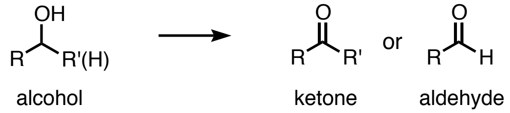
General Introductory References

March, J. In *Advanced Organic Chemistry*, John Wiley and Sons: New York, **1992**, p. 1158–1238.
Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B*, Plenum Press: New York, **1990**, p. 615–664.
Carruthers, W. In *Some Modern Methods of Organic Synthesis 3rd Ed.*, Cambridge University Press: Cambridge, UK, **1987**, p. 344–410.

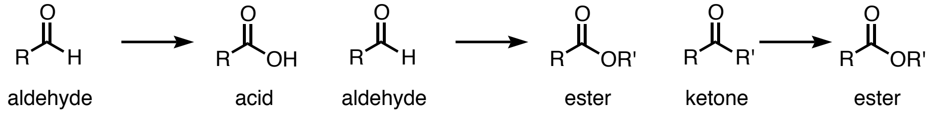
Oxidation States of Organic Functional Groups

The notion of oxidation state is useful in categorizing many organic transformations. This is illustrated by the progression of a methyl group to a carboxylic acid in a series of 2-electron oxidations, as shown at right. Included are several functional group equivalents considered to be at the same oxidation state.

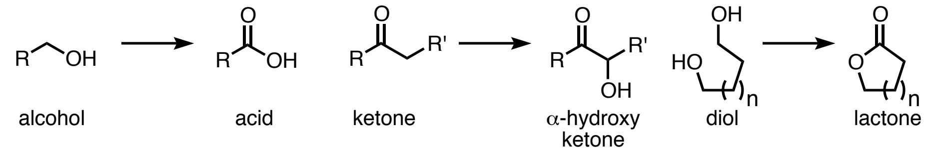
Summary of Reagents for Oxidative Functional Group Interconversions:



- Dimethylsulfoxide-Mediated Oxidations
- Dess-Martin Periodinane (DMP)
- *o*-Iodoxybenzoic Acid (IBX)
- tetra-*n*-Propylammonium Perruthenate (TPAP)
- *N*-Oxoammonium-Mediated Oxidation
- Manganese Dioxide
- Barium Manganate
- Oppenauer Oxidation
- Chromium (VI) Oxidants
- Sodium Hypochlorite
- *N*-Bromosuccinimide (NBS)
- Bromine
- Cerium (IV) Oxidants



Sodium Chlorite Silver Oxide Potassium Permanganate Pyridinium Dichromate (PDC)	Manganese Dioxide–NaCN–CH_3OH Bromine	Bayer-Villiger Oxidation



Ruthenium Tetroxide O_2/Pt Jones Oxidation	Form enolate; Davis Oxaziridine Form enolate; MoOPH Form silyl enol ether; mCPBA	Fetizon's Reagent O_2/Pt *N*-Oxoammonium-Mediated Oxidation

Alkane R-CH_3

organoboranes RCH_2BR_2'
organometallics in general RCH_2M (M = Li, MgX, ZnX...)
organosilanes RCH_2SiR_3'

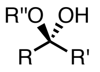
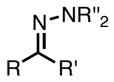
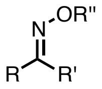
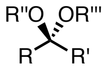
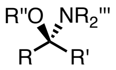
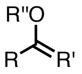
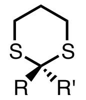
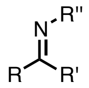
↓

Alcohol R-CH_2OH (R-CH_2X)

alkyl halide X = halide
alkane sulfonate X = OSO_2R'
alkyl azide X = N_3
alkylamine X = NR'_2
alkylthio ether X = SR'
alkyl ether X = OR'

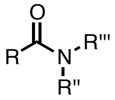
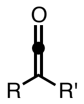
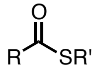
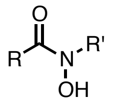
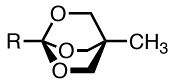
↓

Aldehyde (Ketone) R-CHO (RCOR')

hemiketal (hemiacetal) 
hydrazone 
oxime 
ketal (acetal) 
geminal dihalide RCX_2R'
aminal 
enol ether (enamine) 
dithiane 
imine 

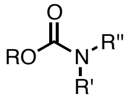
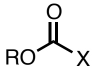
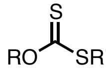
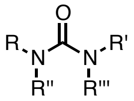
↓

Carboxylic Acid R-CO_2H

ester RCO_2R'
amide 
ketene 
thioester 
trihalomethyl RCX_3
nitrile R–C≡N
hydroxamic acid 
orthoester  (OBO ester shown)

↓

Carbonic Acid Ester ROH + CO_2 ($ROCO_2H$)

carbamate 
alkyl haloformate 
xanthate 
isocyanate R–N=C=O
carbodiimide R–N=C=N–R'
urea 

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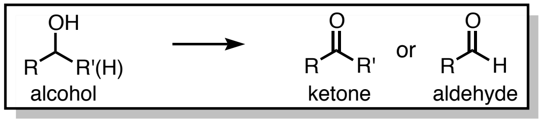


Dimethylsulfoxide-Mediated Oxidations

- Reviews

Lee, T. V. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 291–303.

Tidwell, T. T. *Synthesis* **1990**, 857–870.

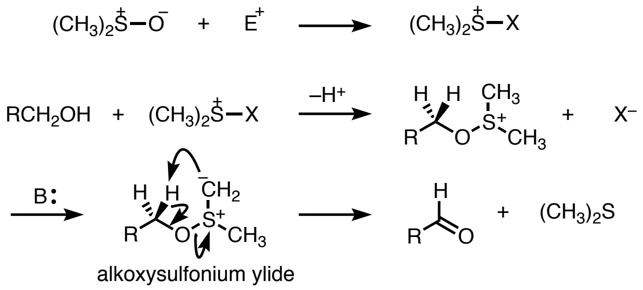
Tidwell, T. T. *Organic Reactions* **1990**, *39*, 297–557.

General Mechanism

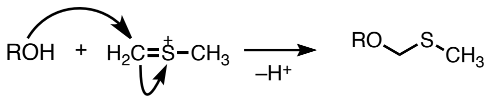
- Dimethylsulfoxide (DMSO) can be activated by reaction with a variety of electrophilic reagents, including oxalyl chloride, dicyclohexylcarbodiimide, sulfur trioxide, acetic anhydride, and *N*-chlorosuccinimide.

- The mechanism can be considered generally as shown, where the initial step involves electrophilic (E^+) attack on the sulfoxide oxygen atom.

- Subsequent nucleophilic attack of an alcohol substrate on the activated sulfoxonium intermediate leads to alkoxysulfonium salt formation. This intermediate breaks down under basic conditions to furnish the carbonyl compound and dimethyl sulfide.

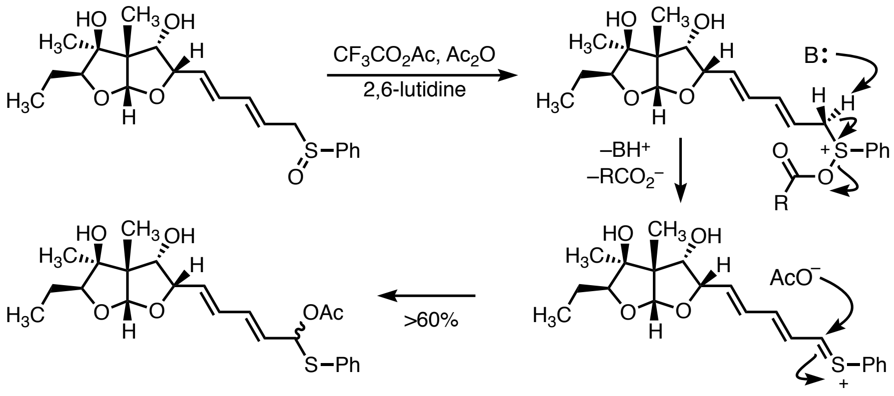


- Methylthiomethyl (MTM) ether formation can occur as a side reaction, by nucleophilic attack of an alcohol on methyl(methylene)sulfonium cations generated from the dissociation of sulfonium ylide intermediates present in the reaction mixture. This type of transformation is related to the Pummerer Rearrangement.



Fenselau, A. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762–1765.

- Pummerer Rearrangement



Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186–4188.

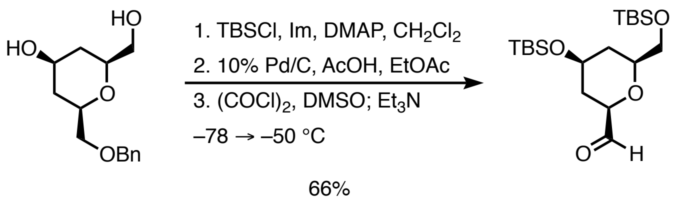
Swern Procedure

- Typically, 2 equivalents of DMSO are activated with oxalyl chloride in dichloromethane at or below –60 °C.

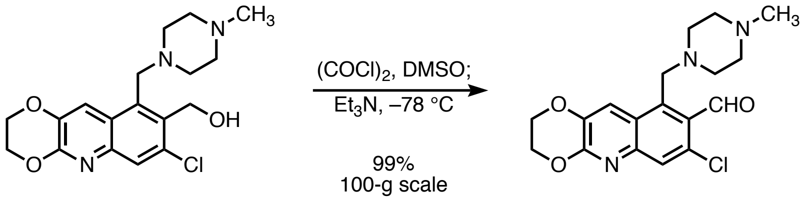
- Subsequent addition of the alcohol substrate and triethylamine leads to carbonyl formation.

- The mild reaction conditions have been exploited to prepare many sensitive aldehydes. Careful optimization of the reaction temperature is often necessary.

Huang, S. L.; Mancuso, A. J.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.



Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2354–2359.



Fang, F. G.; Bankston, D. D.; Huie, E. M.; Johnson, M. R.; Kang, K.-C.; LeHoullier, C. S.; Lewis, G. C.; Lovelace, T. C.; Lowery, M. W.; McDougald, D. L.; Meetholz, C. A.; Partridge, J. J.; Sharp, M. J.; Xie, S. *Tetrahedron* **1997**, *53*, 10953–10970.

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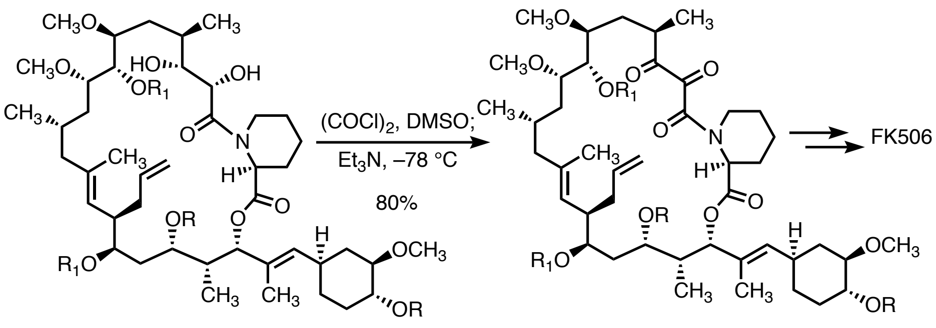
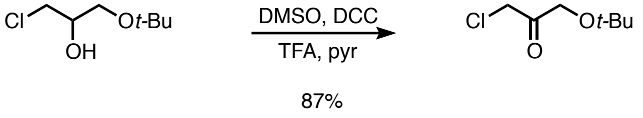


R = TIPS, R_1 = TBS

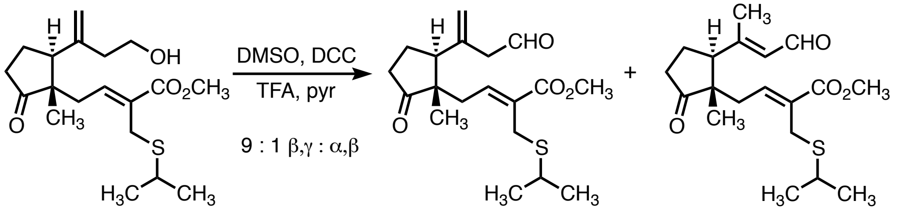
Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998–3017.

Pfitzner-Moffatt Procedure

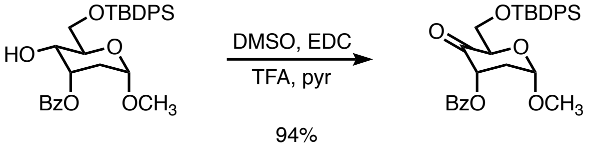
- The first reported DMSO-based oxidation procedure.
- Dicyclohexylcarbodiimide (DCC) functions as the electrophilic activating agent in conjunction with a Brønsted acid promoter.
- Typically, oxidations are carried out with an excess of DCC at or near 23 °C.
- Separation of the by-product dicyclohexylurea and MTM ether formation can limit usefulness.
- Alternative carbodiimides that yield water-soluble by-products (e.g., 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)) can simplify workup procedures.



Corey, E. J.; Kim, C. U.; Misco, P. F. *Org. Synth. Coll. Vol. VI* **1988**, 220–222.



Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565–5576.



EDC = $(CH_3)_2N{-}(CH_2)_3{-}N{=}C{=}N{-}CH_2CH_3 \cdot HCl$

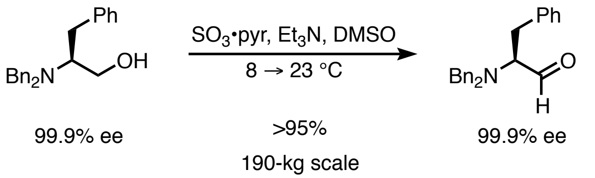
Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1981**, *59*, 870–877.

Parikh-Doering Procedure

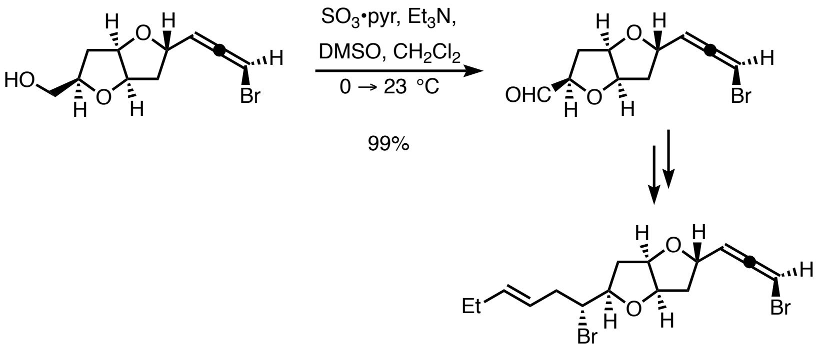
- Sulfur trioxide-pyridine is used to activate DMSO.
- Ease of workup and at-or-near ambient reaction temperatures make the method attractive for large-scale reactions.

Parihk, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

- Examples



Liu, C.; Ng, J. S.; Behling, J. R.; Yen, C. H.; Campbell, A. L.; Fuzail, K. S.; Yonan, E. E.; Mehrotra, D. V. *Org. Process Res. Dev.* **1997**, *1*, 45–54.



(–)-kumausallene

Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3175–3177.

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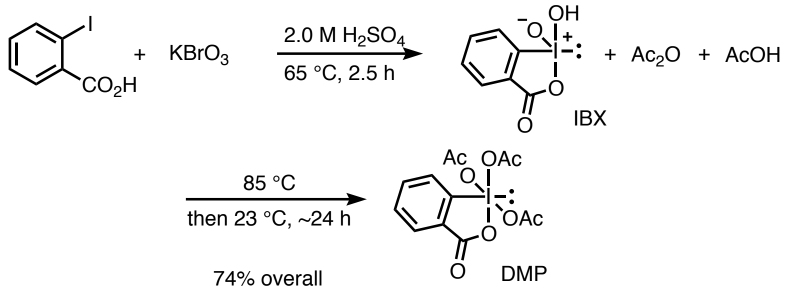
Dess-Martin Periodinane (DMP)

- DMP has found wide utility in the preparation of sensitive, highly functionalized molecules.
- DMP oxidations are characterized by short reaction times, use of a single equivalent of oxidant, and can be moderated with regard to acidity by the incorporation of additives such as pyridine.
- DMP and its precurser *o*-iodoxybenzoic acid (IBX) are potentially heat and shock sensitive and should be handled with appropriate care.

Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *48*, 4155–4156.

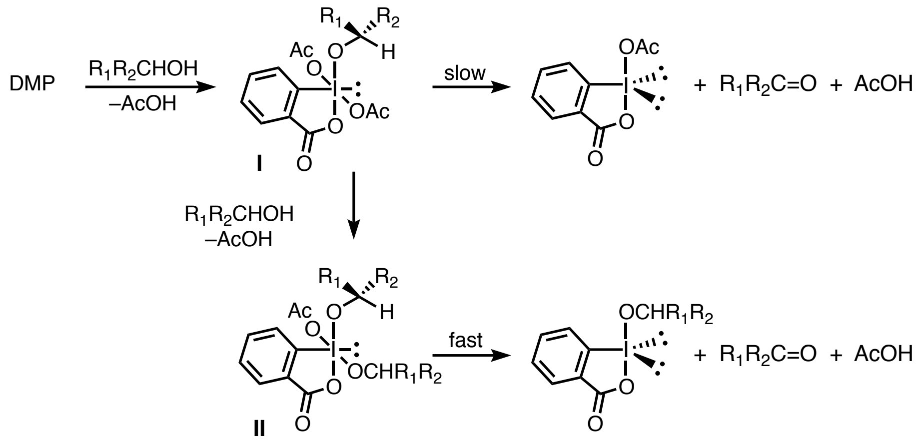
Boeckman, R. K.; Shao, P.; Mulins, J. J. *Org. Synth.* **1999**, *77*, 141–152.

Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, July 16, 3.



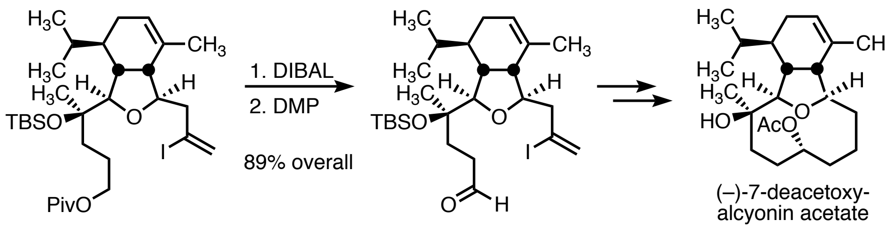
- Addition of one equivalent of water has been found to accelerate the alcohol oxidation reaction with DMP, perhaps due to the formation of an intermediate analogous to **II**. It is proposed that the decomposition of **II** is more rapid than the initially formed intermediate **I**:

Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

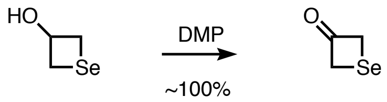


Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

- Examples

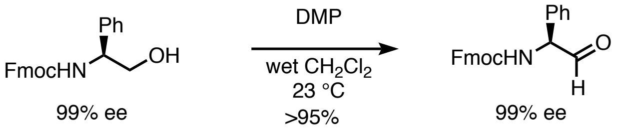


Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683–2686.



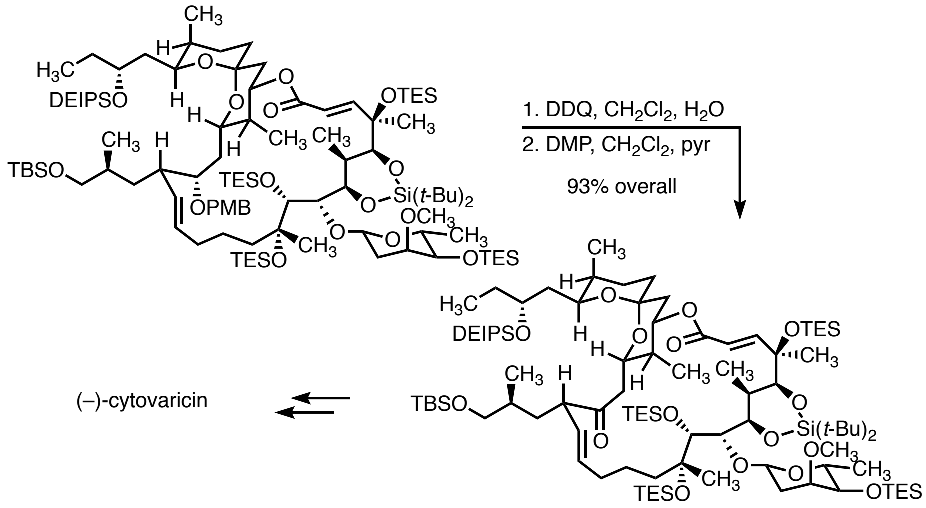
Polson, G.; Dittmer, D. C. *J. Org. Chem.* **1988**, *53*, 791–794.

- For the synthesis of sensitive α-amino aldehydes from the corresponding alcohols, the use of DMP suppresses epimerization.



Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359–1362.

- Use of other oxidants in the following example led to conjugation of the β,γ-unsaturated ketone, which did not occur when DMP was used.



Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

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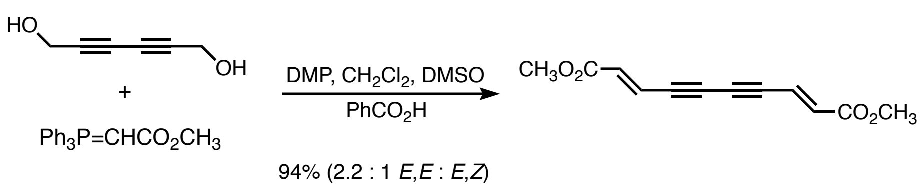
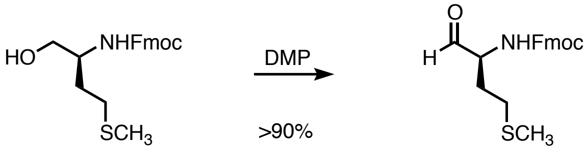
- DMP oxidation in the presence of phosphorous ylides allows for the trapping of sensitive aldehydes.

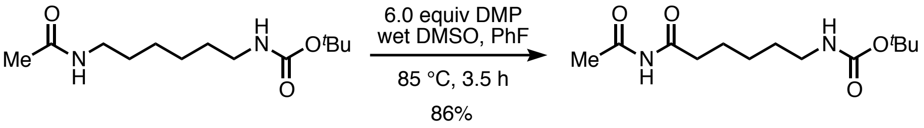


Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376–9378.



Myers, A. G.; Zhong, B.; Kung, D. W.; Movassaghi, M.; Lanman, B. A.; Kwon, S. *Org. Lett.* **2000**, *2*, 3337–3340.

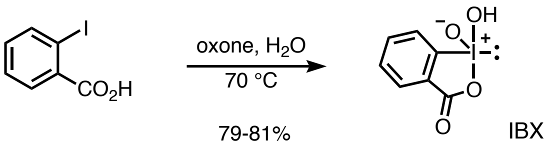
- DMP has been used to oxidize secondary acyclic and macrocyclic amides to the corresponding imides in moist DMSO/fluorobenzene at elevated temperature.



Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992–5997.

o-Iodoxybenzoic Acid (IBX)

- The DMP precursor IBX is gaining use as a mild reagent for the oxidation of alcohols.
- A simpler preparation of IBX has been reported.

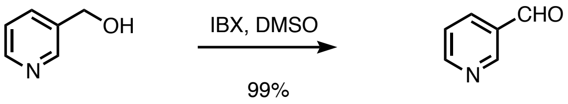


Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

- IBX is used as a mild reagent for the oxidation of 1,2-diols without C-C bond cleavage.

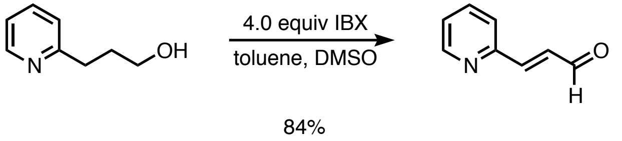
Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

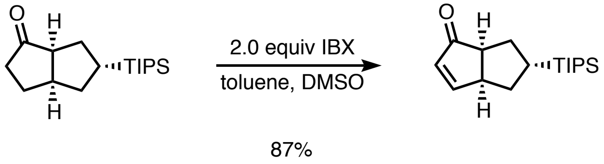
- Pyridines are not oxidized at a rate competitive with the oxidation of a primary alcohol.

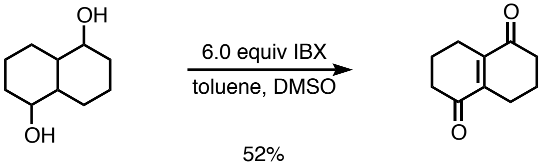


Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

- IBX has been shown to form α,β-unsaturated carbonyl compounds from the corresponding saturated alcohol or carbonyl compound.
- The reproducibility of the results of this and related IBX-mediated oxidations has been found to often depend on the presence of water in the IBX employed (for a discussion, see: http://blog-syn.blogspot.com/2013/03/blog-syn-003a-secret-ingredient.html)







Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.

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tetra-*n*-Propylammonium Perruthenate (TPAP): $Pr_4N^+RuO_4^-$

- Reviews

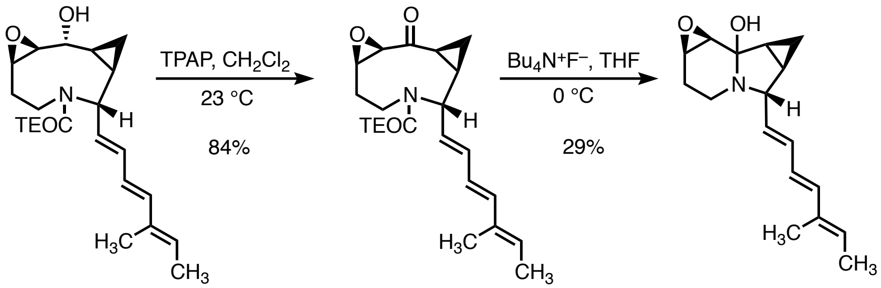
Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.

- Ruthenium tetroxide (RuO_4, Ru(VIII)) and, to a lesser extent, the perruthenate ion (RuO_4^-, Ru(VII)) are powerful and rather nonselective oxidants.
- However, perruthenate salts with large organic counterions prove to be mild and selective oxidants in a variety of organic solvents.
- In conjunction with a stoichiometric oxidant such as *N*-methylmorpholine-*N*-oxide (NMO), TPAP oxidations are catalytic in ruthenium, and operate at room temperature. The reagents are relatively non-toxic and non-hazardous.
- To achieve high catalytic turnovers, the addition of powdered molecular sieves (to remove both the water present in crystalline NMO and the water formed during the reaction) is essential.
- The following oxidation state changes have been proposed to occur during the reaction:

$$\begin{aligned} \text{Ru(VII)} + 2e^- &\rightarrow \text{Ru(V)} \\ 2\text{Ru(V)} &\rightarrow \text{Ru(VI)} + \text{Ru(IV)} \\ \text{Ru(VI)} + 2e^- &\rightarrow \text{Ru(IV)} \end{aligned}$$

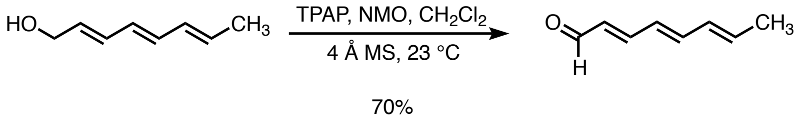
Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

- Examples

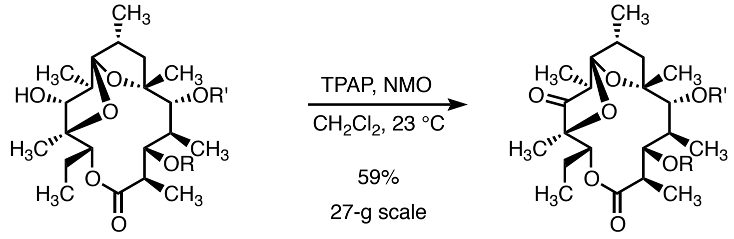


(±)-indolizomycin

Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30–39.

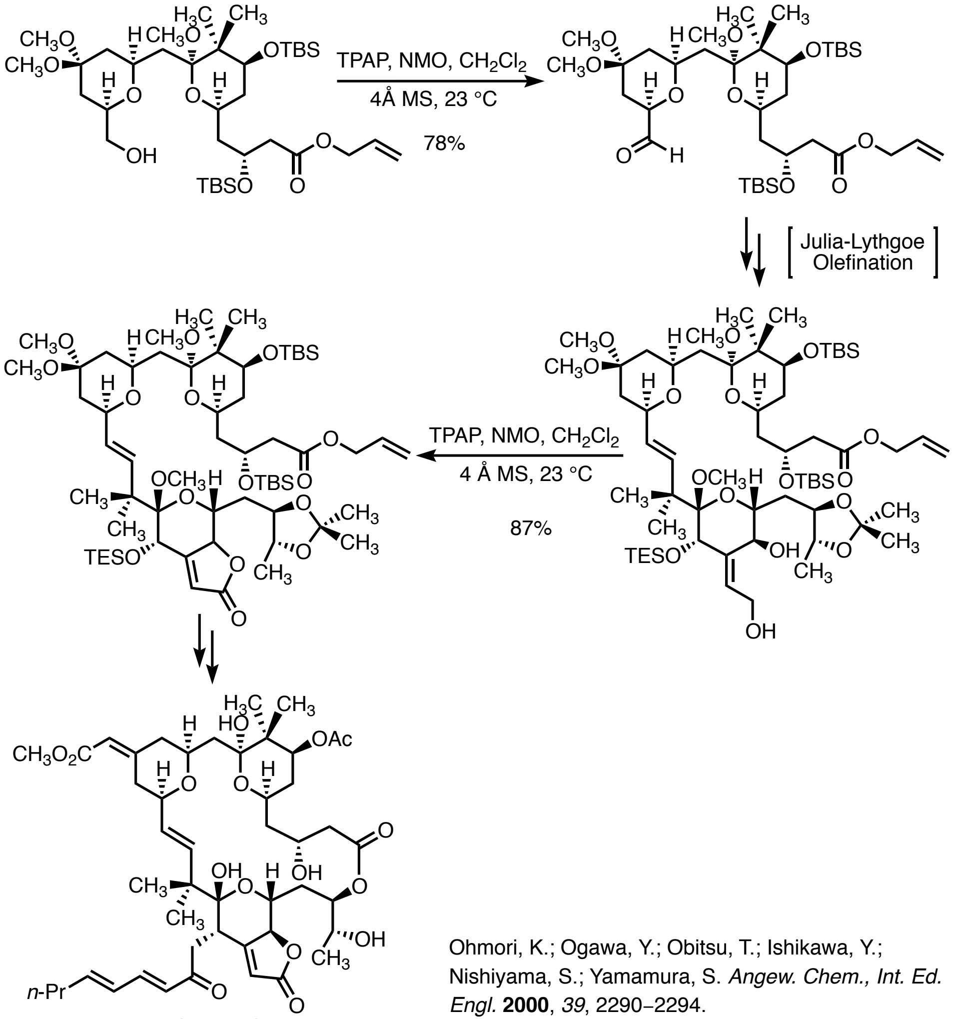


Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145–1174.



R = cladinose, R' = 3-*N'*-demethyl-3'-*N*-phenylsulfonyl desosamine

Jones, A. B. *J. Org. Chem.* **1992**, *57*, 4361–4367.



bryostatin 3

Ohmori, K.; Ogawa, Y.; Obitsu, T.; Ishikawa, Y.; Nishiyama, S.; Yamamura, S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2290–2294.

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N-Oxoammonium-Mediated Oxidation

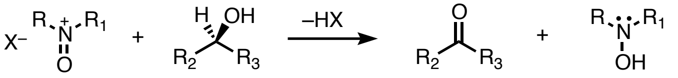
- Reviews

de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.

Bobbitt, J. M.; Flores, C. L. *Heterocycles* **1988**, *24*, 509–533.

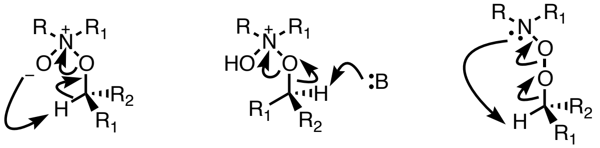
Rozantsev, E. G.; Sholle, V. D. *Synthesis* **1971**, 401–414.

- *N*-Oxoammonium salts are mild and selective oxidants for the conversion of primary and secondary alcohols to the corresponding carbonyl compounds. These oxidants are unstable and are invariably generated in situ in a catalytic cycle using a stable, stoichiometric oxidant.



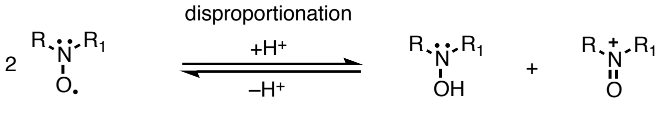
N-oxoammonium salt

- Three possible transition states have been proposed:



Ganem, B. *J. Org. Chem.* **1975**, *40*, 1998–2000.
Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A. *Tetrahedron Lett.* **1986**, *27*, 1119–1122.
Bobbitt, J. M.; Ma, Z. *J. Org. Chem.* **1991**, *56*, 6110–6114.

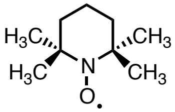
- *N*-Oxoammonium salts may be formed in situ by the acid-promoted disproportionation of nitroxyl radicals. Alternatively, oxidation of a nitroxyl radical or hydroxyl amine can generate the corresponding *N*-oxoammonium salt.



nitroxyl radical

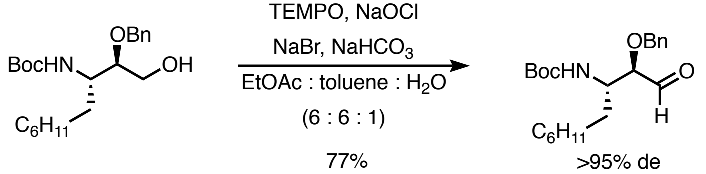
Golubev, V. A.; Sen', V. D.; Kulyk, I. V.; Aleksandrov, A. L. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1975**, 2119–2126.

- 2,2,6,6-Tetramethyl-1-piperidinyloxyl (TEMPO) catalyzes the oxidation of alcohols to aldehydes and ketones in the presence of a variety of stoichiometric oxidants, including *m*-chloroperoxybenzoic acid (*m*-CPBA), sodium hypochlorite (NaOCl), [bis(acetoxy)-iodo]benzene (BAIB), sodium bromite ($NaBrO_2$), and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).



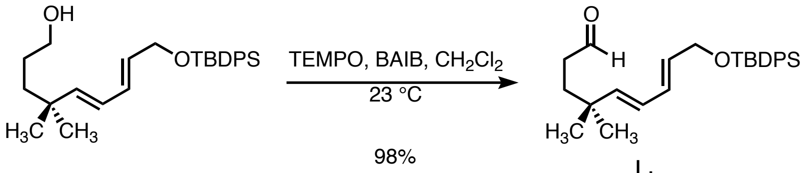
TEMPO

- Examples

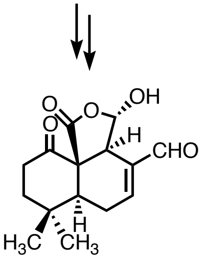


Leanna, R. M.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029–5032.

See also: Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gryza, H.; Prokopoxicz, P. *Tetrahedron* **1998**, *54*, 6051–6064.

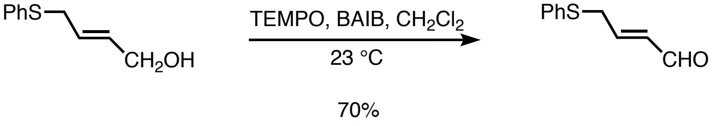


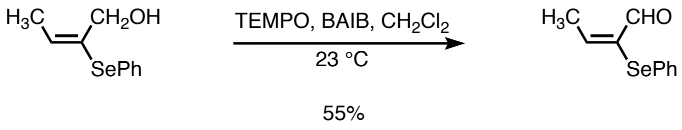
Jauch, J. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2764–2765.



kuehneromycin A

- Selective oxidation of allylic alcohols in the presence of sulfur and selenium has been demonstrated.





De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

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Manganese Dioxide: MnO_2

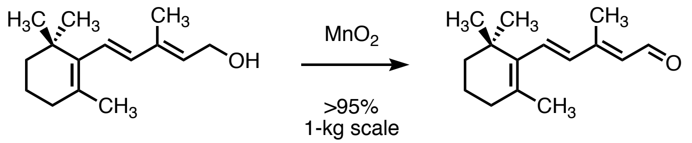
- Reviews

Cahiez, G.; Alami, M. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 231–236.

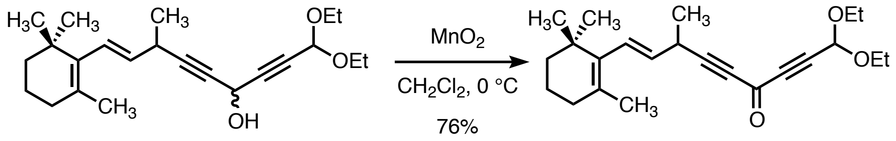
Fatiadi, A. J. *Synthesis* **1976**, 65–104.

Fatiadi, A. J. *Synthesis* **1976**, 133–167.

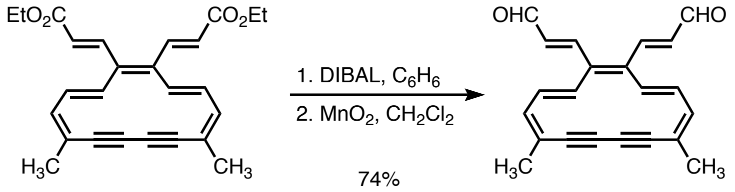
- A heterogenous suspension of active manganese dioxide in a neutral medium can selectively oxidize allylic, benzylic and other activated alcohols to the corresponding aldehyde or ketone.
- The structure and reactivity of active manganese dioxide depends on the method of preparation.
- Active manganese oxides are nonstoichiometric materials (in general MnO_x, $1.93 < x < 2$) consisting of Mn (II) and Mn (III) oxides and hydroxides, as well as hydrated MnO_2.
- Hydrogen-bond donor solvents and, to a lesser extent, polar solvents have been shown to exhibit a strong deactivating effect, perhaps due to competition with the substrate for the active MnO_2 surface.
- Examples



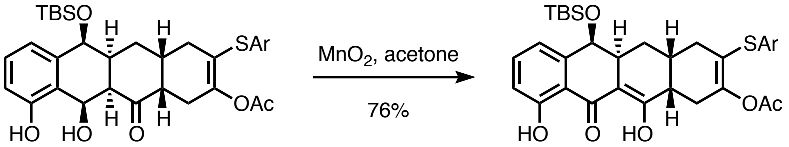
Salman, M.; Babu, S. J.; Kaul, V. K.; Ray, P. C.; Kumar, N. *Org. Process Res. Dev.* **2005**, *9*, 302–305.



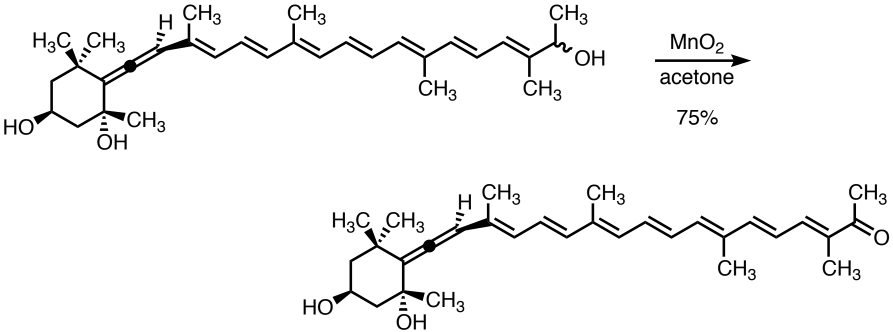
van Amsterdam, L. J. P.; Lugtenburg, J. *J. Chem. Soc., Chem. Commun.* **1982**, 946–947.



Cresp, T. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1975**, 97, 4412–4413.



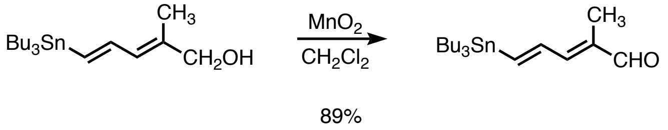
Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252–3265.



paracentrone

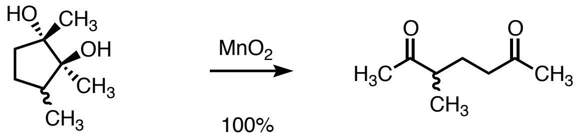
Haugan, J. A. *Tetrahedron Lett.* **1996**, *37*, 3887–3890.

- Vinyl stannanes are tolerated.



Alvarez, R.; Iglesias, B.; Lopez, S.; de Lera, A. R. *Tetrahedron Lett.* **1998**, *39*, 5659–5662.

- Syn or anti vicinal diols are cleaved by MnO_2.



Ohloff, G.; Giersch, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 401–402.

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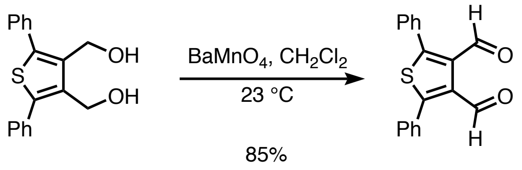
Barium Manganate: $BaMnO_4$

- Review

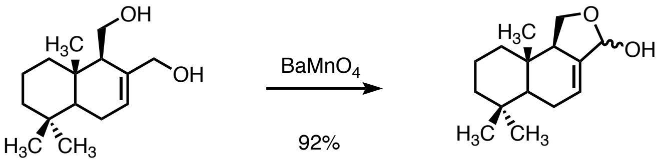
Fatiadi, A. J. *Synthesis* **1987**, 85–127.

- Barium manganate and potassium manganate are deep green salts that can be used without prior activation for the oxidation of primary and secondary allylic and benzylic alcohols.

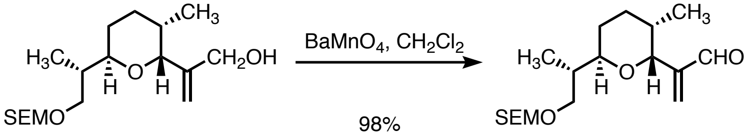
- Examples



Firouzabadi, H.; Mostafavipoor, Z. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 914–917.



Howell, S. C.; Ley, S. V.; Mahon, M. *J. Chem. Soc., Chem. Commun.* **1981**, 507–508.



Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332–347.

Oppenauer Oxidation

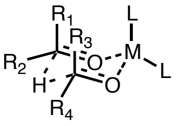
- Review

de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017.

- A classic oxidation method achieved by heating the alcohol to be oxidized with a metal alkoxide in the presence of a carbonyl compound as a hydride acceptor.

- Effectively the reverse of the Meerwein–Pondorff–Verley Reduction.

- The reaction is an equilibrium process and is believed to proceed through a cyclic transition state. The use of easily reduced carbonyl compounds, such as quinone, helps drive the reaction in the desired direction.

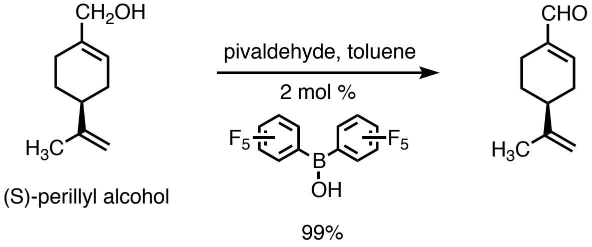


Proposed Transition State

Djerassi, C. *Org. React.* **1951**, *6*, 207.

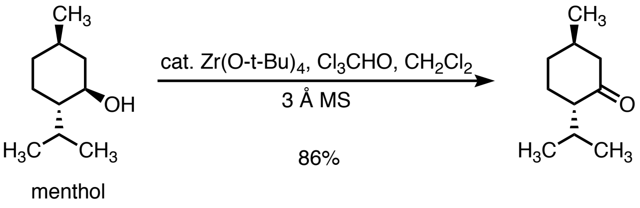
Oppenauer, R. V. *Rec. Trav. Chim. Pays-Bas* **1937**, *56*, 137–144.

- Examples



Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5664–5665.

- Highly reactive zirconium alkoxide catalysts undergo rapid ligand exchange and can be used in substoichiometric quantities.



Krohn, K.; Knauer, B.; Kupke, J.; Seebach, D.; Beck, A. K.; Hayakawa, M. *Synthesis* **1996**, 1341–1344.

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Chromium (VI) Oxidants

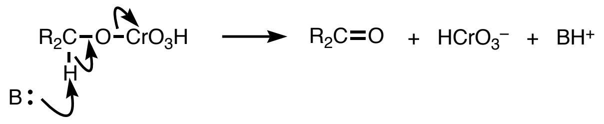
- Reviews

Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 251–289.

Luzzio, F. A. *Organic Reactions* **1998**, *53*, 1–122.

- The mechanism of chromic acid-mediated oxidation has been extensively studied and is commonly used as a model for other chromium-mediated oxidations.

$$R_2CHOH + HCrO_4^- + H^+ \longrightarrow R_2CHOCrO_3H + H_2O$$



Holloway, F.; Cohen, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1951**, *73*, 65–68.

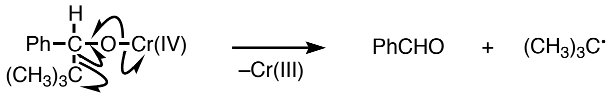
- A competing pathway involving free-radical intermediates has been identified.

$$R_2CHOH + Cr(IV) \longrightarrow R_2\dot{C}OH + Cr(III) + H^+$$
$$R_2\dot{C}OH + Cr(VI) \longrightarrow R_2C{=}O + Cr(V) + H^+$$
$$R_2CHOH + Cr(V) \longrightarrow R_2C{=}O + Cr(III) + 2H^+$$

Wiberg, K. B.; Mukherjee, S. K. *J. Am. Chem. Soc.* **1973**, *96*, 1884–1888.

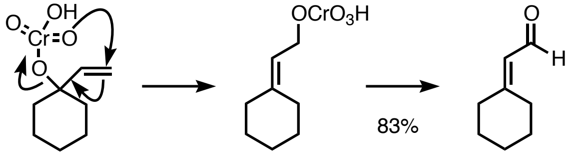
Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1973**, *96*, 1889–1892.

- Fragmentation has been observed with substrates that can form stabilized radicals.



Doyle, M.; Swedo, R. J.; Rocek, J. *J. Am. Chem. Soc.* **1973**, *95*, 8352–8357.

- Tertiary allylic alcohols are known to undergo oxidative transposition.



Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.

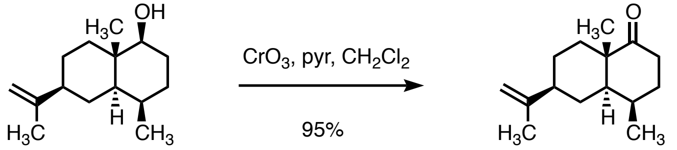
Collins Reagent: $CrO_3 \cdot pyr_2$

- $CrO_3 \cdot pyr_2$ is a hygroscopic red solid which is easily hydrolyzed to the yellow dipyridinium dichromate ($[Cr_2O_7]^{-2}(pyrH^+)_2$).
- Typically, 6 equiv of oxidant in a chlorinated solvent leads to rapid and clean oxidation of alcohols.
- Caution: Collins reagent should be prepared by the portionwise addition of solid CrO_3 to pyridine. Addition of pyridine to solid CrO_3 can lead to a violent reaction.

Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, *30*, 3363–3366.

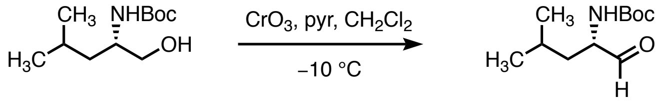
Collins, J. C.; Hess, W. W.; *Org. Synth.* **1972**, *52*, 5–9.

- In situ preparation of the reagent circumvents the difficulty and danger of preparing the pure complex.



Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–4003.

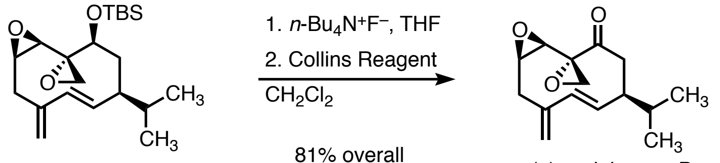
- Examples



>99.5% ee 67% >99.5% ee

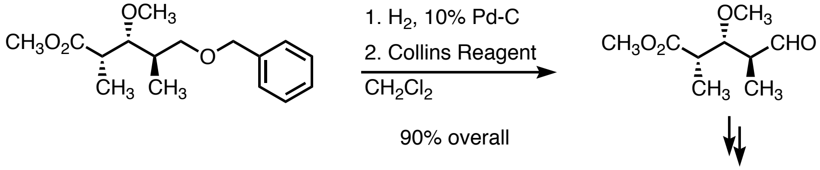
50-g scale

Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016–3018.



(±)-periplanone B

Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493–2495.



(+)-monensin

Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117–2120.

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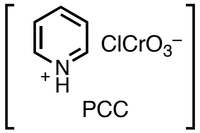
Pyridinium Chlorochromate (PCC, Corey's Reagent)



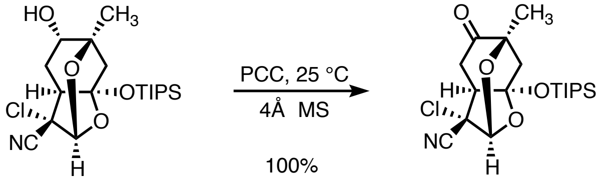
- PCC is an air-stable yellow solid which is not very hygroscopic.
- Typically, alcohols are oxidized rapidly and cleanly by 1.5 equivalents of PCC as a solution in *N*,*N*-dimethylformamide (DMF) or a suspension in chlorinated solvents.
- The slightly acidic character of the reagent can be moderated by buffering the reaction mixture with powdered sodium acetate.

Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *26*, 2647–2650.

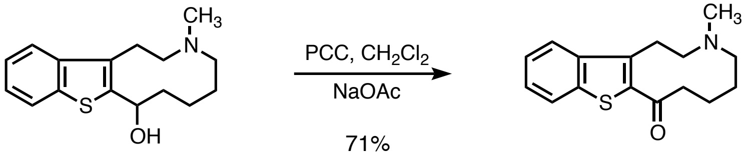
- Addition of molecular sieves can accelerate the rate of reaction.

Antonakis, K.; Egron, M. J.; Herscovici, J. *J. Chem. Soc., Perkin Trans. I* **1982**, 1967–1973.

- Examples

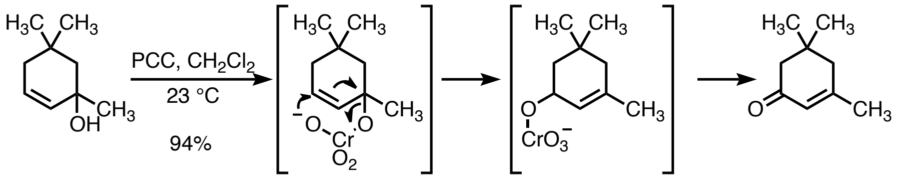


Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871–8872.



Browne, E. J. *Aust. J. Chem.* **1985**, *38*, 756–776.

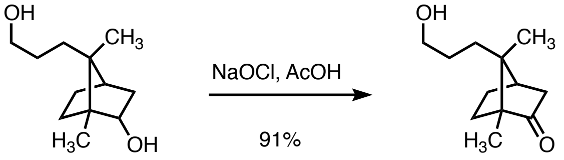
- Treatment of tertiary allylic alcohols with PCC affords enone products via oxidative transposition.



Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.

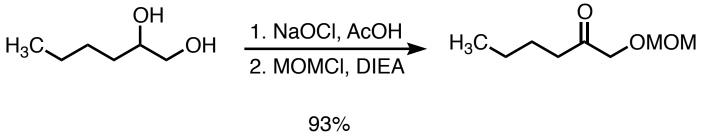
Sodium Hypochlorite: NaOCl

- Sodium hypochlorite in acetic acid solution selectively oxidizes secondary alcohols to ketones in the presence of primary alcohols.
- A modified procedure employs calcium hypochlorite, a stable and easily handled solid hypochlorite oxidant.
- Examples:

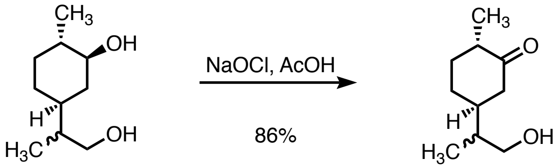


Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647–4650.

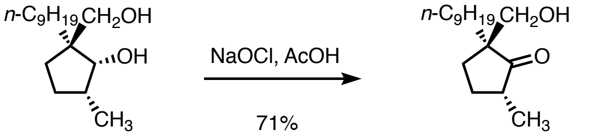
Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 35–38.



Kende, A. S.; Smalley, T. L., Jr.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431–7432.



Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777–12782.



Winter, E.; Hoppe, D. *Tetrahedron* **1998**, *54*, 10329–10338.

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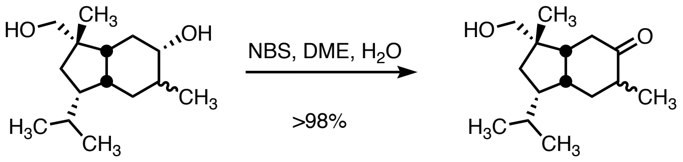
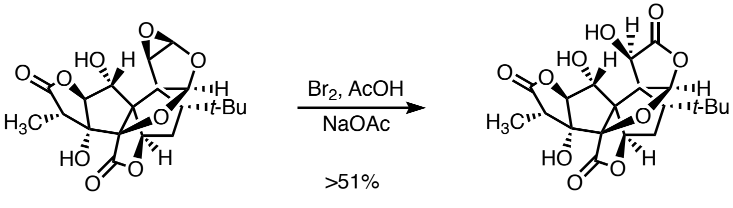
Selective Oxidations Using *N*-Bromosuccinimide (NBS) or Bromine

- NBS in aqueous dimethoxyethane selectively oxidizes secondary alcohols in the presence of primary alcohols.
- Examples:



Corey, E. J.; Ishiguro, M. *Tetrahedron Lett.* **1979**, *20*, 2745–2748.

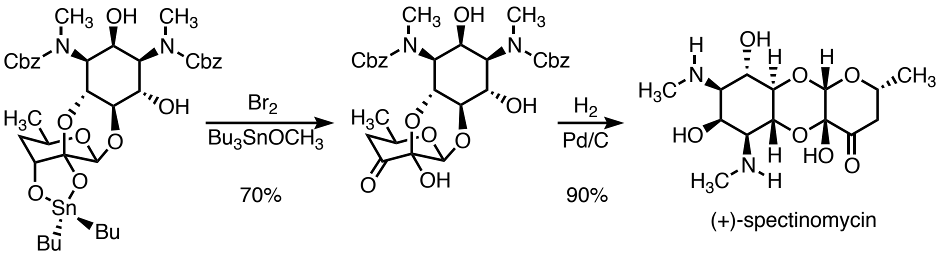
- Bromine has been employed for the selective oxidation of activated alcohols. In the following example, a lactol is oxidized selectively in the presence of two secondary alcohols.



(±)-ginkgolide B

Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453–8463.

- Stannylene acetals are oxidized in preference to alcohols in the presence of bromine:



(+)-spectinomycin

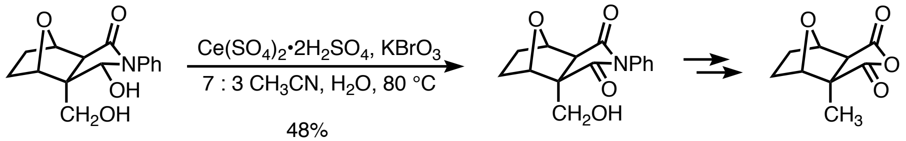
Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839–5841.

Selective Oxidations using Other Methods

- Cerium (IV) complexes catalyze the selective oxidation of secondary alcohols in the presence of primary alcohols and a stoichiometric oxidant such as sodium bromate ($NaBrO_3$).

Tomioka, H.; Oshima, K.; Noxaki, H. *Tetrahedron Lett.* **1982**, *23*, 539–542.

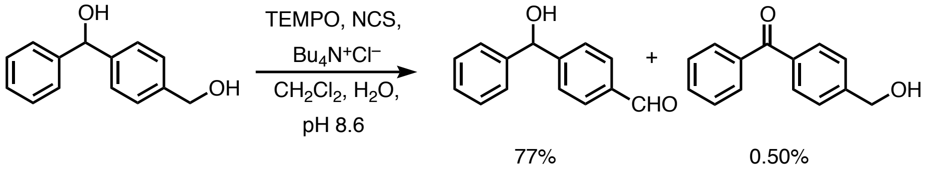
- In the following example, catalytic tetrahydrogen cerium (IV) tetrakissulfate and stoichiometric potassium bromate in aqueous acetonitrile was found to selectively oxidize the secondary alcohol in the substrate whereas NaOCl with acetic acid and NBS failed to give the desired imide.



(±)-palasonin

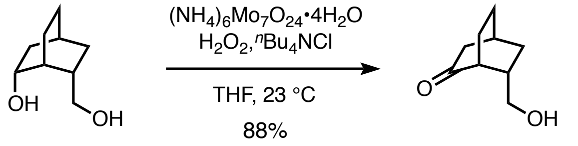
Rydberg, D. B.; Meinwald, J. *Tetrahedron Lett.* **1996**, *37*, 1129–1132.

- TEMPO catalyzes the selective oxidation of primary alcohols to aldehydes in a biphasic mixture of dichloromethane and aqueous buffer (pH = 8.6) in the presence of *N*-chlorosuccinimide (NCS) as a stoichiometric oxidant and tetrabutylammonium chloride ($Bu_4N^+Cl^-$).



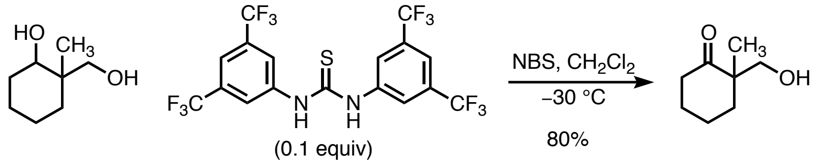
Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452–7454.

- Molybdenum catalysts and H_2O_2 have been used to oxidize secondary alcohols in the presence of primary alcohols:



Trost, B. M.; Masuyama, Y. *Tetrahedron Lett.* **1984**, *25*, 173–176.

- Schreiner's thiourea has been shown to catalyze the selective oxidation of secondary alcohols by NBS:



Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592–1598.

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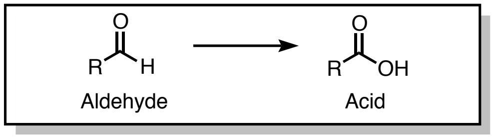


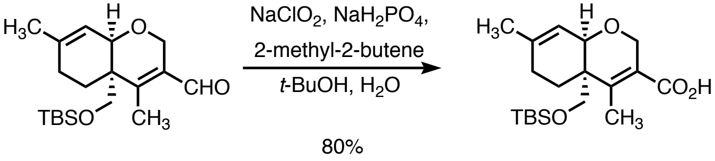
Sodium Chlorite: $NaClO_2$

- Sodium chlorite is a mild, inexpensive, and selective reagent for the oxidation of aldehydes to the corresponding carboxylic acids under ambient reaction conditions.
- 2-methyl-2-butene is often incorporated as an additive and has been proposed to function as a scavenger of any electrophilic chlorine species generated in the reaction.

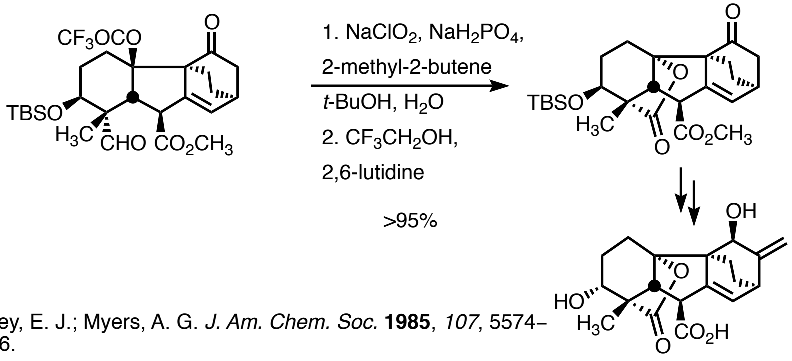
Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888–890.

Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825–4830.

- Examples

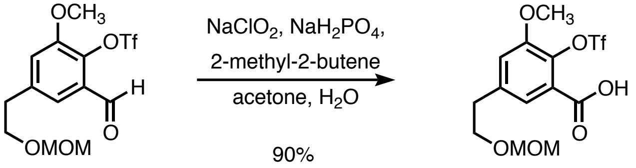


Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825-4830.

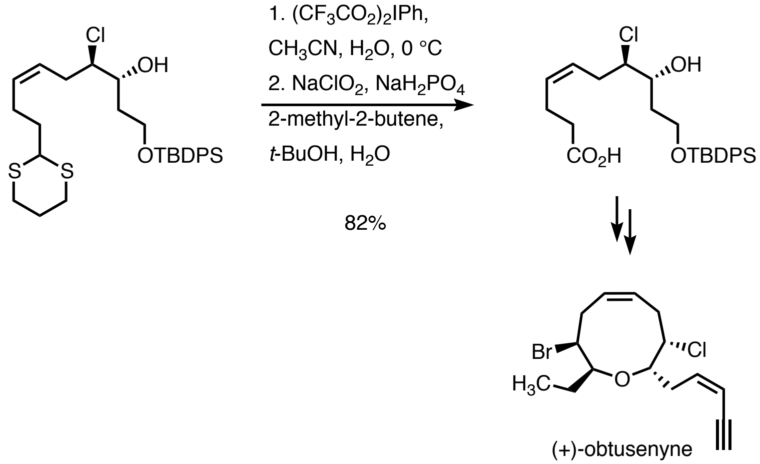


(±)-antheridic acid

Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576.



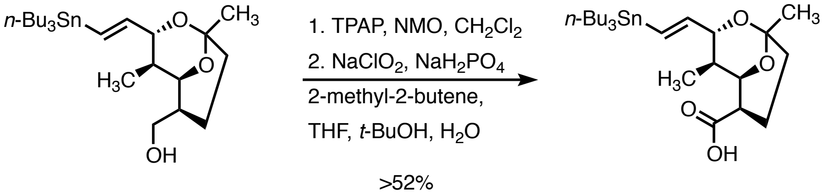
Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004-1015.



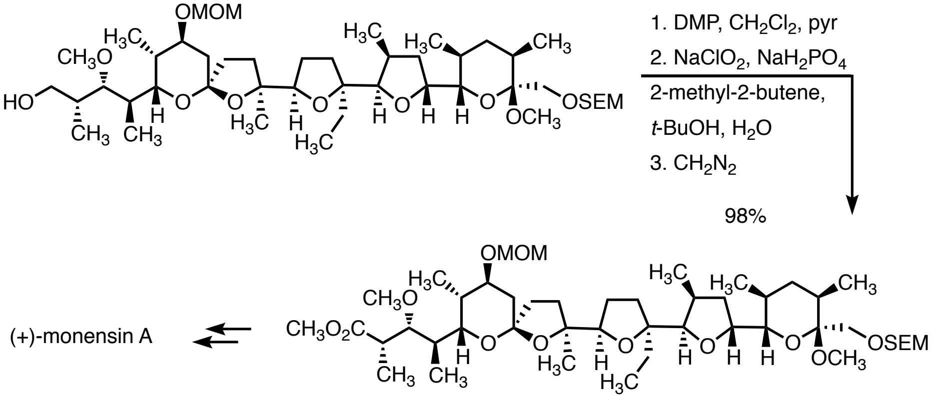
(+)-obtusenyne

Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616–2617.

- The two-step oxidation of an alcohol to the corresponding carboxylic acid is most common.



Nicolaou, K. C.; Ohshima, T.; Murphy, F.; Barluenga, S.; Xu, J.; Winssinger, N. *J. Chem. Soc., Chem. Commun.* **1999**, 809–810.



Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166–7172.

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Potassium Permanganate: $KMnO_4$

Review:

Fatiadi, A. J. *Synthesis* **1987**, 85–127.

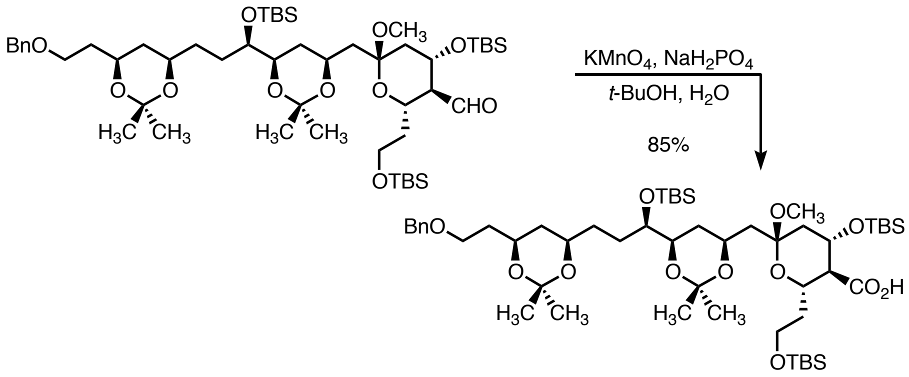
- Potassium permanganate is a mild reagent for the oxidation of aldehydes to the corresponding carboxylic acids over a relatively large pH range. Alcohols, alkenes, and other functional groups are also oxidized by potassium permanganate.

- Oxidation occurs through a coordinated permanganate intermediate by hydrogen atom-abstraction or hydride transfer.

Freeman, F.; Lin, D. K.; Moore, G. R. *J. Org. Chem.* **1982**, *47*, 56–59.

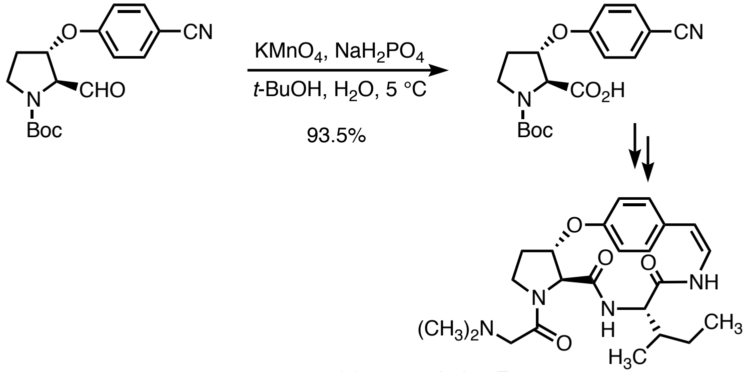
Rankin, K. N.; Liu, Q.; Henrdy, J.; Yee, H.; Noureldin, N. A.; Lee, D. G. *Tetrahedron Lett.* **1998**, *39*, 1095–1098.

- Potassium permanganate in the presence of *tert*-butyl alcohol and aqueous NaH_2PO_4 was shown to effectively oxidize the aldehyde in the following polyoxygenated substrate to the corresponding carboxylic acid whereas Jones reagent, $RuCl_3(H_2O)_n$-$NaIO_4$, and silver oxide failed.



Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

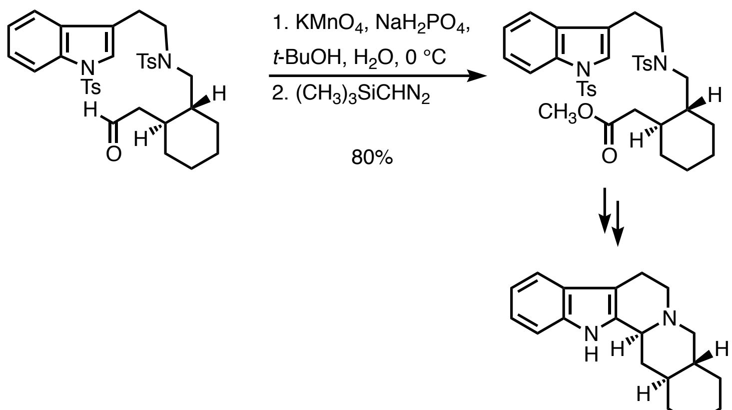
- Examples:



(–)-nummularine F

Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114,* 10181–10189.

- In the following example, a number of other oxidants (including Jones reagent, NaOCl, and RuO_2) failed:



(–)-yohimbane

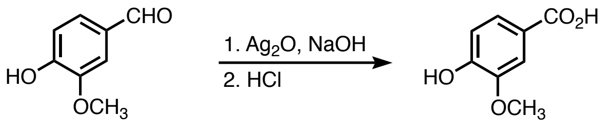
Bergmeier, S. C.; Seth, P. P. *J. Org. Chem.* **1999**, *64,* 3237–3243.

Silver Oxide: Ag_2O

- A classic method used to oxidize aldehydes to carboxylic acids.

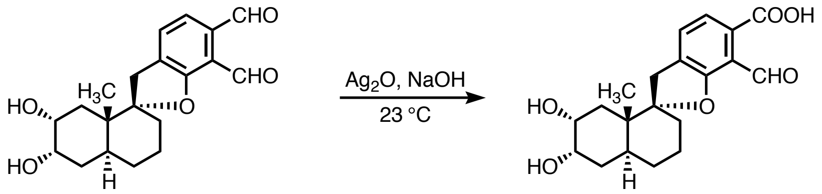
- Cis/trans isomerization can be a problem with unsaturated systems under the strongly basic reaction conditions employed.

- Examples:



vanillic acid

Pearl, I. A. *Org. Synth. IV* **1963**, 972–978.



(±)-K-76 (±)-K-76 monocarboxylic acid

Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553.

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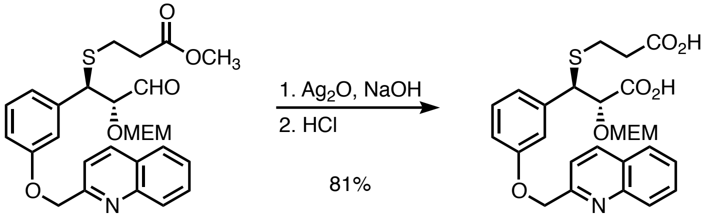
- In the following example, all chromium-based oxidants failed to give the desired acid.



Ovaska, T. V.; Voynov, G. H.; McNeil, N.; Hokkanen, J. A. *Chem. Lett.* **1997**, 15–16.

Pyridinium Dichromate: $(pyrH^+)_2Cr_2O_7$

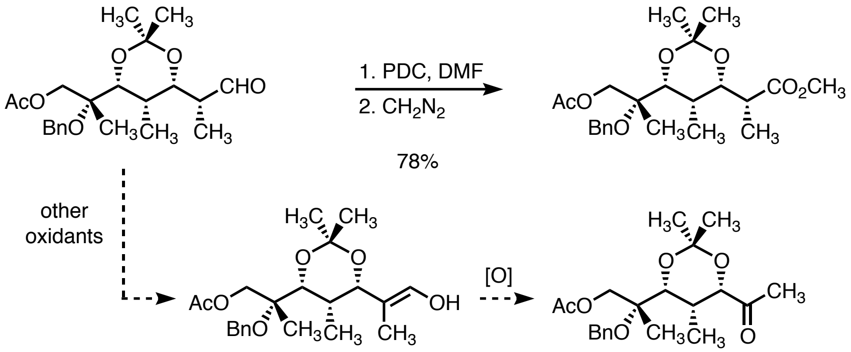
- Review

Ley, S. V.; Madin, A. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 251–289.

- PDC is a stable, bright orange solid prepared by dissolving CrO_3 in a minimun volume of water, adding pyridine and collecting the precipitated product.
- Non-conjugated aldehydes are readily oxidized to the corresponding carboxylic acids in good yields in DMF as solvent.
- Primary alcohols are oxidized to the corresponding carboxylic acids in good yields.

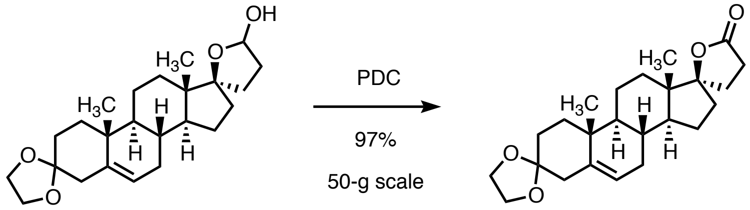
Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399–402.

- In the following example, PDC was found to be effective while many other reagents led to oxidative C-C bond cleavage.



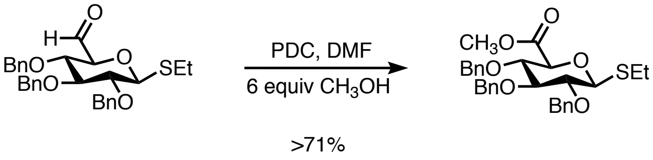
Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095–2105.

- Additional Examples



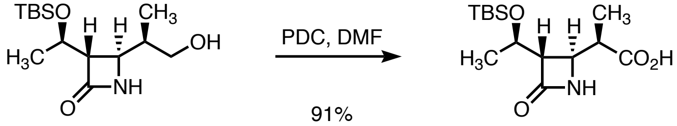
Wuts, P. G. M.; Ritter, A. R. *J. Org. Chem.* **1989**, *54*, 5180–5182.

- PDC can oxidize aldehydes to the corresponding methyl esters in the presence of methanol. It appears that in certain cases, the oxidation of methanol by PDC is slow in comparison to the oxidation of the methyl hemiacetal.
- Attempts to form the ethyl and isopropyl esters were less successful.
- Note that in the following example sulfide oxidation did not occur.



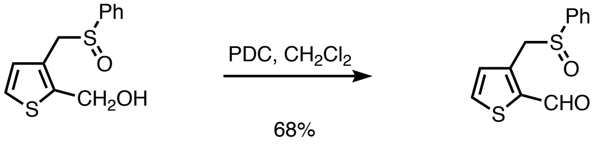
O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235–3236.
Garegg, P. J.; Olsson, L.; Oscarson, S. *J. Org. Chem.* **1995**, *60*, 2200–2204.

- PDC has also been used to oxidize alcohols to the corresponding carboxylic acids.



Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron* **1988**, *44*, 2149–2165.

- However, a suspension of PDC in dichloromethane oxidizes alcohols to the corresponding aldehyde.



Terpstra, J. W.; van Leusen, A. M. *J. Org. Chem.* **1986**, *51*, 230–238.

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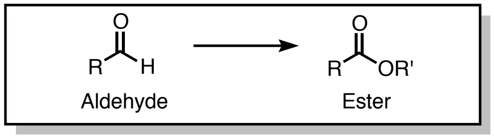
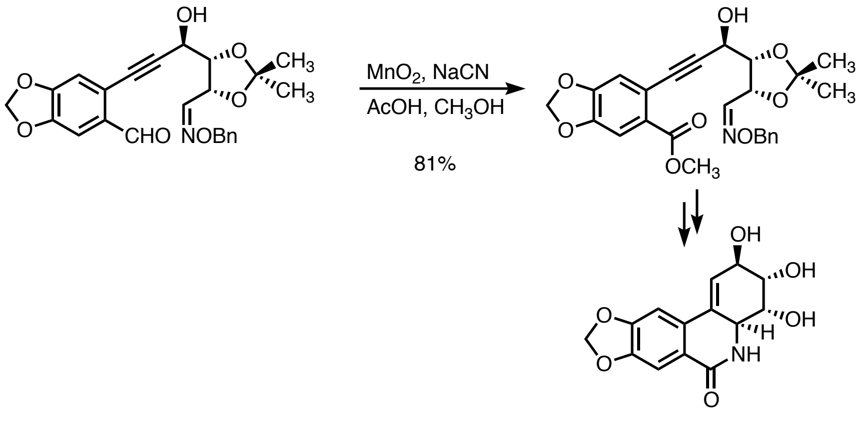


Manganese Dioxide–NaCN–CH_3OH

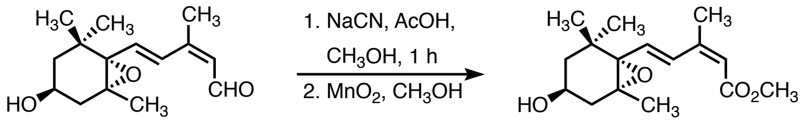
- A convenient method to convert unsaturated aldehydes directly to the corresponding methyl esters.
- Cis/trans isomerization, a problem when other reagents such as basic silver oxide are employed, is avoided.
- The aldehyde substrate is initially transformed into a cyanohydrin intermediate. Subsequent oxidation of the cyanohydrin furnishes an acyl cyanide which is then trapped with methanol to give the desired methyl ester.
- Conjugate addition of cyanide ion can be problematic.
- Examples



(–)-lycoricidine

Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121,* 5176–5190.

- In the following example, stepwise addition of reagents proved to be essential to achieve high yields.



97%

(2Z, 4E)-xanthoxin

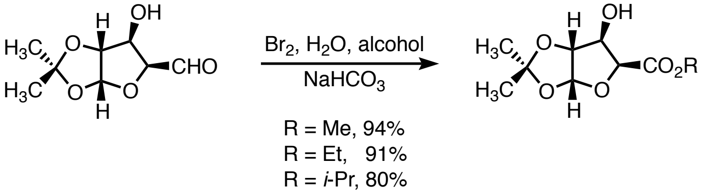
Yamamoto, H.; Oritani, T. *Tetrahedron Lett.* **1995**, *36,* 5797–5800.

Bromine

- Review

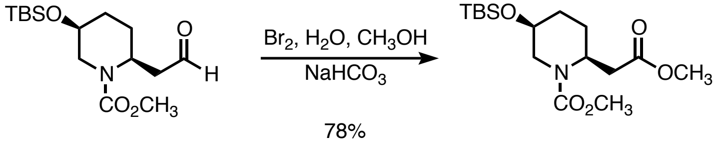
Palou, J. *Chem. Soc. Rev.* **1994**, 357–361.

- Bromine in alcoholic solvents is a convenient and inexpensive method for the direct conversion of aldehydes into ester derivatives.
- Under the reaction conditions employed, secondary alcohols are not oxidized to the corresponding ketones.
- Oxidation of a hemiacetal intermediate is proposed.
- Olefins, benzylidine acetals and thioketals are incompatiable with the reaction conditions.
- A variety of esters can be prepared.
- Examples



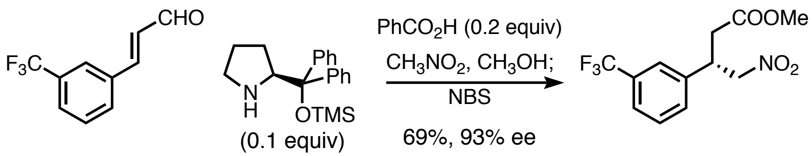
Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29,* 5087–5090.

Lichtenthaler, F. W.; Jargils, P.; Lorenz, K. *Synthesis* **1988**, 790–792.



Herdeis, C.; Held, W. A.; Kirfel, A.; Schwabenländer, F. *Tetrahedron* **1996**, *52,* 6409–6420.

- A variation of this reaction using NBS as oxidant has been employed in tandem with the catalytic enantioselective Michael addition of nitromethane to an enal:



Jensen, K. L.; Poulsen, P. H.; Donslund, B. S.; Morana, F.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 1516–1519.

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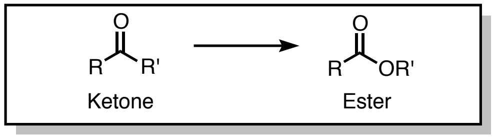


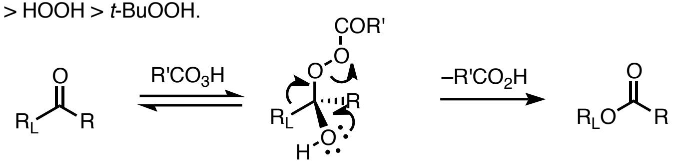
Bayer-Villiger Oxidation

- Reviews

Krow, G. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 671-688.

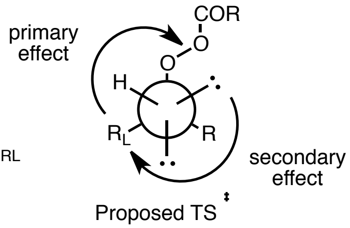
Krow, G. R. In *Organic Reactions*, Paquette, L. A., Ed., John Wiley and Sons: New York, **1993**, *Vol.* 43, p. 251-296.

- A classic method for the oxidative conversion of ketones into the corresponding esters or lactones by oxygen insertion into an acyl C-C bond.
- The migratory preference of alkyl groups has been suggested to reflect their electron-releasing ability and steric bulk.
- Typically, the order of migratory preference is tertiary > secondary > allyl > primary > methyl.
- The reactivity order of Bayer-Villiger oxidants parallels the acidity of the corresponding carboxylic acid (or alcohol): CF_3CO_3H > *p*-nitroperbenzoic acid > *m*-CPBA = HCO_3H > CH_3CO_3H > HOOH > *t*-BuOOH.



R_L = Large Group Criegee Intermediate

- Primary and secondary stereoelectronic effects in the Bayer-Villiger reaction have been demonstrated.

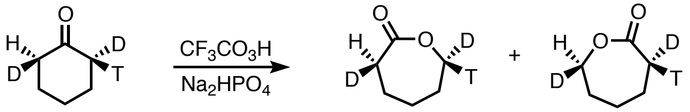


Proposed TS ‡

- Primary effect: antiperiplanar alignment of R_L and $\sigma_{O\text{-}O}$
- Secondary effect: antiperiplanar alignment of O_{lp} and $\sigma^*_{C\text{-}RL}$

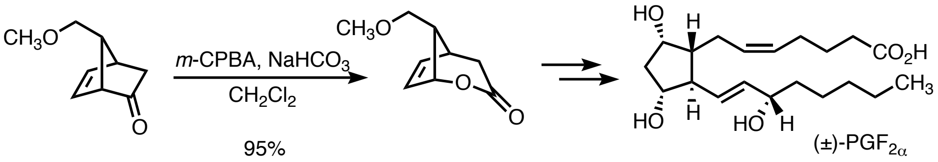
Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2852-2855.

- The Bayer-Villiger reaction occurs with retention of stereochemistry at the migrating center.

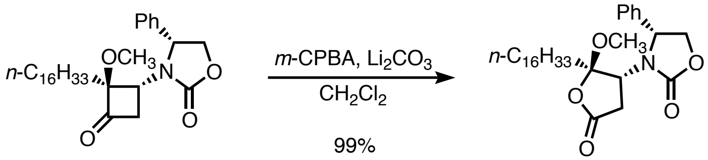


Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878-882.
Gallagher, T. F.; Kritchevsky, T. H. *J. Am. Chem. Soc.* **1950**, *72*, 882-885.

- Examples

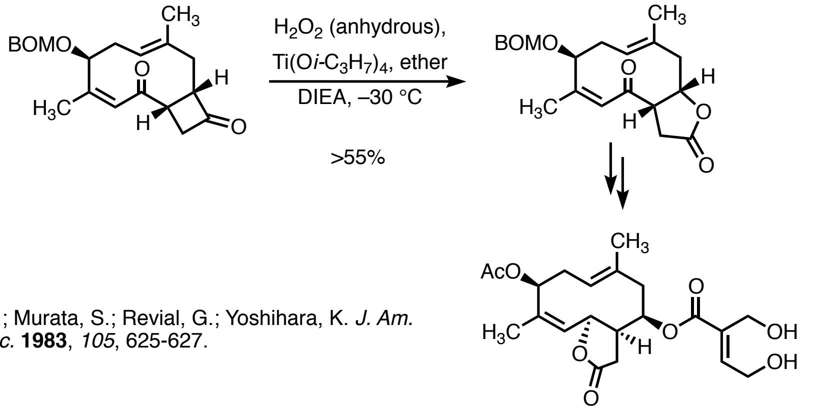


Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675-5677.



Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779-6785.

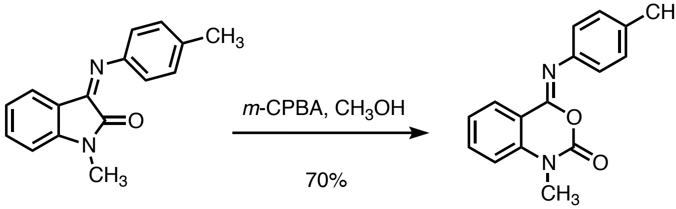
- Selective Bayer-Villiger oxidation in the presence of unsaturated ketones and isolated olefins has been achieved.



Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625-627.

eucannabinolide

- Carbamates have been prepared in some cases.



Azizian, J.; Mehrdad, M.; Jadid, K.; Sarrafi, Y. *Tetrahedron Lett.* **2000**, *41*, 5265-5268.

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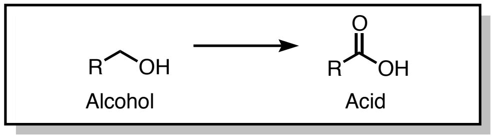


Ruthenium Tetroxide: RuO_4

- RuO_4 is used to oxidize alcohols to the corresponding carboxylic acid. It is a powerful oxidant that also attacks aromatic rings, olefins, diols, ethers, and many other functional groups.

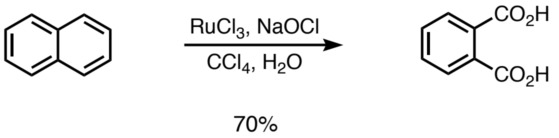
- Catalytic procedures employ 1-5% of ruthenium metal and a stoichiometric oxidant, such as sodium periodate ($NaIO_4$).

- Sharpless has introduced the use of acetonitrile as solvent to improve catalyst turnover. It is proposed to avoid the formation of insoluble Ru-carboxylate complexes and return the metal to the catalytic cycle.

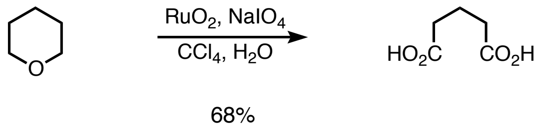
Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838–3840.

Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

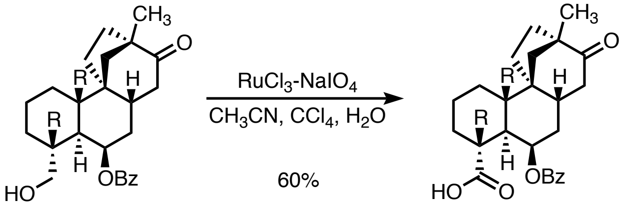
- Examples



Sptzer, U. A.; Lee, D. G. *J. Org. Chem.* **1974**, *39*, 2468–2469.



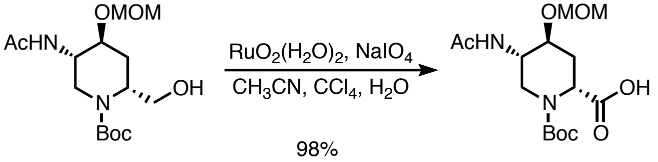
Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205–211.



R = CH_3

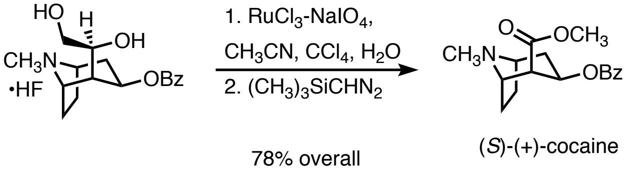
(±)-scopadulcic acid B

Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031–12040.



Clinch, K.; Vasella, A.; Schauer, R. *Tetrahedron Lett.* **1987**, *28*, 6425–6428.

- In the following example, sodium periodate cleaves the 1,2-diol to an aldehyde, which is further oxidized to the corresponding carboxylic acid by RuO_4. The amine is protonated and thereby protected from oxidation.



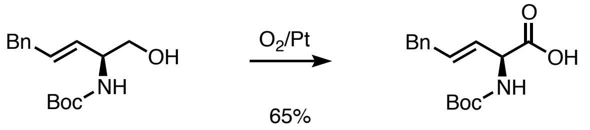
(*S*)-(+)-cocaine

Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773–4775.

Molecular Oxygen

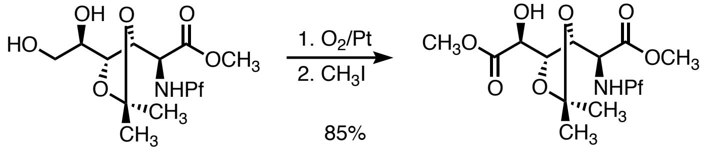
- Molecular oxygen in the presence of a platinum catalyst is a classic method for the oxidation of primary alcohols to the corresponding carboxylic acids.

- Examples



Mehmandoust, M.; Petit, Y.; Larcheveque, M. *Tetrahedron Lett.* **1992**, *33*, 4313–4316.

- Primary alcohols are oxidized selectively in the presence of secondary alcohols.



Pf = 9-phenylfluorenyl

Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394–399.

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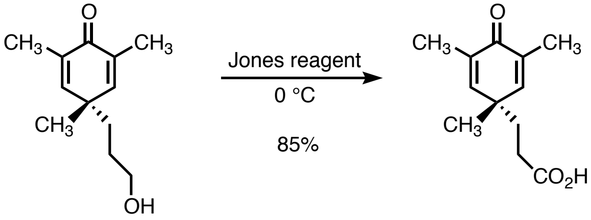
Jones Oxidation

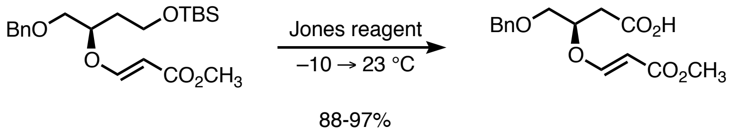
- Jones reagent is a standard solution of chromic acid in aqueous sulfuric acid.
- Acetone is often benefical as a solvent and may function by reacting with any excess oxidant.
- Isolated olefins usually do not react, but some olefin isomerization may occur with unsaturated carbonyl compounds.
- 1,2-diols and α-hydroxy ketones are susceptible to cleavage under the reaction conditions.

- Examples:

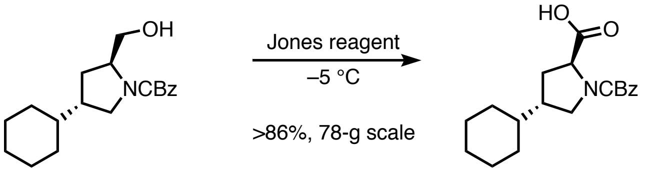


Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Flack, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618–4620.

- Silyl ethers can be cleaved under the acidic conditions of the Jones oxidation.

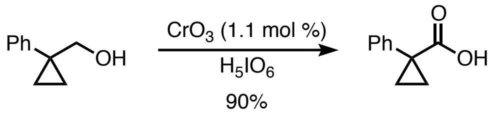


Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3175–3177.



Thottahil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140–3143.

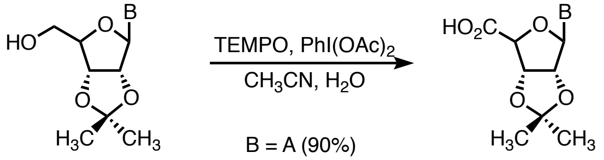
- Toxicity concerns inherent to chromium(VI) species can be minimized by employing CrO_3 as a catalyst in the presence of periodic acid as stoichiometric oxidant.



Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323–5326.

N-Oxoammonium-Mediated Oxidation of Alcohols to Carboxylic Acids

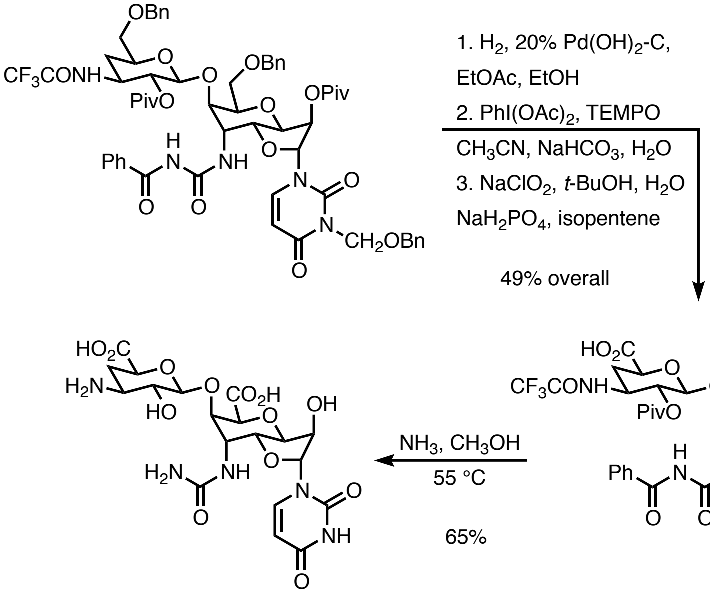
- A general method for the preparation of nucleoside 5'-carboxylates:



B = A (90%)
B = U (76%)
B = C (72%, $NaHCO_3$ added)
B = G (75%, Na salt, $NaHCO_3$ added)

Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.

- A brief follow-up treatment with sodium chlorite was necessary to obtain complete oxidation to the bis-carboxylic acid in the following example.



4-desamino-4-oxo-ezomycin A_2

Knapp, S. K.; Gore, V. K. *Org. Lett.* **2000**, *2*, 1391–1393.

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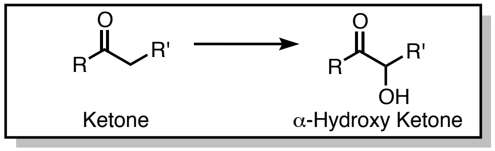


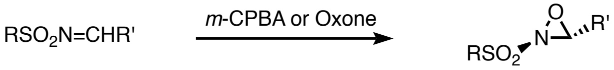
Davis Oxaziridine

- Reviews

Davis, F. A.; Chen, B. *Chem. Rev.* **1992**, *92*, 919–934.

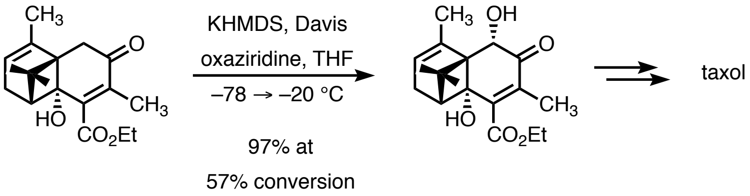
Jones, A. B. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 151–191.

N-Sulfonyloxaziridines are prepared by the biphasic oxidation of the corresponding sulfonimine with *m*-CPBA or Oxone.



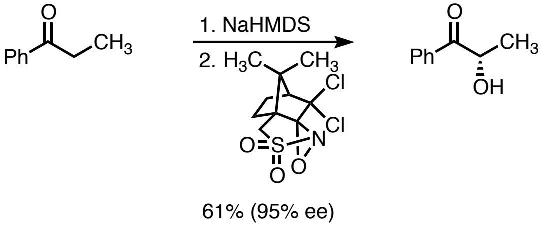
Davis oxaziridine: R = R' = Ph

- Nucleophilic attack by enolates on the electrophilic oxaziridine oxygen furnishes α-hydroxy ketones.
- Potassium enolates are generally the most successful.
- Examples



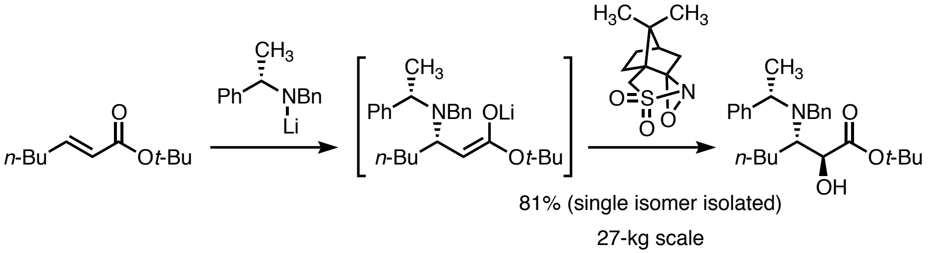
Wender, P. A.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 2757–2758.

- Enantioselective hydroxylation of prochiral ketones has been demonstrated.

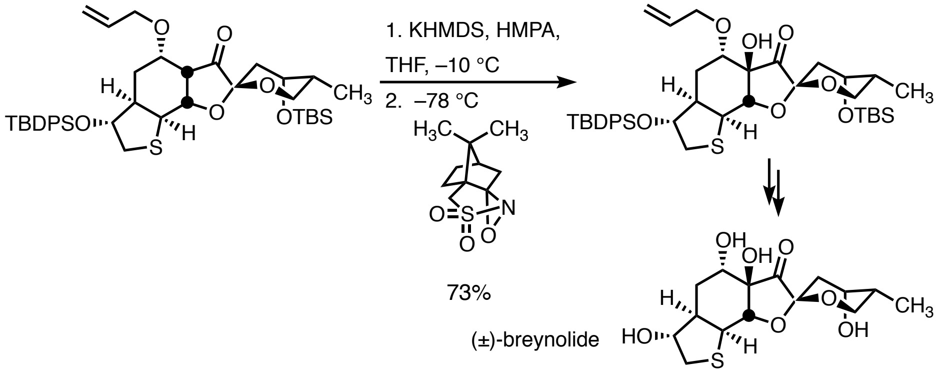


Davis, F. A.; Chen, B. *Chem. Rev.* **1992**, *92*, 919–934.

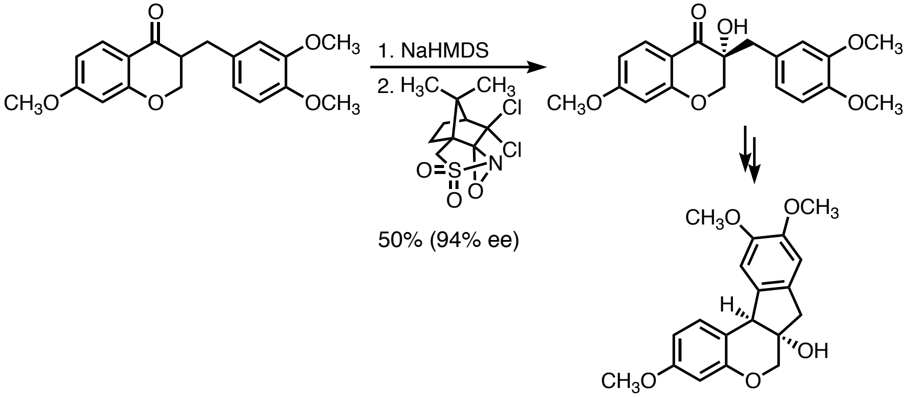
- A related diastereoselective conjugate addition/α-oxidation protocol has been employed on industrial scale for the synthesis of an HCV protease inhibitor.



Traverse, J.; Leong, W. W.; Miller, S. P.; Albaneze-Walker, J.; Hunter, T. J.; Wang, L.; Liao, H.; Arasappan, A.; Trzaska, S. T.; Smith, R. M.; Lekhal, A.; Bogen, S. L.; Kong, J.; Bennett, F.; Njoroge, F. G.; Poirier, M.; Kuo, S.-C.; Chen, Y.; Matthews, K. S.; Demonchaux, P.; Ferreira, A. Patent: WO 2011014494.



Smith, A. B., III; Empfield, J. R.; Rivero, R. A.; Vaccaro, H. A.; Duan, J. J.-W.; Sulikowski, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 9419–9434.



(+)-*O*-trimethylbrazilin

Davis, F. A.; Chen, B. *J. Org. Chem.* **1993**, *58*, 1751–1753.

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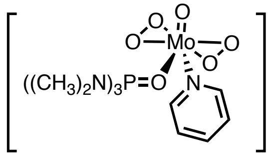
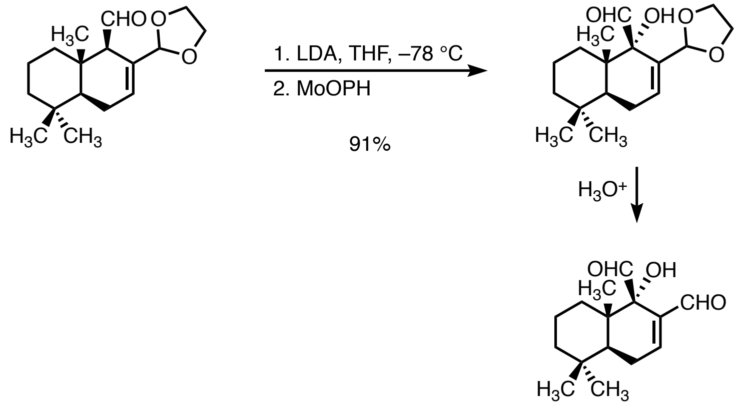
Molybdenum peroxy compounds: MoO_5•pyr•HMPA

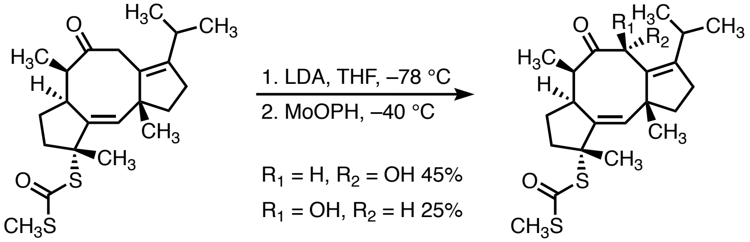


- Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH) is commonly used to oxidize enolates to the corresponding hydroxylated compound.
- It is proposed that nucleophilic attack of the enolate occurs at a peroxyl oxygen atom, leading to O-O bond cleavage.
- β-Dicarbonyl compounds are not hydroxylated.
- Examples



(±)-warburganal

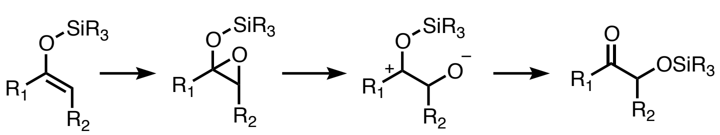
Jansen, B. J. M.; Sengers, H.; Bos, H.; de Goot, A. *J. Org. Chem.* **1988**, *53*, 855-859.



Kato, N.; Okamoto, H.; Arita, H.; Imaoka, T.; Miyagawa, H.; Takeshita, H. *Synlett.* **1994**, 337-339.

Rubottom Oxidation

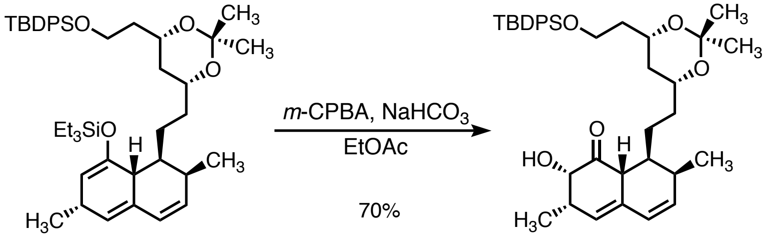
- Epoxidation of a silyl enol ether and subsequent silyl migration furnishes α-hydroxylated ketones.
- Silyl migration via an oxocarbenium ion has been postulated.



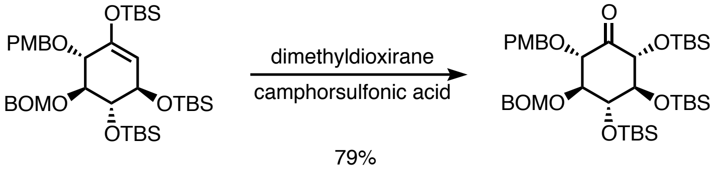
Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319-4322.

Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19-C21.

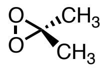
Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427-3429.



Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413-1427.



dimethyldioxirane =



Reddy, K. K.; Saady, M.; Falck, J. R. *J. Org. Chem.* **1995**, *60*, 3385-3390.

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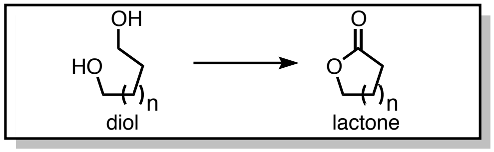


- Review

Procter, G. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p. 312–318.

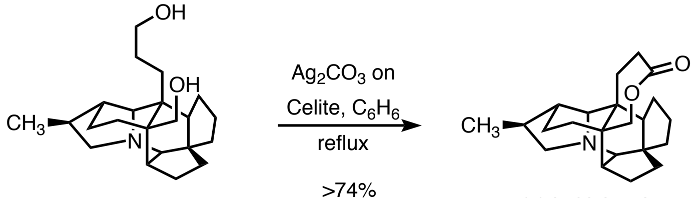
Fetizon's Reagent

- Silver carbonate absorbed on Celite has been found to selectively oxidize primary diols to lactones.

Fetizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc., Chem. Commun.* **1969**, 1102–1118.

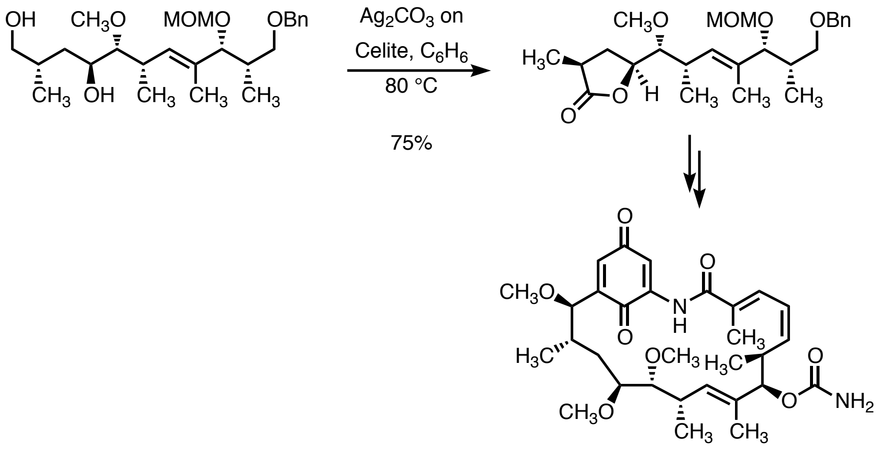
Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, *13*, 4445–4448.

Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523–533.



(±)-bukittinggine

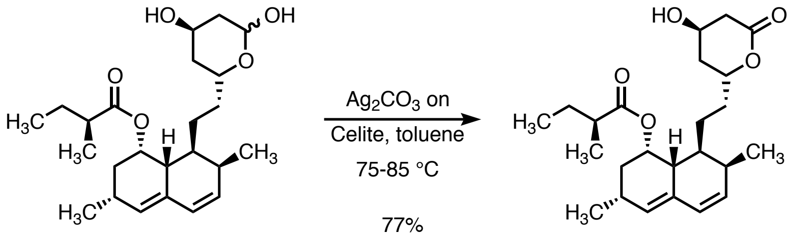
Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575–2585.



(±)-macbecin I

Coutts, S. J.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4305–4308.

- Lactols are oxidized selectively.

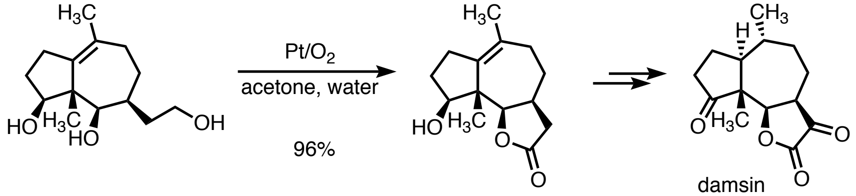


(+)-mevinolin

Clive, D. L. J.; et al. *J. Am. Chem. Soc.* **1990**, *112*, 3018–3028.

Other Methods

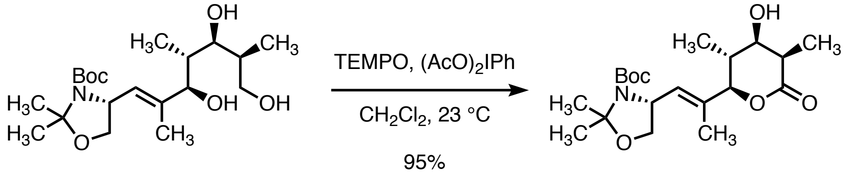
- Platinum and oxygen have been used for the selective oxidation of primary alcohols to lactones.



damsin

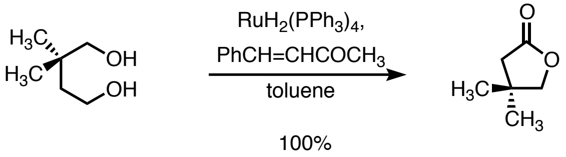
Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379–3380.

- TEMPO has been employed as a catalyst for the preparation of lactones.



Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.*, **2003**, *44*, 57–59.

- Ru complexes have also been employed.



Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034–2039.

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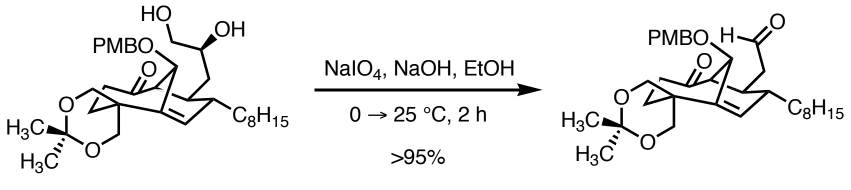
Oxidative Cleavage of Diols

Sodium periodate ($NaIO_4$)

- Reviews:

Wee, A. G.; Slobodian, J. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 420–423.

- One of the most common reagents for cleaving 1,2-diols.



Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202–2211.

Lead Tetraacetate ($Pb(OAc)_4$)

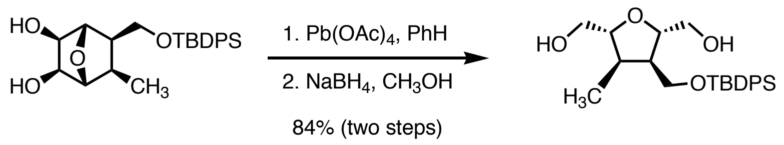
- Reviews:

Mihailovic, M. L.; Cekovic, Z. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents,* Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 190–195.

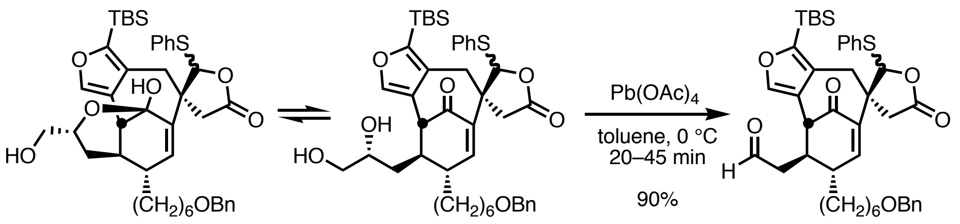
Butler, R. N. In *Synthetic Reagents*, Pizey, J. S., Ed., **1977**, Vol 3, p. 277–419.

Rubottom, G. M. In *Oxidation in Organic Chemistry*, Trahanovsky, W. S., Ed.; Organic Chemistry, A Series of Monographs, Vol 5, **1982**, Part D, p. 1–145.

- A common reagent for the cleavage of diols. However, $Pb(OAc)_4$ is a strong oxidant and can react with a variety of functional groups.
- Examples:

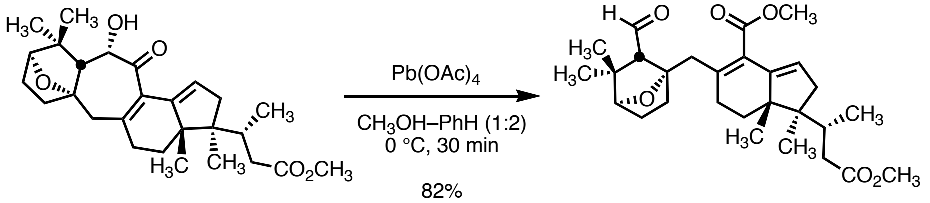


Takao, K.; Watanabe, G.; Yasui, H.; Tadano, K. *Org. Lett.* **2002**, *4*, 2941–2943.



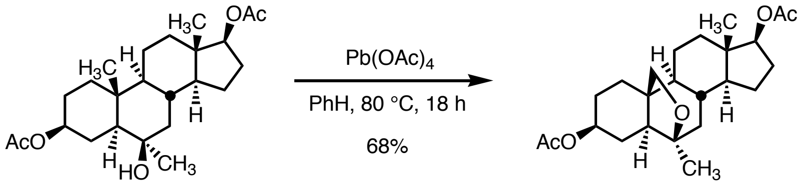
Tan, Q.; Danishefsky, S. J. *Angew. Chem. Int. Ed., Eng.* **2000**, *39*, 4509–4511.

- α-Hydroxyketones can be cleaved as well:



Corey, E. J.; Hong, B. *J. Am. Chem. Soc.* **1994**, *116*, 3149–3150.

- Oxidative cyclizations sometimes occur. This process likely proceeds by a free-radical mechanism involving homolytic cleavage of an RO–Pb bond.



Bowers, A.; Denot, E.; Ibáñez, L. C.; Cabezas, M. A.; Ringold, H. J. *J. Org. Chem.* **1962**, *27*, 1862–1867.

Mihailovic, M. L.; Cekovic, Z. *Synthesis* **1970**, *5*, 209–224.

- In addition, $Pb(OAc)_4$ can oxygenate alkenes, oxidize allylic or benzylic C–H bonds, and has been used to introduce an acetate group α to a ketone.

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Oxidative Cleavage of Alkenes

Ozone

- Reviews:

Berglund, R. A. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 270–275.

Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol 7, p. 543–558, 574–578.

Murray, R. W. In *Techniques and Methods of Organic and Organometallic Chemistry* , Denny, D. B., Ed., Marcel Dekker: New York, **1969**, Vol 1, p. 1–32.

Murray, R. W. *Acc. Chem. Res.* **1968**, *1*, 313–320.

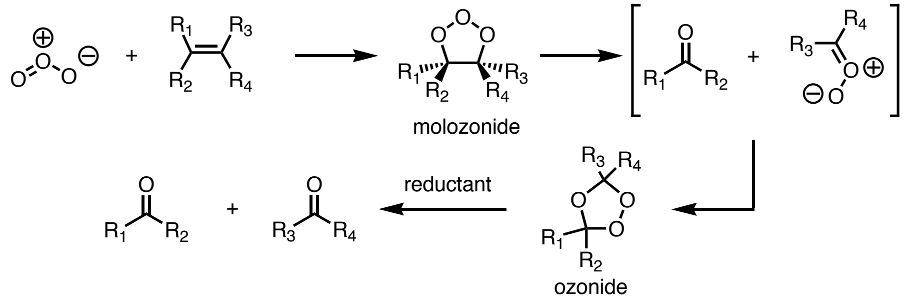
- Ozone is the most common reagent for the oxidative cleavage of olefins.

- The reaction is carried out in two steps:

(1) a stream of O_3 in air or O_2 is passed through the reaction solution at low temperature (0 °C to –78 °C) until excess O_3 in solution is evident from its blue color.

(2) reductive or oxidative work-up.

- Mechanism:



- Considered to be a concerted 3 + 2 cycloaddition of O_3 onto the alkene.

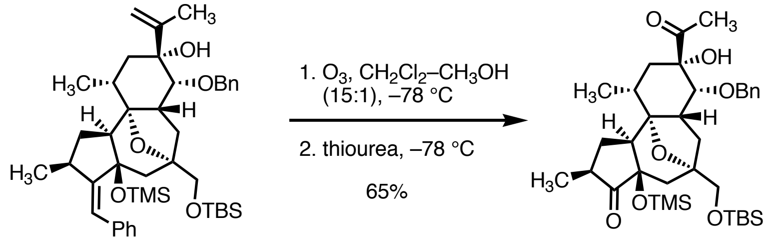
- Because ozonides are known to be explosive, they are rarely isolated and typically are transformed directly to the desired carbonyl compounds.

- Dimethyl sulfide is the most commonly used reducing agent. Others include I_2, phosphine, thiourea, catalytic hydrogenation, tetracyanoethylene, Zn–HOAc, $LiAlH_4$, and $NaBH_4$. The latter two reductants afford alcohols as products.

- Oxidative workup provides either ketone or carboxylic acid products. The most common oxidants are H_2O_2, AgO_2, CrO_3, $KMnO_4$, or O_2.

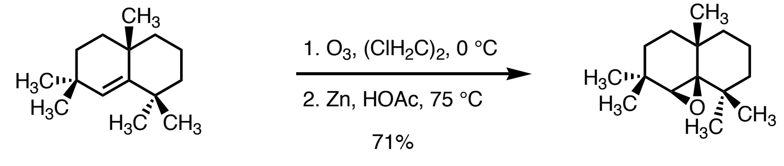
- Alkenes with electron-donating substituents are cleaved more readily than those with electron-withdrawing substituents, see: Pryor, W. A.; Giamalva, D.; Church, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 2793–2797.

- Examples



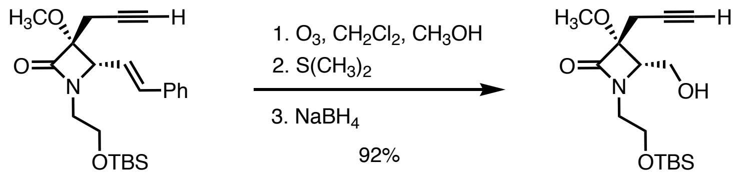
Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.

- Forming the primary ozonide with sterically hindered olefins is difficult, and epoxides can be formed instead:



Hochstetler, A. R. *J. Org. Chem.* **1975**, *40*, 1536–1541.

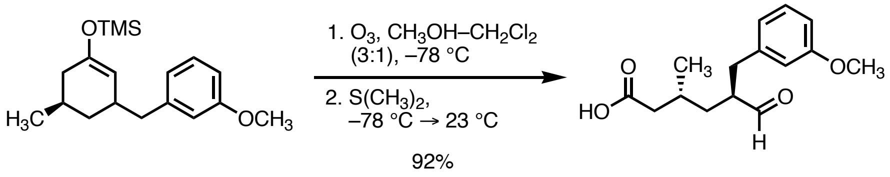
- Alkenes are ozonized more readily than alkynes:



- When a TMS-protected alkyne was used in the example above, the authors observed products arising from ozonolysis of the alkyne as well.

Banfi, L.; Guanti, G. *Tetrahedron Lett.* **2000**, *41*, 6523–6526.

- Ozonolysis of silyl enol ethers can afford carboxylic acids as products:



Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87.

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Oxidative Cleavage of Alkenes

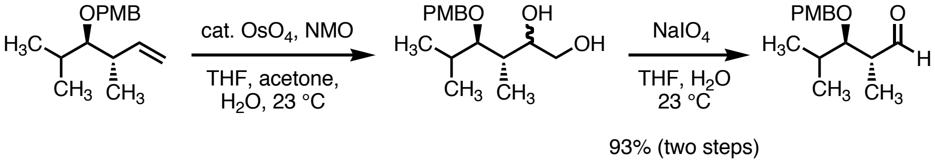
OsO_4, $NaIO_4$

Wee, A. G.; Liu, B. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 423–426.

Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol.* 7, p.564.

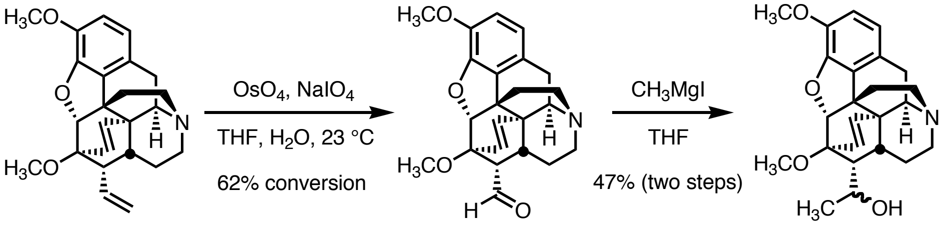
VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

- A two-step procedure involving initial dihydroxylation with OsO_4 to form 1,2-diols, followed by cleavage with periodate.
- This procedure offers an alternative to ozonolysis, where it can be difficult to achieve selectivity for one olefin over another due to difficulties in adding precise quantities of ozone.
- Sharpless dihydroxylation conditions (AD-Mix α/β) can lead to enhanced selectivities.



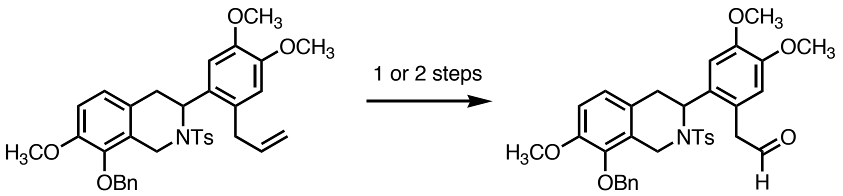
Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Sheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275–4283.

- The procedure is most often performed in two steps, but the transformation is sometimes accomplished in one:



- Notice that in the example above, the less-hindered olefin was cleaved selectively.

Maurer, P. J.; Rapoport, H. *J. Med. Chem.* **1987**, *30*, 2016–2026.



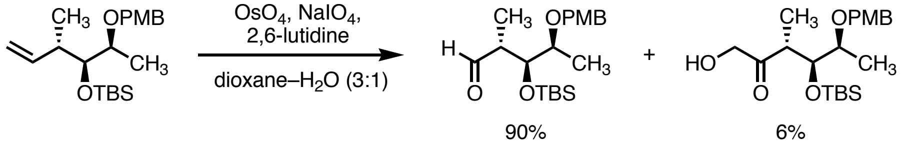
OsO_4 (cat.), $NaIO_4$, THF–H_2O (3:1)..................................77%

1. OsO_4 (cat.), NMO, acetone–H_2O–*t*-BuOH (4:2:1);
2. $NaIO_4$, THF–H_2O (3:1)..89%

- Frequently the two-step protocol is found to be superior to the one-pot procedure. In the example shown, over-oxidation of the aldehyde was observed in the one-pot reaction.

Bianchi, D. A.; Kaufman, T. S. *Can. J. Chem.* **2000**, *78*, 1165–1169.

- An improved one-pot procedure uses 2,6-lutidine as a buffering agent:



- Ozonolysis of this substrate resulted in PMB removal.
- The authors found that without base, the α-hydroxyketone was formed in ~30% yield. Using pyridine as base, epimerization of the aldehyde product was observed.

Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

Oxidative Cleavage of Alkenes

RuO_4

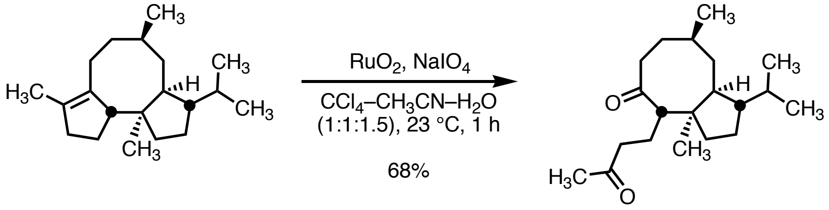
- References:

Martín, V. S.; Palazón, J. M.; Rodríguez, C. M. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 346–353.

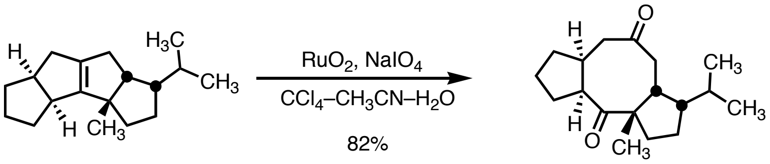
Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol 7, p.564–571, 587.

Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.* **1953**, *75*, 3838–3840.

- RuO_4 is a powerful oxidant that is nevertheless useful in many synthetic transformations.
- RuO_4 has been used to cleave alkenes where other oxidation methods (e.g., O_3, $OsO_4/NaIO_4$) have failed.
- Reaction conditions are relatively mild and usual involving generation of RuO_4 in situ from $RuO_2 \cdot 2H_2O$ or $RuCl_3 \cdot H_2O$ and an oxidant, such as $NaIO_4$.
- Solvent mixtures of CCl_4, H_2O and CH_3CN have been determined to be optimal. CH_3CN is a good ligand for low valent Ru, and it prevents formation of stable Ru(II/III)–carboxylate complexes which remove Ru from the catalytic cycle. See: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
- RuO_4 will also oxidize alcohols (to ketones), ethers (to lactones or to two carboxylic acids), diols (to two carboxylic acids), alkynes (to 1,2-diketones), and aryl rings (to carboxylic acid products). It will also remove aryl and alkyne groups, leaving carboxylic acids.



Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057–3083.



Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319–1321.

Ketone ⟶ α,β-Unsaturated Ketone

See also: *o*-Iodobenzoic Acid (IBX) earlier in handout

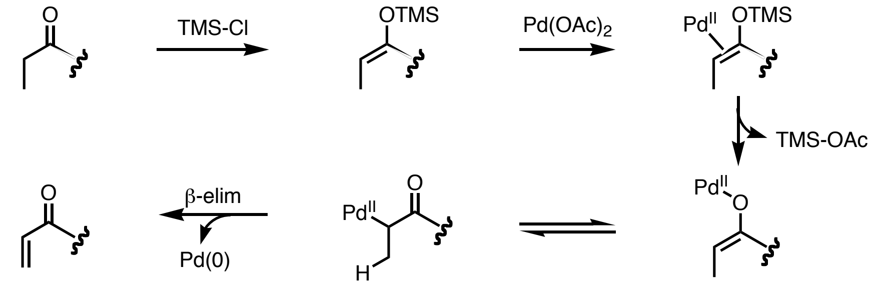
General Reference:

Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 7*, p. 119–149.

Saegusa Oxidation

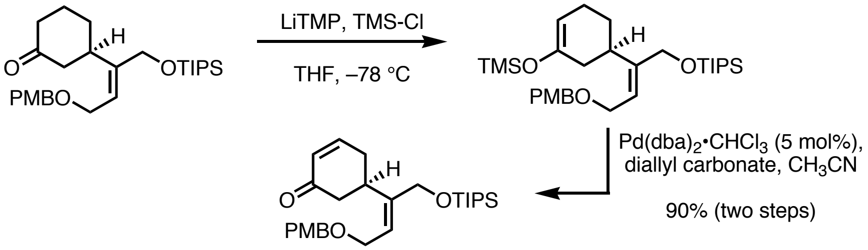
Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

- A two-step procedure involving silyl enol ether formation, followed by treatment with Pd(II).
- The reaction can be performed with stoichiometric Pd(II), or can be rendered catalytic if a terminal oxidant, such as O_2 or *p*-benzoquinone, is used.
- Mechanism:



Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

Porth, S.; Bats, J. W.; Trauner, D.; Giester, G.; Mulzer, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2015–2016



- In this case, diallyl carbonate is used as a terminal oxidant.

Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546–14547.

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Ketone ⟶ α,β-Unsaturated Ketone

Selenation/Oxidation/Elimination

Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis,* Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 7, p. 128–135.

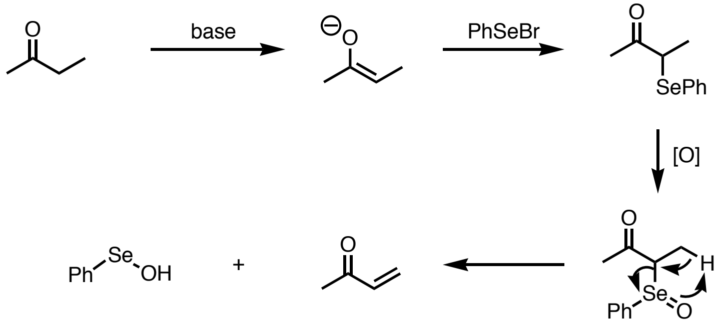
Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979–1982.

Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139.

Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813–5815.

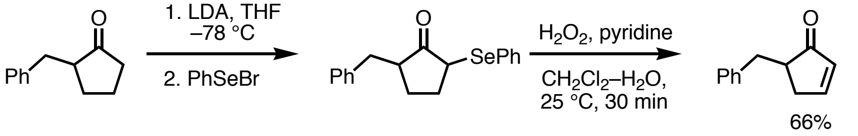
Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

- PhSeBr and PhSeCl can be used to selenate enolates of ketones, esters, lactones and lactams.
- PhSeSePh can be used as well, but ketone enolates are unreactive
- Aldehydes can be selenated via:
  - enol ethers: Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J. *Synthesis* **1979**, 982–984.
  - enamines: Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, *21*, 4417–4420.
  - one-step procedure with PhSeSePh, SeO_2, and a catalytic amount of H_2SO_4: Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1982**, *23*, 4813–4816.
- Mechanism:



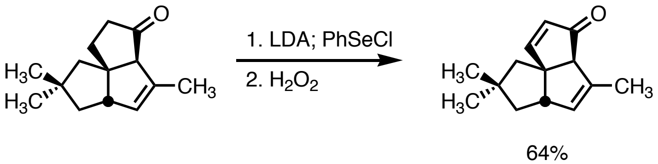
- Common oxidants include H_2O_2, O_3, and $NaIO_4$.
- Elimination is *syn*-specific, see: Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86–87.
- Electron withdrawing groups on the phenyl ring facilitate the elimination step, which can be difficult with primary or β- or γ-branched selenoxides: Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–948.

- Examples:

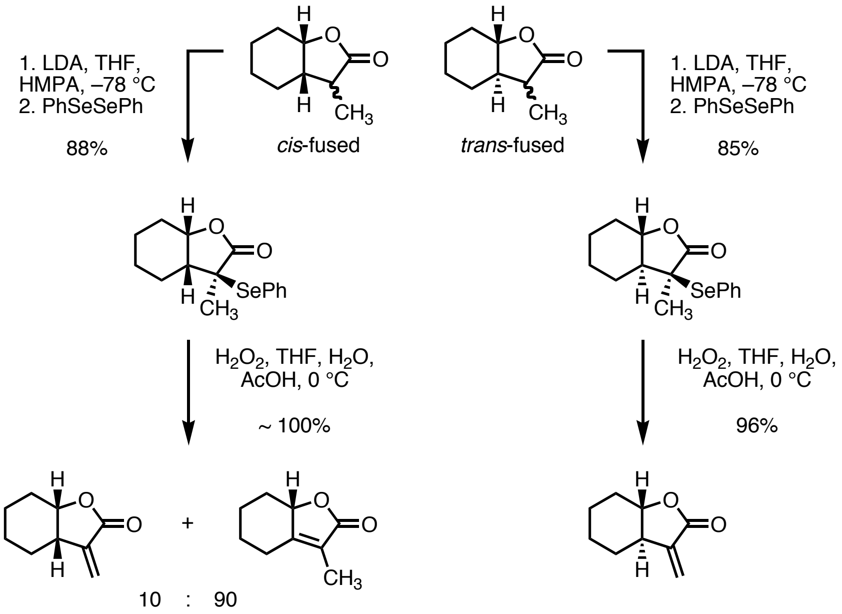


- Generating the enolate under kinetic conditions can allow for formation of the less-substituted double bond.

Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.



Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504–4506.



- The example above illustrates how the stereospecificity (*syn*) of the elimination can be used to achieve selectivity in olefin formation.

Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120–122.

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Alkene → Allylic alcohol

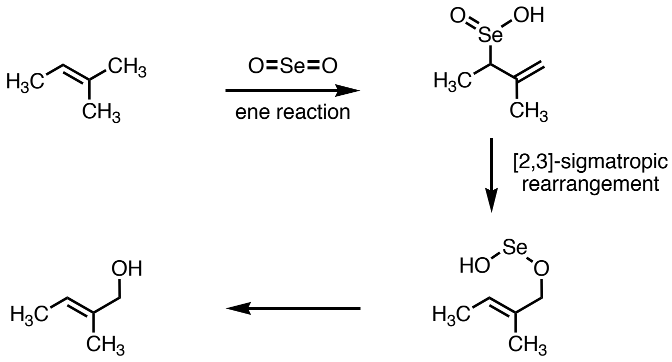
SeO_2

- References

Bulman Page, P. C.; McCarthy, T. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, Vol. 7, p. 84–91, 108–110.

Rabjohn, N. In *Organic Reactions*, **1976**,Vol 24, p. 261–415.

- General method for oxidizing alkenes to allylic alcohols.
- Although the reaction can be performed with stoichiometric SeO_2, catalytic methods employing a stoichiometric oxidant (e.g., *t*-BuOOH) are more frequently used.
- Mechanism:



Singleton, D. A.; Hang, C. *J. Org. Chem.* **2000**, *65*, 7554–7560.

Selectivity:

(a) oxidation typically occurs at the more highly substituted terminus of the alkene

(b) the order of reactivity of C–H bonds is $CH_2 > CH_3 > CH$
[rule (a) takes precedence over rule (b)]

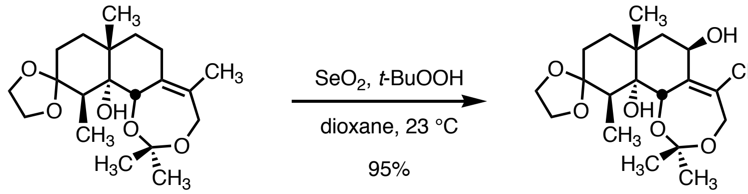
(c) when the double bond is within a ring, oxidation occurs within the ring

(4) *gem*-dimethyl trisubstituted alkenes form (*E*)-α-hydroxy alkenes stereoselectively

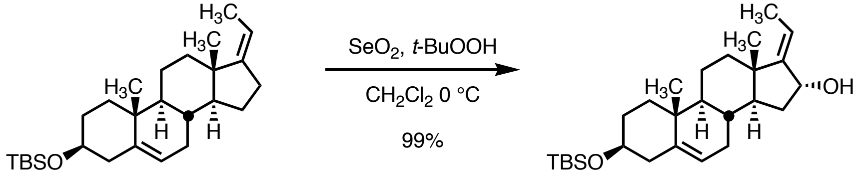
Hoekstra, W. J. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 358–359.

Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 4835–4840.

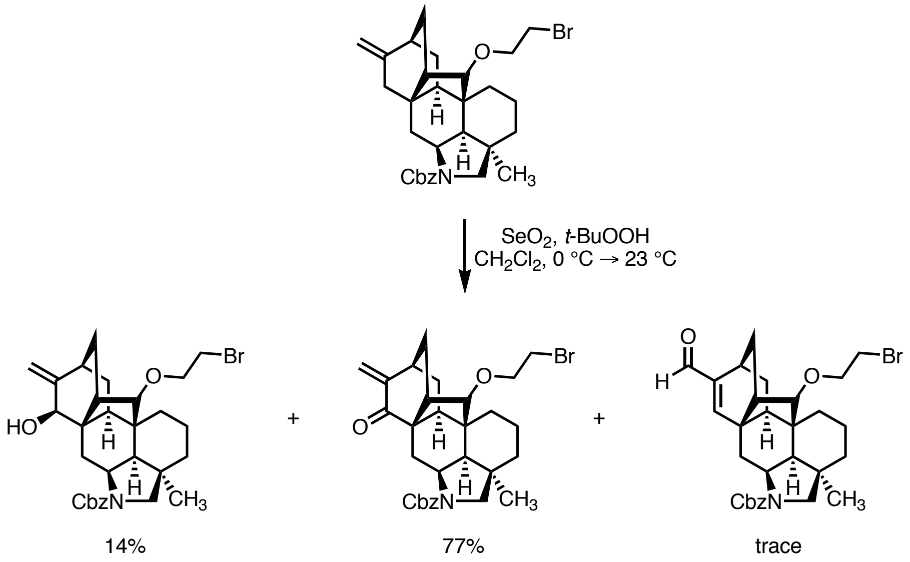
- Examples:



Xia, W. J.; Li, D. R.; Shi, L.; Tu, Y. Q. *Tetrahedron Lett.* **2002**, *43*, 627–630.



Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369–3370.



Muratake, H.; Natsume, M. *Angew. Chem. Int. Ed., Eng.* **2004**, *43*, 4646–4649.

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