Organic synthesis

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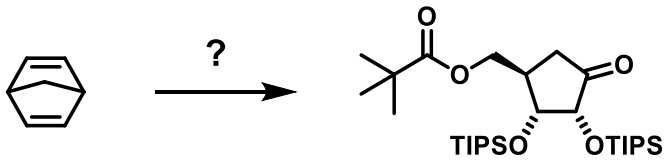
Masaryk University, Brno

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

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)

Organic Reactions

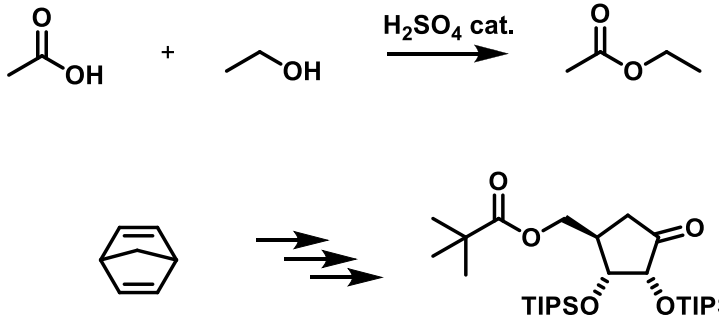
Science of Synthesis

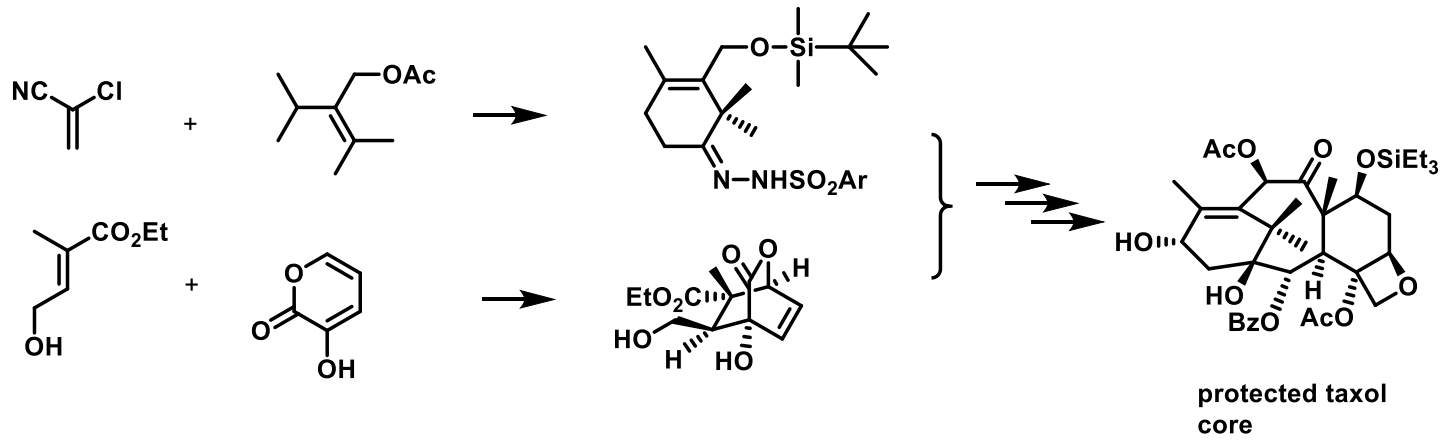
+ additional literature in the central library (organic chemistry section)

starting material → *synthesis* → **product**

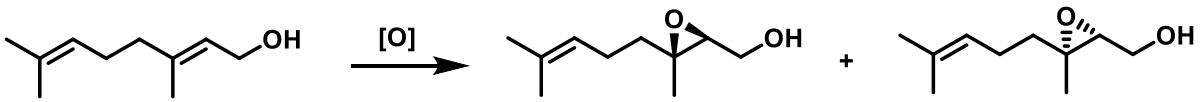
(more complex)

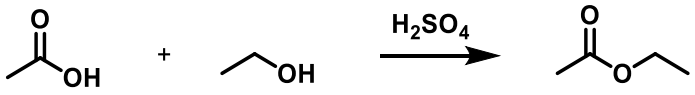
- ***chemoselectivity***
- ***regioselectivity***
- ***stereoselectivity***
- ***cost of reagents***
- ***feasibilty (number of steps, scale up)***

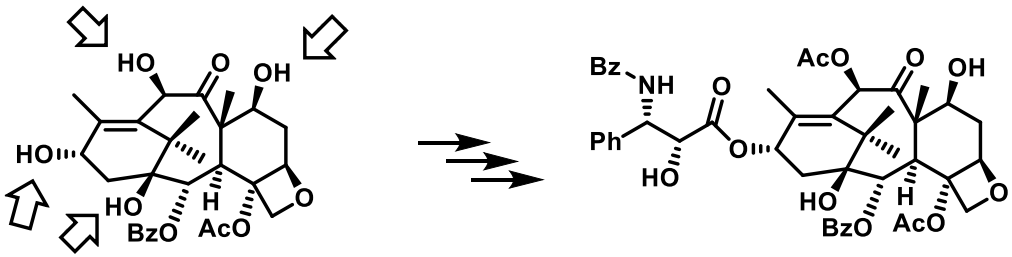




protected taxol core

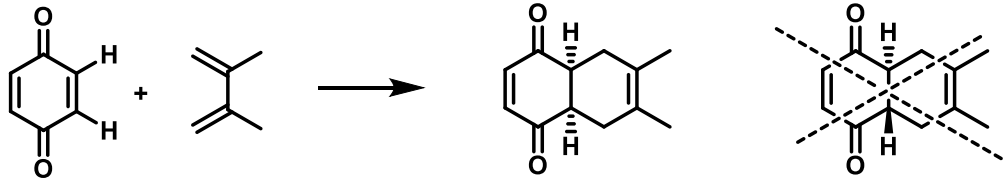


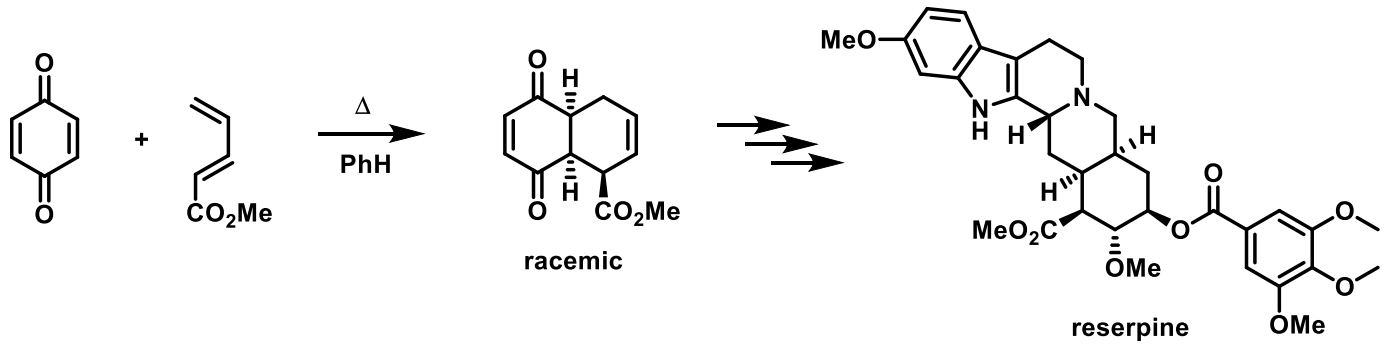




10-deacetyl baccatin III **taxol**

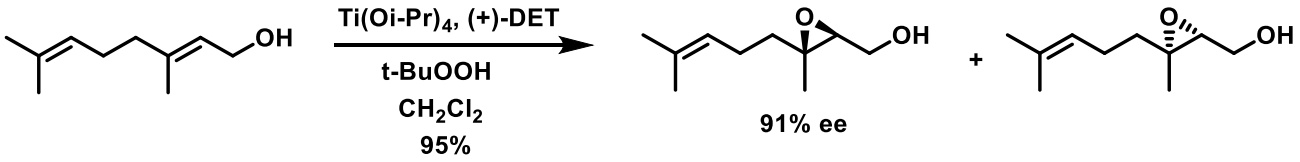
J. Am. Chem. Soc. **1998**, *110*, 5917.



