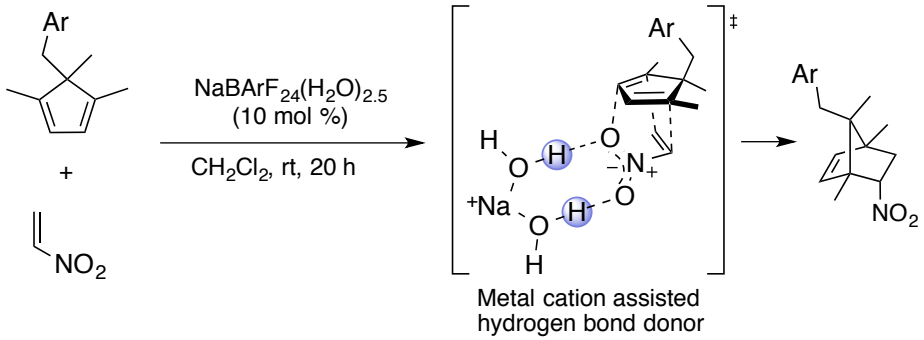


33c

Entry	Diene	Catalyst	Yield[a] (%)
1	**33a**	none	0
2	**33b**	none	25
3	**33b**	$NaBArF_{24}$•$2.5H_2O$	67[b]
4	**33c**	none	11
5	**33c**	(*P*)-**32**	14[c]
6	**33c**	$NaBArF_{24}$•$2.5H_2O$	42[b]

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

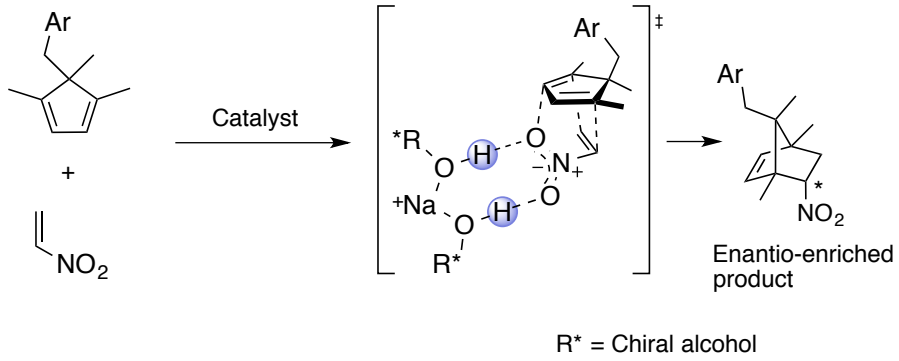
We did an evaluation of these new dienes and observed that they were quite unreactive to nitroethylene (Table 2.9, entries 1,2 and 4) under thermal conditions. Due to the structural similarity between these newly synthesized dienes and 5-substituted pentamethylcyclopentadienes, the observed difference in reactivity was surprising even though the extra alkyl substituents would raise the HOMO. The use of H-bond donor catalyst **32** did not effectively promote the reaction (entry 5) and no enantioselectivity was observed. In 2011, our group discovered 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.[68] As a result, $NaBArF_{24}\cdot 2.5H_2O$ catalyzed the reaction and provided the desired products in satisfactory yields (entries 3 and 6). We believe that the water molecules situated around the sodium cation would act as H-bond donors to sufficiently lower the LUMO of the nitroalkene and catalyze the reaction (Scheme 2.6).



Scheme 2.6 Catalysis of nitroalkene Diels-Alder reaction via $NaBArF_{24}(H_2O)_{2.5}$

2.5 Future studies

Having established that helical chiral H-bond donors can effectively promote the nitroalkene Diels – Alder reaction enantioselectively, we can turn our attention to continuing the synthesis of highly functionalized cyclopentenes. In light of the low reactivity of the 1,4,5,5-tetrasubstituted cyclopentadienes with nitroalkene and low catalytic activity observed with catalyst **32**, an alternative method to provide enantioselectivity is necessary. As such, we reported that the water molecules of the $NaBArF_{24}{\cdot}2.5H_2O$ can be partially replaced by phenol under reflux with toluene with Dean-Stark apparatus. We envision that via this method, a chiral alcohol can be used instead of phenol to replace the resident water molecules, creating a chiral analogue (Scheme 2.7). The catalysis should then occur in a chiral environment enabling the formation of an enantio-enriched product.



Scheme 2.7 Proposed catalysis of nitroalkene Diels-Alder reaction via chiral variant of $NaBArF_{24}(H_2O)_{2.5}$

2.6 Conclusion

We successfully demonstrated that the nitroalkene Diels-Alder reaction could be rendered enantio- and periselective by helical chiral hydrogen bond donor catalysts. To the best of our knowledge, this represents the first asymmetric catalytic nitroalkene Diels-Alder reaction by LUMO-lowering catalysis. We investigated the substrate scope of catalyst **25** using readily available 5-substituted pentamethylcyclopentadienes. Also, a three-step synthesis of a new class of synthetically useful cyclopentadienes was developed.

2.7 Experimental section

2.7.1 General information

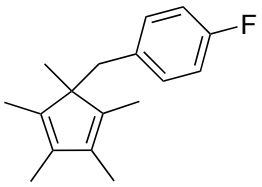
All reactions were carried out in the oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F_{254} 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 using silica gel 60 (mesh 230-400) supplied by Merck.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromenthane (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 the literature.[69] All new compounds synthesized in this chapter have been fully characterized. Known compounds that were been utilized have been cited accordingly.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 (300 MHz ^{1}H), a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), and a Bruker Avance 500 (500 MHz ^{1}H, 125 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, University of Miami.

2.7.2 General procedure for preparation of 5-substituted pentamethylcyclopentadienes

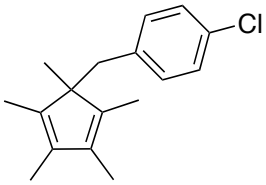
1-Fluoro-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57b)



To a solution of NaHMDS (1.10 g, 5.97 mmol) in THF (12 mL) cooled to 0 °C was added a solution of pentamethylcyclopentadiene (813 mg, 5.97 mmol) in THF (6 mL) drop-wise. The resulting mixture was stirred for 1 h at room temperature, cooled back to 0 °C, and then treated with a solution of 4-fluorobenzyl bromide (1.00 g, 5.37 mmol) in THF (6 mL). The reaction mixture was stirred for 20 h at room temperature, quenched with aqueous NH_4Cl solution (20 mL), and extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, at which time all volatiles, including unreacted pentamethylcyclopentadiene, were removed from the crude reaction mixture. The resulting oil was filtered through a short column of SiO_2 with hexanes, and concentrated in vacuo to afford the title compound as a colorless oil (1.22 g, 93%), which was used in the Diels-Alder reaction (vide infra) without further purification.

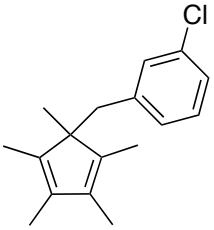
^{1}H NMR (400 MHz, $CDCl_3$) d 6.74 – 6.80 (m, 4H), 2.66 (s, 2H), 1.77 (s, 6H), 1.58 (s, 6H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 161.2 (d, J = 250.0 Hz) 138.9, 134.8, 134.2 (d, J = 3.0 Hz), 129.7 (d, J = 7.8 Hz), 113.6 (d, J = 20.6 Hz), 56.5, 40.7, 21.5, 10.7, 10.3; FTIR (neat) u_{max} 2916, 2854, 1603, 1509, 1447, 1378, 1220, 1157, 1098, 1016, 825, 766 cm^{-1}; GCMS: 244 $[M]^+$

1-Chloro-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57c)



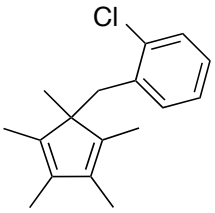
^{1}H NMR (400 MHz, $CDCl_3$) d 7.03 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 2.66 (s, 2H), 1.77 (s, 6H), 1.58 (s, 6H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 138.9, 137.1, 134.9, 131.1, 129.8, 127.1, 56.5, 40.8, 21.6, 10.8, 10.3; FTIR (neat) u_{max} 2917, 2855, 1492, 1445, 1406, 1378, 1265, 1087, 838, 781, 739 cm^{-1}; GCMS: 260 $[M]^+$

1-Chloro-3-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57d)



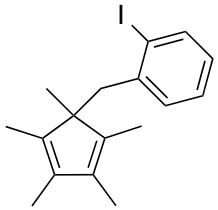
^{1}H NMR (400 MHz, $CDCl_3$) d 6.98 – 7.06 (m, 2H), 6.83 (s, 1H) 6.73 (d, *J* = 4.0 Hz, 1H), 2.67 (s, 2H), 1.78 (s, 6H), 1.61 (s, 6H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 140.6, 138.9, 135.1, 132.7, 128.5, 128.2, 126.7, 125.6, 56.5, 41.0, 21.6, 10.7, 10.3; FTIR (neat) u_{max} 2914, 2855, 1597, 1572, 1479, 1445, 1378, 1205, 1078, 859, 772 cm^{-1}; GCMS: 260 $[M]^+$

1-Chloro-2-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57e)



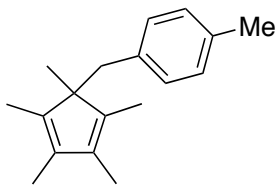
Obtained as colorless oil in 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 1.7, 7.7 Hz, 1H), 6.95-7.04 (m, 2H), 6.78 (dd, J = 1.7, 7.6 Hz, 1H), 2.92 (s, 2H), 1.73 (s, 12H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 137.0, 134.5, 134.0, 129.6, 128.9, 126.9, 126.1, 56.3, 36.2, 23.4, 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 (57f)



Obtained as a white solid in 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]$^{+}$

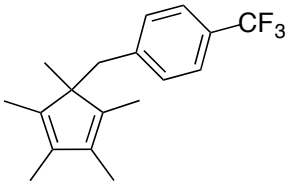
1-Methyl-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57g)



Obtained as a white solid in 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),

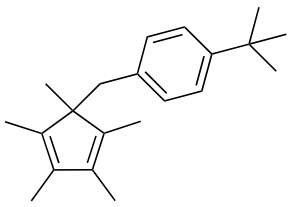
0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.8, 134.9, 134.5, 128.6, 128.0, 56.9, 41.3, 22.0, 21.1, 11.0, 10.5; FTIR (neat) υ_{max} 2968, 2914, 2857, 1657, 1515, 1442, 1378, 1110, 820, 782, 757 cm^{-1}; GCMS: 240 $[M]^+$

1-((1,2,3,4,5-Pentamethylcyclopenta-2,4-dienyl)methyl)-4-(trifluoromethyl)benzene (57h)



Obtained as a white solid in 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 $[M]^+$

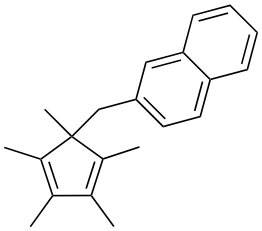
1-tert-Butyl-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57i)



Obtained as light yellow oil in 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,

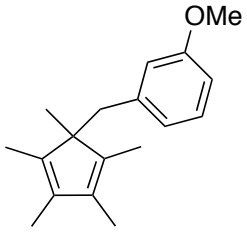
56.7, 41.1, 34.3, 31.4, 21.8, 10.9, 10.4; FTIR (neat) υ_{max} 2960, 2913, 2863, 1516, 1448, 1378, 1363, 1269, 1105, 1020, 834, 785 cm^{-1}; GCMS: 282 $[M]^+$

2-((1,2,3,4,5-Pentamethylcyclopenta-2,4-dienyl)methyl)naphthalene (57j)



Obtained as a white solid in 81% yield; ^1H 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$[M]^+$

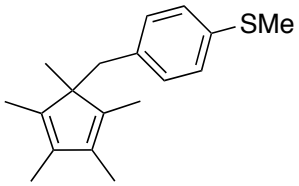
1-Methoxy-3-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57k)



Obtained as a white solid in 84% yield; ^1H 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

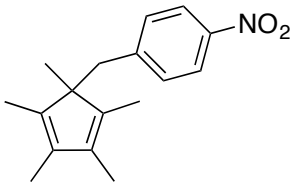
158.8, 140.5, 139.6, 134.6, 128.1, 121.4, 113.8, 111.5, 56.8, 55.1, 41.4, 22.2, 11.0, 10.5; FTIR (neat) υ_{max} 2959, 2915, 2858, 1600, 1584, 1490, 1447, 1378, 1291, 1261, 1153, 1048, 910, 776 cm^{-1}; GCMS: 256 $[M]^+$

Methyl(4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)phenyl)sulfane (57l)



Obtained as a light yellow solid in 87% yield; ^1H 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 $[M]^+$

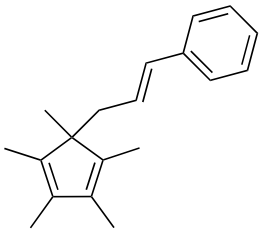
1-Nitro-4-((1,2,3,4,5-pentamethylcyclopenta-2,4-dienyl)methyl)benzene (57m)



Obtained as a bright yellow solid in 10% yield; ^1H 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 (57n)

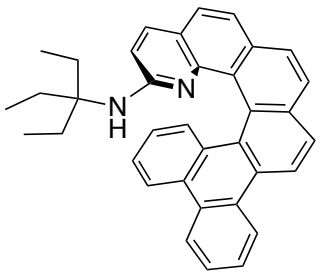


Obtained as colorless oil in 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14-7.28 (m, 5H), 6.30 (d, J = 15.8 Hz, 1H), 5.40-5.47 (m, 1H), 2.34 (dd, J = 1.4, 7.0 Hz, 2H), 1.79 (s, 6H), 1.76 (s, 6H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 138.4, 134.2, 129.9, 128.5, 128.1, 126.7, 126.0, 55.9, 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$[M]^+$

2.7.3 Preparation of 2-amino-1-aza[6]helicenes

All new 11,12-benzo-2-alkylamino-1-aza[6]helicenes were prepared according to the published procedure.[32]

(+)-(*P*)-11,12-Benzo-2-(3-ethylpentan-3-amino)-1-aza[6]helicene (59)

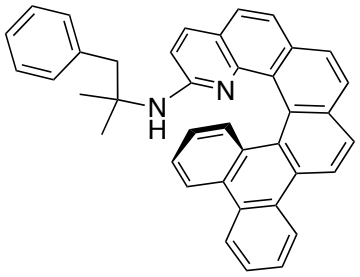


$[\alpha]^{20}_D$ = +2684, c = 0.0005, CH_2Cl_2. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.26 (m, 3H), 8.04 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.26 – 7.38 (m, 6H), 6.85 – 6.89 (m, 2H), 6.32 – 6.36 (m, 1H), 6.08 (d, J = 8.0 Hz, 1H), 0.89 – 1.02

(m, 6H), 0.14 (t, *J* = 8.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$)

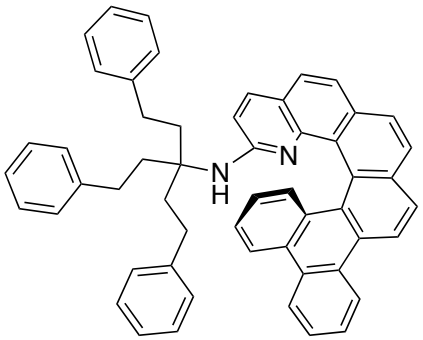
δ 155.0, 145.5, 136.9, 134.0, 133.1, 132.8, 130.63, 130.61, 130.5, 128.4, 127.8, 127.6, 127.1, 127.0, 126.9, 126.6, 126.4, 126.3, 126.2, 125.9, 125.0, 124.4, 124.2, 122.8, 122.79, 121.7, 121.4, 120.6, 107.8, 57.7, 28.0, 7.7; FTIR (neat) υ_{max} 2965, 2927, 1720, 1610, 1520, 1485, 1464, 1360, 1277, 1215, 1131, 837, 747 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{36}H_{33}N_2$ $[M + 1]^+$, expected: 493.2644, found: 493.2638

(-)-(*M*)-11,12-Benzo-2-(2-methyl-1-phenylpropan-2-amino)-1-aza[6]helicene (60)



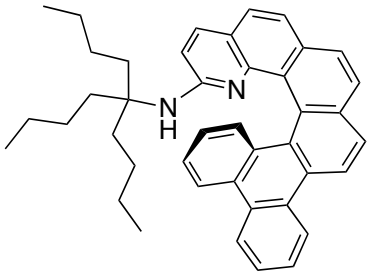
$[\alpha]^{20}_D$ = -2374, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.0, 8.0 Hz, 2H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.0 Hz), 8.01 – 8.04 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.76 (m 5H), 7.29 – 7.31 (m, 1H), 7.08 – 7.16 (m, 3H), 6.75 – 6.79 (m, 3H), 6.49 (d, *J* = 12.0 Hz, 1H), 3.86 (s, 1H), 2.63 (d, *J* = 12.0 Hz, 1H), 2.37 (d, *J* = 12.0 Hz, 1H), 0.98 (s, 3H), 0.88 (s, 3H);^{13}CNMR(100MHz,$CDCl_3$) 155.1, 145.6, 137.9, 136.5, 133.9, 132.9, 132.8, 130.7, 13 0.51, 130.46, 140.44, 128.5, 128.2, 127.7, 127.6, 127.4, 127.0, 126.9, 126.7, 126.5, 126.4, 126.3, 126.0, 125.8, 125.1, 124.6, 124.2, 122.8, 122.7, 122.1, 121.5, 120.7, 109.6, 53.1, 4 6.4, 28.1, 27.0; FTIR (neat) υ_{max} 2972, 1610, 1520, 1484, 1263, 839, 732, 700 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{39}H_{31}N_2$ $[M + 1]^+$, expected: 527.2487, found: 527.2482

(-)-(*M*)-11,12-Benzo-2-(3-phenethyl-1,5-diphenylpentan-3-amino)-1-aza[6]helicene (61)



