

I. Basic Principles

I-P. Oxidations

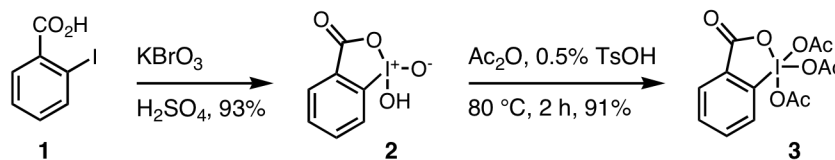
- Alcohols
- Arenes
- Baeyer-Villiger
- Dehydrogenations
- Allylic & Benzylic Dehydrogenations
- Ozonolysis



Alcohol Oxidations

Dess-Martin Oxidation

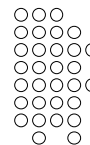
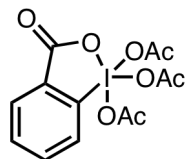
- Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, 113, 7277. The Dess-Martin periodinane **3** is an extremely useful reagent for the conversion of primary and secondary alcohols to aldehydes and ketones at 25 °C. It does not overoxidize aldehydes to carboxylic acids under these conditions and tolerates the presence of furan rings or sulfides and vinyl ethers. It reacts with primary amines to give insoluble products, and reacts slowly enough with secondary amines and sulfides to make it possible to oxidize alcohols in the presence of these functional groups.



In 1993, Ireland and Liu reported an improved procedure for the preparation of the Dess-Martin periodinane (*J. Org. Chem.* **1993**, 58, 2899). **CAUTION! Precursor oxide 2 (IBX) was reported to be explosive under excess heating!**

Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J., "The Dess-Martin periodinane: 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one." *Org. Synth.* **2000**, 77, 141-152.

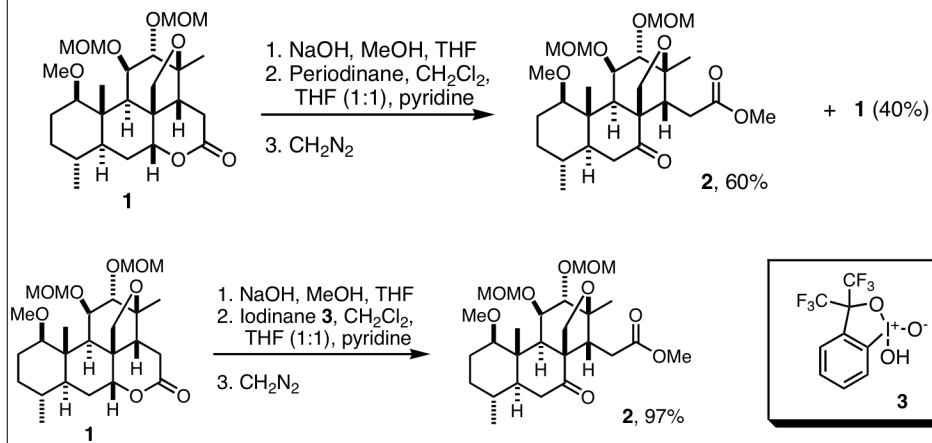




- Impure samples of Dess-Martin periodinane may in many cases provide better results than the pure reagent, since the partially hydrolyzed agent is a more effective oxidant. However, the fully hydrolyzed material is a polymer that seems to have deactivating effects that result in the requirement of multiple equivalents of reagent. Accordingly, when rate enhancement is desired, the pure oxidant may be decomposed with one equivalent of water immediately before or during its use (Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549).

Racemization is minimized with DMP: Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S., "Synthesis of highly epimerizable N-protected α -amino aldehydes of high enantiomeric excess." *Tetrahedron Lett.* **2000**, *41*, 1359-1362.

- Grieco, P. A.; Pineiro-Nunez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606. Oxidation of lactone **1** to ketone **2** with Dess-Martin periodinane buffered with pyridine provided ca. 40% of starting material. Replacement of Dess-Martin periodinane with hydroxyiodinane oxide **3** alleviated these problems since **3** generates water instead of acetic acid during the course of the oxidation reaction:



PCC Oxidation

- Martin, T.; Soler, M. A.; Betancort, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 1570.



- PCC can also be used to effect the rearrangement/oxidation of tertiary allylic alcohols (THL **1998**, *39*, 6521).

- Corey, E. J.; Kania, R. S. *Tetrahedron Lett.* **1998**, *39*, 741.

Oxidation of Activated Alcohols to Aldehydes [MnO₂]

Quesada, E.; Taylor, R. J. K., "One-pot conversion of activated alcohols into terminal alkynes using manganese dioxide in combination with the Bestmann-Ohira reagent." *Tetrahedron Lett.* **2005**, *46*, 6473-6476.



See also:

Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A., "Tandem oxidation processes using manganese dioxide: Discovery, applications, and current studies." *Acc. Chem. Res.* **2005**, *38*, 851-869.

Oxidation of 1° Alcohols to Aldehydes [BaMnO₄]

- Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.

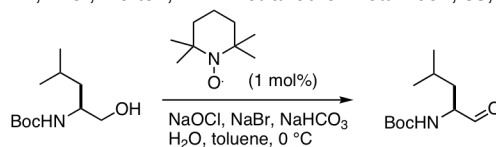


Oxidation of 1° Alcohols to Aldehydes [CrO₂]

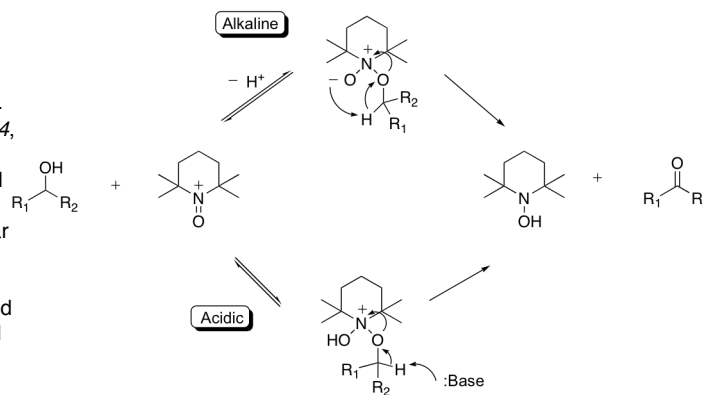
- Lee, R. A.; Donald, D. S., "Magtrieve, an efficient, magnetically retrievable and recyclable oxidant." *Tetrahedron Lett.* **1997**, *38*, 3857-3860. Magtrieve is a form of ferromagnetic CrO₂ produced for magnetic tapes. Reaction mixtures can be decanted and the oxidant retained by holding a magnet to the side of the reaction flask.

Oxidation of 1° Alcohols to Aldehydes [TEMPO]

- Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.



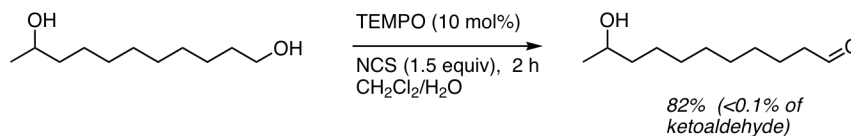
- Two different mechanisms have been postulated (Naik, N.; Braslau, R. *Tetrahedron* **1998**, *54*, 667). In acidic medium, primary and secondary alcohols are oxidized at similar rates, whereas in basic medium, primary, less hindered alcohols are oxidized more rapidly.



Oxidation of 1° Alcohols to Aldehydes [TEMPO]

For a catalytic protocol, see: Bolm, C.; Magnus, A. S.; Hildebrand, J. P., "Catalytic synthesis of aldehydes and ketones under mild conditions using TEMPO/oxone." *Org. Lett.* **2000**, *2*, 1173-1175.

TEMPO/NCS allows for the selective oxidation of primary over secondary alcohols: Einhorn, J.; Einhorn, C.; Ratajzak, F.; Pierre, J.-L., "Efficient and highly selective oxidation of primary alcohols to aldehydes by *N*-chlorosuccinimide mediated by oxoammonium salts." *J. Org. Chem.* **1996**, *61*, 7452-7454.



see also: De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G., "A versatile and highly selective hypervalent iodine(III)/2,2,6,6-tetramethyl-1-piperidinyloxy-mediated oxidation of alcohols to carbonyl compounds." *J. Org. Chem.* **1997**, *62*, 6974-6977. The TEMPO/PhI(OAc)₂ system tolerates sulfides and selenides, dienes, etc.

Another recent and very useful modification is the use of trichloroisocyanuric acid: De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A., "Trichloroisocyanuric/Tempo oxidation of alcohols under mild conditions: A close investigation." *J. Org. Chem.* **2003**, *68*, 4999-5001.

Oxidation of 1° Alcohols to Aldehydes [TPAP]

Lenz, R.; Ley, S. V. *Perkin Trans. 1* **1997**, 3291. Tetra-*n*-propylammonium perruthenate (TPAP)-catalyzed oxidations of alcohols using molecular oxygen as a co-oxidant. Aliphatic aldehydes lead to partial overoxidation to acids.

One of the advantages of TPAP is that it can be used in for amine-containing alcohols (see, for ex. Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542-3545).

- Ali, S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703.

Oxidation of Diols to Lactones [TPAP]

Dong, H.; Zhang, Z.-L.; Huang, J.-H.; Ma, R.; Chen, S.-H.; Li, G., "Practical synthesis of an orally active renin inhibitor aliskiren." *Tetrahedron Lett.* **2005**, *46*, 6337-6340.

**Oxidation of 1° Alcohols to Aldehydes [ADD]**

Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. Oxidation of this alcohol to the carboxylic acid using Jones reagent, chromic acid ($\text{CrO}_3/\text{H}_2\text{SO}_4/\text{HOAc}$), PDC in DMF, $\text{RuCl}_3/\text{NaIO}_4$, purple benzene ($\text{KMnO}_4/n\text{-Bu}_4\text{NBr}/\text{C}_6\text{H}_6$) and PtO_2/O_2 were unsuccessful.



Oxidation of 1° Alcohols to Aldehydes [Swern]

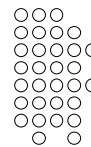
Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.



Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556.

Oxidation of 1° Alcohols to Aldehydes [Swern]

- Smith, A. B.; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 49. The oxalyl chloride-DMSO complex or its decomposition product ($[(\text{Me}_2)_2\text{S}^+\text{-Cl}]\text{Cl}^-$) are thought to be the source of positive chlorine, which reacts with the enol form. Electrophilic chlorination during the Swern protocol can be avoided by using reagents in stoichiometric amounts, or by using the Albright-Goodman or the Pfitzner-Moffat variants.



Oxidation of 1° Alcohols to Aldehydes [Combo-Swern]

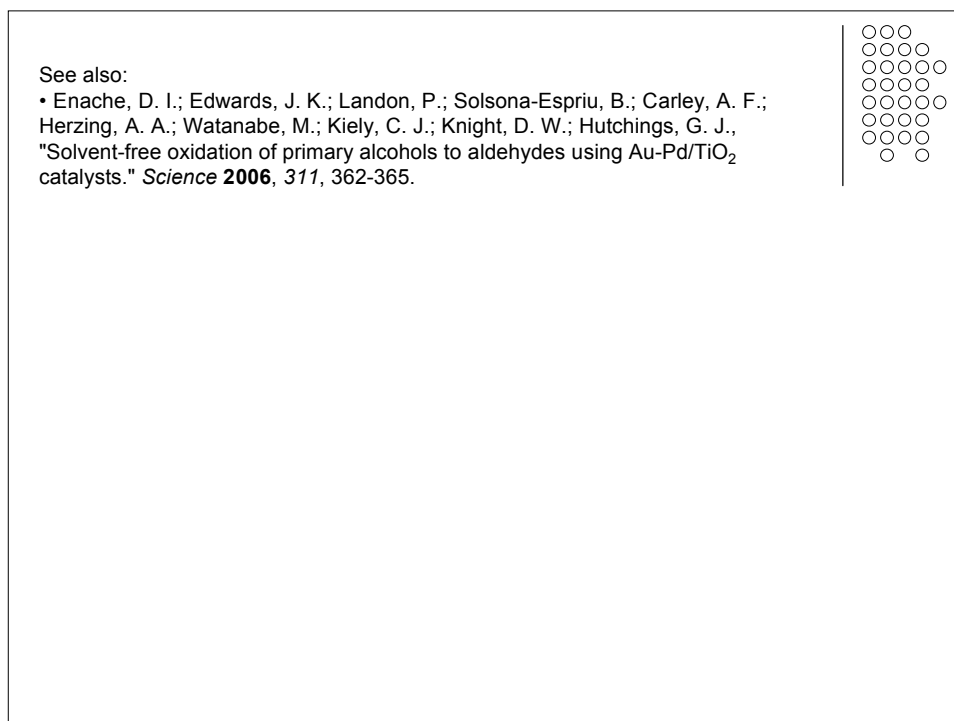
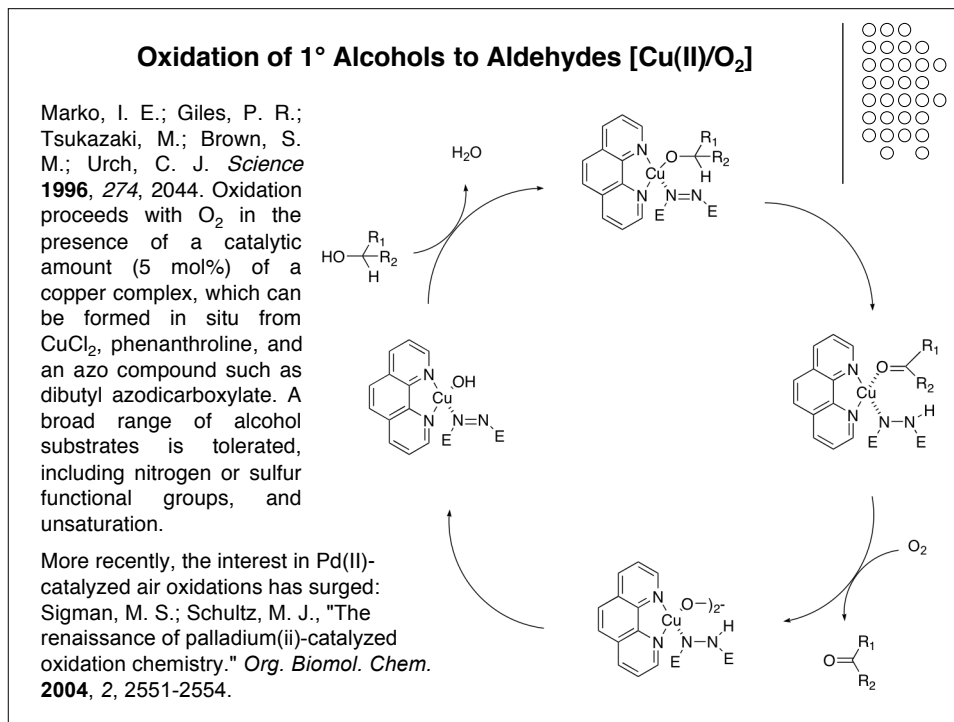
Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677.

**Oxidation of 1° Alcohols to Aldehydes [Parikh-Doering]**

Wipf, P.; Venkatraman, S.; Miller, C. P. *Tetrahedron Lett.* **1995**, *36*, 3639.



Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shioiri, T. *J. Org. Chem.* **1987**, *52*, 1252.



Oxidation of Alcohols to Enones [IBX]

Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S., "A new method for the one-step synthesis of α,β -unsaturated carbonyl systems from saturated alcohols and carbonyl compounds." *J. Am. Chem. Soc.* **2000**, *122*, 7596-7597.

**Oxidation of Diols to Ketones [NaIO₄]**

Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

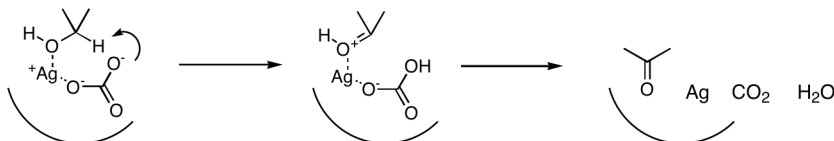
Woodward, R. B. et al. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.



Oxidation of Diols to Lactones [Fetizon]

The rate of oxidation of alcohols by silver carbonate/Celite strongly depends on the solvent and the type of alcohol. More polar solvents and benzene slow the reaction down. Because of their enhanced reactivity, allylic and benzylic alcohols may often be oxidized in CH_2Cl_2 or chloroform; other commonly used solvents are toluene and hydrocarbons. Choice of solvent can be a critical factor in achieving the selective oxidation of a polyol. Proposed mechanism:



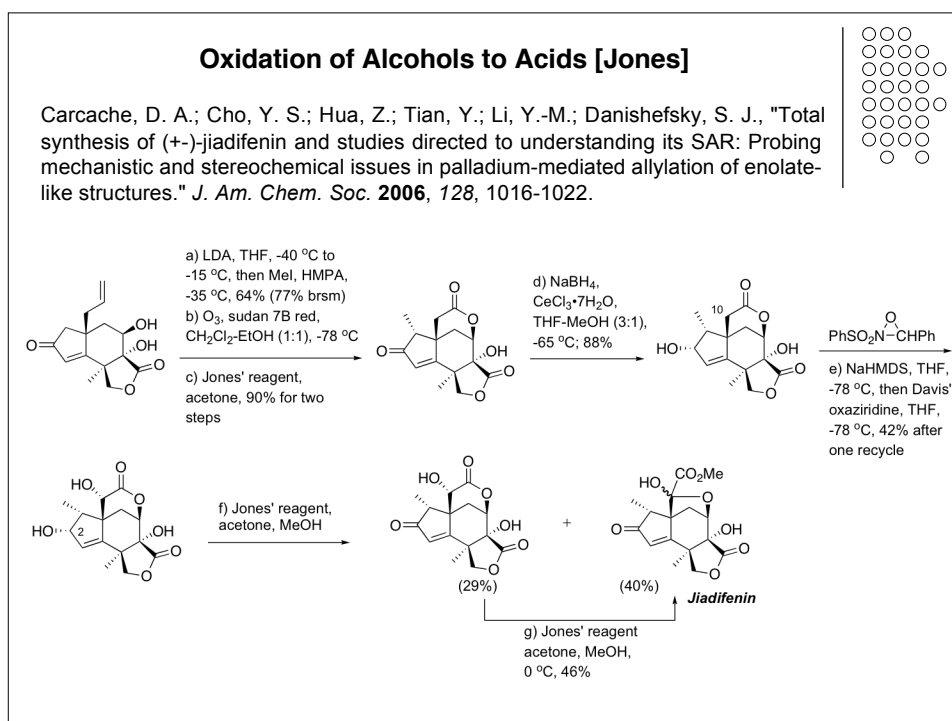
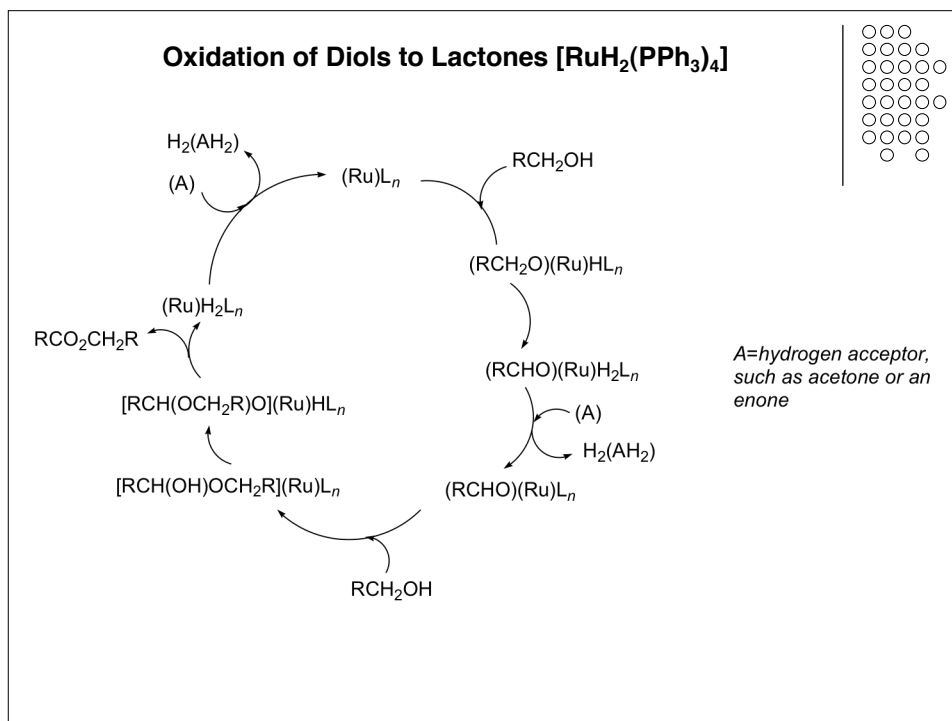
Lange, G. L.; Lee, M. *J. Org. Chem.* **1987**, *52*, 325.



Oxidation of Diols to Lactones [$\text{RuH}_2(\text{PPh}_3)_4$]

Murahashi, S.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H., "Ruthenium-catalyzed oxidative transformation of alcohols and aldehydes to esters and lactones." *J. Org. Chem.* **1987**, *52*, 4319-4327.





Oxidation of Alcohols to Acids [Dess-Martin, NaClO₂]

Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, *2*, 199.



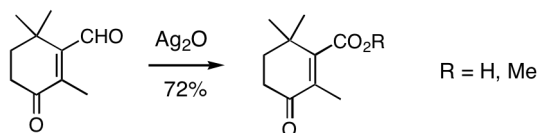
Oxidation of Aldehydes to Acids [NaClO₂]

Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643.



Oxidation of Aldehydes to Acids [Ag₂O]

Silver oxide is usually prepared *in situ* by mixing a solution of silver nitrate and excess sodium hydroxide. Pepperman, A. B. *J. Org. Chem.* **1981**, *46*, 5039.



KMnO₄-H₂SO₄: 14%
 air: 37-46%
 Jones: 55%
 MnO₂-NaCN: 80% (R=Me)

Oxidation of Aldehydes to Esters [MnO₂-NaCN]

Non-conjugated aldehydes are not converted to esters by this treatment, despite the fact that cyanohydrin formation occurs. An important advantage of this reaction is the retention of geometry about the alkene bond, in contrast to Ag₂O oxidation which causes isomerization.

Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
Baudoy, R.; Gore, J. *Synthesis* **1974**, 573.

For more recent applications, see:

Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K., "Esters and amides from activated alcohols using manganese(IV) dioxide: Tandem oxidation processes." *Synthesis* **2003**, 1055-1064.

**Oxidation of Furans to Acids [RuO₄]**

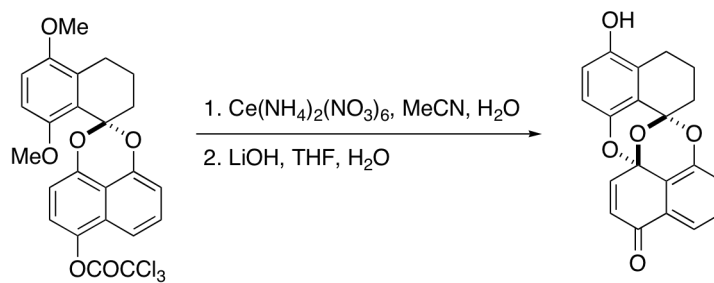
Sasaki, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1997**, *38*, 3013.

**Oxidation of Alkenes to Acids [RuO₄]**

Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

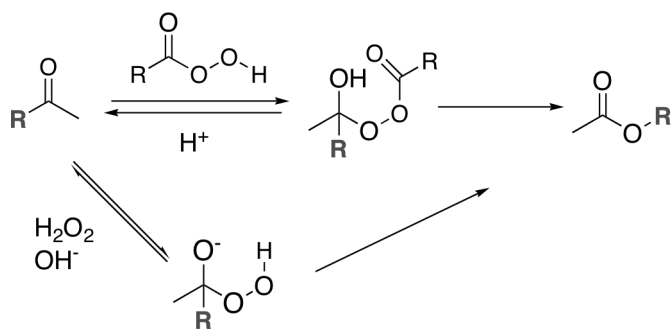
Arene Oxidation Reactions

Chi, S.; Heathcock, C. H., "Total syntheses of (±)-preussomerins G and I." *Org. Lett.* **1999**, *1*, 3.



Bayer-Villiger Oxidations

Ketones react with peroxyacids or hydrogen peroxides to give esters via a C→O rearrangement. Both acid- and base-catalyzed mechanisms have been proposed.

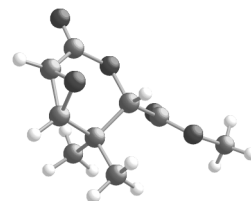


The migratory aptitudes are *t*-alkyl > cyclohexyl = 2°alkyl = benzyl = phenyl > vinylic > 1°alkyl > cyclopropyl > methyl.

Baeyer-Villiger oxidations are highly stereoselective; migration occurs with retention of configuration. Recent work also demonstrates that alkoxyalkyl groups have an extremely high migratory aptitude:

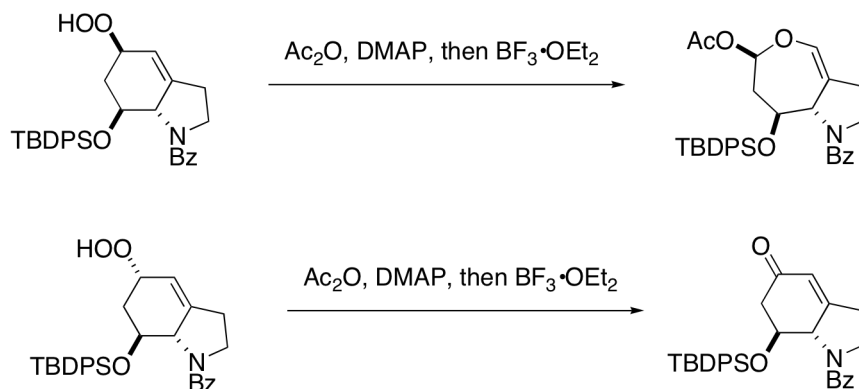
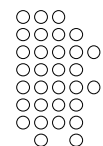
- Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541.

Waller, D. L.; Stephenson, C. R. J.; Wipf, P., "Spiroketal via oxidative rearrangement of enol ethers." *Org. Biomol. Chem.* **2007**, *5*, 58-60.

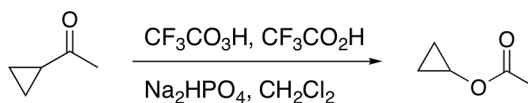
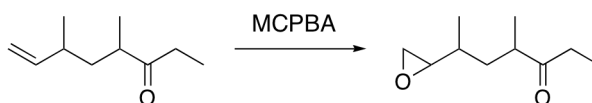
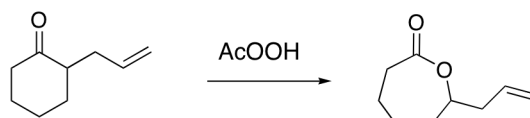


Mechanism:

The bond antiperiplanar to the dissociating peroxide bond is always the bond that migrates, even when electronically disfavored from doing so (Goodman, R. M.; Kishi, Y., "Experimental support for the primary stereoelectronic effect governing Baeyer-Villiger oxidation and Criegee rearrangement." *J. Am. Chem. Soc.* **1998**, *120*, 9392).



When an alkene and a carbonyl are present in the same molecule, an increase in the acidity of the medium favors attack at the carbonyl. Acid-catalyzed side reactions can be suppressed by a phosphate buffer.



Jacobi, P. A.; Herradura, P., "Enantioselective syntheses of (+)- and (-)-blastmycinolactol." *Tetrahedron Lett.* **1997**, *38*, 6621-6624. *Syn*-selective Nicholas-Schreiber condensation. The methyl ketone was unreactive to the usual reagents, including MCPBA, AcOOH, $\text{CF}_3\text{CO}_3\text{H}$, and $\text{PhSe}(\text{O})\text{OH}/\text{H}_2\text{O}_2$. The best results were obtained using bis(trimethylsilyl)peroxide $[(\text{TMSO})_2]$, which was initially introduced by Noyori for the chemoselective oxidation of ketones in the presence of alkene double bonds.



Aldehydes usually give acids, with the exception of electron-rich aldehydes. Migration occurs with retention of configuration.

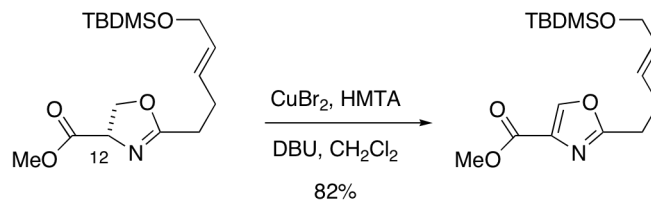
- Wipf, P.; Jung, J.-K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 764.
(An example for a Dakin reaction)



Dehydrogenations

Cyclohexadienes: Corey, E. J.; Lazerwith, S. E., "A direct and efficient stereocontrolled synthetic route to the pseudopterosins, potent marine antiinflammatory agents." *J. Am. Chem. Soc.* **1998**, *120*, 12777.

Oxazolines: Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558;
Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.



Kraus, G. A.; Choudhury, P. K., "The first synthesis of cynandione A." *Synthesis* **2005**, 703-704.



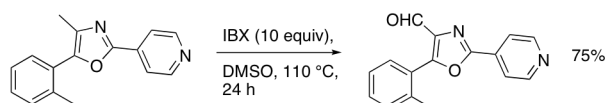
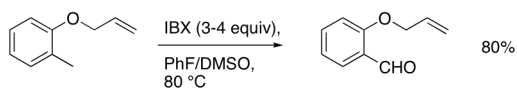
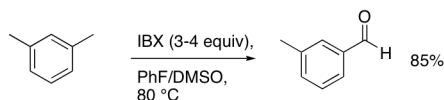
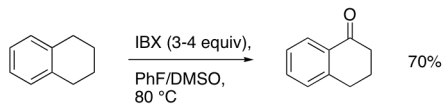
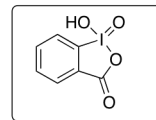
Allylic Oxidations

Limanto, J.; Snapper, M. L., "Sequential intramolecular cyclobutadiene cycloaddition ring-opening metathesis, and Cope rearrangement: Total syntheses of (+)- and (-)-asteriscanolide." *J. Am. Chem. Soc.* **2000**, *122*, 8071-8072.



Benzylic Oxidations

Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L., "Selective oxidation at carbon adjacent to aromatic systems with IBX." *J. Am. Chem. Soc.* **2001**, *123*, 3183-3185.



Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R., "The first stereoselective total synthesis of quinine." *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.



Ozonolysis

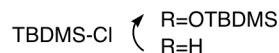
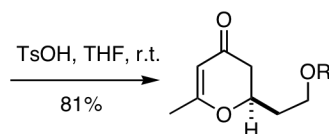
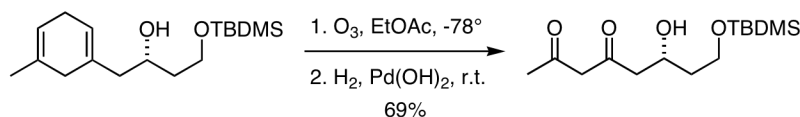
According to the Criegee mechanism, 1,3-dipolar cycloaddition gives a 1,2,3-trioxolane product that rearranges to a 1,2,4-trioxolane (the *ozonide*) by fragmentation into a ketone and a carbonyl oxide followed by a second dipolar addition. In addition to catalytic hydrogenation, LAH, NaBH₄, Zn/AcOH, and Me₂S/MeOH can be used to decompose the ozonide.

1,3-Dipolarophiles, such as ketones, methyl formate, phenanthrene quinone and methyl pyruvate have been employed to trap the carbonyl oxides to give tri- and tetra-substituted ozonides. The goal of these trapping experiments is simply to prepare the ozonides which are difficult to obtain by normal procedures (*Tetrahedron* **1997**, *53*, 5217-5232).

Alkenes can usually be ozonized in the presence of alkynes (since ozone is an electrophilic reagent, it actually prefers alkenes). Non-compatible functional groups are:

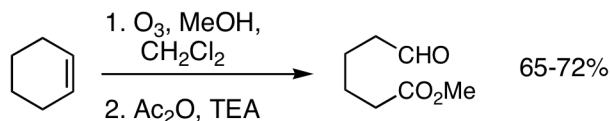
- anilines and other electron-rich aromatic rings.
- thioethers and phosphines
- hydrazones, oximes, enamines

Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558; Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157.



The nonoxidative decomposition of cyclohexene ozonide gives an aldehyde-carboxylate.

- Clause, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

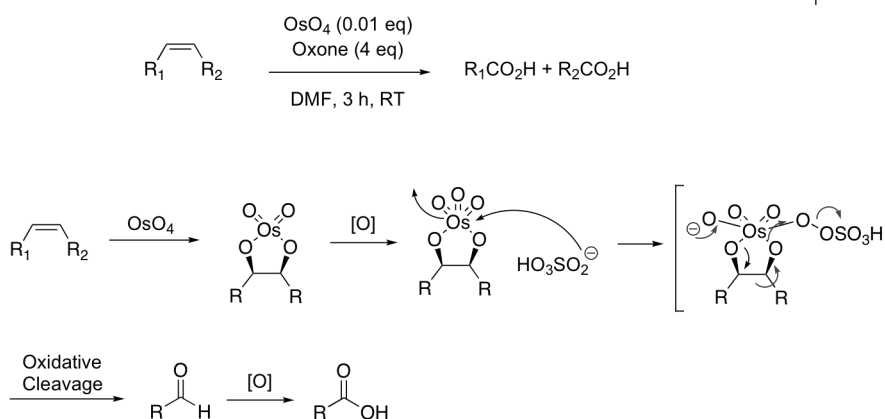


-Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.
The ozonolysis of alkenes in methanolic NaOH or NaOMe with CH_2Cl_2 as a cosolvent leads directly to methyl esters.



-Pyridine serves to attenuate the reactivity of ozone toward electron-rich functional groups such as a PMB-ether:
-Schreiber, S. L. et al. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

Travis, B. R.; Narayan, R. S.; Borhan, B., "Osmium tetroxide-promoted catalytic oxidative cleavage of olefins: An organometallic ozonolysis." *J. Am. Chem. Soc.* **2002**, *124*, 3824-3825.



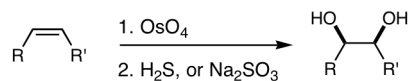
Dihydroxylation Reactions

Noe, M. C.; Letavic, M. A.; Snow, S. L. "Asymmetric dihydroxylation of alkenes."

Org. React. **2005**, *66*, 109-625.

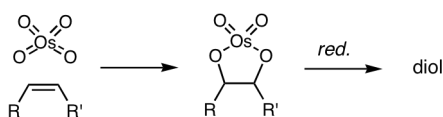
Drudis-Sol, G.; Ujaque, G.; Maseras, F.; Lled, A. "Enantioselectivity in the dihydroxylation of alkenes by osmium complexes." *Top. Organomet. Chem.* **2005**, *12*, 79-107.

cis-Dihydroxylation of alkenes (rep. in 1908):

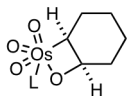


Mech.
:

Criegee:



alternative: [2+2]

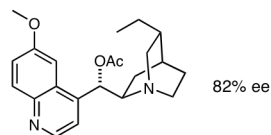
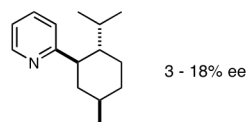
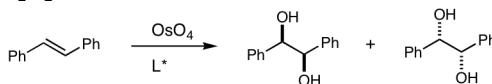


L = py: rate-enhancing
or: chiral ligand

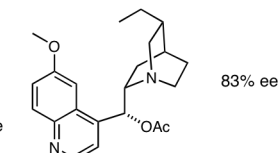
cat. OsO₄; co-oxidant: TBHP, NMO (Upjohn process), K₃Fe(CN)₆ - K₂CO₃.

For the use of a flavin analogue with NMM/H₂O₂ in the Upjohn process, see: Bergstad, K.; Jonsson, S. Y.; Bäckvall, J.-E., "A new coupled catalytic system for dihydroxylation of olefins by H₂O₂." *J. Am. Chem. Soc.* **1999**, *121*, 10424-10425.

chiral ligands:



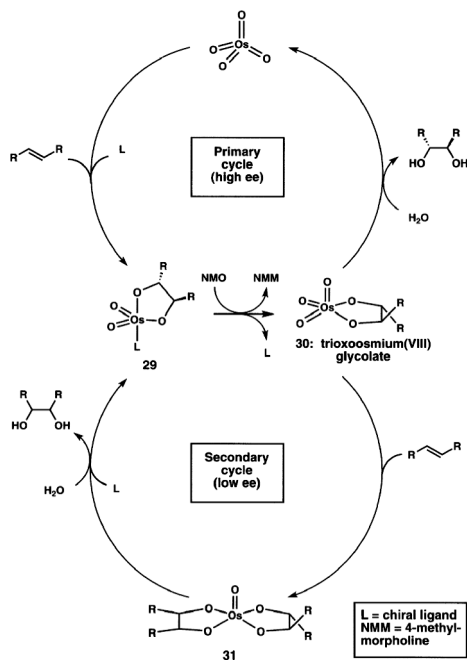
pseudo-enantiomers



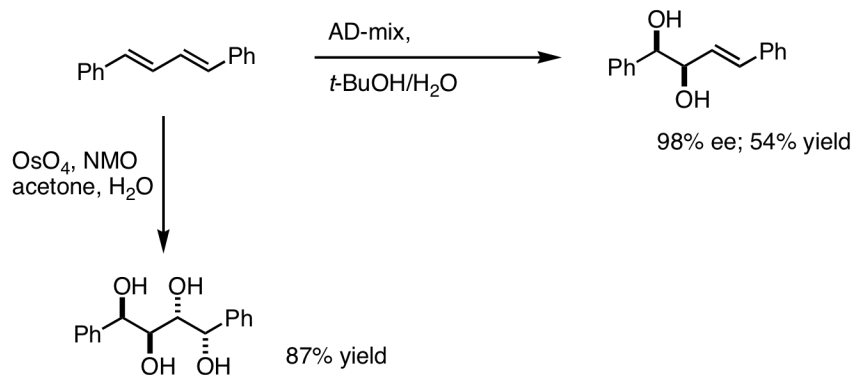
Sharpless Asymmetric Dihydroxylations (SAD)

Chem. Rev. **1994**, *94*, 2483. The two catalytic cycles for AD using NMO as a stoichiometric oxidant; in a monophasic layer, the secondary cycle is fast and decreases ee; in a biphasic layer, dihydroxylation is slower but proceeds with good ee.

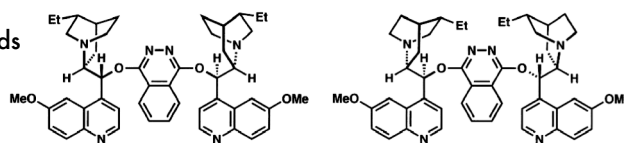
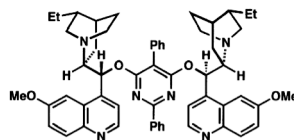
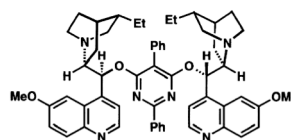
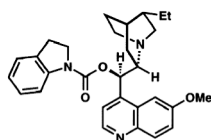
SAAH: O'Brien, P. "Sharpless asymmetric aminohydroxylation: Scope, limitations, and use in synthesis." *Angew. Chem., Int. Ed.* **1999**, *38*, 326-329.



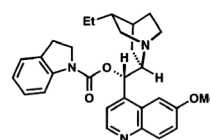
Example from Karl Hale's work:



Alkaloid ligands

32: (DHQ)₂PHAL33: (DHQD)₂PHAL34: (DHQ)₂PYR35: (DHQD)₂PYR

36: (DHQ)IND



37: (DHQD)IND

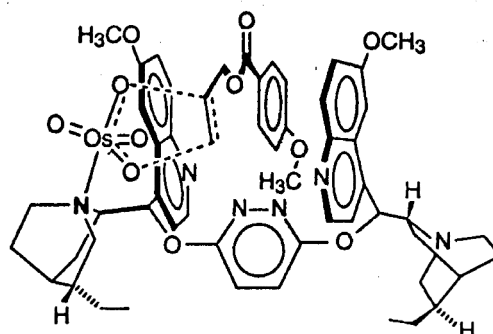
reagents	(DHQ) ₂ PHAL	(DHQD) ₂ PHAL	K ₂ OsO ₂ (OH) ₄	K ₃ Fe(CN) ₆	K ₂ CO ₃
AD-mix α	5.52 g	--	0.52 g	700.0 g	294.0 g
AD-mix β	--	5.52 g	0.52 g	700.0 g	294.0 g



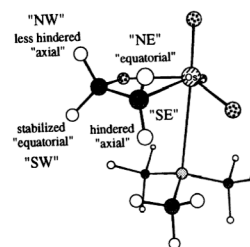
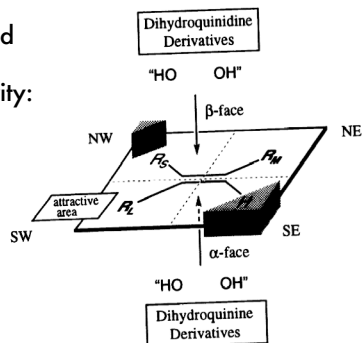
Mechanism(s):

For discussions of possible mechanisms, see: C&EN, November 3, 1997, 23-26 and *J. Am. Chem. Soc.* **1997**, 119, 9907.

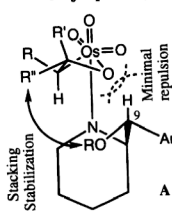
One hypothesis: Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, 118, 319.



Mnemonic device and rationalization for enantiofacial selectivity:

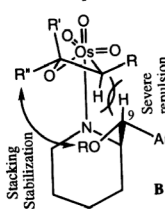


Major pathway



Best isomer (A), leads to (*R*)-diol, good attractive stabilization and minimal repulsion

Minor pathway



Steric repulsion destabilizes this isomer (B), an (*S*)-diol precursor



- Keinan, E. et al. *J. Am. Chem. Soc.* **1993**, *115*, 4891.