

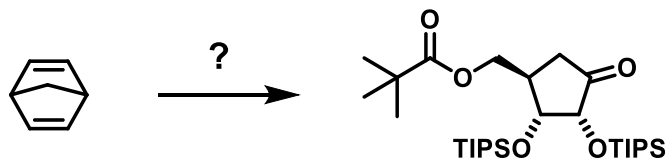
Organic synthesis

Kamil Paruch

Masaryk University, Brno

develop the ability to design viable syntheses of organic compounds of medium complexity

- build database of synthetically useful transformations/reagents
- be able to assess reactivity of organic compounds (i.e. precursors and intermediates)



understand (greater part of) organic syntheses in current literature

lecture (C4450) + seminar (C4455) merged -> lecture with problems to solve/think about

- *three tests during the semester: >50% points in total to pass (= get the credits for) the seminar*
< 50% points in total : make-up test
- *exam: written test (>50% points) followed by oral part*

draw structures & mechanisms

Petr Beňovský: Organická chemie - Organická syntéza, MU Brno 2003

László Kürti, Barbara Czakó: Strategic applications of named reactions in organic synthesis

K. C. Nicolaou et al.: Classics in Total Synthesis

Leo A. Paquette (Ed.): Encyclopedia of reagents for organic synthesis (14 vols), Wiley 2009

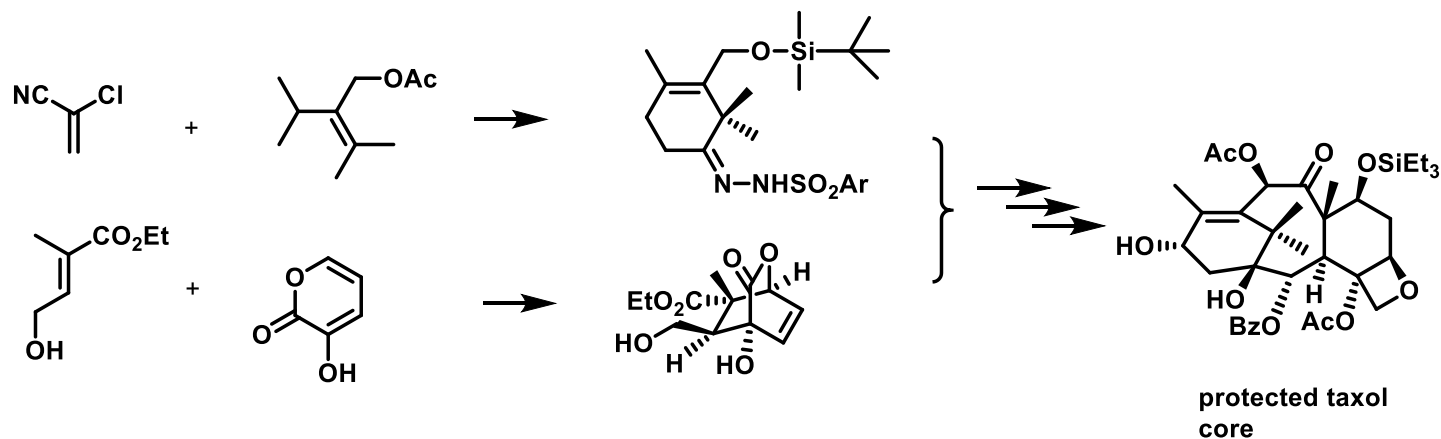
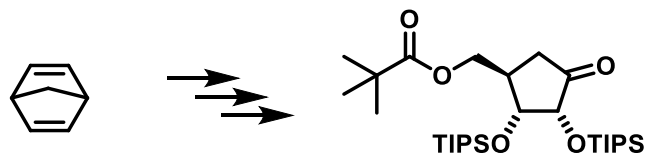
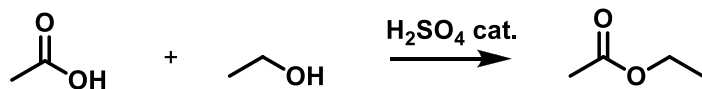
Organic Reactions

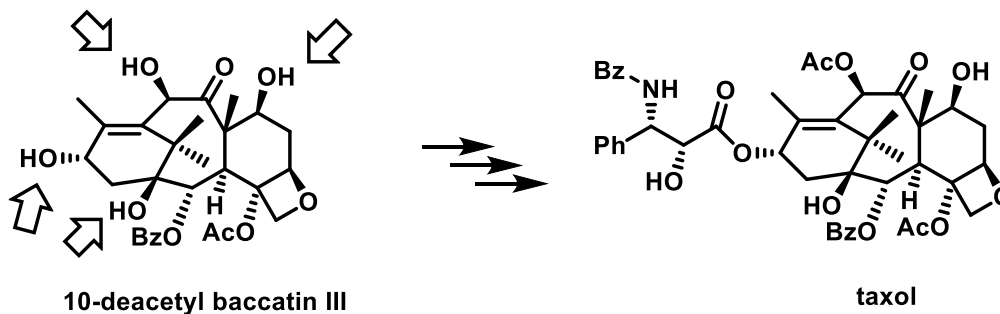
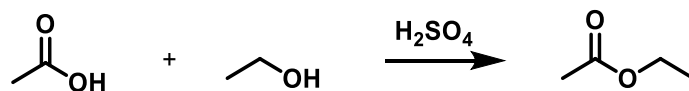
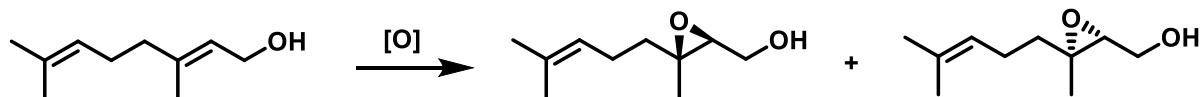
Science of Synthesis

+ additional literature in the central library (organic chemistry section)

