Organic Chemistry CH-401 Course

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Oxidation

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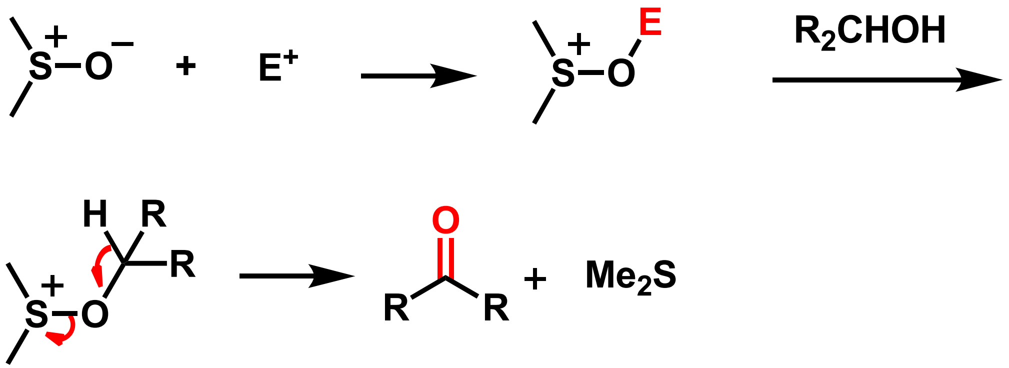
Non-Metal Based Oxidation

Activated Dimethyl Sulfoxide (DMSO)



Electrophiles

$SOCl_2$, $(COCl)_2$, Cl_2, TsCl, $(CH_3CO)_2O$, SO_3/pyridine, CF_3SO_3H

Nucleophiles

ROH, PhOH, $PhNH_2$, $R_2C{=}N\text{-}OH$, Enols

Most of these reactions take place at very low temperature

- Kornblum Oxidation
- Moffatt-Pfitzner Oxidation
- Parikh-Doering oxidation
- Corey-Kim oxidation
- DMSO-Ac_2O
- Swern Oxidation

Non-Metal Based Oxidation

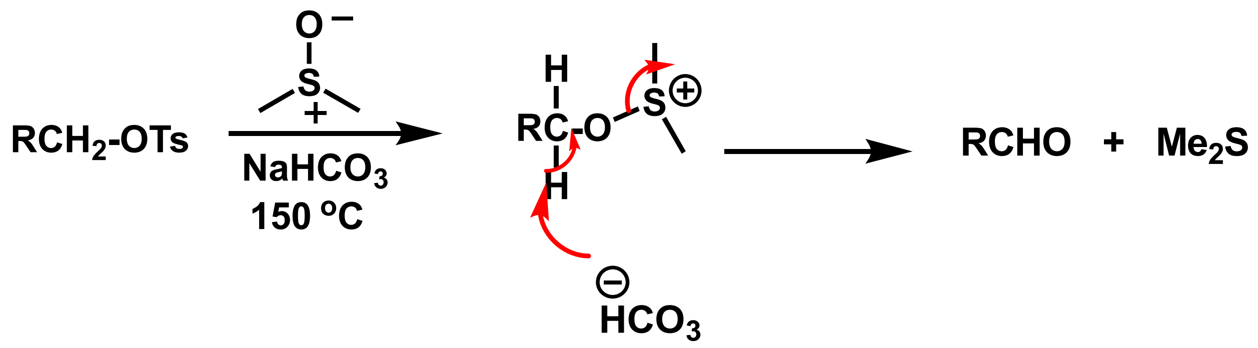
Kornblum Oxidation (1959)

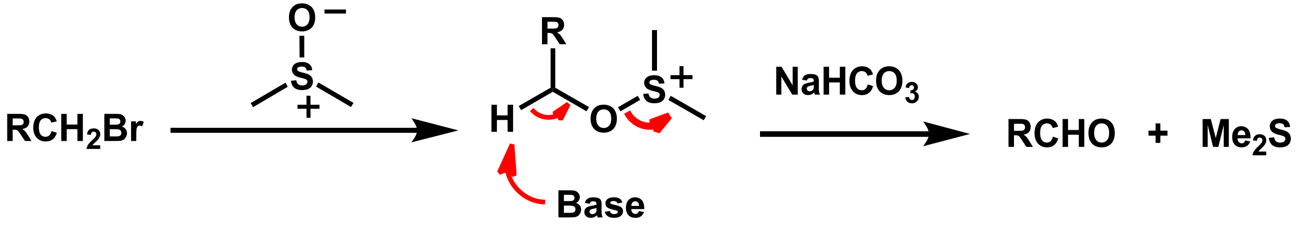
Oxidation of alkyl tosylates/halides to aldehydes

In 1959, Kornblum reported oxidation of primary tosylates with $NaHCO_3$ when heated at 150 °C with DMSO

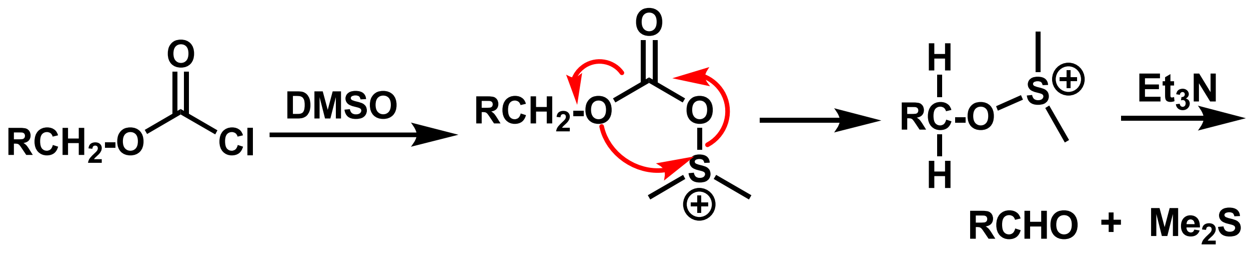
As per the accepted mechanism, in the first step, DMSO displaces the tosylate in a S_N2 fashion to form a sulfenate salt

In the second step, HCO_3^- mediated E_2 elimination takes place to form the aldehyde and Me_2S





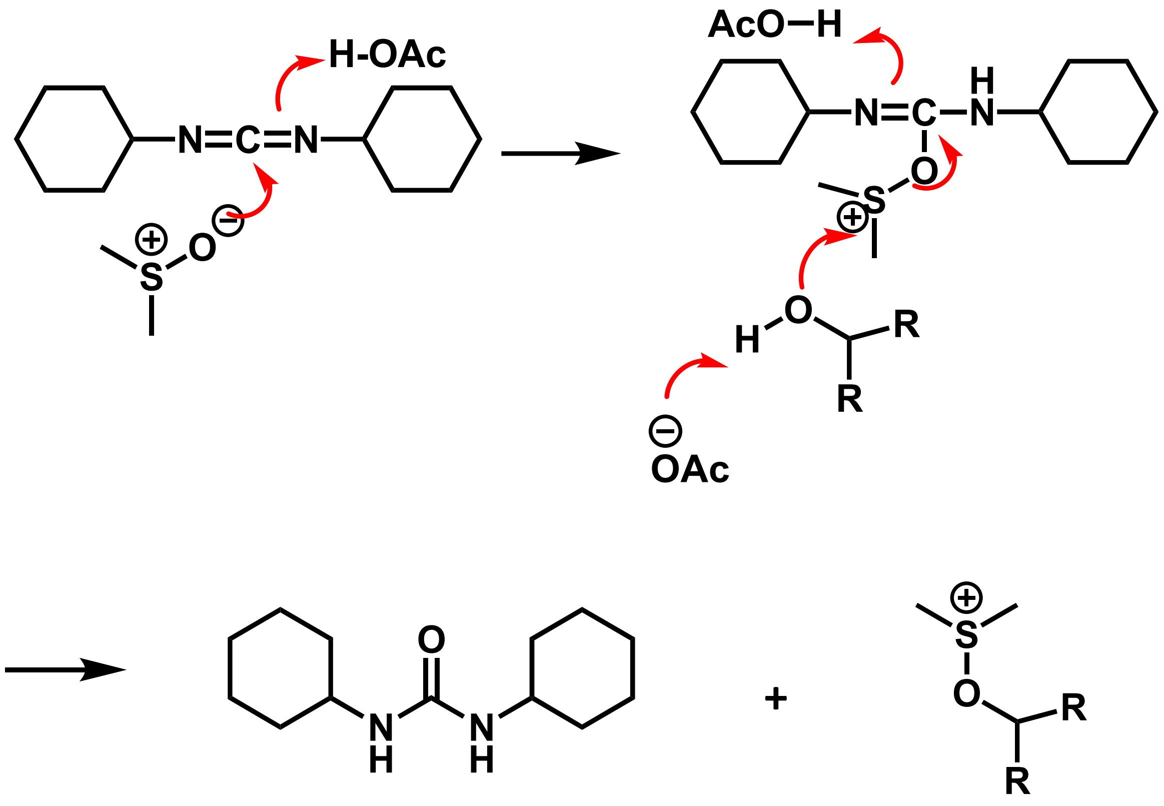
Barton Modification (1964)

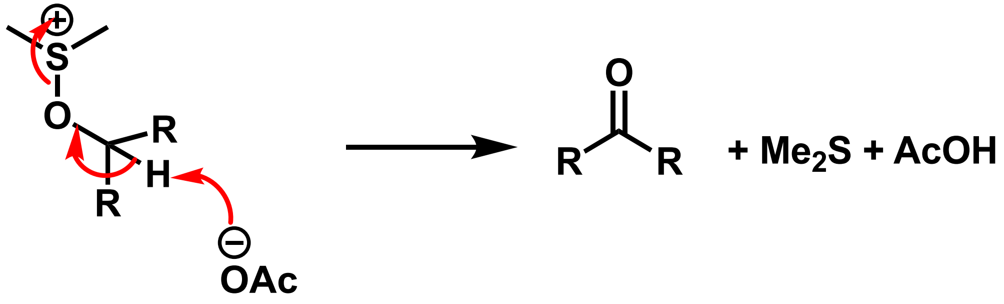


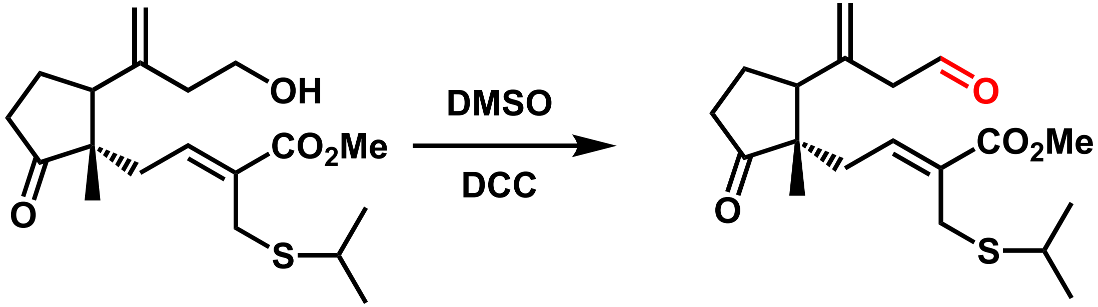
Non-Metal Based Oxidation

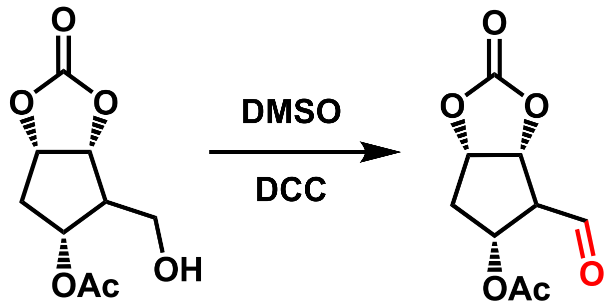
Moffatt-Pfitzner Oxidation (1963)

In 1963, a new process was developed at Syntex for the oxidation of alcohols to corresponding carbonyl groups with DMSO and activated DCC with an acid







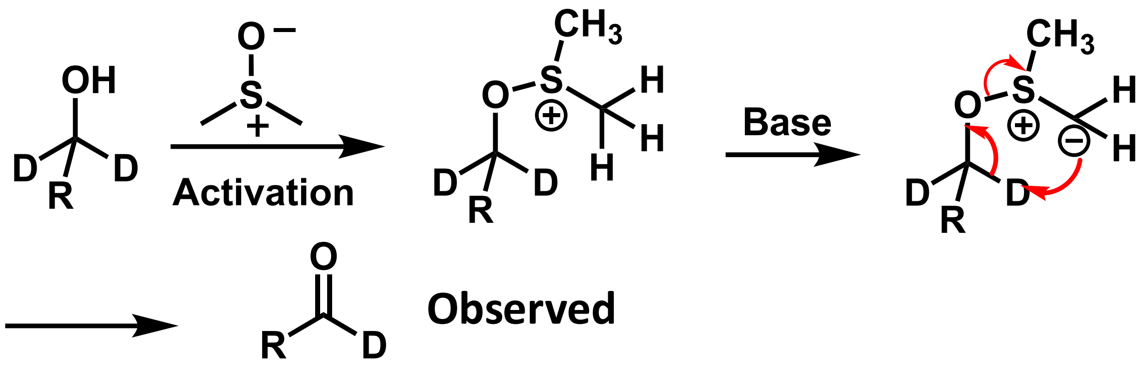


Non-Metal Based Oxidation

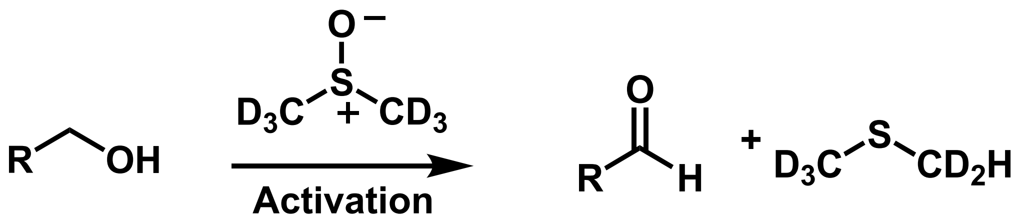
Torsell Mechanism

Torsell demonstrated that DMSO based oxidation do not proceed via intermolecular E_2 elimination but via an intramolecular process involving sulfonium ylide

Experiment 1

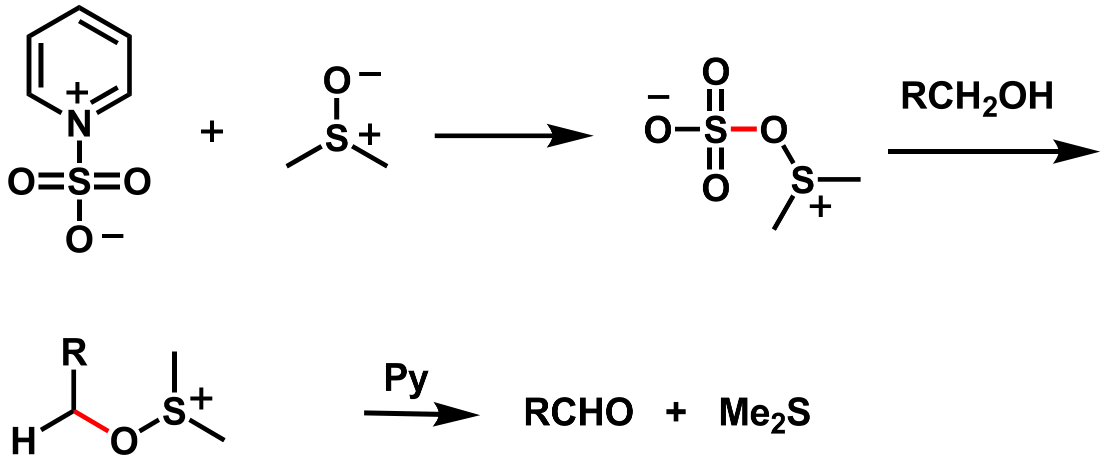


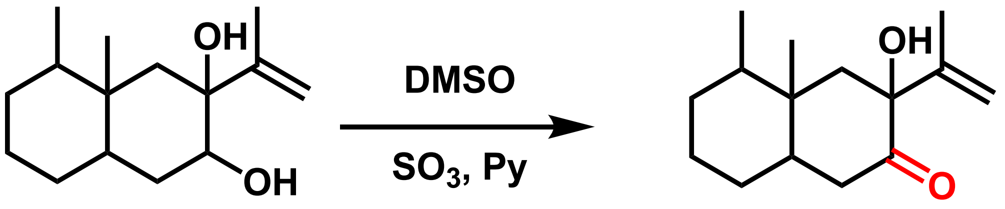
Experiment 2



DMSO-SO_3-Py (Parikh Doering -1967)

In this reaction, pyridine-sulfur trioxide acts as the activator

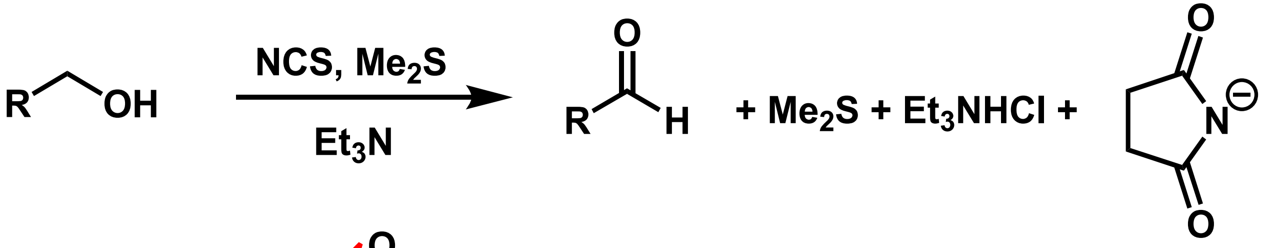


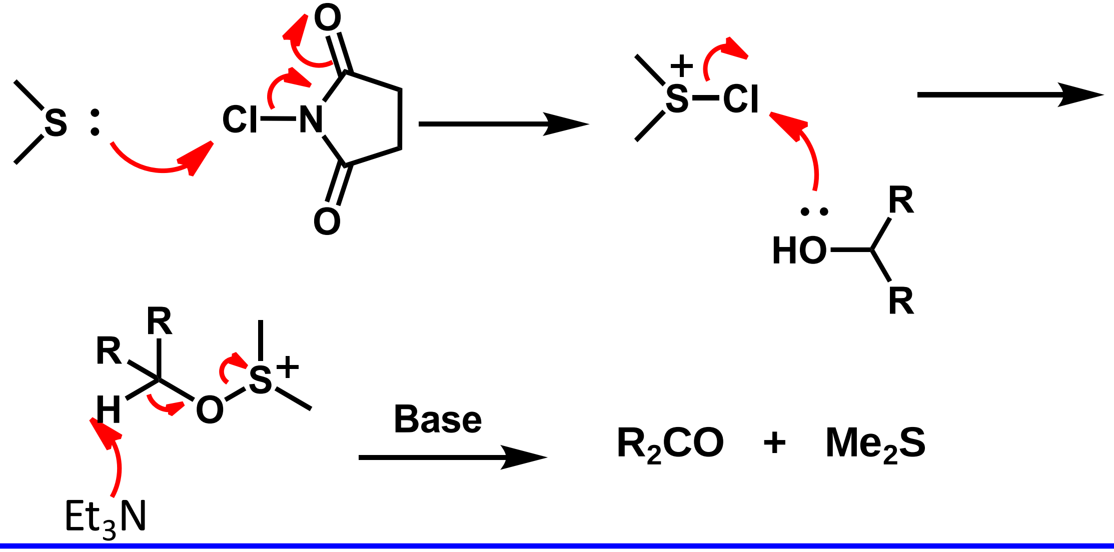


DMSO Based Oxidation

Corey-Kim Oxidation (1972)

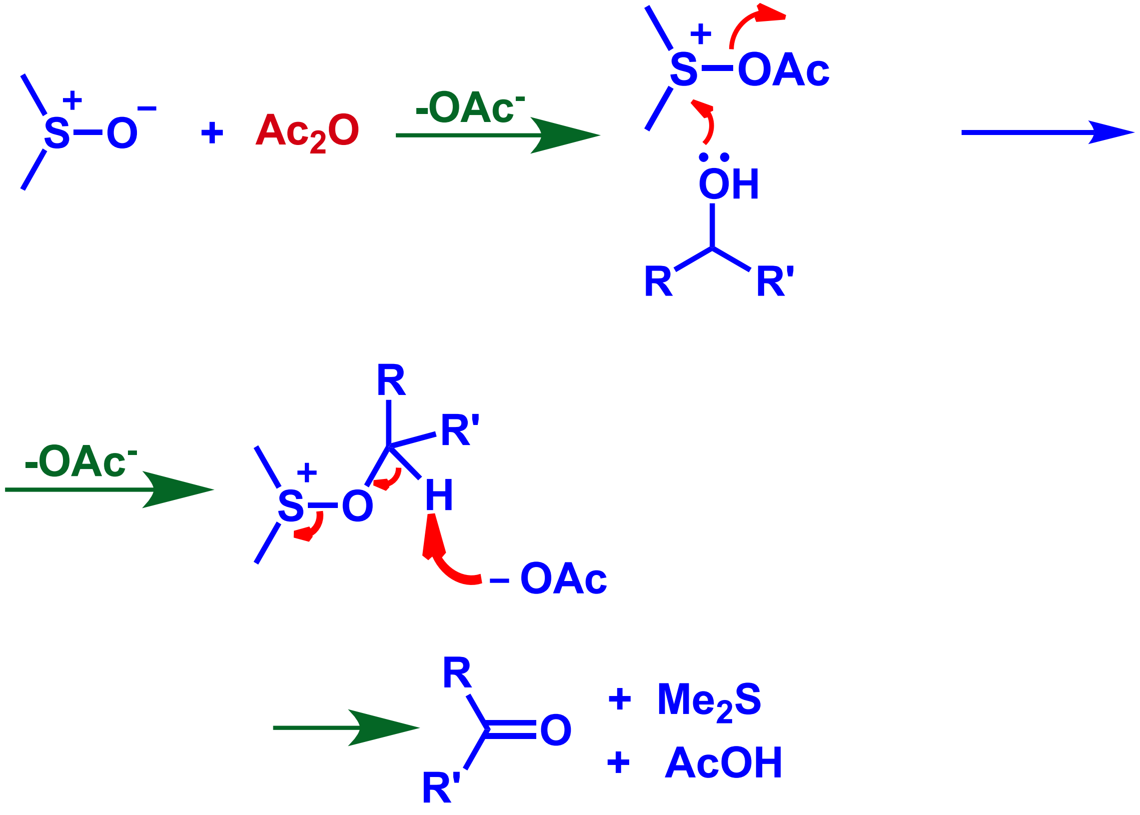
In this reaction NCS (N-chlorosuccinimide) is used to activate the dimethyl sulfide (and not DMSO). Succinimidyl group is the leaving group. Triethylamine is used as the base





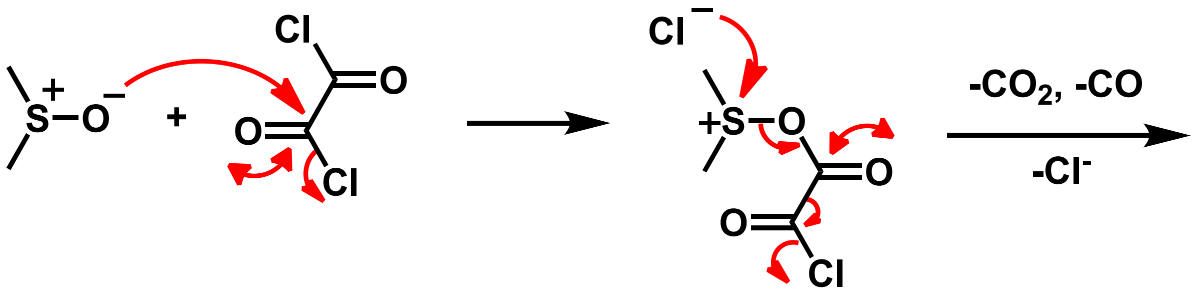
DMSO/Ac_2O

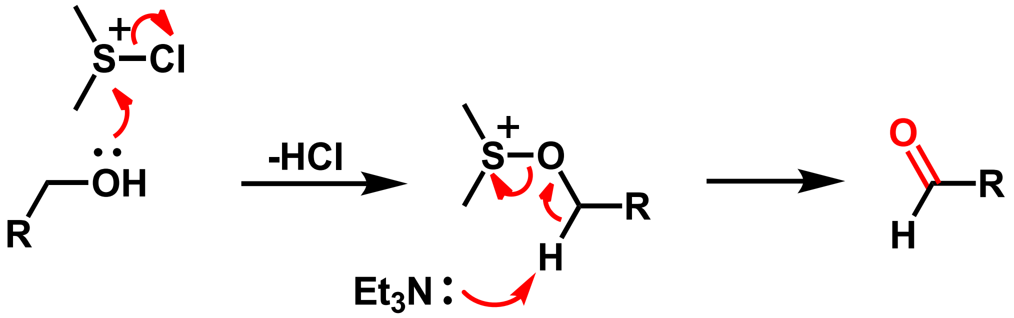
Here, either acetic anhydride or trifluoroacetic anhydride is used as activating agent

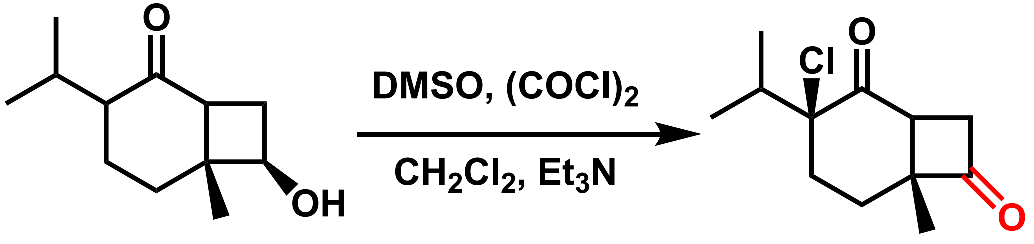


Sometimes, alcohols will be acetylated

Swern Oxidation

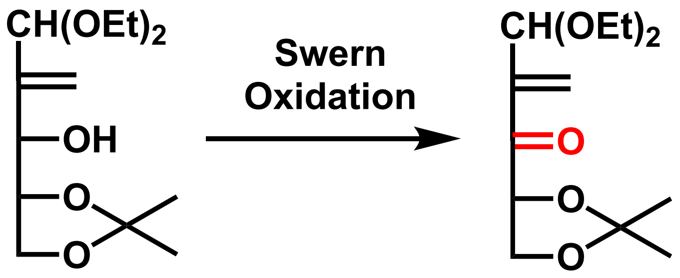




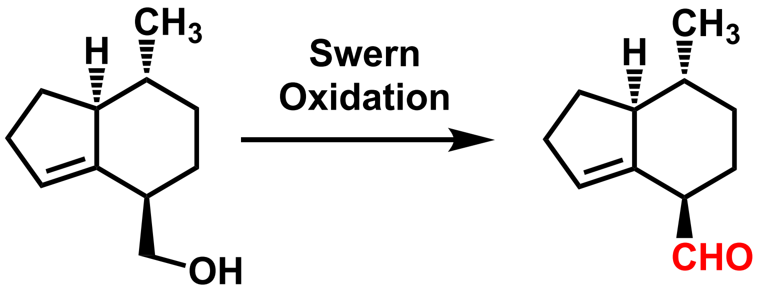


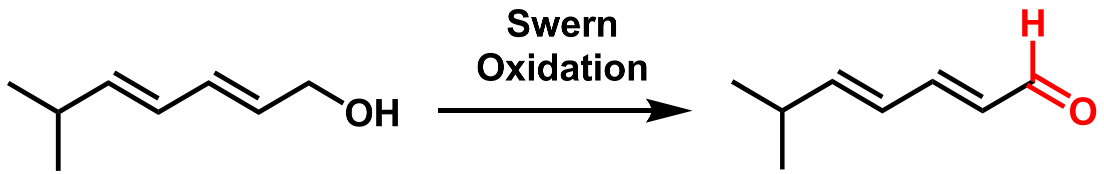
Trifluoroacetic anhydride also can be used instead of $(COCl)_2$

Survives protecting groups

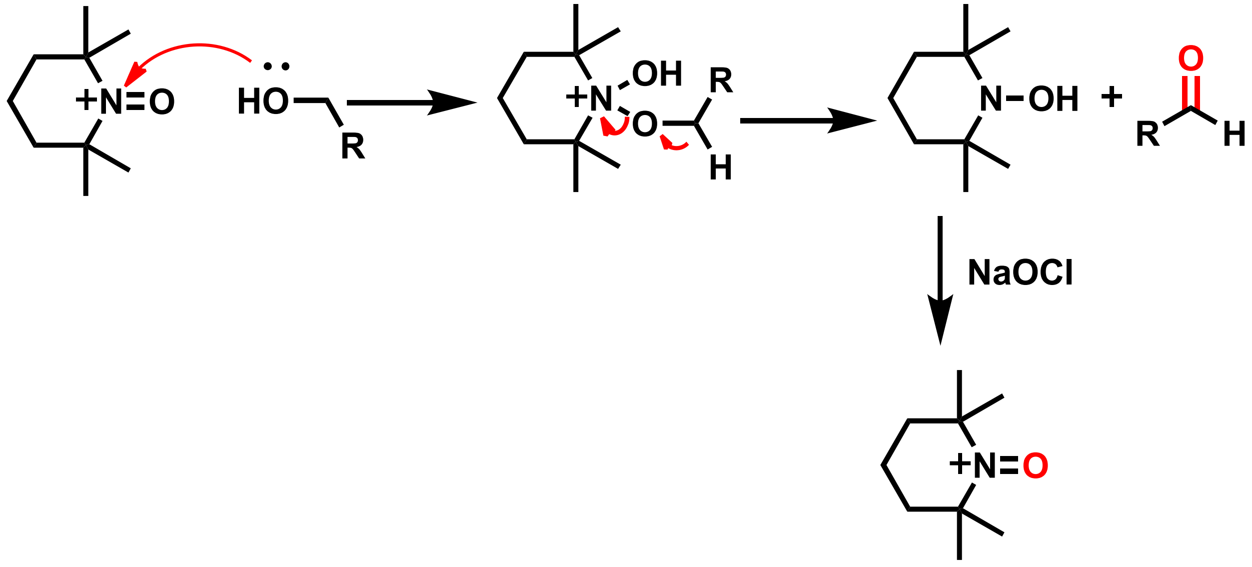


No epimerization of aldehydes





TEMPO (Tetramethylpiperidine N-oxide)



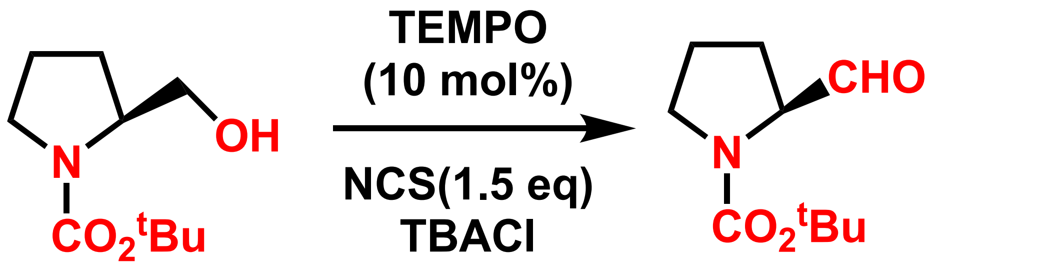
It is a stable nitroxide and is the active reagent in oxidizing alcohols

TEMPO can be used in catalytic amount if NaOCl or NCS is used in stoichiometric amount

$$PhCH_2O(CH_2)_2CH_2{-}OH \xrightarrow[\text{NaOCl}]{\text{TEMPO (2 mol\%)}} PhCH_2O(CH_2)_2{-}CHO$$

This reagent can selectively oxidize primary alcohols in the presence of secondary alcohols

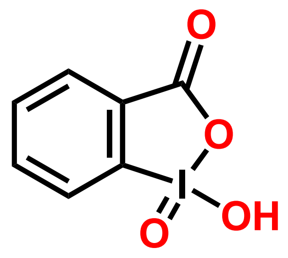
$$CH_3CH(OH)(CH)_8CH_2OH \xrightarrow[\text{NCS(1.5 eq), TBACl}]{\text{TEMPO (10 mol\%)}} CH_3CH(OH)(CH)_8CHO$$



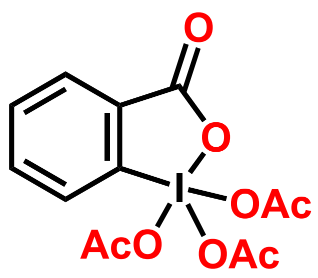
It can also oxidize primary alcohols to carboxylic acids by a subsequent oxidation with hypochlorite ion

$$RCH_2OH \xrightarrow[\text{NaOCl (3 eq), TBACl}]{\text{TEMPO}} RCOOH$$

IBX and Dess Martin Periodinane (DMP)



IBX
(2-Iodoxybenzoic acid)



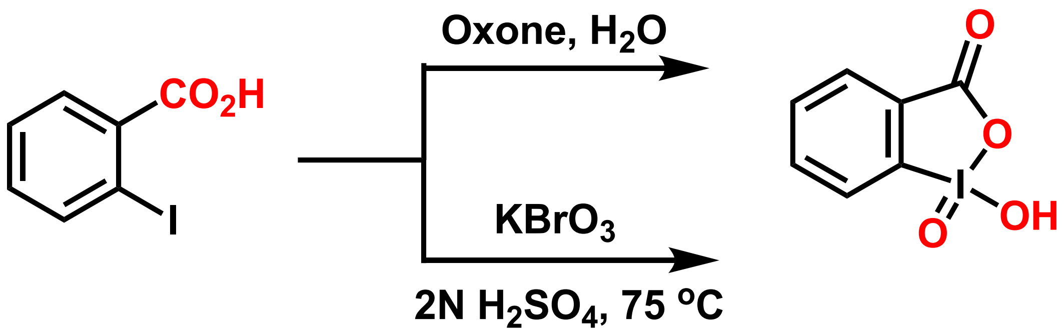
DMP
(Dess Martin Periodinane)

IBX was discovered in 1893 by Hartmann and Meyer but not used due to its remarkable insolubility in organic solvents and explosive nature

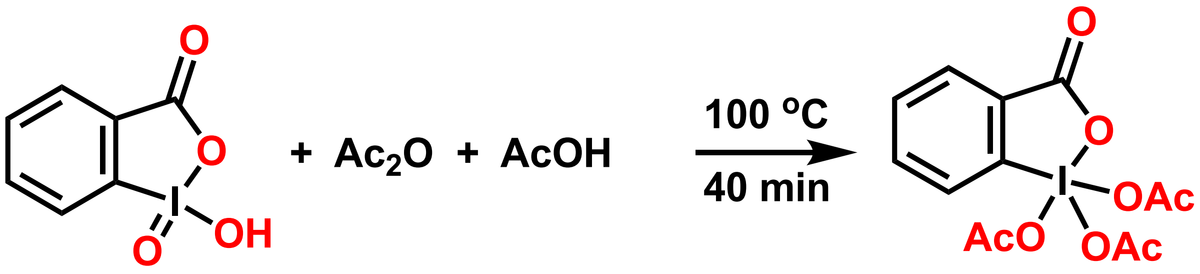
Several groups try to improve its solubility through structural modification or through polymer supported reagents

The most important and useful derivative is its triacetate, known as DMP (Dess Martin Periodinane), which is soluble in organic solvents

Preparation of IBX



Preparation of DMP

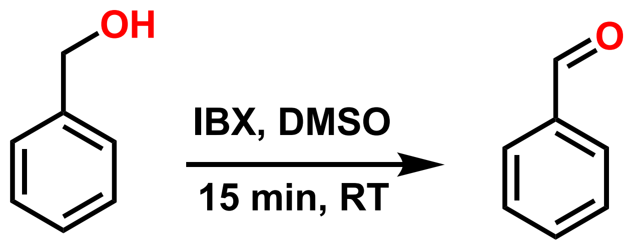


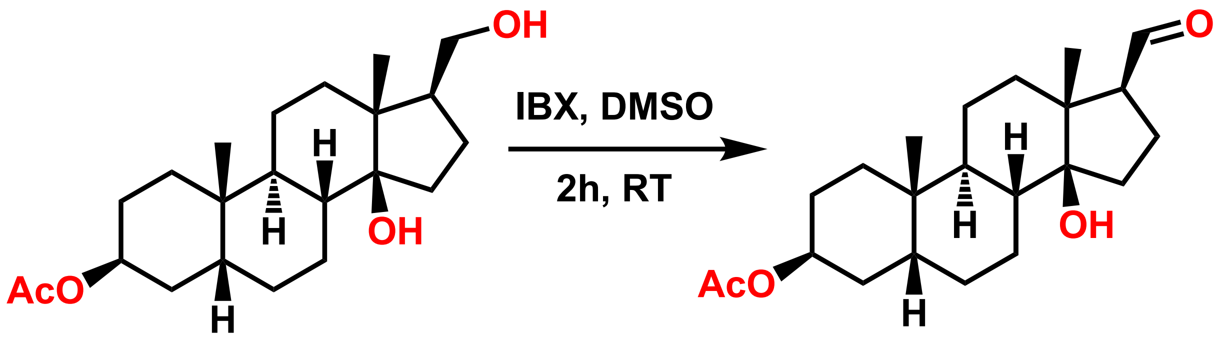
DMP
(Dess Martin Periodinane)

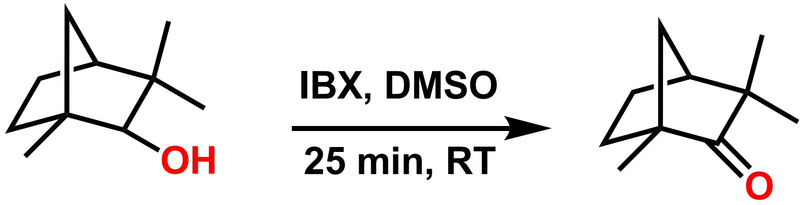
Synthetic Utility of IBX

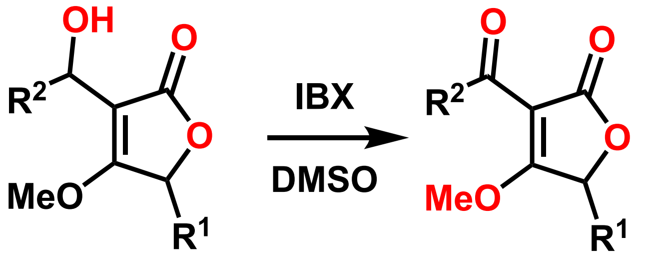
1. Oxidation of primary and secondary alcohols
2. Oxidation of 1,2-diols to 1,2-diketones
3. Oxidation of amino alcohols to aminocarbonyls
4. Deoximation of oximes
5. Deprotection of thioacetals and thioketals
6. Oxidation of phenols to *o*-quinones
7. Aldehydes to Nitriles
8. Oxidation of secondary alcohols to unsaturated ketones

Oxidation of Primary and Secondary Alcohols

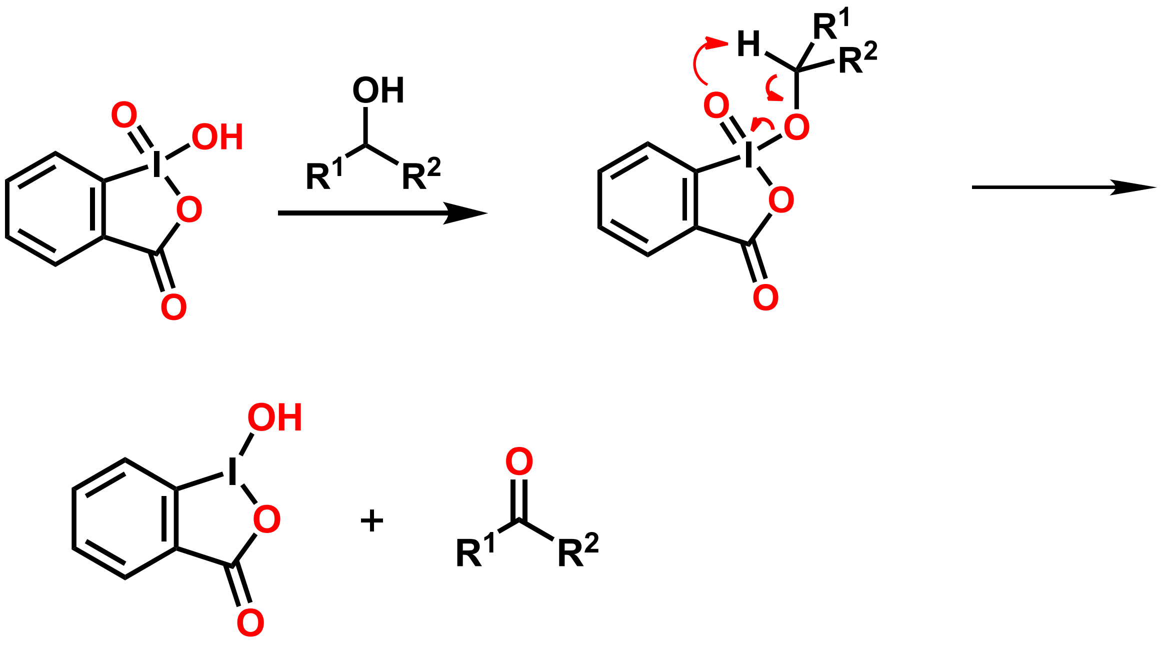


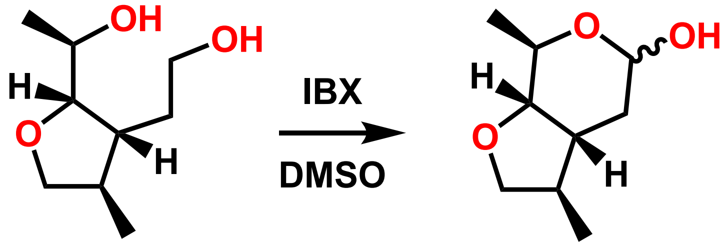






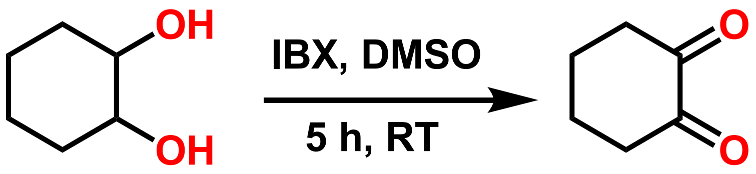
Mechanism

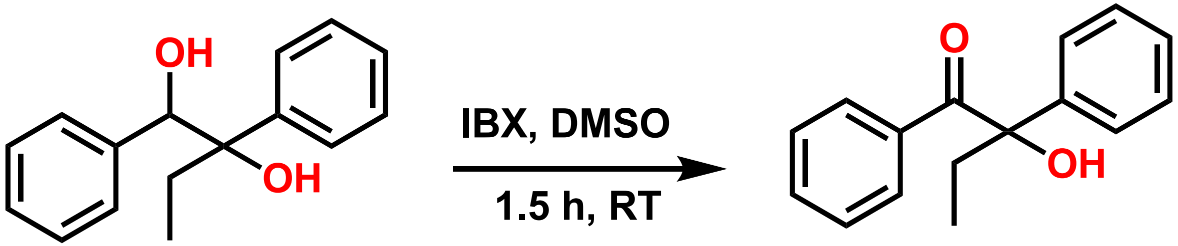


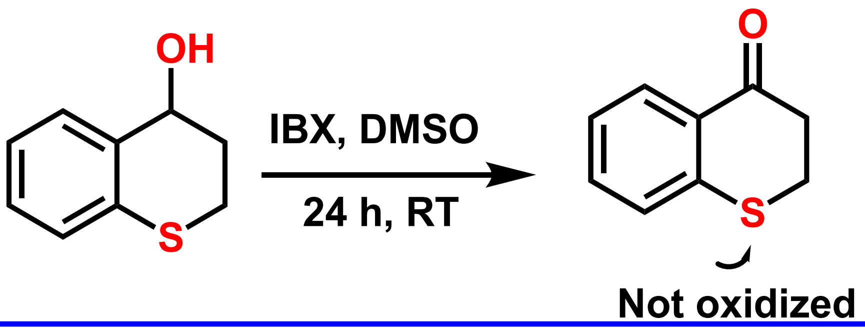


Oxidation of Diols and Aminoalcohols

Oxidation of 1,2-diols

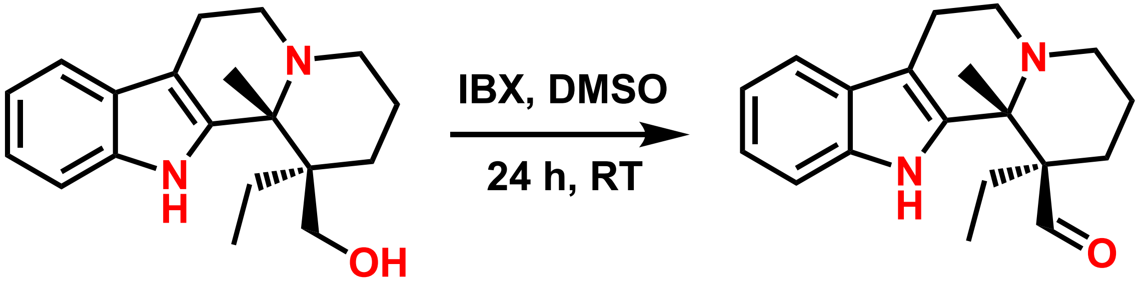






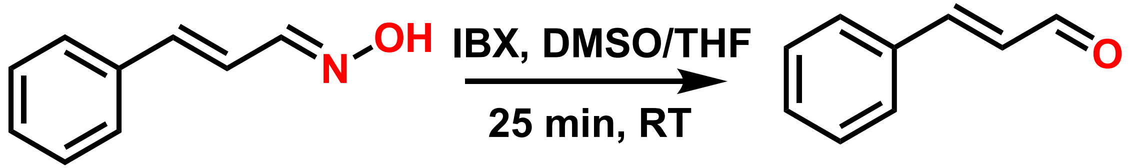
Oxidation of Aminoalcohols

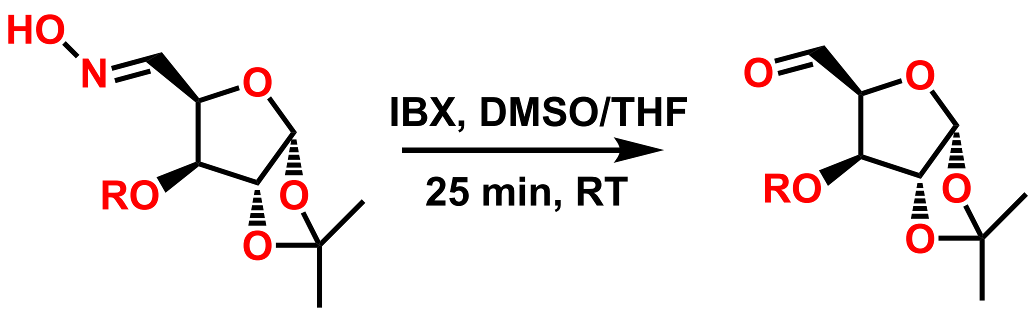
Primary and secondary amines are temporarily protonated befo oxidation

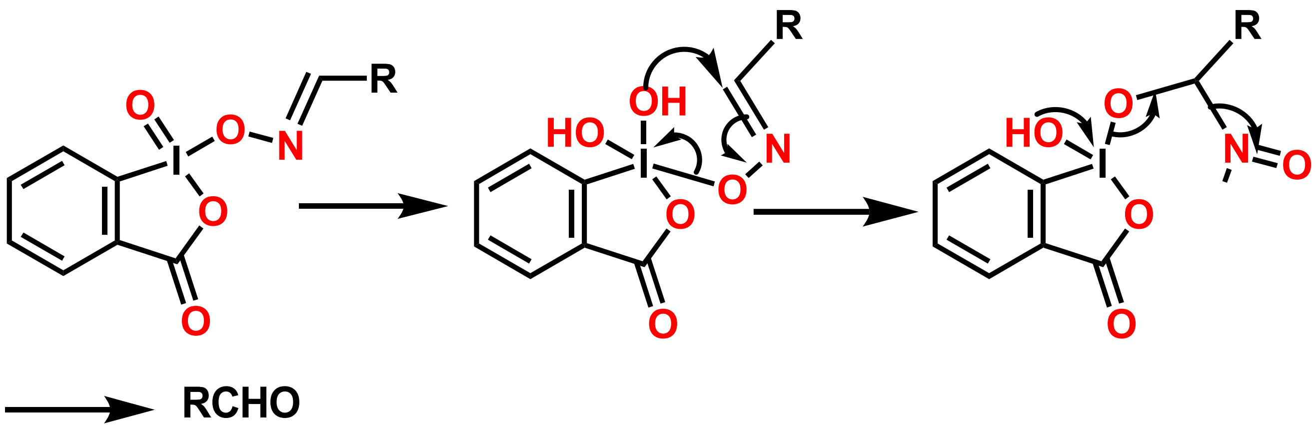


Deoximation and Deprotection

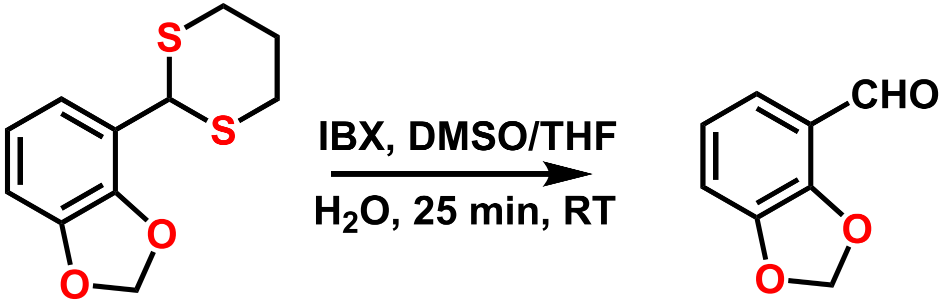
Deoximation of Oximes

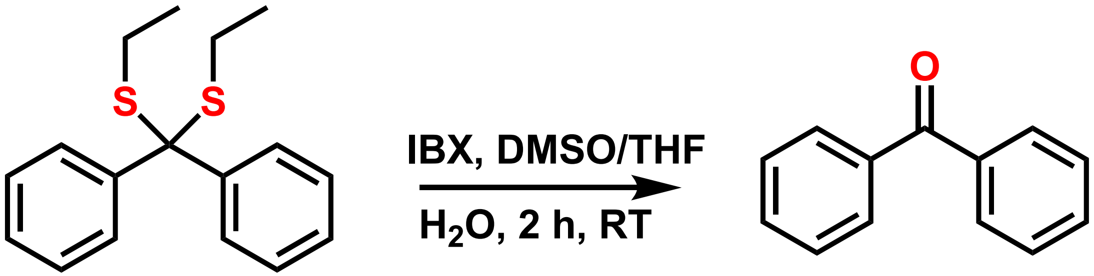


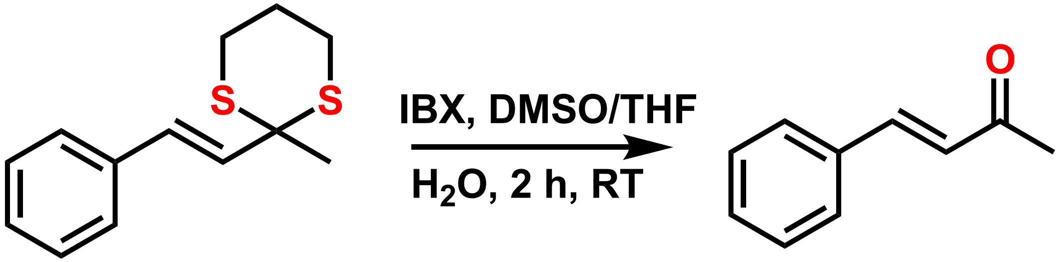


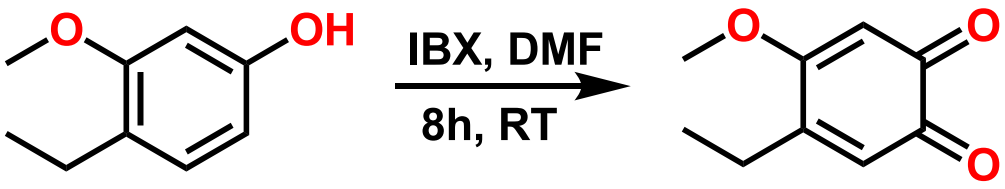


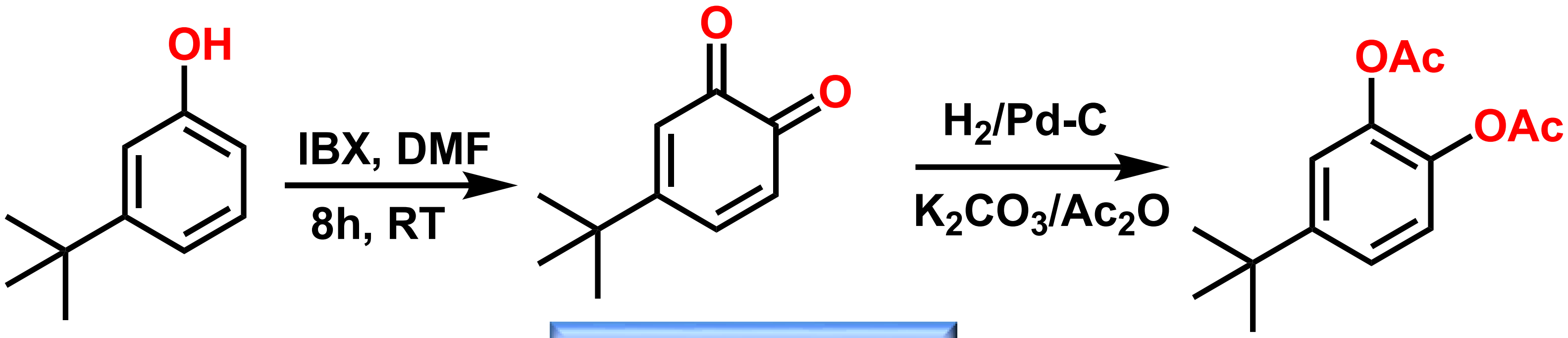
Deprotection of thioacetals & thioketeals



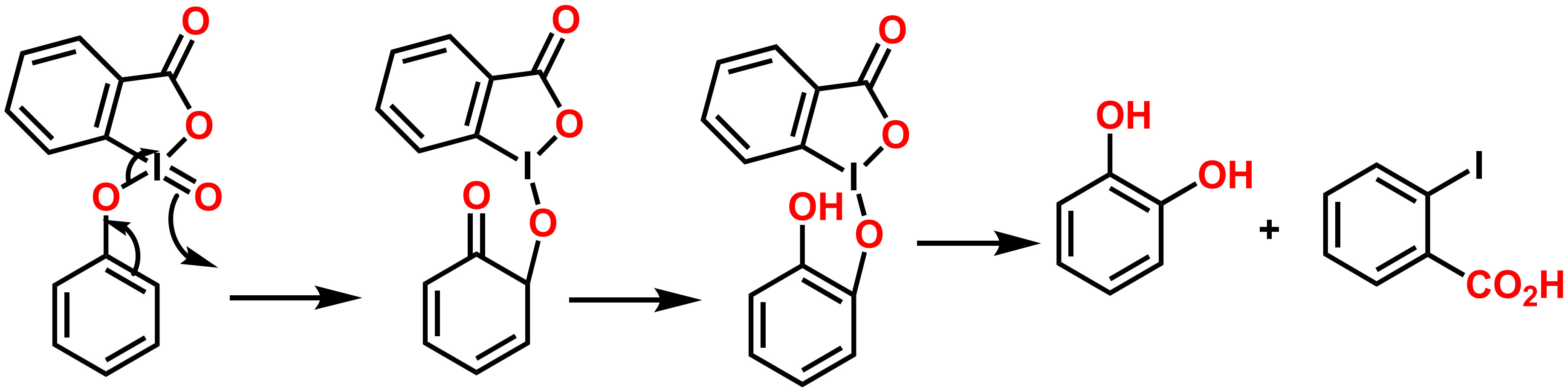




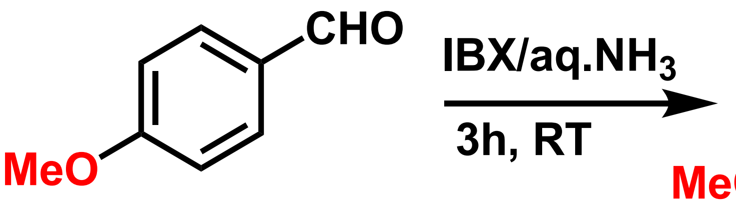

O
OH
IBX, DMF
8h, RT
O
O
O

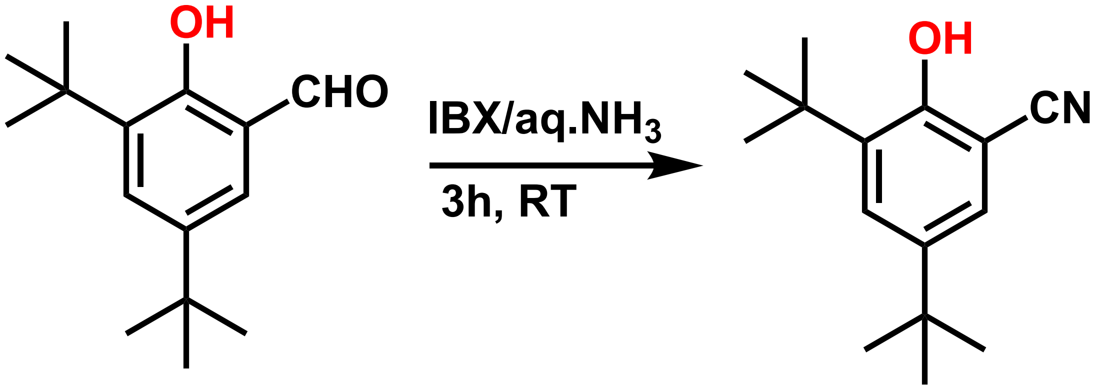

OH
IBX, DMF
8h, RT
O
O
H2/Pd-C
K2CO3/Ac2O
OAc
OAc

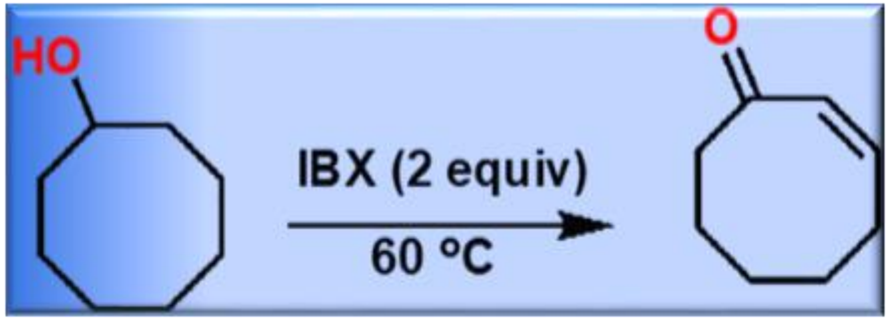
Mechanism

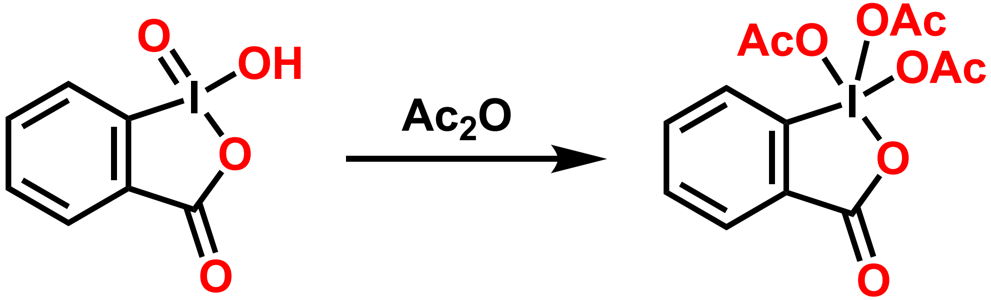

O
O
I
O
O
O
O
I
O
O
O
O
I
OH
O
OH
OH
+
I
CO2H

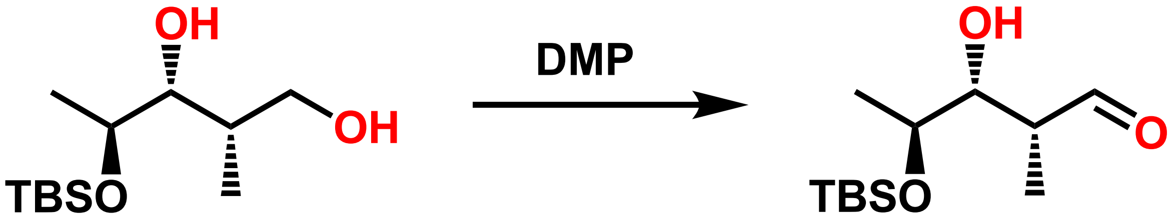
IBX & DMP

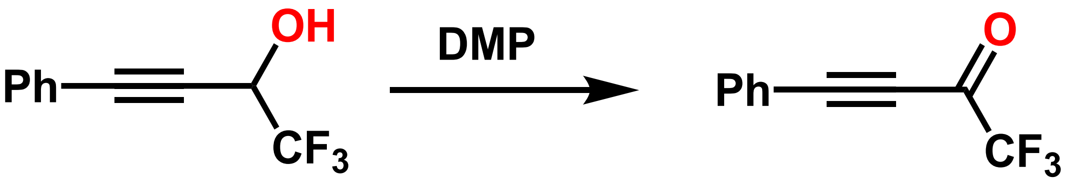

CHO
MeO
IBX/aq.NH_3
3h, RT
CN
MeO

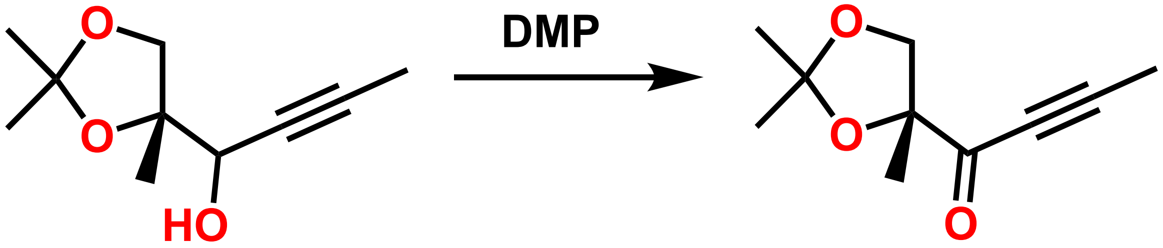

OH
CHO
IBX/aq.NH_3
3h, RT
OH
CN


HO
IBX (2 equiv)
60 °C
O

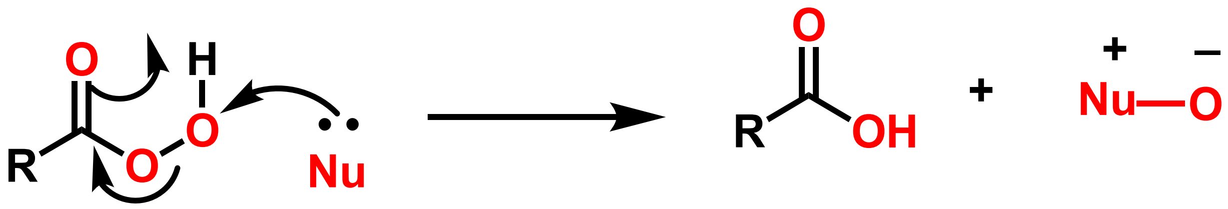

O
OH
I
O
O
Ac_2O
AcO
OAc
OAc
I
O
O


OH
OH
TBSO
DMP
OH
O
TBSO


OH
Ph
CF_3
DMP
O
Ph
CF_3

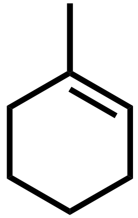

O
O
HO
DMP
O
O
O

Epoxidation



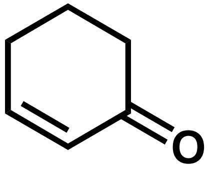
R = EWG
Stabilized

Electron rich substrate and electrophilic reagent



electron rich

Electron deficient substrate and nucleophilic reagent



electron deficient

Electrophilic reagents

1. Peracetic acid
2. Perbenzoic acid
3. *m*-CPBA
4. $KHSO_5$ (Oxone)
5. Dimethyldioxirane (DMDO)

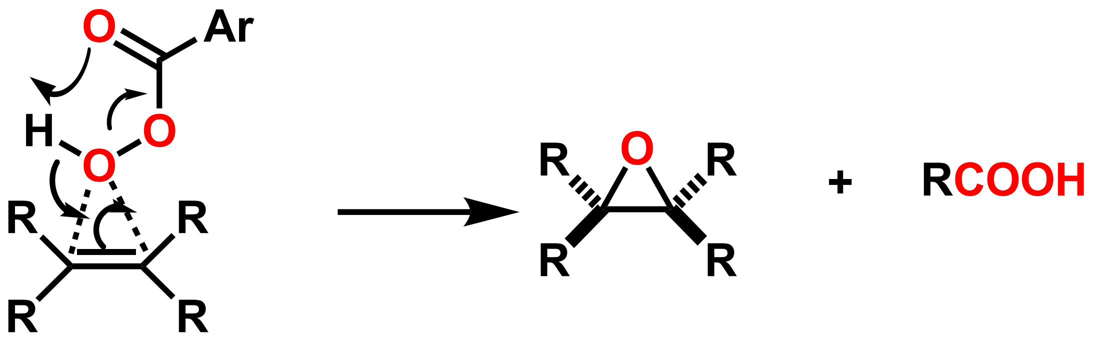
Peracids

Peracids can be prepared from the corresponding acids & H_2O_2

$$RCO_2H + H_2O_2 \longrightarrow RCO_3H + H_2O$$

Peracids

Mechanism



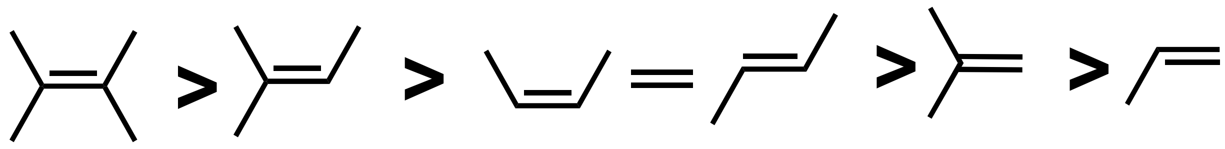
It is believed to be a concerted process

Stereospecific *syn* addition is constantly observed

Epoxides are always *syn*

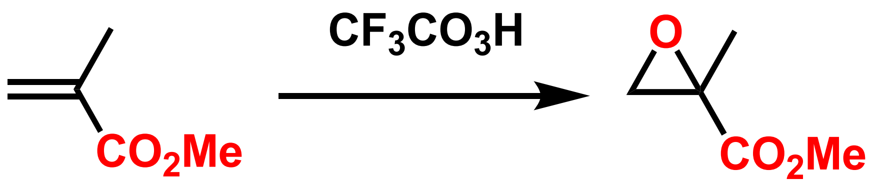
Trans epoxide means substituents are *trans*

The rate of epoxidation



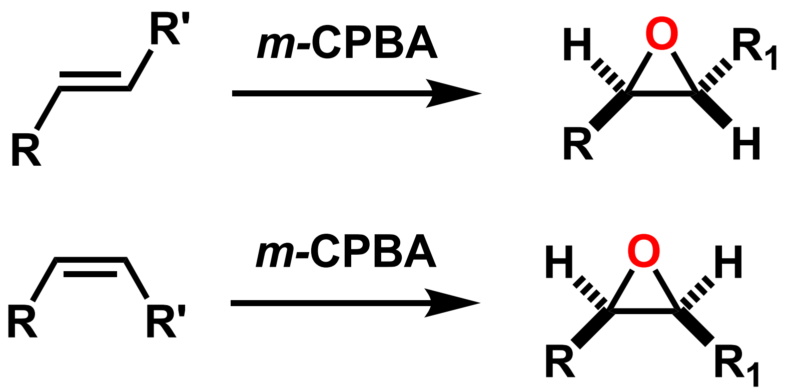
The reactivity of the peracid is increased by EWG's

Strong EWG attached to olefin makes it less reactive

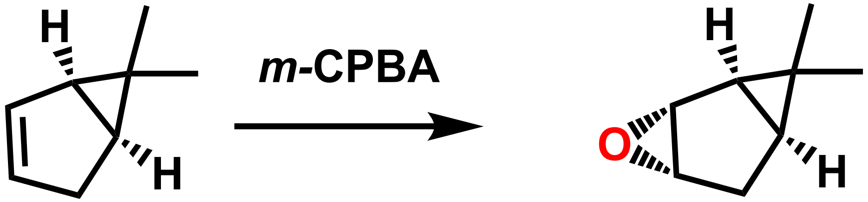


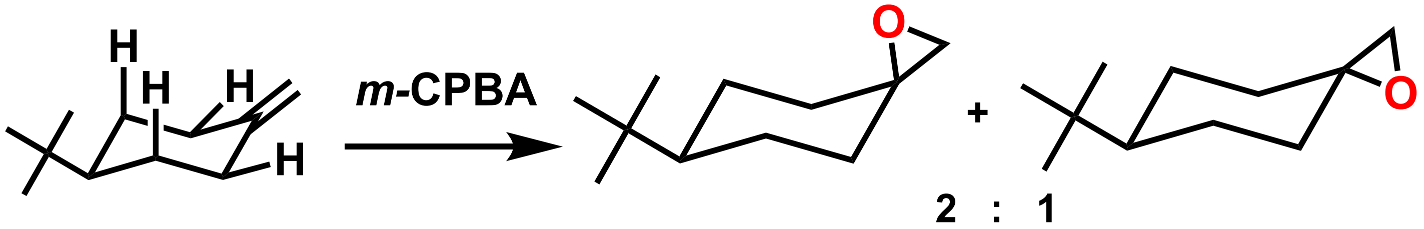
Epoxidation

Stereoselectivity:

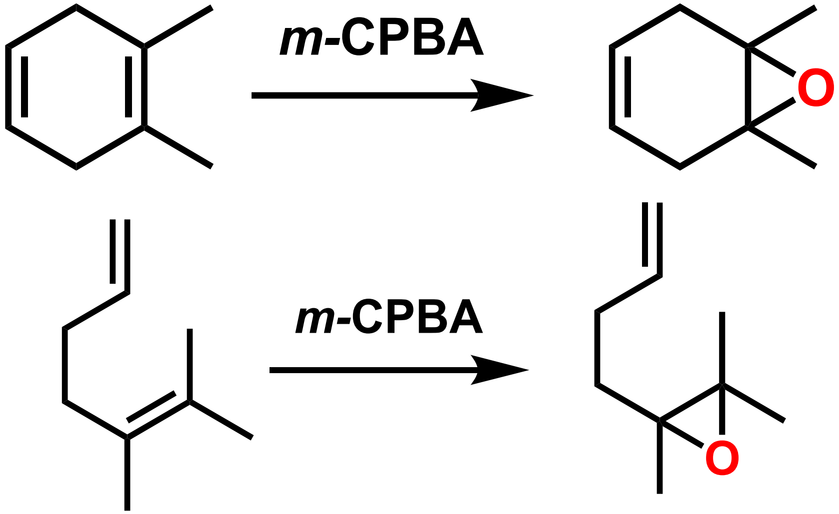


Addition of oxygen comes preferentially from the less hindered side of the molecule



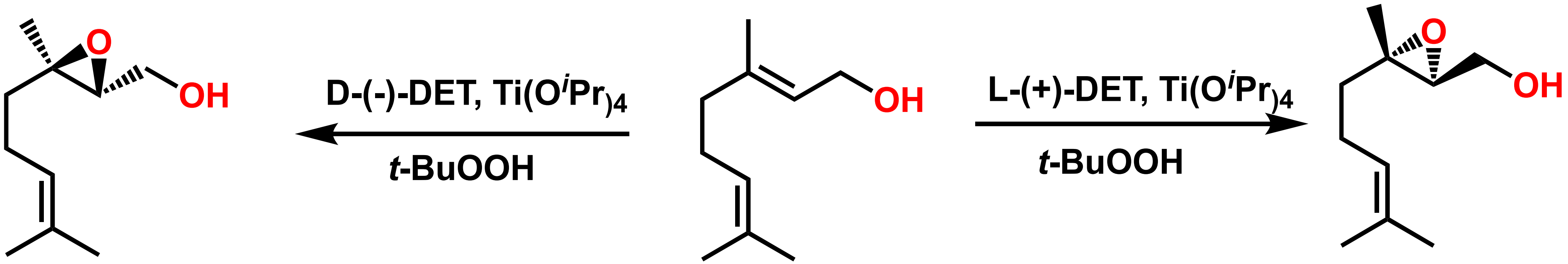


Regioselectivity



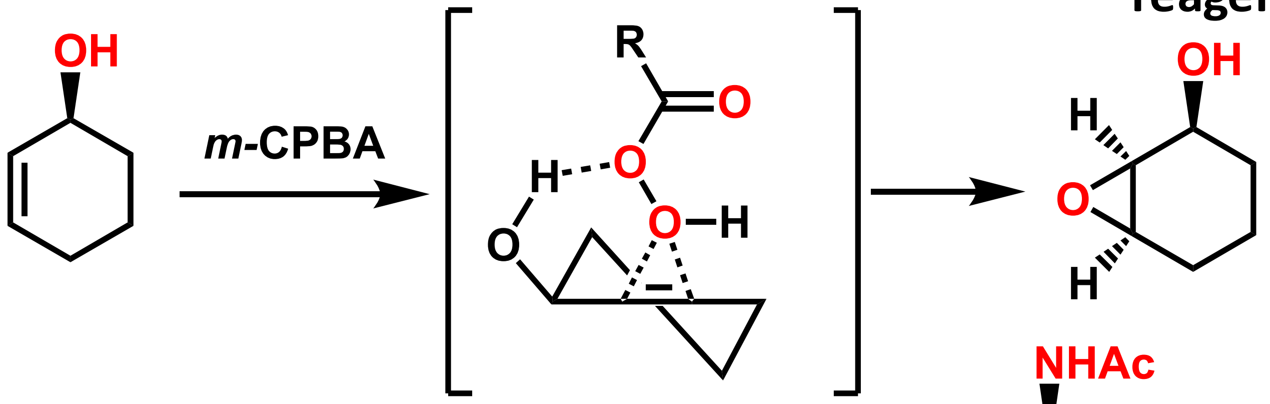
More electron rich double bond participated in epoxidation

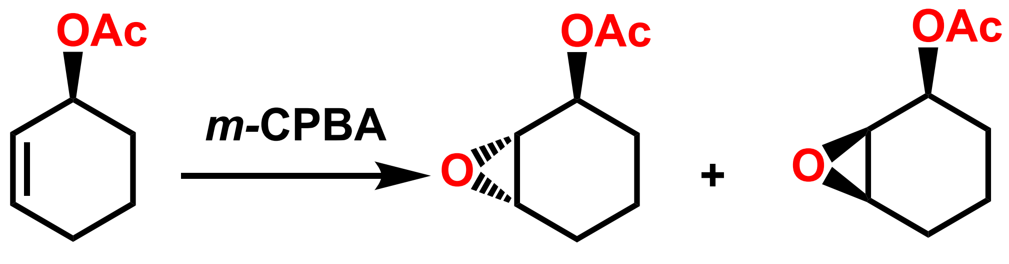
Sharpless Asymmetric Epoxidation



Epoxidation Directed by Polar Group

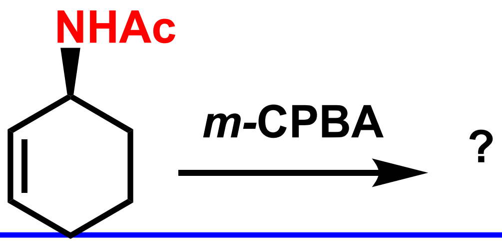
Hydrogen bonding between the hydroxyl group and the reagent stabilizes the transition state



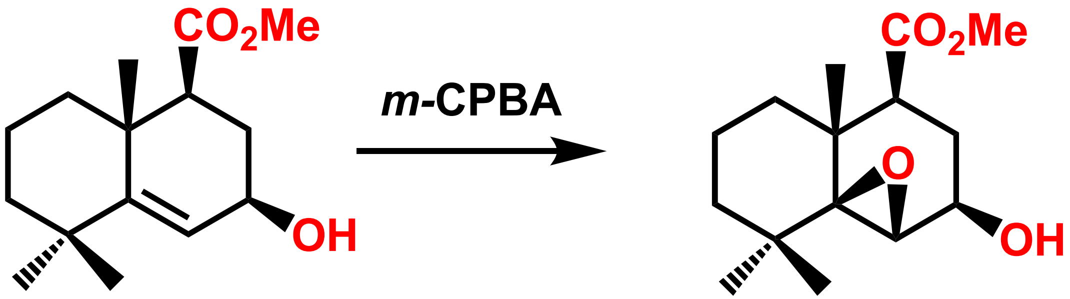


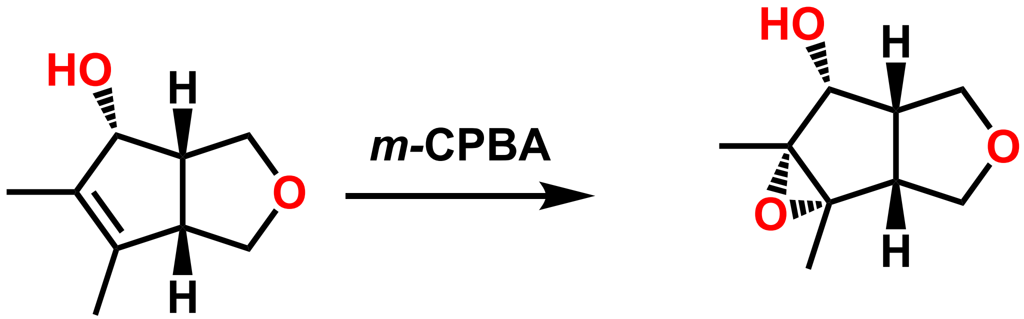
(57:43)

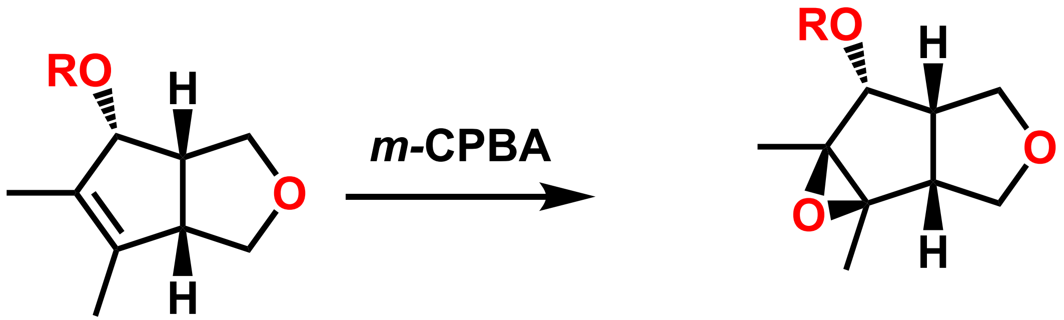
Henbest Epoxidation



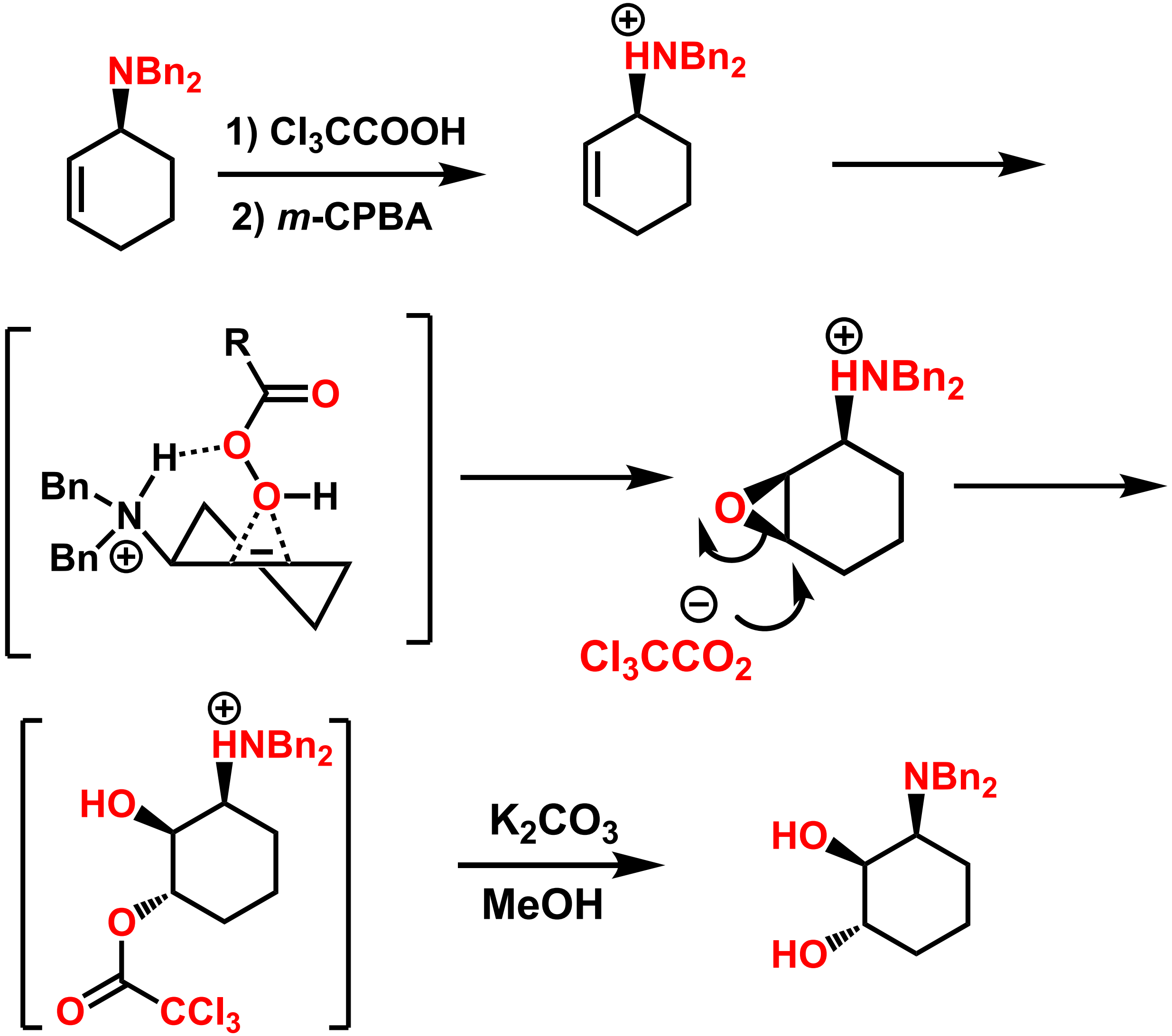
Epoxidation



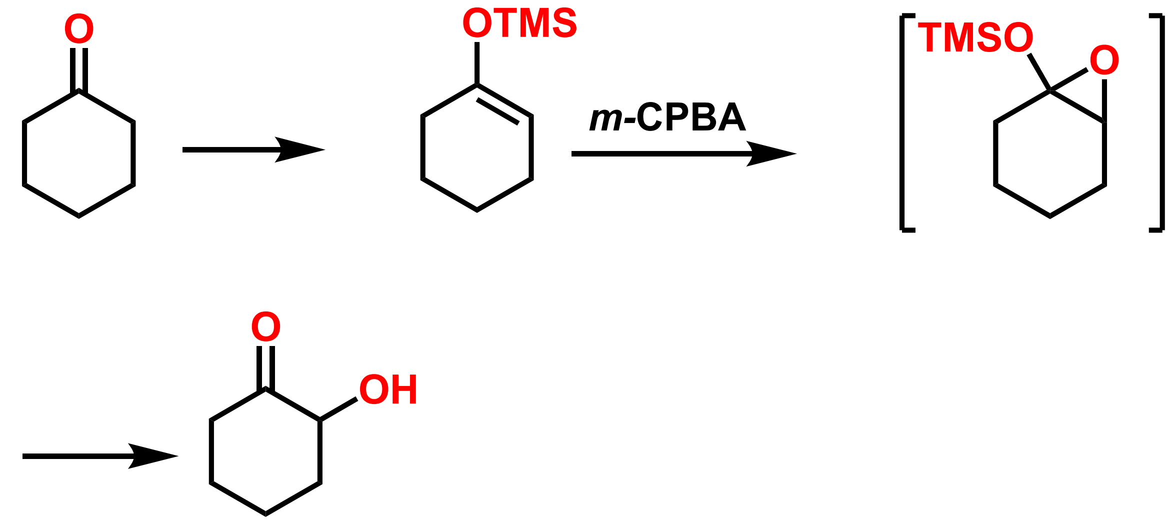


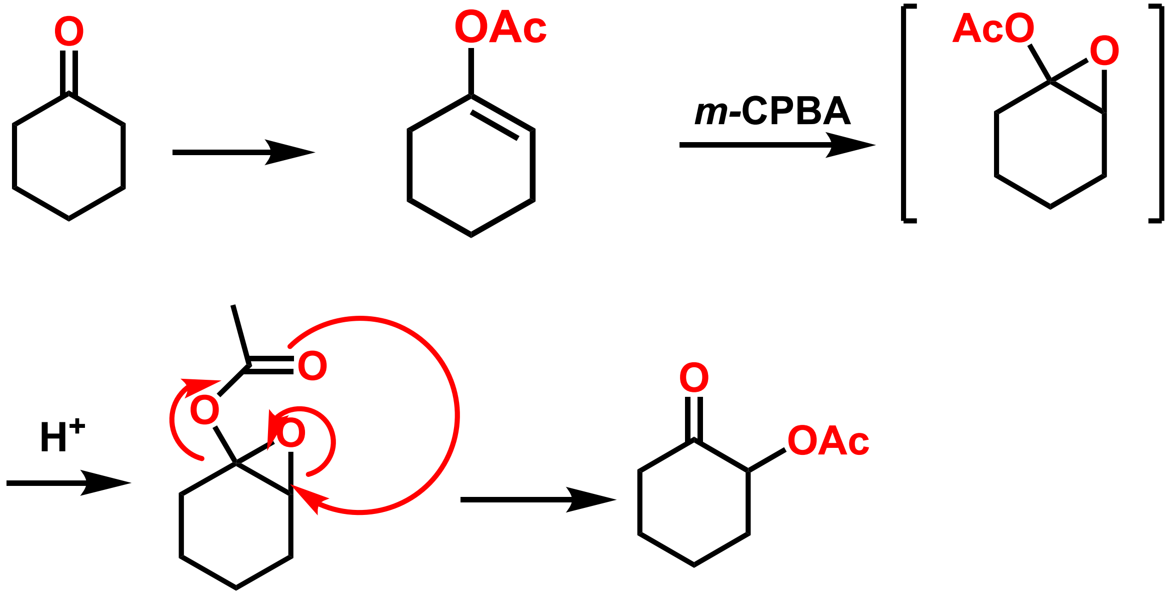


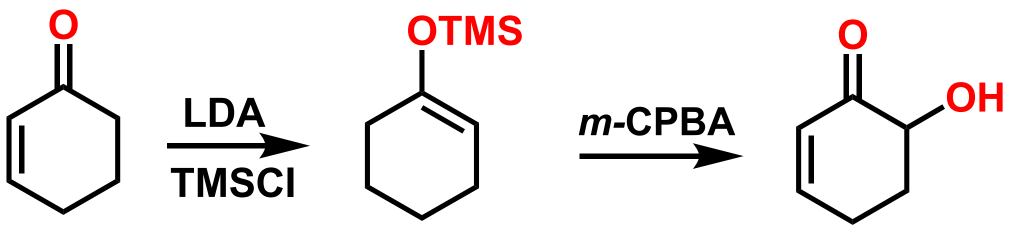
Epoxidation Directed by Ammonium salt

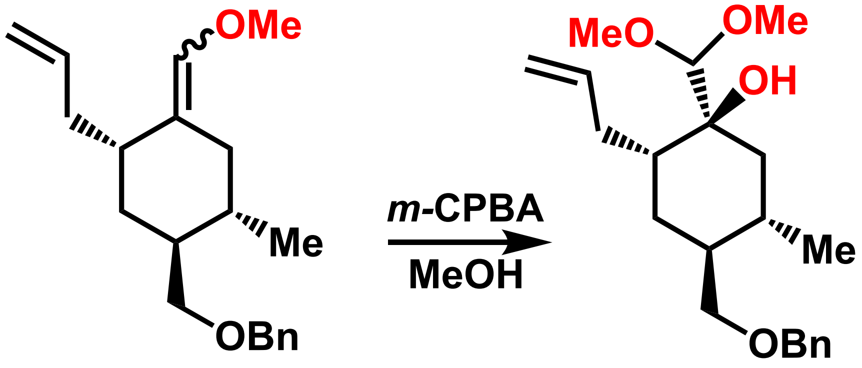


Rubottom Oxidation

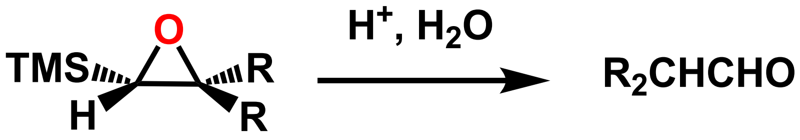








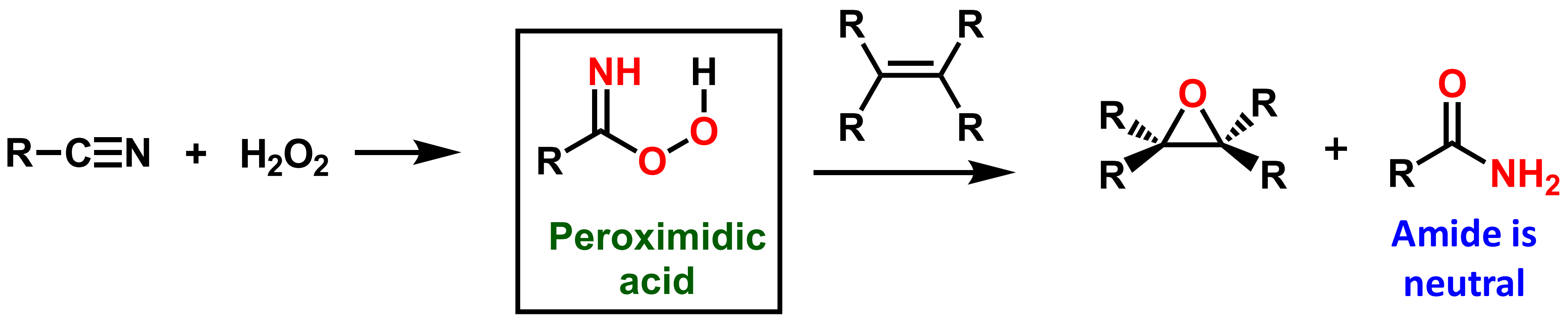
Epoxides derived from vinyl silanes are converted into aldehydes or ketones under mild acidic condition



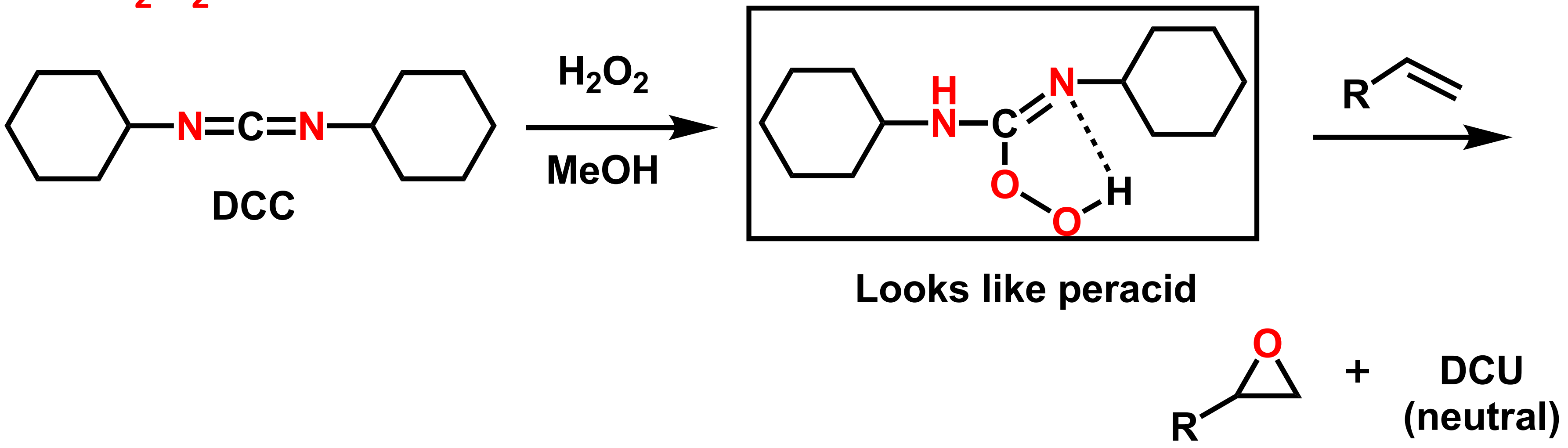
Epoxidation under Neutral Conditions

Epoxidation in non-acidic medium

Nitrile & H_2O_2

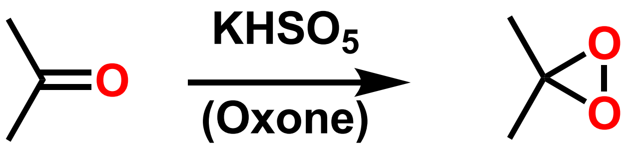


DCC-H_2O_2

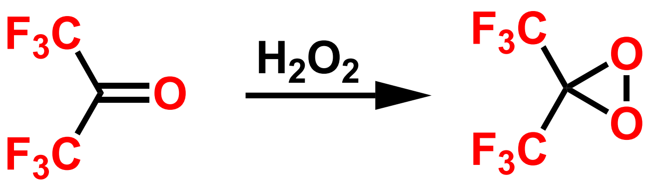


Dioxiranes

Dioxiranes (Murray's reagent)

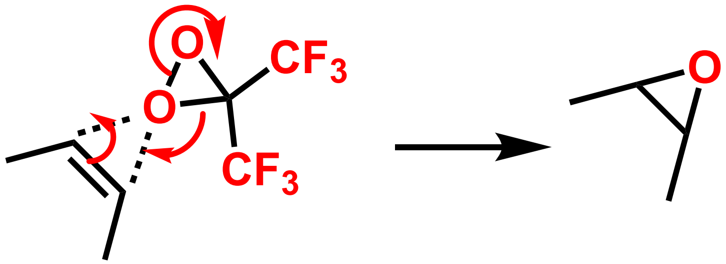


Dimethyldioxirane (DMDO)



More reactive analogue of DMDO

Dioxiranes Mechanism



Utility:

Epoxidation of olefins

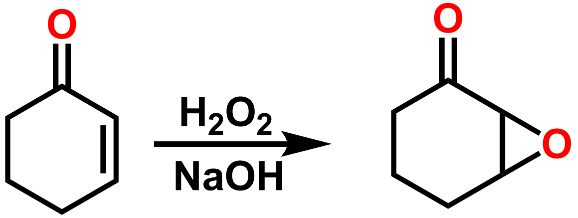
Oxidizes sulfides to sulfoxides & sulfones

Oxidation of amines to amino N-oxides

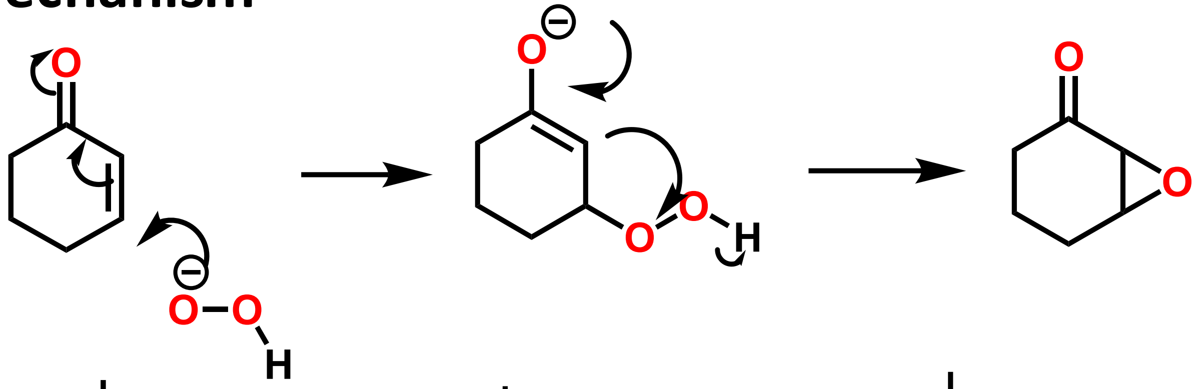
Oxidation of aldehydes to carboxylates

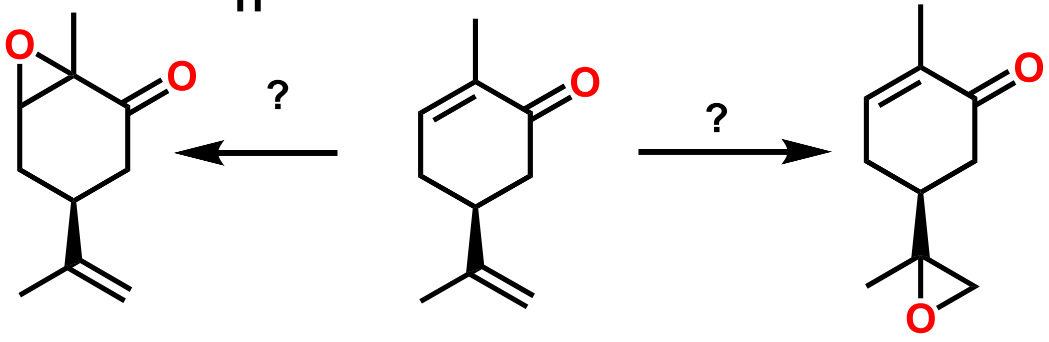
Epoxidation

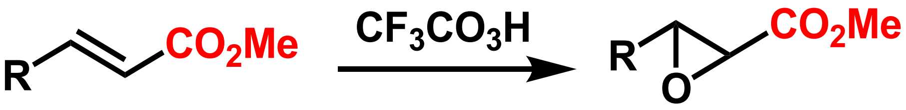
Epoxidation of Electrophilic Alkenes



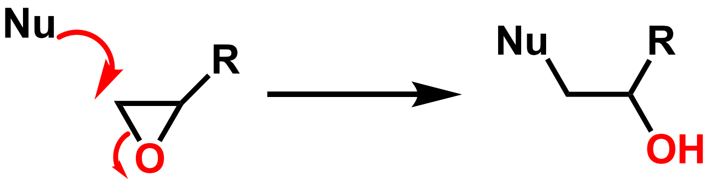
Mechanism

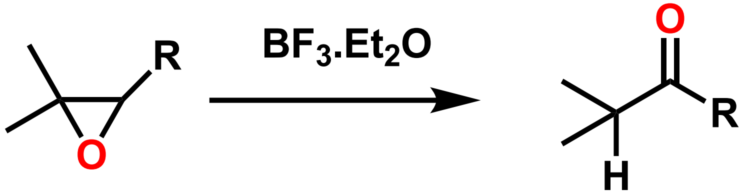


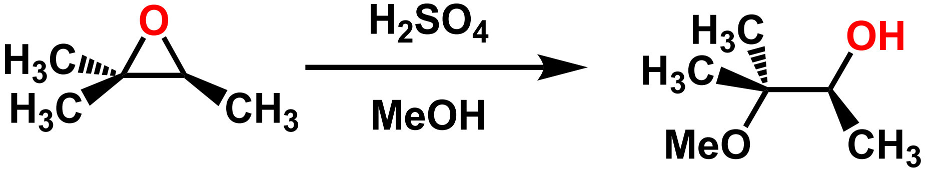


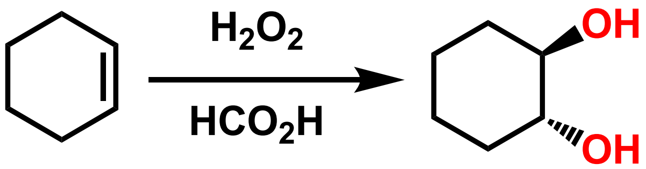


Transformation of Epoxides









Sharpless Asymmetric Epoxidation

1. Regioselective epoxidation of allylic and homoallylic alcohols

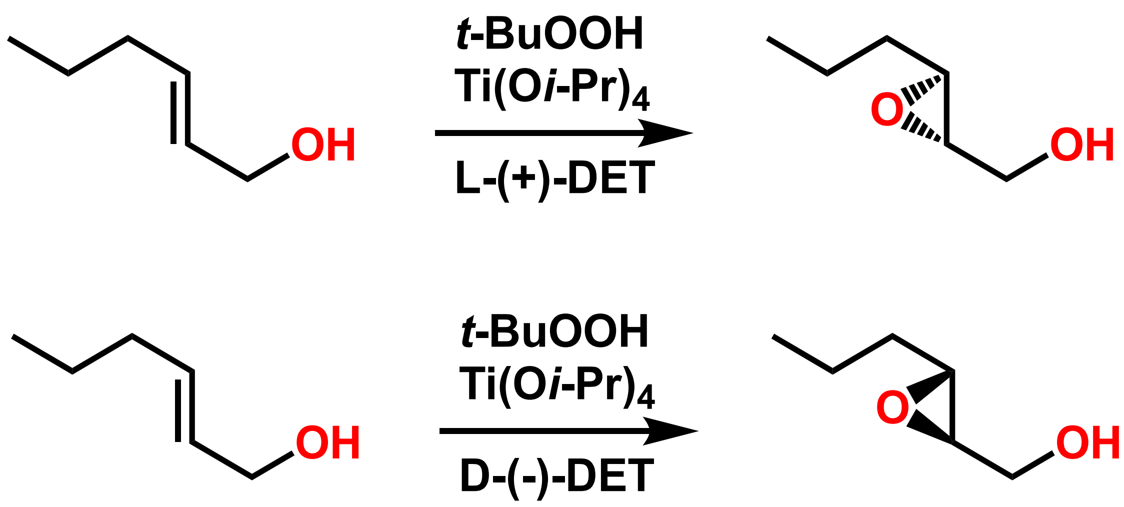
2. Isolated double bonds won't be epoxidized

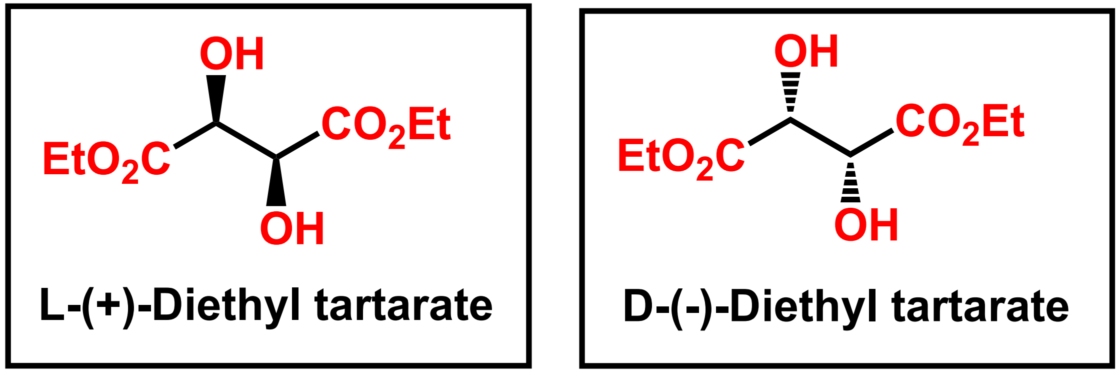
3. Most commonly used oxidant is *t*-BuOOH

4. Catalysts used are: $Ti(Oi\text{-}Pr)_4$, $VO(acac)_2$, $Mo(CO)_6$

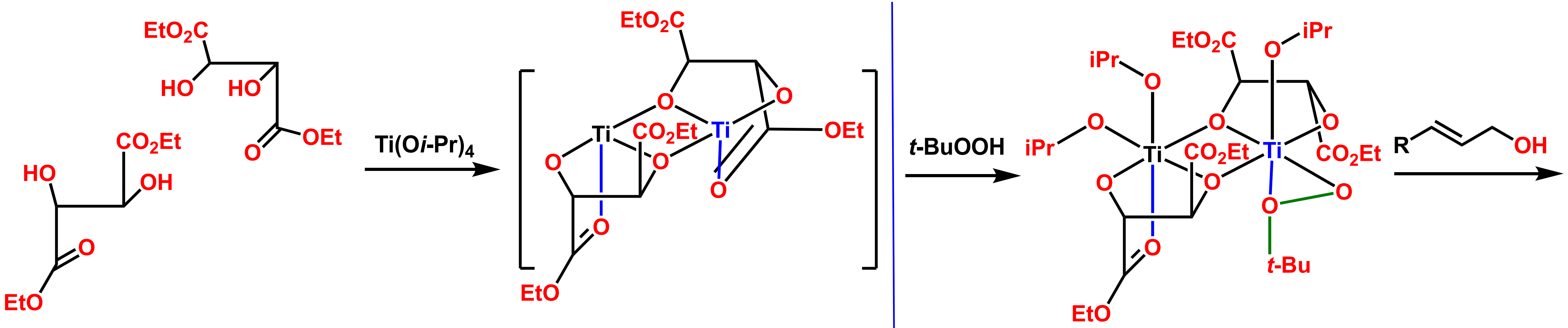
5. Chiral ligands used: DET (Diethyl tartarate) or DIPT (Diisopropyl tartarate)

6. Stereoselectivity occurs with respect to the alcohol

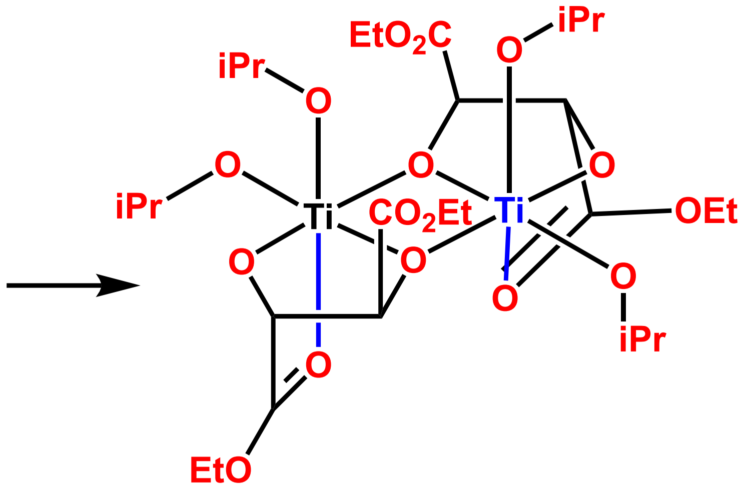




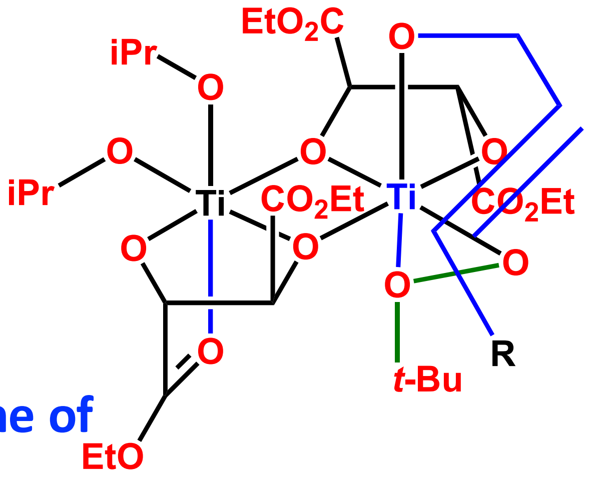
Mechanism of SAE



t-BuOOH replaces one of the –O-*i*Pr groups

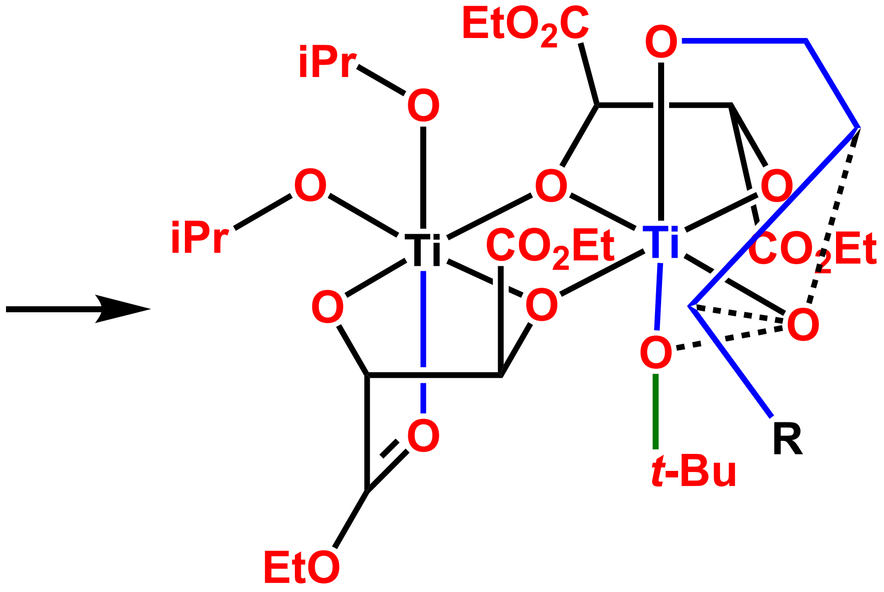


Two Titanium atoms bridged by tartrate ligands

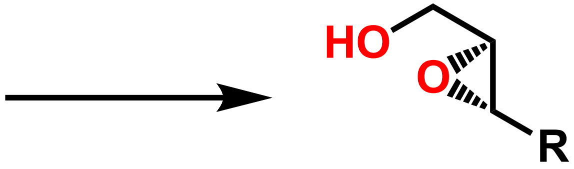


Allyl alcohol replaces one of the –O*i*-Pr groups

Mechanism of SAE



Now, the oxygen atom of the peroxide comes from the α-side of the double bond



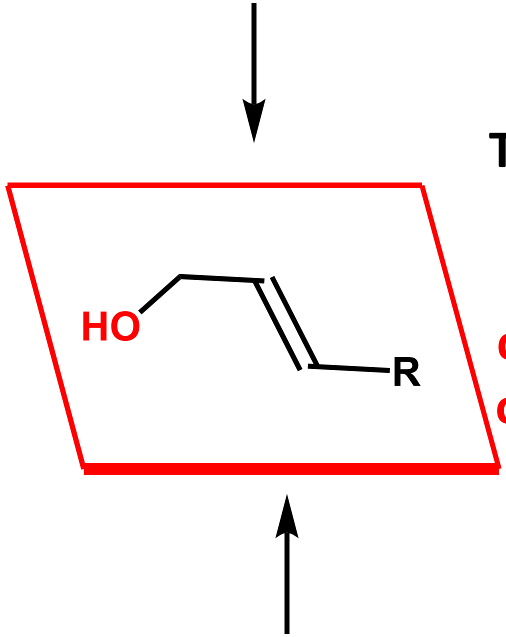
L-tartarate will produce α-epoxide

D-tartarate will produce β-epoxide

Stereochemical Outcome

D-(-)-Diethyl tartrate delivers the oxygen from the top face of the double bond

Keep the allylic alcohol on the top left hand side

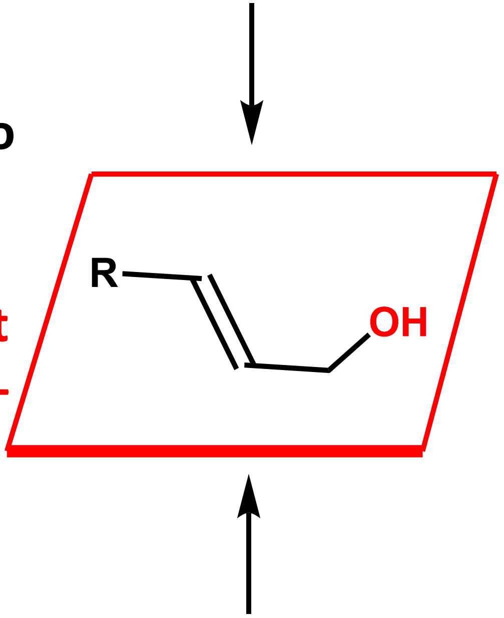


This reaction also can be done with catalytic amount of DET and Ti(O*i*-Pr)$_4$

L-(+)-Diethyl tartrate delivers the oxygen from the bottom face of the double bond

D-(-)-Diethyl tartrate delivers the oxygen from the top face of the double bond

This reaction also can be done with catalytic amount of DET and Ti(O*i*-Pr)$_4$



Keep the allylic alcohol on the bottom right hand side

L-(+)-Diethyl tartrate delivers the oxygen from the bottom face of the double bond

Salient Features

1. Reaction is carried out with 5-10 mol% of Ti catalyst

2. Addition of Molecular Sieves accelerate the reaction

3. Use of stoichiometric amount of Ti catalyst gives much higer '*ee*'

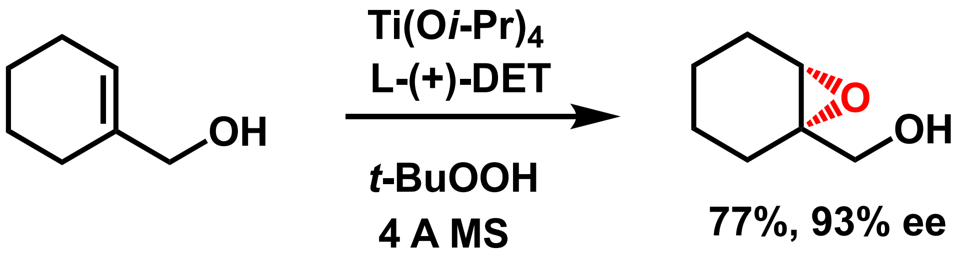
4. Allylic alchols with E-geometry give very good yield and higher *ee*.

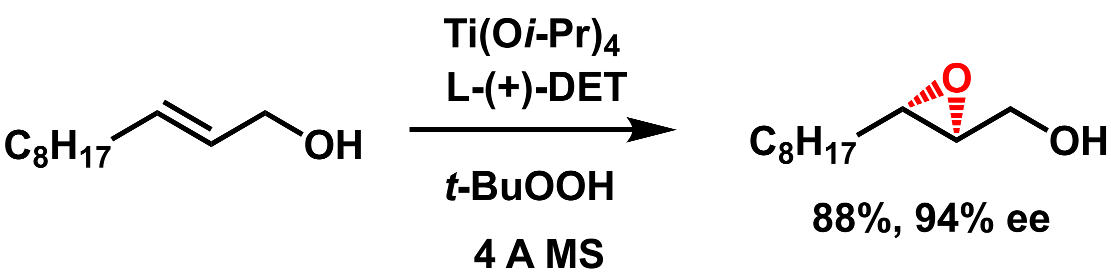
5. Unhindered Z-allylic alcohols are also excellent substrates

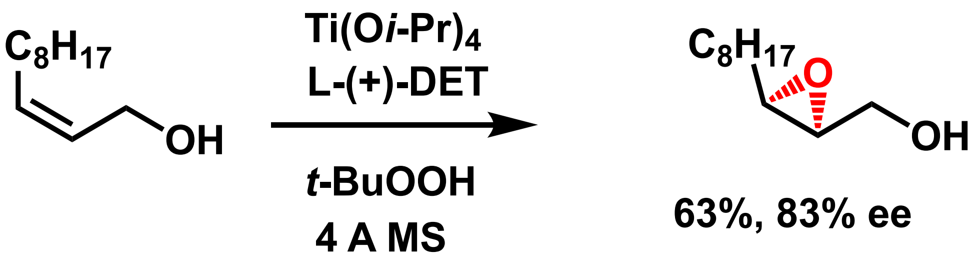
6. Branched Z-allylic alcohols, especially at C4 position give reduced selectivity

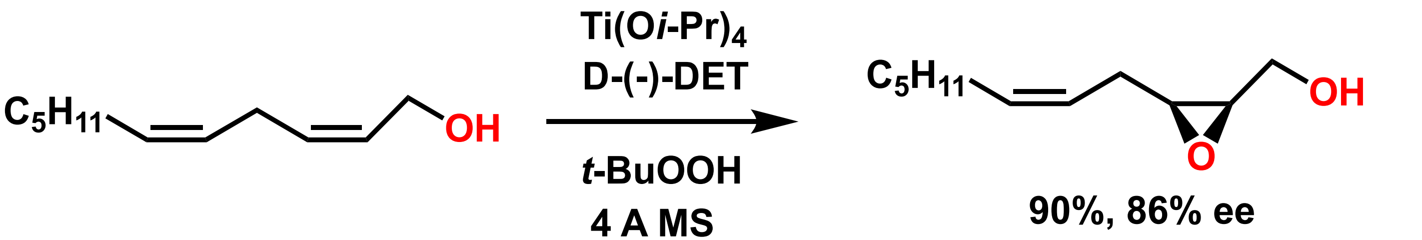
7. Tolerant to the presence of esters, ketones, acetals, enones etc.

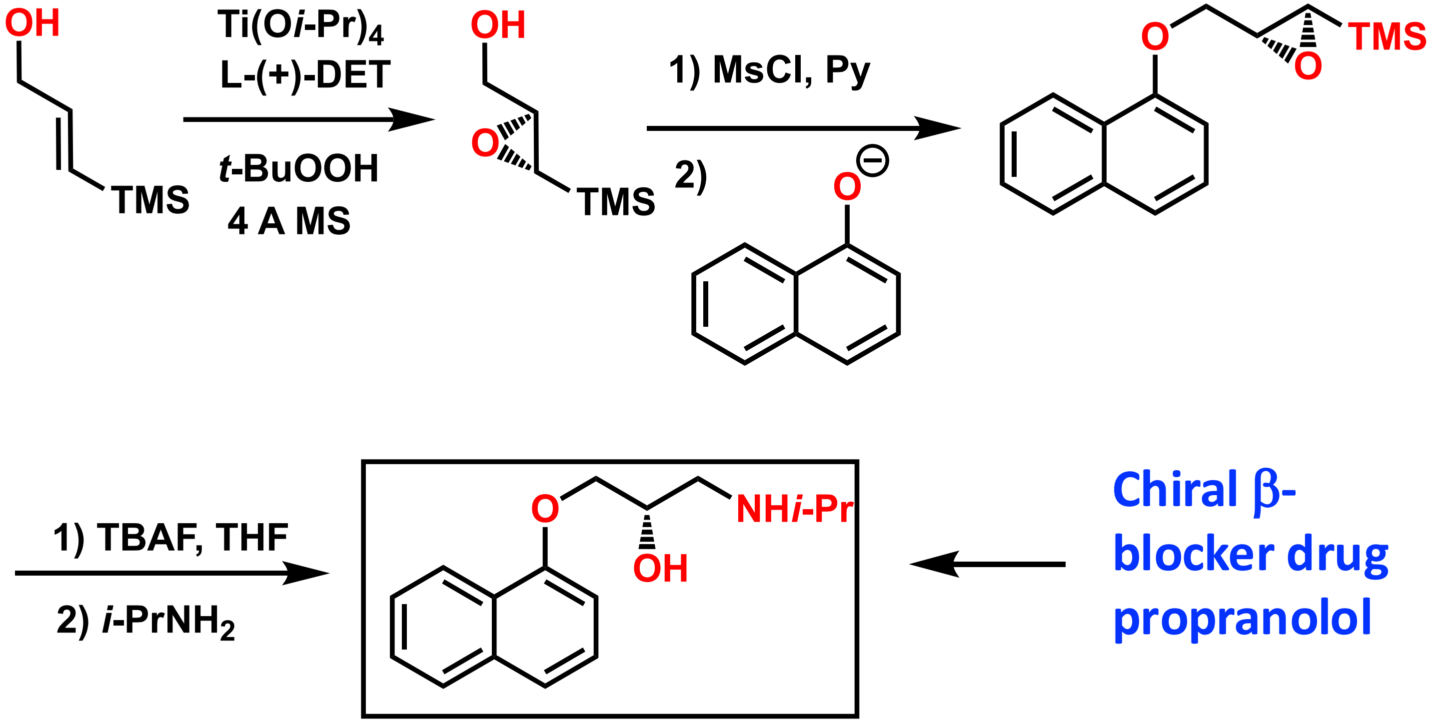
Examples





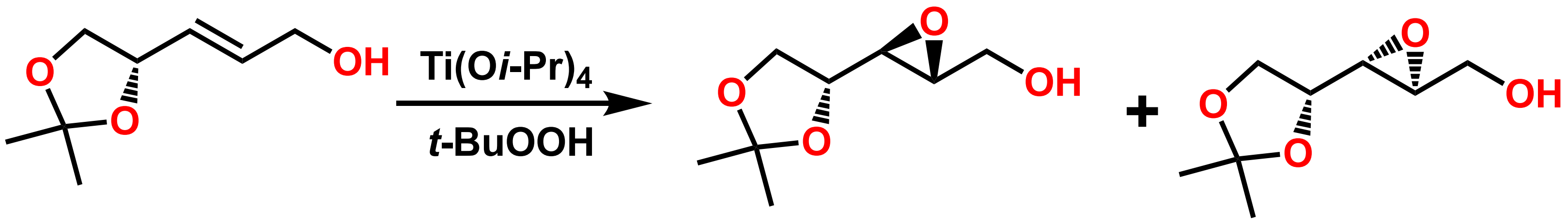






Chiral β-blocker drug propranolol

Matching & Mismatching



No Ligand:	2.3	:	1
(-)-DIPT:	90	:	1
(+)-DIPT:	1	:	22

In the absence of chiral reagent, the chiral center in the substrate controls the diastereoselectivity to a certain extend – (Called Substrate Control)

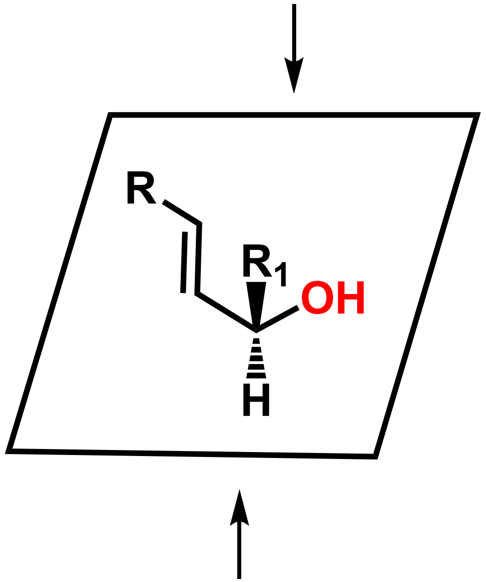
Use of chiral reagents will outweigh the effect of chiral center in the substrate but it could match or mismatch with the stereoselectivity due to the chiral center present in the molecule

Stereoselectivity matched with (-)-DIPT and mismatched with (+)-DIPT

Kinetic Resolution through SAE

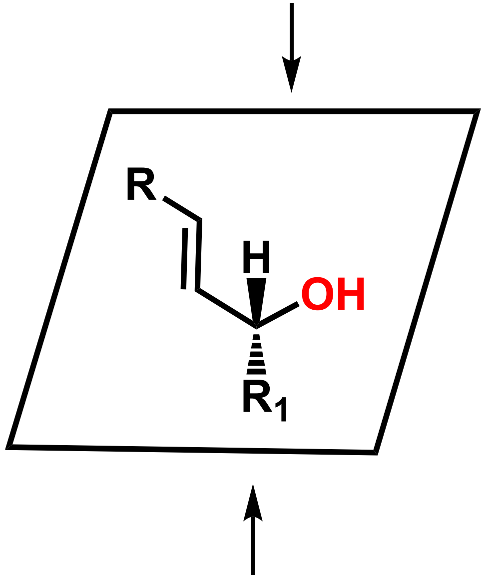
In the case of epoxidation of racemic secondary allylic alcohols, one isomer undergoes epoxidation at a much faster rate than the other

Epoxidation with D-(-)-Diethyl tartrate is slow



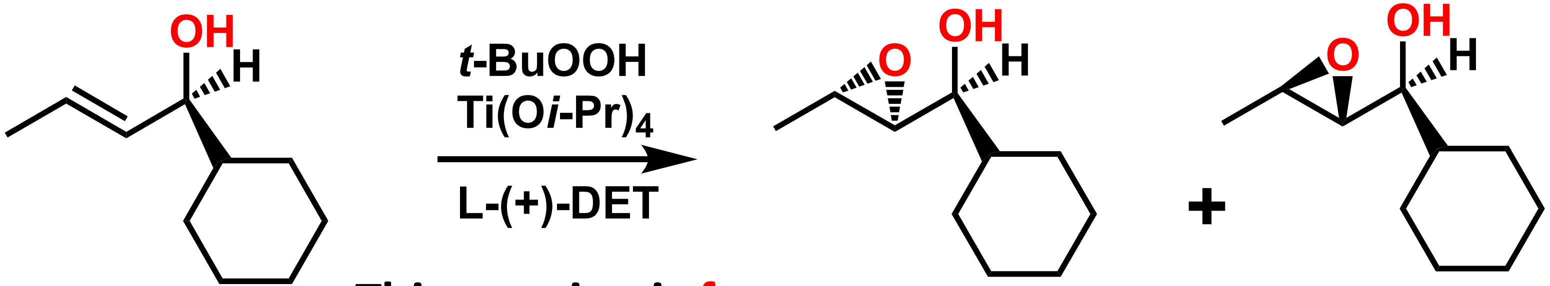
Epoxidation with L-(+)-Diethyl tartrate is fast

Epoxidation with D-(-)-Diethyl tartrate is fast



Epoxidation with L-(+)-Diethyl tartrate is slow

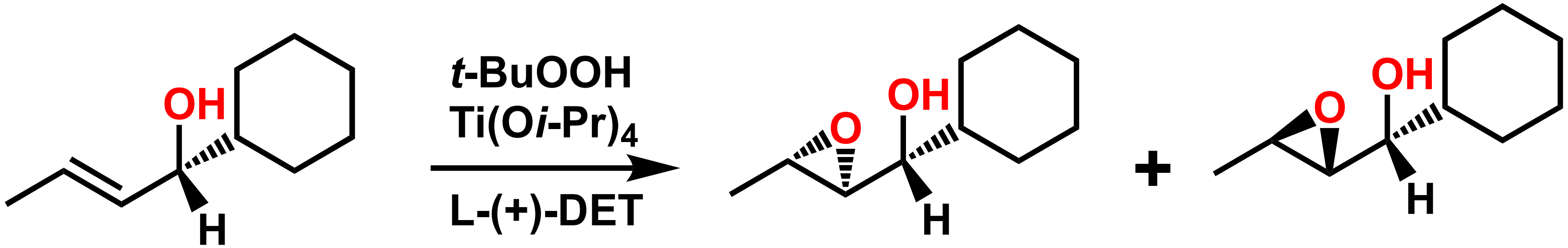
Kinetic Resolution through SAE



X

This reaction is **fast**

A (98 %) : B (2%)



Y

This reaction is **slow**

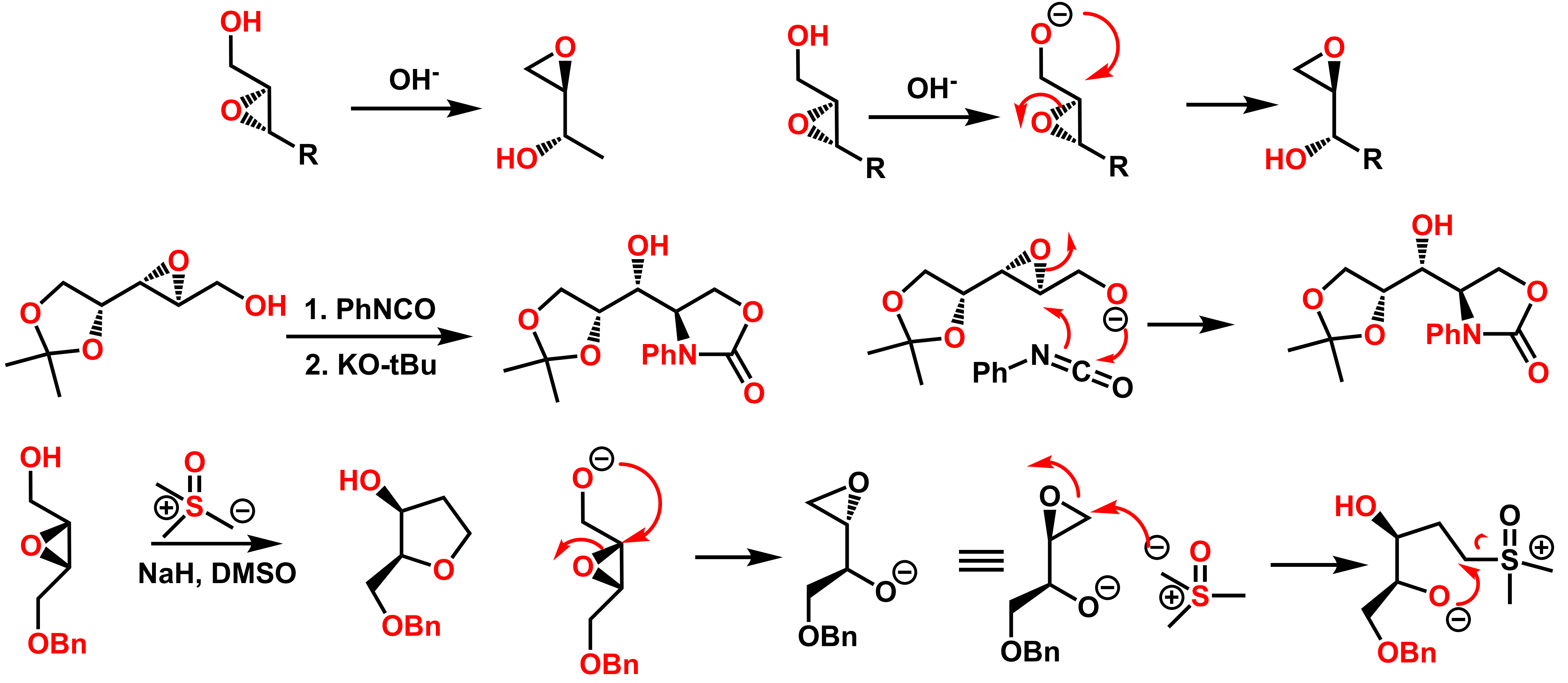
C (62 %) : B (38 %)

If the reaction is run to only 50% conversion, Y is recovered with 95 % optical purity and A is formed with 98% optical purity

Yield of this reaction is limited to less than 50%

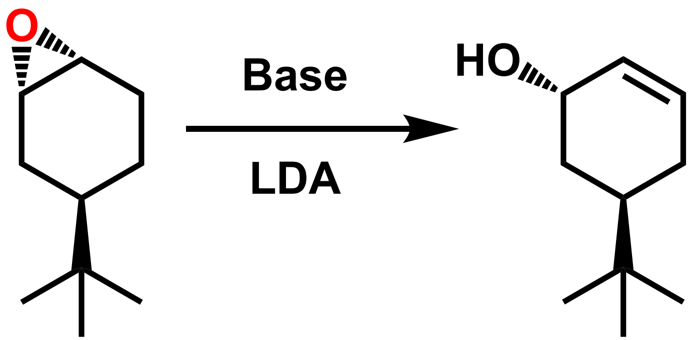
Payne Rearrangement

Payne rearrangement- Base mediated rearrangement of epoxyalcohols

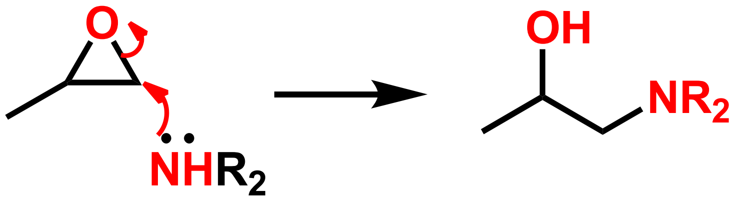


Transformations of Epoxides

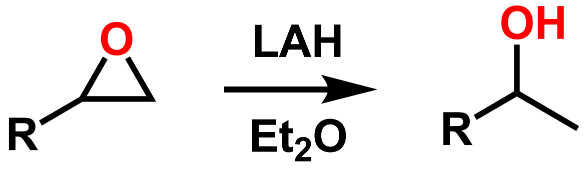
Base catalyzed ring opening of epoxides leads to allylic alcohols



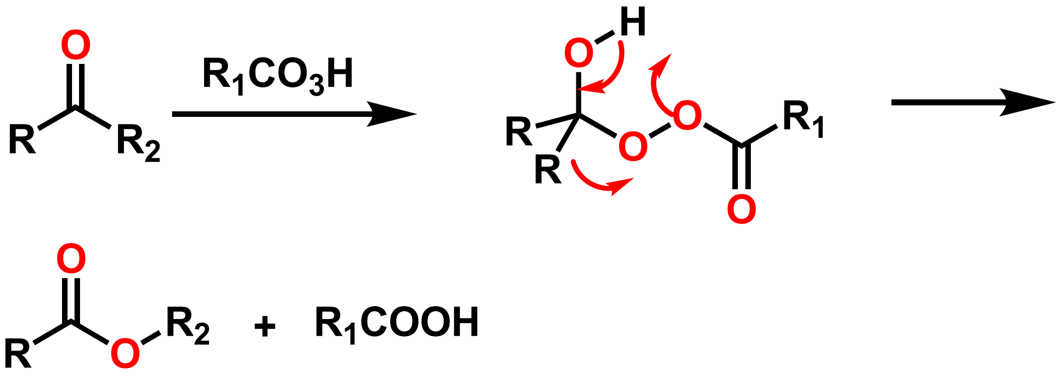
$LiClO_4$, CF_3SO_3Li, $Mg(ClO_4)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$ catalyze the epoxide ring opening.



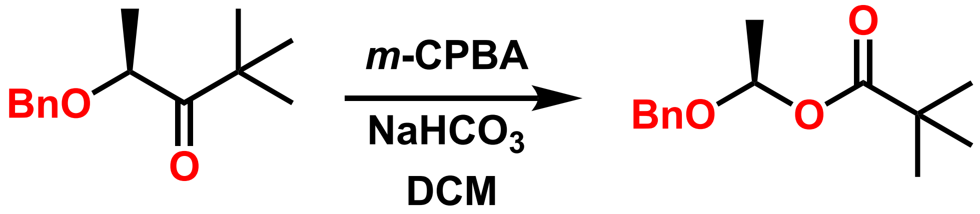
LAH acts as a nucleophilic agent & attacks at the less substituted carbon atom of the epoxide ring. DIBAL-H also serves the purpose

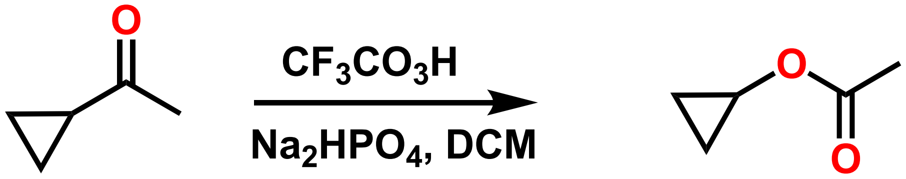


Baeyer Villiger Oxidation

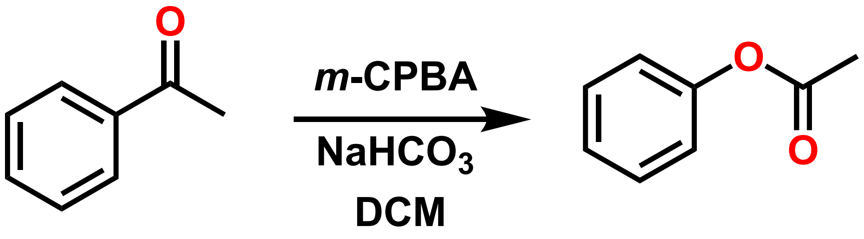


The migratory aptitudes are: Alkoxyalkyl >*t*-Alkyl> cyclohexyl=secondary alkyl=benzyl=Phenyl> vinylic>primary alkyl>cyclopropyl>methyl

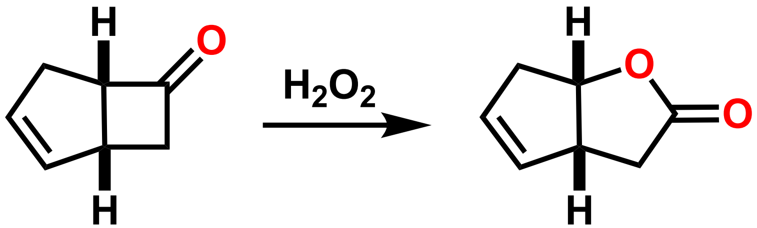




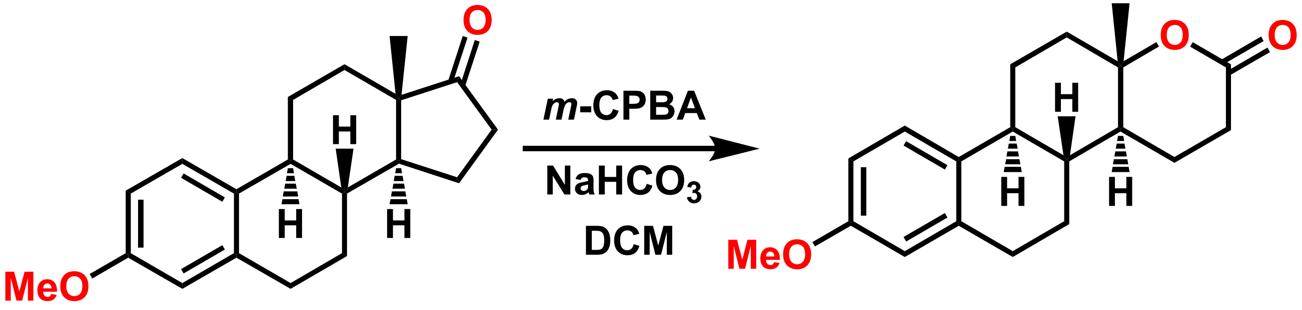
Acid catalyzed side reactions can be suppressed by phosphate buffer



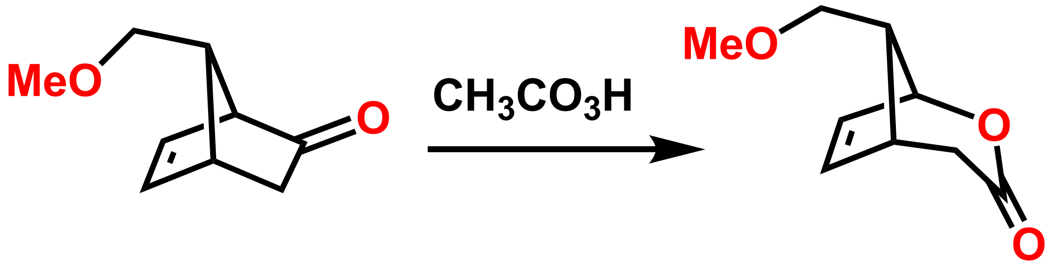
meta directing group ... *ortho & para* directing group

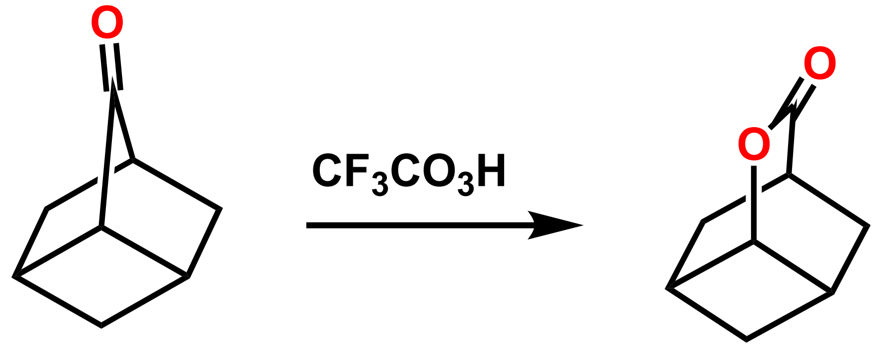


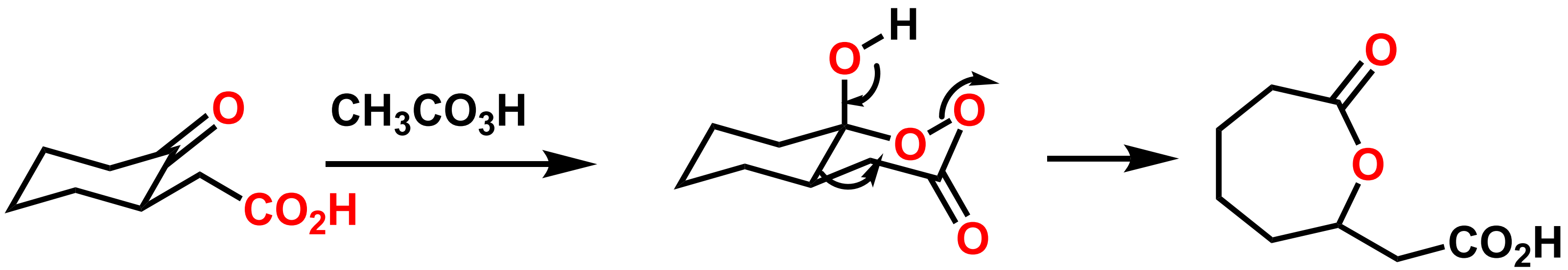
Normally, most ketones do not react with H_2O_2 but the above one does



Baeyer Villiger Oxidation





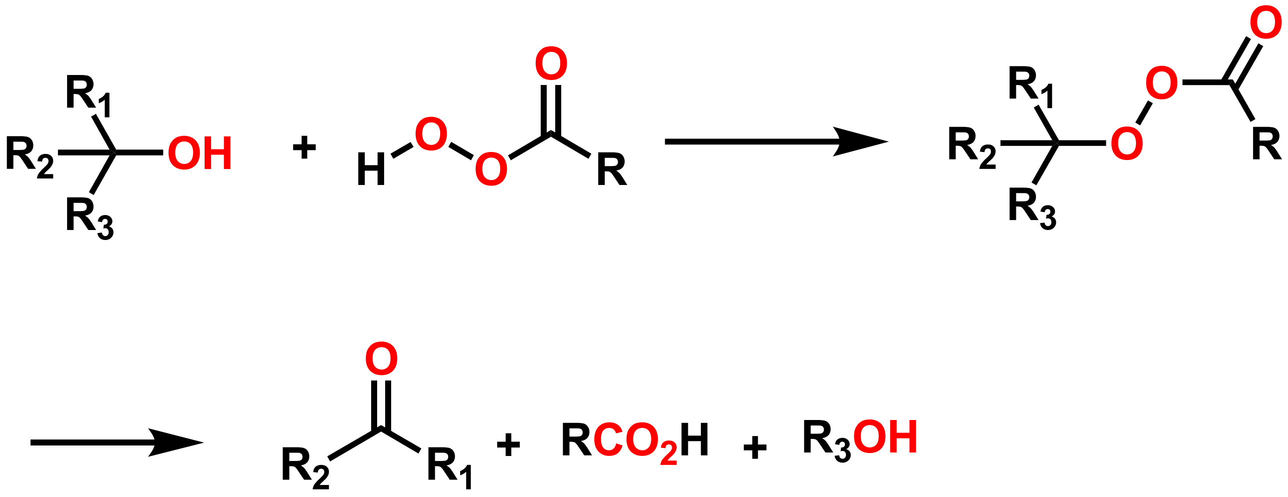


Criegee Rearrangement

This rearrangement was reported by Criegee in 1944

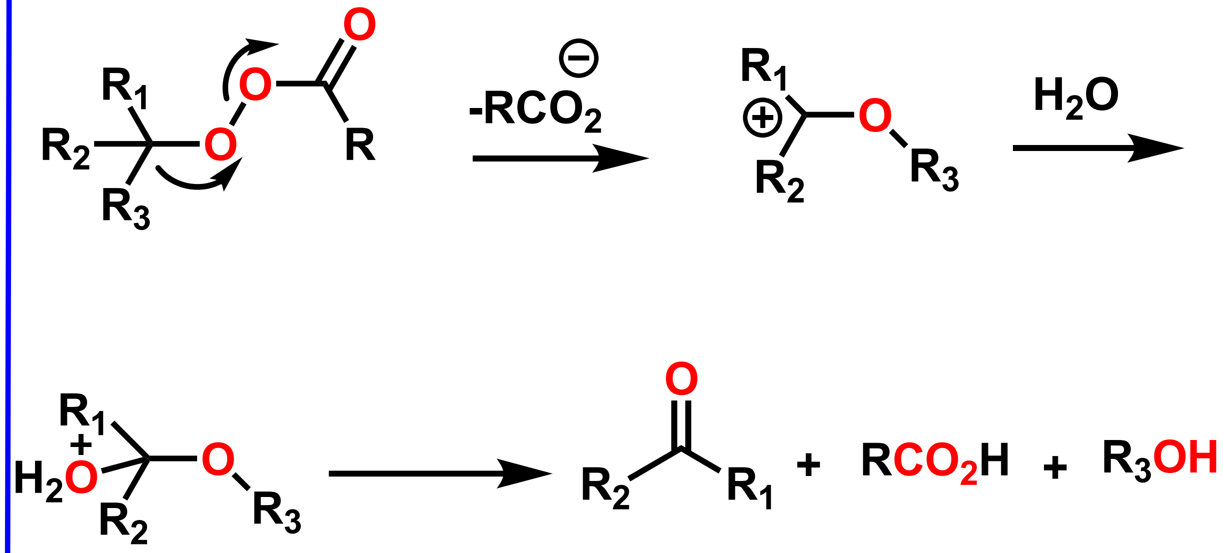
Baeyer Villiger oxidation is a subset of Criegee rearrangement

Rearrangement of peroxyester into ketone, ester or carbonate and alcohol via oxygen insertion

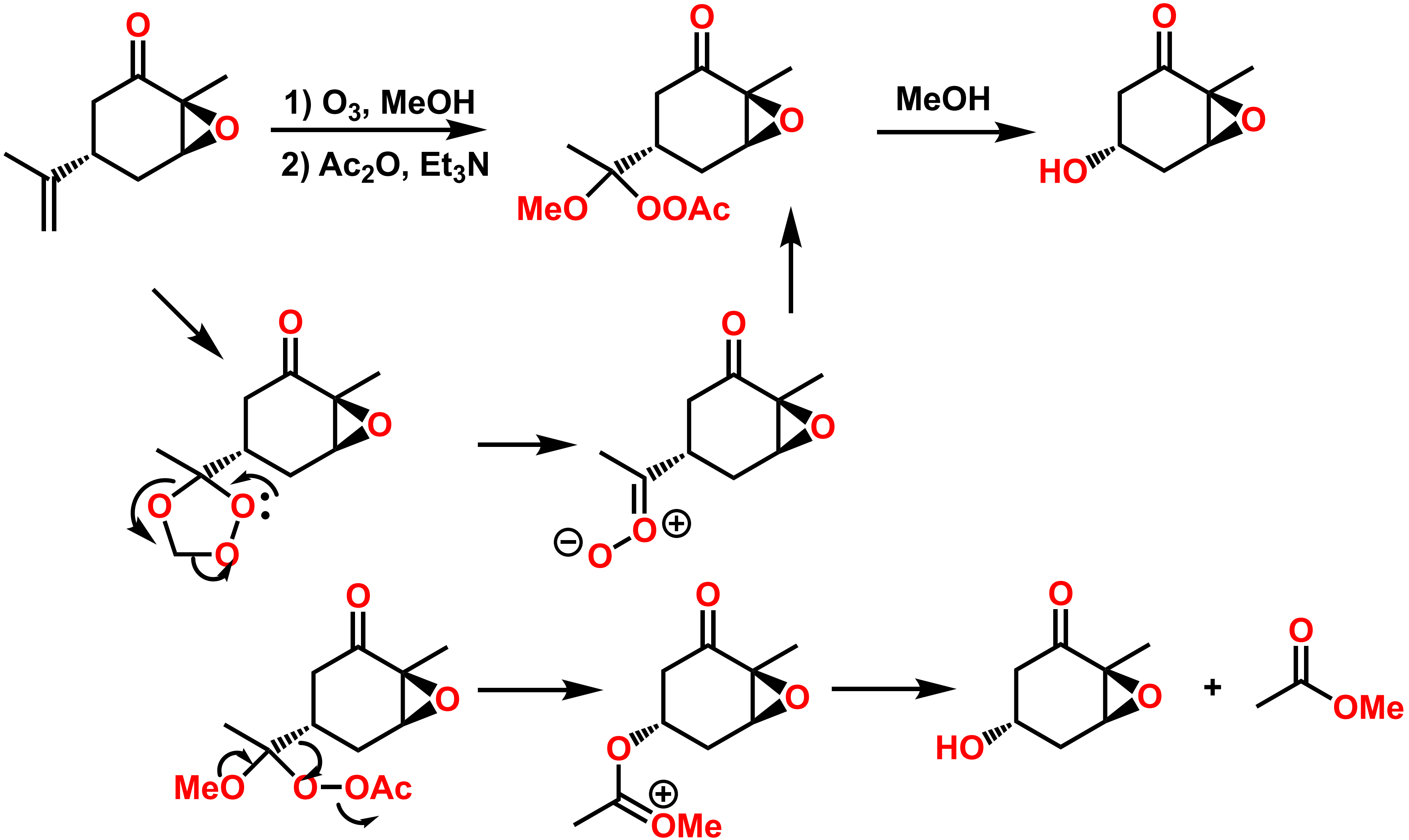


Peroxyesters are prepared by reaction between peracid and tertiary alcohols

Mechanism



Criegee Rearrangement



Oxidation with Singlet Oxygen

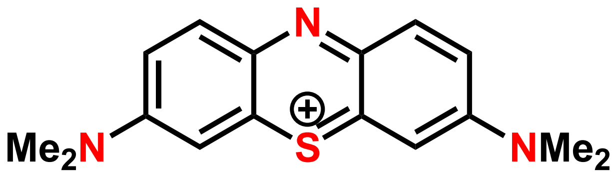
Generation of singlet oxygen:

Photosensitizer + hν ⟶ ^{1}[Photosensitizer]*

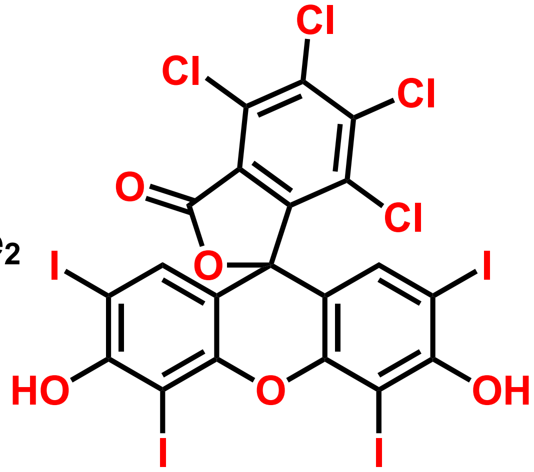
^{1}[Photosensitizer]* ⟶ ^{3}[Photosensitizer]*

^{3}[Photosensitizer]* + $^{3}O_2$ ⟶ Photosensitizer + $^{1}O_2$

Photosensitizers:



Methylene blue

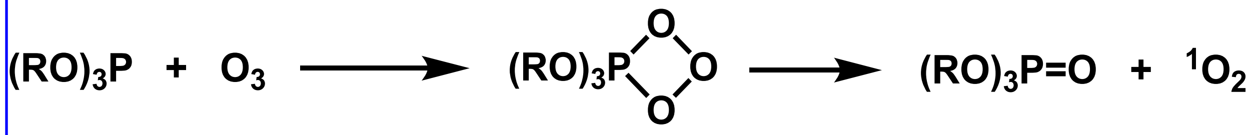


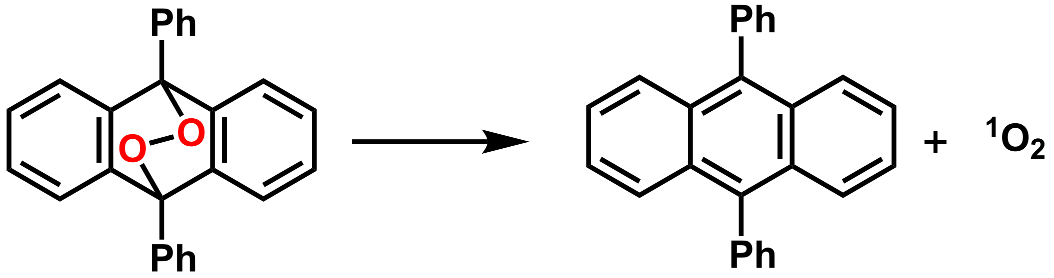
Rose Bengal

Tetraphenylporphyrin

Generation of singlet oxygen:

H_2O_2 + ^{-}OCl ⟶ $^{1}O_2$ + H_2O + Cl^{-}

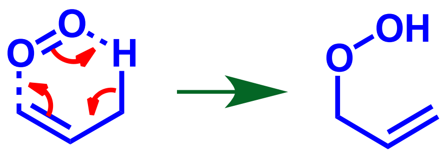




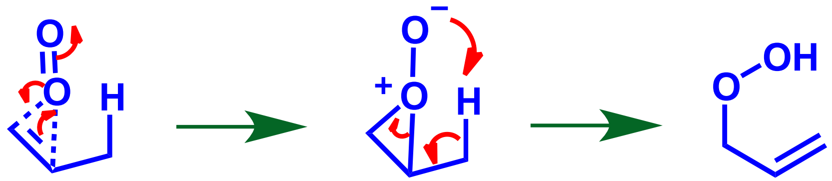
Oxidation with Singlet Oxygen

Mechanism:

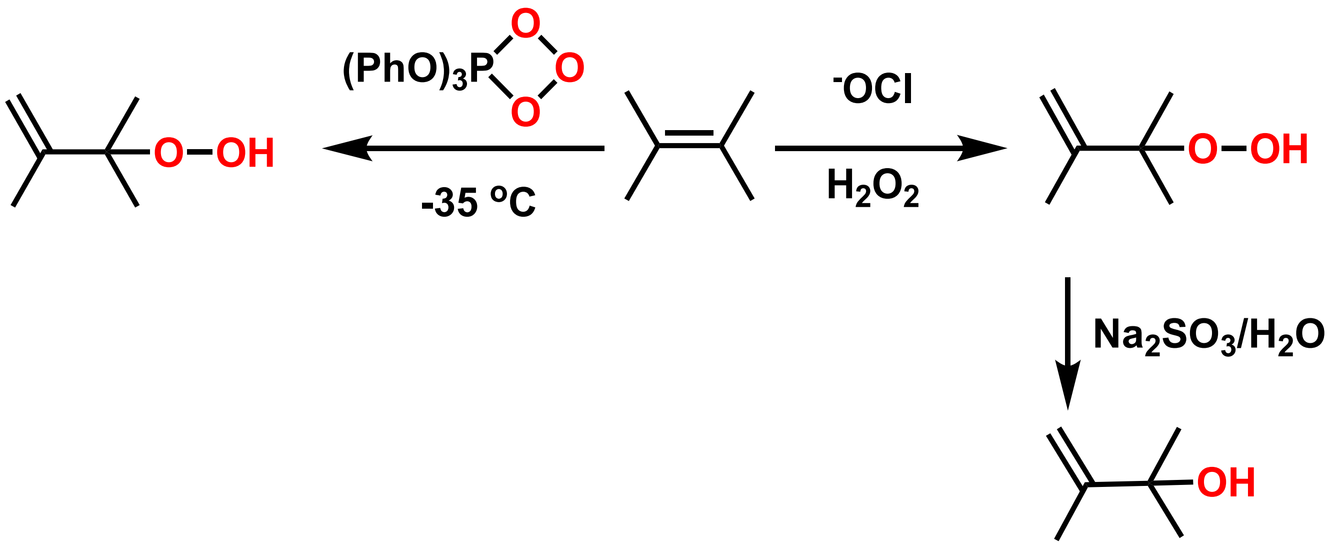
1. Concerted mechanism



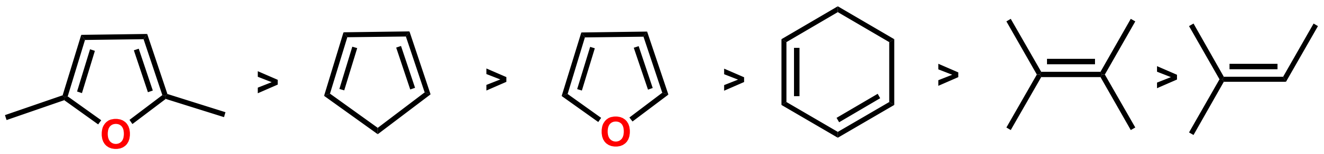
2. Perepoxide-intermediate mechanism



There is a preference for removal of a hydrogen from more congested side of the double bond

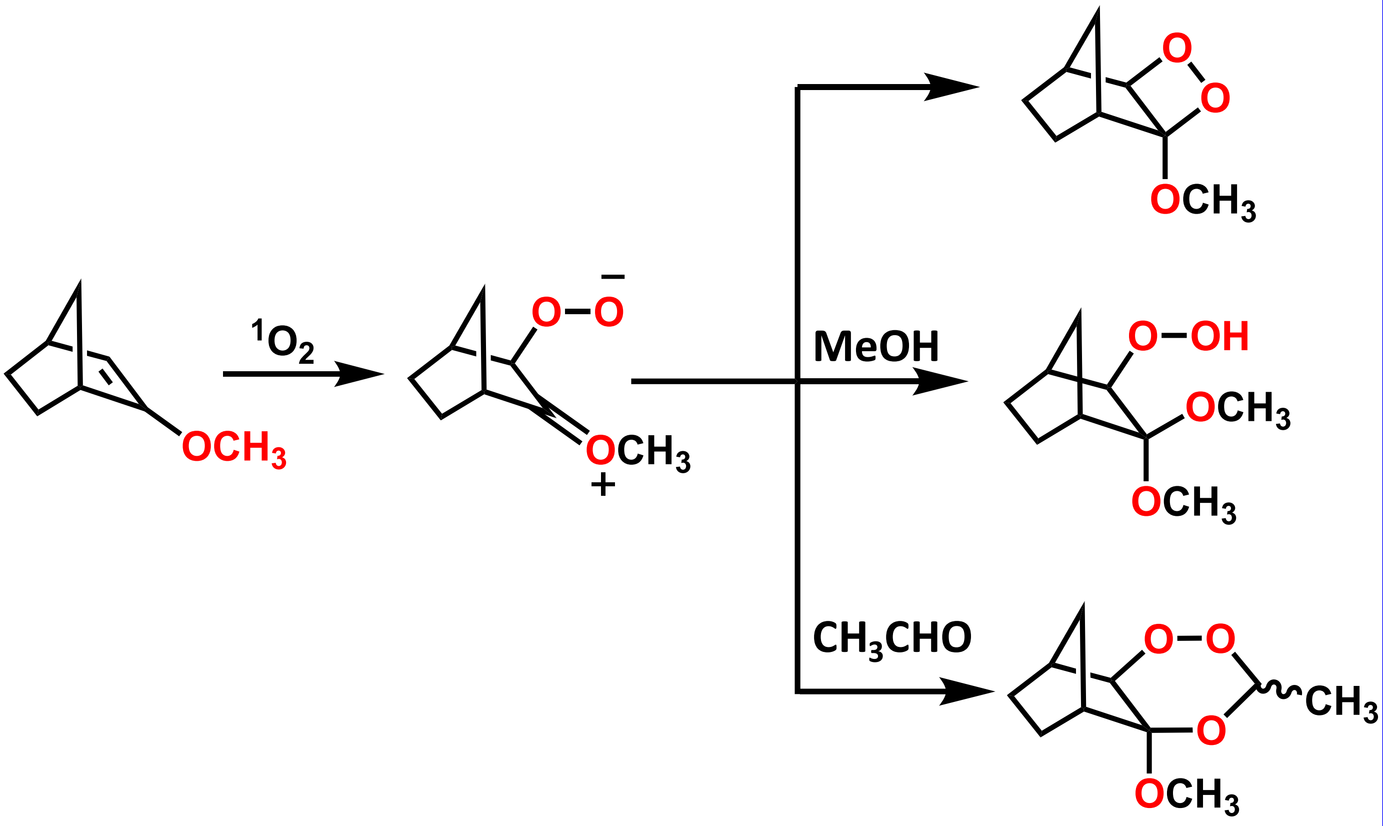


Relative rates of oxidation:

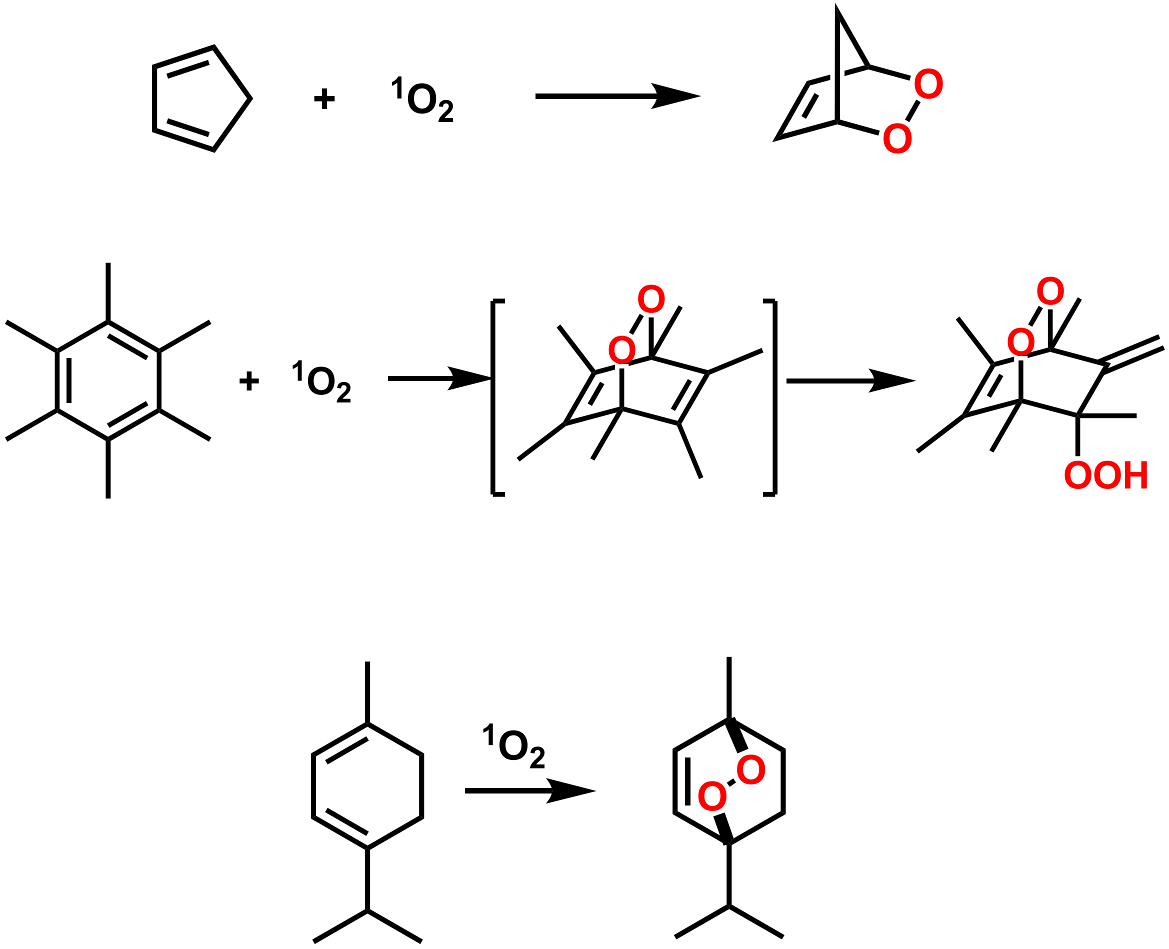


Singlet Oxygen

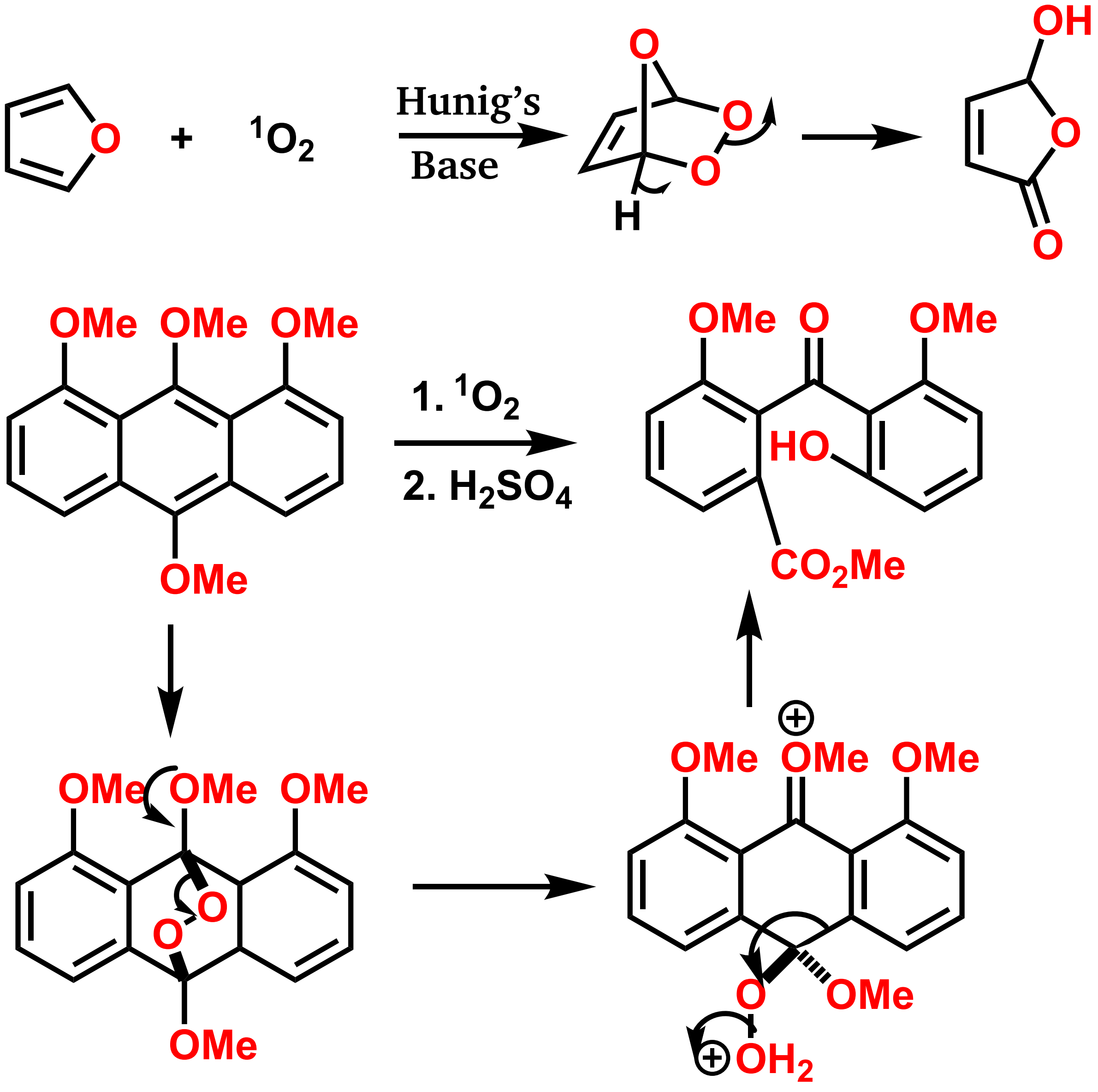
Oxidation with Singlet Oxygen

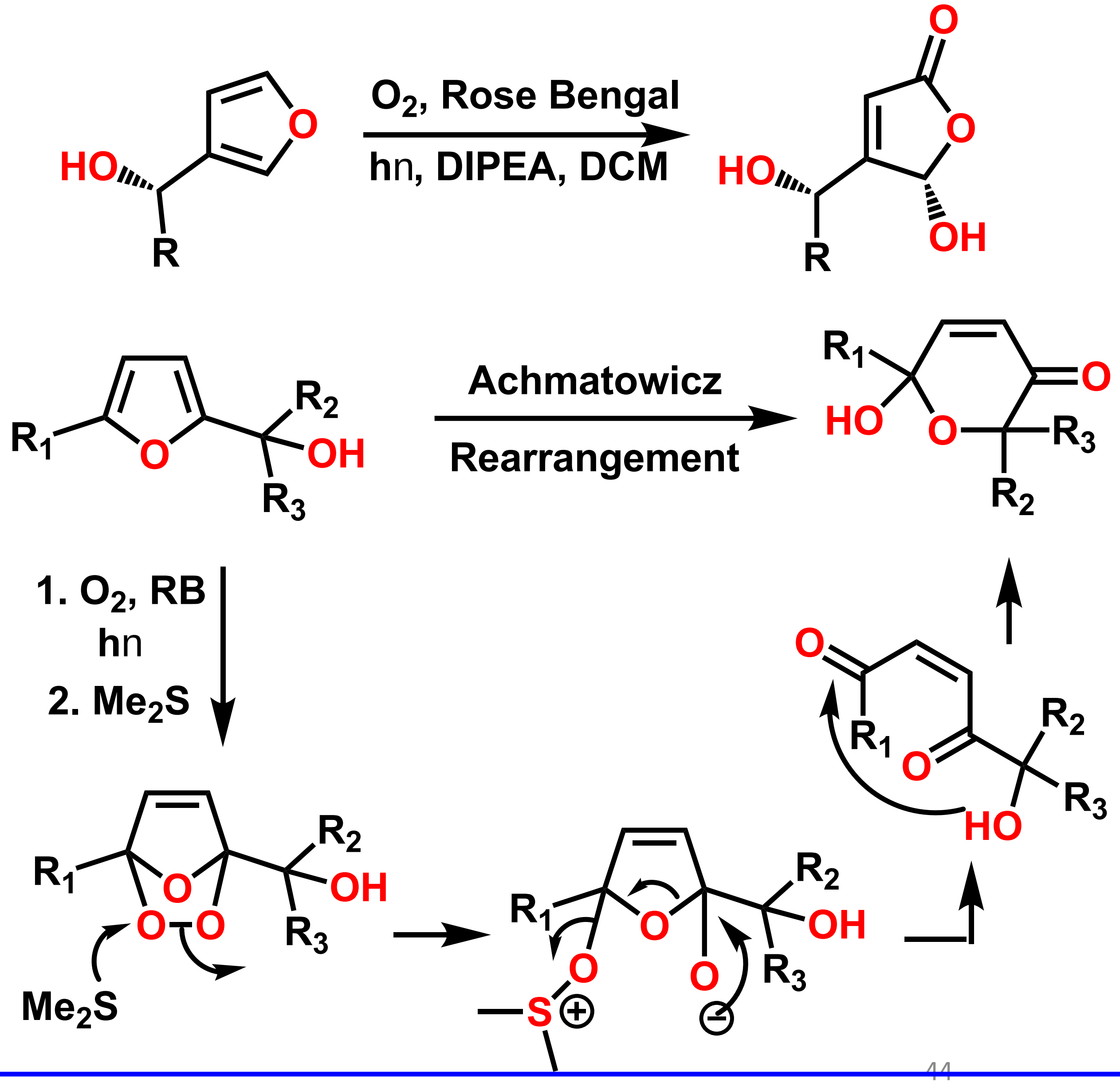


[4+2] with Singlet Oxygen

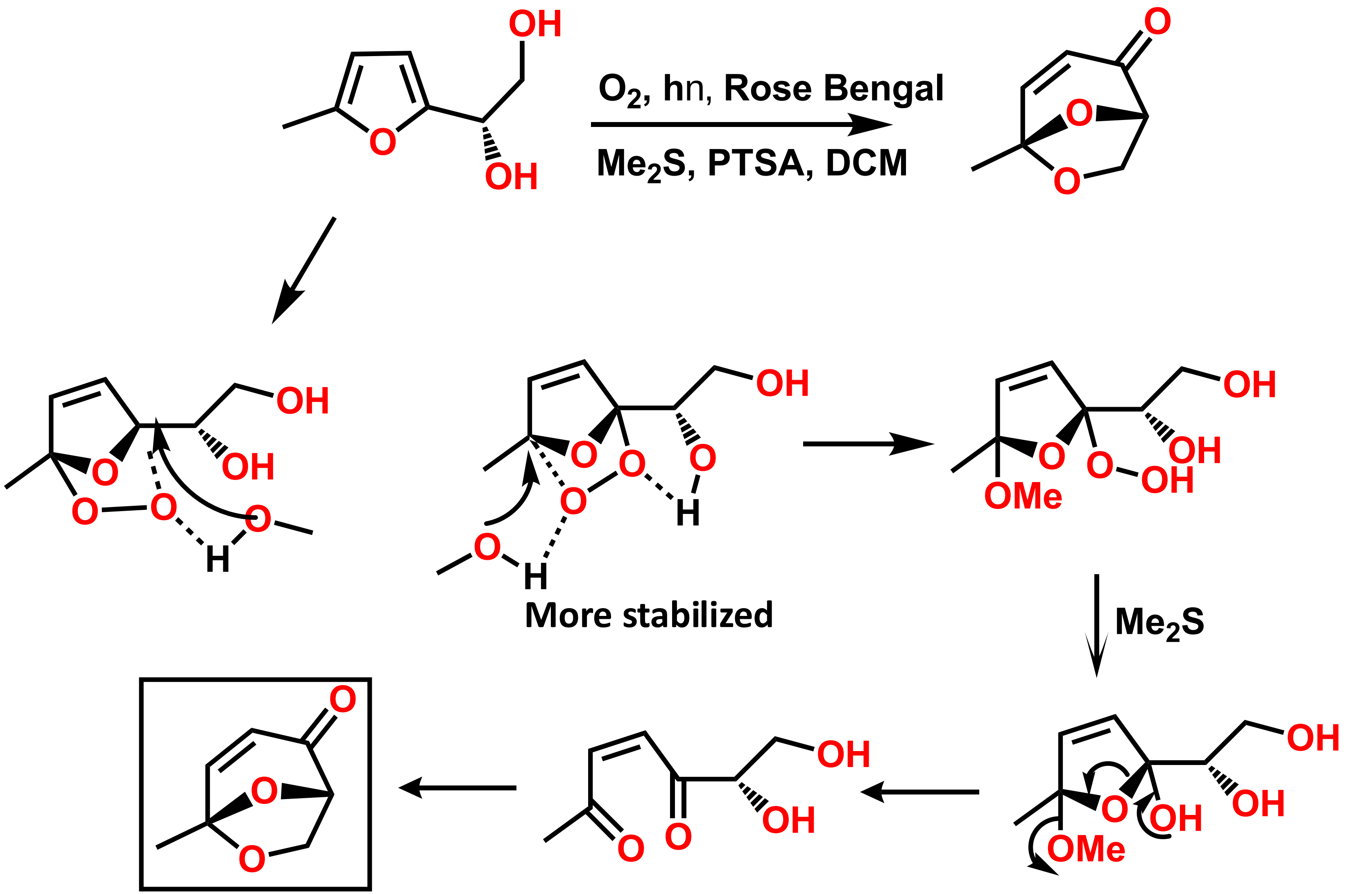


[4+2] with Singlet Oxygen

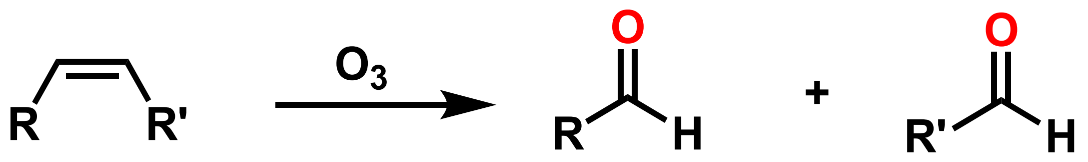




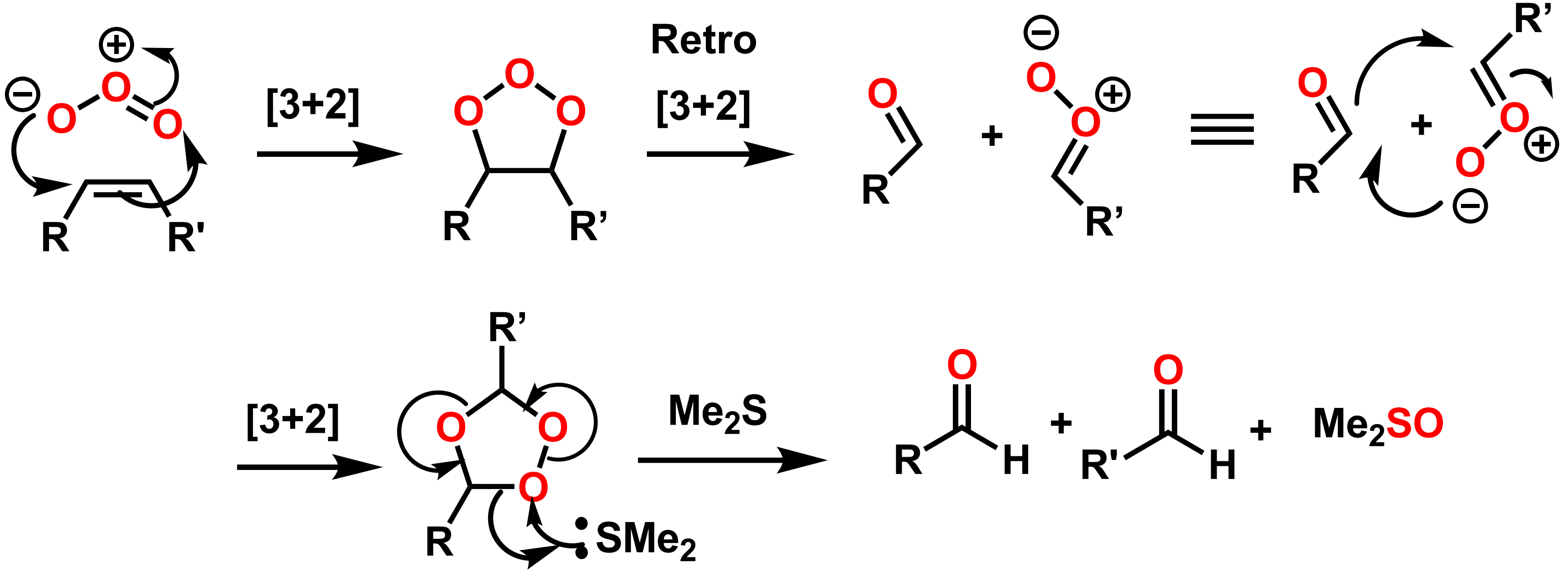
Singlet Oxygen



Ozonolysis



Mechanism



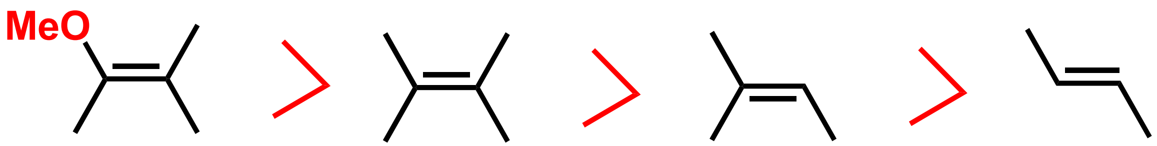
$PPh_3 \longrightarrow Ph_3P{=}O$

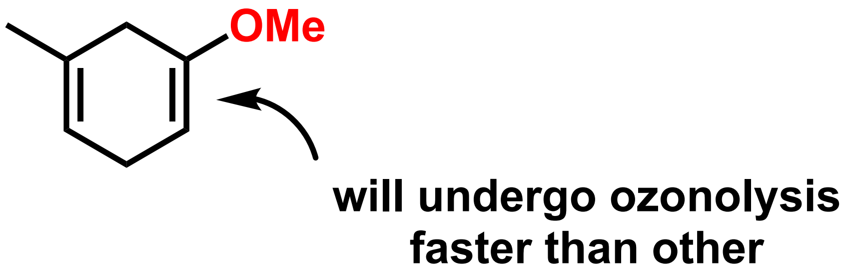
$Zn \longrightarrow ZnO$

Ozonide $\xrightarrow[EtOH]{NaBH_4}$ RCH_2OH

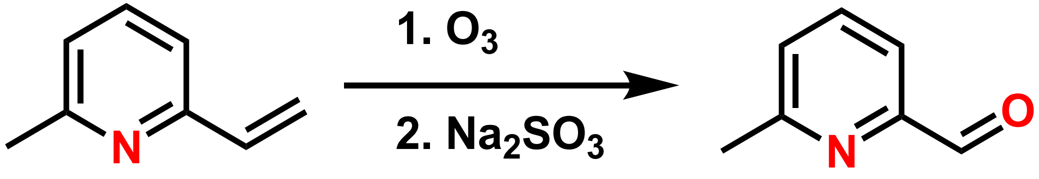
Ozonide $\xrightarrow[AcOH]{H_2O_2}$ RCO_2H

Reactivity

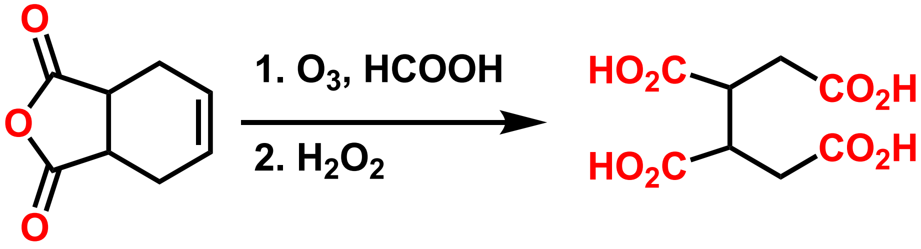




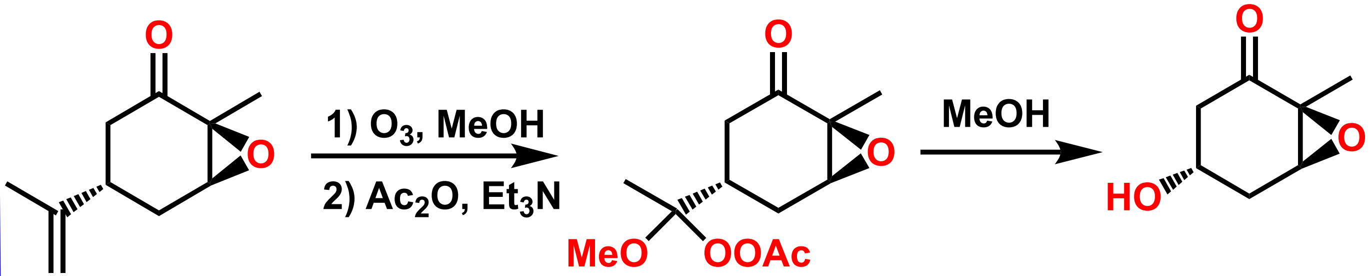
Reductive Work-up



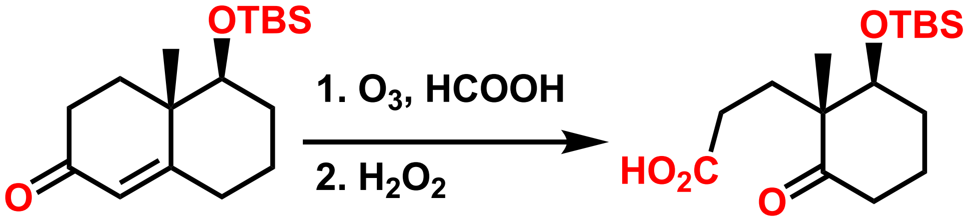
Oxidative Work-up



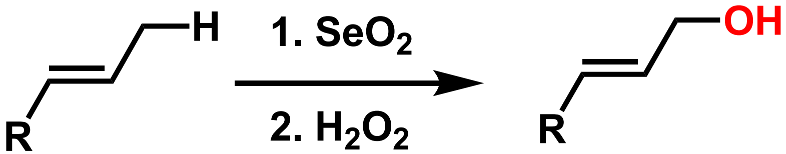
Criegee Rearrangement



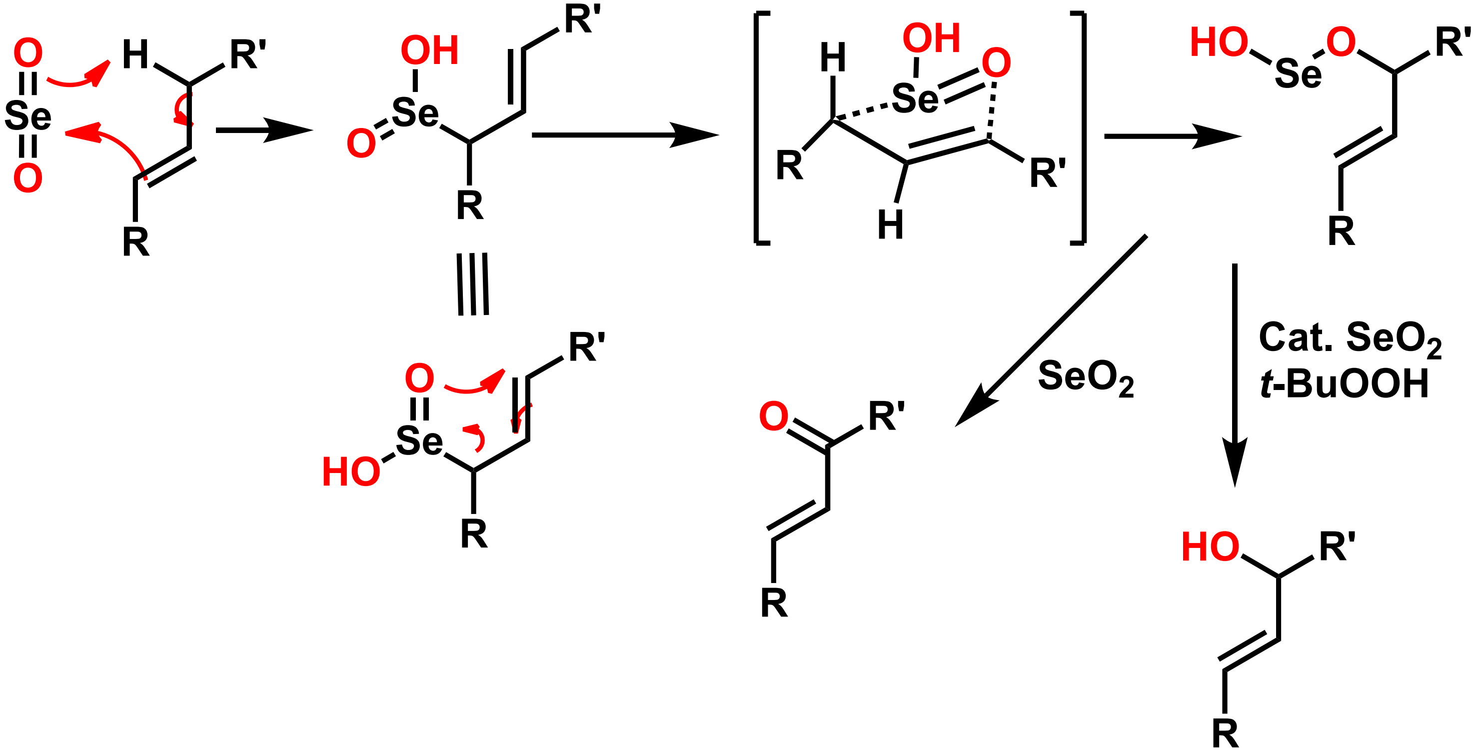
Oxidative Cleavage

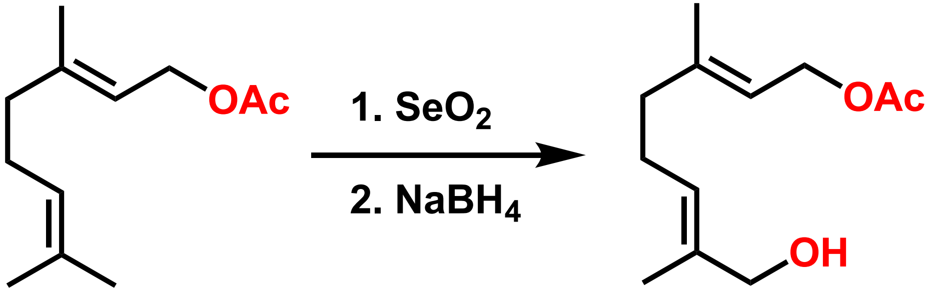


Oxidation with SeO_2

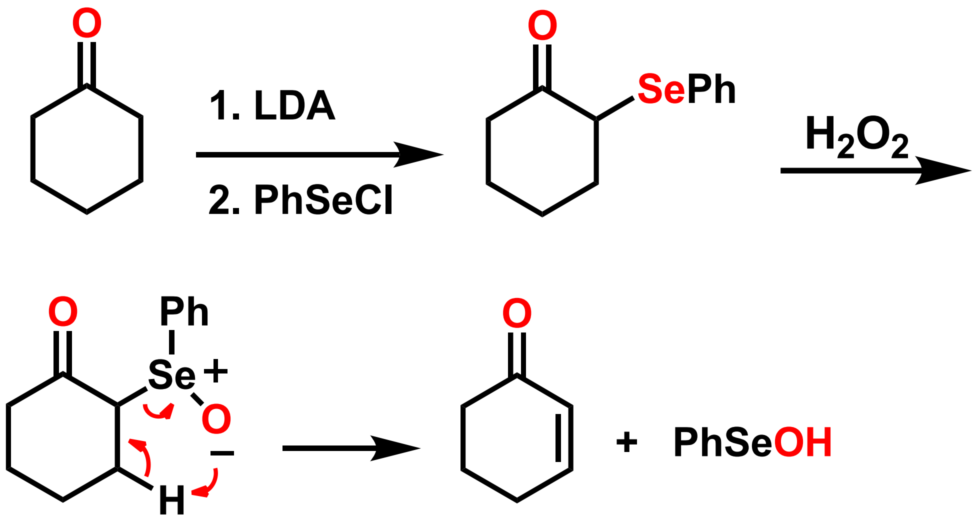


Mechanism:

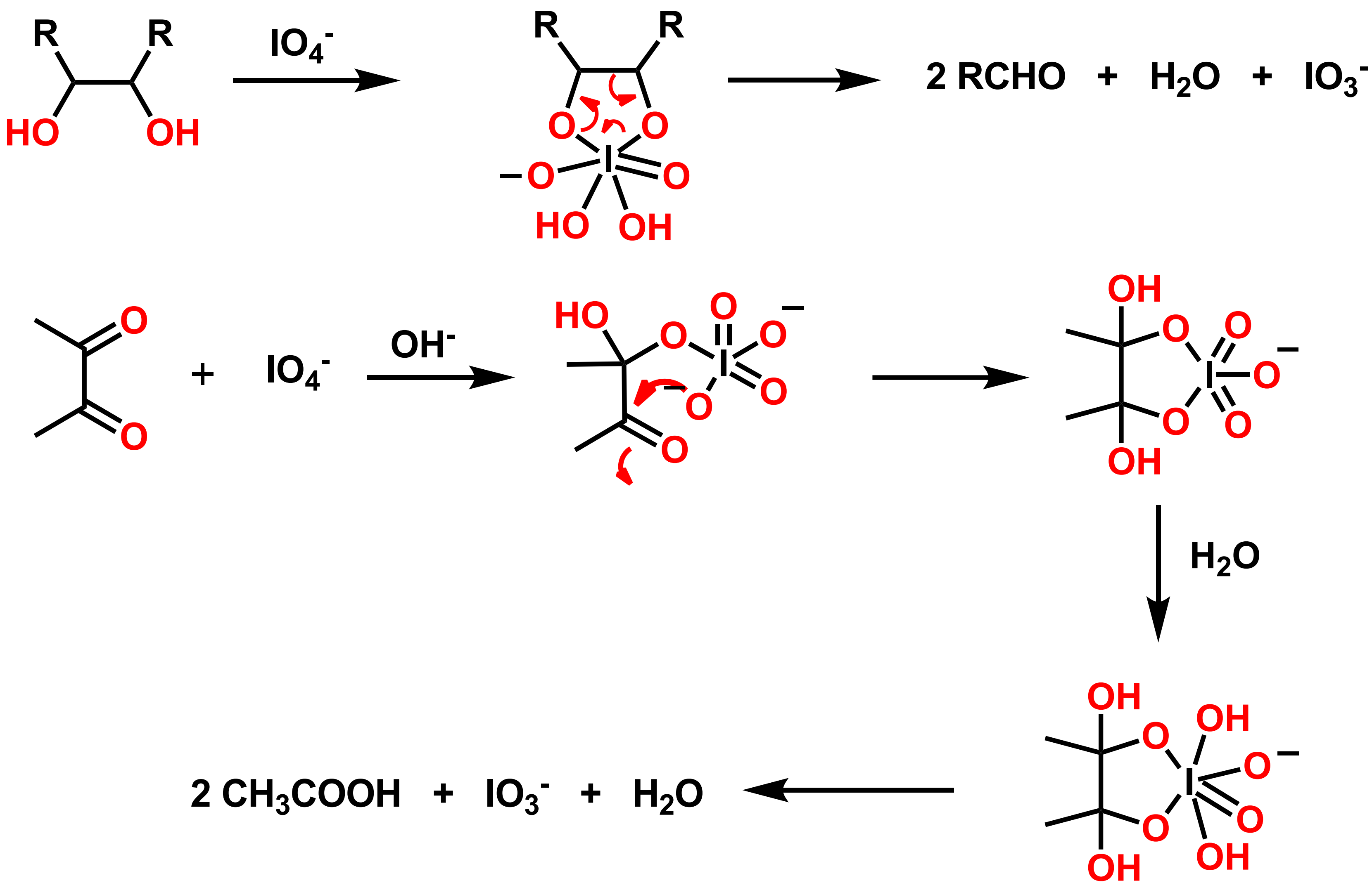




PhSeCl Oxidation

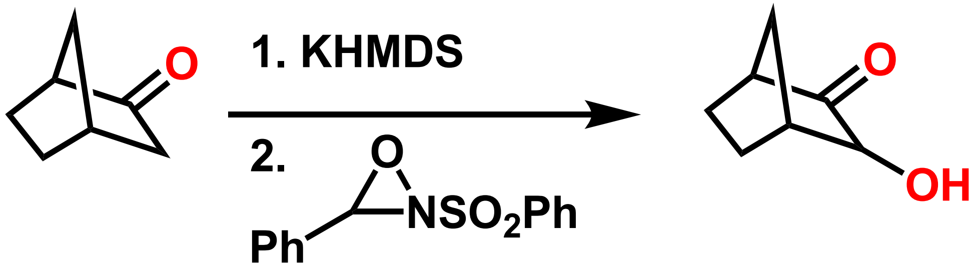


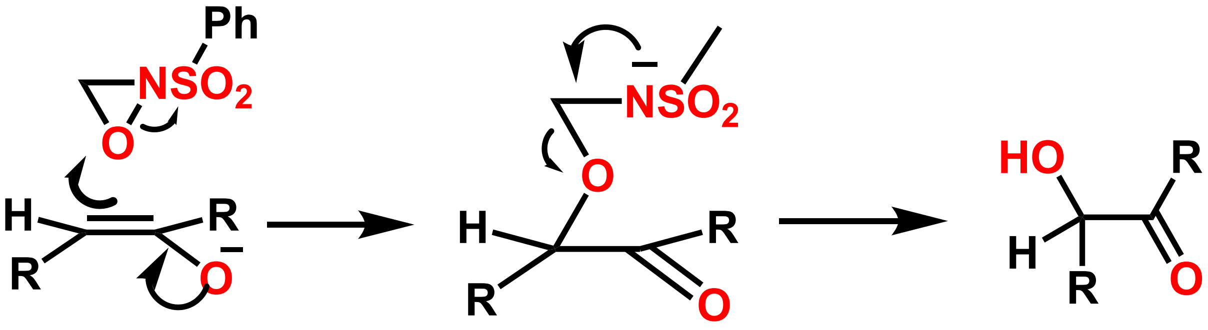
Oxidation with NaIO4



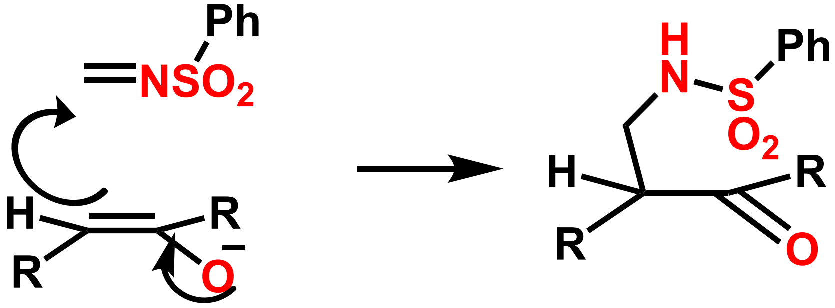
Hydroxylation

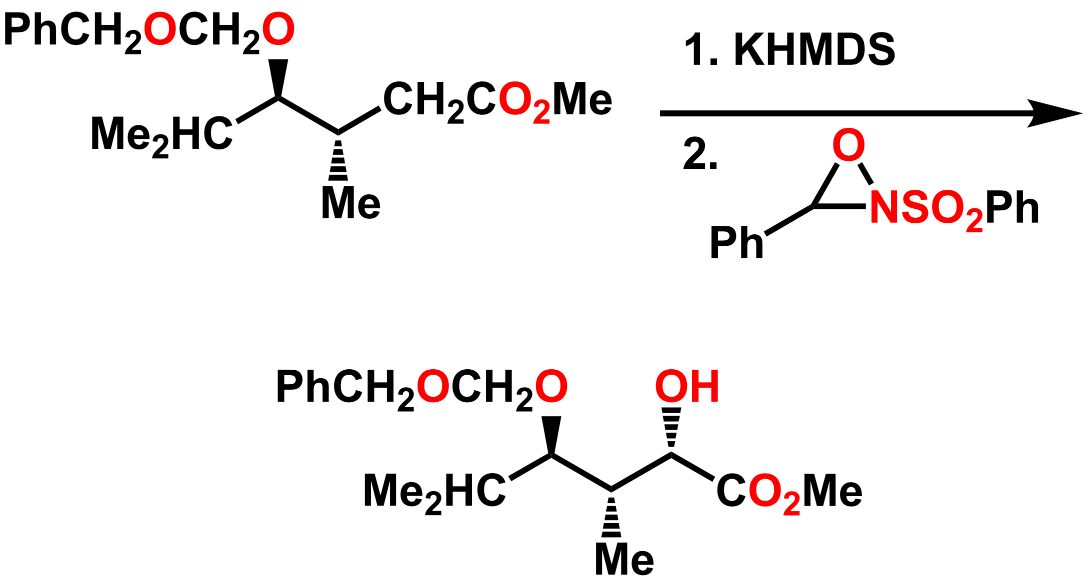
Oxidation with *N*-sulfonyloxaziridines



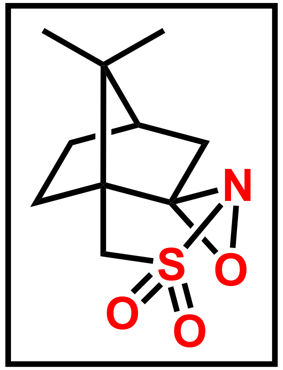


Side product





Asymmetric hydroxylation with Chiral *N*-sulfonyloxaziridines



Barton Reaction

In 1960, Sir Derek Barton reported a photochemical conversion of alkylnitrites to δ-nitrosoalcohols