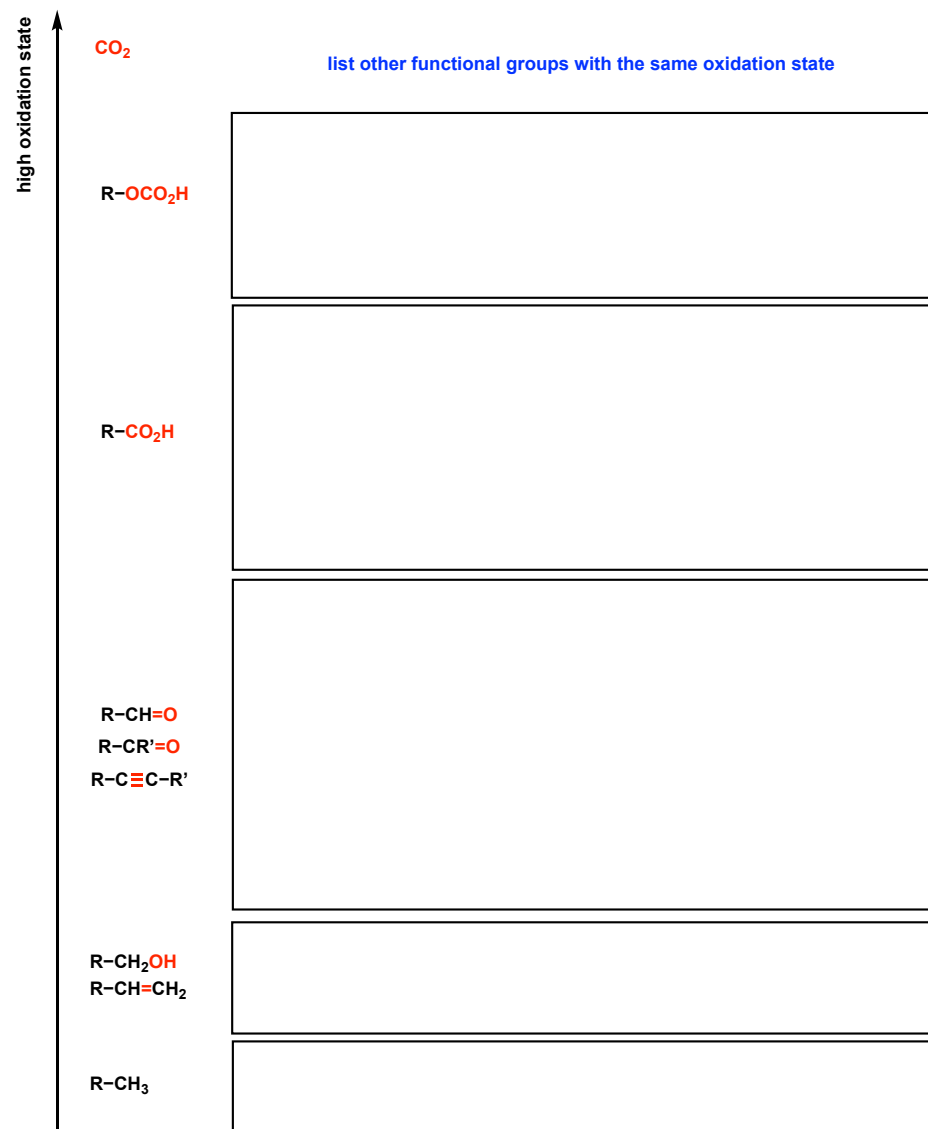
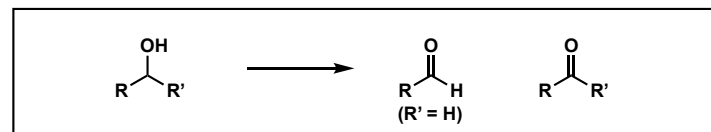


Oxidation: Transformations that increase the oxidation states of a functional group.

Oxidation states in organic molecules

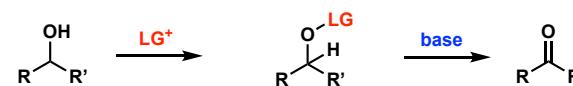


1. Oxidation of alcohol to aldehyde and ketone

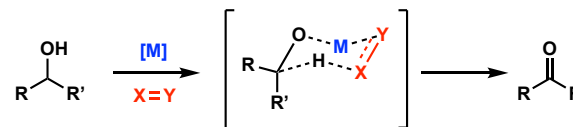


General mechanistic considerations

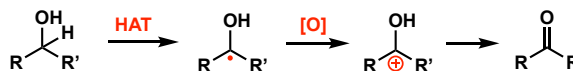
Type I



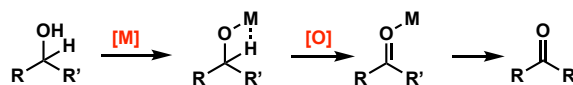
Type II



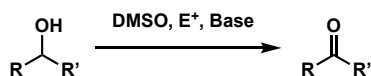
Type III



Type IV



A. DMSO mediated oxidation



Reviews: Chem. Rev. 1967, 67, 247; Tetrahedron 1978, 34, 1651; Synthesis 1981, 165; Org. React. 1990, 39, 297

Conditions:	DMSO, COCl ₂ , Et ₃ N	Swern
	DMSO, DCC, TFA, pyridine	Moffatt-Pfitzner Moffatt JACS 1966, 88, 1762
	DMSO, SO ₃ ·pyr, Et ₃ N	Parikh-Doering
	DMSO, Ac ₂ O	Albright-Goldman

Mechanism (Swern [O] as an example):

Swern T 1978, 34, 1651
Moffatt JACS 1966, 88, 1762

A related reaction: Corey-Kim Oxidation

Me₂S, NCS

Mechanism

Corey JACS 1972, 94, 7586

A possible side reaction

Mechanism

Swern T 1978, 34, 1651

A related reaction: Pummer rearrangement

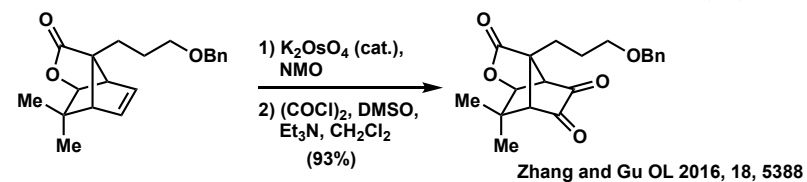
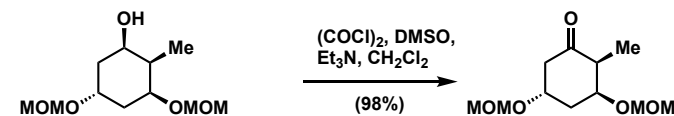
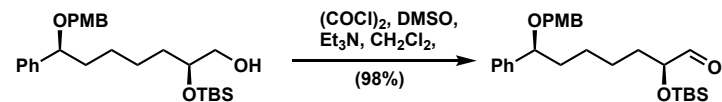
Mechanism

Pummer CB, 1909, 42, 2282

a. Swern oxidation

DMSO, (COCl)₂, Et₃N, low temperature

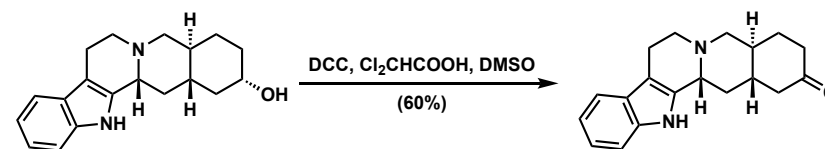
- careful control of T
- work well on both large and small scale (can use excess reagents)
- be careful when concentration is >0.2 M, rxn must be well stirred



