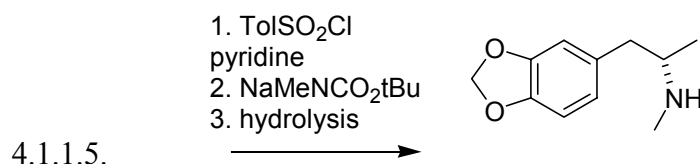
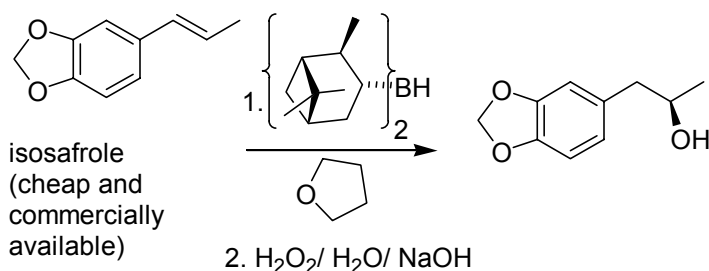
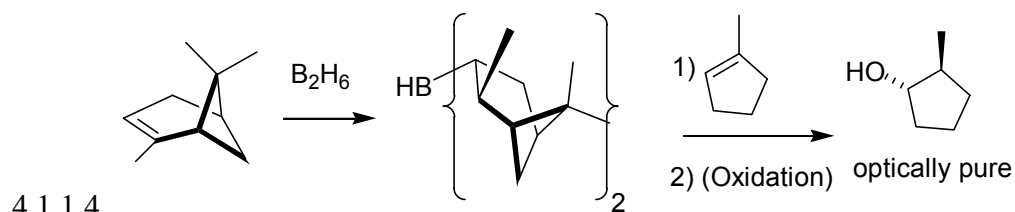


**Alkenes, Important Synthetic Intermediates.**

1. We have discussed the synthesis of alkenes.
  - 1.1. There are many more protocols than the ones we have discussed.
  - 1.2. Some of these you will encounter in your working problems.
  - 1.3. We will discuss more as the semester matures.
  - 1.4. In the synthesis of alkenes one needs to worry about stereocontrol.
    - 1.4.1. Often this is no small task.
    - 1.4.2. We talked about stereocontrol in trisubstituted alkenes and 1,2-disubstituted alkenes.
2. The most important thing to remember regarding stereocontrol and alkene starting materials is: if you can control the stereochemistry in the alkene you can effect from stereocontrol in the product.
  - 2.1. We saw some of this in the discussions of the 3,3-sigmatropic rearrangement, the aldol, the cyclizations, 2,3-sigmatropic rearrangement and the Diels-Alder reaction.
  - 2.2. Keep this in mind as we talk about the reactions of alkenes.
3. Let's now discuss alkenes in the synthetic context in which they are starting materials.
  - 3.1. Where can you go from here?
    - 3.1.1. You can go from flat land achiral to 3D space chiral and/ or polycyclic.
  - 3.2. Many of these reactions should be familiar to you from your previous study of organic chemistry.

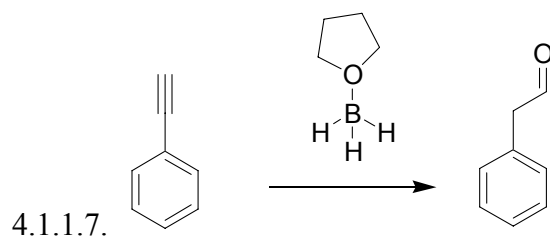




4.1.1.5.1. Hypothetical path above should give ecstasy (*N*-methyl- 3,4-methylenedioxyamphetamine).

4.1.1.5.2. Why should the hydration of the alkene occur with the regiochemistry indicated? The stereochemistry is difficult to predict.

4.1.1.6. Remember that addition of borane to alkynes gives rise to ketones and aldehydes instead of alcohols.

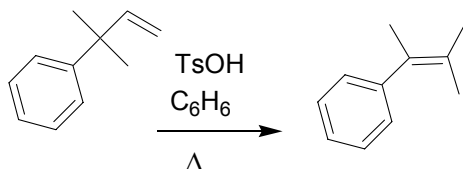


**4.1.2. Markovnikov addition of H<sub>2</sub>O is usually less problematic, Retro 2 in the Figure 1.**

4.1.2.1. Regiochemical problems can arise when R and R<sup>2</sup> are similar.

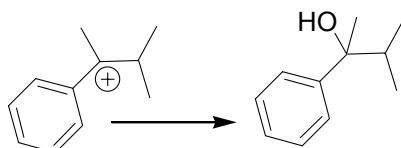
4.1.2.2. If this is attempted with H(+) carbocation rearrangement can dominate the product mixture.

