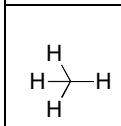
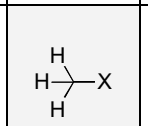
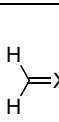
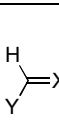
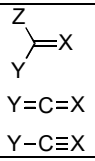
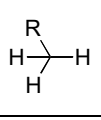
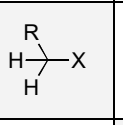
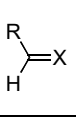
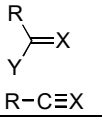
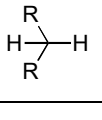
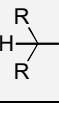
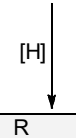
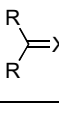
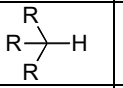
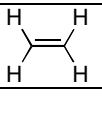
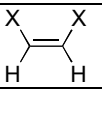
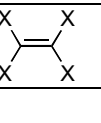
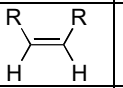
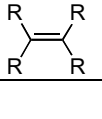
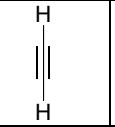
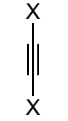
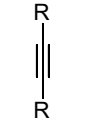
Chapter 18

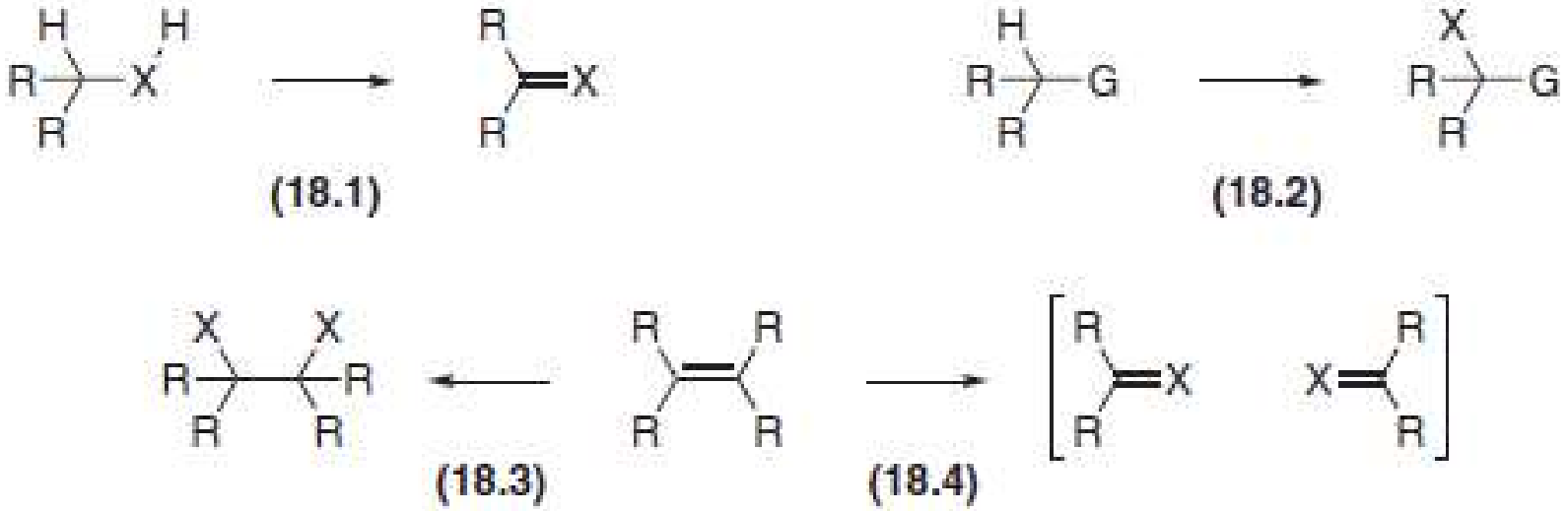
Table 18.1

- oxidations in this table occur left-to-right, or bottom-to-top
- Reductions in this table occur right-to-left or top-to-bottom

Formal Oxidation Number of Carbon

−4	−3	−2	−1	0	+1	+2	+3	+4
			[O] → 					
				[O] ↑ 				
			[H] ← 		[H] ↓ 			
								
								
								
								
								
								

Classes of Oxidations



Classes of Reductions

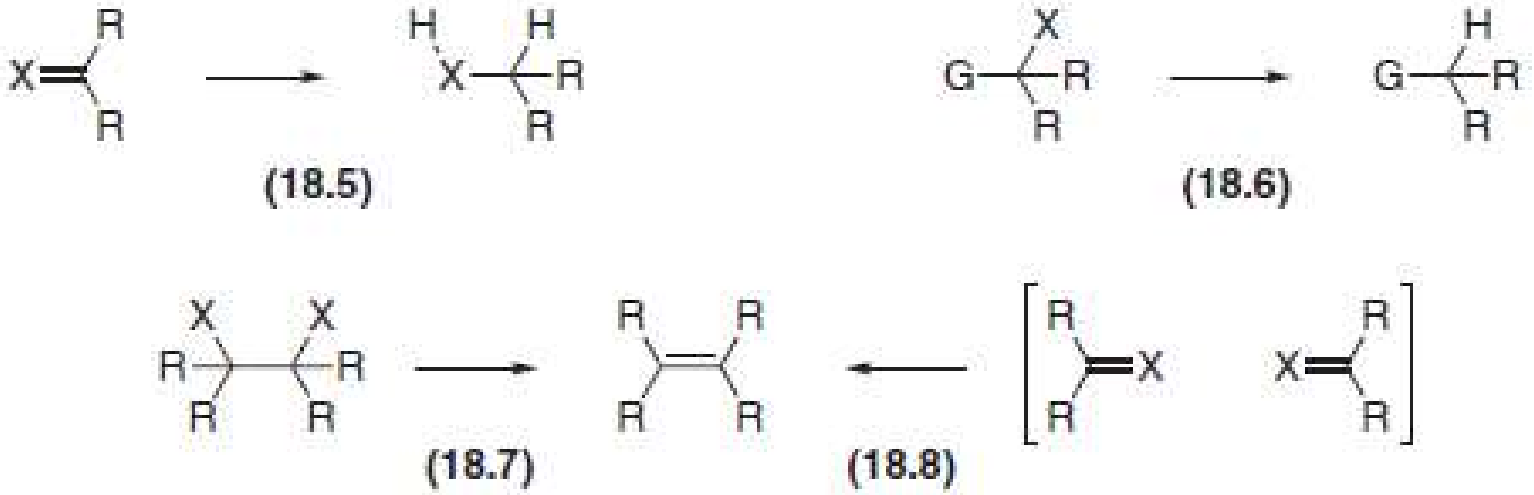


Table 18.2: Common Oxidation Reactions

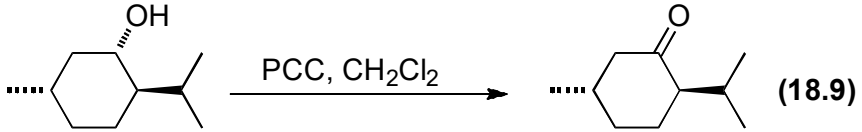
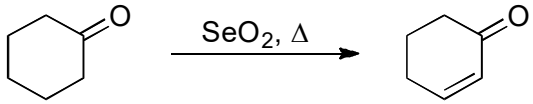
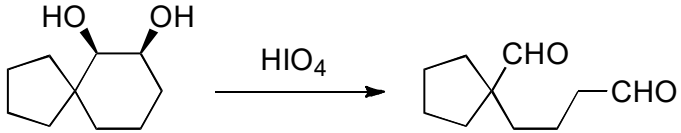
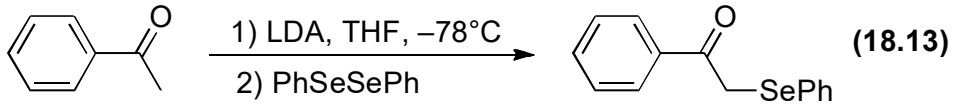
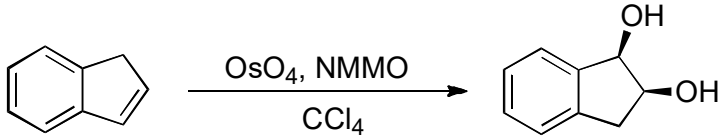
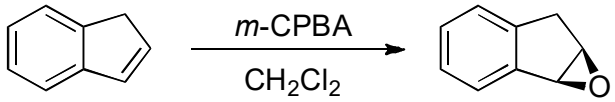
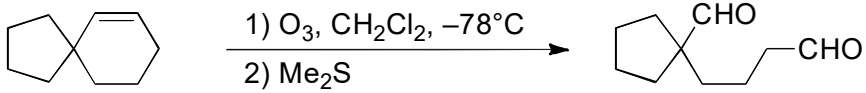
Reaction Type	Example
Alcohol oxidation	 (18.9)
Dehydrogenation	 (18.10)
Oxidative cleavage of glycols	 (18.11)
α-Selenylation	 (18.13)
Hydroxylation	 (18.14)
Epoxidation	 (18.15)
Ozonolysis	 (18.16)

Table 18.3: Common Reduction Reactions

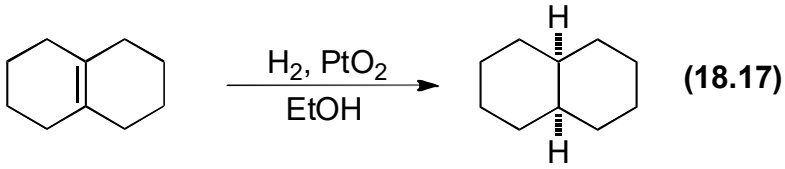
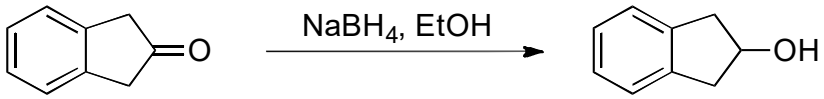
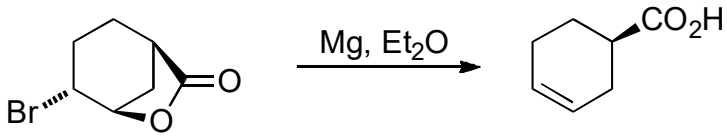
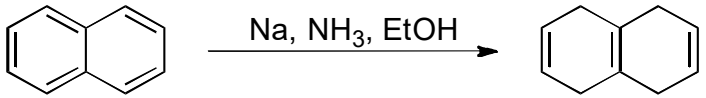
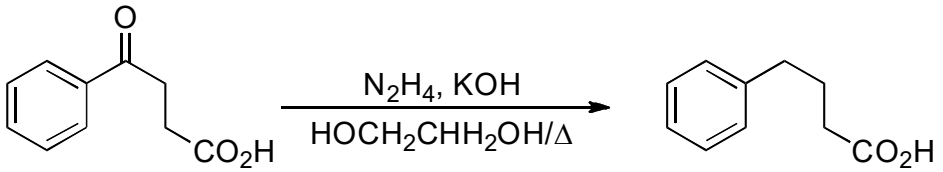
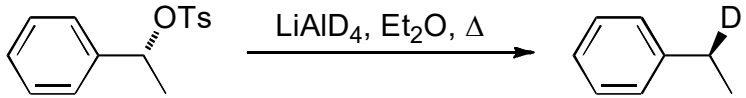
Reaction Type	Example
Catalytic hydrogenation	 (18.17)
Metal hydride reduction	 (18.18)
Reductive elimination	 (18.19)
Dissolving metal (Birch) reduction	 (18.20)
Deoxygenation	 (18.21)
Reductive substitution	 (18.22)

Figure 18.1

- Major classes of oxidation reactions in organic chemistry
  - oxidation of alcohols and aldehydes
  - oxidation of alkene π bonds
  - allylic and benzylic oxidation
  - α-oxidation of carbonyl compounds
  - dehydrogenation of carbonyl compounds
  - oxidative insertion (rearrangements)
  - arene oxidations (ring and side chain)

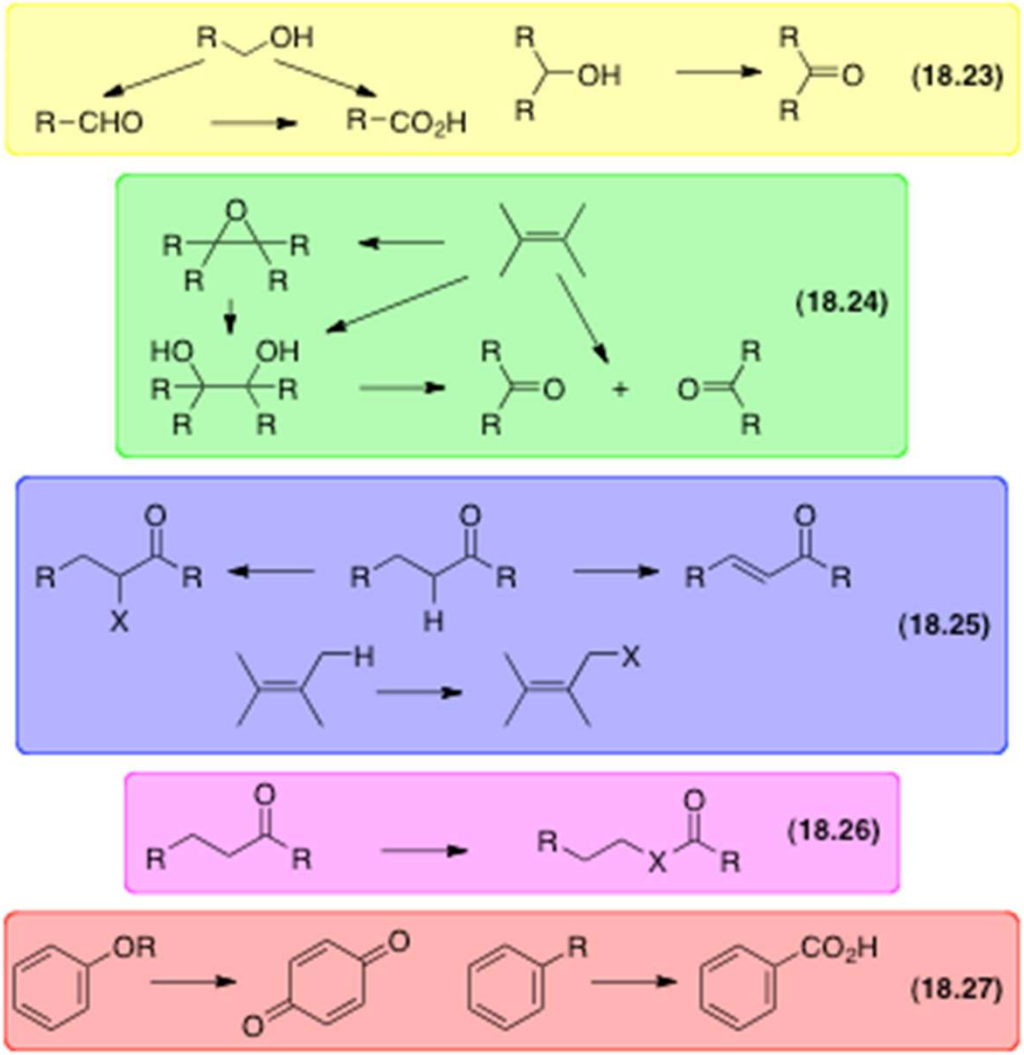
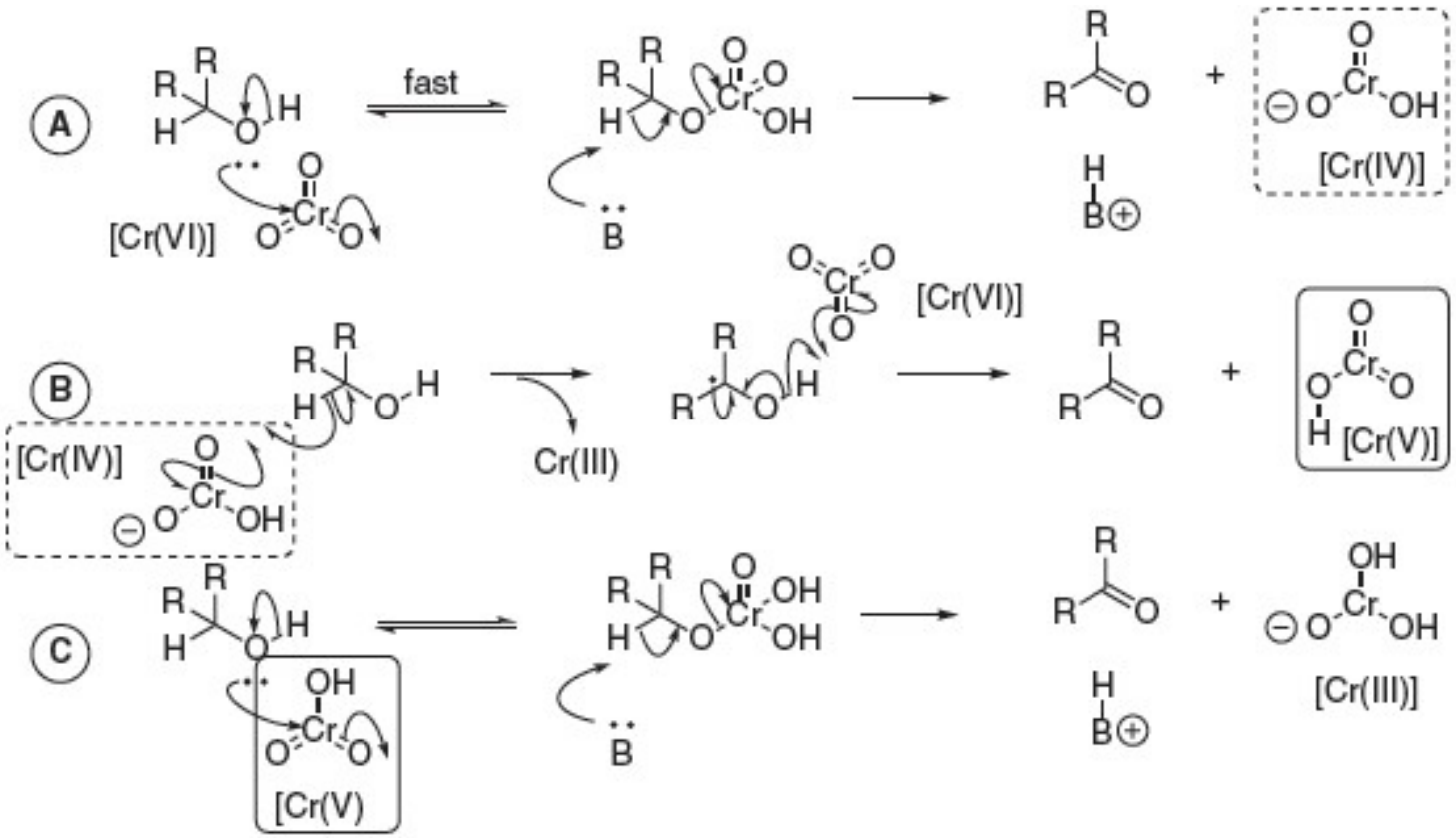


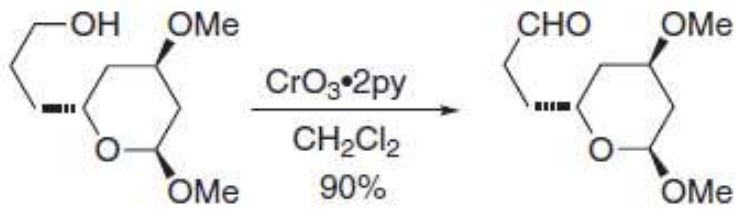
Figure 18.2

The Westheimer mechanism for oxidation of alcohols by chromium (VI)



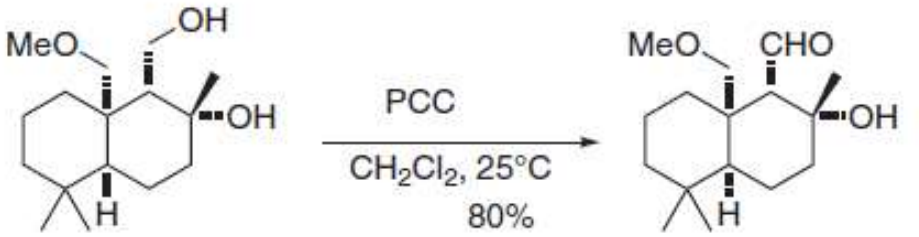
Common Cr (VI) oxidizing reagents

- Collins reagent ($CrO_3 \bullet 2py$, CH_2Cl_2)
- PCC (pyridinium chlorochromate, $pyH^+ ClCrO_3^-$
- PDC (pyridinium dichromate, $(pyH^+)_2 Cr_2O_7^{2-}$



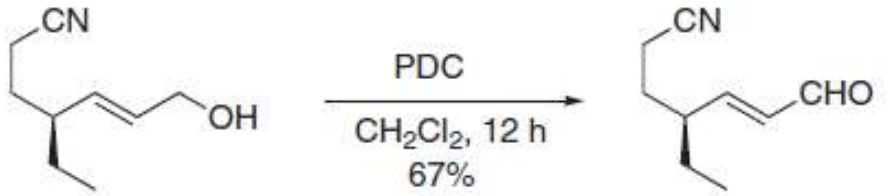
(18.28)

Collins oxidation[6]



(18.29)

Pyridinium chlorochromate[7]



(18.30)

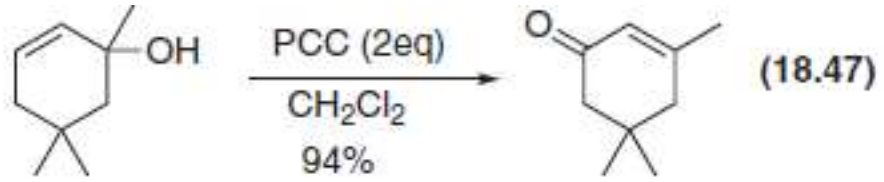
Pyridinium dichromate[8]

Table 18.4: Oxidizing Agents Based on Cr (VI)

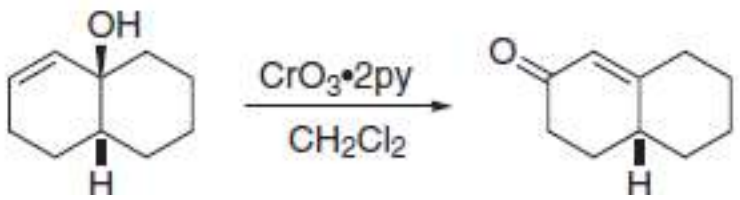
Reagent	Compound Name	Acronym or Reaction Name
$K_2Cr_2O_7/H_2SO_4/H_2O$	chromic acid	Ğ
$K_2Cr_2O_7/ H_2SO_4/ H_2O /Et_2O$	chromic acid	***Brown oxidation***
$CrO_3/ H_2SO_4/ H_2O$ /acetone	chromic acid	***Jones oxidation***
CrO_3/pyridine [C_5H_5N, py]	chromic anhydride	***Sarett oxidation***
CrO_3¥2py	chromic anhydride	***Collins oxidation***
$pyHCrO_3Cl$	pyridinium chlorochromate	PCC
$pyHCrO_3F$	pyridinium fluorochromate	PFC
$(pyH)_2Cr_2O_7$	pyridinium dichromate	PDC
$(C_5H_4)_2HCrO_3Cl$ [$bpyHCrO_3Cl$]	bipyridyl chlorochromate	BPCC
$Me_3SiOCrO_2Cl$	trimethylsilyl chlorochromate	TMSCC

Babler oxidation

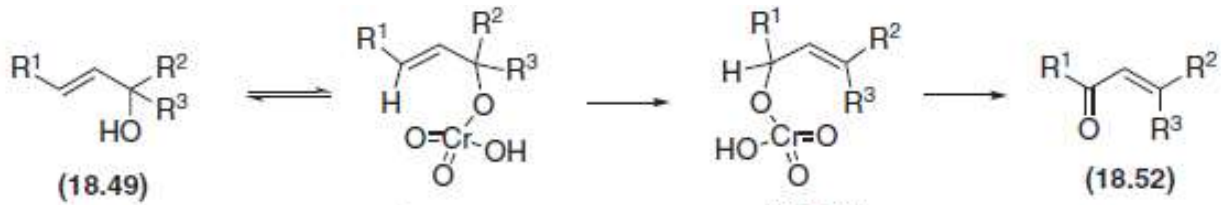
- oxidation of tertiary allylic alcohols by excess PDC or Collins reagent for extended periods of time
- occurs with allylic rearrangement
- Reaction may proceed by heterolysis and subsequent rearrangement of the allylic chromate ester, or by sigmatropic rearrangement of the allylic chromate ester (shown here)



(18.47)

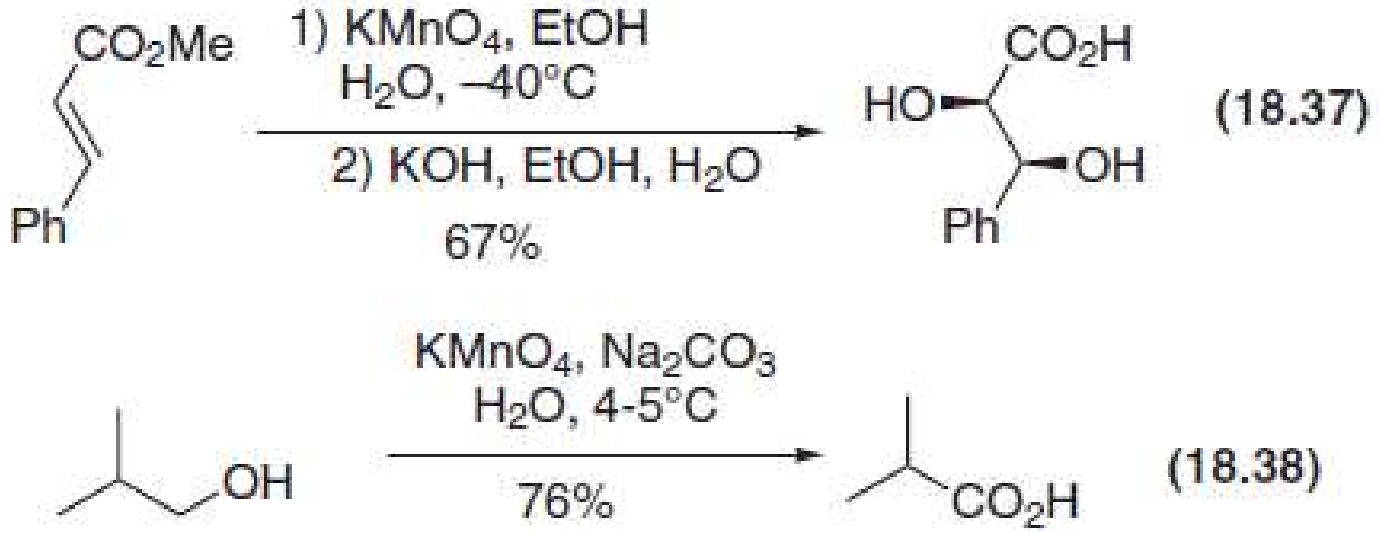


(18.48)



(18.49) (18.50) (18.51) (18.52)

