

Oxidations at Carbon

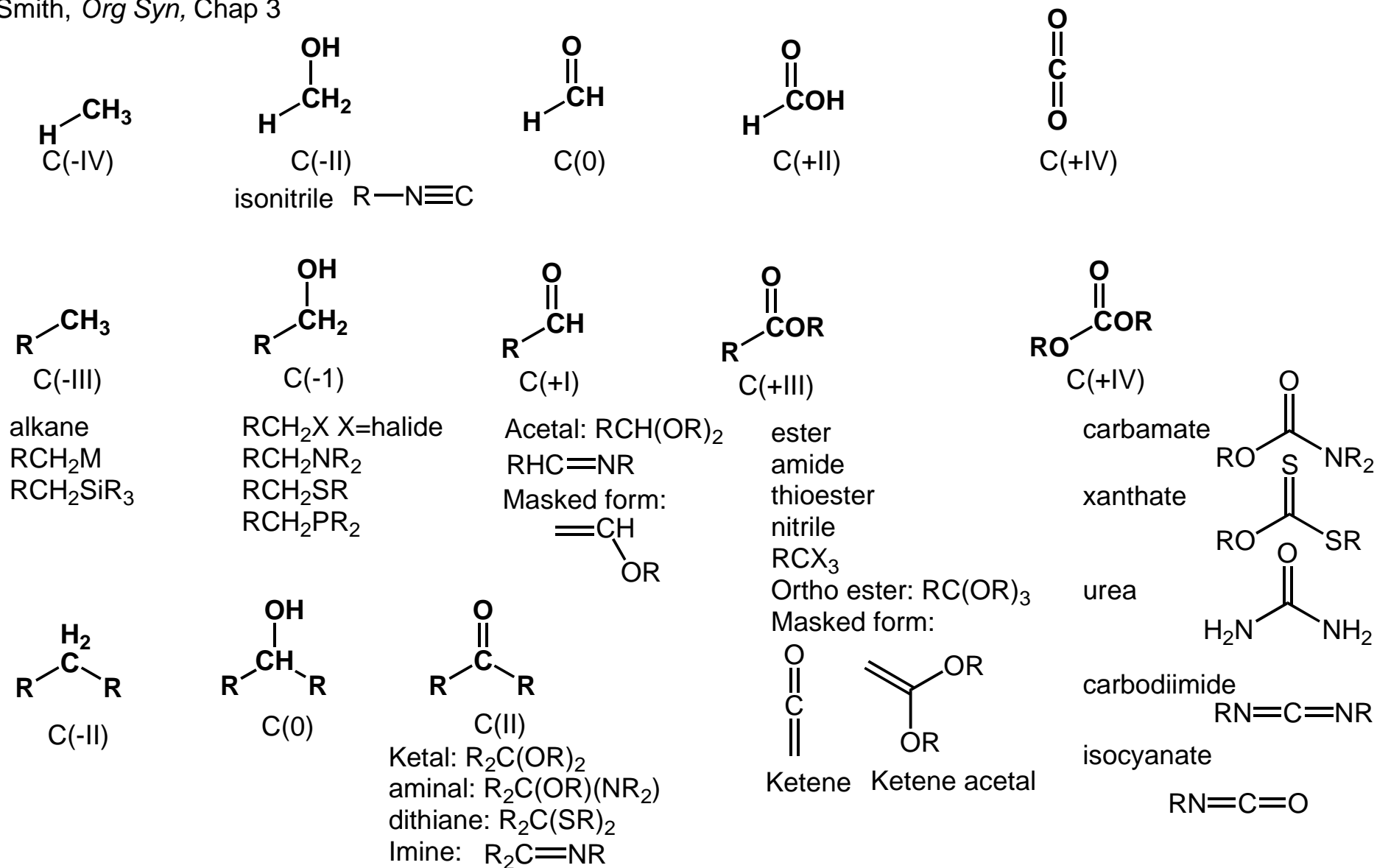
General references

March, *Advanced Org Chem*, 1992, 1158-1238

Trost, *Comp. Org. Syn.* 1991, vol 7

Carey and Sundberg, *Advanced Org Chem*, part B, 615-664

Smith, *Org Syn*, Chap 3



Chromium-based Oxidations

Very powerful oxidants

Many variations on the theme

Reactivity modulated by ligands on Cr (*Org. Rxn.*, **1998**, 53, 1-122)

Likely pretty toxic

H_2CrO_4

Jones reagent

As solution with H_2SO_4 in acetone/water

Very strong and not very selective

Mechanism has been studied extensively

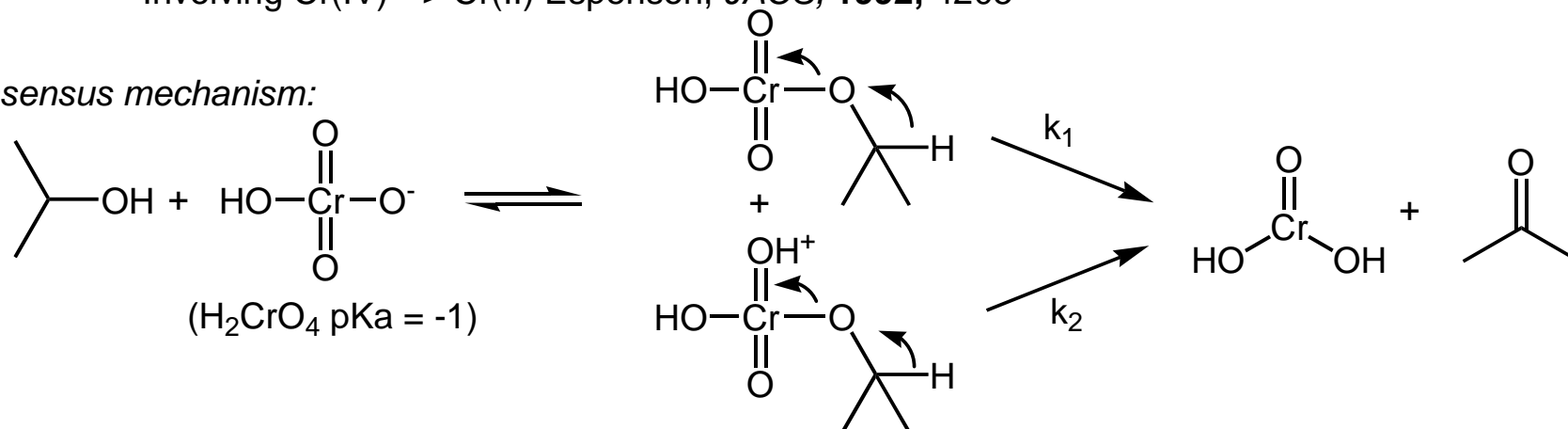
Predominant mechanism likely to be Cr(VI) \rightarrow Cr(IV), taken as prototype for other Cr-based reagents

Mechanism: See Westheimer *J. Phys. Chem.* **1959**, 538; *Chem Rev.* **1949**, 419

Involving radical intermediates: Wieberg, *JACS*, **1974**, 1884

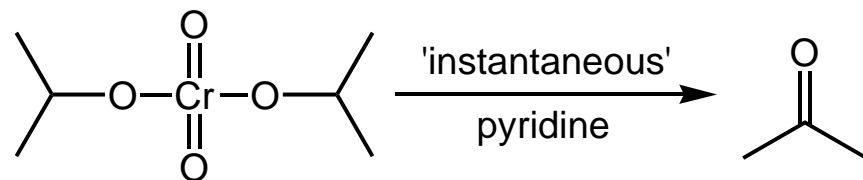
Involving Cr(IV) \rightarrow Cr(II) Espenson, *JACS*, **1992**, 4205

Consensus mechanism:



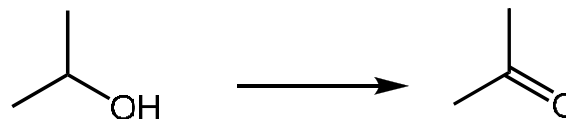
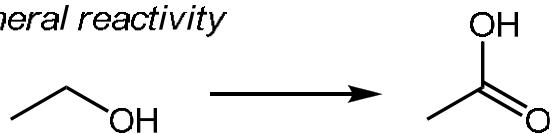
Evidence: $k_{\text{H}}/k_{\text{D}} = 6$

$$\text{rate} = d[\text{Cr(VI)}]/dt = (k_1[\text{H}^+] + k_2[\text{H}^+]^2)[\text{HCrO}_4][\text{ROH}] \quad k_1/k_2 = 0.04$$

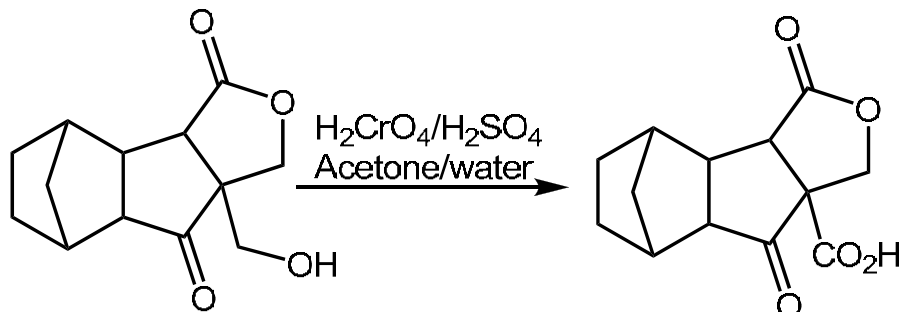


Jones Reagent: Reactivity

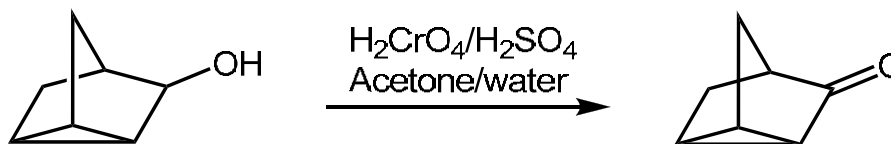
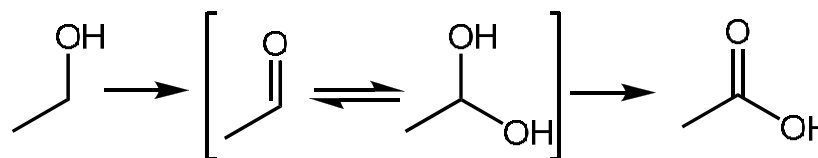
General reactivity



Examples:

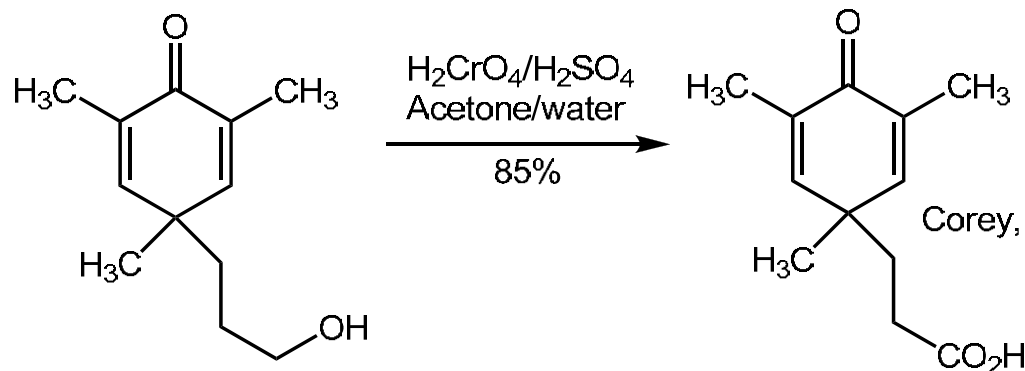


Synthesis, 1990, 235



88%

Mienwald, JACS, 1966, 1292

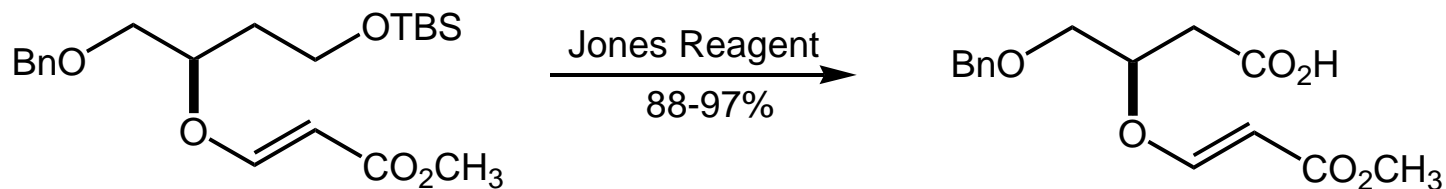
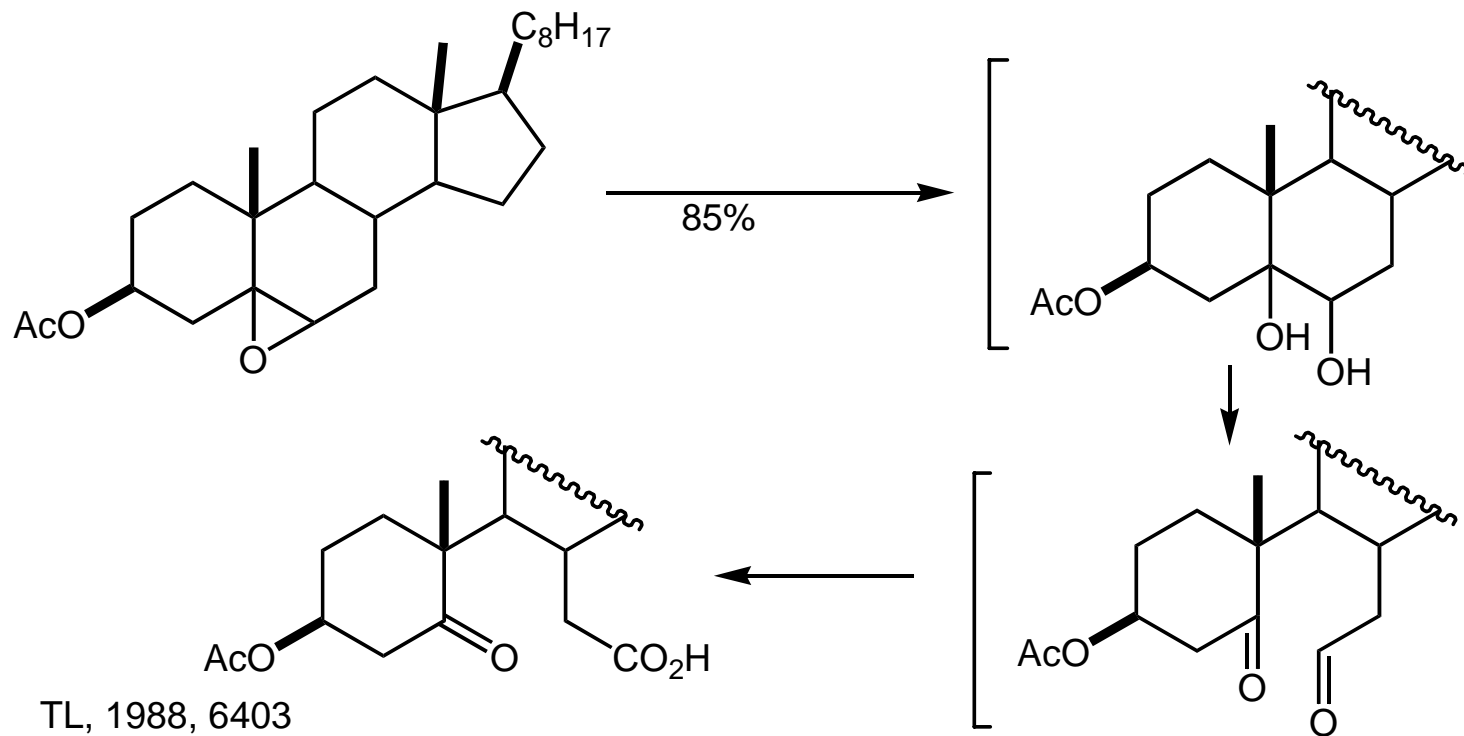


85%

Corey, Falck, et al, JACS, 1978, 4618

Jones Reagent: Reactivity

Jones reagent can promote acid-catalyzed reactions (desilylation, Friedel-Crafts type, olefin migrations, epoxide openings) and diol cleavage, as in the examples below.



P. A. Evans, ACIEE, 1999, 3175

Cr-amine reagents

review: Org. React. 1998, 1-122

added amine helps moderate reactivity of Cr and buffers reaction mixture

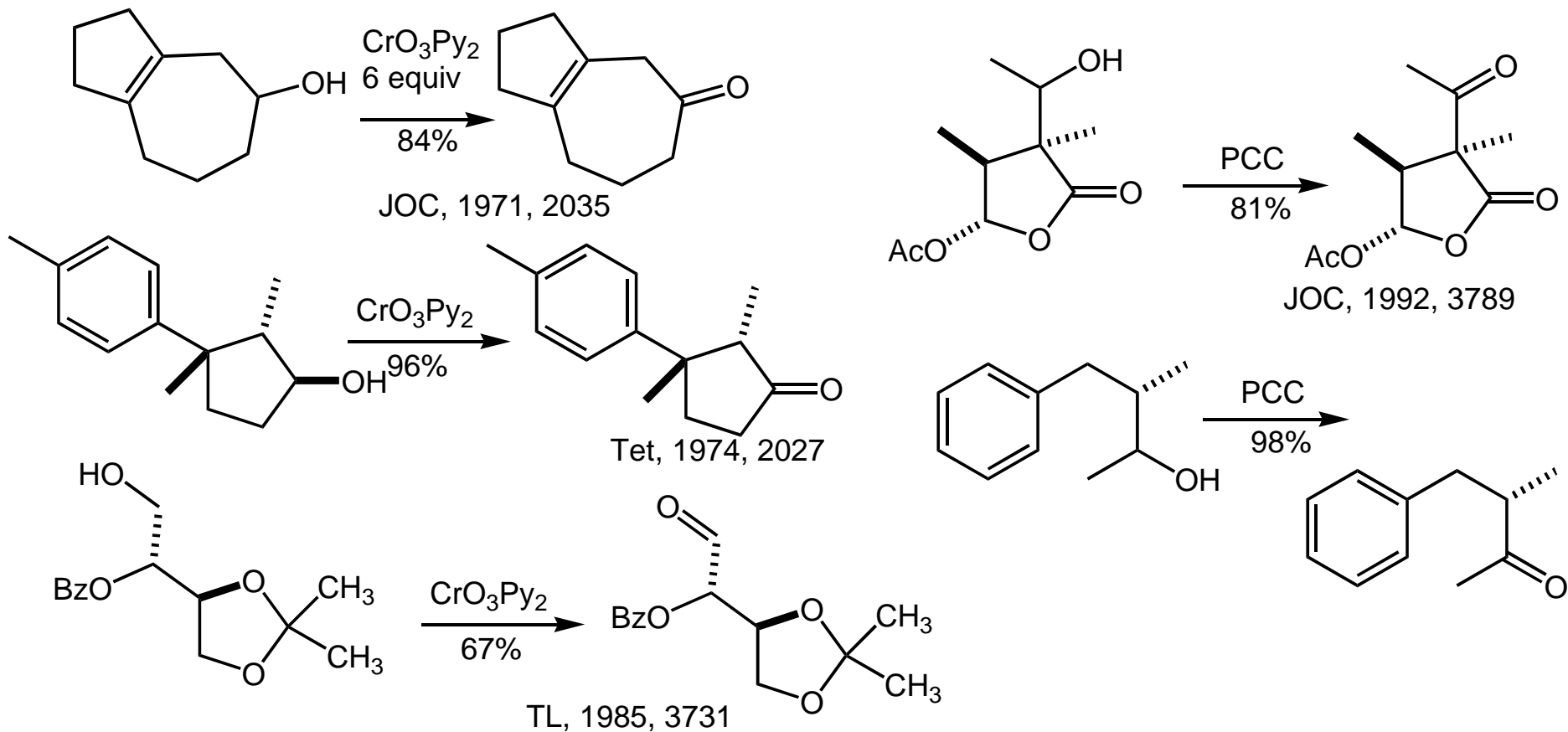
Three common reagents:

CrO_3Py_2 (*Collins Reagent*): hygroscopic, often requires excess, if dry will stop at aldehyde

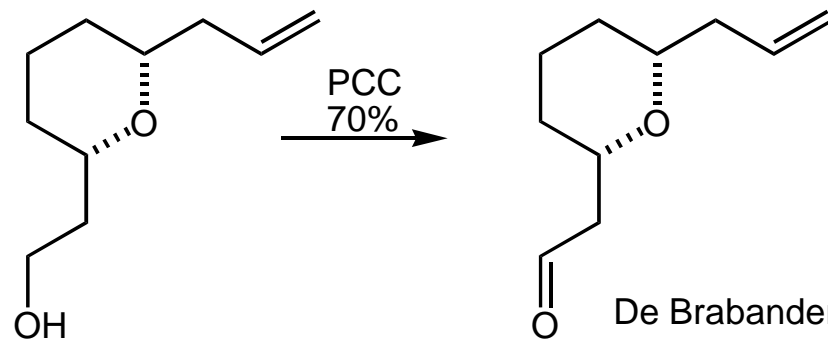
$[\text{ClCrO}_3][\text{PyH}]$ (*pyridinium chlorochromate, PCC, Corey's reagent*): often oxidant of choice for first attempt, used in conjunction with mol sieves (to keep dry and prevent clumping) or Celite (usually 1:1 mass ratio for both); Air stable, not too hygroscopic; will stop at aldehyde

$(\text{PyH}^+)_2\text{Cr}_2\text{O}_7$ (*pyridinium dichromate, PDC*): in CH_2Cl_2 , alcohol to aldehyde; more often used in DMF for alcohol to acid

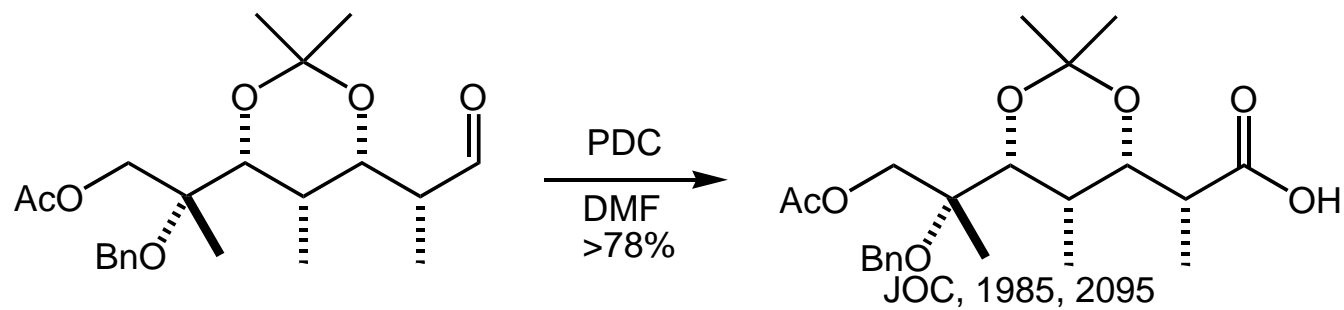
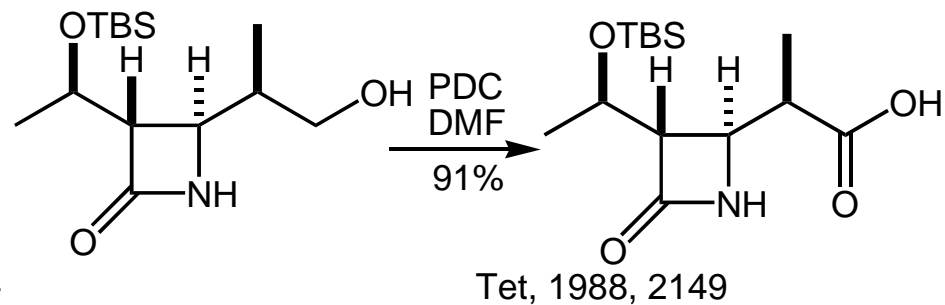
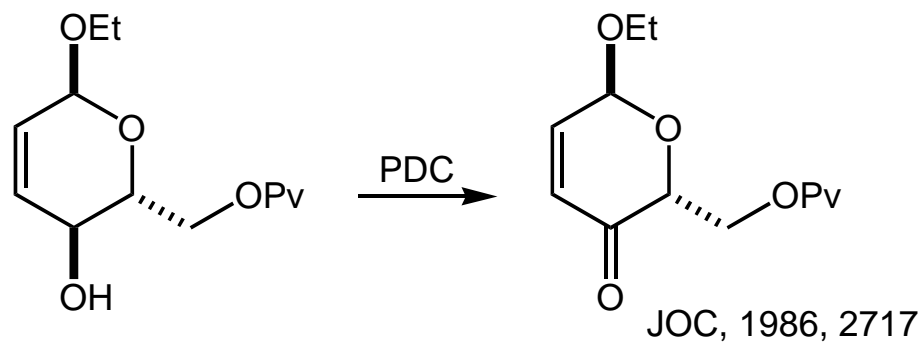
Examples



Cr-amine reagents
examples, cont.

