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STUDY OF DIRHODIUM(II) CATALYZED HETERO-DIELS-ALDER REACTIONS: INVESTIGATIONS OF DIENE INFLUENCE AND SUBSTITUTION PATTERN

by

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ABSTRACT

Studies pertaining to the dirhodium(II) carboxamidate catalyzed hetero-Diels-Alder reaction between 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene and various aldehydes have been carried out. It has been demonstrated that the overall yield, enantioselectivity, and rate of reaction for the hetero-Diels-Alder process are influenced by the substitution pattern of the diene. Collected data has allowed for the evaluation of the structural and electronic properties of the catalysts and for comparisons to be made between several dienes of interest.

The complete synthesis of $Rh_2(4R\text{-dFIBAZ})_4$, a dirhodium(II) carboxamidate catalyst that has shown increased reactivity for diazo decomposition and enhanced selectivity for ylide formation, has been previously reported by our group. Presented herein are the attempts taken to improve the existing synthesis through optimization and scale-up.

CHAPTER 1: The Hetero-Diels-Alder Reaction: Mechanistic Insights, Applications, and Synthetic Importance

I. Introduction

Over the past few decades the HDA reaction has emerged as one of the important methodologies in organic synthesis for the reaction of carbonyl compounds with conjugated dienes.[1] Contributions to the HDA reaction have been provided by a number of talented researchers whose noteworthy efforts have allowed for a deeper understanding of the HDA reaction.[2]

The first chapter of this thesis is devoted to the hetero-Diels-Alder (HDA) reaction itself. Background information pertaining to the mechanistic aspects of the HDA reaction will be provided through explanations of the frontier molecular orbital theory.[2a,3] Additionally, the observed selectivity of the HDA reaction[4] as well as the possible mechanistic pathways[2a] for the reaction will be discussed.

In order to illustrate the importance of the hetero-Diels-Alder reaction from a practical point of view, several natural products will be examined.[5] The HDA reaction provides a viable route in which chiral nonracemic dihydropyrans can be accessed.[1] Those natural products mentioned herein incorporate the HDA reaction in their respective total syntheses.

Finally, contributions to the hetero-Diels-Alder reaction from a select number of researchers will be presented.[2] Examples from the work of some of the leading players in the field of Lewis acid catalyzed HDA reactions will not only demonstrate the efficiency

of the catalyzed process, but will also serve as a comparison for the vast array of catalysts employed.[2]

II. Mechanistic Aspects of the Hetero-Diels-Alder Reaction

In order to provide an understanding of how the HDA reaction takes place on a mechanistic level, the frontier molecular orbital theory for the process will be briefly discussed in this section.

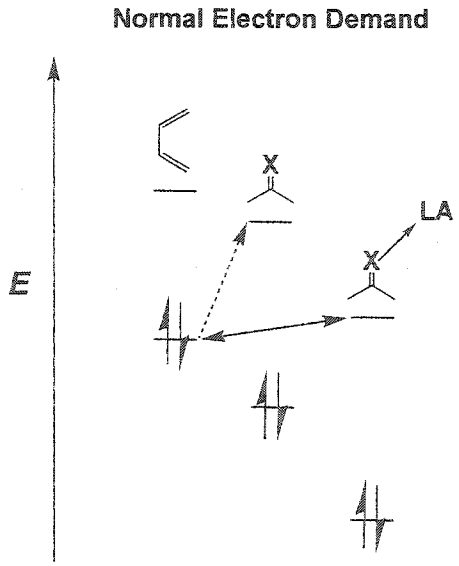
1. Frontier Molecular Orbital Theory

From a mechanistic point of view, two types of [$_{\pi}$4s + $_{\pi}$2s] cycloadditions exist for the hetero-Diels-Alder reaction.[2a,3] The two types of cycloadditions, the normal electron demand HDA reaction and the inverse electron demand HDA reaction, are based on the relative energies of the frontier molecular orbitals (FMOs) of the diene and the dienophile as will be explained.[3,6] For practical purposes, only the normal electron demand HDA reaction will be elaborated on in the following paragraphs. The inverse electron demand case, as it does not pertain to the research that was carried out (see Chapter 2), will not be discussed.

Catalytic enantioselective HDA reactions of carbonyl compounds occur by coordination of the chiral Lewis acid to the carbonyl group, thereby activating the substrate for reaction.[2a,7] At the same time, a chiral environment is created that directs the approaching diene to the substrate from the less sterically hindered face, establishing enantioselectivity in the reaction.[7]

Mechanistically, the normal electron demand reaction is a $HOMO_{diene}$-$LUMO_{dienophile}$ controlled HDA reaction generally occurring between an electron-rich diene and an electron-deficient dienophile (**Figure 1.1**, dashed line).[2a] Without a Lewis acid, the energy difference between $HOMO_{diene}$ and $LUMO_{dienophile}$ is high. When subsequent coordination of the dienophile with a Lewis acid occurs, the FMOs of the dienophile are changed, decreasing the LUMO and HOMO energies (**Figure 1.1**, solid line).[2a] Additionally, a better interaction with the dienophile is achieved, and a lower energy difference between $HOMO_{diene}$ and $LUMO_{dienophile}$ is observed. The Lewis acid therefore has an activating effect for the reaction.[2a]

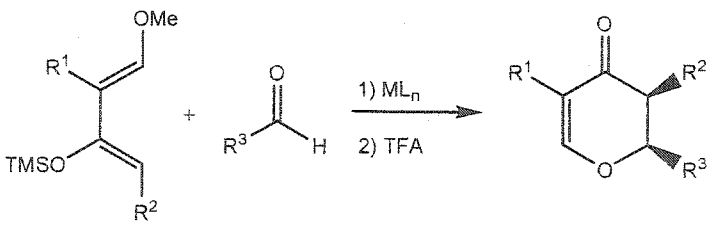
Figure 1.1: A FMO diagram of a normal electron demand hetero-Diels-Alder reaction between a diene and a dienophile with and without a Lewis acid. X = O or a heteroatom.



2. Observed Selectivity in the Hetero-Diels-Alder Reaction

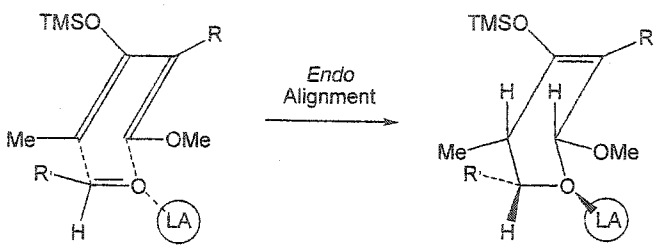
In 1985, Danishefsky and co-workers explained that the formation of *cis* adducts in the hetero-Diels-Alder reactions of the type shown in **Equation 1.1** correlate with an *endo* alignment of the aldehyde R group and the diene.[4] An illustration of the transition state with the *endo* alignment of the aldehyde R group and the diene is provided below in **Figure 1.2**.[4] Danishefsky further explained that there is a reasonable assumption that the Lewis acid catalyst/solvent array would take an *anti* orientation relative to the R group of the aldehyde upon complexation of the carbonyl group.[4] Additionally, if the steric demand of the catalyst/solvent complex is greater than that of the R group, the observed *endo* specificity for the R group may be the result of an *exo* specificity for the catalyst/solvent array.[4]

Equation 1.1: General hetero-Diels-Alder reaction.



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

Figure 1.2: Illustration of the transition state of the HDA reaction with *endo* alignment of the aldehyde and the diene.

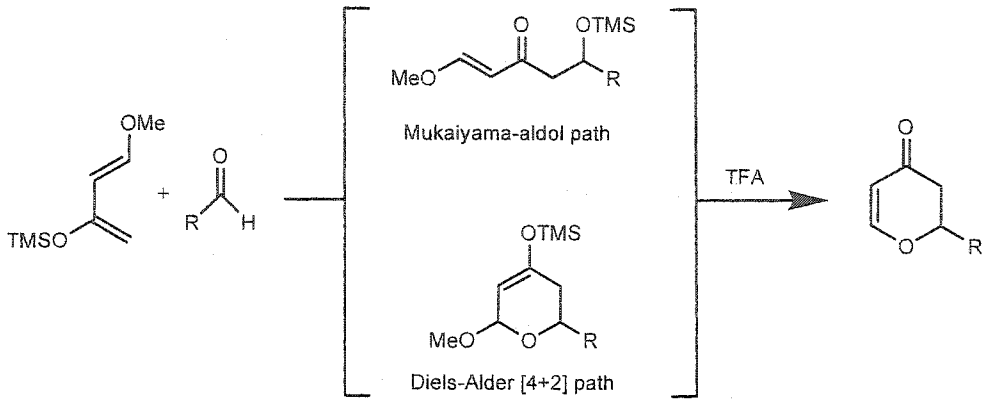


LA = Lewis acid

3. Mechanistic Pathways of the Hetero-Diels-Alder Reaction

The observed mechanistic pathway for the hetero-Diels-Alder reaction of carbonyl compounds and dienes is dependant upon the catalyst employed. Based on the Lewis acid selected for the reaction, two different mechanistic pathways may be observed, namely the Mukaiyama-aldol pathway or the Diels-Alder concerted [4+2] cycloaddition pathway.[2a] The two possible pathways for the HDA reaction are given below (**Figure 1.3**). Additionally, specific examples for each type of pathway will be provided in this section for illustration.

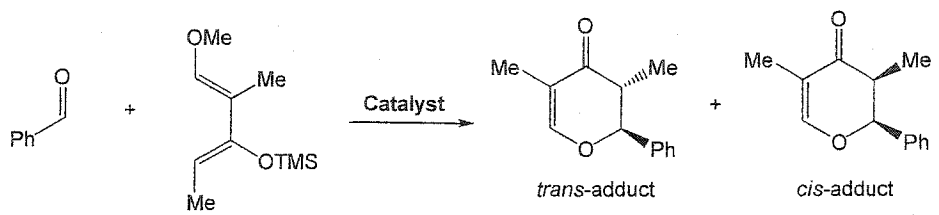
Figure 1.3: Two mechanistic pathways for the hetero-Diels-Alder (HDA) reaction of carbonyl compounds.



The Lewis acid catalyst employed has an affect on the type of intermediate formed during the course of the reaction as previously stated. It is possible to determine if the HDA reaction has gone though the linear intermediate or the cyclic intermediate by ^{1}H NMR analysis of a sample from the reaction prior to treating it with trifluoroacetic acid (TFA).[2a,4] Despite the pathway taken, however, simple treatment of the reaction with TFA will afford the cyclic dihydropyran product.[4] Lewis acid catalysts based on manganese,[8] chromium,[8,9] europium,[10] zinc,[4] aluminum,[11] rhodium, [12] and cerium[13] proceed via the Diels-Alder [4+2] concerted cycloaddition pathway. Alternatively, catalytic systems based on boron[14] or titanium[15] involve the stepwise linear Mukaiyama-aldol pathway. To illustrate the dependence of the mechanistic pathway on the type of catalyst employed, an example from Danishefsky's work follows.

In 1985, Danishefsky and co-workers investigated the reaction between benzaldehyde and 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene catalyzed by both BF_3 and $ZnCl_2$ (**Equation 1.2**).[4]

Equation 1.2: Product dependence based on Lewis acids employed in the hetero-Diels-Alder reaction.



BF_3/TFA	68	23
$ZnCl_2$/TFA	< 2	78

Results from the study revealed that when BF_3 was employed as the catalyst the reaction proceeded through a stepwise Mukaiyama-aldol mechanism giving an initial linear product which, upon treatment with TFA, yielded the *trans*-cycloadduct as the major product.[4] In contrast to results with BF_3, when $ZnCl_2$ was used as an accelerant for the reaction, the *cis*-adduct dominated revealing only trace amounts of the *trans*-product. This gives evidence of an *endo* alignment of the aldehyde R group and the diene as discussed in the preceding section on observed selectivity.[4]

III. Hetero-Diels-Alder Reaction with Unactivated and Activated Aldehydes

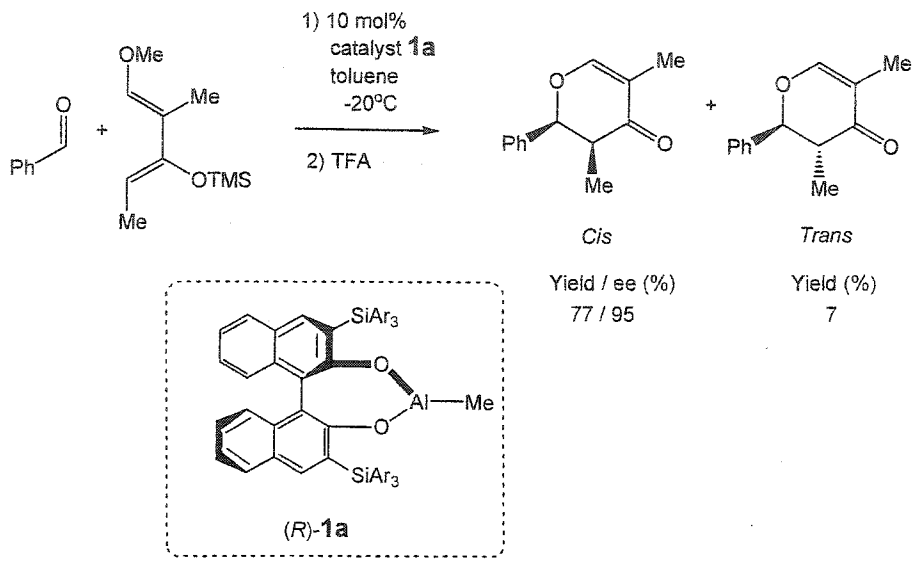
1. Reactions with Unactivated Aldehydes

Carbonyl compounds generally exhibit limited reactivity in the hetero-Diels-Alder reaction with dienes.[2a] Only electron-deficient carbonyl groups such as those found in 1,2,3-triketones, glyoxylates, ketomalonates, and related types of compounds, react with dienes possessing electron-donating groups.[2a]

Unactivated aldehydes usually contain a single carbonyl group (i.e. aromatic aldehydes) that allow only monodentate coordination to the Lewis acid employed.[2a]

Providing an example of a HDA reaction with an unactivated aldehyde, Yamamoto *et al.* in 1988 reacted benzaldehyde and 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene with an aluminum based catalyst **1a**, yielding *cis*-dihydropyranes as the major product in 77 % with enantioselectivities of 95% ee (**Equation 1.3**).[16]

Equation 1.3: Hetero-Diels-Alder reaction of benzaldehyde, an unactivated aldehyde, and a dimethyl analog of Danishefsky's diene.

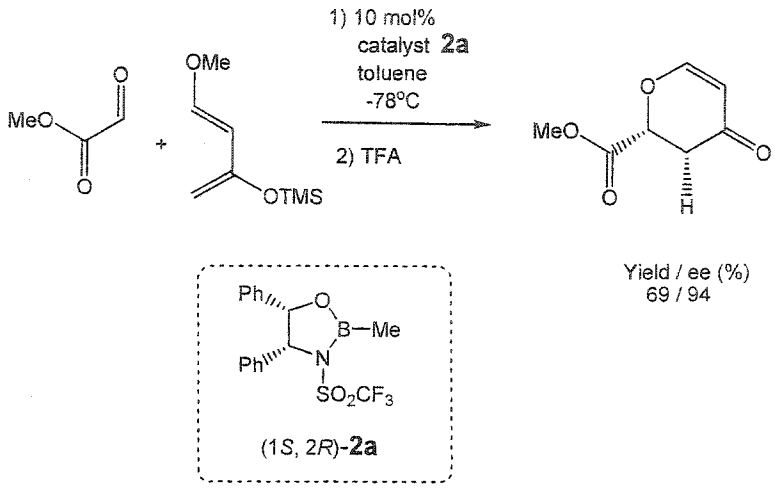


2. Reactions with Activated Aldehydes

Activated aldehydes usually contain two or more carbonyl groups (i.e. glyoxylates) that are able to coordinate in a monodentate or bidentate fashion to the Lewis acid employed. To illustrate the application of an activated aldehyde in the HDA reaction, examples from the work of Mikami and Jørgensen are provided.[2a]

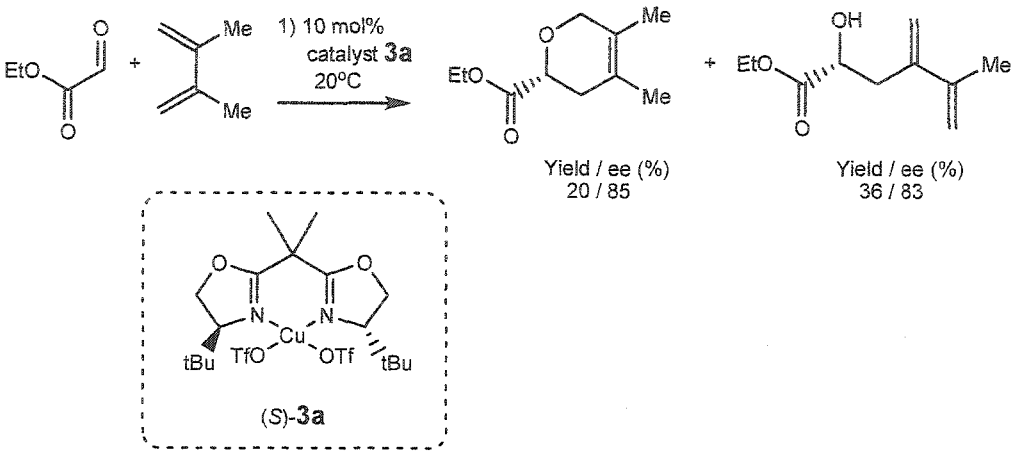
In 1994, Mikami and co-workers reacted methyl glyoxylate with Danishefsky's diene under the influence of a chiral boron catalyst, **2a**. A yield of 69 % was achieved with a corresponding high enantiomeric excess of 94 % (**Equation 1.4**).[17]

Equation 1.4: Hetero-Diels-Alder reaction of methyl glyoxylate, an activated aldehyde, and Danishefsky's diene.



In 1995, Jørgensen used a chiral copper(II) bis-oxazoline catalyst, **3a**, for the reaction of ethyl glyoxylate and 2,3-dimethyl-1,3-butadiene. The HDA cycloadduct was formed in 20 % yield and 85 % ee. Since the substrate contains an allylic C-H bond, an ene reaction can also take place. Here the ene reaction product is produced in 36 % yield and 83 % ee. The ratio of hetero-Diels-Alder to ene product is equal to 1 : 1.8 (**Equation 1.5**).[18]

Equation 1.5: Hetero-Diels-Alder and Ene reactions involving an activated aldehyde.