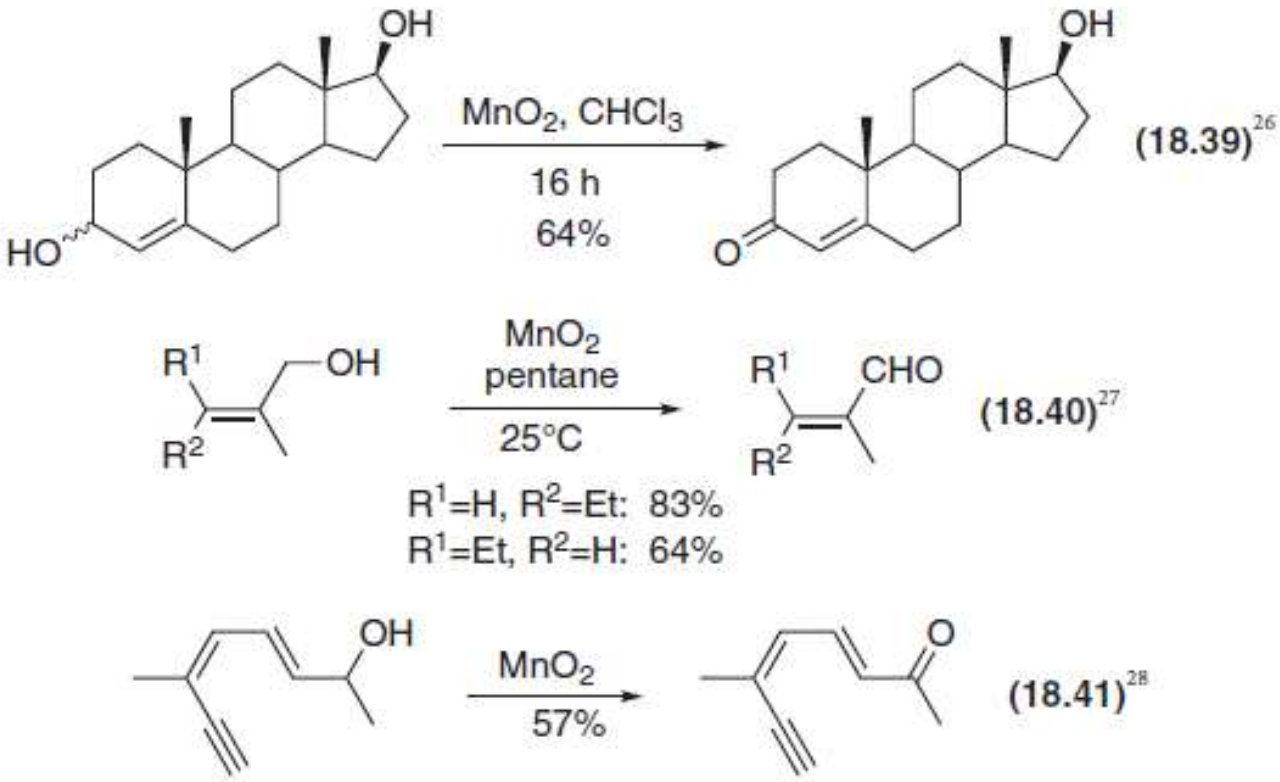
Manganese-based reagents: $KMnO_4$



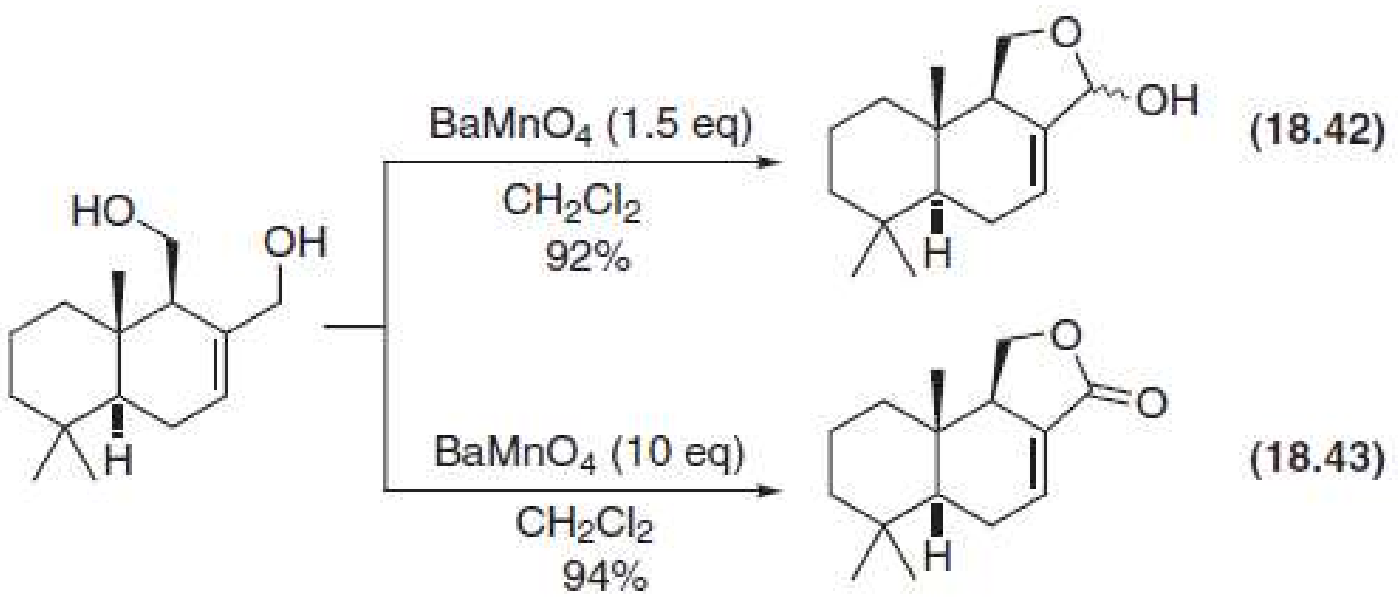
- oxidizes alkenes more rapidly than primary alcohols
- oxidizes aldehydes more rapidly than alcohols
- oxidizes primary alcohols to carboxylic acids

Manganese-based reagents: MnO_2

- Reagent is selective for allylic alcohols
- Reagent is not easy to make reproducibly
- Large excess of reagent is often required



Manganese-based reagents: $BaMnO_4$



- Reagent is similar to manganese dioxide, but more reproducible and easier to make

Other Metal-based Oxidations

- ruthenium (TPAP, $Pr_4N^+ RuO_4^-$)
- silver (Fétizon reagent, Ag_2CO_3-celite)
- vanadium (V_2O_5: may be used with O2 as terminal oxidant)

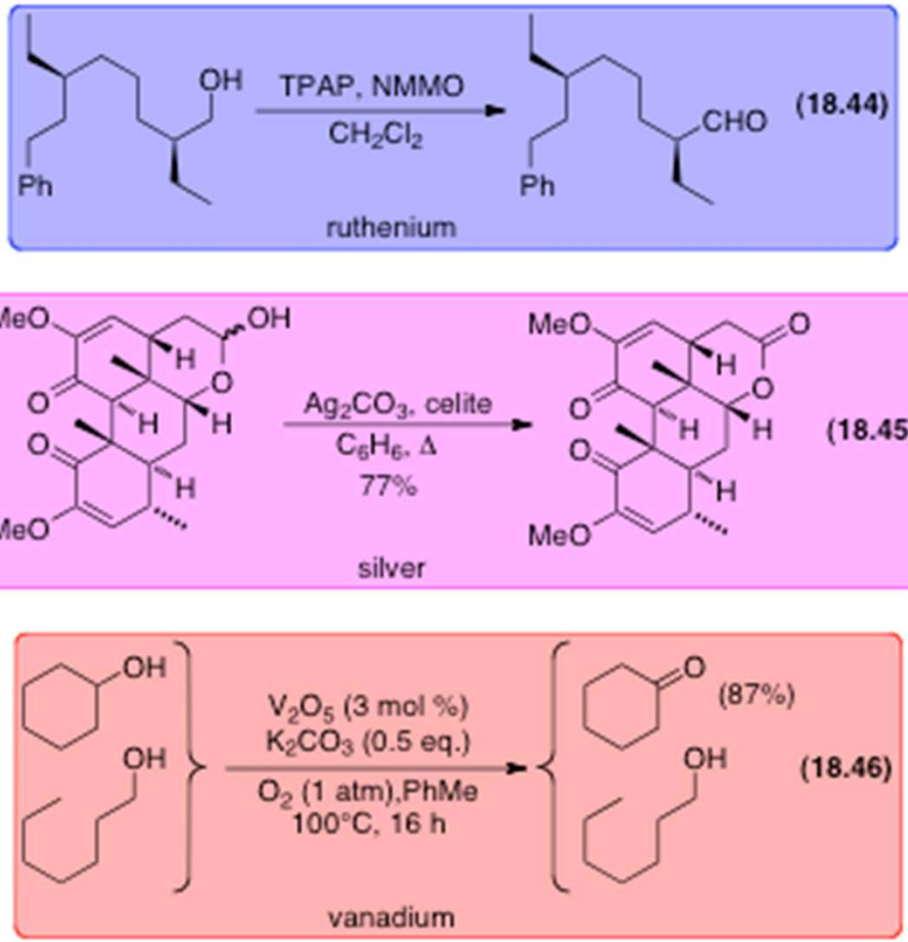


Table 18.5: Oxidizing agents based on dimethyl sulfoxide

Reagent	Name of Reaction
Ac_2O, Me_2SO, 25°C	
$C_6H_{11}N{=}C{=}NC_6H_{11}$ (DCC), CF_3CO_2H, C_6H_6, Me_2SO, py, 25°C	
DCC, H_3PO_4, Me_2SO, 25°C	***Moffatt*** (or ***Moffatt-Pfitzner***)
py•SO_3, Et_3N, Me_2SO, 25°C	***Parikh-Doering***
$(COCl)_2$, Et_3N, Me_2SO, CH_2Cl_2, –78°C	***Swern***

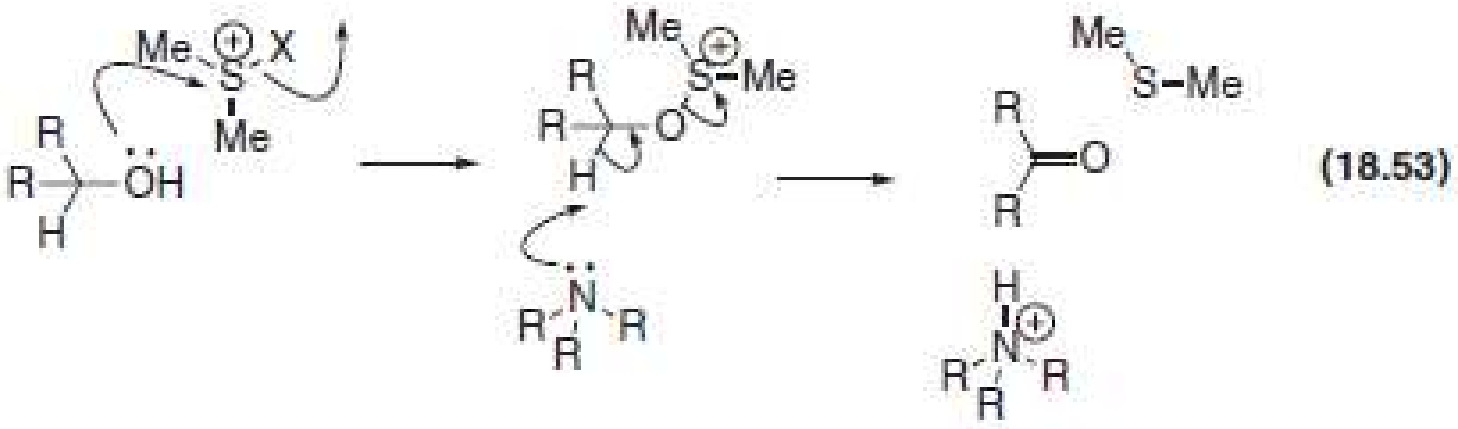
Mechanism of oxidation with dimethyl sulfoxide-based reagents

$$Me_2SO + (COCl)_2 \rightarrow \mathbf{Me_2S^+}\breve{\mathrm{G}}Cl + CO + CO_2 + Cl^{\breve{\mathrm{G}}}$$

$$Me_2SO + RN{=}C{=}NR + H^+ \rightarrow \mathbf{Me_2S^+}\breve{\mathrm{G}}[C(NHR){=}NR]$$

$$Me_2SO + Ac_2O \rightarrow \mathbf{Me_2S^+}\breve{\mathrm{G}}OAc + OAc^{\breve{\mathrm{G}}}$$

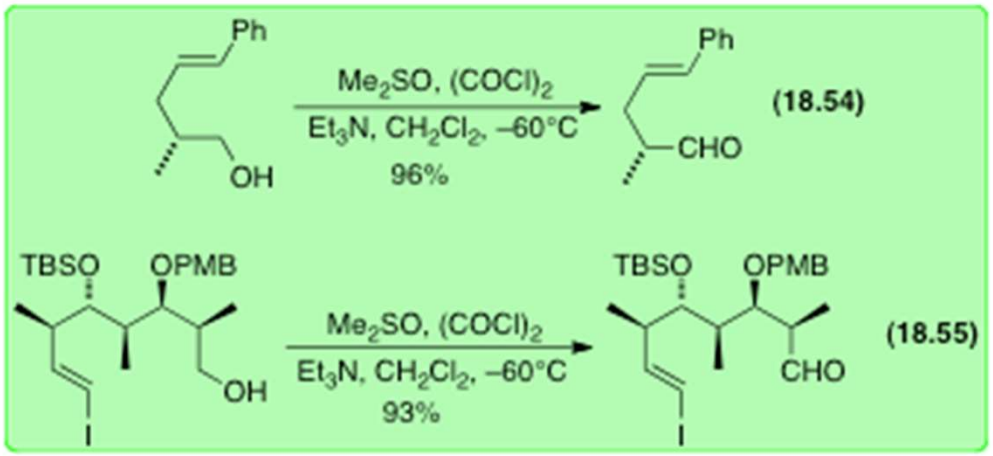
$$Me_2SO + SO_3 \rightarrow \mathbf{Me_2S^+}\breve{\mathrm{G}}OSO_3^{\breve{\mathrm{G}}}$$

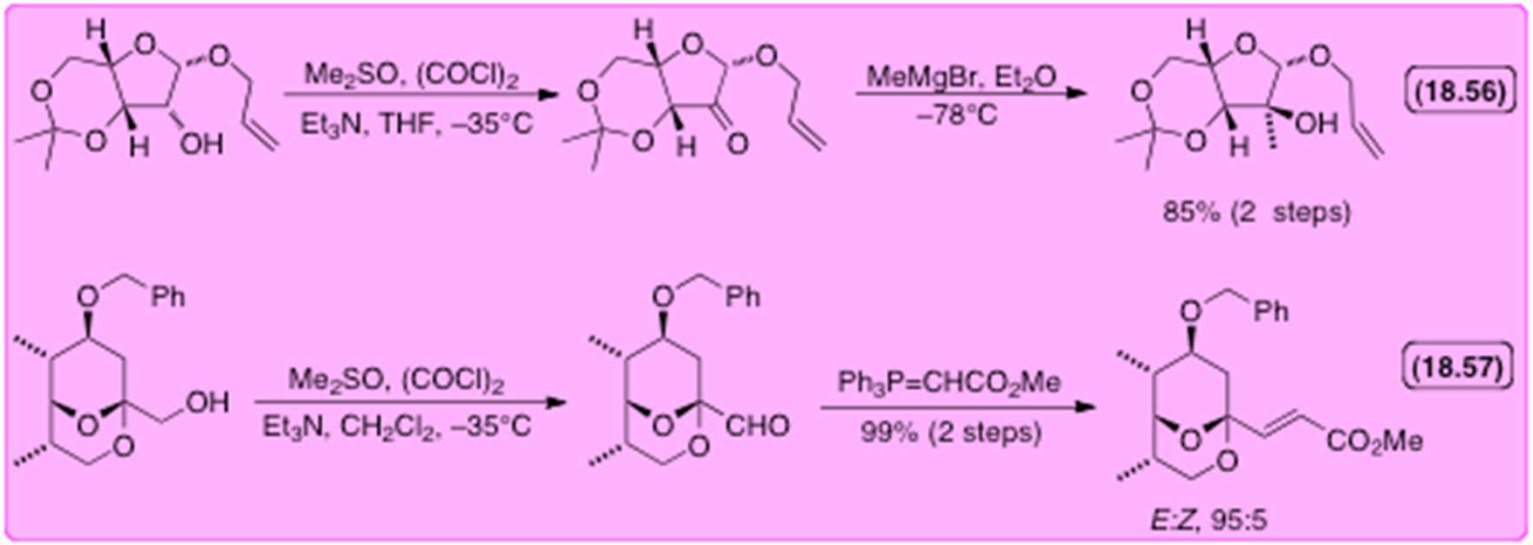


(18.53)

Representative Swern oxidations

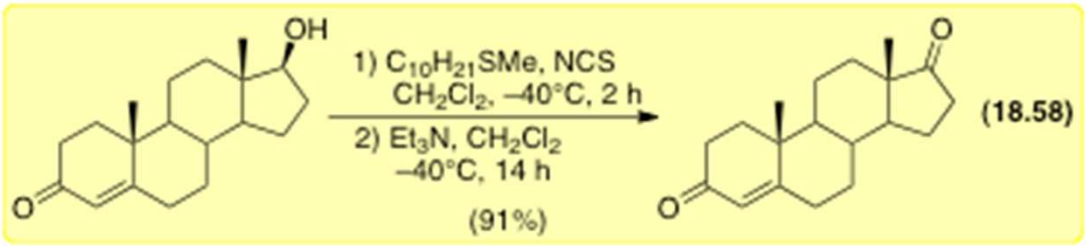
- The Swern oxidation helps prevent epimerization of the aldehyde product
- The initial product of the Swern oxidation can be intercepted *in situ* by appropriate nucleophiles

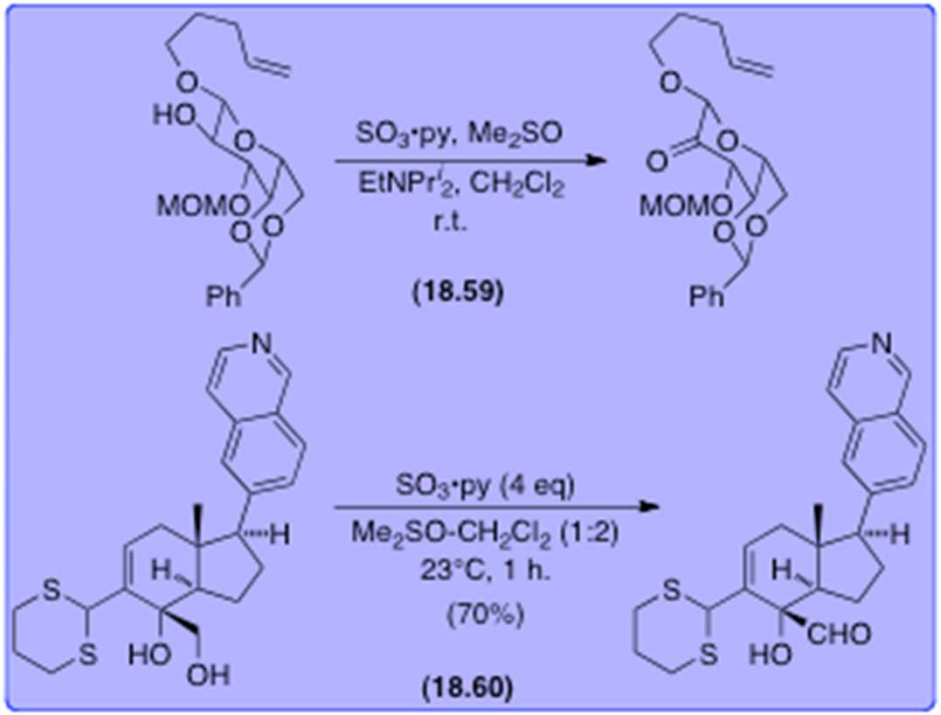




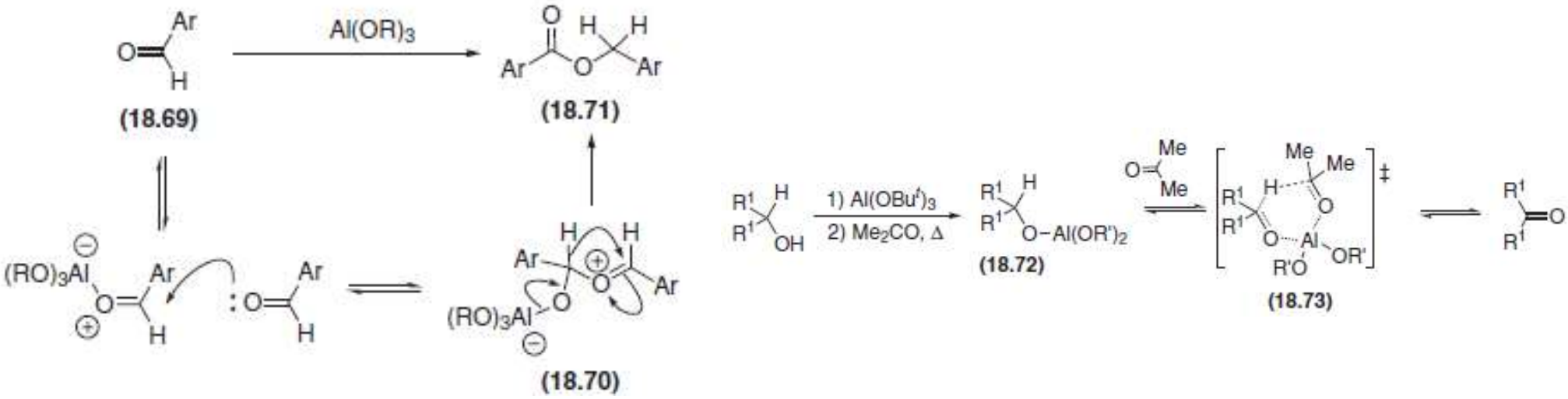
Corey-Kim and Parikh-Doering oxidations

- Corey-Kim oxidation requires a dialkyl sulfide, which can be malodorous
- Parikh-Doering oxidation does not required low temperatures





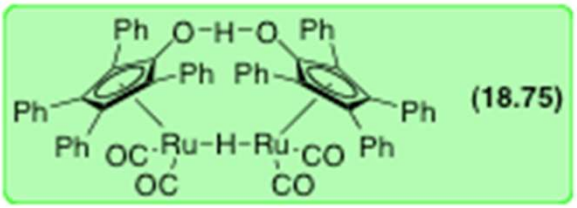
Redox reactions mediated by aluminum alkoxides



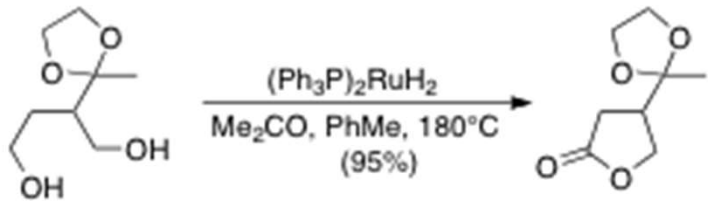
- The Tishchenko reaction is a redox disproportionation reaction catalyzed by an aluminum alkoxide
- The Oppenauer oxidation is the oxidation of an alcohol by hydrogen transfer to a carbonyl acceptor compound (e.g. acetone)

Ruthenium-catalyzed oxidation

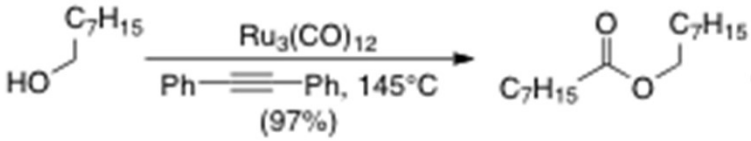
- Low valent ruthenium complexes (e.g. Shvo's catalyst, **18.75**) react with alcohols by initial oxidative addition of the O—H bond to ruthenium, and then reductive elimination of H_2
- Oxidation of primary alcohols to aldehydes is usually followed by ruthenium-catalyzed Tishchenko reactions to give esters (or lactones from diols).



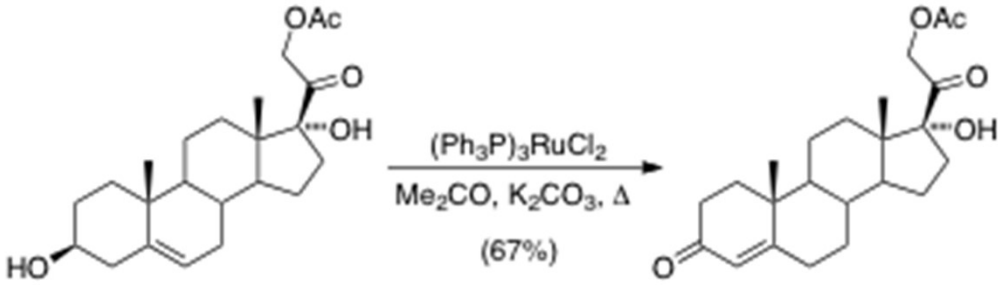
(18.75)



(18.76)



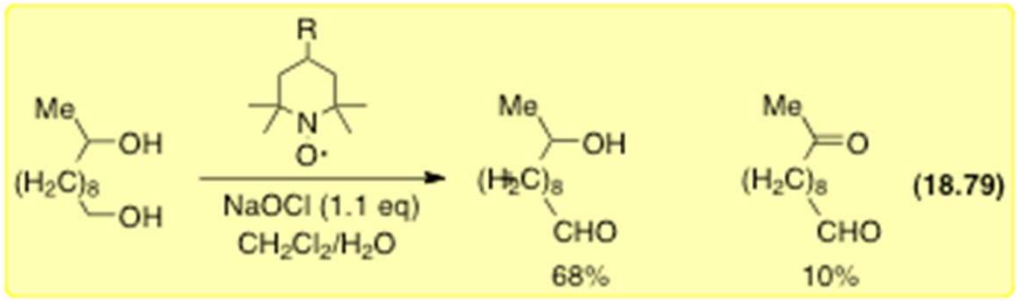
(18.77)

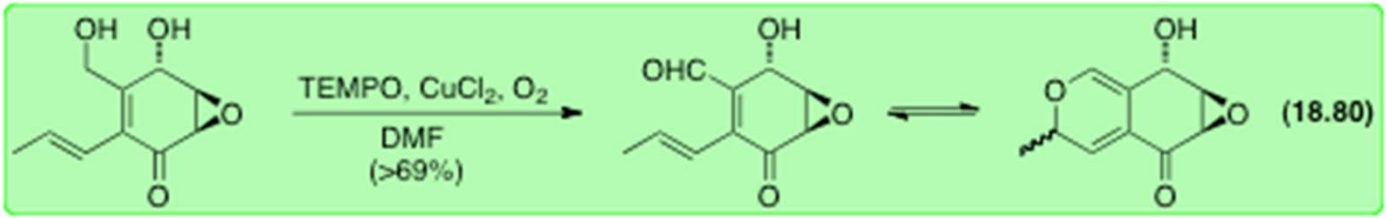


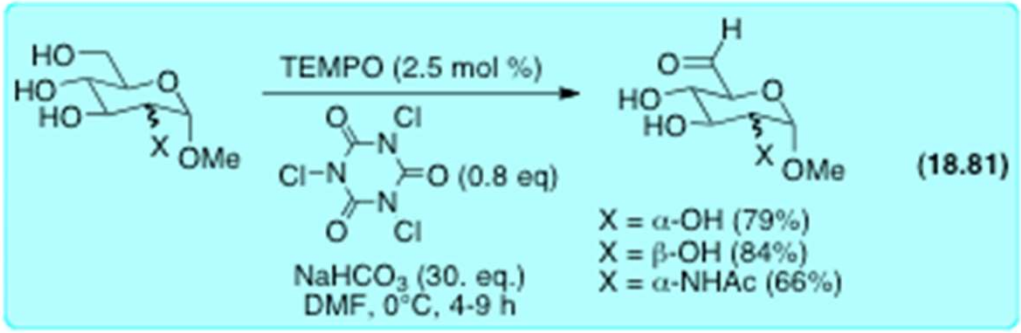
(18.78)

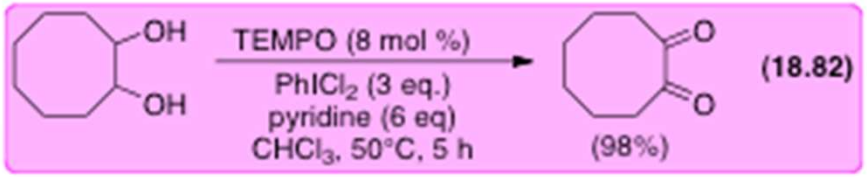
Oxidations with TEMPO and a supporting stoichiometric oxidant

- stoichiometric oxidants
  - NaOCl
  - O_2 ($CuCl_2$)
  - cyanuric chloride
  - $PhICl_2$

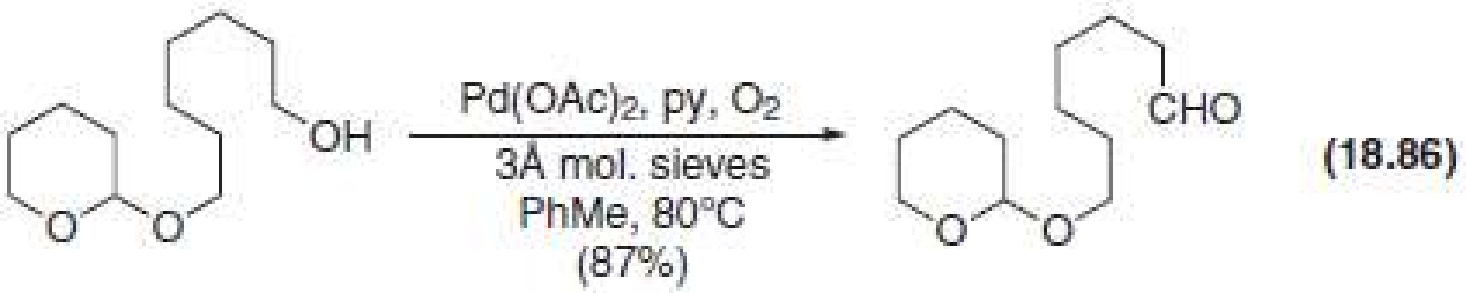






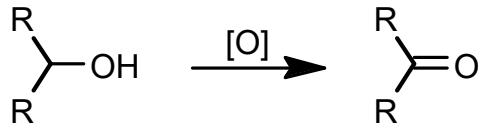


Uemura oxidation



- palladium catalyzes the oxidation of alcohols by means of molecular oxygen
- the reaction is catalyzed by pyridine

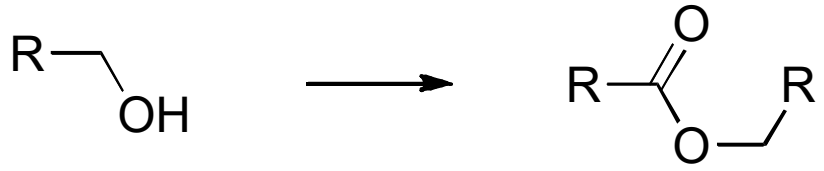
Reaction Synopses: Oxidation of alcohols to aldehydes and ketones



Reagents:

Cr (VI): PCC, CH_2Cl_2; PDC, CH_2Cl_2; CrO_3¥2py, CH_2Cl_2; etc.
Mn (VI): $BaMnO_4$, CH_2Cl_2
Mn (IV): MnO_2, C_6H_6, Δ only)
Mn (VII): $KMnO_4$, $CuSO_4$¥$5H_2O$, Al_2O_3, r.t. (solvent-free)
Ru (VII): TPAP, NMMO, CH_2Cl_2, r.t.
Ag (I): Ag_2CO_3, celite, C_6H_6, Δ
Al (III): Al(O-*i*-Pr)$_3$, Me_2CO, Δ
Ru (II): $(Ph_3P)_2RuH_2$, PhMe, Me_2CO, 180¡C;
Shvo's catalyst, K_2CO_3, Me_2CO, Δ
Me_2SX^+: $(COCl)_2$, Me_2SO, CH_2Cl_2, Et_3N, Ğ60¡C (Swern);
DCC, Me_2SO, CH_2Cl_2 (Pfitzner-Moffatt);
py¥SO_3, Me_2SO, CH_2Cl_2 (Parikh-Doering);
Me_2S, NCS, Et_3N, CH_2Cl_2, Ğ25¡C (Corey-Kim); etc.
Dess-Martin: DMP, CH_2Cl_2(-H_2O); selective for 2¡ ROH over 1¡
TEMPO: TEMPO, CH_2Cl_2, NaOCl, H_2O; TEMPO, CuCl, O_2, DMF; etc.
O_2: O_2, Pd(OAc)$_2$, pyridine, PhMe, 80¡C (Uemura).

