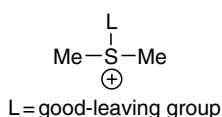


Activated Dimethyl Sulfoxide

2.1. Introduction



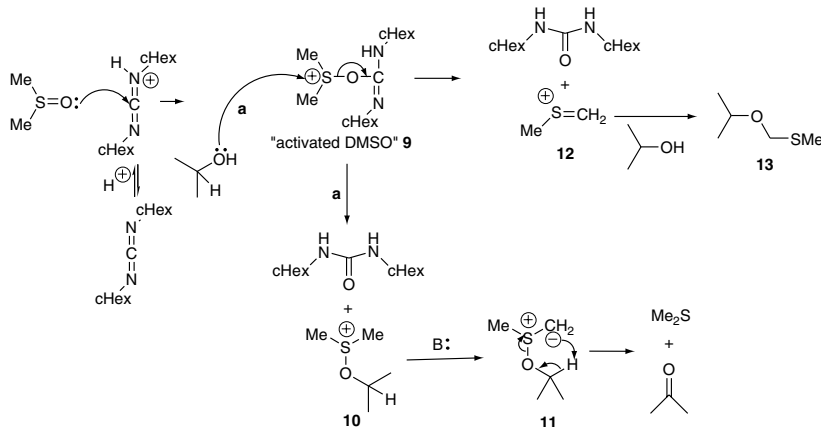
In 1963, Moffatt and Pfitzner¹ published that, at room temperature, treatment of an alcohol dissolved in dry DMSO with dicyclohexylcarbodiimide (DCC), in the presence of a mild acid, leads to the oxidation to the corresponding aldehyde or ketone. This oxidation was remarkable, because it succeeded in 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 loses 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 $\text{H}_2\text{C}=\text{S}(+)\text{-CH}_3$ 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 ^1H -NMR spectra of methylthiomethyl ethers ($\text{R-OCH}_2\text{-SCH}_3$) 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 anhydride³ and phosphorous pentoxide⁷ 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 $\text{SO}_3 \cdot \text{Py}$.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 anhydride⁹ 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 $\text{SO}_3 \cdot \text{Py}$, 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 $\text{SO}_3 \cdot \text{Py}$, 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 Pfizner–Moffatt oxidations”. Sometimes, the name “Moffatt 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 “Pfizner–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 $\text{SO}_3 \cdot \text{Py}$. 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 P₂O₅. 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

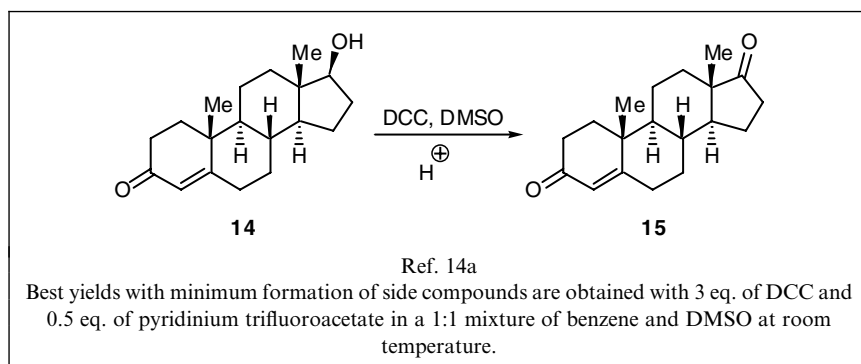
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- 2 (a) Pfitzner, K. E.; Moffatt, J. G.; *J. Am. Chem. Soc.* **1965**, *87*, 5661. (b) *ibid*, 5670.
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2.2. Pfitzner–Moffatt Oxidation (Carbodiimide-Mediated Moffatt Oxidation)

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 oxidation¹⁶ as the default oxidation with activated DMSO. The Pfitzner–Moffatt oxidation¹³—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



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, H₂SO₄ or HClO₄, 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 pK_a inside a narrow window.^{14a} For example, no oxidation occurs with acetic acid (pK_a = 4.76) or trichloroacetic acid (pK_a = 0.66), because their pK_as lay outside the acidity window, while monochloroacetic acid (pK_a = 2.86) leads to a slow and incomplete reaction, and dichloroacetic acid (pK_a = 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 pK_as can lead to very diverse yields of the ketone **15**.