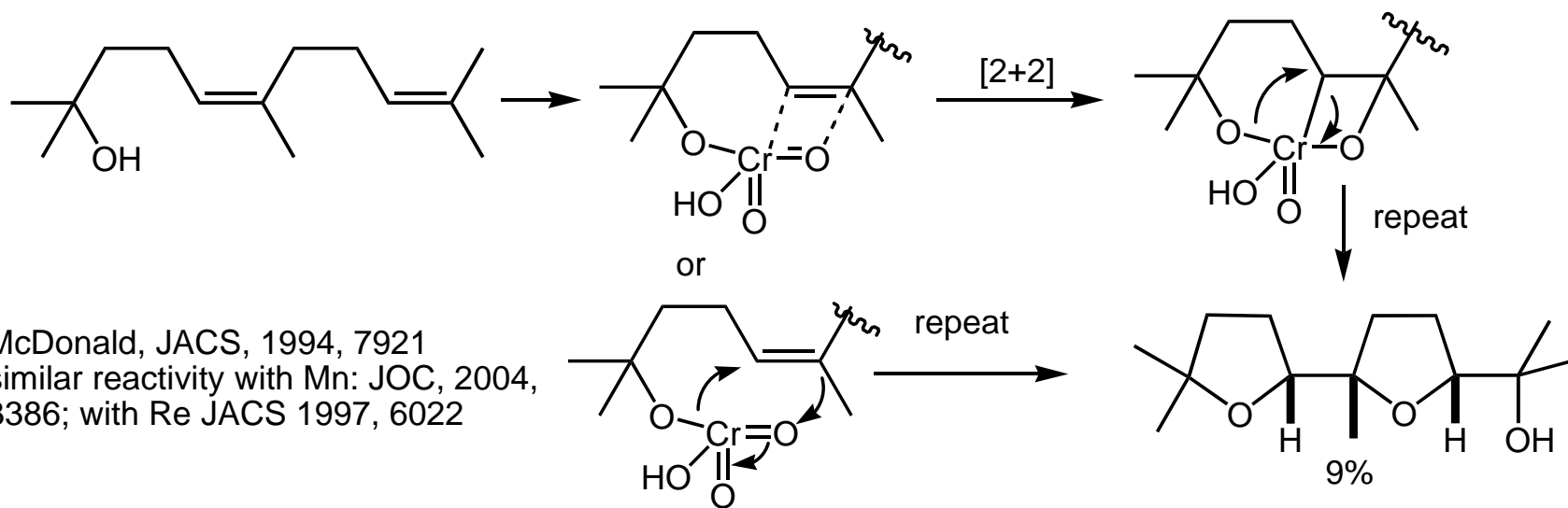
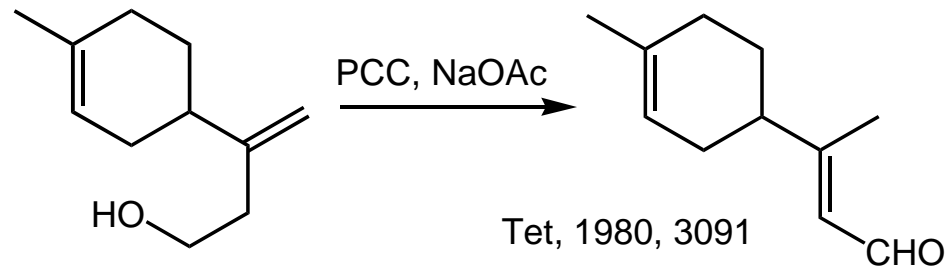
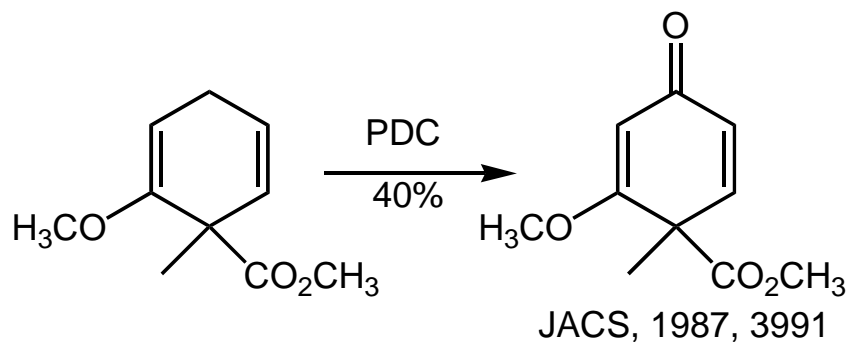
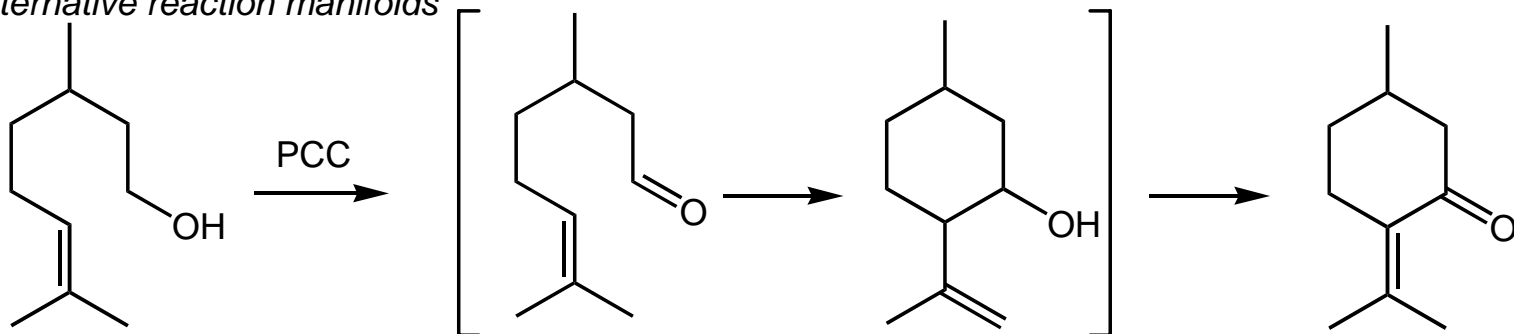


De Brabander, OL, 2002, 481



Cr-amine reagents

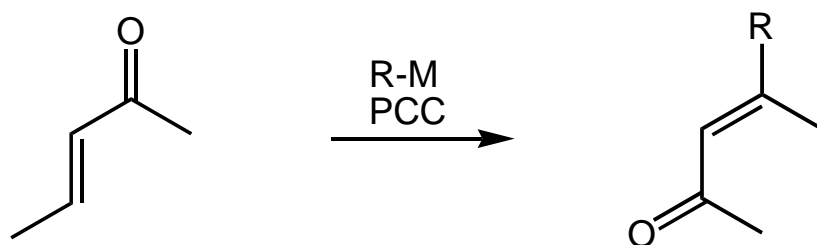
alternative reaction manifolds



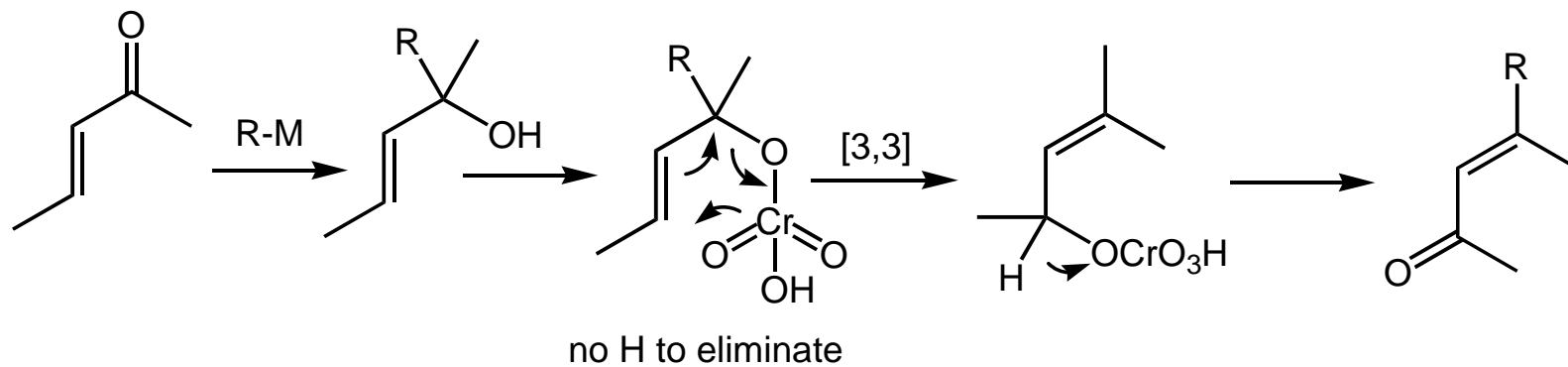
Cr-mediate synthesis of β,β -disubstituted enones

Dauben, JOC, 1977, 682

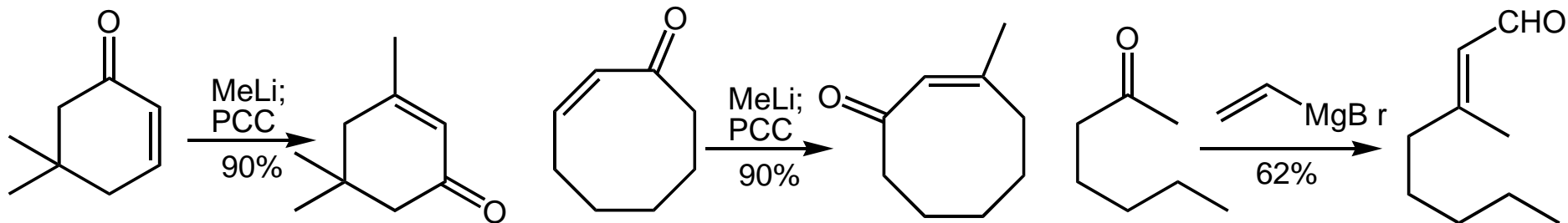
overall transformation:



mechanism

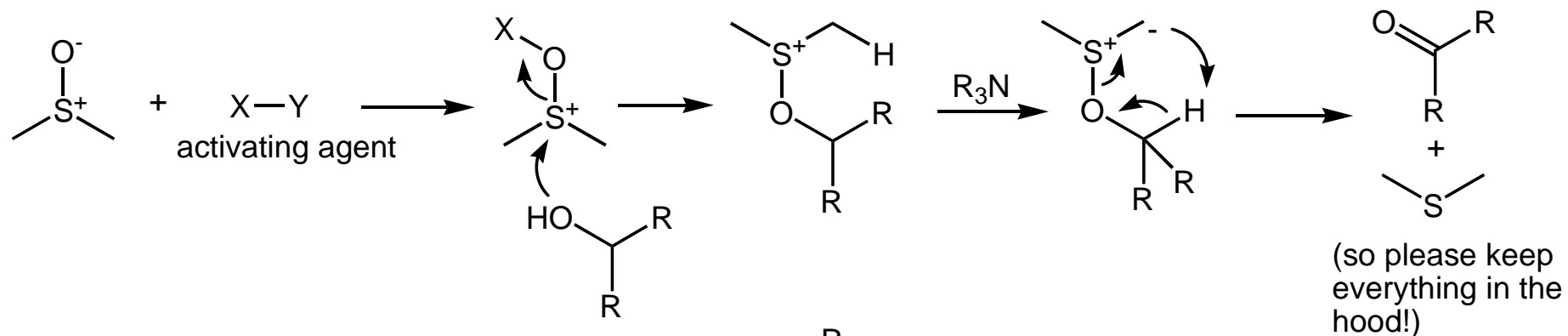


examples

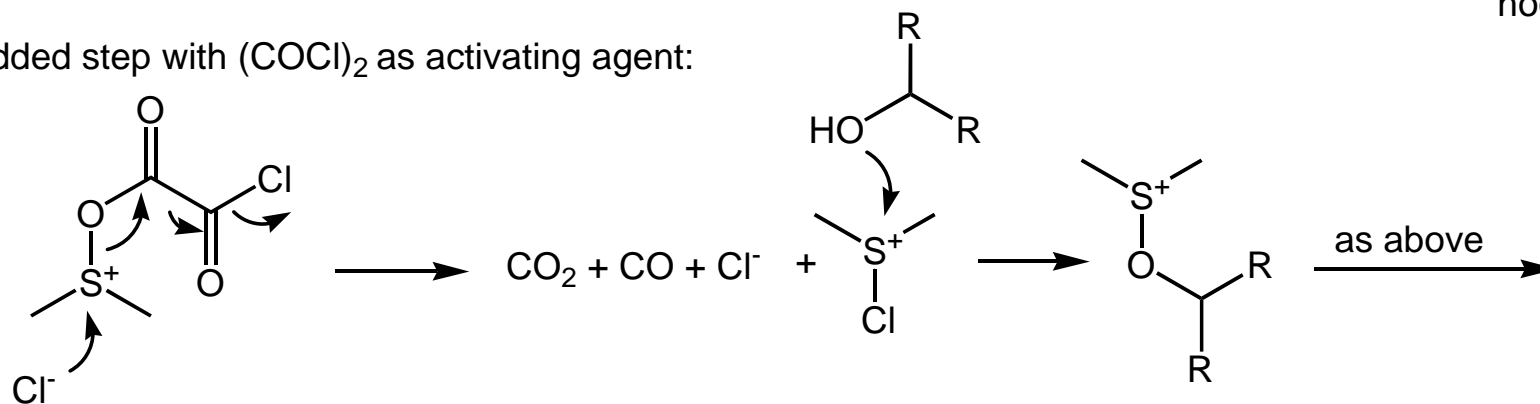


Activated DMSO oxidations

General mechanism



an added step with (COCl)₂ as activating agent:



Many activating agents are available. Some of the more common:

DCC (Pfitzner-Moffatt oxidation) JACS, 1963, 3027

Ac₂O JACS, 1967, 2416

SO₃-Pyridine (Perikh-Doering oxidation) JACS, 1967, 5505

Cl₂ TL, 1973, 919

SOCl₂ Tet, 1978, 1651

(COCl)₂ (Swern oxidation) JOC, 1978, 2480

Activated DMSO oxidations

Applications

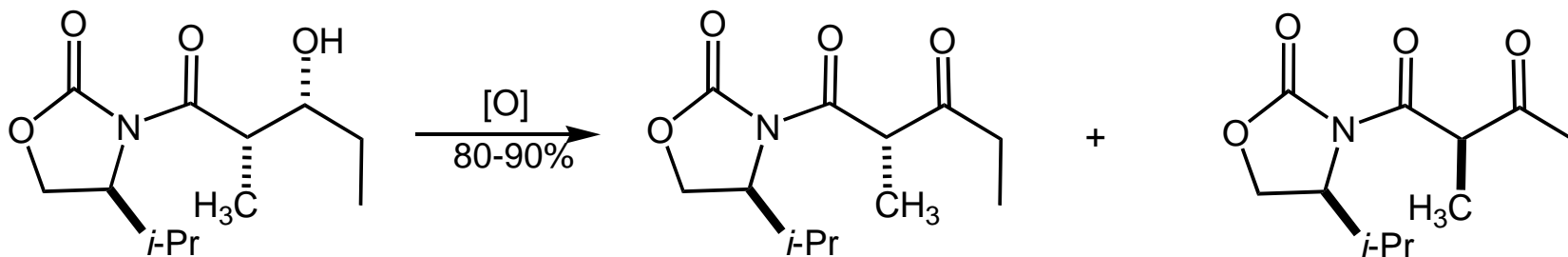
positives

Very mild conditions
Reactions are very fast and reliable
Never go to acid
Inexpensive and nontoxic reagents

negatives

Carbodiimide-derived urea hard to remove in Moffatt
(use of EDCI partially addresses this problem)
Operationally more involved than some other methods
(but still pretty easy)
Pummerer rearrangement can interfere (see below)
DMS angers the biologists

