# SYNTHESIS OF WATER SOLUBLE CATLAYSTS FOR THE ENANTIOSELECTIVE HETERO DIELS ALDER REACTIONS

A Thesis Proposal

by

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ABSTRACT

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A catalyst will be designed, synthesized, purified, and characterized and used to catalyze the Hetero Diels Alder reaction wherein specific stereoisomers will be produced. NMR spectroscopy will be used to determine purification of product. The enantioselectivity and reaction conditions will be determined as well as percent yield. Spartan, a modeling software, will then be used to provide quantitative data over the molecular structure of the Diels Alder reaction.

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# Chapter 1

# INTRODUCTION

## 1.1 Hetero Diels-Alder Reaction

The Diels-Alder reaction is an organic chemical reaction. This reaction usually occurs between a conjugated diene and a substituted alkene that is also called the dieneophile, to form a substituted cyclohexene system. Otto Paul Hermann Diels and Kurt Alder originally first described the Diels-Alder reaction and earned the Nobel Prize in Chemistry.[1] This kind of reaction is especially useful in synthetic organic chemistry as a way for producing 6-membered systems with good control over stereochemical properties.[2]

## 1.2 Chirality

A chiral molecule is a type of molecule that has a non-superimposable mirror image, meaning when the molecules are placed next to each other they are not identical. Having an asymmetric carbon atom as a feature is usually what causes molecules to be chiral. Achiral objects (not chiral) however, are identical to their mirror image. Chirality is a property of matter found all through biological systems, starting from the basic building blocks of life such as amino acids, carbohydrates, and lipids of the human body. An example of chirality is human hands. No matter which way you orient your left and right hands with your palms facing outwards, it will never be possible for both hands to have the same fingers on the same side so the left hand is a non-superimposable image of the right hand.[3] Shown in figure 1 is an example of chirality.

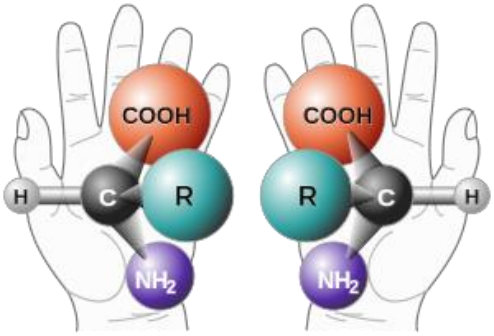


Figure 1. Chirality

Stereoisomers are isomeric molecules that have the same molecular formula and constitution, and their atoms are bonded in the same sequence, but their three-dimensional orientations of their atoms in space are different. Figure 2 demonstrates an example of a pair of stereoisomers.

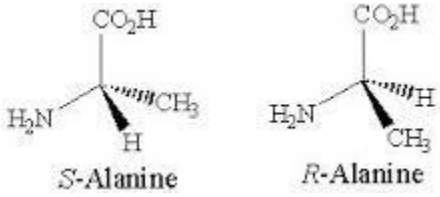


Figure 2. Stereoisomers

Enantioselective synthesis is the synthesis of a compound by using a procedure that favors the formation of a specific enantiomer (one of two stereoisomers that are mirror images of each other and are non-superimposable), or diastereomer (stereoisomers of a compound that have different configurations at one or more of the equivalent stereocenters and are not mirror images of each other). An enantiomeric pair has two molecules that have the same chemical composition and are also drawn the same way in 2 dimensions, however, they can behave very differently in the body and can cause terrible side effects. Because molecules have different enantiomers or diastereomers and the biological activity is very different, enantioselective synthesis is very important in the field of pharmaceuticals. [4,5,6] Shown in Figure 3 are a few examples of enantiomers that are produced through each reaction.

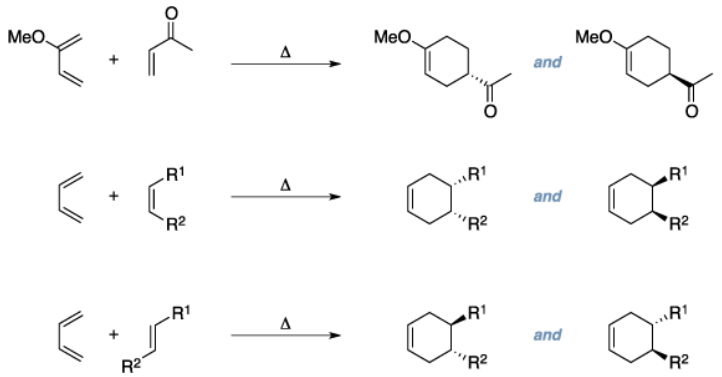



**Figure 3.** A pair of enantiomers are produced through each reaction.

### 1.3 Chiral Drugs in Biological Systems

In an achiral environment, enantiomers of a chiral drug can have identical or similar chemical and physical properties, however, in a chiral environment, one enantiomer may have a chemical and pharmacological behavior that is different than the other enantiomer. This means that when a patient takes the R-enantiomer of a drug, it might not act the same way in the body as the S-enantiomer of the same drug. From this knowledge, it is appropriate to treat the two enantiomers of a given chiral drug as two separate drugs with properties that are not the same unless proven otherwise. Figure 4 illustrates the difference between two enantiomers of a drug using a hypothetical interaction between a chiral drug and its chiral binding site.