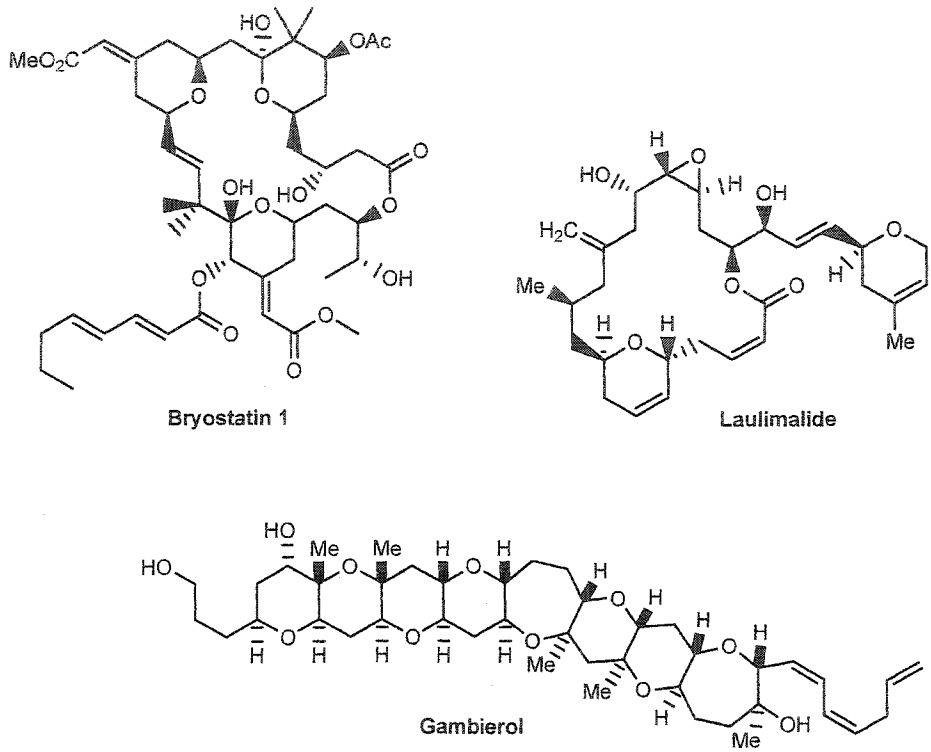


IV. Applications toward Natural Products and Pharmaceutical Targets

As one of the important methodologies in organic synthesis, the hetero-Diels-Alder reaction of carbonyl compounds with conjugated dienes provides a viable route in which chiral nonracemic dihydropyrans can be accessed.[1,2b] As various dihydropyran compounds are present in the structures of many natural products, the hetero-Diels-Alder reaction may be applied to their total synthesis. Briefly discussed in this section are a select number of natural products, each one containing at least one dihydropyran ring. The complete structures of the natural products are provided as well as the key reaction in which dihydropyran formation is achieved (**Figure 1.4**).[5]

Many natural products, as they are found in nature, are frequently hard to isolate from their original sources and often exist in such low abundances that sufficient supplies for biological and pharmaceutical testing remain unfulfilled. The need for substantial quantities of various natural products has, in part, been met through chemical synthesis. The following three compounds illustrate this point.

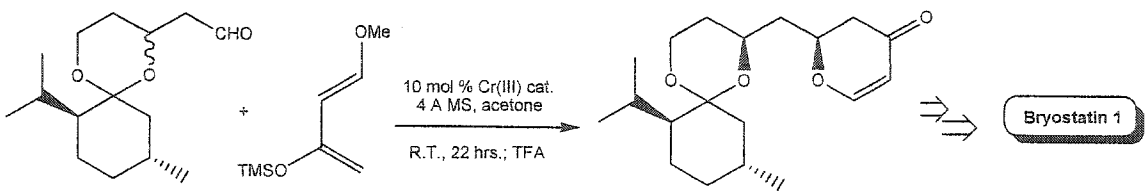
Figure 1.4: Several natural products synthesized by the hetero-Diels-Alder reaction.



Bryostatin 1 belongs to a family of marine natural products which have displayed potent biological activities[19] ranging from the stimulation of immune system responses[20] to acting alongside other oncolytic agents,[21] as well as inhibiting the growth of numerous human cancer cell lines. In 2002, Wender and co-workers employed a HDA cycloaddition reaction with 1-methoxy-3-(trimethylsiloxy)-butadiene (Danishefsky's diene), catalyzed by Jacobsen's Cr(III) catalyst, **8a Equation 1.13**,[22] in their total synthesis (**Equation 1.6**).[5a] This compound has reached the clinical trial stages, as

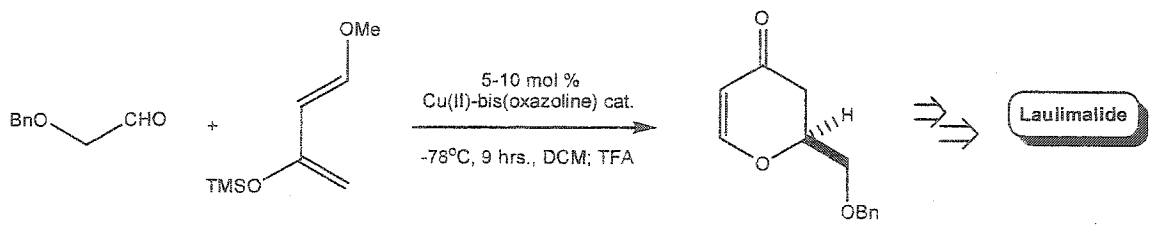
necessary amounts for testing have been realized through a multitude of chemical syntheses by several groups.

Equation 1.6: Hetero-Diels-Alder reaction used in the synthesis of Bryostatin 1.



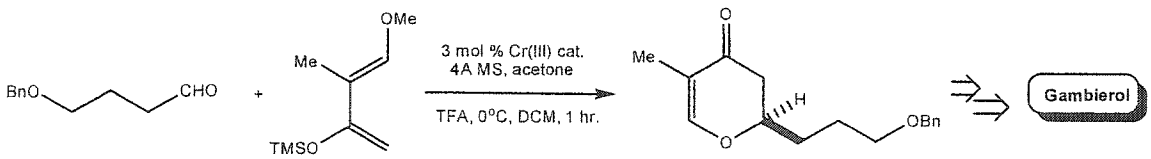
Laulimalide is a 20-membered macrolide comprised of unique structural features with the potential to be used as an anticancer agent. It is isolated from the Indonesian sponge *Hyattella Sp*[23] and the Okinawan sponge *Fasciospongia rimosa.*[24] This compound has been prepared enantioselectively by Ghosh and co-workers in 1997 using a HDA reaction that is catalyzed by a chiral bis(oxazoline)-metal based complex as the key transformation (**Equation 1.7**).[5b]

Equation 1.7: Hetero-Diels-Alder reaction used in the synthesis of Laulimalide.



Gambierol is a marine ladder toxin isolated in 1993 by Yasumoto *et al.*[25] which has exhibited interesting biological activity.[26] It is acquired from the cultured cells of *Gambierdiscus toxicus*,[25] and encompasses 8 ether rings and 18 stereogenic centers.[27] In 2001, Rainier and co-workers synthesized the A-D ring system in which the synthesis included a hetero-Diels-Alder reaction with 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene catalyzed by Jacobsen's Cr(III) catalyst, **8a Equation 1.13**,[22] **(Equation 1.8)**.[5c,28]

Equation 1.8: Hetero-Diels-Alder reaction used in the synthesis of Gambierol.



There are in existence other additional natural products whose total syntheses take advantage of the hetero-Diels-Alder transformation. Those briefly discussed above lend further support to the importance of such a reaction.

V. Chiral Catalysts in Use: Variations in Design

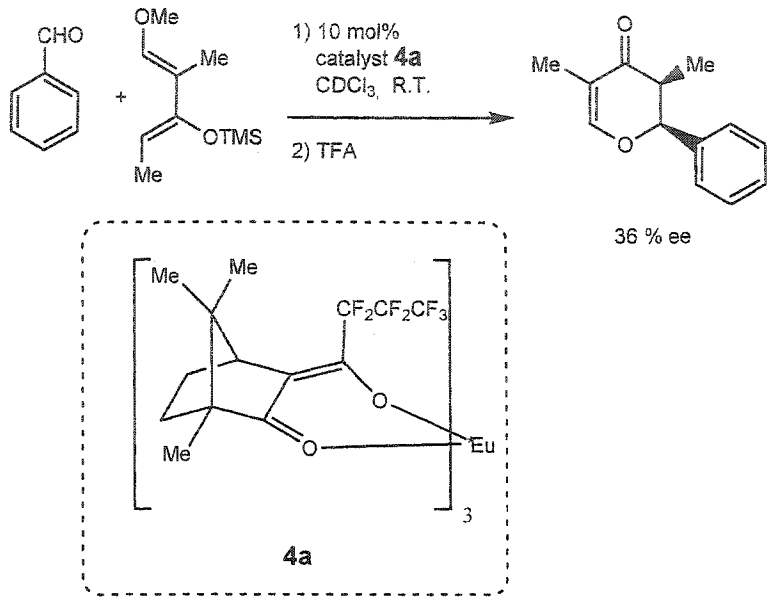
In considering the hetero-Diels-Alder reaction, the absolute configuration of the product can be controlled either with the use of a diene and/or a dienophile containing a chiral auxiliary, or by employing a chiral catalyst.[2a] Chiral catalysts offer the benefit of being efficient and easy to use, in addition to giving rise to adducts with up to four new chiral centers. Reactions accelerated by chiral catalysts usually occur under mild reaction conditions with substoichiometric amounts of chiral materials.[2a] Over the years multiple chiral catalysts have been generated with differing structural characteristics.[2a]

Several researchers have left their mark over time.[2] Contributions they have made to the field have allowed for numerous advances in finding efficient catalytic methods for the hetero-Diels-Alder reaction. Pursuits reflecting their efforts are noteworthy, thus several of these individuals and their work will be briefly discussed in this section.

1. Examples of Various Chiral Catalysts at Work

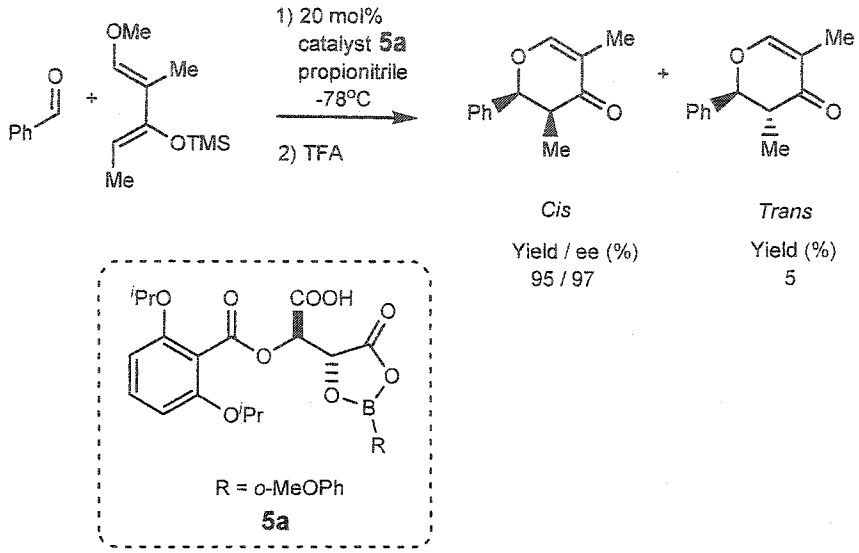
Early on, Danishefsky and co-workers recognized that lanthanide complexes could serve as effective catalysts for the hetero-Diels-Alder reaction.[29] In 1983 he showed that a europium based catalyst, in particular [Eu(hfc)$_3$] catalyst **4a** in 10 mol %, promoted the HDA reaction between 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene and benzaldehyde, giving an ee of 36 % (**Equation 1.9**).[29] Through optimization of reaction conditions and screening of various substrates, Danishefsky was able to achieve enantiomeric excesses of 58 % ee with this catalyst system.[29,30]

Equation 1.9: Hetero-Diels-Alder reaction with Danishefsky's europium catalyst.



Yamamoto and co-workers developed a chiral (acyloxy)borane (CAB) catalyst several years after Danishefsky's report.[31] Prepared in situ from a 1:1 molar ratio of a tartaric acid derivative and phenylboric acid, this catalyst is stable and can be stored at room temperature. In 1992, Yamamoto reported using 20 mol % of catalyst **5a** to catalyze the reaction between benzaldehyde and 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene (**Equation 1.10**). The HDA product was formed in 95 % yield and 97 % ee after being treated with trifluoroacetic acid.[31]

Equation 1.10: Hetero-Diels-Alder reaction with Yamamoto's chiral boron catalyst.

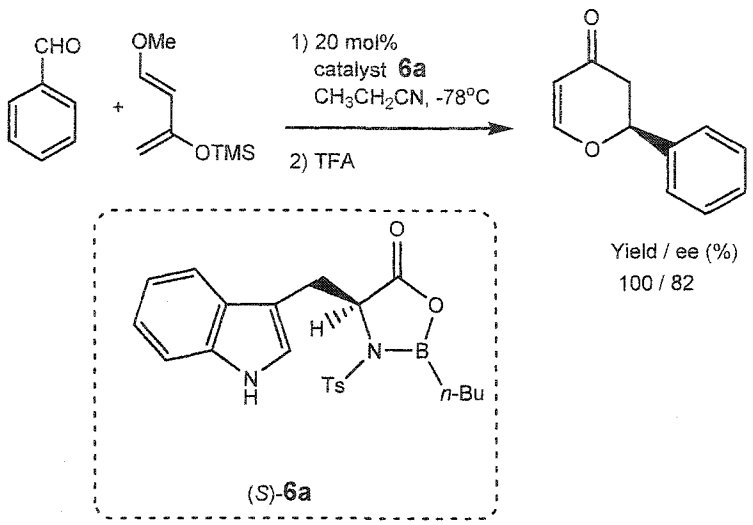


As previously mentioned (**Equation 1.3**), Yamamoto has also developed an aluminum based catalyst capable of carrying out the hetero-Diels-Alder reaction in which enantioselectivities as high as 95 % ee can be achieved with 10 mol % catalyst.[16]

Keeping pace with Yamamoto, in 1992 Corey published his own variant of catalyst that was able to enantioselectively form dihydropyranes. The catalyst presented by Corey's group was an (*S*)-tryptophan derived catalyst (**6a**).[32] Using 20 mol % of catalyst **6a** at a temperature of -78°C and propionitrile as the solvent, benzaldehyde and Danishefsky's diene were converted to the cyclic product once being treated with trifluoroacetic acid (**Equation 1.11**).[32] Corey's group reported a 100 % yield of product with an accompanying enantiomeric excess of 82 % ee. Several other aldehydes were

investigated under the same reaction conditions with yields ranging from 57-87 % and ee's from 67-76 %.

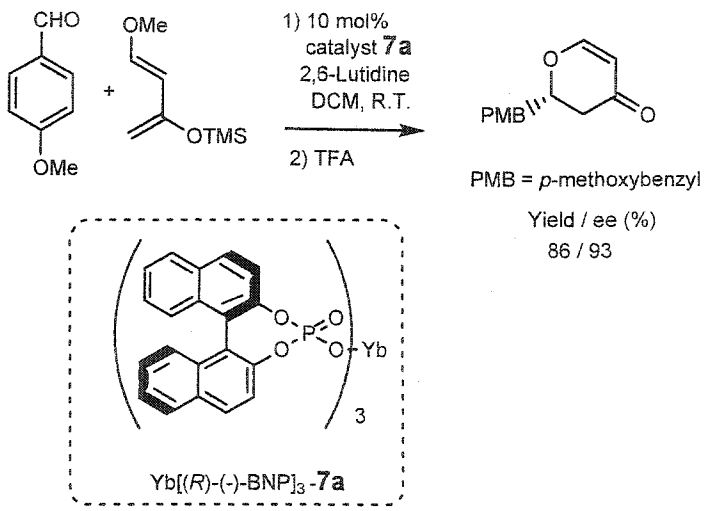
Equation 1.11: Hetero-Diels-Alder reaction with Corey's tryptophan derived catalyst.



Several years after Corey's tryptophan derived catalyst, Inanaga in 1997 followed with a chiral ytterbium(III) phosphate catalyst.[33] At this time Inanaga and co-workers had synthesized a series of trivalent lanthanoids, scandium, and yttrium tris-(*R*)-(-)-1,1'-binaphthyl-2,2'-diyl phosphonates for use as chiral Lewis acids. They discovered that the degree of asymmetric induction largely depended on the ionic radius of the central metal ion of the catalyst, and that the rare earth metal ytterbium complex was the best at exhibiting efficient catalytic activity towards several aldehydes.[33] Using 2,6-lutidine as an additive, the hetero-Diels-Alder reaction between *p*-anisaldehyde and Danishefsky's

diene was carried out at room temperature with 10 mol % Yb[(*R*)-(-)-BNP]$_3$ catalyst **7a**, to afford the corresponding dihydropyran product in 86 % yield and 93 % ee (**Equation 1.12**).[33]

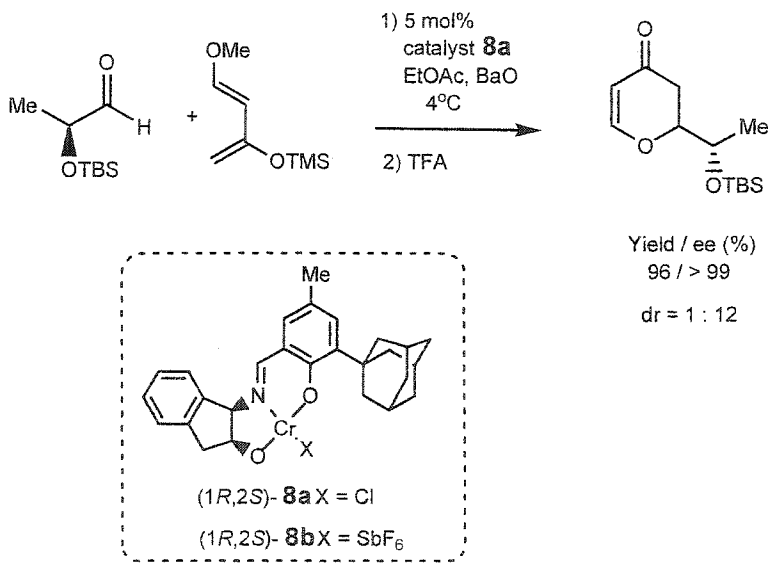
Equation 1.12: Hetero-Diels-Alder reaction with Inanaga's chiral ytterbium catalyst.



