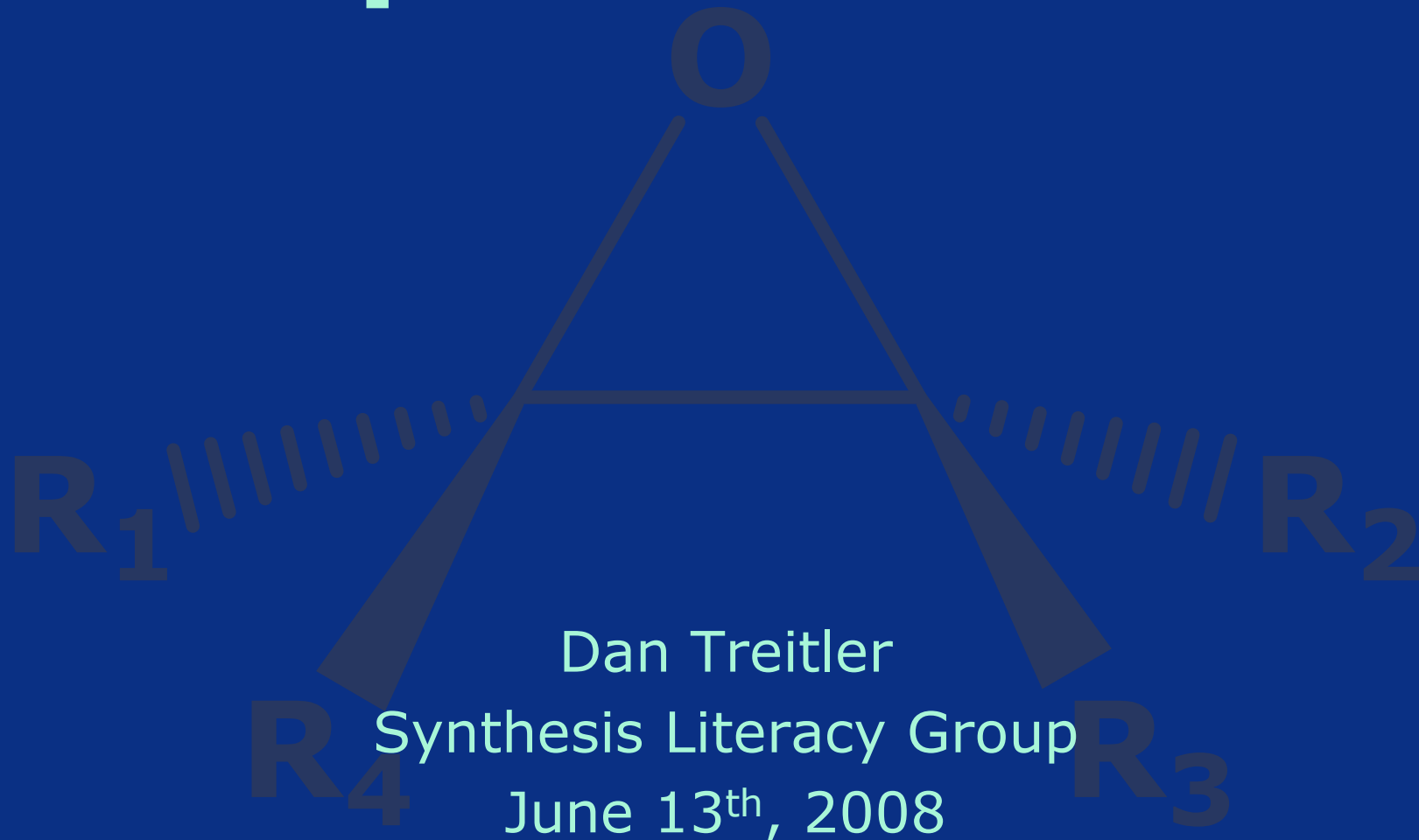


Enantioselective Epoxidations



Overview

I. Organocatalyzed Enantioselective Epoxidation

1. Chiral Hydroperoxides
2. Chiral Sulfur Ylides (Corey-Chaykovsky Conditions)
3. Chiral Dioxiranes

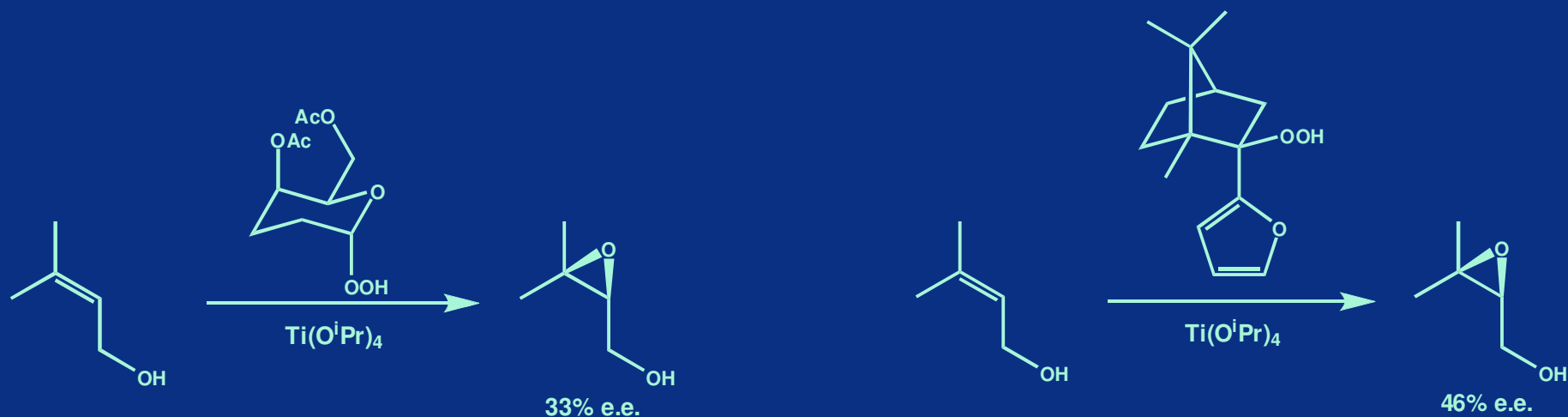
II. Metal Catalyzed Enantioselective Epoxidation

