Oxidation of Alcohols to Aldehydes and Ketones

BASIC REACTIONS IN ORGANIC SYNTHESIS

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Oxidation of Alcohols to Aldehydes and Ketones:
A Guide to Current Common Practice, by Gabriel Tojo and Marcos Fernández

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Springer

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This book is dedicated to the thousands of scientists cited in the references that constructed our present knowledge on the oxidation of alcohols to aldehydes and ketones. Thanks to their collective effort, the preparation of medicines, pesticides, colorants and plenty of chemicals that make life more enjoyable, is greatly facilitated.

Acknowledgements

We thank the staff of the library of the Faculty of Chemistry of the University of Santiago de Compostela (SPAIN) for their most serviceable help in collecting literature for the preparation of this book.

Preface

There is natural selection in the synthetic organic laboratory. Successful reagents find their way into specialized journals and tend to populate the researcher's benches. Sometimes, old species like active manganese dioxide in the oxidation of unsaturated alcohols are so well adapted to a certain reaction niche that they remain unchallenged for a long time. On other occasions, a successful new species like Dess Martin's periodinane enjoys a population explosion and very quickly inhabits a great number of laboratories. On the other hand, the literature is filled with promising new reagents that fell into oblivion because nobody was able to replicate the initial results on more challenging substrates.

Very few synthetic operations in Organic Chemistry match the importance of the oxidation of alcohols to aldehydes and ketones. The present book, which is a monograph on this operation, is not primarily aimed at specialized researchers interested in the development of new oxidants. Rather, it was written with the objective of being a practical guide for any kind of scientist, be it a chemist of whatever sort, a pharmacologyst, a biochemist, or whoever is in the practical need to perform a certain alcohol oxidation in the most quick and reliable way. Therefore, a great emphasis is given to those oxidants that are employed most often in laboratories, because their ubiquity proves that they possess a greater reliability. Reagents appearing in only a few publications, regardless of promising potential, are only briefly mentioned. We prefer to err on the side of ignoring some good reagents, rather than including bad reagents that would lead researchers to loose their precious time.

This book is meant to be placed near working benches in laboratories, rather than on the shelves of libraries. That is why full experimental parts for important oxidations are provided. Although plenty of references from the literature are facilitated, this book was written with the aim of avoiding as much as possible the need to consult original research articles. Many researchers do not have scientific libraries possessing numerous chemical journals ready available, and, many times, although such library might be

available, it is just inconvenient to leave the laboratory in order to consult some reference.

Our aim is to facilitate a little practical help for anybody preparing new organic chemicals.

Abbreviations

Ac	acetyl
acac	acetylacetonate
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOM	benzyloxymethyl
b.p.	boiling point
Bs	benzenesulfonyl
BSA	bis(trimethylsilyl) acetamide
Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
ca.	circa
CA	Chemical Abstracts
CAN	cerium (IV) ammonium nitrate
cat.	catalytic
Cbz or Z	benzyloxycarbonyl
cHex	cyclohexyl
CI	chemical ionization
18-Crown-6	1,4,7,10,13,16-hexaoxacyclo octadecane
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	density
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCAA	dichloroacetic acid
DCC	*N,N*-dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethyl-amine, Hünig's base
DMAP	4-(dimethylamino)-pyridine
DMB	2,5-dimethoxybenzyl
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylforma-mide
DMP	Dess-Martin periodi-nane
DMSO	dimethyl sulfoxide
EDC	16,14e-2,1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride
EE	1-ethoxyethyl
eq.	equivalent
Et	ethyl
Fl	9-phenylfluoren-9-yl
Fmoc	9-fluorenyl methoxycarbonyl
g	gram
glac.	glacial
Glc	glucose

h	hour
IBA	*o*-iodosobenzoic acid
IBX	*o*-iodoxybenzoic acid
imid.	imidazole
i-Pr	isopropyl
L	litre
LDA	lithium diisopropylamide
m	multiplet
M	mol/L
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	(2-methoxyethoxy) methyl
min.	minute
MOM	methoxymethyl
m.p.	melting point
MP	*p*-methoxyphenyl
Ms	mesyl, methanesulfonyl
MS	molecular sieves
MTBE	methyl *t*-butyl ether
MW	molecular weight
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
p.	page
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB or MPM	*p*-methoxybenzyl
PMBOM	*p*-methoxy benzyloxymethyl
PMP	*p*-methoxyphenyl
POM	[(*p*-phenylphenyl)oxy] methyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTFA	pyridinium trifluoroacetate
Py	pyridine
ref.	reflux
Ref.	reference
r.t.	room temperature
SEM	2-(trimethylsilyl) ethoxymethyl
SET	single electron transfer
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy free radical
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
T_i	internal temperature
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSEt	2-(trimethylsilyl)ethyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl, trityl
Ts	*p*-toluenesulfonyl

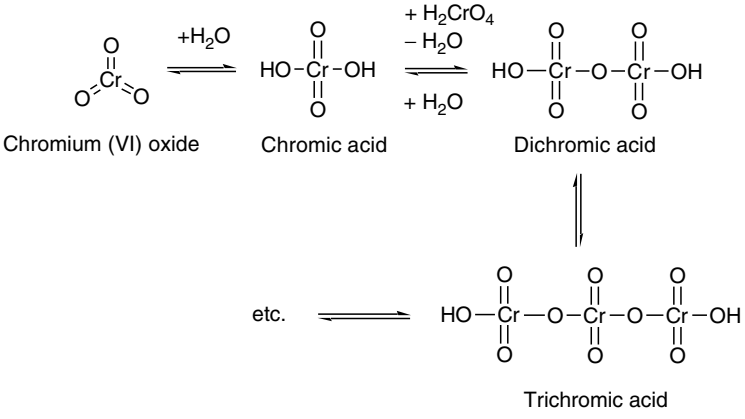
Contents

1

Chromium-based Reagents

1.1. Introduction

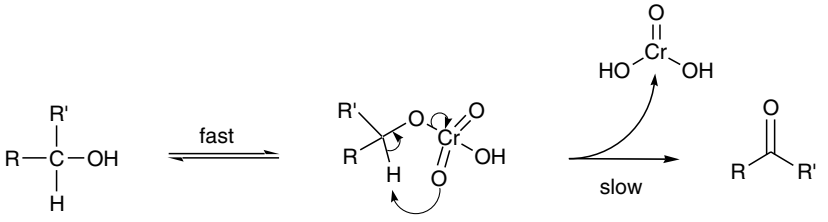
Chromium trioxide (CrO_3) is a strong oxidizing agent that appears in the form of deep-red hygroscopic crystals. Upon solution in water, it forms chromic acid that equilibrates with polymeric anhydrides.[1]



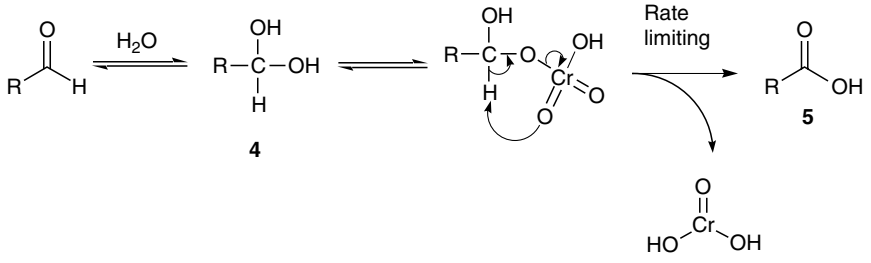
1.1.1. Jones Reagent

Although CrO_3 is soluble in some organic solvents, like *tert*-butyl alcohol, pyridine or acetic anhydride, its use in such solvents is limited, because of the tendency of the resulting solutions to explode.[2,3] Nevertheless, acetone can safely be mixed with a solution of chromium trioxide in diluted aqueous sulfuric acid. This useful property prompted the development of the so-called *Jones oxidation*, in which a solution of chromium trioxide in diluted sulfuric acid is dropped on a solution of an organic compound in acetone. This reaction, first described by Jones,[13] has become one of the most employed procedures for the oxidation of alcohols, and represents a seminal contribution that prompted the development of other chromium (VI) oxidants in organic synthesis.

The mechanism of the oxidation of alcohols with Jones reagent is often depicted as given below.[4]



The alcohol **(1)** is transformed into a chromic acid ester **(2)**, which evolves to an aldehyde or a ketone **(3)**. When an aldehyde is generated, it can react with water to form the hydrate **(4)** that can evolve as in Equation below,[5] resulting in the formation of an acid **(5)**.



Other chromium-based reagents are also found to oxidize alcohols, following a mechanism like the one depicted above for oxidation with chromic acid.[4]

> An interesting consequence of the fast formation of the chromic ester is that, sometimes, chromium-based oxidants counter-intuitively are able to oxidize quicker alcohols possessing a greater steric hindrance, as the initially formed chromic ester releases greater tension on evolving to a carbonyl. Thus, axial alcohols are oxidized quicker than equatorial ones with chromic acid.[6] The reverse—a somehow expected behavior—is observed, for example in oxidations with activated DMSO.[7]

Although Jones oxidation is very useful for the transformation of secondary alcohols into ketones, it can be difficult to stop the oxidation of primary alcohols at the intermediate aldehyde stage.

> Useful yields of aldehydes can be obtained when the proportion of hydrate in equilibrium with the aldehyde is low (see page 12).

1.1.2. Sarett and Collins Reagents

Chromium trioxide reacts with pyridine in a highly exothermic reaction, resulting in the formation of the complex $CrO_3 \cdot 2Py$, which is soluble in organic solvents. A solution of this complex in pyridine is called *Sarett*

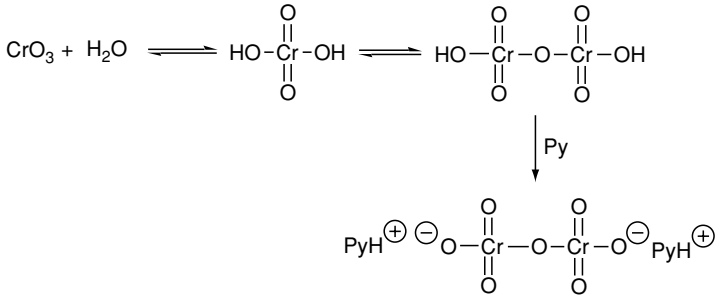
reagent.[2] This reagent is very efficient, not only in the oxidation of secondary alcohols to ketones, but—for its lack of water—also in the oxidation of primary alcohols to aldehydes. A useful modification of the Sarett reagent involves the use of $CrO_3 \cdot 2Py$ dissolved in methylene chloride, forming the so-called *Collins reagent*.[8] This reagent has a number of advantages over Sarett reagent, including the use of a solvent—methylene chloride—that is not as basic as pyridine.

Both, the preparation of Sarett reagent and Collins reagent can be quite dangerous. For instance, during the generation of the $CrO_3 \cdot 2Py$ complex, chromium trioxide must be added over pyridine, as doing an inverse addition leads to an explosion.[9] The $CrO_3 \cdot 2Py$ complex is highly hygroscopic, and can explode in the presence of organic matter. This prompted the development of the Ratcliffe variant[10] of the Collins reaction, in which the $CrO_3 \cdot 2Py$ complex is formed *in situ* in methylene chloride solution, by adding chromium trioxide to a stirred solution of pyridine in methylene chloride. As this variant of the Collins reaction is much safer and convenient than both Sarett reaction and the classic Collins reaction, nowadays it is almost the only one employed in organic synthesis when $CrO_3 \cdot 2Py$ is used.

Chromium trioxide derivatives are very strong oxidizing agents that have the potential to explode in the presence of organic matter. Therefore, we suggest that no substantial changes over the standard oxidation procedures are tested during research. It is particularly dangerous to test non-standard solvents or higher temperatures than recommended. Chromium-based oxidations are mainly done in methylene chloride, which is a solvent very refractory to ignition.

1.1.3. Pyridinium Dichromate (PDC)

When pyridine is added to a solution of chromium trioxide in water, it is possible to obtain a precipitate of the pyridinium salt of dichromic acid, that is pyridinium dichromate (PDC).[11]

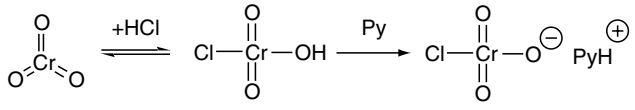


Pyridinium dichromate

This oxidant is a bright-orange solid that is soluble in organic solvents, and very convenient to store and manipulate, because of its lack of hydrophilicity. Pyridinium dichromate (PDC), which is normally used in dichloromethane at room temperature, is a very efficient oxidant able to transform alcohols in aldehydes and ketones in high yield. The absence of water in the reaction media prevents the over-oxidation of aldehydes into carboxylic acids.

1.1.4. Pyridinium Chlorochromate (PCC)

The interaction of CrO_3 with hydrochloric acid, in the presence of water, results in an equilibrium, in which chlorocromic acid is present. Addition of pyridine results in the formation of a precipitate of the pyridinium salt of chlorocromic acid, the so-called pyridinium chlorochromate (PCC).[12]



Chlorochromic acid PCC

This reagent is a yellow-orange solid, which shares many properties with PDC. Thus, non-hygroscopic PCC is very convenient to store, and is able to transform alcohols into aldehydes and ketones in high yield when it is used in dichloromethane solution at room temperature.

1.1.5. Election of Oxidant

The following guidelines can help in the election of a certain chromium-based oxidant in the laboratory:

- Jones oxidation is very easy to carry out, because of the absence of need to keep anhydrous conditions. Furthermore, it is very cheap. It is the oxidation of choice for robust substrates on a big scale. It is neither suitable for very acid sensitive substrates, nor for the preparation of many aldehydes.
- Collins oxidation is very cheap, but has the added experimental difficulty of having to work under anhydrous conditions. Although sometimes it lacks the selectivity of PDC or PCC, it can produce very good yields of aldehydes and ketones in uncomplicated substrates.
- PDC and PCC are more expensive reagents that normally guarantee the best results in difficult cases.

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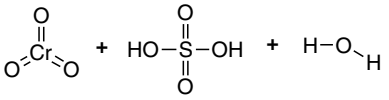
1.2. Jones Oxidation



Chromium trioxide is a strong oxidizing agent, and its use in organic synthesis had to overcome two problems:

- Its lack of solubility in most organic solvents,
- Its tendency to explode in the presence of organic matter.

In 1946, Jones discovered that secondary alcohols could be efficiently oxidized to ketones by pouring a solution of chromium trioxide in diluted sulfuric acid over a solution of the alcohol in acetone.[13] This procedure, which has proved to be quite safe, allows a sufficient contact of the alcohol with chromium oxide derivatives for a reaction to take place. Jones oxidation marked the beginning of the highly successful saga of chromium-based oxidants.

The action of sulfuric acid on chromium trioxide results in a number of equilibria, in which the major specie is chromic acid (see page 1). Thus, Jones conditions are often referred as "chromic acid" in acetone.

> It is also possible to prepare a "chromic acid" solution by treating sodium dichromate ($Na_2Cr_2O_7$) or potassium dichromate ($K_2Cr_2O_7$) with sulfuric acid. Consequently, sodium[14] and potassium[15] dichromate can be used, instead of chromium trioxide, in Jones oxidations.

Jones oxidation is carried out under very convenient experimental conditions with no need to employ a dry environment or an inert atmosphere. It is very useful for the oxidation of secondary alcohols, while it rarely succeeds in the transformation of primary alcohols into aldehydes due to its tendency to cause over-oxidation to carboxylic acids (see page 2).

One obvious limitation of Jones oxidation is the use of acidic conditions that may cause interference with acid-sensitive functional groups. It must be mentioned that, due to the presence of separated organic and aqueous phases, containing respectively the organic substrate and sulphuric acid, such interferences are much less common than expected, and many protecting groups that can be deprotected using acid survive Jones oxidation. The concentration of sulfuric acid can be decreased in order to minimize interferences with acid-sensitive functionalities, although this causes a decrease on the oxidizing power of Jones reagent.[16]

1.2.1. General Procedure for Transformation of Alcohols to Ketones by Jones Oxidation

A 0.15–0.40 volume[a] of concentrated sulfuric acid is added over one volume of a 1.5–4.5 M (150–450 g/L) solution of CrO_3 (MW= 100.0) in water. A fraction of the resulting red solution is dropped over a 0.01–0.5 M stirred solution of the alcohol in acetone.[b] The alcohol causes the reduction of the red Cr (VI) cations to chromium species with a greenish look. A complete oxidation of the alcohol in a short time requires normally between 1.2 and 5.0 equivalents of chromium trioxide. When a TLC analysis shows that most alcohol is consumed,[c, d] the oxidant is quenched by the addition of 0.1–0.4 volumes of 2-propanol.[e] If so desired, the reaction mixture can be neutralized by the addition of saturated aqueous $NaHCO_3$ or diluted NaOH. The resulting mixture is extracted with an organic solvent, such as EtOAc, CH_2Cl_2 or Et_2O. The collected organic solutions are washed with brine, dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a crude ketone that may need some purification.

[a] The use of a more limited quantity of sulfuric acid helps to avoid interferences with acid-sensitive functional groups. On the other hand, this causes a decrease in the oxidizing power of Jones reagent.[16]

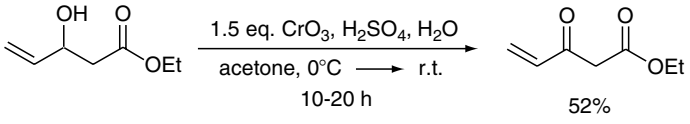
[b] The solution of the alcohol in acetone can be kept either over an ice-water bath or at room temperature during all the reaction. It is also possible to keep the reaction mixture over an ice-water bath during the addition of the chromic acid solution when the major exotherm is expected, and let it reach room temperature afterwards. For reactions on a multigram scale, cooling on an ice-water bath is particularly recommended. During the oxidation of very sensitive substrates, it may be advisable to perform the entire oxidation at a temperature as low as $-20^{\circ}C$.

[c] The consumption of the alcohol can be signaled by the persistence of the red color of the chromium acid solution, which is being dropped into the reaction flask. As the red color of the solution being added is mixed with the green color of the reduced chromium species already present in the reaction flask, it may take some practice to appreciate the color changes. A sheet of white paper, placed bellow a reaction flask made of glass, substantially helps to distinguish these color changes.

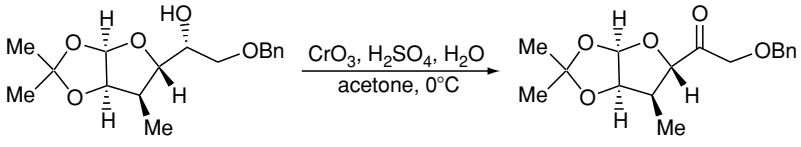
[d] It normally takes between 10 min and 12 h.

[e] Other alcohols, such as MeOH, can also be used. A conspicuous change to deep green color indicates the complete quenching of the chromium (VI) species.

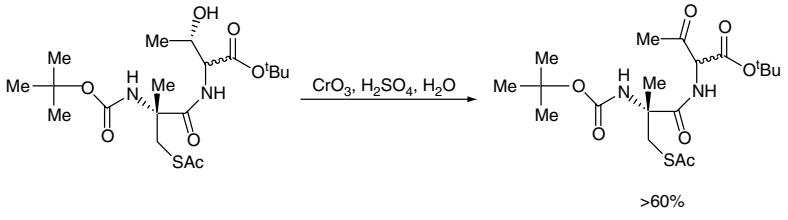
Some successful oxidations of secondary alcohols to ketones, using Jones reagent, are listed bellow:



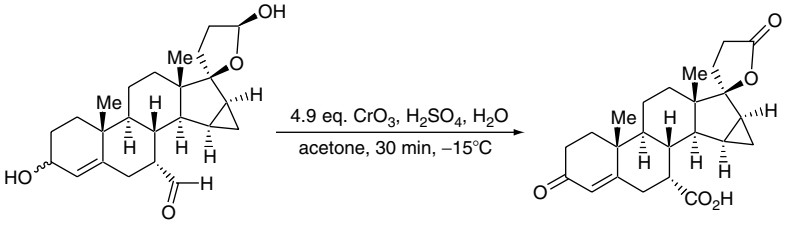
Ref. 3
A detailed description for a multigram scale preparation of an unstable ketone is provided.



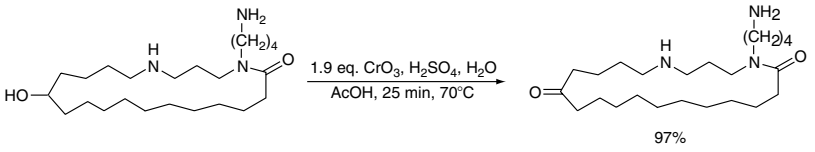
Ref. 17
The internal and the isopropyliden acetals withstand the acidic conditions.



Ref. 18
Both, the very acid-sensitive *t*-butyl ester and the Boc group resist the acidic conditions.

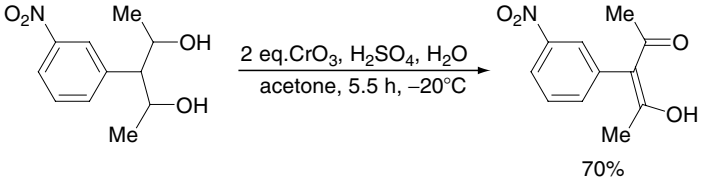


Ref. 19
The simultaneous oxidation of an allylic alcohol, a lactol and an aldehyde is observed.



Ref. 20

The oxidation-sensitive primary and secondary amines remain unaffected, probably due to protonation under the acidic conditions.



Ref. 21

This very difficult oxidation succeded with Jones reagent at very low temperature, while it failed using Swern, Collins, MnO_2, TEMPO, PCC and Dess-Martin conditions. One of the resulting ketones tautomerizes to a very oxidation-sensitive enol.

1.2.2. Protecting Group Sensitivity to Jones Oxidation

Although Jones oxidation is carried out in the presence of aqueous sulfuric acid, functionalities with a high sensitivity to acidic conditions can remain unchanged due to the segregation between the organic and aqueous phases.

Only very acid-sensitive protecting groups are hydrolyzed under the conditions of the Jones oxidation. When free alcohols result from the hydrolysis of very acid-sensitive protecting groups, they are *in situ* oxidized to ketones or carboxylic acids.

It must be mentioned that diverse acid strengths, temperatures and reaction times are used in Jones oxidation, which leads to uneven responses of the same protecting groups.

Most silyl ethers, including the ubiquitous TBS ethers,[22] resist Jones oxidation, with the exception of the very acid-sensitive TMS ethers.[23]

> Anomalous cases are known in which the normally robust TBS ethers are hydrolyzed.[24] Contrastingly, rare instances have been published in which the sensitive TMS ethers remain unchanged[25] under Jones oxdation.

Alkoxyalkyl protected alcohols remain unchanged under Jones oxidation, except those protected with the very acid-sensitive THP group.[26,27b]

> Nevertheless, THP ethers can remain untouched in some cases,[27] while MOM ethers normally resist Jones oxidation[28], and they can be deprotected in some uncommon instances.[29]

Table 1.1. Sensitivity of Alcohol Protecting Groups to Jones Oxidation

Protecting group		Reactivity
Silyl ethers	Remain unchanged: TMS,[25,35] TBS,[22] TIPS,[36] TBDPS[37,23b]	Hydrolysis followed by oxidation to acid or ketone: TMS,[23] TBS[24]
ROCH(R′)–	Remain unchanged: MOM,[28] MEM,[38] BOM,[39] PMBOM,[36b] THP[27]	Hydrolysis followed by oxidation to acid or ketone: THP[26,27b]
Alkyl ethers	Remain unchanged: PMB,[30] ^{t}Bu[31]	Hydrolysis followed by oxidation to acid or ketone: Ph_3C-,[32] p-MeOPh$(Ph)_2$C-[33]
Esters	Remain unchanged	—
Alkylidene protecting diols	Remain unchanged: isopropylidene,[40] benzylidene,[41] cyclohexylidene[42]	—

Benzyl, PMB[30] and *t*-butyl ethers are not affected,[31] while the very acid sensitive trityl and *p*-MeOPh$(Ph)_2$C-ethers are hydrolyzed, and the resulting primary alcohols are oxidized to carboxylic acids.[32,33]

> In fact, it has been reported[34] that benzyl ethers can react with Jones reagent, resulting in the formation of ketones and benzoates. This happens under relatively harsh conditions, and normally no interference from benzyl ethers is observed during the oxidation of alcohols with Jones reagent.

Alcohols protected as esters, and diols protected as cyclic acetals resist Jones oxidation.

It is important to stress that, although MOM, TMS and THP ethers can be hydrolyzed under Jones oxidation, many cases are known in which this does not happen (Table 1.1.).

Depending on substrate and exact reaction conditions, acetals protecting both aldehydes and ketones can resist or be hydrolyzed under Jones oxidation. When the hydrolysis leads to the formation of an aldehyde, an ensuing oxidation to carboxylic acid occurs (Table 1.2.).

Regarding amine protecting groups, both amides and uretanes[49] resist the action of Jones oxidation, including the very acid-sensitive Boc protecting group.[18,47,49]

1.2.3. Functional Group Sensitivity to Jones Oxidation

Aldehydes are oxidized to carboxylic acids by Jones oxidation; although, in certain cases, the oxidation of primary alcohols can be stopped at the aldehyde stage (see page 12).

Table 1.2. Sensitivity of Carbonyl Protecting Groups to Jones Oxidation

Protecting group		Reactivity
Aliphatic acetals	Remain unchanged: dimethyl acetal[43]	Hydrolysis: dimethyl acetal[44]
Cyclic acetals	Remain unchanged: ethylidene acetal[45] 2,2-dimethylpropylidene acetal[45c,46]	Hydrolysis followed by oxidation to acid, or deprotection to ketone: ethylidene acetal[47] propylidene acetal[48]

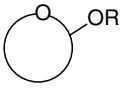
Lactols are oxidized to lactones. Depending on substrate and the precise reaction conditions, sulfides can remain unchanged[51] or be transformed into sulfoxides[52] or sulfones.[53] *O*-Alkyl cyclic hemiacetals including glycosides, both can remain unchanged[54] or suffer oxidation to lactones.[35]

Most epoxides resist Jones oxidation with the exception of the very acid-labile ones,[55] that is the ones able to generate a very stable carbocation on opening.

Amines, pyridines and esters resist Jones oxidation, including the very acid-sensitive *t*-butyl esters.[56] Amines and pyridines withstand Jones oxidation, probably because they are protected by protonation under the reaction conditions.

Normally, nitrocompounds resist[57] the action of Jones reagent. Very rarely, a nitrogroup can suffer activation on contact with Jones reagent, resulting, on being attacked by a nucleophile. This reaction can compete with the normal

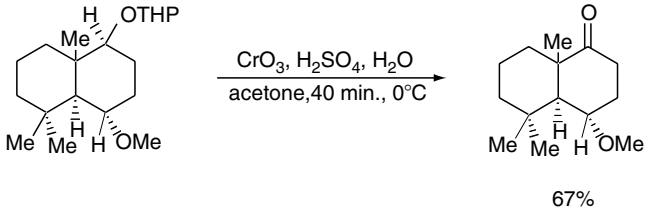
Table 1.3. Sensitivity of Functional Groups to Jones Oxidation

Functional group		Reactivity
Aldehydes	—	Oxidation to acids;[59] nevertheless, sometimes the oxidation of primary alcohols can be stopped at the aldehyde stage[60,61]
Lactols	—	Oxidation to lactones[19,62]
Sulfides	Remain unchanged[56]	Oxidation to sulfoxides[52] or sulfones[53]
	Remain unchanged[54]	Hydrolysis followed by oxidation to acid[63] or lactone[35]
Epoxides	Remain unchanged with the exception of the most acid-sensitive ones[55]	—
Amines and pyridines	Remain unchanged[64]	—
Esters	Remain unchanged, including the very acid sensitive *t*-butyl esters[56]	—

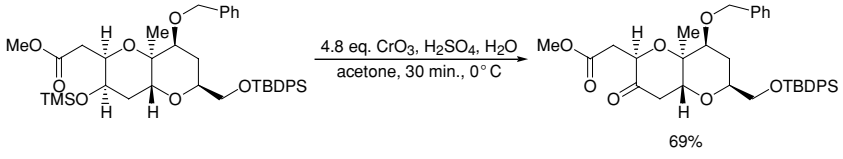
oxidation of the alcohol, only when the alcohol is hindered and the attack on the nitrogroup is favoured by some intramolecular process.[58]

1.2.4. *In situ* Deprotection and Oxidation of Alcohols to Ketones

The sensitivity of some alcohol protecting groups to the acidic conditions of Jones oxidation allow the operation of one-pot reactions, in which deprotection of alcohols is followed by *in situ* oxidation to ketones. Some interesting synthetic applications of this principle are listed bellow:

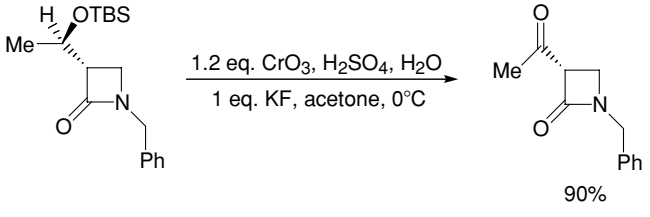


Ref. 26a
The THP ether is hydrolysed and oxidized to ketone under Jones conditions.



Ref. 23b
The TBDPS ether remains unaffected, while the more acid-sensitive TMS ether is hydrolysed and the corresponding alcohol is oxidized to ketone.

The deprotection of the TBS ethers—with the corresponding oxidation to ketones or carboxylic acids—can be purposefully facilitated by the addition of some hydrofluoric acid[65] or KF[66] to the Jones reaction mixture.



Ref. 66
The TBS group is removed with the assistance of potassium fluoride added to the Jones reagent. The resulting alcohol is oxidized to a ketone.

1.2.5. Obtention of Aldehydes by Jones Oxidation

Jones oxidation is generally not useful for the transformation of primary alcohols into aldehydes. This is due to the equilibrium of the aldehydes with the corresponding hydrates in the aqueous media, leading to the subsequent oxidation of the aldehyde hydrates into carboxylic acids. In fact, kinetic studies support the assumption that chromic acid oxidizes aldehydes into carboxylic acids via the corresponding aldehyde hydrates.[5]

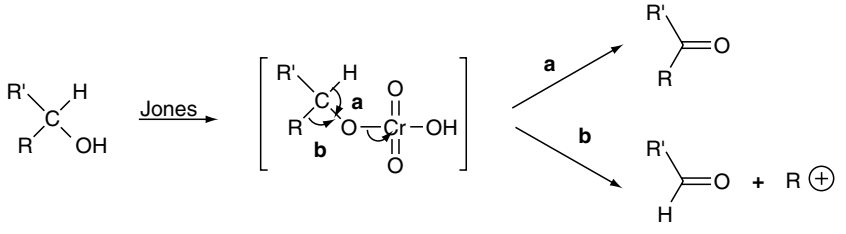
> Nevertheless, in those cases in which the proportion of hydrate in equilibrium with the aldehyde is low, it is possible to obtain a useful yield of aldehyde.[60,61] Electron donating groups,[68,69] conjugation with alkenes and aromatic rings[5] and steric hindrance[69] decrease the proportion of hydrates in equilibrium with aldehydes. This explains the fact that alcohols successfully transformed into aldehydes by Jones oxidation, normally belong to the allyl,[70] benzyl[71] or neopentyl kind.[72]

In simple molecules, it is possible to obtain a good yield of aldehyde—including examples possessing an important proportion of hydrate in equilibrium—by continuous distillation of the aldehyde from the reaction mixture.[73] This procedure only succeeds in the preparation of simple volatile aldehydes.

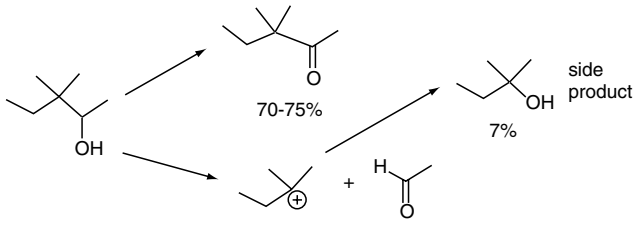
> The obtention of aldehydes can be facilitated by the use of ethyl methyl ketone,[74] instead of acetone, due to the lower polarity of the former, leading to a decreased concentration of aldehyde hydrate.

1.2.6. Side Reactions

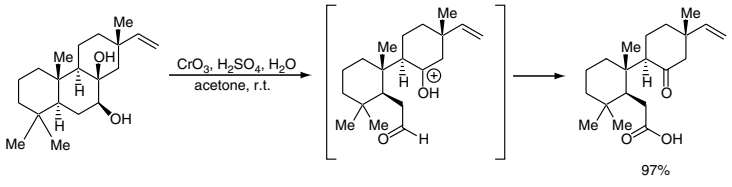
Alcohols, possessing substituents able to stabilize carbocations at the β position, may suffer a carbon-carbon bond breakage as in Equation below (route **b**), competing with the normal transformation to ketones on Jones oxidation (route **a**).[75]



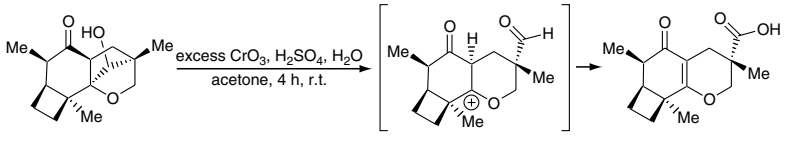
This explains the following side products from oxidation of alcohols with Jones reagent:



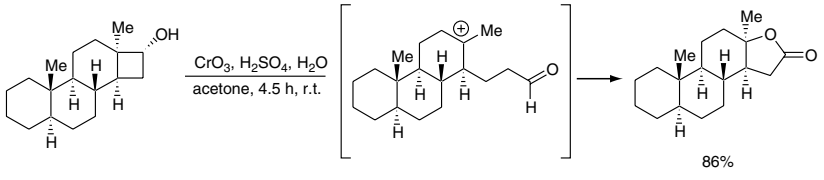
Ref. 76
A carbon-carbon bond breakage leads to a stabilized tertiary carbocation that reacts with water giving a 7% yield of an alcohol.



Ref. 77
A carbocation stabilized on α to a hydroxy group—that is a protonated ketone—is generated by cleavage of a carbon-carbon bond. This also leads to the formation of an aldehyde, which is oxidized *in situ* to a carboxylic acid.



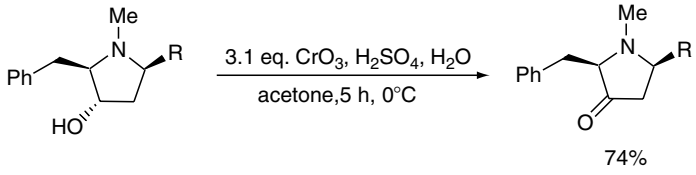
Ref. 78
A carbocation, stabilized by an ether-oxygen, is generated. It looses a proton, leading to an alkene. An aldehyde is also formed that evolves to a carboxylic acid.



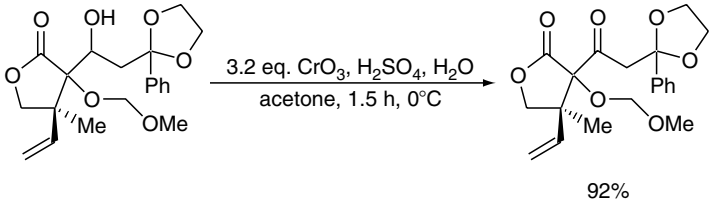
Ref. 79
A naïve look at the product suggests an oxidation to a ketone followed by a Baeyer-Villiger like reaction. The product is best explained by a fragmentation from an intermediate chromate ester, resulting on an aldehyde and a stabilized tertiary carbocation that is transformed into a tertiary alcohol by reaction with water. The hydroxyaldehyde so obtained may evolve to the final lactone either via a lactol or a hydroxyacid.

As the oxidative carbon-carbon bond breakage of alcohols, leading to a stable carbocation, depends not only on the stability of the resulting carbocation but also on very exacting stereoelectronic factors, many cases are known in which alcohols are successfully oxidized to ketones, regardless of apparently easy oxidative carbon-carbon bond breakages. In fact, in synthetic experimental practice, it is recommended not to fail in trying a Jones oxidation because of fear of such side reactions.

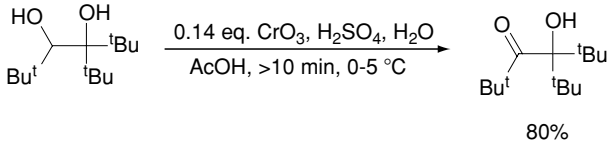
A listing of examples of successful Jones oxidation to ketones on substrates that could be suspected to be prone to oxidative carbon-carbon bond breakage is given bellow:



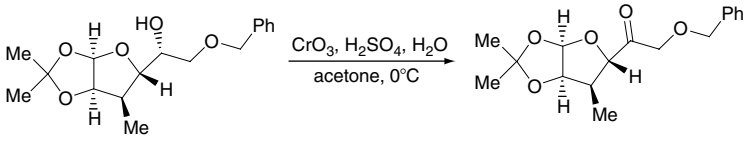
Ref. 80
Probably, the protonation of the nitrogen under the acidic reaction conditions prevents the formation of a cation on α-position to the amine.



Ref. 28a
The carbonyl group strongly destabilizes the carbocation that would be formed on oxidative carbon-carbon bond breakage.



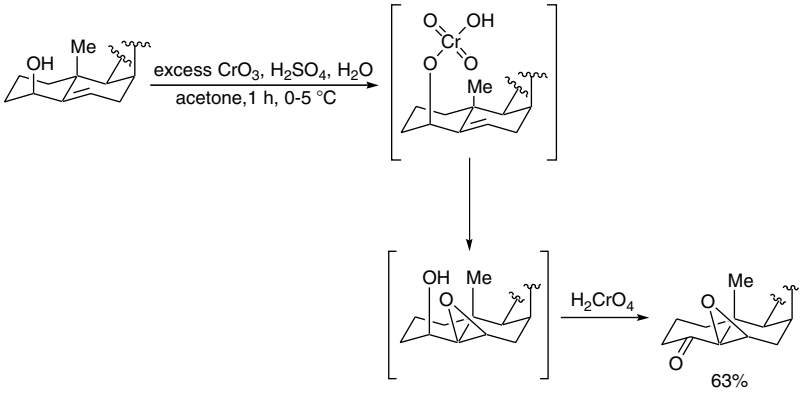
Ref. 81
Steric constraints probably prevent oxidative carbon-carbon bond breakages that would lead to very stable carbocations.



Ref. 82

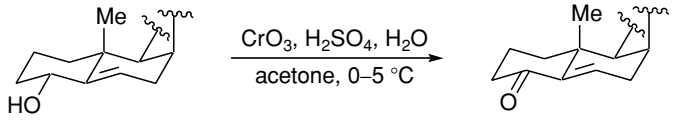
This oxidation succeeds in spite of two potential oxidative carbon-carbon bond breakages that would lead to a carbocation stabilized by ether oxygens.

Sometimes, an alcohol via the corresponding chromate ester may direct a chromium-promoted epoxidation of an alkene. This side reaction, which can happen with other chromium-based oxidants,[83] depends on very exacting stereoelectronic factors to occur.



Ref. 84

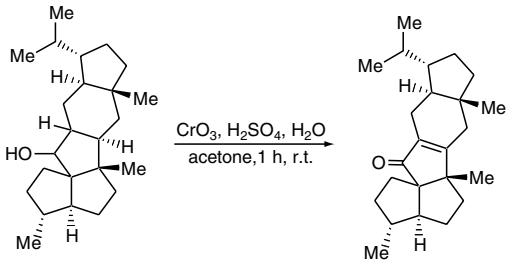
The axial allylic alcohol directs the chromium-promoted epoxidation of the alkene.



Ref. 84

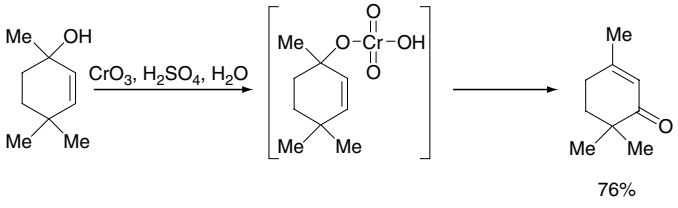
The equatorial alcohol is not able to direct the epoxidation and an uneventful oxidation to ketone occurs.

At times, the carbonyl compound, obtained from the oxidation of an alcohol, suffers a further oxidation, causing the introduction of an olefin conjugated with the carbonyl.



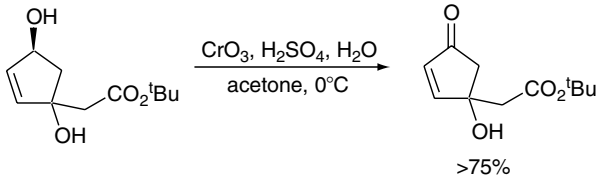
Ref. 85
The treatment of the cyclopentanol under Jones conditions results in an over-oxidation to a cyclopentenone.

Tertiary allylic alcohols form a chromate ester that, as it lacks a hydrogen on α to the alcohol, instead of suffering a normal oxidation to ketone rearranges to an enone. This transformation, which can be brought about by other chromium-based reagents, is normally carried out with PCC when it is purposefully sought at (see page 55).



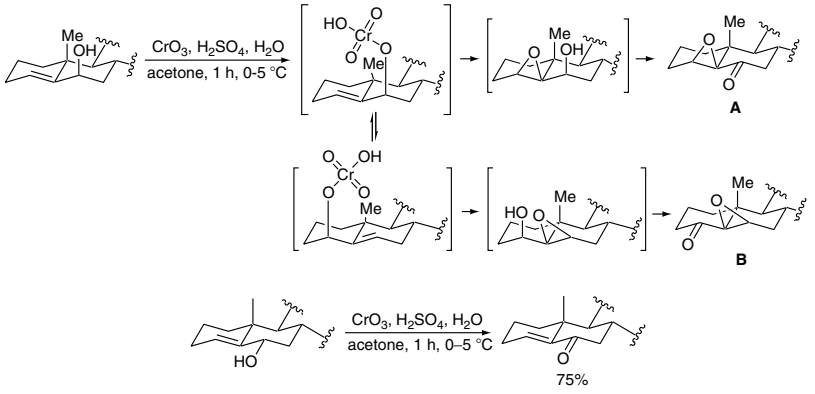
Ref. 86
The tertiary allylic alcohol is transformed by Jones reagent into a rearranged enone.

As the Jones-mediated transformation of tertiary allylic alcohols into enones is normally slower than the oxidation of secondary alcohols into ketones; it is possible to selectively oxidize a secondary alcohol to ketone, without affecting a tertiary allylic alcohol present in the same molecule.



Ref. 87
The secondary alcohol is transformed into a ketone without affecting a tertiary allylic alcohol.

Sometimes, chromate esters from secondary allylic alcohols suffer transposition rather than direct oxidation, and the resulting transposed chromate ester can either produce epoxidation of the alkene, or suffer oxidation yielding a transposed enone.[84]



Ref. 84

The initially formed allylic chromate ester equilibrates with an isomeric chromate ester. Both allylic chromate esters produce the epoxidation of the alkene. The resulting epoxy alcohols are oxidized to epoxy ketones **A** and **B** in a 5:3 ratio. Starting from an equatorial alcohol instead of an axial one, an uneventful oxidation to enone occurs without transposition.

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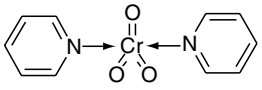
1.3. Collins Oxidation



When chromium trioxide is added over pyridine, the complex $CrO_3 \cdot 2Py$ is formed.[88] This complex, which is soluble in organic solvents, is very efficient in the oxidation of alcohols to ketones and aldehydes. On the other hand, as the complex $CrO_3 \cdot 2Py$ is highly hygroscopic and can explode during its preparation or in contact with organic matter, a number of modifications were made in order to use it in the oxidation of alcohols with the greater safety and experimental simplicity. Thus, in 1953 Sarett *et al.*[89] published that adding chromium trioxide to excess of pyridine results in the formation of a solution of $CrO_3 \cdot 2Py$ in pyridine—the so-called *Sarett reagent*—which is efficient for the transformation of alcohols into aldehydes and ketones. In variance with Jones oxidation, the use of the $CrO_3 \cdot 2Py$ complex allows the

easy oxidation of primary alcohols to aldehydes with little risk of over-oxidation to carboxylic acids. In 1968, Collins[90] first used pre-formed $CrO_3 \cdot 2Py$ dissolved in CH_2Cl_2 for the oxidation of alcohols, which became known as *Collins oxidation*. This method—although suffering from the inconvenience of handling highly hygroscopic $CrO_3 \cdot 2Py$—possesses the advantage over Sarett reagent of avoiding the use of pyridine as solvent, which may interfere with base-sensitive substrates. In 1970, Ratcliffe and Rodehorst[91] described the *in situ* preparation of the complex $CrO_3 \cdot 2Py$ by adding one equivalent of CrO_3 over a solution of two equivalents of pyridine in CH_2Cl_2. This variant of the Collins protocol, as it avoids the dangerous isolation and handling of the very hygroscopic complex $CrO_3 \cdot 2Py$, is nowadays greatly preferred.

Very often, Celite® is added to the Collins solution during the oxidation of alcohols in order to prevent loss of product in chromium precipitates.[92] The addition of acetic anhydride to the Collins solution, first reported by Garegg and Samuelsson,[93] allows a very mild oxidation of alcohols that is particularly suited for sugars and nucleosides. Acetic anhydride helps preventing a β-elimination that may occur during the oxidation of alcohols containing heteroatoms at the β-position.[94]

1.3.1. General Procedure for Oxidation of Alcohols to Aldehydes and Ketones by Collins Oxidation

One equivalent of CrO_3[a] (MW= 100.0) is slowly added over a 0.2–2.0 M solution of 2–2.03 equivalents of dry pyridine (MW= 79.1) in dry CH_2Cl_2.[b]

Very often, ca. 2–7 g of dry Celite® per g of CrO_3 are added—normally before the preparation of the $CrO_3 \cdot 2Py$ complex—in order to avoid loss of product on the chromium precipitates during the work-up. Very frequently, ca. 2–5 equivalents of acetic anhydride (MW = 102.1) are added—normally after the preparation of the $CrO_3 \cdot 2Py$ complex—in order to facilitate a milder reaction, particularly in sugars and nucleosides. It is not common to add both Celite® and acetic anhydride in the same reaction.

After ca. 15–20 min, a 0.02–0.70 M solution of the alcohol in dry CH_2Cl_2 is slowly added. Normally, between 4 and 10 equivalents of the $CrO_3 \cdot 2Py$ complex are used per equivalent of alcohol. When most of the starting alcohol is consumed,[c] two alternative work-ups can be carried out:[d]

Work-up A:

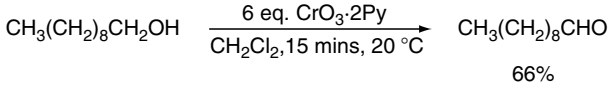
The reaction mixture is filtered through a pad of silica, Florisil® or Celite®. The filtrate is washed with an organic solvent, like Et_2O,

EtOAc or CH_2Cl_2. The collected organic phases may be optionally washed with diluted HCl, diluted aqueous base, brine or saturated $CuSO_4$ solution. The resulting organic solution is dried (Na_2SO_4 or $MgSO_4$) and concentrated.

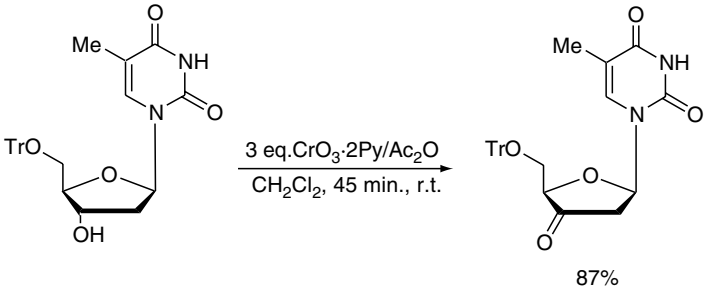
Work-up B:

The reaction mixture is sequentially washed with NaOH (5%), HCl (5%), $NaHCO_3$ (5%) and brine. Adding some ether can help the fractioning. Optionally, the organic phase can be subsequently filtered through Florisil®. The organic phase is dried (Na_2SO_4 or $MgSO_4$) and concentrated.

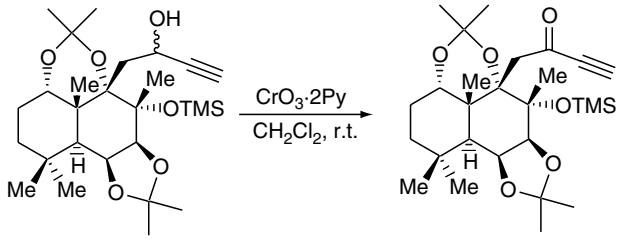
[a] As CrO_3 is hygroscopic, care must be taken to avoid contamination with atmospheric moisture. Water must be avoided from the reaction mixture, for instance, with a $CaCl_2$ tube or with a blanket of an inert gas.
[b] The complete synthetic operations till the work-up can be made at room temperature or at 0°C. Low temperature is particularly advisable on multigram reactions, at least during the initial mixing operations, in which greater exotherms are expected.
[c] It takes normally between 2 min and overnight.
[d] A quick quenching of the oxidation can be done by addition of aqueous Na_2SO_3.



Ref. 95
A detailed description of a Collins oxidation on a multigram scale is provided.

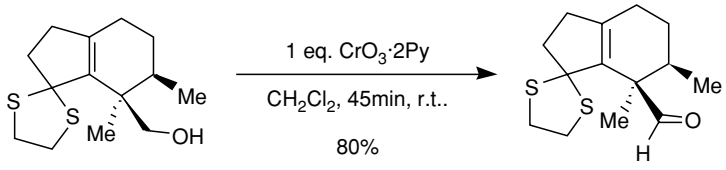


Ref. 94
Failure to add acetic anhydride causes the elimination of thymine, resulting in the formation of an enone.



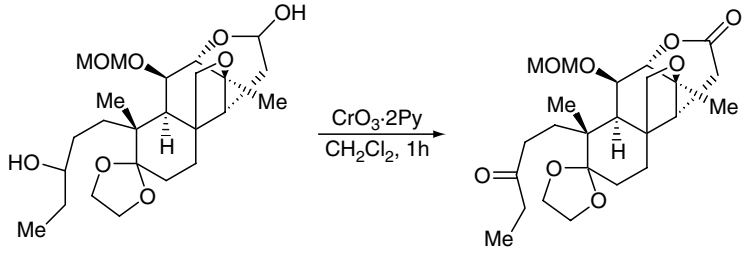
Ref. 96

The Collins oxidation succeeds regardless of the presence of dense functionality, including a labile tertiary TMS ether.



Ref. 97

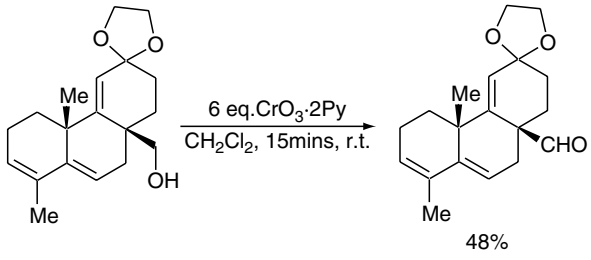
According to the authors "Other chromium-based oxidizing reagents gave consistently lower yields, while the Corey and Swern procedures led to significant decomposition."



Ref. 98

The oxidation of a secondary alcohol to ketone is accompanied by the oxidation of a lactol to lactone.

Collins reagent is used for the introduction of carbonyl groups at allylic positions.[99] This transformation of alkenes into enones is much slower than the oxidation of alcohols, requiring a great excess of $CrO_3 \cdot 2Py$ and prolonged reaction times. Consequently, alcohols can be oxidized to aldehydes and ketones by Collins reagent without interference from alkenes.

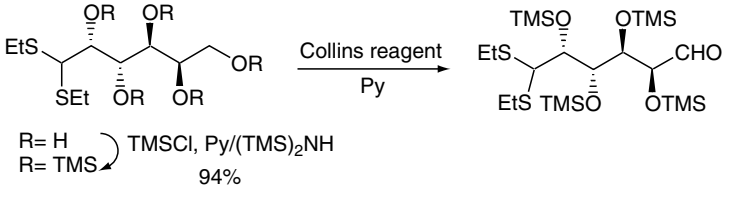


Ref. 100
A hindered primary alcohol is uneventfully transformed into an aldehyde with no interference from allylic oxidations.

Collins reagent can transform tertiary allylic alcohols into rearranged enones,[101] similar to PCC, which is routinely used for this purpose (see page 55). As this reaction is normally slower than the oxidation of primary and secondary alcohols, these can be oxidized with Collins reagent with no interference from tertiary allylic alcohols present in the same molecule.[102]

1.3.2. Functional Group and Protecting Group Sensitivity to Collins Oxidation

Protecting groups, including very labile ones, withstand the action of Collins reagent. The very labile primary TMS ethers are transformed into the corresponding aldehydes.[103] As secondary and tertiary TMS ethers resist the action of Collins reagent, a protocol involving per-silylation followed by Collins oxidation allows the selective oxidation of primary alcohols in the presence of secondary ones.[104]



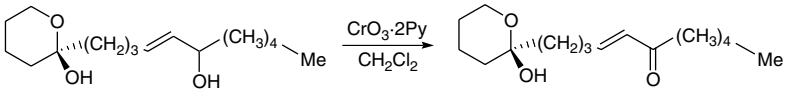
Ref. 104a
The primary TMS ether is selectively transformed into an aldehyde in the presence of secondary TMS ethers.

Although there are many published examples of silyl ethers resisting the action of Collins reagent, there is one report in which a diphenylmethylsilyl (DPMS) ether is transformed into the corresponding aldehyde by $CrO_3 \cdot 2Py$ in CH_2Cl_2.[105]

Most functional groups resist Collins oxidation, including the oxidation-sensitive sulfides[106] and thioacetals.[103] Although Collins reagent can transform alkenes into enones[99] and alkynes into inones,[107] these reactions are slower than the oxidation of alcohols into aldehydes or ketones. Therefore, alcohols can be usually oxidized with no interference from alkenes[108] or alkynes.[109]

Collins reagent is able to transform benzyl ethers into ketones and benzoates.[110] Normally, this causes no interference with the oxidation of alcohols, because the oxidation of benzyl ethers demands more drastic conditions.

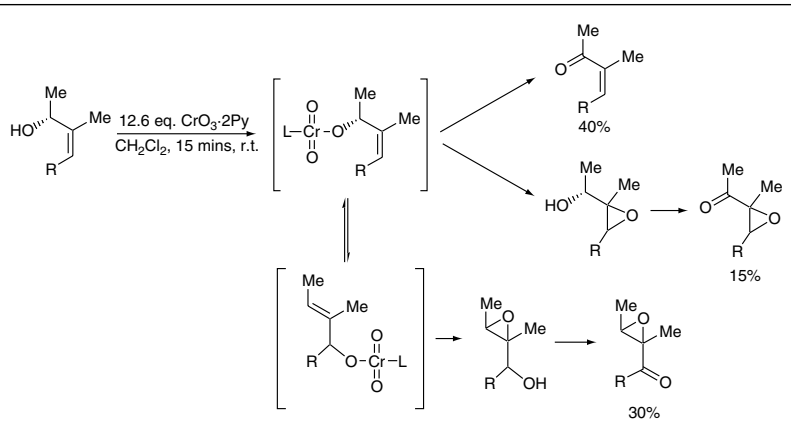
Selenides are oxidized to selenoxides that normally suffer an *in situ* elimination.[111] Amines are destroyed,[112] although its protection as amides or carbamates prevents the reaction with Collins reagent. Lactols are very quickly oxidized to lactones,[113] unless a very great steric hindrance is present.[114] Tertiary lactols suffer oxidation via its opened hydroxyketone form.[115] The oxidation of tertiary lactols may be slow, so that an alcohol can be selectively oxidized.



Ref. 116
An alcohol is selectively oxidized in the presence of a tertiary lactol.

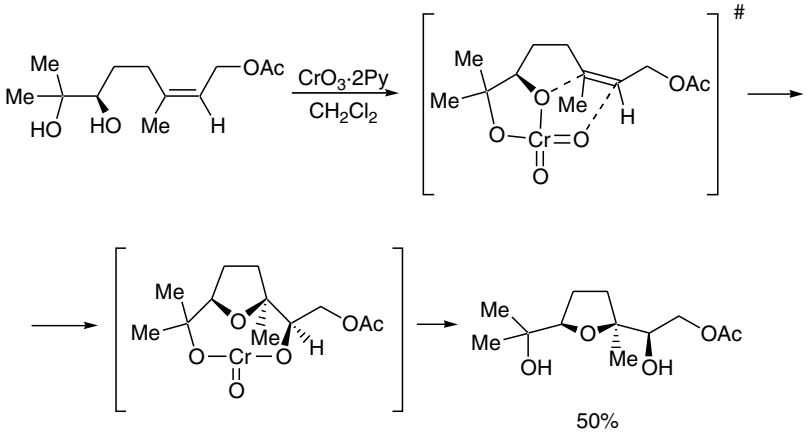
1.3.3. Side Reactions

Similar to Jones reagent, Collins reagent can produce a hydroxy directed epoxidation of allylic alcohols. This side-reaction only occurs in a limited number of allylic alcohols, most of them being oxidized uneventfully to the corresponding enones.[117]



Ref. 118
The expected enone is obtained in 40% yield. A 15% yield of the product, resulting from hydroxy-directed epoxidation followed by oxidation to ketone, is obtained. A third product, obtained in 30% yield, can be explained by the equilibration of the initially formed allylic chromate ester with an isomeric chromate ester that directs the epoxidation of an alkene, giving an epoxy alcohol that is further oxidized to an epoxy ketone.

Sometimes, alcohols can direct the oxidation of alkenes, resulting in highly stereoselective formation of tetrahydrofurans by the action of Collins reagent. Thus, 1,2-diols can form cyclic chromate esters that can intramolecularly oxidize alkenes, positioned so as to allow the operation of five-membered cyclic transition states.[119]



Ref. 119
The 1,2-diol reacts with Collins reagent, producing a cyclic chromate ester that oxidizes intramolecularly the alkene. This results in a highly stereoselective preparation of a tetrahydrofuran.

After oxidations with $CrO_3 \cdot 2Py/Ac_2O$, sometimes compounds possessing strongly coordinating sites, for example nitrogen atoms containing free electron pairs, form complexes with residual chromium salts that can hinder efficient chromatographic purification. Such complexation causes broadening of NMR signals and prevents the corresponding compounds from having sharp melting points and right combustion analyses. A straightforward correlation between complexation tendency and nitrogen basicity may not be present.[120]

Section 1.3. References

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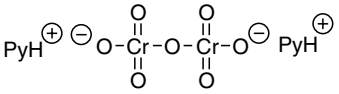
1.4. Pyridinium Dichromate (PDC)



The slow addition of one equivalent of pyridine on a concentrated aqueous solution of CrO_3 leads to the formation of pyridinium dichromate (PDC), which can be precipitated by the addition of 4 volumes of acetone per volume of water and cooling at $-20°C$. Filtration of the precipitate, washing with acetone and drying under vacuum leads to PDC as orange crystals.[121] An explosion can occur during the preparation of PDC. This can be avoided following these guidelines:[122] i) chromium trioxide must be completely dissolved in the concentrated aqueous solution; ii) the temperature must be kept bellow 25°C during mixing of the reagents.

The use of PDC for the oxidation of alcohols was first described in a brief communication by Coates and Corrigan in 1969.[123] Nevertheless, full attention of the synthetic community for this useful reagent was achieved by the publication of Corey and Schmidt in 1979, in which they described the potential of this reagent.[121]

PDC exists in the form of stable bright-orange crystals that remain unaltered by manipulation in the open air. Its lack of hydrophylicity and almost neutral properties facilitate its handling and allows the selective oxidation of alcohols in the presence of very sensitive functional groups.

> Although the presence of pyridinium cations makes PDC slightly acidic, very acid sensitive functionalities are able to withstand the action of PDC. Some sodium acetate can be added as a buffer for a completely acid-free oxidation.[124]

Normally, the oxidation of alcohols to aldehydes or ketones is carried out using a suspension of PDC in CH_2Cl_2 at room temperature. Other organic solvents, such as EtOAc, MeCN, benzene or $CHCl_3$, are occasionally used.

> DMF, which is very efficient in dissolving PDC, or a mixture of DMF and CH_2Cl_2, can also be used as solvent, regardless of the fact that PDF may promote the over-oxidation of certain alcohols into acids, something that may happen even in the absence of added water. In fact, PDC in DMF is very effective for the oxidation of certain primary alcohols into carboxylic acids.[121] This oxidation into carboxylic acids succeeds when the intermediate aldehyde equilibrates with a liberal proportion of hydrate; that is, when the intermediate aldehyde belongs to the aliphatic kind and is not highly hindered. The water necessary for the formation of the intermediate aldehyde hydrate may proceed from the decomposition of PDC. Regardless of the problem of over-oxidation, the use of DMF as solvent, contrary to the more common CH_2Cl_2, can offer some advantages in the obtention of ketones or uncomplicated aldehydes because of its superior solubilizing power.

Mechanistic evidences show that PDC, similar to other chromium-based oxidants, operates via an intermediate chromate ester that evolves to a carbonyl compound in the rate-determining step.[125]

Sometimes, oxidations with PDC can be rather slow. However, the following chemicals can be added in order to achieve a synthetically useful acceleration of this oxidation.

- Molecular sieves (MS)
- An organic acid
- Acetic anhydride

The addition of molecular sieves may produce a substantial acceleration of the oxidation with PDC. Apparently, this acceleration is unrelated with its water-scavenging nature, although best results are obtained when thoroughly activated material is used. Best results are obtained when 3 Å molecular sieves are used.[126]

Acetic acid,[127] pyridinium trifluoroacetate (PTFA)[121] or pyridinium tosylate (PPTS)[128] are often added in order to speed up PDC oxidations. Acetic acid, which is described as superior[127a] and very easy to remove, is used most often. Although this precludes the advantages of using an almost neutral PDC medium, it provides a very useful substantial acceleration of the oxidations. The combined employment of molecular sieves and an acid can provide a synergistic accelerating effect.[127a]

Acetic anhydride also provides a substantial acceleration of PDC oxidations, which is particularly useful in sugar and nucleoside chemistry.[129]

Occasionally, the addition of accelerants may be counterproductive because they may lead to quick unselective oxidations.[127b] In some difficult substrates, good yields are achieved when a balance is reached by the moderate use of accelerants, and some exploratory chemistry is made employing less common solvents, like EtOAc.[127b]

The following experimental tips help to achieve best yields in oxidations of alcohols to aldehydes and ketones with PDC.[127a]

- Finely ground PDC gives best results.
- Although commercial PDC operates in a satisfactory way in most reactions, some cases are reported in which success depends on using freshly prepared PDC.[130]
- Methylene chloride must be dry. Best results are obtained when it is distilled from PDC and stored over molecular sieves.[127a]
- When molecular sieves are added, best results are obtained using 3 Å molecular sieves freshly activated by heating at ca. 320°C during 5 h. Alternatively, they can be stored at 80°C after activation and reactivated for half an hour just before use. Finely ground molecular sieves give best results.
- When acetic acid is added, it must be very dry.

1.4.1. General Procedure for Oxidation of Alcohols to Aldehydes and Ketones with Pyridinium Dichromate (PDC)

Approximately, 1.1–7 equivalents of solid PDC[a] are added over a ca. 0.01–0.30 M solution of the alcohol in dry methylene chloride.[b] The resulting suspension is stirred at room temperature[c] till most of the starting compound is consumed.[d]

Approximately, 0.5–4 g of activated[e] molecular sieves—preferably finely ground 3 Å molecular sieves—per mmol of alcohol can be added in order to accelerate the oxidation. The reaction can also be accelerated by the addition of ca. 0.9–4 equivalents of dry AcOH[f] or 0.75–12 equivalents of acetic anhydride. The simultaneous use of molecular sieves and an organic acid has a synergistic accelerating effect.[g] The addition of ca. 0.5–2.50 g of Celite® or Florisil® per mmol of alcohol can facilitate the work-up. Celite® or Florisil® can be added either at the beginning of the oxidation or ca. 30 min before the work-up.

Two alternative work-ups can be carried out.

Work-up A:

This is the most common work-up. Diethyl ether is added and the precipitate is decanted and washed with ether. The collected organic phases are filtered through a pad of Celite®, silica or Florisil®. Alternatively, decanting the precipitate can be avoided and the mixture, resulting from the addition of ether, can be directly filtered through a pad of silica, Celite® or Florisil®. When the reaction is carried out under dilute conditions, the addition of diethyl ether can be avoided. The organic phase is concentrated giving a residue that may need chromatographic purification. When the reaction is carried out in the presence of added Celite® or Florisil®, a similar work-up is made in which the Celite® or Florisil® is filtered, and no extra filtration through a pad of silica, Celite® or Florisil® is normally needed.

Work-up B:

Diethyl ether is added and the resulting mixture is washed with aqueous phases. The aqueous phases used can be: plain water, aqueous saturated $NaHCO_3$ solution, diluted hydrochloric acid or brine. The collected organic phases are dried ($MgSO_4$ or $NaSO_4$) and concentrated, giving a residue that may need chromatographic purification.

[a] It may be advisable, particularly on multigram scale reactions, to cool down (ca. 10°C) the reaction mixture during the addition of some components in order to prevent exotherms, which are more likely during the addition of PDC, molecular sieves or the acid accelerant.

[b] Occasionally, other apolar organic solvents, like EtOAc, MeCN, benzene or $CHCl_3$, are used. Some dry DMF may be added to increase the solubility of polar alcohols. DMF may also be the only solvent used. When DMF is employed, over-oxidation of primary

alcohols to carboxylic acids may occur, particularly when the intermediate aldehyde equilibrates with a substantial percentage of hydrate (see page 2).

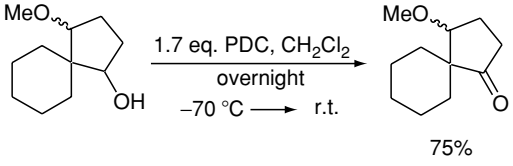
[c] It may be advisable to carry out the oxidation at 0°C when sensitive alcohols, able to be oxidized very quickly, are employed. Alternatively, it can be advisable to accelerate the reaction by heating at 40°C when robust alcohols are oxidized.

[d] It usually takes about 0.5–24 h. Very often, the reaction is very slow unless accelerants are added.

[e] Best results are obtained when molecular sieves are activated by heating at ca. 320°C, at least during 5 h just prior to use. Activated molecular sieves can also be stored at 80°C and re-activated by heating at ca. 320°C during half an hour before use.

[f] Other organic acids, such as pyridinium trifluoroacetate or pyridinium tosylate, can also be used, although acetic acid is very easy to eliminate during work-up, and is reported to give best results in some cases.

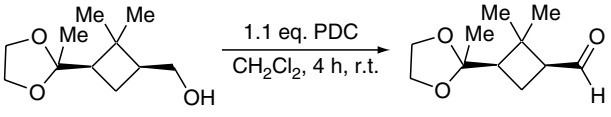
[g] When acetic anhydride is used as accelerant, no other accelerants are added.



75%

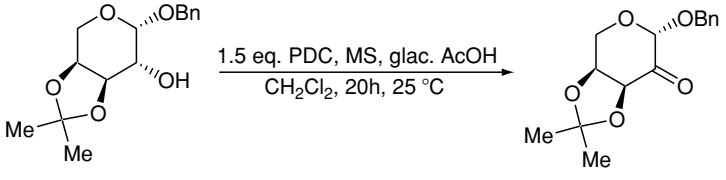
Ref. 131

A detailed description of a multigram scale reaction is provided.



Ref. 132

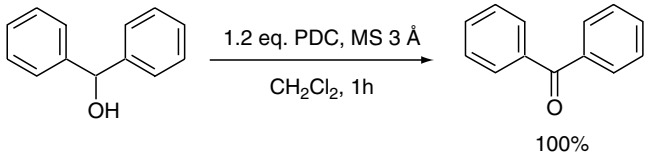
A PDC oxidation, followed by removal of the chromium salts with Florisil®, gives a good yield of an unstable aldehyde. Attempted oxidation using Swern conditions met the problem of decomposition of the aldehyde during column chromatography.



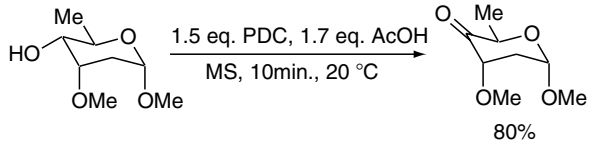
72%

Ref. 133

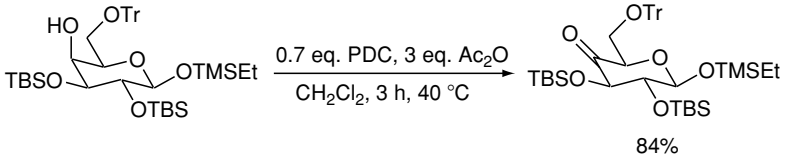
Although an oxidation with Swern reagent gives a better yield, an oxidation with PDC is preferred because it is easier to carry out. Swern oxidation produces ketone contaminated with sulfur-containing impurities, which may interfere with a subsequent hydrogenation.



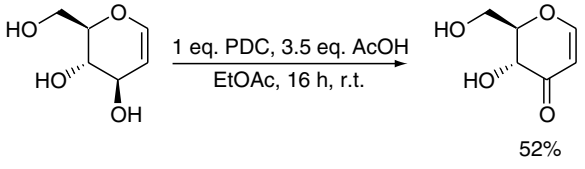
Ref. 134
In the absence of molecular sieves, the oxidation lasts 12 h and no quantitative yield is obtained.



Ref. 127a
In the absence of molecular sieves, the reaction needs 40°C and 2.5 h, giving a 70% yield. In the absence of both molecular sieves and acetic acid, the reaction takes 3 d at 40°C and provides a 70% yield.



Ref. 135
The addition of Ac_2O allows a smooth high-yielding reaction.



Ref. 127b
Molecular sieves are not added because they promote a quick, non-selective oxidation. The addition of acetic acid is needed for a smooth and complete oxidation.

1.4.2. Functional Group and Protecting Group Sensitivity to Oxidation with PDC

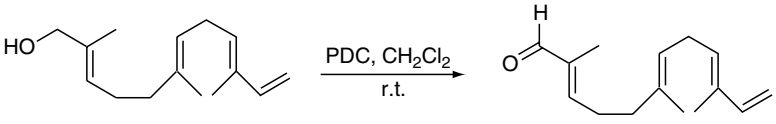
The near neutral character of PDC makes almost all protecting groups, including very acid sensitive ones, resistant to its action.

PDC in DMF is able to perform alcohol desilylation and *in situ* oxidation.[136]

TMS and TBS ethers can be cleaved and oxidized to aldehydes or ketones in a one-pot reaction, employing a standard PDC oxidation in which trimethylsilyl chloride is added.[138]

Although aldehydes can be oxidized to acids by PDC, this reaction normally succeeds only with aldehydes in equilibrium with a substantial proportion of hydrate, and useful reaction speed normally demands the use of DMF as solvent.[121] Sometimes, aldehydes possessing electron withdrawing groups at the α position, which strongly shift the hydration equilibrium to the aldehyde hydrate, can be quickly oxidized to acids even in dry CH_2Cl_2; the water most probably being originated from the decomposition of PDC.[139]

PDC is able to oxidize allylic positions, resulting in the transformation of alkenes into enones. This reaction normally demands heating and is best performed in solvents other than CH_2Cl_2.[140] Very often, *t*-butyl hydroperoxide is added.[141] When a standard procedure for the oxidation of alcohols with PDC is employed, normally no interference with alkenes occurs.

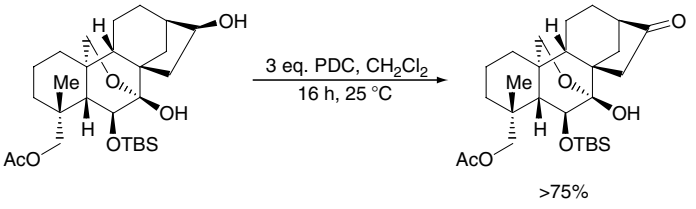


Ref. 142

The oxidation of the alcohol is not affected by the presence of alkenes.

Lactols are easily oxidized to lactones by PDC, under the same standard conditions used for the oxidation of alcohols into aldehydes and ketones. Cases are reported in which a lactol is transformed into a lactone in the presence of an unreacting alcohol,[143] and also conversely where an alcohol is selectively oxidized in the presence of an unreacting lactol.[144]

Lactols derived from hydroxyketones cannot be oxidized to lactones. Theoretically, they could be oxidized to dicarbonyl compounds via the minor hydroxyketone equilibrating with the lactol. In practice, this reaction is usually so slow as to allow the selective oxidation of alcohols with PDC, in the presence of lactols derived from hydroxyketones.

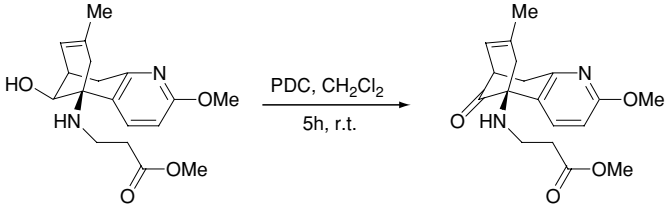


>75%

Ref. 145

No interference is caused from a lactol, which must be in equilibrium with a small amount of a hydroxyketone that could be oxidized with PDC.

Although primary and secondary amines are destroyed by PDC, hindered secondary amines can resist the action of PDC long enough to allow selective oxidation of alcohols.[146]



71%

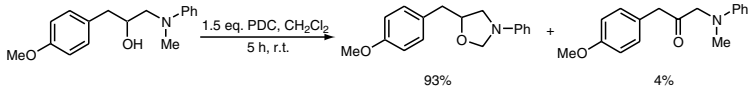
Ref. 147

This reaction succeeds with PDC, with no interference from the hindered secondary amine, while Dess-Martin periodinane and tetra-*n*-propylammonium perruthenate give complex mixtures.

Normally, alcohols can be selectively oxidized with PDC in the presence of tertiary amines.[148] Although *N*-methyl tertiary amines are transformed into formamides by PDC,[149] this reaction is usually slow enough so that selective oxidation of alcohols with PDC can be possible.

Nevertheless, there is one report on the selective transformation of an electron-rich aromatic *N*-methyl tertiary amine into a formamide in the presence of a primary alcohol.[150]

N-Methyl aromatic amines can suffer oxidation by PDC, giving an immonium ion that can be trapped intramolecularly by a neighbouring alcohol.



93% 4%

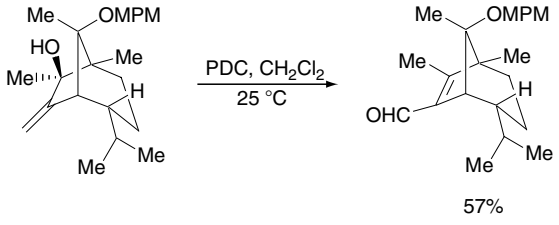
Ref. 151

The ketone is isolated only with a 4% yield. Most of the starting compound reacts via oxidation of the amine to an immonium ion that is trapped by the neighbouring alcohol.

There is one report in which sulfides are oxidized by PDC in aqueous acetic acid; however normally the oxidation of alcohols is quicker, so that selective oxidation of alcohols with PDC is possible in the presence of sulfur containing compounds, such as thiophenes,[153] aryl sulfides,[154] alkyl sulfides[155] and dithioacetals.[156]

Nitrocompounds resist the action of PDC during the oxidation of alcohols.[157] On rare occasions, PDC can promote the attack of nucleophiles on nitro groups, in a similar manner to the one observed with Jones reagent (see page 10).

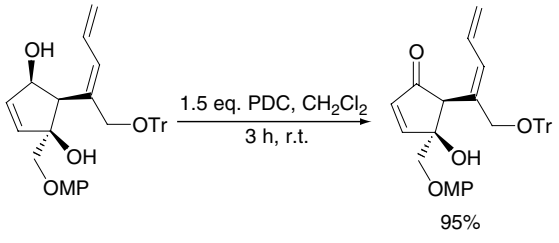
Tertiary allylic alcohols are transformed into transposed enones by PDC under mild conditions.[158]



Ref. 158a

Treatment of the tertiary allylic alcohol with PDC results in transposition of the intermediate chromate ester, producing a transposed enal.

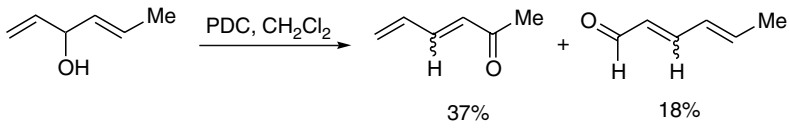
Nevertheless, normally it is possible to selectively oxidize primary and secondary alcohols with PDC without affecting tertiary allylic alcohols.[159]



Ref. 160

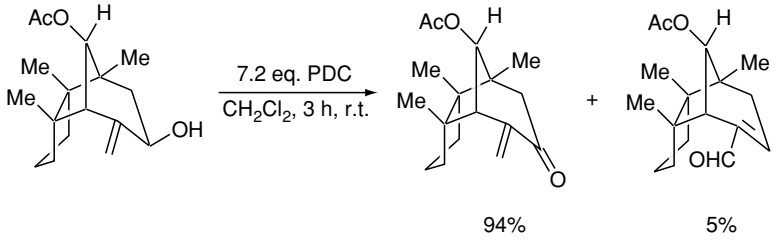
An uneventful oxidation of a secondary alcohol occurs with no oxidative transposition to enone of the tertiary allylic alcohol.

Sometimes, tertiary allylic alcohols interfere with the oxidation of primary and secondary alcohols with PDC, causing low-yielding transformations into the desired aldehydes and ketones.[161] Secondary allylic alcohols occasionally suffer oxidative transposition to enones rather than a direct oxidation.[162]



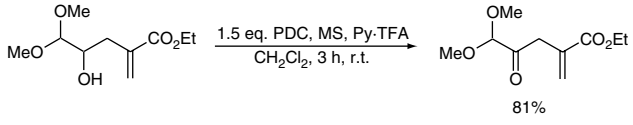
Ref. 162
Rather than a direct oxidation to dienone, the secondary alcohol suffers an oxidative transposition to give a mixture of enone and enal.

PDC has a lesser tendency to effect oxidative transposition of allylic alcohols than other chromium-based reagents.[163]



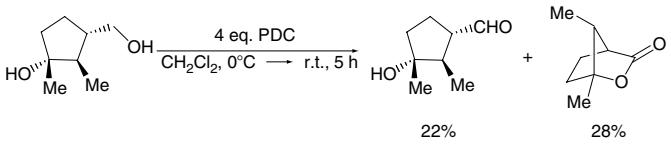
Ref. 163
Oxidation with PCC gives a 5:1 ratio of the desired enone versus an enal resulting from oxidative transposition. The lesser tendency of PDC to effect oxidative transpositions of allylic alcohols allows to improve this ratio to 15:1.

Although oxidation of homoallylic alcohols with PDC normally leads uneventfully to the desired β,γ-unsaturated carbonyl compound,[164] in some cases complex mixtures are obtained.[165] It is quite remarkable that oxidations of homoallylic alcohols with PDC result, only quite exceptionally, in migration of the alkene into conjugation with the resulting carbonyl compound,[166] even in cases where such migration would be greatly favoured by thermodynamics.[167]

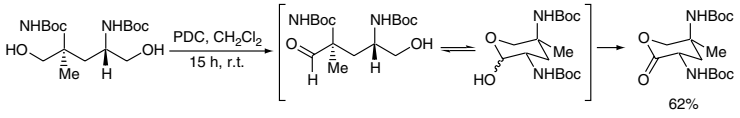


Ref. 164c
No migration of the alkene into conjugation with both carbonyls occurs regardless of very favourable thermodynamics.

Very often, when the treatment of a 1,4- or a 1,5-diol with PDC leads to the initial formation of a hydroxyaldehyde that can equilibrate with a cyclic hemiacetal, the latter is further oxidized to a lactone.[168]

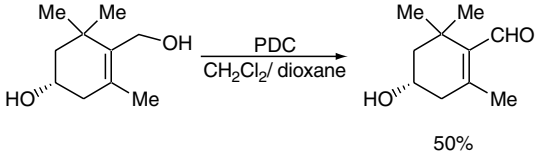


Ref. 169
The expected hydroxyaldehyde is obtained accompanied by a lactone, resulting from the oxidation of a lactol equilibrating with the hydroxylaldehyde.



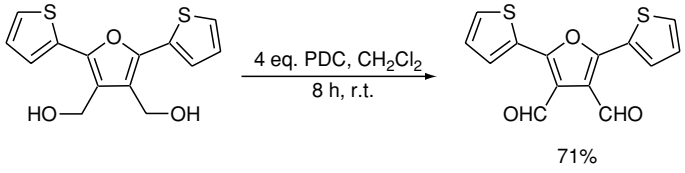
Ref. 170
One of the alcohols is oxidized to an aldehyde, which equilibrates with a lactol that is further oxidized to a lactone.

No lactone formation occurs when the intermediate lactol is disfavoured by geometric constrains.[171]



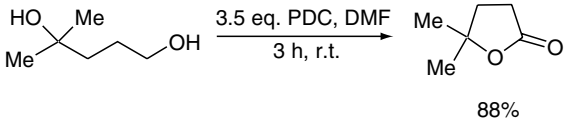
Ref. 172
No further oxidation to lactone occurs for the resulting hydroxyaldehyde is not able to equilibrate with a substantial amount of lactol, that would have to exist in a very unfavourable chair conformation containing a bridgehead alkene.

Sometimes, an uneventful oxidation to dicarbonyl compounds may succeed even when an intermediate lactol looks very favourable.



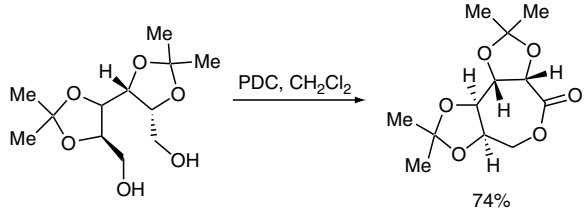
Ref. 153a
An uneventful oxidation to a dialdehyde happens regardless of the intermediacy of a hydroxyaldehyde, that would be expected to equilibrate with a substantial proportion of hemiacetal.

When the formation of the lactone is purposefully looked at, DMF that promotes the oxidation of primary alcohols in carboxylic acids can be used as solvent in PDC oxidations. The resulting hydroxycarboxylic acid would cyclize to a lactone if favoured.[173]



Ref. 174
Oxidation of the primary alcohol with PDC in DMF leads to a hydroxyacid that cyclizes to a stable five-membered lactone.

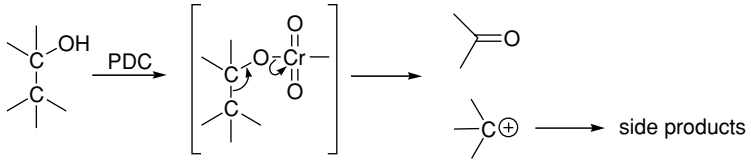
Lactone formation can happen even resulting in the generation of seven-membered lactones, which are usually less favoured than five or six-membered lactones.



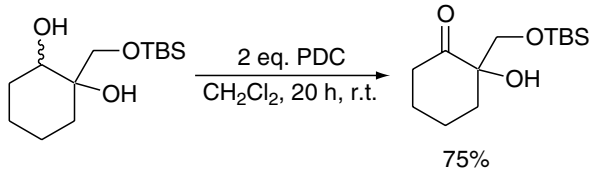
Ref. 175
The intermediate hydroxyaldehyde equilibrates with a sufficient proportion of seven-membered lactol, so that the oxidation of the latter to lactone is more predominant than the oxidation of the intermediate hydroxyaldehyde to dialdehyde.

1.4.3. Side Reactions

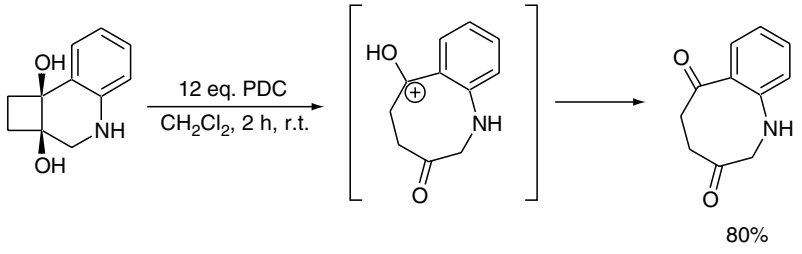
Similar to other chromium-based oxidants, the action of PDC on alcohols, bearing substituents at the α position and able to support stable carbocations, may result in a carbon-carbon bond breakage from the intermediate chromium ester.



This explains, for example, the tendency of some 1,2-diols to suffer oxidative carbon-carbon bond breakage under the action of PDC. Thus, although many 1,2-diols can be uneventfully oxidized to α-hydroxyketones with PDC,[176] very often a cleavage of a carbon-carbon bond occurs, resulting in two carbonyl functionalities.[177] Vicinal tertiary diols, sometimes, are smoothly oxidized to diketones by PDC.[178]

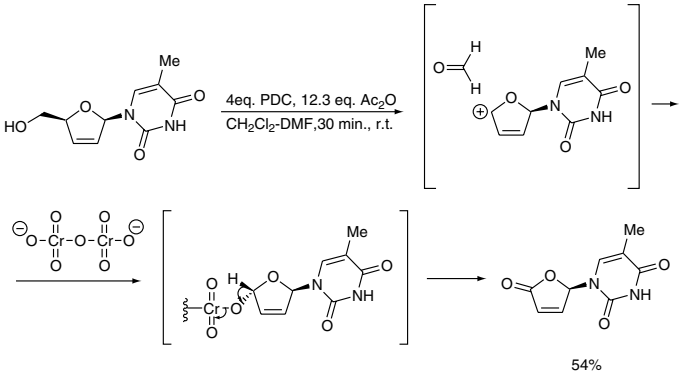


Ref. 176c
No oxidative carbon-carbon bond breakage occurs in spite of the very stable carbocation that could be formed from the intermediate chromate ester.



Ref. 179
The intermediate chromic acid ester, which is most probably formed on the more exposed non-benzylic alcohol, evolves by cleavage of a carbon-carbon bond, resulting in the formation of a ketone and a benzylic cation that yields a second ketone by deprotonation.

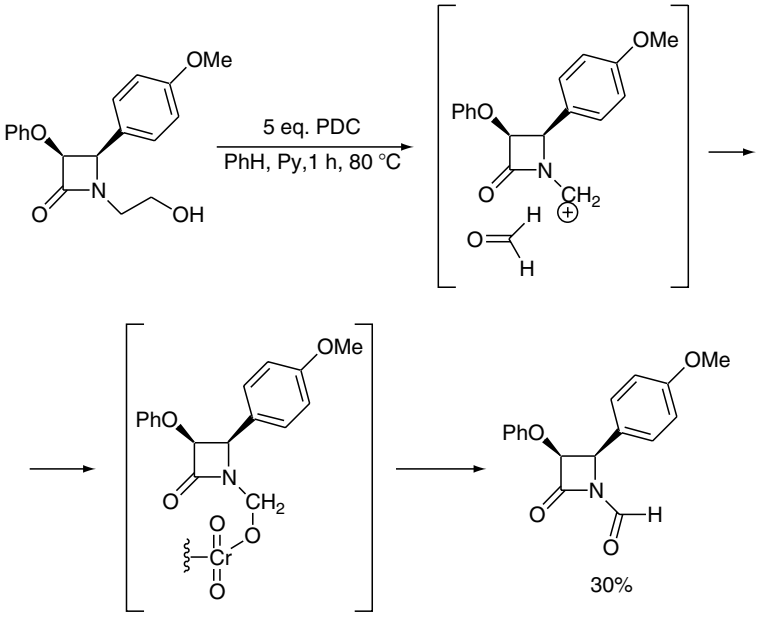
Because of the stabilization of carbocations on α to oxygen atoms, fragmentation can occur in β-alkoxyalcohols via intermediates, similar to the ones resulting from fragmentation of 1,2-diols. In variance to the cations originated from 1,2-diols that normally evolve to ketones by deprotonation, cations originated from β-alkoxyalcohols tend to evolve to esters by oxidation.[180] This further oxidation can be explained by the trapping of these cations with dichromate, resulting in a chromate ester that suffers fragmentation to an ester.



Ref. 129a

The result of this oxidative degradation can be explained by an initial fragmentation leading to formaldehyde, and a cation that can be trapped by reaction with dichromate, resulting in a chromate ester that yields a lactone. The authors of this reaction pursued as much fragmentation as possible, and found that best yields of fragmented product were obtained by the use of Ac_2O as accelerant.

