LEWIS ACID ASSISTED METAL-LIGAND BIFUCTIONAL HYDROGENATION OF AMIDES

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Overview:

In the past decade, metal-ligand bifuctional catalysis has been a growing interest in the field of hydration of polar double bonds. In particular, these catalysts have provided a new mechanistic approach for the direct reduction of carbonyl compounds.[1] The most well studied example of the metal-ligand bifuctional catalysis is Noyori's Ru catalyst shown in figure 1. The hydrogens for the reduction are located on the ruthenium metal and the amine ligand. The hydridic Ru-H and the protic N-H are simultaneously inserted to the carbonyl, which has a partial negative charge on the oxygen and a partial positive charge on the carbon, to form a six member transition state, resulting in an *S* alcohol.[6] This type of catalysis however, has not been effective for amide reductions.

Because of the growing interest in developing mild and catalytic methods for reduction of amides, we propose a modification to the typical Noyori system which is designed to expand metal-ligand bifuctional activity to amide hydrogenations. Amides have a substantial contribution from a polar resonance form where a partial double bond between the carbon of the carbonyl and the nitrogen reduces the carbonyl-like character of this group and prevents normal hydrogenation.[5] It is therefore proposed that a tethered Lewis acid, such as a borane, will interact with the amide nitrogen and minimize the polar resonance contribution to the carbonyl double bond. In this manner the amide will have greater "carbonyl" characteristics, and the reduction could proceed via a concerted transition state resembling the Noyori hydrogenation of ketones. Presented will be the synthesis and future goals of amide reduction activity of catalysts that contain a tethered borabicyclo[3.3.1]nonane fragment.

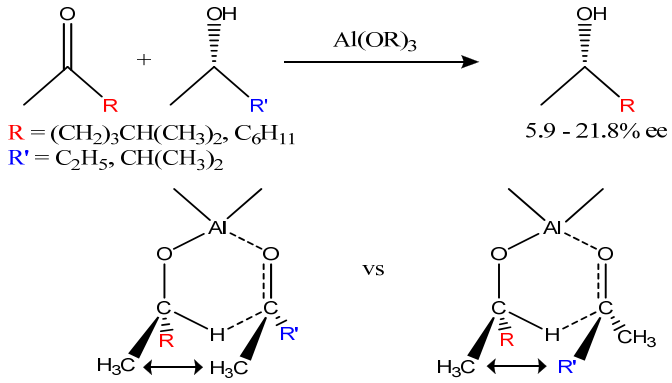
Introduction:

Metal-Ligand Bifuctional Catalyst:

There have been different methods for reducing ketones to alcohols, but the method that has been gaining interest due to its high efficiency, excellent stereoselectivity and mild reaction conditions is metal-ligand bifuctional catalysis. These bifuctional transition metal based catalysts have revealed new mechanistic possibilities for the direct hydrogenation of carbonyl compounds to alcohols.[1] Conceptually,

this catalysis has evolved from a rich tradition of transfer hydrogenation reactions. Catalytic asymmetric transfer hydrogenation was first demonstrated by Doering and Young[2] using an asymmetric version of the Meerwin-Ponndorf-Verley reduction of ketones using chiral alcohol. The classical MPV reduction, which is equilibrium-driven, involves a hydride transfer from a secondary alcohol to a carbonyl substrate that is activated through coordination of a Lewis acidic aluminum center.[3] Doering and Young successfully reduced ketones using a chiral alcohol, (*S*)-2-butanol or (*S*)-3-methyl-2-butanol, in the presence of *rac*-aluminum alkoxides resulting in chiral alcohols. However, enantioselection was low with 5.9-22% ee[1]. Another drawback was that more than stoichiometric amounts of aluminum alkoxides are required to obtain satisfactory yields of the alcohol in reasonable time.[3] Despite the drawbacks, the results strongly suggested that the hydrogen transfer proceeds through a six-membered transition state, which was a significant finding for the mechanism.

Scheme 1. Asymmetric Meerwein-Ponndorf-Verley Reduction



Since 1950, there have been numerous examples of chiral catalyst systems for the asymmetric reduction of ketones. However, the most notable catalyst system, and basis for this research, has been the catalyst system by Noyori, Ikariya and co-workers. In 1995, they introduced a new chiral Ru(II) catalyst that was effective at hydrogenation of aromatic ketones with high enantioselectivity at room temperature.[4] The Ru metal center, bearing N-sulfonylated 1,2 diamines or amino alcohols[1] as chiral

ligands, reduced ketones into the corresponding *S* chiral alcohol. This catalysts system has further proven to also reduce imines.[6]

The structure and mechanism of the Ru catalyst has been studied extensively to understand how the carbonyls are reduced. The active catalyst is a 16 electron amido Ru complex in Scheme 2. The geometry of this type of complex has been described as square planar, distorted trigonal bipyramidal, and two-legged piano stool. In this coordination environment the face of the η^6-arene ligand is perpendicular to the plane defined by N-Ru-N. The Ru-N bond has a bond length between the single and triple bond. Due to this nature, the amido complex readily dehydrogenates 2-propanol to produce an amine hydrido Ru complex as a single diastereomer.[1] The amine hydrido complex is 18-electron with octahedral geometry around the Ru center.[6]

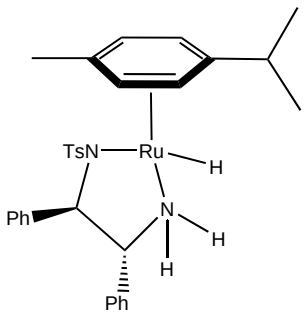
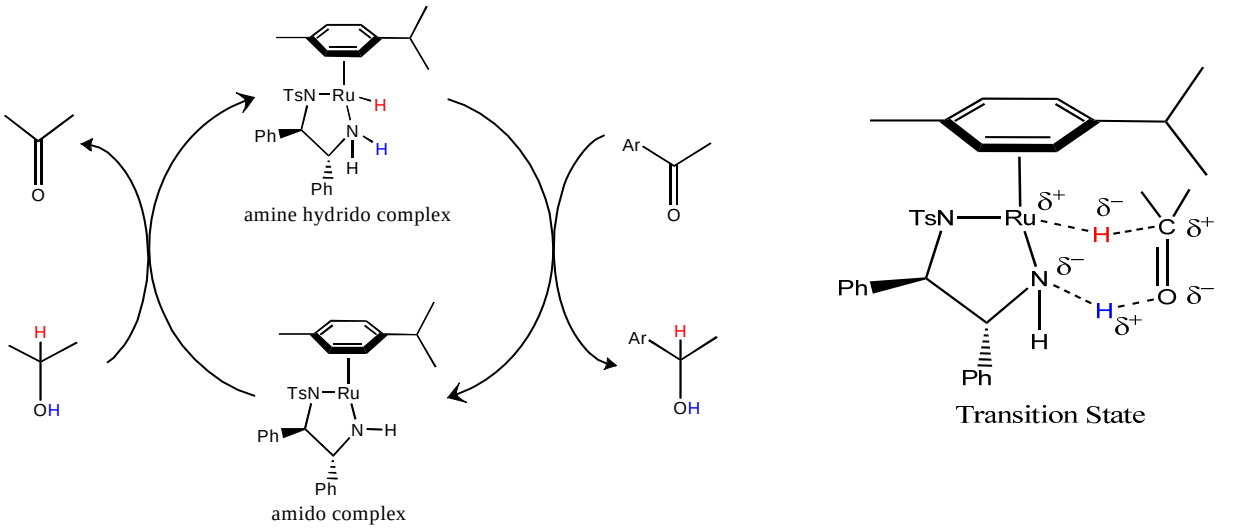


Figure 1. Noyori's chiral Ru(II) catalyst

The high enantioselectivity of the products is attributed to the bond properties of the metal and nitrogen active sites. The hydrogens for the reduction are located on the ruthenium metal and the amine ligand. The N-H unit bound to the metal center exhibits a sufficiently acidic character that is able to easily activate ketones. Due to the electronegative nature of oxygen, electron density is pulled away from the carbon of the carbonyl resulting in a partial negative charge on the oxygen and a partial positive charge on the carbon. The hydridic Ru-H bond lengths as a new H-C (of the carbonyl) bond is formed. Simultaneously, a new bond to the carbonyl oxygen, H-O (of the carbonyl), is formed in what has been shown to be a six-membered pericyclic transition state.[6] Since there is no direct interaction between the carbonyl and the metal, the reaction is able to proceed faster with higher enantiomer purity.[1] After reduction of the ketone, the catalyst is regenerated by a hydrogen source. When 2-propanol is used as the sacrificed hydrogen source, the catalyst is regenerated by the microscopic

reverse of the hydrogenation pathway and the overall hydrogen transfer is driven by the thermodynamics of the hydrogen acceptor-donor pair.

