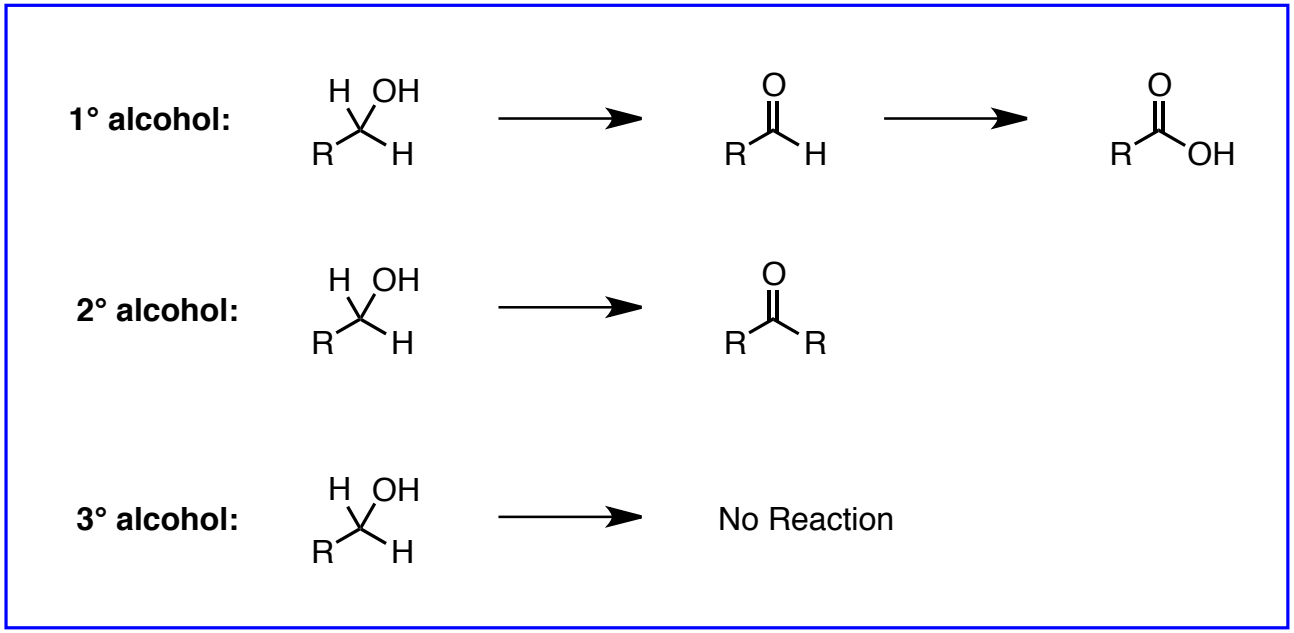
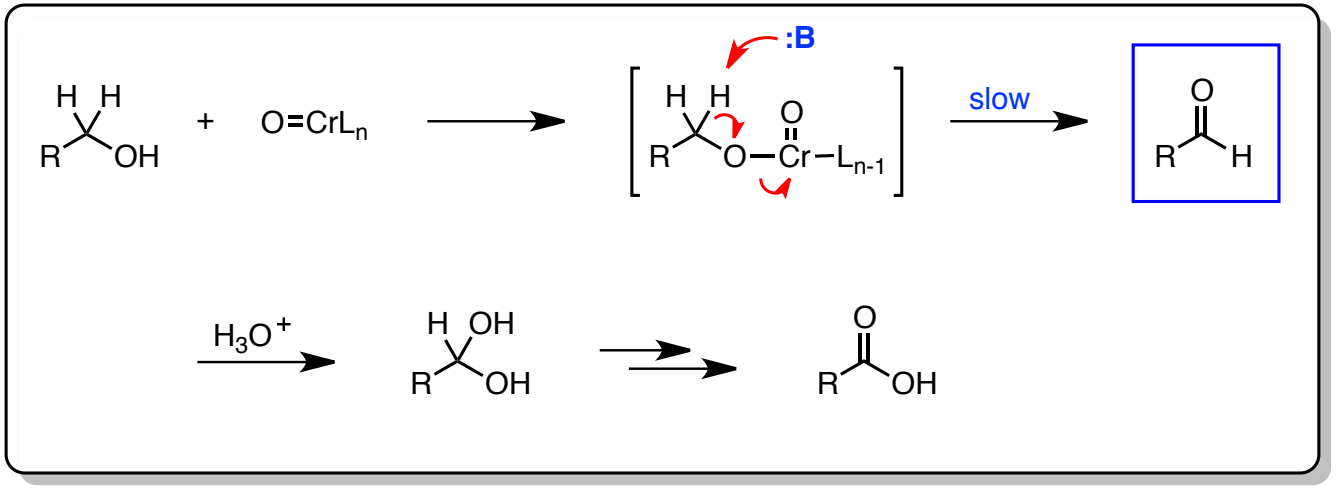
Oxidation of Alcohols



A. Chromium Based Reagents

General Mechanism:



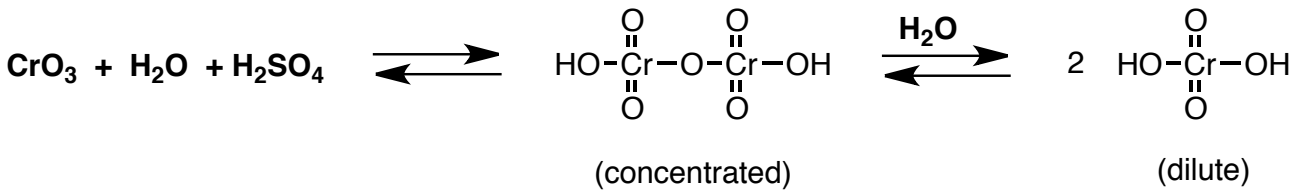
- 1° alcohols: under anhydrous conditions (Collins, PCC, PDC) will stop at aldehyde
- in presence of aqueous acid (Jones), see further (rapid) oxidation to carboxylic acid
- oxidation of 2° alcohols give ketones

- these processes generate chromium waste (toxic)

A. Chromium Based Reagents

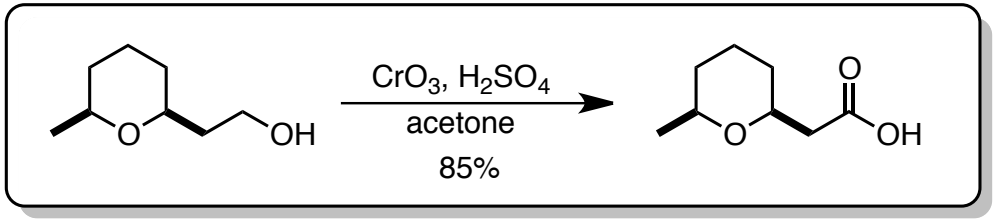
1. CrO_3/H_2SO_4 (aq): Jones Oxidation

- **preparation**



- reagent is shelf stable

- **reactivity**

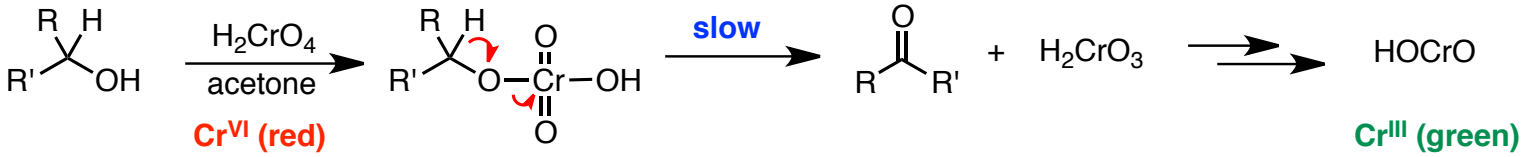


Yamamoto *Tetrahedron* **1990**, *46*, 4595.