1. Asymmetric Weitz-Scheffer Epoxidation
2. Sharpless Epoxidation
3. Jacobsen Epoxidation
4. Katsuki Epoxidation

III. Hydrolytic Kinetic Resolution (HKR)

Chiral Hydroperoxides

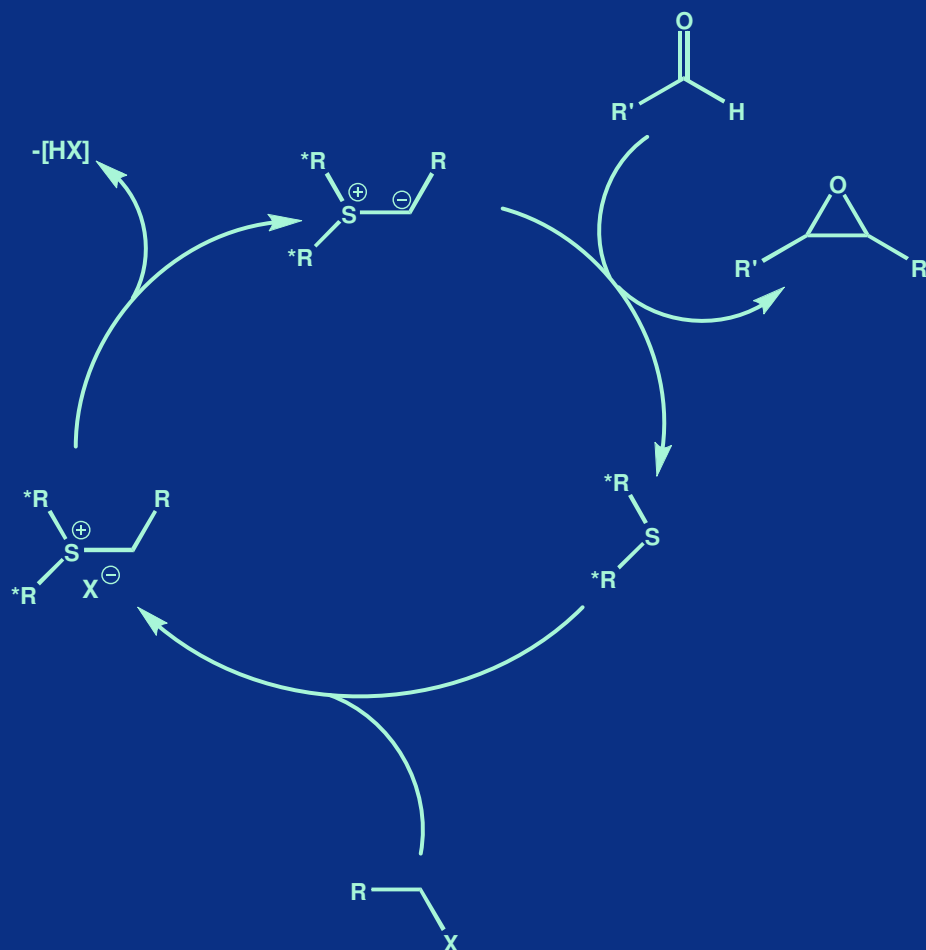
- Simplest approach towards asymmetric epoxidation – generally not spectacular.



H-J Hamann et al., *Chirality*, **1993**, 5, 338.
A. Lattanzi et al., *Chem Comm.* **2003**, 1440.

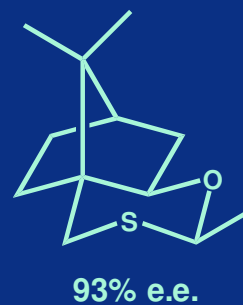
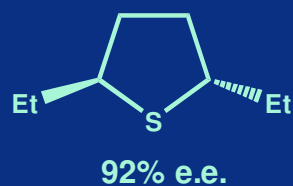
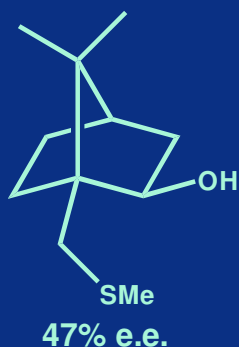
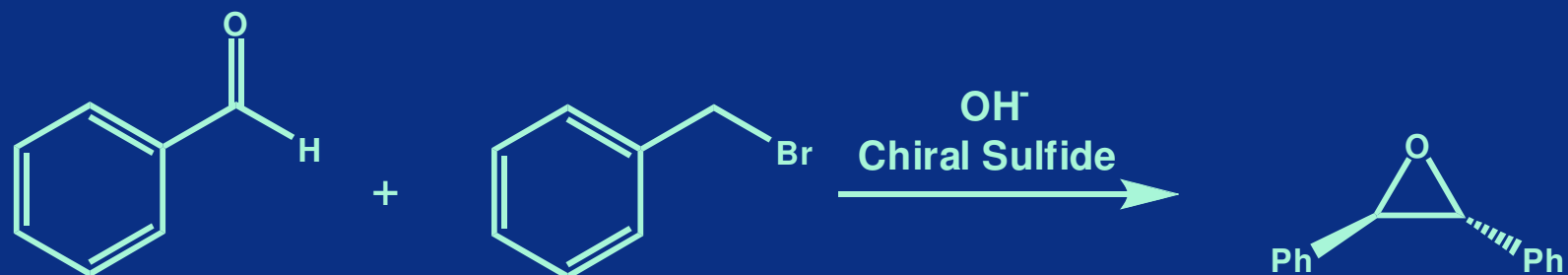
Chiral Sulfur Ylides

Asymmetric variants of the Corey-Chaykovsky reaction (addition of sulfur ylides to aldehydes or ketones) have been devised using chiral sulfides as starting materials.



N. Furukawa et al. *J. Org. Chem.*, **1989**, *54*, 4222.

Chiral Sulfur Ylides



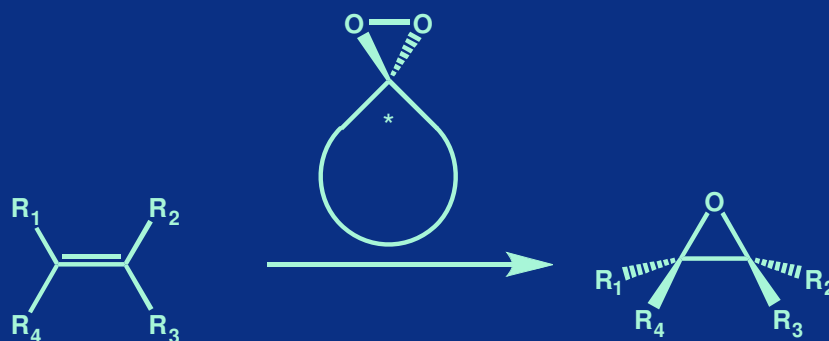
Not applicable to broad substrate scopes. Reaction conditions generally suck (days or weeks).

