ABSTRACT

Title of Dissertation / Thesis:	DIRHODIUM(II) CARBOXAMIDATE CATALYSTS AS LEWIS ACIDS FOR THE HETERO-DIELS-ALDER REACTION.
	Marcela V. Valenzuela, Doctor of Philosophy, 2004
Dissertation / Thesis Directed By:	Professor Michael P. Doyle, Department of Chemistry and Biochemistry

The hetero-Diels-Alder reaction between an aldehyde and a diene provides access to dihydropyrans which are precursors in the chemical synthesis of biologically active natural products. Lewis acid catalysts increase reactivity by activating the carbonyl group of the aldehyde dienophile towards addition. Chiral dirhodium(II) carboxamidates are highly selective Lewis acids that have high turnover numbers in the hetero-Diels-Alder reaction. The reaction between aromatic aldehydes with Danishefsky's diene in the presence of only 0.01 mol % catalyst afforded the corresponding dihydropyran products in high enantioselectivities and yields.

Optimization of reaction conditions led to the discovery that the amount of dihydropyran formed increased at elevated temperatures while maintaining stereoselectivities as high as 98 % ee for aromatic aldehydes extending from *p*-nitro- to *p*-methoxy-benzaldehyde. Aldehydes with electron-donating substituents required longer reaction times in comparison to those having electron withdrawing

substituents. Reactions with aliphatic aldehydes were sluggish in comparison to aromatic aldehydes, however enantioselectivities as high as 86 % were achieved.

A detailed kinetic analysis of the hetero-Diels-Alder reaction, which has not been previously reported, was performed to gain insight into the mechanistic pathway for the dirhodium(II) catalyzed hetero-Diels-Alder reaction**.** Both the equilibrium constants for the association between catalyst and aldehyde and the rates of reaction for various *para*-substituted aldehydes were determined. Kinetic investigations revealed a pronounced electronic influence on the rate of reaction giving a Hammett ρ value of +1.9 (versus σ^+). The reaction rate for *p*-nitrobenzaldehyde is 20 times faster than *p*-chlorobenzaldehyde which is 36 times faster than *p*-anisaldehyde. Aldehydes with higher equilibrium constants for coordination with dirhodium(II) catalyst undergo slower rates of cycloaddition. Detailed kinetic studies established that inhibition of the catalyst by reactant aldehyde is apparent. In addition, reactions exhibit first order dependence on aldehyde and diene, and variable dependence on catalyst.

The dimethyl analogue of the Danishefsky's diene, 1-methoxy-2-methyl-3-trimethylsilyolxy-1,3-pentadiene, reacted with nitro-substituted aromatic aldehydes to form exclusively the *cis*-dihydropyran in high selectivity and yield. The approach of the diene to the catalyst-aldehyde complex is influenced by substitution on the incoming diene. Furthermore, substitution on the diene affects the rate of reaction with *p*-nitrobenzaldehyde. The diastereoselectivity with aromatic aldehydes other than nitro- substituted aldehydes was optimized; however, long reaction times were necessary to obtain high conversion.

DIRHODIUM(II) CARBOXAMIDATE CATALYSTS AS LEWIS ACIDS FOR THE HETERO-DIELS-ALDER REACTION

By

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Dedication

This dissertation is dedicated to my family, my parents Jesus Manuel and Maria Elena Valenzuela, my sister Blondie, my brother Eddie, and my best friend Kyle Woolfolk whom through their constant love and support have encouraged me to succeed, and made my graduate career possible.

Acknowledgements

I am grateful to the many individuals who have contributed to making my graduate career a gratifying and positive experience. Most importantly I would like to thank my research advisor Michael Doyle for taking me into his research group in December of 2000. I was one of his first graduate students and he allowed me the opportunity to work on a new and different research project. In addition, I would like to thank you for your support over the years and for advising me when I needed guidance. Your enthusiasm for chemistry and science is contagious.

I have likewise had the opportunity to work with some talented individuals within the Doyle laboratory. One of those individuals was Dr. Wenhao Hu who helped me get started on the hetero-Diels-Alder project. His assistance and mentoring were instrumental my first year in the group. I would like to thank you for your constant advice and patience with me.

I would like to thank all the members of the Doyle group who I have overlapped with over the years. I want to say thank you for the fond and comical memories at work and for many stimulating conversations. In particular I would like to thank Christine Hedberg and Penglin Huang for working with me on the hetero-Diels-Alder project. It has been a joy working with the both of you and I am glad that I have had the pleasure to really get know you.

I am also grateful to my undergraduate advisor Dr. Jeffery Arterburn for encouraging me to pursue a PhD in organic chemistry and allowing me to work in his research laboratory for three years. Finally I would like to thank my family and friends who have given me the strength and encouragement to never give up.

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List of Abbreviations

DA = Diels-Alder

HDA = hetero-Diels-Alder

TFA = trifluoroacetic acid

ee = enantiomeric excess

TMS = trimethylsilyl

TBDMS = *t*-butyldimethylsilyl

DCM = dichloromethane

GC = gas chromatography

HPLC = high-performance liquid chromatography

THF = tetrahydrofuran

hfc = 3-(heptafluoropropylhydroxymethylene)camphorate

BNP = 1,1'-binaphthyl-2,2'-diyl phosphate

CAN = cerium ammonium nitrate

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Chapter 1: Hetero-Diels-Alder Reaction: Introduction and Background

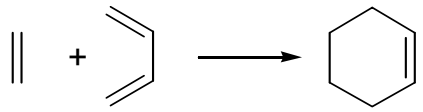
1.1 Introduction

The Doyle laboratory is well known for its contribution to asymmetric catalysis particularly in the area of metal carbene chemistry, utilizing dirhodium(II) carboxamidates.[1] In 2000 we embarked upon a research program which aspired to develop dirhodium(II) carboxamidates as Lewis acids. In particular, we wanted to access the viability of dirhodium(II) as a Lewis acid catalyst in the hetero-Diels-Alder (HDA) reaction. Traditionally this has become a platform from which Lewis acid catalysts are evaluated.

This chapter will focus on the HDA reaction and its application in natural product synthesis. Additionally the mechanism of the hetero-Diels-Alder reaction and factors that must be considered in Lewis acid catalysis will be discussed. Finally, an overview of Lewis acids that have been successfully applied in this reaction will also be provided.

1.2 Overview of the Hetero-Diels-Alder Reaction

In 1928 Otto Diels and Karl Alder discovered one of the cornerstone reactions in organic chemistry for the construction of six-membered rings which now bears their names, the Diels-Alder reaction (DA).[2] In the DA reaction a double bond (dienophile) adds 1,4 to a conjugated diene via a [4 + 2] cycloaddition pathway providing a six membered carbocycle (Eq. 1).



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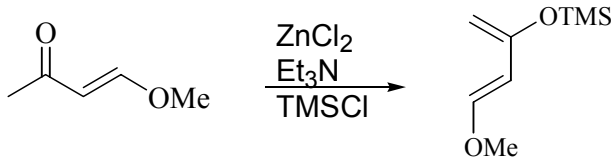
Subsequently, various types of DA reactions have been developed and their application in chemistry covers compounds of academic and industrial interest. Additionally, attention has been focused on the synthetic and mechanistic aspects of the DA reaction and the development and application of the Diels-Alder reaction for the formation of optically active compounds.

Carbon-carbon double bonds are not the only units that can participate in the DA reaction. For example, carbonyl compounds can act as dienophiles and undergo cycloaddition with 1,3-dienes. However, reactions of this type proceed poorly with aliphatic and aromatic aldehydes and ketones unless highly reactive dienes and/or Lewis acid catalysts are used.[3] A Lewis acid is a species that can accept an electron pair from an electron pair donor known as a Lewis base. The concept of activation by a Lewis acid and the parameters that must be considered when employing a Lewis acid will be discussed later in this chapter.

The HDA reaction can transpire in the absence of a Lewis acid; however forcing reaction conditions are generally required. For instance, a trace amount of product is formed when acetaldehyde and isoprene are reacted at 100^{o}C.[4] Electron deficient aldehydes are reactive under thermal reactions in the cycloaddition reaction with alkyl-substituted 1,3-dienes. As an example, chloral will react with simple 1,3-dienes to afford [4 + 2] adducts in reasonable yields.[5]

In 1974, Danishefsky and Kitahara discovered that 1- and 3-alkoxydiene derivates are more reactive than 1,3-butadiene itself in the HDA reaction.[6]

Additionally, the active diene introduces oxygen in the resultant product. Silyl enol ether, 1-methoxy-3-[(trimethylsilyl)oxy]butadiene (**1**), was synthesized from commercially available *trans*-4-methoxy-3-butene-2-one using trimethylchlorosilane in the presence of triethylamine-zinc chloride (Eq. 2).



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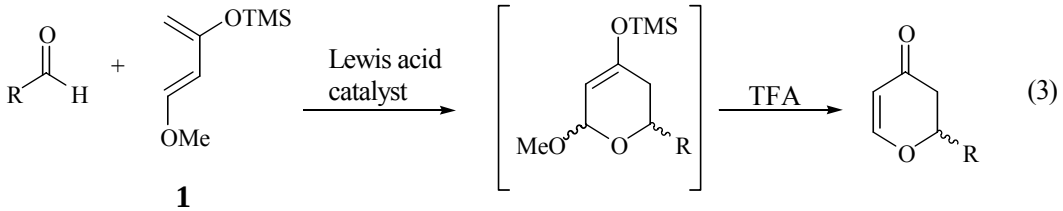
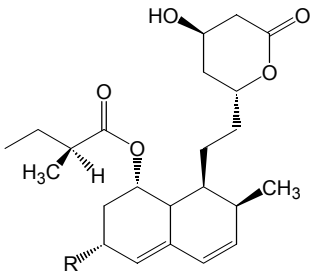


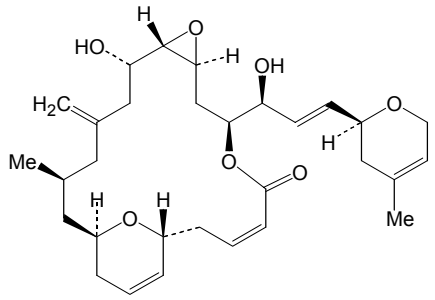
(3)

1

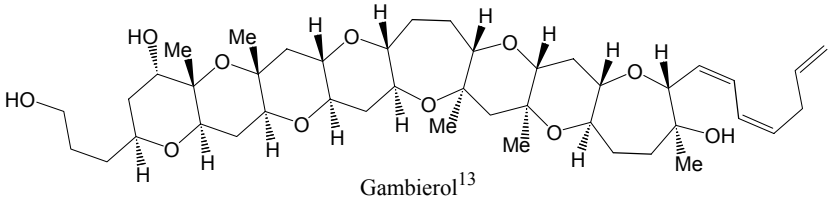
Subsequently, the catalytic enantioselective HDA reaction between aldehydes and diene **1** has became vital for the production of chiral, non-racemic dihydropyrans. (Eq. 3).[3, 9-11] Examples of their application are found in the synthesis of biologically active products with pharmaceutical interest (Scheme 1).[12-15] Included in those examples are compactin and mevinolin, potent inhibitors of sterol biosynthesis.



Compactin,[15] R = H
Mevinolin,[15] R = CH_3



Laulimalide[14]



Gambierol[13]

Scheme 1. Natural products which use a HDA reaction in the synthesis

Two basic strategies in controlling the absolute configuration of product formation in the HDA reaction are: (1) use of a diene or dienophile with an attached chiral auxiliary, and (2) use of a chiral catalyst. The former is more efficient and economic way to control enantioselectivity because it allows direct formation of chiral compounds from achiral substrates using mild conditions and requires only a substoichometric amount of chiral material. Enantioselectivity is obtained when a Lewis acid coordinates to the carbonyl oxygen activating the substrate and providing a chiral environment that forces the diene to approach from the less sterically hindered face.

Since, Danishefsky's initial report of cycloaddition reactions between aldehydes and **1** ("Danishefsky's diene"), catalyzed by Eu(hfc),[34] this transformation has been a standard for evaluating the enantiocontrol of chiral Lewis acid catalysts. Subsequently, several groups have developed other chiral Lewis acids for application in this reaction and will be discussed in more detail later in this chapter.[17-21] In these

reports high selectivity has often been achieved; however, a high catalyst loading leading to low turnover numbers (TON) is required in virtually all cases (TON $\leq$ 50).[7]

There are a few parameters that must be considered when using a chiral Lewis acid for the hetero-Diels-Alder cycloaddition. First, the substrate requires a certain level of reactivity. For example, the carbonyl dienophile should be able to coordinate to the Lewis acid to obtain sufficient reactivity. Second, the choice of metal and ligand is imperative for obtaining high selectivity and reactivity. Next, the Lewis acidity and the structural and electronic properties of the metal and the ligand are equally crucial for enantiocontrol. The ligands attached to the metals are selected to furnish the most effective Lewis acid. Generally, the chiral ligands attached to the metal contain oxygen as the coordinating atom, due to the oxophilicity of Lewis acids.[22]

The concept of activation by a Lewis acid as well as the mechanistic aspects must be understood to develop effective catalysts. The hetero-Diels-Alder reaction is a $HOMO_{diene}$ - $LUMO_{dienophile}$-controlled reaction that occurs between the electron-rich diene and electron deficient dienophile. For example, activation occurs when the lone pair of electrons of the carbonyl oxygen coordinates to the Lewis acid.[23,24] This coordination decreases the LUMO and HOMO energies of the aldehyde. Thus, the difference in energy between the HOMO of the diene and the LUMO of the aldehyde is reduced compared to that for the absence of the Lewis acid leading to better interaction with then diene and accounts for the activation by the Lewis acid (Figure 1).[23,24] Additionally, coordination of the Lewis acid increases the magnitude of the LUMO atomic orbital of the carbonyl, making it more susceptible to the diene. This

polarization may change the reaction pathway from a concerted non-synchronous mechanism to a stepwise mechanism (discussed later in this chapter).[22] The substituents on the reactants and the reaction conditions also effect the mechanism.[22]

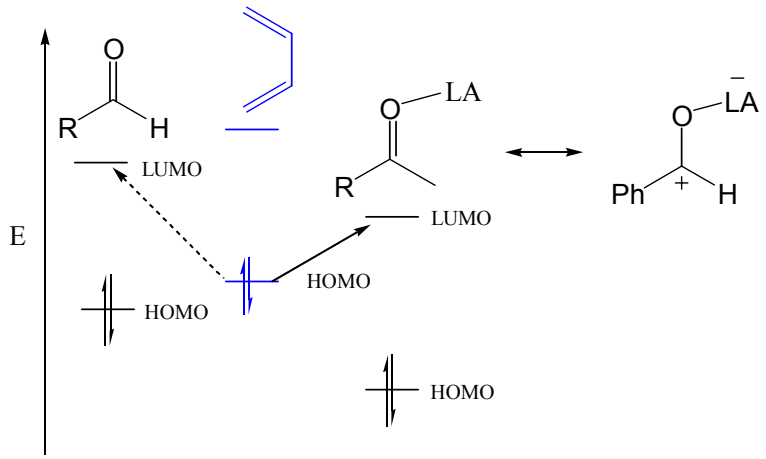


Figure 1. A frontier molecular orbital diagram of the hetero-Diels-Alder reaction in the presence and absence of a Lewis acid.

In the HDA reaction, the stereochemistry of the cycloadduct is dependent on the approach of the substrates during the transition state. For example, a reaction can proceed via an *endo* or *exo* transition state. *Endo* is a stereochemical descriptor in a bicyclic system of a substituent on a bridge that points toward the larger of the two remaining bridges. Lewis acid catalyzed reactions are *endo*-selective due to the preference of the Lewis acid being *exo* as a result of its size (Figure 2).[25] In addition, the Lewis acid and the R group of the carbonyl are proposed to be *trans* to one another.[26] Similarly, the uncatalyzed reaction of aldehydes and a diene demonstrate *endo*-selectivity for the carbonyl substiuent.[27]

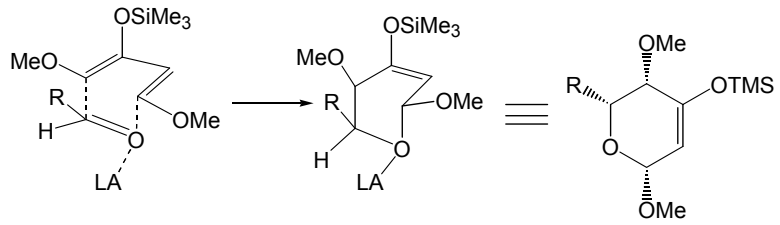


Figure 2. *Endo* selectivity is seen in the Lewis acid catalyzed HDA reaction because the solvated Lewis acid is exo, due to its size.

1.3 Mechanistic Pathways for the Hetero-Diels-Alder Reaction

There are two mechanistic pathways to consider for the hetero-Diels-Alder reaction: (1) a traditional Diels-Alder cycloaddition and (2) formation of the hetero-Diels-Alder adduct via a Mukaiyama-aldol reaction intermediate (Figure 3).[28] The reaction pathway is dependent on the Lewis acid applied. A brief overview of the Lewis acids and their mechanism will be provided.

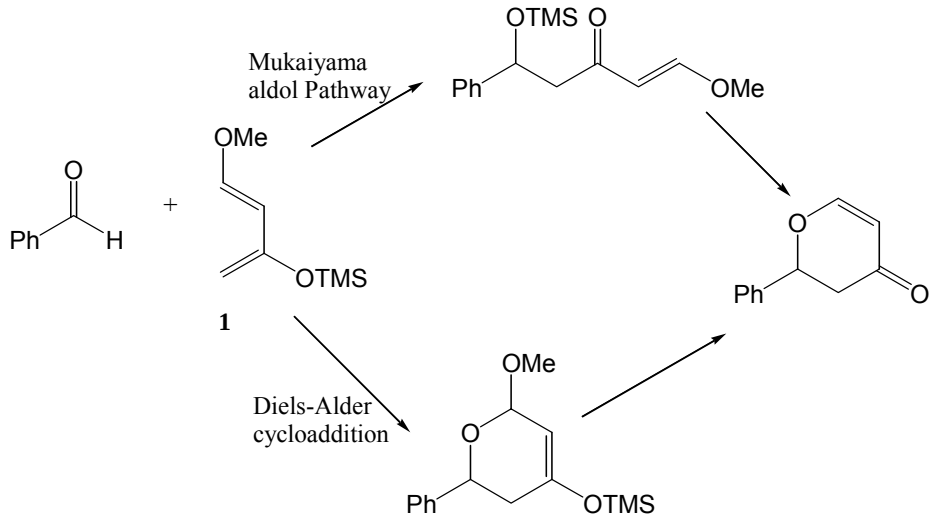
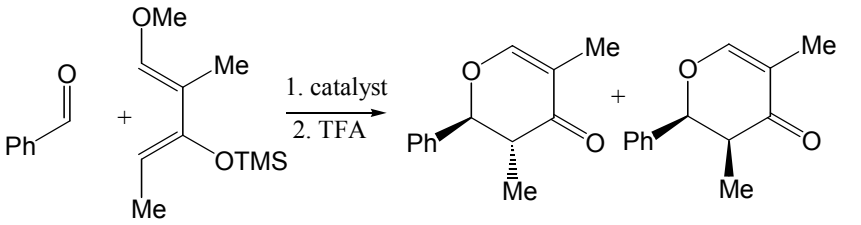


Figure 3. Two mechanistic pathways which can occur via a Lewis acid catalyzed hetero-Diels-Alder reaction

The Diels-Alder pathway occurs via a concerted [4 + 2] cycloaddition yielding a cyclic intermediate. Conversely, the Mukaiyama-aldol reaction pathway occurs via a

stepwise mechanism providing an acyclic intermediate. Upon treatment with trifluoroacetic acid (TFA) the corresponding dihydropyran is formed from both intermediates. Danishefsky and coworkers investigated the influence of different Lewis acids upon diastereoselectivity in reactions between benzaldehyde and 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene (**2**). When the reaction was performed in the presence of the classic Lewis acid BF_3, the reaction proceeded via a stepwise Mukaiyama-aldol pathway leading to dihydropyran products having low diastereoselectivity wherein the major product contained the 2,3-*trans* configuration. Conversely, when $ZnCl_2$ was used as the Lewis acid, the reaction occurred by a concerted [4 +2] cycloaddition providing the 2,3-*cis* product with high diastereoselectivity (Figure 4).[29]



2

Catalyst	*trans*-isomer	*cis*-isomer
BF_3	68	23
$ZnCl_2$	<2	78

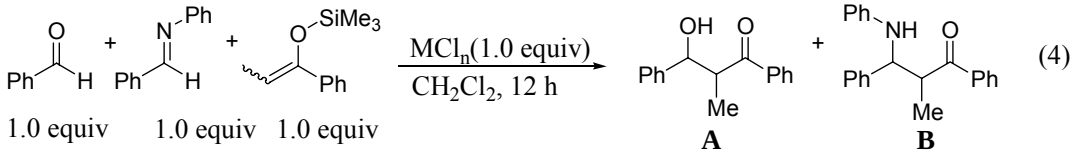
Figure 4. Different Lewis acids catalyze the reaction via two different mechanistic pathways.

While numerous theoretical studies have been undertaken for the Diels-Alder reaction, only a handful of theoretical studies have been investigated for the hetero-Diels-Alder reaction.[30-34] In one of those examples, the Houk laboratory reported that the transition state in the HDA reaction is unsymmetrical, and the C-C and C-O bond lengths were calculated to be 2.133 and 1.998 Å respectively (using *ab initio*

calculations) for the transition state in the reaction between formaldehyde and 1,3-butadiene.[31,32] When the oxygen atom of formaldehyde is coordinated to BH_3 (where BH_3 is *exo*) the transition state is less symmetrical than when the Lewis acid is absent. Specifically, the forming C-C bond length is 0.42 Å longer, while the forming C-O bond length is 0.23 Å shorter than when BH_3 is absent. Additionally, coordination of BH_3 to the carbonyl oxygen resulted in a highly charged transition state wherein a partial positive charge of + 0.37 resides on the diene and a negative charge of –0.65 is present on the formaldehyde oxygen. As a result, the carbonyl group becomes an acceptor of negative charge in the presence of the Lewis acid, and during the transition state, the O-B bond becomes shorter giving rise to a tighter complexation. Finally, Houk determined that the activation energy for the reaction between formaldehyde and 1,3-butadiene is 8.9 kcal mol^{-1}, which is 12.0 kcal mol^{-1} lower in energy than the uncatalyzed reaction.

1.4 Lewis Acidity

Various Lewis acids have been employed in the HDA reaction and many have been chosen based on experimental trial and error. Therefore, understanding Lewis acids on the basis of activity toward their reaction with aldehydes and imines was investigated by Kobayashi and coworkers.[35] As a model for their studies, benzaldehyde, *N*-benzylideneaniline, and silyl enol ether were reacted in the presence of one equivalent of a metal chloride (Eq. 4). After 12 hours, the reaction mixture was quenched and products **A** and **B** were isolated and the yield of each determined.



(4)

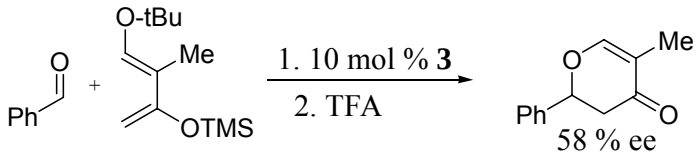
Subsequently, based on the results, the metals were classified as active, weak or inactive for the activation of the aldehyde and/or aldimine. In addition, the groups were divided into aldehyde-selective, aldimine-selective, and neutral. For example, a few of the metal chlorides that were classified as active and aldehyde-selective were: BCl_3, $TiCl_4$, $ZrCl_4$, $GaCl_3$, and $AlCl_3$. Furthermore, Lewis acids that proceeded sluggishly (even at room temperature) were: $CrCl_3$, $RhCl_3$, $MnCl_2$, and VCl_3.

The authors assert that strong Lewis acids didn't necessarily promote reactions smoothly and that observed selectivity (aldehyde or aldimine selectivity) was dependent on the Lewis acid employed. In conjunction with Kobayashi, Cozzi and coworkers reported a deleterious effect (decrease in diastereo- and enantioselectivity) was observed when strong Lewis acids were present in the catalytic enantioselective reaction for the addition of allyl organometallic reagents to aldehydes. However, the presence of weak Lewis acids drives the stereochemistry of the reaction toward a high level of enantio- and diasterocontrol.[36]

1.5 Lanthanide Chiral Lewis Acids for the Hetero-Diels-Alder Reaction

In the early 1980's Danishefsky was the first to recognize that lanthanides, then used mainly as chiral shift reagents in NMR spectroscopy, can be applied as chiral Lewis acids for the HDA reaction with activated dienes.[16] For example, benzaldehyde was reacted with an activated conjugated diene in the prescence of $Eu(hfc)_3$ [Eu = europium, hfc = 3-(heptafluoropropylhydroxymethylene)camphorate]

affording the product in 58 % enantiomeric excess (ee) (Eq. 5). The reaction provided superior results when performed in the absence of solvent and at a reduced temperature.



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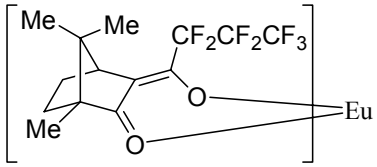

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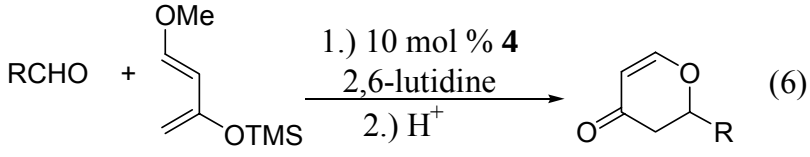
An additional lanthanide metal that has been used as a Lewis acid is ytterbium (Yb). Inanaga and coworkers demonstrated that 10 mol % of ytterbium tris-(*R*)-(-)-1,1'-binaphthyl-2,2'-diyl phosphate (Yb[(*R*)-(-)BNP]$_3$) (**4**) can catalyze the HDA reaction of various aromatic aldehydes in the presence of 2,6-lutidine to give products in 65-93 % ee with moderate to good yields at room temperature (Eq. 6).[37] The addition of one equivalent of 2,6-lutidine to the reaction mixture was necessary to achieve a homogeneous catalyst system.



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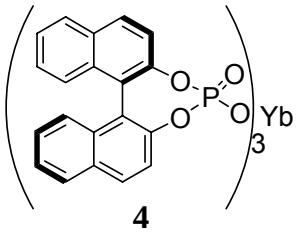
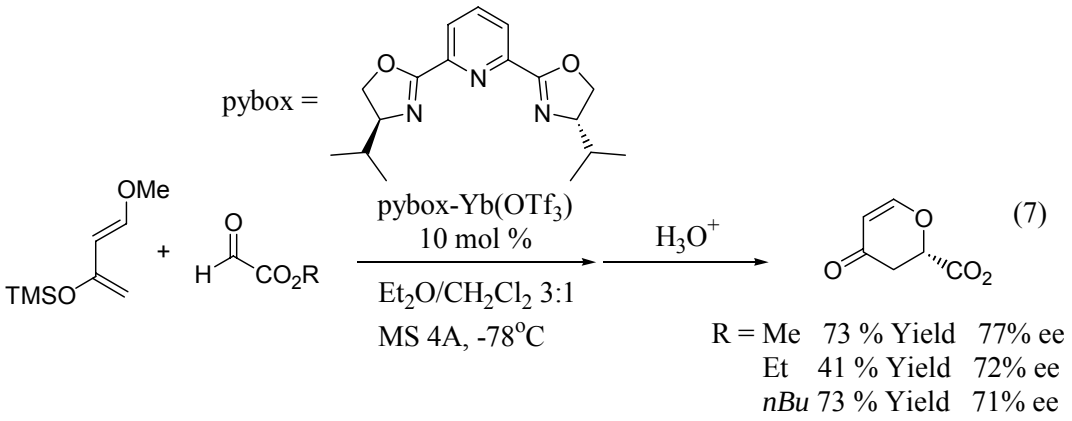


4

Qian and Wang performed the asymmetric HDA reactions of glyoxylate esters and **1** catalyzed by various chiral bis(oxazoline)-lanthanide complexes.[38] The authors determined that the ytterbium triflate/*i*Pr-pybox (equimolar amount) complex was the best catalyst for the reaction (Eq. 7). Elevated levels of enantiocontrol and improved yields were obtained by slow addition of the diene to the less sterically demanding methyl glyoxylate. After the reaction mixture was quenched a 1:1 mixture of Mukaiyama aldol product to pyranone product was obtained.



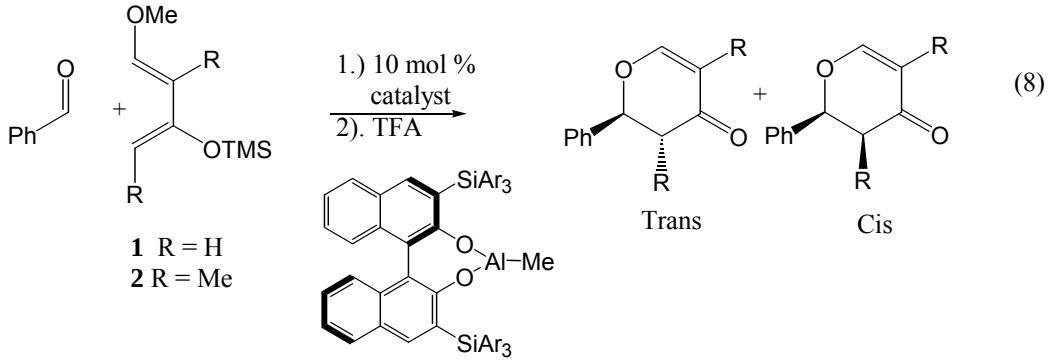
(7)

R = Me 73 % Yield 77% ee
Et 41 % Yield 72% ee
nBu 73 % Yield 71% ee

Inanaga and Furuno developed derivatives of the BNP (**4**) ligand and used them in conjunction with other rare earth organophosphates to give products with excellent enantioselectivities (up to 99 % ee).[39,40] The first example of remarkably high asymmetric amplification (positive nonlinear effect) was observed during the reaction in the metal ion-chiral ligand 1:3 catalytic systerm.[39, 41] Subsequently, Inanaga developed cerium(III)-(*R*)-BNP, which is derived from CAN (cerium ammonium nitrate) and (*R*)-BNP-Na, as a storable chiral Lewis acid for the HDA reaction.[42] Reactions were performed using 10 mol % catalyst to access aromatic dihydropyran products in enantiomeric excess ranging from 80-94 % ee and 46-96 % yield.