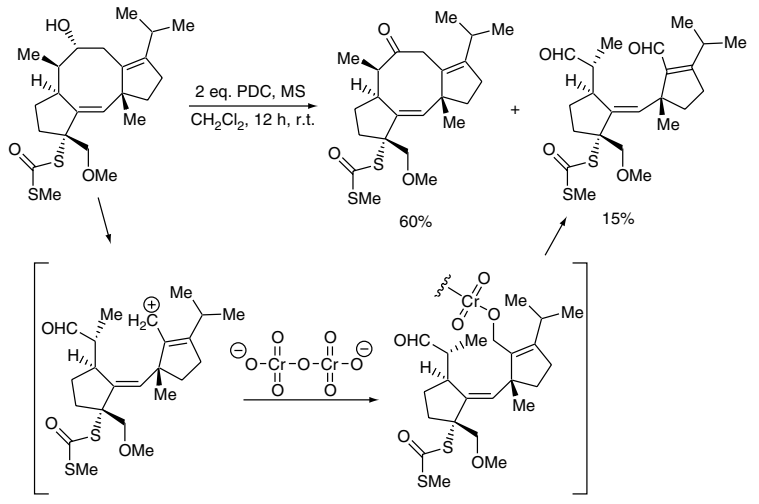
A very similar fragmentation can occur in alcohols possessing a nitrogen atom at the β-position.



Ref. 181

Fragmentation of the initially formed chromate ester gives formaldehyde and an iminium ion that is trapped by dichromate. The resulting chromate ester evolves to a formamide.

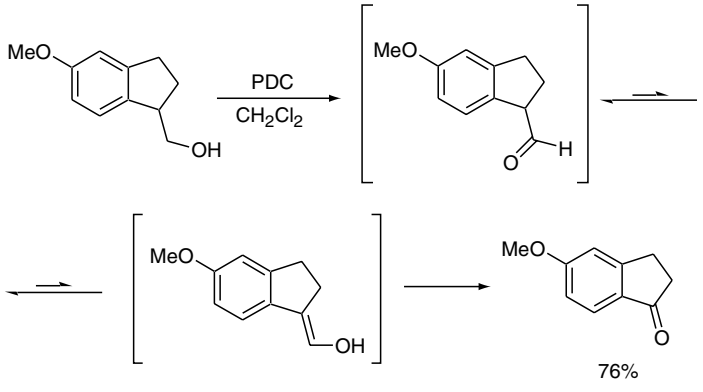
Fragmentation of chromate esters may be also driven by the formation of stable allylic[182] or benzylic[183] cations.



Ref. 182

The expected ketone, obtained in 60% yield, is accompanied by 15% of a fragmentation product, which can be explained as a result from the generation of an allylic carbocation that is trapped by attack of dichromate dianion.

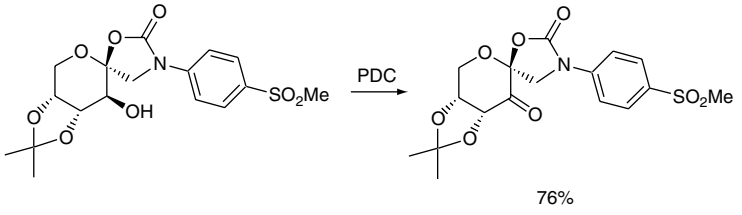
Many other PDC-induced fragmentations can be explained by an alternative mechanism involving a normal oxidation to an aldehyde or ketone, followed by the cleavage of the enol tautomer by PDC.[183a]



Ref. 183a

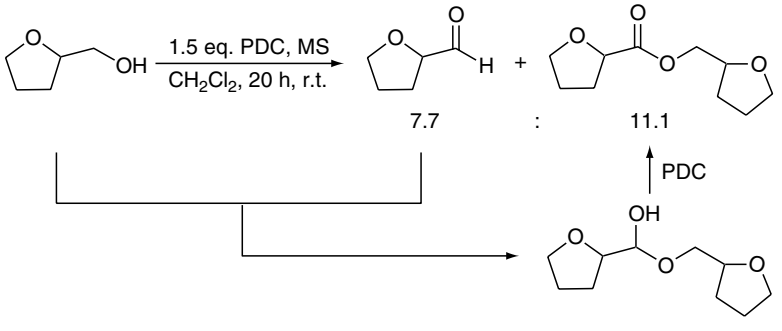
Although a mechanism involving a chromate ester fragmentation to a benzylic cation can be put forward, the authors presented some evidence pointing to a mechanism involving the oxidative cleavage of the enol equilibrating with the initially formed aldehyde.

It is important to stress the fact that no fragmentation needs to occur wherever a stable carbocation can be formed. In fact, there are plenty of reports of successful oxidations of alcohols with PDC, in which no fragmentation happens regardless of the potential formation of very stable carbocations via carbon-carbon bond breakages.[184]



Ref. 184a
No fragmentation occurs regardless of the very stabilized carbocations that it would produce.

Sometimes, treatment of primary alcohols with PDC leads to the formation of dimeric esters[186] arising from the oxidation of acyclic hemiacetals, formed by reaction of the starting alcohol with an intermediate aldehyde.

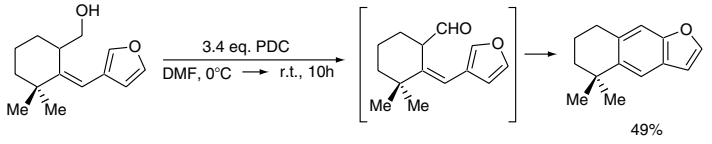


Ref. 185
The aldehyde reacts reversibly with the starting alcohol, producing an acyclic hemiacetal that is oxidized to a dimeric ester.

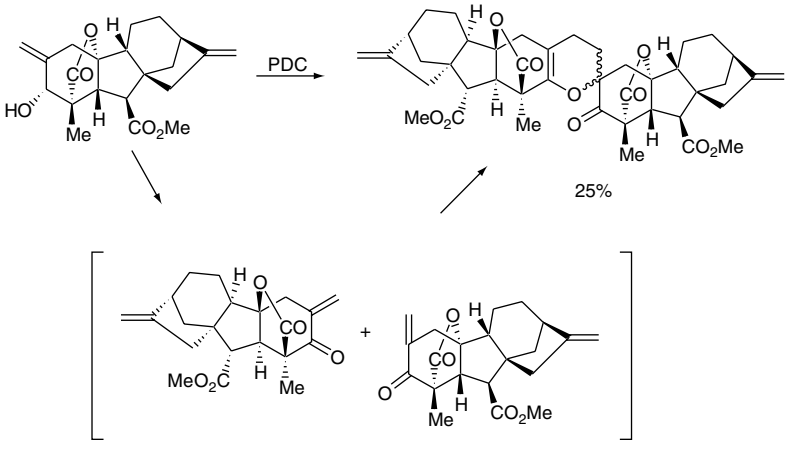
This oxidative dimerization can be minimized by increasing the dilution and adjusting the use of accelerants.[185] Alcohols producing aldehydes, which equilibrate with a substantial proportion of hydrate, tend to be very prone to this side reaction. In fact, the reported examples[186] of this side reaction involve intermediate aldehydes possessing an alkoxy group at the α position, which greatly activates aldehydes to hydration or to hemiacetal

formation by reaction with alcohols. The use of PCC, instead of PDC (see page 74), may help to minimize this side reaction.[186c]

Some examples of further non-oxidative transformations suffered *in situ* by aldehydes and ketones, obtained by PDC oxidation, are listed bellow.



Ref. 187
The intermediate aldehyde suffers an intramolecular Friedel-Crafts reaction by attack of the electron-rich furan ring.



Ref. 188
The desired enone is not isolated because of its tendency to dimerize via a reaction, in which the enone moiety acts as the diene in a hetero Diels-Alder reaction.

Section 1.4. References

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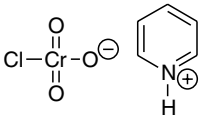
188 Fowles, A. M.; MacMillan, J.; *J. Chem. Soc., Perkin Trans. I* **1988,** *7,* 1973.

1.5. Pyridinium Chlorochromate (PCC)



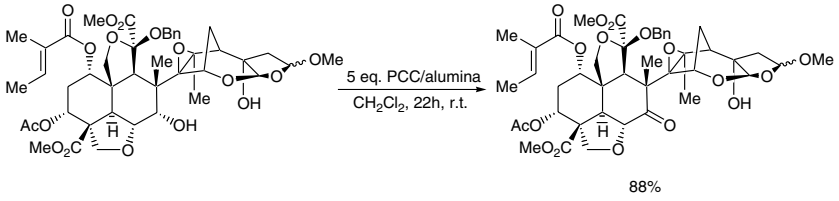
Addition of one equivalent of CrO_3 (MW= 100.0) to 1.1 equivalents of hydrochloric acid (6 N) leads to a homogenous solution containing chlorochromic acid ($ClCrO_3H$). Slow addition of one equivalent of pyridine (MW= 79.1) to this solution, kept at 0°C, leads to the formation of pyridinium chlorochromate (PCC) that separates as yellow-orange crystals. Filtration through a sintered glass funnel, followed by drying in vacuum, allows the isolation of ca. 84% of pure PCC.[12a]

> PCC is usually prepared using the description of Corey and Suggs,[189] although other procedures have been reported.[190,191] Agarwal *et al.* published that preparing PCC by addition of CrO_3 over a pyridinium hydrochloride solution avoids the handling of poisonous chromyl chloride.[192]

Although PCC was first prepared in 1899,[191] its use in the oxidation of alcohols was started as late as in 1975, following a landmark publication by Corey and Suggs,[12a] hence, the name Corey-Suggs reagent, often employed to refer PCC. Corey and Suggs described that most alcohols are oxidized in good yields to aldehydes and ketones using a suspension of PCC in CH_2Cl_2 at room temperature. They also described the addition of NaOAc to the reaction mixture, in order to moderate the slightly acidic character of PCC.

PCC is a stable solid of very moderate hydrophylicity that can be bought and stored for long periods without apparent decomposition. Although commercial PCC operates satisfactorily in most oxidations, cases are reported[193] in which optimum yields are achieved using freshly prepared PCC. In practice, the alternative use of commercial material or

PCC easily prepared in one's own laboratory is largely dependent on personal preferences.



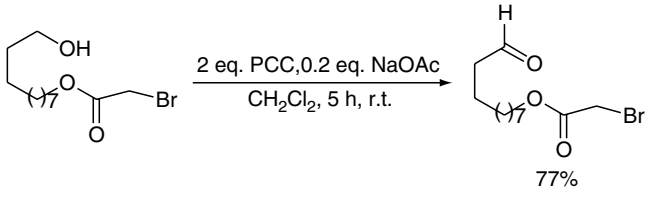
Ref. 193
In this complex substrate, best yields are obtained when freshly prepared PCC is used.

Similar to other chromium-based reagents, kinetic evidence shows that oxidation of alcohols by PCC operates via a chromate ester intermediate that evolves to an aldehyde or ketone in the rate-determining step.[194]

In the vast majority of cases, CH_2Cl_2 is used as solvent in PCC oxidations. Occasionally, other solvents, including benzene,[195] tetrahydrofuran,[196] acetonitrile,[197] chloroform,[192] dioxane,[198] hexane,[199] acetone-CH_2Cl_2[200] or toluene,[201] are used in PCC oxidations. The use of some of these alternative solvents may be advantageous in some substrates.[202] Use of DMF tends to promote the over-oxidation of primary alcohols into carboxylic acids.[203]

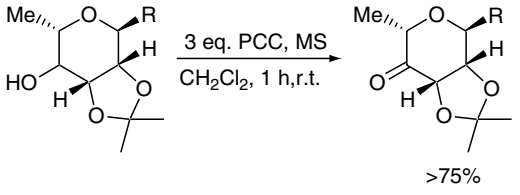
PCC possesses a slight acidity that may interfere in some oxidations of acid-labile compounds. This prompted the widespread routine addition of sodium acetate to the reaction medium.[204] Other buffers used less often include: KOAc,[205] $CaCO_3$,[206] $BaCO_3$,[207] $NaHCO_3$,[208] Na_2HPO_4,[209] pyridine[210] and Na_2CO_3.[211] Calcium carbonate has proved to be particularly useful in avoiding migration into conjugation of alkenes during the oxidation of homoallylic alcohols.[206c]

On occasions, an oxidation with PCC proceeds very quickly at the beginning of the reaction and slows down considerably as the reaction advances. This has been attributed to the formation of an acetal—catalyzed by the acidic nature of PCC—between the product and the starting alcohol.[212]



Ref. 204
The best result is obtained when NaOAc is added to the reaction mixture.

Although PCC allows quicker oxidations than the closely related oxidant PDC; sometimes, it is convenient to add some accelerant, the most commonly used being molecular sieves and the best results are obtained using 3 Å molecular sieves.[134]



Ref. 213

A substantial acceleration is observed when the quantity of molecular sieves is increased from 0.25 to 0.5 g per mmol of alcohol. Further increases in the amount of molecular sieves produce a very moderate increase in velocity.

Other less common accelerants for PCC oxidations include: the addition of organic acids or Ac_2O, as well as sonication with ultrasounds or irradiation with microwaves.

Following kinetic studies that show that PCC oxidations are accelerated by acids, occasionally organic acids, including AcOH,[214] *p*-TsOH,[194a] CSA,[215] PTFA,[216] NH_4OAc,[217] dichloroacetic acid[218] or trichloroacetic acid,[218] are added. Sometimes, this can be counterproductive because, with the acidity of PCC not moderated with a buffer, the medium is made more acidic and, therefore, interferences with acid-sensitive moieties in the substrate can happen. On the other hand, sometimes the extra acidity can help to perform other additional transformations during PCC oxidations. For example, addition of acetic acid allows a one-pot hydrolysis of TMS ethers, followed by oxidation to ketone.[219] On rare occasions, Ac_2O is added to PCC oxidations.[220]

The application of ultrasound may substantially shorten the reaction time in PCC oxidations.[221] Apparently, the ultrasound produces an erosion of the surface of the particles of PCC suspended in methylene chloride and, therefore, accelerate its interaction with the organic substrates.[221a]

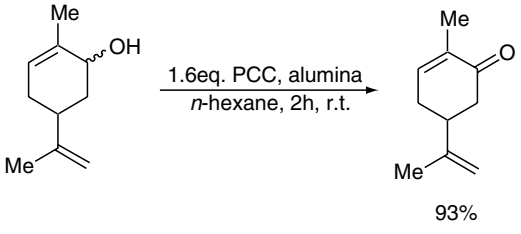
It is claimed that the action of microwaves may very substantially accelerate PCC oxidations, resulting in reactions lasting a few minutes rather than hours.[222] Microwaves may be applied both to suspensions of PCC in a dichloromethane solution of the organic reactant or to the dust, resulting from thoroughly mixing the reactant and PCC in a mortar.

During PCC oxidations, a dark viscous material containing reduced chromium salts is produced, and can interfere in the separation and purification of the product. Very often, solid particles consisting an inorganic material, such as silica gel,[223] Celite®,[224] Florisil®,[225] magnesium sulfate[226] or montmorillonite K10[198] are added to PCC oxidations, so that the reduced

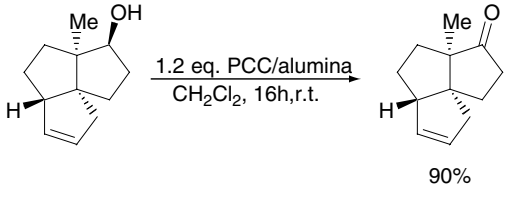
chromium salts are deposited over these solids and are easily removed by filtration. Sometimes, these inorganic materials are simply added to the reaction.[227] On other occasions, these solid particles and PCC are finely ground in a mortar before being added to the solution.[221a] This can help to fragment the PCC particles and, therefore, accelerate the oxidation.[221a] Finally, sometimes PCC is deposited on the solid inorganic particles, by concentrating at the rotary evaporator the solution of PCC possessing suspended solid particles.[223a]

> The work-up of PCC oxidations can be greatly facilitated by the use of the PCC polymeric derivative, poly[vinyl(pyridinium chlorochromate)].[228] Filtration of the polymer and concentration of the organic solution allow an easy isolation of the product.

Alumina has been used in a similar manner. Normally, alumina is added to an aqueous solution of PCC in water, prepared by mixing chromium trioxide, hydrochloric acid (6N) and pyridine. Removal of water leads to the formation of alumina particles covered by PCC, described as PCC on alumina,[229] which is commercially available.[230] Alternatively, it has been described that best results are obtained when alumina and PCC are finely ground in a mortar.[231] The alumina not only helps in the work-up by allowing an easy filtering of the chromium-containing by-products, but also accelerates the oxidation with PCC.[229a]



Ref. 229a
In the absence of alumina, an 82% yield is obtained.



Ref. 232
Low yields are obtained in the oxidation of this congested alcohol with Swern or Jones conditions. While PCC on alumina gives a consistent 90% yield. PCC on other supports, such as Celite® or molecular sieves, gives less than 50% yield.

It is important to note that buffers, accelerants and materials introduced to facilitate the work-up can be used simultaneously. Thus, it is common to use: molecular sieves plus NaOAc,[233] silica gel plus ultrasounds,[221a] Celite® plus NaOAc,[234] AcOH plus molecular sieves,[195b] montmorillonite K10 plus ultrasounds,[198] molecular sieves plus Celite®,[235] Celite® plus AcOH[236] or AcOH plus Celite® plus molecular sieves.[214c]

1.5.1. General Procedure for Oxidation of Alcohols to Aldehydes and Ketones with Pyridinium Chlorochromate (PCC)[237]

Approximately, 1.1–7 equivalents—typically 1.5 equivalents—of solid PCC are added[a, b] over a ca. 0.01–0.25 M solution of the starting alcohol in dry methylene chloride. The resulting mixture is stirred at room temperature[c] till most of the starting compound is consumed.[d]

Very often, ca. 0.2–1.2 g of activated molecular sieves per mmol of alcohol are added in order to accelerate the reaction.

In order to moderate the acidity of PCC, it is very common to add ca. 0.3–1 equivalents of NaOAc.[e]

A solid support, such as silica gel, Celite®, Florisil® (magnesium silicate) or magnesium sulfate, is added, very often in a proportion of ca. 0.3–2 g of solid support per mmol of alcohol, in order to facilitate the work-up.[f]

Occasionally alumina, working both as a solid support—used to facilitate the work-up—and as an accelerant, mixed with PCC is added, in a proportion of ca. 0.4–1.5 g of alumina per mmol of alcohol. Normally, PCC is deposited over the alumina.[g]

Occasionally, ca. 10–20 equivalents of acetic acid[h] are added in order to accelerate the reaction.

Sometimes, the reaction flask is sonicated with ultrasound in order to fragment the surface of the PCC particles and, therefore, accelerate the reaction.

Although in PCC oxidations, it is very common to add simultaneously to the reaction an accelerant, a buffer and a work-up-facilitator; it is not common to employ simultaneously two materials belonging to the same kind, with the exception of the combination of the two accelerants molecular sieve and acetic acid, which are very often used together.

When a TLC analysis shows that most of the starting alcohol is consumed,[d] the solids suspended in the reaction and the chromium species are removed by filtration through a pad[i] of Florisil®, silica gel, alumina or

Celite®, and the pad is washed with an organic solvent, such as ether, CH_2Cl_2, or EtOAc. Sometimes, the solids can be removed by decantation. Other times, it is advisable to add some diethyl ether to the reaction mixture before the filtration, in order to promote the separation of reduced chromium species in a granular form. Occasionally, the reaction mixture is concentrated before the addition of diethyl ether.

Finally, the collected organic phases are concentrated at the rotary evaporator, giving a crude aldehyde or ketone that may need some further purification.

[a] It may be advisable, particularly on multigram scale reactions, to cool down (ca. 5°C) the reaction mixture during the addition of some components in order to prevent exotherms.

[b] Frequently, an inverse addition is preferred, whereby a solution of the alcohol is added to a suspension of PCC in CH_2Cl_2.

[c] It may be advisable to carry out the oxidation at 0°C when sensitive alcohols able to be oxidized very quickly are employed. Alternatively, it may be advisable to accelerate the reaction by heating when robust alcohols are oxidized.

[d] It usually takes between 30 min and 3 days.

[e] Other buffers, such as KOAc, $CaCO_3$, $BaCO_3$, $NaHCO_3$, Na_2HPO_4, pyridine or Na_2CO_3, can also be used. $CaCO_3$ is recommended when avoidance of migration of alkenes into conjugation, during oxidation of homoallylic alcohols, is desired.

[f] Sometimes, PCC and the solid support are simultaneously added in the form of a fine dust, obtained from grinding both materials together in a mortar.

[g] The PCC is deposited over the alumina adopting the following operations:

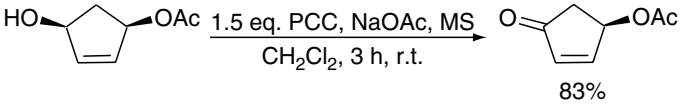
1. One equivalent of pyridine (MW = 79.1) is added over 10 min to a solution of 377 g per liter of CrO_3 (MW = 100.0) in HCl (6 N), kept at 40°C. The solution is cooled at 10°C till a solid is formed, and it is reheated to 40°C in order to dissolve the solid.
2. Alumina—50 g per equivalent of pyridine—is added and the solvent is evaporated at the rotary evaporator. The resulting orange solid is dried in vacuum and is stable in the dark under vacuum during several weeks.

Alternatively, the alumina and the PCC can be added after grinding both in a mortar to a fine dust.

PCC on alumina is commercially available.

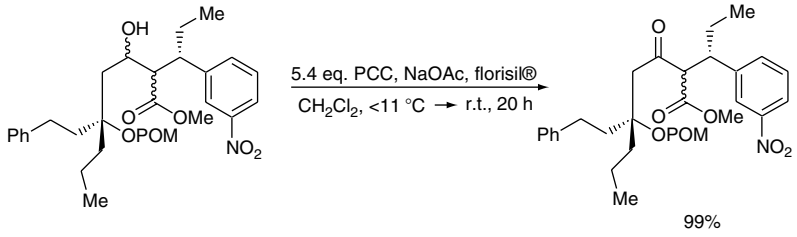
[h] Other organic acids, such as *p*-TsOH, CSA, Py·TFA, NH_4OAc, dichloroacetic or trichloroacetic acid, have been used.

[i] The reduced chromium species can be separated by decantation instead of filtering, but this tends to cause the crude product to be contaminated with chromium.



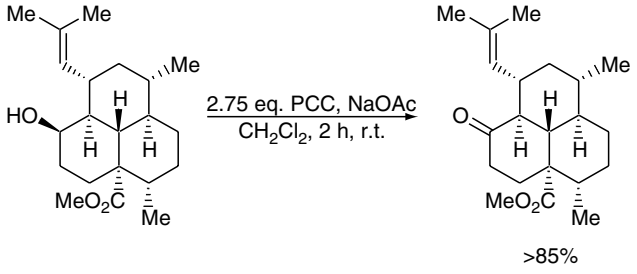
Ref. 238

An oxidation on a multigram scale is described in detail.



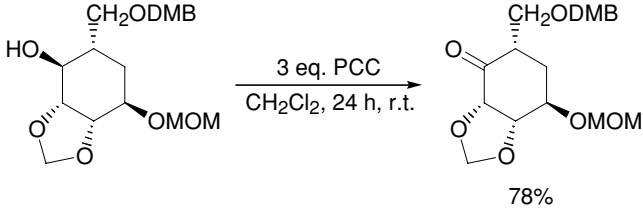
Ref. 239

In this reaction, PCC is preferred over Swern oxidation because it does not require low temperature, it is easy to manipulate and it does not generate bad odour.



Ref. 240

The starting alcohol is very unstable and must be oxidized immediately after its preparation.



Ref. 241

PCC provides a better yield than the Dess-Martin reagent in this oxidation.

1.5.2. Functional Group and Protecting Group Sensitivity to Oxidation with PCC

1.5.2.1. Protecting Groups

All protecting groups resist the action of PCC, including the following very acid-sensitive ones: TMS ether,[242] THP ether,[243] *t*-butyl ether,[244]

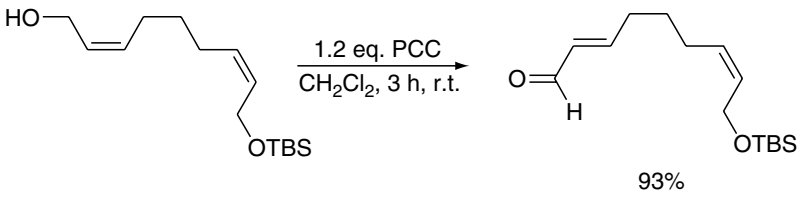
Boc,[245] *t*-butyl ester,[246] trityl ether[247] and even tris(*p*-methoxyphenyl)methyl ether.[248] The oxidation-sensitive PMB normally resists the action of PCC,[249] as well as the sulfur-containing protecting groups dithioacetals[250] and monothioacetals.[251]

Although there are hundreds of reports in the literature in which silyl ethers withstand the action of PCC, there are two references in which a TBS ether is cleaved and oxidized *in situ* to aldehyde[252] or ketone[253] by the action of PCC unaided by added acid. There are also reports of a TMS-protected tertiary allylic alcohol being transformed into the corresponding transposed enone,[254] a labile TES ether being converted into a ketone,[255] and a diphenylmethylsilyl (DMPS) ether being removed[256] by the action of PCC.[254] It has been reported that primary TMS and TES ethers can be selectively transformed in aldehydes in the presence of secondary TMS and TES ethers and under the action of PCC, although the method is often not very effective.[257] Bis-TMS[258] and bis-TBS[259] protected *p*-hydroquinones are transformed into *p*-quinones by the action of PCC.

Although THP ethers[243] resist the action of PCC under the relatively mild conditions used for the oxidation of alcohols, PCC in boiling benzene is able to deprotect THP ethers and perform an *in situ* oxidation of the resulting alcohol to ketone.[260]

1.5.2.2. Alkenes

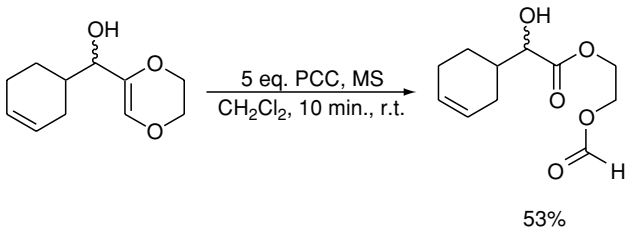
Normally, alkenes do not interfere with the oxidation of alcohols with PCC. Although alkenes do react with PCC, this normally requires quite harsh conditions, and selective oxidations of alcohols are possible.



Ref. 261

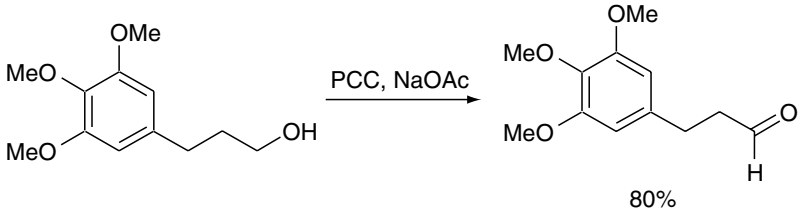
Regardless of the presence of two alkenes, the treatment of the alcohol with PCC leads uneventfully to the desired aldehyde.

Nevertheless, alkoxyalkenes, being very electron-rich olefins, do react quickly with PCC. This produces either the breakage of the carbon-carbon double bond yielding two carbonyl compounds,[262] or the transformation of the alkoxyalkene into an ester or a lactone.[263]



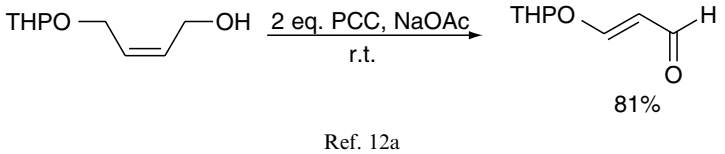
Ref. 262a
The very electron-rich olefin, substituted with two oxygens, is cleaved by PCC, while the alcohol is unaffected.

Normal alkenes—which are particularly not electron-rich—are oxidized at the allylic position by PCC, resulting in the formation of enones.[264] Aromatic compounds suffer a similar reaction at the benzylic positions, yielding aromatic ketones[265] or aromatic aldehydes.[266] These oxidations normally demand quite harsh conditions with excess of PCC, long reaction times and high temperature. Therefore, they hardly compete with the oxidation of alcohols, which is normally made under quite mild conditions.



Ref. 267
The alcohol is oxidized to aldehyde, while no oxidation at the benzylic position occurs, in spite of its strong activation by electron donors on the benzene ring.

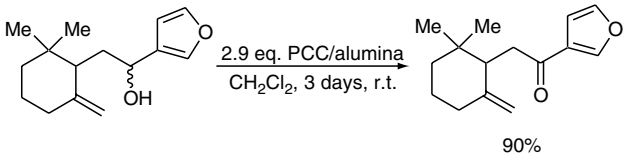
Olefins, belonging to primary allylic alcohols and possessing a (*cis*) configuration, suffer isomerization to the (*trans*) compound during the oxidation of the alcohol to aldehyde with PCC.[268] This isomerization is not avoided by the addition of sodium acetate as buffer.[189]



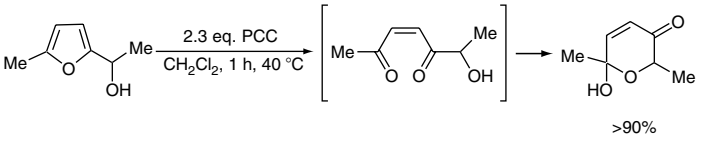
Ref. 12a
The olefin suffers isomerization to a (*trans*)-enal, in spite of the presence of sodium acetate.

1.5.2.3. Furan Rings

PCC oxidatively cleaves furan rings, resulting in the synthetically useful formation of conjugated endiones.[269] The literature contains both, cases in which an alcohol is oxidized by PCC in the presence of an unreacting furan ring[270], as well as contrasting cases in which a furan ring is oxidised by PCC in the presence of an unreacting alcohol.[270]



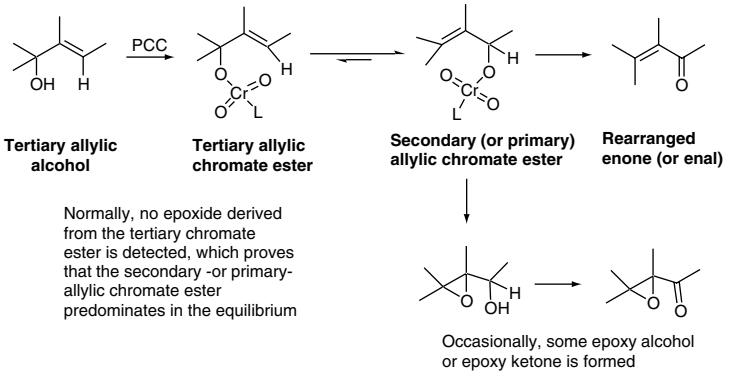
Ref. 270a
The furan ring remains unaffected during the oxidation of the alcohol with PCC.



Ref. 271
PCC cleaves the furan ring, giving a conjugated endione. The unreacted alcohol attacks one of the ketones, yielding a cyclic hemiacetal.

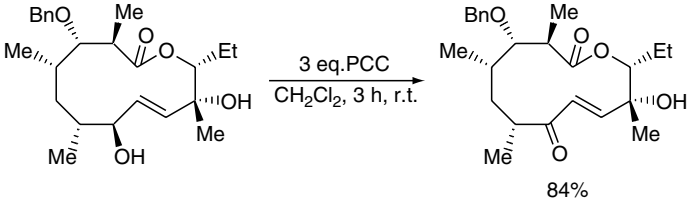
1.5.2.4. Tertiary Allylic Alcohols

PCC reacts with tertiary allylic alcohols, forming an intermediate chromate ester that evolves giving a conjugated enone or enal. Sometimes, the isomeric chromate ester produces the epoxidation of the alkene, giving an epoxy alcohol that can be further oxidized to an epoxy ketone.



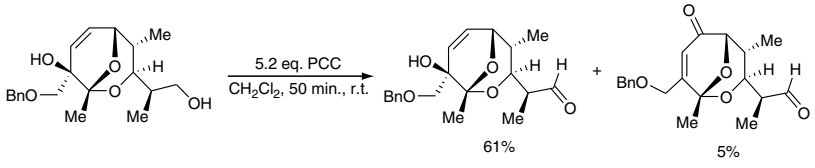
This oxidative transposition of tertiary allylic alcohols into enones or enals is carried out under mild conditions and has ample application in organic synthesis. Although, it can be carried out with other chromium-based reagents (see pages 16 and 35), PCC is the reagent of choice.[272]

Although the PCC-mediated oxidative transposition of tertiary allylic alcohols is carried out under very mild conditions, normally it is possible to selectively oxidize a primary or secondary alcohol to aldehyde or ketone with PCC, without affecting a tertiary allylic alcohol present in the same molecule.[273]

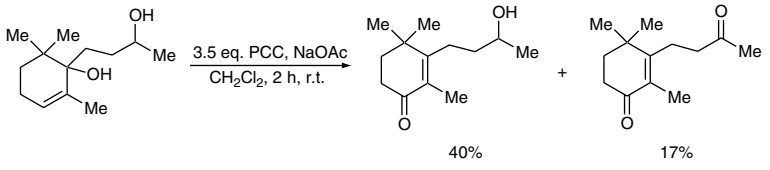


Ref. 273c
A normal oxidation of a secondary alcohol into ketone occurs with no reaction of the tertiary allylic alcohol.

Nevertheless, transposed enones can be formed as minor compounds,[274] and a few times the oxidative transposition can predominate over the normal oxidation of primary or secondary alcohols.[275]

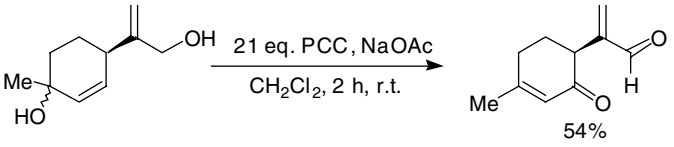


Ref. 274
The main product results from an uneventful oxidation of a primary alcohol. Minor quantities of a product, resulting from an accompanying oxidative transposition of the tertiary allylic alcohol, are obtained.



Ref. 275
This is a rare instance in which an oxidative transposition of a tertiary allylic alcohol predominates over a normal oxidation of a secondary alcohol.

Of course, using excess of PCC allows the operation of both, an oxidative transposition of a tertiary allylic alcohol and a normal oxidation of a primary or a secondary alcohol.[276]

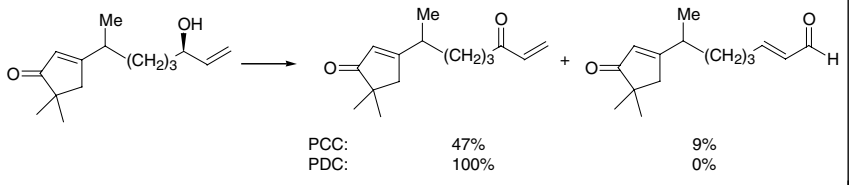


Ref. 276

The oxidation with PCC causes both, a normal oxidation of the primary alcohol and an oxidative transposition of the tertiary allylic alcohol.

1.5.2.5. Secondary Allylic Alcohols

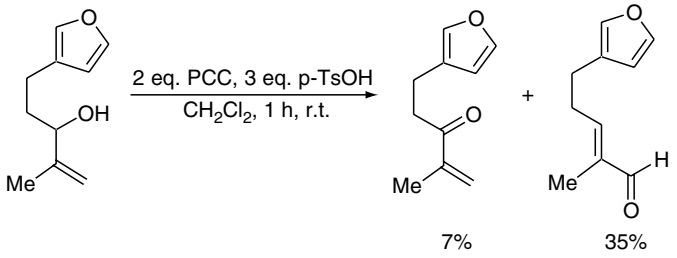
Although secondary allylic alcohols can suffer an oxidative transposition via the corresponding allylic chromate ester, in the same manner that the tertiary allylic alcohols; normally, a direct oxidation to the corresponding enone with no transposition predominates.[277] Nevertheless, minor amounts of enone, resulting from an oxidative transposition, can be formed.[278] The formation of transposed enone may be minimized using the less transposing-prone PDC, instead of PCC.[279]



Ref. 278b

The enone, resulting from a normal oxidation of the secondary alcohol, is obtained together with minor amounts of an enal, resulting from an oxidative transposition when PCC is used. The use of the less transposing-prone PDC allows the obtention of a quantitative yield of the desired untransposed enone.

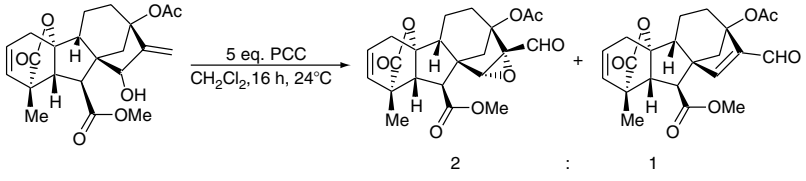
When the oxidative transposition of secondary allylic alcohols is purposefully looked after, it can be fostered by the addition of *p*-toluenesulfonic acid.[280] Most probably, the added acid catalyzes the equilibration of the intermediate allylic chromate esters, allowing the major formation of transposed enone when the corresponding chromate ester is less hindered. This means that an oxidative transposition of a secondary allylic alcohol can only dominate when the thermodynamics of the equilibrating allylic chromate esters are favourable.



Ref. 280a

Thanks to the addition of *p*-TsOH that catalyzes the equilibration of the intermediate allylic chromate ester; the major product is the desired enal, resulting from an oxidative transposition. Failure to add *p*-TsOH leads to the major formation of the untransposed enone, with only minor amounts of enal being generated.

Very hindered secondary allylic alcohols may have a great tendency to suffer oxidative transpositions, even without the help of added acid; a fact undoubtedly due to the release of steric tension, resulting from the transposition of the initially formed chromate ester.[281]



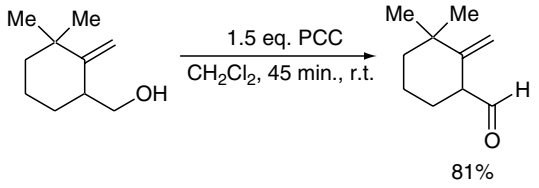
Ref. 281

The initially formed chromate ester, from this very hindered secondary alcohol, suffers a transposition to an isomeric chromate ester. The isomeric chromate ester produces the transposed enal. Alternatively, the transposed chromate ester can produce the epoxidation of the alkene, giving an epoxy alcohol that is further oxidized to an epoxy aldehyde.

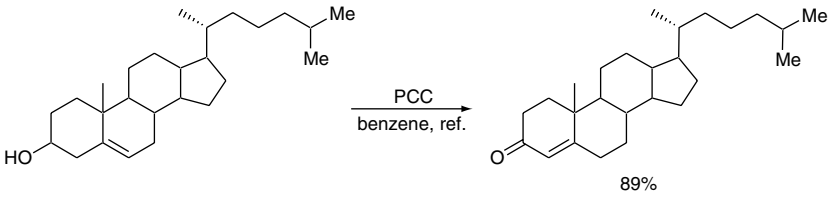
The authors of this book are not aware of any case, in which a primary allylic alcohol suffers an oxidative transposition with PCC. Such case would be most unlikely, because it would involve an equilibrating pair of allylic chromate ester, in which the less stable minor one would evolve to a carbonyl compound.

1.5.2.6. Homoallylic Alcohols

During the oxidation of homoallylic alcohols with PCC, normally no migration of the alkene into conjugation with the resulting carbonyl group is observed, regardless of favourable thermodynamics. Such migration can be occasionally observed when it results in a highly favourable formation of endocyclic alkenes inside 5 or 6-membered rings.[282]



Ref. 283
No migration of the alkene into conjugation is observed during the PCC oxidation, in spite of the fact that the final compound suffers quantitative isomerization to a conjugated enal by simple contact with alumina at room temperature.

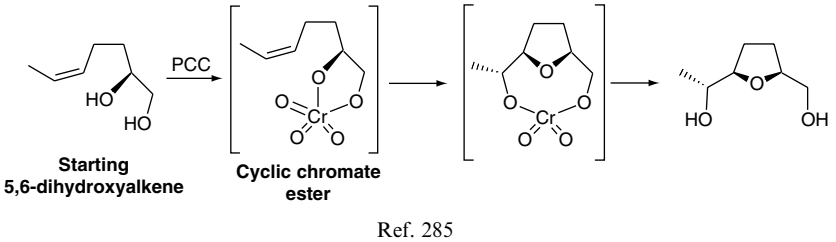


Ref. 282c
Under the relatively energic conditions of PCC in refluxing benzene, migration of the alkene into conjugation with the ketone is observed.

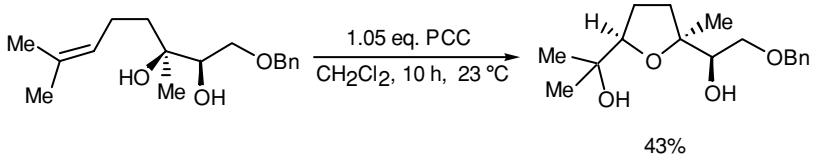
Under oxidation with PCC, migration of alkenes into conjugation with aldehydes or ketones can be avoided by the addition of calcium carbonate (see page 47).

1.5.2.7. 5,6-Dihydroxyalkenes

PCC transforms 5,6-dihydroxyalkenes into tetrahydrofurans in a highly stereoselective manner[284] (see Equation below). This transformation can be explained by the initial formation of a cyclic chromate ester by reaction with the diol moiety, followed by an intramolecular oxidative addition of the chromate ester on the alkene.



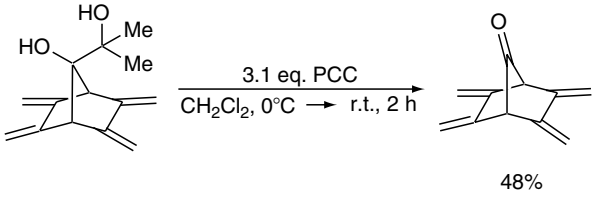
Ref. 285
This reaction has been used in the preparation of complex natural tetrahydrofurans.



Ref. 118

A PCC-induced oxidative formation of a tetrahydrofuran from a 5,6-dihydroxyalkene is used in the total synthesis of the antiviral natural compound venustatriol.

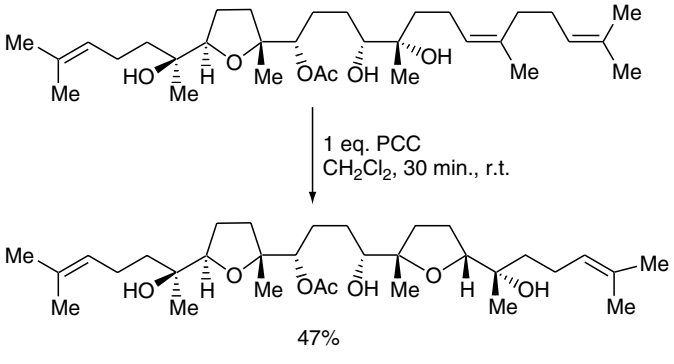
Of course, the PCC-induced formation of tetrahydrofurans from 5, 6-dihydroxyalkenes fails when structural constrains prevent the approach of the intermediate cyclic chromate ester to the alkene.[286]



Ref. 286

No tetrahydrofuran is formed because structural constrains prevent the approach of the intermediate cyclic chromate ester to the alkene. Instead, the chromate ester evolves, producing an oxidative breakage of the 1,2-diol.

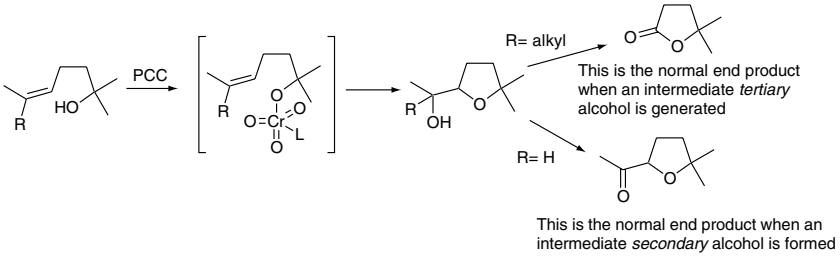
Nonetheless, this formation of tetrahydrofurans from 5,6-dihydroxyalkenes, when possible, demands such mild oxidation conditions that it is possible to prevent further oxidation of the generated alcohols by adjusting the quantity of PCC employed.



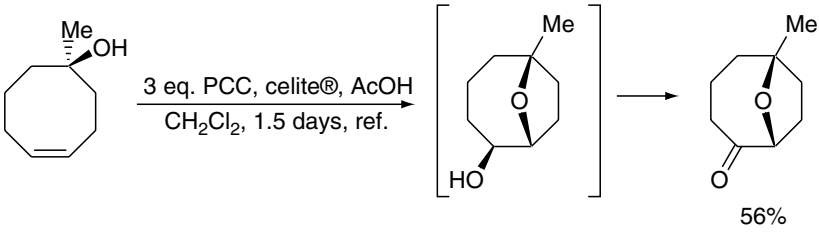
Ref. 284a
Chromium coordinates selectively with the 1,2-diol, forming a stable cyclic chromate ester that evolves producing the formation of a tetrahydrofuran. Observe that no formation of tetrahydrofuran from the alcohol on the left occurs, for this would involve the intermediacy of a less stable simple chromate ester (*vide infra*). The experimental conditions are so mild that no direct oxidation of the secondary alcohol to ketone is observed, either on the starting compound or in the product.

1.5.2.8. 5-Hydroxyalkenes

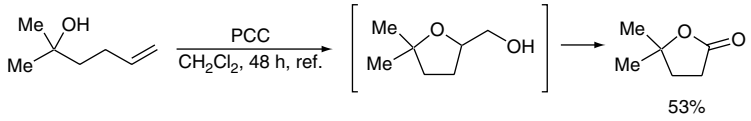
It is possible to make an oxidative cyclization, akin to the one suffered by 5,6-dihydroxyalkenes, starting from 5-hydroxyalkenes.[284a]



However, as the formation of an intermediate simple chromate ester is not as favorable as the generation of the cyclic chromate ester, involved in the oxidation of 5,6-dihydroxyalkenes, this reaction, demands harsher conditions. Therefore, only tertiary 5-hydroxyalkenes may be normally used as starting compounds, otherwise a direct oxidation of the alcohol to an aldehyde or ketone would occur.[287] Because of the harsher conditions involved, very often the resulting 1-hydroxyalkyltetrahydrofuran is further oxidized to a γ-lactone or to a ketone.[288]



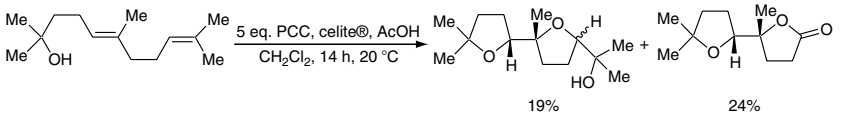
Ref. 289
The intermediate chromate ester interacts with the alkene, producing the formation of a secondary alcohol that is further oxidized to a ketone.



Ref. 288a

The intermediate hydroxymethyltetrahydrofuran is further oxidized to a γ-lactone.

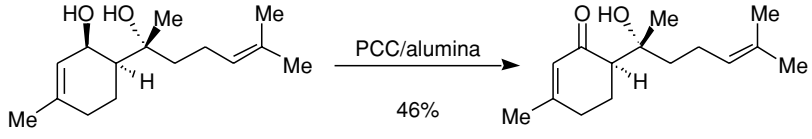
Interestingly, in alcohols containing properly positioned alkenes, it is possible to perform a highly stereoselective tandem formation of tetrahydrofurans.[284a]



Ref. 284a

A tandem formation of two tetrahydrofurans occurs. The resulting alcohol partially suffers an oxidative breakage to a lactone.

As the oxidative cyclization of 5-hydroxyalkenes demands quite harsh conditions, normally it is possible to selectively perform a standard oxidation of a primary or secondary alcohol in other part of the molecule.[290]

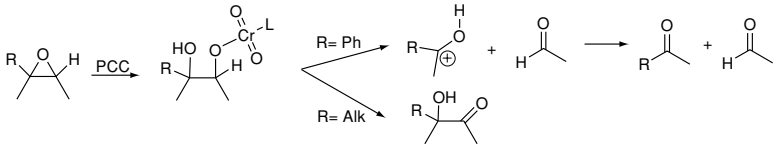


Ref. 290

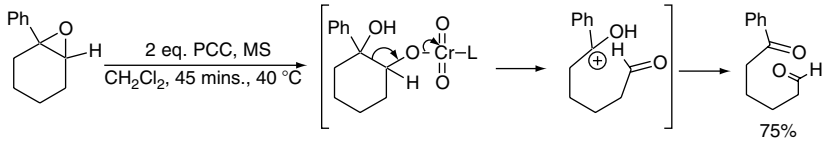
A normal oxidation of the secondary alcohol occurs with no interference with the formation of a tetrahydrofuran on the right part of the molecule.

1.5.2.9. Epoxides

PCC reacts with epoxides, resulting in cleavage either generating two carbonyl compounds or transformation into a α-hydroxyketone.

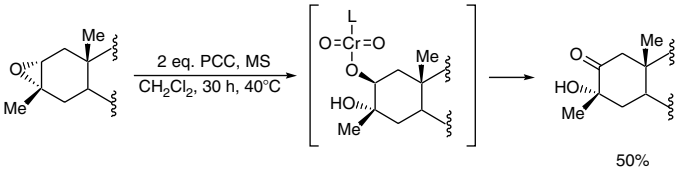


These transformations can be achieved by opening of the epoxide—most probably previously activated by protonation—by attack of chromate. The intermediate chromate may evolve by breakage of a carbon-carbon bond, leading to the formation of an aryl-stabilized cation and a carbonyl compound. Deprotonation of the aryl-stabilized cation leads to a ketone. Alternatively, when there is no aryl group that could stabilize an intermediate cation, the chromate evolves in a standard way to generate a α-hydroxyketone.



Ref. 291

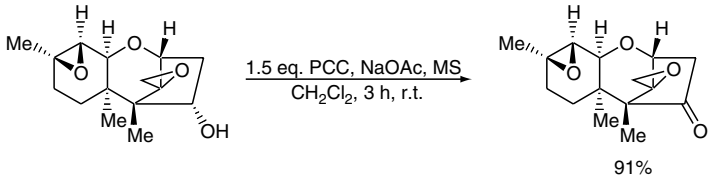
Opening of the epoxide by attack of a chromate anion leads to an intermediate that suffers a carbon-carbon bond breakage, resulting in a stabilized carbocation that evolves to give a dicarbonyl compound.



Ref. 291

A (protonated) epoxide is opened by attack of chromate anion. The intermediate chromate ester generates a α-hydroxyketone.

As the oxidation of epoxides with PCC is relatively slow, it is possible to adjust the oxidation conditions so as to selectively transform an alcohol into an aldehyde or ketone in the presence of an epoxide.[292]

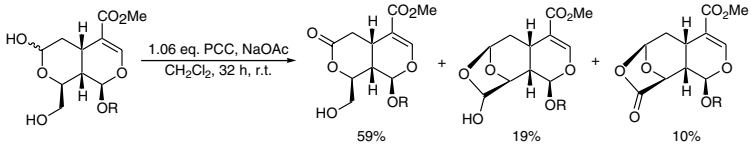


Ref. 292c

An uneventful oxidation of the alcohol to a ketone occurs with no reaction of the epoxides. The buffering of the reaction with NaOAc may help to avoid the oxidative opening of the epoxides.

1.5.2.10. Lactols

PCC very easily oxidizes lactols to lactones.[293] However, at the time of writing, the scientific literature does not contain enough data to assess the relative ability of oxidation of lactols versus alcohols with PCC.

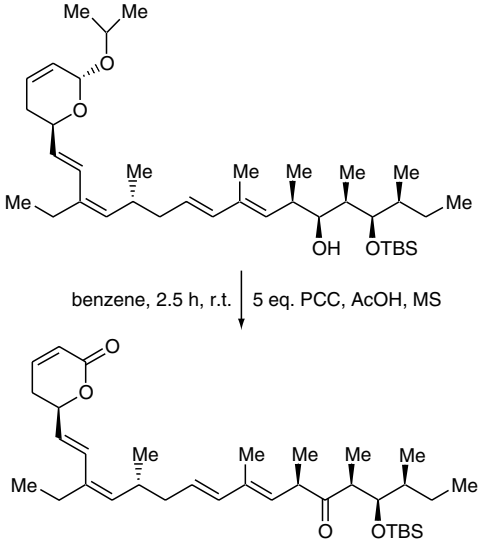


Ref. 294

A 59% yield of the product, originating from the selective oxidation of the lactol, is obtained. Selective oxidation of the primary alcohol to an aldehyde yields two minor compounds. One of them is a lactol resulting from attack of the lactol hydroxyl group on the aldehyde, while the other one is originated from the oxidation of the previously formed lactol.

1.5.2.11. Acetals

Although certain cyclic acetals are transformed into lactones by PCC,[295] sometimes with the help of some added AcOH;[195b] alcohols are routinely oxidized with PCC without affecting acetals in the same molecule.[296]



Ref. 195b

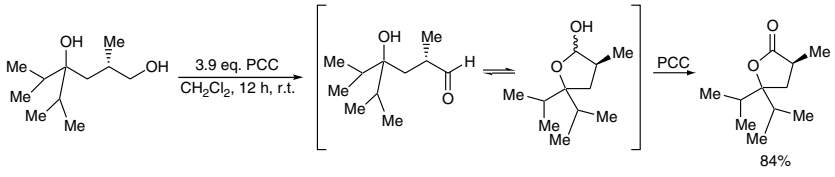
This is a rare case in which an acetal is oxidized by PCC. The presence of acetic acid may promote this oxidation.

1.5.2.12. 1,2-Diols

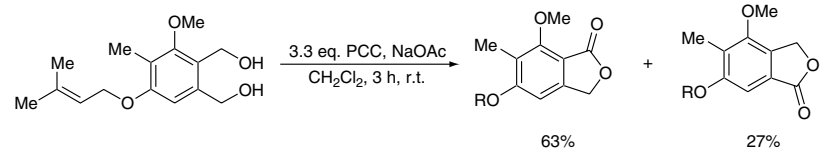
Sometimes, 1,2-diols suffer an oxidative carbon-carbon bond breakage under the action of PCC (see page 60).

1.5.2.13. 1,4-Diols

PCC sometimes transforms 1,4-diols in to γ-lactones; however, at least one of the alcohols in 1,4 diols should be a primary alcohol.[297] This oxidation proceeds via an intermediate γ-hydroxyaldehyde that equilibrates with a lactol, which is transformed in a γ-lactone.

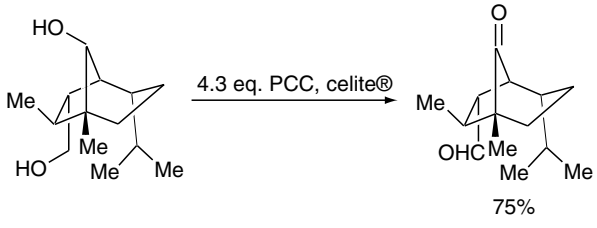


Ref. 297a
The primary alcohol is oxidized to a hydroxyaldehyde that equilibrates with a lactol, which is further oxidized to a lactone.



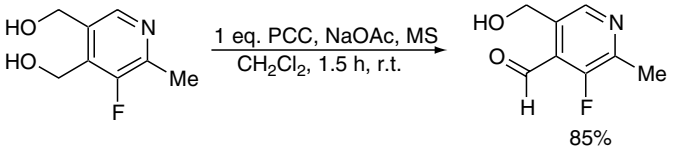
Ref. 297b
Two different isomeric lactones are generated, depending on the benzylic alcohol that is first oxidized by PCC.

No formation of lactone is observed when geometrical constrains prevent the formation of an intermediate lactol.[298]



Ref. 298b
An uneventful oxidation of both alcohols occurs, because geometrical constrains prevent the formation of the intermediate lactol.

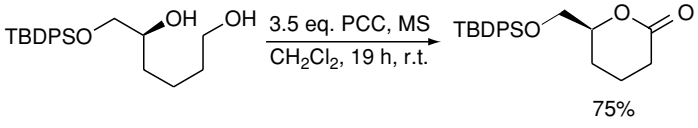
Very often, uneventful oxidations with no formation of lactone are found, even in cases in which the formation of an intermediate stable lactol looks likely.[299]



Ref. 300a
A selective oxidation of one of the alcohols is observed with no lactone formation, in spite of apparent facility in the formation of a lactol.

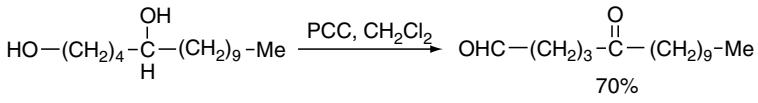
1.5.2.14. 1,5-Diols

With respect to 1,4-diols, a similar behaviour is observed in 1,5-diols, in which one of the alcohols is a primary alcohol. That is, the treatment with PCC may result in the formation of a δ-lactone,[300] although this does not happen when geometrical constrains prevent the formation of an intermediate lactol.[301]



Ref. 300a
The oxidation of the primary alcohol yields a hydroxyaldehyde that equilibrates with a lactol, which is further oxidized to a δ-lactone.

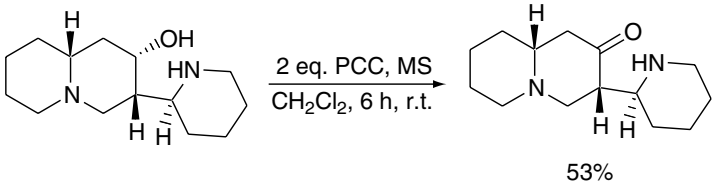
As in the case of 1,4-diols, very often 1,5-diols are oxidized uneventfully with PCC, in spite of the potential formation of apparently stable lactols.[302]



Ref. 302b
Both alcohols are uneventfully oxidized with no formation of lactones, in spite of the potential intermediacy of a lactol.

1.5.2.15. Nitrogen-Containing Compounds

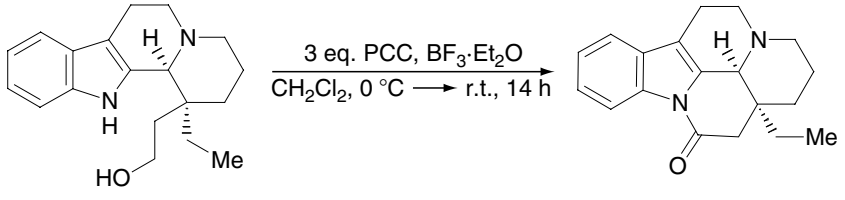
Tertiary and secondary amines can resist the action of PCC, while an alcohol is oxidized.[303] Even so, secondary amines are very often protected against PCC oxidations.



53%

Ref. 304
A selective oxidation of a secondary alcohol with PCC is performed, in the presence of a tertiary and a secondary amine.

Sometimes, an intramolecular hydrogen bond between an alcohol and an amine prevents the oxidation of the alcohol. In such cases, a successful oxidation of the alcohol with PCC can be performed, by blocking the free electron pair of the nitrogen by the addition of one equivalent of $BF_3 \cdot Et_2O$.[305]

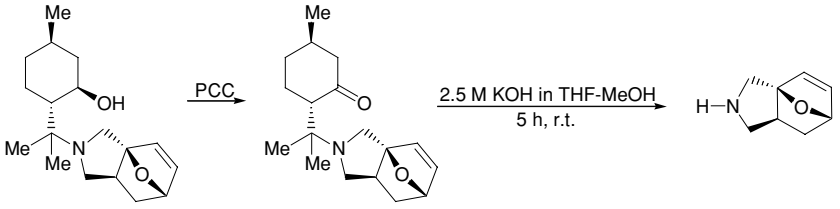


37%

Ref. 305b
$BF_3 \cdot Et_2O$ acts by blocking the free electron pair of the amine that, otherwise, would form a hydrogen bond with the alcohol and prevent its oxidation. The intermediate aldehyde equilibrates with an aminal, that is further oxidized to a lactam.

Although little pursued in the literature, it can be anticipated that addition of one equivalent of $BF_3 \cdot Et_2O$—or other acid—would prevent the interference of amine functionalities in PCC oxidations.

PCC is used to remove menthyl substituents—working as chiral auxiliaries—from amines.[306] The oxidation of menthylamines with PCC leads to β-aminoketones that, on treatment with base, suffer a retro-Michael reaction leading to free amines.

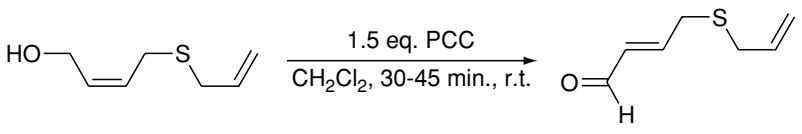


Ref. 306a
The menthyl chiral auxiliary is removed by an oxidation with PCC, in which no interference with the amine occurs, followed by a base-induced retro-Michael reaction.

Normally, nitrocompounds resist[307] the action of PCC; although, on rare occasions, PCC can promote the attack of nucleophiles on nitro groups, in a similar way to the other chromium-based reagents (see pages 10 and 35).

1.5.2.16. Sulfides

Although PCC oxidizes thiols to disulfides[308] and sulfides to sulfoxides,[309] it is possible to selectively oxidize alcohols in the presence of sulfides.[310,311]

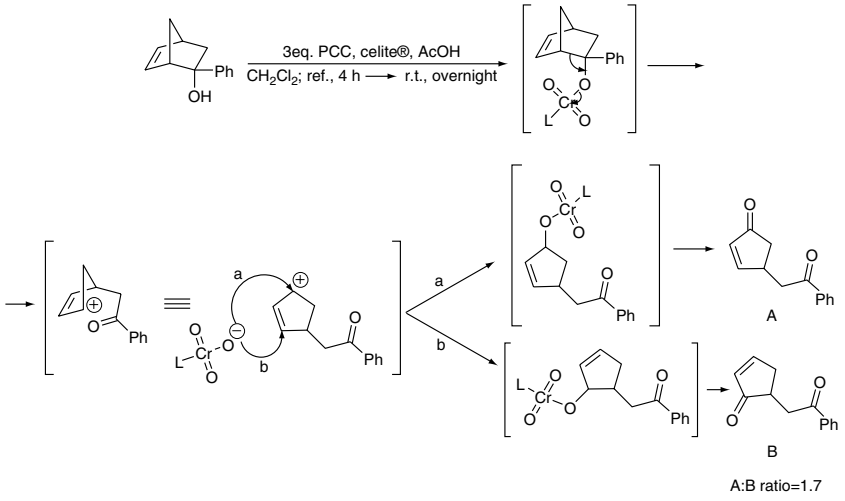


Ref. 268a
A selective oxidation of alcohol to aldehyde is performed in the presence of an unreacting sulfide.

1.5.3. Side Reactions

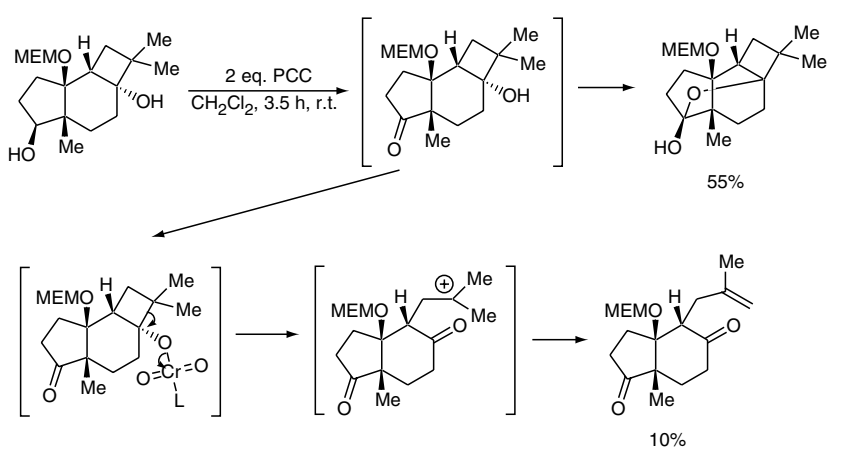
1.5.3.1. Oxidative Breakage of a Carbon-Carbon Bond from an Intermediate Chromate Ester

As in other chromium-based reagents (see pages 12 and 38), sometimes intermediate chromate esters, resulting from a primary reaction between alcohols—including tertiary alcohols—and PCC, evolve by breakage of a carbon-carbon bond when it results in the generation of a stable cation. Stable cations generated in this way include cations located at allylic[236] positions and at tertiary carbons,[312] as well as cations stabilized by nitrogen[313] or oxygen[314] atoms.



Ref. 236

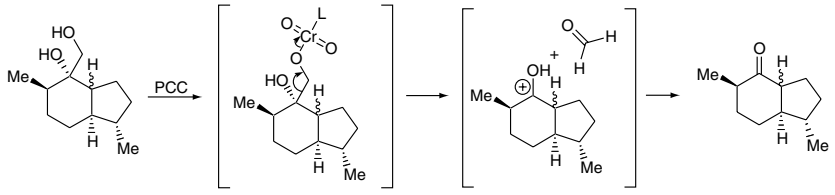
The initially formed chromate ester is fragmented, producing an allylic cation that can be attacked at two positions by a chromate anion. The resulting allylic chromates evolve by producing two isomeric ketones.



Ref. 312

The secondary alcohol is oxidized to a ketone that can be trapped intramolecularly as a cyclic hemiacetal. Alternatively, the tertiary alcohol can react with PCC forming a chromate ester that evolves by a carbon-carbon breakage, facilitated by the formation of a stable tertiary carbocation, and the release of annular tension resulting from the opening of a cyclobutane. The resulting carbocation produces an alkene by deprotonation.

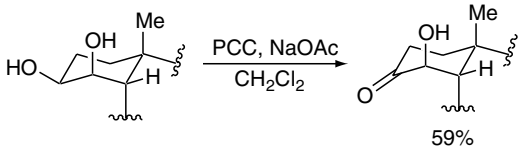
1,2-Diols are particularly prone to this side reaction, as the intermediate cation is very stabilized by the presence of an oxygen atom.



Ref. 314d

A chromate ester, formed upon the primary alcohol, evolves by generating an oxygen-stabilized carbocation and formaldehyde. Deprotonation of the intermediate carbocation yields the final ketone.

It is important to note that the relative velocity of an uneventful oxidation of an alcohol with PCC versus a carbon-carbon bond breakage from a chromate ester, driven by the generation of a stable carbocation, is substantially substrate-dependent, and may change according to stereoelectronic factors, which may be difficult to predict. Thus, many alcohols are successfully oxidized to aldehydes and ketones, regardless of an apparently potential carbon-carbon bond breakage leading to stabilized carbocations.[315] Consequently, failure to try an alcohol oxidation with PCC, because of fear of this side reaction is not recommended.

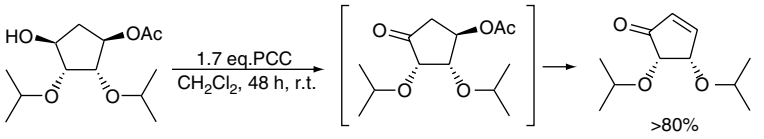


Ref. 315c

A selective oxidation of the equatorial alcohol is achieved, regardless of a potential carbon-carbon breakage from the intermediate chromate ester.

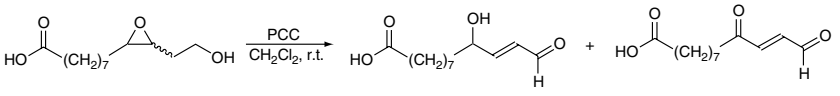
1.5.3.2. Formation of Conjugated Enones (or Enals) by Eliminations Subsequent to Alcohol Oxidation

Sometimes, when the oxidation of an alcohol produces a carbonyl compound, containing a good-leaving group at the β-position, an elimination leading to a conjugated enal or enone occurs. This reaction is facilitated by the presence of better leaving-groups. Thus, elimination is quite common during the oxidation of alcohols containing halogens[316] or carboxylates[317] at the β-position.



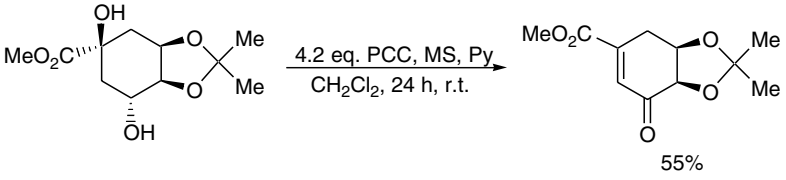
Ref. 317a
The intermediate β-acetoxyketone suffers *in situ* a very easy elimination to a conjugated cyclopentenone.

Eliminations promoted by the formation of the following anions can also happen: alkoxides[318]—including those resulting from the opening of epoxides,[319] hydroxides,[320] sulfinates[321] and sulfenates.[322]



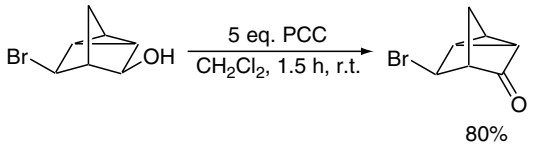
Ref. 319
The oxidation of the primary alcohol is followed by the opening of the epoxide, leading to a γ-hydroxyenal that is further partially oxidized in the alcohol.

When eliminations are purposefully looked after, they can be promoted by the addition of a base, like NaOAc,[323] pyridine[210c] or $BaCO_3$,[316a] to the oxidizing solution.



Ref. 210c
The oxidation of the secondary alcohol is followed by a pyridine-promoted elimination of the tertiary alcohol, presumably via an $E_{1C}B$ mechanism. The elimination is facilitated by the formation of an alkene conjugated with two carbonyls.

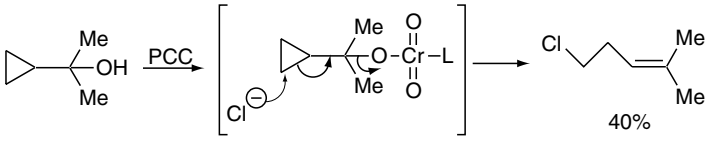
It is important to note that these eliminations normally are explained by an $E_{1C}B$ mechanism; comprising the formation of an enolate, followed by an elimination, demanding proper alignment between p-orbitals containing negative charge, and sigma orbitals linking the leaving-group with the β-carbon. The nature of the substrate may dictate both, an extremely easy orbital alignment or a very difficult one. Thus, such substrates are found, in which eliminations during PCC oxidations are almost impossible to avoid, or it hardly happen.[324] Sometimes, failure to elimination is easily explained by the instability that would have the resulting alkene.[324ii]



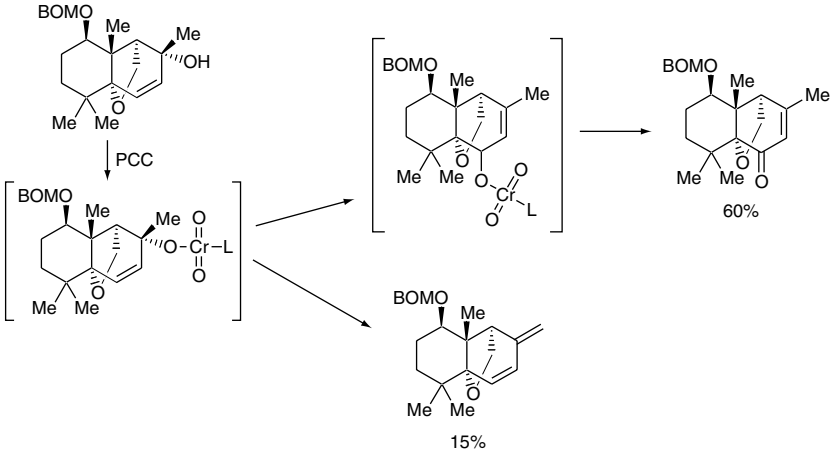
Ref. 324ii
In spite of the fact that bromide is an excellent leaving-group, no elimination occurs for it would lead to a very unstable bridgehead alkene.

1.5.3.3. Chromate as Leaving-Group and Reactions Induced by the Acidic Nature of PCC

Sometimes, side reactions, resulting from the intermediate chromate esters acting as good-leaving groups, occur. They are remarkable because they involve PCC reactions, in which no oxidation happens.

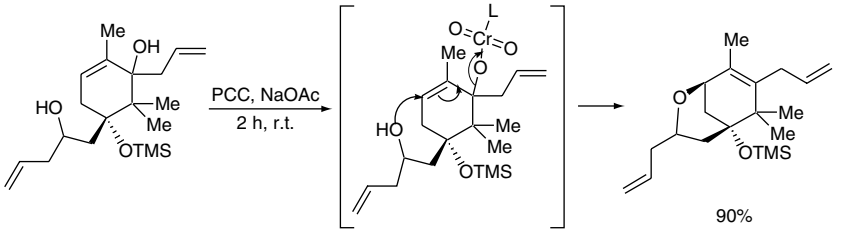


Ref. 325
Formation of a chromate ester is followed by the opening of cyclopropane, driven by attack of chloride and elimination of chromate anion.



Ref. 326
A tertiary allylic alcohol produces the desired transposed enone on treatment with PCC. Minor amounts of a compound arising from elimination of the intermediate chromate ester are also formed.

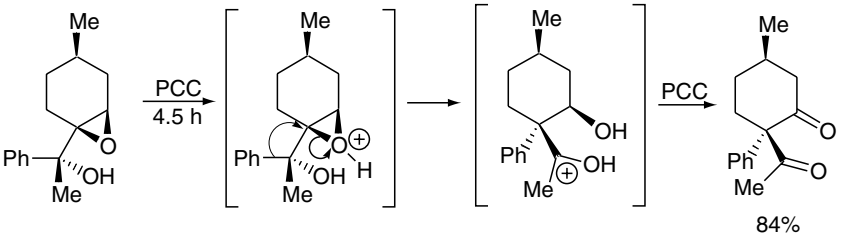
It is often difficult to distinguish whether a hydroxyl acts as a good-leaving group on PCC treatment, resulting from the formation of a chromate ester, or from protonation produced by the acidic nature of PCC. Cases are known in which such PCC induced reactions are not mimicked by treatment with simple acids,[327] suggesting that a chromate ester is acting as leaving-group rather than occuring a reaction induced by the acidic nature of PCC.



Ref. 327

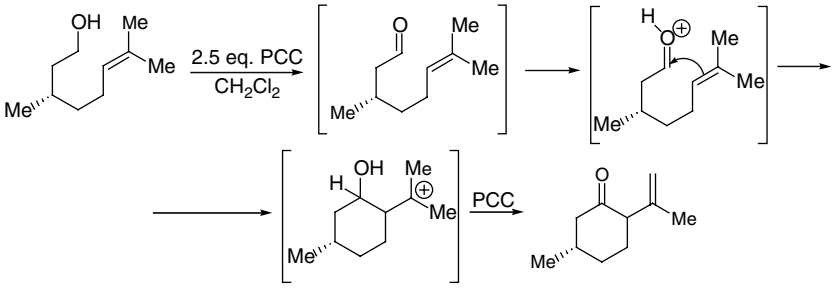
The intermediate chromate ester suffers an intramolecular displacement by attack of a hydroxyl via a S_N2' reaction, instead of the expected transposition, leading to an enone. This is not a simple ether formation, catalyzed by the acidic nature of PCC, for treatment of the starting compound with acids produces complex mixtures containing alkenes, resulting from dehydration of the alcohols.

On other occasions, some PCC-induced reactions are better explained through the use of PCC as a proton source.[328]



Ref. 328

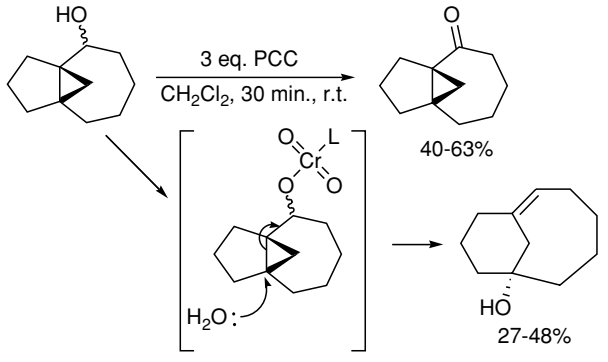
Protonation of the epoxide promotes the migration of a phenyl group that results in opening of the epoxide, and formation of an alcohol and a protonated ketone. Oxidation of the alcohol leads to the final diketone.



Ref. 329

The oxidation of the alcohol produces an aldehyde that, after activation by protonation with PCC is attacked intramolecularly by an alkene. This results in the generation of an intermediate that contains a secondary alcohol and a tertiary carbocation, and evolves to the final olefinic ketone by oxidation and deprotonation.

The following is a PCC-induced reaction with an unclear mechanism:

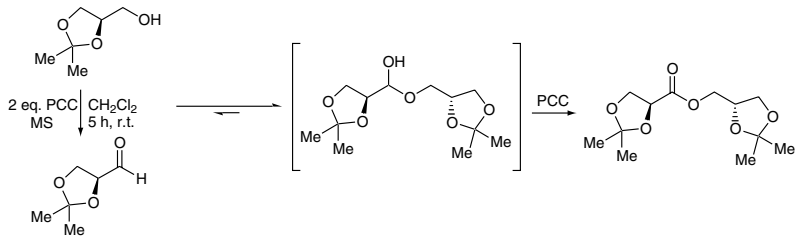


Ref. 330

A ketone, resulting from the normal oxidation of a secondary alcohol, is obtained along with an alkene, resulting from an opening of the cyclopropane. The secondary product can be explained by the intermediacy of either a chromate ester, or a protonated alcohol. Treatment of the starting alcohol with 10% HCl leads to a 87% yield of the secondary product, suggesting a mechanism involving PCC as a proton donor.

1.5.3.4. Oxidative Dimerization of Primary Alcohols

When the oxidation of a primary alcohol with PCC results in the formation of an aldehyde, activated with an electron withdrawing group at the α-position; sometimes, a stable dimeric hemiacetal is formed that is further oxidized to a dimeric ester.[331] This reaction, that can also happen with other chromium-based reagents (see page 42), can be minimized by adjusting the reaction conditions.

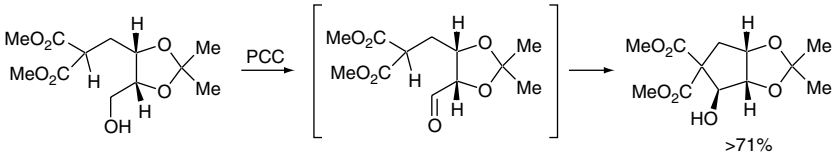


Ref. 331

The aldehyde reacts with the starting alcohol, yielding a stable hemiacetal that can be further oxidized to a dimeric ester. The formation of the dimeric ester can be minimized by the use of high dilution and the slow addition of the alcohol to the oxidant, resulting in a reaction giving an optimized 5:2 ratio of aldehyde to dimeric ester.

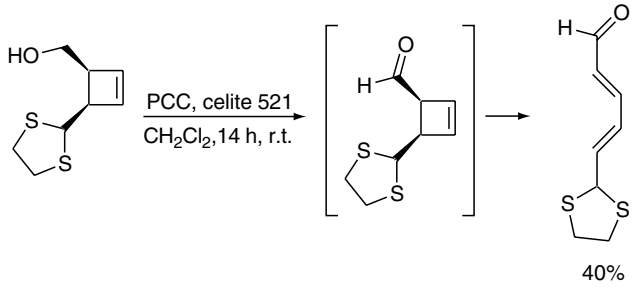
1.5.3.5 Oxidation Products Suffering Subsequent Reactions in Which PCC Plays no Role

Sometimes, oxidation of alcohols with PCC leads to very reactive aldehydes or ketones that suffer subsequent reactions *in situ,* which can be explained without the recourse of a role for PCC.[332]



Ref. 332

The oxidation of the primary alcohol leads to an aldehyde that intervenes *in situ* in a very easy aldol addition, leading to a stable five-membered ring.

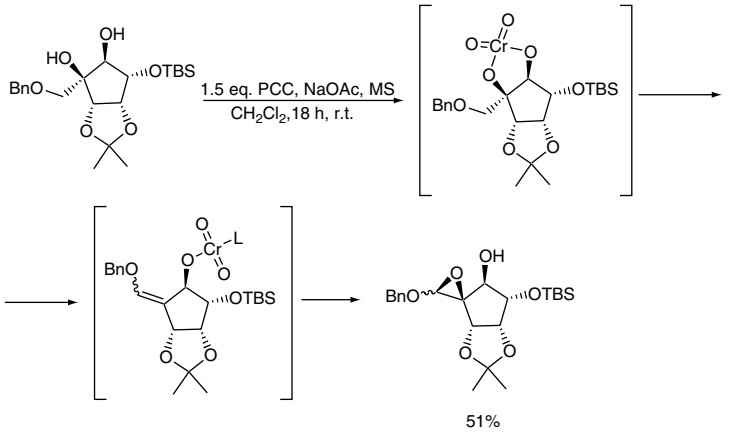


Ref. 333

The concerted disrotatory opening of the cyclobutene is much easier in the aldehyde than in the starting alcohol. Thus, while the alcohol could be easily isolated, its oxidation to aldehyde leads to a cyclobutene that could not be isolated, because it suffers a quick opening of the ring to the final product.

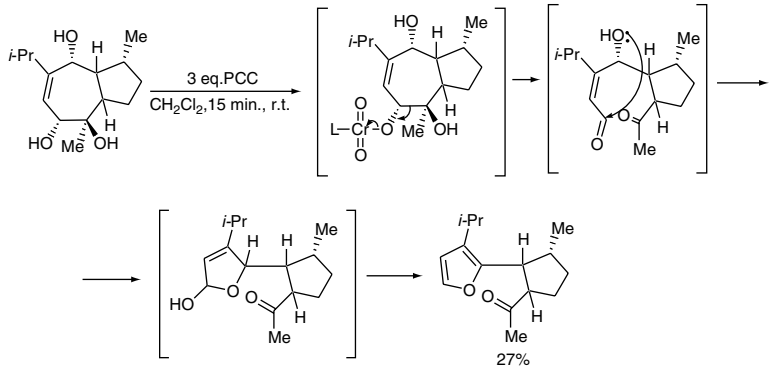
1.5.3.6. Side Reactions in Which Several of the Above Principles Operate

Sometimes, the action of PCC on alcohols leads to products that can be explained by complex mechanism, in which several of the reactivity principles mentioned above act in a sequential manner.[334]



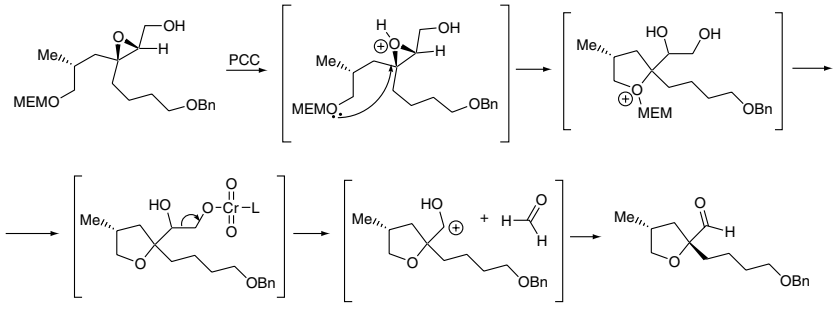
Ref. 334a

This mechanistically fascinating product can be explained by the initial formation of a cyclic chromate ester, facilitated by the formation of a five-membered ring and the (*cis*) relationship in the 1,2-diol. Interestingly, this stable chromate does not evolve resulting in the oxidation of the secondary alcohol, but it suffers elimination producing a very electron-rich benzyloxy alkene that is easily epoxidized intramolecularly by chromium. Observe that the epoxide oxygen enters from the same face than the secondary alcohol.



Ref. 334b

PCC reacts with one of the secondary alcohols, producing a chromate ester that suffers fragmentation, resulting in the generation of an aldehyde and a protonated ketone. The aldehyde is intramolecularly attacked by the remaining secondary alcohol, yielding a lactol that is dehydrated to a furan.



Ref. 334c

This epoxide—previously protonated—is opened by intramolecular attack of the MEM-protected alcohol. The MEM group is lost from the resulting oxonium ion, and the primary alcohol forms a chromate ester that fragments, yielding a protonated aldehyde and formaldehyde.

Section 1.5. References

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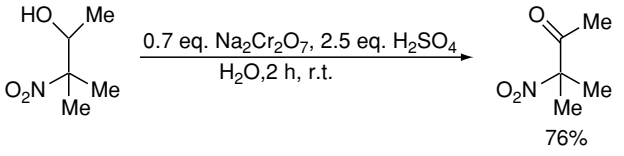
1.6. Other Chromium-Based Oxidants

1.6.1. Chromic Acid

Chromium trioxide in aqueous solution equilibrates with a number of species, and chromic acid, being the most abundant one under acidic conditions (see page 1). Thus, a mixture of chromium trioxide and sulfuric acid is often referred to as a ''chromic acid'' solution. Such solution can also be obtained by the action of sulfuric acid on sodium dichromate ($Na_2Cr_2O_7$) or potassium dichromate ($K_2Cr_2O_7$).

So far, the most common experimental conditions used for the oxidation of alcohols with chromic acid are the so-called Jones oxidation; first described in 1946, in which acetone is used as co-solvent. In fact, the use of chromic acid in the oxidation of alcohols has a long tradition in organic synthesis. As soon as in the 19th century, Beckmann described[335] an oxidation of alcohol with aqueous chromic acid, in which no mixing of phases was

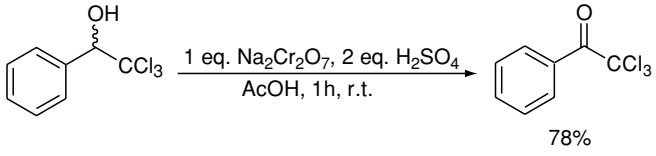
facilitated by the addition of an organic solvent. Such crude procedure, which very often results in a sludge of suspended organic matter in water, may offer sometimes the advantage of avoiding emulsions, and finds occasional use even nowadays.[336]



Ref. 336g

No use of an organic solvent is found in this oxidation, in which chromic acid is generated by the action of sulfuric acid on sodium dichromate.

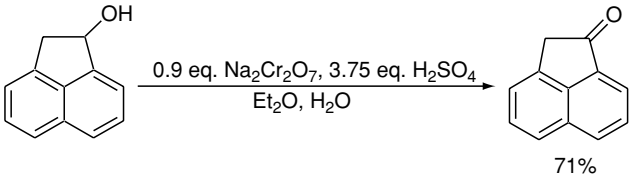
In 1901, Kiliani *et al.*[337] described the use of a solution of chromic acid in acetic acid and water, prepared by mixing sodium dichromate, sulfuric acid, acetic acid and water. The resulting "Kiliani reagent" is occasionally used for the oxidation of alcohols.[338] In 1954, Gastamide[339] described a similar reagent in which no water is added. This procedure was rediscovered in 1989[340] and offers the distinctive advantage of the good solubilizing power of acetic acid for both polar and apolar compounds. Chromic acid in acetic acid—with[341] or without[342b] water included—has been prepared using either sodium[343] or potassium[341] dichromate, or chromium trioxide[342] as the source of chromic acid. A study of the kinetics of oxidation of alcohols with chromic acid in acetic acid has also been made.[344] Occasionally, no sulfuric acid is added to the reaction; in fact, this variant being described earlier than the Gastamide paper. Thus, the use of a mixture of potassium dichromate and acetic acid was first described in 1934, and is referred as the method of Asahina and Ishidate,[345] while the employment of sodium dichromate in aqueous acetic acid was reported in 1948, and has been described as the method of Erne and Erlenmeyer.[346] Fieser reagent, comprised of a suspension of chromic trioxide in anhydrous acetic acid, must also be mentioned.[347]



Ref. 343g

In this oxidation under Gastamide conditions, acetic acid is used as solvent, while chromic acid is generated by the action of sulfuric acid on sodium dichromate.

In 1961, Brown[348] described the oxidation of alcohols, using a two-phase system with aqueous chromic acid and diethyl ether. Brown's oxidation[349] has a work-up, facilitated by the reluctance of ether to form emulsions with materials containing chromium, and although not as popular as Jones oxidation, it is used quite often.

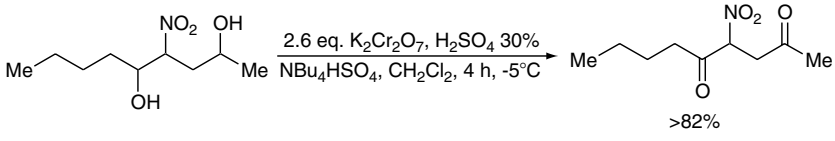


Ref. 349g

A two phase system, consisting of water and diethyl ether, is used in this oxidation under Brown's conditions, in which chromic acid is formed by the action of sulfuric acid on sodium dichromate.

Interestingly, very few examples involving other organic solvents, apart from acetone, acetic acid or diethyl ether, are found in the literature in chromic acid oxidations of alcohols. Rarely used organic solvents include: ethyl acetate,[350] benzene,[351] chlorobenzene,[352] dioxane[353] and DMSO.[354]

Phase-transfer conditions can be used in a two-phase system, consisting of aqueous chromic acid and dichloromethane with tetrabutylammonium bisulfate[355] or benzyltriethylammonium chloride[356] as phase-transfer catalysts.



Ref. 355d

In this oxidation, tetrabutylammonium bisulfate works as a phase transfer catalyst in a two phase system, consisting of water and dichloromethane, in which chromic acid is formed by the action of sulfuric acid on potassium dichromate.