Scheme 2. Interconversion of the Amido and the Amine Hydrido Ru Complex via a Possible Six-Membered Transition State.[1]

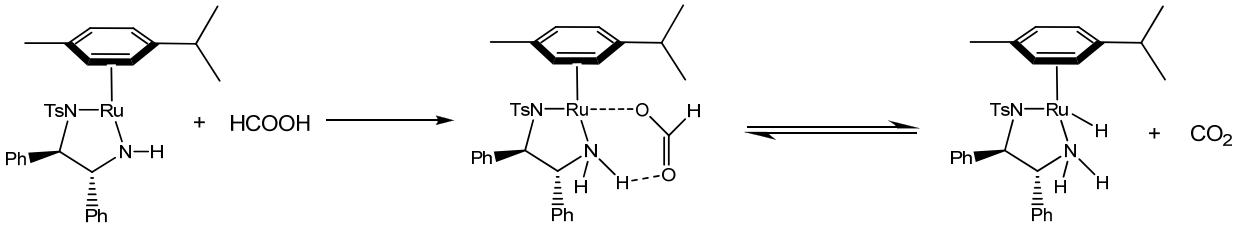


Due to the fact that 2-proponal usually yields satisfactory results in terms of both reactivity and selectivity, it's commonly used as the sacrificial hydrogen donor for catalyst regeneration. Also, it's a particularly safe, non-toxic, easy to use, inexpensive and an environmentally friendly hydrogen source.[1] The byproduct, acetone, is easily removed. However, one of the major drawbacks is that the reaction is reversible. Conversion rates are determined by thermodynamic factors of the system and thus limited. Efficiency is strongly affected by the structures of the ketones substrates and the properties of the hydrogen donors. The equilibrium point is determined by the standard free energy of the system.[7] When the products are exposed to the reaction mixture for extended periods of time, there is a decrease in the enantiomeric purity due to attrition.

Another hydrogen source that would diminish reversibility and increase enantiomeric purity is formic acid, another well-behaving, inexpensive reducing agent.[7] Formic acid is the simplest carrier of hydrogen on a proton and hydride. Its effectiveness has long been recognized by organic chemist. The catalytic asymmetric reduction can overcome the drawbacks of 2-propanol reversibility and in principle

allows hydrogenation to occur at 100% conversion with minimal loss of stereoselectivity. Unlike the mechanism for 2-propanol, the reaction with formic acid proceeds in a stepwise manner. First to occur is the deprotonation of the formic acid which in turns forms an ion pair intermediate, leading to the kinetically favored formate complex.[1] The formate complex transforms to the amine hydrido Ru complex through the decarboxylation of the intermediate is shown in Scheme 3.[8]

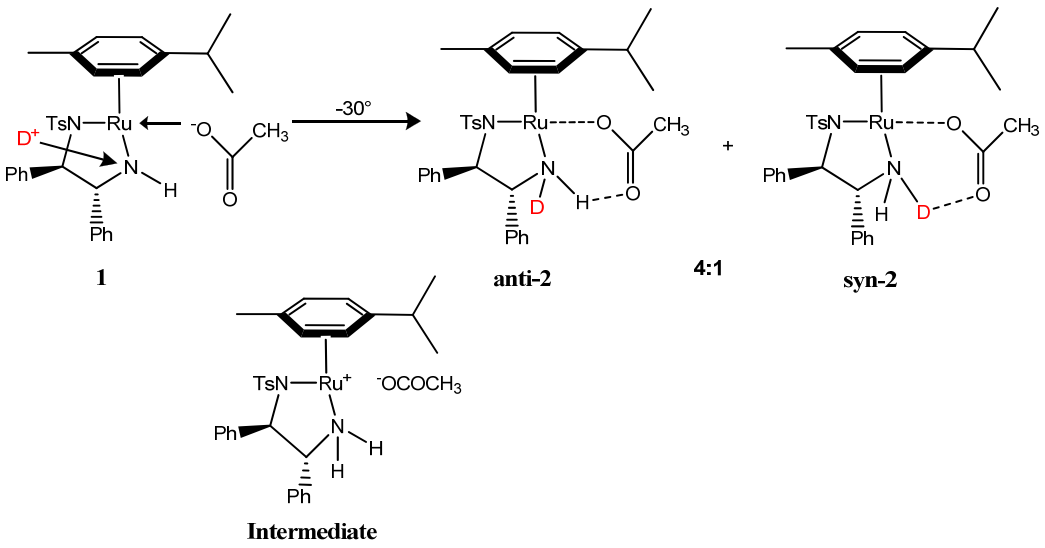
Scheme 3. Proposed Stepwise Mechanism of the Amido Ru Complex with Formic Acid



The carbon dioxide formed can reinsert into amine hydrido Ru complex proceeding to the reverse reaction through the same intermediate or transition state as the forward reaction. To ensure maximum catalyst efficiency, the CO_2 generated in the asymmetric reduction with formic acid should be removed.

To further understand the stepwise mechanism of hydrido Ru complex with formic acid, Takashi Koike and Takao Ikariya used deuterium labeled acetic acid, CH_3COOD, to see where insertion took place. Following the mechanism by ^1H NMR, one equivalent of CH_3COOD and **1** were reacted in CD_2Cl_2 at low temperatures.[8] The ^1H NMR spectrum showed two signals due to NH_2 protons in the deuterated complex at δ = 4.8 and 8.92 ppm with a 1:4 ratio of relative intensity. This ratio indicated that the anti-**2** was preferentially formed at lower temperature as shown below in Scheme 4.[8] When the temperature is increased, decarboxylation occurs to form amine hydrido Ru complex. Based on kinetic data collected[8], there are three possible pathways for the decarboxylation predicted by Koike and Ikariya: 1) formate anion dissociation leading to an ion pair, 2) η^6-arene ring slippage to η^4-arene, or 3) NH_2 ligand dissociation providing a vacant site, followed by β hydrogen elimination.

Scheme 4. Labeling of Formic Acid



A third possible hydrogen source is sodium formate in an aqueous medium. With every industry trying to become more environmentally green, water has the potential for producing less process waste, is safer to operate, and is low cost.[1] The Ru catalyst is insoluble in water but is stable.[1] Jianliang Xiao and colleague demonstrated how asymmetric transfer hydrogenation of aromatic ketones is actually accelerated in water. The ketones of the study were not water soluble and when water is the solvent, the catalyst is partitioned in the substrate and aqueous phases, being more soluble in the substrate.[9] There was only a slight decrease in enantioselectivity, but this green method benefits in terms of activity, selectivity and productivity.

Amide Reduction:

While there has been great stride and improvement for this type of Ru catalyst to reduce ketones and imines, there has been no evidence in the reduction of amides. In 2005, the American Chemical Society, Green Chemistry Institute, and several leading global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable. While the goal of the "pharmaceutical industry is invent medicines that allow patients to live longer, healthier, and more productive lives,"[10] these philosophies need to not come at the cost of the environment. The mission of The Roundtable was to implement the use of green chemistry and green engineering in the global pharmaceutical industry.

Before the use of green chemistry could be enforced, a brainstorming session identified the key mechanisms that needed either improvement or new pathways for desired products. Mild, catalytic amide reduction was one of the major areas that was identified as an immediate need.

After poling the pharmaceutical companies, it was noticed that an enormous amount of medicines and current drug candidates contain at least one basic nitrogen atom.[10] Typically, amide reduction is the common approach to synthesis the necessary amine. Reduction is usually carried out by a hydride reducing reagent such as $LiAlH_4$, DIBAL, RedAl, B_2H_6, Et_3SiH, or polymethylhydroxysilane (PMHS).[10] The Process Chemistry R&D departments of three major pharmaceutical companies completed a survey stating that amides to amines chemical transformations was only used 0.6% of all transformations, however, this number would be significantly higher if safer methods for use on industry scale were available.[11] The survey also indicated that amide reductions was equally split between diborane and hydride reagents. Hydride and borane reagents are hazardous and lead to both complex work-up procedures and high levels of waste.[11]

Lithium aluminum hydride is frequently used since it has the highest hydride density with a molecular weight of 38 with four hydrides per molecule. One of the major drawbacks, however, is the lithium aluminum hydroxide by-product is difficult to separate from the desired product.[10] Chemetall, a bulk supplier specialized in lithium based products, recommends to precipitate and filter the aluminum hydroxide salts. However, this proves to be a slow filtration process and causes product loss. The remaining material forms a cake like mixture which then needs to be disposed. There are two options for disposal, 1) dissolving the cake in water and sending it to a waste water treatment plant, or 2) drying the cake mixture and sending it to a chemical waste dump that accepts solids.[10] Either method chose, both have environmental consequences. The conclusion from The Roundtable discussion was “a generally applicable, safe, environmentally benign and economically viable method for the reduction of amides to amines would have an appreciable benefit to numerous processes.”[10]

There were two new methods mentioned, and while these methods show improvement, there are some shortcomings. One approach has been to use biotransformation to reduce the amide. Bacteria and fungi are known to reduce carboxylic acids to aldehydes or ketones.[12] When this method is applied to amides, hydrolysis is usually the outcome. In recent years, there has been development of anaerobic bacteria, *Clostridium sporogenes*, which reportedly reduces benzamide to benzylamine.[10] There is still uncertainly on the understanding of these complex enzyme-catalyzed processes. The greater challenge is being able to produce the enzymes on a large scale for industry use.

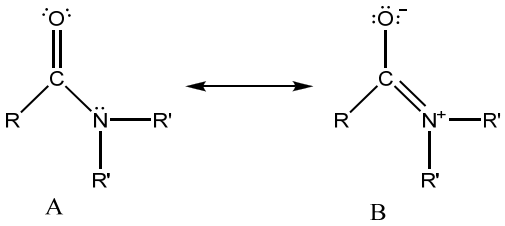
Another approach which has gained more attention is using hydrogen gas. Hydrogen gas is an ideal reductant because the only byproduct is water. For this reason, much emphasis of research has been on the discovery of a transition metal catalyst selective for hydrogenation of amides. With the current examples of catalyst systems available to reduce amides, both high temperature (~150 °C) and pressure (>100 bar) are required.[10] Most pharmaceutical manufacturing plants do not have the necessary equipment to carry out the reactions at these requirements. The development of a mild catalytic hydrogenation that could be carried out at low pressure and temperature would find widespread industrial application.