- 1° alcohol → CO_2H
- rapid reaction
- strongly acidic; not useful for acid sensitive substrates
- reaction can effectively be run as a titration

A. Chromium Based Reagents

- **mechanism**



$R_2CH\text{-}OH + Cr^{(VI)} \rightarrow R_2C{=}O + Cr^{(IV)} + 2\,H^+$

$R_2CH\text{-}OH + Cr^{(IV)} \rightarrow R_2C{=}O + Cr^{(II)} + 2\,H^+$

$Cr^{(II)} + Cr^{(VI)} \rightarrow Cr^{(III)} + Cr^{(V)}$

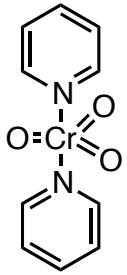
$R_2CH\text{-}OH + Cr^{(V)} \rightarrow R_2C{=}O + Cr^{(III)} + 2\,H^+$

- stoichiometry: $3\,R_2CHOH + 2\,CrO_3 + 6\,H^+ \rightarrow 3\,R_2C{=}O + 2\,Cr^{3+} + 6\,H_2O$

A. Chromium Based Reagents

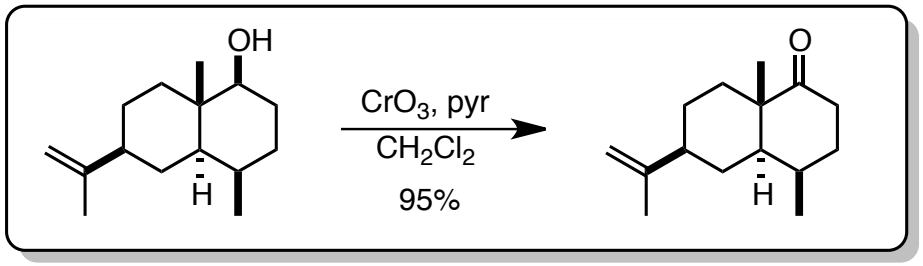
2. CrO_3•pyridine: Collins reagent

- **preparation**

CrO_3 + 2 pyridine →  hygroscopic red crystalline solid → (H_2O) → $(Cr_2O_7)^{2-}(pyrH^+)_2$ (yellow)

- important: add CrO_3 to pyridine (reverse results in strong exotherm!)
- Sarett: *in* situ generation in pyridine
- Collins: isolated solid; reaction in CH_2Cl_2
- Radcliff: *in situ* generation in CH_2Cl_2

- **reactivity**



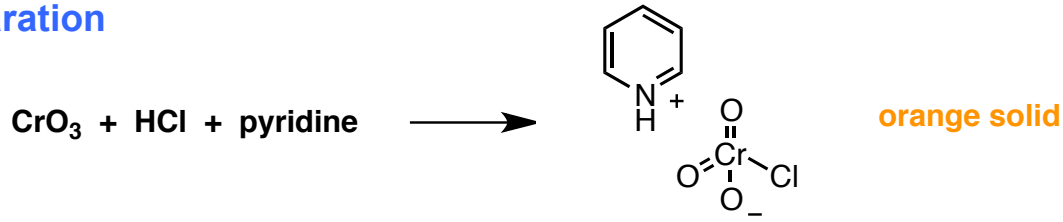
Ratcliffe *JOC* **1970**, *35*, 4000.

- 1° alcohol → CHO
- neutral to slighlty basic; good for acid sensititve substrates
- requires large excess of reagent; anhydrous conditions

A. Chromium Based Reagents

3. Pyridinium Chlorochromate (PCC): Corey-Suggs Oxidation

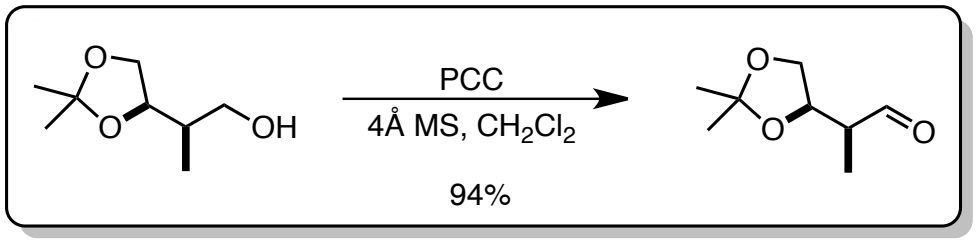
- **preparation**



orange solid

- stable; commercially available
- chloride facilitates formation of chromate ester

- **reactivity**



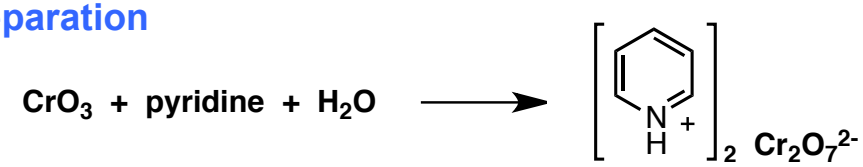
Nicolaou *J. Am. Chem. Soc.* **1988**, *110*, 4672

- 1° alcohol → CHO
- can use in near stoichiometric amounts (ca. 1.5 equiv)
- mild conditions; slightly acidic → can buffer with NaOAc
- add powd MS or Celite to facilitate product isolation
- addition of MS can accelerate rxn rate
- can promote allylic rearrangements

A. Chromium Based Reagents

4. Pyridinium Dichromate (PDC): Corey-Schmidt Oxidation

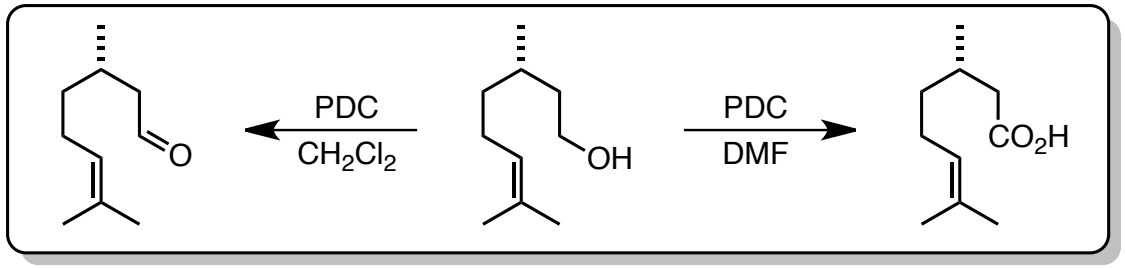
- **preparation**



orange solid

- stable; commercially available

- **reactivity**



Corey *Tetrahedron Lett.* **1970**, *20*, 399.

- product of reaction depends on solvent used

  CH_2Cl_2: 1° alcohol → CHO

  DMF: 1° alcohol → CO_2H (allylic alcohols give CHO)

- oxidizes more slowly than other Cr-based reagents

- mild conditions; less acidic than PCC

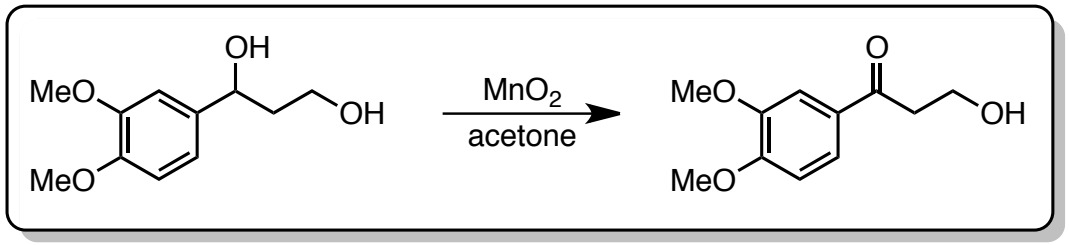
B. Manganese Based Reagents

1. Manganese Dioxide (MnO_2)

- **reagent**

  - dark brown or black solid
  - structure/activity depends on preparation
  - non-stoichiometric material containes Mn(II) and Mn(III) oxides and hydrated species

- **reactivity**



  - selective oxidation of allylic and benzylic alcohols; significant rate difference!
  - 1° alcohol → CHO
  - slow reaction, requires large excess of reagent
  - H bonding solvents show strong deactivating effect; non-polar solvents best
  - mild; no isomerization of double bonds upon oxidiation of allylic alcohols

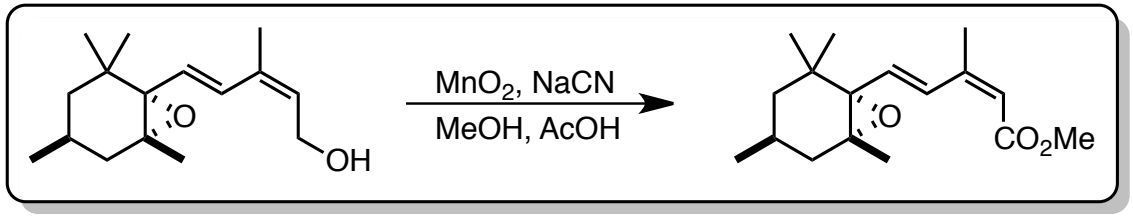
B. Manganese Based Reagents

2. Manganese Dioxide, ROH, NaCN: Corey-Gilman-Ganem Oxidation

- **reagent**

  - modified MnO_2 oxidation

- **reactivity**

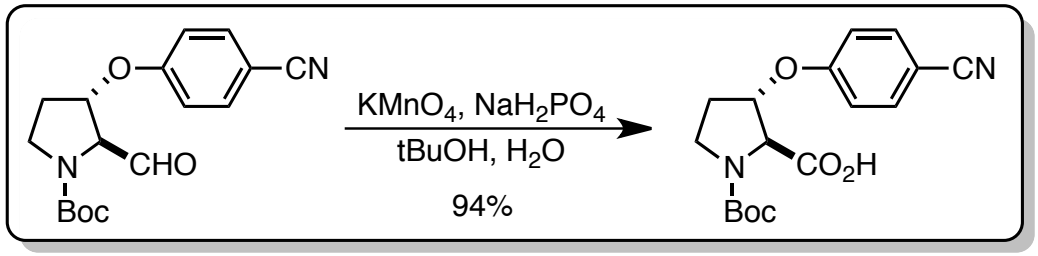


  - direct oxidation of 1° allylic/benzylic alcohols to esters
  - more commonly used for the conversion of conjugated aldehydes to esters

B. Manganese Based Reagents

3. Potassium Permanganate ($KMnO_4$)

- **reactivity**



Joullié *J. Am. Chem. Soc.* **1992**, *114*, 10181.