1.6 Aluminum Chiral Catalysts

Yamamoto and coworkers reported the first reliable and efficient aluminum Lewis acid catalyzed hetero-Diels-Alder reaction.[19,43] The Yamamoto group discovered that (R)-BINOL-AlMe complexes (**5**) were effective Lewis acids for the HDA of unactivated aldehydes with dienes **1** and **2**. Catalyst **5** was generated from $AlMe_3$ and optically pure (*R*)-(+)-3,3'-bis(triarylsilyl)binaphthol.



1 R = H
2 R = Me

(R)-**5**
a. Ar = Ph
b. Ar = 3,5-xylyl

(8)

Diene	Catalyst	Yield %[a]	% ee
1	(R)-4a	71	67
1	(R)-4b	81	81
2	(R)–4a	77 (7)	86
2	(R)–4b	90 (3)	97

[a] Yield in parentheses refers to *trans* isomer

In Yamamoto's study, the major product was found to be the *cis* dihydropyran derived from diene **2** and benzaldehyde (Eq. 8). High yields of 71-90 % and selectivities up to 97 % ee using 10 mol % catalyst loadings were reported. Nonpolar solvents, such as toluene, afforded superior enantioselectivities. In addition, the authors state that the bulky aryl moieties on the silicon ligands provided higher yields and enantioselectivities as a result of a sterically hindered catalyst-aldehyde complex.

The aldehyde in this complex is readily liberated, thereby relieving the steric repulsion and regenerating the catalyst.

The use of BINOL-AlMe catalysts of the type shown in Figure 5 have the possibility to form hypercoordinated aluminum complexes.[20] Wherein the ether oxygen present in the ligand is capable of coordinating to the metal and affecting the enantioselectivity. A trend becomes evident for the ligands in Figure 5. As the steric bulk of the alkoxy group increases (**B** vs. **C**) the % yield and % ee increase.

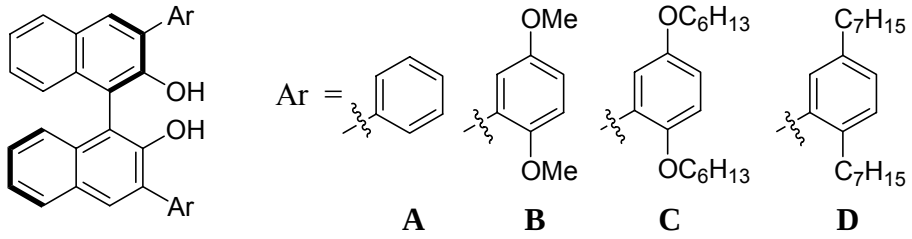


Figure 5. BINOL ligand derivates

The mechanism of the HDA reaction between benzaldehyde and Danishefsky's diene catalyzed by $(MeO)_2AlMe$ and (S)-BINOL-AlMe was determined to proceed via a Mukaiyama-aldol intermediate using semiempirical calculations.[44] First, the catalyst activates benzaldehyde making the carbon atom of the carbonyl more electrophilic. This is followed by nucleophilic attack by the activated diene to the carbonyl carbon, with a transition-state energy of up to 13 kcal mol^{-1} depending on the catalyst and calculation method (Figure 6). A short-lived intermediate is present in which the cationic charge of the diene is stabilized by the oxygen atom of the chiral catalyst (bottom of Figure 6). Secondly ring closure occurs with a significantly lower transition-state energy that leads to the dihydropyran product. The transition states and intermediates for the $(MeO)_2AlMe$ and (S)-BINOL-AlMe catalyzed reactions are similar using both semi-empirical and *ab initio*

calculations. The uncatalyzed reaction proceeds as a concerted reaction with an unsymmetrical transition state with an energy of 27 kcal mol^{-1}.

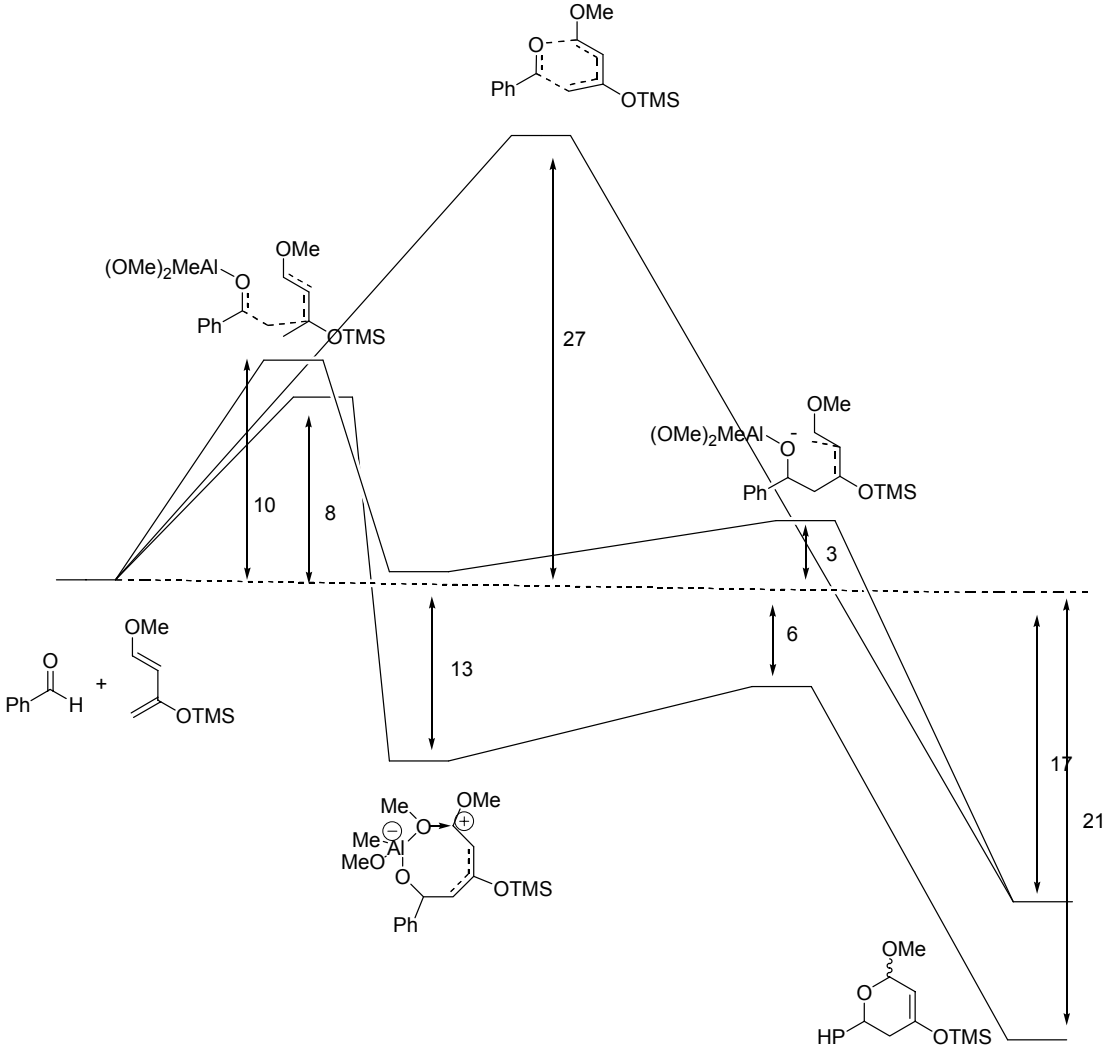
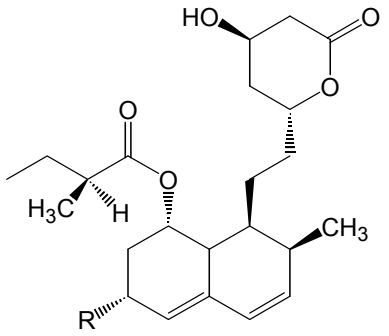


Figure 6.[44] Schematic representation of the energy change for the uncatalyzed HDA reaction and the $(MeO)_2AlMe$ catalyzed reaction of benzaldehyde and **1**. The upper is the results obtained using AM1 calculations and the lower curve is the results found using ab initio calculations.

1.7 Chiral Titanium Complexes

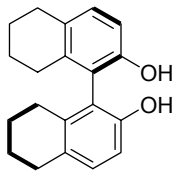
In 1995, Keck and coworkers established that titanium-BINOL complexes can efficiently catalyze the HDA reaction of various aldehydes and Danishefsky diene with ee's up to 97 % using 10 mol % catalyst.[15] Higher selectivities were achieved

with the catalyst generated from (*S*)- or (*R*)-BINOL and Ti(O*i*Pr)$_4$ in a 2:1 ratio in comparison to the catalyst formed in a 1:1 ratio. The authors report that the reaction proceeds via a Mukaiyama-aldol pathway, which was cyclized after treatment with TFA. In addition, using benzyloxyacetaldehyde as the substrate the resulting product was a precursor for biologically active compounds, compactin and mevinolin (**6** and **7**).

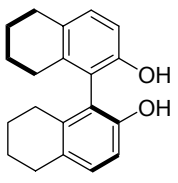


6 Compactin, R = H
7 Mevinolin, R = CH_3

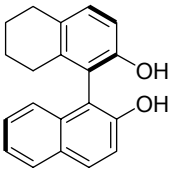
Jiang and coworkers introduced a new titanium(IV) catalyst with a chiral H_8-BINOL ligand (**8**) as Lewis acid for the HDA reaction. [45] The 2,3-dihyrdro-4H-pyran-4-one was produced with ee's of up to 99 % under mild reaction conditions using 20 mol % catalyst. The optimized reaction conditions include using a 1.1 equivalent of **8** to 1.0 equivalent titanium(IV) in toluene at reaction temperatures ranging from 0 and 14^{o}C. Furthermore, decreasing the catalyst loading to 10 mol % considerably reduced the enantioselectivity of the reaction.



8 (R)-H_8-BINOL

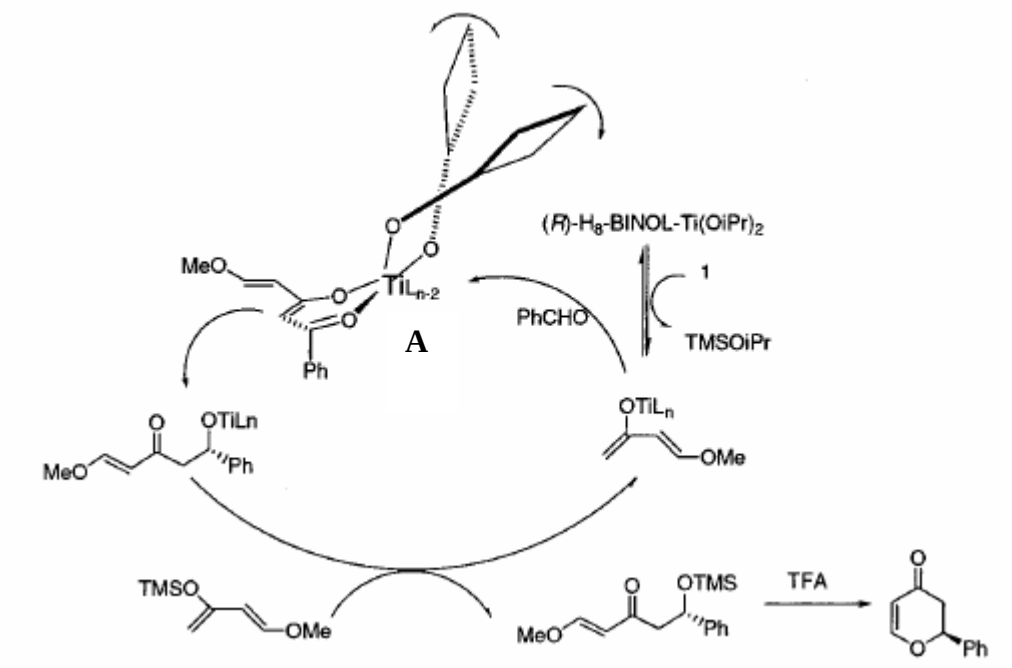


8 (S)-H_8-BINOL



9 (R)-H_4-BINOL

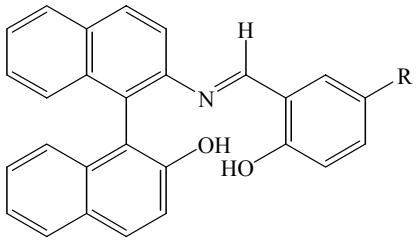
Subsequently in 2002, an extensive study was reported by Feng and Jiang using Ti(IV)-H_8-BINOL complexes as Lewis acids.[46] A range of ligands and Lewis acids was examined, and the authors determined that the Ti(IV)-H_8-BINOL complex is a very effective catalyst for the HDA reaction, leading to products with very high enantioselectivities and yields. The (*R)*-H_4-BINOL (**9**) and (*R)*-H_8-BINOL (**8**) ligands exhibited remarkably enhanced enantiocontrol and reaction rate. This is attributed to a greater steric hindrance of the hydrogen atoms attached to the sp^3 carbon compared to the sp^2 carbon on the naphthalene rings. The dihedral angle of the axial biaryl group in BINOL is crucial for high enantiocontrol and yield in the catalytic system. Ti(IV)-H_8-BINOL (20 mol %) catalyzed the reactions between aromatic aldehydes and **1** with enantioselectivities up to 99 % ee and in good yields. Interestingly, a molar ratio of 1:2 ($Ti(OiPr)_4$: (*R)*-H_8-BINOL) afforded the lowest levels of enantioselectivity. Additionally, the presence of 4 Å molecular sieves increased the product yield, though no affect on enantioselectivity was observed. The mechanism of the reaction occurs via a Mukaiyama aldol adduct which is obtained through a six-membered cyclic transition state (**A**) wherein the diene is linked to the Ti-(*R*)-H_8-BINOL by the C-3 oxygen and the oxygen atom of the aldehyde is associated to the metal (Scheme 2).



Scheme 2. Proposed mechanism of the Ti(IV)-H_8-BINOL catalyzed HDA reaction.

Ding and coworkers have also contributed to the field using titanium(IV) in conjunction with various BINOL ligands for the enantioselective HDA reaction which they reported in 2002.[47] High-throughput screening, with a combinatorial library of 104 chiral titanium complexes, allowed for highly enantioselective catalysts to be developed. Dihydropyrone heterocycles were formed using as little as 0.1-0.005 mol % of **8**/Ti/**9** or **9**/Ti/**9** catalysts. Reactions were performed at room temperature under solvent and molecular sieve free conditions leading to products in quantitative yields and up to 99.8 % ee. At a catalyst loading of 0.005 mol % the product from furfural and Danishefsky's diene was formed in 63 % yield and 96.3 % ee (after 144 hours). This is the lowest reported catalyst loading for a Lewis acid catalyzed asymmetric reaction but the report occurred a year after our report of low catalyst loading (down to 0.01 mol %). Ding also mentions that the reaction mechanism for the catalysis of the **8**/Ti/**9** or **9**/Ti/**9** systems remains unclear.

In 2002 Ding and coworkers reported the effect of additives on the titanium catalyzed HDA reaction.[48,49] The Ding group discovered that both achiral and chiral carboxylic acid additives increased the enantioselectivities of the dihydropyran products catalyzed by tridentate titanium catalysts derived from ligand **9** and Ti(O*i*Pr)$_4$.



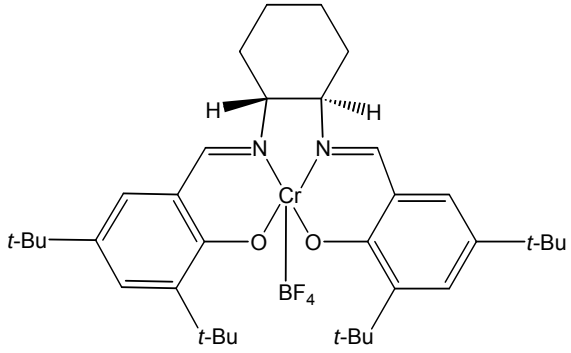
10 R = H, F, or I

Furthermore, the catalytic system exhibits a positive nonlinear effect. As an additive, Naproxen ((*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acd) was found to be particularly effective giving the HDA products up to 97% ee and quantitative yields. Reactions were carried out in the presence of 10 mol % of a 2.0/1.0/0.5 mixture of ligand/Ti(O*i*Pr)$_4$/Naproxen. Ding and coworkers report the mechanism discerned from the crude reaction mixture, before treatment with TFA, revealed that the cyclic intermediate was formed exclusively supporting the concerted [4 + 2] cycloaddition mechanism.

1.8 Chiral Chromium Complexes as Lewis Acids in the HDA Reaction

Catalyst (**11**) provides HDA adducts in good yields and enantioselectivities as shown by Jacobsen and coworkers in 1998.[17] The catalyst promotes the reaction of various aldehydes containing aromatic, aliphatic, and conjugated substituents and Danishefsky's diene with a catalyst loading of 2 mol %.[17] The highest selectivities

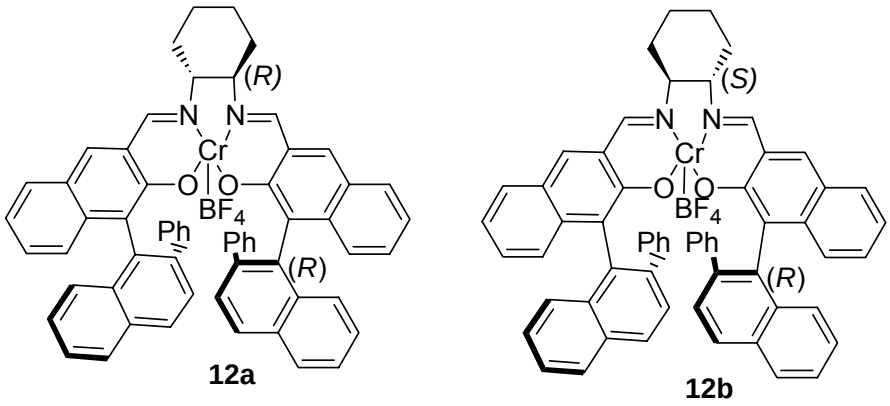
were found with cyclohexanecarboxaldehyde (93 % ee, 71 % yield). Conversely, hexanal provided the lowest selectivity (62 % ee). Molecular sieves (4 Å) proved to be beneficial and provided increased yields and enantioselectivity's. The ^{1}H NMR spectra of the crude reaction mixture before treatment with TFA revealed the cyclic HDA adduct was present. In addition, the Mukaiyama aldol adduct was prepared independently and subjected to the reaction conditions in the presence of the chromium(III) salen catalyst, and no detectable HDA adduct could be observed. The results offer credence that the mechanism occurs via a [4 + 2]-HDA cycloaddition reaction pathway.



11

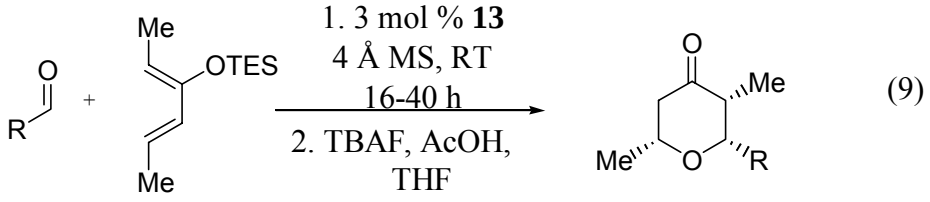
Katsuki and coworkers established that second-generation salen-chromium(III) complexes **12** that bear binaphthyl subunits as a chiral auxiliary can effectively catalyze the reaction between **1** and various aromatic and aliphatic aldehydes with enantioselectivites up to 97 % ee and good yields (88-99 %) using 2.5 mol % catalyst.[50] Before treatment with TFA, ^{1}H NMR analysis reveled that the primary product was the silylated cycloadduct, similar to that found by Jacobsen.[17] Katsuki and coworkers report that second-generation metallosalen complexes can adopt a *cis*-β-structure when a chelating substrate coexists in the reaction mixture.[51]

For example, (*R*,*R*)-(salen)-chromium(III) **12a** will catalyze the reaction of simple aldehydes, while (*R*,*S*)-(salen)-chromium(III) **12b** complexes can better catalyze the reaction of aldehydes bearing a precoordinating group such as $–OCH_3$ or –OBn.



Subsequently, in 1999 the Jacobsen group developed tridentate Schiff base chromium(III) complex (**13**) that has the ability to achieve high enantioselectivities with a broad scope of HDA reactions.[52] Complex **13** can catalyze the reaction between unactivated aldehydes and less nucleophilic dienes (bearing less than two oxygen substituents) with high diastereo- (greater than 95 %) and enantioselectivity using 3 mol % catalyst (Eq. 9). The adamantyl-substituted catalyst afforded superior results with both aliphantic and aromatic aldehydes. Moreover, the hexafluorantimonate catalyst **13a** resulted in faster and more selective reactions (generally >90 % ee), and proceeded without solvent compared to the chloride catalyst **13b**. By IR spectroscopy no measurable complexation between catalyst **13a** and the aldehydes used in the study could be detected, indicating the mild Lewis acidity of the catalyst. Additionally, catalyst **13b** can effectively control the diastereoselectivity of reactions between various chiral aldehydes and **1** with

diastereomeric ratios up to 1:33 (*trans* : *cis*) when 5 mol % of catalyst is employed.[53] The products are formed in yields ranging from 44-99 % at 4°C in ethyl acetate with BaO as the desiccant.



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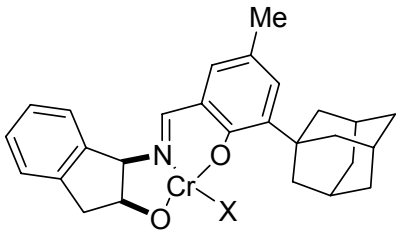
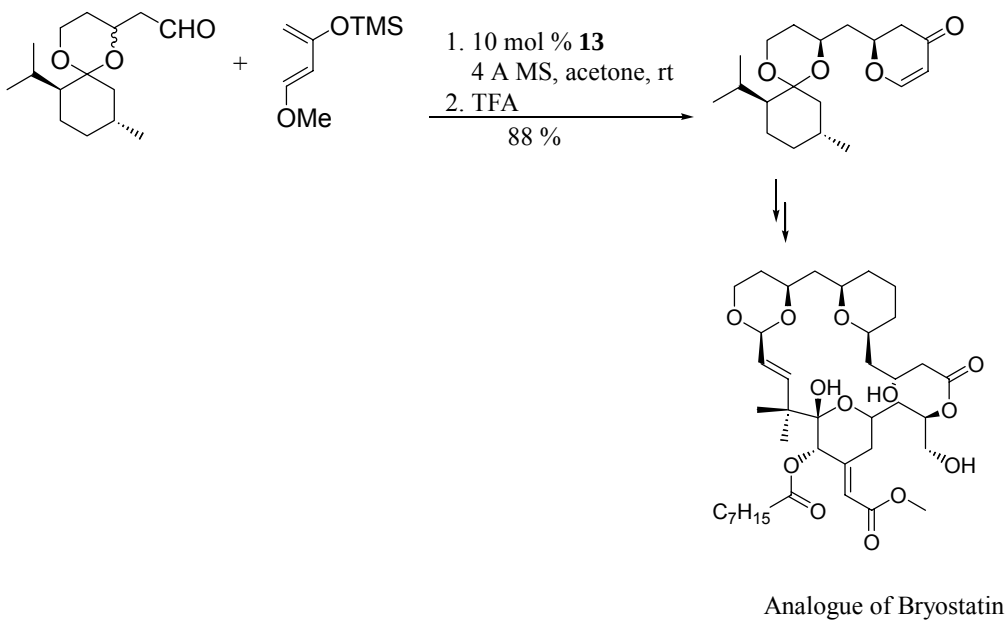


13aX=SbF_6
13b X=Cl

The application of Jacobsen's tridentate chromium(III) catalyst **13** is nicely showcased in the synthesis of a highly potent analogue of Bryostatin, which is a natural product with unique biological activities.[54] The HDA reaction proceeded in good yield and high diastereocontrol (33:1) (Scheme 3). The analogue is over 100-fold more potent than bryostatin at inhibiting the growth of numerous human cancer cell lines.



Analogue of Bryostatin

Scheme 3. Synthesis of a potent analogue of bryostatin

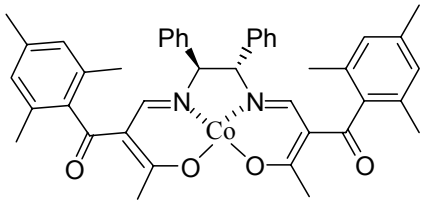
1.9 Zinc as a Chiral Lewis Acid

Since the first HDA reaction between benzaldehyde and **1** promoted by $ZnCl_2$,[55] there have been few reports on the use of a chiral zinc catalyst for the HDA cycloaddition. Ding and coworkers reported that 10 mol % of a (*R*)-3,3'-dibromo-1,1'-bi-2-napthol ligand with Et_2Zn yields products from aromatic aldehydes in 82-99 % yields and 89-98 % ee's.[56] From a BINOL derivative ligand screening it was clear that the enantioslectivity and reactivity of the HDA reaction were influenced by both the electronic influence and steric hindrance of the substituents a the 3,3'-positions of BINOL. High levels of enantiocontrol were found when the reactions were performed at -25°C in toluene. The mechanism for this catalytic system is still under investigation.

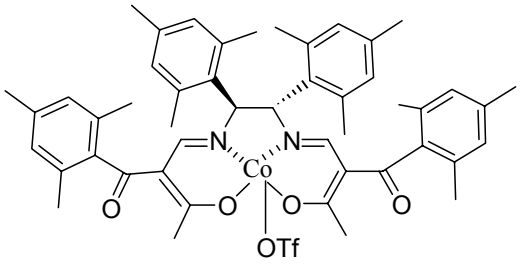
Ding has also demonstrated the ability of a single catalyst to promote two distinct reactions in one pot. For example, the zinc catalyst was used in conjunction with a diimine activator for the enantioselective catalysis of a HDA reaction and diethylzinc addition in one pot.[57] The reaction takes place with high stereoselectivity for both the HDA reaction and diethylzinc addition to aldehydes,

1.10 Cobalt Catalysts as Lewis Acids for the HDA Cycloaddition

Optically active cobalt**(**II) catalysts bearing aldiminato ligands (**14a**) have been shown by Yamada to catalyze the reaction between 1-methoxy-[3-(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene and ortho-substituted arylaldehydes.[58] Regardless of the amount of catalyst used (0.5-10 mol %) the yield and enantiomeric excess of the products remained virtually unchanged (80-96 % yields and 57-62 % ee). However, lower catalyst loadings led to longer reaction times.



14a



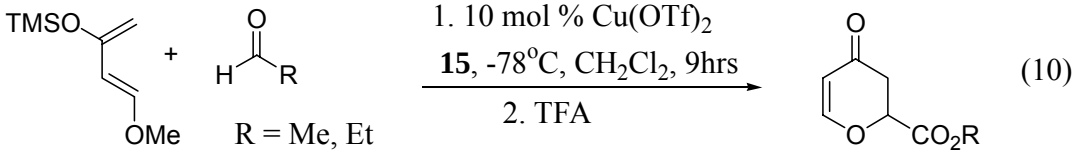
14b

Subsequently, Yamada further increased the catalytic activity of his cobalt catalyst by making the complex cationic and therefore more Lewis acidic. The corresponding optically active cationic cobalt(III) triflate complexes (**14b)** was developed and was able to effectively catalyze the reaction between 1-methoxy-[3-(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene and *p*-nitrobenzaldehyde in 94 % yield and 94 % ee using 5 mol % catalyst.[59] The scope of the reaction could be furthered

extended to include aliphatic aldehydes.[60] As an example, the reaction between 1-methoxy-[3-(*tert*-butyldimethylsilyl)oxy]-1,3-butadiene and octanal catalyzed by 8 mol % of **14b** affords the HDA product in 88 % ee and 89 % yield after 96 hours in DCM at -78°C.

1.11 Copper(II) Catalysts

The reaction of **1** with glyoxylate esters can be catalyzed by 10 mol % bisoxazoline copper(II) complexes affording products in up to 72 % ee and 70 % yield (Eq. 10).[61] After the reaction was quenched, a mixture of Mukaiyama aldol product and pyranone was observed. The observed enantioselectivity's of the HDA adducts are rationalized by a square planar complex of the glyoxalate ester with the Cu(II) catalyst and addition of the activated diene from the less hindered site of the carbonyl group.



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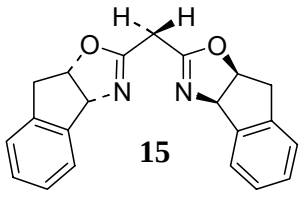
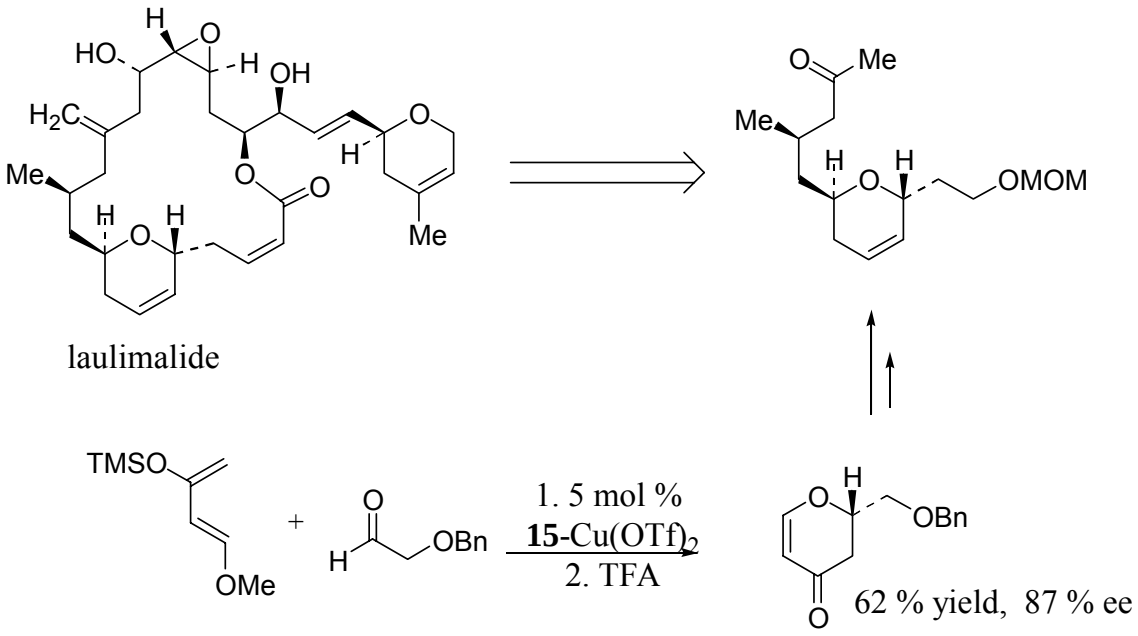


15

The methodology in Eq. 10 was applied in the synthesis of the antitumor agent laulimalide.[14] The constrained catalyst complex derived from $Cu(OTf)_2$ and **15** afforded the dihydropyran precursor in 87 % ee (Scheme 4). The C_3-C_{14} segment of the novel antitumor agent was then synthesized using a Ferrier rearrangement and asymmetric conjugate addition as the key steps.



