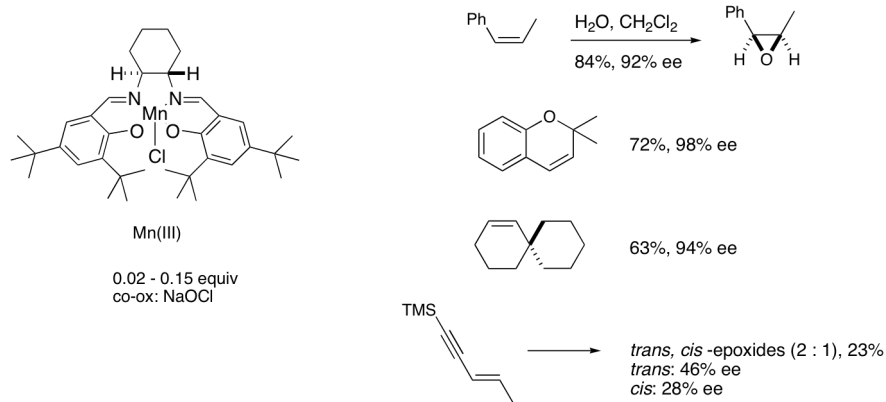


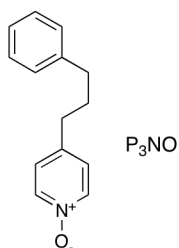
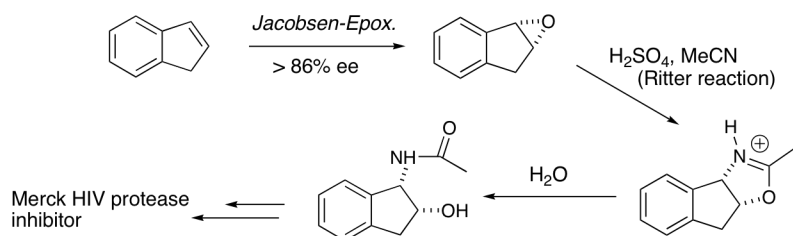
## 9. Jacobsen-Katsuki Epoxidations

Jacobsen, *JACS* **1990**, *112*, 2801; *JACS* **1991**, *113*, 7063; Katsuki, *THL* **1990**, *31*, 7345. Based on Kochi's achiral salen catalyst.

