Oxidations in Organic Synthesis

Oxidation = removal of electrones (hydrogen)

- transformation of FGs to a more oxidized derivatives

FG Transformations

(1) oxidation of alcohols
(2) addition of oxygen at double bonds
(3) allylic oxidation
(4) oxidative cleavage of double bonds
(5) oxidative cleavage of other FGs
(6) oxidations of aldehydes and ketones
(7) oxidation at unfunctionalized positions

Oxidative reagents

(1) transition metal oxidants
(2) O_2, O_3 and peroxides
(3) other reagents

Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

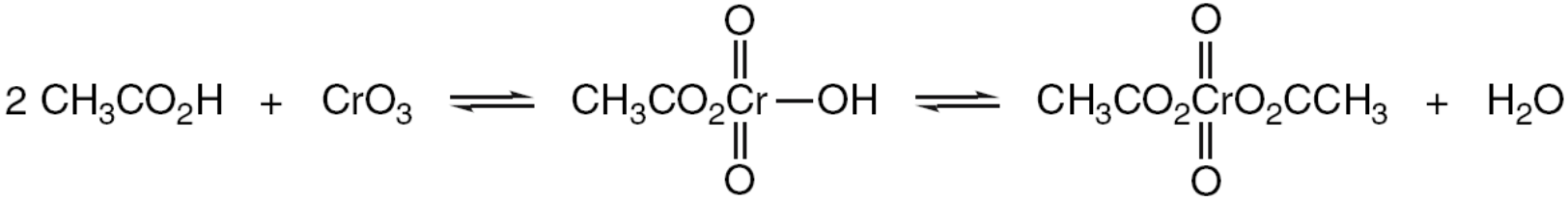
- preparation of aldehydes, ketones, carboxylic acids

A. Transition Metal Oxidants

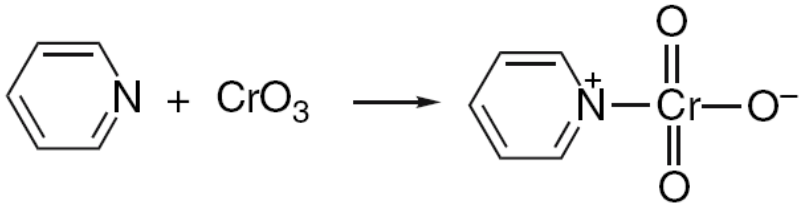
• Chromium (Cr VI)

H_2CrO_4, CrO_3, $Cr_2O_7^{2-}$, toxic

CrO_3/AcOH



CrO_3/py



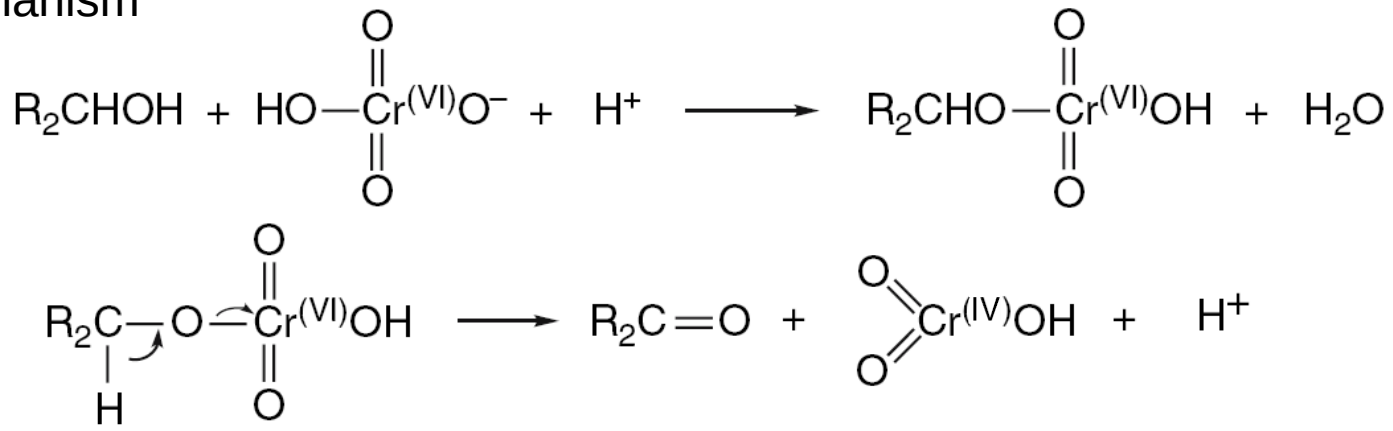
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

A. Transition Metal Oxidants

Cr(VI):

Mechanism



$$R_2CHOH + HO{-}Cr^{(VI)}O^{-} + H^{+} \longrightarrow R_2CHO{-}Cr^{(VI)}OH + H_2O$$

$$R_2C(H){-}O{-}Cr^{(VI)}OH \longrightarrow R_2C{=}O + Cr^{(IV)}OH + H^{+}$$

$$\begin{aligned}
R_2CHOH + Cr(VI) &\longrightarrow R_2C{=}O + Cr(IV) + 2H^{+}\\
R_2CHOH + Cr(IV) &\longrightarrow R_2C{=}O + Cr(II) + 2H^{+}\\
Cr(II) + Cr(VI) &\longrightarrow Cr(III) + Cr(V)\\
R_2CHOH + Cr(V) &\longrightarrow R_2C{=}O + Cr(III) + 2H^{+}\\
\hline
3\,R_2CHOH + 2\,Cr(VI) &\longrightarrow 3\,R_2C{=}O + 2\,Cr(III) + 6\,H^{+}
\end{aligned}$$

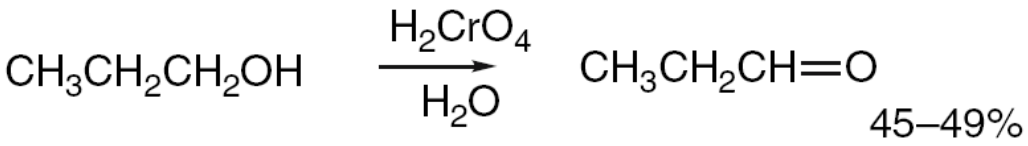
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

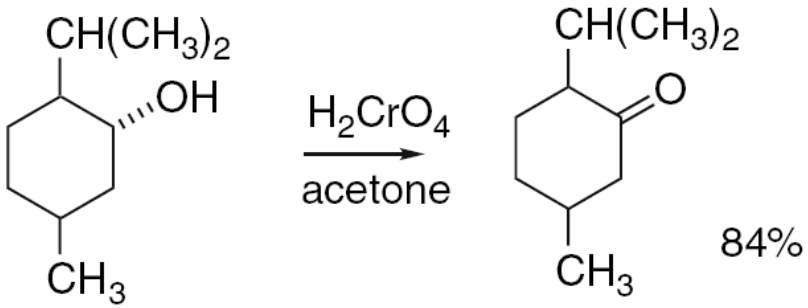
A. Transition Metal Oxidants

Cr(VI):

- primary ROH (**H_2CrO_4/H_2O**)



- secondary ROH (**H_2CrO_4/H_3O^+/acetone**) - *Jones*



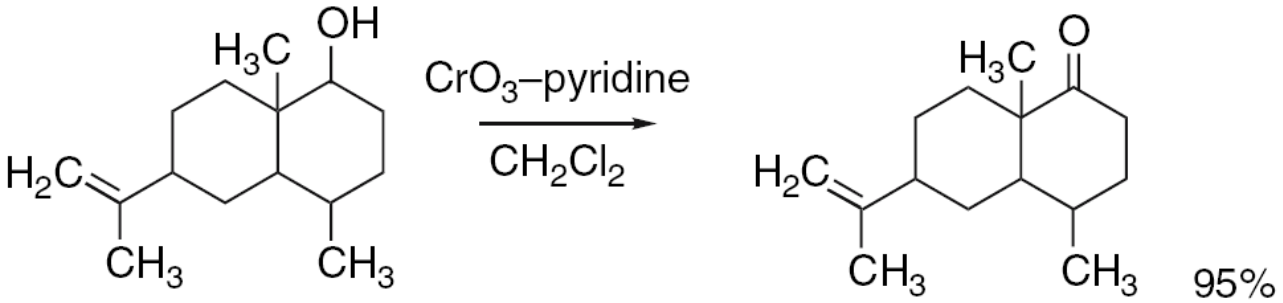
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

A. Transition Metal Oxidants

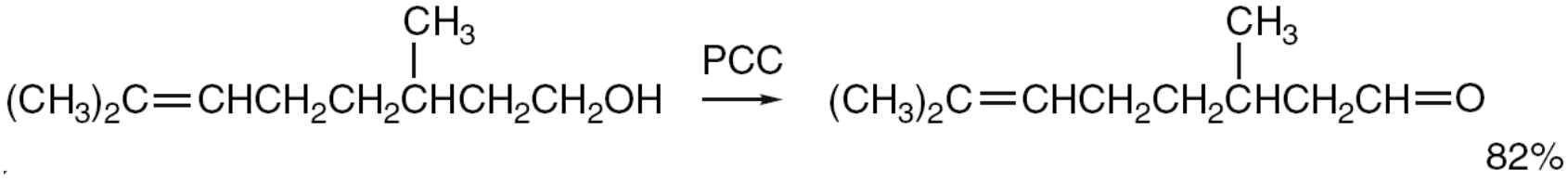
Cr(VI):

- primary and secondary ROH (**CrO_3-py/CH_2Cl_2**) - *Collins*



- **PCC** (primary ROH), **PDC** (secondary ROH)

$$C_5H_5N + HCl + CrO_3 \rightarrow [C_5H_5NH]^+[CrO_3Cl]^-$$



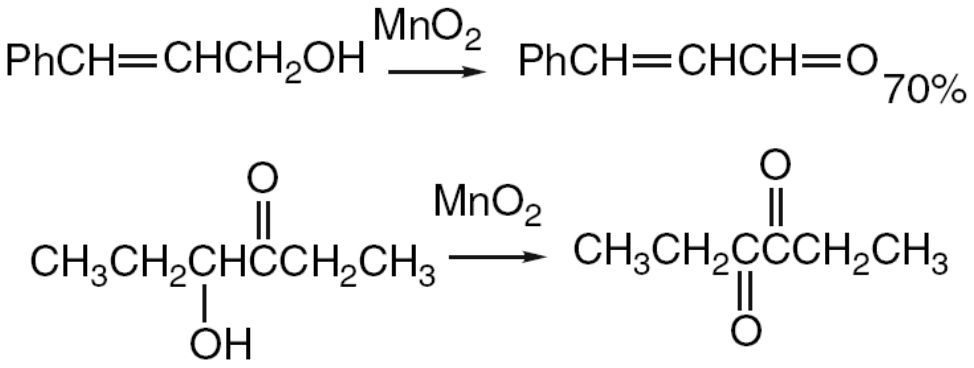
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

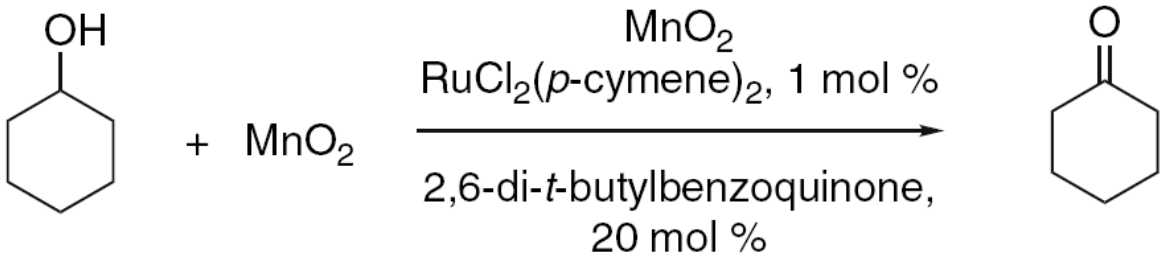
A. Transition Metal Oxidants

- **Manganese (Mn)**

- allylic, benzylic ROH (**MnO_2**)