Amide Resonance:

Before hydrogenation can be attempted on the amide, the structure needs to be examined to determine if there are any potential roadblocks. Significant n-π^* interactions in amides reduces the π character of the carbonyl group, making amide hydrogenation challenging. Amides are generally considered to be weakly basic with the functional group classified as neutral.[13] If an amide is in the presence of a concentrated strong acid, the carbonyl oxygen will be protonated rather than the nitrogen atom. The reasoning for the preference for the carbonyl oxygen is the lack of basicity of the nitrogen due to contribution from its dipolar resonance. Amide structure is understood as a resonance hybrid of

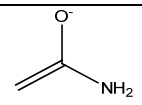
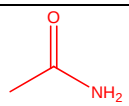
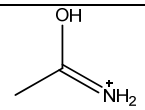
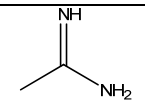
the conventional structure and a structure with a double bond between the carbon and nitrogen shown below.[13]

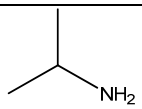
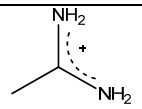
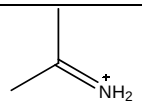
Scheme 5. Amide Resonance



In Carl R. Kemnitz and Mark J. Loewen's 2007 JACS publication, they studied the "Amide Resonance." They explain that the "amide functional group has traditionally been characterized by a restricted C-N bond rotation, coplanarity of the attached atoms, short C-N bond lengths, red-shifted carbonyl stretching frequencies, relative stability toward nucleophilic attack, and protonation at oxygen rather than nitrogen." [5] While there is some dispute among the community for the correct resonance model for amide, Kemnitz and Loewen demonstrated that the best resonance model is where there is a double bond between the carbon and nitrogen (**B**). This was concluded by examining the C-N rotation barriers of different compounds shown in Table 1.

Table 1. Computed C-N Rotation Barriers

Structure	#	$\Delta G^{\ddagger}$ kcal/mol
	1	3.9
	2	15.4
	3	30.3
	4	9.4

Structure	#	$\Delta G^{\ddagger}$ kcal/mol
	5	2.0
	6	21.6
	7	49.4

Rotation barriers for the compounds displayed above were computed using the high accuracy CBS-QB3 method. Acetamide, **2**, has a computed $\Delta G^{\ddagger}$ for C-N bond rotation of 15.4 kcal/mol with a mean absolute error of less than 1 kcal/mol. When compared to the experimental gas-phase $\Delta G^{\ddagger}$ for dimethylacetamide, a value of 15.3 kcal/mol,[5] indicating that the calculated rotation barrier is close to literature values. Isopropyl amine, **5**, has only a single bond between carbon and nitrogen with no carbonyl oxygen present with a calculated barrier of 2.0 kcal/mol. When C-N rotation barriers for amide is compared to compounds **3** or **7**, where a double bond is present between the carbon and nitrogen, the calculated barriers are 30.0 and 49.4 kcal/mol respectively, much greater than amides. From the table, it can be concluded that the C-N rotation barrier is higher than single bond C-N, but lower than C-N double bond. According to the resonance rationale, the large C-N rotation barriers in amides arise from the partial double bond character resulting from the amide resonance.[5]

Goal:

With the growing interest in developing mild and catalytic methods for reduction of amides, we propose a modification to the typical Noyori system with the aim to expand metal-ligand bifuctional activity to amide hydrogenations. Through preliminary data and lack of amide reduction by metal-ligand bifuctional in literature, it is difficult for reduction on the carbonyl to succeed most likely due to polar resonance of the amide. A proposed way to overcome diminish contributions from this amide resonance is to coordinate the nitrogen lone pair with a Lewis acid such as a borane. With decreasing the n-π^* contribution from the amide N to the carbonyl C, the amide will have greater characteristics of a true carbonyl. The reduction could then proceed by proton and hydride transfer to the C=O bond resembling the Noyori hydrogenation of ketones shown in Figure 2.

Miller and coworkers attached a pendant Lewis acid to a rhenium carbonyl complex for their studies of synthesis gas.[14] While their aim was different from ours, it validated our strategy for incorporating an intramolecular borane for Lewis acid assisted amide hydrogenation. The borane would

be tethered to the arene side chain of Noyori's Ru complex. The arm of the tethered borane needs to be long enough so that when the nitrogen of the amide is coordinated, the carbonyl portion can still be reduced by the hydridic Ru-H and the protic N-H. However, the arm cannot be too long that is able to interact with the nitrogens of the ligand on the metal center. Presented is the synthesis completed thus far in the steps of producing the desired catalyst containing a tethered borabicyclo[3.3.1]nonane fragment. In the near future, amide reduction activity of catalysts will be examined and presented.

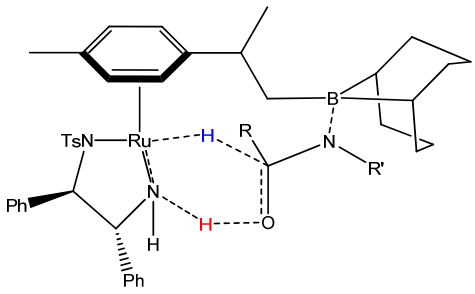
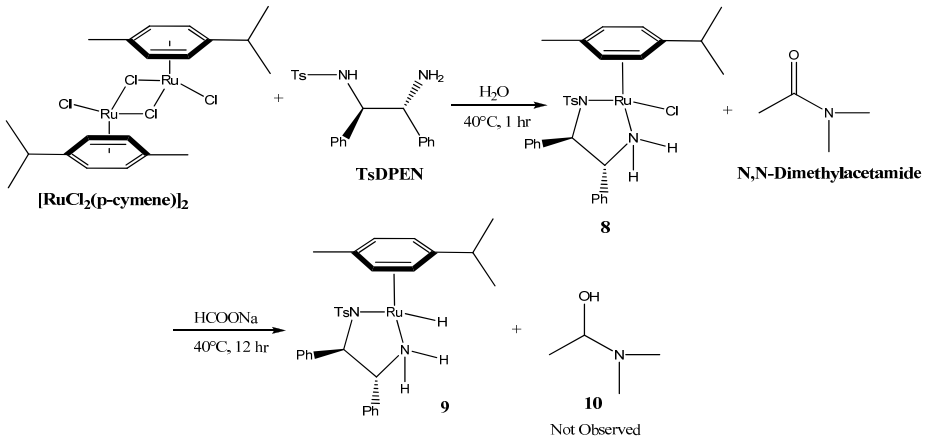


Figure 2. Proposed Transition State of Newly Designed Catalyst

Synthesis:

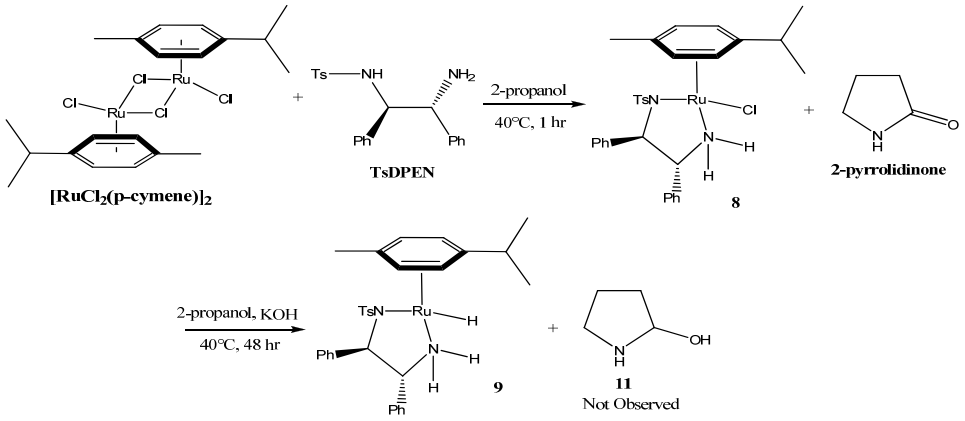
Before moving onto our new catalytic system we examined amide reduction with Noyori's Ru complex as a control reaction. Thus, we attempted the hydrogenation of N,N-Dimethylacetamide with an insitu prepared catalyst starting from the dichloro(p-cymene)ruthenium(II) dimer, (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine as the ligand, and sodium formate as the hydrogen source shown below in Scheme 6.

Scheme 6. Reduction of N,N-Dimethylacetamide



After stirring for several hours at 40°C, ^{1}H NMR spectrum showed only starting material with no evidence of the alcohol product (**10**). A second amide, 2-pyrrolidinone, was tested using the same method as shown above. NMRs were taken after the first hour and at the 20 hour mark; both showing only the presents of the starting amide. The reduction of 2-pyrrolidinone, was attempted again with altering the method by using 2-propanol as the hydrogen source instead of the water and sodium formate shown below in Scheme 7. Similar results to the aqueous hydrogenation were obstained; after 48 hours, NMR indicated only starting material with no evidence of the alcohol product (**11**).