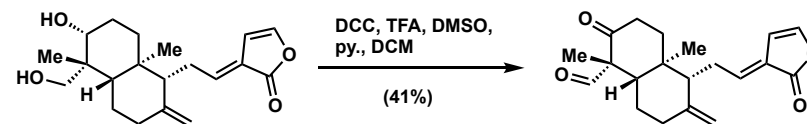
b. Moffatt-Pfitzner oxidation

DMSO, DCC, pyridine/acid

- works well at RT
- work well on both large and small scale (can use excess reagents)
- use of DCC can be operationwise problematic



Y. Qin Chem 2017, 2, 803

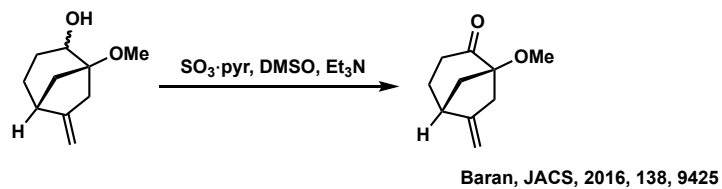
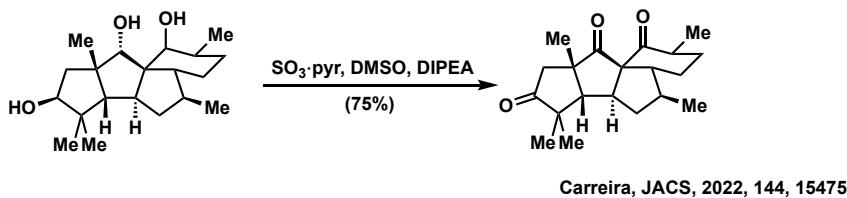


Bioorganic Med. Chem. Lett. 2014, 24, 2353

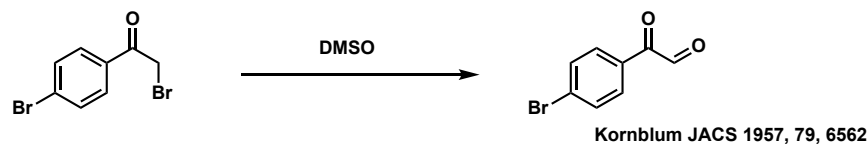
c. Parikh-Doering oxidation

DMSO, SO₃·pyr, Et₃N

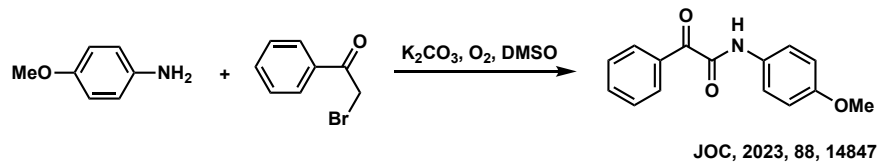
- typically 0 °C to RT
- excess of reagent required
- dump-and-stir
- easy to scale up



d. Kornblum oxidation

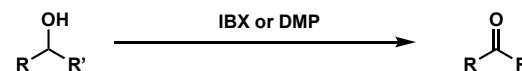


Mechanism:



B. Hypervalent iodine mediated oxidation

IBX and Dess-Martin Periodinane



preparation of reagent

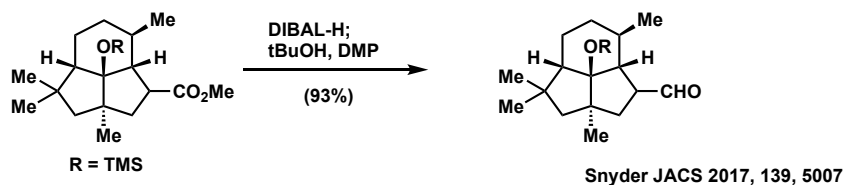
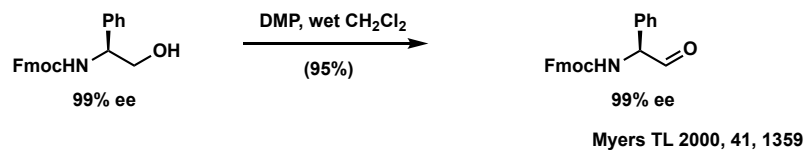
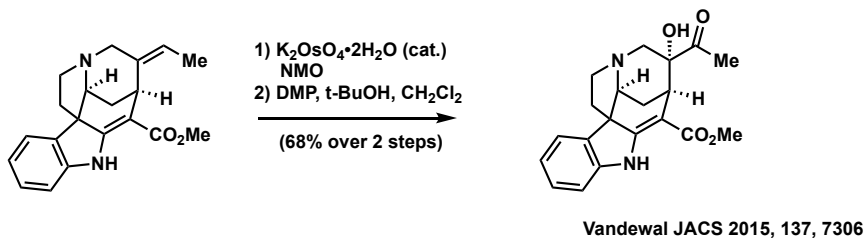
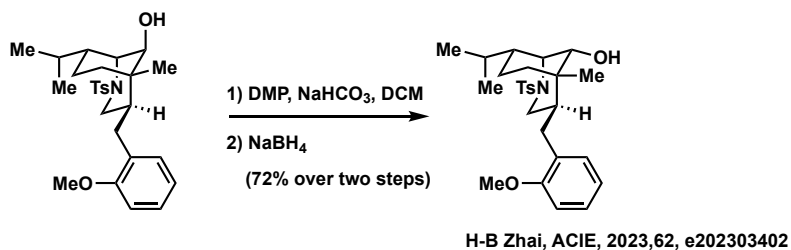
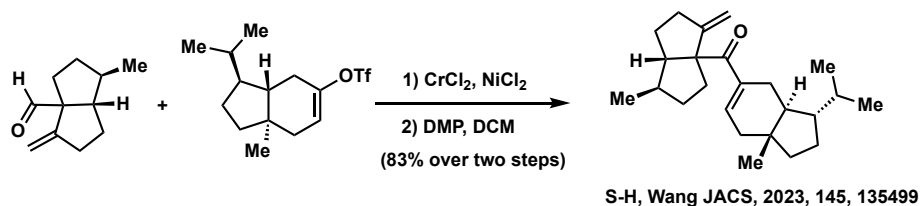
a. Dess-Martin Periodinane (DMP) oxidation

- mild
- short rxn time
- acidity can be buffered with NaHCO₃ or pyr
- sometimes add H₂O or tBuOH to accelerate the rxn

