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Development of New Hydrogen Bond Donor Catalytic Methods and Their Applications to the Diels-Alder Reaction of Nitroalkenes

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DEVELOPMENT OF NEW HYDROGEN BOND DONOR CATALYTIC METHODS AND THEIR APPLICATIONS TO THE DIELS-ALDER REACTION OF NITROALKENES

By

Andreina Aguado Jimenez

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The development of LUMO lowering double hydrogen bond donor catalysts, 2-aminopyridinium, for the Diels-Alder reaction of nitroalkenes is described. In addition, helical chiral 2-aminopyridinium variants were identified as promising asymmetric catalysts for the intermolecular Diels-Alder of nitroalkenes, providing a first example of an enantioselective nitroalkene Diels-Alder reaction by a LUMO lowering strategy.

Additionally, this LUMO lowering strategy has been successfully applied to the intramolecular nitroalkene Diels-Alder reaction to produce the first sub-stoichiometric catalytic process for the intramolecular Diels-Alder reaction of nitroalkenes. This method is capable of accessing a range of stereochemically complex [4.3.0] and [4.4.0] nitrocarbocycles in good yields and high to excellent levels of diastereoselectivity. This methodology highlights the utility of double hydrogen bond donor catalysts, 2-aminopyridinium ions, to access chemical transformations for which traditional Lewis acid catalysis has proved difficult.

We have also developed a synthetic route to planar chiral 2-aminopyridinium ions, a new class of hydrogen bond donor catalysts, and found a convenient way to

optically resolve them. Moreover, this catalyst was found to catalyze the nitroalkene intramolecular Diels-Alder reaction providing the adduct with excellent *endo:exo* selectivities and excellent yields. These planar chiral 2-aminopyridinium catalysts are a promising class of H-bond donor catalysts and in the future can be applied to other synthetically useful transformations.

For My Son
and Husband

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I am forever grateful to my family, my parents, my two brothers, Eno and Anthony, and my baby sister Pao. You have forever believed in me. If not for your love I wouldn't have come this far. I feel profound gratitude toward my in-laws, Yoli, Mimi, and Abuelo. You have loved and treated me as a daughter and I truly feel blessed to have

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Finally I offer my thanks to my husband and my son. You are the pillars that hold me in place! Thanks for your unconditional love. I offer this work to you, I love you.

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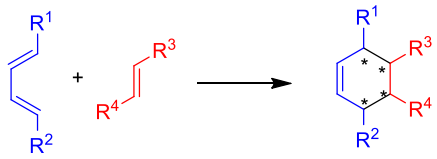
Figure 1.1. Genaral Diels-Alder reaction

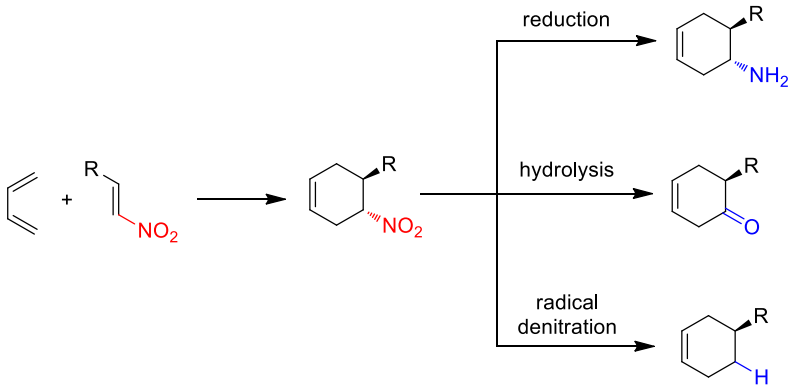


The Diels-Alder reaction, first described in 1928[1] by, teacher student pair, Kurt Alder and Otto Diels, is arguably one of the most powerful transformations in the synthetic chemist's tool box. This [4+2] cycloaddition reaction is especially valuable because in a single step it forms two new bonds, a cyclohexenyl ring, and up to four contiguous stereocenters, in a highly stereoselective and predictable fashion (Figure 1.1). Hundreds of elegant applications of this process to the total synthesis of complex natural products have been reported.[2] In addition, both Lewis acid catalysis[3,4,5,6] and more recently organocatalysis[7,8,9,10,11] have proven to be powerful methods for increasing the rate, diastereoselctivity, and enantioselctivity of carbonyl-based dienophile substrates. However, in contrast to carbonyl-based dienophiles, LUMO lowering catalysis of the Diels-Alder reaction of nitroalkenes has remained quite elusive, despite offering unique advantages due to the synthetic versatility of the nitro group.[12] Therefore, in hopes of taking advantage of these complementary substrates, my group began a research program to address the catalysis of the Diels-Alder reaction of nitroalkenes with the goal of asymmetric applications.

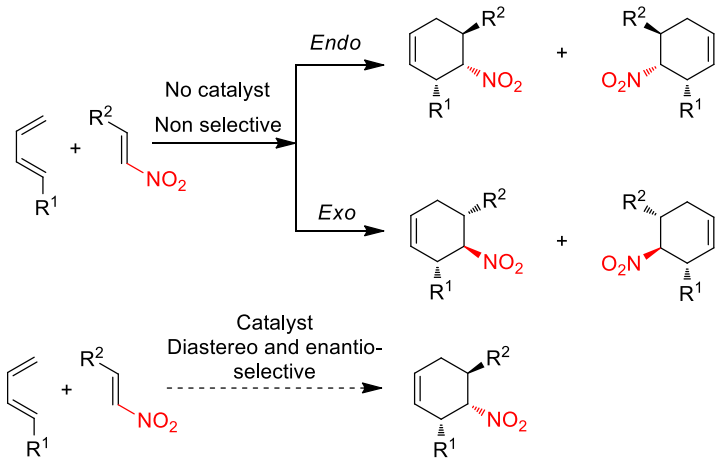
1.1. Background

1.1.1. Catalysis of the Nitroalkene Diels-Alder reaction

Scheme 1.1. Diels-Alder reaction of nitroalkenes

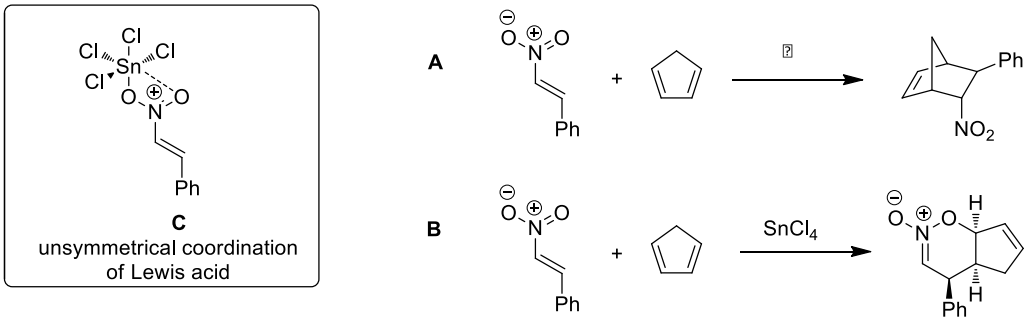


Scheme 1.2. Non selective and selective nitroalkene Diels-Alder reaction



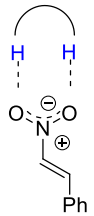
The Diels-Alder reactions of nitroalkenes are highly valuable due to the nitro group's ease of functional group interconversion (Scheme 1.1) and have been frequently employed in the synthesis of complex natural products.[12] From the viewpoint of fine chemicals preparations, there is a growing need to access molecules in selective manner. Therefore, we believe that the merit of this method would be significantly enhanced by a diastereo- and enantioselective catalytic methodology (Scheme 1.2).

Scheme 1.3. Thermal and Lewis acid catalyzed Diels-Alder reaction of β-nitrostyrene

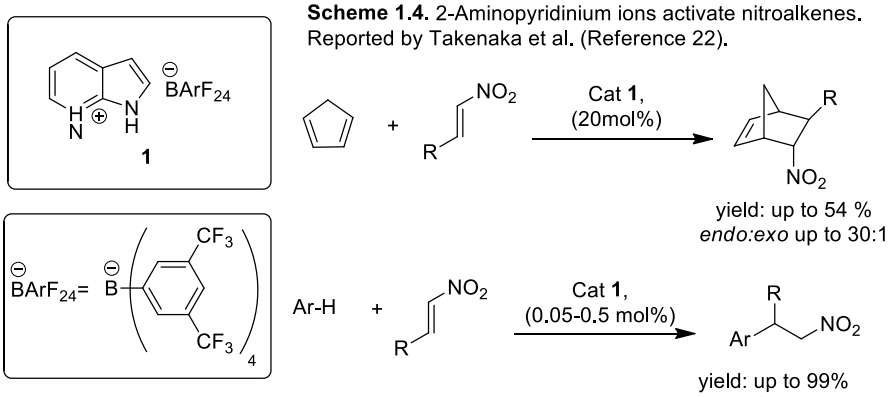


Although the thermal Diels- Alder reactions of nitroalkenes with dienes have been widely studied,[13-19] LUMO lowering catalytic examples of this process have remained remarkably scarce[20] even by simple achiral catalysts. On the other hand, Denmark and co-workers have demonstrated that the catalysis of this transformation with metal centered Lewis acids is challenging. Specifically, they have observed that in the presence of Lewis acids, nitroalkenes undergo the inverse-electron- demand-hetero-Diels-Alder reaction giving rise to nitronates rather than the thermal Diels-Alder product[21] (Scheme 1.3). For the reaction of *trans*-β-nitrostyrene and cyclopentadiene, Denmark et al. rationally suggested that unsymmetrical coordination of the Lewis acid with one of the oxygen atoms of the nitro group serves to localize double bond character in the nitrogen-oxygen (O=N) bond, thus resulting in reversed periselectivity (Scheme 1.3 C).

Figure 1.2. Activation of nitroalkene with double H-bond donor



In light of this, my colleagues hypothesized that a molecule capable of donating two symmetrical hydrogen bonds (H-bond) to a nitroalkene may serve as a catalyst. They envisioned a LUMO lowering, H-bonding complex between the catalyst and the nitroalkene, evenly dispersing the O-N-O bonding array (Figure 1.2). This would enable the nitroalkene to participate as a dienophile. Gratifyingly my colleagues found that double H-bond donors, *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea and 2-benzylaminopyridinium could promote the desired Diels-Alder reaction.

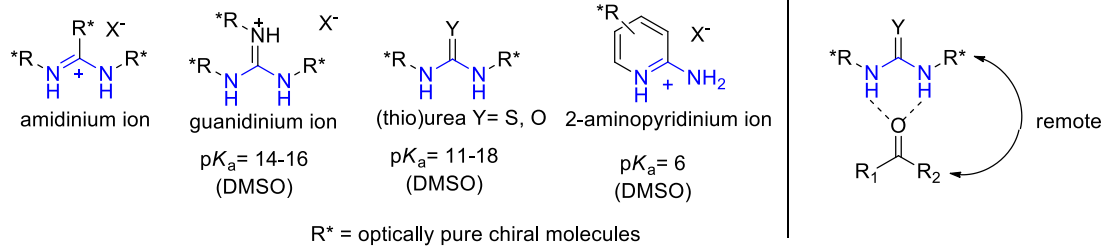


Scheme 1.4. 2-Aminopyridinium ions activate nitroalkenes. Reported by Takenaka et al. (Reference 22).

Subsequently, other 2-aminopyridinium ions were investigated as H-bonding catalysts, and were found to be highly unique. During the course of the study 2-aminopyridinium, 7-azaindolium **1** (Scheme 1.4) was found to be optimum. This catalyst efficiently catalyzes the Diels-Alder reaction of nitroalkenes with the periselectivity opposite to that observed with metal centered Lewis acids affording the product in up to 54% yield and high diastereoselctivity (up to 30:1 *endo:exo*).[22] In addition, this catalyst efficiently activates nitroalkenes toward the conjugate addition of heteraromatic compounds with the lowest catalyst loading for this reaction, known to date (Scheme 1.4).

1.1.2. 2-Aminopyridinium ions vs. other double hydrogen bond donors

Figure 1.3. Double hydrogen bond donors



Over the past decade, electrophilic activation by small-molecule hydrogen bond donors has emerged as an important archetype in enantioselective catalysis.[10,11] Urea and thioureas containing chiral compounds are among the most prominent H-bond donor catalysts, finding diverse applications in a remarkable number of synthetically useful transformations. Their notable success can be attributed to their ability to form two H-bonds to a substrate. This two-point binding is thought to further activate the electrophile and constrain it to a well defined orientation leading to asymmetric induction.

In contrast to urea and thiourea catalytic systems, 2-aminopyridiniums ions[23-30] have been much less investigated as H-bonding catalysts despite offering unique structural opportunities. For one, 2-aminopyridinium ions are more acidic than commonly studied double H-bonding donors (i.e., more reactive) (Figure 1.3). Furthermore, an intrinsic challenge in the design of chiral double H-bonding catalysts is that the chiral element (R* in Figure 1.3) can often only be introduced at sites remote from the H-bonding site due to the directionality of the Hydrogen bonds and what's more, the chiral element and H-bonding site are connected *via* rotary single bonds, which can give rise to conformational ambiguity between the bound substrate and the chiral element. 2-

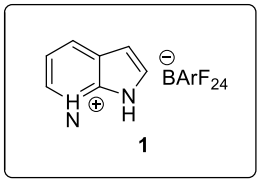
aminopyridinium ions, on the other hand, are devoid of these challenges because the pyridine ring can be modified to extend its reach asymmetrically toward the H-bonding site in a conformationally rigid fashion. It should also be mentioned that many of the successful enantioselective double H-bond donor catalysts have additional functional groups that enables them to interact with incoming heteroatom-containing nucleophiles[10,11] (bifunctional catalysis). These additional interactions, often direct the orientation of nucleophilic addition leading to asymmetric induction. However, because we are interested in the Diels-Alder reactions of nitroalkenes with hydrocarbon dienes these bifunctional catalysts would be ineffective for our substrate systems, highlighting the need for other catalysts systems. In light of the beneficial structural elements of the 2-aminopyridinium ion catalytic core and their new found abilities to efficiently activate nitroalkenes we deemed it wise to further investigate them as H-bonding catalysts.

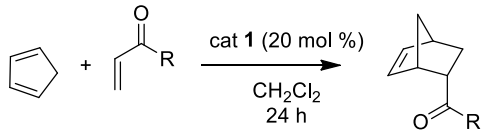
1.2. Results and discussion

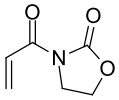
1.2.1. General applicability of 2-aminopyridinium ions as catalysts

My first project was to examine the general applicability of 2-aminopyridinium ions as H-bonding catalysts. To our delight, catalyst **1** proved to activate effectively several commonly used electrophiles for the Diels-Alder reaction (Table 1.1). These preliminary results indicate that 2-aminopyridinium ions are excellent H-bonding catalysts and thus the use of chiral 2-aminopyridinium ion variants for the nitroalkene Diels-Alder reaction is a worthwhile goal.

Table 1.1. 2-Aminopyridinium ion catalyzed Diels-Alder reactions



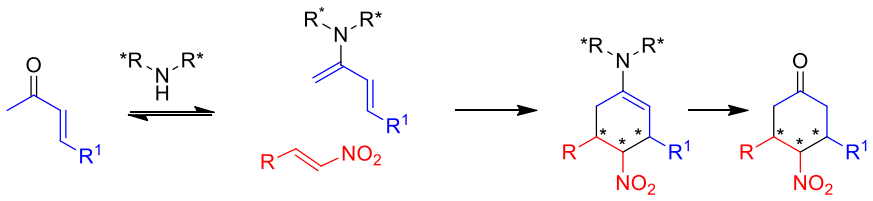


entry[b]	dienophile	temp (° C)	yield (%)[c]	*endo:exo*[d]
1		-20	64(29)[a]	8:1(5:1)[a]
2		-20	99(20)[a]	14:1(9:1)[a]
3		-30	85 (20)[a]	10:1(10:1)[a]

[a] With out catalyst. [b] The reaction is not fully optimized. [c] Yields determined by NMR of crude products using 1,1,2,2-tetrachloroethane as internal standard. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture.

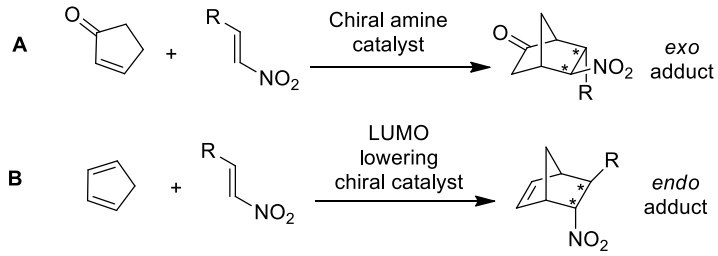
1.2.2. Chiral 2-aminopyridinium as catalysts for the Diels-Alder reactions of β-nitrostyrene

Scheme 1.5. Asymmetric nitroalkene Diels-Alder reactions with unsaturated carbonyl compounds *via* enamines



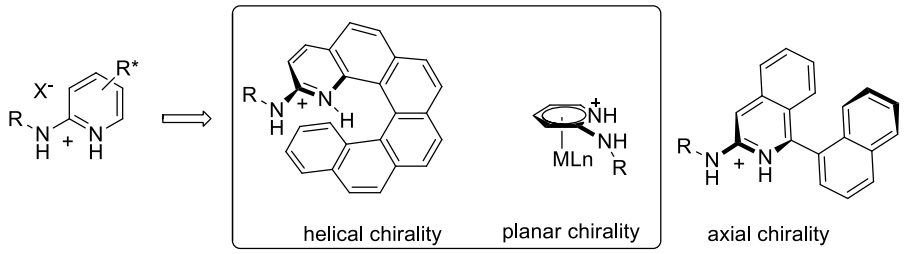
It should be mentioned that current catalytic asymmetric nitroalkene Diels-Alder reactions involve chiral amine catalyzed reactions with α,β-unsaturated carbonyl compounds as dienes, *via* enamine intermediates (Scheme 1.5).[31-34] We believe, however, that an asymmetric LUMO lowering nitroalkene Diels-Alder method would be highly complementary to these existing methods. Specifically, amine catalyzed reactions of α,β-unsaturated carbonyl compounds with nitroalkenes gives rise to *exo* adducts,[32,33] while a LUMO lowering catalyst could allow access to *endo* products (Scheme 1.6).

Scheme 1.6. Asymmetric nitroalkene Diels-Alder reactions



Having identified a catalytic motif (2-aminopyridinium core) that could promote the Diels-Alder reaction of nitroalkenes with high *endo* diastereoselectivity, we set out to examine the potential utility of achiral variants as enantioselective catalysts. Although one could easily obtain chiral 2-aminopyridiniums by coupling optically active amines to the pyridine, for the reasons discussed in section 1.1.2 (Figure 1.3) we have chosen not to study those. Instead we have chosen to focus on examples with desymmetrized pyridine rings. These are generated by integrating the 2-aminopyridinium core into a chiral (helical, planar, or axially) scaffold (Figure 1.4). Because each one of the three possible chirality types (helical, planar, and axial) creates a considerably different chiral space, inherent to its structural features, each one is expected to induce enantioselectivity differently. Therefore, it is always a risk to rely on one family of chiral catalysts when developing novel enantioselective processes. For this reason we decided to investigate at least two of the three possible chirality types; helical and planar. Furthermore, we deemed that the chiral 2-aminopyridinium catalysts should have three necessary features; (1) a well differentiated chiral environment in the vicinity of the reaction site, (2) easily tunable steric surroundings, and (3) robustness for ease of handling.

Figure 1.4. Examples of possible 2-aminopyridnium chiral variants



Catalysts **2a** (Table 1.2), is a helical chiral variant in which the 2-aminopyridinium core has been merged into the chiral framework of helicene. This class of H-bond donor catalysts have proven to be highly enantioselective for Friedel-Crafts alkylation reactions of nitroalkenes.[35] The crystal structure of the helical 2-aminopyridinium HCl salt **2c** (Figure 1.5), in which the 2-aminopyridinium cation forms a double hydrogen bond to the chloride anion, reveals that the helicene backbone creates a well differentiated chiral environment around the vicinity of the hydrogen bonds. For example, the space beneath the two H-bonds is congested or blocked by the helicene framework, while the space above it remains open. This structural feature is highly attractive in an asymmetric catalyst as it suggests that the chiral scaffold may effectively block one face of a bound electrophile from an incoming nucleophile, resulting in asymmetric induction.

Figure 1.5. ORTEP of 2-(1-adamentylamino)-1-azahelicene·HCl
Reported by Takenaka et al. (Reference 35).

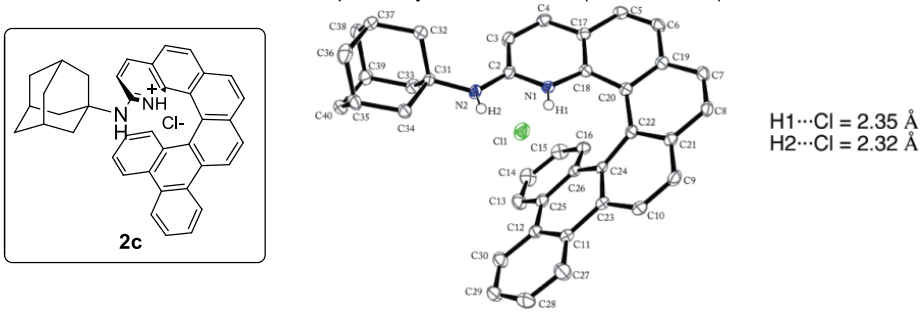
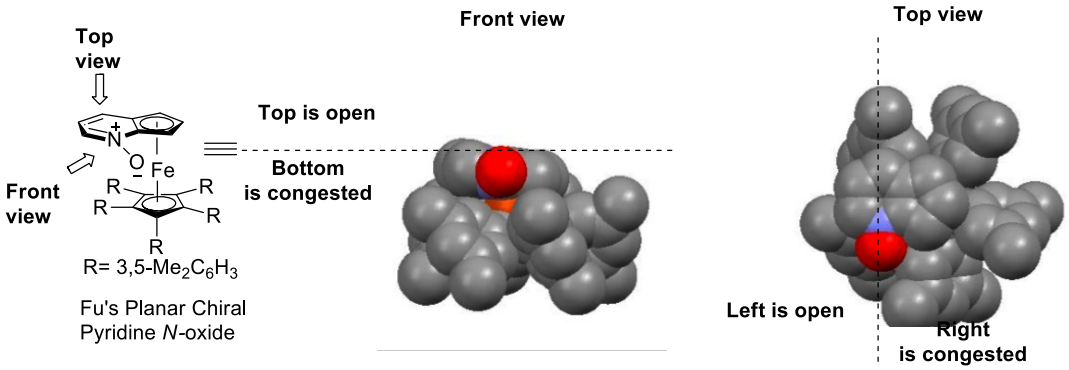
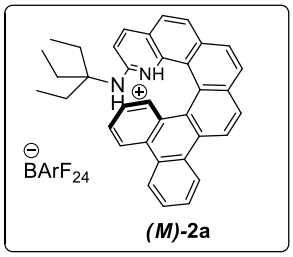


Figure 1.6. X-ray analysis of planar chiral pyridine *N*-oxide. The pyridine ring is well-desymmetrized in terms of top-from-bottom and left-from-right. Reported by Fu et al. (Reference 36).



Catalyst **3** (Table 1.2), a planar chiral 2-aminopyridinium variant, was developed in connection with the nitroalkene intramolecular Diels-Alder project (See Chapter 3) and was synthesized from the chiral ferrocene pyridine *N*-oxide reported by Fu et al.[36] X-ray analysis of the *N*-oxide precursor, indicates that its pyridine ring is also well-desymmetrized in terms of top-from-bottom (Front view, Figure 1.6) and left-from-right (Top view) differentiations.

As described above the structures of both catalysts, **2a** and **3**, have well defined chiral environments. Moreover, it has been demonstrated that the steric surroundings around the pyridine rings of the ferrocene *N*-oxide precursor[36] of **3** and of helical chiral catalyst **2**,[35,37] are highly tunable. Furthermore, they are both robust in terms of ease of handling,[35,37] thereby meeting our three aforementioned requirements. We therefore decided to probe their abilities as asymmetric catalysts for the nitroalkene Diels-Alder reaction.



(M)-**2a**

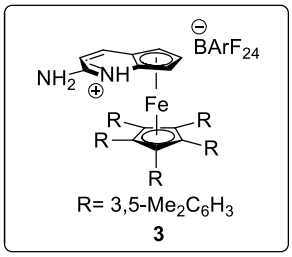


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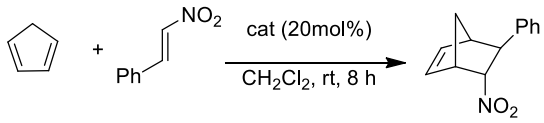
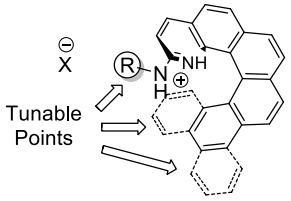
Table 1.2. Evaluation of helical and planar chiral 2-aminopyridinium catalysts



entry	cat	*endo:exo*	yield (%)	ee (%)
1	**2a**	6:1	34	27
2	**3**	20:1	29	7

To our delight 20 mol% of helical catalyst **(*M*)-2a**, promoted the Diels-Alder reaction between cyclopentadiene and β-nitrostyrene with 27% ee. On the other hand, planar catalyst **3** (20 mol %) proved to be less enantioselective, providing the nitroalkene Diels-Alder adduct in 7% ee, although with improved diastereoselectivity. The reaction with helical catalyst **(*M*)-2a** represents a first example of an enantioselective nitroalkene Diels-Alder reaction by LUMO lowering catalysis. Although reactivities remain low modifications to enhance the acidity of the 2-aminopyridinium core may be a *via*ble solution. This may be accomplished by incorporating electron deficient R groups on the 2-amino nitrogen of the pyridine ring (Figure 1.7). Furthermore, since the helicene scaffold can be readily tuned, systematic structural modifications can be made to increase enantioselectivity. It should be mentioned that asymmetric catalysis with helical chiral 2-aminopyridium catalyst was done in collaboration with a post doctoral associate Jenshui Chen.

Figure 1.7. Tunability of 1-azahelicene derivatives



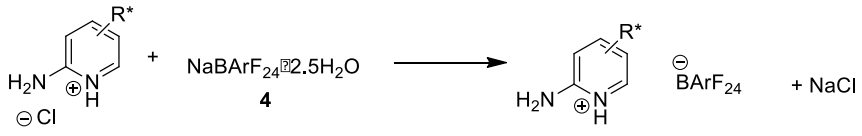
R = electron deficient group

Although, these results were promising indeed, we decided to additionally investigate other possible LUMO lowering achiral catalysts that could activate nitroalkenes.

1.2.3. Sodium Tetrakis [3,5-bis(trifluoromethyl)phenyl]borate complexes as catalysts for the Diels-Alder reaction of β-nitrostyrene

The weakly coordinating and lipophilic anion, Tetrakis [3,5-bis(trifluoromethyl)phenyl]borate ($BArF_{24}$) was first utilized by Kobayashi et al. as a negatively charged phase transfer catalyst in 1981[38] and has since then, found a wide range of applications. In particular, it has enabled the study of highly reactive catalytic, cationic transition-metal complexes.[39]

Scheme 1.7. 2-Aminopyridinium HCl salt counterion exchange with $NaBArF_{24}$ hydrate



2a or **3**

$NaBArF_{24}$ hydrate **4** is used in our laboratory during chiral 2-aminopyridinium catalyst preparations. Specifically, it is used to undergo counter ion exchange with the 2-aminopyridinium hydrochloride salts (Scheme 1.7.). Because, chiral 2-aminopyridinium $BArF_{24}$ salts are used as catalysts without purification subsequent to the counter ion

exchange, it occurred to us that residual $NaBArF_{24}$•$2.5H_2O$ **4** may be catalyzing the background reaction and eroding the enantiomeric excess of the nitroalkene Diels-Alder reaction (Figure 1.8.). We therefore set up control experiments with 10 mol% of **4** and found that $NaBArF_{24}$•$2.5H_2O$ catalyzes the nitroalkene Diels-Alder reaction (Table 1.3.)