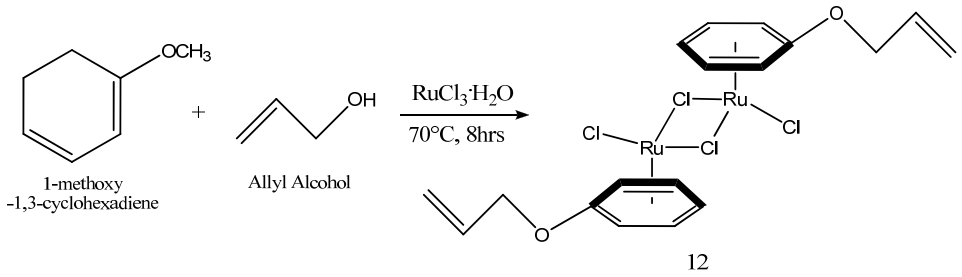
Scheme 7. Reduction of 2-pyrrolidinone with 2-propanol



Having established a baseline with Noyori's ruthenium catalyst, we turned our attention to the design of our new catalyst. Our intention was to tether a Lewis acid to the Noyori catalyst without significantly altering any other part of the catalyst. The first challenge was to find the best method for synthesizing the arene. The arene ligand in these types of piano stool arene ruthenium complexes originate from cyclohexadiene. The reaction of the cyclohexadiene with the hydrated halide, $RuCl_3 \cdot 3H_2O$, results in the oxidation of the arene with simultaneous reduction of Ru (III) to Ru (II), forming the bridging chloro-dimer precursor shown in Scheme 7. In this regard, the cyclohexadiene is both a ligand precursor and a reductant. The first method, shown is Scheme 8, was to add an allylic arm to the diene 1-methoxy-1,3-cyclohexadiene which would be subjected to anti-Markovnikov hydrogenation to place the boronic Lewis acid in close promimity to the Ru center. While the desired product was formed and

confirmed by ^{1}H NMR, the NMR spectrum also showed that numerous side products were also produced. It was determined that separation would be too time consuming and resource intensive, thus a different method would be a better step forward.

Scheme 8. Tethered Arm with Allyl Alcohol



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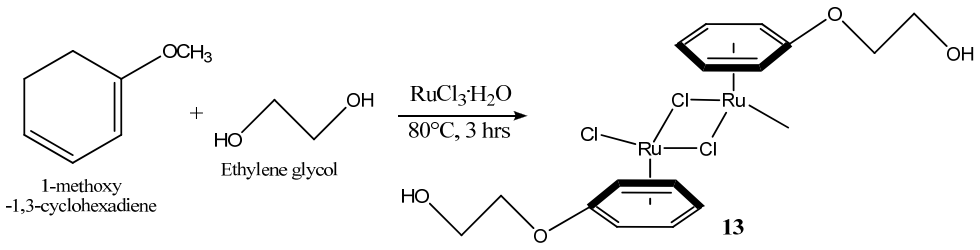
The second method used the same starting cyclohexadiene, but tethers an ethylene glycol arm as shown in Scheme 9. With an alcohol at the end of the arm, a borate ester could exchange in a later step with the established Lewis acid. NMR characterization of the reaction products revealed a mixture which included excess ethylene glycol. Surprisingly, the ethylene glycol could not be removed away after several attempts. At the same time, the borate ester exchange strategy was reconsidered due to doubts about the lability of the B-O bond in alcohol solvents.

Scheme 9. Tethered Arm with Ethylene Glycol



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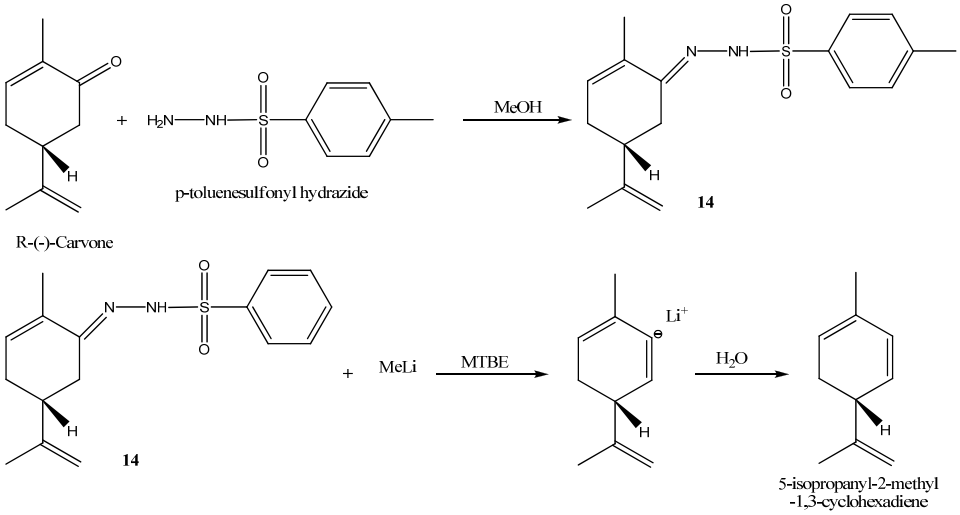
The method that we are currently pursuing is the hydroboration of the terminal double bond of 5-isopropanyl-2-methyl-1,3-cyclohexadiene shown in Scheme 18. This compound contains the requisite functionality to form the desired chloro bridging dimer, Scheme 19. Therefore, our immediate synthesis focus turned to 5-isopropanyl-2-methyl-1,3-cyclohexadiene which we envisioned to be obtained from

the Shapiro reaction of commercially available R-(-)-Carvone (Scheme 10). The Shapiro reaction, a variation on the Bamford-Stevens Reaction, is the base-induced reaction of tosylhydrazones to afford alkenes. R-(-)-Carvone and *p*-toluenesulfonyl hydrazide were stirred in methanol for several hours then allowed to sit over night. The solution was placed in the fridge for a few hours then the bottom of the round bottom flask was scratched which initiated crystal formation. ^{1}H NMR indicated that the desired hydrazide (14) was produced in pure form. After drying on the vacuum line, there was only a small amount of methanol present.

The elimination of the hydrazide was first attempted with the addition of methyllithium (1-2M in ether) and tetramethylethylenediamine as the solvent. After the solution was stirred overnight, it was cooled to -30°C and the addition of water quenched the reaction. Following a typical procedure for the Shapiro reaction, the crude product was extracted with pentane, washed with NaOH, HCl, water and brine, then purified by short path distillation. However when an NMR was taken of the final product, all that could be seen on the spectrum were the solvent peaks. Since TMEDA has a boiling point of 120°C and is soluble in both water and ether, it proved to be too difficult to remove from the product.

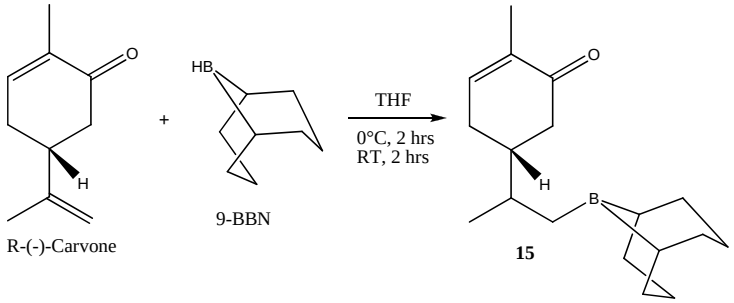
The starting material was made again from the R-(-)-Carvone and *p-toluene*sulfonyl hydrazide, again producing pure crystals. The second attempted at the hydrazide elimination was done with methyl lithium / lithium bromide complex solution in tert-Butyl methyl ether. Since MTBE has a much lower boiling point of 55°C, it was much easier to remove after the completion of the reaction. Reaction scheme of the final method chosen is shown below in Scheme 10. ^{1}H NMR and MS data indicated that the 5-isopropanyl-2-methyl-1,3-cyclohexadiene was formed in pure form.

Scheme 10. Shapiro Reaction



Before attempting the hydroboration of the 5-isopropanyl-2-methyl-1,3-cyclohexadiene we decided to test the regioselectivity of the hydroboration for the terminal double bond by performing the hydroboration on R-(-)-Carvone. Thus, we hydroborated R-(-)-Carvone with 9-Borabicyclo[3.3.1]nonane following the procedure outlined in *Organic Syntheses*.[17] The reaction was monitored by TLC, showing the disappearance of Carvone, and later confirmed by NMR. The NMR showed that although some starting material was still present, the 9-BBN had added to the terminal double bond to produce the tethered arm (15) shown in Scheme 11.