- saturated ROH (**MnO_2+ $RuCl_2$(*p*-cymene)$_2$ + 2,6-di-*t*-butylbenzoquinone**)

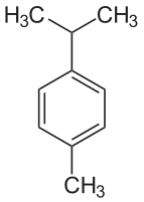


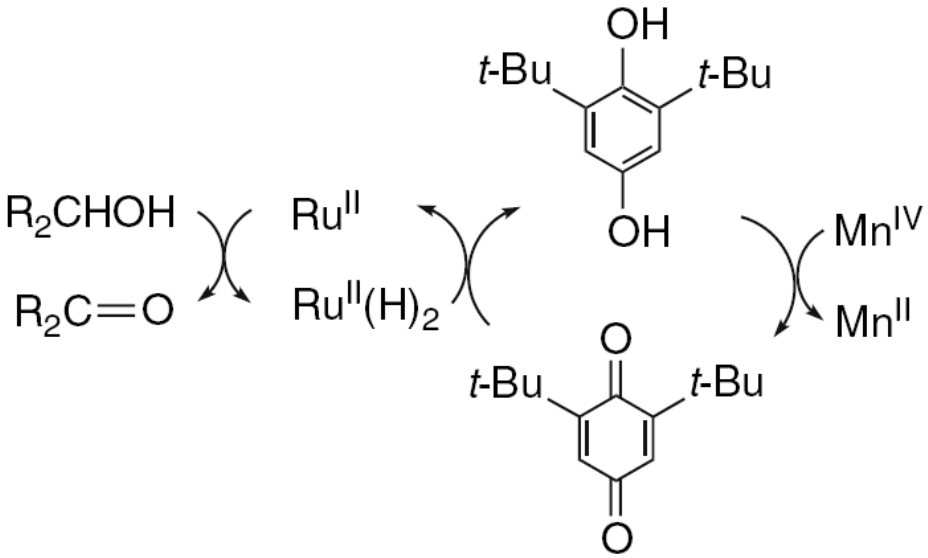
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

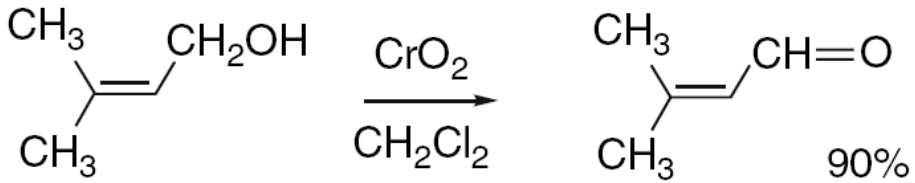
A. Transition Metal Oxidants

- catalytic system:





- allylic, benzylic ROH (CrO_2)



Oxidations in Organic Synthesis

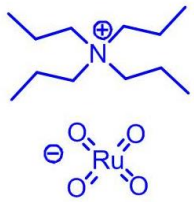
(1) Oxidation of Alcohols

A. Transition Metal Oxidants

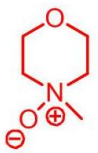
- **Ruthenium**

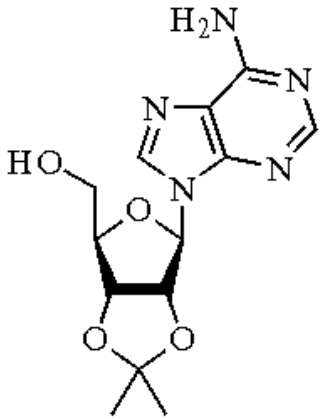
- **RuO_4** ($RuCl_3$ or RuO_2/HIO_4), milder oxidants: OCl^-
- strong oxidant, mild conditions
- modern variant (**TPAP/NMO, H_2O**): $RCH_2OH \rightarrow RCOOH$
-primary ROH (RI)

TPAP:



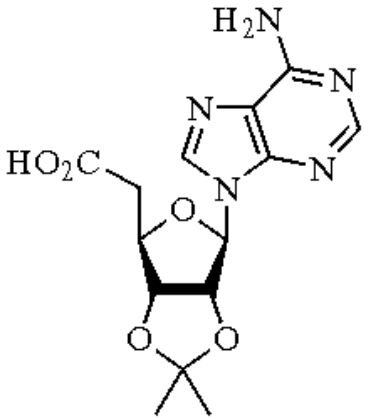
NMO:

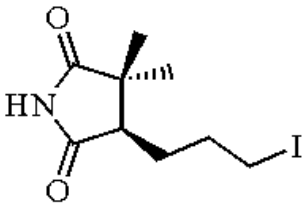




$RuCl_3$, $NaIO_4$
CCl_4, MeCN

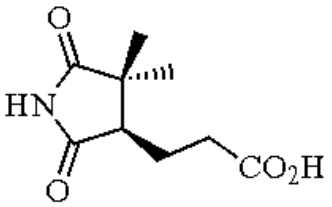
H_2O, rt
>95%

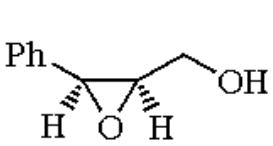




$RuCl_3$, H_5IO_6
CCl_4, MeCN

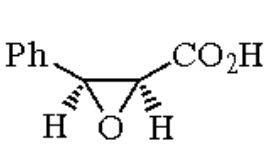
H_2O, rt
>60%

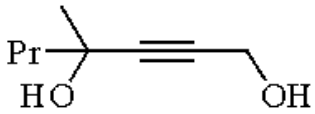




$RuCl_3$, $NaIO_4$
CCl_4, MeCN

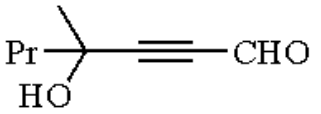
H_2O, rt
75%





$RuCl_3$, $Ca(OCl)_2$

MeCN, H_2O, rt
80%



Oxidations in Organic Synthesis

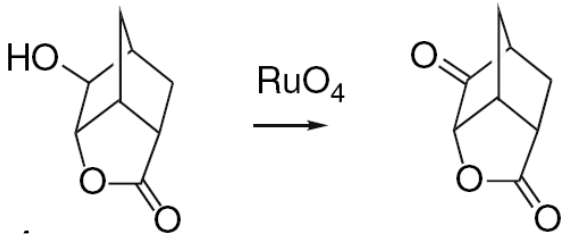
(1) Oxidation of Alcohols

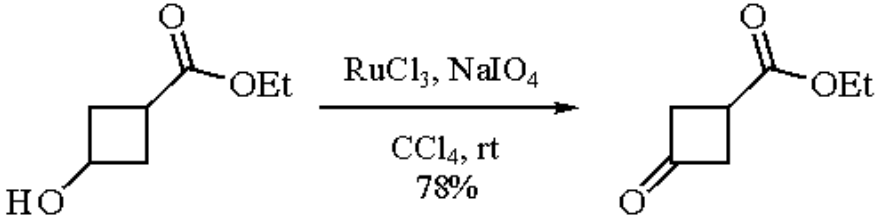
A. Transition Metal Oxidants

- **Ruthenium**

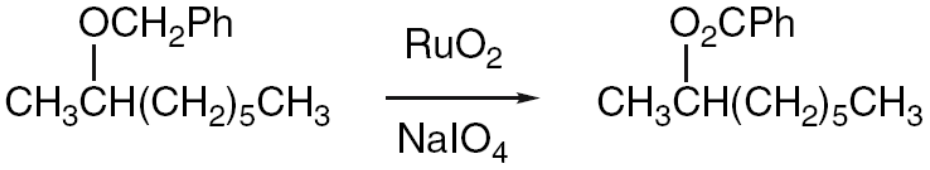
- **RuO_4** ($RuCl_3$ or RuO_2/HIO_4)

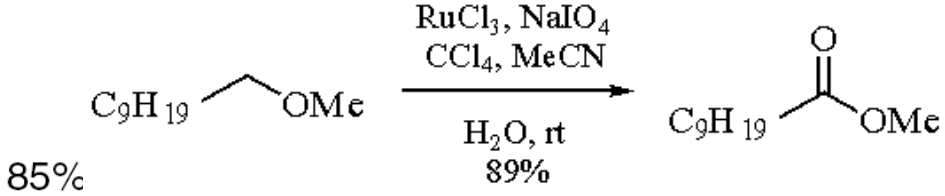
-secondary ROH

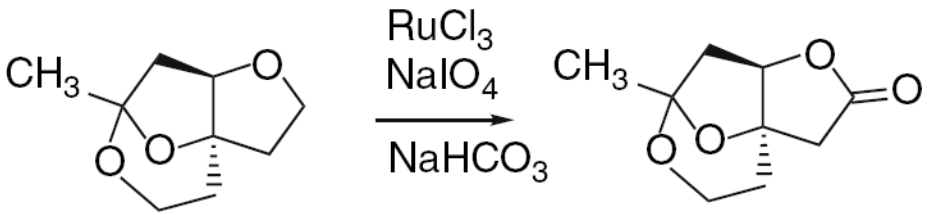




- cyclic ethers (MeOR, EtOR, BnOR)







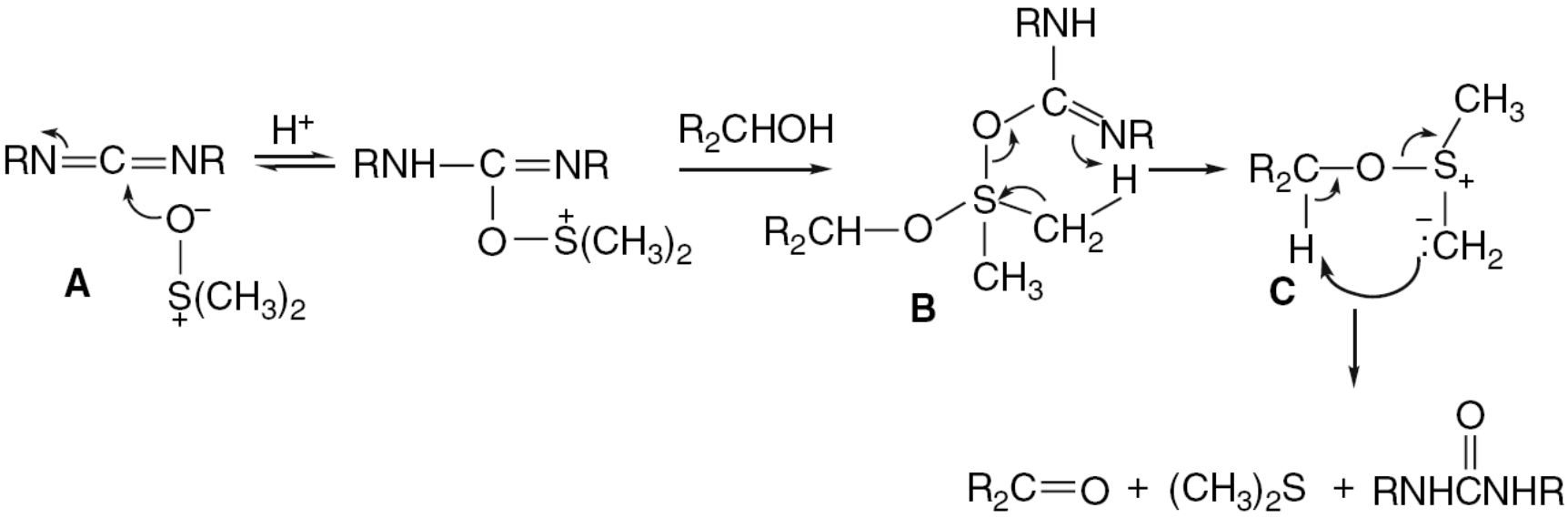
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