Figure 1.8. Chiral 2-aminopyridinium ions vs $NaBArF_{24}$·$2.5H_2O$ as catalyst

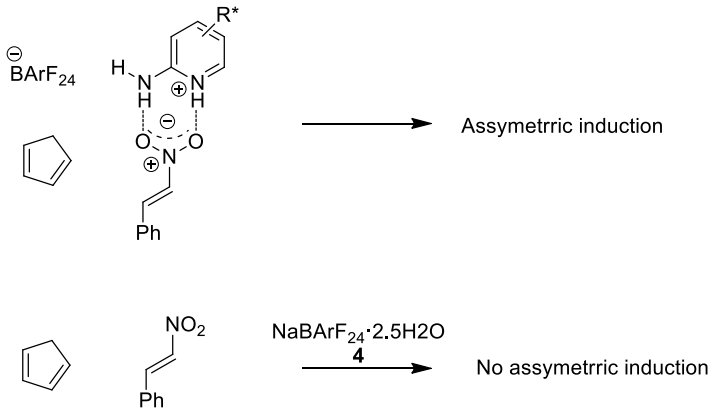
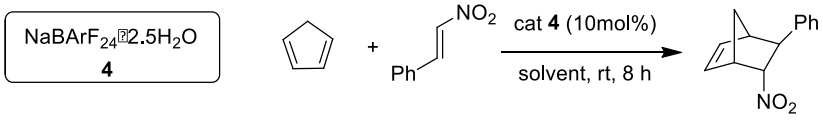


Table 1.3. $NaBArF_{24}$·$2.5H_2O$ as a catalyst for the Diels-Alder reaction of nitralkenes



entry	solvent	yield (%)	*endo:exo*[a]
1	CH_2Cl_2	45	16:1
2	PhMe	52	18:1

[a] Determined by ^1H NMR analysis of the crude reaction mixture.

To gain some mechanistic understanding on the mode of nitroalkene activation we attempted to co-crystallize β-nitrostyrene with $NaBArF_{24}$ hydrate **4**. Unfortunately, our efforts were unfruitful. Liu et al., however, previously reported that $NaBArF_{24}$ hydrate, provides one proton source to initiate the polymerization of vinyl ethers in anhydrous dichloromethane solutions (Scheme 1.8.).[40] The crystal structure of $NaBArF_{24}$

hydrate (Figure 1.9.) reported by Liu et al. shows that sodium coordinates with two trans water molecules and four fluorine atoms from the triflouromethyl groups of four different borate anions. The Na--F interactions are believed to enhance Lewis acidity of Na, thereby polarizing the water molecules. The interactions seen in the solid phase are thought to persist in the solution phase because $NaBArF_{24}•2H_2O$ is known to agglomerate, and not fully dissociate into free anions in dichloromethane.[41]

Scheme 1.8. Polymerization of vinyl ethers. Reported by Lui et al. (Reference 40).

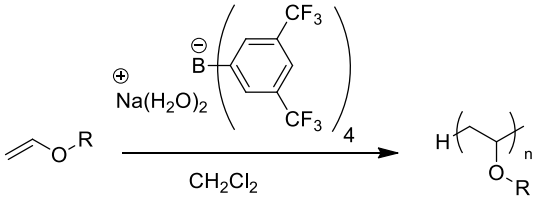
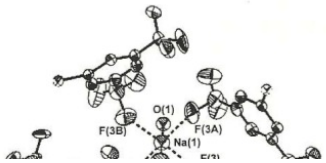


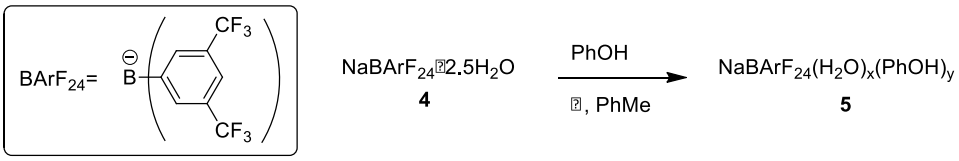
Figure 1. 9. ORTEP plot of $NaBArF_{24}·2H_2O$ Reported by Lui et al. (Reference 40).



In light of Liu's report we hypothesized, that activation of the nitroalkene may be occurring by Lewis acid assisted Brønsted acid catalysis, similar to those developed by Yamamoto and co-workers[42] and that a more acidic complex may enhance the reactivity of the nitroalkene Diels-Alder reaction. To test this hypothesis we aimed to replace the water molecules (pK_a H_2O is 15.7) of $NaBArF_{24}•2H_2O$ complex with more acidic phenol (pK_a PhOH is 9.95 in water). The $NaBArF_{24}•(H_2O)_x(PhOH)_y$ complex was obtained by

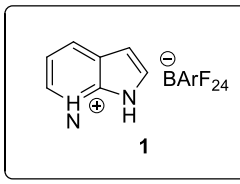
refluxing a mixture of $NaBArF_{24}•2H_2O$ and PhOH (2.5 equiv) in toluene, followed by removal of the solvent (Scheme 1.9.).

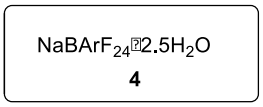
Scheme 1.9. Synthesis of $NaBArF_{24}(H_2O)_x(PhOH)_y$

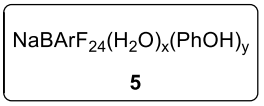


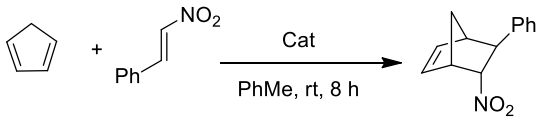
To our delight, $NaBArF_{24}•(H_2O)_x(PhOH)_y$ complex provided improved yields and selectivities as compared to $NaBArF_{24}•2.5H_2O$ (Table 1.4., entry 2). In addition, it is more effective than the 2-aminopyridinium catalyst **1** in identical conditions. Having identified a new catalyst for the nitroalkene Diels-Alder reaction we decided to investigate more challenging nitroalkene-diene Diels-Alder reaction partners.

Table 1.4. $NaBArF_{24}$ complexes as catalysts for the Diels-Alder reaction of nitralkenes









entry	cat (mol %)	yield (%)	*endo:exo*
1	**4**	52	18:1
2	**5**	62	23:1
3[a]	**1**	49	22:1

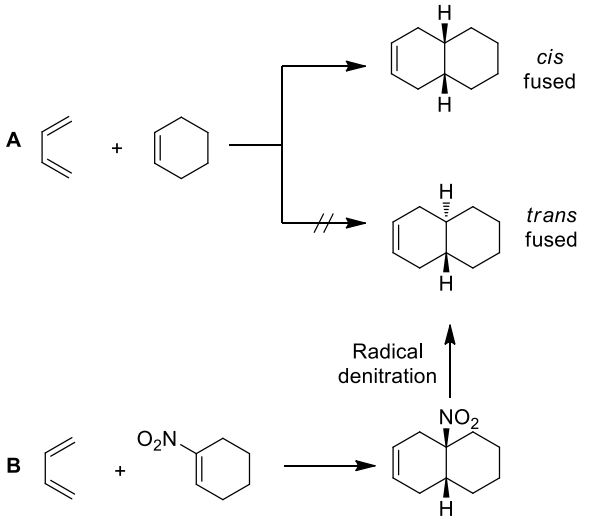
[a] Reported by Takenaka et al. (Reference 22).

1.2.4. Attempts at catalyzing the Diels-Alder reaction 1-nitrocyclohexene with Brønsted acids

As mentioned at the beginning of the chapter the Diels-Alder reaction of nitroalkenes is useful due to the nitro group's ease of functional group interconversion. This process allows access to cyclic and bicyclic motifs that are otherwise difficult to

obtain. Danishefsky and coworkers have elegantly demonstrated the utility of the Diels-Alder reaction of 1-nitrocyclohexene.[43] It is well established that the inter-molecular Diels-Alder reactions provide access to *cis*-fused bicyclic systems (Scheme 1.10A). However, Danishefsky et al. have established a well-designed two step protocol, which provides access to *trans*-fused decalin systems from the Diels-Alder adducts of 1-nitrocyclohexene. As shown in Scheme 1.10B, cycloaddition provides a *cis*-fused bicyclic adduct, bearing a nitro group in the ring junction. Subsequent radical denitration furnishes the *trans* fused system with good selectivity. In a sense 1-nitrocyclohexene serves as an equivalent of *E*-cyclohexene which is otherwise unavailable.

Scheme 1.10. Access to *trans*-fused bicyclic systems *via* the Diels-Alder reaction of 1-nitrocyclohexene. Scheme adapted from Danishefsky et al. (Reference 43).



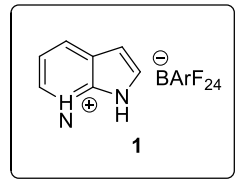
Despite the utility of the above stated protocol, Danishefsky et al. described that the reactivity of 1-nitrocyclohexene with hydrocarbon dienes proved to be a particularly challenging problem. They noticed that at temperatures below 120 °C to 130 °C little or no reaction was observed, and that at temperatures above 140 °C serious degradation of the dienophile, 1-nitrocyclohexene, took place. Fortunately, however, they observed a

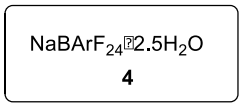
substantial increase in the yield when 2,2,2-trifluoroethanol was employed as a solvent under microwave conditions.

Considering the reactivity challenges and the usefulness of the products, we decided to investigate the capability of newly identified catalyst $NaBArF_{24}$•$2.5H_2O$ **4**, and 2-aminopyridinium catalyst **1** to promote the Diels-Alder of 1-nitrocyclohexene. As a model study we chose the Diels-Alder reaction of isoprene and 1-nitrocyclohexene (Table 1.5).

Regrettably, we observed similar reactivity issues to those described by Danishefsky. At low temperatures little product was observed, while higher temperatures resulted in dienophile decomposition. For instance, after 62 hours at room temperature, in the presence of $NaBArF_{24}$•$2.5H_2O$ **4**, only starting material nitroalkene could be seen by TLC and in the crude NMR (entry 1). Increasing the temperature to 77 °C for 48 hours provided the product in 5% yield and 73% recovered starting material (entry 2). After, 21 hours at 110 °C we obtained 13% yield (entry 3). However, both TLC and crude NMR indicated that the starting material nitroalkene had completely deteriorated. Similar results were obtained in the presence of radical inhibitor hydroquinone, in un-degassed or degassed solvents (entries 4-5). In degassed solvent, radical inhibitor, 2,6-di-*tert*-butyl-4-methyl-phenol (BHT), did not provide any improvements (entry 6). Because Danishefsky reported that a more favorable product distribution relative to decomposition could be obtained in 2,2,2-trifluoroethanol, a final attempt to catalyze the reaction with $NaBArF_{24}$•$2.5H_2O$, in 2,2,2-trifluoroethanol was made. Although we did observe less starting material degradation (30 % remained), catalytic activity remained low, 14% yield (entry 7).

We next examined 2-aminopyridinium **1** as a catalyst for this reaction. However, to our dismay, in degassed toluene and in the presence of either one of the radical inhibitors, only 9% of the Diels-Alder product was observed accompanied by severe starting material decomposition (entries 8 and 9). We therefore concluded that catalysis of this particular transformation with catalyst systems **1** and **4** was highly challenging.





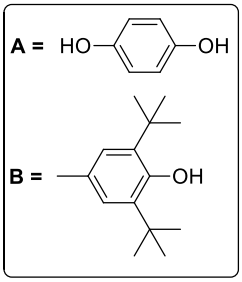
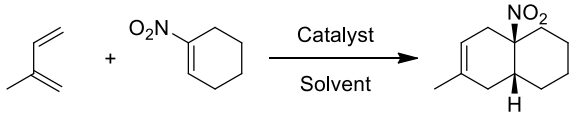


Table 1.5. Catalysis of the Diels-Alder reaction of 1-nitrocyclohexene



entry	catalyst (mol %)	solvent	temp. (°C)	time (h)	radical inhibitor (1 mol %)	yield[b] (%)
1	**4** (10)	PhMe	25	62	-	-
2	**4** (10)	PhMe	77	48	-	5
3	**4** (10)	PhMe	110	21	-	13
4	**4** (10)	PhMe	110	21	**A**	13
5	**4** (10)	PhMe[a]	110	21	**A**	13
6	**4** (10)	PhMe[a]	110	21	**B**	9
7	**4** (10)	CF_3CH_2OH	110	21	-	14
8	**1** (20)	PhMe[a]	110	21	**A**	9
9	**1** (20)	PhMe[a]	110	21	**B**	9

[a] Solvent was degassed by freeze thaw method
[b] Yields determined by NMR of crude products using 1,1,2,2-tetrachloroethane as internal standard

1.3. Summary and outlook

In summary, we have explored helical and planar chiral variants of 2-aminopyridinium ions as asymmetric catalysts for the Diels-Alder reaction of nitroalkenes and consequently identified helical chiral 2-aminopyridinium variants as promising candidates. This provides a first example of an enantioselective nitroalkene

Diels-Alder reaction by LUMO lowering catalysis. Although reactivities remain low, modifications to enhance the acidity of the 2-aminopyridinium core may be a *via*ble solution. This may be accomplished by incorporating electron deficient R groups on the 2-amino nitrogen of the pyridine ring. Furthermore, since the helicene scaffold can be readily tuned, systematic structural modifications can be made to increase enantioselectivity.

Additionally, we have identified $NaBArF_{24}$ complexes as useful rate enhancing catalysts for the Diels-Alder reaction of β-nitrostyrene and cyclopentadiene. Although the mechanism of activation is unclear at this point, we hypothesize that it may be acting as a Lewis acid assisted Brønsted acid catalyst. Finally, we have applied $NaBArF_{24}$•$2.5H_2O$ **4**, and 2-aminopyridinium ion **1** as catalysts to the Diels-Alder reaction of 1-nitrocyclohexene. Unfortunately, we observed little or no increases in the rates of the reactions at low temperatures (25-75 °C) and substantial starting material degradation at temperatures above 100 °C, highlighting the reactivity challenges described by Danishefsky.

1.4. Experimental section

1.4.1. General information

All reactions were carried out in 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 200-400) supplied by E. Merck.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH_2Cl_2), and toluene (PhMe) were freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. Et_2O and THF were freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. *Trans*-β-nitrostyrene and phenol purchased from Sigma-Aldrich were purified by flash chromatography on silica gel. Isoprene was distilled over calcium hydride and stored over Linde type 4Å molecular sieves in a Schlenk flask, and used from there. 1-Nitrocyclohexene was purified by Kugelrohr distillation stored in a Schlenk flask and used from there. Compounds that are not numbered in the main body of the chapter are labeled **S1**, **S2**, ect.

^{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). Fast atom bombardment mass spectra (FABMS) were recorded

with a VG Mass Lab Trio-2 spectrometer, using 3-nitrobenzyl alcohol as matrix. Low resolution mass spectra were recorded using Hewlett Packard 5971A spectrometer. High resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, University of Miami.

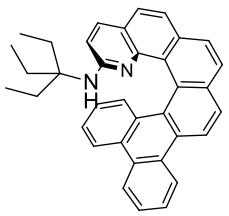
1.4.2. General procedure for Diels-Alder reaction of carbonyl substrates

To a solution of dienophile (0.5 mmol) and catalyst, 7-azaindolium $NaBArF_{24}$ **1**[22] (103 mg, 0.1 mmol), in CH_2Cl_2 (0.5 mL) at the indicated temperature (-20 or 30 °C) was slowly added neat cyclopentadiene (81 μL, 1.0 mmol). The resulting solution was stirred for 24 h at the indicated temperature, followed by the addition of 5 mL of Et_2O, and subsequent concentration *in vacuo*. The ratio of the diastereomers (*endo:exo*) were determined by ^1H NMR analysis of the crude reaction mixture and the yields of the products were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

1.4.3. Preparation of 2-Amino-1-aza[6]helicene

We followed the general procedure previously reported.[35]

(+)-(*P*)-11,12-Benzo-2-(3-ethylpentan-3-amino)-1-aza[6]helicene (S1)



S1

$[\alpha]^{20}_D$ = +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, 1 H), 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.

1.4.4. Procedure for asymmetric nitroalkene Diels-Alder reaction with helical chiral 2-aminopyridinium ions

To a solution of **(*M*)-S1** (73 mg, 0.15 mmol) in CH_2Cl_2 (2.4 mL) was added an Et_2O solution of HCl (1M, 0.18 mL) drop wise at room temperature. The reaction mixture was stirred for 1 h and then concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (2.0 mL), and the concentrated *in vacuo*, the process of which was repeated three times. To the resulting yellow solid was added EtOH (10.1 mL) and $NaBArF_{24}{\cdot}2.5H_20$[39] (131 mg, 0.15 mmol). The mixture was stirred for 1 h at room temperature, filtered through a silica gel plug and was concentrated *in vacuo.* The resulting salt **(*M*)-2a** was used as a catalyst without further purification.

To a solution of *trans*-β-nitrostyrene (0.2 mmol) and catalyst **(*M*)-2a** (54.3 mg, 0.04 mmol) in CH_2Cl_2 (0.3 mL) cooled to 0 °C was added slowly neat cyclopentadiene (33 μL, 0.4 mmol). After 8 h at room temperature the reaction mixture was treated with neat hydrazine hydrate (200 μL). The resulting solution was stirred for 30 min, followed by the addition of 1 mL of Et_2O, and three consecutive washes with 1 mL of water. The organic layer was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

The ratio of diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture (*endo:exo* = 6:1), which was then purified by flash chromatography on silica gel with 2% EtOAc in hexanes to afford the product (14.5 mg, 34%) with 27% ee. All spectral data were identical to the literature values.[22] Enantiomeric ratio was determined by HPLC with a Chiralcel AD-H column equipped with an OD-H guard column (2% isopropanol in hexanes, flow rate = 0.2 ml/min), t_r (minor) = 34.81 min, t_r (major) = 48.49 min.

1.4.5. Procedure for asymmetric nitroalkene Diels-Alder reaction with planar chiral catalyst

To a solution of **74** (chapter 3) (33 mg, 0.043 mmol) in CH_2Cl_2 (3.6 mL) was added an Et_2O solution of HCl (1M, 0.86 mL) drop wise at room temperature. The reaction mixture was stirred for 30 min. and then concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (5.0 mL), and then concentrated *in vacuo*, the process of which was repeated three times. To the resulting solid were added CH_2Cl_2 (0.68 mL), and $NaBArF_{24}\cdot 2.5H_20$ (40. mg, 0.043 mmol) at room temperature. The resulting mixture was stirred for 1 h, and concentrated *in vacuo.* The resulting salt **3** was used as a catalyst without further purification.

To a solution of *trans*-β-nitrostyrene (0.16 mmol) and catalyst **3** (52 mg, 0.032 mmol) in CH_2Cl_2 (0.160 mL) cooled to 0 °C, was added slowly neat cyclopentadiene (26 μL, 0.32 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours, and then treated with neat hydrazine hydrate (65 μL). The resulting solution was stirred for 30 min, followed by the addition of 1 mL of Et_2O, and three consecutive washes with 1 mL of water. The organic layer was then washed with brine, dried over

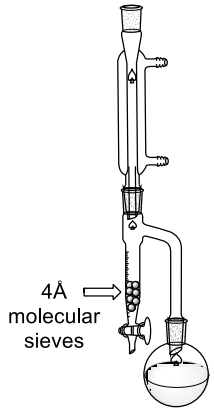
Na_2SO_4 and concentrated *in vacuo*. The ratio of diastereomers was determined by ^1H NMR analysis of the crude reaction mixture (*endo:exo* = 20:1) which was then purified by flash chromatography on silica gel with 2% EtOAc in hexanes to afford the product (10.2 mg, 29%) with 7% ee. All spectral data were identical to the literature values.[22] Enantiomeric ratio was determined by HPLC with a Chiralcel AD-H column equipped with an OD-H guard column (2% isopropanol in hexanes, flow rate = 0.2 ml/min), t_r (minor) = 36.03 min, t_r (major) = 53.3 min.

1.4.6. Procedures for the Diels-Alder reaction of β-nitrostyrene catalyzed by $NaBArF_{24}$•2.5(H_2O)

To a solution of *trans*-β-nitrostyrene (75 mg, 0.5 mmol) and $NaBArF_{24}\cdot 2.5H_20$[39] (47 mg, 0.05 mmol) in solvent (0.5 mL) cooled to 0 °C, was added slowly neat cyclopentadiene (81 μL, 1.0 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours, and then diluted with 1 mL of CH_2Cl_2 followed by the addition of 200 μL MeOH-hydrazine hydrate solution (50:50 mixture by volume). The resulting solution was stirred for 5 min, diluted with 1 mL of water, and extracted three times with CH_2Cl_2. The combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The ratio of diastereomers (*endo:exo)* was determined by ^1H NMR analysis of the crude reaction mixtures, which were then purified by flash chromatography on silica gel with 2% EtOAc in hexanes to afford the products. All spectral data were identical to the literature values.[22]

1.4.7. Procedures for the Diels-Alder reaction of β-nitrostyrene catalyzed by $NaBArF_{24}•(H_2O)_x(PhOH)_y$

Figure 1.10. Glassware set up



A round-bottom flask containing a solution of $NaBArF_{24}·2.5H_20$ (559 mg, 0.60 mmol), PhOH (131 μL, 1.5 mmol) and toluene (12 mL) was equipped with a Dean-Stark apparatus and condenser (Figure 1.10). The side arm with the stop cock of the Dean-Stark apparatus was packed with approximately 3 cm of Linde type 4Å molecular sieves. Under an atmosphere of dry argon, the solution was refluxed for 4 hours, at which time the solvent was drained. The resulting solid was dried under vacuum and was used as catalyst **5** without further purification.

To a solution of *trans*-β-nitrostyrene (75 mg, 0.5 mmol) and **5** (56 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) cooled to 0 °C, was added slowly neat cyclopentadiene (81 μL, 1.0 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours, and diluted with 1 mL of CH_2Cl_2. The mixture was then treated with 200 μL of MeOH-hydrazine hydrate solution (50:50 mixture by volume). The resulting solution was stirred for 5 min, diluted with 1 mL of water, and extracted three times with CH_2Cl_2. The combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The ratio of diastereomers was determined by ^1H NMR analysis of

the crude reaction mixtures (23:1), which were then purified by flash chromatography on silica gel with 2% EtOAc in hexanes to afford the product (67 mg, 62% yield). All spectral data were identical to the literature values.[22]

1.4.8. General procedures for the Diels-Alder reactions of 1-nitrocyclohexene

To a flame dried seal tube containing catalyst and radical inhibitor (10 mol %) was added toluene (degassed three times using the freeze-thaw method), 1-nitrocyclohexene (113 μL, 1.0 mmol), and isoprene (500 μL, 5.0 mmol). The resulting solution was sealed and heated at 110 °C for 21 h behind a blast shield, cooled to room temperature and then concentrated *in vacuo*. NMR yields were determined using 1,1,2,2-tetrachloroethane as an internal standard. Spectral data were in agreement with reported literature values.[44]

CHAPTER 2. DIASTEREOSELECTIVE 2-AMINOPYRIDINIUM ION CATALYSIS OF INTRAMOLECULAR NITROALKENE DIELS-ALDER REACTIONS

Since its discovery in 1928,[1] the Diels-Alder reaction has become one of the most useful transformations in organic chemistry. The intramolecular variant of this process, in which the diene and dienophile are tethered by a connecting chain, holds a similar position of prominence; forming two new C-C bonds, two rings, and up to four contiguous stereocenters in a single step. Furthermore, the process is oftentimes highly stereoselective, generating predictable adducts. Numerous examples in the literature attest to its utility, especially in the construction of stereochemically complex natural products.[45,46]

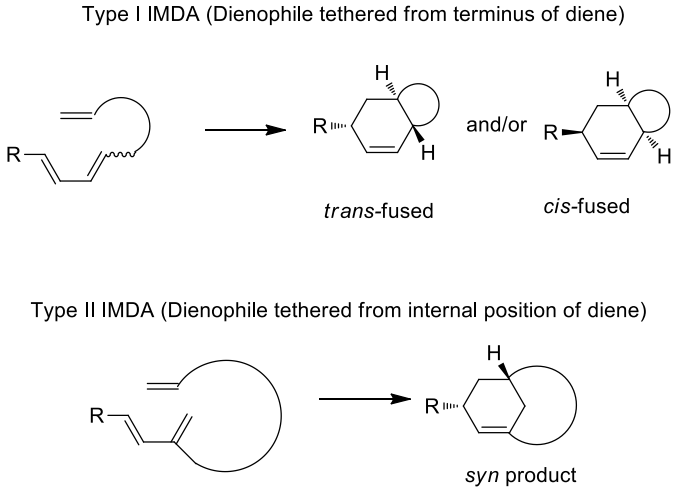
However, despite the prevalent uses of the intramolecular Diels-Alder (IMDA) reaction, examples of the nitroalkene IMDA variant have remained remarkably rare,[47-54] unlike its bimolecular counterpart.[13-16,20] This is especially surprising, when one considers the unique advantage that the nitroalkene IMDA reaction offers. Due to the nitro group's ease of functional group interconversion,[12] nitroalkene IMDA adducts can provide straightforward access to bicyclic motifs that are otherwise difficult to attain. Furthermore, unlike the intramolecular Diels-Alder reactions of carbonyl based substrates, for which Lewis acid catalysis has proven a powerful method of increasing rates and diastereoselectivity,[55] catalytic examples of the nitroalkene intramolecular Diels-Alder variant remain scarce.[47-54] Therefore, in hopes of taking advantage of these highly complementary substrates we initiated a program to address the catalysis of this decidedly promising process.

2.1. Background

The intramolecular Diels-Alder reaction is one of the most efficient and elegant methods for constructing polycyclic ring systems. In a single step, functionalized bicyclic ring systems possessing up to four contiguous stereocenters can be generated from relatively simple triene precursors. Additionally, excellent levels of regio- and diastereoselectivities are oftentimes observed, which together accounts for the numerous applications of this reaction, particularly to the synthesis of natural products.[45,46]

The intramolecular Diels-Alder (IMDA) reaction can be separated into two major classes, Type I and II, identified based on the point of connection between the diene and the dienophile (Figure 2.1.). Type I IMDA reactions involve trienes with the connecting chain attached to the diene terminus, resulting in bicyclic products containing a fused ring junction. Type II IMDA, on the other hand, have dienophiles that are tethered from an internal position on the diene, resulting in the formation of bridged bicycles containing bridgehead double bonds. An excellent comprehensive review has been published on this topic and therefore it will not be discussed here.[56]

Figure 2.1. Type I vs. Type II IMDA



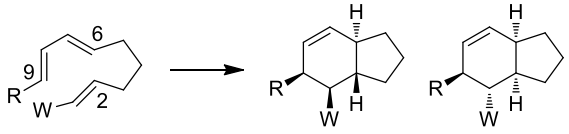
2.1.1. Simple diastereoselection in intramolecular Diels-Alder reactions

The ability to control the regio- and stereoselectivity of the IMDA is critical for their successful applications in synthesis. Fortunately, some important trends in Type I IMDA reactions have been identified. The nature of the diene, dienophile, and tether are all factors that can affect the stereochemical outcome of the reaction.[55] The most significant issue of, Type I trienes, with (*E*)-dienes is that of stereoselectivity, as mixtures of *cis* and *trans*-fused cycloadducts are accessible. Combinations of steric and electronic elements determine the stereochemistry of the IMDA and will be briefly summarized here.