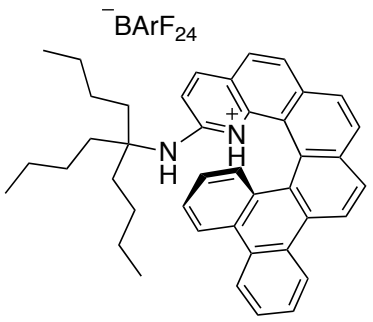
$[\alpha]^{20}_{D}$ = -1780, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.17 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.20 (m, 9H), 6.53 – 6.97 (m, 15H), 6.27 – 6.29 (m, 2H) 6.11 (d, *J* = 8.0 Hz, 1H), 1.78 – 1.98 (m, 6H), 1.23 – 1.37 (m, 6H); ^{13}C NMR (100MHz, $CDCl_3$) 154.4, 145.5, 142.0, 137.3, 134.1, 132.9, 130.7, 130.5, 130.4, 130.1, 128.6, 128.4 , 128.3, 127.7, 127.2, 127.1, 127.0, 126.99, 126.8, 126.5, 126.43, 126.39, 126.1, 125.85, 1 25.3, 124.3 122.9, 122.8, 122.3, 121.6, 120.9, 107.6, 57.2, 38.8, 30.0 (two signals overlap to give one); FTIR (neat) υ_{max} 2932, 1608, 1519, 1454, 1379, 1264, 841, 733, 699 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{54}H_{45}N_2$ $[M + 1]^+$, expected: 721.3583, found: 721.3577

(-)-(*M*)-11,12-Benzo-2-(5-butylnonan-5-amino)-1-aza[6]helicene (62)



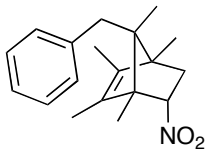
$[\alpha]^{20}_D$ = - 2082, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.67 (m, 3H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.66 – 8.01 (m, 7H), 7.26 – 7.32 (m, 3H), 6.74 – 6.77 (m, 1H), 6.49 (d, *J* = 12.0 Hz, 1H), 0.77 – 1.35(m,27H);^{13}CNMR(100MHz,$CDCl_3$) 154.8, 145.4, 136.8, 134.0, 133.4, 132.8, 130.8, 130.6, 130.5, 128.3, 127.7, 127.5, 127.13, 127.1, 126.9, 126.6, 126.43 126.36, 126.3, 126. 0, 125.1, 124.4, 124.3, 122.8, 122.7, 121.6, 121.3, 120.6, 107.4, 56.9, 36.6, 25.2, 23.0, 13. 9; FTIR (neat) υ_{max} 3400, 2930, 2861, 1609, 1584, 1519, 1485, 1465, 1356, 1263, 1144, 837, 751, 723 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{42}H_{45}N_2$ $[M + 1]^+$, expected: 577.3583, found: 577.3577

2.7.4 General procedure for asymmetric nitroalkene Diels-Alder reaction



To a solution of **62** (72 mg, 0.12 mmol) in CH_2Cl_2 (2.4 mL) was added Et_2O solution of HCl (1M, 0.14 mL) drop-wise at room temperature. The reaction mixture was stirred for 30 min. and then concentrated *in vacuo*. The resulting solid was redissolved in CH_2Cl_2 (2.0 mL), and then concentrated *in vacuo*, the process of which was repeated three times. To the resulting yellow solid were added CH_2Cl_2 (2.6 mL), and $NaBArF_{24}\cdot 2.6H_2O$ (109 mg, 0.12 mmol) at room temperature. The resulting mixture was stirred for 30 min., filtered through a short pad of Celite, concentrated *in vacuo*, and then used in the Diels-Alder reaction without purification.

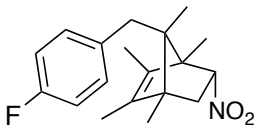
(-)-7-Benzyl-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58a)



A flame-dried test tube was charged with the catalyst (28 mg, 0.02 mmol) and 4 Å molecular sieves (28 mg). To this were added CH_2Cl_2 (0.3 mL) and a solution of nitroethylene[69] (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 (91 mg, 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 (20% benzene in hexanes) to afford the title compound as colorless oil (46 mg, 77%) with 70:30 er. The ligand **5** was recovered by eluting the column with 100% EtOAc (67 mg, 93%), and reused without loss in activity and selectivity.

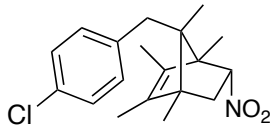
Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (major) = 40.72 min., t_r (minor) = 46.79 min. $[\alpha]^{20}_D$ = -40, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.29 (m, 4H), 7.05 – 7.07 (m, 1H), 4.69 – 4.71 (m, 1H), 2.58 (d, *J* = 12.0 Hz, 1H), 2.49 (d, *J* = 12.0 Hz, 1H), 1.87 – 1.89 (m, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.12 (s, 3H), 0.89 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.1, 131.2, 130.6, 127.8, 125.9, 91.6, 64.0, 63.6, 55.0, 39.2, 37.5, 15.4, 12.4, 11.2, 10.7, 10.1; FTIR (neat) υ_{max} 2943, 1541, 1448, 1382, 1362, 908, 729 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{26}NO_2$ $[M + 1]^+$, expected: 300.1964, found: 300.1958.

(+)-7-(4-Fluorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58b)



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 (minor) = 35.07 min., t_r (major) = 40.37 min. $[\alpha]^{20}_D$ = +32, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 7.02 (m, 2H), 6.89 – 6.94 (m, 2H), 4.70 (dd, *J* = 5.2, 6.4 Hz, 1H), 2.57 (d, *J* = 12.0 Hz, 1H), 2.45 (d, *J* = 12.0 Hz, 1H), 1.88 – 1.90 (m, 2H), 1.69 (s, 3H), 1.47 (s, 3H), 1.12 (s, 3H), 0.87 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, *J* = 243.0 Hz), 139.0, 134.95 (d, *J* = 3.6 Hz), 131.8 (d, *J* = 7.9 Hz), 131.2, 114.6 (d, *J* = 20.6 Hz), 91.5, 63.49, 63.47, 56.0, 38.3, 37.5, 15.3, 12.4, 11.2, 10.7, 10.1;FTIR (neat) υ_{max} 2944, 1541, 1508, 1448, 1383, 1222, 908, 828, 729 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{25}FNO_2$ $[M + 1]^+$, expected: 318.1869, found: 318.1864.

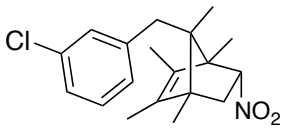
(+)-7-(4-Chlorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58c)



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 (minor) = 44.85 min., t_r (major) = 55.91 min. $[\alpha]^{20}_D$ = +40, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.21 (m, 2H), 6.98 – 7.01 (m, 2H), 4.70 (dd, *J* = 5.2, 6.4 Hz, 1H), 2.57 (d, *J* = 12.0 Hz, 1H), 2.46 (d, *J* = 12.0 Hz, 1H), 1.89 – 1.91 (m, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.14 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

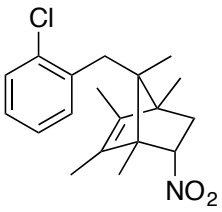
δ 139.0, 137.9, 131.82, 131.8, 131.3, 127.9, 91.4, 64.0, 63.5, 56.0, 38.5, 37.4 15.4, 12.4, 1 1.2, 10.8, 10.1 FTIR (neat) υ_{max} 2942, 1540, 1490, 1447, 1382, 1362, 1091, 1015, 810, 732 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{25}ClNO_2$ $[M + 1]^+$, expected: 334.1574, found: 334.1568.

(+)-7-(3-Chlorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58d)



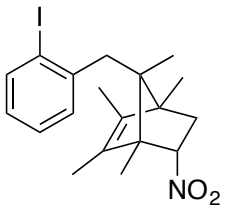
Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (minor) = 57.59 min., t_r (major) = 65.56 min. $[\alpha]^{20}{}_D$ = +28, c = 0.0005, CH_2Cl_2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.21 (m, 2H), 6.98 – 7.01 (m, 2H), 4.70 (dd, *J* = 5.2, 6.4 Hz, 1H), 2.57 (d, *J* = 12.0 Hz, 1H), 2.46 (d, *J* = 12.0 Hz, 1H), 1.89 – 1.91 (m, 2H), 1.69 (s, 3H), 1.48 (s, 3H), 1.14 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.1, 133.6, 131.3, 130.5, 129.0, 128.7, 126.1, 91.4, 63.9, 63.6, 56.0, 39.0, 37.4, 15.5, 12.4, 11.2, 10.7, 10.1 FTIR (neat) υ_{max} 2940, 1596, 1540, 1443, 1382, 1362, 1322, 875, 785 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{25}ClNO_2$ $[M + 1]^+$, expected: 334.1574, found: 334.1587

(1S, 4S, 5S, 7R)-(-)-7-(2-Chlorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58e)



Obtained as a colorless oil in 55% yield with er 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. $[\alpha]^{20}_D$ = - 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, $CDCl_3$) δ 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.

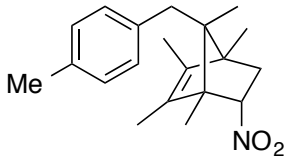
(1S, 4S, 5S, 7R)-(-)-7-(2-Iodobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58f)



Obtained as a colorless oil in 65% yield with er of 60:40. Enantiomeric ratio was determined by converting **10e** into **3** *via* halogen-lithium exchange reaction followed by aqueous work-up, using 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. $[\alpha]^{20}_D$ = - 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,

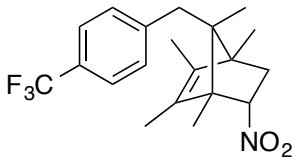
3H), 0.93 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.6, 139.6, 131.9, 131.8, 128.3, 127.9, 103.6, 92.0, 65.0, 64.7, 57.1, 42.3, 37.7, 16.4, 13.5, 12.1, 12.0, 11.0; FTIR (neat) υ_{max} 2943, 1540, 1449, 1382, 1361, 1009, 733, 753 cm^{1}; HRMS (ESI-TOF): Exact mass calcd for $C_{19}H_{24}INNaO_2$ $[M + Na]^+$, expected: 448.0749, found: 448.0760.

(1S, 4S, 5S, 7R)-(-)-1,2,3,4,7-Pentamethyl-7-(4-methylbenzyl)-5-nitrobicyclo[2.2.1]hept-2-ene (58g)



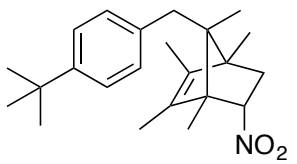
Obtained as a colorless oil in 85% yield with er of 65:35. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (major) = 29.73 min., t_r (minor) = 33.85 min. $[\alpha]^{20}_D$ = - 52, c = 0.0005, CH_2Cl_2. ^{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, $CDCl_3$) δ 139.3, 136.3, 135.6, 131.3, 130.7, 128.7, 96.7, 91.8, 64.3, 63.8, 56.2, 21.1, 15.5, 12.6, 11.4, 11.0, 10.3; FTIR (neat) 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.

(1S, 4S, 5S, 7R)-(-)-1,2,3,4,7-Pentamethyl-5-nitro-7-(4-(trifluoromethyl)benzyl)bicyclo[2.2.1]hept-2-ene (58h)



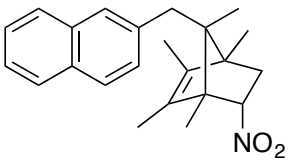
Obtained as a colorless oil in 75% yield with er of 64:36. Enantiomeric ratio was determined by HPLC with a Chiralcel OD-H column equipped with an OD-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (major) = 31.85 min., t_r (minor) = 38.25 min. $[\alpha]^{20}_D$ = - 22, c = 0.0005, CH_2Cl_2. ^{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.

(1S, 4S, 5S, 7R)-(-)-7-(4-tert-Butylbenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58i)



Obtained as a colorless oil in 80% yield with er 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. $[\alpha]^{20}_D$ = - 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.

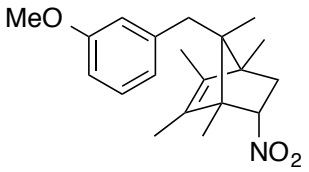
(1S, 4S, 5S, 7R)-(-)-2-((1,2,3,4,7-Pentamethyl-5-nitrobicyclo[2.2.1]hept-2-en-7-yl)methyl)naphthalene (58j)



Obtained as a colorless oil in 83% yield with er of 69:31. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (minor) = 52.69 min., t_r (major) = 69.35 min. $[\alpha]^{20}_D$ = - 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

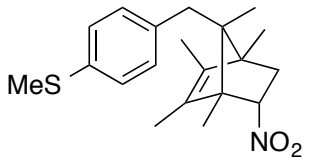
(s, 3H), 1.53 (s, 3H), 1.16 (s, 3H), 0.95 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 137.1, 133.4, 132.1, 131.4, 129.6, 129.0, 127.7, 127.6, 127.3, 126.1, 125.4, 91.7, 64.3 64.1, 56.3, 39.5, 37.7, 15.7, 12.7, 11.5, 11.0, 10.4; FTIR (neat) υ_{max} 2943, 1540, 1382, 1362, 1084, 821, 748 cm^1; HRMS (ESI-TOF): Exact mass calcd for $C_{23}H_{28}NO_2$ $[M + 1]^+$, expected: 350.2120, found: 350.2116.

(1S, 4S, 5S, 7R)-(-)-7-(3-Methoxybenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58k)



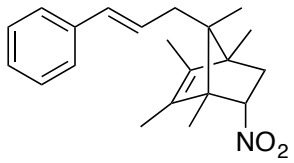
Obtained as a colorless oil in 80% yield with er of 66:34. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (1% *i*PrOH in Hexanes, flow rate = 0.3mL/min), t_r (minor) = 22.48 min., t_r (major) = 25.07 min. $[\alpha]^{20}_D$ = - 30, c = 0.0005, CH_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.

(1S, 4S, 5S, 7R)-(-)-Methyl(4-((1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-en-7-yl)methyl)phenyl)sulfane (58l)



Obtained as a colorless oil in 89% yield with er of 67:33. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (1% iPrOH in Hexanes, flow rate = 0.3mL/min), t_r (minor) = 25.25 min., t_r (major) = 28.71 min. $[\alpha]^{20}_D$ = - 60, c = 0.0005, CH_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.

(1S, 4S, 5S, 7R)-(-)-7-Cinnamyl-1,2,3,4,7-pentamethyl-5-nitrobicyclo[2.2.1]hept-2-ene (58n)



Obtained as a colorless oil in 79% yield with er of 63:37. Enantiomeric ratio was determined by HPLC with a Chiralcel AS-H column equipped with an AS-H guard column (100% Hexanes, flow rate = 0.5mL/min), t_r (minor) = 19.25 min., t_r (major) =

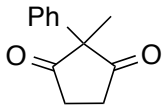
24.89 min. $[\alpha]^{20}_{D}$ = - 54, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.33 (m, 4H), 7.17 – 7.23 (m, 1H), 6.03 – 6.22 (m, 2H), 4.72 – 4.75 (m, 1H), 2.07 – 2.19 (m, 2H), 1.89 – 1.98 (m, 2H), 1.65 (s, 3H), 1.42 (s, 3H), 1.29 (s, 3H), 1.06 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 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.

2.7.5 New dienes synthesis

Synthesis of diones 65

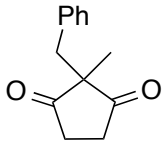
All the diones were synthesized according to the reported procedures. [62,63]

2-Methyl-2-phenylcyclopentane- 1,3-dione (65a):



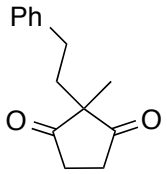
Obtained as pale yellow oil in 68% yield. All spectral data were identical to the literature values [70].

2-Methyl-2-phenemethylcyclopentane-1,3-dione (65b):



Obtained as a light orange solid in 72% yield. All spectral data were identical to the literature values [71].

2-Methyl-2-phenethylcyclopentane-1,3-dione (65c):



Obtained as a brown solid in 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) d 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, $CDCl_3$) d 216.7, 140.9, 128.9, 128.8, 126.7, 56.8, 37.3, 35.5, 31.2, 20.2; FTIR (neat) u_{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

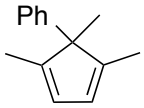
General procedure for the synthesis of dienes 33

The methylenation of diones **65** and the following isomerization of **66** to **33** were carried out with slight modification from the procedures reported in the literature. The reactions were not fully optimized. A typical procedure is as follows:

To a mixture of Mg (3.36 g, 140 mmol) and $TiCl_4$ (7.65 ml, 70 mmol) in CH_2Cl_2 (70 mL) cooled down to 0 °C 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%

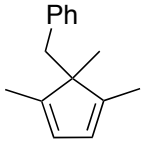
aqueous HI (0.7 ml) was added. The reaction mixture was then stirred vigorously for 20 h in the dark. The reaction was diluted with pentane (20 mL), washed with saturated aqueous $NaHCO_3$, (2 X 15 mL), aqueous $Na_2S_2O_2$, (2 X 15 mL), and brine (15 mL), and the organic phase was dried over a mixture 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 (33a):



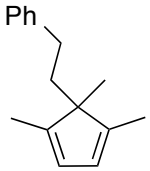
Obtained as a colorless oil in 25% yield based on dione 33a; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.25-7.31 (m, 2H), 7.17-7.21 (m, 1H), 7.03-7.06 (m, 2H), 5.98 (s, 2H), 1.70 (s, 6H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 154.4 (2x), 128.7, 126.4, 126.3, 125.1, 18.8, 13.3 (2x); FTIR (neat) u_{max} 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 (33b):



Obtained as a colorless oil in 28% yield based on dione 33b; ^{1}H NMR (400 MHz, $CDCl_3$) d 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, $CDCl_3$) d 149.4, 138.3, 128.7, 127.6, 126.1, 125.8, 57.2, 41.2, 22.5, 13.4; FTIR (neat) u_{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 (33c):

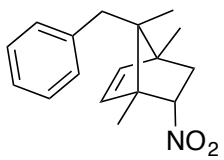


Obtained as a colorless oil in 40% yield based on dione 33c; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24-7.28 (m, 2H), 7.15-7.19 (m, 1H), 7.11-7.13 (m, 2H), 5.99 (s, 2H), 1.95-1.99 (m, 2H), 1.88 (s, 6H), 1.74-1.78 (m, 2H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 149.9, 143,5, 128.6, 128.5, 125.9, 125.5, 56.6, 37.3, 30.5, 22.4, 13.1; FTIR (neat) u_{max} 3061, 3028, 2965, 2931, 2863, 1604, 1496, 1450, 1376, 1030, 911, 821, 748 cm^{-1}; GCMS: 212$[M]^{+}$

2.7.6 General procedure for $NaBArF_{24}$•$2.5H_2O$ catalyzed nitroalkene Diels-Alder reaction

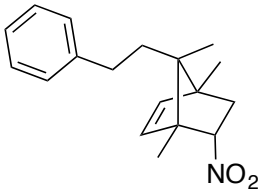
A flame-dried test tube was charged with $NaBArF_{24}$•$2.5H_2O$ (19 mg, 0.02 mmol). To this were added CH_2Cl_2 (0.3 mL) and a solution of nitroethylene (28 mg, 0.4 mmol) in CH_2Cl_2 (0.1 mL). The resulting mixture was cooled to -78 °C, slowly treated with a solution of diene (0.2 mmol) in CH_2Cl_2 (0.3 mL), then the mixture was allowed to warm 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 (67b)



Obtained as a white solid in 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) d 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, $CDCl_3$) d 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) u_{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 (67c)



Obtained as colorless oil in 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) d 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, $CDCl_3$) d 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) u_{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.