- 1° alcohol → CO_2H; also useful for the oxidation of aldehydes
- powerful oxidant; over oxidation/side reactions may be a problem
  → also oxidizes alkenes, 1,2-diols, etc.
- insoluble in organic solvents
- may be successful when other oxidants fail (Jones, AgO, NaOCl).
- R_4NMnO_4 shows similar reactivity and is soluble in organics

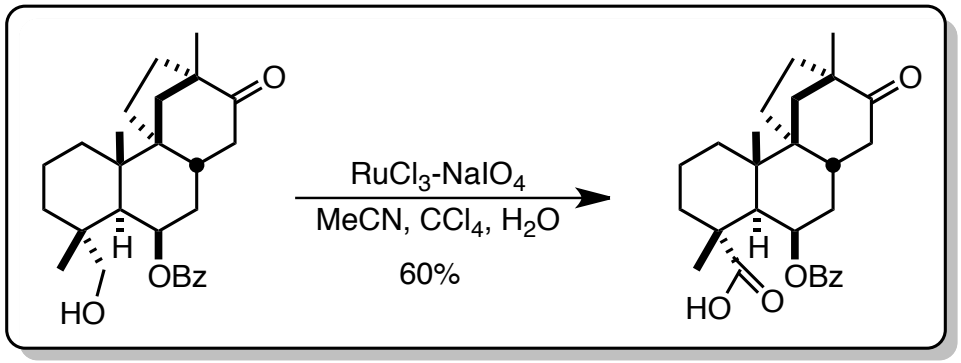
C. Ruthenium Based Reagents

1. Ruthenium Tetraoxide (RuO_4)

- **reagent**

  - toxic
  - catalytic procedures use 1-5% Ru metal with a stoichiometric oxidant

- **reactivity**



Overman *J. Am. Chem. Soc.* **1997**, *119*, 12031.

  - 1° alcohol → CO_2H
  - powerful, non-selective oxidant; will also attack multiple bonds,1,2-diols, ethers, aromatic rings, etc.

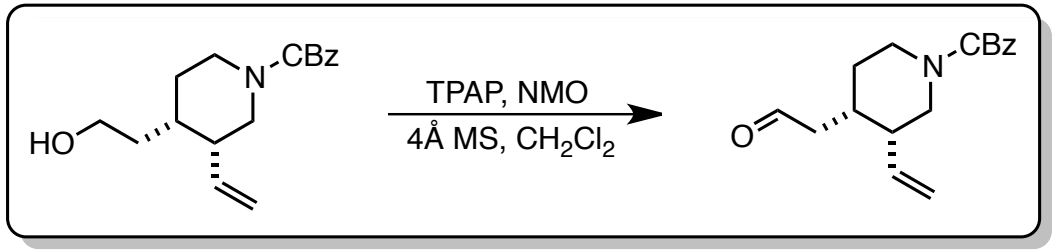
C. Ruthenium Based Reagents

2. Tetra-n-propylammonium Perruthenate ($Pr_4N^+RuO_4^-$): TPAP

- **reagent**

  - developed by Steve Ley (Imperial College → Cambridge)
  - catalytic; used in conjunction with a stoichiometric oxidant (NMO)
  - perruthate salts with a large counterion are mild and selective oxidants

- **reactivity**



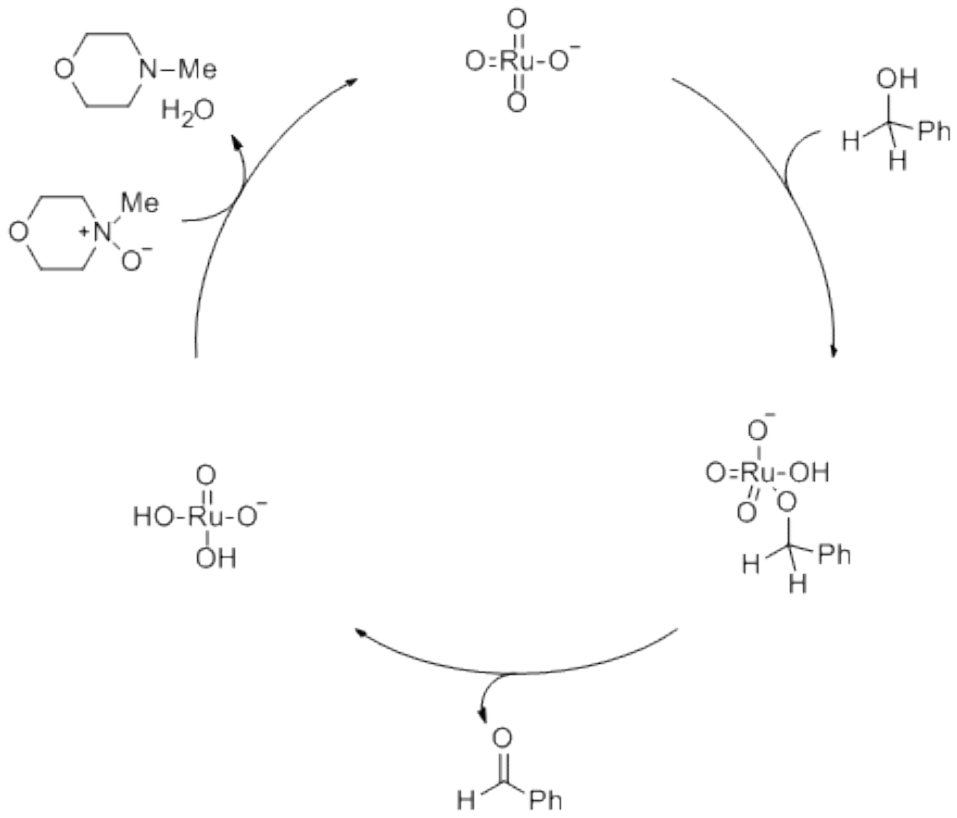
Jacobsen *J. Am. Chem. Soc.* **2004**, *126*, 706.

  - 1° alcohol → CHO
  - mild oxidant; no over oxidation, does not react with multiple bonds
  - use of MS required to remove water and achieve high catalyst turnover
  - modified conditions allow for oxidation of 1° alcohol to carboxylic acid (Stark *Org. Lett.* **2011**, *13*, 4164)