.**Scheme 4.** Formation of the C_3-C_{14} segment of laulimalide

1.12 Summary

In summary, the hetero-Diels Alder reaction has been developed for the synthesis of synthetically useful dihydropyrans which are precursors to biologically active molecules. Uncatalyzed hetero-Diels-Alder reactions require high temperatures or pressures to proceed. However, in the presence of a Lewis acid the HDA reactions can take place under mild conditions. Another advantage of utilizing a chiral Lewis acid is the ability to generate chiral products from achiral substrates using a substoichiometric amount of chiral material.

Two mechanistic pathways are possible in the Lewis acid catalyzed HDA cycloaddition. The reaction can take place via a concerted (Diels-Alder) or stepwise mechanism (Mukaiyama aldol) depending on the Lewis acid employed. Catalysts, zinc chloride and chromium(III)-salen complex promote the reaction via a concerted 4 + 2 cycloaddition. Conversely the Lewis acids that promote the HDA via a

Mukaiyama aldol adduct include: ytterbium-pybox, aluminum-binol, titanium-binol, and copper(II)-bisoxazoline.

A variety of metals such as Eu, Ti, Yb, Cr, Zn, Co, Al etc. have been used as Lewis acids in the reaction between unactivated aldehydes and diene **1**. These catalytic systems have been applied in the natural product synthesis of biologically active compounds. Many of the early reported Lewis acid catalysts required catalyst loadings ranging between 5-10 mol %. However, loading as low as 0.005 mol % have been utilized effectively.

While there has been advancement made in the asymmetric catalysis of the hetero-Diels-Alder reaction, continued investigation is still underway to develop catalysts which are (1) selective for a broad scope of both aliphatic and aromatic aldehydes, (2) effective at low catalyst loadings, and (3) recyclable/reusable. The field also lacks information regarding the exact nature of activation of the Lewis acid toward the aldehyde. Additionally no information has been described with regard to the kinetic and mechanistic details of the reaction.

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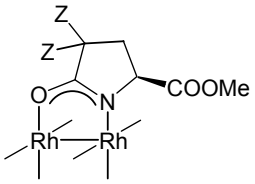
Chapter 2: Dirhodium(II) Catalyzed Hetero-Diels-Alder Reaction

2.1 Introduction

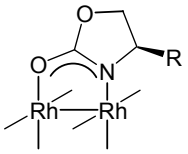
In 2000, the Doyle laboratory began to question if dirhodium(II) carboxamidates **1**-**5** could be successfully utilized as Lewis acids in the hetero-Diels-Alder reaction. There were challenges to be met for the Lewis acid catalyzed asymmetric hetero-Diels-Alder reaction. For instance, few examples of reactions with turnover numbers greater than 50 have been reported, which make their application impractical except on a laboratory scale. We wanted to develop chiral dirhodium(II) carboxamidate catalysts as effective Lewis acids for the hetero-Diels-Alder reaction wherein the criteria of our success in this program included (1) high turnover numbers, (2) high enantioselectivities, and (3) high product yields.

The use of dirhodium(II) carboxamidates (**1**-**5**) as Lewis acids, was inspired by our understanding of several key factors. First, dirhodium(II) carboxamidates posses the ability to coordinate with Lewis bases such as acetonitrile. For example, acetonitrile coordinates to dirhodium(II) with an equilibrium constant of about 100.[1,2] The first equilibrium constant (coordination of acetonitrile to one rhodium center) is larger than the second equilibrium constant (coordination of a second acetonitrile to the catalyst). Secondly, dirhodium(II) catalysts are 16-electron systems (without axial ligands) and exhibit only monodentate coordination with Lewis bases, unlike copper(II)[3] that has the ability to form bidendate complexes. Finally, the weak

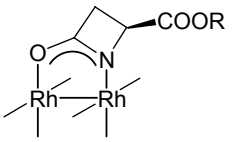
coordination ability of chiral dirhodium(II) carboxamidates with Lewis bases, may be one reason why high turnover numbers are possible.



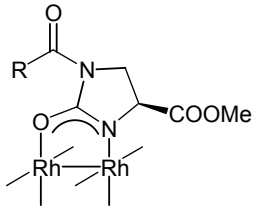
1a Rh_2(5*S*-MEPY)$_4$, Z = H
1b Rh_2(5*S*-dFMEPY)$_4$, Z = F



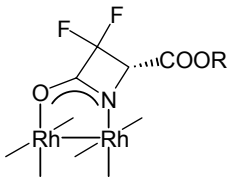
2a Rh_2(4*S*-MEOX)$_4$, R=CO_2Me
2b Rh_2(4*R*-IPOX)$_4$, R=^{I}Pr



3a Rh_2(4*S*-MEAZ)$_4$, R=Me
3b Rh_2(4*S*-IBAZ)$_4$, R=^{i}Bu
3c Rh_2(4*S*-CHAZ)$_4$, R=$^{C}C_6H_{11}$



4a Rh_2(4*S*-MPPIM)$_4$, R=CH_2CH_2Ph
4b Rh_2(4*S*-MACIM)$_4$, R=Me



5a Rh_2(4*R*-dFIBAZ)$_4$, R=^{i}Bu
5bRh_2(4*R*-dFCHAZ)$_4$, R=$^{C}C_6H_{11}$

Each catalyst has a paddlewheel structural motif defined by four bridging carboxamidate ligands about a Rh_2^{4+} core with, preferentially, two nitrogens and two oxygens bound to each rhodium, and the two nitrogens (or oxygens) *cis* to each other (Figure 1). With acetonitrile or benzonitrile coordinated in the axial positions, these air stable complexes typically crystallize as red solids. This *cis*-2,2 conformation is apparent in the crystal structure for Rh_2(4*S*-MPPIM)$_4$ (Figure 2).

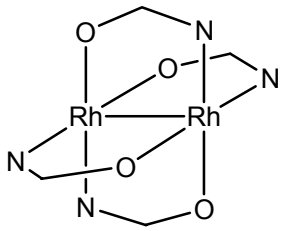


Figure 1. Typical paddlewheel arrangement for dirhodium(II) carboxamidates.

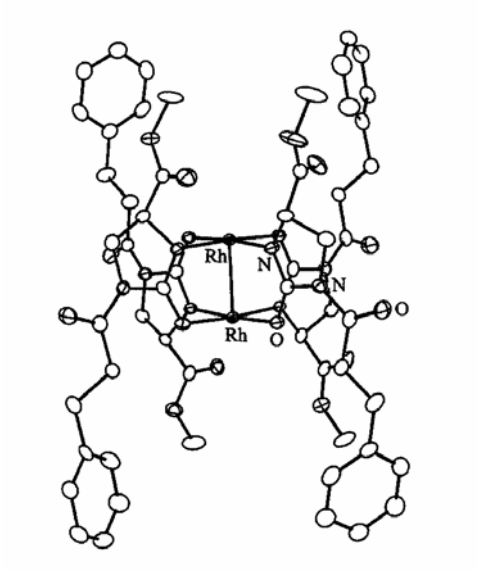
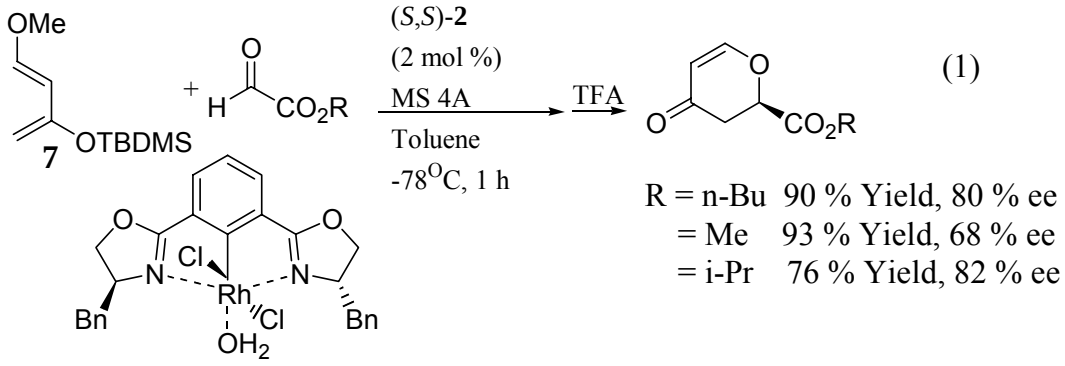


Figure 2. The structure of $Rh_2(4S\text{-MPPIM})_4$ with axial CH_3CN molecules removed.

This chapter will focus predominately on our efforts to employ dirhodium(II) carboxamidates as effective chiral catalysts for asymmetric hetero-Diels-Alder cycloaddition reactions. Optimization of reaction conditions will be explored to achieve high selectivities for a broad range of aromatic aldehydes. Notably, selectivities greater than 90 % ee have been achieved for many aromatic aldehydes using a little as 0.01 mol % catalyst. In addition, the mechanism of the dirhodium(II) catalyzed HDA reaction was studied in great detail and will be discussed. Lastly, included is a discussion of the use of aliphatic aldehydes as dienophiles and their reactivity.

2.2 Background

Employing rhodium catalysts as Lewis acids for organic transformations is not uncommon.[4] However, there are few reports in the literature describing the use of rhodium complexes as Lewis acids in the hetero-Diels-Alder reaction. These reports describe the use of a rhodium(III) and a dirhodium(II) complexes as Lewis acids.



6

In 2001, Nishiyama and coworkers utilized chiral bis(oxazolinyl)phenyl-rhodium(III) aqua complex **6** in the asymmetric HDA reaction of diene **7**, a *tert*-butyldimethylsilyl (TBDMS)-derived diene, and a range of glyoxylates (Eq. 1).[5] Use of the trimethylsilyl-(TMS)-substituted diene led to decomposition of the diene and production of a trace amount of product. Increasing the steric bulk of the ester substituent (R) on the dienophile increased the enantiomeric excess. For example, the enantioselectivity of the reaction with methyl glyoxylate was 68 % ee, which is much lower compared to *iso*-propyl glyoxylate (82 % ee). Interestingly, use of the bulky *iso*-propyl glyoxylate decreased the chemical yield in comparison to methyl glyoxylate (76 % vs. 93 %). The dibromide and difluoride complexes analogous to **6** showed activity similar to the dichloride complex; however, the difluoride complex exhibited slightly higher enantiocontrol (84 % ee vs. 80 % ee). The ^{1}H NMR spectra of the crude reaction mixture revealed no acyclic intermediates. As a result, the Nishiyama laboratory reports the pathway of the HDA reaction catalyzed by **6** proceeds via a concerted [4 + 2] cycloaddition mechanism.

Also in 2001, the Doyle laboratory reported that dirhodium(II) carboxamidates **1-5** catalyze the reaction of Danishefsky's diene with *p*-

nitrobenzaldehyde using as little as 0.01 mol % catalyst (Eq. 2).[6] Typical Lewis acid catalyst loadings reported for the HDA reaction at that time ranged from 2-10 mol %. Dirhodium(II) carboxamidates **1-5** were screened for their selectivity in the reaction given in Equation 2 and the results are given in Table 1.

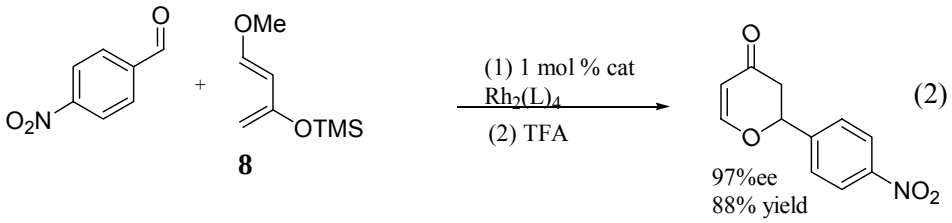


Table 1. Enantioselectivity in catalytic cycloaddition of *p*-nitrobenzaldehyde to Danishefsky diene after 24 hours at room temperature in DCM using 1.0 mol % catalyst.

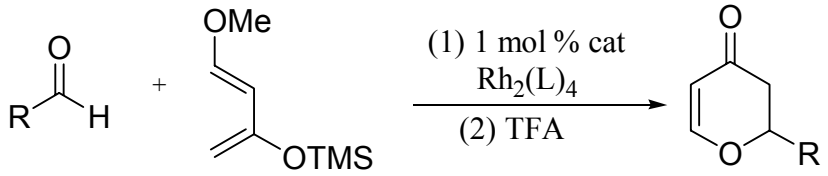
Catalyst	Yield, %	ee, %
Rh_2(5*R*-MEPY)$_4$	53	73
Rh_2(5*S*-dFMEPY)$_4$	53	78
Rh_2(4*S*-MEAZ)$_4$	63	56
Rh_2(4*S*-IBAZ)$_4$	62	66
Rh_2(4*R*-dFIBAZ)$_4$	68	70
Rh_2(4*S*-CHAZ)$_4$	54	61
Rh_2(4*S*-dFCHAZ)$_4$	98	76
Rh_2(4*S*-MACIM)$_4$	76	74
Rh_2(4*S*-MPPIM)$_4$	82	95

Notably, the highest level of enantiocontrol was achieved with Rh_2(4*S*-MPPIM)$_4$ (82 % yield, 95 % ee) and enantioselectivities of the HDA products catalyzed by other dirhodium(II) catalysts range from 56-78 % ee. Conversely, low enantiocontrol was seen with Rh_2(4*S*-MEAZ)$_4$ which provided the HDA adduct in 63 % yield and 56 % ee.

The scope of the HDA reaction with **8** catalyzed by Rh_2(4*R*-dFIBAZ)$_4$ (**5a**) and Rh_2(4*S*-MPPIM)$_4$ (**4a**) was investigated (Table 2). A significant electronic

influence on enantiocontrol is seen from the data of the substituted benzaldehydes. For example, the enantioselectivity increases with increasing electron withdrawing ability from the *para*-substituent. Consequently, enantiomeric excesses beyond 88 % are obtained with aldehyde dienophiles containing electron withdrawing nitro-groups and moderate selectivity was seen with other aldehydes [18-70 % ee using Rh_2(4*R*-dFIBAZ)$_4$].

Table 2. HDA reactions of representative aldehydes with Danishefsky diene.



8

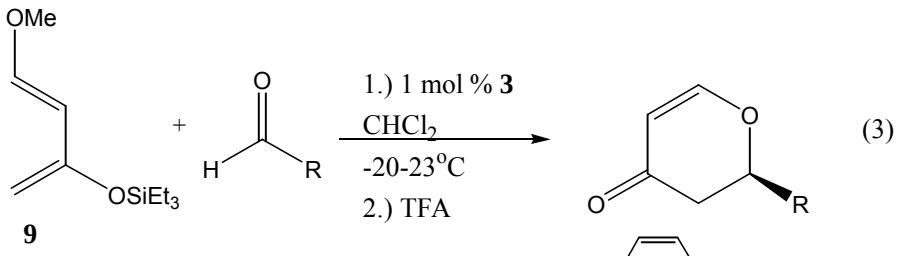
Aldehyde	Catalyst	Yield, %	ee, %
p-$NO_2C_6H_4CHO$	Rh_2(4*R*-dFIBAZ)$_4$	68	70
p-ClC_6H_4CHO	Rh_2(4*R*-dFIBAZ)$_4$	86[a]	65
C_6H_5CHO	Rh_2(4*R*-dFIBAZ)$_4$	50[a,b]	65
p-$MeOC_6H_4CHO$	Rh_2(4*R*-dFIBAZ)$_4$	27[a,b]	18
trans-*p*-$NO_2C_6H_4CH$=CHCHO	Rh_2(4*R*-dFIBAZ)$_4$	33	68
	Rh_2(4*S*-MPPIM)$_4$	41[a]	89
EtOOCCHO	Rh_2(4*R*-dFIBAZ)$_4$	43	54
	Rh_2(4*S*-MPPIM)$_4$	83[a]	10
5-nitrofurancarboxaldehyde	Rh_2(4*R*-dFIBAZ)$_4$	78[a]	80
	Rh_2(4*S*-MPPIM)$_4$	48[a]	93
5-nitrothiophenecarboxaldehyde	Rh_2(4*R*-dFIBAZ)$_4$	98[a]	85
	Rh_2(4*S*-MPPIM)$_4$	81[a]	94

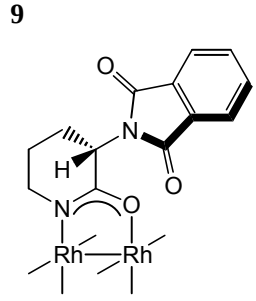
[a] Five molar excess aldehyde was used. [b] Reaction was carried out in refluxing DCM

Initial studies in the Doyle laboratory indicated that chiral dirhodium(II) carboxamidates are viable Lewis acids for the asymmetric HDA reaction. Dirhodium(II) carboxamidate catalysts do not have the same restrictions for catalyst turnover that are common with previously reported Lewis acid catalysts. Rh_2(4*S*-MPPIM)$_4$ (**4a**) catalyzes the reaction between *p*-nitrobenzaldehyde and Danishefsky's

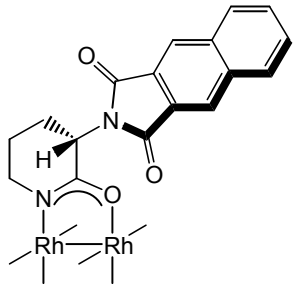
diene with substrate to catalyst ratios (S/C) of up to 10,000; however, a decrease in % ee is seen as the S/C ratio is increased. Further optimization was required to broaden the substrate scope, and decrease the catalyst loading without diminishing the yield or enantioselectivity of the cycloadduct.

Recently in 2004, Hashimoto and coworkers reported that air-stable dirhodium(II) carboxamidate complexes **10,** are effective Lewis acids in the enantioselective HDA reaction of 1-methoxy-3-[(triethylsilyl)oxy]-1,3-butadiene (**9**) and a broad scope of aldehydes leading to products in >90 % ee and good yields (Eq. 3).[7] The ^{1}H NMR spectrum of the crude reaction between *p*-nitrobenzaldehyde and Danishefsky's diene obtained without the use of TFA revealed the exclusive formation of the 2,6-*cis*-dihydropyran, lending evidence that the reaction proceeds *via* a [4+2] mechanism. Aromatic aldehydes including benzaldehyde, *p*-anisaldehyde, and furfural afforded the corresponding dihydropyrans in high yields and with asymmetric induction as high as those found with electron poor *p*-nitrobenzaldehyde. However, aldehydes containing electron donating *para* substituents required longer times to reach completion. In addition, phenylpropargylaldehyde dramatically accelerated the reaction leading to shorter reaction times. The Hashimoto group proposed that the steric interaction between the acetylenic moiety and the phthalimido group protruding toward the rhodium-aldehyde adduct is less severe than the steric interaction with an aromatic ring.





10a Rh_2(*S*-BPTPI)$_4$

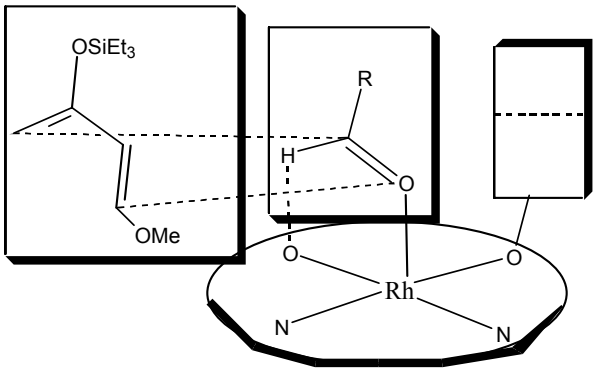


10b Rh_2(*S*-BPTPI)$_4$

Catalyst **10** promoted the HDA cycloaddition smoothly with catalyst loadings of 1.0 mol %. Additionally, Hashimoto reports one example for each HDA reaction promoted with 0.0075, 0.005, and 0.002 mol % catalyst. However, longer reaction times were required at lower catalyst loadings (64 hours for 0.002 mol %).

The stereochemical outcome of the reaction was explained by the Hashimoto laboratory using model **A** shown in Figure 3. In the model, the approach of the diene is from the *endo* mode to avoid intrusion into the rhodium framework. A formyl C-H···O hydrogen bond between the aldehyde C-H and the carboxamidate oxygen atom that is bound to rhodium, a concept proposed by Corey and coworkers, is thought to be favorable.[38] For example, Corey describes that coplanarity of the formyl group and the metal-X subunit to which it is bound in a five membered ring effectively restricts rotation about the donor-acceptor bound between the formyl oxygen and the metal center of the Lewis acid, thus creating an additional organizing element in these complexes.[8] Additionally, this explains the preference of dirhodium(II) carboxamidate catalysts over carboxylate catalysts. For example, the carboxylate

catalysts contain four oxygen atoms bound to rhodium leading to four sets of formyl C-H···O hydrogen bonding interactions possible. Each interaction leads to a competing diastereomeric transition state which lowers enantiomeric excess.



A

Figure 3. Stereochemical model for the aldehyde catalyst-complex

2.3 Optimization of Reaction Conditions

Rh_2(4*S*-MPPIM)$_4$ (**4a**) catalyzed the HDA reaction between *p*-nitrobenzaldehyde and **8** with the highest level of enantiocontrol at room temperature. We were interested in optimizing the reaction conditions for other dirhodium(II) carboxamidate catalysts. Increasing the reaction temperature to 60^{o}C allows for a number of dirhodium(II) catalysts to be used with higher levels of enantiocontrol and higher % yields in comparison to when the reactions are performed at room temperature (Table 3). For example, an increase in the enantioselectivity is observed with Rh_2(5*R*-MEPY)$_4$, Rh_2(5*S*-dFMEPY)$_4$, and Rh_2(*S*-DOSP)$_4$ as the temperature increases. Conversely, the azetidinone based ligands (MEAZ, IBAZ, CHAZ) and Rh_2(4*S*-MPPIM)$_4$ show a decrease in enantiocontrol with increasing reaction

temperature. This phenomenon will be discussed later and can be explained with respect to the competing uncatalyzed background reaction (Chapter 4).

Table 3. Enantioselectivity in catalytic cycloaddition of *p*-nitrobenzaldehyde to Danishefsky diene[a]

Catalyst	yield, %[b]	ee, %[c]
Rh_2(5*R*-MEPY)$_4$	90	88
Rh_2(5*S*-dFMEPY)$_4$	80	90
Rh_2(4*S*-MEAZ)$_4$	84	53
Rh_2(4*S*-IBAZ)$_4$	84	59
Rh_2(4*S*-CHAZ)$_4$	92	53
Rh_2(4*S*-MPPIM)$_4$	95	92
Rh_2(*S*-DOSP)$_4$	94	50

[a] The reactions were carried out at 60°C for 24 hours, with one mol % catalyst using 1 equivalent of aldehyde to 1.2 equivalents of Danishefsky's diene. Treatment with TFA after 24 hours, followed by column chromatography afforded the corresponding dihydropyran. [b] Determined by HPLC using a Chiralpak OD column. [c] Isolated yield after chromatography.

Further efforts were explored to optimize the dirhodium(II) carboxamidate catalyzed HDA reaction (Table 4). For example, increasing the catalyst loading in the reaction from 1 mol % to 10 mol % did not afford any advantage with respect to enantiomeric excess in the reaction between *p*-nitrobenzaldehyde and **8** catalyzed by **1a**. However, at higher catalyst loadings the conversion to HDA adducts was increased and the amount of dihydropyran formed increased (11 % yield with 1 mol % catalyst versus 64 % yield with 10 mol % catalyst after 2 hours). Longer reaction times (60 h) were required to achieve high yields (79 % yield) at 1 mol % of **1a**.

Table 4. Optimization of reaction conditions between *p*-nitrobenzaldehyde and Danishefsky's diene.[a]

catalyst	loading (mol %)	solvent	time (h)	% yield[b]	% ee[c]
Rh_2(S-MEPY)$_4$	1.0	DCM	1.5	11	72
Rh_2(S-MEPY)$_4$	1.0	DCM	60	79	72
Rh_2(S-MEPY)$_4$	10.0	DCM	2	64	70
Rh_2(S-MEOX)$_4$	1.0	DCM	24	82	86
Rh_2(S-MEOX)$_4$	1.0	Acetone	24	24	59
Rh_2(S-MEOX)$_4$	1.0	Nitromethane	24	<10	33
Rh_2(S-MEOX)$_4$	1.0	THF	24	54	92
Rh_2(S-MEOX)$_4$	1.0	THF/DCM	24	62	90

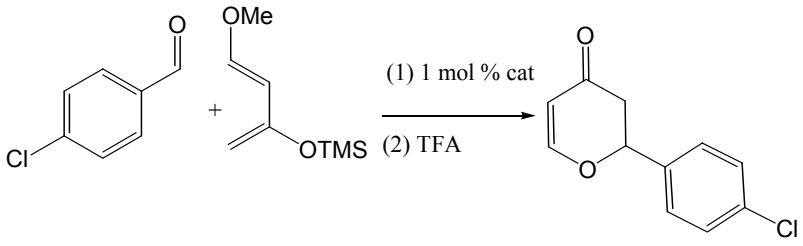
[a] The reactions were carried out at room temperature for the designated time, with the catalyst loading shown, using 1 equivalent of aldehyde to 1.2 equivalents of Danishefsky's diene. Treatment with TFA, followed by column chromatography afforded the corresponding dihydropyran. [b] Isolated yield after chromatography. [c] Determined by HPLC using a Chiralpak OD column (% ee ± 1).

A solvent influence is evident in the HDA reaction between **8** and *p*-nitrobenzaldehyde catalyzed by **2a** (Table 4). For example, reactions conducted in dichloromethane (DCM) generated products in superior yields and selectivities compared to acetone and nitromethane. Additionally, tetrahydrofuran (THF) afforded the dihydropyran in slightly higher enantiomeric excesses in comparison to DCM; however, a lower yield is observed (82 % yield for DCM vs 54 % yield for THF). Furthermore, we observed an increase in the yield is when a 1:5 mixture of THF:DCM was employed (62 % yield); nonetheless, DCM remained the choice solvent giving the products in the highest yield and high selectivity.

Our initial investigations of HDA reactions promoted by dirhodium(II) (at room temperature) demonstrated a significant electronic influence on enantiocontrol. Additionally, reactions carried out at room temperature gave moderate to low selectivities and yields with the exception of *p*-nitrobenzaldehyde. Our efforts focused on optimizing the reaction conditions in order to expand the scope of aromatic aldehydes beyond nitro-substituted aldehydes. The reaction of *p*-chlorobenzaldehyde and Danishefsky's diene was chosen to optimize the reaction

conditions (Table 5). Two catalysts, Rh_2(*R*-MPPIM)$_4$ (**4a**), and Rh_2(*S*-MEOX)$_4$ (**2a**) were examined. Catalyst **2a**, in contrast to **4a**, results in lower selectivities for the HDA reaction at all temperatures shown. Interestingly, the selectivity increased as the reaction temperature increased for both the Rh_2(*R*-MPPIM)$_4$, and Rh_2(*S*-MEOX)$_4$ catalyzed reactions. For example, at 27^{o}C the dihydropyran is formed in 87% ee and 60% yield when using Rh_2(*R*-MPPIM)$_4$ as the catalyst. However, when the temperature is increased to 40^{o}C, the enantiomeric excess and yield of the product increased to 91% ee and 86% yield respectively. Increasing the temperature further to 60^{o}C, increased the % yield slightly (90 %) without markedly affecting the enantioselectivity. Similarly, with **2a** both the yield and the enantioselectivity increased with increasing reaction temperature.

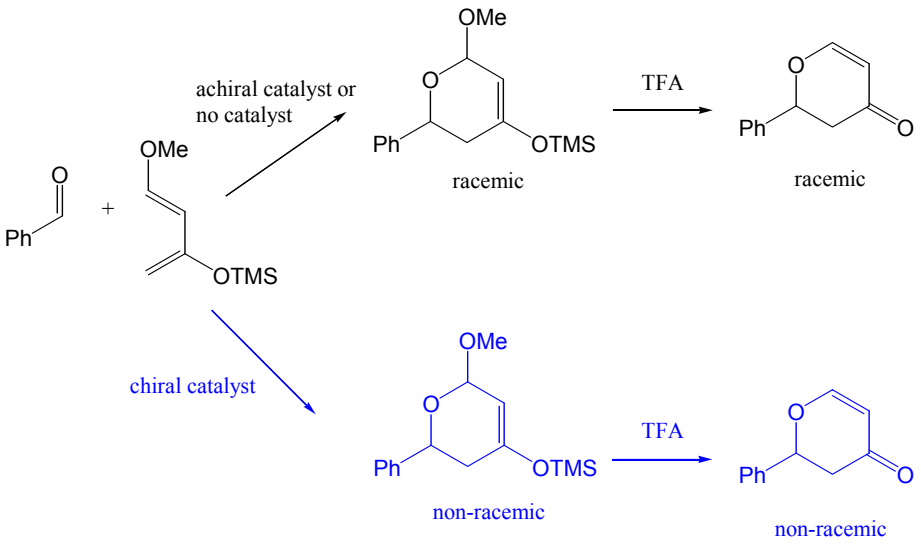
Table 5. Reactions with Danishefsky's diene and *p*-chlorobenzaldehyde[a]



catalyst	Temperature (^{o}C)	% ee[b]	% yield[c]
Rh_2(R-MPPIM)$_4$	27	87	60
Rh_2(S-MPPIM)$_4$	40	91	86
Rh_2(S-MPPIM)$_4$	60	91	90
Rh_2(S-MEOX)$_4$	27	76	75
Rh_2(S-MEOX)$_4$	40	81	81
Rh_2(S-MEOX)$_4$	60	87	88

[a] The reactions were carried out at the designated temperature for 24 hours, with one mol % catalyst using 1 equivalent of aldehyde to 1.2 equivalents of **1**. Treatment with TFA after 24 hours, followed by column chromatography afforded the corresponding dihydropyran. [b] Determined by HPLC using a Chiralpak OD column (% ee ± 1). [c] Isolated yield after chromatography.