Reaction Synopses: Tishchenko and related reactions



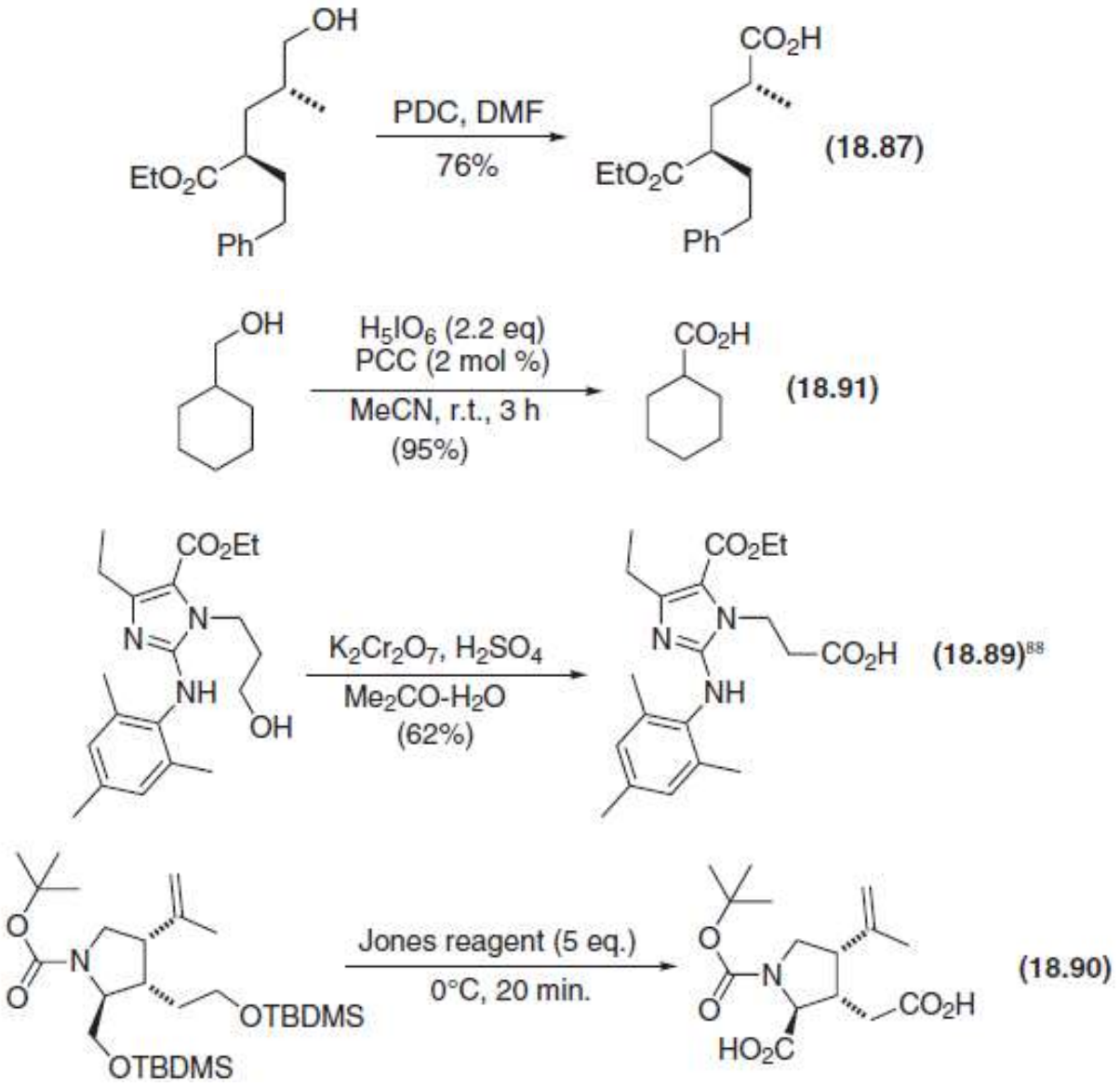
Reagents:

(R=aryl): $Al(OR_3)$, Me_2CO (Tishchenko);

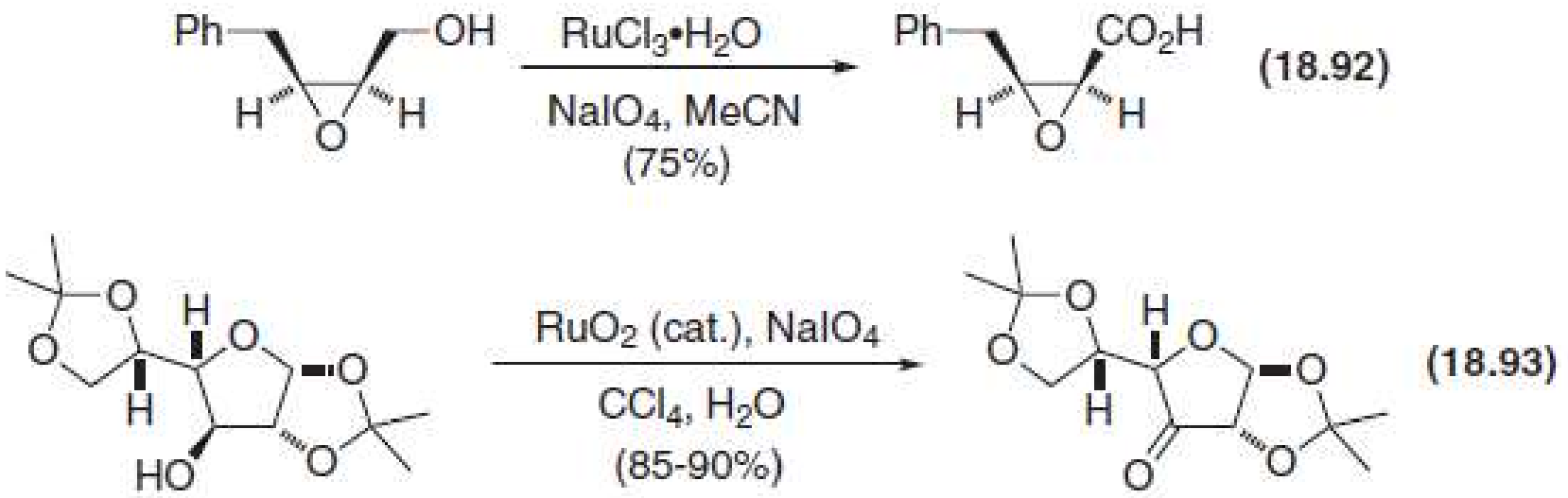
(R=akyl): $Ru_3(CO)_{12}$, PhC≡CPh, Δ

Shvo's catalyst, PhCH=CHCOMe, Δ c

Oxidation of primary alcohols to carboxylic acids with stoichiometric or catalytic Cr (VI) reagents

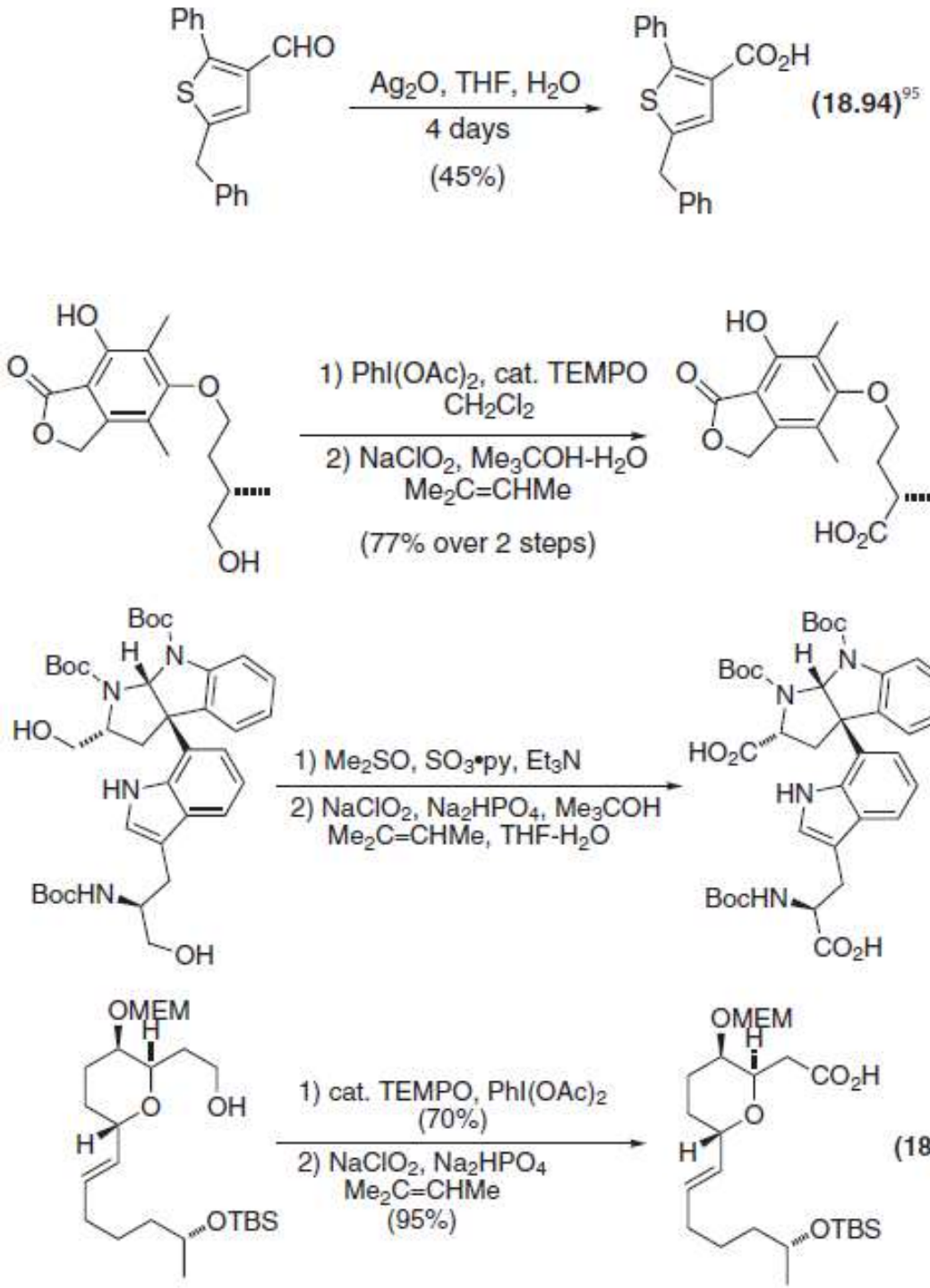


Ruthenium tetroxide oxidation of alcohols

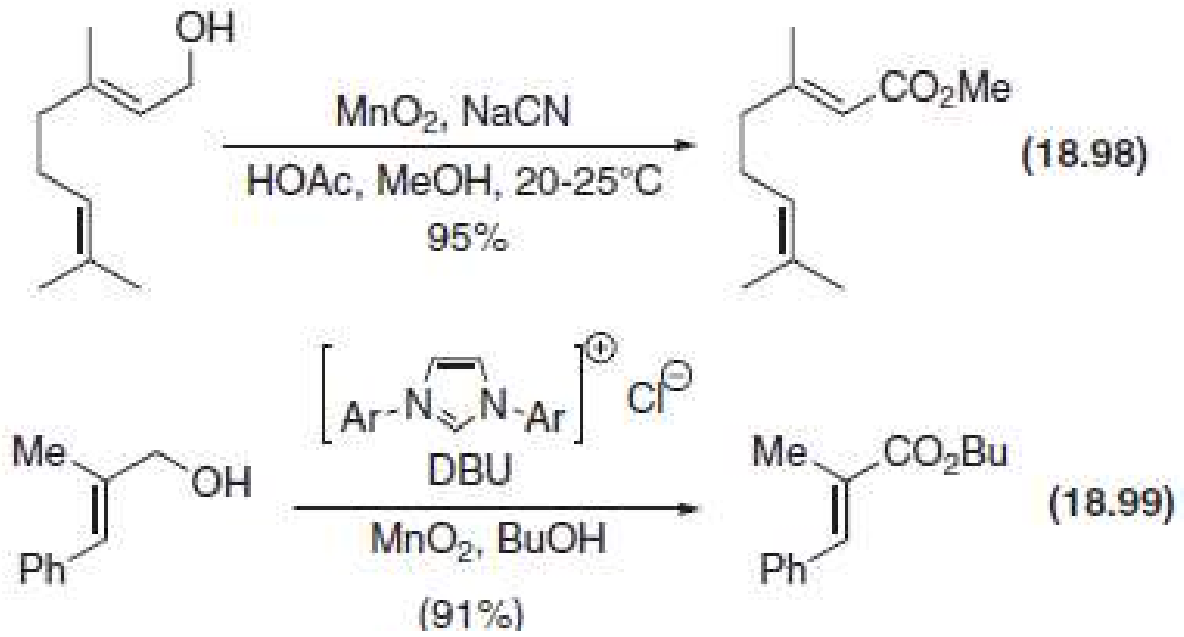


- This very powerful oxidizing agent is almost always prepared *in situ* from a lower-valent ruthenium compound and a strong oxidant ($NaIO_4$ is popular)
- The reagent also attacks alkenes (very rapidly), aromatic rings (moderately fast) and esters and amides (slowly). Epoxides are also fairly resistant to the reagent.

Oxidation of aldehydes to carboxylic acids. The oxidation of primary alcohols to aldehydes is highlighted in red; the oxidation of the aldehydes is highlighted in blue

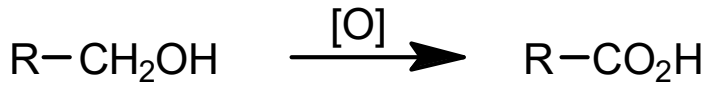


Oxidation of allylic alcohols to conjugated esters



- manganese dioxide is the functional oxidizing agent
- the aldehyde is intercepted by the nucleophile (cyanide anion or the NHC) to give an alcohol that is further oxidized
- the resulting acyl derivative reacts with the alcohol solvent to give the conjugated ester and regenerate the nucleophile.

Reaction synopses: Oxidation of alcohols to carboxylic acids



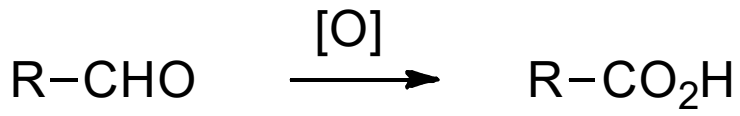
Reagents:

Cr (VI): $K_2Cr_2O_7$, H_2SO_4, H_2O; $K_2Cr_2O_7$, H_2SO_4, acetone, H_2O; CrO_3, H_2SO_4, H_2O, acetone, 0¡C (Jones reagent); PDC, DMF; PCC, H_5IO_6, MeCN; etc.

Mn (VII): $KMnO_4$, H_2O; $KMnO_4$, H_2O, Bu_4NCl, C_6H_6; $KMnO_4$, 18-crown-6,, benzene; etc.

Ru (VIII): RuO_4; $RuCl_3$¥H_2O, $NaIO_4$/MeCN; RuO_2, $NaIO_4$, CCl_4, H_2O; etc.

Reaction synopses: Oxidation of aldehydes to acids or esters

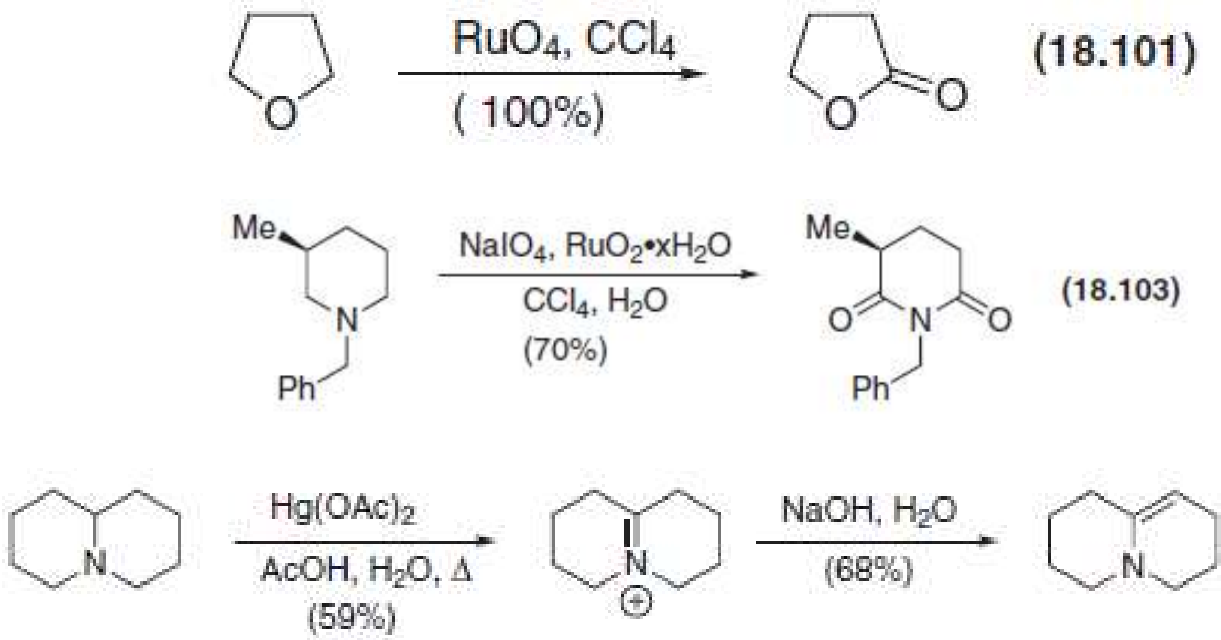


Reagents: $Ag(NH_3)_2OH$, H_2O; Ag_2O, THF, H_2O; etc.

or $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, THF, H_2O

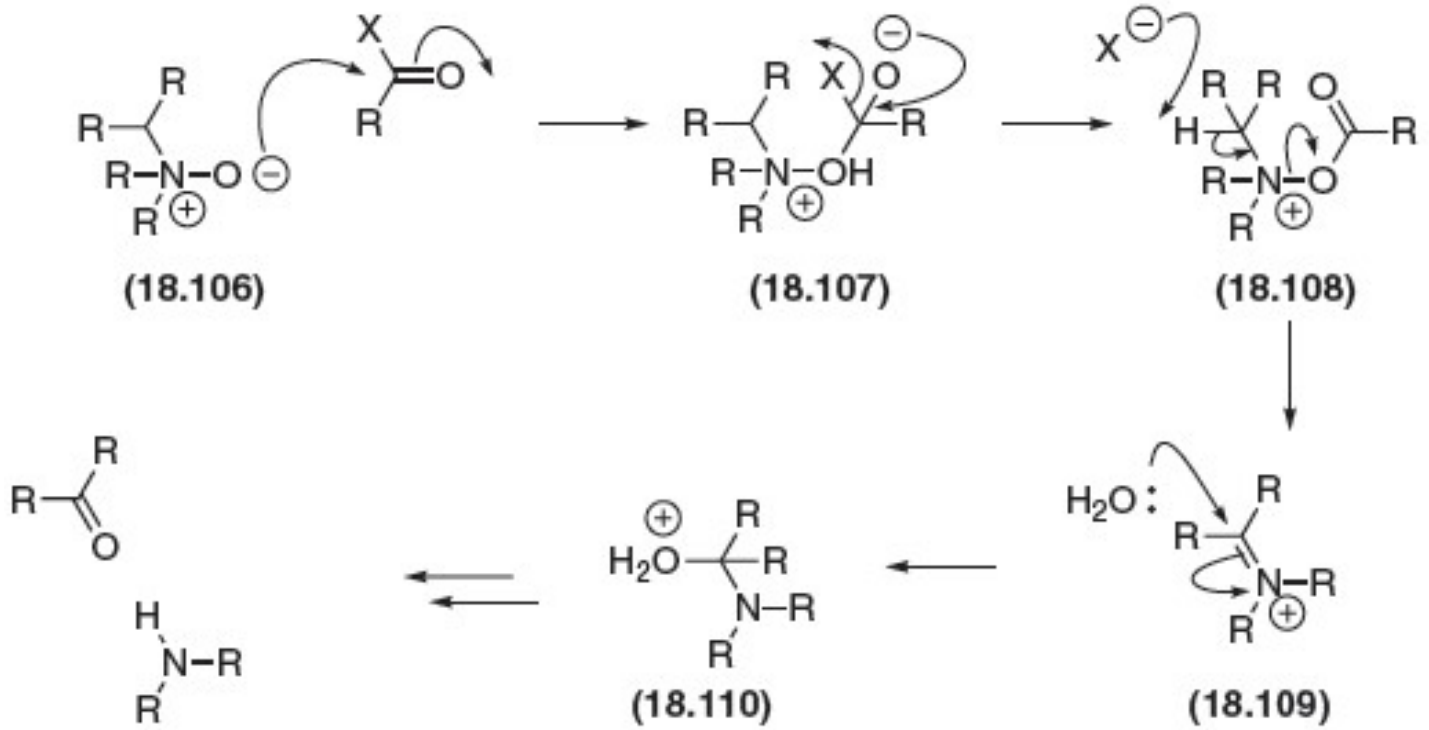
or V_2O_5, H_2O_2, $HClO_4$, MeOH; etc.

Oxidation of ethers and amines



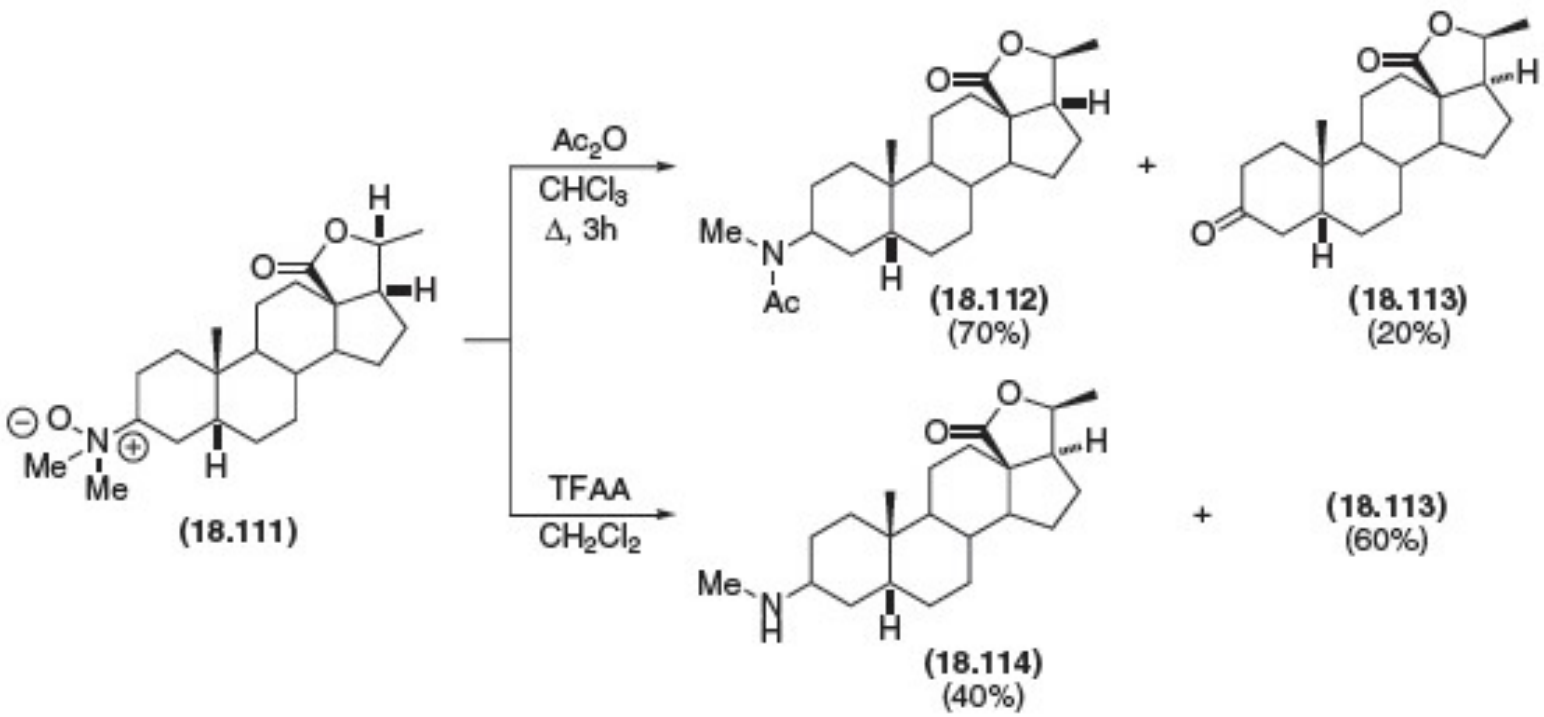
- ruthenium tetroxide oxidizes ethers to esters
- ruthenium tetroxide oxidizes amines to amides or imides
- mercuric acetate oxidizes tertiary amines to iminium ions, which may be further transformed into enamines; the hydrogen removed is *anti* to the nitrogen lone pair

Figure 18.3



- The mechanism of the Polonovski reaction

Figure 18.4

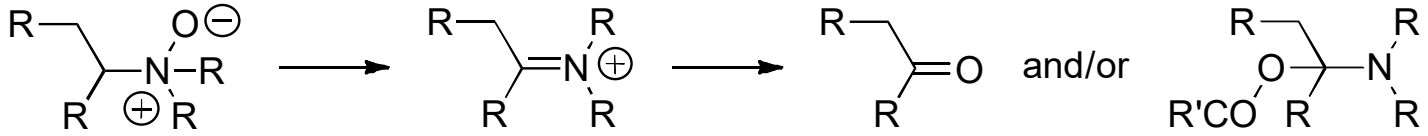


- Comparison of the Polonovski and Potier-Polonovski reactions

Reaction synopses: Oxidation of ethers and amines to esters and amides

Reagents: RuO_4; $RuCl_3$¥H$_2$O, $NaIO_4$, MeCN; RuO_2, $NaIO_4$, CCl_4, H_2O; etc.
or $Hg(OAc)_2$, HOAc, H_2O, Δ (3¡ amines)

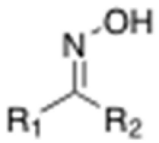
Reaction synopses: Polonovski reaction



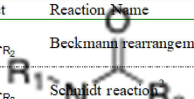
Reagents:

$Ac_2O/CHCl_3/\Delta$; $AcCl/CHCl_3$; etc (Polonovski reaction);
$(CF_3CO)_2O/CH_2Cl_2$ (Polonovski-Potier); etc.

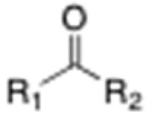
Table 18.6: Oxidative rearrangements



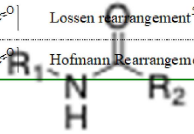
H_2SO_4; H_3PO_4; etc.



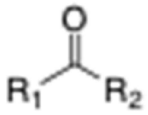
Beckmann rearrangement



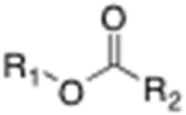
HN_3; etc.



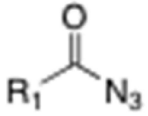
Schmidt reaction



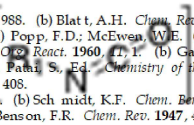
RCO_3H; etc.



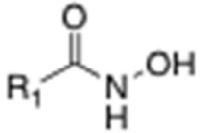
Baeyer-Villiger oxidation



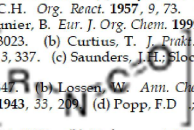
Δ or hν



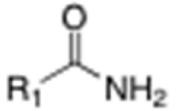
Curtius rearrangement



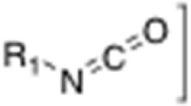
H_2SO_4; $TsCl$; etc.



Lossen rearrangement



Br_2, KOH; etc.



Hofmann rearrangement

Substrate	Reagent	Product	Reaction Name
	H_2SO_4; H_3PO_3; etc.		Beckmann rearrangement[1]
	HN_3; etc.		Schmidt reaction[2]
	RCO_3H; etc.		Baeyer-Villiger oxidation[3]
	Δ or hν		Curtius rearrangement[4]
	H_2SO_4; $TsCl$; etc.		Lossen rearrangement[5]
	Br_2/KOH		Hofmann Rearrangement[6]

[1] (a) Beckmann, E. *Ber. dtsch. chem. Ges.* **1886**, *19*, 988. (b) Blatt, A.H. *Chem. Rev.* **1933**, *12*, 215. (c) Jones, B. *Chem. Rev.* **1944**, *35*, 335. (d) Popp, F.D.; McEwen, W.E. *Chem. Rev.* **1958**, *58*, 370. (e) Heldt, W.Z.; Donaruma, L.G., *Org. React.* **1960**, *11*, 1. (b) Gawley, R.E. *Org. React.* **1988**, *35*, 1. (c) McCarty, C.G. In Patai, S. Ed. *Chemistry of the Carbon-Nitrogen Double Bond* (Wiley: New York, 1970), p. 408.

[2] (a) Schmidt, K.F. *Z. angew. Chem.* **1923**, *36*, 514. (b) Schmidt, K.F. *Chem. Ber.* **1924**, *57*, 704. (c) Wolff, H. *Org. React.* **1946**, *3*, 307. (d) Benson, F.R. *Chem. Rev.* **1947**, *41*, 48. (e) Popp, F.D.; McEwen, W.E. *Chem. Rev.* **1958**, *58*, 370.

