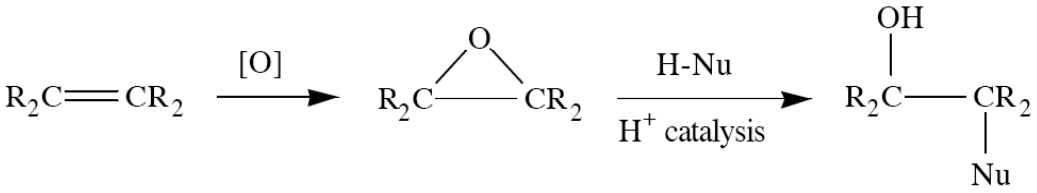
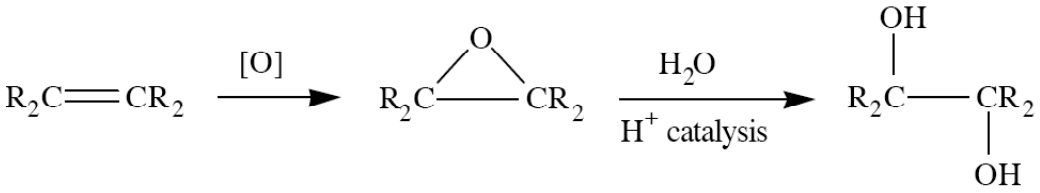
Experiment #3: *Asymmetric Synthesis – The Use of a Chiral Manganese Catalyst for the Enantioselective Epoxidation of Alkenes*

INTRODUCTION

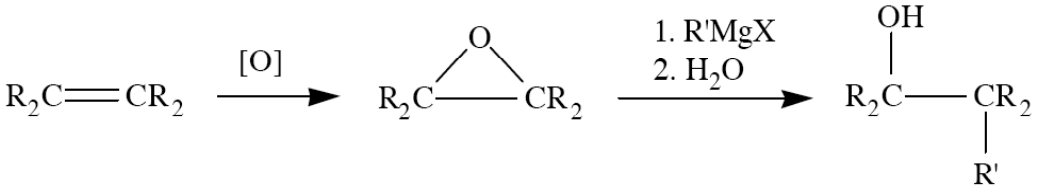
Chemists have discovered and developed many elegant and synthetically useful transformations of carbon-carbon double bonds. One important class of reactions involves the oxidation of olefins (or alkenes) to epoxides, which serve as synthetic intermediates towards a wide variety of oxygen-bearing functionalities.[1] For example, epoxides react with strong nucleophiles (*e.g.* RS^- , RSi^-) under basic conditions and even weak nucleophiles (*e.g.*, H_2O) will react under acidic conditions with opening of the epoxide ring.



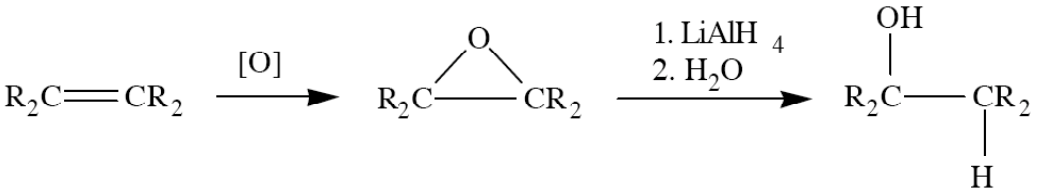
Hydrolysis in dilute mineral acid is a widely used method for the preparation of (*trans*)-1,2-diols from alkenes.



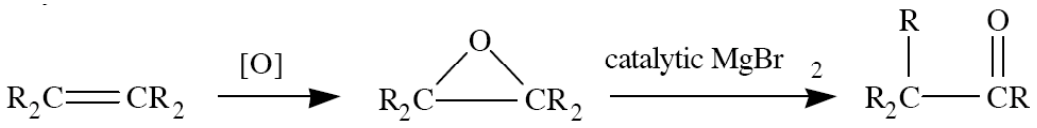
Reactions with carbon nucleophiles such as Grignard reagents and organocuprates lead to ring opening and carbon-carbon bond formation.