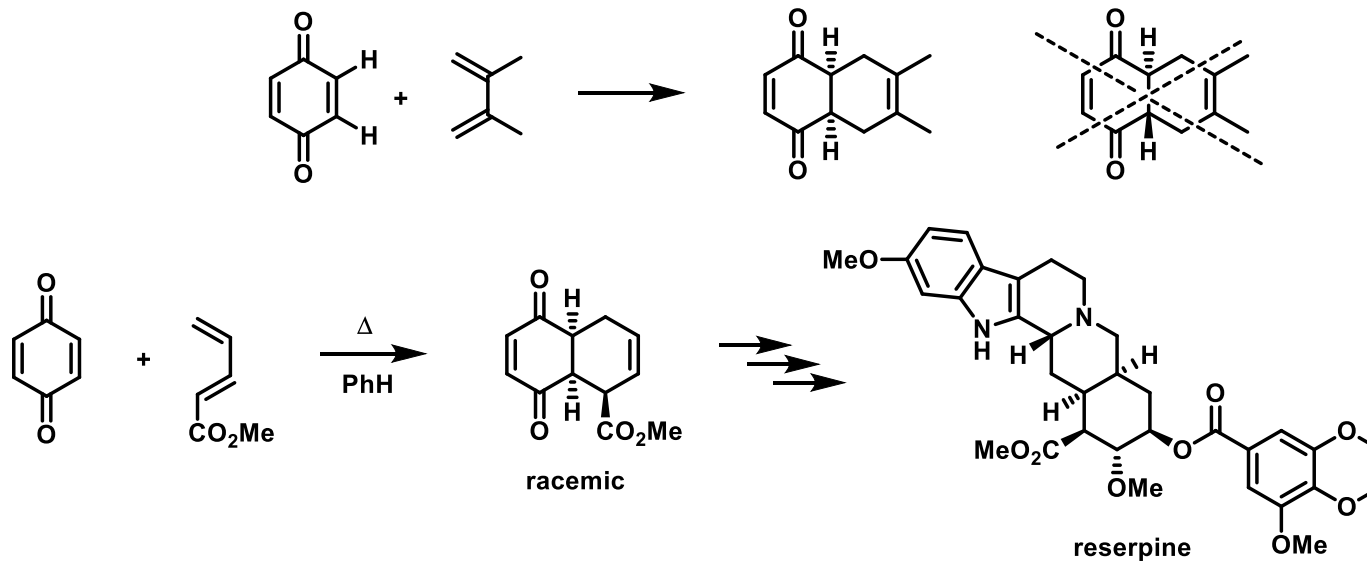
starting material $\xrightarrow{\text{synthesis}}$ product
(more complex)

- *chemoselectivity*
- *regioselectivity*
- *stereoselectivity*
- *cost of reagents*
- *feasibility (number of steps, scale up)*



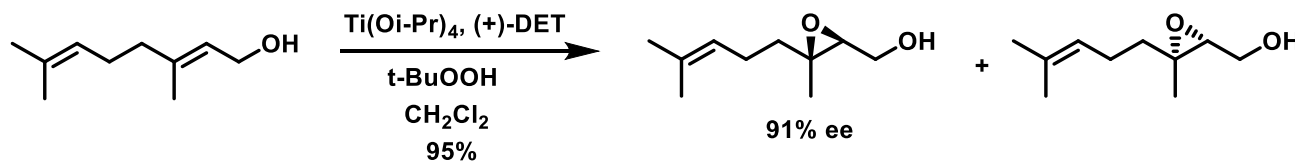


J. Am. Chem. Soc. **1998**, *110*, 5917.

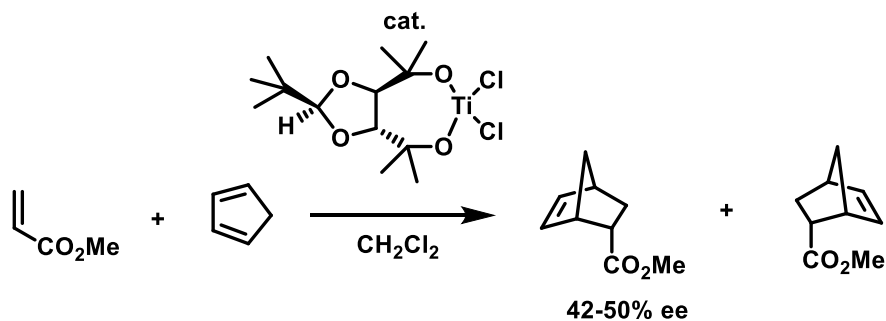


J. Am. Chem. Soc. **1956**, 78, 2657.

enantioselectivity



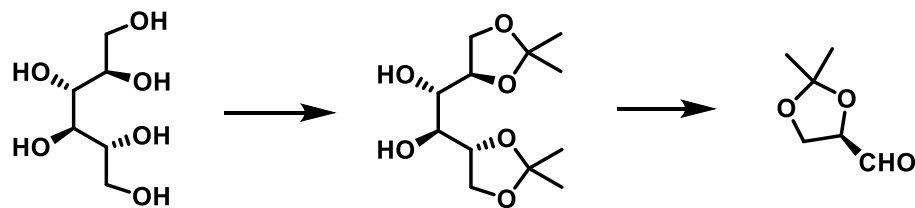
J. Am. Chem. Soc. **1987**, 109, 5765.



Helv. Chim. Acta **1987**, 70, 954.

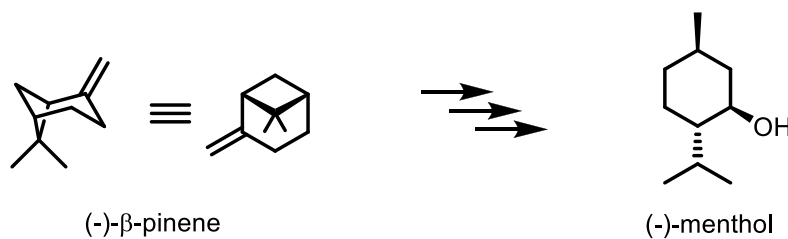
more complex reagents \longrightarrow less complex products

- e.g. easily available natural products, often only one enantiomer



D-mannitol

J. Org. Chem. **1968**, 33, 728.



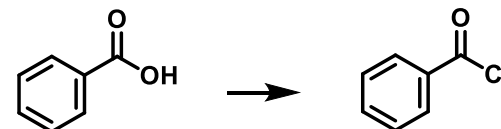
(-)-β-pinene

(-)-menthol

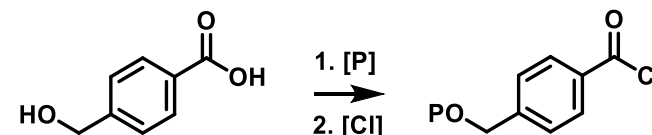
Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, p.343.