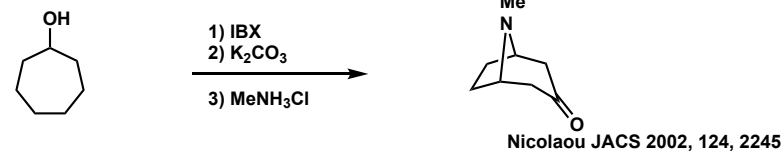
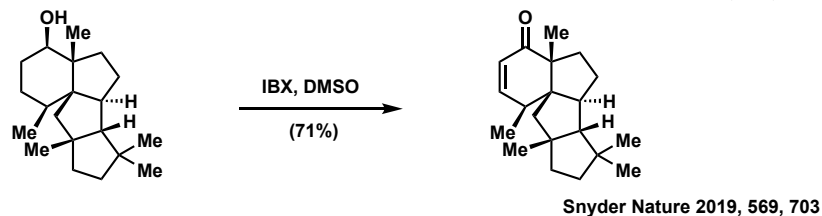
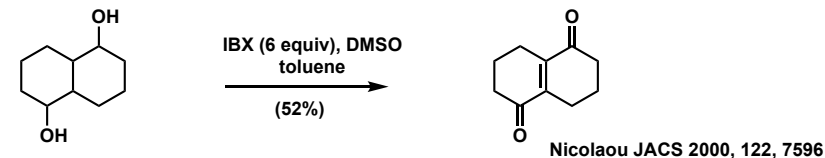
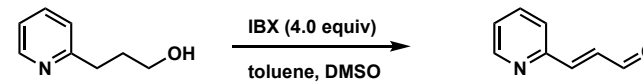
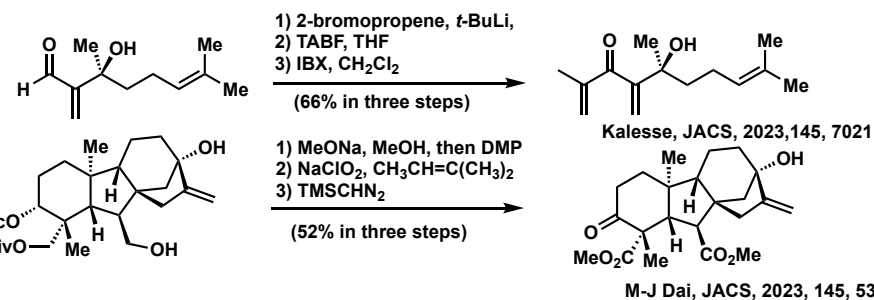
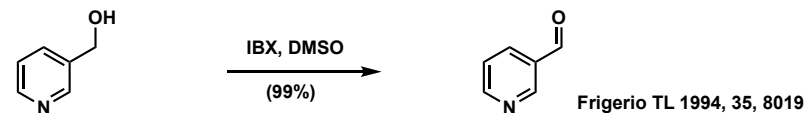
Mechanism

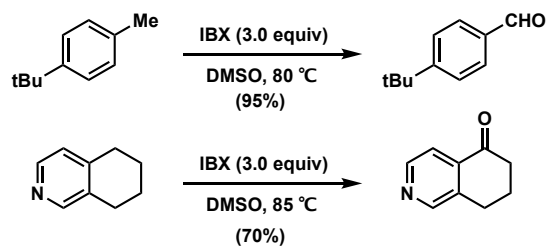
- Addition of H₂O or tBuOH can generate of an intermediate that is analogous to II. II decompose more rapidly than I to give the product.

Dess, D. B.; Martin, J. C. JACS 1991, 113, 7277

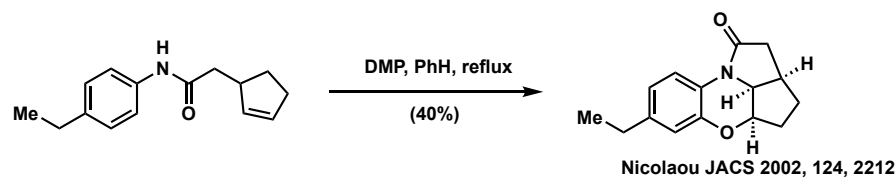
b. *o*-iodoxybenzoic acid (IBX) oxidation

- mild
- often use DMSO as solvent
- can further oxidize ketone/aldehyde to unsaturated carbonyls
- upon heating, IBX can oxidize benzylic positions and promote cyclizations





Nicolaou JACS 2001, 123, 3183



Mechanism

C. Cr(VI)-based oxidation

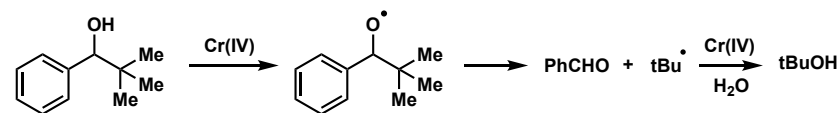
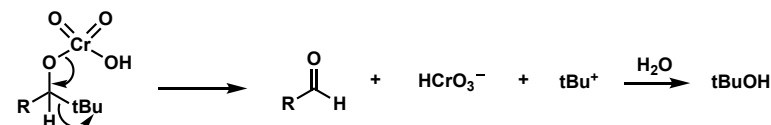
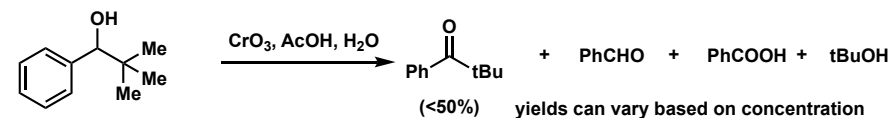
$\text{CrO}_3 \cdot 2\text{pyr}$	Collins reagent
$\text{CrO}_3 \cdot \text{pyr} \cdot \text{HCl}$	PCC
$\text{CrO}_3 \cdot 2\text{pyr} \cdot \text{HCl}$	PDC
$\text{CrO}_3 + \text{H}_2\text{SO}_4$	Jones reagent

Mechanism: Using chromic acid-mediated oxidation as an example:

A competing radical pathway:

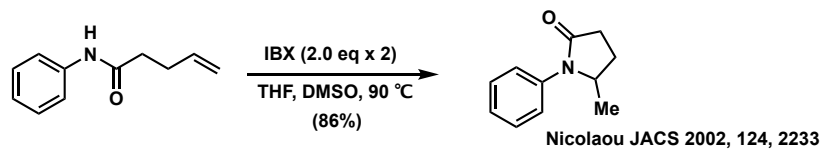
Wiberg JACS 1973, 96, 1884; 1889

- Oxidation of hindered substrate can lead to low yield and generation of by-product



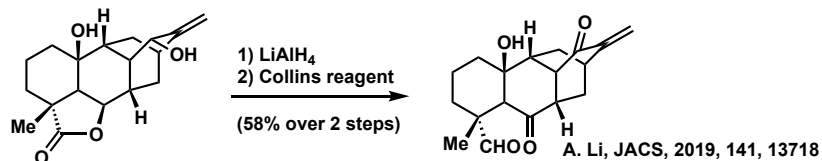
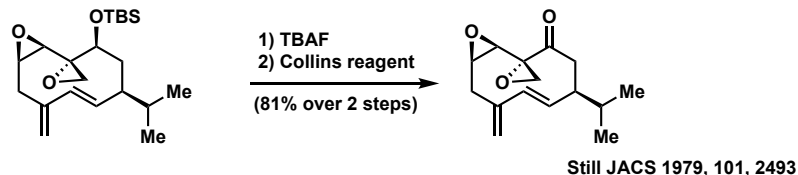
Westheimer JACS 1955, 78, 306