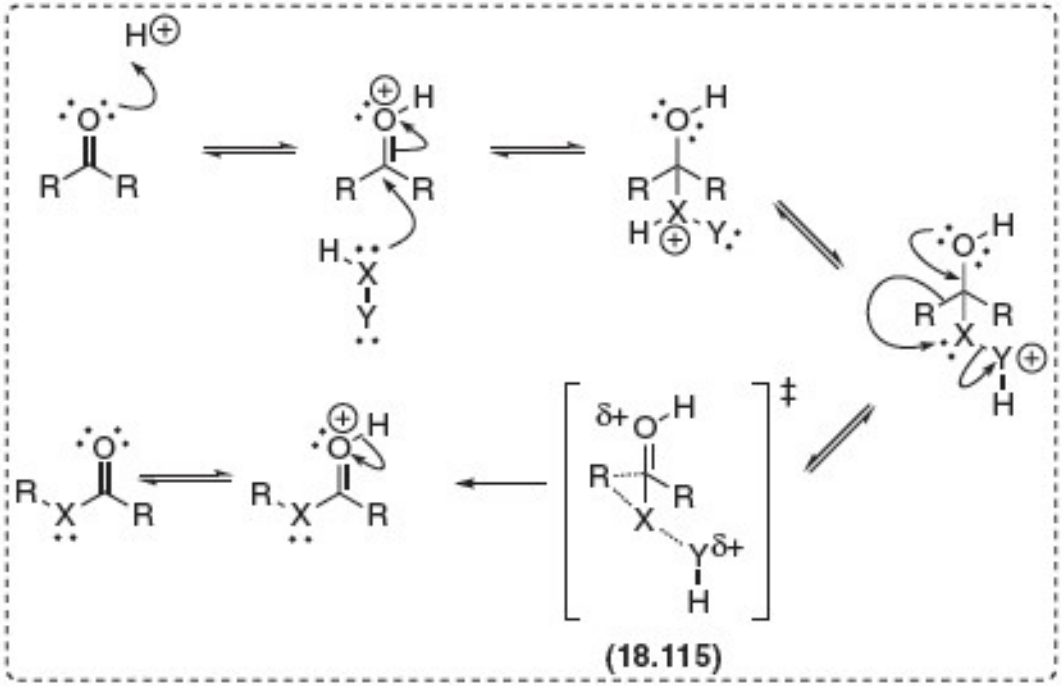
[3] (a) Baeyer, A.; Villiger, V. *Ber Deut. chem. Ges.* **1899**, *32*, 3625. (b) Baeyer, A.; Villiger, V. *Ber Deut. chem. Ges.* **1900**, *33*, 858. (c) Hassall, C.H. *Org. React.* **1957**, *9*, 73. (d) Krow, G.R. *Org. React.* **1993**, *43*, 251. (e) Rentz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737.

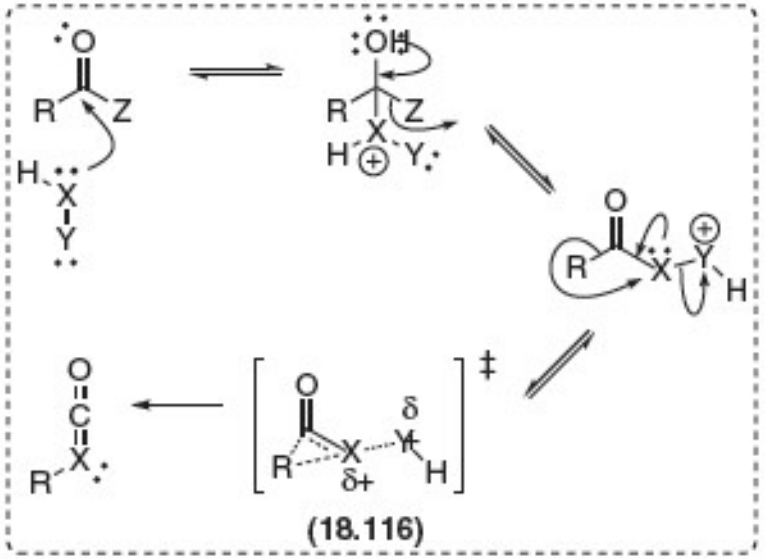
[4] (a) Curtius, T. *Ber. dtsch. chem. Ges.* **1890**, *23*, 3023. (b) Curtius, T. *J. Prakt. Chem.* [2] **1894**, *50*, 275. (b) Smith, P.A.S. *Org. React.* **1946**, *3*, 337. (c) Saunders, J.H.; Slocombe, R.J. *Chem. Rev.* **1948**, *43*, 205.

[5] (a) Lossen, W. *Ann. Chem. Pharm.* **1872**, *161*, 347. (b) Lossen, W. *Ann. Chem. Pharm.* **1875**, *175*, 271, 343. (c) Yale, H.L. *Chem. Rev.* **1943**, *33*, 209. (d) Popp, F.D.; McEwen, W.E. *Chem. Rev.* **1958**, *58*, 370.

[6] (a) Hofmann, A.W. *Ber. dtsch. chem. Ges.* **1881**, *14*, 2725. (b) Hofmann, A.W. *Ber. dtsch. chem. Ges.* **1882**, *15*, 407, 762. (c) Hofmann, A.W. *Ber. dtsch. chem. Ges.* **1884**, *17*, 1406. (d) Hofmann, A.W. *Ber. dtsch. chem. Ges.* **1885**, *18*, 2734. (e) Hofmann, A.W. *Ber. dtsch. chem. Ges.* **1882**, *15*, 752. (f) Franklin, E.C. *Chem. Rev.* **1934**, *14*, 219. (g) Wallis, E.S.; Lane, J.F. *Org. React.* **1946**, *3*, 267.

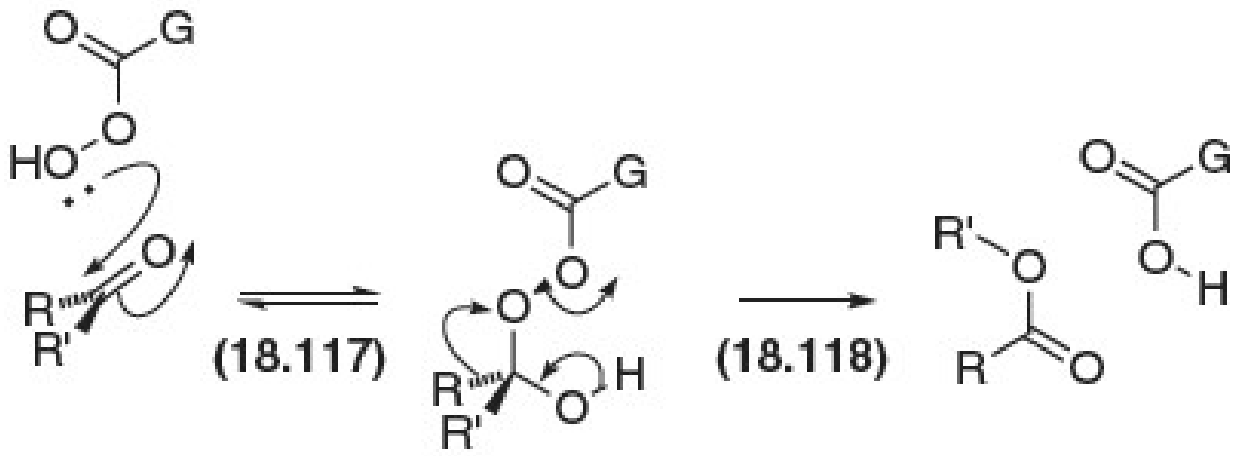
Figure 18.5





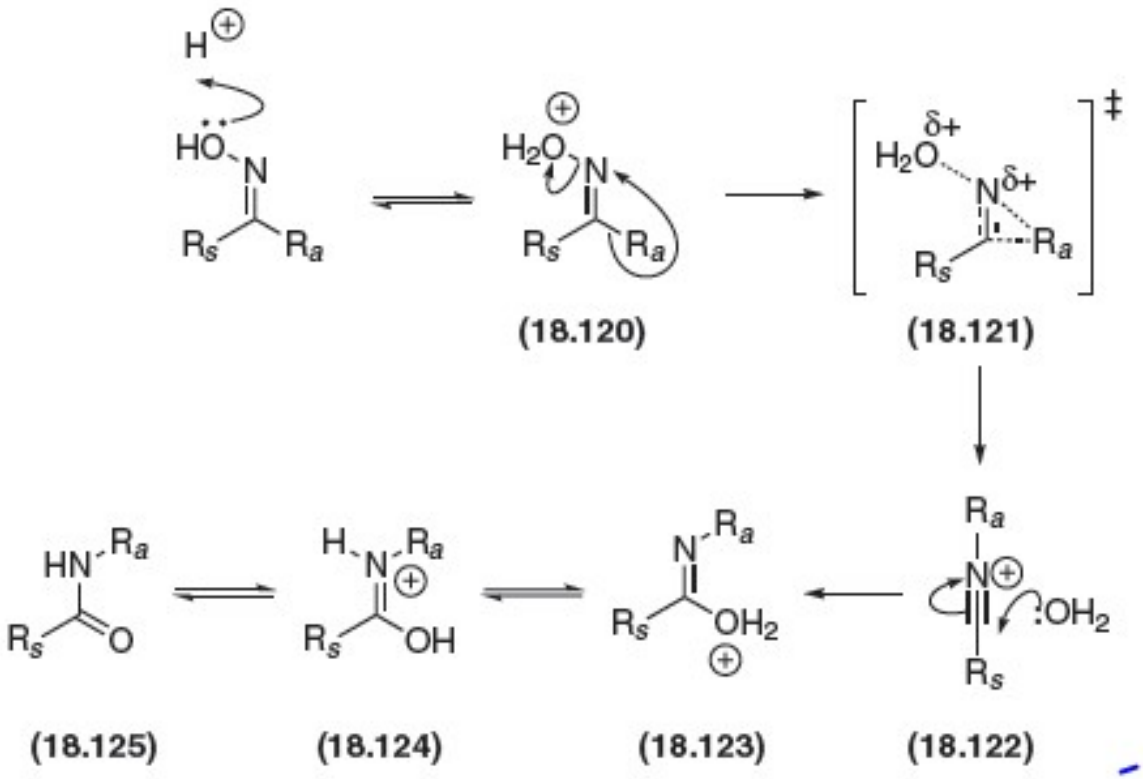
- General mechanisms of oxidative rearrangements
  - rearrangements of ketone derivatives
  - rearrangements of carboxylic acid derivatives

Figure 18.6



- Mechanism of the Baeyer-Villiger oxidation
  - reaction occurs with retention of configuration at the migrating carbon
  - migratory aptitude of groups: 3°R > cyclohexyl≈2°R ≥ $PhCH_2$≈Ph≈vinyl > 1°R > cyclopropyl > Me
  - facilitated by stronger peracids (RCO_3H): R = CF_3 > *c*-$CH{=}CHCO_2H$ > *o*-$C_6H_4CO_2H$ > *p*-$C_6H_4NO_2$ > H ≈ *m*-C_6H_4Cl > C_6H_5 > Me >> Bu

Figure 18.7



- Mechanism of the Beckmann rearrangement
  - group *anti* to the OH group of the oximes migrates preferentially
  - group migrates with retention of configuration at carbon

Representative Beckmann rearrangements

- Rearrangement of cyclohexanone oxime with sulfuric acid gives caprolactam, the key starting material for nylon 6
- As shown in this lower example, mercuric chloride can act as a mild Lewis acid catalyst for the rearrangement

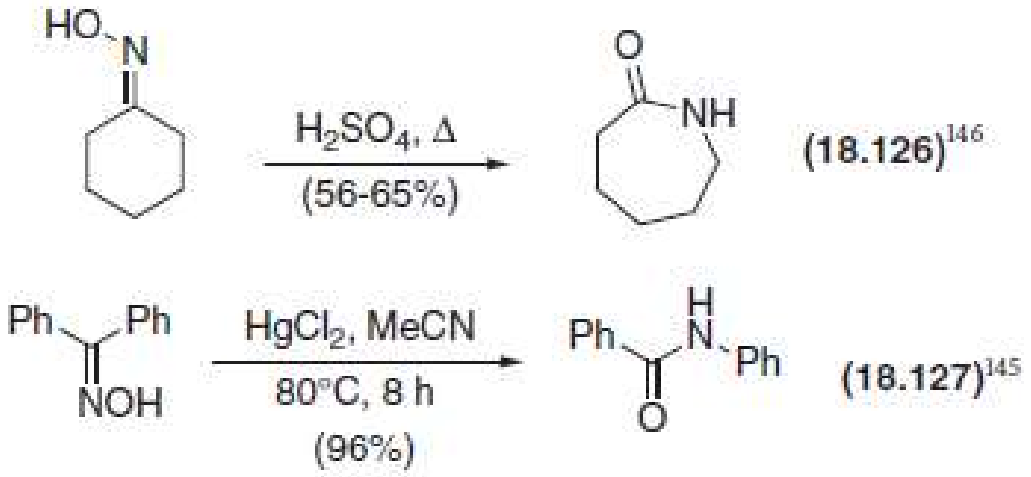
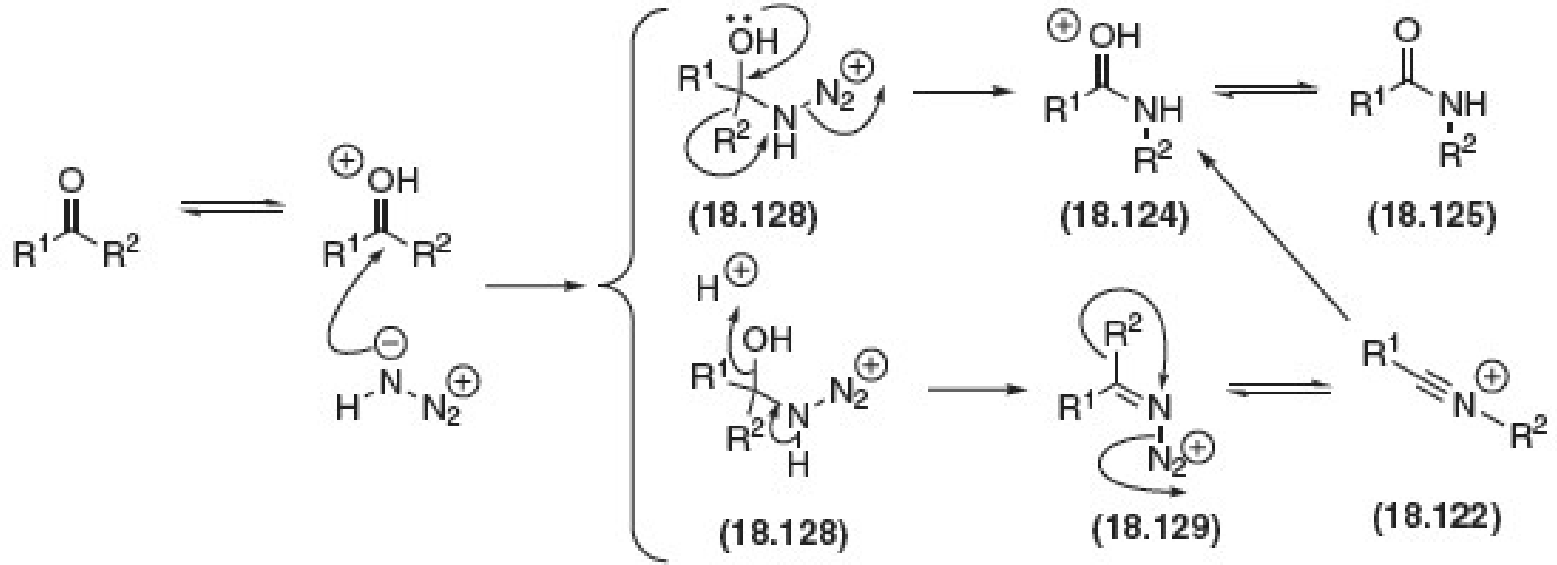
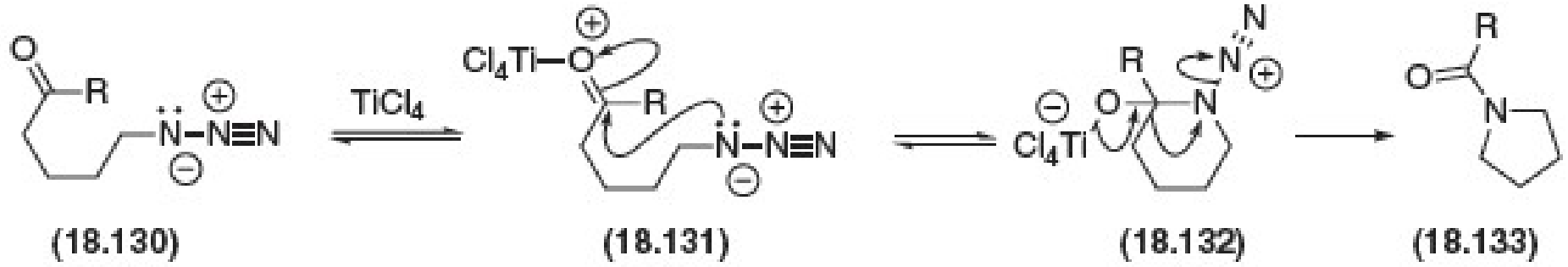


Figure 18.8



- Mechanisms of the Schmidt reaction
  - the rearrangement may proceed by either of two mechanisms
  - the stereochemistry of the migrating group is retained

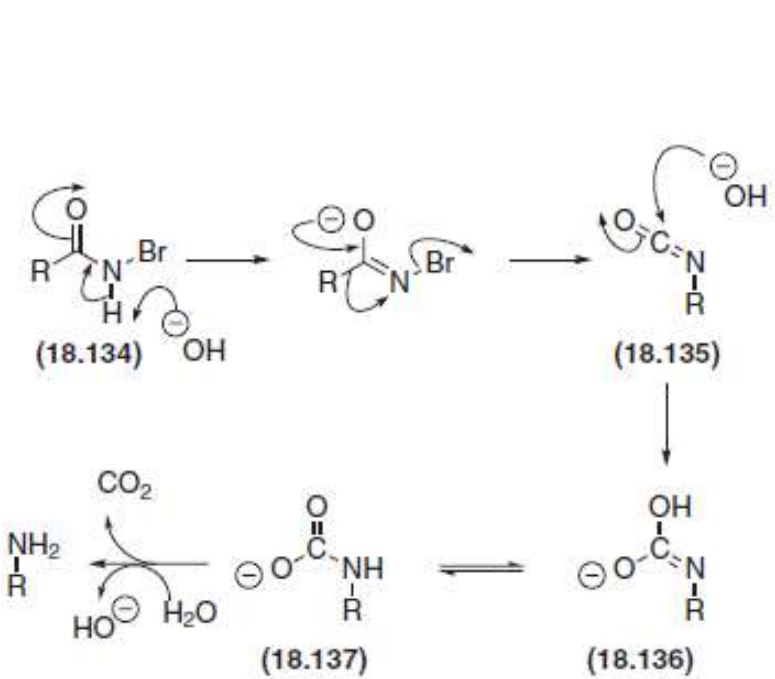
Intramolecular Schmidt-like reaction of an ω-azidoalkyl ketone

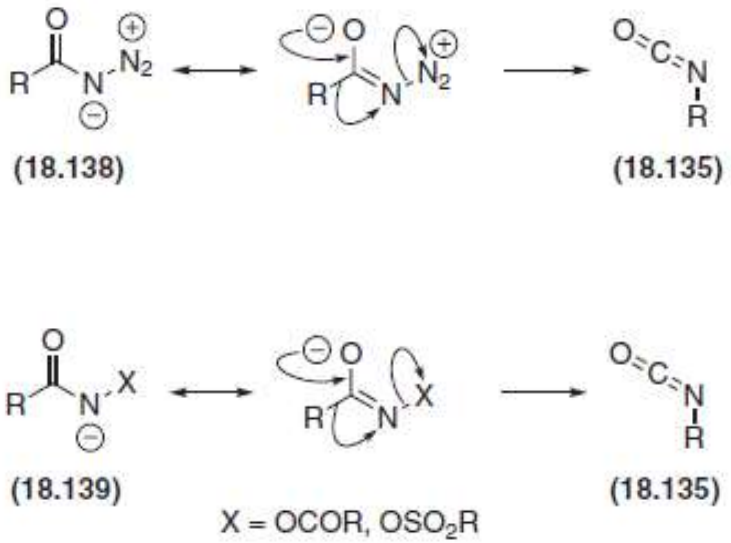


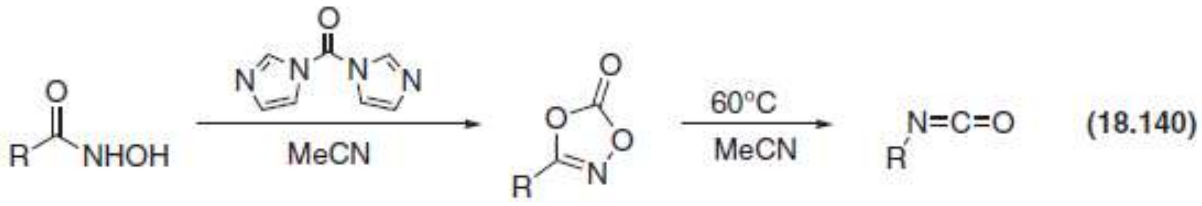
(18.130) (18.131) (18.132) (18.133)

- Reaction proceeds through an *N*-diazonium ion formed by acid-catalyzed addition of the azide group to the carbonyl group
- the rearrangement occurs with retention of configuration at the migrating carbon

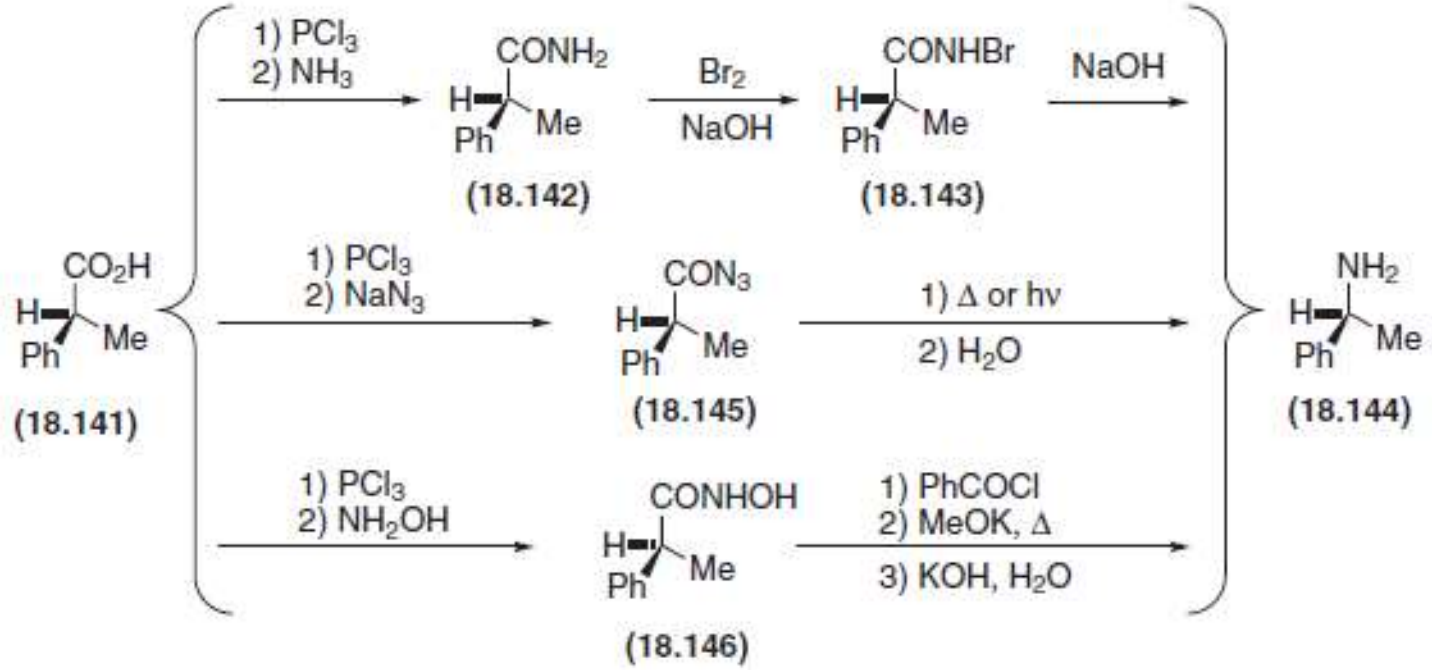
Common mechanistic characteristics of Hofmann, Curtius and Lossen rearrangements





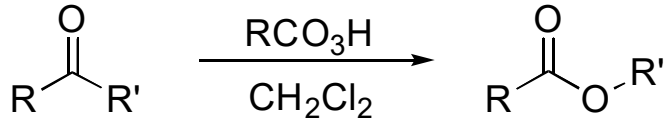


Stereochemistry in Hofmann, Curtius and Lossen rearrangements



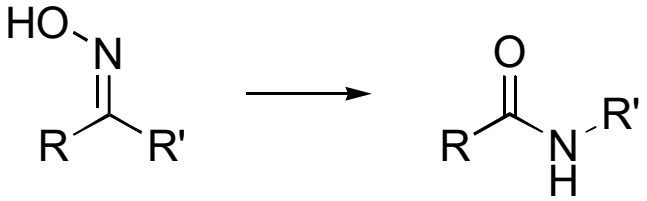
- all rearrangements occur with retention of configuration at the migrating carbon
- color coding is the same as in the previous slide

Reaction synopses: Baeyer-Villiger oxidation (rearrangement)



Reagents:	HCO_3H; $MeCO_3H$; *m*-CPBA; etc.
or	H_2O_2, R_FOH, $PhAsO_3H$; H_2O_2, R_FOH, TsOH; etc.
or	H_2O_2, zeolites; etc.

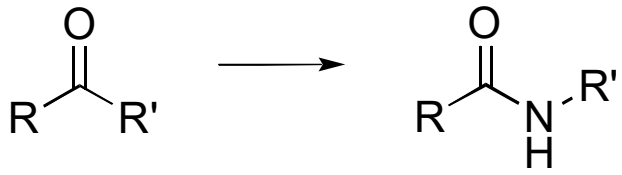
Reaction synopses: Beckmann rearrangement



Reagents: H_2SO_4, H_3PO_4

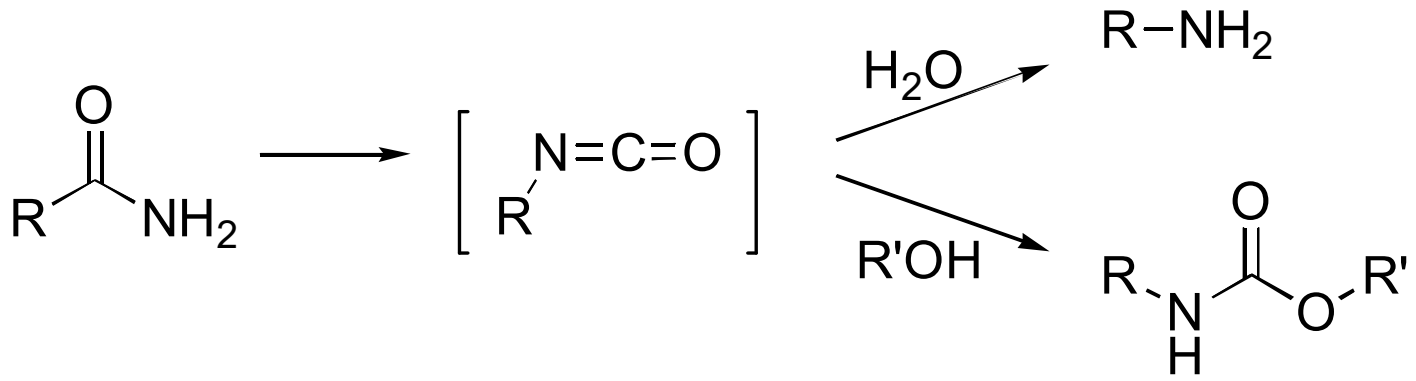
or $POCl_3$, PCl_5, P_2O_5, $SOCl_2$, $(COCl)_2$, cyanuric chloride, Ac_2O, RN=C=NR, RN=C=O; etc.

Reaction synopsis: Schmidt reaction



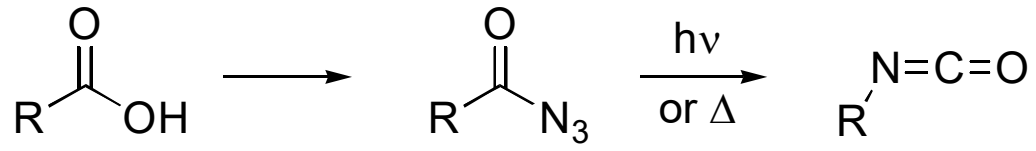
Reagents: HN_3; NaN_3/HCl; Me_3SiN_3/ZnI_2; etc.