Scheme 11. Hydroboration of R-(-)-Carvone



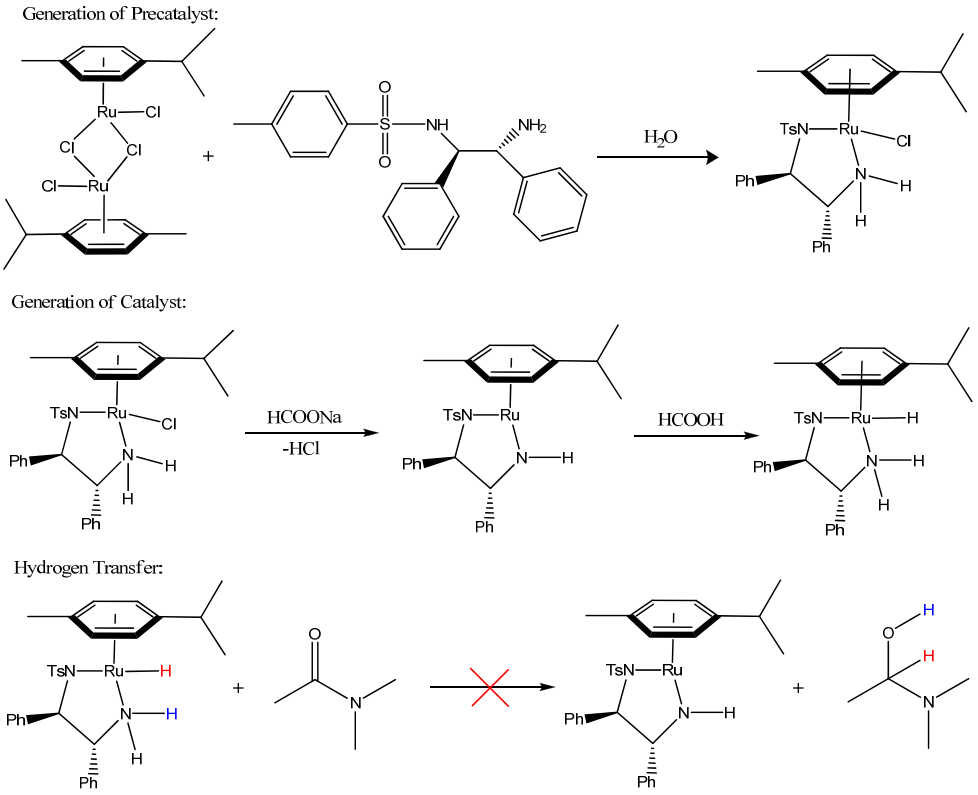
Discussion:

Reduction of amides with Noyori's Ru Catalyst:

Even though there was no evidence of amide reduction by Noyori's Ru catalyst in the literature, these reactions were still carried out to provide a set of control reactions under different conditions in our lab. Two different amides with two different methods were tested. The first amide, N,N-Dimethylacetamide, was chosen because it was just a simple amide. The initial thought was that the simplicity of the amide would be a positive since there would not be any cause of steric hindrance or no other possible coordination sites. However, the simplicity of the amide soon caused some concern. If the initial hemiaminal reduction product did form, and fell apart due to lack of stability, there would be no way to monitor this on the NMR. The possible side products products acetaldehyde and dimethyl amine are volatile and would escape under experimental conditions (Scheme 12 bottom). The NMR only showed evidence of the starting material.

The procedure, adapted from Xiao in *Organic & Biomolecular Chemistry*[9], starts by preparing the pre-catalyst dichloro(p-cymene)ruthenium(II) dimer and the ligand (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine with stirring for one hour at 40°C. After an hour, sodium formate is added along with the substrate (the amide). The sodium formate converts the pre-catalyst to the active catalyst by chloride displacement and CO_2 deinsertion. Normally the active catalyst would then be able to do a hydrogen transfer, however that is not the case with the amide as shown below in Scheme 12. As explained above in the introduction, amide hydrogenation is challenging due to significant n-π^* interactions which reduces the π character of the carbonyl group. With a lack of carbonyl characteristic, the active catalyst is not able to form the pericyclic transition structure shown in Scheme 2.

Scheme 12. Generation of Noyori's Ru Catalyst



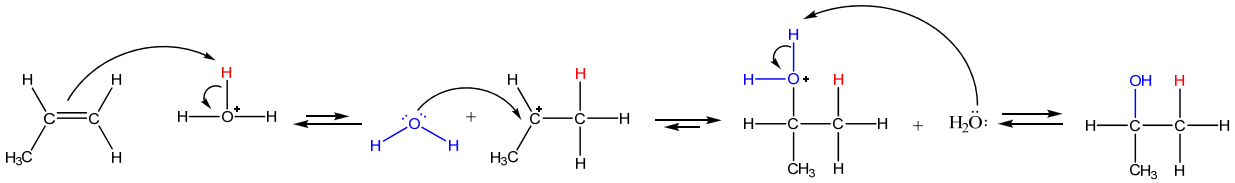
Since it was difficult to fully conclude there was no evidence amide hydrogenation, a different amide was chosen that would not be as volatile and whose hemiaminal decomposition products would be readily identifiable. The second amide tested was 2-pyrrolidinone using the same method as shown above. As indicative with the first amide, after the reaction ran for 48 hours, the NMR showed only evidence of the starting amide. The reaction was setup one more time, but instead of using water and sodium formate, 2-propanol and potassium hydroxide were used. This showed no changes in the outcome, only starting material was present. This provided evidence that a new catalyst is needed to affect amide hydrogenation to form a hemiaminal then ultimately an amine.

Installation of the borane tether:

The first method in designing the new catalysts was to start with 1-methoxy-1,3-cyclohexadiene and allyl alcohol with ruthenium chloride hydrate. The arene on the ruthenium catalyst is initially a cyclohexadiene and is then coordinated to the ruthenium following an initial redox reaction. The cyclohexadiene is oxidized to an arene, and the ruthenium is reduced from ruthenium(III) to ruthenium(II). For this reason, altering the arene portion of the catalysts, requires the synthesis of a modified cyclohexadiene and great caution must be made that the product does not aromatize nor polymerize prior to reaction with ruthenium chloride hydrate.

Initially, allyl alcohol was chosen as the pendant arm off the ring since it has a terminal double bond. Hydroboration of the double bond would form an anti-Markovnikov product. The difference between Markovnikov and anti-Markovnikov products are most easily seen when demonstrating the difference between hydration of alkenes by water versus hydroboration. When water is added to an alkene (in the presence of an acid catalyst), a hydrogen is added to one carbon and a hydroxyl group to the other. The proton adds to the less highly substituted end of the double bond; the resulting carbocation resides on the more highly substituted carbon. After the attack of carbocation by water and loss of a proton, the hydroxyl group is located on the more substituted carbon. The Markovinkov rule states the product in which the new hydrogen has been added is to the less highly substituted end of the double bond.[13]

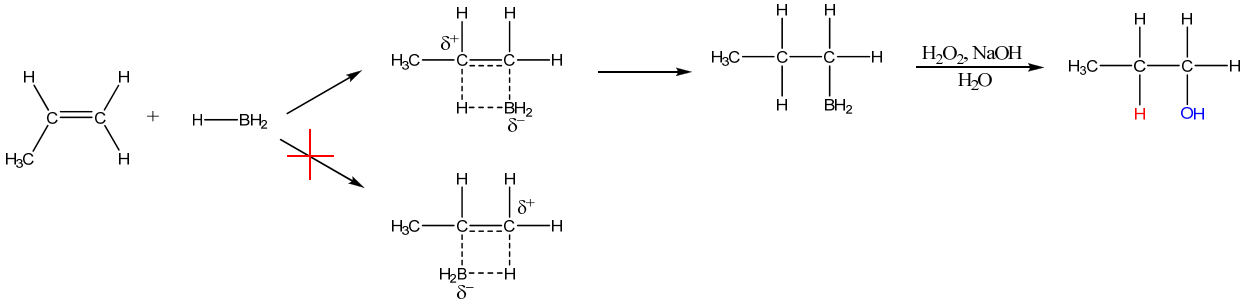
Scheme 13. Hydration of Alkenes by water[13]



Hydroboration on the other hand has the hydrogen added to the more highly substituted end of the double bond forming the anti-Markovinkov product. Borane is an electron-deficient compound with the boron atom having only six valence electrons. Borane is a strong electrophile capable of adding to a

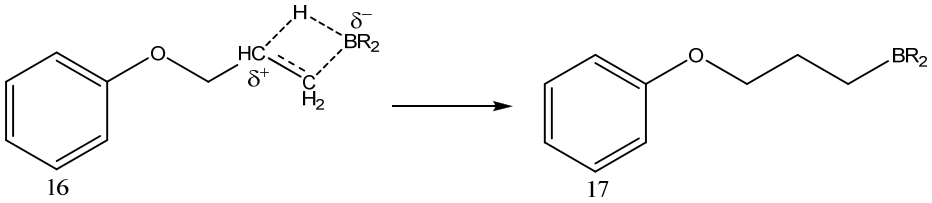
double bond with the boron atom adding to the less substituted carbon. In the transition state, the electrophilic boron atom withdraws electrons from the pi bond causing a partial positive charge on the carbon at the other end of the double bond. With the same principles as described with hydration by water, the partial positive charge is placed on the on the more substituted carbon atom. For this reason, the hydrogen resides on the more highly substituted carbon yielding an anti-Markovnikov product. In work up steps, the boron atom is removed by oxidation using aqueous sodium hydroxide and hydrogen peroxide to replace the boron atom with a hydroxyl group.

Scheme 14. Hydroboration of an Alkene[13]



With the addition of the Lewis acid to the double bond of allyl alcohol, a similar transition state would occur with the borane also yielding an anti-Markovnikov product.

Scheme 15. Insertion of borane to allyl alcohol product



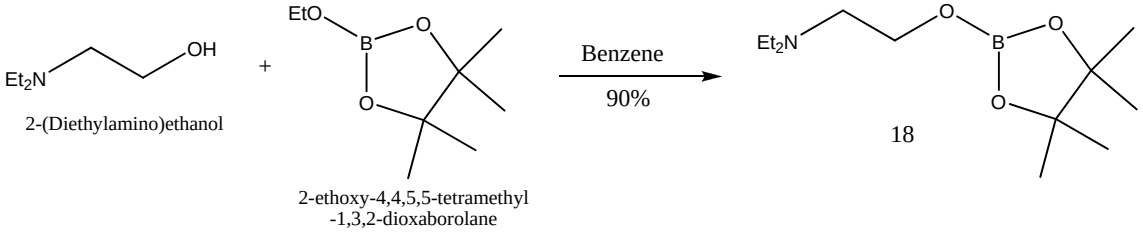
The plan of synthesis was to combine 1-methoxy-1,3-cyclohexadiene and allyl alcohol with the use of ruthenium chloride hydrate. After the reaction ran for 8 hours and placed on the rotary evaporated, the NMR spectrum showed that many side products were produced. A peak at 9.5 ppm indicated that an aldehyde was present, along with peaks in the 6-7 ppm evident of a vinyl alcohol. It was determined that

the double bond at the end of the arm was too reactive and susceptible to polymerization and rearrangement. A new pathway was needed to add the borane Lewis acid to the arene.