Mechanism

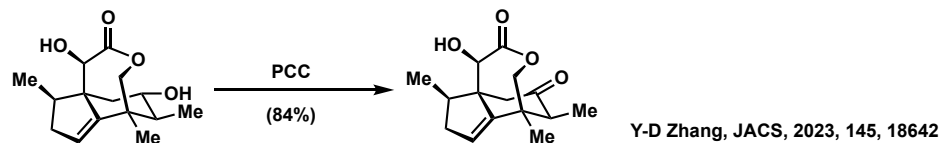
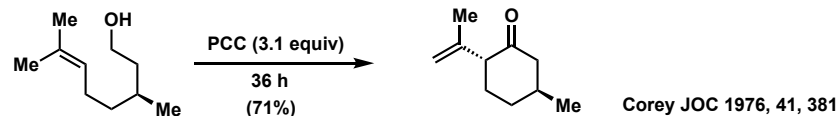
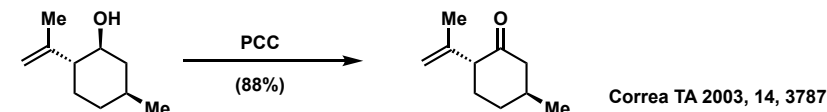


a. Collins reagent ($\text{CrO}_3 \cdot 2\text{pyr}$)

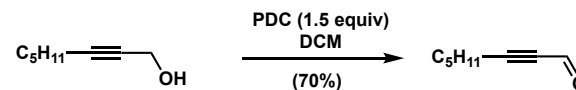
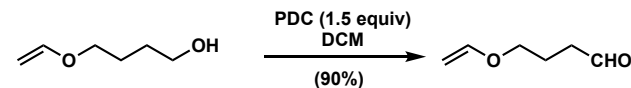
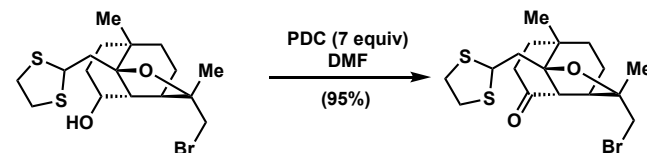
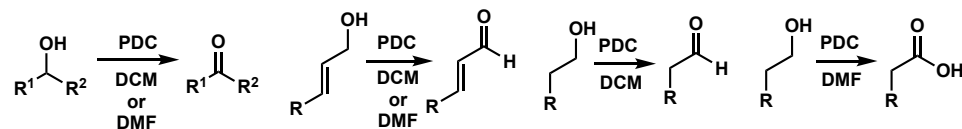
- hygroscopic, suggested in-situ preparation
- mild basic

b. Pyridinium Chlorochromate (PCC) ($\text{CrO}_3 \cdot \text{pyr} \cdot \text{HCl}$)

- bench stable, not hygroscopic
- DMF, CH_2Cl_2 as common solvent
- slightly acidic, can be buffered with NaOAc
- Molecular sieves can accelerate the reaction
- work-up simplified by adding powdered MS or silica gel

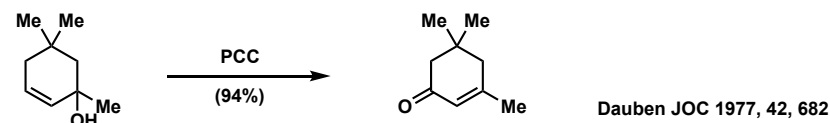
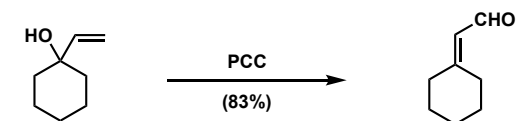
c. Pyridinium Dichromate (PDC) ($(\text{pyrH}^+)_2\text{Cr}_2\text{O}_7$)

- bench stable, not hygroscopic
- DMF, CH_2Cl_2 as common solvent; can impact reaction outcome

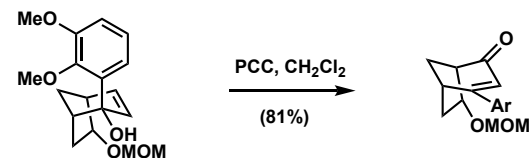
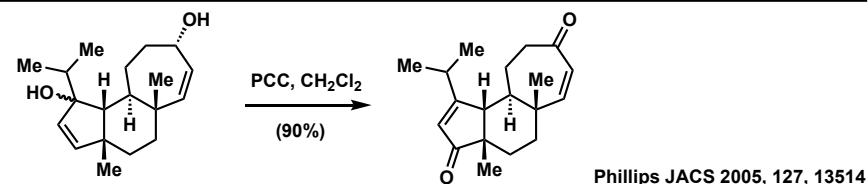


Corey TL 1979, 20, 399

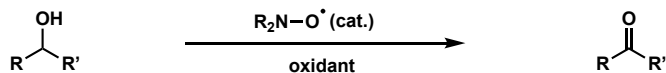
- Tertiary allylic alcohol with PCC afford rearranged enone products



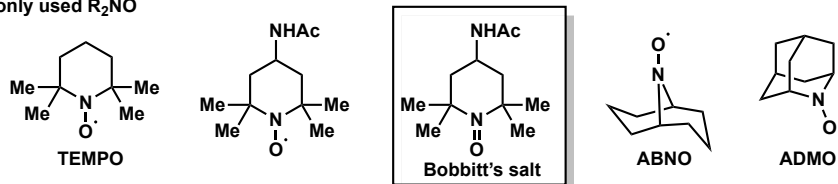
Mechanism



D. N-Oxoammonium based oxidation



- Commonly used $\text{R}_2\text{NO}^\bullet$

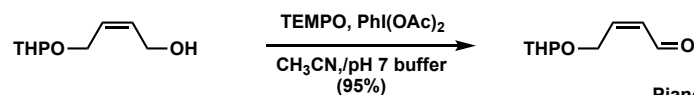
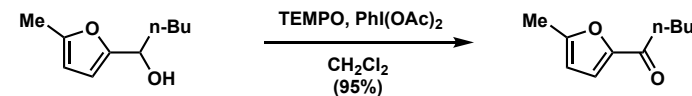
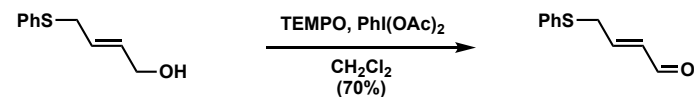


- Oxidant: NaClO , $\text{PhI}(\text{OAc})_2$, *m*-CPBA, NaBrO_2 , oxone, $\text{Cu}(\text{I})$ cat. + O_2 (Stahl oxidation)
- selectivity can be achieved between primary and secondary alcohols
- when CH_3CN was used as solvent instead of CH_2Cl_2 , oxidation of primary alcohol can give acid

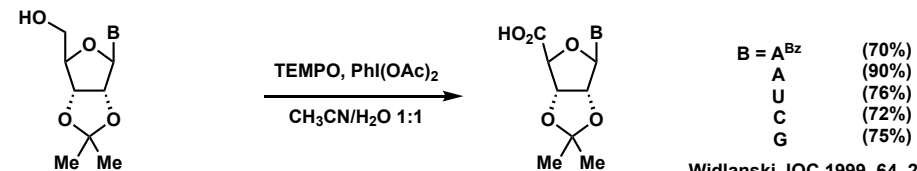
Mechanism

- The mechanism of oxidation under Stahl's conditions is different from the oxoammonium-based reactions. It likely proceed via a concerted electron transfer-substrate oxidation process.