A comparative summary is compiled in Table 2.1 for reports of thermal IMDA cyclizations of several representative (*E,E,E)*-1,6,8- nonatrienes. Houk has previously reported that unsubstituted parent (*E,E,E)*-1,6,8- nonatriene, cyclizes with moderate selectivity to a 24:76 mixture of *trans*- and *cis*-fused cycloadducts (entry 1).[57] Four concerted synchronous transition states are feasible (Figure 2.2.). *Cis*-fused products are

derived from arrangements **6b** and **6d**. In contrast, incorporation of an activating, electron withdrawing group (W), at the dienophile terminus, favors *trans*-fused products (Table 2.1 entries 2-8).[47,58-60] The currently accepted rational for this aspect of stereocontrol is known as asynchronicity,[61] and appears to correlate with a change from a highly synchronous concerted reaction pathway to a concerted asynchronous reaction pathway.

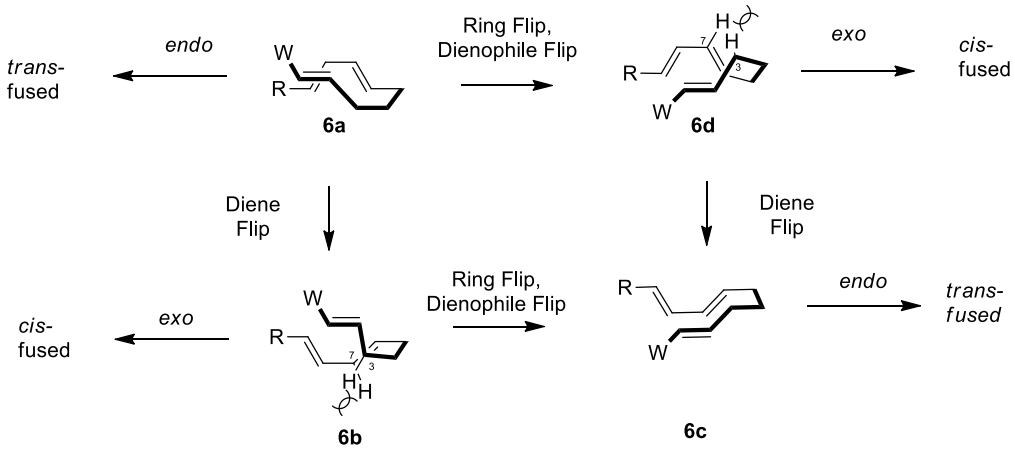
Table 2.1. Comparative analysis of the formations of *trans* and *cis* cycloadducts from (*E*,*E*,*E*)-1,6,8- nonatrienes Table adapted from Roush (Reference 55).



trans *cis*

entry	R	W	temp (° C)	cat	*trans:cis*
1	H	H	160	-	24:76
2	iPr	$CO(NC_4H_8)$	150	-	51:49
3	H	CO_2Me	150	-	60:40
4	iPr	CO_2Me	150	-	72:28
5	Et_2N	CO_2Et	60	-	85:15
6	iPr	COMe	120	-	85:15
7	Me	NO_2	80	-	89:11
8	iPr	CHO	110	-	92:8
9	H	CO_2Me	23	$EtAlCl_2$	>99:1
10	iPr	CO_2Me	23	$EtAlCl_2$	>99:1
11	iPr	COMe	-78	$EtAlCl_2$	>99:1
12	iPr	CHO	-78	$EtAlCl_2$	>99:1

Figure 2.2. Possible transition states of IMDA reaction of (*E,E,E)*-1,6,8- nonatrienes. W = Electron withdrawing group.

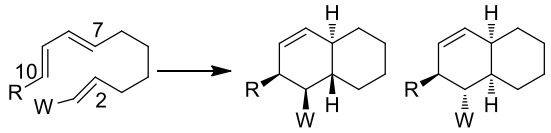


Because introduction of an electron withdrawing group, causes polarization of the dienophilic C=C bond, the LUMO coefficient at C(2) is larger than at C(1). Consequently the developing internal bond between C(2) and C(6) is somewhat more advanced in the transition state, relative to C(1) and C(9). Greater thermodynamic stability of the forming *trans*- 1,2-disubstituted cyclopentane relative to the *cis*-fused cyclopentane accounts for the observed trans selectivity. Specifically, the *trans*-transition state is said to be more energetically accessible due to the presence of unfavorable non bonding interaction between the hydrogens at C(3) methylene and the hydrogen at C(7) in the *trans* transition state. Additionally, Alder *endo* stabilization favors the *trans*-fused products, due to secondary orbital overlap interactions. This model predicts that the selectivity for the *trans*-fused cycloadducts in nonatrienes should increase as polarization of the dienophile or diene increases. Table 2.1 summarizes the results of the IMDA reaction of several nonatrienes. Increases in *trans*-selectivities are indeed observed as the dienophile activating group is changed along the series $CONR_2$ < CO_2Me < COMe <CHO. Lewis acid catalysis additionally augments *trans*-selectivities (entries 9-12). Furthermore,

increases in the size of the HOMO coefficient at C(6), by addition of electron donating groups (i.e. Et_2N) can also enhance *trans* selectivities (entry 5).[60]

Similar trends, although less pronounced were reported for (*E,E,E)*-1,7,9-decatrienes (Table 2.2.). [50,57,58,60-63] Differences in selectivities between the two series are attributed to distinctions in the nona- and decatriene transition states. For the decatriene, both *cis* and *trans* transitions states are essentially unstrained, in the developing chair-like ring (Figure 2.3.). This is unlike the nonatriene cases, where *cis* transition states are decidedly disfavored.

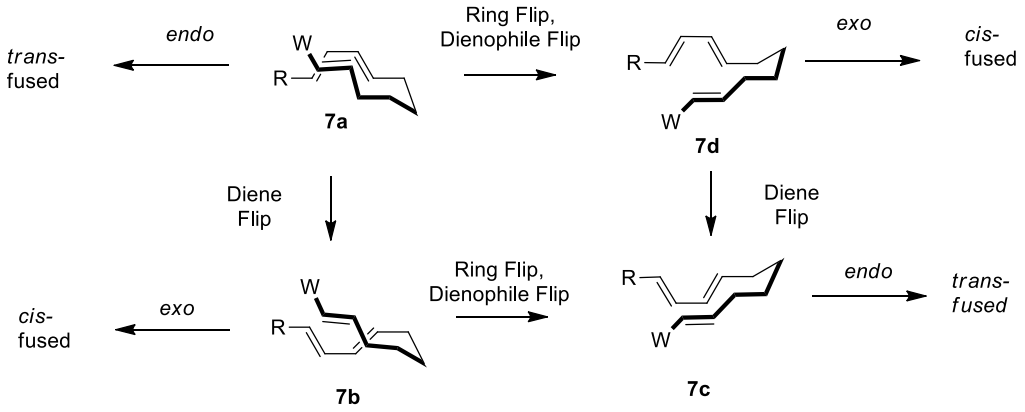
Table 2.2. Comparative analysis of the formations of *trans* and *cis* cycloadducts from (*E,E,E*)-1,7,9-decatrienes. Table adapted from Roush (Reference 55).



trans *cis*

entry	R	W	temp (° C)	cat	*trans:cis*
1	H	H	190	-	47:53
2	H	CO_2Me	155	-	51:49
3	iPr	CO_2Me	160	-	50:50
4	Et_2N	CO_2Et	40	-	55:45
5	iPr	COMe	150	-	67:33
6	Me	NO_2	85	-	70:30
7	iPr	CHO	150	-	75:25
8	iPr	CO_2Me	23	$EtAlCl_2$	88:12
9	iPr	COMe	-78	$EtAlCl_2$	>99:1
10	iPr	CHO	-78	$EtAlCl_2$	>99:1

Figure 2.3. Possible transition states of IMDA reaction of (*E,E,E)*-1,7,9- decatrienes. W = Electron withdrawing group.



The behaviors of (*Z,E,E*)- nona- and decatrienes are also different. For (*E,E,E*)- nonatrienes, Alder *endo* stabilization and asynchronous effects are cooperative, both favoring the *trans*-fused adduct, so increased selectivity occurs with increased dienophile activation. On the other hand, for (*Z,E,E*)- nonatrienes, Alder *endo* stabilization favors *cis*-fused products while asynchronous effects favors *trans*-fused adducts (Figure 2.4). These effects evidently cancel each other out, such that no significant change in selectivity occurs with dienophile activation, or even with Lewis acid catalysis (Table 2.3.). For (*Z,E,E*)- decatrienes, a more significant enhancement of selectivity can be seen with Lewis acid catalysis as compared to the (*Z,E,E*)- nonatrienes counterparts (Table 2.4.). This is due to the fact that asynchronous effects are less pronounced in the decatriene transition states, so that Alder *endo*-stabilization can predominate.

Figure 2.4. Possible transition states of IMDA reaction of (*Z,E,E)*-1,6,8- nonatrienes. W = Electron withdrawing group.

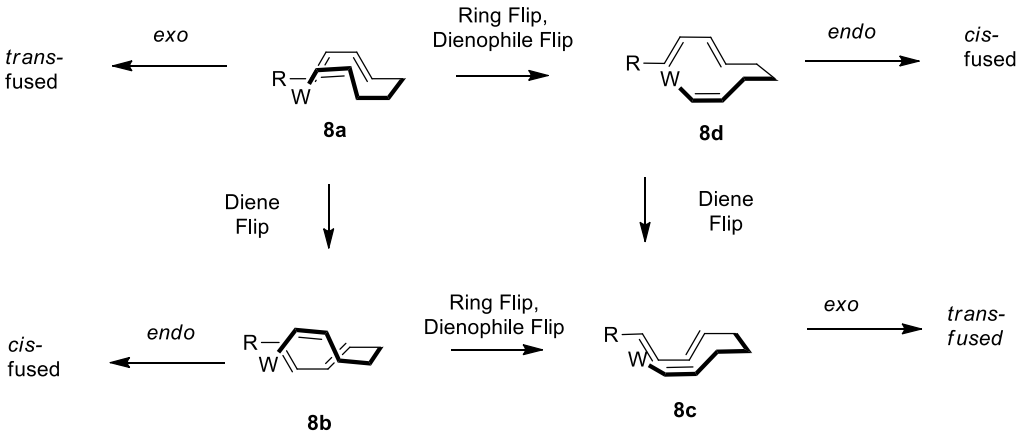
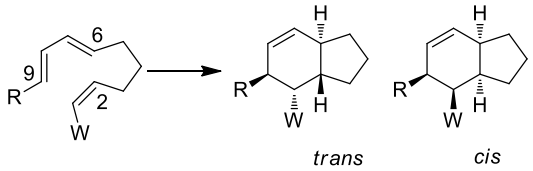
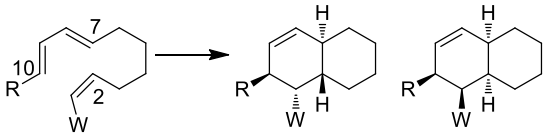


Table 2.3. Comparative analysis of the formations of *trans* and *cis* cycloadducts from (*Z,E,E*)-1,6,8- nonatrienes. Table adapted from Roush (Reference 55).



entry	R	W	temp (° C)	cat	*trans:cis*
1	H	CO_2Me	155	-	51:49
2	iPr	CO_2Me	180	-	55:45
3	Me	NO_2	23	-	53:47
4	H	CO_2Me	23	$EtAlCl_2$	52:48
5	iPr	CO_2Me	23	$EtAlCl_2$	63:37

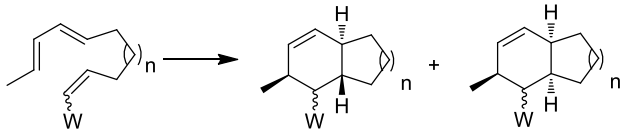
Table 2.4. Comparative analysis of the formations of *trans* and *cis* cycloadducts from (*Z,E,E*)-1,7,9- decatrienes. Table adapted from Roush (Reference 55).



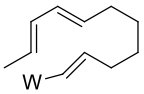
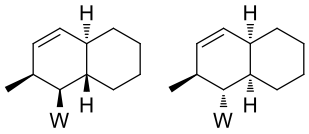
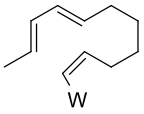
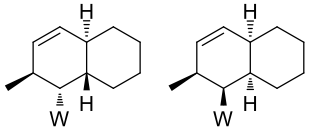
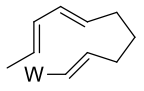
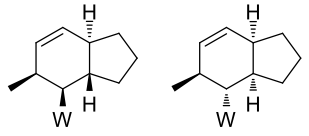
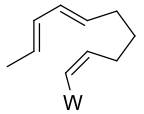
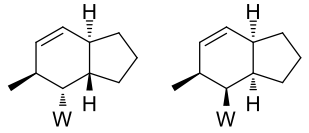
trans *cis*

entry	R	W	temp (° C)	cat	*trans:cis*
1	H	CO_2Me	155	-	51:49
2	iPr	CO_2Me	180	-	55:45
3	iPr	CO_2Me	23	$EtAlCl_2$	<8:92

Table 2.5. IMDA reactions of sulphonyl substituted trienes. Reported by Craig et al. (References 64 and 65).

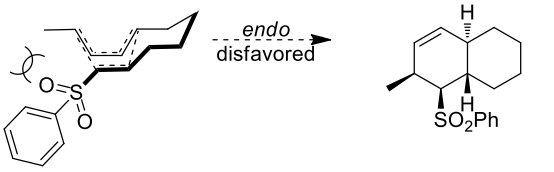


trans *cis*

entry	triene	temp (° C)	Products	*trans:cis*
1		175		1:6
2		165-175		3:1
3		145		1:1
4		165		7:1

It is important to note that while electronic effects certainly play a significant role in determining the stereochemical outcome of the IMDA reaction, steric and conformational effects also exert a significance influence on the course of these reactions. Table 2.5 illustrates how steric effects are capable of overriding the usual preference of terminally activated (*E,E,E)*-nona- and deca-trienes to cyclize to *trans*-fused products. For example, Craig and coworkers have reported that sulfonyl activated (*E,E,E)*-decatriene cyclizes to a 6:1 *cis*:*trans* mixture (entry 1).[64,65] The unusual *cis*-selective nature is attributed to unfavorable steric interactions between the bulky sulphone group and the diene in the *endo*-transition state (Figure 2.5). Similarly, the (*Z,E,E*)-decatriene, was selective toward the more sterically favorable *exo* transition state, providing a 1:3 mixture of *cis* and *trans* (entry 2).

Figure 2.5. Sterically disfavored *endo* transition state. Figure adapted from Craig et al. (References 64 and 65).

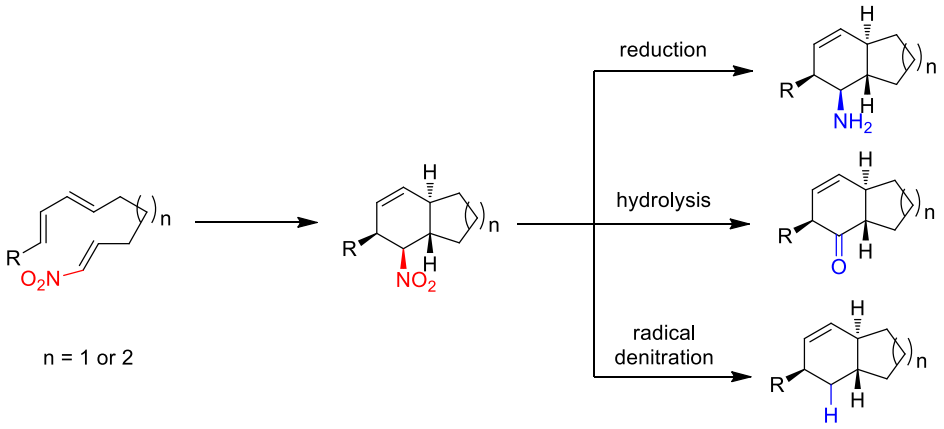


The lower sulfonyl (*E,E,E)*-nonatriene homologue, cyclized to give a mixture of 1:1 *cis*:*trans* cycloadducts (entry 3). The decreased selectivity is attributed to the opposing steric effects (disfavors the *endo*-transition state) and the asynchronous effect (favors the *trans*-fused transition state). The (*Z,E,E*)-nonatriene on the other hand, was *trans*-selective, providing a 1:7 *cis*:*trans* mixture. This reflects the now cooperative nature of the steric effect (favors the *exo* transition state) and asynchronous effect that favors the *trans*-fused adduct.

This is just one example showcasing how sterics can alter the results of the IMDA, but numerous more are encountered in the literature. For a detailed account please refer to the excellent reviews cited herein.[55,66]

2.1.2. Intramolecular Diels-Alder reactions of nitroalkenes

Scheme 2.1. Intramolecular nitroalkene Diels-Alder reaction

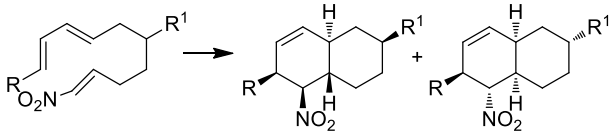


Stereocontrolled access to complex nitrocarbocycles *via* the IMDA reaction of nitroalkenes offers rich synthetic opportunities, especially when one considers the ease of product manipulations, due to the diverse reactivity of the nitro group[12] (Scheme 2.1). In this respect, Kurth and coworkers have investigated the thermal cyclizations of 1-nitro-1,6,8-nonatrienes for the synthesis of perhydroindenes.[47] Furthermore, the merits of the intramolecular nitroalkene Diels-Alder reaction were clearly demonstrated by the elegant synthesis of the AB ring system of zoanthamine alkaloids reported by Williams and coworkers.[50] However, despite the potential utility of the nitroalkene IMDA reaction, examples of this process have remained remarkably scarce,[47-54] presumably due to the lack of its catalytic method.

The use of Lewis acid catalysis has proven to be a powerful method for enhancing the rate and diastereoselectivity of many carbonyl based IMDA substrates[55] and have thus had an enormous impact on chemical synthesis.[45,46,67-69] However, unlike carbonyl based substrates, catalytic examples of the nitroalkene IMDA reaction are limited,[48,50,53,54] and pioneering studies have proven that the catalysis of these substrates by Lewis acids, is extremely challenging.

For example, Williams and coworkers attempted to enhance *endo* selectivity of several (*E*)-1-nitro-1,7,9-decatienes with a variety of Lewis acids.[50] However, the use of $AlMe_3$, BF_3•OEt_2, $TiCl_4$, and $TiCl_2(O^iPr)_2$ all led to low yields (<10 %) of the decalin products and although improved results were achieved with Et_2AlCl only modest yields were obtained (Table 2.7). Furthermore, catalytic quantities of Lewis acids were ineffective, while stoichiometric quantities led to considerable decomposition affording unidentified highly polar materials.

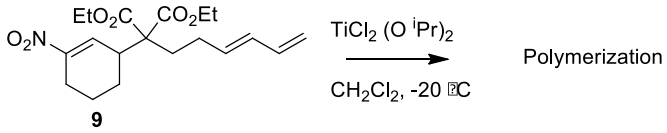
Table 2.6. IMDA reactions of (*E*)-1-nitro-1,7,9-decatienes. Reported by Williams et al. (Reference 50).



entry	R	R^1	temp (° C)	cat (equiv)	yield (%)	*trans:cis*
1	Me	H	85	-	70	70:30
2	Me	H	-78	Et_2AlCl (2)	39	89:11
3	H	Me	85	-	80	73:27
4	H	Me	-78	Et_2AlCl (2)	38	92:8

Similar problematic results were reported by Guy and coworkers. They attempted to catalyze the IMDA reaction of substrate **9** with catalytic quantities of $TiCl_2(O^iPr)_2$ but instead observed polymerization of the triene.[53]

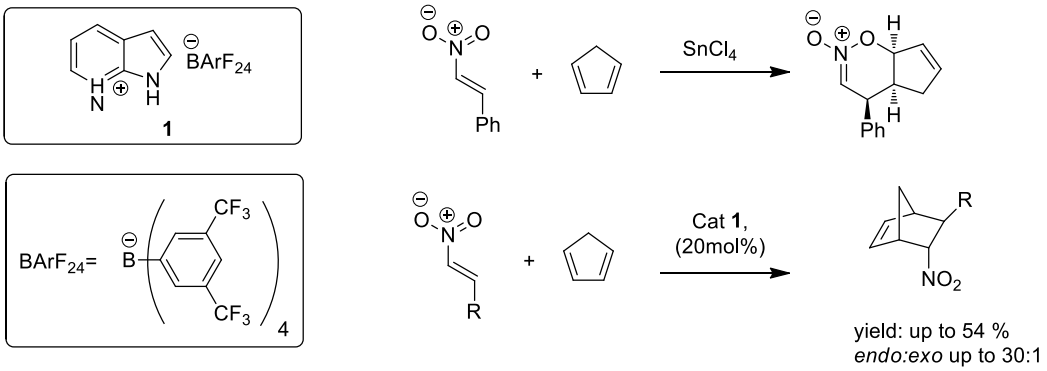
Scheme 2.2. IMDA reaction of substrate **9.**
Reported by Guy et al. (Reference 53).



It should be mentioned here, that the intramolecular inverse electron demand hetero Diels-Alder reaction of nitroalkenes, which provides nitronate intermediates, has been systematically studied by Denmark and coworkers.[21,70,71]

In light of our own findings[22] that Brønsted acids periselectively catalyze the intermolecular nitroalkene Diels-Alder reaction despite the inherent preference of nitroalkenes to undergo the inverse electron-demand hetero Diels-Alder reaction with Lewis acids (Scheme 2.3), we were interested in investigating the effects of Brønsted acids on the intramolecular variant.

Scheme 2.3. Lewis acid vs Brønsted acid catalyzed
Diels-Alder reaction of β-nitrostyrene

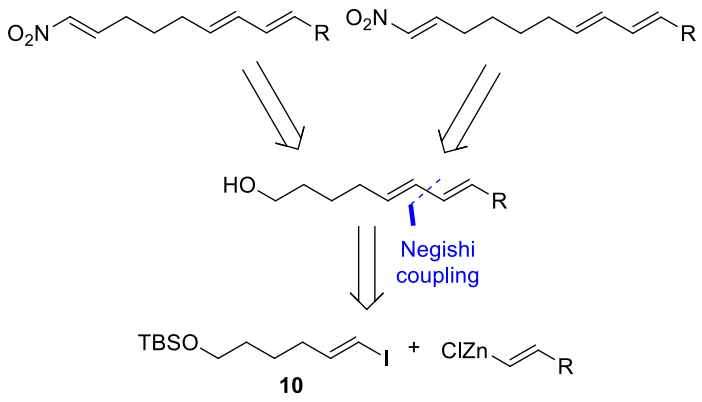


2.2. Results and discussion

2.2.1. Synthesis of 1-nitrotrienes; intramolecular Diels-Alder reaction substrates

It is worthy of mention, that several studies on the catalysis of IMDA reaction have involved tedious syntheses of the substrates, which has oftentimes lead to studies with limited substrate scopes. Fortunately, however we employed a straightforward route to access several nitroalkene IMDA substrates. The synthetic strategy involved a key Negishi cross coupling reaction of known vinyl halide **10**[72] with vinylzincs (Figure 2.6). This provides ready access to a variety of diene intermediates from which we planned to obtain both the 1-nitro-nona and decatrienes IMDA substrates.

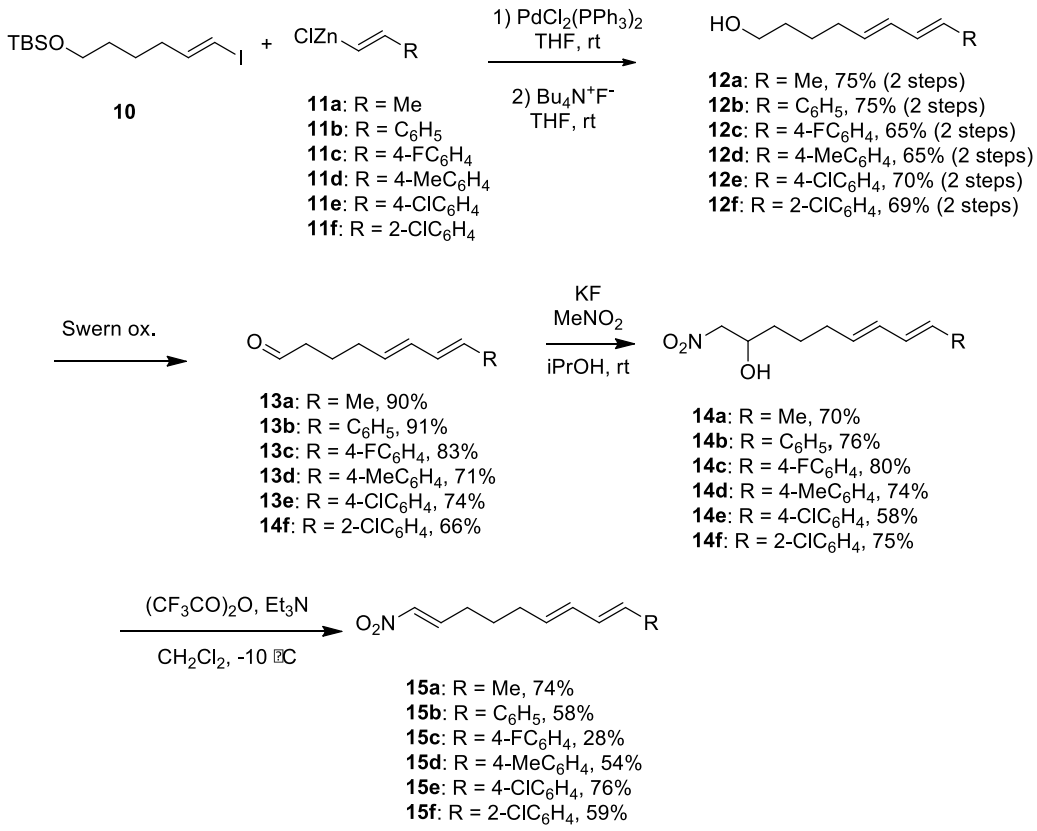
Figure 2.6. Synthetic plan for nitroalkene IMDA substrates



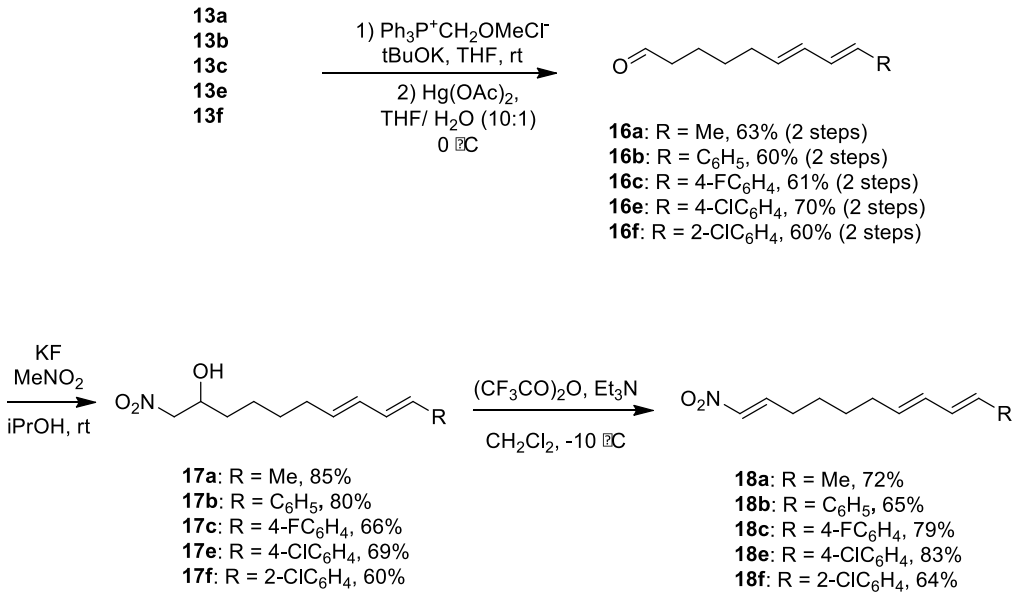
Following our planned synthetic route, and using well known methodologies as outlined in Schemes 2.4 and 2.5, the substrates for the intramolecular Diels-Alder reaction were readily synthesized. Negishi coupling of vinyl iodide **10** with vinylzincs followed by the removal of TBS group provided dienes **12a-f**. Swern oxidation afforded aldehydes **13**. A sequence of Henry reaction[73] and dehydration[74] of the corresponding β-hydroxyl nitroalkanes provided the (*E)*-1-nitro-1,6,8-nonatrienes.