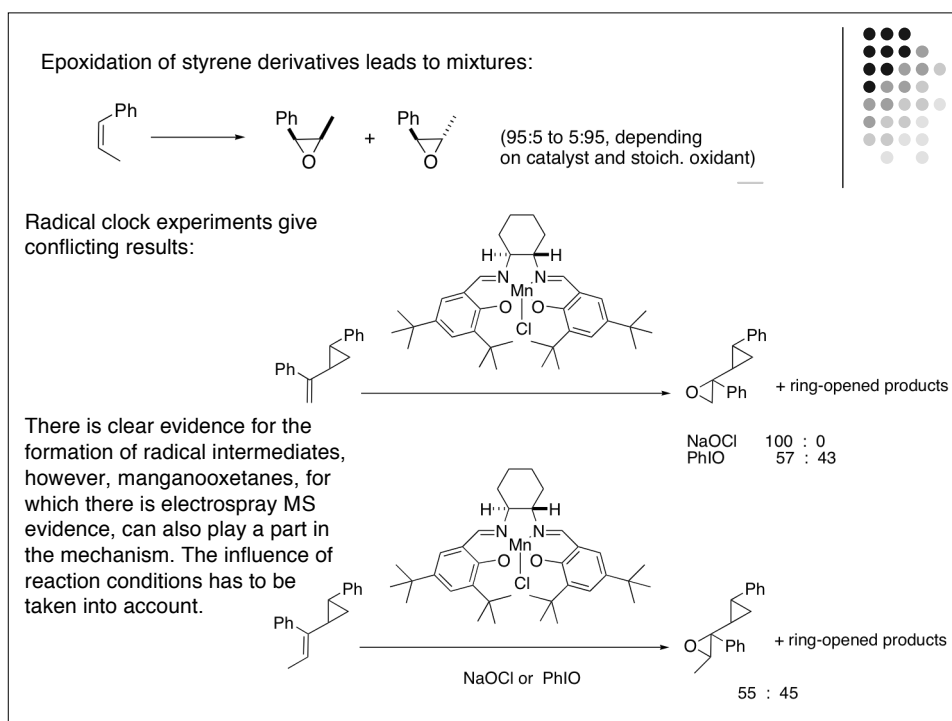
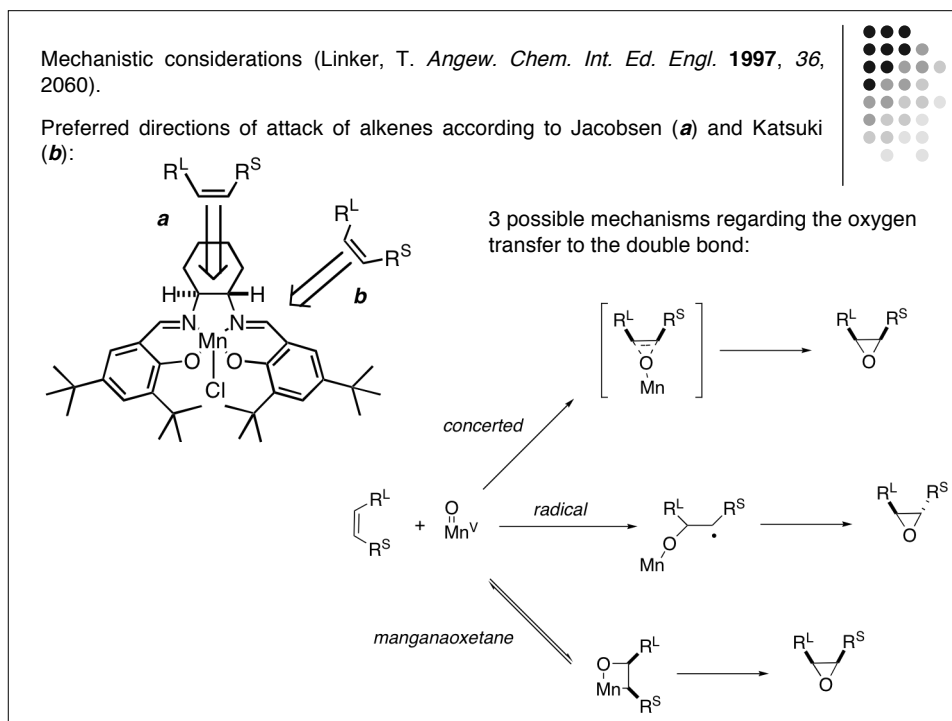
Mcgarrigle, E. M.; Gilheany, D. G., "Chromium- and manganese-salen promoted epoxidation of alkenes." *Chem. Rev.* **2005**, *105*, 1563-1602.



Application in process chemistry (*THL* **1995**, *36*, 3993):

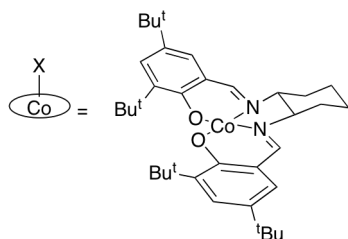


The use of the co-catalyst  $\text{P}_3\text{NO}$  allowed for a decreased charge of the Mn salen catalyst in the Jacobsen epoxidation.  $\text{P}_3\text{NO}$  stabilized the catalyst, increased the rate, and transported bulk oxidant HOCl into the organic phase (*JOC* **1997**, *62*, 2222).

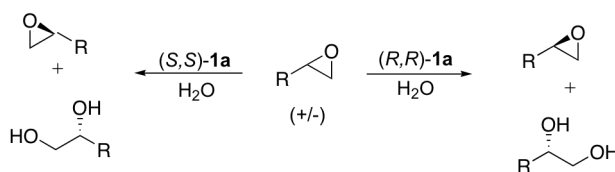


Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N., "Mechanistic investigation leads to a synthetic improvement in the hydrolytic kinetic resolution of terminal epoxides (HKR)." *J. Am. Chem. Soc.* **2004**, *126*, 1360-1362.

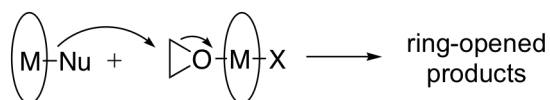
The (salen)-Co(III) complex **1** provides a general and effective method for the preparation of enantioenriched terminal epoxides. **1a** is the most commonly used variant.