C. Ruthenium Based Reagents

2. Tetra-n-propylammonium Perruthenate ($Pr_4N^+RuO_4^-$): TPAP

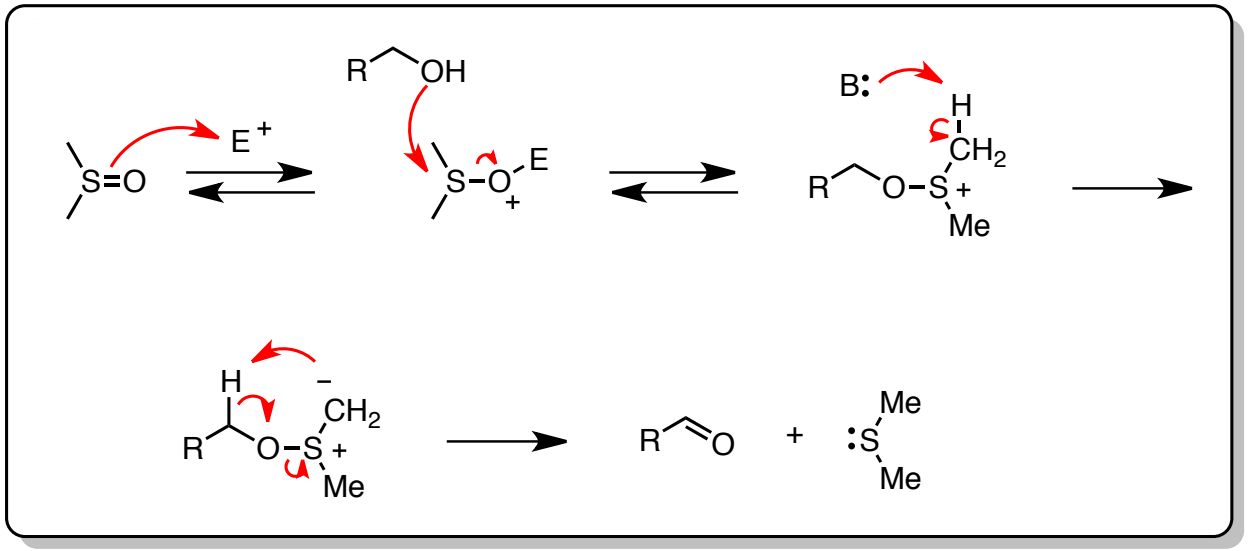
- **mechanism**



http://www.synarchive.com/named-reactions/Ley-Griffith_Oxidation

D. DMSO Based Reagents

General Mechanism:

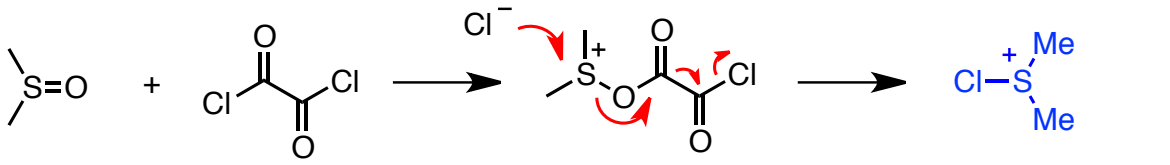


- mild class of reagents
- don't have environmental issues associated with use of Cr based reagents
- no over oxidation → oxidation of 1° alcohols give aldehydes
- oxidation of 2° alcohols give ketones

D. DMSO Based Reagents

1. DMSO, $(COCl)_2$; Et_3N: Swern Oxidation

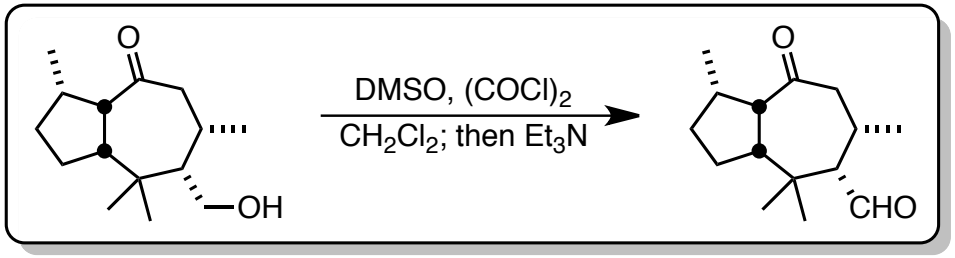
- **activation:**



+ CO_2 + CO + Cl^-

- also TFAA, Ac_2O, $SOCl_2$, Cl_2, P_2O_5

- **reactivity**



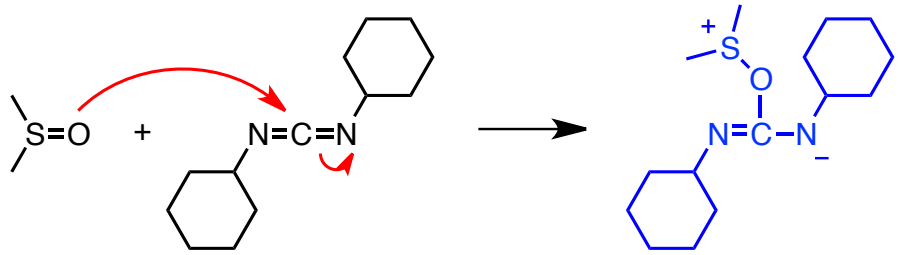
Funk *J. Org. Chem.* **1987**, *52*, 3173.

- 1° alcohol → CHO
- most common of DMSO based reagents
- very mild → run at low temp (-78 to -60°C)
- low sensitivity to steric factors
- preparation of β-alkoxy carbonyl derivatives may be problematic → use Et_2NiPr

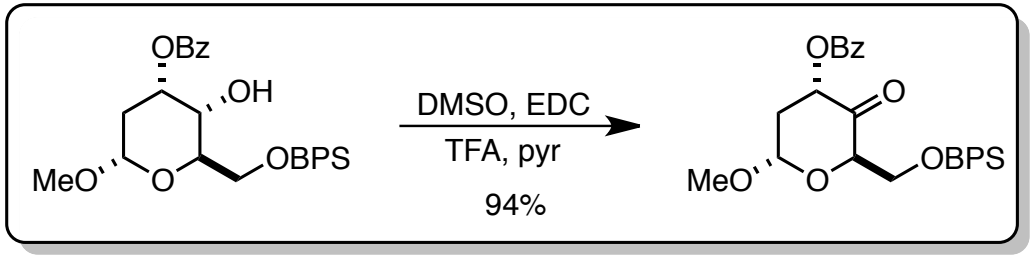
D. DMSO Based Reagents

2. DMSO, DCC, TFA, pyridine: Moffatt Oxidation

- **activation: DMSO + DCC**

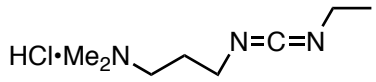


- **reactivity**



Hannessian *Can. J. Chem.* **1981**, *59*, 870.

- 1° alcohol → CHO
- first reported DMSO based oxidant; less commonly used
- separation of by-pyroduct (dicyclohexylurea) can be difficult → use EDC

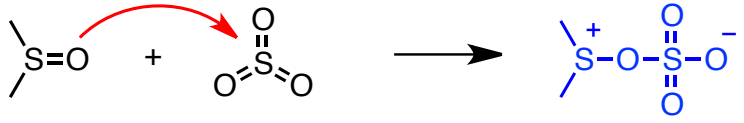


- may result in formation of MTM ethers (side reaction)