Finally, the use of some chromic acid species deposited on silica particles must be mentioned.[357]

Interestingly, in Jones oxidation, chromic acid is almost always generated from chromium trioxide; while in the rest of the chromic acid oxidations, sodium or potassium dichromate are almost exclusively used. This seems to be the result of an irrational tradition originated since the reagents

were first employed in the seminal papers. Chromium trioxide looks a better choice in all oxidations, because of its more economical price.

1.6.2. Chromium Trioxide and Pyridine

Chromium trioxide forms the complex $CrO_3 \cdot 2Py$ on reaction with pyridine. This complex is very effective in the oxidation of alcohols and, depending in the way it is generated, results in different reagents possessing the names of their discoverers. Thus, Sarett reagent,[358] first described in 1953, is formed when chromium trioxide is added over excess of pyridine, resulting in a solution of $CrO_3 \cdot 2Py$ in pyridine. As the preparation of Sarett reagent is tedious and dangerous, in 1962, Cornforth reagent[359] was introduced, whereby chromium trioxide is added to pyridine as an aqueous solution, resulting in a much more comfortable and safe preparation of the complex. Both Sarett and Cornforth reagents suffer from the need to use them in excess in a very basic pyridine solution. These problems were overcome by the use of Collins reagent, in which the complex $CrO_3 \cdot 2Py$ is used in dichloromethane solution. In 1968, Collins[8] described the preparation and isolation of the complex $CrO_3 \cdot 2Py$, that can be stored and later used in dichloromethane solution for the oxidation of alcohols in almost neutral conditions, with no need to use a great excess of oxidant. In 1970, a great experimental improvement on Collins oxidation was introduced by Ratcliffe,[10] by which the complex $CrO_3 \cdot 2Py$ was prepared *in situ* by adding CrO_3 and pyridine to dichloromethane; thus, avoiding the need to isolate and handle the complex $CrO_3 \cdot 2Py$, which is quite hygroscopic. Nowadays, Sarett and Cornforth reagents are rarely used, while Collins oxidations are normally performed using the Ratcliffe variant, in which $CrO_3 \cdot 2Py$ is prepared *in situ*.

1.6.3. Dichromate Salts

So far, the most commonly used dichromate salt in the oxidation of alcohols is pyridinium dichromate (PDC). It possesses the advantages of being soluble in organic solvents, easy to prepare and having some extra reactivity due to the slightly acidic nature of the pyridinium counter-ion. In fact, under proper conditions the cheap and simple inorganic dichromate salts, sodium dichromate ($Na_2Cr_2O_7$) and potassium dichromate ($K_2Cr_2O_7$) are also able to oxidize alcohols, in spite of its lack of solubility in most organic solvents and its decreasing reactivity. Thus, $K_2Cr_2O_7$ can be used as oxidant of alcohols if brought into an organic solution by employing a dipolar organic solvent, like DMF[362] or DMSO,[363] or by using two equivalents of Adogen 464 as phase-transfer reagent in benzene.[364] Even the simple procedure of mixing finely ground potassium dichromate with an alcohol, in the absence of solvent, may result in a useful oxidation.[365] Other alternatives of oxidation of alcohols with neutral sodium or potassium dichromate include, the use of a two-phase system of water and benzene,[351b] and the

employment of a silica-supported reagent.[366] It is important to stress that, when sodium or potassium dichromate are used in the presence of sulfuric acid or other strong acids, the real oxidizing reagent is chromic acid (see page 83).

The oxidation of alcohols with metal dichromates, other than sodium or potassium dichromate, has been little explored. Hydrated zinc dichromate ($ZnCr_2O_7 \cdot 3H_2O$)[367, 368a] and ferric dichromate [$Fe_2(Cr_2O_7)_3$],[368b]—which are very easy to prepare as stable solids—are able to oxidize alcohols in organic solvents.[368] Zinc dichromate is particularly efficient in the transformation of α-hydroxyphosphonates into α-ketophosphonates.[369]

Ammonium dichromates, other than pyridinium dichromate, have been scarcely used in the oxidation of alcohols, regardless of their easy preparation. It seems that the ammonium contra-ion may have a profound effect on the reactivity of the dichromate anion. For instance, the simple ammonium dichromate—$(NH_4)_2Cr_2O_7$—is able to oxidize alcohols only when very exacting experimental conditions are employed.[370] Quinolinium (QDC),[371] isoquinolinium (iQDC),[372] bis(benzyltriethylammonium),[373] 2- and 4-benzylpyridinium,[374] benzimidazolium,[375] *n*-butyltriphenylphosphonium,[376] 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane[377] and naphtyridinium (NapDC)[378] dichromates have been shown to be able to oxidize alcohols. Although little explored, some of them seem to offer some advantages over PDC regarding solubility in apolar solvents and oxidation selectivity.

A compound prepared and first described as nicotinium dichromate (NDC) by Palomo *et al.*,[379] was later shown by X-ray-crystal analysis[380] to be a betainic mixed anhydride of nicotinic and chromic acid (NACAA). Because of its unique structure, it deserves a close scrutiny of its oxidative properties.[381] Replacement of the chloride anion in the quaternary ammonium resin, Dowex 1-X8, for the dichromate anion, leads to a polymer supported dichromate, which is able to make selective benzylic oxidations.[382] Finally, poly[vinyl(pyridinium dichromate)] (PVPDC), a polymeric analogue of PDC, must be mentioned whose use in the oxidation of alcohols allows for a very easy work-up.[383]

1.6.4. Halochromate Salts

Ammonium chlorochromates are prepared by mixing chromium trioxide and an amine in hydrochloric acid, and collecting the crystals. For historical reasons, the most thoroughly used and investigated is pyridinium chlorochromate, although chlorochromates possessing other ammonium cations may offer some advantages. Even though, the oxidizing power resides on the chlorochromate anion, the ammonium part modulates the oxidizing reactivity by providing differential acidic catalyses. Thus, the less acidic *p*-dimethylaminopyridinium chlorochromate (DMAPCC)[384] is a milder oxidant than pyridinium chlorochromate (PCC), and is able to selectively oxidize allylic alcohols. Similarly, quinolinium chlorochromate

(QCC)[385] is able to regioselectively oxidize primary alcohols in the presence of secondary ones. Tetrabutylammonium (TBACC),[386, 387j] butyltriphenylphosphonium (BTPPCC)[388] and benzyltriphenylphosphonium[389] chlorochromates, as they possess no acidic protons, behave as very mild oxidants able to perform selective oxidations on allylic and benzylic alcohols.

On the other hand, isoquinolinium (iQCC),[385b] *p*-methylpyridinium (γ-PCC)[390] and trimethylammonium (TMACC)[391] chlorochromates closely resemble the oxidizing behaviour of PCC. *p*-Methylpyridinium chlorochromate has the distinctive advantage over PCC of containing *p*-methylpyridine that is less toxic than pyridine.

2,6-Dicarboxypyridinium chlorochromate (2,6-DCPCC)[392] possesses an acidic character that allows the *in situ* deprotection and oxidation of alcohols, protected as tetrahydropyranyl and trimethylsilyl ethers. 2,2′-Bipyridinium chlorochromate (BPCC)[393] contains a ligand that complexes efficiently with the reduced chromium species, generated during the oxidation of alcohols, allowing for a substantial simplification of the work-ups. For this reason, it enjoys a popularity among chlorochromates surpassed by only PCC.

Other ammonium chlorochromates, occasionally used in the oxidation of alcohols, include: pyrazinium-*N*-oxide (PzOCC),[378] naphtyridinium (NapCC),[394] pyrazinium (PzCC),[394] tripyridinium hydrochloride (TPCC),[378a] triethylammonium,[378b] imidazolium and 1-methylimidazolium,[194e] and benzyltrimethylammonium (BTMACC)[387j] chlorochromates.

Interestingly, the little studied inorganic chlorochromates, potassium[397] and magnesium[398] chlorochromates are very easy to prepare and are soluble in polar organic solvents, like acetone or acetonitrile. They are able to efficiently oxidize secondary alcohols to ketones, although they provide only low yields of aldehydes on the oxidation of primary alcohols.

Ammonium fluoro and bromochromates can be prepared in an analogous manner than the chlorochromates by mixing chromium trioxide, an amine and the corresponding hydrohalic acid in water, and collecting the crystals. Fluorochromates are less acidic and, therefore, less reactive than chlorochromates, while bromochromates are more acidic and more reactive. Pyridinium fluorochromate (PFC)[387] and quinolinium fluorochromate on alumina[399] have efficiently been used in the oxidation of alcohols as less acidic counterparts of PCC, needing no addition of a buffer. The use of the polymeric analogue of PFC, poly[vinyl(pyridinium fluorochromate)] has also been described.[400] Pyridinium bromochromate (PBC)[401] is a little studied analogue of PCC with a stronger oxidizing power. Quinolinium fluorochromate (QFC)[402] is a very mild oxidant, able to deprotect primary TBS ethers in the presence of secondary ones, thanks to the presence of fluoride. The liberated alcohols are oxidized *in situ* to aldehydes.

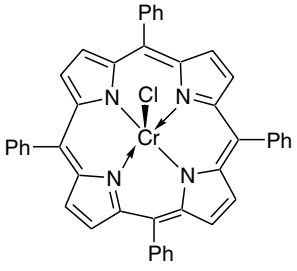
3,5-Dimethylpyrazolinium fluorochromate,[403] isoquinolinium fluorochromate (iQFC)[404] and quinolinium bromochromate (QBC)[405] have also been described as halochromates able to oxidize alcohols.

1.6.5. Oxidations Using Catalytic Chromium Compounds

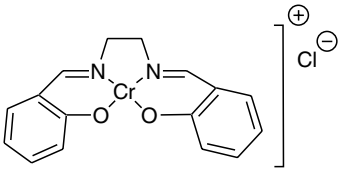
A great effort is dedicated to the development of methodologies for the oxidation of alcohols, involving catalytic quantities of chromium compounds, which are re-oxidized with other oxidants present in excess.[406] Using chromium compounds in catalytic amounts is environmentally sound, and often facilitates the work-ups.

Chromium compounds used in catalytic amounts for the oxidation of alcohols to aldehydes and ketones include:

- Cr(0) compounds, like $Cr(CO)_6$,[407]
- Cr(III) compounds, like Cr(III) hydroxide deposited on montmorillonite,[408] Cr(III) stearate,[409] $Cr(acac)_3$,[409b] Cr(III) on a perfluorinated sulfonic resin (NAFK),[410] chloro(tetraphenylporphyrinate) chromium(III) [(TPP)CrCl] **(6)**[411] and (salen)oxochromium(III) complex **(7)**,[412,413]

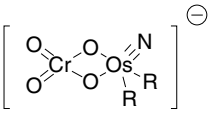


(TPP)CrCl **(6)**



7

- Cr(VI) compounds, like CrO_3,[414] PDC,[415] PCC,[416] $(OCMe_2CH_2CMe_2O)CrO_2$[417] and a chromium substituted aluminophosphate (CrAPO-5),[418]
- Bimetallic complexes containing chromium like **8**.[419]



8

R= CH_2SiMe_3, Me

As oxidants (used in excess), the following reagents were tried: *t*-butyl hydroperoxide,[407,408,410,414,409,418] cumyl hydroperoxide,[414b] hydrogen peroxide,[415c] air,[419] oxygen,[418] peracetic acid,[417] bis(trimethylsilyl)peroxide,[415a,b; 416] sodium perborate,[420] iodosobenzene[411,412,413] and iodosobenzene diacetate.[413]

Table 1.4. Lists the combinations of catalytic chromium compounds and oxidants (used in excess) employed in the oxidation of alcohols to aldehydes and ketones.

Catalytic chromium compound	Oxidant used in excess	Molar ratio chromium compound/oxidant in excess/alcohol	Observations	References
$Cr(CO)_6$	*t*-BuOOH	0.25/3/1	MeCN, 19 h, reflux	407
Cr(III) montmorillonite	*t*-BuOOH	0.025/1.05/1	CH_2Cl_2, 18–20 h, r.t.	408
$Cr(St)_3$	*t*-BuOOH	—	80–125 °C	409
$Cr(acac)_3$	*t*-BuOOH	0.02/2/1	PhH, 6 h, 80 °C	409b
Cr/NAFK	*t*-BuOOH	0.034/4/1	PhCl, 6 h, 85 °C	410
(TPP)CrCl	PhIO	—	r.t.	411
(Salen)oxochromium(III) complex (7)	PhIO	0.15/1.5/1	CH_2Cl_2, 20 °C	392,413
(Salen)oxochromium(III) complex (7)	$PhI(OAc)_2$	0.1/1.5/1	CH_2Cl_2, 1 h, 20 °C	413
CrO_3	*t*-BuOOH	0.05–0.1/1–4/1	CH_2Cl_2, 8–17 h, r.t.,	414
CrO_3	$NaBO_3$	0.1/7/1	$PhH:H_2O$(1:1), 24 h, 60 °C	400
CrO_3	$PhCMe_2OOH$	—	—	414b
PDC	$Me_3SiOOSiMe_3$	0.1/0.5/1	CH_2Cl_2, 0.5 h, 25 °C	415a,b
PDC	H_2O_2	0.1/6/1	0.2 eq. adogen 464, 1,2-dichloroethane, 24 h, 80 °C	415c
PCC	$Me_3SiOOSiMe_3$	—	—	416
$(OCMe_2CH_2CMe_2O)CrO_2$	$MeCO_3H$	—	—	417
CrAPO-5	*t*-BuOOH	0.14/5/10	PhCl, 16 h, 85 °C	418
CrAPO-5	O_2	—	—	418
Bimetallic complexes **8**	air	5 mol% catalyst	MeCN, 72 h, 70 °C	419

Table 1.4. lists the combinations of catalytic chromium compounds and oxidants (used in excess) employed in the oxidation of alcohols to aldehydes and ketones.

Although the oxidations using catalytic chromium compounds are industrially attractive, none of them has found a widespread use in organic synthesis, because its versatility and efficiency in complex substrates have not been demonstrated.

1.6.6. Miscellanea

A suspension of chromium trioxide in dichloromethane, although able to oxidize alcohols, produces a very sluggish and low yielding transformation into aldehydes and ketones, because of the heterogeneous nature of the reaction. The addition of a catalytic amount of a crown ether,[421] or a quaternary ammonium salt,[422] causes a substantial increase in reaction speed and yield. Alternatively, chromium trioxide in a mixture of dichloromethane and diethyl ether is able to oxidize alcohols in good yields, particularly when celite is added to facilitate the work-up.[423] Chromium trioxide deposited on alumina is very efficient in the transformation of 1-hydroxyphosphonates into acyl phosphonates.[424] Recently, it has been reported that solid CrO_3 in a solvent-free system is able to efficiently oxidize liquid primary alcohols to aldehydes.[425] Chromium trioxide intercalated in graphite is able to oxidize primary alcohols in a very good yield, while secondary alcohols are almost inert to this reagent.[426a]

Chromium peroxide (CrO_5), obtained by the oxidation of chromium trioxide with hydrogen peroxide, reacts with amines forming complexes, like 2,2′-bipyridylchromium (BPCP) and pyridinechromium (PCP) peroxides, that oxidize efficiently alcohols to aldehydes and ketones.[426b]

Pyridinium and quaternary ammonium resins react with chromium trioxide, producing polymer-supported complex chromates that oxidize alcohols, and provide a very facile work-up.[427]

The mixture of chromium trioxide with one equivalent of trimethylsilyl chloride, with no solvent added, results in the formation of an explosive red liquid that is soluble in dichloromethane or tetrachloromethane.[428] It is suggested, with no spectroscopic evidence, that it consists of trimethylsilyl chlorochromate [$Me_3Si\text{-}O\text{-}Cr(O)_2\text{-}Cl$]. This compound, which can safely be used in organic solvents, is able to oxidize alcohols to aldehydes or ketones, and interacts with *t*-butyldimethylsilyl ethers producing deprotection, followed by oxidation of the liberated alcohol.[138] Compounds analogue to trimethylsilyl chlorochromate are also able to oxidize alcohols, although they possess lesser reactivity. They can be prepared by reaction of chromium trioxide with dimethyldichlorosilane and diphenyldichlorosilane.[428b]

Chromyl chloride adsorbed on silica-alumina oxidizes alcohols to aldehydes and ketones.[430]

Section 1.6. References

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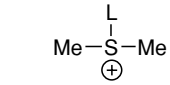
2

Activated Dimethyl Sulfoxide

2.1. Introduction



L = good-leaving group

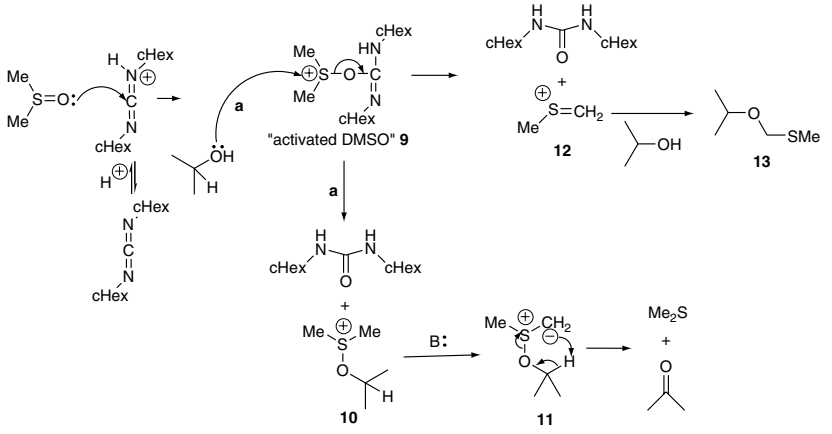
In 1963, Moffatt and Pfitzner[1] published that, at room temperature, treatment of an alcohol dissolved in dry DMSO with dicyclohexylcarbodiimide (DCC), in the presence of a mild acid, leads to the oxidation to the corresponding aldehyde or ketone. This oxidation was remarkable, because it succeeded in sensitive substrates, and no trace of over-oxidation to acid was detected in the oxidation of primary alcohols. Two years later, Moffatt *et al.*[2] and Albright *et al.*[3] almost simultaneously suggested a mechanism for this oxidation, which has been proved to be fundamentally right.[4] According to this mechanism (see Equation below), protonated DCC reacts with DMSO resulting in the formation of a sulfonium species containing a good-leaving group linked to the positive sulfur atom, the so-called "activated DMSO" species **9**. The alcohol displaces the good leaving-group, yielding an alkoxydimethylsulfonium salt **10** that looses a proton, resulting in the formation of the sulfur ylide **11**. Finally, an intramolecular elimination leads to the formation of a carbonyl compound and dimethyl sulfide.

> Dimethyl sulfide is toxic and possesses a very bad odour. Particularly, in reactions with activated DMSO on a very big scale, it may be advisable to destroy the dimethyl sulfide, generated during the reaction, by purging the reaction mixture with a nitrogen flow, and scrubbing the resulting gaseous mixture with aqueous NaOCl.[5]

The "activated DMSO" **9** can also suffer an elimination, resulting in the highly reactive $H_2C{=}S(+)\text{-}CH_3$ species that can react with the alcohol, yielding a methylthiomethyl ether **13** as a side compound. Fortunately, this elimination demands a higher temperature than the normal temperature of oxidation, and a proper control of the temperature minimizes the formation of the methylthiomethyl ether side compound.

Using solvents of low polarity also minimizes the formation of methylthiomethyl ethers.[6] That is why, oxidations with activated DMSO are normally carried out in CH_2Cl_2, a solvent of low polarity possessing good solubilizing power.

The ^{1}H-NMR spectra of methylthiomethyl ethers (R-OCH_2-SCH_3) shows the methyl group as a singlet at ca. 2.1–2.3 ppm, and the methylene group as a singlet or as an AB quartet at ca. 4.6–4.8 ppm.



It was very soon realized that other electrophiles, besides diimides, can "activate" DMSO and allow the oxidation of alcohols. Thus, in 1965, acetic anhydride[3] and phosphorous pentoxide[7] were already suggested as activators by Albright *et al.* and Onodera *et al.*, and in 1967, Doering and Parikh disclosed the use of the complex $SO_3 \cdot Py$.[8] The following years witnessed the exploration of numerous activators, belonging to almost any conceivable electrophile kind. Thus, the Swern team carried out a very active search for an ideal activator that led to the proposal of trifluoroacetic anhydride[9] in 1976, and culminated with the predication of oxalyl chloride in 1978,[10] as the activator of choice in what became known as the Swern oxidation. Nowadays, most research groups use the "Swern oxidation" as the default oxidation when activated DMSO is desired. In fact, oxalyl chloride is the activator guaranteeing probably the best yields in the oxidation of alcohols, and it is now the most commonly used also, regardless of involving a somehow inconvenient experimental procedure, including low temperature and the evolution of highly toxic carbon monoxide. Dicyclohexylcarbodiimide, the complex $SO_3 \cdot Py$, trifluoroacetic anhydride, acetic anhydride and phosphorous pentoxide, in approximate decreasing order of use, are other activators commonly used in oxidations with activated DMSO, and offer alternatives to Swern oxidation, involving many times simpler experimental procedures with a minimum detriment in yield. In the opinion of the authors, the highly successful discovery of the Swern oxidation, rather than closing the chapter of the oxidation of alcohols with activated DMSO, should encourage the quest for

better activators. In fact, many promising alternative activators have been suggested, but little tested by the synthetic organic chemists (see Table 2.2, page 177). Furthermore, some potentially good activators could have been discarded, because of using unoptimized reaction conditions. Very significantly, trifluoroacetic anhydride has been proved to be a magnificent activator at low temperature by Swern *et al.*,[122] while it was previously discarded by Albright *et al.*[3,56] after finding that it is useless at room temperature.

It is important to note that, depending on the activator, the resulting "activated DMSO" will have diverse reactivity. Strong activators, such as oxalyl chloride or trifluoroacetic anhydride, produce highly reactive "activated DMSO", able to oxidize alcohols at very low temperature. The resulting forms of highly reactive "activated DMSO" will also have a tendency to decompose to the methylene sulfonium salt **12** at relatively low temperatures. Thus, strong activators must necessarily be used at low temperatures for best yields. In contrary, mild activators, such as dicyclohexylcarbodiimide, the complex $SO_3 \cdot Py$, acetic anhydride or phosphorous pentoxide, give best results at approximately room temperature, because the resulting forms of "activated DMSO" are less reactive but very advantageously decompose less easily to the methylene sulfonium salt **12**. An important consequence of this pattern of reactivity is that the resistance of unreactive alcohols to oxidation with activated DMSO can hardly be overcome by increasing the temperature.

2.1.1. A Proposal for Nomenclature of Reactions Involving Activated DMSO

Oxidations involving DCC are normally referred as either "Moffatt oxidations" or Pfitzner–Moffatt oxidations". Sometimes, the name "Moffat oxidations" is applied in a broad sense to any reaction involving activated DMSO regardless of the concrete activator employed. Moffatt made the seminal contribution to the oxidations with activated DMSO and explored its mechanism. Therefore, we suggest that oxidations with activated DMSO collectively be called "Moffatt oxidations". The name "Pfitzner–Moffatt oxidation" could be reserved to oxidations involving DCC, or any other carbodiimide as activator. Oxidations with oxalyl chloride are called, according to extensive use, "Swern oxidations". In fact, Swern made an enormous contribution to oxidations with activated DMSO, involving many different activators.[11] Although, his most successful activator was oxalyl chloride, he must also be credited with the suggestion of trifluoroacetic anhydride as activator. Its use, although not as common as the use of oxalyl chloride, is common enough to merit a name to the reaction. We propose, in keeping with common usage, that "Swern oxidation" be used to refer to oxidations in which oxalyl chloride is employed, the name "Omura–Sharma–Swern oxidation" being reserved to oxidations involving trifluoroacetic anhydride. The name "Parikh–Doering oxidation" is normally used for oxidations involving the complex $SO_3 \cdot Py$. This usage is unambiguous and should be kept. No reaction name has normally been employed for oxidations involving acetic anhydride. We suggest that these oxidations be called "Albright–Goldman oxidations". Albright and Goldman were the first to suggest the use of acetic anhydride, and Albright made valuable early contributions to the

oxidations with activated DMSO.[12] The use of phosphorous pentoxide was first briefly mentioned by Albright in 1965, and soon afterwards, Onodera *et al*. published a communication dealing solely with this reagent. Therefore, we suggest the name "Albright–Onodera oxidations" for oxidations involving P_2O_5. When less common activators are used, the corresponding oxidation can be named as Moffatt oxidation mediated by the corresponding activator. For instance, an oxidation induced by triphosgene can be described as a "Triphosgene-mediated Moffatt oxidation".

Corey and Kim described an oxidation,[6a] in which activated DMSO is not generated by activation of DMSO, but by oxidation of dimethyl sulfide. Although, they described only the use of chlorine and *N*-chlorosuccinimide as dimethyl sulfide oxidants, we propose that the name "Corey–Kim oxidations" be applied to alcohol oxidations, in which activated DMSO is generated by oxidation of dimethyl sulfide, regardless of the oxidant employed.

Section 2.1. References

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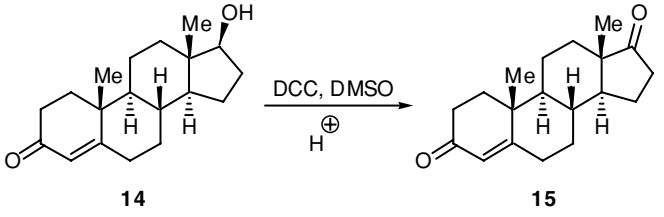
2.2. Pfitzner–Moffatt Oxidation (Carbodiimide-Mediated Moffatt Oxidation)

During some couplings of nucleosides, promoted by dicyclohexylcarbodiimide (DCC), Pfitzner and Moffatt.[13] decided to try dimethyl sulfoxide (DMSO) as solvent. Instead of obtaining the expected couplings, they observed oxidation of alcohols to aldehydes and ketones. These oxidations were very remarkable, because at that time, on the nucleosides tested, no oxidants were known to be able to deliver efficiently the observed aldehydes and ketones. Furthermore, contrary to many other oxidants, no over-

oxidation of aldehydes to carboxylic acids occurred. These serendipitous observations led to a detailed study of the oxidation of alcohols, using DMSO and DCC, that culminated with several landmark publications by Moffatt *et al.*[14,15] in which they determined optimal experimental conditions and performed tests, providing data to propose a consistent mechanism for these oxidations. Very soon other researchers realized that DMSO activators, other than carbodiimides, could be used, and the ensuing research efforts led to a number of oxidation protocols involving activation of DMSO, that culminated with the present employment of oxalyl chloride in the so-called Swern oxidation[16] as the default oxidation with activated DMSO. The Pfitzner–Moffatt oxidation[13]—in which carbodiimides are used for the activation of DMSO—not only represents the seminal contribution to the oxidation of alcohols with activated DMSO, but it is an oxidation method that finds broad use nowadays and possesses a number of advantages, including being very conveniently performed at room temperature.

Initially, Moffatt *et al.* performed optimization studies on the oxidation of testosterone **(14)** to Δ^4-androstene-3,17-dione **(15)**.[14]



14 **15**

Ref. 14a

Best yields with minimum formation of side compounds are obtained with 3 eq. of DCC and 0.5 eq. of pyridinium trifluoroacetate in a 1:1 mixture of benzene and DMSO at room temperature.

A look at the mechanism (page 98) shows that DCC—in order to be attacked by DMSO—needs to be activated by protonation. On the other hand, the reaction fails in the presence of a strong acid, such as HCl, H_2SO_4 or $HClO_4$, because these would prevent the formation of the sulfur ylide.[11] Moffatt *et al.* found that the oxidation of testosterone **(14)** succeeds using mild acids with pKa inside a narrow window.[14a] For example, no oxidation occurs with acetic acid (pKa = 4.76) or trichloroacetic acid (pKa = 0.66), because their pKas lay outside the acidity window, while monochloroacetic acid (pKa = 2.86) leads to a slow and incomplete reaction, and dichloroacetic acid (pKa = 1.25) produces a quantitative oxidation in ten minutes.

In fact, it was observed, regarding the acidic catalyst in the oxidation of testosterone **(14),** that acidity is not the only factor affecting yields, as acids with very similar pKas can lead to very diverse yields of the ketone **15**.

After testing many acids, it was found that ortophosphoric acid (solid anhydrous phosphoric acid) provides the greater acceleration of the oxidation, although its use may not be the most convenient, as it also leads to the formation of greater amounts of side compounds. Pyridinium trifluoroacetate—which can be used in the presence of excess of pyridine for buffering purposes—provides an optimum acceleration of the oxidation without promoting the formation of side compounds. Excellent yields are obtained when 0.5 equivalents of acid are added. A marginal increase in yield can be observed with a lower quantity of acid, at the cost of prolonging the reaction time substantially. Increasing the amount of acid above 0.5 equivalents produces a substantial decrease in yield. Very hindered alcohols are not oxidized employing pyridinium trifluoroacetate as acid. In such cases, some oxidation can be observed by using ortophosphoric acid, although the resulting yields of carbonyl compounds tend to be low, and substantial amounts of side compounds are obtained.

Three equivalents of DCC provide the best yield, while using less equivalents result in a substantial decrease in yield. Adding more than three equivalents of DCC has little influence in the oxidation.

DMSO must be used in excess, because it must attack DCC in competition with the acid and the alcohol. Surpassing the quantity of DMSO above six equivalents has little influence in the yield of the oxidation, although small yield increases are observed with a growing number of DMSO equivalents till an optimum yield is obtained with a 1:1 DMSO-benzene mixture. The use of neat DMSO results in a yield almost as good as using a 1:1 mixture of DMSO and benzene.

Moffatt *et al*. found that the optimized reaction conditions developed for the oxidation of testosterone **(14)**, worked ideally in the oxidation of other alcohols. Later, researchers tended to apply, on reactions run at room temperature on very diverse alcohols, these optimized conditions involving 3 equivalents of DCC or other carbodiimide, 0.5 equivalents of pyridinium trifluoroacetate with some extra pyridine added, and neat DMSO or a mixture of DMSO and benzene as solvent. The only substantial changes to this standard protocol involve the growing use of the water-soluble carbodiimide EDC,[17] instead of DCC, in order to facilitate the work-ups, and the occasional employment of dichloroacetic acid,[18] which proved very effective in the oxidation of some complex polar alcohols, instead of pyridinium trifluoroacetate.

Moffatt *et al*.[13] mentioned that other carbodiimides, such as diisopropylcarbodiimide, can be used in place of DCC. Carbodiimides, other than DCC and EDC, occasionally employed in this oxidation include: diethylcarbodiimide[19] and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.[20] It

must be mentioned that the easily available[21] diethylcarbodiimide is a liquid that generates the water soluble *N,N*'-diethylurea.[22]

It should also be noted that, during the formulation of the standard oxidation protocol by Pfitzner and Moffatt, no study at different temperatures was made, and the only solvent substantially tested was benzene.

Very occasionally, solvents other than benzene, such as toluene,[23] CH_2Cl_2[24] or DME,[25] have been used. It must be mentioned that the use of polar solvents tends to promote the formation of methylthiomethyl ethers in oxidations with activated DMSO.[26] So far, pyridinium trifluoroacetate[27] is the acid most commonly used, while phosphoric[28] and dichloroacetic acid[18] are being used less often. Acids rarely used include: pyridinium tosylate,[29] pyridinium phosphate[30] and pyridinium chloride,[31] which are normally employed in the presence of excess of pyridine.

2.2.1. General Procedure for Oxidation of Alcohols by Pfitzner–Moffatt Method

Three equivalents[a] of a carbodiimide[b] are added over a solution of 1 equivalent of the alcohol and 0.5 equivalents of pyridinium trifluoroacetate[c] in 0.6–40 mL of neat dry DMSO (MW = 78.1, d = 1.10), or a mixture of DMSO and benzene[d], at room temperature.[e] When most of the starting compound has been consumed,[f] the work-up can be made according to the following alternatives:

Work-up A:

The solvent is removed at the rotary evaporator, and the resulting residue is purified by chromatography. It can be advisable to filter the precipitate of *N,N*'-dicyclohexylurea[g]—formed when DCC is used—before removing the solvent. In order to avoid interferences from unreacting carbodiimide, it can be advisable to transform it in the corresponding urea by careful addition of oxalic acid—either solid or in a solution in methanol—to the stirred reaction mixture. Addition of oxalic acid produces a copious evolution of gas that signals the duration of the hydrolysis of the carbodiimide.

Work-up B:

The reaction mixture is fractioned between water and an organic solvent, such as diethyl ether, ethyl acetate or dichloromethane. The organic phase is sequentially washed with water and with an aqueous solution of $NaHCO_3$, dried with Na_2SO_4 or $MgSO_4$ and concentrated. When DCC is used, the resulting residue will contain unreacting DCC and *N,N*'-dicyclohexylurea that will need to be separated by chromatography. Alternatively, most of the highly insoluble urea, which appears as a thick

suspension in water, or in an organic solvent, can be removed at some point during the work-up by filtration. It can be advisable to quench the reaction by transforming the excess of DCC into the corresponding urea, by careful addition of oxalic acid either solid or in a solution in methanol.

[a] Normally, 3 equivalents of carbodiimide are used, although a greater amount can be advisable if the presence of adventitious moisture is suspected. The gratuitous employment of a liberal excess of carbodiimide can lead to a decreased yield, because of the need to separate great amounts of the resulting urea during the work-up.

[b] Normally, DCC (MW = 206.3) is used, although it can be difficult to free the product from the residues of the urea, resulting from the hydrolysis of DCC during the work-up. That is why, the water-soluble carbodiimide EDC [*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride] (MW = 191.7) is finding a growing use instead of DCC.

[c] Very often more than 0.5 equivalents of pyridinium trifluoroacetate (MW = 191.1) are added. This practice is not advisable, as it can lead to a substantial decrease in the yield of the aldehyde or ketone. For instance, during the oxidation of testosterone **(14)**, Moffatt *et al*. found that on changing from 0.5 to 2.0 equivalents of pyridinium trifluoroacetate, a decrease of ca. 20% occurs.[14b] On the other hand, the quantity of pyridinium trifluoroacetate can be diminished to 0.1 equivalents with no erosion of the yield, although leading to a slower reaction.

Pyridinium trifluoroacetate can either be added as such, or formed *in situ* by the addition of pyridine (MW = 79.1, d = 0.98) and trifluoroacetic acid (MW = 114.0, d = 1.48). Very often pyridine is added in an excess of ca. 0.5–2 equivalents relative to trifluoroacetic acid for buffering purposes.

If the substrate possesses a basic site, like an amine, this can neutralize the pyridinium trifluoroacetate and prevent the oxidation. In such cases, 1.5 equivalents of pyridinium trifluoroacetate must be added.

During the oxidation of greatly hindered alcohols, it can be advisable to use 0.5 equivalents of ortophosphoric acid (MW = 98.0) (solid phosphoric acid) instead of pyridinium trifluoroacetate. This causes an acceleration of the oxidation, although it normally leads to greater amounts of side compounds. On some highly polar compounds, the use of 0.5 equivalents of dichloroacetic acid (DCAA) (MW = 128.9, d = 1.47) can provide best results.

[d] Although, normally best yields are obtained using a 1:1 mixture of DMSO and benzene, it can be experimentally more convenient to avoid the use of dry benzene, because neat DMSO delivers normally a yield of carbonyl compound almost as good. On the other hand, if using as little as possible of DMSO (MW = 78.1, d = 1.10) is desired, its quantity can be decreased to about 6 equivalents without a great erosion of the yield.

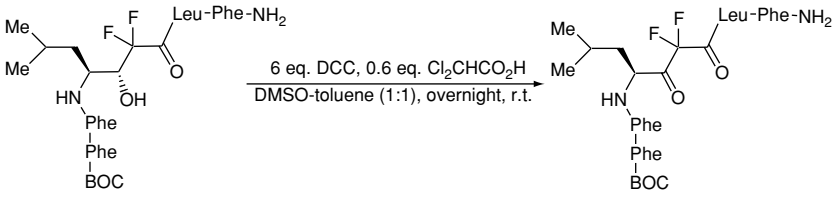
Very little is known about the influence of the use of other solvents on the yield, although it is expected that other aprotic solvents would be as efficient as benzene. Toluene and CH_2Cl_2 are interesting alternatives to the use of carcinogenic benzene, which have been proved to be efficient in this oxidation.

[e] It can be advisable to cool the reaction flask on an ice-water bath during the initial mixture of components on multigram scale oxidations when exotherms can be expected. As the DMSO freezes at 18°C, operations at low temperature must be done in the presence of a co-solvent, like benzene.

[f] Normally, it takes between 1 h and 1 day.

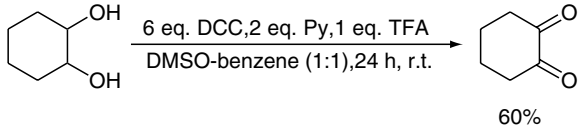
[g] *N,N*'-dicyclohexylurea shows a melting point of 237–238°C.[32] Its ^{1}H-NMR (δ, DMSO-d_6, 500 MHz, ppm) shows the following signals: 5.50 (1H, d, J = 8 Hz), 3.37–3.28 (1H, m),

1.75–1.68 (2H, m), 1.65–1.57 (2H, dt), 1.53–1.47 (1H, dt), 1.29–1.19 (2H, qt), 1.18–1.10 (1H, tt), 1.10–1.00 (2H, qd), and its ^{13}C-NMR (δ, DMSO-d_6, ppm) the following ones: 156.4, 47.3, 32.9, 24.9 and 23.9. A common side compound when pyridinium trifluoroacetate and DCC are used is *N,N'*-dicyclohexyl-*N*-trifluoroacetylurea that shows a melting point of 139°C and the following ^{1}H-NMR (δ): 6.5 (1H, m) and 3.8 (22H, m).[33] DCC possesses a melting point of 34–35°C[34] and the following spectroscopic data: ^{1}H-NMR (δ, $CDCl_3$, ppm): 3.19–3.14 (1H, m), 1.90–1.85 (2H, m), 1.72–1.70 (2H, m), 1.34–1.31 (1H, m), 1.29–1.14 (5H, m); ^{13}C-NMR (δ, $CDCl_3$, ppm): 139.8, 55.7, 34.9, 25.4 and 24.7, Mass spectrum: EM (CI, %) = 207[($M^+ + 1$), 16], 125 (100). The 1-(3-dimethylaminopropyl)-3-ethylcarbodimide shows the following ^{1}H-NMR (δ, D_2O, 60 *MHz*, ppm): 3.27 (t, J = 6.5 Hz), 3.26 (q, J = 7 Hz), 2.28 (t, J = 7 Hz), 2.21 (s), 1.7 (m), 1.21 (t, J = 7 Hz).[35] The hydrosoluble carbodiimide EDC shows a melting point of 111–113°C[36] and the following spectroscopic data: ^{1}H-NMR (δ, $CDCl_3$, 500 MHz, ppm): 7.67 (d, J = 23 Hz), 3.93–3.90 (m), 3.76 (s), 3.61–3.56 (m), 3.38–2.94 (m), 2.66–2.62 (m), 1.99–1.81 (m), 1.03–0.89 (m); ^{1}H-NMR (δ, D_2O, 60 *MHz*, ppm)—mixture of open and cyclic form: 3.86 (t, J = 7 Hz), 3.48 (t, J = 6.5 Hz), 3.41 (s), 3.17 (q, J = 7 Hz), 2.92 (s), 2.2 (m), 1.16 (t, J = 7 Hz).[35] ^{13}C-NMR (δ, $CDCl_3$, 125.8 MHz, ppm): 147.0, 141.1, 139.3, 63.6, 61.6, 55.5, 53.3, 52.5, 43.6, 42.9, 42.6, 41.8, 41.1, 37.3, 26.0, 18.3, 18.1, 16.6, 15.6, 13.5; ^{13}C-NMR (δ, DMSO-d_6, ppm): 158.3 (^{13}CN), 147.7, 141.2 (-NCN-), 62.4 ($^{13}CH_2N$ or $^{13}CH_2N^+$), 60.4, 54.6, 52.9, 51.7, 43.3 ($^{13}CH_3N$), 42.3, 42.0, 40.9, 40.6, 36.5 ($^{13}CH_2N$), 36.3, 33.9, 25.9 ($C^{13}CH_2C$), 25.2, 17.3 ($^{13}CH_3C$), 16.5, 15.6, 13.5.[37]



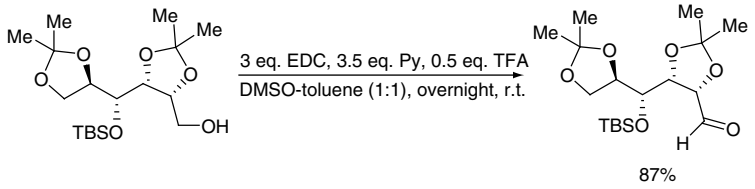
Ref. 23a

This fluorine-containing, oxidation-resistant alcohol is best oxidized by the Pfitzner–Moffatt reaction, using dichloroacetic acid as catalyst. Observe the use of toluene, instead of carcinogenic benzene, as solvent. A Swern oxidation was not reproducible, and caused substantial epimerization of the isobutyl side chain. Collins oxidation was successful, but required a great excess of reagent resulting in some peptide degradation.

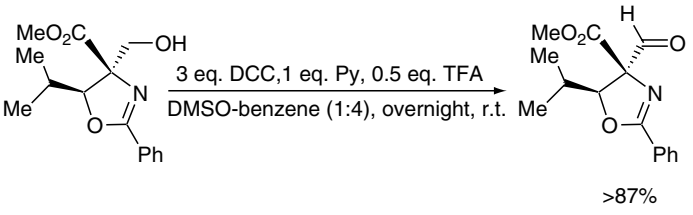


Ref.38

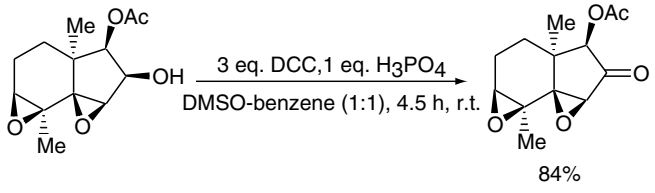
In variance with other oxidants, such as the chromium-based ones, no carbon-carbon bond breakage is observed in the Pfitzner–Moffatt oxidation of this 1,2-diol.



Ref. 23b
The water soluble carbodiimide EDC was used, instead of DCC that caused problems during the purification of the product.



Ref. 39
This oxidation that proved troublesome under a variety of conditions, like Swern, PCC, Dess-Martin and Parikh–Doering, succeeded under Pfitzner–Moffatt conditions.



Ref. 30a
A good yield in the oxidation of this hindered secondary alcohol was obtained employing the Pfitzner–Moffatt method, by using ortophosphoric acid as a strong acidic activator. Collins oxidation delivers only a 38% yield.

2.2.2. Functional Group and Protecting Group Sensitivity to Pfitzner–Moffatt Oxidation

The Pfitzner–Moffatt oxidation is performed in the presence of a carbodiimide that is transformed into a form of "activated DMSO". As both the carbodiimide and the activated DMSO are strong electrophiles, it would seem reasonable to expect that nucleophilic sites in a molecule would interfere with the oxidation. Nevertheless, Pfitzner–Moffatt oxidations very often can be carried out in the presence of thiols,[14b] amines[40] and amides.[23c,d]

Carboxylic acids react under Pfitzner–Moffatt conditions, resulting in the formation of methylthiomethyl esters and *N*-acylureas.[41] Nevertheless, although the authors are not aware of any report involving the selective oxidation of alcohols in the presence of a carboxylic acid, such outcome would be likely with carboxylic acids with little nucleophilicity, as standard Pfitzner–Moffatt oxidations are performed in the presence of trifluoroacetate that is known for not to interfere.

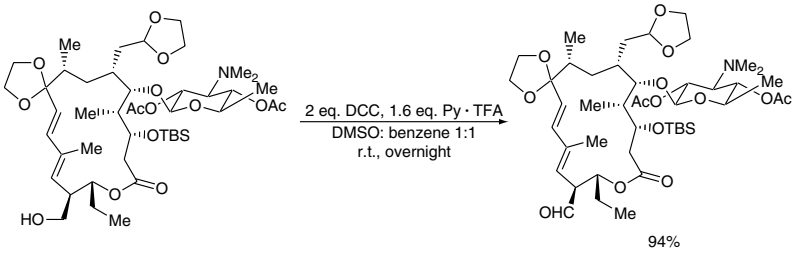
Quite puzzingly, thiols are reported[14b] to be unreactive under Pfitzner–Moffatt conditions, while this being one of the few oxidation methods for alcohols compatible with this functionality. Sulfides also resist the action of Pfitzner–Moffatt oxidations.[42,43]

Some amines react under Pfitzner–Moffatt conditions, yielding an adduct with the carbodiimide or a *S,S*-dimethylsulfilimine, resulting from attack of the amine on activated DMSO. The reactivity of different amines is very diverse, and observed in amines, which are not substantially protonated under the reaction conditions, while they still posses enough nucleophilicity. Thus, tertiary amines do not interfere, while hindered secondary ones seldom do it.

Ref. 44

An eventful oxidation of the secondary alcohol in the presence of a very hindered secondary amine occurs.

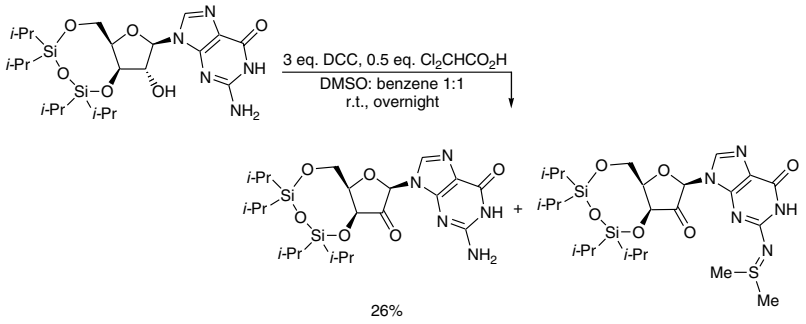
In fact, the interference of amines in Pfitzner–Moffatt oxidations very often results from the trivial fact that basic sites in a molecule can quench the acidic catalyst. In such cases, the oxidations must be carried out by adding an excess of one equivalent of acidic catalyst.



Ref. 40a

In this oxidation, 1.6 equivalents of acidic catalyst are used, instead of the standard quantity of 0.5 equivalents, because one equivalent is quenched by protonation of the amine.

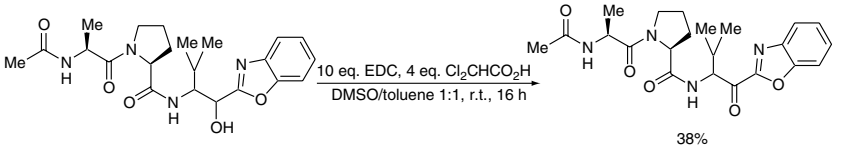
It must be mentioned that the *S,S*-dimethylsulfilimines, resulting from attack of amines on activated DMSO, are very often hydrolyzed back to the free amine during the work-up and thus, their formation may not be detected.



Ref. 45

The expected ketone is obtained accompanied with minor amounts of a *S,S*-dimethylsulfilimine, resulting from reaction of the amine with activated DMSO. Most probably, a greater amount of *S,S*-dimethylsulfilimine is formed, but most of it is hydrolyzed to the desired product during the work-up.

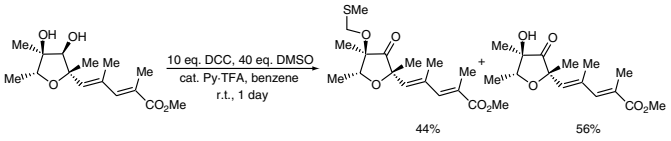
Although amides can react under Pfitzner–Moffatt conditions, resulting in the formation of a number of compounds, including *N*-methylthiomethylamides and *N*-acylsulfilimines,[46] normally, these reactions are slower than the oxidation of alcohols, so that selective oxidations can be possible.[23c,d]



Ref. 23d

An uneventful oxidation of the alcohol occurs with no interference from the amide moieties.

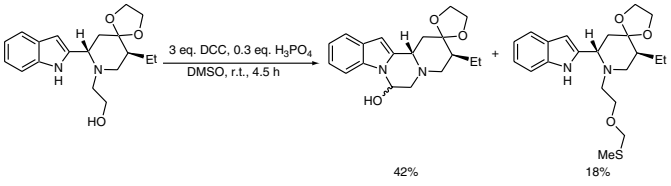
Normally, tertiary alcohols do not interfere with the oxidation of primary or secondary alcohols, although the use of a liberal quantity of reagent can lead to the formation of the methylthiomethyl ether of the tertiary alcohol, accompanying a normal oxidation of a primary or secondary alcohol.[47]



Ref. 47

The use of a liberal quantity of reagent leads to the desired oxidation of the secondary alcohol, being accompanied by the formation of a methylthiomethyl ether on the tertiary alcohol.

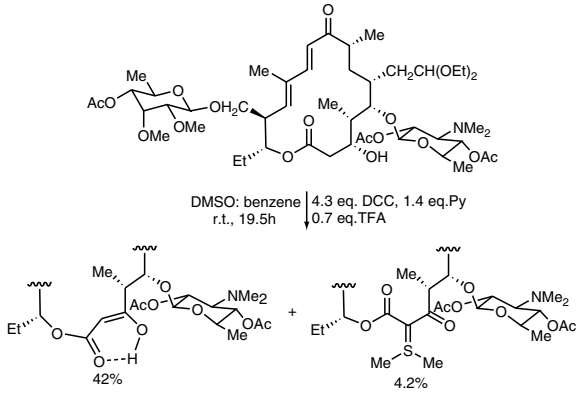
Sometimes, small amounts of methylthiomethyl ethers of primary or secondary alcohols are isolated. As these ethers originate from $H_2C{=}S(+)$-Me, formed by decomposition of activated DMSO that needs relatively high temperature, it is expected that lowering the reaction temperature would minimize the formation of these side compounds.[48]



Ref. 48

The oxidation of the primary alcohol leads to an aldehyde that is isolated as an aminal. Minor amounts of a methylthiomethyl ether are isolated, resulting from the reaction of the alcohol with $CH_2{=}S(+)$-Me that is formed by thermal decomposition of activated DMSO. Interestingly, a Swern oxidation fails to deliver the desire product, because it causes the chlorination of the indole.

Very rarely, those strong carbon nucleophiles, able to survive the presence of an acidic catalyst, can react with activated DMSO.[40c]



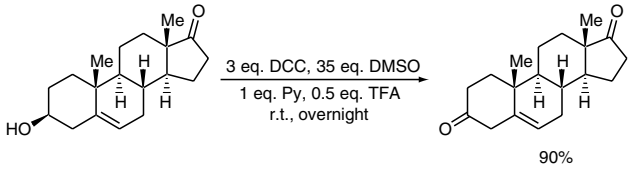
Ref. 40c

Traces of a compound, resulting from attack of an enol on activated DMSO, are obtained in an otherwise successful oxidation of a secondary alcohol.

Pyridinium trifluoroacetate is such a mild acidic catalyst that it can hardly affect acid-sensitive functionalities. Thus, for example the very acid-sensitive Boc-protected amines[49] and *t*-butyl esters,[50] as well as glycosides[51] and acetals,[52] remain unchanged under Pfitzner–Moffatt conditions.

2.2.3. Side Reactions

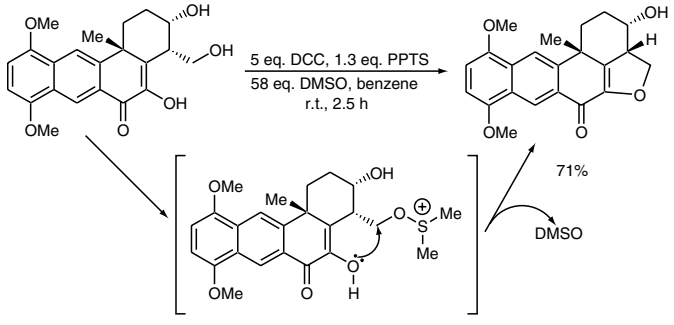
Homoallylic alcohols are oxidized, in the presence of pyridinium trifluoroacetate, with no migration of the alkene into conjugation with the carbonyl, even in cases in which such migration can occur under very mild acidic catalyses. On the other hand, the stronger acid H_3PO_4 is able to produce such isomerizations.[14b]



Ref. 14b

While the use of pyridinium trifluoroacetate as acidic catalyst leads to 90% of the desired unconjugated enone, the employment of the stronger acid H_3PO_4 as catalyst results in the isolation of the desired product contaminated with the corresponding conjugated enone, originating from acid catalyzed migration of the alkene. This migration can also happen under very mild conditions during chromatography on silica gel.

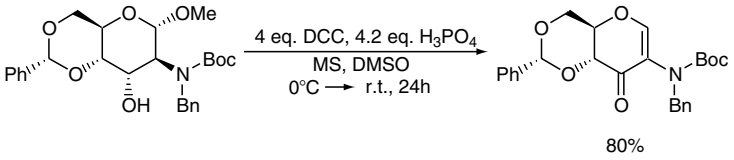
Sometimes, when intramolecular processes are favoured, the intermediate alkoxysulfonium salt suffers displacement from a nucleophile, instead of the expected evolution to an aldehyde or ketone.[53]



Ref. 53

The less hindered primary alcohol reacts selectively with activated DMSO, resulting in the formation of an intermediate alkoxydimethylsulfonium salt. This intermediate, instead of evolving as usual to an aldehyde, produces a cyclic ether by an intramolecular displacement, in which DMSO acts as a good-leaving group.

Sometimes, when the primary product of the oxidation contains a good-leaving group in the β-position relative to the carbonyl, an elimination occurs leading to an enol or an enone.[54]



Ref. 54f

The oxidation of the alcohol is accompanied by elimination of methanol, leading to the formation of an enone.

Section 2.2. References

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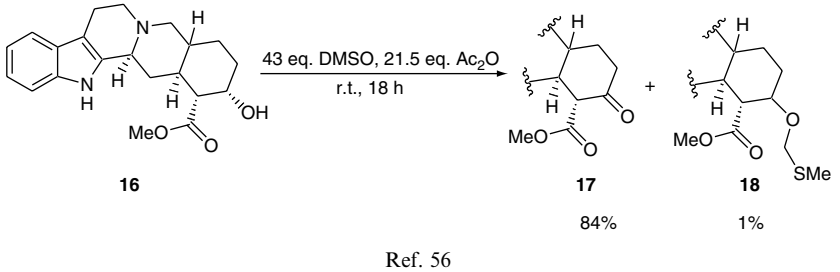
2.3. Albright–Goldman Oxidation (Acetic Anhydride-Mediated Moffatt Oxidation)

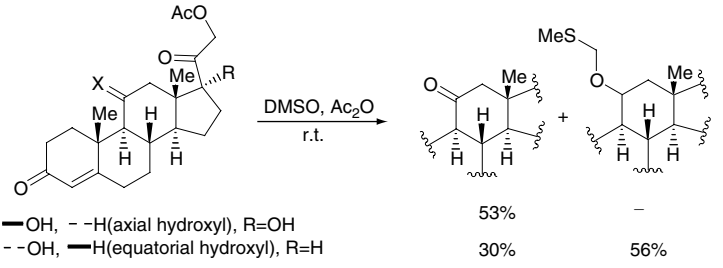
In 1965, Albright and Goldman[3] demonstrated that alcohols are oxidized to aldehydes and ketones by the action of a mixture of DMSO and acetic anhydride at room temperature. Two years later,[56] they presented a full paper, in which optimized conditions for this oxidation were established using yohimbine **(16)** as a model substrate. Thus, it was found that treatment of yohimbine with a mixture of DMSO and Ac_2O produces the desired oxidation to yohimbinone **(17)**, accompanied by formation of the methylthiomethyl ether **18**.



Ref. 56

An optimal yield of 80% of ketone was obtained using 5 equivalents of Ac_2O.

Optimal conditions minimizing the formation of side compounds, consisting on the methylthiomethyl ether and the acetate of the starting alcohol, involve the use of DMSO as solvent mixed with 5 equivalents of Ac_2O. While the amount of the acetate side compound can be minimized by using no more than 5 equivalents of Ac_2O,[56] or lowering the temperature to ca. 5°C;[57] the amount of methylthiomethyl ether is very substrate-dependant, and can be quite substantial. Interestingly, alcohols yielding best yields of aldehyde or ketone are normally very hindered. Apparently, steric hindrance causes a greater retardation on the formation of side compounds than on the desired oxidation.



19 X= ▬OH, - -H(axial hydroxyl), R=OH — 53% —
20 X= - -OH, ▬H(equatorial hydroxyl), R=H — 30% — 56%

Ref. 56

Oxidation of the more sterically hindered axial alcohol is slower, but produces a better yield of the corresponding ketone. The less hindered equatorial alcohol produces a substantial quantity of methylthiomethyl ether.

The Albright–Goldman oxidation protocol is not a good choice as a standard oxidation procedure, because it tends to deliver substantial quantities of side compounds on simple substrates. On the other hand, it may succeed in hindered alcohols resistant to oxidation by other means. In those cases in which the Albright–Goldman oxidation delivers a useful yield of aldehyde or ketone, this oxidation protocol is hardly surpassed in terms of economy and experimental usefulness. Both DMSO and Ac_2O are cheap solvents that are conveniently employed in this oxidation at room temperature or with some heating.

Although Albright and Goldman established the use of 5 equivalents of Ac_2O in DMSO at room temperature, as the optimized conditions for the oxidation of an uncomplicated unhindered substrate, normally a much greater excess of Ac_2O[56] is employed, and sometimes the oxidation is performed by heating rather than at room temperature. This happens because the Albright–Goldman oxidations tends to be used on hindered alcohols where, on one hand, other oxidants are less likely to succeed and, on the other hand, DMSO-Ac_2O tends to yield less amounts of side compounds. On such refractory substrates, the oxidation normally demands the use of a great excess of Ac_2O and, very often, heating above room temperature.

2.3.1. General Procedure for Oxidation of Alcohols by Albright–Goldman Method

A mixture of ca. 20–60 equivalents[a] of acetic anhydride in ca. 0.05–0.4 M solution of 1 equivalent of alcohol in dry DMSO is stirred at room temperature[b] under a blanket of an inert gas, till most of the starting compound is consumed.[c] The work-up can be made according to two alternative protocols:

Work-up A:

After the oxidation, as the reaction mixture consists of products originating from the alcohol mixed with DMSO, Ac_2O, Me_2S and AcOH, the latter being volatile compounds, the crude aldehyde or ketone can be secured by simple concentration in vacuo. Since the removal of the less volatile DMSO may demand heating, and can be unpractical at a multigram scale, this simple protocol is useful for reactions on a small scale resulting in products resistant to heat. Alternatively, it may be useful to eliminate most of the more volatile Ac_2O, Me_2S and AcOH under mild conditions, leaving a residue consisting of product mixed with mostly remaining DMSO that can be subjected to a further work-up according to method B.

Work-up B:

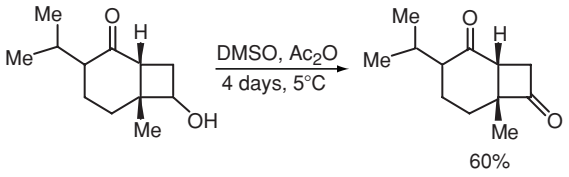
The reaction mixture is mixed with water or ice.[d] This may result in the precipitation of the product that can be separated by filtration. If no precipitation occurs, the product can be extracted with an organic solvent, such as CH_2Cl_2, $CHCl_3$, Et_2O or EtOAc. The organic phase is washed with an aqueous solution of sodium bicarbonate, in order to eliminate acetic acid residues. It can be additionally washed with plain water and/or brine. Finally, the organic phase is dried (Na_2SO_4 or $MgSO_4$), and concentrated to give a crude product that may need further purification.

[a] Although, in unhindered alcohols, it may be advisable to use as less as 2 to 4 equivalents of acetic anhydride in order to minimize the formation of alcohol acetate, as this reaction is normally applied to hindered alcohols which react quite slowly, normally it is recommended to use a very great excess of acetic anhydride.

[b] In alcohols very resistant to oxidation, it may be advisable to heat at ca. 60–100°C. On the other hand, in alcohols prone to suffer acetylation, this side reaction can be minimized by lowering the temperature to ca. 5°C. As the melting point of DMSO is 18°C, freezing can occur at low temperature. It can be avoided by adding a co-solvent, or using a great excess of Ac_2O.

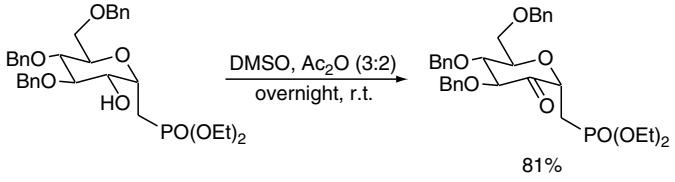
[c] Normally, it takes between 2 and 40 h. If heating is applied, the reaction time can be decreased to as little as 10 min.

[d] Sometimes, an alcohol, such as methanol or ethanol, is added before mixing with water or ice, in order to destroy the Ac_2O. The destruction of the anhydride is performed by stirring with the alcohol at room temperature for about 1 h.



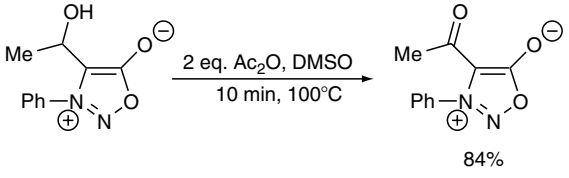
Ref. 57

The reaction is performed at 5°C in order to minimize the acetylation of the alcohol. A Swern reaction causes the α-chlorination of the ketone.



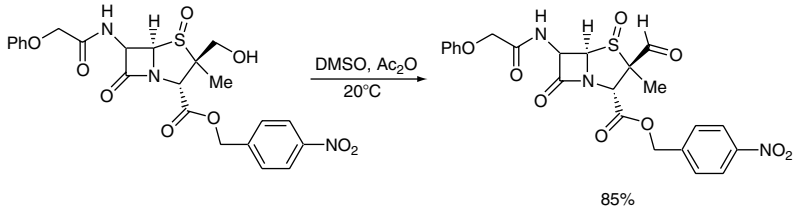
Ref. 58

No epimerization on α to the ketone is observed in the oxidation of this equatorial alcohol, using the Albright–Goldman method.



Ref. 59

This oxidation fails with strong oxidants like dichromate-sulfuric acid, because of decomposition of the sydnone ring, while mild oxidants like MnO_2 cause no reaction. The use of a 1:1 mixture of DMSO and Ac_2O, instead of the conditions indicated above, leads to a 38% yield of the corresponding acetate, and to a decrease in the yield of ketone to 46%.



Ref. 60

An excellent yield in the oxidation of this hindered alcohol is obtained using the Albright–Goldman method.

2.3.2. Functional Group and Protecting Group Sensitivity to Albright–Goldman Oxidation

As the Albright–Goldman oxidation is relatively little used in organic synthesis, the available literature provides a very limited database to know the sensitivity of many moieties to this oxidation protocol.

During this oxidation, acetic acid is produced that could interfere with acid-sensitive molecular fragments. Nevertheless, isopropylidene[61] and benzylidene acetals,[62] as well as glycosides[63] and dioxolanes[64] are known to resist the Albright–Goldman oxidation, probably because no water is present and a small amount of acetic acid is generated.

Tertiary amines,[65] dithioacetals[66] and thioethers[67] resist the action of the Albright–Goldman oxidation. Primary amines are acetylated[68] because of the presence of Ac_2O, although cases are known in which a primary amine remains unaffected,[67c] while a secondary alcohol is oxidized.

Tertiary alcohols react slowly at room temperature with DMSO-Ac_2O, resulting in the formation of a methylthiomethyl ether. In fact, this is one of the standard procedures[69] for the protection of tertiary alcohols as methylthiomethyl ethers; acetic acid being commonly added as catalyst when this reaction is purposefully sought at.[70] One would expect that the greater hindrance of tertiary alcohols versus primary and secondary ones should allow the selective oxidation of the latter. Although, the authors of this book are not aware of examples from such behavior in the literature.

2.3.3. Side Reactions

As mentioned earlier, the most common side reaction during oxidations with the Albright–Goldman protocol is the formation of methylthiomethyl ethers.[71] The other common side reaction is the acetylation of the alcohol. These side reactions can be minimized by limiting the amount of Ac_2O to about 5 equivalents[56] or even less,[59] or by lowering the temperature to ca. 5°C.[57]

When the oxidation results in the formation of a ketone, containing a good-leaving group at the β-position, very often an elimination occurs leading to an enone.[72]

Ref. 72b

The oxidation of the secondary alcohol is followed by elimination of benzoic acid, producing an enone.

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2.4. Albright–Onodera Oxidation (Phosphorous Pentoxide-Mediated Moffatt Oxidation)

In 1965, Albright and Goldman in a communication[73] briefly mentioned that DMSO can be activated with phosphorous pentoxide in the oxidation of alcohols. A few months later, Onodera *et al.*[74] made a report fully centred on this oxidation, in which they described that oxidation of alcohols can be performed by treating a solution of the alcohol in dry DMSO with P_2O_5 at room temperature. In 1987, an important improvement on this oxidation protocol was published by Taber *et al.*,[76] whereby 1.8 equivalents of P_2O_5 are added in a solution of alcohol, 2 equivalents of DMSO and 3.5 equivalents of Et_3N in dry CH_2Cl_2, and the reaction is carried out at room temperature.

The Albright–Onodera oxidation is seldom used in organic synthesis and, therefore, no extensive experimental database is available that would provide information on its scope and limitations. Nonetheless, it must be mentioned that this oxidation tends to be used as a last resort when more common oxidation protocols fail, and in such cases, very often, it proves to be superior than other common oxidants. The Albright–Onodera oxidation is very conveniently carried out at room temperature using very cheap reagents, and resulting in water soluble side compounds that greatly simplify the work-up.

2.4.1. General Procedure of Albright–Onodera Oxidation Using Taber Modification

Two equivalents of dry DMSO and 1.8 equivalents of P_2O_5[a,b] are sequentially added over a stirred ca. 0.2 M solution of 1 equivalent of the starting alcohol in dry CH_2Cl_2, kept over an ice-water bath and under a blanket of an inert gas. The reaction mixture is allowed to react at room temperature till a TLC analysis shows no starting compound.[c] The reaction mixture is cooled again on an ice-water bath and 3.5 equivalents of Et_3N are slowly added. After about ½ h, 10% aqueous HCl is added, and the resulting mixture is extracted with CH_2Cl_2. The organic phase is washed with brine, dried with $MgSO_4$ and concentrated, giving a residue that may need further purification.

[a] CAUTION! Phosphorous pentoxide is extremely caustic on contact with the skin. It must be manipulated using gloves. In case of irritation, the affected area must be immediately flushed with plenty of water.

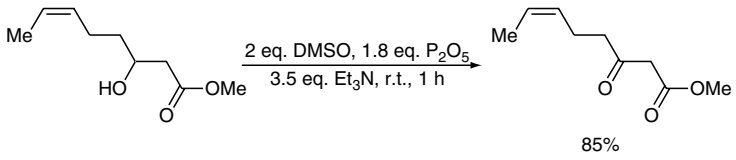
[b] As phosphorous pentoxide is extremely hygroscopic, it must be promptly transferred in order to minimize hydration produced by atmospheric moisture. Phosphorous pentoxide reacts very violently with water producing a copious evolution of heat.

[c] It normally takes between ½ h and 2 h.

88%

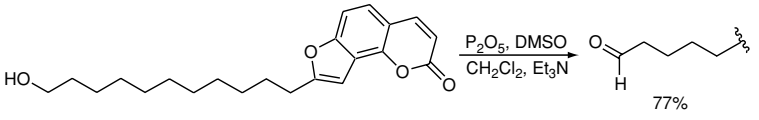
Ref. 76

This α-hydroxy-β-lactam is resistant to usual oxidizing reagents, like PDC, PCC or Swern, but delivers a 88% of the desired ketone by using the Albright–Onodera protocol.



Ref. 75

Treatment of the starting alcohol under Swern conditions gave chlorinated products, while chromic acid gave a low yield, and PCC led to a complex separation of the product from chromium-containing residues. An excellent yield of the desired ketone was obtained by using the Taber modification of the Albright–Onodera oxidation.



Ref. 77

A good yield of the desired aliphatic aldehyde is obtained by the Taber modification of the Albright–Onodera oxidation.

2.4.2. Functional Group and Protecting Group Sensitivity to Albright–Onodera Oxidation

It is known that acetals,[78] β-lactams,[79] TBS ethers[76] and alkenes[75] resist the action of the Albright–Onodera oxidation.

Section 2.4. References

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2.5. Parikh–Doering Oxidation (Sulfur Trioxide-Mediated Moffatt Oxidation)

Parikh and Doering in 1967 described[80] that DMSO can be activated for the oxidation of alcohols, using sulfur trioxide that can be conveniently added to the reaction mixture as complex with pyridine. According to the original

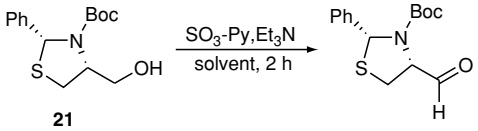
communication, alcohols can be oxidized to aldehydes and ketones by adding a solution of 3–3.3 equivalents of the pyridine sulfur trioxide complex—a commercially available stable solid—in dry DMSO over a solution of the alcohol in dry DMSO, containing 6.5–16.5 equivalents of triethylamine at room temperature. This communication was not followed, as far as the authors of this book are aware, by any full paper on the establishment of optimized conditions to obtain the best yields. Subsequent authors modified the original protocol to fit the oxidation of their own alcohols, and in general, this resulted in applying the following experimental conditions:

- Very often, CH_2Cl_2 is used as a co-solvent. Very variable proportions of DMSO versus CH_2Cl_2 are used. Sometimes, CH_2Cl_2 is a minor component in the mixture, and other times, the oxidation can be successful with as little as 3 eq. of DMSO in a CH_2Cl_2 solution.[81] Minimizing the amount of DMSO may facilitate the work-up. Other co-solvents like THF[82] or $CHCl_3$[83] are occasionally used.
- Most frequently, the reaction is carried out at low temperature rather than at room temperature. It is common to cool down the reaction on an ice-water bath, while a temperature as low as $-12^{\circ}C$[84] can be employed. Sometimes, mixing is done at low temperature, while the proper oxidation is carried out at room temperature. As DMSO solidifies at 18°C, reactions at low temperature must include a co-solvent like CH_2Cl_2.
- Very often, the pyridine sulfur trioxide complex is added as a solid rather than mixed with DMSO, as recommended in the original publication. This is obviously done for experimental convenience. Nevertheless, one must take into account that the pyridine sulfur trioxide complex reacts with alcohols,[85] phenols[86] and other nucleophiles, like amides[87] and amines,[88] resulting in the introduction of a $-SO_3H$ group. That is why, $SO_3 \cdot Py$ must be in contact with DMSO and, therefore, being consumed during the activation of DMSO before it has a chance to react with the alcohol. Mixing $SO_3 \cdot Py$ with DMSO ca. 5–15 min before the addition to the alcohol may guarantee a good yield.[89]
- Some authors reported[89] that, for best yields, scrupulously dry material must be used.

  For example, during the oxidation of *N*-benzyl-3-hydroxy-4-methylpiperidine, a 99% conversion in the oxidation is achieved with starting material containing 0.1% of water, while the conversion decreases to 42% with starting material containing 2% of water.[90a]
- Sometimes, Hünig's base[91]—$EtN(i\text{-}Pr)_2$—is used rather than triethylamine. This hindered base may help to minimize α-epimerization on some sensitive aldehydes and ketones.

The exact reaction temperature may have a profound effect on the yield. For example, during the oxidation of the primary alcohol **21**, a drastic improvement from a 24% to an almost quantitative yield was observed by lowering the temperature from 40 to 10°C. Furthermore, the low temperature

minimized the epimerization of the resulting aldehyde. The test performed at 10°C was made in a DMSO-toluene 5:1 mixture, in order to avoid freezing of the solution.[92]



21

SO_3-Py (equiv.)	Et_3N (equiv.)	Solvent	T (°C)	Yield (%)	de (%)
2.0	2.0	DMSO	40	24	96
2.0	2.0	DMSO	30	58	97
2.0	2.0	DMSO	20	82	97
2.5	2.5	DMSO-toluene(5:1)	10	95	>99

Ref. 92

Lowering the temperature produces a drastic improvement in the yield, and lesser epimerization at the α position of the resulting aldehyde. Toluene is added as a co-solvent at 10°C, in order to avoid freezing of the DMSO solution. Adapted from reference 92 by permission of the American Chemical Society.

These results suggest that the Parikh–Doering oxidation should be routinely tried at 0–10°C, rather than at room temperature, as described in the original paper.

The Parikh–Doering oxidation is conveniently carried out at room temperature or moderately cool temperature. The activator—$SO_3 \cdot Py$—generates side compounds that are very easily removed during the work-up. In variance with other oxidations involving activating DMSO, the Parikh–Doering oxidation rarely delivers substantial amounts of methylthiomethyl ether side compounds.[93] Unlike the Swern oxidation, no chlorinated side compounds are possible.

2.5.1. General Procedure for Parikh–Doering Oxidation

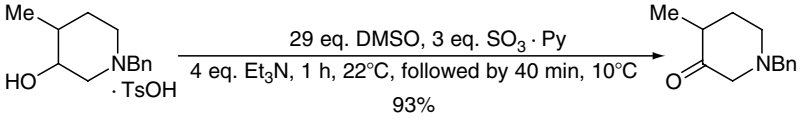
Between 2 and 9—typically 2.9–3.3—equivalents of the complex SO_3.Py (MW=159.2) in a ca. 190–400 mg/mL solution[a] in dry DMSO are slowly added over ca. 0.2–0.6 M solution of 1 equivalent of alcohol in dry DMSO, containing ca. 7–17 equivalents of Et_3N (MW = 101.2, $d = 0.726$).[b] When most of the starting compound is consumed,[c] water is added. This may cause the precipitation of the product, particularly when no co-solvent has been added to the DMSO solution. In that case, the crude product can be isolated by simple filtration, and the DMSO contaminant can be washed away with water. If no precipitation occurs, an organic solvent, like CH_2Cl_2, EtOAc or Et_2O, is added and the organic

phase is decanted and washed with water. Optionally, the organic phase can also be washed with brine, a $NaHCO_3$ aqueous solution and/or a NH_4Cl aqueous solution. Finally, the organic phase is dried with Na_2SO_4 or $MgSO_4$, and concentrated, leaving a residue that may need further purification.

[a] Very often the complex $SO_3 \cdot Py$ is added as a solid rather than in a DMSO solution. Apparently, this is not generally deleterious for the oxidation yield, although the $SO_3 \cdot Py$ complex must be consumed by activating DMSO, before it is able to react directly with the alcohol. Adding the $SO_3 \cdot Py$ solution in DMSO from 5 to 15 min after its preparation may prevent the transformation of the alcohol into the R-OSO_3H species.

[b] The reaction can be carried out at room temperature. Very often, it is done at a lower temperature, typically over an ice-water bath. Temperatures as low as $-12°C$ have been employed. It is also common to mix the reactants at low temperature, and let the reaction be run at room temperature. This is particularly advisable when the reaction is run in multigram scale and exotherms are expected.

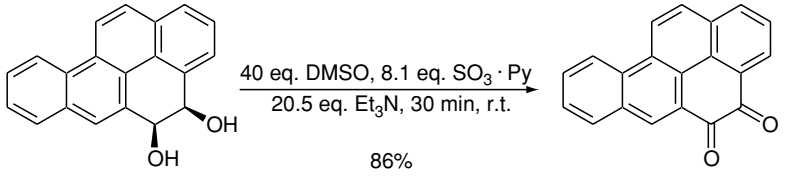
[c] Normally, it takes between 10 min and 2 days, typically ca. 2 h.



93%

Ref. 90

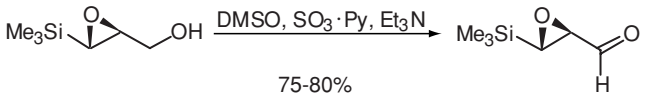
A Parikh–Doering oxidation on 40.9 Kg of starting compound in a 640 L vessel is described. A current of nitrogen is run through the reaction, in order to divert the dimethyl sulfide—generated during the oxidation—to a scrubber containing 13–15% bleach. A Parikh–Doering oxidation is preferred over a Swern oxidation on a big scale, because the former can be carried out under non-cryogenic temperatures, the reagents are easier to handle, and there is a greater flexibility to add more reagent if the reaction does not proceed to completion.



86%

Ref. 89

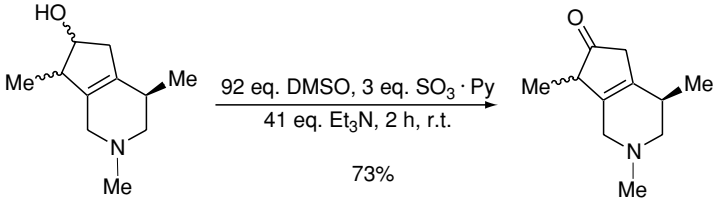
This oxidation presented a serious challenge, because of the tendency of the substrate to suffer dehydration, or oxidative breakage at the benzylic positions. It succeeded under Parikh–Doering conditions, provided that scrupously dry conditions are used, and the reaction of $SO_3 \cdot Py$ with DMSO precedes the interaction with the diol, in order to avoid the formation of a sulfate ester. Thus, the solution of $SO_3 \cdot Py$ in DMSO was prepared 5 min in advance of its use. The application of the closely related Albright–Goldman oxidation led to erratic yields, the diol acetate being the main side product.



75-80%

Ref. 94

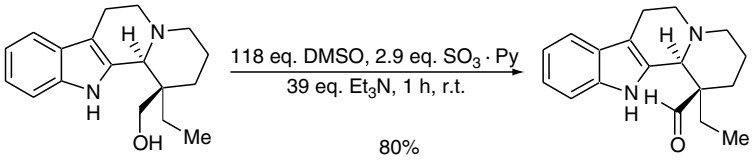
After considerable experimentation, it was found that the Parikh–Doering oxidation provides a good and reproducible yield. Under Swern conditions, yields are erratic with substantial quantities of a product, arising from opening of the epoxide by attack of a chloride ion being formed. PCC did not afford a good yield of alcohol.



73%

Ref. 95

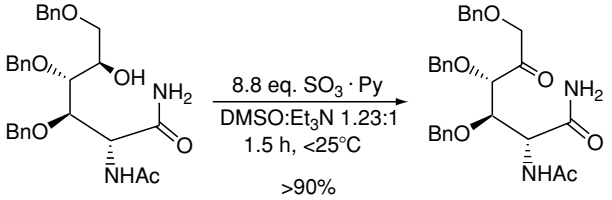
Both PCC and a Moffatt oxidation fail to provide the desired unstable ketone, while the Parikh–Doering oxidation succeeds. Observe that no migration of the alkene into conjugation with the ketone occurs.



80%

Ref. 96

While the Parikh–Doering oxidation succeeds, a Swern oxidation produces chlorination at the activated 3-position of the indole.



>90%

Ref. 97

During the oxidation, an acid-catalyzed cyclization of the product by attack of the nitrogen atoms on the ketone, leading to three different aminals, must be avoided. A Parikh–Doering oxidation gives a good yield of the desired ketone, while PCC, Dess-Martin reagent and Jones oxidation deliver diverse amounts of aminals.

2.5.2. Functional Group and Protecting Group Sensitivity to Parikh–Doering Oxidation

Although the complex pyridine-sulfur trioxide reacts with a number of nucleophiles, including alcohols,[85] amines,[88] amides[87] and phenols,[86] producing the introduction of a $-SO_3H$ group; no such reaction needs to happen during a properly performed Parikh–Doering oxidation, because the complex is consumed by reaction with DMSO before interfering with functional groups in the substrate. In fact, the Parikh–Doering oxidation can be carried out in the presence of nucleophiles, like tertiary alcohols[98] and tertiary amines.[99]

There is a published instance, in which the Parikh–Doering oxidation is made with no interference from a secondary amine.[100]

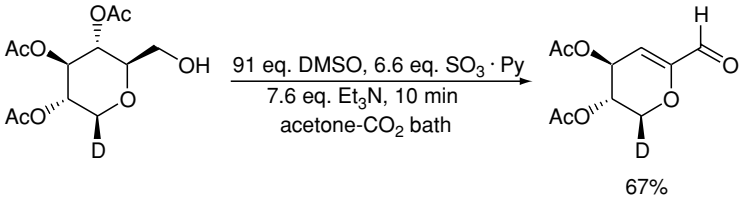
Not surprisingly, acid sensitive functionalities and protecting groups are not modified under Parikh–Doering conditions. Such groups include: acetals,[101] glycosides,[102a] amines protected with Boc[103] and alcohols protected with TMS,[105] TBS,[102] MOM,[106] Tr[107] and *t*-Bu.[108] In spite of the presence of Et_3N, as the Parikh–Doering oxidation is made under anhydrous conditions, functionalities and protecting groups sensitive to base-catalyzed hydrolyses are not affected.

The Parikh–Doering oxidation provides a very high regioselectivity for the oxidation of alcohols. Oxidation-sensitive functionalities, like indoles,[99a,c] sulfides,[109] and selenides;[110] as well as oxidation-sensitive protecting groups, like dithioacetals,[111] PMB[104] and dimethoxybenzyl ethers[109b], do not react.

It must be mentioned that sensitive compounds, like alkyl silanes,[112] alkyl stannanes[113] and vinyl stannanes,[114] are not affected under the conditions of the Parikh–Doering oxidation.

2.5.3. Side Reactions

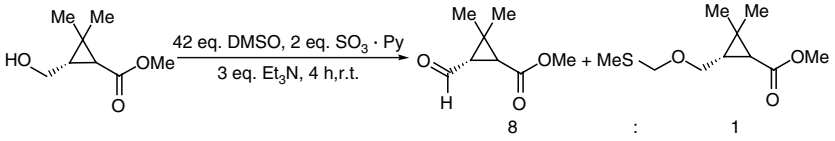
When an aldehyde or ketone, possessing a good-leaving group at the β-position, is obtained during a Parikh–Doering oxidation, very often an elimination occurs, leading to an enal or an enone. Leaving-groups suffering such elimination include acetate[115] and sulfinyl.[116]



Ref. 115b

The oxidation of the alcohol to aldehyde is followed *in situ* by elimination of acetic acid, leading to an enal.

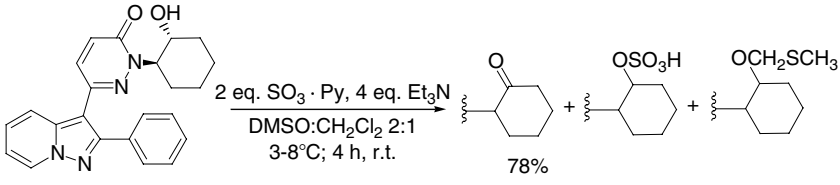
Very rarely, some quantity of methylthiomethyl ether is formed.[93] It must be mentioned that the formation of methylthiomethyl ethers in oxidation with activated DMSO can be minimized by the use of low polarity solvents.[117]



Ref. 93

This is a rare example, in which formation of a methylthiomethyl ether is reported during a Parikh–Doering oxidation.

In a properly performed Parikh–Doering oxidation, the complex $SO_3 \cdot Py$ must not interfere, because it must be completely consumed by reaction with DMSO before the substrate is added. In practice, it can be difficult to avoid the presence of minor amounts of $SO_3 \cdot Py$, that can react with nucleophilic sites in the molecule, including alcohols.



Ref. 118

The desired ketone is obtained together with minor amounts of sulfonated and methylthiomethylated alcohol. This oxidation was made on a pilot-plant scale, resulting in the isolation of multikilograms of ketone. The formation of side compounds was minimized, by operating at 3–8°C with 2 equivalents of $SO_3 \cdot Py$ and 4 equivalents of Et_3N. Although a Swern oxidation was successful, it was not the preferred one, because of the need of low temperature (ca. −60°C). An Ac_2O-mediated oxidation generated substantial amounts of methylthiomethyl ether.

Section 2.5. References

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2.6. Omura–Sharma–Swern Oxidation (TFAA-Mediated Moffatt Oxidation)

The use of trifluoroacetic anhydride for the activation of DMSO in the oxidation of alcohols was first attempted by Albright and Goldman in 1965.[119,120] According to these authors, who tried the reaction at room temperature, trifluoroacetic anhydride is not effective in the activation of DMSO. Later, Swern *et al*. made a detailed study of the interaction of DMSO with TFAA,[121] and proved that the resulting activated DMSO is stable at low temperature and can be used in the oxidation of alcohols. In

three papers published between 1976 and 1978,[122] Swern *et al.* made a profound study on the oxidation of alcohols with DMSO activated with TFAA, resulting in optimized oxidation protocols that are being used nowadays by other researchers.

Neat trifluoroacetic anhydride and DMSO interact in an explosive manner at room temperature.[121] Nevertheless, at low temperature and in the presence of CH_2Cl_2, as solvent and moderator, DMSO and TFAA react almost instantaneously, yielding a white precipitate described as trifluoroacetoxydimethylsulfonium trifluoroacetate **(22)**.

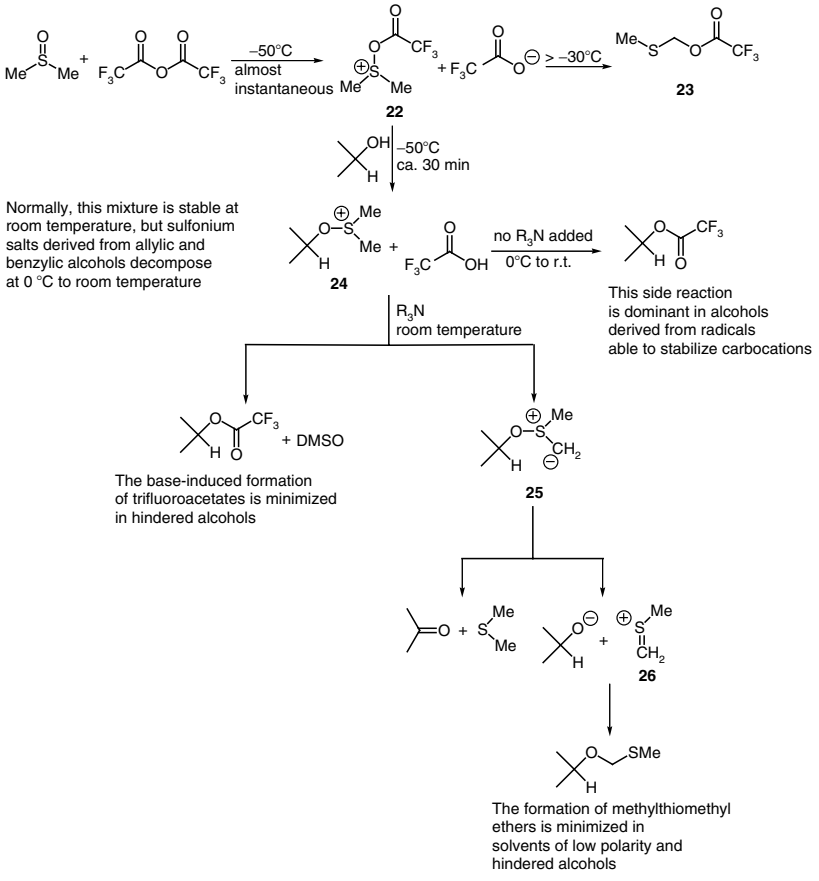
> This form of activated DMSO is stable below −30°C, but suffer a Pummerer rearrangement above this temperature, resulting in the formation of methylthiomethyl trifluoroacetate **(23)**. In fact, compound **23** reacts with alcohols in the presence of an amine, resulting in a very quick trifluoroacetylation. However, this trifluoroacetylation pathway is not operative in a properly performed Omura–Sharma–Swern oxidation, because alcohols are previously transformed in alkoxydimethylsulfonium salts **24**.
>
> Interestingly, although trifluoroacetic anhydride reacts very quickly with alcohols, the reaction with DMSO is even quicker. Therefore, the formation of the activated DMSO species **22** can be made in the presence of the alcohol, resulting in little erosion of the oxidation yield.

Alcohols react with compound **22** at low temperature in ca. 30 min, yielding an alkoxydimethylsulfonium salt **24** and one equivalent of trifluoroacetic acid. This mixture is normally stable at room temperature for several days. Nonetheless, alkoxydimethylsulfonium salts, derived from alcohols whose radicals are able to stabilize carbocations—particularly allylic and benzylic alcohols—suffer solvolyses by the action of trifluoroacetic acid from 0°C to room temperature, already in the absence of an amine, yielding the corresponding trifluoroacetates. This differential stability of alkoxydimethylsulfonium salts, derived from diverse alcohols, dictate different protocols in the Omura–Sharma–Swern oxidation depending on the alcohol (vide infra).