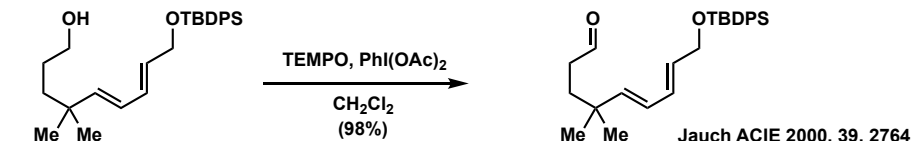
Mechanism



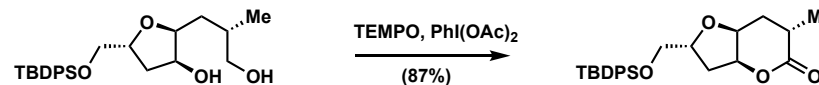
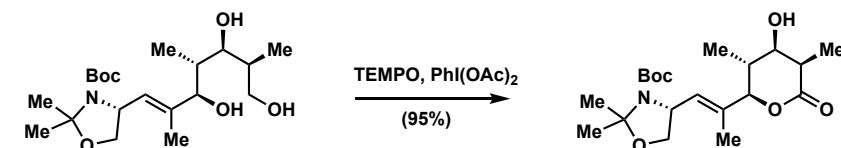
Piancatelli JOC 1997, 62, 6974



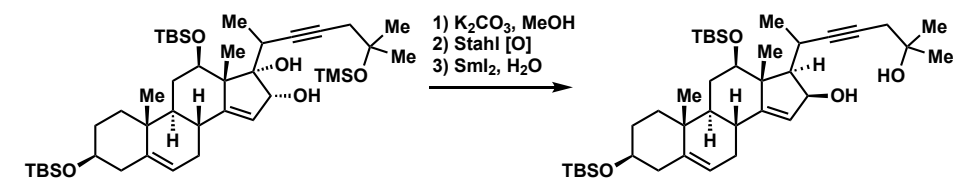
Widlanski JOC 1999, 64, 293



Jauch ACIE 2000, 39, 2764



Forsyth TL 2003, 44, 57



Reisman JACS 2021, 143, 4187

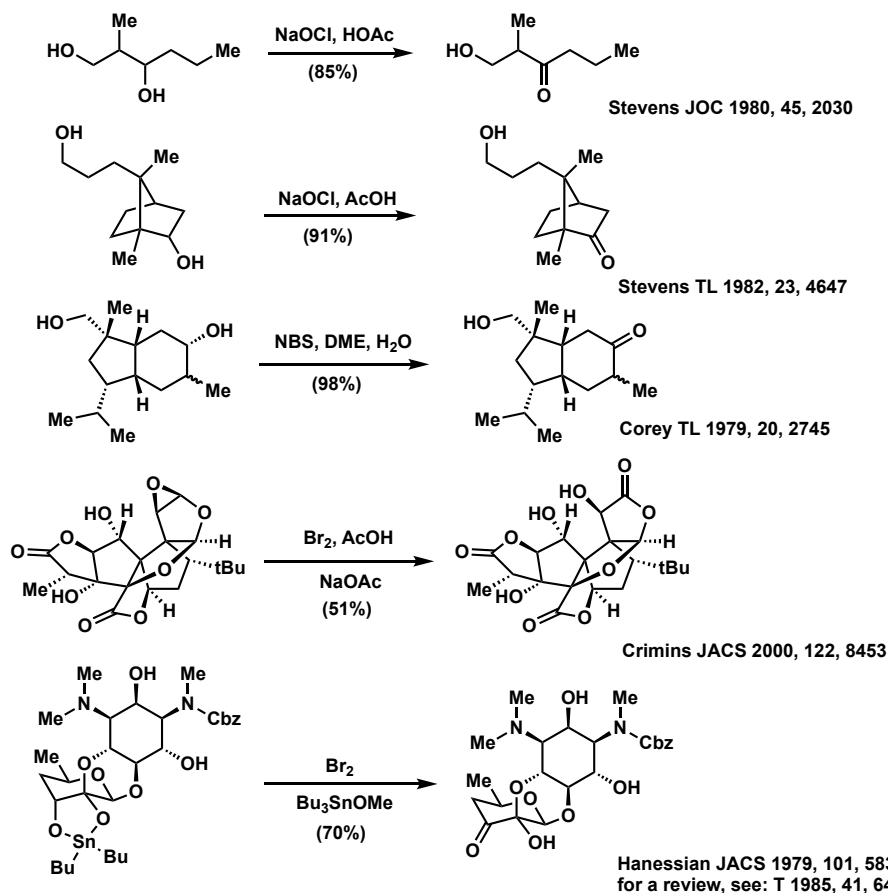
Stahl JACS 2013, 135, 2357; 15742

E. Hypohalite

typical conditions: NaOCl, HOAc NBS, DME, H₂O (Bu₃Sn)₂O, Br₂ NIS, Bu₄NI

- selectively oxidize secondary alcohols in the presence of primary ones
- may be less tolerant towards other functional groups compared with methods A-D
- primary alcohols react slowly to give esters in lower yields

Mechanism



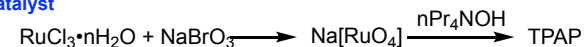
F. tetra-n-Propylammonium Perruthenate (TPAP)

Ley oxidation

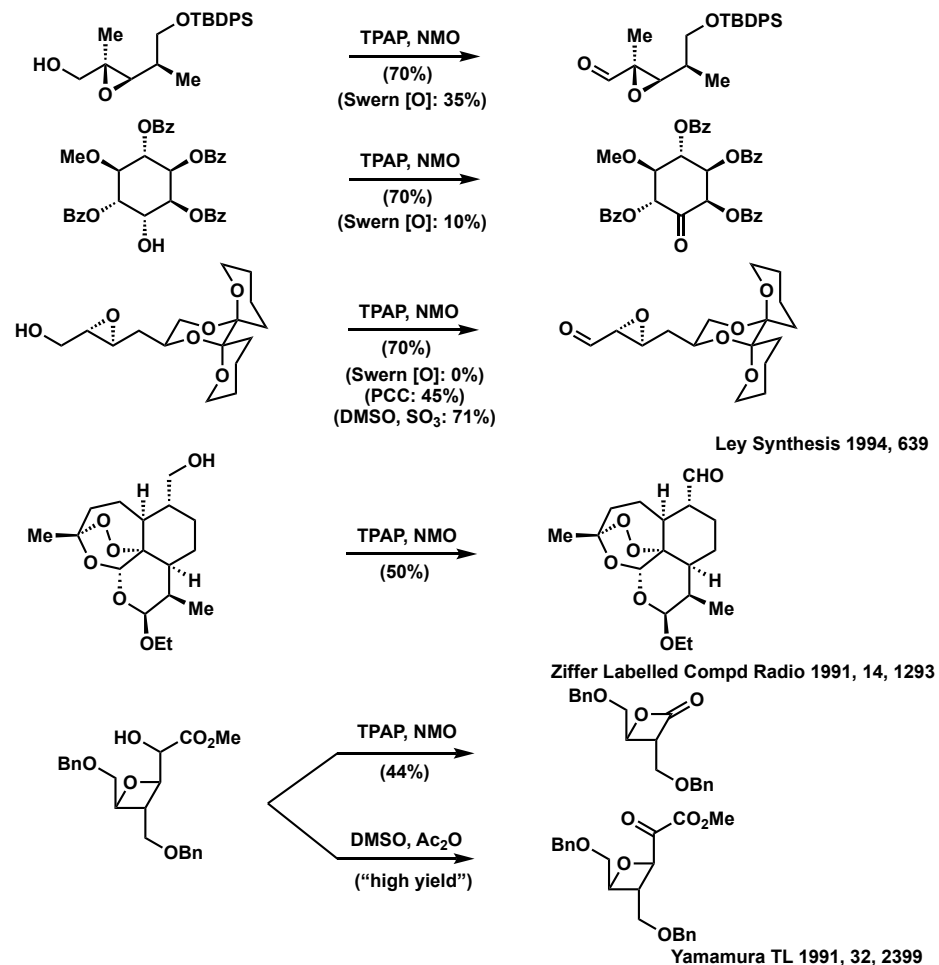
Reviews: Synthesis 1994, 639; Aldrichmca Acta 1990, 23, 13

typical conditions: TPAP (cat.), NMO, MS

preparation of catalyst



- mild, fast and clean
- molecular sieves can accelerate the rxn
- easy work-up
- detailed mechanism not clear



