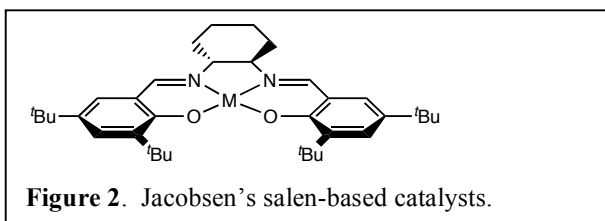
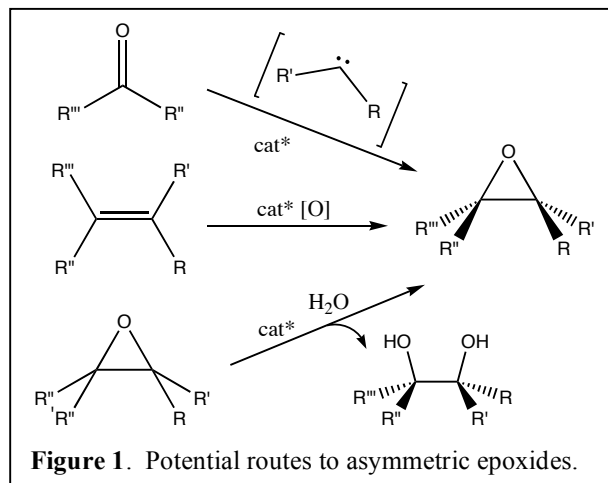


The Hydrolytic Kinetic Resolution – Jacobsen’s Catalyst

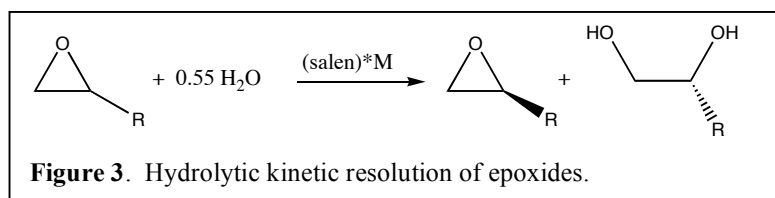
A Cursory Introduction

Enantiomerically pure epoxides are extremely valuable chemical compounds due to controllable but high reactivity of epoxides coupled with the vast array of reactions they can undergo with retention of stereochemical integrity. One can envision a number of direct routes to asymmetric epoxides (Figure 1). Asymmetric carbene addition has never achieved broad applicability due to both the instability of the carbenes, low yields and low enantioselectivities. The most common methods for epoxide formation is controlled addition of activated oxygen to an alkene. For some olefins, this process can be made enantioselective, an achievement for which K. Barry Sharpless was awarded 1/2 of the Nobel prize in 2001. The Sharpless asymmetric epoxidation is restricted to internal olefins with pendent functionality such as an alcohol which helps direct the reaction. In 1990, Jacobsen, fresh of a postdoc with Sharpless and at the beginning of his independent career at UIUC, introduced a system which obviated the use of a directing group, but the enantioselectivities were not phenomenal and yields were not spectacular. Furthermore, terminal olefins were still difficult. Simultaneously and independently, Katsuki (a Sharpless postdoc from ten years prior) revealed a closely related system which suffered the same drawbacks.



makes it a poor choice for industrial processes. Furthermore, the resolution of terminal epoxides remained elusive. Thus the search of a better both a better catalyst and a better nucleophile continued. The hydrolytic kinetic resolution (Figure 3) was discovered due to a fortunate accident. Jacobsen had been working with a reduced form of a chromium-salen complex. Surprisingly, 1,2-epoxyhexane (Figure 3, R = *n*-Bu) proved to be an extraordinarily good substrate. Furthermore, the solid residue isolated from the end of reactions with that substrate worked extraordinarily well to resolve others! Careful investigation led to the discovery that acetic acid, left from the industrial synthesis of epoxyhexane, had served to catalyze

In the mid 1990's, having moved to Harvard, Jacobsen was exploring the use of a variety of metal catalysts all based around a chiral "salen" ligand scaffold (Figure 2). The first breakthrough came with the desymmetrization of *meso* epoxides with Me_3SiN_3 catalyzed by a complex where $\text{M} = \text{CrCl}$ (Figure 3). While it is generally easily controlled on the laboratory scale, the potentially explosive nature of Me_3SiN_3



the air-oxidation of the metal, increasing the activity of the catalyst. At long last, enantiomerically pure terminal epoxides were readily available through a simple two step process – epoxidation of a terminal olefin and selective hydrolysis of one enantiomer of the resulting epoxide. This was an event dramatic enough to warrant publication in *Science*, an extreme rarity for a synthetic methodology.