2.7.7 Assignment of absolute stereochemistry

Absolute configuration of (+)-7-(4-chlorobenzyl)-1,2,3,4,7-pentamethyl-5-nitrobicyclo-[2.2.1]hept-2-ene was assigned on the basis of the X-ray structure of enantiopure **57c** prepared by HPLC (Chiralcel OD-H column, 100% Hexanes, flow rate = 0.5mL/min, tr

of (-)-enantiomer = 44.85 min., tr of (+)-enantiomer = 55.91 min.) as described below. Those of other products were assigned by analogy.

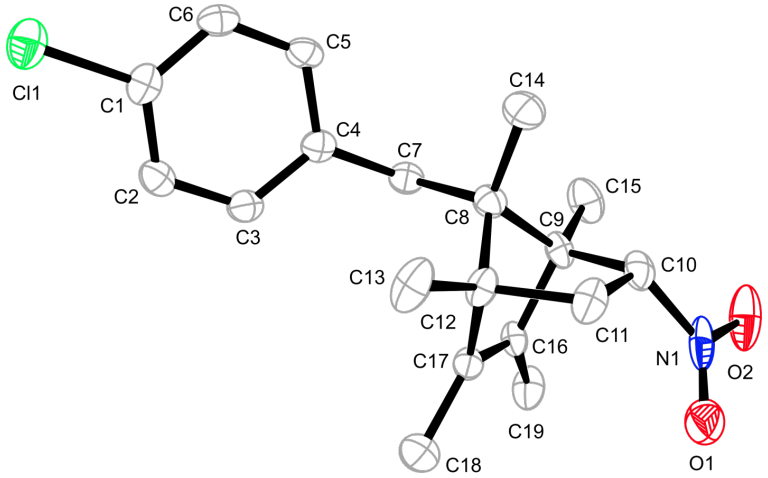


Figure 2.8 An ORTEP of the molecular structure of (+)-enantiomer showing 50 % thermal ellipsoid probability.

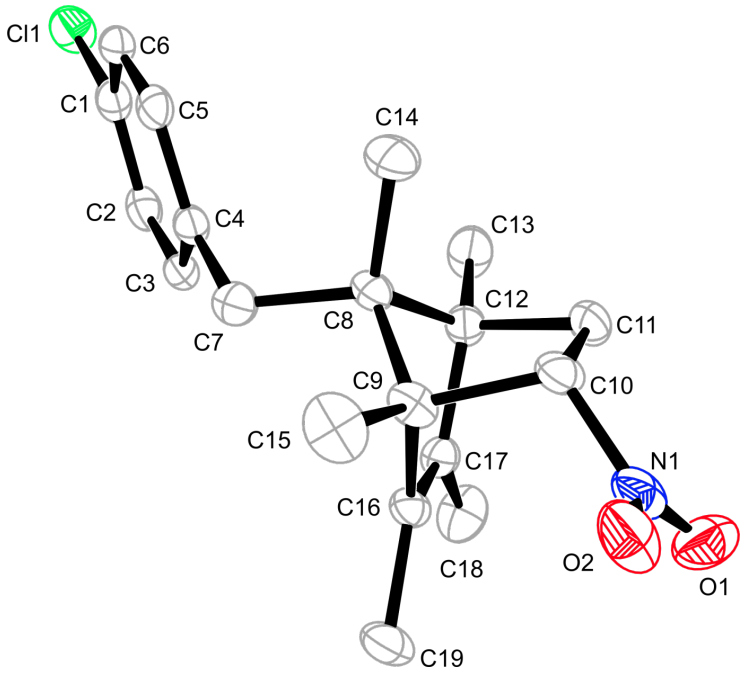


Figure 2.9 An ORTEP of the molecular structure of (-)-enantiomer showing 50 % thermal ellipsoid probability.

Crystallographic analyses:

The data crystals of (+)-enantiomer and (-)-enantiomer were mounted onto the end of a thin glass fiber using Paratone-N. X-ray intensity data were measured with a Bruker SMART APEX2 CCD-based diffractometer using Mo Kα radiation (λ = 0.71073 Å).1 The raw data frames were integrated with the SAINT+ program by using a narrow-frame integration algorithm.1 Corrections for Lorentz and polarization effects were also applied with SAINT+. An empirical absorption correction based on the multiple measurement of equivalent reflections was applied using the program SADABS. The structure was solved by a combination of direct methods and difference Fourier syntheses, and refined by fullmatrix least-squares on F2, by using the SHELXTL software package.2 All non-hydrogen atoms were refined with anisotropic displacement parameters unless otherwise stated. Hydrogen atoms were placed in geometrically idealized positions and included as standard riding atoms during the least-squares refinements. Crystal data, data collection parameters, and results of the analyses are listed in Table S1.

Colorless single crystals of (+)-enantiomer suitable for x-ray diffraction analyses obtained by evaporation of ethanol/water solvent mixture crystallized in the Triclinic crystal system. The structure could only be solved in the chiral space group P1. Attempts to solve the structure in the centrosymmetrical space group $P\bar{1}$ were unsuccessful. Furthermore, ADDSYM/PLATON3 test did not indicate any additional missed symmetry. The Flack x(u) parameter 0.04(3) indicates that the correctenantiomorph has been selected. With Z = 4, there are four formula equivalents of the complex present in the asymmetric crystal unit. All four molecules are the same enantiomer. Colorless single crystals of (-)-enantiomer suitable for x-ray diffraction analyses obtained by evaporation

of isopropanol/water solvent mixture crystallized in the Triclinic crystal system. The structure could only be solved in the chiral space group P1. Attempts to solve the structure in the centrosymmetrical space group P $\bar{1}$ were unsuccessful. Furthermore, ADDSYM/PLATON3 test did not indicate any additional missed symmetry. The Flack x(u) parameter − 0.03(3) indicates that the correct enantiomorph has been selected. With Z = 4, there are four formula equivalents of the complex present in the asymmetric crystal unit. All four molecules are the same enantiomer.

Table 2.10 Crystallographic data for (+)-enantiomer and (-)-enantiomer.

	(+)-enantiomer	**(-)-enantiomer**
Empirical formula	$C_{19}H_{24}NO_2Cl$	$C_{19}H_{24}NO_2Cl$
Formula weight	333.84	333.84
Crystal system	Triclinic	Triclinic
Lattice parameters		
a (Å)	8.3213(4)	8.3206(4)
b (Å)	8.3312(4)	8.3369(4)
c (Å)	25.7701(13)	25.7561(14)
α (°)	93.369(1)	93.355(1)
β (°)	95.301(1)	95.323(1)
γ (°)	93.703(1)	93.682(1)
V ($Å^3$)	1771.42(15)	1771.53(15)
Space group	P1 (#1)	P1 (#1)
Z value	4	4
ρ_{calc} (g / cm^3)	1.252	1.252
μ (Mo Kα) (mm^{-1})	0.225	0.225
Temperature (K)	100	100

$2\Theta_{max}$ (°)	54.0	54.0
No. Obs. ($I > 2\sigma(I)$)	12509	12543
No. Parameters	849	849
Goodness of fit	1.023	1.036
Max. shift in cycle	0.002	0.001
Residuals*:R1; wR2	0.0446; 0.0827	0.0453; 0.0873
Absorption Correction,	Multi-scan	Multi-scan
Max/min	0.9933/0.9194	0.9866/0.9154
Absolute structure Flack parameter	0.04(3)	– 0.03(3)
Largest peak in Final Diff. Map (e^- / $Å^3$)	0.228	0.302

*$R = \Sigma_{hkl}(\,|\,|F_{obs}|-|F_{calc}|\,|)/\Sigma_{hkl}|F_{obs}|$; $R_w = [\Sigma_{hkl}w(|F_{obs}|-|F_{calc}|)^2/\Sigma_{hkl}wF_{obs}^2]^{1/2}$,

$w = 1/\sigma^2(F_{obs})$; $GOF = [\Sigma_{hkl}w(|F_{obs}|-|F_{calc}|)^2/(n_{data} - n_{vari})]^{1/2}$.

CHAPTER 3

Catalysis of the Claisen Rearrangement by Helical Chiral Hydrogen-Bond Donors

The C – C bond forming ability of the Claisen rearrangement makes it useful and powerful method in synthesis. Complex stereochemical motifs can be generated from comparatively simple precursors in a highly predictable manner, which makes this transformation highly valuable. The predictability is reliant upon the pericyclic nature of the mechanism and the inclination of substrates to go through a highly ordered six-membered transition state (Figure 3.1). As a result, it has found considerable use in the total synthesis of natural products containing intricate stereochemical motifs.[72]

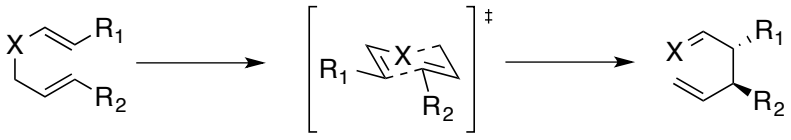


Figure 3.1 Highly ordered six-membered transition state

3.1 Background

3.1.1 Enzymatic catalysis of Claisen rearrangement

The enzyme chorismate mutase catalyzes the [3,3]-sigmatropic rearrangement of chorismate to prephenate with a rate enhancement of about $10^6 – 10^7$ fold. It is a rare example of pericyclic processes occurring naturally. Through substrate labeling[73] and kinetic isotope effect studies[74] it was demonstrated that the uncatalyzed and catalyzed reactions proceed via a chair-like transition state. Analysis of solved X-ray structures for *Bacillus subtilis*[75,76] and *Escheria coli*[77] chorismate mutases and catalytic antibody 1F7[78] bound to an oxabicyclic transition state analogue revealed stabilization of the transition state through a series of electrostatic and hydrogen-bonding interactions. In the active site Arginine and Lysine residues interact with the ether oxygen of the allyl vinyl ether and

the carboxylate functional groups.[79] In *Bacillus subtilis* chorismate mutase mutagenesis studies have shown the cationic H-bond donor Arginine 90 is at a position necessary for catalysis[80,81] (Figure 3.2) stabilizing the negative charge that develops on the oxygen in the transition state and the required chair-like conformation.

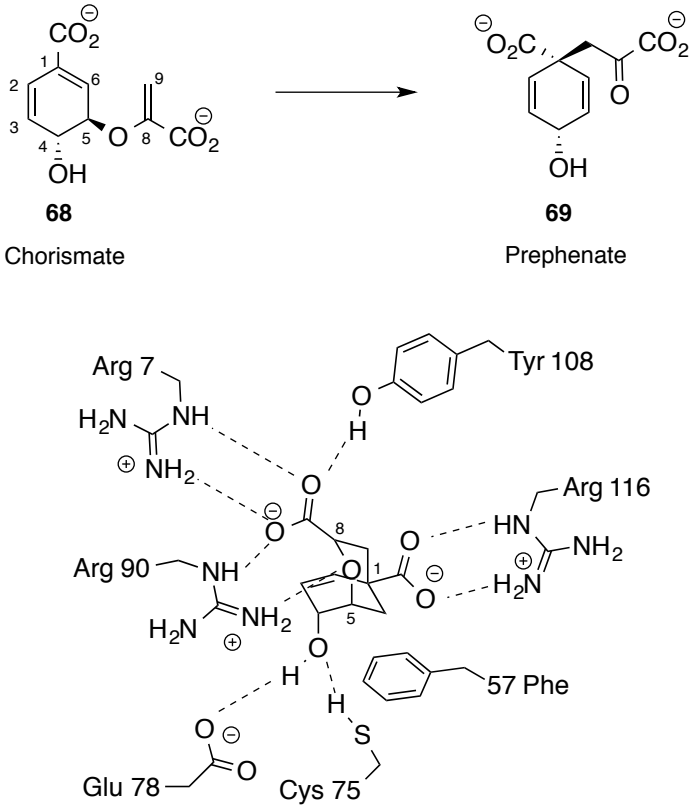
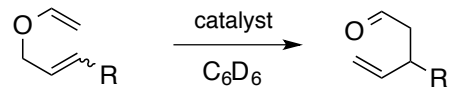


Figure 3.2 Schematic diagram of hydrogen-bonding interactions in *Bacillus subtilis* chorismate mustase bound to oxabicyclic transistion state analogue. Reported by Schultz (Reference 80).

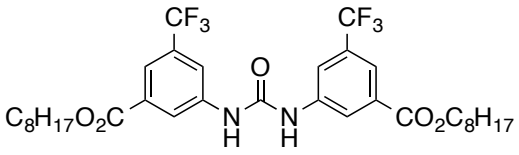
3.1.2 Catalysis of Claisen rearrangement via hydrogen-bond donors

In 1995, Curran demonstrated the acceleration of the Claisen rearrangement of acylic allyl vinyl ethers using diaryl ureas.[82] Rates were observed to be up to 22.4 times faster with 1.0 equivalent of the double H-bond donor urea catalyst.

Table 3.1 Rearangements of allyl vinyl ethers with urea catalyst. Reported by Curran (Reference 82).



70 : R = Ph (all E)
71 : R = OMe (E/Z = 2.6/1)



72

Substrate	Temp. (C)	equiv	k (x 10^{-5} s^{-1})	k_{rel}
70	100	none	0.4	1
70	100	0.2	0.7	1.7
70	100	0.5	1.3	3.1
70	100	1.0	1.8	4.2
71	80	none	0.6	1
71	80	0.1	1.6	2.7
71	80	0.4	3.1	5.0
71	80	1.0	13.7	22.4

As an explanation, Curran proposed a *bis*-hydrogen bonded transition state model for the acceleration effects of the urea catalyst on the Claisen rearrangement. Analogous thioureas that are about 10^6 times more acidic demonstrated a weaker accelerating effect, which suggests that hydrogen bonding and not acidity was crucial for acceleration.

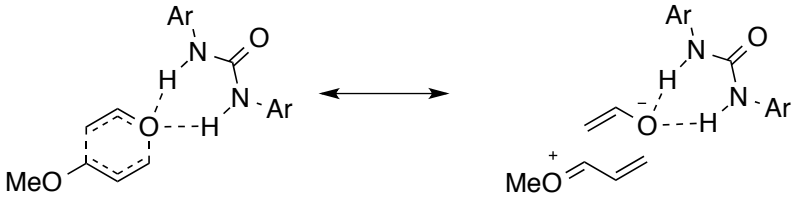


Figure 3.3 *Bis*-hydrogen transistion state model.
Reported by Curran (Refererence 82).

This *bis*-hydrogen bonding model was in agreement with control experiments that illustrated reduced acceleration with single hydrogen bond donor urea catalysts. Also in a large excess of dimethyl sulfoxide (DMSO) the double hydrogen-bond donor urea catalyst was inhibited as it was expected to bind preferentially.

Hiersemann performed a theoretical and experimental study in 2007 for the development of an organocatalytic asymmetric Claisen rearrangement.[83] Using acyclic 2-alkoxycarbonyl-substituted allyl vinyl ether **73** as the model substrate, detailed computational studies showed a chair-like transition state binding in a bidentate fashion to the ether and carboxylate oxygen atoms as having the lowest energy.

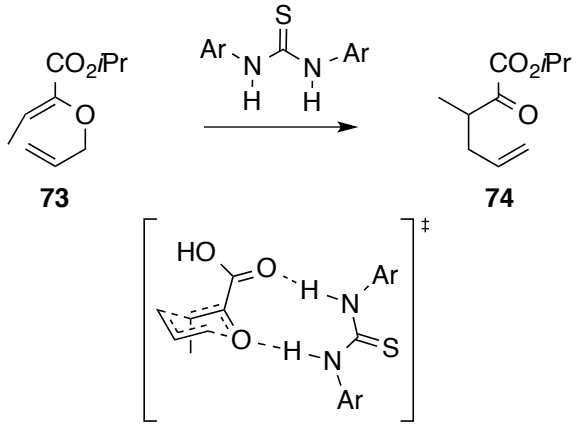
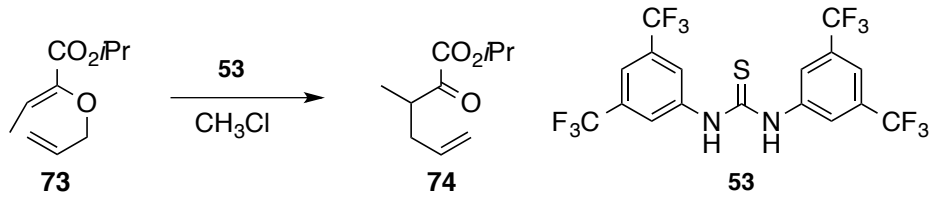


Figure 3.4 Transition state stabilization for Claisen rearrangement by bidentate thiourea coordination. Reported by Hiersemann (Reference 83).