(*E)*-1-Nitro-1,7,9-decatrienes were synthesized analogously from one-carbon elongated aldehydes. It should be mentioned that the dehydration reactions led to exclusive formation of *E*-olefins, as determined by ^{1}H NMR analysis of crude products, and that these nitroalkenes were stable to procedures of flash silica gel chromatography.[54]

Scheme 2.4. Synthesis of (*E)*-1-nitro-1,6,8-nonatrienes



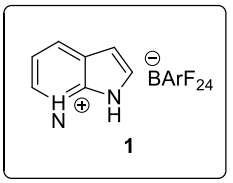
Scheme 2.5. Synthesis of (*E*)-1-nitro-1,7,9-decatrienes



2.2.2. 2-Aminopyridinium ion catalyzed intramolecular Diels-Alder reactions of 1-nitro-nonatrienes

We began our investigations by studying the cyclization of (*E*)-1-nitro-1,6,8-nonatriene **15a** (R = Me) with catalyst **1** which was found to be optimal for the intermolecular nitroalkene Diels-Alder reaction.[22] To our delight it cleanly catalyzed the reaction and provided the product with excellent *endo* selectivity (Table 2.7, entry 1), while an 8.1:1 *endo:exo* ratio was reported for the corresponding thermal reaction.[47] An increase in catalyst loading led to the excellent yield (Table 2.7, entry 1). As described in Chapter 1 we also identified $NaBArF_{24}$•$2.5H_2O$ **4** as an efficient catalyst for the intermolecular nitroalkene Diels-Alder of β-nitrostyrene, and we therefore decided to probe its capabilities for the intramolecular counterpart. To our delight we found that it is also a competent catalyst for this reaction (Table 2.7, entry 3). However, unlike the 7-azaindolium catalyst **1**, increased catalyst loading did not show a beneficial effect on the yield (entry 4). After careful consideration we decided continue our study with 2-

aminopyridinium **1** because we aimed at asymmetric catalysis (See Chapter 1 and 3 for more detailed discussions).



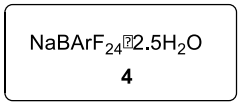
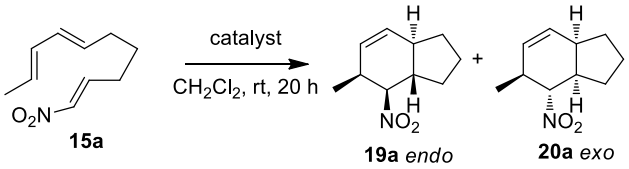


Table 2.7. Evaluation of Brønsted acids for IMDA reactions of (*E*)-1-nitro-1,6,8-nonatrienes

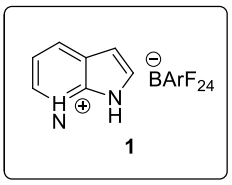


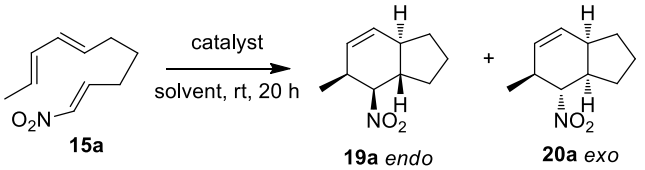
entry	cat (mol %)	yield[a] (%)	*endo*:*exo*[b]
1	**1** (10)	47	>30:1
2	**1** (20)	91	>30:1
3	**4** (10)	87	>30:1
4	**4** (20)	85	>30:1

[a] Yield determined by NMR of crude products, with 1,1,2,2-tetrachloroethane as internal standard. [b] Determined by ^{1}H NMR analysis of the crude product.

In order to optimize the reaction conditions a survey of commonly used solvents was undertaken, and dichloromethane was identified as most favorable (Table 2.8). It is interesting to note the differences in the reactivity in diethyl ether and tetrahydrofuran (THF). Because THF is a better hydrogen bond acceptor, it is proposed that it may be inhibiting the catalyst.

Table 2.8. Screening of solvents for IMDA reaction of (*E*)-1-nitro-1,6,8-nonatriene



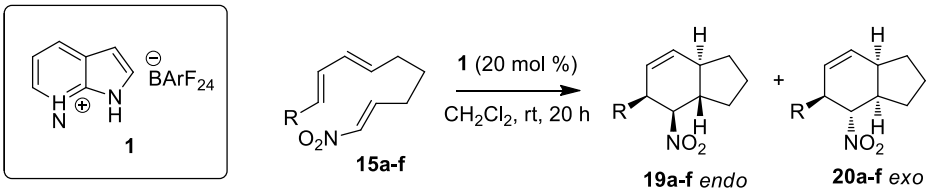


entry	solvent	cat (mol %)	yield[a] (%)	*endo:exo*[b]
1	CH_2Cl_2	**1** (20)	91	>30:1
2	CH_2Cl_2	-	Trace	-
3	MePh	**1** (20)	70	>30:1
4	MePh	-	6	3.3:1
5	Et_2O	**1** (20)	41	>30:1
6	Et_2O	-	8	3.6:1
7	THF	**1** (20)	11	27:1
8	THF	-	10	3.9:1

[a] Yield determined by NMR of crude products, using 1,1,2,2-tetrachloroethane as an internal standard. [b] Determined by ^{1}H NMR analysis of the crude product.

With the optimum conditions in hand, the scope of the reaction was explored (Table 2.9). Both aliphatic and aromatic substrates underwent the reaction cleanly and afforded the product with excellent *endo* selectivities (Table 2.9 entries 1-6). Aromatic substrate containing electron- withdrawing group F was well tolerated, although it provided the adduct with slightly lower yield (entry 3). The aromatic substrate containing electron-donating group provided the IMDA adduct in excellent yield (entry 4). In addition, both *para* and *ortho*-chloro substituents worked well (entries 5 and 6). It is worth noting that these substrates could be used as cross coupling partners for further derivation of the products.

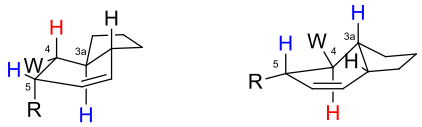
Table 2.9. Substrate scope of IMDA reactions of (*E*)-1-nitro-1,6,8-nonatrienes



entry	triene	R	yield[a] (%)	*endo*:*exo*[b]
1	**15a**	Me	91	>30:1
2	**15b**	C_6H_5	86	>30:1
3	**15c**	4-FC_6H_4	69	>30:1
4	**15d**	4-MeC_6H_4	98	>30:1
5	**15e**	4-ClC_6H_4	72	>30:1
6	**15f**	2-ClC_6H_4	68	>30:1

[a] Isolated yield of products. [b] Determined by ^{1}H NMR analysis of the crude product.

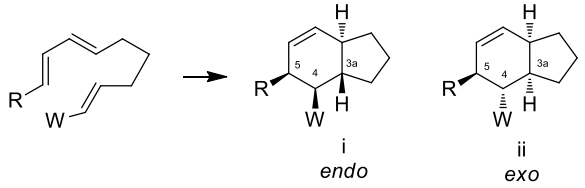
Figure 2.7. Representative diagrams of *cis* and *trans*-fused IMDA adducts of nonatrienes

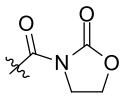


It proved possible to make unambiguous stereochemical assignments for the six cycloadducts by comparing their ^{1}H NMR spectroscopic data with those reported by Roush et al. for the IMDA adducts of nonatriene ester **21** (Table 2.10).[59] Kurth and coworkers previously applied this technique to assign ^{1}H NMR spectroscopic data of nonatriene cycloadducts **19a** and **20a**.[47] The ^{1}H NMR resonances for C(4)-H, the proton α to the W group, are especially indicative of the structure (Figure 2.6) and the data is summarized in Table 2.10. In the *trans*-fused isomer of the ester adduct, C(4)-H appears as a doublet of doublets, with coupling constants $J_{4,5}$ = 7.7 Hz and $J_{3a,4}$ = 11.4 Hz. These

data require that C(3a)-H and C(4)-H occupy axial positions and C(5)-H occupies a pseudo-equatorial position in the cyclohexenyl ring (Figure 2.6 i). For the *cis*-fused adduct, on the other hand a doublet of doublet with coupling constants, $J_{4,5}$ is 10.8 Hz and $J_{3a,4}$ is 11.3, was observed. This data indicates that C(3a), C(4), and C(5) cyclohenyl protons occupy axial positions in the cyclohexenyl ring (Figure 2.6 ii).

Table 2.10. ^{1}H NMR data for C(4)-H nonatriene IMDA adducts



Entry	triene	R	W	i C(4)-H δ (ppm) dd, $J_{4,5}$ & $J_{3a,4}$ (Hz)	ii C(4)-H δ (ppm) dd, $J_{4,5}$ & $J_{3a,4}$ (Hz)
1[a]	**21**	$CH(CH_3)_2$	CO_2CH_3	2.70 7.7 &11.4	2.11 10.8 & 11.3
2	**15a**	CH_3	NO_2	4.68 7.0 & 10.9	3.97 10.2 & 11.2
3	**15b**	C_6H_5	NO_2	4.89 7.3 & 11.4	-
4	**15c**	4-FC_6H_4	NO_2	4.87 7.3 & 11.1	-
5	**15d**	4-MeC_6H_4	NO_2	4.87 7.2 & 11.3	-
6	**15e**	4-ClC_6H_4	NO_2	4.87 7.3 & 11.2	-
7	**15f**	2-ClC_6H_4	NO_2	5.02 7.5 & 10.9	-
8[b]	**22**	C_6H_5		4.29 7.9 &11.4	-

[a] Reported by Roush et al. (Reference 59). [b] Reported by Evans et al. (Reference 75).

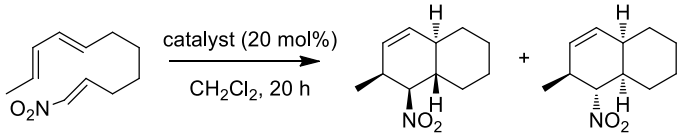
Inspection of Table 2.10 reveals that for all adducts obtained C(4)-H appears as a doublet of doublet with coupling constants in the range of $J_{4,5}$ = 7.2 - 7.9 Hz and $J_{3a,4}$ =

10.9 – 11.4. These coupling constants are consistent with *trans*-fused products. It is important to mention that the C(4)-H of *trans*-fused perhydroindene synthesized by the IMDA reaction of nonatrieneimide **22** (Table 2.10, entry 8)[75] reported by Evans and coworkers, has similar peak multiplicity and coupling constants (doublet of doublet with coupling constants, $J_{4,5}$ = 7.9 Hz and $J_{3a,4}$ = 11.4 Hz). In addition, its structure has been confirmed by X-ray analysis.

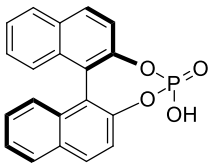
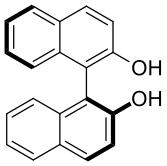
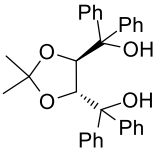
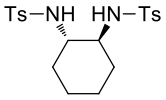
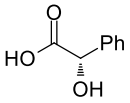
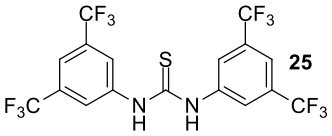
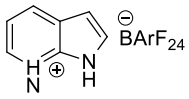
2.2.3. 2-Aminopyridinium ion catalyzed intramolecular Diels-Alder reactions of 1-nitro-decatrienes

We next turned our efforts to the catalysis of 1-nitro-decatrienes. Because it is well established that it is often more challenging to increase the stereoselectivity of the IMDA reaction of decatrienes as compared to their homologous nonatrienes[55,75-77] we deemed it wise to screen several known H-bonding catalysts[10,11] (Table 2.11). For our initial study we chose aliphatic substrate **18a**, for which a 2.3:1 *endo:exo* ratio of products were obtained under thermal conditions.[50] To our delight, double H-bond donors, thiourea **25**[78] and 2-aminopyridinium ion **1**, were found to be efficient catalysts for the reaction (Table 2.11, entries 6 and 7). 2-Aminopyridinium ion **1** provided the best results, affording the product in good yield and high *endo* selectivity. An attempt to increase the selectivity by conducting the reaction at lower temperature, led only to decreased yield. We additionally screened $NaBArF_{24}$•$2.5H_2O$ **4**, as it was found to be effective for the lower homologue nonatriene and the intermolecular nitroalkene Diels-Alder reaction, however it turned out to be less effective in terms of selectivity (entries 9 and 10). Interestingly, $NaBArF_{24}$•$(H_2O)_x(PhOH)_y$, **5**, described in Chapter 1 provided better yield and selectivity than $NaBArF_{24}$•$2.5H_2O$, **4**, did. This may be attributable to the expected higher acidity of the former complex.

Table2.11. Evaluation of Brønsted acids for IMDA reaction of (*E*)-1-nitro-1,7,9-decatriene



18a **23a** *endo* ***24a*** *exo*

entry	cat	temp (°C)	yield[a] (%)	*endo:exo*[b]
1		25	12	5.5:1
2		25	14	5.6:1
3		25	14	5.6:1
4		25	10	5.9:1
5		25	11	5.8:1
6	 **25**	25	60	14:1
7	 **1**	25	77	14:1
8	**1**	0	44	13:1
9	$NaBArF_{24}\cdot 2.5H_2O$ **4**[c]	25	88	8:1
10	**4**[c]	0	27	8:1
11	$NaBArF_{24}(H_2O)_x(PhOH)_y$ **5**[c]	25	93	13:1

[a] Isolated yield of products. [b] Determined by ^1H NMR analysis of the crude product.
[c] 10 mol% catalyst loading.

Of competent catalysts found, (**25**, **1**, **4**, and **5**) we chose to proceed with 2-aminopyridinium ion, **1**, as it would make an excellent catalaphore to build a chiral scaffold around (See Chapter 1 and 3 for more detailed discussions). With this catalyst we examined the scope of the reaction (Table 2.12). To our delight aromatic substrate **18b** afforded the product in good yield, although with slightly decreased *endo* selectivity. Aromatic substrate containing electron- withdrawing group F was also well tolerated, providing the IMDA adduct with high *endo* selectivity (Table 2.12 entry 3). *Para*-chloro aryl substrate provided the product in 53 % yield and 12:1 *endo*:*exo* selectivity (entry 4). We were delighted to find that the *ortho*-chloro aryl substrate **18f** provided the IMDA adduct with excellent *endo* selectivity (entry 5). One possible explanation for the enhanced *endo* selectivity relative to the other substrates may be that additional steric effects are playing a role. Drieding model analysis of the two possible transition states reveals the presence of unfavorable electrostatic repulsion between the chlorine atom and the negative charge of the nitro group in the *exo* transition state (Figure 2.7), perhaps making the *endo* transition state more energetically accessible.

Figure 2.8. Possible transition states of decatriene **18f**

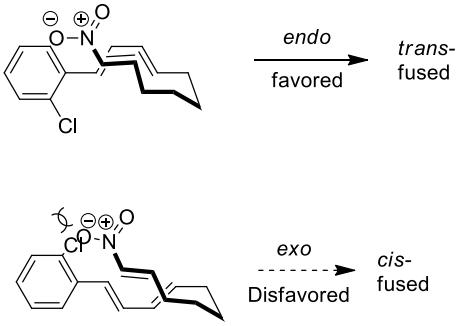
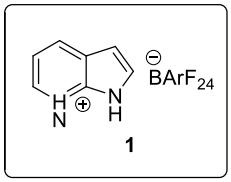
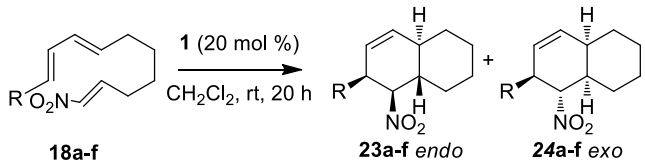


Table 2.12. Substrate scope of IMDA reactions of (*E*)-1-nitro-1,7,9-decatriene



1



18a-f **23a-f** *endo* **24a-f** *exo*

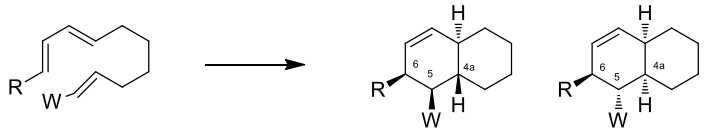
entry	triene	R	yield[a] (%)	*endo:exo*[b]
1	**18a**	Me	77	14:1
2	**18b**	C_6H_5	71	11:1
3	**18c**	4-FC_6H_4	66	16:1
4	**18e**	4-ClC_6H_4	53	12:1
5	**18f**	2-ClC_6H_4	60	>30:1

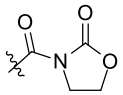
[a] Isolated yield of products. [b] Determined by ^{1}H NMR analysis of the crude product.

Unambiguous stereochemical assignments of the products were made by comparing ^{1}H NMR spectroscopic data with those of the cycloadducts of decatrienimide **26** reported by Evans et al.[75] and of decatriene ester **27** (Table 2.13) reported by Roush et al.[63] The protons α to the W group, C(5)-H, are especially indicative of the structure (Figure 2.8) and the data is summarized in Table 2.13. In the *trans*-fused adduct of decatrienimide **26**, C(5)-H is a doublet of doublet with coupling constants $J_{6,5}$ = 7.1 Hz and $J_{5,4a}$ = 11.4 Hz. These data require that C(4a)-H and C(5)-H occupy axial positions and C(6)-H occupies a pseudo-equatorial position in the cyclohexenyl ring (Figure 2.8 i). The *cis* isomer C(5)-H is also a doublet of doublets, but has coupling constants of values of $J_{6,5}$ = 10 and $J_{5,4a}$ = 11. This would require that C(4a), C(5), and C(6) cyclohenyl protons occupy axial positions in the cyclohexenyl ring (Figure 2.8 ii). NOE data reported by Evans et al. support this analysis.[75] Roush et al. obtained similar peak multiplicity and coupling constants for the IMDA adduct of decatriene ester **26**.[63] In the trans-fused isomer C(5)-H, appears as a doublet of doublets, with coupling constants $J_{6,5}$ = 7.3 Hz

and $J_{5,4a}$ = 11.7 Hz. For the *cis* fused isomer, C(5)-H is a triplet with a coupling constant of J = 10.7 Hz. However, it makes sense that peak multiplicity may actually be a doublet of doublet with two coupling constants of similar magnitude, overlapping to give a triplet. As can be seen from Table 2.13, the major isomers of the cycloadducts obtained from IMDA of 1-nitrodecatriene substrates all have coupling constants that correlate with a *trans*-fused product.

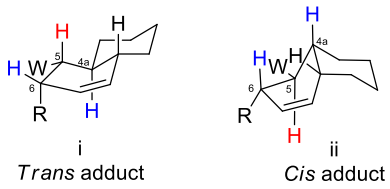
Table 2.13. ^{1}H NMR data for C(5)-H decatriene IMDA adducts



Entry	triene	R	W	i C(5)-H δ (ppm) dd, $J_{5,6}$ & $J_{4a,5}$ (Hz)	ii C(5)-H δ (ppm) dd, $J_{5,6}$ & $J_{4a,5}$ (Hz)
1[a]	**26**	C_6H_5		4.06 7.1 & 11.4	4.56 10.0 & 11.0
2[b]	**27**	$CH(CH_3)_2$	CO_2CH_3	2.60 7.3 &11.7	2.68 t 10.7
3	**18a**	CH_3	NO_2	4.63 6.4 &11.1	4.54 9.9 & 11.9
4	**18b**	C_6H_5	NO_2	4.84 6.7 & 11.6	4.86 9.9 & 12.1
5	**18c**	4-FC_6H_4	NO_2	4.81 6.7 & 11.8	-
6	**18e**	4-ClC_6H_4	NO_2	4.82 6.7 & 11.7	-
7	**18f**	2-ClC_6H_4	NO_2	4.93 6.6 & 11.6	-

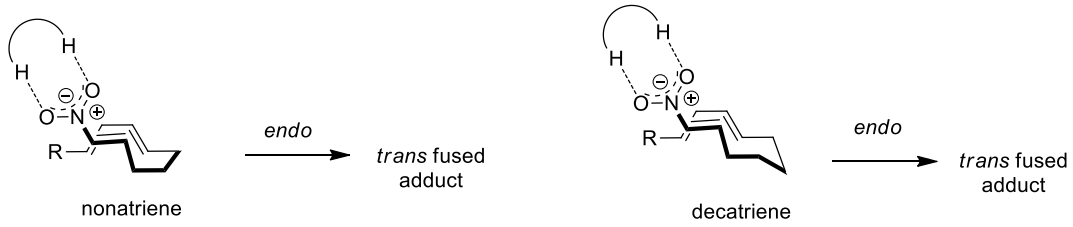
[a] Reported by Evans et al. (Reference 75). [b] Reported by Roush et al. (Reference 63).

Figure 2.9. Representative diagrams of *cis* and *trans*-fused IMDA adducts of decatrienes



2.3. Proposed transition state model

Figure 2.10. Proposed transition state model. 1-Nitro-nona and decatrienes activated by double hydrogen bond donors



From the understanding gained by the intermolecular nitroalkene Diels-Alder reaction studies and from our observation that double hydrogen bond donors catalyze the nitroalkene IMDA reaction we hypothesize that 2-aminopyridinium ion **1** activates 1-nitrotrienes by forming a LUMO lowering double-hydrogen bonding complex to the nitro-group (Figure 2.10).

It is central to mention that selectivity differences observed for 1-nitro-nonatrienes and decatrienes are consistent with the proposed asynchronous nature[55] of the IMDA reaction discussed in Section 2.1.1. For example, as expected decatrienes produced somewhat lower selectivities as compared to the nonatrienes. Given that, both the *cis* and *trans* transition states of decatrienes are unstrained chair conformations, Alder *endo* stabilization plays the most significant role in enhancing diastereoselectivity. On the other hand, all 1-nitro-nonatrienes produced excellent *trans*:*cis* to selectivities (>30:1). This can be attributed to the cooperative nature of Alder *endo* stabilizations and the

asynchronous effects that prefers the *trans* cyclopentane-like transition state due to unfavorable non bonding interactions in the *cis* transition state.

2.4. Summary

To the best of our knowledge, we have developed the first sub-stoichiometric catalytic process for the intramolecular Diels-Alder reaction of nitroalkenes. The study demonstrates that unlike Lewis acid catalysts, double hydrogen bond donor, 2-aminopyridinium ion **1**, is capable of cyclizing a variety of 1-nitrotrienes in good to excellent yields and diastereoselectivities. The reaction has been found to tolerate variation in the diene and tether of the IMDA substrate, thereby allowing access to a range of substituted [4.3.0] and [4.4.0] bicyclic ring systems. Furthermore, the substrates were readily synthesized allowing for the survey to represent one of the most comprehensive substrate studies on the nitroalkene IMDA reaction. Finally, due to the potential utility of bicyclic nitro compounds in synthesis, this process is expected to be highly complementary to IMDA reactions of carbonyl based substrates.

2.5. Experimental section

2.5.1. General information

All reactions were carried out in 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 (TLC) 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 200-400) supplied by E. Merck.

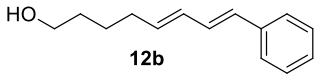
Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH_2Cl_2), and toluene (PhMe) were freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. Et_2O and THF were freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. All the (*E*)-*β*-aryl vinyl halides used for cross coupling reactions were synthesized according to the procedure reported by Charette *et al.*[79] Zinc chloride was flame dried under vacuum before use.[80] Triethylamine, nitromethane, and isopropanol were distilled over calcium hydride and stored over Linde type 4Å molecular sieves, and used from there. DMSO was distilled over calcium hydride under reduced pressure (3.5 mm Hg) and stored over Linde type 4Å molecular sieves, and used from there. Triflouroacetic anhydride was freshly distilled prior to use over phosphorous pentaoxide. Compounds that are not numbered in the main body of the chapter are labeled **S1**, **S2**, ect.

^{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). Fast atom bombardment mass spectra (FABMS) were recorded with a VG Mass Lab Trio-2 spectrometer, using 3-nitrobenzyl alcohol as matrix. Low resolution mass spectra were recorded using Hewlett Packard 5971A spectrometer. High resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, University of Miami.

2.5.2. General procedure for the preparations of 5*E*,7*E*-octadienols (12a-f)

8-Phenyl-5*E*,7*E*-octadienol (12b)



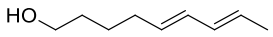
12b

To a solution of (*E)*-(2-iodovinyl)benzene (1.94 g, 8.4 mmol) in ether (17 mL) cooled to -78 °C was added *t*-BuLi solution drop-wise (10.3 mL, 1.64 M in pentane, 16.8 mmol). The resultant solution was stirred for 30 min at -78 °C. To this was added *via* cannula a solution of dry $ZnCl_2$ (2.75 g, 20.5 mmol) in THF (20.5 mL). The mixture obtained was stirred for 5 min at -78 °C, warmed to 23 °C over 25 min, and then added *via* cannula to a mixture of vinyl iodide **10**[72] (1.30 g, 3.83 mmol) and $PdCl_2(PPh_3)_2$ (268. mg, 0.383 mmol) in THF (7.65 mL) at 23 °C. The resultant mixture was stirred and monitored by TLC. After 30 min. the reaction was quenched with saturated NH_4Cl, extracted with ether, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* The crude mixture was filtered through a silica gel plug and washed with 10% benzene in hexanes concentrated *in vacuo* and used in the following step without further purification.

