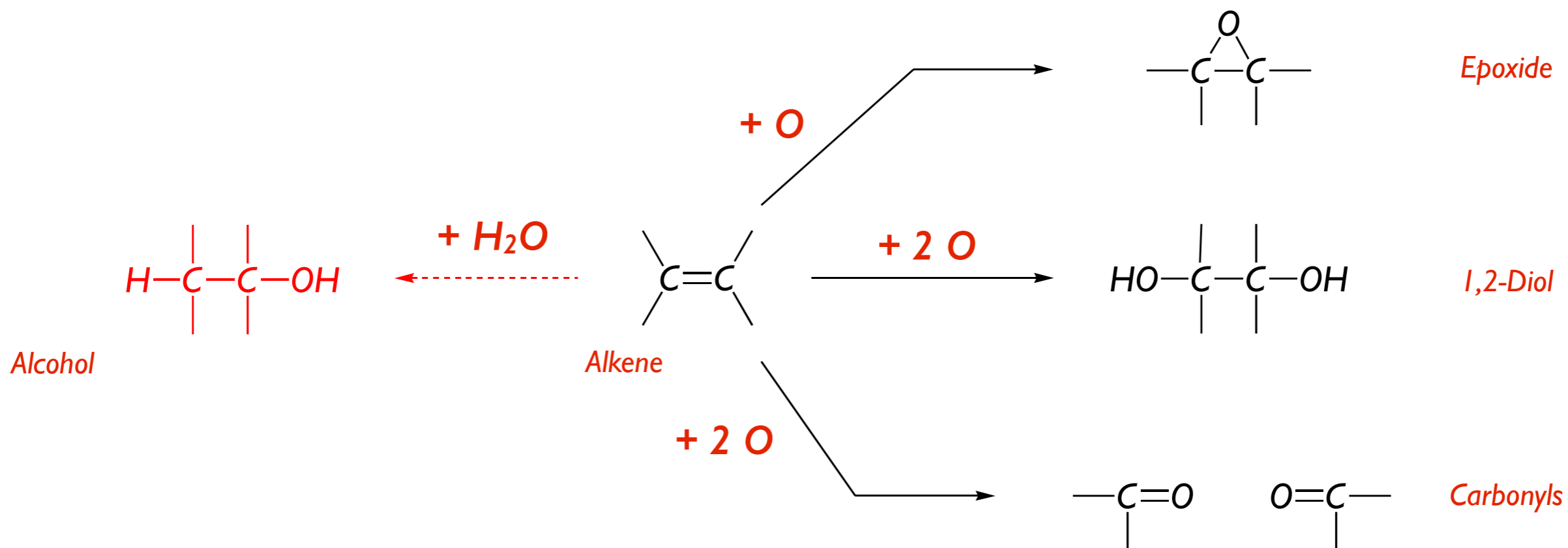
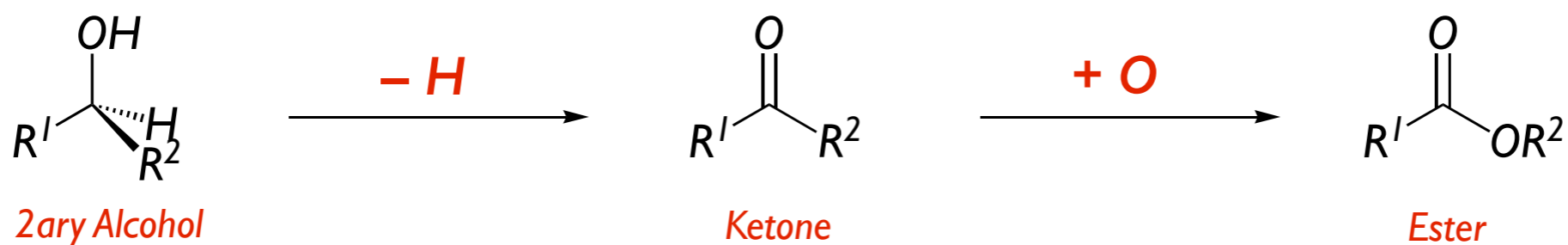
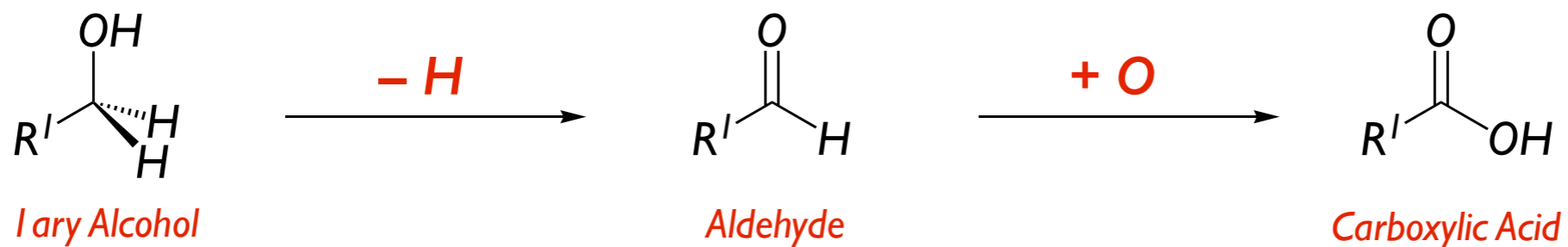
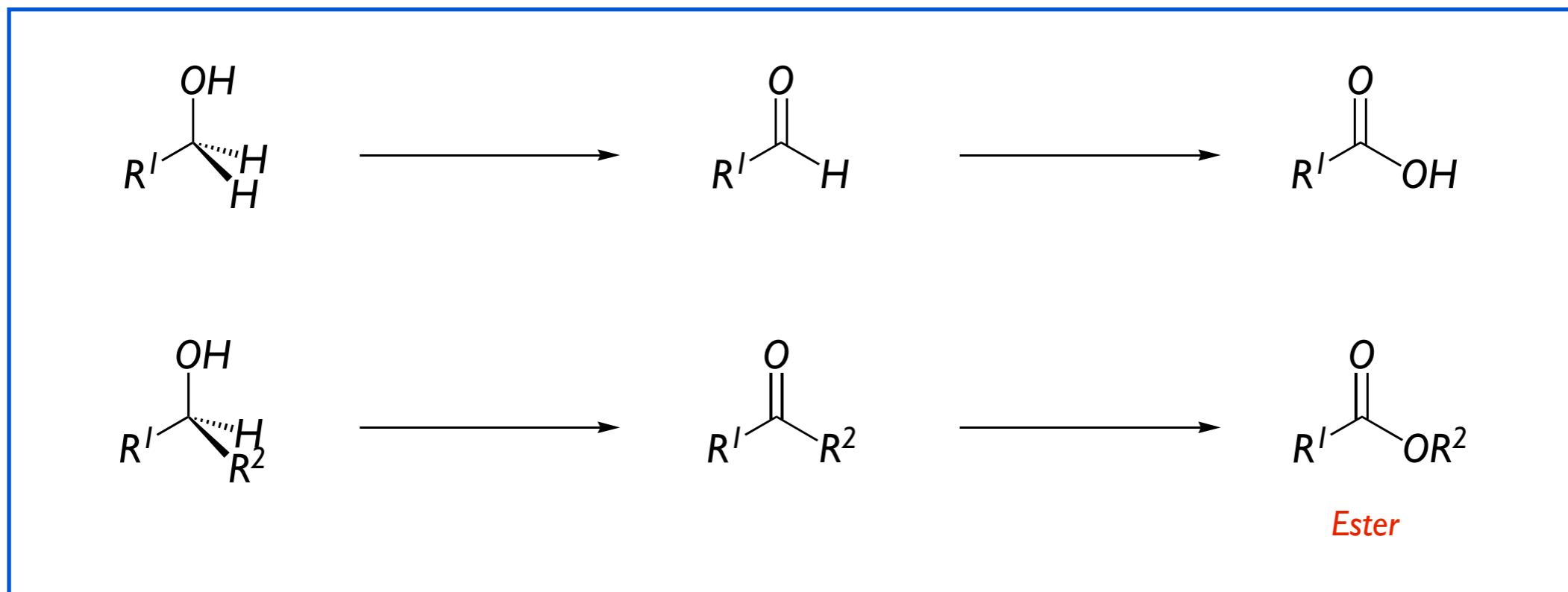




Rouen Cathedral
Claude Monet, 1892-94

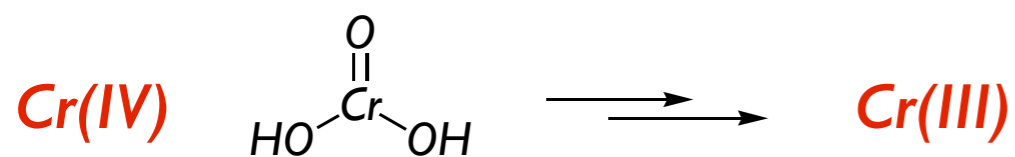
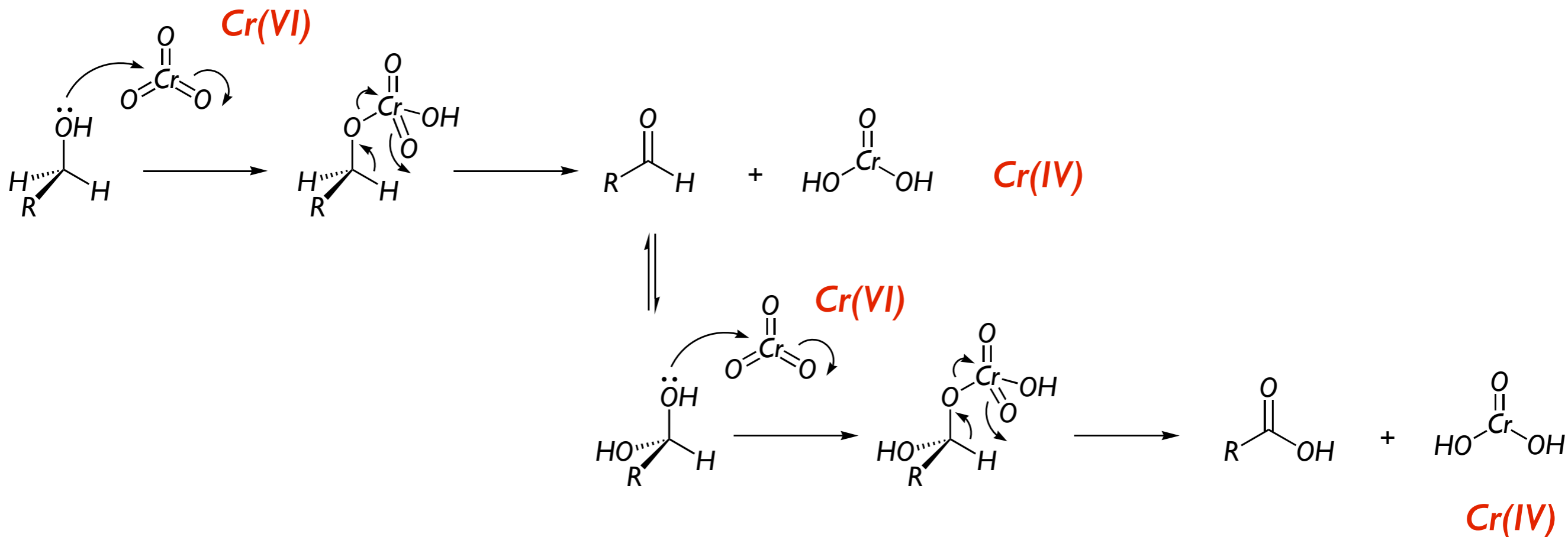
8. Oxidations





- *Cr(VI) Reagents*
- *DMSO/E⁺ Mixtures*
- *Other oxidizing agents*

■ **Cr(VI) Reagents**

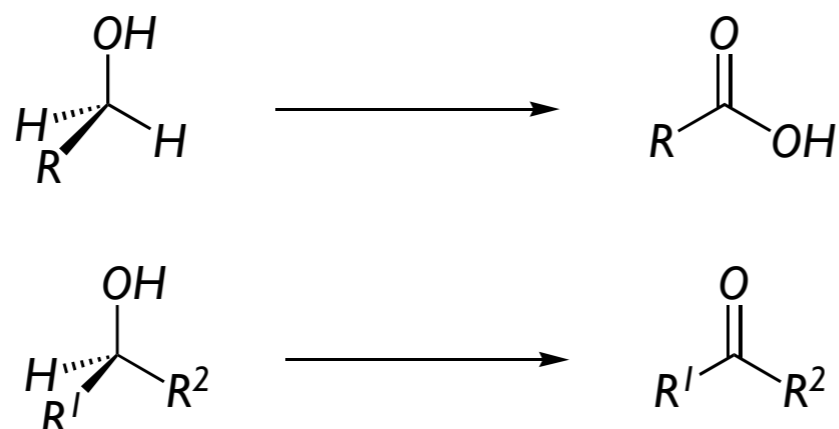


– Overoxidation is a problem

– Aqueous media facilitate the oxidation of the resultant aldehyde

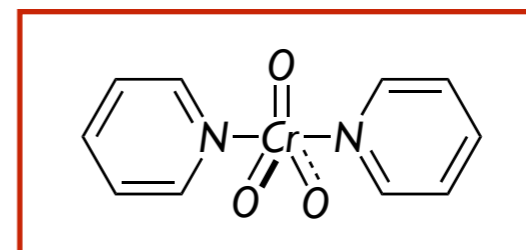
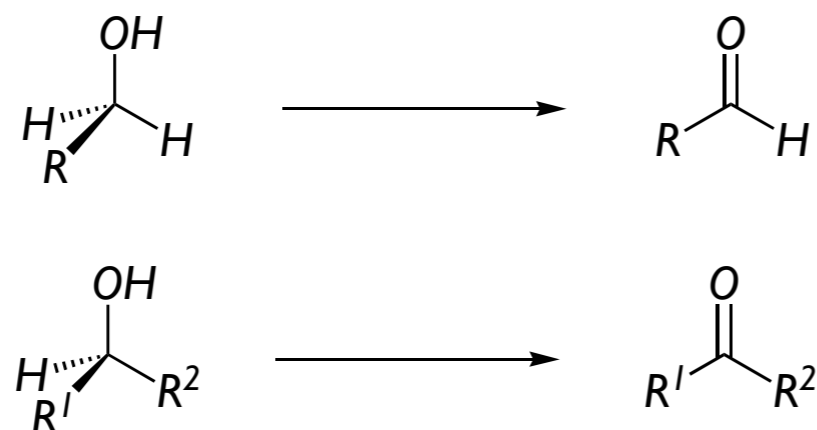
– **Chromium wastes are harmful**

– $\text{CrO}_3/\text{H}_3\text{O}^+$: Jones reagent



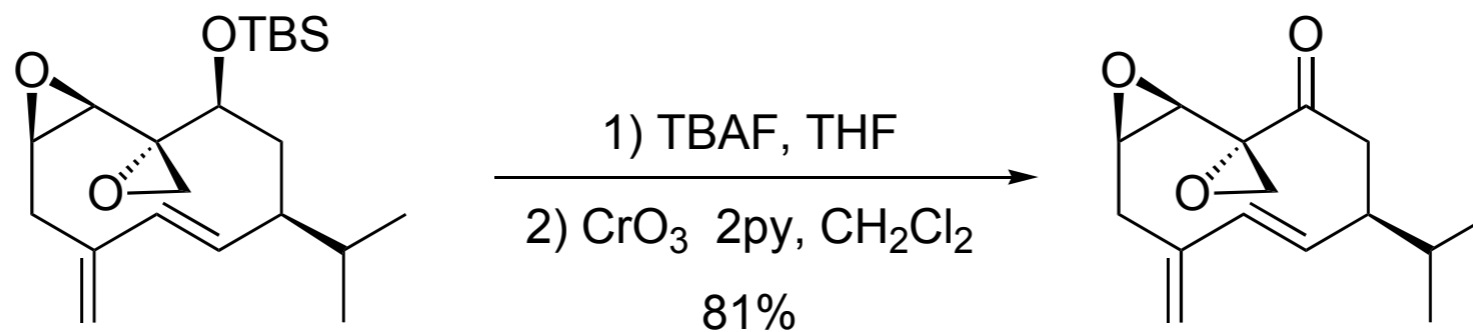
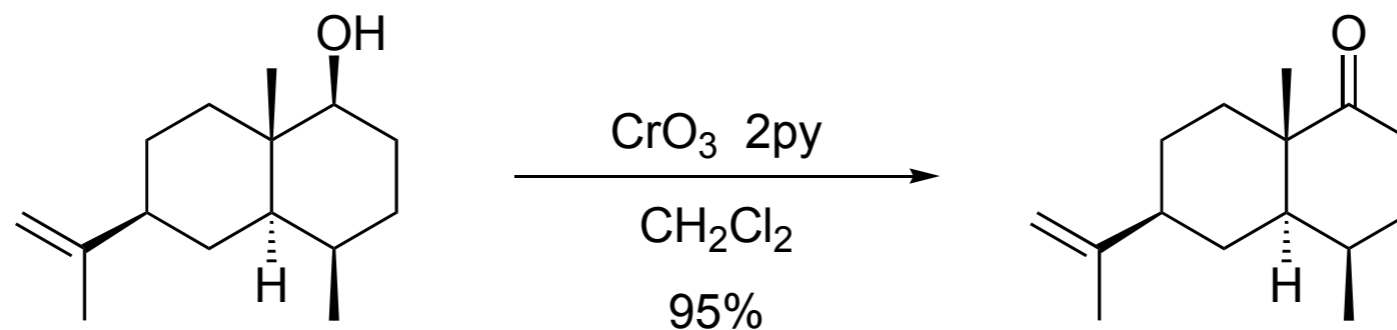
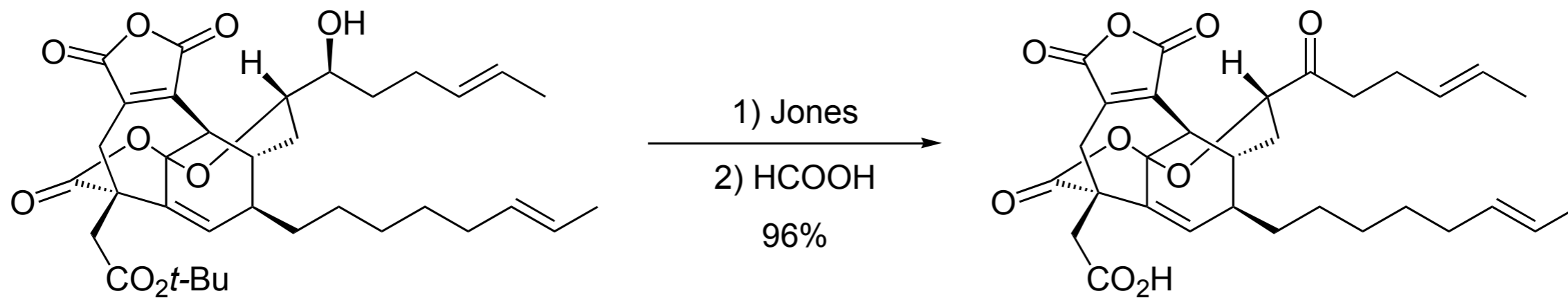
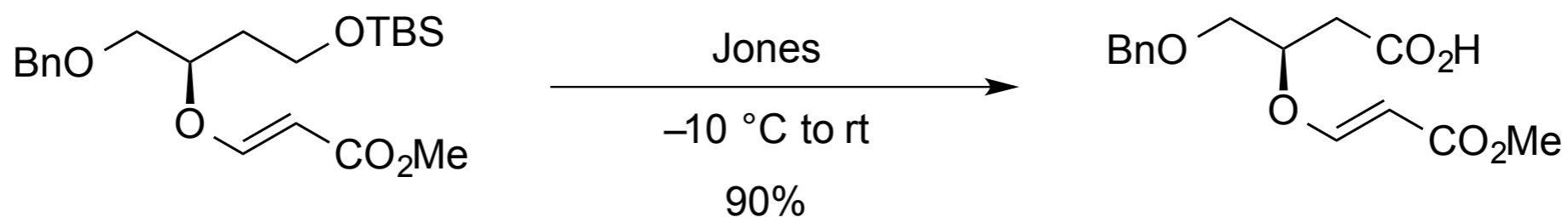
Aqueous media facilitate the oxidation of the resultant aldehyde

– $\text{CrO}_3/2\text{py}$: Collins reagent

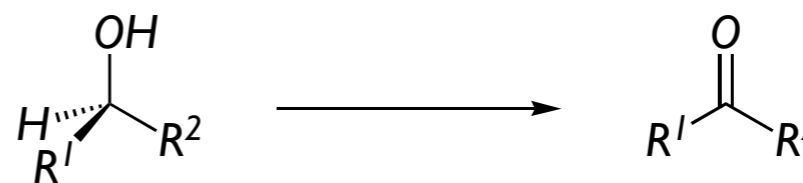
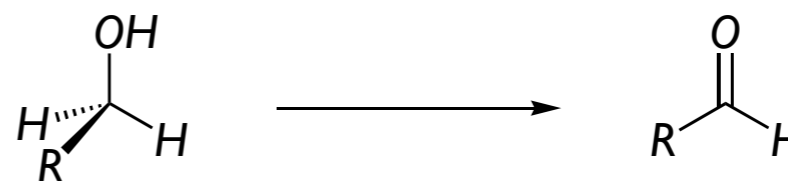
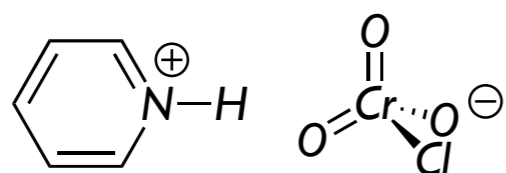


Kinetics are rather slow and high loadings are usually required

These reagents are hygroscopic and can easily catch fire and burn during their preparation, so other commercially available reagents are usually employed



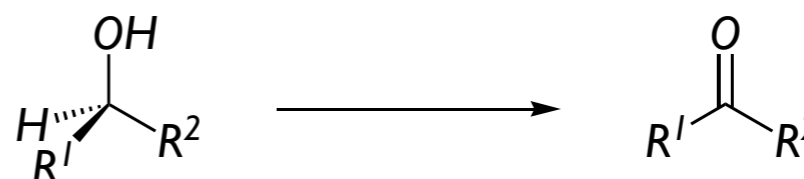
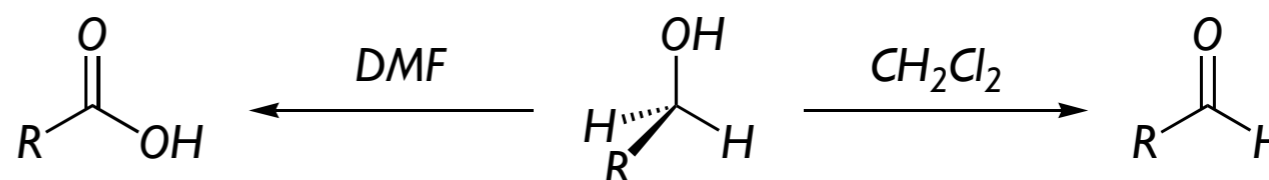
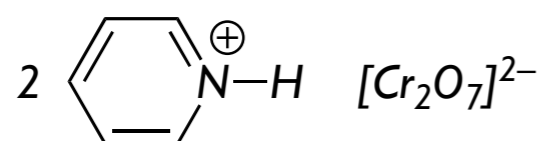
– $[pyH]^+[CrO_3Cl]^-$: pyridinium chlorochromate, PCC

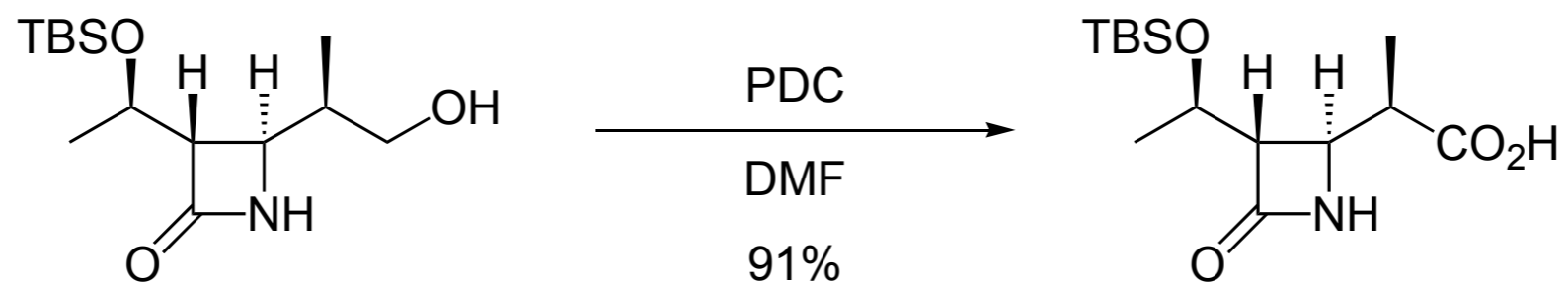
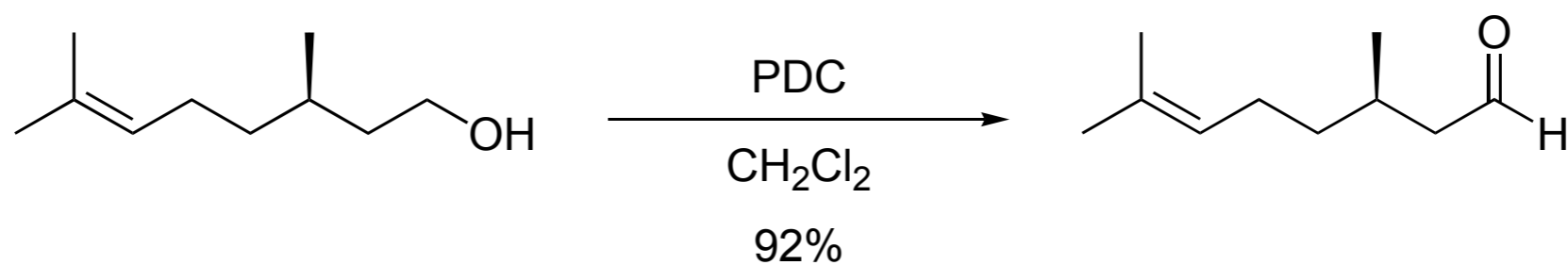
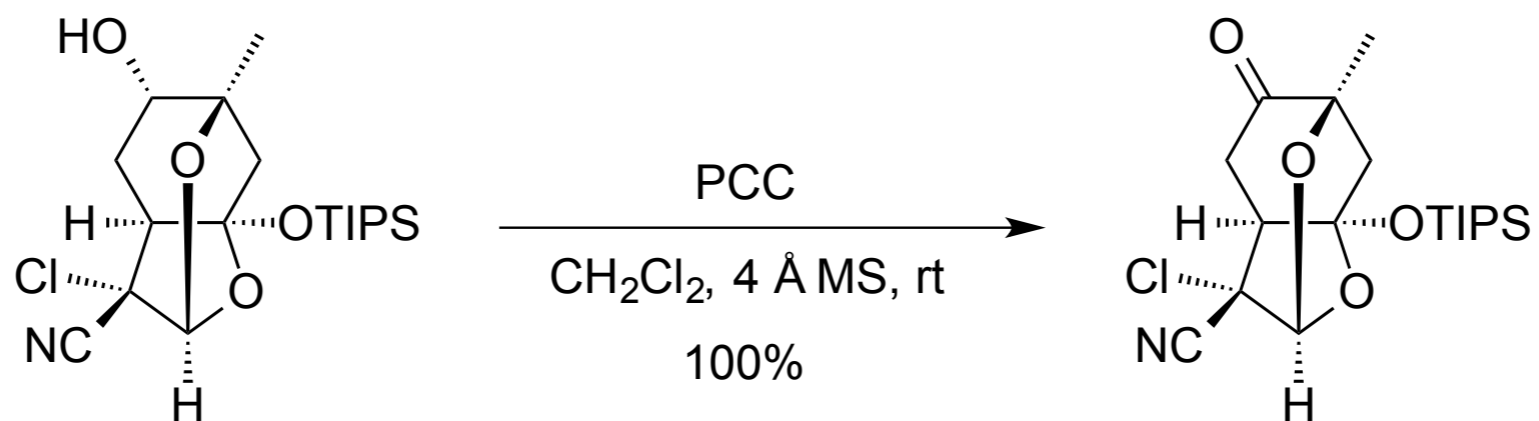
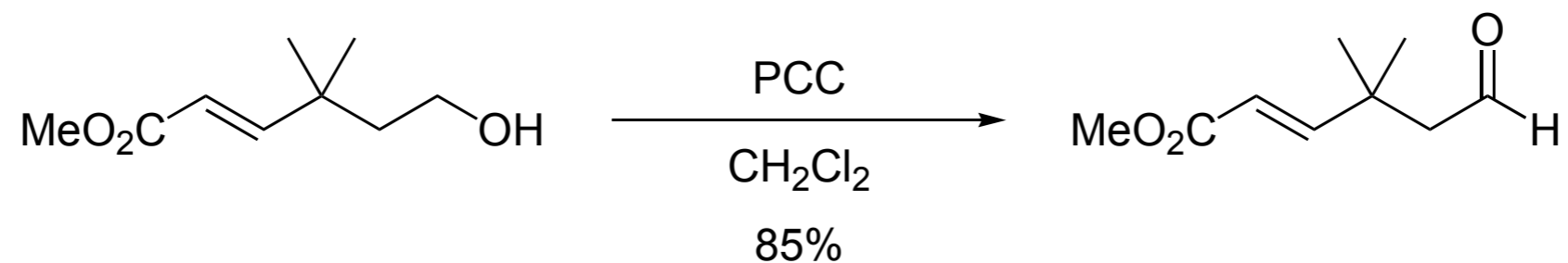