In 1998, and later in 2002, Jacobsen and co-workers introduced several chiral (salen)-Cr(III) and tridentate Schiff base-Cr(III) complexes.[9,22] In 2002, studies pertaining to doubly diastereoselective HDA reactions between Danishefsky's diene and optically active chiral aldehydes, controlled by chiral catalysts, were performed in hopes of providing elaborate dihydropyranone derivatives. Using 5 mol % of their chiral Schiff base-Cr(III) catalyst **8a**, a TBS protected hetero dienophile was reacted with Danishefsky's diene forming the cyclic product in 96 % yield and greater than 99 % ee

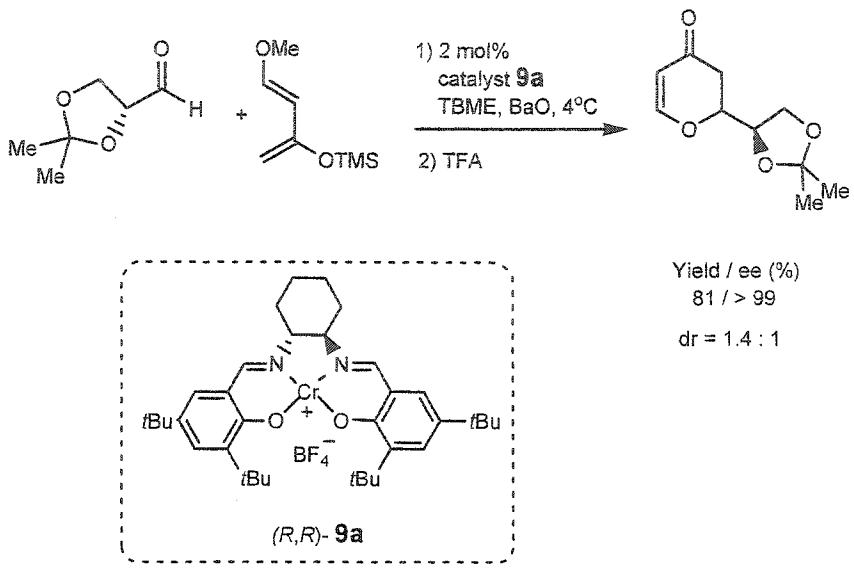
after treatment with TFA; the diastereomeric ratio of products was 1 : 12 (**Equation 1.13**).[22] Using BaO as a desiccant was found to be advantageous to a solution of the catalyst in ethyl acetate, prior to the addition of the aldehyde and diene.

Equation 1.13: Hetero-Diels-Alder reaction with Jacobsen's tridentate Schiff base-chromium(III) catalyst.



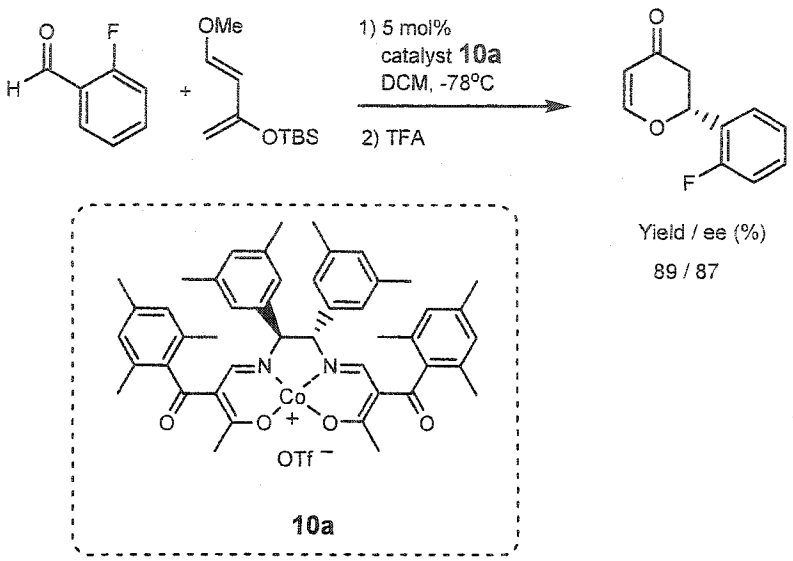
In addition to their Schiff base-Cr(III) complex **8a**, Jacobsen *et al.* also considered a chiral (salen)-Cr(III) catalyst, **9a**.[22] Looking at the more sterically hindered glyceraldehyde, 2 mol % of catalyst **9a** provided the HDA product in 81 % yield and > 99 % enantiomeric excess; the diastereomeric ratio of products was 1.4 : 1. BaO was again the desiccant of choice, however the solvent was changed to *tert*-butyl methyl ether, TBME (**Equation 1.14**).[22]

Equation 1.14: Hetero-Diels-Alder reaction with Jacobsen's (salen)-chromium(III) catalyst.



Yamada and co-workers in 2000 developed an optically active β-ketoiminato cobalt(III) complex capable of successfully catalyzing the hetero-Diels-Alder reaction of both aryl and alkyl aldehydes.[13] Taking a TBS protected variant of Danishefsky's diene, *o*-fluorobenzaldehyde, and 5 mol % of the cationic cobalt(III) triflate catalyst complex **10a**, Yamada and co-workers generated the resulting HDA product in 87 % ee and 89 % yield (**Equation 1.15**).[13]

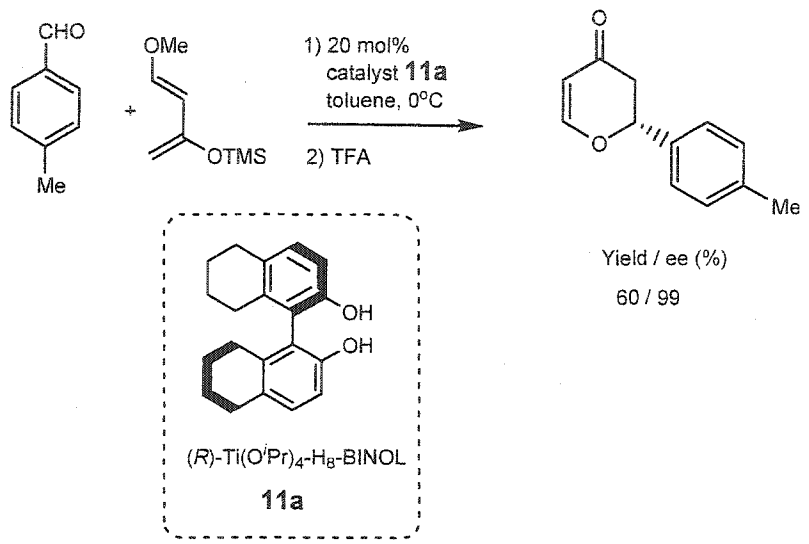
Equation 1.15: Hetero-Diels-Alder reaction with Yamada's chiral cobalt(III) complex.



In 2000 and then in 2002, the research groups of Feng and Jiang working together reported that a chiral titanium(IV)-H_8-BINOL complex was more fruitful at accelerating the HDA reaction of a wide range of aldehydes than was a titanium(IV)-BINOL species.[34,35] Submitting *p*-tolualdehyde to 20 mol % of catalyst **11a** and Danishefsky's diene afforded the cyclic HDA product in a fair 60 % yield and high enantioselectivity of 99 % ee (**Equation 1.16**).[34] Following their good fortune with the titanium(IV)-H_8-BINOL complex in 2000, in 2002 Feng and Jiangs' groups published highly optimized conditions for such a transformation.[35] A series of ligands and various Lewis acids were screened as well as a number of solvents, reaction temperatures, substrates, and

concentration effects.[35] Throughout the study, high enantioselectivities and yields were reached.

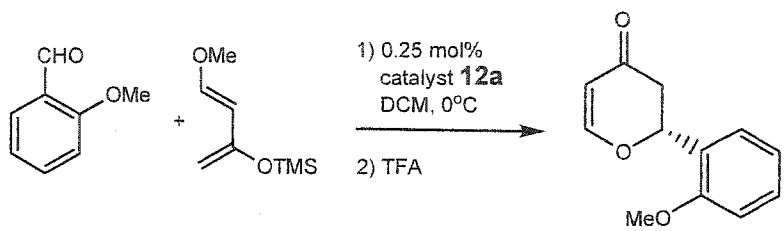
Equation 1.16: Hetero-Diels-Alder reaction with Feng and Jiang's chiral titanium(IV) complex.

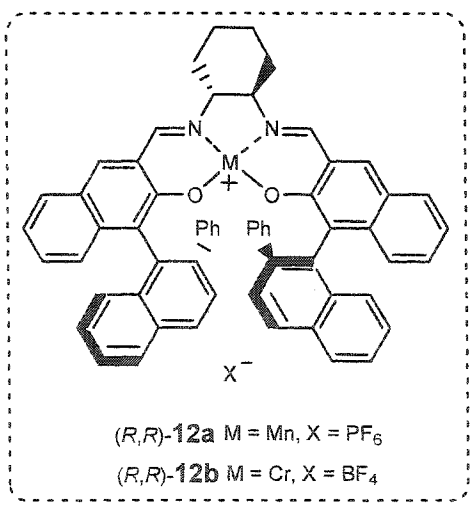


One final contribution to mention comes from Katsuki and co-workers. Previously, in 1999, Katsuki realized that 2 mol % of a (ON^+)(salen)-ruthenium complex could serve as an efficient catalyst for the HDA reaction when carried out under the influence of incandescent light or sunlight.[36] Modest yields of 26-49 % were seen with ee's from 74-83 % for various aldehyde substrates. In 2001, he reported that chiral cationic manganese(III) and chromium(III) metallosalen complexes could be employed as attractive catalysts for asymmetric hetero-Diels-Alder reactions. Under the influence

of a second generation (salen)-manganese(III) complex, 0.25 mol % of complex **12a**, 0°C in DCM, *o*-methoxybenzaldehyde and Danishefsky's diene provided the enantioenriched product in 97 % yield and 68 % ee, no sunlight needed (**Equation 1.17**).[37]

Equation 1.17: Hetero-Diels-Alder reaction with Katsuki's (salen)-manganese(III) complex.





Although not elaborated on here, several other noteworthy contributions have come from Keck and co-workers in 1995 with investigations using a titanium-BINOL based catalyst,[38] as well as from Ding in 2002 with the employment of a tridentate titanium catalyst.[39] Chiral catalysts brought forward by Mikami in 1994 and Jørgensen in

1995 and 1999 have also been presented (**Equation 1.4** and **Equation 1.5**). Although only a few have been selectively discussed in this section, other researchers over the years have also provided worthy insights into the hetero-Diels-Alder reaction. Collectively, they remain invaluable.

VI. Conclusions

Over the past few decades the hetero-Diels-Alder (HDA) reaction has emerged as one of the important methodologies in organic synthesis for the reaction of carbonyl compounds with conjugated dienes. This chapter has been devoted entirely to the HDA reaction in order to provide an overview of its mechanistic aspects, application, and synthetic utility.

Included herein are brief discussions about the frontier molecular orbital theory, the observed selectivity, and the mechanistic pathways for the HDA reaction. For each of these areas examples have been provided. Additionally, the importance of the hetero-Diels-Alder has been addressed. From a practical point of view, the HDA reaction is one way chiral nonracemic dihydropyran products can be accessed. Each of the three natural products furnished herein utilize the HDA reaction to accomplish their respective total syntheses. Finally, contributions to the hetero-Diels-Alder reaction from a select number of researchers have been supplied. Fueled by the advancement of science itself, these researchers have generated many chiral catalysts with differing physical characteristics. Examples from their work, as it applies to the field of Lewis acid catalyzed HDA reactions, have demonstrated the efficiency of the catalyzed process and have allowed for comparisons to be made about the catalysts themselves.

With all things considered, the hetero-Diels-Alder reaction remains one of fundamental tools any organic chemist can employ. Studies with respect to reaction conditions, amount of catalyst used, substrate and reaction scope, and mechanistic probing continue to be on the forefront.

CHAPTER 2: Dirhodium(II) Catalyzed Hetero-Diels-Alder Reactions: Investigations into Diene Influence and Substitution Pattern

I. Introduction

Advances have been made in the hetero-Diels-Alder reaction over the past few decades. As one of the important methodologies in organic synthesis, the HDA reaction of carbonyl compounds with conjugated dienes provides a viable route to chiral nonracemic dihydropyrans.[1] These compounds have applications in the synthesis of natural products as illustrated in Chapter 1.[2]

Several researchers have successfully employed chiral catalysts as Lewis acids to promote the hetero-Diels-Alder reaction;[3] however, improvements in reaction conditions are still needed. Beginning in 2001, we in the Doyle research group have applied chiral dirhodium(II) catalysts to the hetero-Diels-Alder reaction.[4] The development of the dirhodium(II) catalysts will be briefly presented, followed by specific examples of their employment in the HDA reaction to illustrate overall efficiency. Improvements to existing reactions conditions for the HDA reaction are offered by our dirhodium(II) catalysts. By capitalizing on the reactivity of several dirhodium(II) catalysts generated within the group, insights have also been provided with respect to the mechanism of the catalytic transformation.[5-6]

The main focus of this chapter is on the recent studies pertaining to the dirhodium(II) carboxamidate catalyzed hetero-Diels-Alder reaction between 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene and several aldehydes. Experiments have revealed that the overall yields, enantioselectivities, and rates of reaction for the hetero-

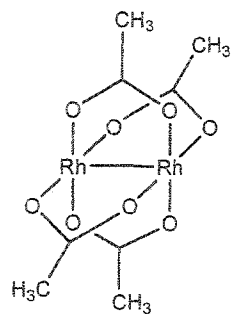
Diels-Alder process are influenced by the substitution pattern of the diene.[6] Steric and electronic interactions with the catalyst also play a role. Reaction rates have been obtained for the HDA reaction of *p*-nitrobenzaldehyde and 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene catalyzed by a variety of dirhodium(II) Lewis acids. This data has allowed evaluation of the structural and electronic properties of the catalysts. Lastly, comparisons between the three dienes of interest, 1-methoxy-3-(trimethylsilyloxy)-butadiene (Danishefsky's diene), 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene, and 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene, have been made with respect to reaction rates.[6] The substitution pattern of the diene was found to influence the rate of the overall reaction. As all of these studies have been the focus of current research, they will therefore be discussed here in some detail.

II. Chiral Dirhodium(II) Carboxamidates in Use

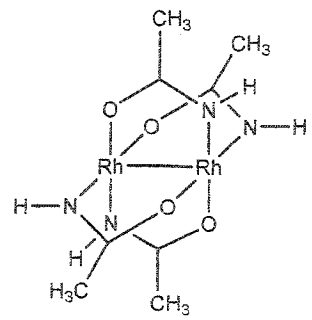
1. Dirhodium(II) Catalyst Structures of the Doyle Group

Dirhodium(II) tetraacetate, prepared and characterized in the 1960's,[7,8] was introduced by Teyssie and co-workers as a catalyst for diazo decomposition in 1973[9] (**Figure 2.1**). Since then, $Rh_2(OAc)_4$ (**1**) has been one of the most widely used catalysts for metal carbene transformations.[10] Exchanging the acetate ligand for other carboxylate ligands changes both the physical and chemical properties of the dirhodium(II) carboxylate to match those of the replacement ligands.[10] In 1986 Bear, with the cooperation of Bernal, reported the first preparations of dirhodium(II) carboxamidates whose parent structure corresponds to dirhodium(II) acetamidate, $Rh_2(acam)_4$ (**2**) (**Figure 2.1**).[11] The bridged structure, resembling that of a paddlewheel, was found by x-ray crystallography to have two oxygens and two nitrogens bound to each rhodium, wherein the two nitrogens are adjacent to each other (*cis*-2,2).[11]

Figure 2.1: Structures of $Rh_2(OAc)_4$ and $Rh_2(acam)_4$.



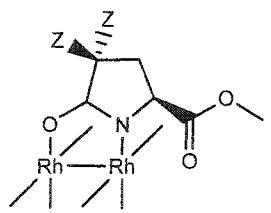
$Rh_2(OAc)_4$
1



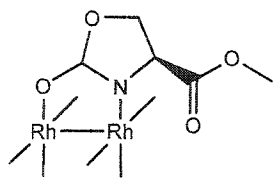
(*cis*-2,2)-$Rh_2(acam)_4$
2

Chiral dirhodium(II) carboxamidates have been prepared by the Doyle group from enantiomerically pure α-substituted carboxamides.[12,13] The ligands that have been employed are based on 2-oxopyrrolidine (**3** and **4**),[14-16] 2-oxazolidinone (**5**),[17,18] *N*-acylimidazolidin-2-one (**6** and **7**),[19,20] and 2-azetidinone (**8** and **9**).[21,22] The structures of the specific catalysts used in the research presented in this thesis are provided below for reference (**Figure2.2**).

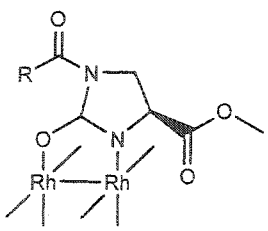
Figure 2.2: Structures of dirhodium(II) carboxamidate catalysts in use.



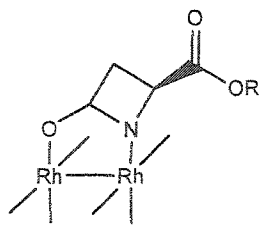
3 Rh_2(5*S*-MEPY)$_4$, Z = H
4 Rh_2(5*S*-dF-MEPY)$_4$, Z = F



5 Rh_2(4*S*-MEOX)$_4$



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



8 Rh_2(4*S*-MEAZ)$_4$, R = Me
9 Rh_2(4*S*-IBAZ)$_4$, R = ^{t}Bu

III. Previous Applications of Chiral Dirhodium(II) Catalysts

A variety of chiral Lewis acid catalysts have been employed in the hetero-Diels-Alder reaction, several of which were discussed in Chapter 1.[3] The HDA reaction has served as a means of evaluating their effectiveness.[4] Despite selectivities that have reached 99 % enantiomeric excess[23] several drawbacks still remain.[4] For example, in order to achieve products with such impressive enantiomeric excesses, either high catalyst loadings [substrate/catalyst (S/C) $\leq$ 50] are needed,[4,24] temperatures as low as -78°C are used,[24,25] or increased reaction times on the order of several days may be required for product formation.[26]

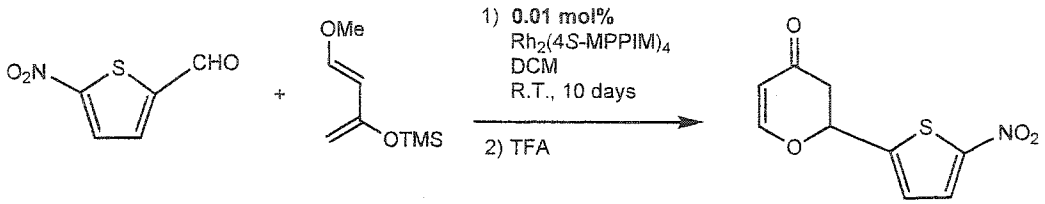
In contributing to the advances of the hetero-Diels-Alder reaction of aldehydes and dienes catalyzed by chiral Lewis acids, we have reported that dirhodium(II) carboxamidates can be successful accelerants as well.[4-6] Briefly discussed in this section are selected results which illustrate the effectiveness of the dirhodium(II) Lewis acid catalysts synthesized within the Doyle research group and their application toward the hetero-Diels-Alder reaction. Examples show the use of lower catalyst loadings, room temperature conditions, and shorter reaction times.