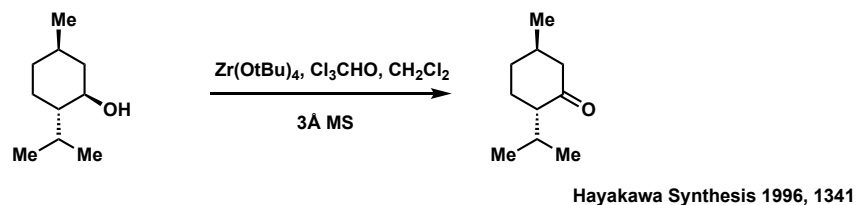
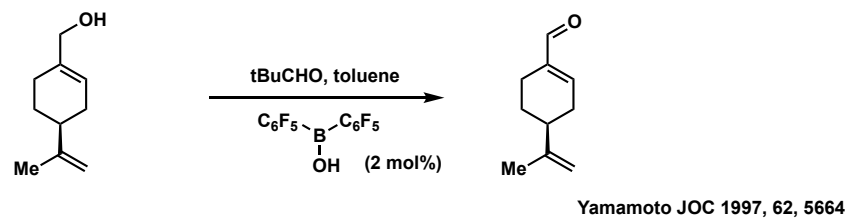
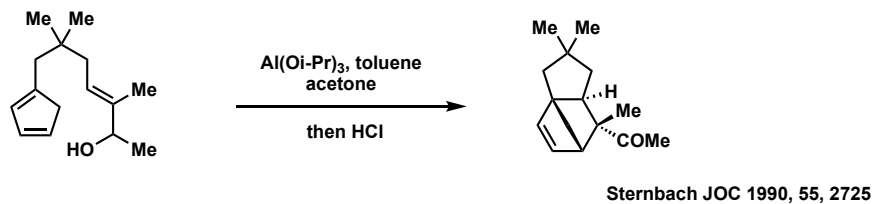
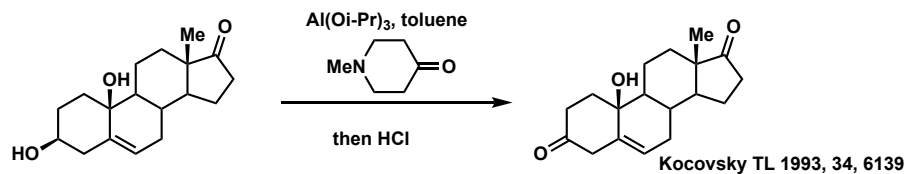
G. Oppenauer Oxidation

Reviews: Synthesis 1994, 1007; Org. React 1951, 6, 207

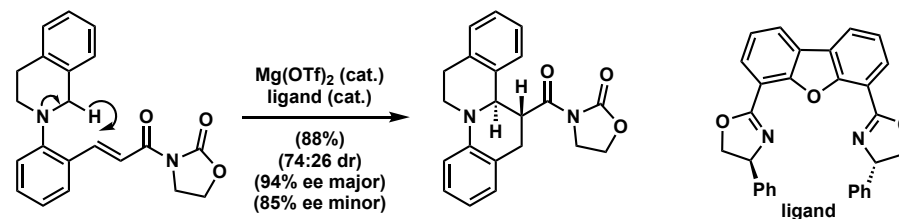
typical conditions: $\text{Al}(\text{O}i\text{-Pr})_3$, excess acetone or other ketones

Mechanism

- an equilibrium reaction
- usually take place on secondary and allylic alcohol

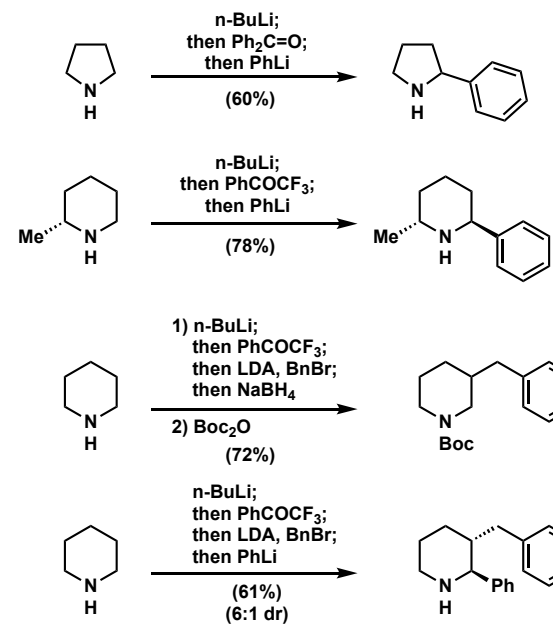


- hydride transfer mechanism can also take place on amines to yield imines

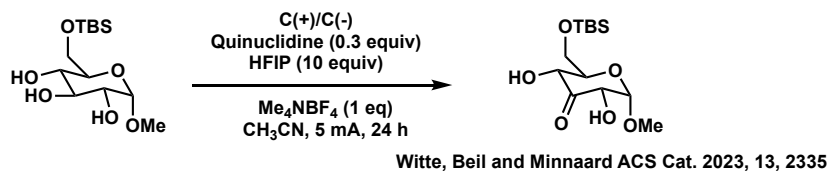


Mechanism

Seidel JACS 2009, 131, 13226



H. HAT-based oxidation



Mechanism

I. Pd-O₂

ref: Uenura JOC 1999, 64, 6750

typical conditions: Pd(OAc)₂ (5 mol%), pyridine (20 mol%), 3A MS, toluene, O₂

- only documented on simple substrates
- Molecular Sieves is important for high yield

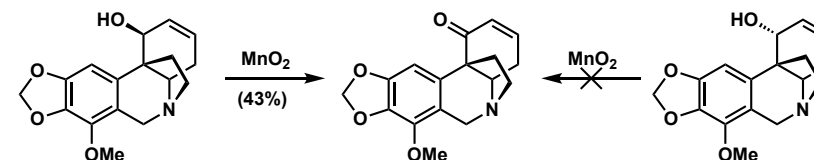
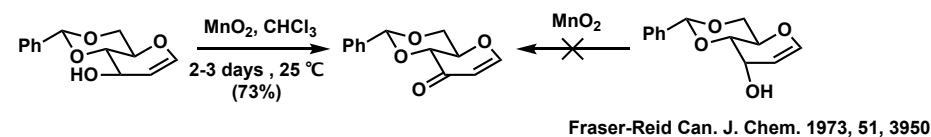
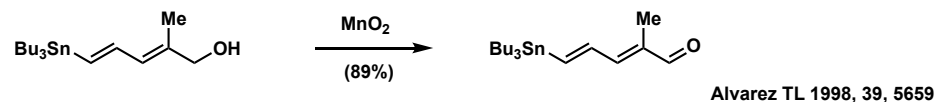
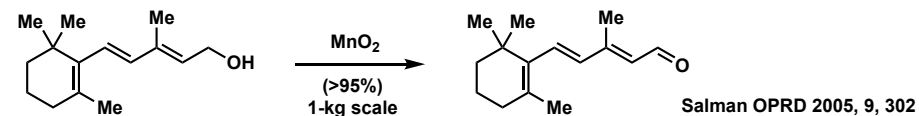
Mechanism