starting material $\xrightarrow{\text{synthesis}}$ product

• *functional groups interconversion*

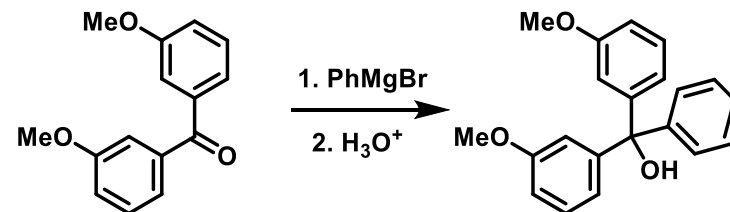


• *protecting groups*

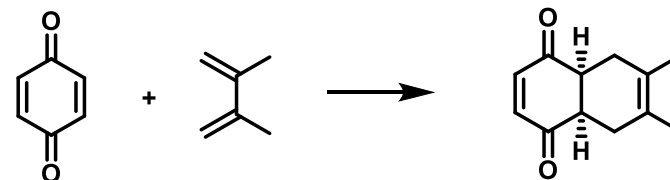


• *single bond formation*

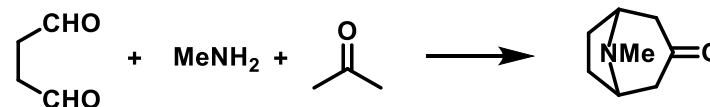
C-C
C-O
C-N
C-S



• *formation of several bonds*



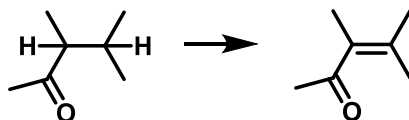
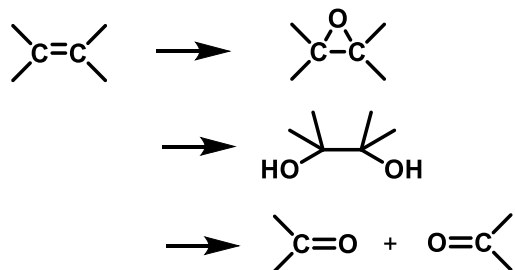
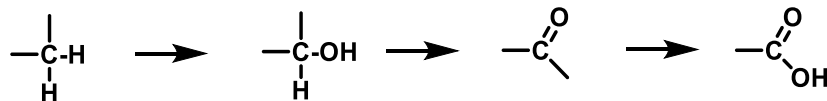
• *multicomponent reactions*
domino reactions

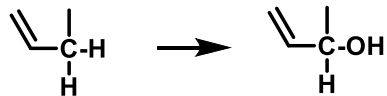
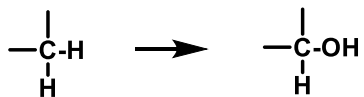


J. Chem. Soc. **1917**, 762.

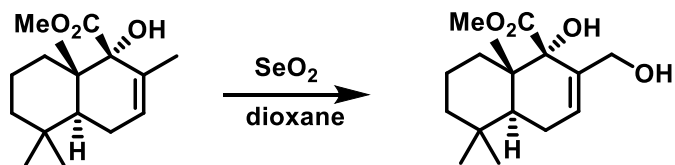
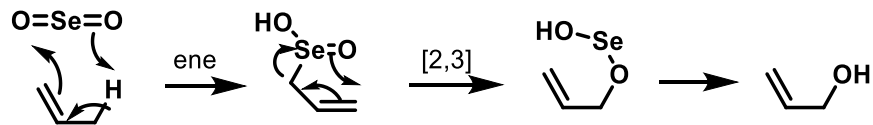
• *solid phase /combinatorial chemistry*

- many syntheses (of complex molecules) include oxidation/reduction steps
- installation of reactive site – e.g. oxidation of alcohol to ketone for subsequent nucleophilic attack
- removal of H or installation of O

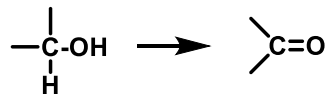


**SeO₂**

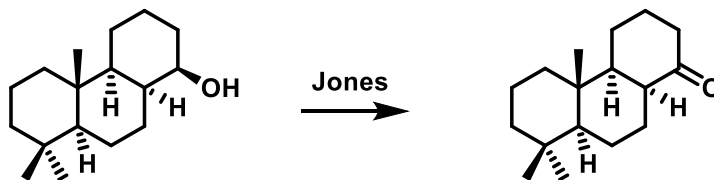
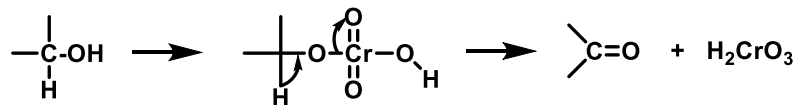
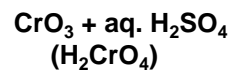
- oxidation on allylic C



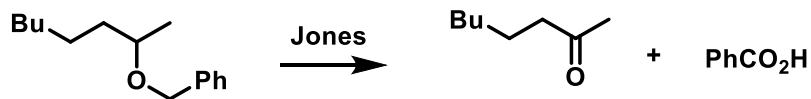
J. Chem. Soc., Chem. Commun. **1987**, 1324.

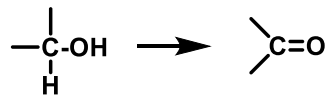


Jones reagent

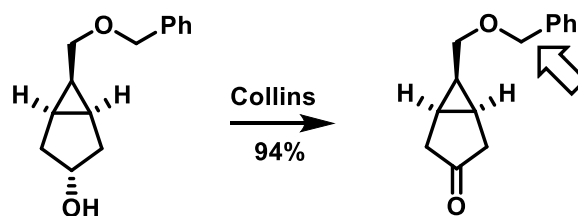
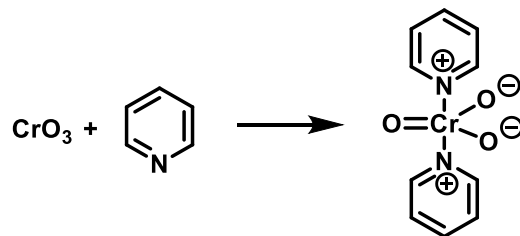
*Tetrahedron Lett.* **1961**, 493.

- acidic conditions; some functional groups not compatible

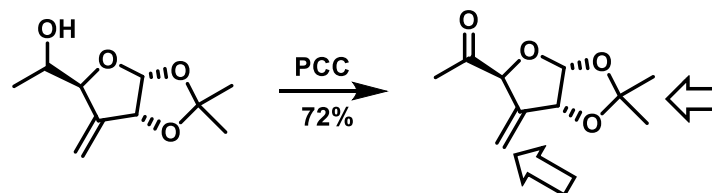
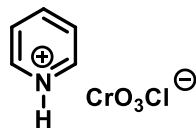
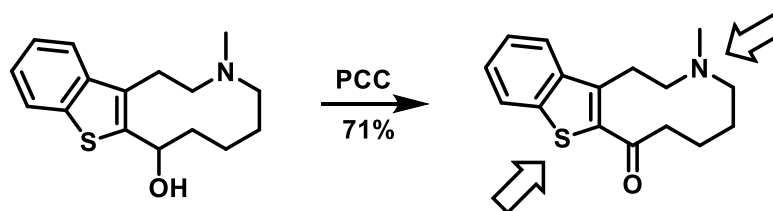
*J. Org. Chem.* **1981**, 46, 1492.

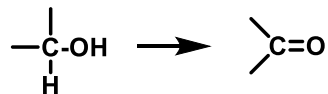


Collins reagent

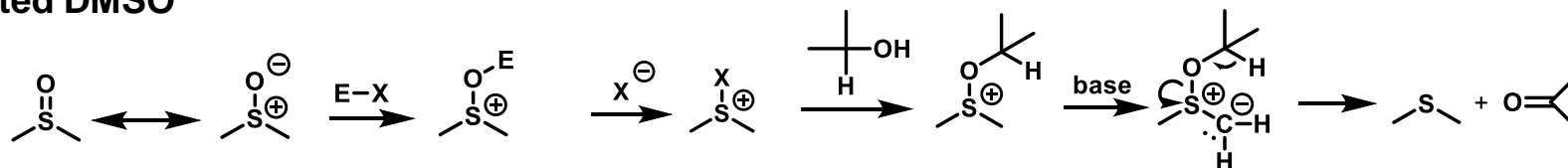
*J. Org. Chem.* **1976**, *41*, 3883.