1. Observed Enhancements to the HDA Reaction with Dirhodium(II) Catalysts

In 2001 we reported that chiral dirhodium(II) catalysts were exceptionally selective when applied to the HDA reaction.[4] As a demonstration of this efficiency, 5-nitro-2-thiophenecarboxaldehyde was reacted with Danishefsky's diene and just 0.01 mol % of Rh_2(4*S*-MPPIM)$_4$ in order to afford the corresponding cyclic product in 81 % yield

and 73 % enantiomeric excess. This result revealed that substrate-to-catalyst loadings of up to 10,000 could be attained, 2 orders of magnitude below the commonly used S/C ratios of 10-50 (**Equation 2.1**).[4]

Equation 2.1: High substrate-to-catalyst ratios exhibited with dirhodium(II) catalysts.

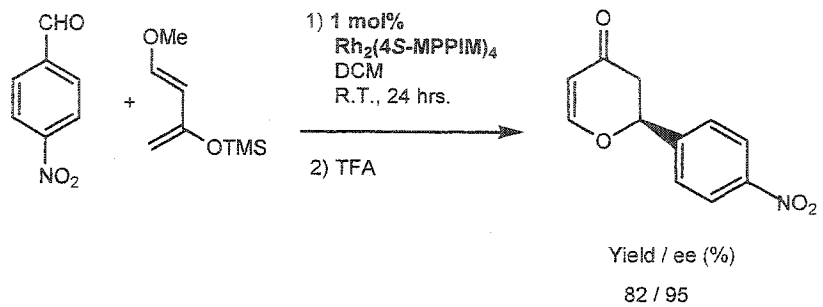


Yield / ee (%)
81 / 73

Additionally, the highest level of enantiocontrol for the hetero-Diels-Alder reaction of *p*-nitrobenzaldehyde and Danishefsky's diene was achieved with $Rh_2(4S\text{-MPPIM})_4$. By reacting the two substrates under the influence of 1.0 mol % of catalyst in dichloromethane at room temperature for a 24 hour period, the HDA adduct was obtained in 82 % yield and 95 % ee (**Equation 2.2**).[4]

Several of the more efficient dirhodium(II) carboxamidate catalysts were also applied to other aldehydes, displaying the varied substrate scope.[4] Similar to the two examples discussed above, the HDA reactions were usually carried out with 1.0 mol % of catalyst at room temperature for 24 hours.[4]

Equation 2.2: Rh_2(4*S*-MPPIM)$_4$ exhibits highest level of enantiocontrol for the HDA reaction of *p*-nitrobenzaldehyde and Danishefsky's diene.



Yield / ee (%)

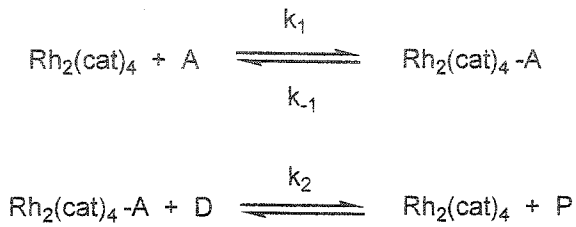
82 / 95

2. Insights into the Rates of Dirhodium(II) Carboxamidate Catalyzed HDA Reactions

The Doyle group in early 2004 reported results of kinetic studies carried out for the hetero-Diels-Alder reaction.[5] Using some of the more selective dirhodium(II) carboxamidate catalysts, studies of the rates of reaction for the HDA process were measured.[5]

The reaction mechanism was proposed to be that outlined in **Scheme 2.1**, where the catalyst (Rh_2L_4) coordinates with the lone pair of electrons on the carbonyl oxygen of the aldehyde (A). This in turn lowers the energy barrier to allow addition of the diene (D) to the catalyst complex, forming the HDA adduct as product (P), and regenerating the catalyst.[5,27]

Scheme 2.1: Reaction mechanism for the dirhodium(II) catalyzed HDA reaction.



As reported in 2004, kinetic studies with both electron-withdrawing and electron-donating *para*-substituted aromatic aldehydes revealed the existence of a strong electronic influence on the rate of the hetero-Diels-Alder reaction.[5] A study in which $Rh_2(4S\text{-MPPIM})_4$ independently catalyzed the HDA reaction of *p*-nitrobenzaldehyde and *p*-anisaldehyde with Danishefsky's diene in chloroform at 60°C was conducted. Results showed that the electron-withdrawing *p*-nitrobenzaldehyde, with a rate constant of $133 \pm 0.7 \times 10^{-3}\ s^{-1}M^{-2}$, reacted greater than 700 times faster than did the electron-donating *p*-anisaldehyde whose rate constant was $0.184 \pm 0.074 \times 10^{-3}\ s^{-1}M^{-2}$ (**Table 2.1**).[5]

Table 2.1: Reaction rates for the HDA reaction with select *para*-substituted aromatic aldehydes and Danishefsky's diene.

Aldehyde	Rate, $10^{-3}\ s^{-1}M^{-2}$	k_{rel}
p-$NO_2C_6H_4CHO$	133 ± 0.7	722
p-$CH_3OC_6H_4CHO$	0.184 ± 0.074	1

Demonstrations of low catalyst loadings for the HDA reaction of either *p*-nitrobenzaldehyde or 5-nitro-2-thiophenecarboxaldehyde and 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene were successful. The $Rh_2(4S\text{-MEOX})_4$ catalyst, at loadings of 1.0 mol %, 0.1 mol %, and even 0.01 mol %, produced the corresponding HDA adduct without large decreases in enantioselectivity.[5] These results further illustrate the exceptional reactivity and selectivity of the dirhodium(II) carboxamidate catalysts as previously seen in the 2001 publication.[4]

IV. Current Research Investigating Diene Influence and Substitution Pattern

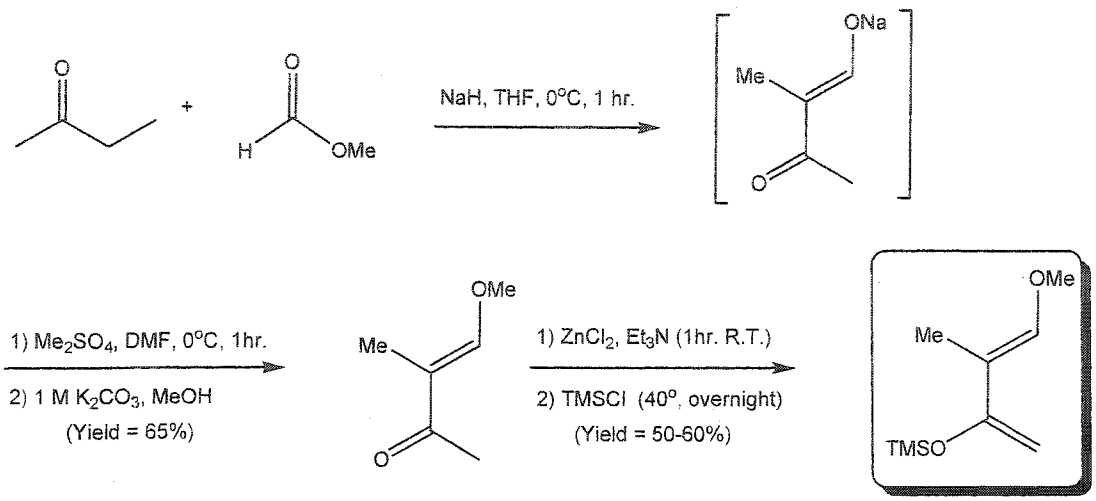
Reports in 2001[4] and 2004[5] have established that dirhodium(II) carboxamidates are highly efficient accelerants for the hetero-Diels-Alder reaction. With the hope of expanding the mechanistic contributions our group has previously reported, new studies have been carried out which are discussed in this section.

Current research has focused on determining the effect substitution of the diene has on the yield, selectivity, and rate of the hetero-Diels-Alder reaction. Experiments with a methyl-substituted variant of Danishefsky's diene, in particular 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene, were conducted. Hetero-Diels-Alder reactions promoted by chiral dirhodium(II) catalysts were carried out with this methyl-substituted diene and several aldehydes. Discussed herein are the results of these experiments. The overall yield, enantioselectivity, and rate of reaction for the hetero-Diels-Alder process are in fact influenced by the substitution pattern of the diene as well as interactions with the catalyst, as will be demonstrated.

1. Synthesis of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene

In order to probe the effects of diene substitution on the dirhodium(II) catalyzed hetero-Diels-Alder reaction, the synthesis of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene was necessary. The overall synthesis of the diene consisted of three steps as outlined below (**Scheme 2.2**).[28,29]

Scheme 2.2: Synthesis of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene.

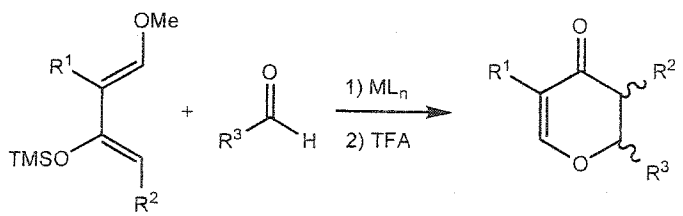


In the initial step, 2-butanone and methyl formate were reacted with sodium hydride in tetrahydrofuran (THF) at 0°C for one hour.[28] The sodium enolate intermediate was not isolated, and addition of dimethyl sulfate (CAUTION: dimethyl sulfate is a known carcinogen and the appropriate precautions were taken with its use) followed (**Scheme 2.2**). Treatment with a 1 M potassium carbonate solution and methanol gave the corresponding ketone (**Scheme 2.2**). Reacting the ketone with zinc chloride, triethylamine, and chlorotrimethylsilane provided a brown residue, which after distillation, provided 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene as reported.[29]

2. General Hetero-Diels-Alder Reaction Investigated

The general hetero-Diels-Alder reaction discussed throughout the remainder of this chapter is given below as a point of reference (**Equation 2.3**). Danishefsky's diene, 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene, will be referred to as diene **1**. Similarly, the dimethyl-substituted version, 1-methoxy-3-(trimethylsilyloxy)-1,3-dimethyl-1,3-butadiene, will be referred to as diene **2**. Finally, the diene of interest, 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene, will be referred to as diene **3**.

Equation 2.3: General HDA reaction under investigation.



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

3. Catalyst Screening Study with *p*-Nitrobenzaldehyde and Diene 3

To ascertain which of the dirhodium(II) carboxamidate catalysts, of the type provided in **Figure 2.2**, would be the most effective for the HDA reaction between *p*-nitrobenzaldehyde and 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**3**), an initial catalyst screening study was in order. *p*-Nitrobenzaldehyde was chosen as previous

studies revealed that a high level of reactivity could be reached among a range of chiral carboxamidate catalysts.[4,5]

The reaction of interest is given below (**Equation 2.4**) in which 1.0 mol % of dirhodium(II) catalyst was reacted with *p*-nitrobenzaldehyde and diene **3** at room temperature in dry dichloromethane for 24 hours. The results for the HDA reaction wherein a variety of chiral dirhodium(II) catalysts were examined are provided as well (**Table 2.2**). Previous experiments have demonstrated that the dirhodium(II) catalyzed HDA reaction proceeds via a Diels-Alder [4+2] pathway, as the product formed before treatment with TFA is the cycloadduct rather than the linear Mukaiyama adduct.[4,5]

Equation 2.4: HDA reaction of *p*-nitrobenzaldehyde and 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (3).

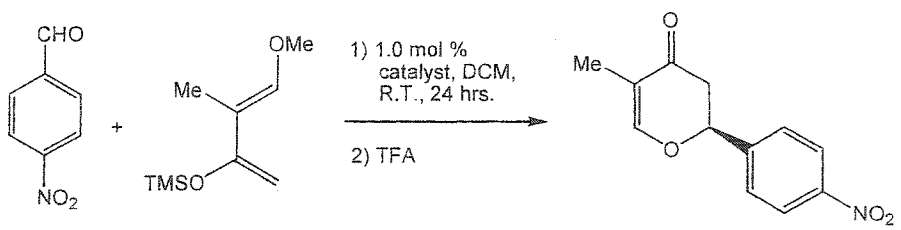


Table 2.2: Catalyst screening study for the HDA reaction of *p*-nitrobenzaldehyde and diene 3 in which various dirhodium(II) carboxamidate catalysts are employed.

Catalyst	Solvent	Yield, %	ee, %
Rh_2(4S-MEOX)$_4$	DCM	66	95
	Toluene	65	93
Rh_2(4S-MACIM)$_4$	DCM	33	45
Rh_2(4S-MPPIM)$_4$	DCM	30	42
Rh_2(4S-IBAZ)$_4$	DCM	58	76
Rh_2(4S-MEAZ)$_4$	DCM	74	53
Rh_2(5S-MEPY)$_4$	DCM	57	66
Rh_2(5S-dFMEPY)$_4$	DCM	67	88
Rh_2(OAc)$_4$	DCM	75	---
NONE	DCM	34	---

Reactions were carried out at room temperature for 24 h.with 1.0 mol% catalyst using 1.0 eq. of aldehyde and 1.3 eq. diene. Treatment with TFA after 24 h , followed by column chromatography afforded the corresponding dihydropyran.
[a] Isolated yield after chromatography.
[b] Determined by HPLC with a Chiralpak OD-H column.

The highest level of enantioselectivity was obtained with the oxazolidinone based Rh_2(4*S*-MEOX)$_4$, which gave a yield of around 66 % and an ee of 95 % (**Table 2.2**). This trend is consistent with previous findings associated with dimethyl diene **2**.[5] As found with diene **3**, Rh_2(4*S*-MPPIM)$_4$ was unsatisfactory in catalyzing the reaction between *p*-nitrobenzaldehyde and diene **2**, and Rh_2(4*S*-MEOX)$_4$ was found to be the most selective catalyst for the HDA transformation.[5]

The two imidazolidinone based dirhodium catalysts investigated were Rh_2(4*S*-MACIM)$_4$ and Rh_2(4*S*-MPPIM)$_4$. Interestingly, the lowest levels of reactivity, reflected

in the % yield of the reaction, and the lowest enantioselectivities, % ee's, were seen with these two catalyst systems. Little difference between these two catalysts was found, as yields between 30-33 % were obtained with ee's in the range of 42-45 % (**Table 2.2**). Also intriguing, Rh_2(4*S*-MPPIM)$_4$, which was previously found to exhibit the highest enantioselectivity (95 % ee) with *p*-nitrobenzaldehyde and Danishefsky's diene **1** (**Equation 2.2**),[4] gave such a poor result here. Rh_2(4*S*-MPPIM)$_4$ was found to be virtually ineffective at catalyzing the reaction between *p*-nitrobenzaldehyde and diene **3**.

From the catalyst screening study (**Table 2.2**) use of Rh_2(5*S*-IBAZ)$_4$ gave a moderate 58 % yield and an enantiomeric excess of 76 % ee. The other azetidinone based catalyst examined, Rh_2(4*S*-MEAZ)$_4$, with a product yield of 74 %, provided the highest yield obtained in the study. However, the ee dropped to 53 % compared to that of Rh_2(5*S*-IBAZ)$_4$.

The pyrolidinone based catalyst Rh_2(5*S*-MEPY)$_4$ gave a yield of 57 % and an enantiomeric excess of 66 % ee, whereas the fluorinated analog Rh_2(5*S*-dFMEPY)$_4$, resulted in an improved yield of 67 % and a much higher ee of 88 % (**Table 2.2**). The enantiomeric excess achieved with Rh_2(5*S*-dFMEPY)$_4$ was the second highest % ee realized under these reaction conditions, second only to Rh_2(4*S*-MEOX)$_4$.

The HDA reaction of *p*-nitrobenzaldehyde and diene **3** catalyzed by $Rh_2(OAc)_4$ was carried out in order to determine appropriate HPLC separation conditions. $Rh_2(OAc)_4$ provided a racemic mixture of *R* and *S* enantiomers of the HDA adduct in 75 % yield (**Table 2.2**).

A brief examination into the influence of the solvent was carried out. The reaction between *p*-nitrobenzaldehyde and **3** was conducted in freshly distilled toluene as well as in dry DCM. Almost identical yields, 66 and 65 %, and similar enantioselectivities, 95 and 93% ee, were seen with both solvents (**Table 2.2**). It appears that under these particular conditions the solvent does not affect the yield and ee, however more than just two solvents are needed to solidify this apparent effect.

To summarize the findings from the catalyst screening study, the imidazolidinone based catalysts gave the lowest product yields (30-33 %) and poorest enantioselectivities (42-45 %). Moderate yields were seen with the pyrolidinones, the azetidinones, and with $Rh_2(4S\text{-MEOX})_4$, the only oxazolidinone investigated. The highest yield of 74 % was obtained with $Rh_2(4S\text{-MEAZ})_4$, whereas the highest enantiomeric excess of 95 % ee was realized with $Rh_2(4S\text{-MEOX})_4$. A brief investigation in which toluene was employed rather than DCM did not reveal any potential solvent effects for the HDA reaction.

4. Catalyst Loading Study with *p*-Nitrobenzaldehyde and Diene 3

The most selective dirhodium(II) carboxamidate catalyst for the HDA reaction between *p*-nitrobenzaldehyde and diene **3** is $Rh_2(4S\text{-MEOX})_4$, as demonstrated by the catalyst screening study. With the employment of this catalyst, an enantiomeric excess of 95 % ee is reached.

Following the catalyst screening study, the catalyst loading of the reaction was explored. The goal of this investigation was to determine if the reactivity and selectivity of the HDA reaction between diene **3** and *p*-nitrobenzaldehyde could be maintained as

the amount of $Rh_2(4S\text{-MEOX})_4$ catalyst was decreased. The results from this study are given below in **Table 2.3**.

Table 2.3: Catalyst loading study for the HDA reaction of *p*-nitrobenzaldehyde and diene 3 in which the amount of $Rh_2(4S\text{-MEOX})_4$ catalyst is decreased.

$Rh_2(4S\text{-MEOX})_4$ Loading, mol %	Yield, % [a]	ee, % [b]
1.0	66	95
0.2	65	93
0.1	63	83

Reactions were carried out at room temperature for 24 h. using 1.0 eq. of aldehyde and 1.3 eq. of diene. Treatment with TFA after 24 h , followed by column chromatography afforded the corresponding dihydropyran.
[a] Isolated yield after chromatography.
[b] Determined by HPLC with a Chiralpak OD-H column.

The HDA reaction of diene **3** and *p*-nitrobenzaldehyde is generally carried out using 1.0 mol % of $Rh_2(4S\text{-MEOX})_4$. To identify whether or not the enantioselectivity of the reaction could be maintained with lower catalyst loadings, the reaction was next looked at using 0.1 mol % of the catalyst (**Table 2.3**). From this initial decrease, a deleterious effect on the enantioselectivity was observed as the ee went from 95 % ee at 1.0 mol % catalyst, to 83 % ee (average of three runs) with 0.1 mol %. Interestingly, even though a decrease in enantioselectivity was observed by lowering the catalyst loading, the yield of the reaction was largely unchanged, 66 % versus 63 %.