Lewis acid catalyzed HDA reactions are generally conducted at lower temperatures ranging from -78°C to 0°C to obtain higher levels of enantiocontrol by suppressing the background reaction (Chapter one). The influence of temperature on the enantioselectivity in the dirhodium(II) catalyzed HDA reaction is explained using Scheme 1. As the temperature increases, the rate of the chiral catalyzed pathway which forms non-racemic products, is greater compared to the rate of the un-catalyzed pathway (background reaction) which leads to racemic products, thereby furnishing higher enantioselectivities for the reaction. This phenomenon is further illustrated with other aromatic aldehydes (Figure 4) wherein an increase in enantioselectivity is observed as the reaction temperatures increases from 40 to 60°C. This occurrence is described in more detail via a kinetic analysis (Chapter 3).



Scheme 1. Two competing reaction pathways in the HDA reaction

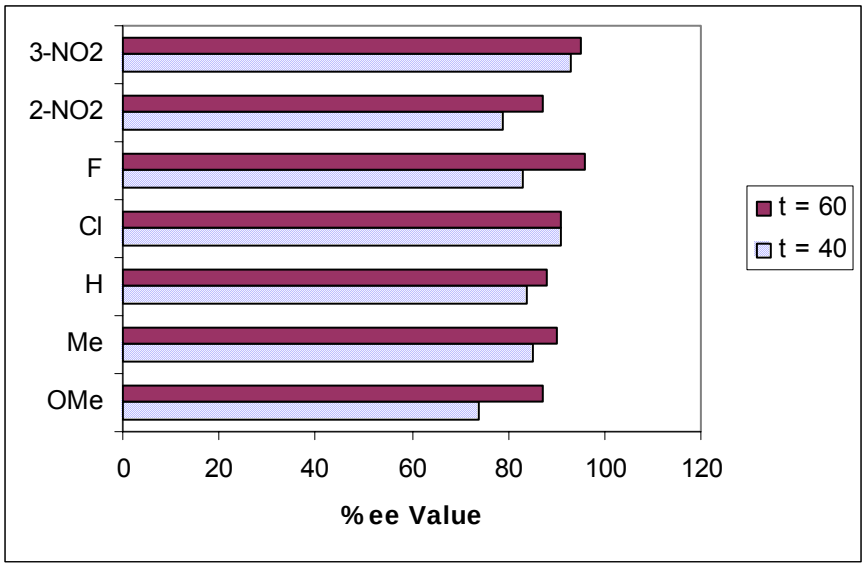


Figure 4. Effect of the reaction temperature on enantioselectivity at 40 and 60°C for a range of aromatic aldehydes.

Notably, others have reported a similar inverse ee/T°C correlation. For example, this relationship has been observed in reactions such as the enantioselective cobalt catalyzed homo Diels-Alder reaction,[9] asymmetric protonation of enolic species,[10] oxazaborolidine-mediated borane reduction of prochiral ketones,[11] and the enantioselective arylation of aldehydes catalyzed by 2-piperidino-1,1,2-triphenylethanol.[12] All attribute this phenomena to the isoinversion principle which was described by Buschmann, Scharf, Hoffmann, and Esser in 1991 and was developed on the basis of Eyring's theory.[13,14] The principle asserts that the enantiomeric excess increases with increasing temperature until a maximum enantioselectivity is observed and from that point either raising or lowering the temperature has deleterious effect on the reaction selectivity (Figure 5a).[12] When a chemical process shows two distinct linear regions for enantioselectivity in the Eyring graph (plot of ln [R/S] as a function of 1/T), the temperature at which the transition from one linear region to the other linear region occurs is called the inversion

temperature. An example of an Eyring graph for the asymmetric protonation of an enolic species is shown in Figure 5b.[10] The inversion temperature is critical for determining the optimal reaction conditions to achieve high enantiocontrol for a catalytic system.

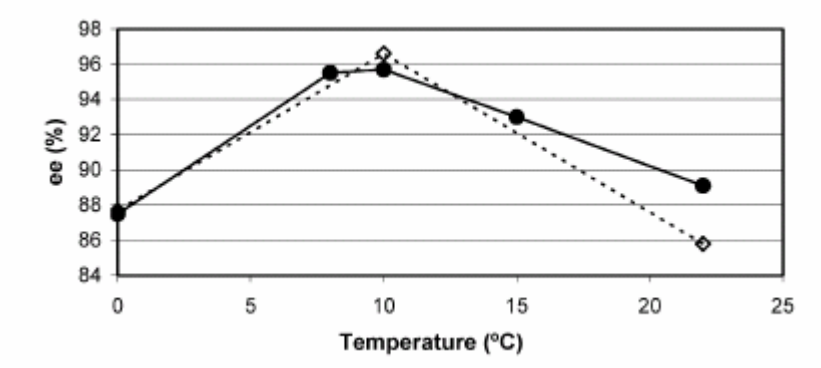


Figure 5a. Example of inversion temperature[12]

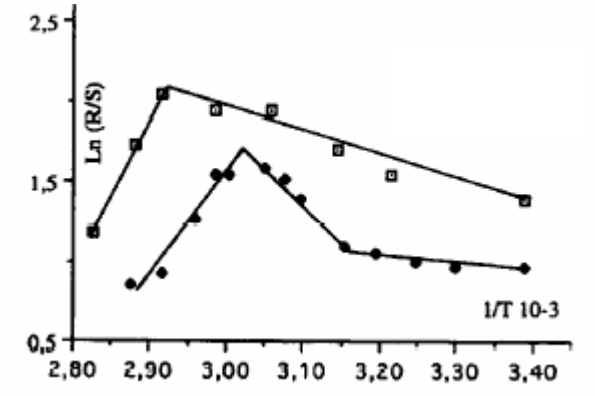


Figure 5b. Example of an Eyring diagram for asymmetric protonation[10]

Dirhodium(II) carboxamidate catalyzed HDA reactions exhibit behavior that can be rationalized according to the isoinversion principle. The influence of reaction temperature on the enantiomeric excess for the reaction between *p*-chlorobenzaldehyde and Danishefsky's diene catalyzed by Rh_2(S-MEOX)$_4$ is exemplified in Figure 6. Increasing the temperature for *para*-substituted aldehydes other than *p*-nitrobenzaldehyde from 25 to 60°C increases the enantioselectivity.

Conversely, increasing the reaction temperature for *p*-nitrobenzaldehyde from 25 to 60°C, leads to a decrease in enantiocontrol from 97 % ee to 92 % ee. Increasing the temperature over 80°C, however, does have a deleterious effect on the quality of the catalyst due to displacement of the chiral ligand over time.[15] Consequently, the inversion temperature for the dirhodium(II) catalyzed HDA reaction would be difficult to determine above 80°C.

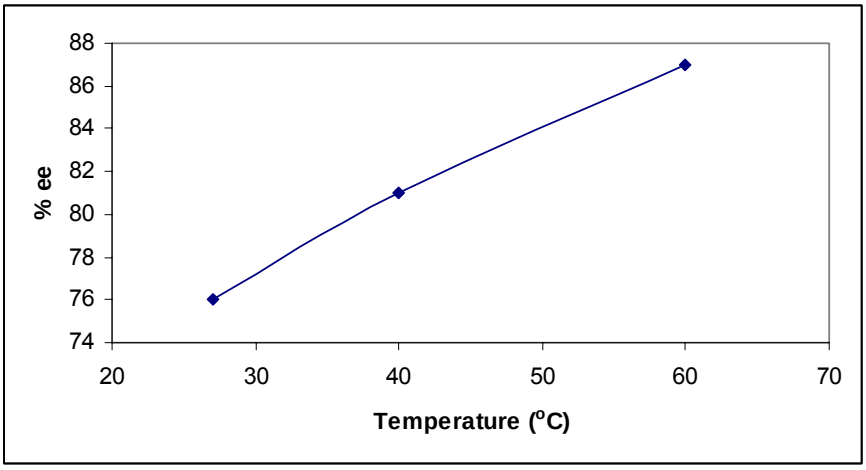


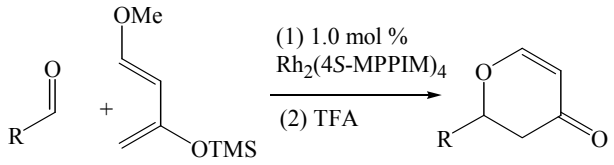
Figure 6. Influence of reaction temperature on the enantiomeric excess for the HDA cycloaddition of *p*-chlorobenzaldehyde and Danishefsky's diene catalyzed by Rh_2(S-MEOX)$_4$

2.4 Aromatic Aldehydes as Dienophiles

Rh_2(4*S*-MPPIM)$_4$ catalyst gave the highest level of enantiocontrol with nitro-substituted aromatic aldehydes. However, selectivity and reactivity were poor for less reactive aromatic aldehydes. After optimization of the reaction conditions with *p*-chlorobenzaldehyde, we discovered that higher temperatures increase the amount of dihydropyran formed without markedly affecting enantioselectivity. Subsequently, enantioselectivities as high as 98 % ee were achieved, using only 1.0 mol % catalyst (at 60°C), with a broad range of aromatic aldehydes and Danishefsky's diene (Table

6). Notably, reactions were carried out under solvent-free and desiccant-free conditions, which is ideal for environmental safety and volumetric productivities.[16]

Table 6. Hetero-Diels-Alder reactions of aromatic aldehydes with Danishefsky diene catalyzed by Rh_2(4*S*-MPPIM)$_4$ [a]



time (days)	temperature (^oC)	R =	% ee[b]	% yield[c]
6	60	*p*-$MeOC_6H_4$	93	47
5	60	*p*-$CH_3C_6H_4$	90	82
2	60	C_6H_5	93	91
1	60	*p*-ClC_6H_4	91	90
1	60	*p*-$CF_3C_6H_4$	92	88
1	40	*p*-$CF_3C_6H_4$	90	86
4	60	*p*-FC_6H_4	96	82
1	60	*p*-$NO_2C_6H_4$[d]	92	95
1	23	*p*-$NO_2C_6H_4$[d]	97	88
2	60	*o*-$NO_2C_6H_4$	84	87
3	60	*m*-$NO_2C_6H_4$	95	66
6	60	2-naphthyl	98	90
6	60	1-naphthyl	88	38
5	60	furfural	84	88

[a] Reactions were carried out at the given temperature under solvent-free conditions, unless stated otherwise, with 1.0 mol % catalyst using 1.0 equivalent of aldehyde to 1.2 equivalents of Danishefsky's diene. Treatment with TFA, followed by column chromatography afforded the corresponding dihydropyran. [b] Determined by HPLC using a Chiralpak OD column (% ee ± 1). [c] Isolated yield after chromatography. [d] Reaction was carried out in 0.5mL of dry DCM.

Enantioselectivities of 90 % or greater were achieved with all *para*-substituted aromatic aldehydes in moderate to good isolated yields. When the nitro group is at the *ortho* position the enantioselectivity decreased in comparison to the *para* position. In addition, the enantioselectivity of *meta*-nitrobenzaldehyde remains high for the formation of the corresponding cyclo-adduct. Benzaldehyde afforded the corresponding dihydropyran in 93 % ee and 91 % yield, while the product from the

more sterically hindered 1-naphthaldehyde was provided in lower enantiomeric excess (88% ee and 38% yield). Furthermore, a steric interaction with the catalyst-aldehyde complex and the diene is apparent when comparing the difference in % ee between the bulkier 1-naphthylaldehyde (88% ee) versus 2-naphthylaldehyde (98% ee).

Clearly, based on the results in Table 6, there is an electronic influence on the reaction times for the dirhodium(II) catalyzed HDA reactions. For example, the electron rich *p*-methoxybenzaldehye requires a longer reaction time in comparison to electron-withdrawing *p*-nitrobenzaldehyde. Hashimoto describes a similar trend in the dirhodium(II) 3-phthalimido-2-piperidinonate catalyzed cycloaddition of substituted aromatic aldehydes and diene **9** (Eq. 3).[7] For instance, aromatic aldehydes including benzaldehyde, and *p*-anisaldehyde, required significantly longer times to reach completion compared to electron-poor *p*-nitrobenzaldehyde.

We continued to optimize the reaction conditions for aromatic aldehydes other than *p*-nitrobenzaldehyde. The use of a polar solvent such as nitromethane decreased the enantioselectivity for the HDA cycloaddition with benzaldehyde and *p*-anisaldehyde. For example, the enantioselectivity for benzaldehyde at room temperature in nitromethane was 75% ee. Additionally, 1,2-dichloroethane afforded lower enantiomeric excesses in comparison to when reactions were performed under solvent free conditions. Similarly, a decrease in the level of enantiocontrol was observed with the use of 4 Å molecular sieves. Our attempts to further optimize the reaction conditions led to either a decrease in the level of enantiocontrol or a decrease in the yield.

2.5 Mechanism

Two distinct mechanistic pathways, the concerted [4 + 2] cycloaddition pathway which occurs via a cyclic intermediate or the Mukaiyama aldol pathway which involves an acyclic intermediate, are possible for the Lewis acid catalyzed HDA reaction. The ^{1}H NMR spectra of the reaction mixture of *p*-nitrobenzaldehyde or benzaldehyde and Danishefsky's diene before treatment with trifluoroacetic acid reveals the exclusive formation of the cycloadduct, thus lending credence for a concerted [4 + 2] mechanism for the HDA reaction catalyzed by dirhodium(II) carboxamidates. Further evidence for the [4 + 2] cycloaddition pathway is provided when the HDA reaction is conducted with the dimethyl substituted diene (Chapter 4).

Similar to the dirhodium(II) carboxamidates catalysts made in the Doyle group, Hashimoto[7] and Nishiyama[5] report that the HDA reactions catalyzed by **6** or **10** proceeds via a concerted [4 + 2] mechanism (Eq. 1 and 3). Hashimoto reports that the ^{1}H NMR spectrum of the crude reaction mixture before treatment with TFA revealed the exclusive formation of the cyclic adduct. In addition, Hashimoto asserts that there is no detectable cyclization of the independently prepared Mukaiyama aldol adduct under the reaction conditions.

2.6 Aliphatic Aldehydes as Dienophiles

Following optimization for the Rh_2L_4 catalyzed HDA reaction with aromatic aldehydes as dienophiles, and enantioselectivities as high as 98 % were obtained; aliphatic aldehydes were examined in the cycloaddition reaction. Initial studies revealed that aliphatic aldehydes were less reactive than aromatic aldehydes with Danishefsky's diene. A closer look at the ^{1}H NMR spectra of the reaction between

octanal and **8** revealed that TMS-derived Danishefsky's diene was decomposing to the α,β-unsaturated ketone at longer reaction times. Consequently, a diene more stable than the TMS-substituted diene **8**, which contains a *tert*-butyldimethylsiloxy (TBDMS) group (**7**), was screened for its reactivity with various aliphatic aldehydes (Table 7).

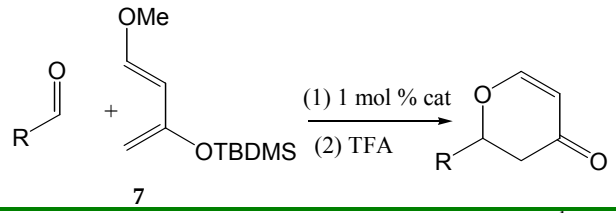
The HDA reaction with aliphatic aldehydes provided dihydropyran products in low to moderate enantioselectivities. In addition, the highest enantiomeric excess was obtained for octanal and diene **7** catalyzed by Rh_2(*S*-MPPIM)$_4$ (86 % ee and 86 % yield) at 60^{o}C under solvent free reaction conditions. Conversely, the TMS-substituted diene **8** afforded significantly lower values (60% ee and 44% yield) under the same reaction conditions. Given there is still unreacted aldehyde present in the ^{1}H NMR after the reaction solution is treated with TFA, it can be concluded that the low yields obtained for aliphatic aldehydes are attributed to slower conversions of the starting materials to products relative to aromatic aldehydes with diene **7**.

Efforts were taken to optimize the reaction between octanal and **7** with the hopes of increasing the yield and enantioselectivity. For example, the catalyst loading was increased to 5 mol %; however, this was not advantageous as the product was formed in 34 % ee and 37 % yield. Furthermore, the addition of 4 Å molecular sieves did not offer an increase in yield nor enantioselectivity.

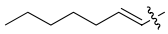
Similar to aromatic aldehydes, the HDA reactions with aliphatic aldehydes provided superior levels of enantioselectivity at elevated temperatures. For example, an increase of enantiomeric excess is observed in the reaction between cyclohexanecarboxaldehyde and **7** when the temperature is raised from 40^{o}C (16%

ee) to 60°C (48% ee). A similar effect is seen for the cycloaddition of diene **7** and octanal wherein the % ee increased from 53 % to 86 % ee (Table 7).

Table 7. Reactions with **1** and aliphatic aldehydes[a]



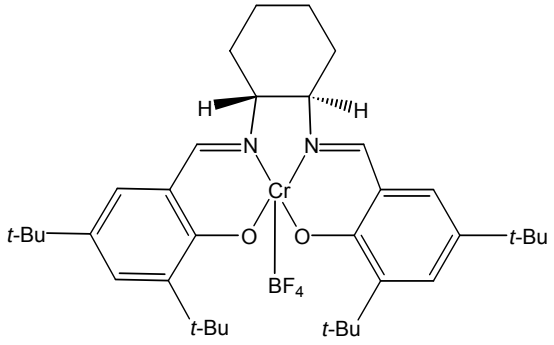
7

R	Temperature (°C)	catalyst	% ee[b]	% yield[c]
n-C_7H_{15}	25	Rh_2(dF-CHAZ)$_4$	46	50
n-C_7H_{15}	50	Rh_2(dF-CHAZ)$_4$	36	68
n-C_7H_{15}	25	Rh_2(R-MEPY)$_4$	13	13
n-C_7H_{15}	25	Rh_2(dF-IBAZ)$_4$	49	5
n-C_7H_{15}	25	Rh_2(dF-MEPY)$_4$	9	17
n-C_7H_{15}	25	Rh_2(R-MPPIM)$_4$	41	9
n-C_7H_{15}	45	Rh_2(R-MPPIM)$_4$	53	49
n-C_7H_{15}	60	Rh_2(S-MPPIM)$_4$	86	86
n-C_7H_{15}	0	chromium(III)-Salen	70	86
n-C_7H_{15}	25	chromium(III)-Salen	71	83
C_2H_5	60	Rh_2(S-MPPIM)$_4$	61	63
cy-C_6H_{11}	60	Rh_2(S-MPPIM)$_4$	48	27
t-Bu	60	Rh_2(S-MPPIM)$_4$	23	<10
	60	Rh_2(S-MPPIM)$_4$	79	36
n-C_7H_{15}	60	Rh_2(S-ODPY)$_4$	32	58

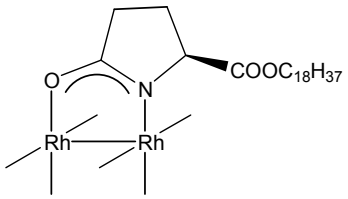
[a] The reactions were performed at designated temperature. All aliphatic aldehydes were performed neat, 1 to 1.2 equivalents of aldehyde to diene was used, in the presence of 1 mol % catalyst. Reaction times were 7 days followed by treatment with TFA, then column chromatography.
[b] Determined by HPLC using a Chiralpak OD column (% ee ± 1)
[c] Isolated yield after chromatography.

We were interested in looking at how catalysts outside of **1**-**5** perform in the HDA reaction of octanal and **7**. In particular we examined a chromium(III)-salen catalyst (**11**) and Rh_2(S-ODPY)$_4$ (**12**). Jacobsen reported that the chromium-salen catalyst can promote the asymmetric HDA with moderate to good

enantioselectivities.[17] Rh_2(S-ODPY)$_4$ was postulated to have favorable interactions with octanal due to the long hydrocarbon chain on the ligand attached to the rhodium metal. However, both catalysts **11** and **12** afforded significantly reduced selectivity's compared to Rh_2(S-MPPIM)$_4$ (70 and 32 % ee vs. 86 % ee). In addition, catalysts bearing electron withdrawing groups such as Rh_2(dFIBAZ)$_4$, Rh_2(dFCHAZ)$_4$, and Rh_2(dFMEPY)$_4$ were examined. Though, Rh_2(dFCHAZ)$_4$ provided the highest yield with moderate selectivity in comparison to the other fluorinated catalysts that afforded the HDA adducts in low yields (<20 %).



11

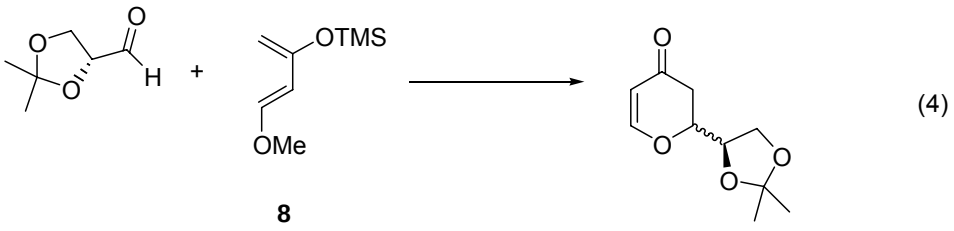


12

A few notable examples of other Lewis acids that catalyze the asymmetric HDA reaction with octanal can be found in the literature. Included in those examples are bis-titanium(IV) catalyst (10 mol % at 0^{o}C),[18] 3-oxobutylideneaminatocobalt complex (8 mol % -78^{o}C),[19] and a titanium(IV) octahydrobinaphthol complex (20 mol % at 23^{o}C)[20] which afforded the resultant dihydropyran in 92, 88, and 96 % ee respectively. The HDA reaction of aliphatic aldehydes catalyzed by dirhodium(II) carboxamidates has been improved from initial investigations; however further optimization is still required. This may be accomplished by increasing the Lewis acidity of the catalysts.

A trend is apparent in the aliphatic aldehydes examined whereby increasing the steric bulk at the α-carbon decreases the % ee and % yield of the HDA product. For example, octanal which has no substitution at the α position provided the highest % yield and ee of product. Cyclohexanecarboxaldehyde, which is substituted at the α-carbon, provided the dihydropyran in decreased % yield and % ee. In addition the reaction is extremely sluggish when pivalaldehyde is used as the dienophile providing less than 10 % yield of product. Maruoka,[18] Keck,[21] and Inanaga[22] also observe a similar trend with their Lewis acids where the sterically less hindered aldehydes lead to higher enantioselectivity.

The ability of chiral dirhodium(II) carboxamidates to control the diastereoselectivity of the HDA was examined using **8** in the presence of a chiral aldehyde. The reaction between 2,2-dimethyl-[1,3]dioxolane-4-carbaldehyde and diene **8** was examined in the presence of both Rh_2(*S*-MPPIM)$_4$ and Rh_2(*R*-MPPIM)$_4$ (Eq. 4). The catalyst enantiomers promoted the reaction with different diastereoselectivities (Eq. 4).

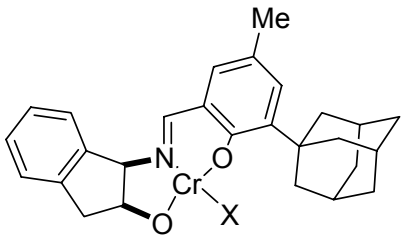


(4)

Rh_2(*S*-MPPIM)$_4$ dr = 1 : 25 (R,R):(S,R) 38% yield
Rh_2(*R*-MPPIM)$_4$ dr = 1 : 5.3 (R,R):(S,R) 62% yield

The matched catalyst/substrate system in this case, Rh_2(*S*-MPPIM)$_4$, provided the highest level of diastereselectivity in this study with a diastereomeric ratio (dr) of 1:25, however the mismatched combination with Rh_2(*R*-MPPIM)$_4$ afforded the

product in a dr of 1:5.3 at 43 ^{o}C in DCM. Jacobsen and Joly describe a similar phenomenon with their chiral Cr(III) catalyst **13** where the matched catalyst affords the same product in a dr of 1:33 and its enantiomer, the mismatched catalyst, affords the product in a dr of 1:1.2 at 4^{o}C in ethyl acetate in the presence of barium oxide as a desiccant.[23] This matched catalyst/substrate methodology offers the advantage to selectively access diastereomeric products by the appropriate use of aldehyde catalyst enantiomers.



13aX=SbF_6
13b X=Cl

2.7 Summary

In summary, the enantioselective HDA reaction between aromatic aldehydes and Danishefsky's diene can be effectively catalyzed using dirhodium(II) carboxamidates under solvent and desiccant free conditions and with uncommonly high turnover numbers (catalyst loadings as low as 0.01 mol %). Optimization of reaction conditions allows various substituted aromatic aldehydes to be catalyzed with enantioselectivities that are greater than 90 % ee. An electronic influence is seen in the reactivity of the *para*-substituted aromatic aldehydes where the more electron rich *p*-anisaldehyde requires longer reaction times compared to electron withdrawing *p*-nitrobenzaldehyde. The dirhodium(II) carboxamidate catalyzed HDA reactions occurs via a [4+2] cycloaddition which is in line with the current accepted mechanism

with rhodium catalysts. Aliphatic aldehydes are less reactive in this catalytic system in comparison to aromatic aldehydes. High levels of diastereocontrol are observed with the matched catalyst/substrate system. Further optimization is necessary in catalyst development to increase the rate of reaction by increasing the Lewis acidity of the dirhodium(II) catalyst.

2.8 Experimental

General. All aldehydes were obtained commercially and purified by distillation or recrystallization prior to their use. Dichloromethane, chloroform and 1,2-dichloroethane were distilled prior to use according to established procedures.[24] Rh_2(4*S*-MPPIM)$_4$ **4a**,[25] Rh_2(4*S*-MEOX)$_4$ **2a**,[1] and chromium catalyst **11**,[17] were prepared according to literature methods. Danishefsky's diene was prepared according to published procedures.[26] All reactions were carried out under a nitrogen atmosphere (by flushing the reaction vial with nitrogen and capping) employing oven and flame dried glassware.

Analytical thin-layer chromatography (TLC) was performed using silica gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, cerium ammonium molybdenate, or iodide. Flash column chromatography was performed using silica gel 60Å (40-63 micron). Analytical normal phase HPLC was performed on a Hewlett-Packard 1100 series chromatograph equipped with a variable wavelength UV detector (254 nm).

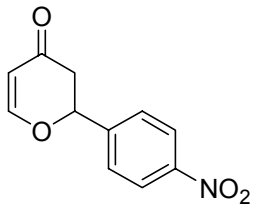
Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ, 0.0 ppm), or with the solvent reference relative to TMS

employed as an internal standard ($CDCl_3$, δ, 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m)], coupling constants [Hz], integration). All NMR spectra were acquired at ambient temperature.

General HDA procedure. Aldehyde (0.50 mmol) was added to an oven-dried 1.5 dram vial along with 1.0 mol % catalyst (0.0050 mmol) after which 0.50 mL of dry solvent was added, and the resulting solution was allowed to mix thoroughly by stirring. (If the aldehyde was a liquid, the reaction was performed without solvent.) Danishefsky's diene (0.70 mmol) was then added, and the solution was stirred at the designated temperature. After the allotted reaction time, the solution was treated with a few drops of TFA and chromatographically purified using a short silica column that removed the catalyst. Enantiomeric excesses (ee) were determined by HPLC analysis with a 0.46 cm X 25 cm Daicel CHIRALPAK OD column.

Following the same procedure mentioned above and the experimental conditions shown in the table (see the text) the following 2-substituted-2,3-dihydro-4H-pyran-4-ones have been prepared.

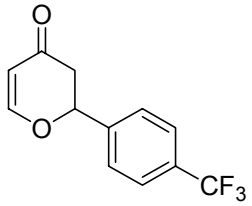
2-(4-Nitrophenyl)-2,3-dihydropyran-4-one:[27]



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 6.1 Hz, 1H), 5.50 (dd, *J* = 6.1, 1.2 Hz 1H), 5.46 (d, *J* = 4.2 Hz, 1H), 2.78 (dd, *J* = 16.8, 13.9 Hz 1H,), 2.65 (ddd, *J* = 16.8, 4.2, 1.2 Hz 1H). HPLC on Chiralpak OD

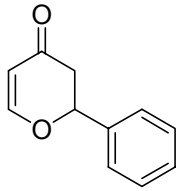
column: t_R 13.54 for minor isomer and 19.63 min for major isomer by using Rh_2(4R-MPPIM)$_4$ catalyst (hexanes/isopropanol = 80/20, flow rate: 1.5 mL/min).

2-(4-Trifluoromethylphenyl)-2,3-dihydropyran-4-one:[28]



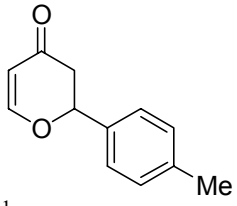
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 6.6 Hz, 1H), 5.49 (dd, *J* = 6.6, 1.2 Hz, 1H), 5.46 (dd, *J* = 14.4, 3.5 Hz, 1H), 2.80 (dd, *J* = 16.8, 14.4 Hz, 1H), 2.64 (ddd, *J* = 16.8, 3.5, 1.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 191.0, 162.6, 141.8, 130.9, 127.6, 126.1, 125.7, 107.5, 80.0, 43.2; HRMS calcd for $C_{12}H_{10}O_2F_3$ (M+1): 243.0633, found: 243.0619. HPLC on Chiralpak OD column: t_R 27.45 min for minor isomer and 40.43 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 98/2, flow rate: 1.0 mL/min).

2-Phenyl-2,3-dihydropyran-4-one:[29]



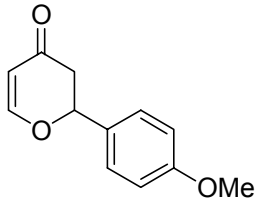
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.65-7.35 (comp, 6H), 5.55 (dd, *J* = 6.0, 0.6 Hz, 1H), 5.43 (dd, *J* = 14.4, 3.0 Hz, 1H), 2.92 (dd, *J* = 16.8, 14.4 Hz, 1H), 2.68 (ddd, *J* = 16.8, 3.0, 0.6 Hz, 1H). HPLC on Chiralpak OD column: t_R 6.46 min for minor isomer and 7.61 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 80/20, flow rate: 1.5 mL/min).