4.1.2.2.1. Sometimes rearrangement is a good thing. Perhaps you are smart enough to plan on the carbocation rearranging to your desired product.



4.1.2.2.2.

4.1.2.2.3. Slightly changing the conditions to more aqueous would give rise to the hydrated material by trapping the carbocation--see below.



4.1.2.2.4.

4.1.3. The cation that forms is the most stable, in this case benzylic and tertiary.

4.1.4. Hopefully in the near future we can talk about syntheses based on carbocation rearrangements. I find this topic fascinating.

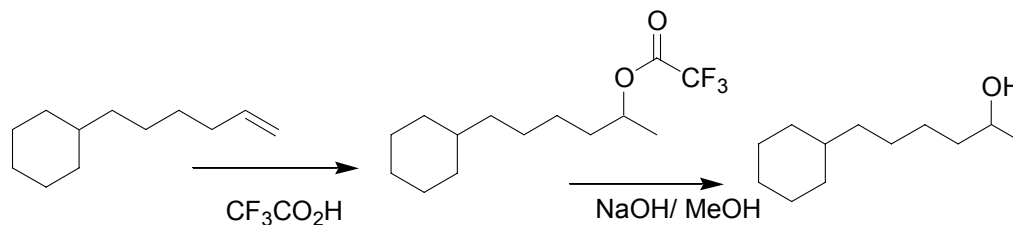
4.1.5. One of the most obvious side reactions of cation based chemistry is polymerization. Usually one can find reaction conditions in which the cation does not polymerize with the starting alkene.

4.1.5.1. Polymer in most of these reactions is usually a side product.

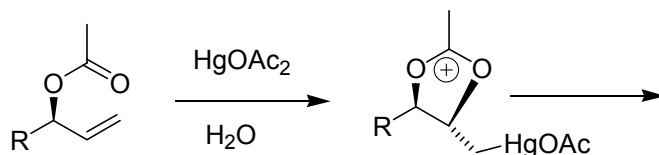
4.1.5.1.1. It happens most often when the cation is stable.

4.1.5.1.2. Polystyrene for example is a very easy polymer to make under acid catalyzed conditions.

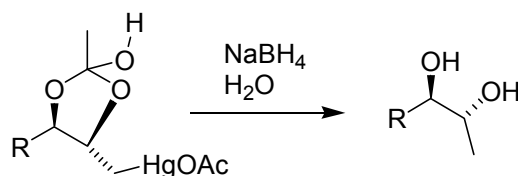
4.1.5.2. Trifluoroacetic acid reacts with the plain vanilla alkene under fairly mild conditions. This followed by saponification under basic conditions results in net addition of H<sub>2</sub>O across the double bond.



4.1.6. Oxy-mercuration is ugly and out of respect for mother earth should only be planned on small scale when not other protocol meets the need.



4.1.7.



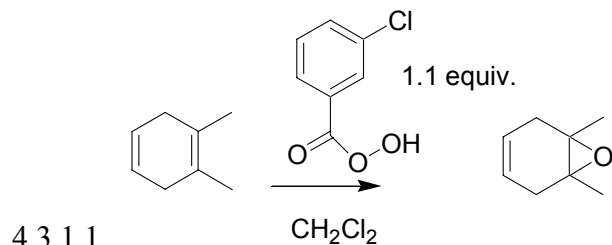
**4.2. Retro 3 (FIG 1) is trivial and is discussed quite a bit in organic one and two.**

4.2.1. Bromohydrins and 1,2-dibromoalkanes are readily available.

4.2.2. There is quite a bit of evidence for the epibromonium ion intermediate.

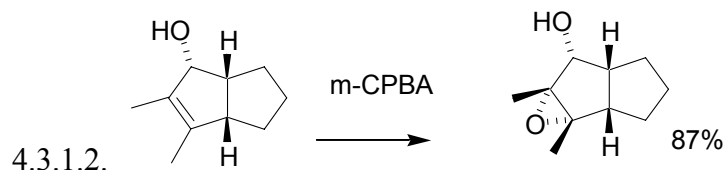
**4.3. Retro 4 (FIG 1) can be accomplished via peroxyacids.**

4.3.1. This protocol gives rise to epoxides, as we have seen; these are important intermediates in organic synthesis.



4.3.1.1.