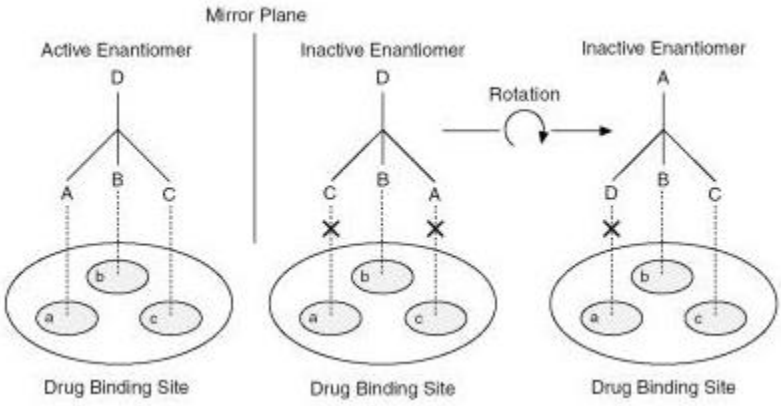



**Figure 4.** Active enantiomer and non-active enantiomer interactions with the binding site.

In this case one enantiomer is biologically inactive while the other enantiomer is active. In order for the drug to have its pharmacologic effect, the portions of the drug labeled A, B and C must interact with the corresponding regions of the binding site labeled a, b and. The active enantiomer of the drug has a 3-dimensional structure that can be aligned with the binding site to allow A to interact with a, B to interact with b and C to interact with c. In contrast, the inactive enantiomer cannot bind in the same way no matter how it is rotated in space. Although the inactive enantiomer has all the same groups A, B, C and D as the active enantiomer, they cannot all be simultaneously aligned with the corresponding regions of the binding site. [7]

**1.4 Catalysis**

Catalysis increases the rate of a chemical reaction by adding a substance into a reaction of two or more reactants called a catalyst, and are often used to give one enantiomer over another enantiomer for chiral reactants. During a reaction, the catalyst is not used up or consumed by the reaction in any way. A catalyst works by lowering the activation energy so that the reactants can cross the barrier to become products. The pH or temperature may either reduce or increase the catalytic activity depending on how high or low they are.[8]

Organocatalysis is one type of catalyst and is advantageous because of their smaller molecular weights and the cost to synthesize is relatively lower compared to the cost of synthesizing other catalysts. They are also stable in most solvents and air and do not involve the use of toxic metals. The ready availability of these organocatalysts also benefit the productions of pharmaceutical intermediates.[9]

Proline has been used as a catalyst and water or ionic liquids can be used as its solvent because of its poor solubility in organic solvents. Using water as a solvent in proline as well as in any catalytic asymmetric reaction is very beneficial because water is a green solvent, meaning

it does not generate hazardous substances, and it is easily accessed. It is also nontoxic as well as nonflammable. Water was first believed to decompose the desired product, however, through many reactions, Breslow discovered that water enhances the performance of the Diels-Alder reactions. After this discovery, water became known as a useful solvent in organic chemistry.[10]

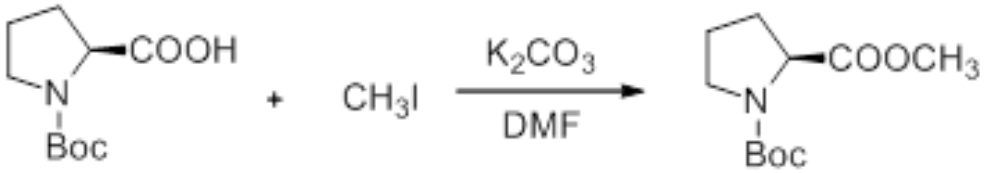
## Chapter 2

## Proposed Work

### 2.1 Synthesis of Catalyst

#### 2.1.1 (S)-1-*tert*-butyl 2-methyl pyrrolidine 1,2-dicarboxylate Synthesis

$K_2CO_3$ (6.41g) will be added to solution of N-boc-L-proline (23.2 mmoles, 5.0g) in dimethylformamide (DMF; 16 mL) and will be stirred for 30 minutes. Carefully, methyl iodide (2.17 mL) will be added drop wise and the reaction will sit overnight. Using ethyl acetate, the product will be extracted and dried over anhydrous potassium sulfate. Using column chromatography, product will be purified using a ration of hexane: ethyl acetate (9:1). The finishing product should be a colorless or yellow oil.[11]