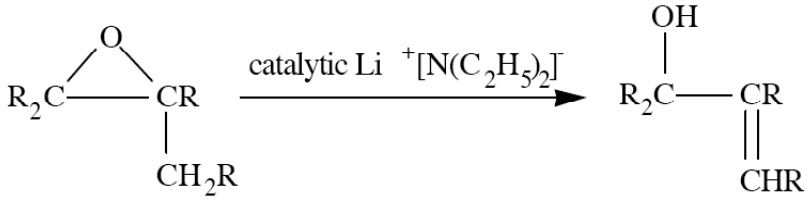
Reductions using aluminum-hydride reagents afford alcohols.



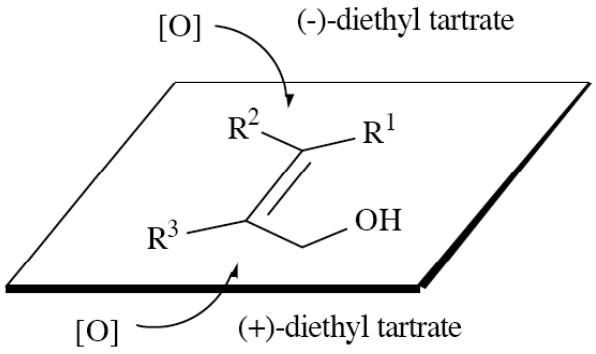
In addition, epoxides undergo Lewis acid-catalyzed rearrangements to carbonyls,



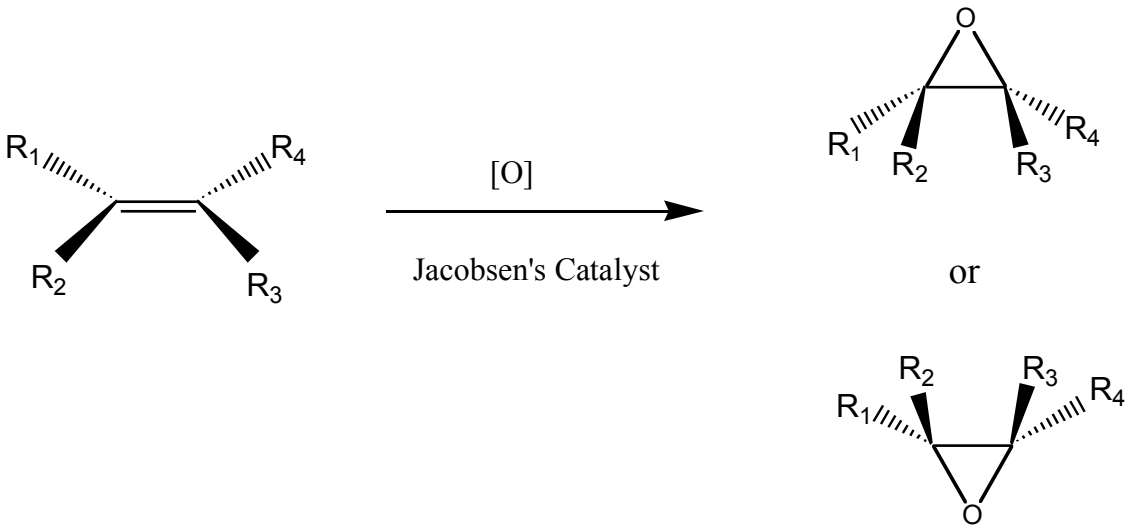
and base catalyzed rearrangements to allylic alcohols.



Traditionally, olefin epoxidations have been accomplished using a variety of peroxy-acids. Since the early 1980's, however, a number of effective transition metal-based catalyst systems have been developed that have significantly extended the scope of these reactions by allowing ***enantioselective*** oxygen transfer to form asymmetric epoxides. The most prevalent of these systems has been the oxidation of prochiral allylic alcohols (which uses *tert*-butyl hydroperoxide in the presence of titanium tetra(isopropoxide) and either (+)- or (-)-diethyl tartrate) to give asymmetric epoxides in high enantioselectivities and yields. This method was developed by K. Barry Sharpless and co-workers (now at Scripps Research Institute) and is commonly referred to as the "Sharpless asymmetric epoxidation". The high enantioselectivity of this reaction is attributed to pre-coordination of the alcohol functional group to the titanium center, which serves to orient the face of the incoming double bond. As such, this reaction is only effective for allylic alcohols, *i.e.*, functionalized alkenes.