PCC

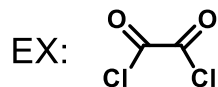
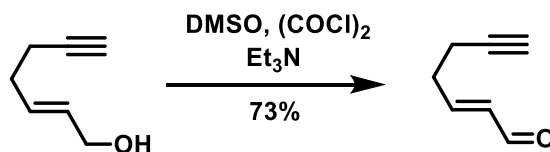
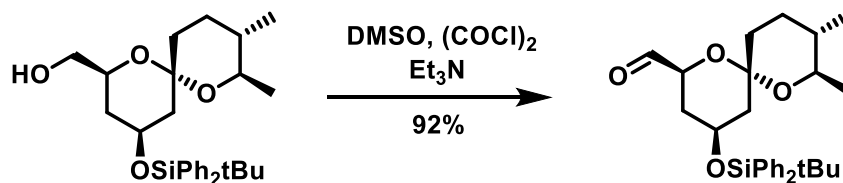
*J. Chem. Soc. Perkin Trans. I* **1985**, *1*.*Chem. Lett.* **1979**, 709.

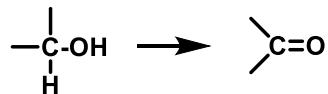


activated DMSO

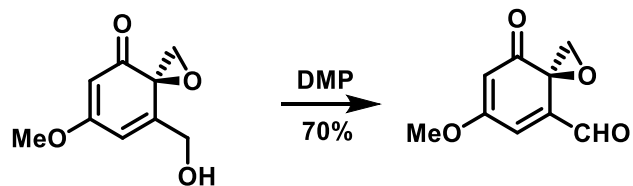
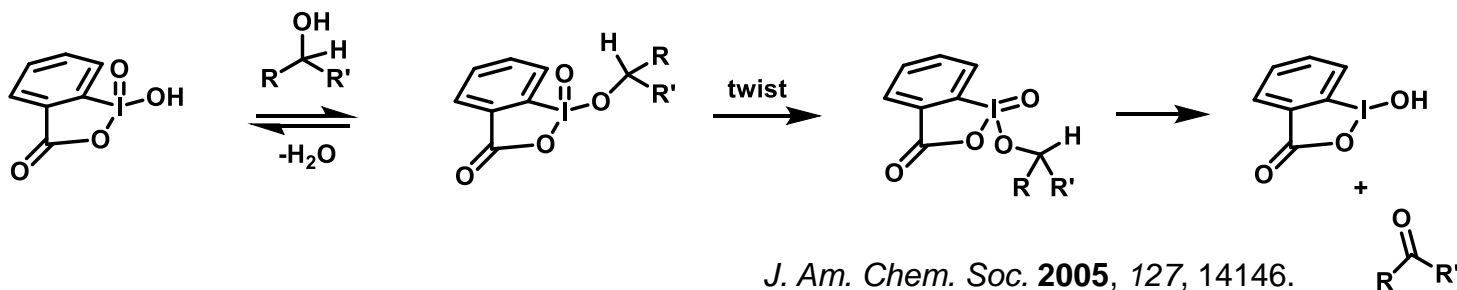
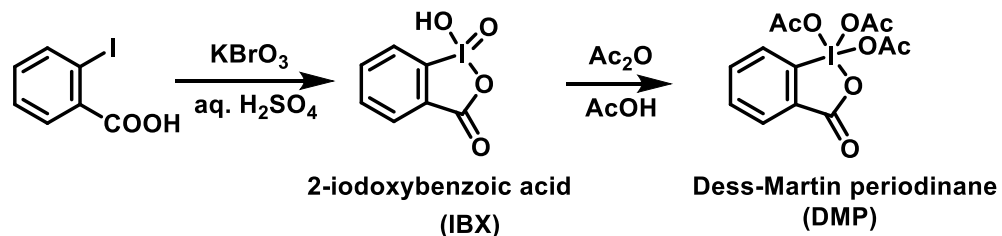
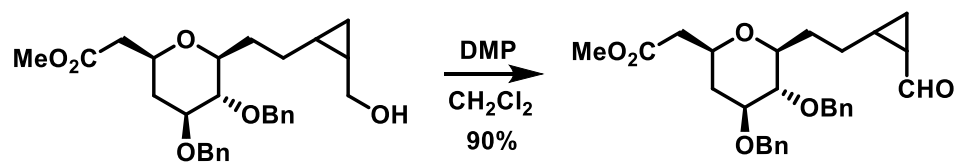


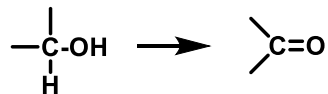
Swern oxidation:

base: amine (Et₃N)*J. Org. Chem.* **1993**, 58, 3912.*J. Am. Chem. Soc.* **1982**, 104, 4708.odorless variant: C₁₂H₂₅S(O)Me *Tetrahedron* **2003**, 59, 8393.



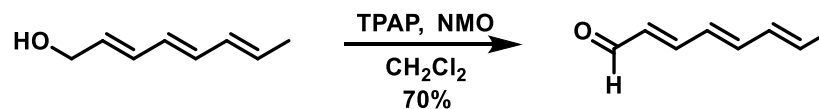
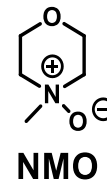
Dess-Martin reagent

*J. Am. Chem. Soc.* **1988**, *110*, 6891.*J. Am. Chem. Soc.* **1990**, *112*, 9645.

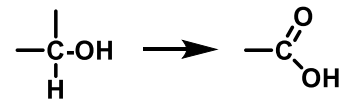
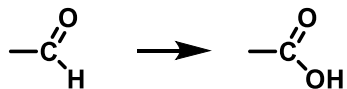


TPAP: $\text{Pr}_4\text{N}^+\text{RuO}_4^-$

- typically used in catalytic amounts
- stoichiometric oxidant: typically NMO

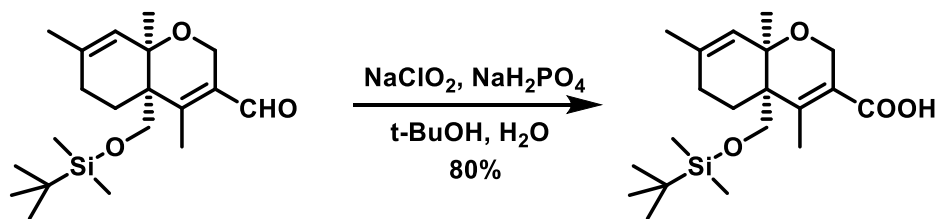


Tetrahedron **1992**, 48, 1145.