B. Other Oxidants (organic)

- **DMSO** (+ electrophilic reagent-TFAA, SO_3, $(COCl)_2$, DCC)

Moffatt oxidation - *mechanism:*

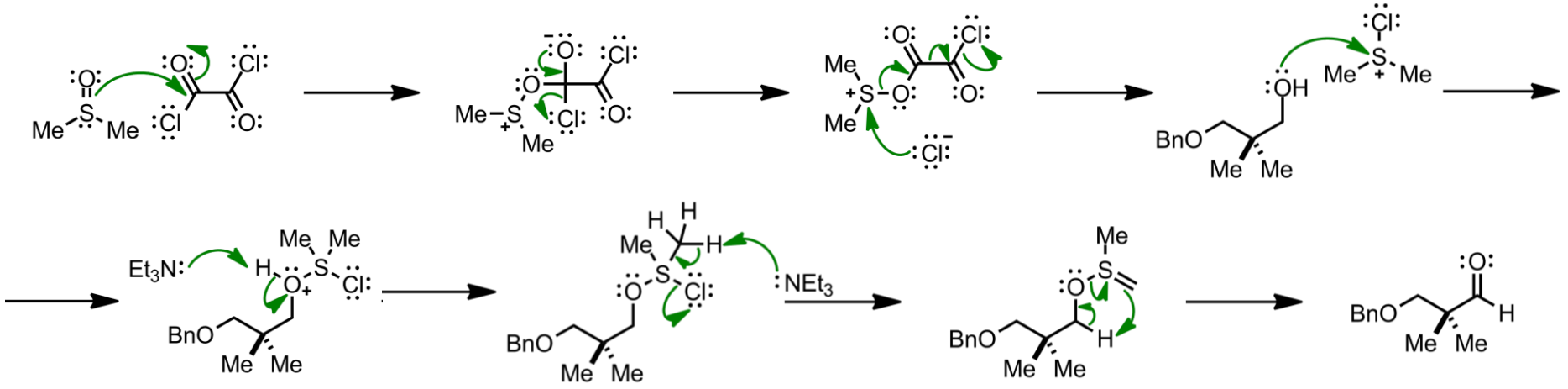


Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

B. Other Oxidants (organic)

- **Swern oxidation** (DMSO/$(COCl)_2$ then Et_3N)



Example

$$(CH_3)_2CHCH{=}CHCH{=}CHCH_2OH \xrightarrow[ClCOCOCl]{DMSO} (CH_3)_2CHCH{=}CHCH{=}CHCH{=}O \quad 93\%$$

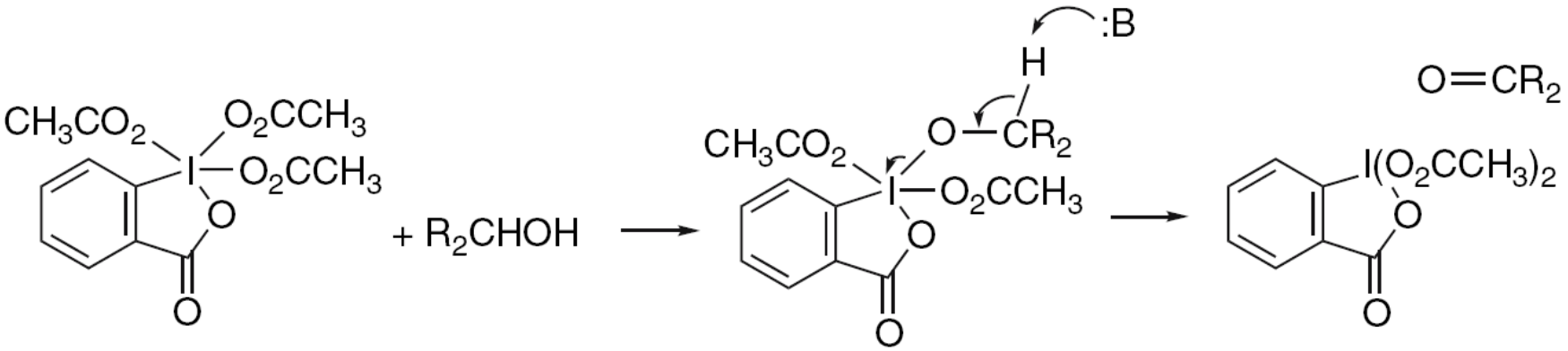
Oxidations in Organic Synthesis

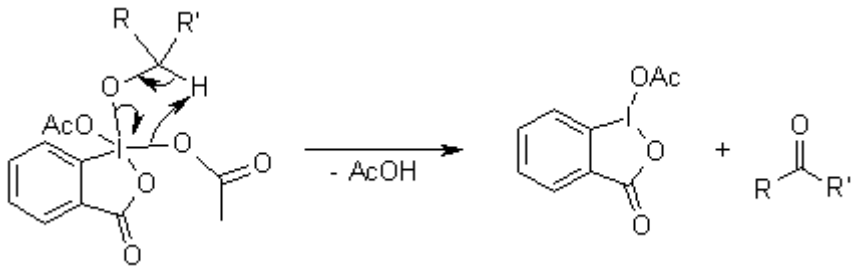
(1) Oxidation of Alcohols

B. Other Oxidants (organic)

- **Dess-Martin Oxidation** (hypervalent iodine (V) compounds)

- primary, secondary ROH
- inert solvents ($CHCl_3$, CH_3CN)





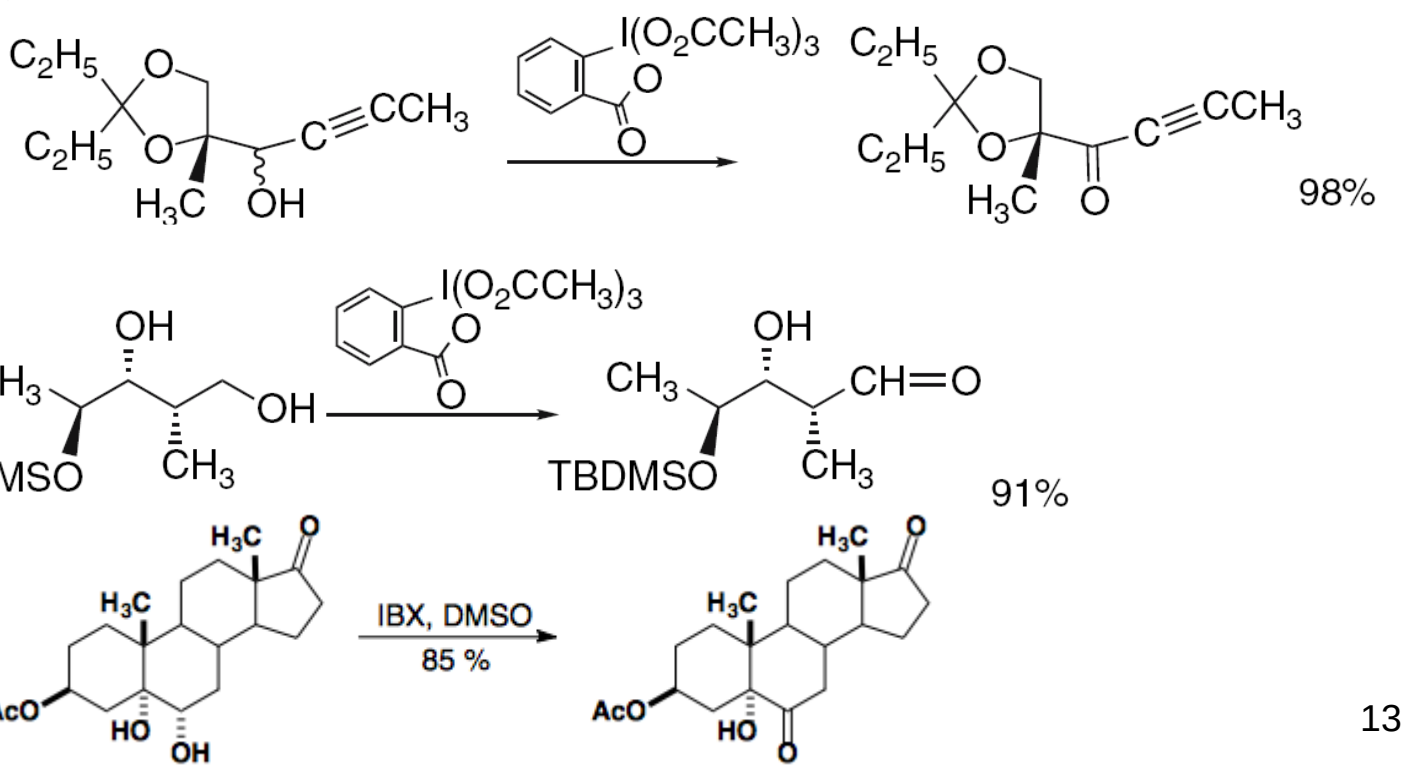
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

B. Other Oxidants (organic)

- **Dess-Martin Oxidation** (hypervalent iodine (V) compounds)
- IBX oxidation

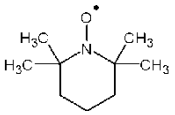
Examples



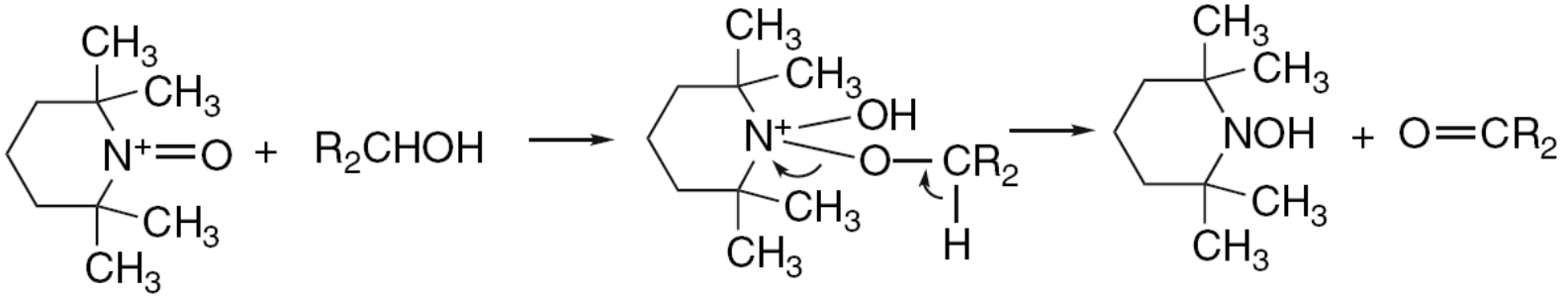
Oxidations in Organic Synthesis

(1) Oxidation of Alcohols

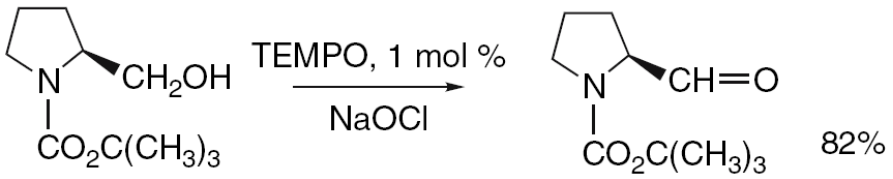
B. Other Oxidants (organic)