The residue was dissolved in THF (6.3 mL) and was cooled to 0 °C, followed by the addition of 1.0 M *n*-Bu_4NF in THF (3.78 mL). The cold bath was removed after 10 min. and was stirred at 23 °C. After 1.5 h the TLC indicated that the deprotection was

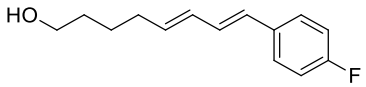
complete. The reaction was then quenched with saturated NH_4Cl and extracted three times with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash chromatography (20% EtOAc/ hexanes) to afford the product (604 mg 75 %). All spectral data were identical to the literature values.[75]

8-Methyl-5*E*,7*E*-octadienol (12a)



The general procedure was followed except that (*E)*-(2-iodovinyl)methyl (2.66 g, 22.0 mmol) and vinyl iodide **10**[72] (5.34g, 15.7 mmol) were used and the crude Negishi product was used without filtering through the silica gel plug prior to the deprotection step (1.66 g, 75 %). All spectral data were identical to the literature values.[64]

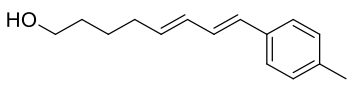
8-(4-Flourobenzene)-5*E*,7*E*-octadienol (12c)



The general procedure was followed except that (*E)*-1-flouro-4-(2-iodovinyl)benzene (2.38 g, 9.59 mmol) and vinyl iodide **10**[72] (1.48 g, 4.36 mmol) were used (637 mg, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.19, 5.8, Hz, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.58 (dd, *J* = 15.6, 10.3 Hz, 1 H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.20 (ddd, *J* = 14.8, 10.6, 0.5 Hz, 1H), 5.80 (dt, 15.1, 6.9 Hz, 1H), 3.66 (br, 2H), 2.18 (q, *J* = 7.0 Hz, 2H), 1.65-1.46 (m, 4H) 1.26 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245 Hz), 135.7, 134.2 (d, *J* = 3.1 Hz), 131.1, 129.4 (d, *J* = 2.1 Hz), 129.4, 127.9 (d, *J* = 7.8 Hz), 115.9 (d, *J* = 21.7 Hz), 63.2, 32.9, 32.6, 25.8; FTIR (neat) υ_{max} 3308, 3012,

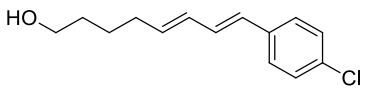
2933,1671, 1597, 1505, 1453, 1413, 1224, 982 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{14}H_{17}FNaO$ $[M+Na]^+$ expected: 243.1156, found: 243.1145.

8-(4-Methylbenzene)-5*E*,7*E*-octadienol (12d)



The general procedure was followed except that (*E)*-1-(2-bromovinyl)-4-methylbenzene (2.9 g, 15.0 mmol) and vinyl iodide **10**[72] (2.32 g, 6.82 mmol) were used (956 mg, 65 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.72 (dd, *J* = 15.6, 10.4 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.21 (dd, *J* = 15.1, 10.4, 1H), 5.80 (dt, 15.1, 7.0 Hz, 1H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 3H), 2.19 (q, *J* = 7.1 Hz, 2H), 1.65-1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 134.9, 134.7, 131.1, 130.3, 129.4, 128.4, 126.2, 62.9, 32.6, 32.3, 25.6, 21.3; FTIR (neat) υ_{max} 3298, 3018, 2928, 2855, 1642, 1605, 1509, 1454, 1351, 997, 984 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{20}NaO$ $[M+Na]^+$ expected: 239.1406, found: 239.1387.

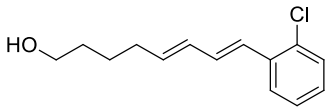
8-(4-chlorobenzene)-5*E*,7*E*-octadienol (12e)



The general procedure was followed except that (*E)*-1-(2-bromovinyl)-4-chorobenzene (3.2 g, 15.0 mmol) and vinyl iodide **10**[72] (2.32, 6.82 mmol) was used and the crude Negishi product was used without filtering through the silica gel plug prior to the deprotection step (1.13 g, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 15.4, 10.4 Hz, 1 H), 6.38 (d, *J* = 15.7 Hz,

1H), 6.21 (dd, *J* = 15.1, 10.4, 1H), 5.84 (dt, 15.1, 7.0 Hz, 1H), 3.67 (dt, *J* = 6.0, 5.5 Hz, 2H), 2.19 (q, *J* = 7.3 Hz, 2H), 1.65-1.45 (m, 4H), 1.22 (t, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ136.3, 136.1, 132.8, 130.8, 130.0, 129.0, 128.8, 127.4, 62.8, 32.7, 32.4, 25.5; FTIR (neat) υ_{max} 3316, 2929, 2861, 1675, 1640, 1590, 1488, 1456, 1404, 1089, 1011, 993 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{14}H_{17}ClNaO$ $[M+Na]^+$ expected: 259.0860, found: 259.0872.

8-(2-chlorobenzene)-5*E*,7*E*-octadienol (12f)

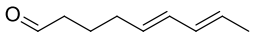


The general procedure was followed except that (*E)*-1-(2-bromovinyl)-2-chorobenzene (3.2 g, 15.0 mmol) and vinyl iodide **10**[72] (2.32, 6.82 mmol) were used and the crude Negishi product was used without filtering through the silica gel plug prior to the deprotection step (1.12 g, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.20 (t, *J* = 7.5, 1H), 7.13 (td, *J* = 7.7, 1.5 Hz, 1H), 6.84 (d, *J* = 15.7 1H), 6.73 (dd, *J* = 15.5, 10.0 Hz, 1H), 6.29 (dd, *J* = 15.1, 10.0 Hz, 1H), 5.87 (dt, *J* = 15.2, 7.1 Hz, 1H) 3.68 (br, 2H), 2.21 (q, *J* = 7.3, 2H), 1.69-1.49 (m, 4H), 1.25 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 133.1, 131.9, 131.1, 129.9, 128.5, 128.2, 126.9, 126.22, 126.16, 63.0, 32.7, 33.4, 25.5; FTIR (neat) υ_{max} 3335, 2931, 2860, 1641, 1589, 1469, 1439, 1049, 1032, 986 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{14}H_{17}ClNaO$ $[M+Na]^+$ expected: 259.0860, found: 259.0861.

2.5.3. General procedure for the preparations of 5*E,* 7*E*-octadienals (13a-f)

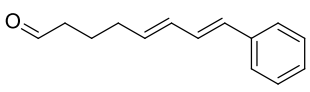
We basically followed the Swern oxidation procedure reported by Evans *et al*.[75]

8-Methyl-5*E,*7*E*-octadienal (13a)



To a solution of oxalyl chloride (2.1 mL, 23.6 mmol) in CH_2Cl_2 (148 mL) at –78 °C was added *via* cannula a solution of DMSO (3.28 mL, 47.2 mmol) in CH_2Cl_2 (30.0 mL) (gas evolution). After 20 min., a solution of alcohol **12a** (1.7g, 11.8 mmol) in 59 mL of CH_2Cl_2 was added *via* cannula. After stirring for 1h at – 78 °C triethylamine (8.3 mL, 59 mmol) was added. The mixture was warmed to 0°C, and stirred for 1h. The reaction was then quenched by the addition of water and extracted three times with CH_2Cl_2. The combined organic layers were then washed with two times with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate and concentrated *in vacuo.* It should be noted that the two sodium bicarbonate washings proved to be necessary; it was observed that the aldehyde decomposed on silica gel if this was not done. The oil was purified by flash column chromatography (1.5% EtOAc/hexane) affording aldehyde **13a** (1.46 g 90 %). Spectral data were in agreement with reported literature values.[47,64] **13a** was used access β-hydroxy nitroalkane **14a** or the corresponding higher homologue aldehyde **16a**.

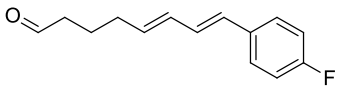
8-Phenyl-5*E,*7*E*-octadienal (13b)



The general procedure was followed except that alcohol **12b** (569 mg, 2.8 mmol) was used. The crude residue was filtered through a short pad of silica gel, washing with 5

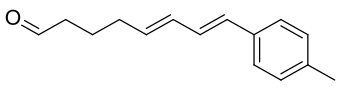
% EtOAc in hexanes. Concentration of the filtrate resulted in 511 mg (91 %) oil, sufficiently pure for use in the next steps. It should be mentioned that aryl aldehydes did not store for prolonged periods so they were synthesized as needed and were therefore not fully characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H), 7.39-7.18 (m, 5H), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.23 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.77 (dt, *J* = 15.1, 7.1 Hz, 1H), 2.48 (dt, 7.3, 1.6 Hz, 2H), 2.21 (q, *J* = 6.8, 2H), 1.78 (m, 1H).

8-(4-Flourobenzene)-5*E*,7*E*-octadienal (13c)



The general procedure was followed except that alcohol **12c** (622 mg, 2.8 mmol) was used. The crude mixture was filtered through a plug of silica gel, eluting with 5 % EtOAc in hexanes. Concentration of the filtrate resulted in a 509 mg (83 %) oil, pure enough for the next steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H), 7.33 (m, 2H), 6.97 (m, 2H), 6.65 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 6.20 (d, *J* = 15.1, 10.4 Hz, 1H), 5.76 (dt, *J* = 15.1, 7.1 Hz, 1H), 2.47 (dt, *J* = 7.3, 1.6 Hz, 2H), 2.20 (q, *J* = 7.1 Hz, 2H), 1.78 (m, 2H).

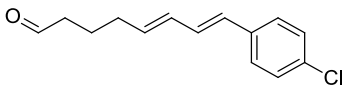
8-(4-Methylbenzene)-5*E*,7*E*-octadienal (13d)



The general procedure was followed except that alcohol **12d** (916 mg, 4.2 mmol) was used. The crude mixture was filtered through a plug of silica gel, eluting with 5 %

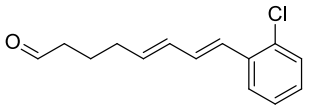
EtOAc in hexanes. Concentration of the filtrate resulted in a 643 mg (71 %) oil, pure enough for the next steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.70 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.21 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.76 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.47 (dt, *J* = 7.3, 1.6 Hz, 2H), 2.33 (s, 3H), 2.19 (q, *J* = 7.0 Hz, 2H), 1.78 (m, 2H).

8-(4-Chlorobenzene)-5*E*,7*E*-octadienal (13e)



The general procedure was followed except that alcohol **12e** (435 mg, 1.8 mmol) was used. The crude mixture was filtered through a plug of silica gel, eluting with 5 % EtOAc in hexanes. Concentration of the filtrate resulted in a 319 mg (74 %) oil, pure enough for the next steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 7.34-7.26 (m, 4H), 6.71 (dd, *J* =15.6, 10.4 Hz, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.22 (dd, *J* =15.1, 10.4 Hz, 1H), 5.79 (dt, *J* = 15.1, 7.1 Hz, 1H), 2.49 (dt, *J* = 7.3, 1.6 Hz, 2H), 2.21 (q, *J* = 7.1, 2H), 1.79 (m, 2H).

8-(2-chlorobenzene)-5*E*,7*E*-octadienal (13f)



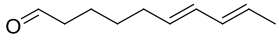
The general procedure was followed except that alcohol **12f** (1.04 g, 4.38 mmol) was used. The crude mixture was filtered through a plug of silica gel, eluting with 5 % EtOAc in hexanes. Concentration of the filtrate resulted in a 681 mg (66 %) oil, pure enough for the next steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 7.55

(dd, *J* = 7.7, 1.2 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.23-7.11 (m, 2H), 6.87 (d, *J* =15.7, Hz, 1H), 6.72 (dd, *J* =15.6, 10.2 Hz, 1H), 6.29 (dd, *J* =15.1, 10.3 Hz, 1H), 5.82 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.48 (dt, *J* = 7.3, 1.6 Hz, 2H), 7.22 (q, *J* = 6.8 Hz, 2H), 1.79 (m, 2H).

2.5.3. General procedures for the preparation of 6*E,* 8*E*-nonadienals (16a-f)

We followed the procedure reported by Lee *et al*.[81]

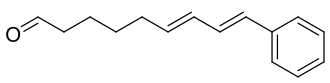
9-Methyl-6*E,8E*-nonadienal (16a)



To a pre-cooled solution (0 °C) of potassium *t*-butoxide (486 mg, 4.34 mmol) and (methoxymethyl)triphenylphosphonium chloride (1.6 g, 4.77 mmol) in THF (18 mL), was slowly added a solution of aldehyde **13a** (300 g, 2.17 mmol) in THF (20 mL). The reaction mixture was stirred for 30 min. at 0 °C, warmed to room temperature and further stirred for 30 min. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ solution. The product mixture was extracted three times with Et_2O, and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The crude enol ether was filtered through a short pad of silica gel, washing with 5% EtOAc/hexanes, concentrated *in vacuo*, and used in the next step. The enol ether was dissolved in 24.4 mL THF and 2.4 mL of H_2O and cooled to 0 °C. Mercury acetate (513 mg, 1.61 mmol) was then added to the solution in one solid portion and the reaction was stirred for 1h at 0 °C, and then treated with saturated aqueous KI solution (24 mL). The product mixture was extracted three times with Et_2O and the combined organic layers were washed two times with saturated aqueous $NaHCO_3$ solution, brine, dried over sodium sulfate and concentrated *in vacuo*. Flash

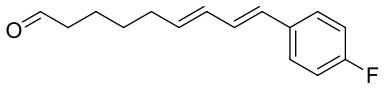
chromatography (2% EtOAc/hexanes) provided the aldehyde **16a** (207 mg, 63 %). All spectral data were identical to the literature values.[82,83]

9-Phenyl-6*E*,8*E*-nonadienal (16b)



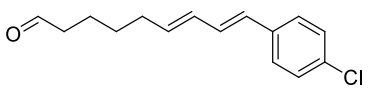
The general procedure was followed with aldehyde **13b** (307 mg, 1.53 mmol) to furnish the product (197 mg, 60%). Spectral data was in agreement with literature values.[75]

9- (4-Flourobenzene)-6*E*,8*E*-nonadienal (16c)



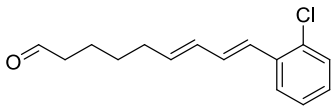
The general procedure was followed with aldehyde **13c** (231 mg, 1.06 mmol) except that the crude aldehyde was filtered through a small silica gel plug, eluting with 5% EtOAc/hexanes to furnish the product (150 mg, 61%) sufficiently pure to be used in the following Henry reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (br, 1H), 7.33 (dd, J = 8.6, 5.8 Hz, 2H), 6.99 (t, J = 8.7 Hz, 2H), 6.65 (dd, J = 15.6, 10.4 Hz, 1H), 6.40 (d, J = 15.7 Hz, 1H), 6.19(d, J = 15.1, 10.4 Hz, 1H), 5.79 (dt, J = 15.1, 7.1 Hz, 1H), 2.47 (dt, J = 7.3, 1.5 Hz, 2H), 2.17 (q, J = 7.2 Hz, 2H), 1.67 (m, 2H), 1.47 (m, 2H).

9- (4-Chlorobenzene)-6*E,8E*-nonadienal (16e)



The general procedure was followed with aldehyde **13e** (203 mg, 0.87 mmol) except that the crude aldehyde was filtered through a small silica gel plug, eluting with 5% EtOAc/hexanes to furnish the product (151 mg, 70%) sufficiently pure to be used in the following Henry reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (br, 1H), 7.28 (m, 4H), 6.71 (dd, *J* =15.6, 10.2 Hz, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 6.19 (dd, *J* =15.1, 10.4 Hz, 1H), 5.81 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.46 (t, *J* = 7.0, Hz, 2H), 2.18 (q, *J* = 6.8, 2H), 1.70 (m, 2H), 1.47 (m, 2H).

9- (2-Chlorobenzene)-6*E,8E*-nonadienal (16f)

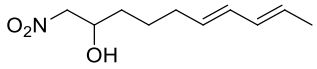


The general procedure was followed with aldehyde **13f** (203 mg, 0.87 mmol) except that the crude aldehyde was filtered through a small silica gel plug, eluting with 5% EtOAc/hexanes to furnish the product (151 mg, 70%) sufficiently pure to be used in the following Henry reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.6 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.34 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.21-7.11 (m, 2H), 6.85 (d, *J* =15.7, Hz, 1H), 6.73 (dd, *J* =15.6, 10.2 Hz, 1H), 6.29 (dd, *J* =15.1, 10.2 Hz, 1H), 5.85 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.46 (dt, *J* = 7.3, 1.7 Hz, 2H), 7.20 (q, *J* = 7.1 Hz, 2H), 1.69 (m, 2H), 1.51 (m, 2H).

2.5.4. General procedure for the preparations of (±)-1-nitro-*E,E*-dien-2-ols

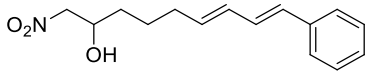
We basically followed the procedure reported by Wollenberg *et al.*[73]

(±)-9-Methyl-1-nitro-6*E*,8*E*-nonadien-2-ols (14a)



To a solution of aldehyde **13a** (2.35 g, 17.0 mmol) in 17.4 mL of isopropanol was added 327 mg of potassium fluoride dihydrate and nitromethane (3.74 ml, 69.6 mmol). After 3.5h the TLC showed one spot for the nitro-alcohol. The reaction was then quenched with saturated aqueous sodium bicarbonate and extracted three times with ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (14 % EtOAc/hexanes) affording the product in 70% (2.37g). Spectral data were in agreement with the literature values.[47]

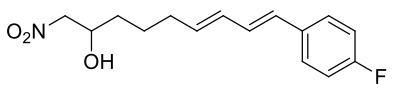
(±)-9-Pheny-1-nitro-6*E*,8*E*-nonadien-2-ols (14b)



The general procedure was followed except that aldehyde **13b** (199 mg, 0.99 mmol) was used to provide the product (197 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.19 (m, 5H), 6.74 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.23 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.78 (dt, *J* = 15.1, 7.1 Hz, 1H), 4.46-4.34 (m, 3H), 2.52 (d, *J* = 4.5 Hz, 1H), 2.21 (q, *J* = 6.7, 2H), 1.69-1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.3, 131.6, 130.8, 129.1, 128.7, 127.4, 126.3, 80.7, 68.6, 33.18, 32.5, 25.0; FTIR (neat) υ_{max} 3323, 3023, 2929, 1548, 1489, 1447, 1424, 1388, 1373, 989,692 cm^{-1}; HRMS (ESI-

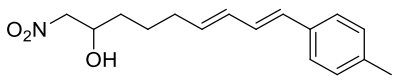
TOF): Exact mass calcd for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$ expected: 284.1275, found: 284.1263.

(±)-9- (4-Flourobenzene)-1-nitro-6*E*,8*E*-nonadien-2-ol (14c)



The general procedure was followed except that aldehyde **13c** (244 mg, 1.18 mmol) was used to provide the product (265 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.6, 5.5, Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 6.20 (d, *J* = 15.0, 10.7 Hz, 1H), 5.77 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.47-4.29 (m, 3H), 2.62 (d, *J* = 4.6 Hz, 1H), 2.20 (q, *J* = 7.2 Hz, 2H), 1.68-1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* = 245 Hz), 134.7, 134.0 (d, *J* = 3.2 Hz), 131.6, 129.8, 129.2 (d, *J* = 2.2 Hz), 128.0 (d, *J* = 7.9 Hz), 115.9 (d, *J* = 21.6 Hz), 81.0, 68.9, 33.5, 32.7, 25.2; FTIR (neat) υ_{max} 3321, 3018, 2926, 1599, 1549, 1505, 1455, 1424, 1231, 989, 832 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{18}FNNaO_3$ $[M+Na]^+$ expected: 302.1163, found: 302.1177.

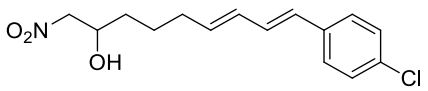
(±)-9- (4-Methylbenzene)-1-nitro-6*E*,8*E*-nonadien-2-ol (14d)



The general procedure was followed except that aldehyde **13d** (253 mg, 1.18 mmol) was used to provide the product (248 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.71 (dd, *J* = 15.6, 10.3 Hz, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.21 (dd, *J* = 15.0, 10.4 Hz, 1H), 5.75 (dt, *J* = 15.1, 7.0 Hz, 1H),

4.45-4.30 (m, 3H), 2.57 (d, *J* = 4.4 Hz, 1H), 2.33 (s, 3H), 2.20 (q, *J* = 6.9 Hz, 2H), 1.69-1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.7, 133.7, 131.6, 130.7, 129.4, 128.1, 126.2, 80.7, 68.6, 33.1, 32.4, 25.0, 21.3; FTIR (neat) υ_{max} 3335, 2929, 1549, 1510, 1455, 1382, 1097, 987, 818 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$ expected: 298.1414, found: 298.1411.

(±)-9-(4-Chlorobenzene)-1-nitro-6*E*,8*E*-nonadien-2-ol (14e)



The general procedure was followed except that aldehyde **13e** (216 mg, 0.92 mmol) was used to provide the product (158 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 6.71 (dd, *J* =15.6, 10.3 Hz, 1H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.20 (dd, *J* =15.1, 10.4 Hz, 1H), 5.80 (dt, *J* = 15.0, 7.1 Hz, 1H), 4.46-4.30 (m, 3H), 2.54 (d, *J* = 4.4 Hz, 1H), 2.20 (q, *J* = 6.7, 2H), 1.69-1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.0, 132.9, 131.3, 129.7, 129.4, 128.9, 127.5, 80.7, 68.6, 33.2, 32.5, 24.9; FTIR (neat) υ_{max} 3344, 2929, 1639, 1548, 1488, 1459, 1381, 1086, 993, 821 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{18}ClNNaO_3$ $[M+Na]^+$ expected: 318.0867, found: 318.0882

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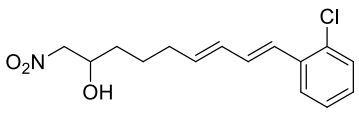
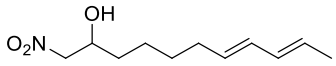
(±)-9- (2-Chlorobenzene)-1-nitro-6*E*,8*E*-nonadien-2-ol (14f)



The general procedure was followed except that aldehyde **13f** (234 mg, 1.0 mmol) was used to provide the product (242 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* =7.8, 1.5 Hz, 1H), 7.34 (dd, *J* =7.9, 1.2 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H),

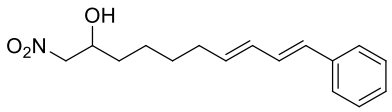
7.14 (td, *J* = 7.6, 1.6 Hz, 1H), 6.86 (d, *J* =15.7, Hz, 1H), 6.73 (dd, *J* =15.6, 10.2 Hz, 1H), 6.29 (dd, *J* =15.1, 10.3 Hz, 1H), 5.83 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.46-4.32 (m, 3H), 2.64 (br, 1H), 7.22 (q, *J* = 6.8 Hz, 2H), 1.69-1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 133.1, 131.6, 131.5, 129.9, 128.3, 126.9, 126.5 126.2, 80.7, 68.6, 33.2, 32.5, 24.9; FTIR (neat) υ_{max} 3430, 2930, 1641, 1549, 1469, 1438, 1379, 988, 749 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{18}ClNNaO_3$ $[M+Na]^+$ expected: 318.0867, found: 318.0889.

(±)-10-Methyl-1-nitro-7*E*,9*E*-decadien-2-ol (17a)



The general procedure was followed except that aldehyde **16a** (4.66 mg, 30.6 mmol) was used to provide the product (5.9 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05-5.96 (m, 2H), 5.63-5.48 (m, 2H), 4.45-4.29 (m, 3H), 2.48 (d, *J* = 4.0 Hz, 1H), 2.08 (q, *J* = 6.4 Hz, 2H), 1.73 (d, *J* = 6.4 Hz, 3H), 1.57-1.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 131.3, 130.9, 127.3, 80.7, 68.7, 33.7, 32.4, 29.1, 24.8, 18.1; FTIR (neat) υ_{max} 3436, 3016, 2928, 2857, 1540, 1431, 1379, 1206, 1095, 987 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ expected: 236.1257, found: 236.1261.

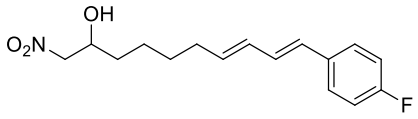
(±)-10-Phenyl-1-nitro-7*E*,9*E*-decadien-2-ol (17b)



The general procedure was followed except that aldehyde **16b** (229 mg, 1.0 mmol) was used to provide the product (220. mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

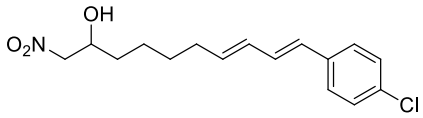
7.39-7.18 (m, 5H), 7.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.22 (dd, *J* = 15.1, 10.5 Hz, 1H), 5.80 (dt, *J* = 15.1, 7.1 Hz, 1H), 4.46-4.31 (m, 3H), 2.54 (d, *J* = 4.7 Hz, 1H), 2.18 (q, *J* = 6.6 Hz, 2H), 1.58-1.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.1, 131.1, 130.5, 129.3, 128.7, 127.3, 126.3, 80.7, 68.7, 33.7, 32.7, 29.1, 24.9; FTIR (neat) υ_{max} 3369, 3020, 2926, 2956, 1552, 1489, 1461, 1419, 1385, 1356, 985, 693 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$ expected: 298.1414, found: 298.1427.

(±)-10-(4-Flourobenzene)-1-nitro-7*E*,9*E*-decadien-2-ol (17c)



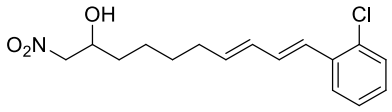
The general procedure was followed except that aldehyde **16c** (139 mg, 0.60 mmol) was used to provide the product (116 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.66 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.40 (*J* = 15.7 Hz, 1H), 6.19 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.79 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.45-4.28 (m, 3H), 2.58 (d, *J* = 4.7 Hz, 1H), 2.17 (q, *J* = 6.5 Hz, 2H), 1.58-1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246 Hz), 135.09, 133.84 (d, *J* = 3 Hz), 130.9, 129.2, 129.1 (d, *J* = 2.4 Hz), 127.7 (d, *J* = 8 Hz), 115.6 (d, *J* = 21 Hz), 80.7, 68.7, 33.7, 32.7, 29.1, 24.8; FTIR (neat) υ_{max} 3376, 3013, 2937, 2860, 1597, 1553, 1505, 1463, 1430, 1386, 1219, 1201, 988, 835 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{20}FNNaO_3$ $[M+Na]^+$ expected: 316.1319, found: 316.1341.

(±)-10-(4-Chlorobenzene)-1-nitro-7*E*,9*E*-decadien-2-ol (17e)



The general procedure was followed except that aldehyde **16e** (128 mg, 0.52 mmol) was used to provide the product (109 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (m, 4H), 6.72 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.20 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.82 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.46-4.32 (m, 3H), 2.62 (d, *J* = 4.4 Hz, 1H), 6.18 (q, *J* = 6.5 Hz, 2H), 1.67-1.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.8, 132.8, 130.8, 129.9, 129.1, 128.8, 127.4, 80.7, 68.8, 33.6, 32.7, 29.0, 24.8; FTIR (neat) υ_{max} 3394, 3011, 2931, 2856, 1642, 1550, 1489, 1459, 1427, 1381, 1209, 1118, 1089, 993, 829 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{20}ClNNaO_3$ $[M+Na]^+$ expected: 332.1024, found: 332.1043.

