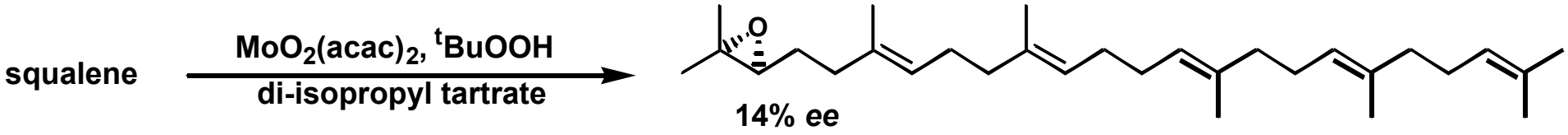
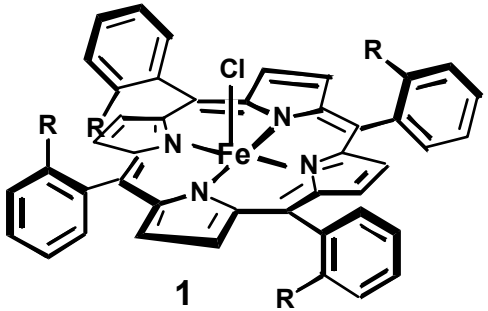
Metal catalysed asymmetric epoxidation of olefins

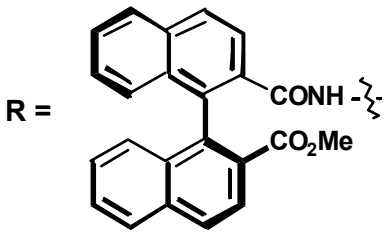
First report: chiral molybdenum peroxo complexes

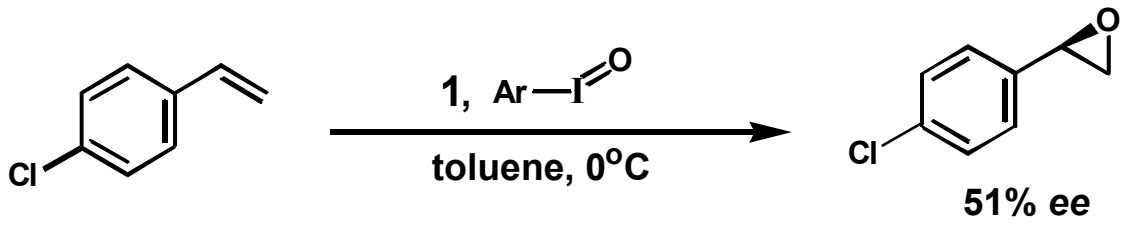


S Otsuka *et al*, *Tetrahedron Lett.* 1979, 3017

Iron porphyrin complexes act as mimics for cytochrome P450 enzymes

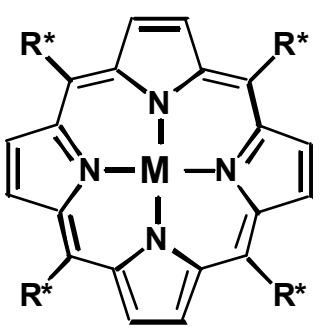




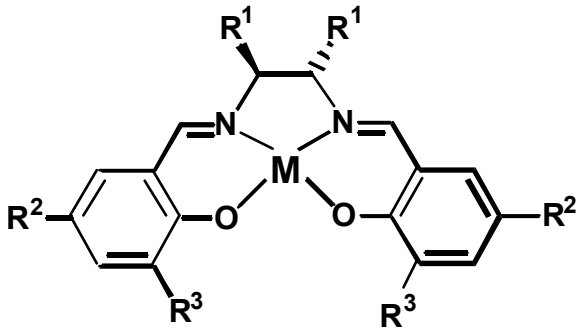


J T Groves *et al*, *J. Am. Chem. Soc.* 1983, *105*, 5791

Metal salen complexes as catalysts for AE reactions



vs.



(E N Jacobsen, T Katsuki)

Advantages of metal salen catalysed AE:

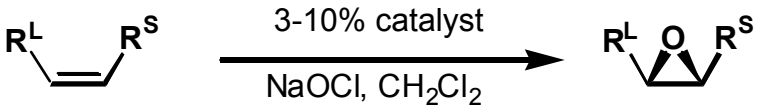
- **Chiral centres close to metal centre**
- **Simple to prepare - substituted salicylaldehyde plus chiral diamine**
- **Relatively stable to oxidation: range of co-oxidants extended**

Achiral metal salen catalysed epoxidations: J K Kochi *et al*, *J. Am. Chem. Soc.* 1985, *107*, 7606

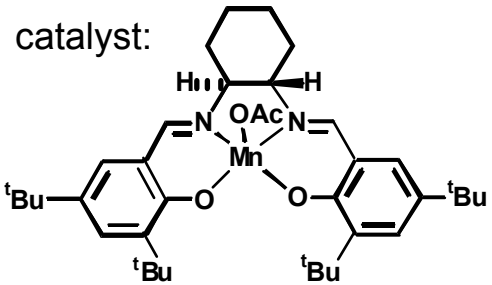
Manganese salen catalysed asymmetric epoxidation of unfunctionalised olefins

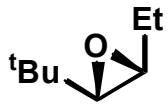
- di-t-butyl substituted chiral manganese salen complexes catalyse the efficient asymmetric epoxidation of *Z*-olefins with good selectivities; the reaction is poor for terminal (low selectivity), *E*- or trisubstituted olefins (low reactivity). Note that the co-oxidant is bleach!

3rd generation:

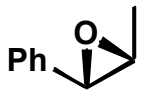


catalyst:

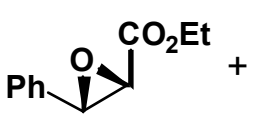




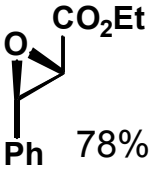
34% *ee*



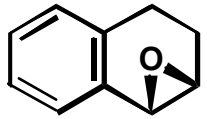
92% *ee*



97% *ee* 4 : 1



78% *ee*

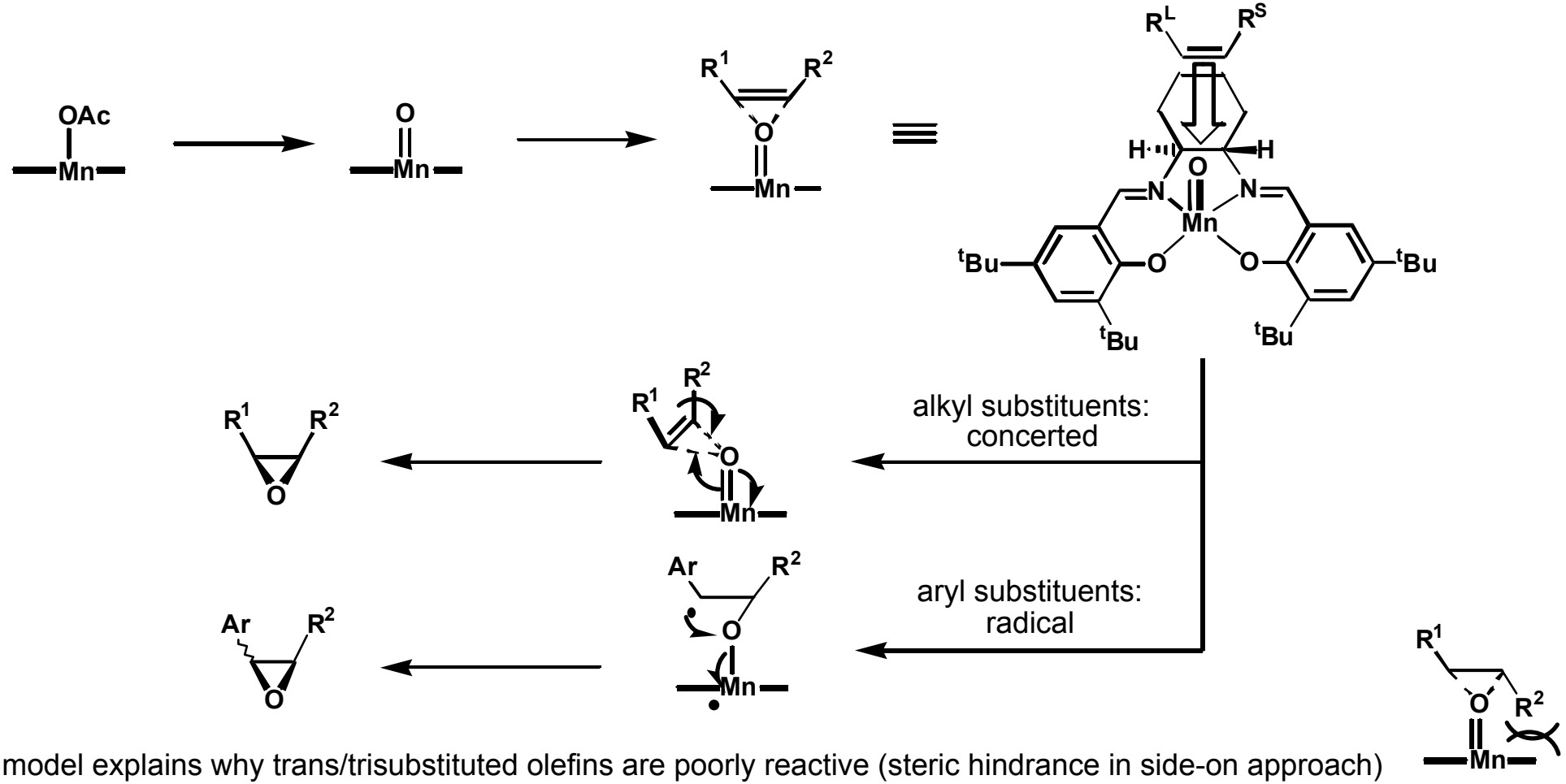


86% *ee*

Jacobsen, *J. Am. Chem. Soc.*, **1991**, *113*, 7063

Manganese salen catalysed asymmetric epoxidation - mechanism and stereochemistry

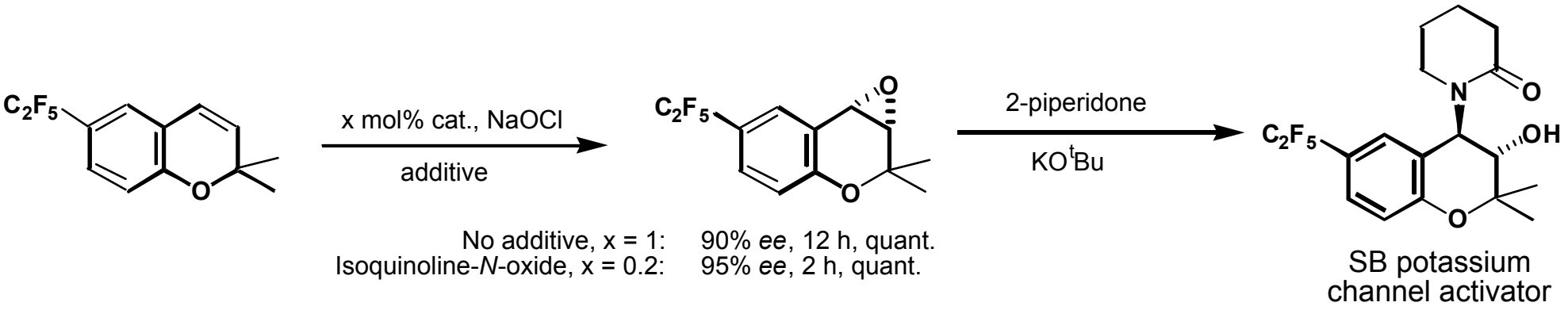
- as seen on the previous slide, dialkyl substituted olefins react with retention of configuration (concerted), whereas acyclic aryl substituted olefins react with loss of geometric purity, suggesting a stepwise radical mechanism



- model explains why trans/trisubstituted olefins are poorly reactive (steric hindrance in side-on approach)
- electron rich olefins are most selective, because their transition state is further along the reaction coordinate

Jacobsen, *J. Am. Chem. Soc*., **1998**, *120*, 948; *Tetrahedron*, **1994**, *50*, 4323