- **TEMPO** 

- TEMPO (cat.)/NaOCl



Examples



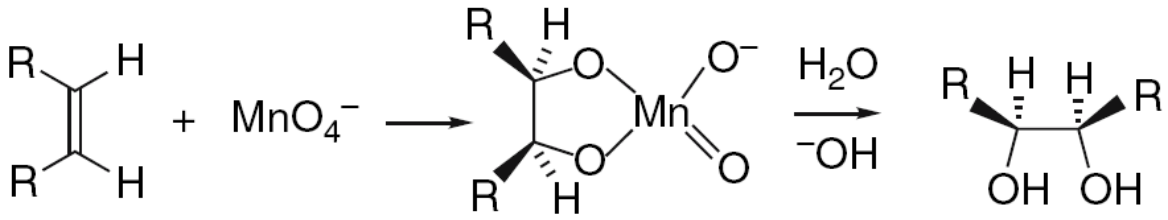
(2) Addition of Oxygen at C=C

A. Transition Metal Oxidants

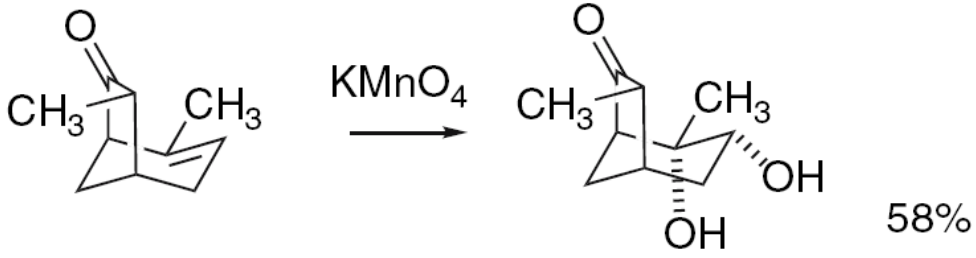
Dihydroxylation of alkenes

- **$KMnO_4/OH^-$**

- *syn* addition



Example



58%

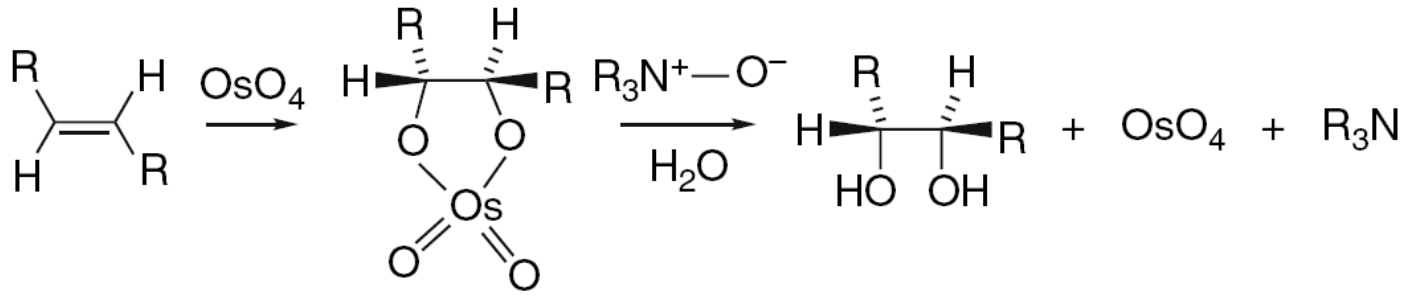
Oxidations in Organic Synthesis

(2) Addition of Oxygen at C=C

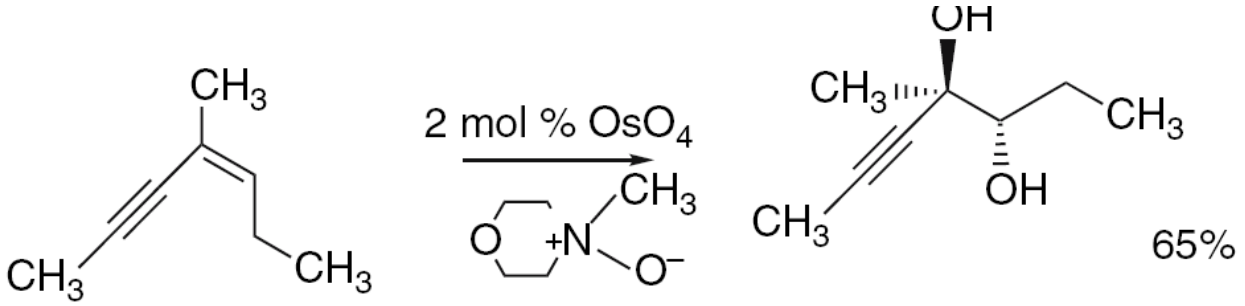
A. Transition Metal Oxidants

Dihydroxylation of alkenes

• **OsO_4/MNO (Upjohn dihydroxylation)**or ***t*-BuOOH (Milas hydroxylation)**
- *syn* addition