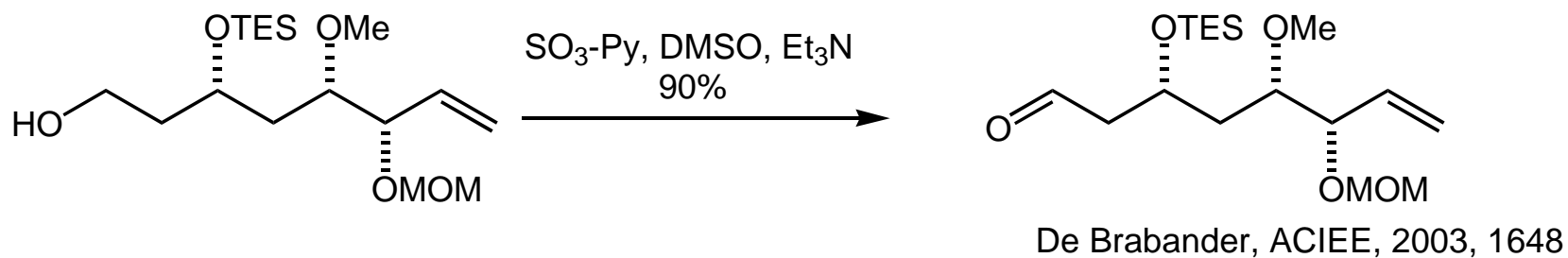
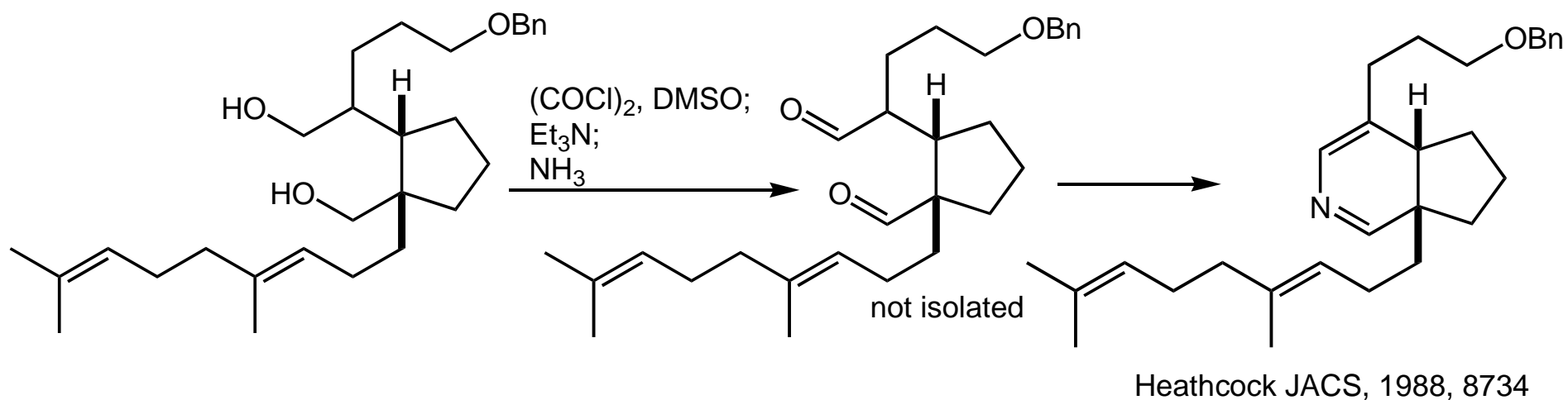
Examples



$[\text{O}]$	Ratio
$\text{CrO}_3, \text{Py}, \text{rt}$	73:27
Jones	79:21
PCC	92:8
PDC, Py, TFA	97:3
$\text{SO}_3\text{-Py}, \text{DMSO}, \text{Et}_3\text{N}, 0^\circ\text{C}$	99:1

Activated DMSO oxidations

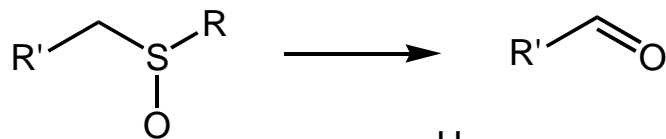
Applications



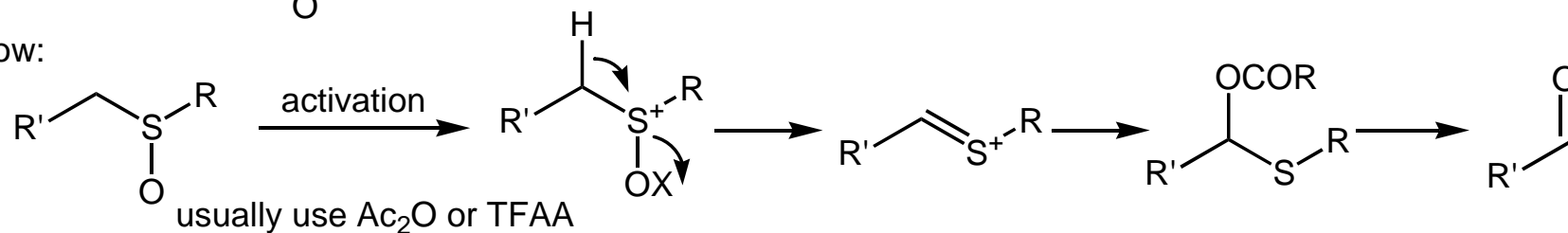
Limitations and Extensions of DMSO-based oxidations: the Pummerer Reaction

review: Org. React. 1991, 157

What:

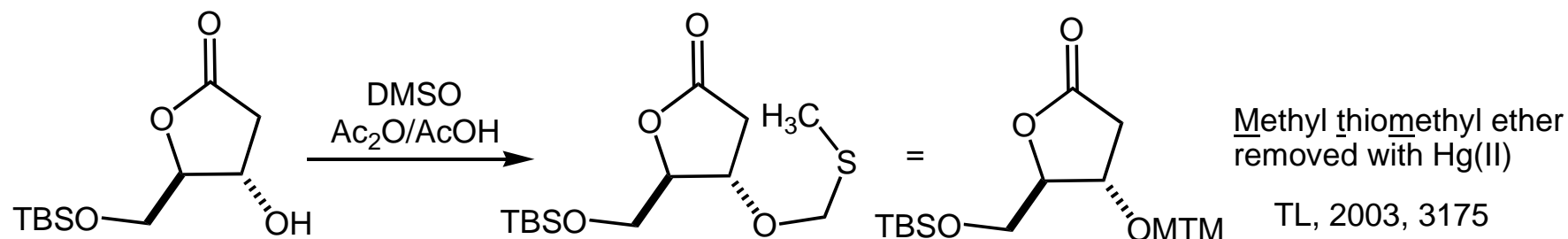


How:

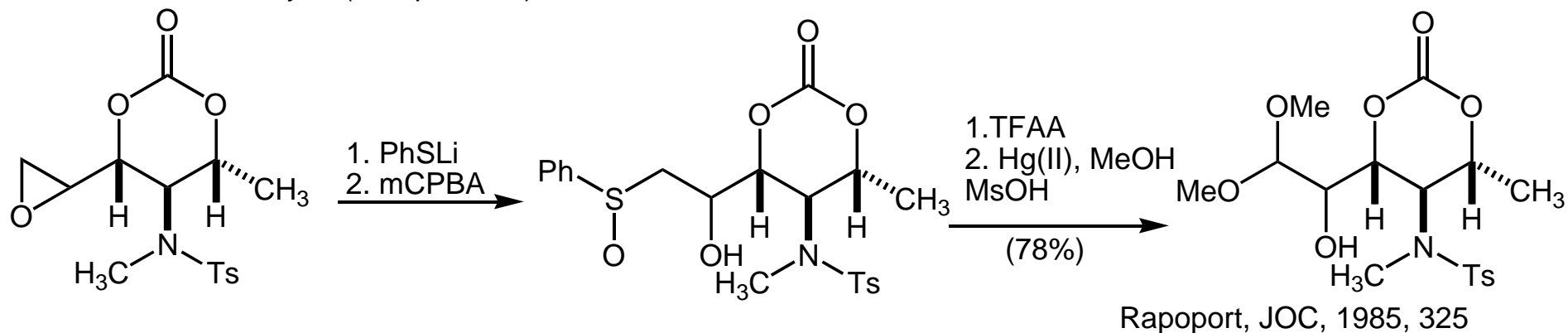


Why:

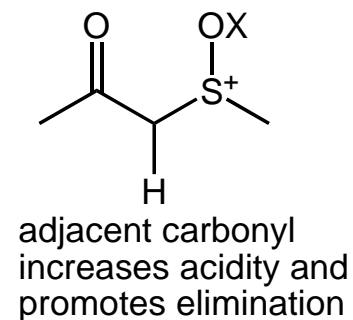
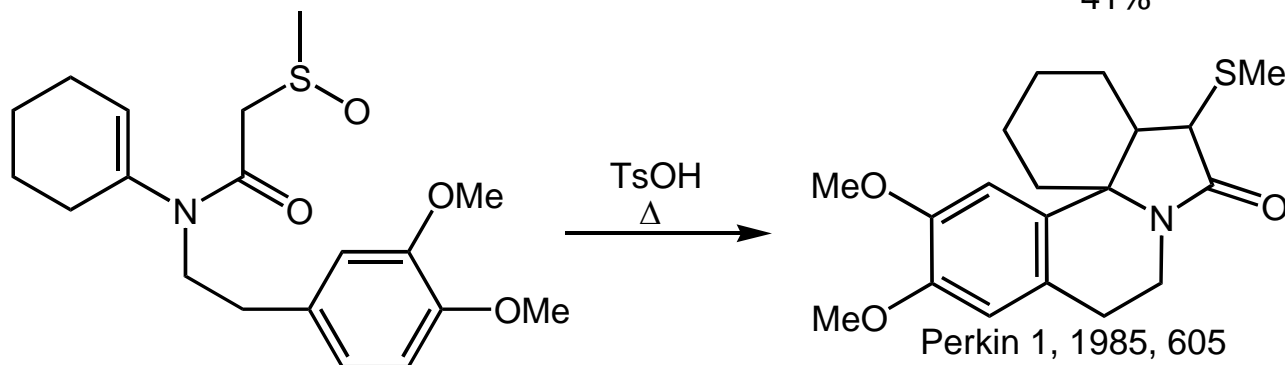
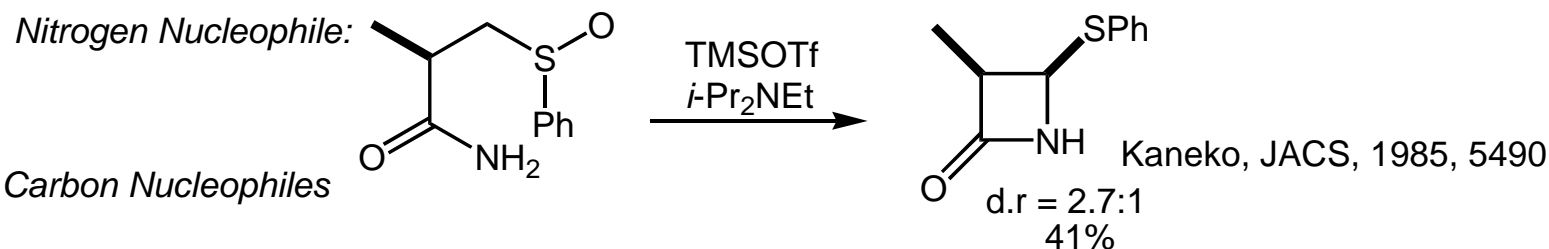
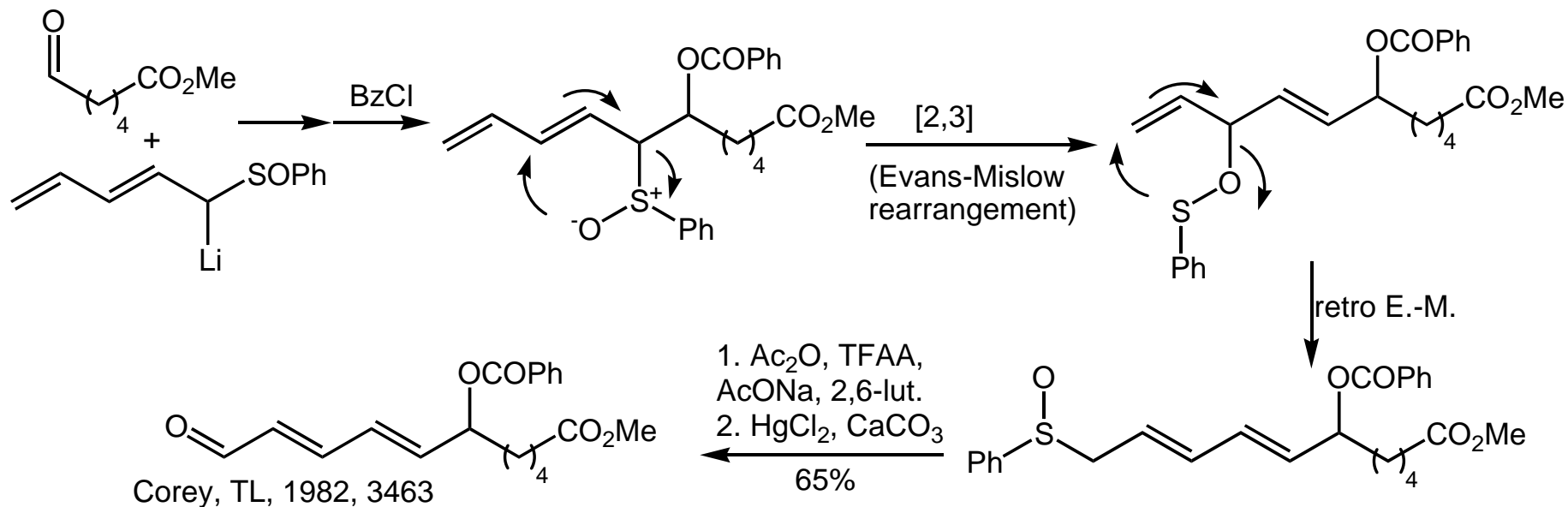
install protecting group



introduce aldehyde (or equivalent):