Reaction synopses: Hofmann rearrangement



Reagents: $Br_2/KOH/H_2O$; $NaOCl/H_2O$; etc.
or $Br_2/ROH/RONa$

Reaction synopses: Curtius rearrangement



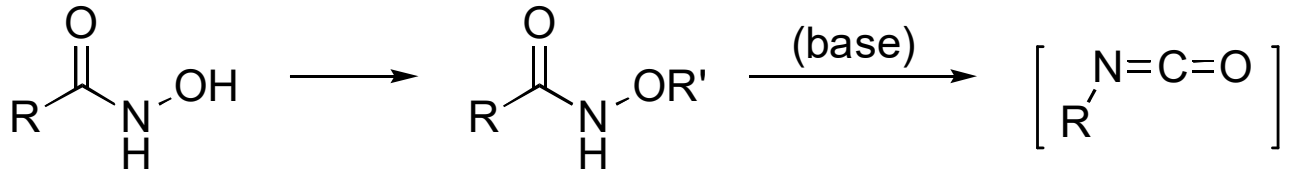
Reagents: 1) PCl_3; 2) NaN_3; 3) Δ

or 1) $ClCO_2Et$, Et_3N, THF; 2) NaN_3, H_2O; 3) hν, PhH

or NaN_3, H_2SO_4, H_2O, Δ

or 1) PCl_3; 2) H_2NNH_2; 3) HONO

Reaction synopses: Lossen rearrangement



Reagents: H_2SO_4; H_3PO_4; etc.

or 1)PhCOCl; 2) KOMe, MeOH, Δ $_2$O, NaOAc, Δ

or 1) TsCl, py; 2) $KOCMe_3$; etc.

or K_2CO_3, Me_2SO, Δ

Table 18.7: Forms of oxidation reactions

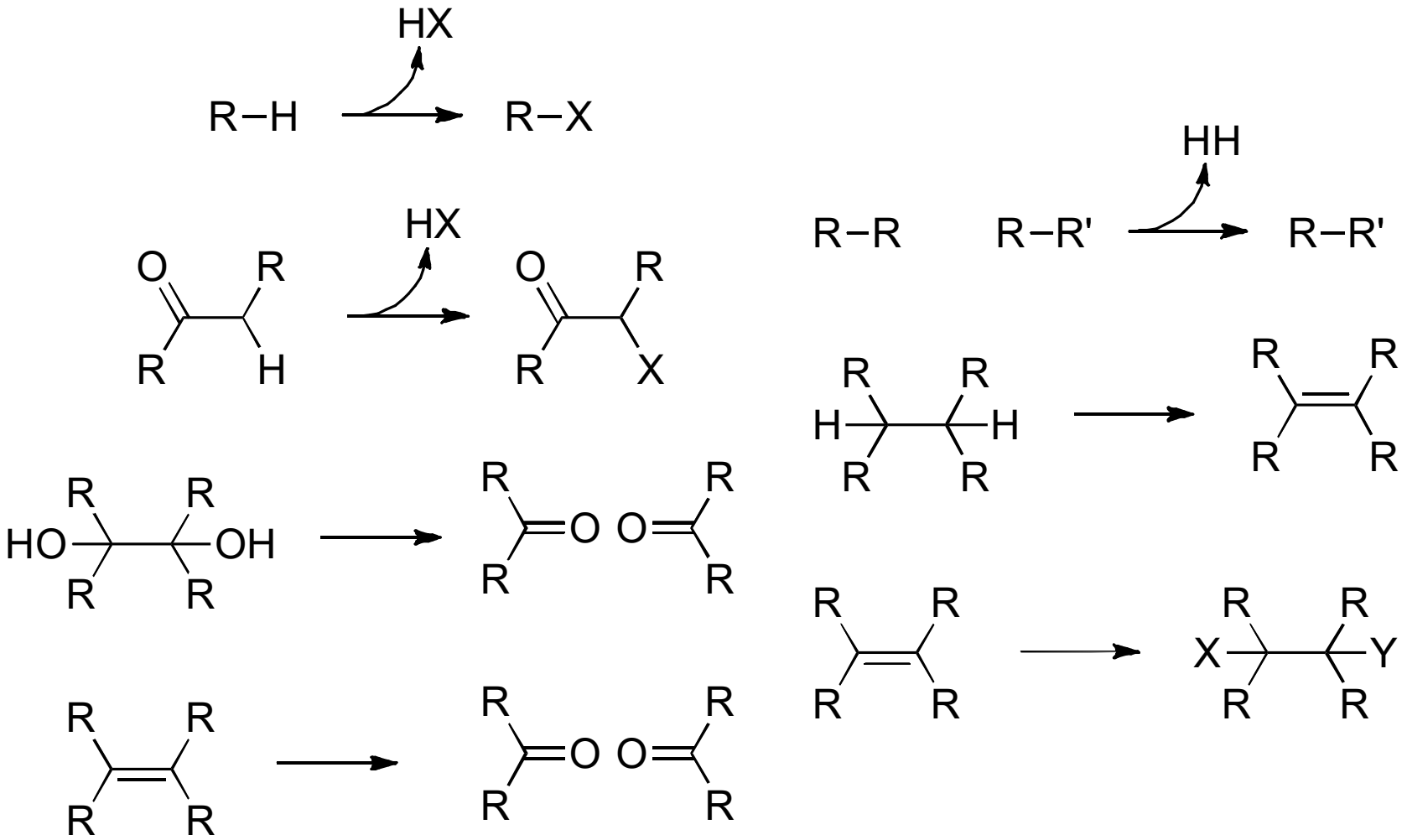
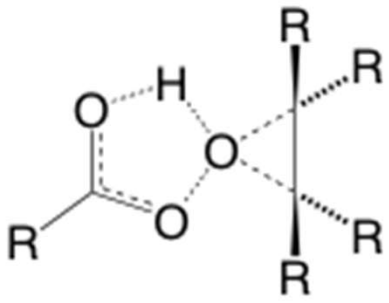
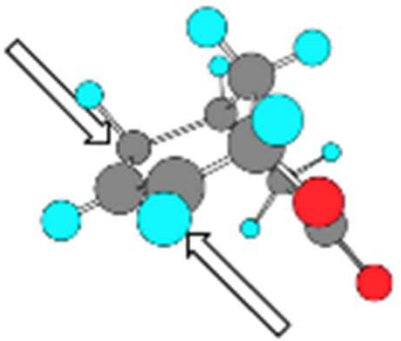
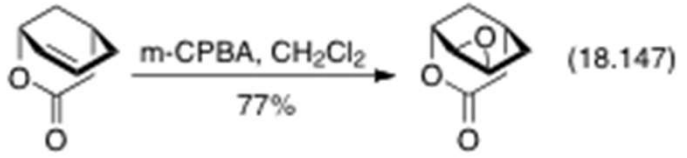
Oxidative substitution	Dehydrogenation
	

Figure 18.9

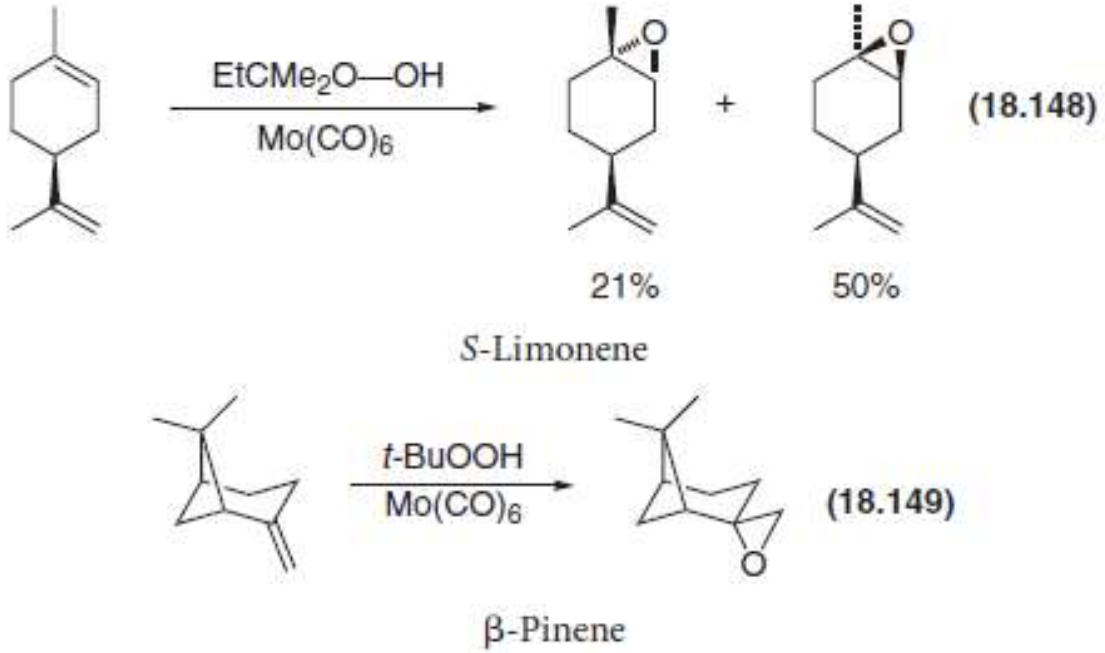
- Transition state for concerted transfer of oxygen in epoxidation
- transfer of oxygen occurs to the less hindered face of the alkene π bond.





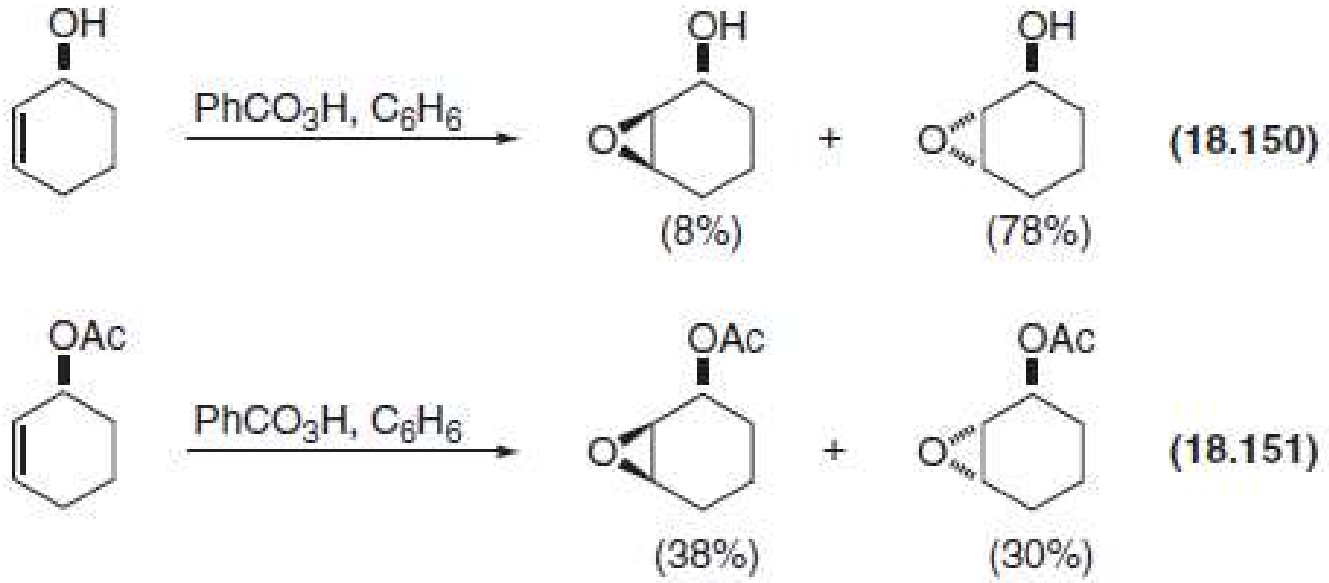


Representative epoxidations with $Mo(CO)_6$ and a hydroperoxide



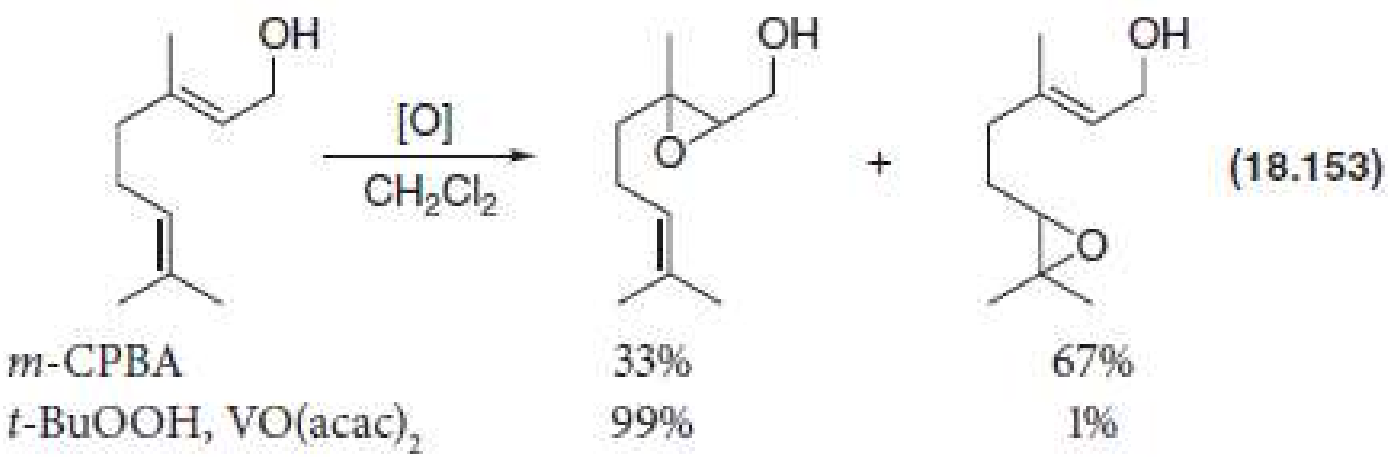
- the more substituted (electron-rich) π bond of a diene reacts more rapidly
- the π bond is attacked from the less hindered face

Effects of hydrogen bonding on epoxide stereochemistry



- a cyclic allylic alcohol will preferentially form the epoxide with the oxygen atoms *cis*.
- a cyclic allylic ether or ester will preferentially form the epoxide with the oxygen atoms *trans*.

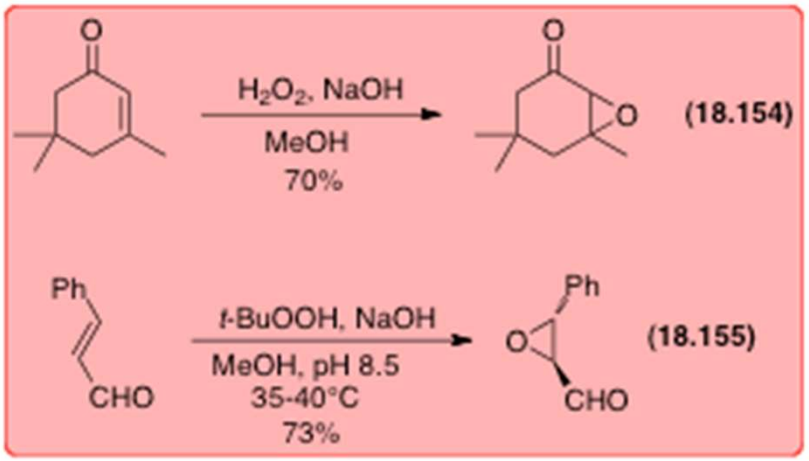
Comparison of peracid and transition metal-catalyzed epoxidations

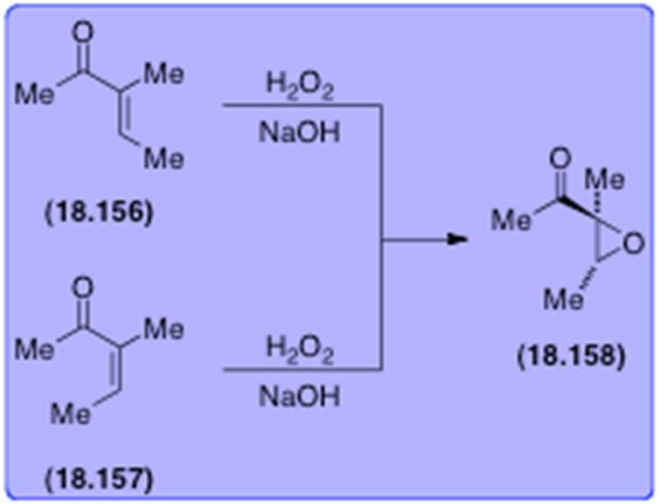


- peracids exhibit a preference for reaction at the more electron-rich π bond, even in a situation where one of the alkenes is part of an allylic alcohol.
- transition metal-catalyzed epoxidations are highly selective for allylic alcohols over isolated alkene π bonds

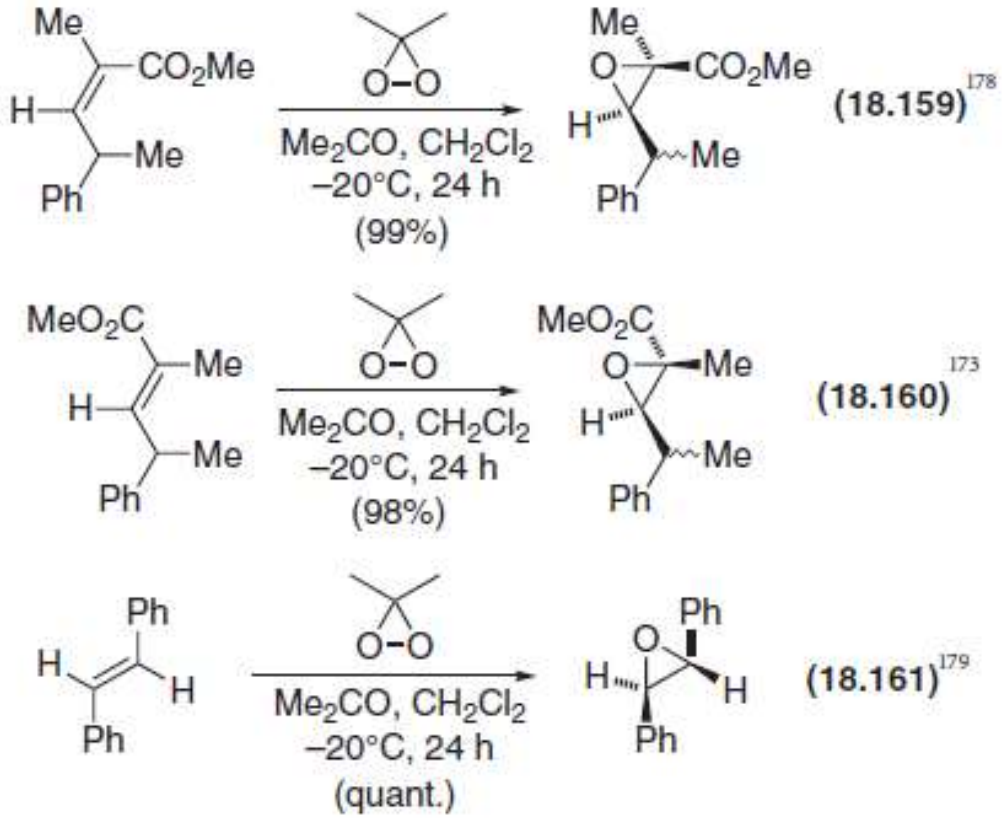
Epoxidation of electron-deficient alkenes

- epoxidation of conjugated carbonyl compounds must be effected using a nucleophilic oxidizing agent (typically the conjugate base of a hydroperoxide)
- epoxidation of the *E* and *Z* isomers of the enone at right gives the same stereoisomer of the major product
  - the reaction proceeds by a stepwise mechanism through initial addition and subsequent displacement of the hydroxide or alkoxide anion in the second step.



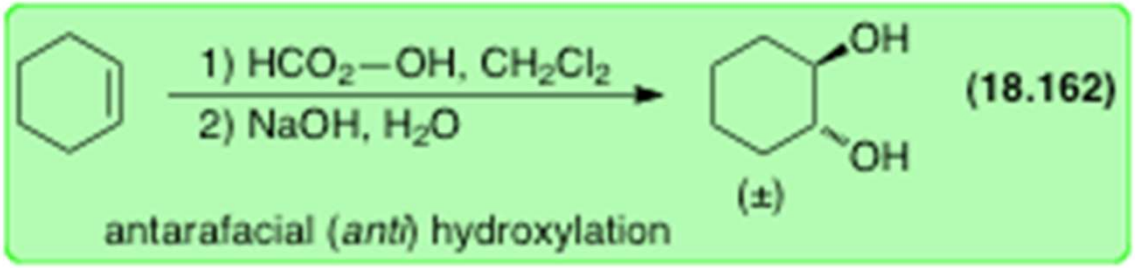


Epoxidations with dimethyldioxirane

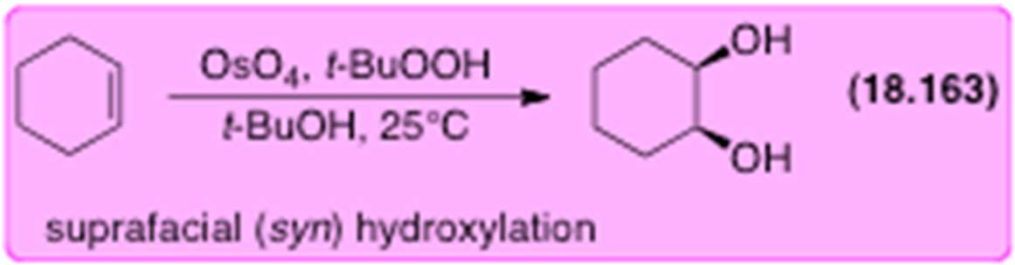


- The stereochemistry of the alkene is preserved in the product
- this reagent will epoxidize both electron-rich and electron-deficient alkene π bonds

Hydroxylation (dihydroxylation) of alkenes



(18.162)

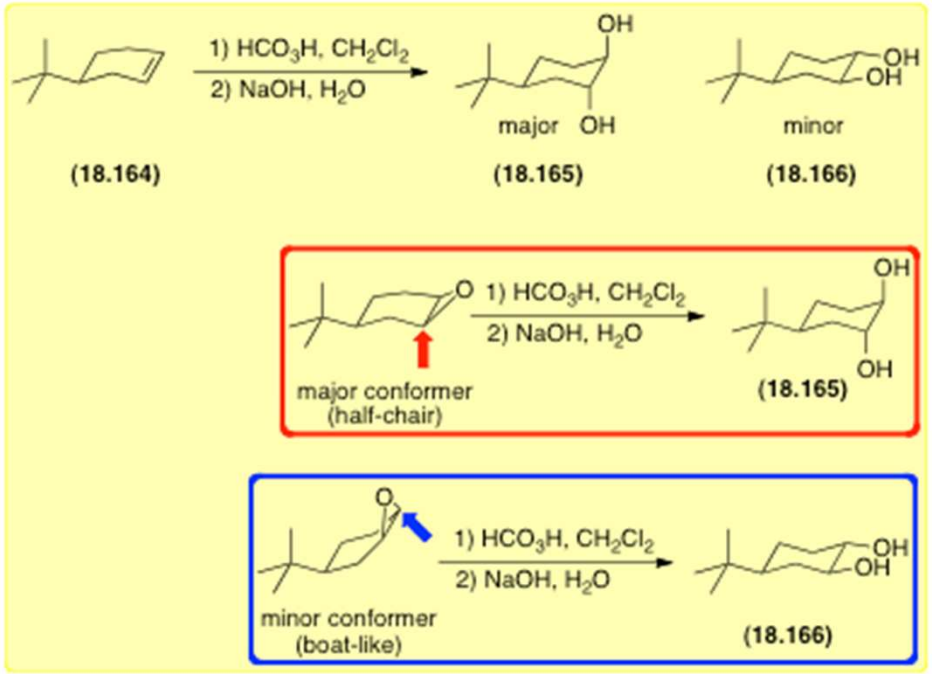


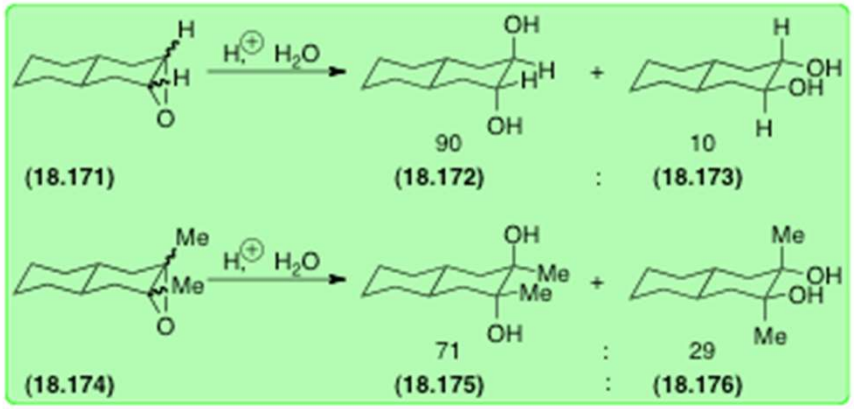
(18.163)

- addition of elements of HO—OH across the π bond
- may be antarafacial (*anti*) or suprafacial (*syn*)

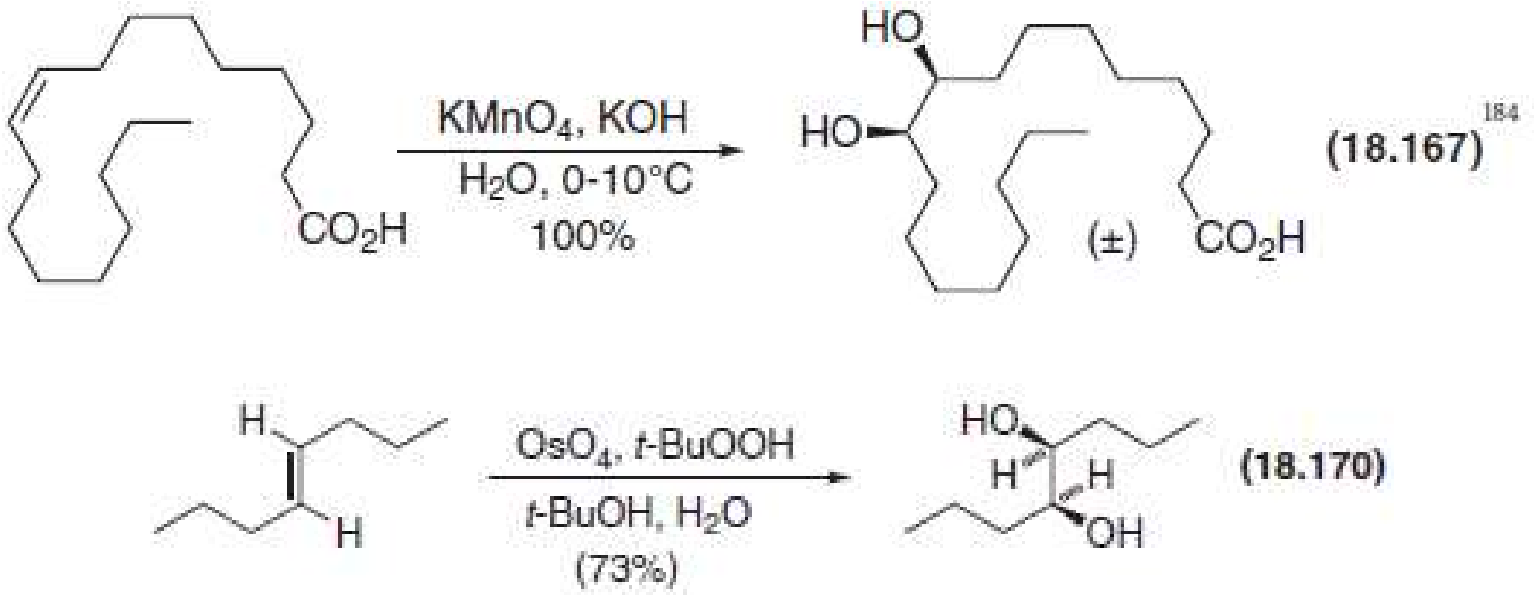
anti-Hydroxylation of cyclohexenes

- reaction proceeds through the epoxide
- epoxides always open *anti*, whether under acid or base conditions
- product should be the *trans*-diaxial diol (both OH groups *anti* in the six-membered ring)
- the *trans*-diequatorial diol may be formed from a boat-like conformation of the epoxide (the epoxide has more conformational flexibility than a typical cyclohexane)
- note how additional substitution on the ring in the acid-catalyzed ring opening reduces the diastereoselectivity





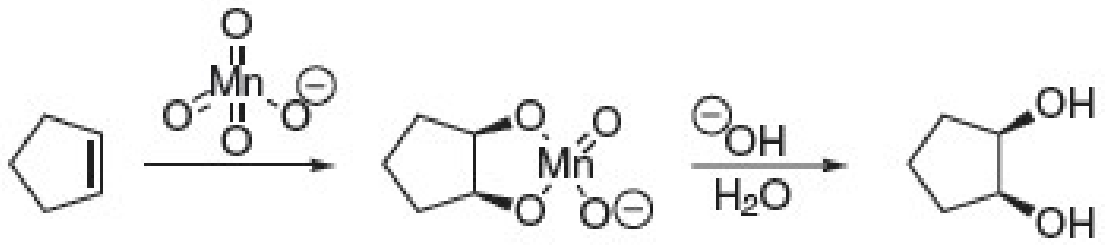
syn-Hydroxylation of alkenes



- both permanganate and osmium tetroxide will accomplish *syn* hydroxylation
- the toxicity and expense of osmium tetroxide have led to the development of catalytic processes where the terminal oxidant is sodium chlorate of an organic hydroperoxide