Example



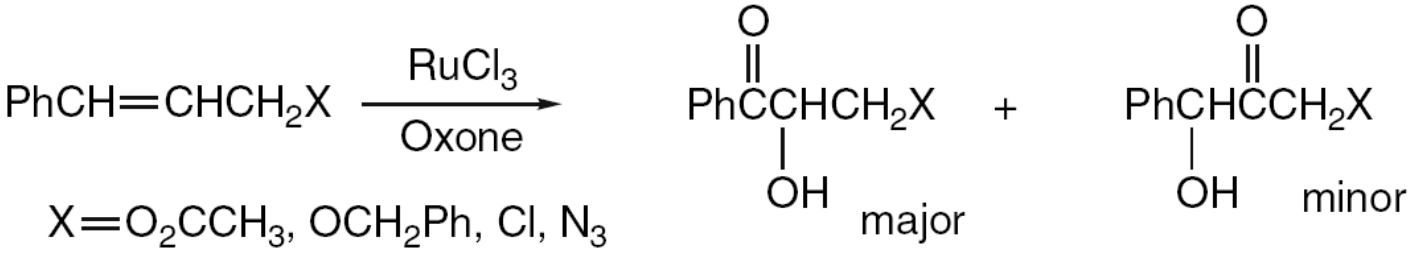
Oxidations in Organic Synthesis

(2) Addition of Oxygen at C=C

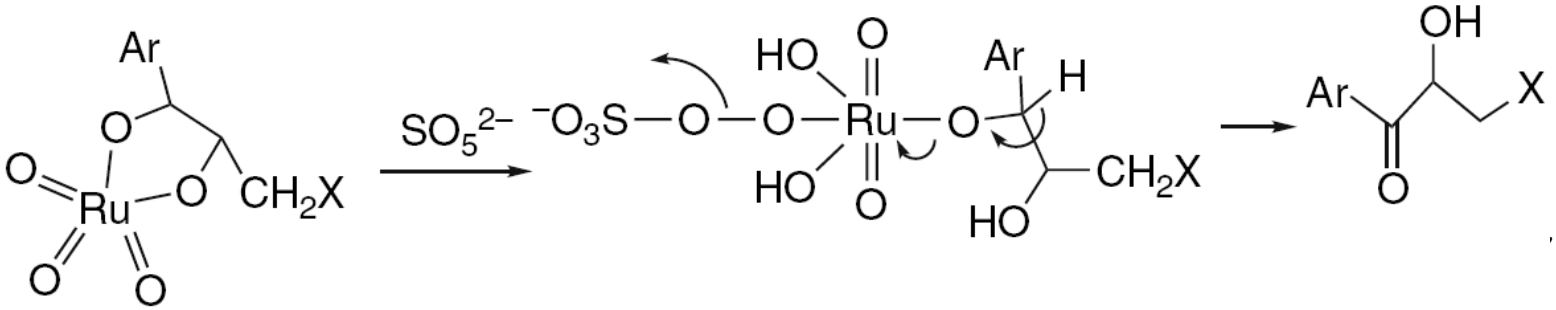
A. Transition Metal Oxidants

Formation of Ketols from Alkenes

- **$RuCl_3$/Oxone** ($KHSO_5$)
- $CH_3CN/EtOAc/H_2O$
- alkenes → ketols



Mechanism

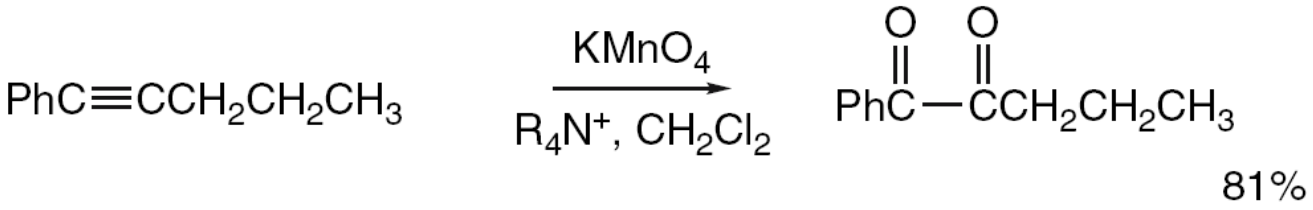


(2) Addition of Oxygen at C=C

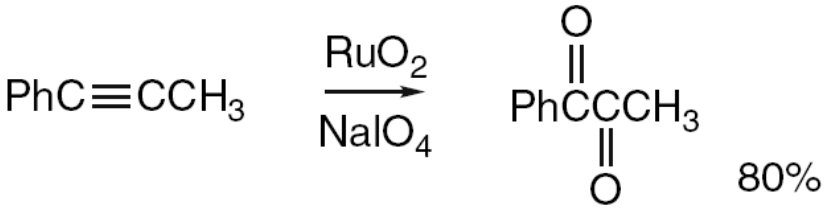
A. Transition Metal Oxidants

Formation of Diones from Alkynes

- **$KMnO_4$**



- **$RuO_2/NaIO_4$**



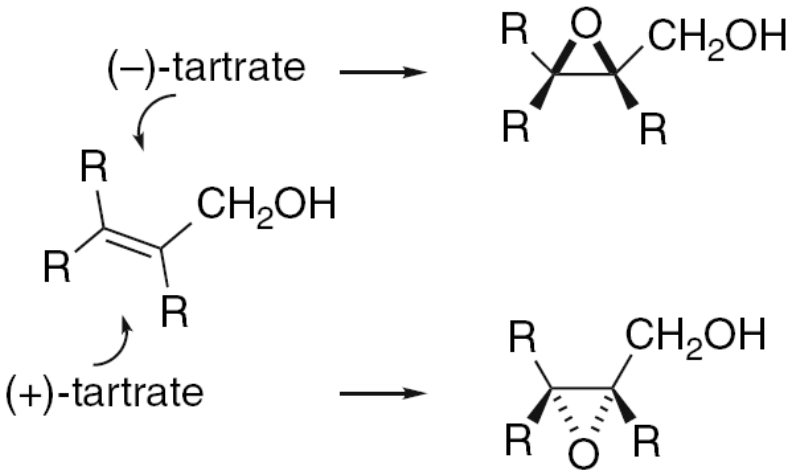
Oxidations in Organic Synthesis

(2) Addition of Oxygen at C=C

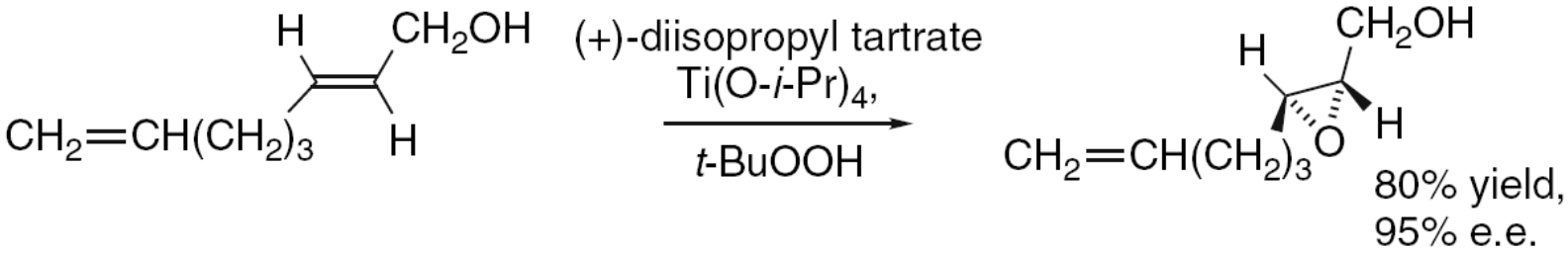
A. Transition Metal Oxidants

Epoxidation of Alkenes

- ***t*-BuOOH/VO(acac)**
- ***t*-BuOOH/Ti(O-*i*-Pr)$_4$**



Example



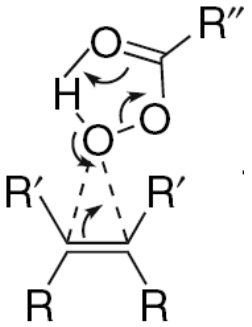
(2) Addition of Oxygen at C=C

B. Peroxidic Reagents

Epoxidation of Alkenes

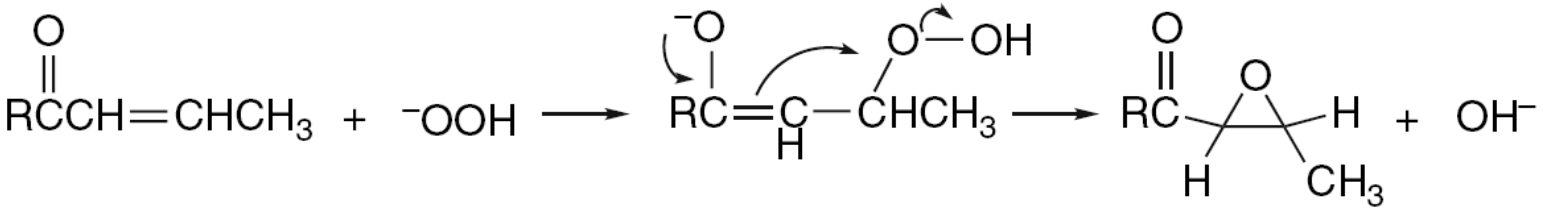
• **MCPBA,** Peroxy Acids, Oxone

- solvents: CH_2Cl_2, MeOH



- ERG substituents of C=C - ↑ **reactivity**
- EWG substituent of peroxy acids - ↑ **reactivity** (CF_3CO_3H)

- electron-poor alkenes (*t*-BuOOH or H_2O_2/OH^-, CF_3CO_3H)



(2) Addition of Oxygen at C=C

B. Peroxidic Reagents

Epoxidation of Alkenes

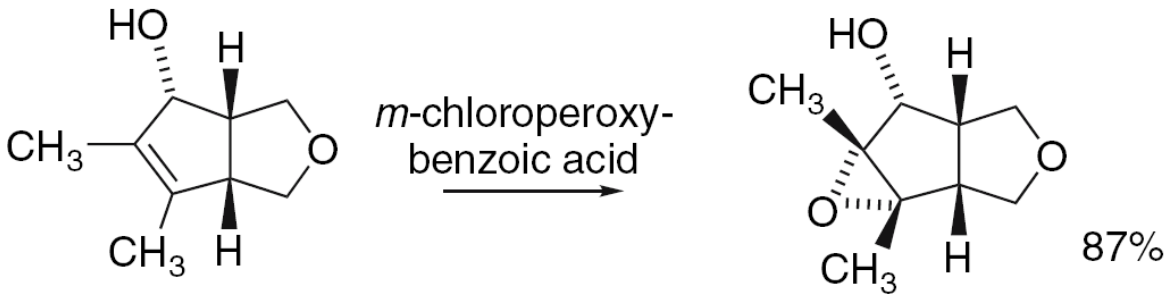
- **MCPBA**

- stereoselectivity:

SAC

α-hydroxyl group – *syn* addition („hydroxy-directing effect“)

Example



Oxidations in Organic Synthesis

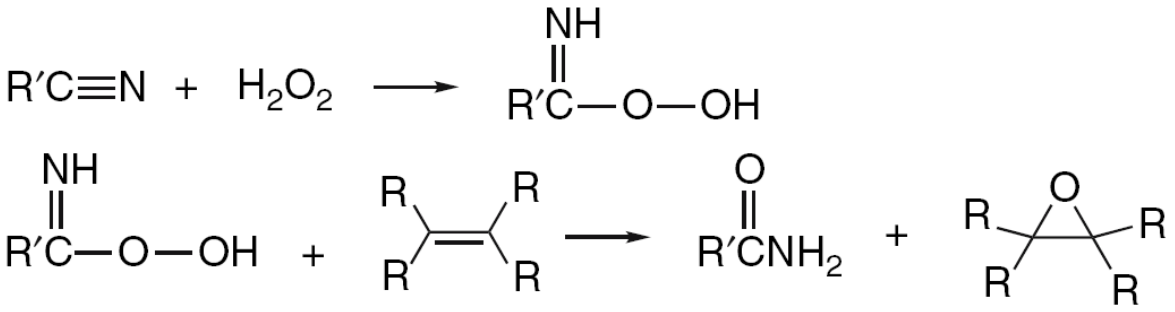
(2) Addition of Oxygen at C=C

B. Peroxidic Reagents

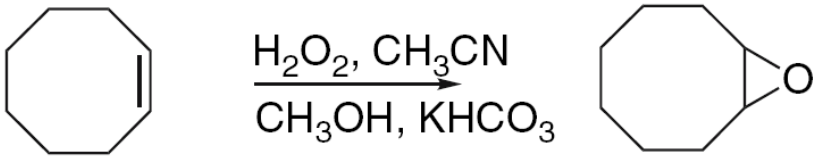
Epoxidation of Alkenes

- **Peroxyimidic Acids**

- to avoid acidic conditions
- „hydroxy-directing effect“



Example



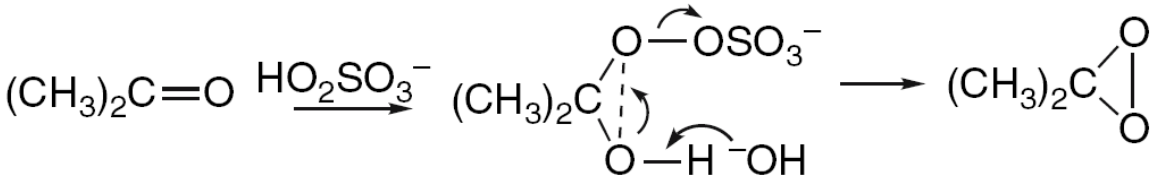
60%

(2) Addition of Oxygen at C=C

B. Peroxidic Reagents

Epoxidation of Alkenes

• **DMDO** (dimethyldioxirane)
- *in situ* (acetone + peroxymonosulfate)



- mechanism similar to MCPBA
- weaker „hydroxy-directing effect“
- stronger SAC
- EWG substituents - ↑ **reactivity**

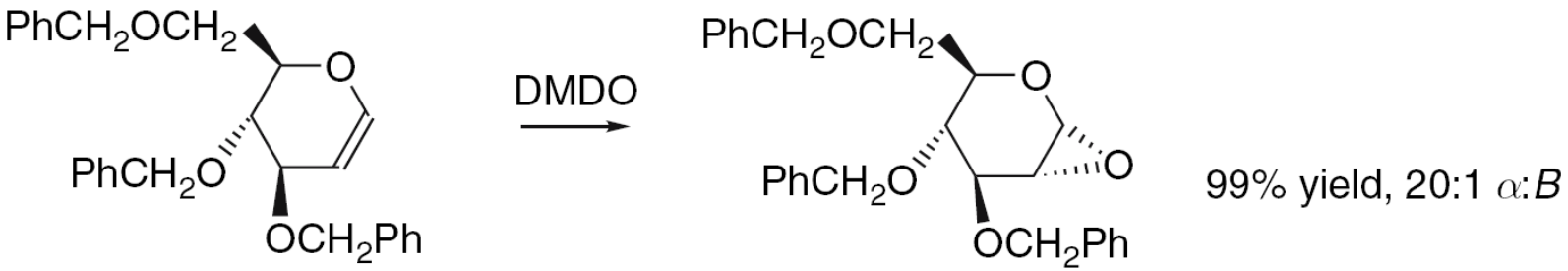
(2) Addition of Oxygen at C=C

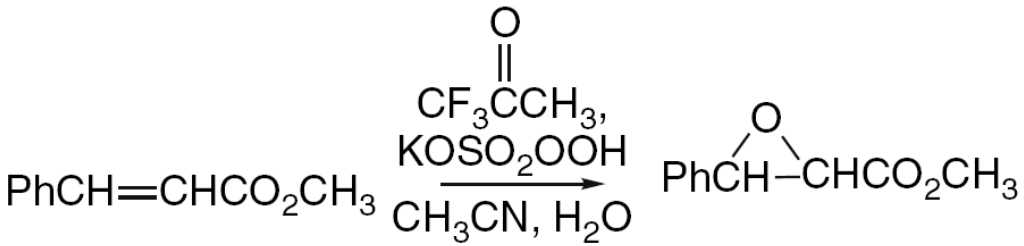
B. Peroxidic Reagents

Epoxidation of Alkenes

- **DMDO**

Examples





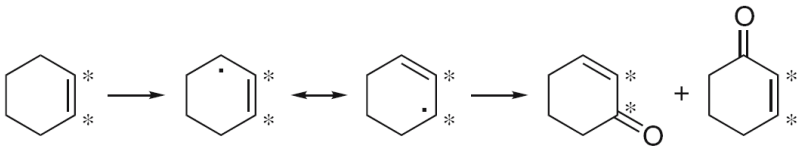
Oxidations in Organic Synthesis

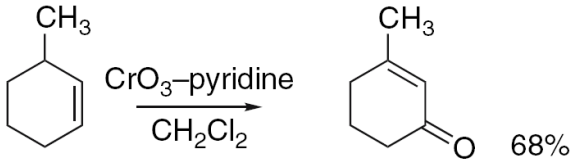
(3) Allylic Oxidations

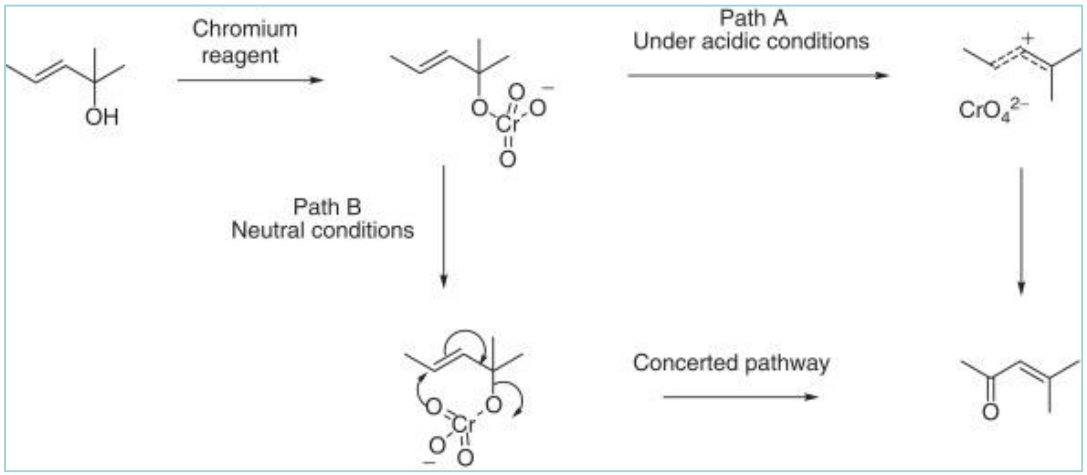
A. Transition Metal Oxidants

CrO_3/py

- various bases
- allylic intermediates

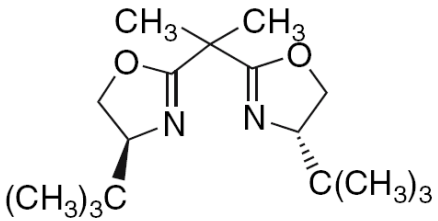






Cu + ligands

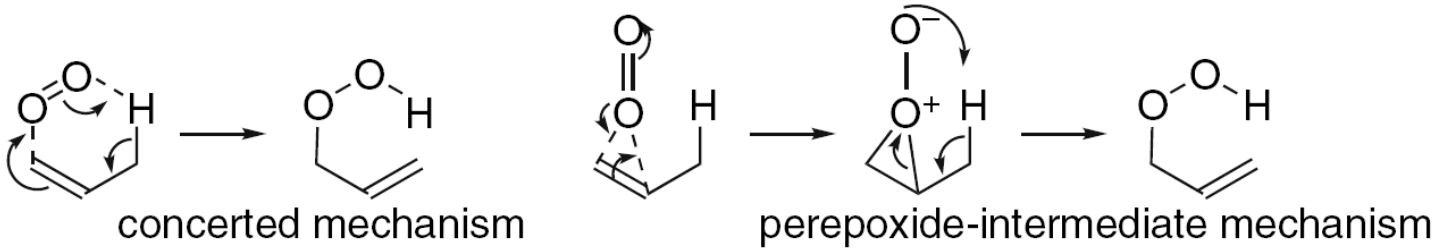
- asymmetric synthesis



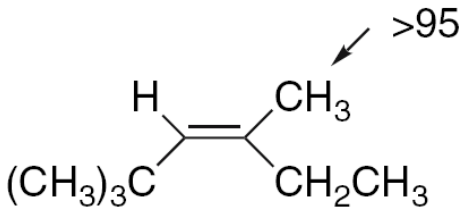
(3) Allylic Oxidations

B. Singlet Oxygen

- removal of allylic H + double-bond shift (*concerted mechanism*)
- reduction of hydroperoxides