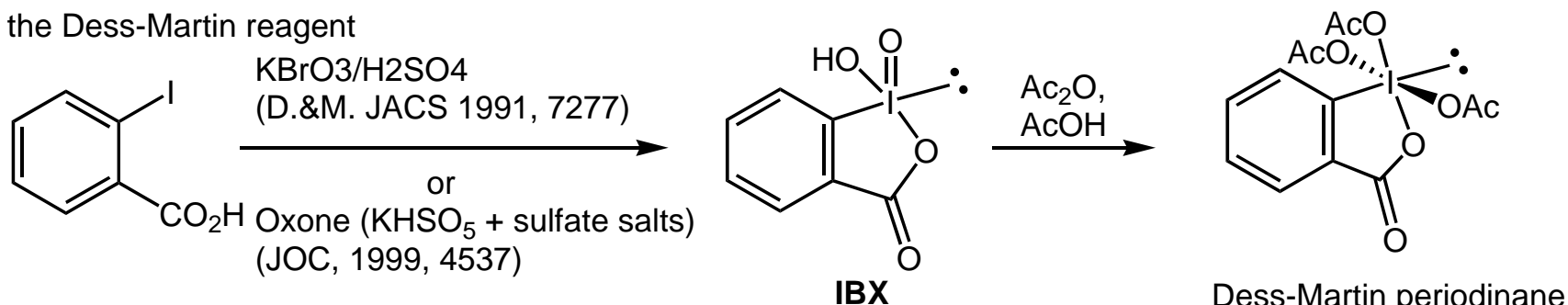


Limitations and Extensions of DMSO-based oxidations: the Pummerer Reaction, cont.



Hypervalent Iodine-based reagents

the Dess-Martin reagent



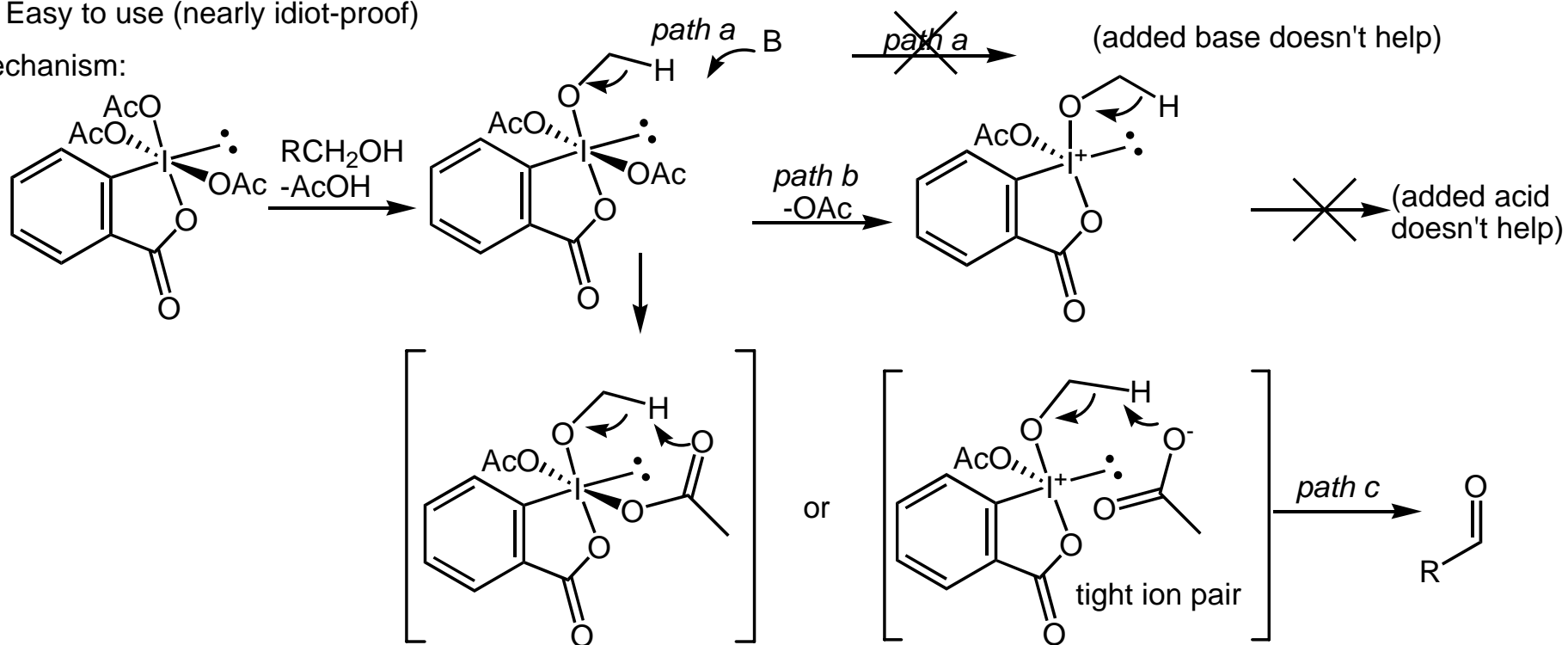
low solubility in most organic solvents (but, see below)
explosive on impact or >200°C

Commercially available

Advantages of DMP:

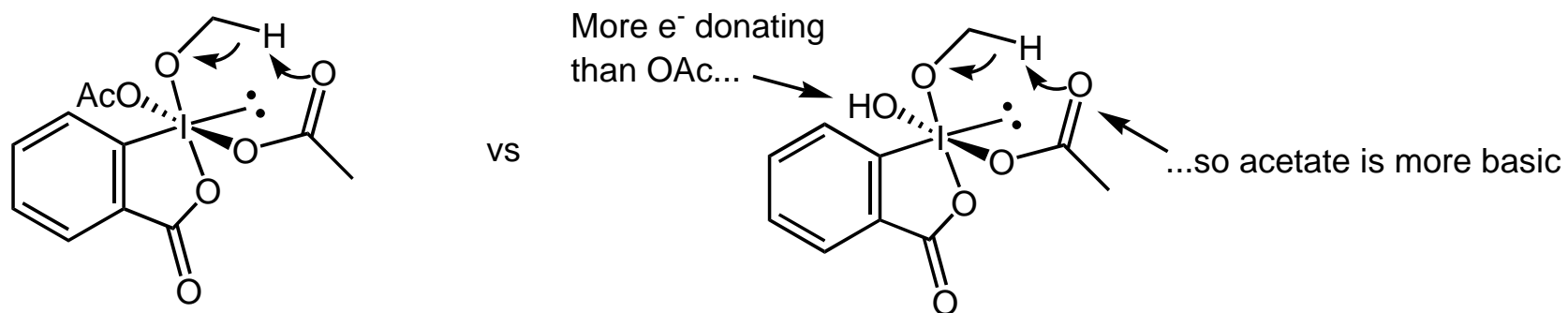
- Reliable with complex molecules
- Often need ~1 equiv
- Effective for 1° or 2° ROH; never go to acid
- Easy to use (nearly idiot-proof)

Mechanism:

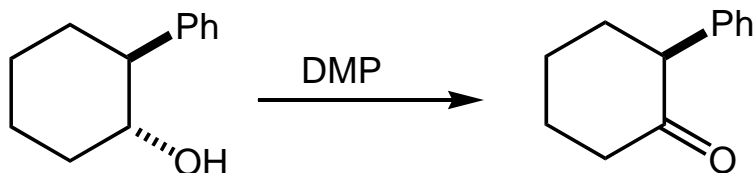


Hypervalent Iodine-based reagents

one equivalent of water was found to accelerate the reaction: Schreiber, JOC, 1994, 7549



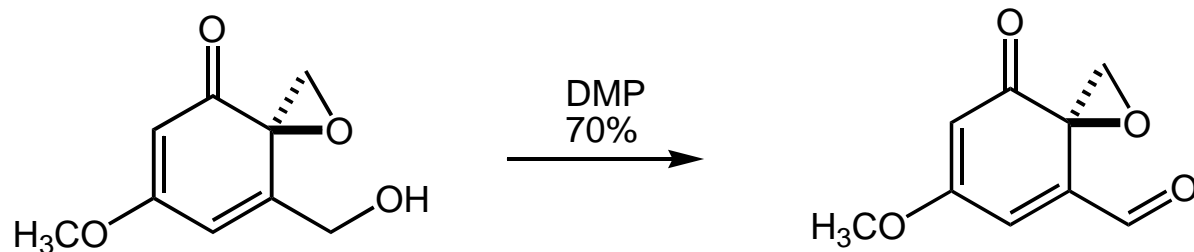
in practice, often easiest to use CH₂Cl₂ out of the bottle (not distilled)



conditions	results
Dry CH ₂ Cl ₂	97%, 14h
1.1 equiv H ₂ O	97% 0.5h

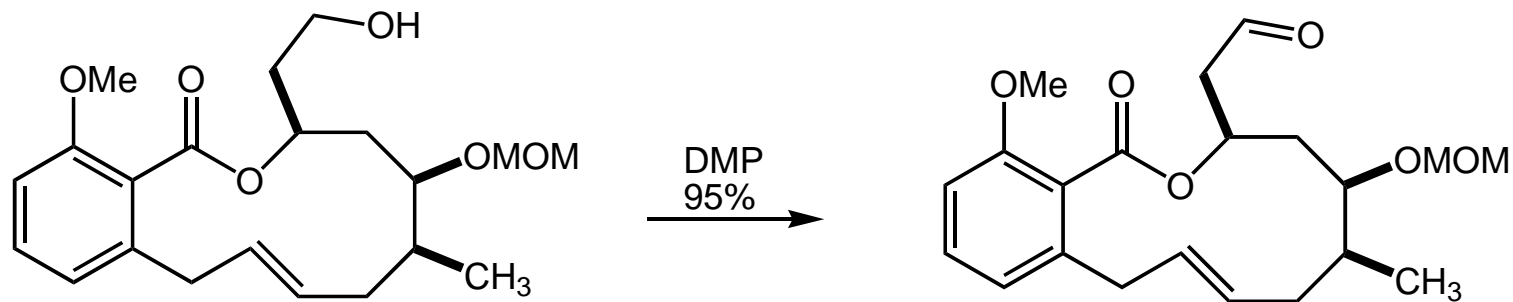
Other examples:

SciFinder search yielded 104,000 hits for DMP

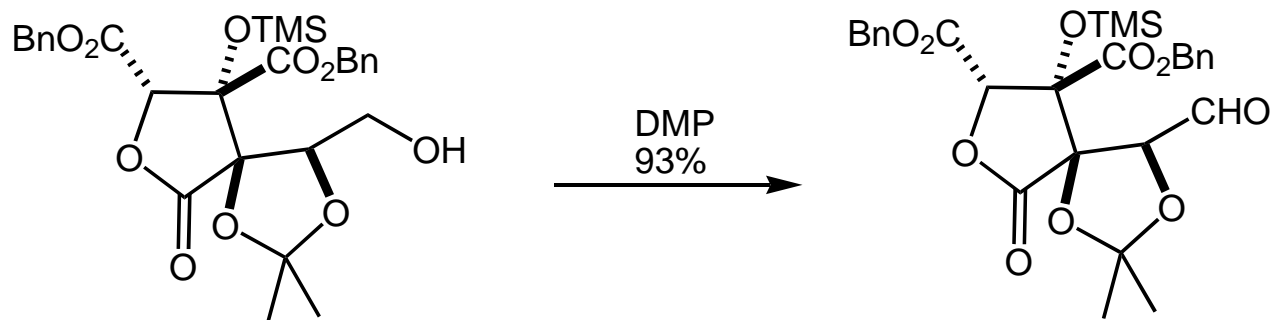


Danishefsky, JACS, 1988, 6890

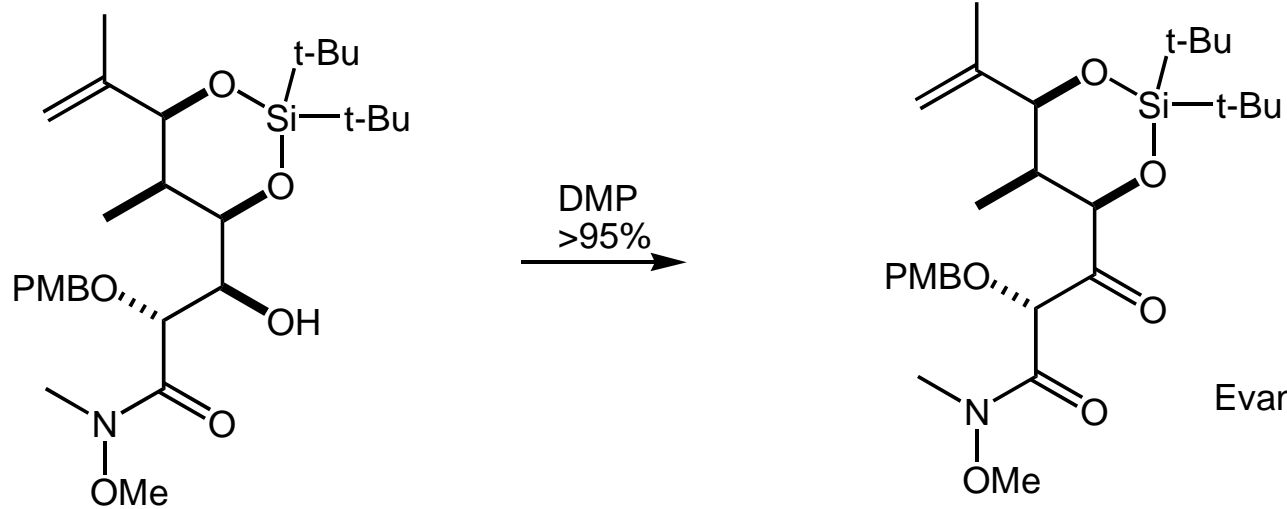
Hypervalent Iodine-based reagents: examples