2-p-Tolyl-2,3-dihydropyran-4-one:[30]



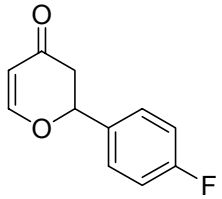
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.51 (d, *J* = 6.0 Hz, 1H), 5.39 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.91 (dd, *J* = 16.5, 14.5 Hz, 1H), 2.64 (dd, *J* = 16.5, 3.5 Hz, 1H), 2.38 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 192.3, 163.2, 138.9, 134.8, 129.5, 126.1, 107.3, 81.0, 43.3, 21.2. HPLC on Chiralpak OD column: t_R 11.54 min for minor isomer and 13.22 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2-(4-Methoxyphenyl)-2,3-dihydropyran-4-one:[31]



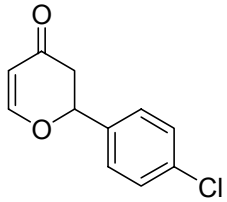
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 6.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 5.52 (d, *J* = 6.0 Hz, 1H), 5.38 (dd, *J* = 14.4, 3.0 Hz, 1H), 3.84 (s, 3H), 2.93 (dd, *J* = 16.8, 14.4 Hz, 1H), 2.63 (ddd, *J* = 16.8, 3.0, 1.2 Hz, 1H). HPLC on Chiralpak OD column: t_R 16.27 min for minor isomer and 18.40 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2-(4-Fluorophenyl)-2,3-dihydropyran-4-one:[32]



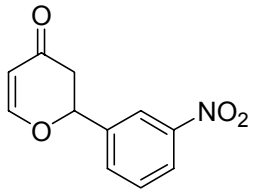
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.0 Hz, 1H), 7.41-7.09 (m, 4H), 5.53 (dd, *J* = 6.0 Hz, 1.1 Hz, 1H), 5.40 (dd, *J* = 14.3, 3.5 Hz, 1H), 2.88 (dd, *J* = 16.8, 14.3 Hz, 1H), 2.65 (dddd, *J* = 16.8, 3.5, 1.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 190.8, 162.61, 162.58, 143.0, 132.7, 126.5, 107.6, 79.7, 43.3; HPLC on Chiralpak OD column: t_R 10.27 min for major isomer and 11.86 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 87/13, flow rate: 1.0 mL/min).

2-(4-Chlorophenyl)-2,3-dihydropyran-4-one:[33]



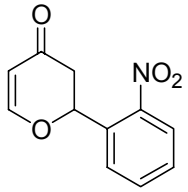
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.1 Hz, 1H), 7.52-7.44 (m, 4H), 5.65 (dd, *J* = 6.1, 1.0 Hz, 1H), 5.55 (dd, *J* = 14.24, 3.57 Hz, 1H), 3.02-2.92 (m, 1H), 2.79-2.72 (m, 1H). HPLC on Chiralpak OD column: t_R 13.57 min for minor isomer and 16.52 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2-(3-Nitrophenyl)-2,3-dihydropyran-4-one:



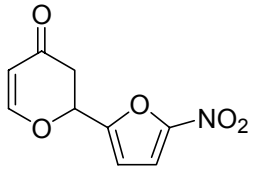
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 6.3 Hz, 1H), 5.61 (d, *J* = 6.3 Hz, 1H), 5.57 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.91 (dd, *J* = 16.5, 14.2 Hz, 1H), 2.77 (dd, *J* = 16.5, 3.2 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 190.8, 162.6, 148.6, 140.0, 131.8, 130.0, 123.7, 121.1, 107.9, 79.6, 43.3. HPLC on Chiralpak OD column: t_R 11.49 min for major isomer and 14.84 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 80/20, flow rate: 1.0 mL/min).

2-(2-Nitrophenyl)-2,3-dihydropyran-4-one:[34]



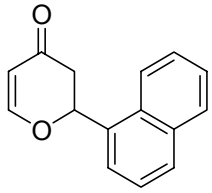
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 6.3 Hz, 1H), 6.09 (dd, *J* = 14.0, 2.5 Hz, 1H), 5.61 (d, *J* = 6.3 Hz, 1H), 3.01 (dd, *J* = 16.5, 2.5 Hz, 1H), 2.79 (dd, *J* = 16.5, 14.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 190.8, 162.5, 134.0, 133.9, 129.5, 128.1, 124.9, 108.0, 43.1, 37.9. HPLC on Chiralpak OD column: t_R 8.29 min for major isomer and 10.32 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 80/20, flow rate: 1.0 mL/min).

2-(5-Nitrofuran-2-yl)-2,3-dihydropyran-4-one:



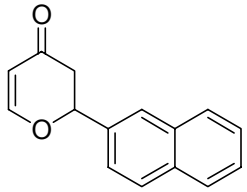
^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.2 Hz, 1H), 7.32 (d, *J* = 3.4 Hz, 1H), 6.68 (d, *J* = 3.4 Hz, 1H), 5.56 (d, *J* = 6.2 Hz, 1H), 5.55 (dd, *J* = 12.3, 4.3 Hz, 1H), 3.07 (dd, *J* = 16.7, 12.3 Hz, 1H), 2.85 (dd, *J* = 16.7, 4.3 Hz, 1H). HPLC on Chiralpak OD column: t_R 16.49 min for minor isomer and 18.58 min for major isomer by using Rh_2(4*R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2-(Naphthalen-1-yl)-2,3-dihydropyran-4-one:[27]



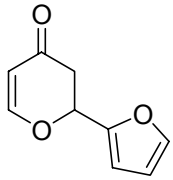
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99-7.86 (m, 3H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.60-7.50 (m, 4H), 6.17 (dd, *J* = 14.2, 3.5 Hz, 1H), 5.61 (d, *J* = 6.0 Hz, 1H), 3.21-3.03 (m, 1H), 2.90-2.83 (m, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 192.5, 163.6, 134.0, 133.4, 130.2, 129.7, 129.3, 126.9, 126.2, 125.5, 124.1, 122.8, 107.7, 78.6, 42.9. HPLC on Chiralpak AD column: t_R 27.94 for major isomer and 33.77 min for minor isomer by using Rh_2(4 *S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 99/1, flow rate: 1.0 mL/min).

2-(Naphthalen-2-yl)-2,3-dihydropyran-4-one:[35]



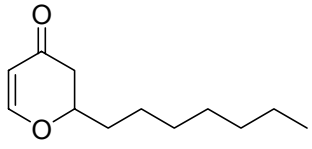
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92-7.85 (m, 4H), 7.56-7.51 (m, 3H), 7.49 (d, J = 3.4 Hz, 1 H), 5.62 (d, *J* = 3.4 Hz, 1H), 5.56 (dd, *J* = 6.3, 1.5 Hz, 1H), 3.01 (dd, *J* = 17.1, 14.6 Hz, 1H), 2.75 (ddd, *J* = 17.1, 3.4, 0.98 Hz, 1H). HPLC on Chiralpak OD column: t_R 16.34 min for minor isomer and 26.34 min for major isomer by using Rh_2(4 *R*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 80/20, flow rate: 1.0 mL/min).

2-(Furan-2-yl)-2,3-dihydropyran-4-one:[36]



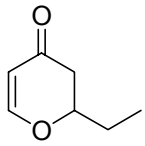
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.5 Hz, 1H), 7.39 (d, *J* = 6.1 Hz, 1H), 6.47-6.41 (m, 2H), 5.52-5.46 (m, 2H), 3.15-3.05 (m, 1H), 2.77-2.70 (m, 1H), HPLC on Chiralpak OD column: t_R 31.20 min for minor isomer and 34.36 min for major isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 95/5, flow rate: 0.5 mL/min).

2-Heptyl-2,3-dihydropyran-4-one:[37]



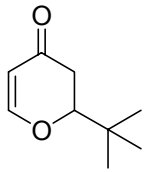
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.0 Hz, 1H), 5.40 (d, *J* = 6.0 Hz, 1H), 4.48-4.32 (m, 1H), 2.52 (dd, *J* = 16.6, 13.7Hz, 1H), 2.43 (dd, *J* = 16.6, 3.9Hz, 1H), 1.89-1.75 (m, 1H), 1.72-1.60 (m, 1H), 1.57-1.19 (m, 10H), 0.94-0.80 (m, 3H). HPLC on Chiralpak OD column: t_R 22.78 min for major isomer and 25.57 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 99/1, flow rate: 0.5 mL/min).

2-Ethyl-2,3-dihydropyran-4-one:[29]



^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 6.0 Hz, 1H), 5.45 (dd, *J* = 6.0, 0.6 Hz, 1H), 4.40-4.34 (comp, 1H), 2.55 (dd, *J* = 16.8, 13.8 Hz, 1H), 2.48 (ddd, *J* = 16.8, 3.6, 0.6 Hz, 1H), 1.84 (hex, *J* = 7.2 Hz, 1H), 1.75 (pentd, *J* = 7.2, 1.8 Hz, 1H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 194.0, 164.4, 106.6, 80.7, 41.0, 27.3, 9.0; MS: 127 (M + 1) (21), 97 (13), 82 (55), 71 (100). HPLC on Chiralpak OD column: t_R 11.39 min for major isomer and 12.41 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 98/2, flow rate: 1.0 mL/min).

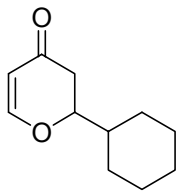
2-*tert*-Butyl-2,3-dihydropyran-4-one:[34]



^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 0.2, 5.0 Hz, 1H), 5.40 (dd, *J* = 1.0, 5.0 Hz, 1H), 4.03 (dd, *J* = 3.0, 15.0 Hz, 1H), 2.53 (dd, *J* = 15.0, 16.0 Hz, 1H), 2.39 (ddd, *J* = 1.0, 3.0 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 163.8, 106.6, 86.9, 37.2, 33.8, 25.4. HPLC on Chiralpak OD column: t_R 6.24 min for major

isomer and 6.86 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2-cyclohexyl-2,3-dihydropyran-4-one:[38]



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.0 Hz, 2H), 5.38 (dd, *J* = 1.0, 6.0 Hz, 1H), 4.16 (ddd, *J* = 14.5, 5.6, 3.4 Hz, 1H), 2.54 (dd, *J* = 16.7, 14.5Hz, 1H), 2.38 (ddd, *J* = 16.7, 3.4, 1.0 Hz, 1H), 1.81-1.64 (m, 6H), 1.27-1.00 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 163.6, 106.9, 83.6, 41.4, 39.2, 28.2, 26.3, 25.9, 25.8. HPLC on Chiralpak OD column: t_R 6.24 min for major isomer and 6.86 min for minor isomer by using Rh_2(4*S*-MPPIM)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 mL/min).

2.9 References

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Chapter 3: Kinetic Study

3.1 Introduction

While extensive kinetic studies have been performed on the Diels-Alder reaction,[1-4] and there have been theoretical investigations pertaining to the mechanism of the catalytic enantioselective hetero-Diels-Alder reaction,[5,6] to our knowledge detailed kinetic studies have not been performed on the Lewis acid catalyzed HDA reaction. However, there have been a small number of kinetic studies reported for the uncatalyzed hetero-Diels-Alder reaction.[7,8] For example, Eckert and coworkers measured the rate constants using fluorescence spectroscopy, for the hetero-Diels-Alder reaction between anthracene and 4-phenyl-1,2,4-triazoline-3,5-dione in supercritical fluid CO_2.[7] Additionally, Rawal reported the rate constants of HDA reactions in different solvents for the reaction between *p*-anisaldehyde and 1-amino-3-siloxybutadiene.[8] Yet neither Eckert nor Rawal utilized a Lewis acid catalyst in their studies.

The dirhodium(II) catalytic system (Chapter 2) provides unique opportunities for evaluation of the Lewis acid catalyzed HDA mechanism because they are readily amenable to determination of equilibrium constants for association between the catalyst and aldehyde as well as to the monitoring of rates for reaction.[9] We wanted to focus on understanding the ability of dirhodium(II) carboxamidates to activate aldehydes toward cycloaddition with Danishefsky's diene. The aldehyde's association to the catalyst would allow us to examine the catalytic ability of the Lewis acid to be used with high turnover numbers. The data obtained from the measured

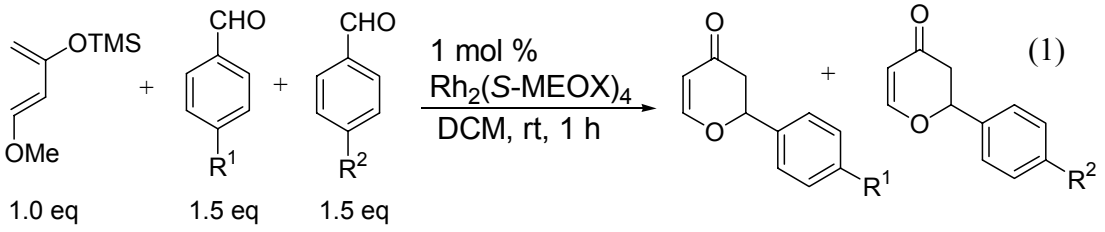
rate constants would allow us to gain insight into other crucial aspects of the dirhodium(II) catalyzed HDA reaction, such as (1) catalyst order in the rate equation, (2) activation energy, and (3) other factors like temperature, solvent, and catalysts that govern the rate of the reaction. Furthermore, we wanted to determine if there is a direct correlation between the rate constant of the reaction and the product enantioselectivity.

This chapter will focus on our efforts to explore the mechanism of the dirhodium(II) catalyzed hetero-Diels-Alder reaction. For the first time, the rates of reaction and equilibrium constants for various *para*-substituted aromatic aldehydes were determined for the Lewis acid catalyzed HDA reaction. In addition, the Hammett plot reveals a direct, pronounced electronic influence on the rate of the reaction. Reaction parameters such as solvent, temperature, and catalyst were examined to determine their effect on the reaction rate for the particular reaction between *p*-nitrobenzaldehyde and Danishefsky's diene. Rates of reaction promoted by catalysts other than dirhodium(II) carboxamidates were examined and will be presented.

3.2 Competition Reactions

We observed in the dirhodium(II) carboxamidate-catalyzed HDA reactions that electron donating aldehydes required longer reaction times relative to electron withdrawing aldehydes (Chapter 2). The difference in reactivity was borne out in a competition experiment wherein two *para*-substituted aromatic aldehydes were allowed to compete directly for the same diene in the presence of a dirhodium(II)

catalyst (Eq. 1). The product ratio in the reaction mixture was subsequently determined by gas chromatography.



1.0 eq 1.5 eq 1.5 eq (1)

1

2 R^1= Cl **3** R^2= NO_2

4 R^1= Me **5** R^2= H

2 : 3	**5 : 2**	**4 : 5**
3 : 97	27 : 73	31 : 69

Initially, we examined the competition reaction between *p*-nitrobenzaldehyde and *p*-chlorobenzaldehyde with Danishefsky's diene (**1**) in the presence of Rh_2(*S*-MEOX)$_4$. From the product ratio it is evident that *p*-nitrobenzaldehyde reacts much faster with Danishefsky diene in comparison to *p*-chlorobenzaldehyde. In fact, the relative product ratios indicate that dihydropyran **3** (from reaction with *p*-nitrobenzaldehyde) is formed more than 25 times faster than **2** (derived from *p*-chlorobenzaldehyde). Similarly, *p*-chlorobenzaldehyde reacted more than 2.5 times faster with **1** relative to benzaldehyde (27:73 for **5**:**2**) and benzaldehyde reacts two times faster than *p*-tolualdehyde (31:69 for **4**:**5**).

Importantly, the competition studies clearly demonstrate a difference in reactivity between various *para*-substituted aromatic aldehydes in the dirhodium(II) catalyzed HDA reaction. We were not surprised by the reactivity differences of aromatic aldehydes in the HDA reaction; however, we were surprised by the large differences between various aldehydes. These sizable differences in reactivity prompted a kinetic study that allowed us to obtain quantitative data for different aromatic aldehydes and

understand how the catalyst activates the aldehyde and how that activation influences both reaction rate and enantioselectivity.

3.3 Kinetic Investigation: Introduction and Procedure

The mechanism of the dirhodium(II) carboxamidate catalyzed HDA reaction is outlined in Scheme 1. Coordination of catalyst (Rh_2L_4) with the lone pair of electrons on the carbonyl oxygen of the aldehyde (Ald) lowers the energy barrier for addition by the diene (D) to the catalyst complex to provide the hetero-Diels-Alder adduct (Pdt) and regenerate the catalyst after product dissociation.[10]

$$Rh_2(cat)_4 + Ald \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Rh_2(cat)_4\text{-}Ald$$

$$Rh_2(cat)_4\text{-}Ald + D \xrightarrow{k_2} Rh_2(cat)_4 + Pdt$$

Scheme 1. Proposed reaction mechanism of dirhodium(II) catalyzed HDA reaction

The association of the aldehyde to the catalyst is in rapid equilibrium (Scheme 1), and the equilibrium constant is given in Eq. 2.

$$K_{eq} = \frac{k_1}{k_{-1}} = \frac{[Rh_2(cat)_4 - Ald]}{[Rh_2(cat)_4][Ald]} \qquad (2)$$

In addition, the rate equation for the mechanism (Scheme 1) is given in Eq. 3.

$$rate = -\frac{d[Ald]}{dt} = \frac{d[Pdt]}{dt} = k_2 K[Ald][D]_0[Rh_2(cat)_4]_0 \qquad (3)$$

The observed rate constant then is $k_{obs} = k_2 K_{eq}[D]_0[Rh_2(cat)_4]_0$ and k_2 can be determined using Eq. 4.

$$k_2 = \frac{k_{obs}/[Rh_2(cat)_4]_0[D]_0}{K_{eq}} \qquad (4)$$

A systematic approach was critical to quickly and efficiently measure the rate and equilibrium constants for mechanism outlined in Scheme 1. The general procedure involved adding aldehyde, biphenyl (GC standard), 1.0 mol % catalyst and 1.0 mL of the appropriate solvent to an oven-dried 2-dram vial. Next, a ten-fold excess of Danishefsky's diene was added, and the solution was stirred under nitrogen at the designated temperature. Subsequently, 100 μL aliquots of the reaction solution were removed at various time increments and added to a second vial containing 1,2-dichloroethane treated with 3-4 drops of TFA. This procedure serves to desilylate both the product and the diene, thereby avoiding further reaction with the aldehyde. The excess TFA was then neutralized with solid sodium bicarbonate, and samples were analyzed by GC. The concentration of aldehyde at each time point was calculated from the predetermined response factor (Eq. 5) that was measured using known concentrations of aldehyde (unknown) and biphenyl (standard). The response factors for *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, benzaldehyde, *p*-tolualdehyde, and *p*-anisaldehyde was 0.483, 0.459, 0.473, 0.716, 0.487 respectively. Additionally, the reaction was allowed to proceed through at least two half-lives and the kinetic data was measured in duplicate or triplicate trials.

$$R.F. = \left(\frac{Area\ U}{Area\ St}\right) \Big/ \left(\frac{Mole\ U}{Mole\ St}\right) \quad \text{U = unknown St = Standard} \qquad (5)$$

Following the kinetic measurement on the sample, the % ee value of the remaining product was measured using HPLC analysis to determine if the selectivity was consistent with that found under typical reaction conditions. Additionally, we monitored the enantioselectivity over time for several kinetic runs and discovered that the selectivity remains constant throughout the kinetic experiment. Extraordinary

efforts were taken to maintain reactant purity since impurities in the catalyst, diene, and aldehyde demonstrably affected both the reaction rate and product selectivity. Rate constants were determined through at least one, and generally two, half-lives and were calculated by linear least-squares regression from the pseudo-first order kinetic plot. The pseudo-first order rate law is rate = k [A] where [A] represents the concentration of aldehyde and k is the rate constant. The concentration versus time equation is given in equation 6.[11]

$$\log \frac{[A]_t}{[A]_0} = \frac{-kt}{2.303} \qquad (6)$$

Rate constants were therefore determined from the slope of the plot of (log $[A]_t/[A]_0$)*1000 vs time (sec). Additionally, the half-life was calculated using the equation $t_{1/2} = 0.693/k$. An example of a kinetic plot is shown for the reaction between *p*-nitrobenzaldehyde and Danishefsky diene at 23^{o}C in a solution of dichloromethane (Figure 1).

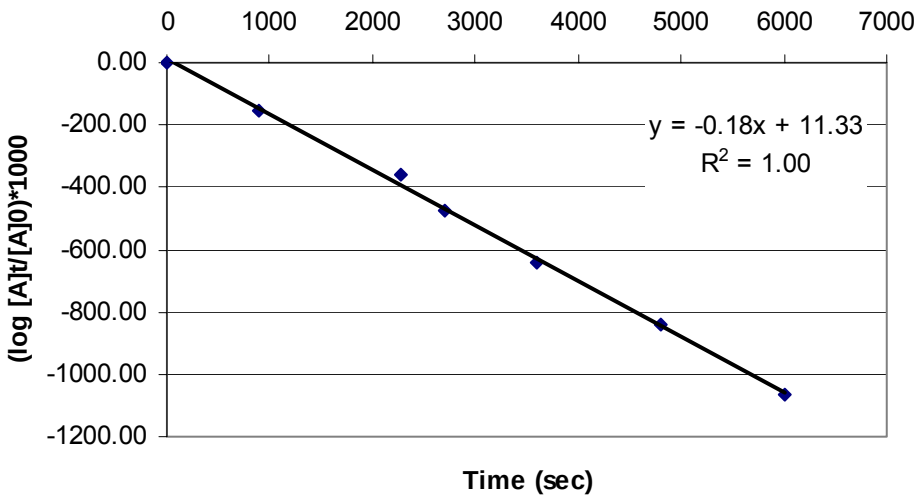


Figure 1. Pseudo-first-order kinetic plot for the reaction between *p*-nitrobenzaldehyde (0.25 M) and Danishefsky's diene (2.5 M) at 23°C in dichloromethane promoted by 1.0 mol % Rh_2(4*S*-MPPIM)$_4$.

Once a systematic approach was established for determination of rate constants, we focused our efforts on the equilibrium constants. These constants were measured on a UV-Vis spectrophotometer.[12] First, the axial-coordinating acetonitrile ligands of the catalysts were removed prior to use; the color change from orange to blue indicated the absence of acetonitrile coordination. Subsequently, the UV-Vis spectrum was analyzed between 400 and 800 nm after sequentially adding microliter aliquots of the aldehyde stock solution to the cuvette containing the catalyst.

Equilibrium constants (K_1) for binding of the aldehyde to the catalyst were determined from a plot of $1/\Delta A$ (A = absorption) versus 1/[aldehyde], which yielded a straight line. K_1 was calculated from the intercept:slope ratio of this best fit line.[12] Wavelengths for the calculation of K_1 were chosen near the isosbestic point, which was 616 nm for *p*-anisaldehyde and benzaldehyde, 580 nm for *p*-chlorobenzaldehyde

and *p*-nitrobenzaldehyde, and 613 nm for *p*-tolualdehyde. An example of the spectral overlay is shown in Figure 2 for *p*-anisaldehyde and Rh_2(4*S*-MPPIM)$_4$. Spectral shifts were not observed with diene or with the cycloaddition product, indicating that these compounds do not significantly coordinate to the dirhodium(II) core.

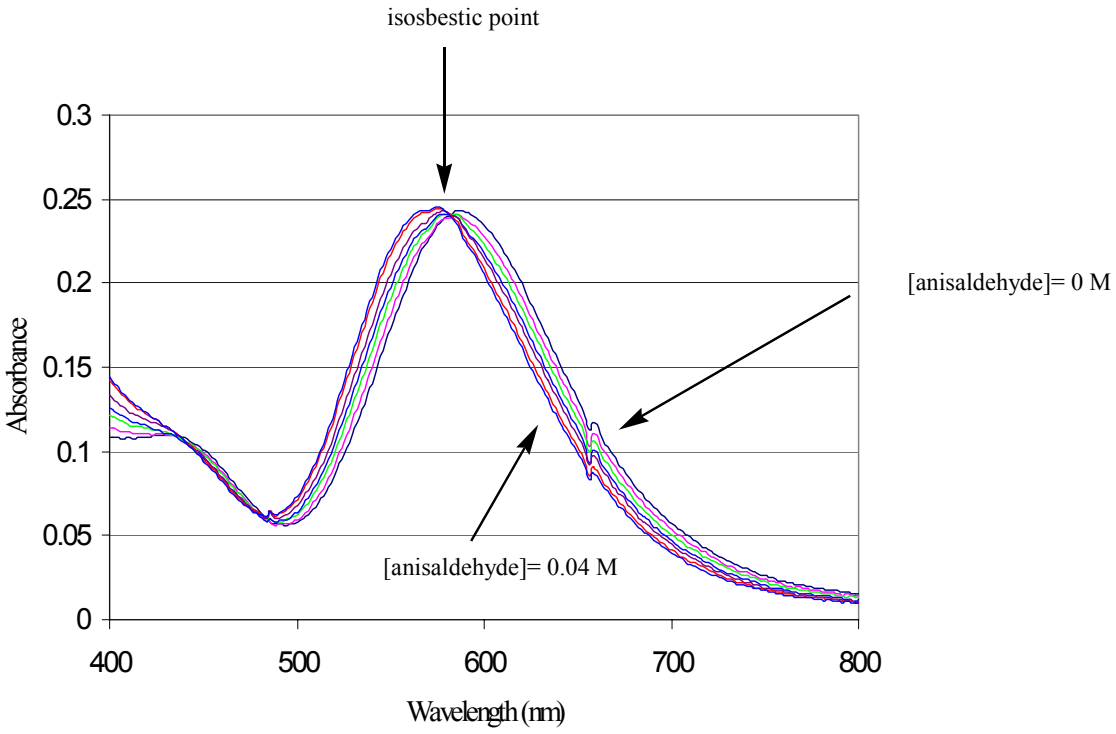


Figure 2. Plot of absorbance vs wavelength for *p*-anisaldehyde using an initial concentration of 0.0024 M for Rh_2(4*S*-MPPIM)$_4$ and incremental concentration changes of 0.0046 M with *p*-anisaldehyde at ambient temperature.

3.4 Rate and Equilibrium Constants

After we established efficient and accurate procedures to determine the rate and equilibrium constants for the proposed mechanism in Scheme 1, we screened several aromatic aldehydes in the HDA reaction. First we examined the rate of the uncatalyzed reaction between *p*-nitrobenzaldehyde and **1** at room temperature. This reaction is relatively slow in comparison to that when Rh_2(4*S*-MPPIM)$_4$ is present

(Figure 3). For example, the half-life of the reaction is 46 hours with no catalyst present (k_2 = 1.66 x 10^{-6} s^{-1} M^{-1}); however, with the mild Lewis acid Rh_2(*S*-MPPIM)$_4$ present the half-life of the reaction is 45 minutes (k_2 = 4.06 x 10^{-2} s^{-1} M^{-2}). This data indicates that the catalyst increases the rate of the reaction by a factor greater than 60. Therefore the highest level of enantiomeric excess possible for Rh_2(*S*-MPPIM)$_4$ at room temperature is 98% ee (taking into consideration the uncatalyzed background reaction), assuming that the catalyst affords the product in 100% ee. This enantioselectivity is consistent with what is observed in the Rh_2(*S*-MPPIM)$_4$ catalyzed reaction between **1** and *p*-nitrobenzaldehyde (Chapter 2).

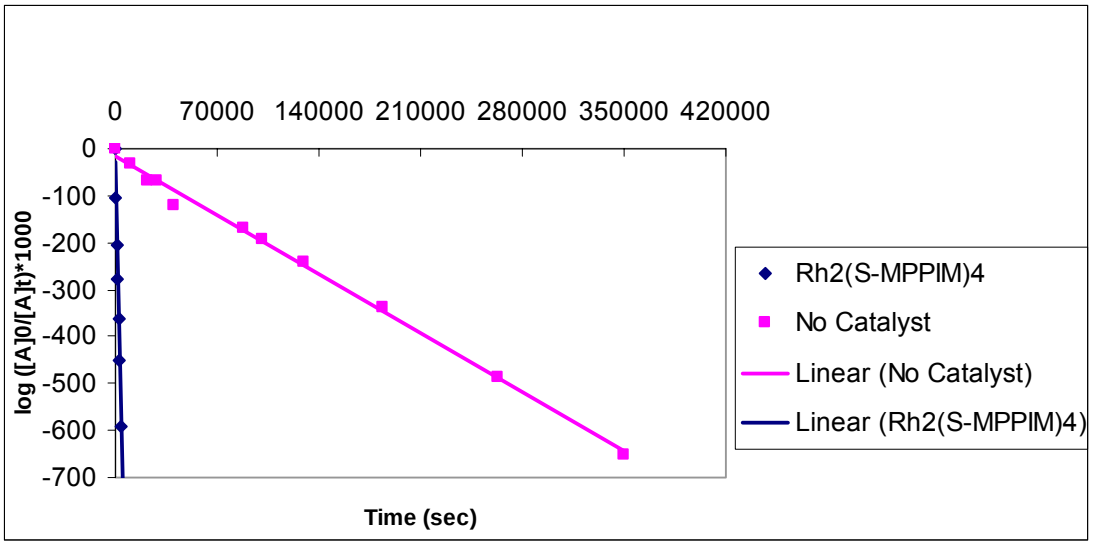


Figure 3. Decrease in the aldehyde concentration for the catalyzed and uncatalyzed reaction of *p*-nitrobenzaldehyde and **1** at 25°C in dichloromethane.

Subsequently, the values for both the association constant and the rate constant ($k_2' = k_2K_{eq} = k_{obs}/[Rh_2(cat)_4]_0[D]_0$) for five aromatic aldehydes catalyzed by Rh_2(4*S*-MPPIM)$_4$ at 60°C were determined (Table 1). The more electron-withdrawing *p*-nitrobenzaldehyde has a reaction rate that is 20 times greater than that

of the *p*-chlorobenzaldehyde, which is itself more than 30 times faster than that for *p*-anisaldehyde. *p*-Anisaldehyde, whose association constant of 74 M^{-1} suggests that catalyst-aldehyde bound complex is more favored at equilibrium than *p*-nitrobenzaldehyde, which has an association constant of 6 M^{-1}. The observation that aldehydes having higher equilibrium constants for coordination with Rh_2(4*S*-MPPIM)$_4$ undergo slower reaction rates for cycloaddition is an unexpected outcome of this study. Apparently, equilibrium coordination is not a contributing factor in rate acceleration for these reactions, and measurement of the "on rates" (rate of aldehyde association with the catalyst, k_1) for coordination may be more informative.