J. MnO₂

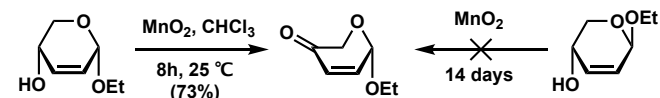
Reviews: Synthesis 1976, 65; 133

typical conditions: MnO₂ (10 wt equiv.), CH₂Cl₂ or CHCl₃, or benzene

- selectively oxidize allylic/benzylic alcohol to aldehyde or ketone
- very mild, needs special preparation and activation techniques (not all commercial ones works well)
- mechanism not clear
- in many cases, for cyclic allylic alcohols, only ones at equatorial position can be oxidized.

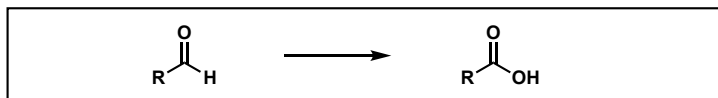


Explanation with 3D structures:



Explanation with 3D structures::

2. Oxidation of aldehyde to carboxylate acid

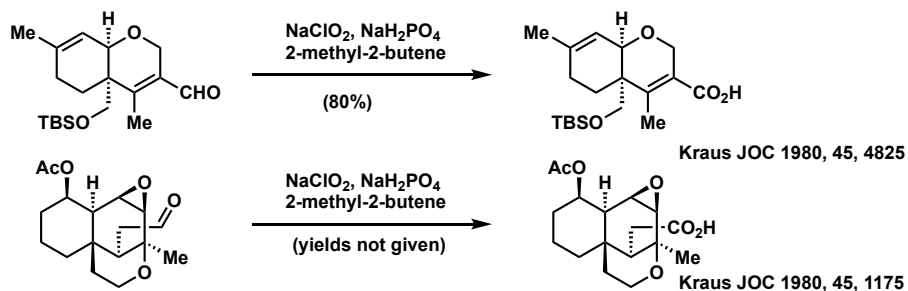


A. Pinnick oxidation

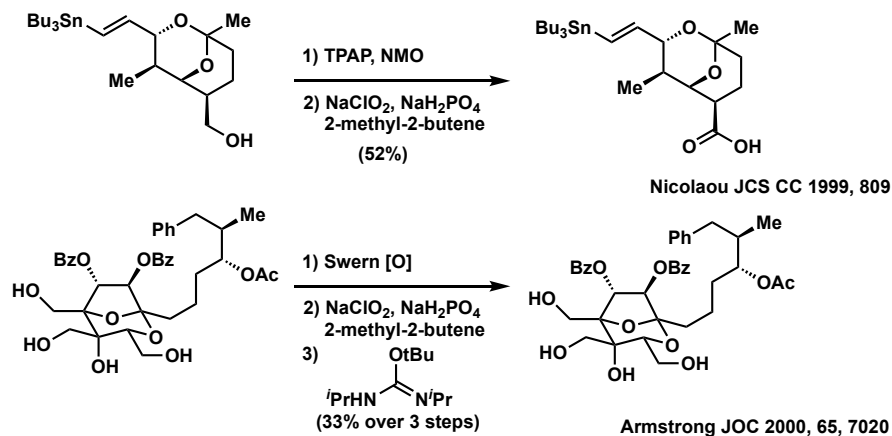
typical conditions: NaClO₂ (1-3 equiv.), 2-methyl-2-butene (10 equiv.), NaH₂PO₄

- mild
- olefin as HClO scavenger

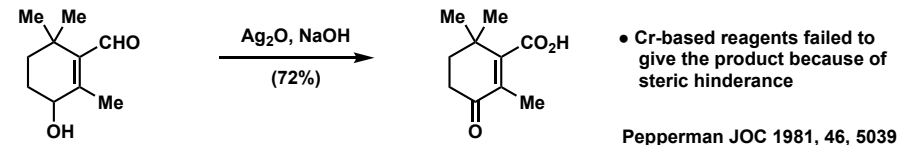
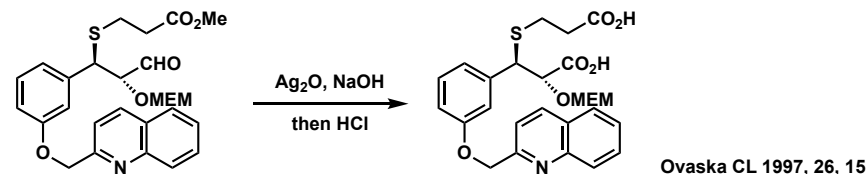
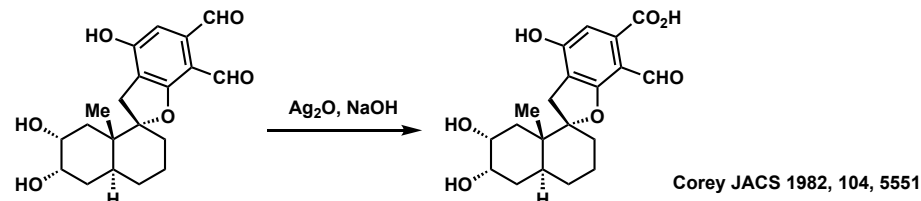
mechanism



- The two-step approach— first oxidize alcohol to aldehyde, then oxidize to acid via Pinnick conditions— is often used in late-stage natural product synthesis, because conditions that directly oxidize alcohol to acid have relatively limited functional group tolerance.

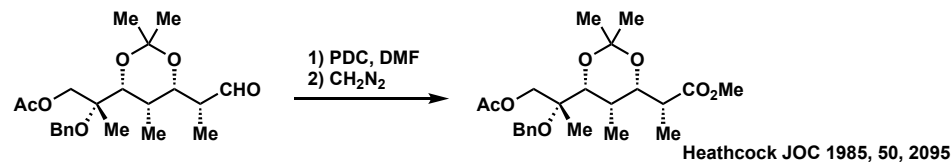
B. Ag₂O

- can oxidize hindered substrate
- conjugated substrates may suffer olefin isomerization due to the basic conditions



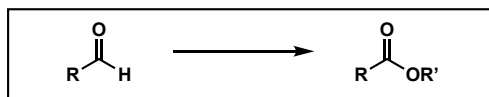
C. PDC in DMF

- PDC in DMF can oxidize non-conjugated aldehyde and non-allylic alcohol to carboxylate acid