De Brabander, JACS, 2002, 3245

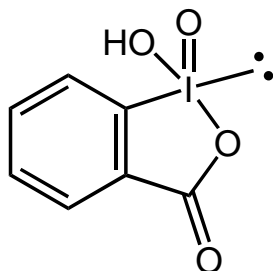


Nicolaou, ACIEE, 1994, 2184



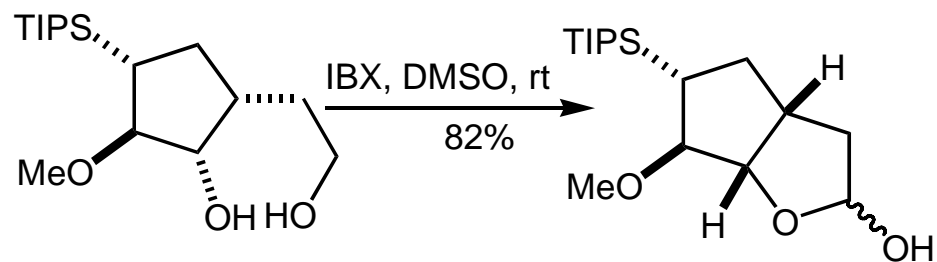
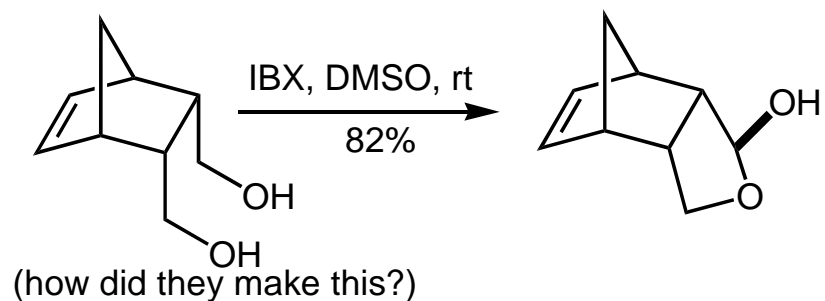
Evans, JACS, 1990, 7001

IBX



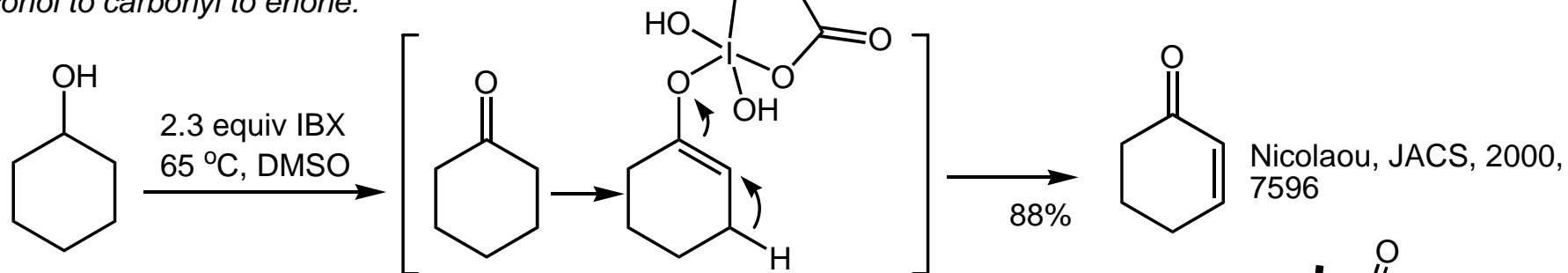
Insoluble in most organic solvents, but somewhat soluble in DMSO. For alcohol to carbonyl, see TL, 1984, 8019 (why did it take 10 years for someone to try DMSO??)

diol to lactone:

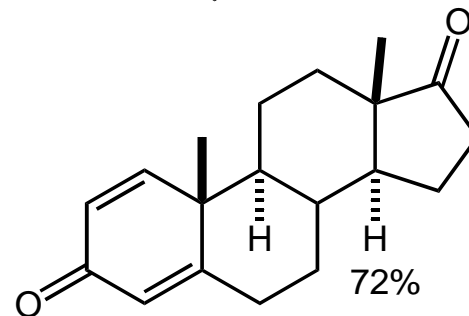
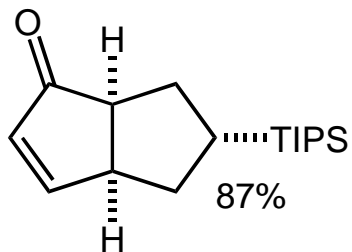
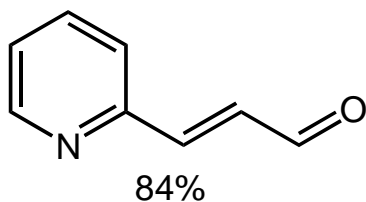


Corey, TL, 1995, 3485

alcohol to carbonyl to enone:



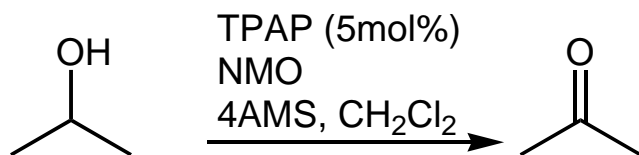
other examples



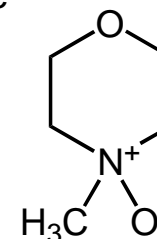
TPAP

reviews: Ley, Synthesis, 1994, 639

Ru(VII) is a strong oxidant
reacts rather indiscriminately as basic, aq solution
Tetra-alkyl ammonium counterion modulates reactivity
most successful recipe:

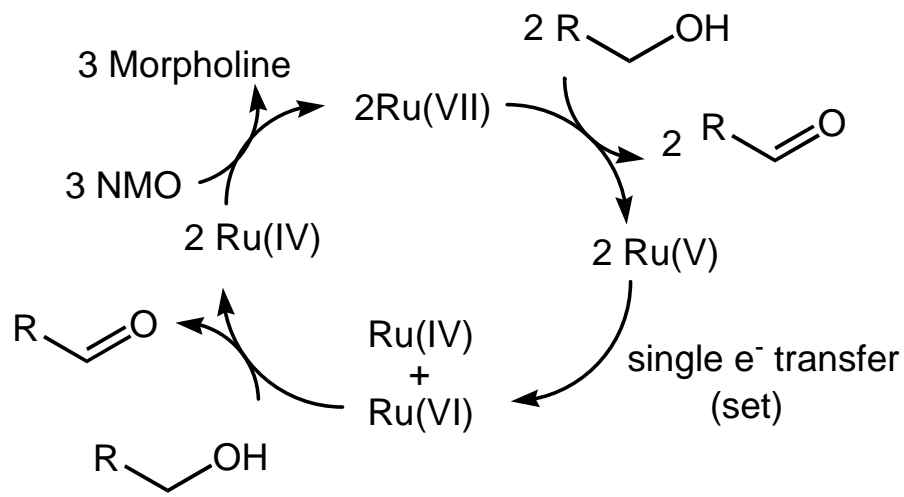
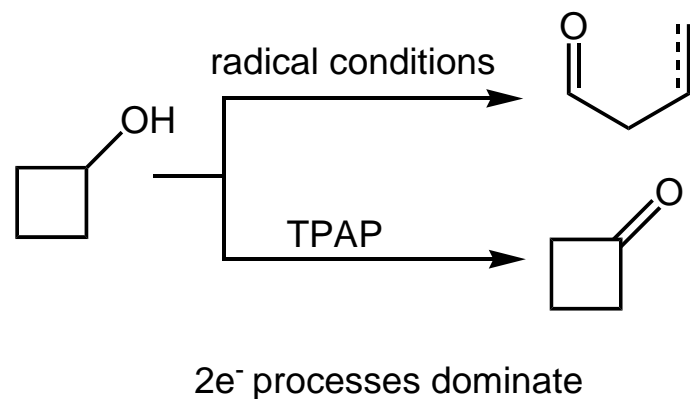


TPAP = [n-Pr₄N][RuO₄] = TetraPropylAmmonium Perruthenate
NMO = N-Methyl Morpholine N-Oxide

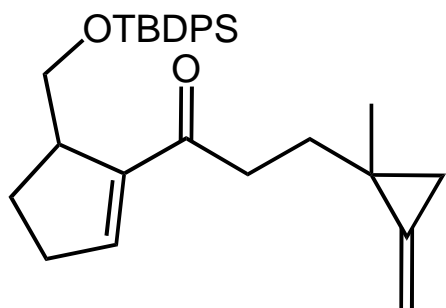
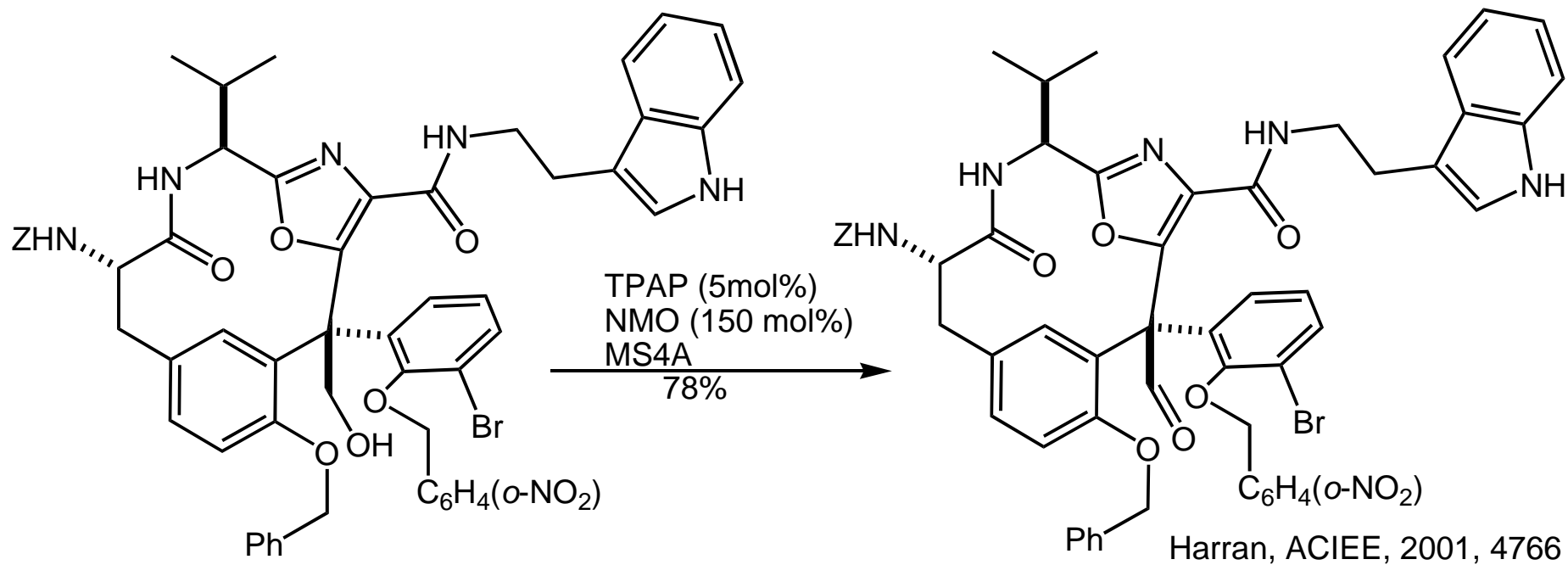


Advantages:
Homogeneous solutions
Easy setup/workup
Suitable for complex molecules

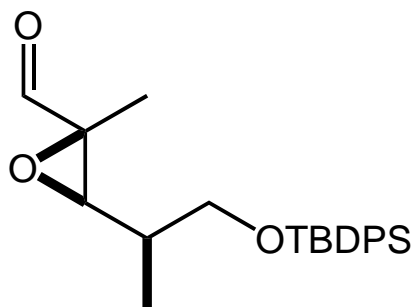
Mechanism: Problem is how to use a 3e⁻ oxidant for a 2e⁻ oxidation?