Process-scale application of manganese salen catalysed asymmetric epoxidation

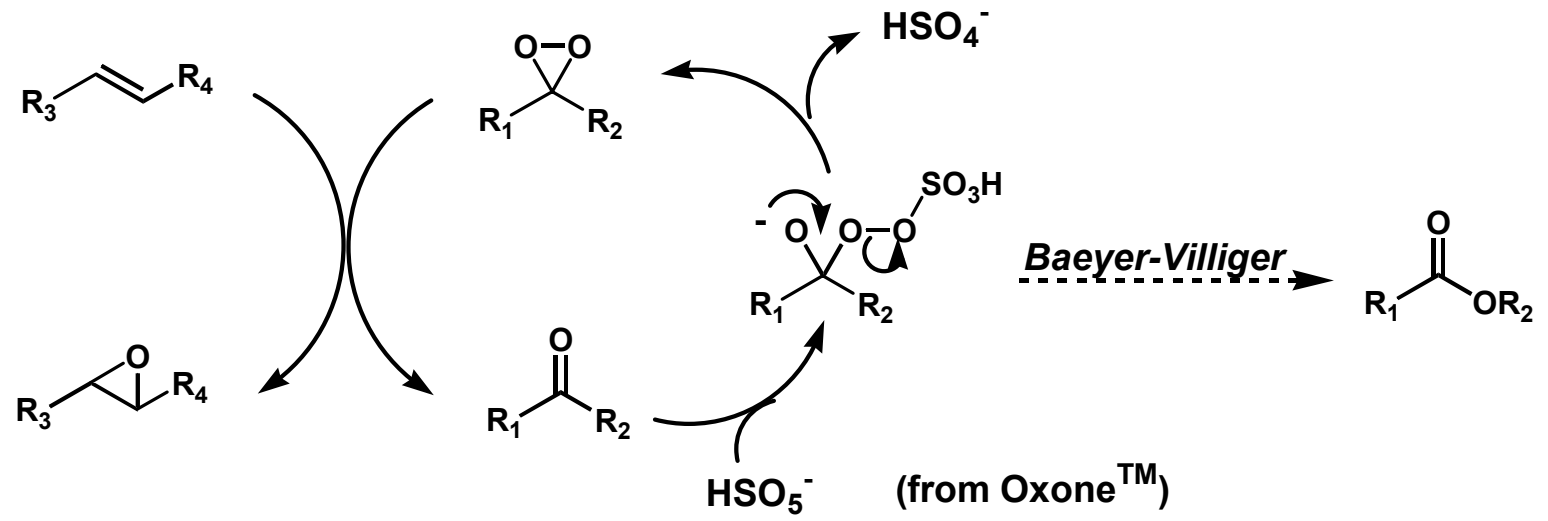


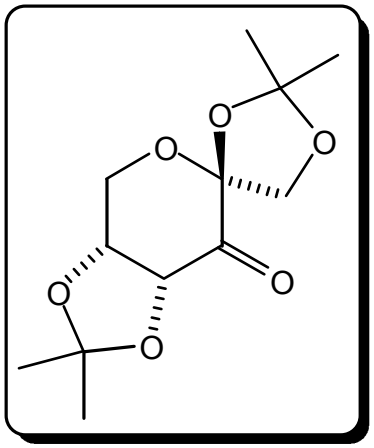
No additive, x = 1: 90% *ee*, 12 h, quant.
Isoquinoline-*N*-oxide, x = 0.2: 95% *ee*, 2 h, quant.

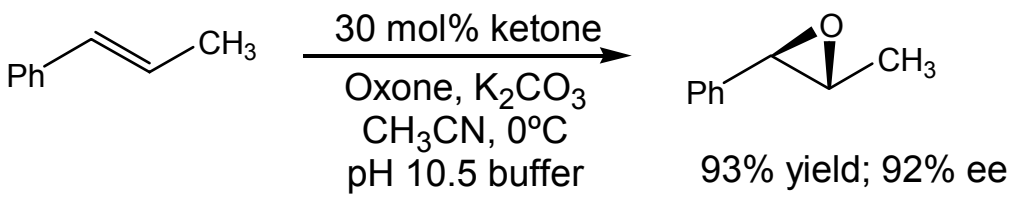
SB potassium channel activator

Tetrahedron Lett., **1996**, *37*, 3895; increase in rate/selectivity of epoxidations with *N*-oxide additives: Jacobsen, *Tetrahedron,* **1994**, *50*, 4223

Dioxirane-Mediated Asymmetric Epoxidation







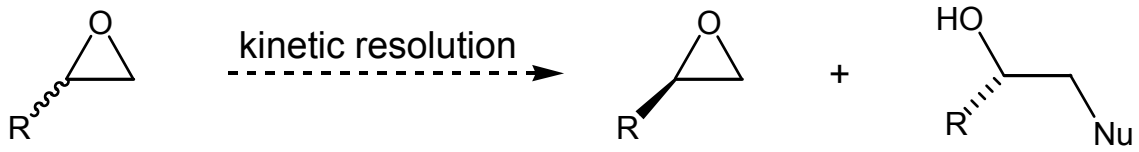
- Preparation: 2 steps from D-fructose (enantiomer available in 5 steps from L-sorbose)
- Excellent enantioselectivities for epoxidation of trisubstituted and *trans*-disubstituted alkenes
- Poor ee for *cis*- and terminal alkenes

- Ketone decomposes by Baeyer-Villiger reaction - cannot be recycled. High pH conditions required.

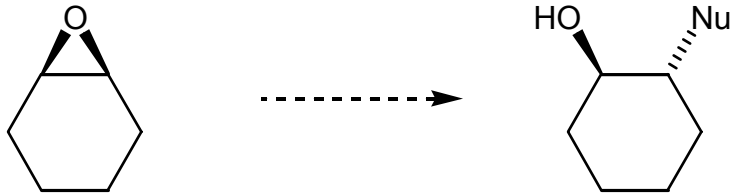
Stable ketones: Armstrong, *Chem. Commun*., **1998**, 621; *Tetrahedron: Asymmetry*, **2000**, *11*, 2057.

Asymmetric Epoxide Ring Opening

- ***Asymmetric ring opening of racemic terminal epoxides***



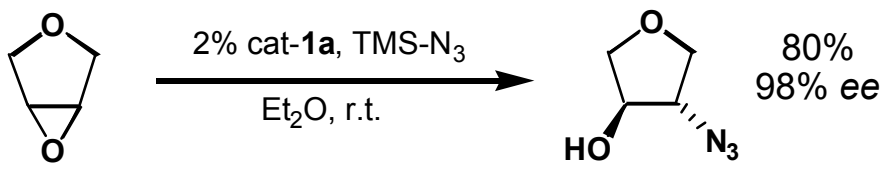
- ***Desymmetrization of meso-epoxides***



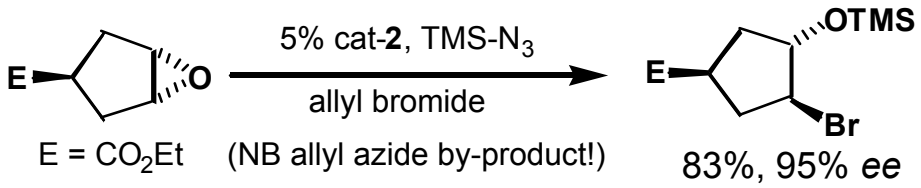
Catalytic asymmetric ring-opening of meso-epoxides

- Asymmetrically substituted *cis*-epoxides are achiral compounds with a meso-plane of symmetry: opening at either carbon produces enantiomeric products. A range of catalysts have been applied to this problem:

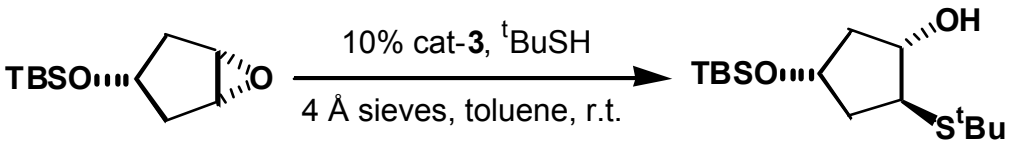
azide as nucleophile[1]