N. Furukawa et al. *J. Org. Chem.*, **1989**, *54*, 4222.

P. Metzner et al. *J. Org. Chem.*, **2005**, *70*, 4166.

V.K. Aggarwal and J. Richardson. *Chem Comm.*, **2003**, 2644.

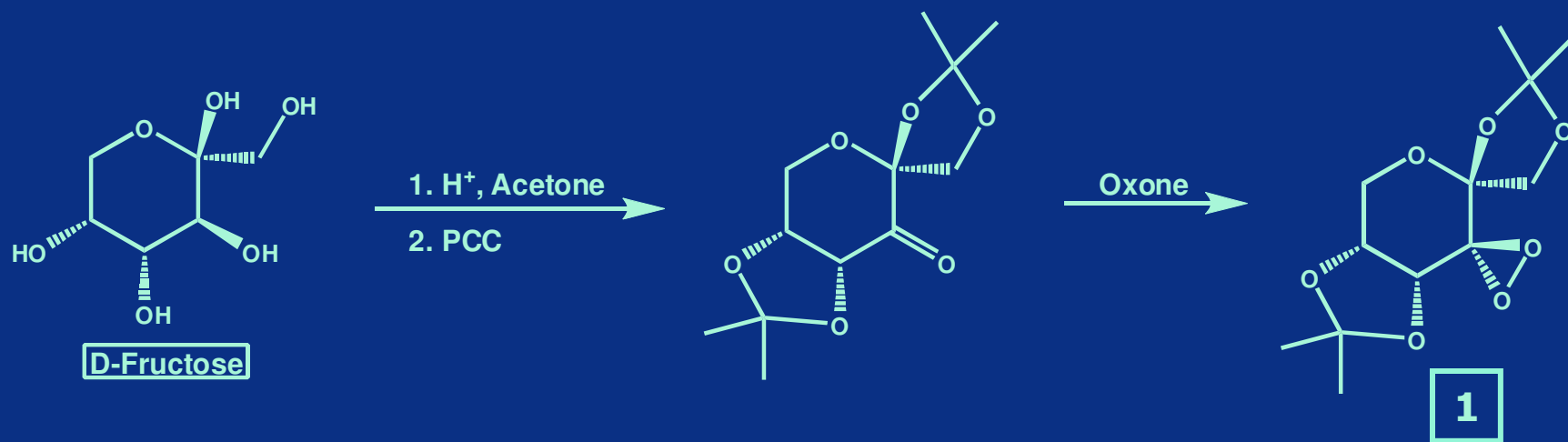
Chiral Dioxiranes



- Generally referred to as Shi Epoxidation, due to major contributions by Yian Shi (Colorado State).

Shi Epoxidation

Synthesis of Organocatalyst:



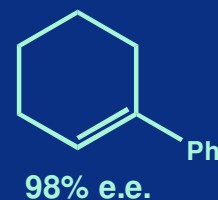
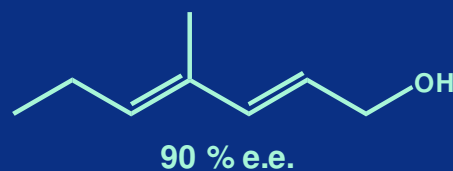
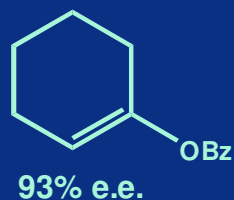
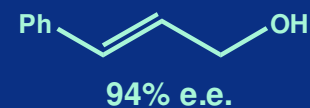
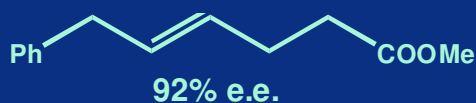
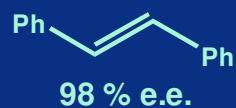
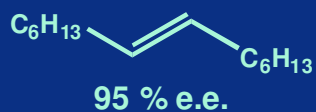
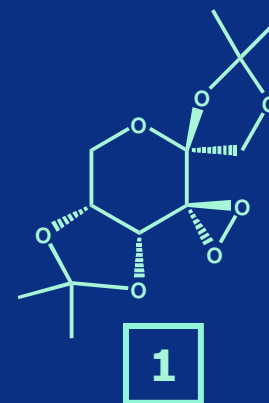
Originally used in stoichiometric amounts (>3 eq), but later discovered that pH optimization (10-11) allowed for use of sub-stoichiometric amounts of **1**.

Y. Shi. et al. *JACS*, **1996**, *118*, 9806.

Shi Epoxidation

Substrate Scope:

- Trans and trisubstituted olefins work very well.
- Normal Conditions: 0.3 eq **1**, 5 eq Oxone, and 6 eq K_2CO_3 in MeCN/ H_2O . 90 mins @ $0^\circ C$.

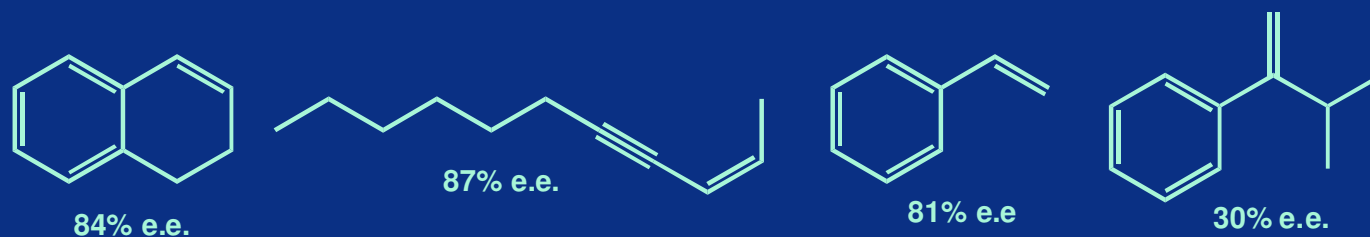
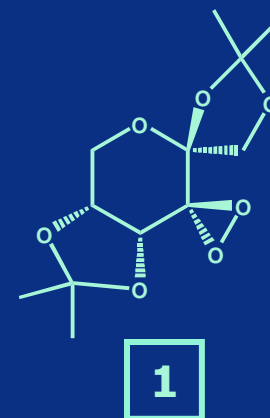


Yields typically good but not great (60-90%)

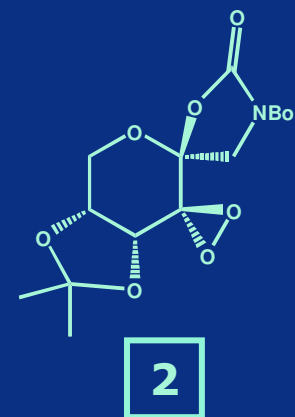
Shi Epoxidation

Cis and Terminal Olefins:

- Catalyst 1 gives rather shitty e.e. values for cis and terminal olefins.
- Catalyst 2 was developed for these substrates – generally results in good but not great e.e.'s.