Determined that an ee above 90 % could still be reached, the loading was increased slightly from 0.1 to 0.2 mol % (**Table 2.3**). With this second approach an ee of 93 % was achieved with a similar yield of 65 %, demonstrating that $Rh_2(4S\text{-MEOX})_4$ can in fact effectively promote the HDA reaction of diene **3** and *p*-nitrobenzaldehyde, even at catalyst loadings as low as 0.2 mol %. Recall that low catalyst loadings (1.0 mol %, 0.1 mol %, and even 0.01 mol %) of the $Rh_2(4S\text{-MEOX})_4$ catalyst were also found to efficiently catalyze the HDA reaction for either *p*-nitrobenzaldehyde or 5-nitro-2-thiophene-carboxaldehyde and Danishefsky's diene **1** without large decreases in enantioselectivity.[5]

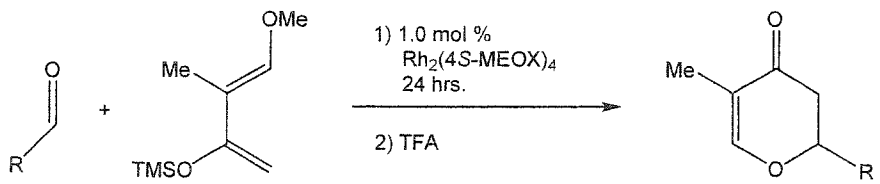
The new findings discussed above, as well as those previously observed,[5] support the trend of exceptional reactivity and selectivity that dirhodium(II) carboxamidate catalysts exhibit.[4]

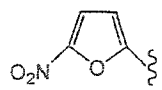
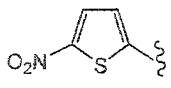
5. Substrate Screening Study for the HDA Reaction with Diene 3

Prior to investigating alternative aldehydes as dienophiles in the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction, a closer examination of the HDA reaction of diene **3** and *p*-nitrobenzaldehyde was needed. With the hope of elevating the modest yield (66%) of the reaction, a slight excess in diene was employed. The data given in **Table 2.4** below reveals that when 2.0 equivalents of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**3**) were reacted with *p*-nitrobenzaldehyde instead of 1.3 equivalents, the yield was improved from a moderate 66 % to a reasonably high 83 %. In both cases, the enantiomeric excess remained unchanged at 95 % ee. Consequently, it appears that an

increase in diene concentration is needed in order for higher yields to be obtained for the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction of *p*-nitrobenzaldehyde and diene 3. By employing 2.0 equivalents of diene, results of 83 % yield and 95 % ee become comparable to the 88 % yield, 97 % ee HDA reaction with diene 1, and the 90 % yield, 96 % ee HDA reaction with diene 2.[5]

Table 2.4: Aldehyde screening study for the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction with diene 3.



R =	Diene, Eqv.	Temperature, °C	Yield, % [a]	ee, % [b]
p-$NO_2C_6H_4$	1.3 2.0	25 25	66 83	95 95
p-$CF_3C_6H_4$ [c]	1.3 1.3	25 60	54 76	86 86
	1.3	25	86	92
	1.3 2.0	25 25	86 89	95 95

Reactions were carried out in DCM at the specified temperature for 24 h. with 1.0 mol % catalyst and 1.0 eq. of aldehyde. Treatment with TFA after 24 h , followed by column chromatography afforded the corresponding dihydropyran.
[a] Isolated yield after chromatography.
[b] Determined by HPLC with a Chiralpak OD-H column.
[c] Solvent free conditions for liquid aldehydes.

With the HDA reaction of *p*-nitrobenzaldehyde and 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene **3** as the exemplary reaction, interest into other aldehydes was sparked. **Table 2.4** provides the results from the room temperature $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reactions of several other aldehydes with diene **3**.

Due to similarities with *p*-nitrobenzaldehyde, α,α,α-trifluoro-*p*-tolualdehyde was reacted with $Rh_2(4S\text{-MEOX})_4$ and diene **3** under solvent free conditions. Initially at 25°C and 1.3 equivalents of diene **3**, the corresponding dihydropyran adduct was formed in a moderate 54 % yield and 86 % ee (**Table 2.4**). As a means of increasing the product yield, the reaction temperature was raised to 60°C. The HDA reaction was successfully catalyzed by $Rh_2(4S\text{-MEOX})_4$ at this temperature. With 1.3 equivalents of diene **3** and solvent free conditions, an enhanced yield of 76 % was observed. The enantioselectivity remained unchanged at 86 % ee.

5-Nitro-2-furaldehyde was also investigated in the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction. At room temperature conditions with 1.3 equivalents of diene **3**, a yield of 86 % was achieved followed by an enantiomeric excess of 92 % ee (**Table 2.4**). Recall that this reaction had been previously investigated with the dimethyl-substituted diene **2** and $Rh_2(4S\text{-MEOX})_4$, giving a 95 % yield and an 84 % ee.[5] When one compares the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA result from this study with diene **3** (92 % ee) and the previous result with diene **2** (84 % ee), it appears that the additional methyl group of diene **2** has an adverse effect on the enantioselectivity of the reaction. Possibly, the additional methyl group of diene **2** presents steric interactions that hinder the dienes' ability to react with the aldehyde-catalyst complex. However, if this is true, one would

think that the differences in enantioselectivities observed with 5-nitro-2-thiophenecarboxaldehyde (discussed next) would follow this same trend. In comparing product yields and enantioselectivities of 5-nitro-2-thiophenecarboxaldehyde with dienes **2** and **3**, one will see that this trend is not applicable.

Related to 5-nitro-2-furaldehyde, 5-nitro-2-thiophenecarboxaldehyde was examined for its reactivity in the hetero-Diels-Alder reaction between 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene **3** mediated by $Rh_2(4S\text{-MEOX})_4$. With 1.3 equivalents of diene at room temperature conditions, a yield of 86 % was achieved (**Table 2.4**). The enantiomeric excess was slightly higher, 95 % ee, than that exhibited with 5-nitro-2-furaldehyde at 92 % ee. Raising the amount of diene **3** to 2.0 equivalents had a minor affect on the yield of the reaction which was increased from 86 % to 89 %. Enantiomeric excesses for both the reactions (1.3 and 2.0 equivalents) remained the same at 95 % ee. Previous investigations of this reaction with $Rh_2(4S\text{-MEOX})_4$ catalyst and diene **2** revealed a 96 % yield of the corresponding adduct in 97 % ee.[5]

From this aldehyde screening study, the single methyl substituent of diene **3** does not exhibit any detrimental effect on the dienes' ability to react with the various aldehyde-$Rh_2(4S\text{-MEOX})_4$ complexes. Reasonable product yields and high enantioselectivities, up to 95 % ee, have been established for several aldehydes in addition to *p*-nitrobenzaldehyde.

6. Kinetic Studies for the HDA Reaction of *p*-Nitrobenzaldehyde and Diene 3

The Doyle group has reported kinetic studies for the $Rh_2(4S\text{-MPPIM})_4$ catalyzed hetero-Diels-Alder reaction between *p*-nitrobenzaldehyde and Danishefsky's diene (**1**).[5] To provide additional insights into the Lewis acid catalyzed hetero-Diels-Alder reaction of aldehydes and substituted dienes, new kinetic studies were performed in conjunction with current research. The results for the HDA reaction between *p*-nitrobenzaldehyde and diene **3**, catalyzed by various chiral dirhodium(II) carboxamidate catalysts, will be discussed herein. It is evident form the results that the structural characteristics of the catalysts themselves have an impact of the rate of the overall reaction.

A. General Guidelines for the Kinetic Studies

The kinetic studies for the various dirhodium(II) catalyzed HDA reactions with *p*-nitrobenzaldehyde and diene **3** were carried out under room temperature conditions. The diene, catalyst, aldehyde, and biphenyl (internal GC standard) were reacted in dry dichloromethane (DCM). At various time intervals throughout the course of the reaction, 100 μL aliquots were removed and added to 4 mL of dichloroethane (DCE). Immediate treatment with trifluoroacetic acid (TFA) followed to desilylate both the product and the diene, after which neutralization with solid sodium bicarbonate occurred. The reaction was allowed to proceed through at least two half-lives.[5] The rate of the catalyzed reaction can easily be monitored with GC analysis by injecting 10 μL of the neutralized sample onto a gas chromatograph. From the GC chromatogram, distinct peaks for the aldehyde and biphenyl internal standard are seen at $t_r \sim 5.90$ minutes and $t_r \sim 6.39$ minutes,

respectively. Eventually, the aldehyde peak at 5.90 minutes decreases and the appearance of a new peak, corresponding to the HDA adduct, is observed at $t_r \sim 14.30$ minutes.

From the GC chromatogram one can therefore calculate the change in the number of moles of aldehyde, or Mole U (**Equation 2.5**). In **Equation 2.5**, U = unknown (aldehyde) and St = standard (biphenyl). The ratio of Area U to Area St is calculated from the area counts provided on the GC chromatogram, the Mole St value is known. The R. F. value, or response factor, for *p*-nitrobenzaldehyde relative to the biphenyl standard was calculated to be 0.483.[5] A pseudo-first-order kinetic plot is generated by plotting the log of the change in the initial and final concentrations of aldehyde, $(\log[A]_t / [A]_0) \times 1000$ vs. the reaction time in seconds (**Figure 2.3**).[5] The rate constant is calculated by linear least-squares regression from the pseudo-first-order kinetic plot using the equation $k = -2.303(m) / 1000$, where "m" is equal to the slope of the line (**Figure 2.3**). By using the following equation, k / (mmol catalyst)(mmol diene), one can calculate the rate constant in terms of the amount of catalyst and diene used. The rate constant is therefore in $sec^{-1}M^{-2}$. The half-life of the reaction is determined by the equation $t_{1/2} = 0.693 / k$.[5] An example of the linear pseudo-first order kinetic plot for the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction between *p*-nitrobenzaldehyde and diene **3** will be discussed herein (**Figure 2.3**).

Equation 2.5: Equation with which the rate of the HDA reaction is calculated.

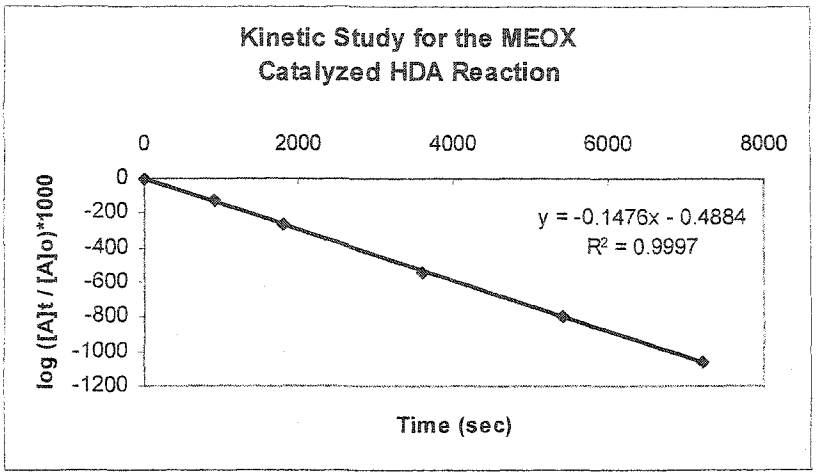
$$\text{Mole U} = \frac{\left(\frac{\text{Area U}}{\text{Area St}}\right)\left(\text{Mole St}\right)}{\text{R.F.}}$$

B. Kinetic Studies for the HDA Reaction of *p*-Nitrobenzaldehyde and Diene 3 Catalyzed by Various Dirhodium(II) Carboxamidates

To provide additional insights into the Lewis acid catalyzed hetero-Diels-Alder reaction of aldehydes and substituted dienes, new kinetic experiments were performed. This section will be dedicated to the kinetic studies carried out and to the mechanistic insights they offer.

The first kinetic study investigated was the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction of *p*-nitrobenzaldehyde and diene **3**. The reaction was allowed to proceed through two half-lives at room temperature as described above. Gas chromatographic analysis of the aliquots removed led to the generation of a pseudo-first-order kinetic plot. The plot generated for this $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction is given below in **Figure 2.3**.

Figure 2.3: Linear pseudo-first-order kinetic plot generated for the Rh_2(4*S*-MEOX)$_4$ catalyzed HDA of *p*-nitrobenzaldehyde and diene 3.



The rate constant for the reaction was calculated from the pseudo-first-order kinetic plot. **Table 2.5** below provides the complete results for each of the dirhodium(II) carboxamidate catalysts investigated for the HDA reaction of *p*-nitrobenzaldehyde and diene **3**. The catalysts, along with their respective rate constants and half-lives (in seconds and in hours), have been presented in order from fastest to slowest. Rate data for the background reaction, in which no catalyst is employed, has been provided beneath **Table 2.5**.

Table 2.5: Kinetic study data for the HDA reaction of *p*-nitrobenzaldehyde and diene 3 catalyzed by various chiral dirhodium(II) carboxamidate catalysts.

Catalyst	Rate Constant [a], k ($\times 10^{-3}$ sec^{-1}M^{-2})	Half-Life [b], $t_{1/2}$ (sec.)	Half-Life, $t_{1/2}$ (hrs.)
Rh_2(4*S*-MEOX)$_4$	56.3 ± 2.6	1977	0.5
Rh_2(4*S*-IBAZ)$_4$	55.6 ± 2.9	2104	0.6
Rh_2(5*S*-MEPY)$_4$	8.2 ± 0.4	13550	3.8
Rh_2(4*S*-MPPIM)$_4$	3.6 ± 0.2	30662	8.5

Reactions were carried out at room temperature in 1.0 mL DCM for the indicated time with 1.0 mol % catalyst, 10.0 eqv. of diene (2.5 M diene solution) and 1.0 eqv. of aldehyde.
[a] Biphenyl was used as a GC internal standard.
[b] Determined after GC injection on a Supelco SPB-5 column.
** The rate of the reaction for *p*-nitrobenzaldehyde and diene **3** with no catalyst present at R.T. is 6.8 ± 0.8 x 10^{-6}sec^{-1}M^{-1}.

A rate constant of 56.3 ± 2.6 x 10^{-3} sec^{-1}M^{-2} was calculated for the Rh_2(4*S*-MEOX)$_4$ catalyzed hetero-Diels-Alder reaction of diene **3** and *p*-nitrobenzaldehyde (**Table 2.5**). An average of three kinetic runs gave a corresponding half-life of 0.5 hours or 1977 seconds, the lowest reaction time observed for any of the dirhodium(II) carboxamidate catalysts examined. This demonstrates the overall efficiency of the Rh_2(4*S*-MEOX)$_4$ catalyst. Comparisons with this highly efficient system will be made with the dienes **1** and **2** in the next section.

Following close behind the Rh_2(4*S*-MEOX)$_4$ catalyzed HDA reaction was Rh_2(4*S*-IBAZ)$_4$. Kinetic studies with Rh_2(4*S*-IBAZ)$_4$ gave a rate constant of 55.6 ± 2.9 x 10^{-3}

$sec^{-1}M^{-2}$ with a half-life of 2104 seconds, 0.6 hours (**Table 2.5**). It is interesting to note that the reaction rate for the azetidinone based catalyst is so close to that of Rh_2(4*S*-MEOX)$_4$. Referring back to **Figure 2.2**, which provides the structures for the dirhodium(II) catalysts, one can see that the isobutyl group of Rh_2(4*S*-IBAZ)$_4$ does not appear to have any detrimental steric effect that would impact the reaction rate. Additionally, the rate of the reaction does not seem to be influenced by ring size. The five-membered ring of the oxazolidinone and the four-membered ring of the azetidinone provided similar rate constants (**Table 2.5**).

The efficiency of the Rh_2(5*S*-MEPY)$_4$ catalyst was also examined in the HDA reaction with *p*-nitrobenzaldehyde and diene **3**. A rate constant of $8.2 \pm 0.4 \times 10^{-3}$ $sec^{-1}M^{-2}$ was calculated from the pseudo-first-order kinetic plot (**Table 2.5**). A corresponding half-life of 13550 seconds or 3.8 hours was determined. This pyrolidinone based catalyst had a reaction rate that fell in between that of Rh_2(4*S*-MEOX)$_4$ and Rh_2(4*S*-MPPIM)$_4$. As one can see from the catalyst structures in **Figure 2.2**, the only difference between MEPY and MEOX is the incorporation of oxygen in the five-membered ring, however, the pyrolidinone based MEPY is not as efficient for the HDA reaction of *p*-nitrobenzaldehyde and diene **3**.

The final catalyst that was examined for its ability to catalyze the HDA reaction between *p*-nitrobenzaldehyde and diene **3** was Rh_2(4*S*-MPPIM)$_4$. For this catalyst a half-life of 30662 seconds or 8.5 hours was obtained, along with a rate constant of $3.6 \pm 0.2 \times 10^{-3}$ $sec^{-1}M^{-2}$ (**Table 2.5**). This catalyst was the most inefficient catalyst of all those examined. In fact, Rh_2(4*S*-MPPIM)$_4$ was so slow in catalyzing this HDA reaction that it

is comparable with the background reaction in which no catalyst is present at all ($t_{1/2}$ = 6.8 ± 0.8 $sec^{-1}M^{-1}$). The catalyst structure provided in **Figure 2.2** shows that the large sterically hindering phenylpropanoyl side arm of this catalyst has very detrimental effects on the coordinating abilities of the aldehyde and diene. Recall that Rh_2(4*S*-MPPIM)$_4$ was found to be the most efficient catalyst for the HDA reaction of *p*-nitrobenzaldehyde and Danishefsky's diene **1**.[4]

Table 2.5 also provides the rate data for the background reaction in which the HDA reaction is carried out in the absence of any accelerant. For this uncatalyzed reaction an average of three runs gave a rate constant of 6.8 ± 0.8 x 10^{-6} $sec^{-1}M^{-1}$ with a half-life of 41332 seconds, 11.5 hours. This has been provided as a point of reference for the catalytic reactions.

Figure 2.4 below provides a graphical summary of the rate constants for all the catalysts examined above. **Figure 2.5** provides a graphical summary of their respective half-lives.

Figure 2.4: Graphical summary of the rate constants for the various dirhodium(II) catalysts examined in the HDA reaction between *p*-nitrobenzaldehyde and diene 3.