The treatment of an alkoxydimethylsulfonium salt **24** with an amine produces a sulfur ylide **25** that can yield an aldehyde or ketone and dimethyl sulfide. Alternatively, **25** can fragment producing the sulfonium species **26** that can generate an undesired methylthiomethyl ether by reaction with alkoxide. Another common side reaction is the displacement of DMSO by attack of trifluoroacetate. These two side reactions—trifluoroacetylation and methylthiomethylation—are normally minimized by adding the amine at room temperature. Therefore, the oxidation of normal alcohols is better made according to the so-called *Procedure C*, whereby although all the operations till the formation of the alkoxydimethylsulfonium salt **24** are made at low temperature, the key intermediate **24** is left to reach room temperature *before* the amine is added. Obviously, *Procedure C* is not suitable for allylic and benzylic alcohols, because they are solvolyzed to the corresponding trifluoroacetates if the alkoxydimethylsulfonium salts **24** are allowed to reach room temperature before adding an amine. In those

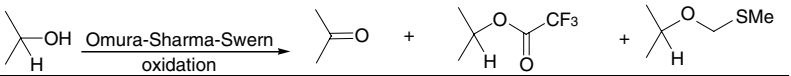
cases, the so-called *Procedure A* must be used, whereby an amine is added at low temperature to the alkoxydimethylsulfonium salt **24**, and the resulting mixture is allowed to reach slowly at room temperature. These results are exemplified in Table 2.1.

Additionally, it must be mentioned that the formation of methylthiomethyl ethers in oxidations with activated DMSO is minimized by the use of solvents of low polarity.[123] Hence, the routine use of CH_2Cl_2—which possesses a good balance of solubilizing power versus low polarity—is practiced in Omura–Sharma–Swern and Moffatt oxidations. The formation of side compounds—both trifluoroacetates and methylthiomethyl ethers—is decreased by using more diluted reaction conditions under *Procedure C*, while concentration has little effect on the yield in oxidations performed under *Procedure A*.[124]



Most Omura–Sharma–Swern oxidations are performed in CH_2Cl_2, although other apolar solvents, like toluene,[125] can be equally effective.

Table 2.1.



Alcohol	Procedure*	Carbonyl (%)	Trifluoroacetate ester (%)	Methylthiomethyl ether (%)
1-Decanol	A	37	35	21
	C	**56**	24	8
Cyclohexanol	A	65	22	12
	C	**73**	17	5
Benzylic alcohol	A	**84**	11	0
	C	42	58	—
Sec-phenetyl alcohol	A	**97**	1	—
	C	0	96	—

* *Procedure A*: DMSO and TFAA are reacted at −78 to −60°C for ca. 10 min producing **22**, which is reacted with the alcohol at −78 to −60°C for ca. 30 min. The amine is added to the resulting solution of alkoxysulfonium salt **24** and the resulting mixture is left to reach slowly at room temperature. *Procedure C*: like *Procedure A* but the solution of the alkoxysulfonium salt **24** is left to reach at room temperature *before* the amine is added.

Because of the propensity to generate side compounds, the Omura–Sharma–Swern oxidation is not a suitable routine oxidation protocol for normal alcohols. Interestingly, however, the formation of side compounds is greatly suppressed during the oxidation of very sterically hindered alcohols. Therefore, this oxidation is particularly suited for secondary alcohols, flanked by bulky groups, and for primary neopentilic alcohols, that is, it gives best yields precisely on those alcohols that are very difficult to oxidize by other means. On such alcohols, the alternative use of either *Procedure A* or *Procedure C* may not be very important, although *Procedure A* is normally preferred, because some side reactions are minimized at low temperature.

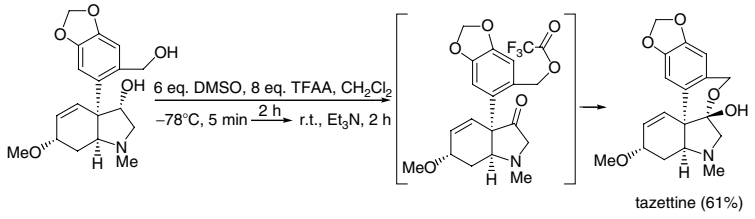
Interesting modifications of the standard *Procedure A* include, allowing a prolonged reaction—till 90 min—of activated DMSO **22** with the alcohol at low temperature, in order to make sure the complete formation of the alkoxysulfonium intermediate **24**,[126] and performing the final steps at ca. −78°C[127] or 0°C[128] rather than at room temperature.

Quite remarkably, although TFAA-activated DMSO is decomposed above −30°C, there is one published report of successful oxidation, in which TFAA is added over a solution of DMSO and the alcohol, kept at −20°C.[125] This oxidation succeeds apparently, because at this temperature, TFAA-activated DMSO suffers decomposition slower than conversion into an alkoxysulfonium salt by attack of the alcohol.

The nature of the amine, used for the decomposition of the alkoxydimethylsulfonium salt, has a great influence in the yield of the aldehyde or ketone. Swern *et al.* proved[122c] that best yields are obtained with hindered amines, like Hünig's base (EtN*i*- Pr_2). Nevertheless, most Omura–Sharma–Swern oxidations are performed using Et_3N instead of Hünig's base, although

with the latter, yields are obtained exceeding 5 to 25 % relative to the use of Et_3N. This is probably due to the fact that most references to the Omura–Sharma–Swern oxidation cite earlier papers[125,123b] where only the use of Et_3N is described, while the use of Hünig's base is mentioned in a later paper[122c] that is less cited. Good yields can also be obtained by using DBU.[129]

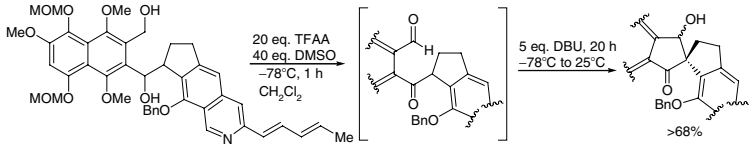
The differential stability of alkoxysulfonium salts, derived from diverse alcohols, and the lesser tendency of hindered alcohols to provide trifluoroacetate side compounds can explain some interesting selective oxidations reported in the literature.[125,130]



Ref. 130

In the last step of the synthesis of the *Amaryllidaceae* alkaloid Tazettine, selective oxidation of a secondary alcohol, in the presence of a benzylic one, can be carried out by allowing the selective decomposition of the less stable alkoxysulfonium salt, derived from the benzylic alcohol. An alternative longer synthetic pathway, involving protection and deprotection of the benzylic alcohol, is avoided. This selective oxidation can be explained by the formation of the alkoxysulfonium salts of both alcohols. These salts are brought to room temperature, resulting in the transformation of the benzylic alcohol in the corresponding trifluoroacetate. The alkoxysulfonium salt from the secondary alcohol evolves to a ketone. Interestingly, no base needs to be added, because of the presence of an amine functionality in the molecule. The hydrolysis of the intermediate trifluoroacetate, and the formation of the hemiacetal probably occur during the work-up.

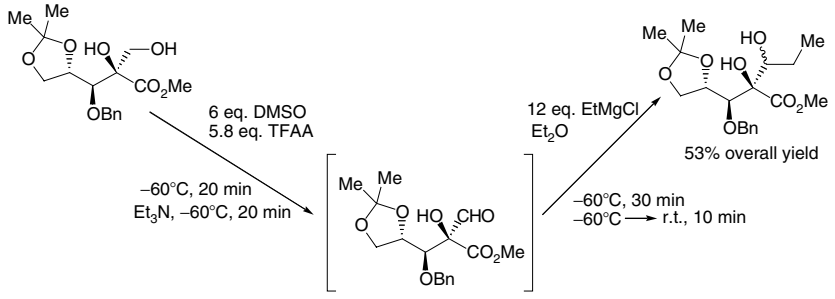
The base added to decompose the alkoxysulfonium intermediate can be used to perform additional reactions *in situ* after the oxidation.



Ref. 129

In this elegantly designed synthetic operation, the oxidation of both alcohols is followed by an *in situ* aldol condensation, promoted by the use of the stronger base DBU rather than the standard Et_3N, and a prolonged reaction time at higher temperature. Interestingly, the use of Et_3N rather than DBU results in the reaction being stopped at the dicarbonyl compound stage. In such case, best yields of the carbonyl compound demand a prolonged (60 min) contact of the base with the bisalkoxysulfonium intermediate at low temperature. This reaction exemplifies a careful experimental design, in which separate optimization of the oxidation and condensation steps were performed.

Interestingly, it is possible to perform an *in situ* addition of a Grignard reagent to a carbonyl compound, obtained by the Omura–Sharma–Swern oxidation.



An aldehyde, obtained by an Omura–Sharma–Swern oxidation, is transformed *in situ* in an alcohol, by reaction with a Grignard reagent.[132]

2.6.1. General Procedure (Procedure A) for Oxidation of Alcohols with Omura–Sharma–Swern Method

Between 1.5 and 7 equivalents—typically 1.5 equivalents—of trifluoroacetic anhydride (MW = 210.0, d = 1.49) are slowly[a] added to a cold[b] and stirred ca. 0.3–2 M solution[c] of 2–11 equivalents—typically 2 equivalents—[d] of dry DMSO (MW = 78.1, d = 1.10) in dry CH_2Cl_2.[e] This results in the formation of a white precipitate, described as the TFAA-activated DMSO compound **22**. After 5–15 min,[f] a ca. 0.05–0.9 M solution of the alcohol in dry DMSO is slowly[a] added. After 15 min-2 h of stirring at low temperature, ca. 3–12 equivalents of Et_3N or Hünig's base (EtN*i*-Pr_2)[g] are slowly added.[h] The reaction mixture is left to reach slowly at room temperature.[i] When most of the starting compound is consumed,[j] the reaction mixture is partitioned between an organic solvent, like CH_2Cl_2 or ether, and water. The organic phase is washed with brine and/or an aqueous solution of saturated $NaHCO_3$, dried with Na_2SO_4 or $MgSO_4$ and concentrated, giving a residue that may need purification.

[a] As TFAA-activated DMSO, that is compound **22**, decomposes above −30°C, care must be taken to avoid exotherms during the addition of trifluoroacetic anhydride or the alcohol. Adding these compounds as a CH_2Cl_2 solution may help to avoid exotherms.

[b] Normally between −78 and −50°C.

[c] The solution of DMSO in CH_2Cl_2 must be prepared at room temperature, because DMSO can freeze when it is dropped on cold CH_2Cl_2.

[d] DMSO must be used in molar excess relative to TFAA, in order to consume all the anhydride that otherwise could cause side reactions. An excessive amount of DMSO can

increase the polarity of the solution, and promote the generation of methylthiomethyl ethers.

[e] Other solvents with low polarity, such as toluene, can be equally effective.

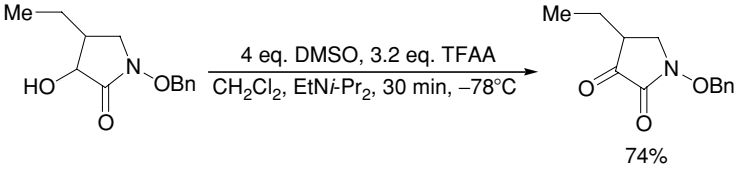
[f] DMSO and TFAA are reported to react instantaneously at −60°C. The resulting activated DMSO is stable at low temperature, at least, during several days. Therefore, little change in the oxidation yield is expected, depending on the time that DMSO and TFAA are in contact at low temperature.

[g] Normally Et_3N is used, although Hünig's base has been proved to give a yield of 5–25% in excess relative to Et_3N.

[h] Alcohols, which are neither allylic, benzylic or greatly hindered, may be best oxidized according to the so-called *Procedure C*, comprised of adding the amine *after* the solution reaches room temperature.

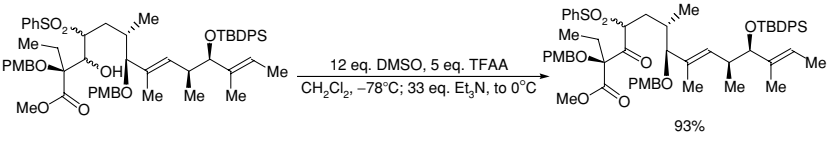
[i] Sometimes, the reaction mixture is left stirring at low temperature, or is left to reach 0°C rather than room temperature. In those cases, very often the reaction is quenched at low temperature with an alcohol, like MeOH or *i*-PrOH, before the work-up.

[j] It takes about 1 h.



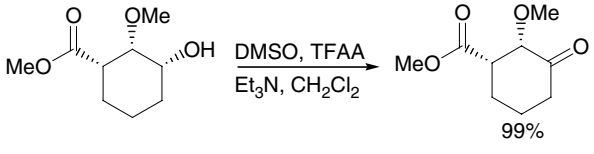
Ref. 132

A Swern oxidation produces the introduction of a methylthio group next to the ketone, while a Omura–Sharma–Swern oxidation, performed at low temperature during all the operations before the work-up, provides the desired ketone in good yield.



Ref. 133

An excellent yield of ketone is obtained in the oxidation of a hindered alcohol, in a molecule adorned with multiple functionalities.



Ref. 134

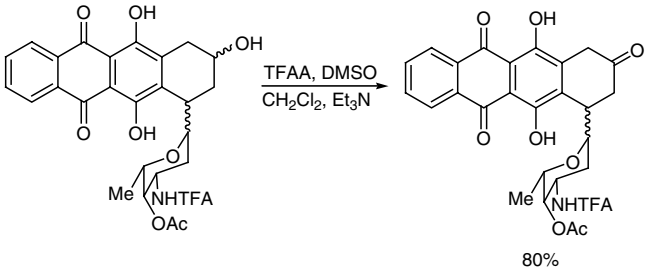
A 99% yield of ketone is obtained via an Omura–Sharma–Swern oxidation, while Dess-Martin periodinane delivers a 73% yield.

2.6.2. Functional Group and Protecting Group Sensitivity to Omura–Sharma–Swern Oxidation

As expected, acid sensitive functionalities, including THP,[135] Tr,[136] TBS[137] and *t*-Bu[138] ethers, orthoesters,[139] acetals[140] and glycosides,[137a,141] as well as Boc-protected[142] amines, are resistant to Omura–Sharma–Swern oxidations.

Normally, functionalities sensitive to basic hydrolyses, like esters, resist this oxidation protocol, because the added amine operates in the absence of water.

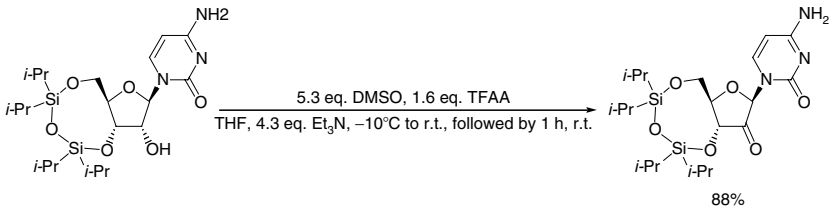
Oxidation-sensitive functionalities other than alcohols are remarkably resistant to the action of the TFAA-mediated Moffatt oxidation. Functional groups resistant to this oxidation include: *p*-methoxybenzyl ethers[133] and esters,[143] sulfides,[143a,144] thioacetals,[145] nitrogen heterocycles[146] and most peculiarly even selenides,[147] and *p*-hydroquinones.[148]



Ref. 148
A very oxidation-sensitive *p*-hydroquinone remains unaffected during an Omura–Sharma–Swern oxidation.

Although very often indoles are recovered unchanged,[149] there are evidences[150] showing that they do react under Omura–Sharma–Swern conditions, producing an intermediate that, in the absence of excess of oxidizing reagent, reverts to starting indole during the work-up. However, this intermediate sometimes may evolve, resulting in the generation of side compounds (see page 137).

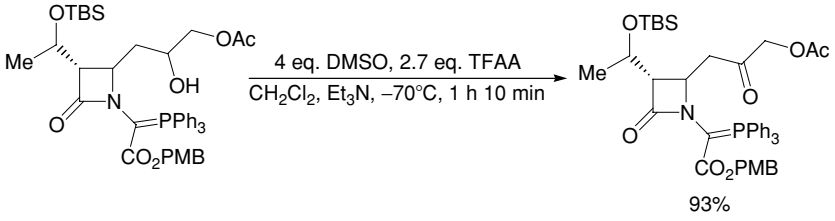
Tertiary[151] amines remain unaffected, and there are examples of unreactive secondary[152] amines, recovered unchanged in Omura–Sharma–Swern oxidations. There is one report[153] of a secondary amine being transformed in a trifluoroacetamide. As trifluoroacetamides are hydrolyzed under very mild basic conditions, one wonders whether the recovery of secondary amines is a result of the hydrolysis of the corresponding trifluoroacetamides during the work-up. During an oxidation in the preparation of the anti-tumour agent FMdC, it was found that an Omura–Sharma–Swern oxidation was unique among other oxidation procedures, because no interference from a primary aromatic amine happened.[154]



Ref. 154

After a substantial exploratory chemistry involving other oxidants, such as Swern, Ac_2O/DMSO, NaOCl, Al(O*t*-Bu)$_3$/acetone, 5% TPAP/NMO and P_2O_5/DMSO, it was found that an Omura–Sharma–Swern oxidation was unique providing a 88% yield of the desired ketone, with no interference from the unprotected primary amine.

It is interesting to note that stabilized phosphoranes[143a,b] and phosphonate[155] anions can resist TFAA-mediated Moffatt oxidations.



Ref. 143a

A TFAA-mediated Moffatt oxidation succeeds in the presence of sensitive moieties, like a β–lactam, and a stabilized phosphorane.

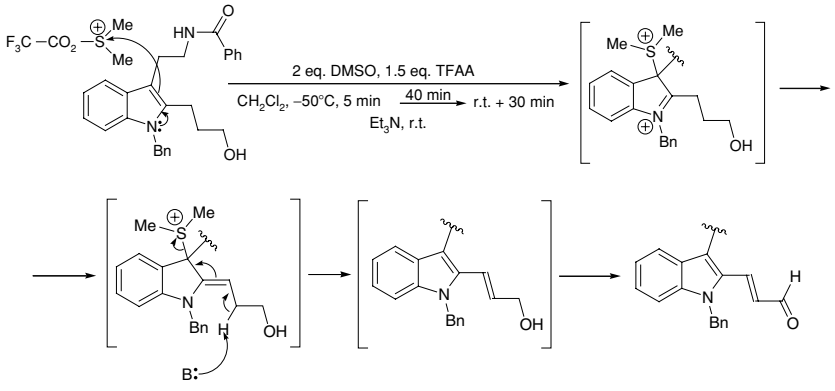
2.6.3. Side Reactions

Very often, alcohols are transformed into the corresponding trifluoroacetates. This side reaction can be very substantial in alcohols possessing radicals able to stabilize carbocations, such as benzylic and allylic alcohols.[122a,b] A proper choice of reaction conditions can result in a minimization of this side reaction (see page 130).

The action of the amine over the alkoxysulfonium intermediate—ROS(+)Me_2—can produce either the desired oxidation, or the generation of $H_2C{=}S(+)$-Me. This compound can react with alcohols, resulting in the formation of methylthiomethyl ethers, R–O–CH_2–S–Me. It can also react with other nucleophilic sites, resulting in the introduction of a methylthiomethyl group. Unhindered alcohols are particularly prone to the generation of methylthiomethyl ethers, whose formation can be difficult to avoid by adjusting reaction conditions. Nevertheless, like other Moffatt oxidations, it

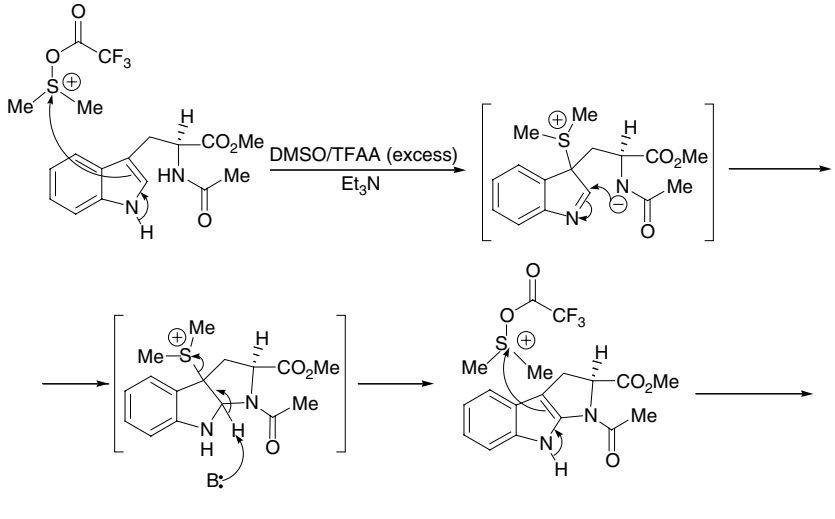
is expected that the use of solvents of low polarity would help to minimize this side reaction.[123]

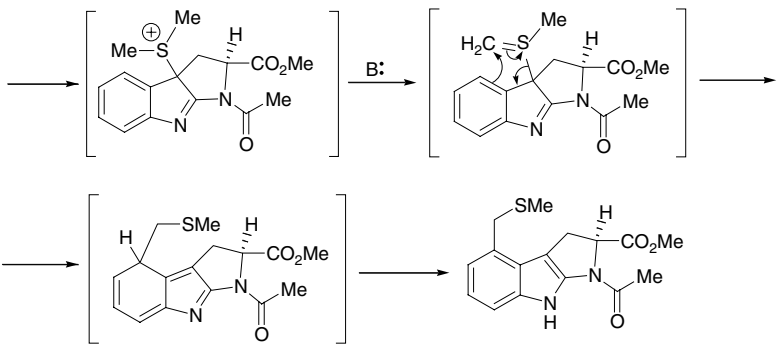
Nucleophiles, other than alcohols, can react with the TFAA-activated DMSO molecule—F_3CCO_2-S(+)Me_2—, indoles being particularly prone to do so.



Ref. 150

The introduction of an unsaturation, conjugated with the aldehyde, can be explained by an initial attack of the indole—via its 3 position—to the activated DMSO molecule. The authors propose a tetravalent sulfur intermediate rather than a sulfonium salt.

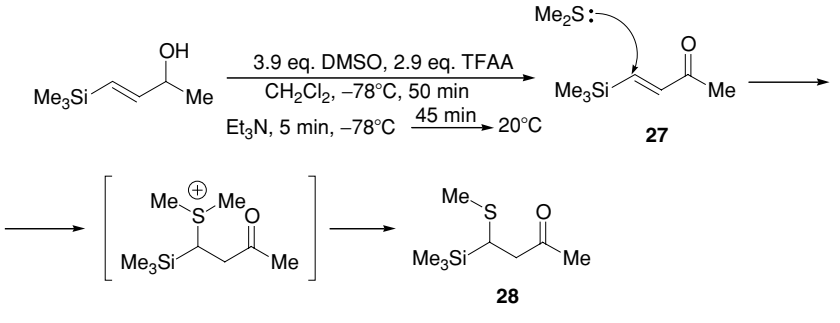




Ref. 150

The initial attack of the indole on the activated DMSO molecule generates an electrophilic intermediate that suffers an intramolecular attack from an amide anion. After the aromaticity being recovered by expulsion of dimethyl sulfide, yielding an intermediate that can be isolated, a second attack of the indole on activated DMSO generates a sulfonium salt. This sulfonium salt, according to the authors, suffers deprotonation, yielding a tetravalent sulfur compound that evolves via a pericyclic reaction, resulting in the introduction of a methylthiomethyl group. An alternative mechanistic proposal, involving the intermediacy of $H_2C = S(+)$-Me, would hardly explain the regioselectivity of the methylthiomethylation.

Sometimes, side products are formed, resulting from attack on electrophilic sites of dimethylsulfide generated from DMSO.

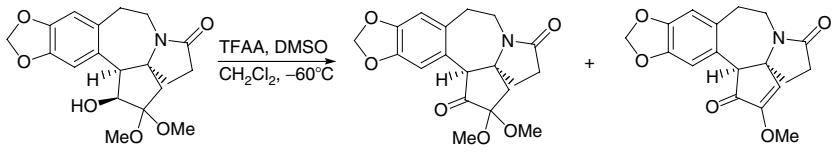


–78°C to 25°C	54%	desired enone **27** + 17% sulfide **28**
–78°C	75%	desired enone **27** + 0% sulfide **28**

Ref. 156

Dimethyl sulfide, generated from DMSO, attacks the enone resulting from the oxidation of the alcohol. A sulfonium salt is generated that decomposes into a sulfur-containing side-compound. Performing the oxidation entirely at –78°C, prevents the undesired attack of dimethyl sulfide.

Sometimes, an elimination occurs when good-leaving groups are present at the α or the β-position of the resulting carbonyl compound.

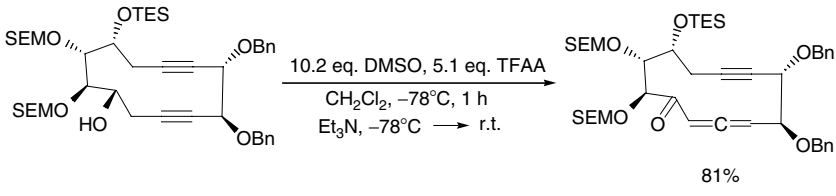


Ref. 157

The desired oxidation product is obtained, contaminated with a compound resulting from elimination of methanol.

It must be mentioned that such eliminations need not to occur, and examples are known in which no carboxylate,[140c,142b] sulfone,[158] or hydroxy[159] groups suffer elimination.

Sometimes, an insaturation migrates into conjugation with the newly formed carbonyl group.



Ref. 160

The oxidation to ketone is followed by isomerization of one of the acetylenes into an allene, resulting in a double-bond being conjugated with the ketone.

However, examples are also known,[135] in which similar migrations do not happen.

Section 2.6. References

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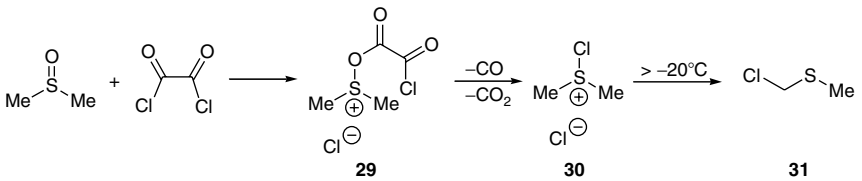
2.7. Swern Oxidation (Oxalyl Chloride-Mediated Moffatt Oxidation)

Few oxidation methods have enjoyed the almost immediate success of the Swern procedure for the oxidation of alcohols. Since the publication of three foundational papers[161] in 1978–79, Swern has become the *de facto* oxidation method by default whenever activated DMSO is desired. It offers the advantage of quite consistent good yields in many substrates, with an operation performed under very low temperature and mild conditions. Swern's procedure consists of the oxidation of an alcohol using DMSO, activated by reaction with oxalyl chloride. According to Swern, oxalyl chloride is the most effective activator of DMSO examined by his group.[162] It must be mentioned that Swern's research team is probably the one that has tried the highest number of DMSO activators for the oxidation of alcohols.

Mechanism

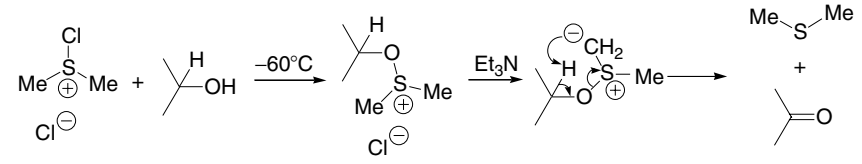
DMSO and oxalyl chloride react in an explosive manner at room temperature. The reaction at $-60^{\circ}C$ is almost instantaneous, resulting in a copious evolution of carbon monoxide and carbon dioxide. As soon as, a drop of a solution of DMSO in CH_2Cl_2 contacts a solution of oxalyl chloride in CH_2Cl_2 at $-60^{\circ}C$, an almost instantaneous reaction takes place, resulting in the formation of chlorodimethylsulfonium chloride **(30)**.



29 30 31

The primary product (**29**) of the reaction of DMSO and oxalyl chloride decomposes very quickly to **30** even at $-140^{\circ}C$.[163] However, the activated DMSO molecule **30** remains stable bellow $-20^{\circ}C$, but decomposes above this temperature to chloromethyl methyl sulfide **(31)**, via the reactive species $H_2C{=}S(+){-}Me$.

During a Swern oxidation, after the formation of the activated DMSO molecule **30**, the alcohol is added at low temperature. The alcohol reacts very quickly with activated DMSO, resulting in the formation of an alkoxydimethylsulfonium chloride **(32)**.



activated DMSO **30** activated alcohol **32** –60°C to room temperature

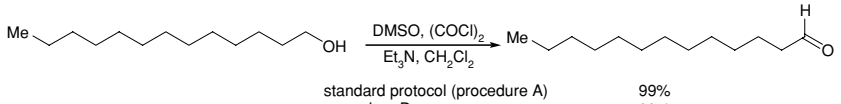
According to the standard protocol (procedure A) as described by Swern *et al.*, the alcohol is allowed to react with activated DMSO for 15 min at low temperature (normally -78 to $-50^{\circ}C$). This is followed by the addition of triethylamine, which reacts with the activated alcohol, while the reaction is left to reach room temperature. This standard protocol, involving the generation of activated DMSO in CH_2Cl_2 at low temperature (ca. $-60^{\circ}C$), followed by activation of the alcohol for 15 min, addition of triethylamine and after 5 min allowing the reaction to heat up slowly to room temperature, is found suitable for most substrates. However, some variations have been introduced to suit the oxidation of diverse alcohols.

Interestingly, oxalyl chloride reacts quicker with DMSO than alcohols. Therefore, although not common,[164] it is possible to generate an activated alcohol by the addition of oxalyl chloride over a mixture of alcohol and DMSO.

Reaction Temperature

For experimental convenience, it may be advisable to carry out the reaction at a maximum temperature. As the activated DMSO molecule—compound **30**—decomposes above $-20^{\circ}C$, it is not possible to use a temperature much higher than this one. On the other hand, the stability of the activated alcohol species **32**, being very diverse depending on the concrete

alcohol involved, dictates different experimental protocols. Thus, in the case of alcohols derived from radicals able to stabilize cations—particularly allylic, propargylic and benzylic alcohols—the corresponding activated alcohol species **32** are expected[165] to decompose at temperatures lower than room temperature. In such alcohols, it is advisable to perform the Swern oxidation at a temperature as low as kinetics would allow. In variance with these alcohols, simple aliphatic alcohols, as demonstrated by Swern *et al.*, can be efficiently oxidized even at $-10^{\circ}C$.[166] However, at this temperature it is necessary to employ excess of activated DMSO to compensate for its decomposition (procedure D). Regardless of the success of the oxidation of simple aliphatic alcohols at $-10^{\circ}C$,—as a higher temperature tends to promote side reactions—it is advisable to try the Swern oxidation on substrates of medium complexity at a low temperature (ca. -78 to $-50^{\circ}C$).



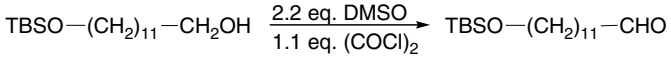
standard protocol (procedure A) 99%
procedure D 98%

standard protocol: alcohol activation, 15 min, –60°C; reaction with Et_3N, 5 min, –60°C followed by –60°C to r.t.

procedure D: like standard protocol, but the activation of the alcohol is done at –10°C.

Ref. 167

In this simple aliphatic alcohol, the use of procedure D involving activation of the alcohol at $-10^{\circ}C$, instead of ca. $-60^{\circ}C$ as in the standard protocol, hardly causes any decrease in yield.



83%

alcohol activation: 1 h, –40°C
5 eq. Et_3N, 1 h, –40°C to 0°C

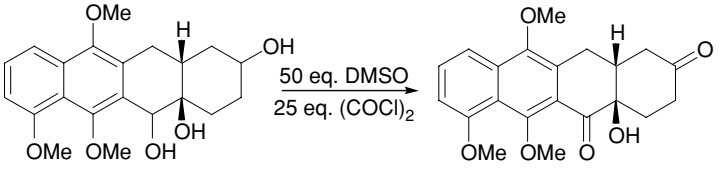
Ref. 168

A temperature higher than usual and a prolonged activation time for the alcohol are employed, in order to make up for the poor solubility of the alcohol in cold CH_2Cl_2.

Alcohol Activation

The observations performed by Marx and Tidwell,[169] regarding alcohol ligand interchange in alkoxysulfonium salts, show that the activation of normal alcohols at low temperature is extremely rapid, being possible to complete in a few minutes at $-60^{\circ}C$. These results show the general correctness of the 15 min time period for the activation of alcohol in the standard protocol. Nevertheless, in difficult oxidations,[170] there are reports claiming that the best yields are obtained when the activation of the alcohol is allowed to run during a prolonged period of 45 minutes. Probably, hindered alco-

hols—or alcohol possessing certain functional group in close proximity to the alcohol functionality—need some extra time for complete activation at low temperature. In fact, the activation of the alcohols in the Swern oxidation is very often performed during much longer than 15 min, as recommended in the standard protocol by Swern *et al.*; activation times as long as 2 h being occasionally described.[171]



81%

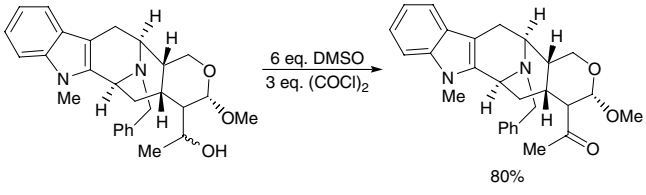
alcohol activation: 45 min at –60°C
115 eq. Et_3N, 15 min –60°C, followed by –60°C to r.t.

Ref. 170

For an effective oxidation of this triol, defined activation time longer than the one employed in the standard protocol must be employed.

It is difficult to anticipate the optimum activation time for the oxidation of a certain alcohol. Hindered alcohols are expected to require more than 15 min. On the other hand, a prolonged activation time, although not deleterious for the oxidation of many alcohols, whose corresponding alkoxydisulfonium chlorides are stable, may promote side reactions, particularly in allylic, benzylic and propargylic alcohols. In such alcohols, it may be advisable to use a very short activation time at a very low temperature, followed by a prolonged reaction with an amine at low temperature.

There are reports in which a prolonged activation time of the alcohol at low temperature is not sufficient for an efficient oxidation, and a higher temperature during the activation must be employed.[172]



80%

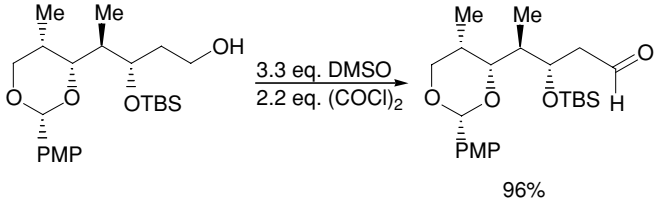
alcohol activation: 1.25 h, –78 to –10°C
14.4 eq. Et_3N, 45 min, –10°C to r.t.

Ref. 172b

In this Swern oxidation, the activation of a very hindered alcohol demands 1.25 h, while the temperature is increased from −78 to −10°C.

Preventing Acid-induced Side Reactions

As activated DMSO and activated alcohols have a certain acidity, a prolonged alcohol activation before the addition of base may cause decomposition of very acid-sensitive functionalities.



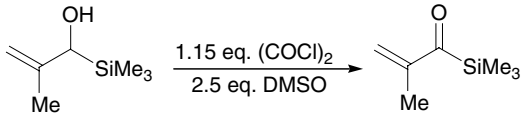
96%

alcohol activation: –78°C
5.6 eq. Et_3N, 30 min, –78°C to r.t.

Ref. 173

Triethylamine must be added immediately after mixing the alcohol and activated DMSO, in order to avoid the acid-catalyzed cleavage of a very sensitive acetal.

The decomposition of acid-sensitive substrates during Swern oxidations can also be explained by the presence of adventitious hydrogen chloride. This can be avoided by the use of freshly distilled oxalyl chloride and carefully dried DMSO.[174]



> 79%

alcohol activation: 1 h, –78°C
5.2 eq. Et_3N, 1 h, –78°C

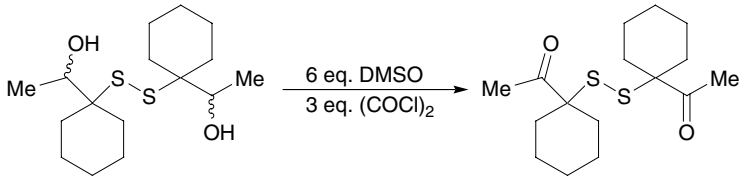
Ref. 174

As traces of HCl promoted the decomposition of the starting compound, adventitious HCl had to be carefully excluded during the Swern oxidation, by using freshly distilled oxalyl chloride and carefully dried DMSO.

Preventing Base-induced Side Reactions

In the standard protocol the transformation of the activated alcohol into the carbonyl compound is done by the action of Et_3N for 5 min,

followed by increasing temperature slowly to room temperature. On some substrates, however, it may be advisable to allow a prolonged contact at low temperature before heating up to room temperature, or even to quench the reaction at low temperature.[175] This is so, particularly when a facile α-epimerization[176] or a β-elimination[177] of the product must be avoided.



96%

alcohol activation: 90 min, –78°C
7.5 eq. Et_3N, 2 h, –78°C
quenching with THF:H_2O (1:1) bellow –60°C

Ref. 175

An almost quantitative yield of diketone is obtained using a modified oxidation protocol, whereby the activated alcohol is in contact with Et_3N for a long time at low temperature, and quenching is performed bellow −60°C. The use of the standard protocol allows the isolation of the diketone in a moderate yield (ca. 60%).

83%

alcohol activation: 25 min, –78°C
5 eq. Et_3N, 1 h, –78°C

Ref. 176a

Quenching is done with saturated aqueous NH_4Cl at −78°C, in order to avoid α-epimerization of the aldehyde.

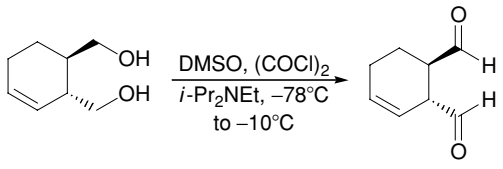
Side reactions, promoted by the acidity of the protons at the α position of the carbonyl of the product, such as α-epimerizations and migration of alkenes into conjugation with the carbonyl, can be mitigated by the use

of the bulkier base diisopropylethylamine (Hünig's base), rather than triethylamine, with a low-temperature quenching.[178] On the other hand, it must be mentioned that using Hünig's base instead of Et_3N, may cause a substantial decrease on the reaction speed.[179]

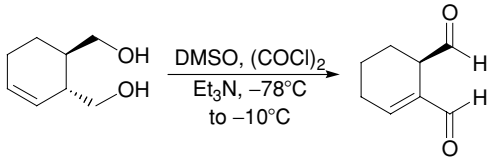
100%

alcohol activation: 15 min, –78°C
8 eq. *i*-Pr_2NEt, 1 h, –78°C, followed by –78°C to –40°C
quenching at –40°C with a neutral phosphate buffer

Ref. 180
In order to avoid a very facile α-epimerization of the aldehyde, the bulky base diisopropylethylamine was used and quenching was performed at −40°C with a phosphate buffer at pH 7.

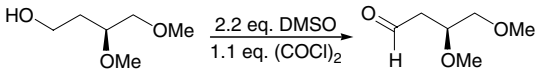


87%



Ref. 178a
The migration of the alkene into conjugation with one of the aldehydes is avoided by the use of Hünig's base, instead of triethylamine. The work-up must be done under cold acidic conditions, followed by washing with a pH 7 buffer solution.

Sometimes, triethylamine causes side reactions, because of its basic strength rather than lack of bulkiness. In such cases, it may be advisable to use a weaker base, such as *N*-methylmorpholine.[181]



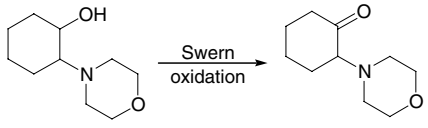
98%

alcohol activation: 25 min, –78°C
3.3 eq. *N*-methylmorpholine, 70°C to 0°C, followed by 2 h, 0°C

Ref. 181a

The use of triethylamine leads to a β-elimination of MeOH from the product. This is avoided by employing the weaker base *N*-methylmorpholine.

With a difficult substrate, in which many bases were tried, Chrisman and Singaram proved that the election of base may have a profound effect on the yield of a certain Swern oxidation. In the substrate tried, the ideal base was neither triethylamine nor Hünig's base, but a base with an intermediate bulkiness.[182]

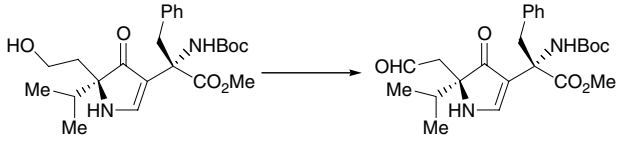


base	%
i-Pr_2NEt	65
Et_3N	68
N-ethylpiperidine	93
N-methylpyrrolidine	57

Ref. 182

An optimum yield is obtained using *N*-ethylpiperidine as base. However, in a very similar substrate, best yields are obtained with *N*-ethylpyrrolidine.

In other substrates, a very strong base, such as DBU, may provide best results.[183]



$(COCl)_2$, DMSO, Et_3N	46%
$(COCl)_2$, DMSO, *i*-Pr_2NEt	87%
$(COCl)_2$, DMSO, DBU	85%

Ref. 183

Although, Hünig's base provided best yield, the use of DBU was preferred, because the product was obtained with a higher purity.

Solvent

Dichloromethane is almost exclusively used as the solvent in Swern oxidations, being tetrahydrofuran[184] very rarely used. This is somehow surprising as some compounds have poor solubility in CH_2Cl_2 at low temperature, and in variance with other Moffatt oxidations, an increase in the solvent polarity in a Swern oxidation seems substantially not to originate side reactions. For example,[162] a 93% yield in the oxidation of 2-octanol was obtained, using the very polar mixture CH_2Cl_2:DMSO (1.3:1) as solvent.

Non-aqueous Work-up

Normally, the work-up of Swern oxidations is carried out by a routine fractioning between an aqueous and an organic phase. Some aldehydes with a high tendency to exist as a hydrate—typically, aldehydes possessing an alkoxy group at the α position—are hydrated during the standard work-up, resulting in a chemical species resistant to react with nucleophiles as aldehydes do. In such cases, it is advisable to perform a non-aqueous work-up, in which an organic solvent is added, the solids are filtered, the resulting solution is concentrated, and the residue is purified with a silica column.[185]

Modified Swern Reagent

The standard Swern oxidation employing DMSO results in the formation of dimethyl sulfide, which is a toxic volatile liquid (b.p. 38°C) with an unpleasant smell. This can be avoided by using other sulfoxides that generate sulfides lacking volatility. Useful alternatives include: dodecyl methyl sulfoxide,[186] 6-(methylsulfinyl)hexanoic acid,[187] sulfoxides containing perfluorated alkyl chains[188] and sulfoxides bound to polymers, such as polystyrene[189] or poly(ethylene)glycol.[190] These variants not only avoid the generation of an unpleasant odour, but also facilitate the work-up. Thus, for example, 6-(methylsulfinyl)hexanoic acid generates a sulfide that is easily separated by chromatography, fluorated sulfoxides produce sulfides that can be extracted with a fluorous solvent, and polymer-based sulfoxides generate sulfide-containing polymers that can be filtered. All these expensive sulfoxides can be regenerated by oxidation of the resulting sulfides.

2.7.1. General Procedure for Oxidation of Alcohols Using Swern Oxidation

From 2 to 11 equivalents[a]—typically 2.2 equivalents—of dry DMSO[b] (MW = 78.1, d = 1.10) are slowly[c] added over a cold[d] stirred ca. 0.2–0.9 M solution of 1.1–5 equivalents—typically 1.1 equivalents—of oxalyl chloride in dry CH_2Cl_2. After the evolution of gas ceased—ca. 1–20 min—,[e] a ca. 0.1–0.5 M solution of 1 equivalent of the alcohol in

dry CH_2Cl_2 is slowly[f] added to the resulting cold[g] solution of activated DMSO. After 5 min to 2 h[h]—typically 15 min—ca. 1.2–16 equivalents—typically 5 equivalents—of triethylamine[i] (MW = 101.2, d = 0.726) are added. After 5 to 120 min[j]—typically 5 min—the reaction is left to reach room temperature.

The reaction is quenched[k] by the addition of either water, a buffer phosphate solution at pH 7, or a slightly acidic aqueous solution, formed, for example, by ca. 10% ammonium chloride, or 0.1–0.5 M sodium bisulfate. The organic phase is separated and the aqueous phase is washed with CH_2Cl_2. At this point, it may be helpful to add some CH_2Cl_2, or other organic solvent, like Et_2O or EtOAc, in order to facilitate the fractioning of phases. The collected organic phases may be optionally washed with water or brine. The resulting organic solution is dried with Na_2SO_4 or $MgSO_4$ and concentrated, giving a residue that may need some purification.

[a] DMSO must be used in excess relative to oxalyl chloride. In the oxidation of substrates with poor solubility in cold CH_2Cl_2, it may be advisable to increase substantially the quantity of DMSO, in order to facilitate the solubility of the alcohol.

[b] The addition of DMSO dissolved in some CH_2Cl_2 may help to avoid local over-heating, as well as the formation of frozen drops of DMSO.

[c] The DMSO reacts very quickly with oxalyl chloride, resulting in a copious evolution of carbon dioxide and carbon monoxide. CAUTION: carbon monoxide is highly toxic, therefore a good hood must be employed. The rate of addition of DMSO must be adjusted to avoid a too quick delivery of gas and heat.

[d] Typically, between −78 and −60°C. The resulting activated DMSO decomposes above −20°C.

[e] As the resulting activated DMSO is stable at low temperature, no effect on the yield of the oxidation is expected by applying a prolonged contact of DMSO with oxalyl chloride.

[f] The speed of the addition of the alcohol solution must be adjusted to avoid exotherms.

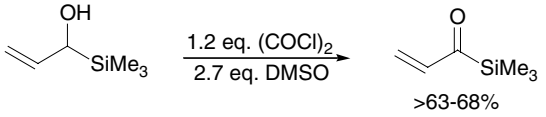
[g] In the oxidation of simple aliphatic alcohols, the solution of activated DMSO may be left to reach as high as −10°C in order to increase the solubility of the alcohol. The routine use of such high temperature is not advisable for it may cause side reactions.

[h] Normally, the activation of the alcohol is complete in a few minutes, although hindered alcohols may need a longer time. As activated alcohols derived from radicals able to stabilize carbocations, like allylic, benzylic and propargylic alcohols, are unstable, in such alcohols it is advisable to perform the activation at very low temperature and to add triethylamine as soon as possible. Substrates with a very high sensitivity to acids can be decomposed, because of the acidic nature of activated DMSO and activated alcohols. In such cases, it is advisable to add Et_3N as soon as possible.

[i] In order to avoid base-induced side reactions, like α-epimerizations on the carbonyl or migration of alkenes into conjugation with the carbonyl, it may be advisable to perform the oxidation using a bulky amine, like diisopropylethylamine (Hünig's base, MW = 129.3, d = 0.742), instead of Et_3N. In such cases, it may also be advisable to quench the reaction at low temperature with an acidic aqueous solution and to wash the organic phase with an aqueous buffer at pH 7.

[j] A prolonged contact of the amine with the activated alcohol is necessary when the quenching of the reaction is done at low temperature, rather than after the reaction is left to reach room temperature.

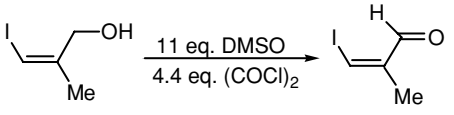
[k] Sometimes, it is advisable to perform a non-aqueous work-up, particularly when aldehydes prone to form hydrates, such as α-alkoxyaldehydes, are obtained. A non-aqueous work-up can be performed by adding an organic solvent, such as acetone, ether or EtOAc, filtering the solids and concentrating the organic solution. The resulting crude material—containing residual triethylamine hydrochloride and DMSO—can be purified by a silica chromatography.



>63-68%

alcohol activation: 1 h, –75°C
5.4-5.8 eq. Et_3N, 1 h, –75°C, followed by –75°C to r.t.

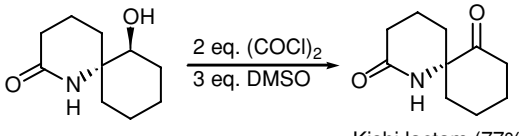
Ref. 191
A description of a Swern oxidation on a multigram scale is provided.



67%

alcohol activation: 30 min, –78°C
1.2 eq. Et_3N, 5 min., –78°C, followed
by –78°C to r.t.

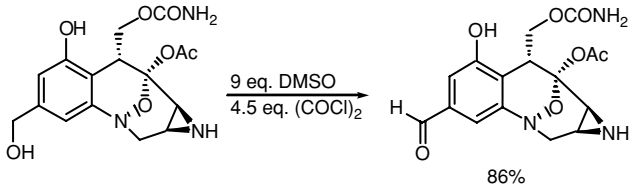
Ref. 192
A highly unstable aldehyde is obtained under Swern conditions, while PCC, PDC, Jones oxidation and Dess-Martin periodinane lead to decomposition.



Kishi lactam (77%)

alcohol activation: 5 min, –78°C
4 eq. Et_3N, 2 h, –78°C and 12 h, 0°C

Ref. 193
In an enantioselective synthesis of a key intermediate for the preparation of poisons from the skin of tropical frogs, a key oxidation was performed under Swern conditions with 77% yield, while PCC provided a 28% yield and Pfitzner–Moffatt oxidation 73% yield.

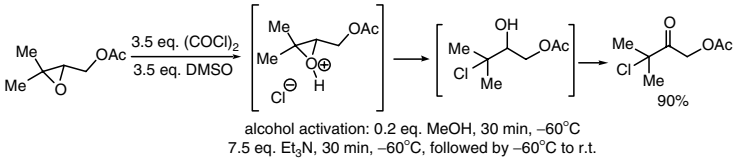


In the preparation of the antitumor compound FR900482, the oxidation of a benzylic alcohol could be done under Swern conditions with 86% yield. Other oxidants, like MnO_2, Collins reagent, PCC, PDC, Dess-Martin periodinane, TPAP and DDQ, gave complex mixtures, probably due to the presence of the naked aziridine functionality and a free phenol.[194]

2.7.2. Functional Group and Protecting Group Sensitivity to Swern Oxidation

As the Swern oxidation is performed under very mild conditions, very acid-sensitive and base-sensitive functional groups are not affected. Adventitious hydrogen chloride—generated, for example, by decomposition of oxalyl chloride—may affect acid-sensitive functionalities. However, this can be avoided by using freshly distilled oxalyl chloride and a very dry DMSO (see page 145). Alterations in acid-sensitive functionalities can also be explained by the acidic nature of activated DMSO and activated alcohols. These alterations can be avoided by adding the base, very promptly after the beginning of the activation of the alcohol (see page 145). In fact, cases of acid-sensitive functional groups being modified, during a properly performed Swern oxidation, are very rare. Swern oxidations are compatible with very acid-sensitive protecting groups, such as THP[195] or trityl[196] ethers.

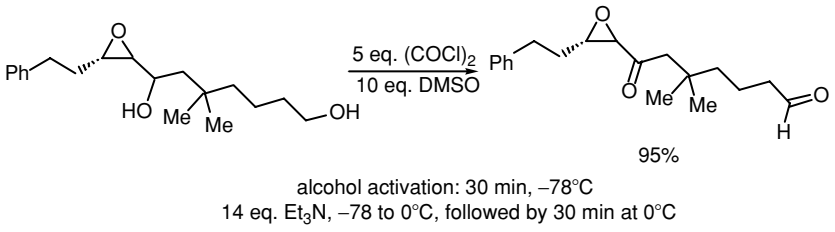
It has been reported that epoxides are transformed in α-chloroketones or α-chloroaldehydes under Swern conditions.[197] According to the authors, depending on the starting epoxide, it may be necessary to add some methanol—that generates HCl by reaction with activated DMSO—for the reaction to occur. This transformation can be explained by an acid-catalyzed opening of the epoxide, resulting in a chloroalcohol that is oxidized to a α-chloroaldehyde or ketone. Adventitious HCl can explain the reaction when no MeOH is added.



Ref. 197b

The HCl generated by the addition of MeOH causes the opening of the epoxide, giving a chloroalcohol that is oxidized to a α-chloroketone.

Under normal Swern conditions, as the oxidation of alcohols is quicker than the reaction with epoxides, it is possible to oxidize alcohols with no interference of epoxides in the same molecule.[198]



Ref. 199

An uneventful oxidation of two alcohols occurs regardless of the presence of an epoxide.

The action of triethylamine may cause base-induced reactions, such as: α-epimerization of carbonyl compounds; isomerization of alkenes into conjugation with carbonyl groups; and, elimination in carbonyl compounds posssessing a good-leaving group at the β-position

These base-induced side reactions can be mitigated by (see page 145):

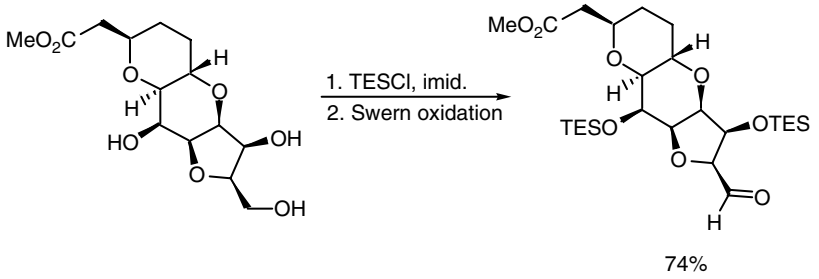
- Using bases, like Hünig's base, which are more hindered than triethylamine
- Using amines, like *N*-methylmorpholine, which are less basic than triethylamine
- Quenching the reaction at low temperature under mild conditions

These reactions only operate on very sensitive substrates, and protecting groups removable under basic conditions normally resist a Swern oxidation.

The Swern oxidation shows a great regioselectivity for the oxidation of alcohols, in the presence of other functionalities with a high sensitivity for oxidants. For example, sulfides, thioacetals, disulfides (see page 146) and even selenides[200] resist the action of Swern oxidation.

Protecting groups that are cleaved by an oxidant, like *p*-methoxybenzyl[201] and dimethoxybenzyl[202] ethers or *p*-methoxybenzylidene[203] and dimethoxybenzylidene[204] acetals, resist the action of oxalyl chloride-activated DMSO.

Primary TMS and TES ethers[205] are deprotected and transformed into the corresponding aldehydes under Swern conditions. Other less labile silyl ethers—such as TBS ethers as well as secondary TMS and TES ethers—, remain unaffected. This allows to perform selective oxidations of primary alcohols in the presence of secondary ones by persilylation of poliols by TMS or TES, followed by selective oxidation of the primary silyl ethers to aldehydes under Swern conditions.



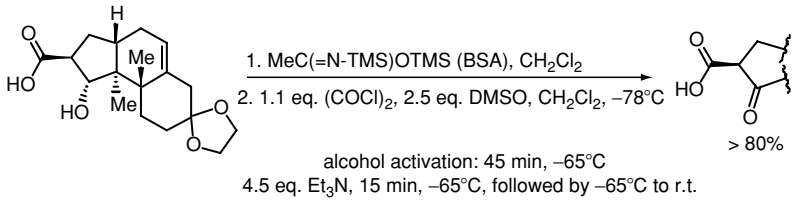
Ref. 205g

A selective oxidation of the primary alcohol, in the presence of two secondary ones, can be performed by persilylation, followed by selective oxidation of the primary TES ether under Swern conditions.

Although the selective oxidation of primary TMS and TES ethers, in the presence of secondary TMS and TES ethers, has been reported by several research groups, there is a contradictory report[205c] showing that 2-octanol TMS ether is oxidized quicker than 1-octanol TMS ether. This rises the concern that the selective oxidation of primary TES and TMS ethers may be the result of a selective acidic hydrolysis, produced by adventitious HCl. This would lead to oxidations with low reproducibility. As the selective oxidation of primary alcohols is an important synthetic operation, this matter deserves a close scrutiny.

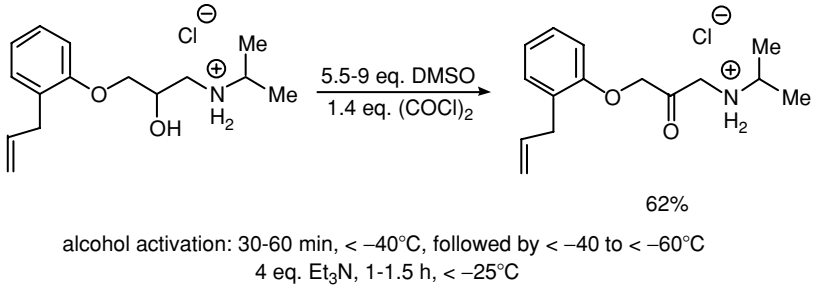
It is possible to oxidize alcohols in the presence of free carboxylic acids.[206] Nevertheless, sometimes better results are obtained if the acid is protected, for example by methylation.[207] Sometimes, free carboxylic acids have a low solubility in cold CH_2Cl_2. In such cases, an *in situ* protection with the silylating agent, bis(trimethylsilyl)acetamide (BSA) normally allows the solubilization of the acid as trimethylsilyl ester, and an easy Swern oxidation. The resulting silylated acid is easily deprotected during the work-up.[208]

Primary and secondary amines react under Swern conditions, resulting in the formation of imines,[209] enamines,[209b] methylthiomethylamines[209b] or iminosulfurans.[210] Hindered secondary amines react very slowly under Swern conditions, so that selective oxidation of alcohols is possible.[194] Particularly, primary amines protected with bulky alkyl groups, such as 9-phenylfluorenil[211] or trityl,[212] resist Swern conditions during the oxidation of alcohols. The selective oxidation of alcohols, in the presence of secondary amines, is facilitated when the amine is present as a protonated species during the activation of the alcohol.



Ref. 208b

Because of the low-solubility of the hydroxyacid in cold CH_2Cl_2, it was treated with 1 equivalent of bis(trimethyl)silylacetamide, till the silylation of the acid functionality caused the solubilization of the starting compound. An ensuing standard Swern oxidation produced an uneventful oxidation of the alcohol, which was followed by a mild TMS carboxylate hydrolysis during the work-up.



Ref. 164

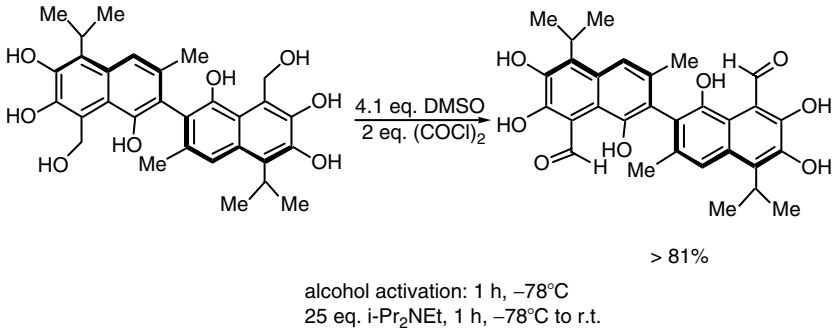
The protection of the amine as a hydrochloride, allows the selective oxidation of the alcohol with 62% yield. However, the protection of the amine is not complete by protonation, because the DMSO present in the medium is basic enough to compete as proton scavenger. A better protection of the amine by the addition of ca. 0.5 eq. of concentrated sulfuric acid, as an extra proton source, allows to increase the yield to 78%.

Tertiary amines normally remain unaffected under Swern conditions.

Primary amides react under Swern conditions, producing the corresponding nitriles[213] and minor amounts of iminosulfurans.[210] Nonetheless, there is some report depicting the selective oxidation of alcohols in the presence of primary amides.[214] Secondary and tertiary amides remain unaffected.

Nitro groups remain unaffected[215] during Swern oxidations, although there is one report in which a nitroalcohol is transformed into a lactone.[216]

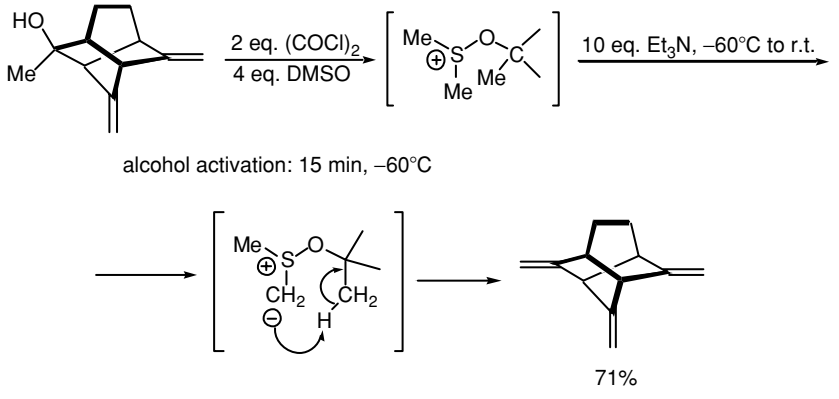
It is possible to oxidize alcohols in the presence of free phenols,[217] although many times phenols are protected for solubilizing purposes.



Ref. 218

In this oxidation of very remarkable selectivity, two benzylic alcohols are transformed into aldehydes, while a hexaphenol with a great tendency to generate a polyquinone remains unaffected.

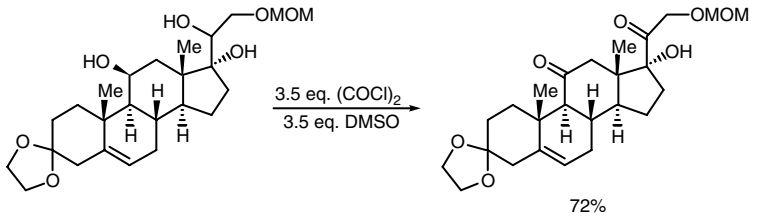
Tertiary alcohols react with activated DMSO, yielding an activated alcohol, that, as it lacks an α-hydrogen, is not able to evolve to a carbonyl compound. Nevertheless, when a β–hydrogen is present, elimination to an alkene can occur under the action of a base.[219]



Ref. 219

No carbonyl compound can be produced, because a sulfur ylide, derived from a tertiary alcohol, cannot abstract a hydrogen via a five-membered transition state. However, an elimination can occur by a hydrogen abstraction via a six-membered transition state.

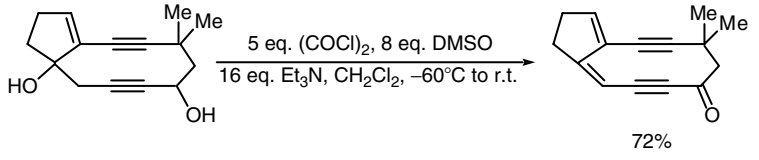
Because of steric constrains, the activation of primary and secondary alcohols is quicker than the activation of tertiary alcohols. Therefore, normally, it is possible to oxidize primary and secondary alcohols, with no interference from elimination reactions of tertiary alcohols present in the same molecule.[220]



Ref. 221

Two secondary alcohols are oxidized with no interference from a tertiary alcohol.

The simultaneous oxidation of a secondary or primary alcohol, and dehydration of a tertiary alcohol can be carried out by using excess of Swern reagent.[222]

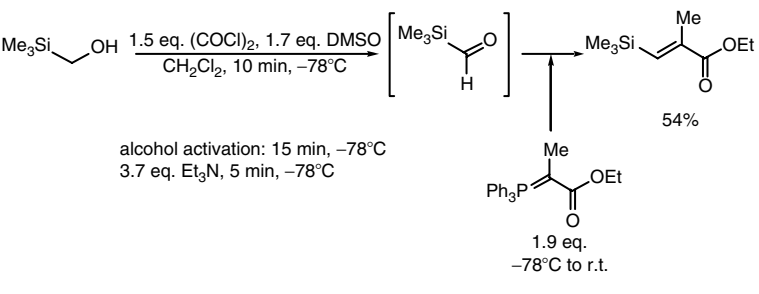


Ref. 222

The purposeful simultaneous oxidation of a secondary alcohol and dehydration of a tertiary alcohol is brought about by the use of excess of Swern reagent.

2.7.3. Reactions Performed *in situ* after a Swern Oxidation

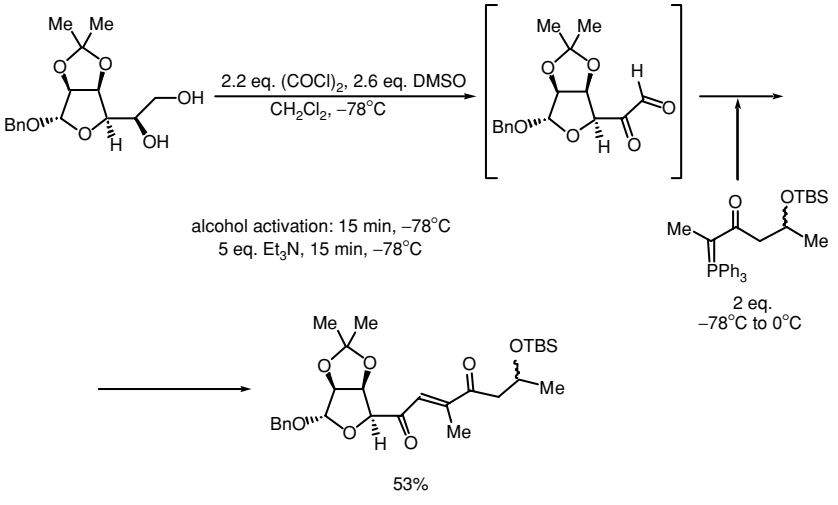
Swern oxidations produce the quite unreactive side compounds carbon monoxide, carbon dioxide, dimethyl sulfide and an amine hydrochloride. Therefore, it is very often possible to perform the *in situ* addition of a nucleophile to the aldehyde or ketone, resulting from the oxidation. This is particularly useful when the aldehyde or ketone is difficult to isolate, because of possessing an unusually high reactivity.



Ref. 223

The highly unstable trimethylsilylformaldehyde is prepared by Swern oxidation at very low temperature. An *in situ* condensation with a stabilized phosphorane delivers a silylolefin. If the solution of trimethylsilylformaldehyde is allowed to reach 0°C, no condensation product is obtained, which proves that trimethylsilylformaldehyde is not stable in solution at 0°C.

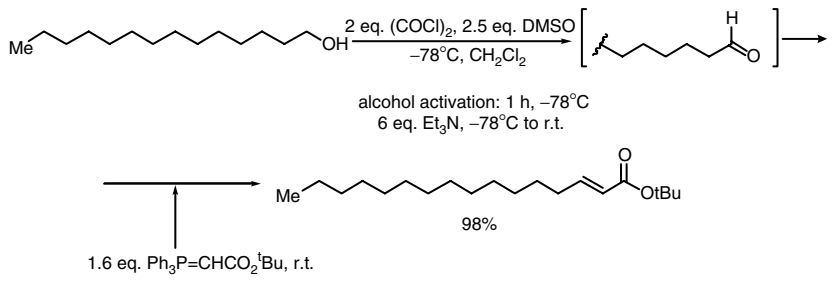
Particularly, the *in situ* condensation of highly reactive aldehydes—generated by Swern oxidation—with stabilized phosphoranes and phosphonate anions is finding ample use in organic synthesis.[224] It must be mentioned that highly reactive aldehydes—for example α-ketoaldehydes, or aldehydes possessing heteroatom substituents at the α-position—are very often difficult to isolate, because of their tendency to be hydrated or to polymerize. At the same time, these highly reactive aldehydes are able to react with stabilized phosphoranes and phosphonate anions at low temperature, while less reactive aldehydes are more refractory to reaction. Therefore, the *in situ* condensation of aldehydes, generated by Swern oxidation, with phosphorous compounds is particularly well suited for operation with reactive aldehydes, while less reactive ones are better isolated before condensation.



Ref. 224b

The hindered, stabilized Wittig reagent is unable to react with ketones, but reacts slowly with normal unhindered aldehydes at elevated temperature. However, it reacts at a reasonable rate with the highly reactive starting α-ketoaldehyde at 0°C. No reaction occurs on the less reactive ketone.

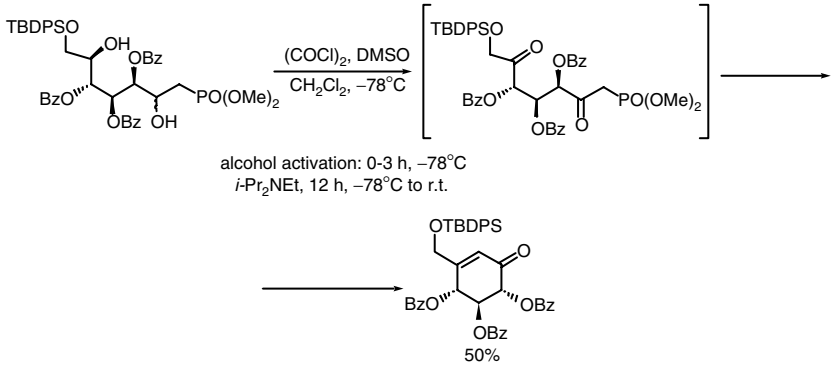
Although many aldehydes with lesser reactivity can be isolated and purified before condensation with phosphorous compounds, often an *in situ* condensation is performed for experimental convenience.[225]



Ref. 225c

Although, the intermediate tetradecanal can be isolated and purified, it is condensed *in situ* with a stabilized phosphorane for experimental convenience.

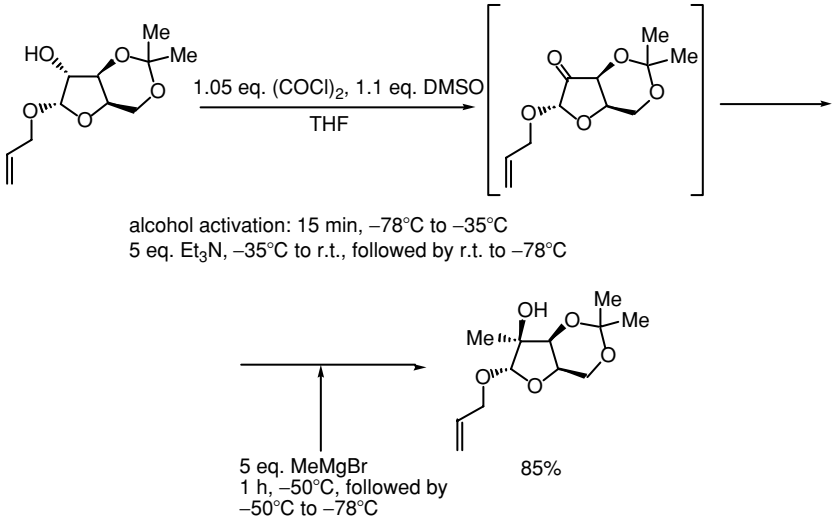
These *in situ* oxidations, followed by condensation with a phosphorous reagent, are normally not possible on ketones, because of their lack of reactivity with stabilized phosphoranes and phosphonate anions. Nevertheless, one-pot condensation with ketones can occur in very favourable cases.[226]



Ref. 226

A spontaneous cyclization occurs by effect of the Hünig's base, added during the decomposition of the activated alcohols. This is a rare case in which a ketone condenses *in situ* with a stabilized phosphonate anion after a Swern oxidation. The condensation is facilitated by the formation of a six-membered ring, and by the relatively high reactivity of a ketone, possessing two activating oxygens at the α-position.

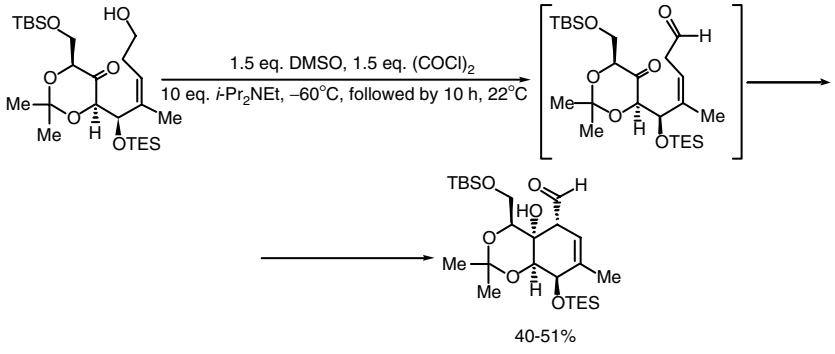
Other nucleophiles reacting *in situ* with aldehydes and ketones, obtained by Swern oxidation, include Grignard reagents[223,184c] and amines.[227]



Ref. 223

A very reactive ketone, obtained by Swern oxidation, is condensed in one-pot with MeMgBr. Other oxidation methods lead to the isolation of the ketone hydrate, which fails to react efficiently with Grignard reagents.

Aldehydes and ketones, obtained by Swern oxidation, may suffer *in situ* intramolecular aldol condensations, resulting in very elegant construction of cycles.[237b]



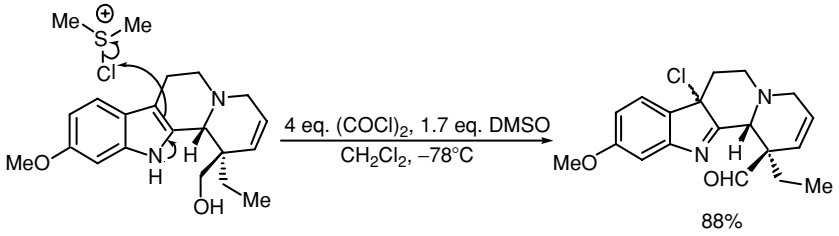
Ref. 237b

A Swern oxidation is followed by an *in situ* aldol condensation, thanks to the use of excess of base. During this very elegant stereoselective construction of a highly functionalized cyclohexene, the hindered base diisopropylethylamine must be used in order to keep the sensitive stereochemistry around the ketone moiety.

2.7.4. Side Reactions

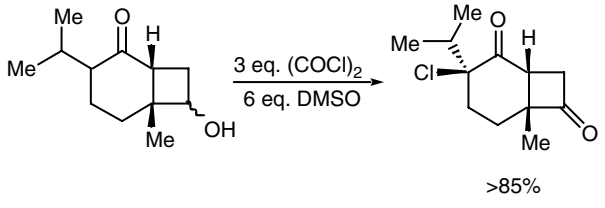
2.7.4.1. Activated DMSO as Source of Electrophilic Chlorine

Nucleophilic sites in a molecule can be chlorinated by attack on the electrophilic chlorine atom, present in activated DMSO. Indoles are particularly prone to suffer this kind of chlorination on the 3-position.[228]



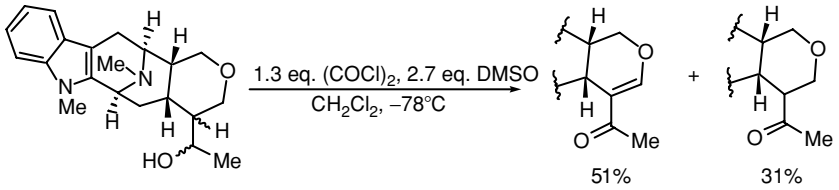
Ref. 228a
A normal oxidation of an alcohol to aldehyde is accompanied by a chlorination of the indole on the 3-position.

Ketones—particularly those with a high proportion of enol form—[229,230] can be chlorinated at the α-position. Using activated DMSO, in stoichiometric amounts, can mitigate the α-chlorination of ketones.[231]



Ref. 231
The desired oxidation of the alcohol was accompanied by α-chlorination of the cyclohexanone. The chlorination could be avoided by using a stoichiometric amount of activated DMSO, or by activating the DMSO with acetic anhydride.

Sometimes, an alkene conjugated with a ketone is introduced during a Swern oxidation.[172a,232] This can be explained by an α-chlorination followed by elimination of HCl.

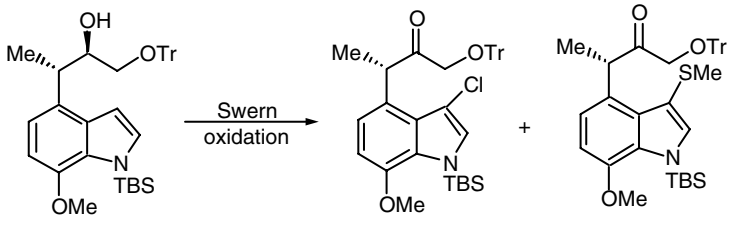


Ref. 172a

The starting alcohol is refractory to reaction using the standard Swern protocol, probably due to steric hindrance. The employment of forcing conditions causes the desired oxidation, as well as the introduction of an alkene conjugated with the resulting ketone. The introduction of the alkene can be explained by an electrophilic α-chlorination, produced by activated DMSO, followed by elimination of HCl.

2.7.4.2. Activated DMSO as Source of Electrophilic Sulfur

A methylthio group can be introduced in a nucleophilic site of a molecule by a reaction, in which activated DMSO can operate as a source of electrophilic sulfur.[228c]



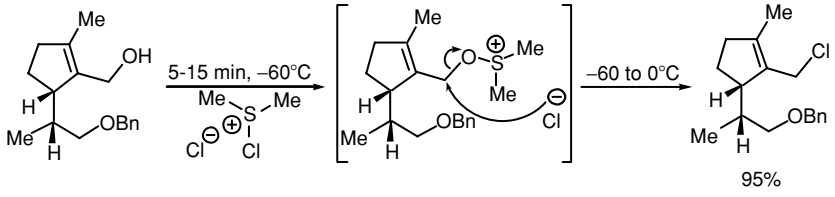
Ref. 228c

The desired oxidation of the alcohol is accompanied by chlorination and methylthiolation at the indole 3-position. The chlorination can be explained by activated DMSO acting as a source of electrophilic chlorine, while the methylthiolation can be caused by activated DMSO operating as a source of electrophilic sulfur. Attack of indole on activated DMSO can result in the introduction of $-S(+)Me_2$, which can be transformed in $-SMe$ by demethylation.

2.7.4.3. Transformation of Alcohols into Chlorides

Activated alcohols are unstable, at least at high temperature, when the corresponding radicals are able to stabilize carbocations, for example in the case of allylic alcohols. The thermal decomposition of activated allylic alcohols leads to the formation of allylic chlorides. This decomposition can

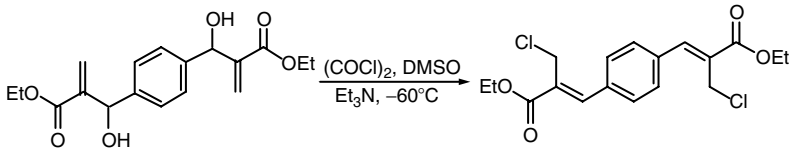
purposefully be brought about, by letting the activated alcohol to heat up with no base added.[233]



Ref. 233

An allylic alcohol is transformed into the corresponding chloride, under very mild conditions, by reaction with activated DMSO, followed by thermal decomposition of the resulting activated alcohol.

Sometimes, the transformation of allylic alcohols into chlorides, by the action of activated DMSO, is so quick that it competes with a normal oxidation.[234]

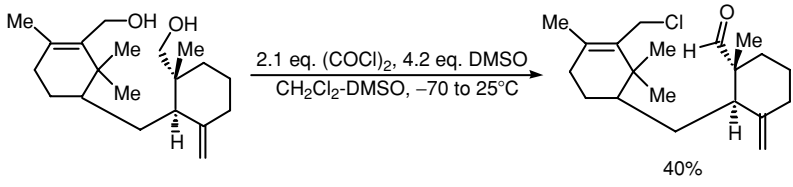


Ref. 234b

No oxidation of the allylic alcohol occurs, because the intermediate activated alcohols evolve very quickly to the corresponding allylic chlorides.

Nonetheless, very often activated allylic alcohols are persistent enough at low temperature, so as to allow a normal Swern oxidation with an added base.[235]

Sometimes, the transformation of allylic alcohols into chlorides, during a Swern oxidation, is brought about by the presence of adventitious HCl.[236]

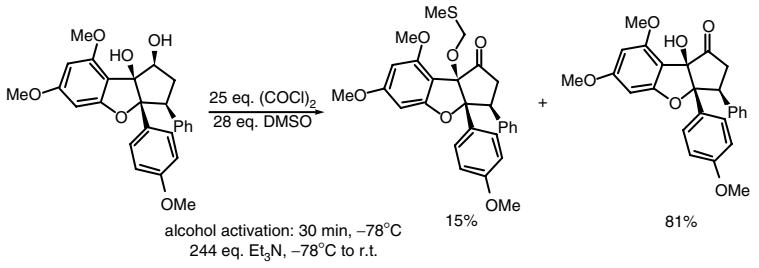


Ref. 236

The use of moist DMSO causes the generation of adventitious HCl, that produces the transformation of the allylic alcohol into an allylic chloride. A properly performed Swern oxidation, under anhydrous conditions, allows the obtention of the desired dialdehyde in 95% yield.

2.7.4.4. Methylthiomethylation

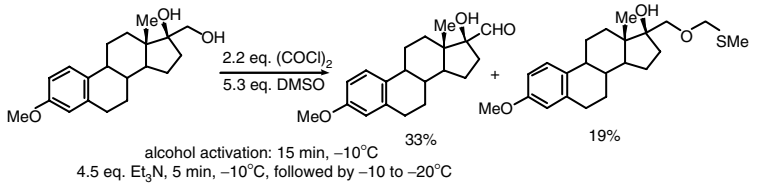
The surplus activated DMSO, which remains unreacted after the activation of the alcohol during a Swern oxidation, decomposes on heating, generating the highly reactive species $H_2C{=}S(+)$-Me (page 97). This species can react with tertiary alcohols present in the molecule, resulting in the formation of a methylthiomethyl ether.[237]



Ref. 237c

The expected oxidation of the secondary alcohol is accompanied by partial methylthiomethylation of the tertiary alcohol.

In fact, it is common to obtain minor amounts of methylthiomethylation of tertiary alcohols during the performance of Swern oxidations of secondary and primary alcohols. The reaction of the tertiary alcohols can be mitigated by avoiding excess of activated DMSO, and performing a low temperature quenching. Very rarely, minor amounts of products are obtained, arising from reaction of secondary or primary alcohols[238] with $H_2C{=}S(+)$-Me. In variance with tertiary alcohols, which are quite hindered, secondary and primary alcohols are expected to be activated very quickly by reaction with activated DMSO. Therefore, no substantial amounts of free secondary or primary alcohols are expected to be present for reaction with $H_2C{=}S(+)$-Me during a properly performed Swern oxidation.



Ref. 238b

This is a rare case of methylthiomethylation of a primary alcohol during a Swern oxidation. A primary neopentilic alcohol, quite resistant to reaction, was treated under Swern conditions at the temperature of $-10°C$. At this temperature, a substantial decomposition of activated DMSO occurred during the activation of the alcohol, resulting in the formation of $H_2C{=}S(+)$-Me that produced the generation of the methylthiomethyl ether side compound.

2.7.4.5. Base-Induced Reactions

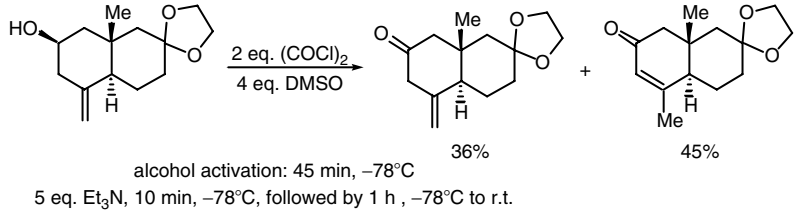
Addition of triethylamine to the activated alcohol, during a Swern oxidation, may produce side reactions, beginning with a deprotonation step. As triethylamine operates at very low temperature, only substrates very sensitive to deprotonation suffer these side reactions. No base-catalyzed hydrolyses are possible because of the absence of water.

The most common side-reactions induced by an initial deprotonation are:

- α-Epimerization of the aldehydes or ketones, resulting from the oxidation,
- Migration of alkenes into conjugation with the aldehydes or ketones, produced during the oxidation,
- Eliminations caused by the presence of a good-leaving group, present at the β-position of the resulting aldehyde or ketone.

α-Epimerization is very common when the aldehydes or ketones, obtained during the Swern oxidation, possess very acidic α-hydrogens; typically, when the α-position is substituted with an electron-withdrawing atom, such as an oxygen or a nitrogen. α-Epimerization can be mitigated by using a bulky base, such as Hünig's base instead of triethylamine, or by performing a low-temperature quenching (see page 146).

The Swern oxidation of homoallylic alcohols leads to a β,γ-unsaturated carbonyl compound, which sometimes suffers an *in situ* base-induced isomerization of the alkene into conjugation with the carbonyl group.[239]



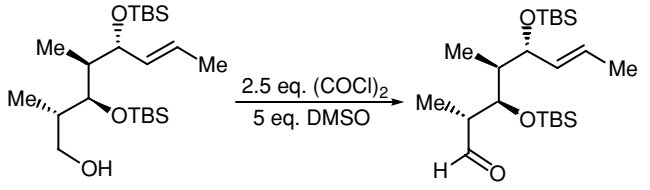
Ref. 239b

A partial migration of an alkene into conjugation with a ketone occurs during a Swern oxidation. The isomerization into conjugation can be purposefully brought about by treating the unconjugated product with DBU in CH_2Cl_2.

It must be mentioned that, most often, no migration of alkenes into conjugation happens during Swern oxidations of homoallylic alcohols.[240] Such migrations can be avoided using a hindered base, such as diisopropylethylamine, or performing a low-temperature quenching (see page 146).

Sometimes, when a Swern oxidation produces a carbonyl compound possessing a good-leaving group at the β-position, an *in situ* elimination occurs, resulting in the generation of a conjugated enone or enal.

Aldehydes and ketones, possessing tertiary alcohols,[241] halides,[209d] epoxides,[242, 243] and sulfonates[244] at the β-position, may suffer such elimination reactions. The use of more hindered or weaker bases than Et_3N (see page 146), and a low-temperature quenching[245] can help to avoid these eliminations.



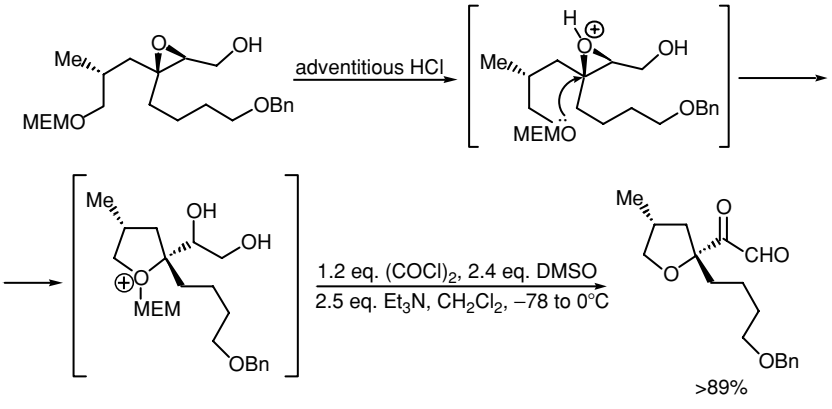
alcohol activation: 1 h, –78°C
7.6 eq. Et_3N, ca. 30 min, –78 to –23°C

Ref. 245

During this Swern oxidation, quenching is done at −23°C, rather than at room temperature, in order to avoid the elimination of a silyloxy group at the β-position of the resulting aldehyde.

2.7.4.6. Acid-Induced Reactions

During Swern oxidations, adventitious HCl may be present either due to the use of impure oxalyl chloride, or due to the hydrolysis of some chlorine-containing chemical, caused by employing wet DMSO. Adventitious HCl may cause acid-induced side reactions on sensitive substrates.[174,246]

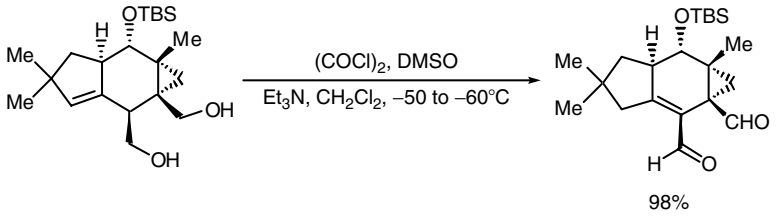


Ref. 246

Adventitious HCl causes the opening of the epoxide by intramolecular attack of a MEM ether. This can be avoided by using freshly distilled DMSO and oxalyl chloride.

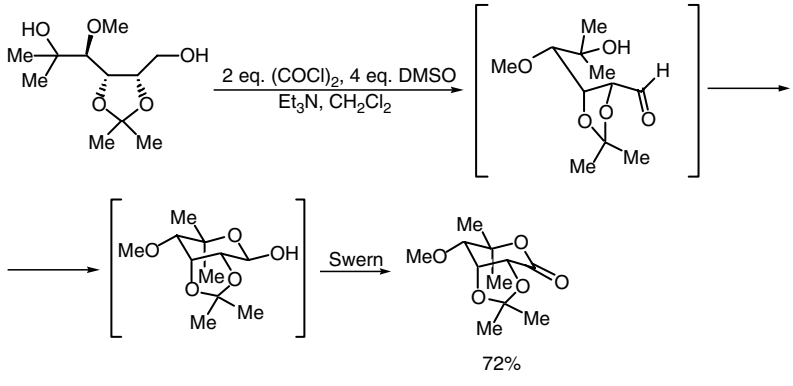
2.7.4.7. Formation of Lactones from Diols

The oxidation of 1,4- and 1,5-diols with many oxidants leads to intermediate hydroxycarbonyl compounds that equilibrate with lactols, which are transformed *in situ* into lactones. This side reaction is very uncommon during Swern oxidations, due to the sequential nature of alcohol activation versus base-induced transformation of the activated alcohol into a carbonyl compound. Thus, during the oxidation of a diol, normally when the first alcohol is transformed into an aldehyde or ketone, the second alcohol is already protected by activation, resulting in the impossibility of formation of a lactol that could lead to a lactone.