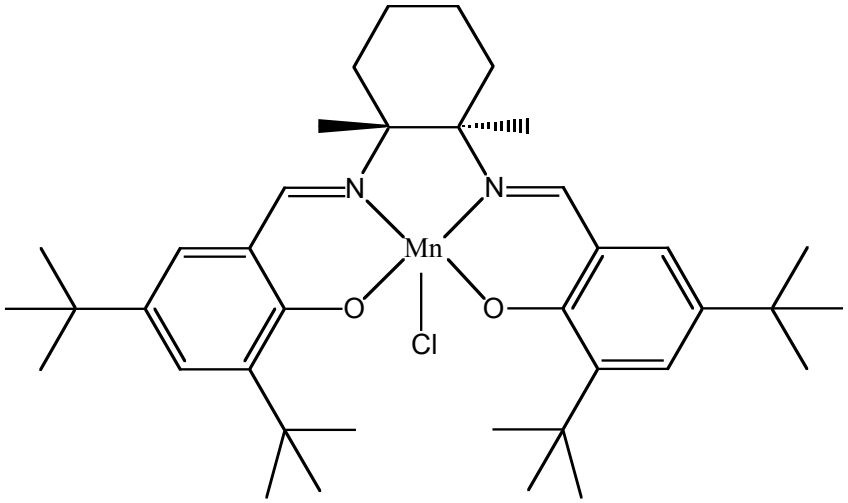


In 1990, Eric N. Jacobsen and co-workers (now at Harvard University) published the first of several important papers on the enantioselective epoxidation of ***unfunctionalized olefins*** catalyzed by chiral manganese complexes.[2] The general reaction is that shown below:



In Jacobsen's systems, the stereoselectivity relies solely on nonbonded interactions, thus lifting the requirement for a pre-coordinating pendant group (such as the alcohols above). In fact, alkyl- and aryl-substituted olefins react with Jacobsen's systems to give the highest enantioselectivity yet realized for nonenzymatic catalysts.

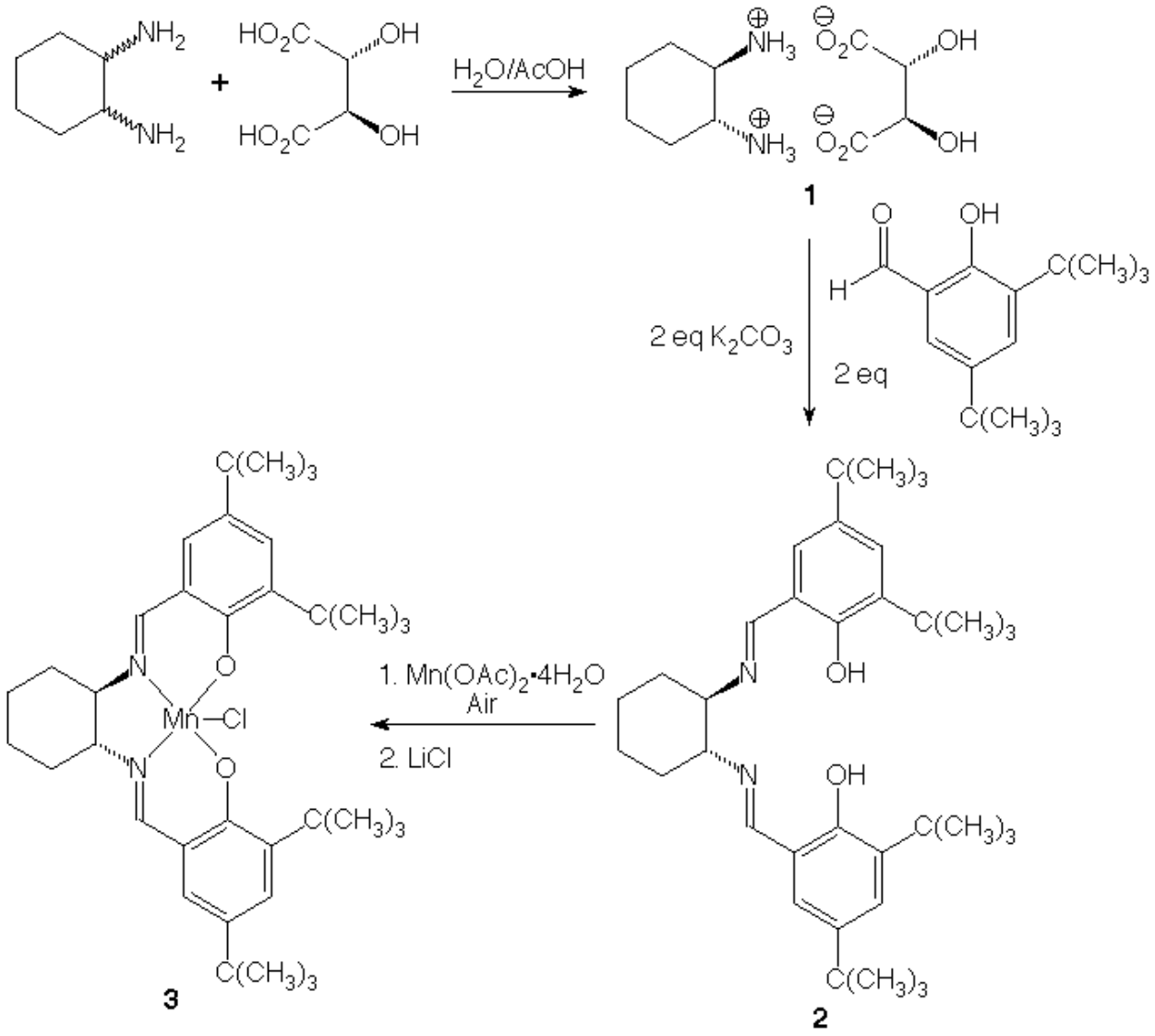
This Chem 346 laboratory experiment involves the synthesis of and experimentation with the most successful catalyst among the many manganese catalysts that Jacobsen and co-workers investigated. The catalyst, now commonly known as Jacobsen's Catalyst has the following structure:



For this extremely useful compound, Eric Jacobsen was awarded the 1994 Fluka Prize for Reagent of the Year. The Fluka Prize is awarded annually for a new compound that

has been shown to be “a reagent of prime importance, useful in organic chemistry, biochemistry, or analytical chemistry.”

Jacobsen’s Catalyst can be prepared in three steps according to reactions shown in Scheme I.

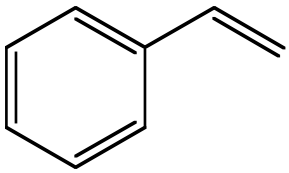


Scheme I

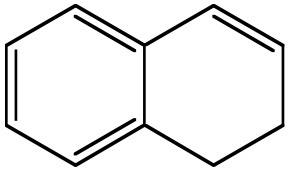
One of the highly attractive aspects of Jacobsen’s Catalyst is that it can be synthesized easily from readily available, low cost starting materials. The first step is a chiral resolution of (*R,R*)-1,2-diaminocyclohexane from a mixture of *cis* and *trans* isomers of the diamine. This is accomplished by using *L*-(+)-Tartaric acid to form diastereomeric salts of the diamine. The relatively low aqueous solubility of the salt of the *R,R* diamine allows it to be crystallized in high enantiomeric purity. In the second step, the tartrate salt of (*R,R*)-1,2-diaminocyclohexane is reacted with two molar equivalents of 3,5-di-

tert-butylsalicylaldehyde to form the diimine (Schiff base). Finally, reaction of the diimine, **2**, with manganese (II) acetate in the presence of lithium chloride and atmospheric oxygen forms [(*R,R*)-*N,N'*-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminato(2-)] manganese (III) chloride.

You will work in pairs and each student pair will investigate the epoxidation of one of the following alkenes using the Jacobsen's Catalyst they prepared. The enantiomeric selectivity of the epoxidation reaction will be determined by gas chromatography (GC) analysis of the resulting epoxide using a chiral GC column. Each group will share the results of their analysis with the other groups.



Styrene



1,2-Dihydronapthalene

Molecular models are extremely useful in the study of reactions of this type. Physical models allow the researcher to visualize various approaches and specific orientations that the alkene can adopt relative to the catalyst as the epoxidation takes place. Each pair of students will build a molecular model of the catalyst and the alkenes being investigated. You should use the models to make predictions regarding enantioselectivity with your substrate and to rationalize your observed results. Note: A good time to build the models is during the one-hour reflux period of the ligand synthesis. Include this analysis in your lab report!