Borate ester - alcohol exchange

The second method for the addition of borane was to do an alcohol-borate ester exchange. In a 1981 article from *Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry*, Duggal and Mehrotra were able to synthesize organic derivatives of boron by doing an alcohol exchange with a borate ester.[15] Borate esters were refluxed with the alkanolamines in equimolar ratios using benzene as the solvent. The progress of the reaction was checked by the estimation of ethanol in the azetrope collected with the help of a fractioning column.[15]

Scheme 16. Borate Ester Exchange



This evidence provided the framework for the second method that was attempted. The second method used the 1-methoxy-1,3-cyclohexadiene (same as previous method), but ethylene glycol instead of allyl alcohol with ruthenium chloride hydrate at 80°C for three hours. An NMR was taken of the final red fine powder. The NMR showed the desired arene on the ruthenium chloride, but there was also free arene present that was not coordinated to the ruthenium chloride. The NMR spectrum also indicated that there was still ethylene glycol present even after multiple purification attempts. Between excess arene and excess ethylene glycol, purification could prove to be difficult. Furthermore, when trying to find a commercially available borate ester to do the borate-alcohol exchange, there seemed to be none available. Upon further investigation into research literature, there was little evidence of borate esters

synthesis. With continued discussion with Dr. Moasser, it was concluded that this method might not be the best choice either. Steps foreseen after the hydroboration would most likely include solvents that would easily break the B-O bond. The best method would be to find another way to add the borane Lewis acid to a double bond via construction of a B-C bond.

Shapiro Elimination/Hydroboration

Once it was decided that the best linkage for placing a boron atom in proximity of Ru was via a C-B bond, cyclohexene compounds were examined that could serve as precursors for hydroboration. The compound chosen that was 5-isopropanyl-2-methyl-1,3-cyclohexadiene which could be synthesized from the commercially available and inexpensive R-(-)-Carvone via the Shapiro reaction. The Shapiro Reaction is a base-induced reaction of tosylhydrazones to afford alkenes. Through this process, ketone or aldehyde is converted to an alkene through an intermediate hydrazone in the presence of two equivalents of strong base.[16] Since R-(-)-Carvone has a ketone with an available alpha hydrogen, the Shapiro Reaction would produce the desired cyclohexadiene.

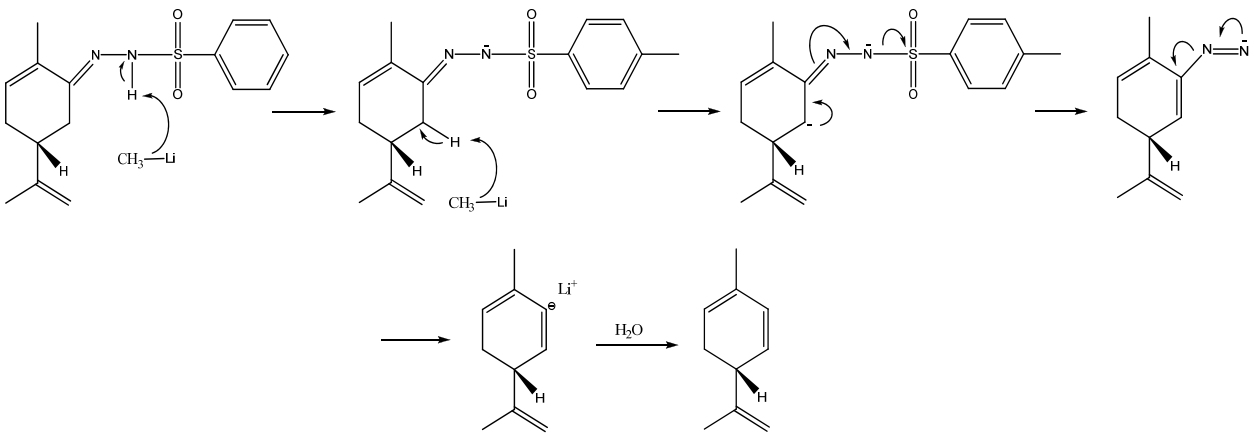
The first part of the Shapiro Reaction is to produce the tosylhydrazone intermediate. R-(-)-Carvone and *p*-toluenesulfonyl hydrazide were combined 1:2 molar ratio in methanol. After stirred for a few hours, the solution sat over night at room temperature. The following morning, the solution was placed in the fridge for a few hours. After warming to room temperature, the bottom of the glass round flask was scratched with a glass rod. Large white crystals crashed out of solution after scratching. After an hour, crystal formation ceased, and the crystals were filtered and washed with 1:1 pentane:ether solution. When the mother solution was placed back in the fridge after filtration, more crystals grew and were again filtered and washed. The only drawback to this reaction was inconsistent yields. This reaction was done numerous times producing yields ranging from 36-58%. Since the reaction is done in a 1:2 molar ratio, at the completion of the reaction there is still excess *p*-toluenesulfonyl hydrazide left. Instead of wasting the material, more R-(-)-Carvone was added to the mother liquor which contained

the excess *p*-toluenesulfonyl hydrazide along with the catalytic *p*-toluene*s*ulfonic acid monohydrate. The *p*-toluenesulfonic acid monohydrate acid-catalyzes the remaining *p*-toluenesulfonyl hydrazide with R-(-)-Carvone. The combined products from the initial self-catalyzed reaction and the second acid-catalyzed reaction showed satisfactory ^{1}H NMR spectra and were used for the next reaction.

Our initial attempt at converting the hydrazide to the alkene employed methyl lithium (1-2M in ether) with tetramethylethylenediamine as the solvent. As explained above, when it came time to remove the solvent, it became problematic. Short path distillation was used to remove the pentane, but since TMEDA has a boiling point of 120°C, and we were concerned that heating the solution at high temperatures would cause the cyclohexadiene to aromatize with no clear pathway to purify the compound.

The second attempted was more successful by using methyl lithium / lithium bromide complex solution in tert-Butyl methyl ether. Two equivalents of the methyl lithium are needed. The first equivalent of the base abstracts the proton from the nitrogen of the hydrazide. Because this proton is more acidic than the alpha carbonyl proton, this attack is most likely first. The second equivalent of base abstracts the alpha carbonyl proton leaving a carbanion.[16] The carbanion proceeds in an elimination reaction, first expelling the tosyl group, followed by nitrogen. The resulting vinyllithium compound is quenched with water to yield the desired alkene.

Mechanism 1. Shapiro Reaction



After the reaction is quench by water, the cyclohexadiene was extracted with MTBE and solvent removed by rotary evaporation to yield a slurry. ^{1}H NMR of this product was consistent with the expect product, however, there was evidence of a minor side product, as well as, residual solvent. Doublets in the 7 ppm range indicated that there was a para substituted aromatic ring present. A thin layer chromatography was performed in 100% hexane to see if the side product could be separated. The two spots that developed were scraped and dissolved in hexane and characterized by mass spectrometry. Although this TLC-MS method is convenient for identifying reaction products, it suffered from contamination arising from the silica gel.

Instead, a small column was prepared in a Pasteur pipette. It was hoped that the desired compound would move with the solvent front and the side product would be retained on the column. Ten fractions were collected each of about ten drops. A thin layer chromatography in 100% hexane was then performed on each fraction to combine similar fractions and characterize. Fractions 2-4 showed a large spot that moved half way with the solvent front. Unexpectedly, in fraction 5 the large spot started to split, and in fractions 6-7 two distinct spots were seen. The final fractions, 8-10 showed no spots at all. Fractions 2-4 were combined and fractions 6-7 were combined to take a mass spectrum. Fractions 2-4 had a mass m/z of 155, this is indicative of the cyclohexadiene plus a sodium adduct (formula weight of the cyclohexadiene is 133 g/mol). There was also evidence that the compound polymerized since

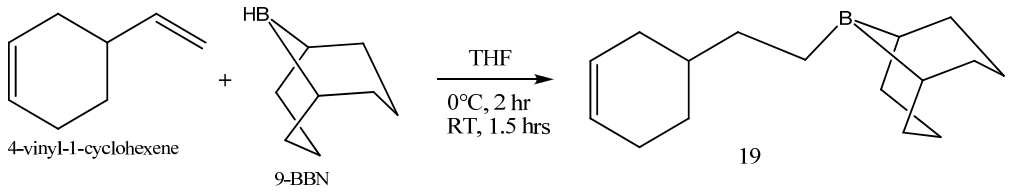
there is peaks at m/z 269 (the dimer), m/z 399 (the trimer), all the way up to m/z 665. Fractions 6-7 had the same peaks present, but also m/z minus 2. This is evidence that the cyclohexadiene aromatized as it spent more time on the silica gel and therefore chromatography on silica cannot be used to purify the material.