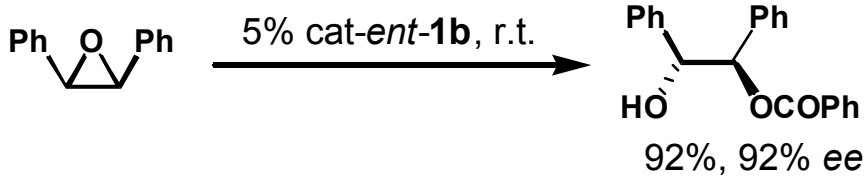
halide as nucleophile[2]



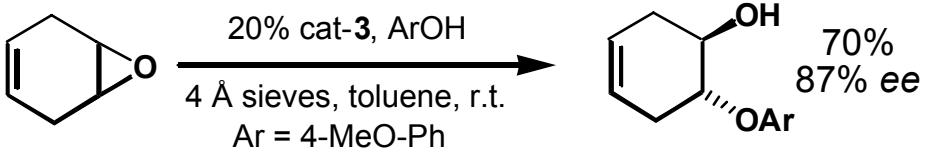
thiol as nucleophile[3]



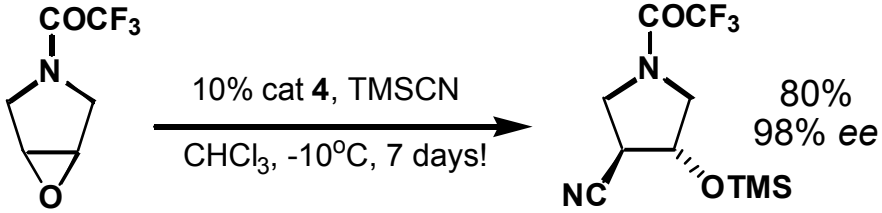
benzoate as nucleophile[4]



phenolate as nucleophile[5]



cyanide as nucleophile[6]

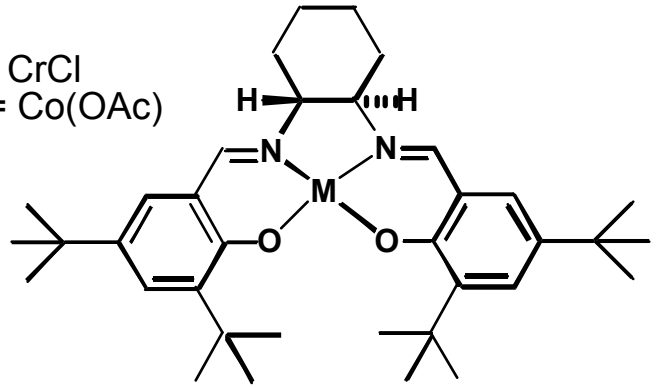


see next slide for catalyst structures and references

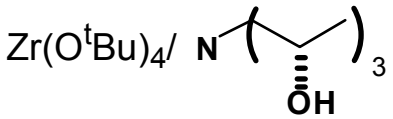
Appendix 1: catalysts for asymmetric ring-opening of meso-epoxides

Catalyst 1:

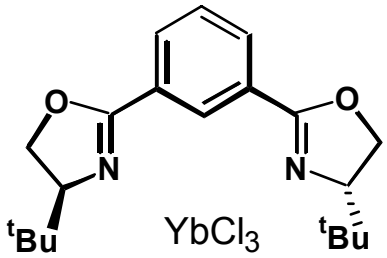
a: M= CrCl
b: M = Co(OAc)



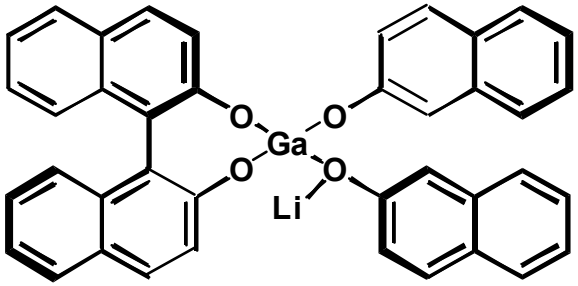
Catalyst 2:



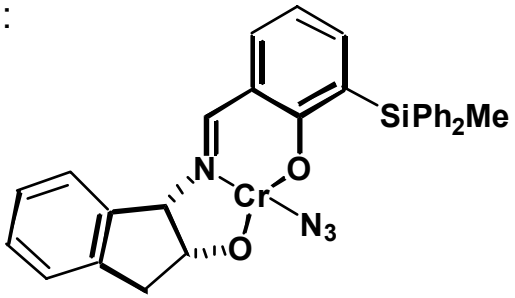
Catalyst 4:



Catalyst 3:



Catalyst 5:

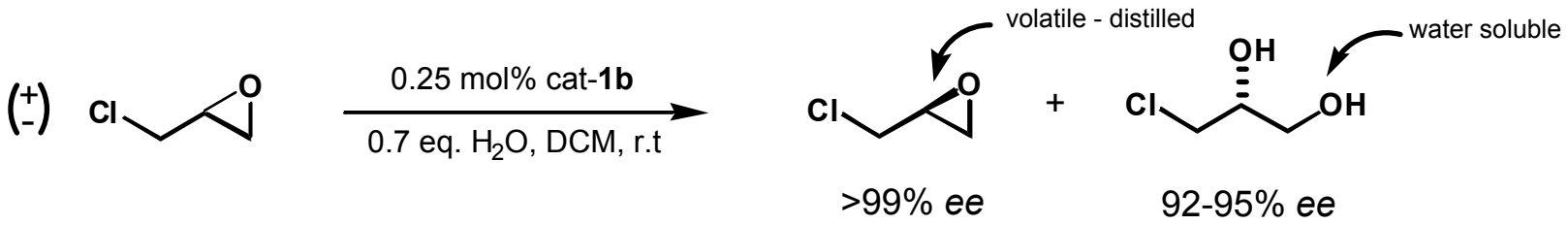


References from slide

1) Jacobsen, *J. Am. Chem. Soc*., **1995**, *117*, 5897; see also Zr catalysis: Nugent, *J. Am. Chem. Soc*., **1992**, *114*, 2768;
2) Nugent, *J. Am. Chem. Soc*., **1998**, *120*, 7139; see also Lewis base catalysis: Denmark, *J. Org. Chem.*, **1998**, *63*, 2428;
3) Shibasaki, *J. Am. Chem. Soc*., **1997**, *119*, 4783; see also Cr catalysis: Jacobsen, *J. Org. Chem.*, **1998**, *63*, 5252;
4) Jacobsen, *Tetrahedron Lett.*, **1997**, *38*, 773; 5) Shibasaki, *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 223;
6) Jacobsen, *Org. Lett*., **2000**, *2*, 1001; see also Ti catalysis: Snapper, Hoveyda, *Angew. Chem., Int. Ed. Engl.*, **1997**, *36*, 1704