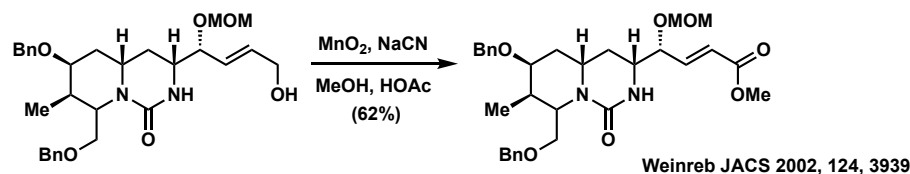
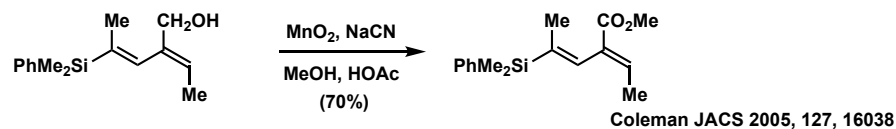
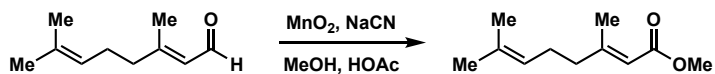
- In the presence of MeOH, methyl ester can be formed. This is only application to methyl ester because oxidation of MeOH by PDC is slow compared to the oxidation of hemiacetal formation

3. Oxidation of aldehyde to ester

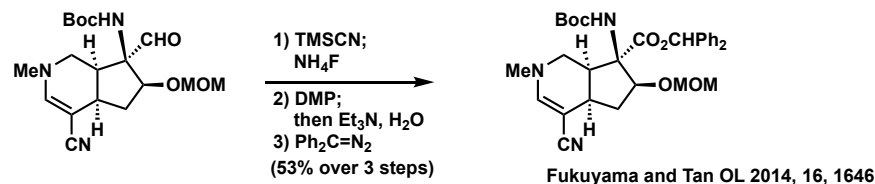
A. MnO₂, NaCN, ROH

- mild
- no olefin isomerization on unsaturated aldehyde

mechanism

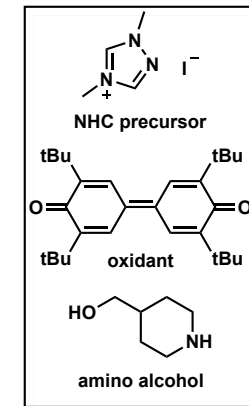
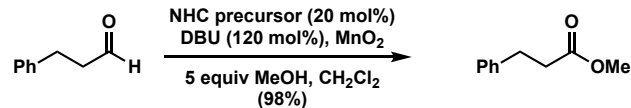
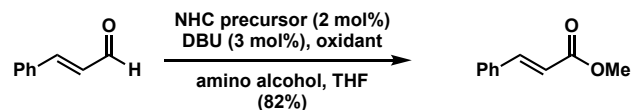
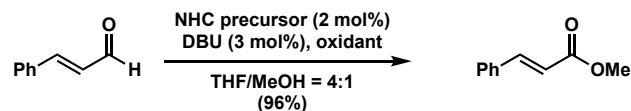
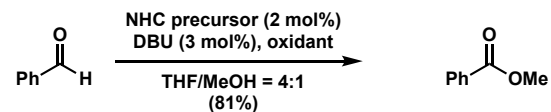


- other stronger oxidant can also oxidize cyanohydrin with separate pot operations



B. NHC catalyzed oxidative esterification

- mechanistically similar to cyanohydrin intermediate
- avoid the use of toxic cyanide
- chemoselectively react with alcohol in the presence of amine



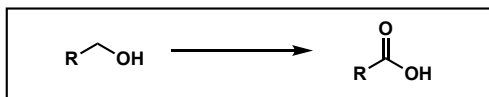
Studer JACS 2010, 132, 1190

Scheidt OL 2008, 10, 4331

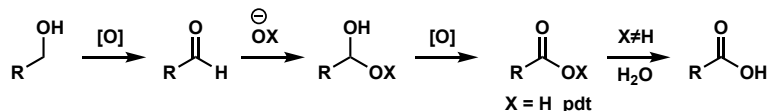
mechanism

NHC organocatalysis has been developed into a huge area with a wide range of transformations.
 Key reviews:
 Enders CR 2007, 107, 5606; Rovis CR 2015, 115, 9307; Bode ACR 2014, 47, 696; Scheidt ACIE 2012, 51, 11686
 Reviews on redox NHC catalysis:
 De Risi CEJ 2023, 29, e202202476; Studer, ACS Cat 2022, 12, 11984

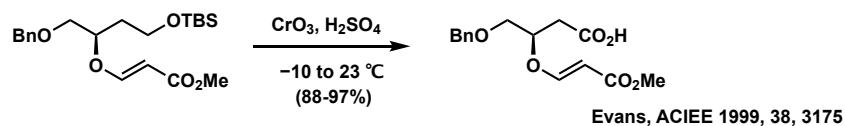
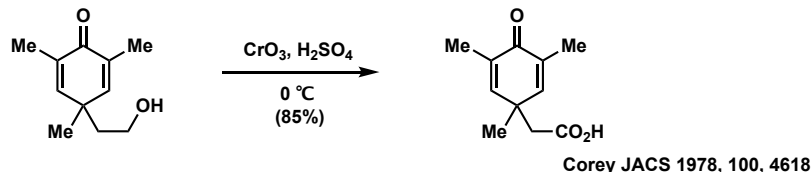
4. Oxidation of alcohol to acid



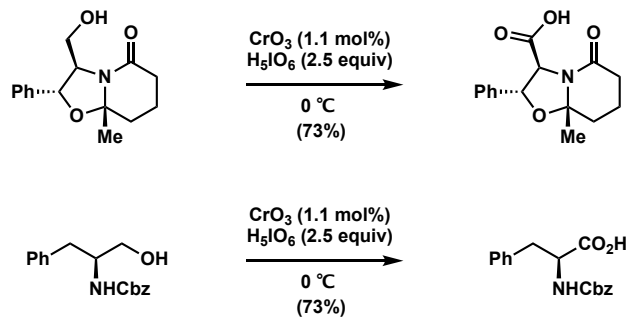
- typically the reaction proceed via an aldehyde intermediate (may not be observed)

A. Jones Oxidation: CrO₃, H₂SO₄

- acetone as a common solvent
- can cleave acid-labile protecting groups

B. CrO₃ (1-2 mol%), H₅IO₆

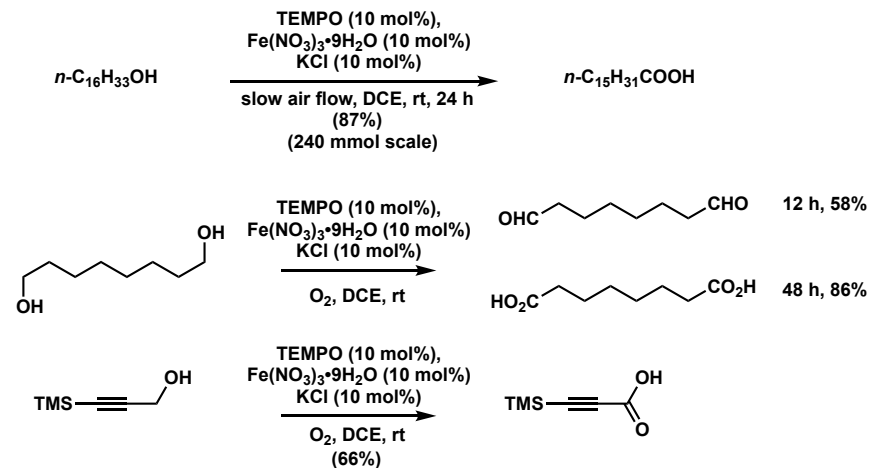
- industrial scale
- no racemization



Zhao TL 1998, 39, 5323

C. TEMPO/Fe(NO₃)₃•9H₂O/MCl (cat.), O₂ or air

Ma Oxidation



mechanism

Ma JACS 2016, 138, 8344