More reactive than the Collins reagent

Somehow Lewis acid character

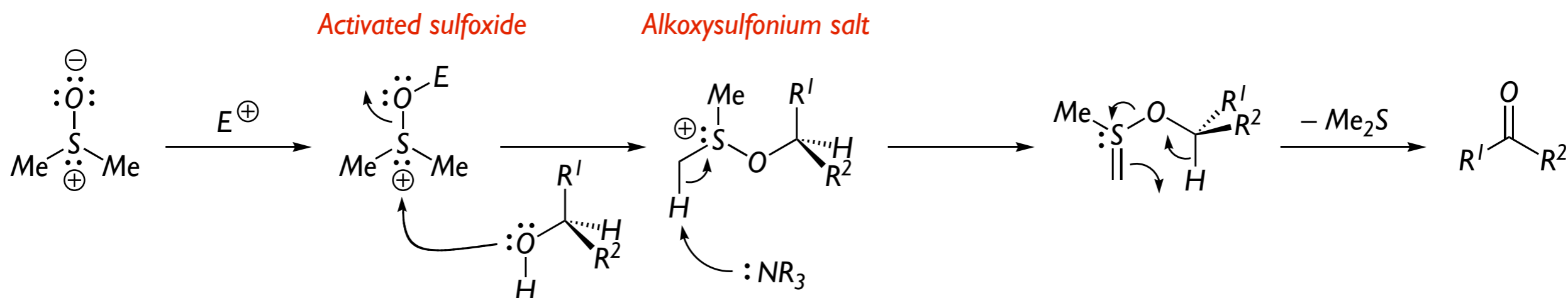
– $2[pyH]^+[Cr_2O_7]^{2-}$: pyridinium dichromate, PDC



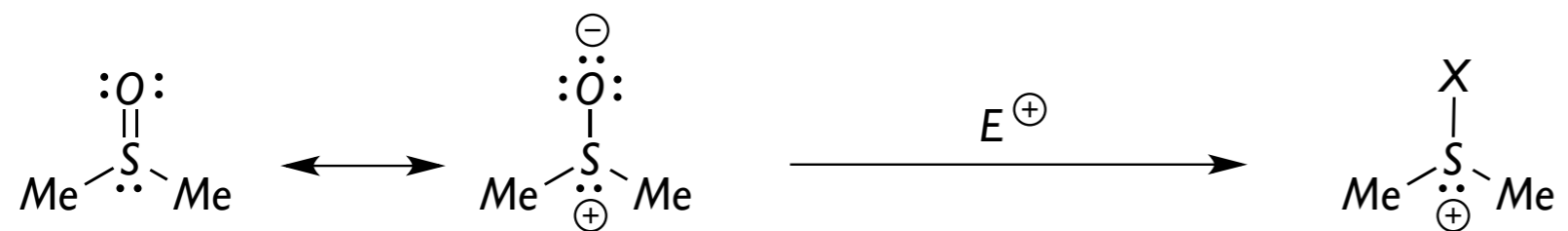


■ DMSO/Electrophile mixtures

- The activation of DMSO with an electrophile gives an alkoxyulfonium salt
- This proceeds through an acid/base and an ene reaction



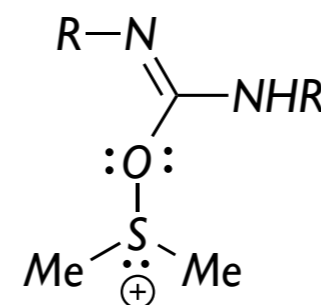
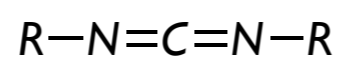
- There is a variety of electrophiles: DCC, $(COCl)_2$, $py-SO_3$,...



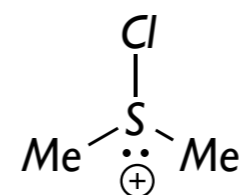
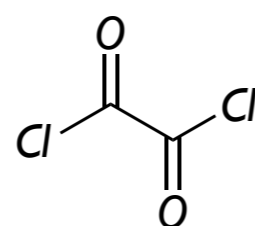
Electrophile

Activated sulfoxide

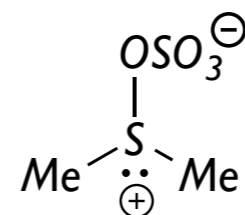
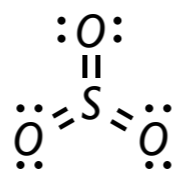
Reaction name



Moffat

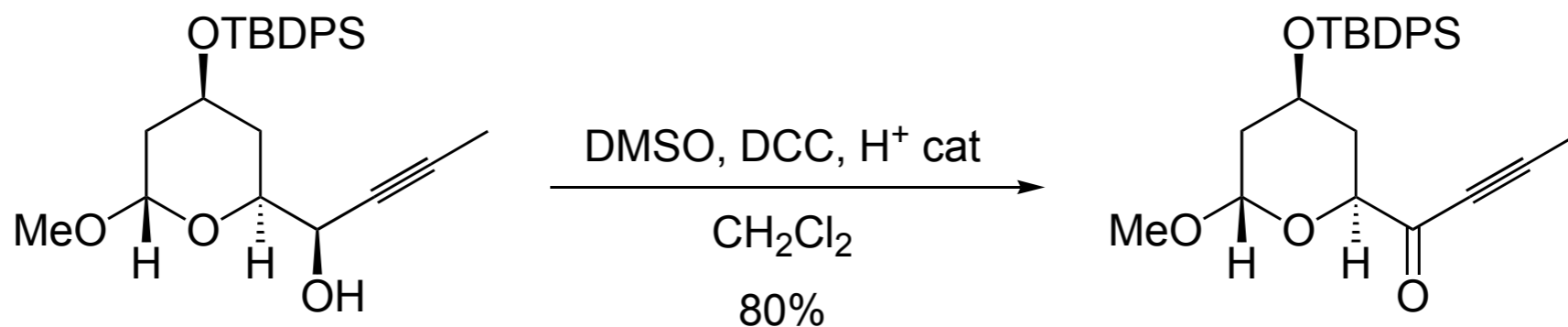
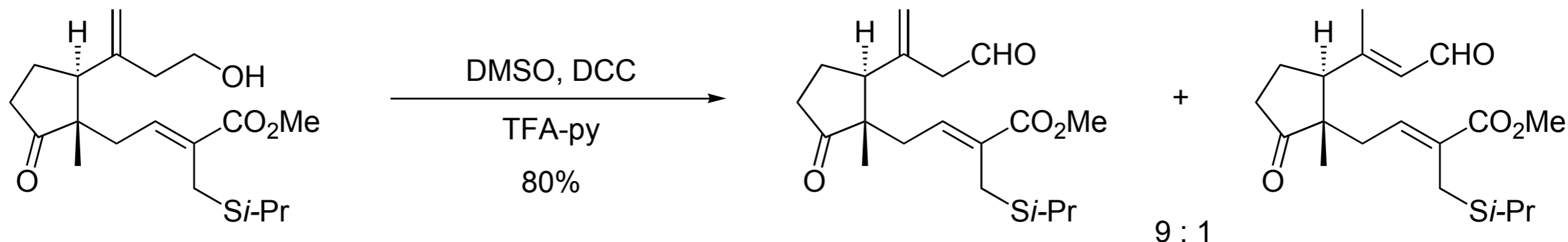
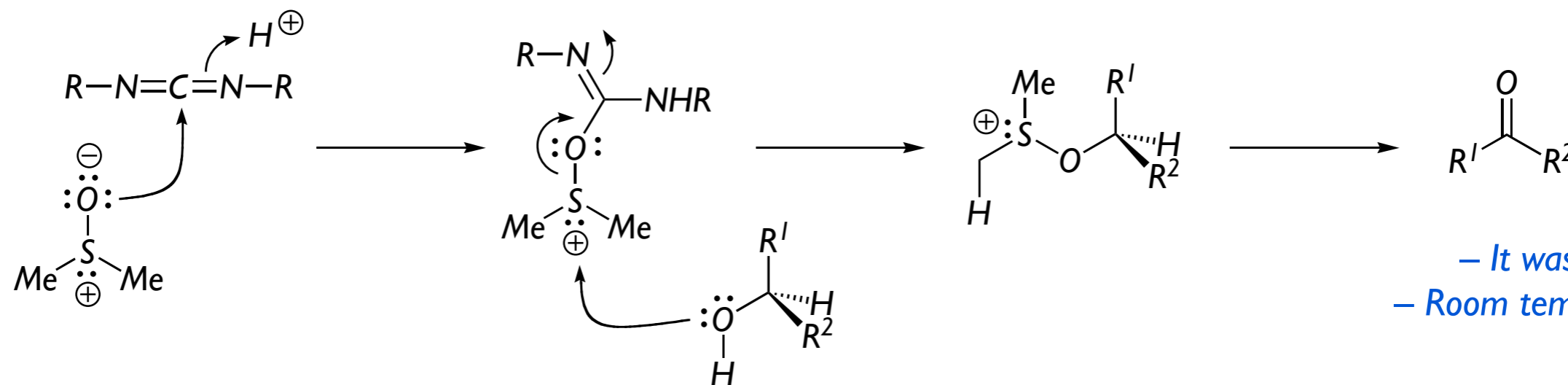


Swern

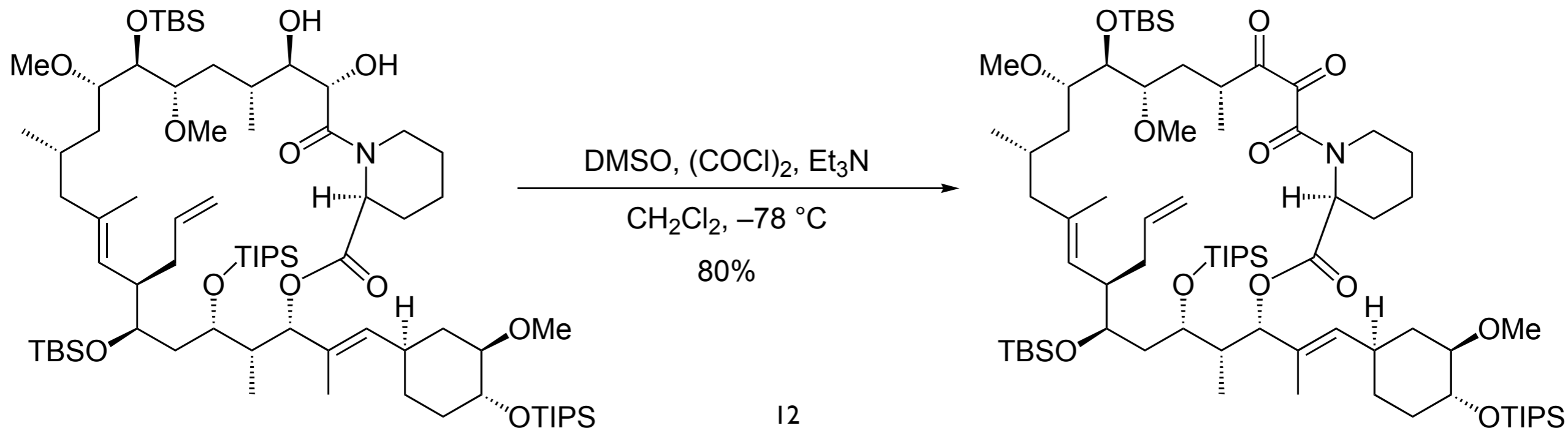
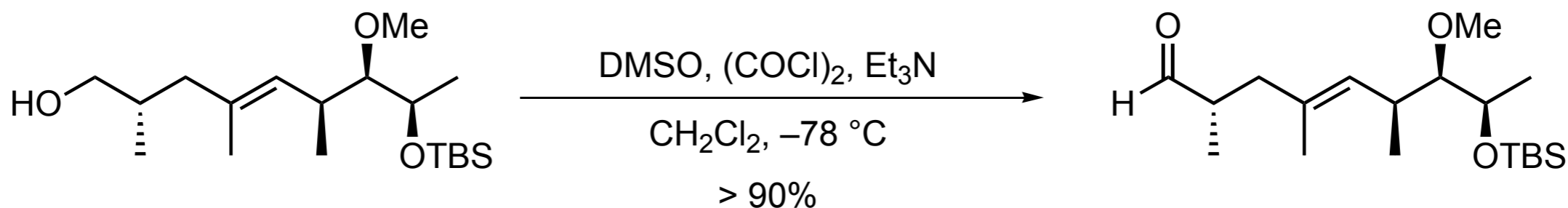
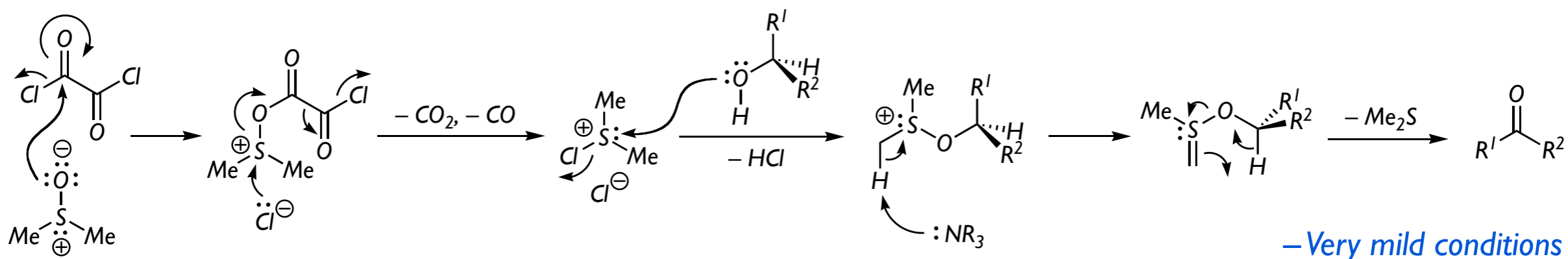


Parikh-Doering

– Moffatt: DCC, cat H⁺



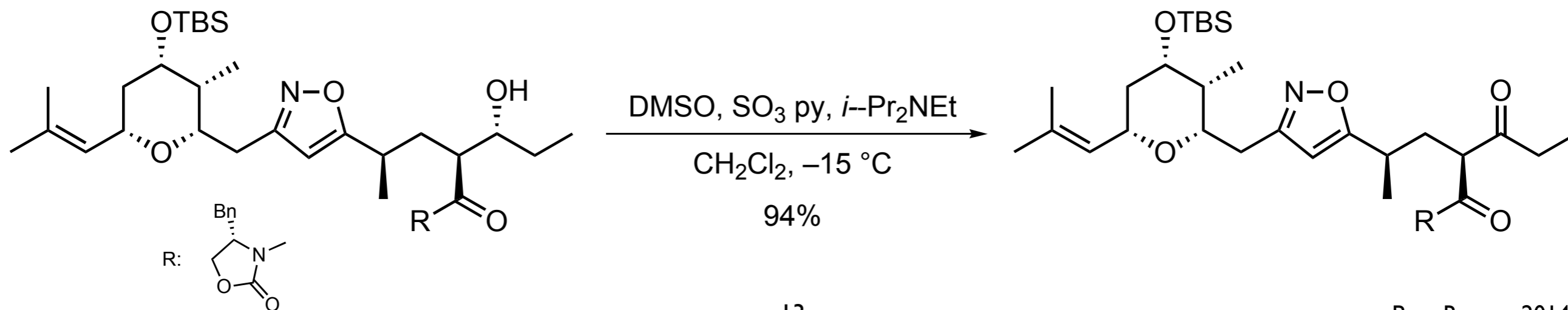
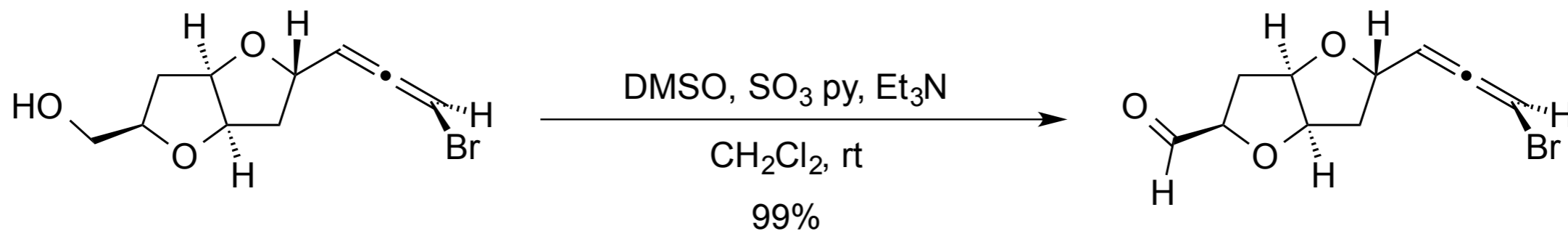
– Swern: $(\text{COCl})_2, \text{Et}_3\text{N}, -78\text{ }^\circ\text{C}$



– Parikh-Doering: $\text{SO}_3 \cdot \text{py}, \text{R}_3\text{N}$

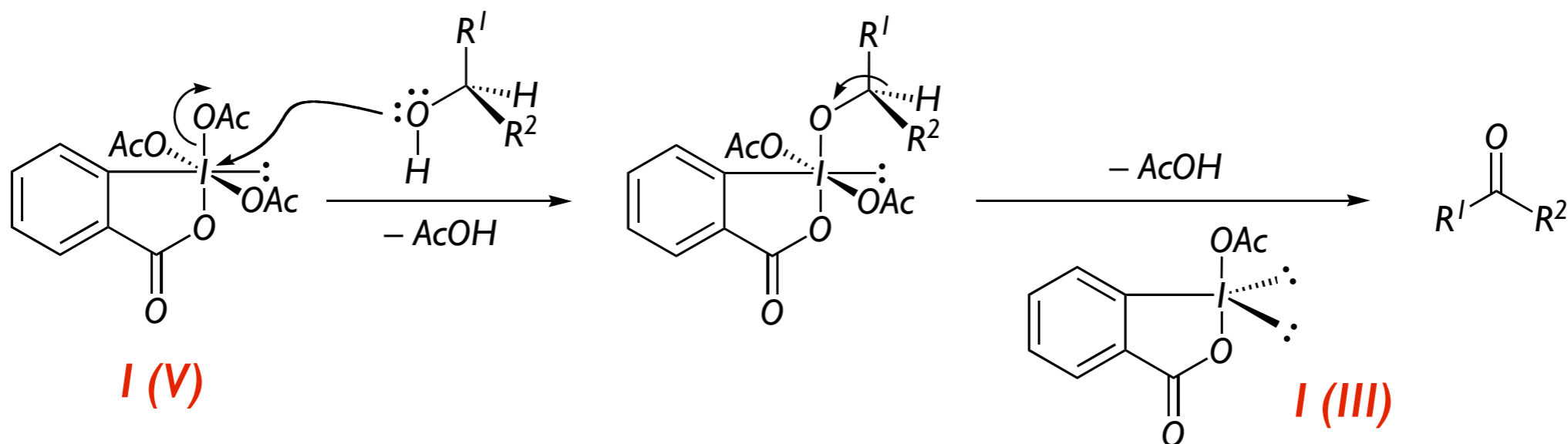
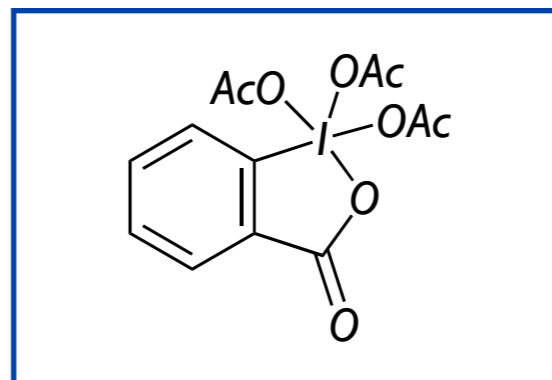
Mechanism?

– Temperature: 0°C , rt
 – Easy work-up

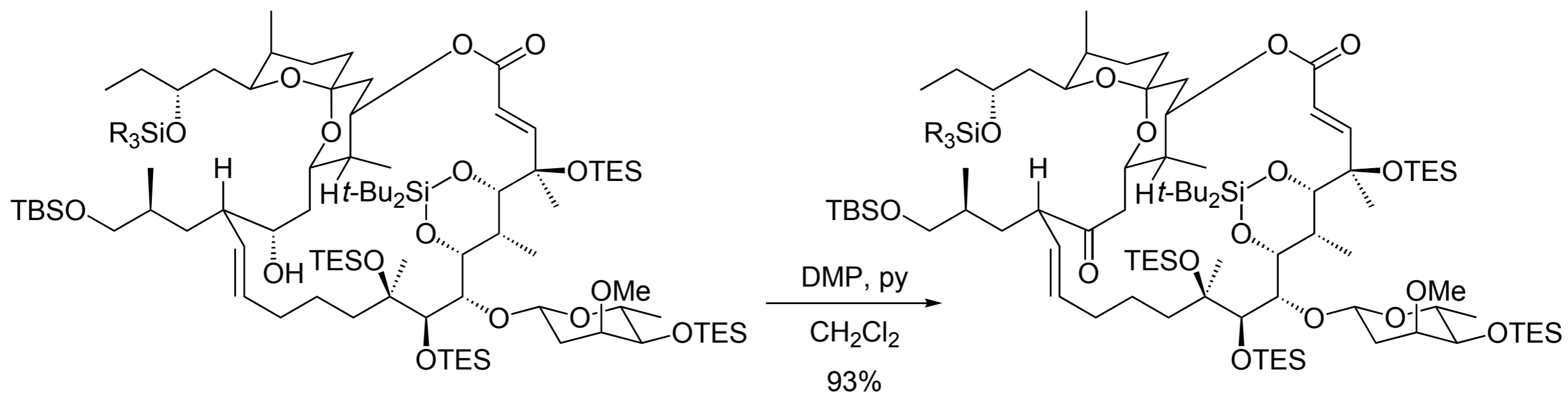
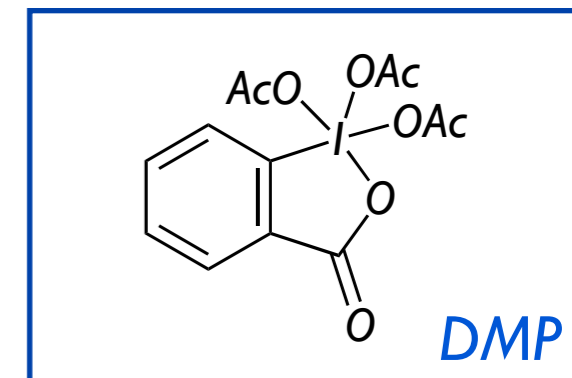
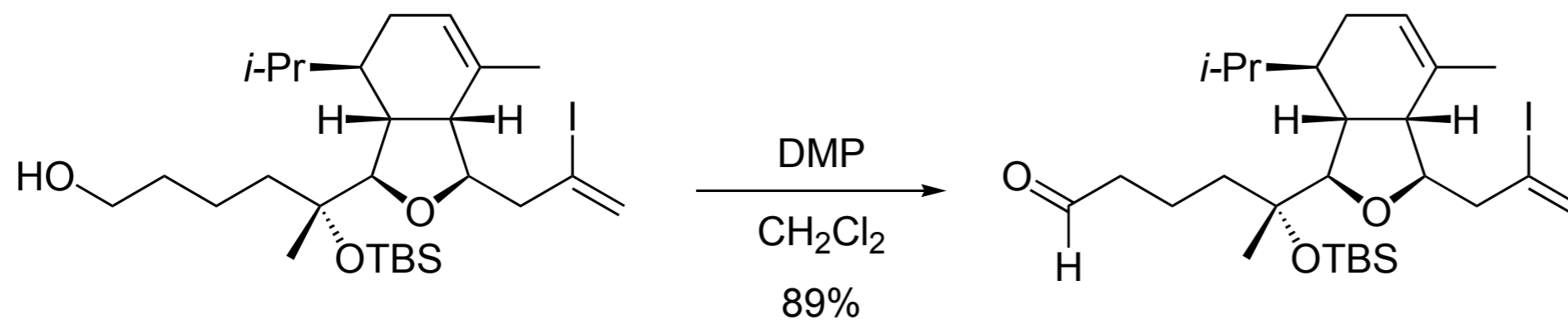