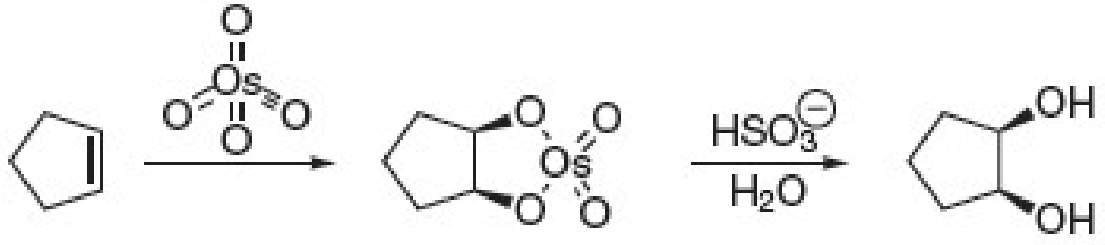
Figure 18.9

- Cyclic ester intermediates in hydroxylation



(18.168)

manganate ester

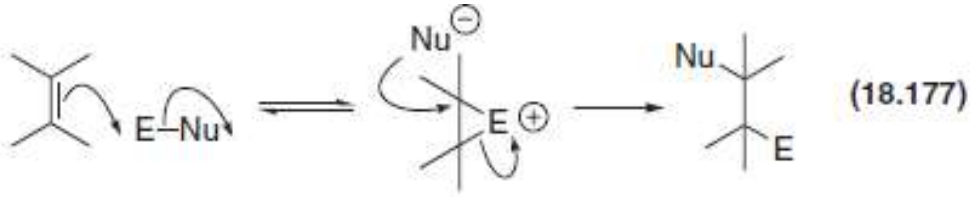


(18.169)

osmate ester

Table 18.10

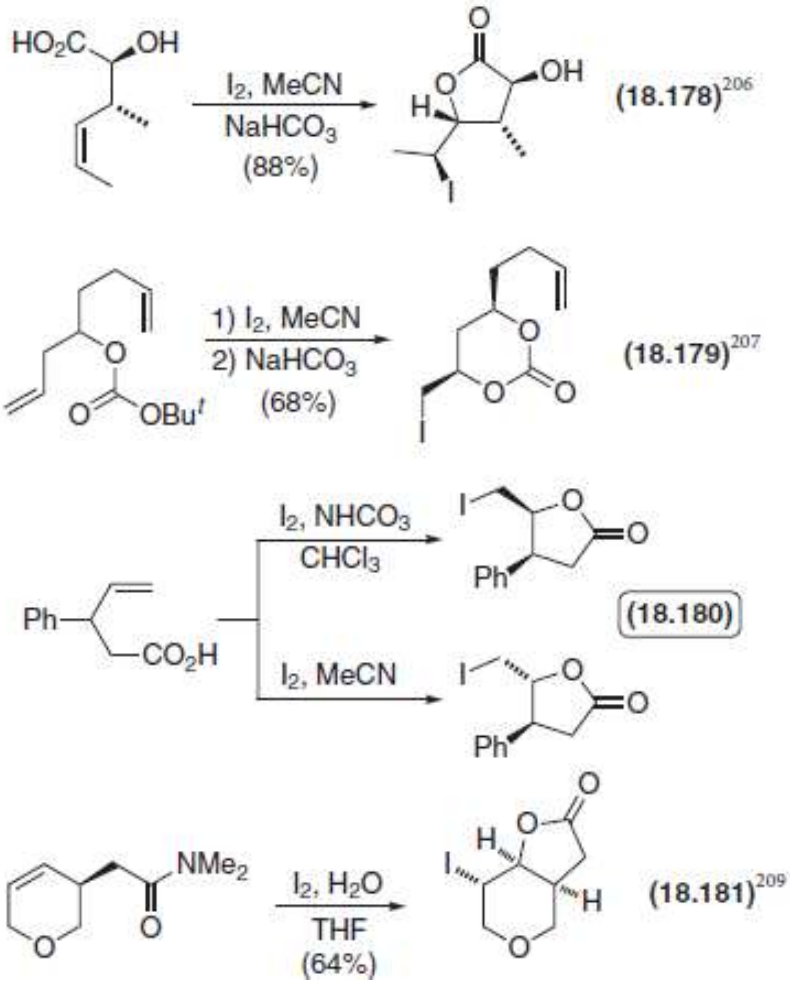
Oxidizing electrophiles that add to alkenes to give *anti* adducts

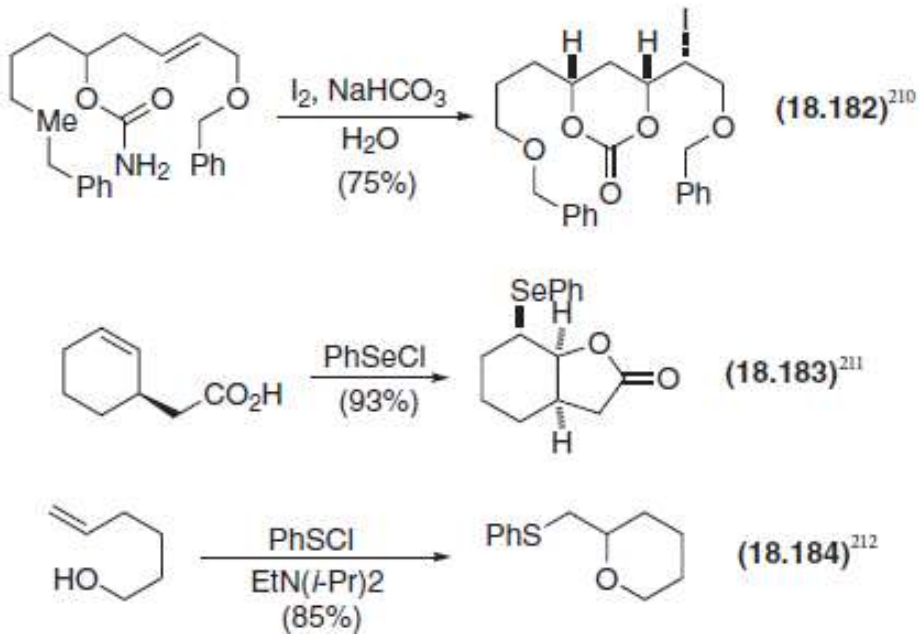


(18.177)

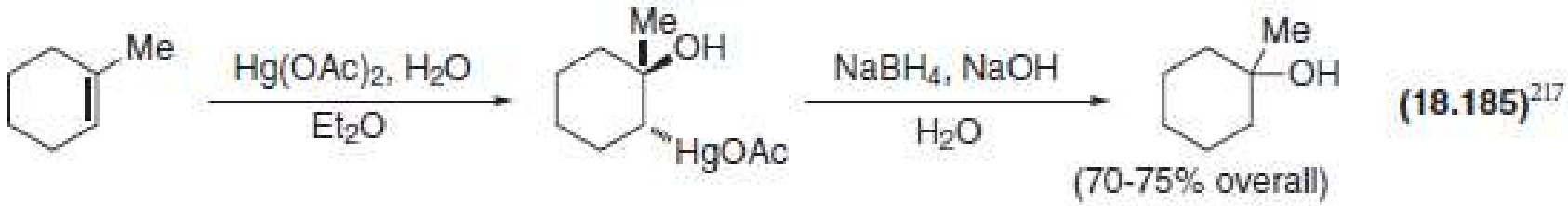
Electrophile (EÑ Nu)	Typical Reagents
XÑ X'	Br_2, CH_2Cl_2; BrCl, CH_2Cl_2; etc.
XÑ OH (XÑ OR)	Br_2, H_2O; NBS, Me_2SO, H_2O; Br_2, MeOH; etc.
BrÑ OH, IÑ OH	$NaBrO_3$ (or $NaIO_4$), $NaHSO_3$, H_2O, MeCN; etc.
XÑ OCOR	Br_2, HOAc; Br_2, NaOAc, MeCN; etc.
RSÑ X	PhSCl, CH_2Cl_2; PhSCl, NaOAc, THF; etc.
RSeÑ X	PhSeCl, CH_2Cl_2; PhSeCl, NaOAc, THF; etc.
IÑ N_3	IN_3, CH_2Cl_2
BrÑ N_3	HN_3, Br_2
IÑ NCO	AgNCO, I_2
XÑ SCN	I_2, $(NCS)_2$; Cl_2, $Pb(SCN)_2$

Representative *anti* additions to alkenes





anti Addition of transition metal electrophiles to alkenes



- the prototypical example of this type of reaction is the oxymercuration step of the oxymercuration-demercuration sequence for preparing alcohols from alkenes by Markovnikov addition of water, without rearrangement

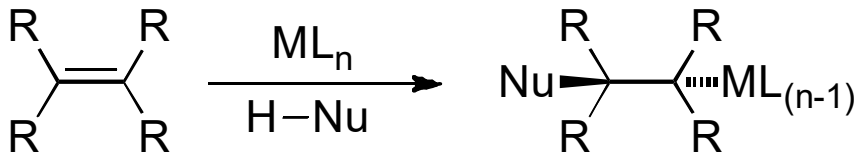
Reaction synopses: Addition of halogens and halogen-like reagents

Reagents: Br_2, CH_2Cl_2; Cl_2, CH_2Cl_2; IN_3; Br_2, H_2O; etc.

or ($Y=CO_2H$): Br_2, $NaHCO_3$, H_2O; I_2, $NaHCO_3$, H_2O; I_2, MeCN; etc.

Stereochemistry: *anti* addition predominates

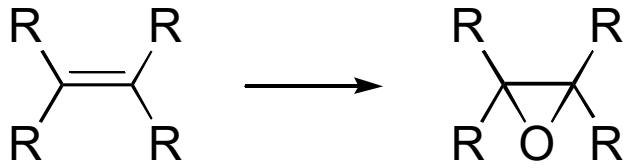
Reaction synopses: Oxymetallation



Reagents: $Hg(OAc)_2$, H_2O, THF; $Hg(OCOR)_2$, ROH;
$Hg(OCOR)_2$, RNHCOR'; $Pd(OAc)_2$, H_2O, MeCN; etc.

Replacement of metal by heteroatom leads to net oxidation

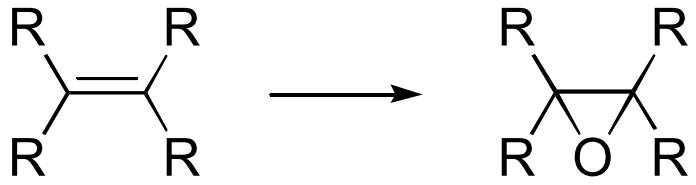
Reaction synopses: Epoxidation of alkenes (Prilezhaev reaction)



Reagents: *m*-CPBA, CH_2Cl_2; HCO_3H, CH_2Cl_2; CF_3CO_3H, CH_2Cl_2; MMPP, CH_2Cl_2; 1) Br_2, H_2O, 2) K_2CO_3, acetone; etc.

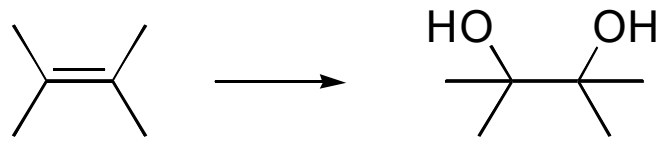
Stereochemistry: overall suprafacial addition to the π

Reaction synopses: Epoxidation of conjugated carbonyl compounds



Reagents: H_2O_2, KOH; Me_3COOH, KOH; Me_2CO_2, Me_2CO; Me_2CO_2, Me_2CO; Me_2CO, Oxone¨; etc.

Reaction synopses: Hydroxylation of alkenes



Stereochemistry: may be either *syn* (suprafacial) or *anti* (antarafacial).

Reagents: *syn*: $KMnO_4$, KOH, H_2O;

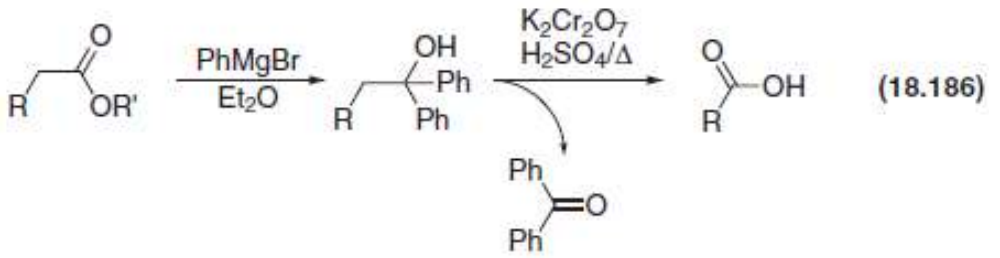
1) OsO_4, 2) KOH or $NaHSO_3$, H_2O;

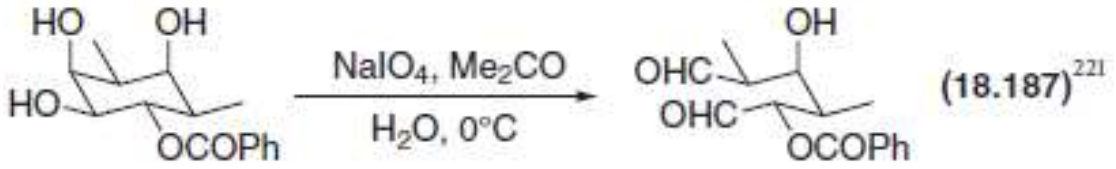
OsO_4, $NaClO_3$, H_2O, CH_2Cl_2; etc.

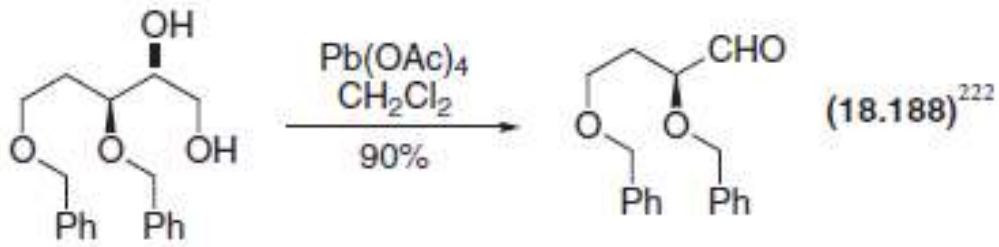
anti: 1) HCO_3H, CH_2Cl_2, 2) $K_2N_2O_2$, H_2O; etc.

Cleavage of 1,2-diols

Cleavage by chromic acid is the end step of the Barbier-Wieland degradation of esters



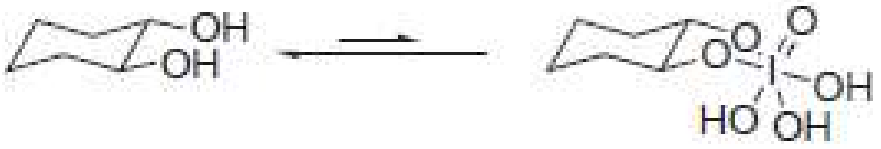




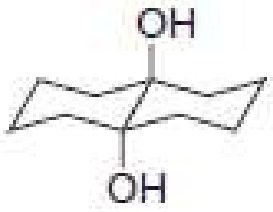
Diol stereochemistry and cleavage

- periodate cleavage requires the formation of a cyclic periodate ester
- *cis*-1,2-cyclohexanediols can readily form a cyclic periodate ester, and react rapidly with periodates
- *trans*-1,2-cyclohexanediols cannot easily form a cyclic periodate ester, and does not react rapidly with periodate
- *trans*-1,2-diols such as **18.191** and **18.192** canot form a cyclic periodate ester. They are not cleaved by periodfate, but are cleaved by lead tetraacetate

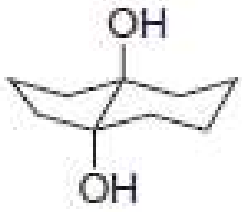
(18.189)



(18.190)

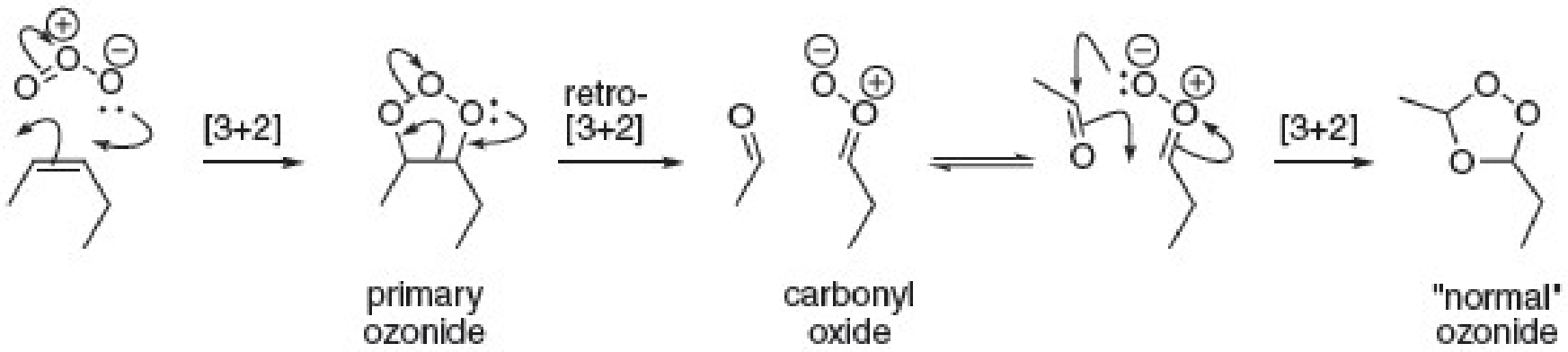


(18.191)



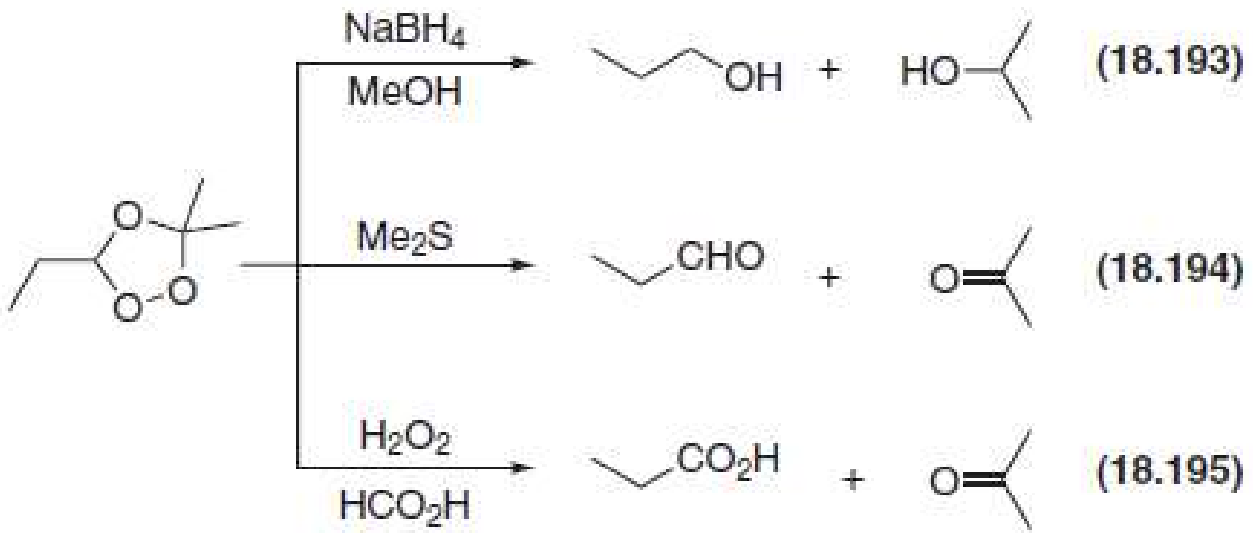
(18.192)

Figure 18.10



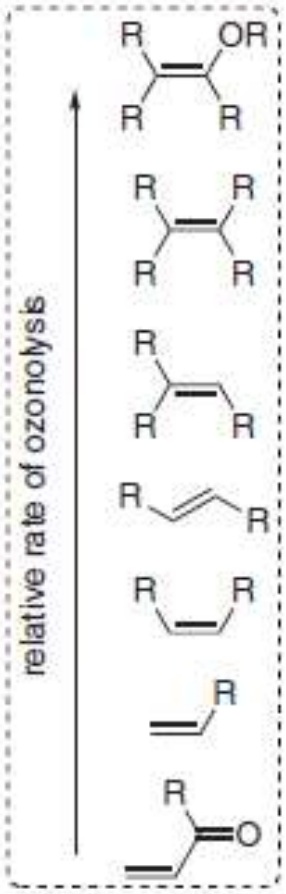
- The Criegee mechanism ofozonolysis

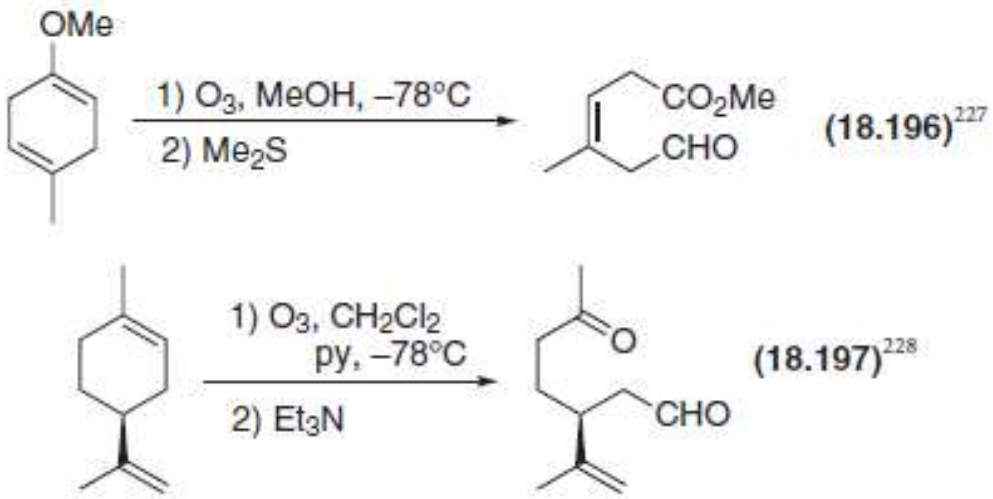
Work-up of ozonolysis



- reduction of the ozonide with sodium borohydride gives the corresponding alcohols
- reduction of the ozonide with dimethyl sulfide or trimethyl phosphite gives aldehydes and ketones
- oxidation of the ozonide with peracids gives ketones and vcarboxylic acids

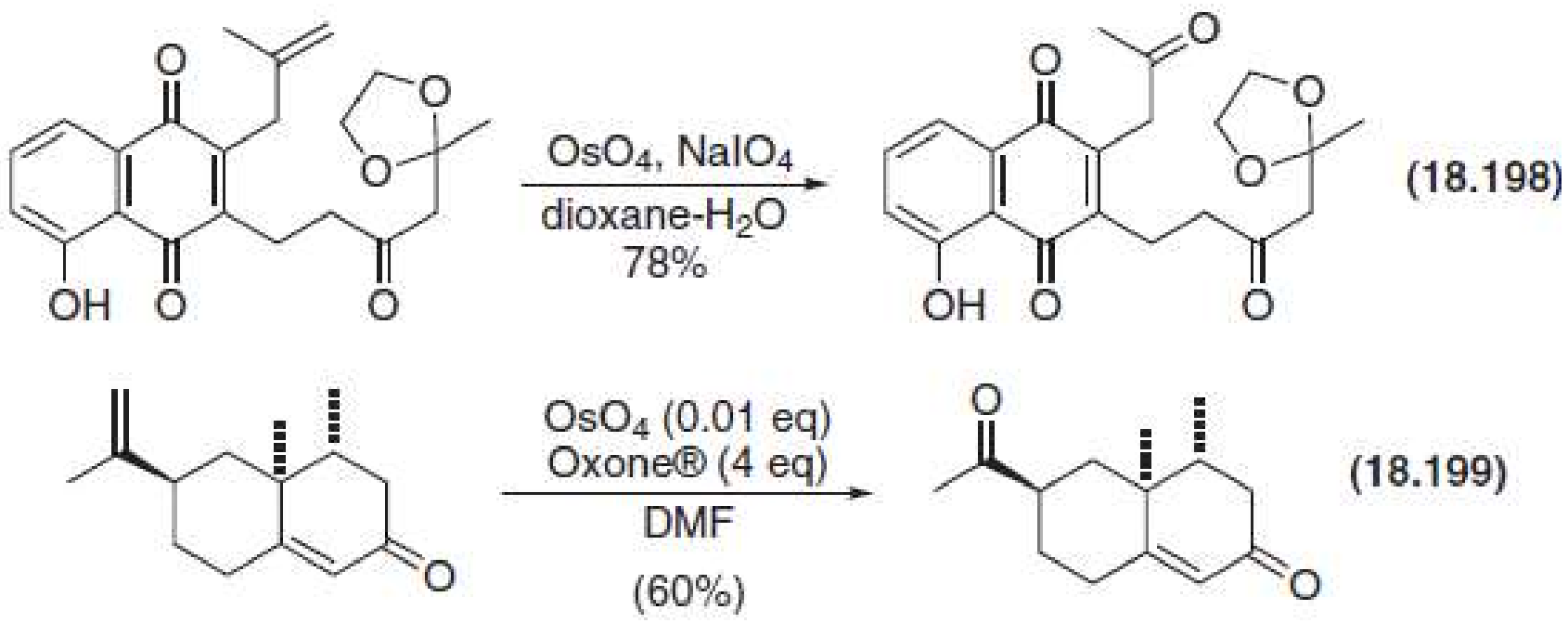
Selectivity in ozonolysis





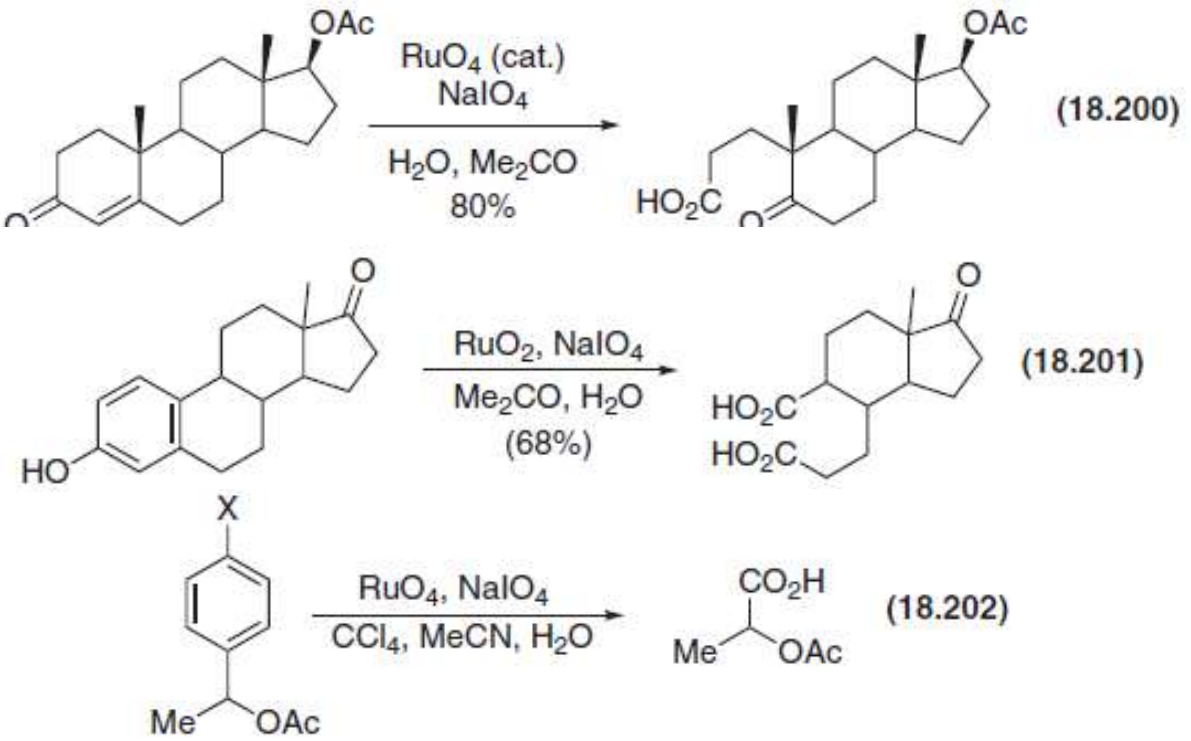
- the most electron rich alkene reacts most rapidly

Lemieux-Johnson cleavage of alkenes



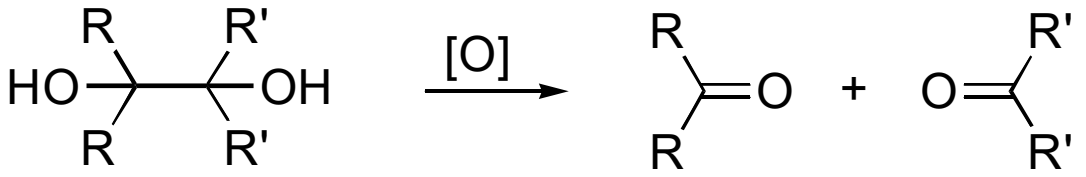
- The reaction is catalytic in osmium tetroxide, with a secondary oxidant to reveal the diol and cleave it

Cleavage of C—C π bonds with ruthenium tetroxide



- ruthenium tetroxide is a much stronger oxidant than osmium tetroxide.
- ruthenium tetroxide will cleave aromatic rings, and oxidizes the double bond in testosterone acetate (**18.200**); osmium tetroxide does not react with this enone.

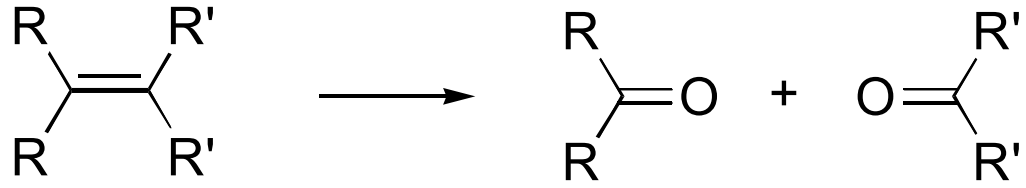
Reaction synopses: Oxidative cleavage of 1,2-diols



Reagents: HIO_4; $Pb(OAc)_4$, CH_3CO_2H; CrO_3; etc.

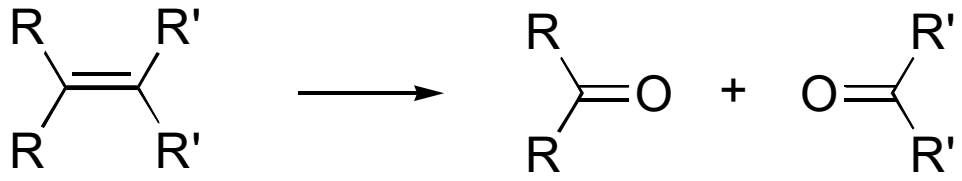
In cyclic systems, *cis*-diols react faster than their *trans* isomers.

Reaction synopses: Ozonolysis



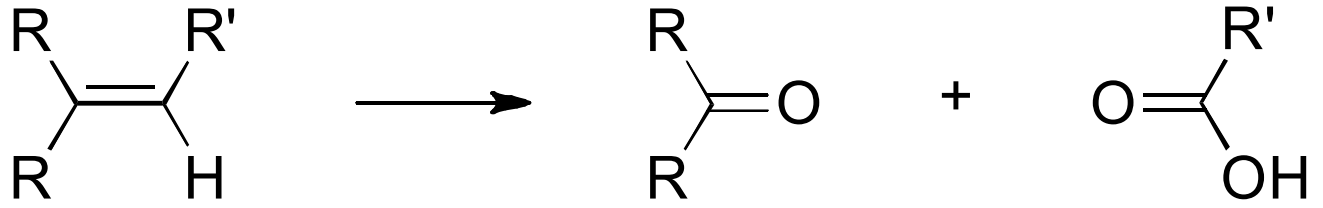
Reagents: 1) O_3, CH_2Cl_2, Ğ78¡C; 2) Zn, H_2O;
or 1) O_3, CH_2Cl_2, Ğ78¡C; 2) Me_2S; etc.
or 1) O_3, CH_2Cl_2, Ğ78¡C; 2) CH_3CO_2OH; etc.