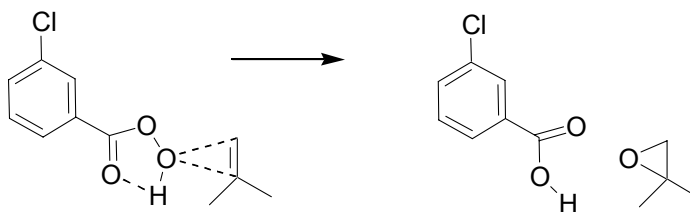
4.3.1.1.1. Why does one double get epoxidized preferentially?



4.3.1.2.

4.3.1.2.1. Alcohols tend to direct the delivery of the oxygen atom, the Henbest effect.

4.3.1.3. Mechanism



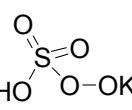
4.3.1.3.1.

4.3.1.3.2. transition state has no intermediates


4.3.1.3.3. delivery of oxene

4.3.1.3.4. We have discussed the chemistry of C, N, O carbene, nitrene and oxene. Isoelectronic.

4.3.1.4. Other reagents capable of epoxidizing alkenes are

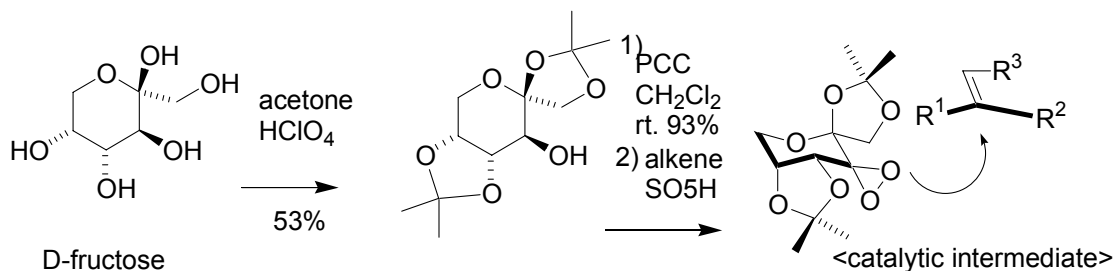
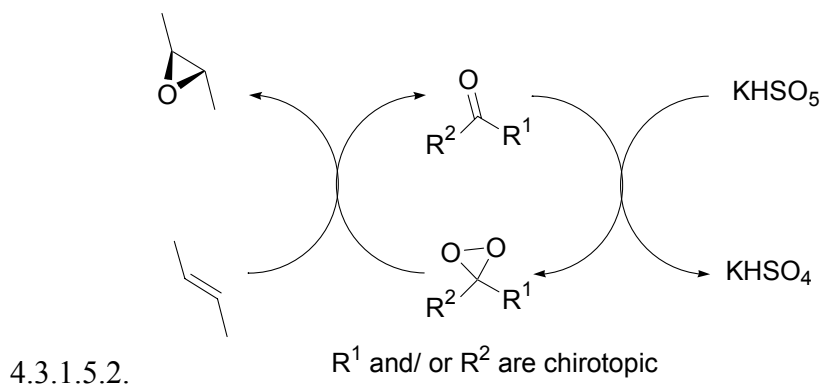
4.3.1.4.1.  Oxone, potassium peroxyhydrogen sulfate