■ Iodine(V)–based reagents

– Dess-Martin Periodinane: DMP

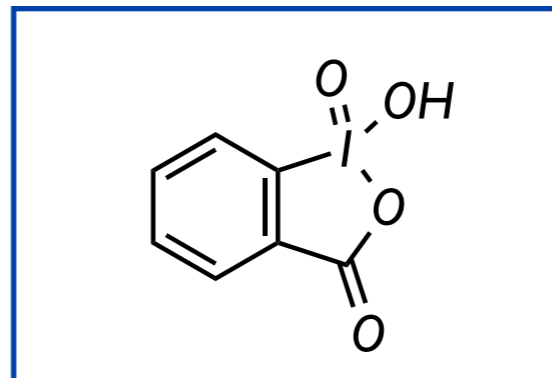


- This is a very mild oxidant that can safely be used in structurally complex and sensitive substrates
- NaHCO_3 or pyridine are often added to moderate the acidity of the reaction mixture
- The addition of one equivalent of water usually enhances the kinetics



■ Iodine(V)–based reagents

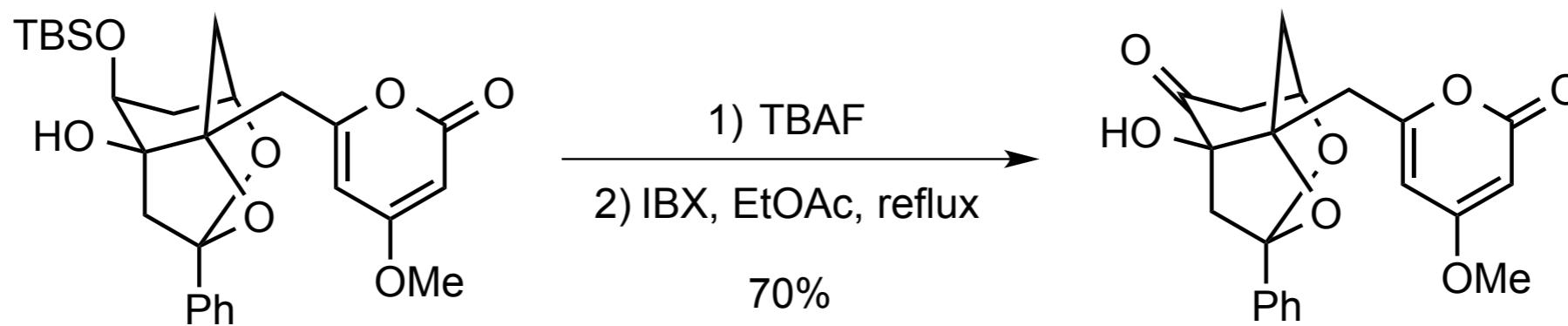
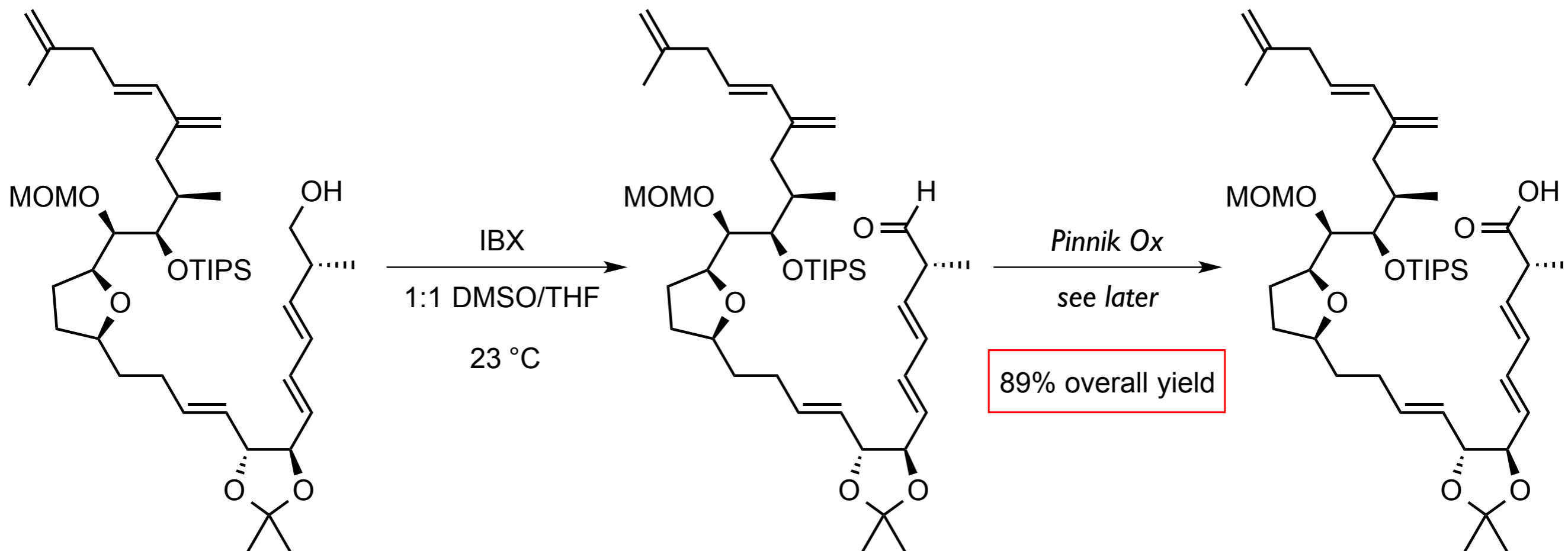
– 2-Iodoxybenzoic acid: IBX



For a review,
Kirsch, S. F. *ACIE* 2011, 50, 1524

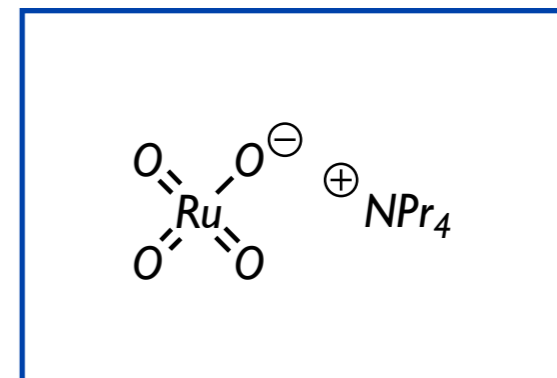
Pros and cons:

- There are safety concerns regarding the potentially violent decomposition upon impact or at high T
- Low solubility in typical organic solvents.
- A mixture of PhCO_2H , $\text{Ph}(\text{COOH})_2$, and IBX (22/29/49) has been developed
- DMSO is the choice or polymer-supported IBX
- Not susceptible to hydrolysis
- Remarkable chemoselectivity: exceptionally mild oxidant for the highly selective transformation of primary and secondary alcohols into carbonyl compounds, and 1,2-diols into hydroxycarbonyls
- Catalytic amounts of IBX can be used in the presence of stoichiometric amounts of ozone

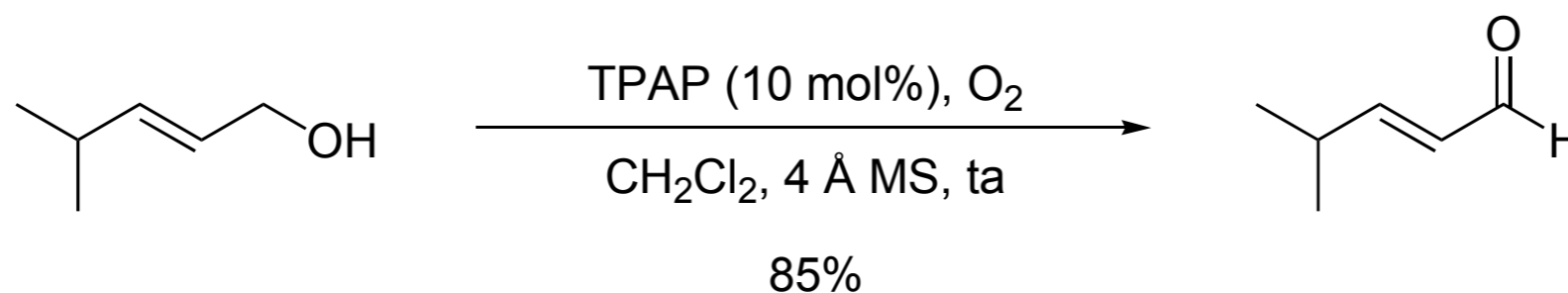
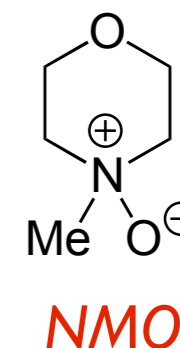
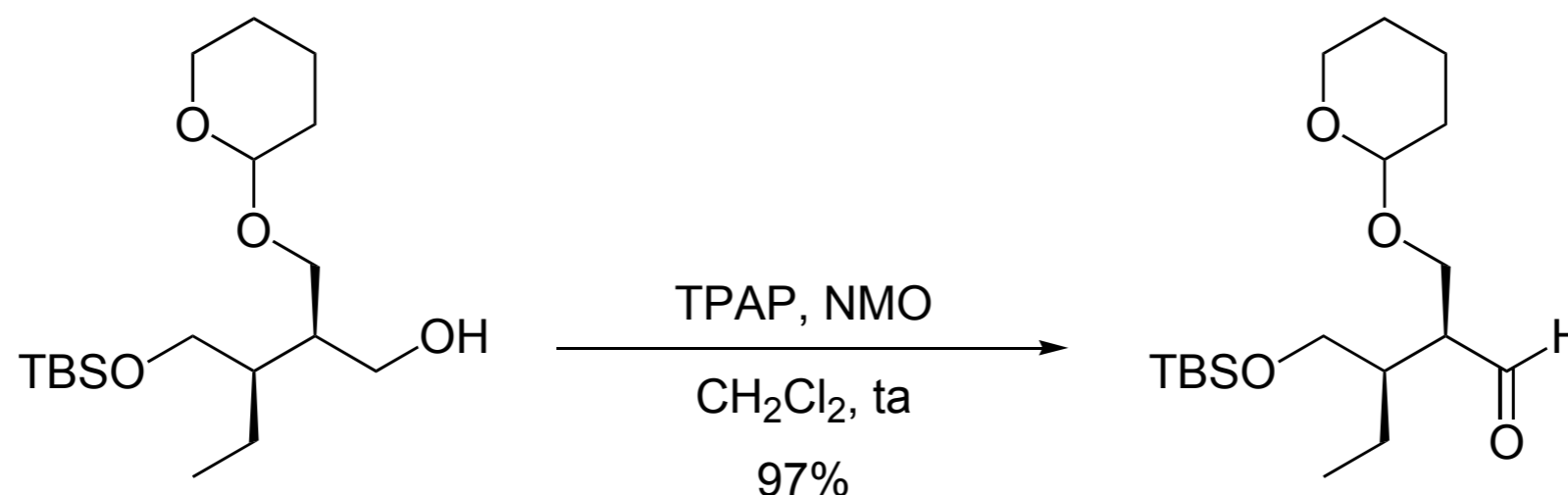


■ *Ruthenium-based reagents*

– *Tetra-*n*-propylammonium perruthenate: TPAP*

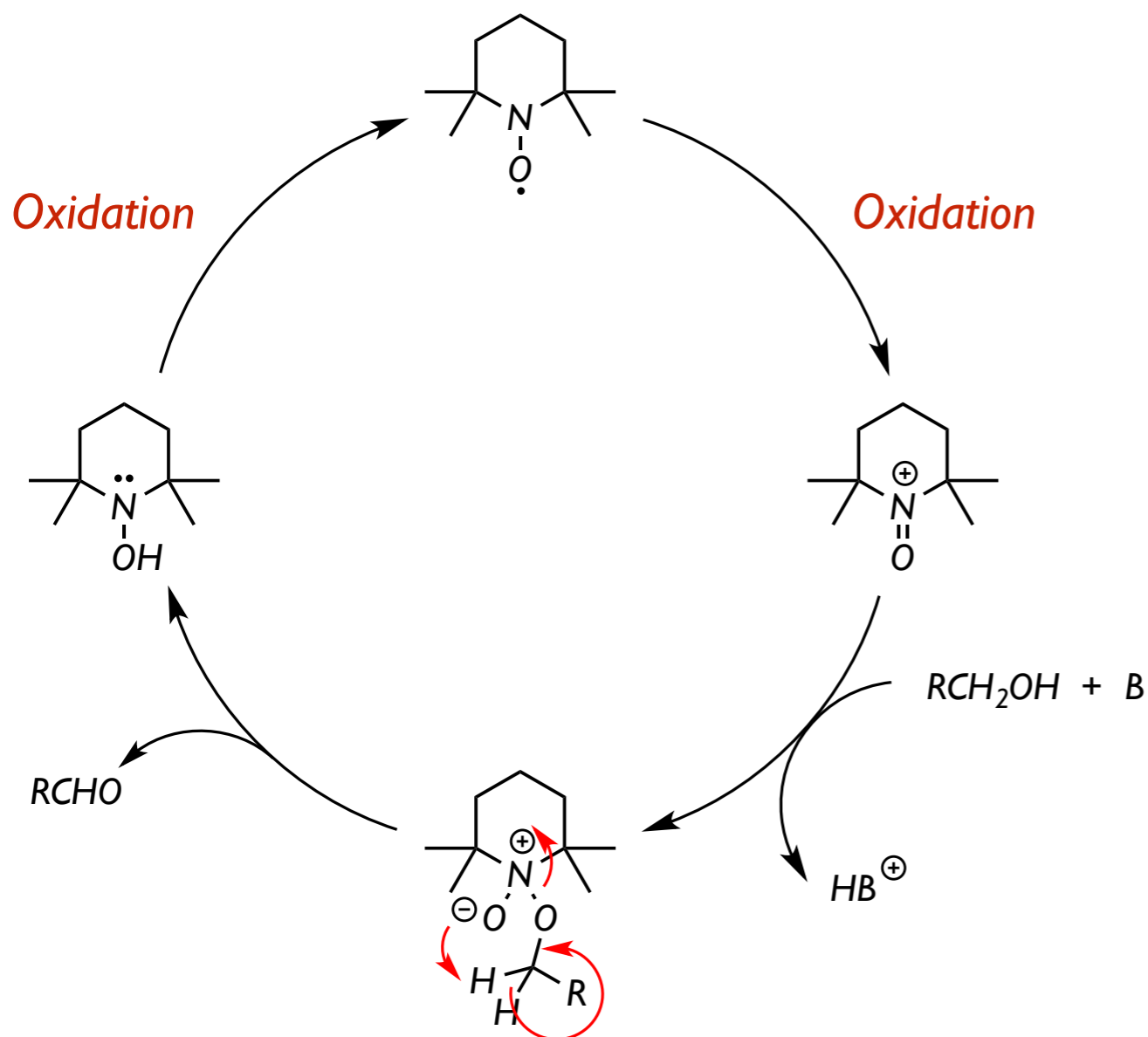
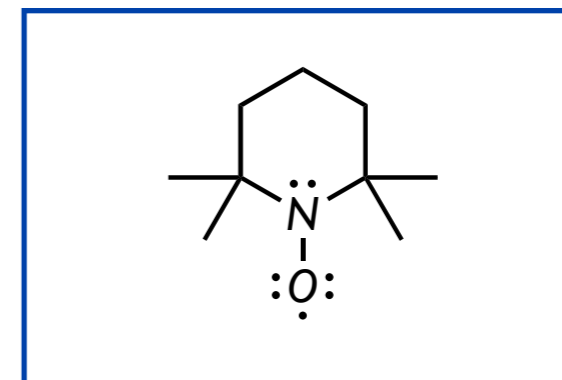


– *Used as catalyst in the presence of stoichiometric amounts of a second oxidant (NMO, O₂)*



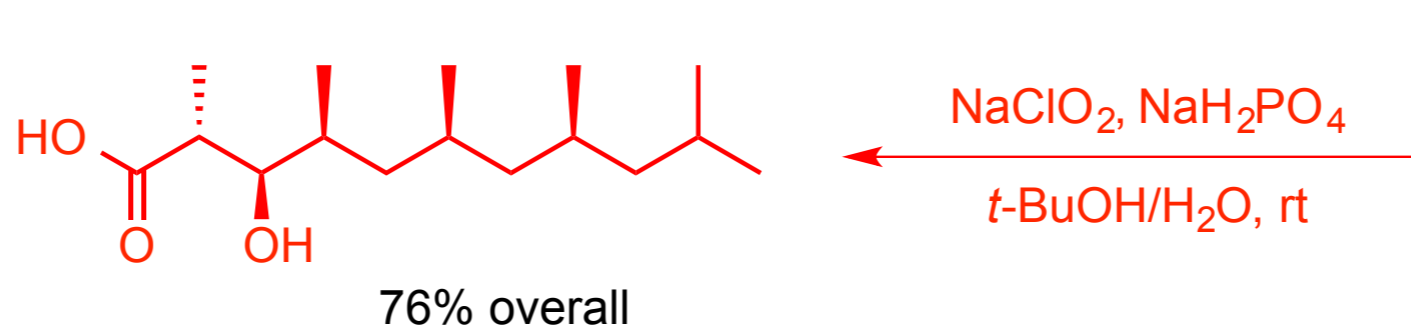
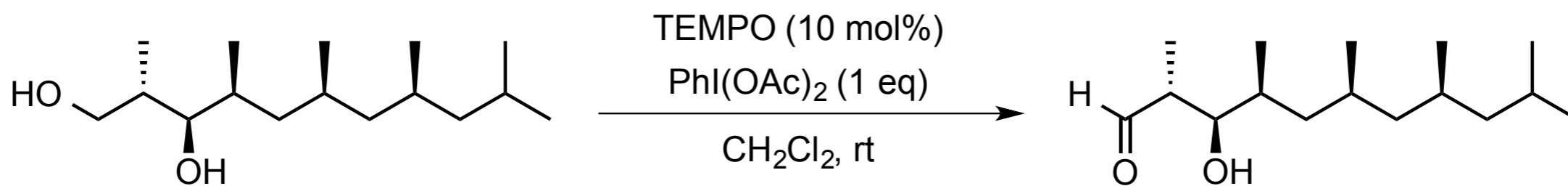
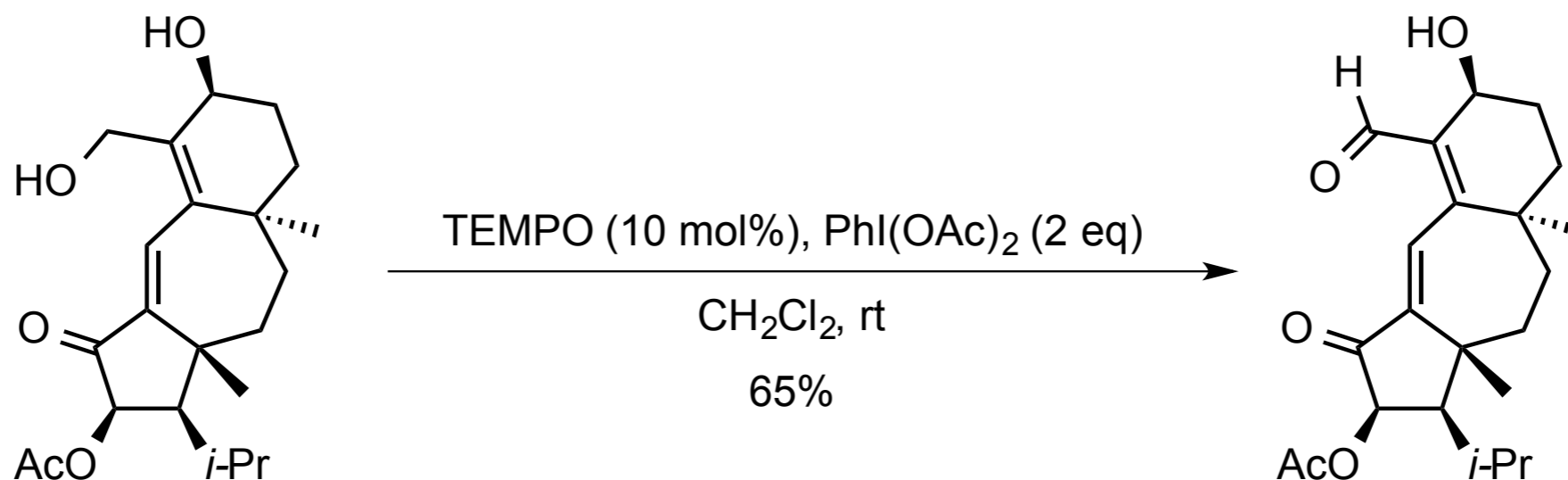
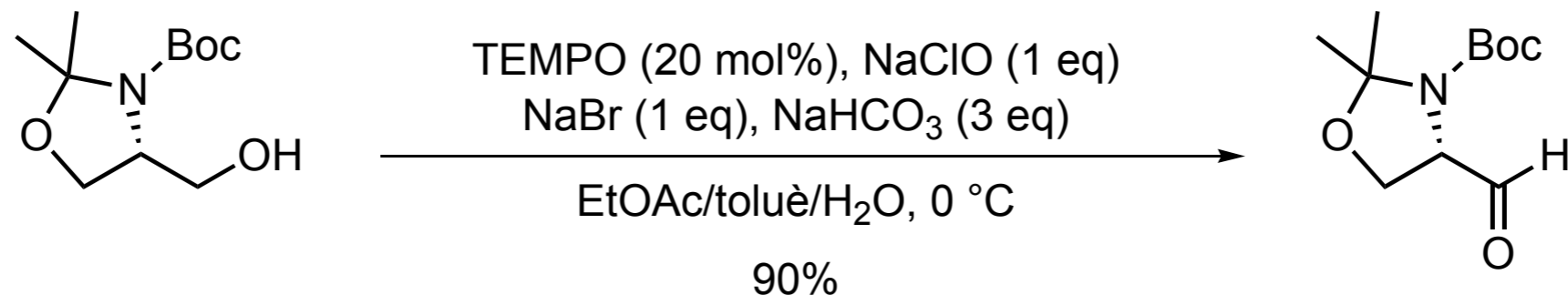
■ Radicals as oxidizing agents

– 2,2,6,6-Tetramethylpiperidinyloxy: TEMPO



- TEMPO is a very mild and chemoselective oxidant: only 1ary and 2ary alcohols are affected
- 1ary Alcohols are oxidized more easily than 2ary Alcohols : chemo- & siteselective
- TEMPO is used under catalytic premises in the presence of stoichiometric amounts of another oxidizing agent as ClO^- , $\text{PhI}(\text{OAc})_2$, or $\text{Cu}(\text{I})/\text{O}_2$
- The mechanism depends on this second reagent

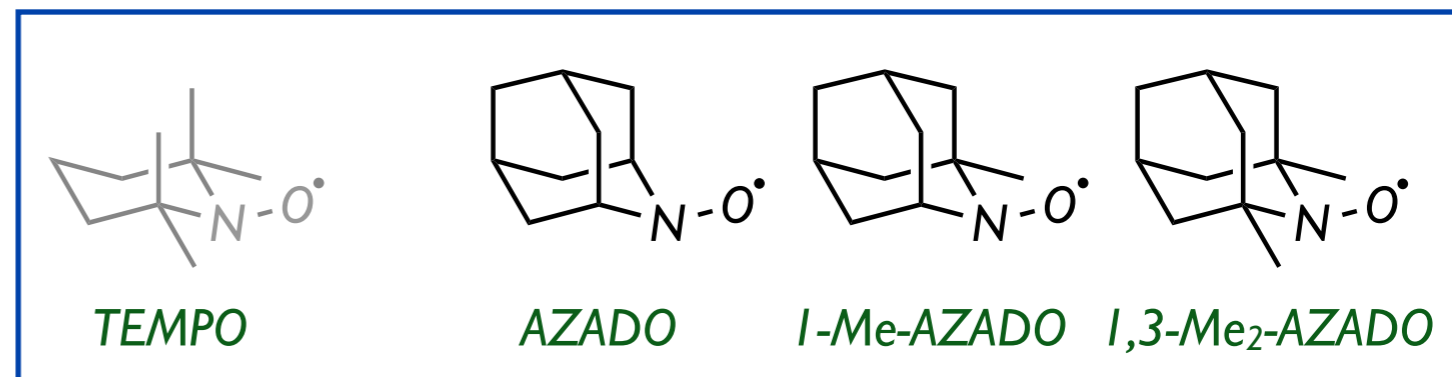
Other mechanisms have been proposed



■ Radicals as oxidizing agents

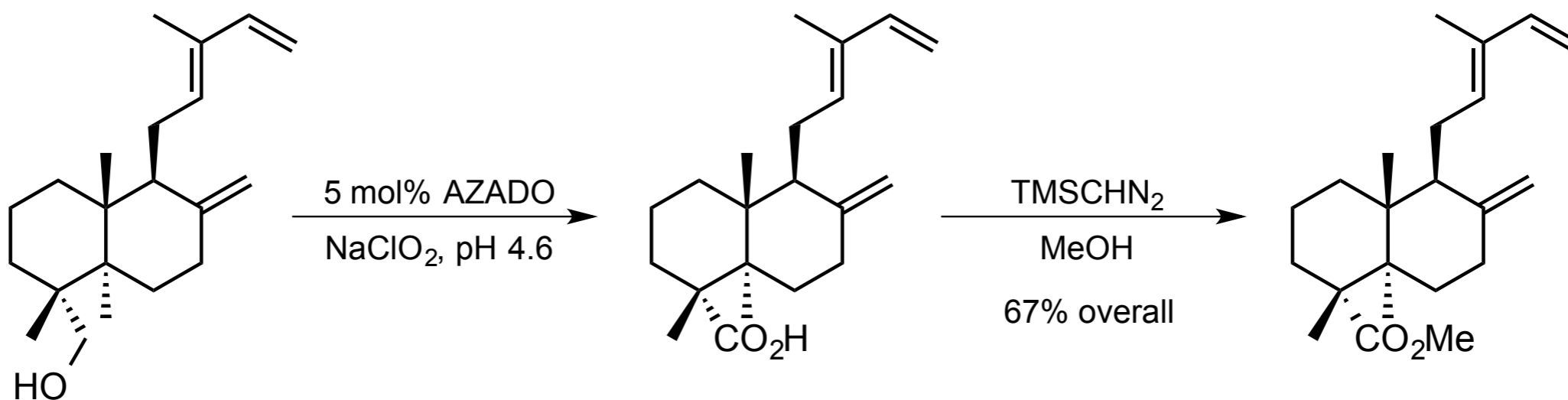
– 2-Azaadamantane N-oxyl radicals:
AZADO

Iwabuchi, Y. JACS 2006, 128, 8412



– Four Me groups flanking the nearby catalytic center in TEMPO prevent bulky substrates forming the key intermediates

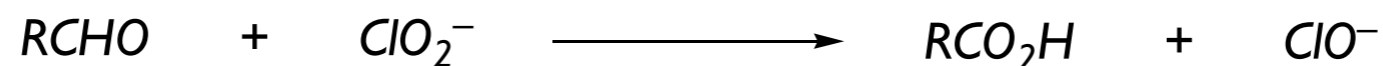
– AZADO family, a structurally less hindered class of nitroxyl radicals, may overcome this problem



