Organic Chemistry CH-401 Course

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Oxidation

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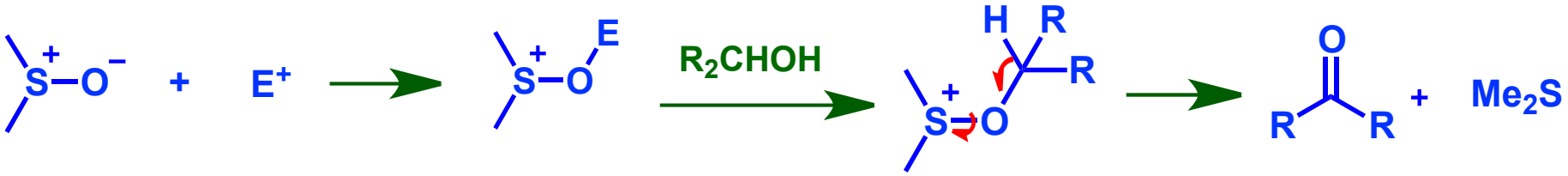
Nonmetal Based Oxidation

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

Swern Oxidation

Moffatt Oxidation

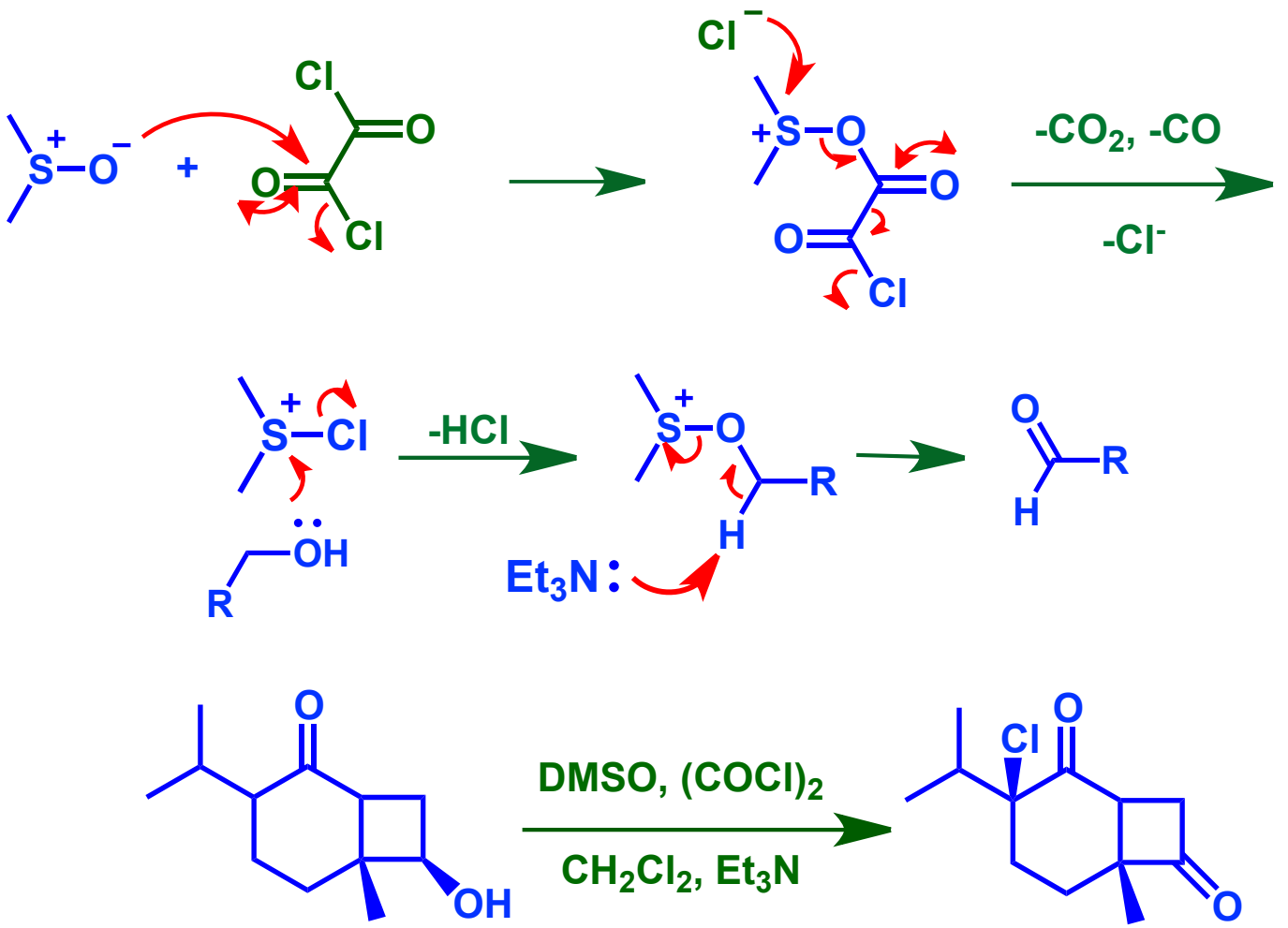
Kornblum Oxidation

Corey-Kim oxidation

DMSO-Ac_20

Most of these reactions take place at very low temperature

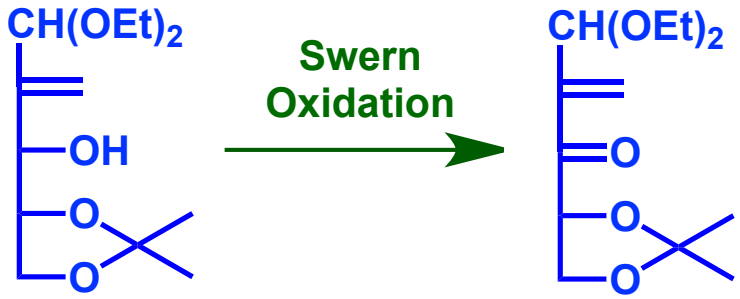
Swern Oxidation



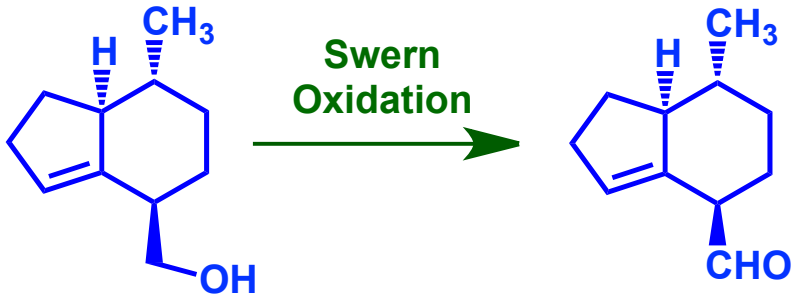
Trifluoroacetic anhydride also can be used instead of $(COCl)_2$

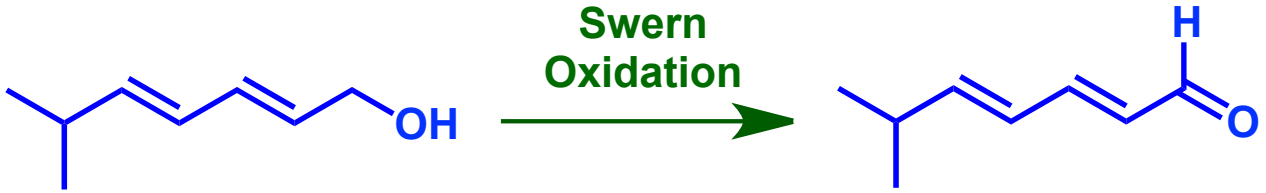
Swern Oxidation

Survives protecting groups

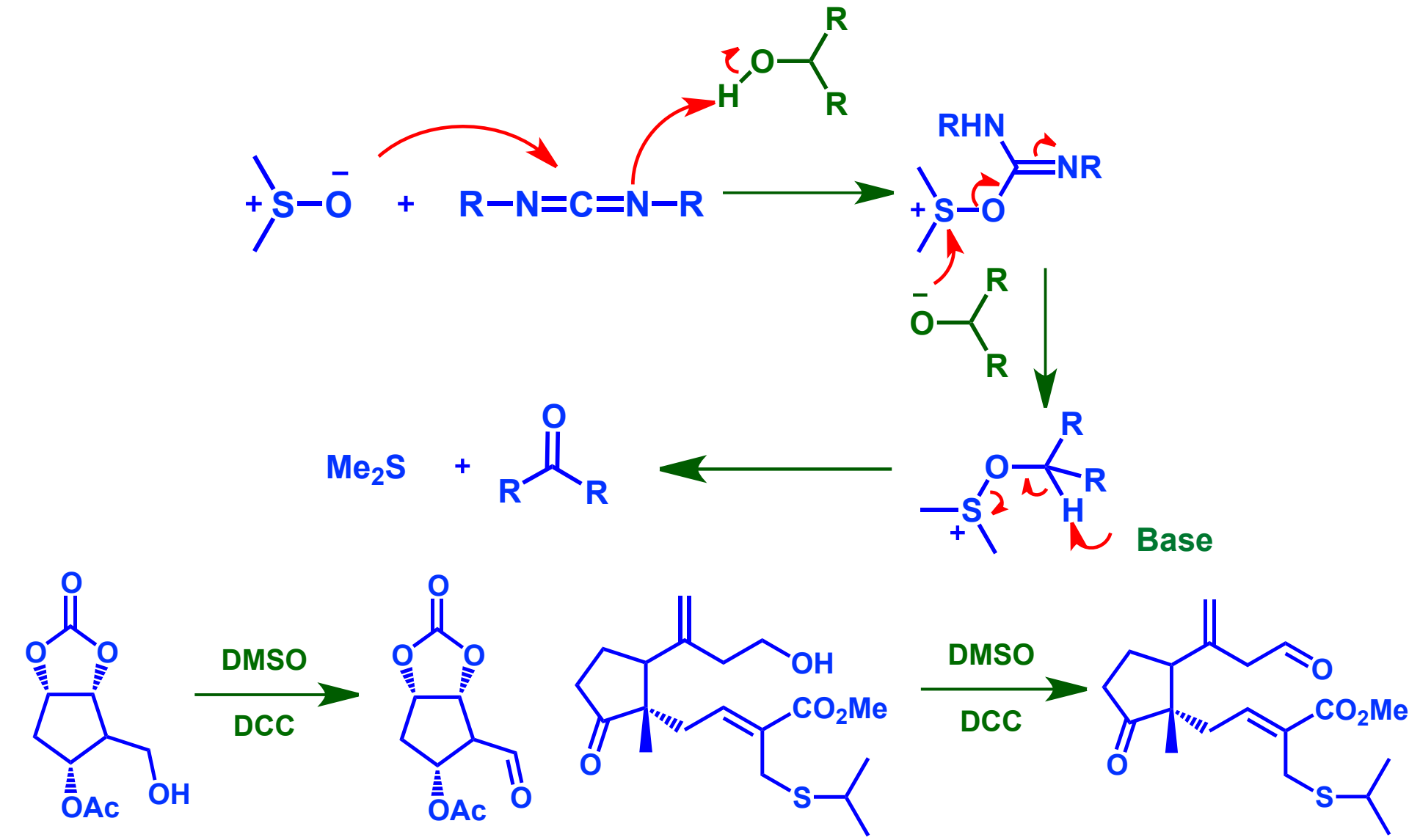


No epimerization of aldehydes

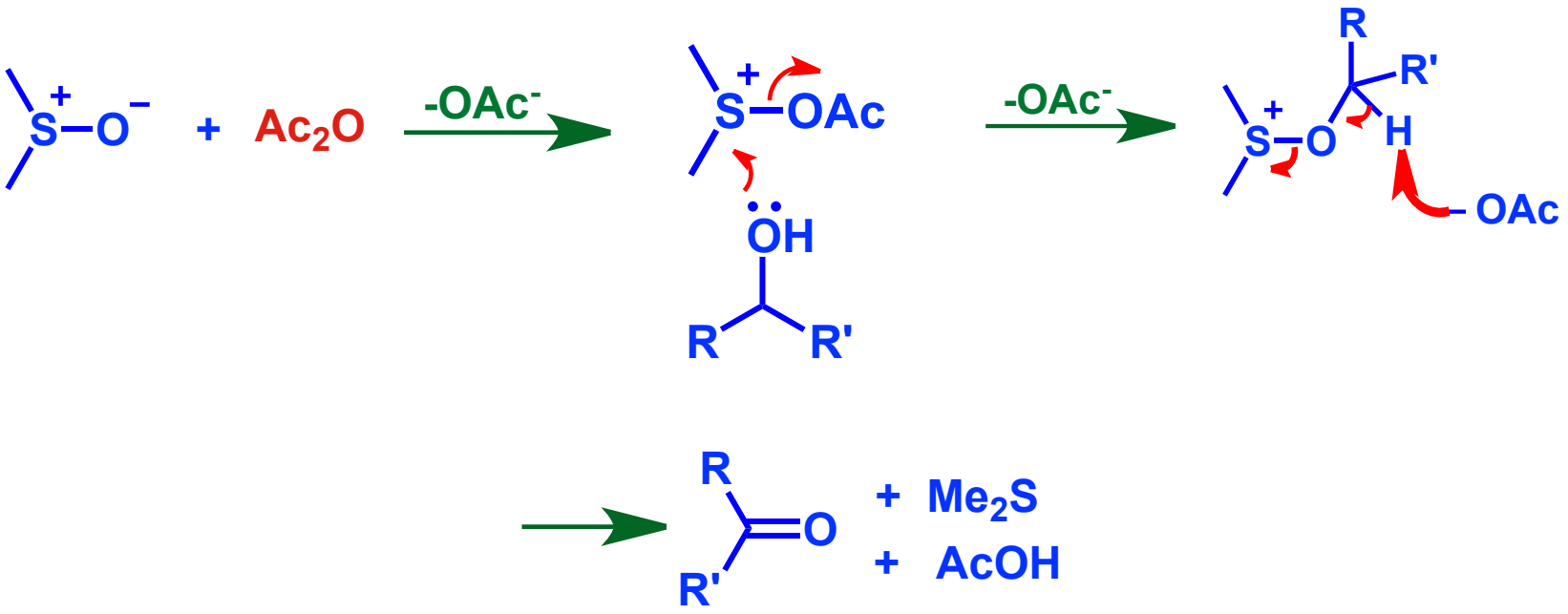




Moffatt Oxidation

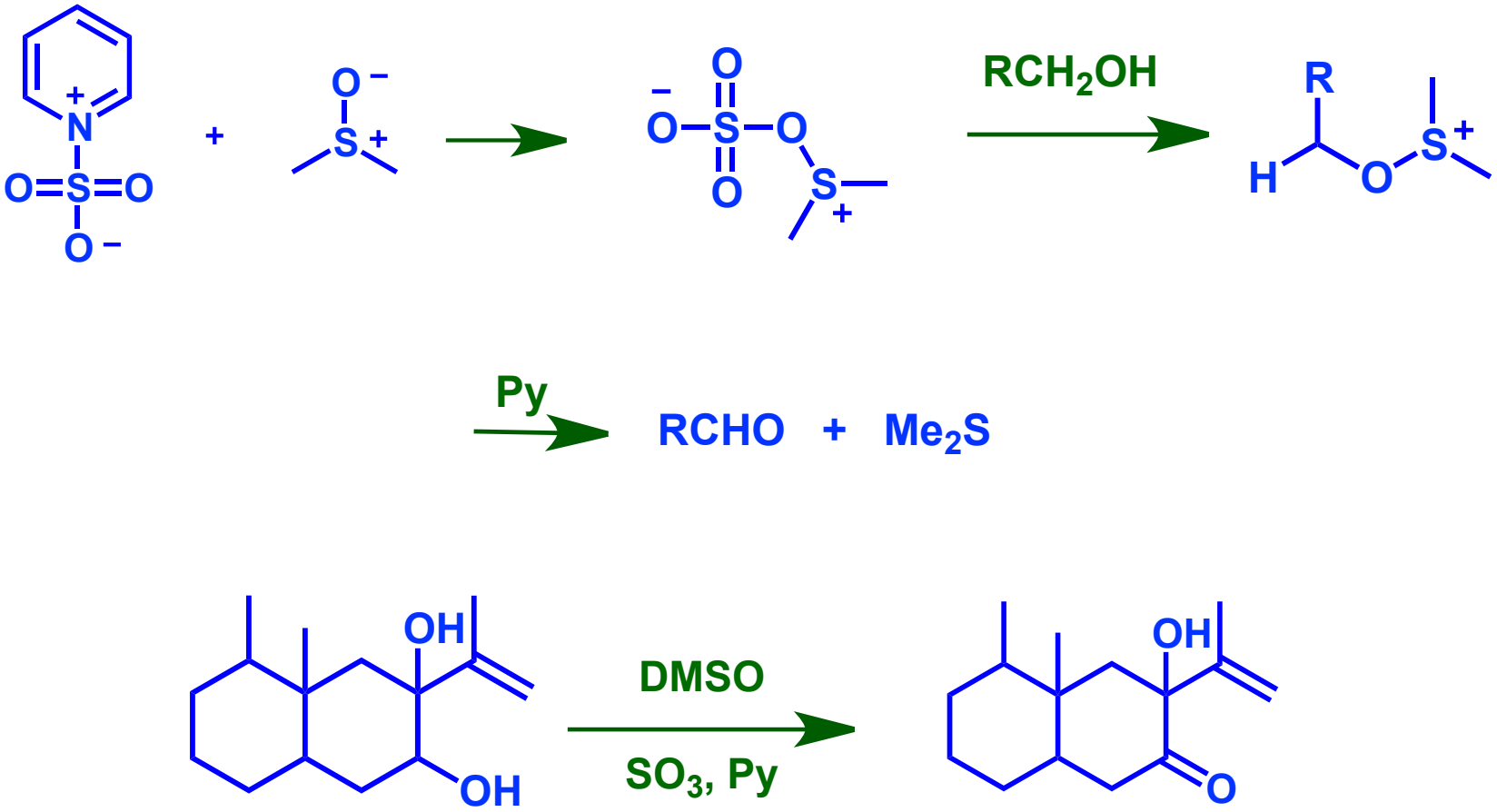


DMSO, Ac_2O



Disadvantage: Alcohol may be acetylated

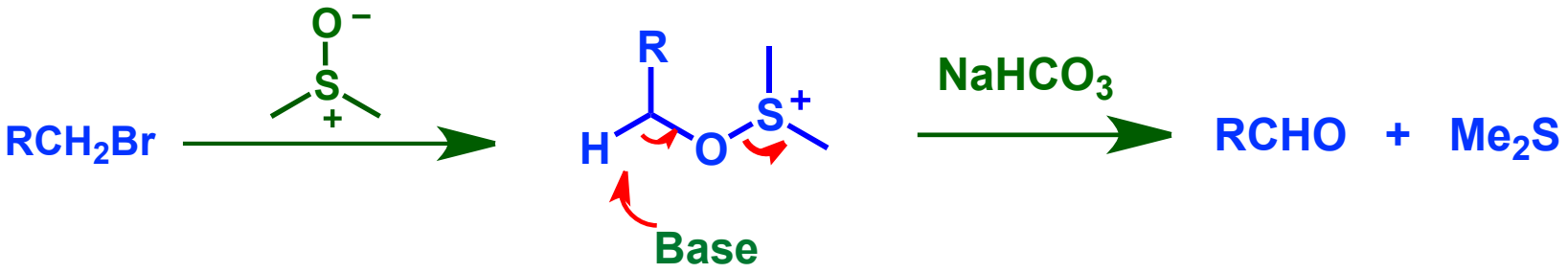
DMSO-SO_3-Py



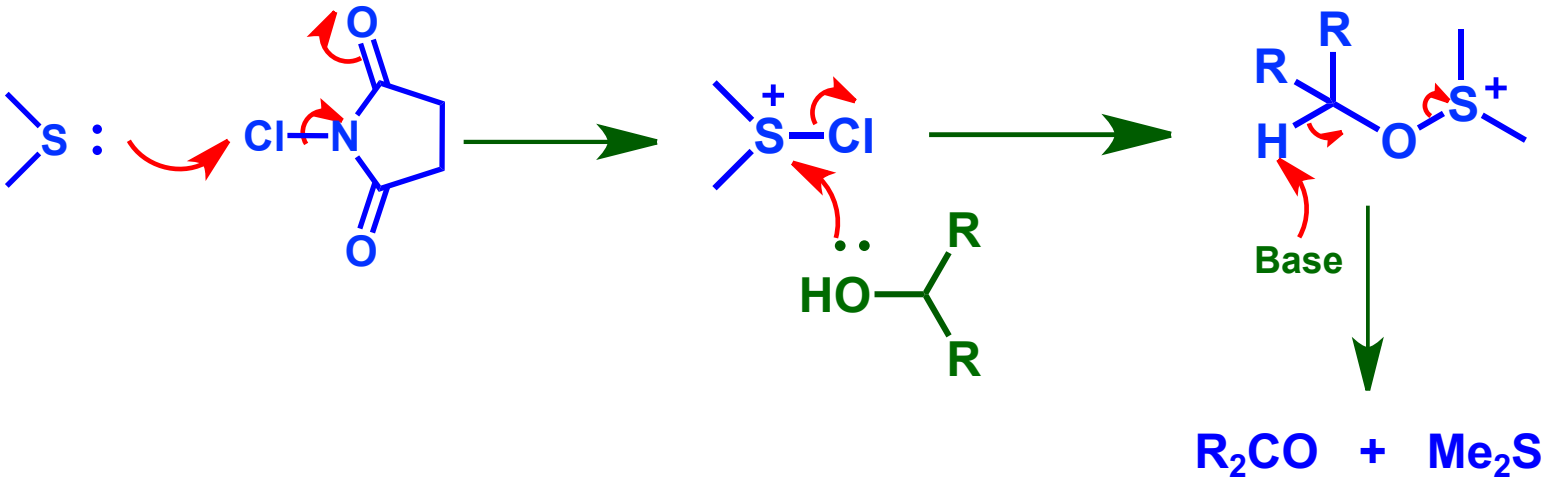
DMSO Based Oxidation

Kornblum Oxidation

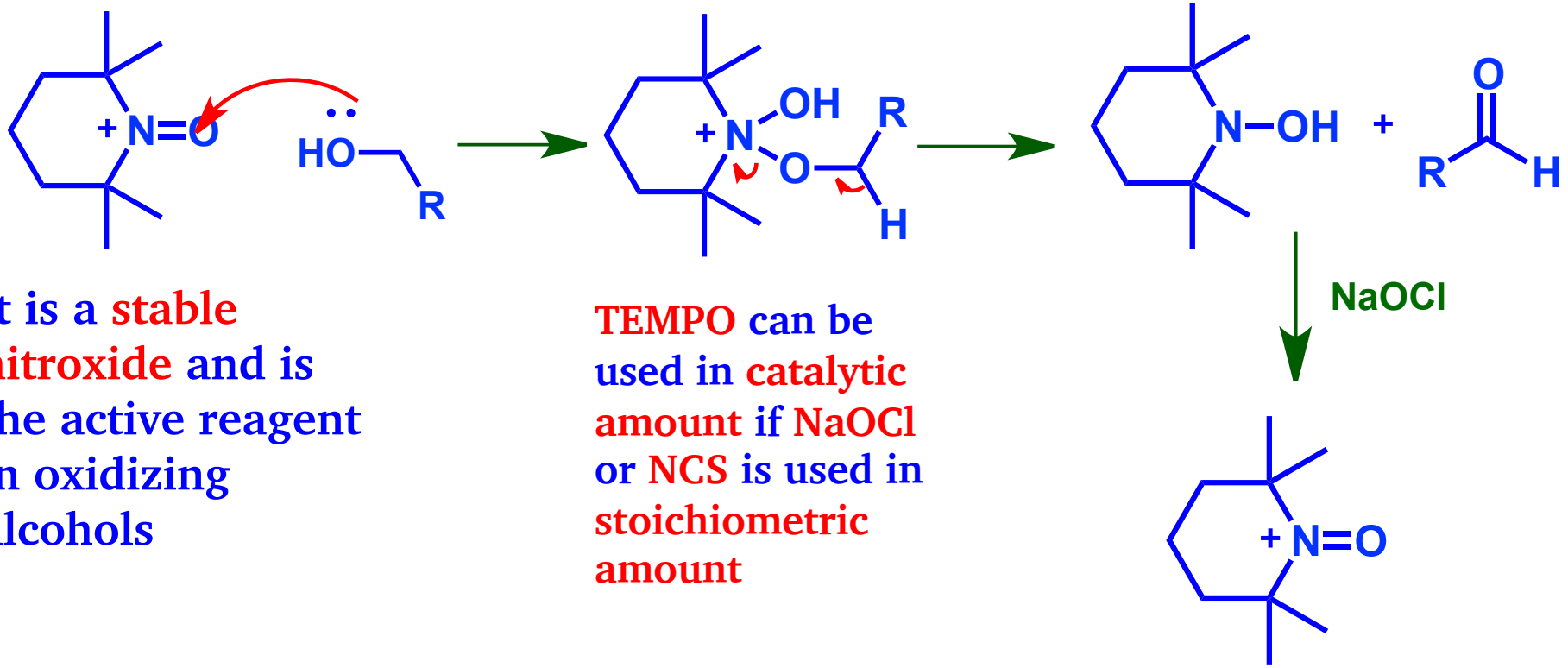
Oxidation of alkyl halides to aldehydes



Corey-Kim Oxidation

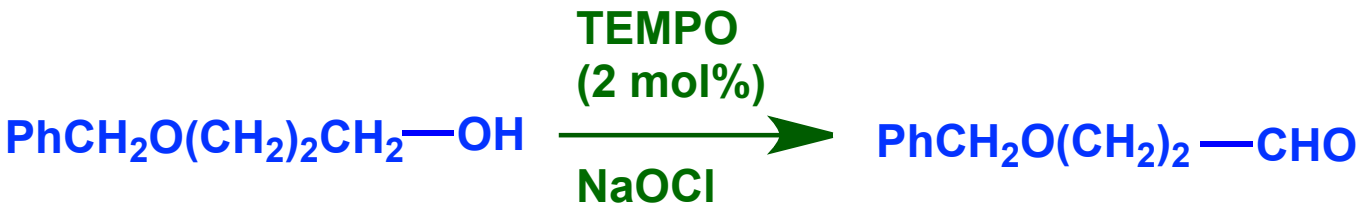


Tetramethylpiperidine nitroxide(TEMPO)



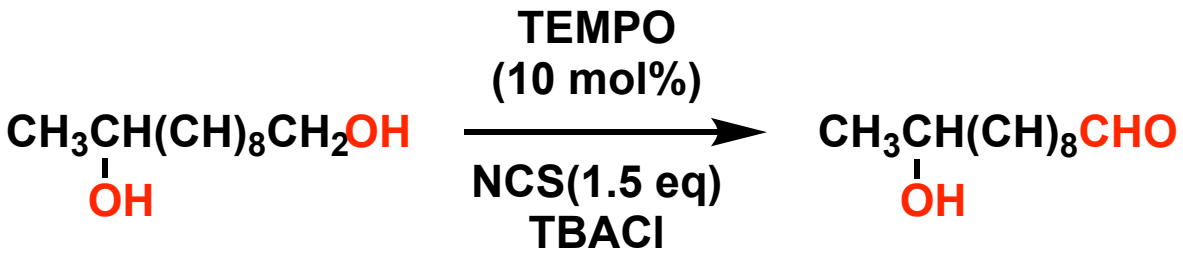
It is a stable nitroxide and is the active reagent in oxidizing alcohols

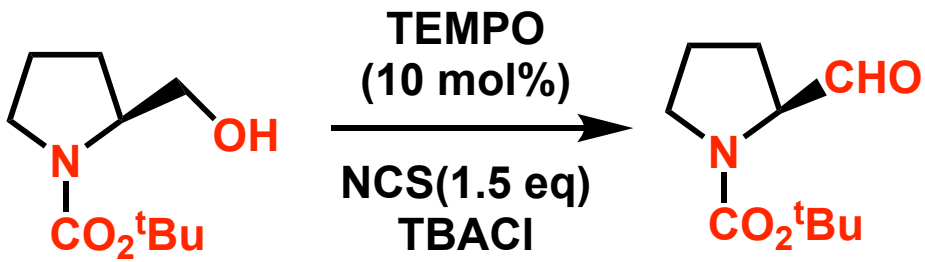
TEMPO can be used in catalytic amount if NaOCl or NCS is used in stoichiometric amount



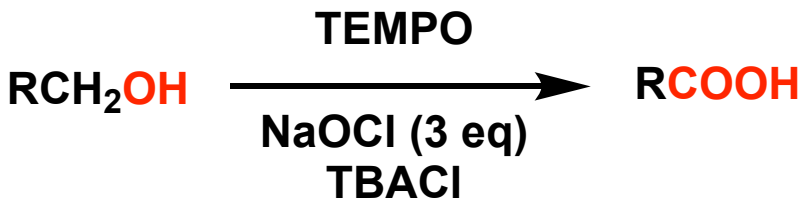
Tetramethylpiperidine nitroxide(TEMPO)

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

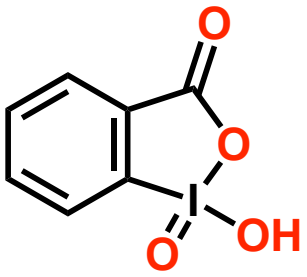




It can also oxidize primary alcohols to carboxylic acids by a subsequent oxidation with hypochlorite ion

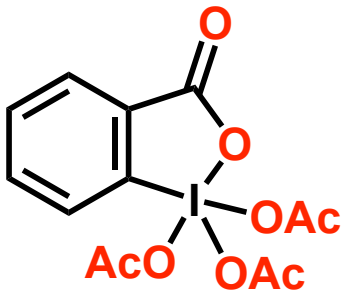


IBX and Dess Martin Periodinane



IBX

(2-Iodoxybenzoic acid)



DMP

(Dess Martin Periodinane)

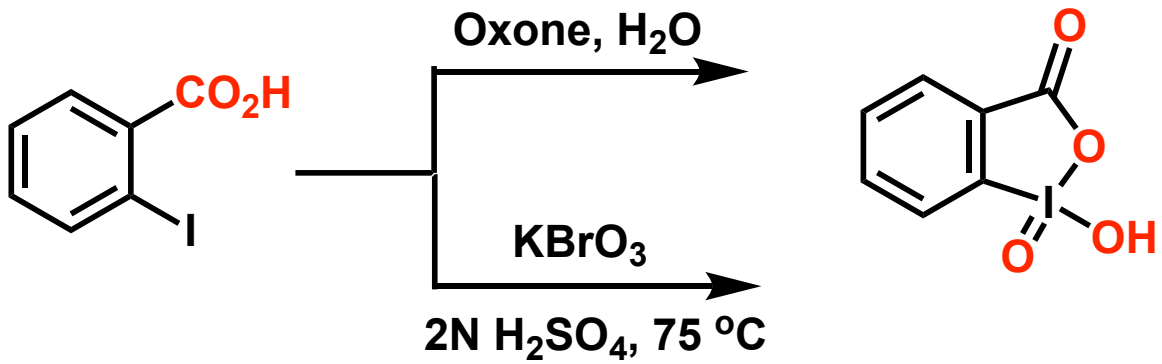
IBX was discovered in 1893 by Hartmann and Meyer but not used due to its remarkable insolubility in organic solvents and explosive nature

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

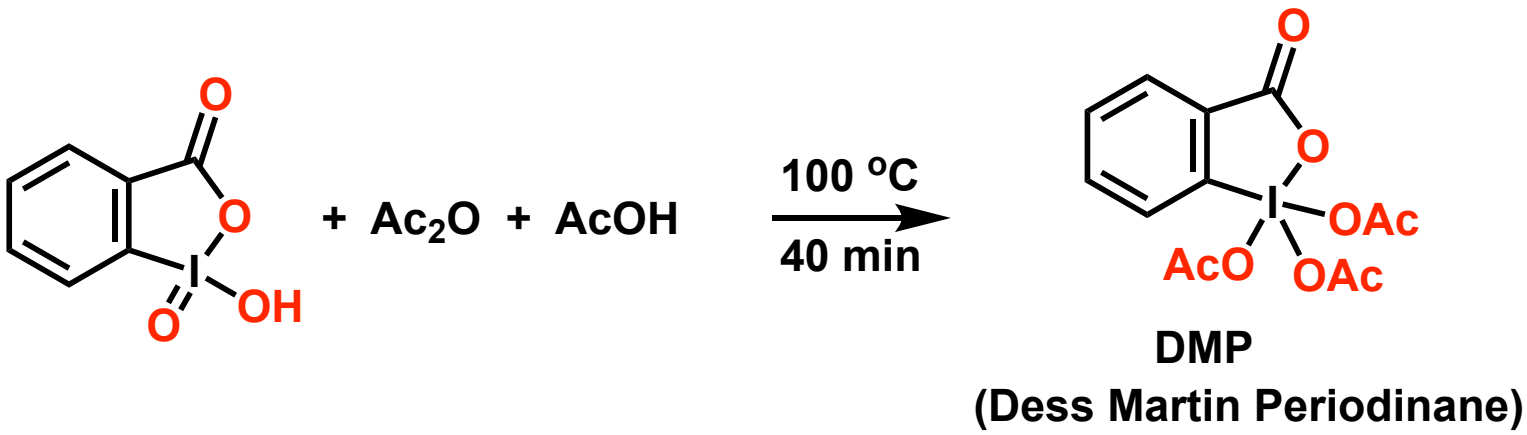
The most important and useful derivative is its triacetate, known as DMP (Dess Martin Periodinane), which is soluble in organic solvents

IBX and Dess Martin Periodinane

Preparation of IBX



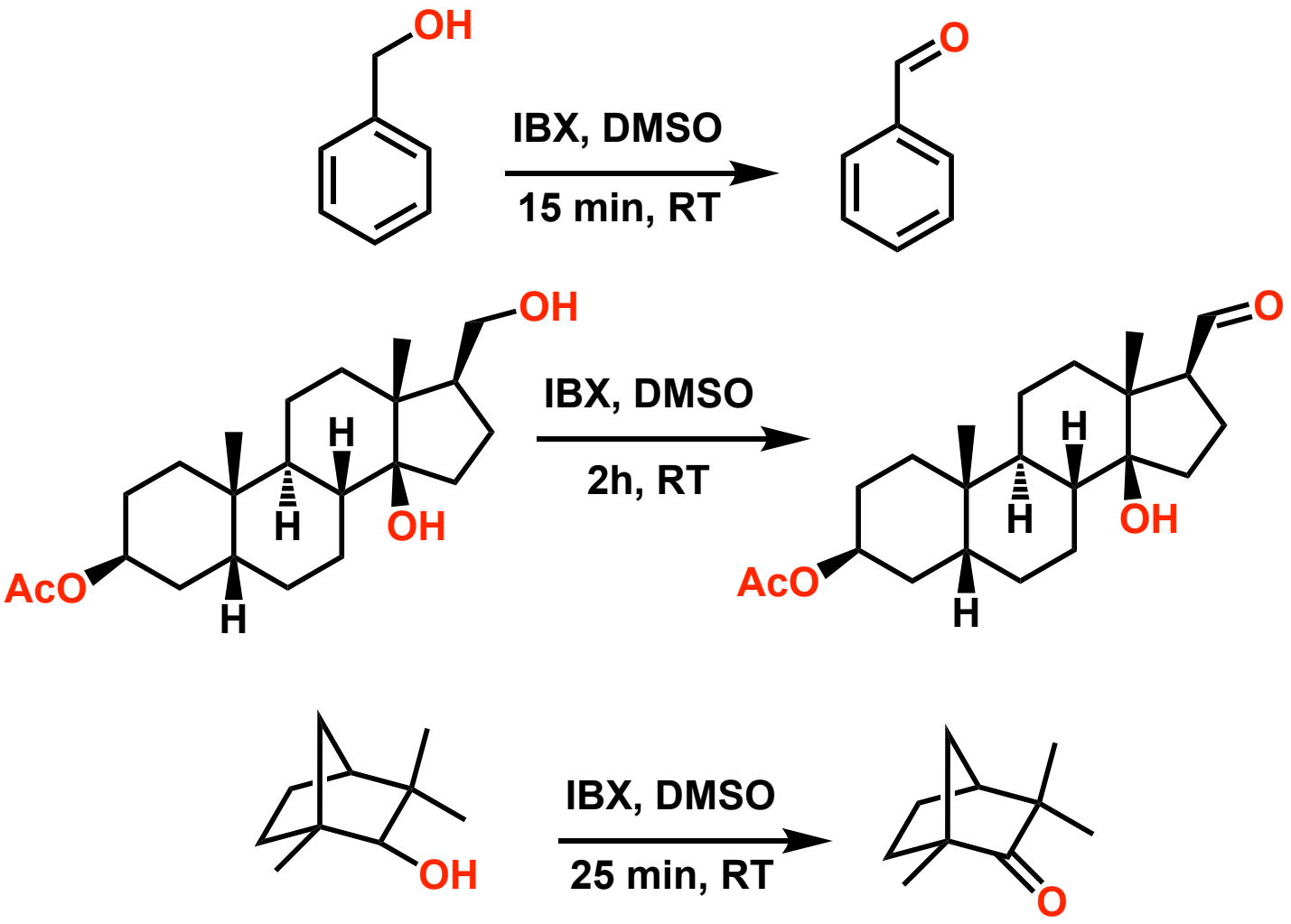
Preparation of DMP



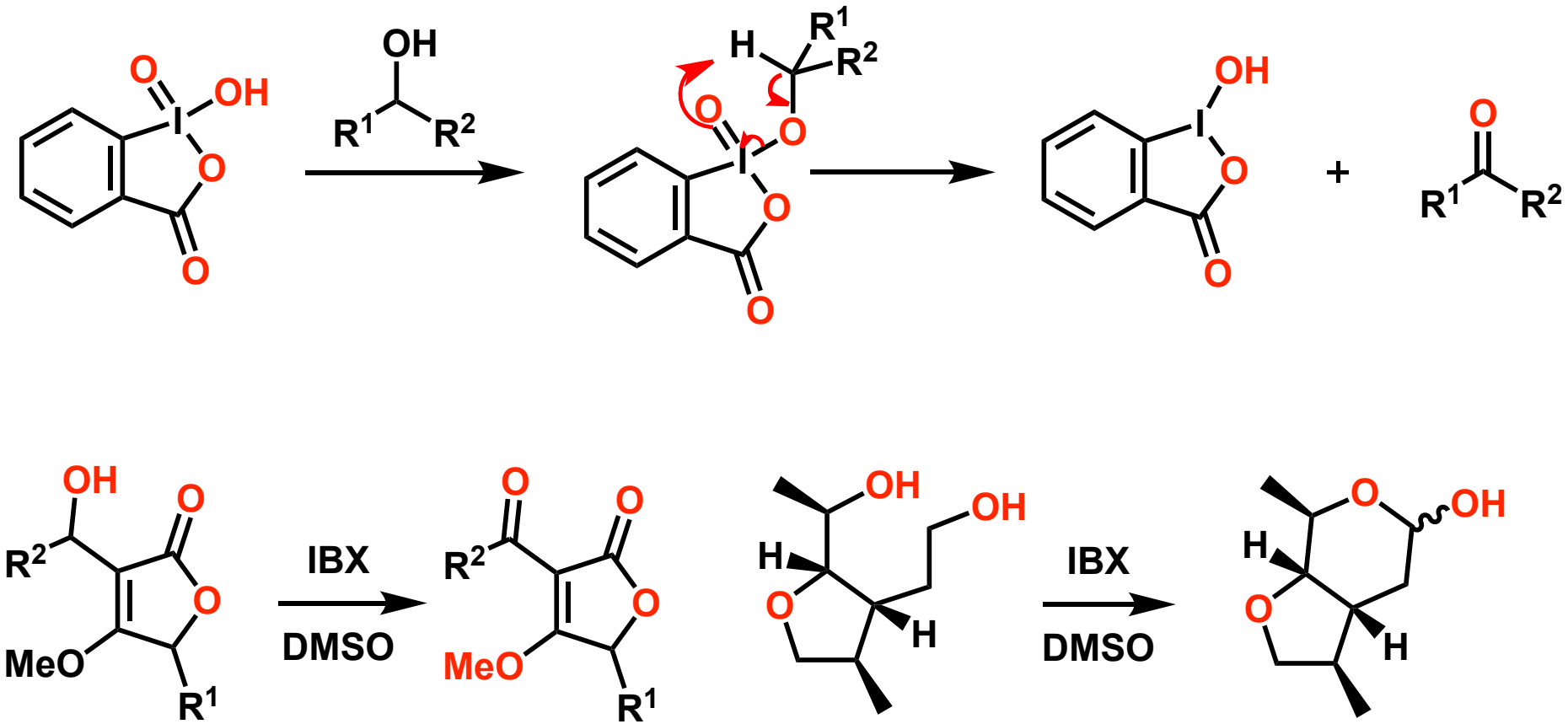
Synthetic Utility of IBX

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

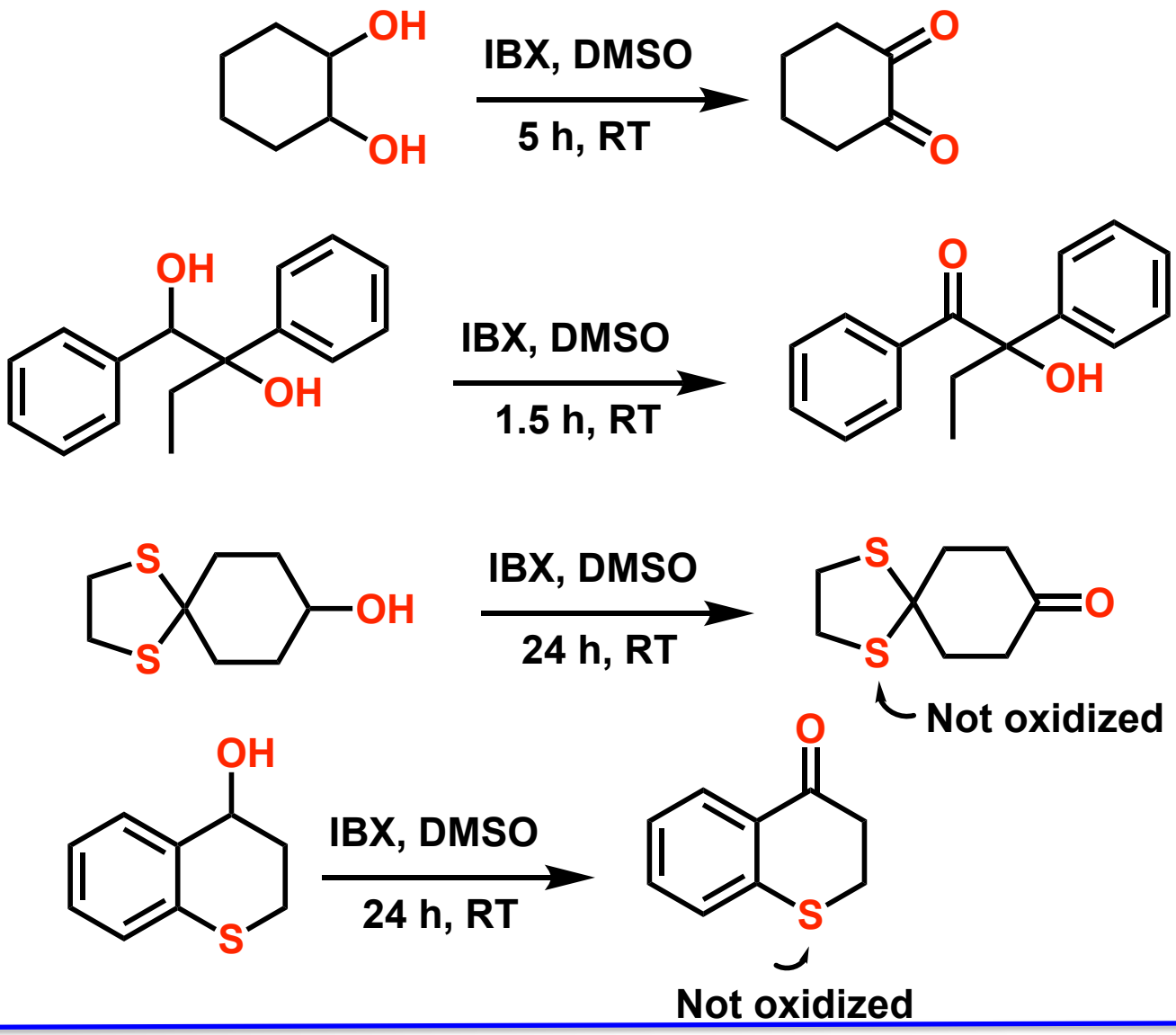
Oxidation of 1° & 2° Alcohols



Mechanism

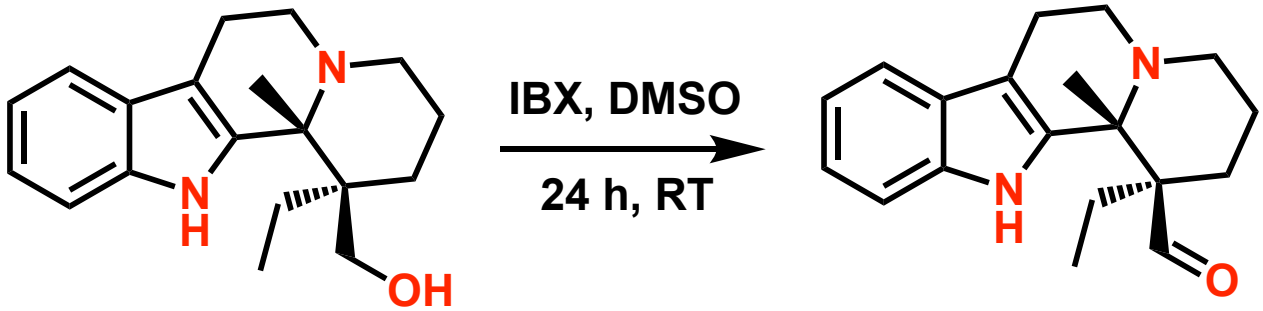


Oxidation of 1,2-diols

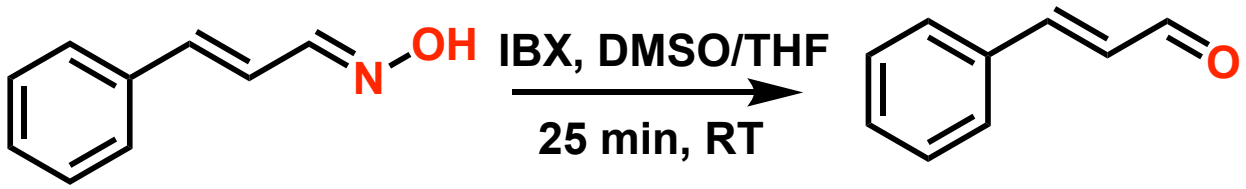


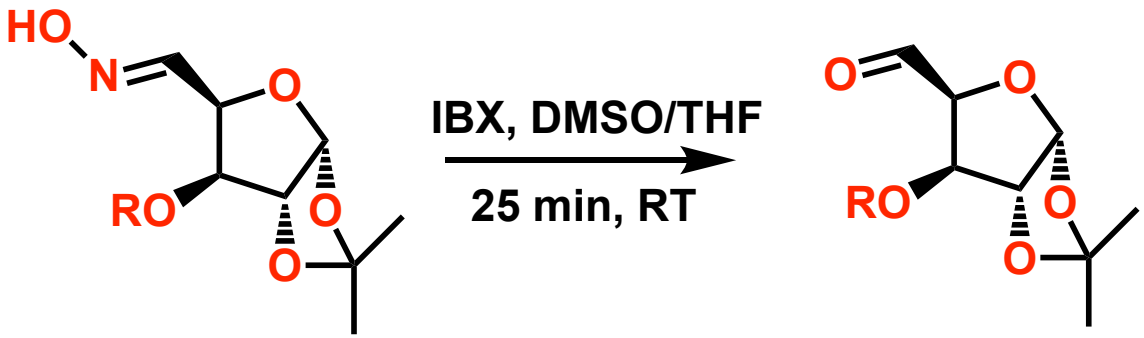
Oxidation of Aminoalcohols

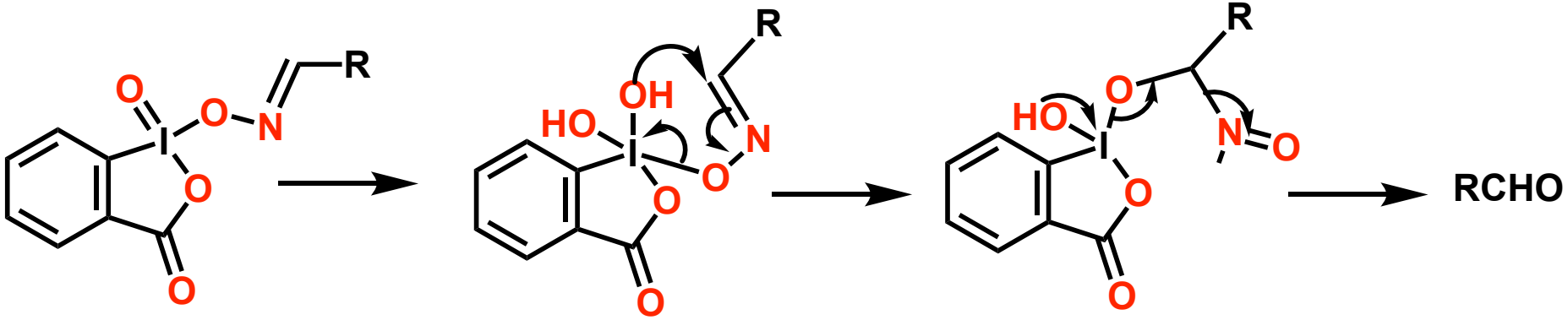
Primary and secondary amines are temporarily protonated before oxidation



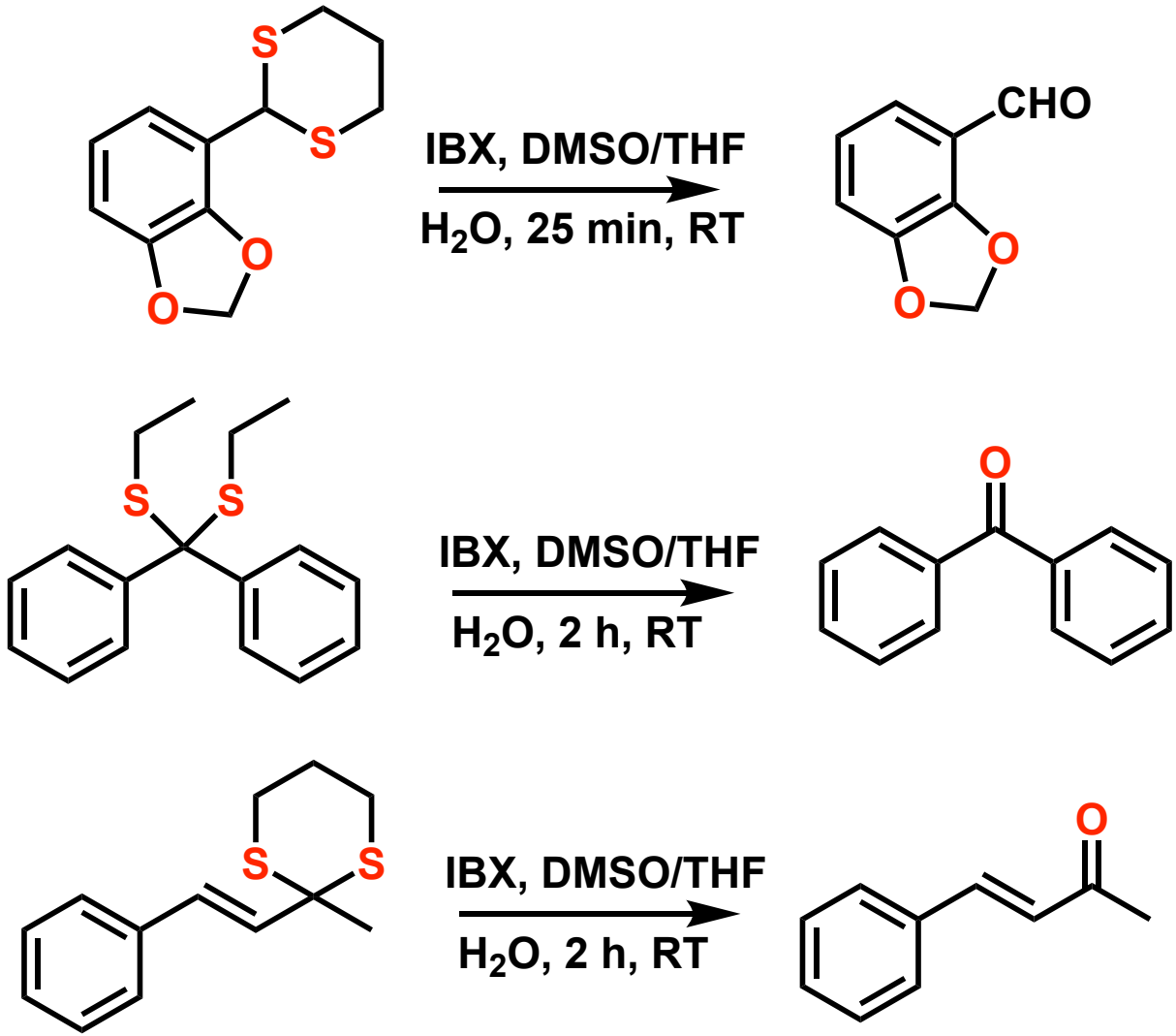
Deoximation of Oximes



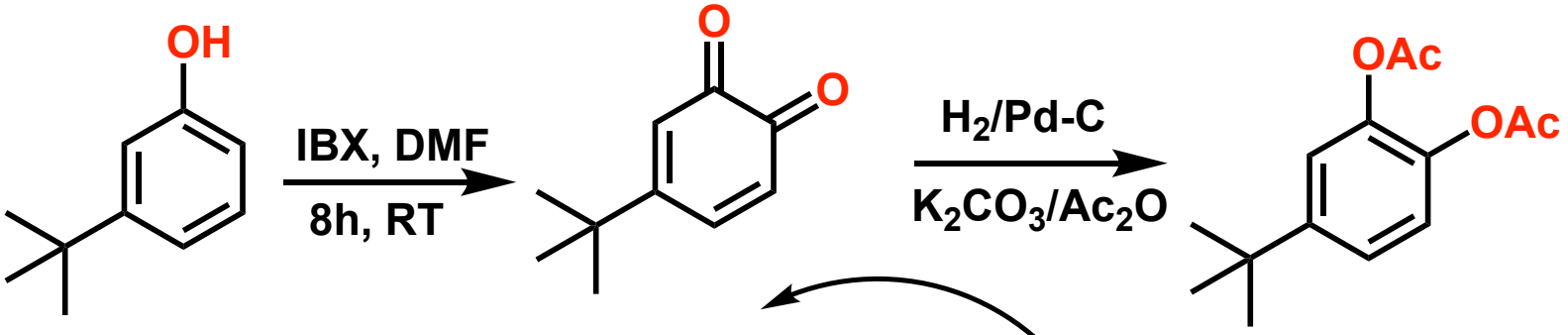




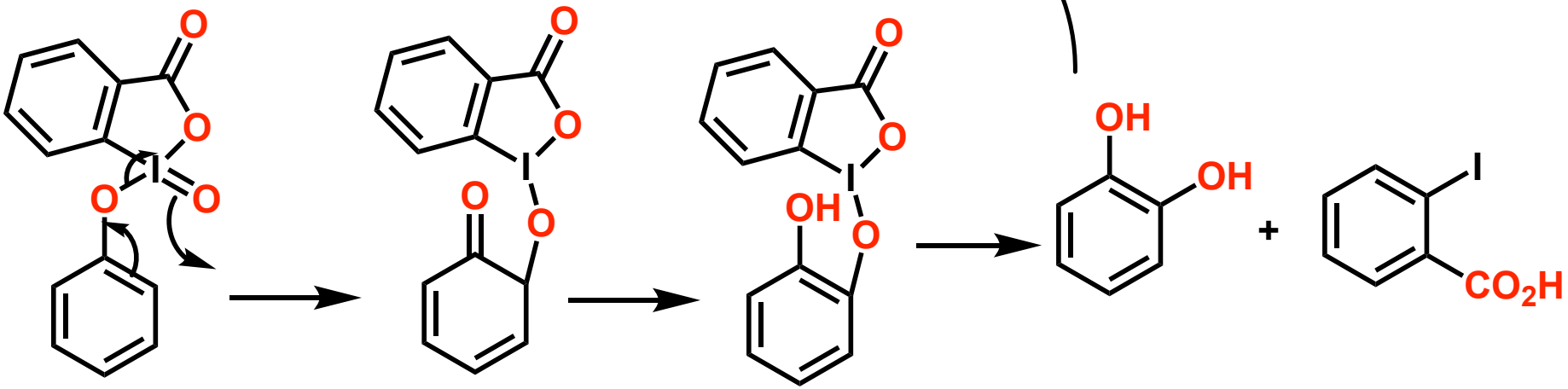
Deprotection of thioacetals & thioketeals



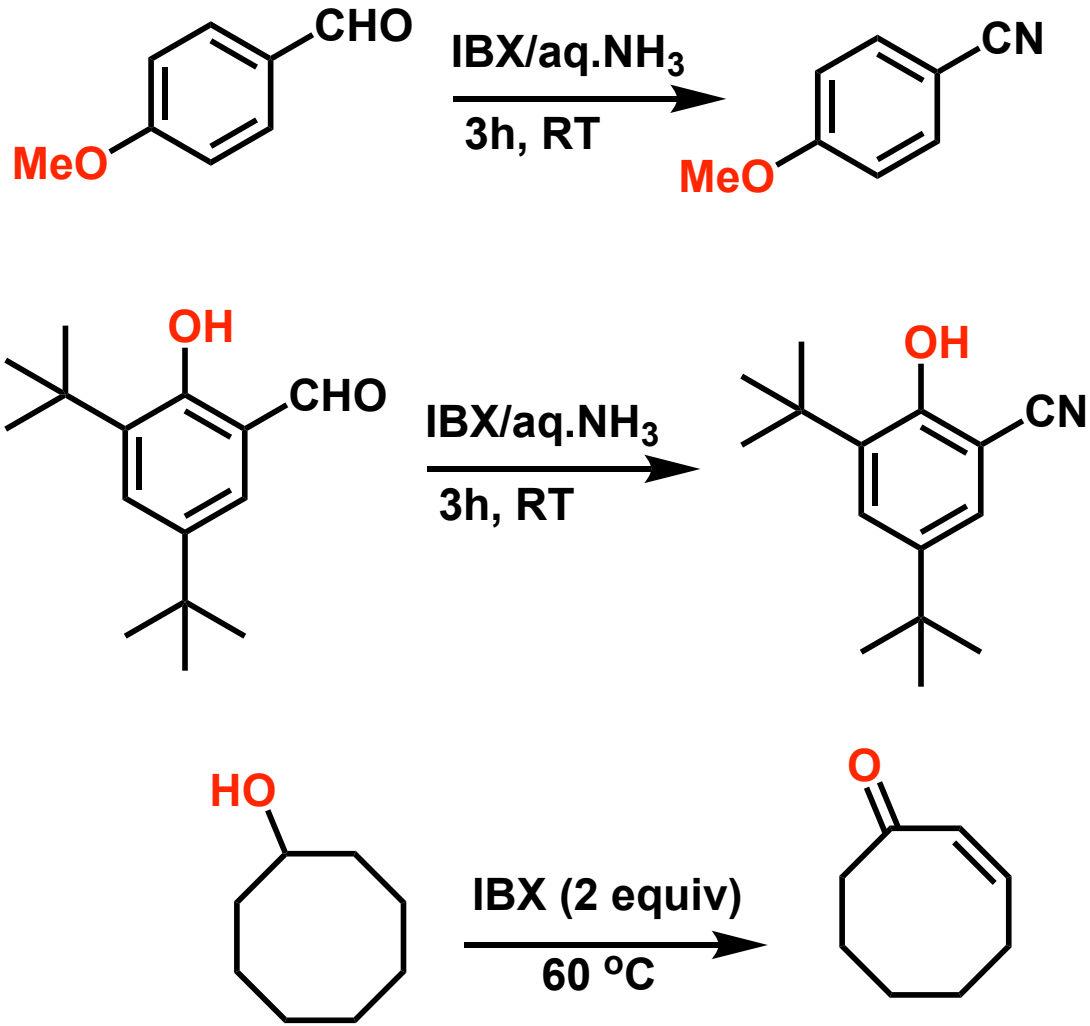
Oxidation of phenols to ortho-quinones



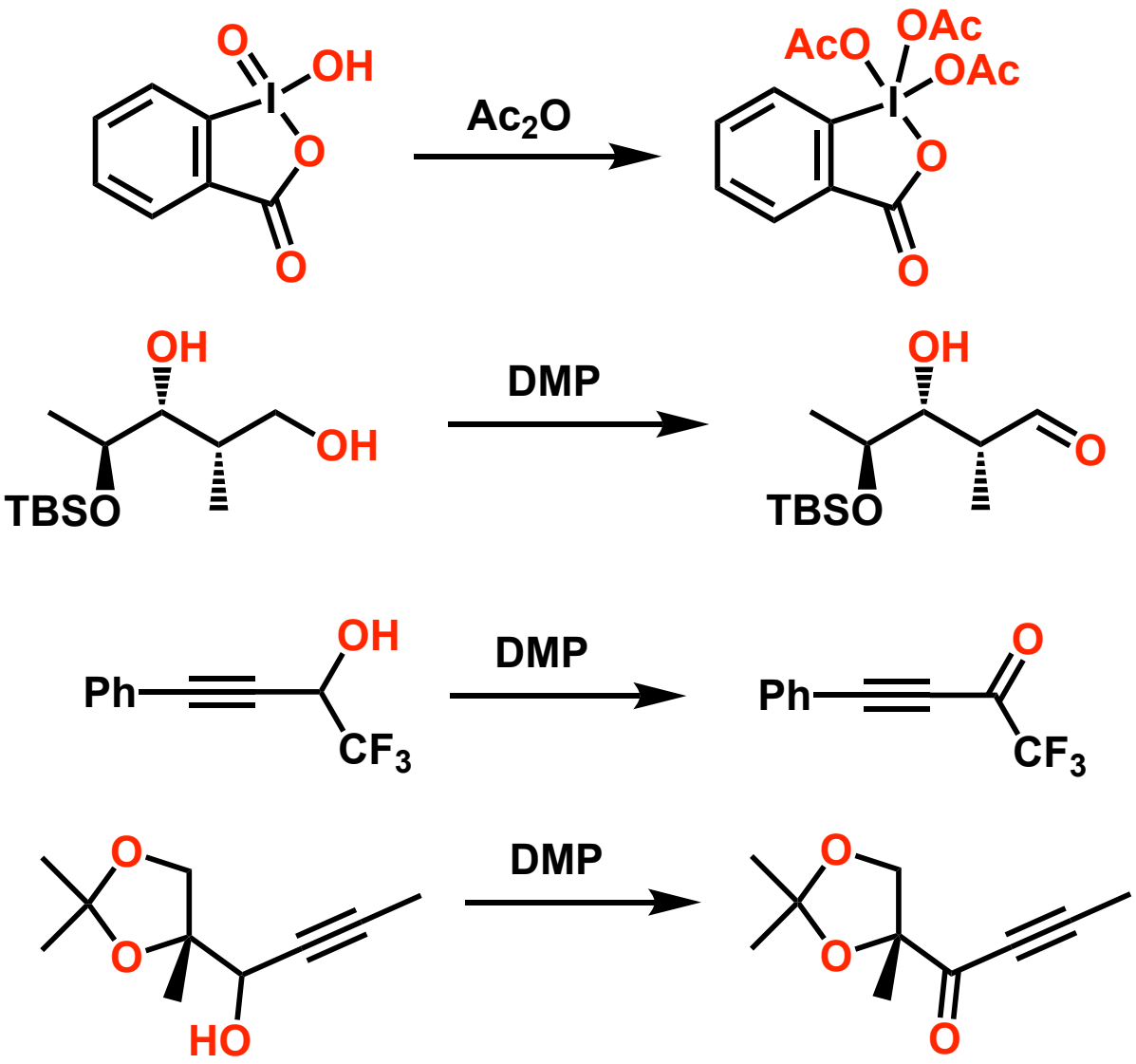
Mechanism



Oxidation of aldehydes to nitriles



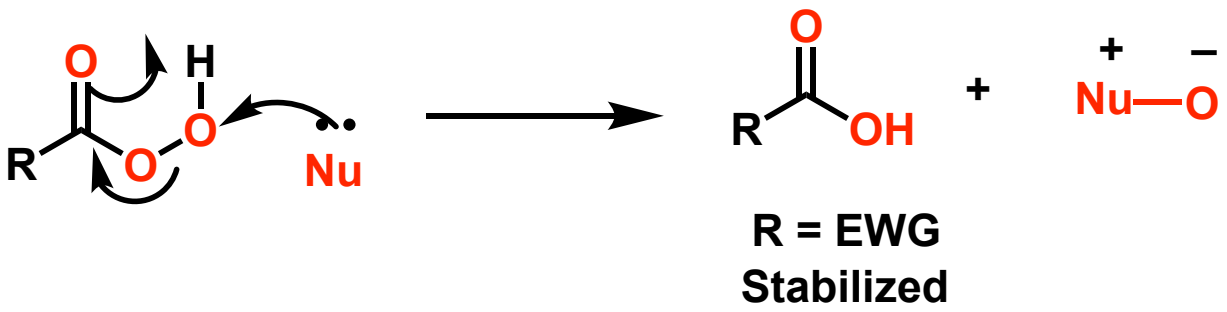
Dess Martin Periodinane



Nonmetal Based Oxidation

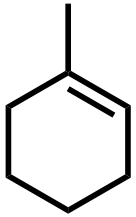
Epoxidation

Epoxidation



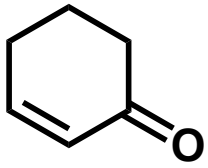
R = EWG
Stabilized

Electron rich substrate and electrophilic reagent



electron rich

Electron deficient substrate and nucleophilic reagent



electron deficient

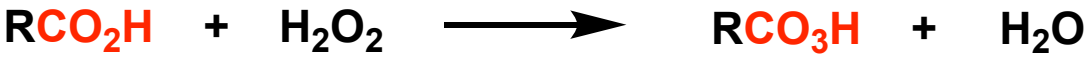
Epoxidation

Electrophilic reagents

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

Peracids

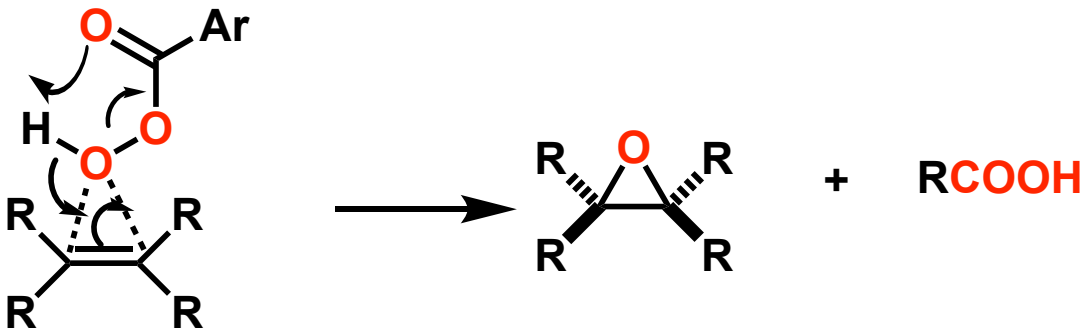
Peracids can be prepared from the corresponding acids & H_2O_2



Epoxidation

Peracids

Mechanism



It is believed to be a concerted process

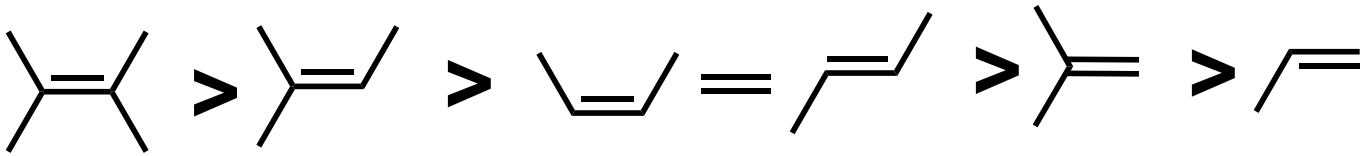
Stereospecific *syn* addition is constantly observed

Epoxides are always *syn*. *Trans* epoxide means substituents are *trans*

Epoxidation

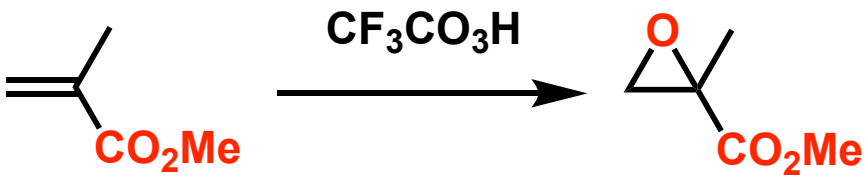
Peracids

The rate of epoxidation



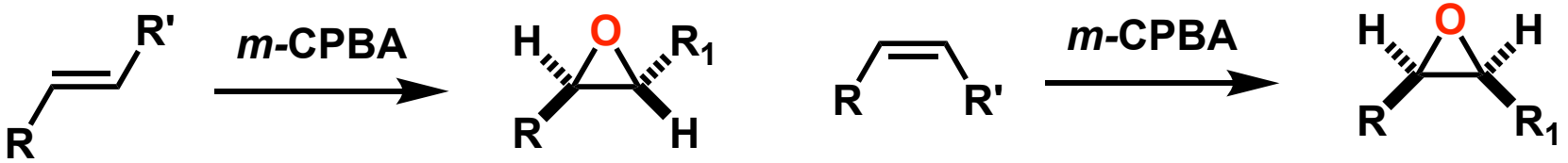
The reactivity of the peracid is increased by EWG's

Strong EWG attached to olefin makes it less reactive

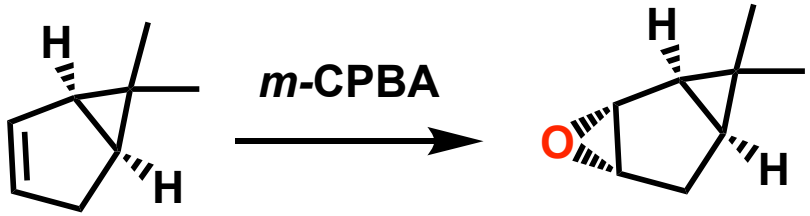


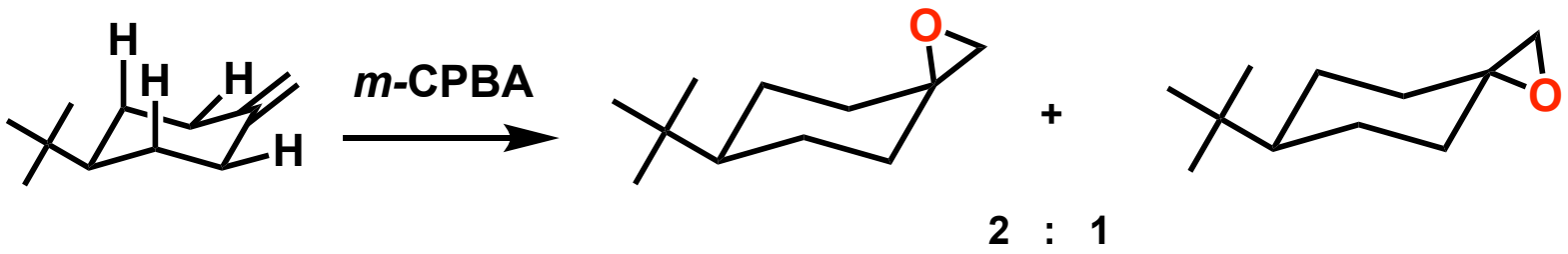
Epoxidation

Stereoselectivity:



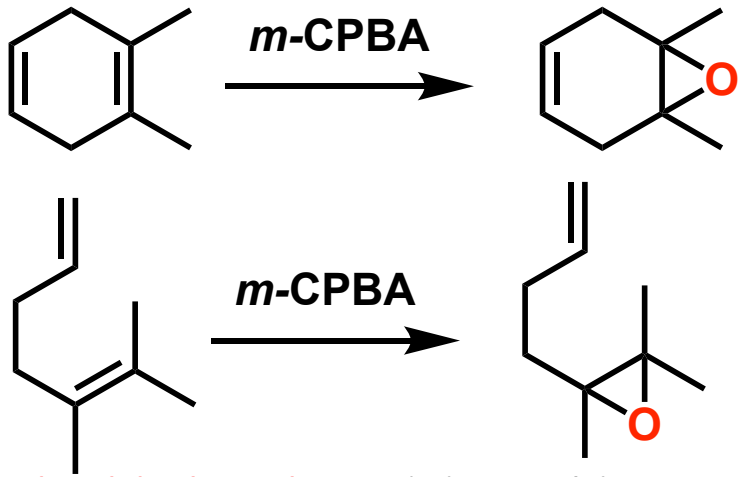
Addition of oxygen comes preferentially from the less hindered side of the molecule





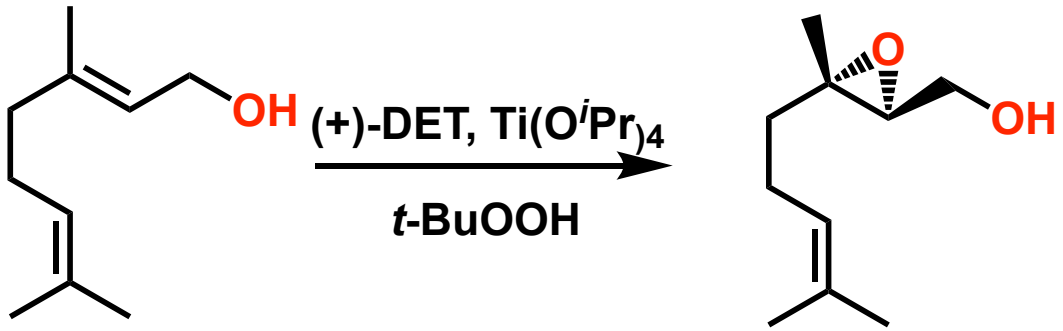
Epoxidation

Regioselectivity:



More **electron rich double bond** participated in epoxidation

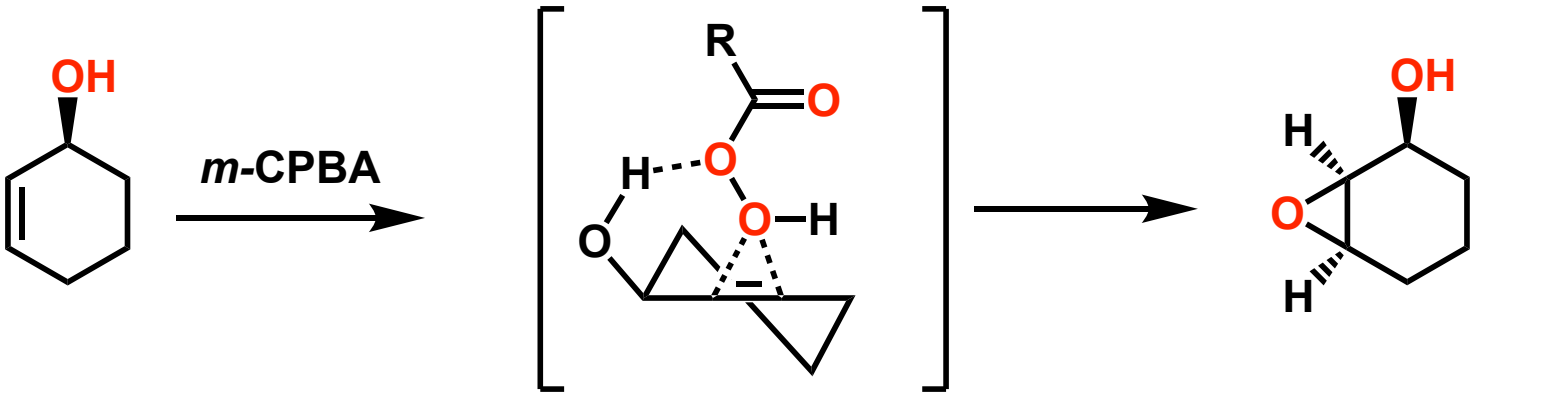
Sharpless Asymmetric Epoxidation:

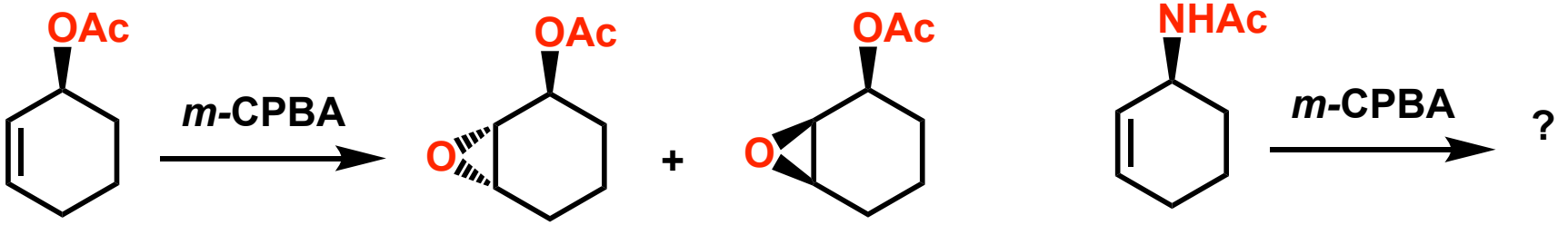


Henbest Epoxidation

Epoxidation Directed by Polar Group

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





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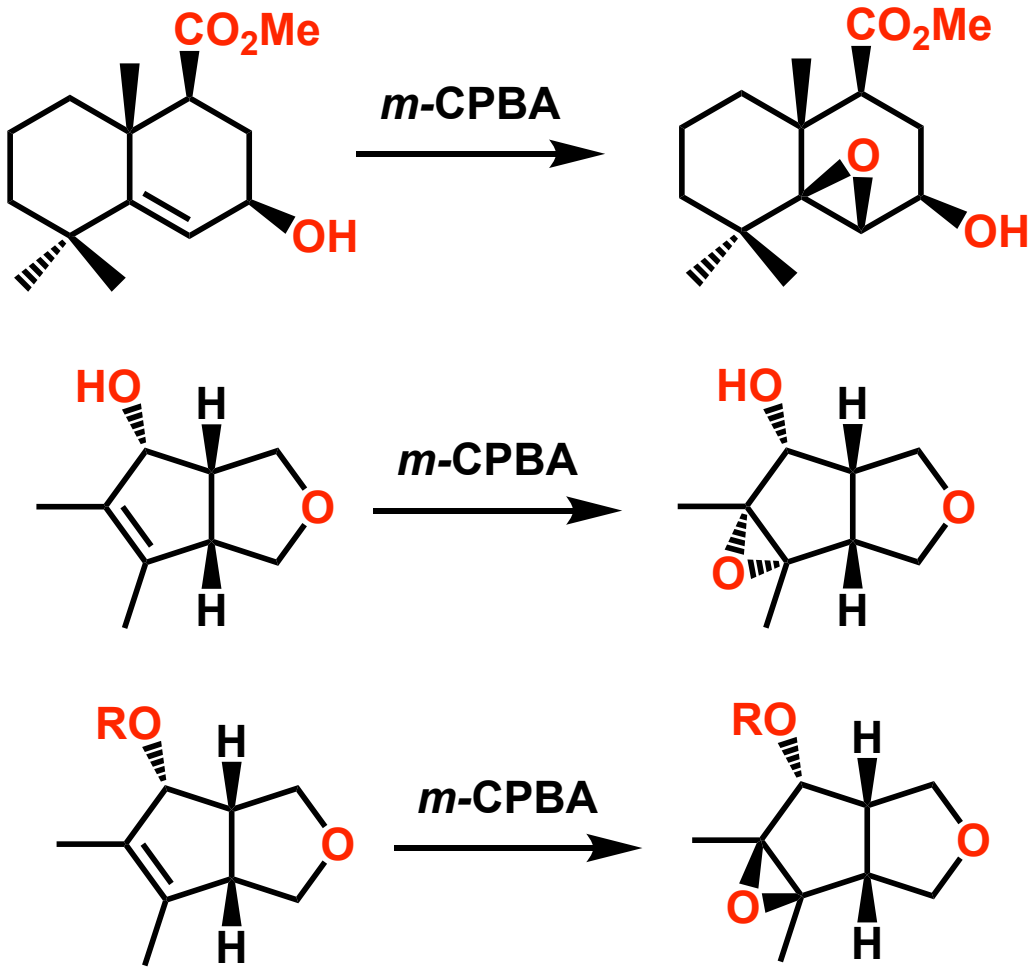
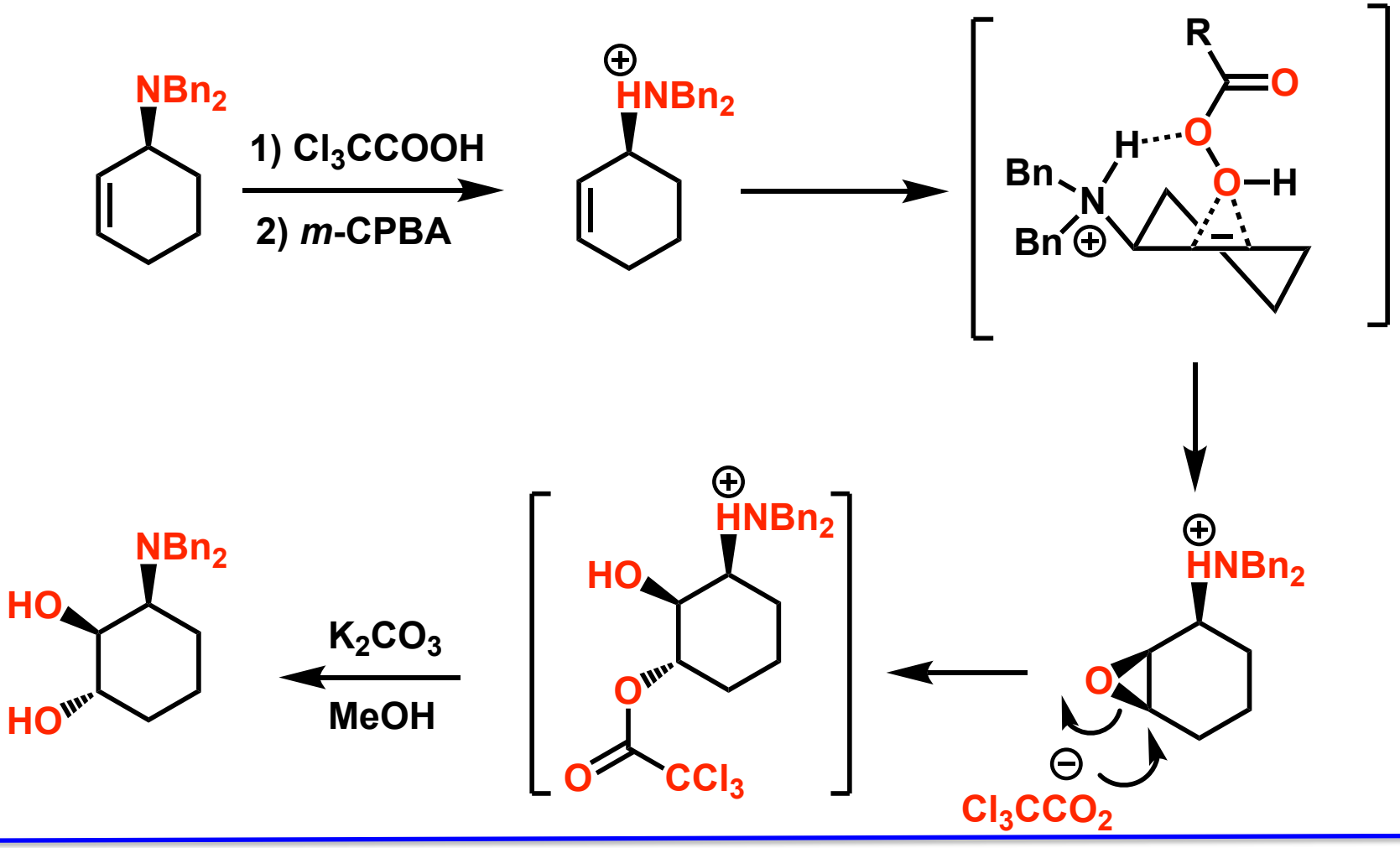
Henbest Oxidation

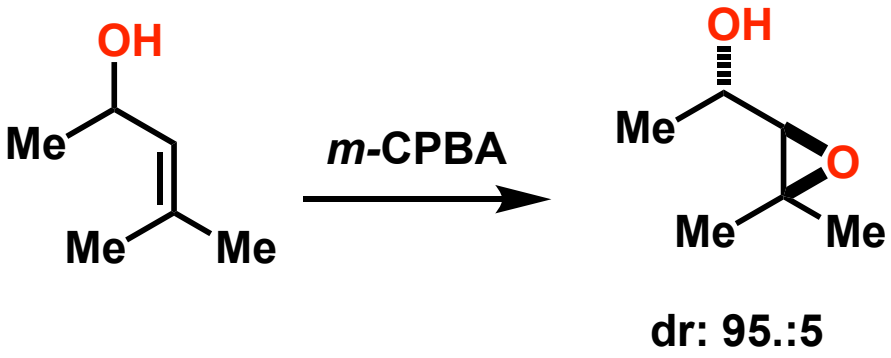


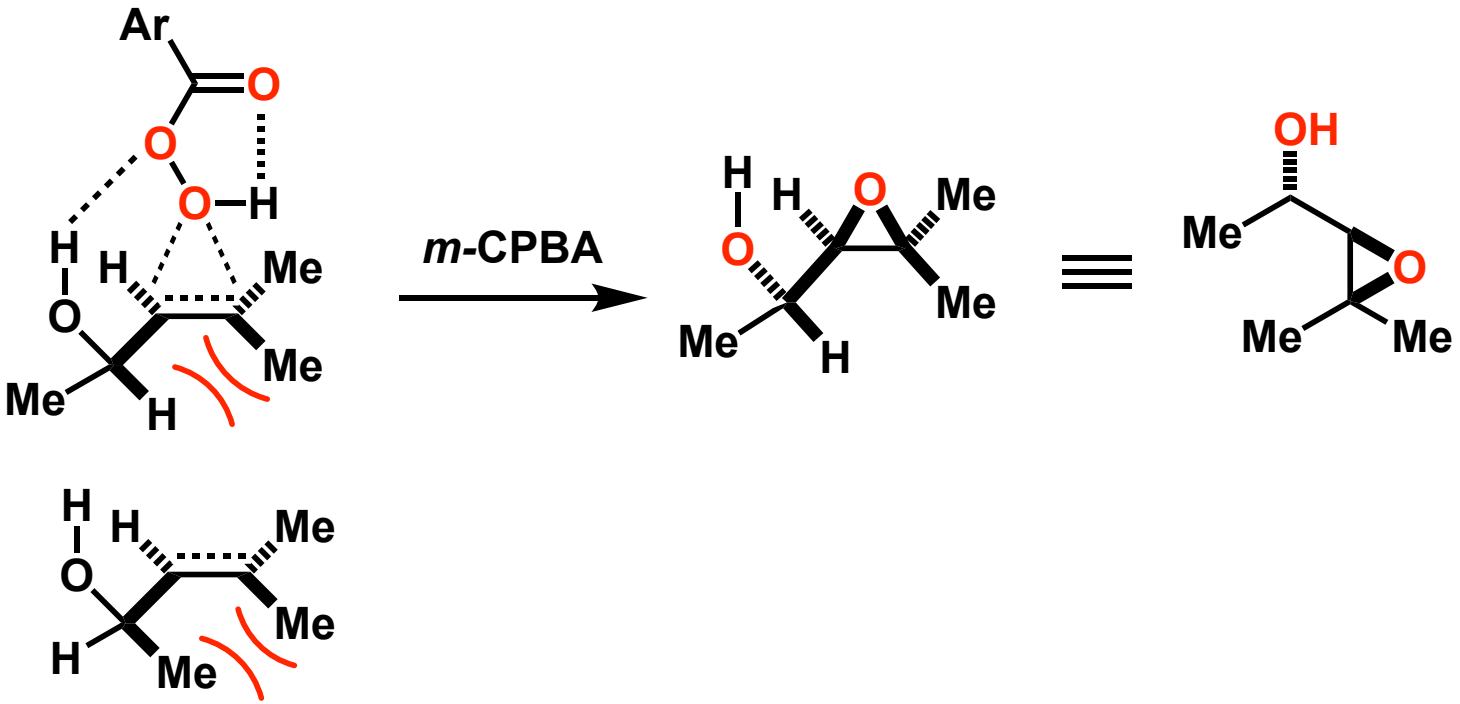
Modified Henbest Oxidation

Epoxidation Directed by Ammonium salt

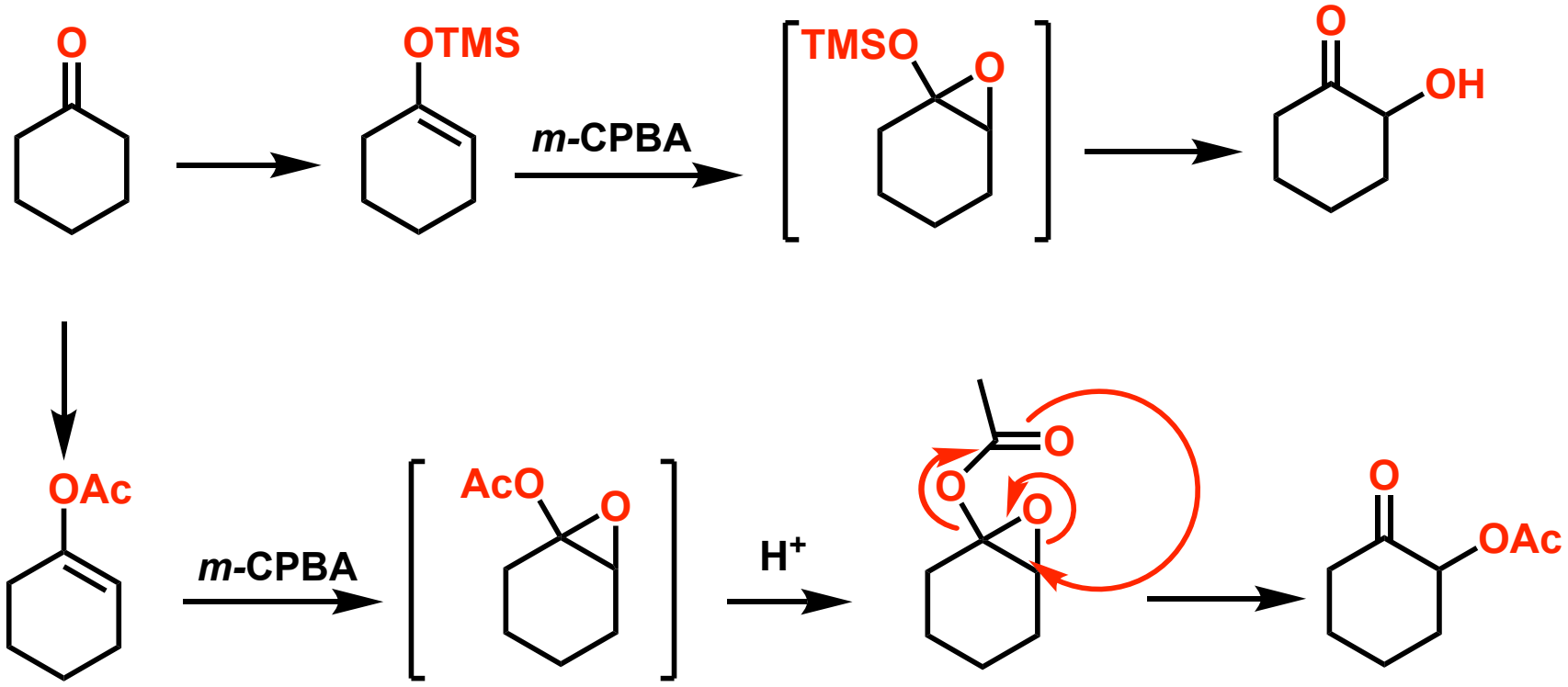


Modified Henbest Oxidation

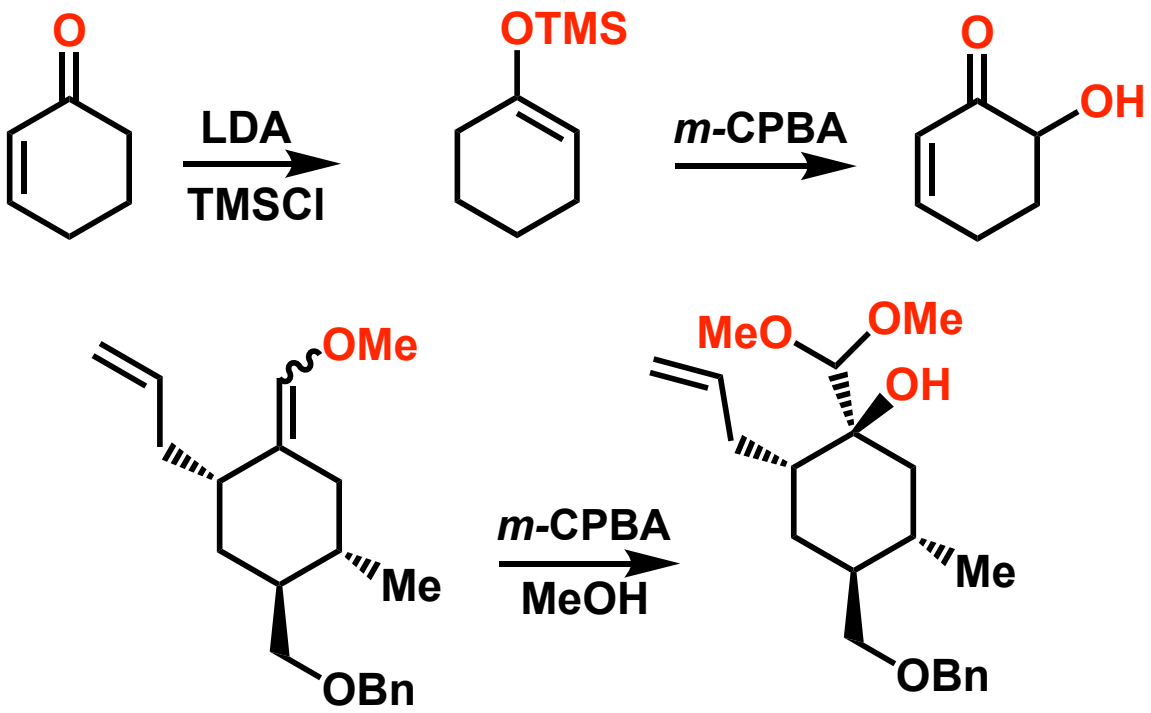




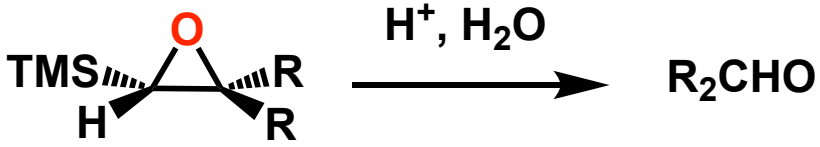
Rubottom Oxidation



Rubottom Oxidation

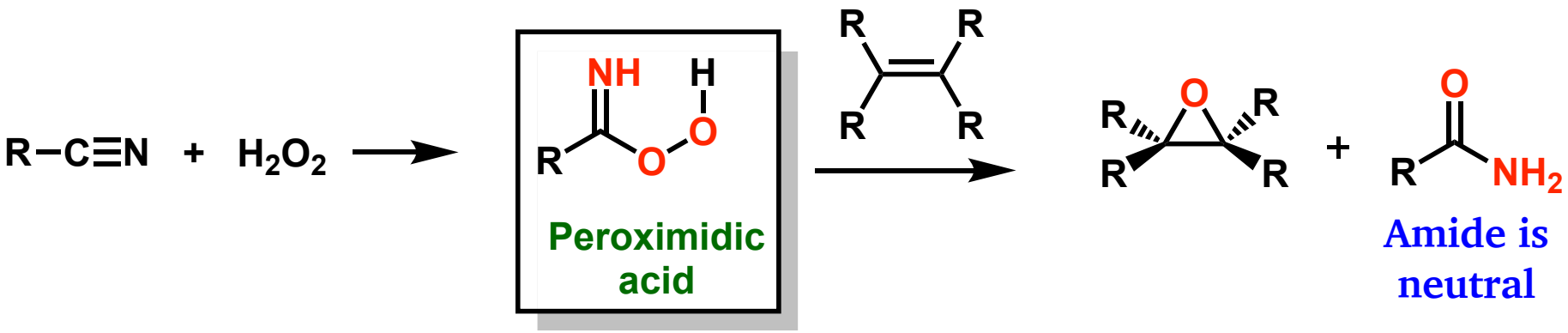


Epoxides derived from vinyl silanes are converted into aldehydes or ketones under mild acidic condition

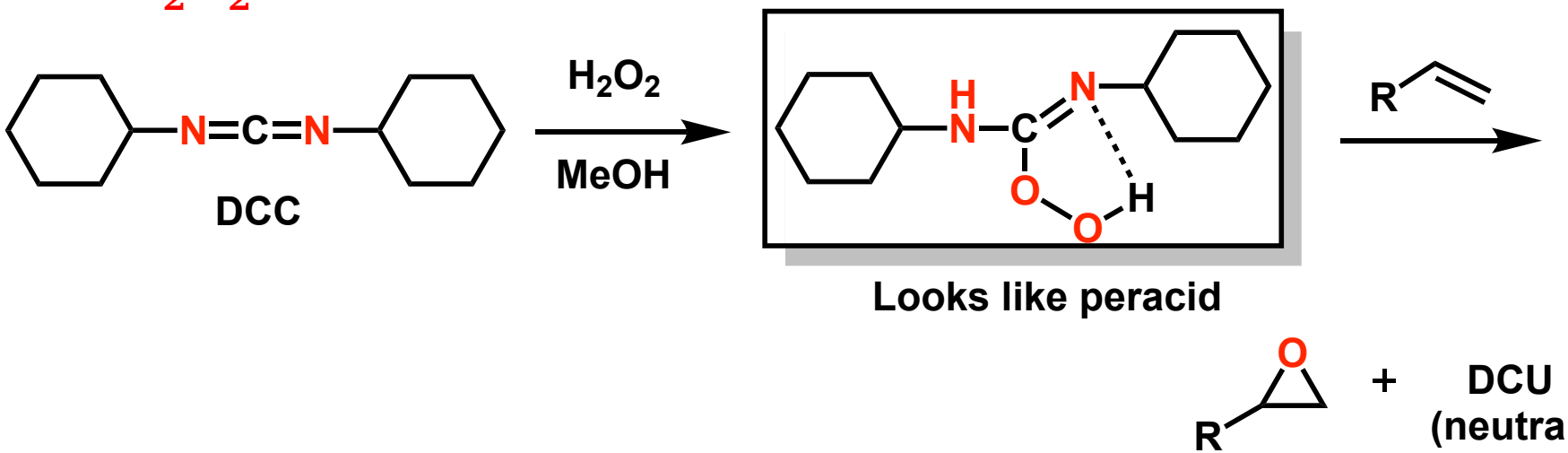


Epoxidation

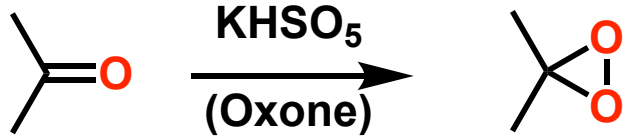
Epoxidation in non-acidic medium Nitrile & H_2O_2



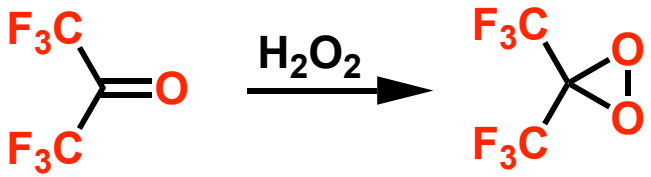
DCC-H_2O_2



Dioxiranes (Murray's reagent)



Dimethyldioxirane (DMDO)



More reactive analogue of DMDO

Utility:

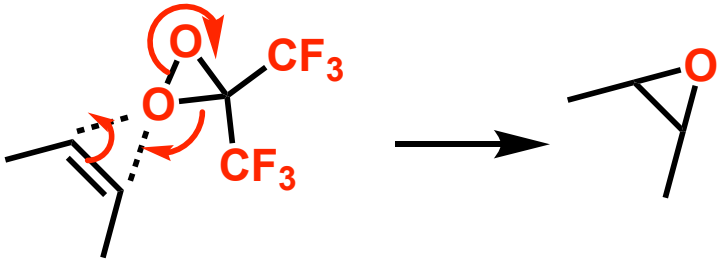
Epoxidation of olefins

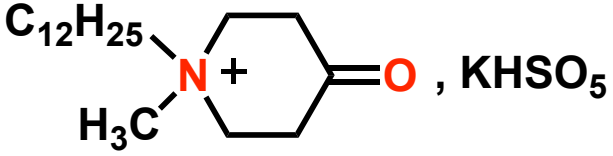
Oxidizes sulfides to sulfoxides & sulfones

Oxidation of amines to amino N-oxides

Oxidation of aldehydes to carboxylates

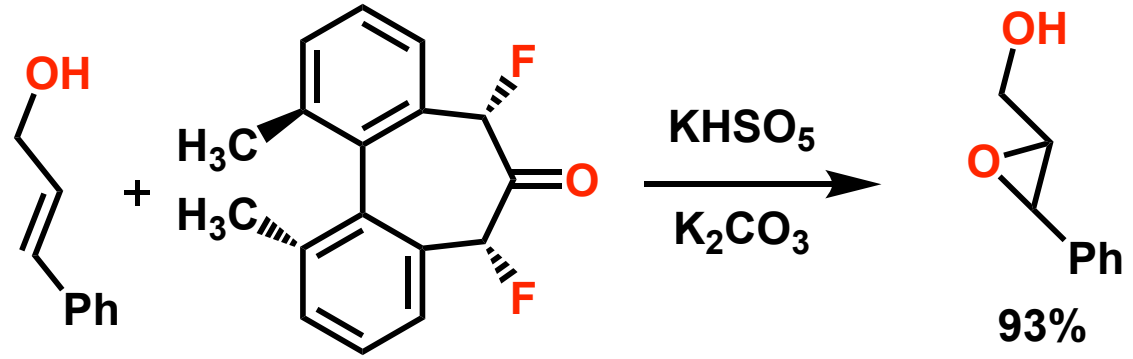
Dioxiranes Mechanism





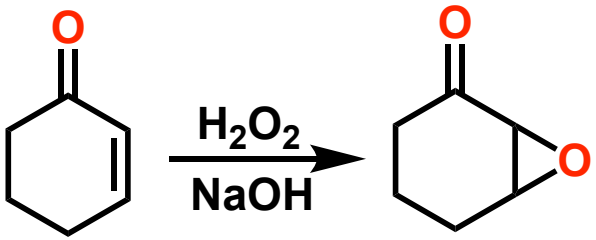
N,N-Dialkylpiperidin-4-one salts are also good catalysts for epoxidation

The quarternary nitrogen enhances the reactivity of the ketone towards nucleophilic addition

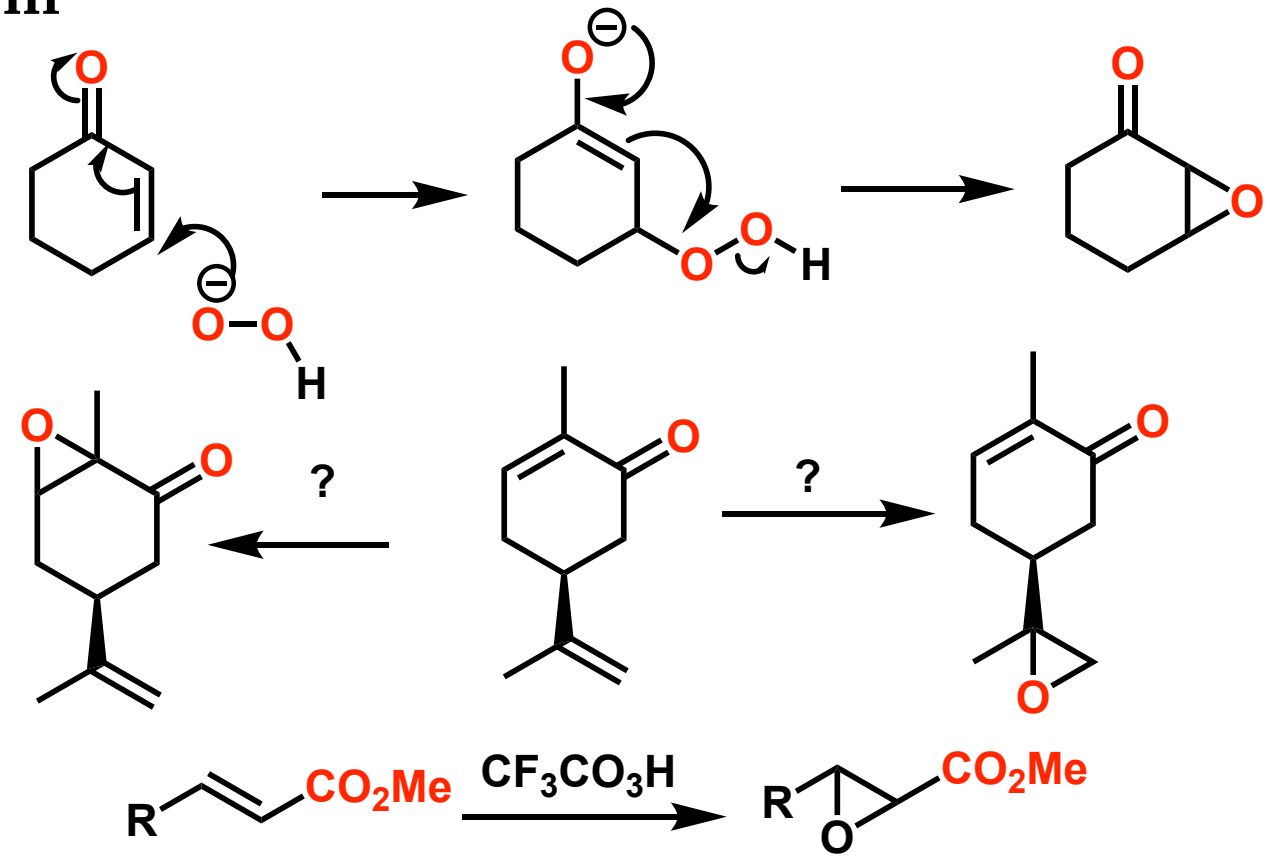


93%
89% ee

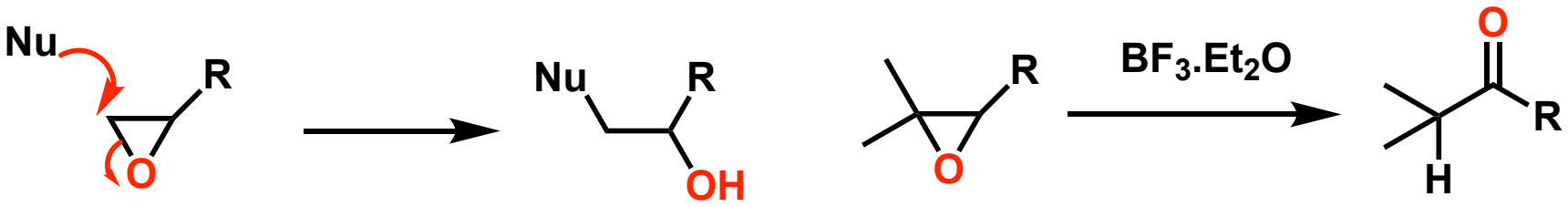
Epoxidation of Electrophilic Alkenes

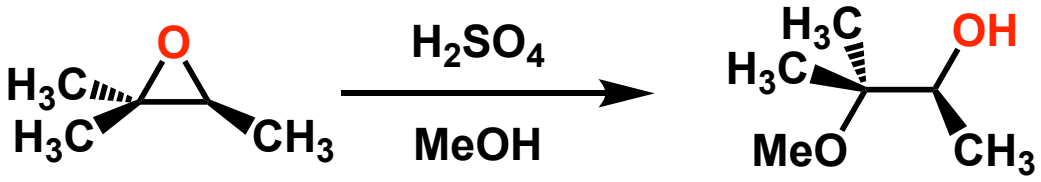


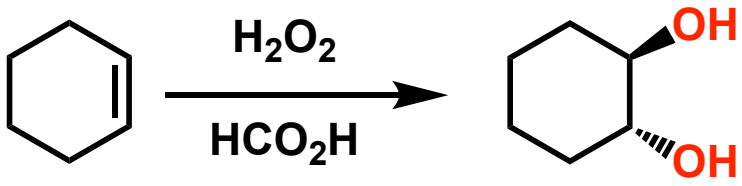
Mechanism



Transformation of Epoxides

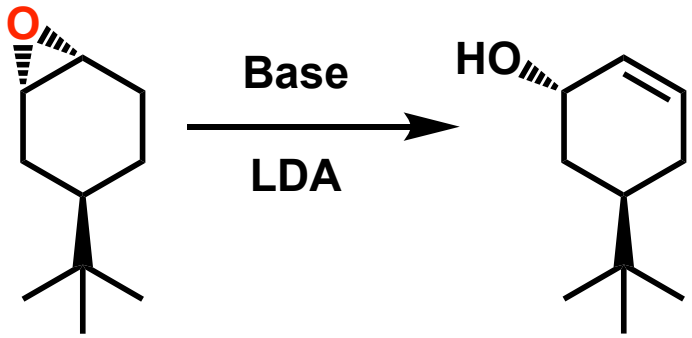




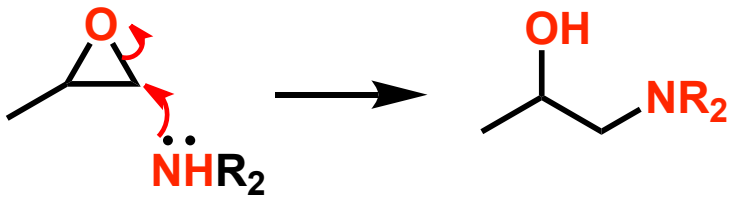


Transformation of Epoxides

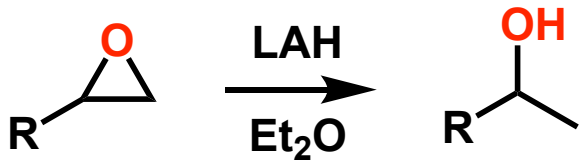
Base catalyzed ring opening of epoxides leads to allylic alcohols



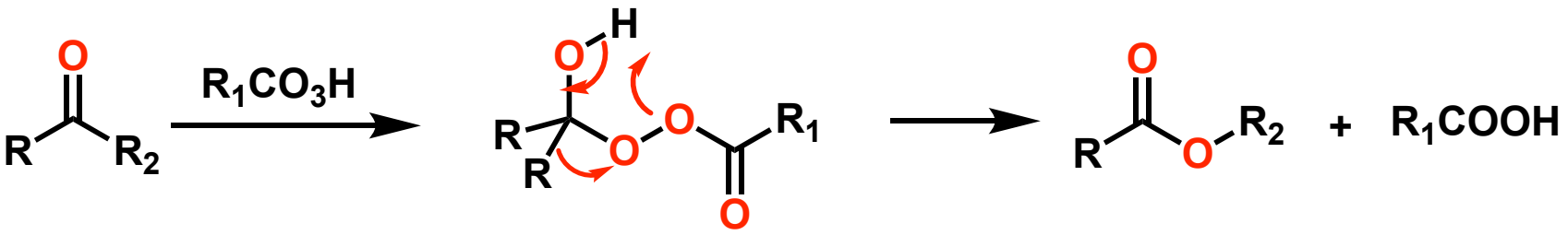
$LiClO_4$, CF_3SO_3Li, $Mg(ClO_4)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$ catalyze the epoxide ring opening.



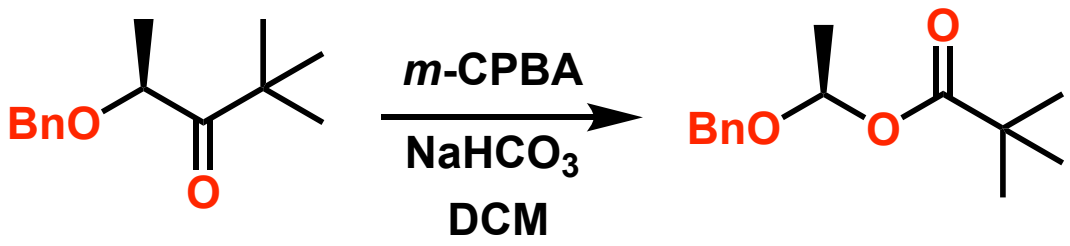
LAH acts as a nucleophilic agent & attacks at the less substituted carbon atom of the epoxide ring. DIBAL-H also serves the purpose

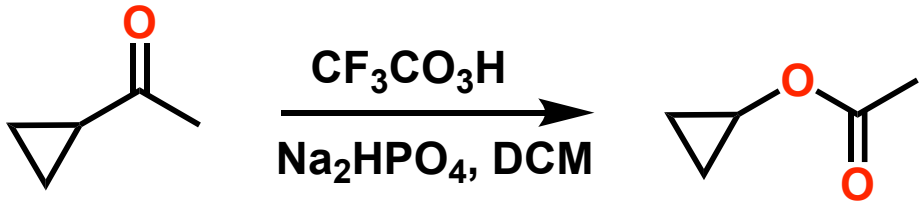


Baeyer Villiger Oxidation



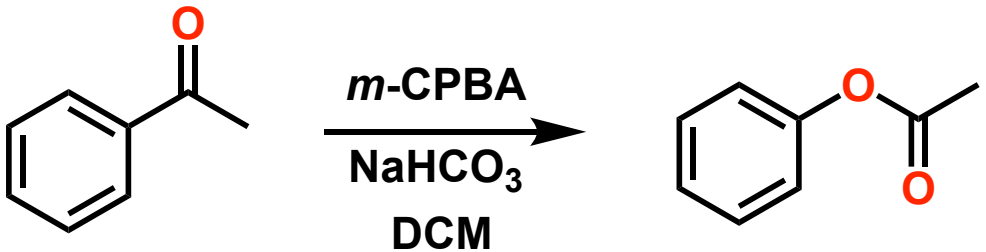
The migratory aptitudes are: Alkoxyalkyl >*t*-Alkyl>cyclohexyl=secondary alkyl=benzyl=Phenyl>vinylic>primary alkyl>cyclopropyl>methyl





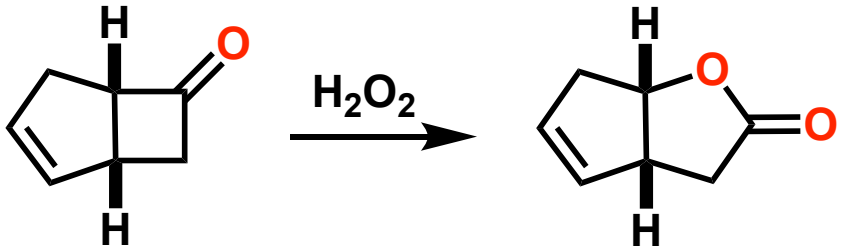
Acid catalyzed side reactions can be suppressed by phosphate buffer

Baeyer Villiger Oxidation

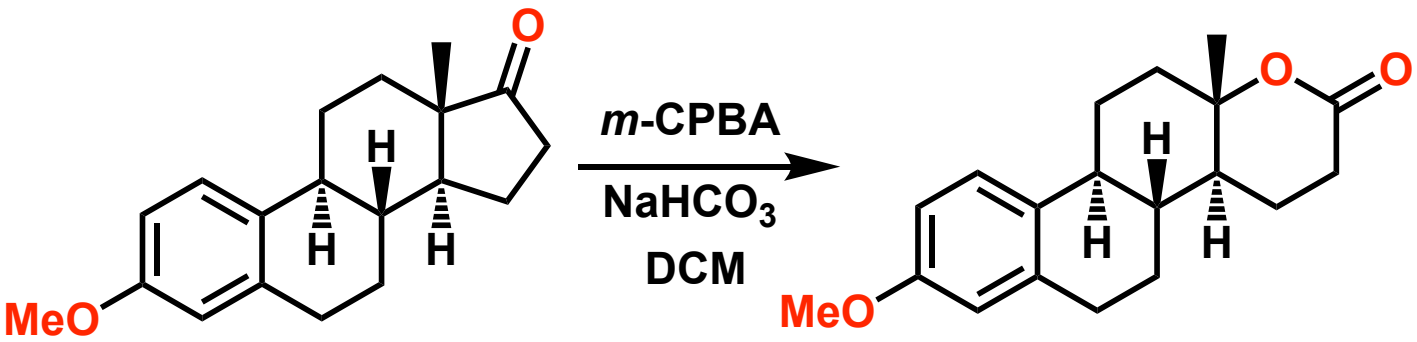


meta directing group

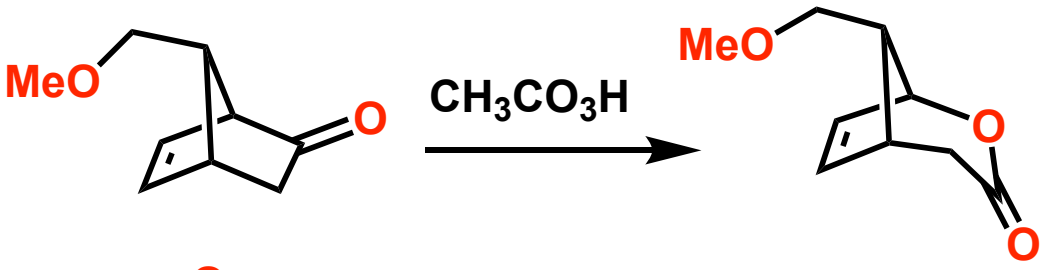
ortho & para directing group

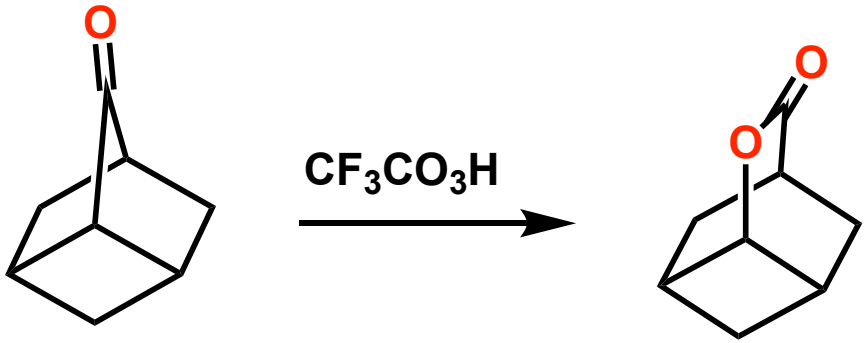


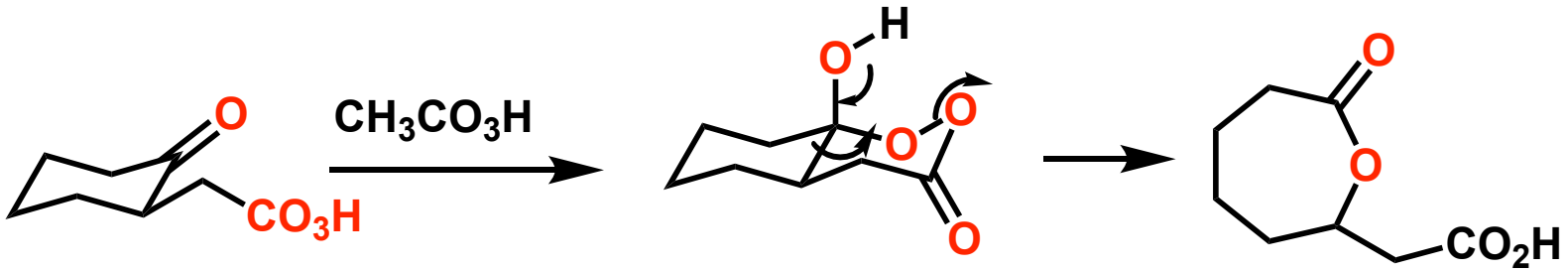
Normally, most ketones do not react with H_2O_2 but the above one does



Baeyer Villiger Oxidation







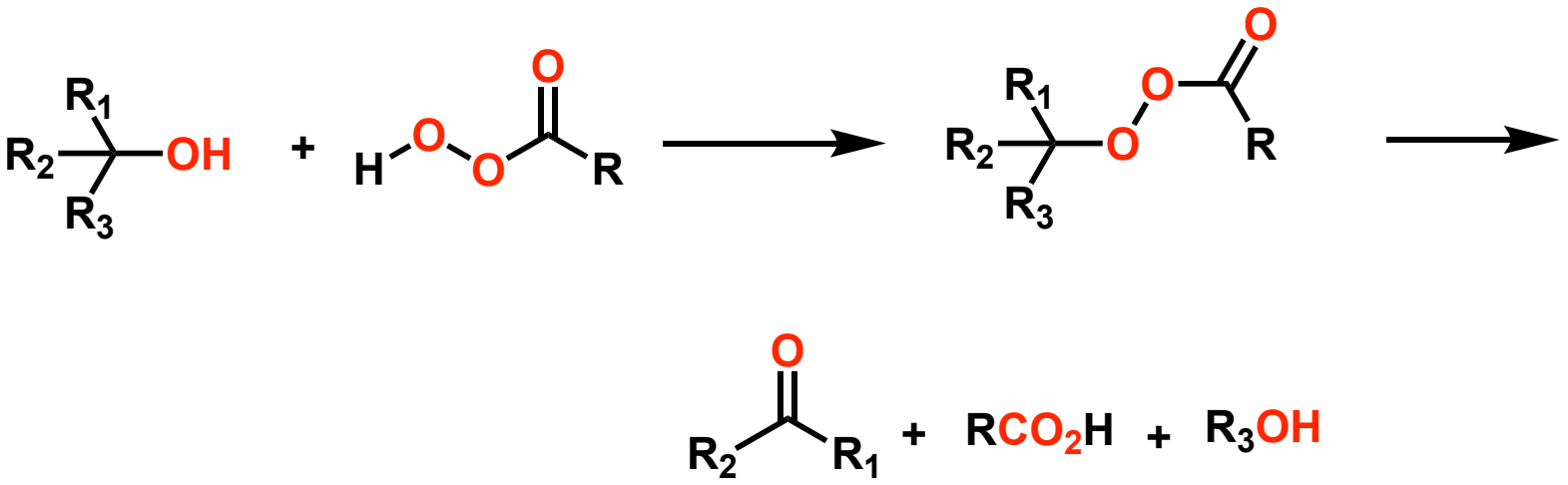
Criegee Rearrangement

This rearrangement was reported by Criegee in 1944

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

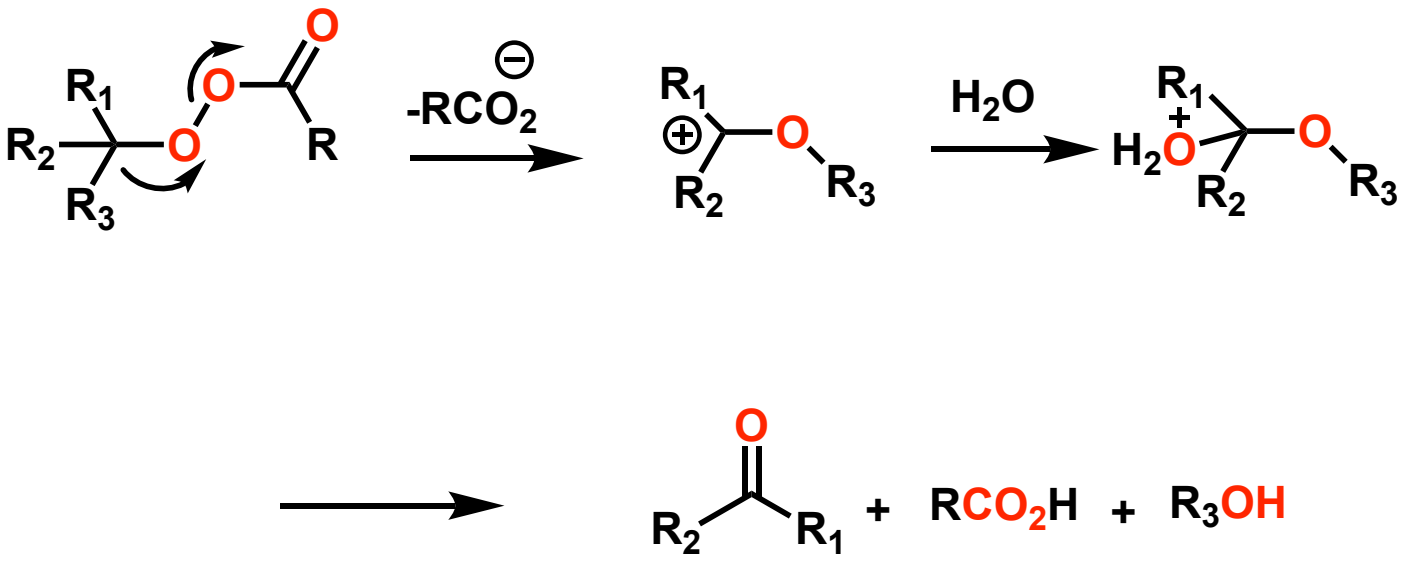
Peroxyesters are prepared by reaction between peracid and tertiary alcohols

Baeyer Villiger oxidation is a subset of Criegee rearrangement

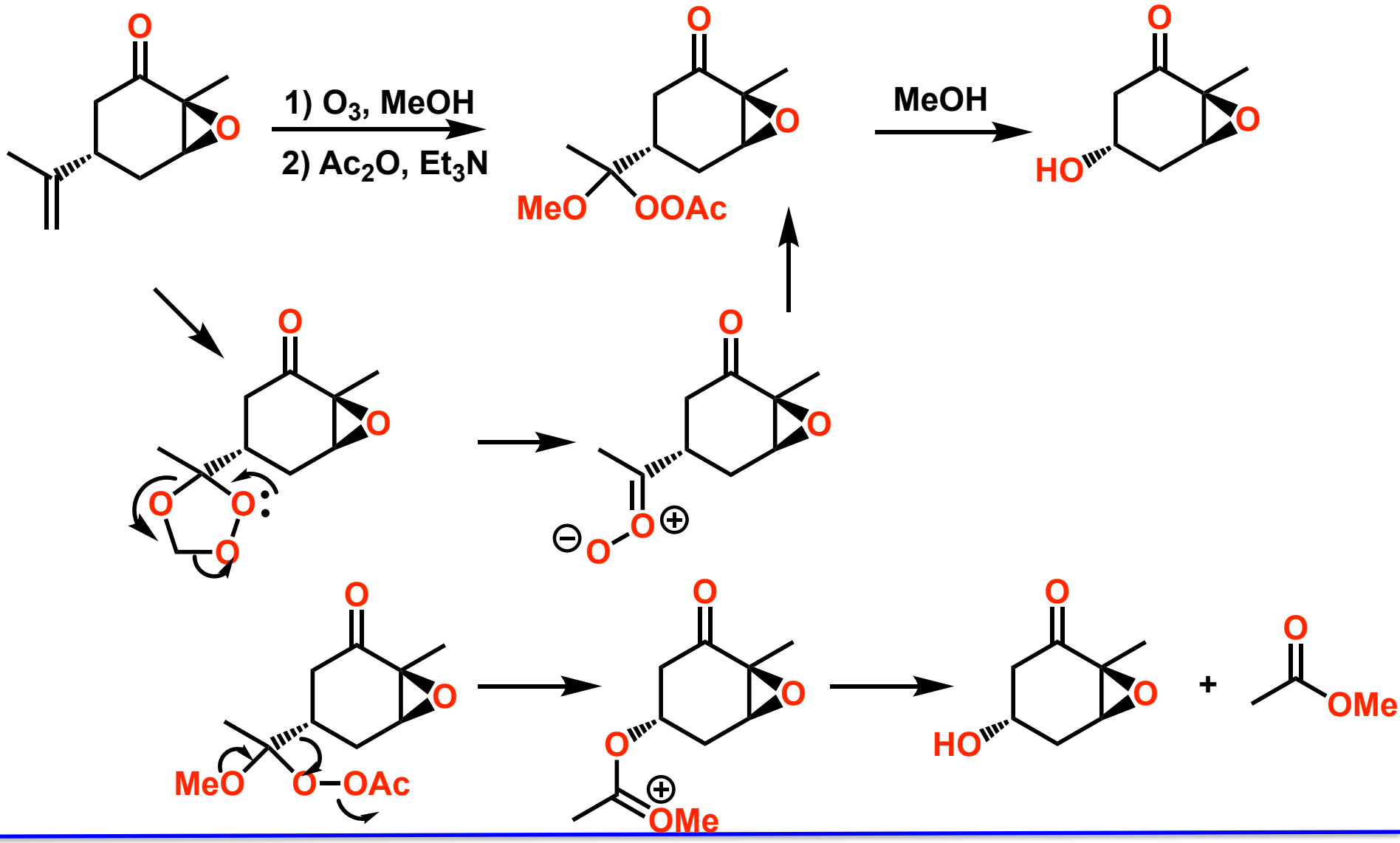


Criegee Rearrangement

Mechanism



Criegee Rearrangement



Oxidation with Singlet Oxygen

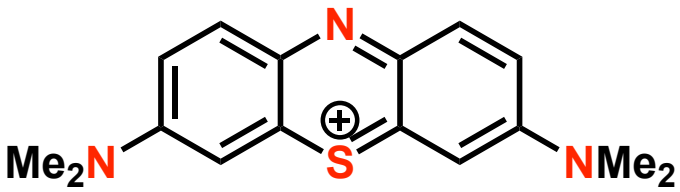
Generation of singlet oxygen:

$$\text{Photosensitizer} + h\nu \longrightarrow {}^1[\text{Photosensitizer}]^*$$

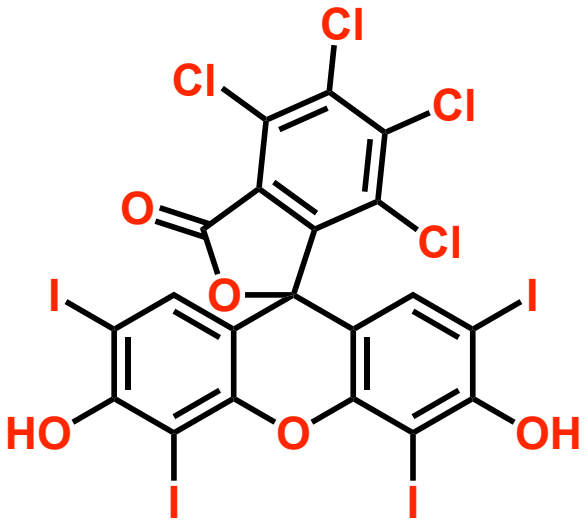
$${}^1[\text{Photosensitizer}]^* \longrightarrow {}^3[\text{Photosensitizer}]^*$$

$${}^3[\text{Photosensitizer}]^* + {}^3O_2 \longrightarrow \text{Photosensitizer} + {}^1O_2$$

Photosensitizers:



Methylene blue

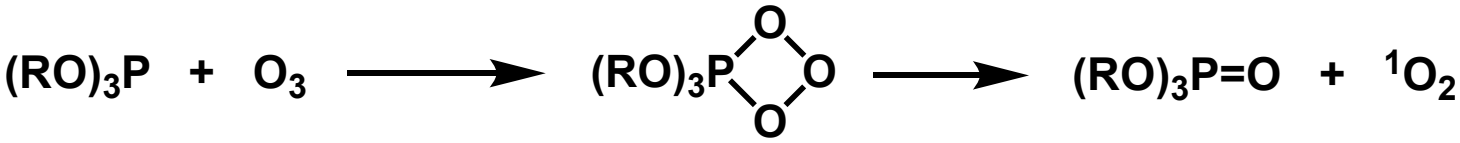


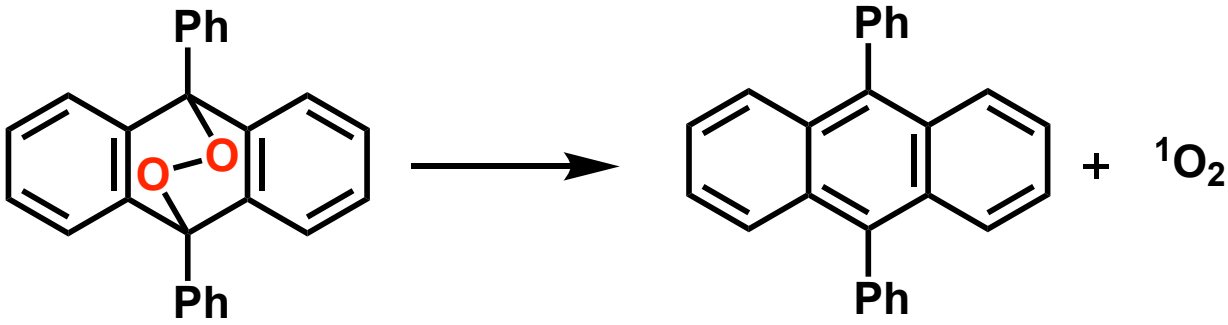
Rose Bengal

Tetraphenylporphyrin

Oxidation with Singlet Oxygen

Generation of singlet oxygen:



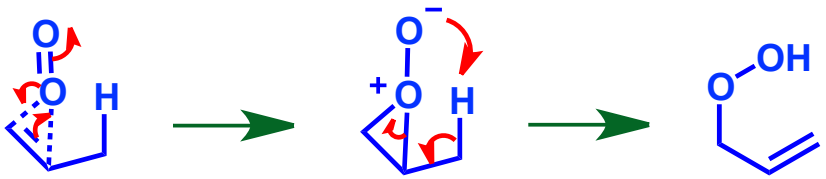


Oxidation with Singlet Oxygen

Mechanism:

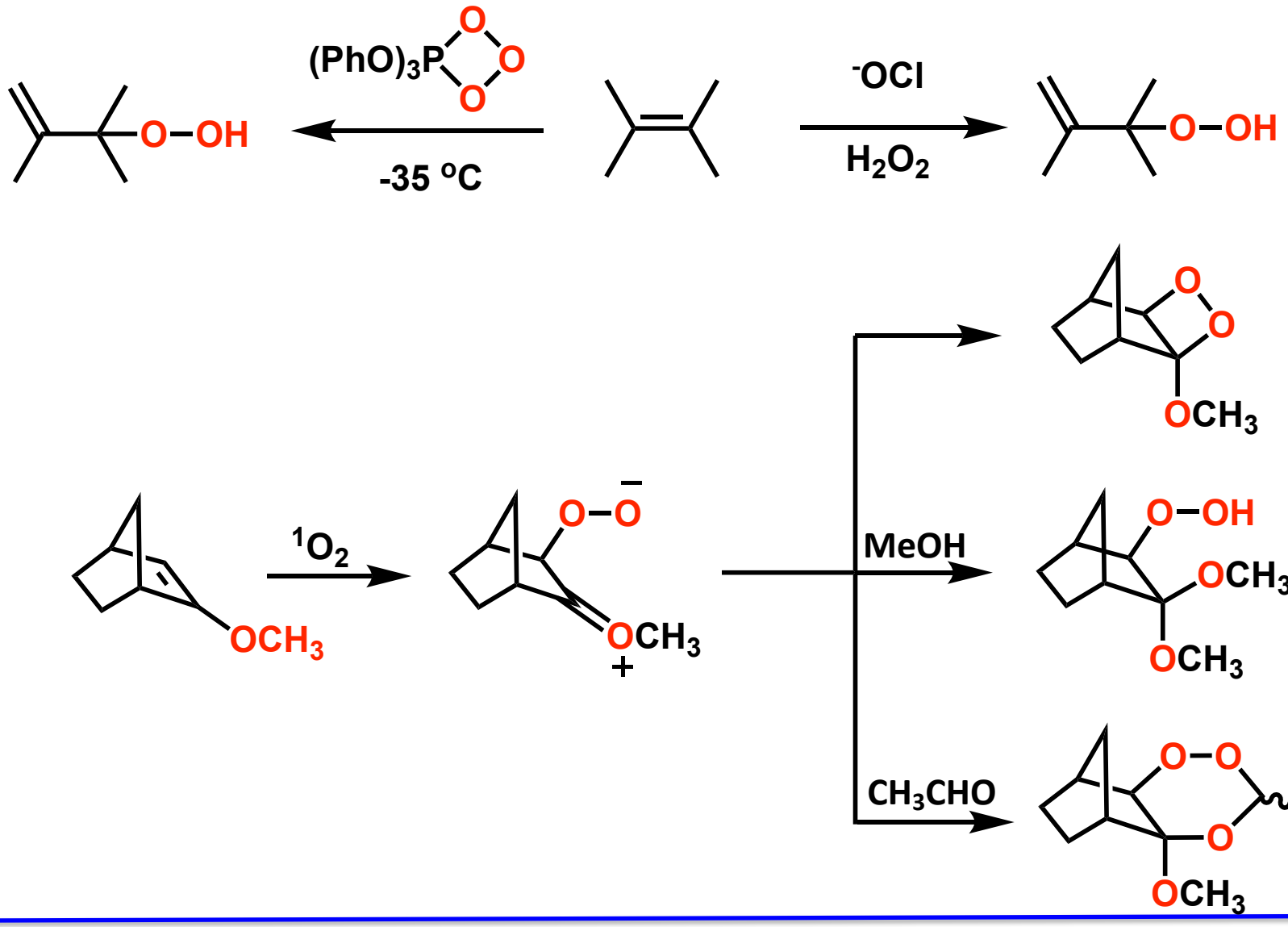
1. Concerted mechanism

2. Perepoxide-intermediate mechanism

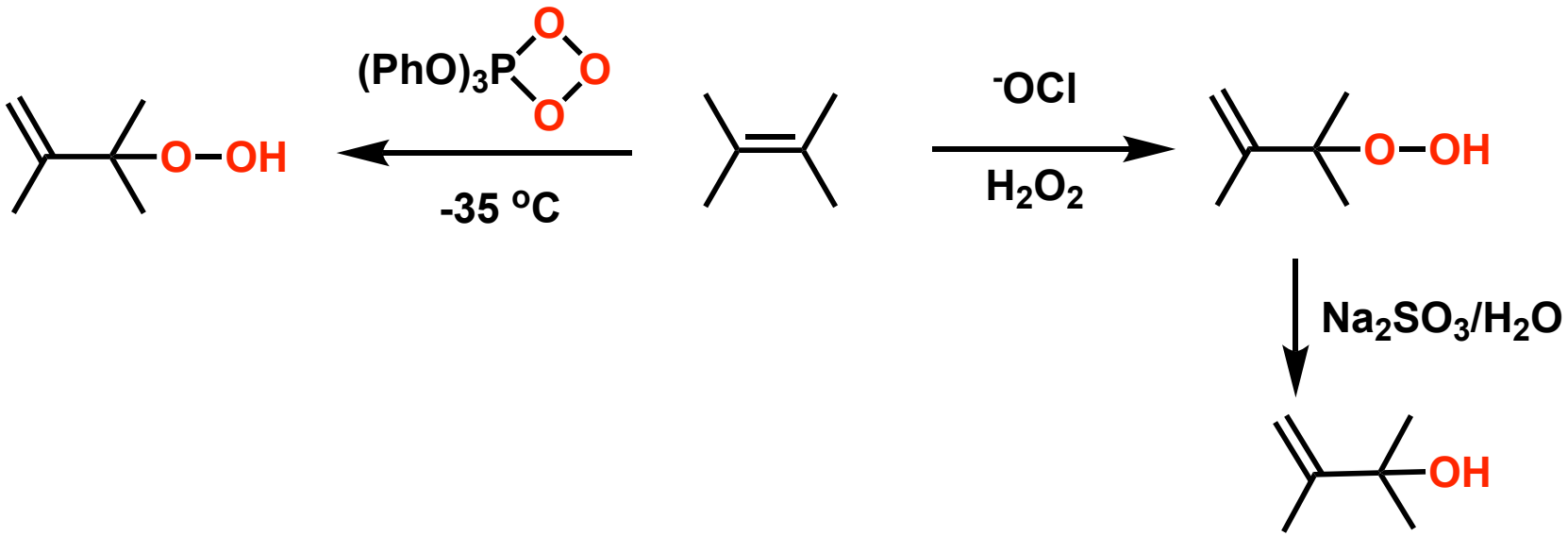


There is a preference for removal of a hydrogen from more congested side of the double bond

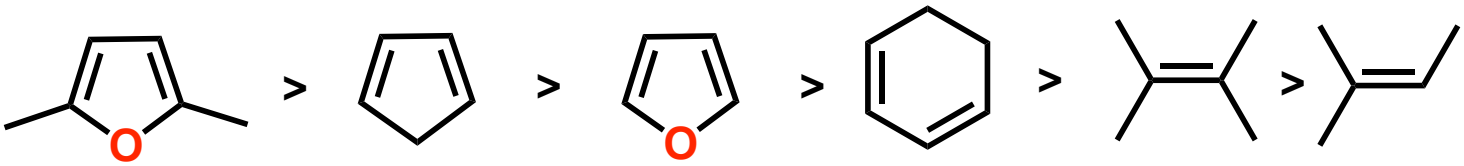
Oxidation with Singlet Oxygen



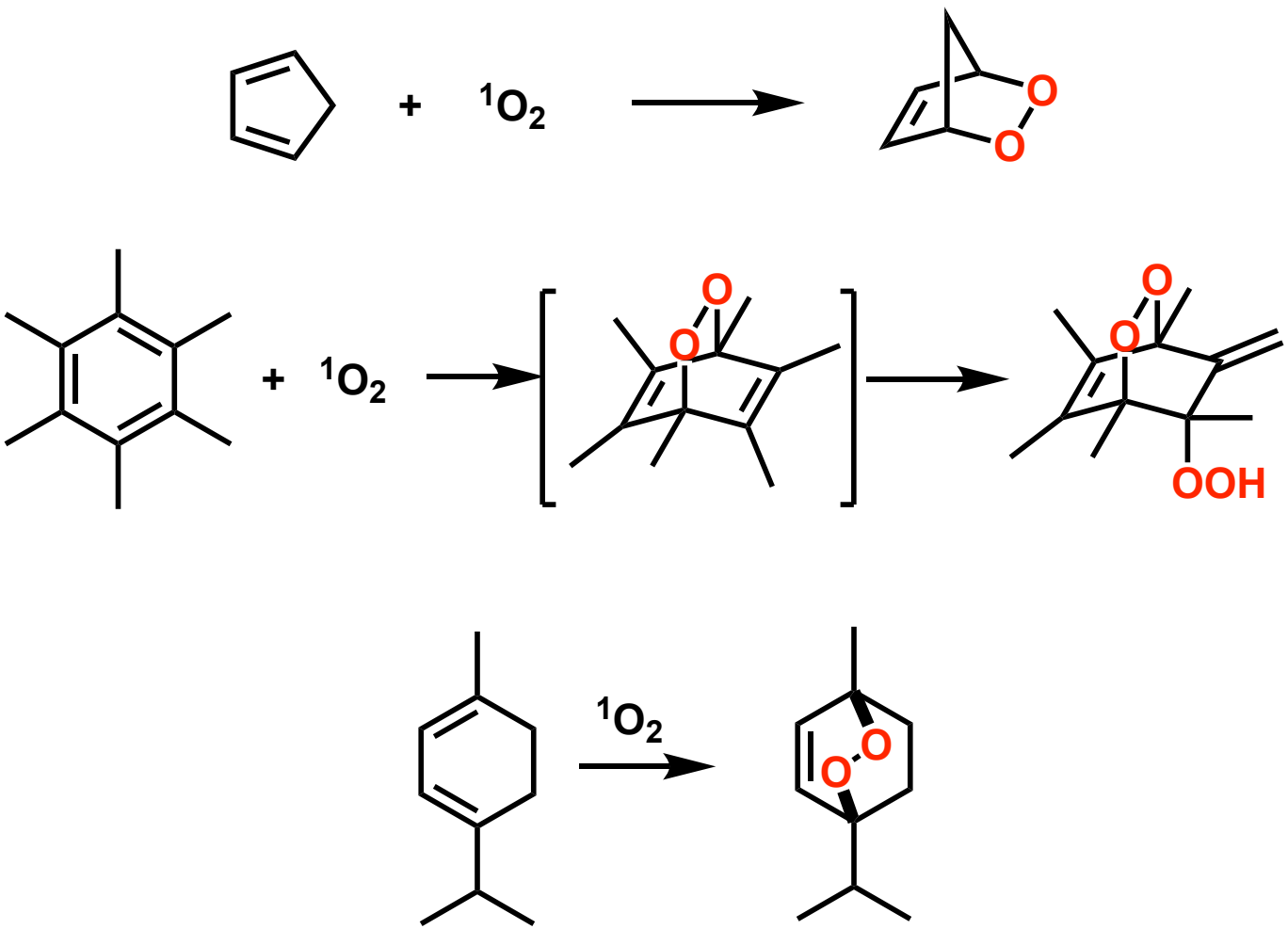
Oxidation with Singlet Oxygen



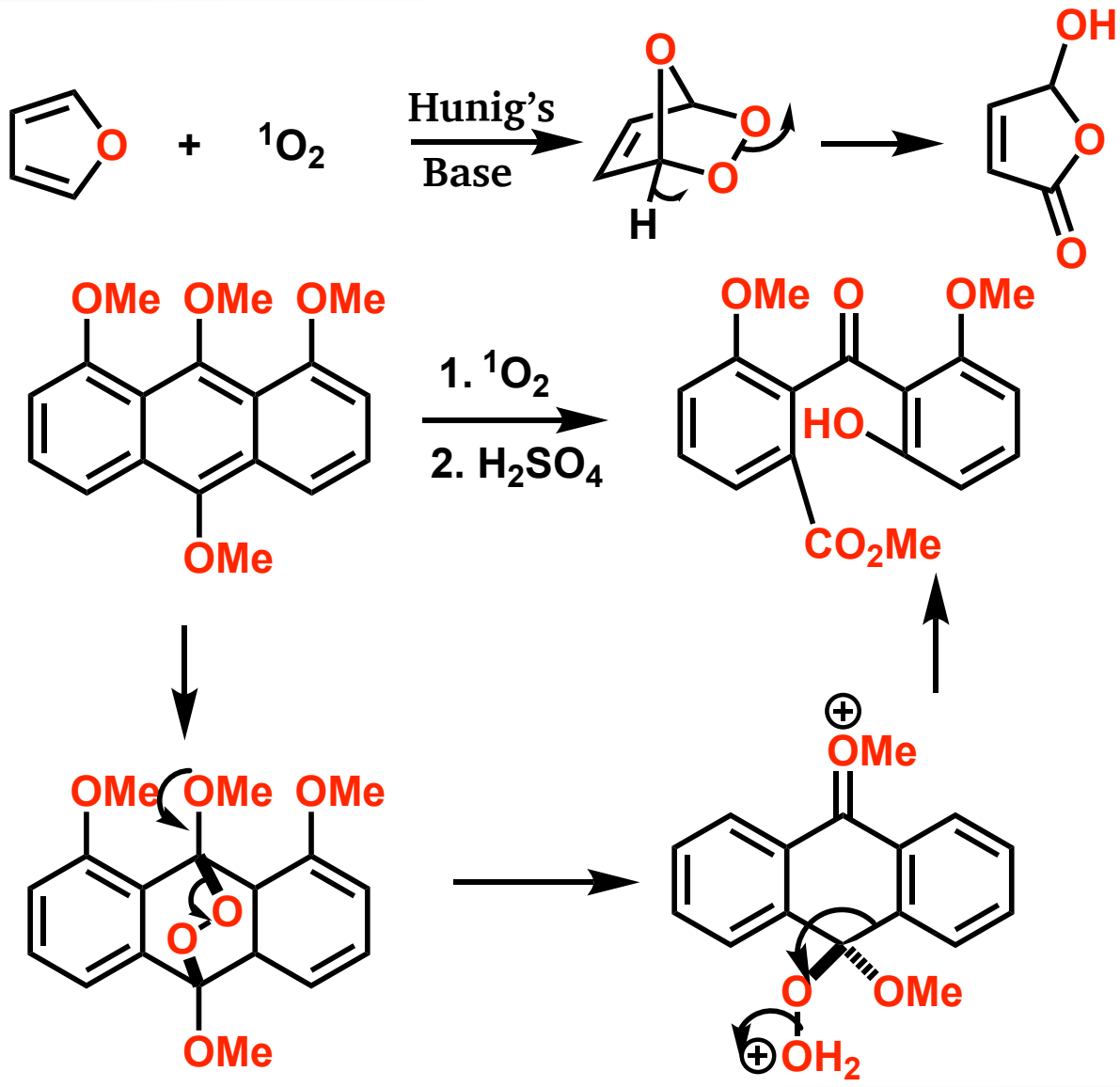
Relative rates of oxidation:



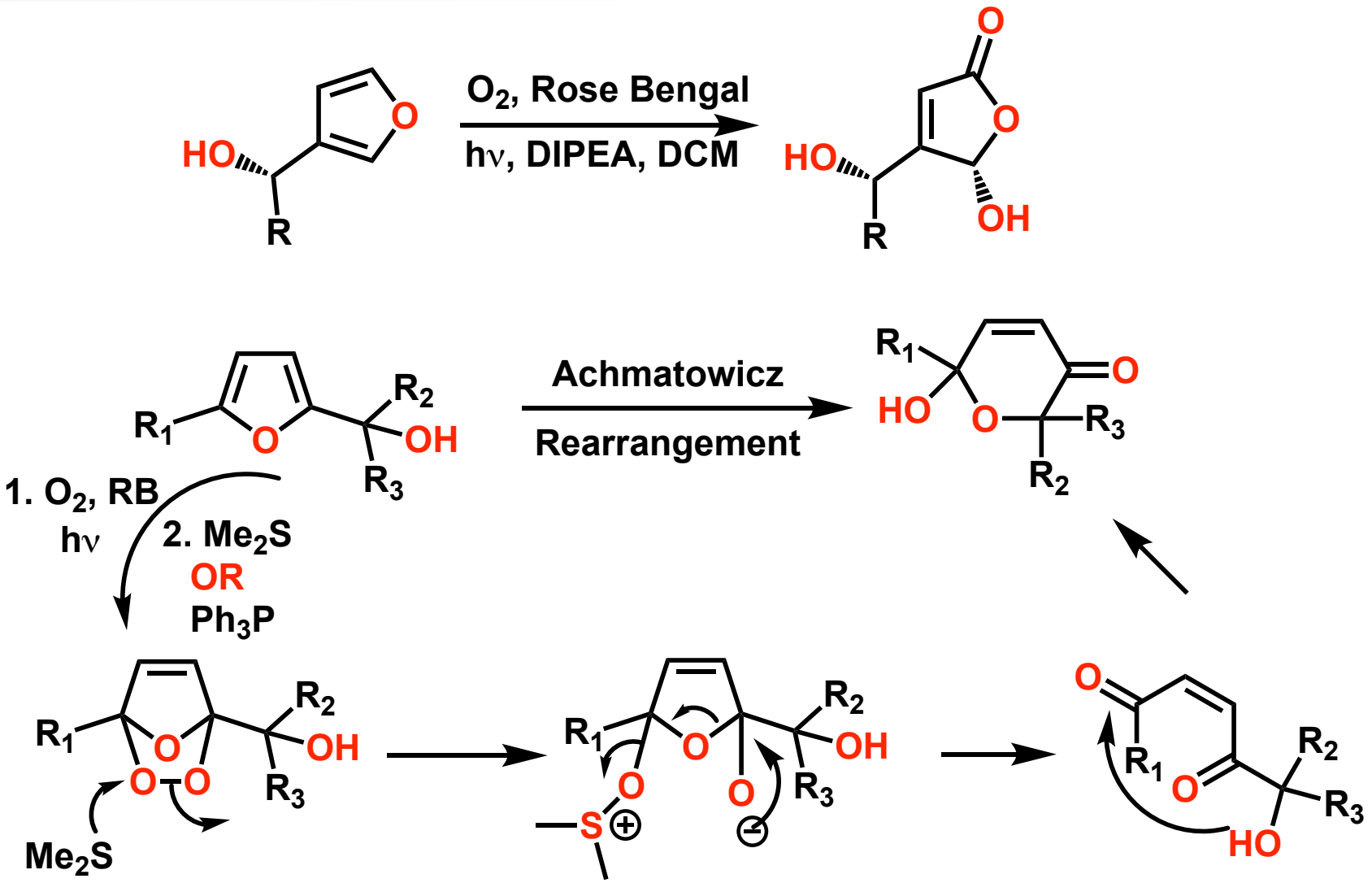
[4+2] with Singlet Oxygen



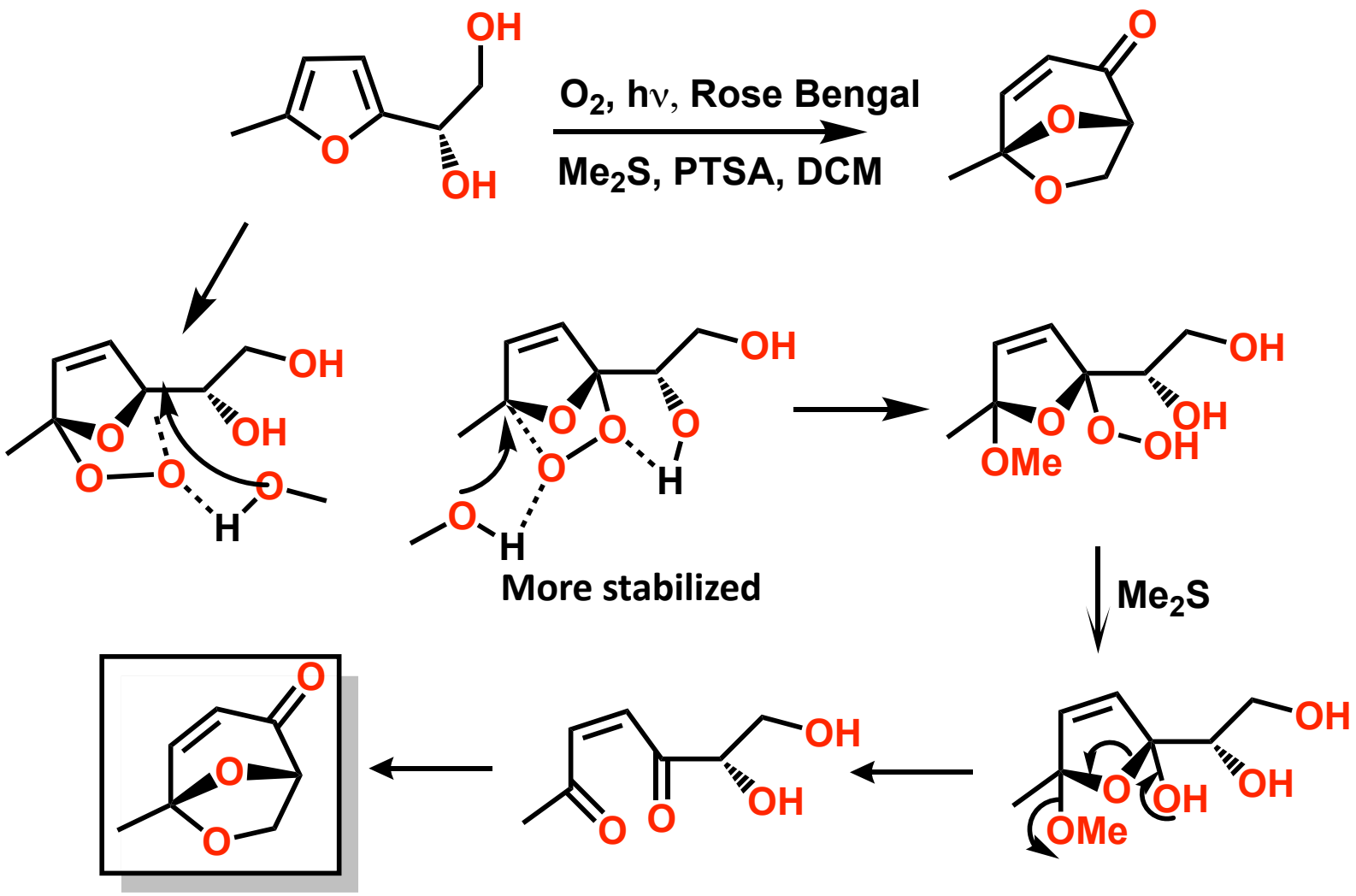
[4+2] with Singlet Oxygen



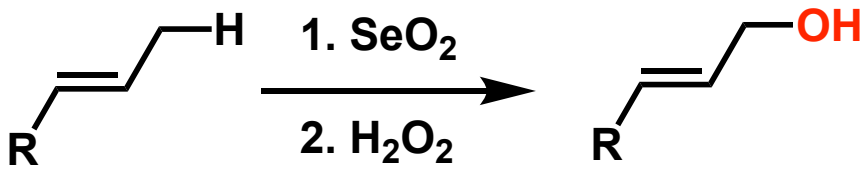
Achmatowicz Rearrangement



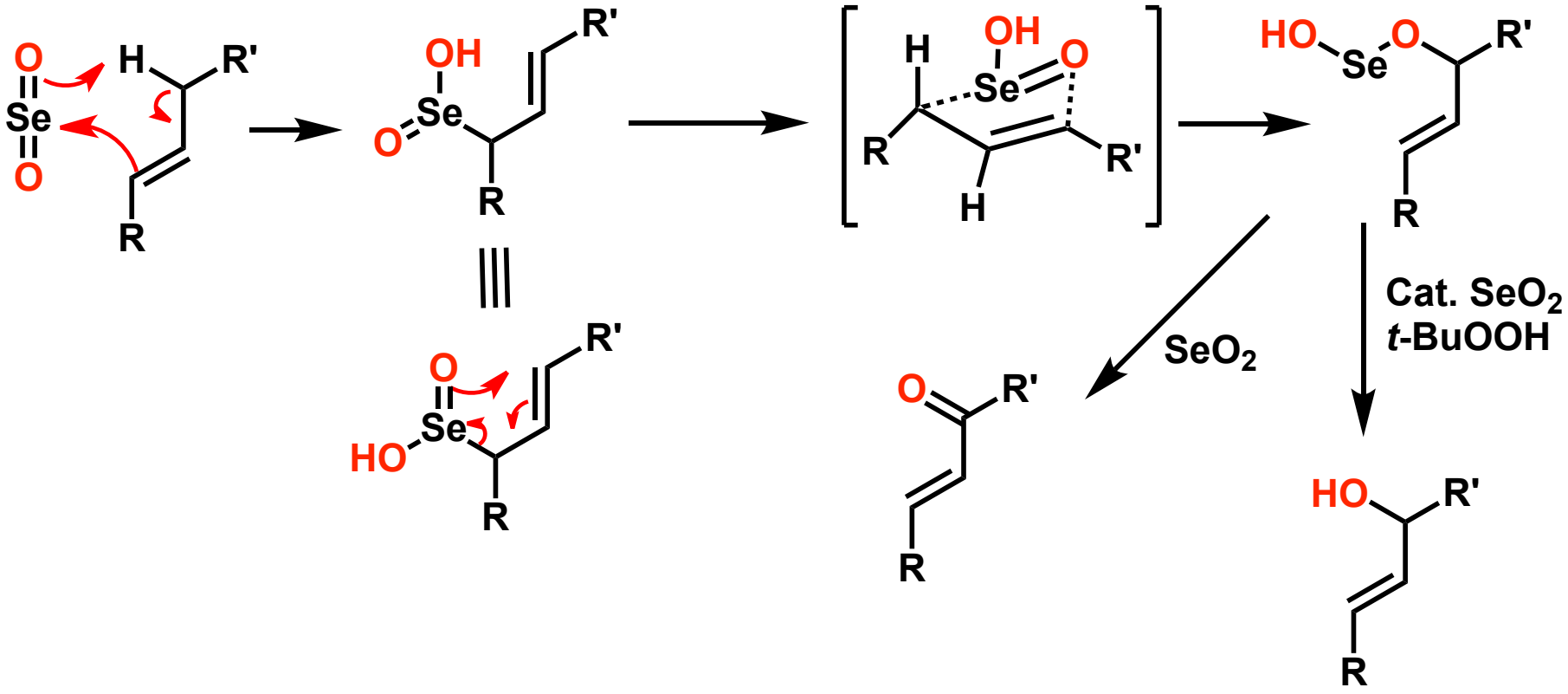
Oxidation with Singlet Oxygen



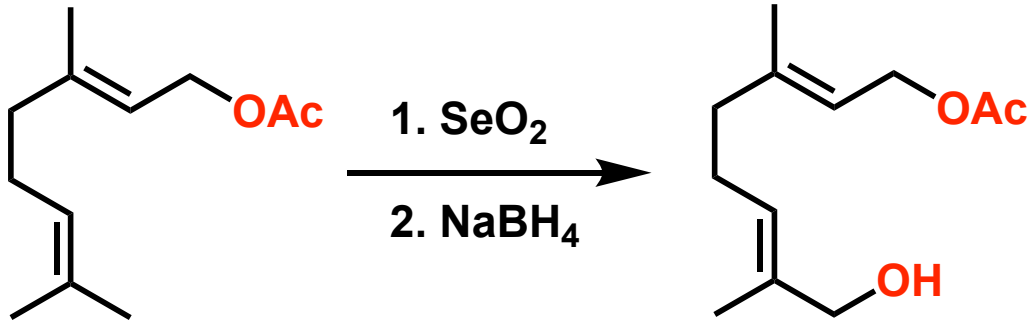
Oxidation with SeO_2



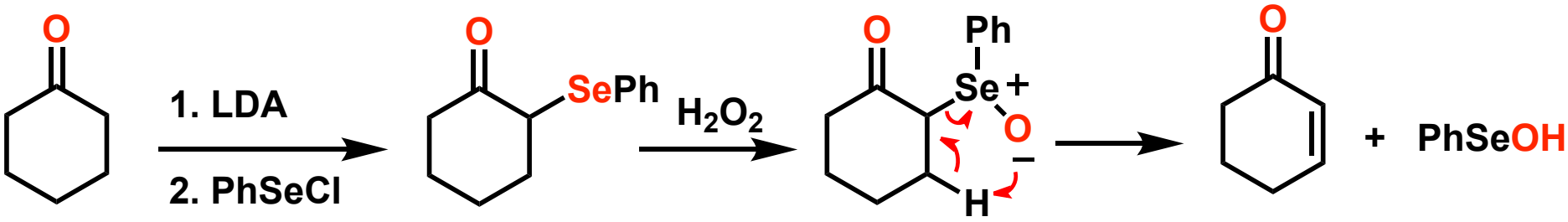
Mechanism:



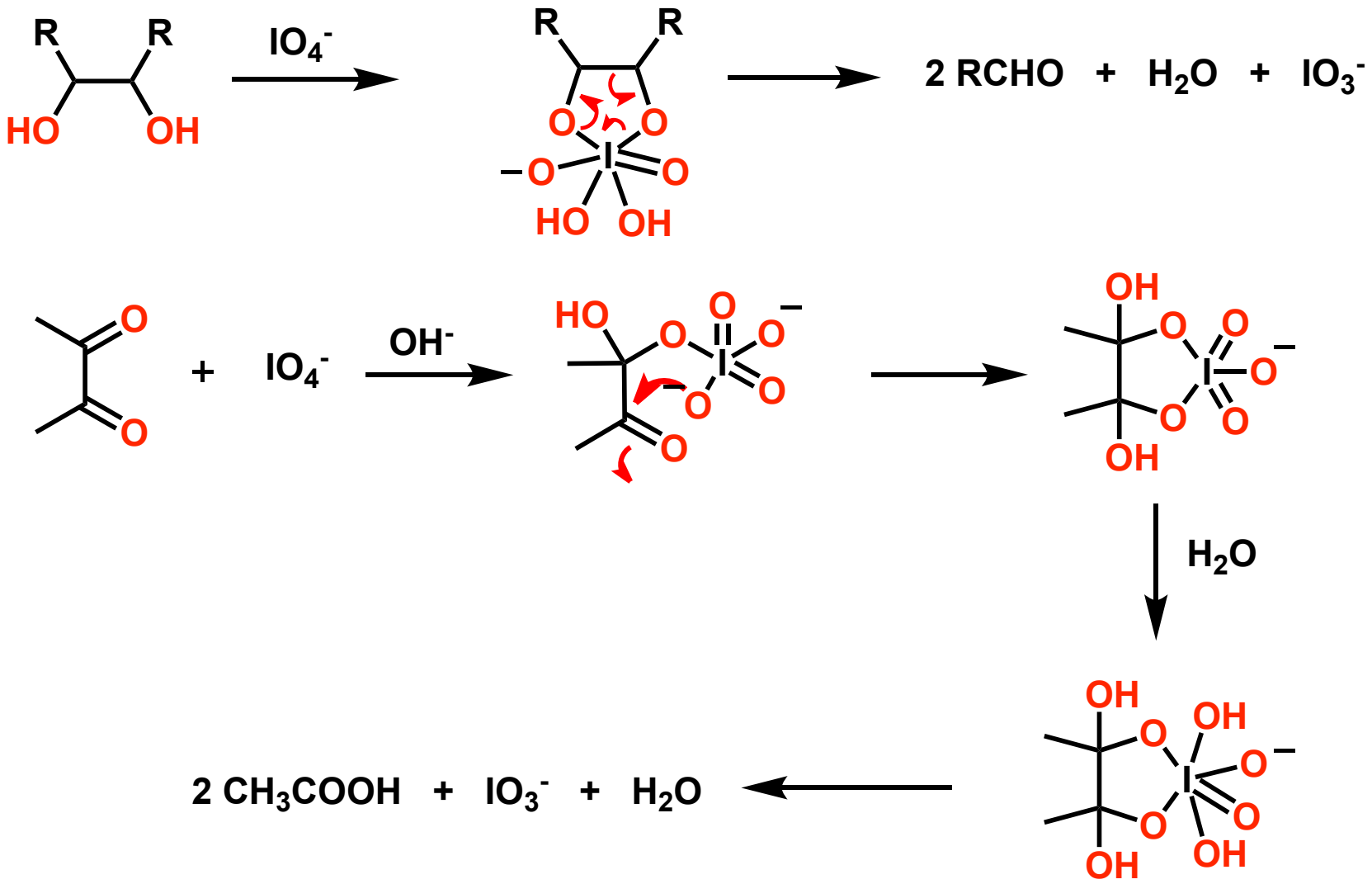
Oxidation with SeO_2



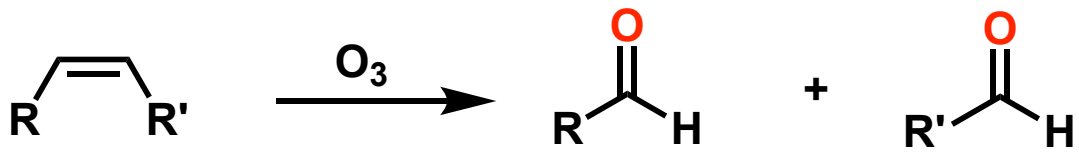
PhSeCl Oxidation



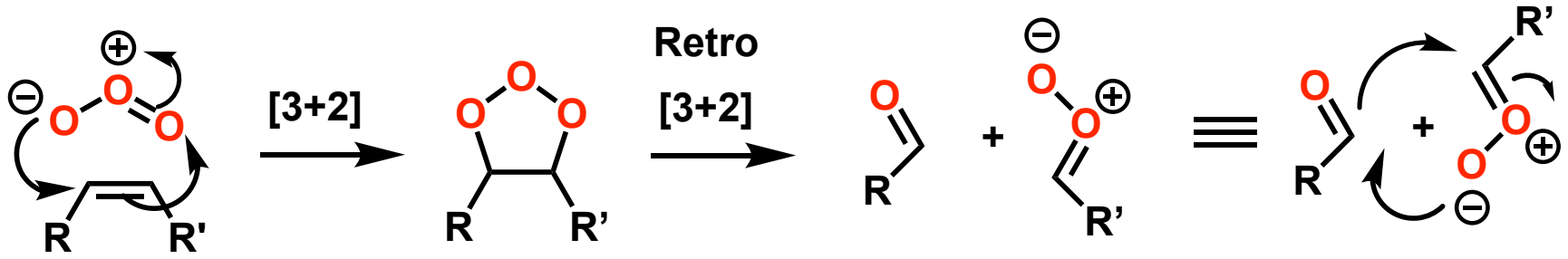
Oxidation with $NaIO_4$

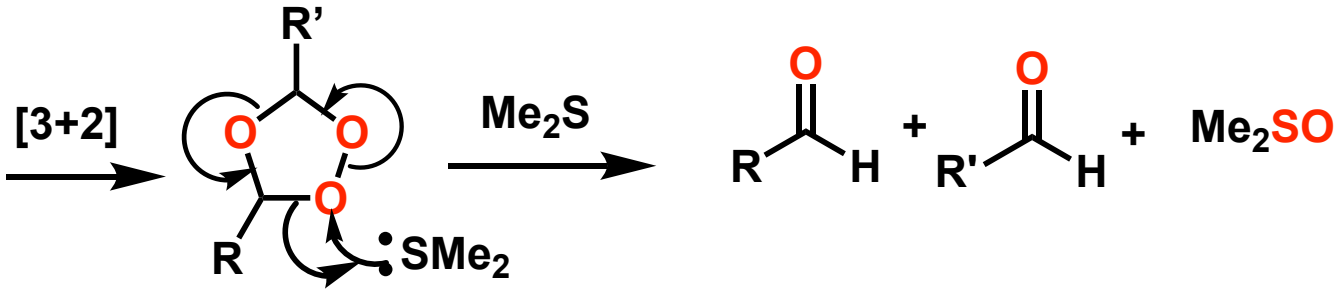


Ozonolysis



Mechanism





PPh_3 → $Ph_3P{=}O$

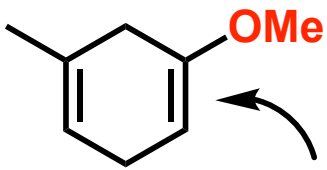
Zn → ZnO

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

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

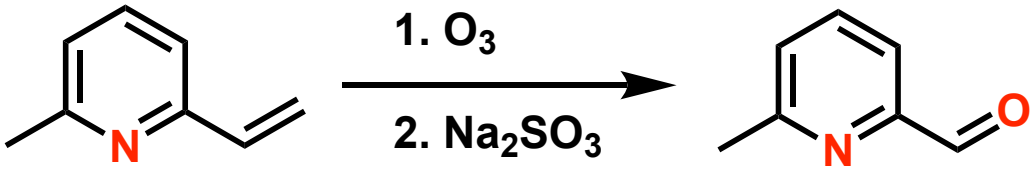
Ozonolysis

Reactivity



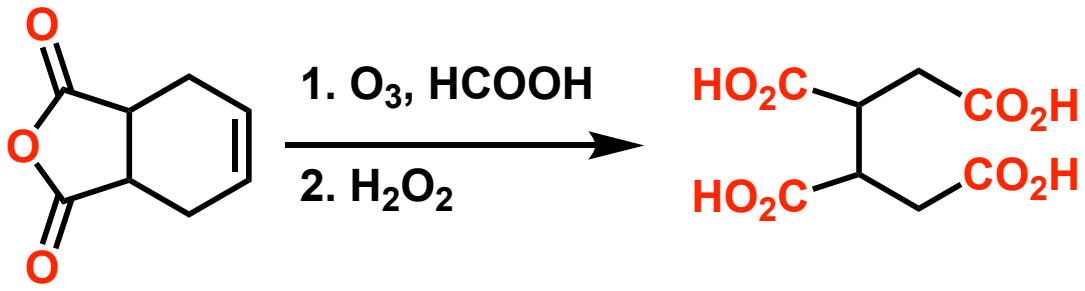
will undergo ozonolysis faster than other

Reductive Work-up

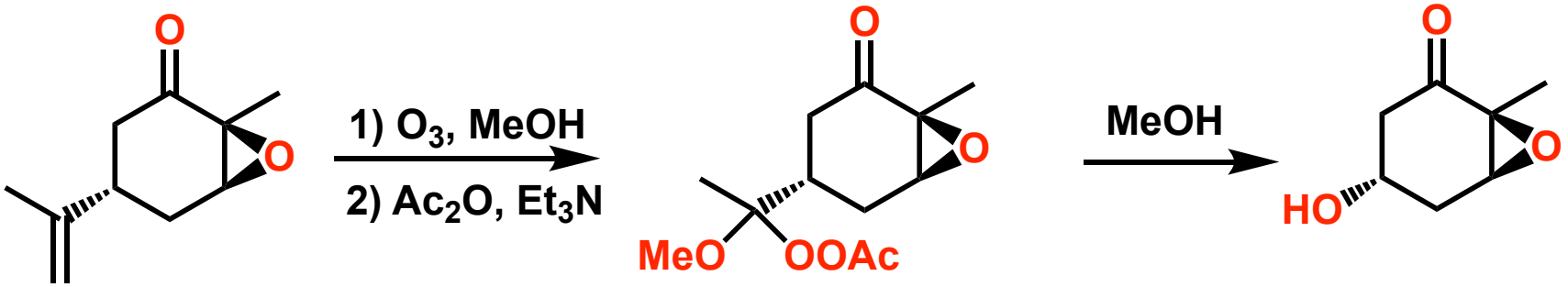


Ozonolysis

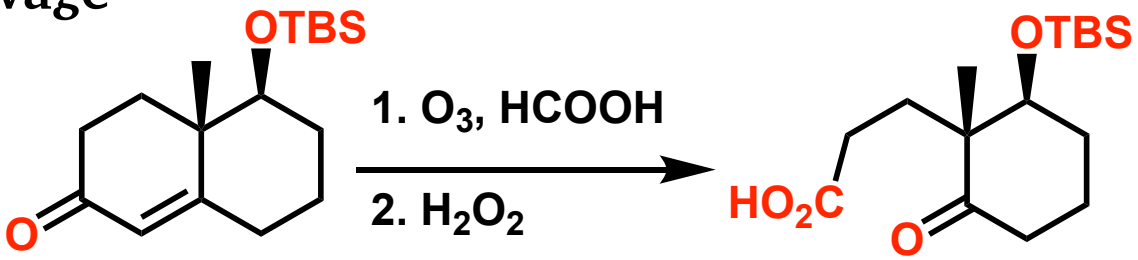
Oxidative Work-up



Criegee Rearrangement

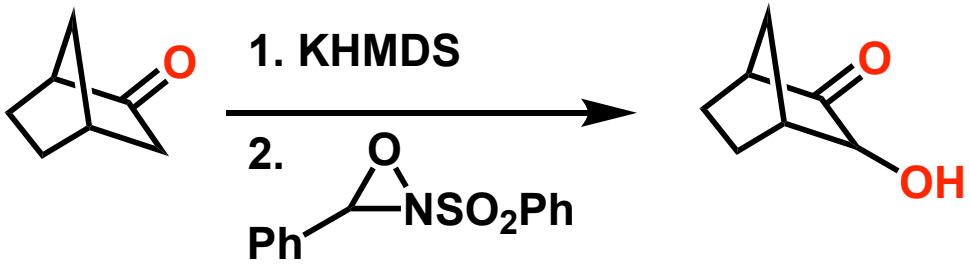


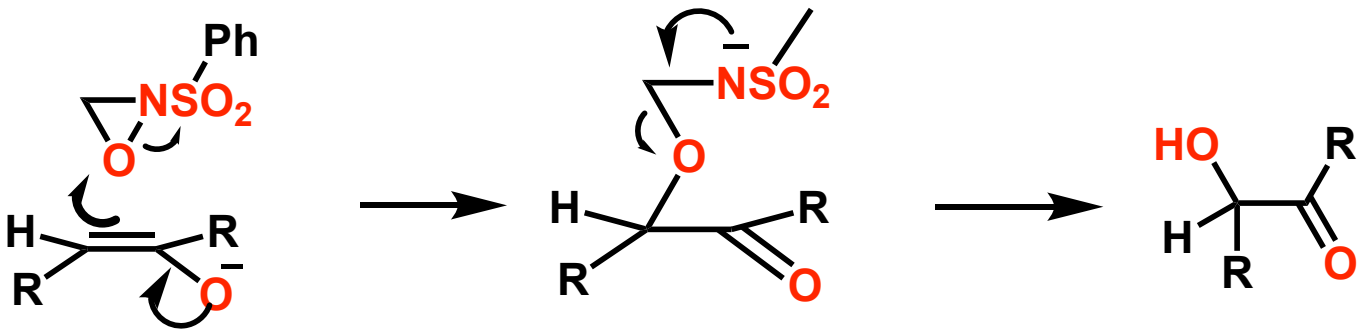
Oxidative Cleavage



Hydroxylation

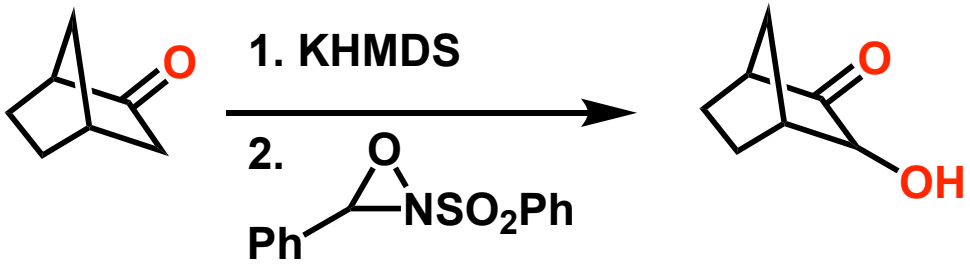
Oxidation with *N*-sulfonyloxaziridines

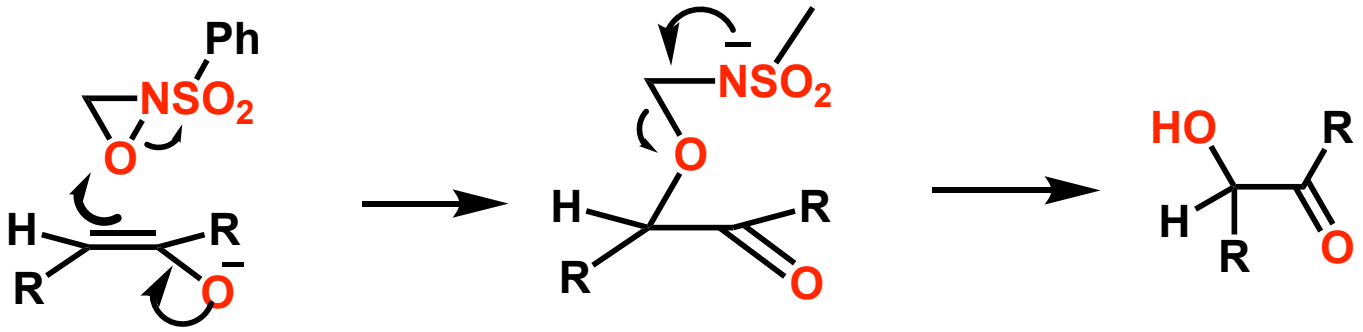




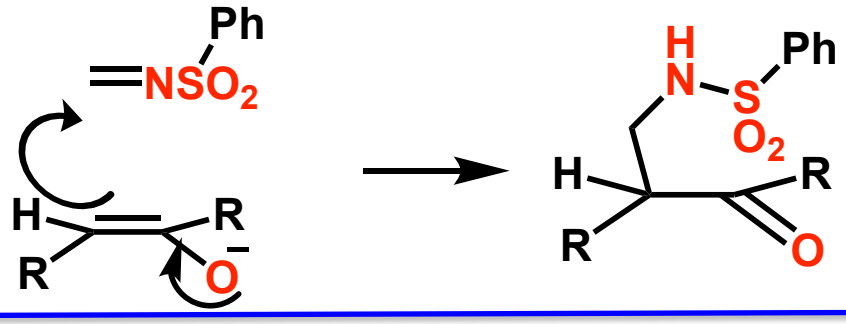
Hydroxylation

Oxidation with *N*-sulfonyloxaziridines



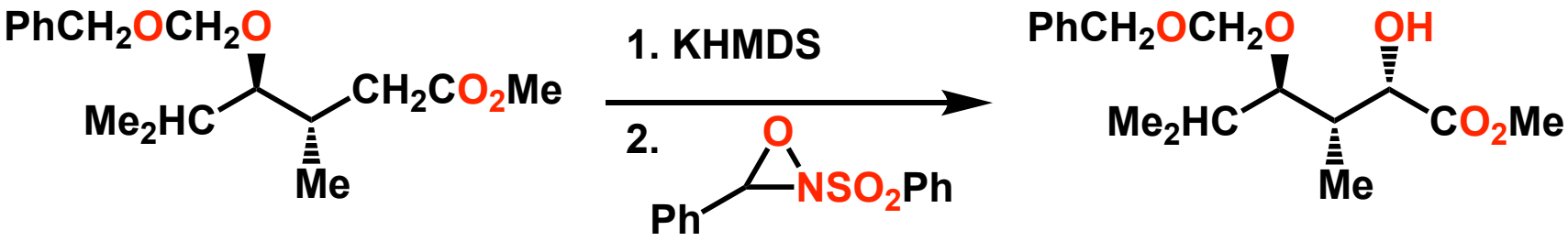


Side product

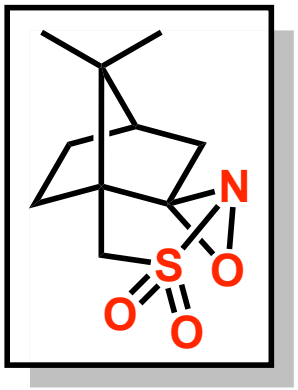


Hydroxylation

Oxidation with *N*-sulfonyloxaziridines



Asymmetric hydroxylation with Chiral *N*-sulfonyloxaziridines



Barton Reaction