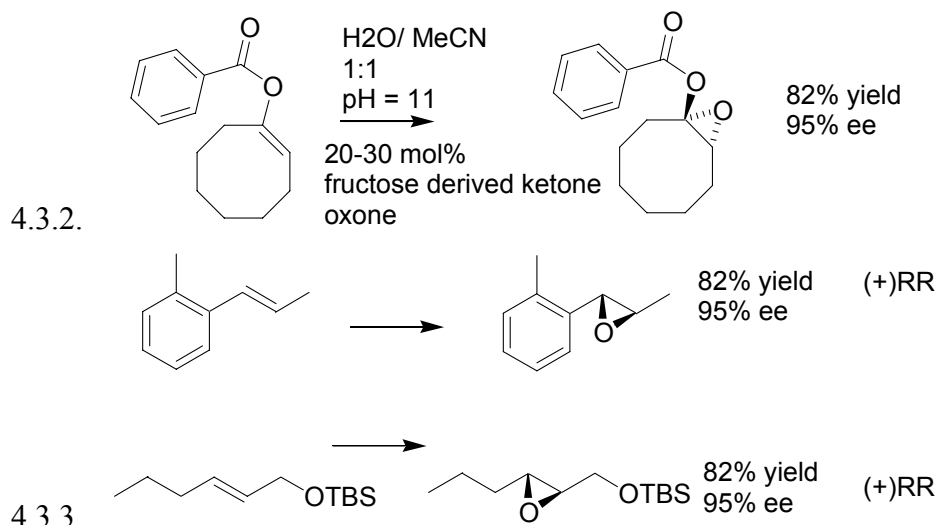
4.3.1.4.2. and peroxytrifluoromethylacetic acid.

4.3.1.4.3. and dimethyldioxirane 

4.3.1.5. Using oxone and a chiral ketone subject to electron withdrawal alkene can be epoxidized.

4.3.1.5.1. Frohn, M.; Shi, Y. "Chiral ketone-catalyzed asymmetric epoxidation of olefins." *Synthesis* **2000**, 1979-2000.





4.3.3.1. Epoxides are important intermediates in the synthesis of complex organic molecules.

4.3.3.1.1. The nucleophilic ring opening in Figure 1 alludes to this utility.

4.3.3.1.2. Usually one needs a Lewis acid as well as a good nucleophile to open epoxides.

#### 4.4. What are the advantages of using the ketone catalytically?

4.4.1. Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259-281.

4.4.2. Atom economy (below from Wikipedia)

4.4.2.1. Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. In an ideal chemical process the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. Atom economy can be written as:

4.4.2.2.  $\% \text{ atom economy} = \frac{\text{MW (desired products)}}{\text{MW (all reactants)}} \times 100\%$

4.4.2.3. Think about the impact on % atom economy of the incorporation of a protecting group in the synthetic scheme.

4.4.3. Atom economy (below from Wikipedia)

4.4.3.1. Note that atom economy can be poor even when chemical yield is 100%, see for instance the Cannizzaro reaction. A Diels-Alder reaction is an example of a potentially very atom efficient reaction. On the other

hand if the desired product has an enantiomer the reaction needs to be sufficiently stereoselective even when atom economy is 100%.

4.4.3.2. Atom economy can also be adjusted if a pendant group is recoverable, for example Evans auxiliary groups. However, if this can be avoided it is more desirable, as recovery processes will never be 100%.

4.4.3.3. Atom economy can be improved upon by careful selection of starting materials and a catalyst system. Atom economy is just one way to evaluate a chemical process, other criteria can include energy consumption, pollutants released and/or price.

#### 4.5. What is the definition of %ee?

4.5.1. enantiomeric excess

4.5.1.1. What percent or fraction is not optically pure?

4.5.1.2.  $\frac{\{[R]-[S]\}}{\{[R]+[S]\}}$

4.5.1.3.A 1: 1 mixture of R:S by this equation gives 0%ee.

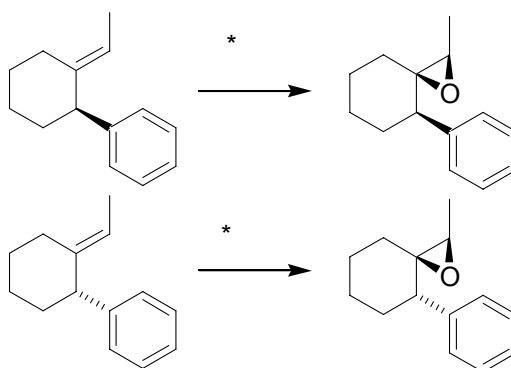
4.5.1.4.likewise an 8:2 mixture of R:S gives  $\frac{\{8-2\}}{\{8+2\}}=60\%ee$

4.5.2. Same principle applies to diastereomeric excess. %de.

#### 4.6. GENERAL PRINCIPLE

##### 4.6.1. Kinetic resolution

4.6.1.1. imagine a racemic mixture of



4.6.1.2.