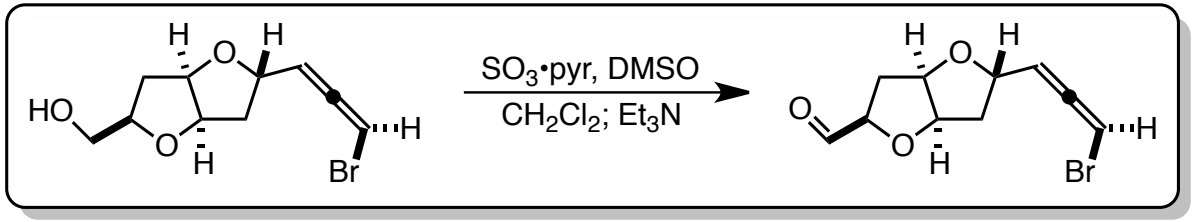
D. DMSO Based Reagents

3. SO_3•pyridine, DMS; Et_3N: Parikh-Doehring

- **activation**



- **reactivity**



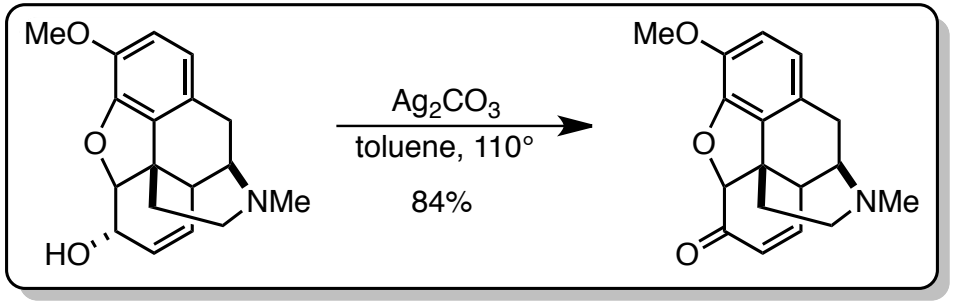
Evans *ACIEE* **1999**, *38*, 3175

- 1° alcohol → CHO
- easy workup; well suited to large scale reactions

E. Silver Based Oxidants

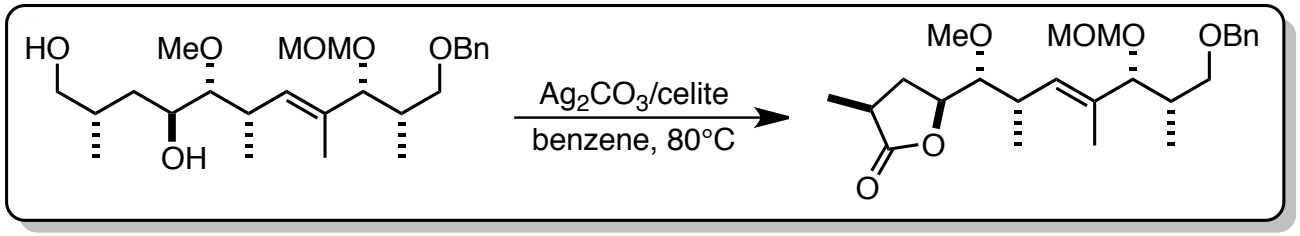
1. Ag_2CO_3/celite: Fetizon's reagent

- **reactivity**



Rappoport - codeine

- 1° alcohol → CHO
- original oxidant modified by Fetizon → adsorb on celite to increase surface area
- neutral conditions; very sensitive to steric factors
- $$$, must use large excess → small scale reactions
- reaction does not proceed through cationic intermediate (no rearrangements, etc.)
- controlled overoxidation possible with some substrates (selective lactol oxidation)

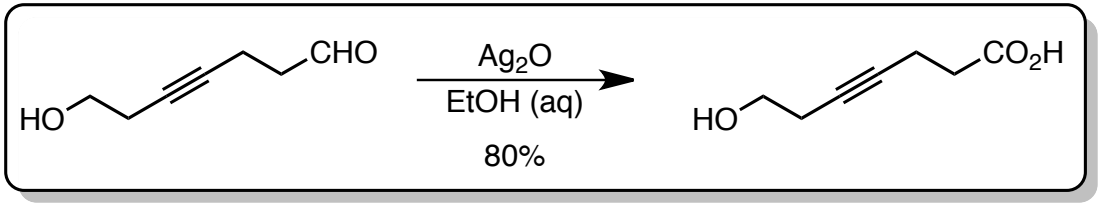


Kallmerten *Tetrahedron Lett.* **1990**, *31*, 4305.

E. Silver Based Oxidants

2. Silver (I) Oxide (Ag_2O)

- **reactivity**



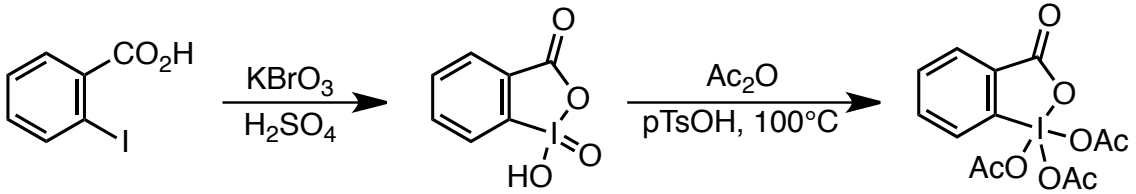
Kitching *JCSP1* **1995**, 1309.

- mild method for the conversion of CHO → CO_2H (in presence of free OH)
- unsaturated aldehydes are problematic (isomerization)
- weak oxidant

F. Other Oxidants

1. Dess-Martin Periodinane

- **preparation**

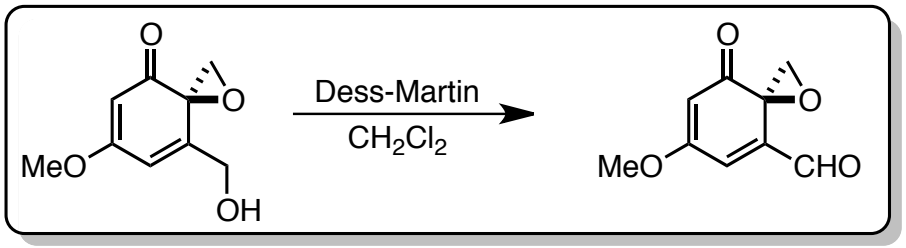


(IBX) shock sensitive

white solid

- can determine quality of reagent by solublity in CH_2Cl_2

- **reactivity**

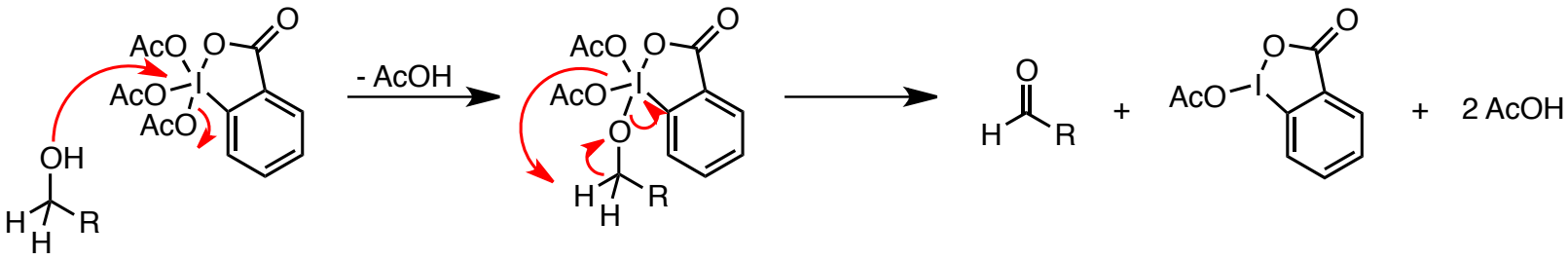


Danishefsky *J. Am. Chem. Soc.* **1991**, *113*, 3850.

- 1° alcohol → CHO
- mild reagent; nearly neutral conditions → gives off AcOH, but can buffer
- will <u>not</u> oxidize N or S

F. Other Oxidants

- **mechanism**

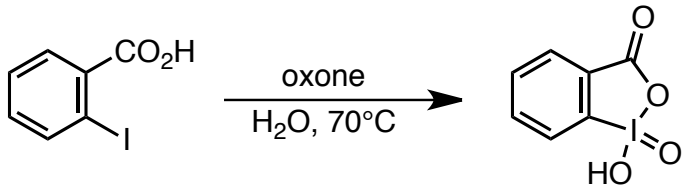


- addition of 1 equiv water accelerates reaction (Schreiber)

F. Other Oxidants

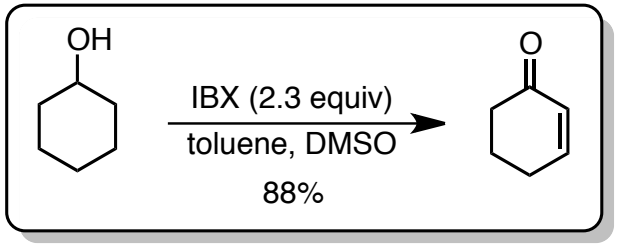
2. *o*-Iodoxybenzoic acid (IBX)

- **preparation**



- intermediate in the synthesis of Dess-Martin periodinane; simpler prep

- **reactivity**



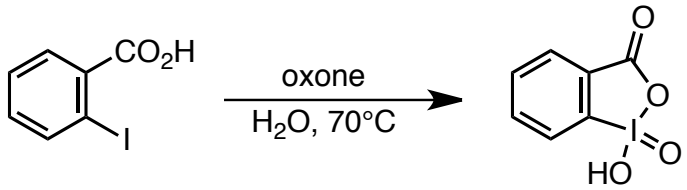
Nicolaou *J. Am. Chem. Soc.* **2000**, *122*, 7596.

- in excess will oxidize alcohols to α,β-unsaturated aldehydes and ketones (or saturated aldehydes/ketones to α,β-unsaturated compounds)
- mild reagent for oxidation of 1,2-diols without oxidative cleavage
- insoluble in most organic solvents, except DMSO or DMSO mixtures

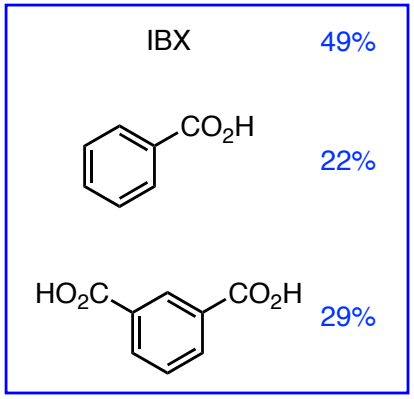
F. Other Oxidants

2. *o*-Iodoxybenzoic acid (IBX)

- **preparation**



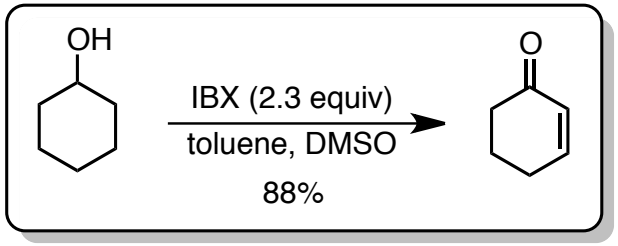
"SIBX"



Quideau *Org. Lett.* **2003**, *5*, 2903.