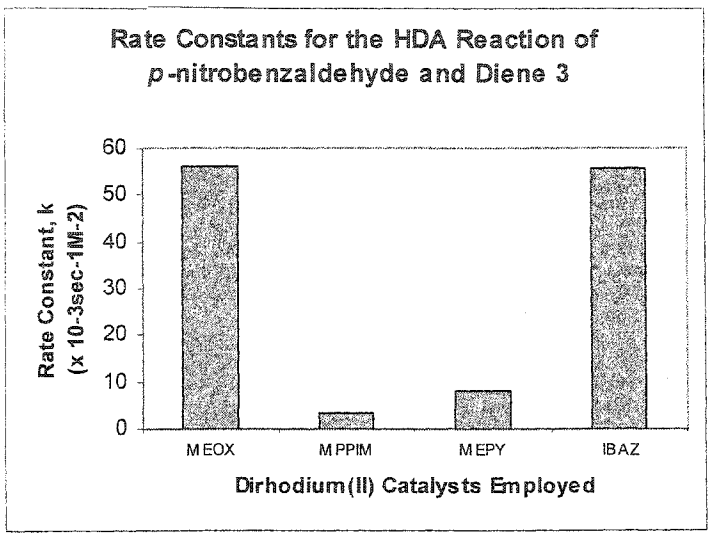
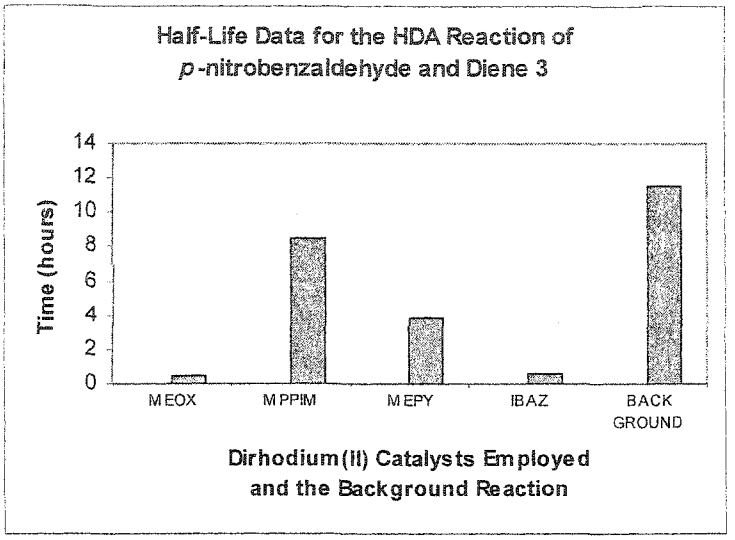


Figure 2.5: Graphical summary of the half-lives of the various dirhodium(II) catalysts employed in the HDA reaction between *p*-nitrobenzaldehyde and diene 3.



In summary, kinetic studies have been carried out to determine the efficiency of the various dirhodium(II) carboxamidate catalysts employed in the hetero-Diels-Alder reaction of *p*-nitrobenzaldehyde and diene **3**. **Figure 2.4** and **Figure 2.5** graphically demonstrate the rate constants and the half-lives for the catalysts. The kinetic studies revealed that Rh_2(4*S*-MEOX)$_4$ was the most effective catalyst for the HDA reaction and that Rh_2(4*S*-MPPIM)$_4$ is the least effective. Comparing the rate data obtained for all of the catalysts and for the background reaction, it is evident that the Rh_2(4*S*-MEOX)$_4$ catalyzed HDA reaction of diene **3** and *p*-nitrobenzaldehyde is 23 times faster than the background reaction, 17 times faster than the Rh_2(4*S*-MPPIM)$_4$ reaction, 8 times faster than the

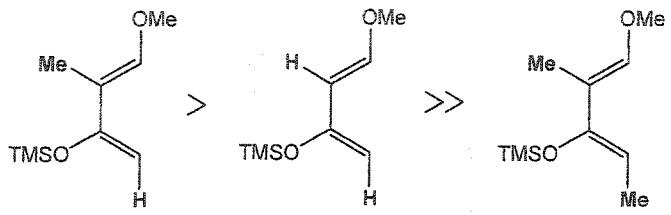
Rh_2(5*S*-MEPY)$_4$ reaction, and that it is almost dead even with the Rh_2(4*S*-IBAZ)$_4$ reaction.

C. Comparison of Dienes 1, 2, and 3 in the Dirhodium(II) Catalyzed Hetero-Diels-Alder Reaction with *p*-Nitrobenzaldehyde

Based on the rate data discussed above for the Rh_2(4*S*-MEOX)$_4$ catalyzed HDA reaction between *p*-nitrobenzaldehyde and diene **3**, one can attempt to compare the overall efficiency of the catalytic process with respect to dienes **1** and **2**.

The Rh_2(4*S*-MEOX)$_4$ catalyzed HDA reaction with *p*-nitrobenzaldehyde and the dimethyl-substituted diene **2** had been previously carried out by a co-worker in early 2004.[5] The calculated rate constant for diene **2** was 6.2×10^{-3} $sec^{-1}M^{-2}$ with a half-life of 18000 seconds or 5.0 hours.[5] A recent publication by our group has included the kinetic studies for diene **3** discussed above in detail, as well as those for the Rh_2(4*S*-MEOX)$_4$ catalyzed HDA reaction of *p*-nitrobenzaldehyde and Danishefsky's diene **1**.[6] Recall that the Rh_2(4*S*-MEOX)$_4$ HDA reaction with diene **3** had a rate constant of 56.3×10^{-3} $sec^{-1}M^{-2}$ and a half-life of 0.5 hours. Danishefsky's diene **1** was found to have a rate constant of 23.1×10^{-3} $sec^{-1}M^{-2}$ and a half-life corresponding to 4500 seconds or 1.3 hours.[6] **Figure 2.6** has been provided below to summarize the rate constant and half-life data for the dienes **1**, **2**, and **3**.

Figure 2.6: Summary of the rate constant and half-life data with $Rh_2(4S\text{-MEOX})_4$ for dienes 1, 2, and 3.



3 **1** **2**

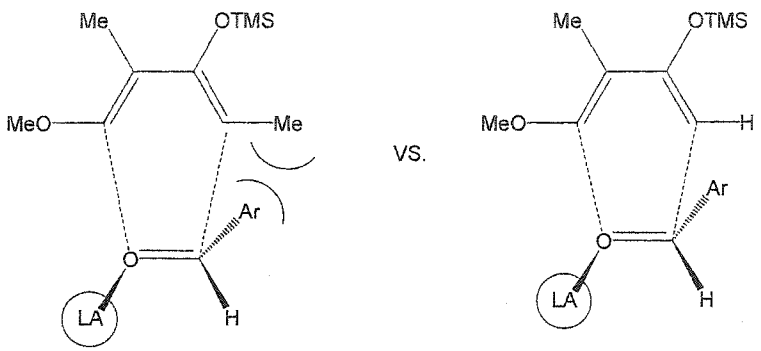
$k = 56.3 \times 10^{-3} sec^{-1}M^{-2}$	$k = 23.1 \times 10^{-3} sec^{-1}M^{-2}$	$k = 6.2 \times 10^{-3} sec^{-1}M^{-2}$
$t_{1/2}$ = 1977 sec	$t_{1/2}$ = 4500 sec	$t_{1/2}$ = 18000 sec
$t_{1/2}$ = **0.5 hrs.**	$t_{1/2}$ = **1.3 hrs.**	$t_{1/2}$ = **5.0 hrs.**

A comparison of the kinetic data for the $Rh_2(4S\text{-MEOX})_4$ catalyzed HDA reaction with *p*-nitrobenzaldehyde and the each of the three dienes reveals some surprising results. The dimethyl-substituted diene **2** was found to have the slowest reaction rate and longest half-life of the three dienes investigated. Danishefsky's diene **1** was found to be faster than diene **2** but interestingly slower than the monomethyl-substituted diene **3**.[6]

Diene **3** was, without a doubt, faster than either of the two dienes which is intriguing. It may be possible that the methyl group of diene **3** is acting like an electron donating group, pushing electrons into the conjugation of the diene, rendering it more reactive towards the aldehyde-catalyst complex. The slower reactivity of diene **2** may be caused by adverse steric interactions of the methyl groups, which in turn minimizes its coordinating abilities toward the aldehyde-catalyst complex.

Figure 2.7 proposes what could be happening between the aldehyde-catalyst complex and dienes **2** and **3**.

Figure 2.7: Mechanistic proposal of possible steric interactions between the aldehyde-catalyst complex and diene 2.



Diene 2 **Diene 3**

Possible steric interactions between the methyl group of diene **2** and the aromatic group of the aldehyde would make coordination difficult for the diene with the aldehyde-catalyst complex (**Figure 2.7**). Adverse steric interactions are not an issue with diene **3**, and coordination of the diene with the aldehyde-catalyst complex may occur more readily (**Figure 2.7**). Further kinetic experiments involving aldehydes other than *p*-nitrobenzaldehyde are needed to determine if this trend in reactivity remains. However, it is evident that the rate of reaction is influenced by the substitution pattern of the diene.

V. Conclusions

Beginning in 2001, the Doyle research group has applied dirhodium(II) catalysts to the hetero-Diels-Alder reaction.[4] The development of the dirhodium(II) catalysts has been presented, and examples of their employment in the HDA reaction have been provided to illustrate their overall efficiency.

The main focus of this chapter has been devoted to recent studies pertaining to the dirhodium(II) carboxamidate catalyzed hetero-Diels-Alder reaction between 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene **3**. Experiments have been carried out to determine the most effective dirhodium(II) carboxamidate catalyst for the HDA reaction of diene **3** and *p*-nitrobenzaldehyde. The $Rh_2(4S\text{-MEOX})_4$ catalyst was found to be the most selective catalyst as enantioselectivities of up to 95 % ee could be reached.

Catalyst loading studies revealed that as little as 0.2 mol % of catalyst could be employed in the reaction without a significant loss in enantioselectivity. Additionally, HDA reactions catalyzed by $Rh_2(4S\text{-MEOX})_4$ were conducted with α,α,α-trifluoro-*p*-tolualdehyde, 5-nitro-2-furaldehyde, and 5-nitro-2-thiophenecarboxaldehyde in order to demonstrate the overall efficiency of the catalyst. Moderate to high yields with enantioselectivities ranging from 86-95 % ee were achieved.

Investigating the kinetics of the reaction between diene **3** and *p*-nitrobenzaldehyde catalyzed by the $Rh_2(4S\text{-MEOX})_4$ catalyst revealed a rate of 56.3×10^{-3} $sec^{-1}M^{-2}$ and a half-life of 0.5 hours. Studies of other dirhodium(II) carboxamidate catalysts showed the $Rh_2(4S\text{-MEOX})_4$ catalyst to be the fastest at promoting the HDA reaction of *p*-

nitrobenzaldehyde and diene **3**. The Rh_2(4*S*-MPPIM)$_4$ catalyst was found to be the least reactive of all the catalysts probed.

Lastly, kinetic data allowed for comparisons between dienes **1**, **2**, and **3**. Subtle differences in the substitution of the diene proved not to be trivial. The monomethyl diene **3** was found to react faster than Danishefsky's diene **1**, both being significantly faster than the dimethyl-substituted diene **2**. Possible steric interactions hindering coordination of diene **2** with the aldehyde-catalyst complex have been proposed. The rate of reaction for the hetero-Diels-Alder process was therefore found to be influenced by the substitution pattern of the diene. Further experiments are needed with other aldehydes in order to determine if this reactivity trend persists, however, these results have recently been published.[6]

VI. Experimentals and Product Characterization

General

All aldehydes were obtained through commercial sources and either purified by recrystallization or distillation prior to their use. Dichloromethane, toluene, and dichloroethane were distilled before use according to established procedures.[30] Rh_2(4*S*-MEOX)$_4$,[17] Rh_2(4*S*-MPPIM)$_4$,[20] Rh_2(4*S*-MACIM)$_4$,[20] Rh_2(4*S*-IBAZ)$_4$,[21] Rh_2(4*S*-MEAZ)$_4$,[22] Rh_2(5*S*-MEPY)$_4$,[14] and Rh_2(5*S*-dF-MEPY)$_4$[16] were prepared according to literature methods. 1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**3**) was prepared and purified by published procedures.[28-29] ^{1}H NMR spectra were obtained as solutions in $CDCl_3$ and are reported downfield from the internal standard, Me_4Si (TMS) using a Bruker 400-MHz spectrometer. Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration. EI-HRMS spectra were obtained on a QP 5000 GCMS instrument.

General Procedure for the hetero-Diels-Alder Reaction

To an oven-dried 1.5-dram vial equipped with stirbar was added the aldehyde (0.25 mmol), 1.0 mol % catalyst (0.0025 mmol), and 0.25 mL dry solvent (if the aldehyde was a liquid, the reaction was conducted in the absence of solvent). The resulting solution was allowed to mix thoroughly with stirring after which 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**3**) (0.33 mmol) was added. The reaction mixture was let to stir at the selected temperature and after the allotted time, the solution

was treated with 3-5 drops of trifluoroacetic acid (TFA). Purification by column chromatography followed with a short silica gel column to remove catalyst. The resulting purified material was concentrated in vacuo to afford product, and the isolated yield was calculated. Enantiomeric excesses (% ee) were determined by HPLC analysis on a Varian Prostar HPLC instrument with a 0.46 x 25-cm Daicel Chiralpak OD-H column.

Kinetic Procedure

To an oven dried 2-dram vial equipped with stirbar was added the aldehyde (0.25 mmol), biphenyl (gas chromatography standard, 0.25 mmol), 1.0 mol % catalyst (0.0025 mmol), and 1.0 mL of dry solvent, giving a 2.5 M diene solution. 1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene (**3**) (2.5 mmol) was then added, timing of the reaction was started, and immediate removal of 100 μL aliquot of the reaction solution as the "time zero" measurement was performed. The reaction was stirred at room temperature and the subsequent removal of 100 μL aliquots of the reaction solution at various time intervals allowed the loss of aldehyde over time to be measured. Each aliquot was added to 4 mL of dichloroethane pretreated with four drops of TFA to desilylate both product and diene, thus ensuring that no further reaction could take place with the aldehyde. The acid was neutralized with solid sodium bicarbonate, and samples were then injected on a Hewlett-Packard 5890A gas chromatograph equipped with a Supelco SPB-5 (30 m, 0.25 mm) column. Gas chromatography conditions were as follows: initial oven temperature = 160°C, helium flow = 80 mL/min., injector temperature = 200°C, and detector temperature = 200°C. The run carried out consisted of 5 minutes at 160°C, after which

ramping at 35°C/minute followed, until a maximum temperature of 240°C was reached. (For *p*-nitrobenzaldehyde, t_r = 5.90 min., biphenyl internal standard, t_r = 6.39 min., and HDA adduct **1a**, t_r = 14.30 min. respectively.)

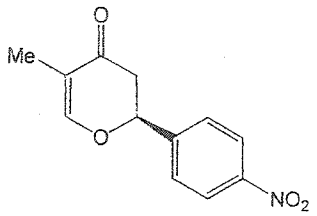
The reaction was allowed to continue through two half lives. Kinetic measurements were conducted in duplicate or triplicate trials. The rate constant, determined through two half lives, was established by linear least-squares regression resulting from the linear pseudo-first-order kinetic plot. The half life was calculated by using the equation $t_{1/2} = 0.693/k$.

Characterization

(2*S*)-2-(4-Nitrophenyl)-5-methyl-2,3-dihydro-4*H*-pyran-4-one

The product was prepared following the procedure outlined above using *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) and 2.0 eqv. (93 μL, 0.50 mmol) of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene. The crude product was purified by column chromatography (silica gel, DCM as eluting solvent) to provide **1a** as a white solid in 83 % yield (48.5 mg, 0.21 mmol); Rf = 0.37 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 0.8 Hz, 1H), 5.49 (dd, *J* = 4.2, 13.6 Hz, 1H), 2.83 (dd, *J* = 13.6, 16.8 Hz, 1H), 2.74 (dd, *J* = 4.2, 16.8 Hz, 1H), 1.72 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 158.8, 145.3, 126.6, 124.1, 114.8, 79.6, 43.2, 10.5. 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

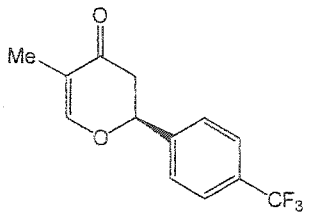
$C_{12}H_{11}O_4N$ (MH^+) 233.0688, found 233.0685. The absolute configuration was not determined.



1a

(2*S*)-2-(4-Trifluoromethyl)-5-methyl-2,3-dihydro-4*H*-pyran-4-one

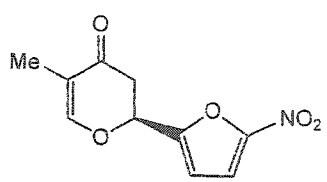
The product was prepared following the procedure outlined above using α,α,α-trifluoro-*p*-tolualdehyde (38 mg, 0.25 mmol) and 1.3 eqv. (53 μL, 0.29 mmol) of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene. The crude product was purified by column chromatography (silica gel, DCM as eluting solvent) to provide **1b** as a white solid in 76 % yield (42.4 mg, 0.17 mmol); Rf = 0.66 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 0.8 Hz, 1H), 5.45 (dd, J = 3.7, 14.2 Hz, 1H), 2.85 (dd, J = 14.2, 16.9 Hz, 1H), 2.72 (dd, J = 3.7, 16.9 Hz, 1H), 1.73 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 159.1, 126.2, 125.8, 114.5, 80.0, 43.2, 10.5. Enantiomeric excess was determined to be 85 % ee by HPLC with a Chiralpak OD-H column (90:10 hexane/^{i}PrOH, 1.0 ml/min): t_r = 8.3 min for major enantiomer; t_r = 12.3 min for minor enantiomer. EI-HRMS *m/z* calculated for $C_{13}H_{11}O_2F_3$ (MH^+) 256.0724, found 256.0711. The absolute configuration was not determined.



1b

(2*S*)-2-(5-Nitrofuryl)-5-methyl-2,3-dihydro-4*H*-pyran-4-one

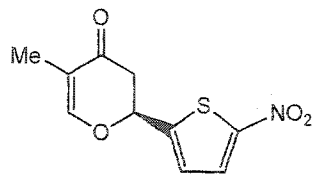
The product was prepared following the procedure outlined above using 5-nitro-2-furaldehyde (38 mg, 0.27 mmol) and 1.3 eqv. (65.5 μL, 0.35 mmol) of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene. The crude product was purified by column chromatography (silica gel, 9:1 hexane/EtOAc as eluting solvent) to provide **1c** as a light yellow solid in 83 % yield (49.5 mg, 0.22 mmol); Rf = 0.36 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 3.6 Hz, 2H), 6.62 (d, J = 3.6 Hz, 1H), 5.49 (dd, J = 4.3, 12.5 Hz, 1H), 3.05 (dd, J = 12.5, 16.8 Hz, 1H), 2.86 (dd, J = 4.3, 16.8 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 158.3, 153.6, 115.5, 112.2, 73.3, 39.4, 31.4, 10.9. Enantiomeric excess was determined to be 92 % ee by HPLC with a Chiralpak OD-H column (90:10 hexane/^{i}PrOH, 1.0 ml/min): t_r = 33.7 min for the major enantiomer; t_r = 40.5 min for the minor enantiomer. EI-HRMS *m/z* calculated for $C_{10}H_9O_5N$ (MH^+) 223.0481, found 223.0476. The absolute configuration was not determined.