- stereoselectivity:
  SAC

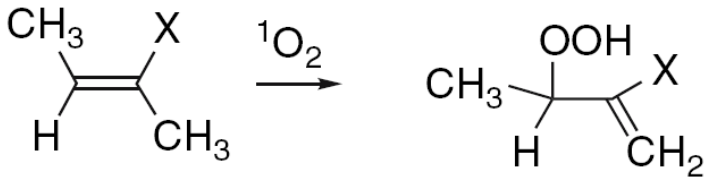


(*„removal of a hydrogen from the more congested side of the double bond“*)

(3) Allylic Oxidations

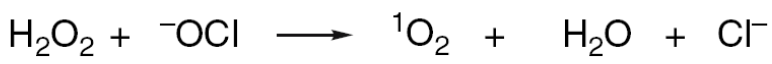
B. Singlet Oxygen

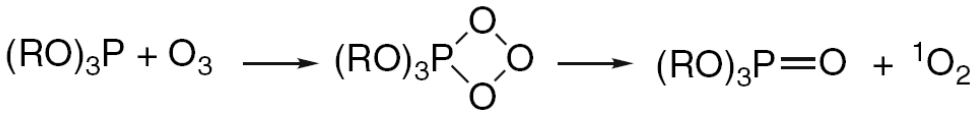
- stereoselectivity:
  strong „hydroxy-directing effect“
  (for all polar groups)

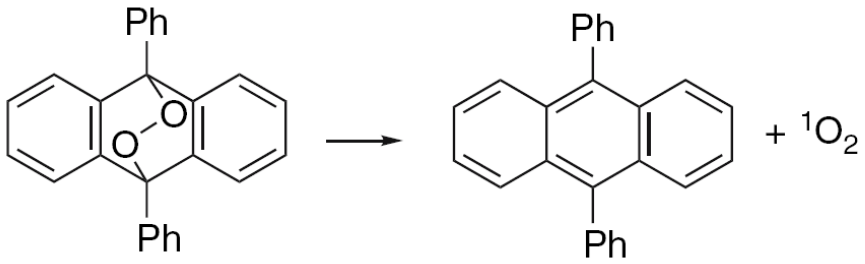


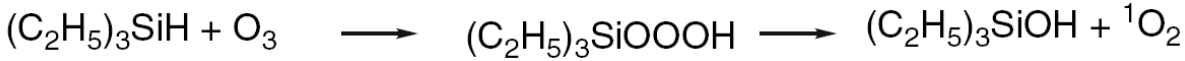
X = CO_2CH_3, CH=O, C≡N, SOPh, $Si(CH_3)_3$, $Sn(CH_3)_3$

- chemical generation of singlet oxygen:





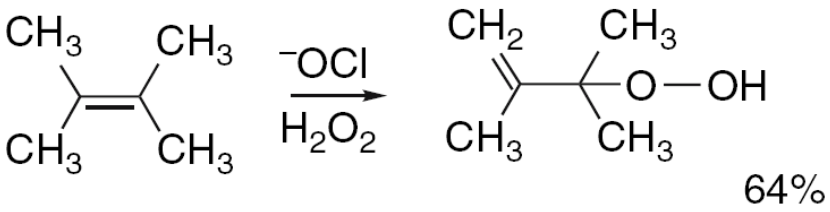


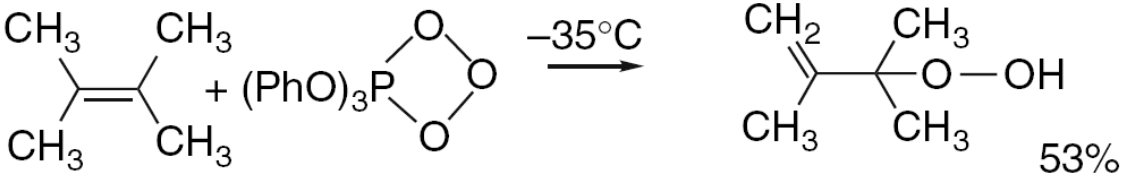


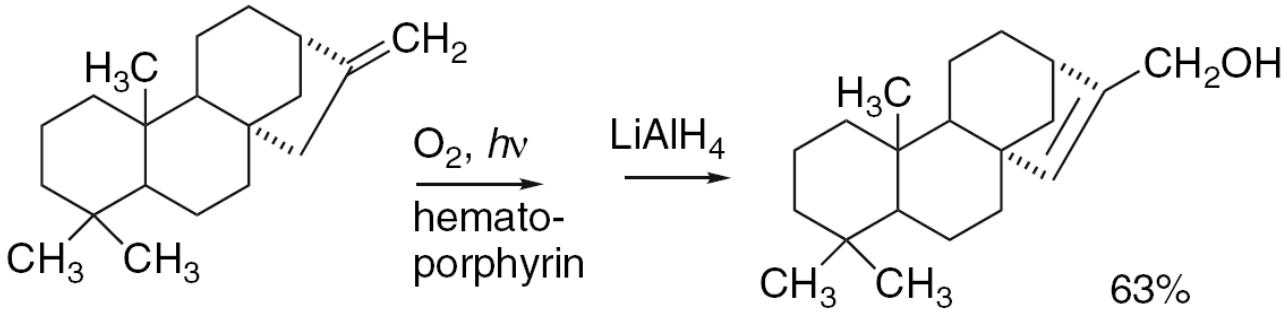
(3) Allylic Oxidations

B. Singlet Oxygen

Examples







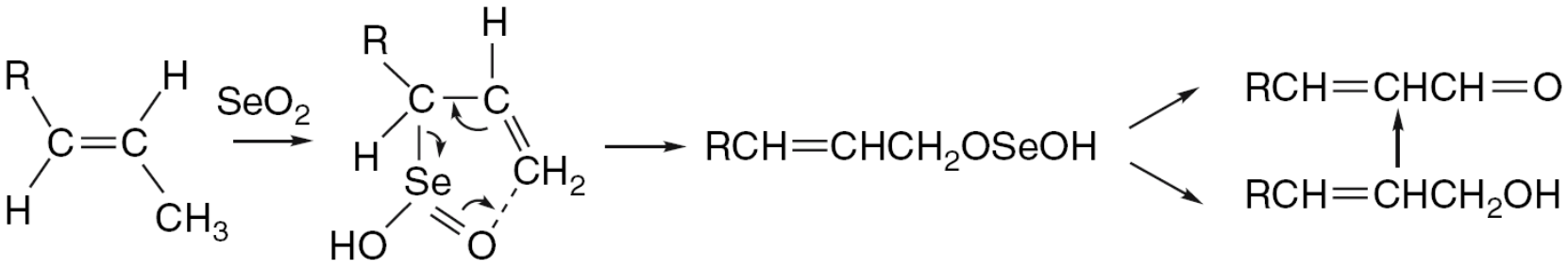
Oxidations in Organic Synthesis

(3) Allylic Oxidations

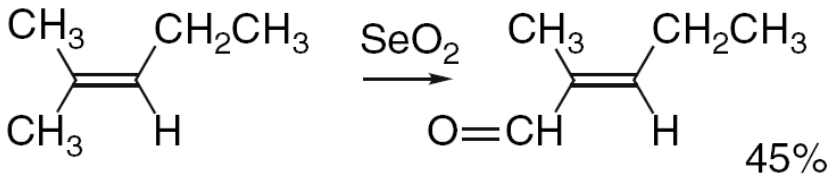
C. Other Oxidants

SeO_2

- „ene“ reaction with SeO_2
- [2,3]-sigmatropic rearrangement
- solvolysis



- practical for:
  gem-dimethyl alkenes (*E*-allylic aldehydes/alcohols are formed)



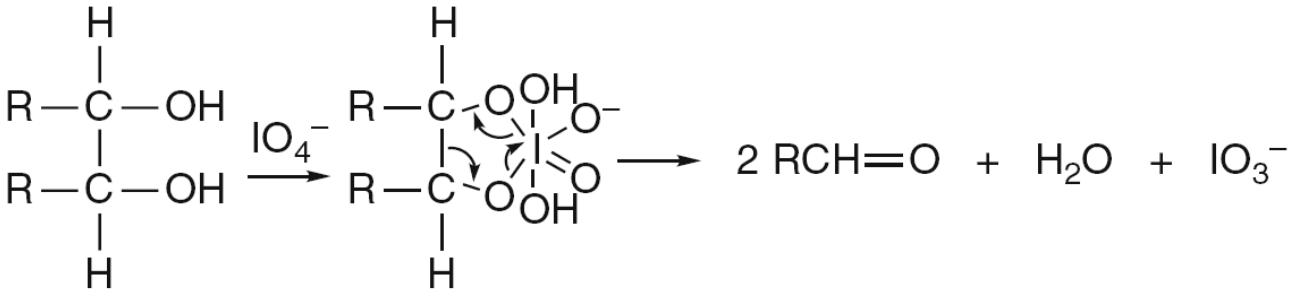
Oxidations in Organic Synthesis

(4) Oxidative Cleavage of C=C

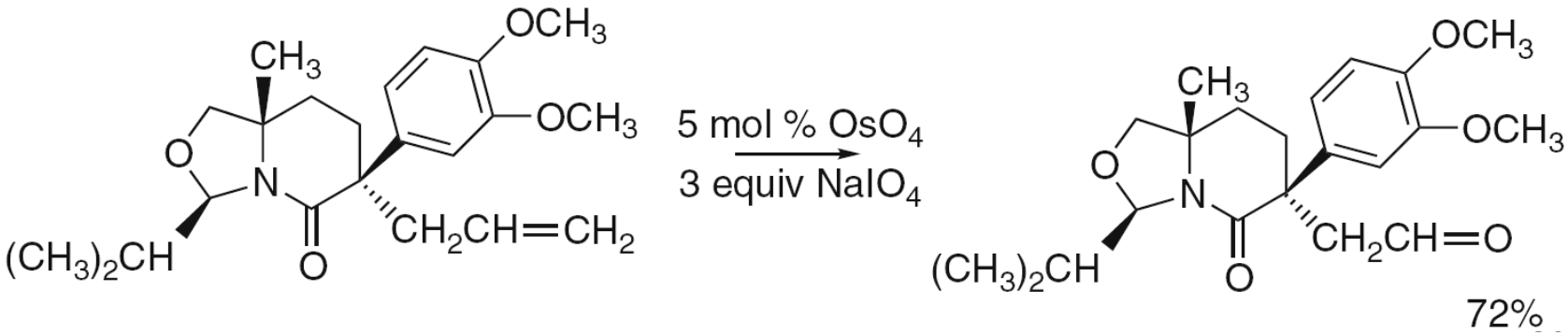
A. Transition Metal Oxidants – Cleavage of C=C