Consequently, the rate acceleration of Claisen rearrangement with achiral 1,3-bis-(3,5-bis(trifluoromethyl)phenyl) thiourea **53** was investigated. Though moderate acceleration was observed with stoichiometric quantities of the thiourea, catalytic results were minimal. As a result, Hiersemann inferred that while thioureas were able to stabilize the transition state, the energy of the conformational changes were too large for the 2-isopropoxycarbonyl-1-methyl-substituted allyl vinyl ether substrate and indicated that the choice of a suitable catalyst/substrate combination is essential for development of catalysis.

Table 3.2 Thiourea accelerated Claisen rearrangement.
Reported by Hiersemann (Reference 83).

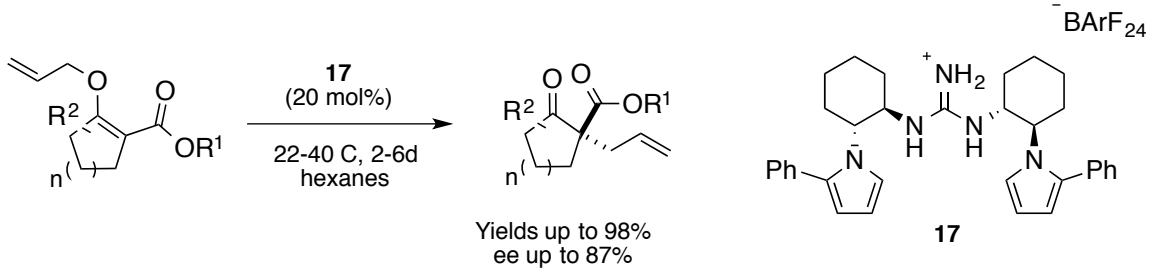


73 **74** **53**

Entry	mol (%)	Temp (C)	time (d)	Conv. (%)
1	0	25	5	10
2	20	25	5	17
3[a]	20	45	0.25	15
4[a]	100	45	1	41
5[a]	100	45	5	84

[a] Reaction performed in sealed tube.

In 2008 Jacobsen demonstrated the first asymmetric catalysis of the Claisen rearrangement of ester substituted allyl vinyl ethers[16] via H-bond donor guanidinium ions.[20] A subsequent study was demonstrated with *O*-allylated β-ketoester substrates (Scheme 3.1).[25] However, the activity of their catalyst was again observed to be low with reaction times of 2 to 6 days. Importantly, Jacobsen proposed that the phenyl substitutions on the pyrrole rings provided cation-π interactions that led to stabilization in the transition state, which was instrumental to enantioselectivity and catalytic activity.



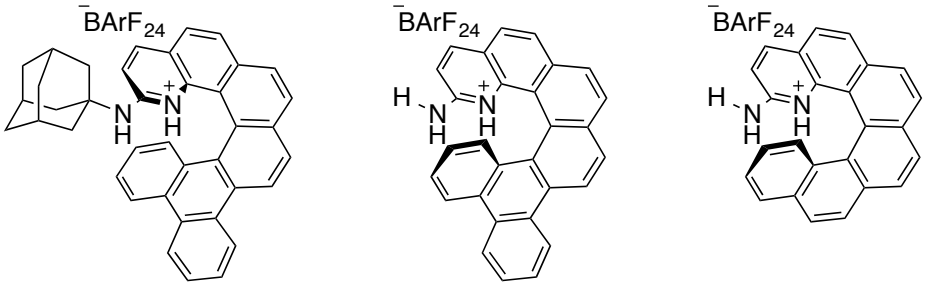
Scheme 3.1 Asymmetric Claisen rearrangement via guanidinium ions.
Reported by Jacobsen (Reference 25).

3.2 Perspective

In light of recent studies, it is evident that hydrogen bond donors can effectively promote the Claisen rearrangement.[20, 25] We became interested in the ability of our helical chiral H-bond donors potential in this transformation. If successful it would provide complimentary means to the limited existing methods through organocatalysis. We hypothesized that the H-bond donor motif of our catalyst would be effective due to its similarity to guanidinium ions. Also, the annulated nature of the helicene framework may be beneficial as the importance of the phenyl group on Jacobsen's guanidinium catalyst was paramount to facilitate cation-π interactions. We chose *O*-allylated methyl 1-indanone-2-carboxylate as our model substrate. It possessed a carboxylate group, which better facilitates a double H-bond donating motif and was experimentally suitable for reaction monitoring and product quantification.

3.3 Results and discussion

To begin our investigation we chose H-bonding catalysts previously developed in our laboratory[32] (Figure 3.5). We were provided with an initial idea of the reactivity and selectivity possessed by this class of catalysts, observing modest yields and low selectivities (Table 3.3).

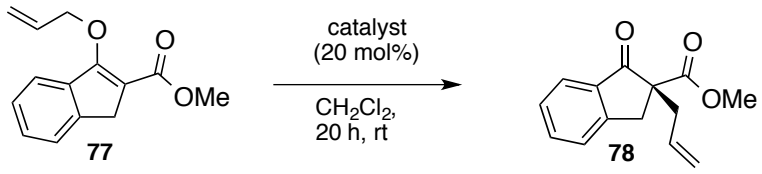


(*P*)-**32** (*M*)-**75** (*M*)-**76**

Figure 3.5 Helical chiral H-bond donor catalysts. Reported by Takenaka (Reference 32).

Beginning with catalyst (*P*)-**32**, which has proven effective for a number of transformations in our laboratory, we obtained the rearrangement product in a yield of 43%, approximately double the conversion of the reaction without any catalyst, and an er, enantiomeric ratio, of 59:41 (18% ee).

Table 3.3 Claisen Rearrangement with H-bond donor catalysts



Entry	Cat.	Yield (%)[b]	er[c]
1	none	20	-
2	(*P*)-**32**	43	59:41
3	(*M*)-**75**	78	33:67
4[d]	(*M*)-**76**	52	45:55

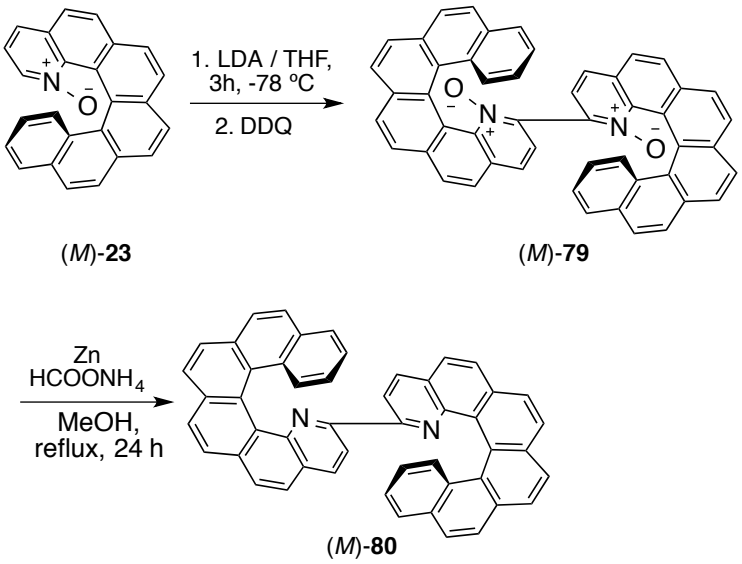
[a] Reaction conditions: 0.1 mmol scale in the presence of 20 mol % catalyst in CH_2Cl_2 (0.5 mL). [b] Yield of islolated products. [c] Determined by chiral HPLC analysis. [d] 4Å Molecular sieve used.

Catalyst (*M*)-**75** showed improved yield (78%) and enantioselectivity (34% ee), leading us to believe that the adamantyl substituent may have negatively affected the reaction due to steric hindrance. The use of an even smaller catalyst (*M*)-**76** produced a lower yield and lower selectivity than its larger counterpart. However, these preliminary results were considered to be promising starting points. The selectivities obtained provided support to show that the rearrangement occurred in a chiral environment. We observed adequate yields and definite enantio-induction with our catalytic systems based on 1-aza[6]helicene scaffolds which have the ability to be tuned.

3.3.1 Development of helical chiral dimer catalysts

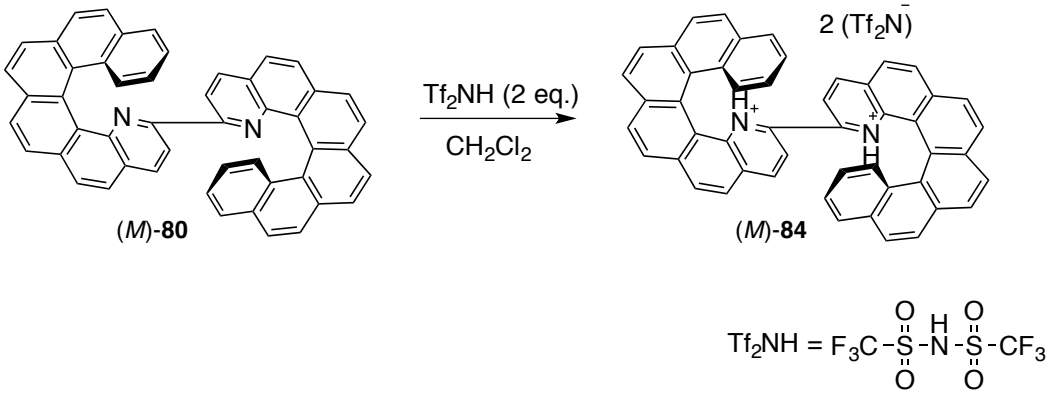
While we observed that our helical chiral H-bond donors can accelerate the Claisen rearrangement for the chosen substrate, our efforts became focused on increasing the selectivity. It was apparent from our results with **75** that the removal of steric bulk resulted in increased enantioselectivity but the use of the smaller **76** showed attenuated results. We hypothesized this [3,3]-sigmatropic rearrangement takes place in the "chiral pocket", a chiral volume of space crafted by the helicene framework,[84] of our helical catalyst via H-bonding interactions. As such, we hypothesized that if this chiral environment can be enhanced, it should have a direct effect on the resultant enantioselectivity of the Claisen rearrangement.

Our investigation comprised of developing a helical dimer as the chiral backbone for our catalyst. We chose to begin with a 1-aza[6]helicene (6 ring) dimer structure, keeping in mind the negative effect of possible steric hindrance with (*P*)-**32** (7 ring), it would be the smaller of the two potential helical structures upon dimerization. Our synthesis of this dimer began with enantiopure 1-azahelicene *N*-oxide (*M*)-**23** which was accessed by methods previously developed in our group.[4] Using modified conditions for the synthesis of Lewis basic bidentate 11,12-benzo-1-aza[6]helicene *N*-oxide catalysts,[85] the dimerization was found to work best with 2.4 equivalents of lithium diisopropylamine (LDA) followed by quenching with 2,4-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). The reduction of dimerized *N*-oxide with zinc and ammonium formate proceeded smoothly to provide the 1-aza[6]helicene dimer product (Scheme 3.2).



Scheme 3.2 Synthesis of 1-azahelicene dimer ligand

With this new ligand in hand (*M*)-**80**, we began the preparation of our double H-bond donor dimer catalysts. (*M*)-**81** and (*M*)-**82** were prepared in a similar fashion to previously reported H-bond donor catalysts in our group[32] with 1 or 2 equivalents of reagents providing the mono or di-protonated species respectively. We were also interested in using a different counter anion to gain insight into any possible effect on yield and selectivity. As such, (*M*)-**83** and (*M*)-**84** could be prepared in situ[86] using trifluoromethanesulfonimide, forming an ion pair after protonation of the ligand (Scheme 3.3).



Scheme 3.3 Preparation of catalyst from dimer ligand

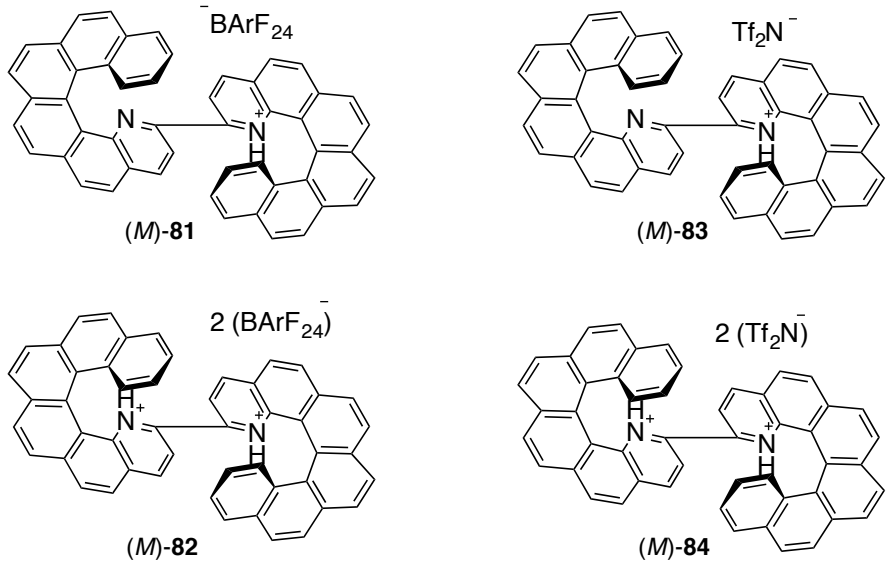
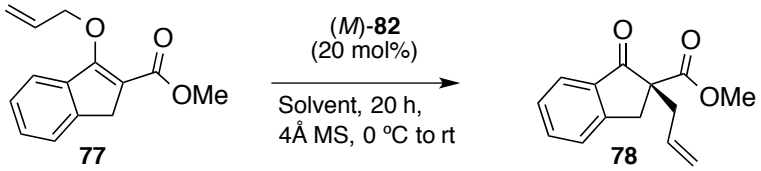


Figure 3.6 Single and double H-bond dimer catalysts with different counter anions

3.3.2 Catalysis of Claisen rearrangement with dimer hydrogen-bond donors

We performed a small solvent screen with new catalyst (*M*)-**82** in light of known effect of solvents on the Claisen rearrangement due to its highly polarized transition state[21] (Table 3.4).

Table 3.4 Solvent effect on rearrangements[a]

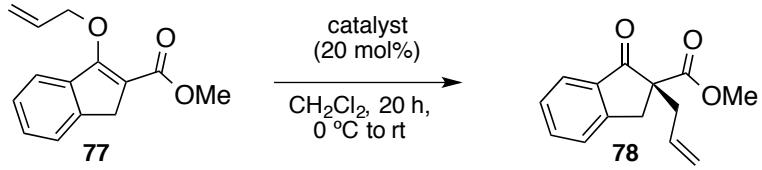


Entry	Solvent	yield (%)[c]	er[d]
1[b]	CH_2Cl_2	96	50:50
2	Hexanes	58	50:50
3	Cyclohexane	50	50:50
4	Benzene	78	50:50
5	TBME	78	50:50

[a] Reaction conditions: 0.05 mmol scale in the presence of 20 mol % catalyst in CH_2Cl_2 (0.25 mL). [b] 0.1 mmol scale. [c] Yield of islolated products. [d] Determined by chiral HPLC analysis

We were pleased to find that the catalyst worked well in both polar and non-polar solvents. The rearrangement proceeded well in dichloromethane providing a very high yield. Good yields were also observed with aromatic solvent benzene and ethereal solvent tert-butyl methyl ether (TBME). This illustrated that it did not affect the activity of the catalyst through H-bonding interactions of the oxygen atom lone pairs. The non-polar hydrocarbon solvents, hexanes and cyclohexane provided lower yields, which may be attributed to the lack of solubility of the catalyst in these solvents. However, we were surprised there was a complete lack of selectivity of our catalyst in all solvents. While the catalytic activity was enhanced by the use of a dimer structure, the enantioselection was completely diminished.

Table 3.5 Claisen rearrangement with different dimer catalysts[a]



Entry	Cat.	Yield w/ No MS (%)[b]	Yield w/ MS (%)[b]
1	(*M*)-**81**	28	50
2	(*M*)-**82**	88	96
3	(*M*)-**83**	14	33
4	(*M*)-**84**	0	62

[a] Reaction conditions: 0.1 mmol scale in the presence of 20 mol % catalyst in CH_2Cl_2 (0.5 mL). [b] Enantiomeric ratio (er) was 50:50. Determined by chiral HPLC analysis

We then investigated the performance of our single H-bond and double H-bond donor dimer catalysts (Table 3.5). It was apparent that the single H-bond catalysts were not very effective with **81** providing low yield and **83** showing no apparent activity. However, their double H-bond donor analogues showed approximately twice the catalytic activity is due more efficient H-bonding between the ether and carboxyl ester oxygen atoms of the *O*-allylated β-ketoester substrate. Interestingly, **84** did not provide any rearrangement product and on further analysis it was observed that substrate was hydrolyzed to the β-ketoester. We believed this may have been a result of adventitious acid[87] as the corresponding reaction conducted with molecular sieve provided the desired rearrangement product in good yield. Indeed all reactions gave increased yields in the presence of molecular sieve that maybe attributed to the removal of impurities. Overall the rearrangement conversions of the catalysts with the non-coordinating $BArF_{24}$ counter anion, (*M*)-**81** and (*M*)-**82** were higher than their respective counterparts, which is in

accord with the acceleration studies of catalysts with based on counter anion coordination. Unfortunately, again no enantioselection was observed for any of the rearrangements. The results led us to believe that there are H-bonding interactions between the dimer catalysts and the substrate and possibly cation-π interactions, sufficiently lower the energy of the transition state, thus resulting in acceleration. It is important to note that the x-ray crystallographic structure of the 11, 12-benzo-1-aza[6]helicene dimer single H-bond donor catalyst was obtained (Figure 3.7).[88]

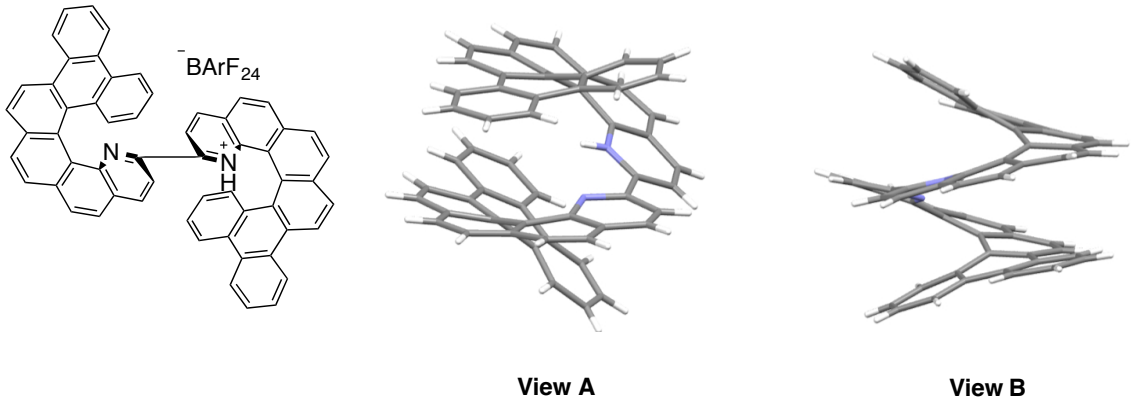


Figure 3.7 X-ray structure of 11,12-benzo-1-aza[6]helicene dimer single H-bond donor catalyst. $BArF_{24}^-$ counter anion not shown for clarity (Reference 88).