Kinetic resolution of racemic epoxides by catalytic asymmetric ring-opening

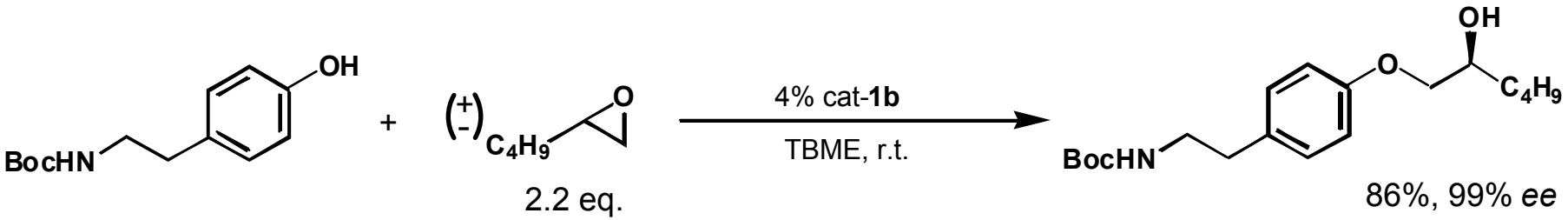
- Meso-epoxides are necessarily a small subset of all possible epoxides. Broader applicability needs a wider range of substrates - but these will all be chiral. Since terminal epoxides are very cheap, a resolution process is viable:



Jacobsen, *Science*, **1997**, *277*, 936; *J. Org. Chem.*, **1998**, *63*, 6776; Tetrahedron Lett., **1999**, *40*, 7303
polymer-supported catalyst: *J. Am. Chem. Soc.*, **1999**, *121*, 4147

- reactions can be run neat; now 1000kg process (Chirex)

- other nucleophiles can also be used:



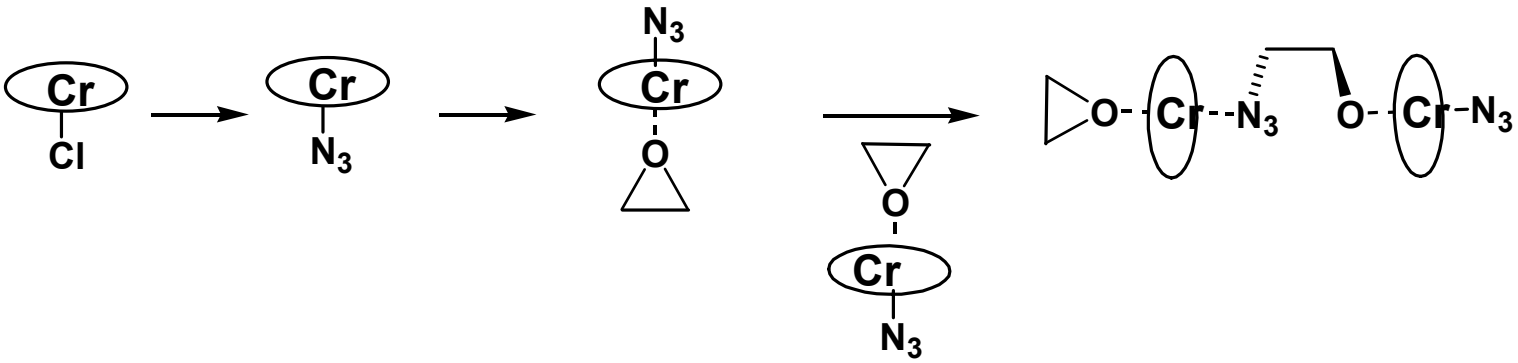
Jacobsen, *J. Am. Chem. Soc.*, **1999**, *121*, 6086
also with azide: *J. Am. Chem. Soc.*, **1996**, *118*, 7420

Reviews of asymmetric epoxide ring opening (meso- and resolution modes): *Acc. Chem. Res.*, **2000**, *33*, 421; *Tetrahedron*, **1996**, *52*, 14361

Mechanism

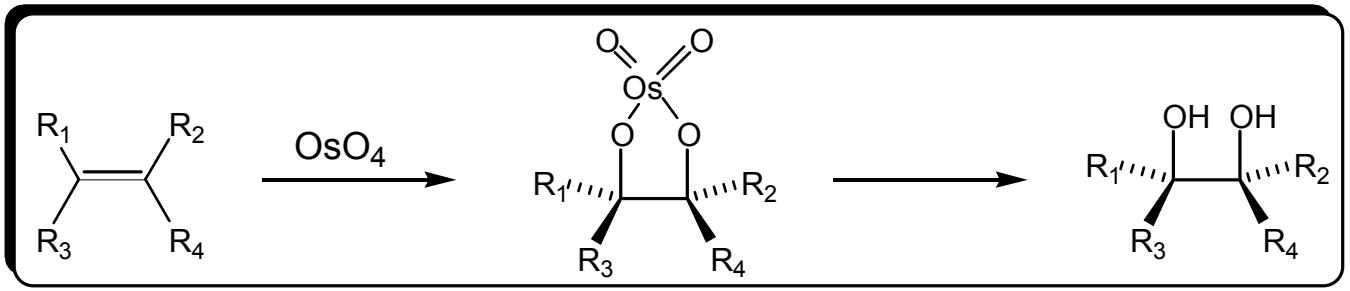
Jacobsen *J. Am. Chem. Soc*. **1996**, *118*, 10924

- Catalyst activates both nucleophile and electrophile



- Tethered dimeric salens give increased rates: *J. Am. Chem. Soc*. **1998**, *120*, 10780.

Alkene Dihydroxylation



Catalytic systems:

• NMO / acetone / H_2O (Upjohn procedure): *Tetrahedron Lett*. **1976**, *23*, 1973.

• $K_3Fe(CN)_6$, K_2CO_3, ^tBuOH / H_2O: Minato, Yamamoto, Tsuji*, J. Org. Chem*. **1990**, *55*, 766.

•Recent catalytic systems:

H_2O_2, cat. flavin, cat. N-methylmorpholine: Backvall, *J. Am. Chem. Soc.* **1999**, *121*, 10424;

• *J. Am. Chem. Soc.* **2001**, *123*, 1365.

• H_2O_2, cat. $V(O)(acac)_2$, NMM, acetone/water: Backvall, *Tetrahedron Lett*., **2001**, *42*, 2569.

• O_2, $K_2[OsO_2(OH)_4]$, ^tBuOH / H_2O:

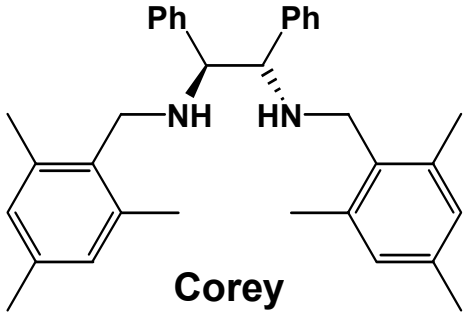
Beller, *Angew. Chem. Int. Ed*. **1999**, *38*, 3026; *J. Am. Chem. Soc*. **2000**, *122*, 10289.