1c

(2*S*)-2-(5-Nitrothiophenyl)-5-methyl-2,3-dihydro-4*H*-pyran-4-one

The product was prepared following the procedure outlined above using 5-nitro-2-thiophenecarboxaldehyde (38 mg, 0.24 mmol) and 2.0 eqv. (90 μL, 0.48 mmol) of 1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-butadiene. The crude product was purified by column chromatography (silica gel, 9:1 hexane/EtOAc as eluting solvent) to provide **1d** as a light orange solid in 89 % yield (51.3 mg, 0.21 mmol); Rf = 0.47 (2:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 4.2 Hz, 1H), 7.28 (d, J = 0.8 Hz, 1H), 6.97 (dd, J = 0.8, 4.2 Hz, 1H), 5.61 (dd, J = 10.7, 17.0 Hz, 1H), 2.91 (dd, J = 6.4, 10.7 Hz, 1H), 2.88 (dd, J = 6.4, 17.0 Hz, 1H), 1.70 (d, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 157.9, 148.7, 128.2, 124.1, 115.3, 110.8, 75.9, 42.5, 10.5. 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 = 18.7 min for the major enantiomer; t_r = 28.9 min for the minor enantiomer. EI-HRMS *m/z* calculated for $C_{10}H_9O_4NS$ (MH^+) 239.0252, found 239.0262. The absolute configuration was not determined.



1d

CHAPTER 3: The Optimization and Scale-Up of $Rh_2(4R\text{-dFIBAZ})_4$: An Enhanced Chiral Dirhodium(II) Carboxamidate Catalyst

I. Introduction

Selectivity enhancement in catalytic reactions may be achieved through ligand modification. Characteristics of the catalyst, such as its inherent reactivity and selectivity, are attributed to the ligand. Modification of the ligand therefore, can change the electronic and steric factors that govern the reaction in general.

The selectivity achieved with dirhodium(II) catalysts has, in part, been developed by modification of their chiral ligands. In 2001, the ligand modification of $Rh_2(4S\text{-IBAZ})_4$ was established by our laboratory.[1] When fluorine was substituted for hydrogen on the carbon position alpha to the carboxamide carbonyl, the reactivity of the catalyst was expected to increase while the selectivity remained comparable to that of the unsubstituted carboxamide.[1] Fluorine substitution had previously been found to influence the reactivity of dirhodium(II) carboxylates.[2,3b]

With the substitution of fluorine for hydrogen onto the alpha positions of $Rh_2(4S\text{-IBAZ})_4$, a novel fluorinated analog, $Rh_2(4R\text{-dFIBAZ})_4$, was synthesized. Fluorine, capable of withdrawing more electron density from rhodium than hydrogen, gave the catalyst more electrophilic character. The more electrophilic catalyst allowed for diazo decomposition to occur at a faster rate than did the unsubstituted parent compound, $Rh_2(4S\text{-IBAZ})_4$.[1] The effectiveness of $Rh_2(4R\text{-dFIBAZ})_4$ has been reported with examples of the increased reactivity for diazo decomposition and the enhanced selectivity

for ylide formation.[1] As an illustration of this increased reactivity and selectivity, examples pertaining to diazo decomposition and ylide formation will be provided.

The complete synthesis of $Rh_2(4R\text{-dFIBAZ})_4$ has been reported.[1] Upon entering the Doyle research group the task of optimizing and scaling-up the synthesis was presented. Described herein are the attempts taken as an initial project to improve the existing synthesis. The optimization and scale-up of a number of steps proved successful. However, one step in particular was not trivial, and because large amounts of time were allocated toward its optimization, the final step wherein the catalyst is prepared was unsuccessful.

II. Reaction Scope and Application of $Rh_2(4R\text{-dFIBAZ})_4$

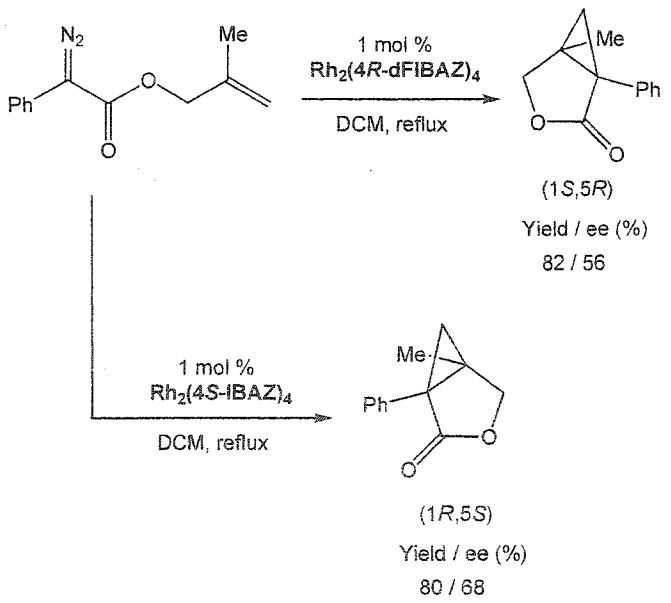
1. Applications toward Diazo Decomposition

Dirhodium(II) compounds containing chiral carboxamidate ligands are effective catalysts toward diazo decomposition of diazoacetates and diazoacetamides.[4] Conversely, these catalyst systems are generally unreactive towards vinyldiazoacetates[5] and diazomalonates[6] as alternative reactions or thermal processes take place instead of the desired catalytic diazo decomposition.[7]

Several studies were carried out to verify whether the modified ligand exhibited higher reactivity. As an initial evaluation, Doyle *et al.* selected the intramolecular cyclopropanation reaction of 2-methyl-2-propen-1-yl phenyldiazoacetate.[1,8] The reaction in which 1.0 mol % of the hydrogen-substituted parent complex $Rh_2(4S\text{-IBAZ})_4$ was employed, reportedly produced the cyclopropane product in 80 % yield and 68 %

enantiomeric excess.[8] Under the influence of 1.0 mol % of the fluorinated complex $Rh_2(4R\text{-dFIBAZ})_4$ and the same reaction conditions, the cyclopropane product was obtained in 82 % yield and 56 % ee (**Scheme 3.1**).[1] The configuration of the cyclopropane product formed with $Rh_2(4S\text{-IBAZ})_4$ and $Rh_2(4R\text{-dFIBAZ})_4$ was opposite because of the configurations of the catalysts employed. Using $Rh_2(4S\text{-IBAZ})_4$ yielded the (1*R*,5*S*) enantiomer as the major product, whereas $Rh_2(4R\text{-dFIBAZ})_4$ yielded the (1*S*,5*R*) enantiomer as the major product.[1]

Scheme 3.1: Cyclopropanation reaction employing chiral $Rh_2(4S\text{-IBAZ})_4$ and $Rh_2(4R\text{-dFIBAZ})_4$.



As can be seen from the results in **Scheme 3.1**, both $Rh_2(4S\text{-IBAZ})_4$ and $Rh_2(4R\text{-dFIBAZ})_4$ produced the cyclopropane product in good yield, moderate enantiomeric

excess, and opposite configuration. Interestingly, when equal amounts of the two catalysts were reacted in the same flask containing 2-methyl-2-propen-1-yl phenyldiazoacetate in refluxing DCM, results revealed that the major enantiomer formed was the (1*S*,5*R*) enantiomer in 43 % enantiomeric excess.[1] This result demonstrated that the modified Rh_2(4*R*-dFIBAZ)$_4$ catalyst was at least eight times more reactive than Rh_2(4*S*-IBAZ)$_4$ at decomposition of 2-methyl-2-propen-1-yl phenyldiazoacetate.[1] The lower ee values seen in this study compared to previous findings were attributed to the differences of reactivity of the intermediate metal carbene formed between 2-methyl-2-propen-1-yl phenyldiazoacetate and Rh_2(4*S*-IBAZ)$_4$ and 2-methyl-2-propen-1-yl phenyldiazoacetate and Rh_2(4*R*-dFIBAZ)$_4$.[1]

2. Applications toward Ylide Formation

The dirhodium(II) catalyzed reaction of allyl iodide and ethyl diazoacetate has been reported (**Equation 3.1**).[9] Under the influence of 1.0 mol % of chiral dirhodium(II) catalysts Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*S*-IBAZ)$_4$, moderate yields of 36-44 % and low enantioselectivities of 0-26 % were seen for product **1** (**Table 3.1**).[1] When Rh_2(4*R*-dFIBAZ)$_4$ was employed as the catalyst, compound **1** was obtained in a comparable yield of 46% and higher enantiomeric excess of 52 % ee (**Table 3.1**).[1]

Equation 3.1: Ylide formation and [2,3]-sigmatropic rearrangement reaction with chiral dirhodium(II) catalysts.

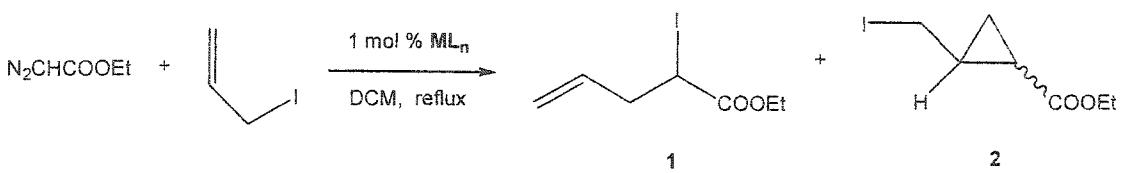


Table 3.1: Reaction of allyl iodide and ethyl diazoacetate catalyzed by chiral dirhodium(II) catalysts.

Catalyst	Product Yield, %	**1** : **2**	**1** % ee	**2** *cis* : *trans*	*cis*-**2** % ee
$Rh_2(OAc)_4$	75	90 : 10	---	45 : 55	---
Rh_2(5*S*-MEPY)$_4$	44	76 : 24	0	37 : 63	44
Rh_2(4*S*-IBAZ)$_4$	36	37 : 63	26	50 : 50	66
Rh_2(4*R*-dFIBAZ)$_4$	46	62 : 38	52	50 : 50	39

The results presented above demonstrate the advantages the $Rh_2(4R\text{-dFIBAZ})_4$ catalyst exhibits, as increased enantiomeric excesses were achieved for the [2,3]-sigmatropic rearrangement and subsequent ylide formation reaction.

Together, the examples provided above for both the intramolecular cyclopropanation reaction as well as the [2,3]-sigmatropic rearrangement reaction illustrate the importance and utility of the modified fluorinated analog, $Rh_2(4R\text{-dFIBAZ})_4$. Overall, enhanced reactivities were exhibited towards diazo, decomposition and selectivities for ylide formation were improved.

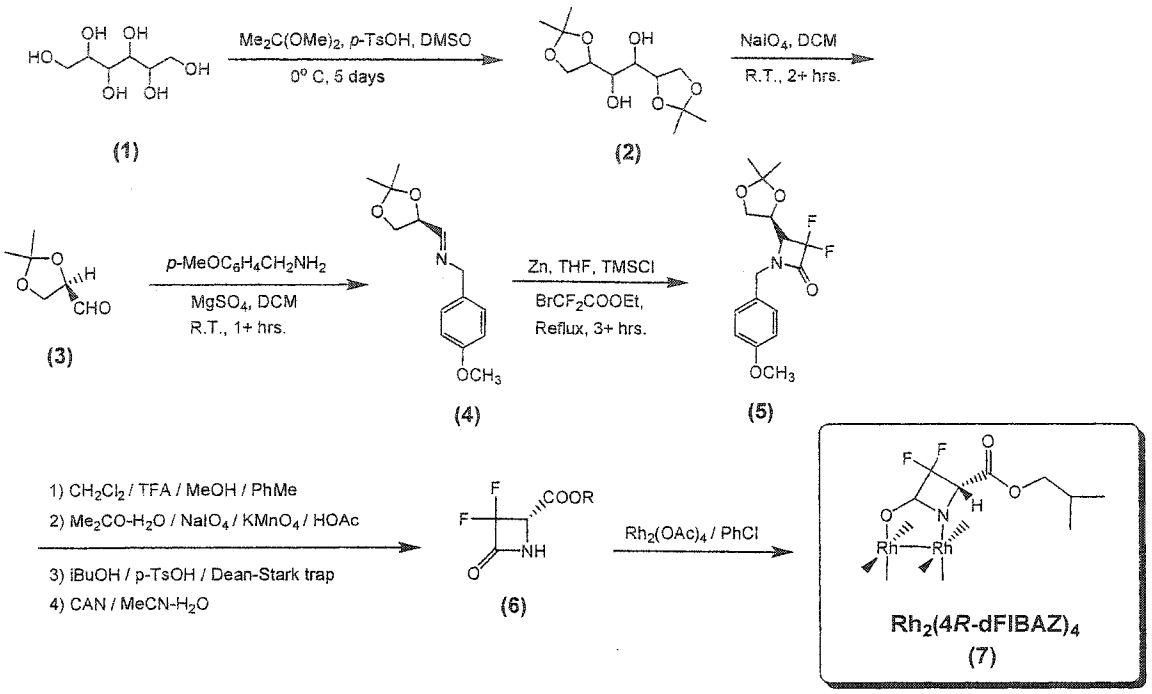
III. Optimization and Scale-up of $Rh_2(4R\text{-dFIBAZ})_4$

With the importance and utility of the $Rh_2(4R\text{-dFIBAZ})_4$ catalyst apparent, optimization of its synthesis would be a worthy task. Described herein are the attempts taken as an initial project to improve the existing synthesis of $Rh_2(4R\text{-dFIBAZ})_4$.[1]

Optimization was initiated with the reaction in which D-mannitol **1** is converted to the corresponding diacetonide (**2**) by reaction with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in dry DMSO. For this step, a temperature of 0°C was found to be most beneficial. With a temperature of 25°C, lower product yields of 42 % were obtained. At elevated temperatures of 50°C, an oily product that was difficult to characterize was produced. However, when the reaction was performed at 0°C for about 5 days, an improvement in yield from 46 % (room temperature)[1] to 76 % was achieved (**Scheme 3.2**). Ameliorating the yield at the onset of the synthetic sequence allowed for larger amounts of material to be produced quickly.

Scale-up of the following step, involving the reaction of diacetonide **2** with sodium periodate to give glyceraldehyde **3**,[10] was increased from a scale of 5.0 g of **2**[1] to 15-20 g. Scale-up of this reaction was not accompanied by any deleterious effect, as **3** was obtained in high 92 % yield.

Scheme 3.2: Synthetic outline for $Rh_2(4R\text{-dFIBAZ})_4$.



The reaction of glyceraldehyde **3** with *p*-methoxybenzylamine at room temperature in DCM to produce the protected imine **4** was scaled-up to 25 g with a corresponding product yield of 90 % (**Scheme 3.2**).

The limiting factor in the synthesis of $Rh_2(4R\text{-dFIBAZ})_4$ remained the Reformatsky reaction in which protected imine **4** reacts with bromodifluoroacetic acid ethyl ester in the presence of zinc and chlorotrimethylsilane to afford the fluorinated lactam **5**. As a means of increasing product yield, from the moderate 55 % usually obtained, several factors were changed. Attempts at varying the molar equivalents of imine **4**, zinc, bromodifluoroacetic acid ethyl ester, and TMSCl employed in the reaction did not result in any detectable improvement in yield of compound **5**. **Table 3.2** has been

provided in order to demonstrate the yields obtained for the Reformatsky reaction when changes to the amounts of the reacting substrates were tried.

Table 3.2: Changes in the amounts of reacting substrates used in the Reformatsky reaction.

Imine (equiv.)	Zn (equiv.)	$BrCF_2COOEt$ (Equiv.)	TMSCl (Equiv.)	Yield (%)
1.0	1.8	1.2	8.0 mL	**55**
1.5	1.8	1.2	8.0 mL	9
1.0	**2.5**	1.2	8.0 mL	13
1.0	1.8	**2.0**	8.0 mL	5
1.0	1.8	1.2	**20.0 mL**	5

Speculation that the source and size of the zinc (for example zinc mesh, zinc dust, etc…) could be influential on the outcome of the reaction led to using different vendors, however this endeavor was also unsuccessful, and no improvement in yield could be realized. Further optimization of this step was not attempted as too much time had already been dedicated to its improvement without measurable gain.

The scale of the reaction wherein lactam **5** is treated with dichloromethane, trifluoroacetic acid, and methanol, affording the corresponding crude diol (**Scheme 3.2**), was increased by a few grams. A subsequent reaction, in which the crude diol reacts with sodium periodate followed by treatment with potassium permanganate and glacial acetic acid, was carried out without further improvement to the reported synthesis[1] (**Scheme 3.2**). The remaining esterification reaction with *iso*butyl alcohol and subsequent ceric ammonium nitrate deprotection (**Scheme 3.2**) rendering formation of compound **6**, was also achieved without change to the previous report (**Scheme 3.2**).[1]

Limitations on time did not permit further improvements or investigations toward optimization. Although several steps were optimized to achieve improved yields, the Reformatsky reaction was not trivial and large amounts of time were allocated toward its optimization. An attempt at making the final catalyst from the ligand that was synthesized was not successful. For this reason, the project was terminated without further attempts to complete the final synthetic step in which the ligand, along with $Rh_2(OAc)_4$, form the catalyst $Rh_2(4R\text{-dFIBAZ})_4$.

IV. Conclusions

The substitution of fluorine for hydrogen on the carbon position alpha to the carboxamide carbonyl resulted in a novel variant of a dirhodium(II) carboxamidate catalyst, $Rh_2(4R\text{-dFIBAZ})_4$.[1] The synthesis of this catalyst was reported in 2001.[1] Studies had previously been carried out by Doyle and co-workers in which a rate enhancement towards diazo decomposition reactions was observed, as well as an increase in selectivity for [2,3]-sigmatropic rearrangement and subsequent ylide formation.[1] Examples that illustrate the observed enhancement have been provided.

An initial project taken upon entering the Doyle research group is described. The goal of this project was to improve the existing synthesis of $Rh_2(4R\text{-dFIBAZ})_4$, previously reported in 2001.[1] Several attempts to ameliorate reactions conditions were successful in increasing yields and allowing for possible scale-up. For example by lowering the reaction temperature for the first step of the synthetic sequence, a higher yield of 76 % compared to the previously reported 46 % could be achieved. This is the highest yield to date for this step. The scale-up of several steps was also carried out wherein 3-fold increases were realized. Consequently, one step in particular was time consuming. Efforts spent trying to improve the Reformatsky reaction were unsuccessful. Despite changing the amount of each of the reacting substrates, no increase in yield could be realized. The project was terminated without successful completion of the final synthetic step in which the ligand and $Rh_2(OAc)_4$ react to form the catalyst $Rh_2(4R\text{-dFIBAZ})_4$, due to the large quantity of time lost in the optimization of the Reformatsky reaction.

V. Experimentals and Product Characterization

General

Dimethylsulfoxide (DMSO), dichloromethane (DCM), and tetrahydrofuran (THF) were distilled prior to use according to established procedures.[11] ^{1}H NMR spectra were obtained as solutions in $CDCl_3$ and are reported downfield from the internal standard, Me_4Si (TMS) using a Varian Unity 300-MHz spectrometer. Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration.