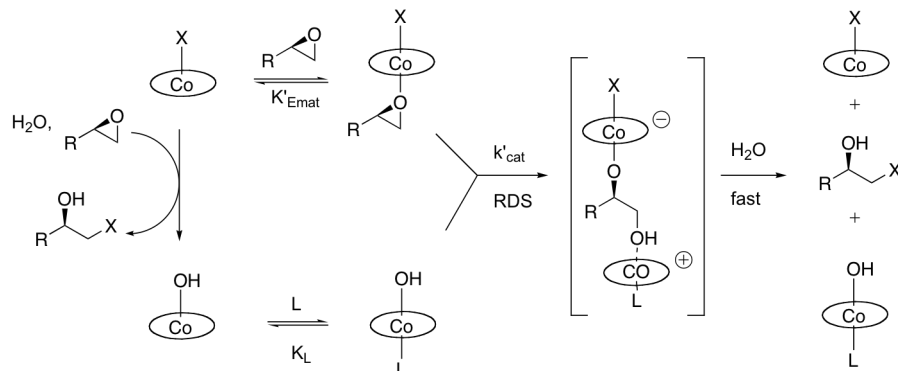
- 1a** X=OAc
- 1b** X=OH
- 1c** X=Cl
- 1d** X=OBz
- 1e** X=OPh
- 1f** X=OTs
- 1g** X=SbF<sub>6</sub>








The catalyst shows a second-order dependence, and a cooperative bimetallic mechanism has been suggested:



Dominant catalytic cycle in HKR reactions (RDS = rate determining step):

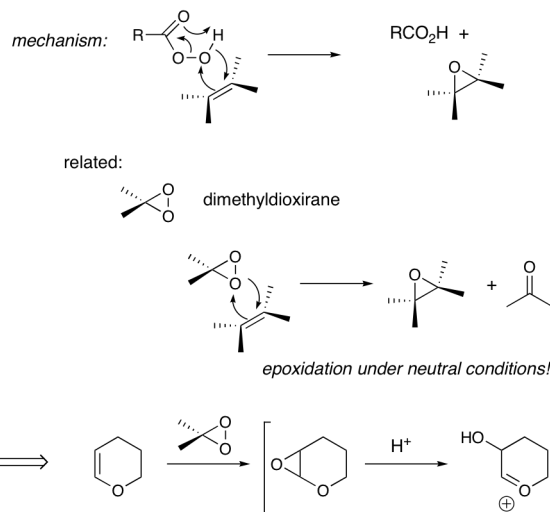


substrate	method <sup>a</sup>	Catalyst (mol %) <sup>b</sup>	Time (h)	Yield (%) <sup>c</sup>
	A	0.5	16	43
	B	0.15	3	44
	B	0.05	16	45
	A <sup>d</sup>	0.5	16	43
	B <sup>d</sup>	0.2	16	42
	A	2.0	24	43
	B	0.5	16	42
	A	0.5	16	47
	B	0.06	16	45
	A	2.0	48	40
	B	1.2	48	39

<sup>a</sup> Method A: Standard, using catalyst **1a**. Method B: Catalyst **1f** added to epoxide (0.1-0.4 mol) and water (0.7 equiv) under solvent-free conditions at room temperature. <sup>b</sup> Catalyst loading based on racemic epoxide. <sup>c</sup> Isolated yield of >99% ee epoxide based on racemate (theoretical maximum yield = 50%). <sup>d</sup> Reaction at 0-4 °C.

## 10. Peracid/Peroxide Epoxidations

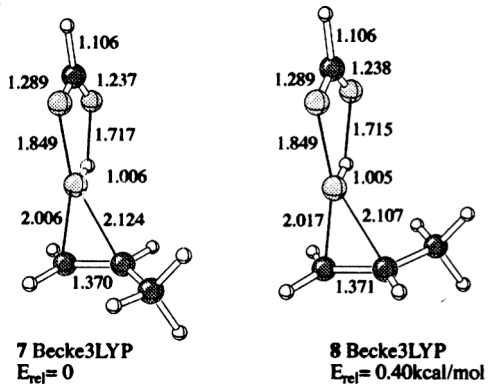
Standard peracids are: MCPBA,  $\text{CH}_3\text{CO}_3\text{H}$ , MMP,  $\text{CF}_3\text{CO}_3\text{H}$ , 3,5-dinitroperbenzoic acid.



Yang, D.; Wong, M.-K.; Yan, Z., "Regioselective intramolecular oxidation of phenols and anisoles by dioxiranes generated in situ." *J. Org. Chem.* **2000**, *65*, 4179-4184.



Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N., "Experimental geometry of the epoxidation transition state." *J. Am. Chem. Soc.* **1997**, *119*, 3385.