While this particular catalyst was not investigated, its structure would be analogous to that of the 1-aza[6]helicene dimers used as catalysts for the Claisen rearrangement. On analysis of the x-ray structure it is clear that the dimer maintains the helical nature throughout the molecular framework. As aforementioned, this helical characteristic acts as the chiral element of the catalyst. The bonding site of the catalyst seems to be within the chiral architecture of the catalyst, which is necessary to induce enantioselectivity (Figure 3.7, View A). In addition, the continuous helical shape would craft a chiral volume of space, or chiral pocket, in which the reaction should occur (Figure 3.7, View B). However, the lack of enantioselection observed in our investigation maybe due to the

formation of the hydrogen bonded chair-like transition state in a space that is distant from or outside of the chiral pocket of the dimer H-bond donor catalyst. The structure of the *O*-allylated β-ketoester substrate may not fit well in the chiral pocket due to steric interactions, forcing it into a different position but one in which it is still hydrogen bonded to the catalyst. As such, the ensuing pericyclic rearrangement would occur in an achiral environment resulting in no enantioselectivity.

3.4 Future studies

In light of these results our future efforts would be centered on expansion of the substrates and developing catalysts to improve the levels of enantioselectivity. The present dimer catalysts should be evaluated with different cyclic and acyclic allyl vinyl ethers to explore the range of its substrate scope. The synthesis of various double H-bond donor dimer catalysts derived from 11, 12-benzo-1-aza[6]helicene ligands will be pursued as can be accessed via the designed synthetic route in (Scheme 3.2) from the respective *N*-oxide and subsequently investigated in the Claisen rearrangement.

3.5 Conclusion

We demonstrated acceleration of the Claisen rearrangement for an *O*-allylated β-ketoester substrate by helical chiral hydrogen bond donor catalysts. Also, we have developed helical chiral dimer H-bond donors, which to the best of our knowledge, is the first of its kind. Our results have shown that double H-bond donor catalysts are more efficient than single H-bond donor analogues in acceleration of the Claisen rearrangement, which is in good agreement with previous studies. Dimer catalysts with this new extended helical framework and the non-coordination $BArF_{24}$ counter anion possess higher activity than those we have previously reported. Although no

enantioselectivity was observed with helical dimer H-bond catalysts, these results provide a platform to further build on our investigation.

3.6 Experimental section

3.6.1 General information

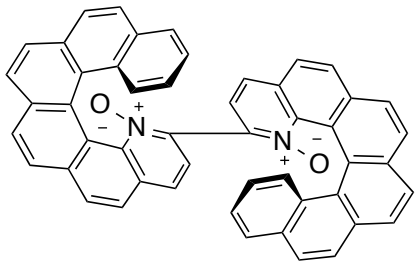
All reactions were carried out in the oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Silicycle pre-coated silica gel plates with 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 using silica gel 60 (mesh 230-400) supplied by Silicycle.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromenthane (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), a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), and a Bruker Avance 500 (500 MHz ^{1}H, 125 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, University of Miami.

3.6.2 Preparation of (*M*)-1-aza[6]helicene *N*-oxide dimer, (*M*)-79

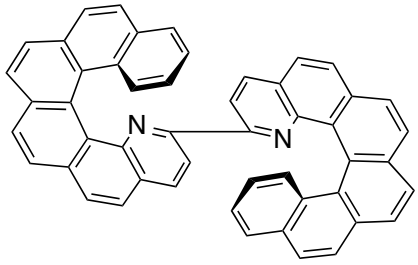


From stock solution containing 210μL (1.5 mmol) of diisopropyl amine in THF (1.0 mL), 100 μL was removed and added to 1.0 mL THF and cooled to -78 degrees Celsius. Then 93μL (0.14 mmol, 1.5M) of *n*BuLi was added resulting solution was stirred for 30 mins at -78 degrees Celsius. The LDA solution was then *quickly* added via syringe to a 20mg (0.06 mmol) 1-azahelicene *N*-oxide solution in THF (1.0 mL) solution, chilled to -78 degrees Celsius. The reaction mixture was stirred for up to 3 hours and monitored by TLC. Reaction was quenched by adding 26mg (0.12 mmol) of 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) pre-chilled at -78 deg. Celsius and stirred for 30 mins. 50% m/v NaOH was added until pH became basic. The resulting mixture was 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 (70% EtOAc in hexanes) to afford the desired product (13 mg, 33%).

$[\alpha]^{20}_D$ = - 8902, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 8.07 (m, 18H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.39 (m, 2H), 7.09 – 7.12 (d, *J* = 12.0 Hz, 2H), 6.49 – 6.70 (m, 2H), 6.04 (d, *J* = 12.0 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.3, 104.2,

139.9, 132.7, 132.3, 131.7, 131.0, 130.2, 129.8, 129.6, 128.7, 127.7, 127.2, 127.1, 125.76, 125.74, 125.4, 125.1, 124.2, 123.7, 123.6, 123.3, 120.1, 99.8; FTIR (neat) υ_{max} 3046, 2925, 2858, 1733, 1463, 1305, 1244, 1096, 846, 834, 789, 739, 698cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{29}N_2O_2$ $[M + 1]^+$, expected: 689.2224, found: 689.2271

3.6.3 Preparation of (*M*)-1-aza[6]helicene dimer, (*M*)-80



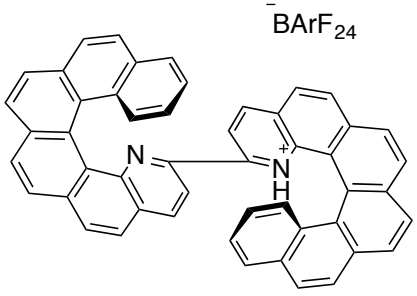
To a solution of 34mg (0.05 mmol) (M)-1-aza[6]helicene *N*-oxide dimer in methanol (25.0 mL) was added Zinc dust (131mg) and ammonium formate (164mg) and heated under reflux conditions for 24 hours. After cooling to room temperature the reaction mixture was filtered through celite and condensed in *vacuo*. It was then redissolved in CH_2Cl_2 and washed with NH_4Cl, $NaHCO_3$ and brine and condensed in *vacuo*. The crude material was purified by flash chromatography on silica gel (30:70:1 EtOAc: Hexanes: NEt_3) to afford the desired product (24 mg, 73%).

$[\alpha]^{20}_D$ = - 6154, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 8.05 (m, 16H), 7.76 – 7.81 (m, 6H), 7.66 – 7.68 (d, *J* = 8.0 Hz, 2H), 6.68 – 6.74 (dd, *J* = 12.0, 24.0 Hz, 2H), 6.58 – 6.61 (d, *J* = 12.0 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 152.4, 145.0, 135.0, 133.6, 133.4, 132.2, 131.5, 131.2, 130.5, 129.4, 128.3, 128.1, 127.6, 127.4, 127.2, 127.0, 126.7, 126.5, 126.39, 126.36, 126.2, 125.8, 124.8, 124.4, 119.3; FTIR (neat) υ_{max} 3044, 2925, 1597, 1575, 1497, 1265, 1074, 851, 831, 792, 742 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{29}N_2$ $[M + 1]^+$, expected: 657.2325, found: 657.2349

3.6.4 Preparation of helical dimer catalysts

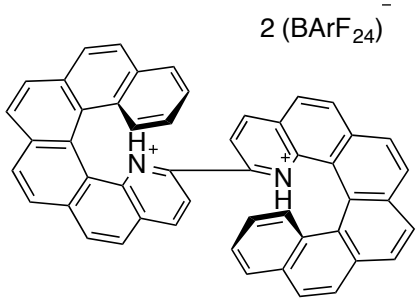
Catalysts (*M*)-**81** and (*M*)-**82** were prepared according to the literature procedure.[32]

(*M*)-1-aza[6]helicenium dimer $BArF_{24}$, (*M*)-81



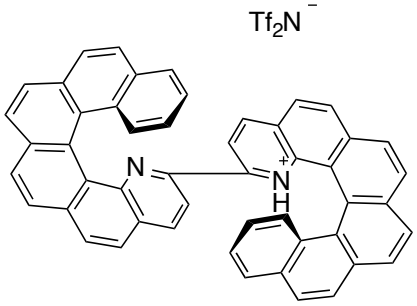
$[\alpha]^{20}_{D}$ = - 5343, c = 0.001, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.48 (d, *J* = 8.0Hz, 2H), 8.39 – 8.41 (d, *J* = 8.0 Hz, 2H), 8.30 – 8.32 (d, *J* = 8.0 Hz, 2H), 8.22 – 8.26 (dd, *J* = 8.0, 18.0 Hz, 4H), 7.92 – 7.94 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.83 (m, 10H), 7.52 – 7.57 (m, 5H), 7.04 – 7.06 (d, *J* = 8.0 Hz, 2H), 6.57 – 6.60 (m, 2H), 6.37 – 6.40 (d, *J* = 12.0 Hz, 2H), 6.27 – 6.30 (m, 4H), 5.79 – 5.81 (d, *J* = 8.4 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 162.7, 162.2, 161.7, 161.2, 142.0, 141.2, 139.9, 135.0, 134.3, 132.1, 131.4, 130.7, 129.7, 129.39 (d, *J* = 3.0 Hz) 129.07 (d, *J* = 3.0 Hz), 128.8, 128.1, 127.9, 127.5, 126.4, 126.1, 125.8, 123.4, 123.2, 122.8, 120.7, 177.7, 116.8; FTIR (neat) υ_{max} 2924, 2854, 1608, 1354, 1276, 1123, 908, 886, 851, 839, 825, 806, 771, 733 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{29}N_2$ $[M + 1]^+$, expected: 657.2325, found: 657.2332

(*M*)-1-aza[6]helicenium dimer $2BArF_{24}$, (*M*)-82



$[\alpha]^{20}_D$ = - 1964, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.49 (d, *J* = 8.0Hz, 2H), 8.39 – 8.42 (d, *J* = 12.0 Hz, 2H), 8.30 – 8.32 (d, *J* = 8.0 Hz, 2H), 8.21 – 8.27 (m, 4H), 7.92 – 7.94 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.83 (m, 20H), 7.52 – 7.57 (m, 10H), 7.04 – 7.06 (d, *J* = 8.0 Hz, 2H), 6.57 – 6.60 (m, 2H), 6.38 – 6.40 (d, *J* = 8.0 Hz, 2H), 6.27 – 6.31 (m, 4H), 5.79 – 5.81 (d, *J* = 8.0 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 162.7, 162.2, 161.71, 161.21, 142.0 141.2, 139.9, 135.3, 135.0, 134.3, 132.2, 131.48, 131.45, 130.7, 129.2 (*J* = 32.0 Hz, 56.0 Hz), 128.1, 128.0, 127.6, 126.5, 126.2, 126.1, 125.9, 125.8, 125.2 (*J* = 3.0 Hz), 124.9, 124.8, 123.4, 123.2, 122.8, 120.65, 117.7 (*J* = 4.0 Hz), 116.7; FTIR (neat) υ_{max} 2935 1708, 1610, 1354, 1276, 1124, 888, 839, 713, 682, 670 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{30}N_2$ $[M]^+$, expected: 658.2398, found: 657.2368

Preparation of catalyst (*M*)-1-aza[6]helicenium dimer Tf_2N, (*M*)-83

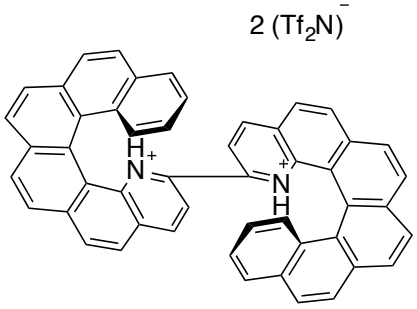


To 11mg (0.02 mmol) of 1-aza[6]helicene dimer was added trifluoromethanesulfonimide (0.018 mmol) from a stock solution in CH_2Cl_2.

$[\alpha]^{20}_D$ = - 6560, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.70– 8.72 (d, *J* = 8.0 Hz, 2H), 8.53 – 8.55 (d, *J* = 8.0 Hz, 2H), 8.40 – 8.42 (d, *J* = 8.0 Hz, 2H), 8.29 – 8.31 (m, 4H), 8.14 – 8.16 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.85 (d, *J* = 8.0 Hz, 2H), 7.07 – 7.09 (m, 2H), 6.60 – 6.64 (m, 2H), 6.40 – 6.42 (d, *J* = 8.0 Hz, 2H), 6.29 – 6.33 (m, 4H), 5.80 – 5.82 (d, *J* = 8.0 Hz, 2H); ^{13}CNMR (100 MHz, CD_2Cl_2) δ 142.6, 141.5, 139.7, 135.4,

134.2, 131.9, 131.8, 131.4, 130.6, 128.2, 128.1, 127.6, 126.5, 126.0, 125.8, 125.5, 125.2, 125.1, 124.9, 124.6, 123.2, 122.8, 121.8, 118.6, 117.6, 115.4; FTIR (neat) υ_{max} 2931, 1608, 1350, 1190, 1137, 1058, 855, 749 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{29}N_2$ $[M]^+$, expected: 657.2325, found: 657.2351

(*M*)-1-aza[6]helicenium dimer 2Tf_2N, (*M*)-84



$[\alpha]^{20}_D$ = - 5316, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.70– 8.72 (d, *J* = 8.0 Hz, 2H), 8.51 – 8.53 (d, *J* = 8.0 Hz, 2H), 8.39 – 8.41 (d, *J* = 8.0 Hz, 2H), 8.27 – 8.30 (m, 4H), 8.13 – 8.15 (d, *J* = 8.0 Hz, 1H), 7.80 – 7.84 (m, 4H), 7.06 – 7.08 (d, *J* = 8.0 Hz, 2H), 6.61 – 6.64 (m, 2H), 6.41 – 6.43 (d, *J* = 8.0 Hz, 2H), 6.29 – 6.31 (m, 4H), 5.82 – 5.84 (d, *J* = 8.0 Hz, 2H); ^{13}CNMR (100 MHz, CD_2Cl_2) δ 142.6, 141.4, 139.7, 135.4, 134.3, 131.9, 131.8, 131.4, 130.6, 128.2, 128.1, 127.56, 126.55, 126.1, 125.9, 125.8, 125.5, 125.1, 124.9, 124.6, 123.2, 122.8, 121.5, 118.3, 117.6; FTIR (neat) υ_{max} 3540, 3081, 2924, 1608, 1349, 1333, 1186, 1135, 1055, 854, 743 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{50}H_{29}N_2$ $[M]^+$, expected: 658.2398, found: 658.2359

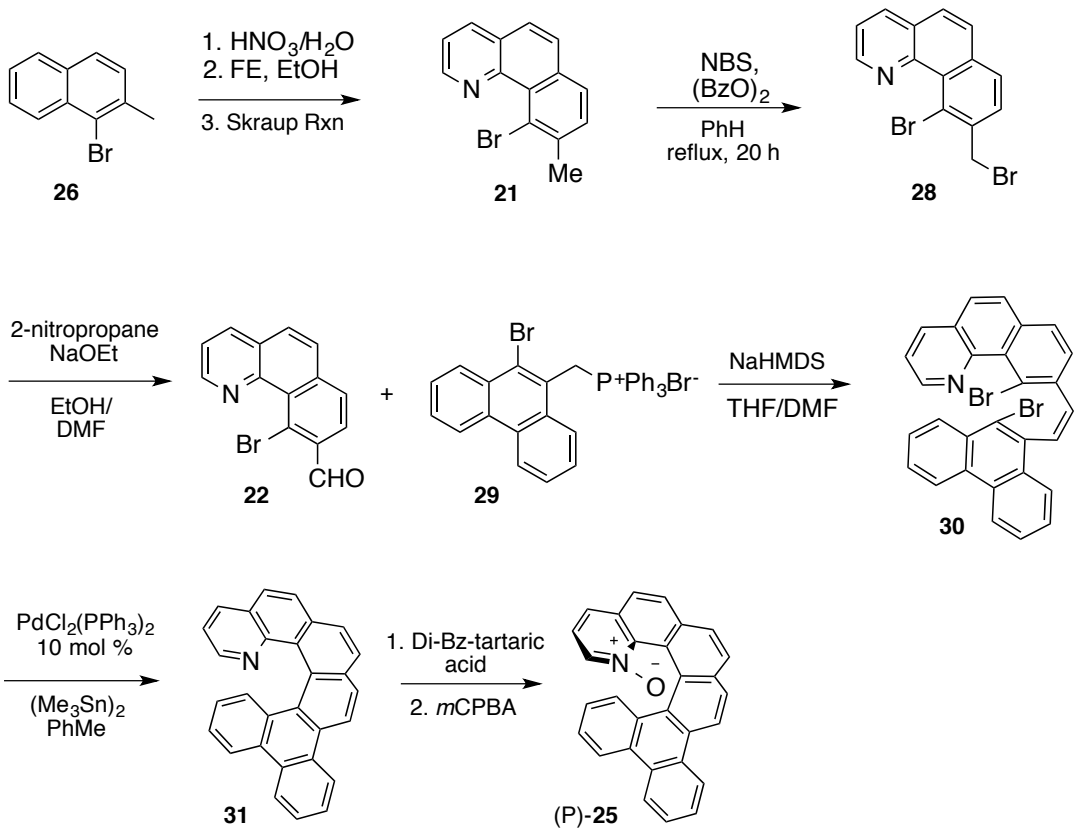
CHAPTER 4

Development of a Third Generation Helicene Synthesis

Helicenes and their derivatives have been long known examples of helical-shaped small molecules. In 1956 Newman demonstrated the first optically active synthesis of hexahelicene.[31] Since then there have been various synthetic strategies and methods to prepare helicenes in substantial quantities. However, in order for helicenes to be utilized as chiral catalytic scaffolds and efficient synthesis that permits structural variation is needed. In 2008 we reported the first application of azahelicenes in asymmetric catalysis.[4] The modular nature of our synthetic route allowed us to modify the bottom half of azahelicene at a late stage. With this in mind, we continued efforts to development a more efficient method.