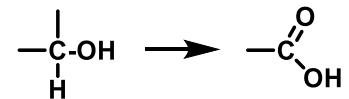
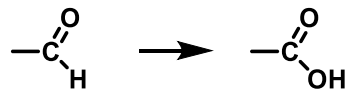


Sodium chlorite: NaClO₂

- selective oxidant, mild conditions (Pinnick oxidation)

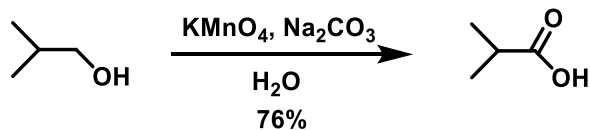


J. Org. Chem. **1980**, *45*, 4825.

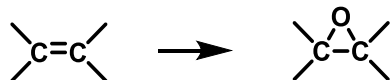


Potassium permanganate): KMnO_4

- strong oxidant; oxidation of alkenes and other functional groups

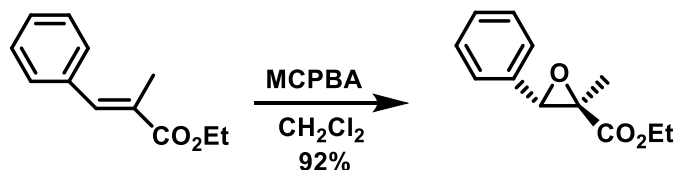
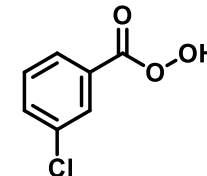


Vogel's Textbook of Practical Organic Chemistry, 5 ed. 1989, p. 668.

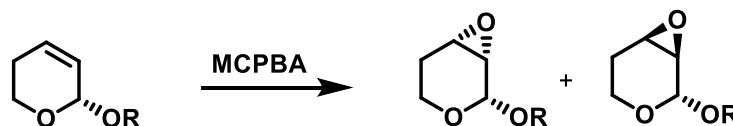


3-chloroperoxybenzoic acid, MCPBA, *m*-CPBA)

- reactivity of alkenes: tetra, trisubst. > disubst. > monosubst.
- stereospecific reaction: syn-addition : cis-alkene -> cis-epoxide
- stereochemistry of epoxidation can be directed by neighboring functional groups

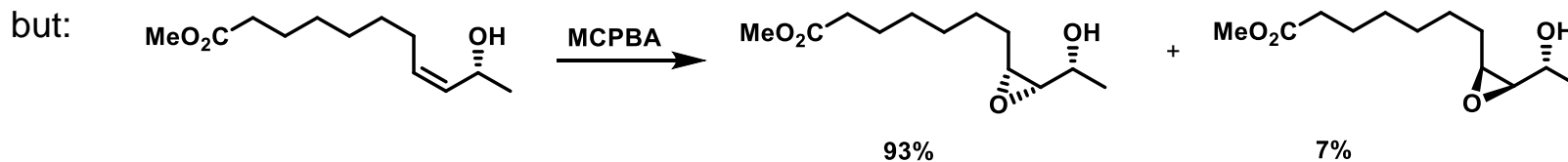


J. Org. Chem. **1966**, 31, 2509.

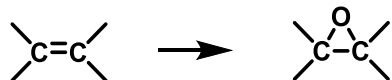


R = Me: 1:3
R = t-Bu: 1:9

Synlett **1991**, 529.



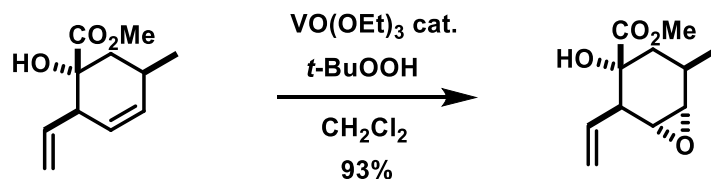
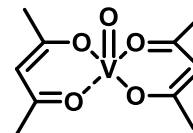
Tetrahedron Lett. **1987**, 28, 5129.



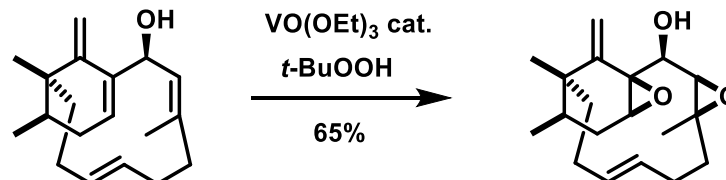
vanadium-based reagents

typically: $\text{VO}(\text{acac})_2 + t\text{-BuOOH}$

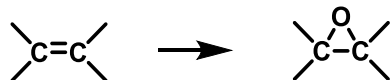
- frequently used for directed epoxidations



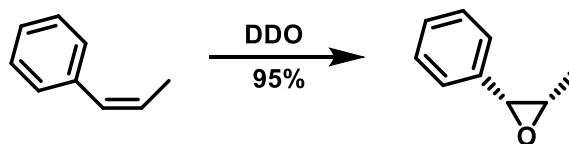
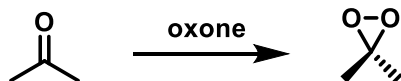
J. Am. Chem. Soc. **2007**, 129, 429.



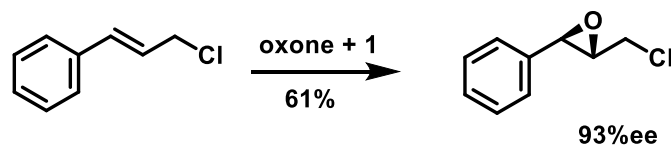
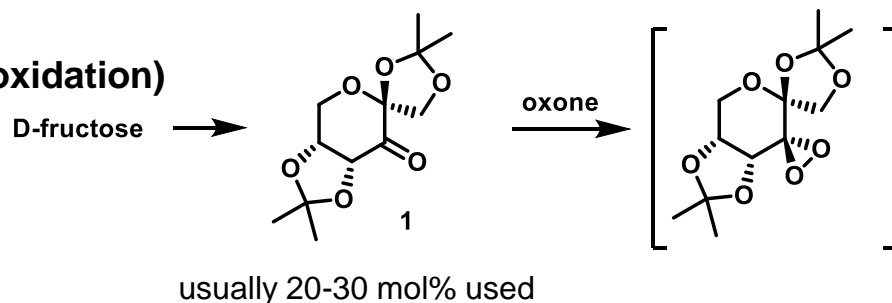
Nature Chemistry **2018**, 10, 938.