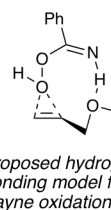
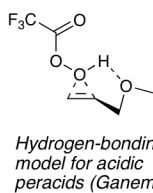
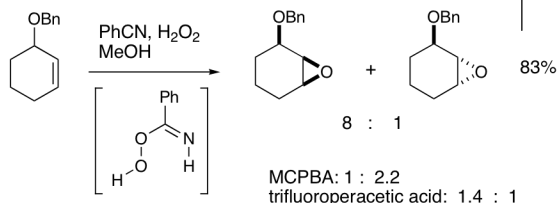


Transition state for DMD: Jenson, C.; Liu, J.; Houk, K., N.; Jorgensen, W. L., "Elucidation of transition structures and solvent effects for epoxidation by dimethyldioxirane." *J. Am. Chem. Soc.* **1997**, *119*, 12982.

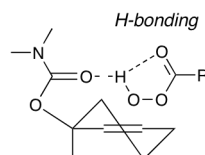
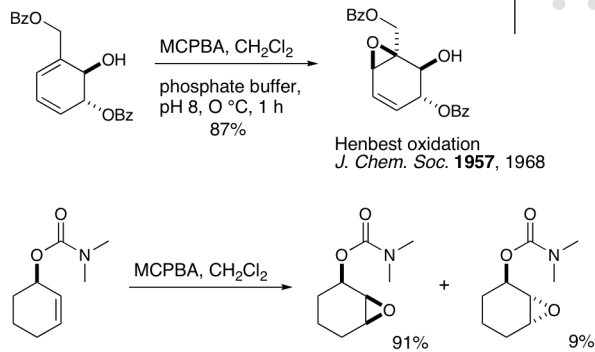
## Epoxidation under Payne conditions:

Bachmann, C.; Gesson, J.-P.; Renoux, B.; Tranoy, I. *Tetrahedron Lett.* **1998**, *39*, 379.

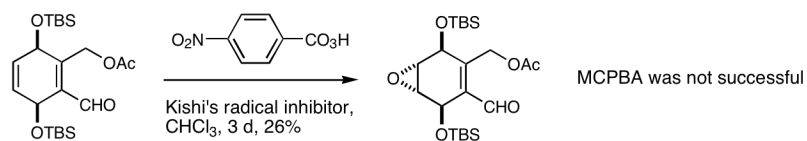
With the less acidic MCPBA, epoxidation of allylic ethers is directed by steric hindrance and is *anti*-selective.



Diastereomeric control in the epoxidation with peracids is quite good, if appropriate directing groups are present, or if the substrate is sterically biased.

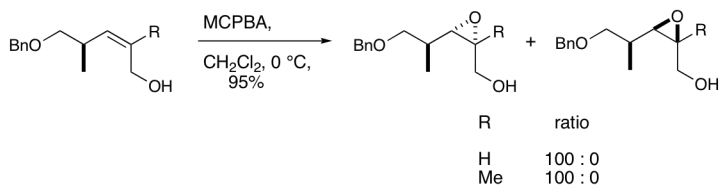
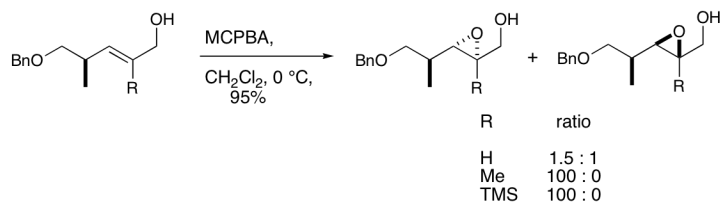


Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.

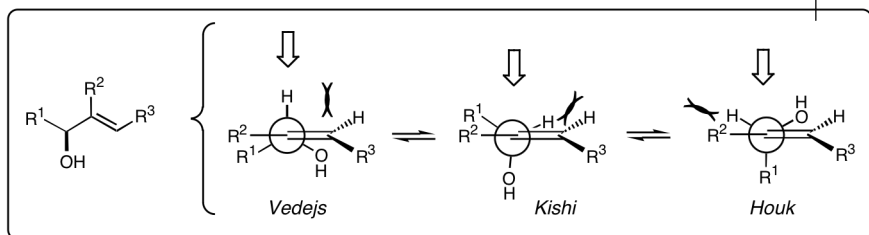


*Diastereocontrol in acyclic substrates:*

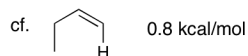
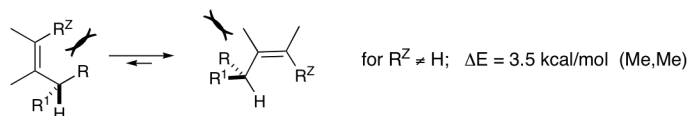
Kishi, Y. et al. *Tetrahedron Lett.* **1980**, *21*, 4229.