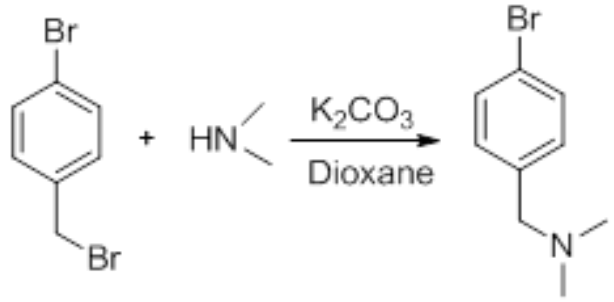

**1** **2**

Scheme 1. Synthesis of Compound 2

#### 2.1.2 1-(4-bromophenyl)-N,N-dimethylmethanamine

Place a solution of 4-bromobenzylbromide (40 mmoles, 10g) in 1, 4-dioxane (30mL) in an ice bath and add potassium carbonate ($K_2CO_3$) (6.6g) and dimethylamine drop wise (18mL) in an ice

bath. The reaction will be stirred for 24 hours at 60°C. Next, using ethyl acetate, extract the product and then use column chromatograph for purification. (hexane: ethyl acetate 10:1) The product will be a yellow/colorless oil.

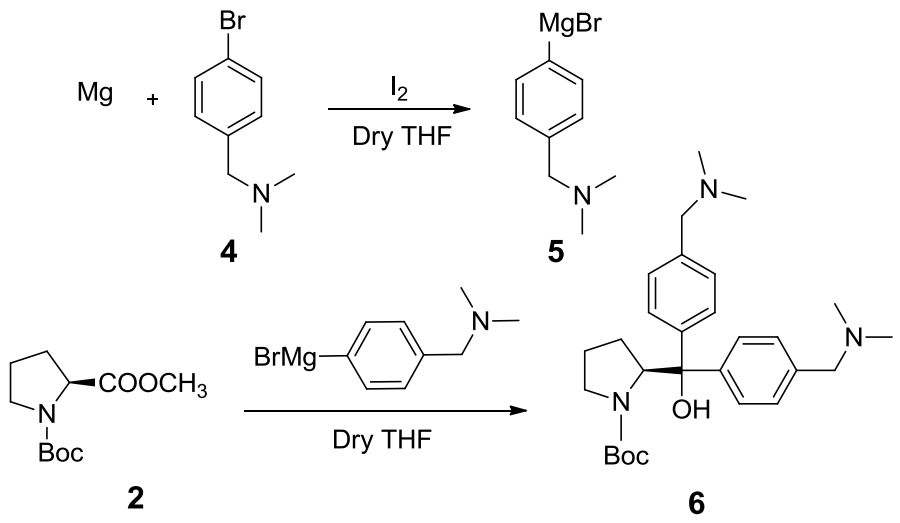



3 4

Scheme 2. Synthesis of Compound 4

### 2.1.3 Grignard Reaction

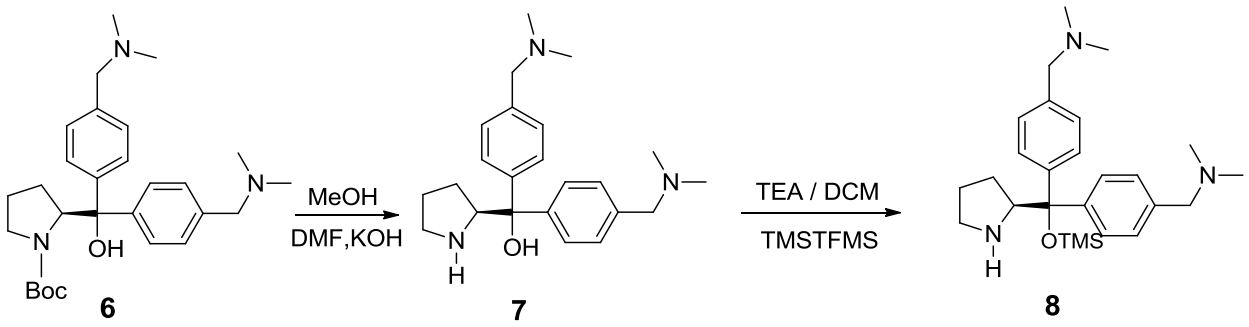
Polish and cut Magnesium (205mmol, 5g) into very fine, small pieces. Add dry tetrahydrofuran (THF, 25 mL) and one small iodine crystal. Then, a solution of 1-(4-bromophenyl)-N,N-dimethylmethanamine (14 mmol, 3.0g) in the solvent, dry THF (5 mL) , is added drop wise. After this is completed, reflux it for about 3 hours and allow it to cool to room temperature. After this is completed add (S)-1-*tert*-butyl 2-methyl pyrrolidine 1,2-dicarboxylate (5.29mmol, 1.14g) in dry THF (5 mL). Allow the reaction to sit overnight and then quench the reaction with saturated ammonium chloride ($NH_4Cl$, 3 mL). Extraction is then done by ethyl acetate. Lastly, column chromatography is applied to the product to purify it (hexane: ethyl acetate 9:1)




