Outline:

Epoxidation
- Condensation approaches
    - Darzens condensation
    - Sulfur ylides
- With organic peroxides
    - Peroxy acids
    - Peroxy iminic acids
    - Dioxiranes
        - DMDO
        - Enantioselective versions
- Metal-catalyzed Approaches
    - $V(O)(acac)_2$
    - Sharpless AE
    - Metal Oxo's
        - MTO
        - Fe, Pt and Mn-based
        - (Salen)Mn Jacobsen AE

Dihydroxylation
- General considerations
- Sharpless AD
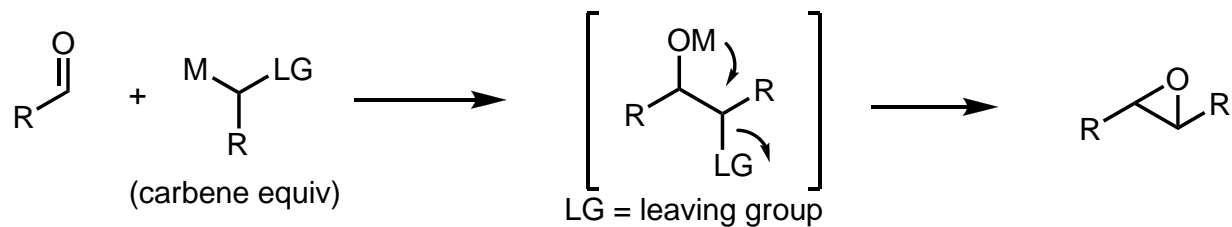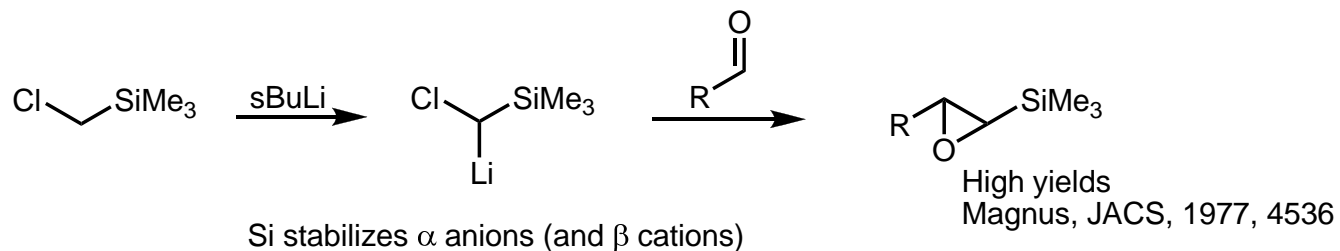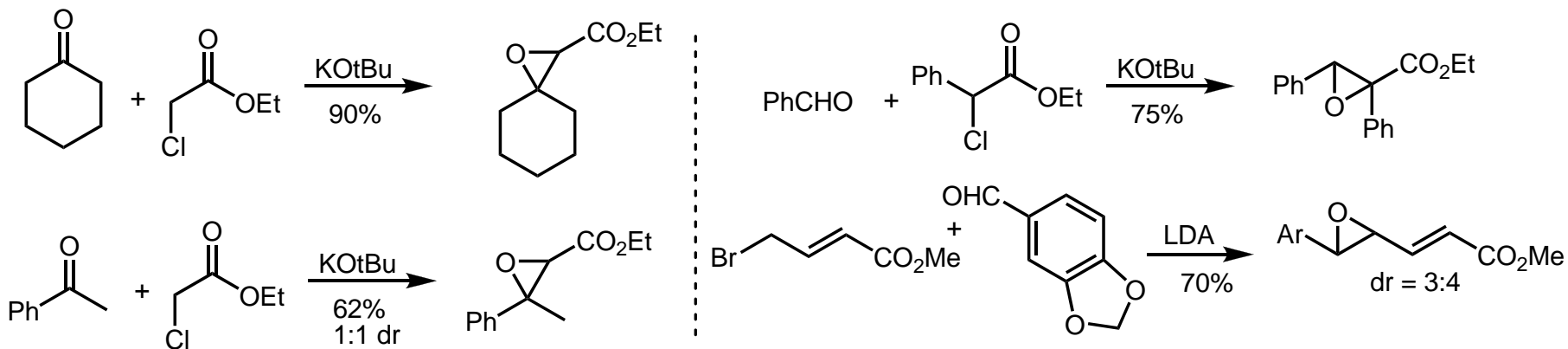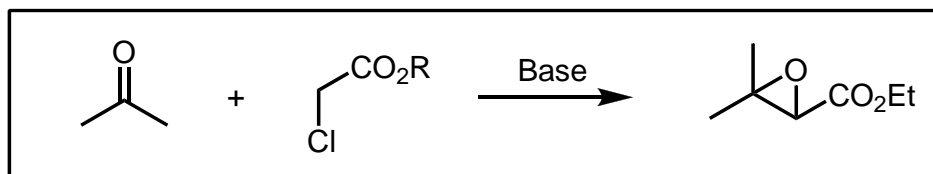   - Conditions and scope
    - Mechanism
    - Applications

Epoxide Ring Opening
- Opening under acid or basic conditions
- Organocopper additions
- Reactions of epoxy alcohols

Condensations: <u>general</u> <u>scheme</u>

(carbene equiv)   LG = leaving group

Darzens condensation

Si stabilizes α anions (and β cations)

High yields
Magnus, JACS, 1977, 4536

Corey-Chaykovsky Epoxidation JACS, 1965, 1353

Two flavors of sulfur ylides are common:

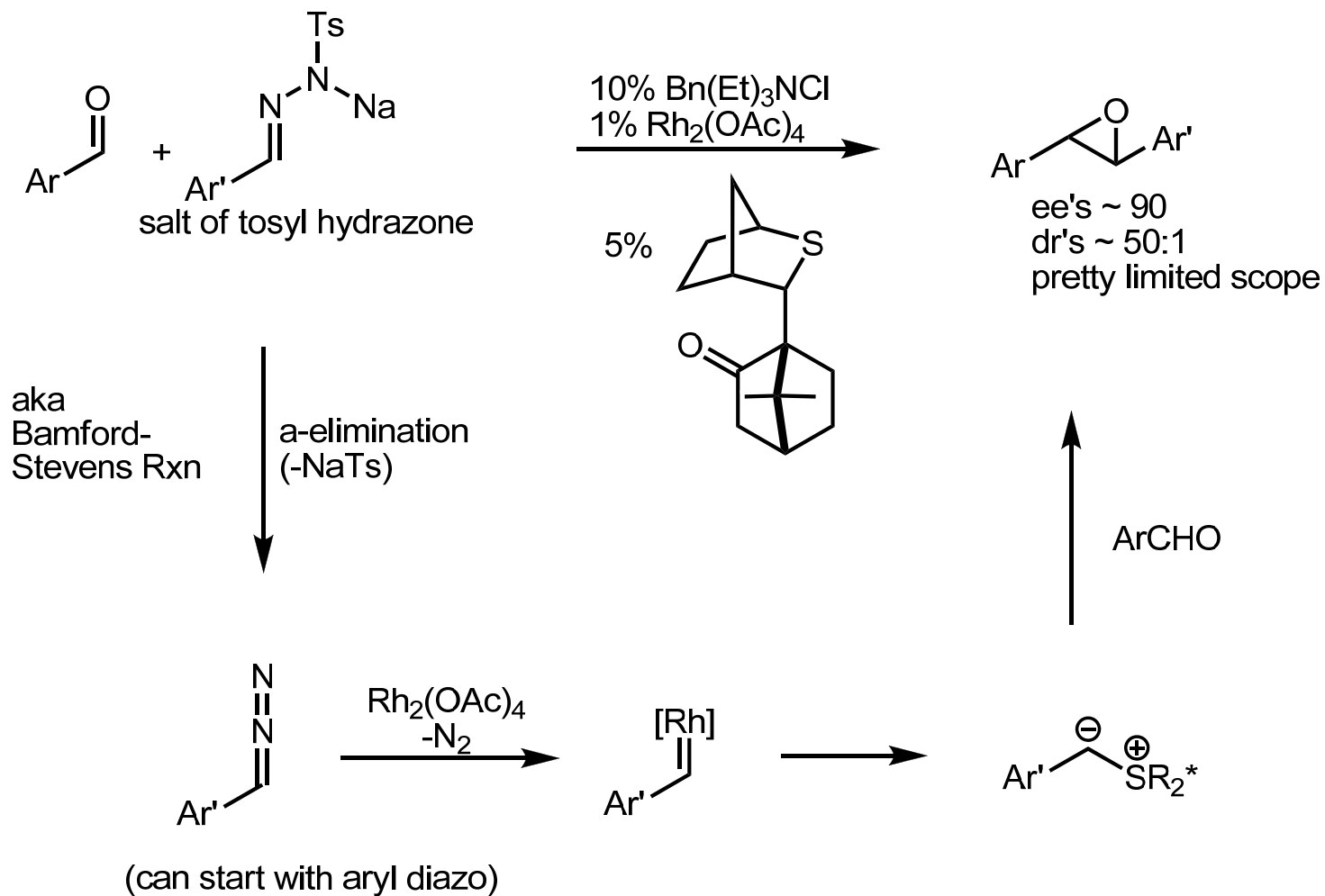$(Me)_2\overset{\oplus}{S}-CH_3$ → dimsyl anion (DMSO/NaH) → $(Me)_2\overset{\oplus}{S}-\overset{\ominus}{CH_2}$
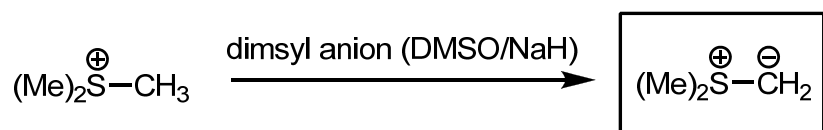
Dimethyl Sulfonium ylide
more reactive
less stable
generated/used low T
adds irreversibly (kinetic product)

$H_2\overset{\ominus}{C}-\overset{O}{\underset{\oplus}{S}}(Me)_2$ ← NaH ← $H_3C-\overset{O}{\underset{\oplus}{S}}(Me)_2$
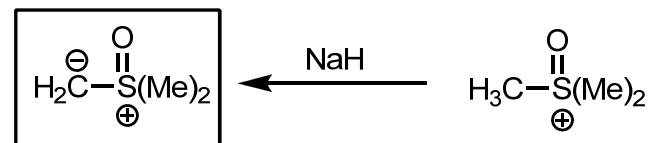
Dimethylsulfoxonium ylide
less reactive
adds reversibly (thermodynamic product)

+ $H_3C-\overset{O}{\underset{\oplus}{S}}(Me)_2\ I^-$ → NaH/DMSO / 50 °C / 67% →

t-Bu → → t-Bu + t-Bu

$(Me)_2\overset{\oplus}{S}-\overset{\ominus}{CH_2}$ 17:83

$H_2\overset{\ominus}{C}-\overset{O}{\underset{\oplus}{S}}(Me)_2$ 100:0

$(Me)_2\overset{\oplus}{S}-\overset{\ominus}{CH_2}$ →

$H_2\overset{\ominus}{C}-\overset{O}{\underset{\oplus}{S}}(Me)_2$ →
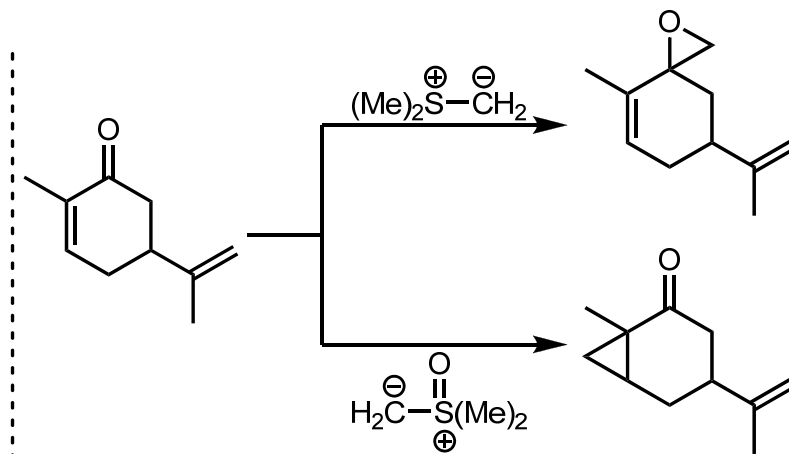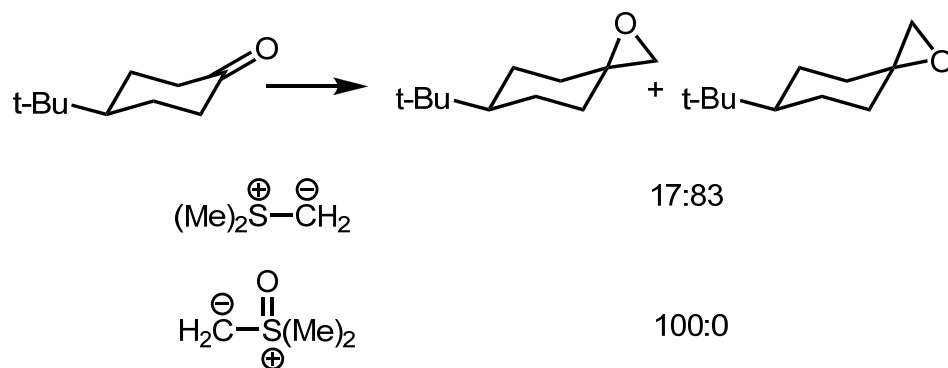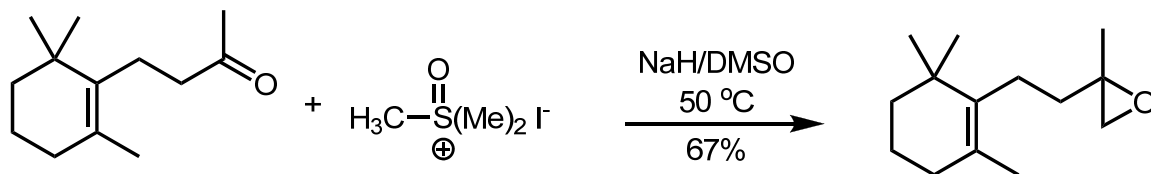
Catalytic generation of and catalytic enantioselective epoxidation with sulfur ylides

salt of tosyl hydrazone

10% Bn(Et)$_3$NCl
1% Rh$_2$(OAc)$_4$

5%

ee's ~ 90
dr's ~ 50:1
pretty limited scope

aka
Bamford-
Stevens Rxn

a-elimination
(-NaTs)

ArCHO

Rh$_2$(OAc)$_4$
-N$_2$

[Rh]

(can start with aryl diazo)

Aggarwal, Chem Rev 2007, 5841

Most common peroxides:
AcOOH, mCPBA, MMPP, Oxone (KHSO$_5$), DMDO
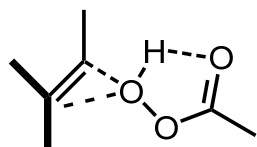
spiro transition state
$\pi_{cc} \rightarrow \sigma^*_{oo}$
$n_o \rightarrow \pi^*_{cc}$
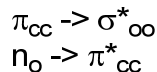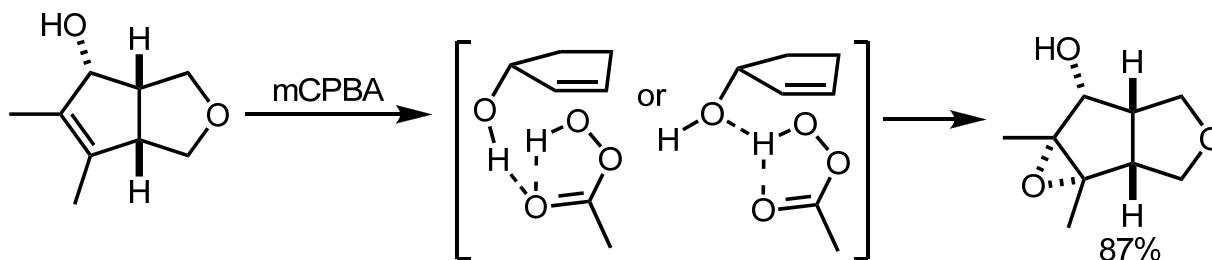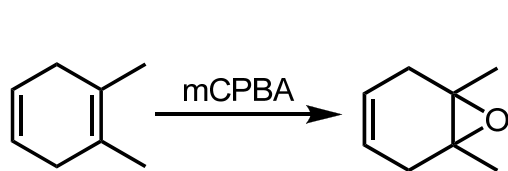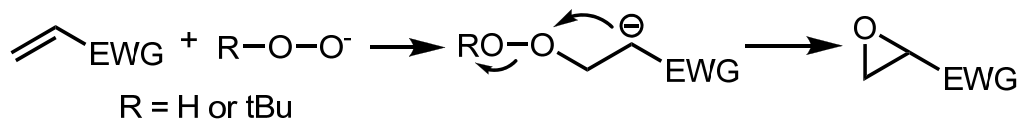
concerted reaction
stereospecific

electrophilic reagents:
rate INCREASES with EDG on olefin
                    EWG on peracid

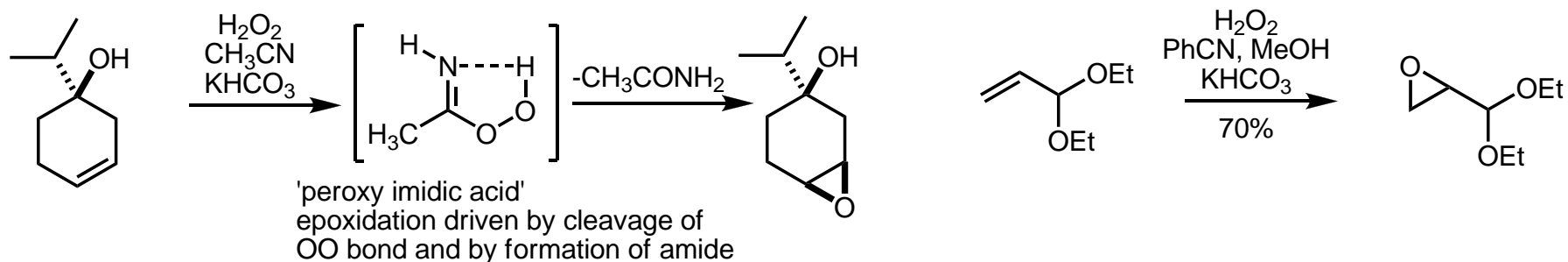EWG on olefin requires basic conditions. Epoxidation via stepwise mechanism:

R = H or tBu

87%

71%
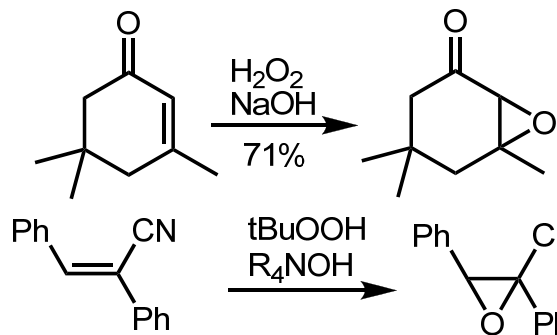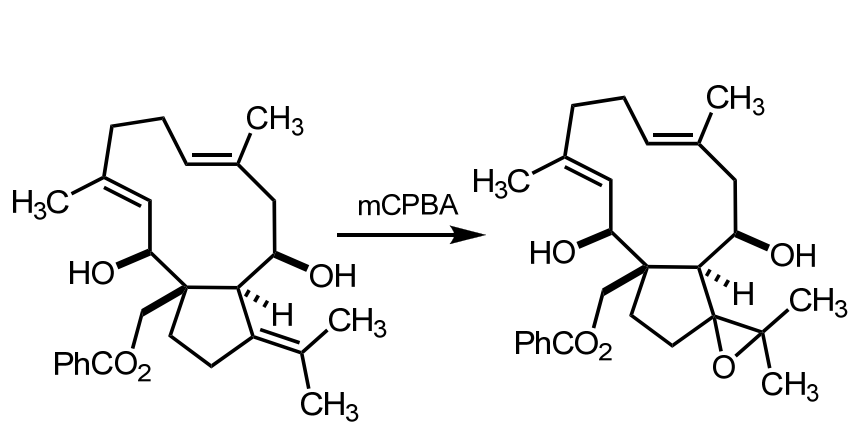
R or electron-poor olefins: generally bad substrates
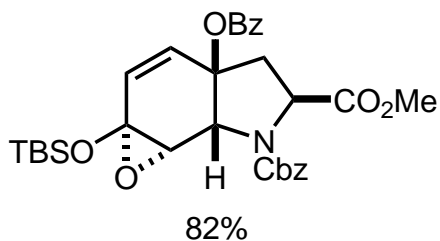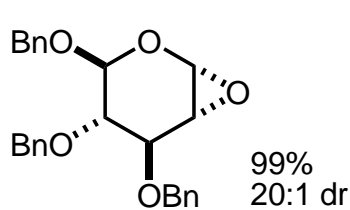
Payne Oxidation: mechanistically similar to peracids, but under basic conditions.