- intermediate in the synthesis of Dess-Martin periodinane; simpler prep

- **reactivity**

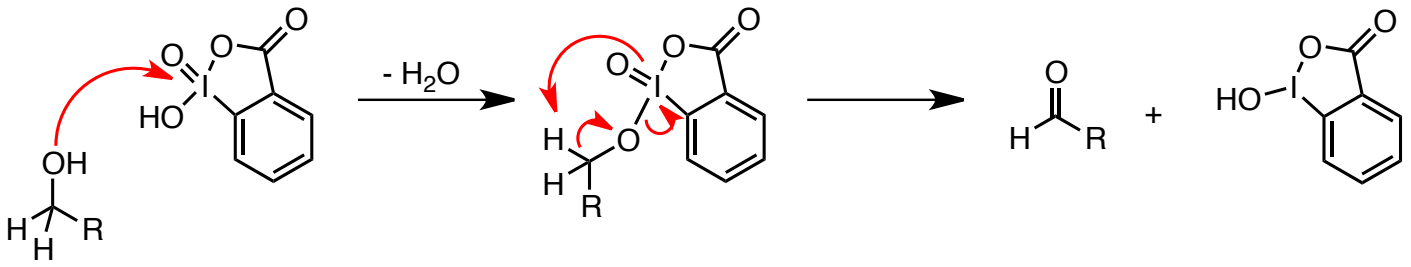


Nicolaou *J. Am. Chem. Soc.* **2000**, *122*, 7596.

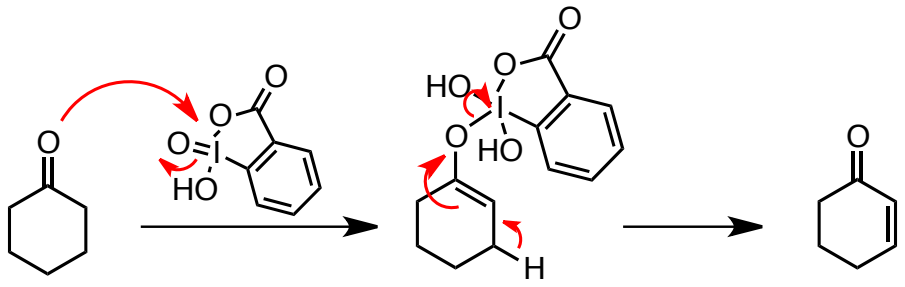
- in excess will oxidize alcohols to α,β-unsaturated aldehydes and ketones (or saturated aldehydes/ketones to α,β-unsaturated compounds)
- mild reagent for oxidation of 1,2-diols without oxidative cleavage
- insoluble in most organic solvents, except DMSO or DMSO mixtures

F. Other Oxidants

- **mechanism**



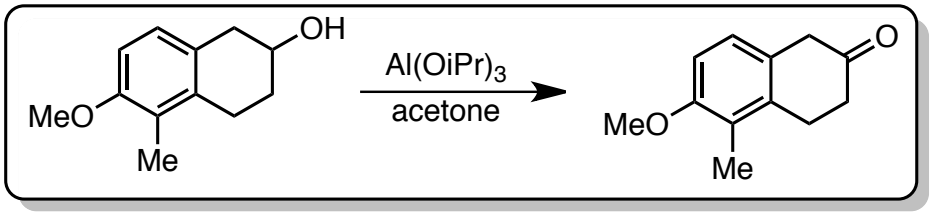
- alcohol oxidation: mirrors Dess-Marin periodinane mechanism



F. Other Oxidants

3. $Al(OiPr)_3$, acetone: Oppenauer Oxidation

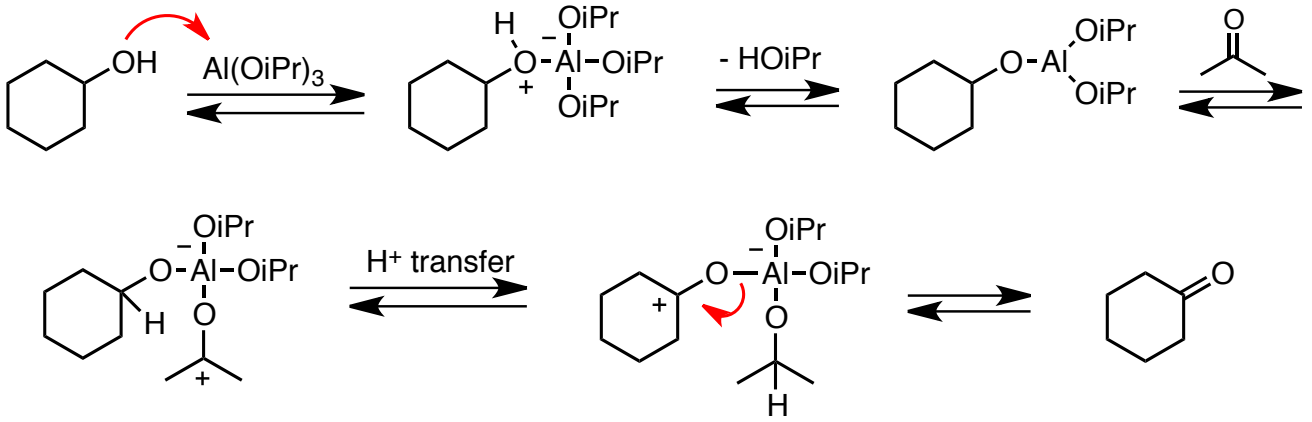
- **reactivity**



Boger *J. Org. Chem.* **1984**, *49*, 4045.

- classical method for alcohol oxidation
- takes advantage of reversible reaction between ketones and metal alkoxides
- mild conditions, infrequently used; does not work well with 1° alcohols

- **mechanism**

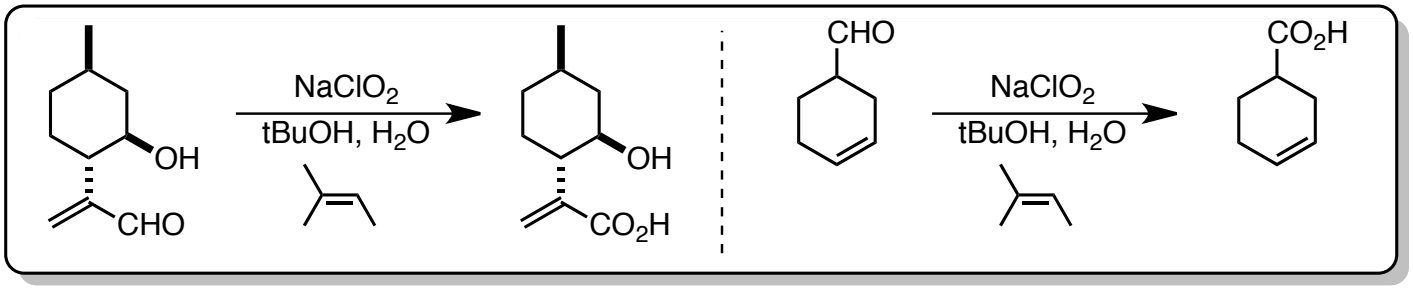


- use of acetone solvent drives reaction to the right

F. Other Oxidants

4. Sodium Chlorite ($NaClO_2$): Pinnick Oxidation

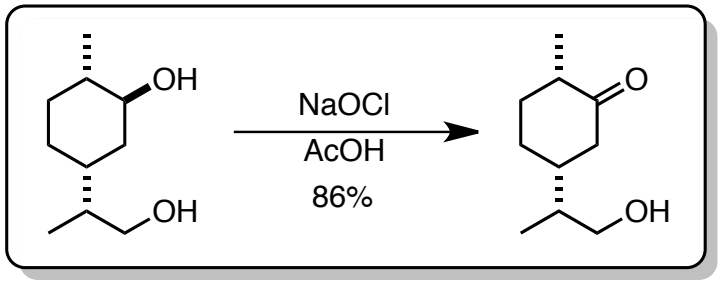
- **reactivity**



- useful method for oxidation of sensitive CHO → CO_2H, esp. α,β-unsaturated CHO
- use hampered by formation of chlorine dioxide
- suppressed by addition of chlorine scavenger (alkene)