Ref. 239c
An eventful oxidation of a 1,4-diol into a dialdehyde occurs, with no interference by the formation of five-membered oxygen-containing products.

However, when one of the alcohols from the diol is a tertiary one—which, therefore, is difficult to protect by activation—formation of lactones is possible.[247]



Ref. 247c
This is a rare case in which a 1,5-diol is transformed into a lactone by a Swern oxidation. The oxidation of the primary alcohol into an aldehyde is followed by the formation of a lactol by attack of the tertiary alcohol. At this point, in spite of the presence of Et_3N, enough activated DMSO is present for the activation of the hydroxy group in the lactol and oxidation to lactone.

Section 2.7. References

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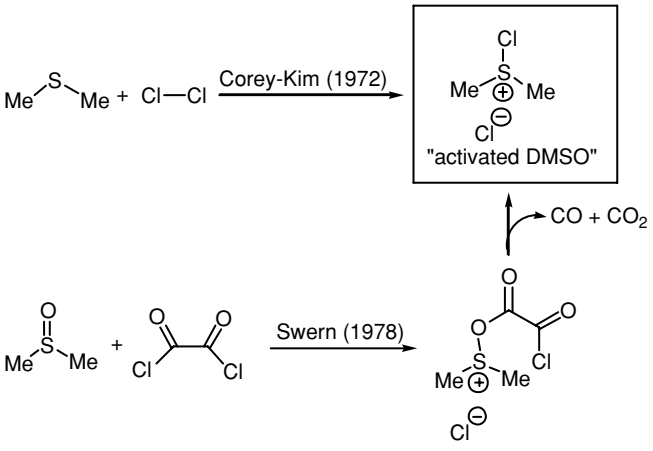
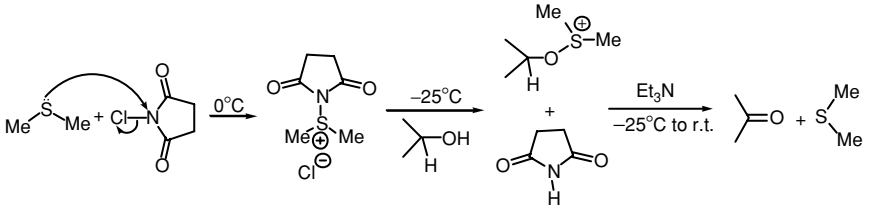
2.8. Corey–Kim Oxidation

In most Moffatt oxidations, ''activated DMSO'' is prepared by the ''activation'' of DMSO in a reaction with an electrophile. On the other hand, in a Corey–Kim oxidation, no DMSO is used in the preparation of ''activated DMSO'', which is obtained by oxidation of dimethyl sulfide.

Thus, Corey and Kim explained in 1972[248] that reaction of dimethyl sulfide with chlorine yields chlorodimethylsulfonium chloride, which is precisely the same species described later[249] as the ''activated DMSO'' species, generated during a Swern oxidation.



As operation with gaseous chlorine is dangerous and inconvenient, Corey–Kim oxidations are normally performed by oxidation of dimethyl sulfide with *N*-chlorosuccinimide rather than with chlorine. This results in the formation of a different kind of ''active DMSO'' species, in which a sulfur-nitrogen bond is present.



This species suffers displacement of a succinimido anion by reaction with an alcohol, resulting in the formation of activated alcohol that can evolve to a carbonyl compound by treatment with triethylamine.

> Interestingly, it is possible to employ diisopropyl sulfide in the place of dimethyl sulfide in Corey–Kim oxidations, in which case primary alcohols can be oxidized in the presence of secondary ones or vice versa, depending on reaction temperature.[250]
>
> Sometimes, better yields are obtained in Corey–Kim oxidations by using methyl phenyl sulfide in the place of dimethylsulfide, a result that can be related with the greater solubility of the sulfoxonium intermediate.[251]

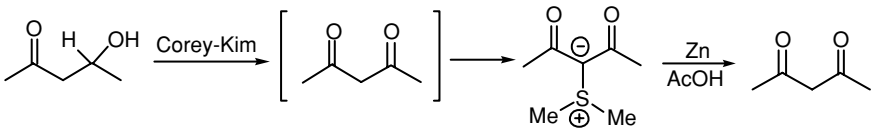
Although the Corey–Kim oxidation is not used as often as the Swern oxidation—probably because of the bad odour of dimethyl sulfide—it offers the advantage of allowing an operation above $-25^{\circ}C$. Typically, NCS (*N*-chlorosuccinimide) and Me_2S are mixed in toluene at $0^{\circ}C$, resulting in the formation of a precipitate of activated DMSO. The reaction mixture is cooled to ca. $-25^{\circ}C$ and the alcohol is added for activation. This is followed by addition of Et_3N and allowing the reaction to reach room temperature.

As in other Moffatt oxidations, a Corey–Kim oxidation may produce minor amounts of methylthiomethyl ethers. These can be minimized by using a solvent of low polarity, like toluene.[248a] Nonetheless, very often dichloromethane is used, because of its better solubilizing power. Almost always triethylamine is used as base.

Because of the high temperature employed in the activation of the alcohols, the Corey–Kim oxidation is not suitable for the oxidation of alcohols, derived from radicals able to stabilize carbocations—particularly allylic and dibenzylic alcohols. In such cases, the activated alcohol is attacked by the chloride anion, resulting in the formation of organic chlorides.[248a]

In fact, Corey–Kim conditions offer a good method for the regioselective transformation of allylic and benzylic alcohols into chlorides, in the presence of other alcohols.[252] The use of *N*-bromosuccinimide in spite of *N*-chlorosuccinimide, quite expectedly, allows the preparation of allylic and benzylic bromides. It must be mentioned that when the transformation of alcohols into chlorides is desired, the activated alcohol is allowed to decompose *in the absence* of triethylamine; whereas, when an oxidation is desired, triethylamine must be added as soon as the alcohol is activated. That is why, some benzylic alcohols can be efficiently oxidized under Corey–Kim conditions,[253] while others can be transformed into benzylic bromides with NBS and Me_2S.[252]

The Corey–Kim procedure is the oxidation method of choice for the transformation of β-hydroxycarbonyl compounds into 1,3-dicarbonyl compounds. Treatment of β-hydroxycarbonyl compounds under Corey–Kim conditions leads to an intermediate 1,3-dicarbonyl compound **33** that reacts *in situ* with activated DMSO, resulting in the generation of a stable sulfur ylide **34**. This sulfur compound can be transformed into the desired 1,3-dicarbonyl compound by reduction with zinc in acetic acid.[254]



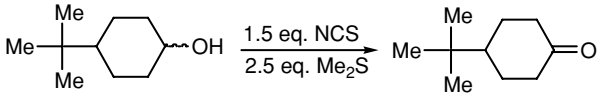
33 34

2.8.1. General Procedure for Oxidation of Alcohols Using Corey–Kim Method

From 2 to 5 equivalents of dimethyl sulfide (CAUTION STENCH, b.p. 38°C, MW = 62.13, d = 0.846) are added over a ca. 0.2–0.7 M solution of ca. 1.5–6.5 equivalents of *N*-chlorosuccinimide (MW = 133.53) in dry toluene[a] at 0°C. A white precipitate of activated DMSO is immediately formed. After ca. 10–30 min, the reaction temperature is lowered to ca. −40 to −20°C—typically −25°C (CCl_4-dry ice bath)—and 1 equivalent of alcohol is slowly added in a ca. 0.2–1.3 M solution in dry toluene.[b] After ca. 0.5–6 h—typically 2 h—, a ca. 2–6 M solution of ca. 1.2–22 equivalents of Et_3N in dry toluene is slowly added and the cooling bath is removed. Optionally, the reaction can be left standing at low temperature for ca. 10 min to 3 h before removing the cooling bath.

The reaction mixture is fractioned by addition of an organic solvent, such as Et_2O or CH_2Cl_2, and an aqueous solvent, like diluted HCl, 1 to 5% saturated $NaHCO_3$, water or brine. The organic phase is separated and optionally washed with water and/or brine. Finally, the organic phase is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a crude oxidation product that may need further purification.

[a] Other solvents like CH_2Cl_2 can be used for solubilizing purposes. More polar solvents facilitate the generation of undesired methylthiomethyl ethers.
[b] A slight exotherm will be generated.



90-93%

alcohol activation: 2 h, –25°C
15 eq. Et_3N, 5 min

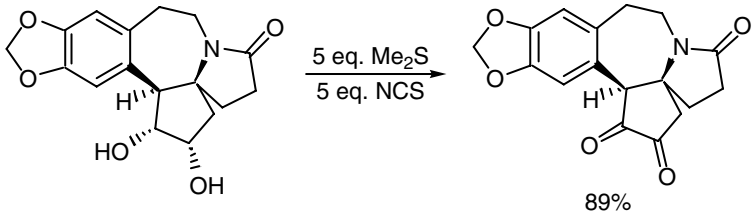
Ref. 255
A detailed description on a multigram scale is provided.[255]

62%

alcohol activation: 1.5 h, –25 °C
1.8 eq. Et_3N, 10 min

Ref. 256

This difficult substrate can be oxidized under Corey–Kim conditions with 62% yield, while other methods such as PCC, PDC, Swern or Jones provide less than 27% yield.

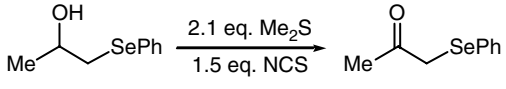


89%

alcohol activation: 1 h, –40°C
8 eq. Et_3N, 1.5 h, –40 to 20°C

Ref. 257

While PCC, Parikh–Doering, Swern or Omura–Sharma–Swern oxidations fail to give the desired diketone, the Corey–Kim method provides a 89% yield.



60%

alcohol activation: 6 h, –20°C
1.5 eq. Et_3N, 5 min

Ref. 258

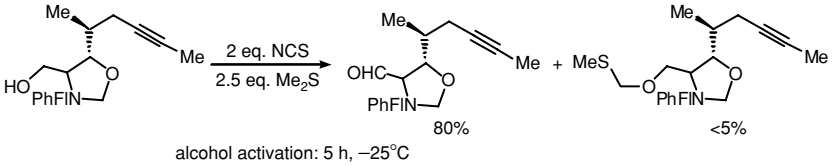
This oxidation on an apparently very simple substrate fails with PCC, PDC, DCC-DMSO and $(F_3C\text{-}CO)_2O$-DMSO, because of the high sensitivity of the selenium atom to suffer oxidation. On the other hand, a Corey–Kim oxidation delivers a 60% of the desired ketone.

2.8.2. Functional Group and Protecting Group Sensitivity to Corey–Kim Oxidations

As the Corey–Kim oxidation is carried out under almost neutral conditions at low temperature, most functional and protecting groups are expected to remain unaffected. As this method did not find exhaustive use in organic synthesis, no ample data are yet available.

2.8.3. Side Reactions

Similar to other Moffatt oxidations, the Corey–Kim method results sometimes in the generation of methylthiomethyl ethers by reaction of alcohols with $H_2C{=}S(+)$-Me, resulting from decomposition of activated DMSO.[259]



Ref. 259b
Less than 5% methylthiomethylation of the alcohol occurs, while the desired ketone is obtained in 80%.

Because of the action of Et_3N on the activated alcohol, some side reactions—beginning with a deprotonation—can happen in sensitive substrates. For example, α-epimerization of sensitive aldehydes and ketones,[260] and migration of alkenes into conjugation with carbonyl groups[261] are occasionally found.

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2.9. Other Alcohol Oxidations Using Activated DMSO

Almost any electrophile, able to react with DMSO, can generate an "active DMSO" species that can be used for the oxidation of alcohols. Dozens of such activators have been described in the literature as shown in Table 2.2. Many of these activators have been the subject of very superficial analyses and, therefore, their potential for Moffatt oxidation of alcohols is not known in detail. Some of these activators—particularly

Table 2.2. Less Commonly Used Electrophiles for the Activation of DMSO

Reagent	Abbrev. or Formulae	Observations
Benzoic anhydride	Bz_2O	Briefly mentioned by Albright[268] as an efficient substitute of Ac_2O
Methanesulfonic anhydride	Ms_2O	Briefly mentioned by Swern[269] and Albright,[268] it delivers from good to excellent yields at $-20^{\circ}C$
p-Toluenesulfonic anhydride	Ts_2O	Briefly mentioned by Albright[268] who reports high yields at $-20^{\circ}C$
Trifluoromethane sulfonic anhydride	Tf_2O	Briefly mentioned by Hendrickson and Schwartzman[270]
Methyl chloroglyoxylate	$CH_3OC(O)C(O)Cl$	Described as efficient, but with no particular advantages over oxalyl chloride[271]
Thionyl chloride	$SOCl_2$	Briefly mentioned by Swern,[269] it provides good to excellent yields at $-60^{\circ}C$
Diphosgene, trichloromethyl chloroformate	$Cl_3COC(O)Cl$	Reported as an alternative to the use of oxalyl chloride with the advantage of being a dense liquid with low volatility[262]

(*Continued*)

Table 2.2. Less Common by Used Electrophiles for the Activation of DMSO—Cont'd

Triphosgene	$(Cl_3CO)_2CO$	White crystalline solid reported as a safe alternative to oxalyl chloride, suitable for large-scale operations[263]
Methanesulfonyl chloride	MsCl	Briefly mentioned by Albright[268] and Swern,[269] Albright reports a slow reaction at −20°C; according to Swern, it provides good yields at room temperature
p-Toluenesulfonyl chloride	TsCl	Briefly mentioned by Albright[268] and Swern,[269] it gives from good to excellent yields between −20 and 5°C
Benzenesulfonyl chloride	BsCl	Briefly mentioned by Albright[268] giving good yield in one oxidation
Cyanuric chloride		Briefly mentioned by Albright[268] and Swern,[269] this surprisingly little used activator is inexpensive and delivers easily elaborated water-soluble salts[272]
Trichloroacetonitrile	$Cl_3C-C\equiv N$	Briefly mentioned by Moffatt[273] as giving a modest yield at room temperature
2-Chloro-1,3-dimethylimidazolinium chloride	DMC	It provides excellent yields in the oxidation of secondary alcohols,[264] and tends to produce chlorination of primary alcohols
Polyphosphoric acid		Briefly mentioned by Albright[268] as a substitute of Ac_2O
Phosphorous trichloride	PCl_3	Briefly mentioned by Swern,[269] it provides from modest to excellent yields at −30°C
Triphenylphosphine dichloride	$Ph_3P{\cdot}Cl_2$	Reported as an alternative to oxalyl chloride, providing from good to excellent yields at −78°C[266]
Triphenylphosphine dibromide	$Ph_3P{\cdot}Br_2$	Reported as an alternative to oxalyl chloride with properties closely resembling $Ph_3P{\cdot}Cl_2$[266]
Phosphorous oxychloride	$POCl_3$	Briefly mentioned by Swern,[269] it provides from modest to excellent yields at −30°C
Acetyl chloride	AcCl	Briefly mentioned by Swern,[269] it provides modest yields at −20°C
Benzoyl chloride	BzCl	Briefly mentioned by Swern,[269] it provides from poor to excellent yields at −20°C
Acetyl bromide	AcBr	Briefly mentioned by Swern,[269] it provides from modest to excellent yields at −60°C
Phenyl dichlorophosphate	$PhOP(O)Cl_2$	It provides from good to excellent yields in oxidations performed from −10°C to room temperature[267]
Diphenyl chlorophosphate	$(PhO)_2P(O)Cl$	Briefly mentioned by Liu and Nyangulu[267a] as a less satisfactory activator than phenyl dichlorophosphate

Diethyl chlorophosphate	$(EtO)_2P(O)Cl$	Briefly mentioned by Liu and Nyangulu[267a] as a less satisfactory activator than phenyl dichlorophosphate
Ethoxyacetylene	$EtO-C \equiv C-H$	Briefly mentioned by Albright[268,274]

oxalyl chloride, which is used in the ubiquitous Swern oxidation—are frequently used in Moffatt oxidations, and have already been described in this book.

Table 2.2. lists activators used less commonly for Moffatt oxidations. The following activators, namely diphosgene,[262] triphosgene,[263] 2-chloro-1,3-dimethylimidazolinium chloride,[264] 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate,[265] triphenylphosphine dibromide and dichloride,[266] and phenyl dichlorophosphate,[267] have been the subject of scientific monographs, in which they are proposed as suitable and convenient alternatives to more routinely used activators, and can offer improved oxidation conditions in some substrates.

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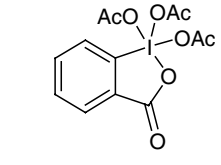
3

Hypervalent Iodine Compounds

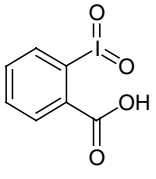
3.1. Introduction

Iodine compounds in a high valence state behave as strong oxidants[1] and, therefore, are good candidates for the oxidation of alcohols. Nevertheless, its use in organic synthesis has been very limited due to its general lack of stability and poor solubility in most organic solvents. The fate of hypervalent iodine compounds in the oxidation of alcohols changed dramatically in 1983 by a landmark publication[2] of Dess and Martin, in which they showed that the hypervalent iodine compound **35**—nowadays known as Dess-Martin periodinane—is able to transform alcohols into aldehydes and ketones in an extraordinary effective manner. Contrary to other hypervalent iodine compounds, Dess-Martin periodinane **(35)** is a stable compound with a high solubility in most organic solvents.

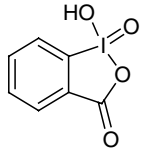
A few years later,[3] it was shown that *o*-iodoxybenzoic acid **(36)**—itself a precursor in the preparation of Dess-Martin periodinane—is able to oxidize very effectively alcohols in DMSO solution. *o*-Iodoxybenzoic acid—normally referred to as IBX—exists mainly as a cyclic form **37**, which crystallizes as a polymer with very low solubility in most solvents with the exception of DMSO. Although, IBX **(36)** was already known in 1893,[4] this ultracentenial reagent found very little use till very recently, when awareness about its solubility in DMSO was raised.



Dess-Martin periodinane **(35)**



o-iodoxybenzoic acid (IBX) **(36)**



37

Section 3.1. References

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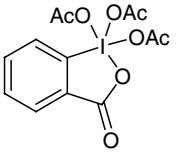
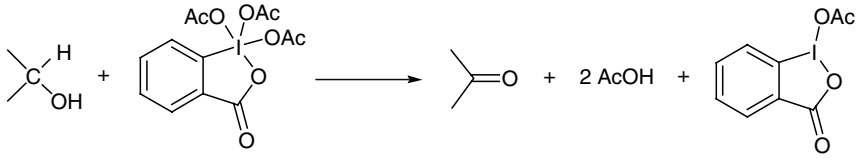
3.2. Dess-Martin Periodinane



In 1983, Dess and Martin published[2] the preparation of the hypervalent iodine compound **35**—Dess-Martin periodinane (DMP)—by treatment of *o*-iodoxybenzoic acid **(36)** with acetic anhydride and acetic acid. This high valent iodine compound, due to the presence of the iodine atom inside a stable five-membered ring and surrounded by organic residues, is very soluble in many organic solvents and possesses a high kinetic stability. It has a very long lifetime under inert atmosphere at room temperature and can be handled in the air with little decomposition due to humidity.

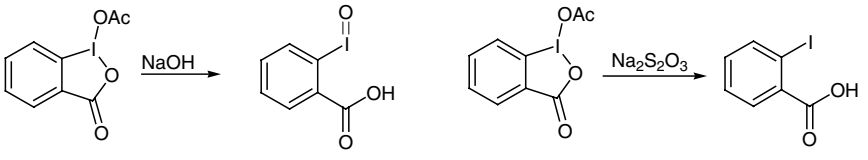
In the foundational paper of Dess-Martin periodinane,[2] it was shown that this compound is very efficient in the oxidation of alcohols in dichloromethane solution at room temperature. While the alcohols are oxidized to the corresponding aldehydes and ketones, Dess-Martin periodinane is transformed into the organic iodinane **38** and acetic acid.



38

Side reactions caused by the acidic nature of acetic acid can be prevented by the addition of a base, such as pyridine or sodium bicarbonate. The periodinane **38** can be removed either by:

- Hydrolysis with 1.3 M NaOH, resulting in *o*-iodosobenzoic acid **(39)** that can be separated by washing with an aqueous sodium bicarbonate solution.
- Treatment with sodium thiosulfate, resulting in reduction to 2-iodobenzoic acid that can be removed by washing with an aqueous sodium bicarbonate solution.



38 *o*-iodosobenzoic acid **(39)** **38** *o*-iodobenzoic acid

It is possible to eliminate very efficiently the by-products derived from Dess-Martin periodinane as well as excess of reagent by a sequential treatment with a thiosulfate-containing resin, followed by a base-functionalized resin. This procedure is very amenable for automation work-ups.[111d]

The *o*-iodosobenzoic or *o*-iodobenzoic acids, recovered from the work-up of oxidations with Dess-Martin periodinane, can be recycled back to this oxidant by oxidation to IBX, followed by transformation of IBX into Dess-Martin periodinane.[2]

It is possible to perform an oxidation with Dess-Martin periodinane under almost neutral conditions by adding pyridine to the reaction flask in order to neutralize the acetic acid, which is generated during the oxidation, and performing the work-up by treatment with sodium thiosulfate in the presence of a sodium bicarbonate buffer.[2]

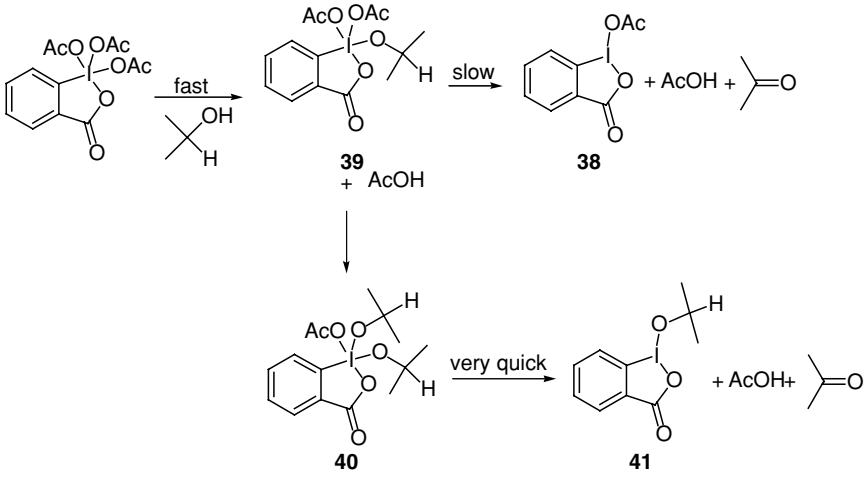
Although the unique effectiveness of Dess-Martin periodinane in the oxidation of complex alcohols was recognized very soon, initially great difficulties were encountered in the preparation of good samples of this reagent. Thus, many researchers were not able to complete the peracetylation of IBX—needed for the preparation of Dess-Martin periodinane—by treatment with acetic anhydride and acetic acid at 85°C as described by Dess and Martin.[2,5] A number of experimental modifications was suggested,[6] culminating in a very detailed description published in the Organic Syntheses journal.[7]

The experimental difficulties were greatly clarified by the discovery of Stevenson *et al*. that IBX can exist in two crystalline forms[8] of very different solubility. Thus, IBX can be present either as a microcrystalline powder in which each microcrystal contains a racemate of IBX that dissolves readily, or as a conglomerate of microscopic crystals of optically active IBX, possessing very slow kinetics for solubilization. During the preparation of IBX, normally a mixture of both crystalline forms is obtained, whose proportion depends on experimental details, like stirring speed, which are difficult to reproduce. As expected, optimum yields of Dess-Martin periodinane are obtained starting from IBX present as the better soluble microcrystalline form. This form can be secured by dissolving IBX in aqueous NaOH and precipitating it by bringing rapidly the pH to 1 by addition of hydrochloric acid.[8]

WARNING:DESS-MARTIN PERIODINANE IS AN EXPLOSIVE COMPOUND. An explosion has been reported during an operation with Dess-Martin periodinane.[9] Although pure Dess-Martin periodinane seems to be refractory to explosion[2] and the explosive properties of this compound

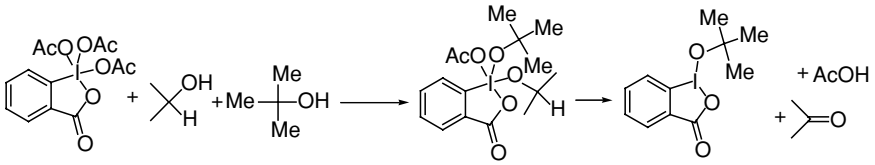
have been attributed to the presence of impurities, Dess-Martin periodinane produces an exotherm during decomposition due to heat;[7] therefore, care must be taken during its handling.

The available ^{1}H-NMR and kinetic data[2,5] regarding oxidation of alcohols with Dess-Martin periodinane are consistent with a mechanism involving the initial displacement of an acetate from Dess-Martin reagent by an alcohol molecule, resulting in the rapid formation of intermediate **39**. This intermediate **39** can evolve very slowly generating the desired carbonyl compound, acetic acid and the monoacetoxyiodinane **(38)**. On the other hand—in the presence of excess of alcohol—two acetoxy ligands can be substituted by two alcohols, resulting in the formation of the intermediate bisalkoxyiodinane **40** that evolves very quickly to the alkoxyiodinane **41**, acetic acid and the desired carbonyl compound.



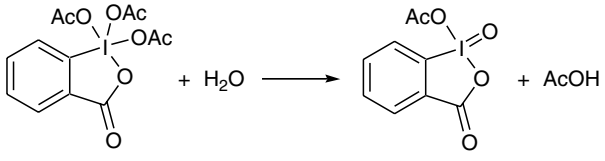
A corollary of this mechanism is that using excess of Dess-Martin periodinane can, in fact, produce a decrease in the speed of the oxidation, while an excess of alcohol causes an acceleration. On the other hand, using excess of alcohol, while providing an acceleration of the oxidation, may produce a decrease in the yield of the carbonyl compound because some of the alcohol is consumed in the generation of the alkoxyperiodinane **(41)**, rather than suffering the desired transformation into the carbonyl compound. This problem can be by-passed by the addition of *tert*-butyl alcohol to the reaction medium.[2] This non-oxidizable alcohol causes an acceleration of the reaction via the formation of the bisalkoxyperiodinane **(42)** that evolves very quickly to the *t*-butoxyperiodinane **(43)**, acetic acid and the desired carbonyl compound. It must be mentioned that when *tert*-butyl alcohol is used for the

acceleration of Dess-Martin periodinane oxidation, it may be necessary to separate the *t*-butoxyperiodinane **(43)** by chromatographic means because this compound is resistant to decomposition by either aqueous base or sodium thiosulfate.



42 **43**

Initially, the use of Dess-Martin periodinane in the oxidation of alcohols was plagued with reproducibility problems and puzzling reports claiming that better yields were obtained using old batches of impure material or performing the oxidation with no exclusion of moisture, something very odd considering that Dess-Martin periodinane is moisture sensitive. Similarly, while Dess and Martin reported that their name-reagent was perfectly soluble in most organic solvents, other authors claimed that they were not able to get clear solutions of Dess-Martin periodinane in organic solvents; although that operated satisfactorily during oxidations.[2,10] This confusing state of affairs was clarified in 1994 by Meyer and Schreiber,[6d] in a very elegant paper, in which they proved that reaction of Dess-Martin periodinane with water results in the formation of the acetoxyiodinane oxide **(44)**, that is able to oxidize alcohols much quicker and efficiently that Dess-Martin periodinane.



44

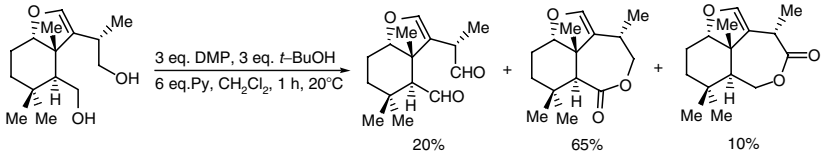
Thus, impure samples of Dess-Martin periodinane containing **44** because of partial hydrolysis of Dess-Martin reagent or incomplete acetylation during its preparation can in fact perform much better during the oxidation of alcohols than very pure samples of Dess-Martin periodinane. Likewise, performing the oxidation in the air or using wet solvents may result in better yields because of the *in situ* generation of periodinane **44**.

For the sake of consistency in the experiments, rather than recommending careless experimental techniques or using impure samples of Dess-Martin periodinane, Meyer and Schreiber suggested modifying the protocol

of the Dess-Martin oxidation, whereby a controlled amount of water is added to the reaction mixture containing a pure sample of Dess-Martin periodinane. This allows the *in situ* generation of the highly reactive periodinane **44** that otherwise is difficult to isolate and store as an effective reagent.

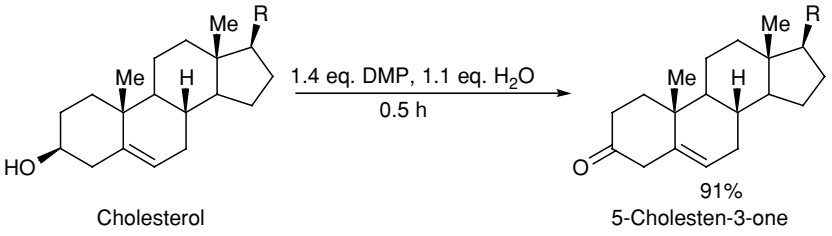
Normally, Dess-Martin oxidations are carried out in CH_2Cl_2, although it succeeds in almost any organic solvent including $PhCF_3$,[11] $CHCl_3$,[12] benzene,[13] toluene,[14] DMSO,[15] DMF,[16] THF,[17] EtOAc[18] and acetonitrile.[19] It is usually performed at room temperature, although it can be carried out at 0°C[20] or higher than room temperature.[21] It must be mentioned that using a high temperature increases the risk of functional groups other than alcohols suffering oxidation.[22]

In order to neutralize the acetic acid produced during the oxidation, very often, sodium bicarbonate[23] or pyridine[24] are added; other bases, like sodium acetate[25] or 2,6-lutidine are less commonly used.[26] Often, water,[27] *tert*-butyl alcohol[28] or trifluoroacetic acid[29] are added in order to accelerate the reaction. Sometimes, the inclusion of water is made in a quite uncontrolled manner by using a "wet" solvent[30] containing an undisclosed amount of water, or by running the reaction unprotected by a blanket of an inert gas.[31] Better reproducibility is expected when a precise amount of water is added to a dry solvent. While one equivalent of water converts Dess-Martin periodinane in the periodinane **44**, which is a better oxidant, adding excess of water may cause the inactivation of all periodinane species able to oxidize alcohols. Performing the oxidation "in the air" is a particularly irreproducible technique because the amount of added water depends on parameters, such as atmospheric humidity, which are difficult to control. Meyer and Schreiber[6d] showed that in a given experiment, while a 20% atmospheric humidity provided enough water to accelerate the reaction, a 75% humidity caused the quick destruction of any oxidizing agent.



Ref. 32

The oxidation of this diol to the corresponding dialdehyde is very difficult due to the tendency to result in two isomeric lactones, via the corresponding intermediate lactols formed from the partially oxidized starting diol. In fact, common oxidants such as Swern, PCC, TPAP or $SO_3 \cdot Py$ do not deliver the desired dialdehyde. After considerable experimentation, it was found that performing the Dess-Martin oxidation in the presence of *t*-BuOH as accelerant and pyridine as acetic acid neutralizer, it was possible to obtain a modest 20% yield of the desired dialdehyde.



Cholesterol

5-Cholesten-3-one

Ref. 6d

In the absence of water, the reaction lasts 8.5 h instead of 0.5 h and the yield is lowered from 91 to 78%. The reaction without water is also less clean due to decomposition of the product under the prolonged reaction time.

3.2.1. General Procedure for Oxidation of Alcohols Using Dess-Martin Periodinane

A ca. 0.05–0.35 M solution of the alcohol[a] in dry[b] CH_2Cl_2,[c] containing 1 to 5 equivalents—typically 1.5 eq.—of Dess-Martin periodinane[d] (MW = 424.14; WARNING: this oxidant can explode) is stirred[e] at room temperature[f] till most of the starting compound is consumed. For a quicker reaction, the following accelerants can be added: water (ca. 1–1.2 eq.), *tert*-butyl alcohol (ca. 0.7–1.5 eq.) or trifluoroacetic acid (ca. 1.5–3 eq.). The possible deleterious effect of acetic acid produced during the oxidation can be prevented by the addition of ca. 10–15 eq. of $NaHCO_3$ or ca. 2.5–3.5 eq. of pyridine. The work-up can be made according to four alternative protocols:

Work-up A: Thiosulfate work-up

In this work-up, the periodinane species **38**[g], resulting from the reduction of Dess-Martin periodinane, is further reduced with sodium thiosulfate to *o*-iodobenzoic acid[h] that is removed with a sodium bicarbonate aqueous solution. The treatment with sodium thiosulfate is normally made in the presence of sodium bicarbonate as buffer. This is the most common work-up because it is done under almost neutral conditions and the organic periodinane **38** is destroyed; thus, avoiding a possible difficult chromatographic separation from the product. The *o*-iodobenzoic acid can be recycled back to Dess-Martin periodinane by oxidation.

The volume of the reaction mixture is normally increased by the addition of an organic solvent, consisting normally in Et_2O and less often in CH_2Cl_2 or EtOAc. An aqueous solution containing sodium thiosulfate (ca. 100–158 g/L, $Na_2S_2O_3$) and $NaHCO_3$ (ca. 100 g/L-saturated) is added and the resulting mixture is stirred for ca. 10–15 min. The organic

phase is separated, dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that may need further purification. Optionally, the organic phase may be washed with water and brine before drying.

Work-up B: Sodium hydroxide work-up

In this work-up, the periodinane species **38**[g]—resulting from the reduction of Dess-Martin periodinane—is hydrolyzed to *o*-iodosobenzoic acid,[i] which is removed in the basic aqueous solution that is used for hydrolysis. This work-up is suitable for substrates that are not sensitive to aqueous base.

Diethyl ether and aqueous NaOH (ca. 0.5–1 N) are added to the reaction flask. The resulting mixture is stirred during ca. 10–15 min. The organic phase is separated, dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that may need further purification. Optionally, the organic phase may be washed with water and brine before drying.

Work-up C: Simple washing with an aqueous solution

In this work-up, no effort is made to separate the periodinane species **38** using chemical means. Normally, the separation is performed by chromatography.

The reaction mixture is washed with an aqueous phase, such as saturated aqueous NH_4Cl or saturated aqueous $NaHCO_3$. Optionally, solids suspended in the reaction mixture can be filtered before the aqueous washing. The addition of an organic solvent such as Et_2O or CH_2Cl_2 may facilitate the washings. The organic phase is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that needs further purification because of the presence of periodinane **38**.

Work-up D: Non-aqueous work-up

As in work-up C, in this work-up, the periodinane **38** is not removed by chemical means. Therefore, it must be separated from the crude at a later stage.

The reaction mixture is filtered through a pad of silica gel, Florisil® or Celite®. The addition of an organic solvent such as Et_2O may facilitate the operation. The filtered solution is concentrated, giving a crude that needs further purification because of the presence of periodinane **38**.

[a] The alcohol can be added—either neat or in solution—to a solution of Dess-Martin periodinane in CH_2Cl_2 or vice versa. The mixing may result in a copious evolution of heat, therefore—particularly on multigram scale—, it may be advisable to perform the mixing slowly, so as to allow for the dissipation of heat, or to cool down the reaction.

[b] Sometimes, wet CH_2Cl_2 is purposefully used in order to accelerate the reaction due to its water content. It must be mentioned that an optimum acceleration is achieved with 1

equivalent of water, and using a wet solvent of unknown water content may result in irreproducible reactions.

[c] Many other aprotic organic solvents of very variable polarity, including $PhCF_3$, $CHCl_3$, benzene, DMSO, DMF, THF, EtOAc and acetonitrile, have been successfully employed in this oxidation.

[d] Pure Dess-Martin periodinane is perfectly soluble in CH_2Cl_2. Partially hydrolyzed samples contain impurities that are not soluble. These partially hydrolyzed samples may, in fact, lead to quicker oxidations. However, the use of Dess-Martin periodinane samples with an unknown extent of decomposition due to hydrolysis is not recommended because this may lead to irreproducible results. Likewise, it is recommended that Dess-Martin periodinane be handled under maximum exclusion of water for the sake of better oxidation reproducibility. Dess-Martin periodinane shows the following spectroscopic data:[5] ^{1}H-NMR ($CDCl_3$, δ): 8.31 (d, J = 8.5 Hz), 8.29 (d, J = 8.5 Hz), 8.07 (t, J = 8.5 and 7.3 Hz), 7.80 (t, J = 8.5 and 7.3 Hz), 2.33 (s) and 2.01 (s); ^{13}C-NMR ($CDCl_3$, δ): 175.7, 174.0, 166.1, 142.4, 135.8, 133.8, 131.8, 126.5, 126.0, 20.4 and 20.3.

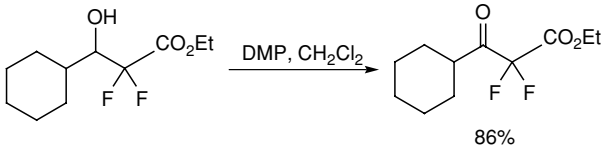
[e] Sometimes, the reaction is performed in the air in order to allow atmospheric humidity to enter into the reaction; therefore, causing an acceleration due to the presence of water. An optimum acceleration is caused by 1 equivalent of water and the quantity of water entering from the air varies greatly depending on experimental factors, such as atmospheric water content, which are very difficult to control. Therefore, it is advisable to run the reaction under a blanket of an inert gas—adding, if desired, a controlled amount of water—rather than in the air.

[f] Sometimes, the reaction is run at 0°C. Very rarely, the reaction is performed at a temperature slightly higher than room temperature—ca. 40–55°C—in order to get some acceleration on refractory substrates.

[g] Periodinane species **38** shows the following ^{1}H-NMR ($CDCl_3$, 300 MHz, δ): 8.25 (dd, J = 7.5 and 1.2 Hz), 8.00 (d, J = 8.1 Hz), 7.92 (dt, J = 7.4 and 1.5 Hz), 7.71 (dt, J = 7.8 and 0.9 Hz) and 2.26 (s).

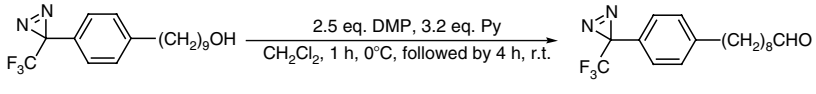
[h] *o*-Iodobenzoic acid (IB) shows the following ^{1}H-NMR (H_2O/*t*-BuOH 7:3 v/v, 400 MHz, δ): 7.87 (d), 7.42 (t), 7.40 (d), 7.10 (td).[33]

[I] *o*-Iodosobenzoic acid (IBA) shows the following ^{1}H-NMR (H_2O/*t*-BuOH 7:3 v/v, 400 MHz, δ): 8.19 (dd), 7.98 (td), 7.89 (d), 7.75 (t).[33]



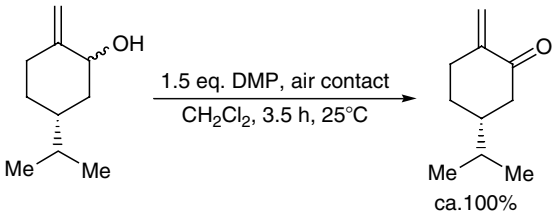
Ref. 34

A Dess-Martin oxidation on a multigram scale is described with precise experimental details.



Ref. 24c

This alcohol containing a very sensitive diazirine moiety can be efficiently oxidized with DMP, while other oxidants like Swern, MnO_2, PCC, PDC and CAN were not successful.



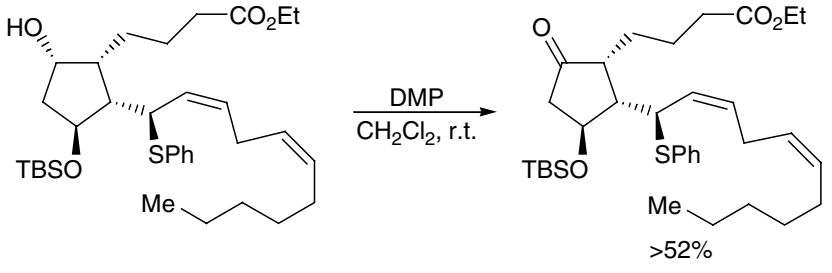
Ref. 31

Obtaining this enone is very difficult because of its tendency to dimerize via a hetero-Diels-Alder reaction. Dess-Martin periodinane provides a quantitative yield, while Ag_2O, Swern or TPAP are much less efficient.

3.2.2. Functional Group and Protecting Group Sensitivity to Dess-Martin Oxidation

According to Dess and Martin,[5] Dess-Martin periodinane reacts slowly with sulfides at room temperature to give complex unidentified products. Nonetheless, as the oxidation of sulfides is slow, normally it is possible to oxidize alcohols in the presence of sulfides.[35]

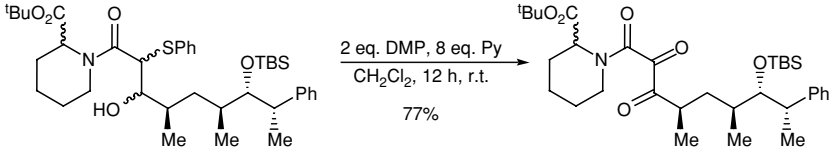
Sometimes, the presence of sulfides causes a decrease in the yield of the oxidation of alcohols with DMP.[36]



Ref. 35a

The presence of a phenyl sulfide causes no interference with the oxidation of the alcohol with Dess-Martin periodinane.

On the other hand, the oxidation of some sulfides with Dess-Martin periodinane provides an unique way to prepare some 1,2,3-tricarbonyl compounds, which are very difficult to obtain.[37]

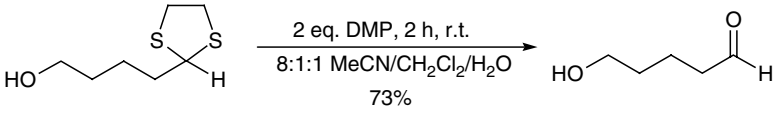


Ref. 37

Both the alcohol and the sulfide are oxidized by Dess-Martin periodinane, resulting in a 1,2,3-tricarbonyl compound that is very difficult to obtain by other means.

1,2,3-Tricarbonyl compounds can also be obtained by treatment of β–hydroxycarbonyl compounds—without a sulfur atom at the α−position—with Dess-Martin periodinane.[38]

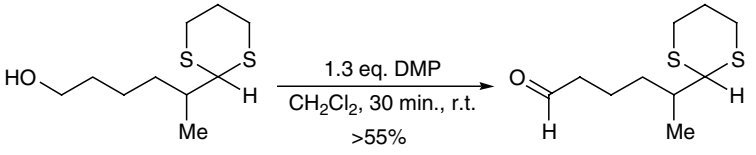
According to Panek *et al.*,[39] thioacetals are hydrolyzed under the action of Dess-Martin periodinane, being possible to perform a selective hydrolysis without affecting an alcohol present in the same molecule. Reaction conditions optimized for the thioacetal hydrolysis involve the use of Dess-Martin periodinane in a $MeCN/CH_2Cl_2/H_2O$ (8:1:1) solvent mixture. Under these conditions, Dess-Martin periodinane behaves as a very efficient reagent for the hydrolysis of thioacetals in complex substrates.



Ref. 39

The alcohol remains unaltered during the hydrolysis of the dithioacetal using Dess-Martin periodinane.

Quite puzzlingly, other authors report the selective oxidation of alcohols in the presence of dithioacetals.[40]

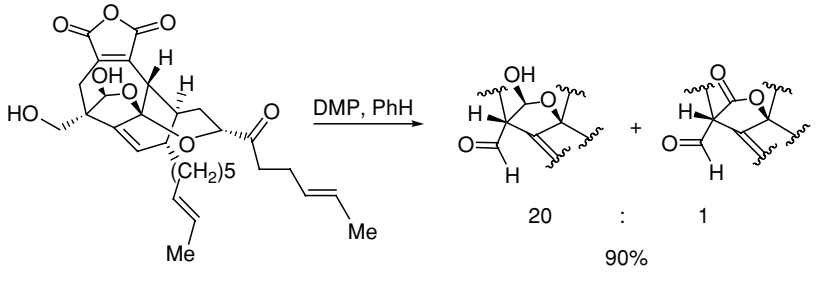


Ref. 40a

The alcohol is selectively oxidized with Dess-Martin periodinane with no interference from the dithioacetal.

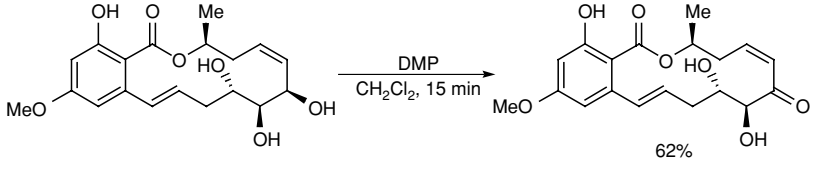
These diverse results can be explained either by the variability of the substrates, or by the influence of minor experimental modifications. Particularly, dichloromethane is the solvent used wherever an alcohol is selectively oxidized, while acetonitrile is the main solvent when a selective dithioacetal hydrolysis is achieved. The presence of water in the reaction media seems to play no role as a selective dithioacetal hydrolysis can be observed under anhydrous reaction conditions after an aqueous work-up.[39]

Dess-Martin periodinane oxidizes lactols to lactones.[41] In molecules containing both an alcohol and a lactol, sometimes it is possible to perform a selective oxidation of the alcohol in the presence of a lactol.[13] Although, a case is known in which this selectivity is reversed and a lactol is oxidized to the corresponding lactone, while an alcohol in the same molecule remains unaffected.[42]



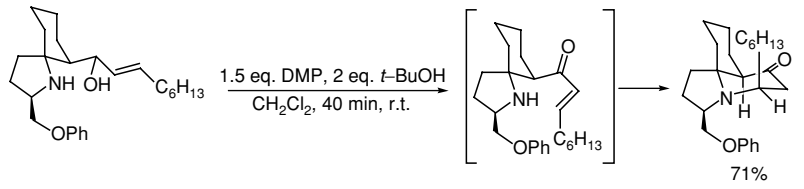
Ref. 13
An alcohol is oxidized with Dess-Martin periodinane, while a lactol remains mostly unaffected.

The Dess-Martin periodinane oxidation of alcohols can be carried out in the presence of free phenols.[43]



Ref. 43a
One of the alcohols is selectively oxidized in the presence of a free phenol.

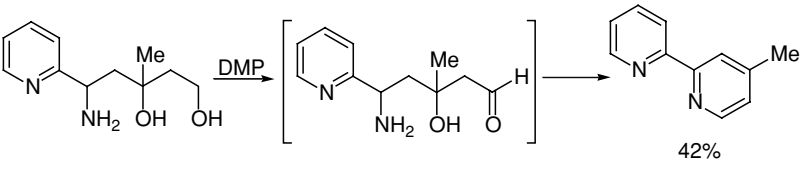
Alcohols can be oxidized in the presence of tertiary[44] or secondary[45] amines. Sometimes, the secondary amines react intramolecularly *in situ* with the functionality resulting from the oxidation of the alcohol.[46]



Ref. 46

A secondary amine remains unaffected, while an alcohol is oxidized with Dess-Martin periodinane. Eventually, the enone, resulting from the oxidation of the alcohol, suffers an *in situ* conjugated attack by the amine.

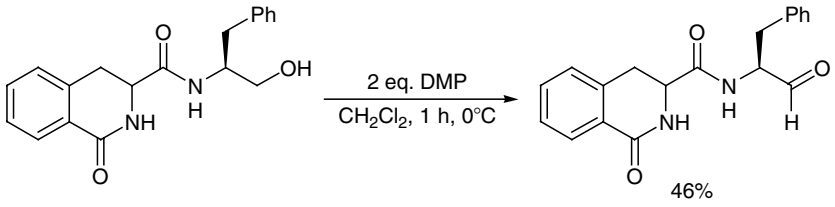
Dess and Martin reported that their name reagent reacts with primary amines giving insoluble products, which are difficult to analyze. Nevertheless, there are several reports of oxidation of alcohols, in which primary aromatic amines remain unaffected.[47] In these cases, when an aldehyde is obtained, sometimes it is attacked by the amine, resulting in the formation of nitrogen heterocycles.[48] There is one report[49] in which an alcohol is oxidized to an aldehyde in the presence of a primary aliphatic amine that reacts *in situ* with the aldehyde.



Ref. 49

Dess-Martin periodinane oxidizes the alcohol without affecting the primary aliphatic amine, which reacts *in situ* with the intermediate aldehyde, resulting in the formation of a new pyridine ring.

Aromatic amides react with Dess-Martin periodinane, resulting in the formation of quinones[50] and azaquinones.[51] These reactions were thoroughly studied by Nicolaou *et al.*, who proved that the resulting azaquinones can be trapped *in situ*, resulting in highly stereoselective construction of skeletons of complex natural products.[52] Normally, Dess-Martin periodinane reacts with aromatic amides at temperatures higher than room temperature. Although, sometimes such reactions occur at room temperature, reaction of Dess-Martin periodinane with alcohols is quicker, and alcohols can be selectively oxidized in the presence of both aromatic[53] and aliphatic[54] amides in the same molecule.



Ref. 53c

The selective oxidation of the alcohol with Dess-Martin periodinane succeeds, in spite of the presence of the amides that react slower.

Oximes are hydrolyzed to aldehydes and ketones with Dess-Martin periodinane in wet CH_2Cl_2. This reaction competes with the oxidation of alcohols, so that selective oxime hydrolyses can be performed in the presence of alcohols.[55] However, *O*-alkyloximes remain unaffected during the oxidation of alcohols.[56]

Normally, nitrocompounds resist[57] the action of Dess-Martin reagent. However, there is one report in which a nitroalcohol is transformed into a lactone, thanks to a very easy intramolecular interaction between the nitro group and the alcohol.[58]

N-Acylhydroxylamines are oxidized to the interesting intermediates acylnitroso compounds by the action of Dess-Martin periodinane.[59]

Dess-Martin periodinane is a sufficiently mild reagent that is very rare for protecting groups to be removed. Protecting groups possessing a very high sensitivity to oxidation, such as *p*-methoxybenzyl[60] and *m,p*-dimethoxybenzyl[61] ethers, and protecting groups with a high sensitivity to acids, such as THP ethers,[62] trityl ethers[63] and TMS ethers,[64] can resist the action of Dess-Martin periodinane.

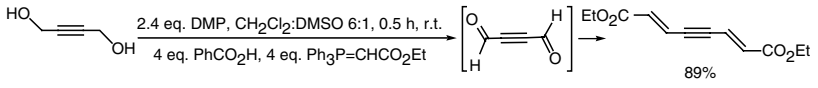
> However, there is one report of partial hydrolysis of a TIPS ether promoted by the acidity of Dess-Martin periodinane.[106a]
>
> Dess-Martin periodinane supported on silica is able to perform the direct transformation of TMS ethers to aldehydes and ketones.[65]

Alkenes can be transformed into epoxides by reaction with Ac-IBX **(44)**, generated by reaction of Dess-Martin periodinane with water.[50b] As the oxidation of alcohols is quicker, it is normally possible to oxidize alcohols with no interference from alkenes.

3.2.3. Reactions Performed *in situ* During Dess-Martin Oxidation

It is possible to perform Dess-Martin oxidations of alcohols in the presence of stabilized phosphoranes or phosphonates.[66] The aldehydes and ketones resulting from the oxidation—when reactive enough—can interact

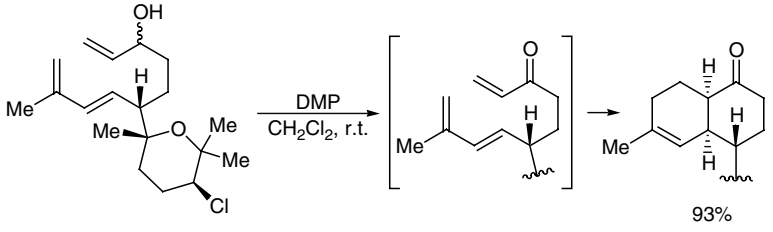
with the phosphorous compounds yielding alkenes in a one-pot reaction. This operation involving the *in situ* generation of aldehydes or ketones, which will react in a Wittig or a Wittig-Horner reaction, is particularly useful when the intermediate aldehydes or ketones are unstable.



Ref. 15a

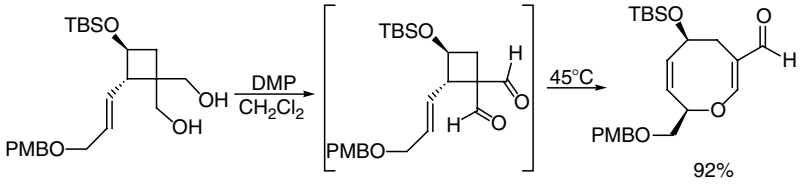
The highly unstable 2-butynedial is generated by a Dess-Martin oxidation in the presence of a phosphorane, resulting in an *in situ* Wittig reaction that provides a very good yield of the desired enediyne. A two step protocol fails to deliver the desired product because of the instability of the intermediate dialdehyde.

Because of the relative inertness of functional groups other than alcohols to Dess-Martin conditions, a Dess-Martin oxidation is a good choice when an *in situ* reaction of the resulting aldehydes or ketones is desired. It is particularly common to use Dess-Martin periodinane in order to generate very reactive aldehydes or ketones that suffer *in situ* concerted reactions, such as Diels-Alder additions,[67] oxy-Claisen reactions,[68] pericyclic processes[69] and concerted hydrogen shifts.[70]



Ref. 67c

During the synthesis of the marine diterpenoid kalihinene X, a key Diels-Alder reaction was employed, which happened *in situ* after the oxidation of an allylic alcohol under Dess-Martin conditions.

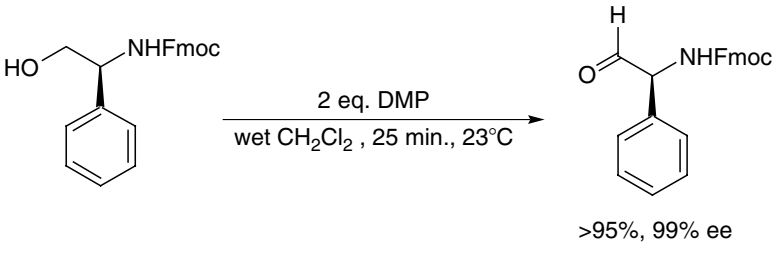


Ref. 68c

The oxidation of a diol under Dess-Martin conditions leads to a dialdehyde that suffers an *in situ* oxy-Claisen rearrangement, resulting in the formation of a dihydrooxocene ring.

3.2.4. Side Reactions

Dess-Martin periodinane has a very low tendency to induce α-epimerization of sensitive carbonyl compounds, being particularly useful in the obtention of epimerization-sensitive aldehydes and ketones without erosion of the enantiomeric or diastereomeric excess.[71] Thus, in a detailed study aimed at finding the ideal oxidant for the obtention of racemization-prone *N*-protected α-aminoaldehydes with a maximum of enantiomeric excess, Dess-Martin periodinane in wet CH_2Cl_2 at room temperature was found to be the oxidant of choice.

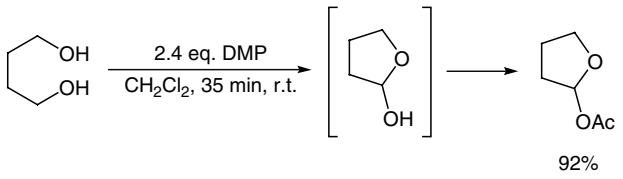


Ref. 71a

In the obtention of this racemization-prone aldehyde, a 99% ee was achieved using Dess-Martin periodinane, while TEMPO yielded material with 95% ee and Swern employing Hünig's base produced material with 50% ee.

The treatment of 1,2-diols with Dess-Martin periodinane may lead either to a 1,2-dicarbonyl compound,[14] or to an oxidative breakage of a C-C bond[14,72] depending on stereoelectronic factors. When a 1,2-dicarbonyl compound is obtained, very often, one of the carbonyl groups tautomerizes to the enol form. Under controlled conditions, very often, it is possible to selectively oxidize one of the alcohols in a 1,2-diol, particularly when this alcohol is an allylic one.[73]

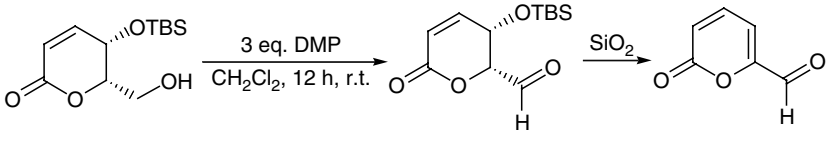
The treatment of 1,4-, 1,5- and 1,6-diols with Dess-Martin periodinane, very often, leads uneventfully to dicarbonyl compounds[74] or to hydroxycarbonyl compounds[75] that are occasionally isolated as lactols.[76] Sometimes, when a lactol is primarily obtained, it suffers a further oxidation to a lactone[32,77] or it is transformed into an acetylated lactol.[78] It has been proved that for the acetylation of lactols, both Dess-Martin periodinane and acetic acid generated during the oxidation must be present. The addition of pyridine does not avoid this reaction.



Ref. 78
The treatment of 1,4-butanediol with Dess-Martin periodinane leads to 4-hydroxybutanal, which equilibrates with a lactol. The lactol is transformed into an acetoxy acetal by the action of the acetic acid generated during the oxidation.

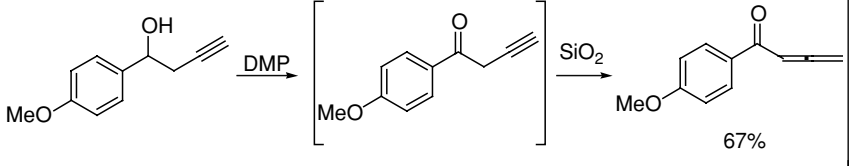
2-Ene-1,4-diols are transformed into furans by Dess-Martin periodinane.[15c]

Sometimes, when an aldehyde or ketone containing a good-leaving group at the β-position is obtained, an *in situ* elimination occurs resulting in the formation of an enal or an enone.[23c] In fact, Dess-Martin oxidations are carried out under very mild conditions and eliminations often happen during silica chromatography rather than during the oxidation.[79]



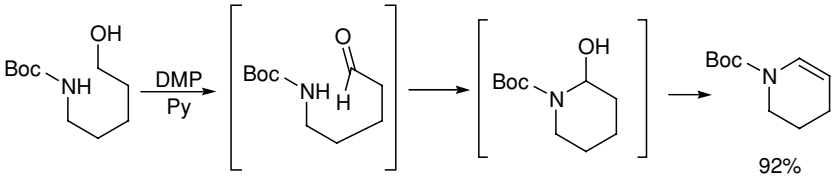
Ref. 23c
A Dess-Martin oxidation delivers an unstable β-silyloxy aldehyde that decomposes to an enal on contact with silica-gel.

Occasionally, alkenes suffer migrations[80] or cis-trans isomerizations[6d] during Dess-Martin oxidations. Such reactions normally only occur under very favourable thermodynamic and kinetic conditions, Dess-Martin reagent being able to deliver compounds containing unstable alkenes that would isomerize on simple contact with silica.



Ref. 81
Examination by NMR of a solution, resulting from the oxidation of a homopropargylic alcohol with Dess-Martin periodinane, shows a clean reaction leading to an unstable unconjugated inone that isomerizes to an allene on contact with silica.

Sometimes, aldehydes or ketones resulting from Dess-Martin oxidation are attacked intramolecularly by nitrogen atoms belonging to diverse functionalities, when such attack results in aminals inside stable medium-sized rings.[82] Sometimes, these aminals suffer dehydration to enamines.



Ref. 82g

The Dess-Martin oxidation of an alcohol delivers an aldehyde that is attacked intramolecularly by a carbamate, resulting in an aminal that suffers dehydration to an *N*-Boc-enamine.

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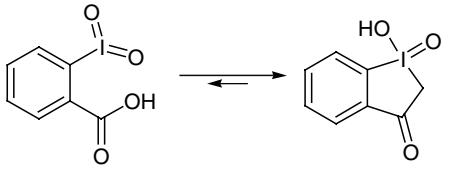
3.3. *o*-Iodoxybenzoic Acid (IBX)



The *o*-iodoxybenzoic acid **(37)** (p. 181)—commonly known as IBX—was prepared for the first time more than a century ago by Hartman and Meyer by oxidation of *o*-iodobenzoic acid with $KBrO_3$.[4] This compound was not explored in organic synthesis for a long time because it was wrongly supposed that its virtual lack of solubility in common organic solvents would preclude any synthetic usefulness. IBX came to the attention of the organic

chemists in the 80's as the direct precursor in the preparation of Dess-Martin periodinane.[2] In 1994, Santagostino *et al.* made the key discovery that DMSO behaves as a unique solvent in its ability to dissolve IBX in a concentration as high as 0.5 M;[3] in such solutions, IBX being able to oxidize alcohols in an extraordinarily efficient and selective manner. In fact, in less than a decade since the seminal paper of Santagostino *et al.*, IBX has proved to be a rather unique alcohol oxidant, able to perform very difficult oxidations that tend to fail using other oxidants. These difficult oxidations include:

- Transformation of 1,2-diols into α-dicarbonyl compounds with no oxidative breakage of a C-C bond.[3,83]
- Oxidation of 1,4-diols to lactols with no over-oxidation to lactones.[84]
- Oxidation of alcohols with a nitrogen-containing functionality at the 4 position, resulting in aminals with no over-oxidation to lactams.[85]
- Oxidation of alcohols with no interference from amines in the same molecule, including the very oxidation-prone primary amines.[83]

Before being used as an alcohol oxidant, IBX found widespread use in the organic laboratories as the precursor of Dess-Martin periodinane. It was found that the efficiency of Dess-Martin periodinane as alcohol oxidant depends substantially on the profile of impurities and the exact manner in which the precursor IBX is prepared. This prompted very detailed studies aimed at finding a protocol delivering IBX of the best quality. Many experimental modifications[86] on the initial preparation of Hartman and Meyer in 1893[4] involving the oxidation of *o*-iodobenzoic acid with $KBrO_3$ were suggested, culminating to a very detailed description being recently published in the Organic Syntheses journal.[7] A preparation of IBX needing the handling of less toxic reagents than the classic ones, was described by Santagostino *et al.* involving the oxidation of *o*-iodobenzoic acid with oxone®.[87]

Stevenson *et al.* discovered that IBX can exist as two different crystalline forms with very different solubilizing kinetics and efficiency in the preparation of Dess-Martin periodinane.[8] Apparently, IBX is normally obtained as a mixture of both crystalline forms in diverse proportions, depending on minor experimental details like stirring speed. Crystals with the more efficient microcrystalline morphology can be obtained by precipitating IBX from a basic aqueous solution by addition of hydrochloric acid.

When IBX is used as a solution in DMSO, the morphology of the original crystals obviously plays no role on the oxidizing efficiency. On the other hand, IBX can be used in the oxidation of alcohols as a suspension in many organic solvents.[88] Although, one would expect that in such case the morphology of IBX crystals must play an important role on the oxidizing efficiency, no such differential behaviour has been reported in the literature.[88a]

WARNING: IBX IS EXPLOSIVE

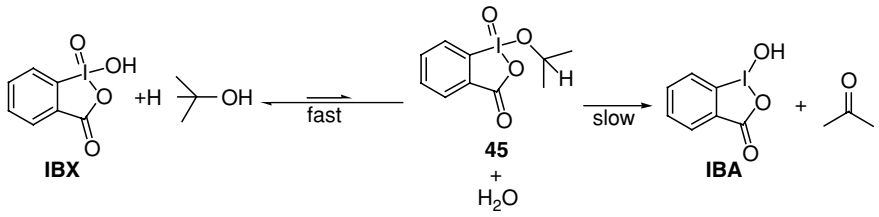
It has been reported that IBX behaves as an explosive similar to trinitrotoluene.[9] Apparently, the tendency to explosion on impact or on heating depends very much on IBX purity,[5,7] being pure samples of reagent much safer. While a wet sample of IBX can explode above 130°C,[7] a pure sample explodes above 200°C.[6c] Very recently, it was discovered that IBX mixed with benzoic and isophthalic acids lacks any explosive property. The corresponding formulation—containing 49% of IBX, 22% of benzoic acid and 29% of isophthalic acid—has been patented as SIBX[89] and it has been claimed that it is a safe alternative to IBX with the same oxidizing efficiency.[88b]

Normally, IBX is dissolved in DMSO for the oxidation of alcohols and the reaction is carried out at room temperature.[3] Sometimes, the addition of co-solvents causes the precipitation of IBX, resulting in a slower but still efficient oxidation that nonetheless, normally would need heating.[83] In fact, IBX oxidations can be carried out using suspensions of IBX in a solvent other than DMSO, in which IBX is virtually insoluble.[83,88a] A substantial acceleration can be achieved by adding a few equivalents of DMSO.

Finney and More have recently proved[88a] that, contrary to intuition, IBX oxidations are more efficiently carried out by using a heated suspension of IBX in various organic solvents rather than using an IBX solution in DMSO at room temperature. This contradicts the general view that IBX must be dissolved for better oxidation ability. After testing several solvents, these authors considered ethyl acetate and 1,2-dichloroethane as the solvents of choice for the oxidation of alcohols using IBX suspensions. These solvents do not react with IBX like THF or toluene, while they are unable to dissolve by-products originating from IBX. This allows an extremely efficient experimental protocol involving the heating of the alcohol in a suspension of IBX with a work-up by simple filtration and concentrating the resulting solution containing solely the desired product. Additionally, this procedure—as all oxidations involving IBX—is not generally affected by the presence of moisture or air, so that the oxidations can most often be done by simple heating in the air using solvents, which need not to be rigorously dried. The general observations of Finney and More were confirmed by Quideau *et al.* employing SIBX, the non explosive formulation of IBX, rather than IBX.[88b]

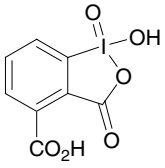
It must be mentioned that Nicolaou *et al.* presented evidences, showing that IBX reacts with some solvents like DMSO or THF—specially under heat—resulting in the transformation of IBX into species possessing the corresponding solvents as ligands.[90] These modified IBX species have a different reactivity profile than IBX in the oxidation of aromatic amides and in the introduction of alkenes conjugated with carbonyls. Therefore, one would expect substantial changes on the pattern of oxidation of alcohols by IBX depending on the solvent employed, although the published data till 2004 seems to suggest that the solvent plays a minor role.[88]

For the oxidation of alcohols with IBX, kinetic evidences are consistent with the following mechanism.[91]



There is an initial fast equilibrium in which the alcohol interacts with IBX, leading to a small concentration of intermediate **45**. This intermediate evolves slowly to IBA and the desired carbonyl compound. As expected, the presence of water displaces the initial equilibrium to the left and produces a decrease on the oxidation speed. Thus, although IBX oxidations can be made in the presence of water, it is better to perform them under dry conditions for maximum velocity.

The water soluble IBX analogue **46** has been prepared.[92] It is capable of oxidizing allylic and benzylic alcohols in water solution with no over-oxidation being observed to acids, in spite of the presence of a great excess of water. The compound **46** is not able of oxidizing aliphatic alcohols. IBX derivatives have been prepared, in which IBX is linked to a silica support[93] or to a resin.[94] These derivatives oxidize alcohols similarly to IBX with the advantage of allowing for easier work-ups.



46

3.3.1. General Procedure for Oxidation of Alcohols with IBX

The alcohol is added[a] to a ca. 0.4–1 M solution[b] of ca. 1–10 equivalents—typically 1.1–3 eq.—of IBX[c] in DMSO.[d,e] In the oxidation of substrates containing a primary or secondary amine, ca. 1–1.5 equivalents of an acid such as TFA must be added for protection. When a TLC analysis shows that most of the starting compound is consumed,[f] the reaction is elaborated according to two alternative protocols:

Work-up A:

The reaction mixture is filtered and concentrated, affording a crude product that may need further purification. This very simple work-up is

well suited for cases in which no DMSO is used, or it is used in very small amounts. It is particularly well adapted for oxidations in which EtOAc or 1,2-dichloroethane are used as the only solvents. These two solvents are not able to dissolve both IBX and the by-products originating from IBX, so that a simple filtration leaves a solution of very pure product.

Work-up B:

Water—or less frequently a neutral aqueous buffer—is added and the precipitate is filtered. The filtrate is extracted with an organic solvent, like Et_2O, EtOAc or CH_2Cl_2. Optionally, the organic phase may be washed with water, a saturated $NaHCO_3$ aqueous solution and/or brine. The organic phase is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that may need further purification.

[a] Normally, the alcohol is added as a concentrated solution in DMSO. Sometimes, it is added as a solution in other organic solvent such as THF. The use of organic solvents other than DMSO may cause the formation of a precipitate of IBX. Oxidations in a two-phase system with precipitated IBX are slower. Therefore, in such cases some heating is recommended.

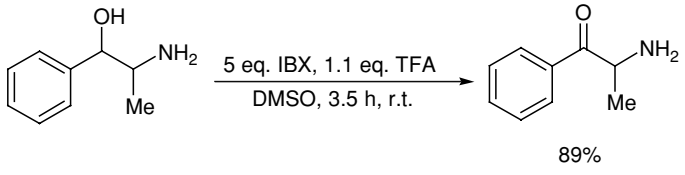
[b] IBX must be stirred for about 5–20 min in DMSO in order to get a ca. 0.4–1 M solution. IBX completely dissolved in DMSO allows for a very quick oxidation that can normally be performed at room temperature over several hours.

[c] IBX shows the following ^{1}H-NMR (DMSO-d_6, 400 MHz, δ): 8.15 (d, 1H, J= 7.9 Hz), 8.02 (d, 1H, J= 14.8 Hz), 7.99 (t, 1H, J= 7.9 Hz) and 7.84 (t, 1H, J= 14.8 Hz).[7]

[d] Sometimes, a co-solvent consisting of an aprotic organic solvent, like THF, EtOAc or 1,2-dichloroethane, is added. In fact, the oxidation can be performed in other solvents or adding only a few equivalents of DMSO. Limiting the quantity of DMSO causes IBX to exist as a suspension that makes the oxidation much slower, resulting in the need to heat. Using lesser amounts of DMSO may be advisable for work-up convenience.

[e] Although, water causes a decrease on the oxidation rate, the oxidation can frequently be carried out in a wet solvent and in the air without a substantial erosion in the yield.

[f] When a reaction mixture containing completely dissolved IBX is used—that is when it contains plenty of DMSO—the oxidation normally lasts about 1–20 h at room temperature. When IBX is present as a suspension, the reaction lasts about 0.5–6 h at 55–80°C.

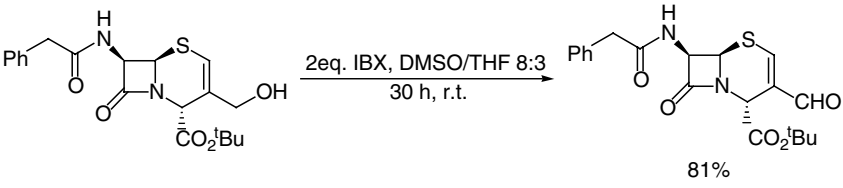


89%

Ref. 83

In this very remarkable oxidation in which the primary amine is protected by protonation with TFA, the reaction succeeds in spite of the presence of a primary amine and the tendency of the molecule to suffer an oxidative C-C bond breakage.

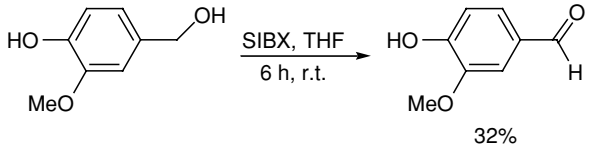
Ref. 85
While oxidants, like PCC, Swern or TPAP give unsatisfactory results, IBX is able to perform this oxidation to aldehyde with no epimerization at the α-position.



Ref. 95
While other oxidants, like MnO_2, PCC, Collins, Moffatt or TEMPO gave low yields or did not react at all, a 81% yield was obtained using IBX.

3.3.2. Functional Group and Protecting Group Sensitivity to Oxidations with IBX

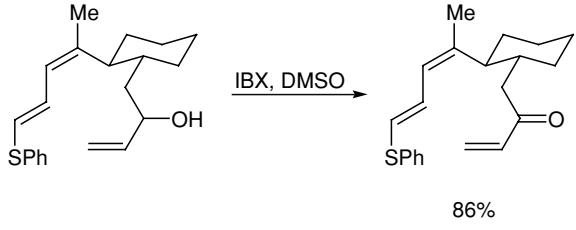
IBX possesses a great selectivity for the reaction with alcohols and the interaction with other functional groups normally demands more severe experimental conditions. According to Santagostino *et al.*,[83] phenols and anilines react with IBX producing complex and dark colored reaction mixtures. Nevertheless, it is possible to selectively oxidize alcohols in the presence of certain phenols that are not very electron rich.[88b]



Ref. 88b
In this oxidation, performed with the non-explosive formulation of IBX called SIBX, interference with the phenol causes the obtention of a moderate yield of aldehyde.

On the other hand, IBX transforms very efficiently *o*-methoxyphenols[88b] and simple phenols[96] into *o*-quinones. Tertiary amines resist IBX oxidations, while primary and secondary ones are unreactive to IBX when protected by protonation.[83] IBX is one of the few known oxidants able to perform alcohol oxidations in the presence of primary aliphatic amines. Amides are normally unreactive to IBX, whereas, *N*-acylanilines and *N*-alkoxycarbonylanilines possessing a free N-H interact with IBX via a single electron transfer to the oxidant, yielding radical-cations that participate in synthetically useful radical cyclizations.[97] These IBX oxidations involving a SET mechanism demand very exacting experimental conditions, which very often involve heating. Therefore, under proper experimental conditions, it is often possible to oxidize alcohols in the presence of *N*-acyl and *N*-acylcarbonylamines.[98]

IBX is able to transform tosylhydrazones and oximes into carbonyl compounds under very mild conditions.[99] It is possible to selectively oxidize alcohols with IBX in the presence of sulfides.[83,100] In fact, IBX has a lesser tendency to oxidize sulfides than Dess-Martin periodinane and in some sulfur-containing substrates it can be the oxidant of choice.[36]



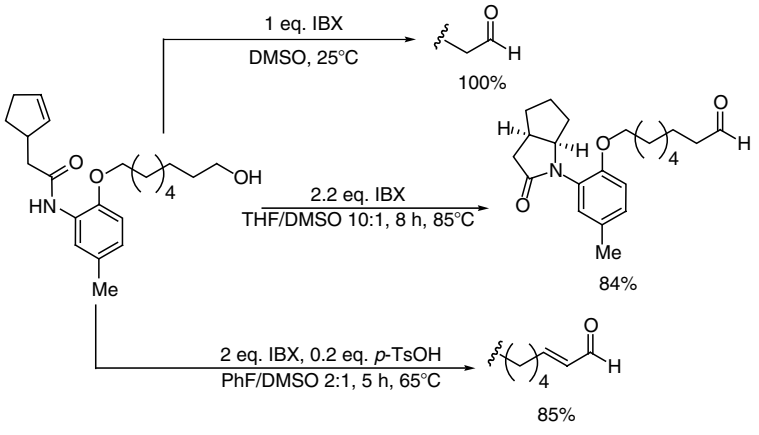
Ref. 36
While Dess-Martin periodinane affords a 44% yield due to over-oxidation products originating from the sulfide, IBX allows the obtention of a 86% yield of the desired product.

Alcohols can be selectively oxidized in the precence of dithioacetals derived from unconjugated ketones.[83,101] On the other hand, the thioacetals at benzylic and allylic positions can be hydrolyzed under very mild conditions with IBX in DMSO in the presence of *traces of water*.[102]

DMSO reacts slowly with IBX at room temperature, resulting in its oxidation to dimethyl sulfone and reduction of IBX to IBA and *o*-iodobenzoic acid.[83] This reaction normally does not interfere with the oxidation of alcohols in DMSO because it is rather slow.

Heating IBX with aldehydes and ketones, results in the introduction of conjugated alkenes in a highly efficient way.[103] This reaction, similar to the reaction of IBX with *N*-acyl and *N*-alkoxycarbonylanilines, usually operates under different experimental conditions than the oxidation of alcohols;

therefore, it is often possible to adjust the oxidation conditions in a certain substrate so as to perform the desired oxidation.



Ref. 98

The alcohol is oxidized to the corresponding aldehyde with 1 equivalent of IBX at room temperature. The use of 2.2 equivalents of IBX at a higher temperature causes the additional interaction with the amide moiety, leading to a radical cation that cyclizes on the alkene. Employing excess of IBX in the presence of *p*-TsOH produces the introduction of an alkene conjugated with the initially formed aldehyde.

IBX allows the introduction of carbonyl groups at benzylic positions in a very efficient way, when it is used as a heated solution in fluorobenzene-DMSO (2:1).[103b,104] This reaction normally does not interfere with the normal oxidation of alcohols because alcohols are oxidized under milder conditions.

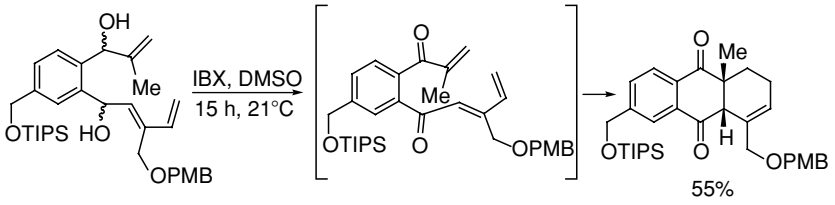
In spite of the slightly acidic nature of IBX,[5] no interference is observed from very acid-sensitive protecting groups, such as TMS ethers[105] or THP ethers.[99a]

Oxidation-sensitive protecting groups, such as PMB ethers,[106] resist the action of IBX under the experimental conditions used for the oxidation of alcohols.

3.3.3. Reactions Performed *in situ* During Oxidation With IBX

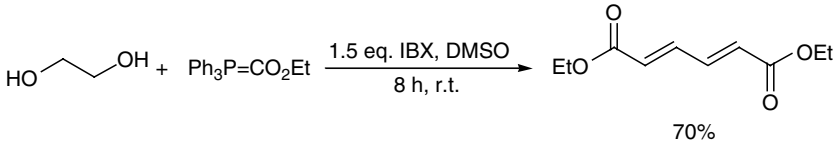
Sometimes, enones—obtained by oxidation of allylic alcohols—suffer Diels-Alder reactions during oxidations with IBX.[106a]

Oxidations of primary alcohols with IBX can be performed in the presence of stabilized Wittig reagents, so that the resulting aldehydes react *in situ* with the Wittig reagents resulting in highly efficient one-pot transformations. This procedure is particularly advisable whenever highly reactive and unstable intermediate aldehydes are involved.[107]



Ref. 106a

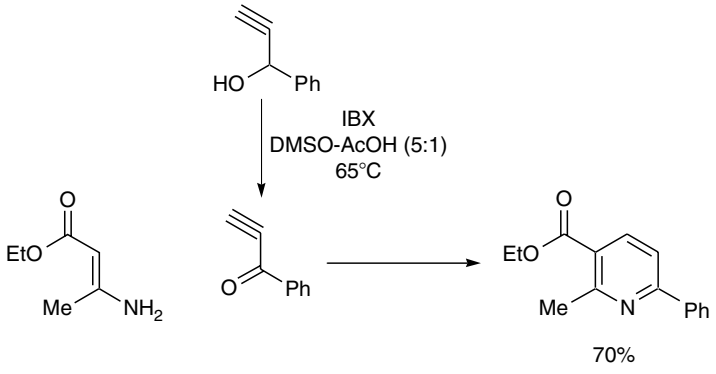
An enone obtained by IBX oxidation suffers an *in situ* intramolecular Diels-Alder reaction. Dess-Martin periodinane produces partial desilylation of the TIPS ether due to its slightly acidic character.



Ref. 107b

The oxidation of 1,2-ethylendiol with IBX leads to highly reactive gliceraldehyde that reacts *in situ* with $Ph_3P = CO_2Et$, resulting in a double Wittig olefination.

Bagley *et al*. performed a number of pyrimidine and pyridine syntheses by condensing an inone—generated *in situ* by oxidation of a propargylic alcohol with IBX—with amidines and β-aminocrotonate.[108]



Ref. 108

The oxidation of a propargylic alcohol with IBX provides an unstable inone that is condensed *in situ* with an ethyl β-aminocrotonate, delivering a pyridine. Acetic acid is added to the reaction mixture in order to promote the condensation.

3.3.4. Side Reactions[109]

Sometimes, over-oxidation of benzylic alcohol to benzoic acid is observed with IBX.[88a] This over-oxidation does not happen in all benzylic alcohols and can be avoided by running the oxidation under anhydrous conditions. In fact, IBX is quite resistant to produce over-oxidation to acids even in the presence of a great excess of water. The water-soluble IBX analogue **46** is able to transform a number of benzylic alcohols into the corresponding benzaldehydes with no over-oxidation to acid, using water as solvent.[92] When the oxidation of alcohol to acid is purposefully looked after, it can be performed with IBX in DMSO with the addition of certain nucleophilic catalysts, such as 2-hydroxypyridine (HYP) or *N*-hydroxysuccinimide (NHS).[110]

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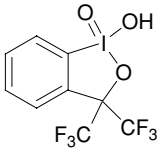
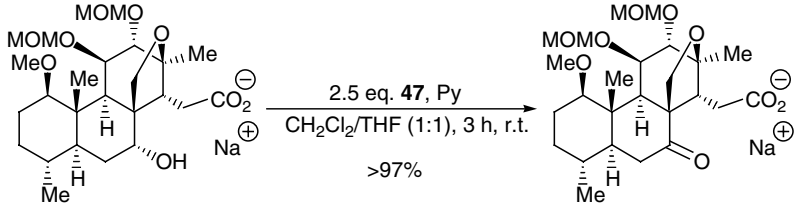
3.4. Other Hypervalent Iodine Compounds Used for Oxidation of Alcohols

The fluorine-containing hypervalent iodine compound **47**, first described by Dess and Martin,[5] finds occasional use in the oxidation of alcohols and is described in some substrates as superior than Dess-Martin periodinane.[111]



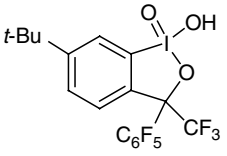
47



Ref. 111b

The use of Dess-Matin reagent leads to partial lactonization, caused by the generation of acetic acid during the oxidation. This is avoided by the employment of compound **47**, which produces water instead of acetic acid during the oxidation.

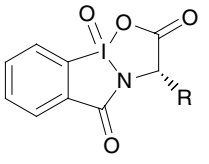
Compound **48** is described as a hypervalent iodine compound possessing the distinctive advantages of being air-stable, non-explosive and soluble in common organic solvents.[112]



48

It can be used for the oxidation of alcohols under experimental conditions similar to the ones employed with Dess-Martin periodinane.

Chiral oxidants **49** are Dess-Martin periodinane analogues able to oxidize alcohols, and possessing a limited ability for the enantioselective oxidation of non-symmetric sulfides.[113]



49

R= Me, $CH_2CH(Me)_2$, *i*-Pr, Bn

Iodosobenzene (PhIO) transforms alcohols into aldehydes and ketones in boiling dioxane in variable yields.[114] This oxidation gives more consistent yields in the presence of an ytterbium catalyst—$Yb(NO_3)_3$—, being particularly efficient in hot 1,2-dichloroethane.[115] The oxidation of alcohols with iodosobenzene can also be carried out in the presence of a ruthenium catalyst, such as $RuCl_2(PPh_3)_3$, resulting in the formation of ketones, aldehydes and carboxylic acids in CH_2Cl_2 at room temperature.[116] Finally, the use of iodosobenzene with KBr as activator in water solution must be mentioned, resulting in the oxidation of secondary alcohols to ketones and primary alcohols to acids.[117]

Iodosobenzene diacetate [IBD, $PhI(OAc)_2$] is able to oxidize benzylic alcohols to benzaldehydes when a solid mixture of iodosobenzene diacetate and the alcohol is irradiated with microwaves. Best results are obtained when iodosobenzene diacetate is supported on alumina.[118] The use of polymer supported iodosobenzene diacetate (PSDIB) simplifies the work-up in the oxidation of benzylic alcohols to benzaldehydes.[119] PSDIB can be employed in the presence of KBr and using water as solvent, resulting in the transformation of secondary alcohols into ketones and primary alcohols into carboxylic acids.[117]

Iodoxybenzene ($PhIO_2$) has been briefly explored in the oxidation of benzylic alcohols to benzaldehydes, giving best results with an acetic acid catalysis.[120] The guanidinium salt of *m*-iodoxybenzoic acid is soluble in CH_2Cl_2 and able to carry out oxidative breakages of 1,2-diols.[120]

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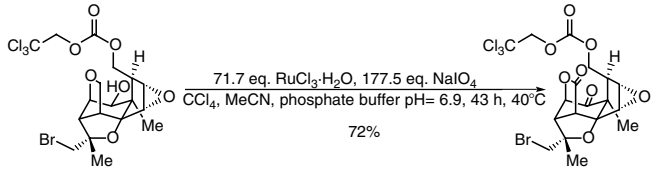
4

Ruthenium-based Oxidations

4.1. Introduction

Interest for ruthenium as an oxidant in Organic Chemistry originated from the supposition that, since ruthenium is bellow osmium in the Periodic Table, ruthenium tetroxide (RuO_4) would have a behaviour resembling osmium tetroxide (OsO_4), which is very useful in the dihydroxylation of alkenes. In fact, although RuO_4 is also able to produce dihydroxylation of alkenes under very controlled conditions, it is a much stronger oxidant than OsO_4. In variance with OsO_4, RuO_4 reacts very violently with common organic solvents, such as benzene, ether or pyridine. RuO_4 must be used in organic solvents refractory to ignition, such as carbon tetrachloride in which it is quite soluble.[1] RuO_4, although not as expensive and toxic as OsO_4, is quite costly and normally used in catalytic amounts with sodium metaperiodate as a secondary oxidant.[2] Because of its very strong oxidizing properties, RuO_4 is used in organic synthesis to perform oxidations for which very few alternative oxidants are available, such as transformation of ethers into esters,[3] degradative oxidation of aromatic appendages into carboxylic acids or even introduction of oxygen atoms on unfunctionalized saturated hydrocarbons. Under controlled conditions, RuO_4 can be useful in some selective oxidations in multifunctional compounds, being occasionally used in some transformations, such as the oxidation of primary alcohols into carboxylic acids—the so-called Sharpless carboxylic acid oxidation—and the oxidative breakage of alkenes into ketones and carboxylic acids.[4] Additionally, RuO_4 is occasionally used in the oxidation of alcohols to aldehydes or ketones,[5] being particularly useful in the oxidation of highly hindered alcohols that are resistant to reaction using other oxidants.



Ref. 6

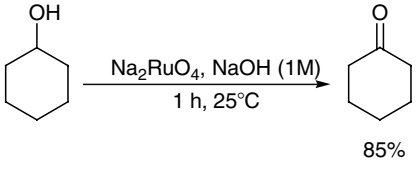
This very hindered secondary alcohol—located in a complex molecule—can be efficiently oxidized to the corresponding ketone in a biphasic system, using RuO_4 generated from $RuCl_3$ and excess of $NaIO_4$. An additional oxidation of a cyclic ether to a lactone occurs under the reaction conditions.

4.1.1. Perruthenate and Ruthenate Ions

As expected, ruthenium compounds possessing a lower oxidation state than RuO_4 (8+), behave as milder oxidants. Thus, both the perruthenate—RuO_4^- (7+)—and the ruthenate—RuO_4^{2-} (6+)—ions are milder oxidants than RuO_4, being able to oxidize alcohols and alkenes but reacting very slowly, if at all, with ethers and benzene rings. The perruthenate ion is unstable in aqueous solution because it produces the oxidation of water. The ruthenate ion suffers dismutation in water, resulting in the generation of perruthenate and ruthenium dioxide.[7] This dismutation can be avoided under very basic conditions with a pH above 12. Although, both aqueous perruthenate and ruthenate can be used for the oxidation of alcohols, this reaction is very limited because of the instability of these ions in water or the need to operate under very basic conditions in the case of the ruthenate ion.

> Polymer supported sodium ruthenate is able to catalyze the oxidation of alcohols with iodosobenzene or tetrabutylammonium periodate in CH_2Cl_2.[8] It is not clear whether the primary oxidant is ruthenate or perruthenate.

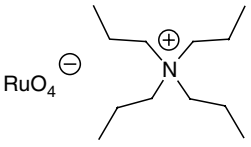
In fact, equilibria between ruthenium ions in different oxidation states in aqueous solution add complexity to the mechanistic analysis of these oxidations. Thus, Burke and Healy presented mechanistic evidences[9] suggesting that putative oxidations of alcohols with ruthenate ion are in fact produced by perruthenate originated by dismutation of ruthenate.