4.6.1.3. Do the two reactions above have the same rates when catalyzed by an optically pure chiral catalyst?

4.6.1.4. remember our previous discussion of matched and mismatched pairs?

4.6.2. Kinetic resolution procedure

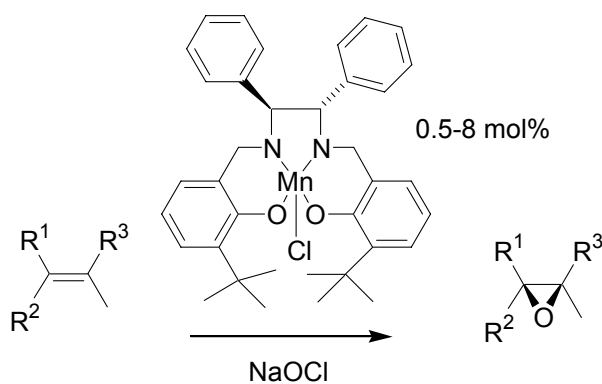
4.6.2.1. Run the reaction on the racemic mixture until about 50-80% of the target enantiomer is consumed.

4.6.2.1.1. The better the selectivity and the less optically pure you need your product to be the further you can run the reaction and get an acceptable result.

4.6.2.1.2. Isolate the optically pure (enriched) product.

4.6.2.1.3. *What would happen if you run the reaction to completion?*

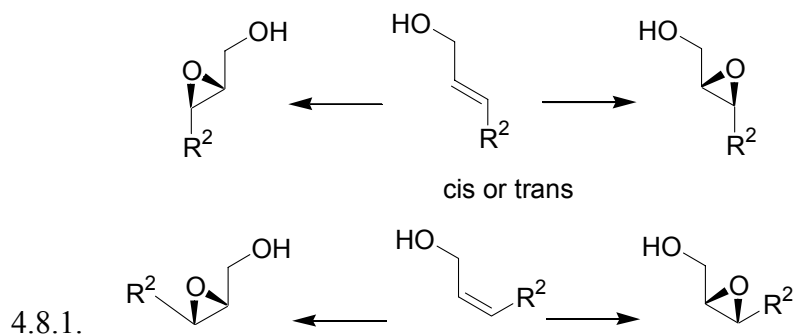
4.7. Another way to accomplish Retro 4 (FIG 1) is via a variety of transition metal peroxo-catalysts



4.7.1.

4.7.2. There are a lot of these salen-derived catalysts.

**4.8. Retro 4 can be controlled stereochemically from allyl alcohol starting materials and Sharpless epoxidation.**



4.8.2. Sharpless epoxidation leads to enantioselective epoxide derivatives of allyl alcohols.

4.8.3. Where do you suppose you might get these in a stereocontrolled fashion?

4.8.3.1. 1,2-disubstited (*E*)

4.8.3.2. 1,2-disubstited (*Z*)

4.8.3.3. 1,1,2-trisubstited

4.8.3.4. Pfenniger, A. "Asymmetric Epoxidation of Allylic Alcohols: The Sharpless Epoxidation." *Synthesis* **1986**, 89.

4.8.3.5. *JACS* **1980** *102* 5974

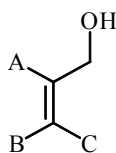
4.8.3.6. *JACS* **1987**, *109*, 5765

4.8.3.7. Johnson, R. A.; Sharpless, K. B. "Asymmetric Oxidation: Catalytic Asymmetric Epoxidation of Allylic Alcohols." In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103-158. QD262 .C356 1993

4.8.4. The breath of asymmetry in Sharpless epoxidation comes from tartaric acid.

4.8.4.1. epoxidation with early transition metals

4.8.4.1.1. Ti(IV), V(V), Mo(VI), W(VI)



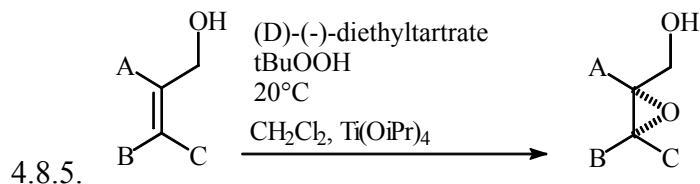
4.8.4.2.