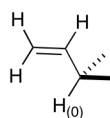
mechanistic consideration of the relative stability of ground state conformational isomers:



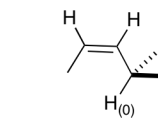
for  $R^2 \neq H$



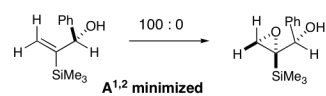
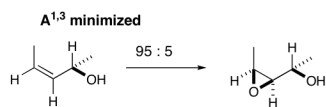
more calc.: Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.



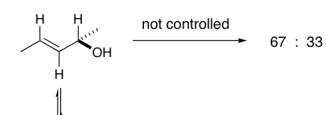
0° : 0 kcal/mol  
70° : 2.60 kcal/mol  
120° : 0.73 kcal/mol  
180° : 2.48 kcal/mol



0° : 0 kcal/mol  
100° : 4.86 kcal/mol  
180° : 3.44 kcal/mol

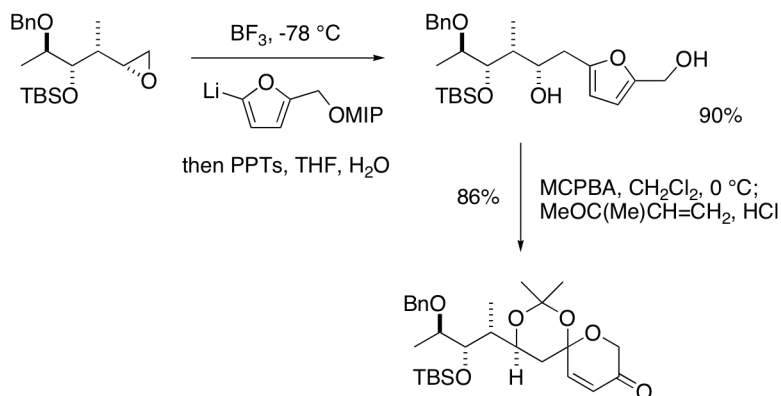


TMS can be used as "chiral auxiliary" (Kishi)





Furan to pyrenone conversion: Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284. Preparation of a *masked aldol* system. An example of the *Achmatowicz* reaction.



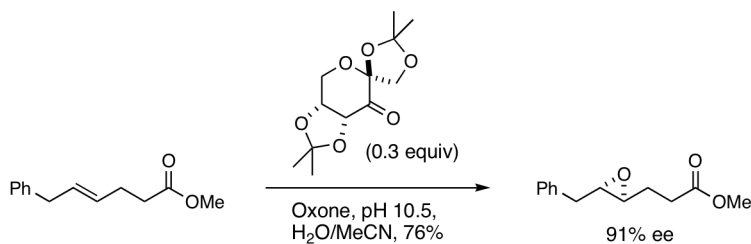
### Catalytic Asymmetric Epoxidation with Chiral Dioxiranes

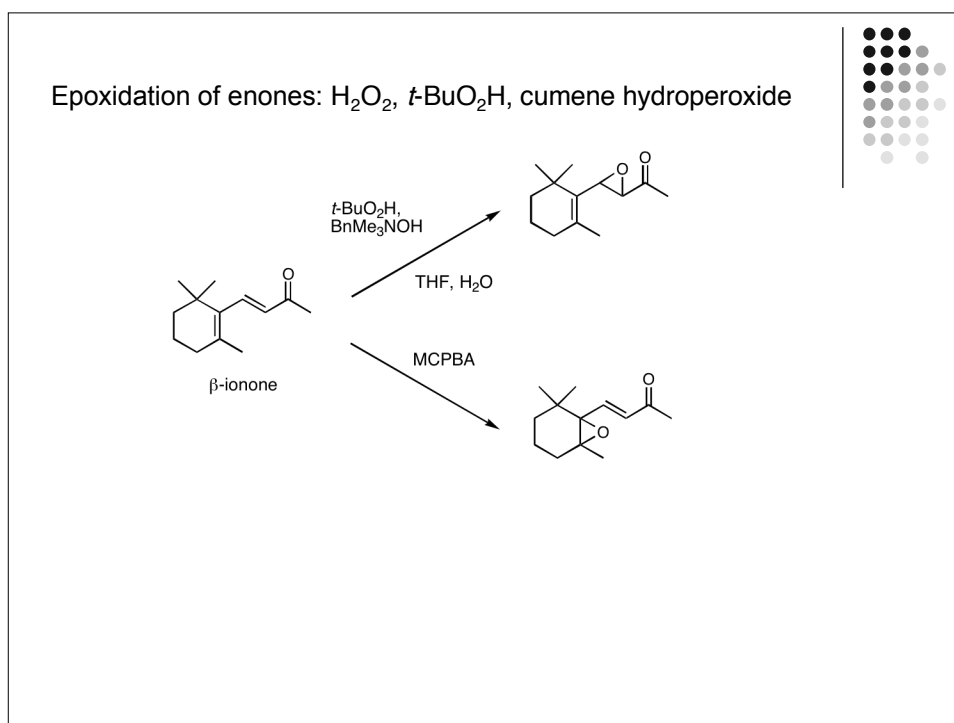
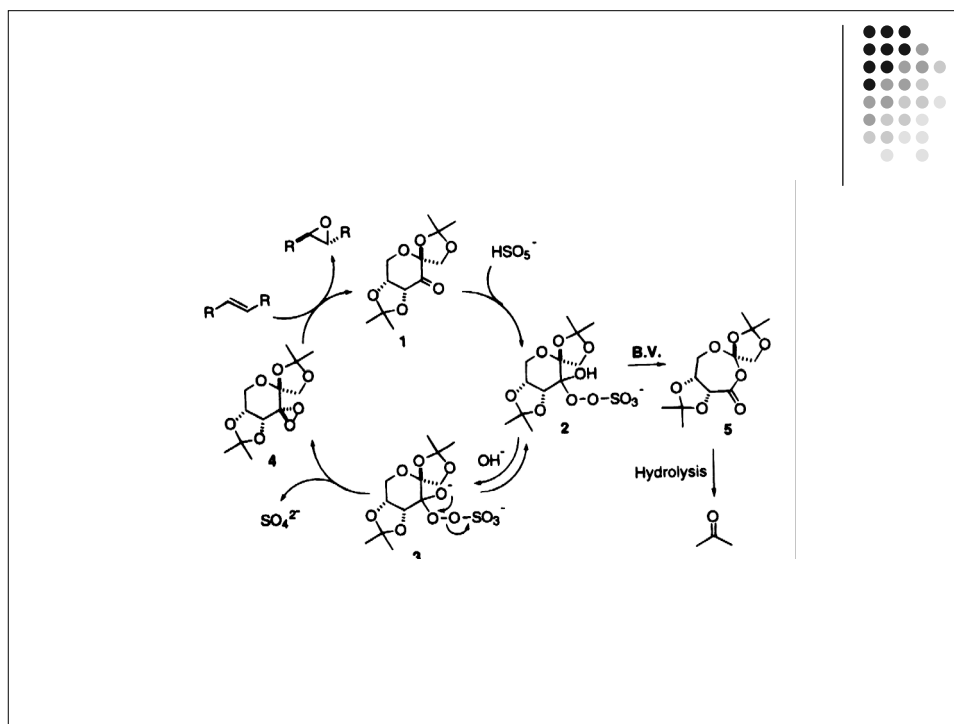
Wang, Z.-Y.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

Biphasic reactions, inexpensive oxidants; turnover and catalytic efficiency need to be improved for this chemistry to become a viable competitor to transition metal catalysts for asymmetric epoxidation. For recent progress, see: *J. Org. Chem.* **1997**, *62*, 8622.

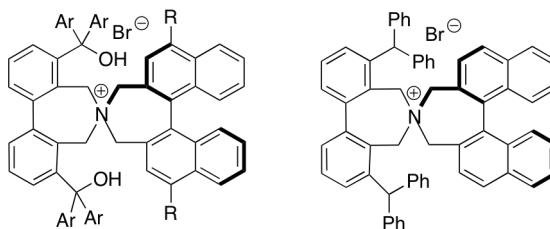
Shi, Y., "Organocatalytic asymmetric - epoxidation of olefins by chiral ketones." *Acc. Chem. Res.* **2004**, *37*, 488-496.

Yang, D., "Ketone-catalyzed asymmetric epoxidation reactions." *Acc. Chem. Res.* **2004**, *37*, 497-505.

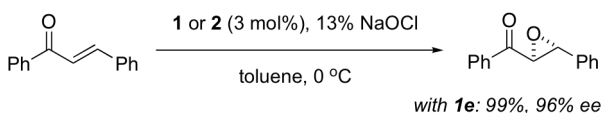




Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K., "Design of new chiral phase-transfer catalysts with dual functions for highly enantioselective epoxidation of  $\alpha,\beta$ -unsaturated ketones." *J. Am. Chem. Soc.* **2004**, *126*, 6844-6845.