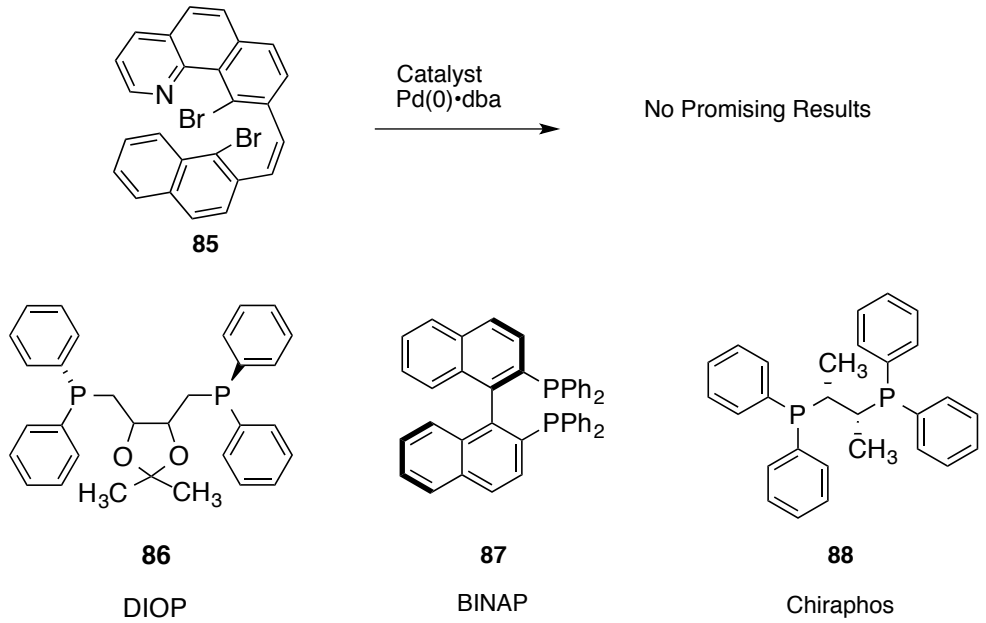
4.1 Background

We recently modified of our azahelicene preparation to address some limitations of the original synthesis but retained its modular nature. The benzoquinoline unit was prepared without the use of cross coupling reagents and can typically be synthesized in quantities of about five grams and stored without degradation. It can then be coupled with readily available screen units. The optical resolution of 11, 12-benzo-1-aza[6]helicene is acquired through chiral HPLC or diastereomeric salts with optically pure dibenzoyl-tartaric acid. Subsequent, basification provides it in approximately 85% ee after which a simple recrystallization affords the optically pure form.



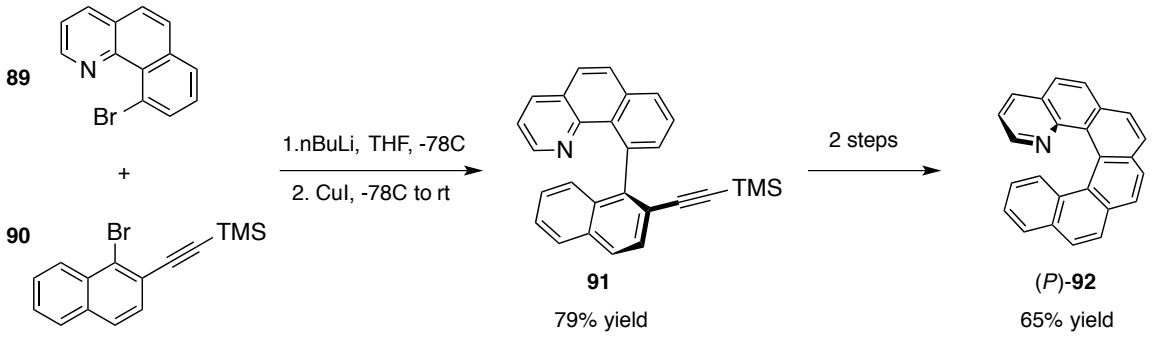
Scheme 4.1 Second generation synthesis of 1-azahelicenes. 11,12-Benzo-1-aza[6]helicene shown as a representative example. Reported by Takenaka (reference 32).

Initially, we were aware of how time consuming and tedious the resolution step can be. To this end, we then attempted to access 1-azahelicene **31** in an enantioselective manner by use of well known chiral reagents for the intramolecular cyclization step. Unfortunately, we observed no promising results and did not proceed in a rigorous investigation of the transformation at that time. (Scheme 4.2)



Scheme 4.2 Formation of 1-aza[6]helicene with chiral ligands

Recently Fuchter and his coworkers demonstrated a new synthetic route to asymmetric azahelicenes. The key intermediate was formed by using a copper-mediated cross-coupling reaction between a benzo[*h*]quinoline unit and functionalized naphthalene. The stereochemistry was derived through formation of the sterically hindered biaryl product.[89] This axial chirality was preserved in following transformations to provide asymmetric 1-azahelicenes and varying derivatives.



Scheme 4.3 Synthesis of 1-azahelicene via copper-mediated cross coupling. Reported by Fuchter (Reference 89).

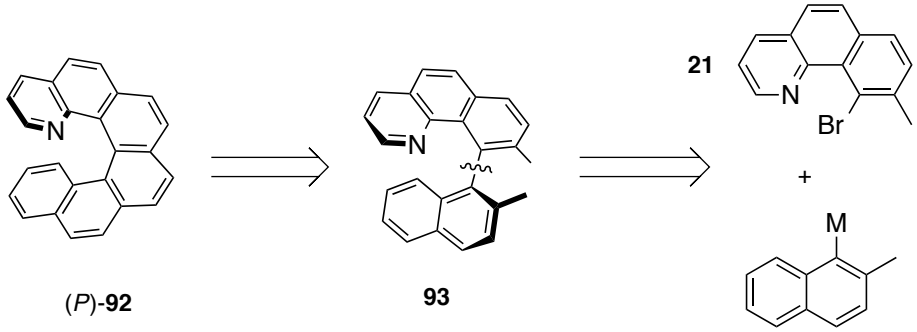
4.2 Perspective

The expansion of interest in helicenes is becoming more apparent with reported studies in fields such as nonlinear optics,[90] electro-optical switches,[91] molecular recognition[92,93] and catalysis. [4,32,94,95] We have established that molecules with helical topology based on 1-azahelicene framework can be highly effective chiral and catalytic scaffolds for unrelated transformations. With continued studies and enhancement, the possibility of these helical organocatalysts being used in total synthesis of medicinal compounds may arise.

This increased interest and our group's desire for our catalyst to possess general applicability necessitates improving the efficiency of our 1-azahelicene synthesis. Even though our second-generation synthesis can readily provide 1-azahelicenes on a multi-gram scale, the optical resolution via tartaric acid (crystallization of diastereomeric salts) or chiral HPLC separation can be viewed as a bottleneck. As such, a third-generation synthesis attempting to decrease the number of steps involved and circumvent the problem of resolution was devised.

In light of Fuchter's work, we decided to reinvestigate our synthetic route to access 1-azahelicenes. On retrosynthetic analysis, we envisaged disconnecting to a key biaryl species **93** via an intramolecular coupling reaction, a transformation that is well developed.[96,97,98] Further disconnection of the aryl – aryl bond of intermediate **93** would lead to bromobenzoquinoline unit **21,** readily available in our group and functionalized naphthalenes. However, we were wary of the difficulty in accessing intermediate **63** as it is a sterically hindered biaryl analogous to 2,2'-dimethyl-1,1'-binaphthyl. Although there have been numerous examples of biaryls formation through well-developed coupling

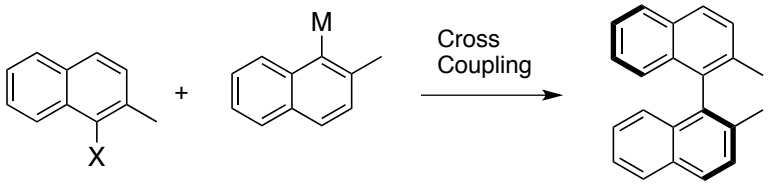
methods, 2,2'-dimethyl-1,1'-binaphthyl remains notoriously difficult to synthesize as is evidenced by select examples in the literature.



Scheme 4.4 Retrosynthetic analysis of 1-aza[6]helicene

The enantioselective synthesis of 2,2'-dimethyl-1,1'-binaphthyl via cross coupling methods has been demonstrated by Hayashi (Kumada),[99] Espinet (Negishi)[100] and more recently by Uozumi (Suzuki)[101] all in high yield and enantioselectivity. On this basis we believe that the challenge to access the biaryl intermediate can be overcome thus effectively expediting the preparation of enantiopure 1-azahelicenes. Therefore paving the way toward an asymmetric third generation synthesis.

Table 4.1 Asymmetric cross coupling of 2,2'-dimethyl-1,1'-binaphthyl by Hiyama, Espinet and Uozumi.

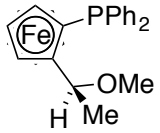


Kumada - X = Br, M = MgBr
Negishi - X = Br, M = ZnCl
Suzuki - X = I, M = $B(OH)_2$

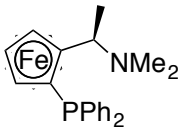
94

Method	Coupling	Ligand	Catayst	Yield	ee (%)
Hiyama	Kumada	**95**	Ni	74	95[a]
Espinet	Negishi	**96**	Pd	95	85
Uozumi	Suzuki	**97**	Pd	98	90

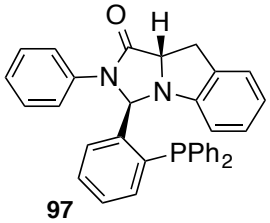
[a] (R) configuration



95



96

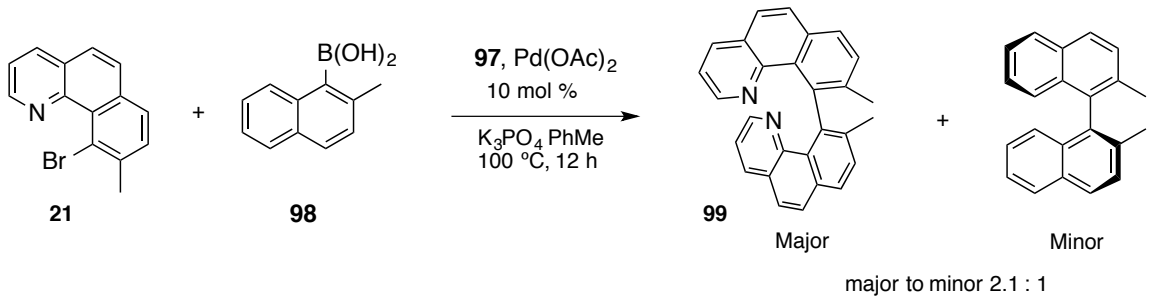


97

4.3 Results and discussion

4.3.1 Suzuki coupling

Our investigation began with the evaluation of known effective catalyst ligand developed by Uozumi for asymmetric Suzuki coupling. We studied this ligand using the Suzuki, Negishi and Kumada cross coupling methods. We began with the Suzuki cross coupling but these conditions but unfortunately our initial attempts did not provide any desired product. Interestingly, the benzoquinoline dimer and 2,2'-dimethyl-1,1'-binaphthyl were observed as products instead. The benzoquinoline dimer was formed as the major product at approximately twice that of the minor 2,2'-dimethyl-1,1'-binaphthyl product.



Scheme 4.5 Synthesis of biaryls via Suzuki coupling

Mechanistically, Suzuki coupling requires the addition of a base, potassium phosphate in this case, to activate the boronic acid species to facilitate the transmetallation step (Figure 4.1).[102] This requirement of a base makes the transmetallation step a slow one. The preceding step, oxidative addition of palladium to benzoquinoline, would mean that there is the presence of a reactive benzoquinoline-palladium (II) species.

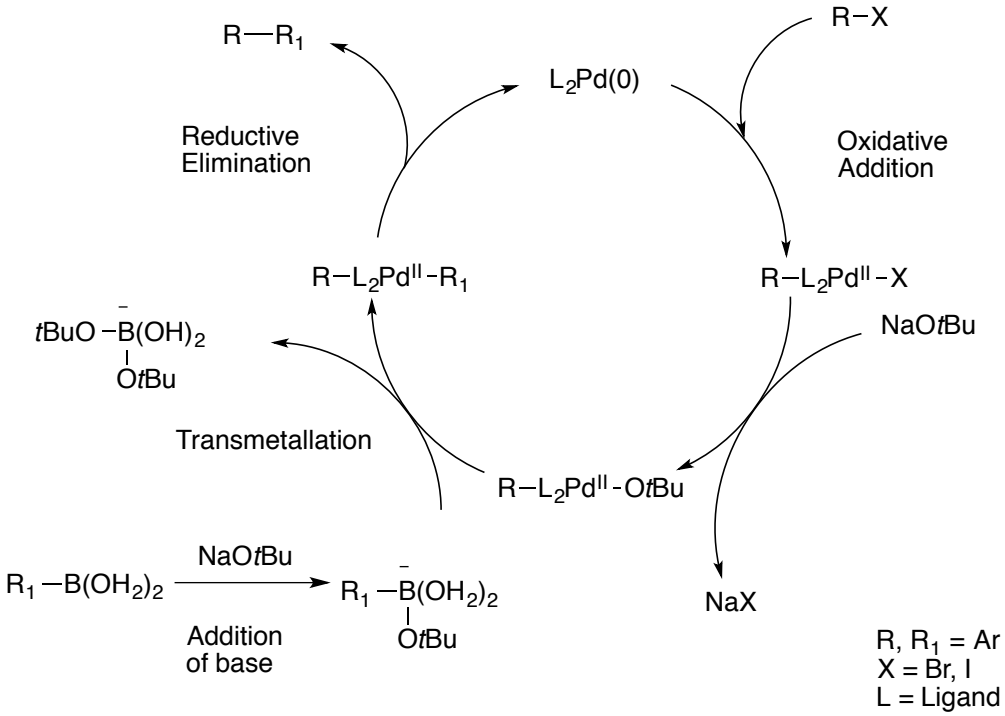


Figure 4.1 Catalytic cyclye for Suzuki coupling.

Interestingly, analogous benzo[*h*]quinoline, and 8-methylquinoline are known to form dimeric complexes in the presence of a palladium source (Figure 4.2 A and B).[103] This

occurs through proton abstraction and is very similar to the cyclopalladation process.[104,105] The analogous nature of **21** to these reported compounds allows for the formation of a dimeric complex (Figure 4.2 C) due to the cyclopalladation process. As a result, we believe a reductive elimination would lead to the formation of benzoquinoline dimer **99**.

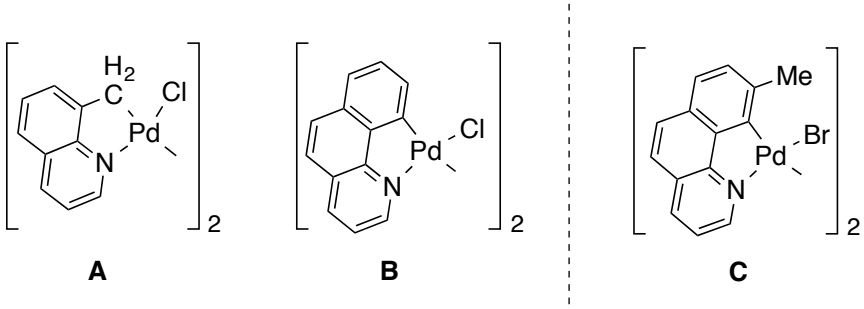
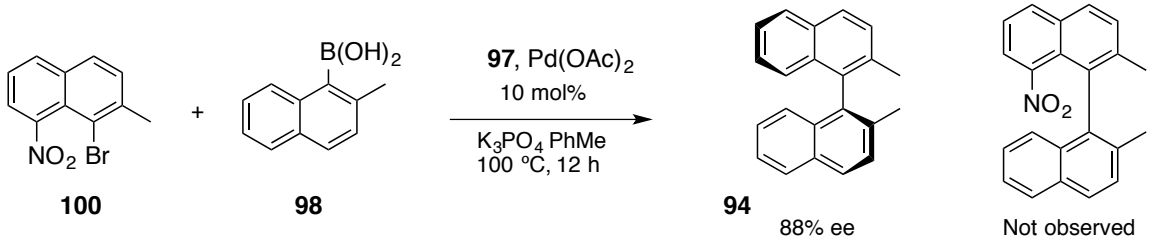


Figure 4.2 Dimeric complexes

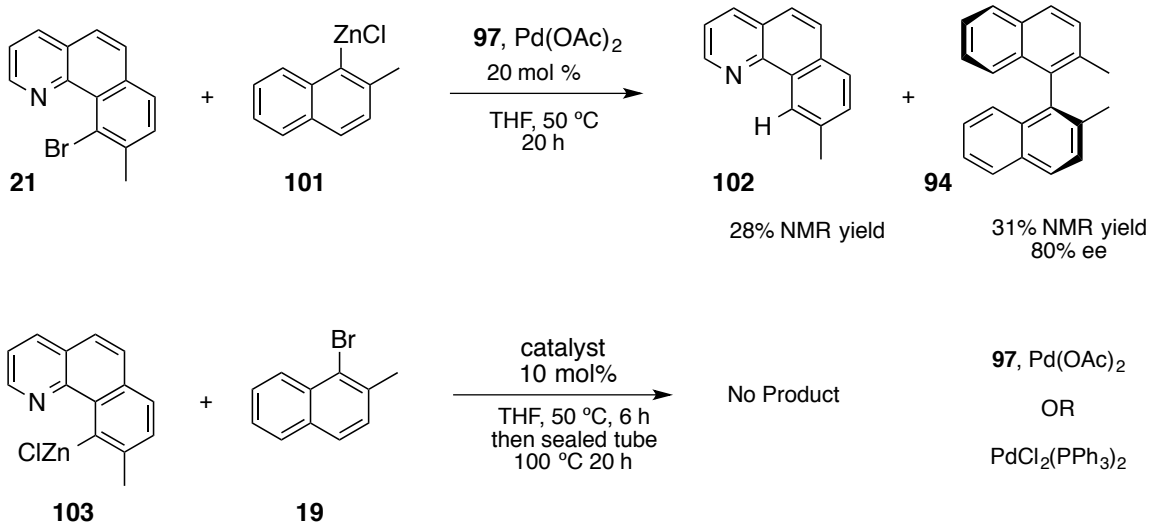
In an effort to circumvent this problem, we then decided to use 1-bromo-2-methyl-8-nitronaphthalene **100** as a coupling partner instead of **21**. This naphthalene should not have the problem of cyclopalladation, is sterically less demanding than **21** and would be able to undergo subsequent transformations to form the desired intermediate after the biaryl formation. However, the 2,2'-dimethyl-1,1'-binaphthyl was the only product observed. While we successfully prevented the formation of the benzoquinoline dimer, the favored reaction pathway was observed to be the homo-coupling of boronic acid **98** to yield **94**.