4.8.4.2.1. ABC and the olefin and the CH<sub>2</sub> are all coplanar

4.8.4.2.2. if you could add reagents (form bonds selectively from the  $\alpha$  or the  $\beta$  face), you would create stereogenic centers and a chiral molecules.

4.8.4.2.3. The  $\alpha$  and the  $\beta$  faces of the molecule are prochiral

4.8.4.2.4. This is said of any sp<sup>2</sup> center that would create chirotopic environment upon hybridization to sp<sup>3</sup>.



4.8.5.1. Same proc with the (L)-(+)-DET give other enantiomer

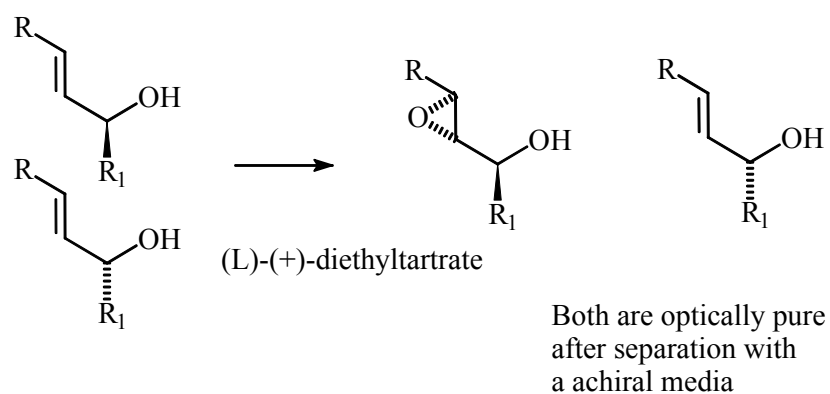
4.8.5.2. The alcohol function determines the enantioselectivity (facial selectivity of the reagent)