$OsO_4/NaIO_4$ (**Lemieux-Johnson oxidation**)

- Lemieux reagent (*$KMnO_4/NaIO_4$*)
- crucial



Example

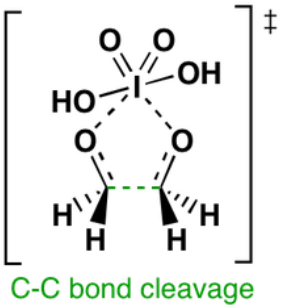


Oxidations in Organic Synthesis

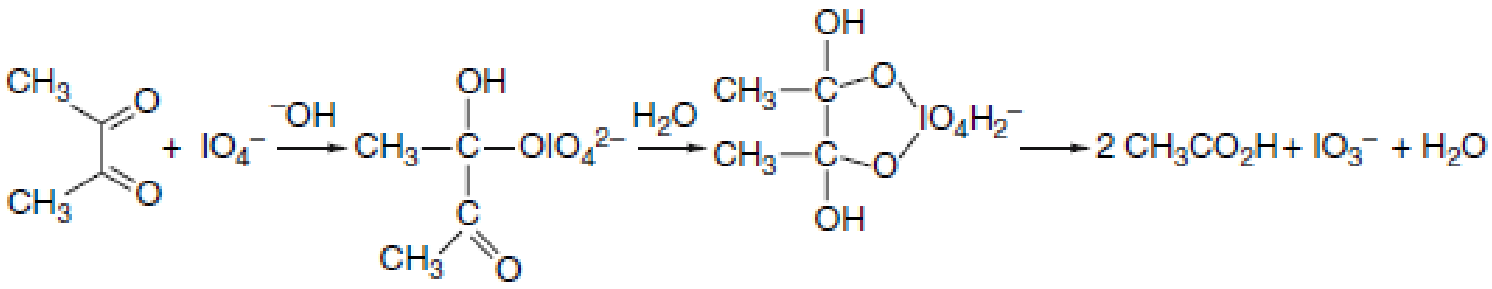
(4) Oxidative Cleavage of C=C

A. Transition Metal Oxidants – Cleavage of Glycols

HIO_4 or IO_4^- (**Malaprade oxidation)**



- formation of aldehydes and ketones
- mild conditions, high yields (better to ozonolysis)
- α-hydroxy/keto carboxylic acids not cleaved
- cyclic intermediate crucial for cleavage, otherwise oxidation



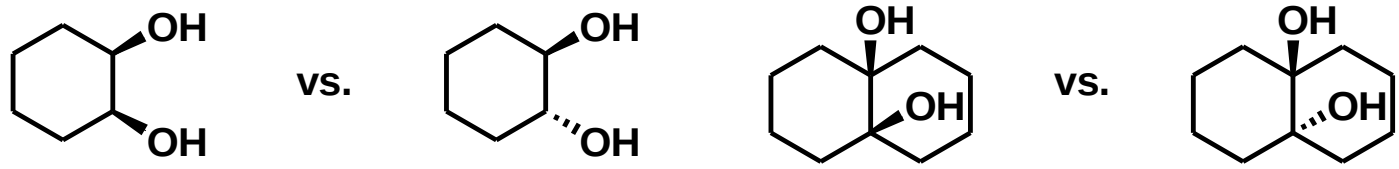
Oxidations in Organic Synthesis

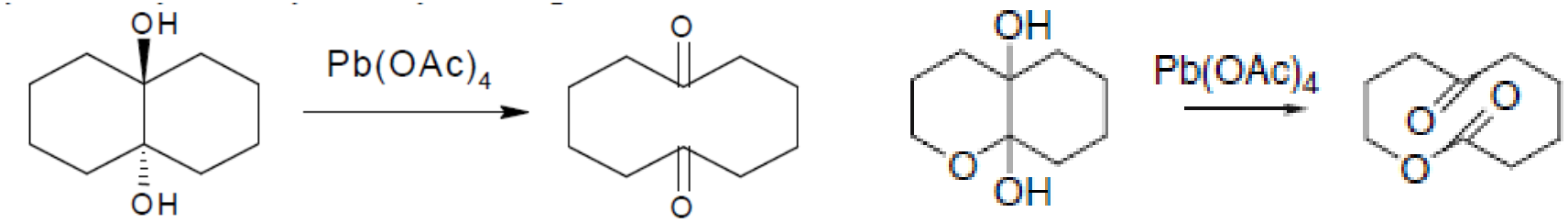
(4) Oxidative Cleavage of C=C

A. Transition Metal Oxidants – Cleavage of Glycols

$Pb(OAc)_4$ in AcOH (**Criegee oxidation**)

- not only via cyclic intermediates, (radical mechanism)
- cleave α-amino alcohols, α-hydroxy carbonyls, and α-keto acids
- stereochemistry important
- *trans*-diols slower then *cis*-diols (1:100)



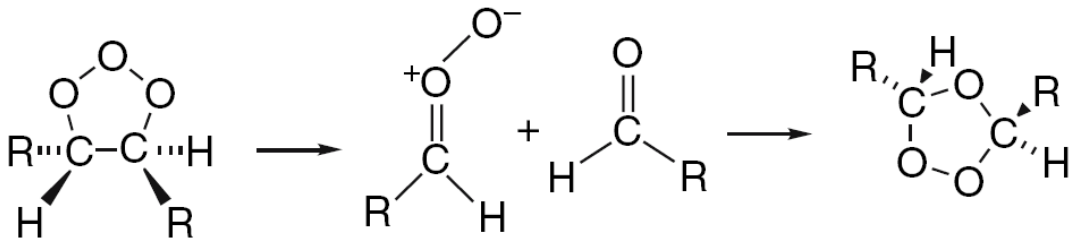


Oxidations in Organic Synthesis

(4) Oxidative Cleavage of C=C

B. Ozonolysis

Mechanism:
- 1,3-dipolar cycloaddition
- fragmentation
- recombination



Work up:
- hydrolysis
- reduction (Me_2S, Zn, Ph_3P, Na_2SO_3, NaI)
- reduction ($NaBH_4$)
- oxidation (H_2O_2)

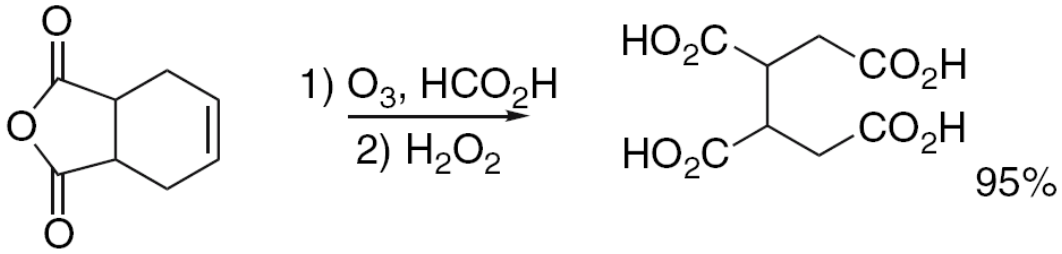
Trapping of intermediates:
- RONa
- reactive carbonyl compounds

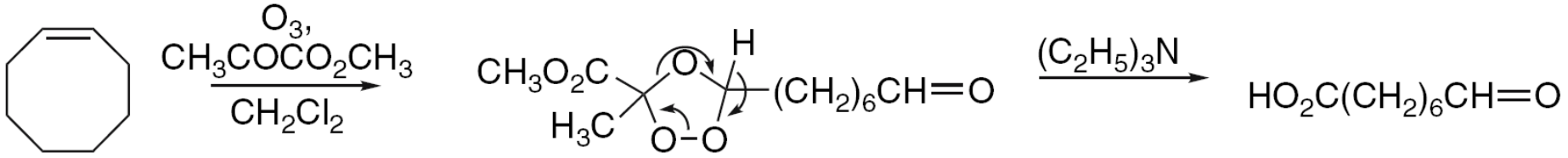
Oxidations in Organic Synthesis

(4) Oxidative Cleavage of C=C

B. Ozonolysis

Examples





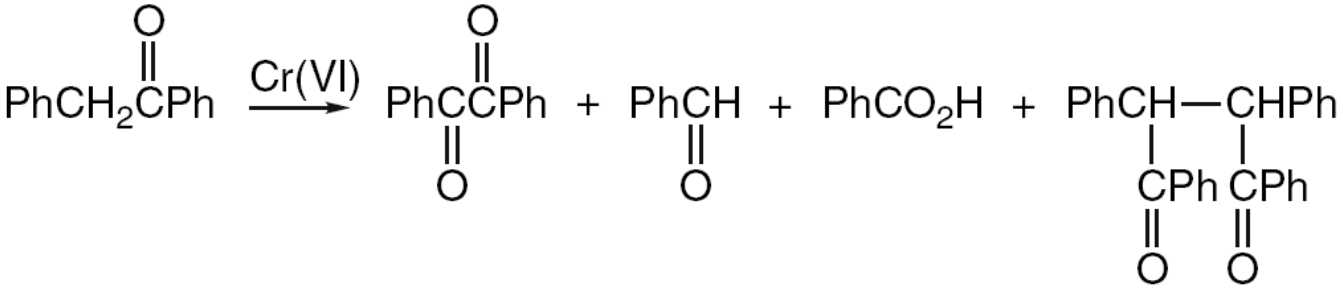
Oxidations in Organic Synthesis

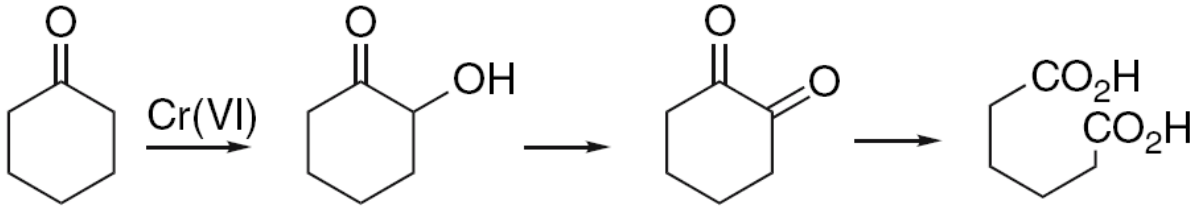
(5) Oxidations of Aldehydes and Ketones

A. Transition Metal Oxidants

Ketones

- vigorous conditions
- oxidative-cleavage products
- oxidative-dimeric product
- etc.