Table 1. Experimental rate and equilibrium constants of the hetero-Diels-Alder reaction catalyzed by Rh_2(4*S*-MPPIM)$_4$ at 60°C in $CHCl_3$[a]

Aldehyde	k_2' x 10^{-3} (s^{-1} M^{-2})	k'_{rel}	K_{eq} (M^{-1})
p-$NO_2C_6H_4CHO$[b]	133 ± 0.7	722	6 ± 2
C_6H_5CHO	9.7 ± 0.13	53	65 ± 6
p-ClC_6H_4CHO	6.6 ± 0.35	36	24 ± 3
p-$CH_3C_6H_4CHO$	0.87 ± 0.17	5	62 ± 4
p-$MeOC_6H_4CHO$	0.18 ± 0.07	1	74 ± 5

[a] The reactions were carried out at 60°C in $CHCl_3$ with 1.0 mol% Rh_2(*S*-MPPIM)$_4$ and 1.0 equivalent of aldehyde to 10 equivalents of Danishefsky's diene. [b] The rate of the reaction for *p*-nitrobenzaldehyde and Danishefsky's diene with no catalyst present at 60°C is 1.66E-06 s^{-1} M^{-1} in $CHCl_3$.

The rate constants (k_2) for the HDA reactions between the aldehydes in Table 1 and Danishefsky's diene, were calculated using Eq. 4 (Table 2). The largest value for k_2 is seen with *p*-nitrobenzaldehyde (22 s^{-1} M^{-1}), which is more than 9,000 times faster than that of *p*-anisaldehyde (0.0024 s^{-1} M^{-1}). Notably, the calculated rate constant for *p*-chlorobenzaldehyde (117 s^{-1} M^{-1}) is larger than that of benzaldehyde (63 s^{-1} M^{-1}); however the equilibrium constant of benzaldehyde is greater than that of *p*-chlorobenzaldehyde.

Table 2. Calculated rate constants for the $Rh_2(4S\text{-MPPIM})_4$ catalyzed HDA reactions.

Aldehyde	k_2 (s^{-1} M^{-1})	k_{rel}
p-$NO_2C_6H_4CHO$	22	9167
C_6H_5CHO	0.15	63
p-ClC_6H_4CHO	0.28	117
p-$CH_3C_6H_4CHO$	0.014	6
p-$MeOC_6H_4CHO$	0.0024	1

To determine the substituents' electronic effect, a Hammett plot was generated from the rate constants of *para*-substituted aldehydes. The Hammett equation is log $k/k_0 = \sigma\rho$, where k = rate constant for a *para*-substituted (X) aldehyde and k_0 = rate constant for the non substituted aldehyde (benzaldehyde), σ is the substituent constant for a given substituent X, and ρ is the reaction constant. This reaction constant is determined from the slope of the best fit line on the plot of log k/k_0 vs σ. If the substituent can stabilize the transition state mainly through resonance effects then a σ^+ value will give a better correlation. The Hammett plot (Figure 4) versus σ^+ was found to give a ρ value of +1.9 ($R^2 = 0.97$). This result indicates that the transition state is destabilized by electron-donating groups and therefore there is decrease in the rate of the reaction. The ground state is accelerated by the electron-withdrawing group thru induction making the carbonyl carbon more electrophilic. Previously, we determined that dirhodium(II) carboxamidates catalyze the HDA reaction via a [4 + 2] cycloaddition pathway (Chapter 2); however, the ρ value suggests that the mechanism involves an asynchronous cycloaddition transition state.

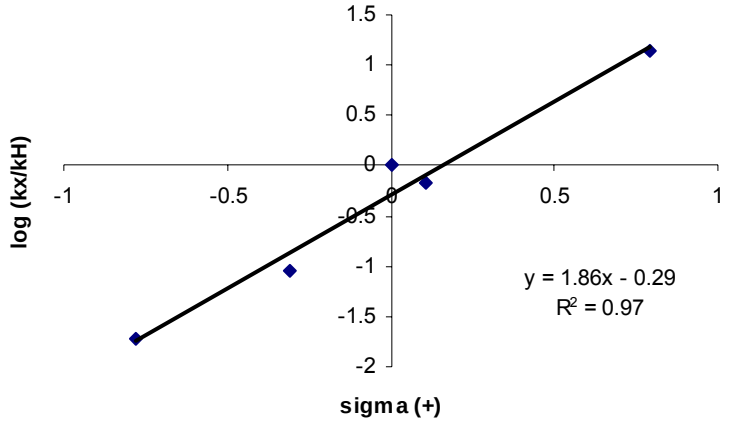


Figure 4. Hammett plot for Rh_2(4*S*-MPPIM)-catalyzed cycloaddition reactions.

3.5 Inhibitors

p-Anisaldehyde was expected to be an inhibitor for the reaction of *p*-nitrobenzaldehyde and **1** given the significantly larger equilibrium constant. When equal amounts of both *p*-nitrobenzaldehyde and *p*-anisaldehyde are used at 25°C in the presence of Rh_2(4*S*-MPPIM)$_4$, only *p*-nitrobenzaldehyde reacts with Danishefsky's diene, but the rate is markedly slower (1.87×10^{-2} $s^{-1}M^{-2}$) than that without *p*-anisaldehyde (4.87×10^{-2} $s^{-1}M^{-2}$). Additionally with Rh_2(4*S*-MPPIM)$_4$, the rate constant decreases as the concentration of *p*-anisaldehyde increases relative to constant catalyst and *p*-nitrobenzaldehyde concentrations (Figure 5). This trend is not limited to Rh_2(4*S*-MPPIM)$_4$: Rh_2(4*S*-MEOX)$_4$ exhibits a similar relationship wherein both the rate constants and the enantioselectivities decrease as the concentration of *p*-anisaldehyde is increased (Figure 6). For example, the enantioselectivity is 80% ee when no *p*-anisaldehyde is present; however, when 5 equivalents of *p*-anisaldehyde

(relative to *p*-nitrobenzaldehyde) is added the enantioselectivity decreases to 53% (Figure 6b).

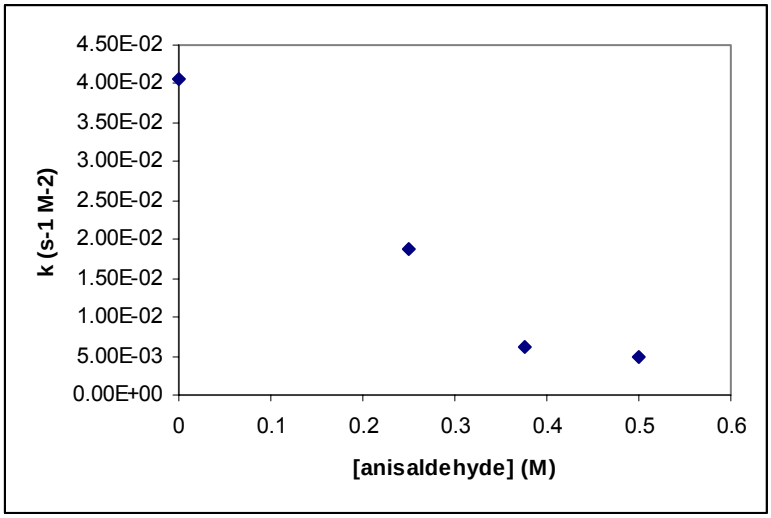


Figure 5. Rate constants of the Rh_2(4*S*-MPPIM)$_4$ catalyzed cycloaddition of *p*-nitrobenzaldehyde and Danishefsky's diene as a function of increasing *p*-anisaldehyde concentration.

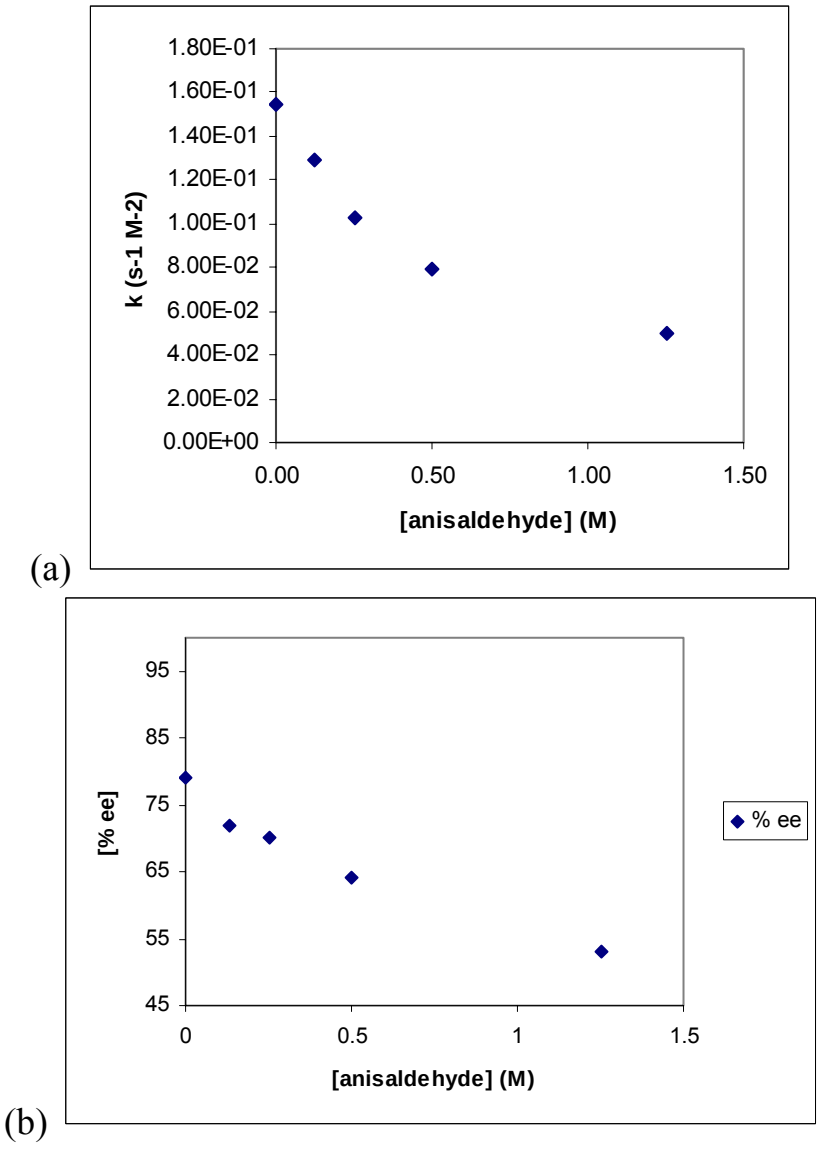


Figure 6. Rate constants (a) and enantioselectivity (b) of the Rh_2(4*S*-MEOX)$_4$ catalyzed cycloaddition of *p*-nitrobenzaldehyde and Danishefsky's diene as a function of increasing *p*-anisaldehyde concentration.

The coordinating acetonitrile ligands of the stock catalyst also act as an inhibitor; however, there is less than 15% increase in the rate constants when acetonitrile is removed compared to when this ligand is not effectively removed. Alternately, the addition of pyridine (1.0 equivalent to catalyst) to the catalytic system shuts down the catalyst rendering it unproductive, presumably by coordination (tight

binding) in the catalysts axial sites. Notably, neither reactant diene nor product shows evidence of coordination with the catalyst: the UV-vis spectrum of these solutions remains unchanged.

3.6 Order of Catalyst in the Rate Equation

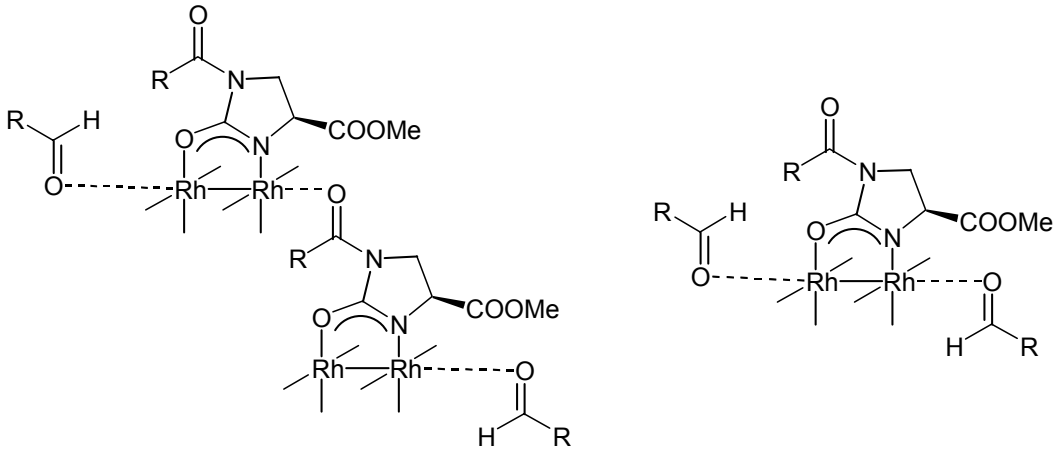
From the studies in section 3.4, the dirhodium(II) catalyzed HDA reaction is first order with respect to diene and aldehyde; however, the order with respect to the catalyst was unknown. We believed that the determination of the catalyst order in the rate equation would shed some light on the mechanistic details of this reaction; therefore, the order with respect to the catalyst was determined. Kinetic studies were carried out at different concentrations of Rh_2(4*S*-MPPIM)$_4$ over a range of 0.2 to 5.0 mol% at 40^{o}C in dichloromethane for the reaction between *p*-nitrobenzaldehyde and **1**. Surprisingly, a catalyst order of 1.4 was found from the linear display (R^2 = 0.995) (Table 3) warranting further investigation. When chloroform was used as solvent in the reaction between **1** and *p*-nitrobenzaldehyde at 40^{o}C, the reaction order decreased by one half (to 0.7). Additionally, the catalyst order remained virtually unchanged in chloroform when the reaction temperature was raised to 60^{o}C (providing an analogous order of 0.8). Similarly, when Rh_2(4*S*-MEOX)$_4$ promotes the reaction between **1** and *p*-nitrobenzaldehyde the catalyst order is 0.8. This suggests that the difference in catalyst order is mainly attributable to the solvent employed.

Table 3. Order of dirhodium(II) carboxamidate catalyst for the reaction between *p*-nitrobenzaldehyde and Danishefsky's diene.[a]

catalyst	temp (^{o}C)	solvent	order
Rh_2(4*S*-MPPIM)$_4$	40	CH_2Cl_2	1.4
Rh_2(4*S*-MPPIM)$_4$	40	$CHCl_3$	0.7
Rh_2(4*S*-MPPIM)$_4$	60	$CHCl_3$	0.8
Rh_2(4*S*-MEOX)$_4$	60	$CHCl_3$	0.8
Rh_2(4*S*-MEOX)$_4$	40	CH_2Cl_2	0.7

[a] The reactions were carried out with 1.0 equivalent of aldehyde to 10 equivalents of Danishefsky's diene.

A catalyst order of 1.4 suggests the possibility of active catalyst aggregates and, not only that, but suggests (because the order is between 1 and 2) that both the catalyst "monomer" and aggregate are both reactive. A fractional order of 0.7 is indicative that each rhodium center acts independently and catalyzes the reaction at different rates. An observed fractional order of the catalyst is not uncommon in the literature.[12-14] For example, previously known systems (not catalyzed HDA reactions) report that the observed fractional order kinetics resulted from aggregation of the active catalytic species,[13] a pre-equilibrium involving anion dissociation from the metal center,[14] and the catalyst existing as an unreactive dimer which has to dissociate before reacting.[15] Dirhodium(II) catalysts have the possibility to form complexes similar to those shown in Figure 7, wherein complexes similar to **A** would lead to catalyst orders greater than one and **B** would provide catalysts orders less than one. Additionally, the occurrence of aldehyde-catalyst complexes **A** and **B** is clearly dependent on the solvent employed. Future studies can elucidate the factors that govern association of the aldehyde to the catalyst. For example, investigation of the equilibrium constants in various solvents and with other dirhodium(II) catalysts is forthcoming to the pool of data on the HDA mechanism.



A **B**

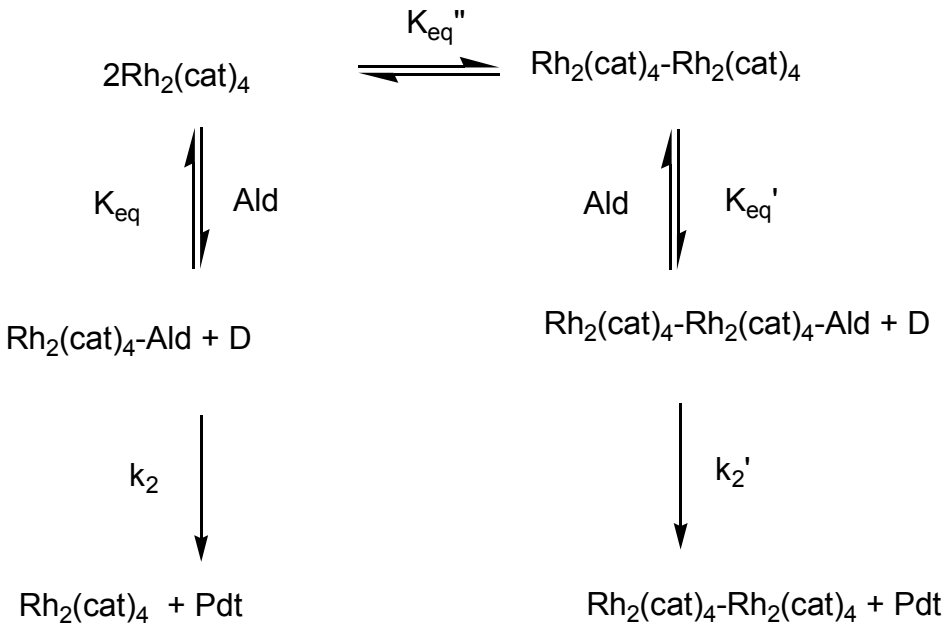
Figure 7. Possible structures of aldehyde catalyst complexes for dirhodium(II) catalyzed HDA reactions.

As mentioned earlier, reactant inhibition is observed with dirhodium(II) catalysts since aldehydes readily associate with dirhodium(II) carboxamidate catalysts. The order of Rh_2(4*S*-MPPIM)$_4$ in reactions of Danishefsky's diene with *p*-nitrobenzaldehyde in the presence of an equimolar amount of *p*-anisaldehyde was 0.9 (R^2 = 0.996). In contrast to an order of 1.4 (without *p*-anisaldehyde) indicating inhibition of the catalyst with added aldehyde (section 3.5). Furthermore, the decrease in catalyst order from 1.4 to 0.9 can be attributed to *p*-anisaldehyde coordinating to the axial site of a rhodium metal center rather than the ligand from another catalyst molecule. This is in contrast to what Evans and coworkers have shown, that competitive inhibition of catalyst from the product is possible in the Diels-Alder reaction catalyzed by chiral bis-oxazoline ligands.[2]

The catalyst order suggests a more complex mechanism than the one we originally proposed (Scheme 1), therefore a revised and more complex mechanism is provided (Scheme 2). The mechanism in Scheme 2 involves the association of two catalyst molecules to provide a new active catalyst aggregate with an equilibrium

constant of K_{eq}''. Both the catalyst aggregate and the monomer are active catalysts in the HDA reaction. The observed rate constant for the mechanism in Scheme 2 is given in Eq. 7 with the assumption that the observed rate constant is determined by the sum of the catalyst aggregates (that is $\Sigma\ k_2^n K_{eq}^n [Ald][D]_0[Rh_2(cat)_4]_0^n$ where n = the number of catalyst molecules).

$$k_{obs} = [diene]_0\ (k_2 K_{eq}[Rh_2(cat)_4 - [Rh_2(cat)_4\text{-}\ Rh_2(cat)_4]] + k_2' K_{eq}' K_{eq}''[Rh_2(cat)_4]^2) \quad (7)$$



Scheme 2. Revised mechanism for the dirhodium(II) catalyzed HDA

3.7 Influence of Solvent on Reaction Rate and Enantioselectivity

Compared to the numerous reports in the literature on reaction optimization by changing the solvent in the Lewis acid catalyzed HDA reaction,[16] rate studies of these reactions have not been investigated. However, reports do exist describing the influence of solvent on the reaction rate for the Diels-Alder and the uncatalyzed HDA reaction.[6,8] For example, Rawal and Huang observed a significantly higher HDA reaction rate in chloroform compared to other aprotic organic solvents (using *p*-

anisaldehyde, 1-amino-3-siloxy-1,3-butadiene, and no catalyst).[8] The increased reaction rate was attributed to a C-H···O hydrogen bond between chloroform and the carbonyl oxygen of the aldehyde, rendering the carbonyl group a stronger dienophile. This activation (provided by hydrogen bonding) was explained by noting that the cycloaddition was accelerated to a greater extent in protic solvents. Engberts and coworkers also describe a solvent effect on the rate constant for the copper(II) catalyzed Diels-Alder reaction between cyclopentadiene and 3-phenyl-1-(2-pyridyl)-2-propen-1-ones.[4]

A kinetic analysis provides the ability to clearly understand the factors influencing the reaction rate. As mentioned in Chapter 2, the solvent has a direct influence on both the enantioselectivity and yield of the reaction between **1** and *p*-nitrobenzaldehyde. Additionally, we observed that the order of the catalyst in the rate equation is dependent on the solvent employed. We embarked upon a study of the reaction parameters by screening different solvents and examining their influence on reaction rate for the dirhodium(II) catalyzed HDA reaction.

To precisely assess the solvents influence, we examined the rate of the hetero-Diels-Alder reaction between Danishefsky's diene and *p*-nitrobenzaldehyde in a variety of solvents at 40^{o}C (Table 4). Upon initial investigation, it is evident that the enantioselectivities and rate constants do not correlate with the solvent's dielectric constants. In contrast, Jørgensen and coworkers demonstrated that a linear relationship exists between the enantiomeric excess and the dielectric constant for the chiral bis(phenyloxazoline)copper(II) catalyzed HDA reaction.[17] Also, the reaction proceeded 3 times faster in chloroform in comparison to nitromethane. Chloroform

was rigorously purified according to literature prior to use;[18] thus, the higher rate in chloroform cannot simply be explained by the presence of trace amounts of acid. High levels of enantiocontrol for the dirhodium(II) catalyzed HDA reaction are seen with toluene and dichloromethane; however, the reaction proceeded 2 times faster in dichloromethane. This observation indicates there is not a direct correlation between reaction rate and enantioselectivity. A similar observation is seen later in the text when different dirhodium catalysts are examined.

Table 4. Rates of HDA reaction catalyzed by $Rh_2(4S\text{-MEOX})_4$[a]

solvent	dielectric constant	k (s^{-1}) x 10^{-4}	$t_{1/2}$ (min)	% ee[b]
Toluene	2.4	2.0	57	84
Chloroform	4.8	4.5	26	78
Dichloromethane	9.1	4.3	27	85
Nitromethane	35.9	1.4	83	65

[a] The reactions were carried out at 40°C in designated solvent with 1.0 mol % $Rh_2(S\text{-MEOX})_4$ and 1.0 equivalent of *p*-nitrobenzaldehyde to 10 equivalents of Danishefsky's diene. [b] Determined by HPLC with a Chiralpak OD-H column.

3.8 Influence of Reaction Temperature and Activation Energy

Optimization of the reaction conditions for the dirhodium(II) catalyzed HDA reaction (Chapter 2) revealed that the percent yield significantly increased as the temperature was increased. We investigated the influence of temperature on the rate constant and determined the corresponding activation energy. Not surprisingly, the rate constant increases as the temperature increases for the $Rh_2(4S\text{-MPPIM})_4$ catalyzed reaction between *p*-nitrobenzaldehyde and Danishefsky's diene (Table 5). The reaction at 60°C proceeded 4 times faster than that performed at room temperature. Gugelchuk and Doherty-Kirby have observed a similar trend in the nickel-catalyzed inverse homo-Diels-Alder reaction of methyl vinyl ketone and 7-substituted norbornadienes.[1]

Table 5. Experimental rate constants (in s^{-1} M^{-2}) of the HDA reaction between *p*-nitrobenzaldehyde and Danishefsky's diene at different temperatures.[a]

Temperature (^oC)	Rate Constant (s^{-1} M^{-2})
0	$8.7 \times 10^{-3} \pm 0.002$
25	$4.1 \times 10^{-2} \pm 0.01$
45	$1.1 \times 10^{-1} \pm 0.002$
60	$1.6 \times 10^{-1} \pm 0.04$

[a] The reactions were carried out at the designated temperature with 1.0 mol % Rh_2(*S*-MPPIM)$_4$ and 1.0 equivalent of *p*-nitrobenzaldehyde to 10 equivalents of Danishefsky's diene.

The activation energy for the HDA reaction between *p*-nitrobenzaldehyde and **1** was determined from the rate constants at different temperatures (Table 5). In 2001, Jørgensen and coworkers examined the transition state energy for the uncatalyzed reaction between benzaldehyde and Danishefsky's diene using AM1 calculations and reported the activation energy to be 27 kcal mol^{-1}.[5] The activation energy for the Rh_2(4*S*-MPPIM)$_4$-catalyzed reaction between *p*-nitrobenzaldehyde and **1** was determined using the Arrhenius equation from the plot of ln k_{obs} vs 1/T [k_{obs} is k[diene]$_0$[catalyst]$_0$ (Figure 8) and T is given in degrees Kelvin]. Using this equation, the activation energy was calculated to be 21 kcal/mol for the catalyzed reaction. The activation energy for the uncatalyzed reaction was determined to be 46 kcal/mol; however, this result requires further investigation because it was calculated using only two temperature points (25 and 60 ^oC).

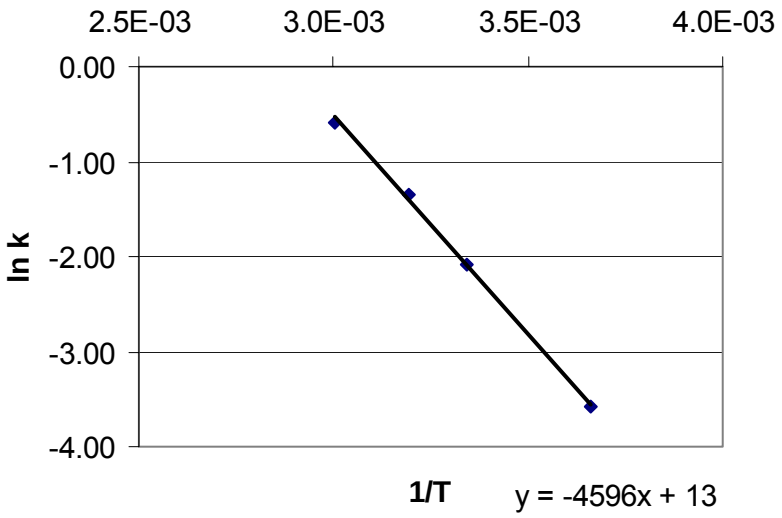


Figure 8. Arrhenius plot of ln k_{obs} vs. 1/T.

From the data in Table 5 both the enthalpy and entropy of activation can be determined for the HDA reaction. The enthalpy of activation ($\Delta H^{\ddagger}$) is the difference in bond energies between the reactants and the transition state. The entropy of activation ($\Delta S^{\ddagger}$) is the difference in entropy between the reactants and the transition state. The enthalpy ($\Delta H^{\ddagger}$), which was determined from the equation $E_a = \Delta H^{\ddagger} - RT$, was calculated to be 20 kcal mol^{-1} and the entropy change ($\Delta S^{\ddagger}$) was subsequently determined to be -33 eu (Eq. 8) . The latter value indicates a positive entropy change (from order to disorder) and is energetically favorable for the formation of products in the dirhodium(II) catalyzed HDA reaction. Similar $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ values are seen for the Diels-Alder reaction.[1]

$$\Delta S^{\neq} = \frac{\Delta H^{\neq}}{T} + R \ln \frac{hk_r}{KkT} \qquad (8)$$

3.9 Influence of Dirhodium(II) Catalyst

A screening of the dirhodium(II) carboxamidate catalysts on hand revealed that Rh_2(4*S*-MPPIM)$_4$ and Rh_2(4*S*-MEOX)$_4$ afforded the highest levels of enantiocontrol for the HDA reaction of **1** with aromatic and aliphatic aldehydes (Chapter 2). We wanted to understand the ability of dirhodium(II) carboxamidates to catalyze effectively the hetero-Diels-Alder reaction and synthesize new catalysts which are more active (i.e. have higher rate constants) without sacrificing enantioselectivity. Additionally, we were curious to determine if a direct relationship exists between rate constant and enantioselectivity for the HDA reaction. Therefore we asked the following question: do ligands attached to the metal center affect the reaction rate and, in turn, how does the ligand or reaction rate affect the enantioselectivity? Thus, a careful investigation of dirhodium(II) carboxamidates was undertaken, and their rate constants were determined for the reaction between **1** and *p*-nitrobenzaldehyde. Subsequently, the enantiopurity of the dihydropyran formed from the carboxamidate catalyzed reaction was weighed against the corresponding rate constant to determine if there is a correlation.

The influence of the ligand was first examined for the reaction between *p*-nitrobenzaldehyde and **1** at 60^{o}C in chloroform (Figure 9). The data shown in Figure 9 reveals that the azetidinone catalyst, Rh_2(IBAZ)$_4$, catalyzes the cycloaddition 4 times faster than the pyrrolidinone based catalyst, Rh_2(MEPY)$_4$ (which is the catalyst with the slowest reaction rate). Catalysts Rh_2(Oct)$_4$, Rh_2(MEOX)$_4$, and Rh_2(MPPIM)$_4$, have similar reaction rate constants ranging from 0.133 to 0.163 s^{-1} M^{-2}. Notably the highest enantiocontrol is provided by Rh_2(MPPIM)$_4$; however this

catalyst does not have the largest rate constant. Additionally, $Rh_2(IBAZ)_4$ affords the dihydropyran product in the lowest level of enantiopurity; however, $Rh_2(IBAZ)_4$ catalyzes the HDA reaction with the faster rate. This suggests a relationship does not exist between reaction rate and enantiocontrol.