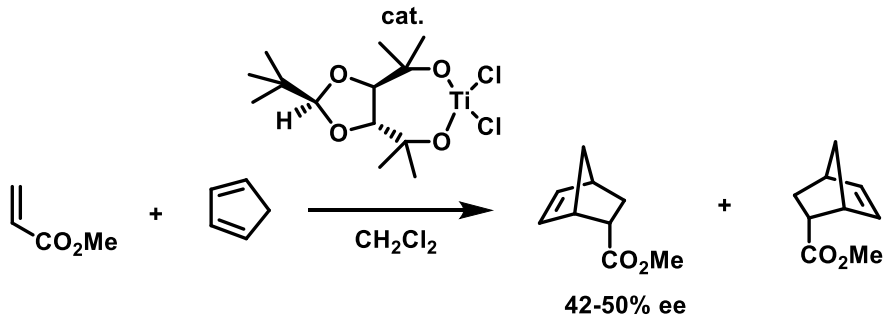


*J. Am. Chem. Soc.***1956**, 78, 2657.

enantioselectivity



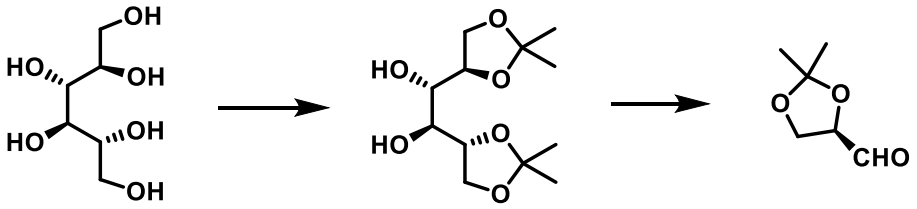
J. Am. Chem. Soc. **1987**, *109*, 5765.



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

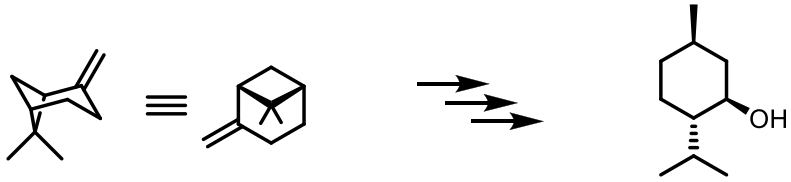
more complex reagents → **less complex products**

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



D-mannitol

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

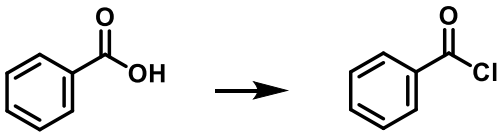


(-)-β-pinene (-)-menthol

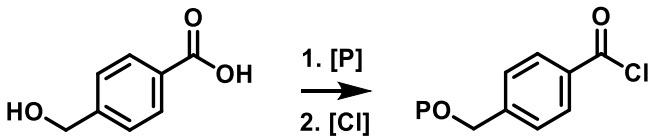
Nicolaou, K. C.; Sorensen, E. J. Classics in Total Synthesis, p.343.

starting material → *synthesis* **product**

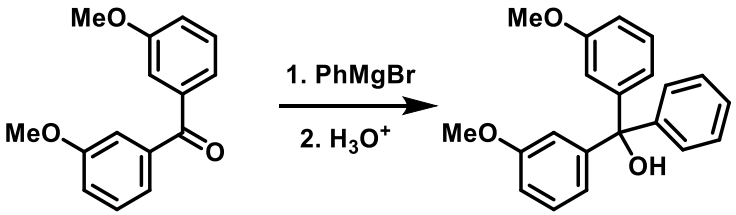
- ***functional groups interconversion***



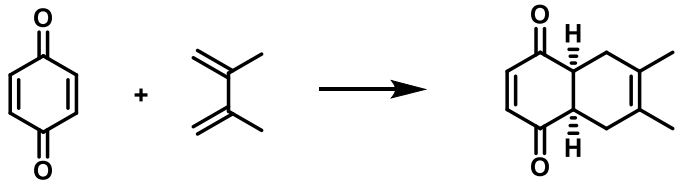
- ***protecting groups***



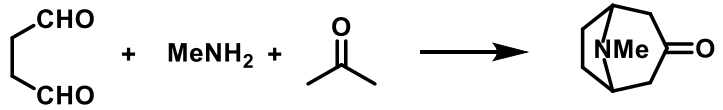
- ***single bond formation*** ***C-C*** ***C-O*** ***C-N*** ***C-S***



- ***formation of several bonds***



- ***multicomponent reactions***
  domino reactions

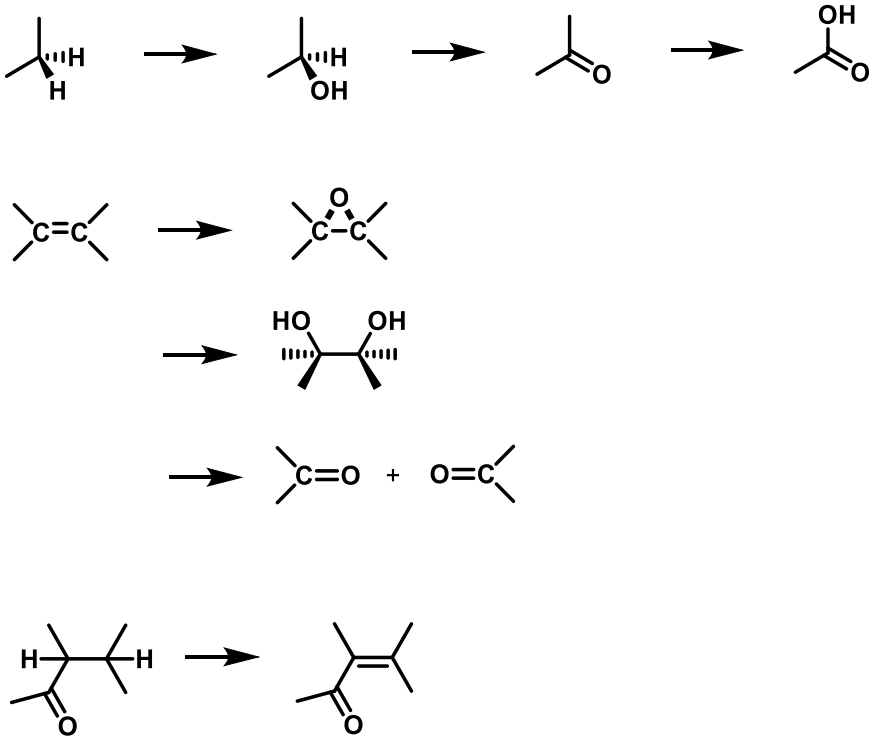


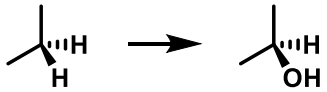
J. Chem. Soc. **1917**, 762.

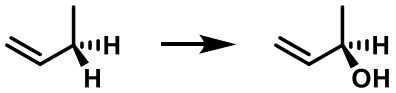
- ***solid phase /combinatorial chemistry***

- 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



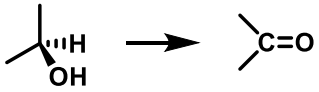




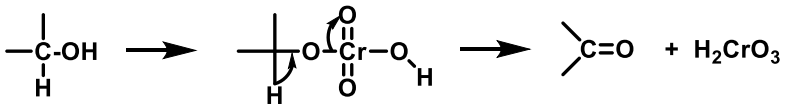
SeO_2

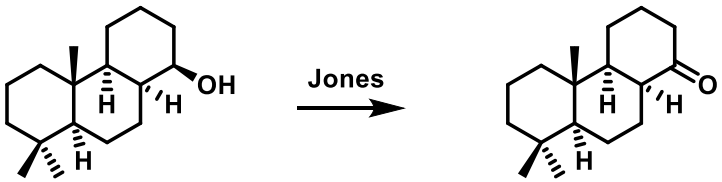
- oxidation on allylic C

Oxidation



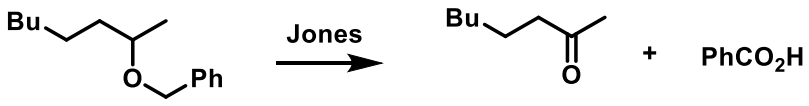
Jones reagent CrO_3 + aq. H_2SO_4 (H_2CrO_4)



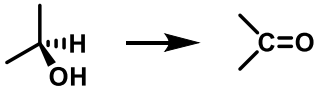


Tetrahedron Lett. **1961**, 493.