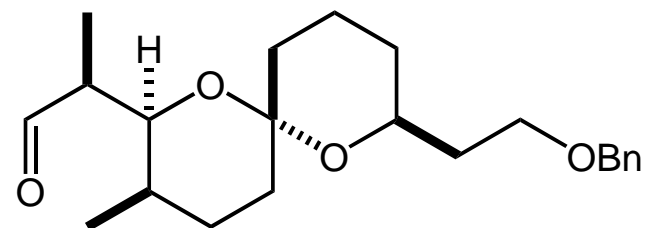
TPAP: examples



TPAP: 70%
Swern: 38%
MnO₂: 0%



TPAP: 70%
Swern: 35%

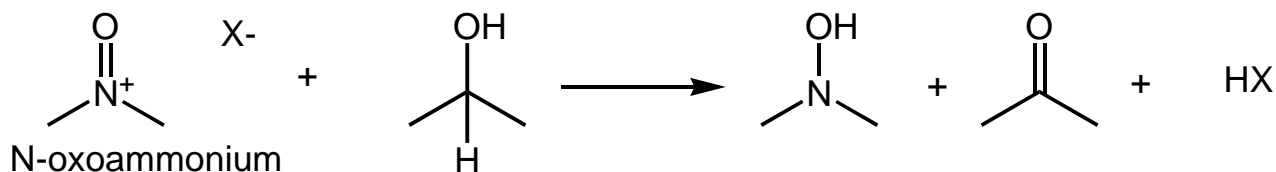


TPAP: 91%

N-oxoammonium mediated oxidations

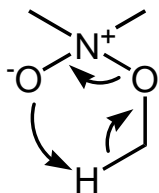
reviews: *Synthesis*, 1996, 1153; *Heterocycles*, 1988, 509

overall transformation:

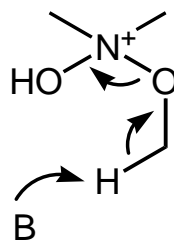


Mechanism:

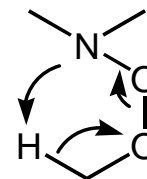
3 proposals in the literature



similar to Cope elimination



similar to Hofmann elimination

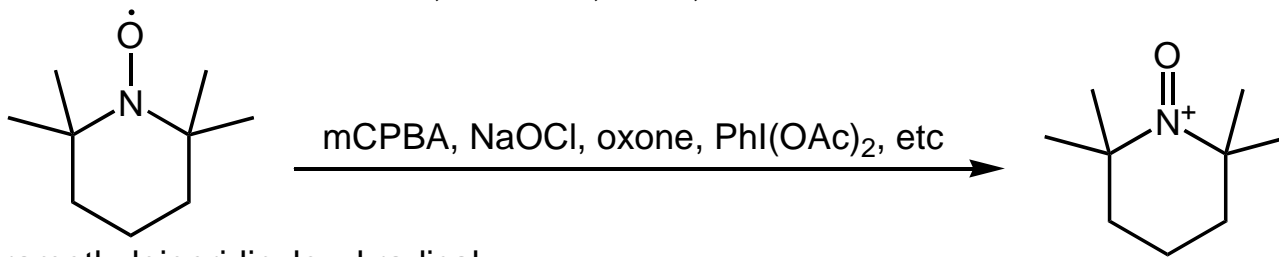


Ganem, *JOC*, 1975, 1998-2000; Semmelhack, *TL*, 1986, 1119; Bobbitt, *JOC*, 1991, 6110

N-oxoammonium salts are too unstable to store; always prepared in situ using catalytic nitroxyl radical and stoichiometric oxidant.

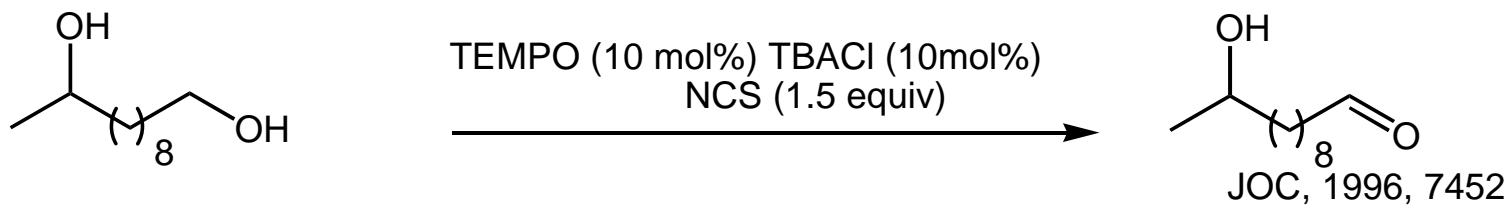
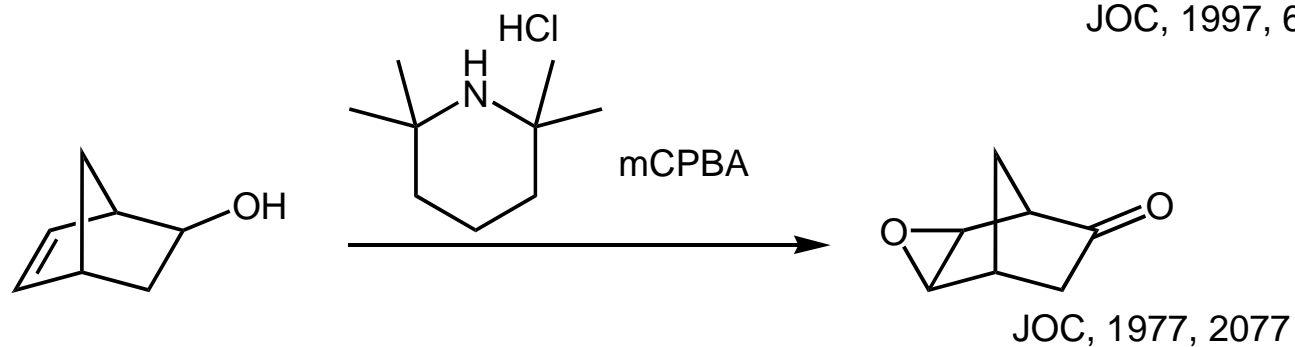
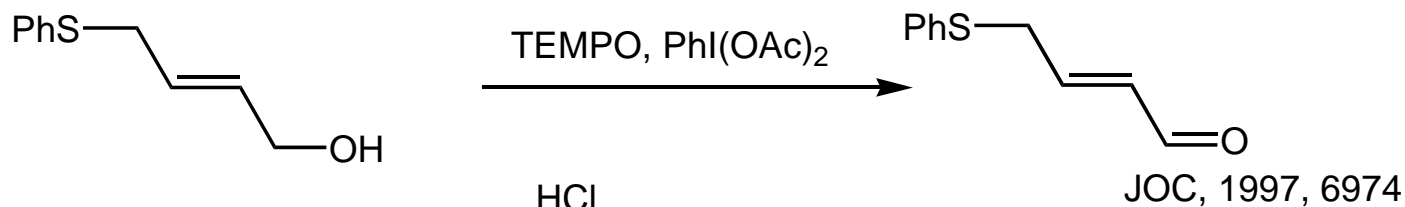
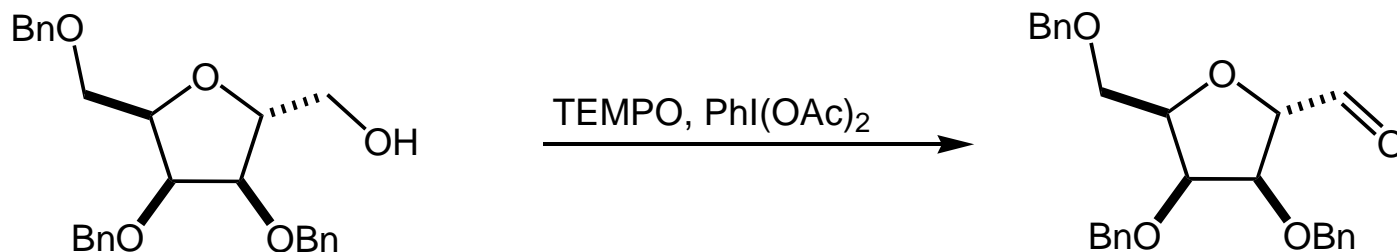
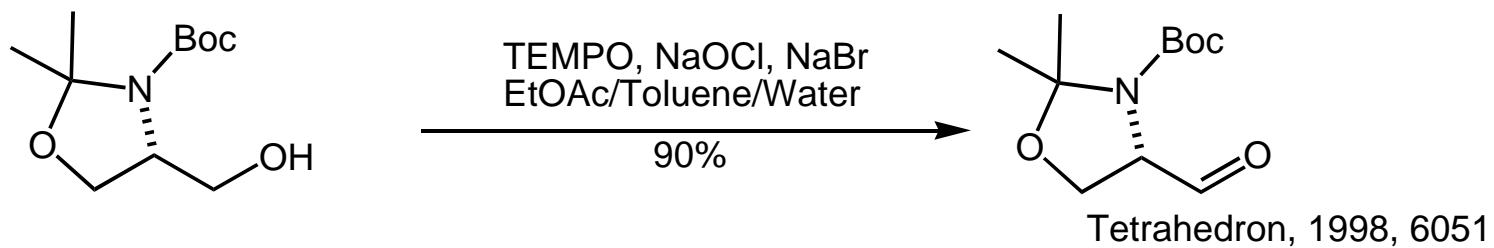
TEMPO is most successful. Catalyzes oxidation of 1° and 2° alcohols to aldehydes and ketones.

For a list of stoichiometric oxidants, see *JOC*, 1997, 6974



2,2,6,6 tetramethylpiperidinyloxy radical
(TEMPO)

N-oxoammonium mediated oxidations: examples



MnO₂

Metal oxide used for selective oxidation of allylic and benzylic alcohols; other pathways available

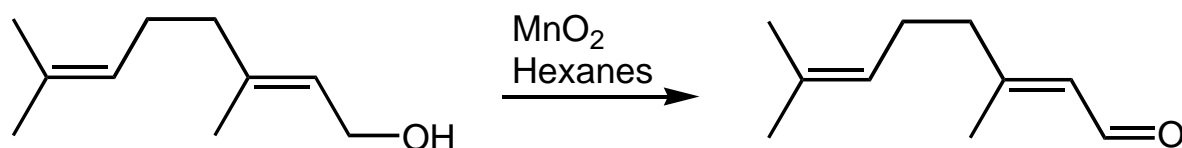
'MnO₂' only an approximation, really MnO_x where 1.93 < x < 2

Old batches can go bad; for preparation recipes, see *Encyclopedia of Reagents for Organic Synthesis*

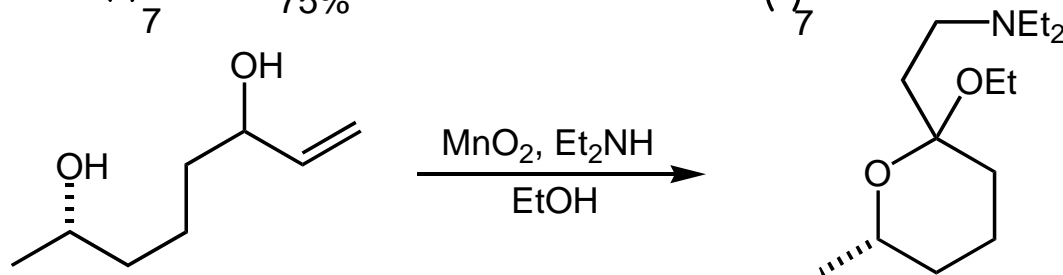
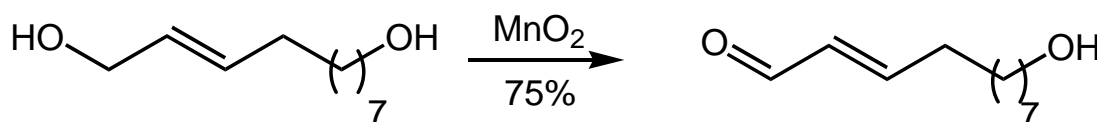
Et₂O or hydrocarbon solvents most common

Alcoholic solvents slow reaction, so can be used to enhance selectivity

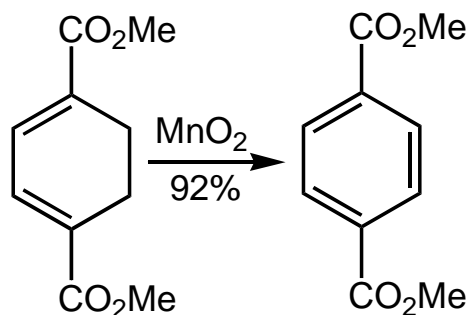
Usually use excess (5:1 by wt good starting point)