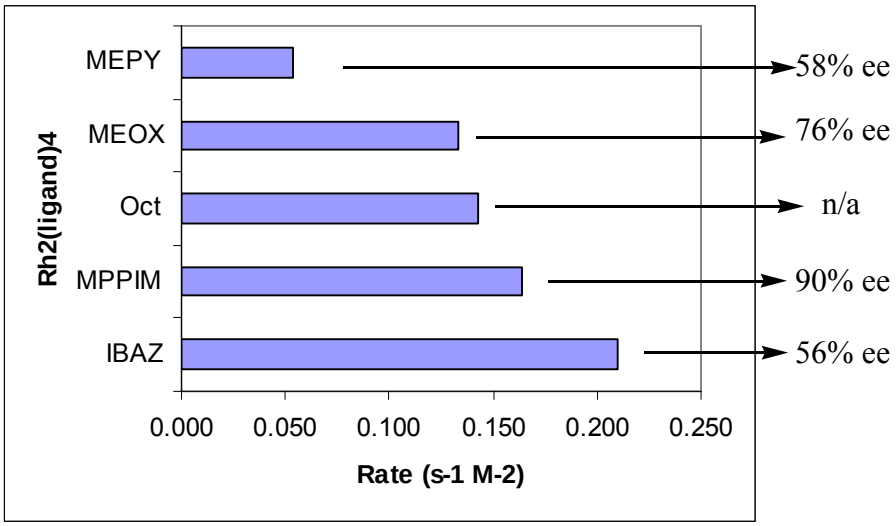
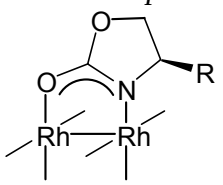


Figure 9. Rates and enantioselectivity of dirhodium(II) carboxamidate catalysts for the HDA reaction between *p*-nitrobenzaldehyde and Danishefsky's diene in $CHCl_3$ at 60^oC

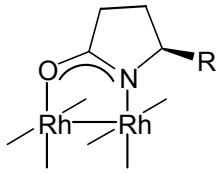
The effect of substituents directly attached to a base ligand on reaction rate was subsequently explored. For example, the role of the carboxylate carbonyl group was examined in the oxazolidinone based ligands. Interestingly, $Rh_2(IPOX)_4$, and $Rh_2(PHOX)_4$, in which an isopropyl and a phenyl group (respectively) replaces the carboxylate group present in $Rh_2(MEOX)_4$, afford much lower rate constants and stereocontrol (Table 6). This outcome suggests the special role of the carboxylate in determining both the enantioselectivity and rate of the reaction. Notably, $Rh_2(PHOX)_4$ affords the dihydropyran product in a measurably higher enantioselectivity in comparison to $Rh_2(IPOX)_4$; however, the rate constants are comparable. This again indicates a direct correlation does not exist between reaction

rate and enantioselectivity. Replacing the carboxylate with a carboxamide ($Rh_2(DMAP)_4$) does not offer any advantage with respect to reaction rate or stereocontrol.

Table 6. Rate constants and enantioselectivity of dirhodium(II) carboxamidate catalyzed cycloaddition of *p*-nitrobenzaldehyde and Danishefsky's diene.[a]



$Rh_2(4R\text{-IPOX})_4$, R=^{i}Pr
$Rh_2(4R\text{-PHOX})_4$, R=Ph
$Rh_2(4S\text{-MEOX})_4$, R=CO_2Me



$Rh_2(5S\text{-MEPY})_4$, R=CO_2Me
$Rh_2(5S\text{-DMAP})_4$, R=$CONMe_2$

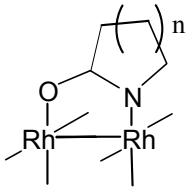
catalyst	k (s^{-1} M^{-2})	$t_{1/2}$ (min)	% ee[b]
$Rh_2(IPOX)_4$	0.054	34	6
$Rh_2(PHOX)_4$	0.047	39	54
$Rh_2(MEOX)_4$	0.13	14	76
$Rh_2(MEPY)_4$	0.053	35	58
$Rh_2(DMAP)_4$	0.042	44	35

[a] The reactions were carried out at 60°C in chloroform with 1.0 mol % catalyst and 1.0 equivalent of *p*-nitrobenzaldehyde to 10 equivalents of Danishefsky's diene. [b] Determined by HPLC with a Chiralpak OD-H column.

The screened dirhodium(II) carboxamidates all contain a five-membered ring ligand directly attached to the dirhodium core except for the azetidinone catalyst, which has a four-membered ring backbone. This azetidinone catalyst [$Rh_2(IBAZ)_4$] catalyzes the reaction between *p*-nitrobenzaldehyde and **1** at a faster rate overall compared to catalysts that contain five-membered rings (Figure 9). A six-membered ring carboxamidate ligand is present in Hashimoto's catalyst (Chapter 1). This system appears to be more active than $Rh_2(4S\text{-MPPIM})_4$, a phenomenon which is manifested by shorter reaction times of the former.[19] We embarked upon a study of the ring size of the carboxamidate ligands that are the most active for catalysts in the HDA reaction.

Using the parent achiral catalysts we investigated the relationship between ligand ring size and reaction rate (Table 7). Notably, the reactivity of the catalyst with respect to the ring size of the ligand attached to the dirhodium(II) core is 5 > 7 > 6 according to the reaction rate constants. In addition, the five-membered $Rh_2(Pyr)_4$ catalyzes the reaction 3 times faster than the six-membered catalyst $Rh_2(VALPY)_4$, which was the slowest of the catalysts examined. Attempts at synthesizing the four-membered carboxamidate were unsuccessful; however, we feel that the azetidinone catalyst would have a higher rate constant than the pyrolidinone catalyst (based on the results shown in Figure 9). The results in Table 7 suggest that the reactivity of Hashimoto's catalyst is most likely a consequence of the phthalimido group present on the carboxamidate ligand.

Table 7. Effect of ring size on the rate constants of the dirhodium(II) catalyzed cycloaddition of *p*-nitrobenzaldehyde and Danishefsky's diene.[a]



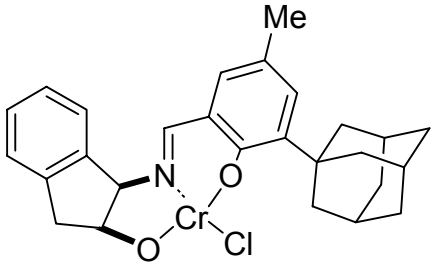
n =1 $Rh_2(Pyr)_4$
n =2 $Rh_2(VALPY)_4$
n =3 $Rh_2(CAPY)_4$

n	k (s^{-1} M^{-2})	k_{rel}	$t_{1/2}$ (min)
1	0.10	2.8	19
2	0.036	1.0	51
3	0.068	1.9	27

[a] The reactions were carried out at 60°C in chloroform with 1.0 mol % catalyst and 1.0 equivalent of *p*-nitrobenzaldehyde to 10 equivalents of Danishefsky's diene.

3.10 Other Lewis Acid Catalysts

We have also examined the mechanistic details for two other catalysts known to promote the hetero-Diels-Alder reaction. Initially, the rate data was obtained for the reaction between *p*-nitrobenzaldehyde and Danishefsky diene catalyzed by Jacobsen's catalyst **6.**[20,21] Notably, the rate constant for the reaction between *p*-nitrobenzaldehyde and **1** catalyzed by 1.0 mol% of catalyst **6** at 25°C is 3.49 x 10^{-1} ± 0.003 $s^{-1}M^{-2}$. Similar to $Rh_2(MPPIM)_4$, **6** catalyzes the cycloaddition of *p*-nitrobenzaldehyde and **1** twenty-two times faster than it catalyzes benzaldehyde and **1**. The catalyst order of **6** at 25°C was found to be 2.2 (R^2 = 0.9913) with catalyst loadings ranging between 0.2 mol% and 1.0 mol%. This order is consistent with preliminary evidence reported by Jacobsen and coworkers, wherein they describe the fact that the catalyst operates in a dimeric form.[22] Remarkably, no association was seen between **6** and *p*-tolualdehyde via NMR spectral shifts. Additionally, no isosbestic point was seen in the UV-Vis spectrum of **6** and *p*-anisaldehyde or *p*-nitrobenzaldehyde, unlike the spectrum recorded for $Rh_2(4S\text{-}MPPIM)_4$ (Figure 2).



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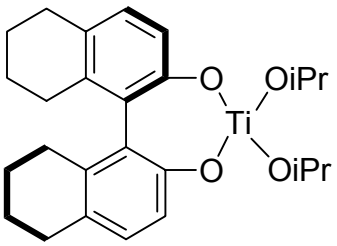

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In addition to the results for Jacobsen's catalyst **6**, no isosbestic point was observed with titanium(IV) catalyst **7** with *p*-anisaldehyde, benzaldehyde, or *p*-nitrobenzaldehyde. Similarly, Feng and Jiang have reported no change in the ^1H NMR spectrum or IR spectrum between **7** and a 5-fold excess of benzaldehyde.[23]

These results confirm there is no measurable interaction between **7** and the aldehyde. We did discover however, that there is a very modest association between catalyst **7** (1:1 ligand:metal ratio) and **1** of 1.1 M^{-1}. This association is probably related to the formation of the active species, described by Feng and Jiang,[23] that catalyzes the hetero-Diels-Alder reaction via a Mukaiyama aldol process (Chapter one). Interestingly, no association to the diene was observed when a 2:1 ligand:titanium(IV) mixture was examined suggesting a 2:1 ligand:metal complex forms with no labile ligands. Notably, the rate is significantly faster when a 1:1 mixture of ligand to metal is employed, in comparison to a 2:1 mixture. Additionally when 2 mol% catalyst (2:1 ligand:metal) is used, the half life is approximately 23 min; however, a 1:1 ligand to metal ratio provides a half life that is less than 6 min. This phenomenon concurs with Feng and Jiang, who report that optimal yields and stereoselectivities are obtained using a 1.1:1 binol : titanium mixture. Therefore, a 1:1 ligand to metal ratio allows for association with the diene and leads to superior reaction rates because the active catalyst intermediate readily forms; however, with a 2:1 ligand to metal ratio, no association to the diene is observed because the catalyst forms stable complex in which 2 ligands are directly attached to titanium.

3.11 Conclusion

Since the inception of this research program in the Doyle laboratory, using dirhodium(II) carboxamidate catalysts to promote the hetero-Diels-Alder reaction has been explored with a degree of success. Capitalizing on previously reported kinetic studies performed on the Diels-Alder reaction, we have explored, for the first time in the field, equilibrium and rate constants for the Lewis acid catalyzed HDA reaction.

By performing kinetic studies on the dirhodium(II) catalyzed HDA reaction, key factors that influence reaction rate have been identified. We have likewise provided a systematic approach and framework for a detailed kinetic study. In addition, we have elucidated catalyst structure-activity relationships. The results obtained in our study portray a more complex process than what is presently understood and suggests the need for more extensive evaluation of the basic tenants of Lewis acid catalysis in the HDA reaction. Questions still remain with regard to the factors that govern enantiocontrol in the Lewis acid catalyzed HDA reaction. The answer to these questions would allow the development of superior chiral catalysts. Dirhodium(II) catalysts uniquely offer the opportunity to investigate multiple mechanistic aspects of the Lewis acid catalyzed hetero-Diels-Alder reaction under very well-defined conditions.

Preliminary competition studies indicate a difference in the rate of reaction for various *para*-substituted aldehydes. Subsequently, we developed a kinetic analysis that allows for a quick and efficient determination of rate constants by monitoring the loss of aldehyde over time via gas chromatography. In addition, equilibrium constants for aldehyde-catalyst binding were readily measured with a UV spectrophotometer. Kinetic measurements for reactions with *para*-substituted aromatic aldehydes demonstrate a pronounced electronic influence on the rate of the HDA reaction with a Hammett ρ value of +1.9. Additionally, *p*-nitrobenzaldehyde reacts more than 700 times faster than does *p*-anisaldehyde.

The variable reaction rate order with respect to the catalyst in dirhodium(II)-catalyzed reactions raises questions concerning the exact role of the catalyst. We feel

the fractional order is related to a complex interplay of catalyst aggregation, competitive inhibition by reacting aldehyde, and solvation. However, further studies are required to fully understand the interactions between aldehyde and catalyst.

Dirhodium(II) catalyst screening studies suggest that the rate for the HDA reaction is dependent on both the electronic influence of the ligand [Rh_2(IBAZ)$_4$ vs. Rh_2(MEPY)$_4$] as well as the ring size of the carboxamidate [Rh_2(Pyr)$_4$ vs. Rh_2(VALPY)$_4$]. These observation are important for future development of new catalysts that are reactive toward effectively catalyzing the asymmetric HDA reaction. However, there is not a clear correlation between reaction rate and enantioselectivity, and factors that govern enantioselectivity must still be probed.

We also examined two catalysts outside of dirhodium(II) and examined their association constants and determined their rate constants in the HDA reaction. The chromium catalyst **6** which is reported to catalyze the HDA reaction via a [4 + 2] cycloaddition, exhibits similar reaction trends to dirhodium(II) and has a reaction rate order of 2.2. Titanium catalyst **7** has a measurable association to Danishefsky's diene, which is consistent with its proposed Mukaiyama aldol mechanism.

3.12 Experimental

General. All aldehydes were obtained commercially and purified by distillation or recrystallization prior to their use. Dichloromethane, chloroform and dichloroethane were distilled prior to use according to established procedures.[18] Rh_2(4*S*-MPPIM)$_4$ **9a**,[24] Rh_2(4*S*-MEOX)$_4$ **7a**,[25] chromium catalyst **6**,[22] and titanium(IV) catalyst **7**[23] were prepared according to literature methods. Danishefsky's diene was prepared according to published procedures.[26] All reactions were carried out under a nitrogen

atmosphere (by flushing the reaction vial with nitrogen and sealing with a cap) employing oven- and flame-dried glassware.

Analytical normal phase HPLC was performed on a Hewlett-Packard 1100 series chromatograph equipped with a variable wavelength UV detector (but operated at 254 nm). Analytical GC was performed on a Hewlett Packard 5890 GC equipped with a Supelco SPB-5 column (30 m, 0.25 mm) and a flame ionization detector. Equilibrium constants were measured on a HP 8453 UV-Vis spectrometer at room temperature.

Competition reactions. To an oven-dried 1 dram vial was added aldehyde #1 (0.75 mmol), aldehyde #2 (0.75 mmol), Danishefsky's diene (0.50 mmol), 1 mol% (0.005 mmol) $Rh_2(4S\text{-}MEOX)_4$, and 3 mL of dichloromethane. The reaction was allowed to stir at 25^{o}C for 1 hour, and then 0.1 ml of the reaction solution was removed and treated with TFA. The product ratio was analyzed using gas chromatography.

Kinetics. To an oven-dried 2 dram vial was added aldehyde (0.25 mmol), biphenyl (GC standard, 0.25 mmol), 1.0 mol % catalyst and 1.0 mL of the appropriate solvent. Danishefsky's diene (2.5 mmol) was then added, and the solution was stirred at the designated temperature. The loss of aldehyde over time was measured by removing 100 μL aliquots from the solution and adding each of them to 4 mL of dichloroethane treated with 3-4 drops of trifloroacetic acid to desilylate both the product and the diene, thereby quenching the reaction. The acid was then neutralized with solid sodium bicarbonate, and samples were analyzed by GC. The reaction was allowed to proceed through at least two half-lives. Measurements were determined in duplicate or triplicate trials during the kinetic run. After each kinetic run was complete the

enantioselectivity of the reaction was determined using HPLC to ensure that the selectivity was consistent with that found in the non-kinetic experiment. The rate constant (determined through at least one and, generally, two half lives) was calculated by linear least-squares regression from the linear pseudo-first order kinetic plot.

Catalyst order. The general kinetic procedure was followed; however, the catalyst loadings were varied between 0.2 – 5.0 mol%.

Equilibrium constants. The axially-coordinated acetonitrile ligands of the catalysts were removed by dissolving the catalyst in 1,2-dichloroethane and removing the volatiles under reduced pressure, followed by heating the solid to 60^{o}C under vacuum (<1 mm Hg) overnight prior to use. The color change from orange to blue indicated the absence of acetonitrile coordination. Aldehyde stock solutions were prepared by dissolving appropriate amounts of aldehydes in dichloroethane. The acetonitrile-free catalyst solid was dissolved in 4.00 mL of dichloroethane, and 3.00 mL of the solution was transferred to a cuvette by syringe. A UV-Vis spectrum was measured between 400 nm to 800 nm. Sequentially, 5.0 μL aldehyde stock solution (for *p*-chlorobenzaldehyde and *p*-nitrobenzaldehyde, 10.0 μL) was added to the cuvette. The addition/UV-Vis spectrum measurements process was repeated 10 times.

3.13 References

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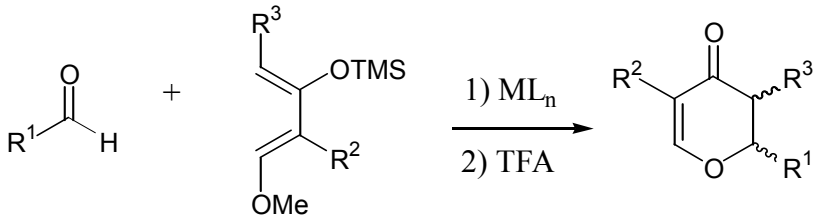
Chapter 4: Influence of the Diene

4.1 Introduction

The hetero-Diels-Alder (HDA) reaction of aldehydes and 1-alkoxy-3-trialkylsiloxy-1,3-butadiene (Danishefsky's diene, **1**) mediated by chiral Lewis acids provides synthetically useful dihydropyran derivatives (Eq. 1).[1]



(1)

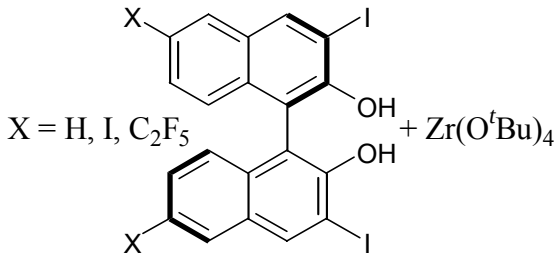
4

1 R^2=R^3= H
2 R^2=R^3= Me
3 R^2=Me, R^3=H

The focus of most investigations has been on **1**, although a few studies have employed other substituted derivatives, including **2** and **3**, with the advantage of providing information on diastereocontrol as well as enantiocontrol.[2-7] For example, Danishefsky and coworkers investigated the influence of different Lewis acids upon diastereoselectivity in reactions between benzaldehyde and 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene (**2**).[8] When performed in the presence of the classic Lewis acid BF_3, this reaction proceeded via a stepwise Mukaiyama aldol pathway leading to dihydropyran products having low diastereoselectivity. However, when $ZnCl_2$ was used as the Lewis acid, the reaction occurred by a concerted [4 +2] cycloaddition giving products with high diastereoselectivity. The major product from

the BF_3-catalyzed reaction had the 2,3-trans configuration. Conversely, the major product from the $ZnCl_2$-catalyzed reaction gave the 2,3-cis product.

The use of a chiral metal-based Lewis acids in the reaction between benzaldehyde and **2** affords 2,3-*cis*-disubstituted pyranone derivatives. The exception is Kobayashi's zirconium catalyst **5**, but in this case the reaction occurs via the stepwise Mukaiyama aldol pathway which affords *trans* products selectively.[3] The intermediate aldol adduct, which was carefully isolated and exhibited high *anti*-selectivity (*syn*/*anti* = 8/92), was easily cyclized under acidic conditions to give the HDA product in a *cis*/*trans* ratio of 8/92. Steric repulsion between the methyl group of the enolate and the zirconium catalyst explains the observed *anti* selectivity in an open-chain transition state model.[9,10]



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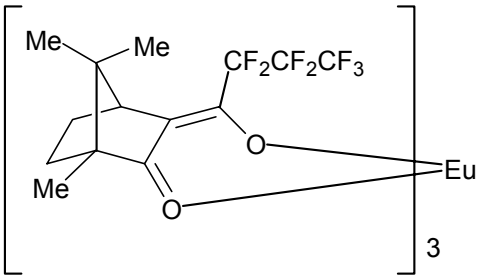

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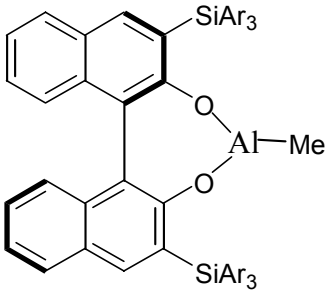

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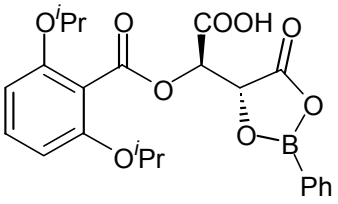


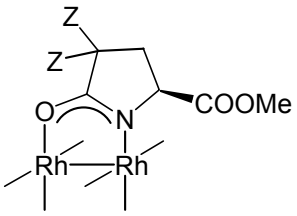
8

The use of chiral catalysts to effect enantioselective hetero-Diels-Alder reactions with diene **2** has seen a tremendous amount of success over the past 20 years. Initial efforts in 1983 by Danishefsky and coworkers generated the HDA adduct in 36 % ee for the reaction with benzaldehyde and **2** in the presence of a $Eu(hfc)_3$ catalyst (**6**).[7] Five years later a report by the Yamamoto group, described asymmetric cycloaddition reactions of aromatic and aliphatic aldehydes with **2** using bis(triarylsilyl)binaphthol aluminum complexes as catalysts (**7**). Notably high enantioselectivities ranging between 86-97 % ee were observed for the major *cis* adduct.[6] Yamamoto and coworkers later developed a different system based on a chiral (acyloxy)borane catalyst **8** derived from a tartaric acid derivative that provided dihydropyran products in up to 97 % ee.[4] Recently, Kobayashi et al, reported the first catalytic asymmetric *trans*-selective HDA reaction using a chiral zirconium catalyst **5**.[3] Enantioselectivities as high as 98 % ee were achieved with 10 mol % catalyst.

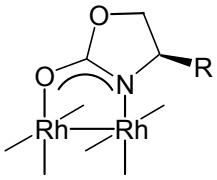
The literature precedent over the past several years documents an increasing array of chiral catalysts for the HDA reaction with **2**. However, there have been few studies that explain the effect of substitution on the diene for the HDA cycloaddition reaction. Furthermore, substitution on the diene and its influence on reaction rate, enantioselectivity, and approach to the aldehyde-catalyst complex, have not been explored in the literature. Additionally, challenges still remain in the HDA cycloaddition with **2** regarding practical catalyst loadings, and high stereoselectivities. We embarked upon an investigation to explore the influence of substitution on the diene and provide solutions to the challenges still remaining with respect to **2**.

4.2 Dimethyl Diene and Nitro-substituted Aromatic Aldehydes

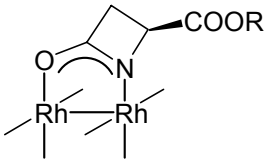
We have reported that dirhodium(II) carboxamidates catalyze the HDA reaction of simple aldehydes and Danishefsky's diene (**1**) via a concerted [4 + 2] cycloaddition pathway with catalyst loadings as low as 0.01 mol % (Chapter 2).[11] Dimethyl-substituted diene **2** has also been used to test the mechanistic pathway for the hetero-Diels-Alder reaction with *cis* stereochemistry being indicative of the [4+2] cycloaddition pathway.[12] As our research into dirhodium(II) carboxamidate catalyzed HDA reactions unfolded, we sought to further investigate the mechanism and the influence of the diene in the catalytic system.



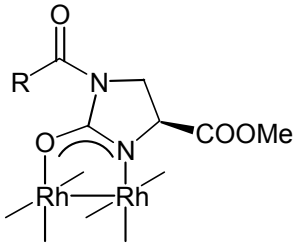
9 Rh_2(5*S*-MEPY)$_4$, Z = H
10 Rh_2(5*S*-dFMEPY)$_4$, Z = F



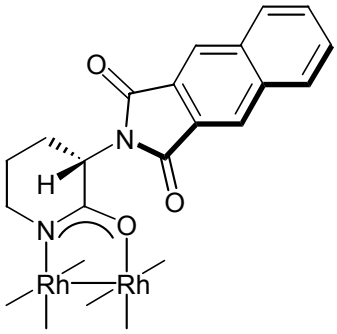
11 Rh_2(4*S*-MEOX)$_4$, R=COOMe
12 Rh_2(4*R*-IPOX)$_4$, R=^{I}Pr



13 Rh_2(4*S*-MEAZ)$_4$, R=Me
14 Rh_2(4*S*-IBAZ)$_4$, R=^{i}Bu



15 Rh_2(4*S*-MPPIM)$_4$, R=CH_2CH_2Ph
16 Rh_2(4*S*-MACIM)$_4$, R=Me



17 Rh_2(*S*-BPTPI)$_4$

At the outset of our investigation, the reaction between diene **2** and *p*-nitrobenzaldehyde was examined at room temperature in the presence of 1.0 mol % of dirhodium(II) catalysts **9**-**16**. In previous studies with **1**, use of Rh_2(4*S*-MPPIM)$_4$ led to the highest levels of enantiocontrol (Chapter 2). However, when the same catalyst was used in the reaction with dimethyl analog **2** and *p*-nitrobenzaldehyde, the nearly racemic 2,3-*cis* product was formed (Table 1). The low level of enantiocontrol is thought to occur because of steric interactions between the catalyst's *N*-3-

phenylpropanoyl attachment and the incoming diene, rendering the asymmetric catalysis pathway ineffective and allowing the uncatalyzed background reaction to dominate (Figure 1).

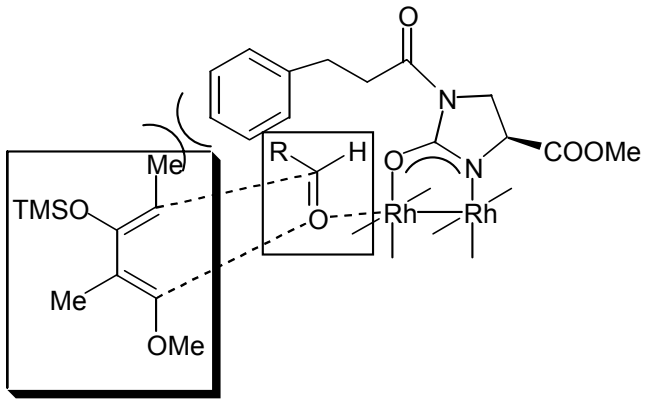


Figure 1. Interaction of diene **2** and Rh_2(4*S*-MPPIM)$_4$-aldehyde complex

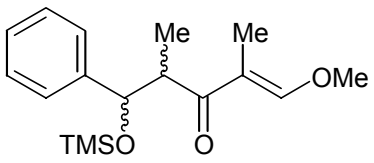
The reaction in which no catalyst is present proceeds with less than 24 % conversion of the aldehyde and a diastereomeric ratio for **4** of 7 : 93 (*trans* : *cis*) after 40 hours, analogous to results with Rh_2(4*S*-MPPIM)$_4$ which also gave product with very low enantiocontrol. When 1.0 mol % of the less sterically demanding Rh_2(4*S*-MACIM)$_4$ (**16**) was used, an increase in enantioselectivity was observed (40 % ee with **16** vs. 8 % ee with **15**). However, the highest level of enantiocontrol was observed when Rh_2(4*S*-MEOX)$_4$ (**11**) was used as a Lewis acid catalyst, giving 2,3-*cis*-dihydropyran **4** in 90 % yield and 96 % ee. Interestingly, Rh_2(4*S*-IPOX)$_4$ (**12**), in which an isopropyl group replaces the carboxylate group present in Rh_2(4*S*-MEOX)$_4$, gives much lower stereocontrol (also in Table 1), demonstrating the special role of the carboxylate in controlling enantioselectivity.[13]

Table 1. Enantioselectivity in Catalytic Cycloaddition of *p*-Nitrobenzaldehyde to 1-Methoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene[a]

catalyst	yield (%)[b]	ee (%)[c]
Rh_2(4S-MEPY)$_4$	63	48
Rh_2(4S-dFMEPY)$_4$	78	81
Rh_2(4S-MEOX)$_4$	90	96
Rh_2(4S-IPOX)$_4$	86	17
Rh_2(4S-MEAZ)$_4$	80	38
Rh_2(4S-IBAZ)$_4$	<30	23
Rh_2(4S-MPPIM)$_4$	38	8
Rh_2(4S-MACIM)$_4$	51	40
none[d]	<24	n/a

[a] Reactions were carried out at room temperature for 24 hours with 1.0 mol % catalyst in a solution of dry CH_2Cl_2 with 1.0 eq of *p*-nitrobenzaldehyde and 1.2 eq of diene, followed by treatment with TFA to afford the *cis* dihydropyran. [b] Isolated yield after column chromatography. [c] Determined by HPLC with a Chiralpak OD column. [d] Reaction time is 40 hours.

The diastereoselectivity for the HDA reaction of diene **2** is indicative of the predominant mechanistic pathway. The dirhodium(II) compounds shown in Table 1 catalyze the formation of the *cis*-substituted dihydropyran from *p*-nitrobenzaldehyde with diastereocontrol greater than 5:95 lending further credence to the operation of the [4 + 2] cycloaddition pathway. Furthermore, the ^{1}H NMR of the reaction solution prior to treatment with TFA does not reveal the presence of the acyclic adduct (**18**) anticipated from the Mukaiyama aldol pathway. Recently, Hashimoto and coworkers found similar diastereoselectivities in reactions between *p*-nitrobenzaldehyde and **2** using 1.0 mol % of their interesting Rh_2(*S*-BPTPI)$_4$ catalyst **17** (Figure 1) whose activity appears to exceed that of Rh_2(4S-MPPIM)$_4$ (**15**).[14] Using **17**, they report essentially complete *cis*-diastereoselectivity and an enantiomeric excess of 97 %.