EXPERIMENTAL

General. The following catalyst preparation and epoxidation procedures are general and may be scaled to the amount of starting compounds available. All solvents may be used without further purification. All reactions should be carried out in a fume hood, if possible.

A. Catalyst Preparation

Resolution of a chiral diamine – Isolation of (R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate. In a 150 mL beaker, *L*-(+)-Tartaric acid (7.5 g, 0.05 mol) is dissolved in 25 mL of distilled water. The solution is stirred as 11.4 g (12.2 mL, 0.10 mol) of 1,2-diaminocyclohexane (a mixture of *cis* and *trans* isomers) is added slowly in one portion. (Note: The addition of the diamine is exothermic.) The solution is initially cloudy, but complete dissolution is observed within minutes. After dissolution is complete, 5.0 mL of glacial acetic acid is added in one portion. Product begins to

precipitate from solution shortly after the addition, and it continues to precipitate resulting in a thick suspension. The reaction mixture is cooled in an ice/water bath. After sitting for at least 30 minutes in the ice bath, the product is isolated by suction filtration. The solid is washed with 5.0 mL of ice cold water followed by 4 x 5 mL portions of room temperature methanol. The product is purified by recrystallization from hot water. The crude solid is dissolved in a minimum amount of (near boiling) hot water. Any residual solid (or foam) that does not readily dissolve after the bulk of the solid has dissolved is filtered off by gravity filtration of the hot solution. (Note: Use fluted filter paper and a powder funnel.) The solution is allowed to crystallize slowly as it cools to room temperature. The solution is cooled in an ice bath to induce further crystallization. If crystallization does not occur, 1-2 mL of methanol are added to reduce the solubility. The crystalline product is collected by suction filtration. A second crop of crystals can usually be collected by adding more methanol to the filtrate.

Ligand Synthesis – Preparation of (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine. A 100 mL, round bottom flask equipped with a magnetic stir bar is charged with (*R,R*)-1,2-diaminocyclohexane mono-(+)-tartrate salt (1.11 grams, 4.20 mmol), 1.16 grams of potassium carbonate and 6.0 mL of water. The mixture is stirred until dissolution is achieved, and then 22 mL of ethanol are added. The flask is equipped with a reflux condenser, and the cloudy mixture is heated to reflux with a heating mantle. A solution of 3,5-di-*tert*-butylsalicylaldehyde (2.0 grams, 8.50 mmol) dissolved in 10 mL of ethanol (Note: this requires heating carefully on a hot plate) is added through the condenser with a Pasteur pipette. The pipette and beaker are then rinsed with 2.0 mL of hot ethanol. After heating at reflux for one hour, heating is discontinued. Water (6.0 mL) is added and the mixture is cooled in an ice bath and left to stand in the ice bath for 30 minutes. The yellow solid is collected by suction filtration and washed with about 5 mL of ethanol. The solid is dissolved in 25 mL of methylene chloride, and the solution is washed with 2 x 5 mL of water, followed by 5 mL saturated aqueous NaCl. The organic layer is dried over Na_2SO_4, and then filtered (or decanted) to remove the drying agent. The solvent is removed by evaporation to yield the product as a yellow solid that is characterized by mp, IR, and $[\alpha]_D$. The reference melting point is 200-203 °C.

Analysis of the Resolution of 1,2-Diaminocyclohexane by Polarimetry. In order to determine the success of your resolution of 1,2-diaminocyclohexane, you will measure the optical activity of your (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamine. (The Jacobsen ligand that you prepared above.) Weigh accurately 0.5-1.0 g of your Jacobsen ligand and then dissolve it in CH_2Cl_2 to make a final volume of 10 mL (use a volumetric flask). Determine the optical rotation of this solution. (Your TA will demonstrate proper use of the polarimeter.) Calculate the specific rotation for your sample and compare it to the reported value: $[\alpha]_D^{20}$=-315°.