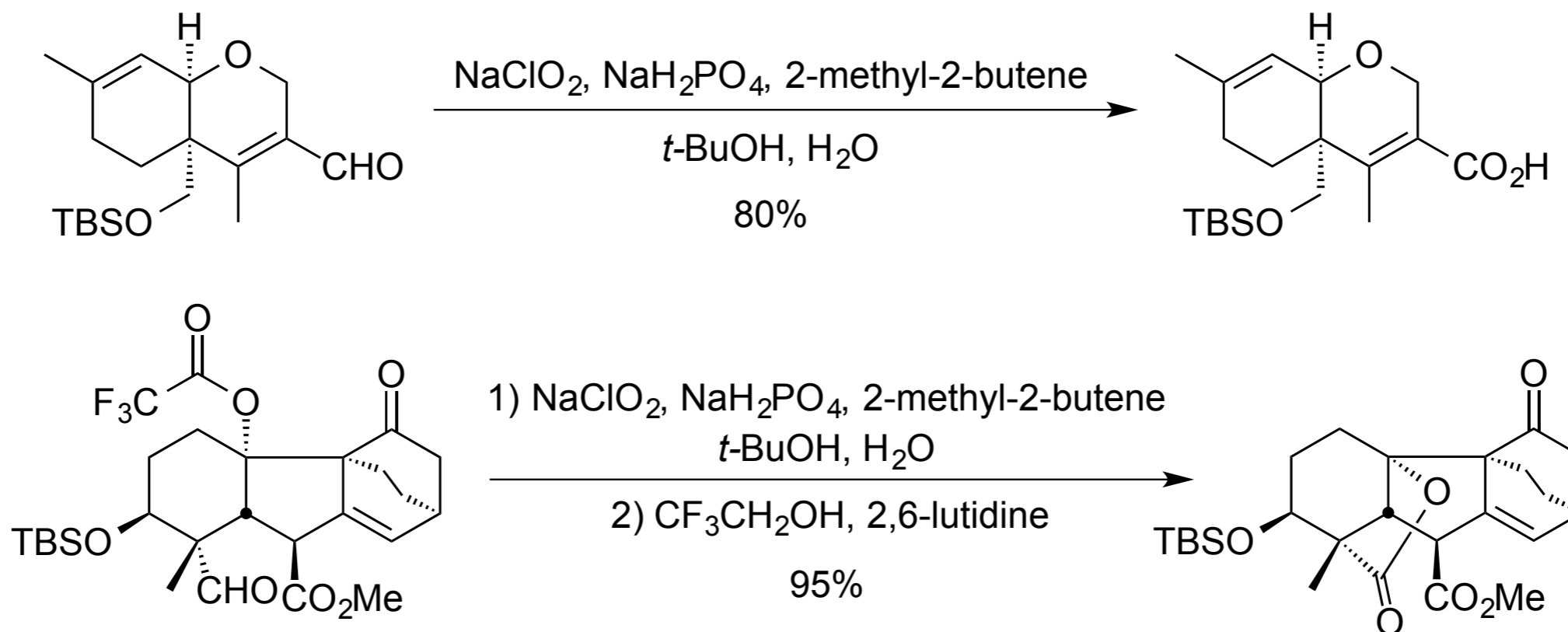
Structurally hindered alcohol

Sodium chlorite acts as the stoichiometric oxidant and transforms the resulting aldehyde into a carboxylic acid. See next slide

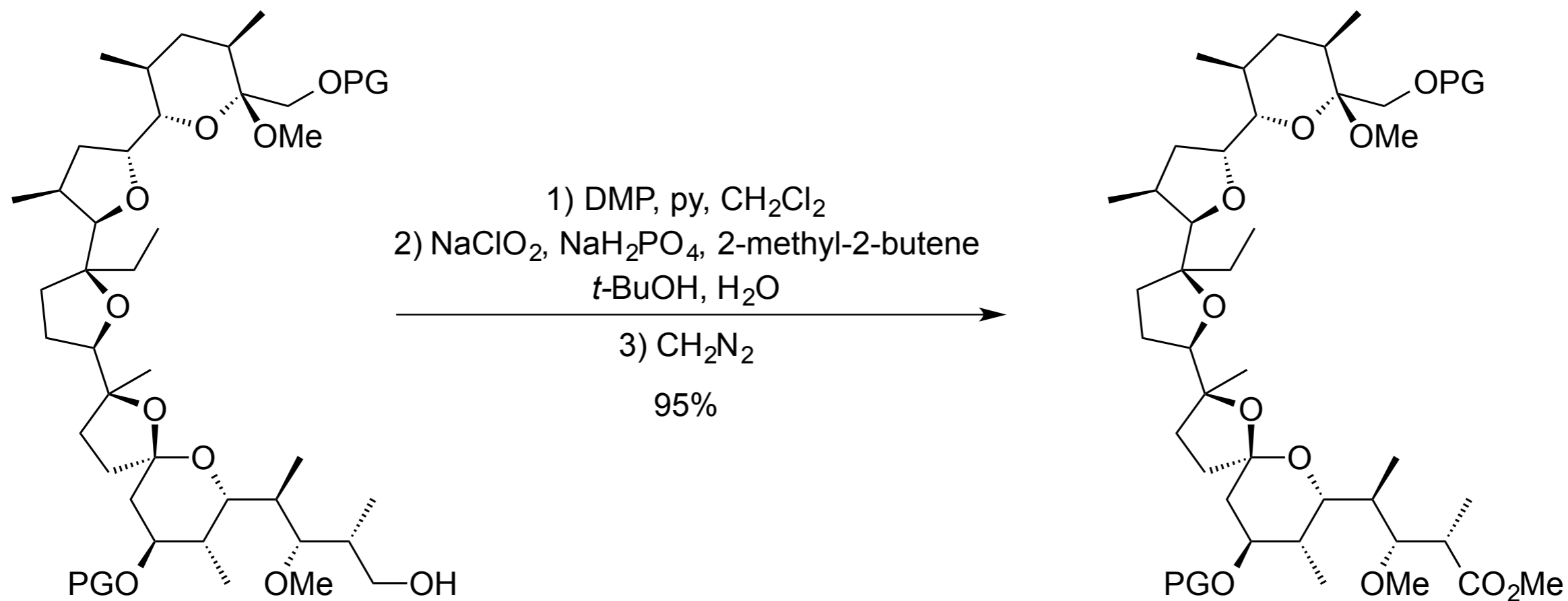
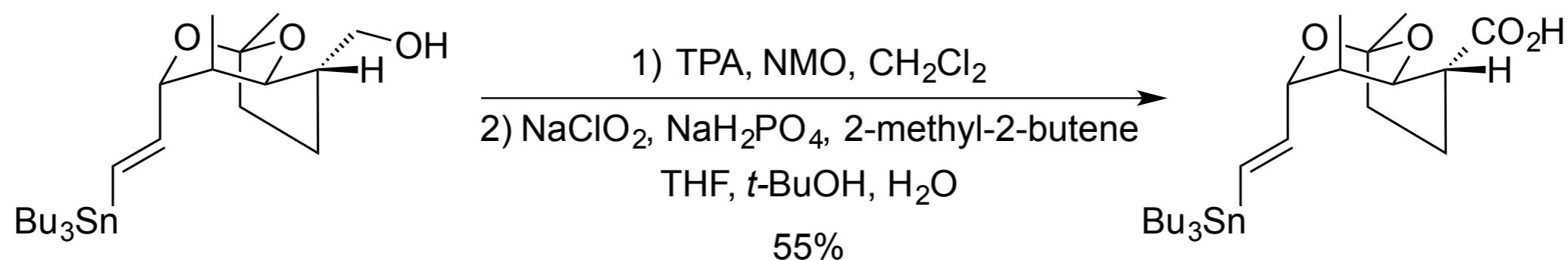
■ *Pinnick oxidation: sodium chlorite, NaClO₂:*



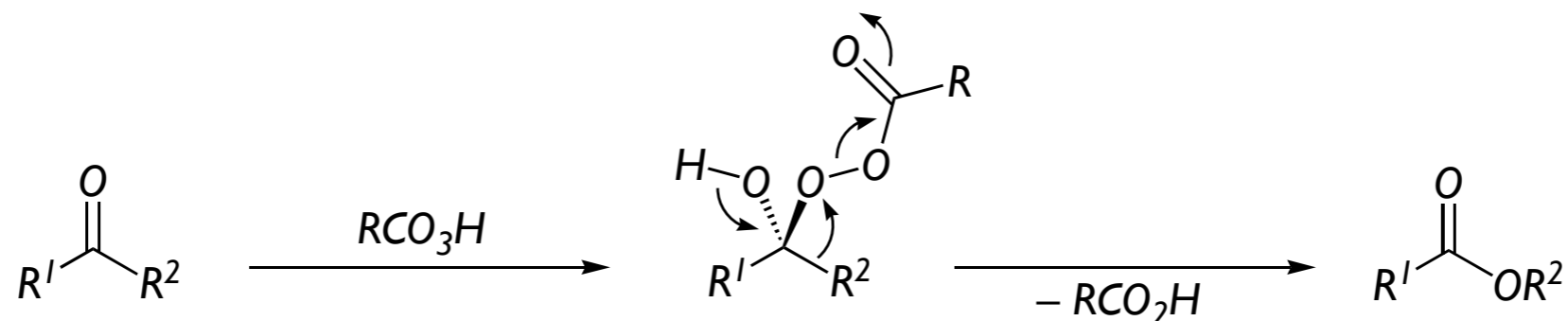
- Sodium chlorite is a cheap, mild, and chemoselective oxidizing reagent: only aldehydes are affected
- 2-Methyl-2-butene is usually added to remove the resultant sodium hypochlorite



– Pinnik oxidation is often the second step of an oxidizing sequence
 leading from primary alcohols to carboxylic acids



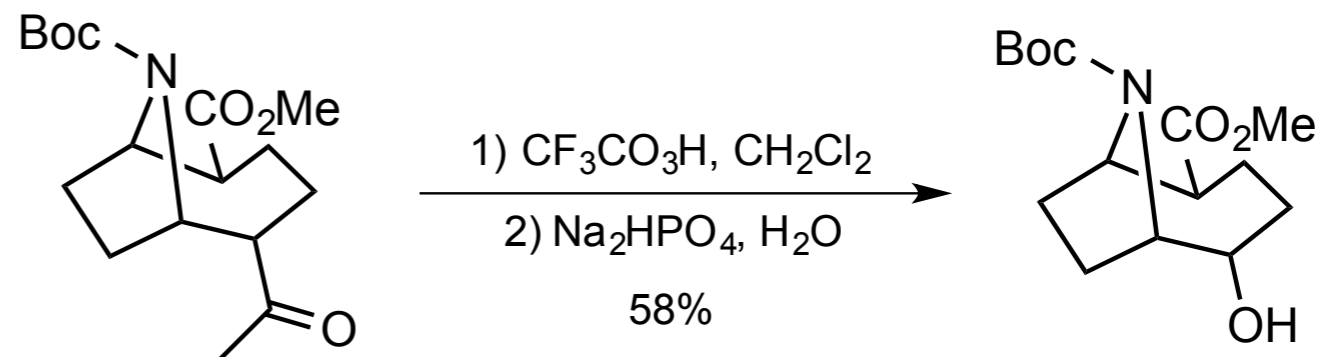
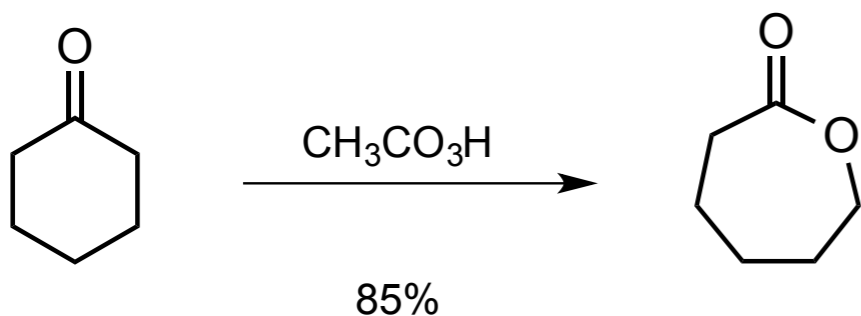
■ *Baeyer-Villiger oxidation: Peracids, RCO_3H :*



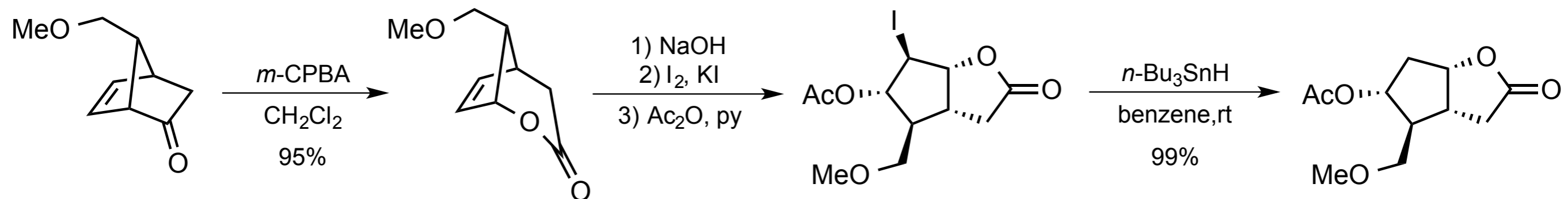
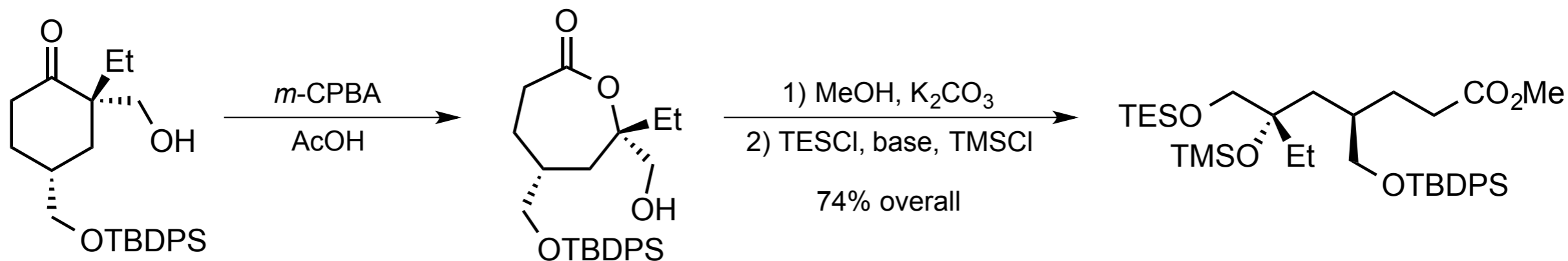
(H) > tertiary > secondary > benzyl \approx phenyl > vinyl > primary > Me

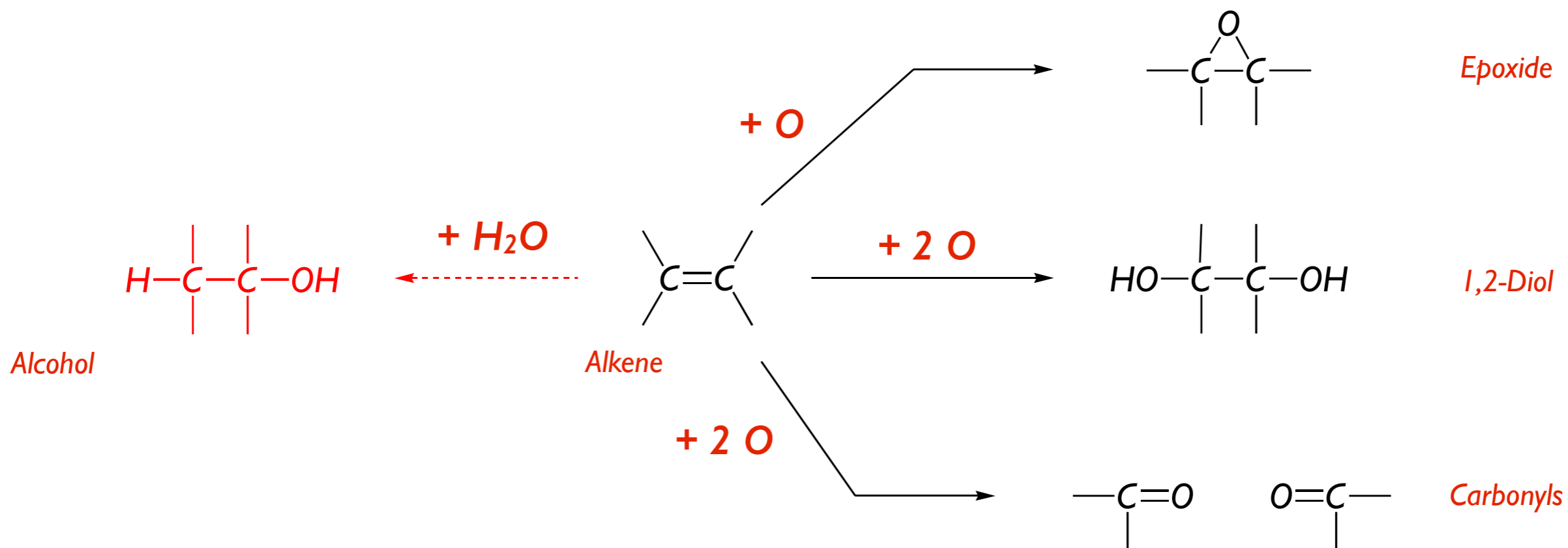
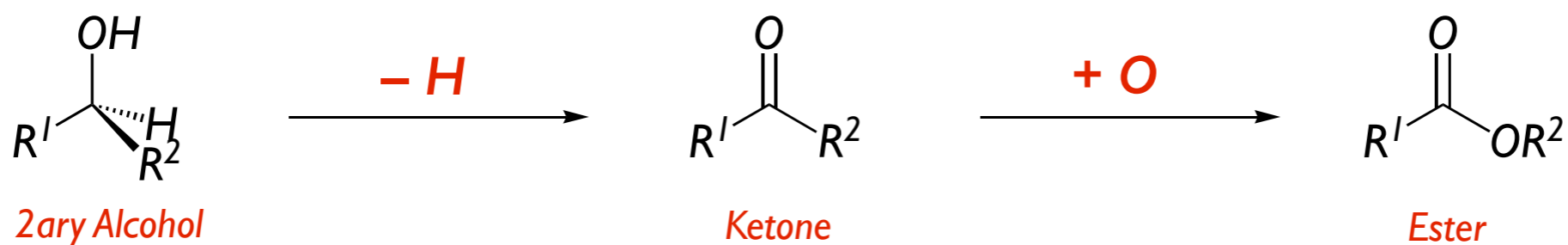
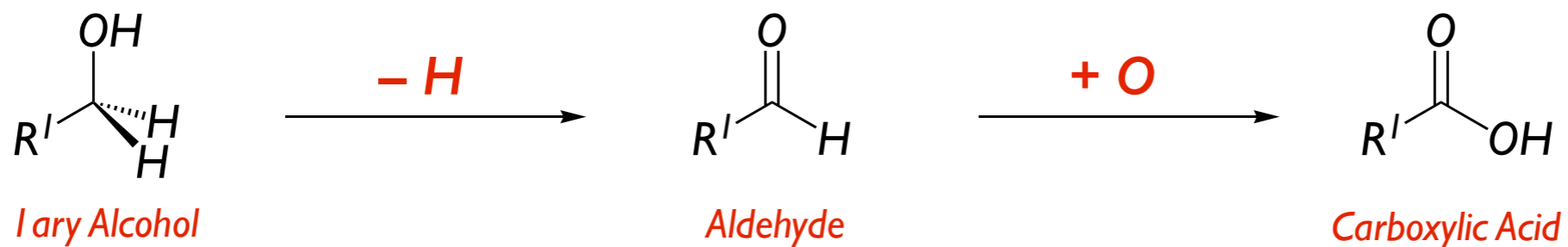
- *Although steric factors can come in to play, the propensity to migrate is enhanced by EDG groups*
 - *Migration of R^2 proceeds with retention of the configuration*
 - *The oxidation is catalyzed by acids*
- *Electronically poor peracids and electronrich ketones give faster oxidations*
 - *Peracids react with olefines very easily*

– A variety of peracids can be used ...

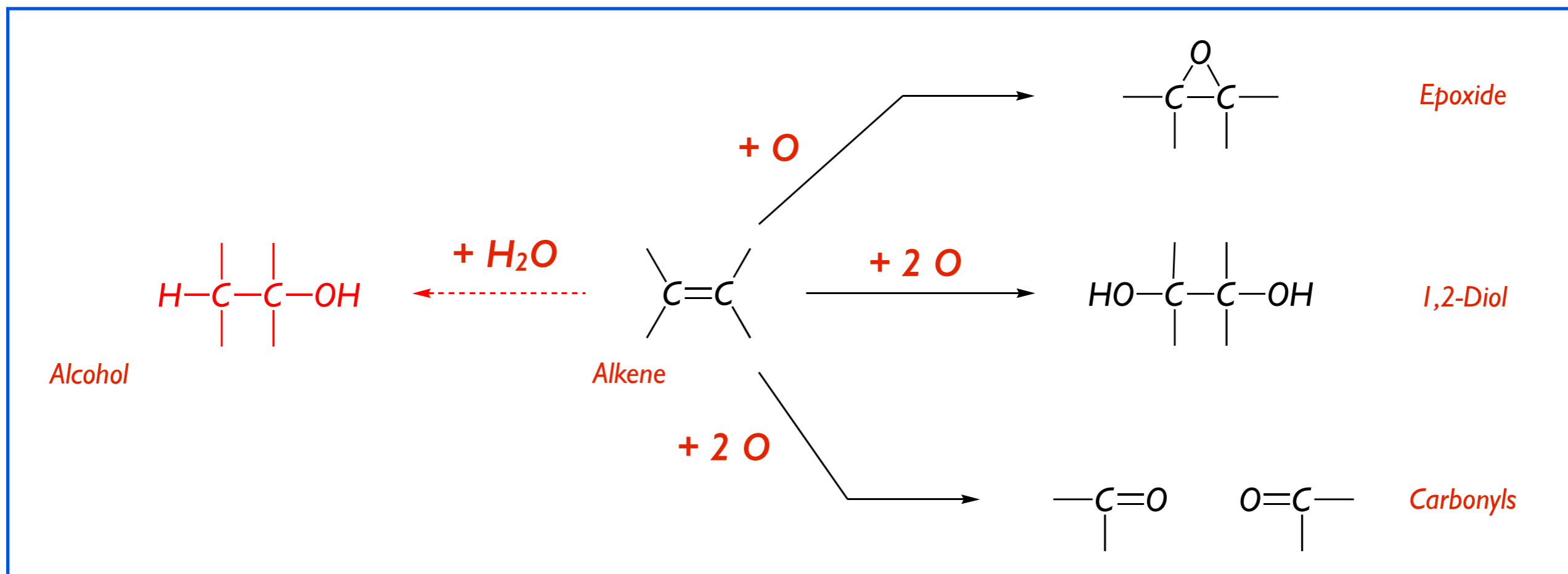


... but *m*CPBA is the most common one



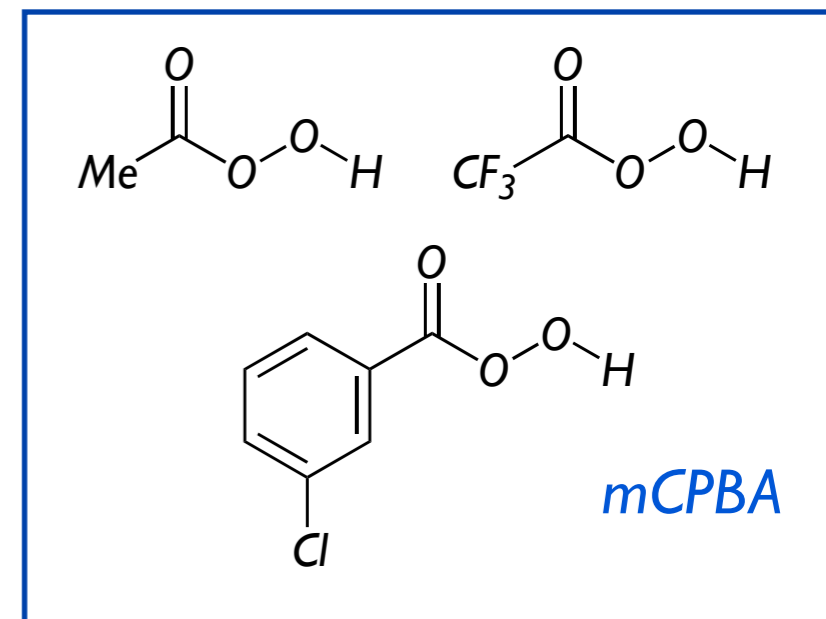
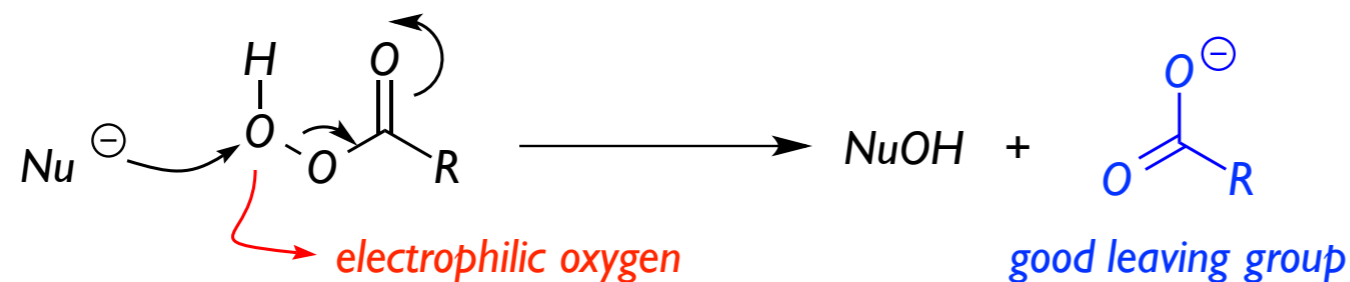


- *Epoxidation of alkenes*
- *Dihydroxylation of alkenes*
- *Other oxidations*

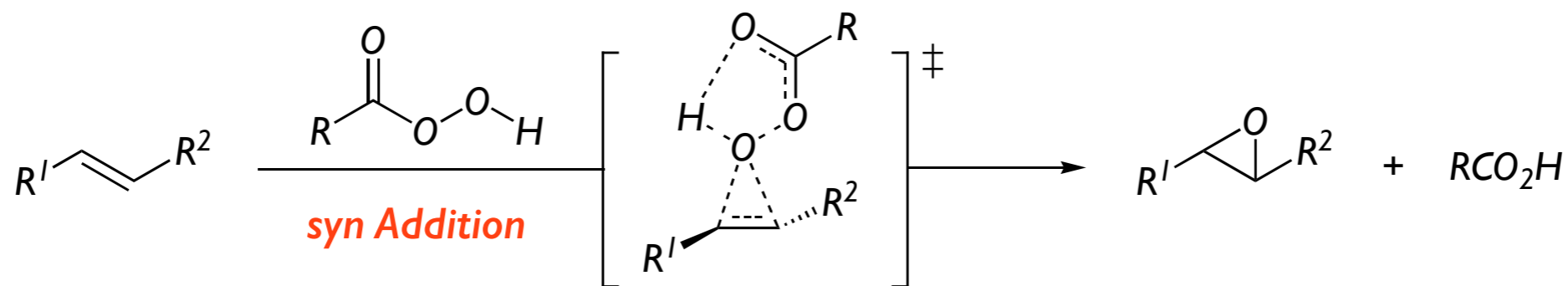


■ *With peracids*

– The third oxygen of peracids has a remarkable electrophilic character and the carboxylate is a good leaving group ...