Ref. 10

An aqueous solution of sodium ruthenate is able to oxidize cyclohexanol. These reaction conditions are hardly appropriate for routine employment in the laboratory because of the high price of Na_2RuO_4 that is used stoichiometrically and of the need to perform the reaction in aqueous 1M NaOH in order to avoid the dismutation of sodium ruthenate. Some mechanistic studies suggest that the real oxidant could be perruthenate,[9] present in very small amounts and in equilibrium with ruthenate regardless of the very basic conditions.

The perruthenate ion can be made soluble in organic solvents by using the tetra-*n*-propylammonium contraanion, that is by employing tetra-*n*-propylammonium perruthenate (TPAP) **(50)**.



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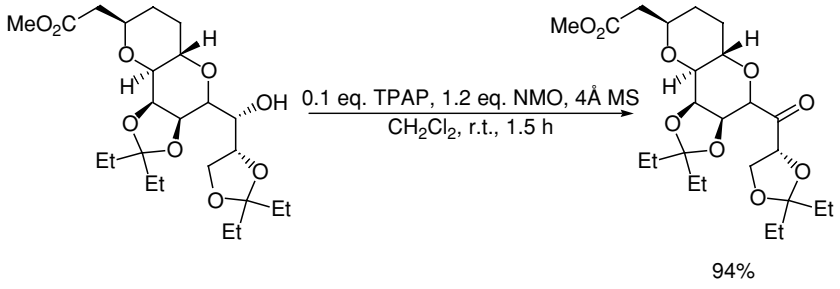
Tetra-*n*-propylammonium perruthenate

Griffith, Ley *et al.*[11] discovered that, in variance with the instability and complex behaviour of perruthenate and ruthenate ions in aqueous solution, TPAP in organic media is quite stable and behaves as a very good oxidant for alcohols. Normally, it is employed in catalytic quantities in dry CH_2Cl_2 with addition of *N*-methylmorpholine *N*-oxide (NMO) as the secondary oxidant. Catalytic TPAP in the presence of NMO is able to oxidize alcohols to adehydes and ketones under very mild conditions in substrates adorned by complex functionalities, and it has become one of the routine oxidants for alcohols in most Synthetic Organic Chemistry laboratories.



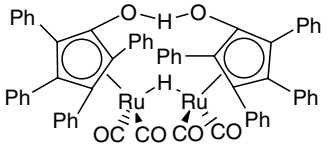
Ref. 12

This complex alcohol is efficiently oxidized to the corresponding ketone, using Ley's conditions with catalytic TPAP in the presence of excess of NMO. PCC and Dess-Martin periodinane are not as effective.

4.1.2. Ruthenium Compounds in Lower Oxidation State

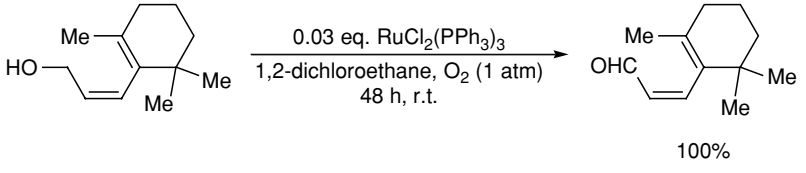
Many compounds containing ruthenium in lower oxidation states can behave as oxidants for alcohols, usually in catalytic quantities in the presence of a secondary oxidant. This includes simple inorganic ruthenium compounds, such as $RuCl_3$,[13,17,19g] RuO_2[14] and $Ru_3(CO)_{12}$,[13a,19g,19l,15] as well as ruthenium complexes containing organic ligands, such as $RuCl_3$-$Co(OAc)_2$,[16] $Ru_3O(OAc)_7$,[17] *cis*-$(NH_3)_4$Ru(II)-2-acetylpyridine,[18] $RuCl_2(CO)_2(PPh_3)_2$,[19l] $RuCl_2(PPh_3)_3$,[19] [RuCl(OAc)$(PPh_3)_3$]-hydroquinone-[Co(salophen)(PPh_3)],[20] $RuClH(PPh_3)_3$,[17] $RuH_2(CO)(PPh_3)_3$,[19n] RuH_2

$(PPh_3)_4$,[21,19n] $RuH(OAc)(PPh_3)_3$,[17,19b] $RuBr_2(PPh_3)_3$,[19b] $Ru(OCOCF_3)_2(CO)(PPh_3)_2$,[22] $[Ru_2O_6(C_5H_5N)_4] \cdot 3.5H_2O$,[23] $[Ru_3O(O_2CR)_6L_3]^n$ (R= Me or Et; L = H_2O or PPh_3; n = 0, 1),[24] ruthenocene,[19l] (η4-tetracyclone) $RuH_2(CO)_2$[25] and compound **51**.[19o,p]



51

Although some of these oxidants are very efficient in the oxidation of alcohols, its employment is seriously limited because of the high price of ruthenium compounds. That is why, a great research effort is being dedicated to the development of oxidizing systems containing a low-valence ruthenium compound in catalytic amounts and a cheap and environmentally friendly secondary oxidant, such as oxygen, hydrogen peroxide, bleach, NMO, iodosobenzene, phenyliodosodiacetate or trimethyl peroxide. Although, at the time of this writing, none of the oxidizing methods involving low-valence catalytic ruthenium compounds has found a widespread use in Synthetic Organic Chemistry, this field is advancing very quickly and could lead in the near future to the discovery of an environmentally benign and very convenient method for the oxidation of alcohols both in the laboratory and on an industrial scale. It is not unconceivable that a certain stable low-valence ruthenium complex could catalyze with a high turnover the selective oxidation of complex alcohols in a solution in the open air. In this way, atmospheric oxygen could be the secondary oxidant in a very cheap and clean procedure, in which water would be delivered.



Ref. 26

This allylic alcohol is smoothly oxidized to the corresponding aldehyde under an atmosphere of oxygen, thanks to the addition of a catalytic quantity of $RuCl_2(PPh_3)_3$.

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4.2. Ruthenium Tetroxide

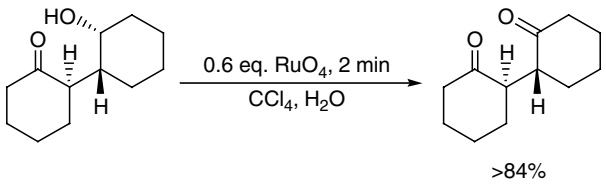
RuO_4

RuO_4 is a poisonous[27] and volatile solid (m.p. 25°C) with a high solubility in apolar organic solvents.[1] In a biphasic water-carbon tetrachloride system, RuO_4 partitions between both phases resulting in a 59 times higher concentration in the CCl_4 phase.[28] RuO_4 is a very strong oxidant that reacts very violently with flammable organic solvents, consequently it must be used in highly halogenated organic solvents such as CCl_4, $CHCl_3$ or CH_2Cl_2.

> However, some flammable solvents such as cyclohexane may be suitable for some operations involving catalytic RuO_4.[29]

In 1958, Berkowitz and Rylander[3] described that stoichiometric RuO_4 reacts very quickly with alcohols resulting in the oxidation of secondary alcohols—including very hindered ones—to ketones and primary alcohols to carboxylic acids. A solution of RuO_4 in CCl_4 can be easily prepared by reacting an aqueous solution of sodium metaperiodate ($NaIO_4$) with hydrated ruthenium dioxide (RuO_2) and extracting the aqueous phase with CCl_4. The concentration of RuO_4 in CCl_4 is easily determined by adding isopropanol and weighing the resulting black precipitate of RuO_2.[2b] As RuO_4 is volatile and poisonous, this material is very conveniently manipulated as a solution in CCl_4, which is stable for more than one year.[1]

Stoichiometric RuO_4 dissolved in CCl_4 is a neutral and extremely efficient reagent for the oxidation of hindered secondary alcohols. The reaction takes place in a matter of minutes at room temperature and is easily monitored by the appearance of a black insoluble precipitate of RuO_2. RuO_4 is seldom employed in stoichiometric amounts in organic synthesis due to its very high price. On the other hand, because of the efficiency of RuO_4 in CCl_4 to carry out the oxidation of hindered secondary alcohols under mild conditions, this reagent may be considered the reagent of choice for the oxidation of *valuable* hindered secondary alcohols.



Ref. 30a
A very mild and quick oxidation with excess of RuO_4 allows the obtention of a diketone with no epimerization.

In 1963, Nakata[2b] described the catalytic oxidation of alcohols with RuO_4, involving a biphasic water-CCl_4 system in the presence of excess of $NaIO_4$ and 1–10 mol% of RuO_4. This procedure, although sometimes not as efficient as the use of stoichiometric RuO_4,[5e] offers the advantage of economy and safety due to the catalytic employment of expensive and poisonous RuO_4, and is the preferred method of oxidation of alcohols using RuO_4.

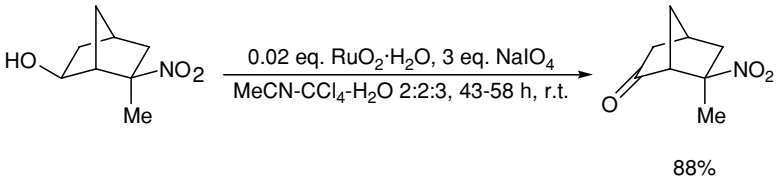
In fact, the description by Nakata of the use of catalytic RuO_4 in the oxidation of alcohols is predated by an article by Pappo and Becker[30b] in 1956, that is seldom cited because it was published in a journal of limited distribution.

Although $NaIO_4$ or KIO_4 are the secondary oxidants used in the vast majority of cases in which alcohols are oxidized with catalytic RuO_4, the employment of sodium hypochlorite (NaOCl),[31] sodium bromate ($NaBrO_3$)[32] or Cl^+, electrolytically generated by oxidation of chloride ion,[33] have also been reported.

In 1965, Parikh and Jones[34] published a modification of Nakata's procedure in which RuO_4—rather than being independently prepared—is generated *in situ* by oxidation with excess of $NaIO_4$ of catalytic hydrated RuO_2, which is commercially available and much safer than RuO_4. Lawton *et al.*[35] in 1969 introduced some slight modifications on this procedure, whereby a $CHCl_3$-H_2O biphasic system is used with KIO_4 as secondary oxidant and K_2CO_3 being added to adjust the pH.

In 1981, Sharpless *et al.*[36] mentioned the advantage of adding some acetonitrile to oxidations involving catalytic RuO_4. Apparently, in oxidantions in which some carboxylic acid is present from the outset or is generated in some amount, however small, the formation of ruthenium carboxylates inactivates the oxidation capability of catalytic ruthenium. Acetonitrile displaces the carboxylates as ruthenium ligands and, therefore, prevents the inactivation of the catalyst. Optimum results are obtained employing CCl_4-MeCN-H_2O in a solvent ratio of (2:2:3). Sharpless reports the use of hydrated ruthenium trichloride as the precursor of RuO_4, although hydrated RuO_2 is mentioned as equally effective.

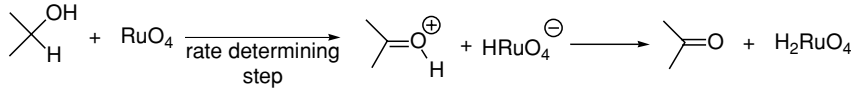
Morris Jr. and Kiely[37] in 1987 noted a great acceleration in the oxidation of alcohols, with catalytic RuO_4 in a biphasic system, upon addition of 1% molar benzyltriethylammonium chloride (BTEAC) as a phase-transfer catalyst.



Ref. 38

The oxidation of this alcohol employing catalytic RuO_4 under Sharpless' conditions is very simple to perform and more satisfactory than a Swern oxidation, which is quite demanding experimentally.

One molecule of RuO_4 is able to oxidize two molecules of a secondary alcohol to the corresponding ketone, while RuO_4 is transformed into RuO_2. Mechanistic evidences show that the rate determining step involves a hydride transfer from the alcohol to the oxidant as in the following Equation.[39]



4.2.1. General Procedure for Oxidation of Secondary Alcohols with Stoichiometric RuO_4

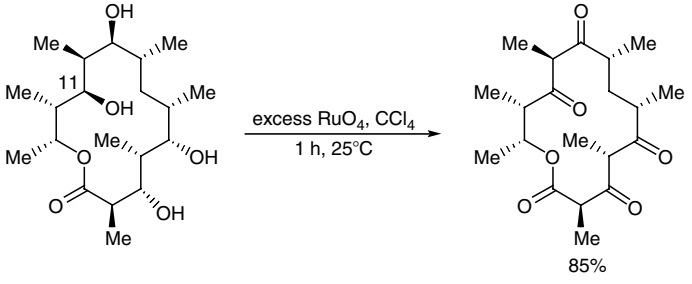
A solution[a] of 3.2 g of sodium metaperiodate ($NaIO_4$, MW = 213.89) in 50 mL of water, kept over an ice-water bath, is added over a suspension of 0.4 g of hydrated ruthenium dioxide[b] (RuO_2) in CCl_4. The resulting mixture is vigorously stirred at 0°C till the black suspension of RuO_2 disappears and a bright yellow solution of RuO_4 in CCl_4 is formed. The CCl_4 solution is separated and shaken with a fresh sodium metaperiodate solution (1.0 g/50 mL) till the yellow color of the CCl_4 phase persists. The resulting solution of RuO_4 in CCl_4—that will possess a ca. 0.037 M concentration—is separated and dried ($MgSO_4$), and can be stored for more than one year at low temperature in the presence of some crystals of sodium metaperiodate.

The concentration of RuO_4 in CCl_4 can be estimated from the amount of RuO_2 formed when 0.5 mL of propan-2-ol are added to 2.0 mL of a ruthenium tetroxide solution. The precipitate of black RuO_2 must be separated, washed with CCl_4 and water, and thoroughly dried by heating under vacuum.

A solution of ca. 0.5 to 0.7 equivalents of RuO_4[c] in CCl_4—prepared as above—is dropped over a ca. 0.2–1.5 M stirred solution of the alcohol in CCl_4[d] kept at room temperature.[e] When most of the alcohol is consumed,[f] excess of propan-2-ol is added to destroy the remaining RuO_4. The

black precipitate of RuO_2 is filtered and washed with an organic solvent[g], such as CCl_4, $CHCl_3$ or acetone. The collected organic phases are concentrated, giving a residue of ketone that may need further purification.

[a] Due to the toxicity and volatility of RuO_4, all the operations must be carried out in a well-ventilated hood using rubber gloves to prevent skin contact.
[b] Hydrated RuO_2 from different vendors contain diverse proportions of water. RuO_2 with a high water content possesses a maximum reactivity and is consumed in less than 1 h. The efficient generation of RuO_4 may fail if RuO_2 with a low water content is employed. Hydrated RuO_2 (54%) from Engelhard Corporation (www.engelhard.com) is reported to be very efficient in the generation of RuO_4 (see reference 40).
[c] One mol of RuO_4 is able to oxidize 2 moles of secondary alcohol.
[d] The reaction can also be carried out in $CHCl_3$, CH_2Cl_2 or Freon 11 (CCl_3F). The solvent must be free from oxidizeable material. For instance, ethanol-free $CHCl_3$ must be used.
[e] Due to the toxicity and volatility of RuO_4, it is not recommended to heat above room temperature. Sometimes, it is advisable to cool the solution of the alcohol at 0°C or at a lower temperature for milder reaction conditions.
[f] It takes approximately from 2 min to 12 h. The beginning of the reaction is signalled by the appearance of a black precipitate of RuO_2. The consumption of RuO_4 is indicated by the disappearance of a bright yellow color.
[g] Some organic compounds may remain adsorbed on RuO_2. Sometimes, it may be necessary to perform a continuous extraction of the RuO_2 with a hot organic solvent in order to recover most of the product.



Ref. 41

After trying many oxidizing conditions, this labile polyketide lactone could be obtained by the employment of RuO_4 that was able to perform the oxidation of four alcohols, including the one on C-11 that was resistant to oxidation with chromic acid.

Ref. 5c

A RuO_4 oxidation affords the desired ketone, while $CrO_3 \cdot Py$ delivers an enone resulting from elimination of methanol from an intermediate ketone.

4.2.2. General Procedure for Oxidation of Alcohols with Catalytic RuO_4

Between 0.02 and 0.25 equivalents[a] of either hydrated RuO_2[b] or hydrated $RuCl_3$ are added to a biphasic system consisting in a ca. 0.2–0.7 M solution of 1 equivalent of the secondary alcohol in CCl_4 or $CHCl_3$,[c] and a ca. 0.4–1.7 M solution of 0.58 to 5 equivalents[d] of either $NaIO_4$ or KIO_4 in water.[e, f] Optionally, ca. 0.2–0.4 eq. of K_2CO_3 may be added to adjust the pH.[g] Optionally, ca. 0.05 to 0.2 eq. of $PhCH_2Et_3NCl$ (BTEAC) can be added as an accelerating phase-transfer catalyst.

The resulting mixture is vigorously stirred.[h] When most of the starting alcohol is consumed,[i] very often the reaction is quenched by the addition of excess of propan-2-ol—or more rarely an aqueous solution of $Na_2S_2O_3$—and the reaction mixture is filtered through a pad of Celite®. The organic phase is separated—optionally washed with aqueous $NaHCO_3$ and brine—, dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that may need purification.

[a] In the oxidation of highly hindered secondary alcohols, sometimes it may be necessary to increase the quantity of RuO_2 or $RuCl_3$ to a value as high as 70 equivalents, in which case the reaction fails to be catalytic in ruthenium.

[b] Normally, the RuO_2 is very quickly transformed into RuO_4 by the action of metaperiodate, as signalled by the disappearance of the black precipitate of RuO_2. RuO_2 containing a small proportion of hydrated water may react very slowly (see note b in the experimental description using stoichiometric RuO_4).

[c] Other halogenated solvents resistant to oxidation, such as CH_2Cl_2 or Freon 11 (CCl_3F), can also be employed.

[d] When a highly hindered secondary alcohol resistant to oxidation demands the use of an excess of RuO_2 or $RuCl_3$, the secondary oxidant—$NaIO_4$ or KIO_4—must be employed in a great excess, which may be as high as 170 equivalents.

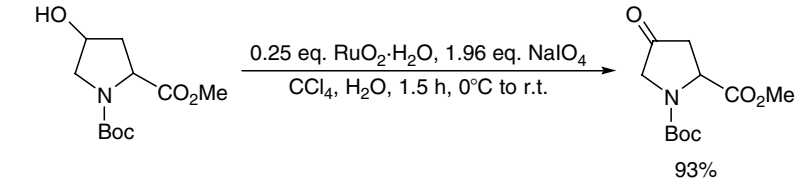
[e] When carboxylic acids are present in the reaction, either as starting compound or being generated during the reaction, even in very small amounts, the ruthenium catalyst may be deactivated due to the formation of ruthenium carboxylates. This can be avoided by the addition of acetonitrile that efficiently competes with carboxylates as a ligand for ruthenium. In such cases, best results are obtained using CCl_4-MeCN-H_2O in a (2:2:3) ratio.

[f] In fact, no water is needed in this oxidation, being metaperiodate suspended in an organic solvent able to generate RuO_4 (see Ref. 42). When this scarcely employed experimental variant is used, it is possible to oxidize primary alcohols to aldehydes with no overoxidation to carboxylic acids.

[g] The pH can also be adjusted with a phosphate buffer.

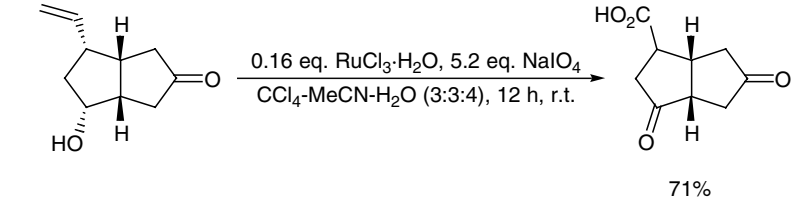
[h] Normally, the reaction is performed at room temperature, although occasionally it is done over an ice-water bath for milder conditions.

[i] It usually takes between 1 h and 2.5 days.



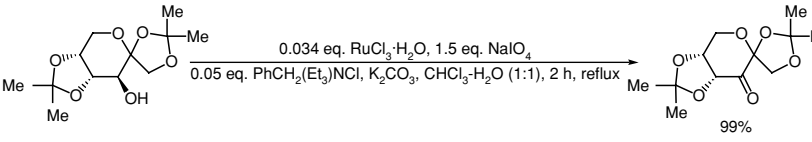
Ref. 43

Catalytic RuO_4 provides a 93% yield of very pure ketone, while Swern oxidation—which is cheaper but less convenient from the experimental point of view—gives a 70% of ketone that needs chromatographic purification.



Ref. 44

An oxidation with catalytic RuO_4 under Sharpless' conditions allows the simultaneous formation of a ketone and the breakage of an olefin delivering a carboxylic acid.



Ref. 45

This hindered alcohol is conveniently oxidized on a large scale with catalytic RuO_4 under phase-transfer conditions with a very good yield.

4.2.3. Functional Group and Protecting Group Sensitivity to Ruthenium Tetroxide

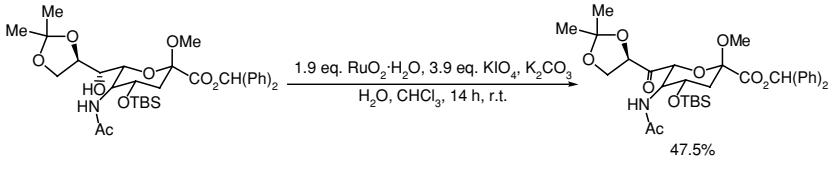
RuO_4 is a very reactive reagent that is employed not only for the oxidation of secondary alcohols to ketones and primary alcohols to carboxylic acids,[36] but also to perform the following transformations:

- Oxidation of alkenes and alkynes—sometimes with oxidative breakage of the carbon-carbon multiple bond—affording 1,2-diols,[46,47] α-hydroxyketones,[46] diketones,[46] aldehydes,[3a,46] ketones[46] or carboxylic acids[31,44,46,29]

- Degradative oxidation of aromatic rings into carboxylic acids[4b] and oxidation of aromatic compounds to quinones[2a]
- Oxidation of ethers to esters[3a,6]
- Introduction of hydroxy groups on unfunctionalized alkanes[48]
- Oxidation of sulfides into sulfoxides[1] and sulfones[1]
- Oxidation of aldehydes to acids[3a]
- Transformation of oximes into ketones[49]

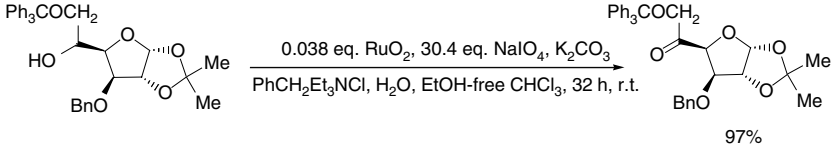
Additionally, it must be mentioned that RuO_4 degrades amines[3a] and can transform amides into imides.[3a]

The high reactivity of RuO_4 against many functionalities, might lead to think that RuO_4 is an inefficient oxidant for secondary alcohols in multifunctional compounds. In fact, the oxidation of alcohols is particularly rapid, so that a selective oxidation of secondary alcohols with RuO_4 in the presence of unreactive esters and lactones,[50] carbonates,[6] carbamates,[43] amides,[52h,j,54] ketones,[2b, 44] phenyl rings,[5c,d,e, 50g,51] furan rings,[42] acetals,[52] carboxylic acids,[34b] cyanides,[42] cyclopropanes,[52e] epoxides,[6] glycosides,[52h,j,53,54,45] trityl ethers,[52e,37] benzylic ethers[37,53] and TBS ethers,[52h,j,54] is possible.



Ref. 52j

A hindered secondary alcohol is oxidized with RuO_4 in a polyfunctional molecule adorned by an amide, a silyl ether, phenyl rings, an ester and acetals.

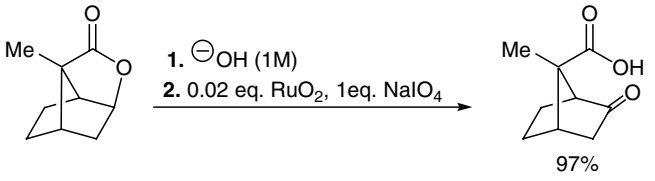


Ref. 37

Ruthenium tetroxide is able to oxidize a hindered secondary alcohol in the presence of several phenyl rings, ethers and an acetal.[37]

Although lactones normally resist the action of RuO_4, it is possible to perform an *in situ* hydrolysis of the lactone with one equivalent of base, followed by oxidation of the resulting hydroxyacid to a ketoacid.[34b] This procedure works efficiently in the oxidation of hydroxyacids, including those

that are very difficult to isolate because of its propensity to cyclize to a stable lactone.



Ref. 34b

The addition of 1 equivalent of aqueous base produces the *in situ* generation of a hydroxyacid that is oxidized to a ketoacid with RuO_4. The intermediate hydroxyacid is very difficult to isolate because of its tendency to cyclize to the starting lactone.

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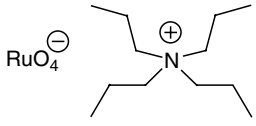
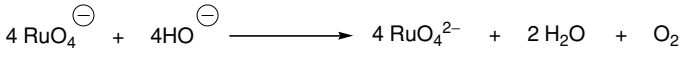
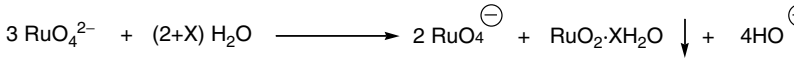
4.3. Tetra-*n*-Propylammonium Perruthenate (TPAP) (Ley Oxidation)



As expected, inorganic perruthenates, like sodium perruthenate ($NaRuO_4$) or potassium perruthenate ($KRuO_4$), are soluble in water and insoluble in apolar organic solvents. On the other hand, the perruthenate ion (RuO_4^-) is unstable in aqueous solution because it produces the oxidation of water according to the following Equation.[55]



The resulting ruthenate ion (RuO_4^{-2}) is stable under strongly aqueous basic conditions. Otherwise, it decomposes according to the next Equation below[7,56] resulting in a dismutation to perruthenate ion (RuO_4^-) and hydrated RuO_2 that appears as a black insoluble precipitate.



It is possible to oxidize alcohols using the perruthenate[57] or the ruthenate[10,58] ion in aqueous solution, but because of the instability of these ions in water, the identification of the genuine oxidant is open to discussion.[59]

A milestone in the routine employment of perruthenate in the oxidation of alcohols was established with the publication by Griffith, Ley *et al.* in 1987 on the catalytic use of tetra-*n*-propylammonium perruthenate (TPAP).[11] The presence of the tetra-*n*-propylammonium cation renders this compound soluble in apolar media and allows the existence of a high concentration of perruthenate ion in organic solvents. The tetra-*n*-propylammonium perruthenate is easily prepared and can be employed catalytically in CH_2Cl_2 solution in the oxidation of alcohols to ketones and aldehydes, using *N*-methyl morpholine *N*-oxide (NMO) as the secondary oxidant.

> Griffith, Ley *et al.* also described the tetra-*n*-butylammonium perruthenate (TBAP); since it is more difficult to prepare, its use is not as convenient as the employment of TPAP.

Oxidations are typically performed at room temperature in CH_2Cl_2, using only 5 mol% of TPAP as being quite expensive, in the presence of ca. 1.5 equivalents of NMO. The addition of molecular sieves is often very beneficial, since they remove both the water formed during the reaction and present in NMO, which normally is hydrated.

TPAP can react very violently with alcohols. For example mixing TPAP with methanol can produce flames.[69c]

> *N*-methylmorpholine *N*-oxide covalently linked to a polymer can be employed, so that it facilitates the recovery of the secondary oxidant.[60]

The catalytic TPAP used in the reaction is able to perform a limited number of catalytic cycles, since it decomposes as the reaction proceeds. During the oxidation of hindered or valuable alcohols, it may be necessary or advisable to increase the quantity of catalyst, or even to employ it in stoichiometric amounts.[61]

> Because of the high price of TPAP, research is being made in order to develop new protocols and modified reagents that allow the recovery of perruthenate—present as TPAP or in other compounds—after oxidation of alcohols. Proposed alternatives include employing TPAP in the presence of ionic salts,[62] on an Amberlist anion exchange resin[63] or on a silicate.[69b,c,d]

Some oxidations performed in CH_2Cl_2 fail to go to complexation. In such cases it may be advisable to add some acetonitrile,[61b] that is know to complex with ruthenium and avoid inactivation of the metal by union with other ligands.[36] In fact, acetonitrile can be used as the sole solvent, although employing CH_2Cl_2 containing 10% of acetonitrile allows a more suitable work-up. Other solvents such as acetone[64] or THF[65] have also been used. Although oxidations with TPAP are normally done at room

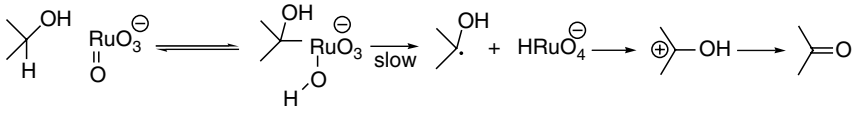
temperature, sometimes it may be advisable to perform them at 0°C[66] for greater selectivity.

TPAP oxidation can be accelerated by ultrasounds.[67]

Gaseous oxygen can be employed, instead of NMO, as secondary oxidant in TPAP oxidations. This environment-friendly secondary oxidant, although not used routinely in synthetic organic laboratories, is very attractive for the industrial point of view and is the subject of active research, both in combination with TPAP[68] and with several forms of supported perruthenate.[69]

Sodium hypochlorite can be used as secondary oxidant in the presence of TPAP but in this case the primary oxidant is reported to be RuO_4, instead of the perruthenate ion.[70] This oxidizing system is much more energetic than the standard TPAP/NMO system and is able to transform ethers into esters.[71]

Lee and Congson[59e] studied the oxidation of alcohols with *aqueous* perruthenate, proposing the following mechanism:



An initial addition of a ruthenium-oxygen double bond to a α-C—H bond leads to an intermediate containing a carbon-ruthenium bond. This bond suffers a homolytic scission leading to a carbon radical, which is oxidized to a carbocation that provides a carbonyl group by deprotonation.

It is open to speculation whether the same mechanism would apply to the more common oxidations with TPAP, in which the perruthenate ion operates in an apolar environment.

Lee *et al.*[72] studied the kinetics of the oxidation of alcohols with TPAP in CH_2Cl_2. Although, they did not propose any mechanism, they made the interesting discovery that the reaction behaves in an autocatalytic fashion. Thus, after an initial induction period, there is a great acceleration of the oxidation speed, till a decrease in the concentration of the reactants leads to a slowing up of the oxidation. It is proposed that colloidal RuO_2, formed by the reduction of the perruthenate ion, accelerates the reaction by acting as a catalyst via a mechanism in which some ligands complex with RuO_2. This explains the retardant effect in TPAP oxidations caused by water, which can compete with other ligands for complexation with RuO_2.

An important corollary of these observations is that sudden exotherms can happen during TPAP oxidations, particularly on a multigram scale.

4.3.1. General Procedure for Oxidation of Alcohols with TPAP

Between 0.02 and 0.15—typically 0.05—equivalents[a] of TPAP (MW = 351.43) are slowly[b] added to a ca. 0.02–0.3 M solution of the alcohol in CH_2Cl_2,[c] containing ca. 0.2–0.7 g of 4 Å molecular sieves[d] per mmol of alcohol and ca. 1.1 to 2.5—typically 1.5—equivalents of *N*-methylmorpholine *N*-oxide (NMO, MW = 117.15).[e] The resultant mixture is stirred at room temperature[f] till most of the alcohol is consumed.[g] This is followed by a work-up that can be carried out according to two alternative protocols:

Work-up A:

The reaction mixture is filtered through a pad of Celite® or silica gel and the resulting solution is concentrated, providing a residue that may need further purification. When the oxidation is performed in the presence of acetonitrile as solvent, as it tends to wash residual TPAP through the Celite® or silica pad, it is advisable to evaporate the solvents and add some CH_2Cl_2 before the filtering.

Work-up B:

The reaction mixture is washed with a saturated Na_2SO_3 aqueous solution, a saturated $CuSO_4$ aqueous solution and, optionally, with brine. Sometimes, it is advisable to add some organic solvent like CH_2Cl_2 or EtOAc, in order to facilitate the washings. The organic phase is dried ($MgSO_4$) and concentrated, giving a residue that may need further purification.

[a] Less equivalents of TPAP are needed in the oxidation of benzylic or allylic alcohols. Hindered secondary alcohols need a greater quantity of TPAP and, in extreme cases or when dealing with very valuable alcohols, it may be advisable to use a stoichiometric quantity of TPAP. In such cases no NMO needs to be added.

[b] The oxidation is catalyzed by a dark material—presumably RuO_2—that is generated by the initial reduction of the perruthenate ion and shows an autocatalytic behaviour with an induction period followed by a very fast oxidation. This may result in a sudden and very vigorous oxidation that may be dangerous, particularly on a multigram scale. Therefore, no substantial quantities of TPAP must be left to accumulate before the formation of the dark material—that catalyzes the reaction—is conspicuous.

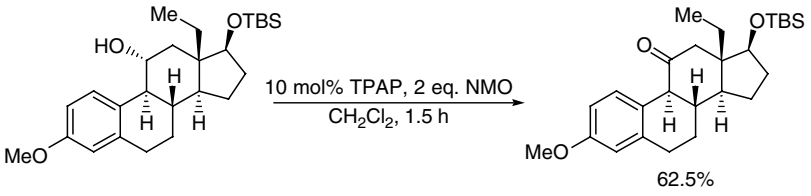
[c] Sometimes the reaction is retarded by the complexation of certain ligands with the active ruthenium species. This is prevented by the addition of acetonitrile that competes efficiently as a ligand for ruthenium. Acetonitrile can be employed as the sole solvent, although the use of a 10% of acetonitrile in CH_2Cl_2 is equally effective and the corresponding oxidation is easier to elaborate.

[d] It is advisable to add molecular sieves as desiccant because water retards the reaction, although it does not stop it. Best results are obtained with finely ground activated 4 Å molecular sieves.

[e] NMO is sold in a hydrated form. As water retards the oxidation, it may be advisable to dry the NMO by treating a solution in CH_2Cl_2 with $MgSO_4$, or by heating the NMO under vacuum during ca. 4 hours at 90°C.

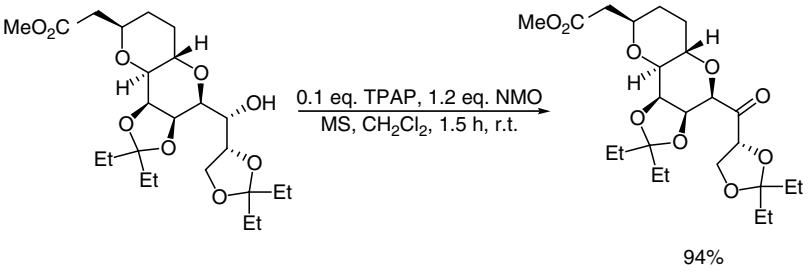
[f] Sometimes the reaction is performed at 0°C for milder conditions.

[g] It normally takes between 30 min and 12 h.



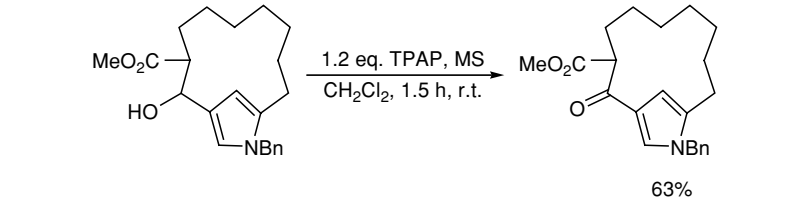
Ref. 73

A 62.5% yield of the desired ketone with no epimerization at the α-position is obtained, employing catalytic TPAP as oxidant. Other oxidizing conditions, including Collins, Sarett, Oppenauer and Swern oxidations, as well as PCC, fail to deliver an acceptable yield of ketone.



Ref. 74

While PCC produces an oxidative C-C bond breakage and Dess-Martin oxidation provides a modest 15% yield, an oxidation with catalytic TPAP yields a 94% of the desired ketone.



Ref. 75

With PDC or under Swern conditions, the sensitive pyrrole ring is destroyed, while catalytic TPAP provides a 63% yield of the desired ketone.

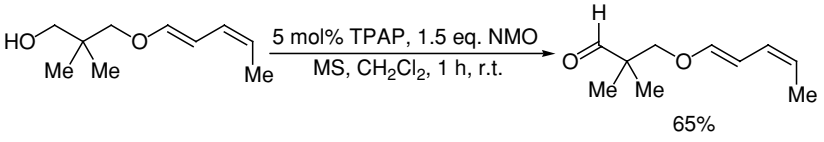
4.3.2. Functional Group and Protecting Group Sensitivity to Oxidation with TPAP

Due to the neutral and very mild conditions used in TPAP oxidations, virtually all protecting groups remain unaffected, including the very oxidant-sensitive PMB ethers[77] and *p*-methoxybenzylidene acetals;[78] and the very acid-sensitive TMS ethers.[76]

Functional groups able to withstand TPAP oxidations include esters, ethers, amides, epoxides, alkynes, urethanes and even alkenes.[61b] It is quite remarkable that alkenes are resistant to TPAP because they are known to react with *aqueous* perruthenate ions.[79]

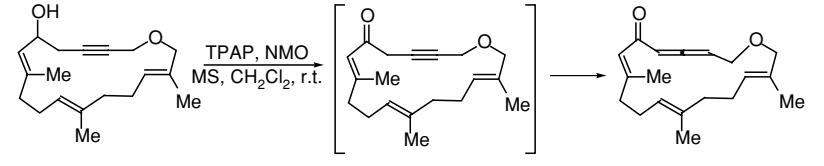
There is one report in which 1,4-cyclohexadienes are transformed into cyclohexadienones under the action of TPAP.[80]

It is possible to oxidize alcohols even in the presence of enol ethers,[81] which are compounds possessing electron-rich alkenes with a great oxidation sensitivity.



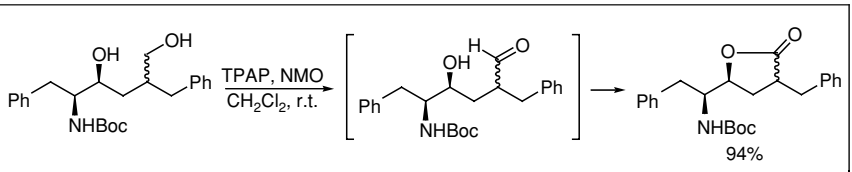
Ref. 81
The oxidation of a hindered primary alcohol succeeds in spite of potential competition from reaction with a very oxidation-prone enol ether.

During the oxidation of homoallylic and homopropargylic alcohols with TPAP, normally no migration of the alkene into conjugation with the carbonyl group occurs,[82] unless the resulting unconjugated enone has a great tendency to isomerize to a α, β-unsaturated ketone.[83] Although, it was stated[84] that homoallylic alcohols are oxidized with TPAP in a slow and inefficient manner, many successful oxidations of such alcohols with TPAP have been performed.



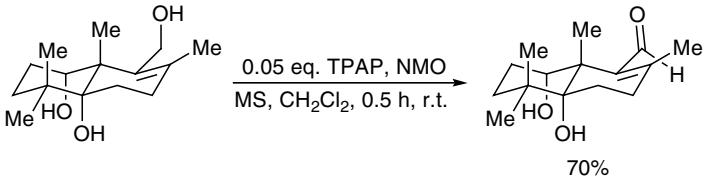
Ref. 83
This is a rare case in which an alkene migrates into conjugation with a carbonyl group during an oxidation with TPAP. Other oxidants, such as Swern or PCC, produce the same isomerization.

TPAP oxidizes lactols to lactones.[85] Treatment of 1,4- and 1,5-diols with TPAP, in which one of the alcohols is a primary one, leads to an intermediate hydroxyaldehyde that normally is transformed into a lactone[86] via an intermediate lactol. No transformation into lactone occurs when the formation of the intermediate lactol is not permited by geometric constraints.[87]



Ref. 86d

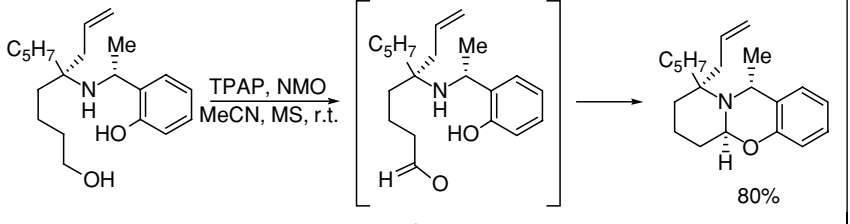
A quicker oxidation of the primary alcohol leads to a hydroxyaldehyde that equilibrates with a lactol, which is transformed into the final lactone by further oxidation.



Ref. 87a

A primary allylic alcohol is oxidized in the presence of a secondary alcohol. No further oxidation to lactone occurs for it would have to happen via a lactol that is greatly disfavoured on geometric grounds.

Alcohols can be oxidized with TPAP in the presence of tertiary amines.[88] Secondary amines are transformed into imines under the action of TPAP.[89] At the time of writing, the scientific literature contains no data regarding the possibility of performing selective oxidation of alcohols in the presence of secondary or primary amines, with the exception of the following example in which a secondary amine is trapped by reaction with an aldehyde, resulting from the selective oxidation of a primary alcohol.[90]

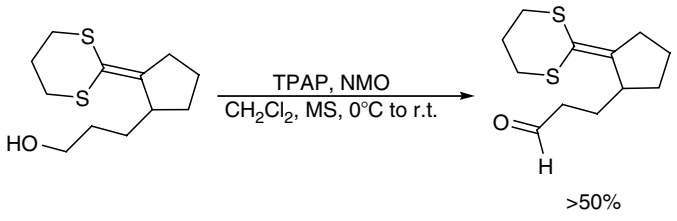


Ref. 90

An alcohol is oxidized with TPAP in the presence of a secondary amine and a free phenol. The resulting aldehyde is trapped by reaction with the amine and the phenol.

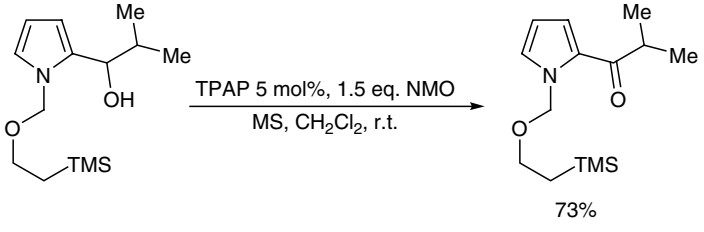
Hydroxylamines are efficiently oxidized to nitrones with TPAP.[91] Although aromatic nitrocompounds resist the action of TPAP,[92] aliphatic nitrocompounds can suffer oxidation.[93]

TPAP oxidizes sulfides[94] to sulfones. There is one published example in which an alcohol is oxidized in the presence of an unreacting ketene dithioacetal.[81b]



Ref. 81b
The sulfur functionality is not altered during the oxidation of a primary alcohol with TPAP.

It is possible to oxidize alcohols with TPAP in the presence of free phenols.[95] Although, there is one instance in which it has been published that, unless a phenol is acetylated, an oxidation with TPAP fails.[73] Oxidation-prone heterocycles, such as pyrroles[96] and indoles,[97] are not affected by TPAP during the oxidation of alcohols.

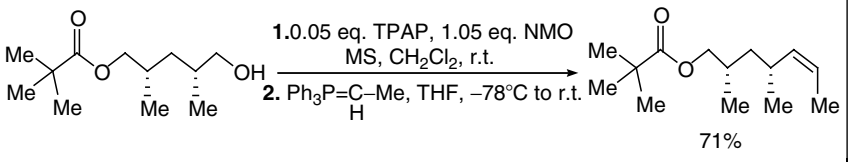


Ref. 98
An oxidation with TPAP succeeds in the presence of a very sensitive pyrrole, while Swern oxidation and PCC fail to deliver the desired ketone.

Organometallic compounds possessing carbon-tin bonds can resist he action of TPAP during the oxidation of alcohols.[99]

4.3.3. Reactions Performed *in situ* During Oxidation with TPAP

It is possible to perform the oxidation of an alcohol with TPAP and to bring together the resulting reaction mixture with a solution of phosphorane, in order to carry out a one-pot oxidation followed by Wittig reaction.[100] It is important to note that—in variance with similar protocols using other oxidants, like MnO_2,[101] $BaMnO_4$,[102] Swern,[103] Dess-Martin periodinane[104] or *o*-iodoxybenzoic acid—[105] this one-pot reaction including TPAP succeeds in the oxidation of non-benzylic alcohols and allows Wittig reactions using non-stabilized ylides employed in a moderate excess.

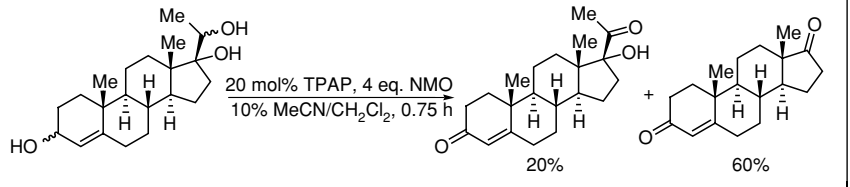


Ref. 100

Bringing together the reaction mixture, resulting from the oxidation of an alcohol with TPAP, with a solution containing a non-stabilized phosphorous ylide allows to perform a Wittig reaction with no need to isolate an intermediate aldehyde.

4.3.4. Side Reactions

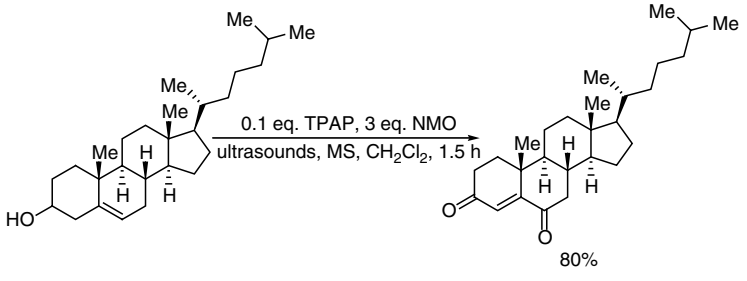
Sometimes, TPAP produces the oxidative scission of carbon-carbon bonds in α-hydroxyketones.[73]



Ref. 73

TPAP produces the oxidation of two alcohols yielding only a 20% of the desired dione. Additionally, a 60% yield of a compound resulting from an oxidative carbon-carbon bond breakage is obtained.

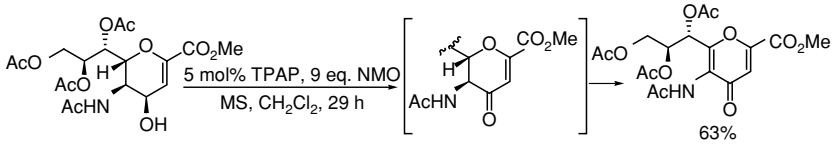
When ultrasounds are applied in order to accelerate the oxidation of homoallylic alcohols with TPAP, over-oxidation to conjugated enediones can occur.[73,67]



Ref. 67

Treatment of cholesterol with TPAP under the action of ultrasounds leads to over-oxidation to an enedione.

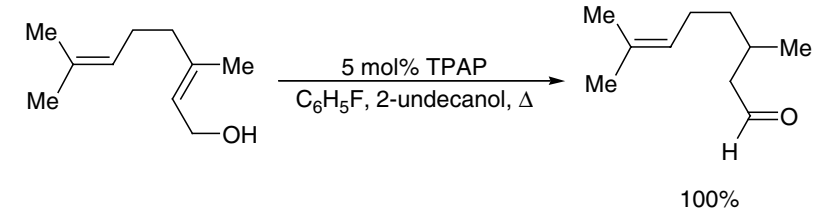
In rare cases, ketones obtained by the oxidation of alcohols with TPAP suffer an *in situ* over-oxidation, resulting in the introduction of an alkene conjugated with the ketone.[106] For example, this happens when thermodynamics are greatly favored by aromatization.



Ref. 106b

The oxidation of an alcohol with TPAP produces a ketone that suffers an *in situ* over-oxidation to a very stable γ-pyrone.

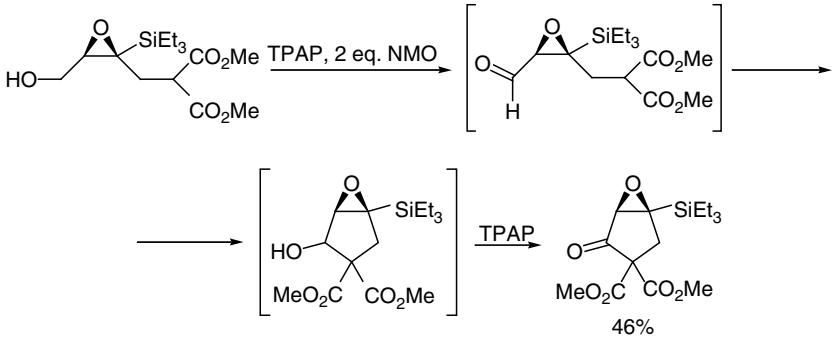
TPAP is able to produce the isomerization of allylic alcohols into saturated ketones and aldehydes.[107] This reaction is not performed under the standard conditions for the oxidation of alcohols, employing NMO as secondary oxidant, and is only efficient under very exacting experimental conditions.



Ref. 107

TPAP causes the isomerization of an allylic alcohol into an aldehyde. Best results are obtained using fluorobenzene as solvent, in the absence of a secondary oxidant and in the presence of undecan-2-ol.

Sometimes, aldehydes obtained by TPAP oxidations suffer *in situ* intramolecular transformations in substrates with a great predisposition to do so. Examples found in the literature include retro-Claisen rearrangements,[108] dipolar additions on enals,[106a] and attack of malonates[109] and indole rings[11] on aldehydes.



Ref. 109
An aldehyde resulting from the oxidation of an alcohol with TPAP, suffers an *in situ* intramolecular attack by a malonate, resulting in a secondary alcohol that is further oxidized to a ketone.

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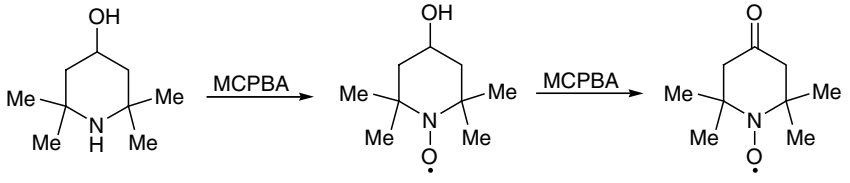
5

Oxidations Mediated by TEMPO and Related Stable Nitroxide Radicals (Anelli Oxidation)

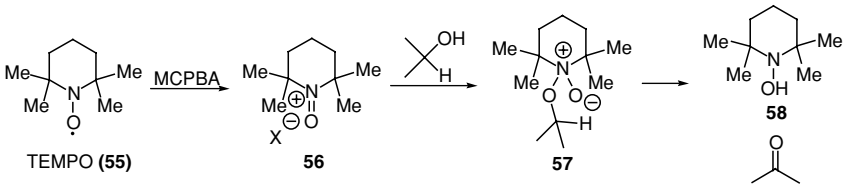
5.1. Introduction

During the 70's, Cella *et al*. treated the hindered secondary amine **52** with *m*-chloroperbenzoic acid, with the intention of transforming it into the nitroxide **53**.[1] Unexpectedly, the oxidation of the amine functionality was accompanied by the transformation of the alcohol moiety into a ketone, resulting in the formation of compound **54**.

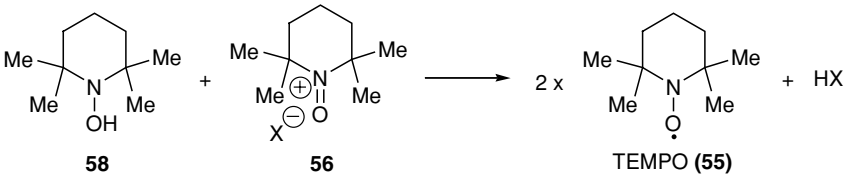


52 **53** **54**

As peracids react very sluggishly with alcohols, it was apparent that the presence of a nitroxide was playing an important role in the oxidation of the alcohol into a ketone. This seminal serendipitous observation led to the development of the first description of the oxidation of alcohols mediated by catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (**55**), published almost simultaneously by Cella *et al*.[2] and Ganem.[3] These authors presented two papers with remarkably similar contents, in which alcohols were oxidized by treatment with MCPBA in CH_2Cl_2 at room temperature in the presence of a catalytic amount of TEMPO **(55)**. In both papers, a plausible mechanism is presented, whereby *m*-chloroperbenzoic acid oxidizes TEMPO **(55)** to an oxoammonium salt **56**. This oxoammonium salt **56**, as detailed in Ganem's paper, can react with the alcohol producing an intermediate **57**, which can deliver a carbonyl compound by a Cope-like elimination.



The resulting hydroxylamine **58** can further react with the oxoammonium salt **56**, resulting in the formation of two equivalents of TEMPO that, therefore, is able to re-enter into a catalytic cycle.



This mechanism is consistent with the ability of stoichiometric oxoammonium salts to oxidize alcohols, a fact that was already published in 1965 by Golubev *et al.*,[4] and was later confirmed by other researchers.[5]

As soon as, it was learnt that oxoammonium salts, which are unstable compounds, are very efficient in the oxidation of alcohols, and that they can be generated *in situ* by treating catalytic TEMPO, or related compounds, with MCPBA acting as a secondary oxidant, it became apparent that other secondary oxidants would be more practical than MCPBA in Synthetic Organic Chemistry. MCPBA is a very energetic oxidant that reacts with many functionalities including alkenes and ketones.

> Nevertheless, Cella *et al.* have proved that employing MCPBA as secondary oxidant in TEMPO-mediated oxidations may have a number of advantages when a one-pot oxidation of an alcohol with a concurrent alkene epoxidation or a Baeyer-Villiger oxidation is desired.[6] The use of MCPBA as a secondary oxidant in TEMPO-mediated alcohol oxidations was recently reviewed.[7]

Thus, Semmelhack *et al.*[8] in 1983 published the oxidation of alcohols by an oxoammonium salt, generated by electrooxidation of catalytic TEMPO; and, in 1984, Semmelhack *et al.*[9] published a similar oxidation of alcohols, in which catalytic TEMPO is oxidized by Cu (II), which itself can be used in catalytic quantities, being generated by the oxidation of catalytic Cu (I) by excess of gaseous oxygen.

Section 5.1. References

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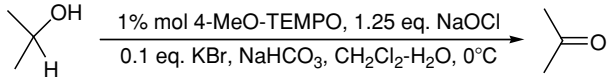
5.2. TEMPO-mediated Oxidations

In 1987, Anelli *et al.* published a landmark paper[10] on TEMPO-mediated oxidations, which signalled the beginning of the routine employment of catalytic oxoammonium salts in the oxidation of alcohols. In this paper, a protocol was established, whereby alcohols can be oxidized to aldehydes and ketones in a biphasic CH_2Cl_2-water medium, containing ca. 1% mol of a TEMPO related stable nitroxide radical, excess of bleach (NaOCl), KBr and $NaHCO_3$. Usually, CH_2Cl_2 is used in the biphasic system. Other organic solvents more rarely employed include THF[11] and PhMe-EtOAc.[12] Under these conditions, primary alcohols are transformed in 3 min at 0°C into the corresponding aldehydes, while secondary alcohols are transformed into ketones in 7–10 min.



Anelli's protocol for the TEMPO-mediated oxidation of alcohols

$NaHCO_3$ must be added in order to achieve a pH of ca. 8.6–9.5 because commercial bleach possesses a very basic pH = 12.7 that greatly retards the reaction.

> Sometimes, it is advisable to adjust the pH of the biphasic system at 6.5–7.5 by the addition of 0.1 N HCl, in order to avoid base-induced side reactions.[13]

Potassium bromide produces an accelerating effect that has been attributed to the generation of HOBr, which is a stronger oxidant than HOCl. Interestingly, the oxidation proceeds at a higher speed at 0°C than at room temperature, a fact that can be explained by the instability of the primary oxidant—that is an oxoammonium salt—above 0°C.

Oxoammonium salts react with water resulting in the generation of hydrogen peroxide.[14] This side reaction is minimized at 0°C. A substantial amount of heat is evolved in oxidations following Anelli's protocol; therefore, on multigram scale reactions it may be very difficult to keep a temperature as low as 0°C. In such cases, an efficient oxidation can be achieved at 10–15°C, a temperature in which the decomposition of oxoammonium compounds does not compete substantially with the desired oxidation of alcohols.[15]

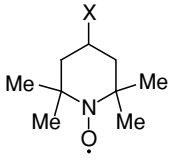
Under the standard protocol, the over-oxidation of aldehydes into carboxylic acids is very slow.

In fact, TEMPO inhibits the auto-oxidation of aldehydes by molecular oxygen and, therefore, there is no need for an inert atmosphere.[28] TEMPO **(55)** was found to be a stronger inhibitor of the over-oxidation to carboxylic acids than the 4-MeO-TEMPO analogue **59**.[18a]

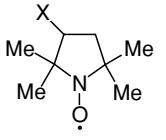
Anelli's TEMPO-mediated oxidation can be accelerated by the addition of a quaternary ammonium salt, like Aliquat 336, acting as a phase transfer catalyst. This can be advisable in the oxidation of hindered secondary alcohols but can encourage the over-oxidation of primary alcohols to carboxylic acids.[16]

Although TEMPO **(55)**, which is very easy to prepare[17] and quite cheap—specially considering that it is employed in very small quantities—, is the most commonly used stable nitroxide radical. Other TEMPO related nitroxide radicals, such as 4-MeO-TEMPO[18] **(59)** and 4-AcHN-TEMPO[5d, 12] **(60)** can also be employed.

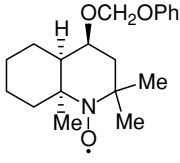
Less commonly used TEMPO-related nitroxyl radicals include 4-$PhCO_2$-TEMPO[19] **(61)**, 4-NC-TEMPO[20] **(62)**, **63**,[20] 4-(4-^{t}Bu$C_6H_4CO_2$)-TEMPO[19c] **(64)**, **65**,[19c] **66**[19c] and **66a**.[21]



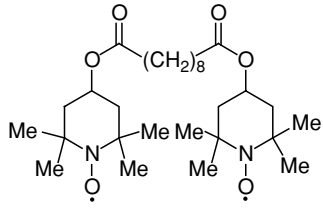
59: X= MeO-
60: X= AcHN-
61: X= BzO-
62: X= NC-
64: X= 4-^{t}BuPhCO$_2$–



65: X= $BzOCH_2$–
66: X= MeO_2C-



66a



63

Additionally, the use of unsymmetrical TEMPO analogues, able to perform enantioselective alcohol oxidations[22] and silica-supported TEMPO,[23] must be mentioned.

Apart from sodium hypochlorite, a number of alternative secondary oxidants for TEMPO-mediated alcohol oxidations can be employed. These include cerium (IV) ammonium nitrate (CAN),[24] trichloroisocyanuric acid (TCCA),[25] oxone®,[26] MCPBA,[2,3,7] $PhI(OAc)_2$,[27] *N*-chlorosuccinimide,[28] sodium bromite,[29] electrooxidation,[8,21] H_5IO_6[26] and a polymer-attached diacetoxybromide (I) complex.[30]

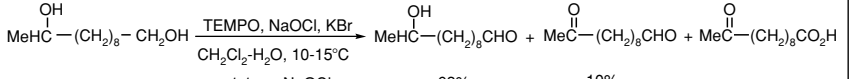
The aerobic oxidation of alcohols mediated by TEMPO, used in combination with other catalysts, such as $CuBr \cdot Me_2S$,[31] $RuCl_2(PPh_3)_3$[32] or the enzyme laccase,[33] must also be mentioned.

One important limitation of TEMPO-mediated oxidations, under Anelli's conditions, originates from competing reactions produced by HOCl, generated *in situ* from NaOCl. This problem can be solved by the use of [bis(acetoxy)iodo]benzene (BAIB) as a secondary oxidant following the protocol of Piancatelli and Margarita[27] which has proved to be particularly efficient in difficult substrates,[34] and it is a highly recommended alternative to Anelli's procedure when oxidations with oxoammonium salts are desired.

The use of [bis(acetoxy)iodo]benzene as secondary oxidant in TEMPO-mediated oxidations was first reported in 1997 by Piancatelli, Margarita *et al.*[27] In the foundational paper, it was stated that the reaction "... can be performed in an open flask without any particular precautions, e.g. inert atmosphere or dry solvents ...". In fact, not following these particular precautions could be mandatory, as Mickel *et al.*[35] found that, in the oxidation of a difficult substrate on a big scale, results were not reproducible unless 0.1 equivalents of water are added to the reaction mixture. One advantage of the employment of [bis(acetoxy)iodo]benzene is that, iodobenzene, a rather inert side compound, is generated, which needs not be removed before performing many subsequent reactions.

Interestingly, using Anelli's protocol for the oxidation of alcohols allows quite selective oxidation of primary alcohols in the presence of secondary ones, which is effective in both transforming primary alcohols into aldehydes[36, 37] and having a complete oxidation of primary alcohols into carboxylic acids.[38]

Stoichiometric oxoammonium salts have proved to be able to selectively oxidize less hindered secondary alcohols in 1,2-diols containing two secondary alcohols.[39]



1.1 eq. NaOCl	68%	10%	-
2.2 eq. NaOCl	-	69%	-
3.6 eq. NaOCl + Aliquat 336	-	-	57%

Ref. 36a

Using 1.1 equivalents of NaOCl, the selective oxidation of the primary alcohol occurs. With, 2.2 equivalents of NaOCl, the main reaction product results from the oxidation of both alcohols, giving a ketoaldehyde. Finally, employing 3.6 equivalents of NaOCl, and including Aliquat 336 as a phase-transfer catalyst that greatly accelerates the reaction, a complete oxidation of the secondary alcohol to ketone and the primary alcohol to a carboxylic acid occurs.

Two interesting recent modifications of Anelli's protocol involve the employment of silica-supported TEMPO[40] and a kind of polymer-immobilized TEMPO (PIPO).[41] PIPO is easily prepared from a cheap polymer called Chimassorb 944 that is used as an antioxidant and light stabilizer for plastics.

5.2.1. General Procedure for Oxidation of Alcohols with TEMPO-NaOCl (Anelli's Protocol)

A two phase system consisting of: a) a ca. 0.2–2.9 M solution of 1 equivalent of the alcohol in CH_2Cl_2, containing ca. 0.2–5% mol—typically 1–2% mol—of TEMPO[a] (MW = 156.25),[b] and b) a ca. 0.02–2.6 M solution of ca. 0.02–0.5 equivalents—typically 0.1 equivalents—of KBr (MW = 119.01) or NaBr (MW = 102.9) in water, is vigorously stirred over a water-ice bath (0°C) or an ice-salt bath (−10°C).[c] Over this two phase system, ca. 1.09–1.4 equivalents of NaOCl in a fresh solution, prepared by adjusting a ca. 5–13% aqueous solution of NaOCl to a pH of 8.6–9.5 by addition of an aqueous solution of $NaHCO_3$,[d] are slowly added.[e] When most of the starting compound is consumed,[f] the organic phase is separated and the aqueous phase is washed with CH_2Cl_2. The collected organic phases are washed with a sodium thiosulfate aqueous solution and water or brine. Optionally, the collected organic phases may be washed with a solution of ca. 0.2–2.5 equivalents of KI (MW = 166.01) in 10–20% hydrochloric acid, before washing with the sodium thiosulfate solution. Finally, the organic solution is dried (Na_2SO_4 or $MgSO_4$) and concentrated, giving a residue that may need further purification.

[a] Other TEMPO-related nitroxyl radicals, such as 4-MeO-TEMPO, 4-AcO-TEMPO or 4-AcHN-TEMPO, can also be used.

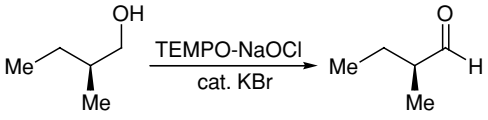
[b] Ca. 0.05 equivalents of a phase transfer catalyst, such as Aliquat 336 (tricaprylmethylammonium chloride), can be added in order to accelerate the oxidation. This can promote over-oxidation of aldehydes into carboxylic acids.

[c] It is convenient to keep the internal temperature as low as practical because the primary oxidant—consisting of an oxoammonium salt—is decomposed by reaction with water at a higher temperature.

[d] Ca. 0.1–0.4 equivalents of $NaHCO_3$ (MW = 84.01) are needed.

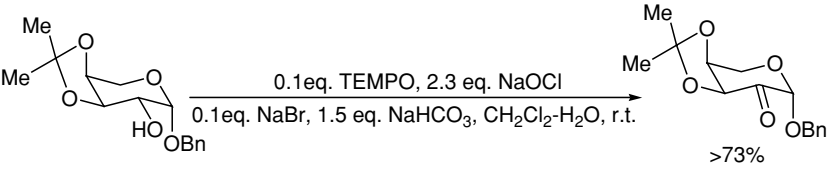
[e] The reaction is highly exothermic, therefore the NaOCl solution must be added at such a rate so as to avoid the internal reaction temperature to exceed 10–15°C, a temperature at which the decomposition of the primary oxidant—consisting of an oxoammonium salt—by reaction with water still does not compete substantially with the oxidation of the alcohol. While in oxidations on a very small scale, the NaOCl solution can be added at once, on a multigram scale, it may be necessary to perform the addition during a period in excess of 1 h.

[f] The oxidation of primary alcohols to aldehydes is normally complete in ca. 3 min, while the oxidation of secondary alcohols to ketones normally takes 7–10 min. Therefore, a few minutes of stirring—after the addition of NaOCl is finished—normally suffices for a complete oxidation. Nevertheless, it is common to allow the reaction to proceed for as long as 1–1.5 h after the addition of NaOCl. An excessive reaction time can promote the over-oxidation of aldehydes into carboxylic acids.



oxidant	%yield	% ee
PCC	45	55
SO_3·Py	56	87
Swern	63	90
Dess-Martin	75	90
TEMPO-NaOCl	82	93

Ref. 42
An oxidation with TEMPO-NaOCl provides the desired aldehyde with the best yield and with a greatest level of enantiomeric excess (ee) comparing with other common oxidants (see table above). Adapted from reference 42 by permission from Georg Thieme Verlag.

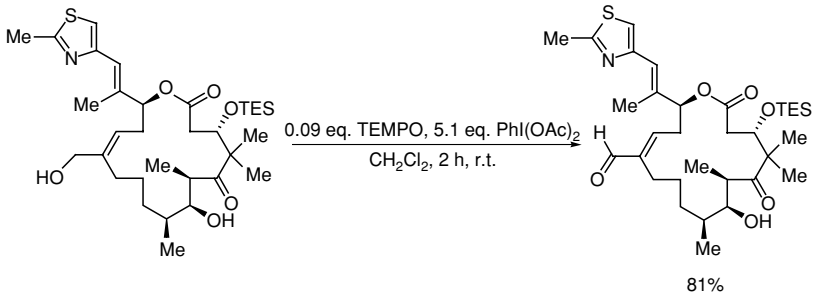


Ref. 43
An oxidation with TEMPO-NaOCl is preferred over oxidations with Swern or CrO_3 because it delivers the desired ketone as a purer product and in a higher yield.

5.2.2. General Procedure for Oxidation of Alcohols with TEMPO-PhI(OAc)$_2$ (Protocol of Piancatelli and Margarita)

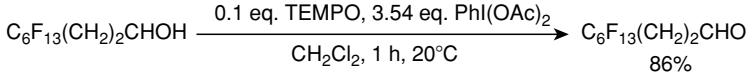
A ca. 0.04–1 M solution of the alcohol in CH_2Cl_2,[a] containing 0.09–0.2 equivalents—typically 0.1 equivalents—of TEMPO (MW = 156.25) and 1.1–5 equivalents—typically 1.1 equivalents—of $PhI(OAc)_2$ (BAIB, MW = 322.1), is stirred at room temperature till most of the starting alcohol is consumed.[b] Then, some CH_2Cl_2 may be optionally added in order to facilitate subsequent washings. The reaction mixture is washed with an aqueous sodium thiosulfate solution. Optionally, the organic phase can be washed with aqueous $NaHCO_3$ and brine. Finally, the organic solution is dried (Na_2SO_4) and concentrated, giving a residue that may need further purification.

[a] There is no need to employ dry CH_2Cl_2 and the reaction may be run in the open air.
[b] It normally takes about 2–12 h.



Ref. 34c

A selective oxidation of a primary alcohol, in the presence of a secondary one in a complex substrate, is achieved by using an oxoammonium salt as primary oxidant under the protocol of Piancatelli and Margarita.



Ref. 34e

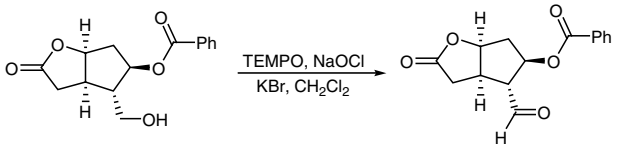
After considering many other oxidants—including Dess-Martin periodinane, Swern, PCC and TEMPO/NaOCl—TEMPO in the presence of $PhI(OAc)_2$ was selected because of economy, convenience and yield.

5.2.3. Functional Group and Protecting Group Sensitivity to Oxidations Mediated by TEMPO

TEMPO-mediated oxidations can be performed under almost neutral conditions. Therefore, acid- and base-sensitive functionalities and protecting groups can remain unchanged during TEMPO-mediated oxidations.

Although TEMPO-mediated oxidations under Anelli's protocol are routinely performed at a slightly basic pH of 8.6–9.8,[10] obtained by buffering the bleach solution with $NaHCO_3$, sometimes, in order to avoid base-induced side reactions, it is advisable to adjust the pH at 6.5–7.5 by adding an acid.[13] A proper adjustment of the pH for example allows to obtain carbonyl compounds without α-epimerization in difficult substrates in which other common oxidants fail.[42]

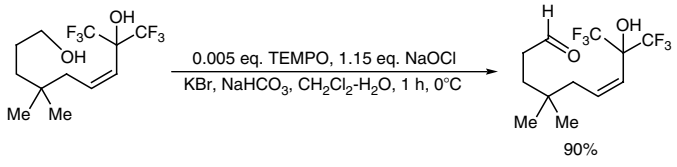
It is important to note that under the slightly basic conditions (pH 8.6–9.8) employed under the standard Anelli's protocol, many base-sensitive functional groups remain unaffected, including the ubiquitous ester groups.[44] On the other hand, it may be advisable to limit the reaction time in order to minimize the hydrolysis of acetates.[16]



Ref. 44e
The benzoate and the lactone are not hydrolyzed under standard Anelli's conditions, regardless of the presence of water under mild basic conditions.

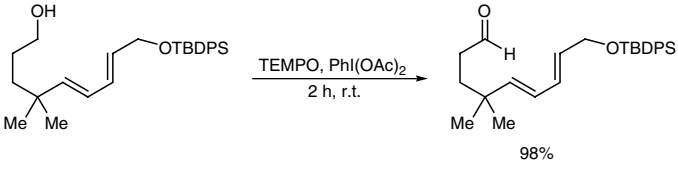
The most serious limitation of TEMPO-mediated oxidations under Anelli's conditions is posed by the presence of HOCl—generated *in situ*—as a secondary oxidant, a quite reactive chemical that adds to olefins and produces electrophilic chlorination in many electron-rich substrates.

Anelli's protocol is not generally compatible with the presence of olefins,[10] although the less reactive olefins conjugated with electron-withdrawing groups, like carbonyls, are not affected,[45] and occasional examples in which normal olefins remain unchanged during the oxidation of alcohols are found in the literature.[13]



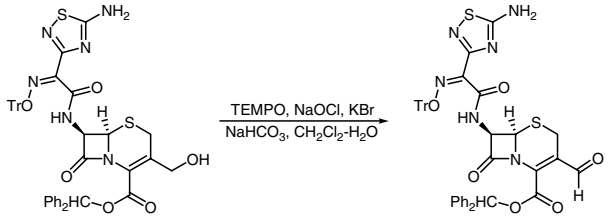
Ref. 13
This a rare case in which an olefin fails to react with HOCl during the oxidation of an alcohol under Anelli's protocol.

Side reactions caused by the presence of HOCl during Anelli's oxidations can be avoided by using a different secondary oxidant. For instance, the experimental conditions of Piancatelli and Margarita, employing $PhI(OAc)_2$ as a secondary oxidant, are compatible with the presence of olefins.[46]



Ref. 46a
In variance with Anelli's conditions, TEMPO-mediated-oxidations—under the protocol of Piancatelli and Margarita—are compatible with the presence of olefins.

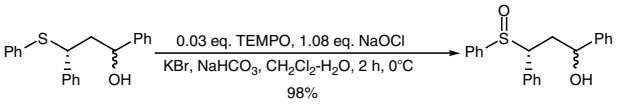
A literature survey shows a limited number of examples, in which amines remain unchanged[47] during the oxidation of alcohols with TEMPO. These include one example in which an alcohol is oxidized even in the presence of a more oxidation-prone primary amine.[44d]



Ref. 44d

This is a rare case in which an alcohol is selectively oxidized in the presence of a primary amine.

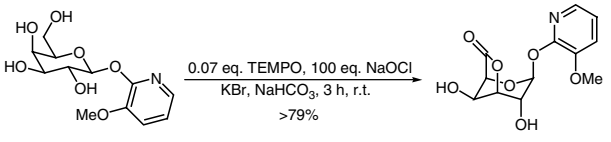
Sulfides are transformed very easily into sulfoxides during TEMPO-mediated oxidations. It is even possible to oxidize sulfides without affecting alcohols in the same molecule.[48]



Ref. 48

A sulfide is selectively oxidized under Anelli's conditions with no reaction on the secondary alcohol.

Lactols are easily transformed into lactones in TEMPO-mediated oxidations.[49] When the oxidation of a diol leads to a hydroxyaldehyde that is able to equilibrate with a hemiacetal, the latter is further oxidized to a lactone.[50] Interestingly, as TEMPO-mediated oxidations can be very selective in favouring oxidations of less hindered alcohols, lactone formation from diols can be very regioselective.[50c]

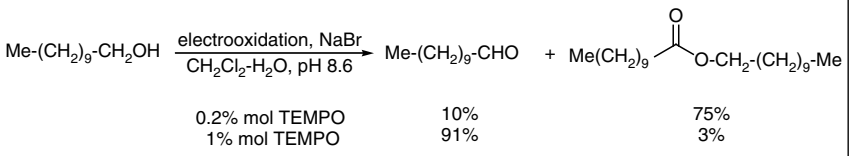


Ref. 50c

There is an initial regioselective oxidation of the primary alcohol into an aldehyde. The aldehyde equilibrates with a lactol that is oxidized to a lactone. Thus, the initial regioselective oxidation of the primary alcohol allows a very selective formation of a lactone in the presence of two unreacting secondary alcohols.

5.2.4. Side Reactions

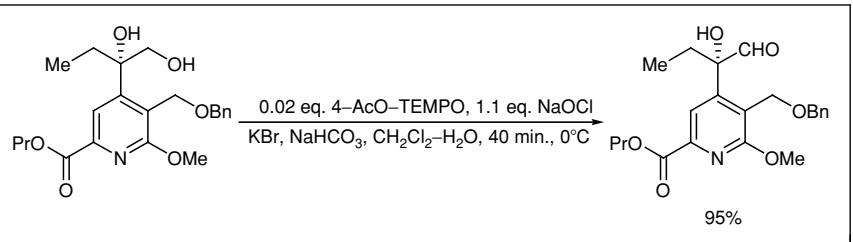
During the oxidation of primary alcohols with oxoammonium salts, sometimes dimeric esters are formed.[20a] This can be minimized by increasing the quantity of TEMPO.



Ref. 20a

An oxoammonium salt operating as a primary oxidant is generated by oxidation of catalytic TEMPO with Br_2, which, in turn, is formed by electrooxidation of bromide anion. The formation of a dimeric ester side-compound is minimized increasing the quantity of TEMPO.

1,2-Diols may suffer an oxidative C-C bond breakage under Anelli's oxidation, unless the quantity of NaOCl is carefully controlled.



Ref. 44b

The amount of NaOCl must be carefully controlled in order to avoid an oxidative breakage of a carbon-carbon bond in the starting 1,2-diol.

The HOCl used as secondary oxidant under Anelli's conditions can add to olefins[10] and react as an electrophilic chlorinating agent.

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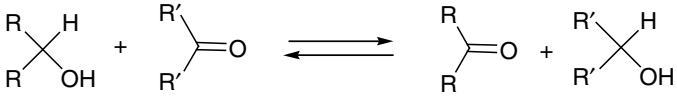
6

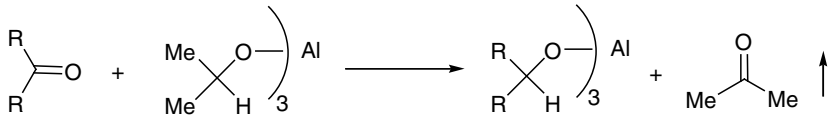
Oxidations by Hydride Transfer from Metallic Alkoxide

6.1. Introduction

At the beginning of the 20th century, Meerwein,[1] Ponndorf[2] and Verley[3] showed that alcohols and carbonyl compounds can equilibrate as in Equation below under the action of Al^{3+} alkoxides.



Very soon, it was found that the equilibrium could be shifted to one side by employing aluminium isopropoxide and removing the volatile acetone on the right of the Equation below.



In this way, an aldehyde or ketone could be reduced to the corresponding alcohol after hydrolysis of the resulting aluminium alkoxide. This reaction is known as the Meerwein-Ponndorf-Verley reduction.

Section 6.1. References

1 Meerwein, H.; Schmidt, R.; *Lieb. Ann. Chem*. **1925,** *444,* 221; **CA** 19:3251.
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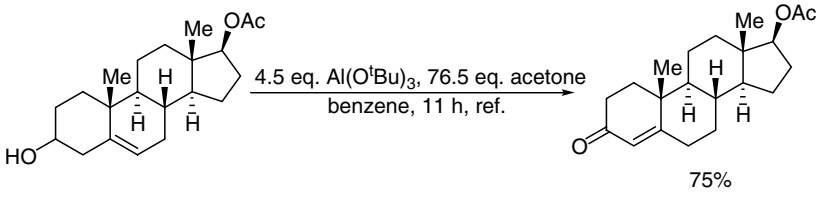
6.2. Oppenauer Oxidation

6.2.1. Experimental Conditions

Shifting the equilibrium so as to oxidize a valuable alcohol, rather than to reduce a valuable carbonyl compound, is more demanding from the experimental point of view. In this case, the removal of the alcohol, resulting from the reduction of a cheap aldehyde or ketone used as oxidant, meets the problem of alcohol being less volatile than the corresponding carbonyl compound. Nevertheless, the practical realization of such oxidation was proved by Oppenauer in 1937.[4]



Ref. 4

In the foundational paper of Oppenauer, the equilibrium is shifted to the oxidation of the sterol, thanks to the use of a great excess of acetone and to some very favourable thermodynamics in which an alkene enters into conjugation with the resulting ketone.

Oppenauer was able to shift the equilibrium towards the oxidation of a number of sterols, by employing an excess of cheap acetone as oxidant and taking advantage of some very favourable thermodynamics in oxidations, in which an alkene enters into conjugation with the resulting ketone.

> In the vast majority of cases, the equilibrium in Oppenauer oxidations is shifted to the right by employing an excess of oxidant. When aldehydes or ketones with a certain volatility are formed during Oppenauer oxidations, it is possible to shift the equilibrium by removing the product by distillation under reduced pressure, while oxidants with a low volatility, such as benzaldehyde, cinnamaldehyde or piperonal, are used.[5] This experimental procedure, although very suitable for multigram scale reactions, is seldom employed because of the inconvenience of running a reaction while a distillation under vacuum is performed.

The so-called Oppenauer oxidation proved to be extremely successful in the oxidation of sterols. On the other hand, its application—in the original formulation—to the obtention of ketones outside the field of steroids and to the preparation of aldehydes met a more limited success because of less favourable thermodynamics and side reactions, induced by the basic character of the aluminium alkoxides.

The position of the equilibrium in the first equation (under 6.1) is controlled by the oxidation potential of the carbonyl compounds. Ketones and aldehydes with a high oxidation potential oxidize alcohols favourably

Table 6.1[a]

Carbonyl compound	E_0 (oxidation potential, mV)
Diphenoquinone	954
1,4-Benzoquinone	715
1,3-Dimethoxyacetone	350
Chloral	277
Formaldehyde	257
Acetaldehyde	226
ω- Piperidinoacetophenone	203
Benzaldehyde	197
Methoxyacetone	189
Cyclohexanone	162
Δ^5- Cholesten-3-one	153
Acetone	129
Benzophenone	129
Cyclopentanone	123
Acetophenone	118
Fluorenone	117
Diethyl ketone	110
Diisobutyl ketone	102
Camphor	82
Δ^4- Cholesten-3-one	63

[a] Taken from ref. 6. The experimental estimations of oxidation potentials from this reference may not be completely accurate; therefore, this Table provides only a rough approximation of the oxidation equilibria in carbonyl compounds. Cf. ref. 7.

whose corresponding carbonyl compounds possess a lower oxidation potential. Table 6.1 shows a number of oxidation potentials.[6]

Obviously, a greater difference in oxidation potentials causes an equilibrium with a maximum displacement on one side. For example working with equimolar amounts at room temperature, a 10 mV difference in oxidation potential produces a mixture containing 40.5% of the carbonyl compound with the greater oxidation potential and 59.5% of the compound with the lesser oxidation potential. With a 100 mV oxidation potential difference, the corresponding figures are 98% and 2%. Equilibria can be further shifted in the desired direction by employing an excess of carbonyl compound operating as oxidant.

Inspection of Table 6.1 shows that the classical oxidation of sterols on the alcohol at the 3-position, using acetone as oxidant, works efficiently; thanks to the migration of the alkene. Thus, the oxidation of cholesterol with acetone ($E_0 = 129\,mV$) must proceed via the thermodynamically disfavoured Δ^5-cholesten-3-one ($E_0 = 153\,mV$) that evolves to the very stable Δ^4-cholesten-3-one ($E_0 = 63\,mV$). In fact, acetone lacks oxidizing power for the obtention of many ketones as well as for the preparation of virtually all aldehydes.

It has been suggested that in Oppenauer oxidations using acetone, the genuine oxidant is one product, resulting from the autocondensation of acetone, possessing a higher oxidation potential.[8]

Not surprisingly, nowadays most Oppenauer oxidations are carried out employing cyclohexanone as oxidant because—for structural reasons—this ketone possesses an exceptionally high oxidation potential among ketones. Similarly, *N*-methyl-4-piperidone is used quite often because it possesses an oxidation potential close to cyclohexanone, while it is very easy to remove together with its reduction product from the reaction mixture by washing with aqueous acid.[9]

Although, a general trend exists with quinones for having a very high oxidation potential, ketones, possessing low oxidation potentials, and aldehydes positioned in the middle, quite similar compounds may in fact show very diverse oxidation potentials. For example, camphor—which is a substituted cyclohexanone—possesses a very low oxidation potential of 82 mV, differing greatly from the oxidation potential of 162 mV for cyclohexanone. Interestingly, contrary to intuition, conjugation with alkenes or aromatic rings has little effect on oxidation potentials of aldehydes and ketones. For example the oxidation potentials of acetone, acetophenone and benzophenone differ in less than 12 mV. The introduction of electron-withdrawing substituents close to the carbonyl group produces a substantial increase of the oxidation potential. This is conspicuous in the series acetone (129 mV), methoxyacetone (189 mV) and 1,3-dimethoxyacetone (350 mV). This explains why alcohols, whose oxidation results in the formation of aldehydes or ketones possessing the moiety –(C=O)-C-X where X is a heteroatom, are refractory to oxidation under Oppenauer conditions.[10]

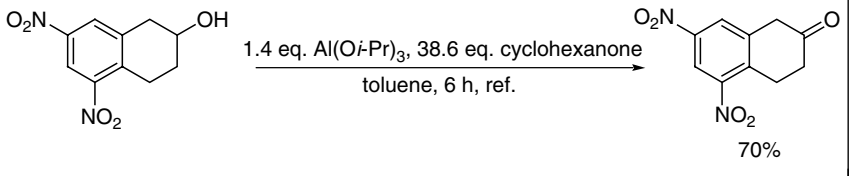
A naïve look at Table 6.1 would suggest that aldehydes, quinones and some ketones, like 1,3-dimethoxyacetone, would operate as very good oxidizing agents, allowing for example the preparation of aldehydes. In fact, these compounds possessing very high oxidation potentials are more reactive than simple ketones like cyclohexanone and tend to produce many side reactions, like aldol condensations.

p-Benzoquinone is occasionally employed as oxidant in Oppenauer oxidations.[11] It can operate at room temperature[12] and the oxidation can be carried out using a catalytic amount under an atmosphere of oxygen that recycles the generated hydroquinone back into *p*-benzoquinone.[13] Both *p*-benzoquinone and hydroquinone are very reactive and tend to produce side compounds.[6c] On the other hand, *p*-benzoquinone has a tendency to promote over-oxidations.[14]

Normally, Oppenauer oxidations are performed employing Al^{3+} cations as catalyst because aluminium alkoxides possess a good balance of a desired high hydride transfer capability versus a low propensity to promote undesired base-induced reactions, like aldol condensations and Tischtschenko reactions. In the reaction, as originally described by Oppenauer, aluminium *t*-butoxide is used as catalyst,[4] because its high basicity allows a very favourable equilibrium towards the formation of the aluminium alkoxide of the alcohol whose oxidation is desired. However,

nowadays the employment of aluminium isopropoxide is preferred, because it is cheaper and much easier to prepare.[15] The less favorable equilibrium for the generation of the alkoxide of the starting compound and the interference in the oxidation-reduction equilibria of isopropanol, do not seem to greatly detract from the final oxidation yields.

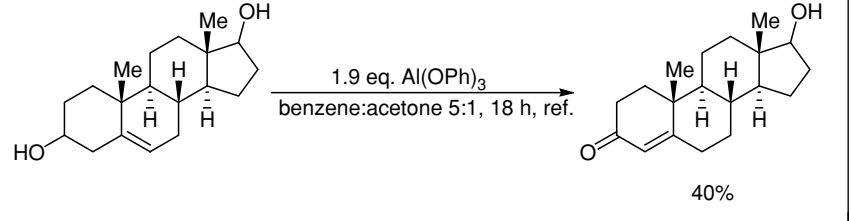
Freshly distilled aluminium isopropoxide exists as the so-called "melt" form, which is a thick liquid that solidifies over several weeks.[16] The resulting crystals represent the "solid" form that can also be obtained by crystallization from a solution in an organic solvent. In the "melt" form, aluminium isopropoxide exists as a trimer, while in the "solid" form it exists as a tetramer. Interestingly, when the "melt" form is dissolved in benzene at room temperature, the transformation of trimer into tetramer is much slower than in the neat[17] and it has been shown that trimers and tetramers may possess quite different chemical behaviour.[18] The "melt" form possesses the practical advantage of showing greater solubility in organic solvents and can be easily generated from the "solid" form by heating. As long as the authors of this book are aware, in no case a different behaviour of the "melt" versus the "solid" was reported in Oppenauer oxidations, although such outcome could be expected. Occasionally, aluminium phenoxide is used in Oppenauer oxidations. Quite puzzlingly, although it leads to a disfavored equilibrium with a small percentage of reacting aluminium alkoxide, it is reported as allowing Oppenauer oxidations under milder conditions.[19]



Ref. 20

This alcohol is oxidized using an Oppenauer reaction under typical conditions with aluminium isopropoxide and cyclohexanone in boiling toluene.

Because of the subtle energetic factors, allowing the oxidation of a certain alcohol employing the Oppenauer conditions, it is possible to carry out regioselective oxidations based solely on thermodynamics.[21]

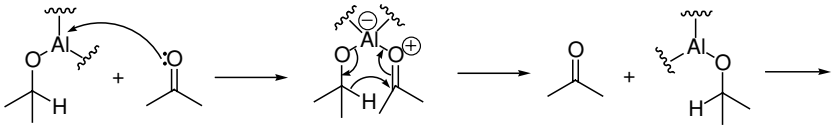


Ref. 19a

A selective oxidation of a cyclohexanol is achieved in the presence of a cyclopentanol using acetone, which is a very mild oxidant.