Catalyst synthesis. A 100 mL three-neck flask equipped with a magnetic stirrer and reflux condenser is charged with 1.0 g of (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-

1,2-cyclohexanediamine and 25 mL of absolute ethanol. The mixture is heated to reflux for 20 minutes and then 2.0 equivalents of solid $Mn(OAc)_2 \cdot 4H_2O$ are added in one portion. After refluxing for an additional 30 minutes, the reaction flask is fitted with a gas bubbling tube extending down into the solution and air is bubbled through at a slow rate while continuing to heat at reflux for 1 hour. At this point, the air bubbler tube is removed and 3 equivalents of LiCl are added in one portion. After refluxing for an additional 30 minutes, the heating mantle is removed, the solution is transferred to a 100 mL round bottom flask, and the solvent is removed by rotary evaporation. The crude product is redissolved in 25 mL of dichloromethane and washed twice with water and once with saturated aqueous NaCl. The organic phase is dried (Na_2SO_4) and approximately 30 mL of heptane is added. The dichloromethane (but not the heptane) is removed by rotary evaporation and the brown slurry is cooled in an ice bath for 30 minutes. The brown solid is collected by vacuum filtration and allowed to air dry. The reference melting point is 324-326 °C. The filtrate is evaporated to dryness on a rotary evaporator, and the residue of crude product is saved.

B. Enantioselective Epoxidation Using Jacobsen's Catalyst

General Procedure: A solution of 0.05 M Na_2HPO_4 (5 mL) is added to 12.5 mL of commercial household bleach (Clorox). The pH of the resulting buffered solution (~0.55 M in NaOCl) is adjusted to pH 11.3 by addition of approximately 1 drop of 1 M NaOH solution. The buffered bleach solution is then added to a solution of alkene (0.5 g) and Jacobsen's Catalyst (10 mole %) dissolved in 5 mL of CH_2Cl_2 in a 50 mL Erlenmeyer flask equipped with a stir bar. The flask is capped with a stopper, and the two-phase mixture is stirred vigorously at room temperature. The progress of the reaction is monitored by TLC. (30-40% CH_2Cl_2 in hexane is a good eluent with which to start.) To obtain a TLC sample, turn the stirrer off and let the two phases separate. Use a pipette to remove a drop or two from the lower organic layer. Place this solution in a small sample vial and spot on the TLC plate. Visualize using a UV lamp. When the starting material is gone and the epoxide product is clearly visible (usually within 2 hours), remove the stir bar and add approximately 50 mL of hexane. Separate the brown organic phase, wash it twice with saturated NaCl solution, and dry it (Na_2SO_4). Filter and remove the solvent. The epoxide is purified by dissolving it in a small volume of hexane and passing it through a silica gel micro column. The micro column is prepared by placing a small glass wool plug in the tip of a Pasteur pipette and adding about 5 cm of silica gel (40-60 μm) to the pipette. The hexane solution of the epoxide is transferred onto the micro column and immediately eluted with excess hexane (30-40 mL). After passing through the micro column, the hexane is removed by rotary evaporation to isolate the purified epoxide. The purified epoxide is analyzed by ^1H NMR. Note reference NMR spectra provided for the alkenes and their epoxides.

C. Chiral GC Analysis

We will use a chiral gas chromatography (GC) column to separate and quantify the ratio of enantiomers produced in the Jacobsen epoxidation. In chiral GC analysis the column

contains a single enantiomer of a chiral substance. The two enantiomers of your epoxide interact differently with this chiral substance, and thus elute from the column at different times. The appropriate GC conditions for each epoxide will be labeled on the GC. To prepare your product, make a sample of approximately 10 mg/mL in CH_2Cl_2 and inject 1 μL of this sample on the GC. (Alternatively, you may use your NMR sample in $CDCl_3$ with appropriate dilution.) Be sure to note all important GC parameters for your report.

Some Questions to Consider When Writing Your Lab Report:

1. Elaborate on the statement that the highest ee's should be imparted to *cis*-olefins bearing one large and one small substituent.

2. Would you expect the (*S,S*)-catalyst to give the same or a different enantiomer as the (*R,R)*)-catalyst for a given olefin? Why? What can you expect for the ee's?

3. Considering the %ee results obtained for each alkene, propose an epoxidation mechanism describing the spatial orientation and line of approach of each alkene to the catalyst. Use molecular models to develop and check your mechanism.

REFERENCES

1) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed, Cambridge University Press, New York, NY, section 6.3: "Oxidation of Carbon-Carbon Double Bonds".

2) Zhang, W.; Loebach; J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803, and references cited therein.

3) Larrow, J. L.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939-1942, and references cited therein.

4) Jacobsen, E. N. "Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins" In *Catalytic Asymmetric Synthesis* I. Ojima, Ed.; VCH: New York, 1993.