A mini distillation apparatus was set up with a u-tube to see if that would allow for a method of purification. A few drops of the solution were place in the bottom of the u-tube and heated with a heat gun. Vapors were collected in a round bottom flask and cooled by an ice bath. NMR was taken of the distillate, showing that both the cyclohexadiene and aromatic compound were present. Because of the instability of the cyclohexadiene and the fact that the primary reaction product was already fairly clean, it was decided that this material will be used in the next reaction without further purification.

Hydroboration of Carvone

A tested hydroboration of R-(-)-Carvone with 9-Borabicyclo[3.3.1]nonane was carried out prior to consuming the 5-isopropanyl-2-methyl-1,3-cyclohexadiene. Reaction conditions were similar to the hydroboration of 4-vinyl-1-cyclohexene reported in *Organic Syntheses* in 1993. When this procedure was tested on the R-(-)-Carvone, ^{1}H NMR indicated that boration at the terminal bond did take place regioselectively, with no indication of reduction of the internal double bond or the carbonyl. The next step is to attempt this procedure on the cyclohexadiene previously designed.

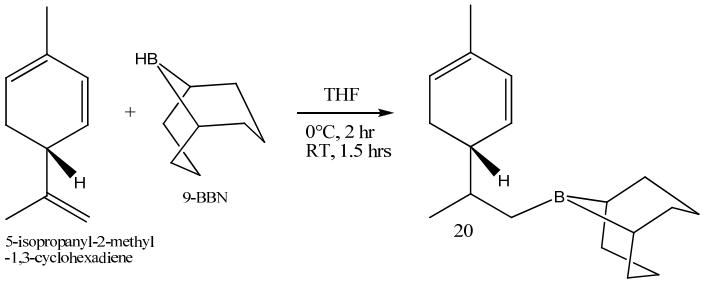
Scheme 17. Hydroboration of 4-vinyl-1-cyclohexene



<u>Future Work:</u>

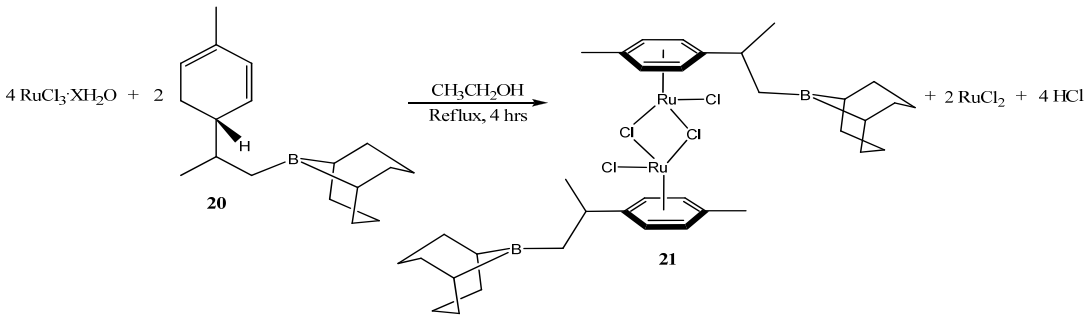
Great strides and some setbacks have been taken thus far for the design of a new metal-ligand bifuctional catalyst for the hydration of amides. Different methods were attempted in designing the arene portion of the catalyst. Now that the best method for this has been determined, the next step is to attach the Lewis acid to the cyclohexadiene. The same procedure will be used as the one completed on R-(-)-Carvone. Since the tetrahydrofuran is a neutral solvent (with a pH of 7), there should not be a risk of aromatizing of the cyclohexadiene.

Scheme 18. Hydroboration of 5-isopropanyl-2-methyl-1,3-cyclohexadiene



After the 9-Borabicyclo[3.3.1]nonane is added to the 5-isopropanyl-2-methyl-1,3-cyclohexadiene, the newly designed 5-[1-(9-borabicyclo[3.3.1]monylmethyl)ethyl]-2-methyl-1,3-cyclohexadiene (20) will be ready to coordinate to ruthenium chloride hydrate. This step will follow the method used by M. A. Bennett and colleagues' to coordinate α-phellandrene to ruthenium trichloride hydrate.[18] For the intended synthesis, four equivalents of the ruthenium chloride hydrate and two equivalents the cyclohexadiene with the Lewis acid attached will be refluxed in ethanol for four hours to yield a dimer. After filtration and drying, the arene will be coordinated to the ruthenium.

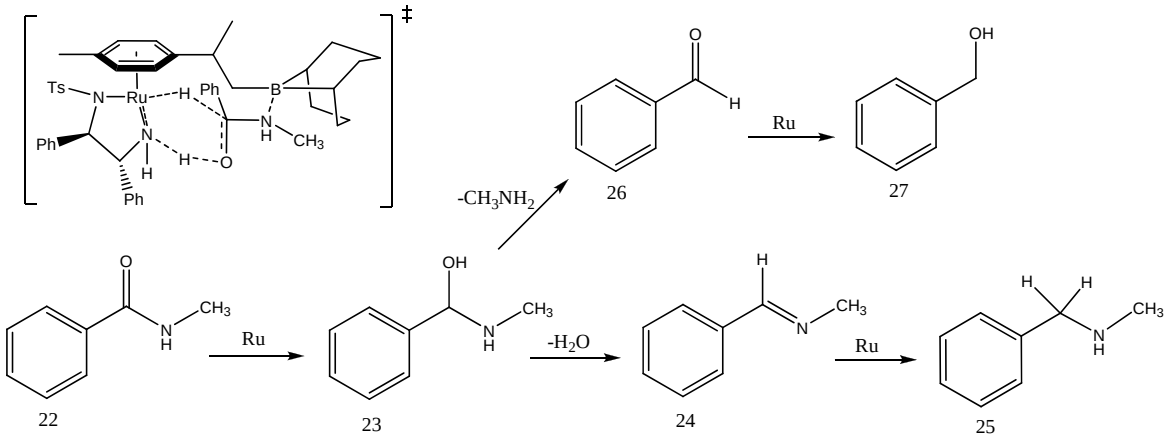
Scheme 19. Generating RuCl dimer



The next step will be to apply the ligand to the ruthenium chloride dimer to form the pre-catalyst. The ligand choice will not change from Noyori's Ru complex which is TsDPEN ((1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine). Previously, the ruthenium chloride dimer and ligand were combined in solvent (water or isopropanol) for an hour, and the substrate (a ketone) and base are added to initiate hydrogenation. We will take this approach in preparing the pre-catalyst insitu for catalytic reactions. For detailed structural studies we will isolate and fully characterize the pre-catalyst. One of the potential road blocks that can be foreseen, is that the nitrogens on the ligand may become coordinated to the boron atom instead of the ruthenium. It is hoped that the ligand will have a higher affinity for the ruthenium metal center over the boron atom.

Once the Lewis acid assisted metal-ligand bifuctional pre-catalyst is synthesized, the next step is for amide hydrogenation. Before this can be attempted, an appropriate amide needs to be chosen. There are multiple pathways that are possible for hydrogenation to occur. Since aromatic compounds are easily characterized with NMR and well known, that is the best place to start. N-Methylbenzamide is an appropriate model compound since all its possible reaction products after initial hydrogenation can be readily characterized. Scheme 20 shows the possible pathways and products.

Scheme 20. Possible Pathways for Amide Hydrogenation



The transition state shown in Scheme 20, is what we envision for amide hydrogenation. The lone pair of the nitrogen would coordinate to the borane Lewis acid reducing the amide polar resonance, then allowing carbonyl portion to be reduced by the hydridic Ru-H and the protic N-H. If this does occur, the amide would be reduced from an amide to an hemiaminal (23). However, hemiaminals are not relatively stable and most likely not isolatable. There are two are two possible pathways from here. The ideal pathway would be that dehydration to occur next. With the loss of water, N-Benzylidenemethylamine (24) is formed. It has been shown in literature that imines can also be reduced by Noyori's Ru catalyst. Therefore, the imine could be reduced further to the amine producing N-Benzylmethylamine (25), achieving the ultimate goal. The second possible pathway is loss of methylamine and benzaldehyde (26) formation. Benzaldehyde can then be reduced further by the ruthenium catalyst to form benzyl alcohol (27). While this would not be the pathway of interests to achieve the goal of the project, it would demonstrate that the ruthenium catalyst does in fact hydrogenate the amide. Since all the possible products are known and characterized compounds, ^{1}H NMR could be used to determine which pathway most likely took place. A possible way to take the project a step further would be to attempt amide reduction with Noyori catalyst and free Lewis acid. A comparison of an intermolecular and intra molecular Lewis acid assisted hydrogenation can shine more light on the potential applications of ligand non-covalent interactions in transition metal catalyst.