(±)-10-(2-Chlorobenzene)-1-nitro-7*E*,9*E*-decadien-2-ol (17f)



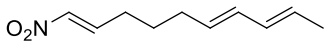
The general procedure was followed except that aldehyde **16e** (162 mg, 0.65 mmol) was used to provide the product (122 mg, 60.%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* =7.8, 1.5 Hz, 1H), 7.34 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.21 (td, *J* = 7.5, 0.9 Hz, 1H), 7.13 (td, *J* =7.6, 1.6 Hz, 1H), 6.85 (d, *J* = 15.7 Hz, 1H), 6.73 (dd, *J* = 15.6, 10.2 Hz, 1H), 6.28 (dd, *J* = 15.1, 10.2 Hz, 1H), 5.85 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.45-4.32 (m, 3H), 2.62 (br, 1H), 2.19 (q, *J* = 6.5 Hz, 2H), 1.60-1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.6, 133.1, 131.8, 131.1, 129.9, 128.2, 126.9, 126.21, 126.18, 80.7, 68.7, 33.6,

32.7, 29.0, 24.8; FTIR (neat) υ_{max} 3441, 2930, 2858, 1642, 1550, 1468, 1440, 1380, 1033, 987, 749, 695 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{20}ClNNaO_3$ $[M+Na]^+$ expected: 332.1024, found: 332.1039.

2.5.4. General procedure for the preparations of 1-nitro-*E,E,E*-nona and decatrienes

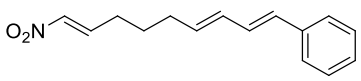
We basically followed dehydration procedures reported by Denmark *et al*.[74,84]

9-(Methyl)-1-nitro-*1E,6E,*8*E*-nonatriene (15a)



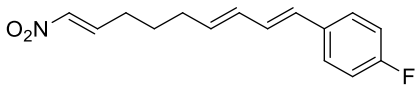
To a solution of nitro alcohol **14a** (60.0 mg, 0.301 mmol) in CH_2Cl_2 (331 μL) cooled to -20 °C was slowly added a solution of Triflouroacetic anhydride (316 μL, 1M in CH_2Cl_2, 0.316 mmol). After two minutes a solution of Et_3N (316 μL, 2M in CH_2Cl_2, 0.632 mmol) was added. The reaction mixture was stirred for an additional 1.5 h and then diluted with 1 mL of CH_2Cl_2 and 1 mL of water. The product mixture was extracted three times with CH_2Cl_2, and the combined organic layers were washed twice with saturated aqueous sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was quickly purified by flash chromatography (2% EtOAc/hexanes) to provide the 1-nitro-nonatriene (40. mg, 74%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. Spectral data was in agreement with literature values.[47]

9-(Phenyl)-1-nitro-*1E,6E,*8*E*-nonatriene (15b)



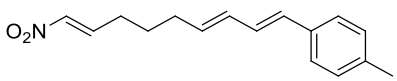
The general dehydration procedure was followed with nitro alcohol **14b** (50.0 mg, 0.191 mmol) to provide the 1-nitro-nonatriene (27 mg, 58%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.21 (m, 6H), 7.00 (dt, *J* = 13.4, 1.6 Hz, 1H), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 6.24 (dd, *J* = 14.8, 10.4 Hz, 1H), 5.77, (dt, *J* = 15.2, 7.2 Hz, 1H), 2.31 (ddt, *J* = 7.6, 7.6, 1.2 Hz, 2H), 2.23 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.67 (tt, *J* = 7.6, 7.6 Hz, 2H).

9-(4-Flourobenzene)-1-nitro-*1E,6E,*8*E*-nonatriene (15c)



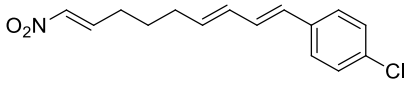
The general dehydration procedure was followed with nitro alcohol **14c** (60.0 mg, 0.215 mmol) to provide the 1-nitro-nonatriene (16 mg, 28%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 3H), 7.02-6.97 (m, 3H), 6.66 (dd, *J* = 15.4, 10.6 Hz, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.20 (dd, *J* = 14.9, 10.2 Hz, 1H), 5.75 (dt, *J* = 15.1, 6.8 Hz, 1H), 2.34-2.18 (m, 4H), 1.71-1.62 (m, 2H).

9-(4-methylbenzene)-1-nitro-*1E,6E,*8*E*-nonatriene (15d)



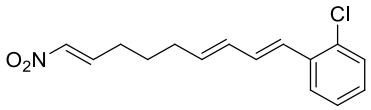
The general dehydration procedure was followed with nitro alcohol **14d** (61 mg, 0.222 mmol) to provide the 1-nitro-nonatriene (31 mg, 54%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 3H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.98 (d, *J* = 13.5 Hz, 1H), 6.70 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.45 (d, *J* = 15.5 Hz, 1H), 6.22 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.73 (dt, *J* = 15.0, 7.5 Hz, 1H), 2.34-2.86 (m, 5H), 2.21 (q, *J* = 7.2 Hz, 2H), 1.66 (tt, *J* = 7.5, 7.5 Hz, 2H).

9-(4-Chlorobenzene)-1-nitro-*1E,6E,*8*E*-nonatriene (15e)



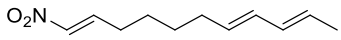
The general dehydration procedure was followed with nitro alcohol **14e** (66 mg, 0.222 mmol) to provide the 1-nitro-nonatriene (47 mg, 76%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.99 (d, *J* = 13.4 Hz, 1H), 6.71 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 6.22 (dd, *J* = 15.1, 10.4 Hz, 1H), 5.78 (dt, *J* = 15.1, 7.1 Hz, 1H), 2.31 (ddt, *J* =7.5, 7.4, 1.27 Hz, 2H), 2.22 (dt, *J* = 7.3, 7.3 Hz, 2H), 1.66 (tt, *J* = 7.4, 7.3 Hz, 2H).

9-(2-Chlorobenzene)-1-nitro-*1E,6E,*8*E*-nonatriene (15f)



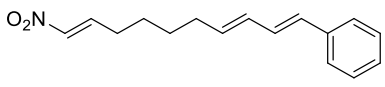
The general dehydration procedure was followed with nitro alcohol **14f** (66 mg, 0.222 mmol) to provide the 1-nitro-nonatriene (37 mg, 59%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (d, *J* = 7.7 Hz, 1H), 7.36-7.11 (m, 4H), 7.00 (dd, 13.4, 1.5, *J* = Hz, 1H), 6.88 (d, *J* = 15.6 Hz, 1H), 6.72, (dd, *J* = 15.6, 10.1 Hz, 1H), 6.31 (dd, *J* = 15.1, 10.1 Hz, 1H), 5.82 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.35-2.20 (m, 4H), 1.67 (tt, *J* = 7.5, 7.3 Hz, 2H).

10-(Methyl)-1-nitro-*1E,7E,*9*E*-decatriene (18a)



The general dehydration procedure was followed with nitro alcohol **17a** (434 mg, 1.91 mmol) to provide the 1-nitro-decatriene (268 mg, 72%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 1H), 6.98 (dt, *J* = 13.4, 1.5 Hz, 1H), 6.06-5.95 (m, 2H), 5.65-5.46 (m, 2H), 2.27 (ddt, *J* = 7.3, 7.3, 1.4 Hz, 2H), 2.09 (q, *J* = 7.0 Hz, 2H), 1.73 (d, *J* = 5.8 Hz, 3H), 1.57-1.41 (m, 4H).

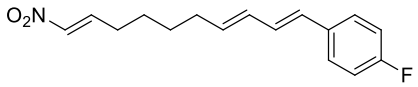
10-(Phenyl)-1-nitro-*1E,7E,*9*E*-decatriene (18b)



The general dehydration procedure was followed with nitro alcohol **17b** (50 mg, 0.182 mmol) to provide the 1-nitro-decatriene (31 mg, 65%) which was used immediately

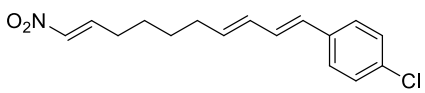
for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.18 (m, 6H), 6.99 (*J* = 13.4 Hz, 1H), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.22 (dd, *J* = 15.1, 10.3 Hz, 1H), 5.78 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.33-2.15 (m, 4H), 1.61-1.48 (m, 4H).

10-(4-Flourobenzene)-1-nitro-*1E,7E,*9*E*-decatriene (18c)



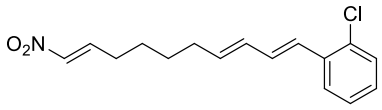
The general dehydration procedure was followed with nitro alcohol **17c** (65 mg, 0.222 mmol) to provide the 1-nitro-decatriene (31 mg, 79%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 3H), 7.01-6.97 (m, 3H), 6.66 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.42 (d, *J* = 15.7 Hz, 1H), 5.78 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.30 (q, *J* = 7.3 Hz, 2H), 2.18 (q, *J* = 7.7 Hz, 2H), 1.58-1.46 (m, 4H).

10-(4-Chlorobenzene)-1-nitro-*1E,7E,*9*E*-decatriene (18e)



The general dehydration procedure was followed with nitro alcohol **17e** (69 mg, 0.222 mmol) to provide the 1-nitro-decatriene (54 mg, 83%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.34 (m, 5H), 6.98 (dt, *J* = 13.4, 1.5 Hz, 1H), 6.71 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.20 (dd, *J* = 15.1, 10.5 Hz, 1H), 7.80 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.29 (q, *J* = 7.0 Hz, 2H), 2.18 (q, *J* = 7.1 Hz, 2H), 1.58-1.47 (m, 4H).

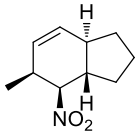
10-(2-Chlorobenzene)-1-nitro-*1E,7E,*9*E*-decatriene (18f)



The general dehydration procedure was followed with nitro alcohol **17f** (64 mg, 0.207 mmol) to provide the 1-nitro-decatriene (39 mg, 64%) which was used immediately for the intramolecular nitroalkene Diels-Alder reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.0, 1.4 Hz, 1H). 6.99 (d, *J* = 13.4 Hz, 1H), 6.86 (d, *J* = 15.7 Hz, 1H), 6.73 (dd, *J* = 15.7, 10.0 Hz, 1H), 6.29 (dd, *J* = 15.1, 10.0 Hz, 1H), 5.84 (dt, *J* = 15.1, 7.0 Hz, 1H), 2.30 (q, *J* = 7.2 Hz, 2H), 2.20 (q, *J* = 6.8 Hz, 2H), 1.62-1.49 (m, 4H).

2.5.4. General procedures for the intramolecular nitroalkene Diels-Alder reaction

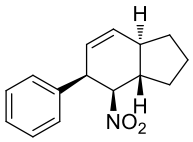
[4.3.0]-nitro-bicycle (19a)



To a solution of triene **15a** (23 mg, 0.13 mmol) in CH_2Cl_2 (250 μL) cooled to 0 °C was added catalyst **1** (26 mg, 0.025 mmol, 20 mol %) in one portion under an atmosphere of dry argon. After stirring for 5 min. at 0 °C, the reaction was allowed to warm to 25 °C. After 20 h, the reaction was diluted with CH_2Cl_2, followed by the addition of 50 μL CH_2Cl_2-hydrazine monohydrate solution (50:50 mixture by volume). The resulting solution was stirred for 5 min., diluted with water, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The ratio of diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture (*endo:exo* = > 30:1), which was then purified by

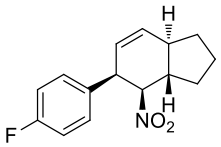
flash chromatography on silica gel (2% EtOAc/hexanes) to provide the product (21 mg, 91%). Spectral data were in agreement with the literature values.[47]

[4.3.0]-nitro-bicycle (19b)



The general procedure was followed with triene **15b** (10. mg, 0.043 mmol) and catalyst **1** (9 mg, 0.0086 mmol), to give the pure product (9 mg, 86%) with *endo:exo* of >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 3H), 7.18-7.16 (m, 2H), 6.13 (d, *J* = 9.8 Hz, 1H), 6.63 (ddd, *J* = 9.6, 4.0, 2.4 Hz, 1H), 4.89 (dd, *J* = 11.4, 7.3 Hz, 1H), 4.24 (m, 1H), 2.16-1.71 (m, 6H), 1.49-1.39 (m, 1H), 1.28-1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 130.6, 129.6, 128.5, 128.2, 127.5, 91.2, 46.8, 44.7, 40.8, 29.1, 27.3, 22.2; FTIR (neat) υ_{max} 3026, 2950, 2872, 1541, 1492, 1454, 1372, 780.5, 701.4 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{17}NNaO_2$ $[M+Na]^+$ expected: 266.1151, found: 266.1156.

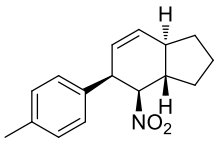
[4.3.0]-nitro-bicycle (19c)



The general procedure was followed with triene **15c** (12. mg, 0.048 mmol) and catalyst **1** (10 mg, 0.0095 mmol), to give the pure product (10 mg, 69%). *Endo:exo* was >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 6.13 (d, *J* = 9.8

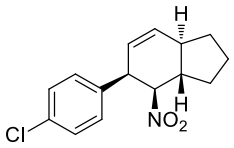
Hz, 1H), 5.60 (m, 1H), 4.87 (d, J = 11.1, 7.3 Hz, 1H), 4.27-4.21 (m, 1H), 2.10-1.79 (m, 6H), 1.48-1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 246 Hz), 132.8 (d, J = 3 Hz), 131.1 (d, J = 8.2 Hz), 130.8, 127.4, 115.5 (d, J = 21.3 Hz), 91.1, 46.0, 44.6, 40.7, 29.1, 27.3, 22.2; FTIR (neat) υ_{max} 2963, 2872, 1729, 1603, 1540, 1506, 1375, 1297, 1222, 1160, 1099, 841, 697 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{16}FNNaO_2$ $[M+Na]^+$ expected: 284.1057, found: 284.1065.

[4.3.0]-nitro-bicycle (19d)



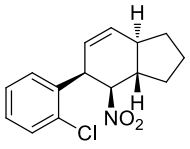
The general procedure was followed with triene **15d** (15.2 mg, 0.059 mmol) and catalyst **1** (12 mg, 0.0118 mmol) to give the pure product (14.9 mg, 98%). *Endo:exo* was >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.2 Hz, 1H), 6.11 (d, J = 9.7 Hz, 1H), 6.0 (ddd, J = 9.2, 4.0, 2.1 Hz, 1H), 4.87 (dd, J = 7.2, 11.3 Hz, 1H), 4.22-4.18 (m, 1H), 2.31 (s, 3H), 2.19-1.77 (m, 6H), 1.50-1.40 (m, 1H), 1.29-1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 134.0, 130.4, 129.4, 129.3, 127.6, 91.2, 46.5, 44.6, 40.8, 29.1, 27.3, 22.2, 21.2; FTIR (neat) υ_{max} 3022, 2937, 2870, 1537, 1512, 1382, 1371, 828, 802, 756 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{19}NNaO_2$ $[M+Na]^+$ expected: 280.1308, found: 280.1332.

[4.3.0]-nitro-bicycle (19e)



The general procedure was followed with triene **15e** (17.3 mg, 0.063 mmol) and catalyst **1** (13 mg, 0.013 mmol) to give the pure product (12.4 mg, 72%). *Endo:exo* was >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.1 (d, *J* = 8.4 Hz, 2H), 6.14 (d, *J* = 9.7 Hz, 1H), 5.58 (ddd, *J* = 9.7, 4.0, 2.6 Hz, 1H), 4.88 (dd, *J* = 11.2, 7.3 Hz, 1H), 4.22-4.20 (m, 1H), 2.12-1.79 (m, 6H), 1.48-1.41 (m, 1H), 1.29-1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 134.3, 131.1, 130.8, 128.7, 127.0, 91.0, 46.1, 44.6, 40.7, 29.1, 27.3, 22.2; FTIR (neat) υ_{max} 2953, 2872, 1545, 1488, 1409, 1456, 1372, 1092, 1014, 805, 670 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{16}ClNNaO_2$ $[M+Na]^+$ expected: 300.0762, found: 300.0775.

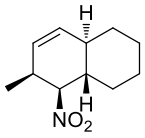
[4.3.0]-nitro-bicycle (19f)



The general procedure was followed with triene **15f** (17 mg, 0.061 mmol) and catalyst **1** (13 mg, 0.013 mmol) to give the pure product (12 mg, 68%). *Endo:exo* was >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.27-7.18 (m, 2H), 6.14 (d, *J* = 9.6 Hz, 1H), 5.53 (dt, *J* = 9.4, 3.1 Hz, 1H), 5.02 (dd, *J* = 10.9, 7.5 Hz, 1H) 4.99-4.96 (m, 1H),

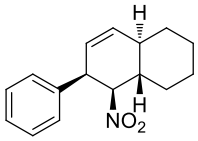
2.27-2.03 (m, 3H), 1.86-1.79 (m, 3H), 1.49-1.43 (m, 1H), 1.32-1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 135.2, 131.6, 130.8, 129.9, 129.1, 127.7, 126.7, 90.3, 44.1, 42.2, 41.6, 29.2, 27.1, 22.2; FTIR (neat) υ_{max} 3064, 3026, 2986, 2957, 2871, 2831, 1535, 1470, 1453, 1463, 1280, 776, 749 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{15}H_{16}ClNNaO_2$ $[M+Na]^+$ expected: 300.0762, found: 300.0789.

[4.4.0]-nitro-bicycle (23a)



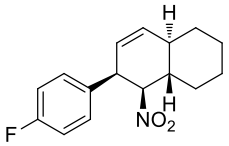
The general procedure was followed with triene **18a** (12 mg, 0.063 mmol) and catalyst **1** (13 mg, 0.013 mmol) to afford the product (12 mg, 77%). *Endo:exo* was 14:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. *Endo* isomer (major): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (ddd, *J* = 9.8, 2.8, 4.5 Hz, 1H), 5.41 (d, *J* = 9.8 Hz, 1H), 4.63 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.92-2.84 (m, 1H), 1.85-1.77 (m, 6H), 1.39-1.14 (m, 4H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.0, 128.8, 91.1, 41.7, 38.0, 34.2, 32.6, 28.4, 26.4, 25.9, 16.8; ; FTIR (neat) υ_{max} 3026, 2926, 2855, 1543, 1450, 1374, 1277, 721 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{11}H_{17}NNaO_2$ $[M+Na]^+$ expected: 218.1151, found: 218.1163.

[4.4.0]-nitro-bicycle (23b)



The general procedure was followed with triene **18b** (16.1 mg, 0.063 mmol) and catalyst **1** (13 mg, 0.013 mmol) to afford the product (12 mg, 71%). *Endo:exo* was 11:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. *Endo* isomer (major): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.30 (m, 3H), 7.15-7.13 (m, 2H), 5.76 (d, *J* = 9.7 Hz, 1H), 5.63 (ddd, *J* = 9.8, 4.4, 2.6 Hz, 1H), 4.84 (dd, *J* = 11.6, 6.7 Hz, 1H), 4.07-4.04 (m, 1H), 1.96-1.72 (m, 6H), 1.43-1.26 (m, 3H), 1.02-0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 133.0, 129.4, 128.5, 128.2, 125.2, 91.6, 45.9, 41.6, 37.5, 32.7, 28.4, 26.4, 25.8; FTIR (neat) υ_{max} 3028, 2925, 2854,1546, 1492, 1450, 1370, 775, 699 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{19}NNaO_2$ $[M+Na]^+$ expected: 280.1308, found: 280.1310.

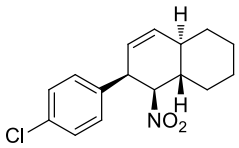
[4.4.0]-nitro-bicycle (23c)



The general procedure was followed with triene **18c** (17.2 mg, 0.063 mmol) and catalyst **1** (13 mg, 0.013 mmol) to afford the product (11 mg, 66%). *Endo:exo* was 16:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. *Endo* isomer (major): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.76 (d, *J* = 9.8 Hz, 1H), 5.61 (ddd, *J* = 9.8, 4.4, 2.7 Hz, 1H), 4.81 (dd, *J* = 11.8, 6.7 Hz, 1H), 4.06-4.03 (m, 1H), 1.96-1.72 (m, 6H), 1.40-1.23 (m, 3H), 1.03-0.96 (m, 1H); ^{13}C

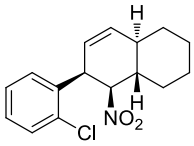
NMR (100 MHz, $CDCl_3$) δ 162.7 (d, *J* = 246), 133.2, 132.98 (d, *J* = 2.9), 130.9 (d, *J* = 8.2), 125.1, 115.5 (d, *J* = 21.3), 91.4, 45.1, 41.5, 37.4, 32.7, 28.3, 26.4, 25.8; FTIR (neat) υ_{max} 2927, 2856, 1604, 1546, 1506, 1371, 1223, 1159, 839,789, 694 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{18}FNNaO_2$ $[M+Na]^+$ expected: 298.1214, found: 298.1222.

[4.4.0]-nitro-bicycle (23e)



The general procedure was followed with triene **18e** (19 mg, 0.066 mmol) and catalyst **1** (14 mg, 0.013 mmol) to afford the product (10 mg, 53%). *Endo:exo* was 12:1, as determined by ^1H NMR analysis of the crude reaction mixture. *Endo* isomer (major): ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.78 (d, *J* = 9.8 Hz, 1H), 5.59 (ddd, *J* = 9.8, 4.4, 2.6 Hz, 1H), 4.82 (dd, *J* = 11.7, 6.7 Hz, 1H), 4.05-4.01 (m, 1H), 1.96-1.71 (m, 6H), 1.44-1.22 (m, 3H), 1.03-0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 134.2, 133.4, 130.7, 128.7, 124.8, 91.3, 45.2, 41.5, 37.5, 32.7, 28.3, 26.4, 25.8; FTIR (neat) υ_{max} 2927, 2855, 1546, 1490, 1371, 1092, 1015, 834, 732 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{18}ClNNaO_2$ $[M+Na]^+$ expected: 314.0918, found: 314.0925.

[4.4.0]-nitro-bicycle (23f)



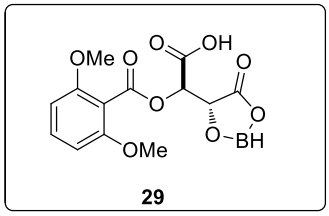
The general procedure was followed with triene **18f** (18.7 mg, 0.064 mmol) and catalyst **1** (13 mg, 0.013 mmol) to afford the product (11 mg, 60%). *Endo:exo* was >30:1, as determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 4H), 5.79 (d, *J* = 9.7 Hz, 1H), 5.54 (ddd, *J* = 9.6, 4.5, 2.6 Hz, 1H), 4.93 (d, *J* = 11.6, 6.6 Hz, 1H), 4.85-4.82 (m, 1H), 1.97-1.78 (m, 6H), 1.44-1.26 (m, 3H), 1.09-1.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.3, 133.3, 131.8, 129.7, 129.0, 126.6, 125.3, 90.9, 41.7, 40.6, 38.4, 32.6, 28.0, 26.3, 25.7; FTIR (neat) υ_{max} 3026, 2927, 2855, 1547, 1470, 1442, 1375, 1292, 1055, 1036, 752, 732 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{16}H_{18}ClNNaO_2$ $[M+Na]^+$ expected: 314.0918, found: 314.0939.

CHAPTER 3. THE DEVELOPMENT OF NEW PLANAR CHIRAL 2-AMINOPYRIDINIUM IONS AND ASYMMETRIC METHODS FOR THE INTRAMOLECULAR NITROALKENE DIELS-ALDER REACTIONS

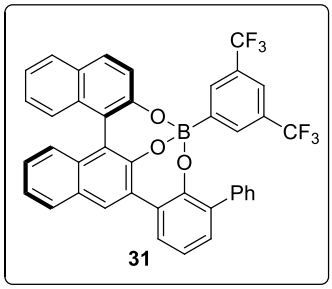
Few reactions lend themselves more readily to the rapid generation of molecular complexity than the intramolecular Diels-Alder reaction. Its ability to generate up to four stereocenters and functionalized bicyclic ring systems, in a highly stereoselective and predictable fashion, has led to its widespread application in solving complex synthetic challenges.[45,46] However, in contrast, to the bimolecular Diels-Alder reaction, for which there are a large number of asymmetric variants reported,[85-87] there are relatively few examples in the literature of enantioselective catalytic intramolecular Diels-Alder (IMDA) reactions.[77,88-96] This is surprising because, the optically rich adducts generated by the IMDA reaction, have proven to be useful synthetic building blocks, lending themselves to additional amplification of molecular complexity, thereby enabling the enantioselective total synthesis of natural products.[92,93,96] Furthermore, catalytic enantioselective IMDA reactions have only involved carbonyl based substrates, and in a number of these examples, very few substrates have been examined, since they are often treated as an extension of the intermolecular Diels-Alder reaction. To the best of our knowledge there are no reported examples of a catalytic asymmetric nitroalkene IMDA reaction, presumably due to the lack of its catalysis method. Considering the potential utility of nitrocarbocycles in synthesis, due to the versatility of the nitro group,[12] we believe a catalytic asymmetric version of this reaction would broaden the scope of the IMDA reaction. This plus having previously developed a highly diastereoselective nitroalkene IMDA method,[97] we were prompted to begin a program to address the asymmetric catalysis of the nitroalkene IMDA.

3.1. Background

3.1.1. Enantioselective intramolecular Diels-Alder reactions

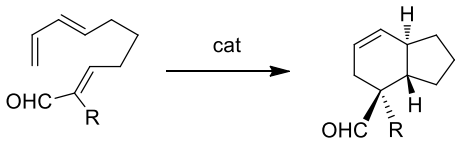


29



31

Table 3.1. Catalytic asymmetric IMDA reactions. Reported by Yamamoto et al. (References 88 and 89).



30a-b

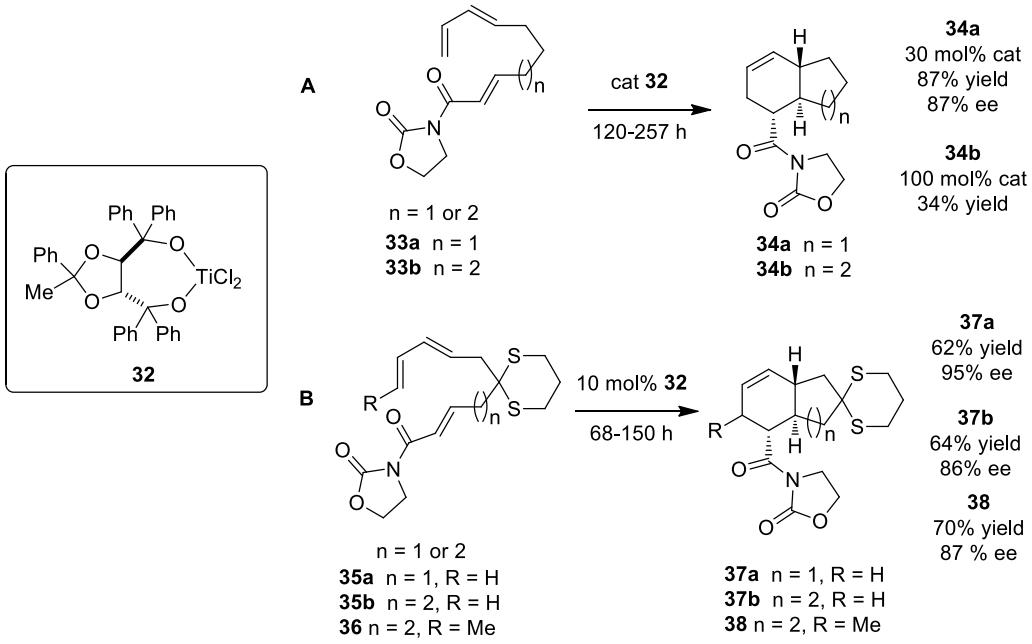
entry	triene	R	cat (mol %)	yield (%)	*endo:exo*	% ee
1	**30a**	Me	**29** (10)	84	99:1	92
2	**30b**	H	**29** (10)	74	99:1	46
3	**30b**	H	**31** (30)	95[a]	>99:1	80

[a] Opposite enantiomer to the one shown was obtained

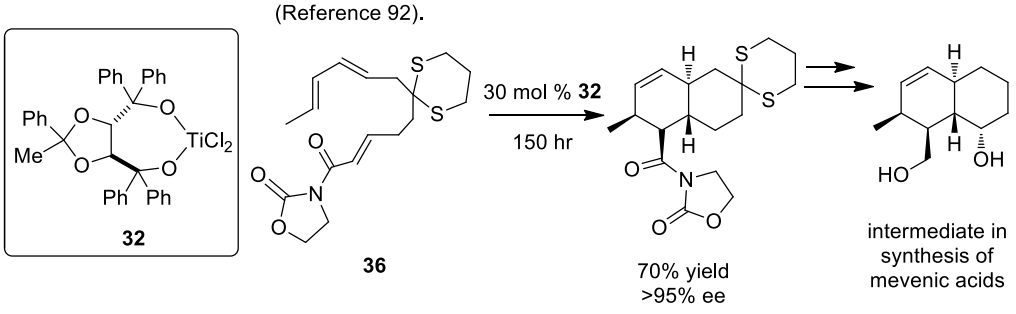
This section will provide a brief historical overview on the catalytic asymmetric Type I IMDA reactions of carbonyl based substrates. It is surprising to note that considering the vast number of reports on the enantioselective catalysis of intermolecular Diels-Alder reactions[85-87] there are relatively few examples of the intramolecular variant. Yamamoto was one of the first groups to successfully employ the use of chiral Lewis acids to catalyze an asymmetric IMDA reaction.[88] They found that chiral acyloxyborane complex (CAB) **29** could affect triene **30** to produce the desired [4.3.0] bicycle in good yield and with excellent diastereo- and enantiocontrol (Table 3.1. entry 1). It was found, however, that this catalyst system was not generally applicable, as cyclization of analogous trienal substrate lacking the α-methyl group proceeded in only 46% ee (entry 2). Yamamoto and coworkers later reported that Brønsted acid-assisted Lewis acid (BLA) **31** could address this shortcoming, providing the product in 95 % yield, as a single

diastereomer in 80 % ee.[89] Although several intermolecular Diels-Alder substrates were studied, trienal **31** was the only IMDA substrate examined.