5. Sodium Hypochlorite (NaOCl): Stevens Oxidation

- **reactivity**



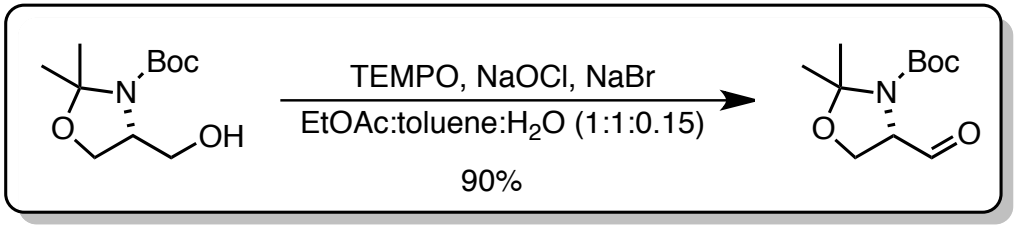
Corey *J. Am. Chem. Soc.* **1998**, *120*, 12777.

- selective oxidation of 2° alcohols
- modified procedure uses calcium hypochlorite – a stable solid

F. Other Oxidants

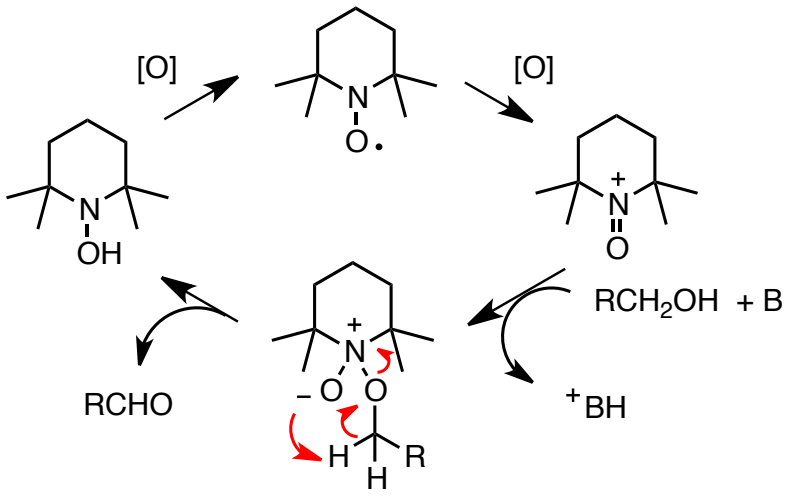
6. TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy):

- **reactivity**

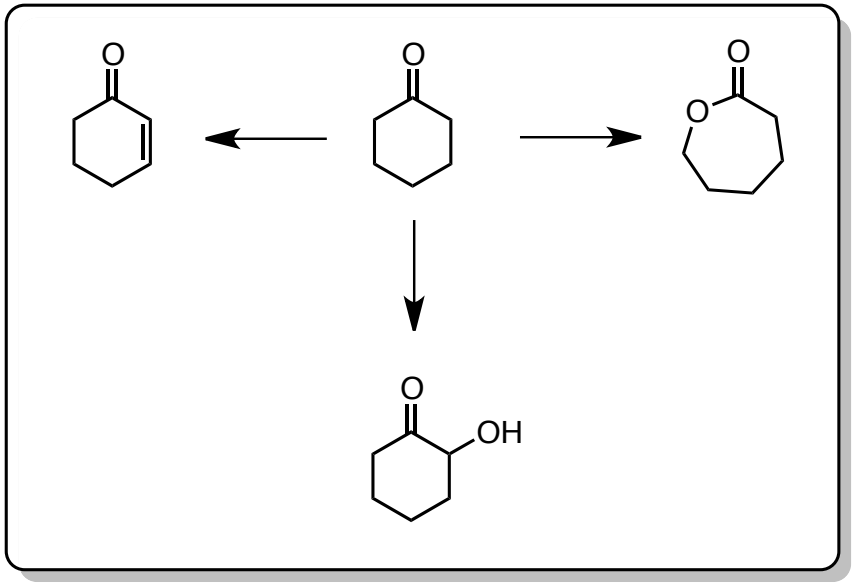


- 1° alcohol → CHO
- used in presence of stoichimetric oxidant (mCPBA, NaOCl, $PhI(OAc)_3$, oxone, etc.
- works best in simple systems
- selective oxidation of alcohols in presence of S or Se

- **mechanism**



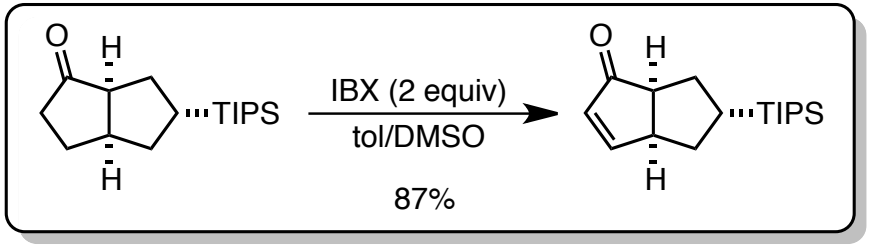
Oxidation of Ketones



Ketone → Enone

1. IBX

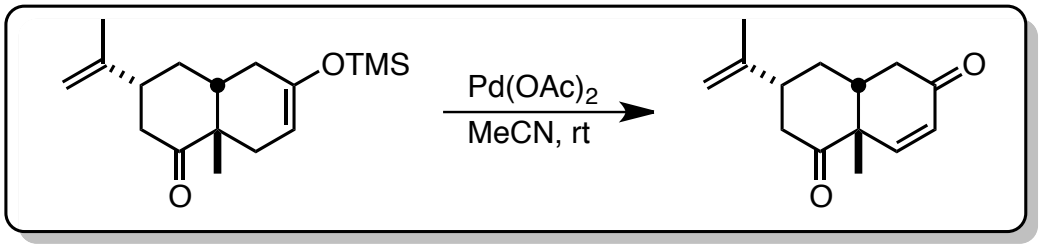
- **reactivity**



- Nicolaou *J. Am. Chem. Soc.* **2002**, *124*, 2245.

2. Saegusa Oxidation

- **reactivity**



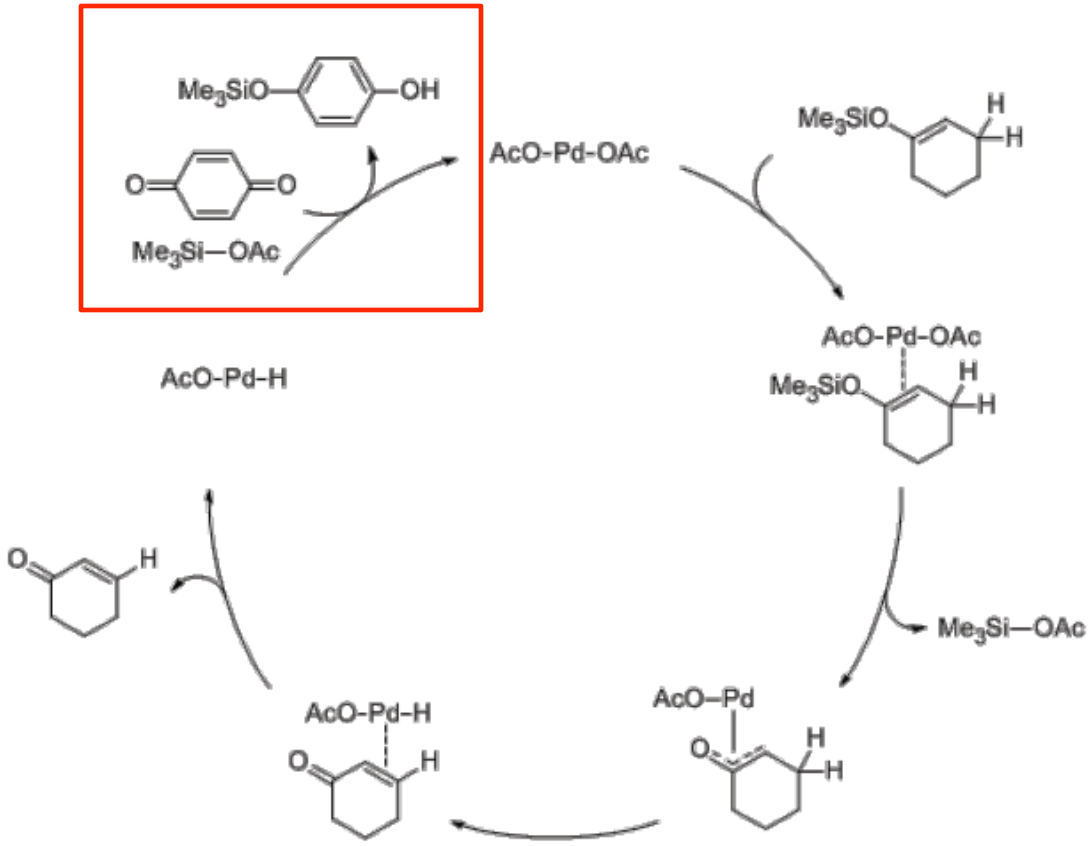
Danishefsky *J. Am. Chem. Soc.* **2008**, *130*, 13765.