Scheme 4.6 Synthesis of biaryls via Suzuki coupling with new coupling partner

4.3.2 Negishi coupling

Next we investigated Negishi coupling conditions for our substrates. The possibility of forming the benzoquinoline dimer **99** was minimized as no base is required for activation in the Negishi coupling mechanism and as such the transmetallation step is faster than in Suzuki coupling. While the dimerized side product was not formed, neither was the desired biaryl, with the 2,2'-dimethyl-1,1'-binaphthyl and benzo[*h*]quinoline **102** being observed as products. We believe that the apparent decomposition of the benzoquinoline unit **21** resulting in the formation of **102**, may have occurred at the oxidative addition or transmetallation step. This decomposition is seemingly equal to the rate of formation of the 2,2'-dimethyl-1,1'-binaphthyl formed as a result of homo-coupling of naphthalene unit **101**.



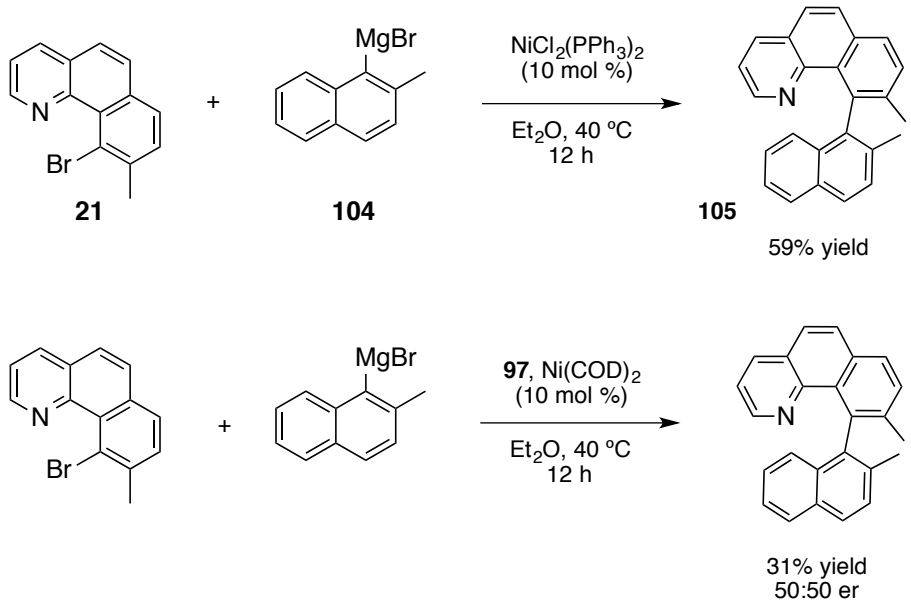
Scheme 4.7 Synthesis of biaryls via Negishi coupling.

Initially we used the naphthalene unit to generate the zinc halide species, in further efforts, we then alternated to the benzoquinoline to form the zinc halide species **103**. In this instance no product of any kind was observed. We suspect that this may have been a result of lone pair coordination of the nitrogen atom to the zinc metal due to their

proximity in the benzoquinoline unit **103**. This would lead to a reduced reactivity of the species, resulting in no product formation. Subsequently, the reaction was then carried out with achiral ligand-catalyst system, $PdCl_2(PPh_3)_2$ and the same result was observed.

4.3.3 Kumada coupling

We then investigated Kumada coupling conditions for our substrates. With our initial efforts we were pleased to find the desired compound was formed in 59% yield using an achiral catalyst, $NiCl_2(PPh_3)_2$.

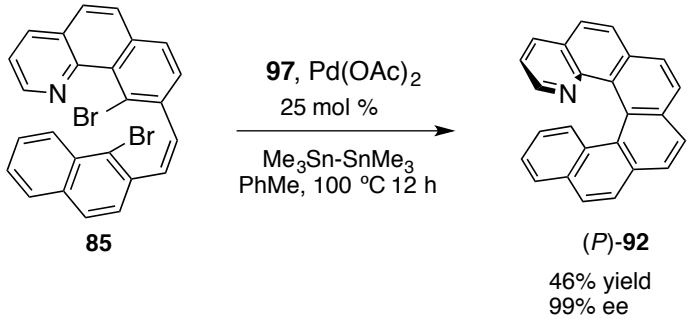


Scheme 4.8 Synthesis of biaryl via Kumada coupling.

However, with the use of **97** a yield of 31% was obtained but no enantioselectivity was observed. The decrease in yield may have been a result of the bulky cyclooctadiene ligand on the Nickel source, which may cause negative steric interactions in an already sterically demanding system. While the lack of enantioselection may be due to a number of factors, it is important to note that naphthalene unit **104** is a Grignard reagent and can possibly react with the carbonyl functional group of **97** and render the catalyst ineffective.

4.3.4 Enantioselective intramolecular cyclization

Not to be deterred by these results, we decided to reinvestigate the asymmetric cyclization step of 1-aza[6]helicene using Uozumi's ligand **97** under Stille-Kelly conditions. The effectual nature of Uozumi's ligand for intermolecular cross – coupling indicated that it may well be applicable in an intramolecular variant. While the use of aforementioned chiral reagents was unproductive, to our delight, the reaction proceeded in 46% yield and 99% ee with **97**. Although the yield was modest which again may be due to the sterically demanding nature of the compound **85**, we were pleased that the transformation was highly selective and provided near enantiopure product. The remarkably high level enantioselectivity shows that the catalyst binds to the substrate almost exclusively in one fashion, leading to the formation of one predominant enantiomer as the product.



Scheme 4.9 Enantioselective cyclization via Stille-Kelly coupling

4.4 Future studies

The asymmetric cross coupling with our substrates should be systematically investigated with the use of the chiral ligands developed by Hiyama and Espinet for 2,2'-dimethyl-1,1'-binaphthyl. Once an effective catalyst has been identified, the various coupling methods can then be investigated to indicate which provides the best results for the key intermediate. The synthetic route will be followed to access 1-aza[6]helicene. As

such, structural analogs of our substrates can then be investigated in the synthesis of other 1-azahelicenes. Also, the formation of 1-aza[7]helicene can be investigated by using the intramolecular cyclization with Uozumi's ligand and the respective precursor.

4.5 Conclusion

We have attempted to further streamline access to 1-azahelicenes by designing a third generation synthesis. Although our efforts to accomplish this synthesis have been generally ineffective, the racemic desired product was obtained through Kumada coupling. We believe continued investigation of chiral catalysts will eventually facilitate this transformation enantioselectively, allowing us to retain the modular nature akin to our present synthetic route to 1-azahelicenes. Thus far we have shown the last step of the second generation synthesis of 1-aza[6]helicene can be prepared with high selectivity thereby eliminating the need for resolution by tartaric acid or semi-preparative chiral HPLC separation.

4.6 Experimental section

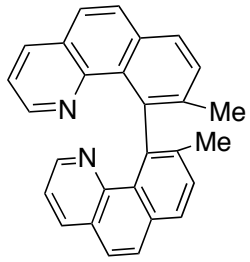
4.6.1 General information

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 using silica gel 60 (mesh 230-400) supplied by Silicycle.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromenthane (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), a Bruker Avance 400 (400 MHz ^{1}H, 100 MHz ^{13}C), and a Bruker Avance 500 (500 MHz ^{1}H, 125 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, University of Miami.

4.6.2 2,2'-Dimethyl benzoquinoline dimer (99)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.91 (m, 8H), 7.64 – 7.61 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.53 (d, *J* = 9.0 Hz, 2H), 7.02 – 6.98 (dd, *J* = 4.2, 7.8 Hz, 2H), 1.87 (s, 6H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 147.9, 146.8, 143.1, 134.6, 134.3, 133.4, 130.6, 129.6, 128.8, 126.7,

126.0, 124.2, 120.1, 21.0; FTIR (neat) υ_{max} 3041, 2918, 1588, 1555, 1509, 1437, 1392, 906, 839, 735, 652 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{28}H_{20}N_2$ $[M + 1]^+$, expected: 385.1699, found: 385.1702.

References

1. Diels, O.; Alder, K., Synthesen In Der Hydroaromatischen Reihe. *Justus Liebigs Annalen Der Chemie* **1928,** *460* (1), 98-122.

2. Ono, N., Conversion Of Nitro Compounds Into Other Compounds. In *The Nitro Group In Organic Synthesis*, John Wiley & Sons, Inc.: 2002; Pp 159-181.

3. Claisen, L., Über Umlagerung Von Phenol-Allyläthern In C-Allyl-Phenole. *Berichte Der Deutschen Chemischen Gesellschaft* **1912,** *45* (3), 3157-3166.

4. Takenaka, N.; Sarangthem, R. S.; Captain, B., Helical Chiral Pyridine *N*-Oxides: A New Family Of Asymmetric Catalysts. *Angewandte Chemie International Edition* **2008,** *47* (50), 9708-9710.

5. Yates, P.; Eaton, P., Acceleration Of The Diels-Alder Reaction By Aluminum Chloride. *Journal Of The American Chemical Society* **1960,** *82* (16), 4436-4437.

6. Corey, E. J., Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, And Applications. *Angewandte Chemie International Edition* **2002,** *41* (10), 1650-1667.

7. Kagan, H. B.; Riant, O., Catalytic Asymmetric Diels Alder Reactions. *Chemical Reviews* **1992,** *92* (5), 1007-1019.

8. Denmark, S. E.; Kesler, B. S.; Moon, Y. C., Inter- And Intramolecular [4 + 2] Cycloadditions Of Nitroalkenes With Olefins. 2-Nitrostyrenes. *The Journal Of Organic Chemistry* **1992,** *57* (18), 4912-4924.

9. Çelebi-Ölçüm, N.; Ess, D. H.; Aviyente, V.; Houk, K. N., Lewis Acid Catalysis Alters The Shapes And Products Of Bis-Pericyclic Diels−Alder Transition States. *Journal Of The American Chemical Society* **2007,** *129* (15), 4528-4529.

10. Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas III, C. F., Amine-Catalyzed Direct Diels–Alder Reactions Of α,β-Unsaturated Ketones With Nitro Olefins. *Tetrahedron Letters* **2002,** *43* (21), 3817-3820.

11. Sundén, H.; Rios, R.; Xu, Y.; Eriksson, L.; Córdova, A., Direct Enantioselective Synthesis Of Bicyclic Diels–Alder Products. *Advanced Synthesis & Catalysis* **2007,** *349* (17-18), 2549-2555.

12. Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y., In Situ Enamine Activation In Aqueous Salt Solutions: Highly Efficient Asymmetric Organocatalytic Diels–Alder Reaction Of Cyclohexenones With Nitroolefins. *Angewandte Chemie International Edition* **2009,** *48* (21), 3821-3824.

13. Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P., Organocascade Reactions Of Enones Catalyzed By A Chiral Primary Amine. *Angewandte Chemie International Edition* **2009,** *48* (39), 7196-7199.

14. Bartelson, K. J.; Singh, R. P.; Foxman, B. M.; Deng, L., Catalytic Asymmetric [4 + 2] Additions With Aliphatic Nitroalkenes. *Chemical Science* **2011,** *2* (10), 1940-1944.

15. Maruoka, K.; Banno, H.; Yamamoto, H., Asymmetric Claisen Rearrangement Catalyzed By Chiral Organoaluminum Reagent. *Journal Of The American Chemical Society* **1990,** *112* (21), 7791-7793.

16. Abraham, L.; Czerwonka, R.; Hiersemann, M., The Catalytic Enantioselective Claisen Rearrangement Of An Allyl Vinyl Ether. *Angewandte Chemie International Edition* **2001,** *40* (24), 4700-4703.

17. Hiersemann, M.; Abraham, L., The $Cu(OTf)_2$- And $Yb(OTf)_3$-Catalyzed Claisen Rearrangement Of 2-Alkoxycarbonyl-Substituted Allyl Vinyl Ethers. *Organic Letters* **2000,** *3* (1), 49-52.

18. Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M., The Catalytic Diastereo- And Enantioselective Claisen Rearrangement Of 2-Alkoxycarbonyl-Substituted Allyl Vinyl Ether. *Advanced Synthesis & Catalysis* **2004,** *346* (11), 1281-1294.

19. Linton, E. C.; Kozlowski, M. C., Catalytic Enantioselective Meerwein−Eschenmoser Claisen Rearrangement: Asymmetric Synthesis Of Allyl Oxindoles. *Journal Of The American Chemical Society* **2008,** *130* (48), 16162-16163.

20. Uyeda, C.; Jacobsen, E. N., Enantioselective Claisen Rearrangements With A Hydrogen-Bond Donor Catalyst. *Journal Of The American Chemical Society* **2008,** *130* (29), 9228-9229.

21. Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Curran, D. P.; Peck, D. R., Synthesis And Claisen Rearrangement Of Alkoxyallyl Enol Ethers. Evidence For A Dipolar Transition State. *Journal Of The American Chemical Society* **1987,** *109* (4), 1160-1170.

22. Cramer, C. J.; Truhlar, D. G., What Causes Aqueous Acceleration Of The Claisen Rearrangement? *Journal Of The American Chemical Society* **1992,** *114* (23), 8794-8799.

23. Sehgal, A.; Shao, L.; Gao, J., Transition Structure And Substituent Effects On Aqueous Acceleration Of The Claisen Rearrangement. *Journal Of The American Chemical Society* **1995,** *117* (45), 11337-11340.

24. Uyeda, C.; Jacobsen, E. N., Transition-State Charge Stabilization Through Multiple Non-Covalent Interactions In The Guanidinium-Catalyzed Enantioselective Claisen Rearrangement. *Journal Of The American Chemical Society* **2011,** *133* (13), 5062-5075.

25. Uyeda, C.; Rötheli, A. R.; Jacobsen, E. N., Catalytic Enantioselective Claisen Rearrangements Of *O*-Allyl β-Ketoesters. *Angewandte Chemie International Edition* **2010,** *49* (50), 9753-9756.

26. Denmark, S. E.; Fan, Y., Catalytic, Enantioselective Aldol Additions To Ketones. *Journal Of The American Chemical Society* **2002,** *124* (16), 4233-4235.

27. Bolm, C.; Zehnder, M.; Bur, D., Optically Active Bipyridines In Asymmetric Catalysis. *Angewandte Chemie International Edition In English* **1990,** *29* (2), 205-207.

28. Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P., Quinox, A Quinoline-Type *N*-Oxide, As Organocatalyst In The Asymmetric Allylation Of Aromatic Aldehydes With Allyltrichlorosilanes: The Role Of Arene–Arene Interactions. *Angewandte Chemie International Edition* **2003,** *42* (31), 3674-3677.

29. Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M., The Scope Of Catalytic Asymmetric Hydroboration/Oxidation With Rhodium Complexes Of 1,1′ -(2-Diarylphosphino-1-Naphthyl)Isoquinolines. *Chemistry – A European Journal* **1999,** *5* (4), 1320-1330.

30. Tao, B.; Fu, G. C., Application Of A New Family Of P,N Ligands To The Highly Enantioselective Hydrosilylation Of Aryl Alkyl And Dialkyl Ketones. *Angewandte Chemie International Edition* **2002,** *41* (20), 3892-3894.

31. Newman, M. S.; Lednicer, D., The Synthesis And Resolution Of Hexahelicene. *Journal Of The American Chemical Society* **1956,** *78* (18), 4765-4770.

32. Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A., Helical Chiral 2-Aminopyridinium Ions: A New Class Of Hydrogen Bond Donor Catalysts. *Journal Of The American Chemical Society* **2010,** *132* (13), 4536-4537.

33. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G., The Diels–Alder Reaction In Total Synthesis. *Angewandte Chemie International Edition* **2002,** *41* (10), 1668-1698.

34. Hayashi, Y., Catalytic Asymmetric Diels-Alder Reactions. In *Cycloaddition Reactions In Organic Synthesis*, Wiley-Vch Verlag Gmbh: 2001; Pp 5-55.

35. Payette, J. N.; Yamamoto, H., Cationic-Oxazaborolidine-Catalyzed Enantioselective Diels–Alder Reaction Of α,β-Unsaturated Acetylenic Ketones. *Angewandte Chemie International Edition* **2009,** *48* (43), 8060-8062.