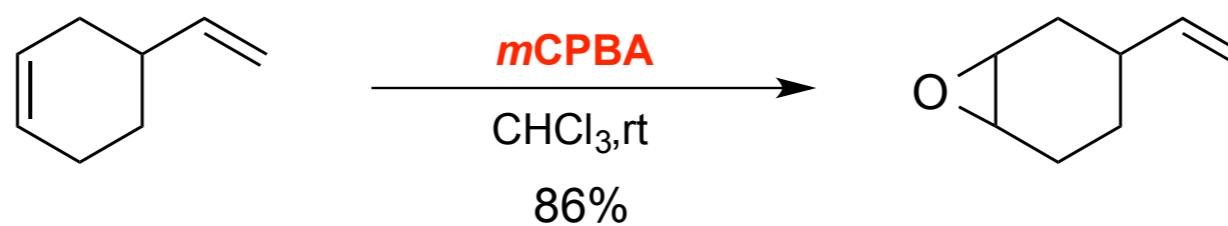
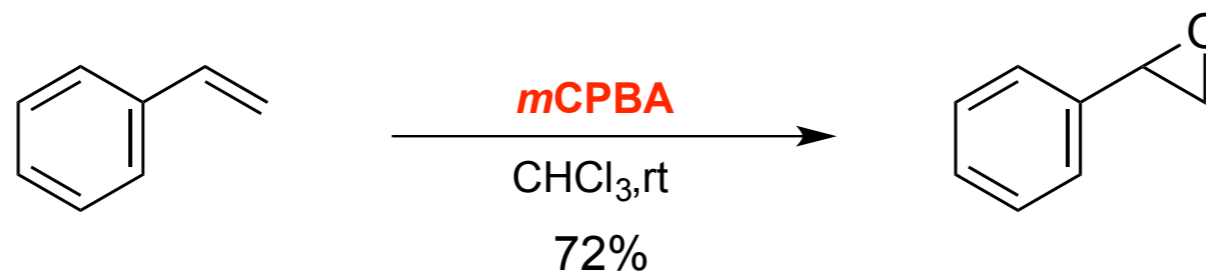
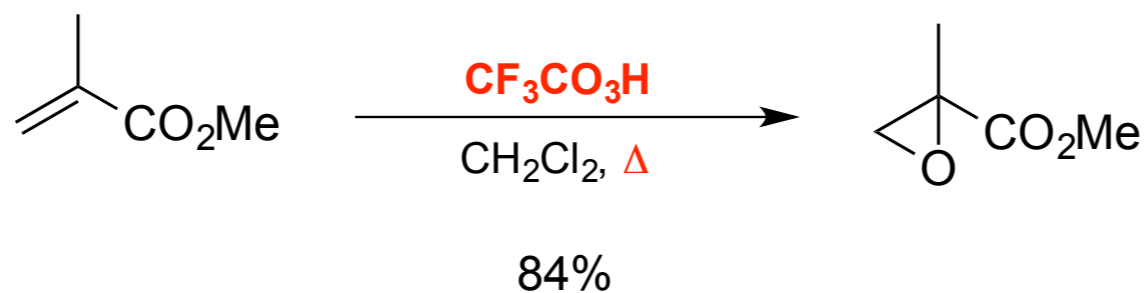
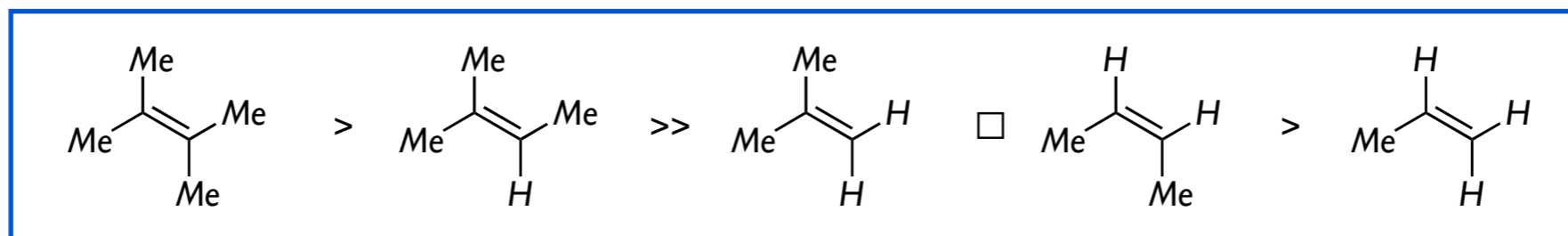


– Since alkenes have a nucleophilic character (remember electrophilic additions to C=C), they react with peracids and an oxygen is transferred in a *syn* concerted step.



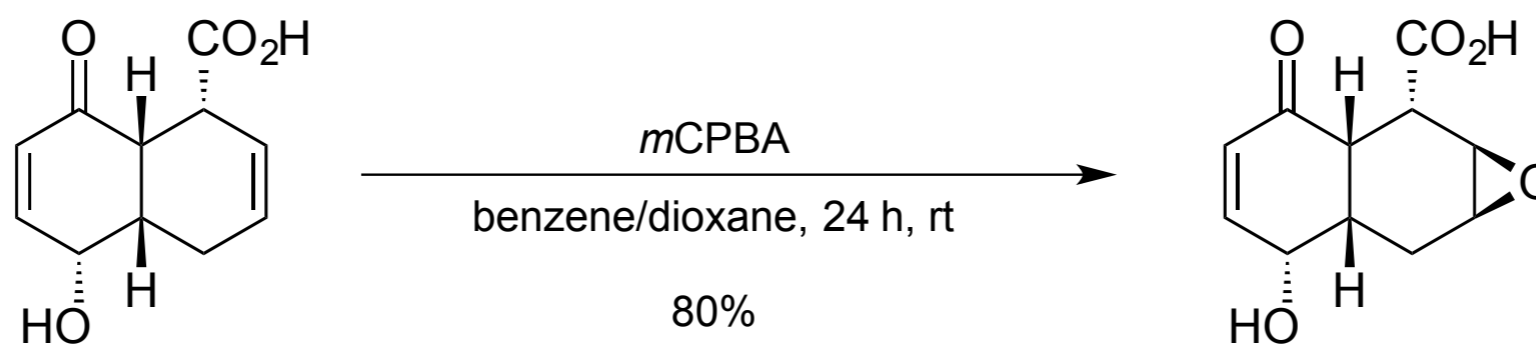
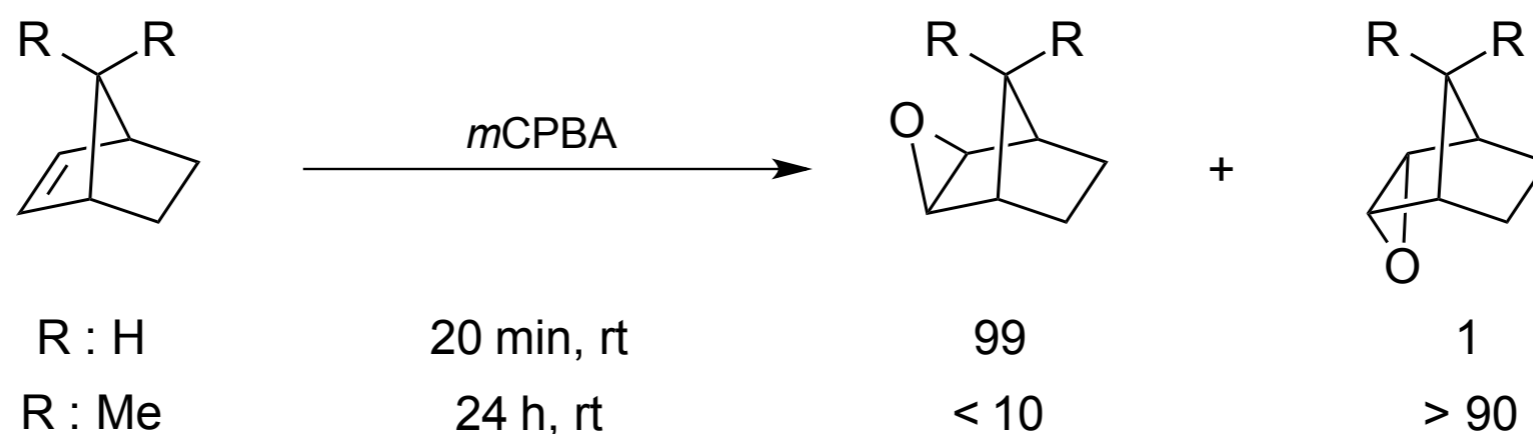
– This epoxidation is sensitive to electronic effects.

It proceeds faster with electronically poor peracids ($\text{CF}_3\text{CO}_3\text{H} > m\text{CPBA} > \text{CH}_3\text{CO}_3\text{H}$) and electronically rich alkenes



– This epoxidation is also sensitive to steric effects.

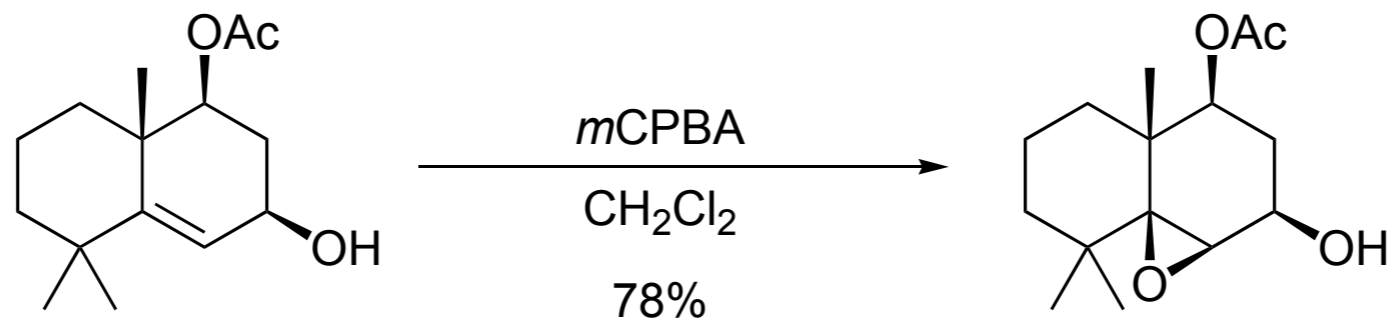
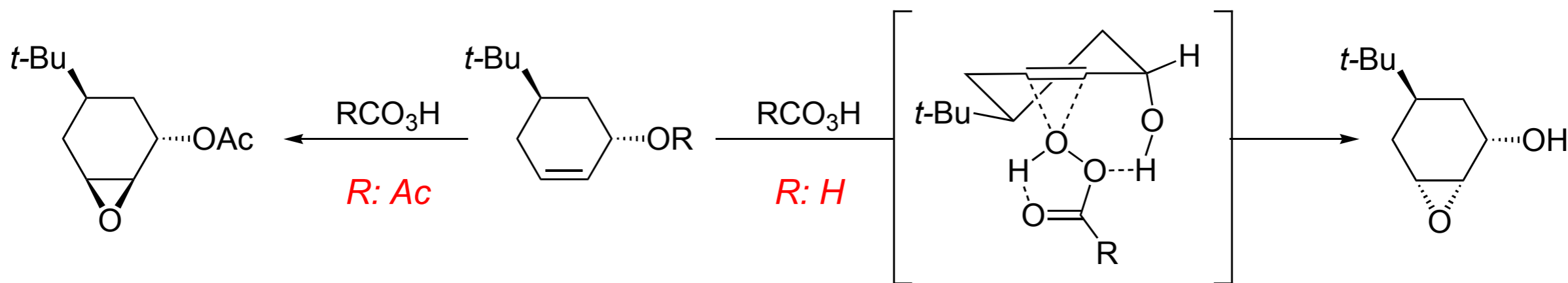
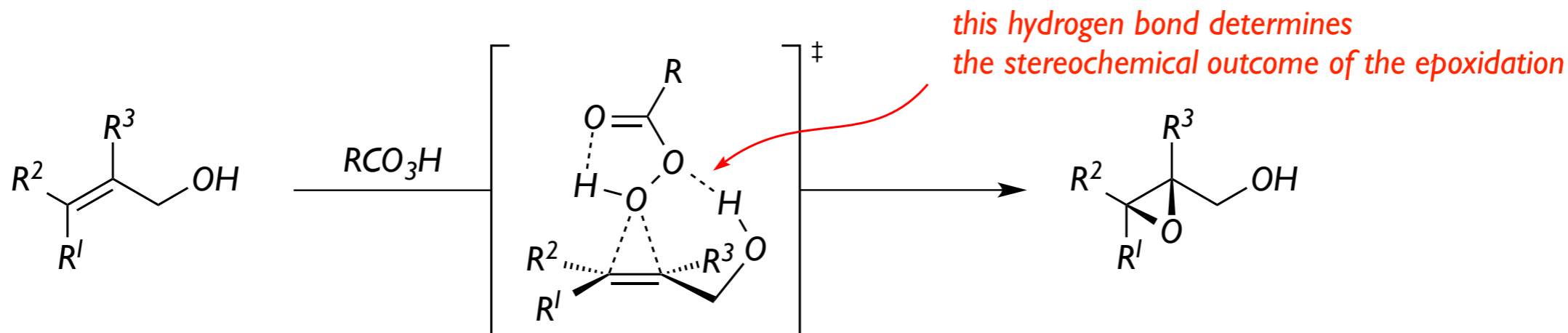
The peracids generally approach from the less hindered side of the olefin ...



... unless other functional groups near the olefin can direct the orientation of the incoming reagent

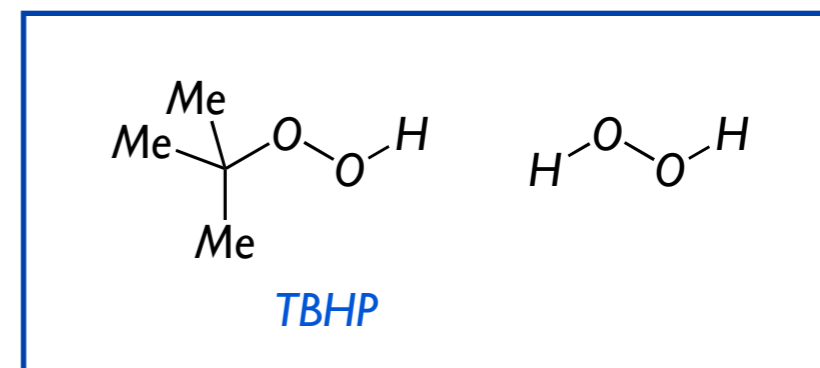
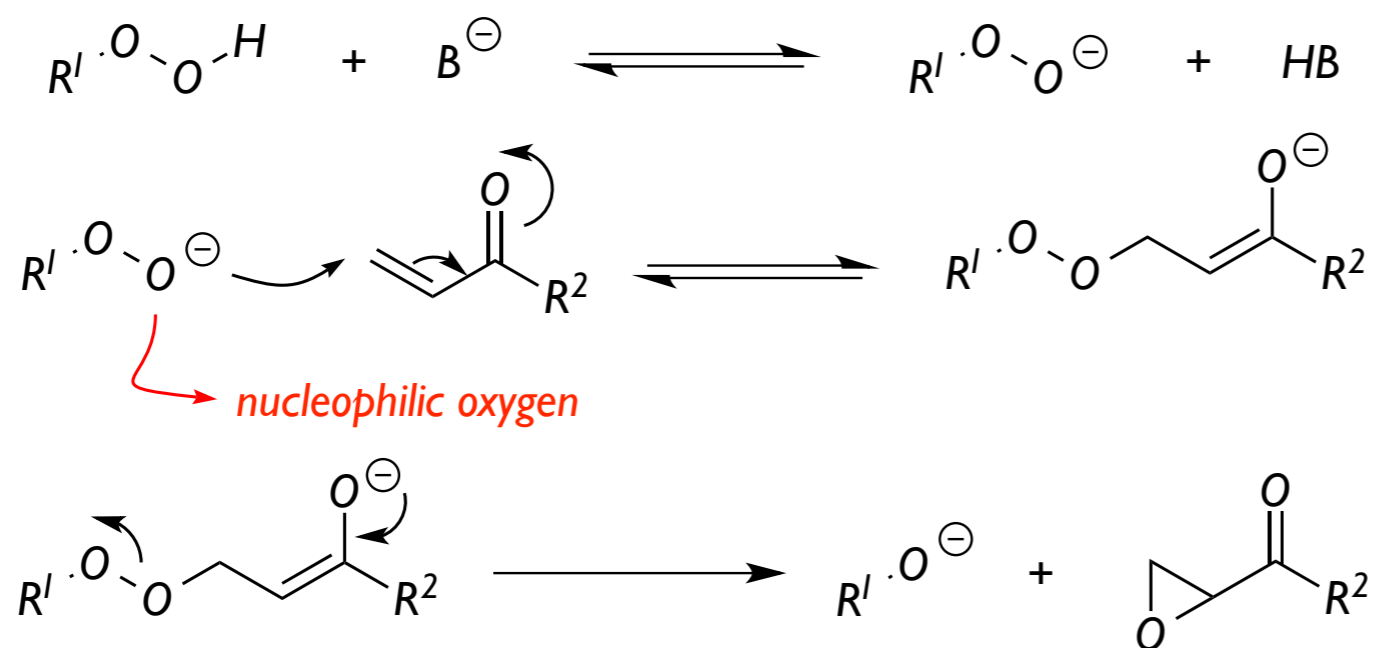
– This happens in allylic and homoallylic alcohols:

hydroxyl group can direct the approach of the peracids overcoming the steric hindrance of the system

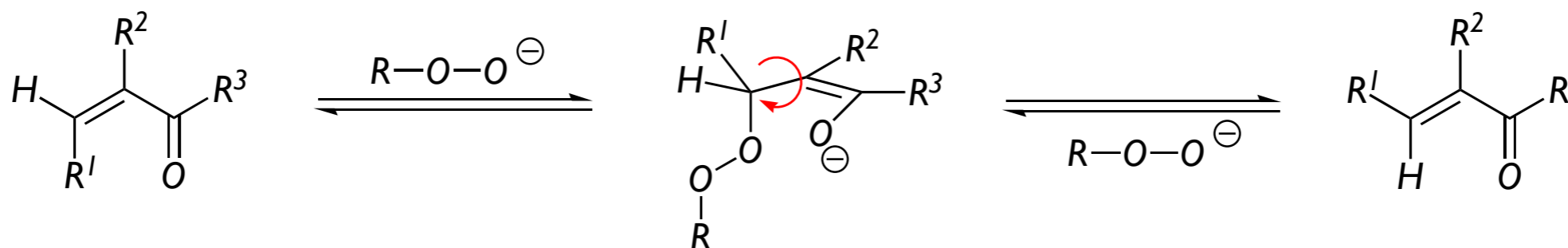


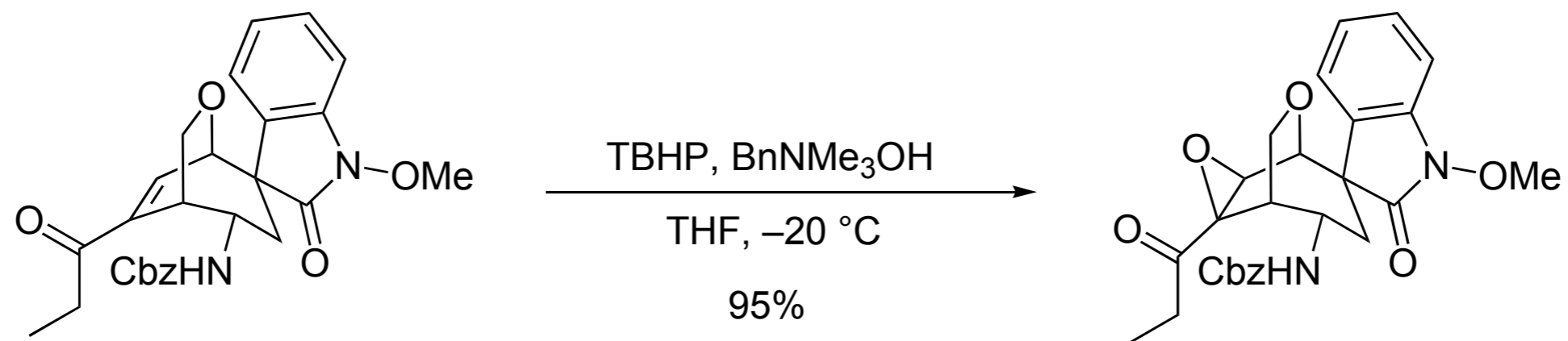
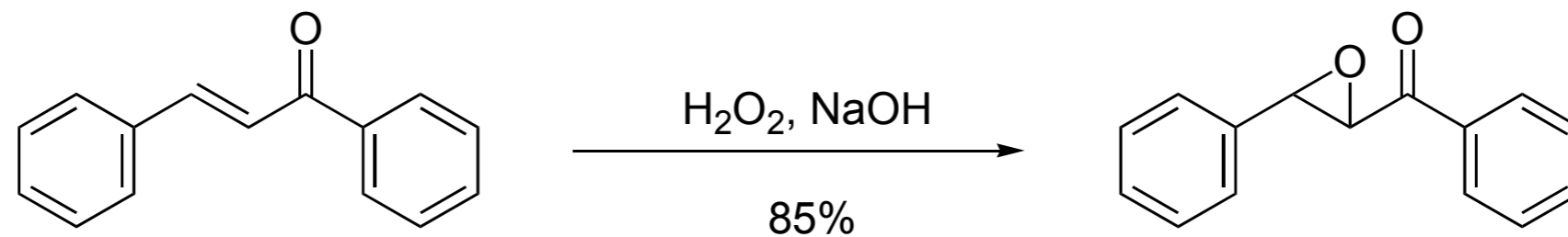
■ With peroxides and bases: $ROOH / OH^-$

– Is it possible to transfer any nucleophilic oxygen?



– The geometry of the alkene does not control the configuration of the resulting epoxide because it is a stepwise process

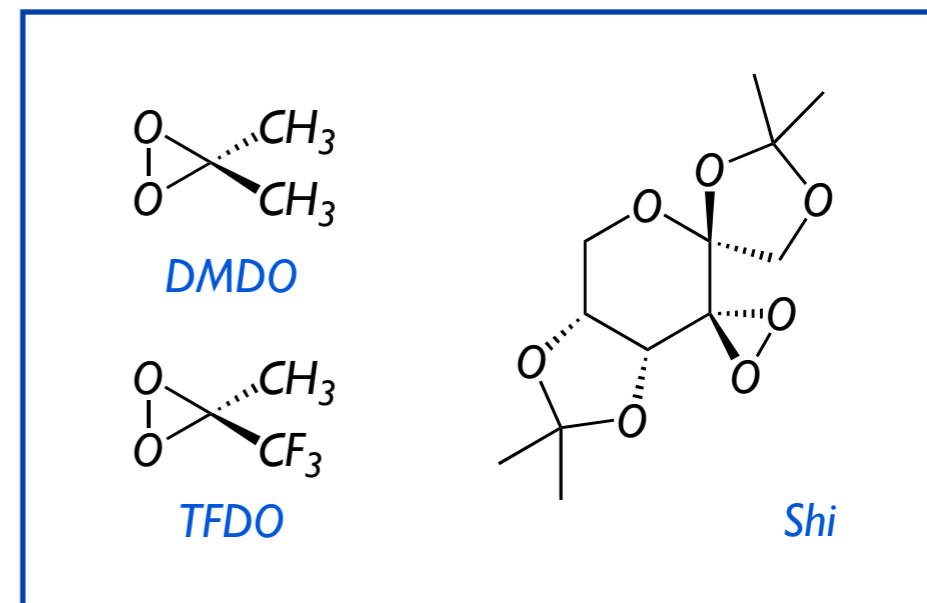
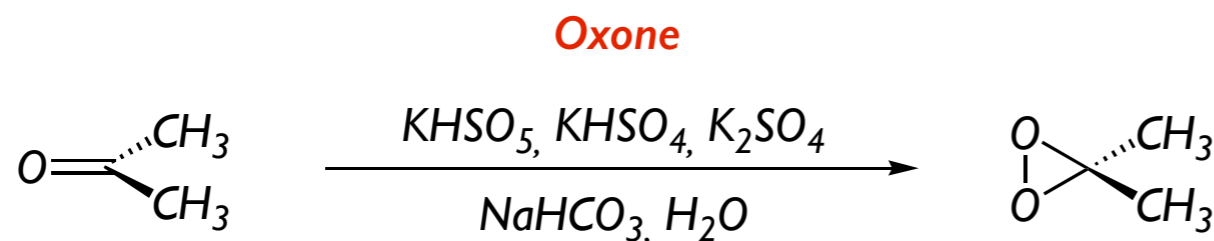




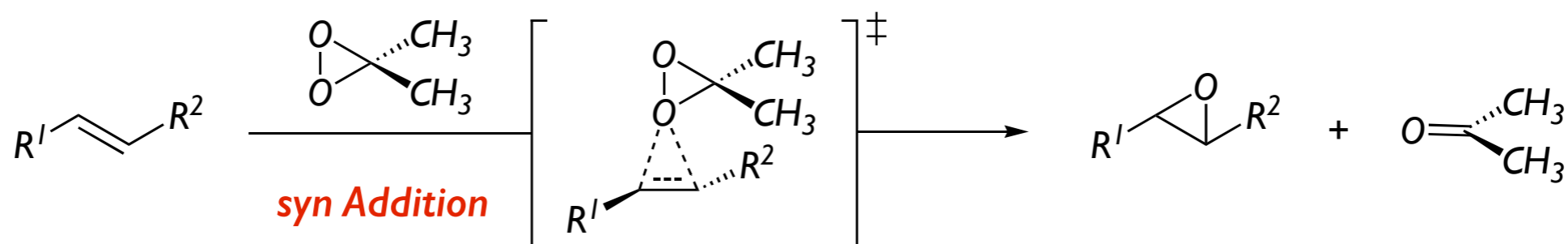
■ *With peroxides in a neutral medium: dioxiranes*

- *Dioxiranes are three membered–rings peroxides*
- *They can be prepared by oxidation with Oxone.*