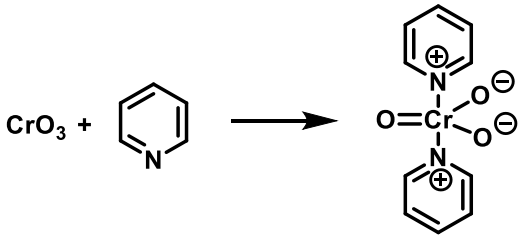
- **acidic conditions; some functional groups not compatible**

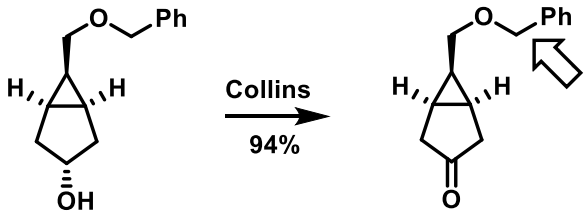


J. Org. Chem. **1981**, *46*, 1492.



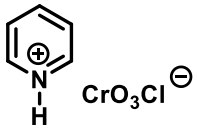
Collins reagent

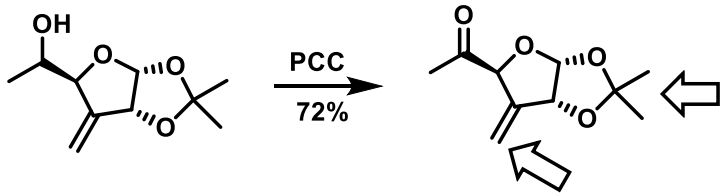




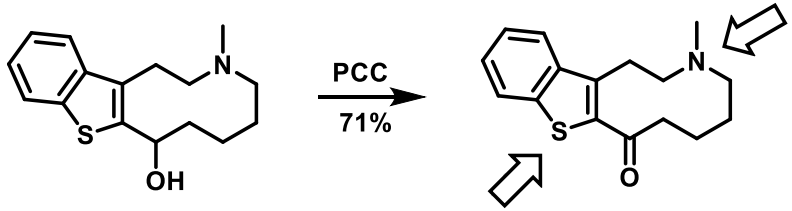
J. Org. Chem. **1976**, *41*, 3883.

PCC

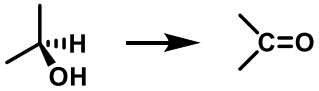




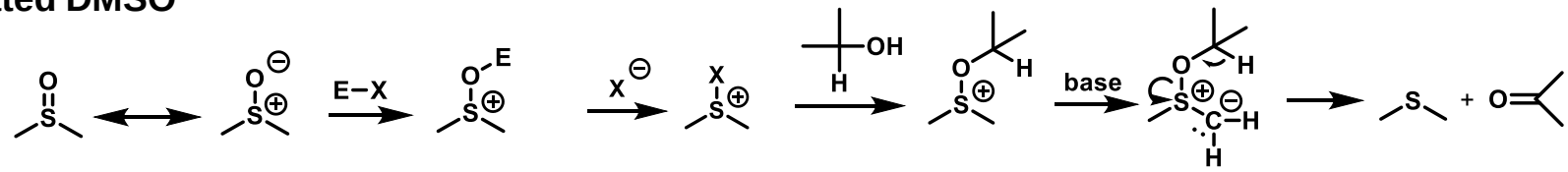
J. Chem. Soc. Perkin Trans. I **1985**, 1.



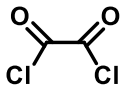
Chem. Lett. **1979**, 709.

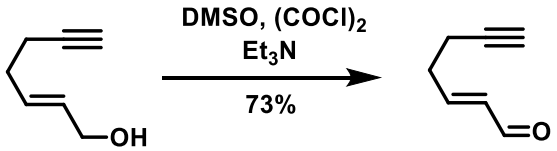


activated DMSO

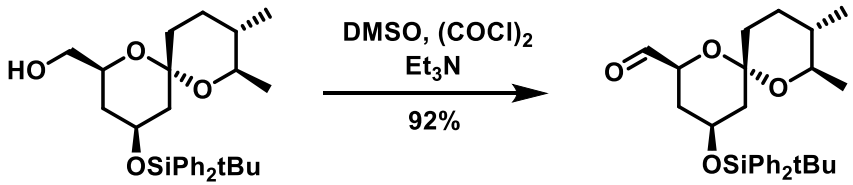


note: Pummerer rearrangement – mechanistically similar

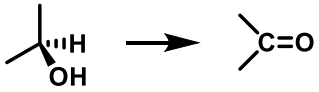
Swern oxidation: EX:  base: amine (Et_3N)



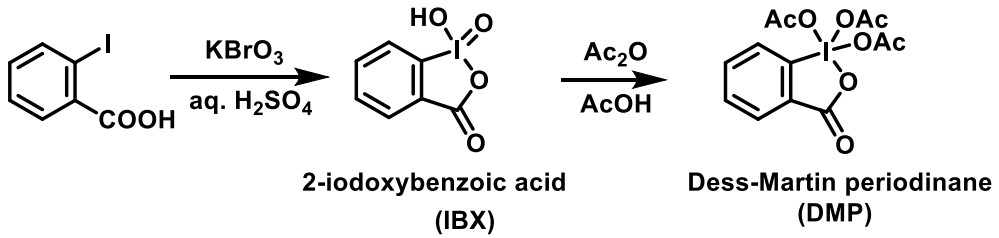
J. Org. Chem. **1993**, *58*, 3912.

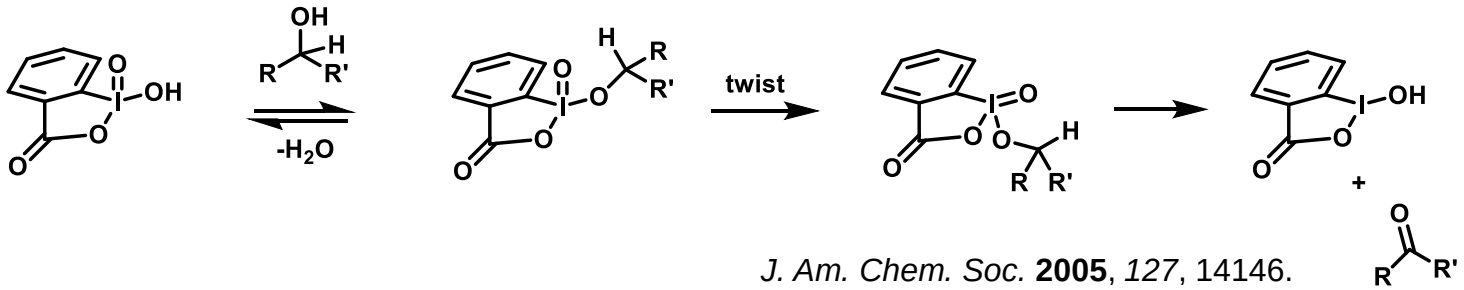


J. Am. Chem. Soc. **1982**, *104*, 4708.

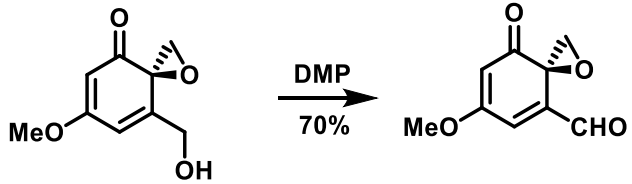


Dess-Martin reagent

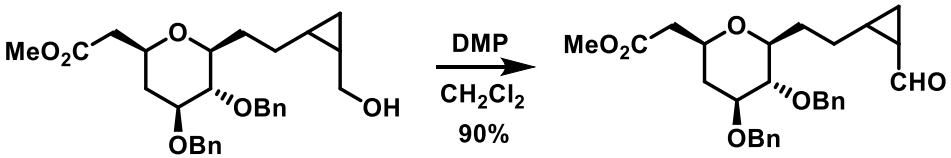




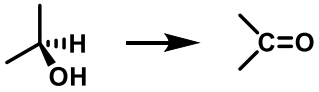
J. Am. Chem. Soc. **2005**, *127*, 14146.



J. Am. Chem. Soc. **1988**, *110*, 6891.

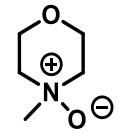


J. Am. Chem. Soc. **1990**, *112*, 9645.

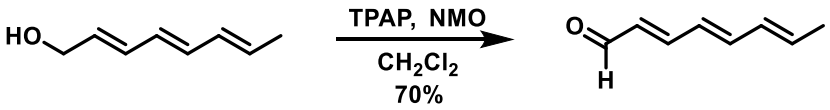


TPAP: $Pr_4N^+RuO_4^-$

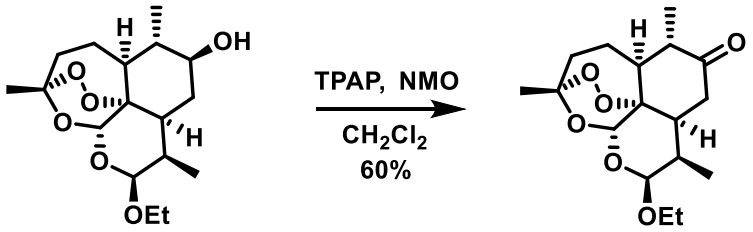
- typically used in catalytic amounts
- stoichiometric oxidant: typically NMO



NMO

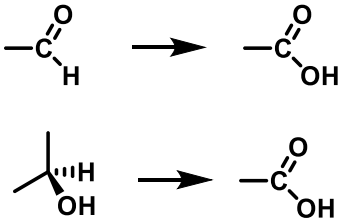


Tetrahedron **1992**, *48*, 1145.



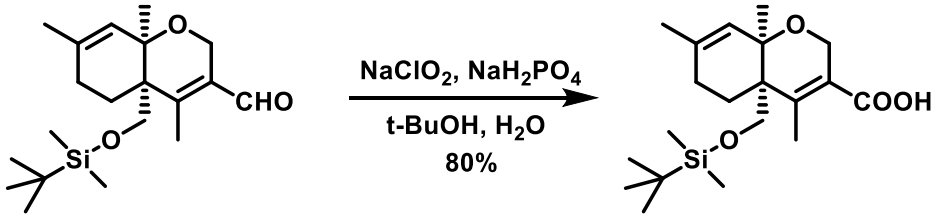
artemisinine core

J. Chem. Soc. Perkin Trans. I **1992**, 979.

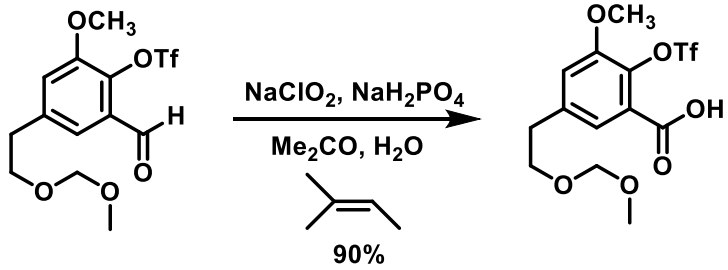


Sodium chlorite: $NaClO_2$

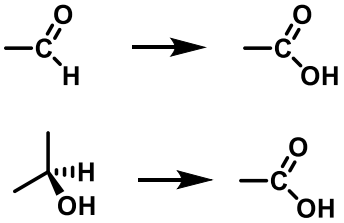
- selective oxidant, mild conditions (Pinnick oxidation)



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

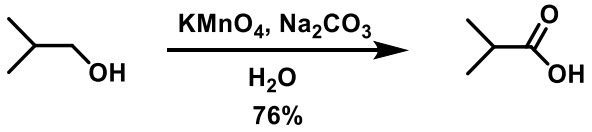


J. Am. Chem. Soc. **1994**, *116*, 1004.

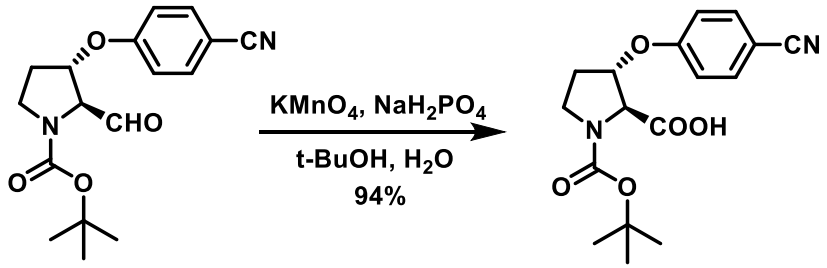


Potassium permanganate): $KMnO_4$

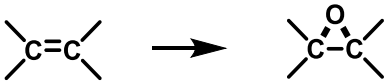
- strong oxidant; oxidation of alkenes and other functional groups



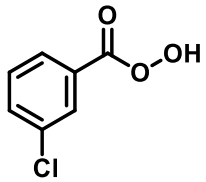
Vogel's Textbook of Practical Organic Chemistry, 5 ed. 1989, p. 668.



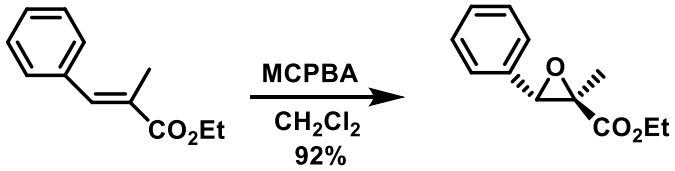
J. Am. Chem. Soc. **1992**, *114*, 10181.



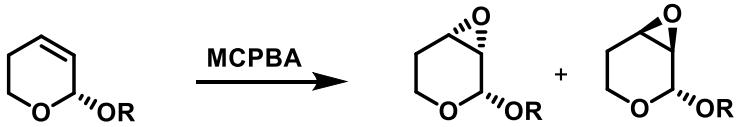
3-chloroperoxybenzoic acid, MCPBA, *m*-CPBA)



- 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



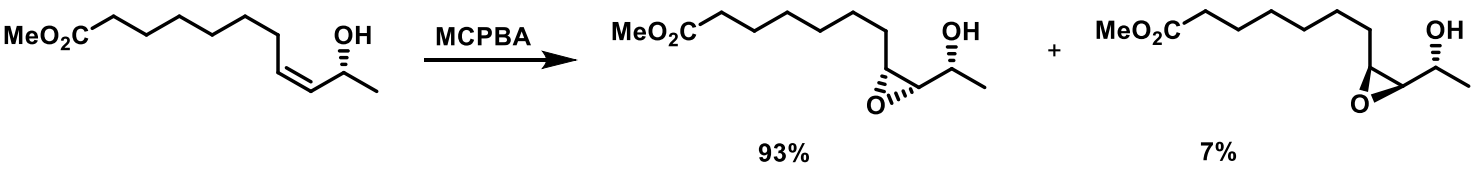
J. Org. Chem. **1966**, *31*, 2509.



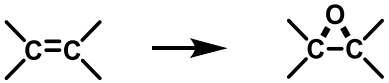
R = Me: 1:3
R = t-Bu: 1:9

Synlett **1991**, 529.

but:

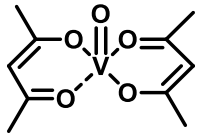


Tetrahedron Lett. **1987**, *28*, 5129.

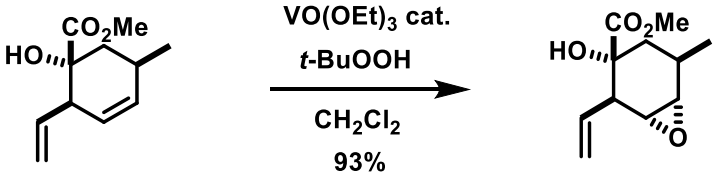


vanadium-based reagents

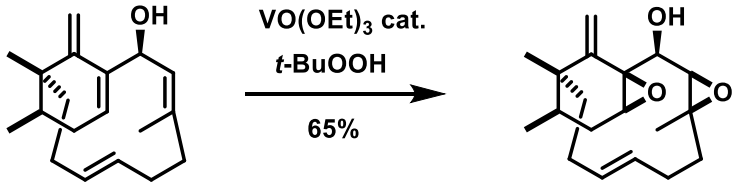
typically: $VO(acac)_2$ + *t*-BuOOH



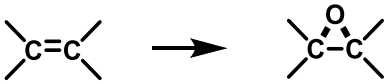
• frequently used for directed epoxidations



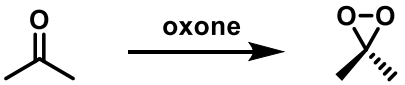
J. Am. Chem. Soc. **2007**, *129*, 429.

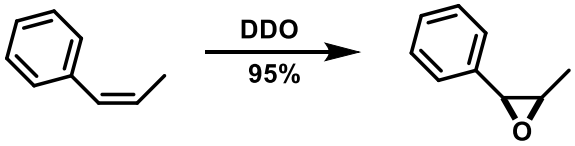


Nature Chemistry **2018**, *10*, 938.

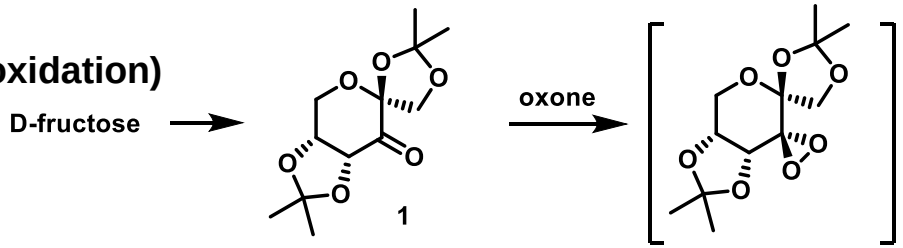


dimethyldioxirane (DDO)

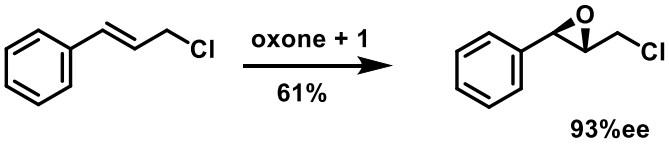




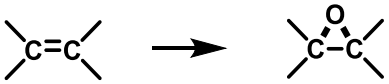
asymmetric variant (Shi epoxidation)



usually 20-30 mol% used



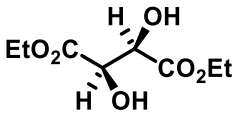
J. Am. Chem. Soc. **1996**, *118*, 9806.
J. Am. Chem. Soc. **1997**, *119*, 11224.



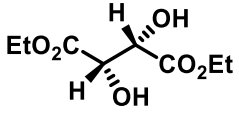
enantioselective

Sharpless asymmetric epoxidation: Ti(Oi-Pr)$_4$, + t-BuOOH + *optically pure* ester of tartaric acid of allylalcohols

- allyl alcohol binds to chiral Ti complex

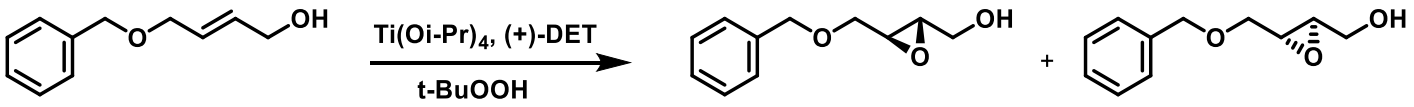


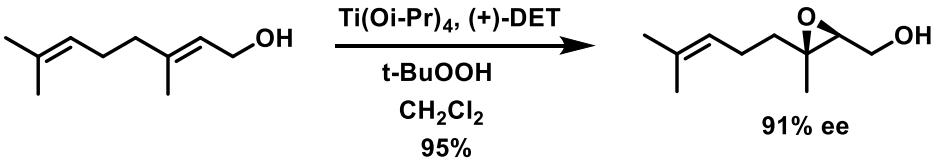
L



D

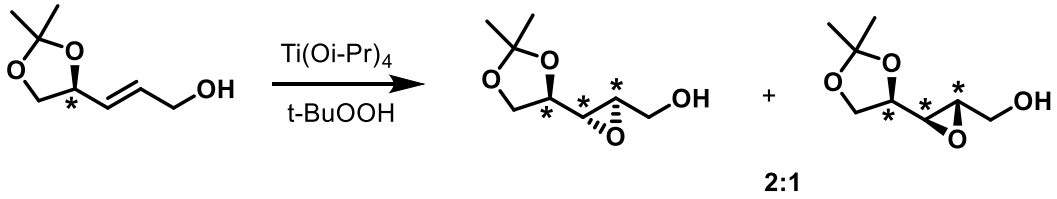
DET

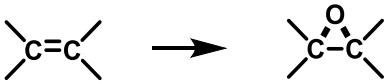




J. Am. Chem. Soc. **1987**, *109*, 5765.

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

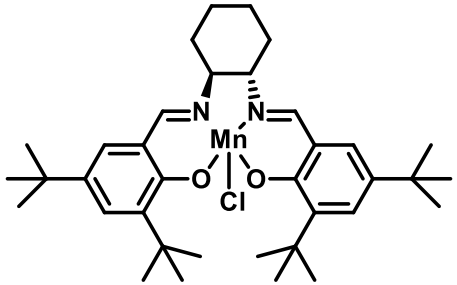




enantioselective

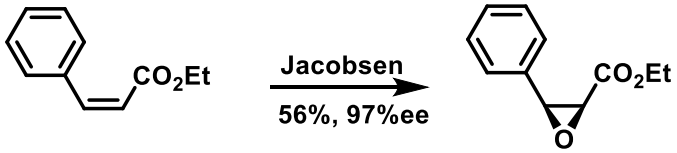
Jacobsen asymmetric epoxidation

- substrate does not have to contain allylic alcohol

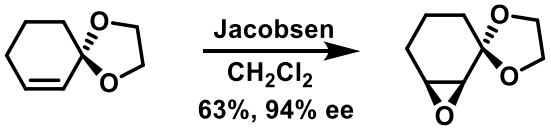


+ NaOCl

catalyst



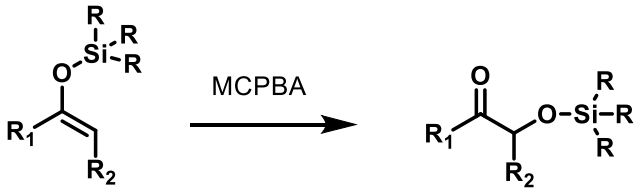
J. Org. Chem. **1992**, *57*, 4320.

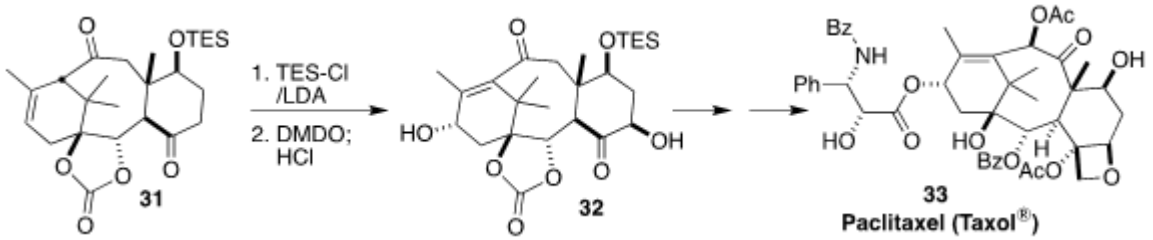


J. Am. Chem. Soc. **1991**, *113*, 7063.

?

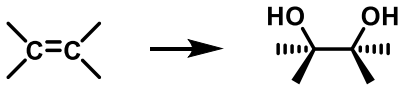
suggest the mechanism of Rubottom oxidation



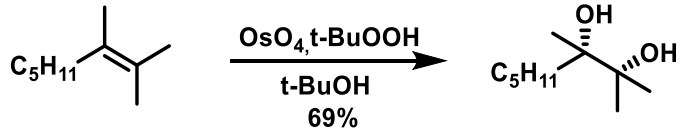


- DMDO was particularly selective in the epoxidation of the bis enol ether derived from **31**, leading to the diol **32**

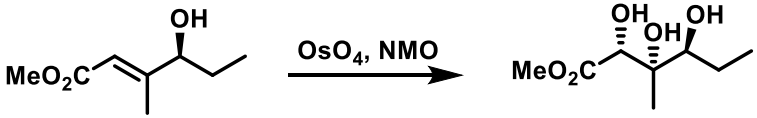
Org. Lett. **2022**, *24*, 202.

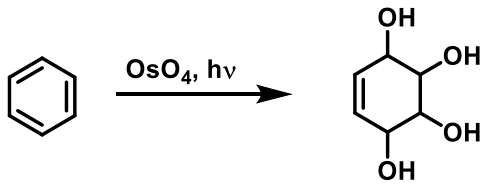


OsO_4; OsO_4 + NMO; OsO_4 + t-BuOOH



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

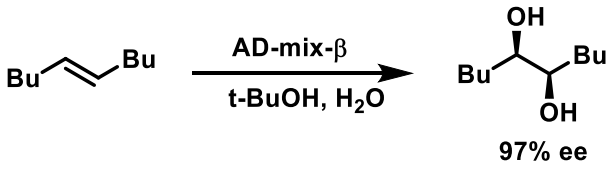


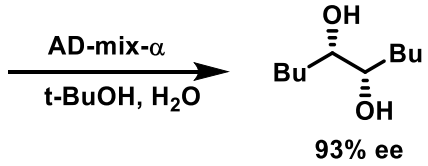


Angew. Chem. Int. Ed. Engl. **1995**, *34*, 2031.

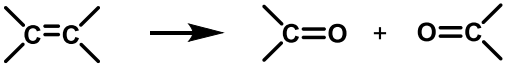
asymmetric (Sharpless) dihydroxylation: AD-mix $K_3Fe(CN)_6$ + K_2CO_3 + $K_2OsO_2(OH)_4$ + $(DHQD)_2$-PHAL

stoichiometric oxidant — **catalytic amt.** — **chiral ligand**



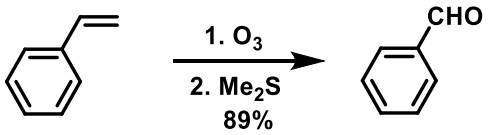


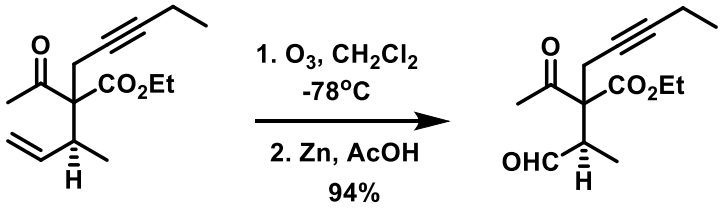
J. Org. Chem. **1992**, *57*, 2768.



ozone: O_3

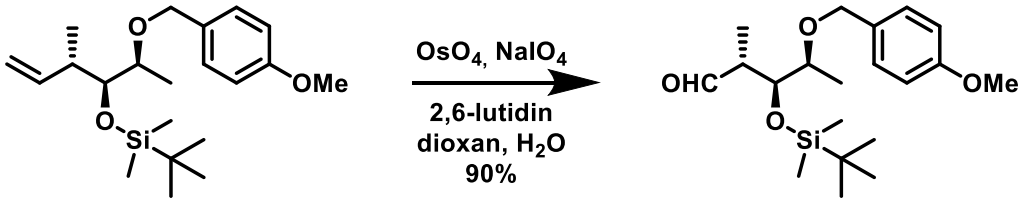
- generated from O_2 by el. discharge





Tetrahedron Lett. **1974**, 1387.

OsO_4 + $NaIO_4$

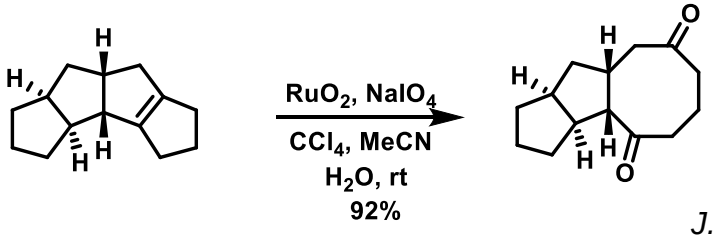


Org. Lett. **2004**, *6*, 3217.

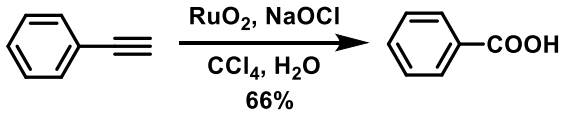
reaction with O_3 : cleavage of the PMB group

RuO_4: RuO_2 + $NaIO_4$

- strong oxidant
- often oxidizes other reactive sites



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



Tetrahedron Lett. **1971**, 2941.

Capturing primary ozonides for a *syn*-dihydroxylation of olefins

Nat. Chem. **2023**, *15*, 1262.

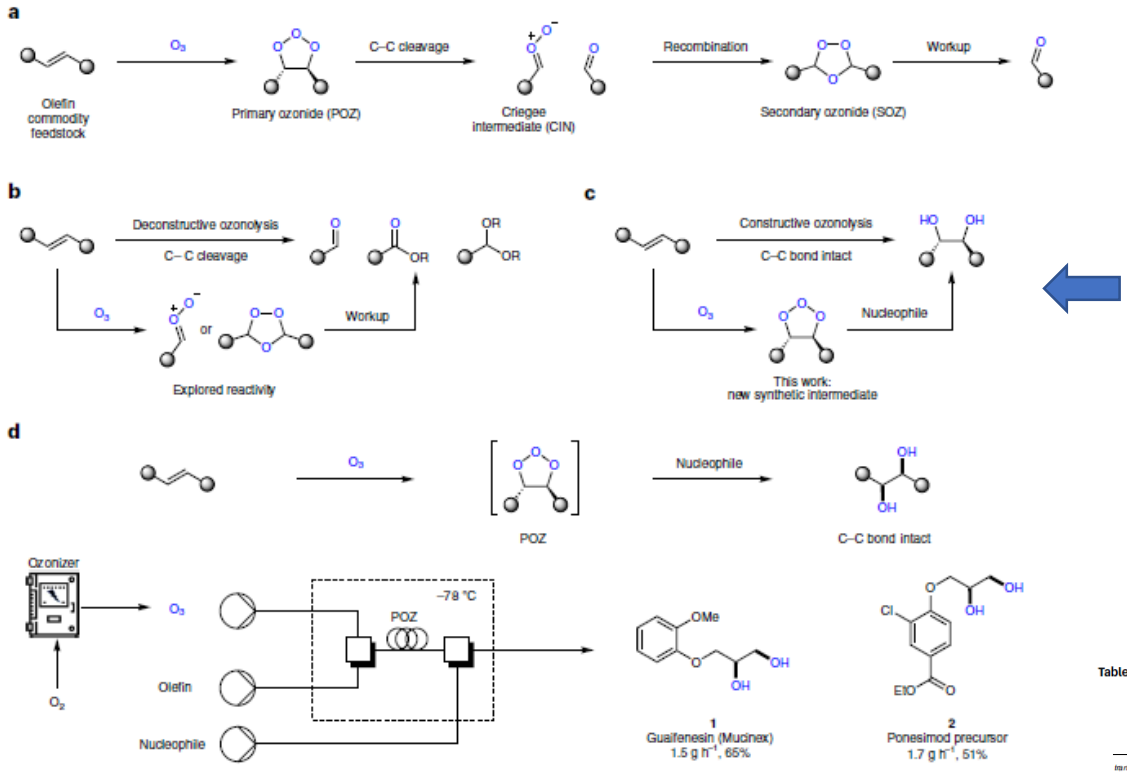
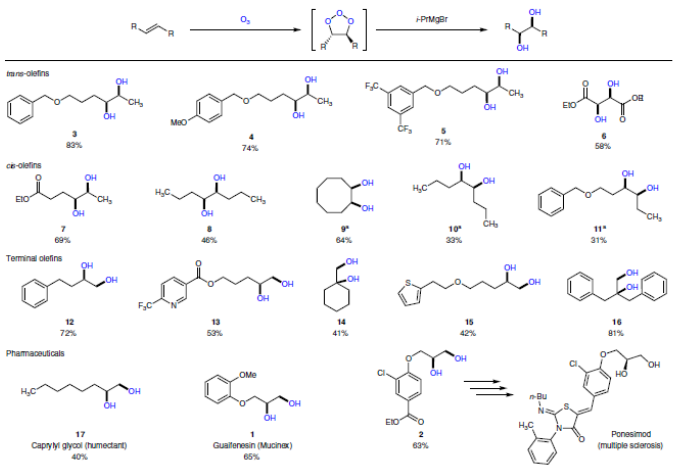
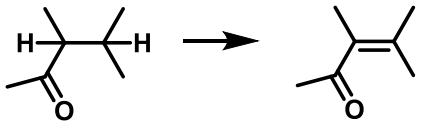


Fig. 1 | Applications of olefin ozonolysis. a, Mechanism of ozonolysis. **b**, Deconstructive approaches to ozonolysis gives aldehydes, ketones, esters, acetals and other functional groups through C–C cleavage. **c**, Nucleophilic capture of POZs enables C–O bond formation without C–C cleavage. **d**, Continuous flow allows for the capture of POZs for a green *syn*-dihydroxylatic with virtually no peroxide accumulation. Ozone is generated from elemental oxygen using an ozonizer that supplies ozone in solution for the generation of POZs in continuous flow reactors.

Table 1 | Green *syn*-dihydroxylation of olefins through constructive ozonolysis



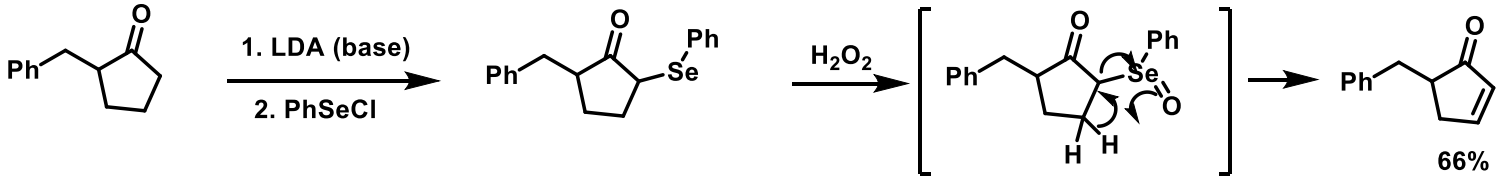
Standard reaction conditions used the olefin (0.50 mmol, 1.0 equiv.) dissolved in diethyl ether (5 ml) cooled to −116 °C and treated with O_3. Isopropyl magnesium bromide (*i*-PrMgBr) solution (2.50 mmol, 5.0 equiv.) was added followed by a general aqueous workup to yield the glycol product. Yields are an average of two runs. [a]Reactions were performed at −130 °C using cyclopentyl methyl ether as solvent.



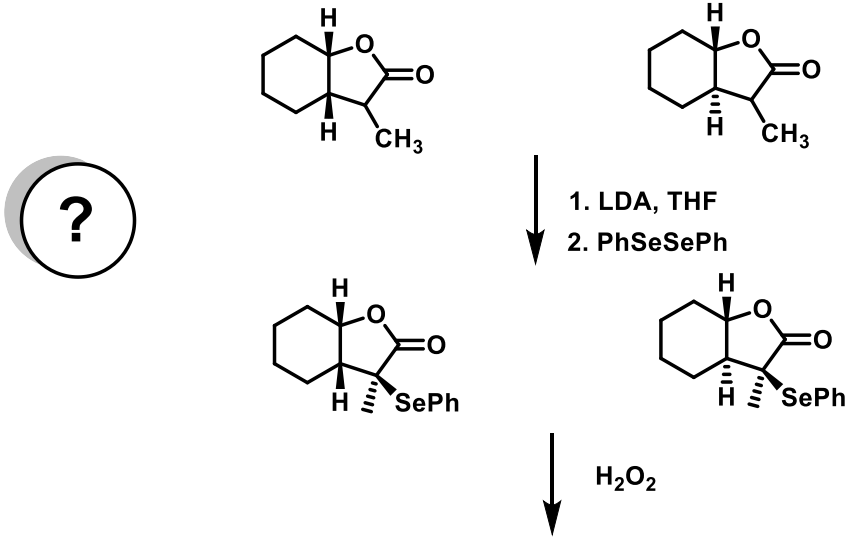
selenation-oxidation-elimination

PhSeCl

- proceeds as *intramolecular syn- elimination*

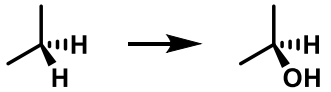


J. Am. Chem. Soc. **1982**, *104*, 4502.

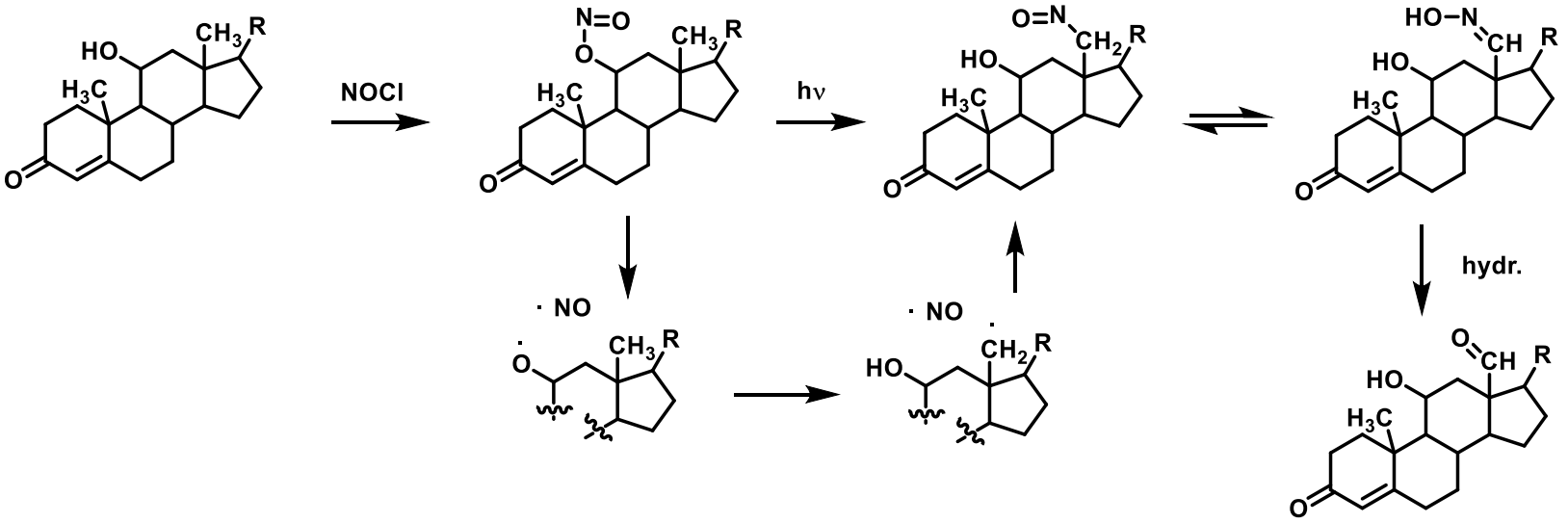


structure of products?

J. Org. Chem. **1974**, *39*, 120.

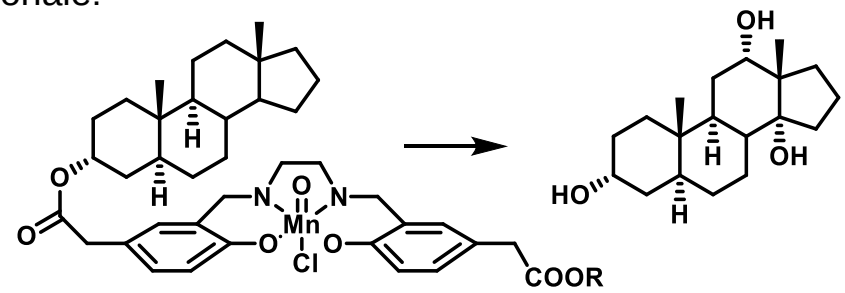


Barton reaction; remote oxidation



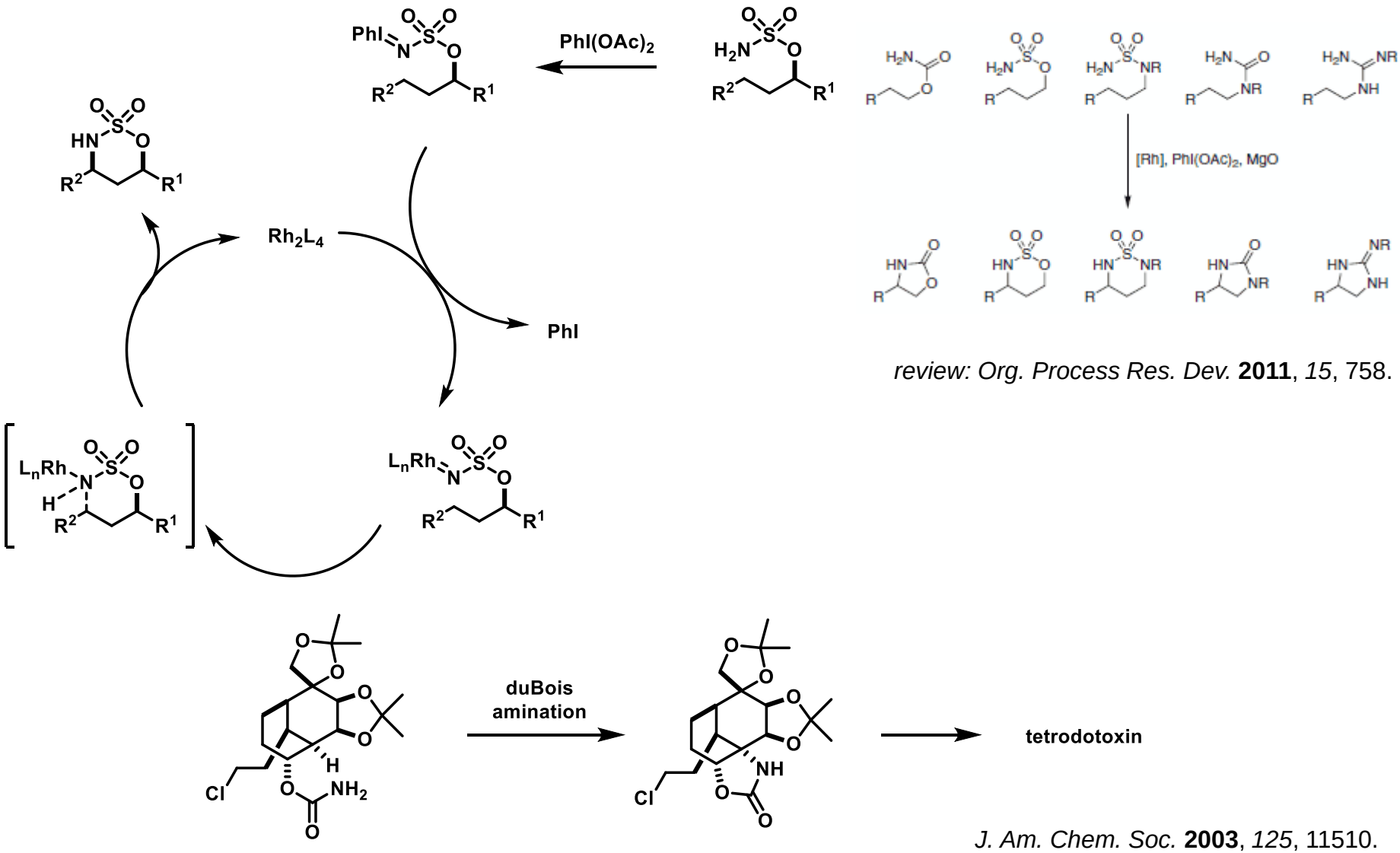
J. Am. Chem. Soc. **1961**, *83*, 4083.