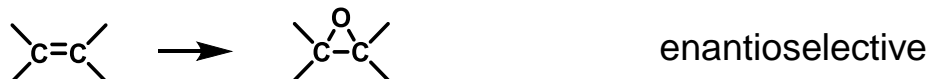
dimethyldioxirane (DDO)



asymmetric variant (Shi epoxidation)

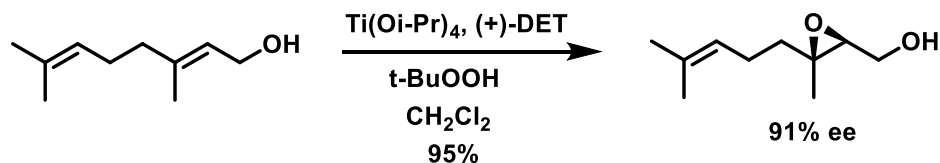
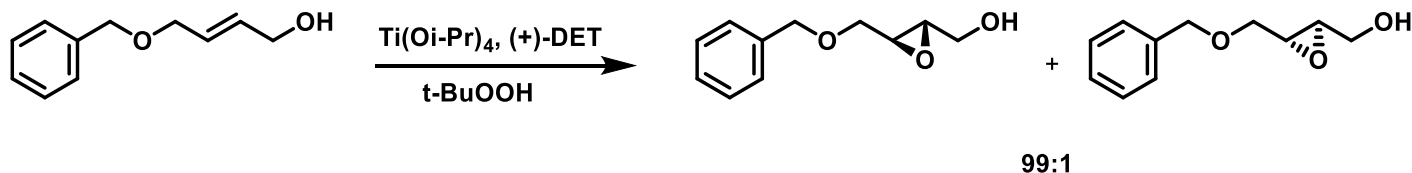
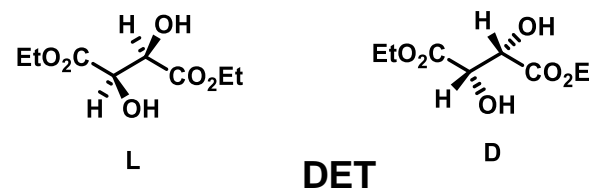


J. Am. Chem. Soc. **1996**, *118*, 9806.
J. Am. Chem. Soc. **1997**, *119*, 11224.



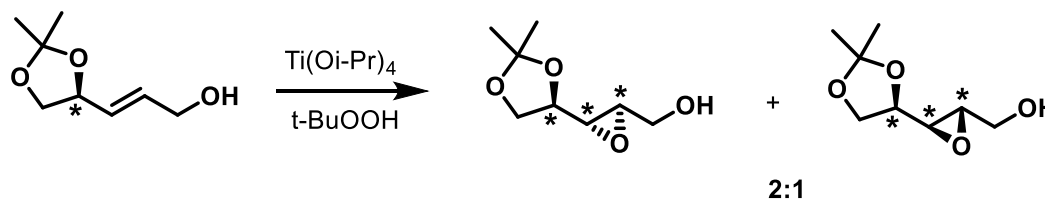
Sharpless asymmetric epoxidation: $\text{Ti}(\text{Oi-Pr})_4$, + t-BuOOH + *optically pure* ester of tartaric acid of allyl alcohols

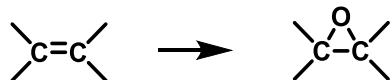
- allyl alcohol binds to chiral Ti complex



J. Am. Chem. Soc. **1987**, 109, 5765.

without chiral ligand, but on chiral substrate (*substrate control*):

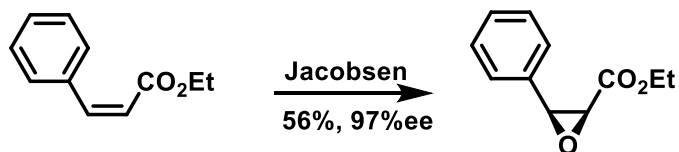
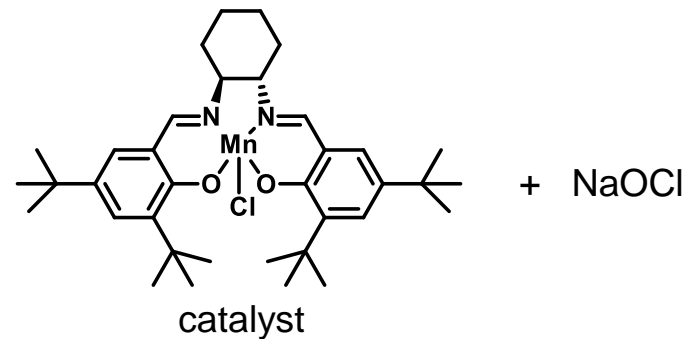
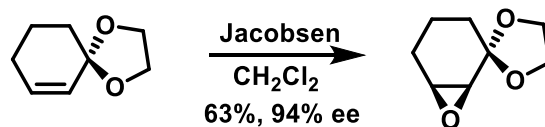


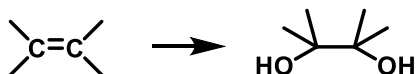


enantioselective

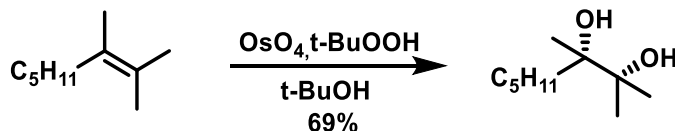
Jacobsen asymmetric epoxidation

- substrate does not have to contain allylic alcohol

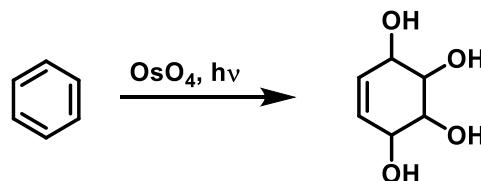
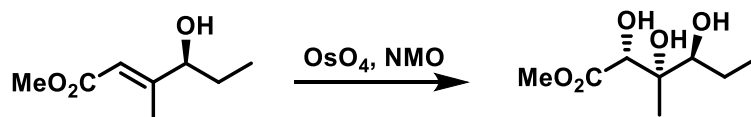
*J. Org. Chem.* **1992**, *57*, 4320.*J. Am. Chem. Soc.* **1991**, *113*, 7063.



OsO_4 ; $\text{OsO}_4 + \text{NMO}$; $\text{OsO}_4 + t\text{-BuOOH}$



J. Am. Chem. Soc. **1976**, 98, 1986.



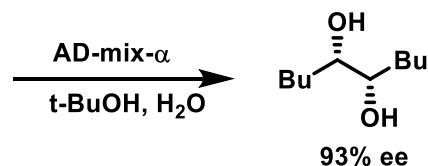
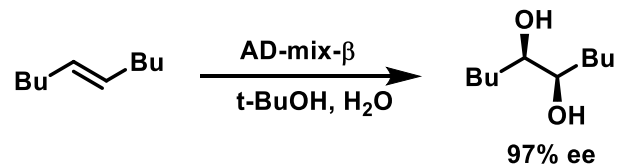
Angew. Chem. Int. Ed. Engl. **1995**, 34, 2031.

asymmetric (Sharpless) dihydroxylation: AD-mix $\text{K}_3\text{Fe}(\text{CN})_6 + \text{K}_2\text{CO}_3 + \text{K}_2\text{OsO}_2(\text{OH})_4 + (\text{DHQD})_2\text{-PHAL}$

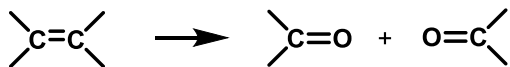
↑
stoichiometric oxidant

↑
catalytic amt.