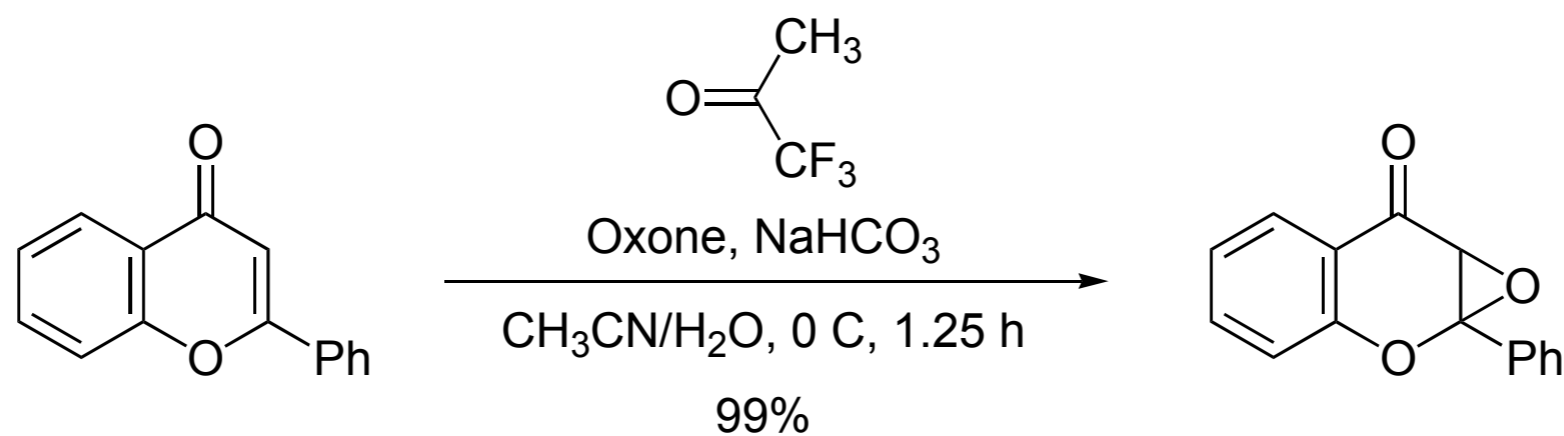
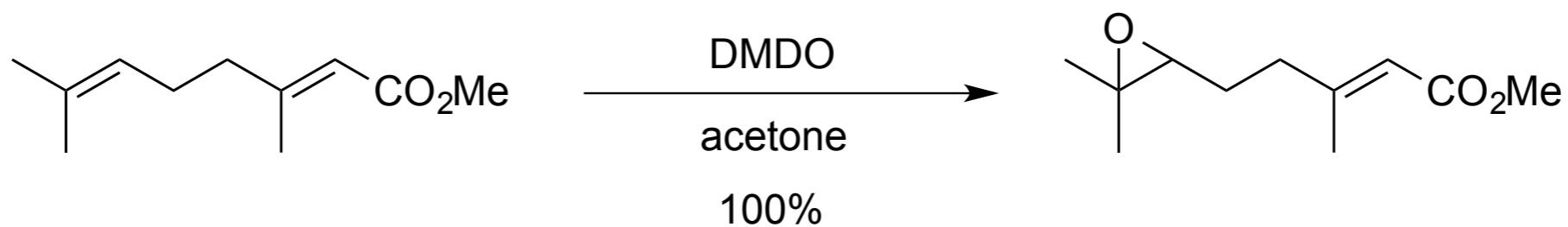
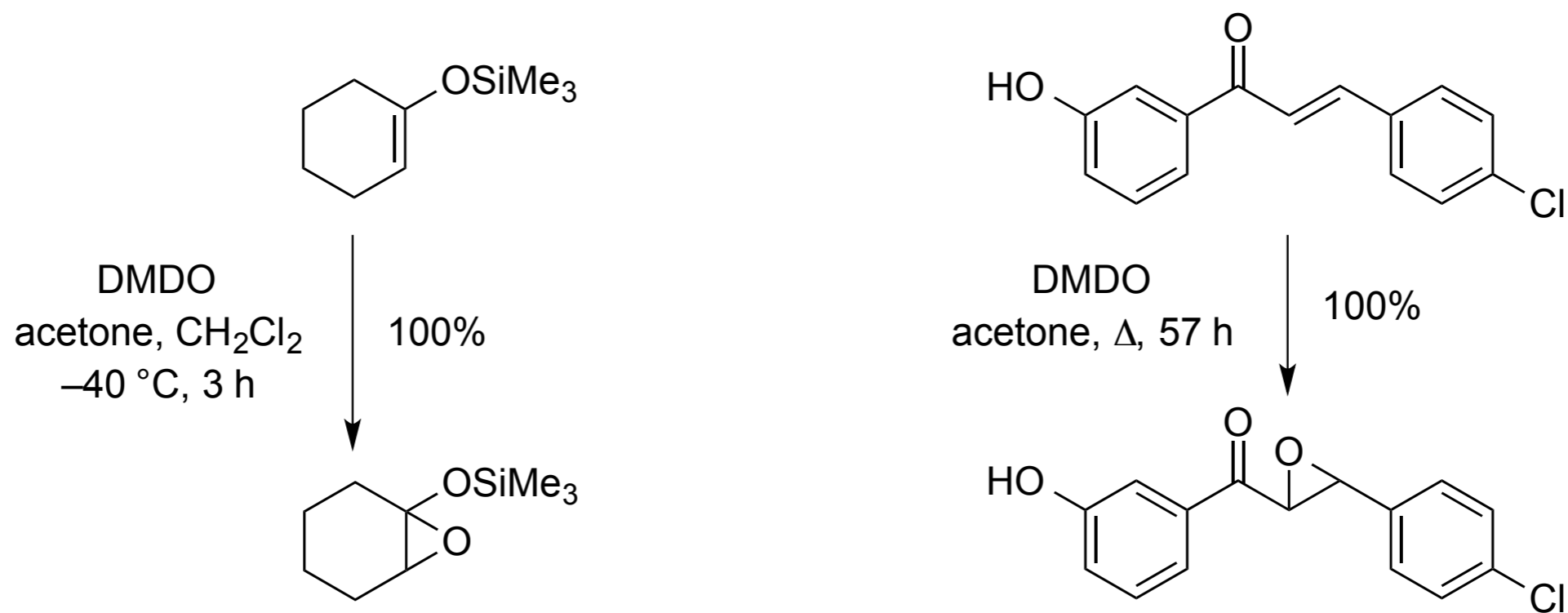
They can be isolated in solution or prepared in situ

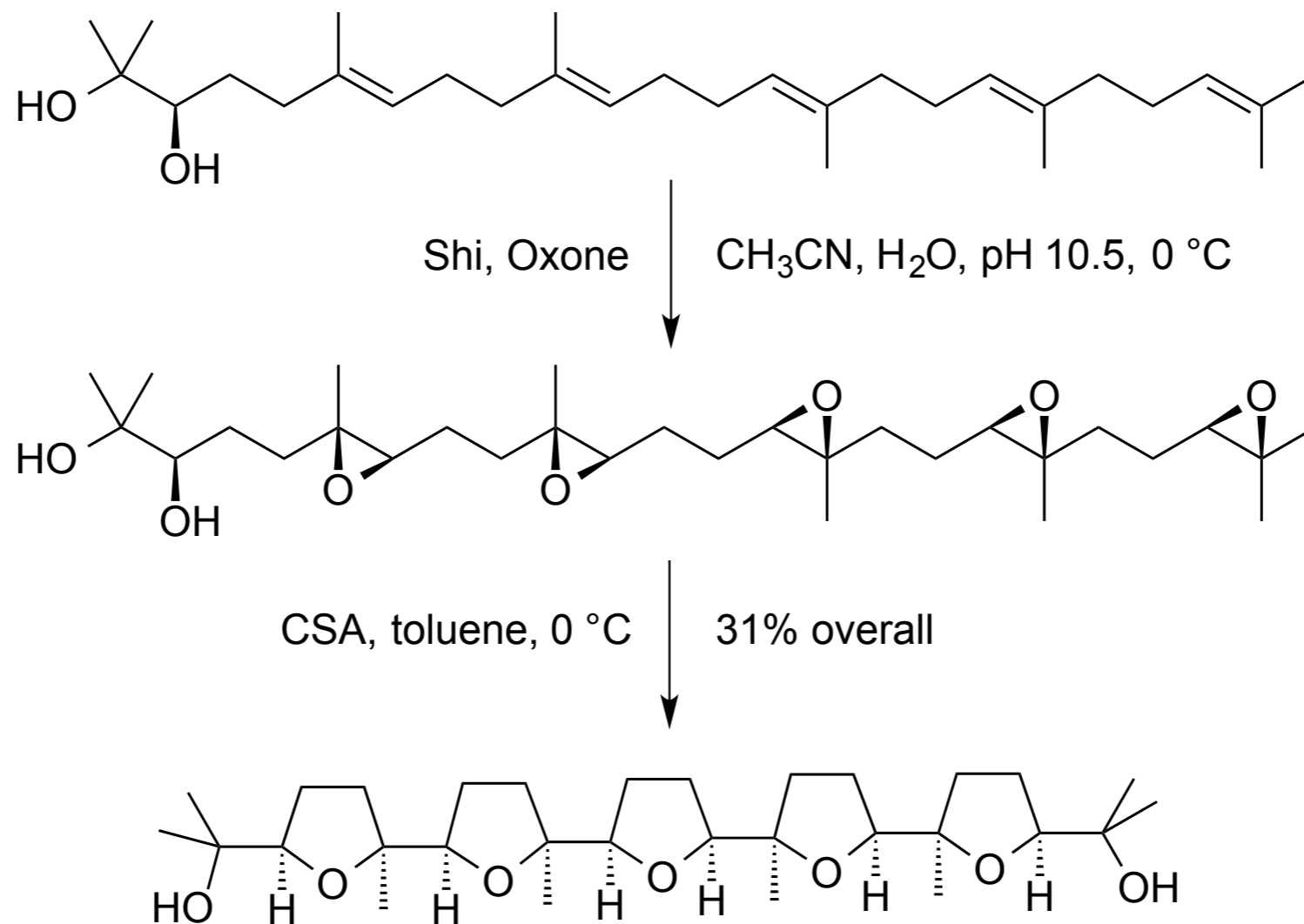
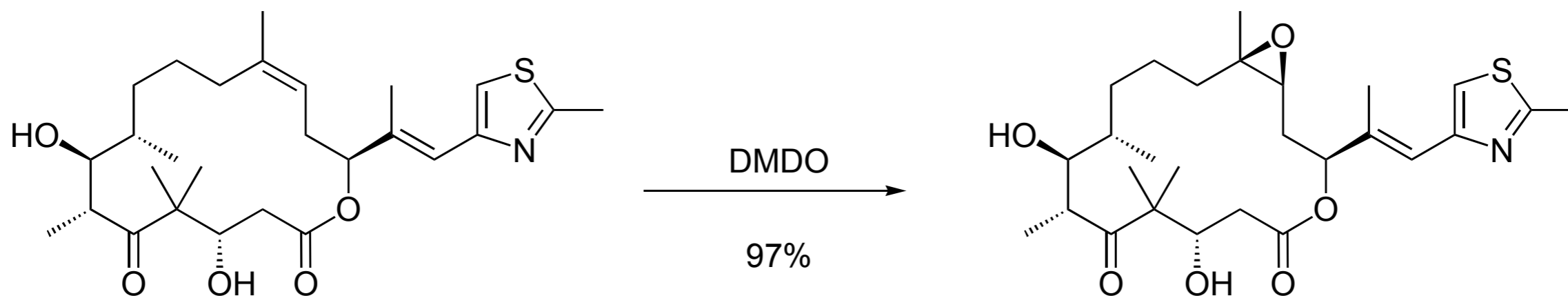


- *The epoxidations are carried out under very mild conditions*
- *The reduced system is a carbonylic compound: acetone in the case of DMDO!*

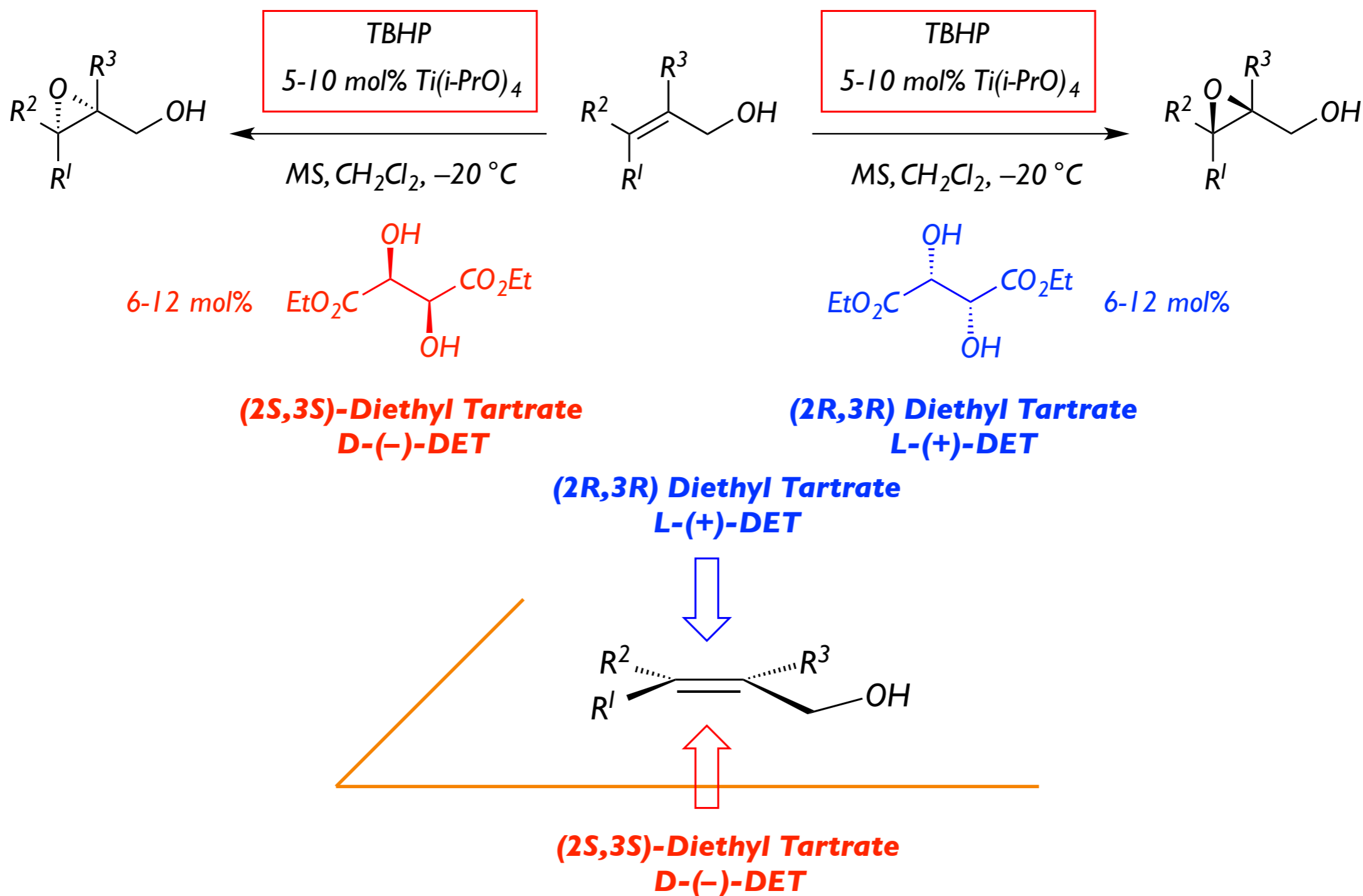


- *Dioxiranes show an strong electrophilic character: electronrich alkenes are easily oxidized*
- *They are no compatible with amines or sulfur-derived compounds*

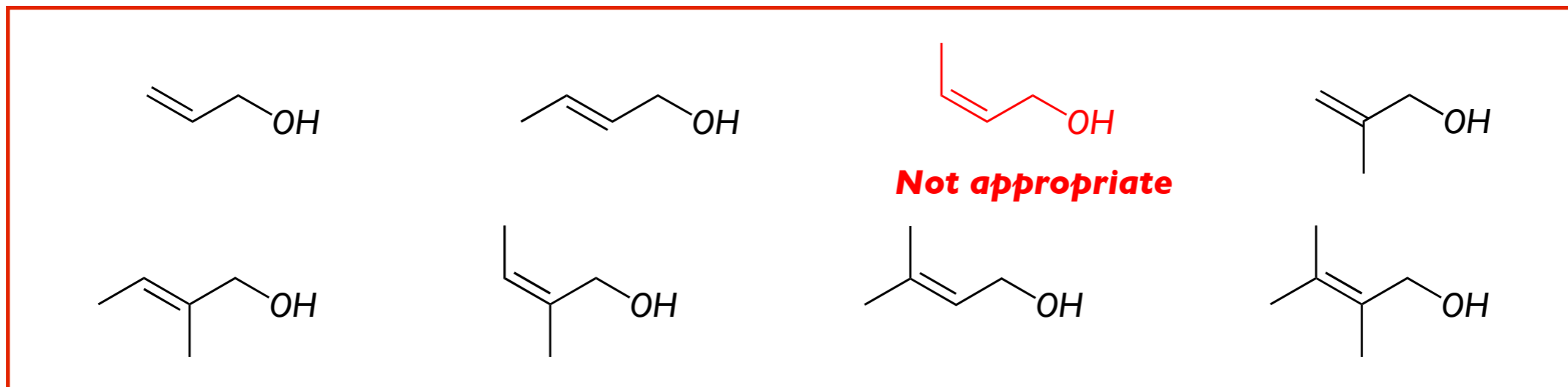


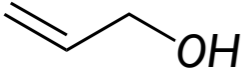
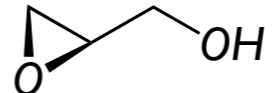
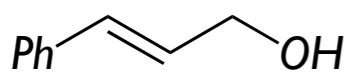
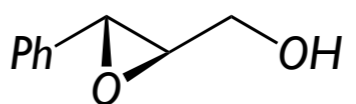
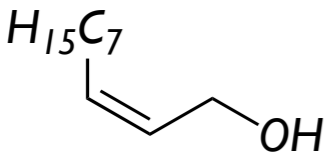
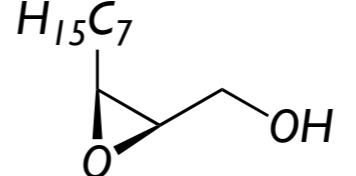
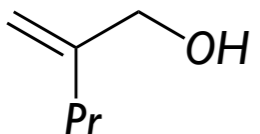
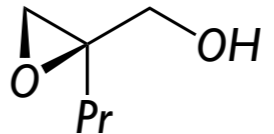


■ **Enantioselective epoxidation of allylic alcohols: Sharpless epoxidation**

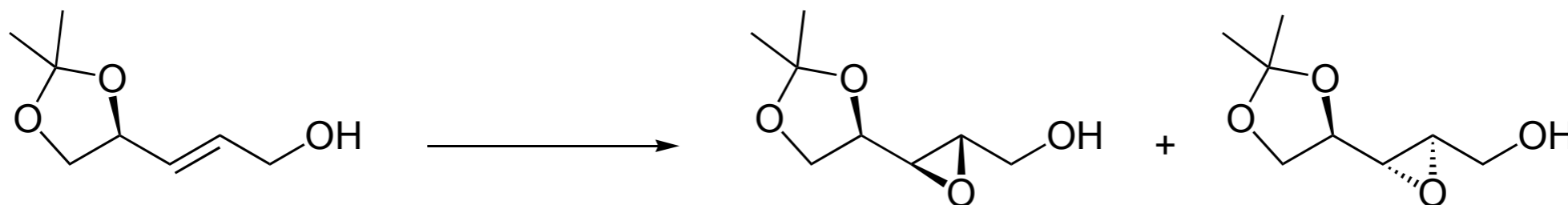


– Unless disubstituted *Z* alkenes, any other alkene can be submitted to Sharpless AE



	5 mol % TiL_4	(+)-DIPT	0 °C 2 h		90% ee	65%
	5 mol % TiL_4	(+)-DIPT	-20 °C 3 h		> 98% ee	89%
	10 mol % TiL_4	(+)-DET	-10 °C 24 h		86% ee	74%
	5 mol % TiL_4	(+)-DET	-10 °C 12 h		95% ee	88%

- The asymmetric induction imparted by the TBHP, TiL₄, tartrate system is pretty high



*m*CPBA

1 : 1.4

TBHP, Ti(*i*-PrO)₄

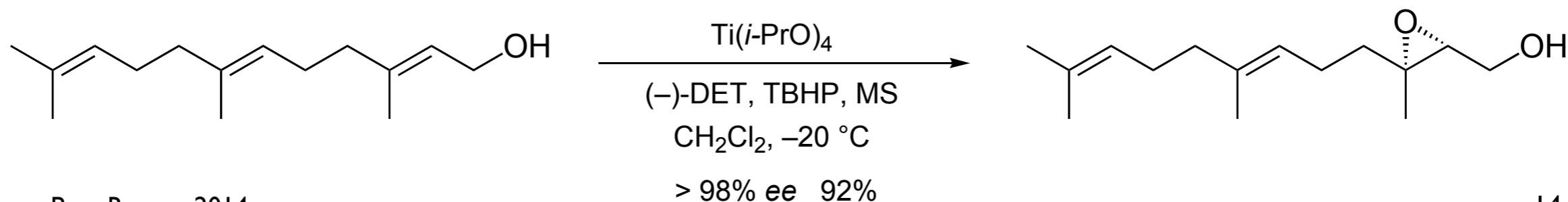
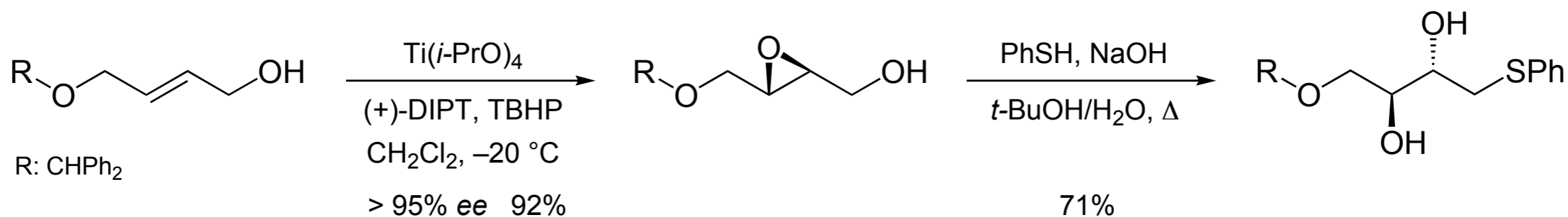
1 : 2.3

TBHP, Ti(*i*-PrO)₄, (-)-DIPT

1 : 90

TBHP, Ti(*i*-PrO)₄, (+)-DIPT

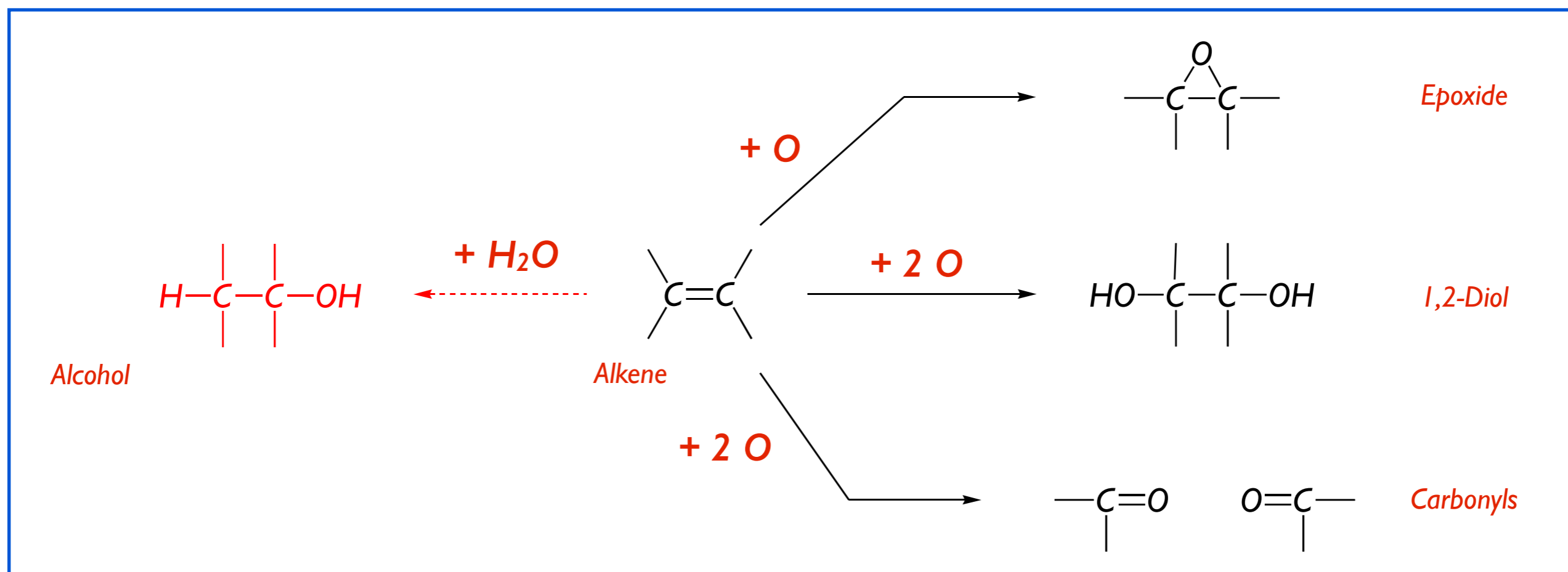
22 : 1



- *Epoxidation of alkenes*

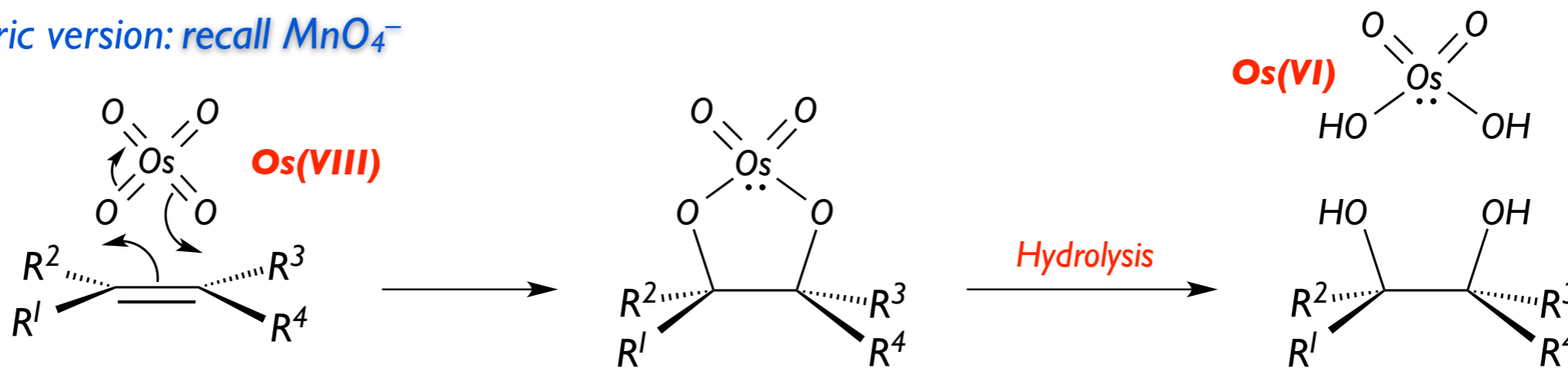
- *Dihydroxylation of alkenes*

- *Other oxidations*



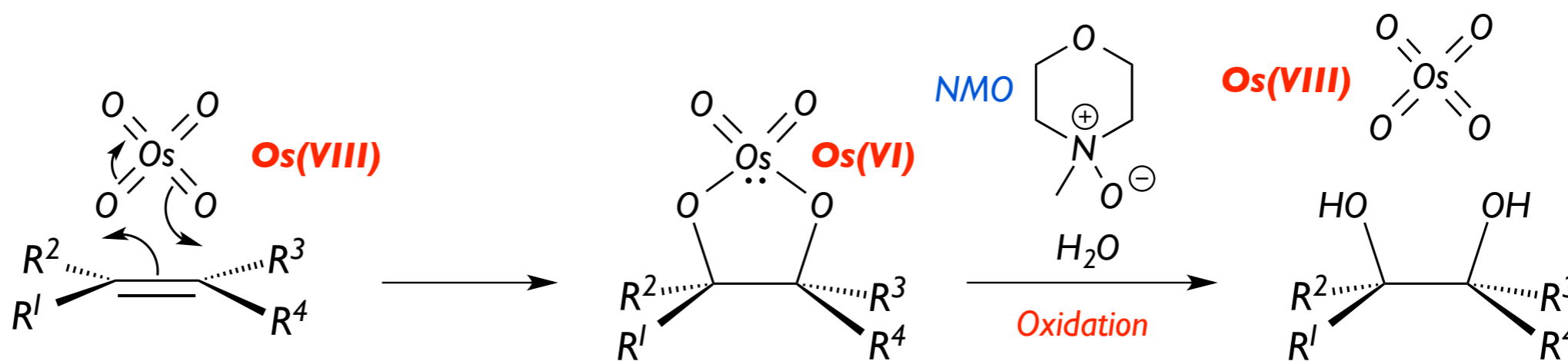
■ *syn* Diols with OsO_4

Stoichiometric version: recall MnO_4^-



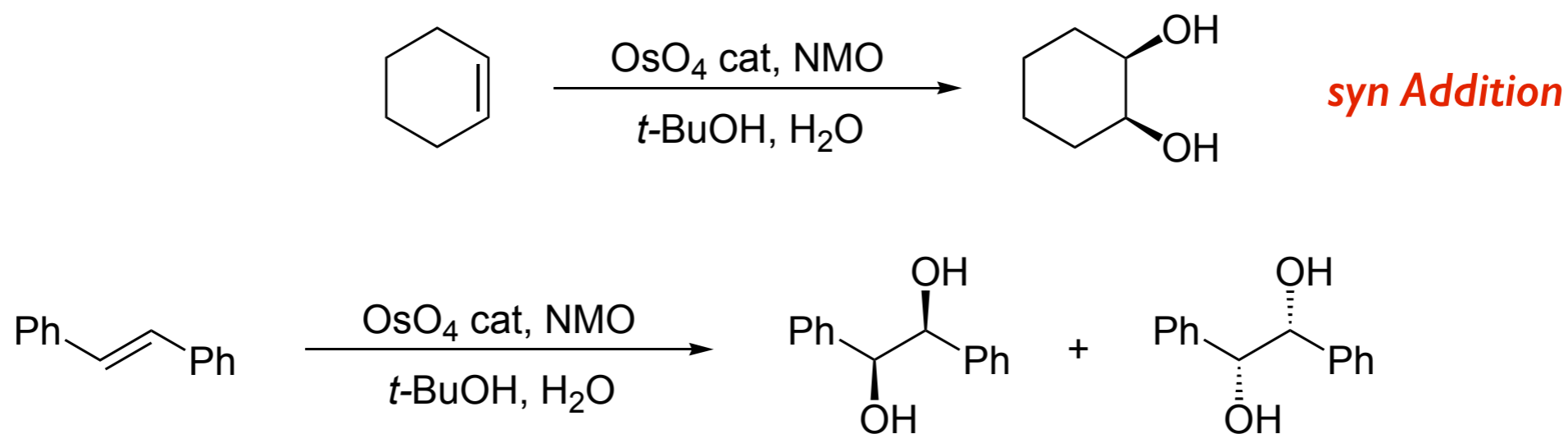
syn Addition

Catalytic version: OsO_4 is costly and toxic, so it is advantageous to use it as catalyst with a cooxidant (NMO)