36. Snyder, S. A.; Corey, E. J., Concise Total Syntheses Of Palominol, Dolabellatrienone, β-Araneosene, And Isoedunol Via An Enantioselective Diels−Alder Macrobicyclization. *Journal Of The American Chemical Society* **2005,** *128* (3), 740-742.

37. Wilson, R. M.; Jen, W. S.; Macmillan, D. W. C., Enantioselective Organocatalytic Intramolecular Diels−Alder Reactions. The Asymmetric Synthesis Of Solanapyrone D. *Journal Of The American Chemical Society* **2005,** *127* (33), 11616-11617.

38. Li, F.; Tartakoff, S. S.; Castle, S. L., Total Synthesis Of (−)-Acutumine. *Journal Of The American Chemical Society* **2009,** *131* (19), 6674-6675.

39. Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. I., Absolute Stereochemistry Of Citrinadins A And B From Marine-Derived Fungus. *The Journal Of Organic Chemistry* **2005,** *70* (23), 9430-9435.

40. King, S. M.; Calandra, N. A.; Herzon, S. B., Total Syntheses Of (−)-Acutumine And (−)-Dechloroacutumine. *Angewandte Chemie International Edition* **2013,** *52* (13), 3642-3645.

41. Pettersson, M.; Knueppel, D.; Martin, S. F., Concise, Stereoselective Approach To The Spirooxindole Ring System Of Citrinadin A. *Organic Letters* **2007,** *9* (22), 4623-4626.

42. Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K., Nitroethylene As A Versatile Ketene Equivalent. Novel One-Step Preparation Of Prostaglandin Intermediates By Reduction And Abnormal Nef Reaction. *Journal Of The American Chemical Society* **1974,** *96* (16), 5261-5262.

43. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W., Stereo-Controlled Synthesis Of dl-Prostaglandins F2.Alpha. And E2. *Journal Of The American Chemical Society* **1969,** *91* (20), 5675-5677.

44. Doyle, A. G.; Jacobsen, E. N., Small-Molecule H-Bond Donors In Asymmetric Catalysis. *Chemical Reviews* **2007,** *107* (12), 5713-5743.

45. Taylor, M. S.; Jacobsen, E. N., Asymmetric Catalysis By Chiral Hydrogen-Bond Donors. *Angewandte Chemie International Edition* **2006,** *45* (10), 1520-1543.

46. Takemoto, Y., Recognition And Activation By Ureas And Thioureas: Stereoselective Reactions Using Ureas And Thioureas As Hydrogen-Bonding Donors. *Organic & Biomolecular Chemistry* **2005,** *3* (24), 4299-4306.

47. Sigman, M. S.; Jacobsen, E. N., Schiff Base Catalysts For The Asymmetric Strecker Reaction Identified And Optimized From Parallel Synthetic Libraries. *Journal Of The American Chemical Society* **1998,** *120* (19), 4901-4902.

48. Wenzel, A. G.; Jacobsen, E. N., Asymmetric Catalytic Mannich Reactions Catalyzed By Urea Derivatives: Enantioselective Synthesis Of β-Aryl-β-Amino Acids. *Journal Of The American Chemical Society* **2002,** *124* (44), 12964-12965.

49. Yoon, T. P.; Jacobsen, E. N., Highly Enantioselective Thiourea-Catalyzed Nitro-Mannich Reactions. *Angewandte Chemie International Edition* **2005,** *44* (3), 466-468.

50. Raheem, I. T.; Jacobsen, E. N., Highly Enantioselective Aza-Baylis–Hillman Reactions Catalyzed By Chiral Thiourea Derivatives. *Advanced Synthesis & Catalysis* **2005,** *347* (11-13), 1701-1708.

51. Schuster, T.; Kurz, M.; Göbel, M. W., Catalysis Of A Diels−Alder Reaction By Amidinium Ions. *The Journal Of Organic Chemistry* **2000,** *65* (6), 1697-1701.

52. Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W., Axially Chiral Amidinium Ions As Inducers Of Enantioselectivity In Diels−Alder Reactions. *Organic Letters* **2000,** *2* (2), 179-181.

53. Tsogoeva, Svetlana B.; Dürner, G.; Bolte, M.; Göbel, Michael W., A C_2-Chiral Bis(Amidinium) Catalyst For A Diels−Alder Reaction Constituting The Key Step Of The Quinkert−Dane Estrone Synthesis. *European Journal Of Organic Chemistry* **2003,** *2003* (9), 1661-1664.

54. Takenaka, N.; Sarangthem, R. S.; Seerla, S. K., 2-Aminopyridinium Ions Activate Nitroalkenes Through Hydrogen Bonding. *Organic Letters* **2007,** *9* (15), 2819-2822.

55. Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A., Catalytic Enantioselective Friedel–Crafts Alkylation Of Indoles With Nitroalkenes By Using A Simple Thiourea Organocatalyst. *Angewandte Chemie International Edition* **2005,** *44* (40), 6576-6579.

56. Narcis, M. J.; Sprague, D. J.; Captain, B.; Takenaka, N., Enantio- And Periselective Nitroalkene Diels-Alder Reaction. *Organic & Biomolecular Chemistry* **2012,** *10* (46), 9134-9136.

57. Ben Romdhane, H.; Baklouti, M.; Chaâbouni, M. R.; Grenier-Loustalot, M. F.; Delolme, F.; Sillion, B., Polypentamethylnadimides Obtained By Diels–Alder Reaction. *Polymer* **2002,** *43* (2), 255-268.

58. Peng, Z.; Narcis, M.; Takenaka, N., Enantio- And Periselective Nitroalkene Diels-Alder Reactions Catalyzed By Helical-Chiral Hydrogen Bond Donor Catalysts. *Molecules* **2013,** *18* (8), 9982-9998.

59. Adam, W.; Jacob, U.; Prein, M., Importance Of Steric Effects In The [4 + 2] Cycloaddition Of 5-Substituted Pentamethylcyclopentadienes. *Journal Of The Chemical Society, Chemical Communications* **1995,** (8), 839-840.

60. Baranovsky, A. V.; Bolibrukh, D. A.; Khripach, V. A.; Schneider, B., Diels–Alder Reaction Of Androsta-14,16-Dien-17-yl Acetates With Nitroethylene: Product Distribution And Selected Adduct Transformations. *Steroids* **2013,** *78* (2), 282-287.

61. Schwartz, C. E.; Curran, D. P., New Tandem Radical Cyclizations Directed Toward The Synthesis Of Crinipellin A. *Journal Of The American Chemical Society* **1990,** *112* (25), 9272-9284.

62. Crane, S. N.; Burnell, D. J., The $BF_3 \cdot Et_2O$-Catalyzed Reaction Of 1,2-Bis[(Trimethylsilyl)Oxy]Cyclobutene And Analogues With Aromatic Ketones. *The Journal Of Organic Chemistry* **1998,** *63* (4), 1352-1355.

63. Jenkins, T. J.; Burnell, D. J., Lewis Acid Catalyzed Geminal Acylation Reaction Of Ketones With 1,2-Bis[(Trimethylsilyl)Oxy]Cyclobutene: Direct Formation Of 2,2-Disubstituted 1,3-Cyclopentanediones. *The Journal Of Organic Chemistry* **1994,** *59* (6), 1485-1491.

64. Lombardo, L., Methylenation Of Carbonyl Compounds With Zn-CH_2Br_2-$TiCl_4$. Application To Gibberellins. *Tetrahedron Letters* **1982,** *23* (41), 4293-4296.

65. Peng, F.; Danishefsky, S. J., Total Synthesis Of (±)-Maoecrystal V. *Journal Of The American Chemical Society* **2012,** *134* (45), 18860-18867.

66. Hibino, J.-I.; Okazoe, T.; Takai, K.; Nozaki, H., Carbonyl Methylenation Of Easily Enolizable Ketones. *Tetrahedron Letters* **1985,** *26* (45), 5579-5580.

67. Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C., Dichloromethane Activation. Direct Methylenation Of Ketones And Aldehydes With CH_2Cl_2 Promoted By Mg/$TiCl_4$/THF. *Organic Letters* **2004,** *6* (26), 4961-4963.

68. Aguado, A.; Takenaka, N., Intramolecular Nitroalkene Diels-Alder Reaction Catalyzed By Brønsted Acids. *Synlett* **2011,** *2011* (9), 1259-1261.

69. Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R., Nitroethylene: A Stable, Clean, And Reactive Agent For Organic Synthesis. *The Journal Of Organic Chemistry* **1980,** *45* (7), 1185-1189.

70. Wu, Y. J.; Strickland, D. W.; Jenkins, T. J.; Liu, P. Y.; Burnell, D. J., Formation Of 2,2-Disubstituted 1,3-Cyclopentanediones From Ketals With 1,2-Bis(Trimethylsilyloxy)Cyclobutene. *Can. J. Chem.* **1993,** *71* (9), 1311-1318.

71. Jenkins, T. J.; Burnell, D. J., Lewis-Acid Catalyzed Geminal Acylation Reaction Of Ketones With 1,2-Bis((Trimethylsilyl)Oxy)Cyclobutene - Direct Formation Of 2,2-Disubstituted 1,3-Cyclopentanediones. *J. Org. Chem.* **1994,** *59* (6), 1485-1491.

72. Peterson, E. A.; Overman, L. E., Contiguous Stereogenic Quaternary Carbons: A Daunting Challenge In Natural Products Synthesis. *Proceedings Of The National Academy Of Sciences Of The United States Of America* **2004,** *101* (33), 11943-11948.

73. Copley, S. D.; Knowles, J. R., The Uncatalyzed Claisen Rearrangement Of Chorismate To Prephenate Prefers A Transition State Of Chair-Like Geometry. *Journal Of The American Chemical Society* **1985,** *107* (18), 5306-5308.

74. Addadi, L.; Jaffe, E. K.; Knowles, J. R., Secondary Tritium Isotope Effects As Probes Of The Enzymic And Nonenzymic Conversion Of Chorismate To Prephenate. *Biochemistry* **1983,** *22* (19), 4494-4501.

75. Chook, Y. M.; Gray, J. V.; Ke, H.; Lipscomb, W. N., The Monofunctional Chorismate Mutase From Bacillus Subtilis: Structure Determination Of Chorismate Mutase And Its Complexes With A Transition State Analog And Prephenate, And Implications For The Mechanism Of The Enzymatic Reaction. *Journal Of Molecular Biology* **1994,** *240* (5), 476-500.

76. Chook, Y. M.; Ke, H.; Lipscomb, W. N., Crystal Structures Of The Monofunctional Chorismate Mutase From Bacillus Subtilis And Its Complex With A Transition State Analog. *Proceedings Of The National Academy Of Sciences* **1993,** *90* (18), 8600-8603.

77. Lee, A. Y.; Karplus, P. A.; Ganem, B.; Clardy, J., Atomic Structure Of The Buried Catalytic Pocket Of Escherichia Coli Chorismate Mutase. *Journal Of The American Chemical Society* **1995,** *117* (12), 3627-3628.

78. Haynes, M.; Stura, E.; Hilvert, D.; Wilson, I., Routes To Catalysis: Structure Of A Catalytic Antibody And Comparison With Its Natural Counterpart. *Science* **1994,** *263* (5147), 646-652.

79. Cload, S. T.; Liu, D. R.; Pastor, R. M.; Schultz, P. G., Mutagenesis Study Of Active Site Residues In Chorismate Mutase From Bacillus Subtilis. *Journal Of The American Chemical Society* **1996,** *118* (7), 1787-1788.

80. Kienhöfer, A.; Kast, P.; Hilvert, D., Selective Stabilization Of The Chorismate Mutase Transition State By A Positively Charged Hydrogen Bond Donor. *Journal Of The American Chemical Society* **2003,** *125* (11), 3206-3207.

81. Wiest, O.; Houk, K. N., Stabilization Of The Transition State Of The Chorismate-Prephenate Rearrangement: An Ab Initio Study Of Enzyme And Antibody Catalysis. *Journal Of The American Chemical Society* **1995,** *117* (47), 11628-11639.

82. Curran, D. P.; Kuo, L. H., Acceleration Of A Dipolar Claisen Rearrangement By Hydrogen Bonding To A Soluble Diaryl Urea. *Tetrahedron Letters* **1995,** *36* (37), 6647-6650.

83. Kirsten, M.; Rehbein, J.; Hiersemann, M.; Strassner, T., Organocatalytic Claisen Rearrangement: Theory And Experiment. *The Journal Of Organic Chemistry* **2007,** *72* (11), 4001-4011.

84. Narcis, M. J.; Takenaka, N., Helical-Chiral Small Molecules In Asymmetric Catalysis. *European Journal Of Organic Chemistry* **2014,** *2014* (1), 21-34.

85. Chen, J.; Captain, B.; Takenaka, N., Helical Chiral 2,2′ -Bipyridine N-Monoxides As Catalysts In The Enantioselective Propargylation Of Aldehydes With Allenyltrichlorosilane. *Organic Letters* **2011,** *13* (7), 1654-1657.

86. Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K., Chiral 1,1‘-Binaphthyl-2,2‘-Diammonium Salt Catalysts For The Enantioselective Diels−Alder Reaction With Α-Acyloxyacroleins. *Organic Letters* **2006,** *8* (11), 2229-2232.

87. Terada, M.; Ikehara, T.; Ube, H., Enantioselective 1,4-Addition Reactions Of Diphenyl Phosphite To Nitroalkenes Catalyzed By An Axially Chiral Guanidine. *Journal Of The American Chemical Society* **2007,** *129* (46), 14112-14113.

88. The 11,12-Benzo-1-Aza[6]Helicene Dimer Single H-Bond Donor Catalyst Was Not Used In Any Experiments. Its Characterization And X-Ray Crystallogrphic Data Is Not Included

89. Weimar, M.; Correa Da Costa, R.; Lee, F.-H.; Fuchter, M. J., A Scalable And Expedient Route To 1-Aza[6]helicene Derivatives And Its Subsequent Application To A Chiral-Relay Asymmetric Strategy. *Organic Letters* **2013,** *15* (7), 1706-1709.

90. Verbiest, T.; Elshocht, S. V.; Kauranen, M.; Hellemans, L.; Snauwaert, J.; Nuckolls, C.; Katz, T. J.; Persoons, A., Strong Enhancement Of Nonlinear Optical Properties Through Supramolecular Chirality. *Science* **1998,** *282* (5390), 913-915.

91. Nuckolls, C.; Shao, R.; Jang, W.-G.; Clark, N. A.; Walba, D. M.; Katz, T. J., Electro-Optic Switching By Helicene Liquid Crystals. *Chemistry Of Materials* **2002,** *14* (2), 773-776.

92. Wang, D. Z.; Katz, T. J., A [5]Helol Analogue That Senses Remote Chirality In Alcohols, Phenols, Amines, And Carboxylic Acids. *The Journal Of Organic Chemistry* **2005,** *70* (21), 8497-8502.

93. Xu, Y.; Zhang, Y. X.; Sugiyama, H.; Umano, T.; Osuga, H.; Tanaka, K., (P)-Helicene Displays Chiral Selection In Binding To Z-DNA. *Journal Of The American Chemical Society* **2004,** *126* (21), 6566-6567.

94. Crittall, M. R.; Rzepa, H. S.; Carbery, D. R., Design, Synthesis, And Evaluation Of A Helicenoidal DMAP Lewis Base Catalyst. *Organic Letters* **2011,** *13* (5), 1250-1253.

95. Dreher, S. D.; Katz, T. J.; Lam, K.-C.; Rheingold, A. L., Application Of The Russig−Laatsch Reaction To Synthesize A Bis[5]helicene Chiral Pocket For Asymmetric Catalysis. *The Journal Of Organic Chemistry* **2000,** *65* (3), 815-822.

96. Grandbois, A.; Collins, S. K., Enantioselective Synthesis Of [7]Helicene: Dramatic Effects Of Olefin Additives And Aromatic Solvents In Asymmetric Olefin Metathesis. *Chemistry – A European Journal* **2008,** *14* (30), 9323-9329.

97. Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J., Preparation Of Helicenes Through Olefin Metathesis. *Angewandte Chemie International Edition* **2006,** *45* (18), 2923-2926.

98. Gingras, M.; Dubois, F., Synthesis Of Carbohelicenes And Derivatives By "Carbenoid Couplings". *Tetrahedron Letters* **1999,** *40* (7), 1309-1312.

99. Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y., Asymmetric Synthesis Catalyzed By Chiral Ferrocenylphosphine-Transition-Metal Complexes. 6. Practical Asymmetric Synthesis Of 1,1'-Binaphthyls Via Asymmetric Cross-Coupling With A Chiral [(Alkoxyalkyl)Ferrocenyl]Monophosphine/Nickel Catalyst. *Journal Of The American Chemical Society* **1988,** *110* (24), 8153-8156.

100. Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B., Asymmetric Negishi Reaction For Sterically Hindered Couplings: Synthesis Of Chiral Binaphthalenes. *Tetrahedron: Asymmetry* **2006,** *17* (18), 2593-2595.

101. Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A., Asymmetric Suzuki–Miyaura Coupling In Water With A Chiral Palladium Catalyst Supported On An Amphiphilic Resin. *Angewandte Chemie International Edition* **2009,** *48* (15), 2708-2710.

102. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions Of Organoboron Compounds. *Chemical Reviews* **1995,** *95* (7), 2457-2483.

103. Hartwell, G. E.; Lawrence, R. V.; Smas, M. J., The Formation Of Palladium(II)- And Platinum(II)-Carbon Bonds By Proton Abstraction From Benzo[h]quinoline And 8-Methylquinoline. *Journal Of The Chemical Society D: Chemical Communications* **1970,** (15), 912.

104. Minatti, A.; Muniz, K., Intramolecular Aminopalladation Of Alkenes As A Key Step To Pyrrolidines And Related Heterocycles. *Chemical Society Reviews* **2007,** *36* (7), 1142-1152.

105. Vicente, J.; Saura-Llamas, I., Ortho-Palladation Of Primary Amines: The Myth Dispelled. *Comments On Inorganic Chemistry* **2007,** *28* (1-2), 39-72.