Jacobsen has proceeded to exploit this ligand framework, and some variations on it, to enantioselectively catalyze a broad range of reactions including an array of nucleophilic epoxide opening reactions, hydrocyanation of aldehydes and imines, conjugate addition of HCN, aldol variations and Diels-Alder variations, to name a few. In fact, the ligand shown in Figure 2 has become known simply as "Jacobsen's ligand". The technologies developed in Jacobsen's lab have been commercialized by Rhodia ChiRex, a joint venture between Jacobsen and global chemical giant Rhodia. The catalysts have been used in many pharmaceutical syntheses and, it sometimes seems, by nearly every synthetic organic chemist alive. Other

researchers too numerous to name have also used these ligands and catalysts in developing other reactions too numerous to count. Truly it is a phenomenal impact for an accidental discovery barely a decade old.

Leading References

Asymmetric Epoxidation:

Gilheany & McGarrigle, *Chem. Rev.* **2005**, *105*, 1563-1602

Sharpless *Angew. Chem. Int. Ed.* **2002**, *41*, 2024-2031 [Nobel lecture]

Jacobsen *et. al.*, *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803

Katsuki *et. al.*, *Tetrahedron Lett.* **1990**, *31*, 7345-3748

Enantioselective Ring Openings/Hydrolytic Kinetic Resolution:

Jacobsen *et. al.*, *J. Am. Chem. Soc.* **1995**, *117*, 5897-5898

Jacobsen *et. al.*, *Science*, **1997**, *277*, 936-938

Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421-431 [the story of the accidental discovery]

Larrow & Jacobsen, *Topics Organomet. Chem.* **2004**, *6*, 123-152 [chiral salen-metal catalysts]

Project Description:

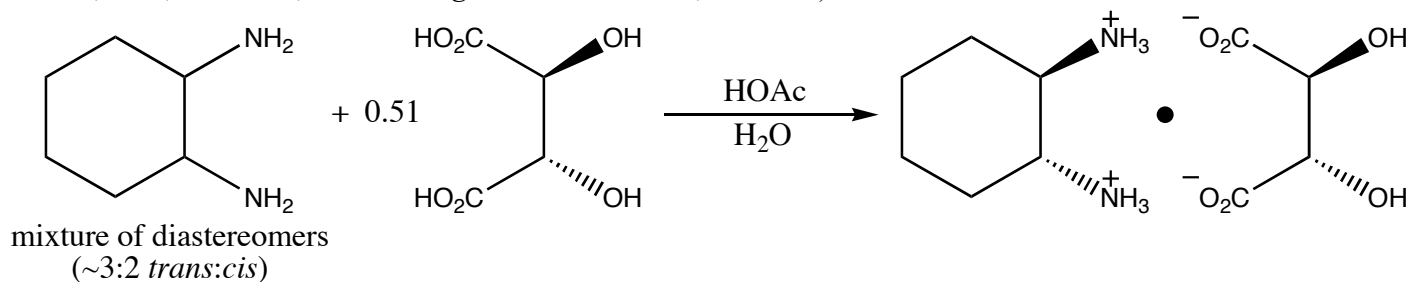
In this project you will build, from the ground up, a highly efficient catalyst for the hydrolytic kinetic resolution (HKR) of epoxides. The ultimate measure of your success will be the enantiomeric purity of the epoxide you resolve. This is a challenging but achievable task and I look forward to celebrating your successes.