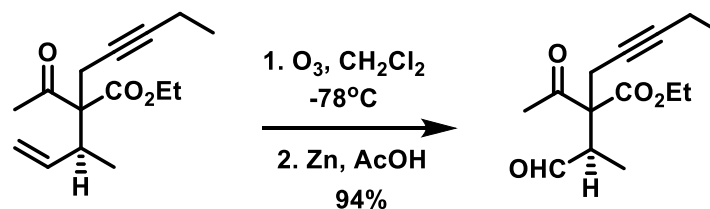
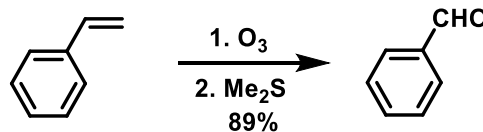
↑
chiral ligand



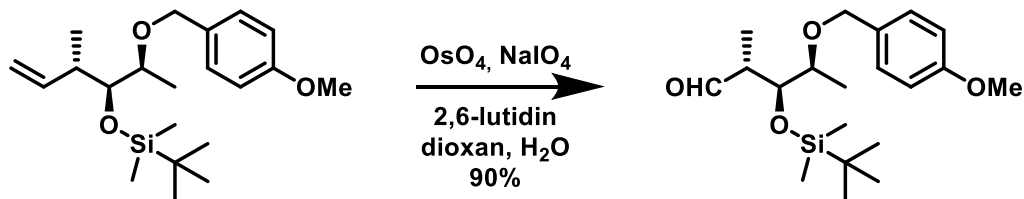
J. Org. Chem. **1992**, 57, 2768.

**ozone: O₃**

- generated from O₂ by el. discharge



Tetrahedron Lett. **1974**, 1387.

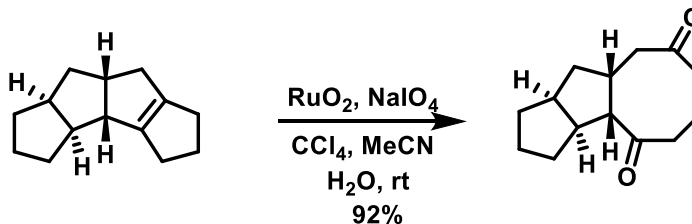
OsO₄ + NaIO₄

Org. Lett. **2004**, 6, 3217.

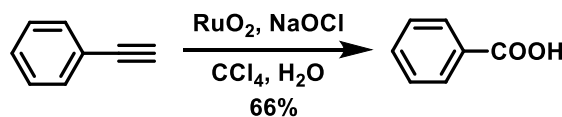
reaction with O₃: cleavage of the PMB group

RuO₄: RuO₂ + NaIO₄

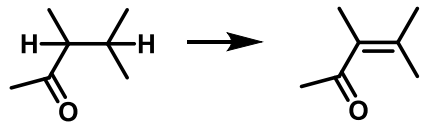
- strong oxidant
- often oxidizes other reactive sites



J. Chem. Soc., Chem. Commun. **1986**, 1319.



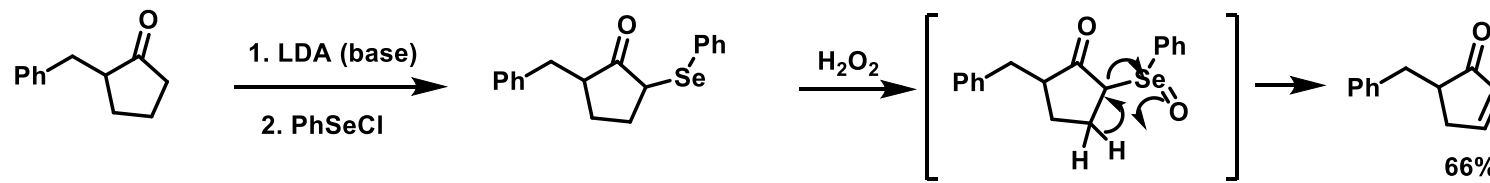
Tetrahedron Lett. **1971**, 2941.



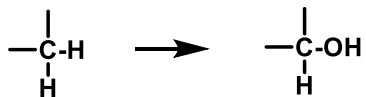
selenation-oxidation-elimination

PhSeCl

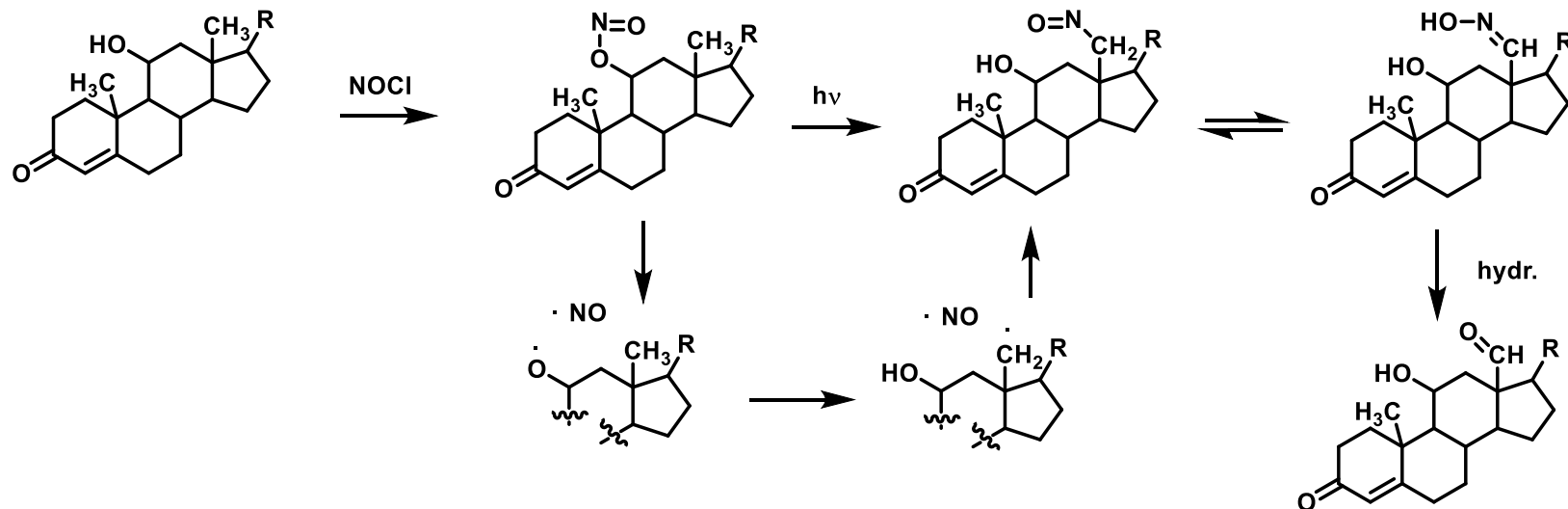
- proceeds as *intramolecular syn-elimination*