4.8.6. Applications

4.8.6.1. asymmetric epoxidation of prochiral allylic alcohols

## 4.8.6.2. kinetic resolution of racemic allylic alcohols

4.8.6.2.1. see above for an explanation of kinetic resolution



## 4.8.7. Advantages of Sharpless Asymmetric Epoxidation:

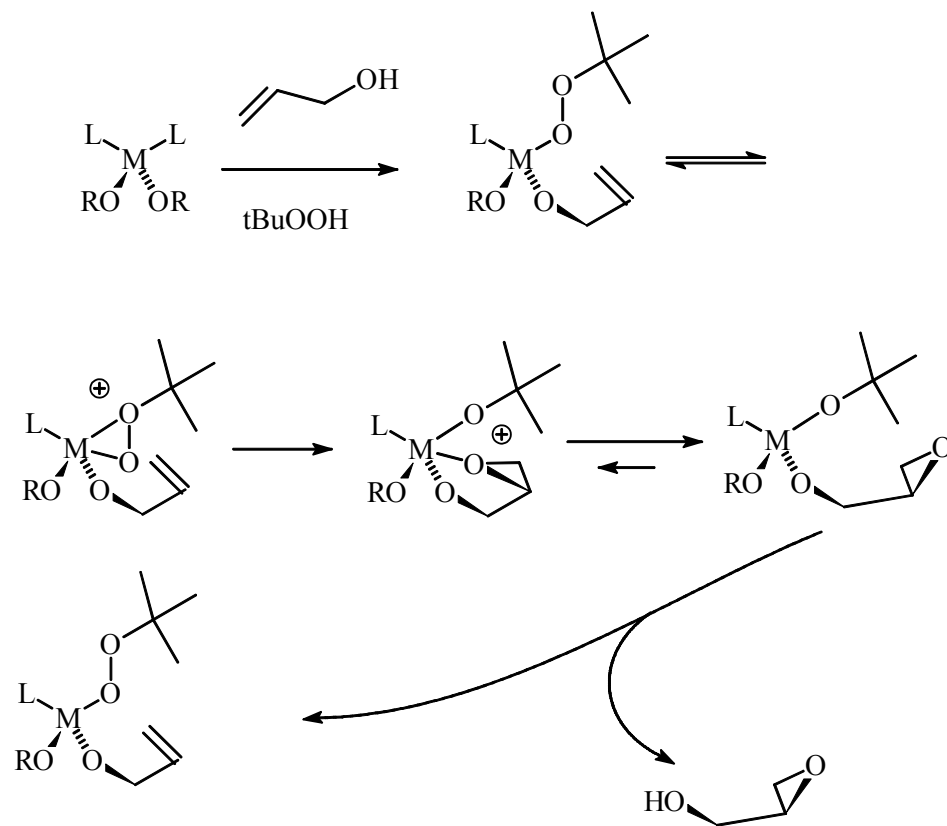
4.8.7.1. simple and cheap

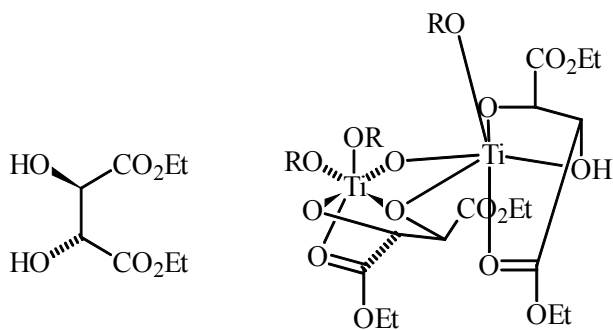
4.8.7.2. reliable (large C give unreliable results)

4.8.7.2.1. greater than 95% ee

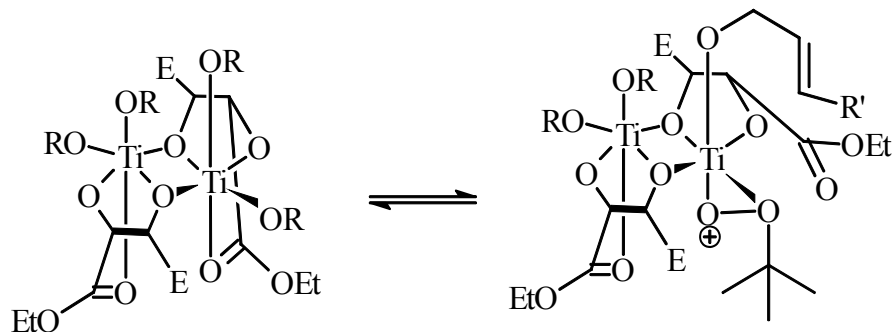
4.8.7.2.2. predictable

4.8.7.2.3. almost insensitive to preexisting stereogenicity





The Tartrate-bound catalyst

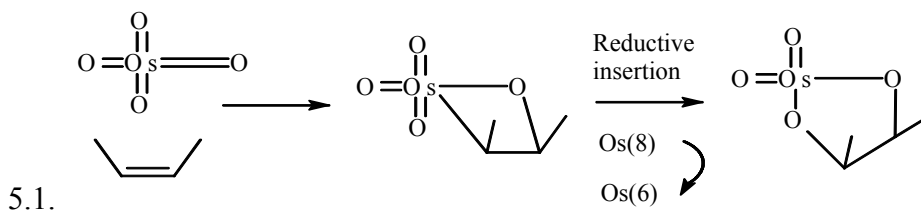


4.8.7.3. Upon chemical contact with the Tartrate-bound catalyst, the peroxide and the allylic alcohol exchange ligands with the isopropoxide.

4.8.8. Epoxides are important intermediates in synthesis.

4.8.8.1.1.