1,2 : 5,6-Diisopropylidene-D-mannitol (2)

A mixture of D-mannitol **(1)** (10.0 g, 0.055 mol), *p*-toluenesulfonic acid (0.47 g, 2.75 mmol) and 2,2-dimethoxypropane (12.5 mL, 0.102 mol) in dry dimethylsulfoxide (DMSO) (20 mL) was stirred for two hours in an ice bath at 0°C under nitrogen, after which the flask was removed from the ice bath and placed in the refrigerator. After 5 days at 10°C the reaction solution was poured into 100 mL of 5% $NaHCO_3$. The mixture was extracted with ethyl acetate (4 x 100 mL) and the extracts were concentrated under reduced pressure until a solid mass resulted. Hexanes (80 mL) were added followed by gentle heating to ensure that all of the solid had dissolved. After cooling to room temperature, the solution was placed in the refrigerator overnight (~10°C). The resulting crystalline material was collected by filtration, washed with 80 mL of cold hexanes, and dried to give 10.9 g of crude diacetonide **2** as a white powder, (0.042 mol, 76 % yield); m.p. = 110-112°C, Lit. = 118-120°C,[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22-4.09 (comp,

1H, 4H), 3.97 (dd, J = 8.4, 5.8 Hz, 2H), 3.74 (t, J = 5.8 Hz, 2H), 2.66 (s, 2H), 1.41 (s, 6H), 1.36 (s, 6H).

2,3-*O*-isopropylidene-D-glyceraldehyde (3)

To a stirred solution of **2** (15.0 g, 0.057 mol) in CH_2Cl_2 (100 mL) was added sodium periodate (24.5 g, 0.114 mol) followed by a saturated solution of sodium bicarbonate (6.0 mL). The biphasic mixture was stirred at room temperature under nitrogen for two hours. Anhydrous magnesium sulfate (20.0 g) was added, and stirring was continued for 20 minutes. The resulting thick slurry was filtered through a plug of celite and thoroughly rinsed with CH_2Cl_2 (50 mL). The CH_2Cl_2 solution was concentrated under reduced pressure to provide 13.8 g of crude aldehyde **3** as a colorless oil, (0.053 mol, 92 % yield).

(4R)-1-(4'-Methoxybenzyl)-3,3-difluoro-4-(1'R-1',2'-*O*-isopropylideneethyl) azetidin-2-one (5)

To aldehyde **3** was added anhydrous magnesium sulfate (23.0 g) followed by *p*-methoxybenzylamine (13.0 g, 0.095 mol) via syringe pump over 30 minutes. After complete addition, another 30 minutes passed, and the resulting slurry was filtered. The filtrate was washed with CH_2Cl_2 (2 x 30 mL) and then concentrated under reduced pressure to produce 23.6 g of imine **4** as a yellow/orange oil, (0.095 mol, 90 % yield).

Imine **4** was then subjected to the Reformatsky reaction. One day prior to carrying out this reaction, the zinc dust employed was reactivated. The appropriate amount of zinc

was weighed and placed in a beaker equipped with a stir bar. Deionized water was then added to completely cover the zinc dust. Concentrated HCl was added dropwise until the zinc-water mixture went from a dark gray color to clear. The mixture was stirred vigorously at room temperature for ten minutes. The clumps of zinc were then collected by filtration, washed with deionized water (30 mL), ethanol (30 mL), and diethyl ether (30 mL). The activated zinc was placed in the oven for 1 hour to dry and then stored overnight in a dessicator.

To activated zinc dust (10.6 g, 0.163 mol) in dry THF (130 mL) was added 1,2-dibromoethane (1.6 mL) The resulting mixture was stirred under refluxing conditions for 30 minutes. After cooling to room temperature, chlorotrimethylsilane (6.5 mL) was added by syringe. The mixture was stirred at room temperature for 30 minutes and then heated to reflux. In a separate round bottom flask, the crude imine (17.0 g, 0.068 mol) was dissolved in THF (40 mL) and bromodifluoroacetic acid ethyl ester (24.8 g, 0.123 mol) was added. This mixture was then added over a 2 hour period via syringe pump to the refluxing mixture of zinc in THF. After complete addition of the imine and bromodifluoroacetic acid ethyl ester, stirring continued for 1 hour at refluxing conditions. The reaction mixture was allowed to come to room temperature, and unreacted zinc was removed by filtration. The mixture was concentrated under reduced pressure, and the *syn*-lactam (**5**) was isolated as a yellow oil after purification by column chromatography on silica gel (hexane : ethyl acetate = 20 : 1, 15 : 1, 10 : 1, and 5 : 1) producing 10.6 g of material (0.032 mol, 48 % yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.22 (comp, 2H),

6.88-6.86 (comp, 2H), 4.86 (d, J = 14.7 Hz, 1H), 4.24-4.16 (comp, 3H), 3.80 (s, 3H), 3.73-3.69 (comp, 2H), 1.38 (s, 3H), 1.35 (s, 3H).

(4R)-1-(4'-Methoxybenzyl)-3,3-difluoro-4-(isobutyloxycarbonyl)azetidin-2-one

To γ-lactam **5** was added 232 mL of 6 : 3 : 1 CH_2Cl_2/TFA/CH_3OH (139 : 70 : 23 mL). The mixture was stirred at room temperature for 1 hour after which the solvent was evaporated under reduced pressure. Toluene (70 mL) was added to the residue and then evaporated in order to remove any residual TFA. The residue was purified by column chromatography on silica gel (hexanes : ethyl acetate = 2 : 1 to 1 : 2) giving the crude diol as a yellow oil (**step 1**).

To the crude diol was added a mixture of 340 mL of a 3 : 1 acetone/H_2O (255 : 85 mL) mixture. To this was added $NaIO_4$ (10.7g, 49.8 mmol). The resulting mixture was stirred at room temperature for 2 hours. $KMnO_4$ (11.4 g, 72.1 mmol) was then added followed by glacial acetic acid (11 mL). The deep purple mixture was stirred at room temperature for 3 hours and was then filtered. The filter cake was washed with acetone until the eluent was clear. To the eluent was added a 40 % $NaHSO_3$ solution with stirring, rendering the purple solution colorless. The aqueous eluent was extracted with ethyl acetate (2 x 100 mL), and the resulting organic layer was washed with brine (40 mL), then dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the crude acid as a yellow/orange oil (**step 2**).

To the crude acid were added benzene (75 mL), 2-methyl-1-propanol (19 mL), and *p*-toluenesulfonic acid (0.27 g, 1.40 mmol). The resulting solution was heated to

reflux in an oil bath with stirring until water ceased to evolve in a Dean-Stark apparatus. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (hexanes : ethyl acetate = 20 : 1), producing 1.57 g of product as a light yellow oil (**step 3**), (4.80 mmol, 34 % yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.93 (d, J = 14.8 Hz, 1H), 4.25 (dd, $J_{F,H}$ = 6.9, 2.5 Hz, 1H), 4.22 (dd, J = 14.8, 1.8 Hz, 1H), 4.05 (dd, J = 10.5, 7.6 Hz, 1H), 3.98 (dd, J = 10.5, 7.6 Hz, 1H), 3.82 (s, 3H), 2.00-1.96 (m, 1H), 0.96 (d, J = 6.9 Hz, 6H).

2-Methyl-1-propyl 3,3-difluoro-2-oxaazetidine-(4R)-carboxylate (6)

To the above *N*-protected azetidinone (0.44 g, 1.35 mmol) was added 12 mL of 2 : 1 CH_3CN/H_2O (8 : 4 mL). The resulting solution was cooled to 0°C in an ice-water bath. To the cooled mixture was added solid ceric ammonium nitrate (2.95 g, 5.38 mmol) and stirring continued at 0°C for 1 hour. The bright orange reaction mixture was then allowed to come to room temperature, after which stirring continued for an additional 3 hours. The mixture was extracted with ethyl acetate (2 x 50 mL) and the organic layer was washed with water (10 mL) and brine (20 mL), then dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (hexanes : ethyl acetate = 10 : 1), giving 0.14 g of the deprotected product **6** as a light yellow oil (**step 4**); (0.676 mmol, 50 % yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s, 1H), 4.60 (dd, $J_{F,H}$ = 6.4, 3.5 Hz, 1H), 4.08 (dd, J = 10.5, 6.8 Hz, 1H), 3.90 (dd, J = 10.5, 6.8 Hz, 1H), 2.01-1.91 (m, 1H), 0.93 (d, J = 6.4 Hz, 6H).

Dirhodium(II) Tetrakis[2-methyl-1-propyl-2-oxa-3,3-difluoroazetidine-4(*R*)-carboxylate] (7)

The final synthetic step in which ligand and $Rh_2(OAc)_4$ react to form $Rh_2(4R\text{-}dFIBAZ)_4$ catalyst was attempted but not accomplished. The catalyst however, may be prepared, purified, and characterized by standard methods.[1,8,13,14]

REFERENCES

CHAPTER 1

[1] For example: (a) Boger, D. L.; Weinreb, S. H. *Hetero-Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: New York, 1996. (c) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, 190, 1. (d) Tietze, L. F. *Curr. Org. Chem.* **1998**, 2, 19.

[2] Reviews: (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, 39, 3558-3588. (b) Waldmann, H. *Synthesis* **1994**, 535. (c) Boger, D. L. In *Comprehensive Organic Synthesis*: Trost B. M., Ed.; Pergamon Press: Oxford, **1991**, 5, 451. (d) Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, 273-297. (e) Danishefsky, S. J. *Aldrichimica Acta* **1986**, 19, 59-69.

[3] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry,* Verlag Chemie, Weinheim, **1970**.

[4] Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, 107, 1246-1255.

[5] For example: (a) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacôte, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, 124, 13648-13649. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, 38, 2427-2430. (c) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, 3, 2919-2922.

[6] For example: Fleming, L. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, **1977**.

[7] Doyle, M.P.; Valenzuela, M.; Huang, P. *PNAS*, **2004**, 101, 15, 5391-5395.

[8] Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, 57, 845-851.

[9] Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, 63, 403-405.

[10] Bednarski, M.; Maring, C.; Danishefsky, S. J. *Tetrahedron Lett.* **1983**, 24, 3451-3454.

[11] Togni, A. *Organometallics* **1990**, 9, 3106-3113.

[12] Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, 123, 22, 5366-5367.

[13] Kezuka, S.; Mita, T.; Ohtusuki, M.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824-825.

[14] Motoyama, Y.; Koga, Y.; Nishiyama, H. *Tetrahedron* **2001**, 57, 853-860.

[15] Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, 2, 49-52.

[16] Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, 110, 310-312.

[17] Motoyama, Y.; Mikami, K. *J. Chem. Soc. Chem. Commun.* **1994**, 1563-1564.

[18] For example: (a) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, 32, 605-613. (b) Jørgensen, K. A.; Johannsen, M. *J. Org. Chem.* **1995**, 60, 5757-5762.

[19] For example: (a) Mutter, R.; Wills, M.; *Bioorg. Med. Chem.* **2000**, 8, 1841-1860. (b) Pettit, G. R. *J. Nat. Prod.* **1996**, 59, 812-821.

[20] For example: (a) Oz, H. S.; Hughes, W. T.; Rehg, J. E.; Thomas, E. K. *Microb. Pathog.* **2000**, 29, 187-190. (b) Scheid, C.; Prendiville, J.; Jayson, G.; Crowther, D.; Fox, B.; Pettit, G. R.; Stern, P. L. *Cancer Immunol. Immunother.* **1994**, 39, 223-230.

[21] For example: (a) Mohammad, R. M.; Wall, N. R.; Dutcher, J. A.; Al-Katib, A. M. *Clin. Cancer Res.* **2000**, 6, 4950-4956. (b) Wang, S.; Wang, Z.; Boise, L. H.; Dent, P.; Grant, S. *Leukemia* **1999**, 13, 1564-1573.

[22] Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, 4, 1795-1798.

[23] For example: (a) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, 53, 3642. (b) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, 53, 3644.

[24] For example: (a) Jefford, C. W.; Bernrdinelli, G.; Tanaka, J-I.; Higa, T. *Tetrahedron Lett.* **1996**, 37, 159. (b) Tanaka, J-I.; Higa, T.; Bernrdinelli, G.; Jefford, C. W. *Chemistry Lett.* **1996**, 255.

[25] Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, 115, 361.

[26] Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, 40, 97.

[27] Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, 123,

6702-6703.

[28] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, 38, 2398.

[29] Bednarski, M.; Maring. C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, 24, 3451-3454.

[30] Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, 105, 6968-6969.

[31] Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, 57, 1951-1952.

[32] Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, 33, 6907-6910.

[33] Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 1, 79-80.

[34] Wang, B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605-1606.

[35] Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, 67, 2175-2182.

[36] Mihara, J.; Hamada, T.; Takeda, T.; Irie, R.; Katsuki, T. *Synlett* **1999**, 7, 1160-1162.

[37] Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, 57, 845-851.

[38] Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, 60, 5998-5999.

[39] Yuan, Y.; Long, J.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, 8, 5033-5042.

CHAPTER 2

[1] For example: (a) Boger, D. L.; Weinreb, S. H. *Hetero-Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: New York, 1996. (c) Waldmann, H. *Synthesis* **1994**, 535. (d) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, 190, 1. (e) Tietze, L. F. *Curr. Org. Chem.* **1998**, 2, 19.

[2] For example: (a) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacôte, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, 124, 13648-13649. (b) Ghosh, A. K.; Mathivanan, P. Cappiello, *J. Tetrahedron Lett.* **1997**, 38, 2427-2430. (c) Cox, J. M.; Rainier, J.

D. *Org. Lett.* **2001**, 3, 2919-2922.

[3] Reviews: (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, 39, 3558-3588. (b) Boger, D. L. In *Comprehensive Organic Synthesis*: Trost B. M., Ed.; Pergamon Press: Oxford, **1991**, 5, 451. (c) Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, 273-297. (d) Danishefsky, S. J. *Aldrichimica Acta* **1986**, 19, 59-69.

[4] Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, 123, 22, 5366-5367.

[5] Doyle, M.P.; Valenzuela, M.; Huang, P. *PNAS*, **2004**, 101, 15, 5391-5395.

[6] Valenzuela, M.; Doyle, M. P.; Hedberg, C.; Hu, W.; Holstrom, A. *Synlett*, **2004**, 13, 2425-2428.

[7] Nazarova, L. A.; Chernyaev, I. I.; Morozova, A. S. *Zh. Neorgan. Khim.* **1965**, 10, 539-541.

[8] Cotton, F. A.; Curtis, N. F.; Harris, C. B.; Johnson, B. F. G.; Lippard, S. J.; Mague, J. T.; Robinson, W. R.; Wood, J. S. *Science* **1964**, 145, 1305-1307.

[9] Paulissenen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1973**, 2233-2236.

[10] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[11] Ahsan, M. Q.; Bernal, I.; Bear, J. L. *Inorg. Chem.* **1986**, 25, 260-265.

[12] Doyle, M. P. *Russ. Chem. Bull* **1994**, 43, 1770-1782.

[13] Doyle, M. P. *Aldrichimica Acta* **1996**, 29 (1), 3-11.

[14] Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, 115, 9968-9978.

[15] Doyle, M. P.; Winchester, W. R.; Simonsen, S. H.; Ghosh, R. *Inorg. Chim. Acta* **1994**, 220, 193-199.

[16] Doyle, M. P.; Hu, W.; Phillips, I. M.; Moody, C. J.; Pepper, A. G.; Slawin, A. M. Z. *Adv. Synth. Catal.* **2001**, 343, 112-117.

[17] Doyle, M. P.; Dyatkin, A. B.; Protopopova, M. N.; Yang, C. I.; Miertschin, C.S.; Winchester, W. R.; Simonsen, S. H.; Lynch, V.; Ghosh, R. *Recl. Trav. Chim. Pays*

Bas **1995**, 114, 163-170.

[18] Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Müller, P.; Bernardinelli, G.; Ene, D.; Motallebi, S. *Helv. Chim. Acta* **1993**, 76, 2227-2235.

[19] Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, 117, 5763-5775.

[20] Doyle, M. P.; Zhou, Q.; Raab, C. E.; Roos, G. H. P.; Simonsen, S. H.; Lynch, V. *Inorg. Chem.* **1996**, 35, 6064-6073.

[21] Doyle, M. P.; Zhou, Q.; Simonsen, S.; Lynch, V. *Synlett* **1996**, 697-698.

[22] Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, 1145-1147.

[23] For example: (a) Joly, G.D.; Jacobsen, E. N. *Org. Lett.* **2002**, 4, 1795-1798. (b) Wang, B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605-1606.

[24] For example: (a) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, 57, 1951-1952. (b) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, 33, 6907-6910.

[25] For example: Kezuka, S.; Mita, T.; Ohtusuki, M.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824-825.

[26] For example: (a) Wang, B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605-1606. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, 60, 5998-5999.

[27] Fu, Y.; Tsai, S.; Huang, C.; Yen, S.; Hu, W.; Yu, S. *J. Org. Chem.* **2003**, 68, 3068-3077.

[28] Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 18, 1787-1788.

[29] Danishefsky, S.; Yan, C.; Singh, R.; Gammill, R.; McCurry, P.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, 101, 7001-7008.

[30] Perrin, D. D. & Armarego W. L. F. in *Purification of Laboratory Chemicals*, **1988**, (Pergamon, Oxford), 3rd Ed.

CHAPTER 3

[1] Doyle, M. P.; Hu, W.; Phillips, I. M.; Moody, C. J.; Pepper, A. G.; Slawin, A. M. Z. *Adv. Synth. Catal.* **2001**, 343, 112-117.

[2] (a) Doyle, M. P. in *Catalysis by Di- and Polynuclear Metal Cluster Complexes* (Eds.: Adams, R. D.; Cotton, F. A.), Wiley-VCH, New York, **1998**, pp. 249-282. (b) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1797-1815.

[3] (a) Cotton, F. A.; Falvello, L. R.; Gerards, M.; Snatzke, G. *J. Am. Chem. Soc.* **1990**, 119, 8979-8980. (b) Doyle, M. P.; Mahaptro, S. N.; Caughey, A. C.; Chinn, M. S.; Colsman, M. R.; Harn, N. K.; Redwine, A. E. *Inorg. Chem.* **1987**, 26, 3070-3072.

[4] (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, 98, 911-935. (b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, 54, 7919-7946.

[5] (a) Davies, H. M. L. *Curr. Org. Chem.* **1998**, 2, 463-468. (b) Davies, H. M. L.; Doan, B. D. *J. Org. Chem.* **1999**, 64, 8501-8508.

[6] Müller, P.; Fernandez, D. *Helv. Chim. Acta.* **1995**, 78, 947-957.

[7] Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, **1998**.

[8] Doyle, M. P.; Davies, S. B.; Hu, W. *Organic Lett.* **2000**, 2, 1145-1148.

[9] Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, 120, 7653-7654.

[10] Jackson, D. Y. *Synth. Comm.* **1988**, 18, 337-341.

[11] Perrin, D. D. & Armarego W. L. F. in *Purification of Laboratory Chemicals*, **1988**, (Pergamon, Oxford), 3rd Ed.

[12] Chittenden, G. J. F. *Carbohydr. Res.* **1980**, 84, 350-352.

[13] Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Syn.* **1996**, 73, 13-24.

[14] Doyle, M. P.; Davies, S. B.; Hu, W. *J. Chem. Soc., Chem. Commun.* **2000**, 867-868.