6.2.2. Mechanism

The available experimental data supports a mechanism for the Oppenauer oxidation, involving an initial complexation of a carbonyl group with the aluminium from an aluminium alkoxide, followed by a rate-determining hydride transfer via a six-membered transition state.[22]



Oppenauer oxidations, employing aluminium alkoxides, must be carried out in organic solvents unable to compete with the carbonyl group for complexation with aluminium. Although, originally benzene was the most commonly used solvent, nowadays toluene is greatly preferred because it is less toxic and has a higher boiling point that allows quicker oxidations. Occasionally, the reaction is performed in boiling xylenes. These aromatic solvents have the advantage of allowing the removal of water—which inhibits the Oppenauer oxidation because of complexation with aluminium—by azeotropic distillation. Normally, the reaction is carried out at the reflux temperature of the solvent during many hours. In some sensitive substrates, it may be advisable to perform the oxidation at room temperature, although this can demand several weeks.[23]

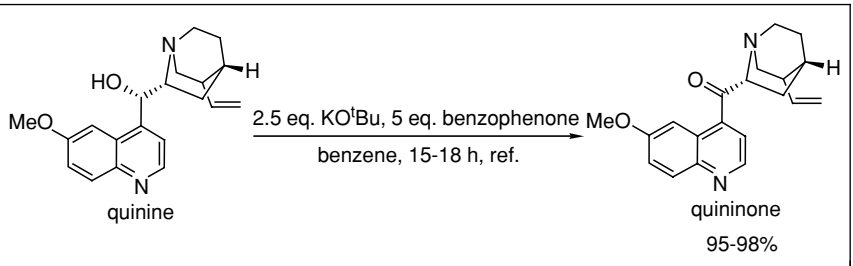
> Oppenauer oxidation, using alkoxides other than aluminium, operates via a hydride transfer mechanism similar to the one depicted in the above Equation, although a complexation of the metal with the carbonyl group may not be present.[22d] Evidence for a radical mechanism was put forward in the case of the interaction between lithium isopropoxide and benzophenone.[24]

The Oppenauer oxidation presents two important limitations: on one side it is unable to oxidize certain alcohols because of unfavourable thermodynamics, and on the other side, base-induced reactions between the oxidant and the product may become dominant. That is why, it is seldom employed for the obtention of aldehydes because these compounds react readily under basic conditions. On the other hand, although aluminium alkoxides promote aldol condensations, many base-sensitive functional groups such as most esters—but not formates—[25] resist its action.

6.2.3. Oxidations Using Sodium or Potassium Alkoxides

Apart from aluminium, many other metals were tested in Meerwein-Ponndorf-Verley reductions and Oppenauer oxidations during the early years of research on hydride transfer from alkoxides.[26] A consensus was

reached, in which aluminium alkoxides were considered superior and were used in the vast majority of cases. Nonetheless, the occasional employment of sodium or potassium alkoxides must be mentioned. For example, Woodward *et al*. found that the important substrate quinine is resistant to oxidation under standard Oppenauer conditions, probably because of adverse thermodynamics, but it can be oxidized with potassium *t*-butoxide and benzophenone in boiling benzene.[10b]

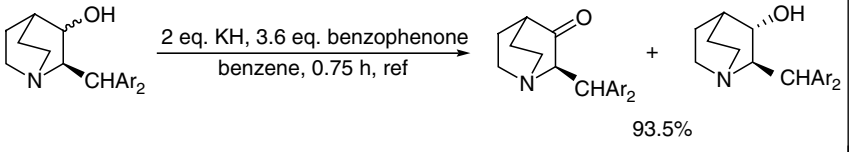


Ref. 10b

Quinine remains unchanged with aluminium alkoxides employing the standard Oppenauer protocol, while it is oxidized in good yield by using KO^{t}Bu to generate a potassium alkoxide that transfers a hydride to benzophenone, according to Woodward's modification of the method of Oppenauer.

The Woodward modification of the Oppenauer oxidation is occasionally used on substrates that fail to be oxidized under the standard protocol,[27] although it possesses the serious limitation of the strongly basic medium generated by potassium *t*-butoxide.

An alcohol can be quantitatively transformed into a sodium or potassium alkoxide with NaH or KH. These alkoxides can sometimes transfer a hydride to a suitable hydride-acceptor[28] in a quite selective manner.[29]

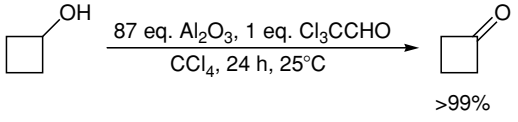


Ref. 29a

A selective oxidation of only one diastereomeric alcohol is achieved in a very elegant manner by forming the corresponding potassium alkoxides with excess of KH, followed by treatment with benzophenone. A hydride transfer to benzophenone occurs from the alkoxide able to deliver a hydride from a less congested location. The reverse reaction of reduction of the resulting ketone is avoided by trapping this ketone by formation of its enolate with excess of KH.

6.2.4. Recent Developments

Posner *et al.* found that commercial aluminium oxide is able to promote the oxidation of alcohols employing chloral as hydride acceptor.[30] The reaction operates at room temperature in inert solvents like CCl_4 and surprisingly no base-induced condensations are reported. Basically, the same experimental conditions were later applied for the oxidation of cyclobutanol,[31] a compound with a great propensity to fragmentation under the action of other oxidants.

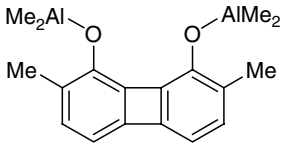


Ref. 31
A modified Oppenauer oxidation, using activated neutral chromatographic alumina and chloral in CCl_4 at room temperature, allows the oxidation of cyclobutanol in good yield. Other oxidants have a tendency to produce fragmentation of cyclobutanols.

Chemically modified Al_2O_3,[32] and an aluminium and magnesium carbonate[33] have been studied in Oppenauer oxidations employing oxidants other than chloral.

Rathke *et al.* showed[34] that electron-withdrawing groups linked to the aluminium atom in aluminium alkoxides increase the Lewis acidity of the aluminium and facilitate its complexation with carbonyl groups. This effect, first observed in 1958 by Gál and Kraznai in chloroaluminium isopropoxide,[35] results in an acceleration of the hydride transfer in Oppenauer oxidations. Thus, the addition of 1 equivalent of trifluoroacetic acid to aluminium isopropoxide results in the formation of $CF_3CO_2Al(O\textit{i}\text{-}Pr)_2$. This is a highly active catalyst that allows Oppenauer oxidations to be run at 0°C in benzene. Regrettably, the utility of this catalyst is very limited because it greatly promotes condensations, leading to a high proportion of side compounds. Nevertheless, Akamanchi and Chaudhari were able to oxidize a number of secondary alcohols[36] employing diisopropoxyaluminium trifluoroacetate and 4-nitrobenzaldehyde as hydride acceptor. Under these modified Oppenauer conditions, oxidations occur at room temperature in benzene, although primary alcohols are not affected.

Very recently, Maruoka's team developed two highly sophisticated and efficient aluminium compounds for the Oppenauer oxidation of alcohols. Thus, the complex aluminium phenoxide **67**, containing two aluminium atoms, is able to catalyze—in a quantity as low as 5 mol%—the oxidation of alcohols with pivalaldehyde at room temperature.[37]



67

It must be mentioned that about 1 equivalent of aluminium isopropoxide is needed in Oppeanuer oxidations using the classical protocol. Supposedly, compound **67** reacts with the alcohol, resulting in an aluminium alkoxide able to form a complex in which both free electron pairs of the oxygen atom in pivalaldehyde are coordinated with aluminium atoms, resulting in a very efficient activation of pivalaldehyde as hydride acceptor via a mechanism represented in Figure 6.1:

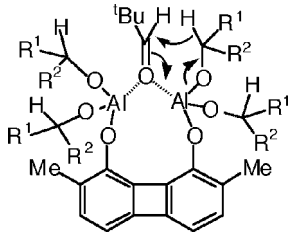
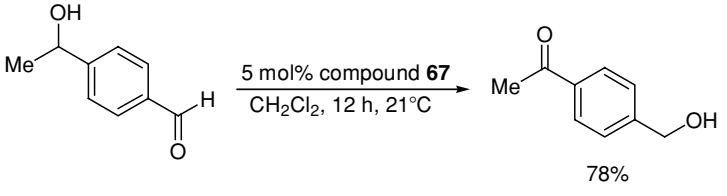


Figure 6.1

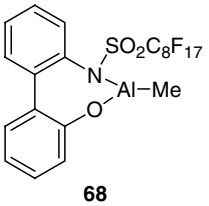
Regardless of the veracity of the proposed assembling depicted in Figure 6.1, the fact remains that the catalyst **67** is highly efficient in the promotion of Oppenauer oxidations under mild conditions and have been employed in a very elegant way in oxidation-reduction transformations, in which in the same molecule a secondary alcohol is oxidized while an aldehyde is reduced with no addition of external redox reagents.



Ref. 37b

In this very elegant transformation induced by aluminium compound **67** present in a 5 mol% proportion, an aldehyde operates as a hydride acceptor in the oxidation of a secondary alcohol present in the same molecule.

Maruoka's group also developed the extremely active aluminium compound **68**,[38] which in a proportion as low as 1 mol% is able to promote the oxidation of alcohols with pivalaldehyde or acetone at room temperature. Oppenauer oxidations employing catalyst **68** succeed in a variety of secondary and primary alcohols, providing yields of aldehydes and ketones above 80% in a consistent way. Only lineal primary aliphatic alcohols fail to be cleanly oxidized to the corresponding aldehydes.



68

Kagan *et al.*[39] have shown that alkoxides of metals belonging to the lantanides are able to promote Oppenauer oxidations in catalytic amounts. Thus, 10 mol% *t*-BuOSmI$_2$ is able to induce the oxidation of a number of alcohols in variable yields in the presence of a variety of aldehydes and ketones as oxidants.[39a] Yb(O*i*-Pr)$_3$ in a 5 mol% quantity is able to catalyze the oxidation of 1-phenylethanol to acetophenone in 98% yield with butan-2-one as oxidant.[39b] Other lantanides provided a lower yield.

A number of zirconium compounds are able to catalyze Oppenauer oxidations. For example, zirconium dioxide, when properly conditioned, is able to promote the oxidation of alcohols in variable yields[40] and it is reportedly superior than Al_2O_3. Other zirconium compounds able to induce Oppenauer oxidations in catalytic amounts include Cp_2ZrH_2,[41] $Cp_2Zr(O\textit{i}\text{-}Pr)_2$,[41b] $Zr(O\textit{t}\text{-}Bu)_4$[42] and $Zr(O\textit{n}\text{-}Pr)_x$ on SiO_2.[42]

Yamamoto *et al.* have shown that the boron compound $(C_6F_5)_2BOH$, in a quantity as low as 1 mol%, is able to promote the oxidation of allylic and benzylic alcohols with pivalaldehyde at room temperature.[43] This result is not surprising considering the similitude of the electronic structure of boron and aluminium.

Sometimes, reactions in which an alcohol is oxidized by hydride transfer to a metallic cluster, resulting in the formation of a metallic hydride that subsequently transfers a hydride to a sacrificial aldehyde or ketone, are described as Oppenauer oxidations.[44] In the opinion of the authors, the name "Oppenauer oxidation" should be reserved for oxidation of alcohols in which a hydride is *directly* transferred from a metallic alkoxide to an aldehyde or ketone acting as oxidant.

6.2.5 General Procedure for Oppenauer Oxidation Under Standard Conditions

Between 0.5 and 4 equivalents—typically 1.0 equivalents—of aluminium isopropoxide[a] are added to a ca. 0.015–0.9 M solution of the alcohol in toluene,[b,c] to which between 3 and 200 equivalents—typically 10 to 40 equivalents—of cyclohexanone[d] or *N*-methyl-4-piperidone have been previously added. The reaction mixture is refluxed[e] till most of the starting compound is consumed.[f] Water or diluted aqueous acid is added to the cold reaction mixture. The organic phase is separated and washed with a saturated aqueous solution of sodium bicarbonate, water and brine. These operations may be facilitated by the addition of an organic solvent like EtOAc or chloroform. The precipitation of aluminium salts may interfere in the separation of phases. This can be avoided by two alternative work-ups. The first one consists of adding slightly more than 3 equivalents of water per equivalent of aluminium alkoxide to the cold reaction mixture, thus causing the separation of solid aluminium hydroxide, which can be separated by centrifugation and washed with an organic solvent. The second work-up involves washing the cold reaction mixture with a saturated aqueous solution of sodium potassium tartrate, which is able to keep the aluminium ions in solution.

Finally, the organic phase that was previously washed with aqueous phases and dried (Na_2SO_4 or $MgSO_4$) is concentrated, giving a crude residue that may need further purification.

[a] Aluminium *t*-butoxide can also be used. Although, it can be more effective than aluminium isopropoxide because it leads to a more favourable equilibrium towards the desired intermediate aluminium alkoxide, its employment is not very common because it is more difficult to prepare and more expensive than aluminium isopropoxide. Aluminium phenoxide and potassium *t*-butoxide are occasionally used. Potassium *t*-butoxide is a very energetic reagent that allows Oppenauer oxidations to proceed on alcohols refractory to oxidations in the presence of aluminium alkoxides. As it is a very basic reagent, its employment must be reserved to cases in which base-induced side reactions are not expected to become dominant.

[b] The presence of water inhibits the Oppenauer oxidation because it competes with the carbonyl group of the oxidant for complexation with aluminium. Water may be absent *ab origene* from the reaction mixture by using dry solvents and reagents. Alternatively, water can be removed from the reaction mixture by azeotropic distillation, employing a Dean-Stark, or by separating a portion of the refluxing solvent at the beginning of the reaction. Normally, this azeotropic separation of water is made before the addition of the aluminium alkoxide, in order to avoid the formation of aluminium hydroxide. Occasionally, water is removed from the reaction mixture before the addition of the aluminium alkoxide, by stirring the mixture with ca. 200 mg of activated molecular sieves 4 Å per mmol of alcohol during about 2 h at room temperature.

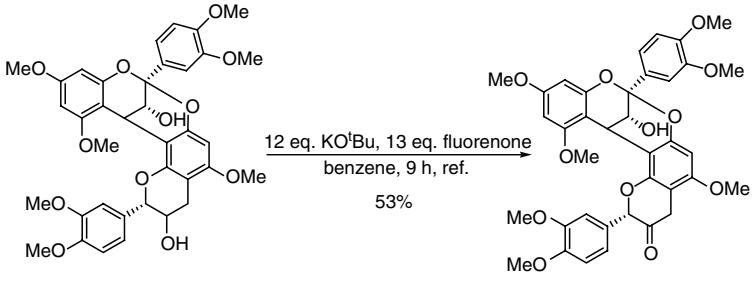
[c] Although, the reaction is normally carried out in boiling toluene, other solvents able to form an azeotrope with water, such as benzene or xylenes, can also be used.

[d] Cyclohexanone is the most common oxidant because it is cheap, easy to remove and possesses a strong oxidizing power. *N*-methyl-4-piperidone is finding an increased

employment, although it is more expensive than cyclohexanone, because side compounds resulting from condensations of the product with *N*-methyl-4-piperidone are easily removed by washing with aqueous acid. Acetone is occasionally used, although it does not possess an oxidizing power as strong as cyclohexanone. Other oxidants possessing a higher oxidizing power include *p*-quinone, chloral and fluorenone. Its employment is more limited because they tend to promote many side reactions.

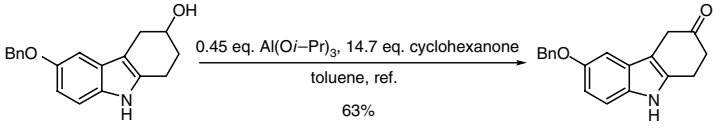
[e] For milder conditions, the reaction can be performed at room temperature, although this can lead to reaction time in excess of weeks.

[f] Normally, it takes between 30 min and 24 h. As expected, reactions in higher boiling solvents finish in a shorter time.



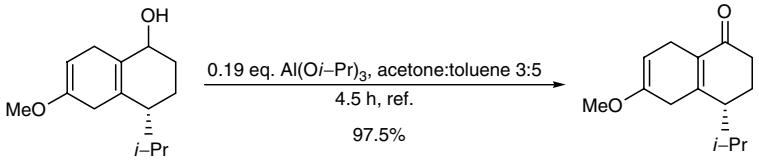
Ref. 45

A selective oxidation of the secondary alcohol presenting less steric hindrance for the transfer of a hydride to the bulky fluorenone is achieved by employing the Woodward's modification of the Oppenauer protocol.



Ref. 46

The alcohol in this sensitive indole could be oxidized to the desired ketone by heating with cyclohexanone and aluminium isopropoxide. A very similar substrate could no be oxidized efficiently after trying a wide variety of reagents.[47]

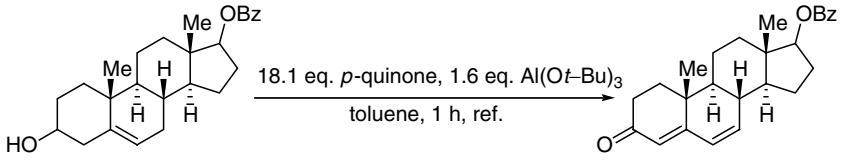


Ref. 48

A very mild Oppenauer oxidation using acetone and aluminium isopropoxide allows the obtention of the desired ketone, while pyridine-chromic acid or manganese dioxide produce, aromatization of the ring on the left.

6.2.6. Functional Group and Protecting Group Sensitivity to Oppenauer Oxidation

Oxidations under Oppenauer conditions are highly selective for alcohols, normally resulting other functionalities sensitive to oxidation unchanged. This happens because the Oppenauer oxidation operates via a mechanism involving a hydride transfer from a metallic alkoxide, which is very specific for alcohols. Over-oxidations have been described only for situations in which very reactive oxidants, such as *p*-quinone, are employed.[14]

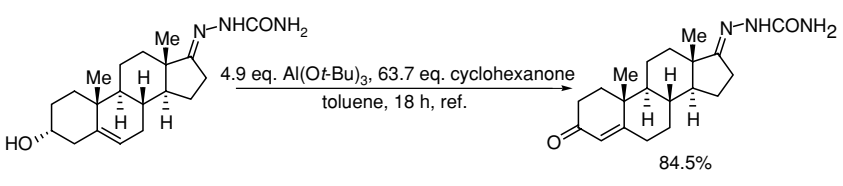


Ref. 14

The Oppenauer oxidation of a ster-3-ol employing the strong oxidant *p*-quinone, instead of the more usual acetone, cyclohexanone or *N*-methyl-4-piperidone, produces an over-oxidation resulting in the formation of a dienone, instead of the usual enone.

The aluminium alkoxides present in the Oppenauer oxidation can cause some base-induced side reactions. Thus, quite typically during the oxidation of sterols possessing homoallylic alcohols, a migration of the alkene into conjugation with the resulting ketone is observed (see pages 256 and 259).[4]

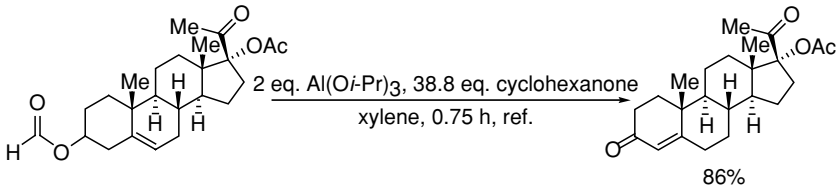
Aluminium alkoxides very often promote aldol condensations between the aldehyde or ketone, resulting from the oxidation, and the carbonyl compound used as the oxidant. That is why, Oppenauer oxidations are seldom employed for the obtention of aldehydes, as these compounds have a greater tendency than ketones to be involved in aldol condensations. Likewise, although Oppenauer oxidation can be made in the presence of ketones,[49] it may be advisable to protect them, for example as semicarbazones.[50]



Ref. 50

A ketone is protected as semicarbazone during an Oppenauer oxidation, in order to avoid interferences from base-induced condensations.

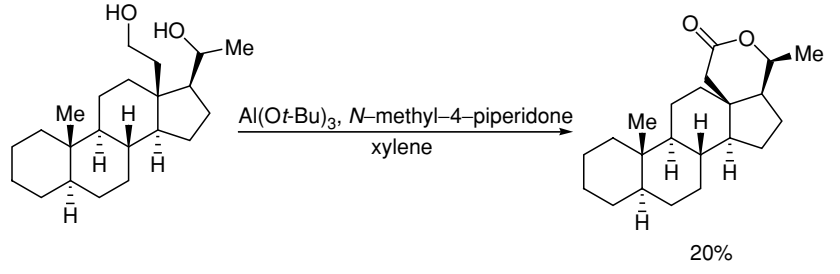
Although aluminium alkoxides are able to promote base-induced reactions, the basic conditions involved are not extremely strong and many base-sensitive functional groups remain unaffected during Oppenauer oxidations, including alkyl halides,[51] epoxides[52] and most esters.[53] On the other hand, the very sensitive formate esters are hydrolyzed under Oppenauer conditions and the resulting alcohols are oxidized *in situ*.[25]



Ref. 25a

Under the Oppenauer conditions, a formate is hydrolyzed resulting in an alcohol that is oxidized *in situ* to a ketone. Observe that an acetate and a ketone in the same molecule resist the basic reaction conditions.

Sometimes, diols are transformed into lactones under the action of the Oppenauer oxidation.[54]



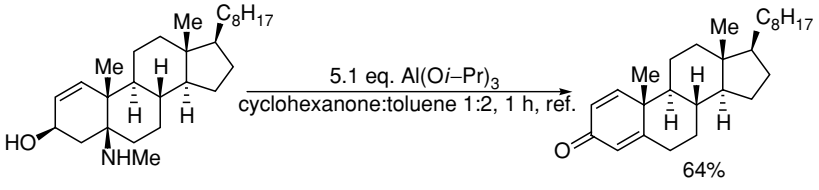
Ref. 54

The treatment of a 1,5-diol under Oppenauer conditions leads to a lactone, presumably formed via an intermediate hemiacetal.

Most amines remain unchanged under the action of Oppenauer oxidations.[55] Some alcohols possessing amino groups in the same molecule resist oxidation under standard Oppenauer conditions employing aluminium alkoxides.[10a,b] There was speculation that this was caused by inactivation of the aluminium alkoxides by complexation of the aluminium with the amines. Later, it was proved that this is not the case, sometimes being amines closely positioned to alcohols able to avoid alcohol oxidation via destabilizing the corresponding ketones by an inductive effect.[10c,56] Interestingly, while such alcohols possessing a closely-positioned amine resist oxidation under standard Oppenauer conditions using aluminium alkoxides, they can be oxidized

by the Woodward modification of the Oppenauer oxidation employing potassium *t*-butoxide.[10b,27]

There is one report,[57] in which a tertiary amine suffers a complex fragmentation, initiated by the oxidation of the amine into an immonium salt upon the action of Oppenauer conditions. There is also one example,[58] in which a secondary amine suffers elimination by the action of an aluminium alkoxide.

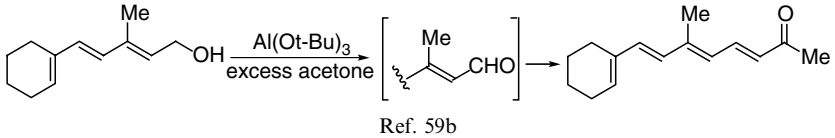


Ref. 58

An Oppenauer oxidation leads to a β-aminoketone that suffers an *in situ* elimination of the amine.[58]

6.2.7. Reactions Performed *in situ* During an Oppenauer Oxidation

A common side reaction during Oppenauer oxidations consists of the base-catalyzed condensation of the carbonyl compound, resulting from the oxidation, with the carbonyl compound used as oxidant. Sometimes, advantage is taken from this side reaction for synthetic purposes. For example, oxidation of primary alcohols with an aluminium alkoxide and acetone results in the formation of an intermediate aldehyde that condenses with acetone, resulting in a synthetically useful formation of an enone.[59]



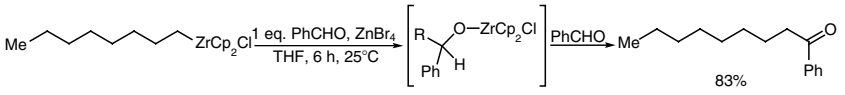
Ref. 59b

During a synthesis of vitamin A, a primary allylic alcohol is treated with $Al(Ot\text{-}Bu)_3$ and acetone, resulting in an intermediate aldehyde that condenses *in situ* to form a synthetically useful methylenone.

Similarly, Nakano *et al*. have prepared a number of alkylidenecycloketones by the oxidation of primary alcohols with cycloketones in the presence of Cp_2ZrH_2, which operates in a similar manner as aluminium alkoxides.[60]

The Oppenauer oxidation is a common side reaction during the condensation of organometallic compounds with aldehydes and ketones, something that very often comes as a surprise for the unaware chemist. This has been observed in condensations of diverse organometallic species, for example chromium,[61] Zr[62] and Mg[63] organometallics. This side reaction

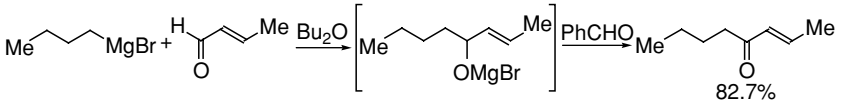
during the condensation of organometallics with aldehydes and ketones has been exploited for synthetic purposes for it allows the formal acylation of carbanionic synthons.[62,63] Thus, Srebnik and Zheng performed the formal acylation of a number of organozirconium species by condensation with aldehydes under $ZnBr_2$ catalysis, resulting in the formation of an zirconium alkoxide that is oxidized *in situ* by the excess of the aldehyde.[62]



Ref. 62

A benzoylation of an organozirconium compound is achieved by condensation with benzaldehyde, followed by the *in situ* Oppenauer oxidation of the resulting zirconium alkoxide by excess of benzaldehyde.

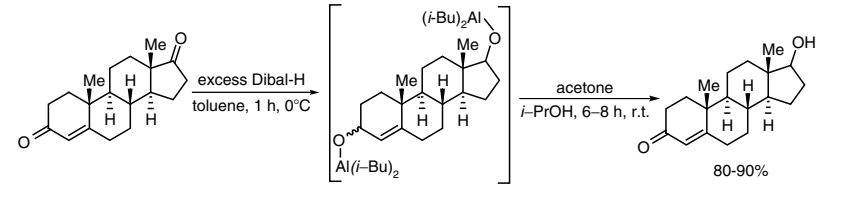
Similarly, Byrne and Karras have proved that magnesium alkoxides, resulting from the condensation of Grignard reagents with aldehydes, can be oxidized *in situ* by adding an excess of a carbonyl compound as oxidant. The reaction gives best yields with benzaldehyde as oxidant in a solvent like Bu_2O having limited complexation ability for magnesium cations.[63]



Ref. 63

A Grignard reagent is condensed with an aldehyde resulting in a magnesium alkoxide that is oxidized *in situ* by the addition of benzaldehyde.

In a very elegant way, Eder performed the regioselective reduction of a dione by treatment with excess of Dibal-H, resulting in the formation of a bisaluminium alkoxide that was selectively oxidized under Oppenauer conditions providing a cyclohexenone, while a cyclopentanol remained unchanged.[64]

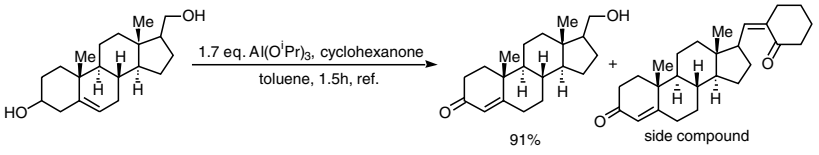


Ref. 64

The selective reduction of the cyclopentanone is achieved by the reduction of both ketones with excess of Dibal-H, resulting in a bisaluminium alkoxide that is regioselectively oxidized under Oppenauer conditions by the addition of acetone.

6.2.8. Side Reactions

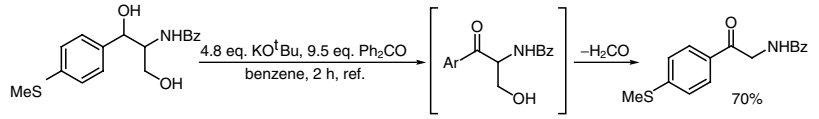
The most common side reactions during Oppenauer oxidation consist of base-induced condensations of the aldehyde or ketone, generated during the oxidation, with the carbonyl compound used as oxidant.[65] This side reaction is particularly prominent during the obtention of aldehydes because they are generally more reactive in aldol condensations than ketones. Furthermore, aldehydes very often suffer Tischtschenko condensations,[66] resulting in the formation of dimeric esters during Oppenauer oxidations. That is why, the Oppenauer oxidation is seldom useful for the preparation of aldehydes.



Ref. 65c

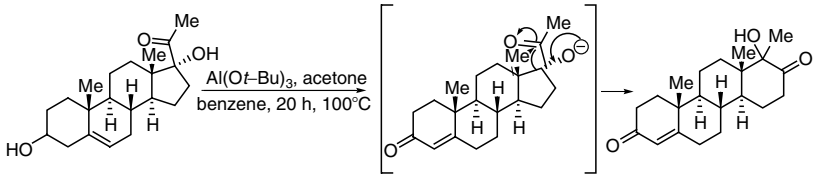
A selective oxidation of a secondary alcohol is achieved by the Oppenauer oxidation of a sterol. A primary alcohol is partially transformed in an aldehyde that condenses *in situ* with cylohexanone employed as oxidant.

Other base-induced side reactions occurring during Oppenauer oxidations include retro-aldol condensations[67] and ring-expansions in α-hydroxyketones.[68]



Ref. 67

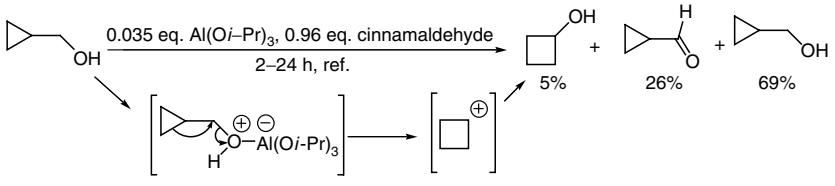
An Oppenauer reaction produces the selective oxidation of a secondary alcohol, leading to a β-hydroxyketone that suffers a retro-aldol condensation under the basic reaction conditions, resulting in the evolution of formaldehyde.



Ref. 68

During a standard oxidation of a ster-3-ol by the Oppenauer protocol, a cyclopentanol suffers a base-induced ring-expansion.

Sometimes, side reactions during Oppenauer oxidations can be explained by the Lewis acidity of the aluminium atom in aluminium alkoxides.[69]



Ref. 69

The oxidation of cyclopropanecarbinol under Oppenauer conditions using cinnamaldehyde as oxidant leads to the desired aldehyde contaminated with cyclobutanol, which probably arises from a ring expansion promoted by a complexation of the alcohol with the aluminium atom operating as a Lewis acid.

Section 6.2. References

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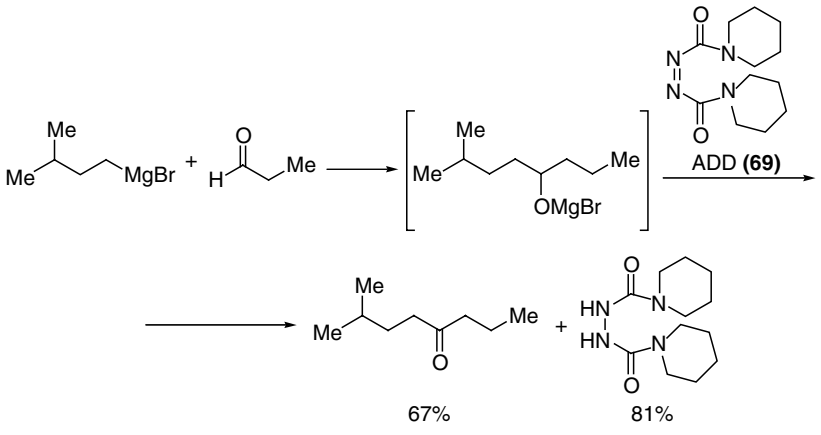
6.3. Mukaiyama Oxidation

In 1968, Mukaiyama *et al.*[70] discovered that magnesium alkoxides—generated by reaction of Grignard reagents with aldehydes—when treated *in situ* with 1,1'-(azodicarbonyl)dipiperidine (ADD) (**69**), suffer oxidation to the corresponding ketones.

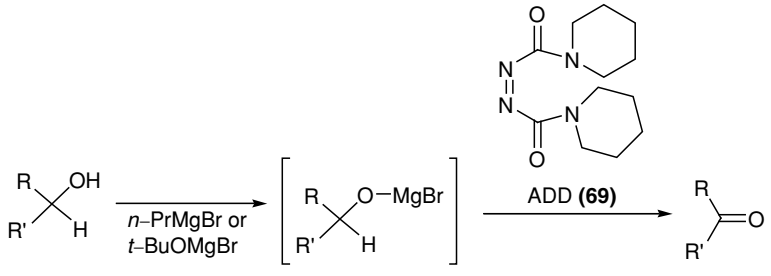


Ref. 70

Reaction of a Grignard reagent with propanal leads to a bromomagnesium alkoxide that is oxidized *in situ* by treatment with ADD.

In this paper, the published yields were modest and the full versatility of the procedure was not checked. However, this paper established the conceptual principle that magnesium alkoxides could be efficiently oxidized in the presence of good hydride abstractors, such as 1,1′-(azodicarbonyl)dipiperidine (ADD), via a hydride transfer resembling the mechanism of the Oppenauer oxidation.

Nine years later, in 1977,[71] Mukaiyama *et al.* published a full account on the oxidation of magnesium alkoxides with ADD. Thus, magnesium alkoxides were generated by the treatment of alcohols with either *n*-propylmagnesium bromide, or *t*-butoxymagnesium bromide, and reacted *in situ* with ADD at room temperature, resulting in good yields of the desired aldehydes or ketones.



Although the magnesium alkoxides can generally be formed by the action of Grignard reagents with alcohols, it may be preferable to employ *t*-BuOMgBr in molecules containing functionalities sensitive to attack by

Grignard reagents. *t*-BuOMgBr is easily generated *in situ* by reaction of *t*-butanol with a Grignard reagent.

Although the Mukaiyama oxidation is not in the top list of the most frequently used alcohol oxidants, the authors of this book have decided to pay full attention to this procedure because it succeeds in very sensitive organometallic compounds, where most other oxidants fail. The Mukaiyama oxidation operates via a somehow unique mechanism involving a hydride transfer from a metal alkoxide to a very good hydride acceptor, which resembles the Oppenauer oxidation. In variance with the Oppenauer oxidation, the Mukaiyama protocol involves much milder conditions and it does not promote as easily base-induced side reactions.

6.3.1. General Procedure for Mukaiyama Oxidation

Initially, the alcohol is transformed into an alkoxymagnesium halide, according to two alternative protocols:

Protocol A.

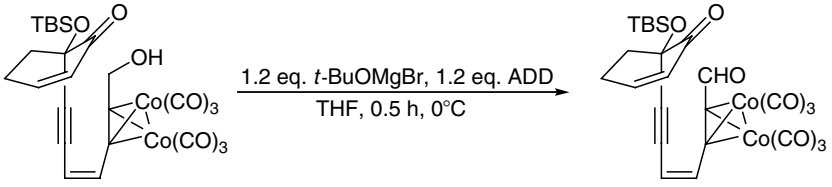
From 1.1 to 1.4 equivalents of a Grignard reagent[a] in a ca. 0.4 M solution in THF are slowly added[b] to a stirred ca. 0.04–0.2 M solution of the alcohol in dry THF.[c] After at least 15 min., ADD is added.

Protocol B.

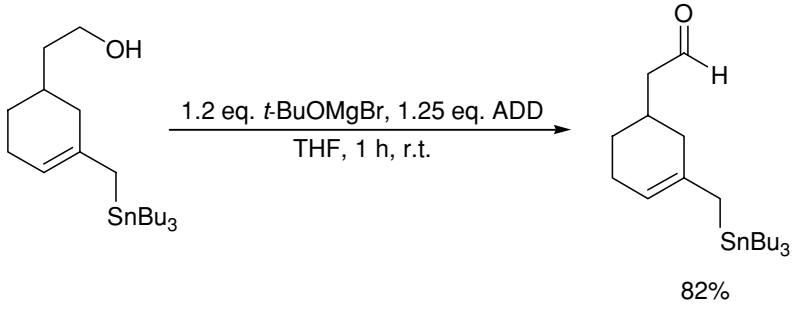
Ca. 1.2–3 equivalents of *t*-butanol, either neat or in a ca. 0.2–0.6 M solution in dry THF, are mixed with ca. 0.98–1.0 equivalents of a Grignard reagent[a] per equivalent of *t*-butanol, the Grignard reagent being contained in a ca. 0.2–0.4 M solution in THF. After at least 3 min., the resulting solution of *t*-butoxymagnesium bromide is mixed with 1 equivalent of the alcohol contained in a ca. 0.1–1.7 M solution in THF.[d] After at least 10 min., ADD is added.

From 1.1 to 3 equivalents of 1,1′-(azodicarbonyl)dipiperidine (ADD, MW = 252.31), either as a solid or as a ca. 0.1–0.7 M solution in dry THF, are mixed with the solution of the alkoxymagnesium halide, and the resulting mixture is stirred at room temperature[e] till most of the alkoxide is consumed.[f] Brine—or, alternatively, water or a NH_4Cl saturated aqueous solution—is added to the reaction. The resulting mixture is extracted with an organic solvent, such as Et_2O, EtOAc or CH_2Cl_2. The organic phase is washed with a saturated $NaHCO_3$ aqueous solution and/or brine. Drying with $MgSO_4$ or Na_2SO_4 is followed by removal of the solvent in vacuum, giving a residue that may need further purification.

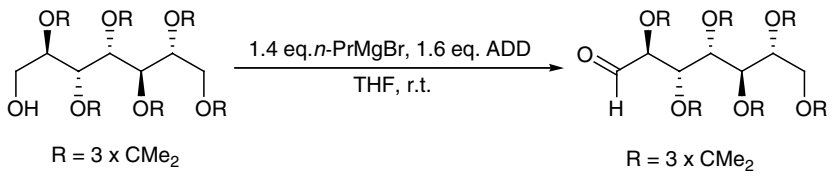
[a] The nature of the Grignard reagent is expected to have little influence in the oxidation. Normally, a commercially available or an easily prepared Grignard reagent, such as ethyl, *n*-propyl, allyl or *i*-propylmagnesium bromide, is employed.
[b] Occasionally, an inverse addition, whereby the solution of the alcohol is added over the solution of the Grignard reagent, is performed.
[c] Normally, the alkoxymagnesium halide is generated at room temperature, although it may be advisable, particularly on a multigram scale, to mix the alcohol and the Grignard reagent at low temperature.
[d] Normally, all the operations during the generation of the alkoxymagnesium halide following protocol B are performed at room temperature, although occasionally they are done at 0 °C for milder conditions.
[e] Occasionally, the reaction is performed at 0 °C for milder conditions.
[f] Normally, it takes from 15 min. to 2.5 h.



Ref. 72
The oxidation of this very sensitive substrate can be carried out by the Mukaiyama procedure with a 81% yield in a scale greater than 100 g.



Ref. 73
The obtention of this very labile product, containing an allylstannane and an aldehyde in the same molecule, was tried unsuccessfully using many oxidizing conditions. Eventually, this product could be prepared following a Mukaiyama oxidation. The basic conditions were essential to avoid protiodestannylation. The product could not withstand chromatography or distillation.



Ref. 74

After trying many oxidizing conditions, it was found that the Mukaiyama procedure is the most suitable. The oxidation also succeeds employing a Swern oxidation, although the corresponding work-up is more difficult.

6.3.2. Functional Group and Protecting Group Sensitivity to Mukaiyama Oxidation

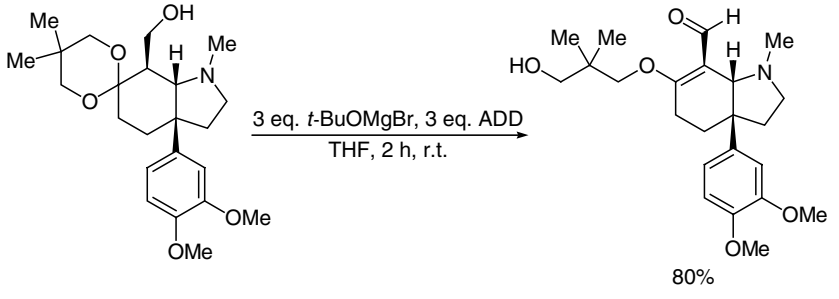
The slightly basic conditions of the Mukaiyama oxidation are particularly well-fitted for oxidations in compounds containing organometallic moieties. These include allylstannanes,[75] π-allylmolibdenum compounds,[76] alkyne $Co(CO)_6$ complexes[77] and diene $Fe(CO)_3$ complexes.[78]

Many base-sensitive functionalities, such as carbonates[79] or epoxides,[75b] resist the mild basic conditions of the Mukaiyama oxidation.

6.3.3. Side Reactions

There is one example in which an ethoxyethyl (EE) protecting group is removed from a phenol during a Mukaiyama oxidation. According to the authors, this deprotection is promoted by a selective complexation of one oxygen with a magnesium atom.[80]

When a carbonyl compound containing a good-leaving group at the β-position is obtained, a base-induced elimination can occur.[81]



Ref. 82

An elimination of an alkoxide at the β-position happens during a Mukaiyama oxidation.

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7

Fétizon's Reagent: Silver Carbonate on Celite®

7.1. Introduction

Ag_2CO_3/celite®

In 1955, Rapoport *et al.*[1] showed that silver carbonate—when prepared from aqueous silver nitrate and sodium bicarbonate—is able to oxidize some alcohols in refluxing benzene under neutral conditions. The preparation of the resulting active silver carbonate involved time-consuming filtering and washing steps. In 1961, King *et al.*[2] showed that less reactive commercial silver carbonate was equally effective under more stringent conditions, using refluxing toluene or xylene.

An important breakthrough in the oxidation of organic compounds with silver carbonate happened in 1968, when Fétizon *et al.*[3] showed that when silver carbonate is generated from aqueous silver nitrate and sodium carbonate (or potassium bicarbonate) in the presence of Celite®, a form of silver carbonate on Celite® is generated that is very easily filtered and washed, and possesses an enhanced reactivity. The resulting so-called Fétizon's reagent is normally employed in refluxing benzene for the heterogeneous oxidation of alcohols to aldehydes and ketones. Fétizon's reagent is a very mild oxidant, possessing very diverse oxidation capabilities for alcohols differing in minor structural features. It is therefore a very useful, although expensive oxidant for alcohols, whenever very mild conditions or selective oxidations of polyols are required.

Section 7.1. References

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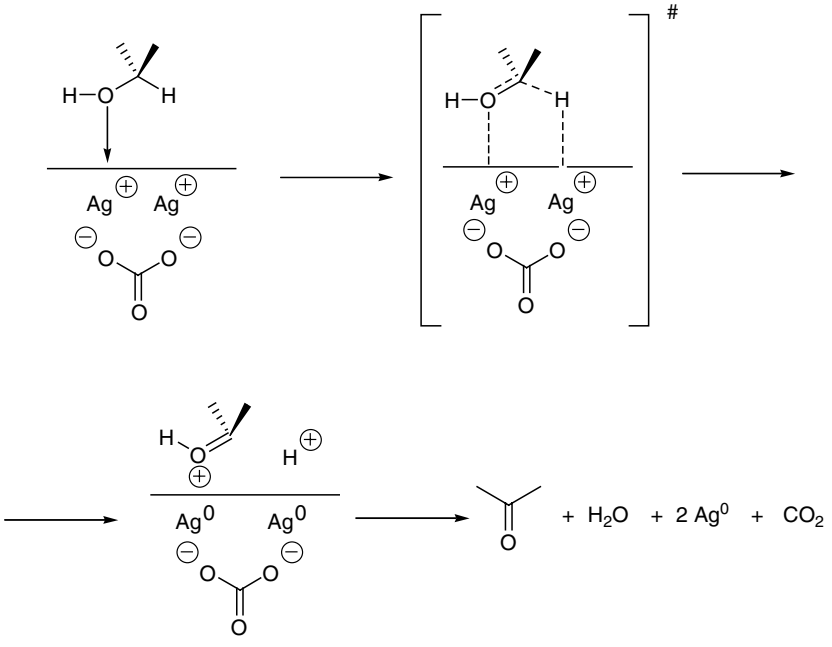
7.2. Fétizon's Oxidation

The available experimental data[4] are consistent with the following mechanism for the oxidation of alcohols with silver carbonate on Celite®:

- The alcohol is reversibly chemisorbed on the surface of silver carbonate.
- The plane of the H-C-O-H atoms adopts a perpendicular arrangement against the surface of an oxidant particle.
- The oxidation proceeds via a highly symmetric transition state whereby the oxygen from the alcohol complexes with a silver cation, while another silver cation interacts with the hydrogen at the α-position of the alcohol (see below).
- The resulting stoichiometry of the reaction is:

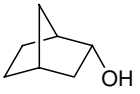
$$R_2CHOH + Ag_2CO_3 \rightarrow R_2C{=}O + 2Ag^0 + H_2O + CO_2.$$



The initial chemisorption step can be prevented by many ligands including quite weak ones. Thus, Fétizon's oxidation must be performed in very apolar solvents because even solvents with very weak basicity, such as ethyl acetate or methyl ethyl ketone, severely inhibit the oxidation.[4c] That is why, Fétizon's oxidation is routinely performed in boiling benzene, which is

a very apolar solvent with the added advantage of allowing the elimination of water produced during the oxidation by azeotropic distillation. The water generated during the oxidation can compete with the alcohol for chemisorption on the surface of the oxidant particles and greatly retard the consumption of the alcohol.

Interestingly, when solvents possessing a lower polarity than benzene—such as heptane—are employed, a substantial acceleration of the oxidation can be observed. Thus, endo-2-norbornanol **(70)** is oxidized 11 times faster in heptane than in benzene.[5] In fact, even weak ligands such as alkenes can produce a substantial slowing of the oxidation. For example, endo-2-norbornenol **(71)** reacts 50 times slower than endo-2-norbornanol **(70)** with Fétizon's reagent.[5]



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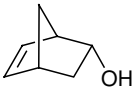


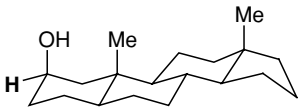
71

Unsurprisingly, examples from successful oxidations of alcohols possessing other polar functionalities with Fétizon's reagent are quite absent from the literature.

Optimum oxidation conditions involve a maximum of silver carbonate surface available for chemisorption. That is why, increasing the amount of Celite® on which silver carbonate is precipitated produces a higher rate of oxidation. Although, above a value of 900 g of Celite® per mol of silver carbonate, a slight decrease of oxidation speed is observed resulting from a dilution effect.[4c]

The chemisorption of the alcohol on the silver carbonate surface, being a heterogeneous process, depends on efficient mechanical mixing; something that is influenced, for example, by stirring speed and vigorous boiling. This causes variable oxidation speeds on reactions with Fétizon's reagent performed under conditions as identical as possible.[4b] Completely faithful replication of results must not be expected for the oxidation of alcohols with Fétizon's reagent.

Although a certain acceleration of oxidation speed is observed for unsaturated alcohols versus saturated ones[3] and for secondary alcohols versus primary ones,[6] the major factor affecting oxidation velocity is the accessibility of the alcohol α-hydrogen to the surface of the oxidant. Thus, the 5α-androstan-2β-ol **(72)**, possessing a readily accessible α-hydrogen on an unhindered equatorial position, is oxidized 25 times faster than the 2α epimer **(73)**, having an axial α-hydrogen close to an axial methyl group.



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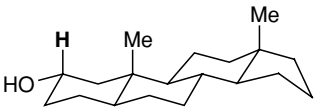
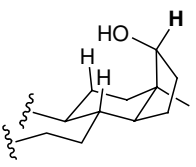
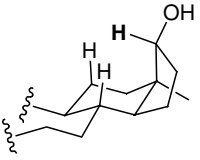


73

Similarly, compound **74** is oxidized 6 times quicker than the epimer **75** that possesses a less accessible α-hydrogen.[4c]

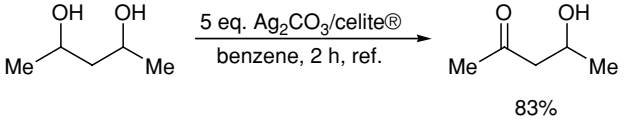


74



75

Because of the mildness of Fétizon's reagent and its sensitivity to minor structural features, this oxidant is particularly well-suited for the monooxidation of symmetric diols[7] and for the oxidation of 1,2-diols in which one of the alcohols is tertiary.[8]



Ref. 6a

The use of Fétizon's reagent allows the monooxidation of a symmetrical diol with 83% yield.

7.2.1. Preparation of Fétizon's Reagent[9]

The Celite® support is purified by washing with MeOH, containing 10% of concentrated HCl, and with distilled water till neutrality. Finally, it is dried at 120°C.

30 g of Celite® are added to a stirred solution of 34 g (200 mmol) of silver carbonate (MW = 275.75) in 200 mL of distilled water. A solution of 30 g (105 mmol) of Na_2CO_3 (MW = 286.14), or, alternatively, 21 g (210 mmol) of $KHCO_3$ (MW = 100.12) in 300 mL of distilled water are slowly added to the stirred suspension. Stirring is continued for 10 min after the addition was complete, and the resulting yellow-green precipitate is filtered and dried at the rotary evaporator during several hours. The resulting silver carbonate on Celite® contains about 1 mmol of silver carbonate per 0.57 g.

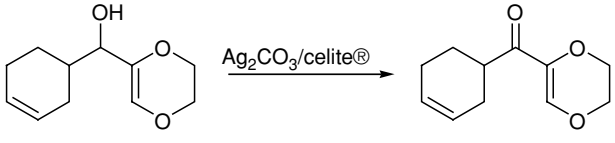
7.2.2. General Procedure for Oxidation of Alcohols with Fétizon's Reagent

From 1 to 10 g (ca. 5–15 equivalents)—typically 3 g—of silver carbonate on Celite® per mmol of alcohol are added to a ca. 0.01–0.15 M solution of the alcohol in dry[a] benzene.[b] The resulting suspension is refluxed till most of the starting alcohol is consumed.[c] The suspended solid is filtered, employing filter paper or a pad of Celite®, and washed with benzene or other organic solvent. Concentration of the organic solution at the rotary evaporator yields the crude carbonyl compound that may need further purification.

[a] Wet benzene can be used, in which case the water present must be eliminated by removal of a portion of benzene at the beginning of the distillation. As water is produced during the oxidation, it may be advisable to remove it continuously by performing an azeotropic distillation with an attached Dean-Stark apparatus.

[b] A higher boiling aromatic hydrocarbon, such as toluene, xylenes or chlorobenzene, can be employed for a quicker reaction. Very apolar solvents, such as heptane, can be very effective.

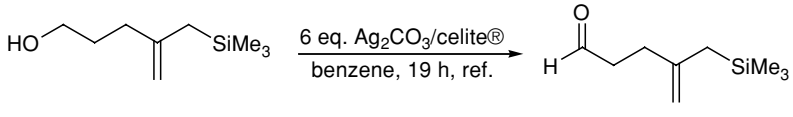
[c] It normally takes between 1 and 26—typically 3—hours. Hindered alcohols may not react at all.



54%

Ref. 10

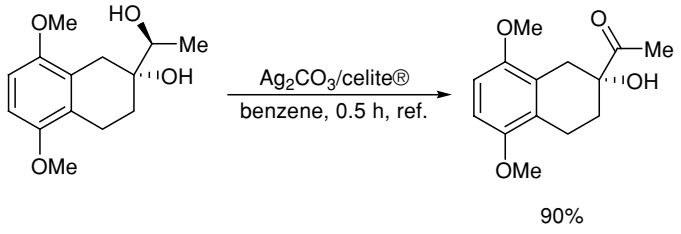
An alcohol is oxidized with Fétizon's reagent in the presence of a very oxidation-sensitive dialkoxy alkene that, for instance, suffers selective cleavage with no reaction on the alcohol moiety on contact with PCC.



100%

Ref. 11

The oxidation of this alcohol can be carried out employing Fétizon's reagent under simple experimental conditions with quantitative yield. Alternatively, a Swern oxidation can be used resulting in 92% yield.



Ref. 8a

A Fétizon's oxidation allows the obtention of the desired α-hydroxyketone with a 90% yield, while Collins reagent, PCC and PDC produce an oxidative breakage of a C-C bond, Jones and Moffatt oxidations yield complex mixtures and a Corey-Kim oxidation returns unreacted material.

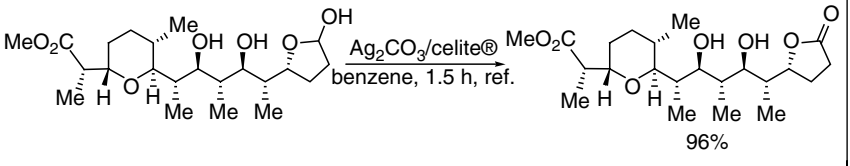
7.2.3. Functional Group and Protecting Group Sensitivity to Fétizon's Oxidation

As Fétizon's oxidation is carried out under neutral conditions, acid- and base-sensitive protecting groups resist its action. The oxidation-sensitive *p*-methoxybenzyl (PMB) protecting group resists the action of Fétizon's reagent.[12]

Phenols suffer oxidation to quinones and oxidative dimerizations under the action of silver carbonate on Celite®.[13]

Tertiary propargylic alcohols suffer a very easy fragmentation under the action of Fétizon's reagent.[14]

Fétizon's reagent has a great tendency to oxidize lactols to lactones, relative to the oxidation of primary and secondary alcohols.[4c] Therefore, this reagent is very often able to transform lactols into lactones in the presence of unreacting alcohols.[15]

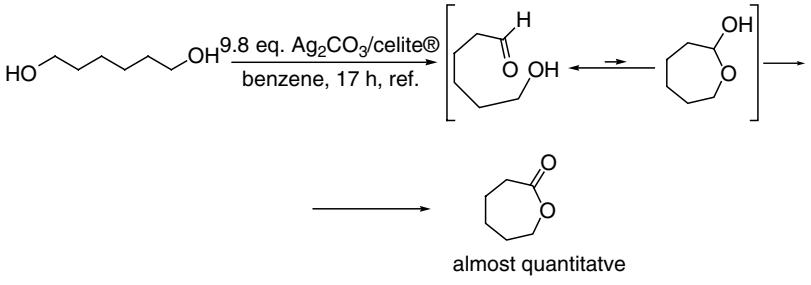


Ref. 15a

A lactol is selectively oxidized to a lactone with a 96% yield in the presence of two alcohols using Fétizon's reagent.

A corollary of this selectivity is the very easy transformation of diols into lactones with silver carbonate on Celite®.[16] During the oxidation of a diol with Fétizon's reagent, as soon as an intermediate hydroxyaldehyde is able to equilibrate with a certain proportion of hemiacetal—even if present

in a very small amount—the hemiacetal can be selectively oxidized to a lactone. Thus, not only 1,4- and 1,5-diols are transformed into respectively γ- and δ-lactones, but also 1,6-diols can be converted into seven-membered lactones,[16b] which are more difficult to obtain with other reagents.



Ref. 16b

The treatment of 1,6-hexanediol with Fétizon's reagent leads to an intermediate hydroxyaldehyde that equilibrates with a small amount of hemiacetal, which is further oxidized to an ε-lactone.

α–Diols possessing the CHOH-CHOH moiety can either suffer an uneventful oxidation to an α-diketone or a C-C bond breakage with Fétizon's reagent, depending on minor structural differences.[17]

Halohydrins are transformed into epoxides or into transposed products on contact with silver carbonate on Celite®.[18]

Although amines can react with Fétizon's reagent resulting in the formation of enamines[19] or imminium cations that can be trapped *in situ*,[20] it is very often possible to oxidize alcohols without affecting tertiary amines in the same molecule.[21]

7.2.4. Side Reactions

1,3-Diols are sometimes transformed with Fétizon's reagent into an intermediate β-hydroxycarbonyl compound, which suffers water elimination resulting in the formation of an enone.[6a]

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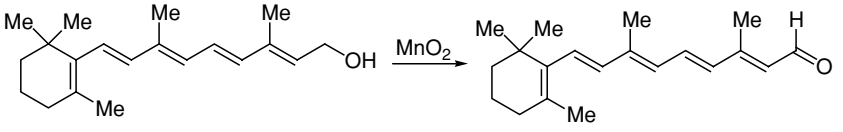
8

Selective Oxidations of Allylic and Benzylic Alcohols in the Presence of Saturated Alcohols

8.1. Introduction

MnO_2

In the 40's, during studies on the preparation of retinene, Ball *et al*. needed to oxidized vitamin A **(76)** to the corresponding aldehyde **77**.



vitamin A **(76)** **77**

A small yield of the aldehyde was obtained using potassium permanganate. Therefore, they embarked on a detailed exploration on the experimental conditions for best yield. It became apparent that best results were obtained when a dark precipitate of MnO_2 was formed by decomposition of potassium permanganate in aqueous solution.[1] In fact, it was found that vitamin A **(76)** could be efficiently oxidized by shaking a solution in light petroleum in the presence of an excess of suspended manganese dioxide. Different types of manganese dioxide showed very diverse oxidizing efficiency. It was very fortunate that they prepared manganese dioxide in a finely divided very active form by mixing aqueous solutions of manganese sulfate ($MnSO_4$) and potassium permanganate ($KMnO_4$), because the commercial samples were much less efficient.

> Active manganese dioxide was used by Canonica in 1947[2] for the oxidation of oximes into nitrocompounds before the seminal publication of Ball *et al.* on the oxidation of vitamin A **(76)**. Canonica prepared active manganese dioxide by reacting $MnCl_2$ with $KMnO_4$. In fact the oxidation power of precipitated manganese dioxide is known since the 1870's.[3]

Section 8.1. References

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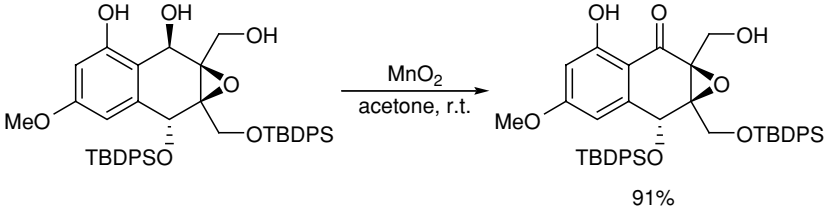
8.2. Manganese Dioxide (MnO_2)

Manganese dioxide very soon became a widely used standard oxidant for the transformation of allylic and benzylic alcohols into aldehydes and ketones.[4] It offers very mild conditions and is extremely selective for allylic and benzylic alcohols when it is not employed at a high temperature. On the other hand, the work-up of oxidations with MnO_2 is very simple, involving just filtration of suspended solid and elimination of solvent.

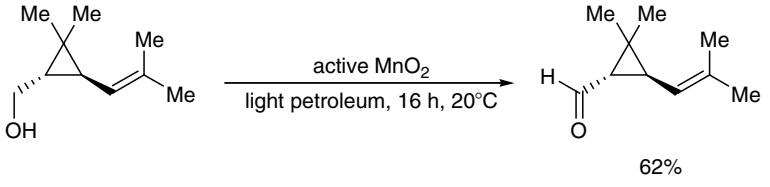
One important property of MnO_2 is its very high selectivity for the oxidation of allylic and benzylic alcohols versus saturated alcohols. Although, MnO_2 is able to oxidize saturated alcohols,[5] this reaction involves prolonged heating, while the oxidation of allylic and benzylic alcohols is normally carried out during a few hours at room temperature. Not surprisingly, MnO_2 is the most common oxidant for the selective oxidation of allylic and benzylic alcohols in the presence of saturated alcohols. On the other hand, because of the efficiency of this reagent and the simple experimental protocols involved in its use, MnO_2 is a good choice for the standard oxidation of allylic and benzylic alcohols. Also, when no selectivity is needed because of the absence of other alcohols.



Ref. 6
A secondary benzylic alcohol is selectively oxidized with active MnO_2 at room temperature in the presence of an aliphatic primary alcohol and a free phenol.

The selectivity of active MnO_2 for the oxidation of allylic and benzylic alcohols can be explained either by the formation of a π-complex between the olefin or the aromatic ring in the alcohol,[24b] and some Lewis acid site on the surface of MnO_2 particles or by the favourable thermodynamics involved in the formation of a carbonyl conjugated with an unsaturated system.[7] Interestingly, alcohols, whose oxidations result in carbonyls conjugated with cyclopropane rings,[8] or alcohols possessing heteroatoms closely

positioned to the alcohol functionality and able to form complexes with Lewis acid sites,[9] can be oxidized under very mild conditions with active MnO_2.



Ref. 8a

A cyclopropylmethyl alcohol behaves against active MnO_2 similarly to an allylic alcohol, resulting in the formation of a cyclopropanecarbaldehyde under very mild conditions.

The oxidizing power of MnO_2 depends widely on the exact preparation of the material.[10] Thus, its reactivity can vary from MnO_2 in the form of the crystalline mineral pyrolusite, which is almost completely unable to oxidize alcohols at room temperature, to highly active forms that are dangerous because they may cause the spontaneous inflammation of organic solvents.[11]

> The activity of a certain sample of manganese dioxide can be measured either by the method of Weedon and Woods,[12] involving oxidation of cynnamic alcohol in petroleum ether at 20°C, or by the method of Fatiadi,[4b] involving reaction with benzenhexol.

Obviously, for the sake of consistency and reproducibility, it is advisable to adhere to an accepted standard protocol for the preparation of samples of MnO_2 possessing a suitable oxidizing power. Attenburrow *et al.*[13] described in 1952, a detailed procedure for the preparation of MnO_2 by mixing aqueous manganese sulfate and potassium permanganate in a basic medium. Some modifications of this procedure, involving changes in the pH of the reaction medium and in the isolation of dry MnO_2, were later suggested by other authors.[14] The employment of Attenburrow manganese dioxide, either prepared as in the original protocol or according to some of its modifications, is advisable because it facilitates the replication of synthetic results in diverse laboratories.

> A number of vendors offer samples of active manganese dioxide prepared according to poorly disclosed procedures, which nevertheless are very efficient in the selective oxidation of allylic and benzylic alcohols. Although, good oxidation yields can be obtained using such samples of MnO_2, it may be advisable to describe in scientific journals oxidations performed with MnO_2 prepared in the researcher's own laboratory using clearly disclosed procedures. Chemical journals are depositories of experimental data that can be very useful in many years to come. There is no guarantee that a certain chemical company will provide consistent samples of MnO_2 during a very prolonged time.

Very often, even in the best chemical journals, oxidations are described in which no information whatsoever is given regarding the nature of the active MnO_2 employed. Referees and editors must be aware in order to avoid this to happen.
Because of the time-consuming preparation of Attenburrow active manganese dioxide, the use of a number of more readily available types of active MnO_2 was proposed. These include employing:

- MnO_2 prepared by thermal decomposition of manganese carbonate or oxalate[11]
- Crystalline MnO_2 activated with ultrasounds[15] or by heating with nitric acid[16]
- MnO_2 deposited on charcoal[17] or on alumina[18]
- MnO_2 deposited on silica[19] or on bentonite,[20] used with no solvent and applying microwaves

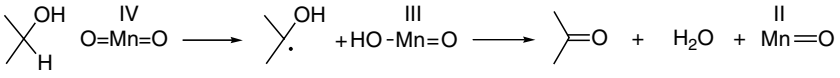
The use of so-called chemical manganese dioxide (CMD), which is employed in the manufacture of batteries and available at a low price, is particularly interesting,[21] although some lack of reproducibility in oxidations with CMD has been attributed to unequal oxidizing power of CMD samples of diverse commercial origin.[22]

Studies on the mechanism of oxidation of alcohols with MnO_2 have met a number of difficulties including: i) the heterogeneous nature of the reaction, and ii) the very diverse oxidation power of MnO_2 samples of different origin. Additionally, there is no absolute certainty regarding the chemical nature of the real reagent in the oxidation of allylic alcohols with excess of MnO_2 at room temperature. A number of circumstantial evidences point to the involvement of a chemical species different from MnO_2. Thus, MnO_2 must be employed in an excess, raising the possibility that an impurity present in small amounts is the real oxidant. Furthermore, the best results are obtained using MnO_2 with a content of water 4–8%[4a] and MnO_2 samples containing a greater amount of impurities tend to be the most chemically active.[23] Regardless of these facts, different researchers focused on the involvement of plain MnO_2 in order to offer a mechanistic view on the oxidation of alcohols with the active reagent.

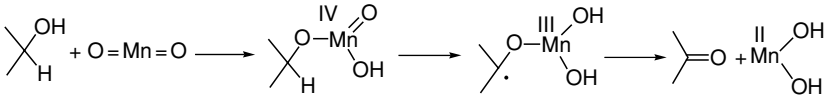
There are less doubts regarding the involvement of plain manganese dioxide in reactions carried out at temperatures higher than room temperature. At high temperatures, there is no need to employ such a great excess of MnO_2 and the origin of the reagent seems not to be so important.

The experimental facts are consistent with a mechanism involving the complexation of the alcohol on the surface of MnO_2 particles, perhaps aided by the presence of foreign ions,[24] followed by oxidation and desorption of the carbonyl compound.[1] This explains that the oxidations of allylic and benzylic alcohols are best performed in apolar solvents that do not compete with the alcohols for adsorption on MnO_2 particles, and the fact that MnO_2 samples possessing particles with a greater surface tend to have the greatest activity.[24b]

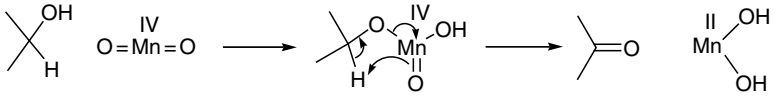
Pratt and van de Castle[14c] suggested a radical mechanism because it is consistent with the limited influence of diverse electron-releasing and –withdrawing groups on the *para* position of benzylic alcohols during its oxidation with active manganese dioxide, something that excludes charged intermediates. A mechanism via radicals, as in Equation below, was not contradicted by subsequent experimental data,[25] including the observation of a very high isotopic effect during the oxidation of deuterated benzylic alcohols,[26] and was favoured by several research groups.



On the other hand, Hall and Story[27] in 1967 presented evidences of the involvement of an intermediate manganese ester. This prompted the proposal by Goldman[26] of a refined radical mechanism, as in the following Equation below, including such intermediate.



Alternatively, according to Kwart and George,[28] the available experimental data are coherent with a hydrogen transfer by way of a cyclic five-membered transition state. A mechanism as in Equation below would be consistent both with a manganese ester intermediate and with the five-membered transition state suggested by Kwart and George.



Interestingly, it has been proved that MnO_2 can catalyze the oxidation of certain alcohols with gaseous oxygen.[29]

The selective oxidation of benzylic and allylic alcohols with active manganese dioxide in the presence of saturated alcohols is normally carried out by stirring or shaking a solution of the alcohol in an organic solvent in the presence of 5–20 equivalents of suspended active MnO_2.

Due to the great excess of active MnO_2 employed, the bulk of MnO_2 is not consumed during the oxidation of alcohols. This allows the recycling of used active MnO_2 by simple heating at 110°C during 24 h.[30]

The reaction is best done using a solvent as apolar as possible because polar solvents compete with the alcohol by interaction on the surface of the

MnO_2 particles. Saturated hydrocarbons, like petroleum ether, pentane, hexane or cyclohexane, are excellent choices because of its negligible interaction with MnO_2. Although, as these saturated hydrocarbons possess a limited solubilizing power for many organic compounds, oxidations with MnO_2 are most often carried out in dichloromethane, chloroform or diethyl ether. More polar solvents can be used nevertheless in MnO_2 oxidations, in spite of the resulting partial inactivation of active MnO_2. Thus, solvents like acetone, EtOAc, benzene, toluene, THF, dioxane, MeCN and even DMF or DMSO can be employed in oxidations with MnO_2 at room temperature. The use of alcohols, such as MeOH, EtOH or *i*-PrOH, is not advisable because they strongly compete with the substrate for adsorption on the surface of the MnO_2 particles.[31] Partial deactivation of MnO_2 was observed with acetone, EtOAc and DMSO. MeCN suffers slow hydrolysis to acetamide on contact with active MnO_2.[4b] THF is slowly oxidized with MnO_2, resulting in the formation of 1,4-butanediol.[25b]

Interestingly, oxidation of alcohols with active MnO_2 can be performed with no solvent.[32] Under these conditions, aliphatic secondary alcohols can be oxidized at room temperature and with reasonable yields.[33]

It is not advisable to employ a temperature higher than room temperature during the selective oxidation of allylic and benzylic alcohols with MnO_2 in the presence of saturated alcohols, because partial oxidation of the saturated alcohols can occur. When no such regioselectivity is needed, mild heating can be applied in order to accelerate the oxidation of refractory unsaturated alcohols. Care must be taken in order to avoid overheating because at high temperatures active manganese dioxide behaves as a very strong oxidant able to react with many functionalities, including aromatic compounds[38a] and olefins.[34]

Some unsaturated alcohols resist reaction with MnO_2 due to steric reasons. Sometimes, epimeric unsaturated alcohols possess very different reactivities versus active MnO_2, which points to the possible involvement of little-investigated stereoelectronic effects.[35]

During the oxidation of alcohols with active MnO_2, water is produced that can partially inactivate the active MnO_2 or generate a brown mud. This can be avoided by performing the oxidation in a boiling aromatic solvent[14c] with azeotropic elimination of water, or—without any need to heat—by adding activated molecular sieves.[21d,e] Interestingly, the azeotropic elimination of water does not remove water molecules strongly bound to the MnO_2, which are necessary for the oxidation activity of this oxidant.[36]

An interesting experimental modification of the standard protocol for the oxidation of unsaturated alcohols with active manganese dioxide, first described by Wald in 1948,[37] involves the percolation of a solution of the alcohol through a column of active MnO_2.[10c]

Preparation of Attenburrow Manganese Dioxide

A 3.3 M aqueous solution of manganese sulfate monohydrate[a] ($MnSO_4 \cdot H_2O$, MW = 169.02) and 1170 mL of a 40% NaOH aqueous solution are simultaneously added to a hot stirred 1.0 M aqueous potassium permanganate ($KMnO_4$, MW = 158.04) solution. The beginning of the addition of both solutions is coincidental in time, while the $MnSO_4 \cdot H_2O$ solution is poured for 60 min and while the 40% NaOH solution is added for 45 min[b] The temperature of the $KMnO_4$ solution is set at 80°C at the beginning of the addition of the $MnSO_4 \cdot H_2O$ and 40% NaOH solutions. Heat is evolved and the $KMnO_4$ solution must be kept at 80–90°C. Once the addition of the $MnSO_4 \cdot H_2O$ solution is finished, the reaction mixture is stirred at 80–90°C during additional 60 min.

The resulting suspension of MnO_2 is filtered while still hot[c] and washed with a copious amount of hot water till the filtrate is almost neutral to litmus.[d,e]

The MnO_2 is dried in an oven at 105–125°C during 2–3 days,[f] with occasional grinding of the material.

It is advisable to store the MnO_2 at low temperature in a stoppered bottle in order to delay ageing.[38b]

[a] The tetrahydrate can also be used.

[b] According to the original Attenburrow protocol, both solutions are poured along 60 min. Pratt *et al.*[38] reported that adding the 40% NaOH solution during the first 45 min results in the formation of MnO_2 particles, which are easier to filter and wash. This avoids the need to separate the MnO_2 by centrifugation.

[c] Some authors let the MnO_2 suspension to stand overnight before the separation of MnO_2.[39] This may result in ageing of the MnO_2 and some loss of activity.

[d] Failure to make a thorough washing with water may result in MnO_2 producing unwanted side reactions in base-sensitive substrates.[39]

[e] It is advisable to perform the water washings within one day in order to obtain MnO_2 with the highest activity.[39]

[f] Both under- and over-drying result in MnO_2 of significant lesser activity.[13] MnO_2 of the highest activity is found to contain 4–8% of water.[4a] While some authors recommend to heat the MnO_2 at 125°C during 24 h[38b] or during more than 2 days,[14c,38a] others[40] recommend not to exceed 105°C. Quite expectedly, authors, subjecting the MnO_2 to heating at 125°C, recommend to let the MnO_2 to equilibrate with atmospheric moisture during several days,[14c,38] undoubtfully in order to compensate for the excess of water removed during heating at 125°C.

It is not recommended to employ organic solvents to dry the MnO_2 because this may produce loss of activity.[5b]

8.2.1. General Procedure for Selective Oxidation of Allylic, Benzylic and Propargylic Alcohols with MnO_2

A suspension of ca. 6–50 equivalents, typically 5–20 equivalents, of active MnO_2 in a ca. 0.02–0.2 M solution of the alcohol in a dry[a] organic solvent[b] is vigorously[c] shaken at room temperature[d] till most of the unsaturated alcohol is oxidized.[e]

The reaction mixture is filtered either using filter paper or a Celite® pad. The MnO_2 is washed with plenty of hot organic solvent and the collected organic phases are concentrated.

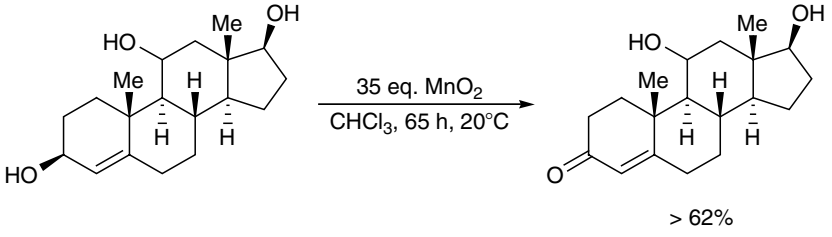
[a] For the highest activity, active MnO_2 must contain a precise amount of water. The addition of surplus water in the solvent may produce deactivation.

[b] Apolar organic solvents give best results because they do not compete with the alcohol for adsorption on the MnO_2 particles. Ideally, the oxidation can be carried out in very apolar solvents, like petroleum ether, pentane, hexane or cyclohexane. Because these solvents have a limited solubilizing power for many organic compounds, normally the oxidation of unsaturated alcohols is performed in CH_2Cl_2 or chloroform because these solvents offer a good balance of solubilizing power versus apolarity. Other solvents less frequently used for oxidation with active MnO_2 include Et_2O, acetone, EtOAc and benzene. Oxidation with active MnO_2 can be performed in more polar solvents, such as THF, dioxane, MeCN, and even MeOH or water. THF and MeCN are known to react slowly with active MnO_2.

[c] The reaction mixture must be vigorously shaken for maximum reaction speed.

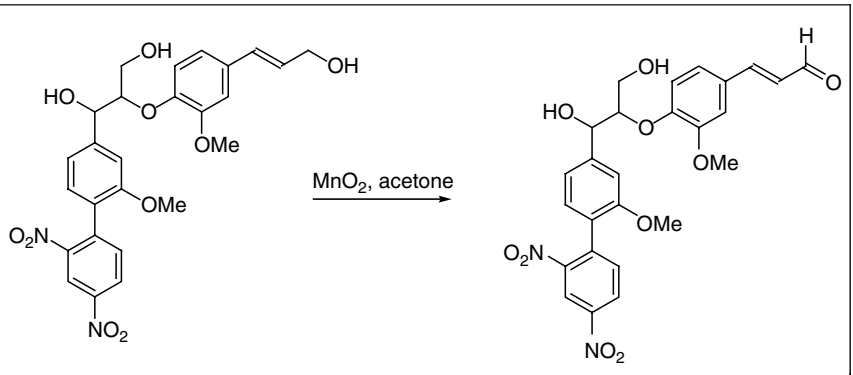
[d] Increasing the temperature above room temperature is not advisable, regardless of a convenient shortening of reaction time, because aliphatic alcohols can be oxidized with MnO_2 above room temperature at an appreciable rate.

[e] Normally, it takes about 1–70 h. A substantial longer reaction time is necessary in the oxidation of hindered allylic and benzylic alcohols. Benzylic alcohols tend to demand longer oxidation times than allylic alcohols.



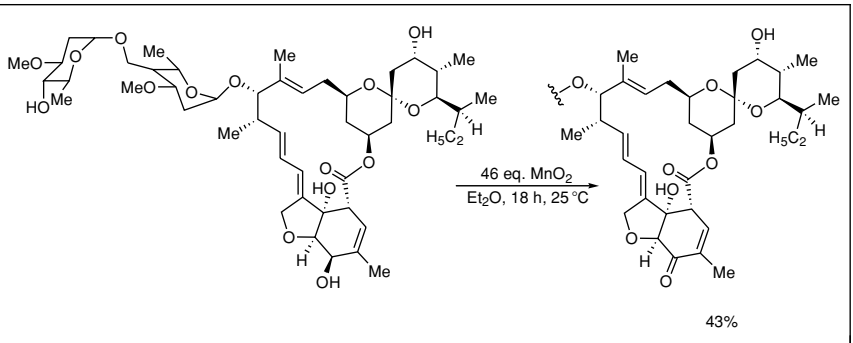
Ref. 14a

An allylic alcohol is regioselectively oxidized with active MnO_2 at room temperature in the presence of two saturated alcohols.



Ref. 41

A primary allylic alcohol is oxidized in the presence of a secondary benzylic alcohol and a primary saturated alcohol. The selectivity in the oxidation of the allylic alcohol versus the benzylic one is due to steric factors plus the fact that active MnO_2 tends to oxidize allylic alcohols quicker than benzylic ones.



Ref. 42

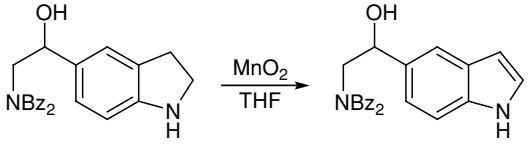
In this complex substrate adorned with many functional groups including secondary saturated alcohols and a tertiary allylic alcohol, it is possible to selectively oxidize a secondary allylic alcohol employing active MnO_2 in Et_2O.

8.2.2. Functional Group and Protecting Group Sensitivity to Oxidation with MnO_2

Not surprisingly, the oxidation power of active MnO_2 depends very strongly on the temperature. Thus, although active MnO_2 at a high temperature behaves as a very strong and unselective oxidant; when it is used at room temperature, it is highly selective for the oxidation of allylic and benzylic alcohols. It is very important to highlight this fact, because a literature search reveals that MnO_2 is able to oxidize many functionalities, including amines[43] and alkenes,[34] while at the same time it is possible to perform selective oxidations of allylic and benzylic alcohols with MnO_2 in

the presence of most other functional groups, provided that the reaction temperature is not high.

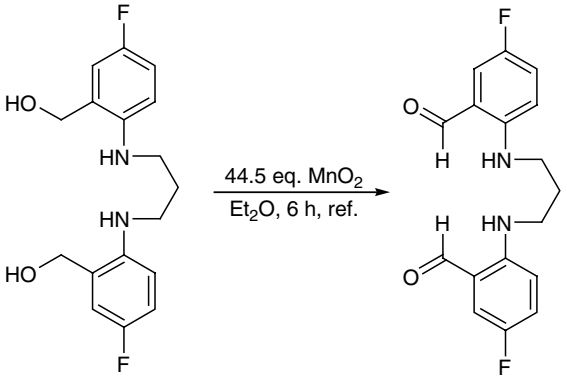
The reactivity of amines versus active MnO_2 increases in the order of tertiary<secondary<primary amine. Thus, normally tertiary amines do not interfere[44] with the selective oxidation of allylic and benzylic alcohols, unless the alcohols are very hindered.[45] Secondary amines tend not to interfere,[46] although cases are known in which secondary amines are selectively oxidized[47] with active MnO_2 in the presence of these alcohols.



95%

Ref. 47

In this interesting case, a secondary amine, which is very oxidation-sensitive because of its tendency to be aromatized to an indole, is selectively oxidized with active MnO_2 in the presence of a benzylic alcohol.



80%

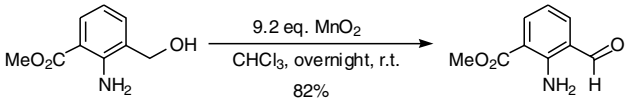
Ref. 46a

Two benzylic alcohols are selectively oxidized with active MnO_2 in the presence of two secondary amines. In a similar compound, possessing two methoxy substituents in the place of the two fluorine atoms, the corresponding oxidation provides a modest 34% yield of the desired dialdehyde. This happens because the methoxy substituents render the amines more oxidation-sensitive.

The number of published selective oxidations of allylic or benzylic alcohols with active MnO_2 in the presence of primary amines is very limited.[48] The published cases involve aromatic primary amines possessing an

electron-poor aromatic ring; that is, successful cases of selective oxidations involve those primary amines that possess lesser sensitivity to oxidation.

Amines tend to react with carbonyl groups resulting from oxidation of alcohols when this leads to formation of stable cyclic imines.[49]

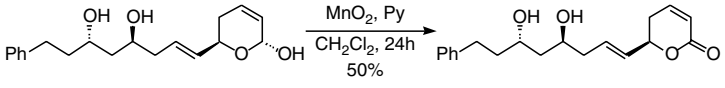


Ref. 48b

A benzylic alcohol is selectively oxidized with active MnO_2 in the presence of a primary amine. This primary amine is relatively refractory to oxidation because it is a hindered electron-poor aniline.

1,2- and 1,4-diphenols, not surprisingly, are very easily oxidized by active MnO_2 to the corresponding quinones.[21d] Other phenols require harsher conditions for the oxidation with MnO_2, resulting in oxidative dimerizations[21d] or formation of quinones.[50] There are several published examples in which allylic or benzylic alcohols are selectively oxidized in the presence of free phenols (see pages 290 and 300).[51]

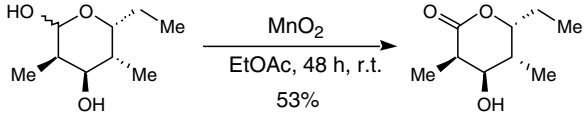
Unsurprisingly, lactols possessing the hydroxy group at an allylic position are easily oxidized with active MnO_2 at room temperature in the presence of unreacting saturated alcohols.[52]



Ref. 52a

An allylic lactol is oxidized to the corresponding lactone with active MnO_2 in the presence of two secondary saturated alcohols.

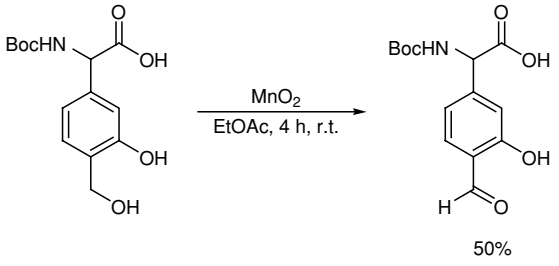
Interestingly, saturated lactols are quite easily oxidized to lactones with active MnO_2; thus, being possible to oxidize such lactols in the presence of unreacting saturated alcohols.[53]



Ref. 53b

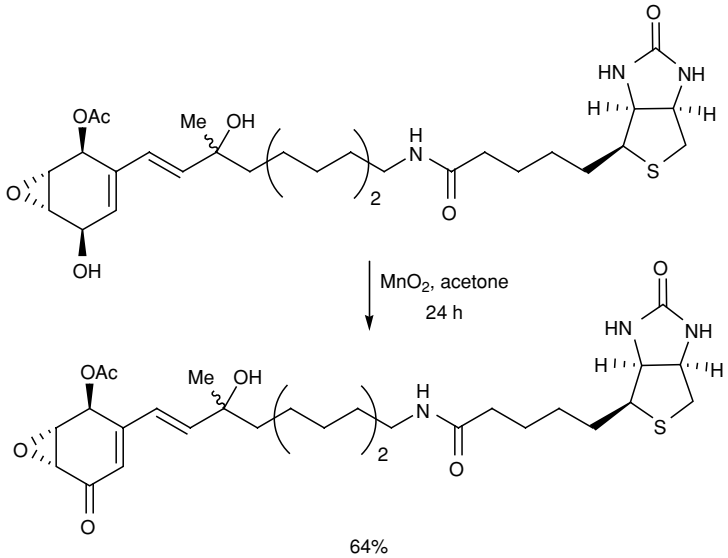
Active MnO_2 is able to oxidize a saturated lactol at room temperature in the presence of a saturated secondary alcohol.

Normally, it is possible to perform selective oxidation of allylic and benzylic alcohols with MnO_2 in the presence of free carboxylic acids.[54] α-Hydroxycarboxylic acids suffer an oxidative breakage on contact with active MnO_2.[55]



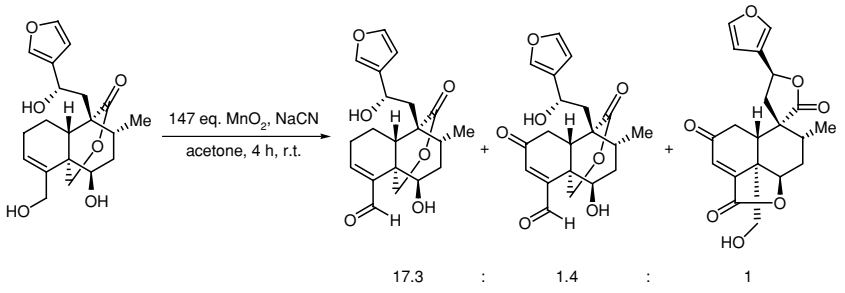
Ref. 54c
A benzylic alcohol is selectively oxidized with active MnO_2 in the presence of a free acid and a free phenol.

Most sulfur compounds resist the action of active MnO_2 at low temperature. For instance, organic sulfides resist active MnO_2 during the oxidation of allylic and benzylic alcohols.[57] Thiols, being sulfur compouds with a greater oxidation sensitivity, are oxidized to disulfides.[56]



Ref. 57c
An allylic alcohol is selectively oxidized with active MnO_2 in a complex substrate in the presence of an aliphatic sulfide.

Alkenes are normally inert to active MnO_2 under the mild reaction conditions used in the oxidation of unsaturated alcohols. Nevertheless, occasionally minor amounts of enones resulting from the oxidation of alkenes at the allylic position are obtained.[34b]



Ref. 34b

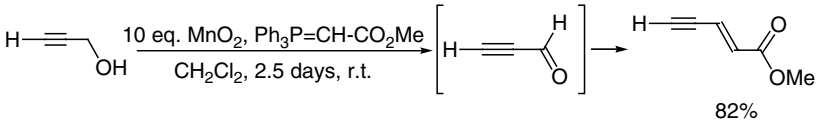
The major compound from this oxidation corresponds to the expected selective oxidation of the allylic alcohol. Minor amounts of compounds are obtained, resulting from: 1- an oxidation at an allylic position, resulting in the transformation of an alkene into an enone; 2- an oxidation of a lactol in equilibrium with the major hydroxyaldehyde, and 3- a translactonization.

Because of the almost neutral character of active MnO_2, this reagent does not affect protecting groups with sensitivity to basic or acid conditions. Although, MnO_2 is slightly basic, specially when it is not thoroughly washed with water during its preparation,[39] base-sensitive substrates, such as acetate esters,[58] resist its action during the oxidation of allylic and benzylic alcohols.

Oxidation-sensitive protecting groups, such as *p*-methoxybenzyl ethers[59] and esters,[60] resist the action of active MnO_2 during the oxidation of allylic and benzylic alcohols.

8.2.3. Reactions Performed *in situ* During Oxidations with MnO_2

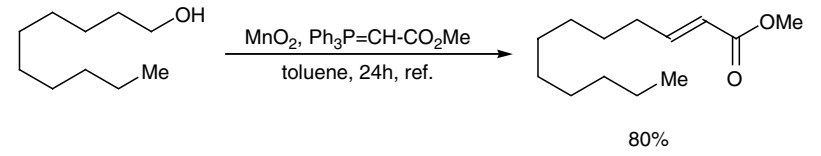
It is possible to subject aldehydes and ketones obtained by oxidation with MnO_2 to subsequent reactions in the same pot, thanks to the mildness of MnO_2, which is compatible with many reagents. For example, aldehydes and ketones obtained using MnO_2 can be reacted *in situ* with stabilized phosphoranes.[61] This protocol was first described by Taylor and Wei, who found that allylic, propargylic and benzylic primary alcohols could be directly transformed into unsaturated esters by oxidation with active MnO_2 in the presence of a stabilized phosphorane of the kind $Ph_3P{=}CR\text{-}CO_2R'$.



Ref. 61a, 62

A domino protocol in which an intermediate aldehyde—obtained employing active MnO_2—is reacted *in situ* with a stabilized phosphorane, avoids the need to isolate propynal, which is a lachrymator that polymerizes "with almost explosive force" on exposure to pyridine or alkalies.

Interestingly, Taylor's team later proved that the tandem MnO_2 oxidation-Wittig reaction also succeeds, not only with "semi-activated" alcohols—like cyclopropylmethanols—and alcohols possessing heteroatoms at the α-position—but also with saturated alcohols. Quite puzzlingly, the tandem reaction of saturated alcohols with active MnO_2, followed by *in situ* reaction with stabilized phosphoranes, succeeds under experimental conditions in which no efficient oxidation of aliphatic alcohols is observed in the absence of a Wittig reagent. The authors speculate that MnO_2 on contact with saturated alcohols leads to an equilibrium, containing a small proportion of aldehyde, that is shifted to the right by reaction of the aldehyde with a Wittig reagent.[7]



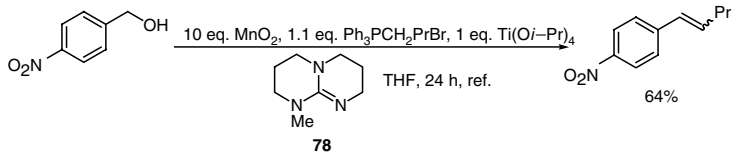
Ref. 7

An aliphatic alcohol is oxidized with active MnO_2, producing an aldehyde that reacts *in situ* with a stabilized phosphorane. The overall yield of the desired unsaturated ester is 80%. Curiously, the oxidation of the alcohol with MnO_2 under the same reaction conditions and in the absence of phosphorane delivers only a 12% of the corresponding aldehyde.