Reaction synopses: Lemieux-Johnson oxidation reactions



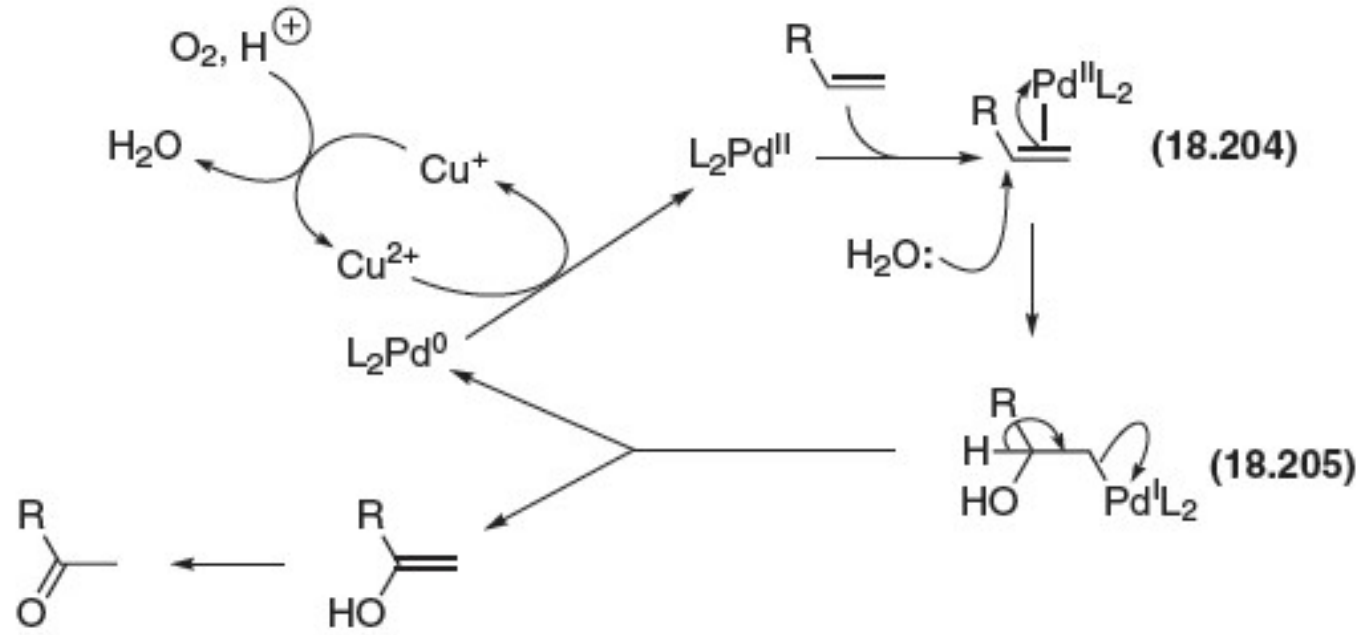
Reagents: OsO_4, $NaIO_4$, CCl_4, H_2O; etc. to give aldehydes;
or OsO_4, Oxone¨, DMF; etc. to give acids

Reaction synopses: Ruthenium tetroxide oxidations



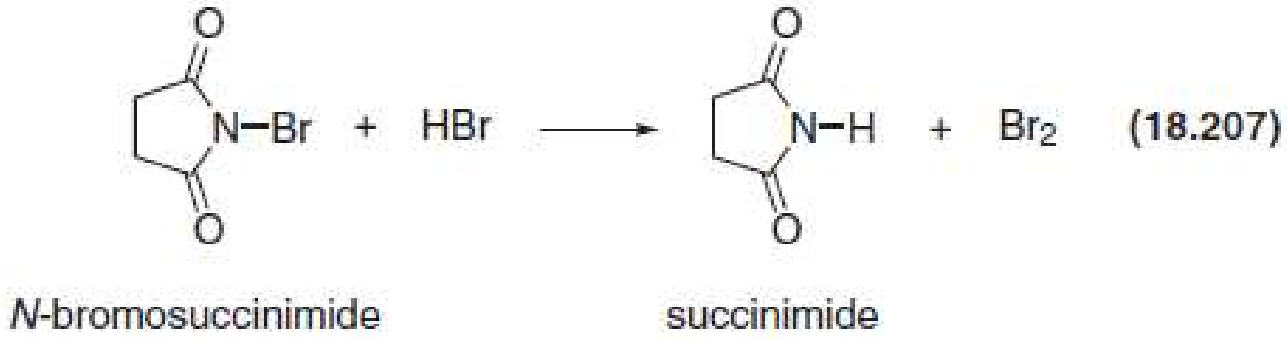
Reagents: RuO_4, CCl_4; RuO_4, Me_2CO, H_2O;
or (RuO_2 or $RuCl_3$), $NaIO_4$, CCl_4, H_2O.

Figure 18.11

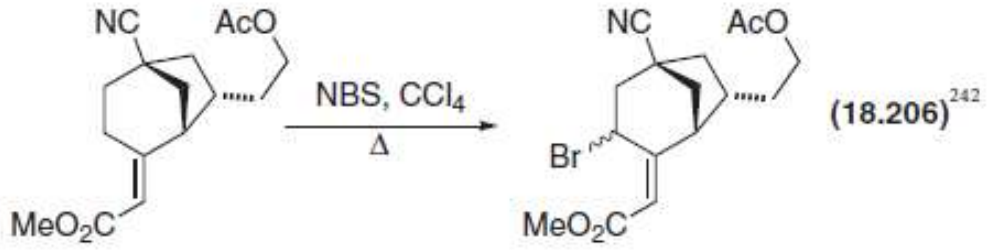


- The catalytic cycle of the Wacker oxidation of 1-alkenes

Allylic halogenation

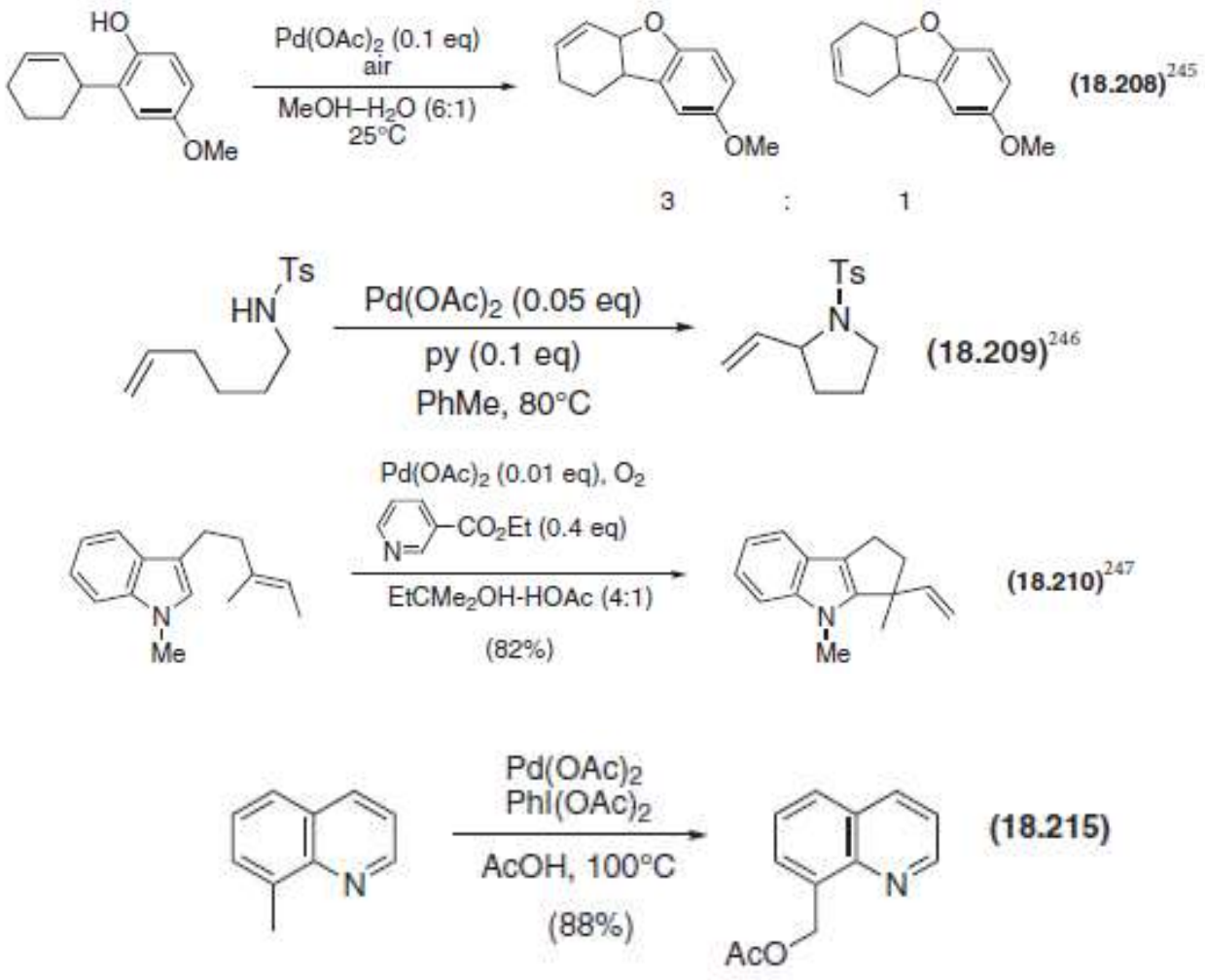


N-bromosuccinimide serves as a source of elemental bromine

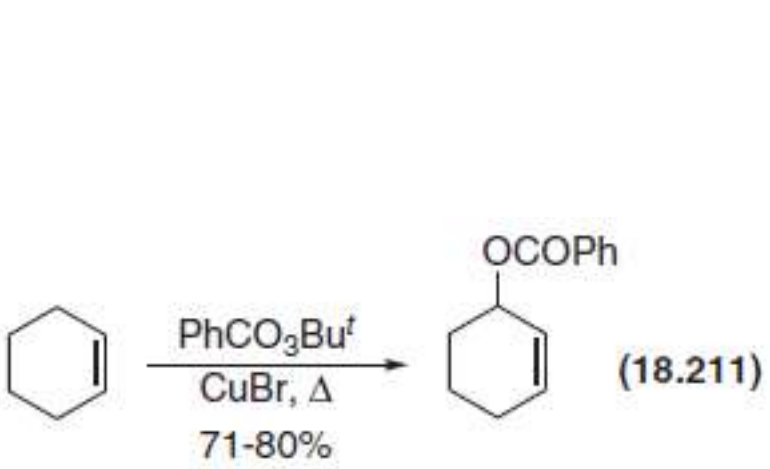


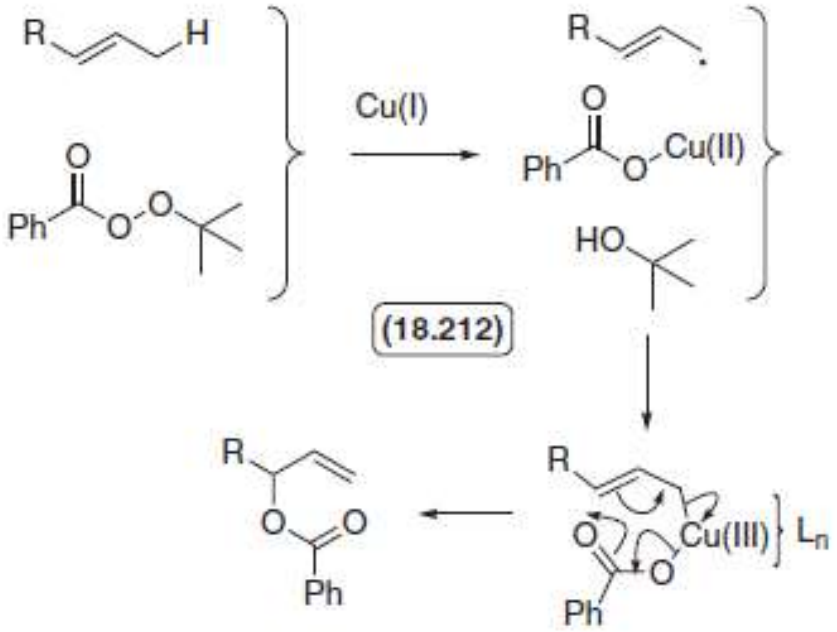
Allylic oxidation with Pd (II)

these reactions most likely proceed through the η^3-allylpalladium complex



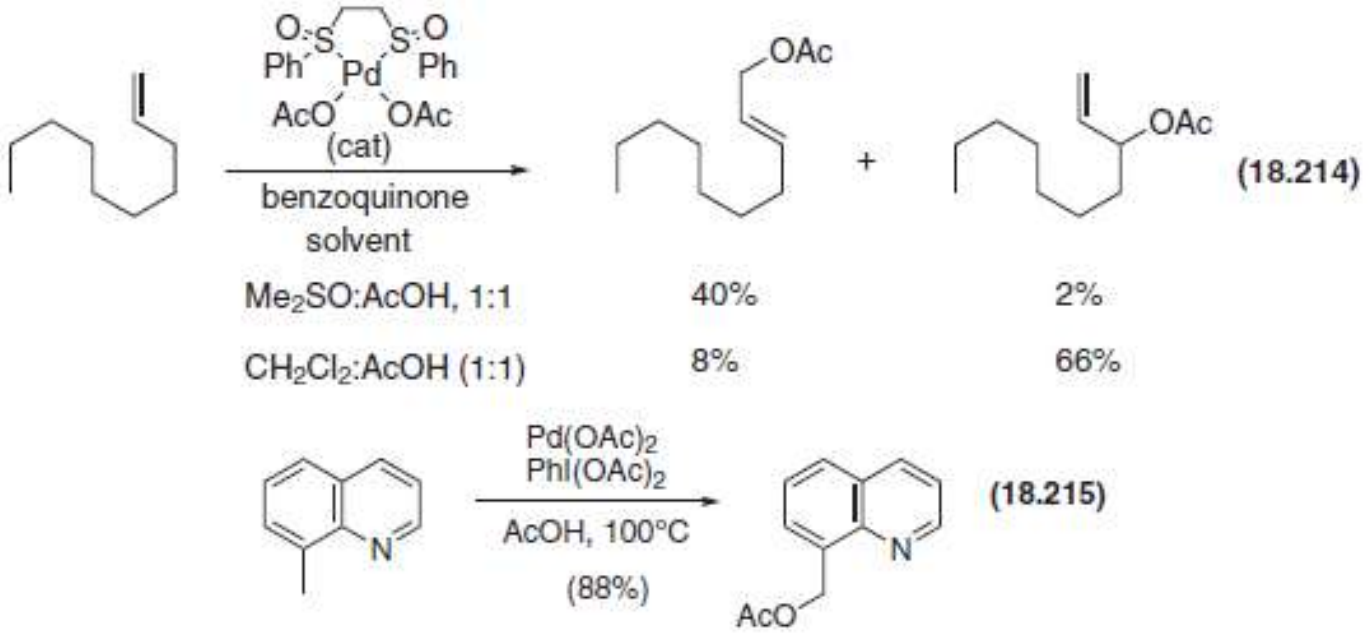
Allylic oxidation with Cu (I) and a *tert*-butyl perester





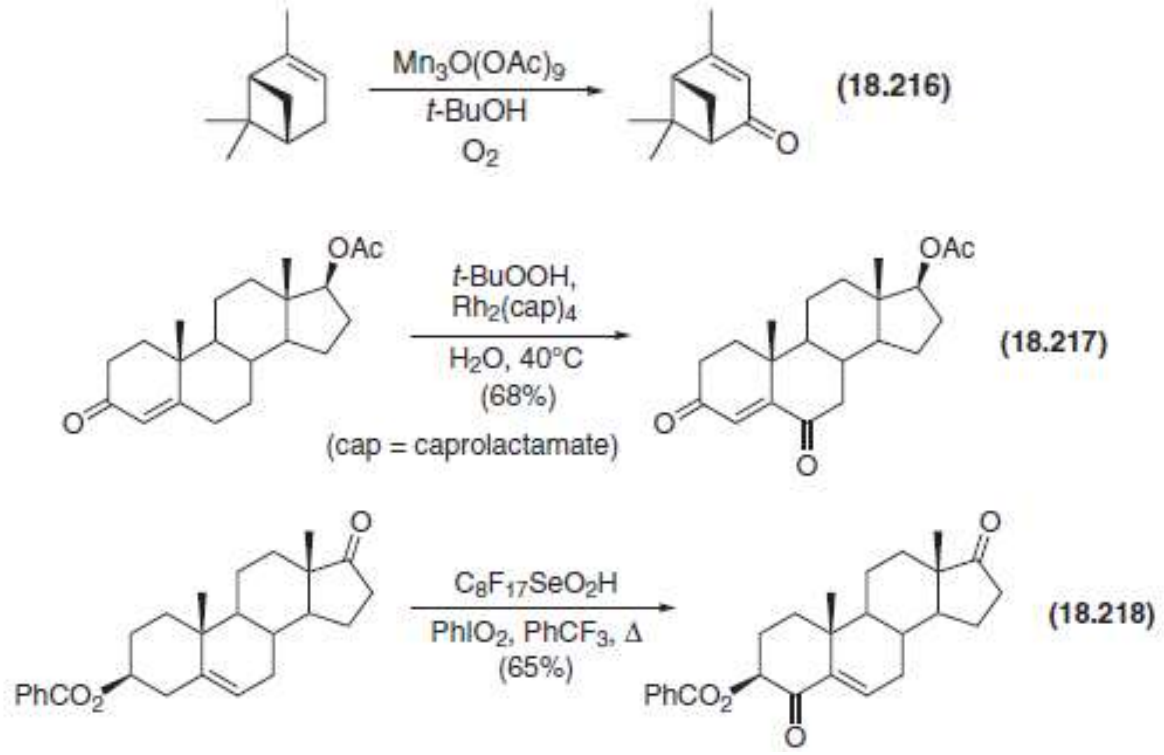
- the product with the less substituted double bond tends to dominate the reaction mixture from terminal alkenes

Pd-catalyzed allylic oxidation



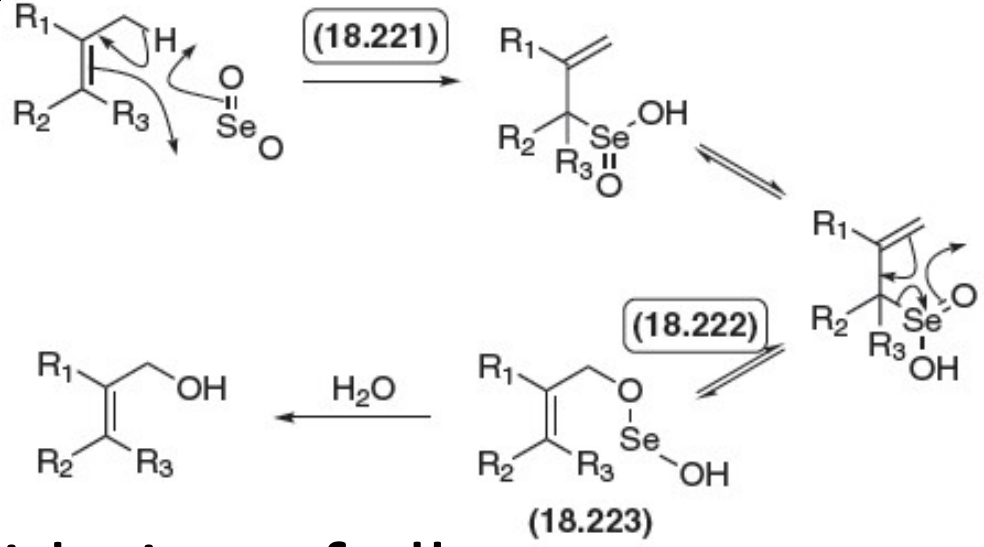
- Suitable terminal oxidants allow the palladium (II) acetate to be used in catalytic amounts.
- The regiochemistry of the product is often determined by the exact experimental conditions

Oxidation of alkenes to enones

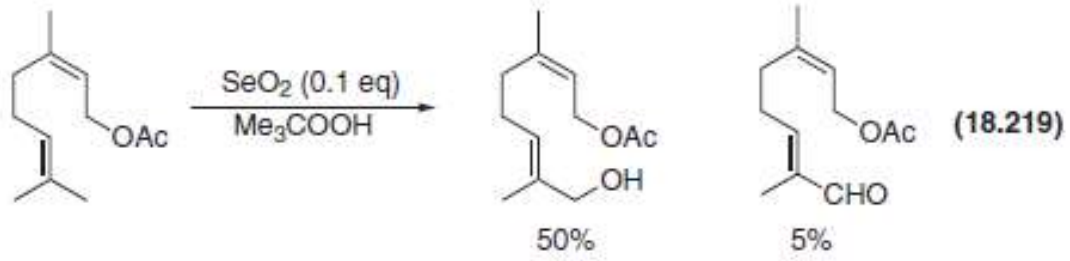


- Oxidation can be accomplished with Mn (III), a hydroperoxide with a Rh (II) complex, or by a seleninic acid with a suitable terminal oxidant

Figure 18.12

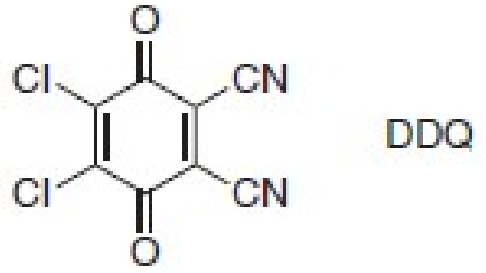


- Mechanism of selenium dioxide oxidation of alkenes

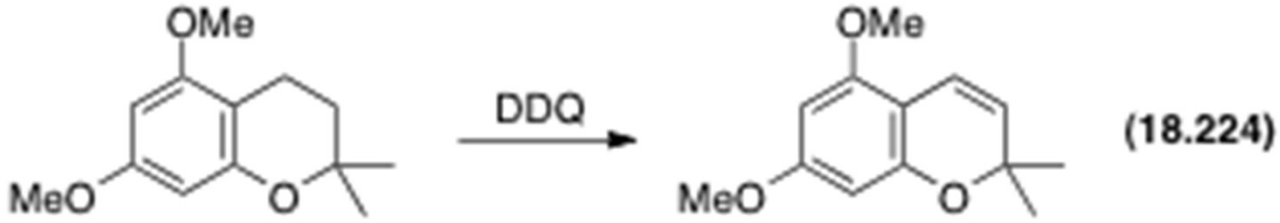


- the major product of a selenium dioxide oxidation is the allylic alcohol

Dehydrogenation



DDQ



(18.224)

- substrate must have a benzylic or allylic hydrogen, or a carbonyl group with an available α-hydrogen

α-Halogenation of carbonyl compounds under acidic conditions

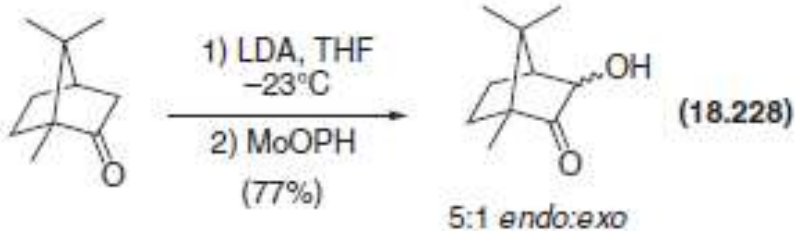
(18.226)

(18.227)

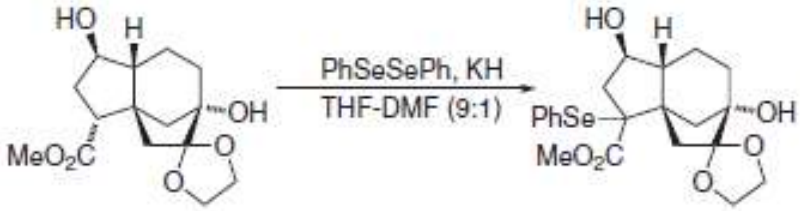
- halogenation is controlled under acidic conditions to give the monohalo product
- under basic conditions, polyhalogenation at ther same carbon occurs
- The Hell-Volhard-Zelinskii reaction can be used to prepare α-haloacids

Other oxidations at the α carbon

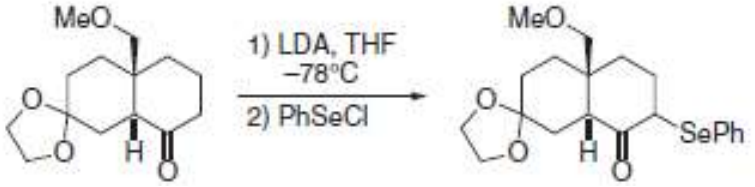
- lithium enolates may be oxidized by a variety of reagents
  - MoOPH gives the α-hydroxyketone
  - diselenides and selenenyl chlorides give the α-selenylketone
  - the analogous α-sulfenylketones can be made using disulfides or sulfenyl chlorides



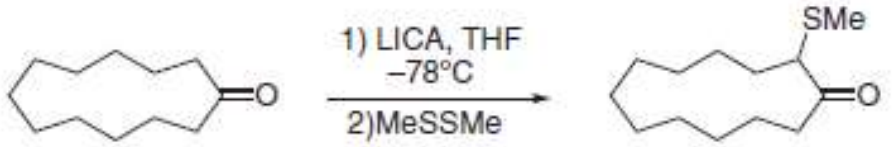
(18.228)



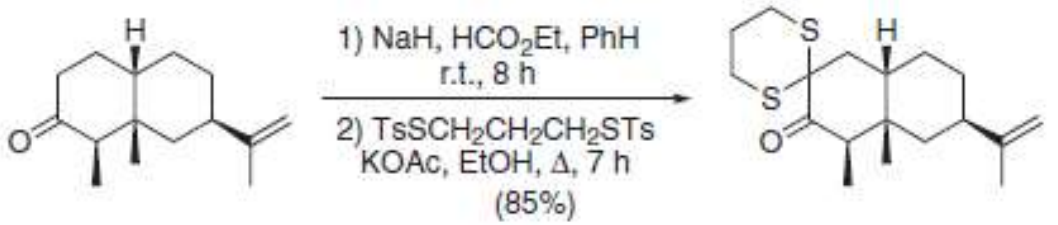
(18.229)[276]



(18.230)[277]



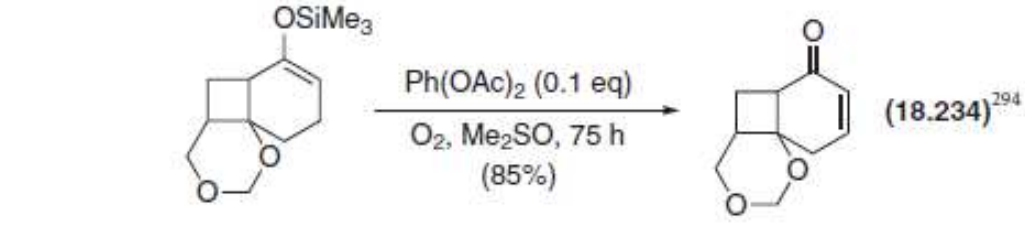
(18.231)[278 (a)]



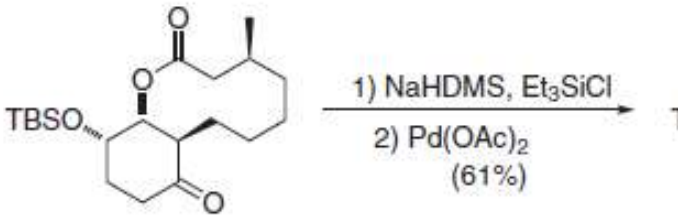
(18.232)

The Saegusa Oxidation

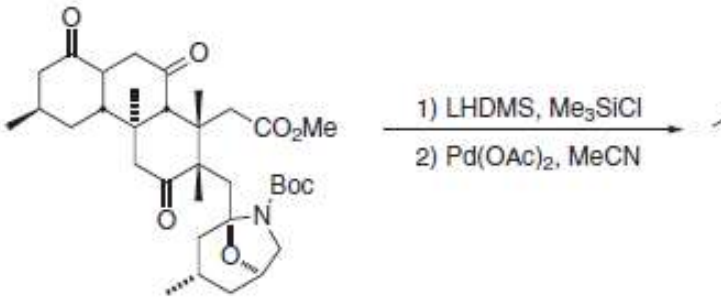
- the reaction converts an enol silyl ether to an enone
- the active oxidizing agent is Pd (II)
- on small scale, it is most convenient to use the Pd reagent stoichiometrically
- on larger scale, a hydrogen atom acceptor such as 1,4-benzoquinone is used as a terminal oxidant, with the Pd (II) in catalytic amounts
- molecular oxygen is a suitable terminal oxidant in the presence of dimethyl sulfoxide



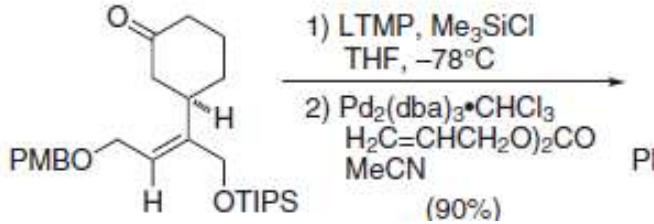
(18.234)[294]



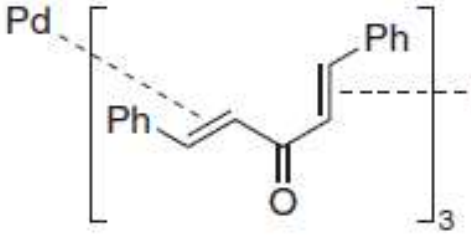
(18.235)[290]