Scheme 3. Synthesis of Compound 6

### 2.1.4 Removal of Boc-Protection and Substitution by TMS

Add the product from step 3, dry methanol (10 mL), dry dimethyl sulfoxide (30mL) and potassium hydroxide (50 mmol, 2.8g). Allow the reaction to stir overnight at 60°C. Afterwards, quench it with distilled water, allow it to cool down to room temperature, and use hexane for extraction. Allow the product to dry in the desiccator for 2 days and then dissolve it in anhydrous dichloromethane (25 mL). Add triethylamine (1.04 mL) and cool reaction to 0°C. Next, add trimethylsilyl trifluoromethanesulfonate (7.5 mmol, 1.3g, 1.1 mL) drop wise, then stir reaction for about 5 hours. Use column chromatography (triethylamine: ethyl acetate 1:19) to purify the product. [12,13]




Scheme 4. Synthesis of Compound 8

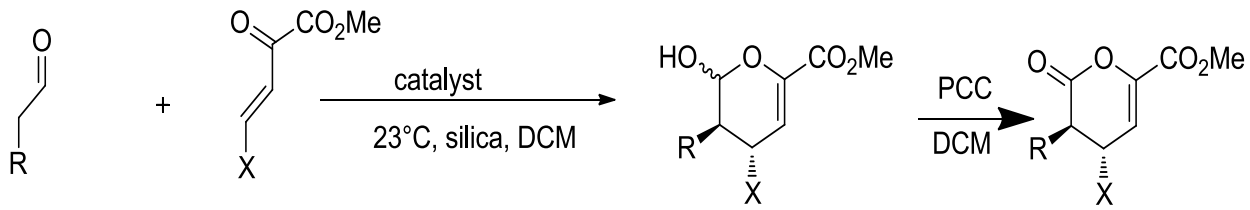
### 3. Synthesis of Enone for Diels Alder Reaction

Add a solution of potassium hydrate (24 g, 0.429 mol) in 75 mL of methanol to a solution of pyruvic acid (20 mL, 0.286 mol), and substituted or unsubstituted benzaldehyde (0.286 mol) in 15 mL of methanol stirring in an ice bath. Add 50 mL of base solution slowly and keep the reaction temperature below 25˚C. Remove the ice bath and add the rest of the base solution quickly. Yellow precipitate will form. Keep the reaction temperature at 30˚C for one hour and then at zero overnight. Filter the yellow crystals and wash twice with cold methanol and once with ether. Air dry the yellow crystals to afford the potassium salt.

Add 24 mL of acetyl chloride to 140 mL of methanol in a 3-necked round bottom flask at zero to generate hydrochloric acid. Add potassium salt (0.1 mol) and stir for 30 minutes; then remove the ice bath. Reflux the mixture overnight after 2 hours. Evaporate the reaction mixture and extract the yellow solid with 50 mL of water two times with 50 mL of dichloromethane. Wash the combined organic phases with 50 mL of saturated sodium carbonate and then 50 mL of water. Dry with anhydrous potassium sulfate and evaporate. The yellow crystals will be obtained by recrystallization from methanol or enthanol.

### 4. Diels Alder Reaction Using Catalyst

The synthesized catalyst will be used in the Hetero Diels-Alder reaction to produce specific enantiomers.




*R = various alkyl groups*
*X = different aromatic groups*

Scheme 5. Synthesis of Diels Alder Reaction with Catalyst

## 5. Computational Analysis of Diels Alder Reactions Using Spartan

Spartan from Wavefunction is a general purpose modelling software that uses modern computational methods to provide researchers with quantitative data on a molecular structure, energy, reactivity, selectivity and a wide range of molecular properties. Quantum chemical calculations have been used to provide detailed information about mechanisms and how products are distributed in chemical reactions just by calculations or in transition states. Spartan is made to provide a great amount of different graphical models with a selection of density functional models. It is designed to reduce the possibility of human error as well as to guide the interpretation of output. The products of the Diels alder reaction will be computed into Spartan to determine the lengths between each atom, the bond angles, and the properties of each molecule.

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