Similar results were observed by Davies and McKervey in the tandem MnO_2 oxidation-Wittig reaction of alcohols derived from β-aminoacids, which can somehow be considered to belong to a "semi-activated" kind.[30]

It is important to note that this tandem MnO_2 oxidation-Wittig reaction is particularly useful when the intermediate aldehydes are difficult to isolate. For example, it allows successful Wittig reactions on α-ketoaldehydes,[61e] which are compounds inconvenient to isolate because of their very high reactivity.

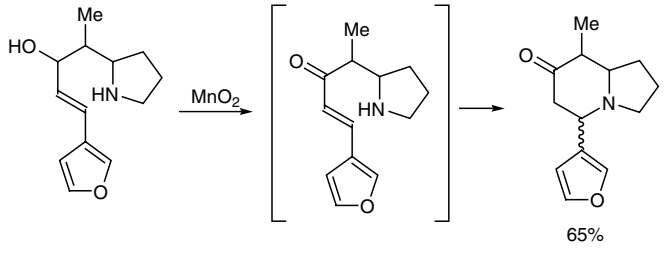
Very recently, Taylor's team,[61f] after considerable exploratory chemistry, found experimental conditions whereby tandem MnO_2 oxidation-Wittig reaction operations can be performed using non-stabilized Wittig reagents. Best results are obtained employing pre-dried active MnO_2 in the presence of Ti(O*i*-Pr)$_4$, and 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) **(78)** acting as a strong base.



Ref. 61f

In this example, a successful tandem MnO_2 oxidation-Wittig reaction is achieved, using a non-stabilized ylide, thanks to the employment of pre-dried MnO_2, the guanidine **(78)** as base and $Ti(Oi\text{-}Pr)_4$.

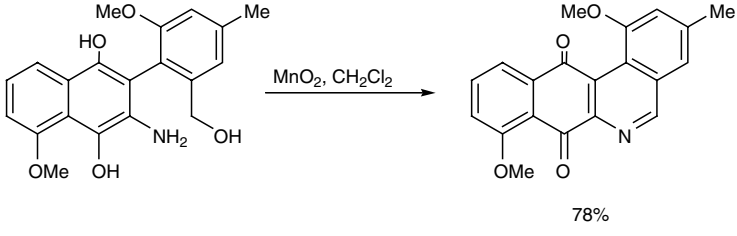
When an oxidation with MnO_2 leads to an enone containing a properly positioned amine, an intramolecular conjugated addition of the amine to the enone can occur, resulting in a useful one-pot oxidation followed by heterocycle formation.[63]



Ref. 63a

During the preparation of a Nuphar alkaloid, a molecule containing an allylic alcohol and a secondary amine is treated with active MnO_2. This results in the formation of an enone that suffers an *in situ* intramolecular conjugated addition of the amine.

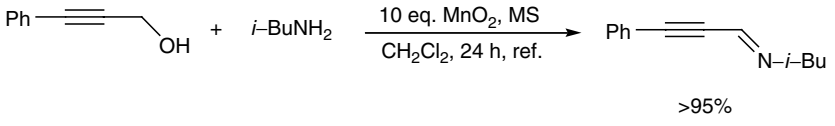
During the formation of aldehydes or ketones with active MnO_2, sometimes an amine condenses intramolecularly resulting in the formation of imines.[49]



Ref. 49

A benzylic alcohol is selectively oxidized with MnO_2 in the presence of a primary amine. The amine condenses intramolecularly with the resulting aldehyde, leading to the formation of an imine. Furthermore, MnO_2 oxidizes a hydroquinone to a *p*-quinone.

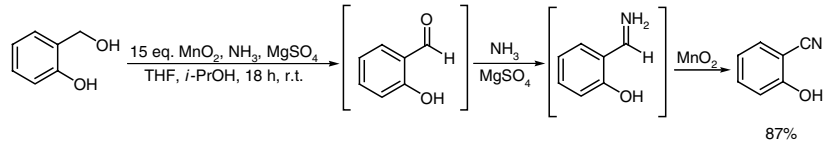
Taylor and Blackburn proved[64] that the *in situ* condensation of an aldehyde with an amine can be made to occur in an intermolecular fashion. Thus, treatment of primary allylic, propargylic and benzylic alcohols with active MnO_2 in the presence of diverse primary amines and molecular sieves in boiling CH_2Cl_2 leads to the selective oxidation of the alcohols in the presence of the primary amines and to the formation of the corresponding imines by reaction of the alcohols with the intermediate aldehydes.



Ref. 64

A propargylic alcohol is selectively oxidized with active MnO_2 in the presence of a primary aliphatic amine. The resulting alcohol condenses with the amine, thanks to the action of the added molecular sieves as dehydrating agent, leading to the formation of an imine in a very good yield.

It is possible to make a one-pot transformation of primary unsaturated alcohols into nitriles by adding a solution of NH_3 in isopropanol to a mixture of the alcohol, active MnO_2 and magnesium sulfate in THF. The unsaturated alcohol is initially oxidized to an aldehyde that condenses with ammonia—with the assistance of $MgSO_4$ operating as a dehydrating agent—delivering an imine that is further oxidized to a nitrile with MnO_2.[65]



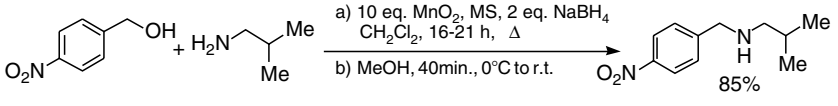
Ref. 65

A benzylic alcohol is transformed with active MnO_2 in a benzaldehyde that condenses *in situ* with ammonia, in the presence of $MgSO_4$ as dehydrating agent, delivering an imine that is oxidized to a nitrile with active MnO_2.

As a further exhibition of juggling chemistry, Taylor's team proved[66] that it is possible to perform an additional *in situ* reaction by reducing the imine with polymer-supported cyanoborohydride (PSCBH)[64] or, more conveniently, with plain $NaBH_4$.[66b] Thus, for example treatment of a mixture of an unsaturated primary alcohol, a primary amine, molecular sieves and MeOH in CH_2Cl_2 with active MnO_2 leads to the oxidation of the alcohol to an aldehyde that condenses with the amine providing an imine, which in turn is reduced with $NaBH_4$, resulting in the formation of

a new amine. The last reaction, involving a reduction with $NaBH_4$ in CH_2Cl_2, is greatly accelerated by the addition of MeOH at the end of the protocol.

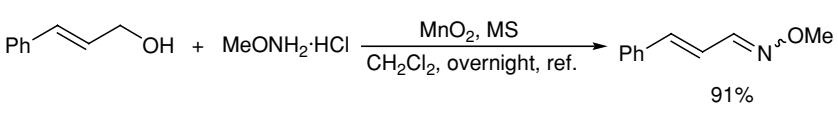
It may seem shocking that an oxidant—MnO_2—and a reducing agent—$NaBH_4$—are acting simultaneously in the same medium. In fact, this is not exactly the case, because $NaBH_4$ is very insoluble in CH_2Cl_2 and it hardly reacts while the MnO_2 oxidation is occurring. Once the action of MnO_2 has finished, MeOH is added in order to solubilize the $NaBH_4$, thus allowing the reduction of the imine.



Ref. 66b

In this very elegant transformation an alcohol and an amine are treated with a mixture of active MnO_2, $NaBH_4$ and molecular sieves. The following reactions occur *in situ*: 1- selective oxidation of the benzylic alcohol with active MnO_2 in the presence of a primary amine; 2- condensation of the amine with the resulting benzaldehyde, induced by the presence of molecular sieves, and 3- reduction of the resulting imine to an amine with $NaBH_4$. MeOH is added after the first two reactions are complete, in order to solubilize the $NaBH_4$ and allow the reduction of the imine to the final amine.

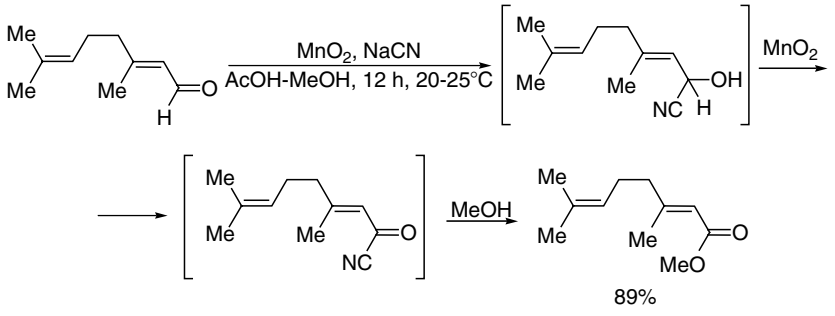
The above reactions are successful because MnO_2 is a mild oxidant that is compatible with primary aliphatic amines, which are quite sensitive to oxidation. Interestingly, the mildness of MnO_2 can be challenged a step further by performing oxidations in the presence of hydroxylamines, which are compounds with a great sensitivity for oxidation. Thus, Taylor and Kanno proved[67] that it is possible to prepare *O*-methyloximes by oxidation of unsaturated alcohols with active MnO_2 in the presence of $MeONH_2 \cdot HCl$ and molecular sieves. This protocol seems to illustrate the tolerance limit of MnO_2 versus oxidizeable nitrogen compounds, because the *O*-methylhydroxylamine must be protected as a hydrochloride and the reaction fails with other hydroxylamines.



Ref. 67

The oxidation of an allylic alcohol with active MnO_2 leads to an aldehyde that condenses *in situ* with $MeONH_2 \cdot HCl$ in the presence of molecular sieves, producing an *O*-methyloxime.

Not surprisingly, active MnO_2 is able to oxidize unsaturated cyanohydrins, resulting in the generation of acyl cyanides. Interestingly, both the formation of the cyanohydrins by reaction of aldehydes with cyanide, and the hydrolysis of acyl cyanides with MeOH, resulting in the formation of methyl esters, can be carried out *in situ* with the MnO_2 oxidation. Thus, Corey *et al*. proved[68] that aldehydes can be directly transformed into methyl esters by treatment with NaCN and active MnO_2 in a mixture of acetic acid and methanol. This represents a useful protocol for the oxidation of unsaturated aldehydes to esters.

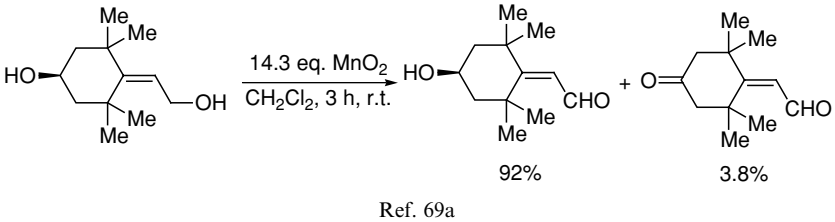


Ref. 68

Treatment of an unsaturated aldehyde with a mixture of NaCN and MnO_2 in AcOH-MeOH, leads to the initial formation of a cyanohydrin that is oxidized with active MnO_2 to an acyl cyanide, which is further hydrolyzed on contact with methanol, resulting in the formation of a methyl ester.

8.2.4. Side Reactions

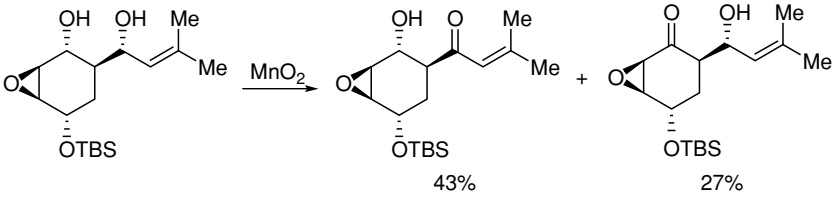
Although active MnO_2 presents a very high selectivity for unsaturated alcohols versus saturated ones when it is employed under mild conditions, sometimes minor amounts of aldehydes or ketones resulting from the oxidation of saturated alcohols are obtained.[69]



Ref. 69a

During the selective oxidation of an allylic alcohol with active MnO_2, a minor amount of product arising from additional oxidation of a saturated alcohol is obtained.

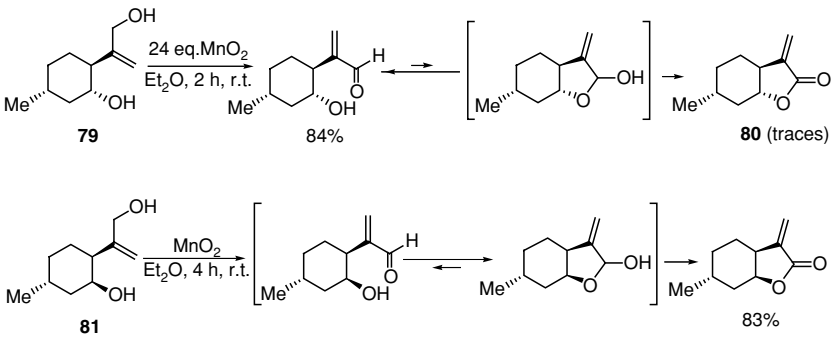
Unsurprisingly, greater amounts of oxidation at a saturated alcohol can be observed when the unsaturated alcohol is subject to steric hindrance.[69b]



Ref. 69b

Treatment of a hindered allylic alcohol with active MnO_2 provides a modest yield of enone resulting from the desired selective oxidation, while a 27% yield of ketone arising from the sole oxidation of an aliphatic alcohol is obtained.

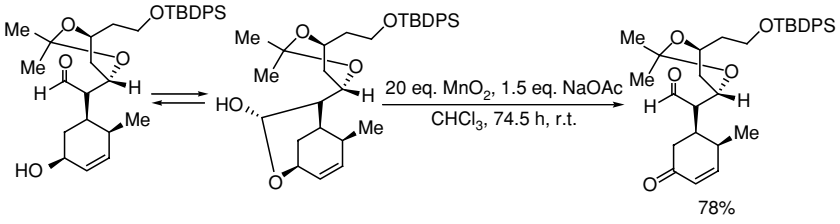
During selective oxidations of 1,4- and 1,5-diols with active MnO_2, sometimes the unreacting alcohol forms a lactol by interaction with the carbonyl group resulting from the oxidation of an unsaturated alcohol. This lactol can be further oxidized to a lactone.[70]



Ref. 70a

The oxidation of 7**9** with active MnO_2 provides a good yield of the desired enal resulting from selective oxidation of the allylic alcohol. Only traces of the undesired lactone **80**—arising from oxidation of a lactol—are obtained because the corresponding lactol is present in a very small amount in the equilibrium. The oxidation of **81** under similar conditions results in a good yield of a lactone arising by the oxidation of an intermediate lactol, which is present in a high proportion in equilibrium with a hydroxyaldehyde that is the primary oxidation product. This primary oxidation product can be isolated in a low yield by limiting the reaction time.

It is important to emphasize that no oxidation of lactol to lactone occurs whenever an easily detectable amount of lactol is present because lactols can react slower than unsaturated alcohols.[71]

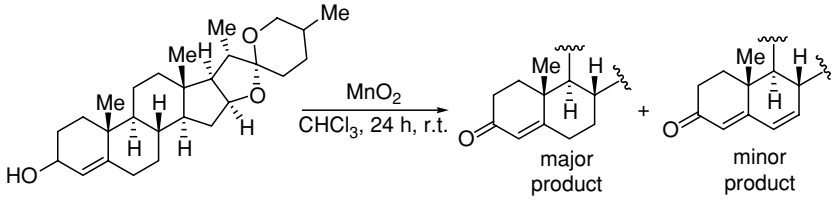


Ref. 71

When an equilibrating mixture of a hydroxyaldehyde and a lactol is treated with MnO_2, a good yield of product arising from the oxidation of an allylic alcohol is obtained due to the lower reactivity of the lactol in equilibrium.

The over-oxidation of primary unsaturated alcohols to carboxylic acids with active MnO_2 is surprisingly seldom described in the literature, in spite of the fact that benzaldehydes are known[72] to be transformed into benzoic acids with MnO_2, although quite slowly. Presumably, the formation of minor amounts of carboxylic acids during MnO_2 oxidations is not normally detected because carboxylic acids may remain strongly adsorbed on the surface of the MnO_2 particles.

On rare occasions, the enone, resulting from an oxidation with active MnO_2, is further oxidized producing a dienone.[14b]

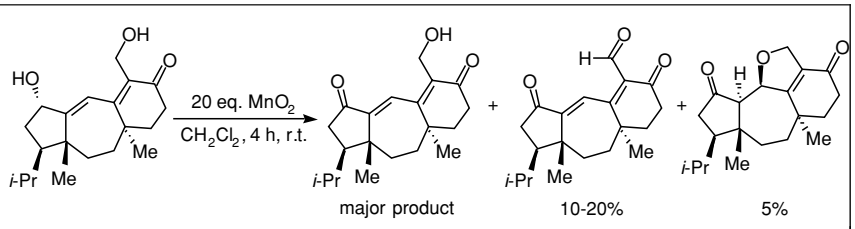


Ref. 14b

The oxidation of an allylic alcohol with active MnO_2 delivers minor amounts of a dienone resulting from additional oxidation of the desired enone.

Sometimes, an alkene *cis-trans* isomerization is observed during the oxidation of allylic alcohols with active MnO_2. This side reaction occurs during the oxidation of allylic alcohols with many different oxidants. In fact, active MnO_2 is quite refractory to induce such isomerizations,[73] when alkene isomerizations must be avoided being the oxidant of choice. The addition of Na_2CO_3 and the performance of the oxidation at 0°C help to prevent such isomerizations.[74]

Sometimes, enones arising from the oxidation of allylic alcohols with active MnO_2 suffer intramolecular conjugated addition from amines (see page 303), or alcohols properly[75] positioned inside the same molecule.



Ref. 75

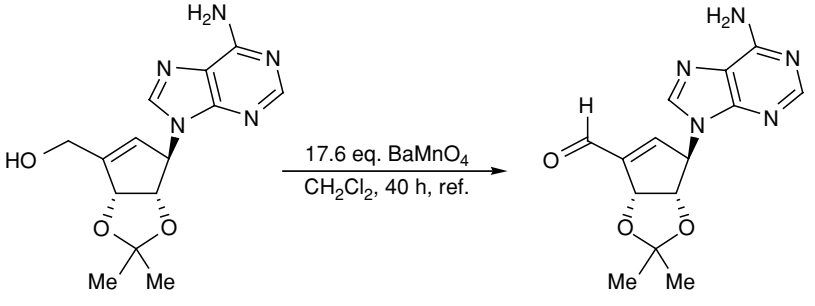
The oxidation of a diol with active MnO_2 produces the selective oxidation of an allylic alcohol as the major reaction pathway, with a 10–20% of product arising from oxidation of both alcohols and 5% of a product resulting from an intramolecular attack of an alcohol on the enone being the primary oxidation product.

8.2.5. Barium Manganate: More Reactive and Reproducible Alternative to Active MnO_2

Barium manganate ($BaMnO_4$) was a little known oxidant in organic synthesis till Firouzabadi *et al.* published in 1978–83 two foundational papers[76] showing that it behaves against alcohols in a similar way as active MnO_2.

> $BaMnO_4$ can be prepared by reacting $KMnO_4$, $BaCl_2$, NaOH and KI in an aqueous solution[76a] or by fusing MnO_2 with KOH, resulting in the formation of potassium manganate (K_2MnO_4) that is reacted with $Ba(OH)_2$ in an aqueous solution.[76b]

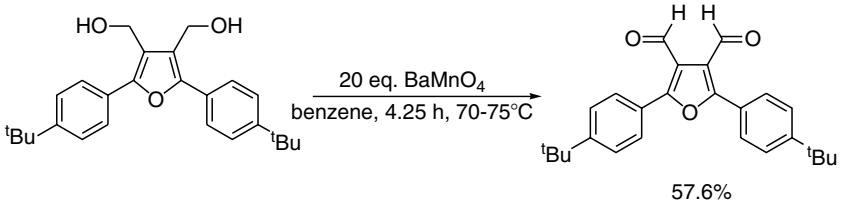
Like active MnO_2, $BaMnO_4$ is a solid that is used in excess as a suspension in an inert organic solvent like CH_2Cl_2 for the oxidation of alcohols, producing a quicker oxidation of unsaturated alcohols than saturated ones. On the other hand, $BaMnO_4$ is a commercially available material that reportedly does not need a special activation and no different chemical behaviour has been communicated from samples of diverse origin.



Ref. 77

This allylic alcohol is efficiently oxidized with $BaMnO_4$, while Swern, Moffatt, TPAP and PDC oxidations do not provide the desired aldehyde.

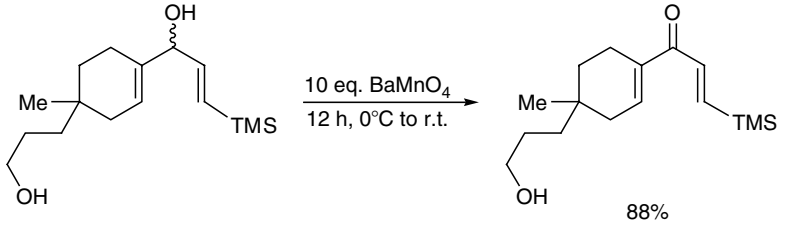
$BaMnO_4$ is particularly well-suited for the transformation of bis-benzylic alcohols into *o*-bisformyl aromatic compounds without the generation of substantial quantities of lactone.[78]



Ref. 78c

An aromatic diol is oxidized with $BaMnO_4$ providing a 58% of the desired bisfuraldehyde. Although, a Swern oxidation provides a 75% yield, the employment of $BaMnO_4$ is preferred because of experimental simplicity.

$BaMnO_4$ is not only an interesting alternative for active MnO_2 in the oxidation of allylic,[79] benzylic[80] and propargylic[81] alcohols—when no selectivity is needed—but it can also be used for the selective oxidation of unsaturated alcohols in the presence of saturated ones in the same molecule.[82]



Ref. 82b

An allylic alcohol is selectively oxidized with $BaMnO_4$ in the presence of a primary saturated alcohol. The authors describe $BaMnO_4$ as the reagent of choice for this transformation.

Normally, oxidations with $BaMnO_4$ are performed at room temperature or in refluxing CH_2Cl_2. Other solvents occasionally employed include benzene,[83] $CHCl_3$[84] and dioxane.[85] Interesting experimental variants during $BaMnO_4$ oxidations include: applying ultrasounds in order to accelerate the reaction,[86] employing the solid mixture $BaMnO_4$-Al_2O_3-$CuSO_4 \cdot 5H_2O$,[87] making the oxidation in the absence of solvent[88] and applying microwaves on a mixture of alcohol and $BaMnO_4$ deposited on montmorillonite or SiO_2 in the absence of solvent.[89]

Similar to MnO_2, $BaMnO_4$ is able to oxidize functional groups other than alcohols, including primary amines,[76b] anilines,[76b,83a] imidazolines,[90] saturated hemiacetals[91] and thiols.[84a,88b]

It is possible to carry out an *in situ* Wittig reaction with a stabilized phosphorous ylide and an aldehyde obtained by a $BaMnO_4$ oxidation of a primary benzylic or allylic alcohol.[77]

8.2.6. General Procedure for Selective Oxidation of Allylic, Benzylic and Propargylic Alcohols in Presence of Saturated Alcohols, using Barium Manganate ($BaMnO_4$)

A suspension of ca. 5–20 equivalents—typically 10 equivalents—of dry powdered barium manganate ($BaMnO_4$, MW = 256.28) in a ca. 0.02–0.08 M solution of the alcohol in dry CH_2Cl_2,[a] is stirred at room temperature[b] under an inert atmosphere till most of the starting compound is consumed.[c]

The reaction mixture is filtered through a pad of Celite® or, alternatively, employing filter paper or a pad of silica. The resulting solution is concentrated, giving a residue that may need further purification.

[a] Other inert organic solvents, like benzene, chloroform or dioxane, can be employed.

[b] The reaction can be accelerated by heating at reflux. This may be advisable when no regioselective oxidation of an unsaturated alcohol is needed. Otherwise, it is better to perform the oxidation at room temperature in order to increase the regioselectivity in the oxidation of unsaturated alcohols versus saturated ones. On a big scale, it may be advisable to add slowly the $BaMnO_4$ over the solution of the alcohol kept at 0°C in order to avoid exotherms.

[c] It usually takes between 1 and 40 h, typically 10 h.

Section 8.2. References

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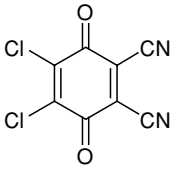
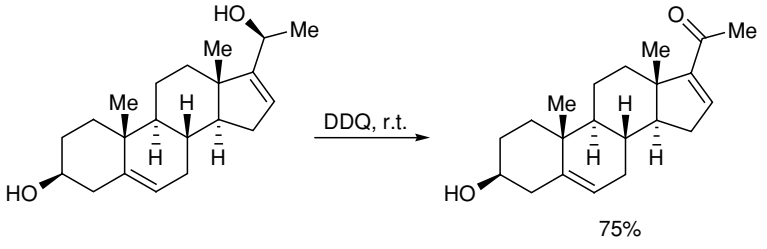
8.3. 2,3-Dichloro-5,6-dicyano-*p*-quinone (DDQ)



In 1956, Braude *et al*.[92] showed that treatment of allylic, benzylic and propargylic alcohols with *o*-chloranil (tetrachloro-1,2-benzoquinone) **(82)** provided the corresponding aldehydes and ketones. Under the mild conditions employed, involving room temperature or refluxing ether, saturated alcohols remained unaffected.

In 1960, Burn et al.[93] found that 2,3-dichloro-5,6-dicyano-*p*-quinone (DDQ) **(83)** was able to perform the regioselective oxidation of allylic sterols in the presence of saturated alcohols in dioxane or benzene at room temperature.



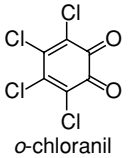
Ref. 93
An allylic alcohol is regioselectively oxidized in the presence of a saturated alcohol with DDQ at room temperature.

Subsequent authors confirmed the utility of DDQ in the oxidation of allylic[94] alcohols and extended the scope of this oxidation to benzylic[95] and propargylic[96] ones. Nowadays, among quinones, DDQ is the preferred one for the oxidation of unsaturated alcohols because it possesses a very high

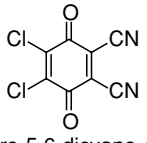
oxidation potential that causes the oxidations to be very quick and high yielding.

p-Chloranil (tetrachloro-1,4-benzoquinone) **(84)** is a readily available and cheap alternative to DDQ that has not found the same widespread use. *p*-Chloranil possesses a lower oxidation potential—$E^0 = 0.70$ versus $E^0 = 1.0$ for DDQ—resulting in a lower yield during the oxidation of unsaturated alcohols, under comparable experimental conditions.[97] On the other hand, the milder reagent *p*-chloranil, when used under harsher conditions than DDQ, sometimes provides a better yield on the oxidation of allylic alcohols because of its mildness and greater selectivity.[95e]

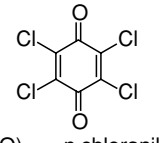
Interestingly, the simple *p*-quinone **(84a)** is also able to oxidize certain unsaturated alcohols under harsh conditions.[98] Because of its lower oxidation potential, *p*-quinone only oxidizes unsaturated alcohols devoid of steric hindrance and able to generate very stabilized carbocations. Thus, it is able to react with primary cinnamyl alcohols but not with secondary cinnamyl alcohols, simple allylic alcohols and benzylic alcohols.



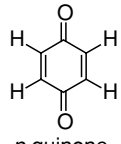
o-chloranil
(82)



2,3-dichloro-5,6-dicyano-*p*-quinone(DDQ)
(83)



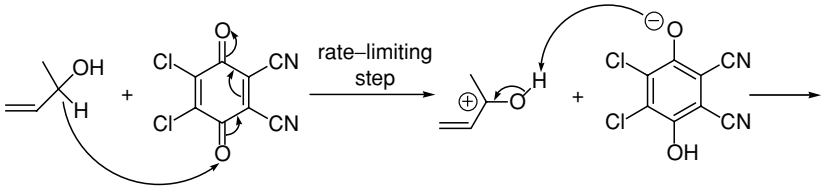
p-chloranil
(84)

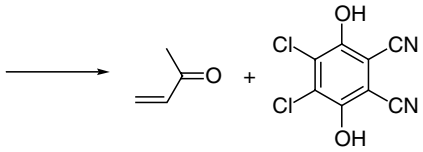


p-quinone
(84a)

While the oxidation of unsaturated alcohols with DDQ is normally done at room temperature or under gentle heating, saturated alcohols are quite resistant to reaction demanding prolonged heating at high temperature.[99] In fact, under the energetic reaction conditions necessary for the oxidation of saturated alcohols, ketones react with DDQ via the corresponding tautomeric enols, resulting in the introduction of unsaturations conjugated with the ketones. Consequently, the oxidation of saturated alcohols with DDQ produces over-oxidation to unsaturated ketones.[100]

As early as in 1956, Braude *et al.*[92] suggested that the selective oxidation of unsaturated alcohols with the quinone *o*-chloranil **(82)**, can be explained by the intermediacy of a resonance-stabilized cation resulting from a hydride abstraction. Later, detailed mechanistic studies confirmed this hypothesis[94c,95e] in oxidations performed with the more common quinone DDQ.

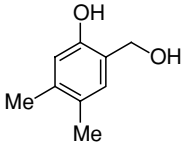




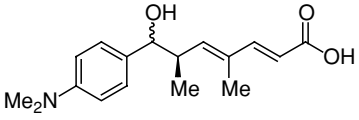
The speed of alcohol oxidation with DDQ correlates with the following factors:

- Stability of the intermediate cation
- Alignment of the C-H bond—from which a hydride will be abstracted—with the π-system of the neighbouring unsaturation
- Steric exposure

As expected, the oxidation of alcohols resulting in more stable intermediate carbocations is quicker. This effect is particularly noticeable in the case of substituted benzylic alcohols, existing a good correlation between σ values in *p*-substituted benzylic alcohols and oxidation velocity.[95e] Thus, alcohol **85** possessing a phenol at the *ortho* position able to strongly stabilize a benzylic cation, reacts with DDQ almost instantaneously at room temperature, delivering an 89% yield of the corresponding benzaldehyde. Similarly, benzylic alcohol **86** possessing an amine at the *para* position is oxidized with DDQ in 5 min at room temperature.[101] In variance, alcohol **87**, possessing a sulfonyl group at the *para* position that strongly destabilizes the intermediate cation, reacts very slowly with DDQ, resulting in a 14% yield of the corresponding aldehyde after 5 weeks at room temperature.[95f]



85



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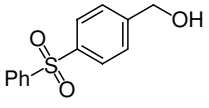
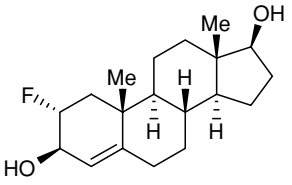


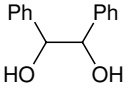
87

Because of the very facile oxidation of benzylic alcohols possessing phenol at the *ortho* or *para* position, DDQ has been described as the preferred oxidant in those cases over other oxidants, such as MnO_2.[95f]

Electron-withdrawing groups close to the alcohol functionality may likewise destabilize intermediate carbocations and result in very slow oxidations. For instance, sterol **88** is oxidized with DDQ at the allylic alcohol two hundred times slower than the corresponding compound lacking the fluorine atom,[94c] and the treatment of hydrobenzoin **(89)** with DDQ results in the oxidation of a single alcohol because a second oxidation would involve a carbocation highly destabilized by the presence of a carbonyl group.[95f]

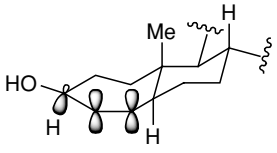


88

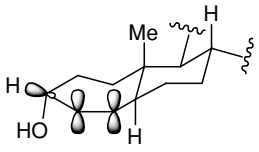


hydrobenzoin **(89)**

Normally, pseudo-equatorial alcohols in cyclohexenols are oxidized quicker than pseudo-axial ones.[94c] For example, 3β-hydroxycholest-4-ene **(90)** is oxidized 7.3 times quicker than the 3α isomer **(91)**. This can be explained by the lowering of the transition state energy during the hydride transfer due to the better overlap between the σ C-H bond and the alkene π-system. This energy lowering being greater in the pseudo-equatorial isomer due to a better orbital overlap.



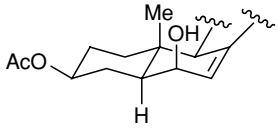
90



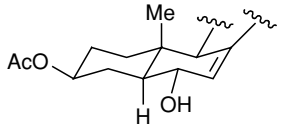
91

Interestingly, the reverse trend is observed with other oxidizing agents, such as chromic acid. Thus, chromic acid is known to oxidize quicker axial alcohols, which is explained by the release of steric congestion exerted by 1,3-*trans*-diaxial interactions.[102] Apparently, a proper orbital alignment plays a greater role in DDQ oxidations than the release of steric congestion.

However, in molecules where the axial alcohol is subject to very severe steric interactions, the release of steric tension may become the major factor affecting DDQ oxidation velocity. For example, the 3β-acetoxy-6β−hydroxy-5α-cholest-7-ene **(92)** is oxidized faster than the corresponding 6α isomer **(93)**.



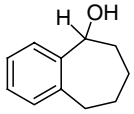
92

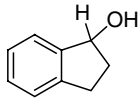


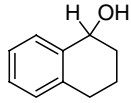
93

During the oxidation of benzylic benzocycloalkanols, the angle between the benzylic C-H bond and the aromatic plane is found to be well

correlated with DDQ oxidation speed, resulting in an increased oxidation speed as this angle approaches 90°.[95c]

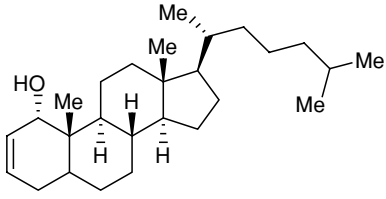






angle between the benzylic C-H bond and the aromatic plane	48°	72°	82°
relative oxidation rate	1	103.6	758

Quite unsurprisingly, apart from stereoelectronic factors, DDQ oxidation of unsaturared alcohols is also subject to steric factors. For instance, the highly hindered allylic alcohol **94** could not be oxidized with DDQ in benzene at room temperature, being necessary to employ Jones oxidation.[103]



94

Normally, oxidations of unsaturated alcohols with DDQ are performed by stirring a solution of the alcohol in an organic solvent with DDQ at room temperature. The most common solvents for this reaction

Table 8.1

Solvent	Solubility of DDQ g/L	Solubility of 2,3-dichloro-5, 6-dicyanohydroquinone g/L
CH_2Cl_2	21	0.4
Benzene	68	0.6
EtOAc	570	120
^{t}BuOH	12	38
THF	660	260
AcOH	65	3.5
Dioxane	180	1.8

Adapted from reference 104 by permission of the American Chemical Society.

are dioxane and benzene because these solvents offer the greatest difference in solubilizing power for DDQ versus the DDQ hydroquinone (Table 8.1).[104] Thus, as the reaction proceeds, the DDQ in solution is transformed into the corresponding hydroquinone that precipitates. This minimizes possible deleterious effects produced by the acidity of the hydroquinone and facilitates the work-up because most of the hydroquinone can be removed by a simple filtration. Nonetheless, DDQ oxidations of unsaturated alcohols can succeed in a variety of solvents including, with approximate order of decreasing use: CH_2Cl_2, THF, toluene, MeCN, $CHCl_3$, CCl_4, $(ClCH_2)_2$, and even AcOH and H_2O.[105]

The solvent may have an important influence in the oxidation speed of unsaturated alcohols with DDQ, although a correlation with solvent properties may be difficult to find. The following yields of ketone were obtained during the oxidation of 1-phenylpropan-1-ol in different solvents during a limited time and under the same reaction conditions: benzene (15%), dioxane (15%), THF (16%), EtOAc (20%), chlorobenzene (26%), CH_2Cl_2 (33%) and $CHCl_3$ (51%).[95e]

> Normally, dry solvents are employed in the oxidation of unsaturated alcohols with DDQ. This is done because DDQ is decomposed by water.[94c] On the other hand, the use of wet solvents may not be deleterious, as a mixture of CH_2Cl_2 and water is routinely employed for the deprotection of *p*-methoxybenzyl (PMB)[106] and 3, 4-dimethoxybenzyl (DMPM)[106] ethers with DDQ, and, when this deprotection leads to an unsaturated alcohol, a prolonged reaction allows a successful oxidation of the alcohol to a ketone.[107]
>
> Since the DDQ hydroquinone is quite weakly acidic and—if a proper solvent is chosen—only a very small proportion remains in solution, DDQ oxidations are performed under almost neutral conditions. Nevertheless, a slow equilibration of isomeric acetals has been described in a DDQ oxidation.[108]

Thanks to the easy removal of the precipitated DDQ hydroquinone after a DDQ oxidation, it is very practical to recover the pricey DDQ by oxidizing the corresponding hydroquinone with nitric acid.[109]

DDQ is a very interesting alternative for the employment of the more common active MnO_2 in the oxidation of unsaturated alcohols. DDQ seems to offer a greater selectivity in the oxidation of unsaturated alcohols versus saturated ones, as signalled by the absence of reports in the literature of unwanted oxidations of saturated alcohols with DDQ. Admittedly, the work-up of active MnO_2 oxidations can hardly be simpler, involving a plain filtration of MnO_2. On the other hand, the work-up of DDQ oxidations can be very convenient, involving just filtering of the DDQ hydroquinone and some washing with basic solutions.

DDQ is an oxidant with a very high tendency to abstract hydride ions whenever a stable cation is produced. This results in the easy oxidation *inter alia* of benzylic positions in electron-rich aromatics[110] and enol ethers.[111]

8.3.1. General Procedure for Selective Oxidation of Unsaturated Alcohols in Presence of Saturated Alcohols Using DDQ

Approximately 1–2.7 equivalents—typically 1.3 equivalents—of DDQ (MW = 227.01) are added over a ca. 0.02–0.5 M solution of the unsaturated alcohol in dry[a] dioxane or benzene.[b] The resulting mixture is stirred at room temperature[c] till most of the starting alcohol is consumed.[d] The precipitated DDQ hydroquinone is filtered[e] and the resulting solution is washed[f] with a saturated $NaHCO_3$ aqueous solution, a ca. 4% NaOH solution or a diluted sodium dithionite aqueous solution. Finally, the organic phase is dried with sodium sulfate or magnesium sulfate and concentrated, giving a residue[g] that may need further purification.

[a] It may not be deleterious to employ a wet solvent (see page 320).

[b] Dioxane and benzene are very often used because they possess a good solubilizing power for DDQ, while the DDQ hydroquinone has a very low solubility in these solvents. Other organic solvents may be equally effective.

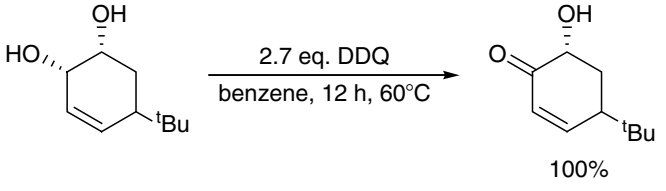
[c] For best selectivity, it is better to perform the oxidation at room temperature, although it may be necessary to apply a gently heating during the oxidation of substrates of low reactivity.

[d] It normally takes between 2 and 30 h—typically 12 h—.

[e] Failure to filter the DDQ hydroquinone means that a more thorough washing of the reaction mixture must be done.

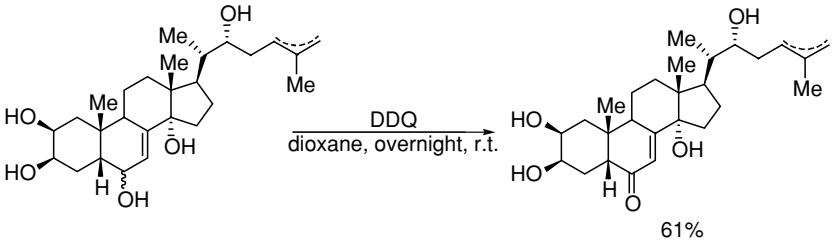
[f] Failure to wash the solution in order to eliminate most of the DDQ hydroquinone and surplus DDQ means that the final residue will probably need a more careful chromatographic purification.

[g] The crude product may contain residues of DDQ or the corresponding hydroquinone. DDQ shows a melting point of 213–215°C[112] and the following spectroscopic data: ^{13}C-NMR (δ, benzene-d_6, ppm): 169.2, 141.0, 125.1 and 109.5. The DDQ hydroquinone presents the following spectroscopic data: ^{13}C-NMR (δ, acetone-d_6, ppm): 151.5, 129.0, 113.5 and 102.8.[113]



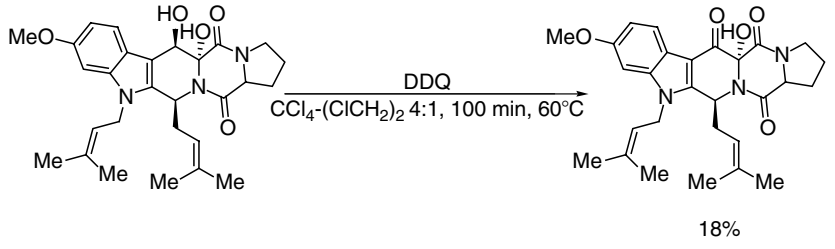
Ref. 114

The treatment of this diol with DDQ leads to the quantitative selective oxidation of the allylic alcohol, while MnO_2 produces an aromatization to the corresponding catechol in 90% yield.

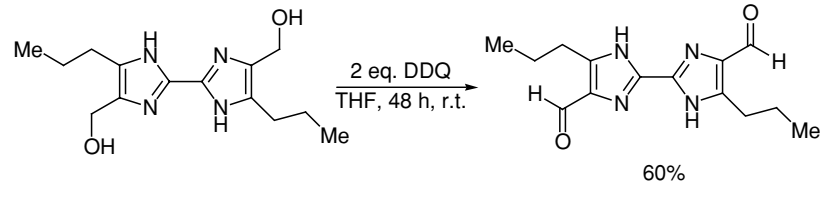


Ref. 115
An allylic alcohol is selectively oxidized with 61% yield in the presence of three saturated secondary alcohols.

DDQ is not only a useful reagent for the selective oxidation of unsaturated alcohols in the presence of saturated ones but it can also provide useful oxidation yields in cases in which no regioselectivity is needed during the oxidation of unsaturated alcohols.



Ref. 116
This complex alcohol could be oxidized with a modest yield employing DDQ under very exacting conditions. According to the authors, "we tried many oxidation conditions ... but all attempts failed except DDQ oxidation".



Ref. 117
A DDQ oxidation provides a 60% yield of the desired dialdehyde, while a Collins oxidation produces a modest 20% yield and MnO_2 and Swern oxidation were ineffective.

8.3.2. Functional Group and Protecting Group Sensitivity to Oxidation with DDQ

DDQ is a potent hydride abstractor with a great tendency to produce oxidations when an intermediate stable carbocation can be formed. That is why DDQ is able to remove *p*-methoxybenzyl (PMB),[106] 3,4-dimethoxybenzyl (DMPM)[106] and 2,4-dimethoxybenzyl (DMB)[118] protecting groups under very mild conditions.

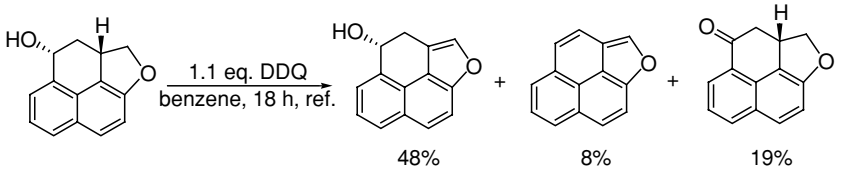
> Interestingly, there are evidences showing that in some cases the deprotection of *p*-methoxybenzyl-protected allylic alcohols with DDQ in a wet solvent operates via a stable allylic cation rather than a benzylic one.[119]

DDQ is able to transform directly TMS allyl ethers into the corresponding carbonyl compounds.[120] The reaction is accelerated by the addition of AcOH that may produce the hydrolysis of the TMS ether prior to the oxidation.

Furthermore, DDQ oxidizes under mild conditions other substrates able to easily release hydrides, such as enol ethers,[111] and certain hydrocarbons, such as tropilidene.[121]

DDQ oxidations are made under almost neutral conditions. Therefore, both base- and acid-sensitive protecting groups and functionalities need not be altered in the presence of DDQ. During DDQ oxidations, the corresponding hydroquinone is generated, which possesses a slight acidity that normally does not cause any interference. However, some acid-catalyzed isomerization of an acetal was observed on a prolonged oxidation with DDQ.[108]

DDQ is able to aromatize many cyclic compounds.[122] Although, aromatizations sometimes compete with the oxidation of unsaturated alcohols,[123] they normally require harsh conditions and selective oxidations of unsaturated alcohols are possible.[124]



Ref. 123

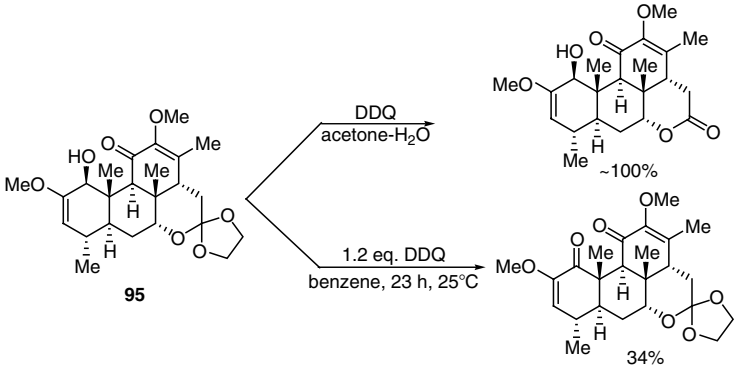
DDQ produces the aromatization of a dihydrofuran, as well as dehydration and oxidation of a benzylic alcohol.

Ref. 124
An unsaturated alcohol is oxidized with DDQ with no interference from a dihydrothiophene, which could be aromatized.

DDQ is employed for the introduction of unsaturations conjugated with aldehydes and ketones.[125] This reaction proceeds via the enol tautomers[97] and demands very harsh conditions.

Although phenols are oxidized with DDQ,[126] benzylic alcohols activated by phenol groups react so quickly with DDQ—delivering high yields of aldehydes or ketones—that this reagent is proposed as the best one for the oxidation of this kind of benzylic alcohols.[127]

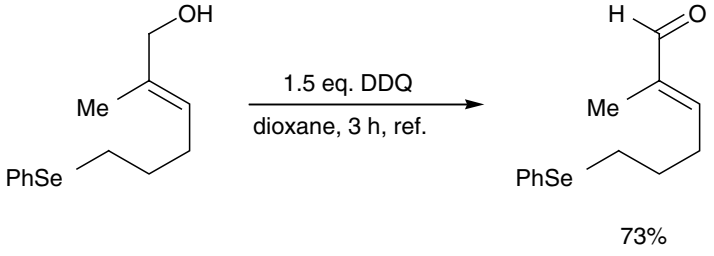
Orthoesters are hydrolyzed on contact with DDQ via a mechanism in which apparently the acidity of the DDQ hydroquinone plays no role. Interestingly, it is possible either to hydrolyze an orthoester in the presence of an unsaturated alcohol, using wet acetone as solvent, or oxidize an unsaturated alcohol in the presence of an orthoester, employing anhydrous benzene as solvent.[128]



Ref. 128
Treatment of compound **95** with DDQ produces the hydrolysis of the orthoester when wet acetone is used as solvent and the oxidation of the allylic alcohol when dry benzene is employed. Apparently, the mechanism of the orthoester hydrolysis involves a charge-transfer intermediate, with no influence from the acidity of the generated DDQ hydroquinone.

Tertiary amines normally resist the action of DDQ during the oxidation of unsaturated alcohols.[129] There is no enough published data on the oxidation of unsaturated alcohols in the presence of secondary or primary amines to infer sufficient information regarding resistance of these amines.

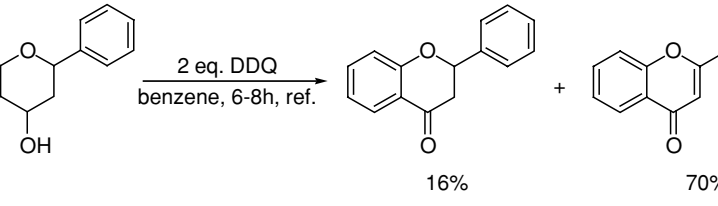
Because of the mechanism of action of DDQ, sulfides and selenides are expected not to react with DDQ during the mild conditions used in the oxidation of unsaturated alcohols. There is one published example in which an alcohol is oxidized with DDQ in the presence of a selenide.[130]



Ref. 130
An unsaturated alcohol is oxidized with DDQ in the presence of a very oxidation-sensitive selenide.

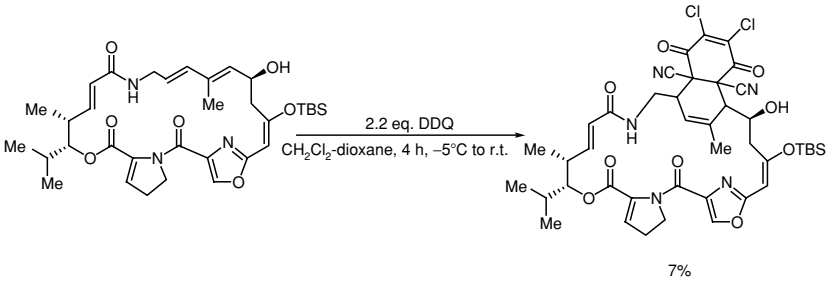
8.3.3. Side Reactions

If heat is applied during the oxidation of unsaturated alcohols with DDQ, an over-oxidation resulting in the introduction of an unsaturation conjugated with the carbonyl group can happen.[131]



Ref. 131a
Treating a flavanol with DDQ in refluxing benzene results in a simple oxidation with 16% yield, and oxidation to enone with a 70% yield.

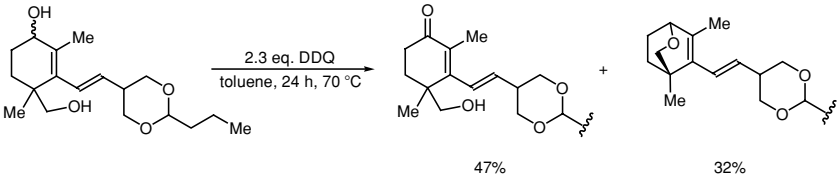
DDQ is a good acceptor in Diels-Alder reactions and it sometimes behaves as such in substrates possessing dienes, instead of producing an oxidation of an unsaturated alcohol.[132]



Ref. 132

The DDQ rather than behaving as an oxidant by producing the desired oxidation of the allylic alcohol, reacts with a diene producing a Diels-Alder adduct.

Sometimes, probably due to the acidity of the DDQ hydroquinone generated during DDQ oxidations, unsaturated alcohols can generate allylic cations that can be trapped with nucleophiles.[133]



Ref. 133

Treatment of an allylic alcohol with DDQ provides the expected enone accompanied by a cyclic ether, resulting from the intramolecular attack of a saturated alcohol on an allylic cation, presumably generated by the action of acid on the starting allylic alcohol.

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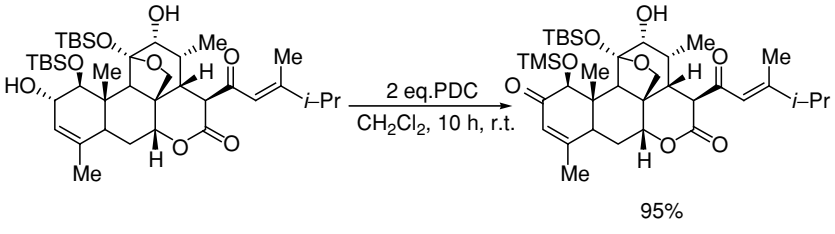
8.4. Other Oxidants

Chromium-based oxidants tend to react quicker with unsaturated alcohols, although the difference of oxidation speed with saturated alcohols is normally not sufficient for synthetic purposes. Nevertheless, the chromium-based reagent pyridinium dichromate (PDC) possesses a mildness and, therefore, a relative greater selectivity that allows its occasional employment for selective oxidations of allylic and benzylic alcohols.[134]



Ref. 134d

PDC is able to perform the selective oxidation of an allylic alcohol in the presence of a saturated one with a 95% yield.

The oxidative potency of dichromates and chlorochromates decreases under less acidic conditions. This is so, for example, when a less acidic ammonium salt is included as counter-ion of a dichromate or chlorochromate anion. Thus, a number of ammonium dichromates and chlorochromates possessing a milder oxidative potency has been described with the specific purpose of allowing very selective oxidations of unsaturated alcohols in the presence of saturated ones. These selective dichromates and chlorochromates include: bis(benzyltriethylammonium)dichromate,[135] tetramethylethylenediammonium dichromate (TMEDADC),[136] imidazolium dichromate (IDC),[137] *N*,*N*-dimethylaminopyridinium chlorochromate (DMAPCC),[138] 1-(benzoylamino)-3-methylimidazolium chlorochromate (BAMICC)[139] and butyltriphenylphosphonium chlorochromate (BTPPCC).[140]

The same principle of moderating the acidity in order to achieve a greater selectivity for the oxidation of unsaturated alcohols is applied in the use of: PCC in a CH_2Cl_2 solution containing 2% of 3,5-dimethylpyrazole (DMP),[141] complexes of *n*-butylammonium chlorochromate (BACC) with 18-crown-6,[142] and the solid support-bound 1-aminoimidazolium chlorochromate.[143]

> Some alcohol oxidants, such as Dess-Martin periodinane,[144] that find common employment as oxidants for all kinds of alcohols, may find a certain preference for the oxidation of unsaturated alcohols.

A number of other oxidants has been described for the selective oxidation of unsaturated alcohols. These include:

- $KMnO_4/ZrOCl_2 \cdot 8H_2O$[145]
- Catalytic potassium ruthenate (K_2RuO_4) in the presence of potassium peroxodisulfate ($K_2S_2O_8$) and Adogen 464 under phase-transfer conditions[146]
- bis(Trinitrocerium)chromate[147]
- An IBX analogue containing a water-solubilizing carboxy group that allows oxidations in water[148]
- Copper (II) acetate[149]
- Potassium ferrate (K_2FeO_4), either under phase-transfer conditions[150] or in the K_2FeO_4-Al_2O_3-$CuSO_4 \cdot 5H_2O$ solid mixture[151]
- Molecular oxygen in the presence of monodispersed palladium nanoclusters generated by treatment of Pd_4 $phen_2(CO)_2(OAc)_4$ with a metal nitrate[152]
- Poly(2-vinylpyridine) or poly(4-vinylpyridine) supported chromium peroxide[153]

Additionally, the employment of the K_2MnO_4-Al_2O_3-$CuSO_4 \cdot 5H_2O$ mixture for the selective oxidation of benzylic alcohols[154] and the use of selenium dioxide on silica—in the presence of *t*-butyl hydroperoxide—for the selective oxidation of primary allylic alcohols[155] must be mentioned. Furthermore, some giant palladium cluster complexes are able to catalyze specifically the oxidation of primary allylic alcohols with molecular oxygen, while they possess a very low catalytic activity for the oxidation of secondary allylic and benzylic alcohols.[156]

Zinc and copper nitrates on silica gel are able to oxidize benzylic and saturated secondary alcohols but not aliphatic primary alcohols.[157] On the other hand, $ZrO(OAc)_2$ is able to catalyze, under the action of *t*-BuOOH, the oxidation of benzylic alcohols—both primary and secondary—and primary saturated alcohols to aldehydes and ketones, while secondary saturated alcohols are very unreactive.[158]

Regrettably, although some of the above oxidants show a remarkable selectivity, as reported in the corresponding foundational papers, its use is not at all widespread in Synthetic Organic Chemistry, probably, because

its efficiency has not been compared in several independent research laboratories.

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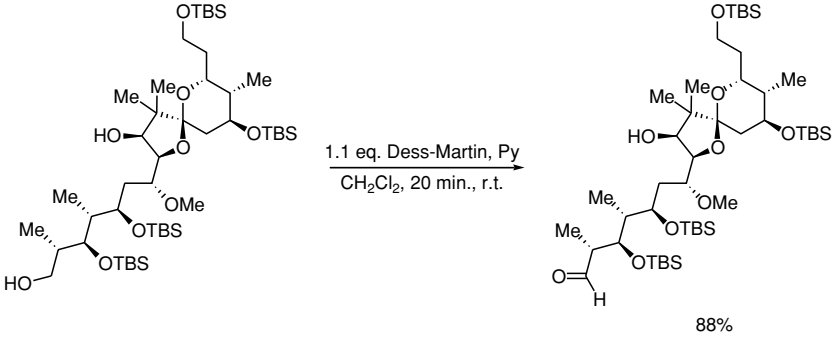
9

Selective Oxidations of Primary Alcohols in Presence of Secondary Alcohols

9.1. Introduction

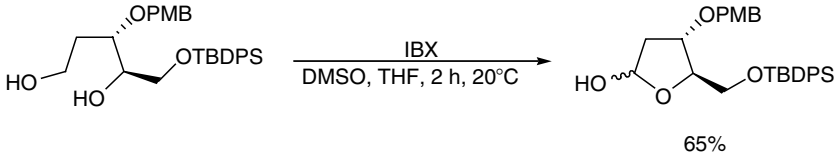
Primary alcohols possess a substantially less crowded environment than secondary ones. Thus, in the absence of dominant electronic factors, many oxidants tend to react quicker with primary alcohols. These include many common oxidants, like TPAP,[1] PCC,[2] Parikh-Moffatt,[3] Dess-Martin,[4] IBX[5] and Swern,[6] that are sometimes able to perform selective oxidations of primary alcohols in useful yields, regardless of the fact that they were not devised for this purpose.



Ref. 4

A selective oxidation of a primary alcohol in the presence of a secondary one in a complex substrate can be done with 88% yield with Dess-Martin periodinane. The authors comment that "Selective oxidation of the primary alcohol proved to be unexpectedly straightforward. Thus, treatment with Dess-Martin periodinane afforded aldehyde with 88% yield, with complete selectivity for the primary alcohol. Despite the large number of documented applications of this mild oxidation, no study has yet addressed its potential for selective oxidations of sterically differentiated diols".

It must be mentioned that IBX is particularly useful in selective oxidations of primary alcohols, leading to hydroxyaldehydes present as lactols.[5]



Ref. 5b

IBX performs the selective oxidation of a primary alcohol, leading to a hydroxyaldehyde that is isolated as a lactol that, interestingly, does not suffer a further oxidation to a lactone.

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9.2. TEMPO-mediated Oxidations

For a detailed account of TEMPO-mediated oxidations see chapter 5.

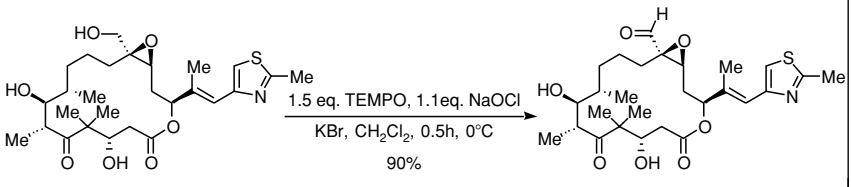
Among common alcohol oxidants, TEMPO-mediated oxidations have been the subject of a close scrutiny, aimed at finding optimum conditions for the selective oxidation of primary alcohols. In fact, TEMPO-mediated oxidations, that is oxidations in which an oxoammonium salt acts as a primary oxidant, have a great tendency to operate quicker with primary alcohols, regardless of the secondary oxidant employed and the exact experimental conditions.

When a TEMPO-mediated oxidation of an 1,4- or 1,5-diol leads to an hydroxyaldehyde able to equilibrate with a lactol, the lactol is normally further oxidized to a lactone.[7]

A scant look at the facts might suggest that the selective oxidation of primary alcohols in TEMPO-mediated oxidations can be explained solely on steric grounds. Things are not so simple, as it was found[8] that the primary oxidants, that is oxoammonium salts, when used stoichiometrically, react quicker with primary alcohols when present as oxoammonium chlorides, while the reverse selectivity, that is selective oxidation of secondary alcohols, is observed when oxoammonium bromides are employed.

The very common TEMPO-mediated Anelli's protocol for the oxidation of alcohols, involving a biphasic CH_2Cl_2-water mixture containing catalytic TEMPO, or an analogue thereof, and sodium hypochlorite as a secondary oxidant, shows a great selectivity for the oxidation of primary alcohols in the presence of secondary ones[9] and has found some use in Synthetic Organic Chemistry.[10]

Selective oxidations of primary alcohols can also be achieved employing less common variants of the Anelli's protocol, such as those involving silica-supported TEMPO[11] and polymer-immobilized TEMPO.[12]

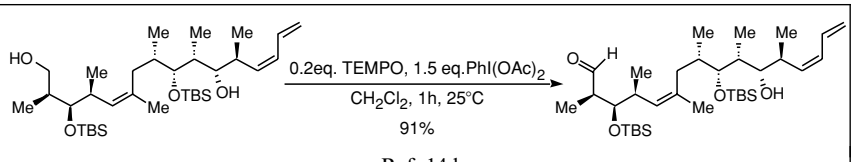


Ref. 10b

A primary alcohol is transformed into an aldehyde in the presence of two secondary alcohols with 90% yield in a complex substrate. An attempted selective oxidation with TPAP/NMO failed because of reaction at the thiazole ring.

In 1997, Piancatelli *et al.*[13] showed that TEMPO in combination with [bis(acetoxy)iodo]benzene (BAIB) as a secondary oxidant presents an exceptional selectivity for the oxidation of primary alcohols in the presence of secondary ones. These results were confirmed by other researchers during the preparation of complex organic compounds.[14]

For some important experimental details during TEMPO-BAIB oxidations, see pages 245 and 247.



Ref. 14d

A primary alcohol is selectively oxidized in the presence of a secondary one with a 91% yield on a multigram scale reaction by using TEMPO-PhI(OAc)$_2$.

Other TEMPO-mediated oxidations reported to possess selectivity for the oxidation of primary alcohols versus secondary ones, include oxidations involving $CuCl_2/O_2$,[15] $NaBrO_2$,[16] NCS[17] and trichloroisocyanuric acid[18] as secondary oxidants.

Systems involving oxoammonium salts, electrolitically generated from TEMPO[19] or employed in stoichiometric amounts,[8] can also show useful selectivities for the oxidation of primary alcohols. The use of stoichiometric oxoammonium salts is sometimes more satisfactory in the selective oxidation of primary alcohols than the employment of catalytic TEMPO systems.[20]

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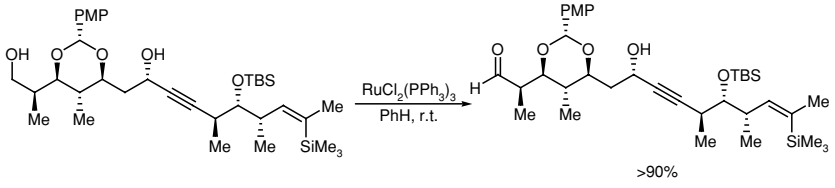
9.3. $RuCl_2(PPh_3)_3$

In 1981, Oshima *et al.*[21] reported that stoichiometric $RuCl_2(PPh_3)_3$ in benzene shows a remarkable selectivity for the oxidation of primary alcohols in the presence of secondary ones. This was confirmed by other researchers in the preparation of complex organic compounds.[22]



Ref. 22f

A primary alcohol is selectively oxidized with $RuCl_2(PPh_3)_3$ in a complex substrate in the presence of a secondary alcohol, a vinyl silane and an oxidation-sensitive *p*-methoxybenzylidene protecting group. According to the authors "... a variety of oxidative conditions were employed... The use of modified Ley's oxidation protocol (TPAP/NMO, MeCN; then H_2O) as well as the use of 4-MeO-TEMPO/NaOCl oxidation conditions caused decomposition of the substrate. Fortunately, selective oxidation worked extremely well using $RuCl_2(PPh_3)_3$ in benzene."

Selective oxidations with stoichiometric $RuCl_2(PPh_3)_3$ are normally carried out simply by stirring a solution of the alcohol in benzene at room temperature in the presence of the oxidant. The addition of 2 equivalents of K_2CO_3 may improve the reaction.[22g]

Due to the high price of $RuCl_2(PPh_3)_3$, a number of protocols employing this reagent in catalytic amounts in the presence of a secondary oxidant have been tried. Successful selective oxidations of primary alcohols can be achieved using the following secondary oxidants: TMSOOTMS,[23] *N*-methylmorpholine *N*-oxide[24], molecular oxygen plus catalytic hydroquinone[25] or catalytic TEMPO.[26]

Although useful selectivities can be achieved with catalytic $RuCl_2(PPh_3)_3$, best results are sometimes obtained using this oxidant in stoichiometric amounts.[23a]

9.3.1. General Procedure for Selective Oxidation of Primary Alcohols in Presence of Secondary Alcohol Employing $RuCl_2(PPh_3)_3$

A ca. 0.01–0.05 M solution of the alcohol in benzene,[a] containing[b] ca. 1.5–2.6 equivalents of $RuCl_2(PPh_3)_3$, is stirred at room temperature till most of the starting alcohol is consumed.[c] The reaction mixture is

concentrated and the residue purified by silica gel chromatography. Alternatively, the ruthenium residues can be removed prior to the chromatographic purification by either subjecting the reaction mixture to washing with cold water and drying (Na_2SO_4), or passing the reaction mixture through a pad of silica.

[a] Toluene can also be used.
[b] It may be convenient to add 2 equivalents of K_2CO_3.[22g]
[c] It normally takes between 1.5 h and 3 d.

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9.4. Other oxidants

A number of diverse oxidizing systems, which do not yet find ample use in organic synthesis, are reported to possess a certain selectivity for the oxidation of primary alcohols. These include:

- $NaNO_2/Ac_2O$[27]
- Cp_2ZrH_2/cyclohexanone or benzophenone[28]
- Molecular oxygen/[$CuBr_2$(2,2′-bipyridine)]/TEMPO/K^tOBu[29]
- $ZrO(OAc)_2/{}^tBuOOH$[30]
- Molecular oxygen/[$N(n\text{-}Bu)_4$][$Os(N)(CH_2SiMe_3)_2Cl_2$][31]
- Quinolinium chlorochromate[32]
- CrO_3 intercalated in graphite[33]

Interestingly, when a Corey-Kim oxidation (Me_2S/NCS) is performed with diisopropyl sulfide, instead of dimethyl sulfide, primary alcohols are selectively oxidized at 0°C, while lowering the temperature to −78°C causes the selective oxidation of secondary alcohols.[34]

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9.5. Selective Oxidation of Primary Alcohols via Silyl Ethers

A number of oxidants are able to selectively transform silyl ethers derived from primary alcohols into aldehydes in the presence of silyl ethers derived from secondary alcohols. This allows to perform selective oxidations, whereby persilylation of polyols is followed by the selective oxidation of primary silyl ethers, resulting in the formation of aldehydes possessing secondary alcohols protected as silyl ethers. As expected, the mild transformation of primary silyl ethers into aldehydes is only possible with silyl ethers that are not exceedingly robust, such as TMS, TES and TBS ethers.

Oxidants able to directly transform primary silyl ethers into aldehydes include:

- Collins reagent (TMS ethers), see page 24
- Quinolinium fluorochromate (TBS ethers)[35]
- Swern (TMS and TES ethers), see page 153

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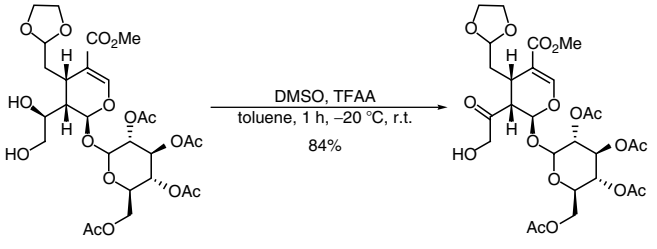
10

Selective Oxidations of Secondary Alcohols in Presence of Primary Alcohols

10.1. Introduction

Primary alcohols possess a considerably less congested environment than secondary ones. Therefore, it may seem contradictory that a certain oxidant could be able to perform the selective oxidation of secondary alcohols. On the other hand, the oxidation potential of aldehydes is generally higher than the one of ketones (see page 257). This means that thermodynamics usually favor the oxidation of secondary alcohols over primary ones and mild oxidants have a tendency to react quicker with secondary alcohols. Other factors that promote the selective oxidation of secondary alcohols include the intermediacy of alkyl hypohalides, which are less stable when derived from secondary alcohols, and the operation of a mechanism involving a hydride transfer, leaving a carbocation located at the α position of an alcohol that possesses a higher stability in secondary alcohols.

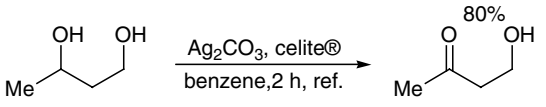
Some standard alcohol oxidants that may not have been originally devised for selective oxidations are able, in favourable substrates, to oxidize secondary alcohols in the presence of primary ones.[1] Thus, cases are known in which Corey-Kim oxidation,[2] TFAA-activated DMSO,[1b] Collins reagent[2] or PDC[1b] show a certain preference for the oxidation of secondary alcohols.



Ref. 1b

This diol possesses a high tendency to suffer a selective oxidation of the secondary alcohol, which can be performed with 84% using DMSO activated with TFAA or with a lower yield with PDC. According to the authors, who intended to make a selective oxidation of the primary alcohol, "however, all attempts to selectively oxidize the primary hydroxy function in the presence of the secondary hydroxy group failed."

Among common alcohol oxidants, Fétizon's reagent—due to its mildness—is particularly well-suited for the selective oxidation of secondary alcohols (see page 283).



Ref. 3

Fétizon's reagent is able to oxidize an unhindered secondary alcohol in the presence of a primary one in an 80% yield.

On the other hand, Fétizon's reagent is very sensitive to steric hindrance and no selective oxidation of secondary alcohols is possible in many complex substrates.[4]

Section 10.1. References

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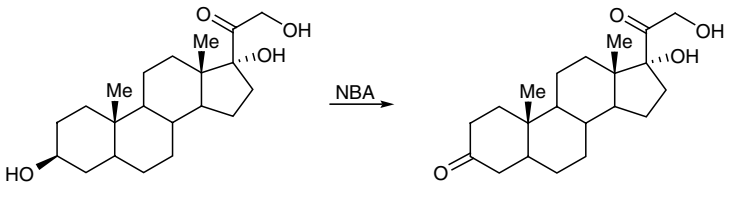
10.2. Reaction with Electrophilic Halogen Sources

In 1943, Reich and Reichstein[5] described the oxidation of secondary steroidal alcohols with *N*-bromoacetamide (NBA) in aqueous *tert*-butyl alcohol or acetone. Subsequently, *N*-bromoacetamide found ample use in the oxidation of secondary alcohols in the steroid field.[6]

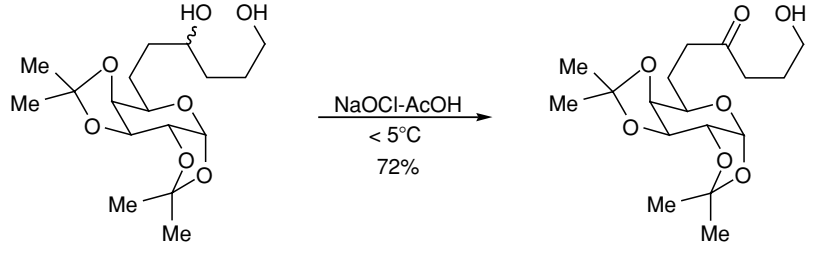
In 1952, Kritchevsky *et al.*[7] reported the selective oxidation of a secondary alcohol in the presence of a primary one with *N*-bromoacetamide. In 1954, Jones and Kocher highlighted[8] the importance of being able to carry out selective oxidations of secondary alcohols with *N*-bromoacetamide, which was employed later by other authors for this purpose.[9]



Ref. 9b

A secondary alcohol is oxidized in the presence of a primary one with *N*-bromoacetamide.

In 1980, Stevens *et al.*[10] reported that a plain solution of sodium hypochlorite, which is easily available as "swimming pool chlorine", is able to efficiently oxidize secondary alcohols in a solution in acetic acid, while primary alcohols react very slowly. Two years later, this research team published[11] a more detailed account on the ability of NaOCl/AcOH to perform the selective oxidation of secondary alcohols in the presence of primary ones. Stevens' oxidant became one of the standard reagents for the selective oxidation of secondary alcohols.[12]



Ref. 12a

A secondary alcohol is oxidized in the presence of a primary one using Stevens' procedure with sodium hypochlorite in acetic acid.

Other reagents, providing a source of electrophilic halogen, able to selectively oxidize secondary alcohols include molecular chlorine,[13] molecular bromine,[13c] 3-iodopyridine dichloride,[13a] trichloroisocyanuric acid (TCIA),[14] the complex HOF·MeCN[15] and tetraethylammonium trichloride.[16]

10.2.1. General Procedure for Selective Oxidation of Secondary Alcohols in Presence of Primary Alcohol, Using Stevens' Protocol (Sodium Hypochlorite in Acetic Acid)

Approximately 1.05–3[a] equivalents of sodium hypochlorite (MW = 74.44) in an aqueous ca. 1.8 M [b] solution are slowly added over 15–30 min.[c] to a ca. 0.6–1.4 M stirred solution of the diol in acetic acid. When most of the starting alcohol is consumed,[d] a saturated $NaHCO_3$ aqueous solution is added and the resulting mixture is extracted with an organic solvent such as ether or CH_2Cl_2. The organic phase is washed with water, dried ($MgSO_4$) and concentrated, providing a hydroxyketone that may need further purification.

[a] Limiting the quantity of oxidant to 1.05–1.1 equivalents allows the use of the iodide-starch test to signal the end of the oxidation.

[b] Sodium hypochlorite aqueous solutions, possessing a ca. 1.8–2.2 M concentration, are sold in hardware stores as "swimming-pool chlorine". The concentration of NaOCl decreases by about 20% per month when the solutions are kept at room temperature.[11] Keeping the NaOCl solutions at low temperature helps retarding the degradation.

The concentration can be measured against a potassium iodide solution (Pontius method)[17] according to the equation:

$$3ClO^- + I^- \rightarrow IO_3^- + 3Cl^-$$

The end-point of the titration is measured by the persistence of intermediate I_2 in the solution, signalled by the blue color of a starch-iodide complex. 10 mL of 0.2% starch and at least 3 g of $NaHCO_3$ are added to 50 mL of the sodium hypochlorite aqueous solution. A titration is performed by dropping a standard 0.02 M potassium iodide solution. The end of the titration is signalled by the persistence of the blue color of the starch-iodide complex.

[c] Heat is evolved during the addition of sodium hypochlorite, therefore, it is advisable to occasionally employ an ice-water bath in order to keep the reaction temperature at ca. 20–25°C. Alternatively, the ice-water bath can be continuously used in order to keep the reaction temperature bellow 5°C for a milder oxidation.

[d] It normally takes between 0.5 and 3 h. The end of the oxidation can be determined employing the iodide-starch test, provided that a limited excess of 1.05–1.1 equivalents of sodium hypochlorite has been used. Alternatively, the reaction can be followed by TLC. When a liberal excess of sodium hypochlorite is employed, it is advisable to quench the reaction by the addition of isopropanol or a sodium thiosulfate solution.

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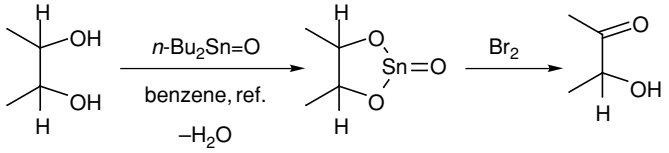
10.3. Oxidation of Intermediate Alkyltin Alkoxides

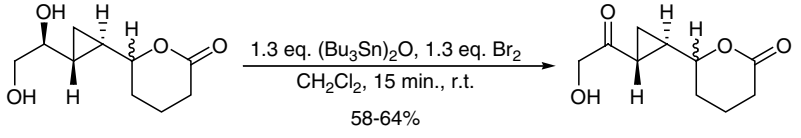
In 1974, David[18] reported that cyclic stannylenes **(97)**, formed by reaction of 1,2-diols **(96)** with dibutyltin oxide—*n*-Bu_2SnO—in refluxing benzene with azeotropic elimination of water, reacted with Br_2 in solution at room temperature at titrating speed, leading to α-hydroxyketones **(98)**.



96 **97** **98**

Subsequent researchers confirmed these results and extended the reaction to the oxidation of acyclic stannane derivatives, prepared by using Et_3SnOMe[19] or, most often, $(Bu_3Sn)_2O$.[20] Additionally, it was discovered that the oxidation of the tin alkoxides can also be brought about with *N*-bromosuccinimide (NBS).[21] An important improvement on the oxidation step occurred when it was noticed that the HBr generated during the oxidation can produce the hydrolysis of the intermediate tin alkoxide, leading to lower yields.[22] This can be avoided by the addition of HBr quenchers, such as Et_3SnOMe,[23] molecular sieves[24] or pinacol dibutylstannylene.[22a] Molecular sieves are often used both to promote the formation of tin alkoxides and to quench the HBr generated during the oxidation step.

In 1976, Ueno and Okawara highlighted the fact that no oxidation of primary saturated alcohols to aldehydes via tin alkoxides had been reported in the literature and published a procedure for the selective oxidation of secondary alcohols.[25] Interestingly, rather than performing the oxidation on pre-formed tin alkoxides, these researchers subjected a mixture of the diol and $(Bu_3Sn)_2O$ in CH_2Cl_2 to the action of Br_2. Regardless of the fact that no complete formation of tin alkoxides is secured and no HBr quencher is added, this method may provide useful yields of hydroxyketones during the selective oxidation of diols.[26]

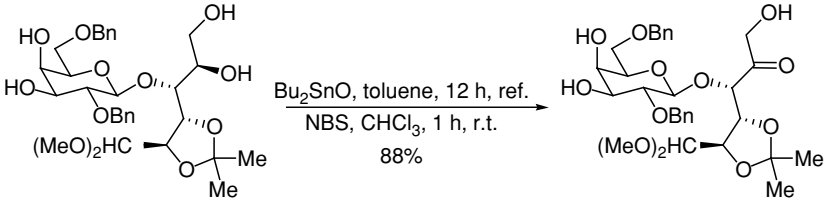


Ref. 26

The selective oxidation of the secondary alcohol is performed by dropping a bromine solution on a mixture of $(Bu_3Sn)_2O$ and the diol in CH_2Cl_2. Although, no complete formation of bis-tin alkoxide is secured and the generated HBr—that may cause the hydrolysis of tin alkoxides—is not quenched, a useful yield of hydroxyketone is obtained.

Subsequent researchers introduced substantial improvements on the Ueno and Okawara's protocol of selective oxidations via tin alkoxides and broadened considerably the scope of its application.[22a, 24b,c] Thus, it was established that good yields in the selective oxidation of diols—and even triols and tetrols—can be achieved in two steps: i) pre-formation of a tin alkoxide, by reaction with either $(Bu_3Sn)_2O$ or Bu_2SnO with elimination of water by molecular sieves or azeotropic distillation of water; ii) treatment of the tin alkoxide with Br_2 or NBS in the presence of a HBr quencher.

While the reaction with $(Bu_3Sn)_2O$ leads to acyclic stannyl derivatives, that is $ROSnBu_3$, reaction with Bu_2SnO leads to cyclic stannylene derivatives. It could be expected that cyclic stannylene derivatives would lead to oxidations with a higher regioselectivity, particularly considering that these compounds exist as dimers in which different oxygens possess a very diverse coordinating environment.[22a] Likewise, Bu_3SnO would seem to be particularly well-suited for the selective oxidation of 1,2- and 1,3-diols that form stable 5- and 6-membered stannylene derivatives. Nonetheless, the fact is that best results are very often obtained by employing $(Bu_3Sn)_2O$, rather than Bu_2SnO.[22a] Although, in the case of polyols, Bu_2SnO may provide extremely good regioselectivities, thanks to the selective formation of stable cyclic stannylenes by regioselective reactions with a certain 1,2- or 1,3-diol moiety in a molecule.



Ref. 27

In this tetrol, a single secondary alcohol is oxidized with 88% yield thanks to the formation of the most stable cyclic stannylene intermediate by the regioselective reaction of Bu_2SnO with one of the 1,2-diol moieties in the molecule.

10.3.1. General Procedure for Selective Oxidation of Secondary Alcohols in Presence of Primary Alcohols by Treatment of Intermediate Tin Alkoxides with Bromine or *N*-Bromosuccinimide

A tin alkoxide is generated[a] by removal of water from a ca. 0.01–0.3 M— typically 0.15 M— solution of the alcohol in an organic solvent,[b] in the presence of ca. 1.05–2 equivalents—typically 1.1 equivalents—of either $(Bu_3Sn)_2O$ (MW = 596.1) or Bu_2SnO (MW = 248.94),[c] by azeotropic

distillation[d] with a Dean-Stark apparatus or by refluxing[e] in the presence of ca. 1 g of activated molecular sieves per mmol of alcohol. The solvent is removed at the rotary evaporator[f] and the crude tin alkoxide is dissolved in CH_2Cl_2 or $CHCl_3$ so as to get a ca. 0.2–0.4 M solution. Approximately, 1–1.5 equivalents of a HBr quencher, such as Et_3SnOMe or pinacol dibutylstannylene, are added.[g] From 1 to 2.6 equivalents—typically 1.2 equivalents—of Br_2 (MW = 159.82, d = 3.102) or NBS (MW = 177.99) in a ca. 0.5–1 M solution in CH_2Cl_2 or $CHCl_3$ are slowly added to the stirred solution.[h] Stirring is continued till most of the starting compound is consumed.[i]

When Br_2 is used as oxidant, the excess can be destroyed by the addition of cyclohexene. The reaction mixture is concentrated at the rotary evaporator and the crude residue purified by silica gel chromatography. Alternatively, a crude material, which may need further purification, can be isolated by filtering the reaction mixture through a pad of silica or Celite® and removing the solvent in vacuo.

[a] It is possible to carry out a selective oxidation by adding Br_2 or NBS to a mixture of the alcohol and the stannylating agent in an organic solvent without securing the complete generation of a tin alkoxide. Nevertheless, this may lead to a decreased yield.

[b] Benzene or toluene can be employed when water is eliminated by azeotropic distillation. CH_2Cl_2 or $CHCl_3$ are suitable solvents when the removal of water is made with molecular sieves.

[c] $Bu_2Sn{=}O$ produces the formation of cyclic stannylene derivatives and it is used in 1,2- or 1,3-diols because they lead to stable 5- and 6-membered cycles.

[d] The complete formation of the tin alkoxide is signalled by the end of the removal of water and it normally takes about 12 h.

[e] Polyols are very often insoluble in CH_2Cl_2 or $CHCl_3$. Therefore, the formation of the tin alkoxide can often be monitored by the dissolution of the starting polyol. Normally, the formation of the tin alkoxide takes between 2 and 3 h.

[f] When CH_2Cl_2 or $CHCl_3$ are used as solvent, they do not need to be removed.

[g] Failure to add a HBr quencher may lead to the partial hydrolysis of the tin alkoxide and a lower yield in the selective oxidation. Excess of molecular sieves or stannylating agent employed in the formation of the tin alkoxide may operate as HBr quenchers during the tin alkoxide oxidation.

[h] The reaction may be kept at room temperature. Alternatively, for milder reaction conditions, it may be cooled on an ice-water bath.

[i] It normally takes a few min when Br_2 is employed as oxidant, and ca. 0.5–1 h when NBS is used.

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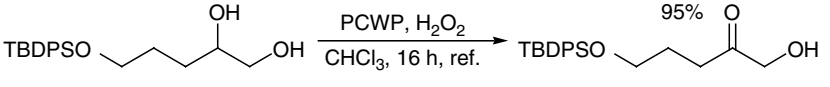
10.4. Other Oxidants

Certain molybdenum complexes, such as $MoO(O_2)(PhCONPhO)_2$[2] and the peroxo-molybdenum compound derived from tris(cetylpyridinium) 12-molybdophosphate and hydrogen peroxide (PCMP),[28] are able to selectively oxidize secondary alcohols. PCMP is able to perform selective oxidations in catalytic amounts in the presence of hydrogen peroxide as secondary oxidant.[29]

Other molybdenum complexes able to catalyze the selective oxidation of secondary alcohols are: ammonium molybdate in the presence of H_2O_2,[30] benzyltrimethylammonium tetrabromooxomolybdate in the presence of *t*-BuOOH[31] and molybdenum hexacarbonyl in the presence of catalytic cetylpyridinium chloride and stoichiometric *t*-BuOOH.[32]

Several compounds of tungsten, which is a transition metal closely related to molybdenum, are able to catalyze the selective oxidation of secondary alcohols with hydrogen peroxide as secondary oxidant. These include: tris(cetylpyridinium) 12-tungstophosphate,[33] peroxotungstophosphate (PCWP)[34] and Na_2WO_4 in the presence of a phase transfer catalyst.[35] Tungstophosphoric acid is able to catalyze the selective oxidation of secondary alcohols in the presence of ferric nitrate as secondary oxidant.[36]



Ref. 34b

A very good yield of hydroxyketone results from the regioselective oxidation of a secondary alcohol using hydrogen peroxide in the presence of catalytic peroxotungstophosphate.

Cerium (IV) ammonium nitrate (CAN)[37] and a cerium (IV) impregnated resin[38] are able to catalyze the selective oxidation of secondary alcohols with sodium bromate ($NaBrO_3$). Stoichiometric cerium bromate—$Ce(BrO_3)_3$, prepared *in situ* from barium bromate and cerium (III) sulfate, is also able to perform selective oxidations of secondary alcohols.[39]

Other transition metal compounds able to catalyze the selective oxidation of secondary alcohols include: $VO(acac)_2$ with *t*-BuOOH as secondary oxidant,[40] a polystyrene-supported (catecholato)oxorhenium complex in the presence of DMSO,[41] and a mixture of ferric nitrate and ferric bromate that catalyzes the oxidation of secondary alcohols with air.[42]

Other oxidizing systems based on metals that can carry out regioselective oxidations of secondary alcohols on a catalytic quantity are: a titanium-doped zeolite in the presence of H_2O_2[43] and the hydrotalcite Ru-Co-Al-CO_3 HT in the air.[44]

The following systems based on metals can oxidize in a non-catalytic quantity the secondary alcohols in the presence of primary ones: copper and zinc nitrate on Celite®,[45] and the solid mixtures K_3FeO_4-Al_2O_3-$CuSO_4 \cdot 5H_2O$[46] and $BaMnO_4$-Al_2O_3-$CuSO_4 \cdot 5H_2O$.[47]

Chloral or benzaldehyde in the presence of dehydrated alumina[48] and $Al(O^tBu)_3$ in the presence of *t*-BuOOH,[49] are oxidizing systems reminiscent of Oppenauer oxidations that can perform regioselective oxidations of secondary alcohols.

A classical Corey-Kim oxidation sometimes shows a certain preference for the oxidation of secondary alcohols.[2] Additionally, a Corey-Kim oxidation, in which diisopropyl sulfide is employed in the place of dimethyl sulfide, presents a preference for the oxidation of primary alcohols at 0°C and secondary alcohols at −78°C.[50]

Both, sodium bromite ($NaBrO_2$)[51] and sodium bromate ($NaBrO_3$)[52] are able to carry out selective oxidations of secondary alcohols in the absence of an added catalyst under properly devised experimental conditions.

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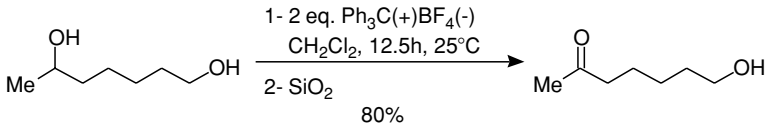
10.5. Selective Oxidations of Secondary Alcohols via Protection of Primary Alcohols

It is possible to perform the regioselective protection of primary alcohols in the presence of secondary ones with almost any protecting group, thanks to the substantially less crowded environment of primary alcohols. This allows to operate a three step synthetic strategy, whereby the regioselective protection of a primary alcohol is followed by the oxidation of a secondary alcohol and deprotection of the primary one. Although, this strategy is time-consuming and perhaps not very elegant, it may be very efficient in certain cases. Examples of this strategy include the use of silyl[53] and trityl[53a] ethers.

The employment of trityl trifluoroborate is particularly interesting. This reagent is able to introduce trityl groups on both primary and secondary alcohols[54] and to selectively oxidize secondary trityl ethers to ketones in the presence of primary trityl ethers.[55] Thus, treatment of diols with trityl trifluoroborate leads to tritylation of both alcohols followed by oxidation of the secondary trityl ether, resulting in the formation of a ketone possessing a trityl-protected primary alcohol. A work-up by mild acidic hydrolysis provides the deprotection of the primary trityl ether and formation of a hydroxyketone.[54]



Ref. 54

Trityl trifluoroborate produces the tritylation of both alcohols and the regioselective oxidation of the resulting secondary trityl ether. The primary trityl ether is hydrolyzed on contact with silica gel during the work-up, resulting in the formation of an 80% yield of the desired hydroxy-ketone.

Section 10.5 References

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