Approximate Timeline:

<i>Step</i>	<i>Suggested characterizations</i>	<i>Suggested scale</i>	<i>Approximate time (weeks)</i>	
Resolution & characterization of diaminocyclohexane	m.p., optical rotation, ¹ H-NMR	~20 g tartaric acid	1.5	3 – 4
Ligand synthesis & characterization	¹ H-NMR, m.p., optical rotation	5 g aldehyde	1.5	
Catalyst synthesis & characterization	¹ H-NMR, m.p.?	available ligand	1 – 1.5	5
Resolution & characterization of epoxybutane	¹ H-NMR, GC, optical rotation	~100 ml epoxide	1.5 – 2	

Resolution & Characterization of Diaminocyclohexane

(Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.*, **1994**, *59*, 1939-42)



The first step in this process is to isolate enantiomerically pure (*R,R*)-1,2-diaminocyclohexane as a salt with (+)-tartaric acid. Here are some of the important questions you should be thinking about:

1) The ceiling temperatures of the reaction at each step is the determining factor for enantiomeric purity of the product – how will you control the rate of addition of each compound and how will you try to target the correct ceiling temperatures?

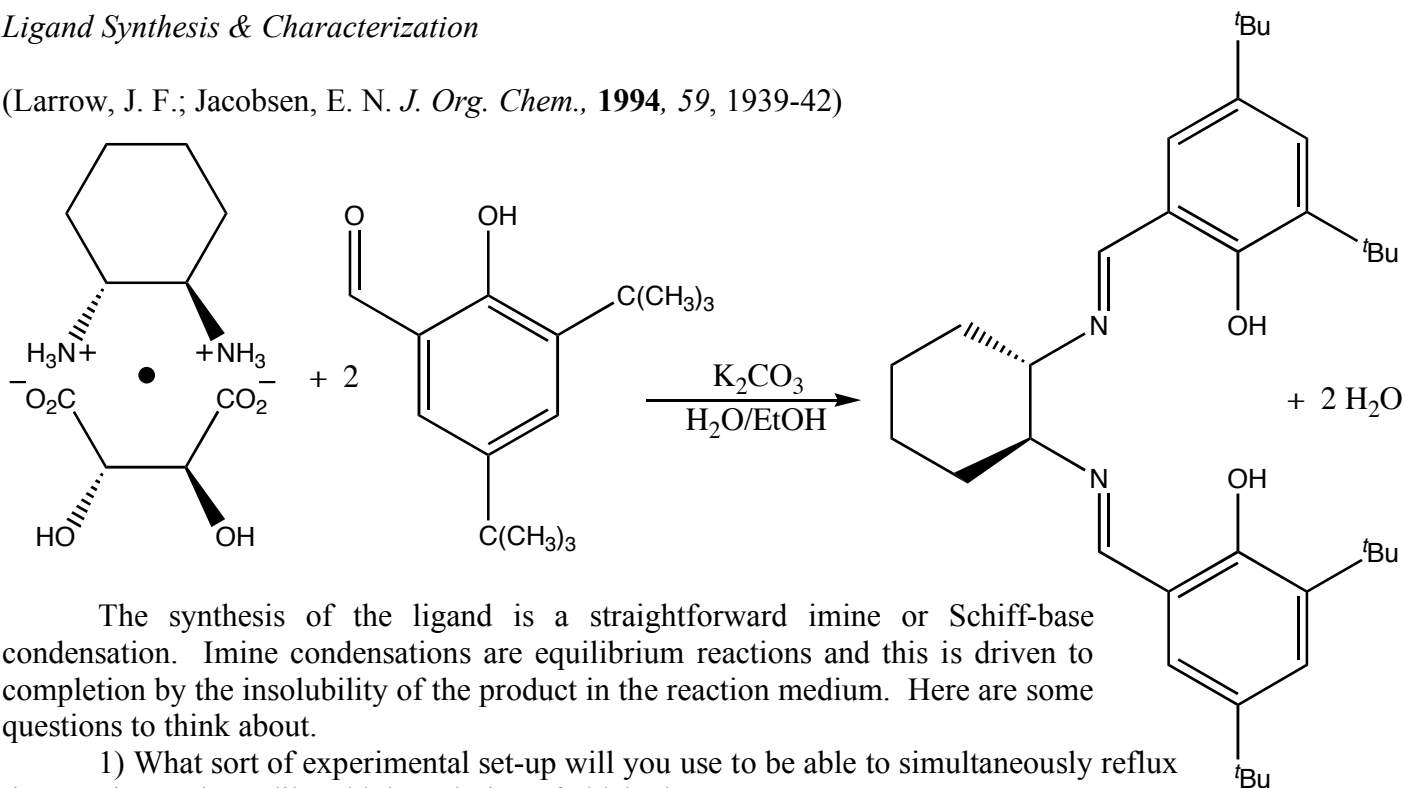
2) Characterization of the product is very important as the enantiomeric purity of this compound is one of only two factors which will determine the enantiomeric purity of a substrate on which the catalyst is eventually used. Where can you find information about the physical properties of this compound?