'peroxy imidic acid'
epoxidation driven by cleavage of
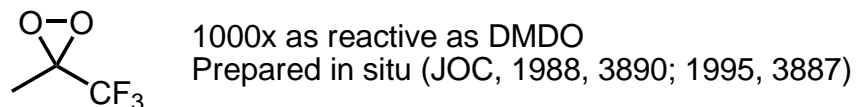OO bond and by formation of amide

Dimethyl Dioxirane: Very strong oxidant; very easy to use
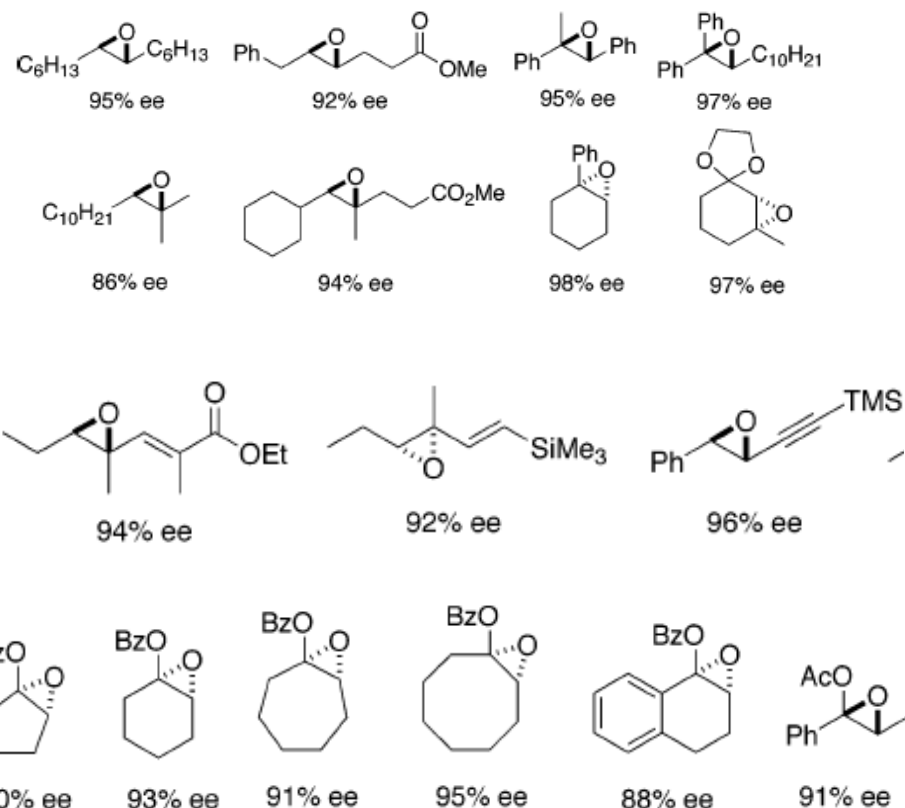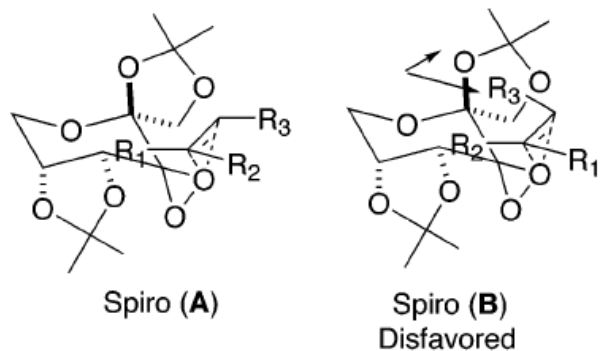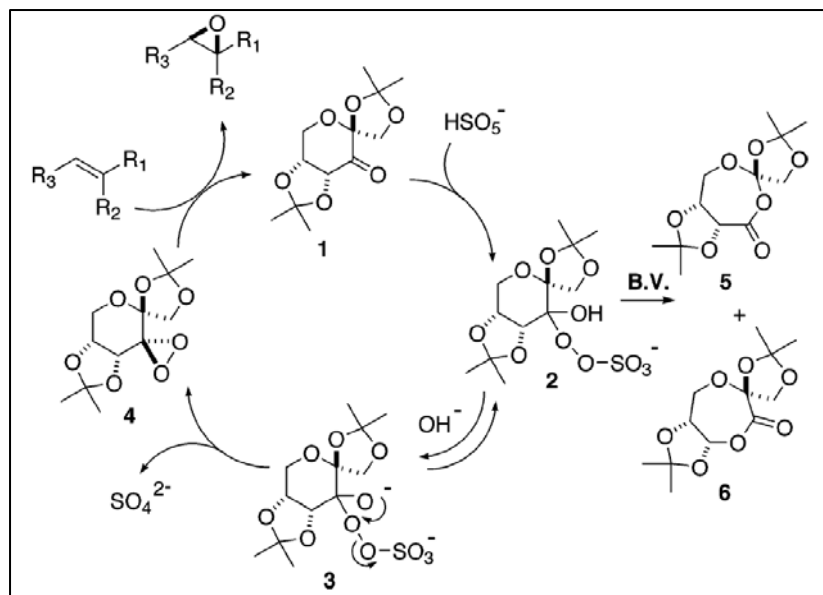Organic Reactions, 2002, vol 61, p219 - ref includes prep for DMDO and experimental conditions for use.
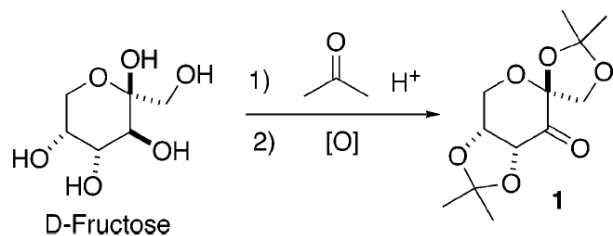
prep:

sold as oxone: $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$

Can be prepared in situ or as ~0.1M soln in acetone
Like peracids, reacts via spiro transition state
Most useful for prep of sensitive epoxides b/c byproduct is acetone

99%
20:1 dr

82%

DMDO
quant.

BF_3; DMDO
85%

72%
note: e- poor; no B.V. oxidation
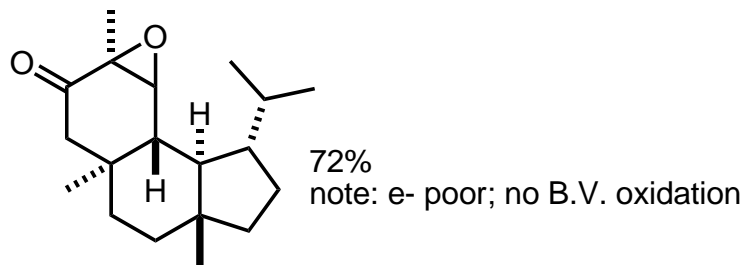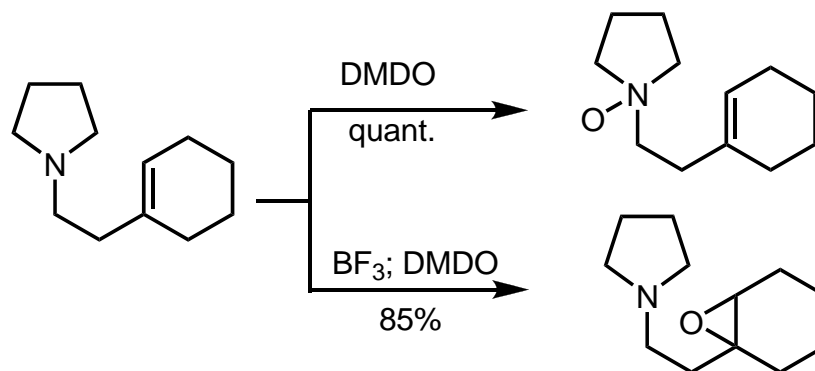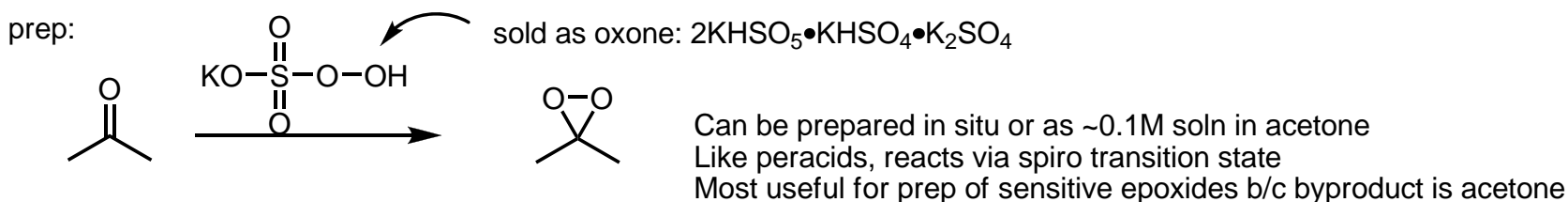
For even more horsepower:

1000x as reactive as DMDO
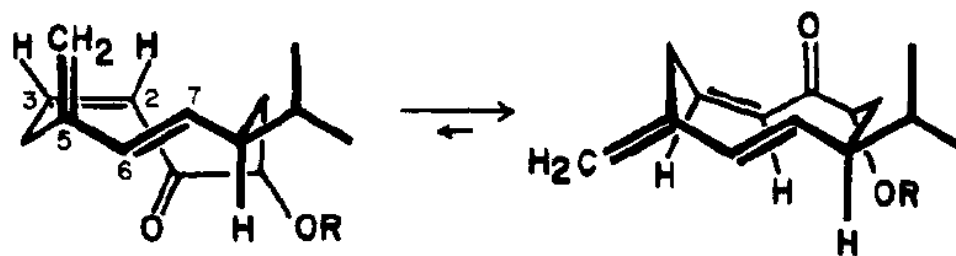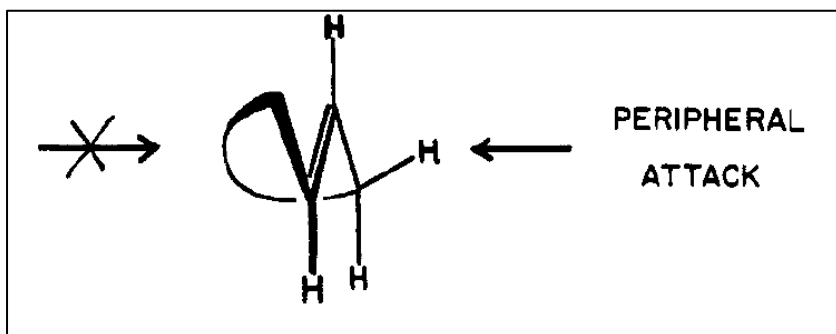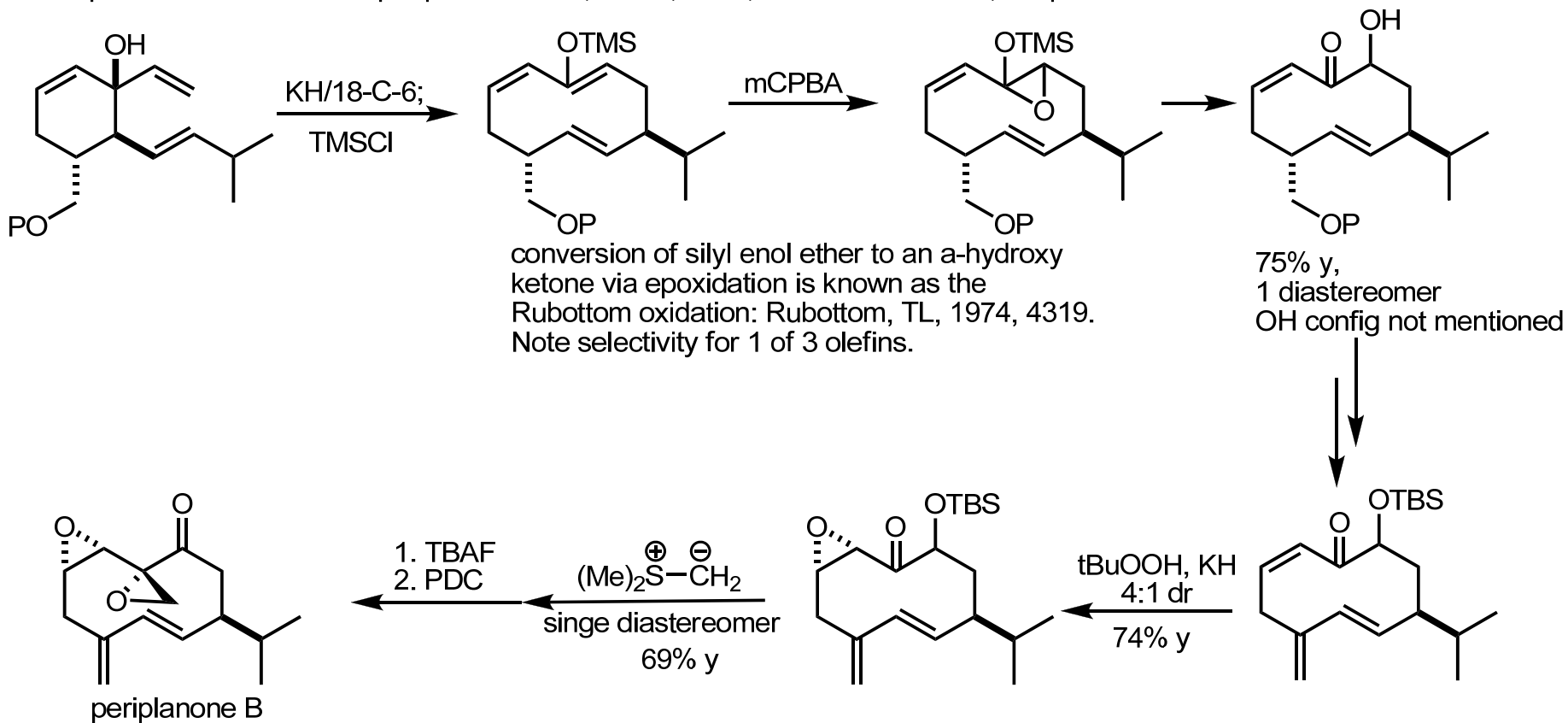Prepared in situ (JOC, 1988, 3890; 1995, 3887)

Several groups have developed chiral ketones as catalysts for asymmetric epoxidation. The most successful has been the Shi epoxidation. The catalyst is easily prepared from fructose and displays broad generality. Shi, Accts, 2004, 488

D-Fructose

95% ee   92% ee   95% ee   97% ee

86% ee   94% ee   98% ee   97% ee

94% ee   92% ee   96% ee

BzO
80% ee   93% ee   91% ee   95% ee   88% ee   91% ee

Spiro (A)   Spiro (B)
                  Disfavored

Principle drawbacks:
requires slow addition of two reagent solutions
Enantiomeric catalyst more difficult to access
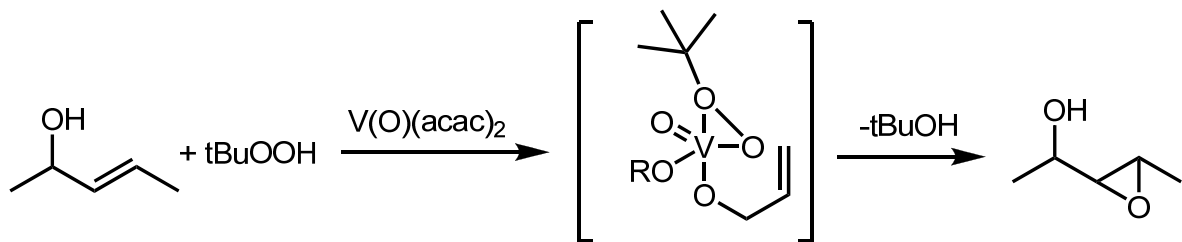
But: one of the most effective catalysts for AE.

Several epoxidations en route to periplanone: Still, JACS, 1979, 2493 and Classics, chap 13.

conversion of silyl enol ether to an a-hydroxy
ketone via epoxidation is known as the
Rubottom oxidation: Rubottom, TL, 1974, 4319.
Note selectivity for 1 of 3 olefins.

75% y,
1 diastereomer
OH config not mentioned

periplanone B

1. TBAF
2. PDC

(Me)₂S–CH₂
singe diastereomer
69% y

tBuOOH, KH
4:1 dr
74% y

PERIPHERAL
ATTACK

S-trans configuration favored for dienes

Ox to V^V under rxn conditions
induced proximity
activation of peroxide

Sharpless, JACS, 1973, 6136
Review: Evans, Chem Rev. 1993, 1307
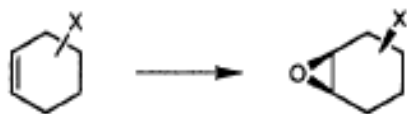
Substrate	$k_{rel}^{a,b}$ (diastereoselectivity^c)		
	peracid	Mo(CO)$_6$	VO(acac)$_2$
(cyclohexene)	1.00	1.00	1.00
(cyclohexenol)	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)

Key point: V and Mo show increased
reactivity and high selectivity

Entry	Substrate	Selectivity	Entry	Substrate	Selectivity
1		9 : 1 (α)	4		single epoxide (α)
2		single epoxide (β)	5		>200 : 1 (β)
3		1 : 1			

Key points: VO(acac)$_2$ reliable, chemoselective
and stereoselective

ca. 40° (vs mCPBA ~ 120°)

Preferred conformation
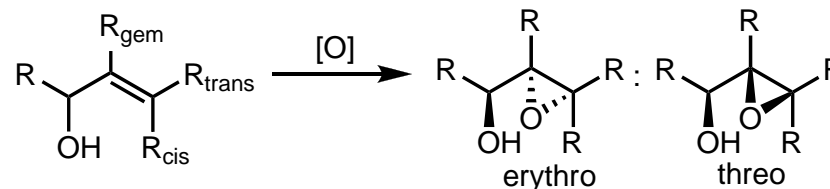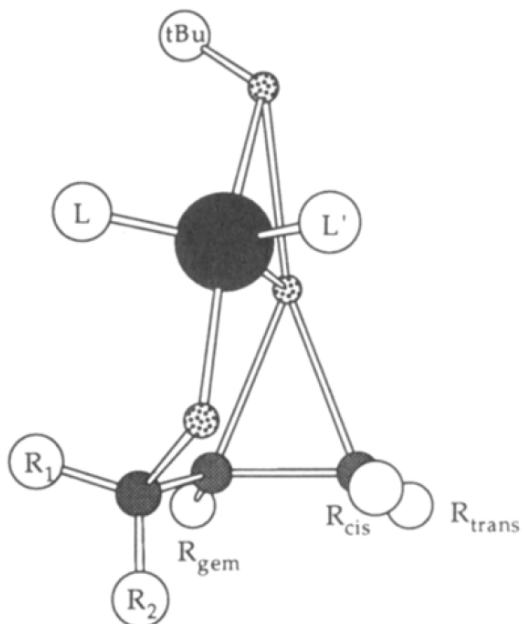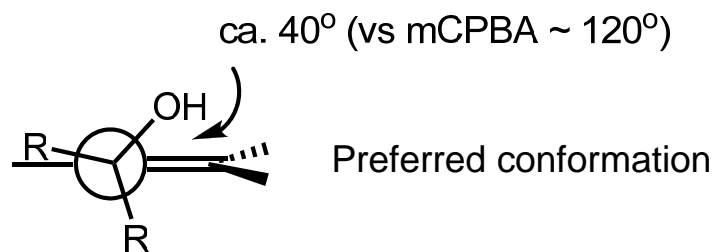
Entry	Substrate	VO(acac)$_2$	Mo(CO)$_6$	m-CPBA
1		4 : 1	1 : 1	1 : 1.5
2		19 : 1	5 : 1	1 : 1
3		2.5 : 1	1 : 1.5	1 : 1.7
4		1 : 2.4	1 : 5	1 : 19
5		1 : 5	1 : 19	1 : 19

For table: R1 = Me → threo; R2 = Me → erythro
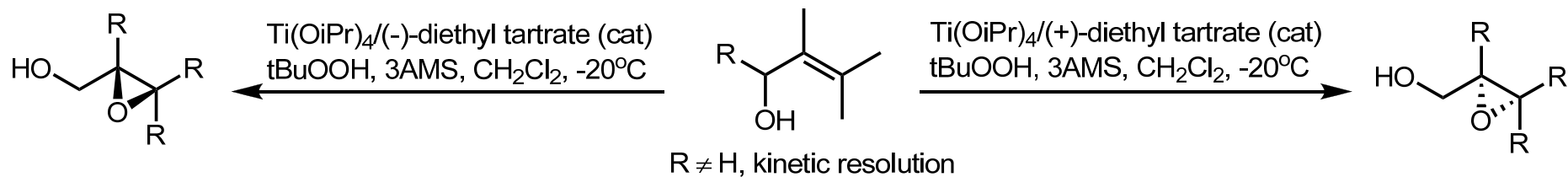Can use conformational analysis to understand and predict
A$_{1,3}$ strain between R$_2$ and R$_{cis}$ favors threo
A$_{1,2}$ strain between R$_{gem}$ and R$_1$ favors erythro
Interaction b/w L and R$_1$ favors erythro
σ_{C-R2}→π^* favors erythro

Ti(OiPr)$_4$/(-)-diethyl tartrate (cat)
tBuOOH, 3AMS, CH$_2$Cl$_2$, -20°C

R ≠ H, kinetic resolution

Ti(OiPr)$_4$/(+)-diethyl tartrate (cat)
tBuOOH, 3AMS, CH$_2$Cl$_2$, -20°C

See lecture notes from Synthesis and Catalysis

See handout from Andrew Myers

From Sharpless, Masamune, Science, 1983, vol 220, 949; see also Tet, 1990, 254.
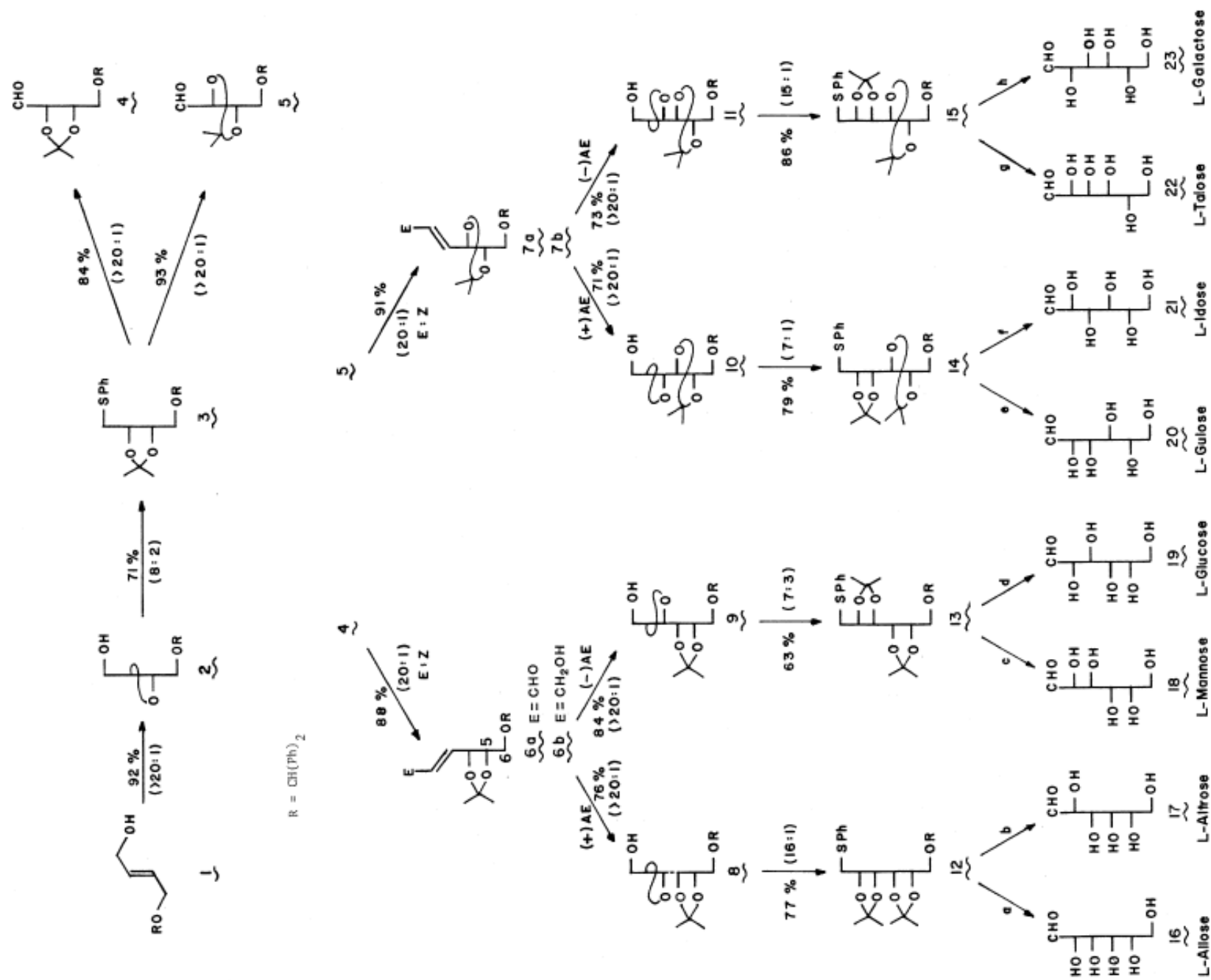
Fig. 2. Synthesis of L-hexoses. For a, c, e, and g, 1 = Pummerer reaction, 2 = Dibal, 3 = deprotection. a: 1 (90 percent), 2 (81 percent), 3 (90 percent). c: 1 (90 percent), 2 (95 percent), 3 (90 percent). e: 1 (87 percent), 3 (84 percent). g: 1 (71 percent), 2 (77 percent), 3 (61 percent). For b, d, f, and h: 1 = Pummerer reaction, 2 = potassium carbonate and methanol, 3 = deprotection. b: 1 (90 percent), 2 (48 percent), 3 (see (11)). d: 1 (90 percent), 2 (60 percent), 3 (20 percent). f: 1 (87 percent), 2 (66 percent), 3 (85 percent). h: 1 (71 percent), 2 (41 percent), 3 (27 percent).

Much research has gone into mimicking cytochrome P450, natures oxidant. The objectives are generally three-fold: 1) Identify highly reactive catalysts. 2) use H2O2 as the terminal oxidant and 3) induce asymmetry.

Cytochrome P450 mechanism

Fe superoxide

Fe peroxide

Fe hydroperoxide

Fe (IV) Oxo
(Ligand radical)

Fe(V) Oxo
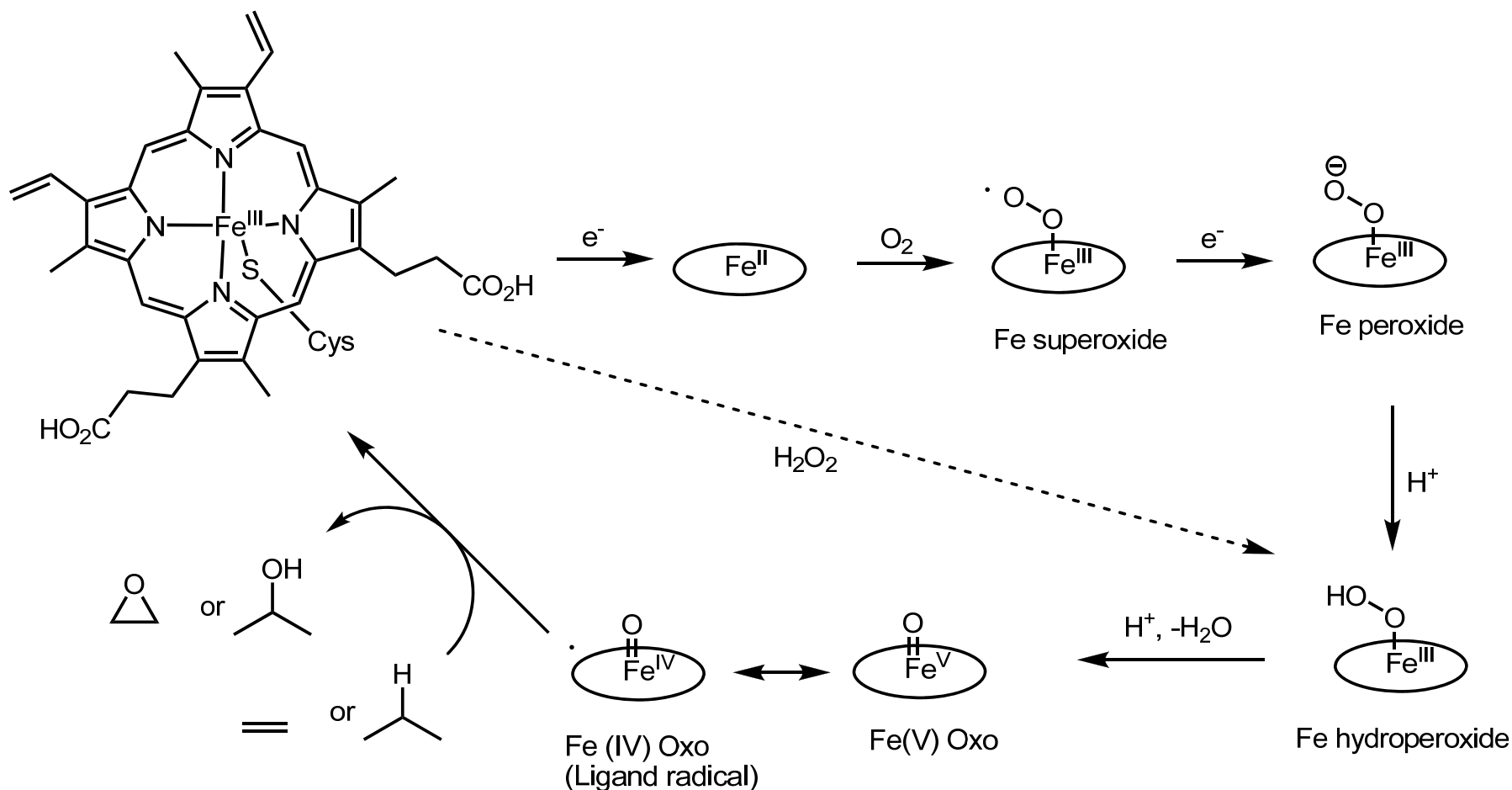
successive electron transfer steps can be avoided by using H_2O_2

Rev on epox with H2O2: Chem Rev 2003, 2457.

MTO: methyl trioxorhenium
Hermann, ACIEE, 1991, 1638

MTO, Re(VII), ~$120/g (Aldrich)
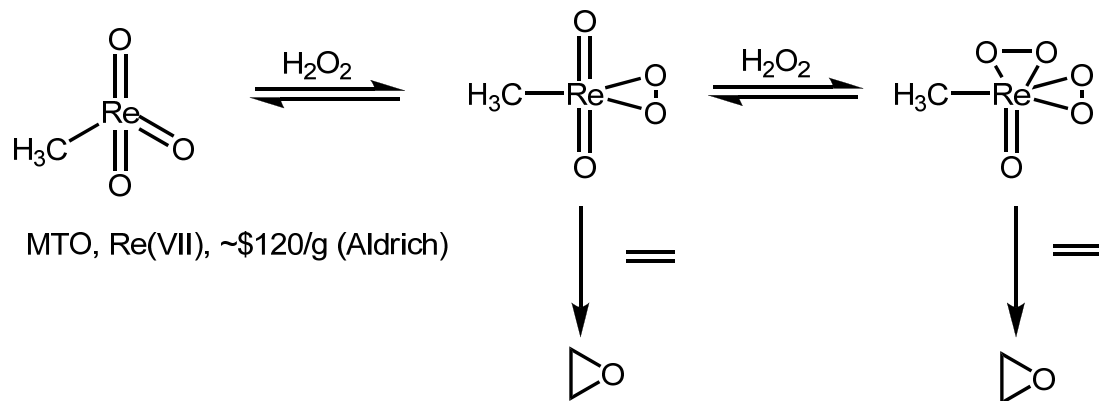
Beneficial effect of added pyridine
Sharpless, JACS, 1997, 6187
    Faster reaction
    Prevents cat decomp
    Buffers reaction
    Sharpless favors py as ligand; no asymmetric version

0.5% MTO, 12% py (amount is critical)
1.5 equiv 30% aq H_2O_2
CH_2Cl_2 or CH_3NO_2

stereospecific
high yields
mild conditions

92%

96:4 dr   82% (48h)
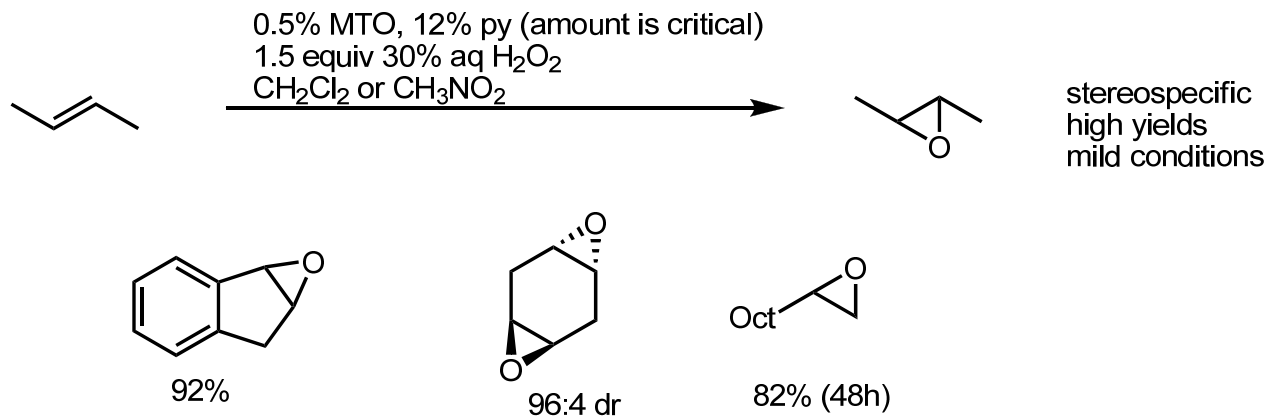
TMTACN: Trimethyl-triazacyclononane (TACN)

Discovered by group from Unilever (oxidative stain removal)
De Vos, TO, 1998, 3221

TMTACN (0.15%), MnSO$_4$ (0.1%), Oxalic acid (0.3%)

H$_2$O$_2$ (1.3 equiv)
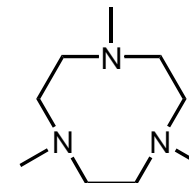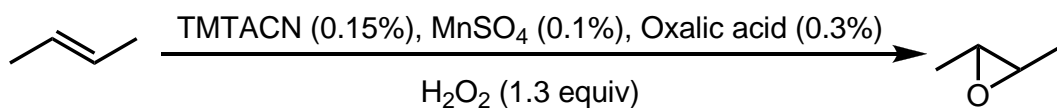
TMTACN
Expensive ligand (difficult to make)
Mostly GC yields
Minimal Functionality demonstrated

Fe-based system
White, Doyle, Jacobsen, JACS, 2001, 7194

Fe[SbF$_6$]$_2$

AcOH, H$_2$O$_2$
CH$_3$CN
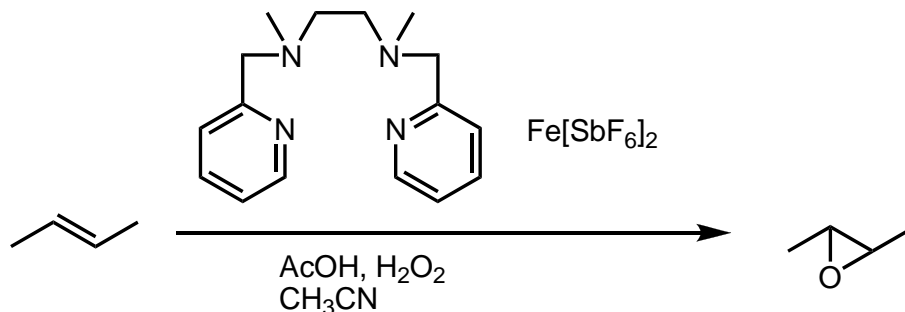
Assembles into di-iron core (2 AcO bridges)
Mimic of MMO
Good yields for terminal olefins
Little functionality allowed

Pt-based system
Strukul, JACS, 2007, 7680
Asymmetric version: JACS, 2006, 14006

Ph$_2$
P OH$_2$ OTf
Pt
(2 mol%)
P C$_6$H$_5$
Ph$_2$

H$_2$O$_2$ (1 equiv)
H$_2$O/DCE
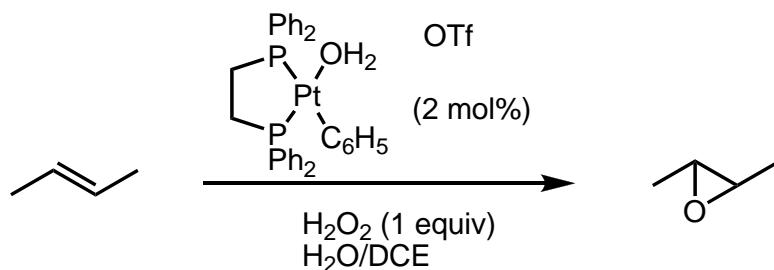
Propose addition to Pt-coordinated olefin, but details
   have evolved
Good yields for terminal, unhindered olefins
Very sensitive to sterics and electronics

Background: Collman (review: Science, 1993, 261, 1404) showed metal porphyrin complexes could catalyse epoxidation
Kochi (JACS 1986, 2309) showed that (salen)Mn and (Salen)Cr complexes could catalyze epoxidation
Burrows (JACS, 1988, 4087) showed that (salen)Ni complexes could catalyze epoxidation
Katsuki (TL, 1990, 7345) showed moderate enantioselectivity with (salen)Mn complexes

Ligand synthesis:

SALicylaldehyde
deriviative

Ethylene diamine (**EN**)
derivative

salen ligand

Catalytic epoxidation:

C_{sp2} ⟍R + NaOCl
(pH 10-13)

0.1 - 4 mol%

C_{sp2} ⟍R

- -

87-98% ee
JACS, 1991, 7063

92-98%ee   up to 97%ee
JOC, 1994, 4378
TL, 1995, 5123

>90%ee
trans epoxide!
TL, 1991, 6533
JOC, 1993, 6939

>80%ee

80's
JACS, 1994, 9333
TL, 1995, 5457
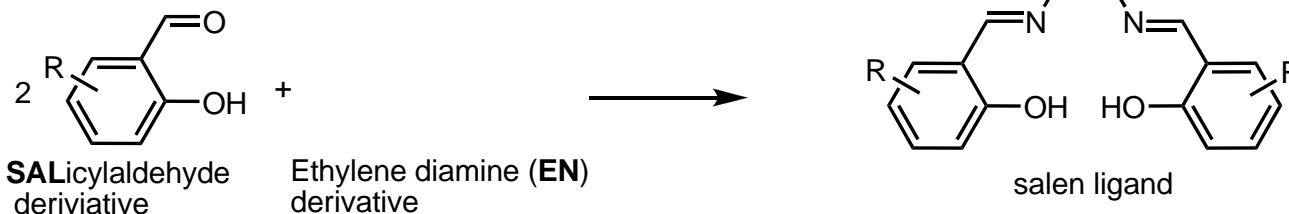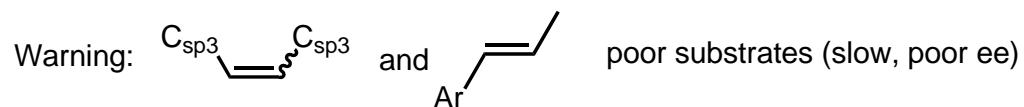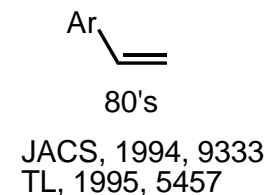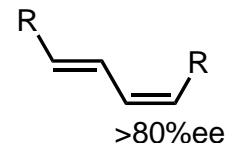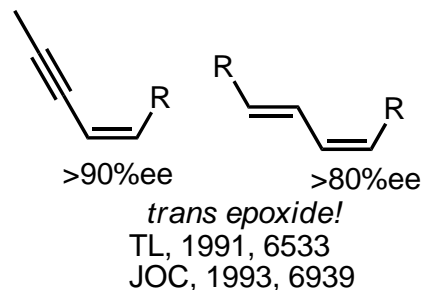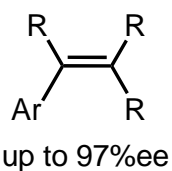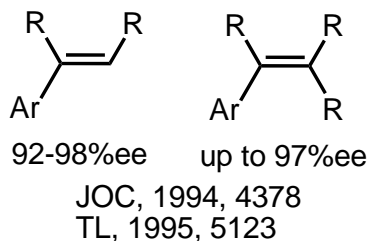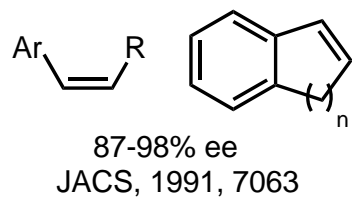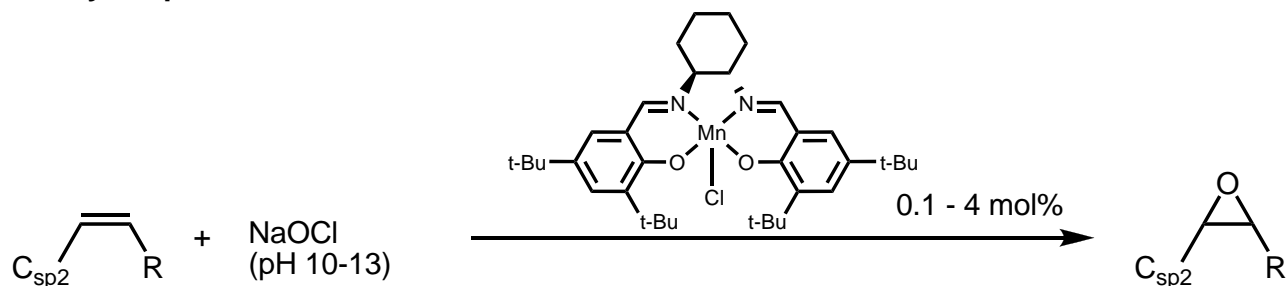
Warning: C_{sp3}⟍═⟋C_{sp3} and Ar⟍═⟋ poor substrates (slow, poor ee)   Review: Chem Rev. 2005, 1563

amine oxides in Jacobsen AE:
TL, 1996, 3271

Known as Ritter reaction
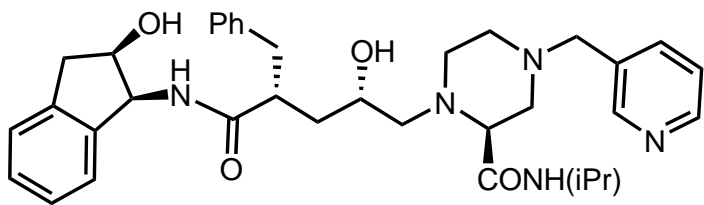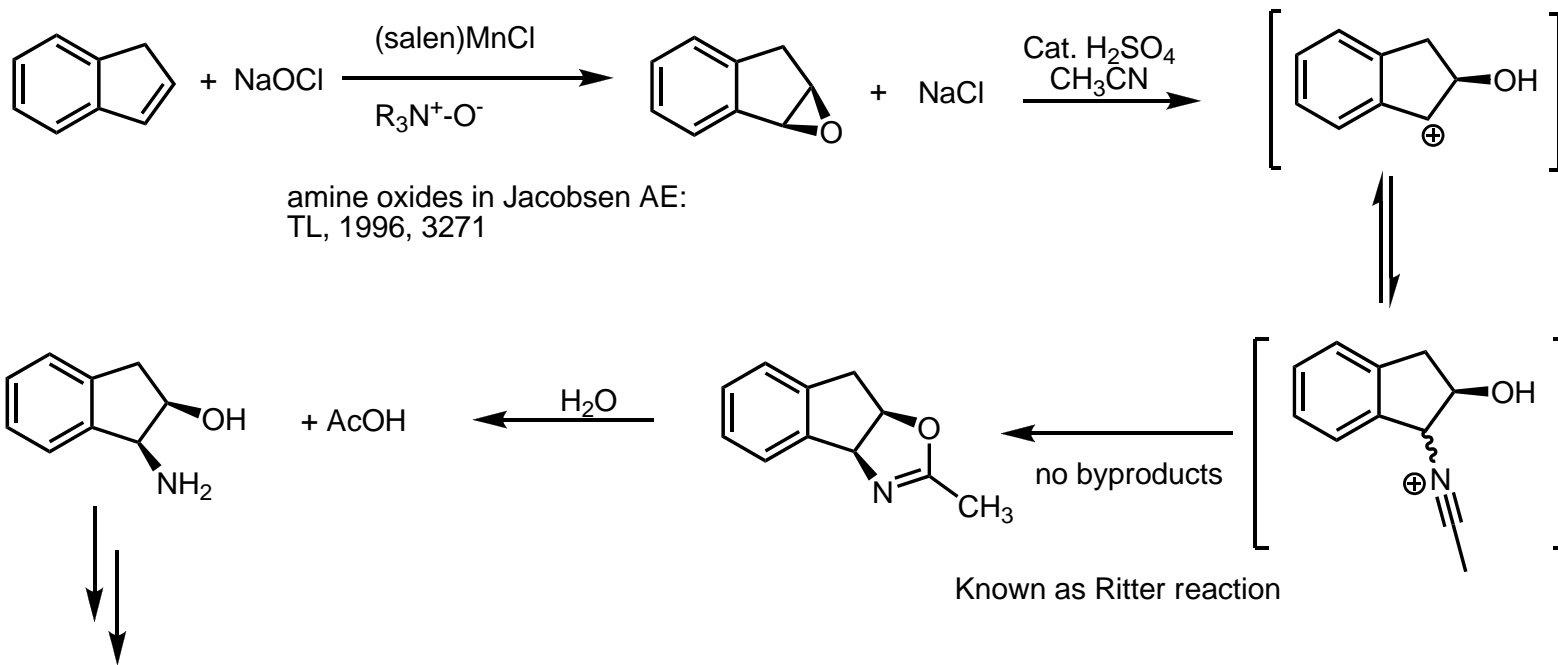
Indinavir - HIV protease inhibitor
(Merck)

Senanayake, Reider, Jacobsen, Org. Syn, 1999, 76.

in general, three different mechanisms possible for metal oxo epoxidation:

[2+2]

$$M^n=O \; + \; || \; \longrightarrow \; \text{(metallaoxetane)} \; \longrightarrow \; M^{n-2} \; + \; \text{(epoxide)}$$

concerted

$$M^n=O \; \longrightarrow \; M^n \; \longrightarrow \; M^{n-2} \; + \; \text{(epoxide)}$$

electron transfer

$$\longrightarrow \; M^{n-1} \; \longrightarrow \; M^{n-2} \; + \; \text{(epoxide)}$$
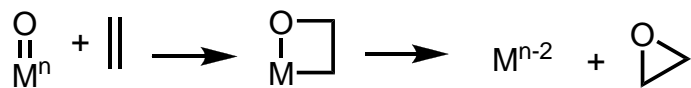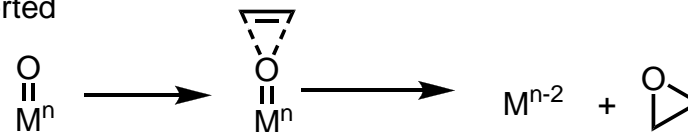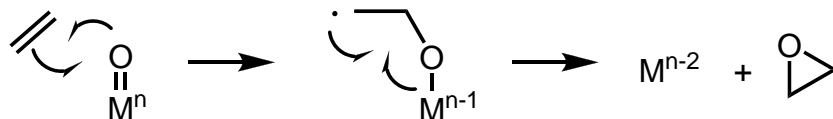
Experimental data:

secondary KIE's

$k_H/k_D = 0.82$

$k_H/k_D = 1.00$

$k_H/k_D = 0.91$

$k_H/k_D = 0.90$

Sp2 -> Sp3

Sp2

Mn
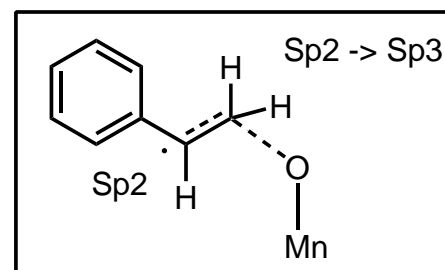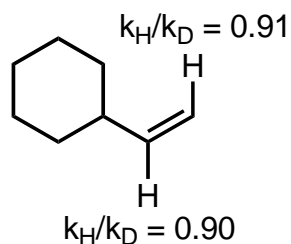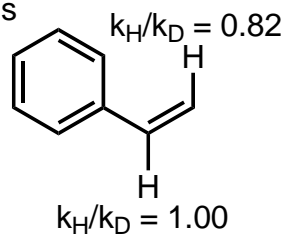
Recall enynes and dienes

$$\text{cis} \; \xrightarrow{\text{(salen)MnO}} \; \text{Mn}^{iv} \; \longrightarrow \; M^{n-1} \; \longrightarrow \; \text{trans}$$

Radical traps
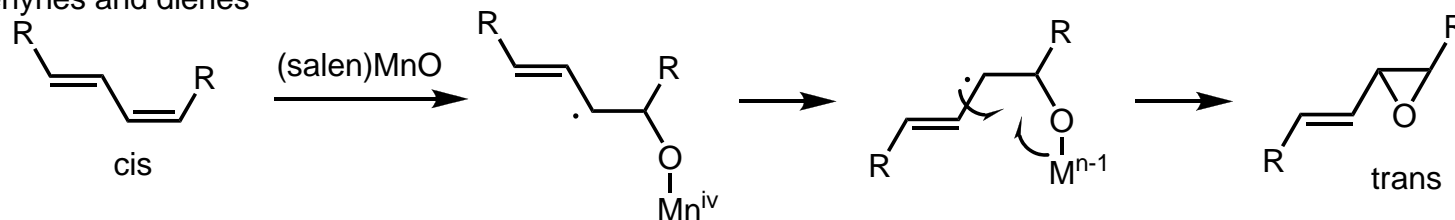
$$\xrightarrow[\text{NaOCl}]{\text{(salen)MnCl}} \; \longrightarrow \; \text{various ring-opened products}$$
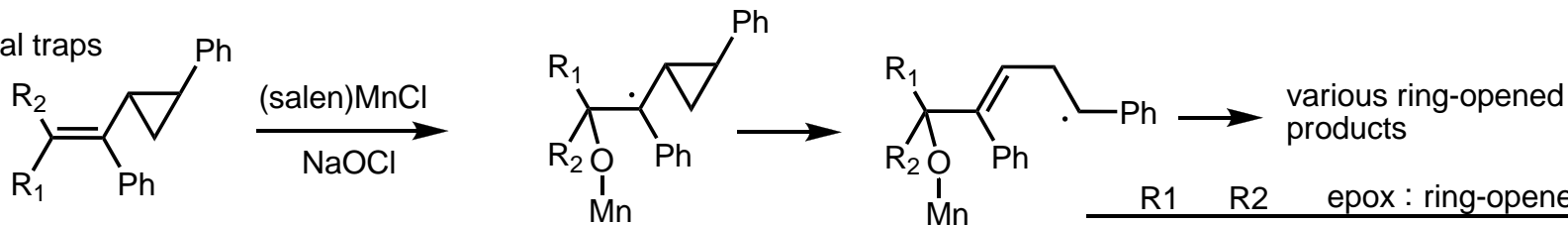
Norby, Akermark, ACIEE, 1997, 1723
Note: these authors interpret the data in terms of a [2+2] mechanism

R1	R2	epox : ring-opened
H	Me	100:0
Me	H	56:44

Three common classes of epoxide ring-opening reactions

Nucleophilic addition
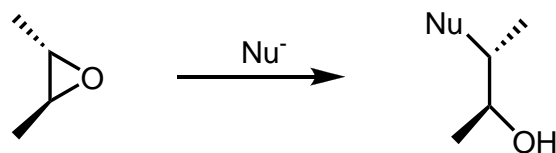
generally stereospecific

Isomerization
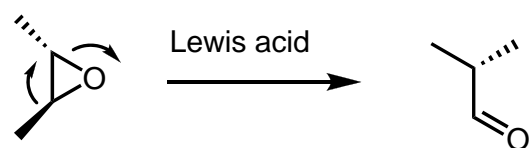
generally stereospecific

Elimination
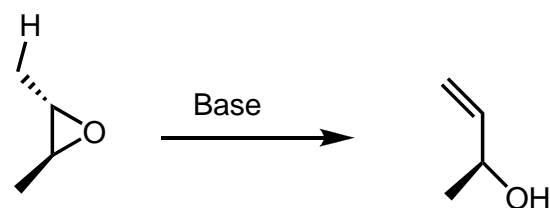
Stereoretentive

General considerations:

Addition to more stable partial cation
Common for solvolysis
Common with strong Lewis or protic acids
Total SN1 = loss of stereochemistry

Addition to less hindered C
Often good reaction for H-, RO-, RS-, CN-, N3-, R2N
Common with weak Lewis acids (esp R2N, CN-
Stereospecific
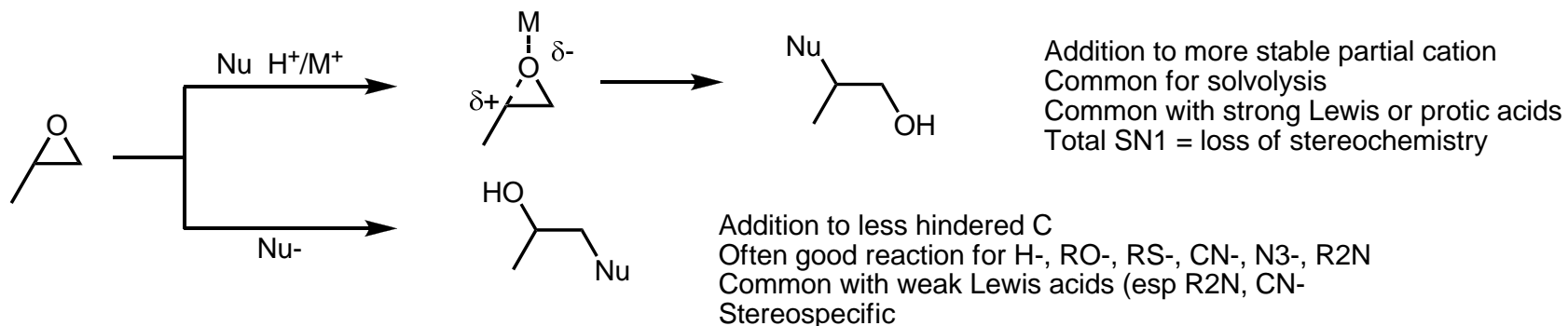
Generally, bond-breaking more advanced than bond-making with epoxides.

Regioselectivity: cation-stabilizing groups can alter selectivity

X = NO2   1:>99
X = OMe   >99:1   TL 2004, 9265

BF$_3$-Et$_2$O   80:20
LiClO$_4$ 6:94   TL, 1991, 6617

endo   exo
(anti-Baldwin)   (Baldwin)

R =

R	ratio
CO_2R (saturated)	0:100
CO_2R (alkene)	60:40
vinyl	100:0

Nicolaou, JACS, 1989, 5330
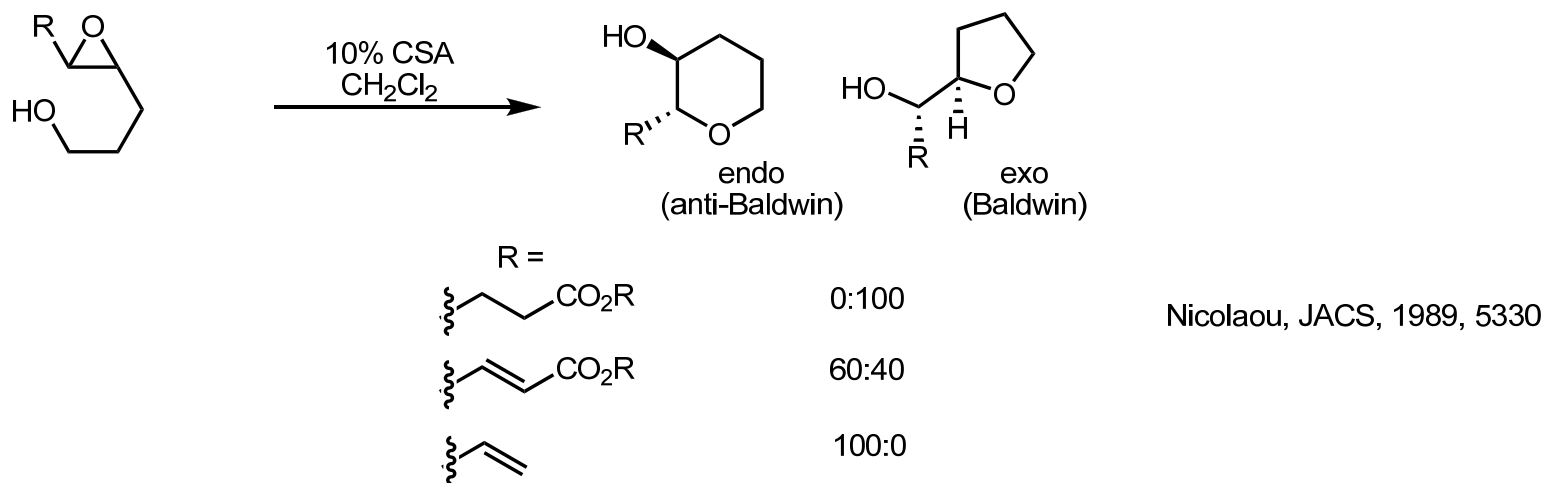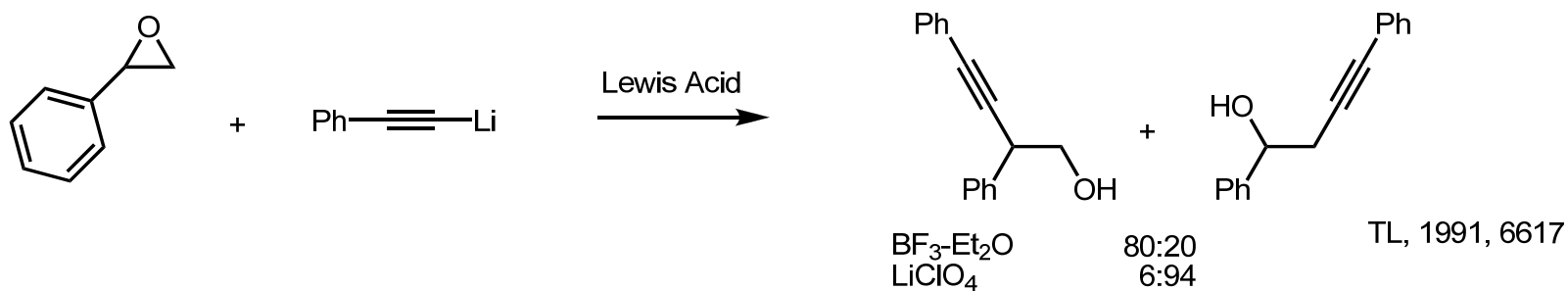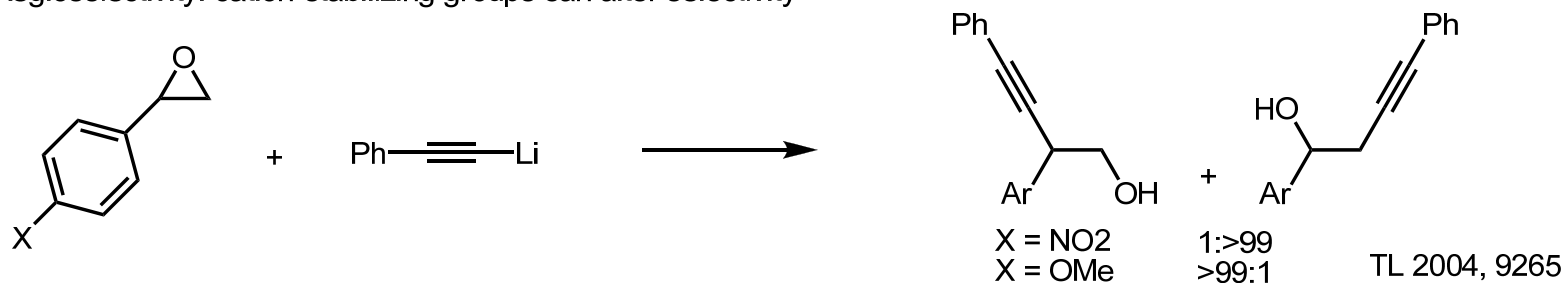
Furst-Plattner Rule: experimentally observed that cyclohexene oxides react such that the nucleophile approaches along an axial trajectory.

path a

twist-boat-like TS
+ ~5 Kcal/mol

disfavored

path b

Chair-like TS

favored

Furst, Helv Chem Acta, 1949, 275
Barton, " 1954, 4284
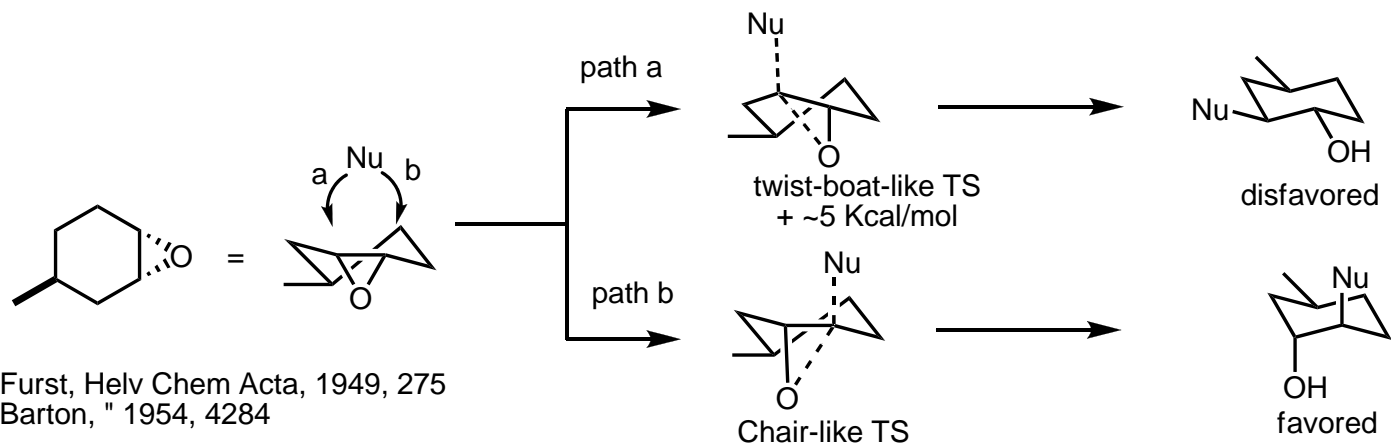
Notes: Faster-forming product may be less stable product
Same analysis applies to conjugate additions, additions to halonium
   ions, additions to cyclic imines.
Also known as 'trans-diaxial rule' for obvious reasons

H_2O, cat. H_2SO_4

$LiAlH_4$

MeOH
H^+

$LiAlH_4$

MeOH
H^+
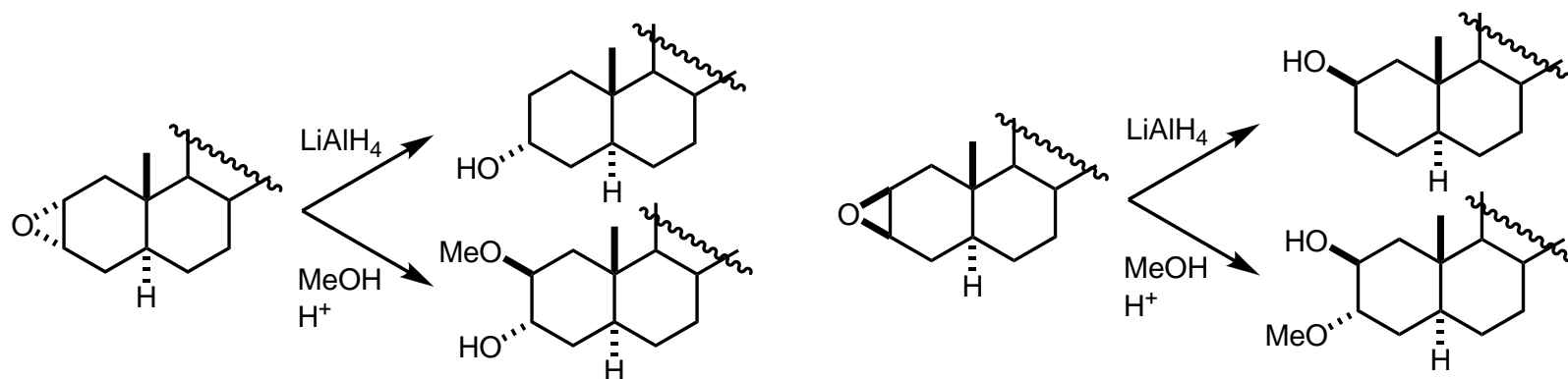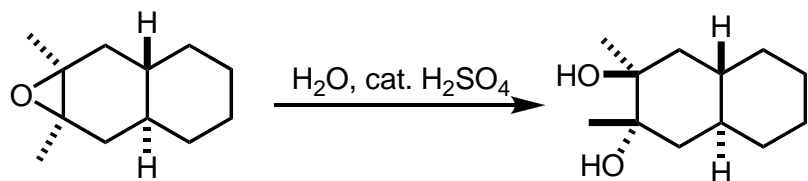
Addition of carbon-centered nucleophiles usually involves organocopper chemistry
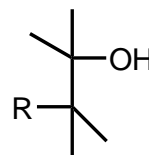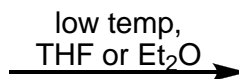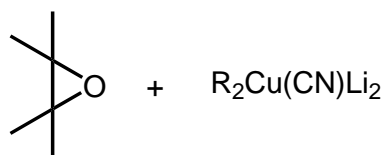
Review: Lipshutz, Tet, 1984, 5005.
Generally high yielding, stereospecific
Addition to less substituted C
Often waste 1 equiv R

Problems:
Tetrasubstituted
Hindered trisubstituted
Vinyl epoxides (good Sn2')

Epoxide	Cuprate /(equiv.)	Conditions[a]	Product(s)	Ratio	Yield (%)[I]
	n-Bu₂Cu(CN)Li₂ (1.1) 38	-20°C, 2 h		—	95[c]
	38 (1.3)	-40°C, 2 h		85 : 8	93
	38 (1.3)	-20°C, 2 h		—	96
	38 (2.0)	0°C, 6 h		—	74[c,d]
	38 (1.3)	0°C, 3 h		1:1	61
	38 (3.0)	0°C, 6 h	—	—	e
	Et₂Cu(CN)Li₂ (2.0)	0°C, 6 h		—	98
	n-Pr₂Cu(CN)Li₂ (2.0)	0°C, 8 h		—	86[c]
	Ph₂Cu(CN)Li₂ (2.0) 39	r.t. 10 h		—	98
	39 (1 1)	-45°C, 1.5 h		3.4 : 1[f]	96
	(⌇)₂Cu(CN)Li₂ (1.3) 40	0°C, 5 h		—	94

base

OH

Payne rearrangement
(Major from SAE)   (Major from SAE - KR)

Nu

0.5N KOH, Et$_2$NH
slow

0.5N KOH, Et$_2$NH
Fast

Sharpless
Aldrichimica Acta, *16*, **1983**, 67
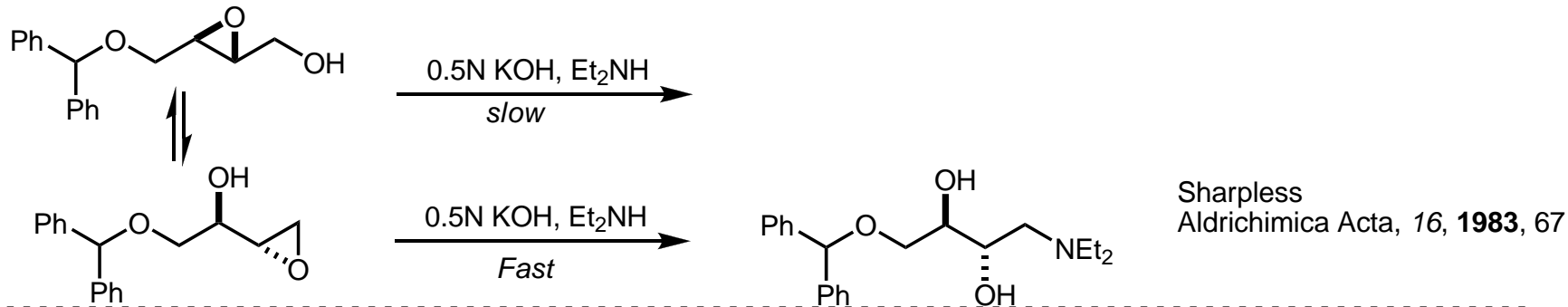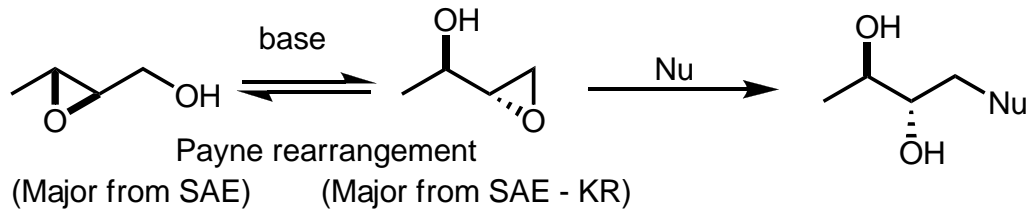
Lewis-Acid promoted addition:
  Sharpless, JOC, 1985, 1557, 1560

+ NuH

1.5 equiv Ti(OiPr)$_4$

generally >5:1 regioselectivity
Nu = R$_2$NH, ROH, RSH, TMSN$_3$,
 KCN, NH$_4$X, NH$_4$OBz
Ti increases rate and selectivity

e.g. w/Et$_2$NH: +Ti 20:1 (90%y)
                -Ti 3.7:1 (4%y)

X = OH, NHBn   Nu = Et2NH

+Ti	1:20
-Ti	6:1

origin of selectivity:
orbital overlap? Least motion? Charge distribution?

[CH$_3$OCH$_2$CH$_2$O]AlH$_2$Na

1   **2**
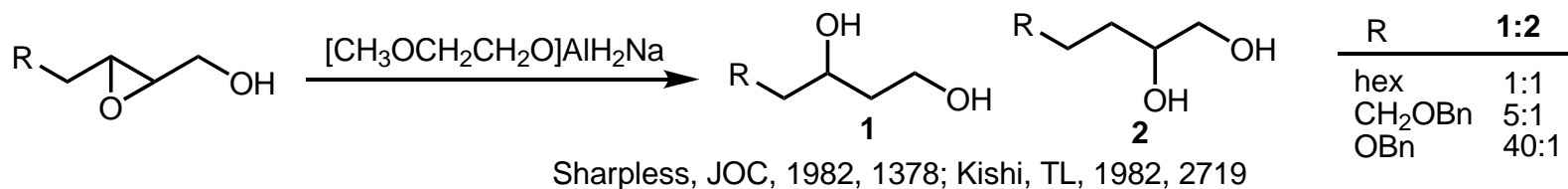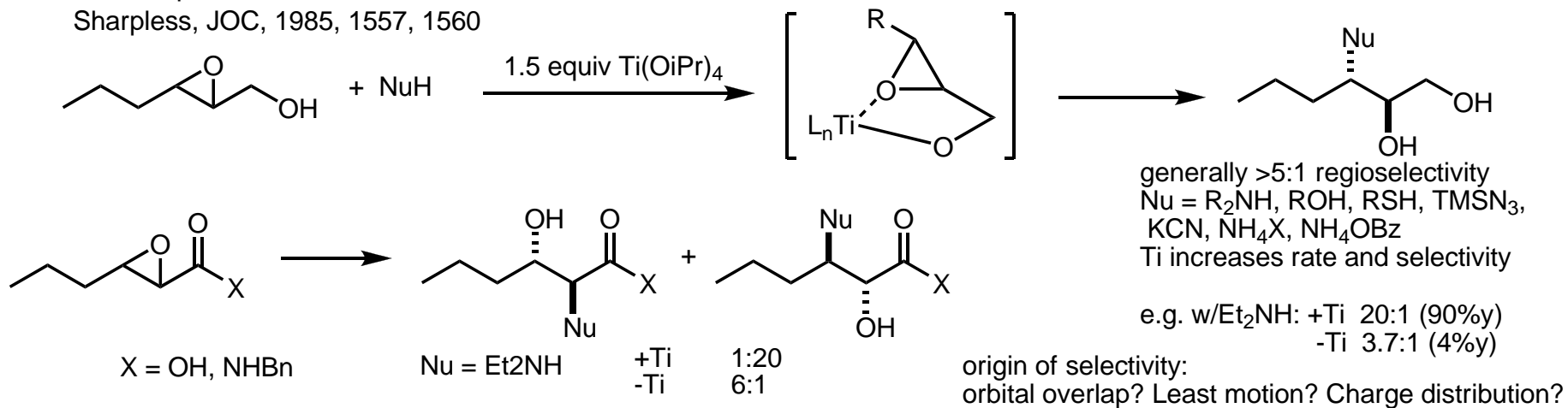
Sharpless, JOC, 1982, 1378; Kishi, TL, 1982, 2719

R	**1:2**
hex	1:1
CH$_2$OBn	5:1
OBn	40:1

Lewis-acid catalyzed rearrangement of epoxides
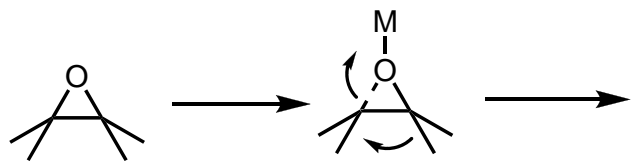
Rearrangement to more stable carbocation
Often high degree of stereospecificity

10% MeAl(OAr)$_2$
'Yamamoto's catalyst'

OAr =

cat. MeAl(OAr)$_2$
88%

Yamamoto, JACS, 1989, 6431

cat. MeAl(OR)$_2$
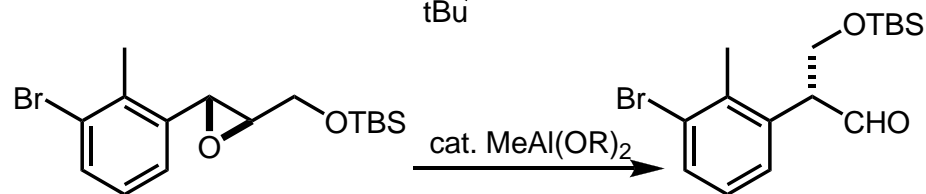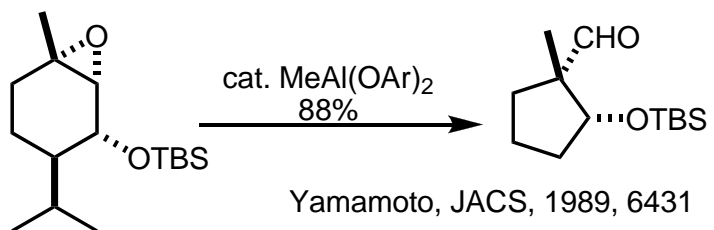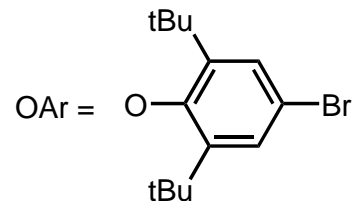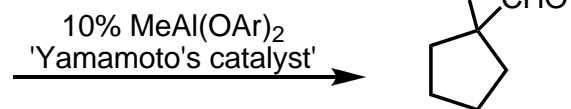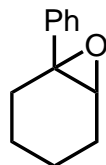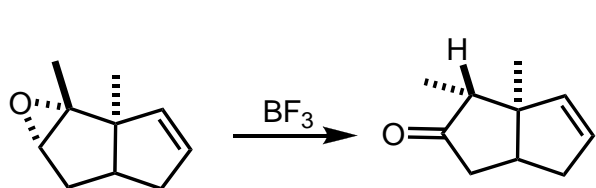
Chen, JACS, 2009, ASAP

Yb(OTf)$_3$

TsOH

88% ee

90% ee

Shi, JACS, 1999, 4080
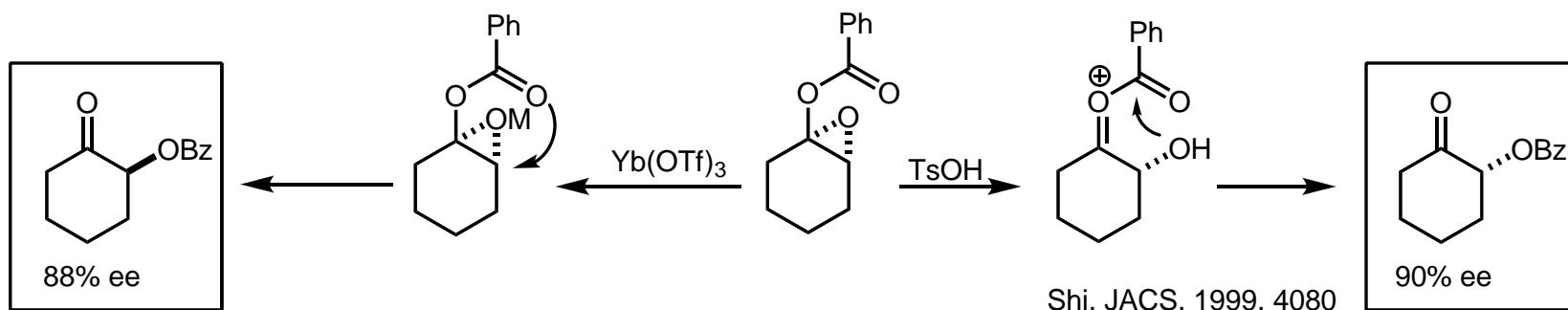
Deprotonation
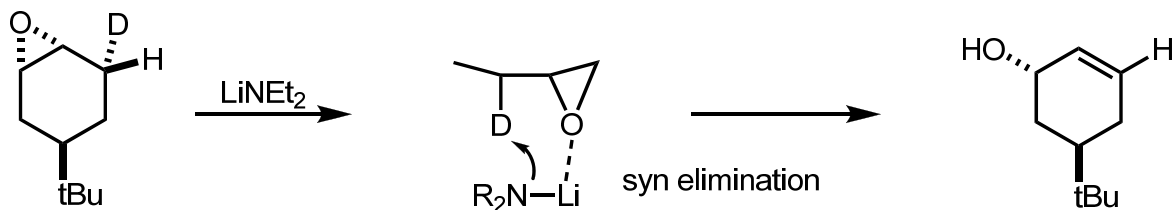
milder conditions:
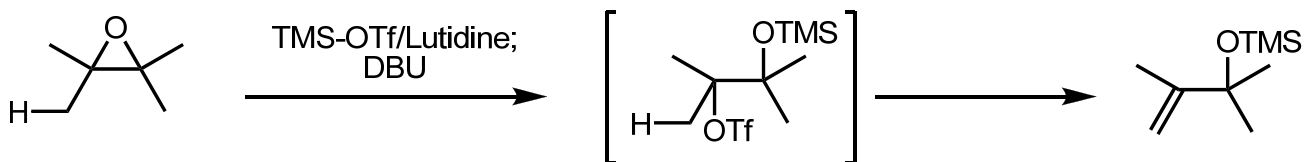
intermediate observed by NMR
OTf addition to more substituted carbon
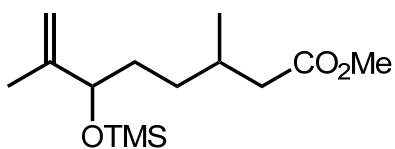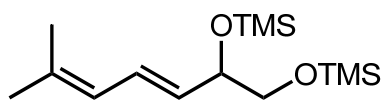
79% (only isomer) 66% (from epoxy alcohol) 87% 59%
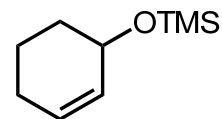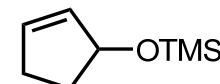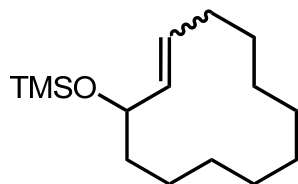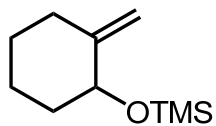
38% 80% (more substituted C,
more accessible H)   100%
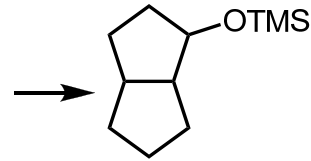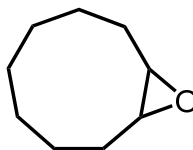
poor substrates: acyclic di- or
mono-substituted epoxides

Noyori, JOC, 1979, 2738.

Addition/oxidation/elimination

Perkin I, 1979, 1358
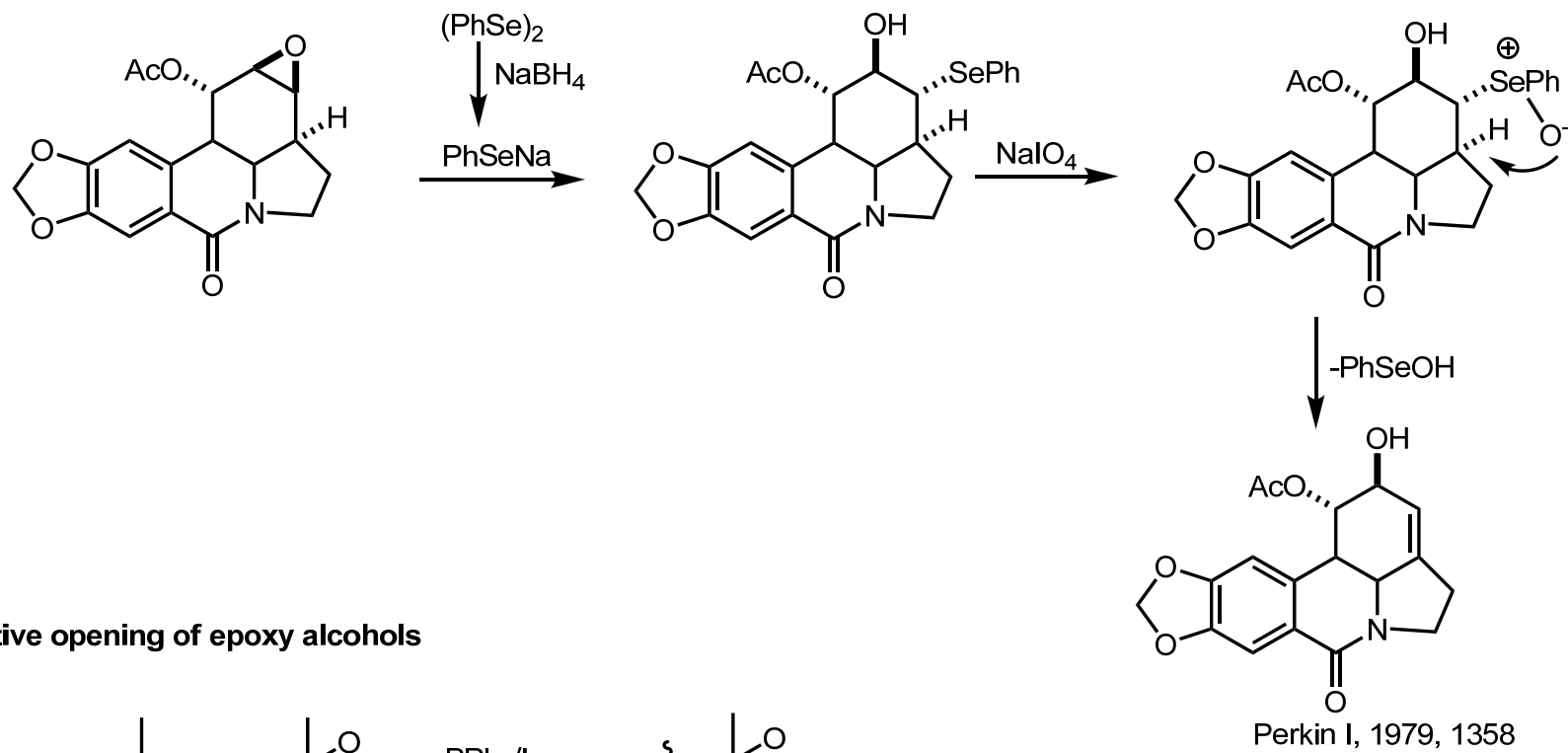
Reductive opening of epoxy alcohols

TL, 1982, 5413

Dihydroxylation: general scheme
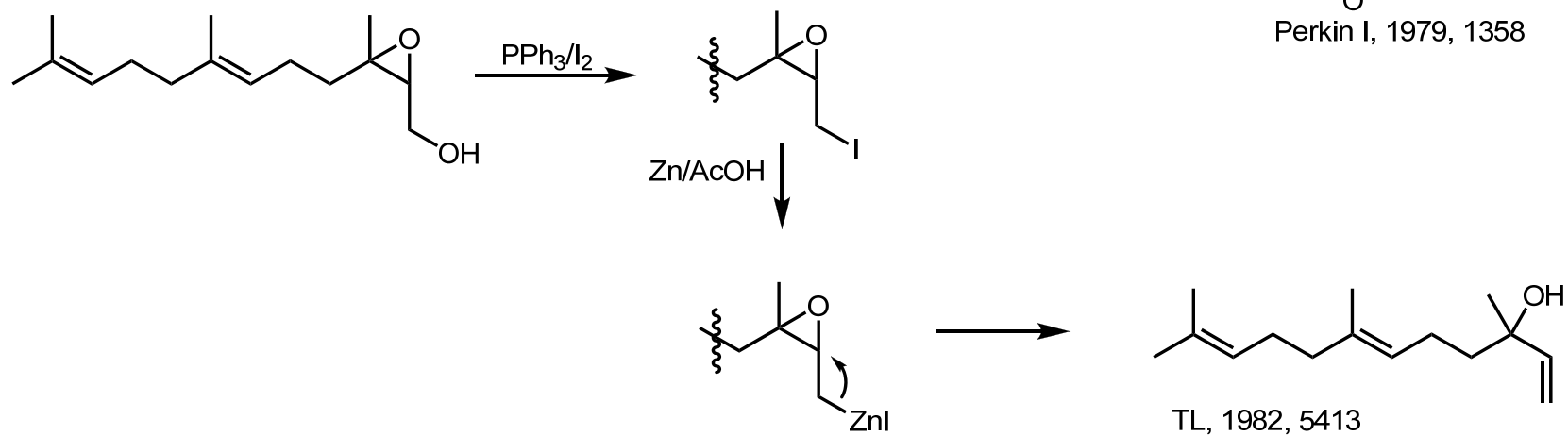
RuO$_4$, KMnO$_4$, OsO$_4$ most common
Stereospecific (cis-dihydroxylation)
Diol cleavage potential side reaction
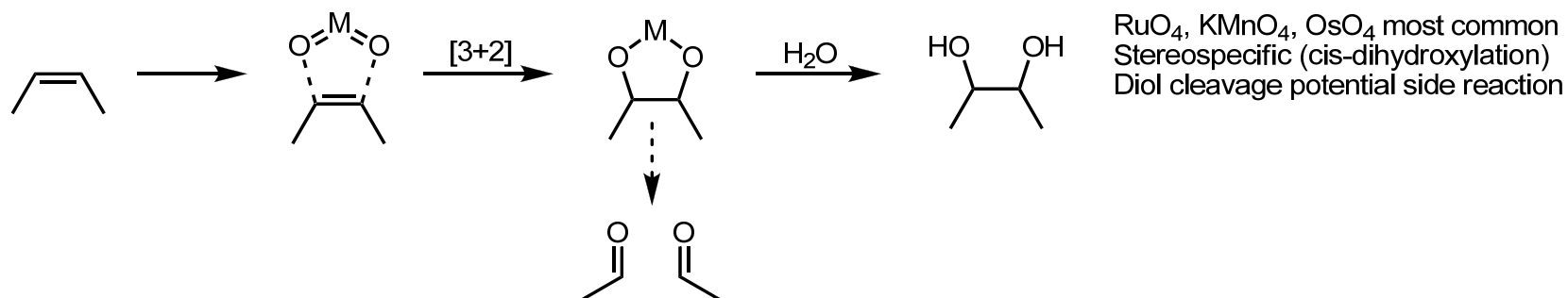
KMnO$_4$ - some uses; mostly replaced by OsO$_4$

KMnO$_4$
58%

KMnO$_4$
R$_4$NX

81%

KMnO$_4$
57%

Chem Comm. 2005, 5636
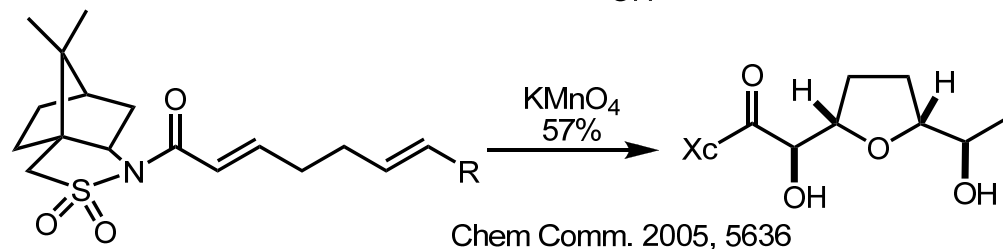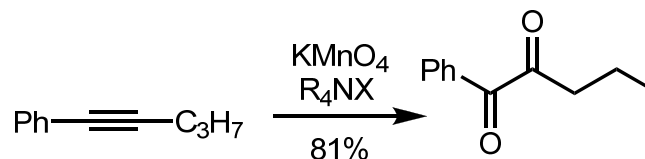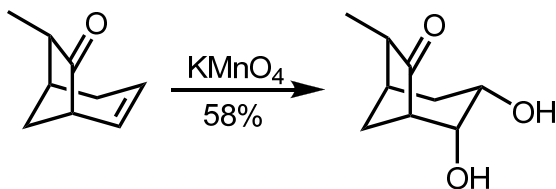
RuO$_4$ - generated in situ from RuCl$_3$ (cat.) and NaIO$_4$

Stark, OL, 2006, 3433

Scheme 3.   RuO$_4$-Catalyzed Oxidative Cyclization

6

0.2 mol % RuCl$_3$,
NaIO$_4$ on wet silica,
THF, 0 °C, 6 h

via

83% (>98 : 2 dr)

2
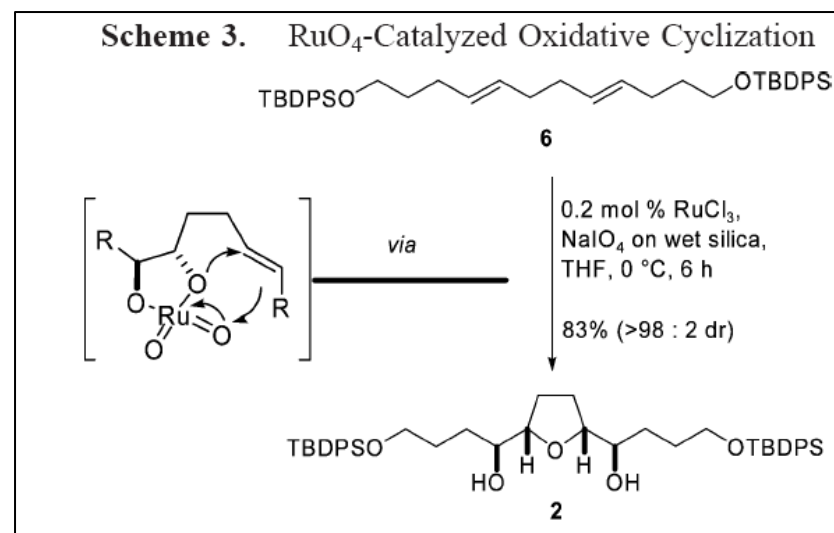
Best conditions for dihydroxylating olefin: Upjohn conditions

1 mol% OsO$_4$, 1.05 equiv NMO
H$_2$O/Acetone
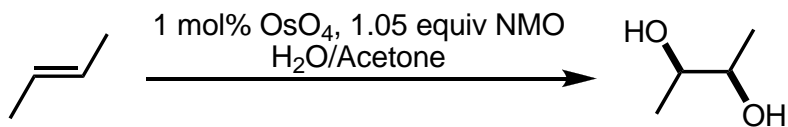
NMO:
Catalytic Os
Easy workup ([H-], H+)
R3N may accelerate rxn

Upjohn Co
TL, **1976**, p1973

Os(VIII)

Os(VI)

Os(VI)
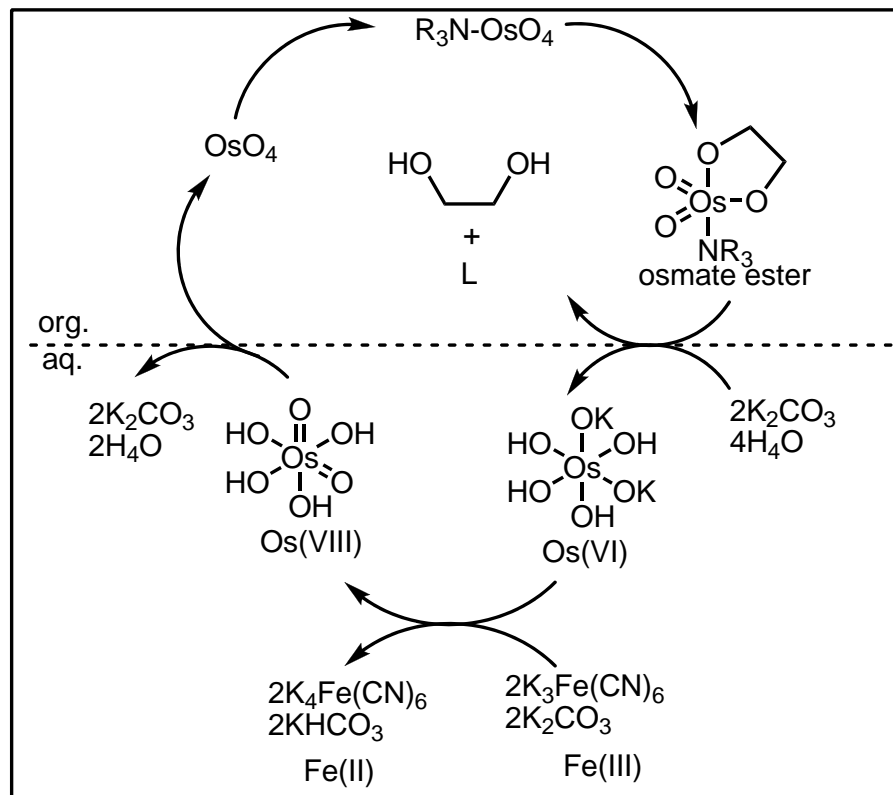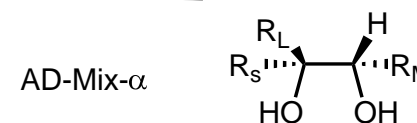
Os(VI)

H$_2$O

N-methyl-morpholine-N-Oxide
(NMO)

(from cis olefin)
>95%

25%

91%

79%

78%

65%
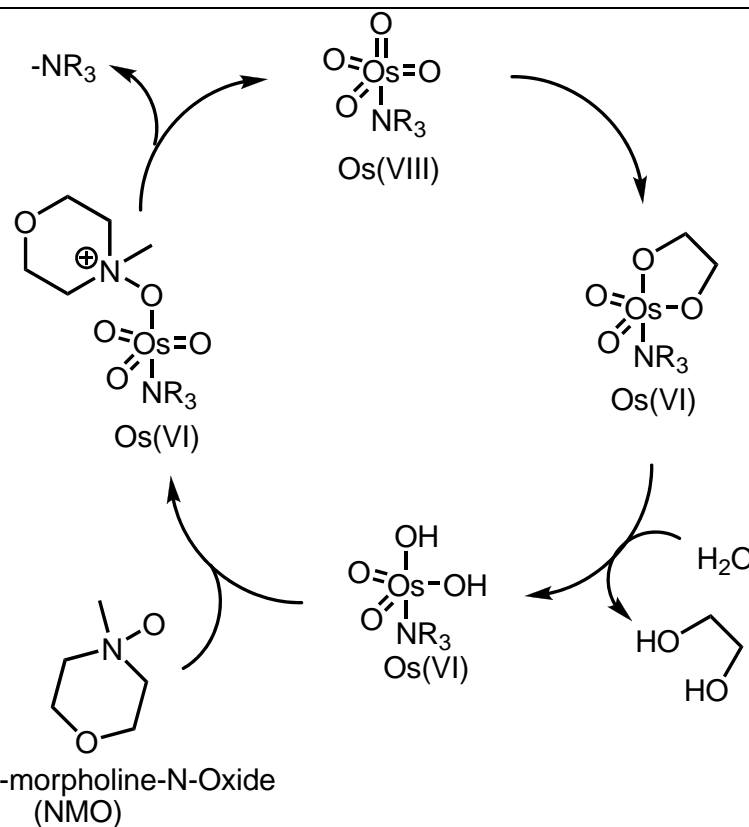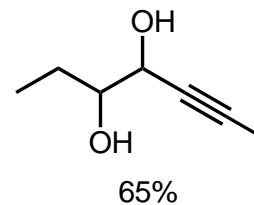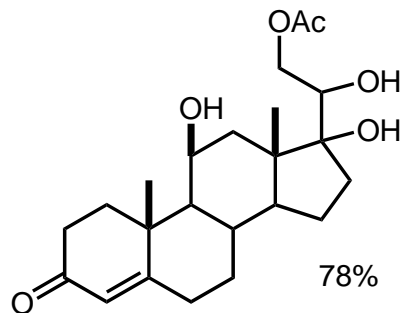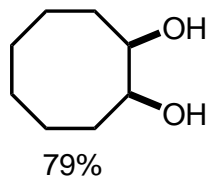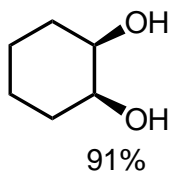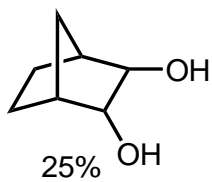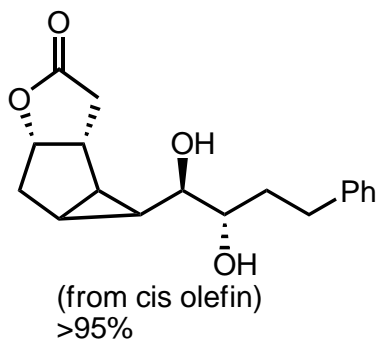
Sharpless asymmetric dihydroxylation
Shapless, Chem Rev 1994, 2483.

General considerations:
Strategy based on observation that tertiary amines accelerate reaction.
Monodentate ligand required for turnover
Ligands based on cinchona alkaloids
Simple experimental protocol
One of the most general enantioselective reactions
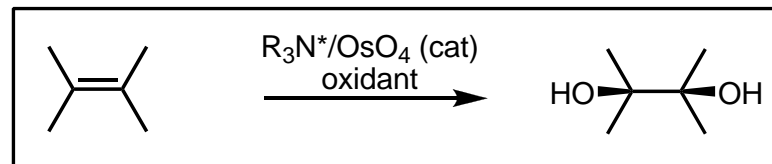
R_3N^* =
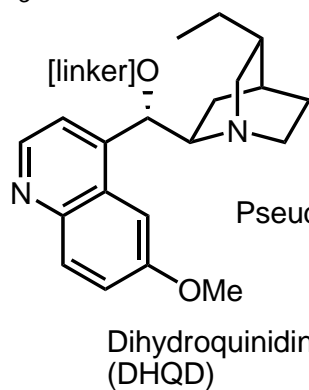
Pseudo-enantiomers
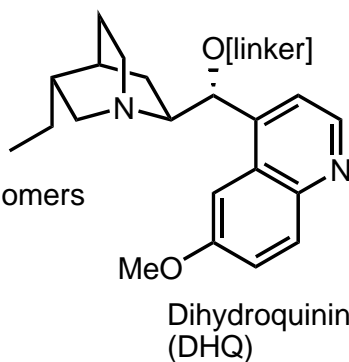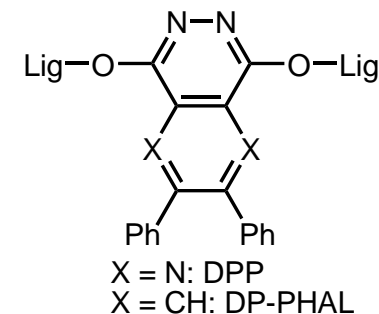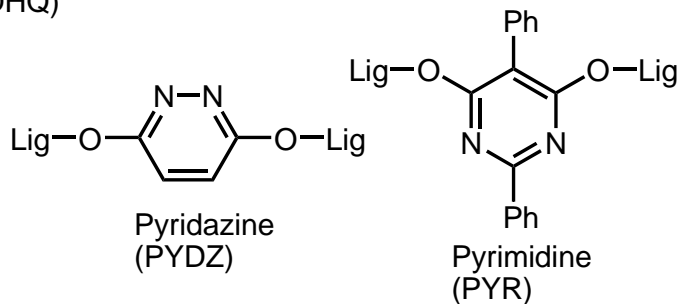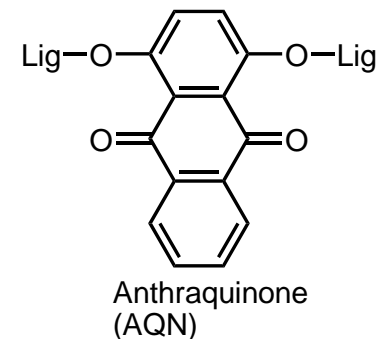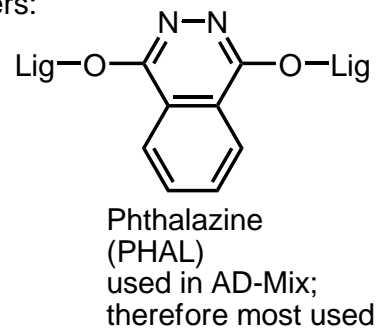
Dihydroquinidine (OH)
(DHQD)

Dihydroquinine (OH)
(DHQ)

Linkers:

Phthalazine
(PHAL)
used in AD-Mix;
therefore most used

Anthraquinone
(AQN)

Pyridazine
(PYDZ)

Pyrimidine
(PYR)

X = N: DPP
X = CH: DP-PHAL

AD-Mix α (Lig = DHQ)
AD-Mix β (Lig = DHQD)

$\begin{cases} K_3Fe(CN)_6 & 0.94 \text{ g (3 equiv)} \\ K_2CO_3 & 0.41 \text{ g (3 equiv)} \\ \text{Lig-PHAL} & 7.8 \text{ mg (1 mol\%)} \\ K_2OsO_2(OH)_4 & \underline{0.74 \text{ mg (0.2 mol\%)}} \\ & 1.36 \text{ g} \end{cases}$

tBuOH:H$_2$O (1:1)

1 mmol

AD-Mix-β

AD-Mix-α

AD-Mix-β

AD-Mix-α

R$_3$N-OsO$_4$

OsO$_4$

HO   OH

+

L

osmate ester

org.
aq.

2K$_2$CO$_3$
2H$_4$O

Os(VIII)

Os(VI)

2K$_2$CO$_3$
4H$_4$O

2K$_4$Fe(CN)$_6$
2KHCO$_3$

Fe(II)

2K$_3$Fe(CN)$_6$
2K$_2$CO$_3$

Fe(III)

net reaction

$=\!=$ + 2H$_2$O + 2K$_2$CO$_3$ + 2K$_3$Fe(CN)$_6$
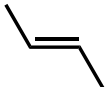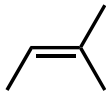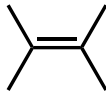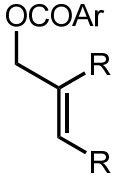
HO   OH

+ 2KHCO$_3$ + 2K$_4$Fe(CN)$_6$
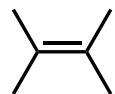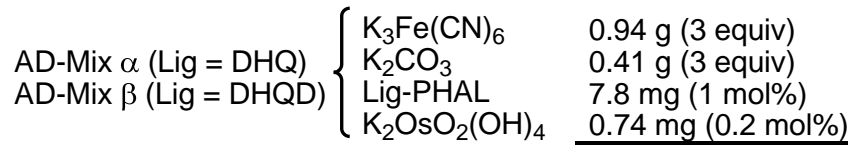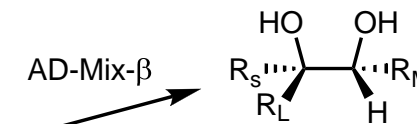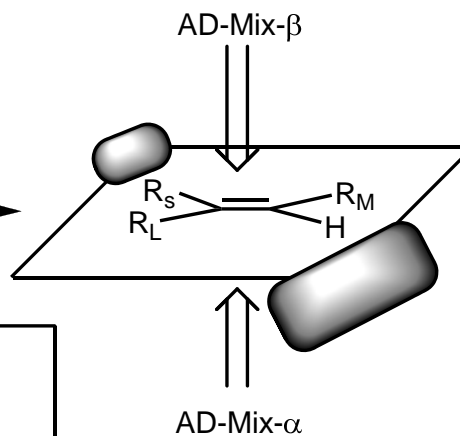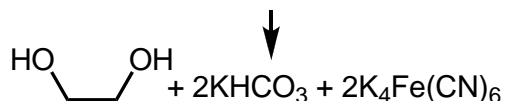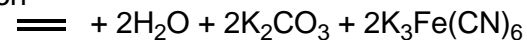
Proposals to rationalize stereochemistry:
Corey, JACS, 1995, 10805; 1996, 319
Sharpless, JACS, 1994, 8470

OMe   OMe

2
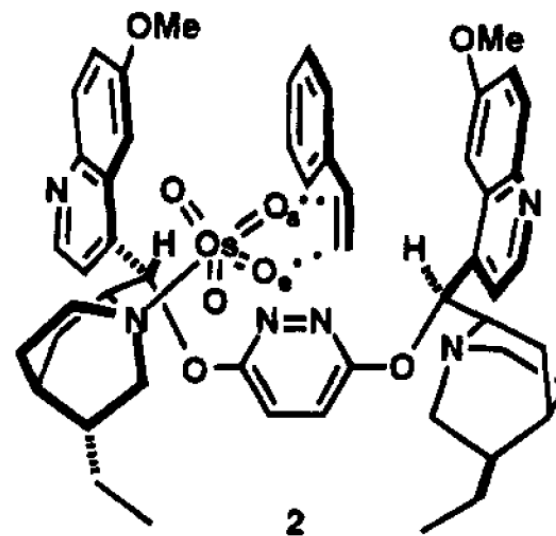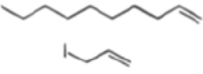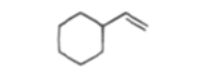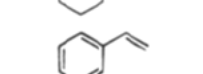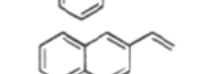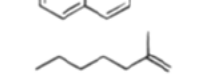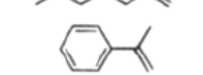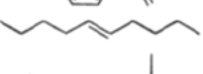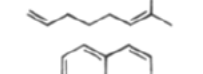
Ready   Sharpless Asymmetric Dihydroxylation: scope

Class							terminal, 1,1-, tri, and trans-di
Best Ligand	PYR DPP	PHAL DP-PHAL DPP	PD-PHAL	PHAL	PHAL DP-PHAL	PYR PHAL	PYDZ
common ee range (%)	80 - 99	70	20-80	>90	>90	20-97	>95

Chem Rev. 1994, 2483 and
JACS, 1995, 10805

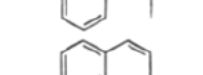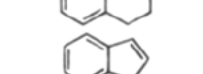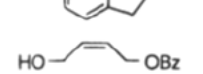| Olefin	1a (1b) (PHAL)	2a (2b) (PYR)	3a (3b) (DPP)	4a (4b) (DP-PHAL)
	79; R	88; R	78; R	80; R
	84; R (80; S)	89; R (76; S)	89; R (81; S)	87; R (85; S)
	63; S	70; S	68; S	77; S
	64; R (66; S)	92; R (87; S)	59; R (65; S)	67; R (73; S)
	88; R	96; R	89; R	91; R
	97; R (97; S)	80; R	99; R (97; S)	98; R (96; S)
	99; R		>99.5; R	97; R
	78; R	76; R	78; R	81; R
	94; R (93; S)	69; R	96; R (92; S)	94; R (94; S)
	97; R,R (93; S,S)	88; R,R	96; R,R (94; S,S)	97; R,R (97; S,S)
	98; R (95; S)	87; R	98; R (94; S)	99; R (91; S)
	35; 1R, 2S		68; 1R, 2S	63; 1R, 2S
	15; 1R, 2S	7; 1R, 2S	40; 1R, 2S	56; 1R, 2S
	42; 1R, 2S	35; 1R, 2S	20; 1R, 2S	53; 1R, 2S
	64; 1S, 2R		82; 1S, 2R	73; 1S, 2R

Shapless, JOC, 1995, 3940

A non-linear Eyring plot is taken as evidence for a stepwise mechanism. Sharpless interpreted these data to support a mechanism involving [2+2] cycloaddition (to yield an osmaoxetane) followed by ring expansion.

4: R = R' = n-Butyl
5: R = Ph, R' = H
6: R = n-Octyl, R' = H

P = e.r.

Sharpless, ACIEE, 1993, 1329
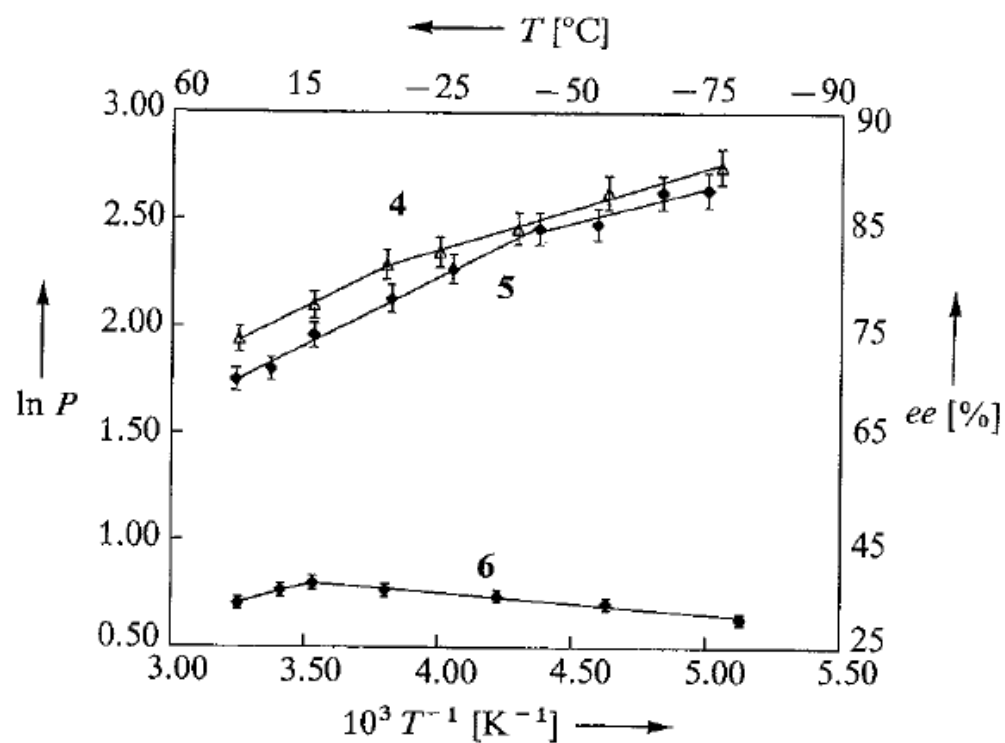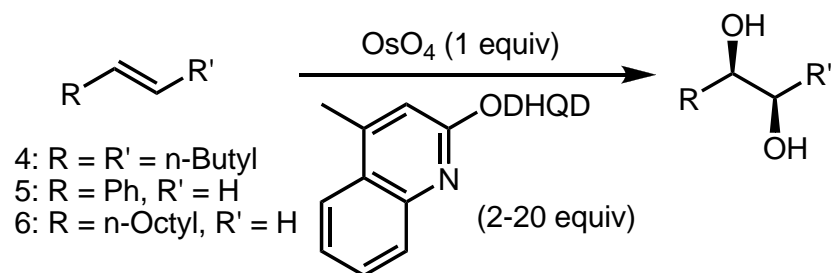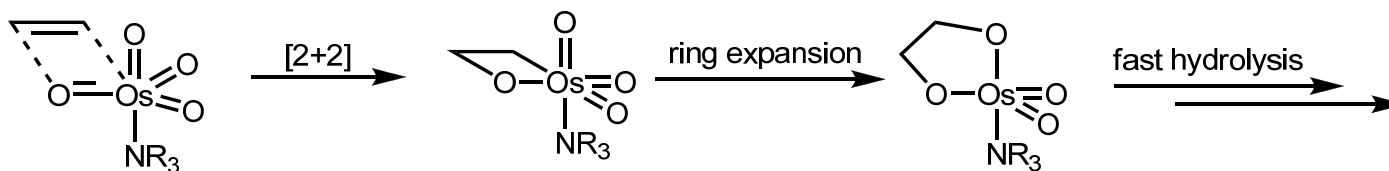
Corey observed enzyme-like kinetics which he interpreted in terms of reversible binding followed by rate-limited [3+2] cycloaddition (aka Criegee mechanism).

JACS, 1996, 319
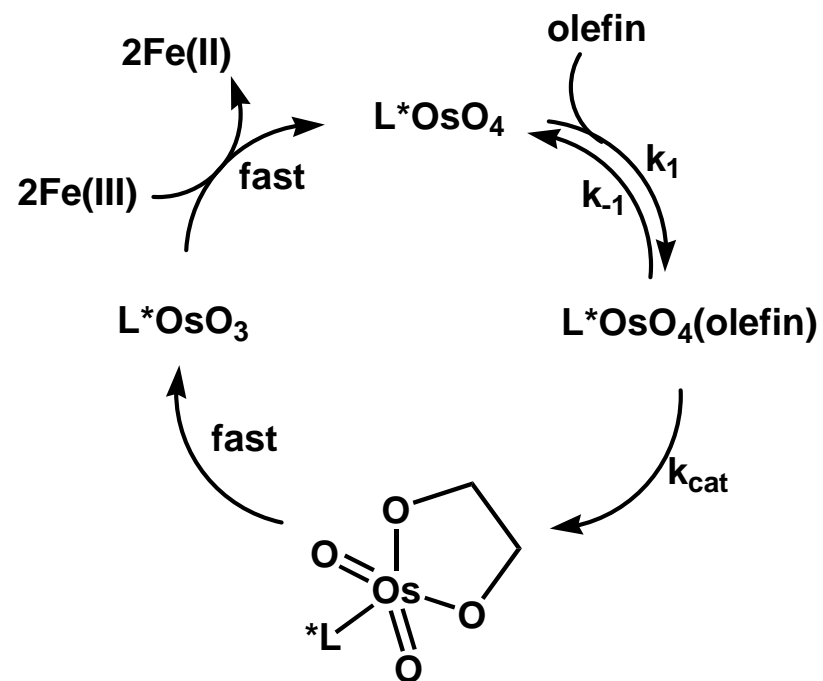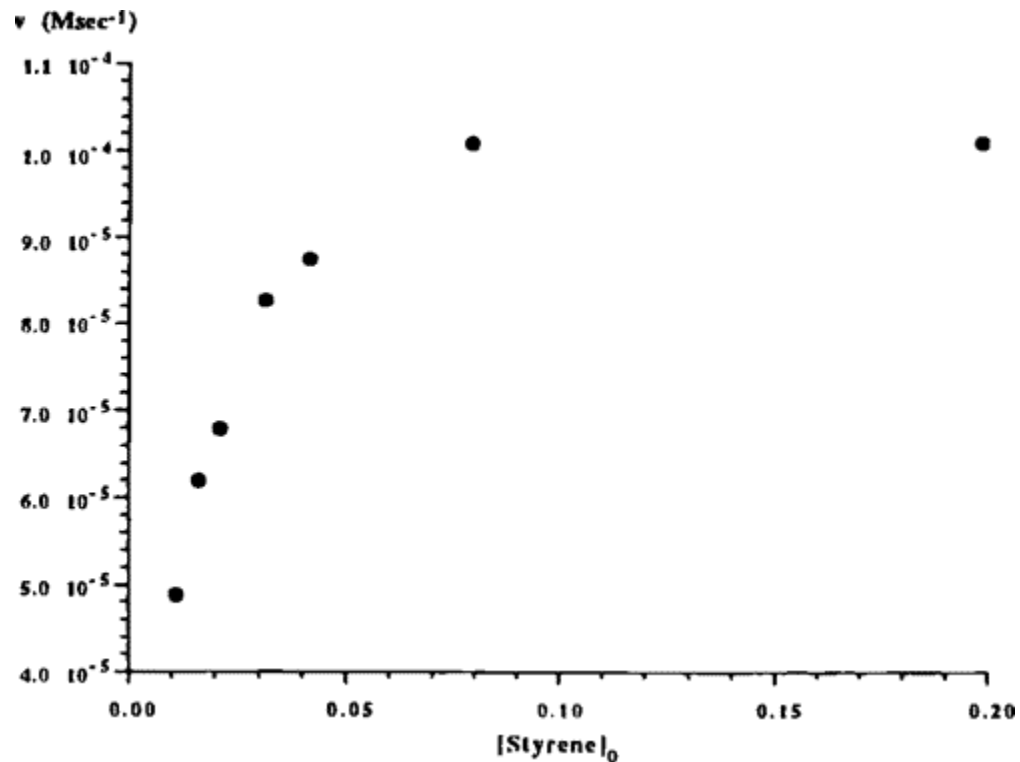
Houk, Singleton and Sharpless performed natural abundance KIE studies of the dihydroxylation of tBu ethylene. The data are more consistent with a concerted [3+2] addition. JACS, 1997, 9907
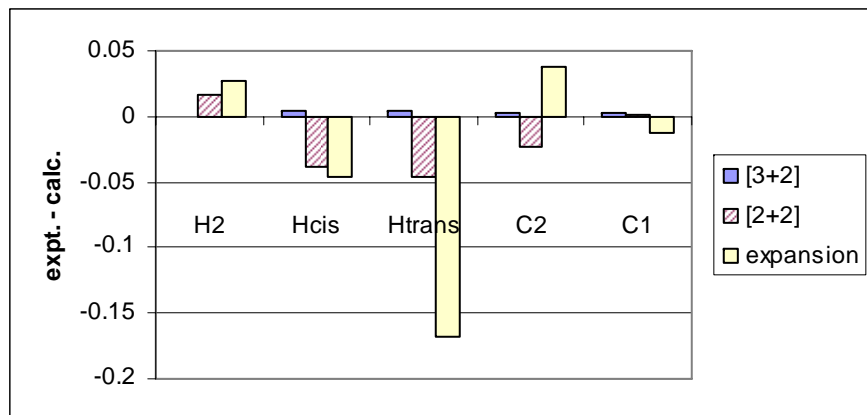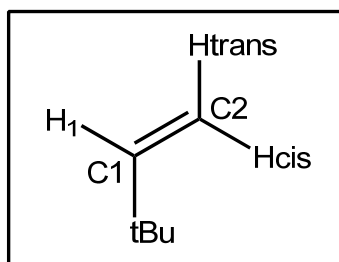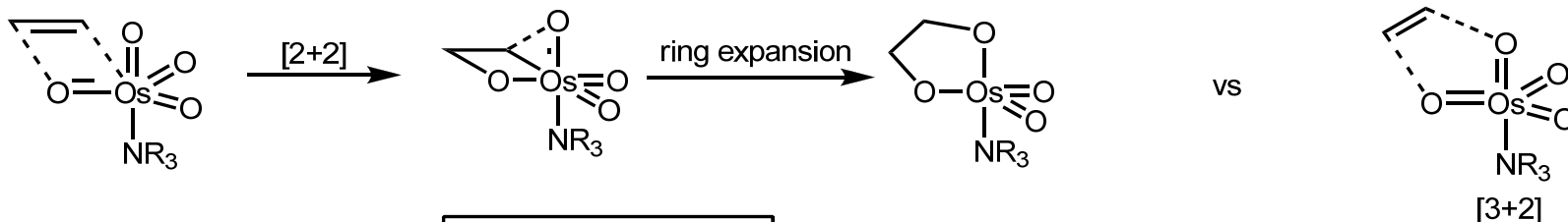

|	H_{C2}	H_{cis}	H_{trans}	C_2	C_1
			Calculated[a]		
			(a) "(3 + 2)"		
2	0.907	0.913	0.921	1.025	1.025
3	0.909	0.912	0.921	1.025	1.024
		(b) Formation of an Osmaoxetane			
6	0.892	0.957	0.972	1.050	1.026
7	0.885	0.962	0.980	1.051	1.025
8	0.832	0.927	0.937	1.046	1.021
			(c) Ring-Expansion		
9	0.880	0.964	1.094	0.989	1.039
10	0.933	0.976	1.068	0.984	1.047
			Experiment[b]		
1	0.906(9)	0.919(5)	0.925(7)	1.027(1)	1.028(3)
2	0.908(4)	0.917(8)	0.926(14)	1.026(3)	1.025(3)

'no other known organic reaction comes close to achieving such enormous scope coupled with such great selectivity.' – Sharpless in Chem Rev.
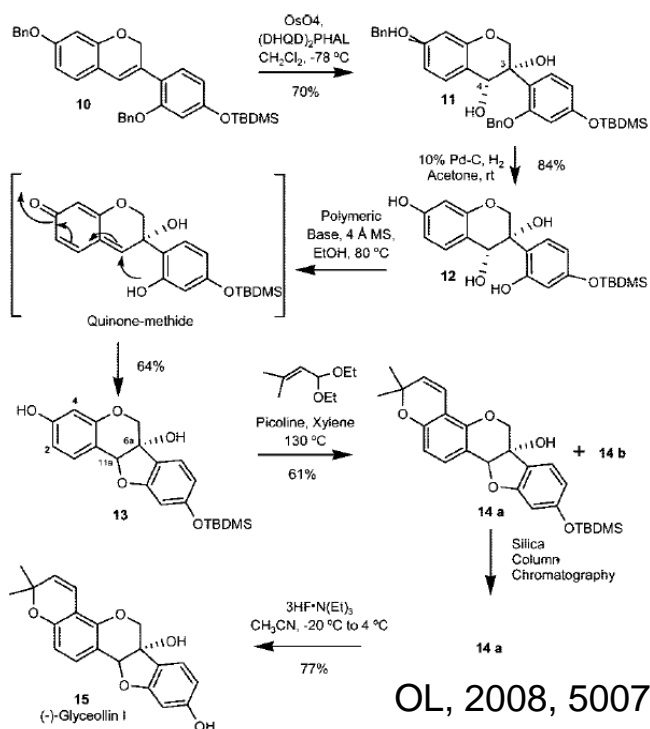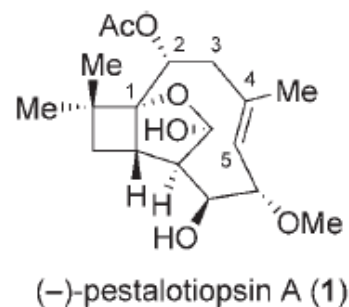

OL, 2008, 5007 (95% ee)
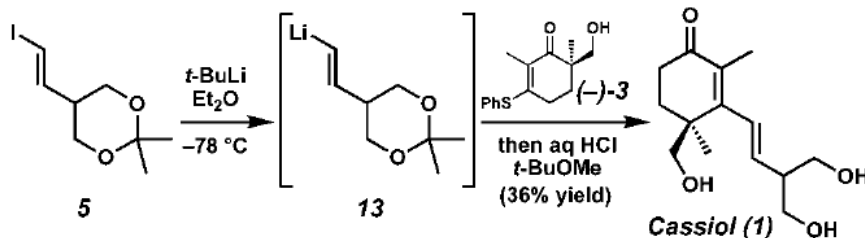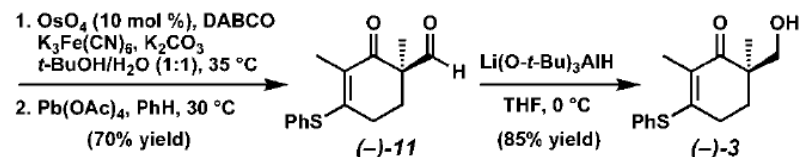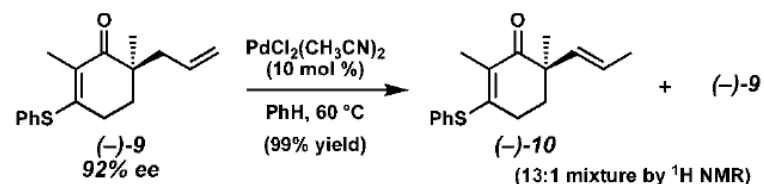
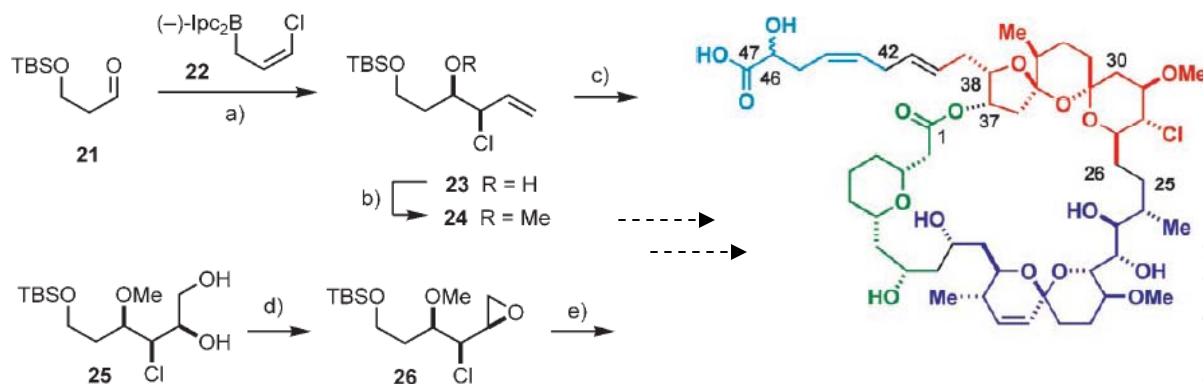OL, 2009, 293. Often AD-Mix is best way to do dihydroxylation regardless of stereochemistry
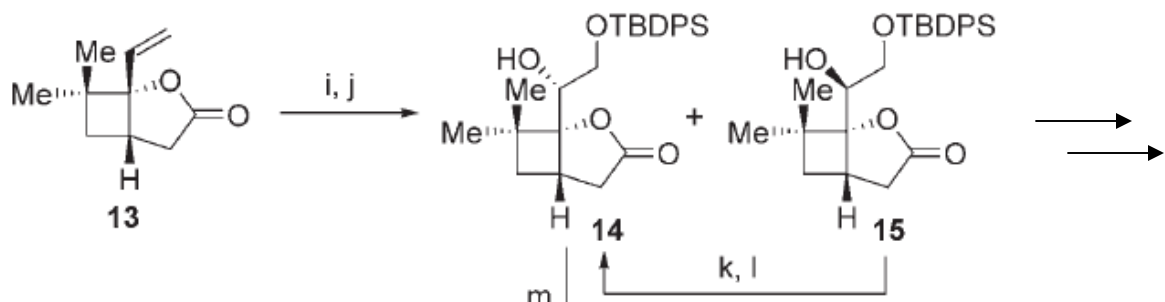
d.r. 4:1 (15 major); [O]/[H-]: 9:1 (14 major); ACIEE, 2008, 3426

Diol-to-epoxide is common application of AD. 'd' in scheme is 1. TsCl. 2. K_2CO_3 Furstner, ACIEE, 2006, 5510, From the conclusion:

macrolide is now covered. Nevertheless, we are well aware that this venture is no more but an auspicious start for the conquest of this challenging natural product because of the as of yet unanswered stereochemical issues delineated in the introduction. Undaunted, however, we are now actively pursuing possible end games with the hope of reaching this monumental target soon.

Scheme 2. Asymmetric Desymmetrization of Diene 10[a]
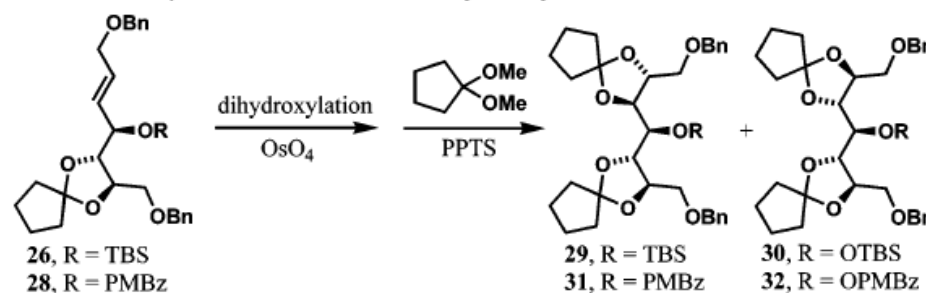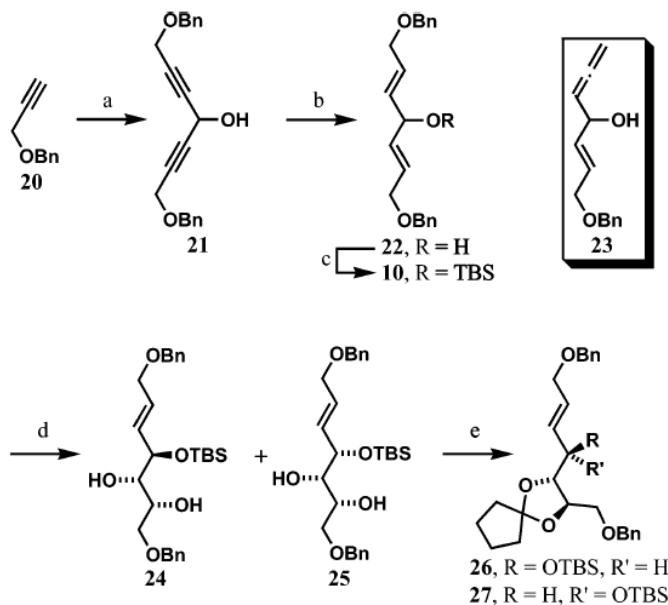
entry	substrate	conditions	yield of 29 + 30 (%)	29:30 (or 31:32)
1	26	NMO	82	1:2
2	26	(DHQD)₂PHAL	78	1:6
3	26	(DHQ)₂PHAL	nd[a]	1:2
4	28	NMO	80	1:3
5	28	(DHQD)₂PHAL	65	1:2
6	28	(DHQ)₂PHAL	nd	1:8

Synthesis of amphidinolide A: Trost, JACS, 13589.
In scheme 2: d: 11:1 24/25, 90%ee.