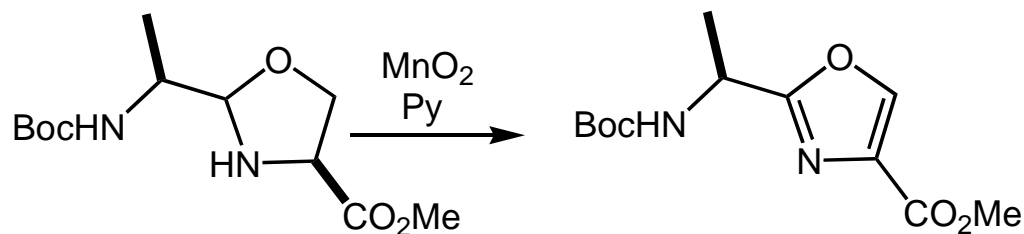
Corey, JACS, 1968, 5616



other reactions:



diol cleavage can be a problem



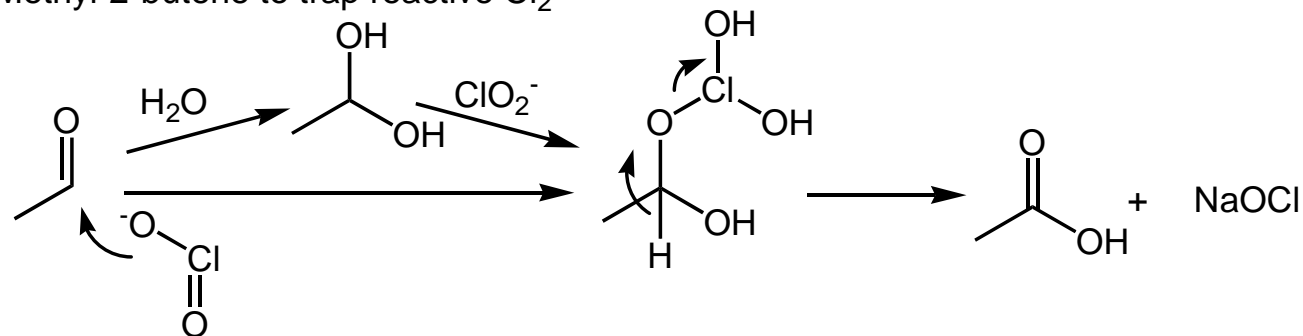
Sodium Chlorite (NaClO_2)

Reagent of choice for aldehyde \rightarrow acid

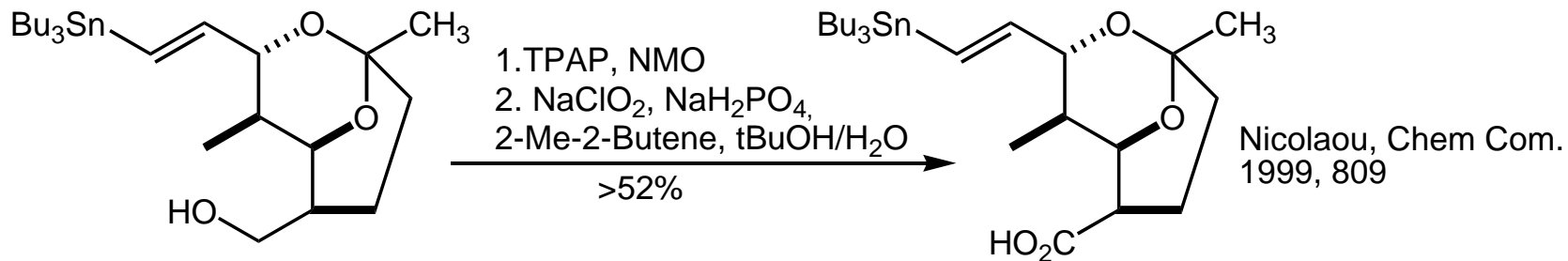
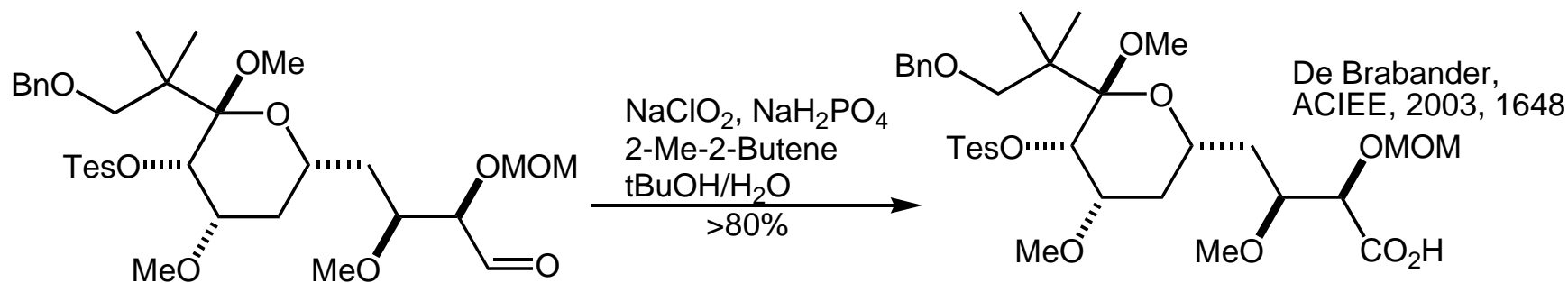
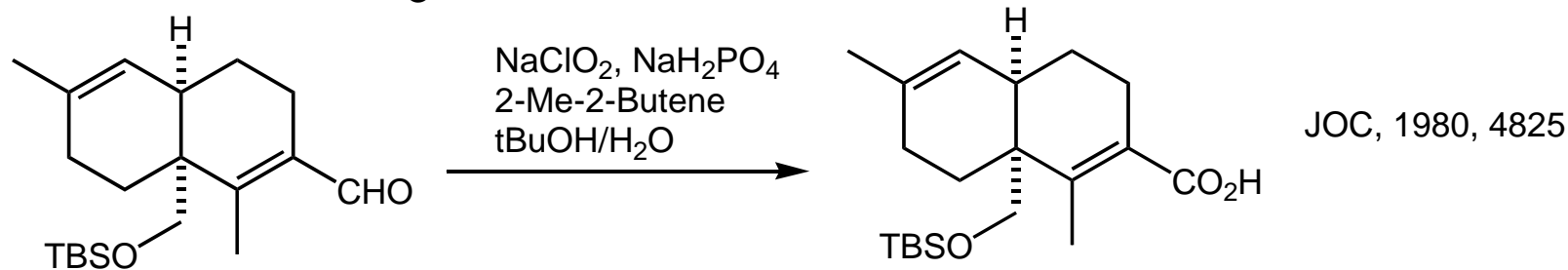
Often see 2 step (e.g. Swern + NaClO_2) rather than Jones Oxidation

Usually include 2-Methyl-2-butene to trap reactive Cl_2

mechanism:

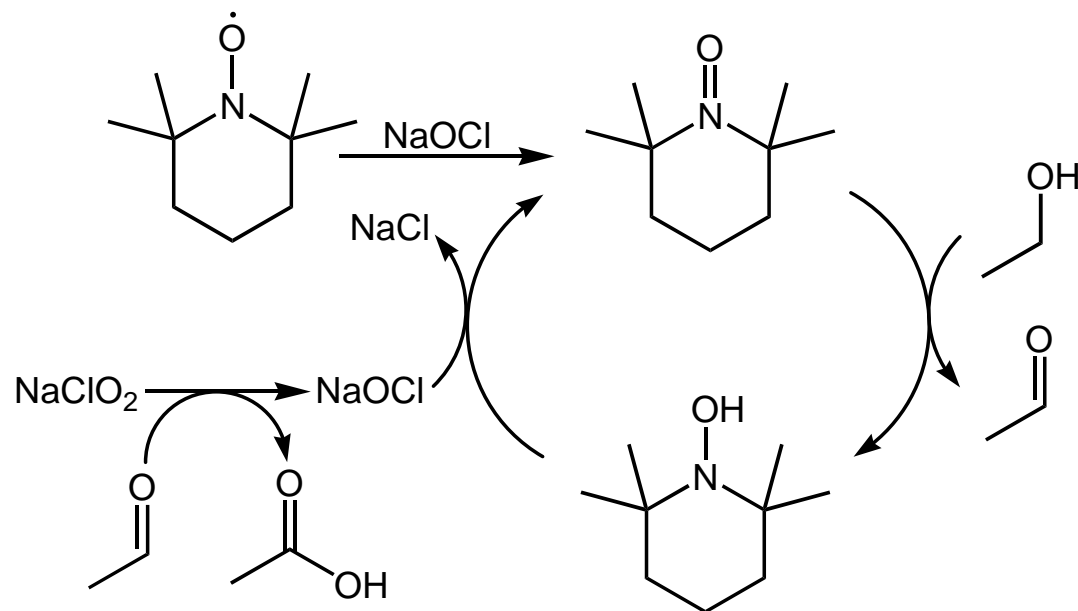
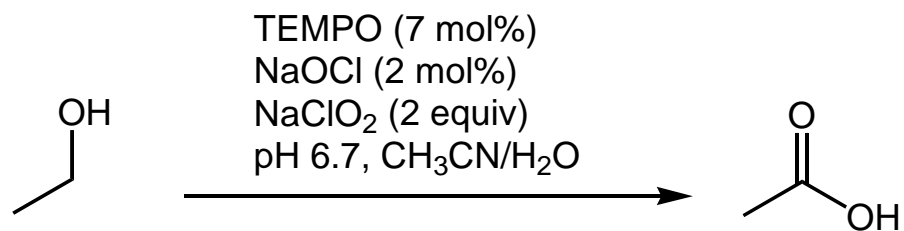


examples:

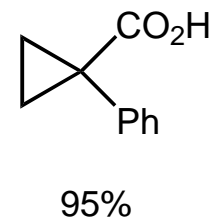
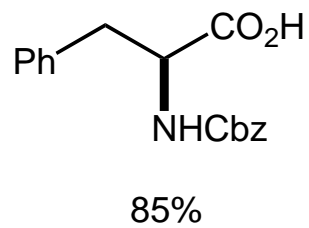
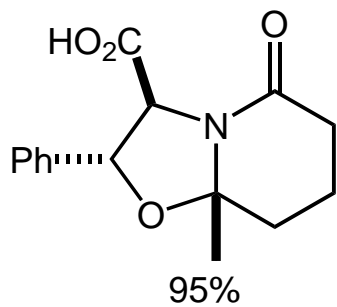


NaClO₂/TEMPO

A one pot method for alcohol --> acid has been developed by Merck Process
JOC, 1999, 2564

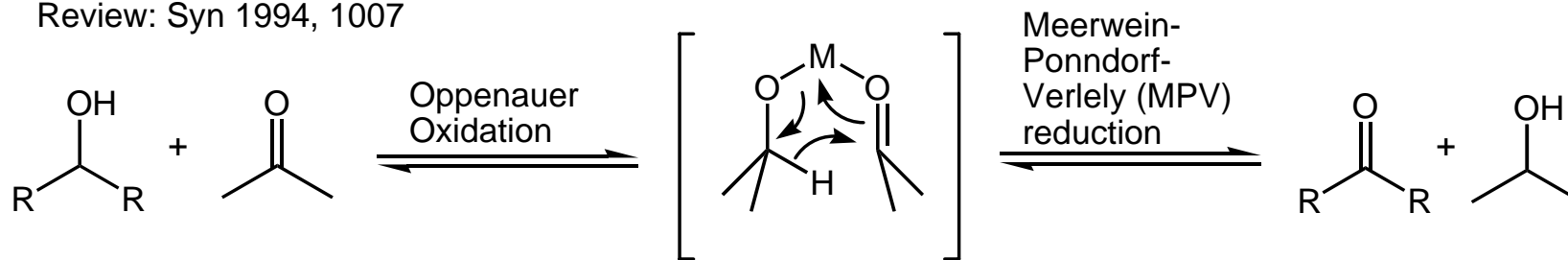


Examples



Oppenauer Oxidation

Review: Syn 1994, 1007



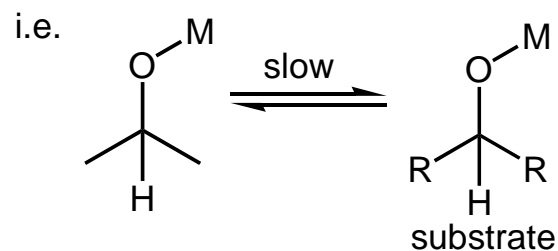
M is usually hard Lewis acid
Al, Zr, Ti, La most common
-Lewis acid activation of carbonyl
-Alkoxide formation
-Preorganization

Oppenauer and MPV infrequently used

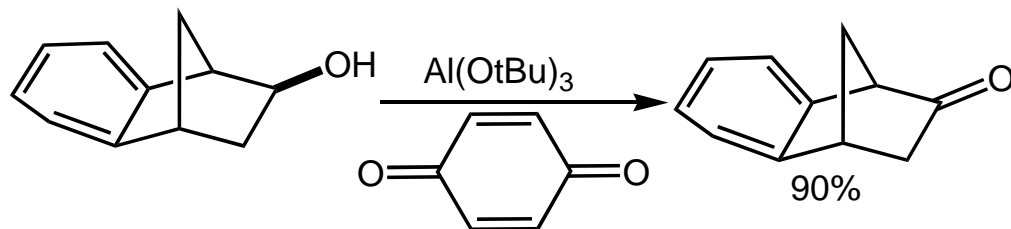
Mild conditions, never go to acid

Thermodynamic control

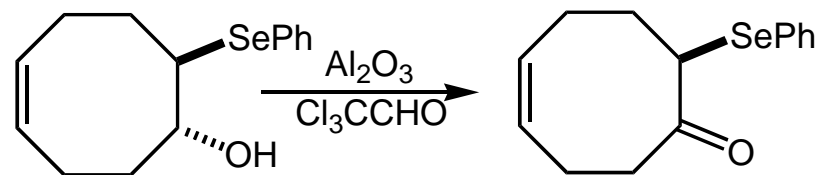
Can see product inhibition (requires high [catalyst]):



examples



JACS, 1960, 1240



TL, 1977, 3227