3) We will not be using the same method as Jacobsen, but rather will attempt to use melting point and optical rotation. Each method of characterization has its own flaws. On what factors does melting point rest? How will you control them as accurately as possible? How about for optical rotation?

Notes:

Ligand Synthesis & Characterization

(Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.*, **1994**, *59*, 1939-42)



The synthesis of the ligand is a straightforward imine or Schiff-base condensation. Imine condensations are equilibrium reactions and this is driven to completion by the insolubility of the product in the reaction medium. Here are some questions to think about.

1) What sort of experimental set-up will you use to be able to simultaneously reflux the reaction and steadily add the solution of aldehyde?

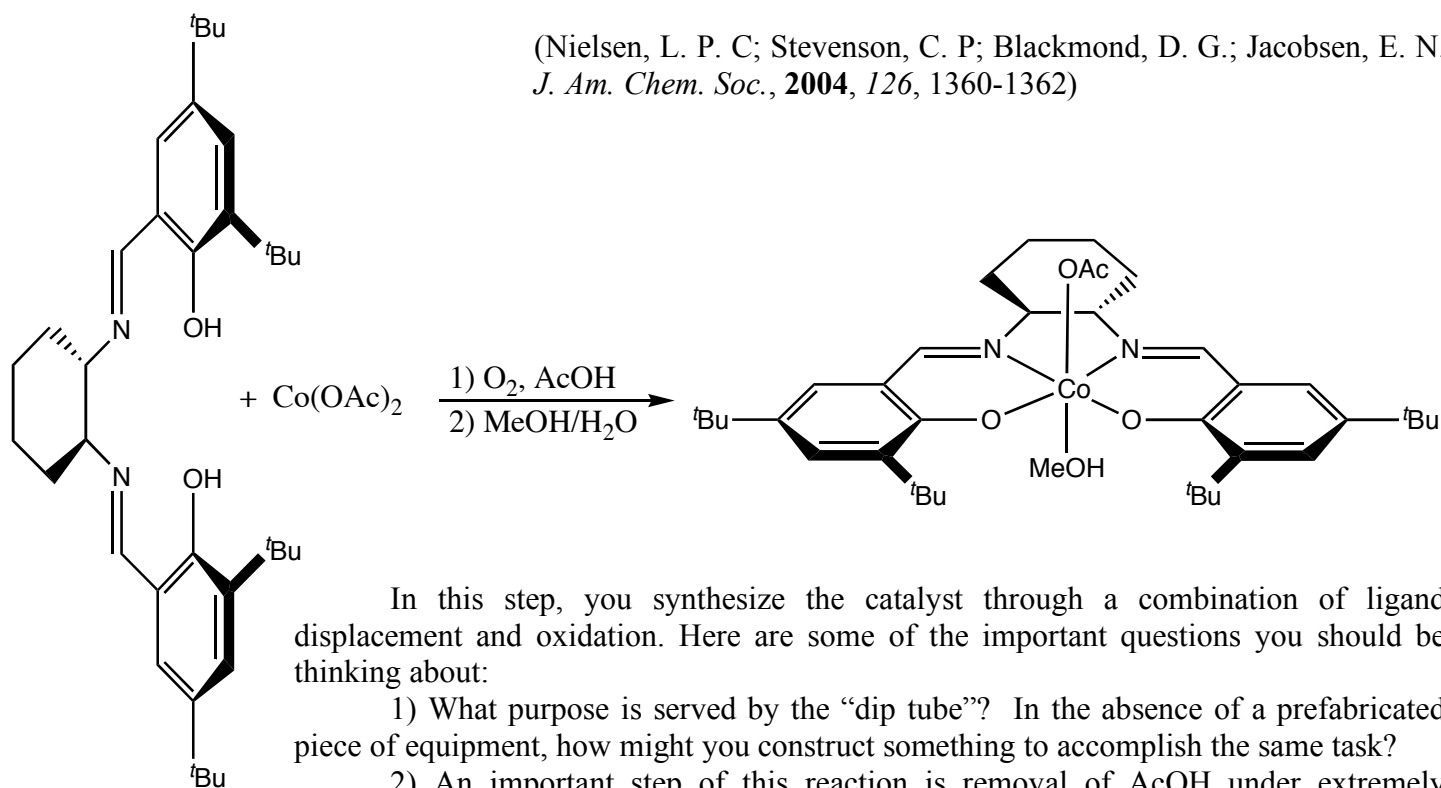
2) The procedure calls for the crude product to be redissolved in CH_2Cl_2 and washed with water and brine. How will you accomplish this?