Wirth, *Angew. Chem. Int. Ed*. **2000**, *39*, 334.

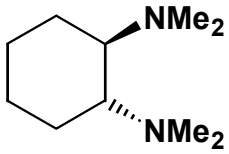
Evolution of Asymmetric Dihydroxylation

Pyridine, tertiary amines accelerates dihydroxylation by OsO_4…….

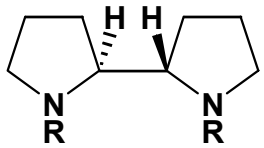
- Chiral pyridines (Sharpless 1979): poor affinity for OsO_4
- Chiral diamines: bind too tightly to OsO_4, forming stable chelates - so cannot be used *catalytically* (but can give excellent enantioselectivities)



Corey

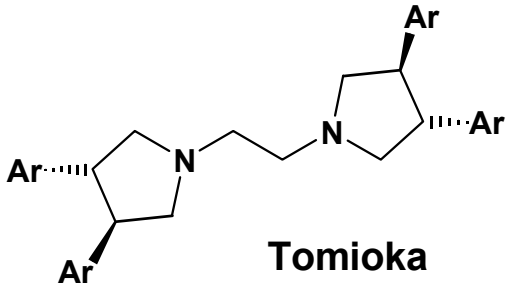


Snyder



(R = neohexyl)

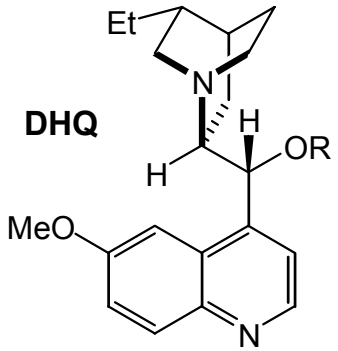
Hirama



Tomioka

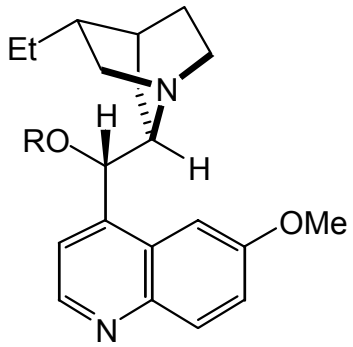
Quinidine / quinuclidine derivatives.....

Sharpless:



DHQ

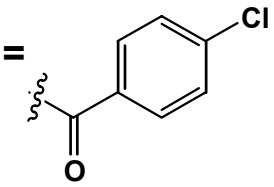
R = H, CLB



DHQD

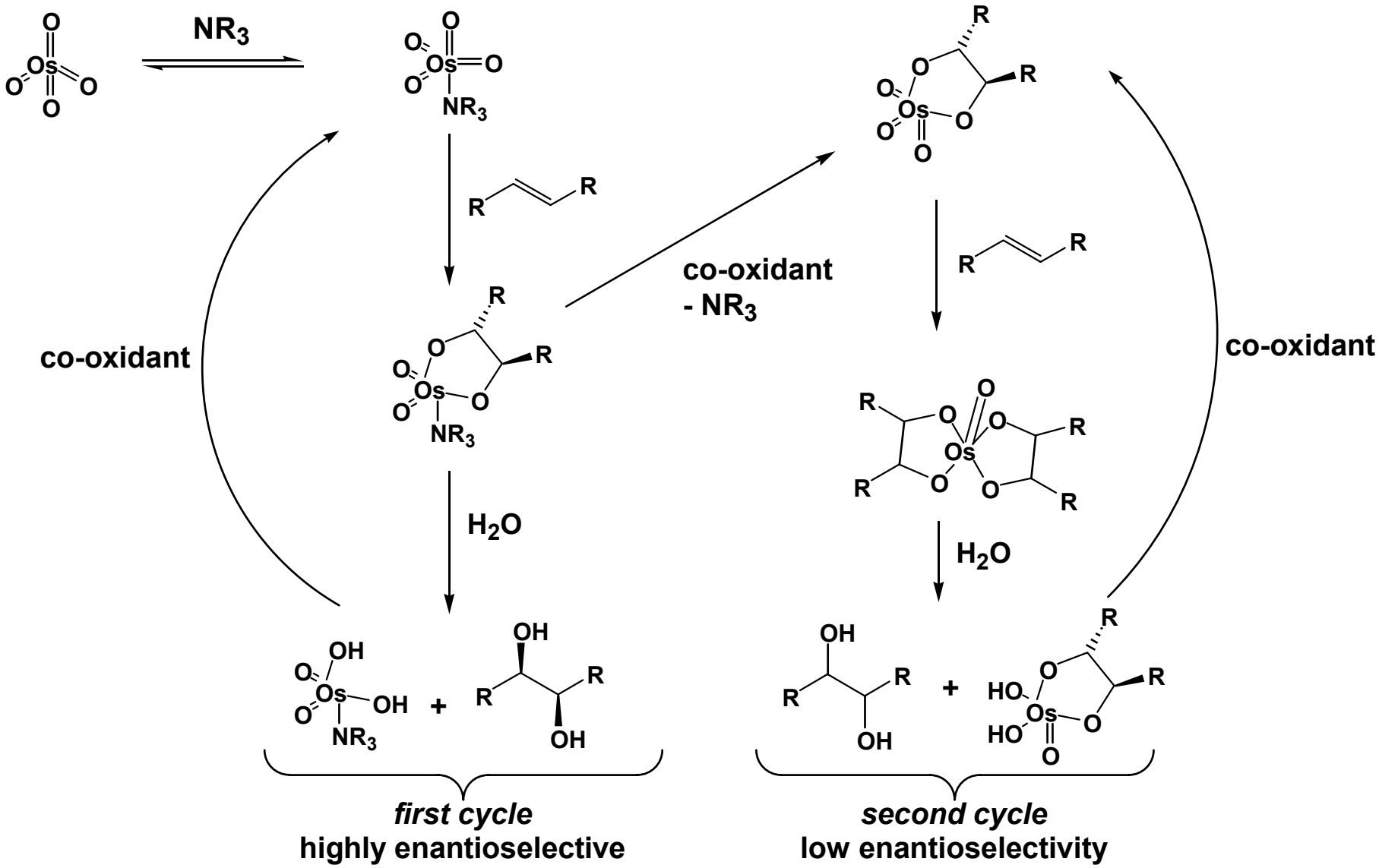
R = H, CLB

CLB =



Good ee obtained using NMO co-oxidant (Upjohn) system. But…..ee often lower for catalytic reaction than stoichiometric. Mechanistic studies showed this to be due to a two-cycle catalytic mechanism……

Catalytic Cycles for Cis-Dihydroxylation



To avoid second cycle:

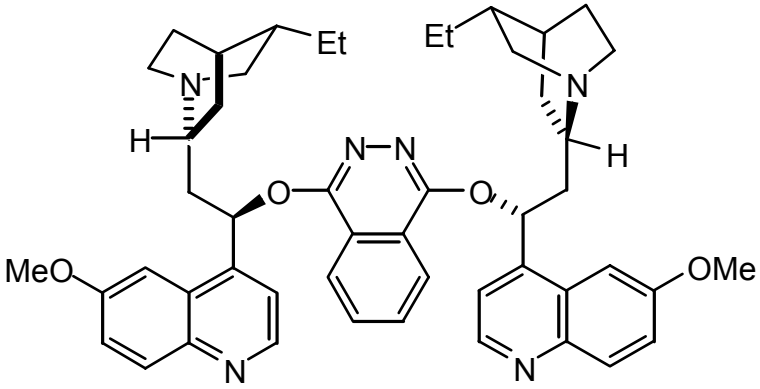
With NMO acetone/water system, add alkene slowly (inconvenient)

Better: use biphasic (^{t}BuOH/H_2O), ferricyanide co-oxidant system: co-oxidant is in different phase to osmate ester, thus preventing second cycle

Sharpless Catalytic Asymmetric Dihydroxylation

Review: Sharpless, *Chem. Rev*. **1994**, *94*, 2483

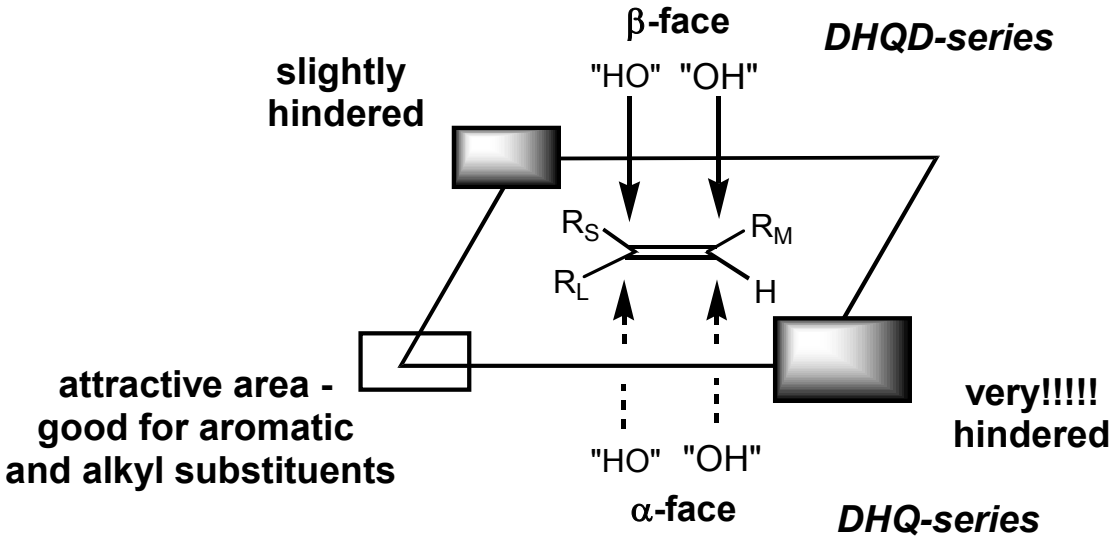
AD-Mix:
$K_2OsO_2(OH)_4$ (non-volatile Os source): 0.2 mol%
$(DHQD)_2PHAL$ or $(DHQ)_2PHAL$: 1 mol%
$K_3Fe(CN)_6$: 3 eq
K_2CO_3: 3 eq



$(DHQD)_2$-PHAL (in β-mix)

Add 1:1 tBuOH: water, alkene, 0°C;
Often supplement $K_2OsO_2(OH)_4$ to make 1%
$MeSONH_2$ (1 eq) to accelerate hydrolysis of intermediate osmate ester (unless alkene is terminal)

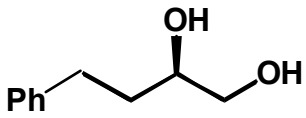
Importance of pH control: improved rates for internal olefins at pH 12 (no $MeSO_2NH_2$); higher ee for terminal olefins at pH 10: Beller, *Tetrahedron Lett.* **2000,** *41,* 8083.



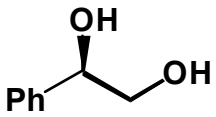
Structural effects in asymmetric dihydroxylation reactions

(all reactions shown carried out with $(DHQD)_2$-PHAL; figure in parentheses is *ee*)

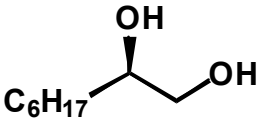
*terminal olefins**



(84)

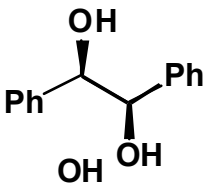


(97)

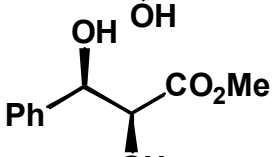


(84)

trans-disubstituted olefins



(99.8)



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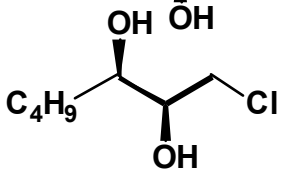
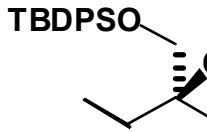
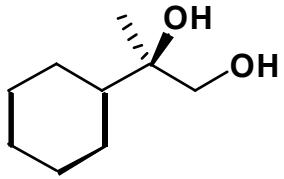


(94)

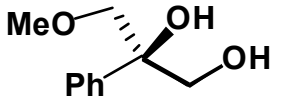
1,1-disubstituted olefins



(91)

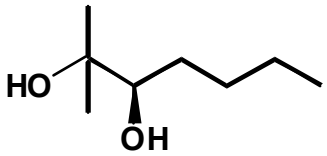


(69)*



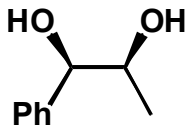
(97)

trisubstituted olefins



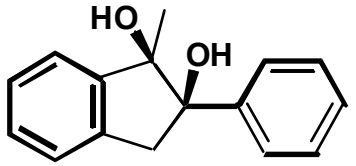
(98)

cis-disubstituted olefins



(72)