J. Am. Chem. Soc. **1982**, *104*, 4502.

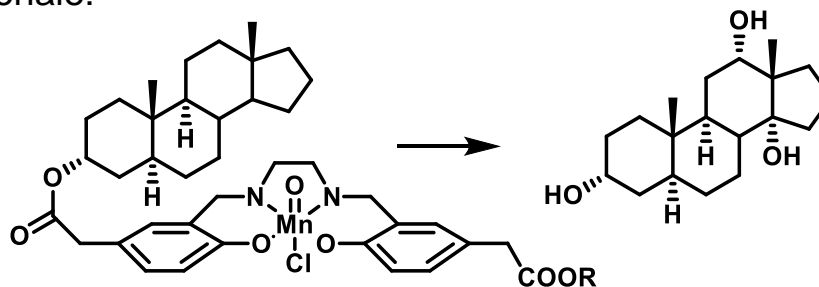


Barton reaction; remote oxidation



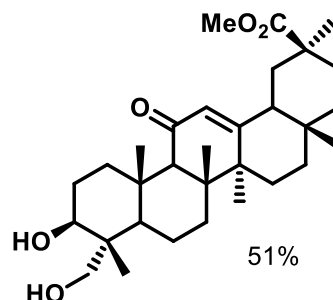
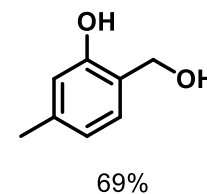
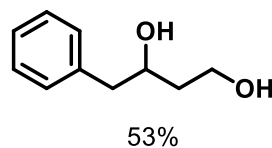
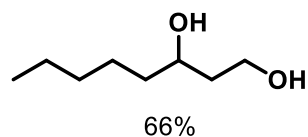
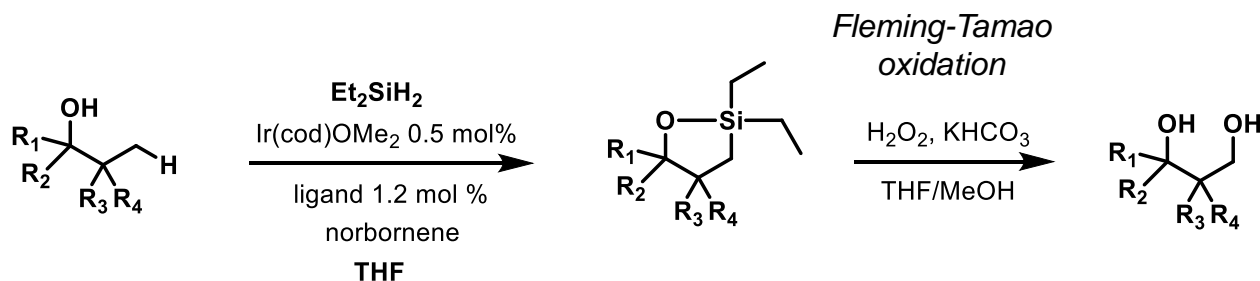
J. Am. Chem. Soc. **1961**, 83, 4083.

similar rationale:



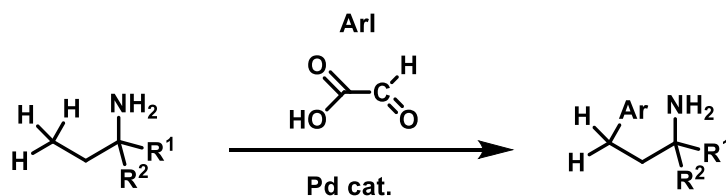
J. Am. Chem. Soc. **1993**, 115, 11648.

direct oxidation of *unactivated* C-H bond („C-H activation“)



J. F. Hartwig et al. *Nature* **2012**, 483, 70.

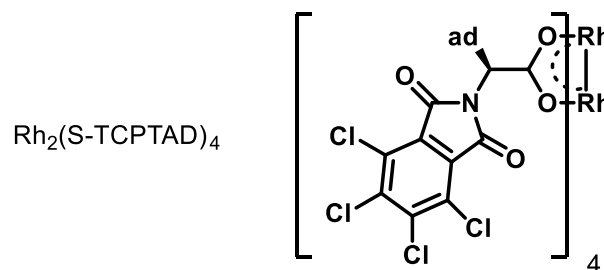
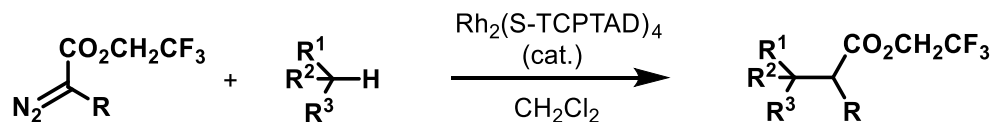
similar concept: site-selective arylation of primary aliphatic amines (catalytic transient directing group)



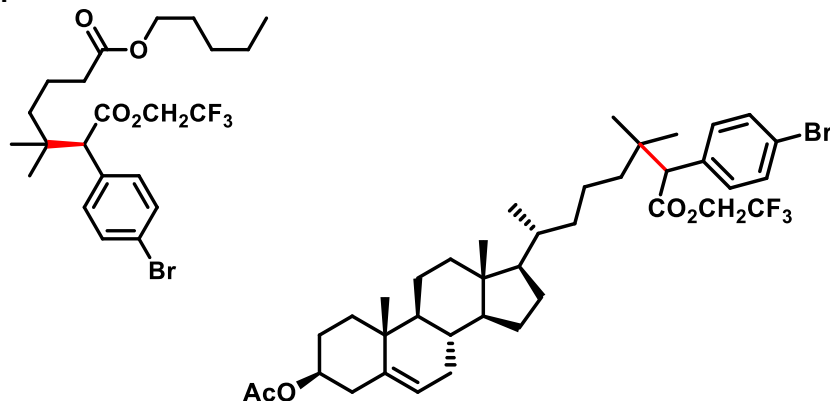
Nature Chemistry **2017**, 9, 26.

site-selective functionalization of tertiary C-H bond

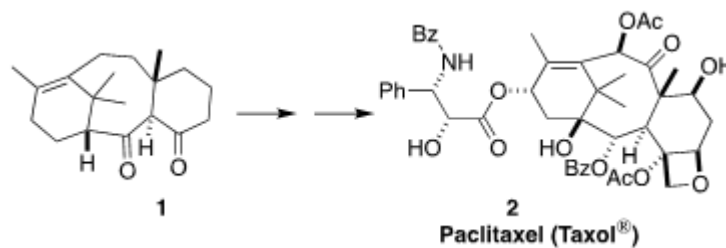
- (stereoselective) manipulation of most accessible tert. C-H bond



e.g.

H. M. L. Davies et al. *Nature* **2017**, 551, 609.

Baran's synthesis of taxol: tour de force in oxidation chemistry



J. Am. Chem. Soc. **2020**, *142*, 10526.
J. Org. Chem. **2020**, *85*, 10293.