syn Addition

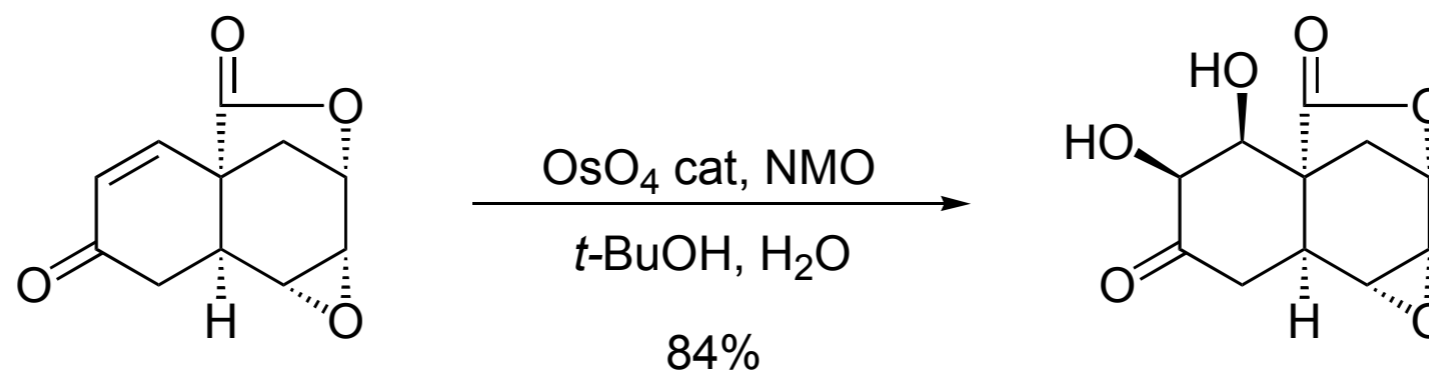
- OsO_4 is costly, toxic, and volatile! The only interesting way to use it is under catalytic premises



Racemic mixture

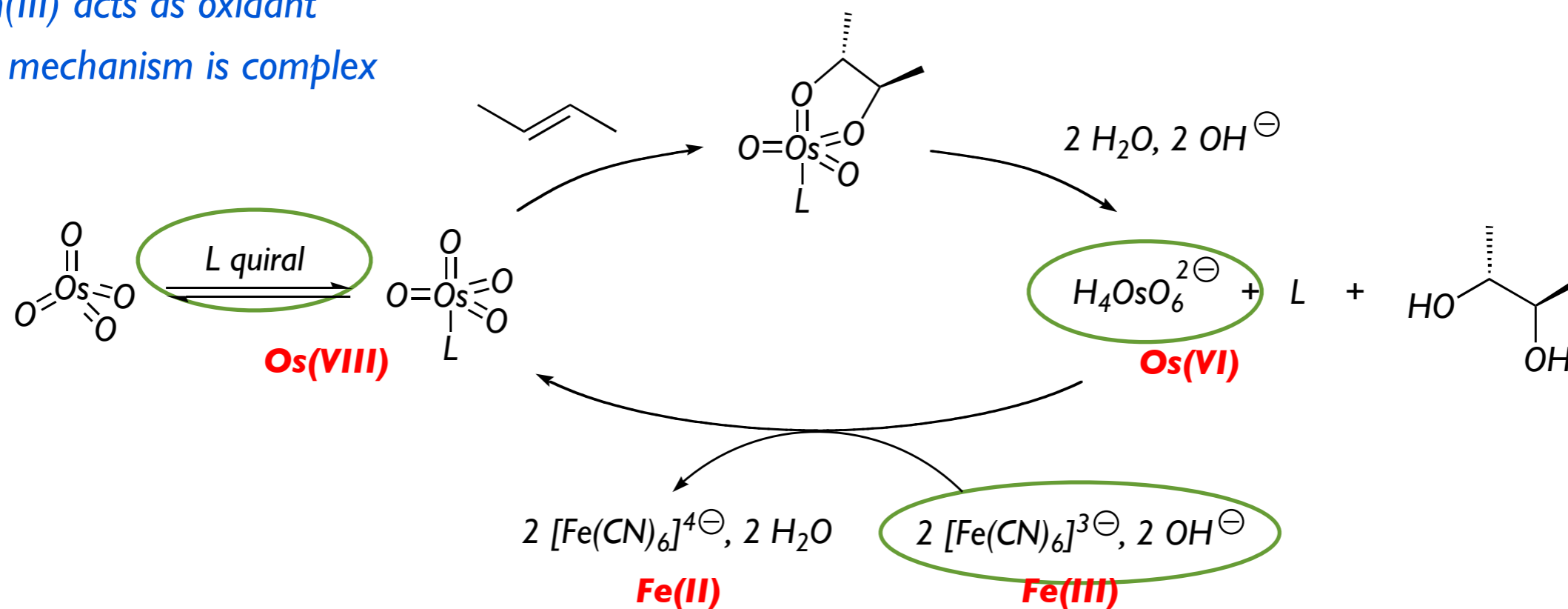
Is it possible to obtain a diol stereoselectively?

Substrate-controlled dihydroxylation

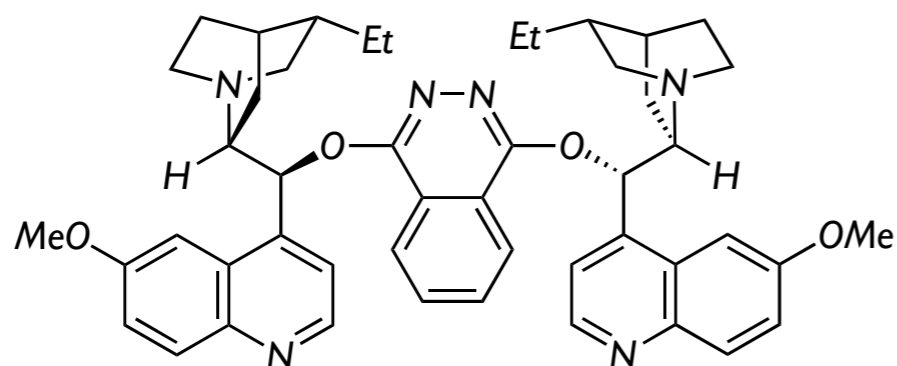


■ Sharpless enantioselective dihydroxylation

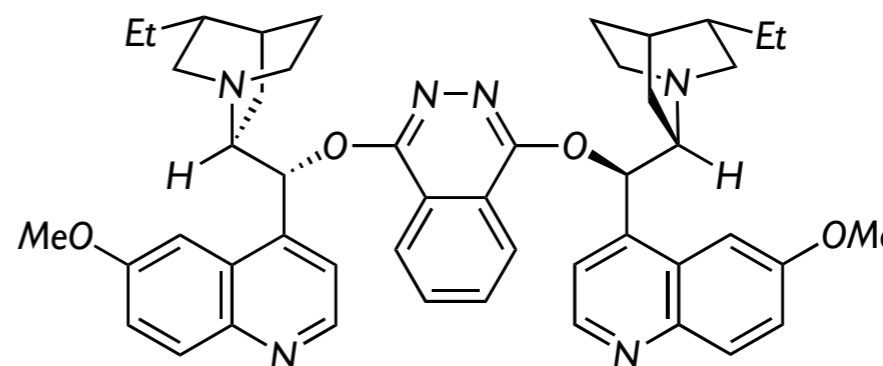
- Asymmetric Sharpless dihydroxylation uses osmium(VIII) complexes containing chiral tertiary amines as ligands
- Iron(III) acts as oxidant
- The mechanism is complex



Chiral tertiary amines



(DHQD)₂-PHAL



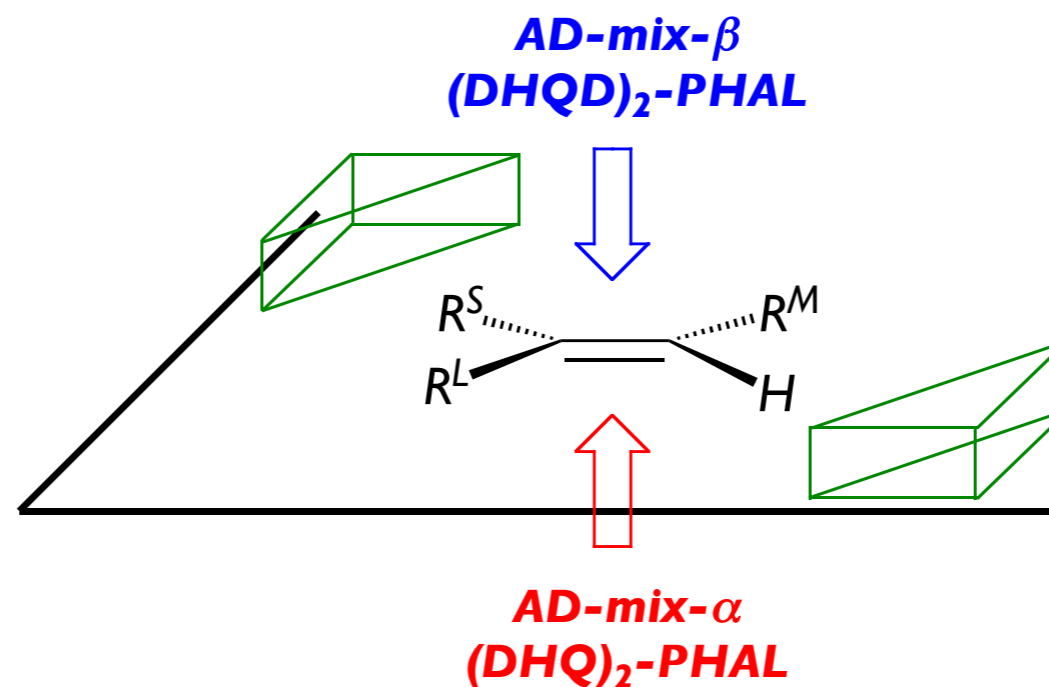
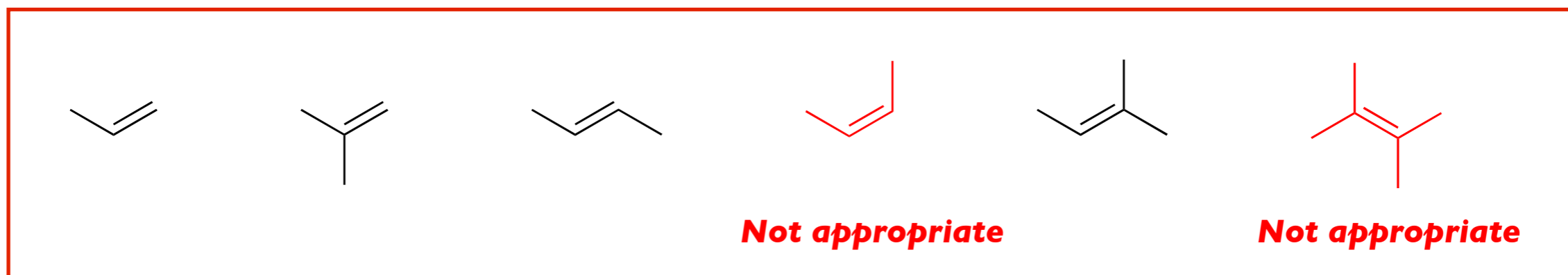
(DHQ)₂-PHAL

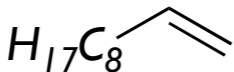
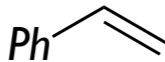
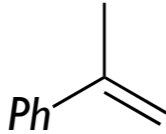
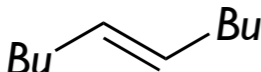
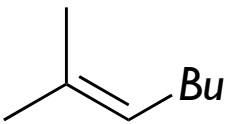
– Commercially available mixtures of oxidants and ligands are commonly used

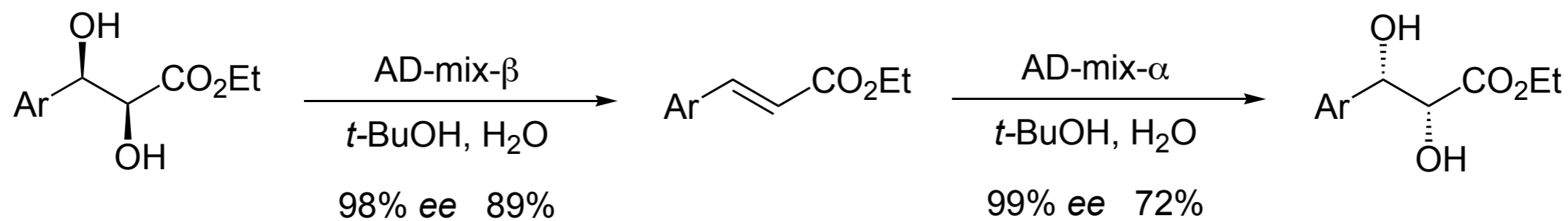
AD-mix- α : $K_2[H_4OsO_6]$, (DHQ)₂-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3

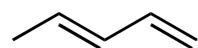
AD-mix- β : $K_2[H_4OsO_6]$, (DHQD)₂-PHAL, $K_3[Fe(CN)_6]$, K_2CO_3

– The most suitable alkenes for the Sharpless AD are

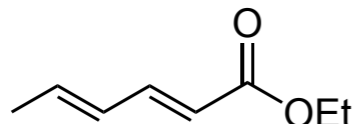
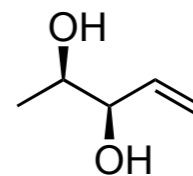


	<i>AD-mix-a</i> <i>(DHQ)₂-PHAL</i>	<i>AD-mix-b</i> <i>(DHQD)₂-PHAL</i>
	ee %	ee %
	80 (S)	84 (R)
	97 (S)	97 (R)
	93 (S)	94 (R)
	93 (S)	97 (R)
	95 (S)	98 (R)

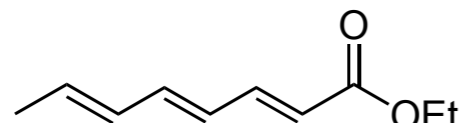
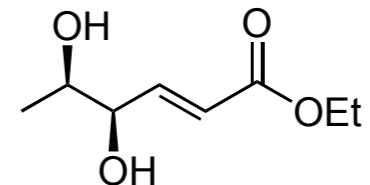




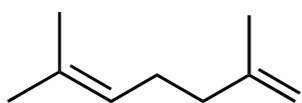
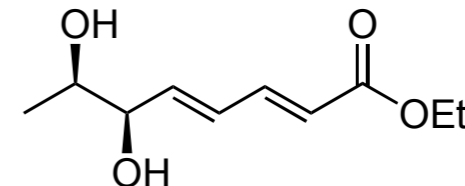
AD-mix- β
93% ee 78%



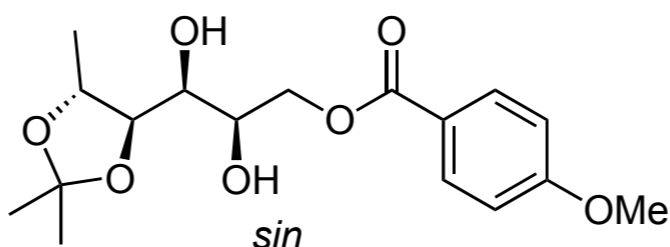
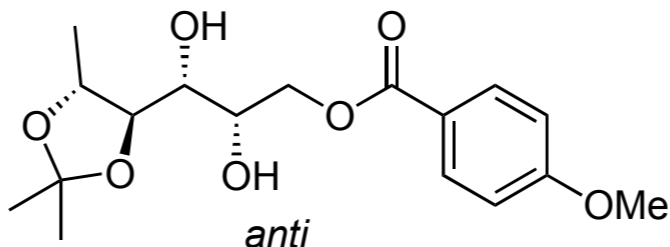
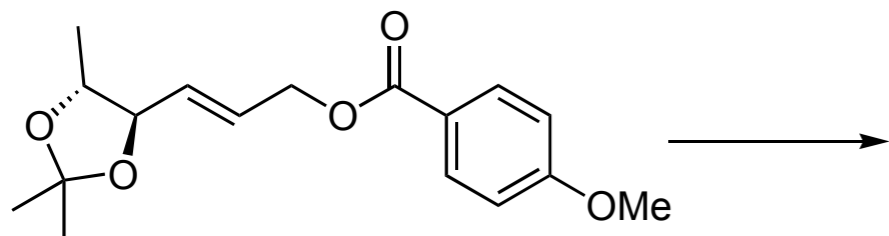
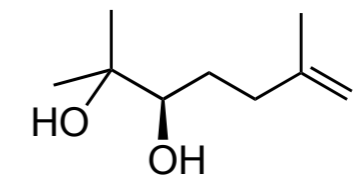
AD-mix- β
92% ee 78%



AD-mix- β
95% ee 93%



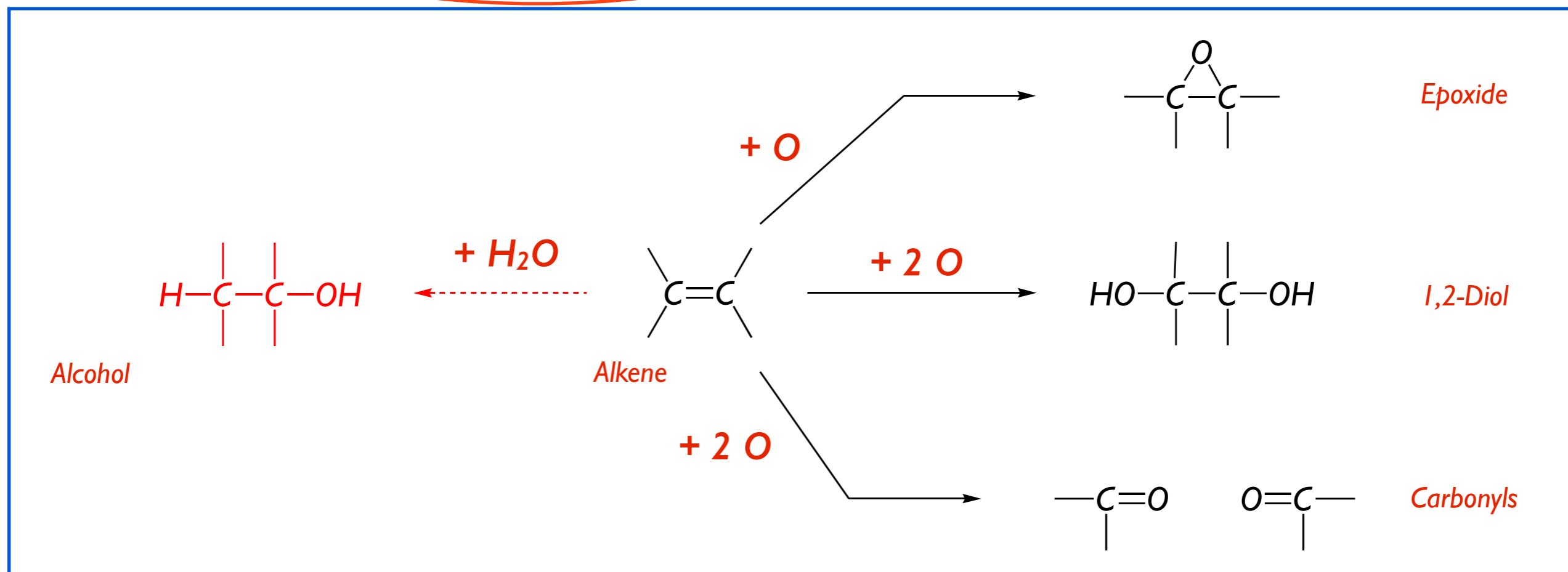
AD-mix- β
98% ee 70%



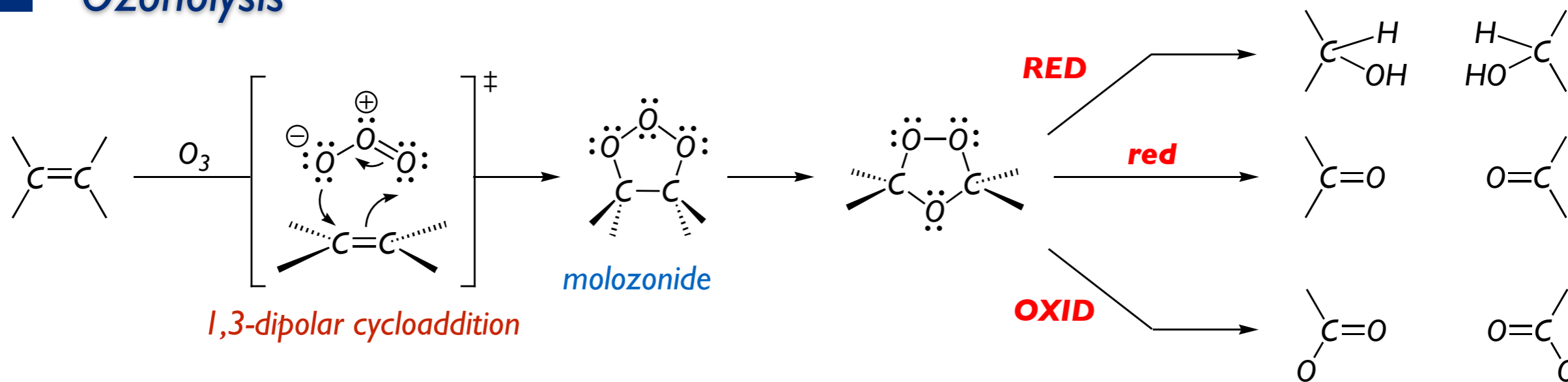
OsO ₄ – NMO	AD mix α	AD mix β
------------------------	-----------------	----------------