Scheme 3.1. Asymmetric IMDA reactions of trienimides. Reported by Narasaka et al. (References 91 and 92).



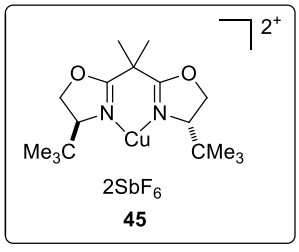
Scheme 3.2. Synthesis of hydronaphthalene core of mevinic acid family of natural products via IMDA reaction. Reported by Narasaka et al. (Reference 92).



Narasaka and coworkers undertook a more extensive study of the asymmetric IMDA reactions and found that Ti-TADDOL complex **32** was capable of catalyzing the IMDA reaction of several trieneimides (Scheme 3.1. A and B).[91] Although reactions required high catalyst loading and long reaction times, reactivity could be increased by

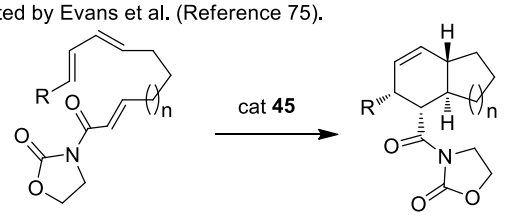
modifying the substrates to incorporate a dithiane moiety on the tether (Scheme 3.1.B), presumably due to the Thorpe-Ingold effect.[98] He later demonstrated the potential utility of this methodology in the elaboration of one of these IMDA adducts into the hydronapthalene core of mevinic acid family of natural products (Scheme 3.2).[92]

A more elaborate IMDA study was reported in 1997 by Evans and coworkers. They demonstrated the successful application of C_2-symmetric Cu(II)-*tert*-butyl-bis(oxazoline) catalyst **45** complex to the IMDA reaction of trieneimides (Table 3.2.).[75] Unsubstituted and phenyl-substituted [4.4.0] and [4.3.0] bicyclic ring systems were constructed with good yields and good to excellent levels of asymmetric induction (with the exception of entry 2). Synthetic manipulations of cycloadduct **44** could be achieved to synthesize the marine natural product (-)-Isopulo'upone **46**, clearly demonstrating the synthetic utility of this system.



45

Table 3.2. Cu (II) *tert*-butyl-bis(oxazoline) catalyzed IMDA reactions. Reported by Evans et al. (Reference 75).

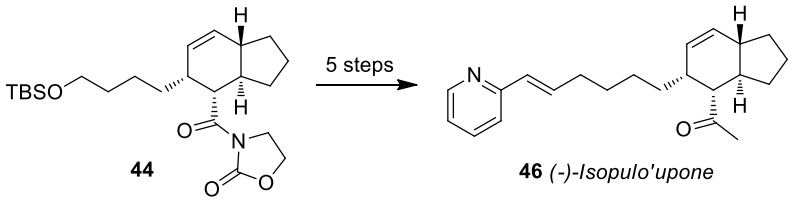


n = 1 or 2
39 R = H
40 R= Ph
41 R= $(CH_2)_4$OTBS

n = 1 or 2
42 R = H
43 R= Ph
44 R= $(CH_2)_4$OTBS

entry	triene	n	product	cat (mol %)	yield (%)	*endo:exo*	% ee
1	**39a**	1	**42a**	10	89	>99:1	86
2	**39b**	2	**42b**	10	<20	-	-
3	**40a**	1	**43a**	5	86	>95:5	92
4	**40b**	2	**43b**	5	97	84:16	97
5	**41**	1	**44**	5	81	>99:1	96

Scheme 3.3. Enantioselective synthesis of *(-)-Isopulo'upone.* Reported by Evans et al. (Reference 75).

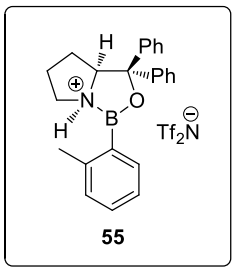


44 **46** *(-)-Isopulo'upone*

Later, in 2003 Corey and coworkers reported that N-Protonated chiral oxazaborilidine catalyst **55** could promote the asymmetric IMDA reaction of trienals and esters with high to excellent levels of enantioselectivity (Scheme 3.4. A-C).[77] It is worth mentioning that this report represents the first example of an enantioselective IMDA reaction of triene esters, which are known to be significantly less reactive than their aldehyde counterparts.

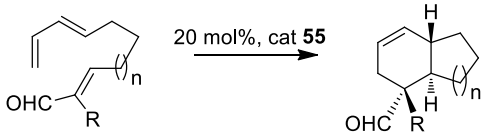
Corey and Snyder have showcased the synthetic utility of this technology. They reported that macrobicyclization *via* a catalytic enantioselective IMDA reaction could provide the key bond constructing step in an efficient synthetic pathway to several natural products belonging to the dolabellane family (Scheme 3.5).[99] Interestingly, the use of simple achiral Lewis acids such as Me_2AlCl, $MeAlCl_2$, or $EtAlCl_2$ did not promote the reaction but led only to removal of silyl protecting group and/or polymerization.

Scheme 3.4. N-Protonated chiral oxazaborilidine catalyzed IMDA reactions. Reported by Corey et al. (Reference 77).



55

A



n = 1 or 2
30a n = 1, R = Me
30c n = 1, R = Br
48 n = 2, R = Me

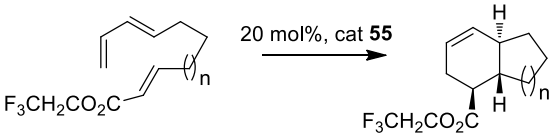
n = 1 or 2
49a n = 1, R = Me
49c n = 1, R = Br
50 n = 2, R = Me

49a
93% yield
endo:exo 99:1
90% ee

49c
82 % yield
endo:exo 99:1
94% ee

50
90% yield
endo:exo 2:1
80% ee *endo*
89% ee *exo*

B



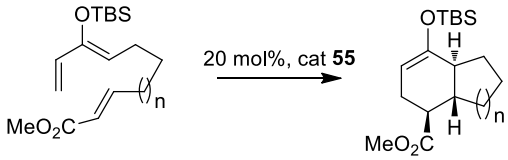
n = 1 or 2
51a n = 1
51b n = 2

n = 1 or 2
52a n = 1
52b n = 2

52a
75% yield
endo:exo 99:1
93% ee

52b
45% yield
94% ee

C



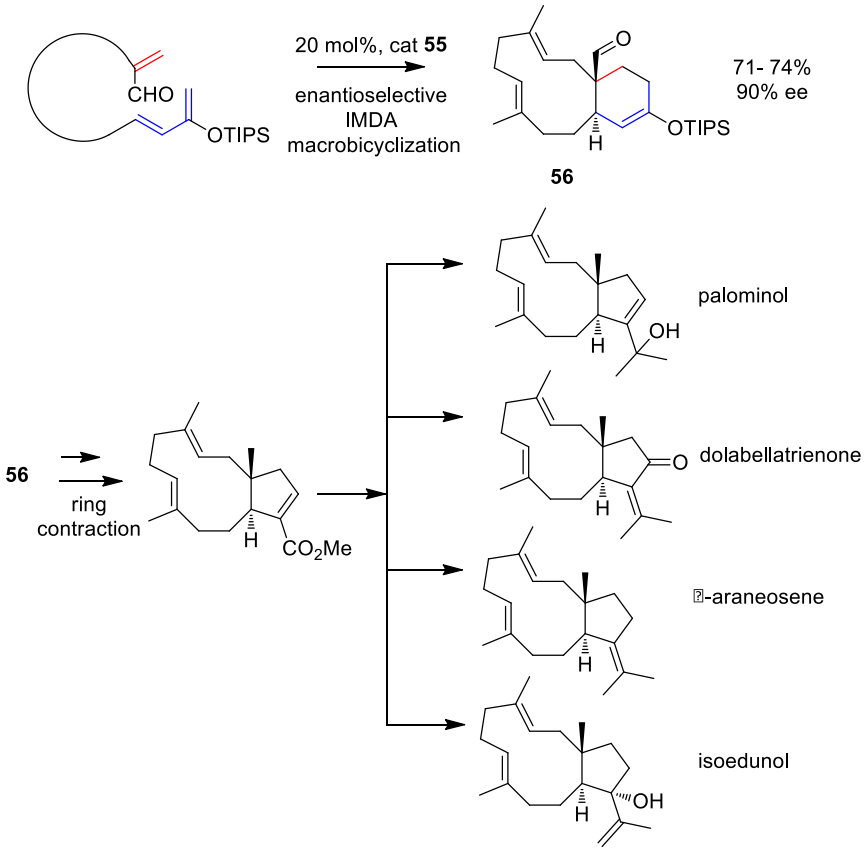
n = 1 or 2
53a n = 1
55b n = 2

n = 1 or 2
54a n = 1
54b n = 2

54a
93% yield
endo:exo >99:1
96% ee

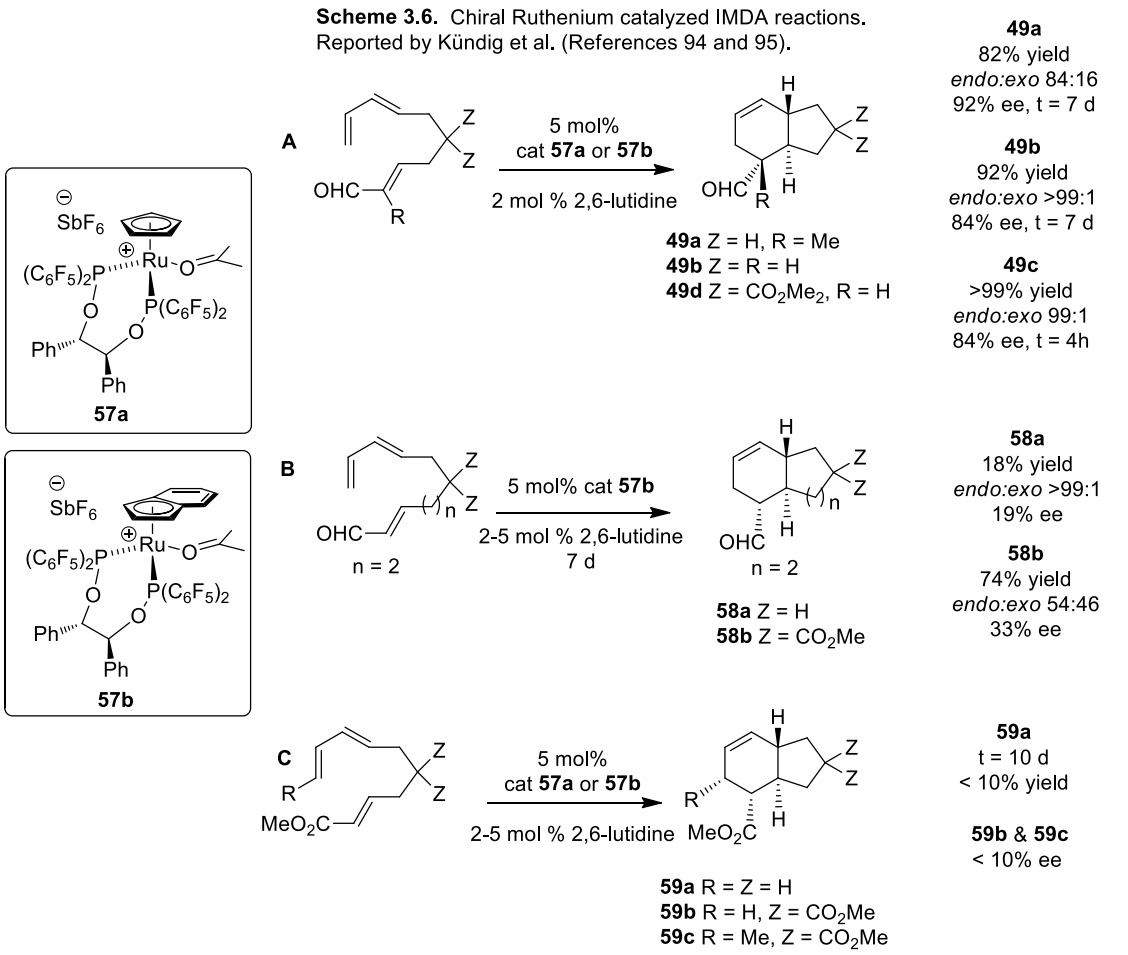
54b
52% yield
endo:exo 4:1
90% ee *endo*

Scheme 3.5. Synthesis of natural products in the dolabellane family *via* catalytic enantioselective IMDA reactions. Reported by Corey et al. (Reference 99).



Kündig and coworkers, recently reported that C_2-symmetric, single point binding, chiral ruthenium complexes **57**, could promote the IMDA reaction of trienals and triene esters. Although the nonatrienals exhibited long reaction times (7 days), good yields were obtained, along with good levels of asymmetric induction (Scheme 3.6 A).[94,95] Furthermore, reactivities could be significantly enhanced by modifying the substrates to incorporate a dimethylmalonate moiety on the tether (4 h reaction time). Asymmetric catalysis of decatrienals and nonatriene esters, on the other hand, proved to be more challenging with this catalyst system. Specifically, decatrienals and nonatriene esters, both cyclized with low product yields and enatioselectivities, and while incorporation of

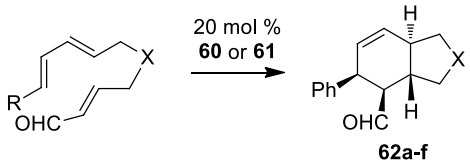
dimethylmalonate moiety increased reactivity, background reactions competed with the catalytic process resulting in low ee's (Scheme 3.6 B and C).

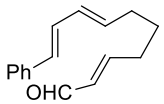
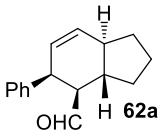
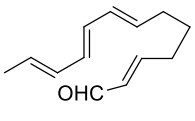
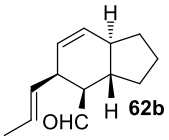
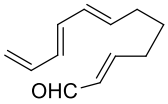
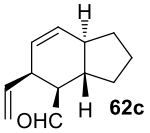
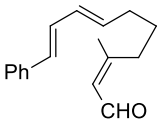
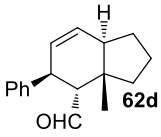
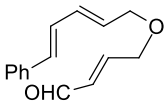
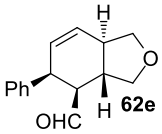
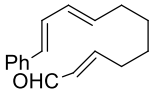
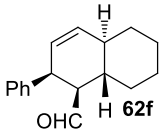
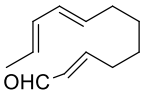
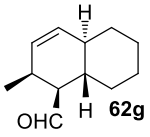


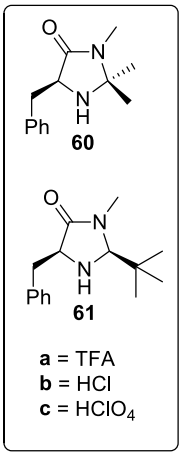
The most comprehensive substrate study on the asymmetric catalytic IMDA reported to date, was conducted by MacMillan and coworkers.[96] They demonstrated that organocatalysts, imidazolidinones **60**-**61** are effective at cyclizing a variety of trienals with excellent selectivities, *via* LUMO-lowering iminium activation. The reaction was found to tolerate variation in diene, tether, and dienophile components of the IMDA substrate, allowing access to a range [4.3.0] and [4.4.0] bicycles (Table 3.3.). Furthermore, the enantioselective IMDA reaction (Table 3.3., entry 7) provided the key

bond construction in the enantioselective synthesis of natural product (-)-solananpyrone, illustrating the efficacy of this method (Scheme 3.7.).

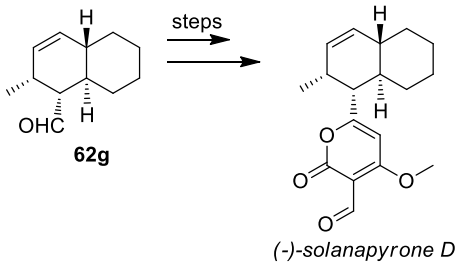
Table 3.3. Enantioselective organocatalyzed IMDA reactions of trienals. Reported by MacMillan et al. (Reference 96).



entry	triene	product	cat	yield (%)	*endo:exo*	% ee
1			**61a**	85	>20:1	93
2			**61a**	75	>20:1	94
3			**60** **61**	<10	-	-
4			**60b**	76	1:>20	94
5			**60c**	79	>20:1	94
6			**61c**	70	>20:1	92
7			**61a**	71	>20:1	90



Scheme 3.7. Enantioselective synthesis of *(-)-solanapyrone D* from IMDA adduct **62g**. Reported by MacMillan et al. (Reference 96).



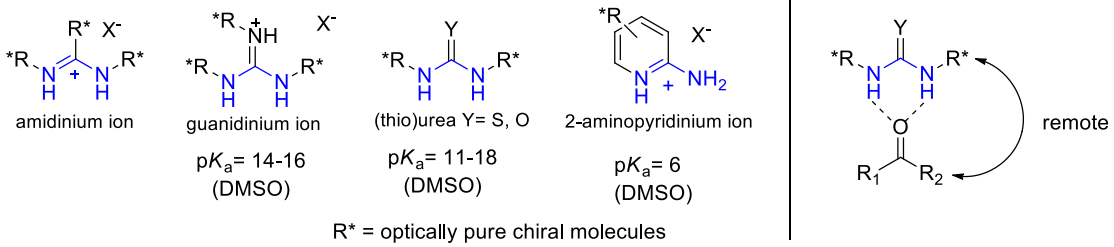
Although the studies discussed above have significantly advanced the field of asymmetric catalytic intramolecular Diels-Alder reactions, further developments can still be made. Examples of an enantioselective catalytic nitroalkene IMDA reaction have not been reported, even though they are expected to be highly complementary to methods of carbonyl based substrates, due to the synthetic versatility of the nitro group. In view of our own findings, that 2-aminopyridinium ions could cyclize the nitroalkene IMDA of 1-nitro-nona and decatrienes in good yields and diastereoselectivity (Chapter 2), we became interested in applying asymmetric variants of 2-aminopyridinium ions to these reactions in hopes of developing a useful asymmetric catalytic nitroalkene intramolecular Diels-Alder reaction.

3.1.2. 2-Aminopyridinium ions vs. other double hydrogen bond donor catalysts

In recent years, enantioselective synthesis and electrophile activation by small-molecule chiral hydrogen bond (abbre*via*ted H-bond) donors has become an important focal point in the area of asymmetric catalysis.[10,11] Among chiral H-bonding catalysts, urea and thiourea containing compounds are perhaps the most generally applicable catalysts, finding uses in a remarkable variety of enantioselective transformations. Much of their notable success can be attributed to their ability to form two H-bonds to a substrate. This two-point binding is thought to further activate a substrate and constrain it

to a well defined orientation necessary for asymmetric induction. Amidinium,[23,100-102] pyridinium[24-29] and guanidinium[10,11] ions are a few other examples of chiral catalysts previously reported that are capable of donating two H-bonds.

Figure 3.1. Double hydrogen bond donors**.** Amidinium ions; guanidinium ions; (thio)urea; 2-aminopyridinium ion

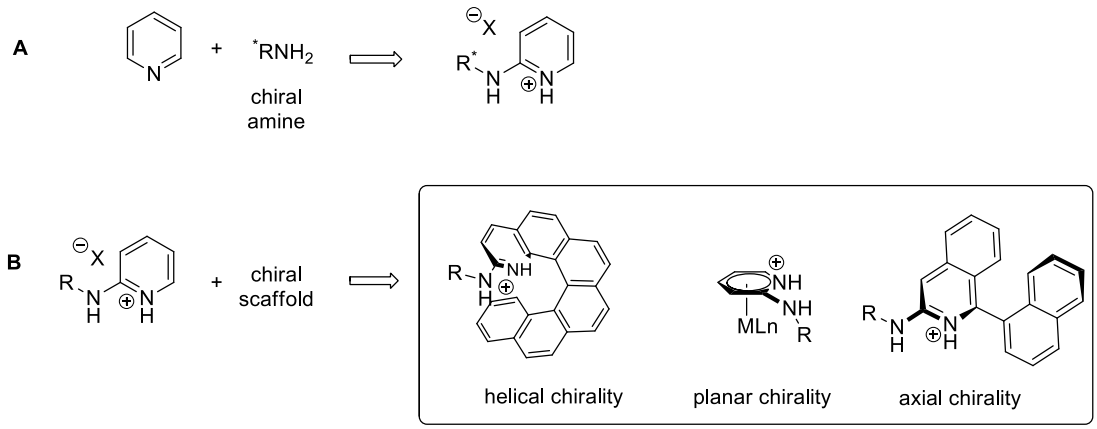


In acute contrast to (thio)ureas, 2-aminopyridinium ions have been much less explored as H-bonding catalysts,[23-30] despite offering unique structural advantages. An intrinsic challenge in the design of chiral double H-bonding catalysts is that the chiral element (R* in Figure 3.1) can often only be introduced at sites remote from the H-bonding site due to the directionality of the Hydrogen bonds. In addition, the chiral element and H-bonding site are connected *via* a rotary single bond, which can give rise to conformational ambiguity between the bound substrate and the chiral element. 2-aminopyridinium ions, on the other hand, are devoid of these challenges because the pyridine ring can be modified to extend its reach asymmetrically toward the H-bonding site in a conformationally rigid fashion. Furthermore, 2-aminopyridinium ions are more acidic (Figure 3.1) than commonly studied double H-bonding donors (i.e., more reactive).

3.2. Results and discussion

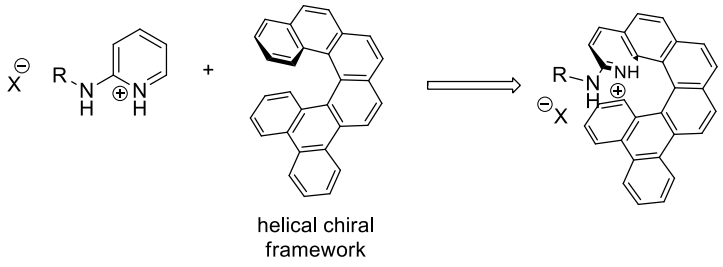
3.2.1. Helical chiral 2-aminopyridinium ions as catalysts for the nitroalkene intramolecular Diels-Alder reaction

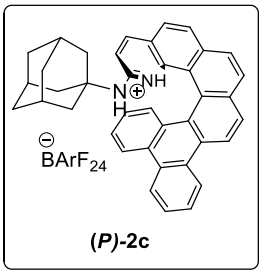
Figure 3.2. Examples of possible 2-aminopyridnium chiral variants



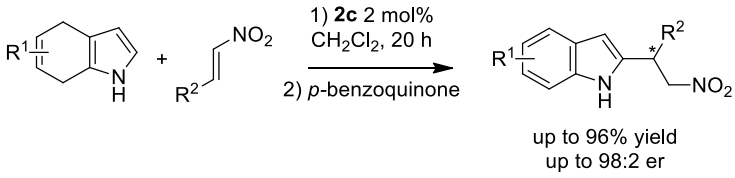
One way to synthesize chiral 2-aminopyridinium ions is to couple the pyridine with optically active amines (Figure 3.2 A). In this way, a number of chiral catalysts can easily be generated. However, for the aforementioned reasons (Section 3.1.2.; Figure 3.1), we have chosen to directly desymmetrize the pyridine ring, by incorporating the 2-aminopyridinium core into a chiral scaffold, which can be done effectively in three different ways (Figure 3.2. B, helical, planar, or axial).

Figure 3.3. Helical chiral 2-aminopyridinium ions



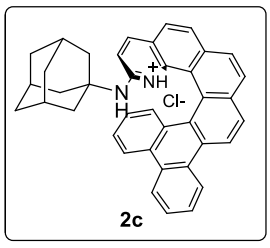


Scheme 3.8. Catalytic enantioselective addition of 4,7-dihydroindoles to nitroalkenes by helical chiral 2-aminopyridinium ions. Reported by Takenaka et al. (Reference 35).



My colleagues have recently developed chiral 2-aminopyridinium variants by merging the 2-aminopyridinium catalytic core into the inherently chiral framework of helicene (Figure 3.3) and these catalysts have proven to be highly enantioselective for addition reactions of 4,7-dihydroindoles to nitroalkenes (Scheme 3.8).[35] The crystal structure of the helical 2-aminopyridinium HCl salt **2c**, reveals a double hydrogen bond between the 2-aminopyridinium cation and the chloride anion (Figure 3.4) in which the bottom half of the helicene framework effectively covers the space beneath the two hydrogen bonds. This suggests that the chiral scaffold may effectively block one face of an electrophile. Moreover, my colleagues have demonstrated that the steric environment around the pyridine rings of 1-azahelicenes are easily tuned (Figure 3.5.)[35,37] and these catalysts are robust in terms of ease of handling. Therefore, we became interested in applying these helical chiral 2-aminopyridinium ion catalysts to an asymmetric nitroalkene IMDA reaction study.

Figure 3.4. ORTEP of 2-(1-adamentylamino)-1-azahelicene·HCl. Reported by Takenaka et al. (Reference 35).