Experimental Section:

Hydrogenation of N,N-Dimethylacetamide[9]

A suspension of Dichloro(p-cymene)ruthenium(II) dimer (3.0mg, 0.005mmol, Aldrich) along with (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine (5.0mg, 0.014mmol, Aldrich) in water (2ml) were placed into a 50ml Schlenk flask and degassed three times by method of freeze-pump-thaw. Flask was placed under nitrogen, sealed and solution stirred for one hour at 40°C. Solution turned from a clear color with brown precipitate to a yellow colored solution with yellow precipitate. Sodium formate (340mg, 5.0 mmol) and N,N-Dimethylacetamide (97µl, 1.0 mmol) were then introduced. Mixture was degassed three times and stirred at 40°C for a period of time under nitrogen. NMR was taken at 1 hr, 2 hr, 18hr. There was no change in the three NMRs, only presence of starting amide and solvent. ^{1}H NMR (CD_3OD): δ 2.05 (s, 3H, CH_3), δ 3.03 (s, 6H, $N(CH_3)_2$)

Hydrogenation of 2-pyrrolidinone[9]

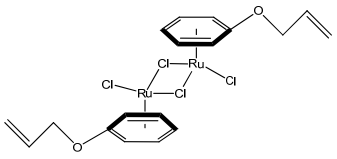
A suspension of Dichloro(p-cymene)ruthenium(II) dimer (3.0mg, 0.005mmol, Aldrich) along with (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine (5.0mg, 0.014mmol, Aldrich) in water (2ml) were placed into a 50ml Schlenk flask and degassed three times by method of freeze-pump-thaw. Flask was placed under nitrogen, sealed and solution stirred for one hour at 40°C. Sodium formate (340mg, 5.0 mmol) and 2-pyrrolidinone (76µl, 1.0 mmol) were then introduced. Mixture was degassed three times and stirred at 40°C for a period of time under nitrogen. NMR taken at 1 hr, 4 hr, 20 hr. There were no changes in the NMRs, only the presence of the starting amide and water. ^{1}H NMR (D_2O): δ 1.99 (m, 2H, CH_2), δ 2.18 (t, 2H, N-CH_2), δ 3.25 (t, 2H, CO-CH_2), δ 8.28 (s, 1H, NH).

Hydrogenation of 2-pyrrolidinone with 2-propanol[19]

A suspension of Dichloro(p-cymene)ruthenium(II) dimer (30.62mg, 0.05mmol, Aldrich) along with (1S,2S)-(+)-N-p-tosyl-1,2-diphenylethylene-diamine (36.65mg, 0.100mmol, Aldrich) in 2-propanol (20ml) were placed into a 100ml Schlenk flask and degassed three times by method of freeze-pump-thaw. Flask

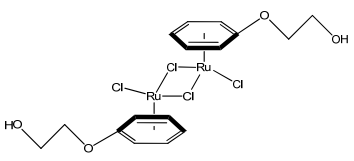
was placed under nitrogen, sealed and solution stirred for one hour at 40°C. Solution was orange/amber in color. In a separate flask, potassium hydroxide (2.8 mg, 0.05mmol), 2-pyrrolidinone (380µl, 5.0mmol) and 2-propanol (50ml), were degassed three times by method freeze-pump-thaw and nitrogen transferred via a cannula needle to the flask containing the ruthenium mixture. Mixture was stirred for 2 days at 40°C. Solution became a homogeneous red color with no precipitate. Solution was placed on the rotorary evaporator to remove solvent. Solvent could not be remove to dryness. There were no changes in the NMR, only the presence of the starting amide and 2-propanol. ^{1}H NMR (CDCl3): δ 2.14 (m, 2H, CH_2), δ 2.31 (t, 2H, N-CH_2), δ 3.46 (t, 2H, CO-CH_2), δ 6.43 (s, 1H, NH).

1-methoxy-1,3-cyclohexadiene and Allyl Alcohol[20]



A solution of ruthenium trichloride hydrate (311mg, 1.5mmol) and 1-methoxy-1,3-cyclohexadiene (1.05ml, 9mmol) in allyl alcohol (5ml) was degassed three times by method of freeze-pump-thaw. Solution was refluxed for 8 hours at 70°C. After the first hour, solution turned from a dark brown to a dark red in color. After 8 hours, there was no precipitate, therefore diethyl ether was added. Immediately, precipitate formed that was red in color. Solution was filtered and the filtrate was placed on the rotavap resulting in an oily red substance. NMR was taken of both the oily substance and precipitate. Precipitate was non-conclusive, expected product was not present. ^{1}H NMR ($CDCl_3$) of oily substance indicated a bunch of side products. Wide, broad peaks from 1 ppm – 4 ppm are indefinable most likely due to polymerization. Peaks between 6 ppm- 7 ppm indicate a vinyl alcohol and peak at 7 ppm indicate an aromatic compound. Peak at 9.5 ppm indicate an aldehyde.

1-methoxy-1,3-cyclohexadiene and Ethylene Glycol[20]



A solution of ruthenium trichloride hydrate (622mg, 3.0mmol) and 1-methoxy-1,3-cyclohexadiene (3.52ml, 30mmol) in ethylene glycol (12ml) was degassed three times by method of freeze-pump-thaw. Solution stirred for 3 hours at 80°C. After 1 hour, solution turned from brown to bright red color. After solution sat overnight under nitrogen, solution became lighter in red color with precipitate. Solution was filtered and washed with methanol and dried on vacuum line yielding a dark red fine powder. Filtrate was placed in fridge and filtered again. NMR was taken of solid. ^{1}H NMR (d_6-DMSO): δ 3.72 (t, 4H, CH_2), δ 4.21 (t, 4H, CH_2), δ 5.37 (t, 2H, Ph), δ 5.56 (d, 4 H, Ph), δ 6.15 (t, 4 H, Ph). Impurities at δ 3.17 (s, 3H, CH_3OH), δ 3.33 (s, 4H, CH_2), δ 3.31 (s), δ 5.97 (s)

Shapiro Reaction with TMEDA[21]

A solution of *p*-toluen*e*sulfonylhydrazide (12.29g, 66mmol) in methanol (330 ml) was added R-(-)-carvone (5.16ml, 33mmol). Solution was stirred for three hours at room temperature and then sat over night. After sitting over night, there was no precipitate, and the solution was placed in the fridge for a few hours. Upon removing from the fridge, the bottom of the flask was scratched with a glass rod. Large white 'snow' like crystals crashed out of solution. If filtrate was placed back in the fridge, more crystals would be present. Solution was filtered and washed with 1:1 pentane:ether and dried on vacuum line (36-58% yield). To the filtrate solution, R-(-)-carvone (5.16ml, 33mmol) was added with *p*-toluenesulfonic acid mono hydrazide (1.1625g, 8.70mmol). Solution was stirred for an hour and crystals formed without sitting or scratching. Crystals are much smaller and solution turned a slight yellow color. NMR from both methods resulted in the same spectrum. ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 3H, CH_3), δ 1.81 (s, 3H, CH_3), δ 2.42 (s, 3H, CH_3), δ 1.9 (dd, 2H, CH_2), δ 2.3 (m, 2H, CH_2), δ 2.42 (s, 3H, CH_3), δ 2.56 (dd, 1H, CH), δ 4.78 (s, 1H, C=CH_2), δ 4.80 (s, 1H, C=CH_2), δ 6.15 (d, 1H, C=CH), δ 7.2 (s, 1H, NH), δ 7.6 (dd, 4H, Ph)
A suspension of (14) (2.35g, 7.4mmol) in tetramethylethylenediamine (71ml, 0.1M) was in a round bottom flask and sealed under nitrogen. Methyl lithium in 1-2M ether (10ml, 15.4 mmol) was added drop wise to suspension at 0°C. After 2ml added, solution became homogeneous. Solution turned colors

yellow, orange, to finally dark red. Solution stirred at room temperature overnight under nitrogen. Solution was cooled to -30°C and quenched with water then extracted with pentane. Solution turned from dark red to yellow. Organic layer was washes with 3M NaOH, 1N HCl, water and brine then finally dried $MgSO_4$. Short path distillation was attempted to concentrate solution but no solid was produced. NMR was non-conclusive.

Shapiro Reaction with MTBE[22]

A solution of *p*-toluenesulfonylhydrazide (12.29g, 66mmol) in methanol (330 ml) and the added R-(-)-carvone (5.16ml, 33mmol) was prepared the same way as described in "Shapiro Reaction with TMEDA." A suspension of (14) (1.05g, 3.3mmol) in tert-butyl methyl ether (33ml, 0.1M) was stirred at room temperature under nitrogen. A 1.5M solution of Methyl lithium as a complex with LiBr in diethylether (6.67ml, 9.90mmol) was added drop wise via a syringe. Solution became homogeneous then change colors from dark orange to light orange. The reaction was stirred at room temperature for 1 hr. then cooled to 0°C before quenched with water. There was large release of gas and solution turned to white. Product was extracted with MTBE, and washed with water. Organic layer was tried over $MgSO_4$. Solution was placed on the rotavap, but solvent not removed to dryness. ^{1}H NMR ($CDCl_3$): δ 1.78 (d, 6H, CH_3), δ 2.25 (m, 1H CH), δ 2.9 (dd, 2H, CH_2), δ 4.76 (s, 1H, C=CH_2), δ 4.78 (s, 1H, C=CH_2), 5.53 (m, 1H, C=CH), δ 6.75 (m, 2H, CH=CH). Impurities: δ 5.06 (s), δ 5.37 (s), δ 7.3 (d, Ph) Purification was attempted by short column and distillation, but these lead to atomization.

Hydroboration of Carvone[23]

A solution of R-(-)-Carvone (3.45ml, 22mmol) in tetrahydrofuran (10ml) was sealed in a round bottom flask, flushed with nitrogen, and cooled to 0°C. A 0.5 M solution of 9-BBN (9-borabicyclo[3.3.1]nonane) in tetrahydrofuran (45ml, 22mmol) was added drop wise through a pressure equalizing addition funnel to a stirring solution for 1 hr. Solution was stirred for an additional hour after 9-BBN was added at 0°C, then stirred for 2 hrs at room temperature. Solution was rotavap to produce a concentrated pale yellow

solution. ^{1}H NMR taken in $CDCl_3$ shows both starting material and the apparent product. Because THF is overwhelming and the solvent could not be removed to dryness, it's difficult to assign peaks. However, the shift of peaks from the starting material indicates that Hydroboration did occur.

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