(1.9 : 1) 88% (54 : 1) 86% (1 : 35) 86%

- *Epoxidation of alkenes*
- *Dihydroxylation of alkenes*
- *Other oxidations*

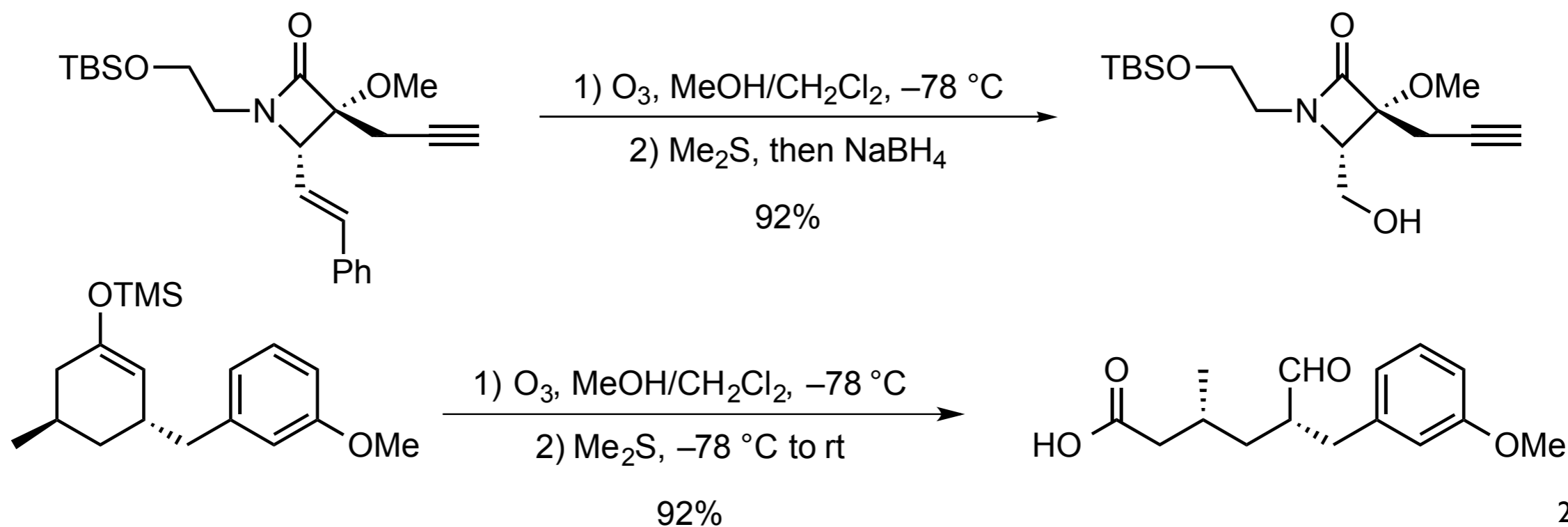


Ozonolysis

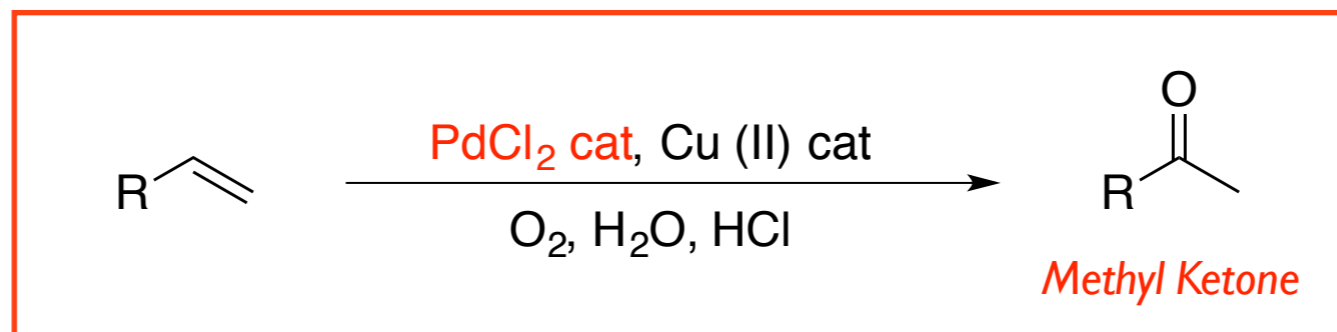


This is a mild, reliable, and minimal side products or waste producing process

RED: NaBH_4 , Zn/AcOH . red: Me_2S , Ph_3P . OXID: H_2O_2

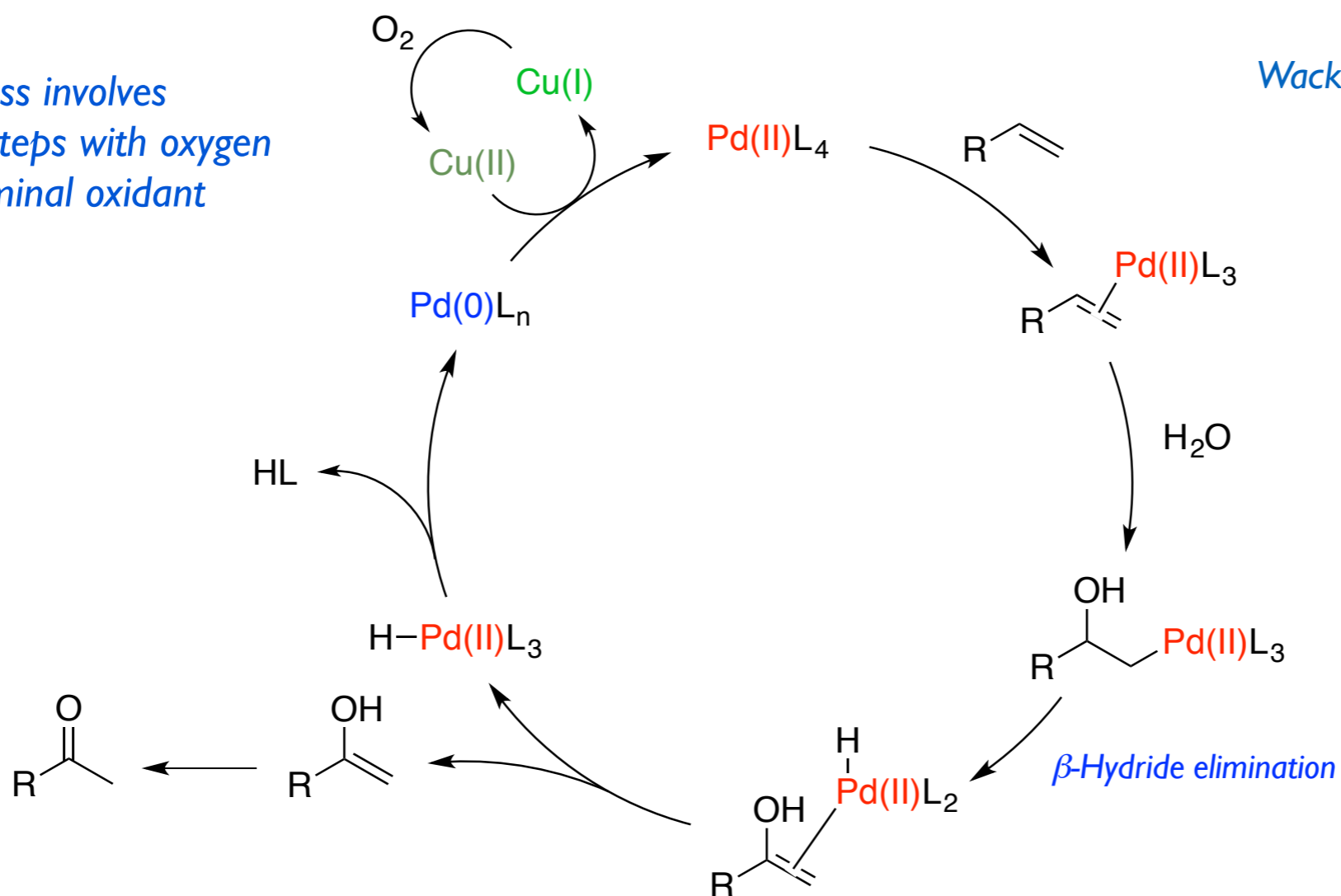


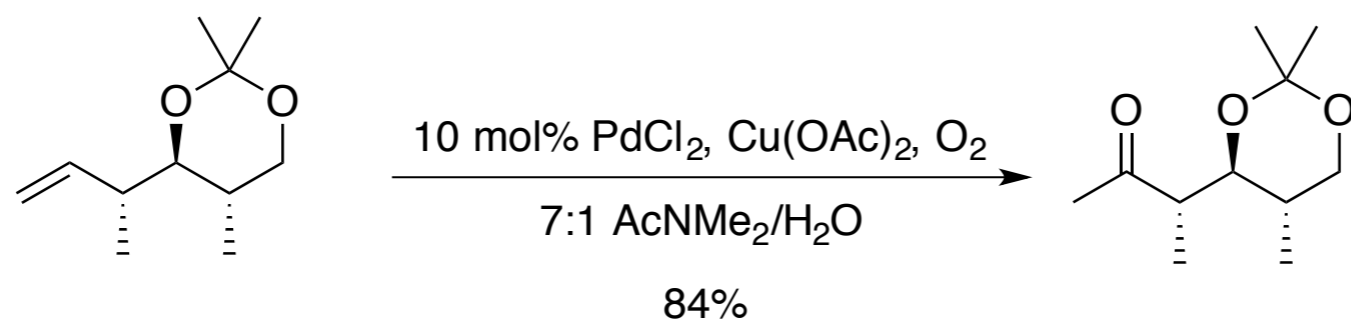
Wacker Process



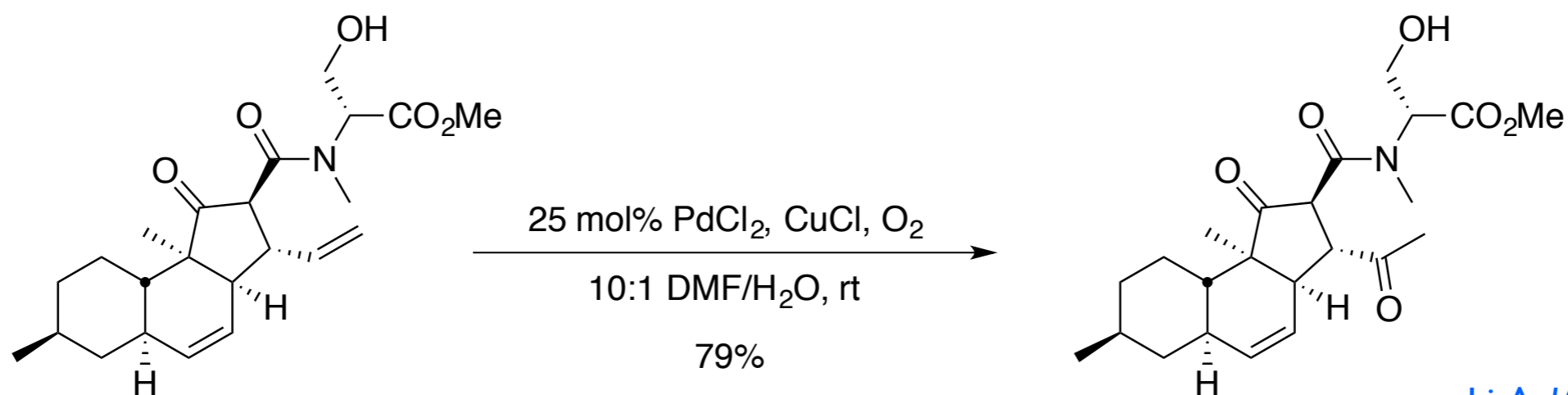
This Wacker process involves a series of redox steps with oxygen serving as the terminal oxidant

Originally developed by Wacker Chemie in the 50s and 60s



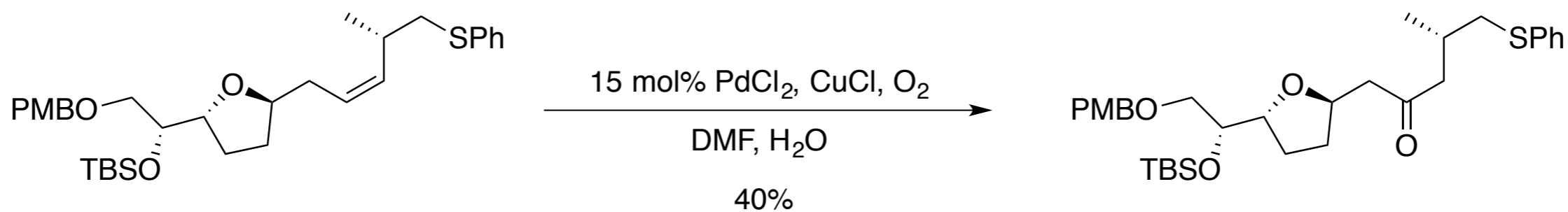


Smith, A. B, III. *JACS* 1999, 121, 10648



Li, A. *JACS* 2012, 134, 920

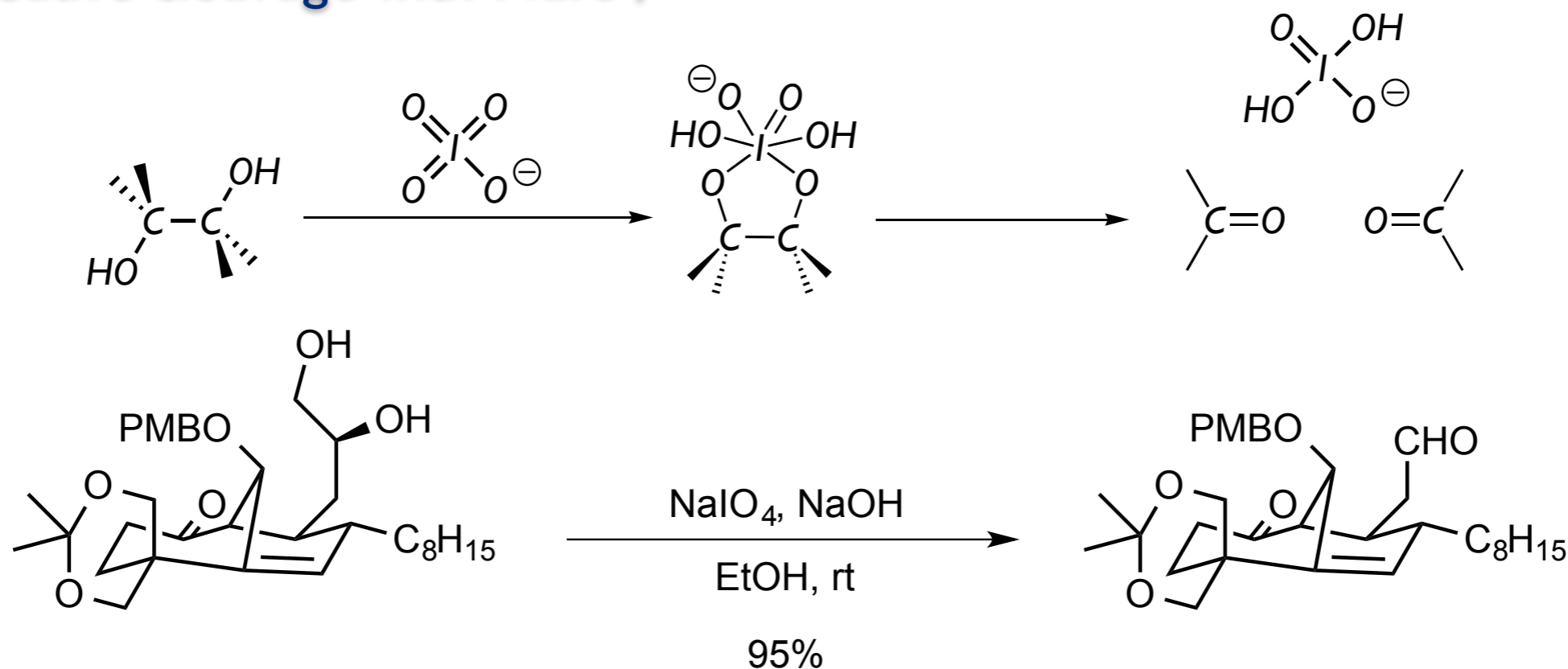
Occasionally, highly regioselective Wacker oxidations of internal alkenes are possible ...



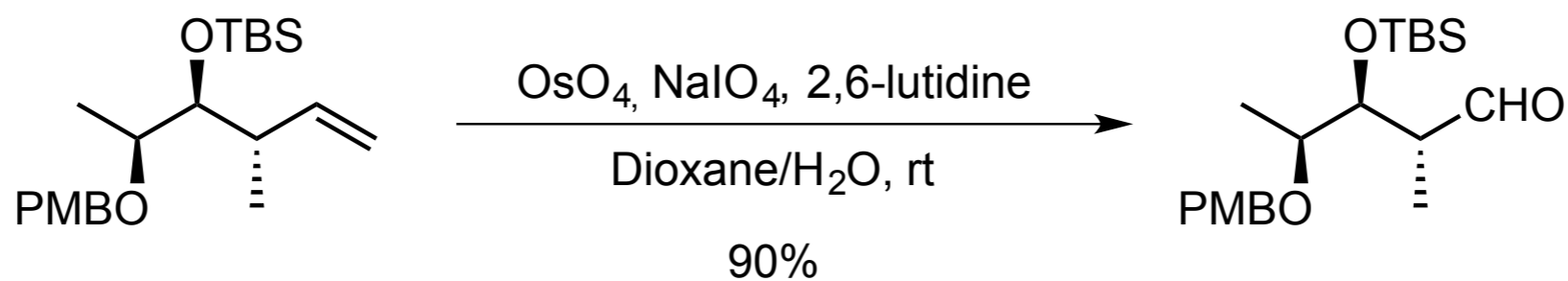
Forsyth, C. J. *OL* 2013, 15, 1178

For an interesting analysis, see: Grubbs, R. H. *ACIE* 2014, 53, 8654

■ Oxidative cleavage with NaIO_4



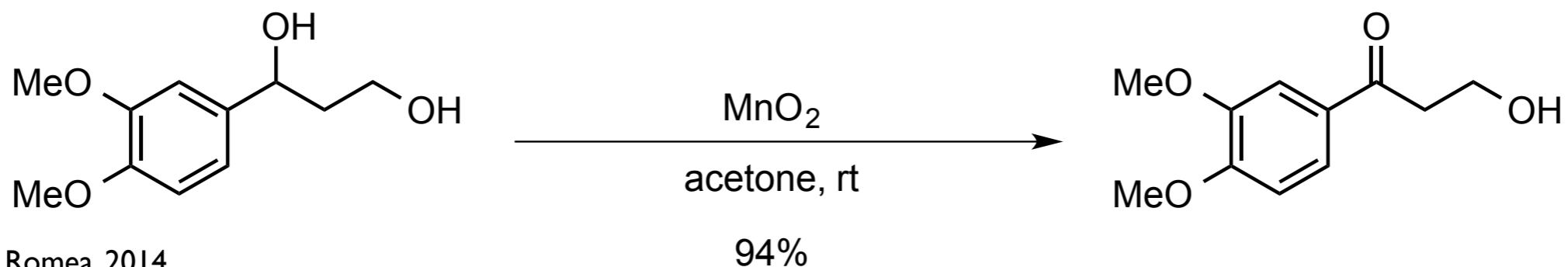
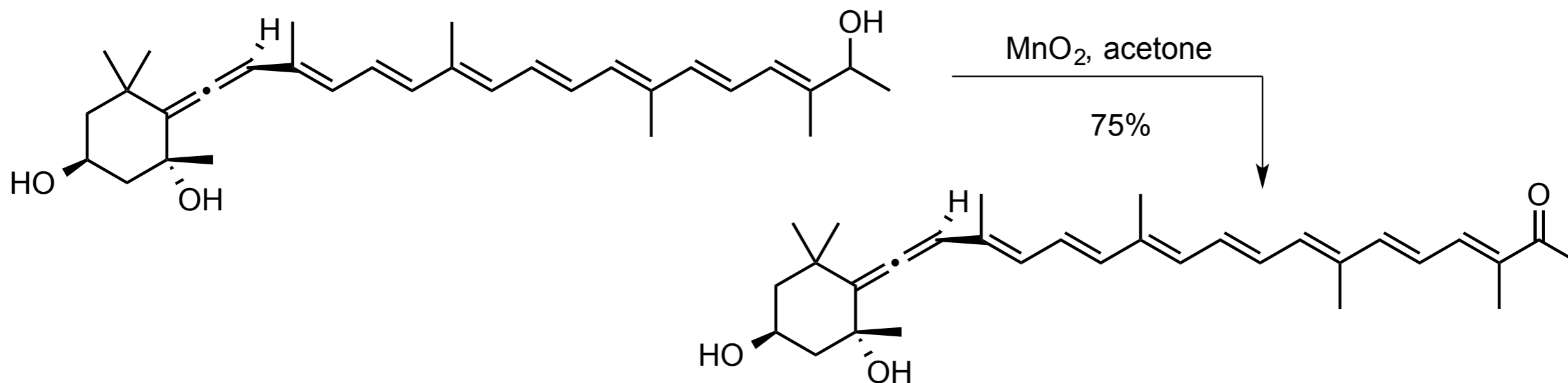
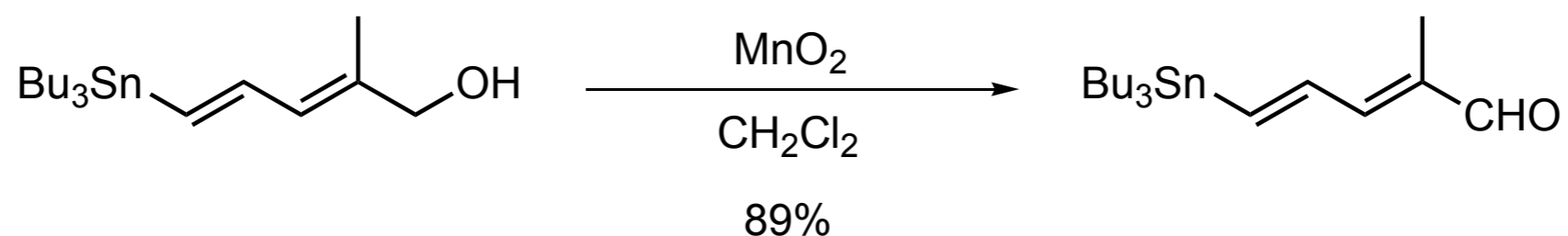
– When using with OsO_4 , alkenes can be transformed into carbonyls



NOTE: $\text{RuO}_2/\text{NaIO}_4$ pair works in a similar manner

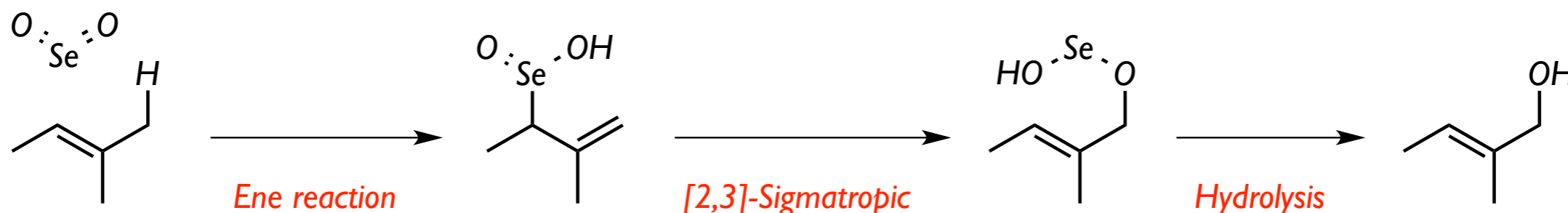
■ Oxidation of allylic and benzylic alcohols with MnO_2

– A heterogeneous mixture of MnO_2 under neutral conditions can selectively oxidize allylic, benzylic, and other activated alcohols to the corresponding aldehydes or ketones



■ Oxidation of allylic positions with SeO_2

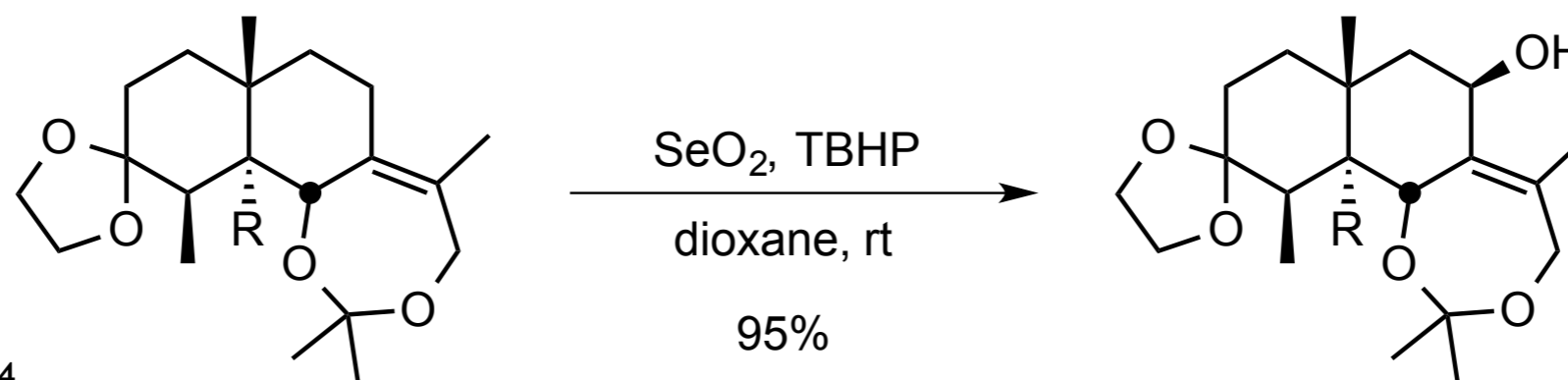
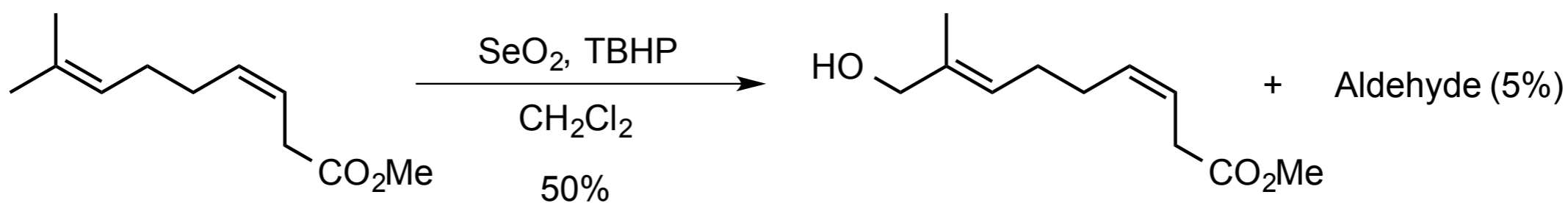
– Allylic positions can be oxidized with stoichiometric SeO_2 or cat SeO_2/TBHP



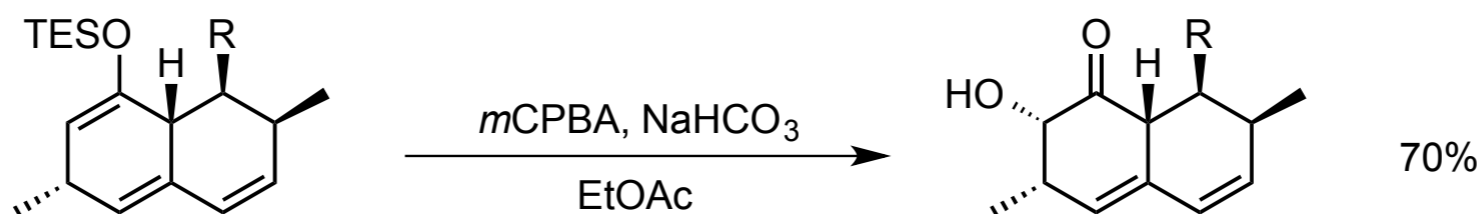
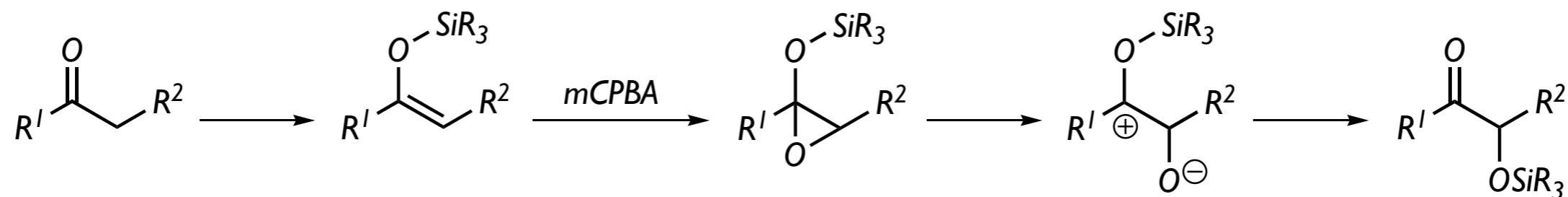
– The oxidation usually affects the most substituted part of the double bond

– Reactivity ranking: $\text{CH}_2 > \text{CH}_3 > \text{CH}$

– Risk: overoxidations



■ Oxidation with *m*CPBA: Rubottom oxidation



■ Oxidation with Pd(II): Saegusa process