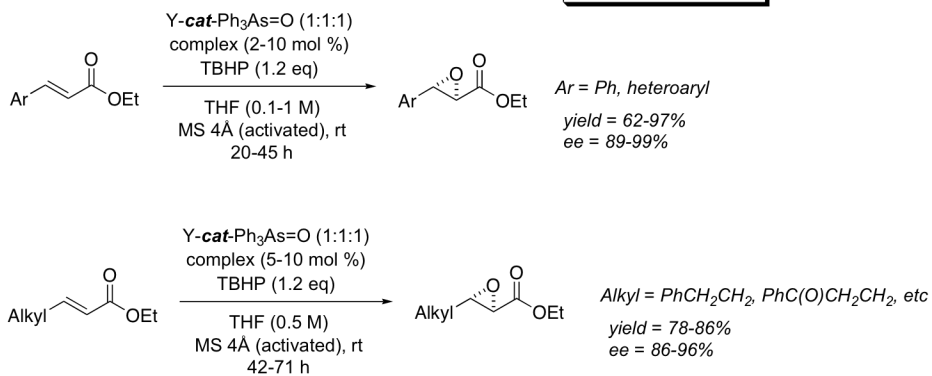
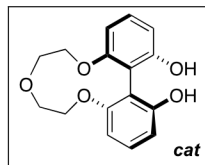


- 1a** (Ar=Ph, R=H)  
**1b** (Ar=4-CF<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>, R=H)  
**1c** (Ar=3,5-(MeO)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, R=H)  
**1d** (Ar=3,5-Ph<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>, R=H)  
**1e** (Ar=R=3,5-Ph<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)



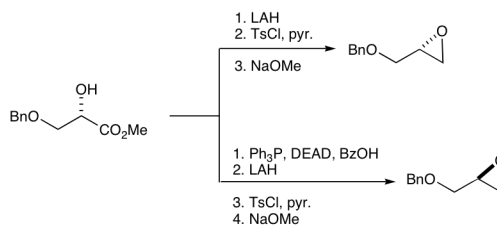
Presently limited to aryl or *t*-Bu ketones

Takei, H.; Tsuji, R.; Ohshima, T.; Shibasaki, M., "Catalytic asymmetric epoxidation of  $\alpha,\beta$ -unsaturated esters using an yttrium-biphenyldiol complex." *J. Am. Chem. Soc.* **2005**, *127*, 8962-8963.



## 11. Alternative Methods for Epoxide Formations

Epoxides from diols:



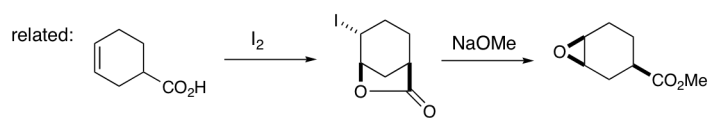
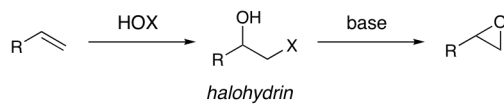
Martin, T.; Soler, M. A.; Betancort, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 1570.

Gardinier, K. M.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 7098. The basic transesterification required with standard esters in the final step of the Sharpless conversion of vicinal diols into epoxides (Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515) was incompatible with the target molecule (cryptophycin).

Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284.



Via halohydrins:

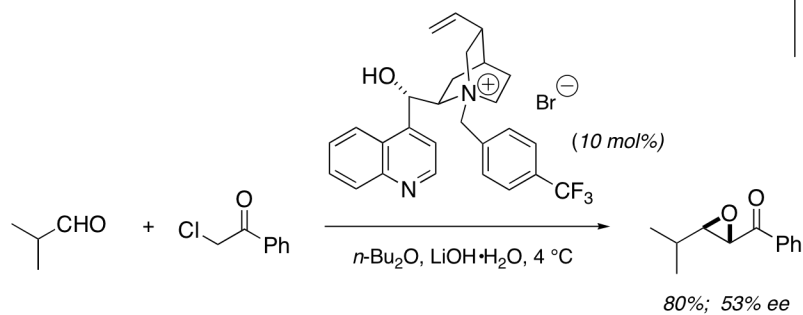


Cardillo-Epoxidation (*TH* **1990**, *46*, 3321):

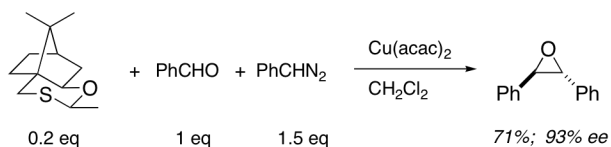
Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 187.