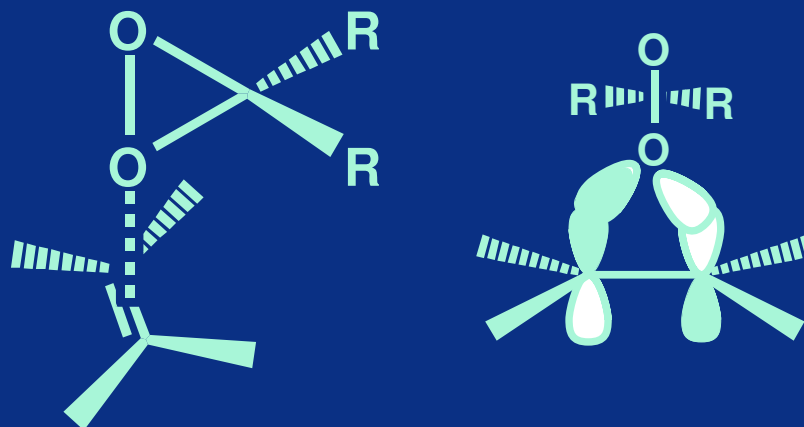
(Olefin must be conjugated)



Shi Epoxidation

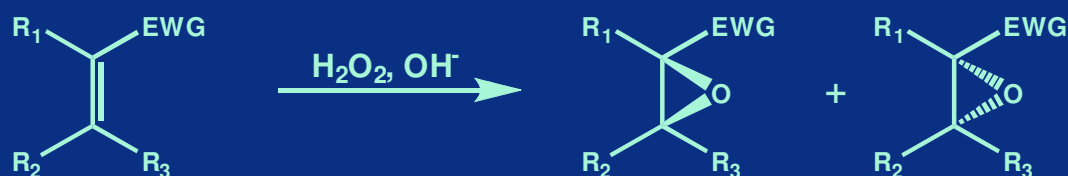
Mechanism:

Spiro transition state is favored due to orbital overlap between $\text{NB}_{(\text{O})}$ and $\pi^*_{(\text{C}=\text{C})}$



The chiral nature of the two R's makes approach from one face more favorable.

Asymmetric Weitz-Scheffer

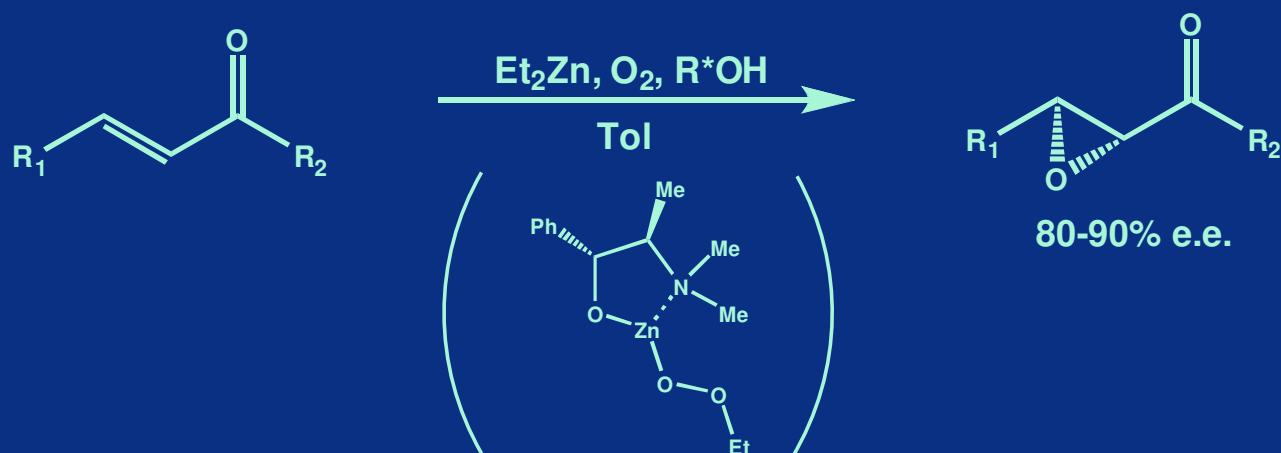


Asymmetric variants:

- EWG is almost always a ketone.
- Alternative to an asymmetric aldol reaction.

Asymmetric Weitz-Scheffer

- Enders Method:

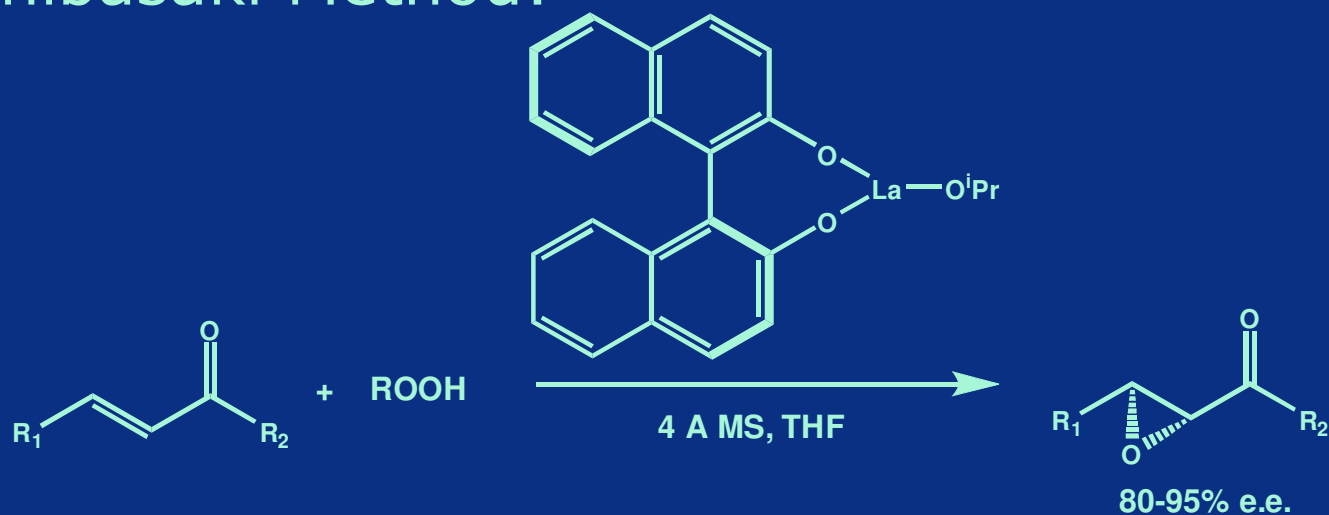


Pros: Oxygen as stoichiometric oxidant.

Cons: Not very broad substrate scope (R_2 must be Ph or other large group for good enantioselectivity).

Asymmetric Weitz-Scheffer

- Shibasaki Method:

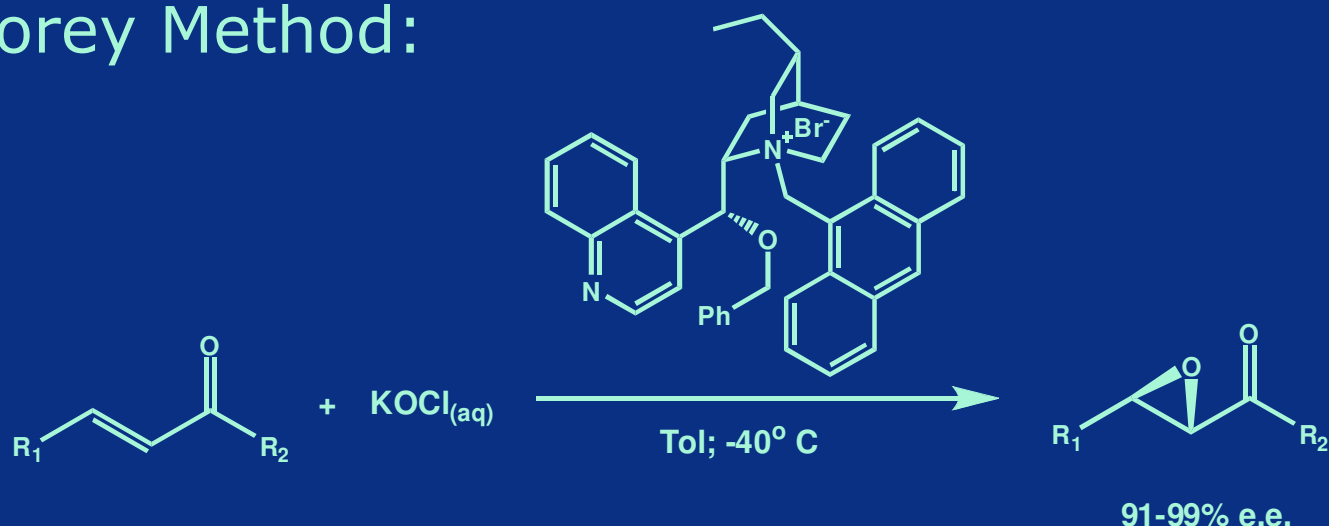


Pros: Catalytic in L-M complex (≤ 5 mole %), Broader substrate scope than Enders method.

Cons: Expensive catalyst; mechanism poorly understood (active catalyst is presumed to be oligomeric).

Asymmetric Weitz-Scheffer

- Corey Method:



Pros: Catalytic in ligand (0.1 eq.), consistently high e.e. values.

Cons: R_2 must be aryl. Ligand is not particularly cheap or easy to come by. Reaction conditions are annoying.

E.J. Corey and F-Y Zhang. *Org. Lett.*, **1999**, 1(8), 1287.

E.J. Corey et al. *Tet. Lett.*, **1996**, 37(11), 1735.

Asymmetric Weitz-Scheffer

Summary:

- Enders method (Pseudoephedrine, ZnEt_2 , O_2).
- Shibasaki method ($\text{La(O}^i\text{Pr)}_3$, Binol, ROOH, 4A MS).
- Corey method (Crazy complex ligand, KOCl).

All give good to excellent enantiomeric excesses for α,β -unsaturated ketones; overall, the Shibasaki method seems to be the most practical.

Sharpless Epoxidation



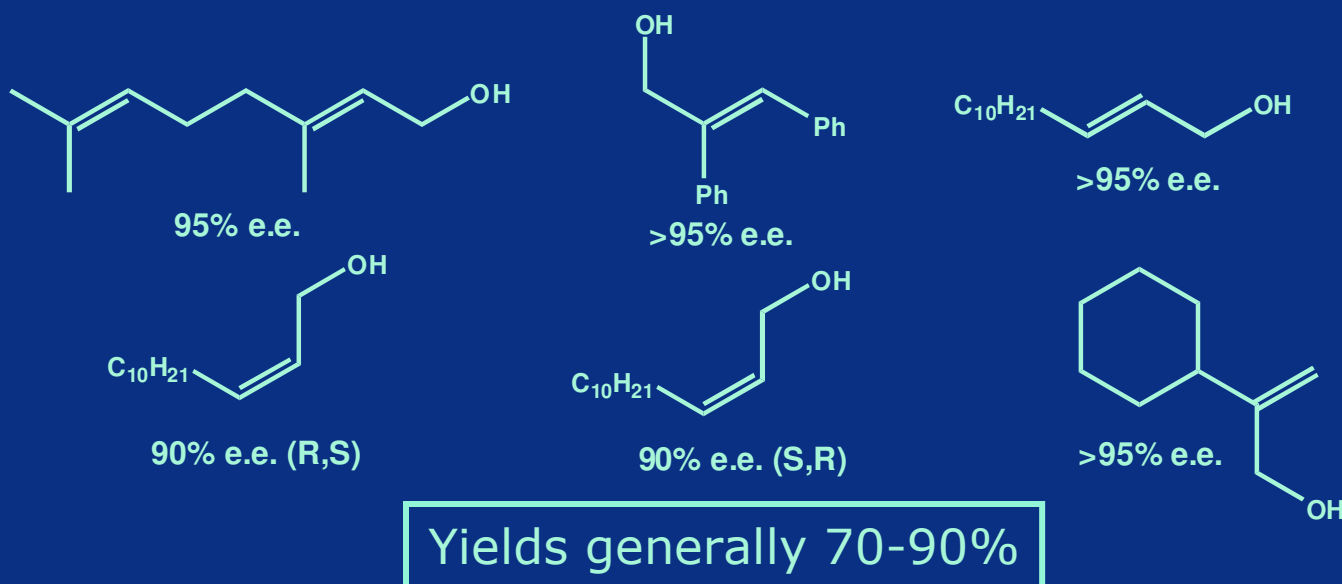
- The first method of enantioselective epoxidation (1980) to give e.e. values >80%.
- Fantastically versatile – works for nearly any substrate.

K.B. Sharpless and T. Katsuki. *JACS*, **1980**, *102*(18), 5974.

Sharpless Epoxidation

Substrate Scope:

- Works for mono-, di-, tri-, and tetrasubstituted olefins.
- Negligible drop in e.e. for cis vs. trans or internal vs. terminal olefins.



K.B. Sharpless and T. Katsuki. *JACS*, **1980**, *102*(18), 5974.

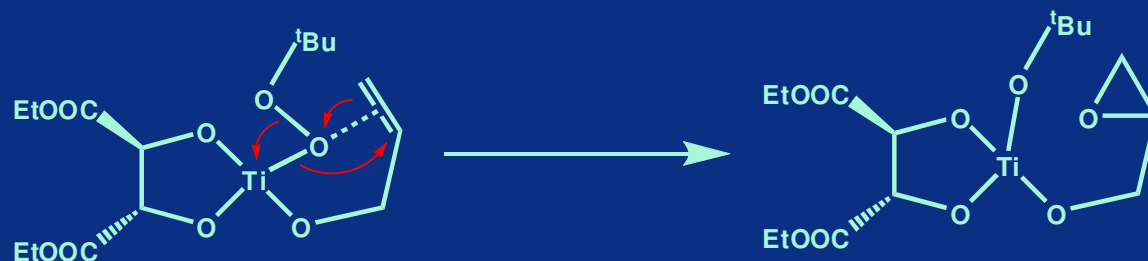
Sharpless Epoxidation

Mechanism:

Mechanism has been debated pretty fiercely:

Corey: "In the course of a study directed at improving the diastereoselectivity of epoxidation of isopropylvinyl carbinol, Katsuki and Sharpless made the felicitous discovery that a mixture of $\text{Ti}(\text{OLPr})_4$, $t\text{-BuOOH}$, and (R,R) -(+)-diethyl tartrate selectively epoxidized one enantiomer of this allylic alcohol."

Sharpless: "As yet, evidence supporting a single hypothesis to the exclusion of the others has not been obtained. It must be noted, however, that a recent proposal by Corey featuring an ion-pair transition state is inconsistent with the observed kinetic rate expression."

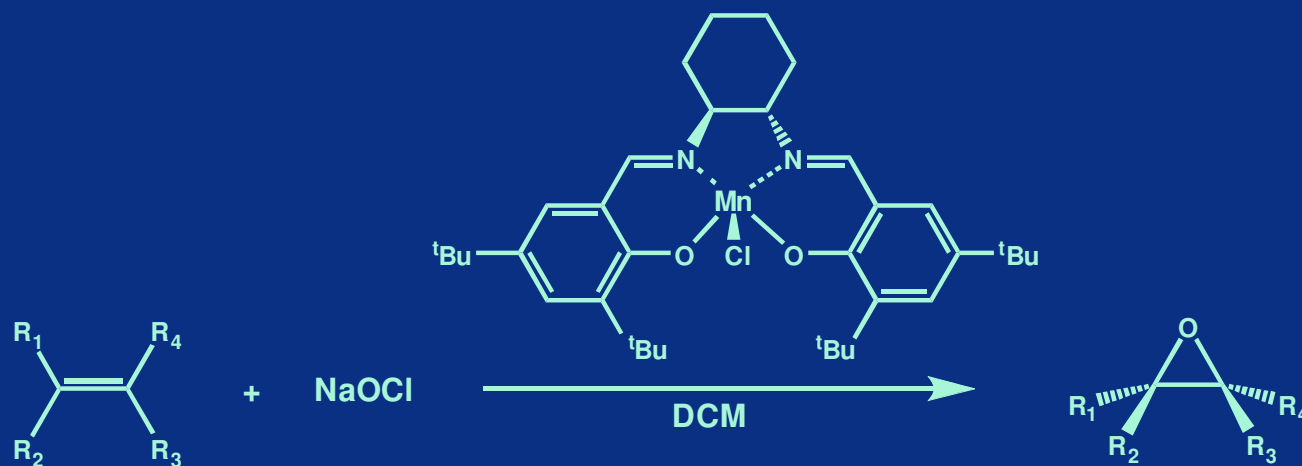


E.J. Corey. *J. Org. Chem.*, **1990**, 55(6), 1693.

M.G. Finn and K.B. Sharpless. *JACS*, **1991**, 113, 113.

A. Pfenninger. *Synthesis*, **1986**, 89.

Jacobsen Epoxidation



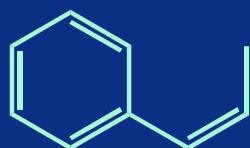
The first metal-catalyzed epoxidation to result in high e.e. values for alkenes without allylic OH groups.

E.N. Jacobsen et al. *JACS*, **1991**, *113*, 7063.

Jacobsen Epoxidation

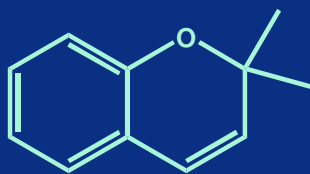
Substrate Scope:

- Applicable to most cis-olefins. A small number of conjugated trisubstituted and tetrasubstituted olefins also work (not general).
- Also works for electron deficient olefins (enones) but requires higher catalyst loading and longer reaction times.

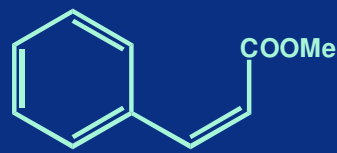


92% e.e.

(2% cat. Loading)

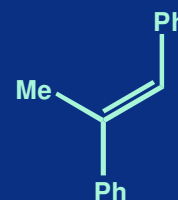


98% e.e.

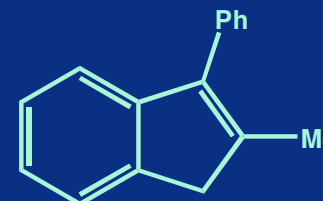


89% e.e.

(10% cat. Loading)



93% e.e.



86% e.e.

Yields generally 60-80%

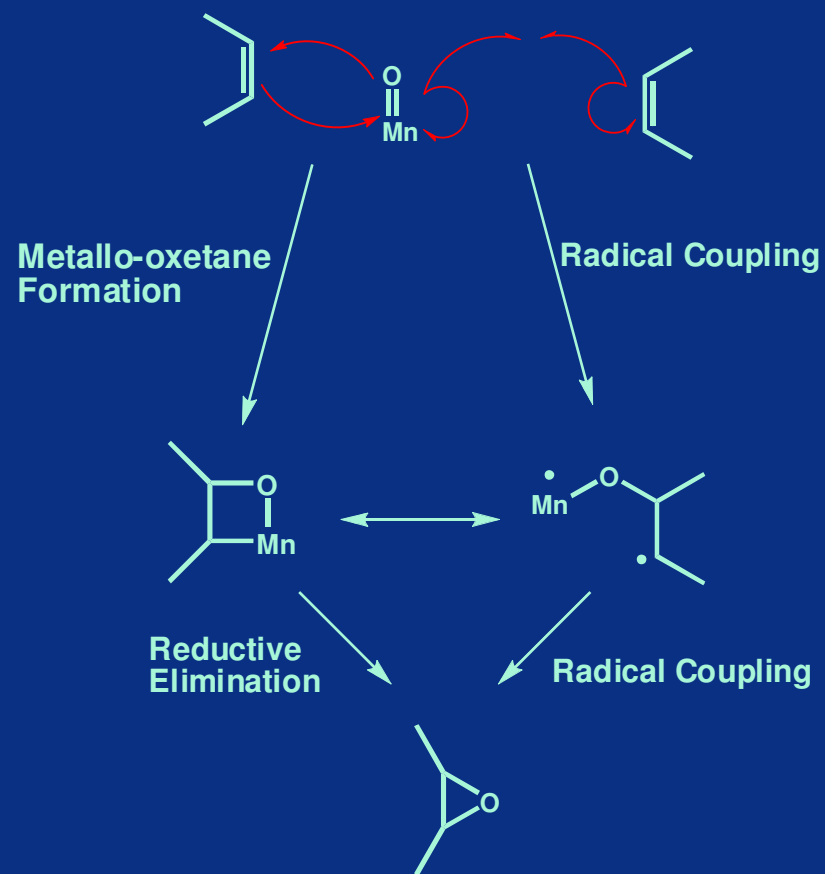
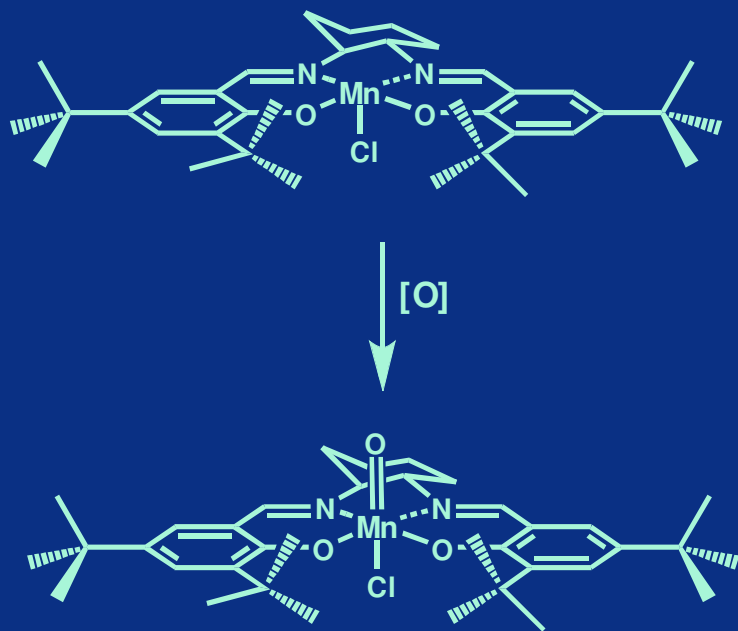
E.N. Jacobsen et al. *JACS*, **1991**, *113*, 7063.

E.N. Jacobsen and B.D. Brandes. *J. Org. Chem.*, **1994**, *59*, 4378.

E.N. Jacobsen and B.D. Brandes. *Tetrahedron Lett.*, **1995**, *36*(29), 5123.

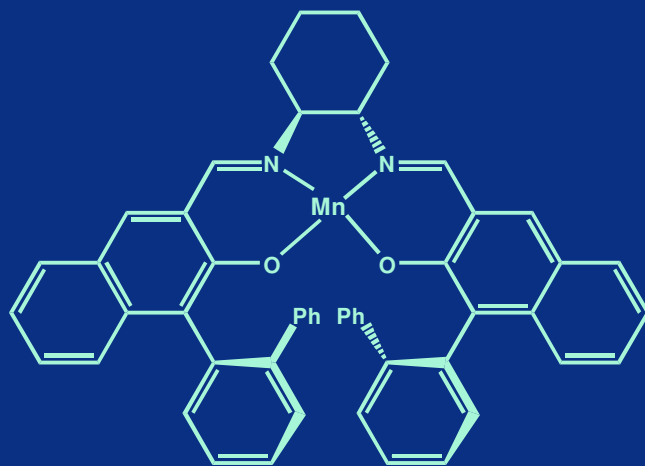
Jacobsen Epoxidation

Mechanism:

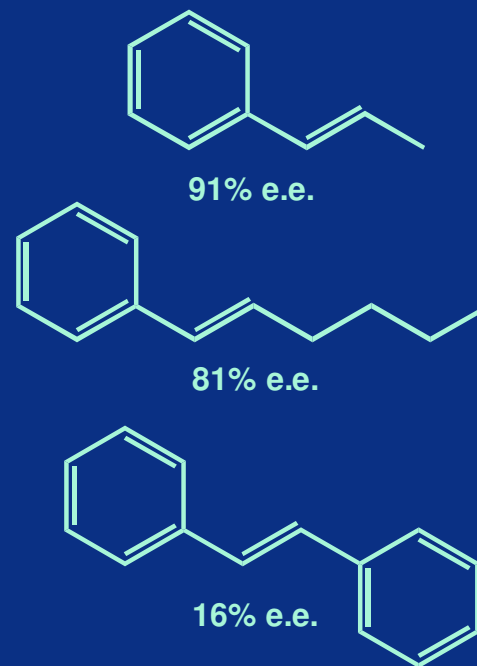


Katsuki Epoxidation

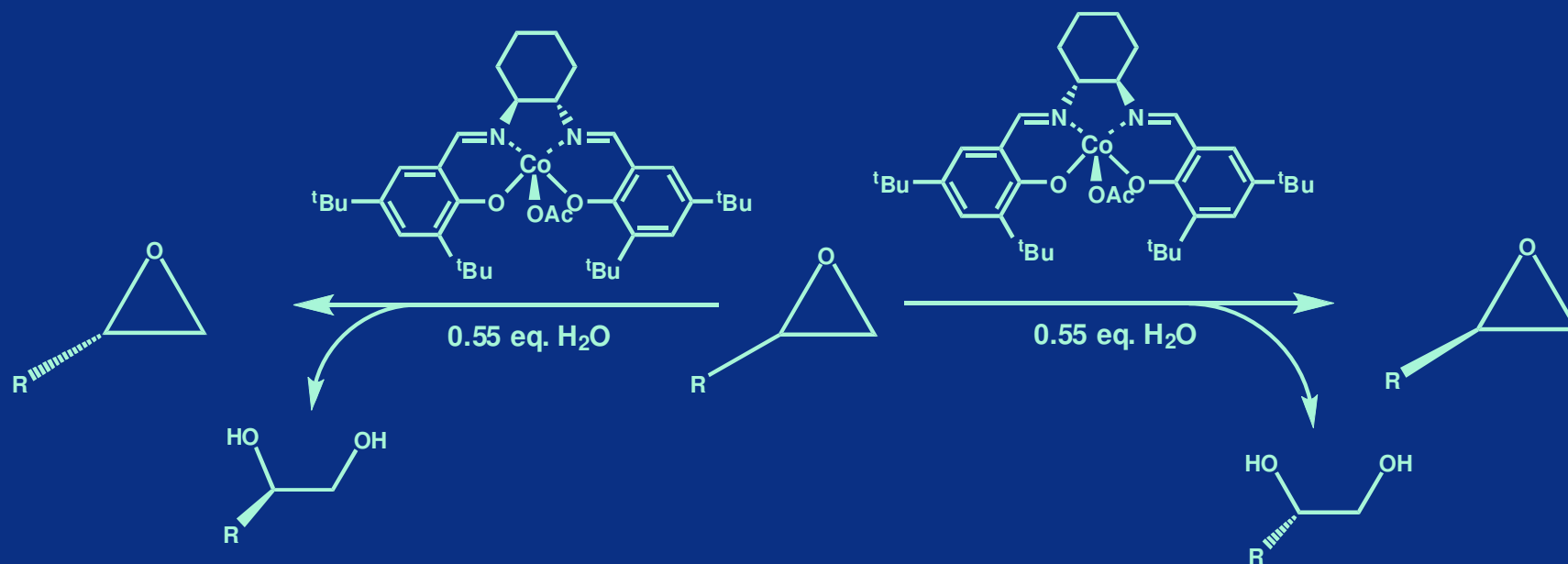
Related epoxidation – more complex catalyst with more steric bulk allows for enantioselective epoxidation of some *trans*-alkenes.



Katsuki's Catalyst



Jacobsen's Hydrolytic Kinetic Resolution (HKR)

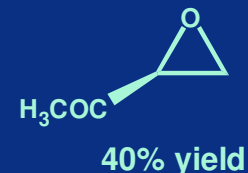
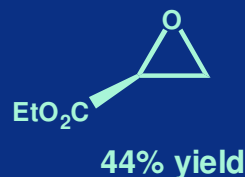
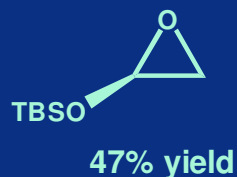
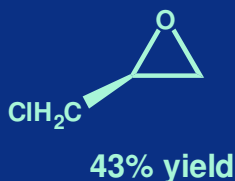
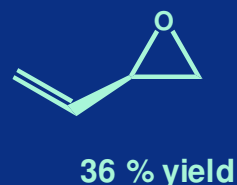
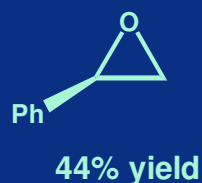
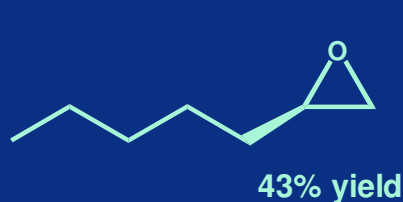


(R,R)-cat gives R-epoxide; (S,S)-cat gives S-epoxide (assumes side-chain is lower priority than CH₂O).

Jacobsen's Hydrolytic Kinetic Resolution (HKR)

Substrate Scope:

- Only for terminal olefins, but works remarkably well in the presence of most functional groups.



All >99% e.e. with catalyst loadings from 0.5 mol% to 2 mol%

Jacobsen's Hydrolytic Kinetic Resolution (HKR)

Pros:

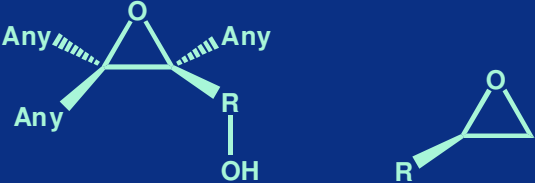


- Equivalents of water added can be varied to optimize for yield or e.e.
- Reaction is very easy to set up – not air-sensitive, often requires no solvent, the only reagents are acetic acid and water, and purification is a joke.
- Both enantiomers of the catalyst are commercially available (Strem - \$25 per gram) and can be recycled easily and essentially indefinitely.

Cons:

- Only viable substrates are terminal olefins.
- Maximum yield is around 50% - unless you really care...

E.N. Jacobsen et al. *JACS*, **2002**, *124*(7), 1307.

Summary: Recommended Methods

<p>Allylic or Terminal</p>	 <p>Sharpless Jacobsen HKR</p>
<p>Di- or Tri-substuted</p>	 <p>Jacobsen Shi Shi Jacobsen</p>
<p>Electron Deficient</p>	 <p>Shibasaki Shibasaki Jacobsen</p>
<p>S.O.L.</p>	