3) Regarding characterization, the same questions noted above apply.

Notes:

Catalyst Synthesis & Characterization

(Nielsen, L. P. C; Stevenson, C. P; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **2004**, *126*, 1360-1362)



In this step, you synthesize the catalyst through a combination of ligand displacement and oxidation. Here are some of the important questions you should be thinking about:

1) What purpose is served by the “dip tube”? In the absence of a prefabricated piece of equipment, how might you construct something to accomplish the same task?

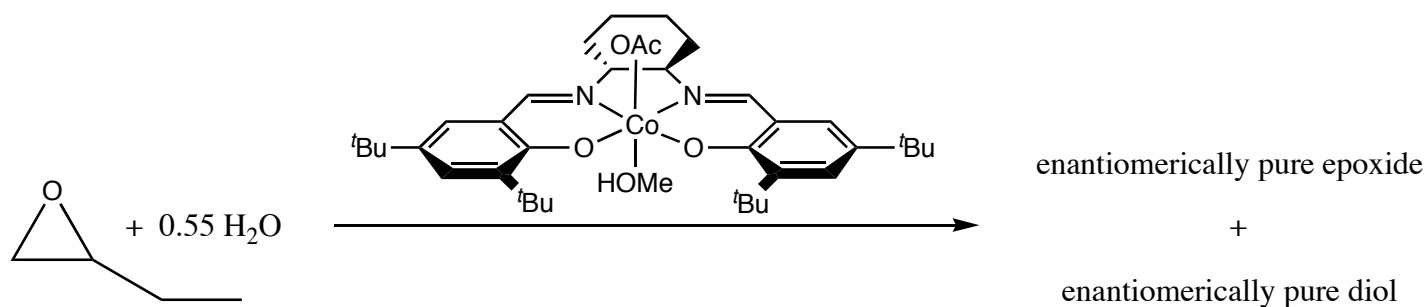
2) An important step of this reaction is removal of AcOH under extremely reduced pressure (“high vac”). What physical hazards might this introduce and how can you minimize them? What dangers does this introduce with respect to yield and how can you minimize them?

3) What is the oxidation state of the metal at the beginning of the reaction and at the end of the reaction? How will the NMR be impacted by the respective oxidation states? How would residual $\text{Co}(\text{OAc})_2$ impact the NMR of the product?

Notes:

Epoxide Resolution & Characterization

(Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936-938)



In this step you will use your hard-won catalyst in the hydrolytic kinetic resolution of 1,2-epoxybutane (α -butylene oxide). In the highly enantioselective, bimolecular rate determining step, the one molecule of catalyst delivers nucleophilic hydroxide to one enantiomer of epoxide bound to another molecule of catalyst yielding an enantiomerically pure diol. The other enantiomer of epoxide is left behind, unhydrolyzed. Here are some questions you should consider.

1) Consider the Arrhenius rate expression. What is the relationship between rate and temperature? Assume that the only difference between reacting with one enantiomer of epoxide versus the other is the activation energy. How does higher temperature impact the difference between relative reaction rates? How does lower temperature impact that difference?

2) How will you accurately measure and control the actual temperature of your reaction as it proceeds?

3) You will purify the desired product by distillation. What other species are in the reaction mixture? What information do you need to know about these species?

4) Sometimes, to make a distillation proceed at lower temperatures, experimentalists will use reduced atmosphere techniques. If the product boils from the distillation flask at lower temperature, it also boils from the receiving flask at lower temperature. What experimental measure can one take to avoid loss of product from the receiving flask?

Notes: