中国科学技术大学
University of Science and Technology of China

Oxidation

Courtesy of Prof. Xi-Sheng Wang

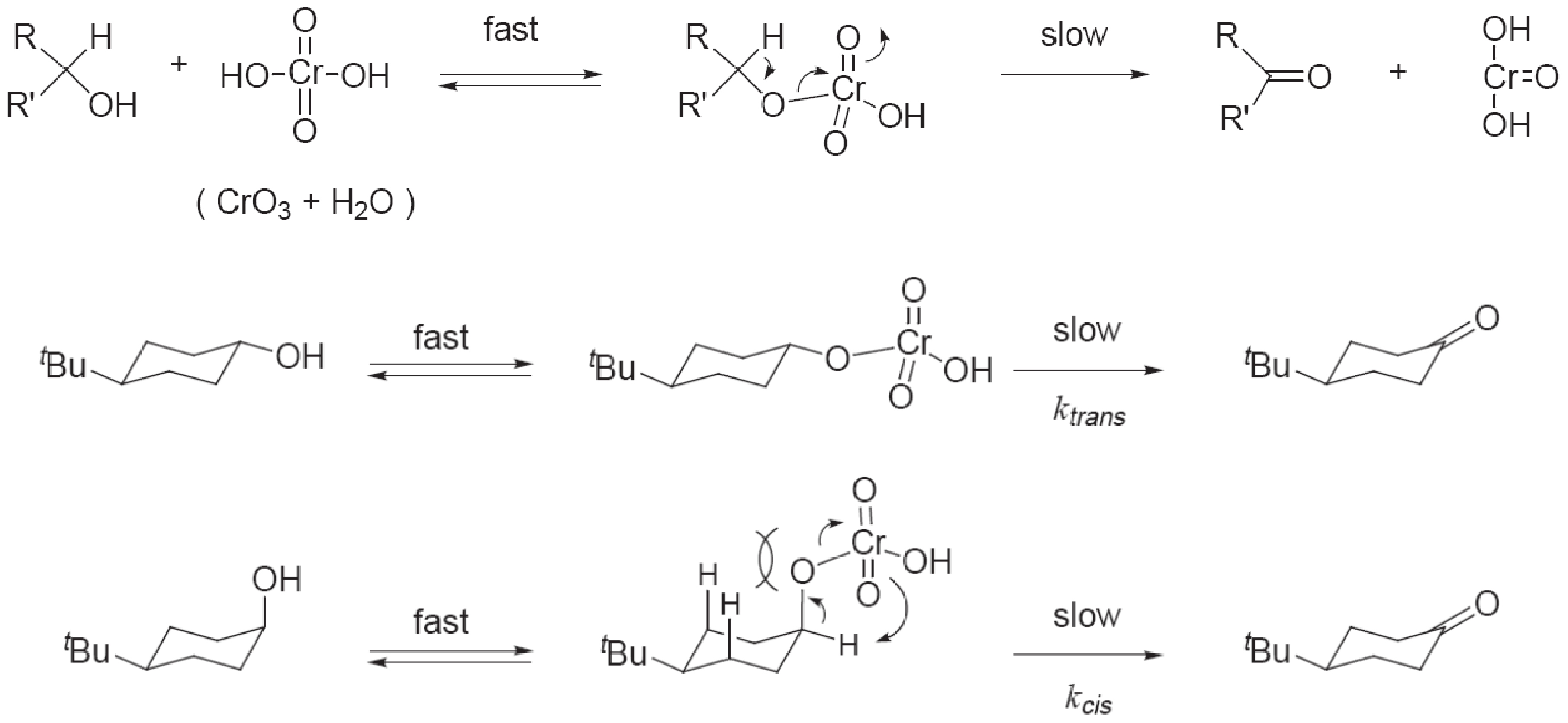
徐航勋

Email: hxu@ustc.edu.cn https://staff.ustc.edu.cn/~hxu

中国科学技术大学高分子科学与工程系

Oxidation of Alcohols

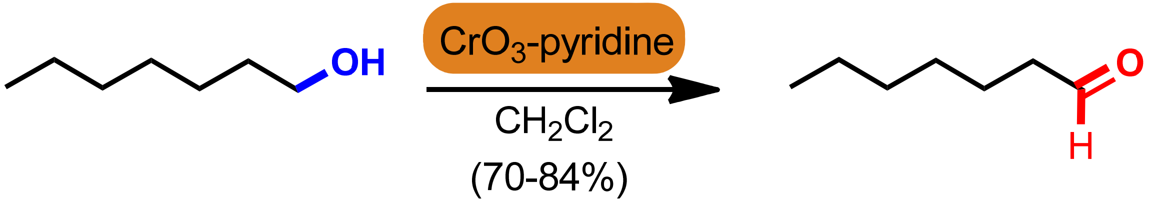
❑ Chromium (Cr) Reagents:



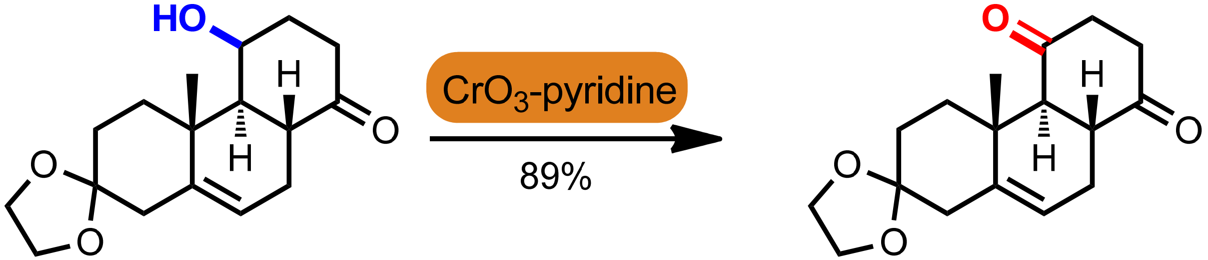
$$k_{cis}/k_{trans} = 4$$

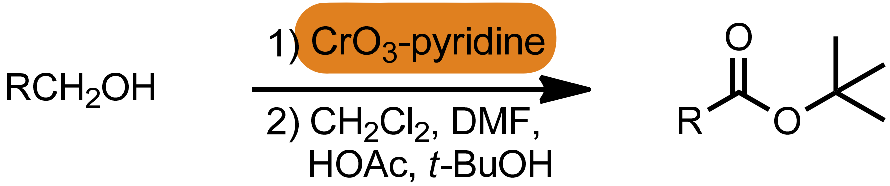
The Collins Reagent: CrO_3•2Py

- CrO_3-Pyridine$_2$, alkaline oxidant
- Hygroscopic (吸湿性强）, red crystalline complex
- Can also be isolated and stored, but usually generated *in situ* by CrO_3 + pyr (**Sarett Reagent**). Note: Add CrO_3 to pyr, not pyr to CrO_3 (inflames)
- Good for acid sensitive substrates
- **Ratcliff modification**: *in situ* preparation and use in CH_2Cl_2.



Notes:
- ➢ No over oxidation.
- ➢ Double and triple bond tolerated.





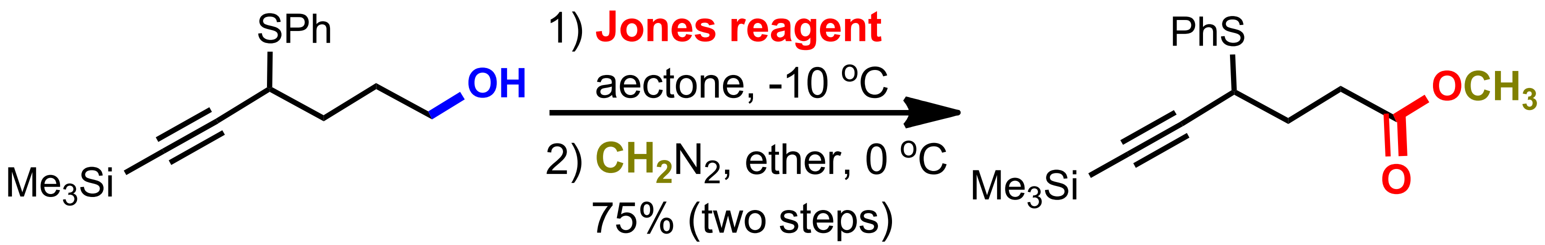
❖ General except for ArCHO

The Jones Oxidation

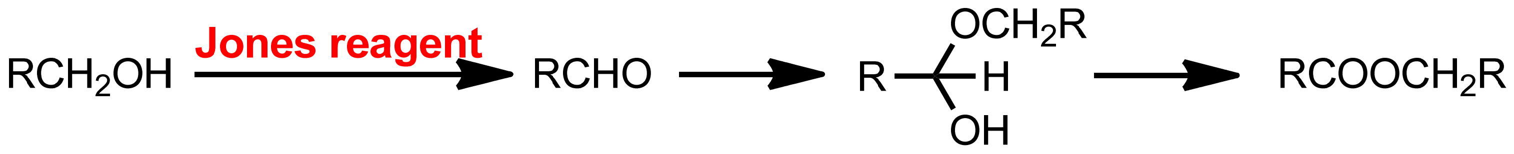
- ❑ A standard solution of chromic acid in aqueous sulfuric acid:

CrO_3 in aq. H_2SO_4/acetone

- ❑ Acetone solvent serves to protect substrate from over oxidation
- ❑ Not good for oxidations of acid sensitive substrates
- ❑ Acidic oxidation conditions, H^+ catalyzed reactions possible



➢ Another common side reaction for primary alcohol oxidation:



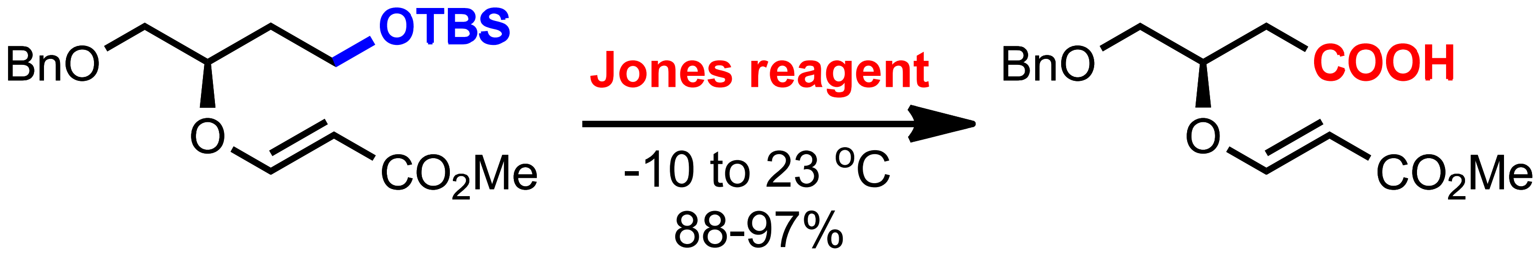
$$RCH_2OH \xrightarrow{\text{Jones reagent}} RCHO \longrightarrow R-\overset{OCH_2R}{\underset{OH}{C}}-H \longrightarrow RCOOCH_2R$$

hemiacetal
(半缩醛)

ester

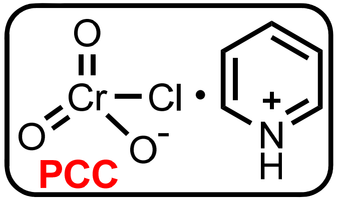
Solution: run under diluted reaction conditions to circumvent esterification.

The Jones Oxidation



(–)-CP-263,114

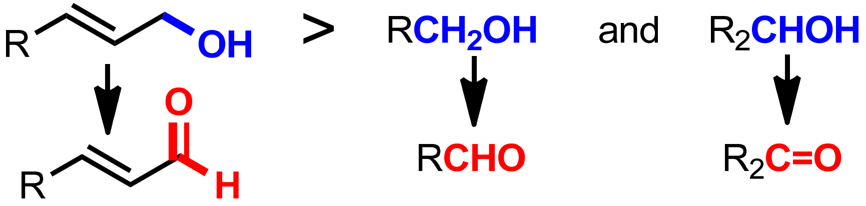
Pyridinium Chlorochromate (PCC)



← CrO_3/6 M HCl/pyridine (1:1:1)

- Chloride facilitates formation of chromate ester (slow step in oxidation reaction)
- Stable, Commercially available reagent

- Reaction usually carried out in CH_2Cl_2
- Rates:



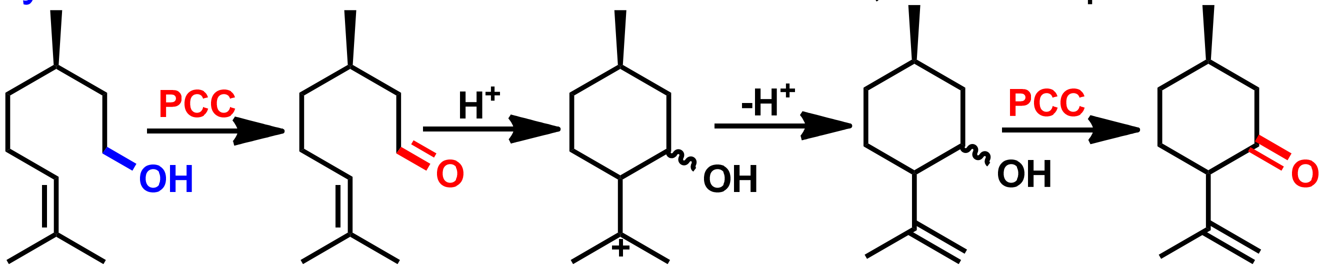
RCH_2OH and R_2CHOH

$RCH_2OH \rightarrow RCHO$

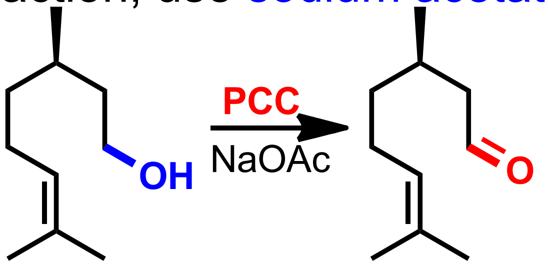
$R_2CHOH \rightarrow R_2C{=}O$

No over oxidation

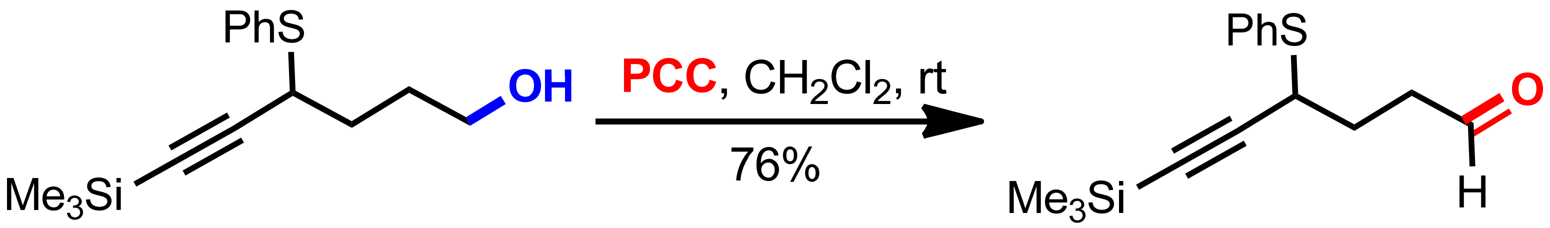
- Usually only need 1-2 eq. of Cr(VI) reagent (Jones & Collins usually require 6 eq.)
- PCC slightly acidic which can cause side reactions , for example:



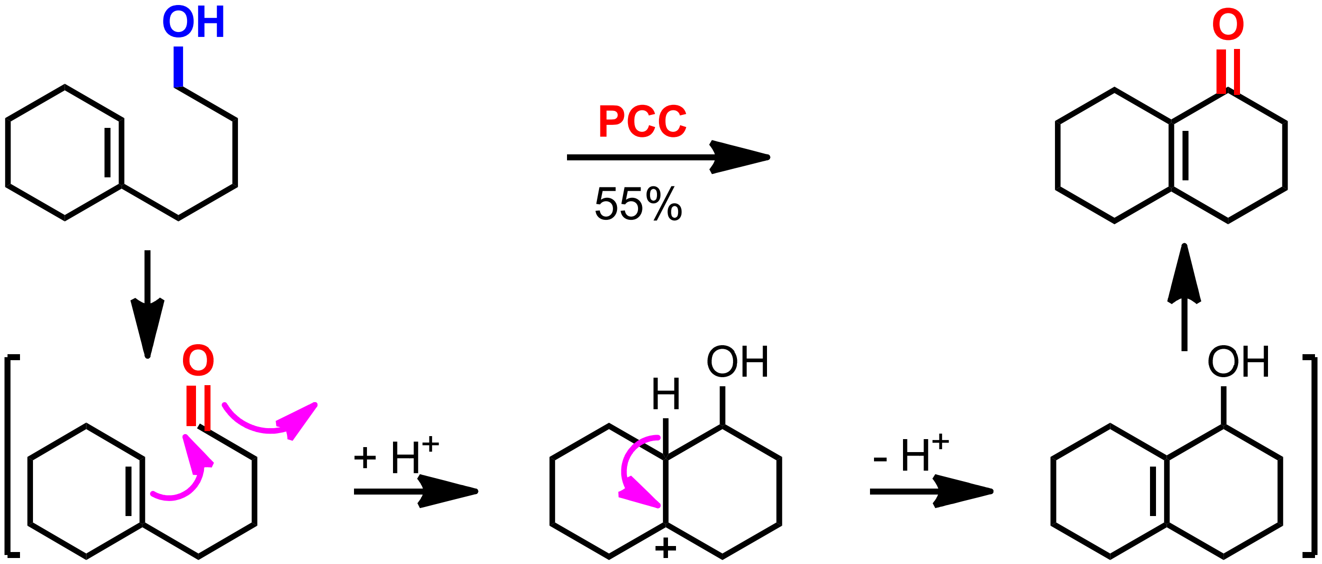
- To avoid H^+ catalyzed side reaction, use sodium acetate buffer:



Pyridinium Chlorochromate (PCC)

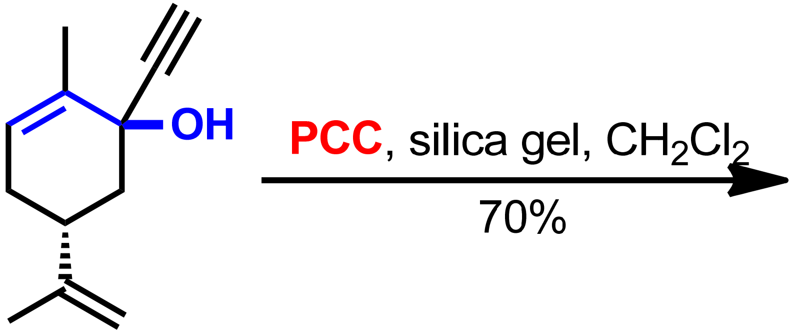


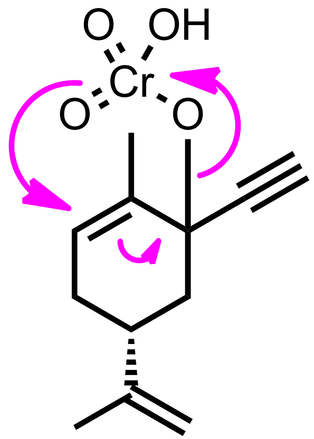
- Can take advantage of acidity in PCC reaction:



Pyridinium Chlorochromate (PCC)

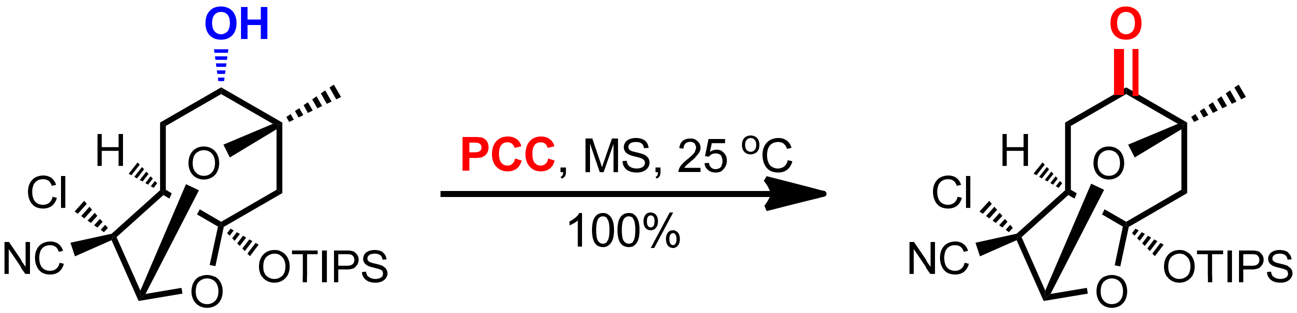
- Oxidation of 3º, allylic alcohols:



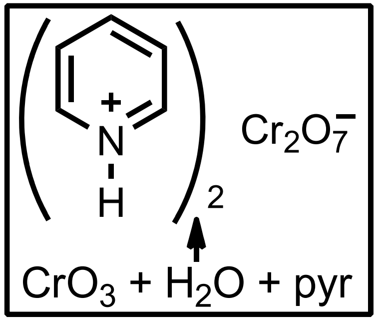


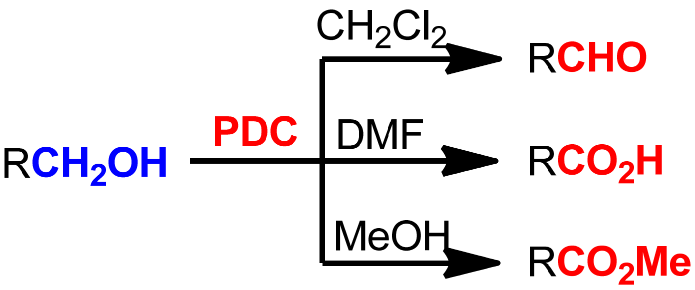
[3,3]-sigmatropic arrangement

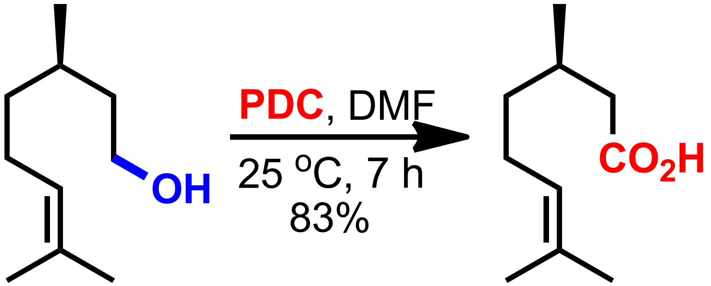
- 3 Å MS accelatate rate of oxidation (PCC and PDC):



Pyridinium Dichromate (PDC)

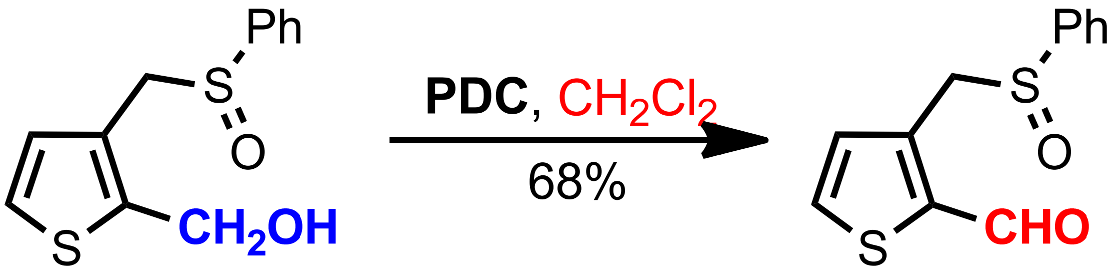


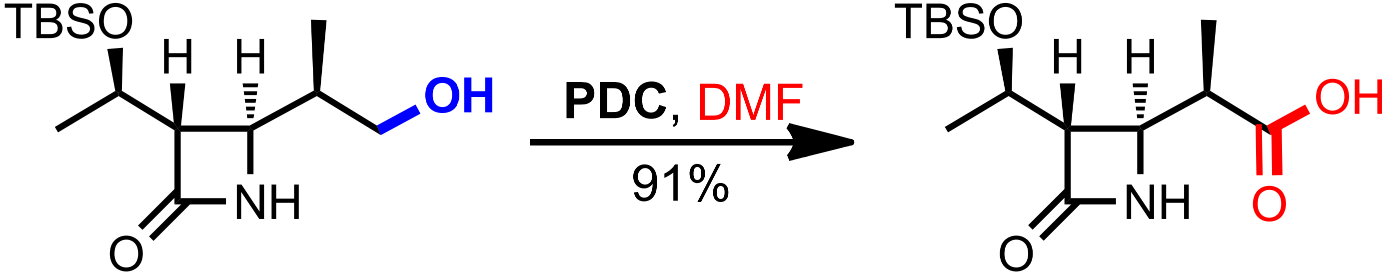




- Stable, commercially available reagent
- Not as acidic as PCC
- Oxidations slower than PCC or other oxidation reagents
- Can **selectively oxidize 1° alcohols** to aldehyde or carboxylic acid depending on solvent
- 2° alcohols oxidize only slowly and sometimes require an acid catalyst (pyridinium trifluoroacetate or 3Å MS)
- Other related reagents include nicotinium dichromate, quinolinium dichoromate, and imidazolium dichromate
- **Note: Cr based reagents will oxidize amines and sulfides**. Substrates with these functional groups must be oxidized with other reagents (PDC will sometimes leave sulfides unaffected).

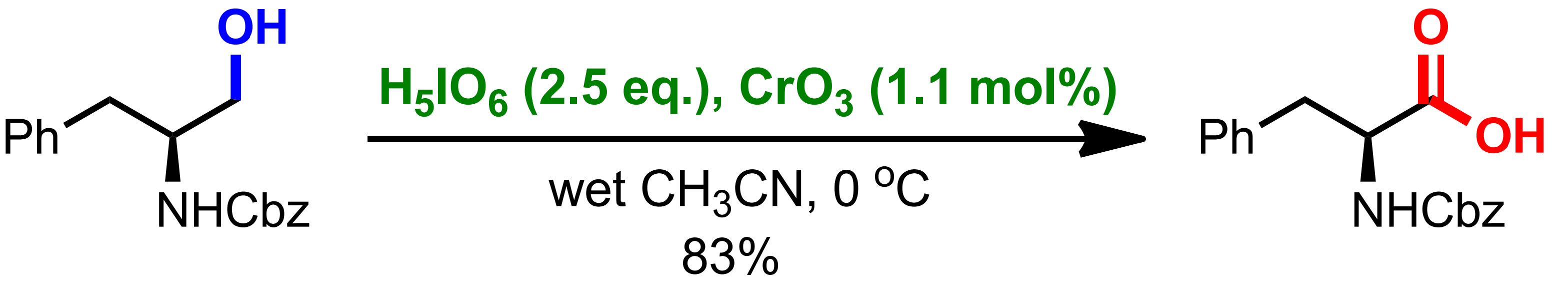
Pyridinium Dichromate (PDC):
Selective Oxidation to Aldehyde or Carboxylic Acid

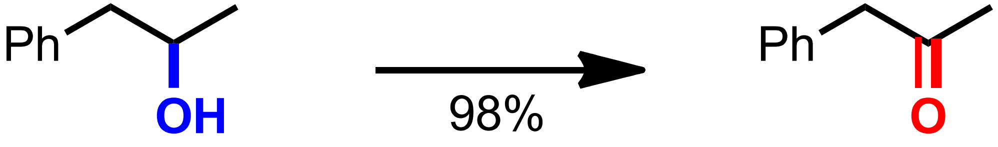




CrO_3-H_5IO_6

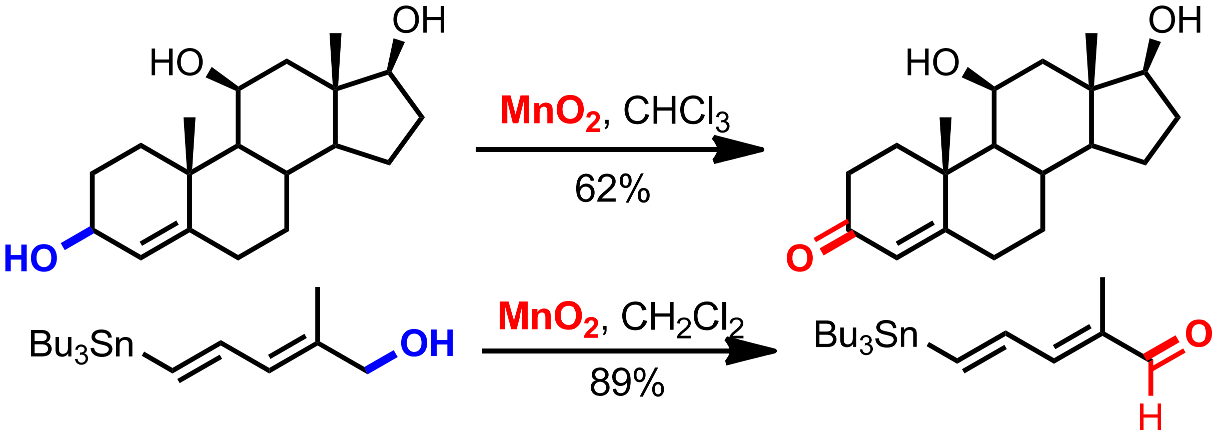
- **Catalytic CrO_3 (1-2%,** industrial scale chromium-based oxidations)



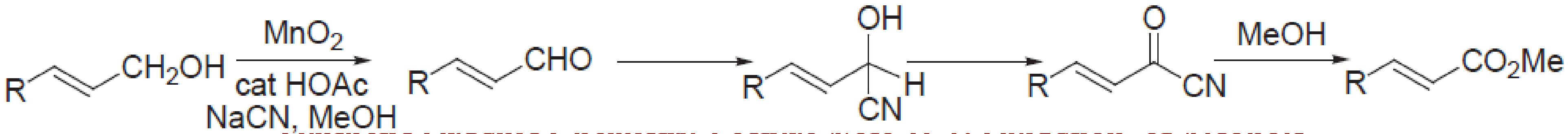


Manganese Dioxide (MnO_2)

- **Very mild oxidizing reagent**, **special "activated"** MnO_2 preparation required
- **Selectively oxidizes allylic and benzylic alcohols to aldehyde or ketone**

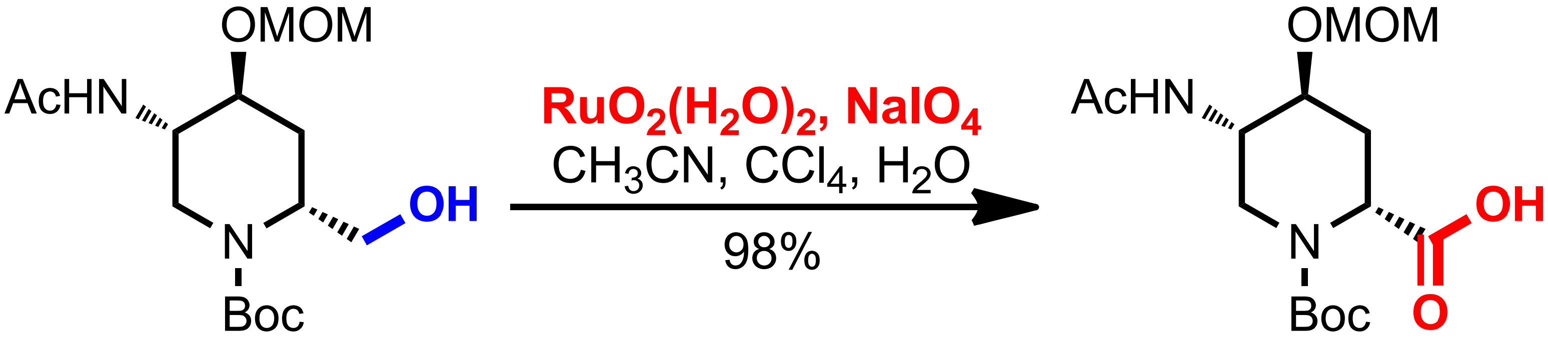


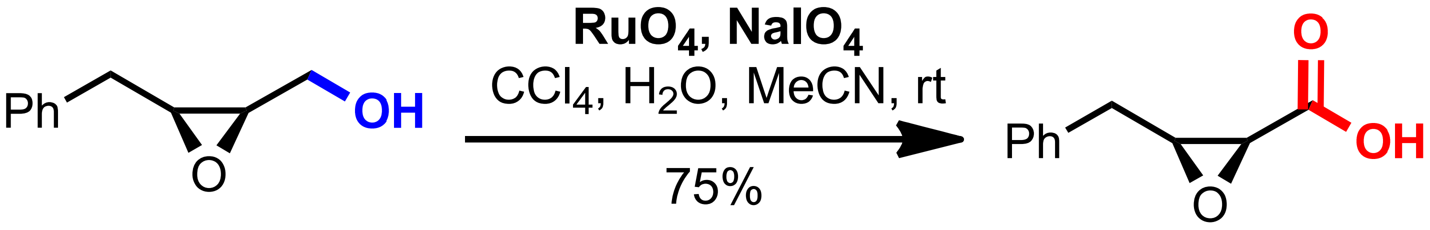
- Requires **nonpolar solvent** (CH_2Cl_2, $CHCl_3$, pentane, benzene, etc.)
- Oxidizing reagent : substrate = **10:1** (10 wt. equiv.)
- No **isomerization (异构化）** of conjugated double bond. Cr-based reagent will cause problems due to H^+ catalysis
- Chemical MnO_2 (CMD), commercially available, also works well
- **NiO_2**: alternative reagent that behaves similar to MnO_2
- Oxidize alcohol to ester, no isomerism of C=C bond



Ruthenium Tetroxide (RuO_4)

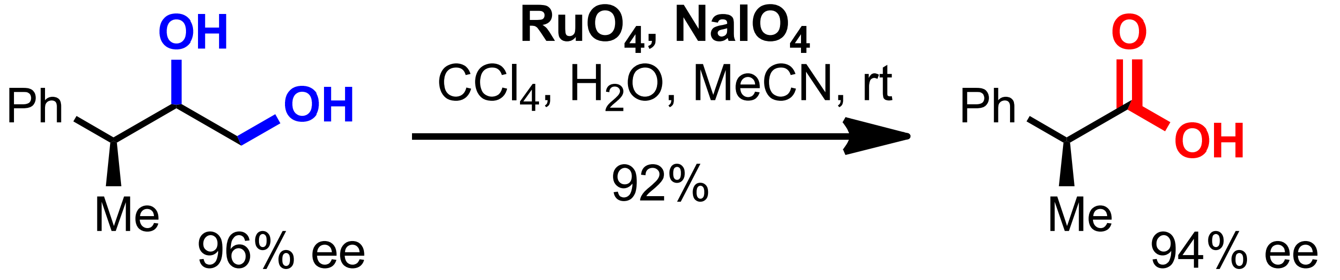
- ❑ Catalytic procedures employ 1-5% of ruthenium metal and a stoichiometric oxidant, such as sodium periodate ($NaIO_4$)
- ❑ *In situ* generation from RuO_2-$NaIO_4$ (or NaClO) or from $RuCl_3$-H_5IO_6

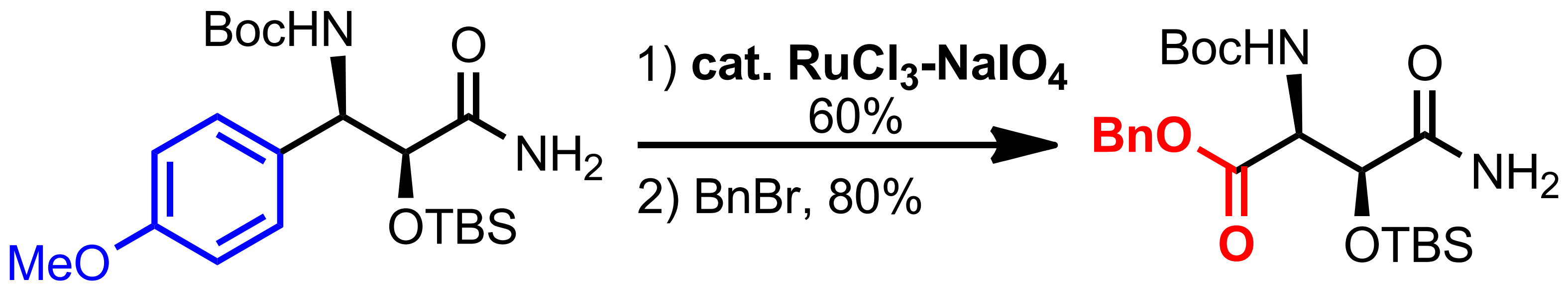




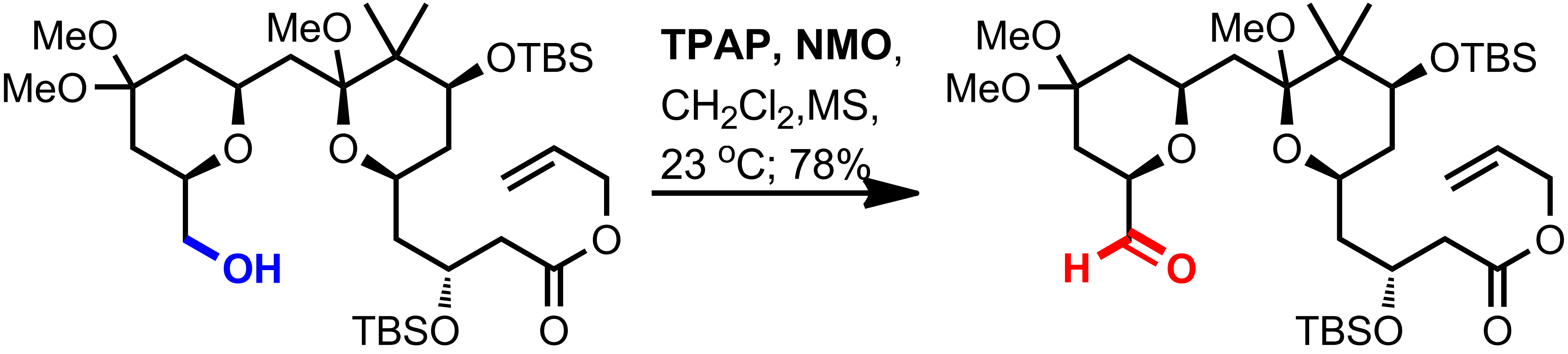
Ruthenium Tetroxide (RuO_4)

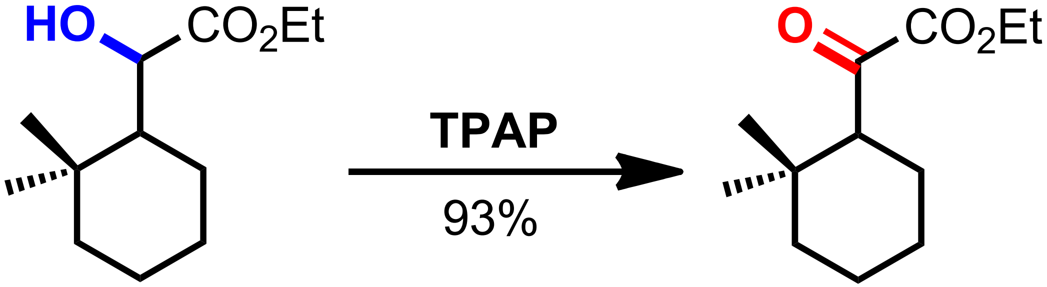
Note: RuO_4 **attacks C=C bonds** and will **cleave 1,2-diols** often used to **cleave aromatic rings**:

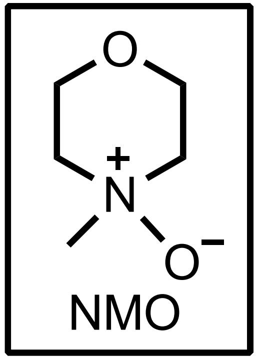




Tetra-*n*-propylammonium Perruthenate (TPAP, *n*-Pr_4N^+ RuO_4^-)

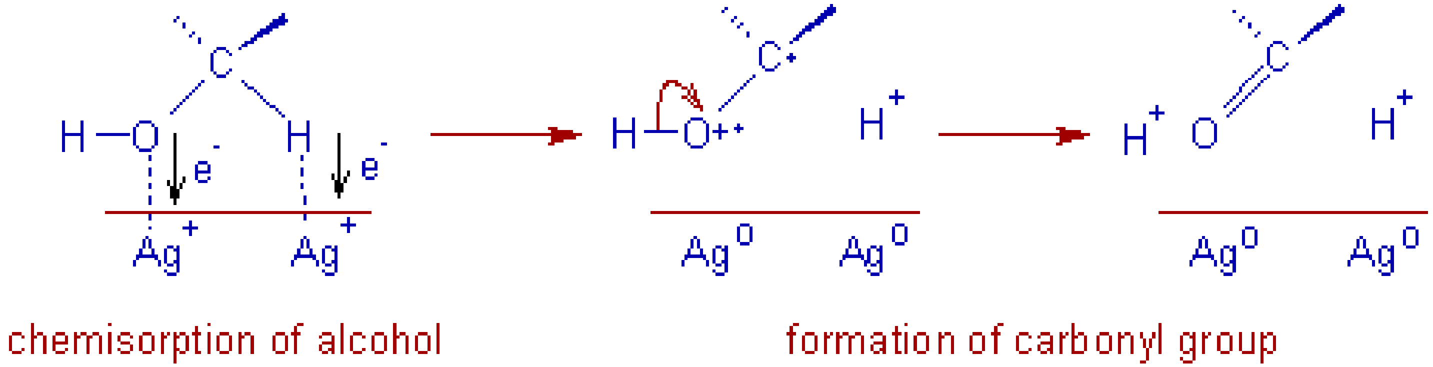


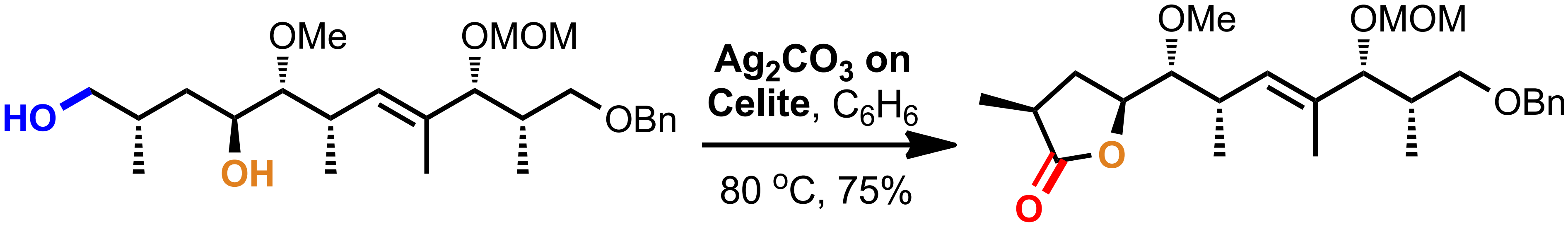




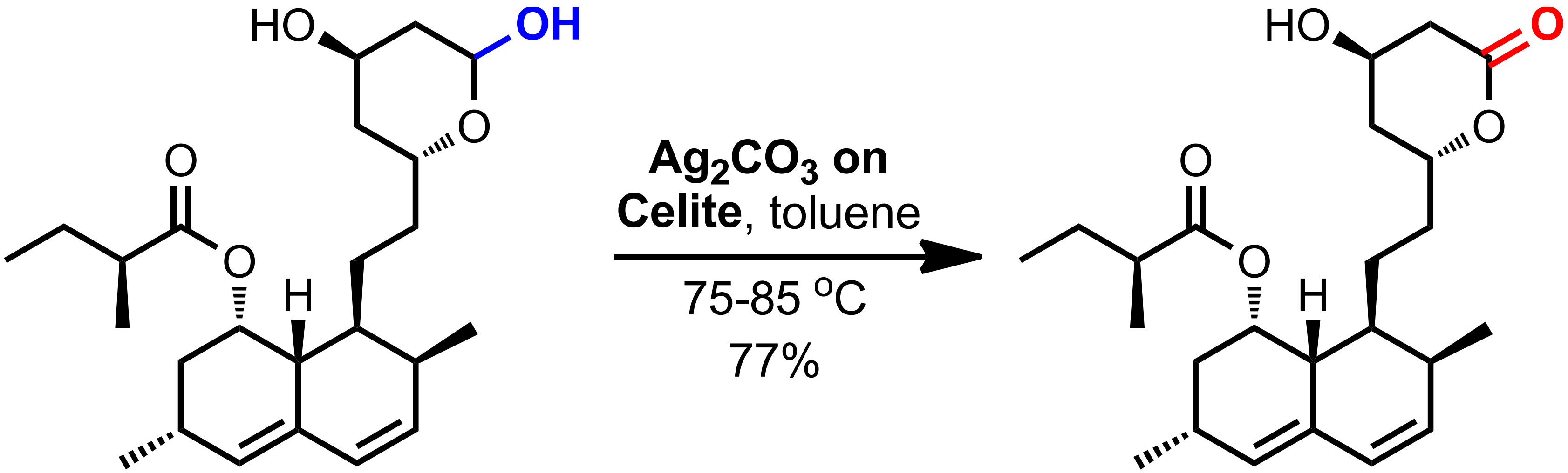
The Fétizon's Reagent

- ☐ Ag_2CO_3 on Celite
- ☐ Reaction Mechanism:





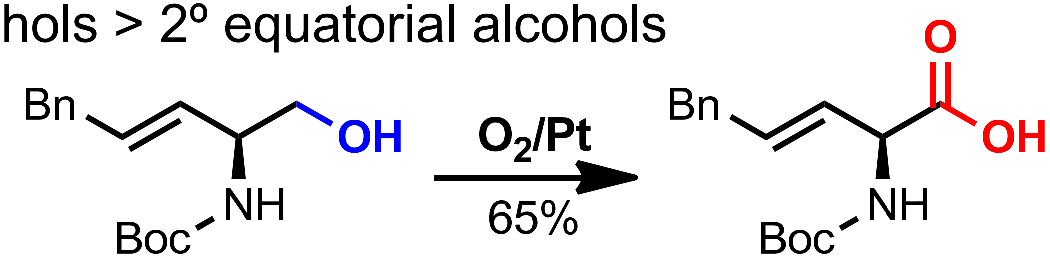
The Fétizon's Reagent

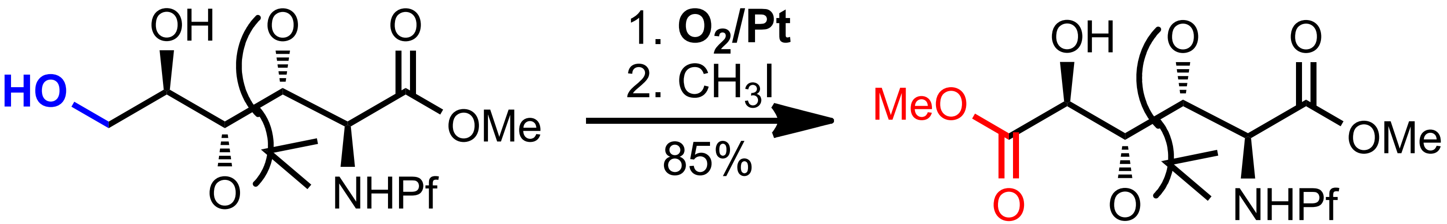


(+)-mevinolin

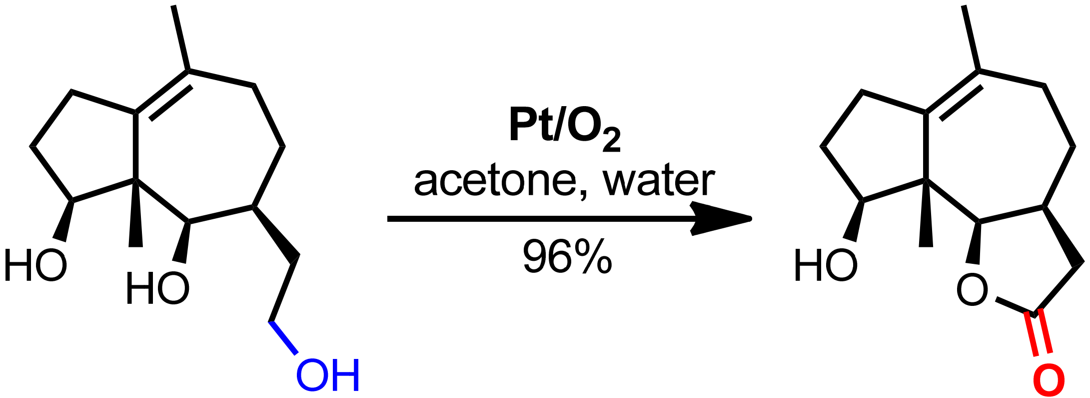
O_2/Pt

- ☐ Good for oxidation of **1° alcohols directly to carboxylic acids**
- ☐ 1° alcohols > 2° alcohols
- ☐ 2° axial alcohols > 2° equatorial alcohols



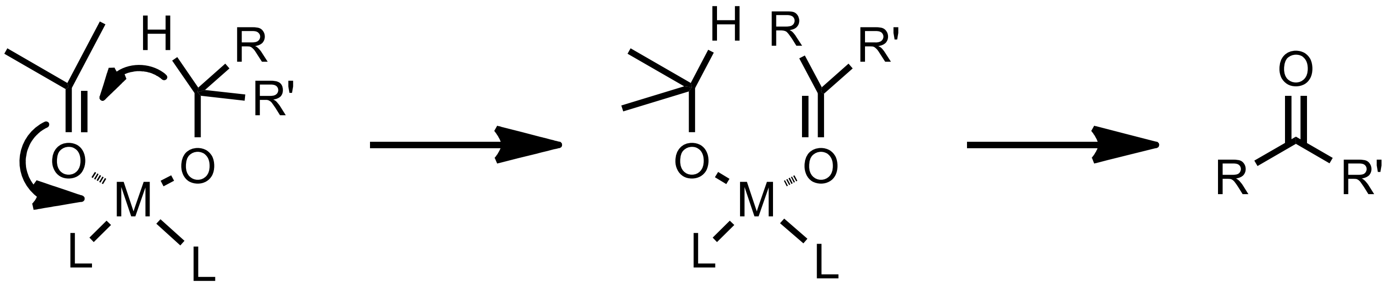


Pf = 9-phenylfluorenyl



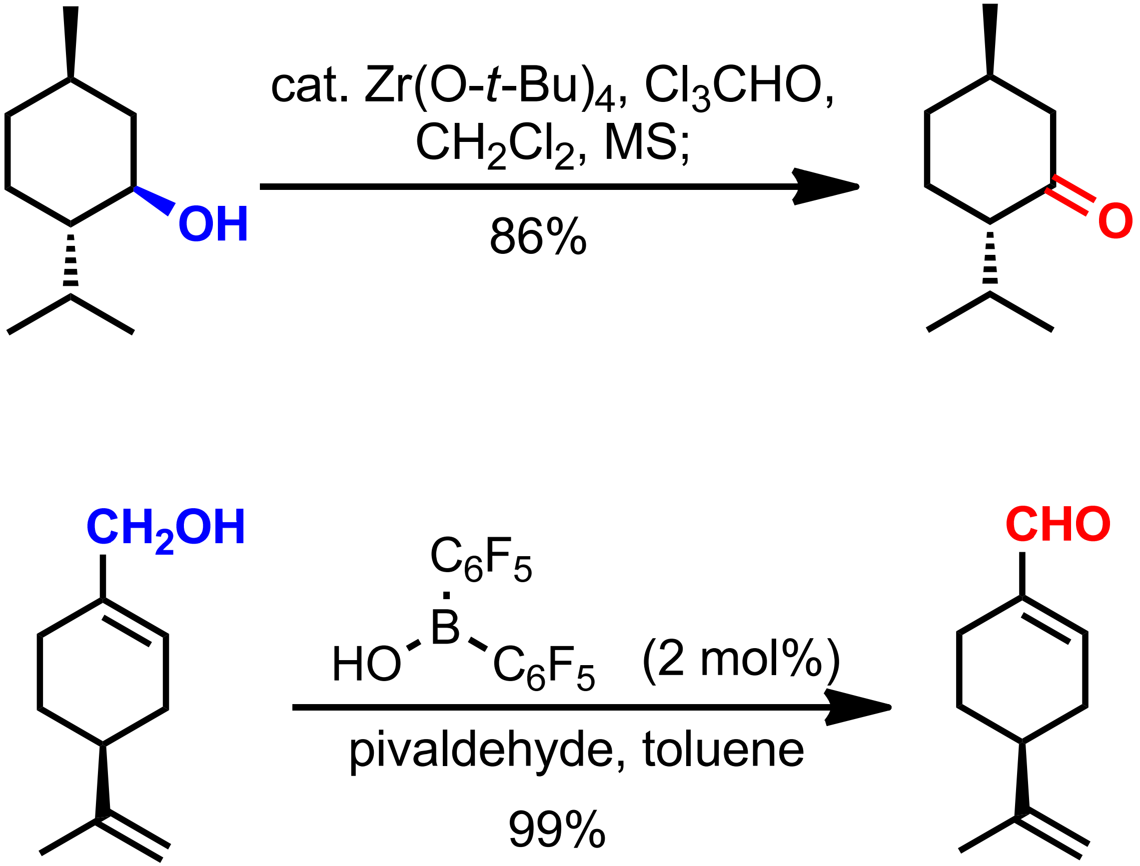
The Oppenauer Oxidation

- ☐ A classic oxidation method achieved by heating the alcohol to be oxidized with a metal alkoxide in the presence of a carbonyl compound as a hydride acceptor (the reverse of the Meerwein-Pondorff-Verley Reduction).
- ☐ The reaction is **an equilibrium process** and is believed to proceed through a cyclic transition state.

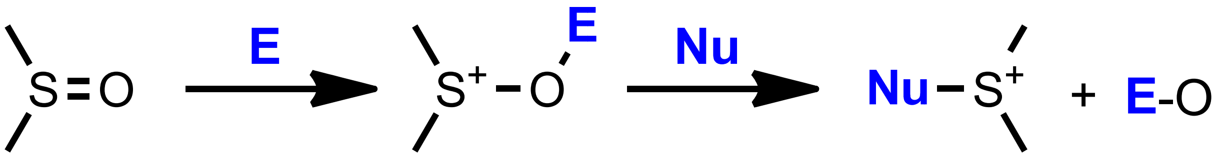


- ☐ Suitable for oxidation of 2° alcohol in the presence of **1° alcohol which do not react**
- ☐ Good for oxidation of substrates containing easily oxidized functional groups

The Oppenauer Oxidation



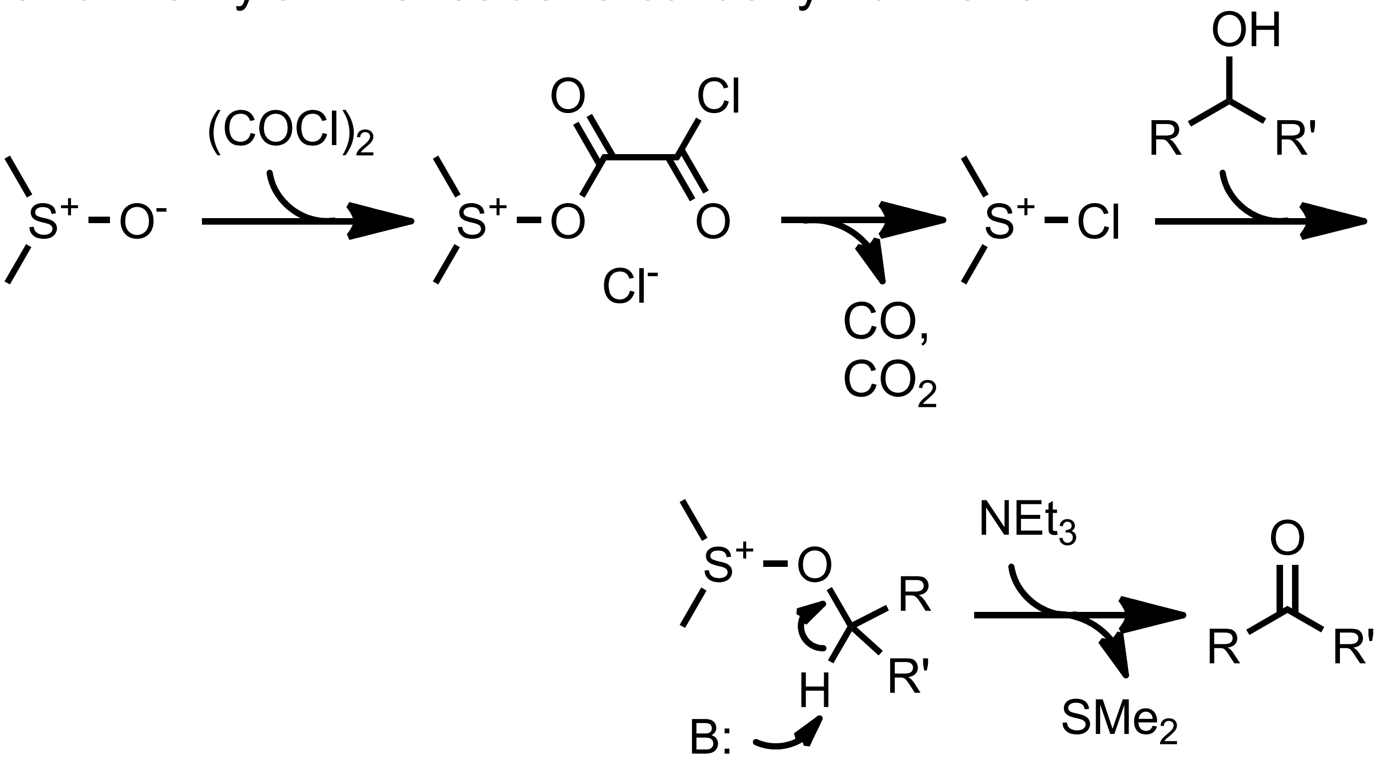
Non-Metal Based Reagents
Dimethylsulfoxide (DMSO)-Mediated Oxidations



- ❑ **E** = $(CF_3CO)_2O$, $SOCl_2$, $(COCl)_2$, Cl_2, $(CH_3CO)_2O$, TsCl, MsCl, SO_2/pyridine, F_3CSO_2H, PO_5, H_3PO_4, Br_2
- ❑ **Nu** = R-OH, Ph-OH, $R-NH_2$, RC=NOH, enols（烯醇）

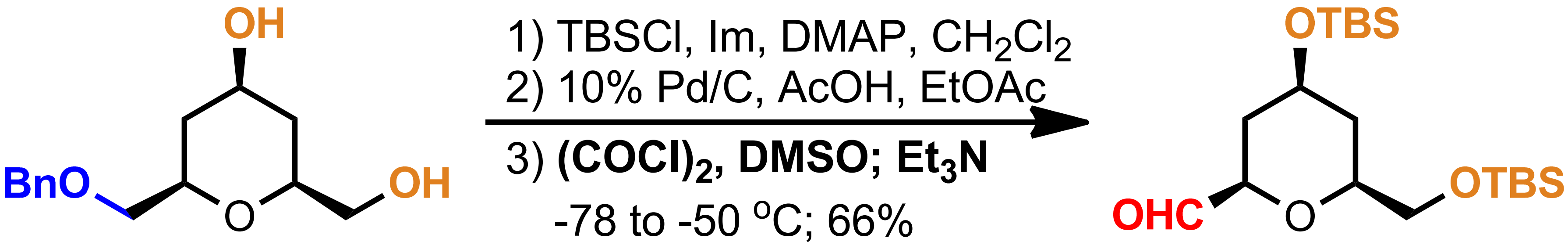
The Swern Oxidation

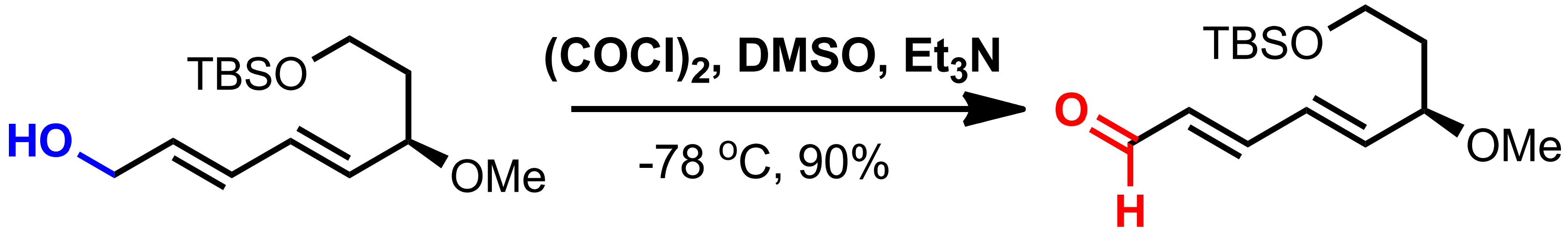
- Typically, 2 equivalents of DMSO are activated with oxalyl chloride in dichloromethane at or below –60 ºC. Subsequent addition of the alcohol substrate and triethylamine leads to carbonyl formation.



- DMSO-$(COCl)_2$; DMSO-TFAA; DMSO-Ac_2O (Albright-Goldman reagent); DMSO-SO_3/Pyr, DMSO-$SOCl_2$; DMSO-Cl_2.

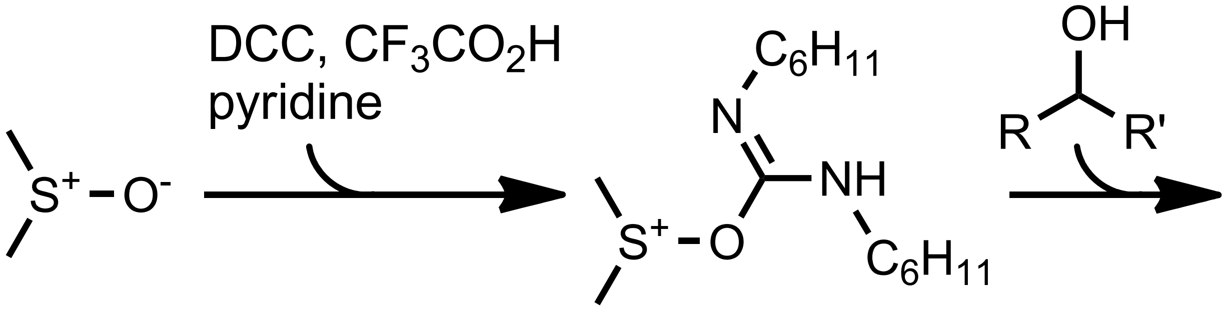
The Swern Oxidation

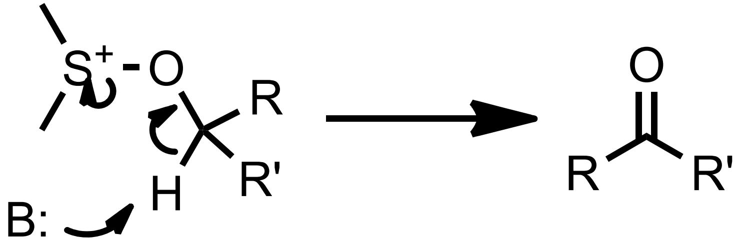


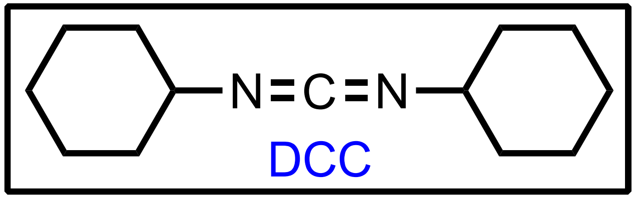


The Moffatt-Pfitzner Oxidation (DCC-DMSO)

- The first reported DMSO-based oxidation procedure.
- Dicyclohexylcarbodiimide (DCC) functions as the electrophilic activating agent in conjunction with a Brønsted acid promoter.

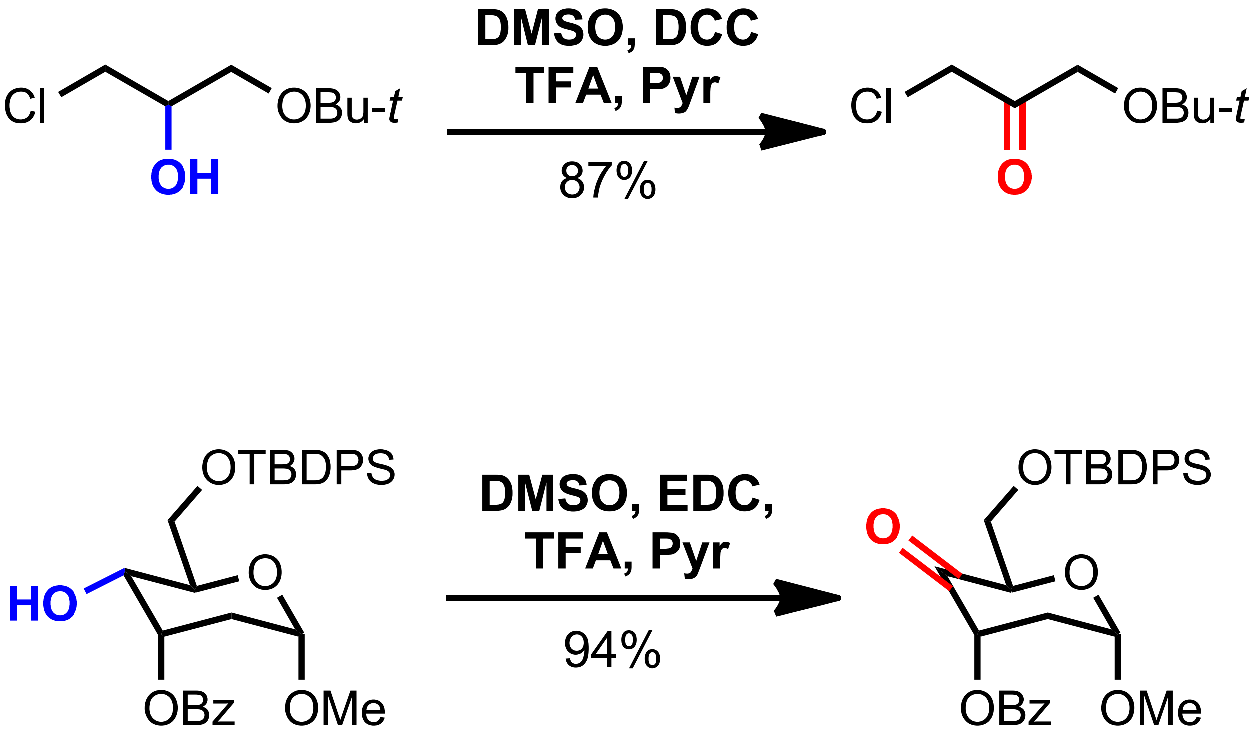






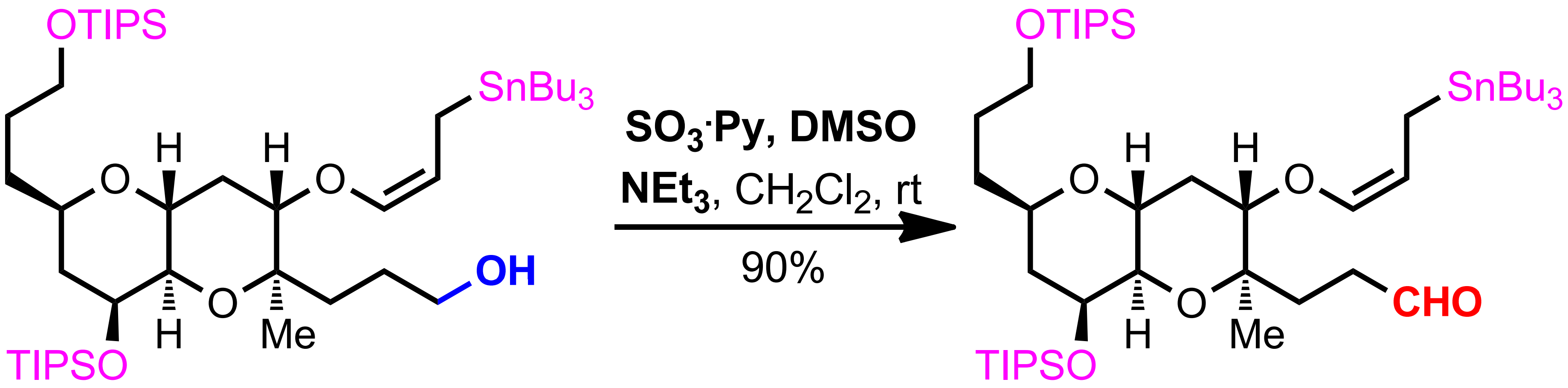
DCC

The Moffatt-Pfitzner Oxidation (DCC-DMSO)



The Parikh-Doering Oxidation

❑ **Sulfur trioxide-pyridine** is used to activate DMSO

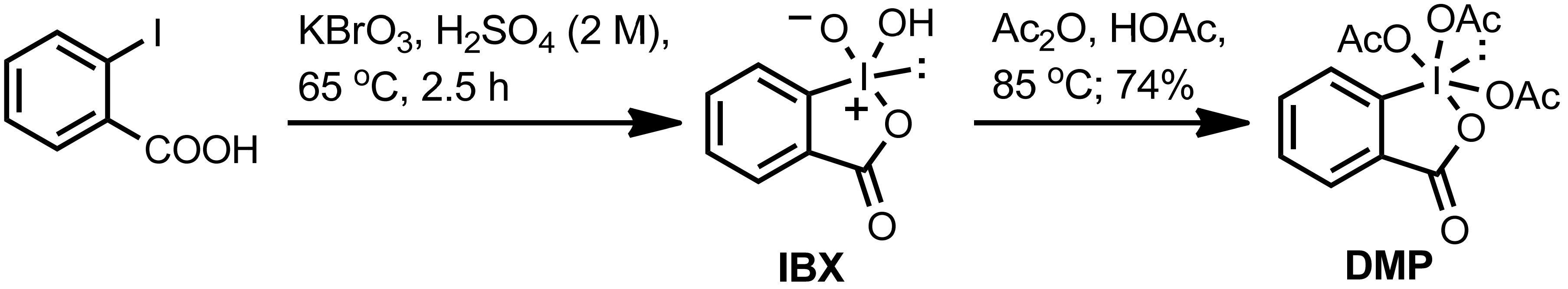


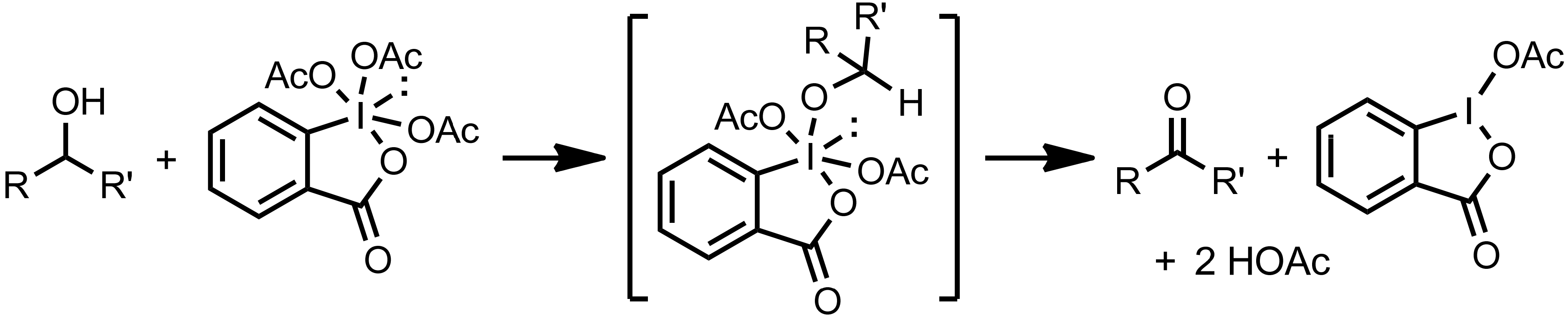
The Dess-Martin Periodinane (DMP)

- periodinane (五价碘）
- CH_2Cl_2, 25 ºC

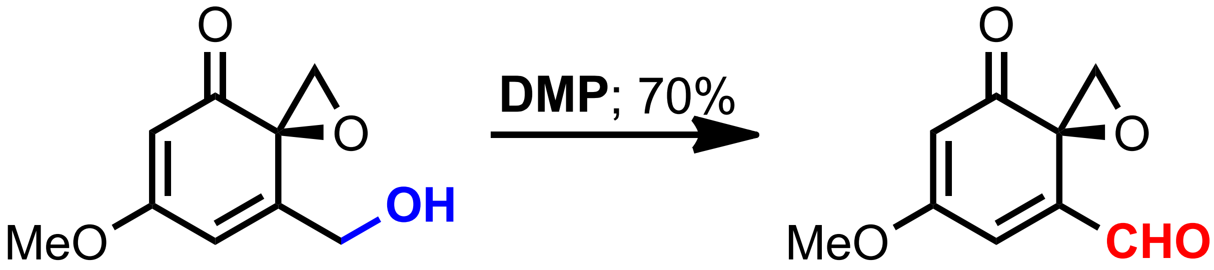
$$RCH_2OH \xrightarrow{DMP} RCHO$$

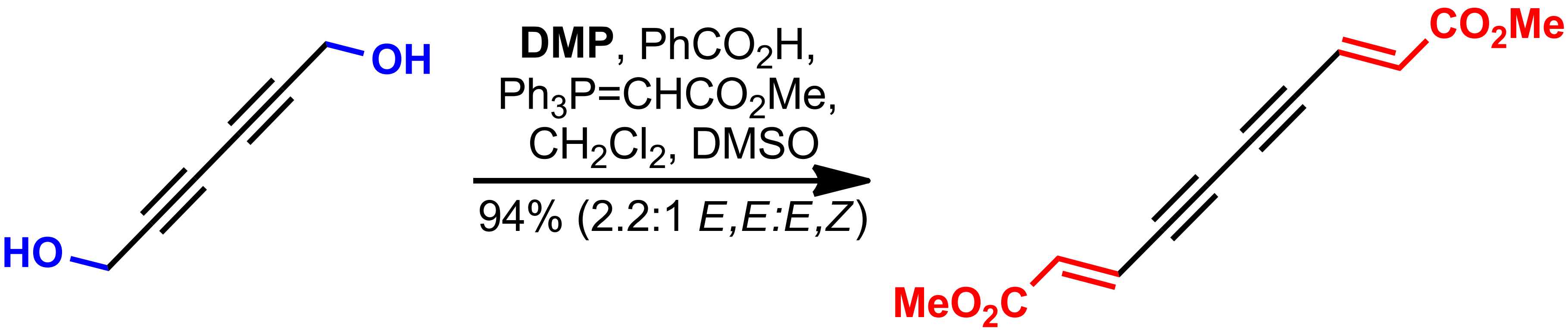
$$R_2CHOH \longrightarrow R_2C{=}O$$





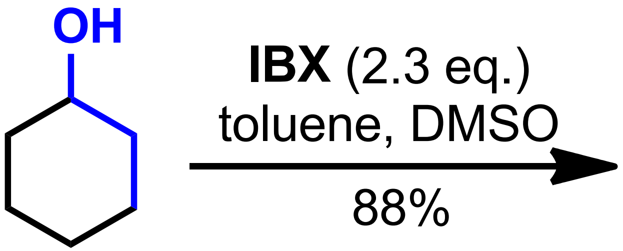
The Dess-Martin Periodinane (DMP)

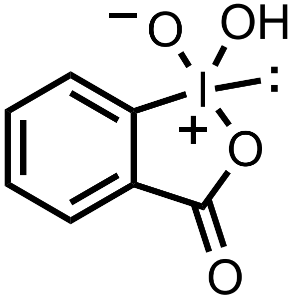




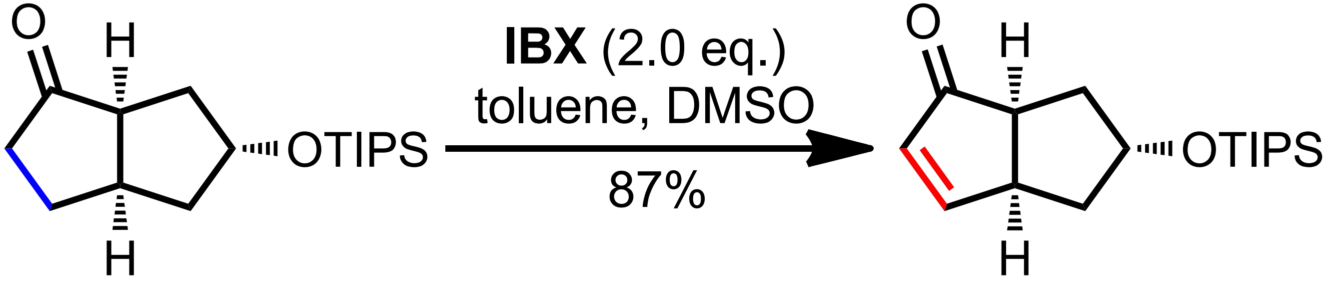
o-Iodoxybenzoic Acid (IBX)

- Precursor (前体）to Dess-Martin reagent
- Insoluble in almost all organic solvents but is soluble in DMSO and oxidation in this solvent work effectively (25 ºC).

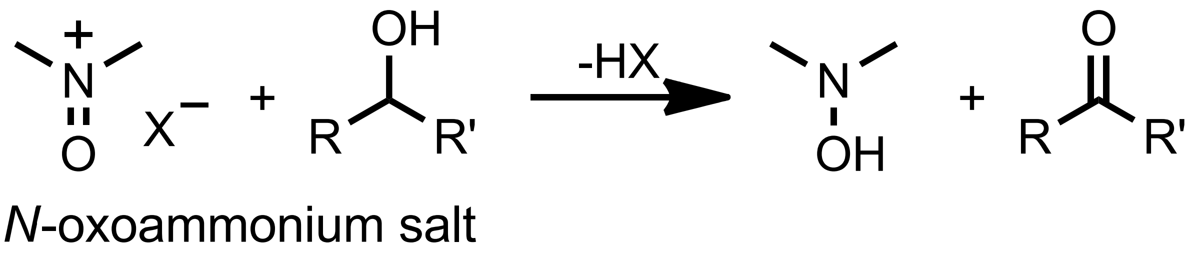




IBX

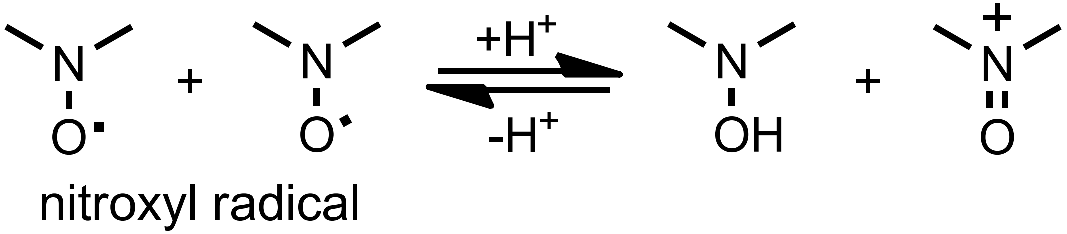


N-Oxoammonium Salt

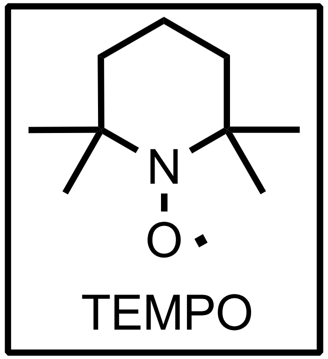


❑ Unstable and are invariably generated *in situ* in a catalytic cycle using a stable, stoichiometric oxidant.

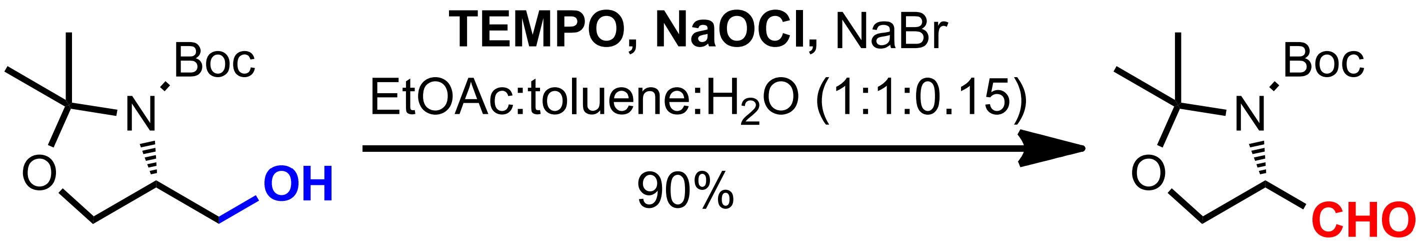
❑ May be formed *in situ* by the acid-promoted disproportionation（歧化）of nitroxyl radicals.



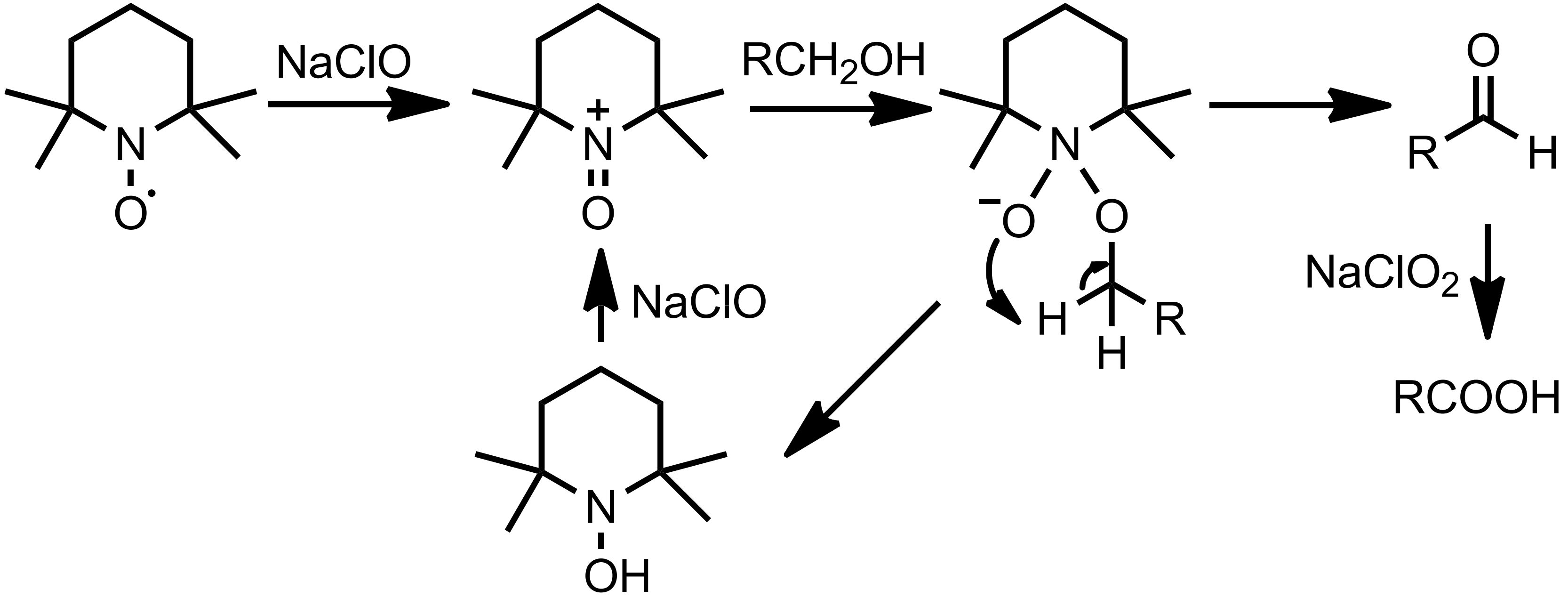
TEMPO



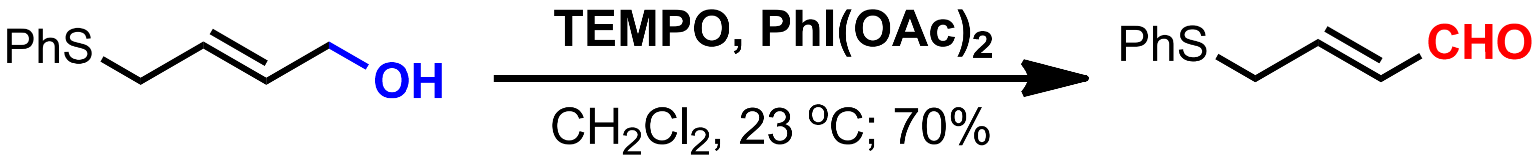
- ❑ With NaOCl , NaBrO$_2$, Ca(OCl)$_{2,}$ et. al.

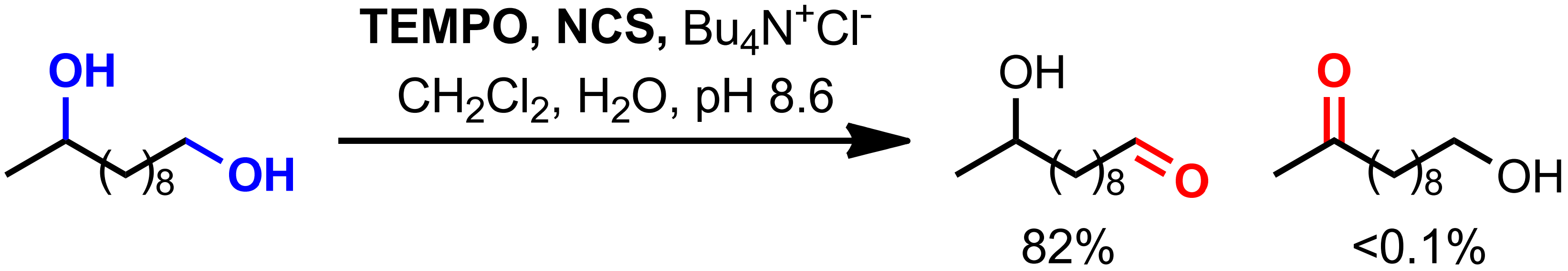

TEMPO, NaOCl, NaBr
EtOAc:toluene:H_2O (1:1:0.15)
90%

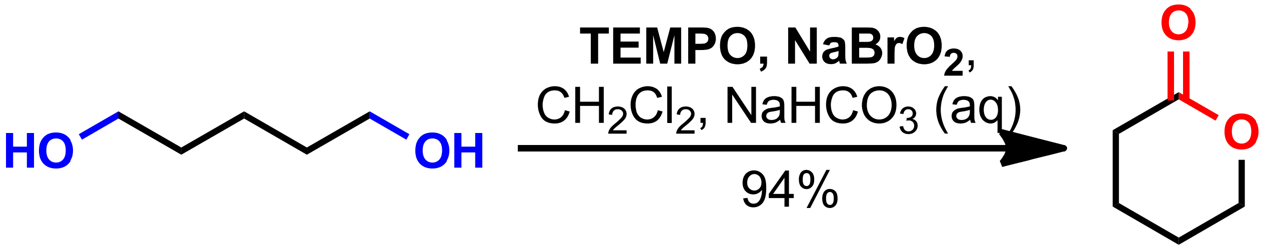
- ❑ Mechanism:



TEMPO


PhS
OH
TEMPO, PhI(OAc)$_2$
CH$_2$Cl$_2$, 23 °C; 70%
PhS
CHO


OH
8
OH
TEMPO, NCS, Bu$_4$N$^+$Cl$^-$
CH$_2$Cl$_2$, H$_2$O, pH 8.6
OH
8
O
82%
O
8
OH
<0.1%

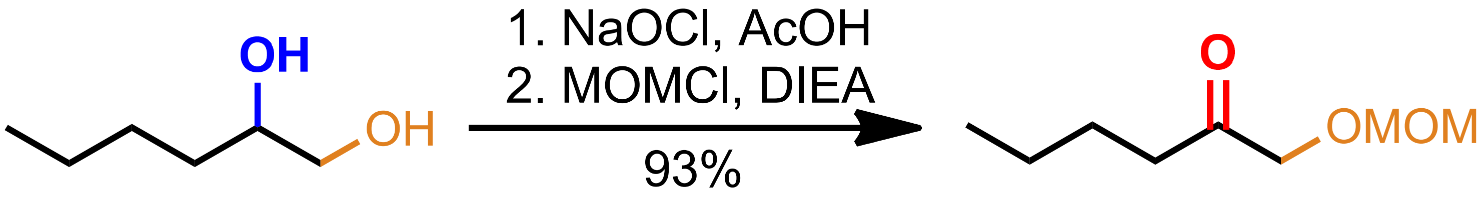

HO
OH
TEMPO, NaBrO$_2$,
CH$_2$Cl$_2$, NaHCO$_3$ (aq)
94%
O
O

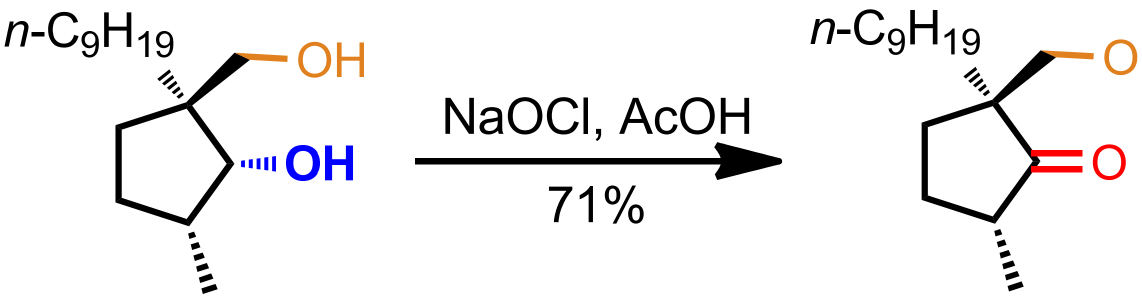
Sodium Hypochlorite: NaOCl

- Used primarily to oxidize alcohols to carboxylic acids

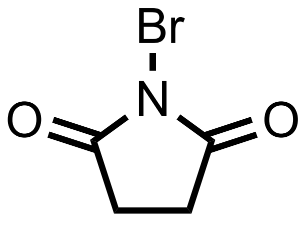
$$\mathrm{RCH_2OH} \longrightarrow \mathrm{RCHO} \longrightarrow \mathrm{RCO_2H}$$

- In acetic acid solution, it selectively oxidizes 2º alcohols rather than 1º alcohols.
- A Modified procedure employs $Ca(ClO)_2$: stable, easy handled, solid.

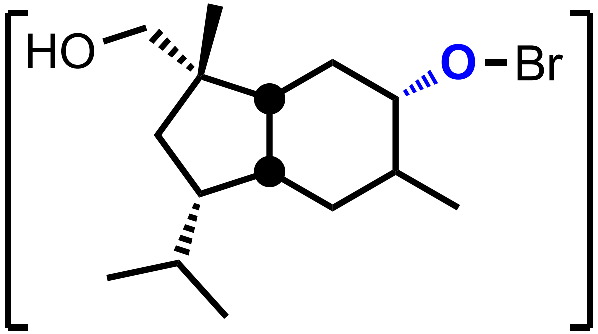


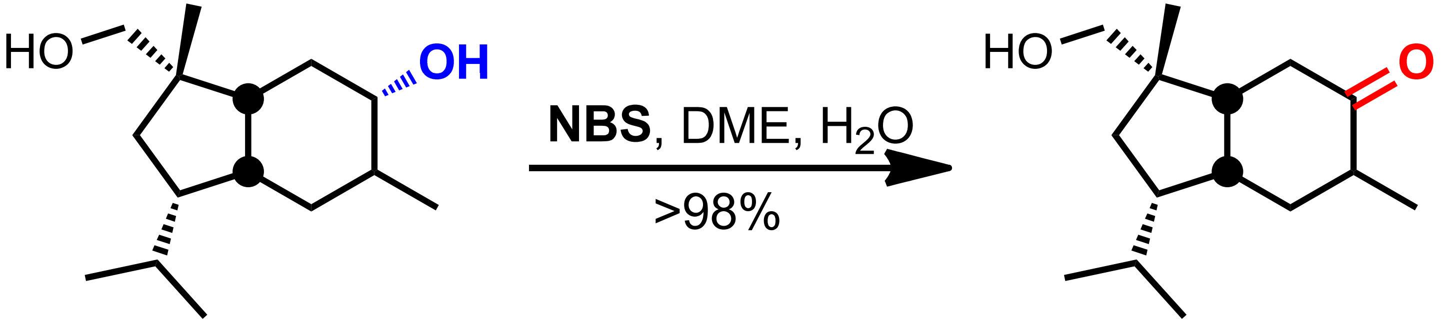


N-Bromosuccinimide (NBS) or Bromine



NBS

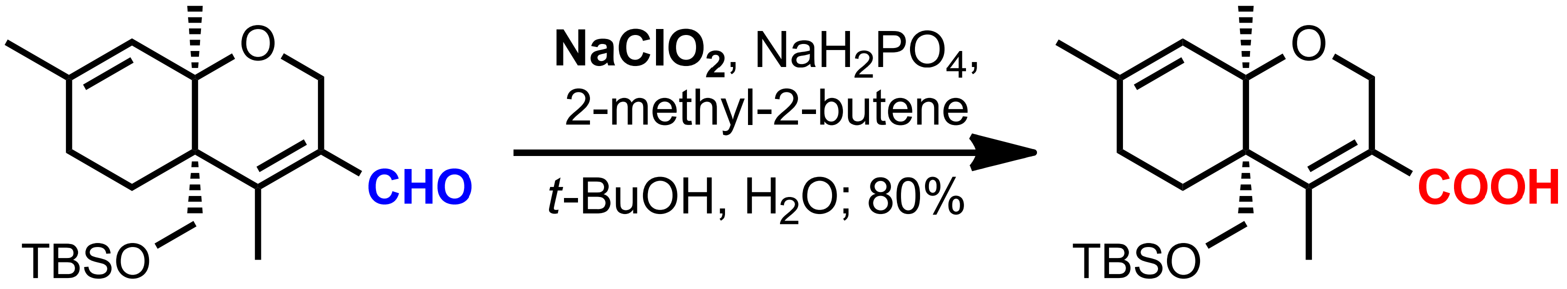




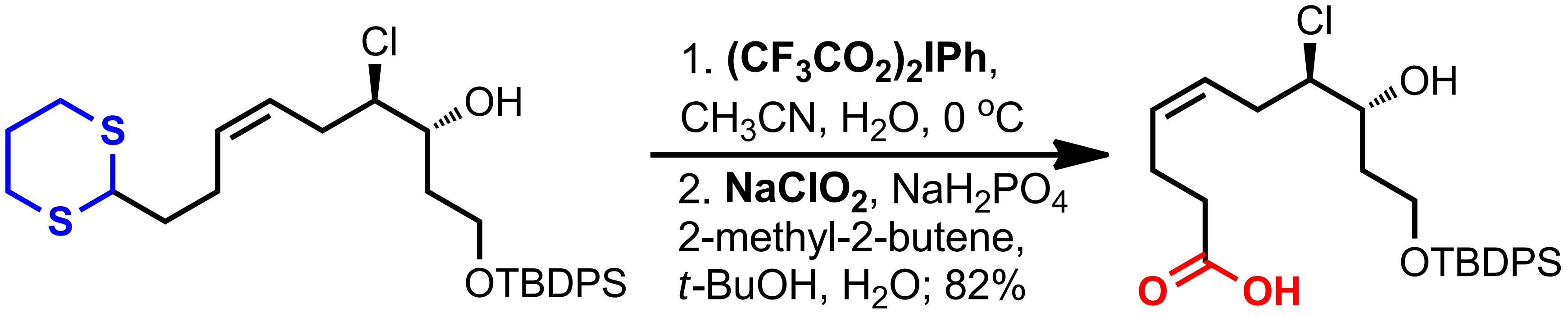
Oxidation of Aldehydes

❑ Sodium Chlorite: $NaClO_2$; Calcium Chlorite: $Ca(ClO_2)_2$

- ➢ Good for oxidation of sensitive **aldehydes to carboxylic acids**
- ➢ Becoming the method of choice for the oxidation of RCHO to RCO_2H
- ➢ Two-step procedures for RCH_2OH to RCO_2H (i.e., MnO_2, Swern, Dess-Martin for RCH_2OH to RCHO and $NaClO_2$ for RCHO to RCOOH most often better than single step reagent conversions.)
- ➢ Scavengers (捕捉剂）are often added to trap （捕捉）or eliminate positive Cl species leading to byproducts. Typical scavengers are resorcinol (间苯二酚) , 2-methyl-2-butene, DMSO, H_2NSO_3H.

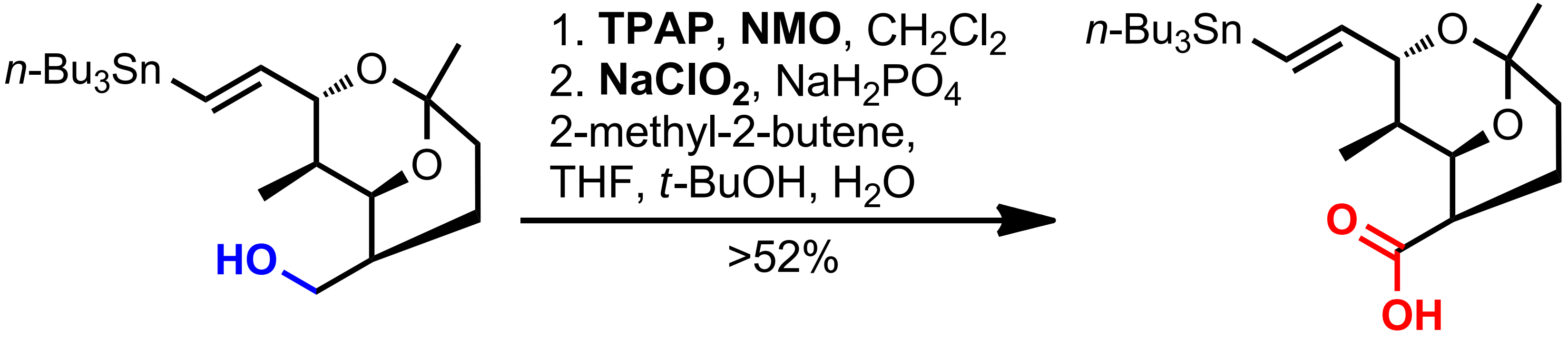


Oxidation of Aldehydes



1. **$(CF_3CO_2)_2IPh$**, CH_3CN, H_2O, 0 °C

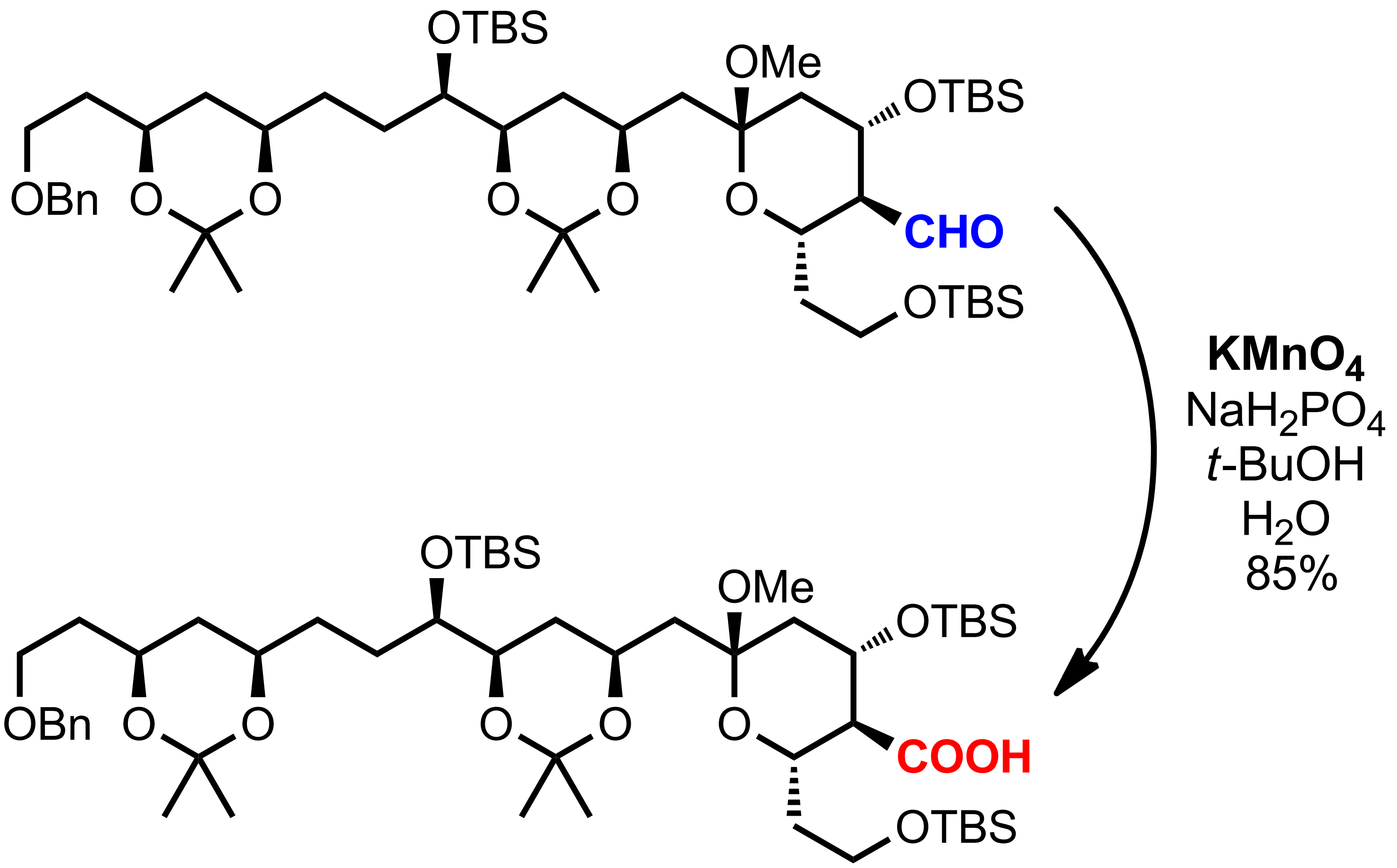
2. **$NaClO_2$**, NaH_2PO_4 2-methyl-2-butene, *t*-BuOH, H_2O; 82%



1. **TPAP, NMO**, CH_2Cl_2
2. **$NaClO_2$**, NaH_2PO_4 2-methyl-2-butene, THF, *t*-BuOH, H_2O

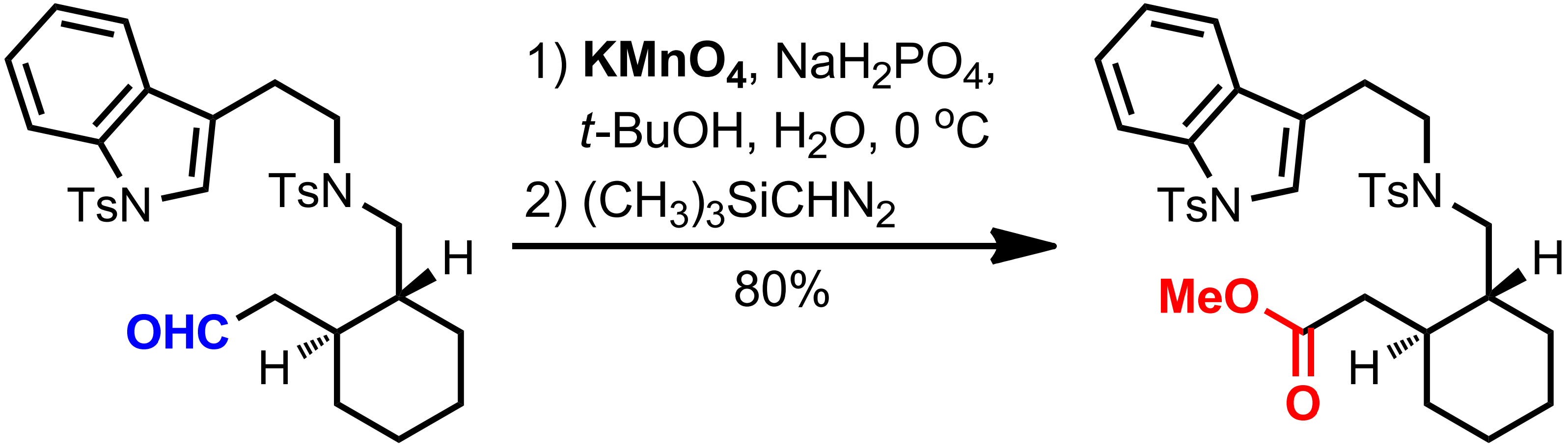
>52%

Potassium Permanganate: $KMnO_4$



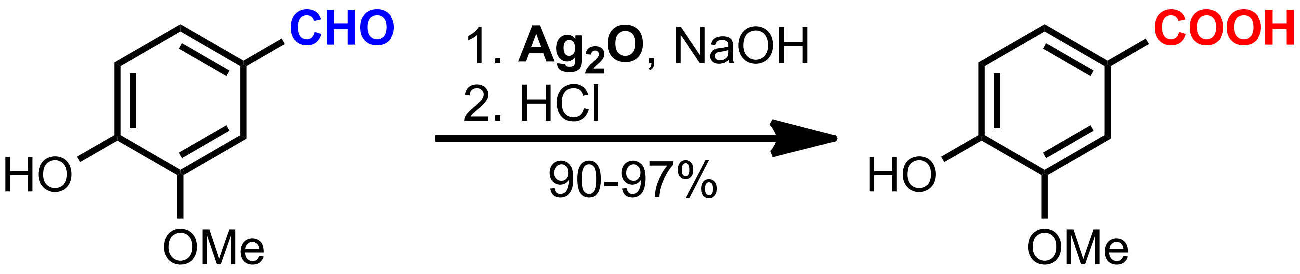
$KMnO_4$
NaH_2PO_4
t-BuOH
H_2O
85%

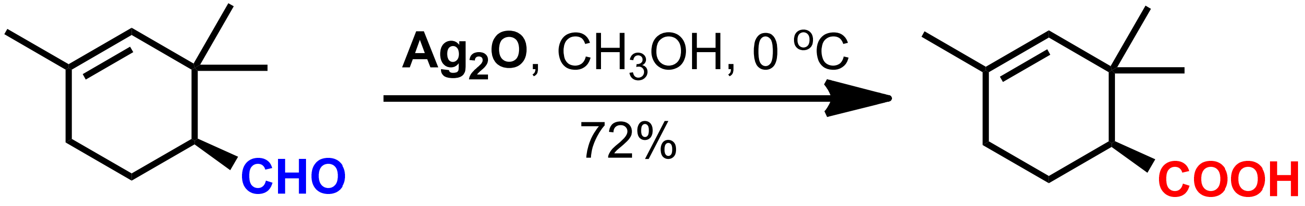
Potassium Permanganate: $KMnO_4$



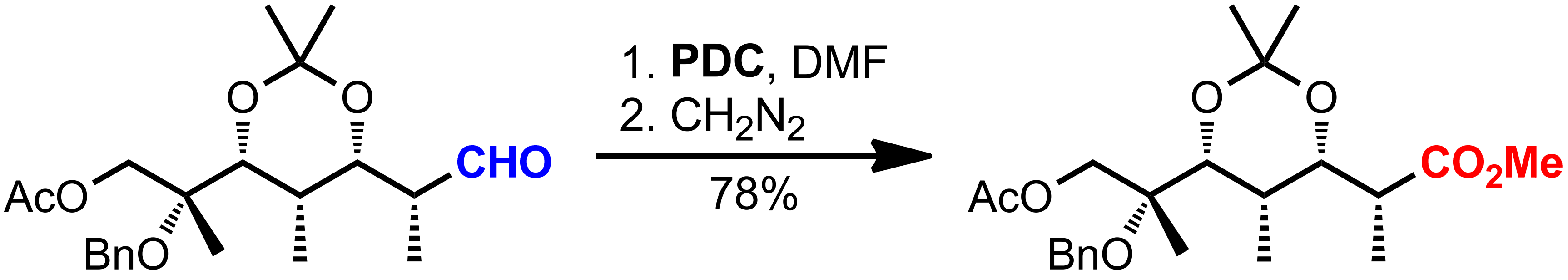
- ☐ A number of other oxidants (including Jones reagent, NaOCl, and RuO_2) failed.

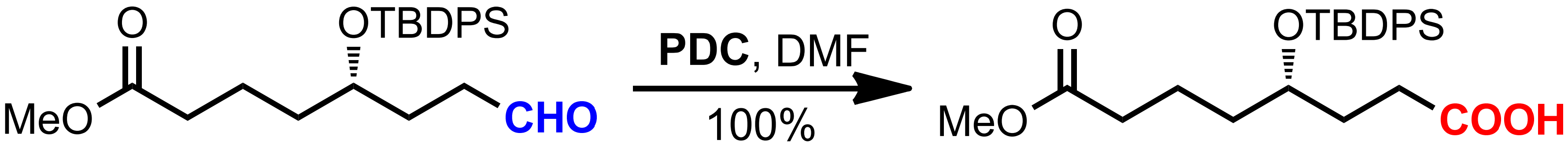
Silver Oxide: Ag_2O



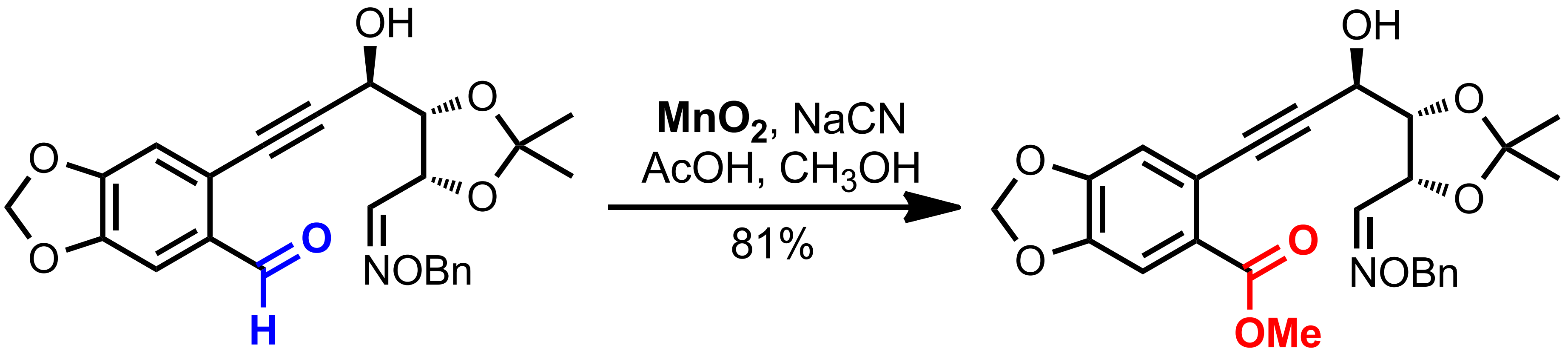


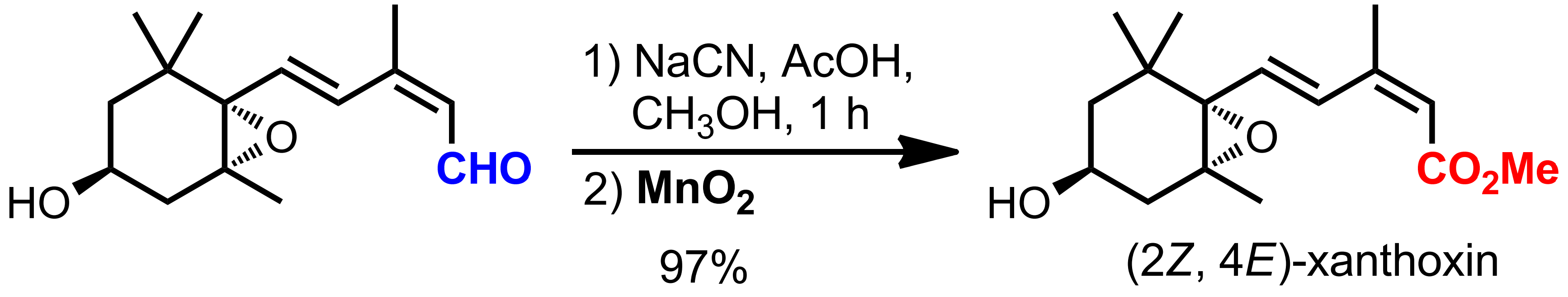
Pyridinium Dichromate (PDC)





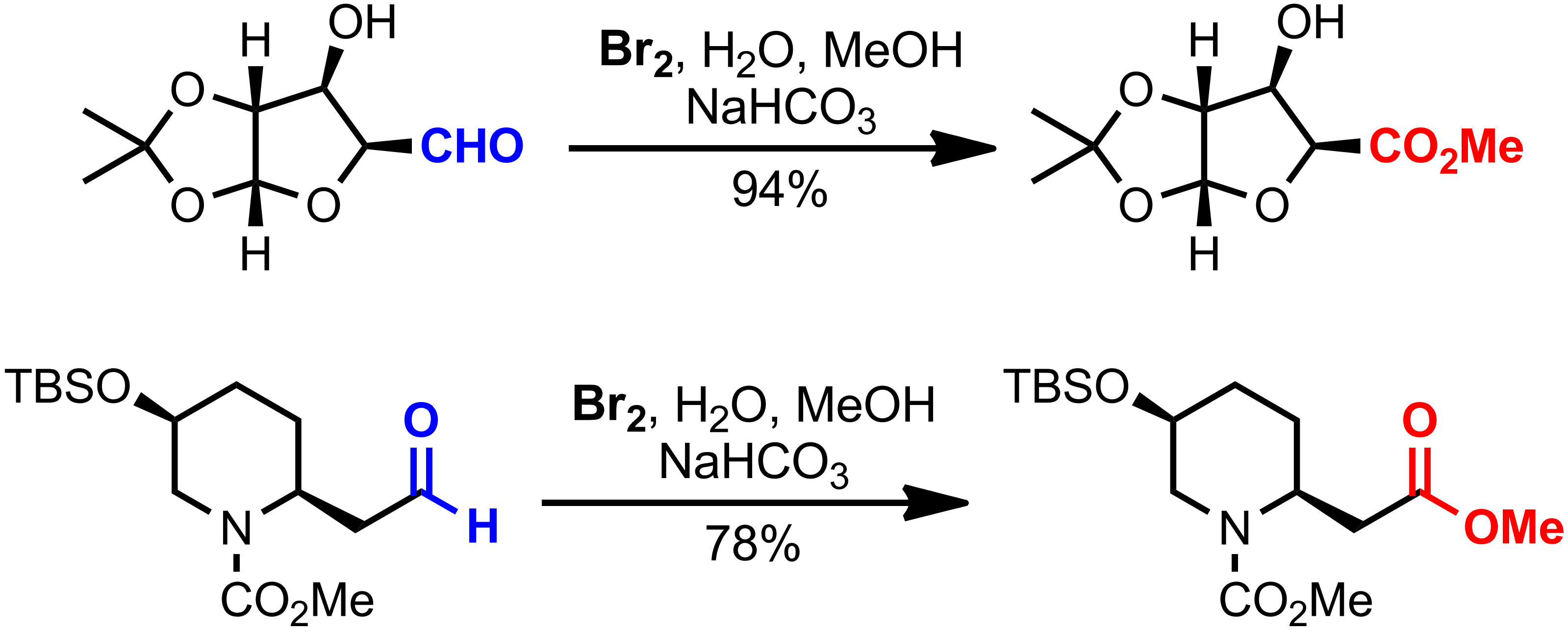
Corey-Gilman-Ganem Oxidation





Bromine

- Direct conversion of aldehydes to ester derivatives.
- Secondary alcohols are not oxidized to ketones.
- Oxidation of a hemiacetal intermediate is proposed.
- Olefins, benzylidine acetals and thioketals did not work.



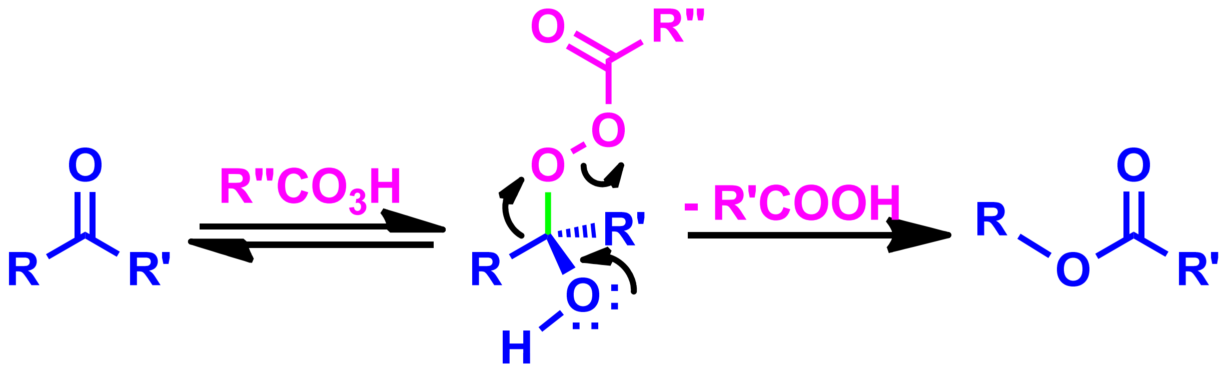
Oxidations of Ketones

Bayer-Villiger Oxidation

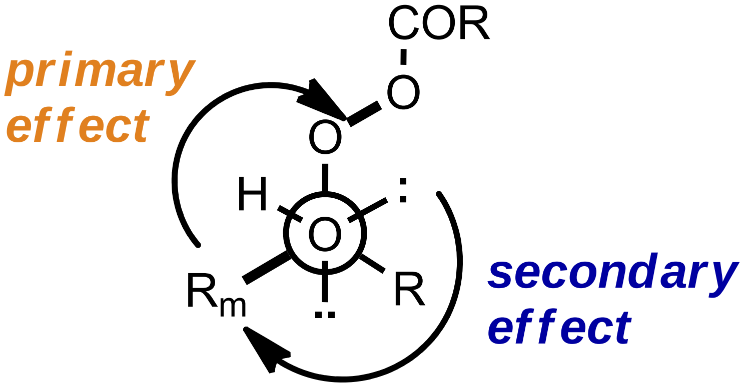
Mechanism:

Peracid nucleophilic addition reaction

A. Baeyer received the 1905 Nobel Prize in Chemistry for his work on dyes (indigo). He also discovered barbituric acid and named it after his girlfriend Barbara.



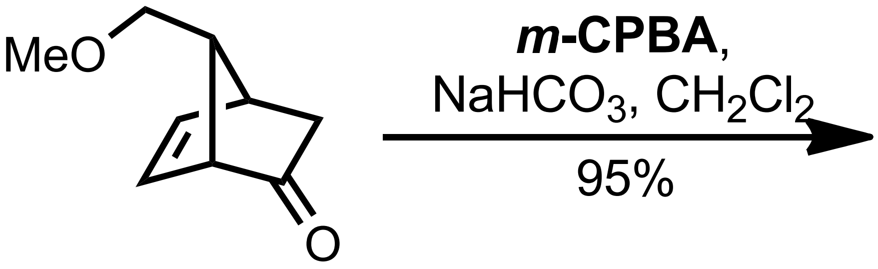
- ☐ Alkyl group that migrates (迁移）does so with rention of configuration
- ☐ The more electron-rich (most-substituted) alkyl group migrates in preference (in general): *t*-alkyl > *s*-alkyl > benzyl > phenyl > *n*-alkyl > methyl

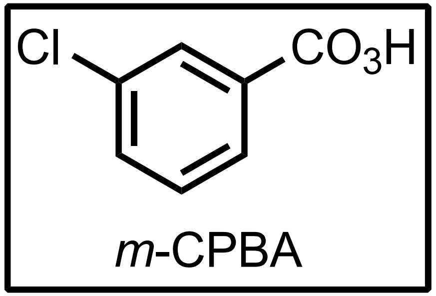


Proposed TS‡

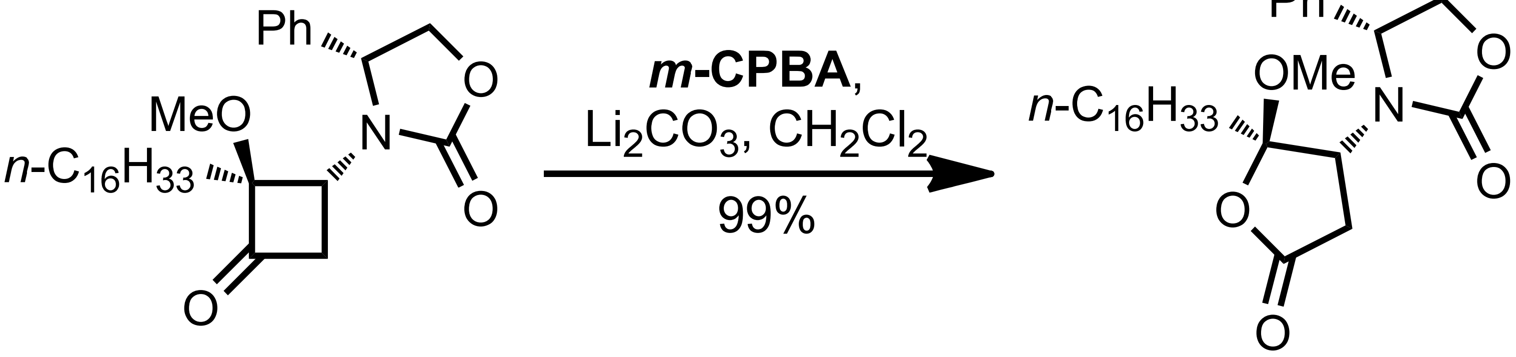
- ☐ ***Primary effect:*** **antiperiplanar arrangement** of C-R_m bond and the breaking O-O bond
- ☐ ***Secondary effect:*** Hydroxyl lone pair or O-H bond **antiperiplanar** to the migrating C-R_m bond.

Oxidations of Ketones

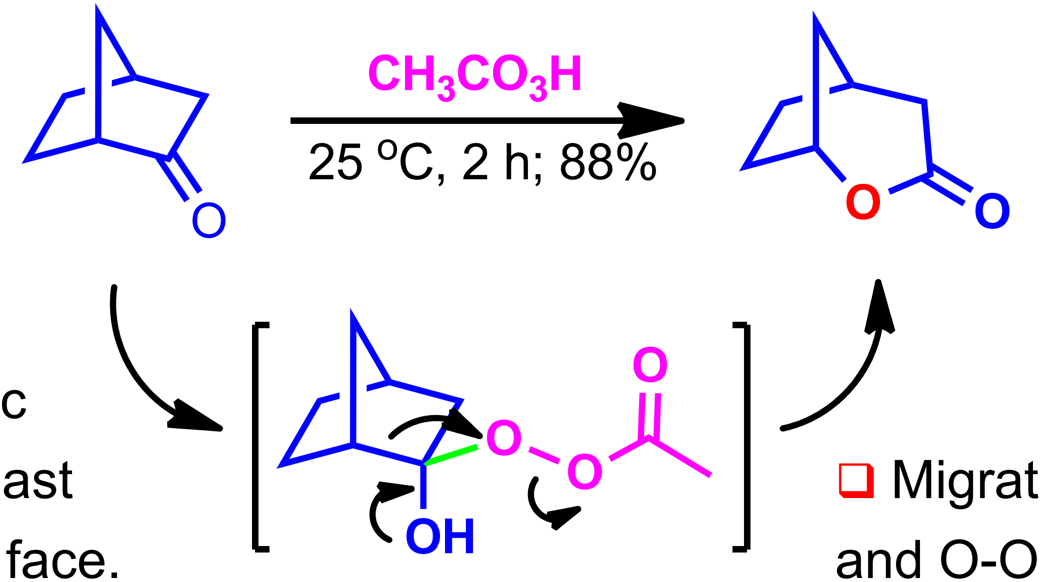




m-CPBA



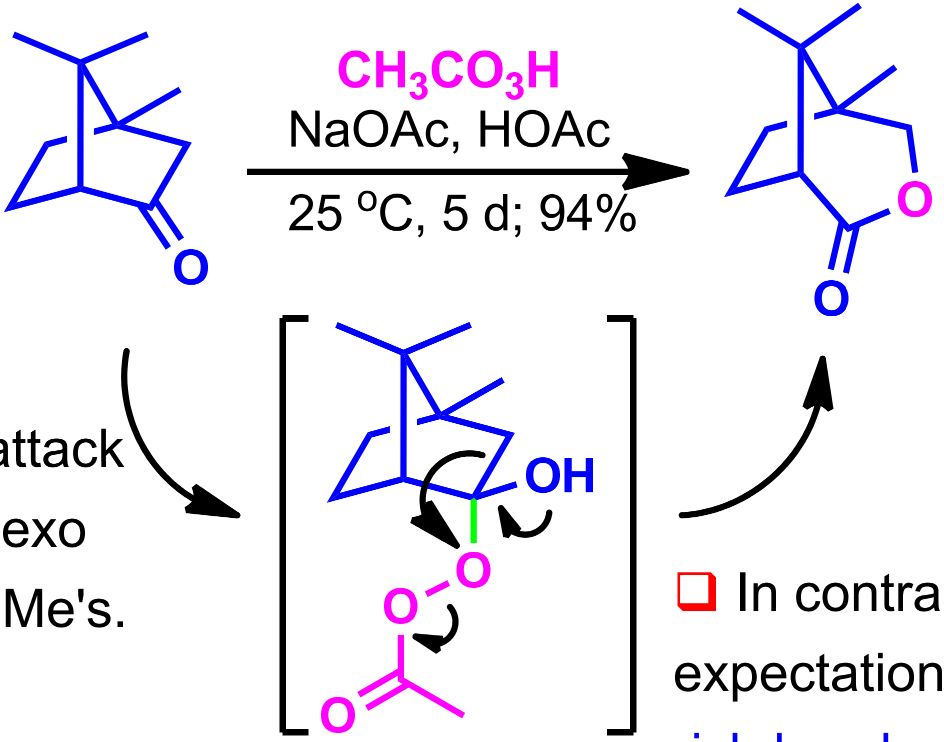
Oxidations of Ketones



- ❑ Nucleophilic attack from least hindered exo face.

- ❑ Migrating C-C bond and O-O bond must be **antiperiplanar** (stereoelectronic requirement).

Oxidations of Ketones



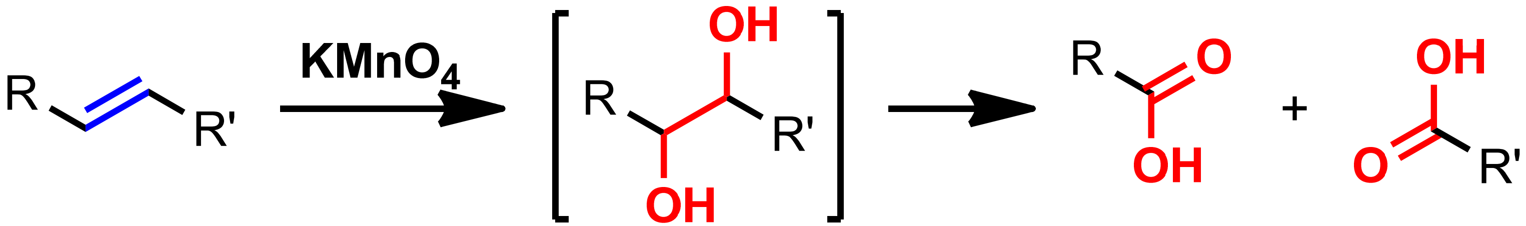
- ❑ Nucleophilic attack from endo face, exo face blocked by Me's.

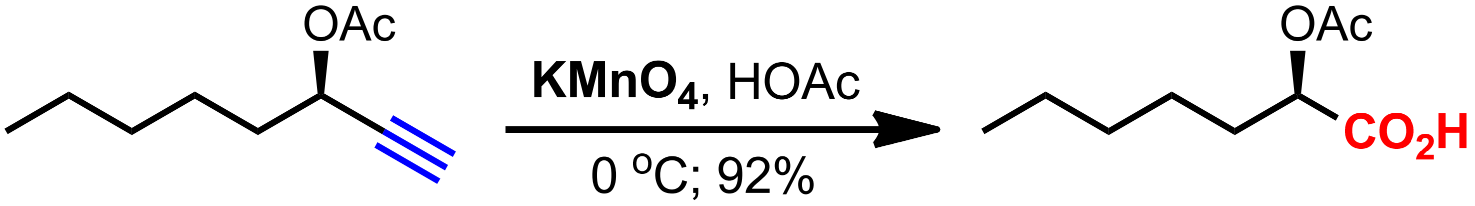
- ❑ In contrast to simple expectations, the less electron-rich bond migrates due to stereoelectronic considerations.

- ❑ Reaction much slower than norbornone.

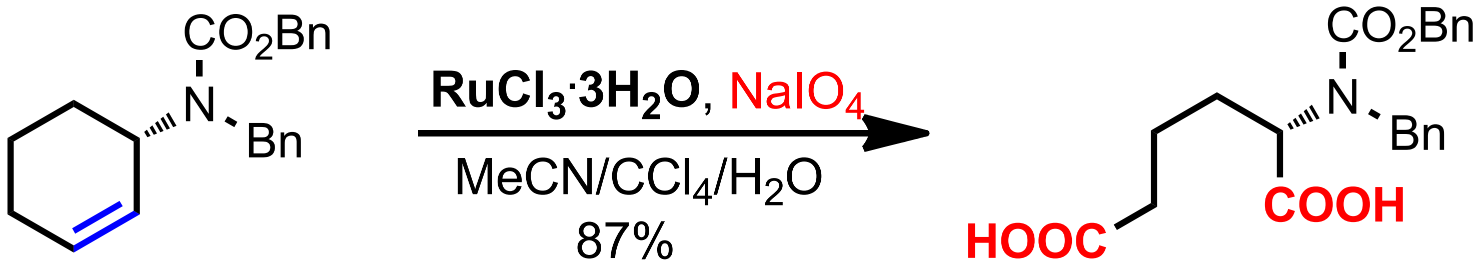
Oxidative Cleavage of C-C Multiple Bonds

- ❑ Potassium Permanganate ($KMnO_4$)





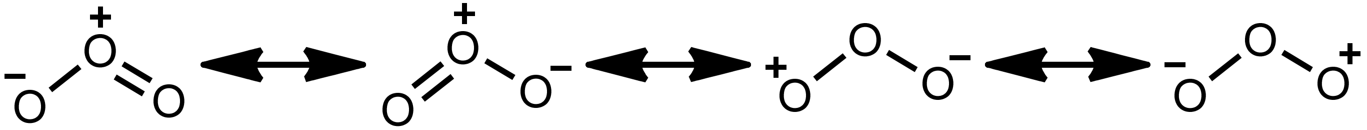
Ruthenium Reagents



Ozonolysis（臭氧化）

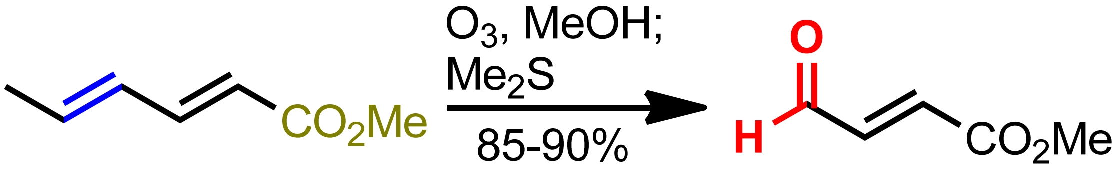
P. Crutzen, M. Molina, and F. S. Rowland shared the 1995 Nobel Prize in Chemistry for their work in atmospheric chemistry, particularly concerning the formation and decomposition of the protective ozone layer.

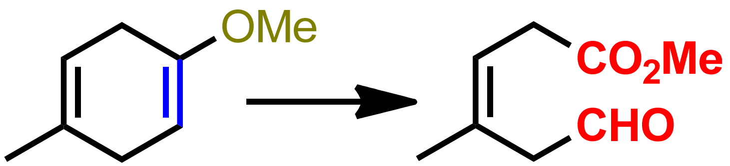
❑ **Ozone**: A resonance species with four contributors



❑ Electrophilic reagent, rate: electron-rich > neutral > electron-deficient olefine

❑ Chemoselectivity:





❑ O_3 exhibits very light color, ozonolysis complete when color persists

❑ Controlled ozonolysis (very reactive agent): KI-starch: characteristic blue color, O_3 sensitive dyes with varying reactivities and detect color disapperance

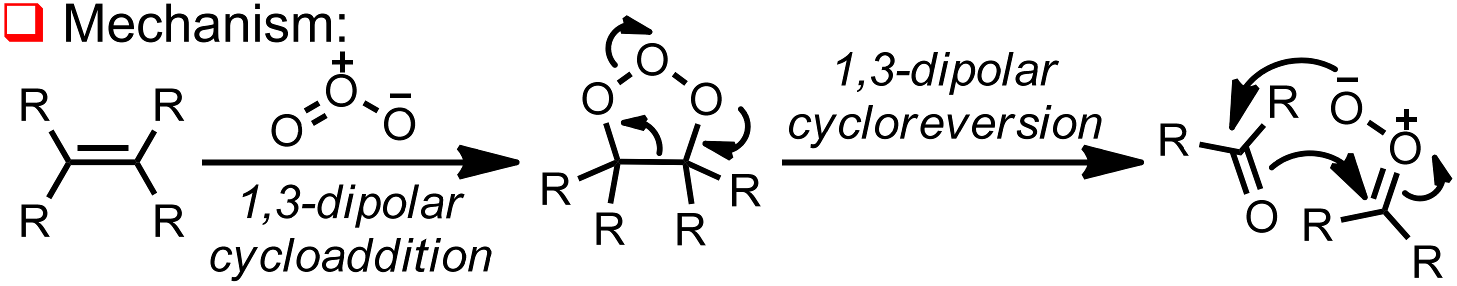
❑ Oxidative workup: H_2O_2, $KMnO_4$, Cr(VI), RuO_4 → ketones, carboxylic acids

❑ Reductive workup: $NaBH_4$, $LiBH_4$ → alcohols

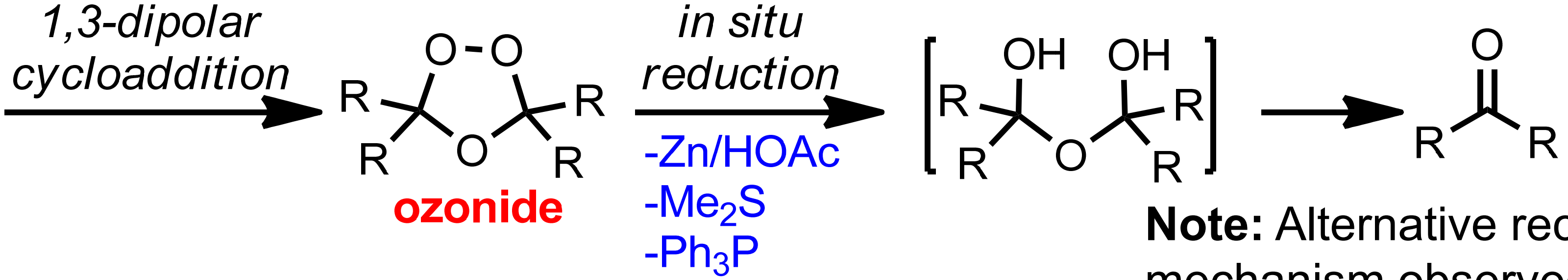
Me_2S, Ph_3P, Zn/HOAc, $NH_2C(=S)NH_2$, H_2, Pd/$CaCO_3$ → aldehydes, ketones

Ozonolysis（臭氧化）

- Mechanism:

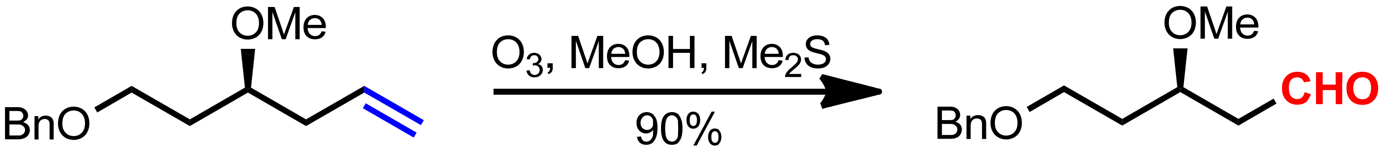


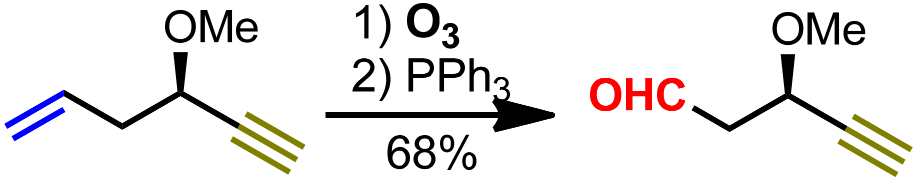
carbonyl oxide
(Criegee zwitterion)
(两性离子）



Note: Ozonide（臭氧化物） **explosive** when isolated or concentrated

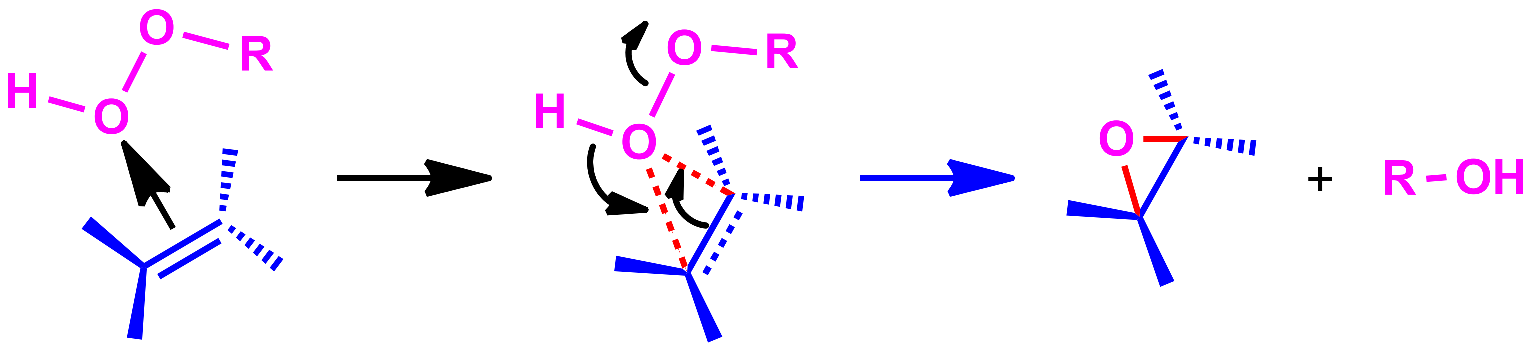
Note: Alternative recombination mechanism observed with ketone vs aldehyde ozonides.





Epoxidation Reactions:
Peroxide Induced Epoxidations

❑ Mechanism:

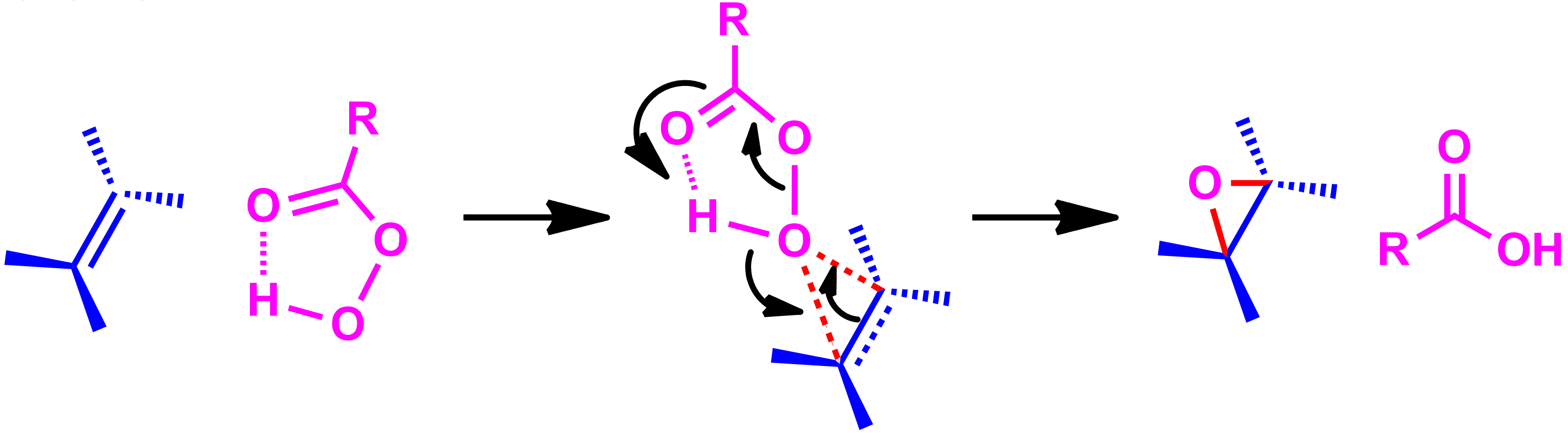


➢ The oxidizing power of the epoxide is inversely related to the pKa of the conjugate acid generated by loss of the leaving group (ROH):

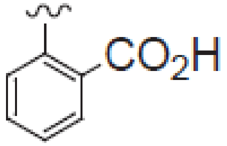
ROOH < H_2O_2 < RCOOOH.

Peracid Epoxidation

- ❑ Mechanism:

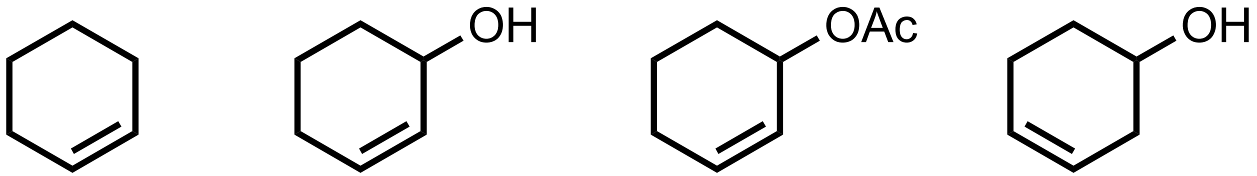


- ❑ Peracid Reactivity:

Rate increases: R =	CH_3	<	C_6H_5	<	*m*-ClC_6H_4	<	H	<	*p*-$NO_2C_6H_4$	<		<	CF_3
pK_a of acid (RCO_2H):	4.8		4.2		3.9		3.8		3.4		2.9		0

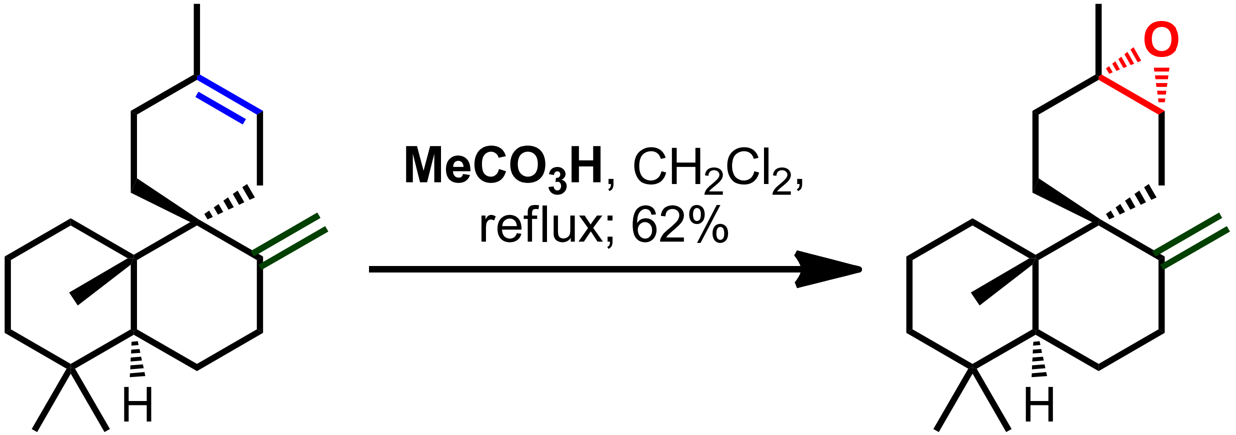
➢ The lower the pK_a, the greater the reactivity (i.e., the better the leaving group).

Reaction Rates

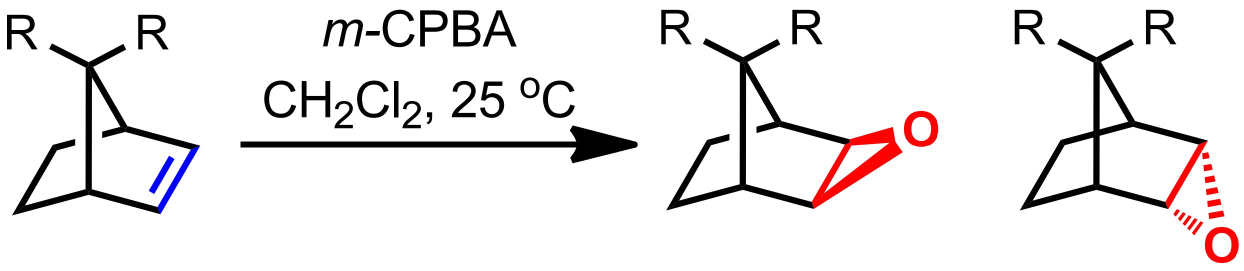


k_{rel} 1.00 0.55 0.046 0.42

- ❑ Reaction rates are governed by **olefin nucleophilicity**.



Stereochemistry

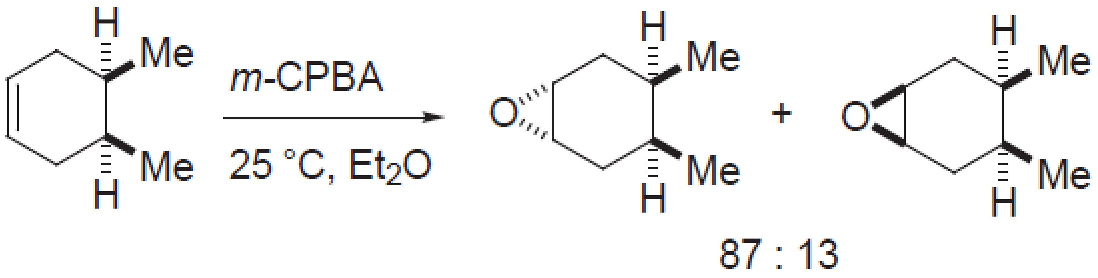


R = **H**	20 min	99%	1%
R = **Me**	24h	<10%	90%

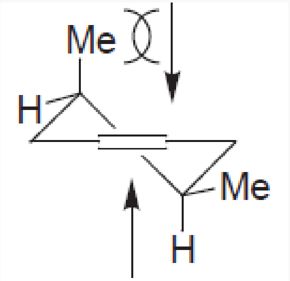
- ☐ Stereochemistry of olefin is maintained: diastereospecific.
- ☐ Reaction rate is insensitive to solvent polarity implying concerted mechanism without intermediacy of ionic intermediates.
- ☐ Less hindered face of olefin is epoxidized.

Diastereoselectivity

❑ Endocyclic Olefins:

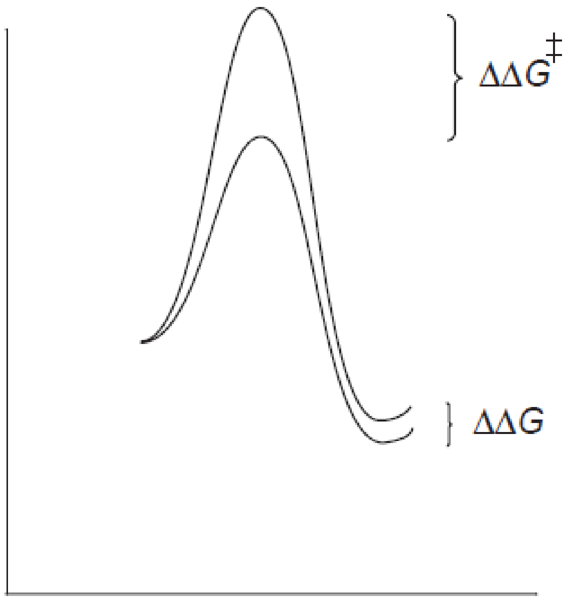


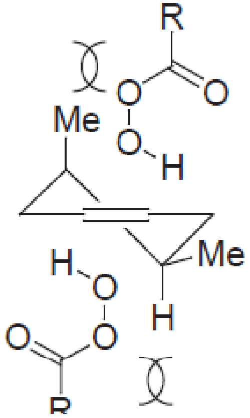
❑ Destabilizing steric interaction between reagent and axial Me

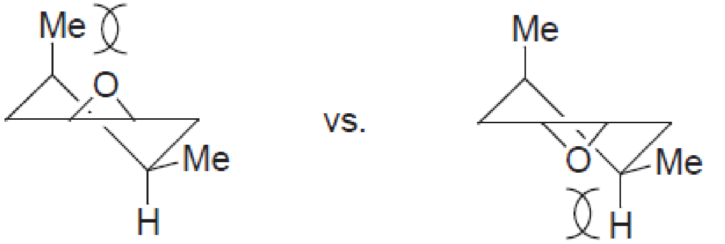


❑ Attack principally from this face

❑ Small difference for products: but larger difference for reagent approach in transition state.

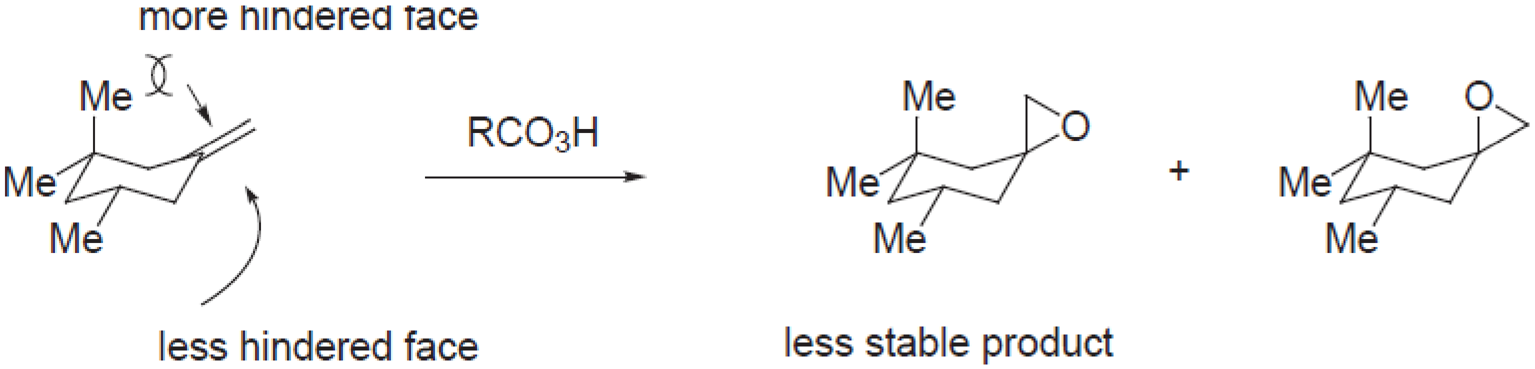






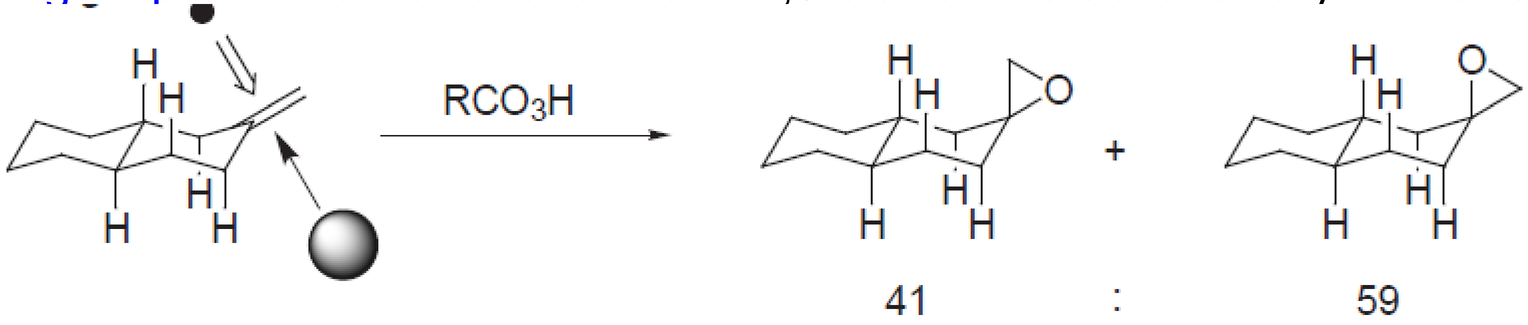
Diastereoselectivity

- Exocyclic Olefins:



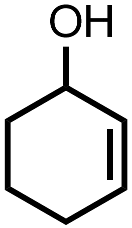
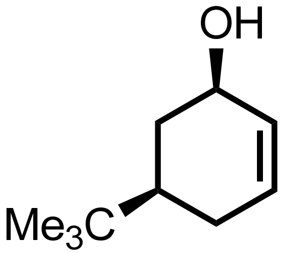
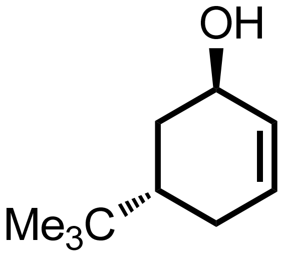
– Solvent dependent	CCl_4	75%	25%
	C_6H_6	80%	20%
	CH_2Cl_2 or $CHCl_3$	83%	17%

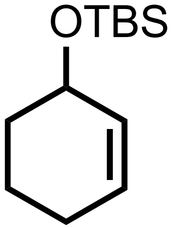
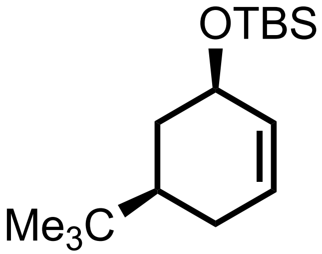
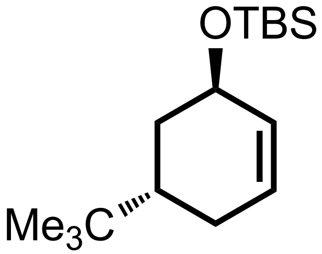
- The effective size of the reagent increases with increasing solvent polarity, i.e., the solvation shell (溶剂化层) of the reagent increase in size.
- Small reagent preference: axial attack and 1,3-diaxial interactions vary with size of the reagent.



- Large reagent preference: equatorial attack and 1,2-interactions (torsional strain) are relatively invariant with the size of the reagent. (扭转张力)

Directed Epoxidations

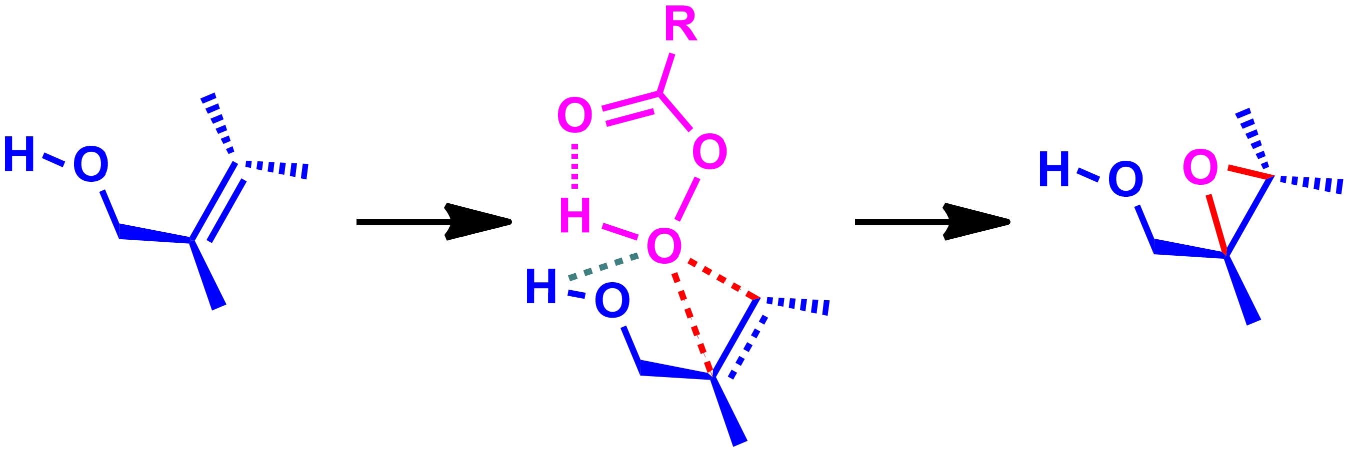
Substrate	*m*CPBA *Syn*:*Anti*	CF_3CO_3H *Syn*:*Anti*
	24:1	50:1
	24:1	100:1
	5:1	100:1

Substrate	*m*CPBA *Syn*:*Anti*	CF_3CO_3H *Syn*:*Anti*
	1:7	5:1
	1:8	12:1
	1:4	1:6

Ganem, *Tetrahedron Lett.* **1985**, *26*, 4895.

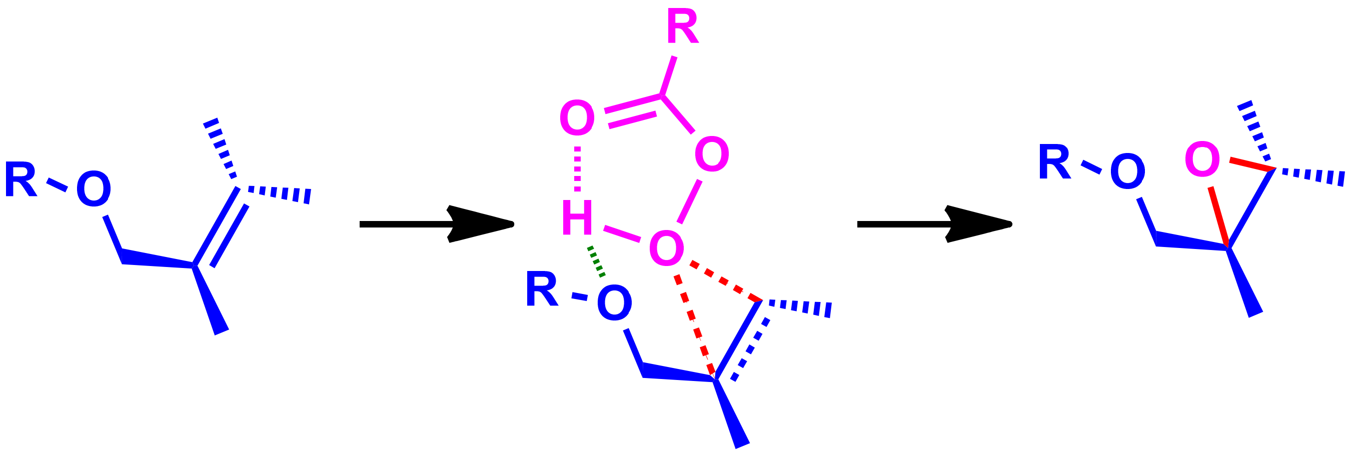
Substrate as H-bond donor (Henbest)

❑ Require allylic or homoallylic（高烯丙基）alcohol



Peracid as H-bond donor (Ganem)

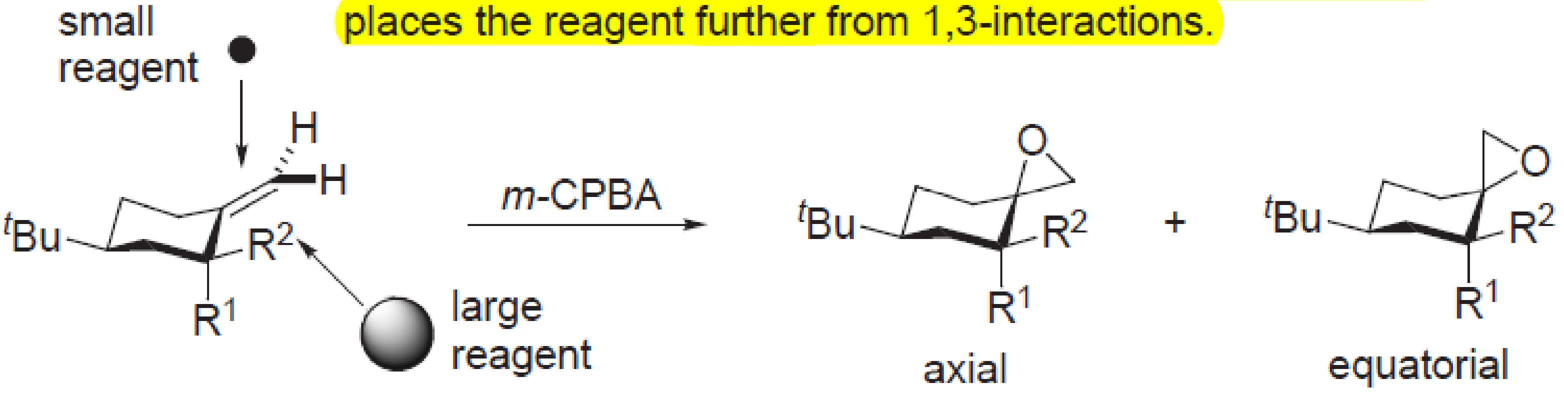
- ❑ Require more acidic peracid, both allylic alcohols and ethers OK



Diastereoselectivity

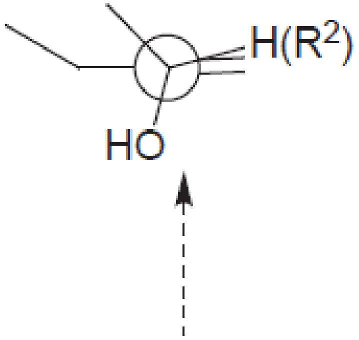
❑ Allylic Alcohols (exocyclic):

Early transition state and the asynchronous bond formation places the reagent further from 1,3-interactions.

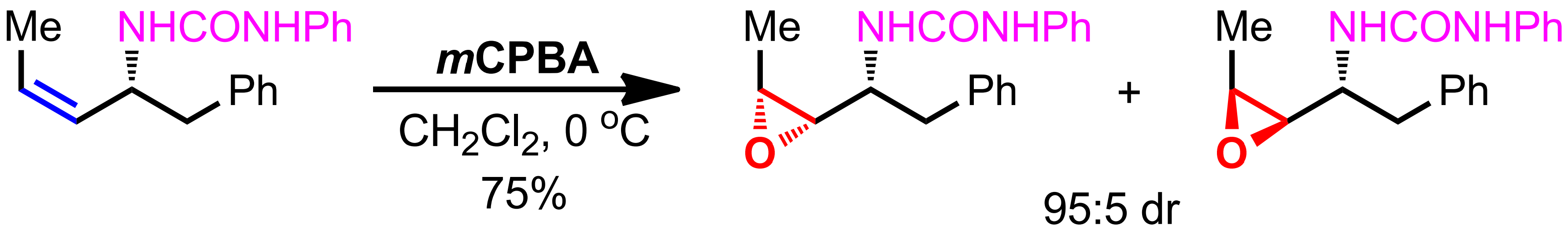


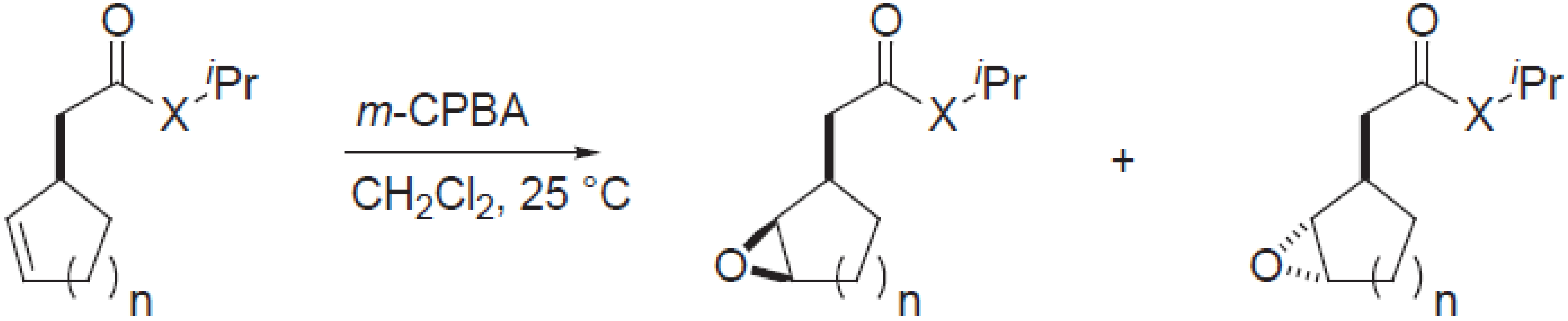
R^1	R^2		
H	H	69 : 31	
H	OH	60 : 40	Equatorial substitution
H	OCH_3	60 : 40	
$\boxed{CH_3}$	OCH_3	88 : 12	
H	OAc	75 : 25	
OH	H	11 : 89	axial OH directs epoxidation to the syn-face of the exocyclic double bond
OH	CH_3	13 : 87	
OCH_3	H	83 : 17	
OCH_3	CH_3	83 : 17	

Axial substitution blocks equatorial reagent delivery



Diastereoselectivity: Directed Epoxidation by NH



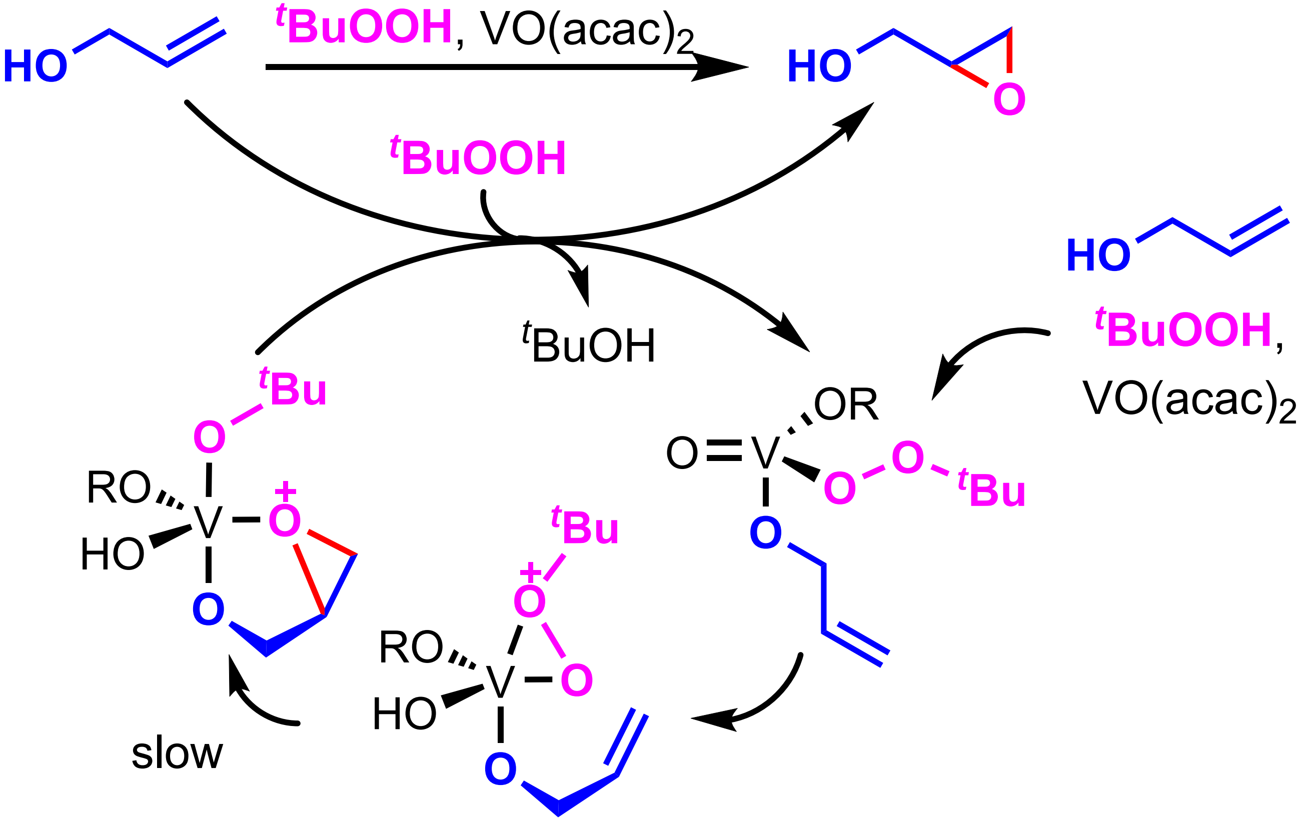


n = 1, X = NH	80%	20	1
X = O		3	1
n = 2, X = NH		20	1
X = O		3	1

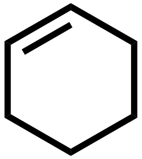
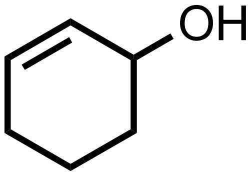
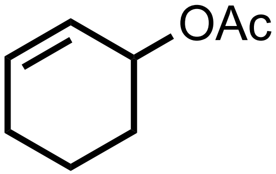
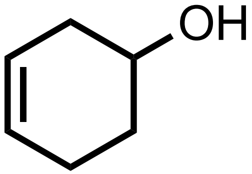
- ❑ Presence of H-bonding, directing substituent enhances rates and yield.

The Sharpless Epoxidation

- ❑ Reviews: *Org. React.* **1996**, *48*, 1-299.
- ❑ Catalysts: $VO(acac)_2$, $Mo(CO)_6$, $Ti(O\textit{i}\text{-}Pr)_4$;
- ❑ Oxidants: *t*-BuOOH, $PhC(CH_3)_2OOH$;
- ❑ Regioselective epoxidation of allylic and homo-allylic alcohols;
- ❑ Will not epoxidize isolated double bonds;
- ❑ Epoxidation occurs stereoselectively with respect to the alcohol.

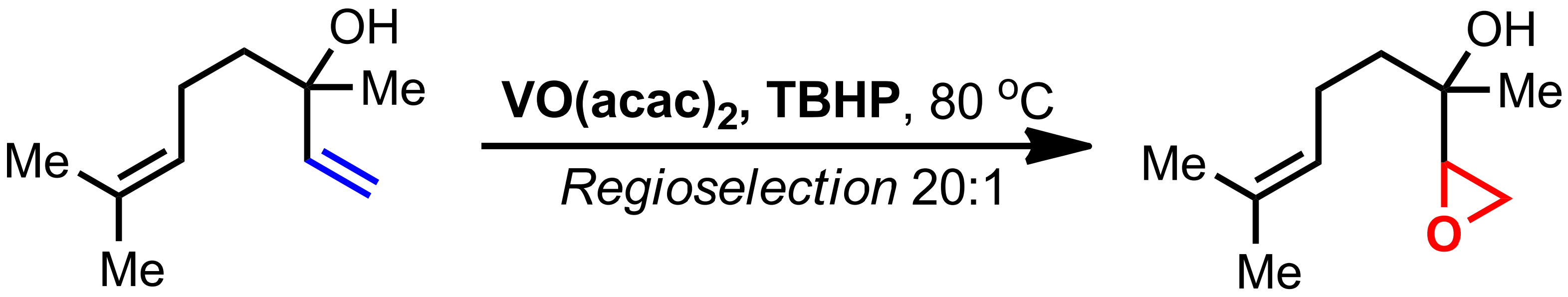


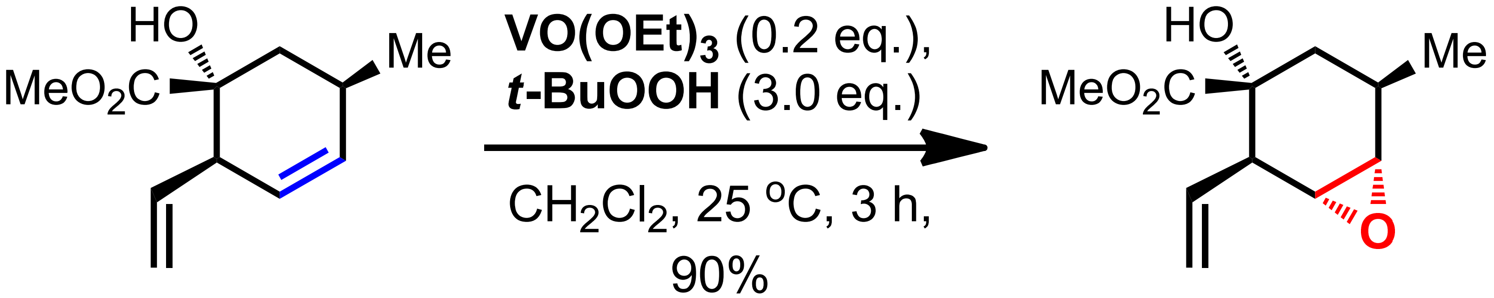
Relative Rate and Diastereoselectivity

Substrate	*m*CPBA	TBHP/Mo(CO)$_6$	TBHP/VO(acac)$_2$
	1.00	1.00	1.00
	0.55 (92:8)	4.5 (98:2)	>200 (98:2)
	0.046 (37:63)	0.07 (40:60)	--
	0.42 (60:40)	11.0 (98:2)	10.0 (98:2)

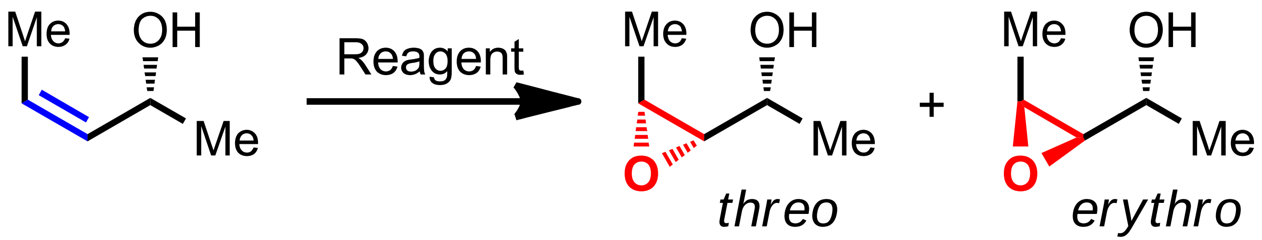
1) The relative rate data apply only to a given column.
2) Values in parenthesis refer to the ratio of *syn*:*anti* epoxide.

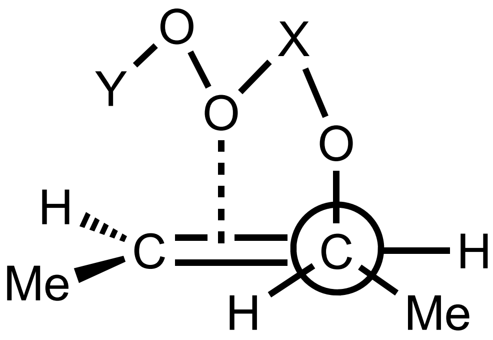
Regioselectivity



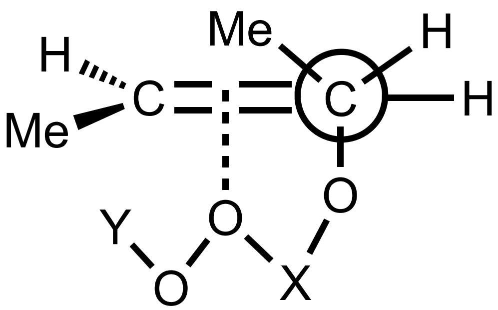


Diastereoselectivity





Major TS



Minor TS

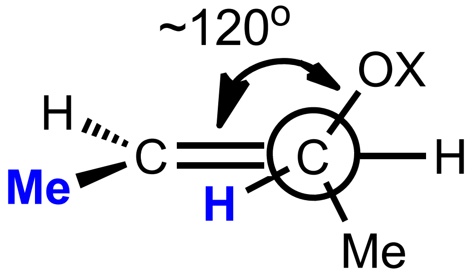
Reagent	*threo:erythro*
MCPBA	95:5
TBHP/VO(acac)$_2$	71:29
TBHP/Mo(CO)$_6$	84:16

X = H, V, Mo ...

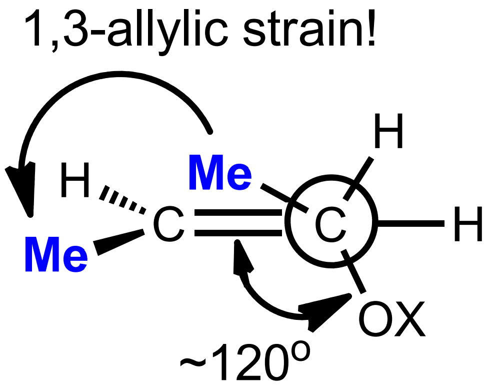
Y = RCO, *t*-Bu

Diastereoselectivity

- RCO$_3$H Transition States and Bite Angles:

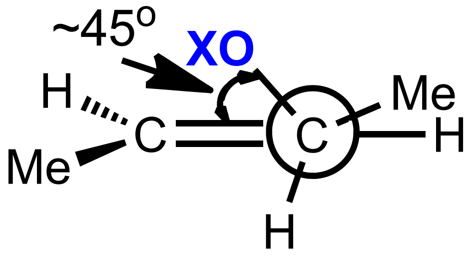


Major TS

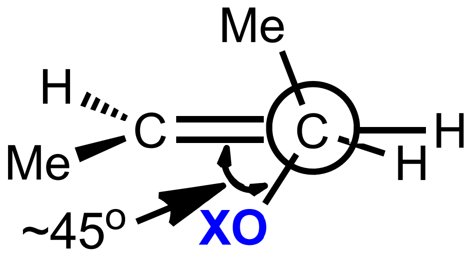


Minor TS

- V Transition States and Bite Angles:



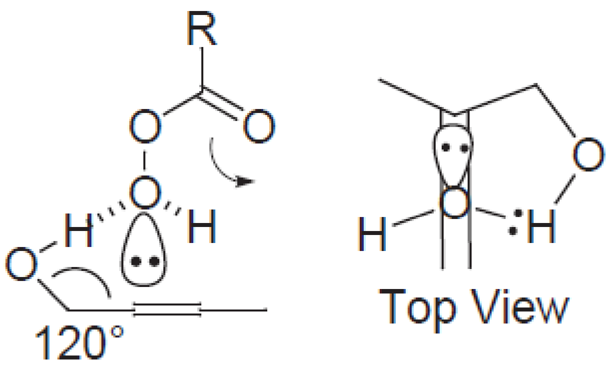
Major TS



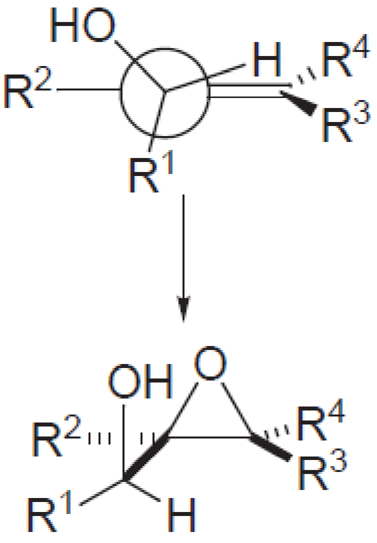
Minor TS

Refined Model for Peracid Mediated Epoxidation

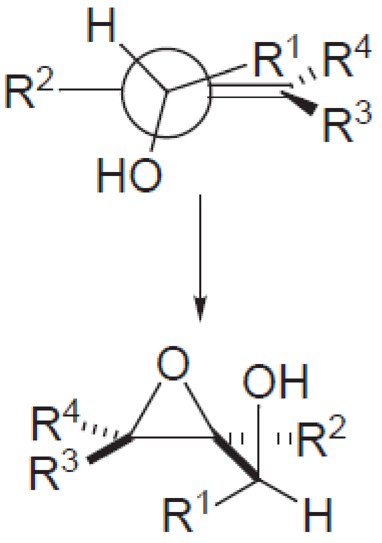
- Trans antiperiplanar arrangement of O-O bond with alkene C=C.
- H-bonding to distal oxygen of peroxide through the lone pair out of the plane of reaction.
- Lone pair in plane of reaction provides π*-lone pair (n-π*)stabilization.
- Secondary isotope effect suggests that the formation of the C-O bonds is asynchronous.



❑ Eclipsed Conformations in *m*-CPBA Epoxidation:

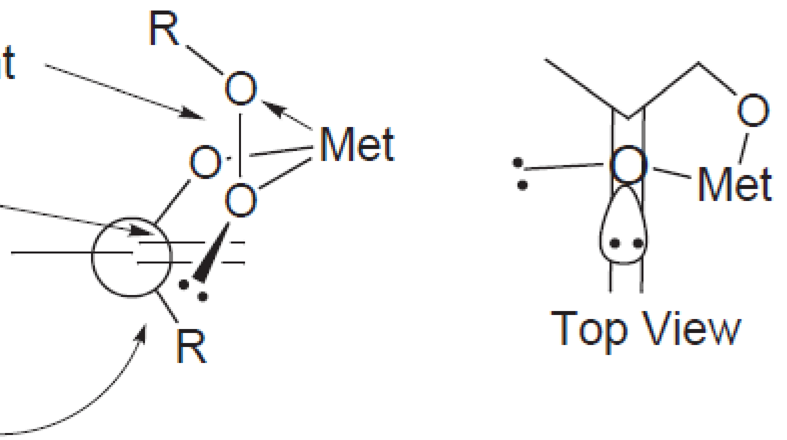


threo product



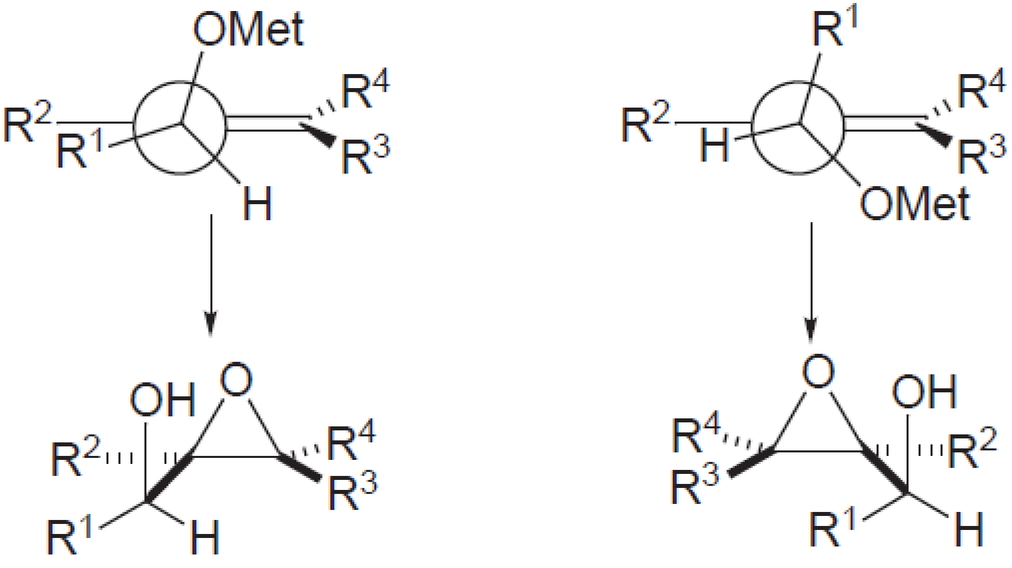
erythro product

Refined Model for Transition-metal Catalyzed Epoxidation



1. *Trans* antiperiplanar arrangement
2. 50° dihedral angle
3. In-plane lone pair
4. Lone pair bisects C=C bond

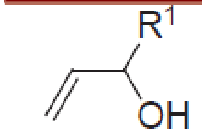
❑ Bisected Conformations in Metal-Catalyzed Epoxidation:



Threo Product

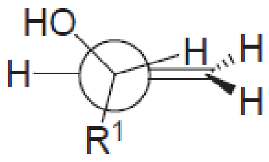
Erythro Product

Diastereoselectivity



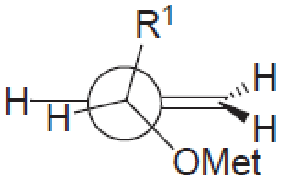
		threo	erythro
R^1 = Me	*m*-CPBA	60	40
	VO(acac)$_2$, ^{t}BuOOH	20	80
= Et	*m*-CPBA	61	39
	VO(acac)$_2$, ^{t}BuOOH	20	80
= ^{i}Pr	*m*-CPBA	58	42
	VO(acac)$_2$, ^{t}BuOOH	15	85

H vs. alkyl eclipsing interaction with double bond has little to no effect on selectivity. H eclipsing interaction slightly more stable.

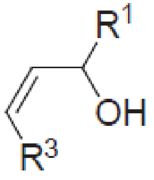


threo

H,H eclipsing in *erythro* T.S. favored over H,alkyl eclipsing in *threo* T.S.

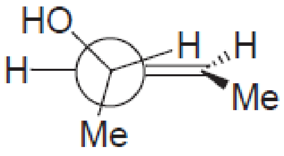


erythro

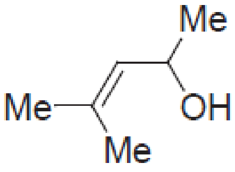


		threo	erythro
R^1,R^3 = Me	*m*-CPBA	95	5
	VO(acac)$_2$, ^{t}BuOOH	71	29

Large 1,3-allylic strain avoided.

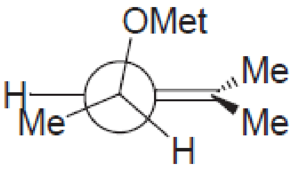


threo



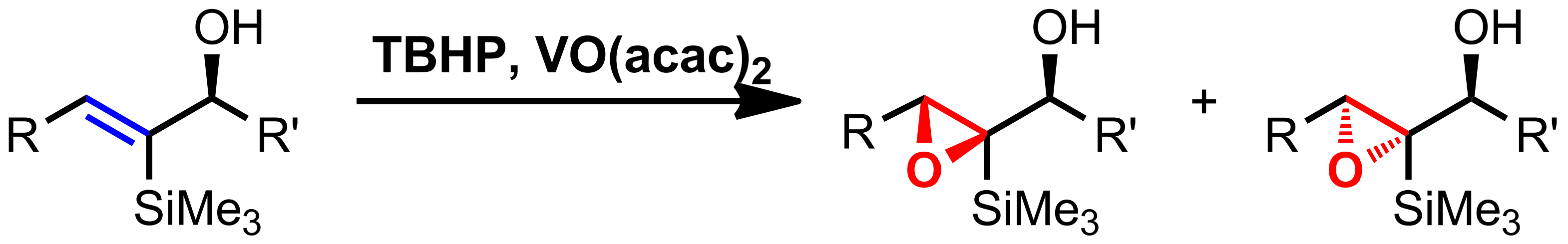
	threo	erythro
m-CPBA	95	5
VO(acac)$_2$, ^{t}BuOOH	86	14

Large 1,3-allylic strain avoided.



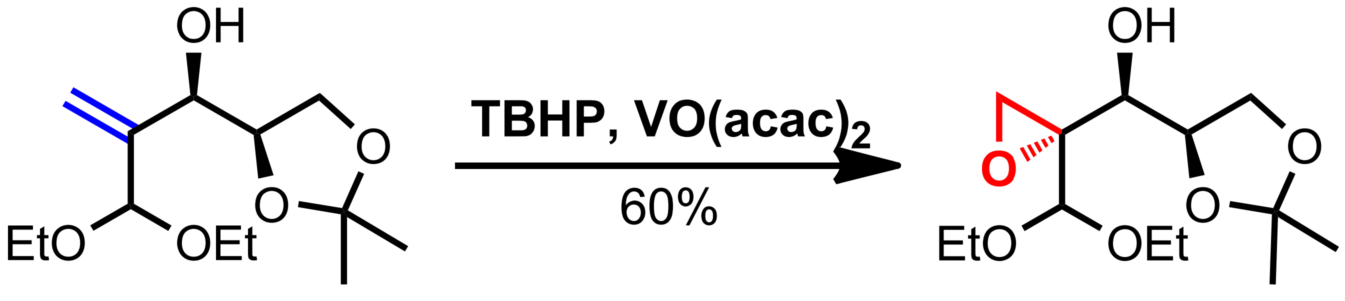
threo

Diastereoselectivity

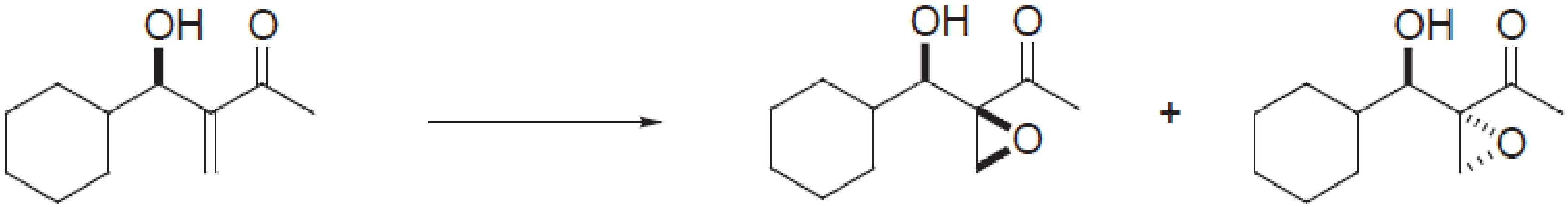


R	R'	Yield%	Ratio
H	Bu	84	1:99
C_5H_{11}	Me	70	1:99

Diastereoselectivity

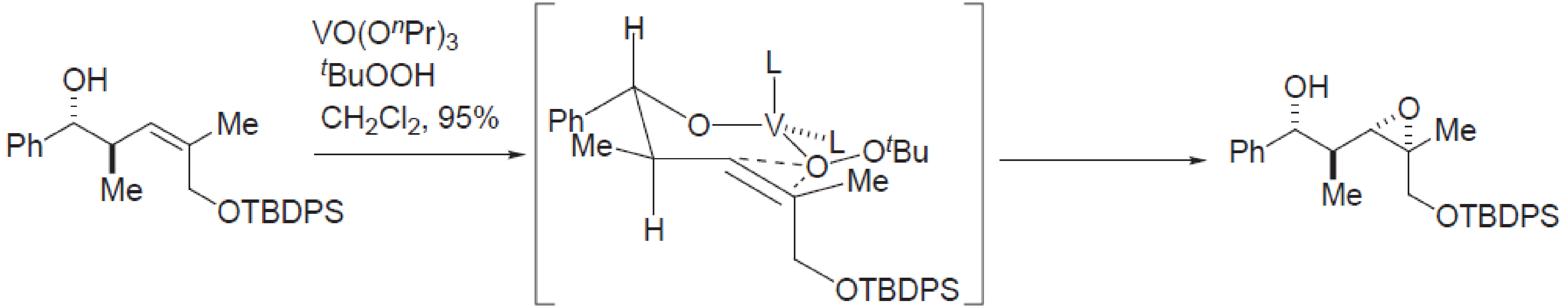


only isomer



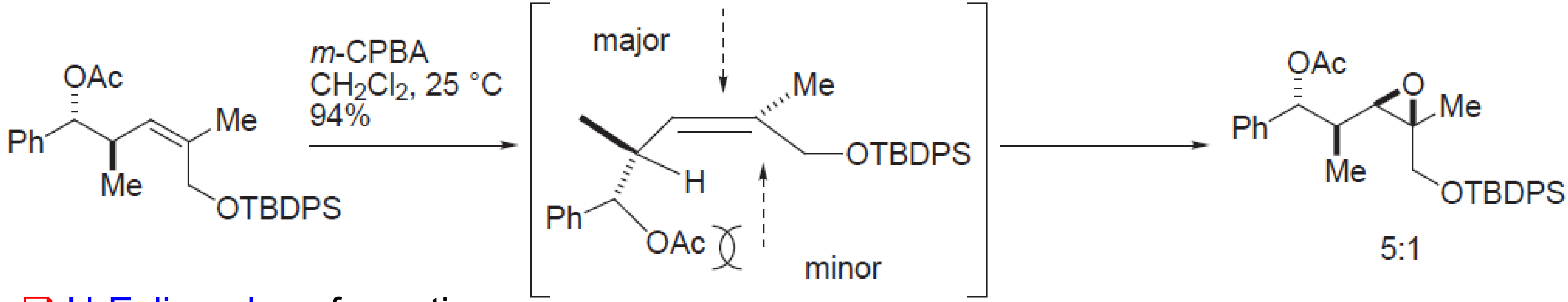
H_2O_2 / NaOH / MeOH / 0 °C	40	:	60
Ti(^{i}PrO)$_4$ / ^{t}BuOOH / CH_2Cl_2 / –15 °C	>99	:	1

Homoallylic Alcohols



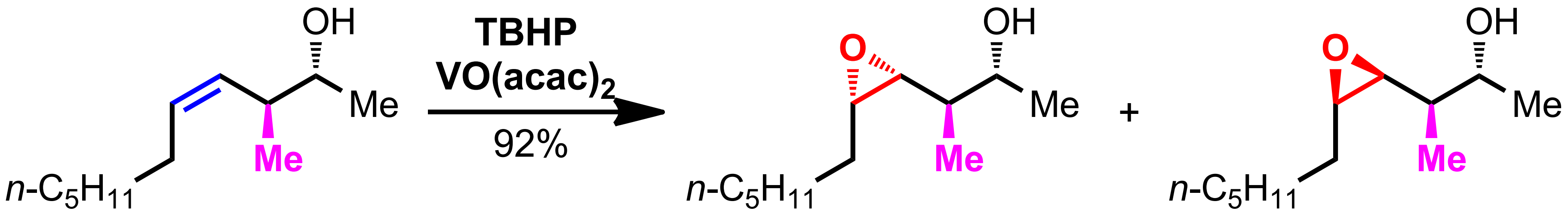
- Alternative chair has two axial substitutes.
- Intramolecular oxygen delivery occurs through most stable chair-like transition state.

vs.

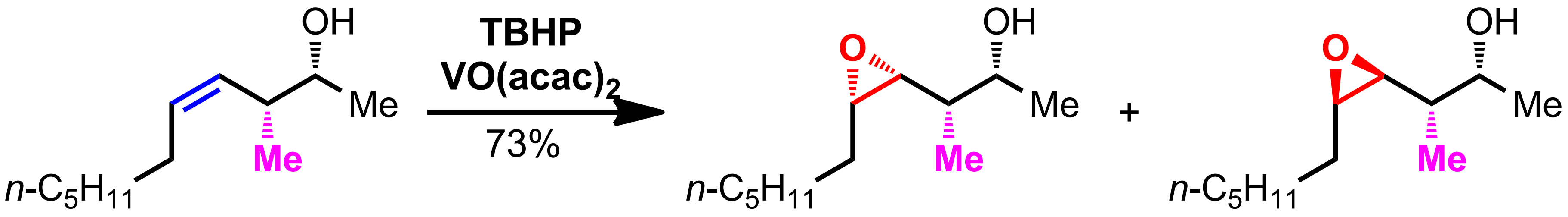


- H-Eclipsed conformation
- Epoxidation from least hindered face
- Not a directed epoxidation!
- Diastereoselectivety still good and through H-eclipsed conformation.

Homoallylic Alcohols

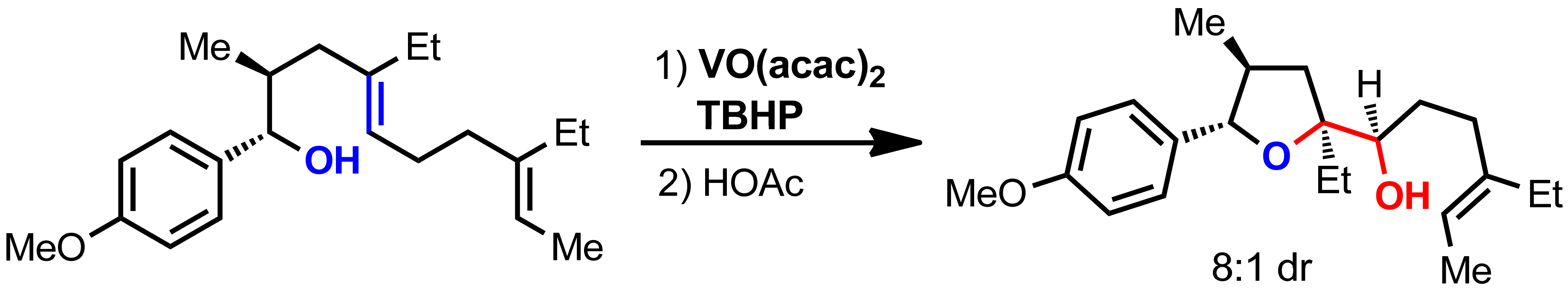


104:1 dr



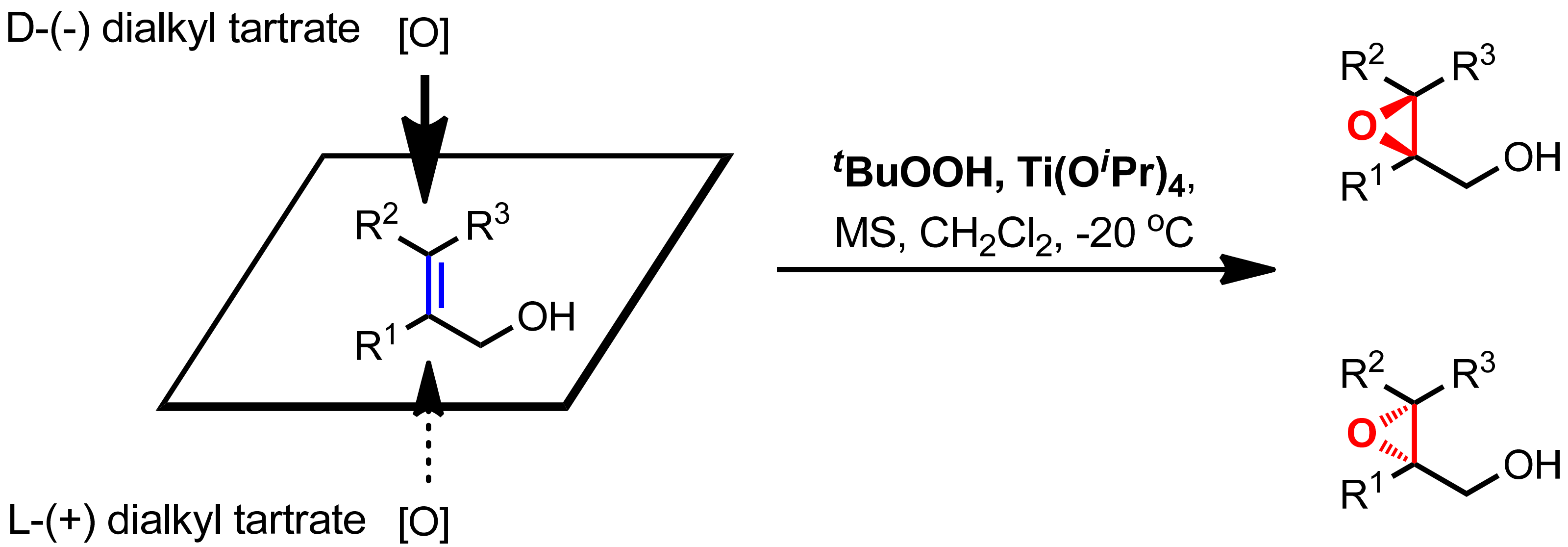
1:70 dr

Homoallylic Alcohols



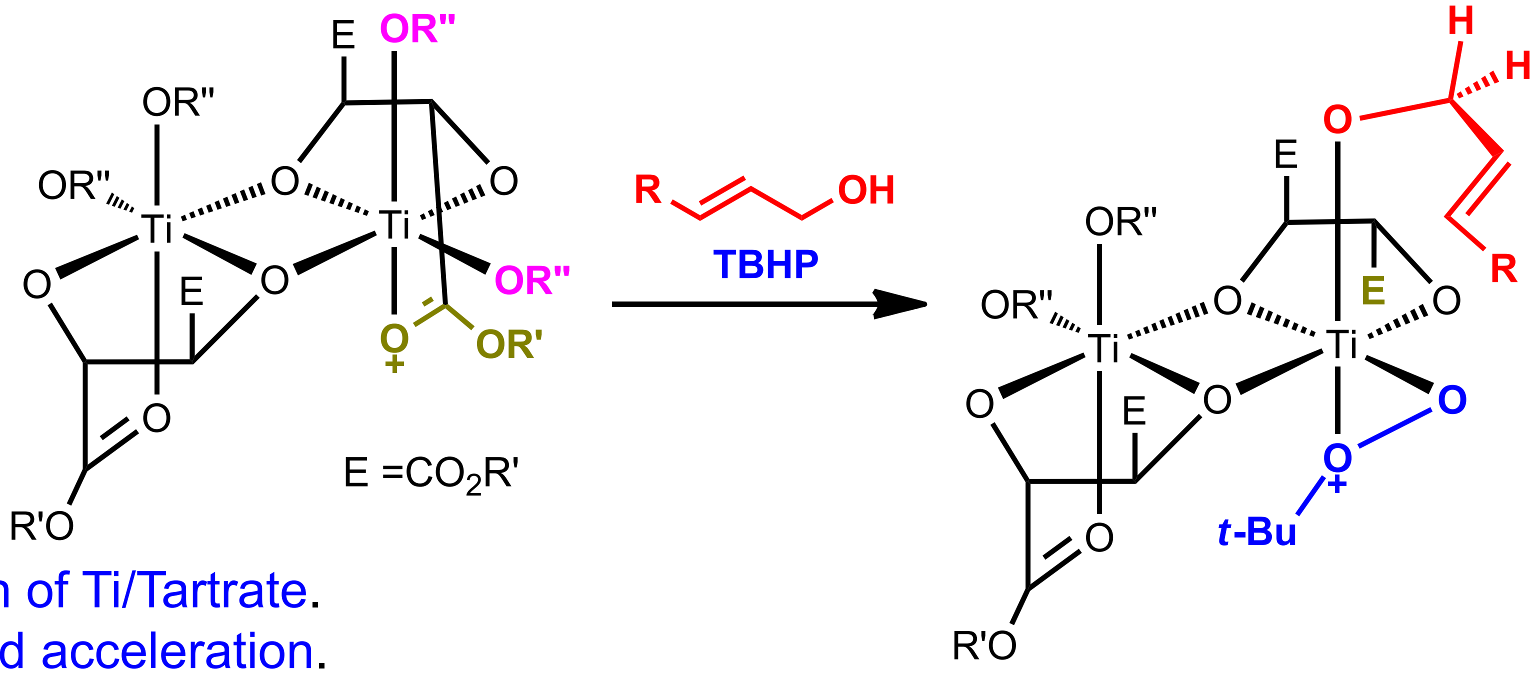
8:1 dr

The Sharpless Asymmetric Epoxidation



R =Me, D-(-)-dimethyl tartrate (DMT)	R =Me, L-(+)-DMT
R =Et, D-(-)-diethyl tartrate (DET)	R =Et, L-(+)-DET
R =^{i}Pr, D-(-)-diisopropyl tartrate (DIPT)	R =^{i}Pr, L-(+)-DIPT

Proposed Transition State

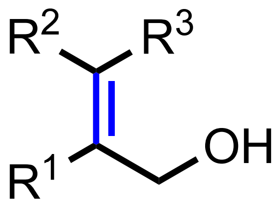


- ❑ Match of Ti/Tartrate.
- ❑ Ligand acceleration.
- ❑ Steric and stereoelectronic features control enantioselectivity.

➢ **Stereoelectronic**: 1) Alkyl peroxide is activated by bidentate coordination to the Ti(IV) center; 2) The olefin is constrained to attack the coordinated peroxide along the O-O bond axis; 3) The epoxide C-O bonds are formed simultaneously.

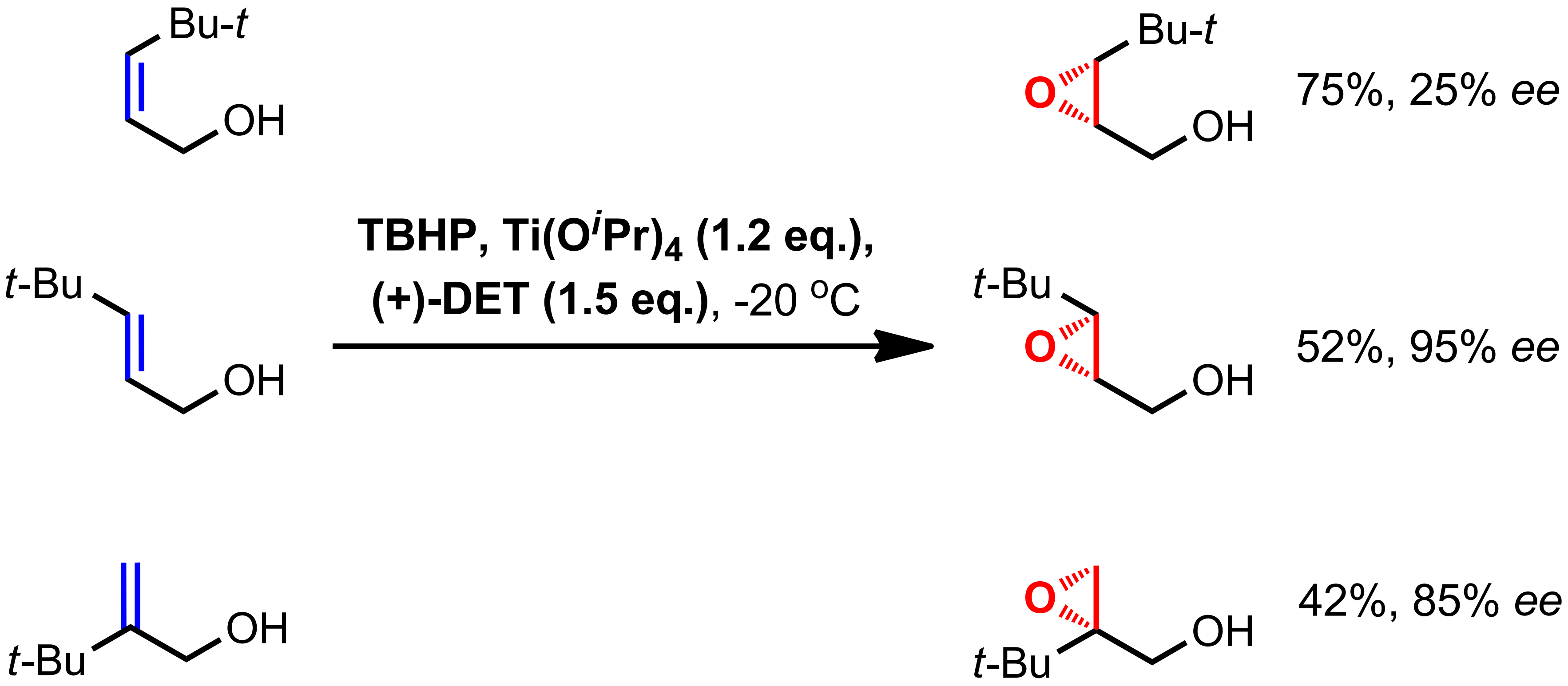
➢ **Steric factors**:1) Bulky hydroperoxide is forced to adopt a **single orientation** when bound; 2) Allylic alkoxides is restricted to reaction at a single coordination site on metal center.; 3) Efficient catalytic turnover provided by the labile（不稳定的）coodinated ester, permitting rapid alkoxide-alcohol exchange.

Substrate Scope



R^1	R^2	R^3	Tartrate	ee%
H	H	Me	(+)-DIPT	92
H	H	CH_2OBn	(-)-DET	92
H	H	$CH_2CH{=}CHC_5H_{11}$	(+)-DMT	94
H	Me	H	(+)-DIPT	92
H	^{i}Pr	H	(+)-DET	94
H	$CH{=}CH_2$	H	(+)-DIPT	>91
H	$(CH_2)_3CH{=}CH_2$	H	(+)-DET	95
H	CH_2CH_2OTBS	Me	(-)-DET	95
H	$CH_2CH{=}CHMe_2$	Me	(+)-DET	95
Me	H	H	(-)-DET	>95
Me	H	^{n}Bu	(+)-DET	89
Me	Me	H	(+)-DET	94
Me	CH_2OBn	H	(-)-DIPT	90
Me	Ph	Bn	(+)-DIPT	94
CH_2OBn	H	H	(-)-DET	>95
cyclohexyl	H	H	(+)-DET	>95
$R^1, R^2 = (CH_2)_2$		H	(+)-DET	93
$R^1, R^2 = (CH_2)_{10}$		Me	(+)-DIPT	94

Geometry and Substituents of Olefins



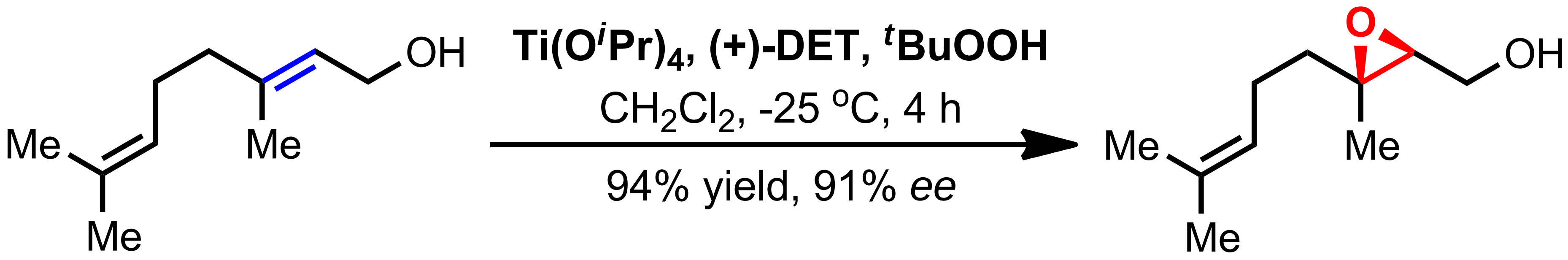
TBHP, Ti(O^{i}Pr)$_4$ (1.2 eq.), (+)-DET (1.5 eq.), -20 °C

75%, 25% *ee*

52%, 95% *ee*

42%, 85% *ee*

Regioselectivity



Ti(O^{i}Pr)$_4$, (+)-DET, ^{t}BuOOH

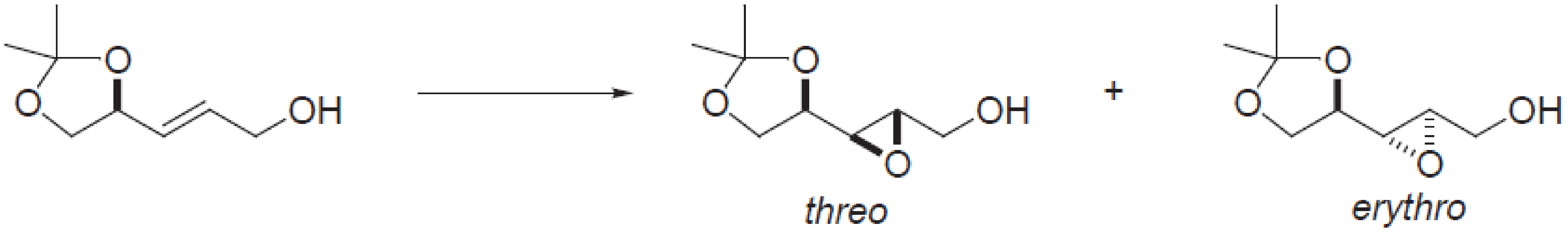
CH_2Cl_2, -25 °C, 4 h

94% yield, 91% *ee*

“Reagent-Control” & “Substrate-Control”

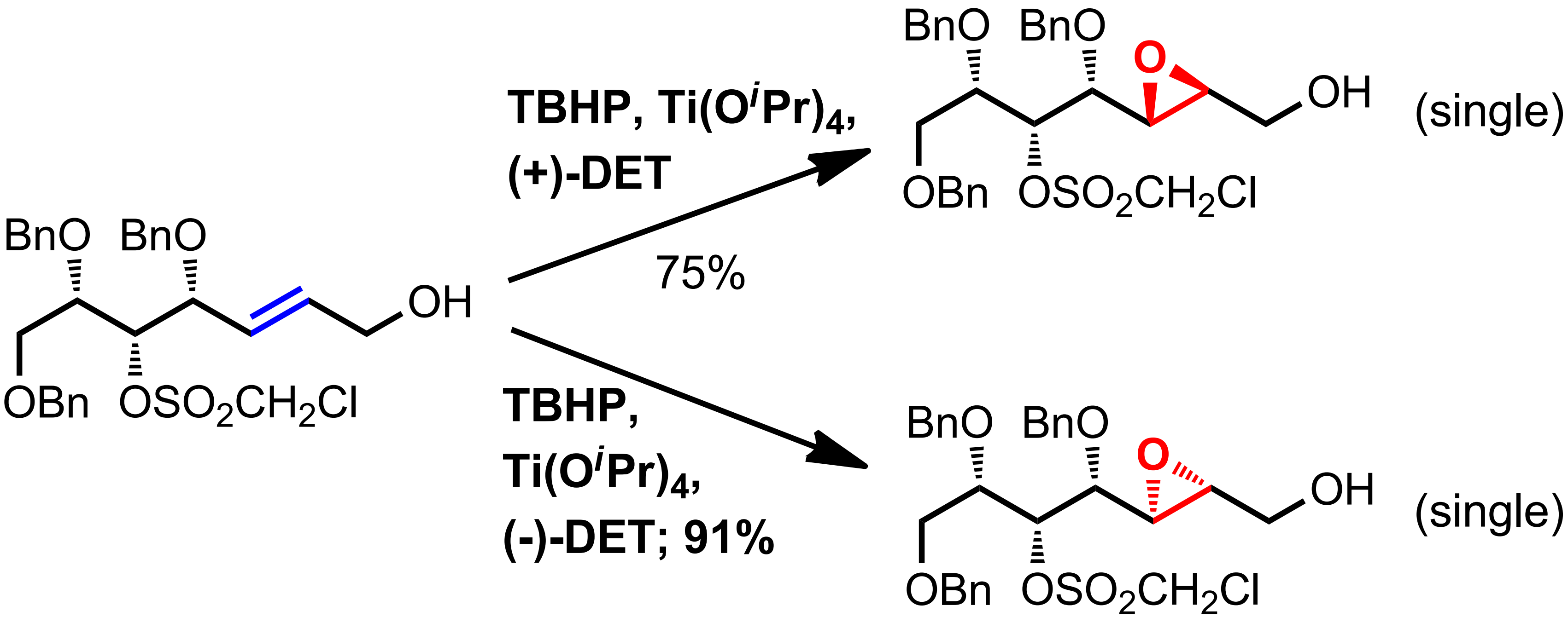
❑ “Reagent-control” Strategy: selection of reagent dictates ultimate absolute stereochemistry of products irrespective of stereofacial bias of substrate.

❑ “Substrate-control” Stategy: stereochemistry of reaction products dictated by the inherent stereofacial bias of the substrate.

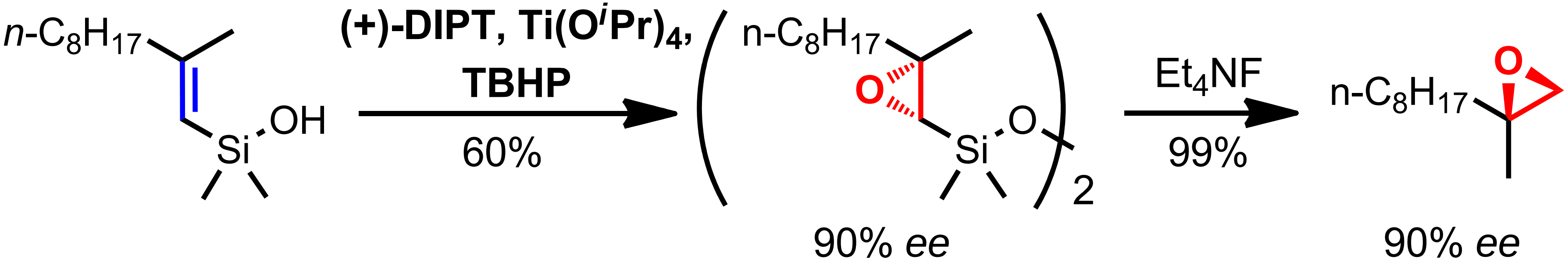


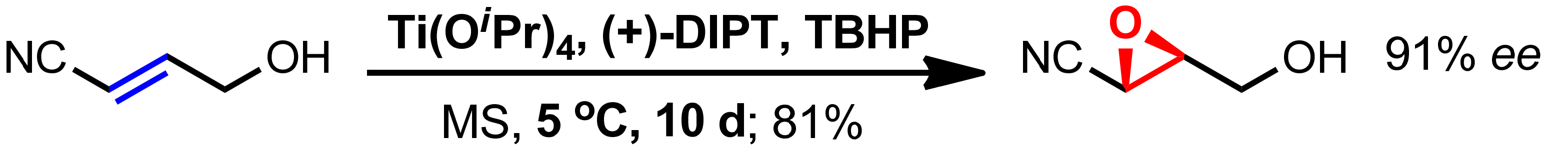
Reagent	Product Ratio (*threo*:*erythro*)	
m-CPBA	1 : 1.4	achiral reagents "substrate control"
$VO(acac)_2$–TBHP	1 : 1.8	
$Ti(O^iPr)_4$–TBHP	1 : 2.3	
$Ti(O^iPr)_4$–(–)-tartrate–TBHP	1 : 90	"matched pair"
$Ti(O^iPr)_4$–(+)-tartrate–TBHP	22 : 1	"mismatched pair" "reagent control"

Reagent-Control

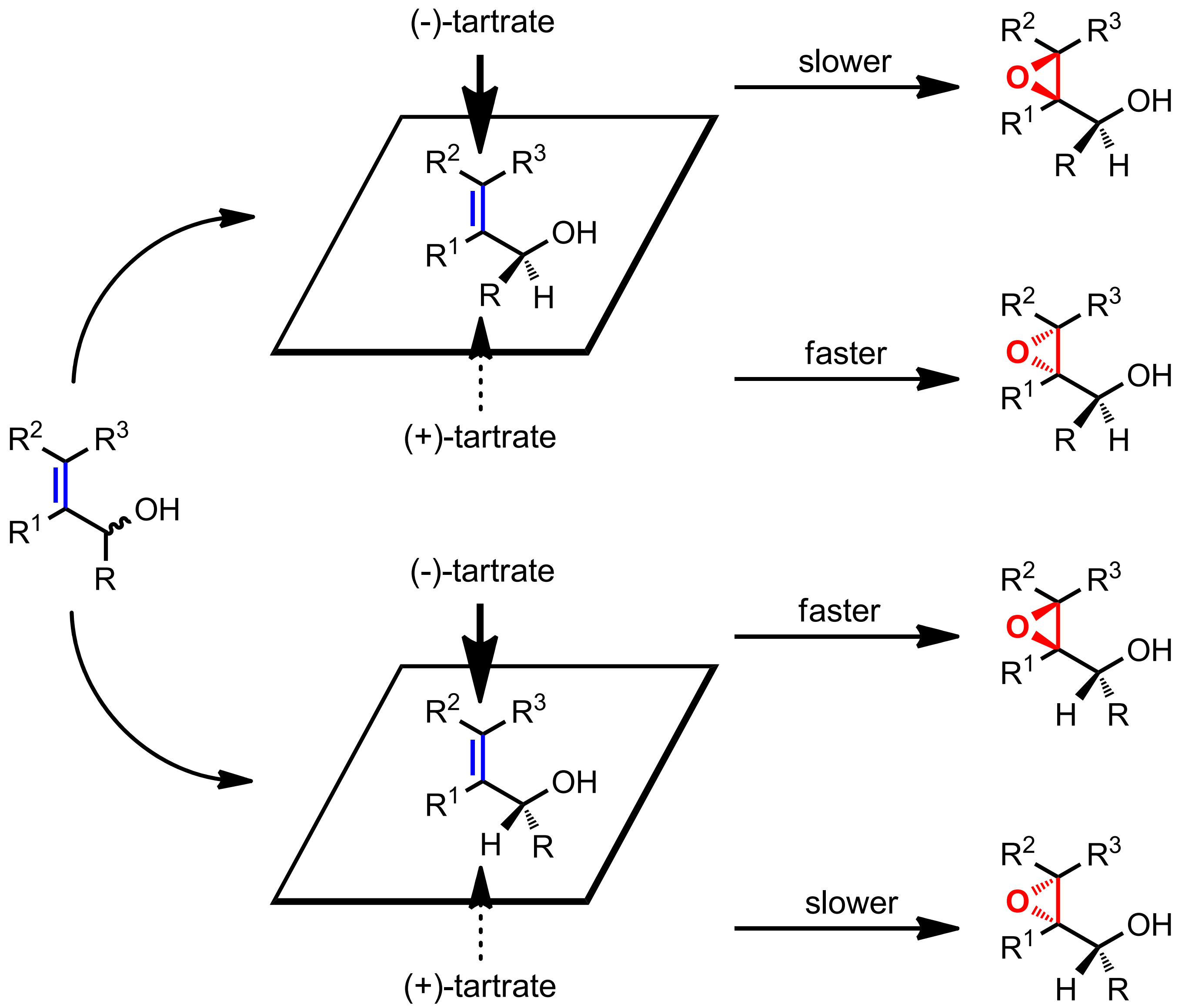


Reagent-Control

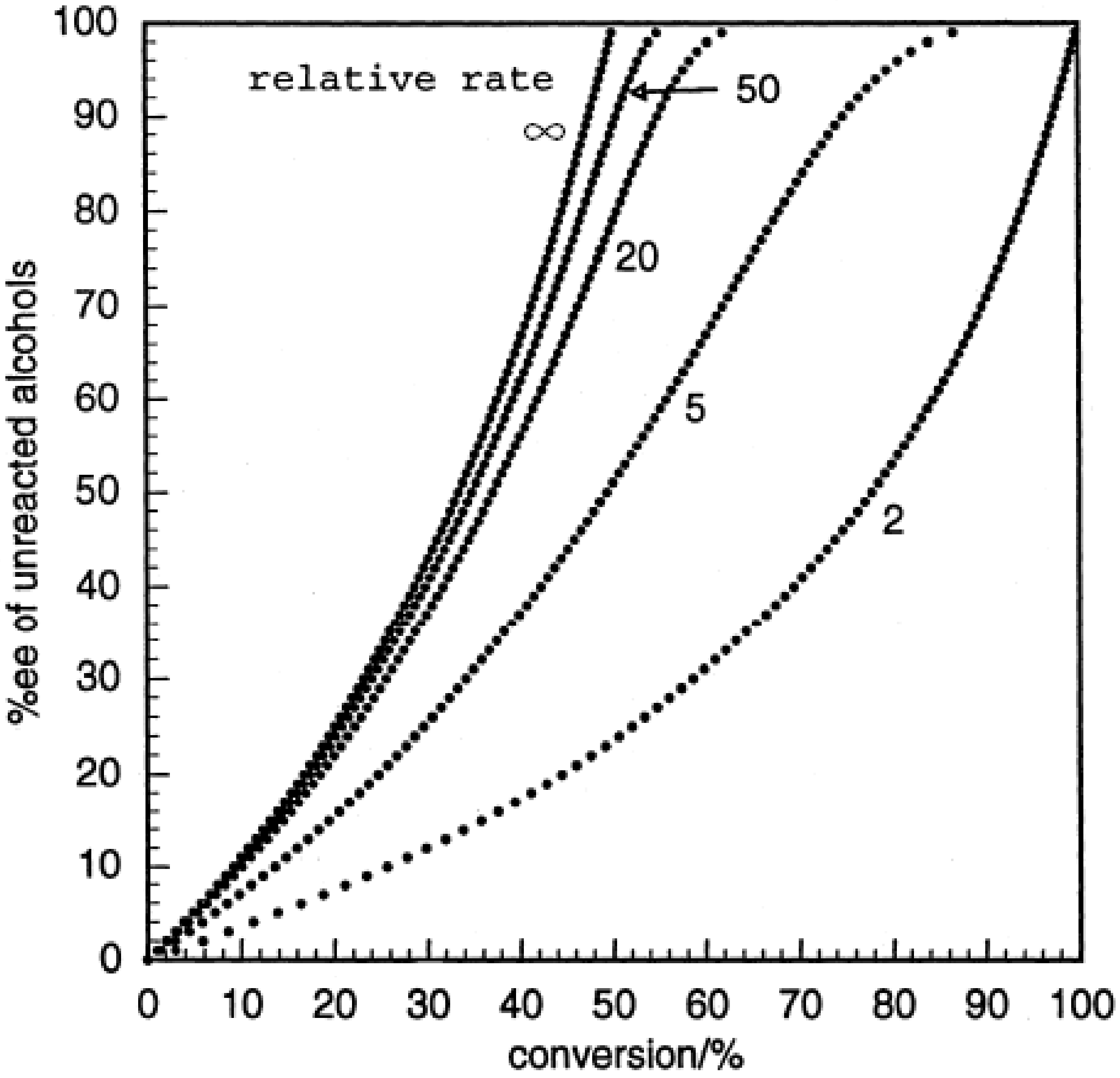




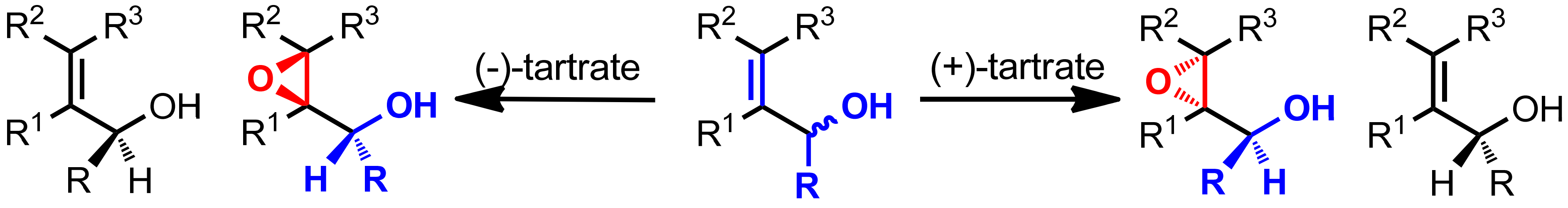
Kinetic Resolution of Allylic Alcohols

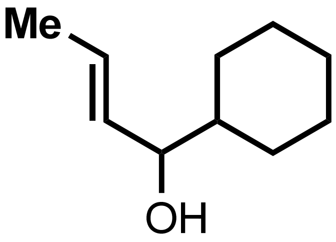


Kinetic Resolution of Allylic Alcohols

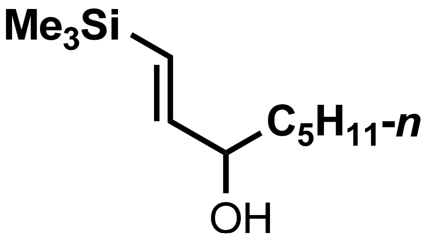


Kinetic Resolution of Allylic Alcohols

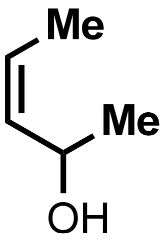




k_{rel} =104

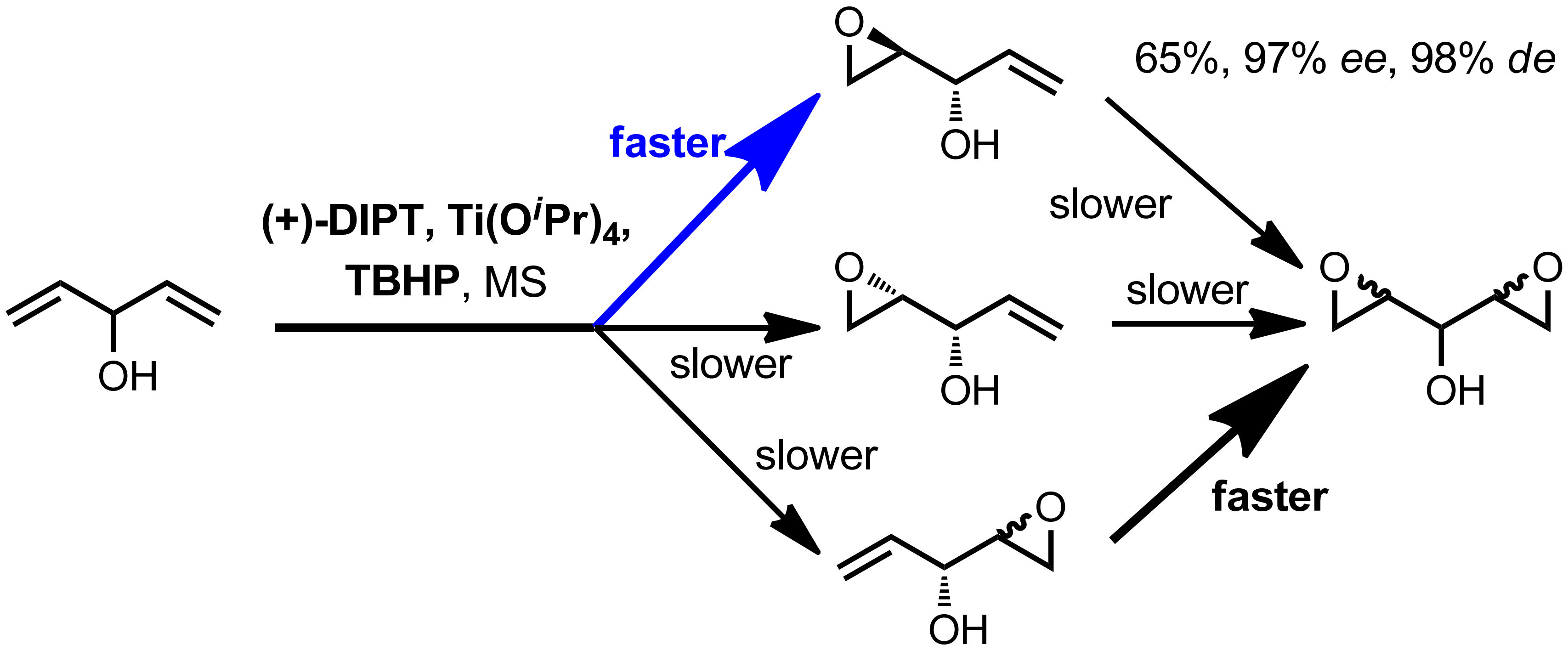


k_{rel} =700



k_{rel} =20

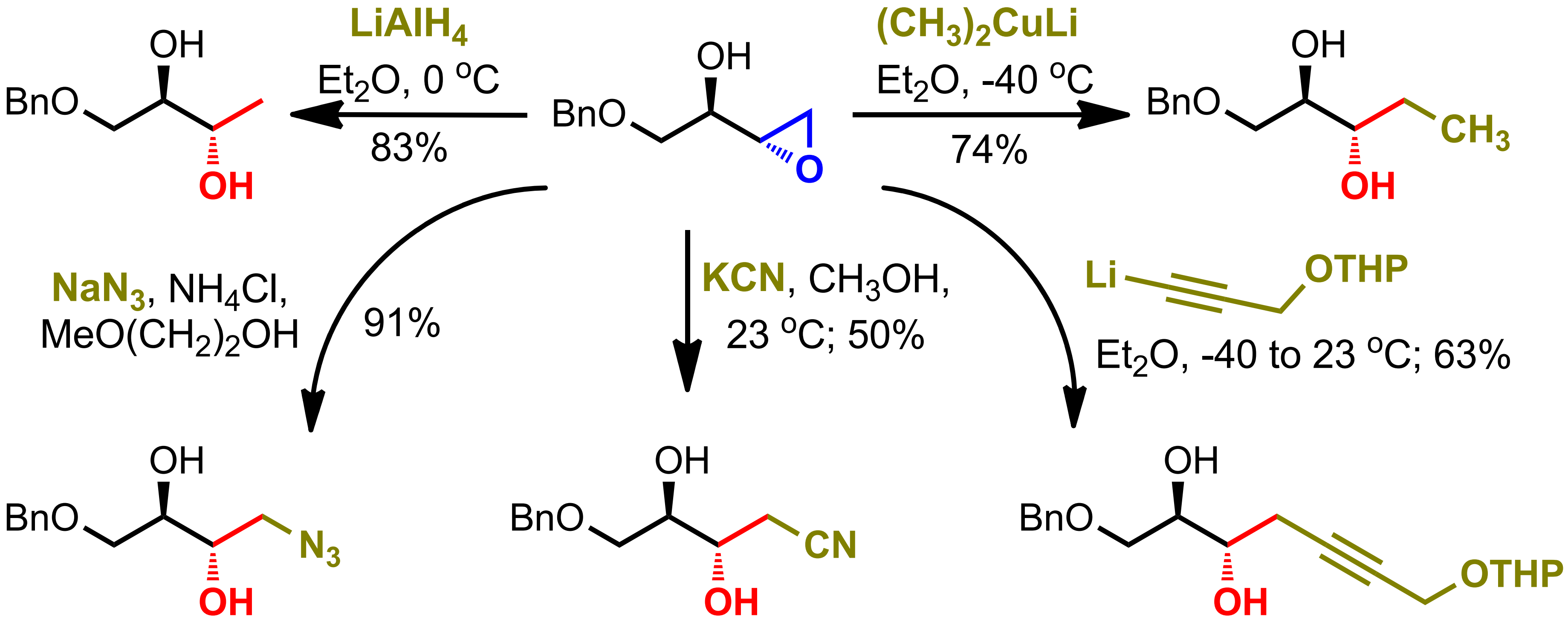
Kinetic Resolution of Allylic Alcohols

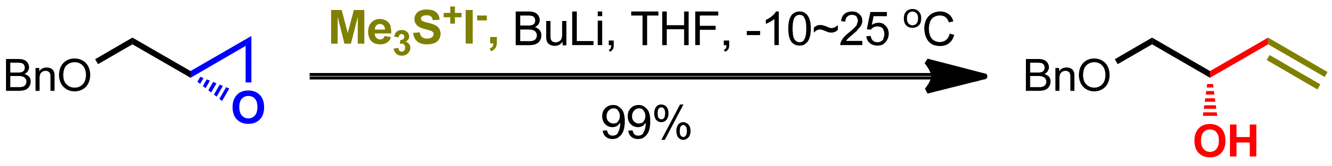


- ❑ The *ee* of the major *anti*-epoxy alcohol was observed to increase (84, 93, >97% *ee*) as the reaction time was extended (3, 24, 140 h).

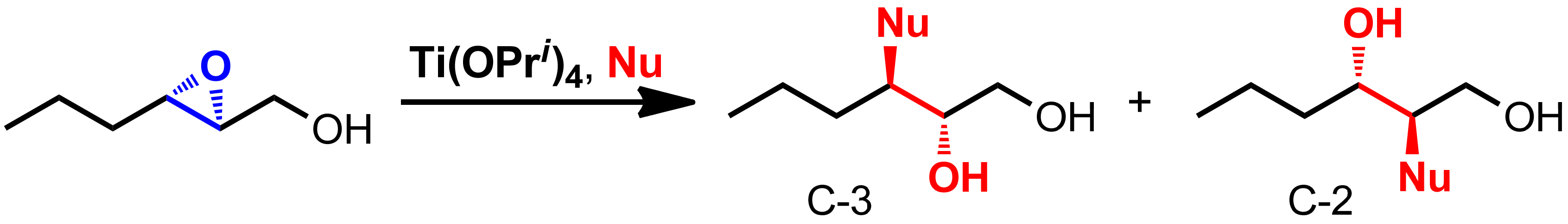
Nucleophilic Opening of Epoxides

- ❑ Nucleophilic opening of terminal epoxides is often **highly regioselective**.

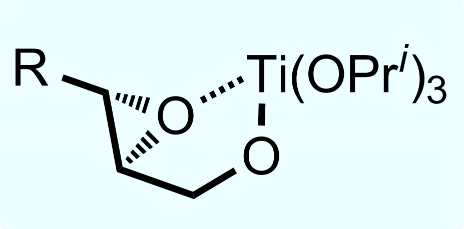




Nucleophilic Opening of Epoxides



- ☐ **Ti(OPr-*i*)$_4$** can **catalyze** the addition of nucleophiles to C-3 of 2,3-epoxy alcohols:

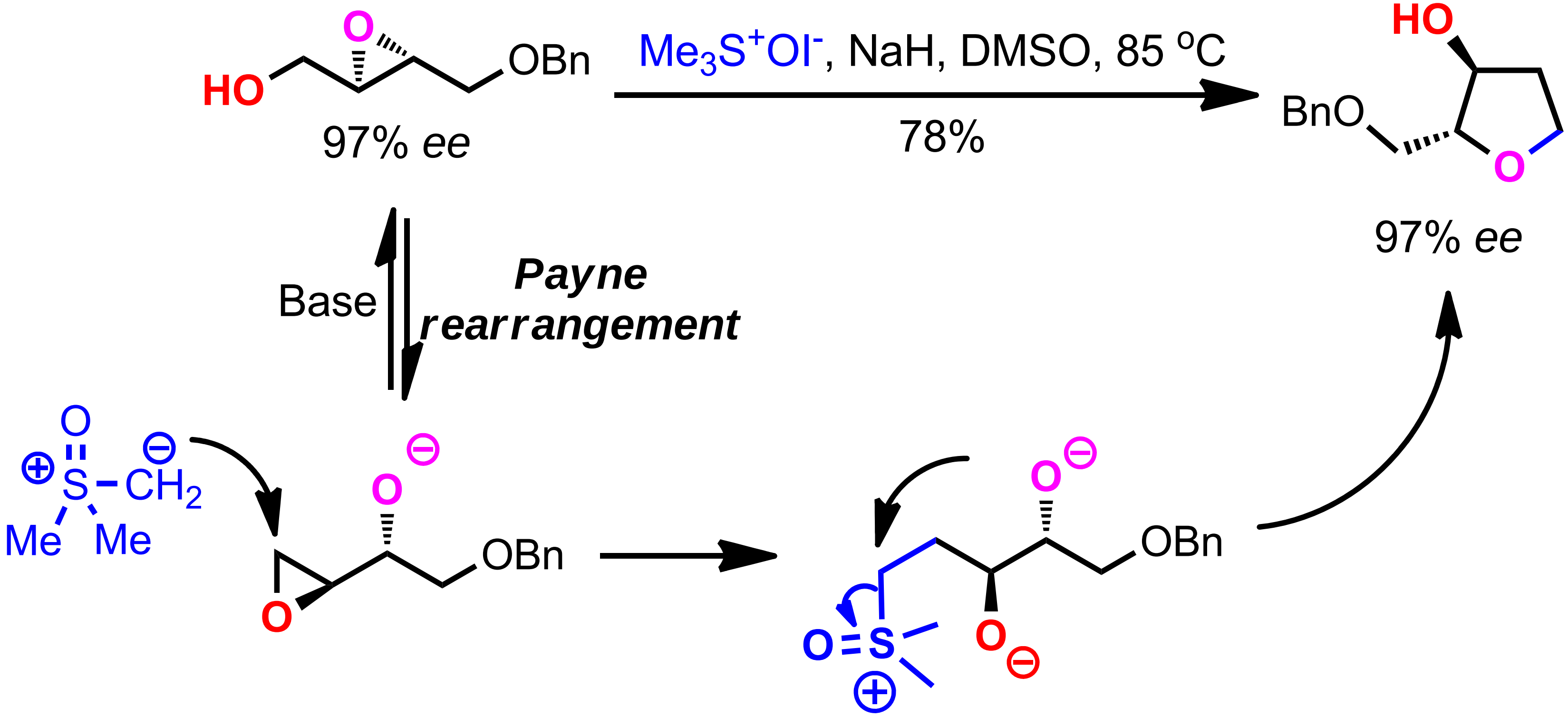


Nu	Ti(O^{i}Pr)$_4$ (eq.)	C-3:C-2	yield (%)
Et$_2$NH	0	3.7 : 1	4
Et$_2$NH	1.5	20 : 1	90
i-PrOH	0	--	0
i-PrOH	1.5	100 : 1	88
(allyl)$_2$NH	1.5	100 : 1	96
allyl alcohol	1.5	100 : 1	90
NH$_4$OBz	1.5	100 : 1	74
NH$_4$OAc	1.5	65 : 1	73
KCN	1.7	2.4 : 1	76

Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

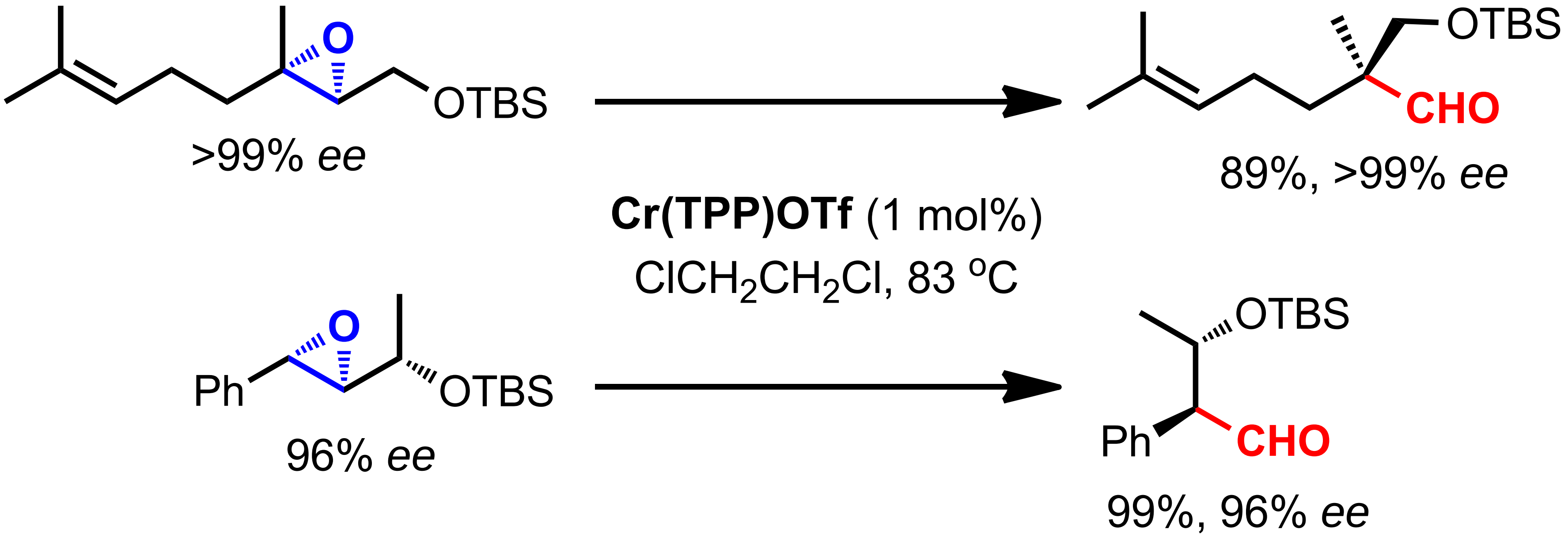
Nucleophilic Opening of Epoxides

- ❑ Dimethylsulfoxonium methylide: heat stability, reactivity, easy preparation.
- ❑ Access to 2,3-disubstituted THF.
- ❑ Highly diastereoselective and enantioselective fashion.
- ❑ The stereochemistry is translated fully.

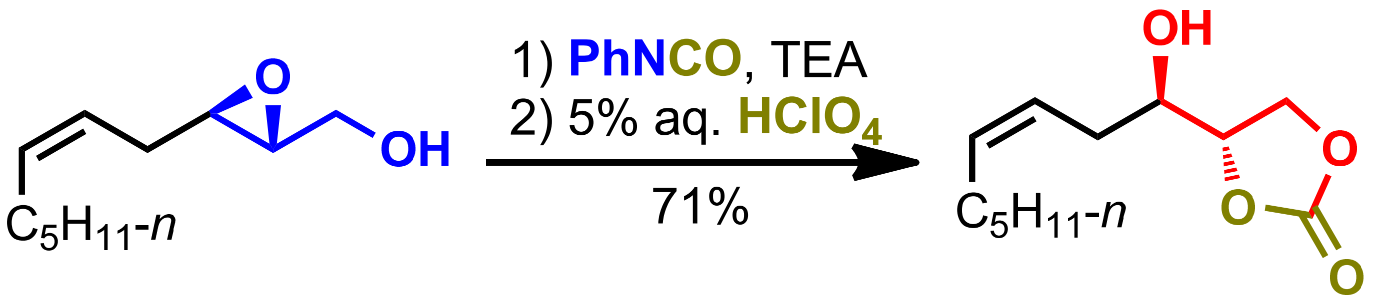


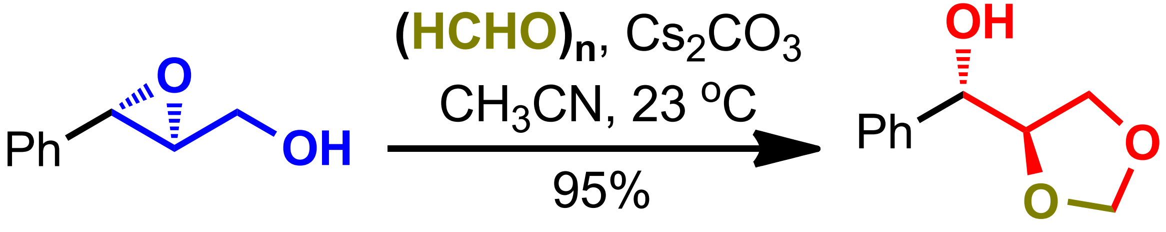
Rearrangement

- Catalyst: a high-valent metalloporphyrin complex, Cr(TPP)OTf (chromium(III) tetraphenylporphyrin triflate), 1-20mol% laoding.
- Alkyl migration.
- The yield and regio- and stereoselectivity are generally good to high.

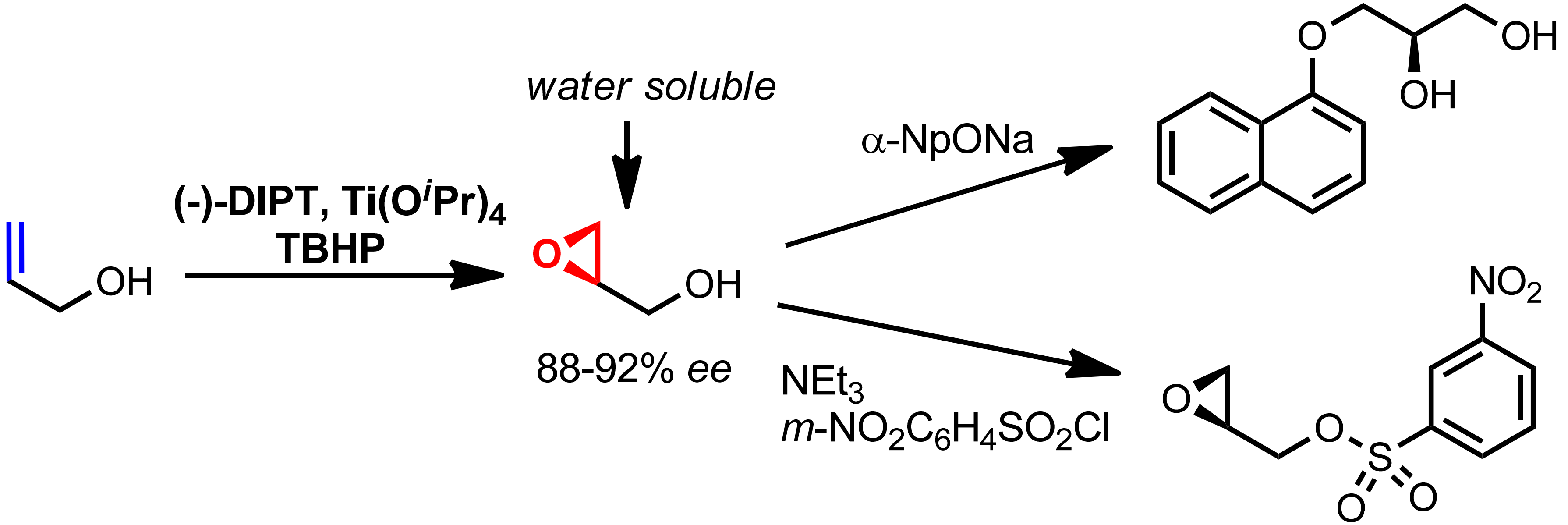


Internal Nucleophiles



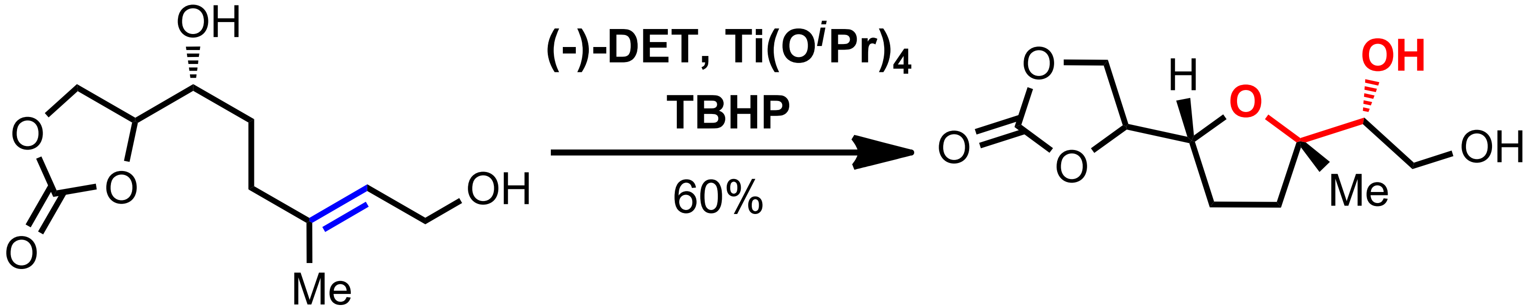


Open the Epoxy Alcohol *in situ*

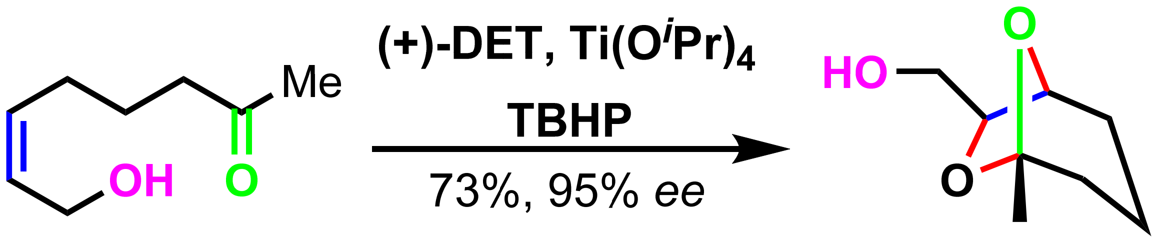


J. Org. Chem. **1986**, *51*, 3710; 5413.

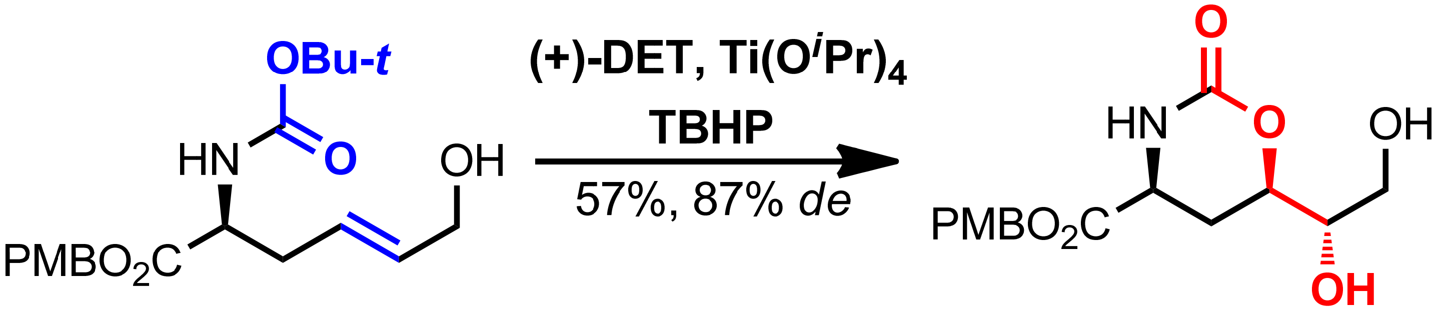
Intramolecular Ring Opening



J. Org. Chem. **1984**, *49*, 2582.



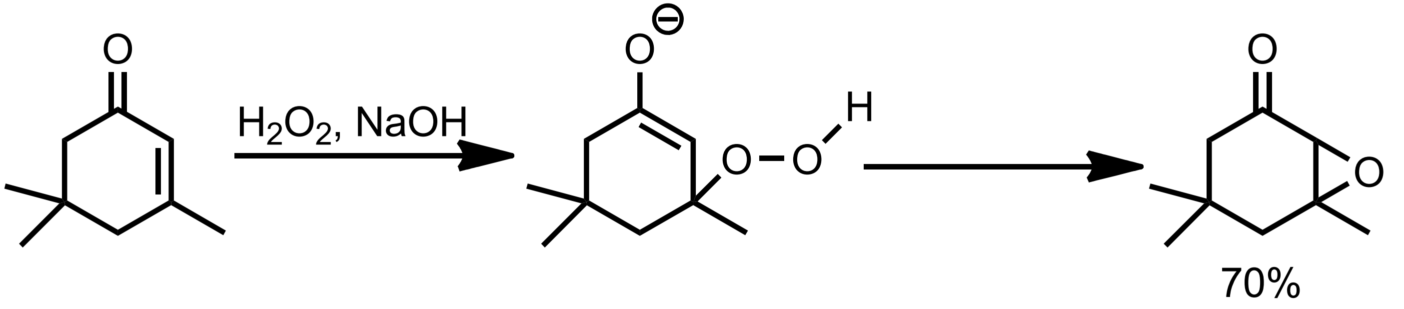
J. Org. Chem. **1982**, *47*, 5384.



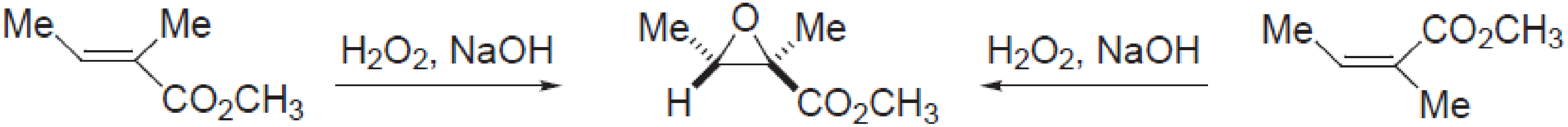
Tetrahedron Lett. **1987**, *28*, 3605.

H_2O_2, NaOH

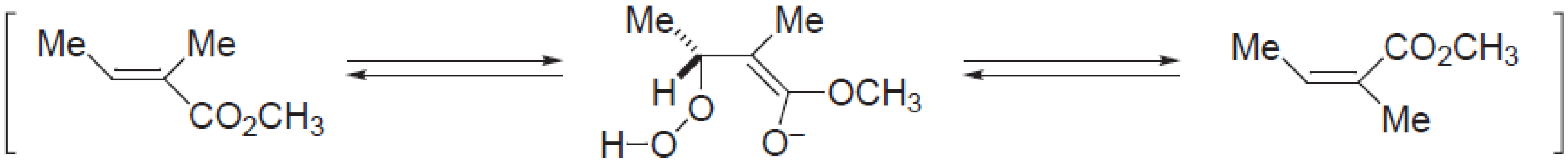
- ❑ Mechanism:



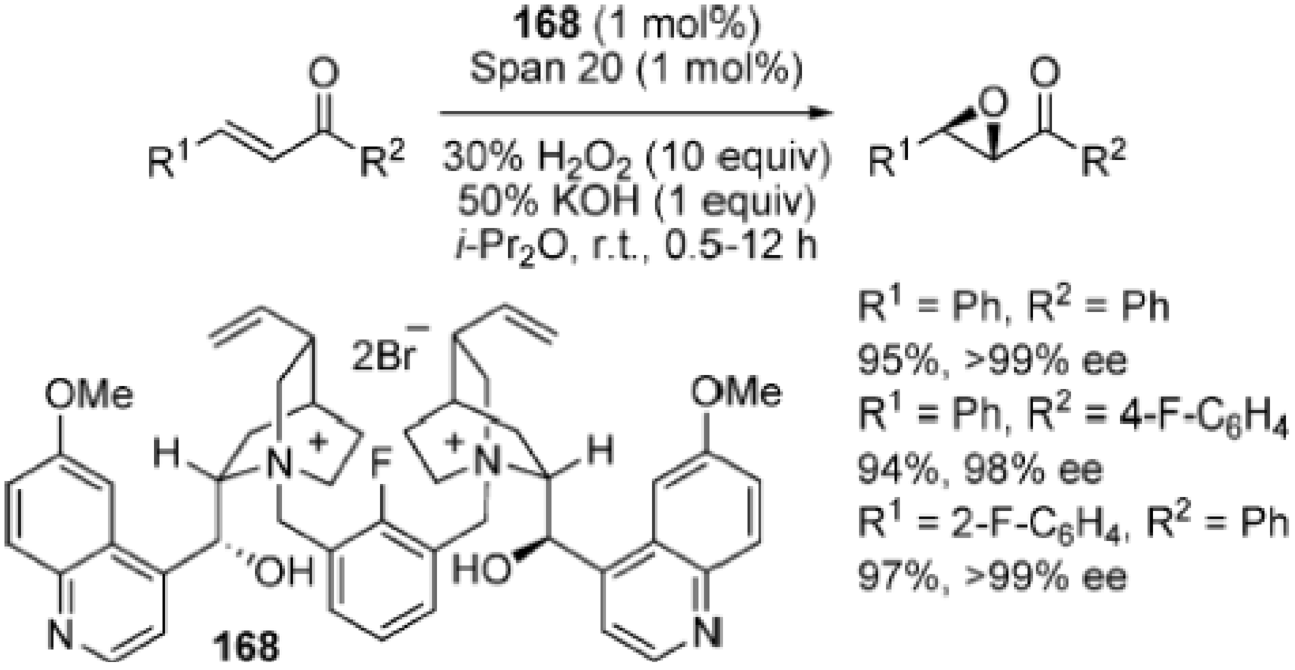
- ❑ **Diastereoselctive**, but not diastereospecific: a single stereoisomer of the product is formed which bears no relationship to the reactant.



via a **reversible process**:



Asymmetric Phase-Transfer Catalysis

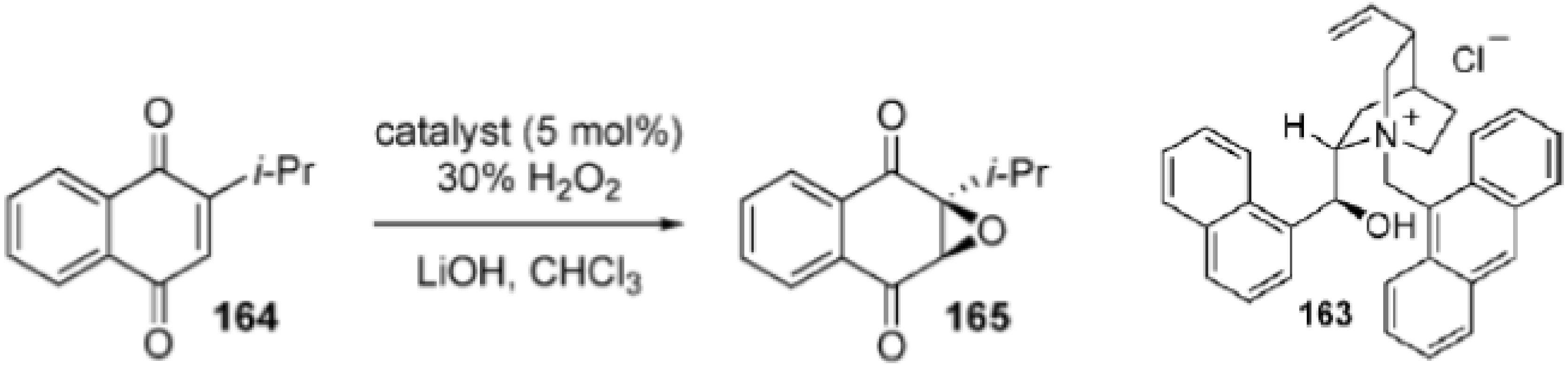


168 (1 mol%)
Span 20 (1 mol%)

30% H_2O_2 (10 equiv)
50% KOH (1 equiv)
i-Pr_2O, r.t., 0.5-12 h

R^1 = Ph, R^2 = Ph
95%, >99% ee
R^1 = Ph, R^2 = 4-F-C_6H_4
94%, 98% ee
R^1 = 2-F-C_6H_4, R^2 = Ph
97%, >99% ee

168



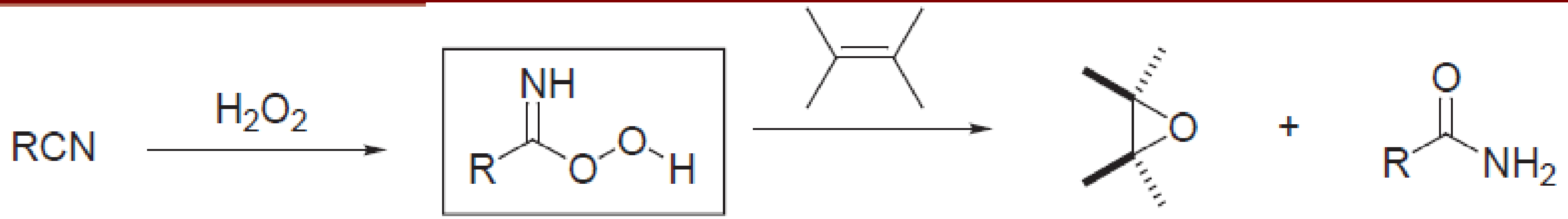
catalyst (5 mol%)
30% H_2O_2

LiOH, $CHCl_3$

164 **165** **163**

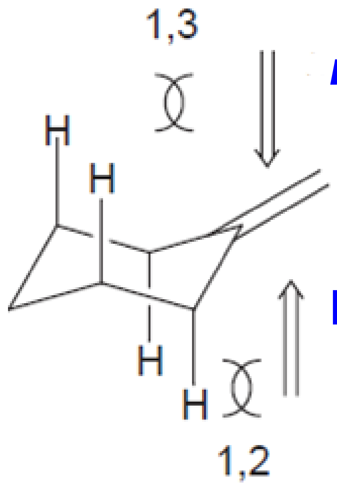
with **163** (0 °C, 5 h; r.t., 12 h) : 75%, 84% ee

Peroxyimidate



- Permits the use of neutral reaction conditions.
- Behaves as a large reagent and approaches from the equatorial face of an exocyclic double bond.

small reagent	⟸	*m*-CPBA	59	41
large reagent	⟸	PhCN / H_2O_2	14	86



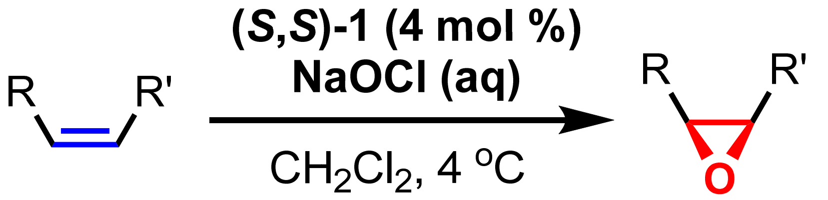
***m*-CPBA**

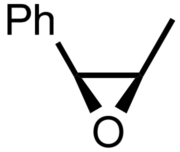
small reagent, but the interaction will increase with the size of the reagent.

$PhCN/H_2O_2$

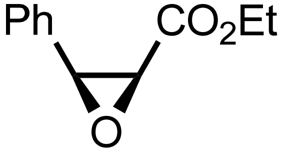
larger reagent, but the interaction will not vary with size, predominately equatorial attack.

Jacobsen Asymmetric Epoxidation

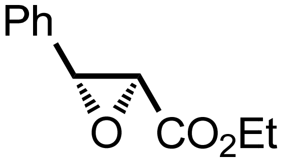




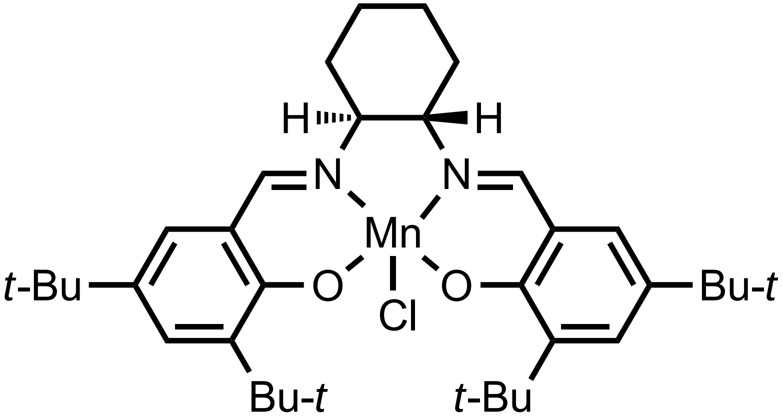
77%, 92% *ee*



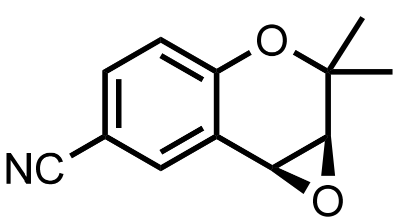
52%, 97% *ee*



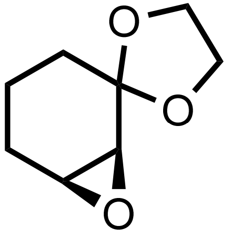
15%, 78% *ee*



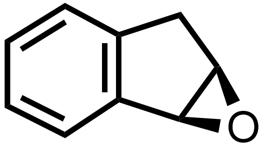
(*S*,*S*)-**1**



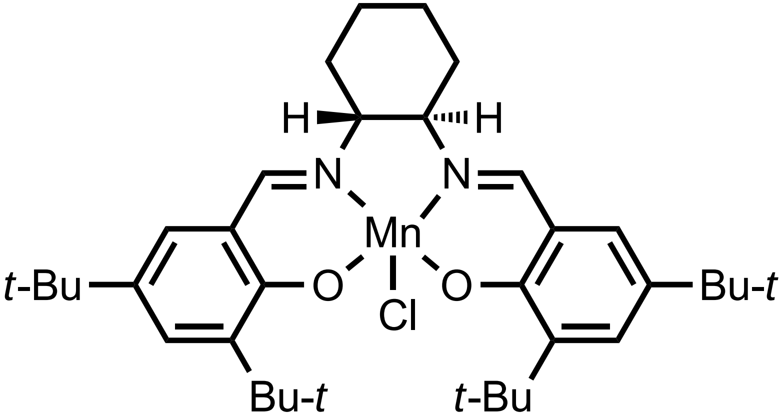
96%, 97% *ee*



63%, 94% *ee*



79%, 84% *ee*

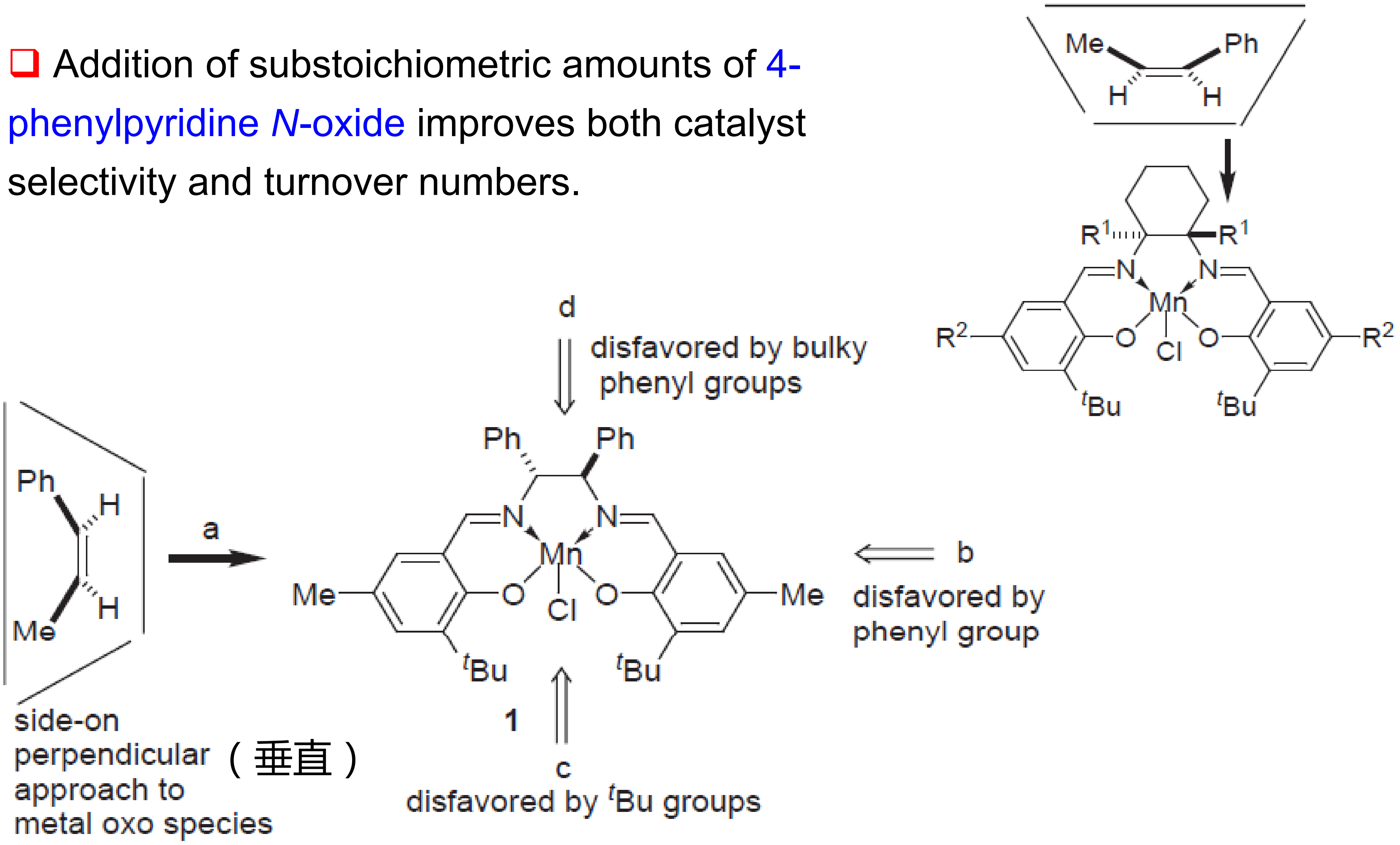


(*R*,*R*)-**1**

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

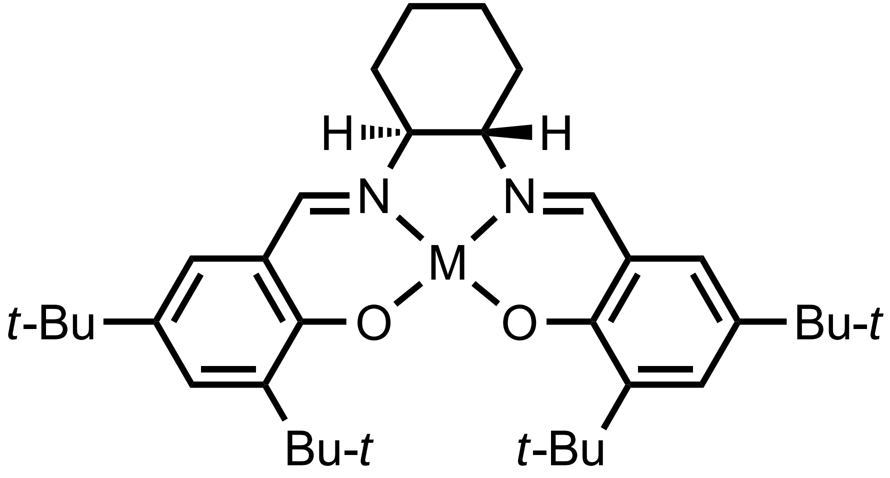
Jacobsen Asymmetric Epoxidation

- ❑ Addition of substoichiometric amounts of 4-phenylpyridine *N*-oxide improves both catalyst selectivity and turnover numbers.



Hydrolytic Kinetic Resolution (HKR)

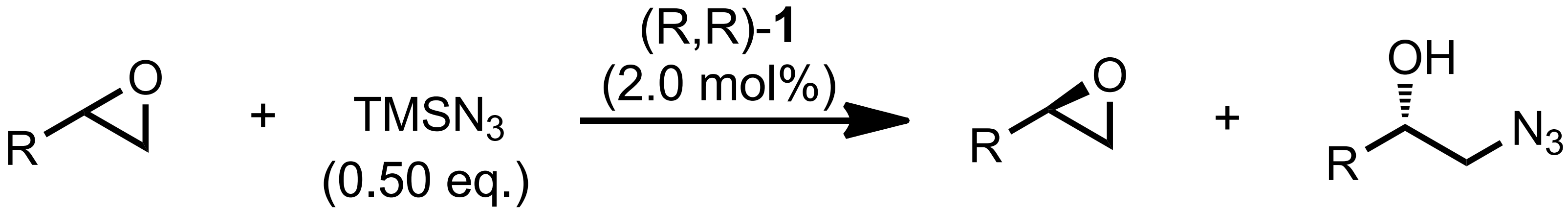
R	k_{rel}
Me	>400
CH_2Cl	50
$(CH_2)_3Me$	290
Ph	20
$CH=CH_2$	30



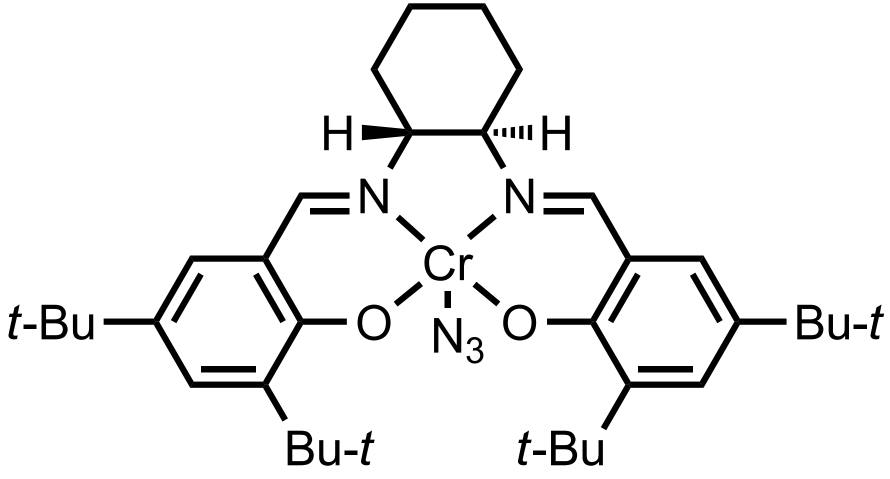
M =Co(OAc)(OH_2), (*S*,*S*)-**1**

Jacobsen, E. N. *Science* **1997**, *277*, 936.

Kinetic Resolution of Terminal Epoxides with Trimethylsilyl Azide



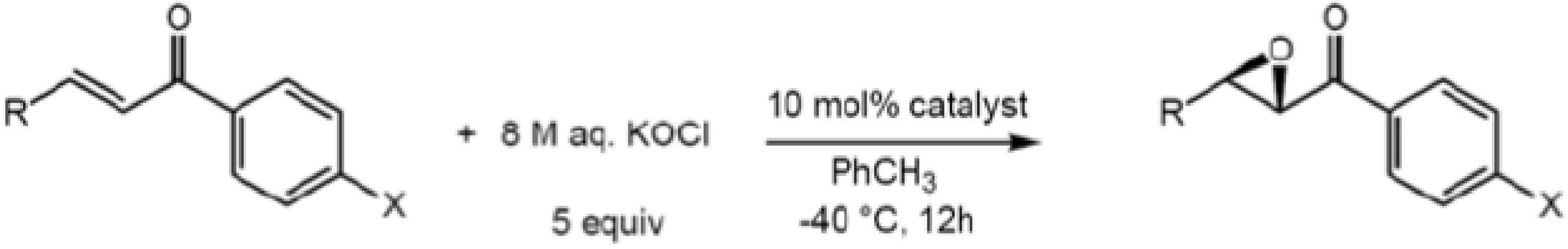
R	k_{rel}
CH_2Cl	100
CH_2CN	45
$CH(OEt)_2$	44
CH_2Ph	71



(R,R)-**1**

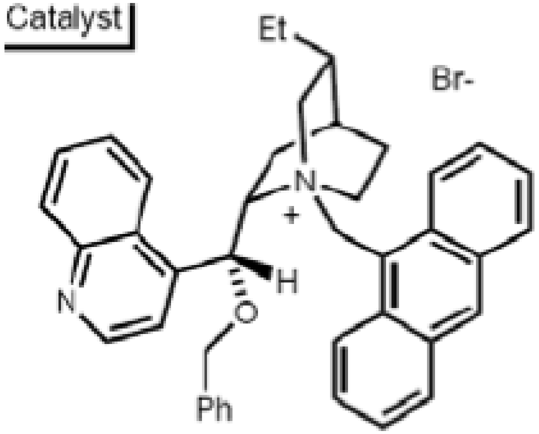
Jacobsen, E. N. *J. Am. Chem. Soc*. **1996**, *118*, 7420.

Asymmetric Catalysis with PTC



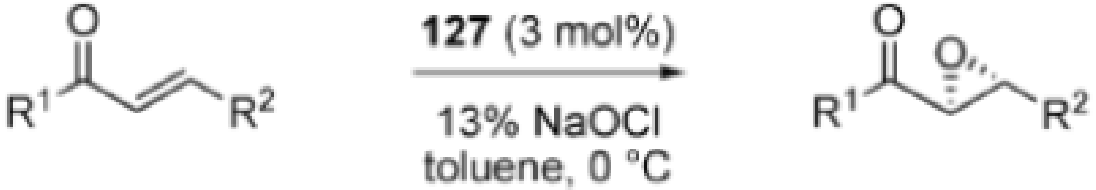
R	X	%ee	% yield
Ph	H	93	96
Ph	F	98	93
p-NO_2Ph	H	94	90
pentyl	F	91	90
C_6H_{11}	H	94	85
p-MeOPh	H	95	70
β-Napht	H	93	87

Catalyst

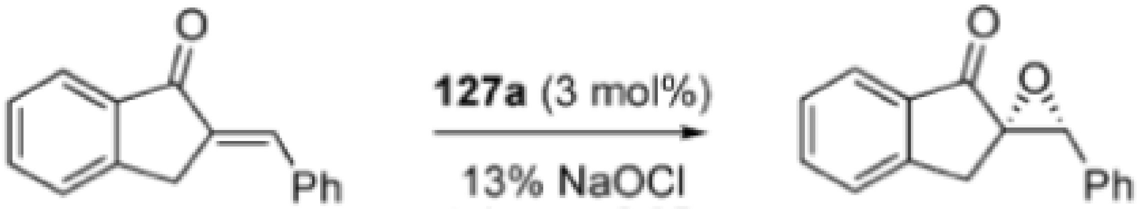


Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

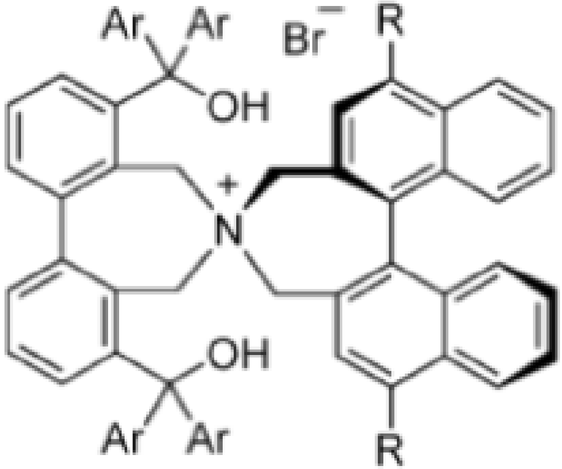
Asymmetric Catalysis with PTC



$R^1 = R^2$ = Ph with **127a** : 99%, 96% ee
R^1 = *t*-Bu, R^2 = Ph with **127b** : 99%, 92% ee
R^1 = *t*-Bu, R^2 = *c*-Hex with **127b** : 80%, 96% ee



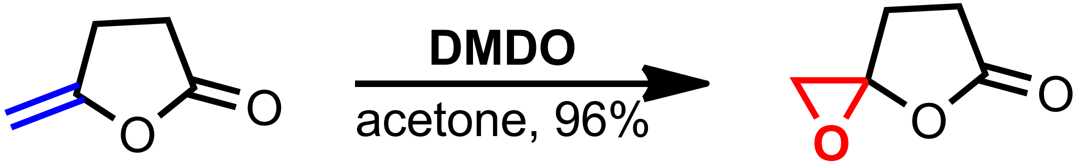
91%, 99% ee

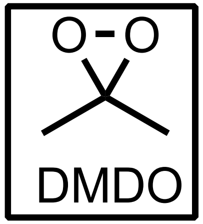


127a (Ar = R = 3,5-Ph_2-C_6H_3)
127b (Ar = 3,5-Ph_2-C_6H_3, R = H)
127c (Ar = Ph, R = H)
127d (Ar = 4-CF_3-C_6H_4, R = H)
127e (Ar = 3,5-$(MeO)_2$-C_6H_3, R = H)

Dimethyl Dioxirane (DMDO)

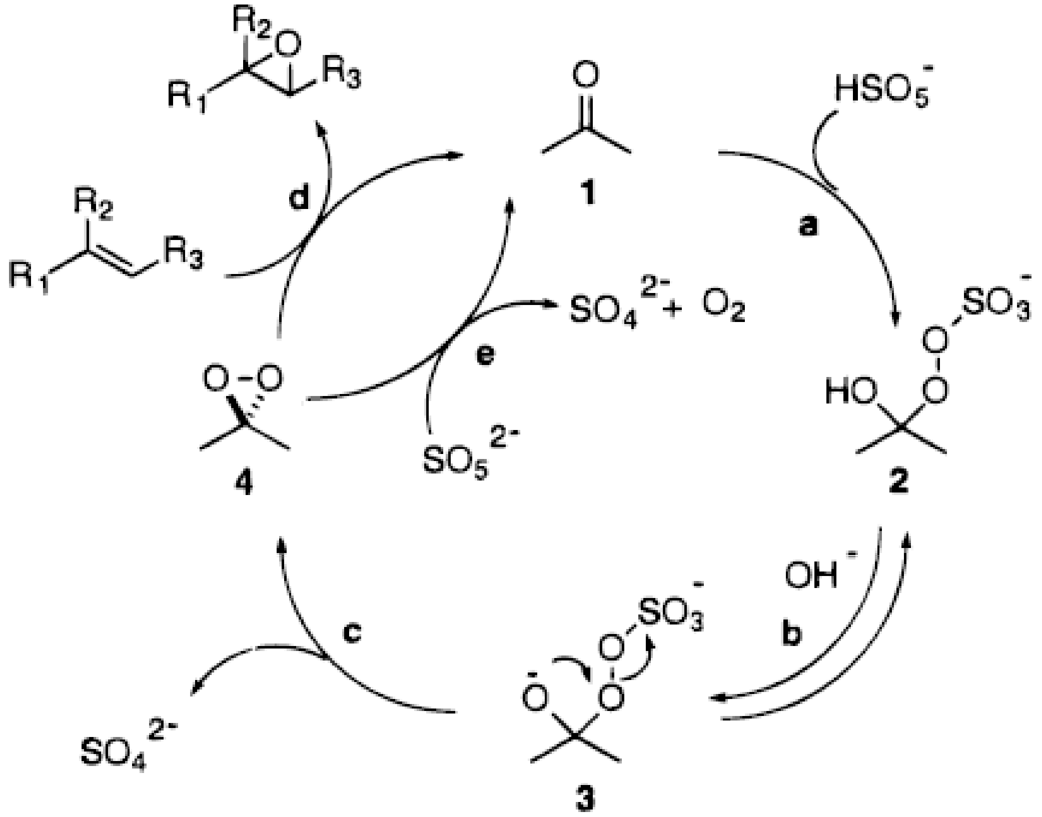
- Peracid reaction suffers from **H^+** catalyzed epoxide opening.





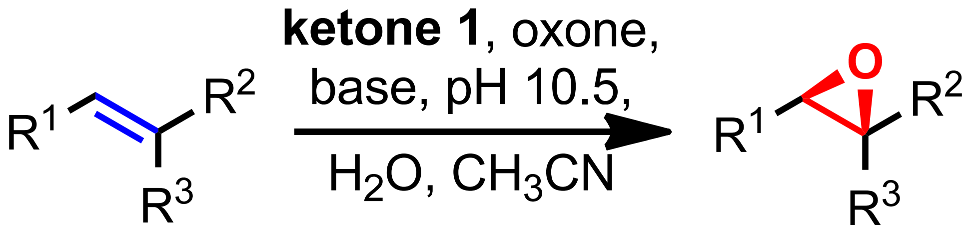
- A mild neutral reagent.

- Cycle with DMDO prepared *in stit*u from acetone-oxone :



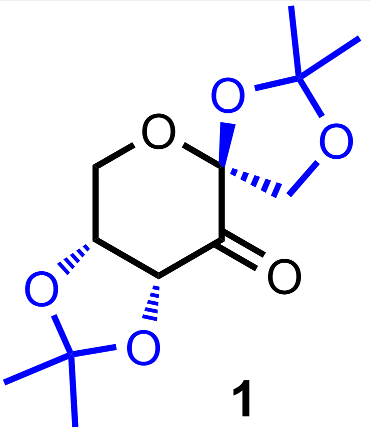
- pH dependence: rate at pH 11 > 7, acetone-oxone.

Shi Asymmetric Epoxidation



ketone 1, oxone, base, pH 10.5,

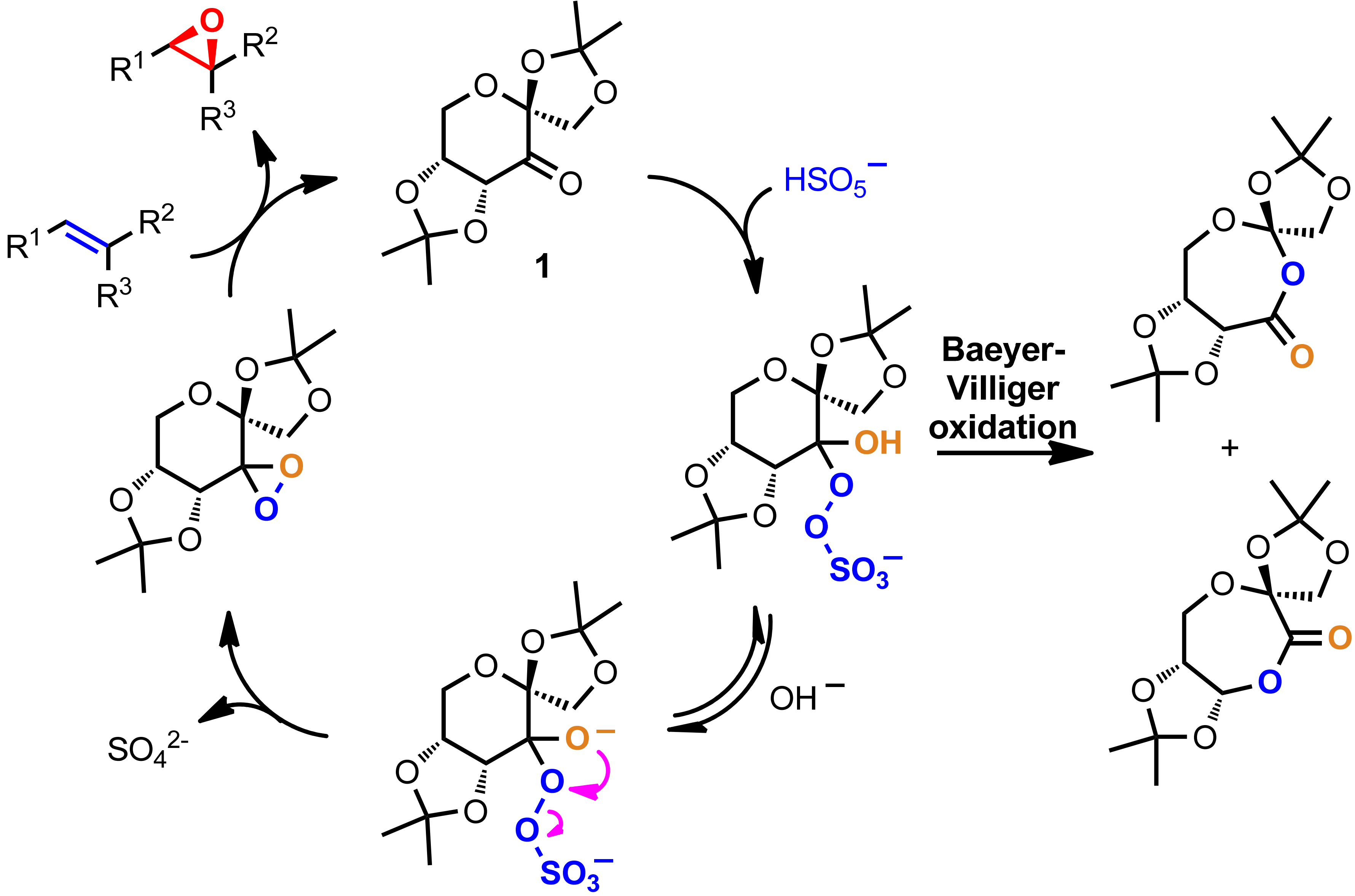
H_2O, CH_3CN



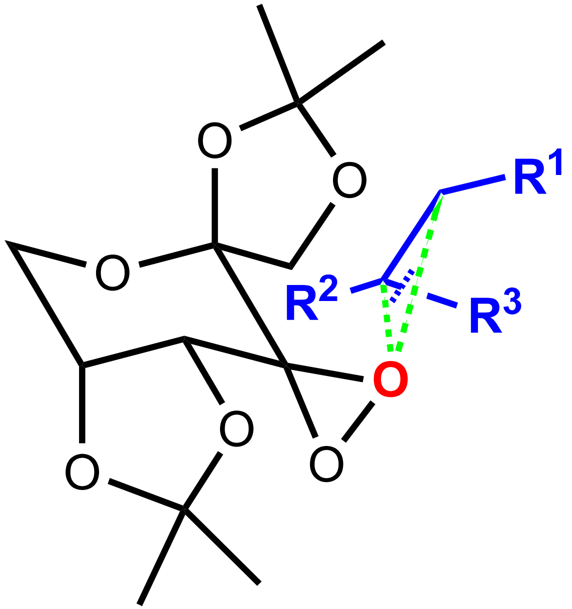
1

- Ketone **1** can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1 $KHSO_5$:$KHSO_4$:K_2SO_4) is used as the stoichiometric oxidant.
- pH = 10.5
- Reaction temperatures range from –10 to 20 ^{o}C.

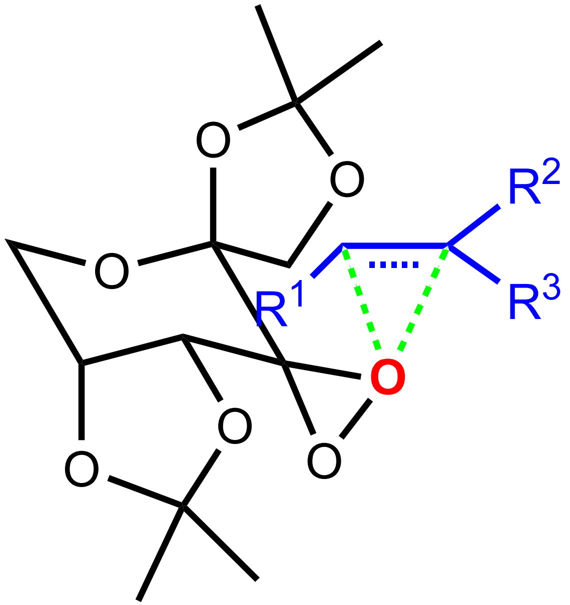
Shi Asymmetric Epoxidation: Mechanism



Spiro and Planar TS



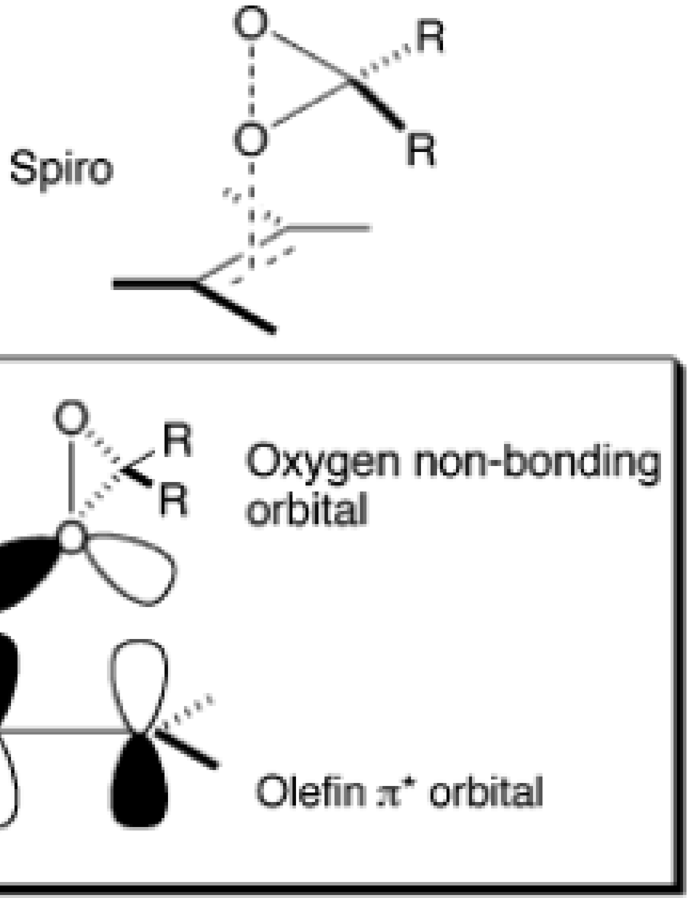
spiro

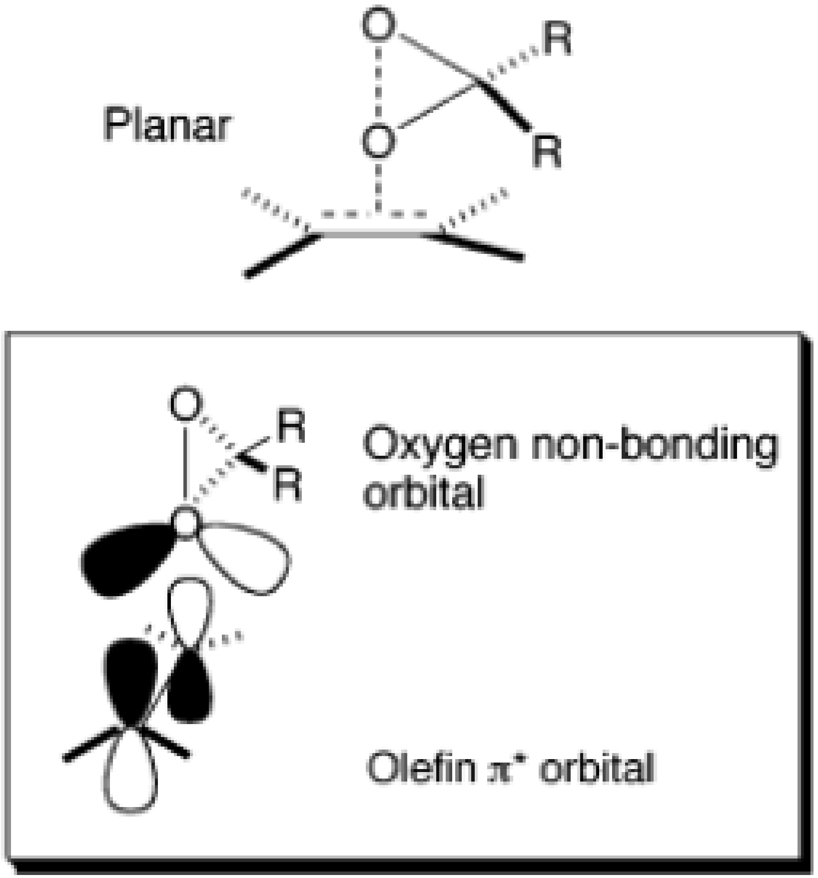


planar

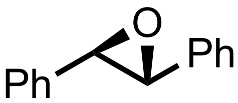
- The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the π* orbital of the olefin.

Spiro and Planar TS

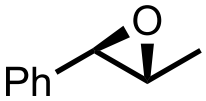




Epoxidation Examples with Ketone 1



98% *ee*



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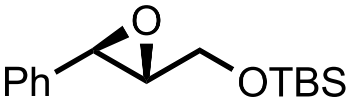
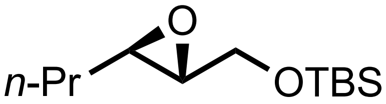


94% *ee*



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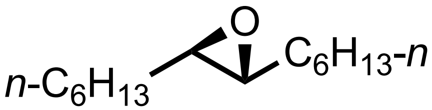

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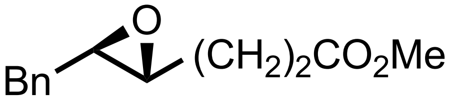

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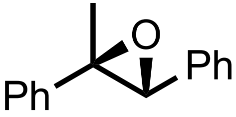

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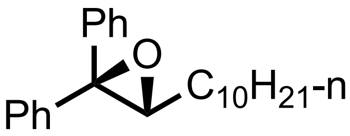

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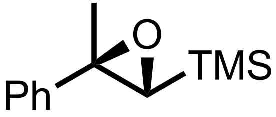

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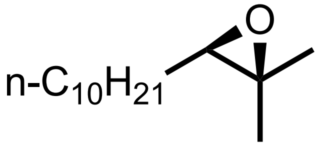

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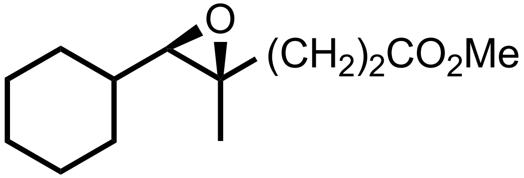

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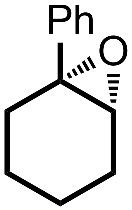

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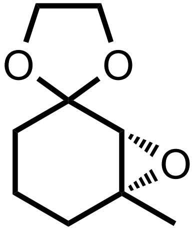

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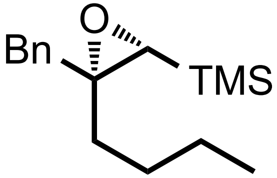

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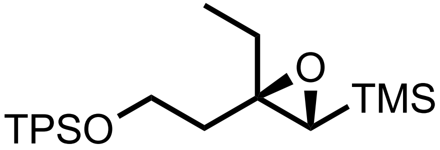

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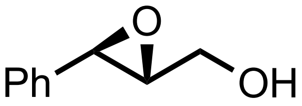

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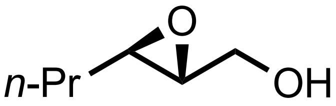

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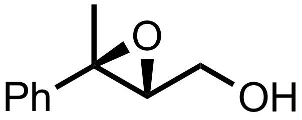

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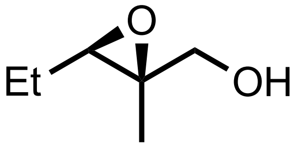

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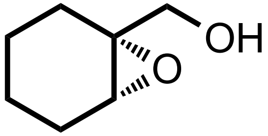
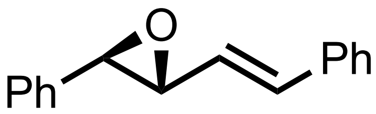


94% *ee*

Conjugated Dienes and Enynes



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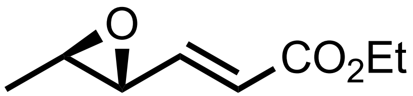

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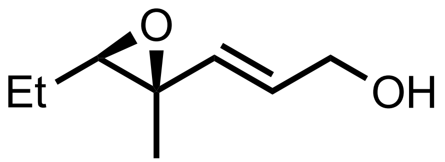

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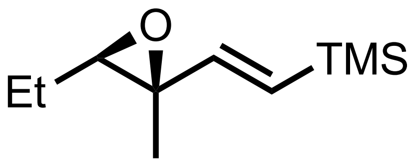

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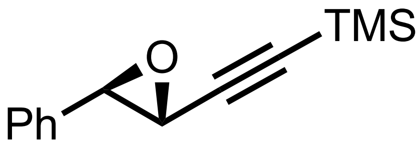

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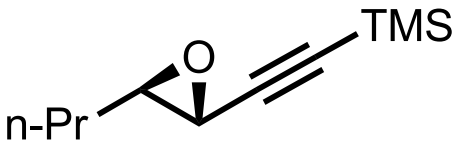

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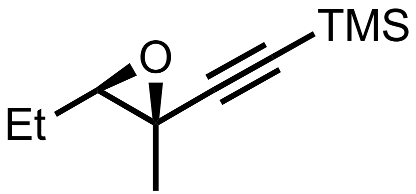

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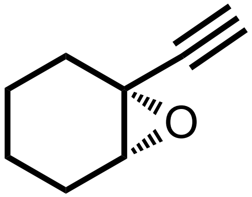
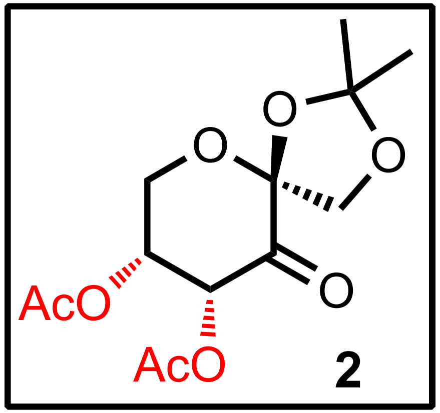
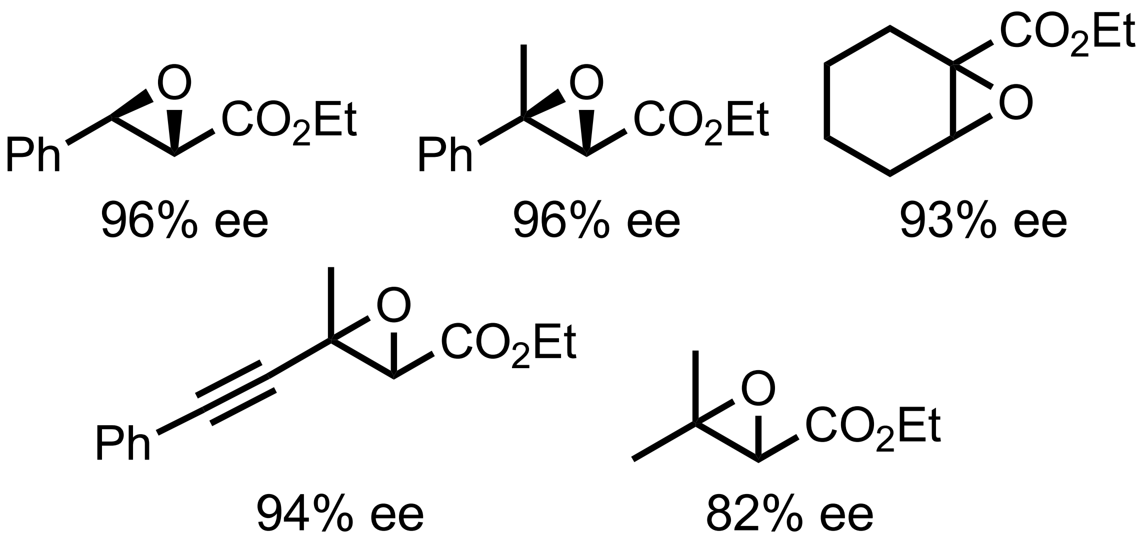


93% *ee*

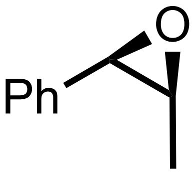
Epoxidation of α,β-Unsaturated Esters with Ketone 2

- The original **Shi catalyst** decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient α,β-unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.

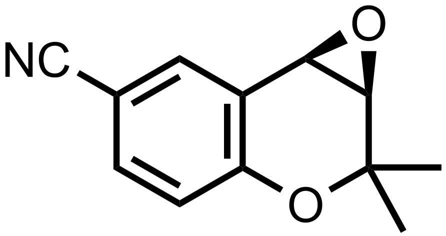




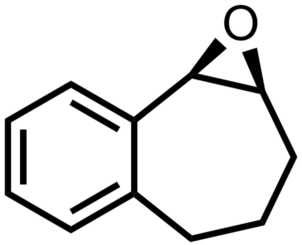
Epoxidation of *cis* and Terminal Olefins with Ketone 3



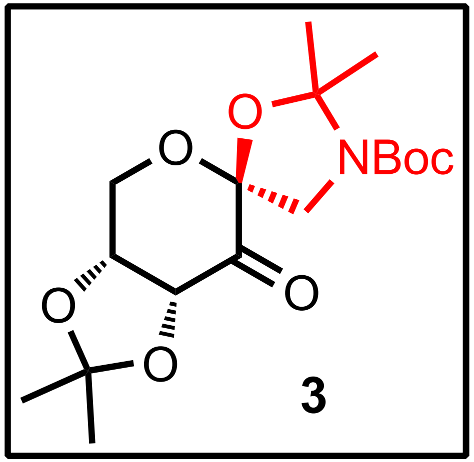
91% ee



91% ee



91% ee



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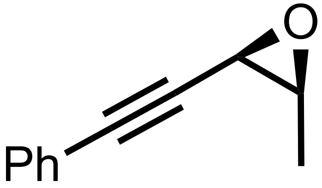
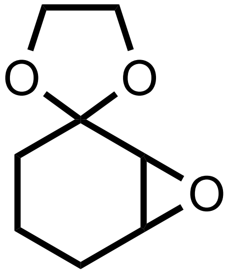
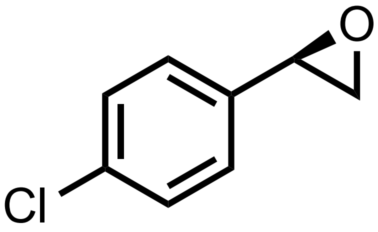


91% ee

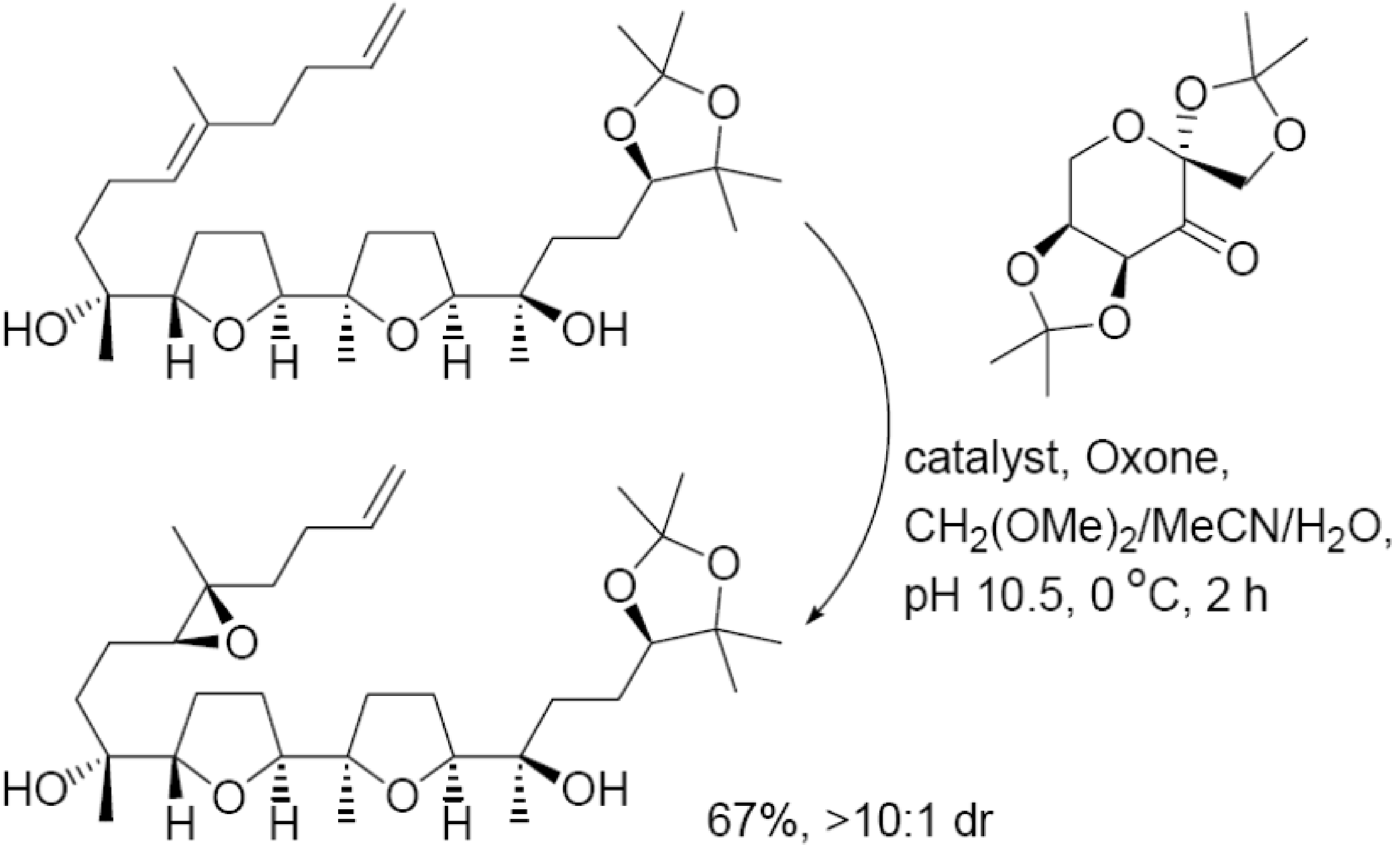


97% ee



85% ee

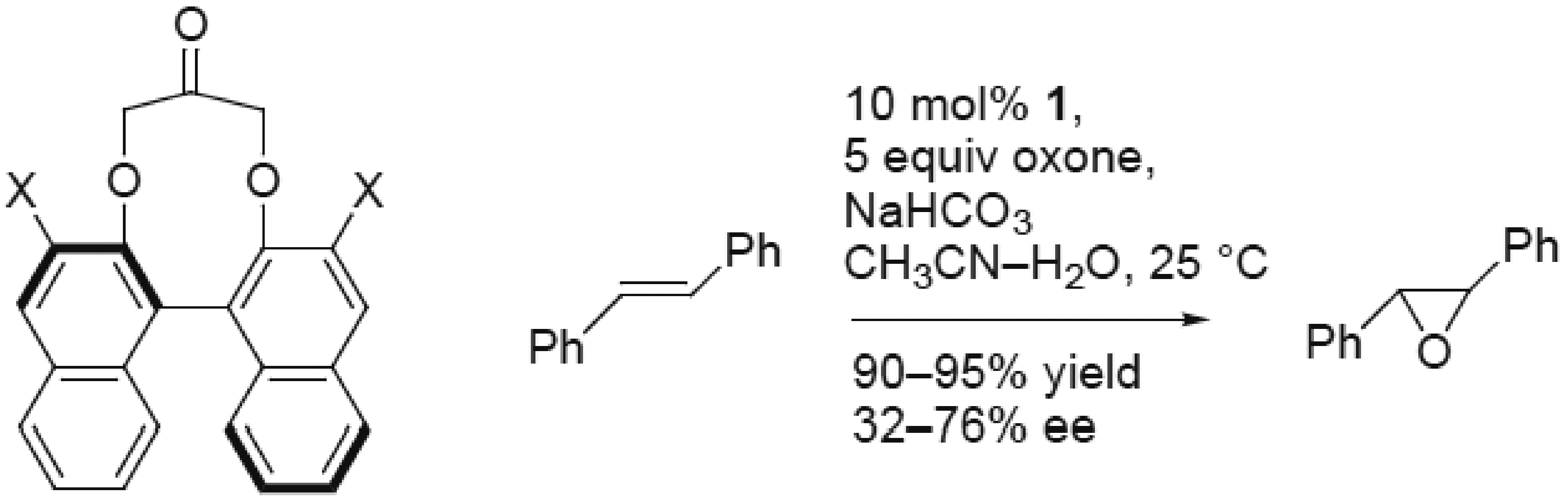
An Application of Shi Catalyst

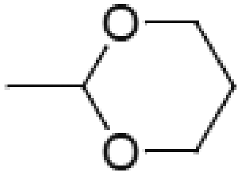


catalyst, Oxone,
$CH_2(OMe)_2/MeCN/H_2O$,
pH 10.5, 0 °C, 2 h

67%, >10:1 dr

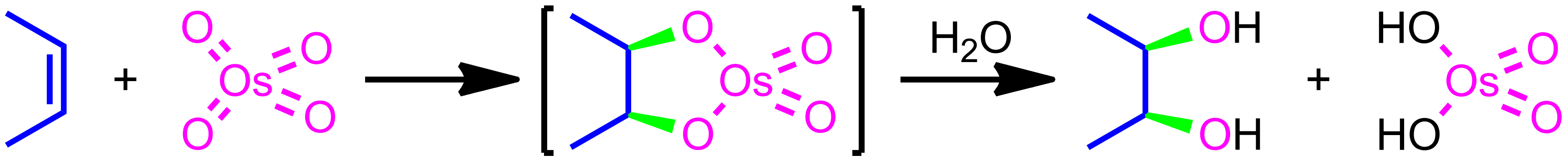
Chiral Dioxirane from BINOL



1	X = H	47% ee	**5**	X = Me	56% ee
2	X = Cl	76% ee	**6**	X = CH_2OCH_3	66% ee
3	X = Br	75% ee	**7**	X = 	71% ee
4	X = I	32% ee	**8**	X = $SiMe_3$	44% ee

Dihydroxylation of Olefins

- Dihydroxylation with Osmium Tetroxide (OsO_4)



Os (VIII)
ectrophilic,
large reagent

Os (VI)
Diastereospecific

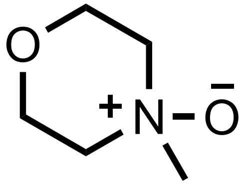
cis-1,2-diol

Os (VI)

- OsO_4 is an **electrophilic** reagent, and it behaves as a **large** reagent.
- **Strained, unhindered** olefins react faster than unstrained, sterically hindered olefins.
- **Electron-rich** olefins react faster than electron-deficient olefins.
- **Diastereospecific**, with attack on the C=C from the least hindered face.

➢ OsO_4 is expensive, volatile（挥发性的）, and toxic.

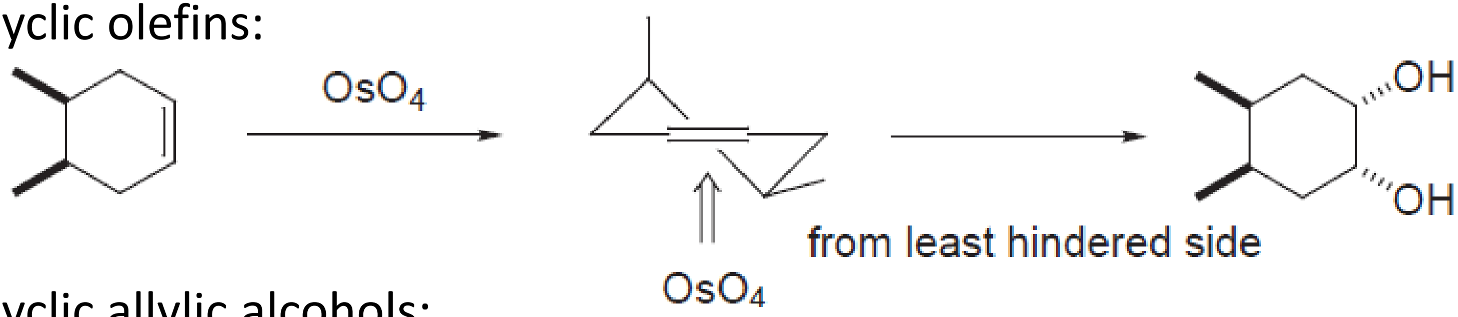
Cooxidants:



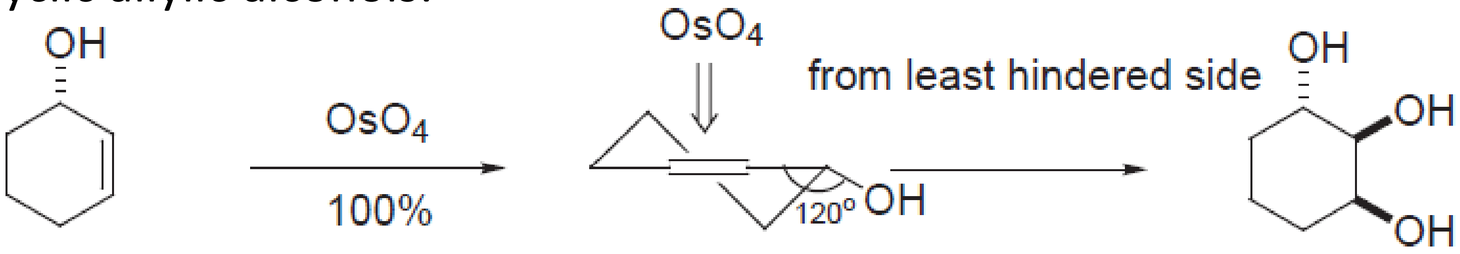
$K_3Fe(CN)_6$

Diastereoselectivity

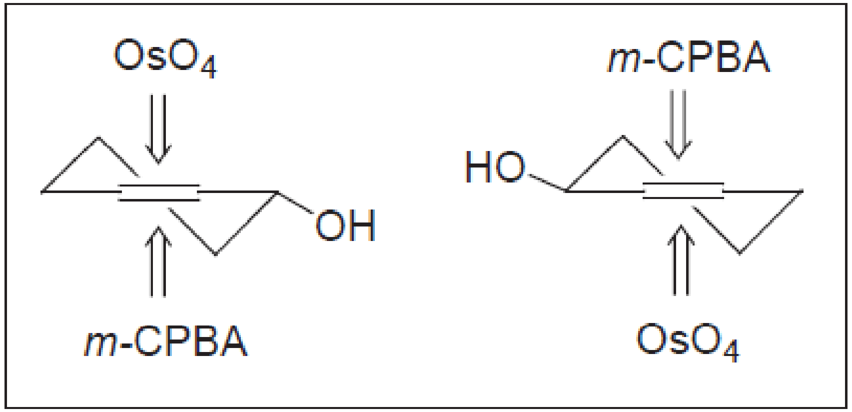
- ☐ Endocyclic olefins:

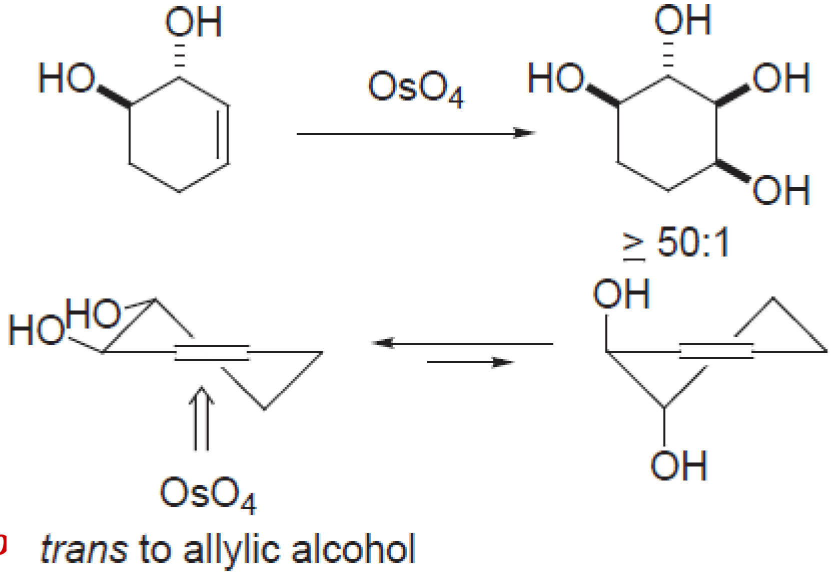


- ☐ Endocyclic allylic alcohols:



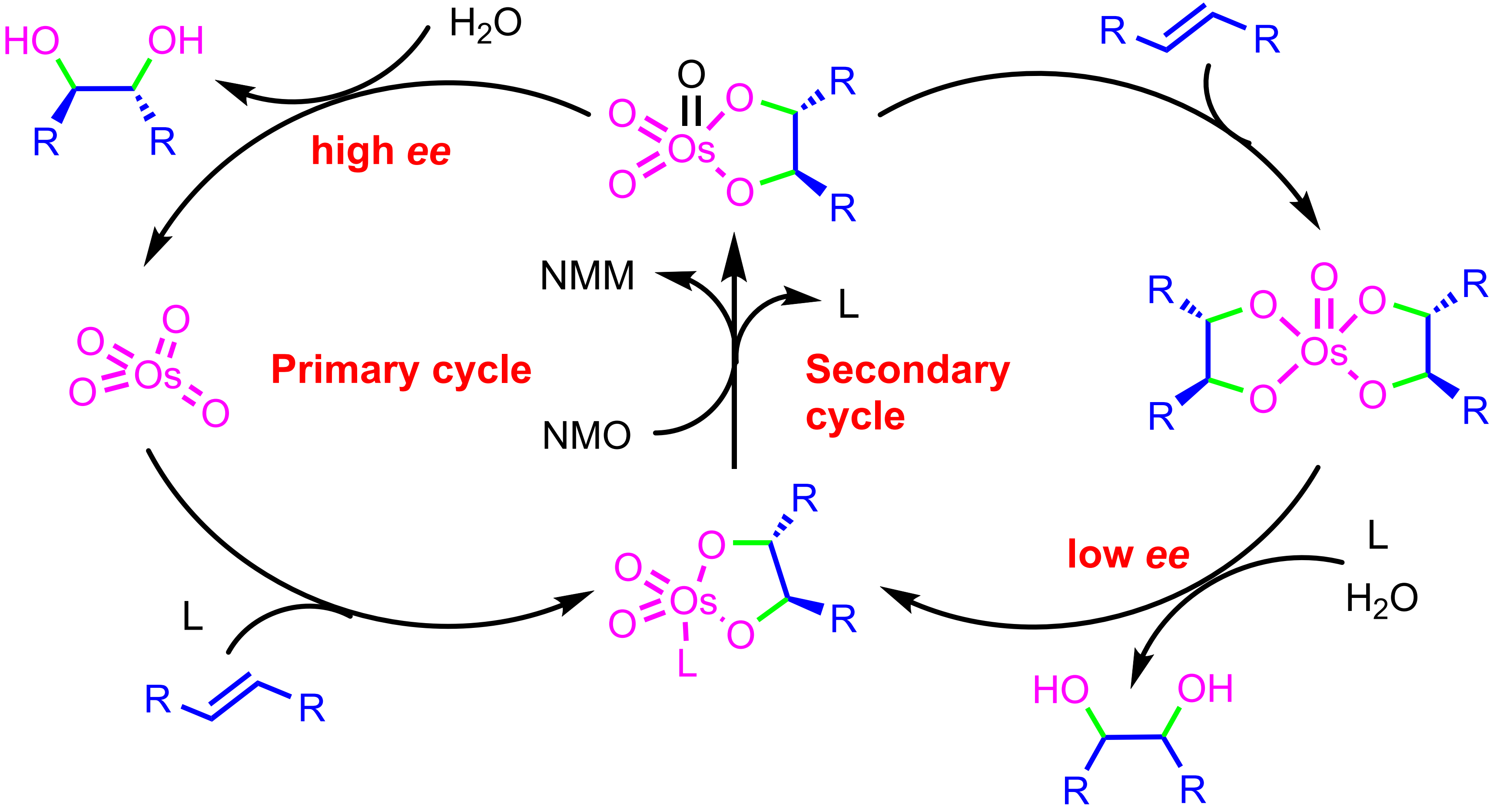
Note: *m*-CPBA comes in *cis*, but OsO_4 comes in *trans* to the allylic –OH.



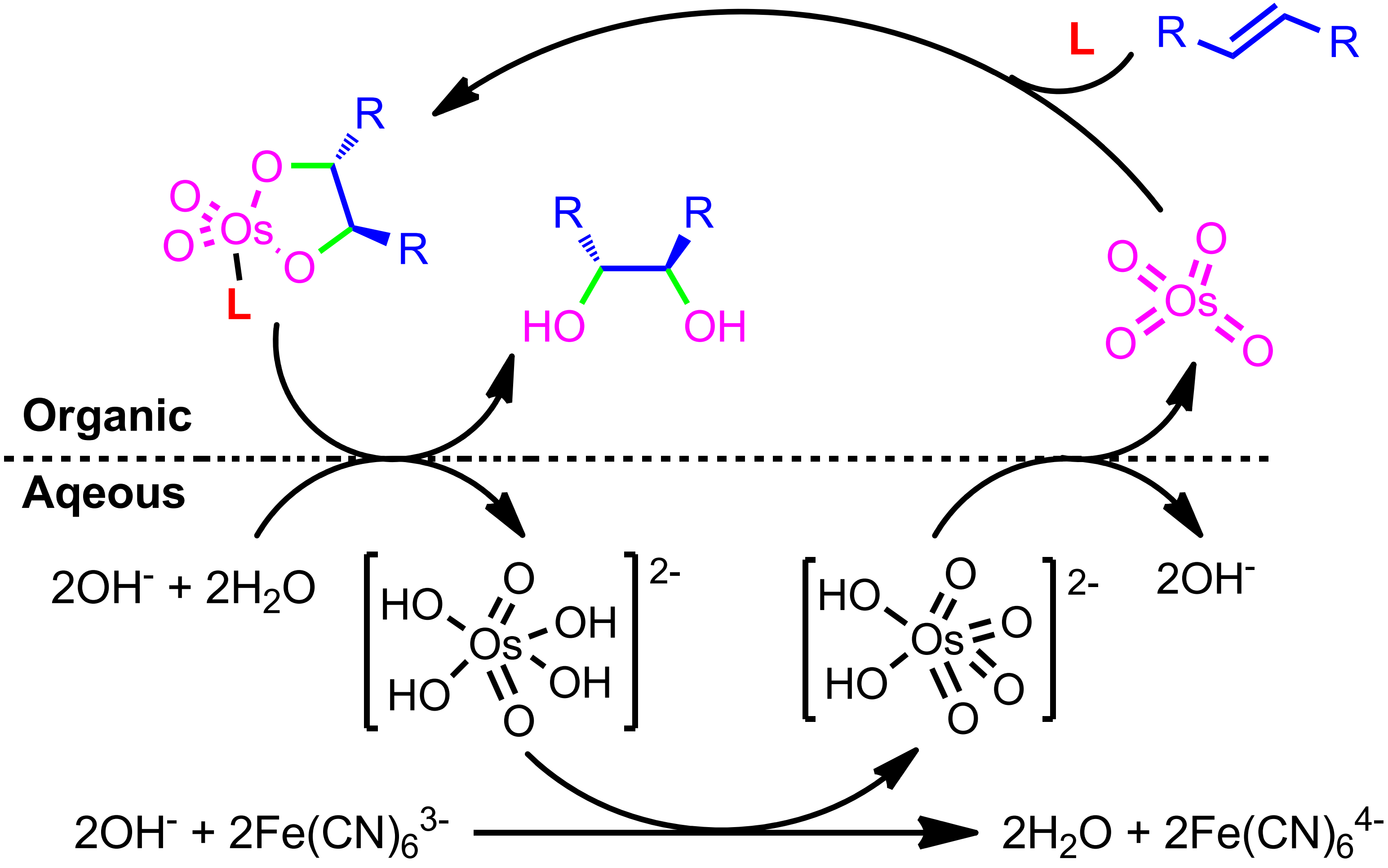


Sharpless Asymmetric Dihydroxylation (AD)

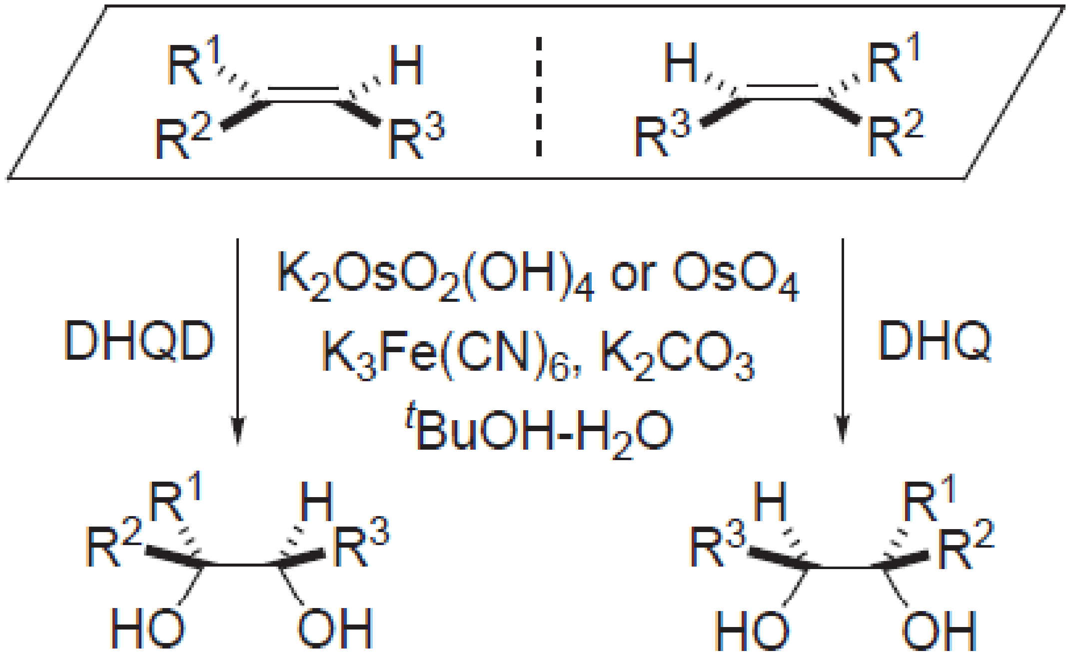
- Using NMO as the Cooxidant



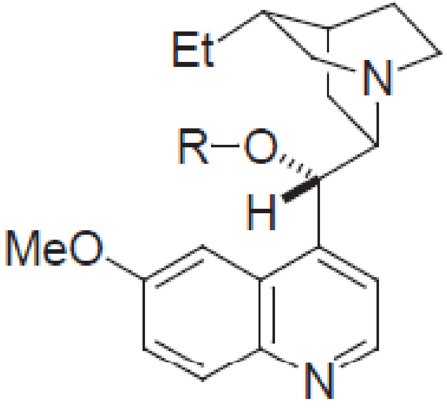
Using $K_3Fe(CN)_6$ as the Cooxidant



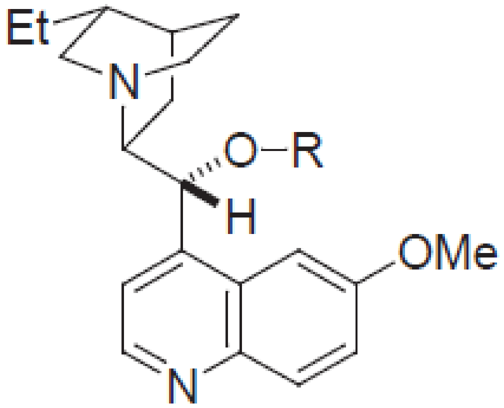
Mnemonic Device（记忆模型）



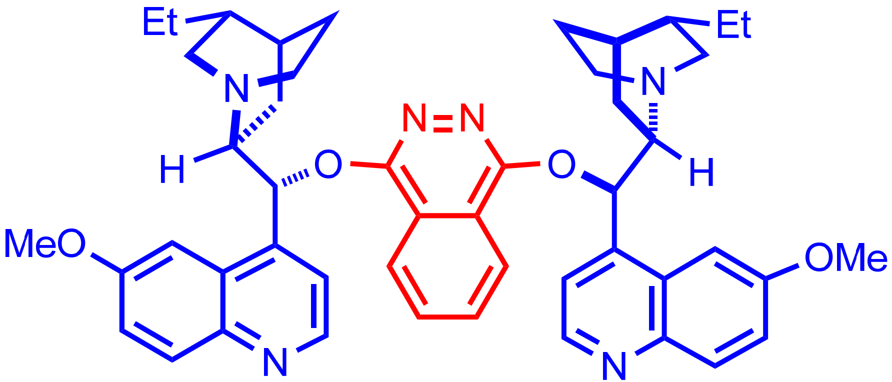
DHQD: dihydroquinidine
(R = H)



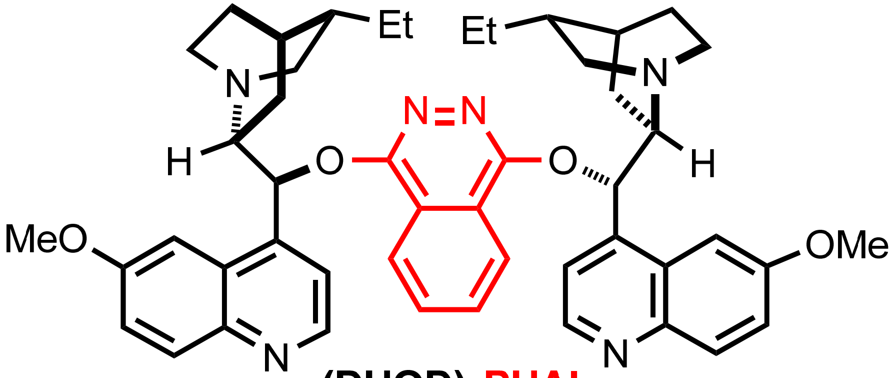
DHQ: dihydroquinine
(R = H)



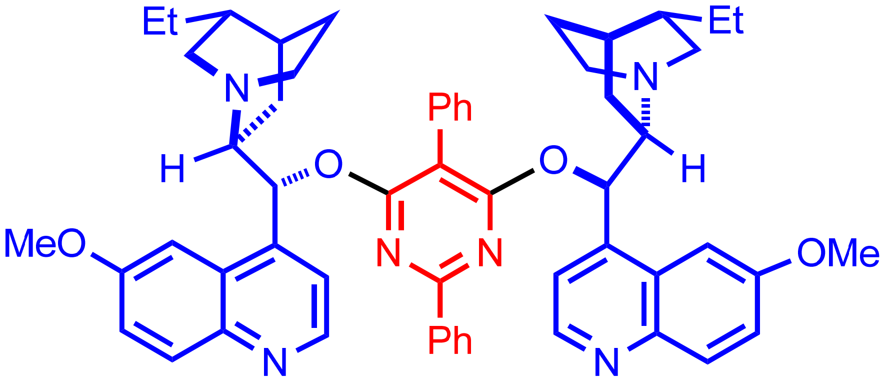
C$_2$-Symmetric, Pseudo-Enantiomeric Ligands



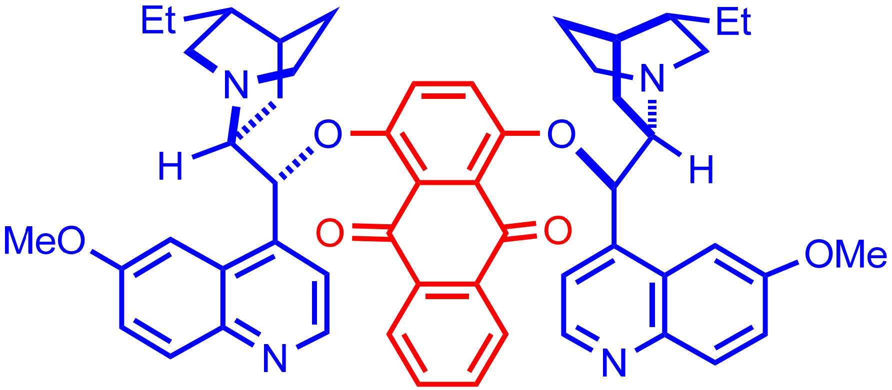
(DHQ)$_2$PHAL



(DHQD)$_2$PHAL



(DHQ)$_2$PYR



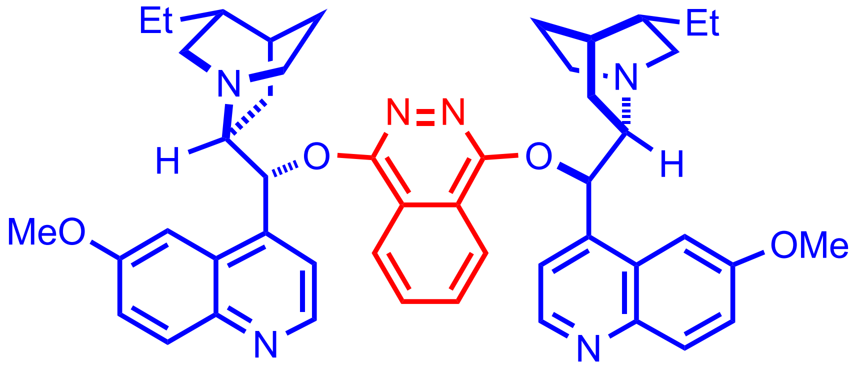
(DHQ)$_2$AQN

AD-mix Reagents

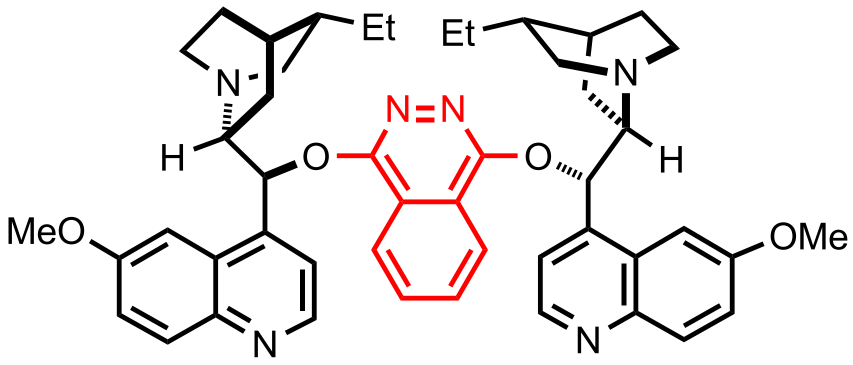
- 1.4 g AD-mix-α will oxidize 1 mmol olefin, contains: 0.98 g $K_3Fe(CN)_6$ (3 mmol), 0.41 g K_2CO_3 (3 mmol), 0.0078 g $(DHQ)_2PHAL$ (0.01 mmol), 0.00074 g $K_2OsO_2(OH)_4$ (0.002 mmol)

- AD-mix-β contains $(DHQD)_2PHAL$ as the ligand.

- Conditions: *t*-BuOH/H_2O (1:1), 0 °C, 6-24 h. For non-terminal olefins, the addition of $MeSO_2NH_2$ leads to faster reaction.

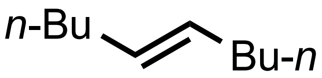
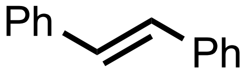
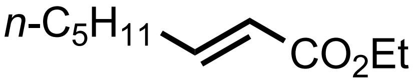
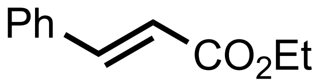
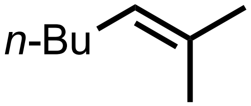
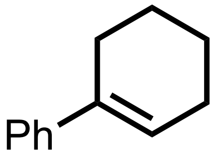
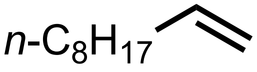


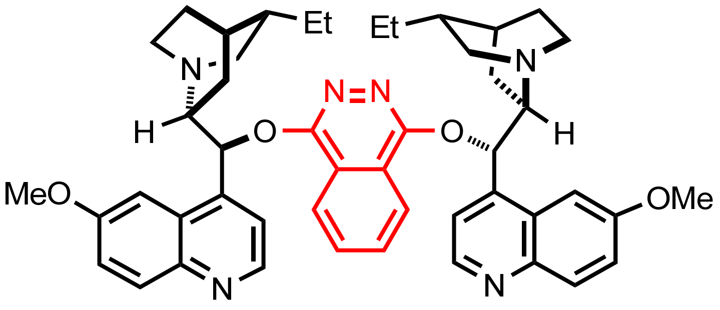
$(DHQ)_2PHAL$



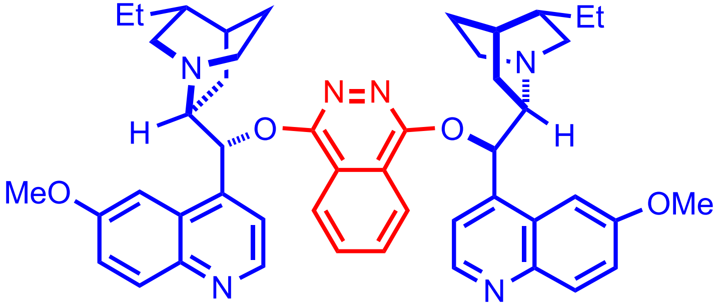
$(DHQD)_2PHAL$

Sharpless AD of Olefins

olefin	ligand	ee (%)	configuration
	$(DHQD)_2PHAL$	97	*R*,*R*
	$(DHQ)_2PHAL$	93	*S*,*S*
	$(DHQD)_2PHAL$	>99	*R*,*R*
	$(DHQ)_2PHAL$	>99	*S*,*S*
	$(DHQD)_2PHAL$	99	2*S*,3*R*
	$(DHQ)_2PHAL$	96	2*R*,3*S*
	$(DHQD)_2PHAL$	97	2*S*,3*R*
	$(DHQ)_2PHAL$	95	2*R*,3*S*
	$(DHQD)_2PHAL$	98	*R*
	$(DHQ)_2PHAL$	95	*S*
	$(DHQD)_2PHAL$	99	*R*,*R*
	$(DHQ)_2PHAL$	97	*S*,*S*
	$(DHQD)_2PHAL$	97	*R*
	$(DHQ)_2PHAL$	97	*S*
	$(DHQD)_2PHAL$	84	*R*
	$(DHQ)_2PHAL$	80	*S*

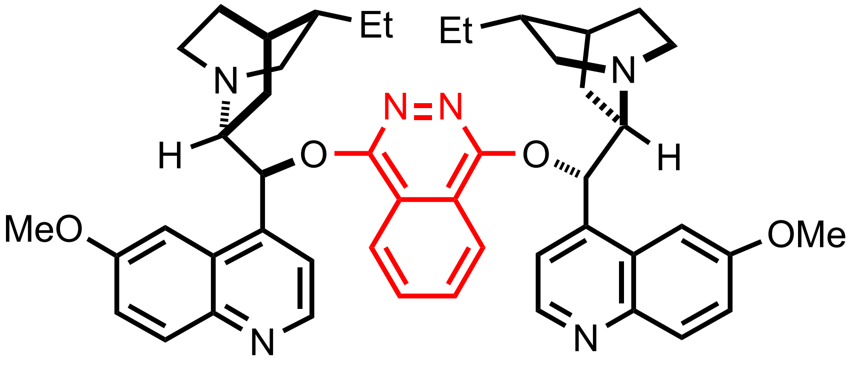


$(DHQD)_2PHAL$

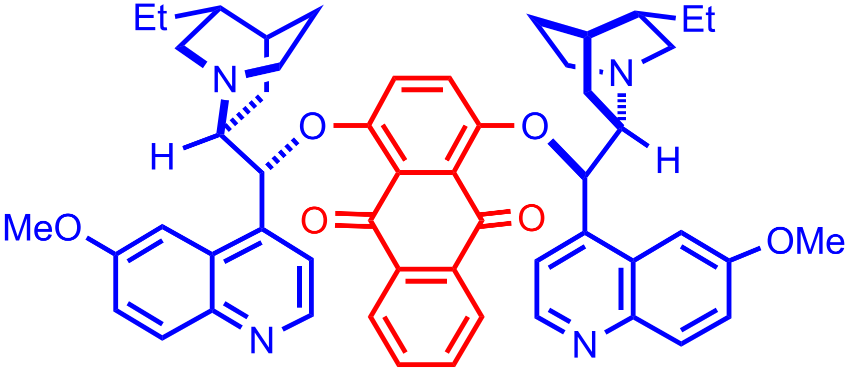


$(DHQ)_2PHAL$

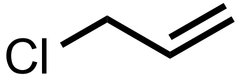
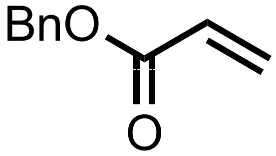
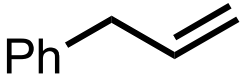
Ligand $(DHQD)_2AQN$



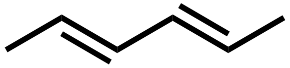
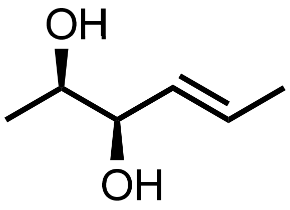
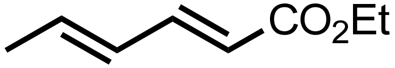
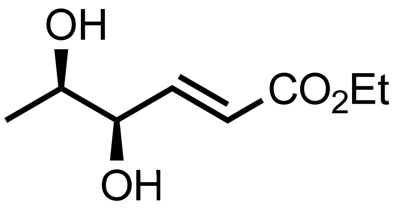
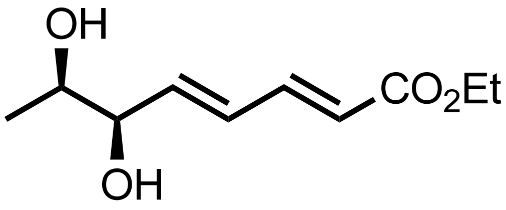
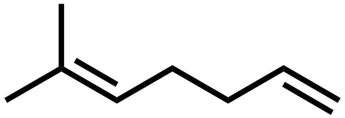
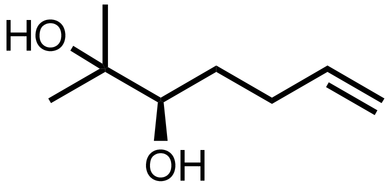
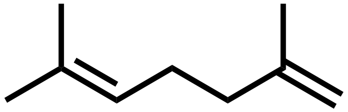
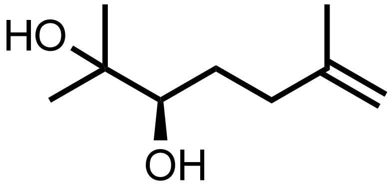
$(DHQD)_2$PHAL



$(DHQ)_2$AQN

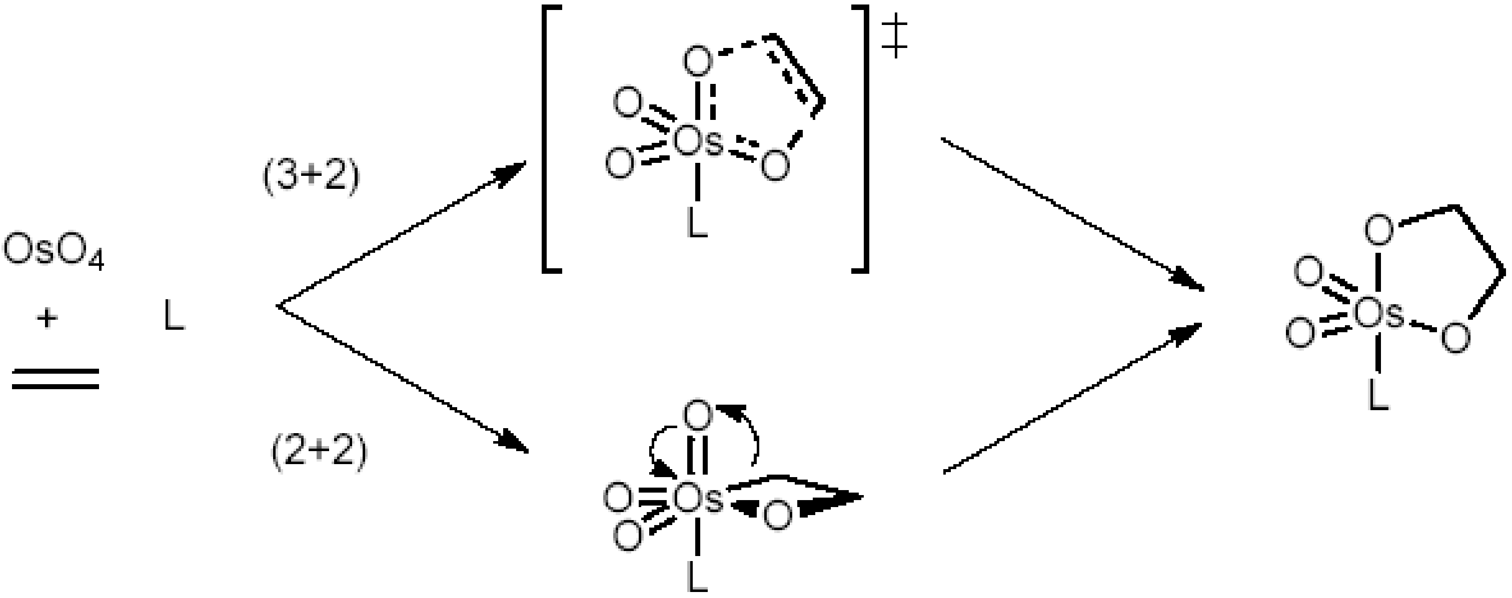
	$(DHQD)_2$PHAL	$(DHQD)_2$AQN
	63% *ee*	90% *ee*
	77% *ee*	88% *ee*
	44% *ee*	78% *ee*

Regioselectivity of AD with Dienes: Using $(DHQD)_2PHAL$ as the Ligand

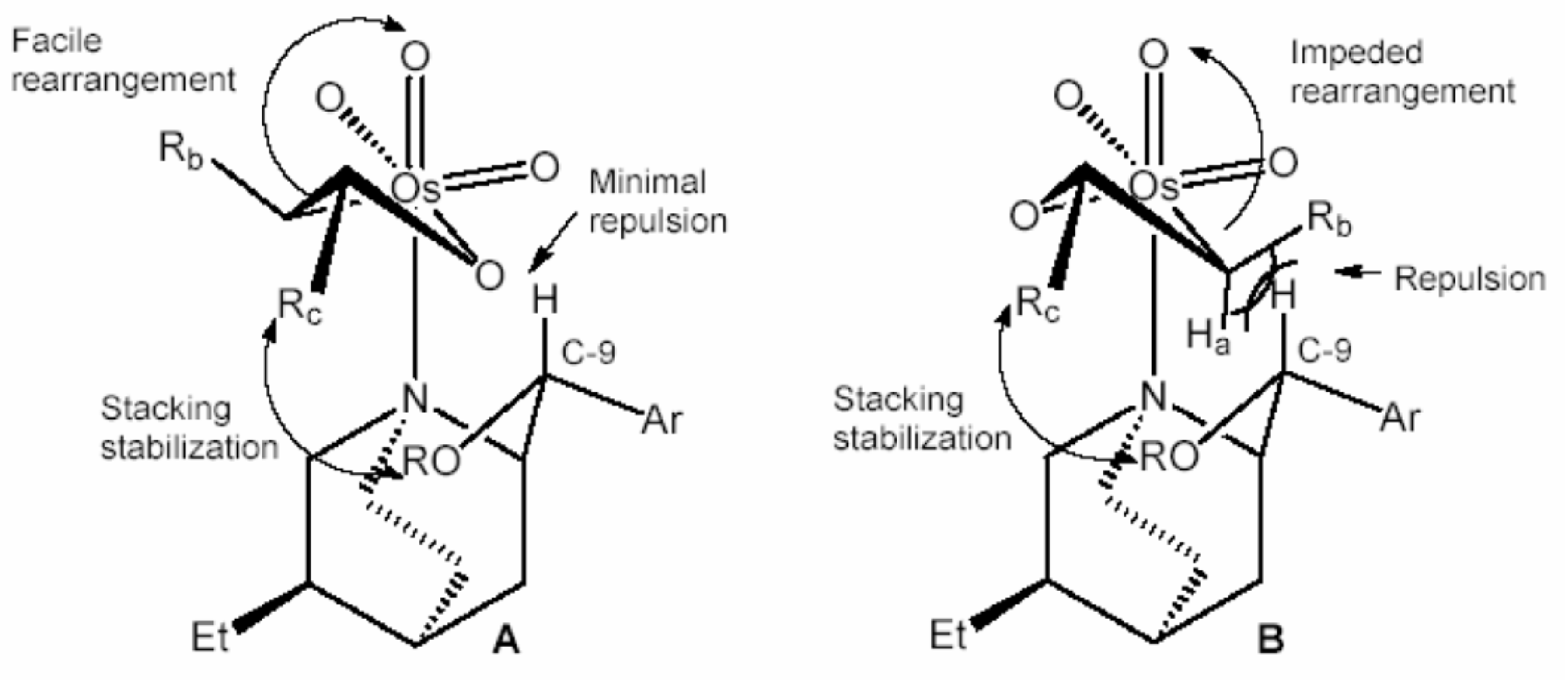
olefin	product	yield (%)	*ee* (%)
		78	93
		78	92
		93	95
		73	98
		70	98

Origin of the Enantioselectivity

- ❑ The explanation of the high enantioselectivity in the AD reaction has been divided into two proposals, one by Sharpless and another by Corey.

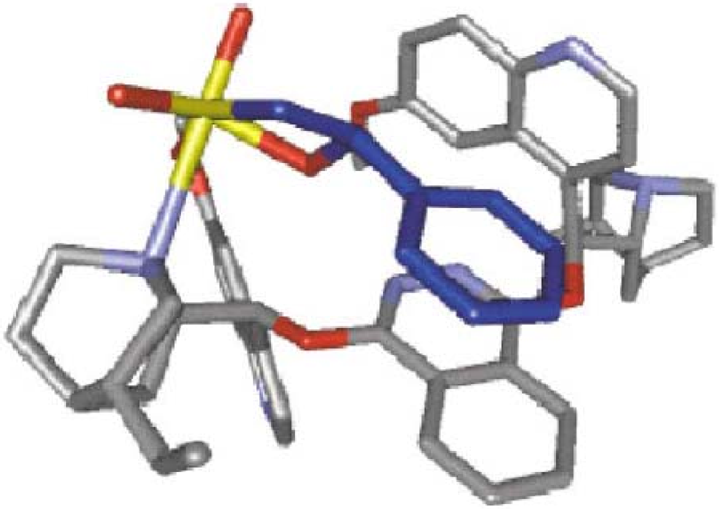


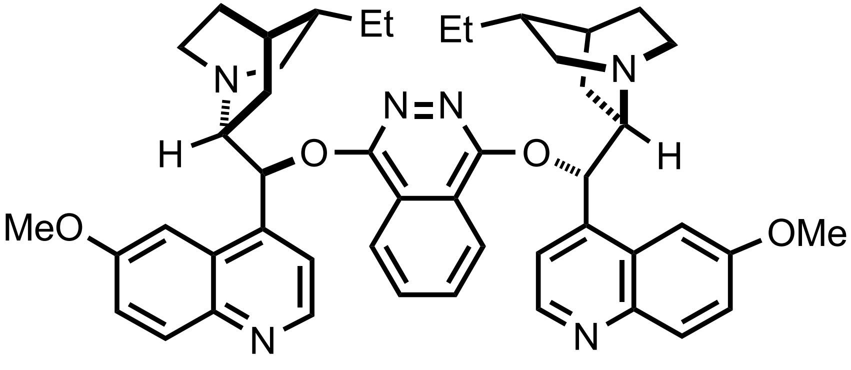
The Sharpless Model



- ☐ Proposed intermediates in the AD process using DHQD ligands

3-Dimensional Model

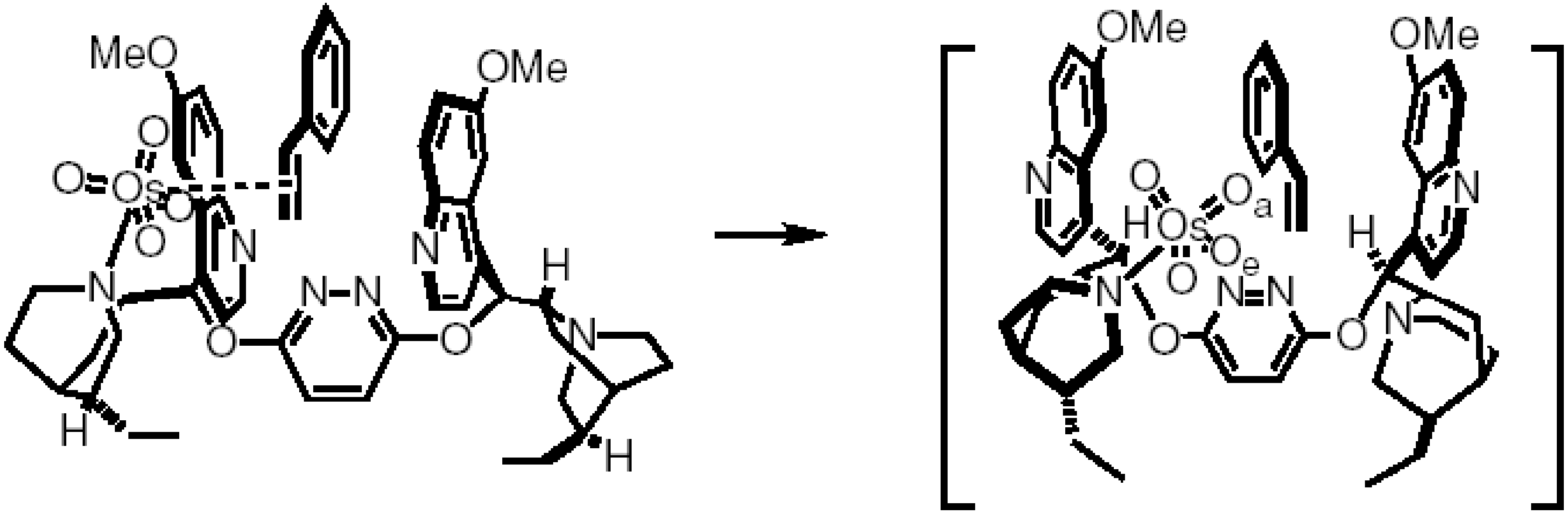




(DHQD)$_2$PHAL

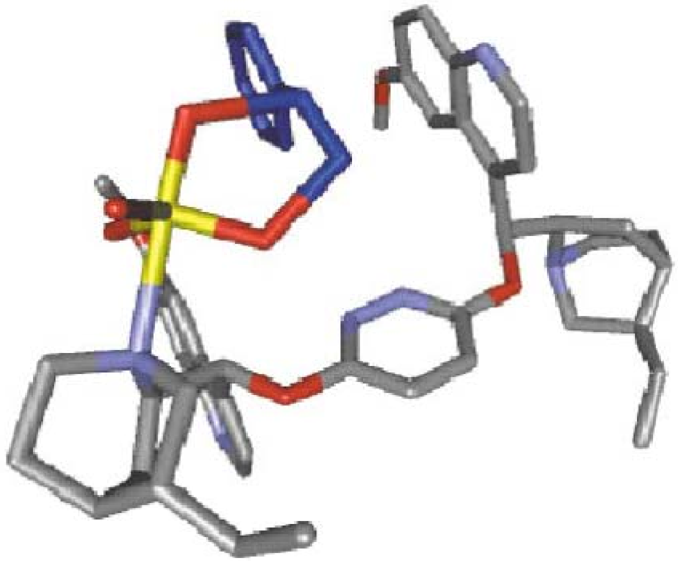
The (DHQD)$_2$PHAL-bound osmaoxetane derived from styrene

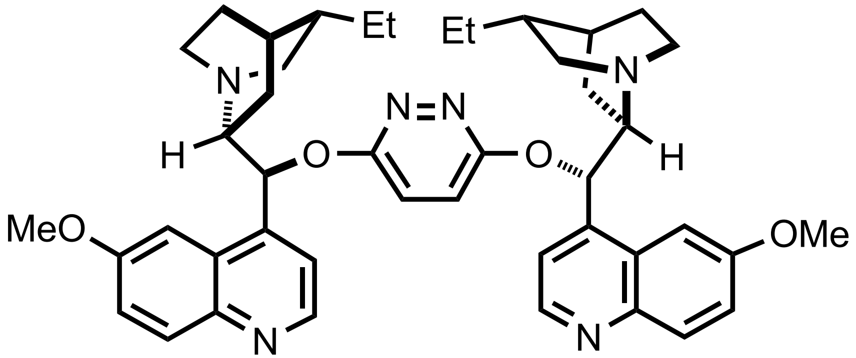
The Corey Model



Corey proposes a U-shaped binding pocket

The Corey Model

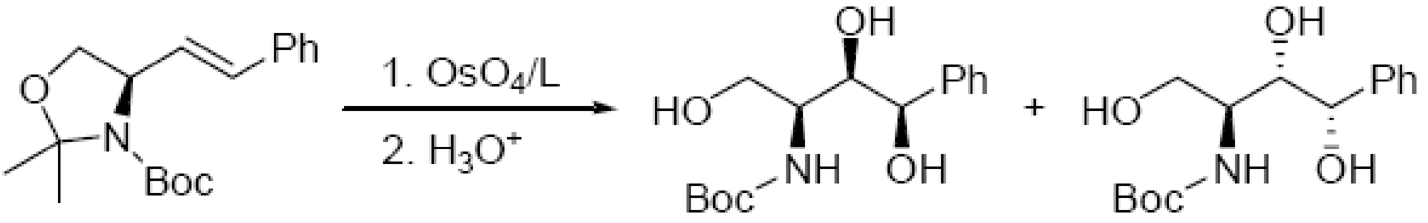




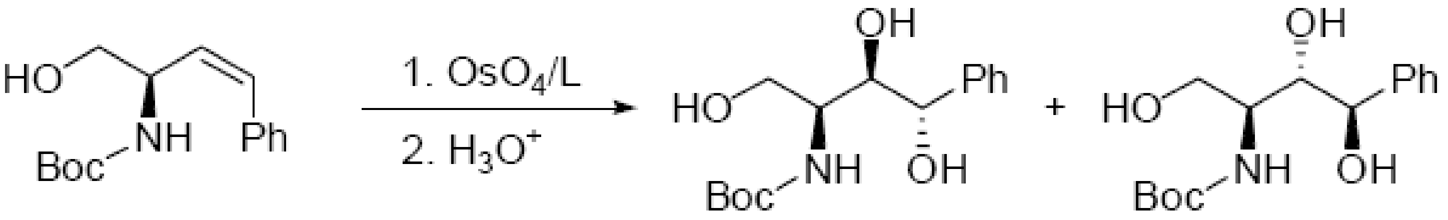
$(DHQD)_2PDZ$

- ❑ A 3-dimensional representation of the transition state for **styrene in the $(DHQD)_2$PDZ-OsO_4 complex** calculated by combined quantum mechanics: molecular mechanics

The Double Diastereocontrolled AD

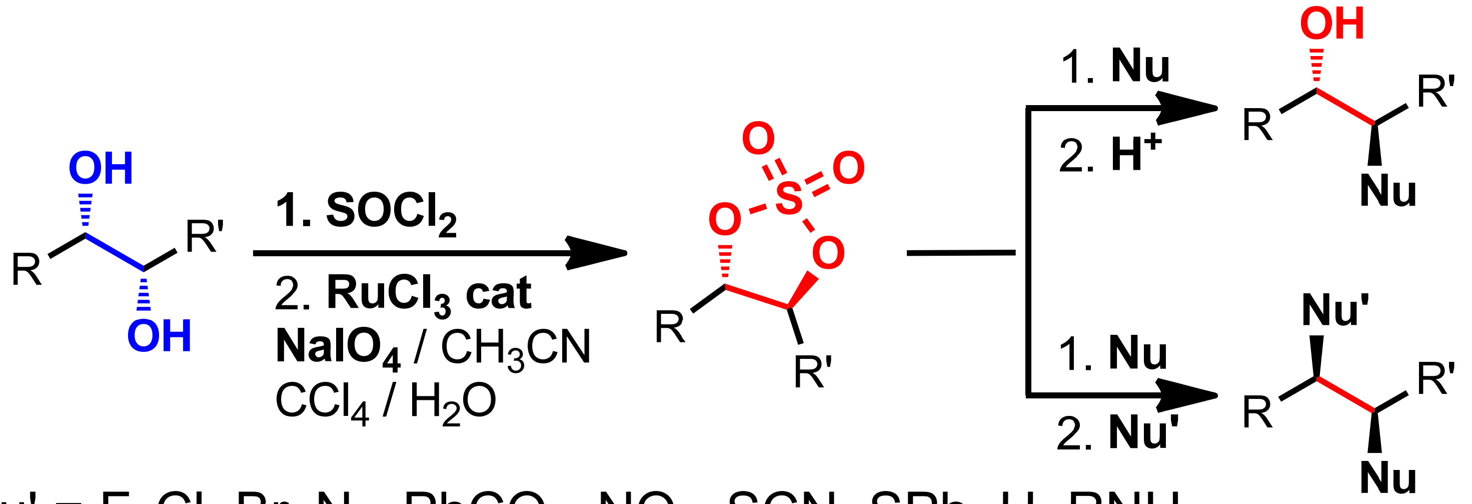


Ligand	Yield (%)	Ratio
none	71	45:55
$(DHQ)_2PHAL$	70	1:99
$(DHQD)_2PHAL$	60	99:1

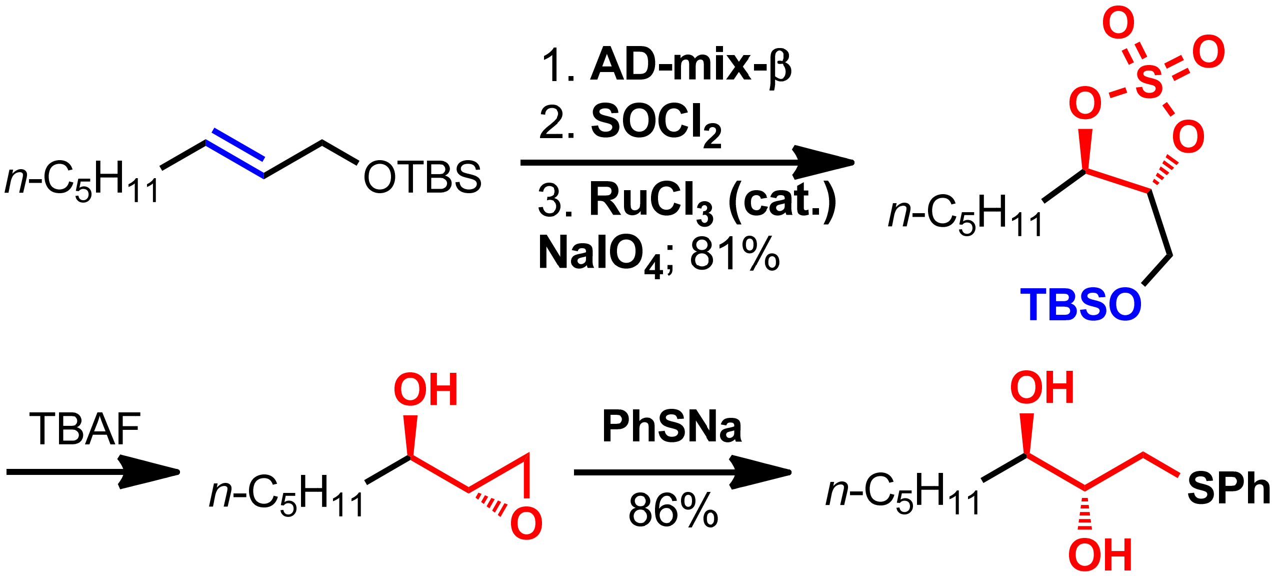


Ligand	Yield (%)	Ratio
none	92	71:29
$(DHQ)_2PHAL$	55	86:14
$(DHQD)_2PHAL$	55	16:84

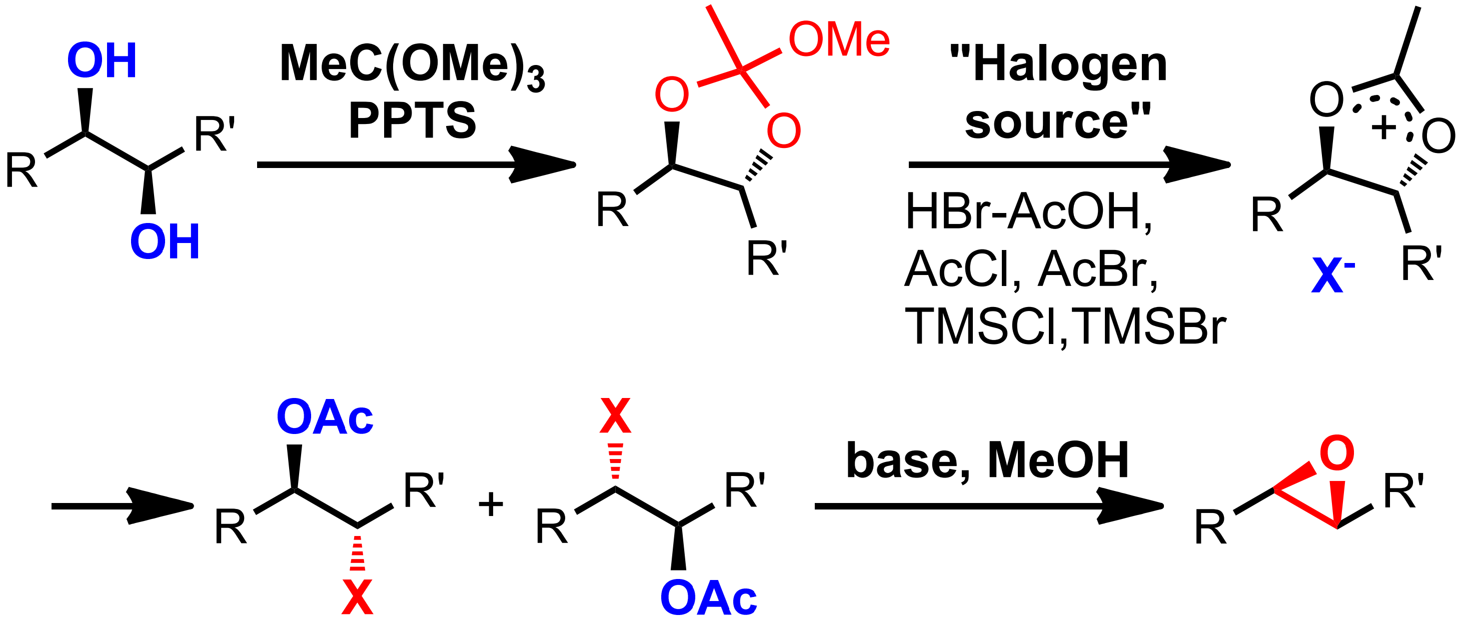
Cyclic Sulfates

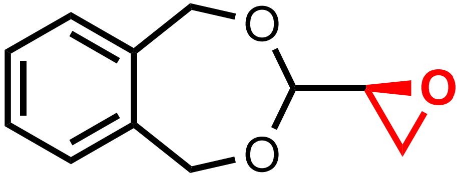


- ❑ Nu, Nu' = F, Cl, Br, N_3, $PhCO_2$, NO_3, SCN, SPh, H, RNH_2, ...



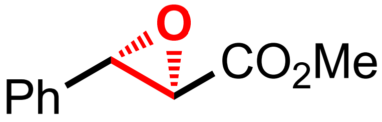
Epoxides from Diols



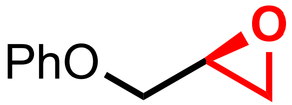


96% *ee*

97% *ee*

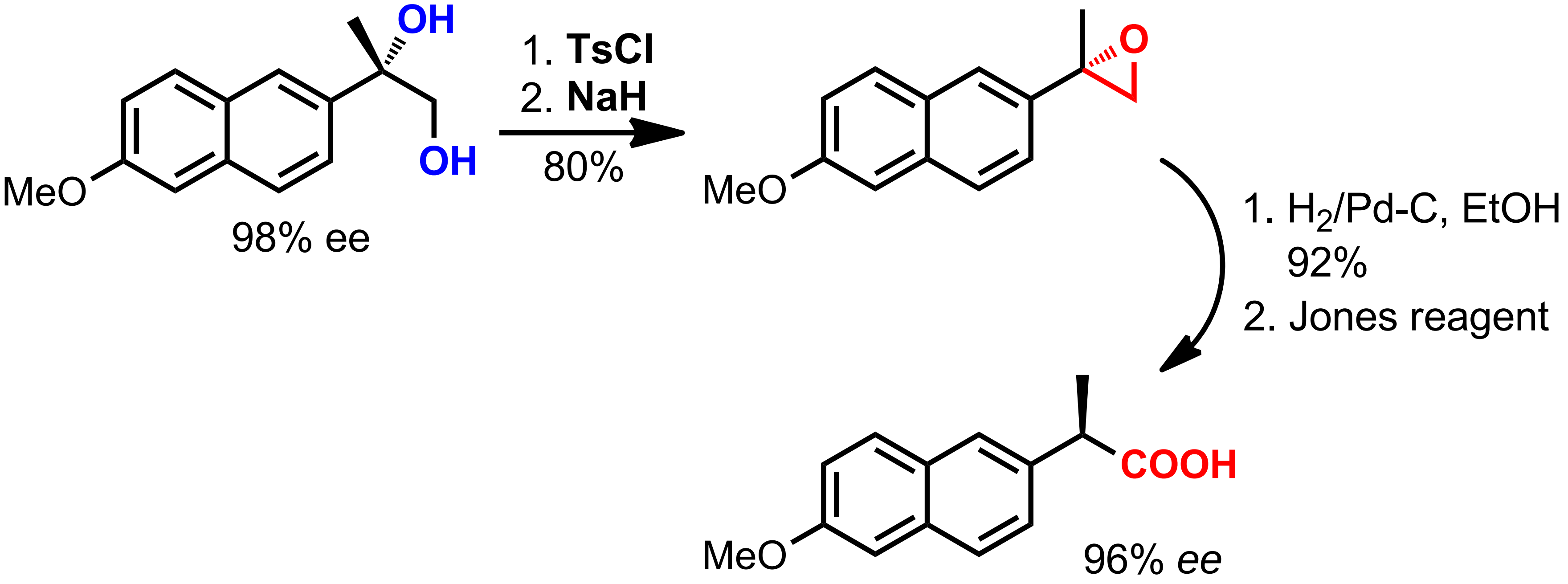


99% *ee*



89% *ee*

Epoxides from Diols



98% ee

1. **TsCl**
2. **NaH**

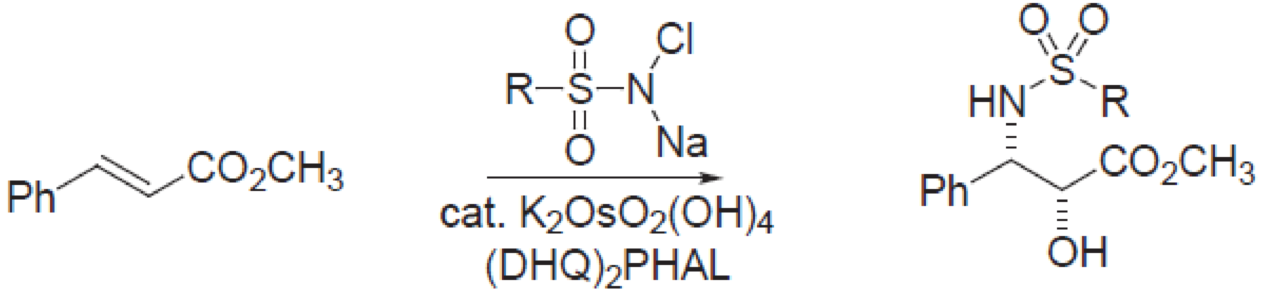
80%

1. H_2/Pd-C, EtOH
   92%
2. Jones reagent

96% *ee*

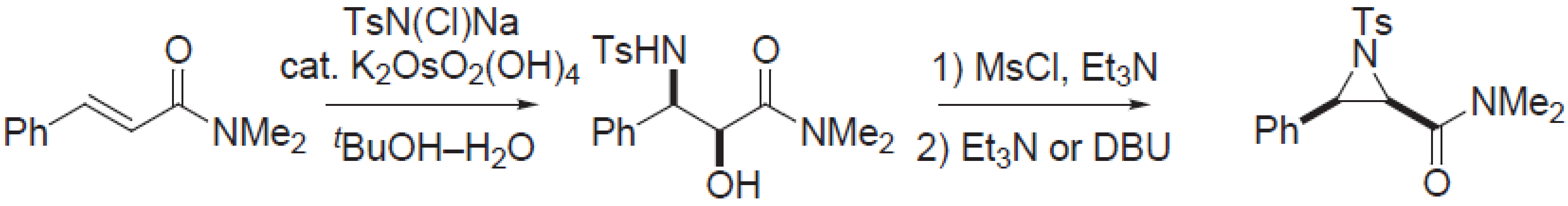
Sharpless Asymmetric Aminohydroxylation (AA): Sulfonamide Variant

- ❑ α,β-unsaturated esters:



R =			
p-Tol	1:1 $CH_3CN–H_2O$	81% ee (64%)	Reductive cleavage of sulfonamides requires harsh conditions (Birch reduction, Red-Al, or 33% HBr/AcOH).
Me	1:1 $^nPrOH–H_2O$	95% ee (65%)	
	1:1 $^nPrOH–H_2O$	70% ee (48%) 83:17 regioselectivity	← Sulfonamide cleaved with Bu_4NF in CH_3CN

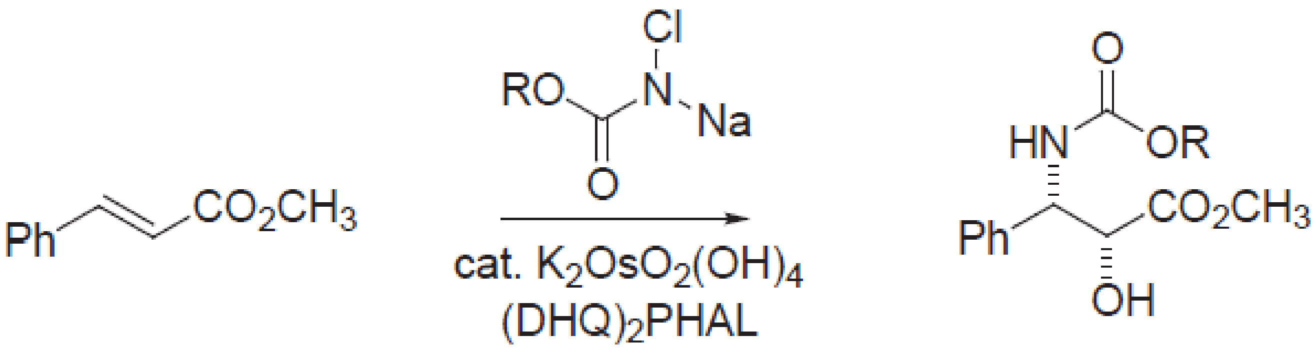
- ❑ α,β-unsaturated amides: no enantioselection, AA gives racemic products.
- ❑ Reaction works well without ligand.



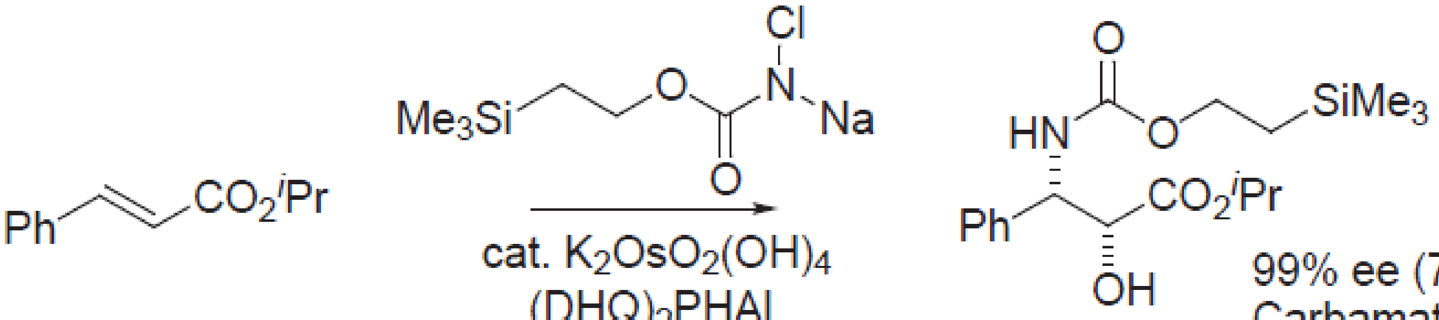
5:1 regioselectivity, racemic (94%)

Sharpless Asymmetric Aminohydroxylation (AA): Carbamate（氨基甲酸酯） Variant

- ☐ α,β-unsaturated esters:



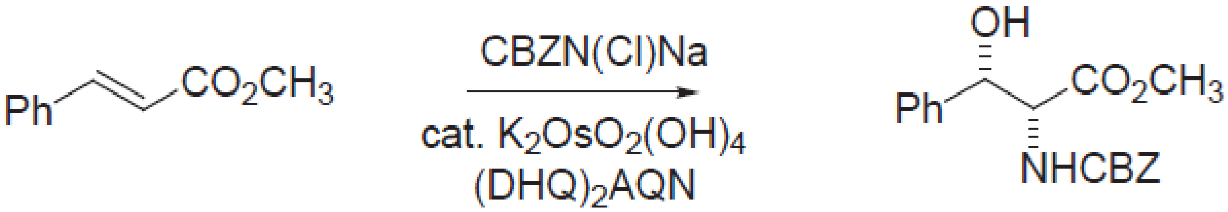
R =	Bn	1:1 ^{n}PrOH-H_2O	94% ee (65%)	← Amine can be deprotected by hydrogenolysis.
	Et	1:1 ^{n}PrOH-H_2O	99% ee (78%)	
	^{t}Bu	2:1 ^{n}PrOH-H_2O	78% ee (71%)	← Amine can be deprotected by acid.



99% ee (70%)
Carbamate cleaved with
Bu_4NF in CH_3CN.

Reversal of Regioselectivity Using $(DHQ)_2$AQN Ligand

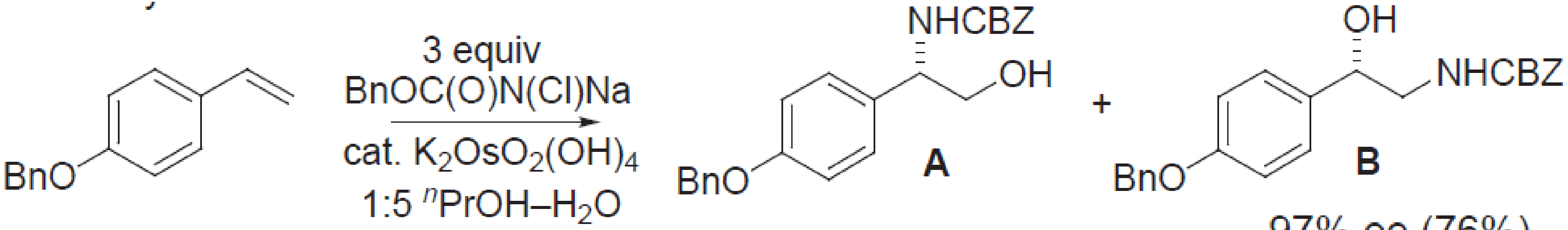
- ❑ α,β-unsaturated esters:



95% ee (58%)
79:21 regioselectivity

- ➢ Reversal of regioselectivity using $(DHQ)_2$AQN ligand.

- ❑ Styrenes:



97% ee (76%)
88:12 **A**:B

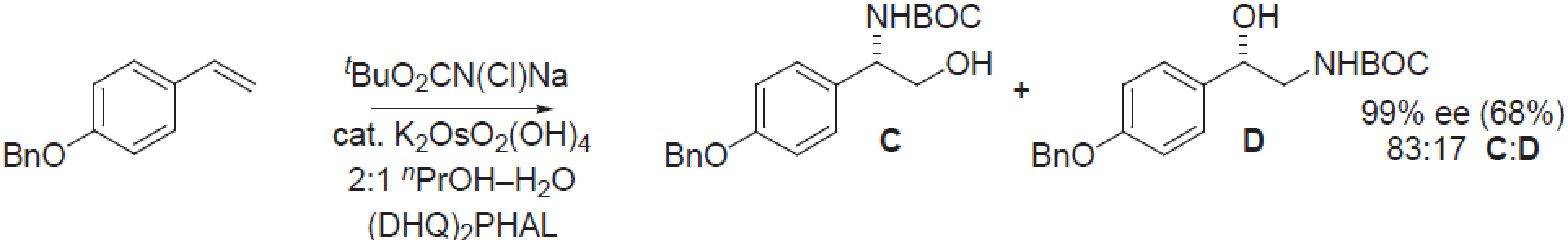
- ➢ Influence of ligand and solvent on regioselectivity:

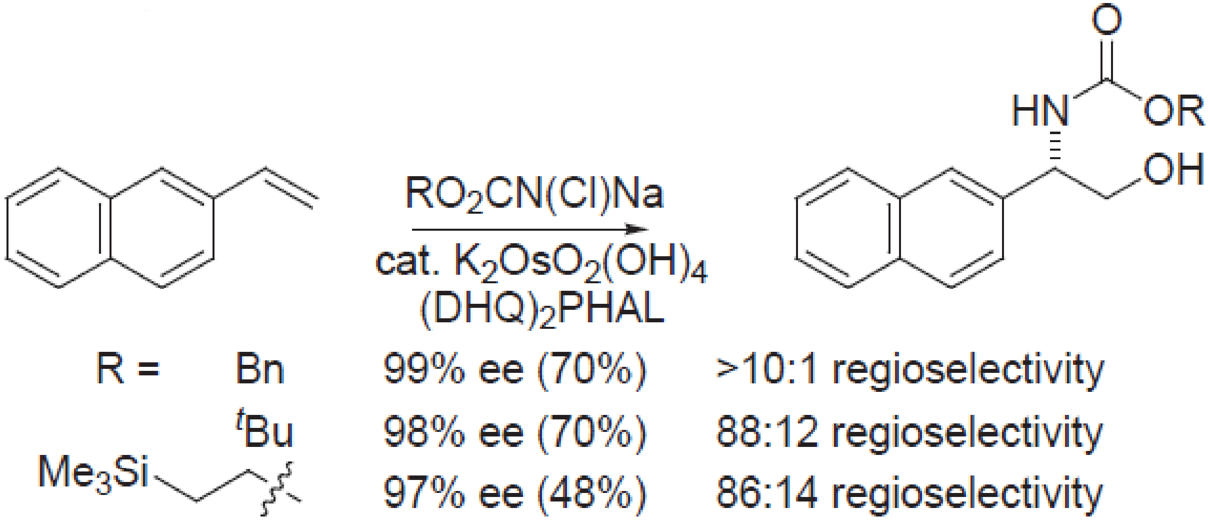
ligand	solvent	**A:B**
$(DHQ)_2$PHAL	$^nPrOH–H_2O$	88:12
$(DHQ)_2$AQN	$CH_3CN–H_2O$	25:75

- However, enantioselectivities for **B** regioisomers are poor (0–80% ee).

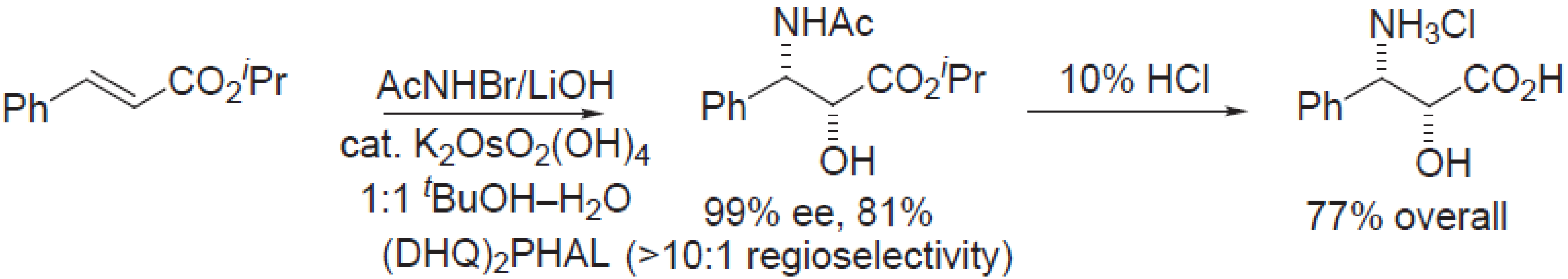
Reversal of Regioselectivity Using $(DHQ)_2AQN$ Ligand: *t*-Bu Carbamate

- ❑ *t*-Bu carbamate based AA affords slightly poorer regioselectivities and yields compared to benzyl carbamate series, but enantioselectivities approach 100% in both cases.





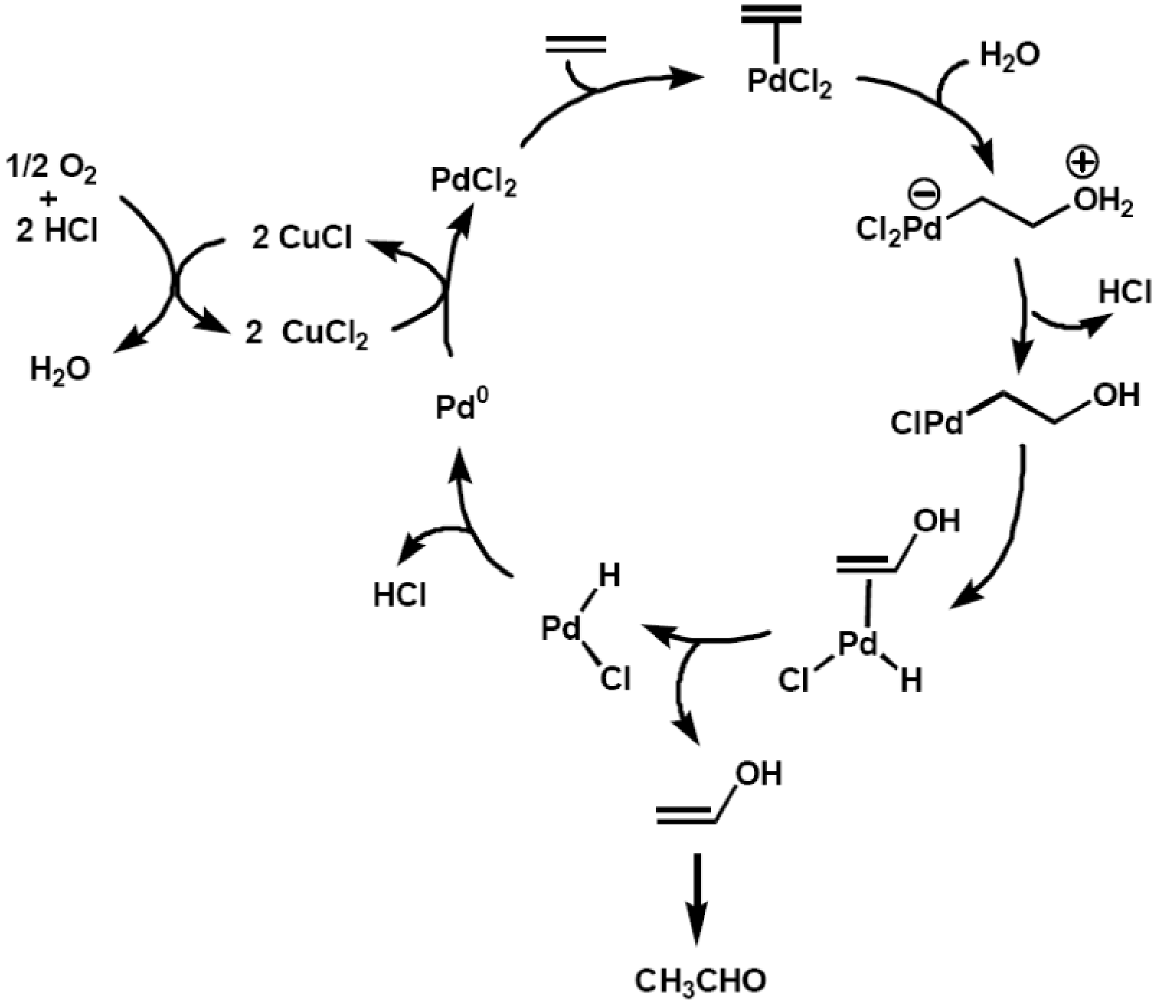
Amide Variant



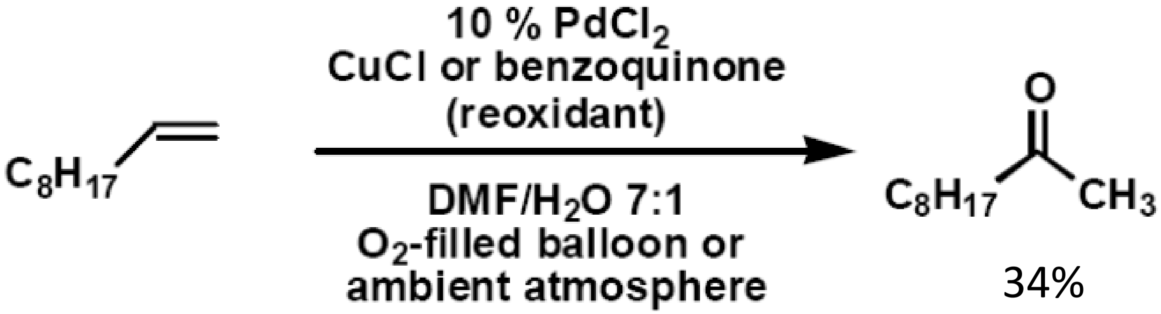
Wacker Oxidation

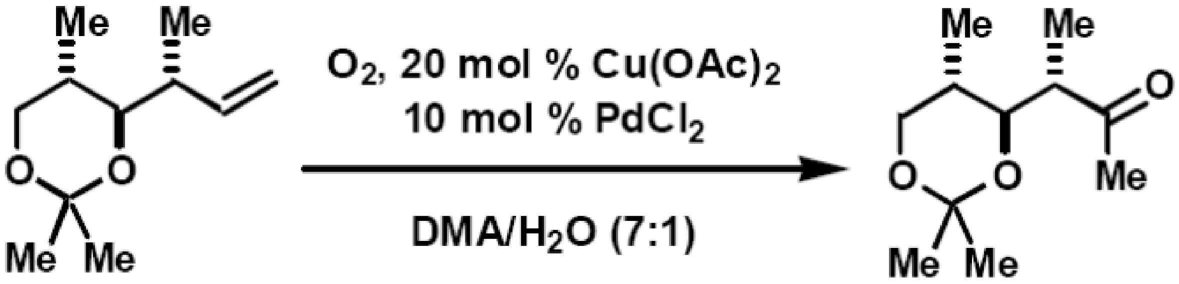
- ❑ Wacker process for the commercial production of acetaldehyde:

- ❑ Mechanism:



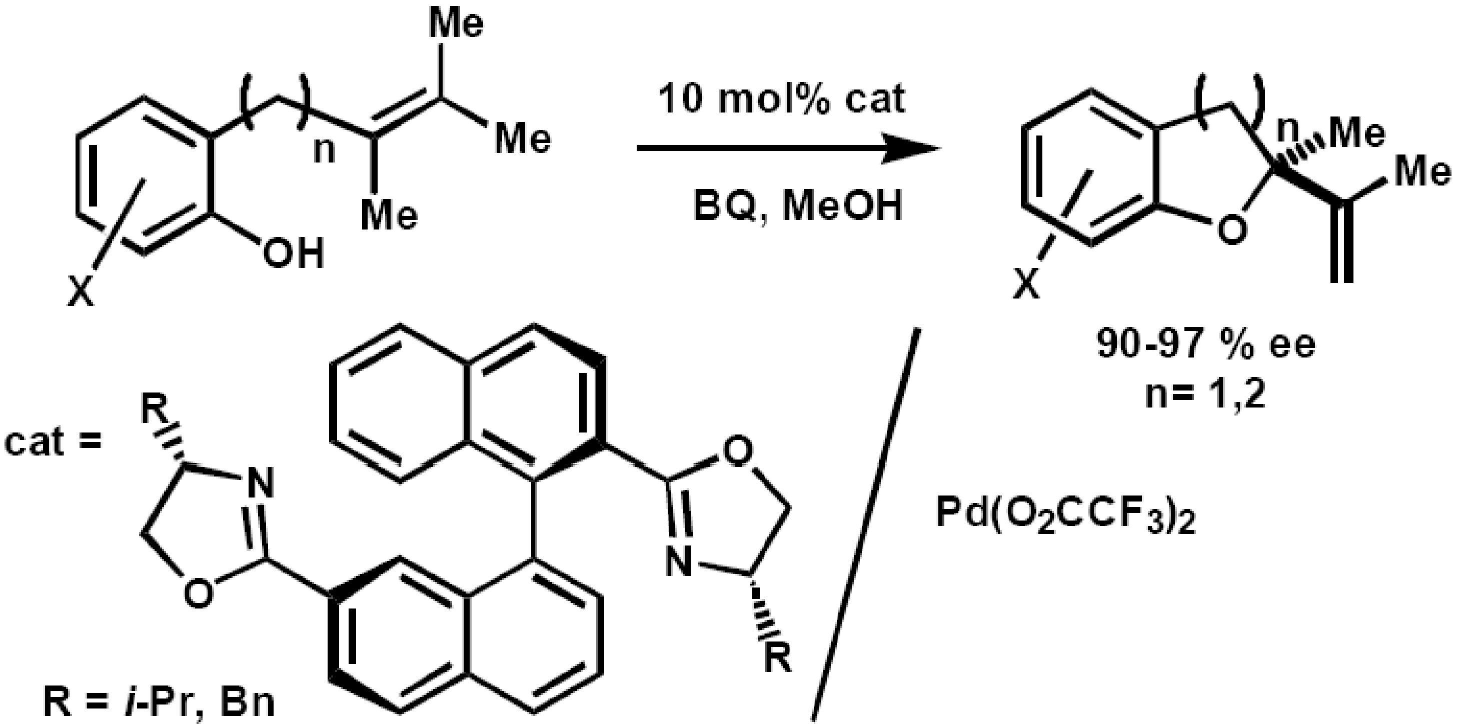
Wacker-Type Reactions



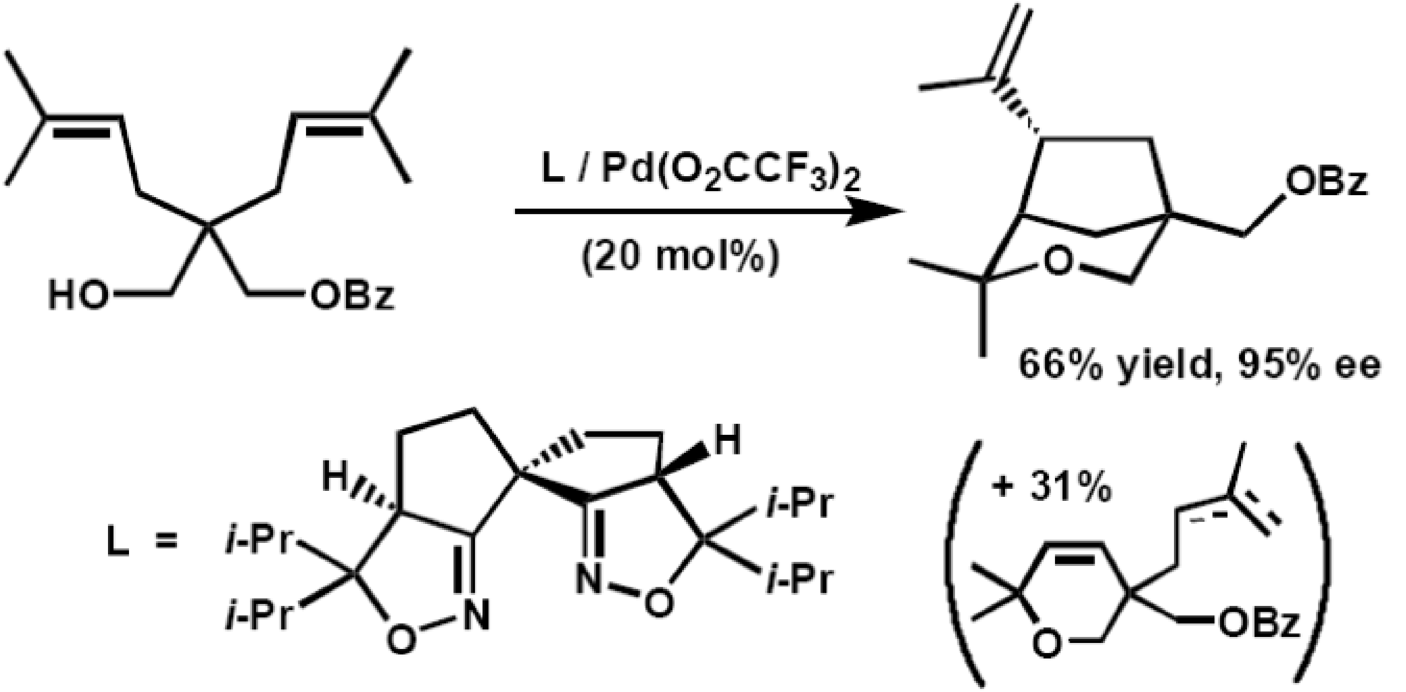


Smith *JACS* **1999**, *121*, 10468

Enantioselective Wacker-Type Reactions

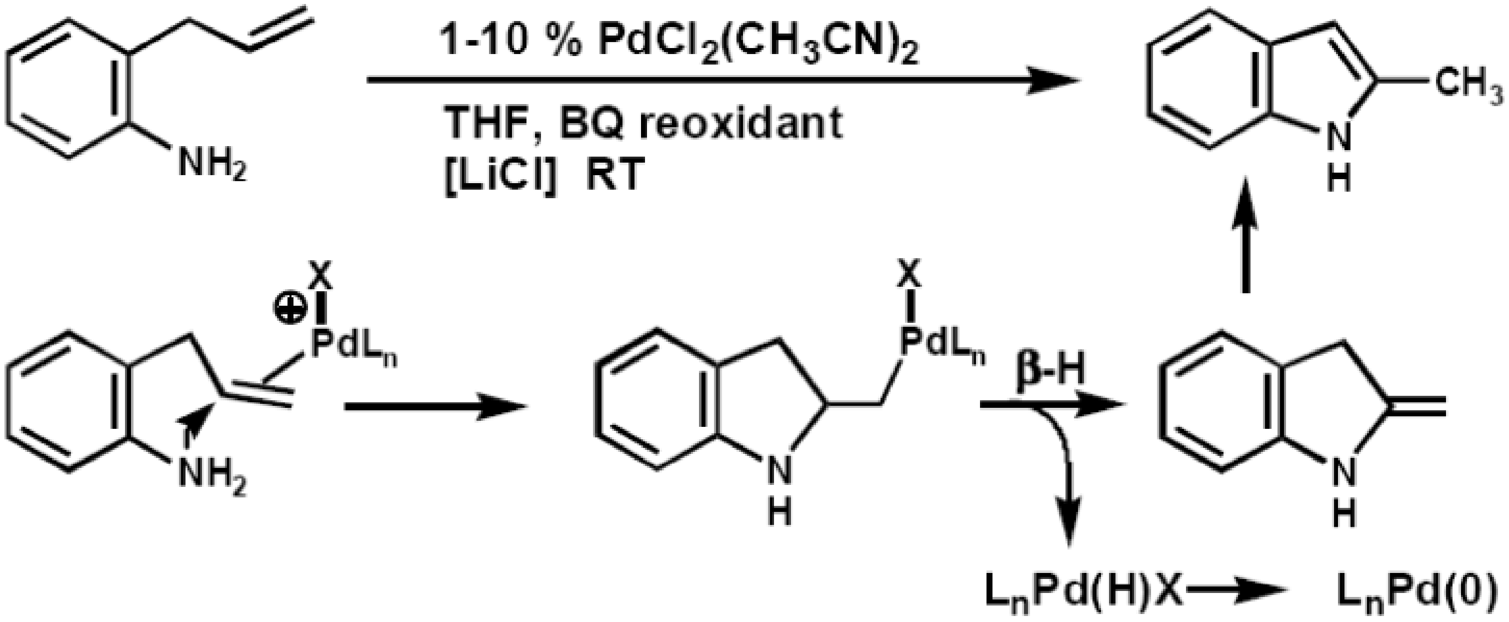


Enantioselective Wacker-Type Reactions

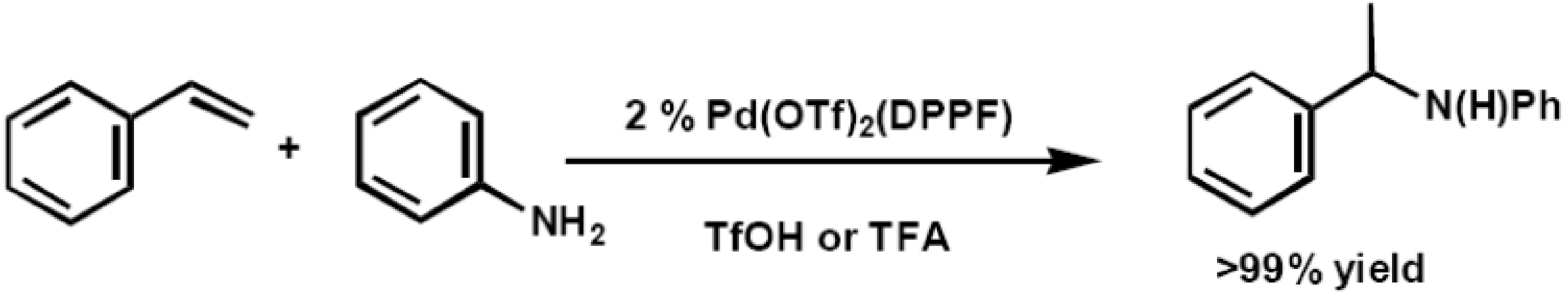


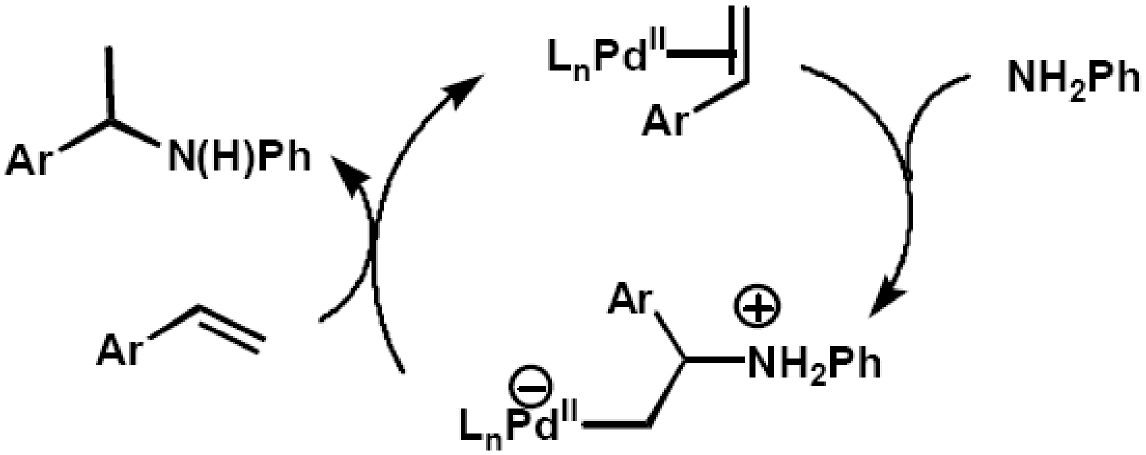
Sasai *JACS* **2001**, *123*, 2907

Using Nitrogen Nucleophiles

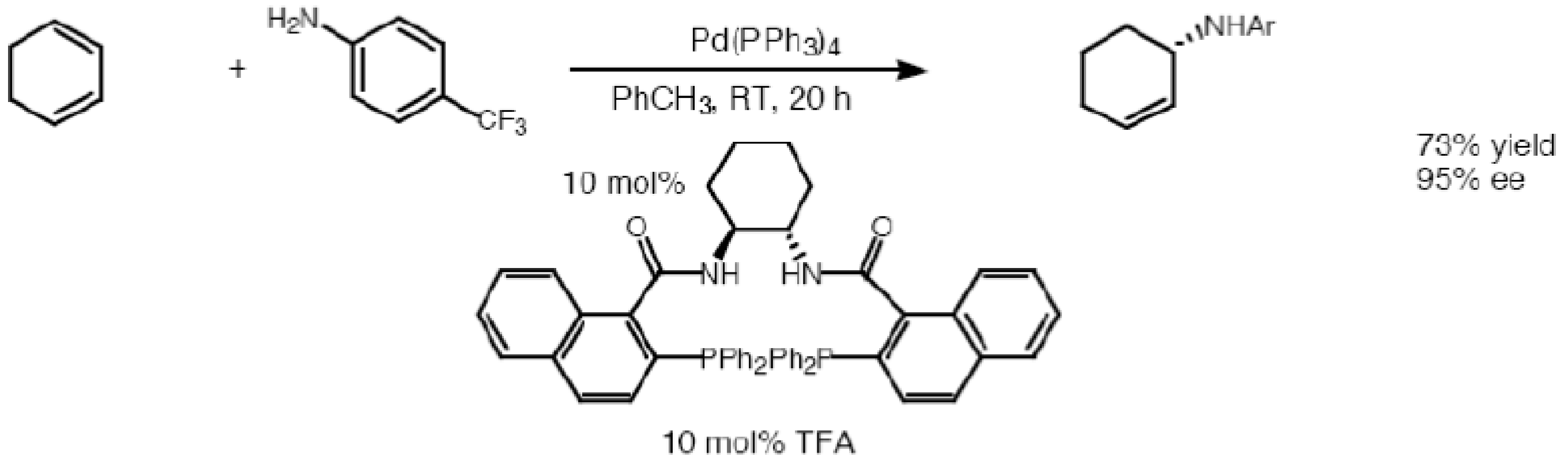


Using Nitrogen Nucleophiles

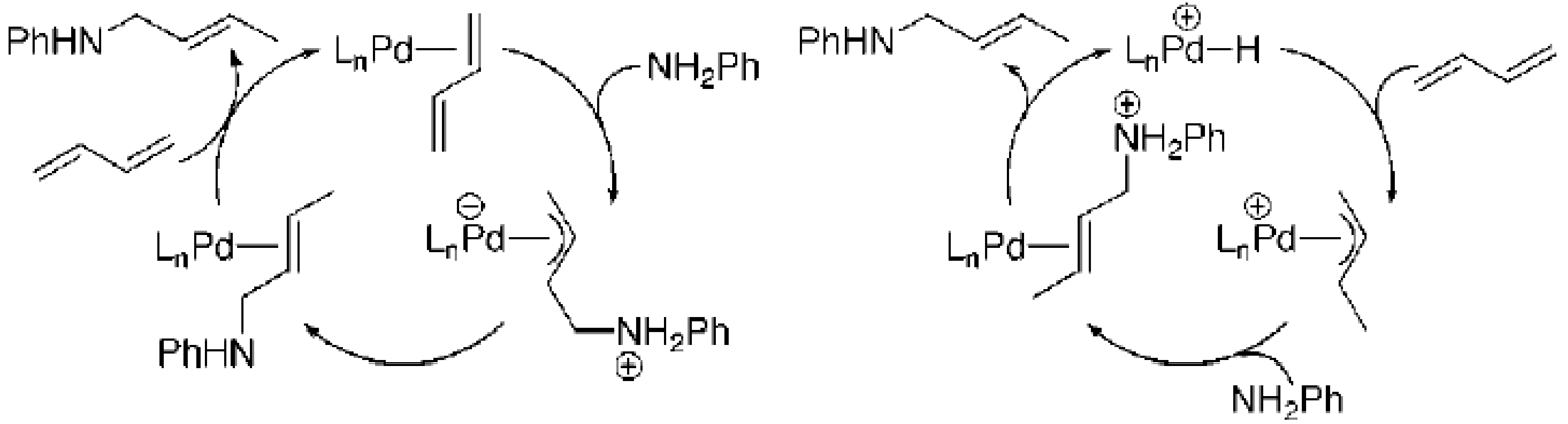




Catalytic Asymmetric Variant



- ❑ Possible Mechanism of Hydroamination in the Absence and Presence of Acid:



Hartwig, J. *J. Am. Chem. Soc*. **1996**, *118*, 7420.