(18.236)[291]

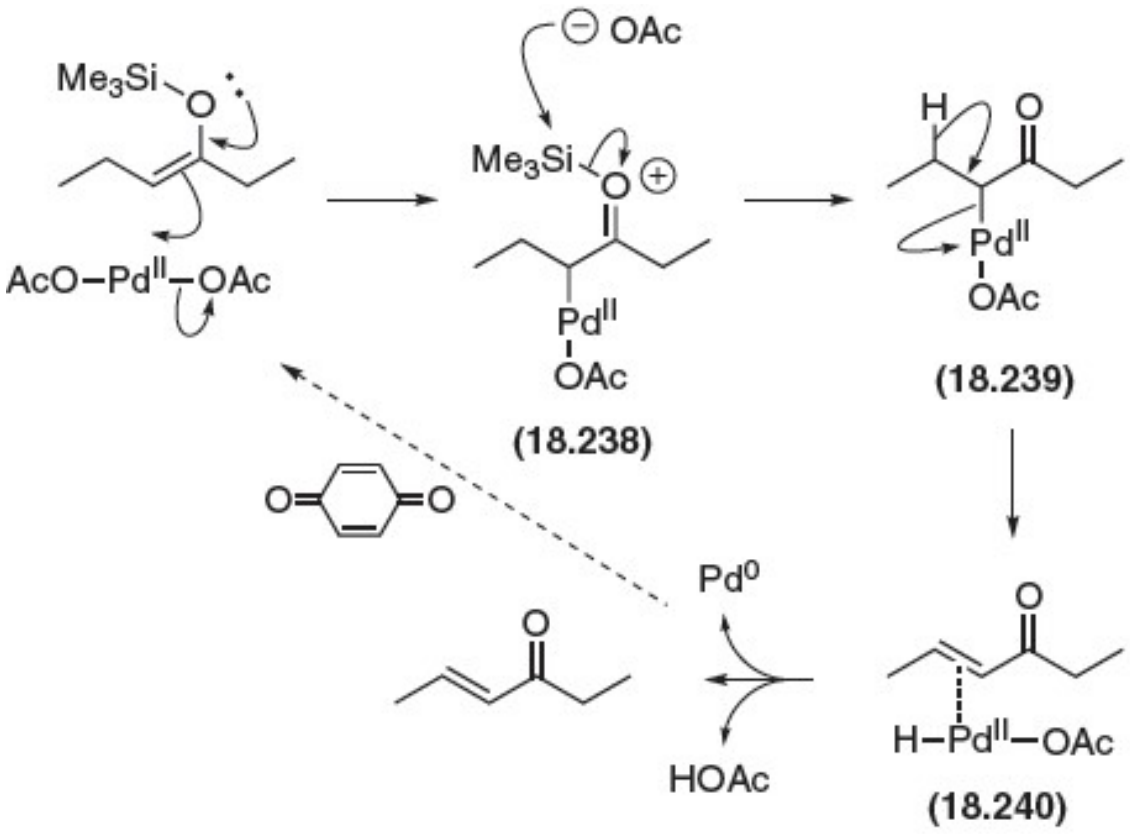


(18.237)[292]



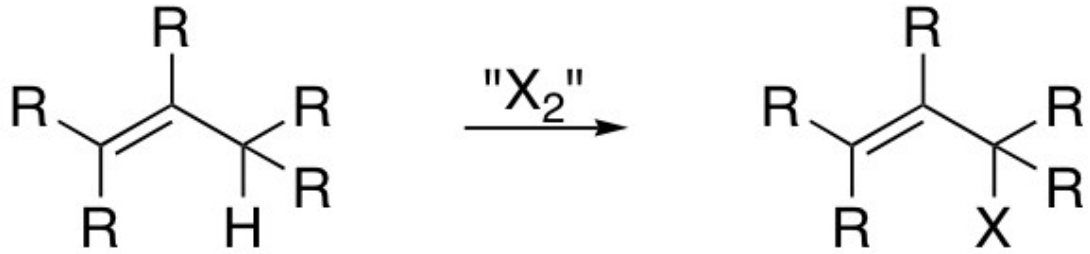
(18.241)

Figure 18.14



- Reaction pathway proposed for the Saegusa oxidation

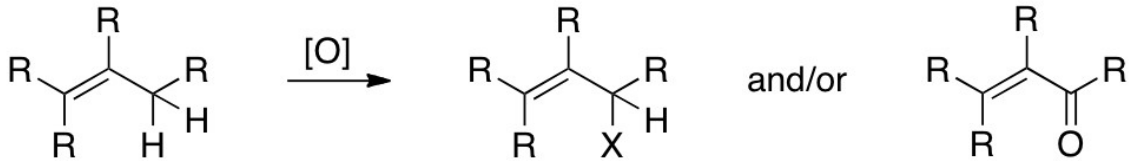
Reaction synopses: Allylic halogenation



Reagents: Br_2, hν; Cl_2, hν; etc.

or NBS, CCl_4, Δ; NCS, CCl_4, Δ; etc.

Reaction synopses: Allylic oxidation



Reagents: RCO_2OBu^t, Cu^+, Δ (R '= OCOR; occurs with allylic rearrangement)

SeO_2 (R' = H; occurs without allylic rearangement)

SeO_2, Me_3COOH; SeO_2, NaOCl; etc.

R_FSeO_2H, $PhIO_2$, $PhCF_3$, Δ;

Bu^tOOH, $BiCl_3$, MeCN; (similar reactions with Cu, Co, Mo, V, etc. as metal);

O_2, hν, Rose Bengal (X=OOH; allylic rearrrangement)

DDQ, CH_2Cl_2;

$Mn_3O(OAc)_9$, Me_3COH, O_2;

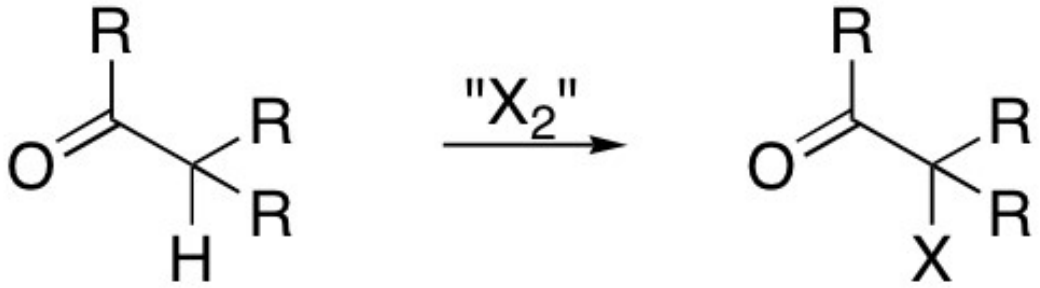
$(PhSOCH_2)_2Pd(OAC)_2$, benzoquinone, solvent

(solvent = AcOH, Me_2SO 1:1 allylic rearrangement)

(solvent = AcOH, CH_2Cl_2 1:1 no allylic rearrangement);

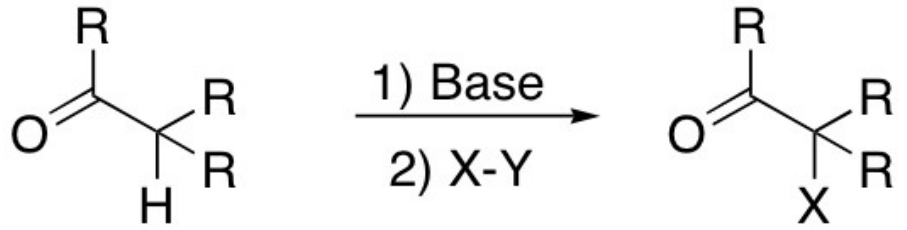
O_2, $Co(py)_2Br_2$, MeCN; or O_2, CoL_2, Me_2CHCHO, MeCN

Reaction synopses: α-Halogenation



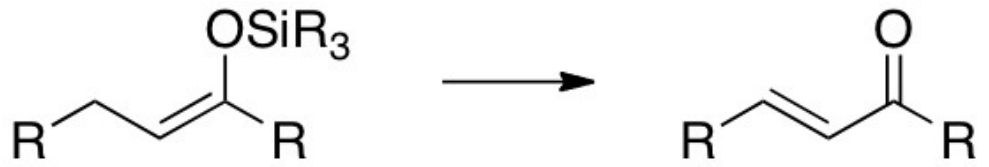
Reagents: Br_2, HOAc; Cl_2, HOAc; etc.

Reaction synopses: α-Selenylation and sulfenylation



Base: LDA, THF, –78°C; NaH, THF; KH, THF; etc.
X—Y: PhSeCl; PhSeBr; PhSeSePh; PhSCl; PhSBr; RSSR; etc.

Reaction synopses: α-Hydroxylation



Reagents: $Pd(OAc)_2$, MeCN, *p*-benzoquinone; P

or $Pd(OAc)_2$; MeCN

or $Pd_2(dba)_3 \bullet CHCl_3$, MeCN, ($H_2C$=CH-

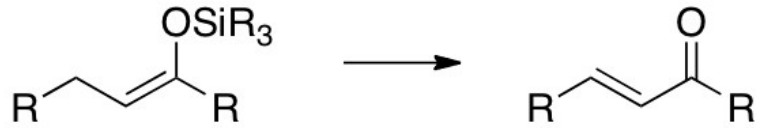
Reaction synopses: Dehydrogenation of carbonyl compounds

Reagents: $Pd(OAc)_2$, MeCN, *p*-benzoquinone; $Pd(OAc)$

or $Pd(OAc)_2$; MeCN

or $Pd_2(dba)_3 \bullet CHCl_3$, MeCN, $(H_2C{=}CH\text{-}CH_2O)_2$

Dehydrosilylation of enol ethers (Saegusa oxidation)

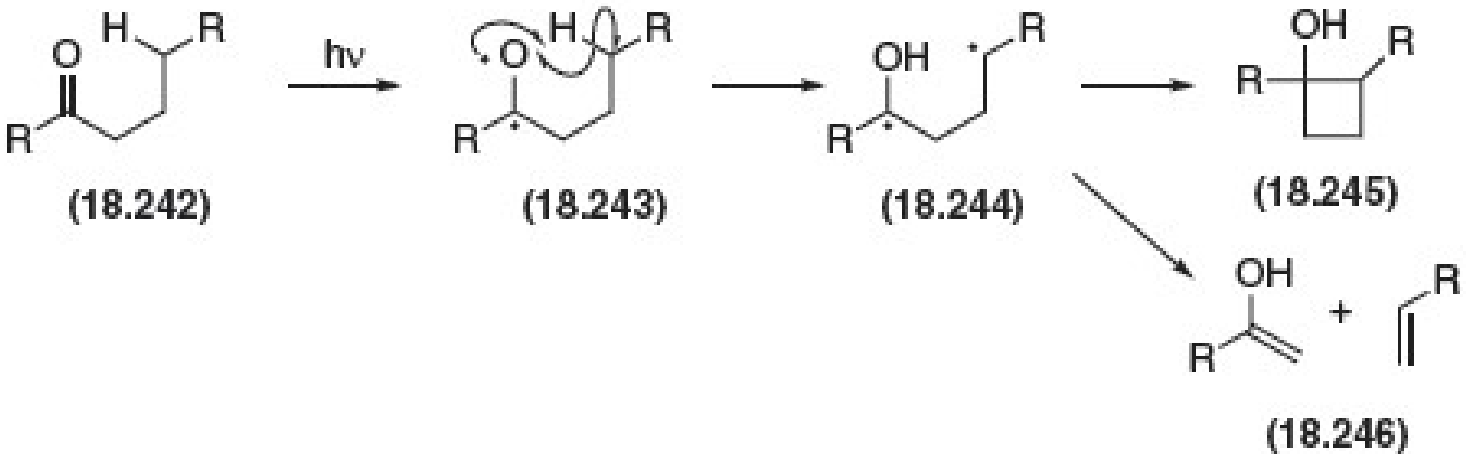


Reagents: $Pd(OAc)_2$, MeCN, *p*-benzoquinone; $Pd(OAc)_2$; Me_2SO; O_2

or $Pd(OAc)_2$; MeCN

or $Pd_2(dba)_3 \bullet CHCl_3$, MeCN, $(H_2C{=}CH\text{-}CH_2O)_2CO$

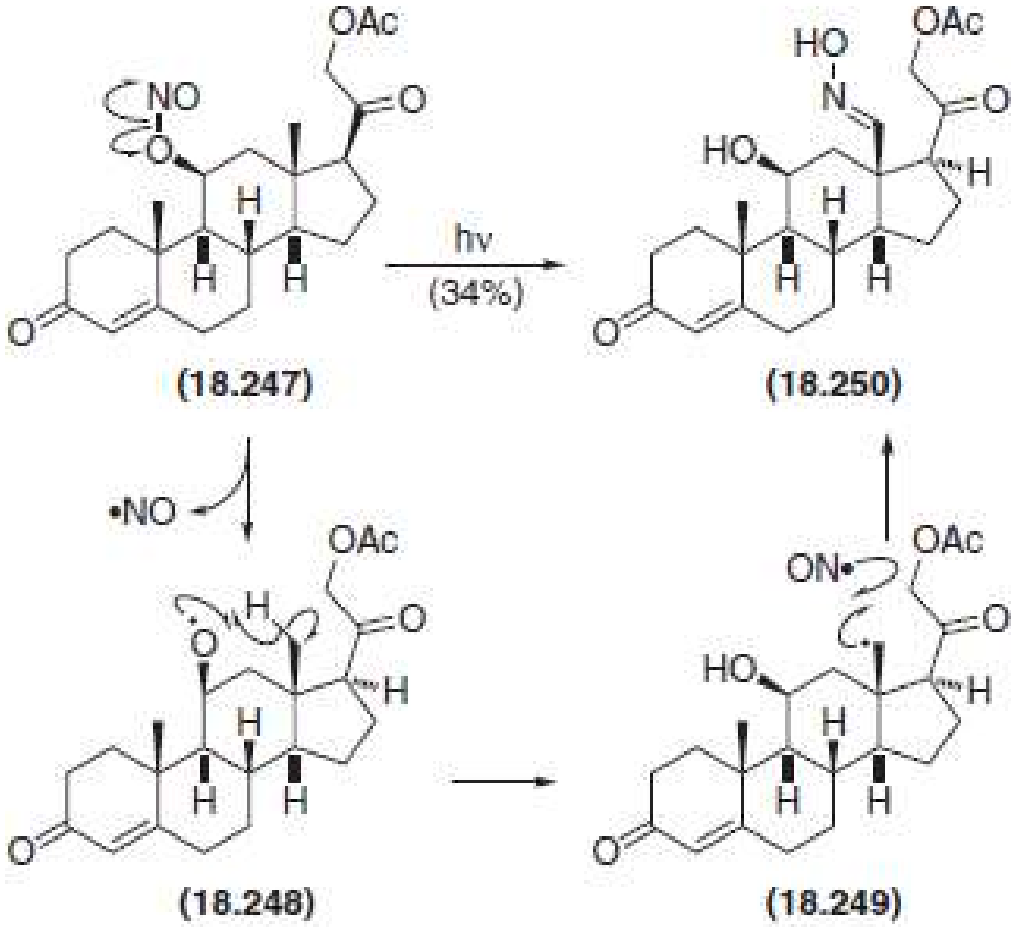
The Norrish Type II photochemical reaction of a ketone



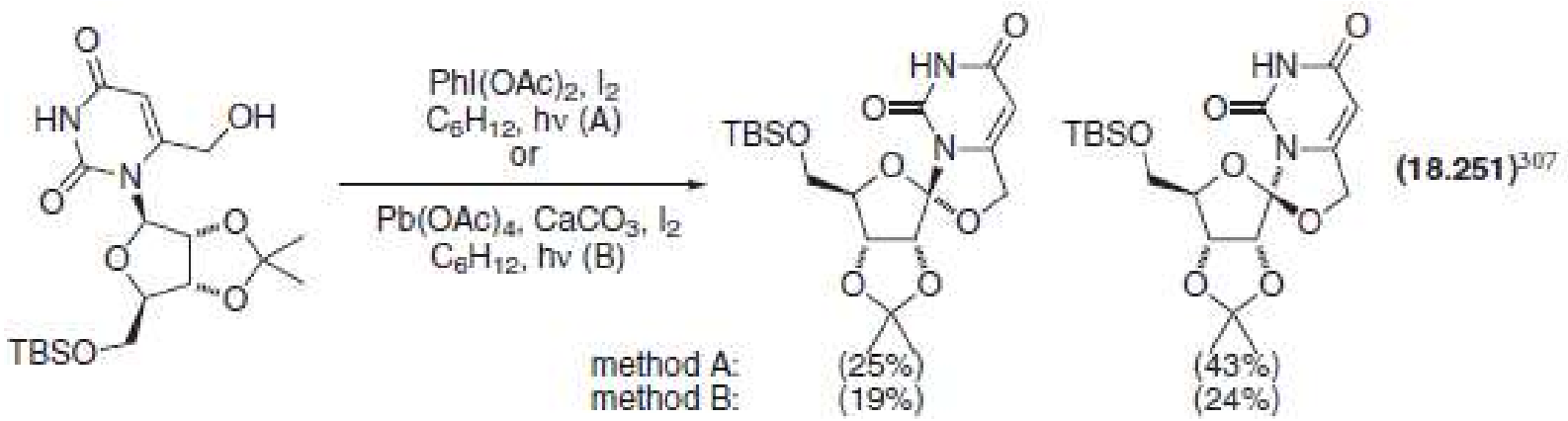
- The initial step of the reaction leads to a triplet diradical rfom the carbonyl group
- This is followed by an intramolecular hydrogen atom transfer through a six-membered transition state
- The final step involves the collapse of the diradical to the cyclobutanol

The Barton synthesis of aldosterone

- homolysis of a nitrite ester gives an alkoxy radical that abstracts a hydrogen atom from carbon through a six-membered transition state
- trapping of the resultant radical by nitric oxide gives a nitrosoalkane that then tautomerizes to the oxime

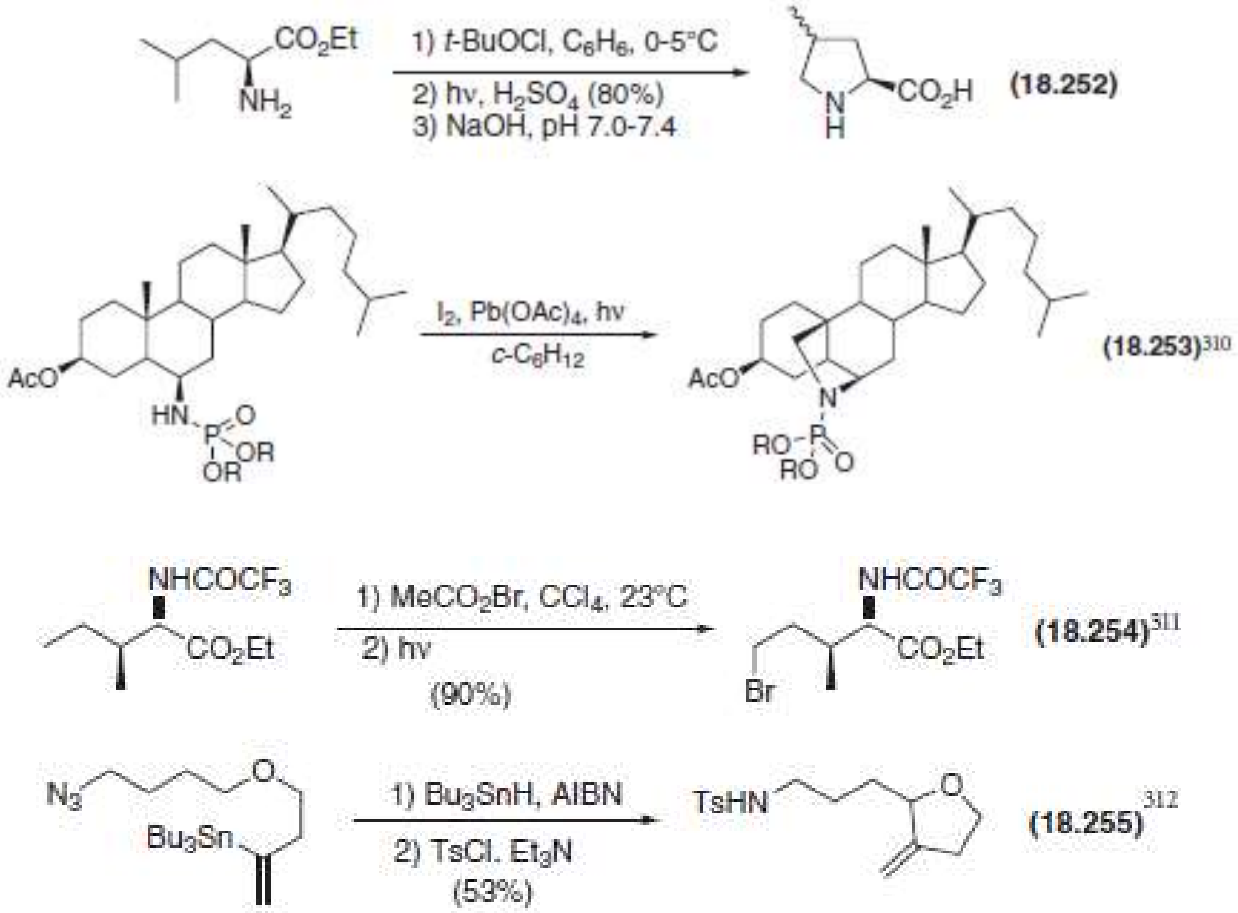


Hypoiodite homolysis and intramolecular hydrogen atom transfer

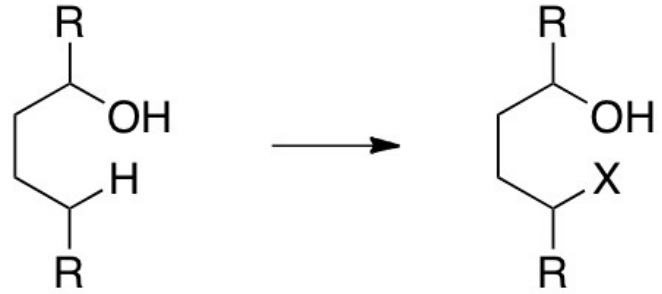


- The alcohol is first converted to the corresponding hypoiodite, R—O—I, which homolyzes to an alkoxy radical that abstracts the hydrogen from carbon.
- The alkyl radical is trapped by the iodine atom (or an iodine molecule) to give the alkyl iodide.
- In the reaction shown here, the product isolated is not the iodoamine, but is the tetrahydrofuran derivative formed by S_N1 displacement of the halide anion.

Variations on the Hofmann-Löffler-Freytag reaction



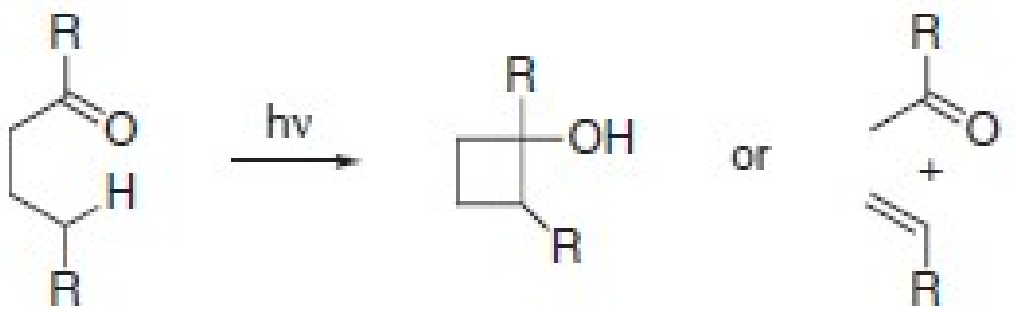
Reaction synopses: Intramolecular hydrogen atom transfer



Reagents: 1) NOCl, pyridine; 2) hν (Barton reaction);
or 1) I_2, $Pb(OAc)_4$; 2) hν (hypoiodite reaction);
or I_2, $PhI(OAc)_2$, cyclohexane, hν;
etc.

Products may react with base to give tetrahydrofuran derivatives

Reaction synopses: Norrish Type II photoreaction



Reaction synopses: Hofmann-Löffler-Freytag reaction

Reagents: 1) *t*-BuOCl; 2) hν (X= X=H_2, Y=alkyl, Z=halogen);

or 1) $MeCO_2Br$; 2) hν (X=O, Y=H, Z=halogen);

or $Pb(OAc)_4 / I_2$ / cyclohexane / hν (X=O, Y=H, Z=halogen);

Products may react with base to give pyrrolidine derivatives.

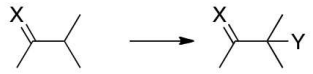
Catalog of Oxidation Reagents-1

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	PCC, PDC; CrO_3, py; CrO_3, py, CH_2Cl_2; etc.	*thiol, sulfide, 1,2-diols can be a problem; 1,3-diols can be a problem*
	Swern reagent, Moffatt-Pfitzner reagent, Corey-Kim reagent, etc.	*primary and secondary amines can interfere by reacting with the dehydrating agent*
	$Al(O\text{-}t\text{-}Bu)_3$, Me_2CO, Δ	reaction is reversible
	TPP (Ley reagent)	often gives higher yields than Swern oxidations
	DMP, IBX, etc.	can be used in ionic liquids; tolerates most functional groups
	TEMPO, NaOCl; etc.	
	Ag_2CO_3, celite	expensive—usually reserved for small-scale reactions
	$Pd(OAc)_2$, py, O_2	reaction is catalytic in Pd; py is essential

Catalog of Oxidation Reactions-2

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	Jones reagent	1,2- and 1,3-diols; aldehydes
	$KMnO_4$; Bu_4NMnO_4, PhH; etc.	alkenes; aldehydes; "purple benzene" is an extremely powerful oxidant
	CrO_3 (cat), H_5IO_6	same as Jones reagent
	RuO_4; $RuCl_3$, $NaIO_4$; etc.	alkenes; ethers and amines
	PDC, DMF	
	$NaClO_2$, *t*-BuOH, H_2O, $Me_2C{=}CHMe$	Two-stage oxidation of primary alcohols is preferred way to make a carboxylic acid
	Ag_2O, NH_3, H_2O	highly selective, but expensive
	MnO_2	reagent can be difficult to make with reproducible activity
	$BaMnO_4$	Reagent is easier to make and needs less than than MnO_2
	PDC, EtOAc	Reagent can be used to oxidize 1,2-diols where one OH is allylic

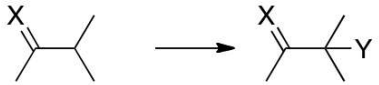
Catalog of Oxidation Reactions-3

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	1) LDA, then 2) Y_2 or YBr	X=O; Y=RS, RSe; etc.; *cannot be used to halogenate carbonyl compounds*
	X_2, HOAc	X=Cl, Br
	1) LDA, then 2) oxaziridine	Y=OH; product is chiral if a chiral oxaziridine is used
	*m*-CPBA (X=O); 1) NH_2OH, then 2) H_2SO_4 or TsCl, py; HN_3	*alkenes*; reactions proceed with retention of configuration at migrating center
	KOH, Br_2 ($X=NH_2$)	
	1) NH_2OH, 2) TsCl, 3) base (X=Cl, OR)	reactions proceed with retention of configuration at migrating center.
	1) $(COCl)_2$, 2) NaN_3, 3) Δ or hν (X=OH)	

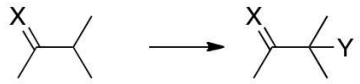
Catalog of Oxidation Reactions-4

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	1) LDA, then 2) Y_2 or YBr	X=O; Y=RS, RSe; etc.; *cannot be used to halogenate carbonyl compounds*
	X_2, HOAc	X=Cl, Br
	1) LDA, then 2) oxaziridine	Y=OH; product is chiral if a chiral oxaziridine is used
	*m*-CPBA (X=O); 1) NH_2OH, then 2) H_2SO_4 or TsCl, py; HN_3	*alkenes*; reactions proceed with retention of configuration at migrating center
	KOH, Br_2 (X=NH_2)	reactions proceed with retention of configuration at migrating center.
	1) NH_2OH, 2) TsCl, 3) base (X=Cl, OR)	
	1) $(COCl)_2$, 2) NaN_3, 3) Δ or hν (X=OH)	

Catalog of Oxidation Reactions-5

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	1) LDA, then 2) Y_2 or YBr	X=O; Y=RS, RSe; etc.; *cannot be used to halogenate carbonyl compounds*
	X_2, HOAc	X=Cl, Br
	1) LDA, then 2) oxaziridine	Y=OH; product is chiral if a chiral oxaziridine is used
	*m*-CPBA (X=O); 1) NH_2OH, then 2) H_2SO_4 or TsCl, py; HN_3	*alkenes*; reactions proceed with retention of configuration at migrating center
	KOH, Br_2 ($X=NH_2$)	
	1) NH_2OH, 2) TsCl, 3) base (X=Cl, OR)	reactions proceed with retention of configuration at migrating center.
	1) $(COCl)_2$, 2) NaN_3, 3) Δ or hν (X=OH)	

Catalog of Oxidation Reactions-6

Transformation	Reagents	*Incompatible Functional Groups*; Other Limitations or Features
	1) LDA, then 2) Y_2 or YBr	X=O; Y=RS, RSe; etc.; *cannot be used to halogenate carbonyl compounds*
	X_2, HOAc	X=Cl, Br
	1) LDA, then 2) oxaziridine	Y=OH; product is chiral if a chiral oxaziridine is used
	*m*-CPBA (X=O); 1) NH_2OH, then 2) H_2SO_4 or TsCl, py; HN_3	*alkenes*; reactions proceed with retention of configuration at migrating center
	KOH, Br_2 ($X=NH_2$)	
	1) NH_2OH, 2) TsCl, 3) base (X=Cl, OR)	reactions proceed with retention of configuration at migrating center.
	1) $(COCl)_2$, 2) NaN_3, 3) Δ or hν (X=OH)	