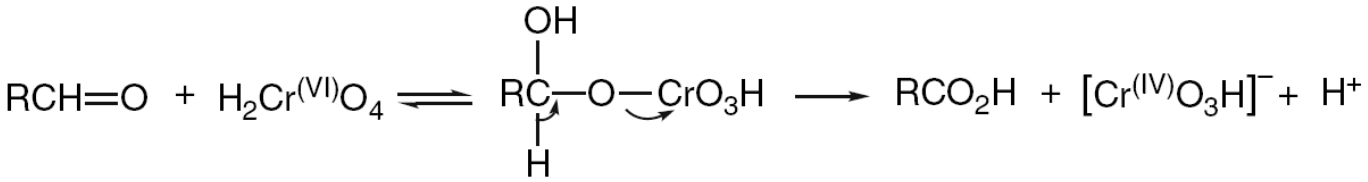
(5) Oxidations of Aldehydes and Ketones

A. Transition Metal Oxidants

Aldehydes

$KMnO_4$, H_2CrO_4

- rate-determining step



- additives: *t*-BuOH, NaH_2PO_4

$NaClO_2$

- supported on resins, silica

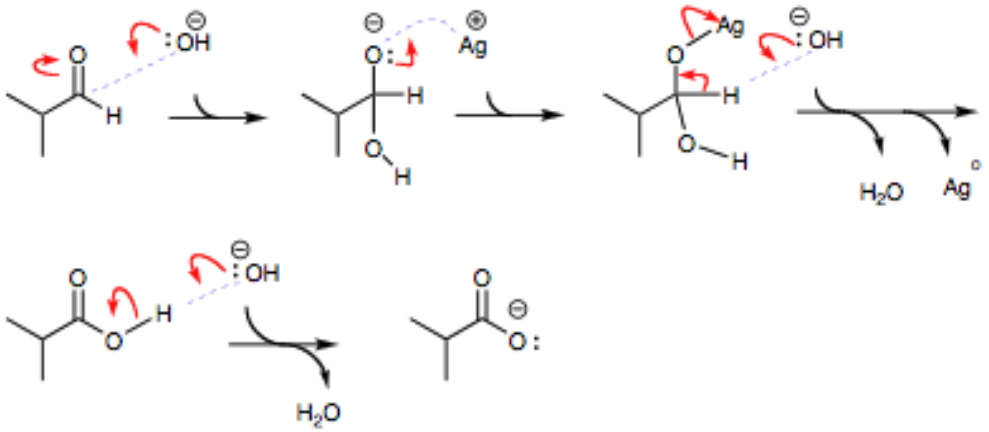
Oxidations in Organic Synthesis

(5) Oxidations of Aldehydes and Ketones

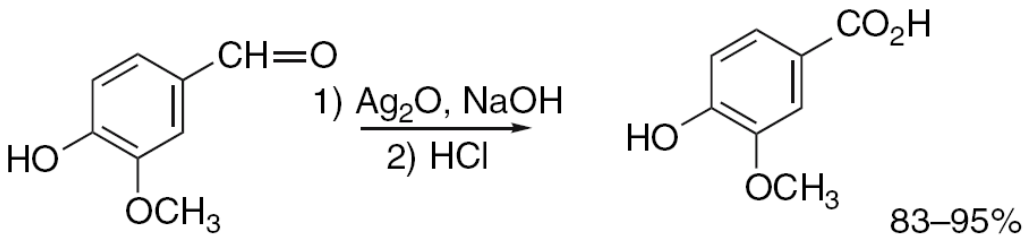
A. Transition Metal Oxidants

Aldehydes

Ag_2O
- basic conditions
- *Tollens*
- acidification



Example



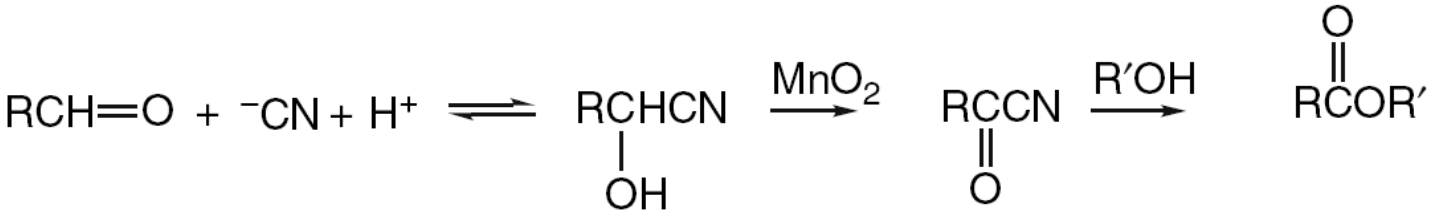
(5) Oxidations of Aldehydes and Ketones

A. Transition Metal Oxidants

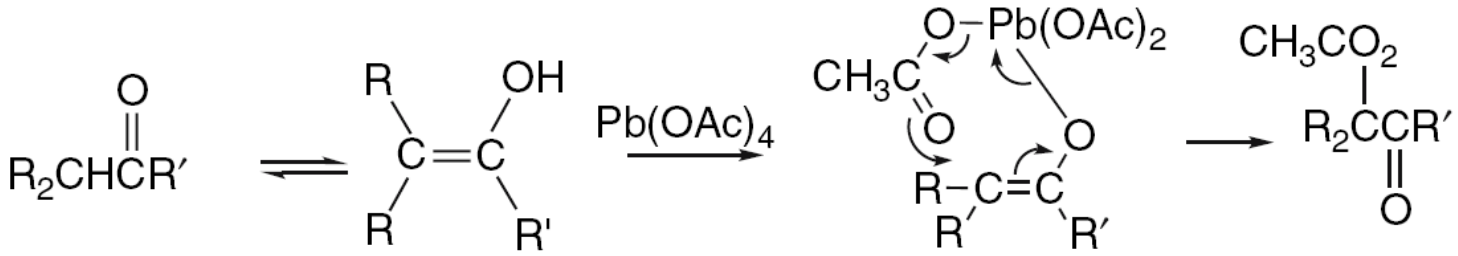
Aldehydes and Ketones

MnO_2/$^-$CN

- acidic conditions
- *cyanohydrines* → *acyl cyanides*
- solvolysis



$Pb(OAc)_4$

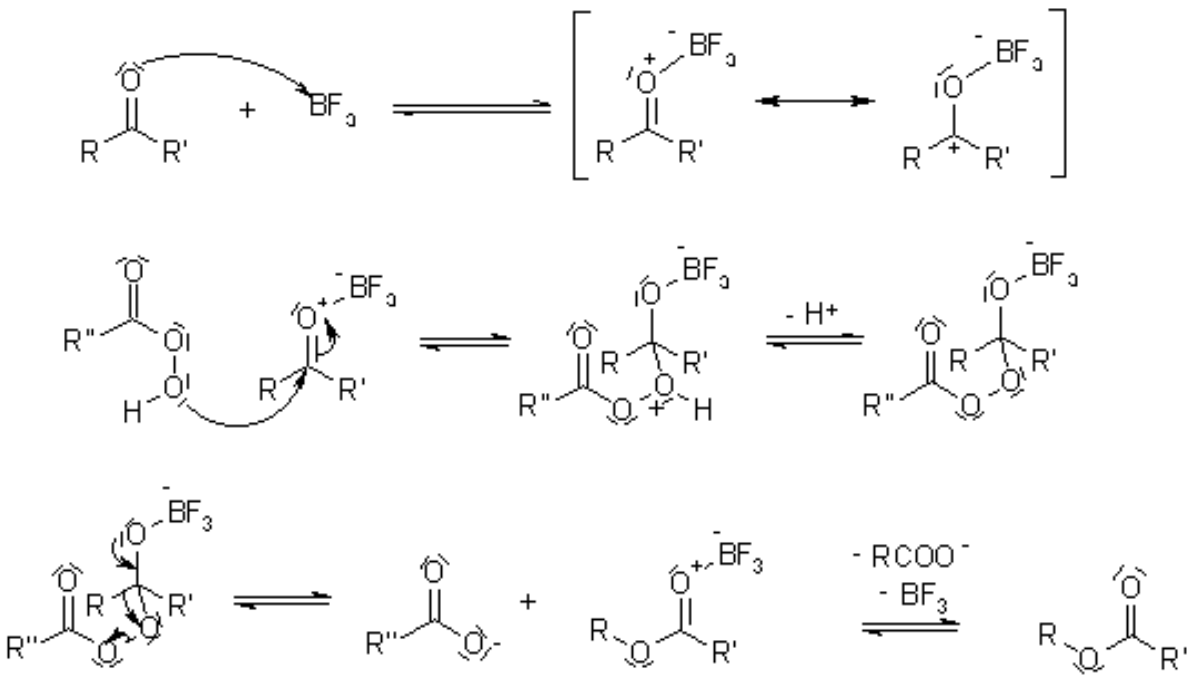


(5) Oxidations of Aldehydes and Ketones

B. Peroxidic Oxidants

Baeyer-Villiger Oxidation of Ketones

- insertion of oxygen
- peroxy compounds + LA (BF_3, $Sc(OTf)_3$, $Bi(OTf)_3$)



Oxidations in Organic Synthesis

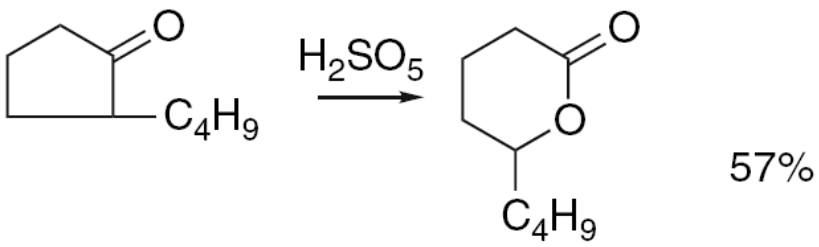
(5) Oxidations of Aldehydes and Ketones

B. Peroxidic Oxidants

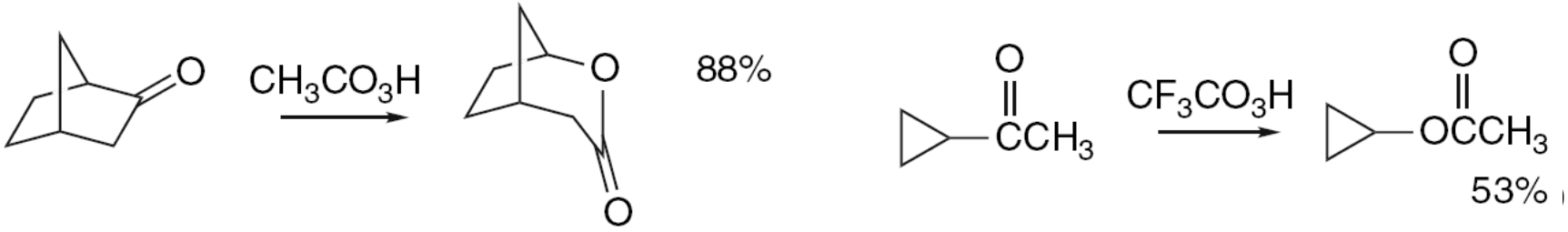
Baeyer-Villiger Oxidation of Ketones

- O−O heterolysis-migration
- general order of migration:

tert-alkyl,*sec*-alkyl > benzyl, phenyl > *pri*-alkyl > cyclopropyl > methyl



57%



53%

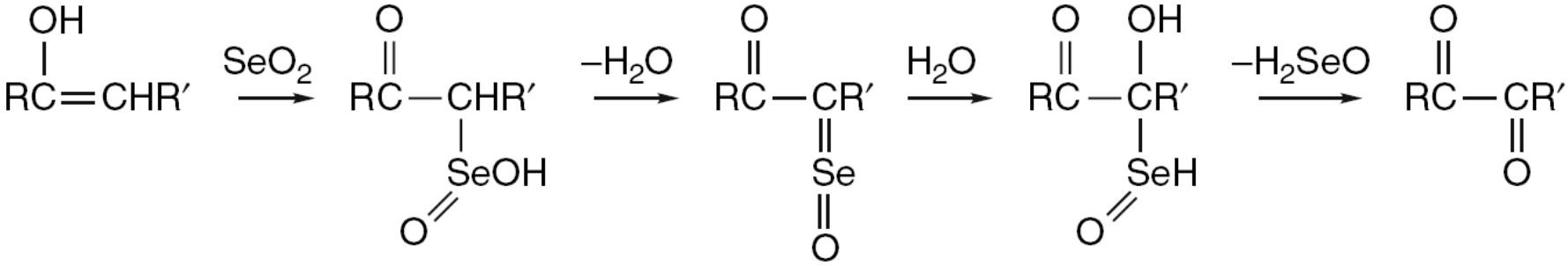
(5) Oxidations of Aldehydes and Ketones

C. Other Oxidants

SeO_2

- aldehydes, ketones → α-dikarbonyl compounds

Mechanism



Examples