Arai, S.; Shioiri, T., "Catalytic asymmetric **Darzens condensation** under phase-transfer-catalyzed conditions." *Tetrahedron Lett.* **1998**, *39*, 2145.



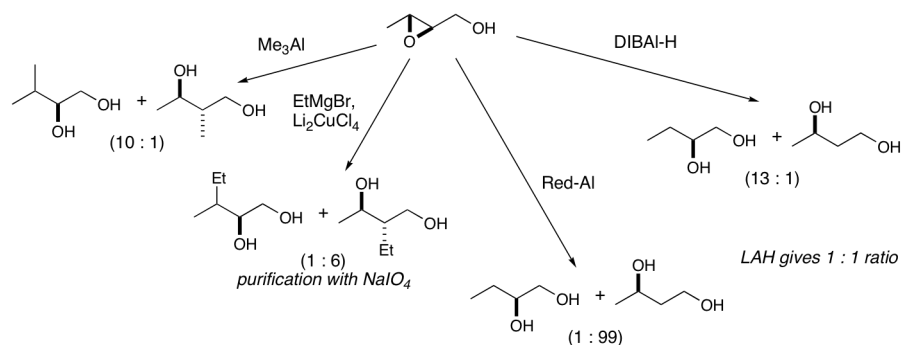
**Corey-Chaykovski Reaction:** Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R., "Catalytic Asymmetric Epoxidation of Aldehydes. Optimization, Mechanism, and Discovery of Stereoelectronic Control Involving a Combination of Anomeric and Cieplak Effects in Sulfur Ylide Epoxidations with Chiral 1,3-Oxathianes." *J. Am. Chem. Soc.* **1998**, *120*, 8328-8339.



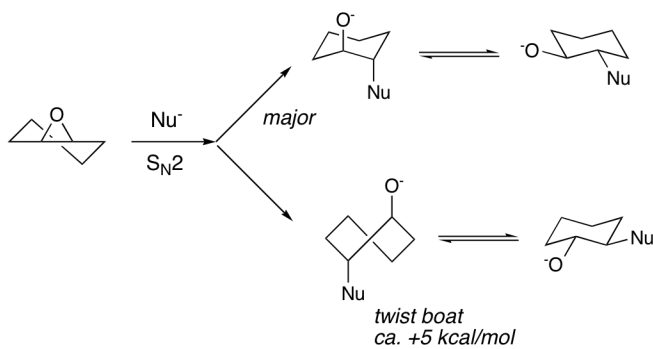
Aggarwal, V. K.; Winn, C. L., "Catalytic, asymmetric sulfur ylide-mediated epoxidation of carbonyl compounds: Scope, selectivity, and applications in synthesis." *Acc. Chem. Res.* **2004**, *37*, 611-620.

## 11. Epoxide Opening Reactions

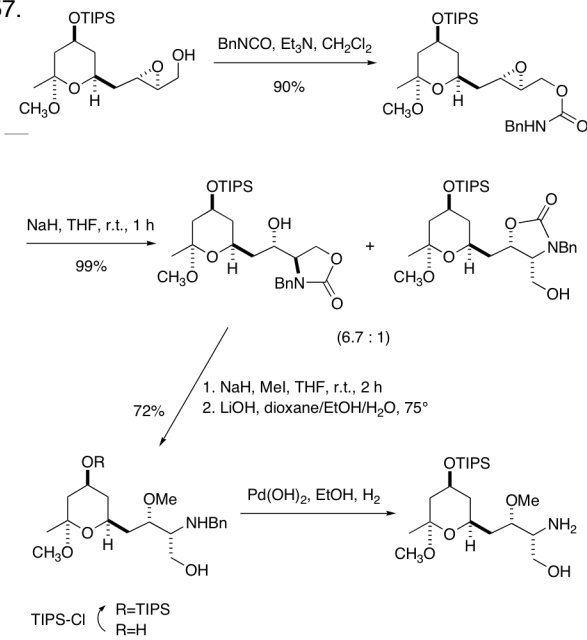
Review: Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.



on rings: *trans*-diaxial opening is preferred (Fürst-Plattner rule):



Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558; Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.





Yamamoto, H. et al. *J. Am. Chem. Soc.* **1989**, *111*, 6431.