**5. Retro 5 can be controlled stereochemically by using Sharpless dihydroxylation**



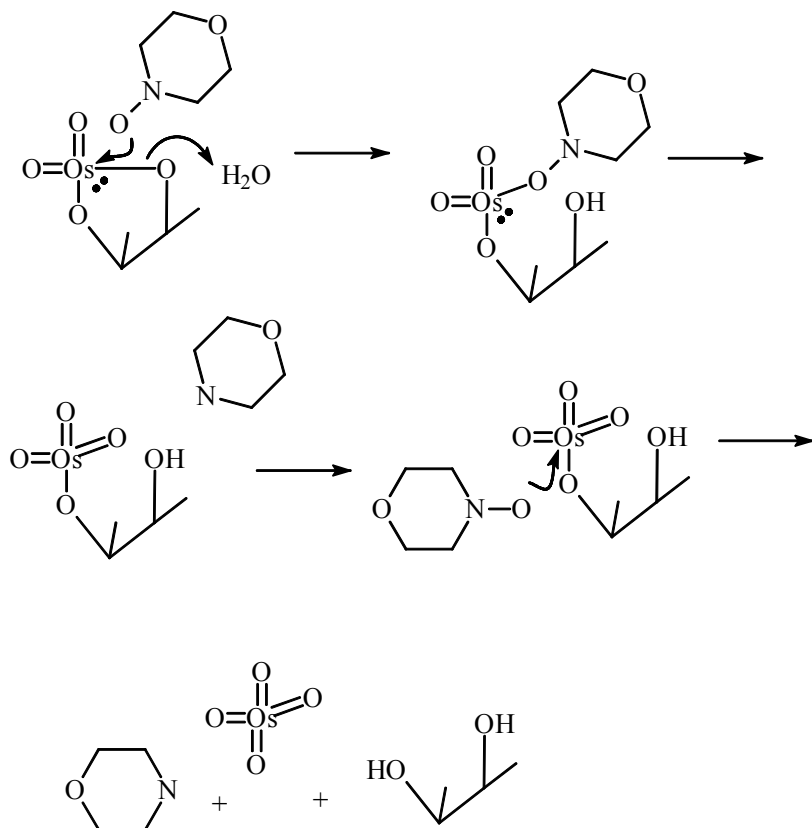
5.2. Criegee discovered that  $\text{OsO}_4$  is reduced by alkenes

5.2.1. Reaction is usually run in neutral aq conditions

5.2.2. The last product shown is an ester (an osmate ester)

5.2.3.  $\text{Os}(0)$  evolves upon stoichiometric reduction

5.2.4. However, in the presence of certain [O] agents the reaction runs catalytic in Os



### 5.2.5. Accounting of electrons

5.2.5.1. Two electron reduction of Os. Upon reductive insertion of O into the Os-C bond after 2+2 addition.

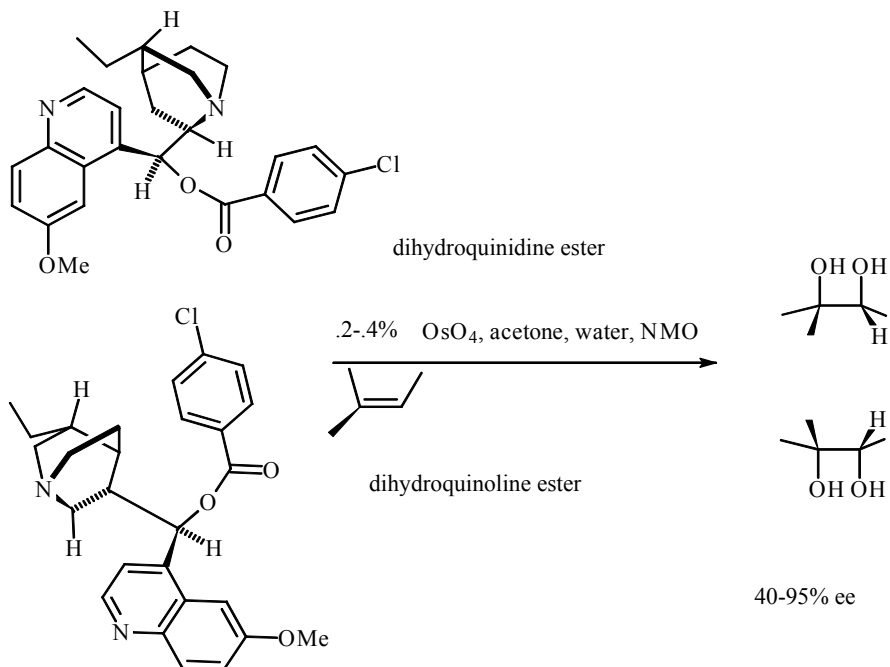
5.2.5.1.1. The microscopic reverse of this mechanism from kinetic data is observed for Re in the 7+ oxidation state--isoelectronic with Os in the 8+ oxidation state.

5.2.5.2. The two electrons came from the alkene

5.2.5.3. The organic substrate went up in oxidation state

5.2.5.4. Nitrogen center goes from +1 to 0

5.2.5.4.1. Thus two nitrogen oxides are needed.



5.2.6.

6. We have discussed Retro 6 in Figure 1 briefly, Simmons-Smith cyclopropanation.

There is much more to say.

6.1. For a preview see: "Transition Metal Carbene Complexes: Cyclopropanation."

Doyle, M. P. In *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982-1994*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12; pp 387-420.