similar rationale:



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

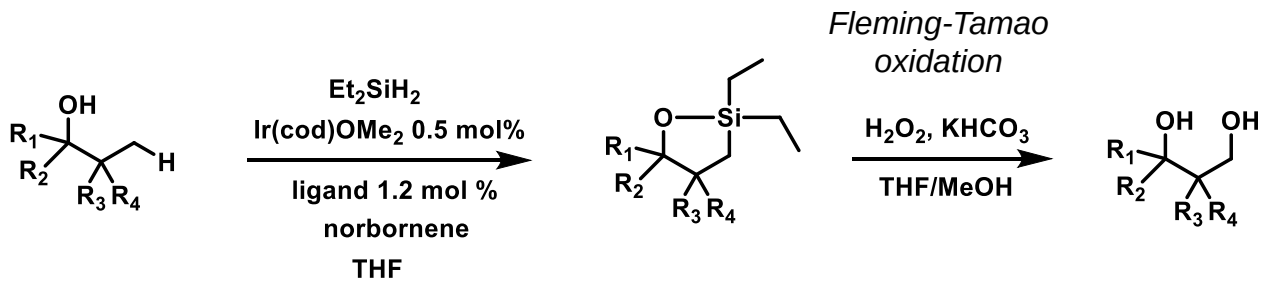
duBois amination

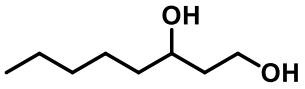


review: Org. Process Res. Dev. **2011**, *15*, 758.

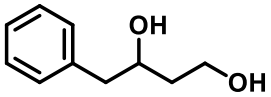
J. Am. Chem. Soc. **2003**, *125*, 11510.

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

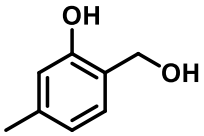




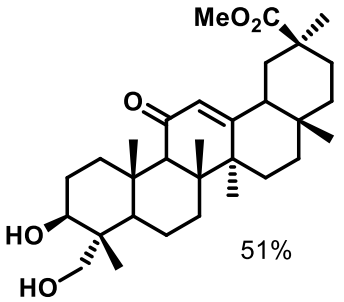
66%



53%



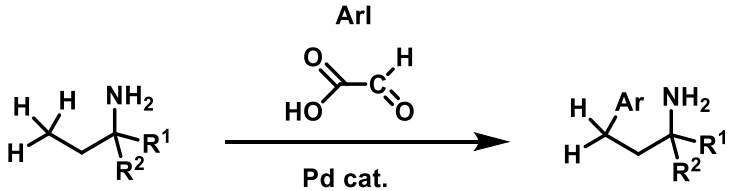
69%



51%

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

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

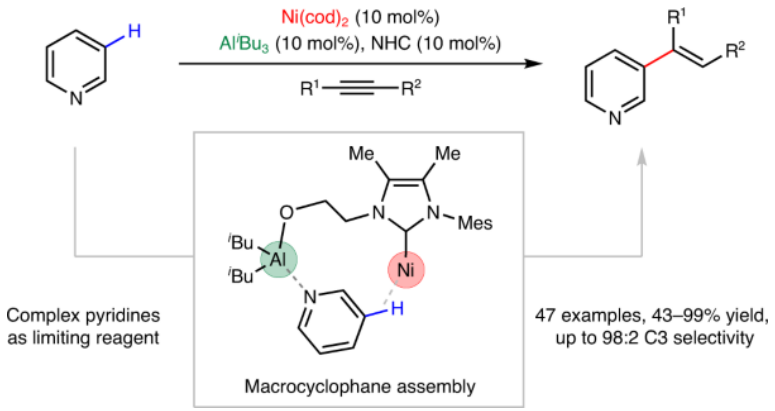


Nature Chemistry **2017**, *9*, 26.

- **analogous strategy can be used in other transformations…**

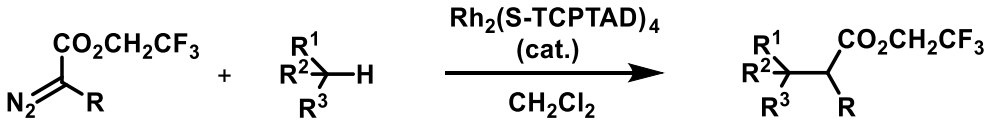
A directive Ni catalyst overrides conventional site selectivity in pyridine C–H alkenylation
Nature Chemistry **volume 13**, pages1207–1213 (2021)Cite this article

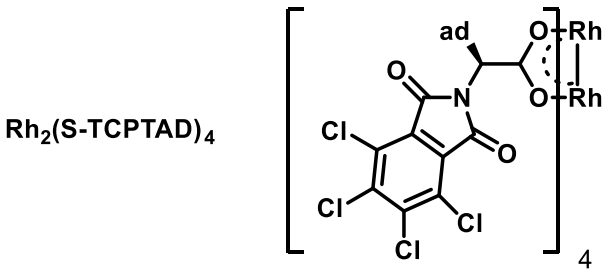
Abstract
Achieving the transition metal-catalysed pyridine C3−H alkenylation, with pyridine as the limiting reagent, has remained a long-standing challenge. Previously, we disclosed that the use of strong coordinating bidentate ligands can overcome catalyst deactivation and provide Pd-catalysed C3 alkenylation of pyridines. However, this strategy proved ineffective when using pyridine as the limiting reagent, as it required large excesses and high concentrations to achieve reasonable yields, which rendered it inapplicable to complex pyridines prevalent in bioactive molecules. Here we report that a bifunctional N-heterocyclic carbene-ligated Ni–Al catalyst can smoothly furnish C3–H alkenylation of pyridines. This method overrides the intrinsic C2 and/or C4 selectivity, and provides a series of C3-alkenylated pyridines in 43–99% yields and up to 98:2 C3 selectivity. This method not only allows a variety of pyridine and heteroarene substrates to be used as the limiting reagent, but is also effective for the late-stage C3 alkenylation of diverse complex pyridine motifs in bioactive molecules.



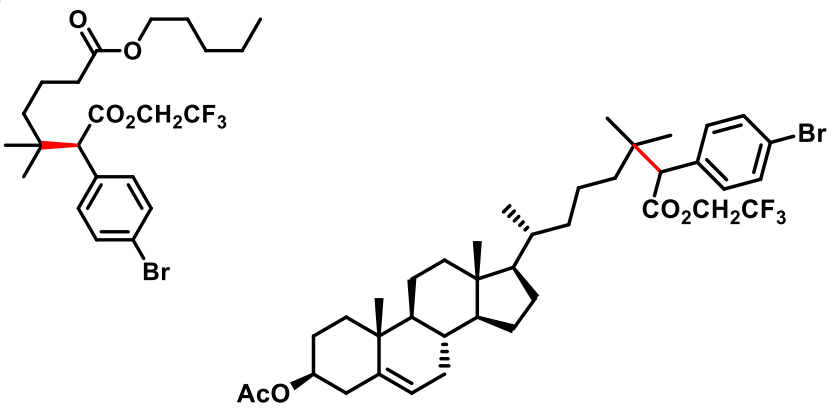
site-selective functionalization of tertiary C-H bond

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





e.g.



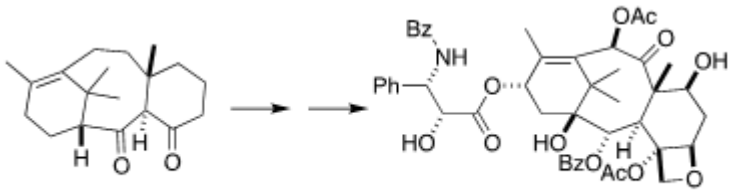
H. M. L. Davies et al. *Nature* **2017**, *551*, 609.

Stereochemical editing logic powered by the epimerization of unactivated tertiary stereocenters

Y.-A. Zhang et al. *Science* **2022**, *378*, 383.

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

Paclitaxel (Taxol®) (**2**) has become a mainstay of cancer chemotherapy.
Phil S. Baran of Scripps/La Jolla developed a two-stage route to **2**, based on the preparation and oxidation of **1**
(*J. Am. Chem. Soc.* **2020**, *142*, 10526, DOI: 10.1021/jacs.0c03592; *J. Org. Chem.* **2020**, *85*, 10293, DOI: 10.1021/acs.joc.0c01287).



1 **2**
Paclitaxel (Taxol®)