- Saegusa *J. Org. Chem. Soc.* **1978**, *43*, 1011.
- most often stoichimetric in Pd, but use of cat Pd in presence of stoichimetric oxidant is known (see, for example: Lebel *JOC* **2013**, *78*, 776)

Ketone → Enone

2. Saegusa Oxidation

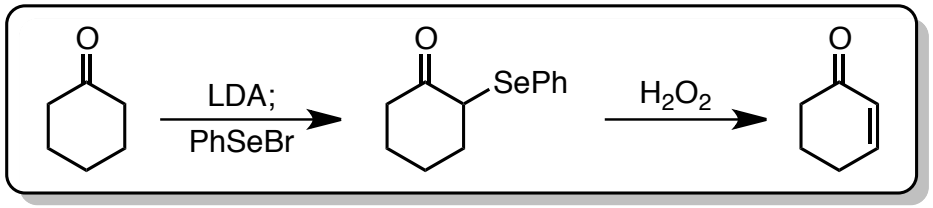
- **mechanism**



Ketone → Enone

3. Selenoxide Elimination

- **reactivity**

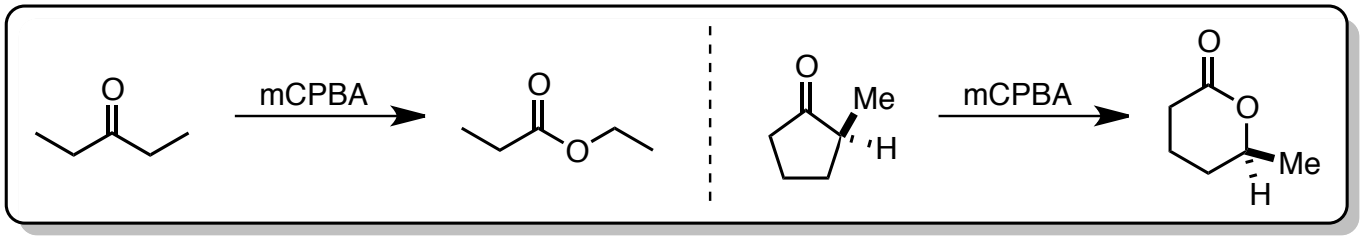


- other oxidants include $NaIO_4$, O_3, mCPBA, etc.

Ketones → Esters/Lactones

1. Baeyer Villager Oxidation

- **reactivity**

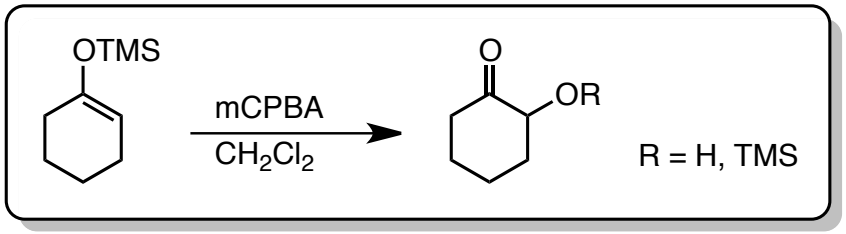


- reaction of ketone with peracids (mCPBA, trifluoroperacetic acid, peracetic acid)
- migration occurs at more highly substituted (more electron rich) position:
- migratory aptitude: 3° > 2° > benzyl > Ph > 1° > cyclopropyl > Me > H
- stereochemistry is retained
- note peracids react with other functionality (alkenes, amines, sulfides, etc.)

Alpha Hydroxylation

1. Rubottom Oxidation

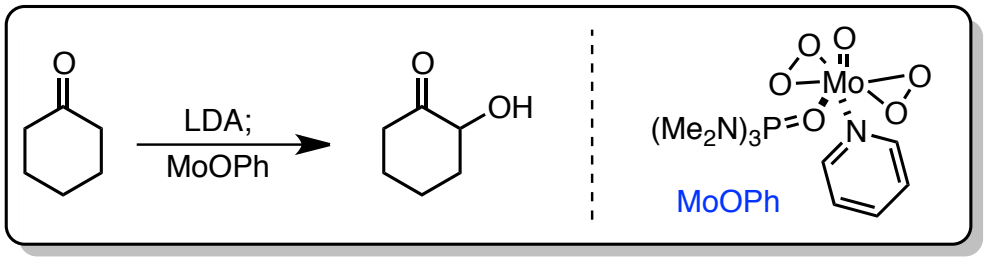
- **reactivity**



- Rubottom *Tetrahedron Lett.* **1974**, *15*, 4319.
- epoxidation of silyl enol ether, followed by silyl migration
- dimethydioxirane (DMDO) can also be used for epoxidation

2. MoOPh Oxidation

- **reactivity**

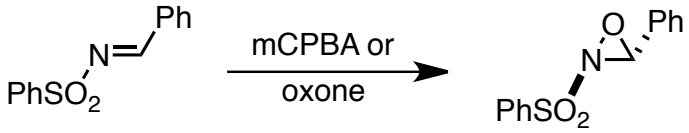


- MoOPh = MoO5•pry•HMPA
- attack of enolate at peroxyl oxygen atom leads to O-O bond cleavage

Alpha Hydroxylation

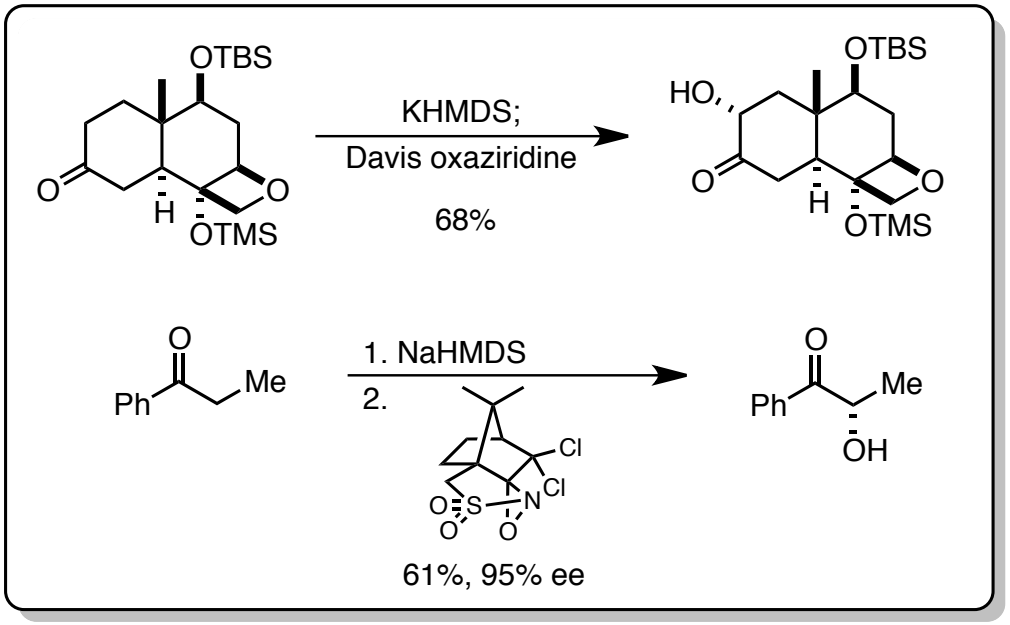
3. Davis Oxaziridine

- **preparation**



- N-sulfonyloxaziridines prepared by oxidation of corresponding sulfonimine
- chiral reagents are known

- **reactivity**



- nucleophilic attack of enolate on electrophilic oxaziridine oxygen
- potassium enolates tend to work best