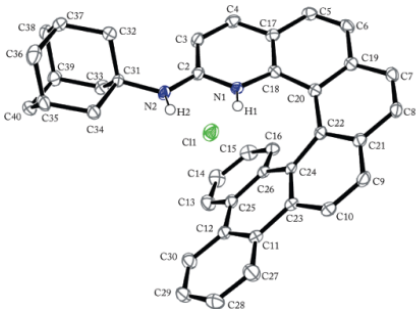
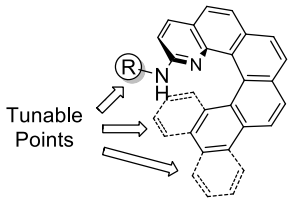
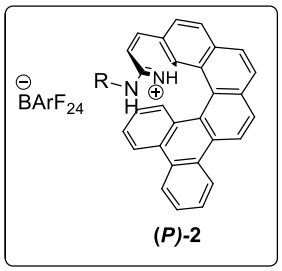


Figure 3.5. Tunability of 1-azahelicene derivatives



As a model substrate, we chose nonatriene **15a** (Chapter 2) because achiral 2-aminopyridinium ion **1** was able to catalyze its reaction with excellent levels of diastereoselectivity. To our delight, helical 2-aminopyridinium **2b** efficiently cyclized the reaction with excellent levels of *endo* selectivity (Table 3.4 entry 1). Unfortunately however, no asymmetric induction was observed. Previous studies conducted in our group, on the addition of 4,7-dihydroindoles to nitroalkenes, showed that enantioselectivity could gradually be increased with increasing degree of alkyl substitution on the R group attached to the 2-amino pyridine nitrogen of 1-azahelicene.[35] Taking this into account, we decided to additionally examine helical catalysts **2a** and **2c** (Table 3.4 entries 2 and 3). Regrettably no significant improvements were observed in enantioselectivities, suggesting that this catalyst class could not adequately provide an effective chiral environment for this transformation. Nevertheless, it can comfortably be said that helically chiral 2-aminopyridinium catalysts are capable of effectively activating the nitroalkene component of the IMDA substrate, producing the adduct in excellent *endo* selectivities.



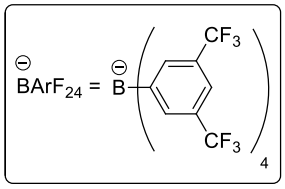
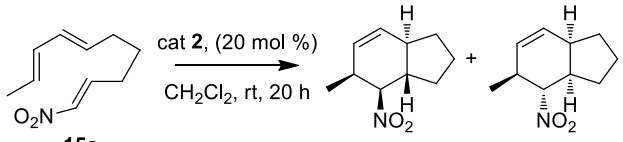
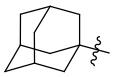


Table 3.4. Evaluation of helical chiral 2-aminopyridinium ions on the of IMDA of (*E*)-1-nitro-1,6,8-nonatriene



entry	cat	R	yield[a] (%)	*endo*:*exo*[b]	% ee
1	**2b**	H	62	>30:1	0
2	**2a**		65	>30:1	6
3	**2c**		66	>30:1	6

[a] Isolated yield of products. [b] Determined by ^{1}H NMR nalysis of the crude product.

3.2.2. Development of new planar chiral 2-aminopyridinium catalysts

Each chirality type (helical, axial, or planar) can create significantly different chiral spaces due to their inherent structural features and are hence expected to induce enantioselectivity differently. Subsequently, it is always a risk to rely on one family of chiral catalysts when developing novel enantioselective processes.[103] Therefore, we deemed it wise to develop a planar chiral 2-aminopyridinium variant as a *via*ble alternative for an asymmetric nitroalkene IMDA reaction.

Figure 3.6. X-ray analysis of planar chiral pyridine *N*-oxide. The pyridine ring is well-desymmetrized in terms of top-from-bottom and left-from-right. Reported by Fu et al. (Reference 36).

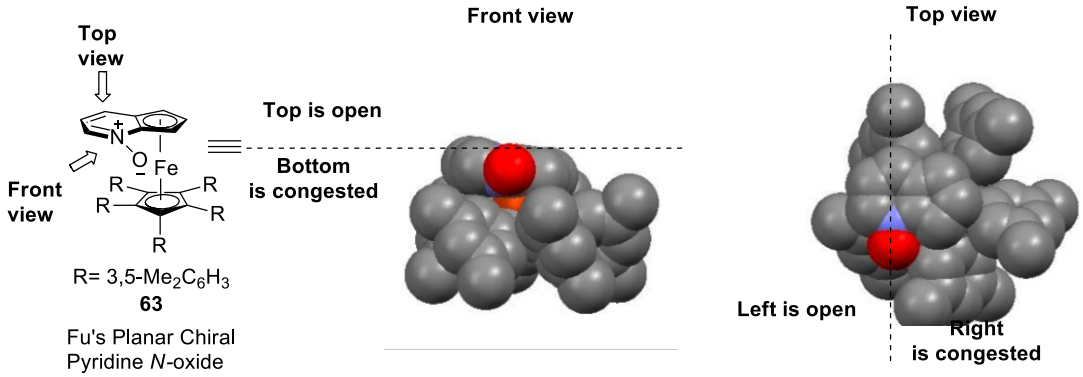
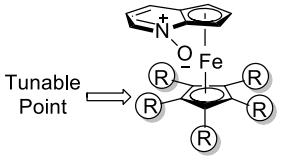


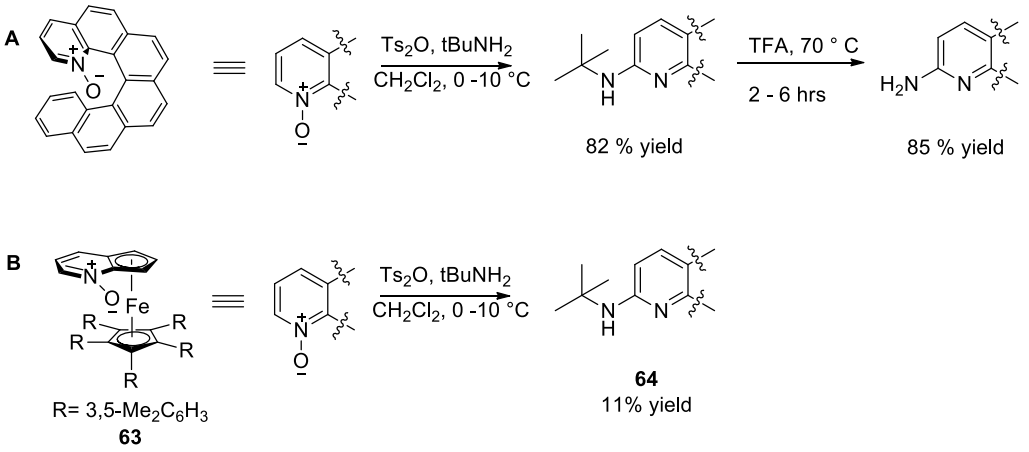
Figure 3.7. Tunability of Fu's planar chiral pyridine *N*-Oxides



After considering a number of planar chiral molecules reported,[36,104-106] we became interested in planar chiral pyridine *N*-oxide **63** developed by Fu and coworkers, because its crystal structure reveals that the pyridine ring is well-desymmetrized in terms of top-from-bottom (Front view, Figure 3.6) and left-from-right (Top view) differentiations. Moreover, Fu and coworkers have demonstrated that the steric environment around its pyridine ring is easily tunable (Figure 3.7) and that this ferrocence complex is robust in terms of ease of handling.[36] We deemed that these structural features were important for creating an effective chiral environment around the reaction center of the corresponding 2-aminopyridinium catalyst. We therefore decided to develop a synthetic route to a planar chiral 2-aminopyridinium catalyst based on Fu's catalyst.

In order to synthesize the planar chiral 2-aminopyridine, we initially employed the amination method used for helical chiral analogues in our group (Scheme 3.9 A).[35,107] However, this amination method was not proficient for the planar chiral pyridine *N*-oxide, affording the desired product **64** in only 11 % yield (Scheme 3.9 B). Instead, a significant amount of a side product was isolated. Nuclear magnetic resonance (^{1}H NMR) and fast atom bombardment mass spectrometry (FAB MS) of the isolated side product suggest that the ferrocene moiety remained intact, but were inconclusive in identifying its structure. Attempts to crystallize the compound for X-ray analysis were not fruitful.

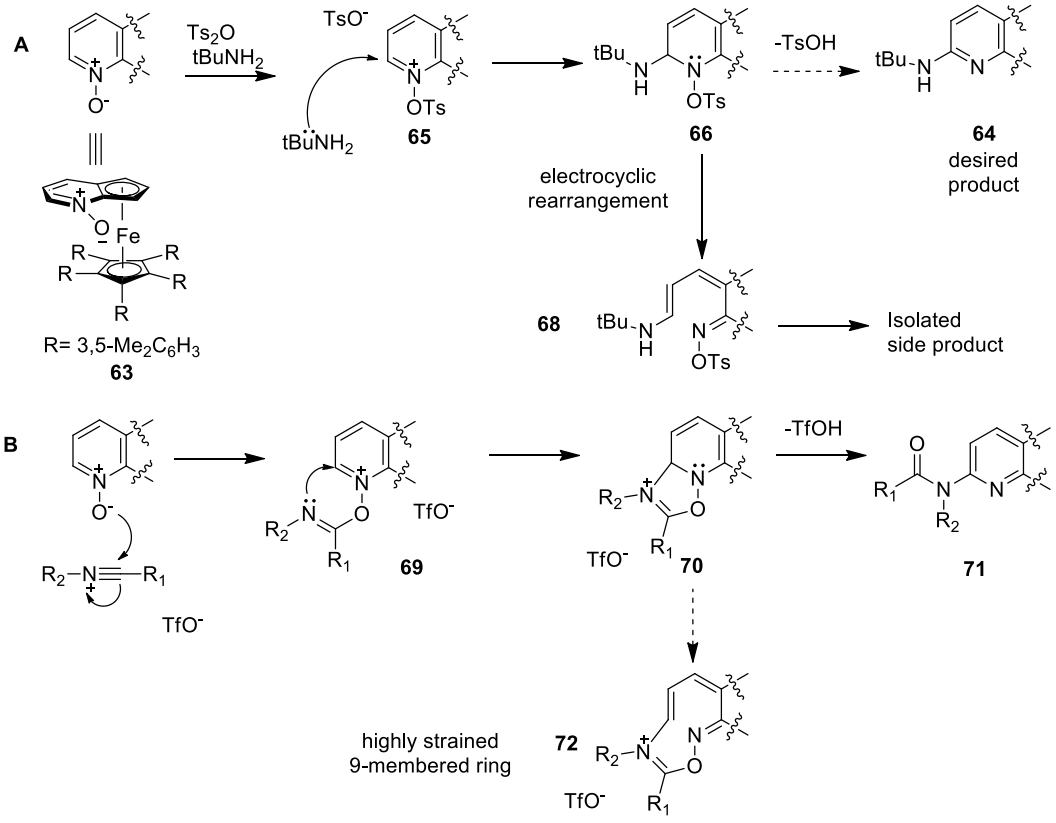
Scheme 3.9. Amination of pyridine *N*-oxides



We hypothesized that amine adduct **66** underwent electrocyclic rearrangement to give a putative intermediate **68**, from which the aforementioned side product was formed (Scheme 3.10 A). Therefore, we considered different amination methods that might stop this hypothesized pathway. The method we chose involves an intra-molecular amination step to produce bicyclic intermediate[108] **70** (Scheme 3.10, intermediates **66** and **70** are corresponding structures). Our notion was that **70** was unlikely to undergo electrocyclic

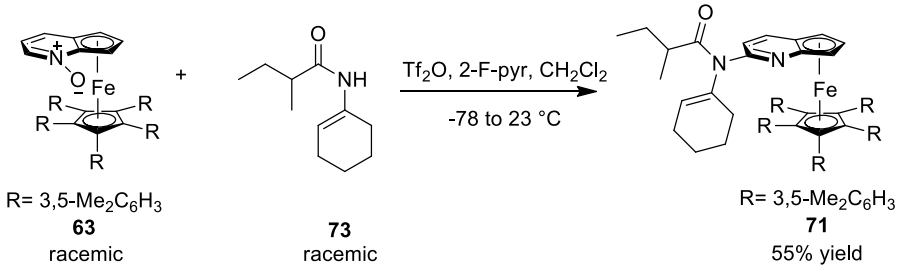
rearrangement because it would produce a highly strained unsaturated, 9-membered ring **72**, thereby leading to the desired product **71**.

Scheme 3.10. Mechanistic considerations of amination reactions

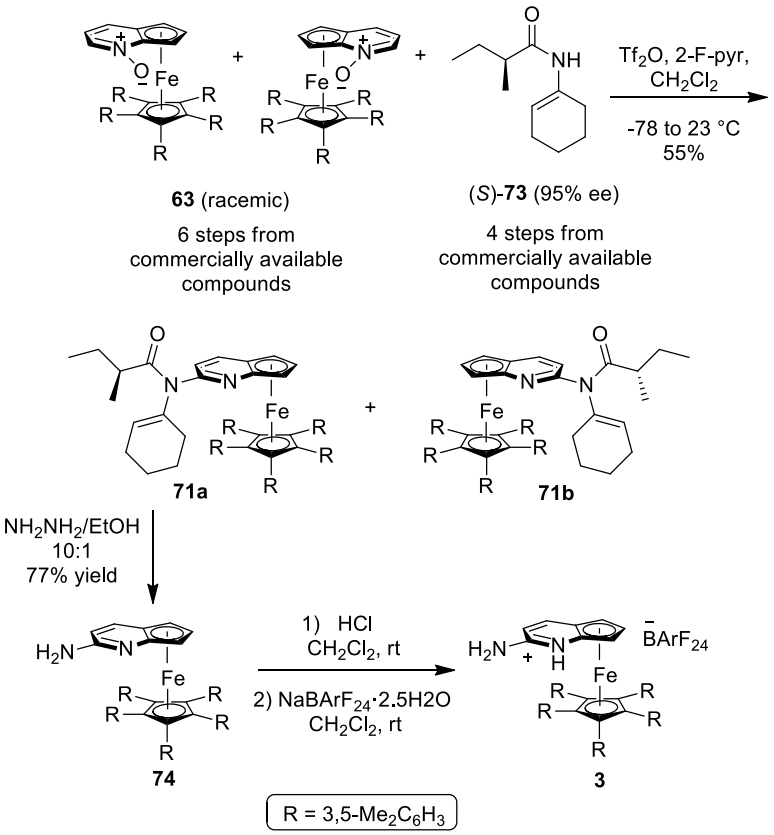


To our delight, this method provided the desired product **71** in 55% yield (Scheme 3.11). Furthermore, we serendipitously found that the two diastereomers formed were fully separable on silica gel. This means that if we use enantiopure **73**, we can optically resolve the catalysts by column chromatography allowing us to avoid non-tri*via*l, optical resolution by chiral HPLC.

Scheme 3.11. Amination of planar chiral pyridine *N*-oxide



Scheme 3.12. Synthesis of enantiopure planar chiral 2-aminopyridinium catalyst. Absolute steriochemistry has not been determined



Using enatio-enriched **73** we obtained optically pure diastereomers and separated them on silica gel. We took one of the diastereomers of **71** and went on to obtain the 2-aminopyridinium TFPB catalyst. Deprotection of the 2-amino group by NH_2NH_2-EtOH (10:1) gave the free 2-aminopyridine **74** in 77% yield. Treatment of the 2-aminopyridine

with HCl followed by immediate counterion exchange with $NaBArF_{24}$ hydrate furnished the catalyst, which were used without further purification (Scheme 3.12).

3.2.3. Planar chiral 2-aminopyridinium ions as catalysts for the nitroalkene intramolecular Diels-Alder reaction

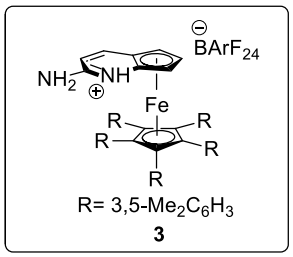
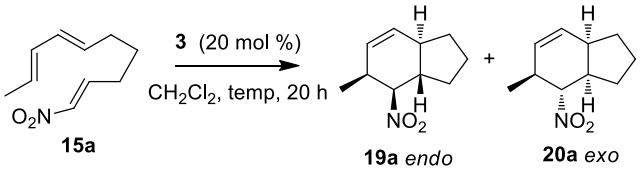


Table 3.5. Evaluation of planar chiral 2-aminopyridinium ions on the of IMDA of (*E*)-1-nitro-1,6,8-nonatriene



entry	temp (°C)	yield[a] (%)	*endo:exo*[b]	% ee
1	25	95	>30:1	0
2	0	51	>30:1	0
3	-20	20	>30:1	0

[a] Isolated yield of products. [b] Determined by ^{1}H NMR analysis of the crude product.

With the optically pure planar chiral catalyst in hand we probed its ability to enantioselectively catalyze the nitroalkene IMDA reaction of substrate **15a**. To our delight, the planar 2-aminopyridinium efficiently catalyzed the reaction, affording the product in excellent yield and with excellent levels of *endo* selectivity. It is worth mentioning that in terms of reactivity, it was more efficient than the helical chiral variants (yields 62-66 %). Unfortunately, however, no enantioselectivity was observed. Lowering the reaction temperatures led only to decreased yields. These results indicate that the planar chiral 2-aminopyridinium ion **3** effectively catalyzes the reaction but do not provide an effective chiral environment for this particular transformation. Nevertheless, it

indicates that planar chiral 2-aminopyridinium ions are a promising class of new H-bond donor catalysts.

3.3. Summary

In summary, we have identified helical chiral 2-aminopyridinium **2a-c** as LUMO lowering catalysts for the nitroalkene intramolecular Diels-Alder reaction. Although they were unable to cyclize the reaction enantioselectively, they provided the IMDA adduct in good yields and in excellent levels of diastereoselectivity. Furthermore, we have established a synthetic route to planar chiral 2-aminopyridinium catalysts, and found a convenient way to optically resolve them. Additionally, this catalyst was found to catalyze the nitroalkene IMDA providing the adduct with excellent *endo:exo* selectivities and excellent yields. These planar chiral 2-aminopyridinium catalysts are a promising class of H-bond donor catalysts and in the future can be applied to other synthetically useful transformations. In impending enantioselective intramolecular Diels-Alder studies, axially chiral 2-aminopyridiniums ions may be investigated as they are *via*ble alternatives to helical and planar chiral variants.

3.4. Experimental section

3.4.1. General Information

All reactions were carried out in 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 (TLC) 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 200-400) supplied by E. Merck.

Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane (CH_2Cl_2), and toluene (PhMe) were freshly distilled over calcium hydride under an atmosphere of dry argon prior to use. Et_2O and THF were freshly distilled over sodium/benzophenone under an atmosphere of dry argon prior to use. Trifluoromethanesulfonic anhydride was freshly distilled prior to use over phosphorous pentaoxide. Compounds that are not numbered in the main body of the chapter are labeled **S1**, **S2**, ect.

^{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). Fast atom bombardment mass spectra (FABMS) were recorded with a VG Mass Lab Trio-2 spectrometer, using 3-nitrobenzyl alcohol as matrix. Low resolution mass spectra were recorded using Hewlett Packard 5971A spectrometer. High

resolution mass spectra were obtained at Mass Spectrometry Laboratory, Department of Chemistry, University of Miami.

3.4.2. General procedure for asymmetric nitroalkene IMDA reaction with helical chiral 2-aminopyridinium ions (Table 3.4)

Entry 2

To a solution of ***(P)*-S1** (Chapter 1) (73 mg, 0.15 mmol) in CH_2Cl_2 (2.4 mL) was added an Et_2O solution of HCl (1M, 0.18 mL) drop wise at room temperature. The reaction mixture was stirred for 1 h and then concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (2.0 mL), and the concentrated *in vacuo*, the process of which was repeated three times. To the resulting yellow solid was added EtOH (10.1 mL) and $NaBArF_{24}{\cdot}2.5H_20$[39] (131 mg, 0.15 mmol). The mixture was stirred for 1 h at room temperature, filtered through a short pad of silica, washed with 4% MeOH in CH_2Cl_2, and was concentrated *in vacuo.* The resulting salt ***(P)*-2a** was used as a catalyst without further purification.

To a solution of triene **15a** (11. mg, 0.063 mmol) in CH_2Cl_2 (125 µL) cooled to 0 °C was added catalyst ***(P)*-2a** (17 mg, 0.0125 mmol, 20 mol %) in one portion under an atmosphere of dry argon. After stirring for 5 min. at 0 °C, the reaction was allowed to warm to 25 °C. After 20 h, the reaction was diluted with CH_2Cl_2, followed by the addition of 50 µL CH_2Cl_2-hydrazine monohydrate solution (50:50 mixture by volume). The resulting solution was stirred for 5 min., diluted with water, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The ratio of diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture (*endo:exo* = > 30:1), which was then purified by

flash chromatography on silica gel (2% EtOAc/hexanes) to provide the product (7 mg, 65%). Spectral data were in agreement with the literature values.[47] (6% ee) Enantiomeric ratio was determined by HPLC with a Chiralcel OJ-H column equipped with an OD-H guard column (2% isopropanol in hexanes, flow rate = 0.5 ml/min), t_r (minor) = 10.25 min, t_r (major) = 12.85 min.

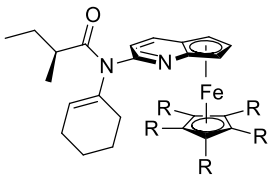
Entry 1

The general procedures were followed with ***(P)*-2b**[35] (12 mg, 0.0094), and **15a** (9 mg, 0.047 mmol), to give the cycloadduct (5.2 mg, 62%) with *endo:exo* = > 30:1, 0% ee.

Entry 3

The general procedures were followed with ***(P)*-2c**[35] (17 mg, 0.0125), and **15a** (13 mg, 0.047 mmol), to give the cycloadduct (8.0 mg, 66%) with *endo:exo* = > 30:1, 6% ee.

3.4.3. Synthesis of (+)-71

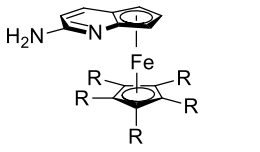


R= 3,5-$Me_2C_6H_3$
Absolute steriochemistry has not been determined

We followed the amination procedure reported by Movassaghi[108] and coworkers. Trifluoromethanesulfonic anhydride (89 μL, 0.52 mmol) was added *via* syringe to a solution of (*S)-N*-cyclohexenyl-2-methylbutanamide[108] (95 % ee) (86.5 mg, 0.48 mmol) and 2-fluoropyridine (49 μL, 0.575mmol, 1.20 equiv) in dichloromethane (1 mL) at –78

°C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, a solution of **63** *N*-oxide[36] (739 mg, 0.95 mmol) in 1 mL dichloromethane, was added. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 1.5 hr, triethylamine (1 ml) was added, and the mixture was diluted by the addition of dichloromethane (10 mL). The resulting mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and were concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (2.5 → 20% ethyl acetate in hexanes) to provide the amide product (247 mg, 55 %), and recovered pyridine planar chiral *N*-oxide[36] **63** (388 mg, 0.5 mmol). The two amide diastereomers were fully separable on silica gel, and the slower eluting diastereomer was used to obtain the planar chiral 2-aminopyridinium catalyst. The slower eluting diastereomer: $[\alpha]^{20}_{D}$ = + 1240, c = 0.0005, CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.3, Hz, 1H), 7.20 (d, *J* = 9.6, Hz, 1H), 6.71 (s, 5H), 6.54 (s, 10H), 5.35 (s, 1H), 5.05 (s, 1H), 4.66 (s, 1H), 4.15 (s, 1H), 2.06 (m, 1H), 2.07 (s, 30 H), 2.07-1.25 (m, 10H), 1.07 (d, *J* = 6.6, Hz, 3H), 0.86 (t, *J* = 7.16, Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 155.2, 138.6, 135.8, 135.4, 130.3, 127.6, 127.1, 118.8, 86.0, 79.8, 78.6, 69.7, 66.1, 65.1, 61.7, 40.7, 29.9, 28.2, 24.9, 22.6, 21.6, 21.4, 18.2, 12.4; FTIR (neat) υ_{max} 3038, 3002, 2963, 2917, 2858, 1673, 1597, 1514, 1437, 1374, 1223, 847, 812 704 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{64}H_{68}FeN_2O$ $[M+1]^+$, expected: 937.4756, found: 937.4782.

3.4.4. Synthesis of planar chiral 2-aminopyridinium ((+)-74).



R= 3,5-$Me_2C_6H_3$
Absolute steriochemistry has not been determined

The slower eluting amide diastereomer (+)-**71** was used in the deprotection step. We followed the procedure reported by Boger *et al*. Five mL of 98 % Hydrazine was added to a solution of (+)-**71** (145 mg, 0.16 mmol) in EtOH (500 μL) under Argon. The reaction mixture was warmed to 115˚ C in a sealed vessel for 30 minutes. The mixture was cooled to room temperature, diluted with ether (100 mL), and quenched by adding saturated $NaHCO_3$ solution (100 mL). It was then extracted with ether (3 x 100 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacou*. The crude compound was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford pure (+)-**74** as a pink solid (92 mg, 77%). $[\alpha]^{20}_D$ = + 852, c = 0.0005, CH_2Cl_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 1H), 6.72 (s, 5H), 6.54 (s, 10H), 6.40 (d, *J* = 9.0 Hz, 1H), 4.65 (s, 1H), 4.46 (s, 1H), 4.37 (br s, 2H), 4.07 (s, 1H), 2.08 (s, 30H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 140.5, 135.6, 135.5, 130.4, 127.3, 127.0, 112.9, 86.0 67.3, 66.0, 64.5, 60.5, 24.4; FTIR (neat) υ_{max} 3494, 3392, 3002, 2914, 2861, 1732, 1617, 1598, 1522, 1481, 1426, 1395, 847, 705 cm^{-1}; HRMS (ESI-TOF): Exact mass calcd for $C_{53}H_{53}FeN_2$ $[M+1]^+$, expected: 773.3554, found: 773.3572.

3.4.5. General procedure for asymmetric nitroalkene IMDA reaction with planar chiral 2-aminopyridinium ions (Table 3.5)

To a solution of **(+)-74** (33 mg, 0.043 mmol) in CH_2Cl_2 (3.6 mL) was added an Et_2O solution of HCl (1M, 0.86 mL) drop wise at room temperature. The reaction mixture was stirred for 30 min. and then concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (5.0 mL), and then concentrated *in vacuo*, the process of which was repeated three times. To the resulting solid were added CH_2Cl_2 (0.68 mL), and $NaBArF_{24}\cdot 2.5H_20$ (40. mg, 0.043 mmol) at room temperature. The resulting mixture was stirred for 1 h, and concentrated *in vacuo.* The resulting salt **3** was used as a catalyst without further purification.

To a solution of triene **15a** (11. mg, 0.063 mmol) in CH_2Cl_2 (125 μL) cooled to 10 °C below the indicated reaction temperature was added catalyst **3** (21 mg, 0.0125 mmol, 20 mol %) in one portion under an atmosphere of dry argon. After stirring for 5 min., the reaction was allowed to warm to reaction temperature. After 20 h, the reaction was diluted with CH_2Cl_2, followed by the addition of 50 μL CH_2Cl_2-hydrazine monohydrate solution (50:50 mixture by volume). The resulting solution was stirred for 5 min., diluted with water, and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The ratio of diastereomers was determined by ^1H NMR analysis of the crude reaction mixture (*endo:exo* = > 30:1), which was then purified by flash chromatography on silica gel (2% EtOAc/hexanes) to provide the product. Spectral data were in agreement with the literature values.[47] Enantiomeric ratio was determined by HPLC with a Chiralcel OJ-H column equipped with an OD-H guard column (2% isopropanol in hexanes, flow rate = 0.5 ml/min), t_r (minor) = 10.25 min, t_r (major) = 12.85 min.

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