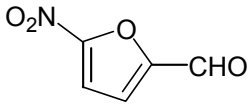
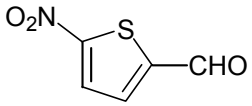
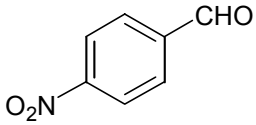


18

We were interested in obtaining a quantitative comparison between dienes **1** and **2** in order to understand the effect of substitution at R^2 and R^3. The rate constant for the reaction between **2** and *p*-nitrobenzaldehyde catalyzed by Rh_2(4*S*-MEOX)$_4$ (**7**) at room temperature in CH_2Cl_2 is slower than that using the Danishefsky diene **1** by a factor of 3.7 (k = 6.19 x 10^{-3} $s^{-1}M^{-2}$ for **2** vs 23.1 x 10^{-3} s^{-1} M^{-2} for **1**). This decrease in rate is most likely due to steric interactions between the diene and the aldehyde-catalyst complex. Kobayashi and coworkers also noted that disubstituted diene **2** was less reactive in their systems.[2]

The Rh_2(4*S*-MEOX)$_4$ (**11**) catalytic system, which was optimum for reactions with *p*-nitrobenzaldehyde, was subsequently applied to the asymmetric HDA reaction with other nitro-substituted aromatic aldehydes. With dimethyl derivative **2** reactions of representative reactive aldehydes, 5-nitro-2-furancarboxaldehyde, 5-nitro-2-thiophenecarbox-aldehyde and *p*-nitrobenzaldehyde, catalyzed by Rh_2(4S-MEOX)$_4$, afforded the corresponding 2,3-*cis* products exclusively (Table 2).[11a] The use of other dirhodium(II) carboxamidates did not prove to be more advantageous for 5-nitro-2-furancarboxaldehyde or 5-nitro-2-thiophenecarboxaldehyde. For example, Rh_2(4*S*-dFMEPY)$_4$ and Rh_2(4*S*-dFIBAZ)$_4$ provided the dimethyl-substituted dihydropyran in 80 and 64 % ee, respectively for 5-nitro-2-furancarboxaldehyde.

Table 2. Enantioselectivity in Catalytic Cycloaddition of **2** with Nitro-substituted Aldehydes Catalyzed by $Rh_2(4S\text{-}MEOX)_4$[a]

Aldehyde	time	temperature	yield (%)[b]	ee (%)[c]
	1 day	25	95	90
	1 day	25	96	97
	1 day	25	90	96

[a]Reactions were carried out at room temperature with 1.0 mol % catalyst in a solution of dry CH_2Cl_2 with 1.0 eq of aldehyde and 1.2 eq of diene for 24 h at 25°C, followed by treatment with TFA to afford the *cis* dihydropyran. [b]Isolated yield after column chromatography [c]Determined by HPLC with a Chiralpak OD column [d]Reaction was performed without solvent.

The ability to minimize catalyst loading is imperative in asymmetric catalysis. We are able to effectively catalyze the hetero-Diels-Alder reaction with catalyst loadings as low as 0.01 mol % for the reaction between diene **2** and 5-nitro-2-thiophenecarboxaldehyde catalyzed by $Rh_2(4S\text{-}MEOX)_4$. The yield remains unchanged (when catalyst loadings are decreased from 1.0 mol % to 0.01 mol %. The enantioselectivity does not change by decreasing the catalyst loading from 1.0 mol % to 0.1 mol %; however, enantioselectivity decreases at 0.01 mol % to 86 % (Figure 2) suggesting that the limit has been reached in competition with the background reaction.

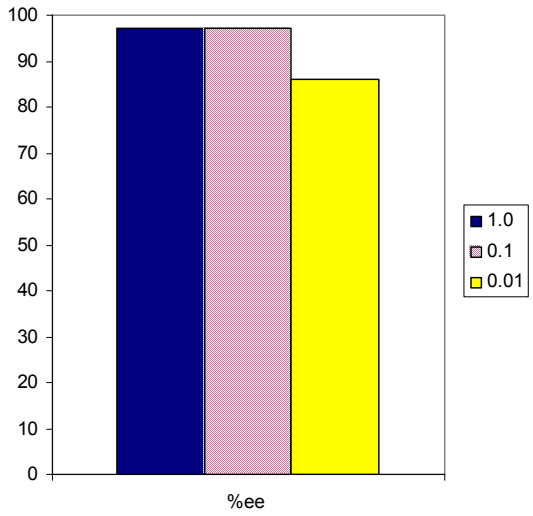


Figure 2. Enantioselectivity of product mixtures reaction between diene **2** and 5-nitro-2-thiophenecarboxaldehyde catalyzed by $Rh_2(4S\text{-MEOX})_4$ using 1.0 mol %, 0.1 mol %, and 0.01 mol % catalyst loadings.

4.3 Dimethyl Diene and para-Substituted Aromatic Aldehydes

Kinetic investigations for the reactions between Danishefsky's diene and *para*-substituted aromatic aldehydes revealed a pronounced electronic influence on the rate of the reaction (Chapter 3) with a Hammett ρ value of +1.9 (versus σ^+).[11a] A similar phenomenon is seen with diene **2** with respect to reaction times. For example, nitro- substituted aromatic aldehydes reacted with diene **2** in good yields and selectivities at ambient temperatures; however, when other *para*-substituted aldehydes were investigated, low % yields and % ee's were obtained even at 40°C (Table 3). The diastereoselectivity for the cycloaddition with **2** decreases with electron-donating *para*-substituents. The product arising from *p*-tolualdehyde has a diastereomeric ratio (dr) of 82:18 (*cis*:*trans*) versus 90:10 for the product of *p*-chlorobenzaldehyde and **2**.

Table 3. Reaction of aromatic aldehydes and **2** in the presence of Rh_2(R-MEOX)$_4$[a]

aldehyde	time (d)	*cis*:*trans*	% ee[b]	% yield[c]
p-$CH_3C_6H_4$	6	82:18	26	27
C_6H_5	6	85:15	21	17
p-ClC_6H_4	6	90:10	0	38
p-$NO_2C_6H_4$[d]	1	100:0	87	90

[a] The reactions were carried out at 40°C, with 1 mol % catalyst, and in a solution of dry CH_2Cl_2 using 1 equivalent of aldehyde to 1.2 equivalents of **2**. Treatment with TFA, followed by column chromatography, afforded the corresponding dihydropyran. [b] Determined by HPLC using a Chiralpak OD column for the major isomer. [c] Isolated yield after chromatography. [d] Reaction was performed at room temperature.

We set out to optimize the diastereomeric ratio and enantioselectivity for the reaction between *p*-chlorobenzaldehyde and **2**. The diastereoselectivity was dependent on solvent, and reaction temperature (Table 4). Reactions were performed at 60°C due to the lower reactivity of diene **2** relative to **1**. However, as the reaction temperature is increased (in toluene), diastereoselectivity decreases without detectable diminution in enantiocontrol. The solvent was found to have a direct and measurable influence on diastereoselectivity. Toluene offers the highest levels of diastereocontrol, but diastereoselectivity decreased as the solvent's dielectric constant increased. Interestingly, the highest level of enantiocontrol is seen when no solvent is present (72 % ee). No improvement in the dr was observed with other dirhodium(II) carboxamidate catalysts. For example, Rh_2(5*S*-dFMEPY)$_4$ (**10**) provided the dimethyl-substituted dihydropyran in a 90:10 (*cis*:*trans*) dr in toluene at 60°C.

Table 4. HDA reaction of *p*-chlorobenzaldehyde and **2** catalyzed by Rh_2(4*S*-MEOX)$_4$[a]

temp (^{o}C)	solvent	dielectric constant	time (d)	yield (%)[b]	dr (*cis*:*trans*)[c]	ee (%)[d]
60	$CHCl_3$	4.8	5 days	22	94 : 6	14
40	Toluene	2.4	5 days	58	99.5 : 0.5	36
60	Toluene	2.4	5 days	95	98 : 2	38
60	CH_3NO_2	35.9	5 days	29	85 : 15	63
60	DCE	16.7	5 days	36	89 : 11	18
60	none	---------	7 days	84	96 : 4	72

[a] Reactions were carried out at the given temperature with 1.0 mol % Rh_2(*S*-MEOX)$_4$ with 1.0 eq of aldehyde and 1.2 eq of diene, followed by treatment with TFA. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC with a Chiralpak OD column.

With the optimized reaction conditions on hand, the HDA cycloadditions of other aromatic dienophiles and **2** were investigated. Benzaldehyde and *p*-tolualdehyde provided dihydropyran products in high diastereoselectivities with moderate enantioselectivity. For example, the *cis* diastereomer is formed exclusively in 86 % yield for the reaction between benzaldehyde and diene **2** in toluene at 60^{o}C; however, the enantiomeric excess is only 28 %. *p*-Anisaldehyde required long reaction times (29 % conversion after 7 days in $CHCl_3$ at 60^{o}C) and as a result, the dr was not determined owing to a small amount of product.

4.4 Mono Methyl Diene and Nitro-substituted Aromatic Aldehydes

1-Methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene[15] (**3**), previously used in the asymmetric aza-Diels-Alder reaction,[16] has not been extensively investigated in the hetero-Diels-Alder reaction with aldehydes. To investigate the influence of substitution pattern on the diene, **3** was reacted with *p*-nitrobenzaldehyde in the presence of dirhodium(II) carboxamidate catalysts (Table 5). Diene **3**, having a methyl substituent at R^2, was thought to behave similarly to **1** given that it lacked a methyl group at R^3. Our model (Figure 1) states that apparent steric repulsion

between the incoming diene and the *N*-3-phenylpropanoyl moiety of Rh_2(4*S*-MPPIM)$_4$ arises from substitution at R^3. When Rh_2(4*S*-MPPIM)$_4$ was employed as a catalyst for **3** and *p*-nitrobenzaldehyde a low level of enantiocontrol was seen in comparison with the outcome of reactions catalyzed by Rh_2(4*S*-MEOX)$_4$ or Rh_2(4*S*-dFMEPY)$_4$ (similar to results from reactions with diene **2**). Rh_2(4*S*-MEOX)$_4$ affords the mono-methyl substituted dihydropyran in 95 % ee, and 66 % yield (Table 5). As stated earlier, Rh_2(4*S*-MACIM)$_4$ offered higher enantioselectivities for diene **2** compared to Rh_2(4*S*-MPPIM)$_4$ (40 % ee vs. 8 % ee): the same is not true for diene **3**.

Table 5. Enantioselectivity in the catalytic cycloaddition of *p*-nitrobenzaldehyde and diene **3.**[a]

catalyst	yield (%)[b]	ee (%)[c]
Rh_2(4*S*-MEPY)$_4$	57	66
Rh_2(4*S*-dFMEPY)$_4$	67	88
Rh_2(4*S*-MEOX)$_4$	66	95
Rh_2(4*S*-MEAZ)$_4$	74	53
Rh_2(4*S*-IBAZ)$_4$	58	76
Rh_2(4*S*-MPPIM)$_4$	30	42
Rh_2(4*S*-MACIM)$_4$	33	45

[a] Reactions were carried out at room temperature for 24 hours with 1.0 mol % catalyst in a solution of CH_2Cl_2 with 1.0 eq of aldehyde and 1.2 eq of diene, followed by treatment with TFA to afford the dihydropyran. [b] Isolated yield after column chromatography [c] Determined by HPLC with a Chiralpak OD-H column

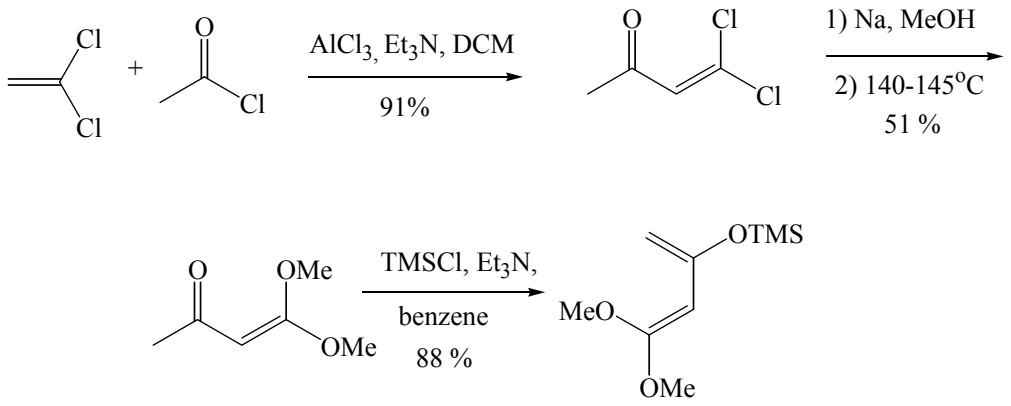
In addition to exploring the influence of arenealdehyde substituents on selectivity, we also wanted to examine the rate of the reaction. The rate constant (k = 56.3 X 10^{-03} $s^{-1}M^{-2}$) for the reaction between diene **3** and *p*-nitrobenzaldehyde is similar to that for diene **1**. However, the rate constant is greater than that for diene **2** by a factor of 9. Therefore the reactivity of the diene towards cycloaddition in the dirhodium(II) catalyzed HDA cycloaddition is as follows: **3** > **1** >> **2**.

When the scope of the reaction was examined with **3** a similar substituent-derived electronic effect was seen in comparison to **2**. Electron donating groups

decrease the reactivity of the aldehyde. Christine Hedberg in our group is presently working on optimizing the reaction conditions for various aldehyde dienophiles and diene **3**. These studies will elucidate the scope of the reaction with **3** and provide further kinetic information with regards to catalyst influence, reaction temperature, and the relationship between the diene and aldehyde-catalyst complex.

4.5 Brassard Diene

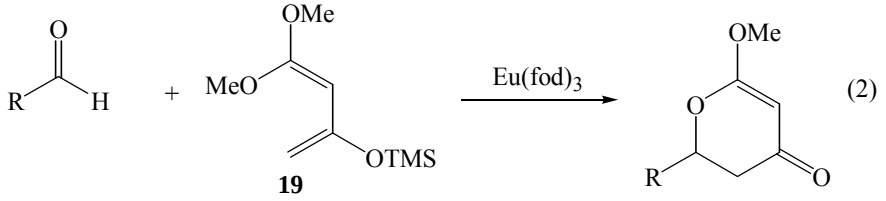
We next wanted to examine the electronic influence of the diene substituents on dirhodium(II) catalyzed HDA using the Brassard diene (**19**). We were interested to determine the reactivity of **19** in comparison to **1** for the HDA cycloaddition. The Brassard diene was synthesized according to the steps outlined in Scheme 1.[17] Due to it's instability, diene **19** was stored in the freezer as a liquid, and for longer storage in benzene in a solid matrix.



Scheme 1. Synthesis of Brassard Diene[17]

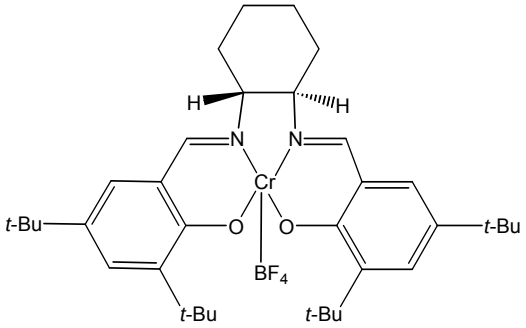
The Danishefsky[18a] group and Castellino[18b] group have reported reacting diene **19** with different aldehydes in the presence of a $Eu(fod)_3$ catalyst. Danishefsky et al report that the trioxygenated diene reacts with benzaldehyde or *n*-heptanal to

afford the corresponding dihydropyrones in 85 % and 73 % yield respectively (Eq. 2). He observed no evidence for the intermediacy of an acyclic product; however, the matter was not examined in detail. Castellino and Sims investigated a range of aliphatic aldehydes with diene **19**. They observed product yields ranging from 69-87 % at room temperature with catalyst loadings between 1-10 mol %.



Notably, there are no reports in the literature for the use of diene **19** with a chiral Lewis acid. Initially, the reaction of **19** and *p*-nitrobenzaldehyde in the presence of 1.0 mol % $Rh_2(OAc)_4$ afforded the dihydropyran adduct in 59 % yield. Representative chiral dirhodium(II) carboxamidates were then screened for the reaction between **19** and *p*-nitrobenzaldehyde (Table 6). Low levels of enantiocontrol were observed for all catalysts examined. Unfortunately, the background reaction (where no catalyst is present) takes place at a faster rate than that of the catalyzed reaction pathway [that leads to non-racemic products (Chapter 2.3)]. In fact, the dirhodium(II) catalyst apparently retards the conversion with Brassard diene leading to lower yields when the carboxamidate is present (48 % yield with $Rh_2(MEPY)_4$ versus 81 % yield without catalyst). Jacobsen's Cr(III)-salen catalyst **20** was also examined and results similar to dirhodium(II) were obtained (4 % ee and 55 % yield). We were hopeful that **19**, whose HDA reactivity surpasses **1**, would be beneficial in the reaction with aliphatic aldehydes that are less reactive towards cycloaddition. However, the aliphatic aldehyde octanal behaved similarly in the HDA reaction to *p*-

nitrobenzaldehyde, wherein the reaction proceeds well in the absence of a Lewis acid leading to product in 96 % yield.



20

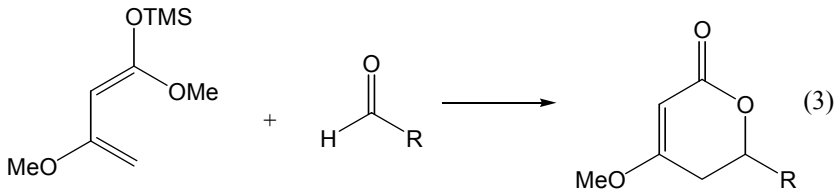
Diene **19** is exceptionally reactive in comparison to **1**. Attempts at obtaining enantioselectivity with **19**, such as lowering the reaction temperature, increasing the catalyst loading, and changing the reaction solvent, were unsuccessful. The enantioselective cycloaddition **19** with ketone dienophiles may be worthwhile to investigate due to their lower reactivity in the HDA reaction.

Table 6. Reaction of various aldehydes with Brassard diene **19**.[a]

Aldehyde	Catalyst	% Yield[b]	% ee[c]
p-nitrobenzaldehyde	Rh_2(5*R*-MEPY)$_4$	48	2
p-nitrobenzaldehyde	Rh_2(4*S*-MPPIM)$_4$	58	3
p-nitrobenzaldehyde	Rh_2(S-MEOX)$_4$	60	5
p-nitrobenzaldehyde	No catalyst	81	-
octanal	Rh_2(4*S*-MPPIM)$_4$	77	3
octanal	Rh_2(S-MEOX)$_4$	63	1
octanal	No catalyst	96	-

[a] Reactions were carried out at room temperature for 24 hours with 1.0 mol % catalyst in a solution of CH_2Cl_2 with 1.0 eq of aldehyde and 1.2 eq of diene, followed by treatment with TFA to afford the dihydropyran. [b] Isolated yield after column chromatography [c] Determined by HPLC with a Chiralpak OD column

Perhaps a superior diene to investigate (that is similar electronically to **19)** is diene **21** which was also reported by Brassard.[19] Diene **21** has been reacted with aliphatic aldehydes in the presence of Eu(hfc)$_3$ to give non-racemic products (Eq. 3).[20]



Recently Feng and coworkers described using a chiral tridentate Schiff base (titanium(IV)) complex to catalyze the reaction between aromatic aldehydes and **21** with selectivities up to 99 % ee.[21] The Feng group, however, did not provide details that elucidate the mechanism. Given the literature precedent, diene **21** may be more reactive toward aliphatic aldehydes in comparison to **1** with dirhodium(II) carboxamidate catalysts. However, the double substitution at the diene terminus may have deleterious consequences for the enantioselectivity as a consequence of steric repulsion between the aldehyde-catalyst complex and the incoming diene. The reactivity of **21** is expected to be similar to **19** but the interaction of **21** with dirhodium(II) catalysts is unknown.

4.6 Summary

The highly stereoselective HDA reaction between nitro-substituted aromatic aldehydes, or *p*-chlorobenzaldehyde and **2** is effectively catalyzed by Rh_2(4*S*-MEOX)$_4$ under mild conditions with catalyst loadings as low as 0.01 mol %.[22] The HDA reaction with **2** directly provides the 2,3-*cis*-disubstituted pyran, indicating the reaction clearly proceeds via a [4+2] cycloaddition pathway. High enantioselectivity and high diastereoselectivity are seen for aromatic aldehydes and diene **2** under the optimized catalytic conditions. Diastereoselectivity is influenced notably by the catalyst that is employed, the temperature at which the reaction is performed, and the polarity of the solvent.

The approach of dienes **2** and **3** to the aldehyde-catalyst complex is affected by the *N*-acyl group present in imidazolidinone-ligated catalysts, which provides unfavorable steric interactions. Importantly, Rh_2(4*S*-MEOX)$_4$ (**11**) and Rh_2(4*S*-dFMEPY)$_4$ (**10**) give the highest levels of enantioselectivity in the reaction between **2** or **3** and *p*-nitrobenzaldehyde. The reactivity of the dienes is **3** > **1** >> **2,** according to their rate constants. The methyl substituent at the 4-position (R^3) decreases the reactivity of the diene by a factor of approximately 4.

The Brassard diene **19** is more reactive than **1** in the HDA reaction. The reaction of **19** and *p*-nitrobenzaldehyde or octanal occurs with high yield in the absence of a Lewis acid. Dirhodium(II) carboxamidate and chromium(III) catalysts retard the conversion leading to lower yields compared to the situation when no catalyst is employed. Attempts at optimizing reaction conditions to obtain high enantioselectivity were unsuccessful for diene **19**.

4.7 Experimental

General. All aldehydes were obtained commercially and purified by distillation or recrystallization prior to their use. Dichloromethane, toluene, chloroform, nitromethane and dichloroethane were purified prior to use according to established procedures.[23] Rh_2(4*S*-MPPIM)$_4$ **9a**[24] and Rh_2(4*S*-MEOX)$_4$ **7a**[25] were prepared according to literature methods. Dienes **2**,[26] **3**,[27] and **19**[17] were prepared according to published procedures. All reactions were carried out under a nitrogen atmosphere (by flushing the reaction vial with nitrogen and capping) employing oven and flame dried glassware.

Analytical thin-layer chromatography (TLC) was performed using silica gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, cerium ammonium molybdenate, or iodide. Flash column chromatography was performed using silica gel 60Å (40-63 micron). Analytical normal phase HPLC was performed on a Hewlett-Packard 1100 series chromatograph equipped with a variable wavelength UV detector (but operated at 254 nm) and a Varian Prostar HPLC instrument equipped with a dual wavelength UV detector (254 nm). Analytical GC was performed on a Hewlett Packard 5890 GC equipped with a Supelco SPB-5 column (30 m, 0.25 mm) and a flame ionization detector.

Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ, 0.0 ppm), or with the solvent reference relative to TMS employed as an internal standard ($CDCl_3$, δ, 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), composite (comp)], coupling constants [Hz], integration). All NMR spectra were acquired at ambient temperature.

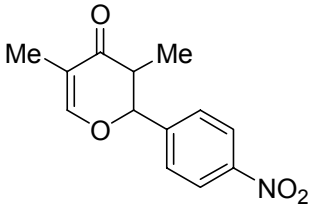
Kinetics. To an oven-dried 2 dram vial was added aldehyde (0.25 mmol), biphenyl (GC standard, 0.25 mmol), 1.0 mol % catalyst and 1.0 mL of the appropriate solvent. The diene (2.5 mmol) was then added, and the solution was stirred at the designated temperature. The loss of aldehyde over time was measured by removing 100 μL aliquots from the solution and adding each of them to 4 mL of 1,2-dichloroethane treated with 3-4 drops of trifloroacetic acid to desilylate both the product and the diene, thereby avoiding further reaction with the aldehyde. The acid was then

neutralized with solid sodium bicarbonate, and samples were injected on the GC. The reaction was allowed to proceed through at least two half-lives. Kinetic measurements were determined in duplicate or triplicate trials.

General HDA procedure. Aldehyde (0.50 mmol) was added to an oven-dried 1.5 dram vial along with 1.0 mol % catalyst (0.0050 mmol) after which 0.50 mL of dry solvent was added, and the resulting solution was allowed to mix thoroughly by stirring. (If the aldehyde was a liquid, the reaction was performed without solvent.) Diene (0.70 mmol) was then added, and the solution was stirred at the designated temperature. After the allotted reaction time, the solution was treated with a few drops of TFA and chromatographically purified using a short silica column that removed the catalyst. Enantiomeric excesses (ee) were determined by HPLC analysis with a 0.46 cm X 25 cm Daicel CHIRALPAK OD column.

Following the same procedure mentioned above and the experimental conditions shown in the table (see the text) the following 2-substituted-2,3-dihydro-4H-pyran-4-ones have been prepared.

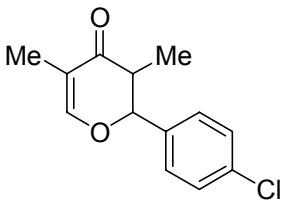
3,5-Dimethyl-2-(4-nitrophenyl)-2,3-*cis*-dihydropyran-4-one:[14]



^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.33 (s, 1H), 5.49 (d, J = 3.0 Hz, 1H), 2.58 (qd, J = 7.5, 3.0 Hz, 1H), 1.68 (s, 3H), 0.81 (d, J = 7.5 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 196.4, 158.0, 147.6, 144.0, 126.3, 123.8, 113.1, 81.8, 45.3, 10.6, 9.9; HRMS calcd for $C_{13}H_{14}NO_4$ (M+1): 248.0923,

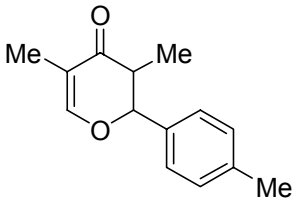
found: 248.0920. HPLC on Chiralpak OD column: t_R 11.48 for major isomer and 23.42 min for minor isomer by using Rh_2(5*S*-dFMEPY)$_4$ catalyst (hexanes/isopropanol = 90/10, flow rate: 1.0 ml/min).

3,5-Dimethyl-2-(4-chloro-phenyl)-2,3-dihydropyran-4-one:[3]



^{1}H-NMR (300 MHz, $CDCl_3$) *trans* isomer δ 7.4-7.3 (m, 4H), 7.30 (s, 1H), 4.89 (d, *J* = 13.0 Hz, 1H), 2.74 (qd, *J* = 13, 6.8 Hz, 1H), 1.72 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); *cis* isomer δ 7.2-7.4 (m, 5H), 5.44 (d, *J* = 3.0 Hz, 1H), 2.56 (qd, *J* = 7.3, 3.0 Hz, 1H), 1.74 (s, 3H), 0.88 (d, *J* = 7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *trans* isomer δ 194.5, 158.5, 136.1, 134.8, 128.9, 128.7, 113.3, 86.0, 44.7, 10.7, 10.3; *cis* isomer δ 197.3, 158.5, 135.3, 133.8, 128.7, 126.8, 112.7, 82.2, 45.5, 10.6, 9.9; HPLC on Chiralpak OD column: t_R 14.17 and 26.62 min by using Rh_2(4*S*-MEOX)$_4$ catalyst hexanes/isopropanol = 97.6/2.4, flow rate: 0.6 ml/min).

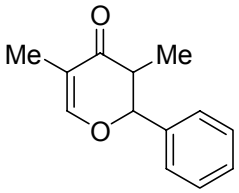
3,5-Dimethyl-2-(*p*-tolyl-phenyl)-2,3-dihydropyran-4-one:[4a]



^{1}H-NMR (300 MHz, $CDCl_3$) *trans* isomer δ 7.3-7.2 (m, 5H), 4.87 (d, *J* = 13.0 Hz, 1H), 2.80 (qd, *J* = 13, 6.8 Hz, 1H), 2.73 (s, 3H), 1.72 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); *cis* isomer δ 7.37 (s, 1H), 7.3-7.2 (m, 4H), 5.43 (d, *J* = 3.1 Hz, 1H), 2.57 (qd, *J* =

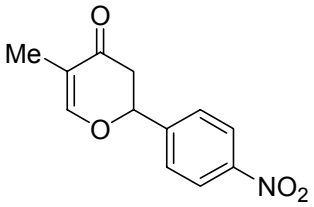
7.3, 3.3 Hz, 1H), 2.37 (s, 3H), 1.74 (s, 3H), 0.90 (d, J = 7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *trans* isomer δ 195.1, 158.8, 138.9, 134.6, 129.3, 127.3, 113.0, 86.8, 44.6, 21.2, 10.7, 10.4; *cis* isomer δ 197.9, 158.9, 137.7, 133.8, 129.1, 125.4, 112.4, 83.0, 45.7, 21.1, 10.7, 9.9; HPLC on Chiralpak OD column: t_R 15.97 and 18.18 min by using Rh_2(4*RS*-MEOX)$_4$ catalyst hexanes/isopropanol = 97.6/2.4, flow rate: 0.6 ml/min)

3,5-Dimethyl-2-(phenyl)-2,3-dihydropyran-4-one:[8]



^{1}H-NMR (300 MHz, $CDCl_3$) *trans* isomer δ 7.5-7.3 (m, 5H), 7.31 (s, 1H), 4.91 (d, J = 13.0 Hz, 1H), 2.80 (qd, J = 13.0, 6.7 Hz, 1H), 1.73 (s, 3H), 0.92 (d, J = 6.7 Hz, 3H); *cis* isomer δ 7.5-7.3 (m, 5H), 7.26 (s, 1H), 5.47 (d, J = 3.2 Hz, 1H), 2.60 (dq, J = 7.4, 3.2 Hz, 1H) 1.74 (s, 3H), 0.90 (d, J = 7.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) *trans* isomer δ 194.9, 158.7, 137.5, 129.0, 128.7, 127.3, 113.1, 86.9, 44.7, 10.7, 10.3; *cis* isomer δ 197.7, 158.8, 136.8, 128.5, 127.9, 125.4, 112.5, 82.9, 45.7, 10.7, 9.9; HPLC on Chiralpak OD column: t_R 22.57 and 26.88 min by using Rh_2(4*RS*-MEOX)$_4$ catalyst hexanes/isopropanol = 97.6/2.4, flow rate: 0.6 ml/min)

5-Methyl-2-(4-nitrophenyl)-2,3-dihydropyran-4-one



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, J = 0.8 Hz, 3H), 2.74 (dd, J = 4.2, 16.8 Hz, 1H), 2.83 (dd, J = 13.6, 16.8 Hz, 1H), 5.49 (dd, J = 4.2, 13.6 Hz, 1H), 7.36 (d, J = 0.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 8.27 (d, J = 8.8 Hz, 2H). Enantiomeric excess was determined to be 95 % ee by HPLC with a Chiralpak OD-H column (80:20 hexane/^{i}PrOH, 1.0 ml/min): t_r = 16.6 min for major enantiomer; t_r = 26.8 min for minor enantiomer. EI-HRMS *m/z* calculated for $C_{12}H_{11}O_4N$ (MH^+) 233.0688, found 233.0685.

4.8 References

1. See Chapter 1 and references therein for a detailed discussion of Lewis acid catalyzed hetero-Diels-Alder reactions.

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