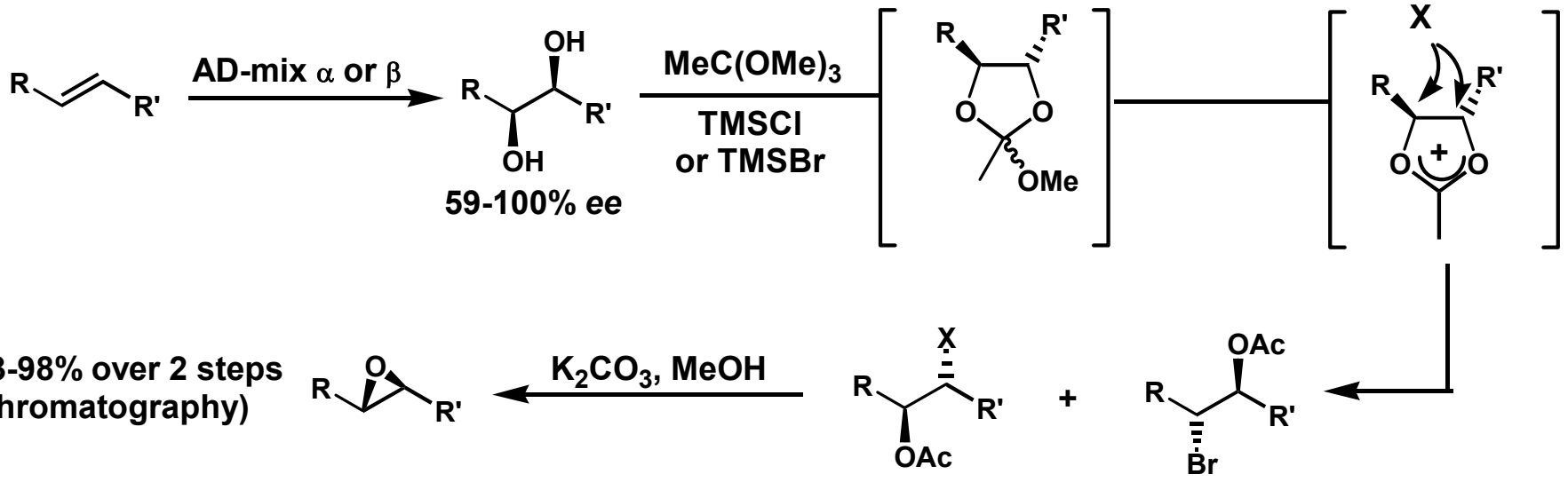
tetrasubstituted olefins



(75)

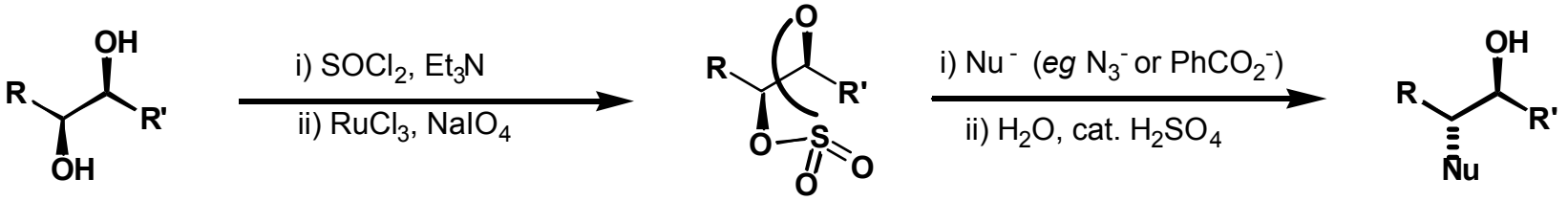
* - an alternative anthraquinone-derived spacer offers superior ee's for terminal olefins and those bearing only alkyl substituents. See *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 448

Epoxides via catalytic asymmetric dihydroxylation

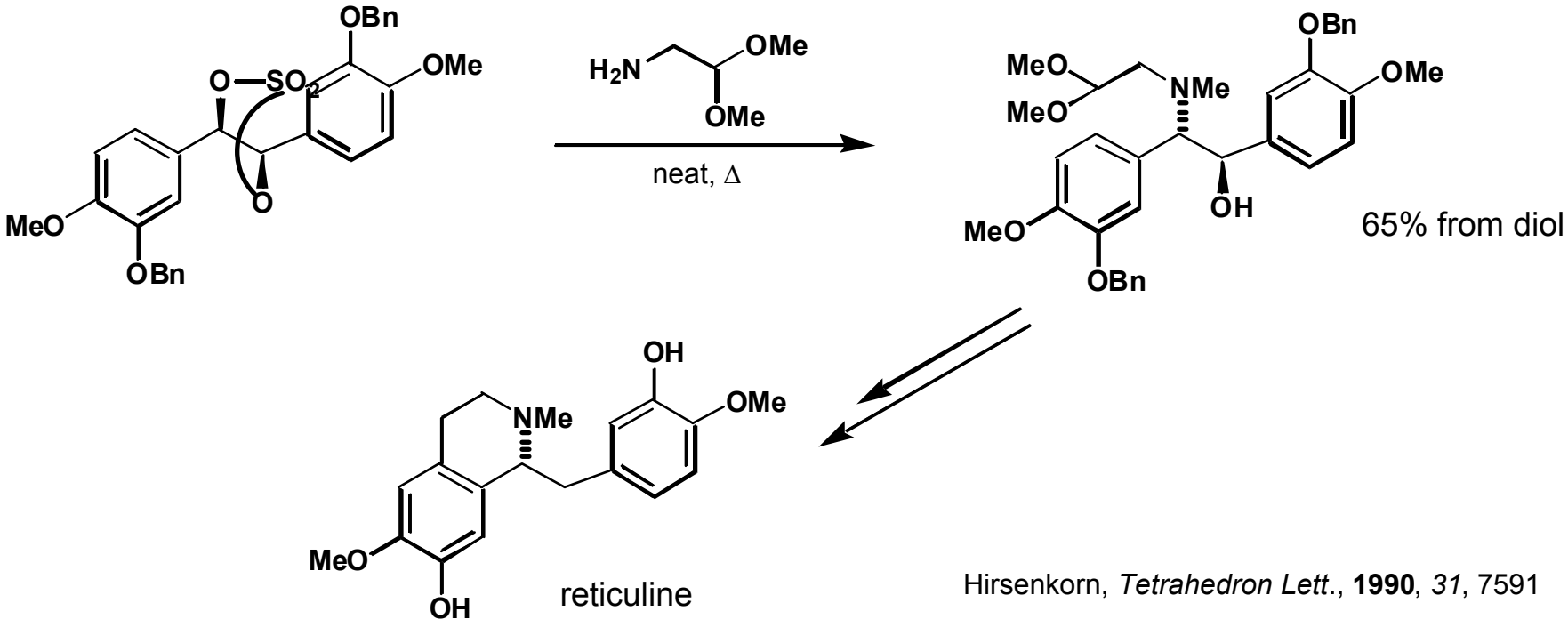


K B Sharpless *et al*, *Tetrahedron*, 1992, *48*, 10515

Cyclic sulfates as epoxide equivalents



Sharpless,*Tetrahedron Lett.*, **1989**, 30, 655



Hirsenkorn, *Tetrahedron Lett.*, **1990**, *31*, 7591