After testing many acids, it was found that orthophosphoric 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 orthophosphoric 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: diethylcarbodiimide¹⁹ and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate.²⁰ It

must be mentioned that the easily available²¹ 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 trifluoroacetate²⁷ is the acid most commonly used, while phosphoric²⁸ and dichloroacetic acid¹⁸ are being used less often. Acids rarely used include: pyridinium tosylate,²⁹ pyridinium phosphate³⁰ 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 orthophosphoric 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.

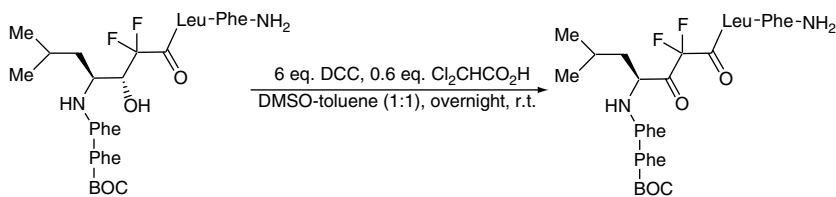
Very little is known about the influence of the use of other solvents on the yield, although it is expected that other aprotic solvents would be as efficient as benzene. Toluene and CH₂Cl₂ are interesting alternatives to the use of carcinogenic benzene, which have been proved to be efficient in this 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.

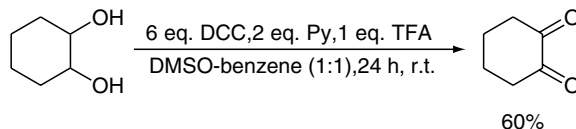
^g *N,N'*-dicyclohexylurea shows a melting point of 237–238°C.³² Its ¹H-NMR (δ, DMSO-d₆, 500 MHz, ppm) shows the following signals: 5.50 (1H, d, *J* = 8 Hz), 3.37–3.28 (1H, m),

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 ^1H -NMR (δ): 6.5 (1H, m) and 3.8 (22H, m).³³ DCC possesses a melting point of 34–35°C³⁴ and the following spectroscopic data: ^1H -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-ethylcarbodiimide shows the following ^1H -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°C³⁶ and the following spectroscopic data: ^1H -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); ^1H -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 ($-\text{NCN}-$), 62.4 ($^{13}\text{CH}_2\text{N}$ or $^{13}\text{CH}_2\text{N}^+$), 60.4, 54.6, 52.9, 51.7, 43.3 ($^{13}\text{CH}_3\text{N}$), 42.3, 42.0, 40.9, 40.6, 36.5 ($^{13}\text{CH}_2\text{N}$), 36.3, 33.9, 25.9 ($\text{C}^{13}\text{CH}_2\text{C}$), 25.2, 17.3 ($^{13}\text{CH}_3\text{C}$), 16.5, 15.6, 13.5.³⁷



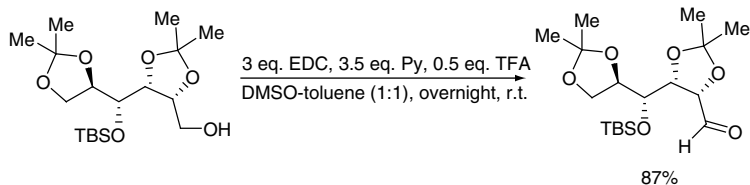
Ref. 23a

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.



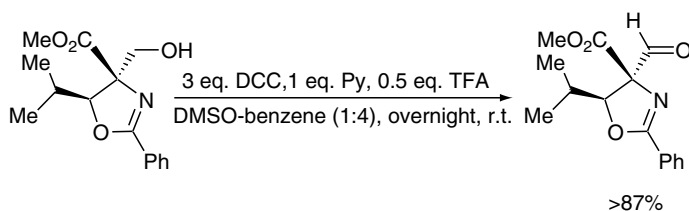
Ref. 38

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.



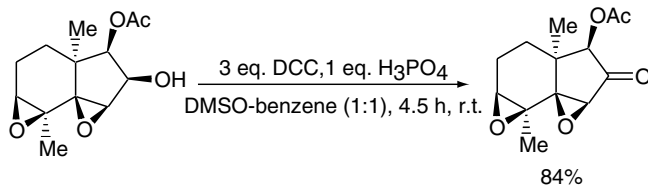
Ref. 23b

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 orthophosphoric acid as a strong acidic activator. Collins oxidation delivers only a 38% yield.

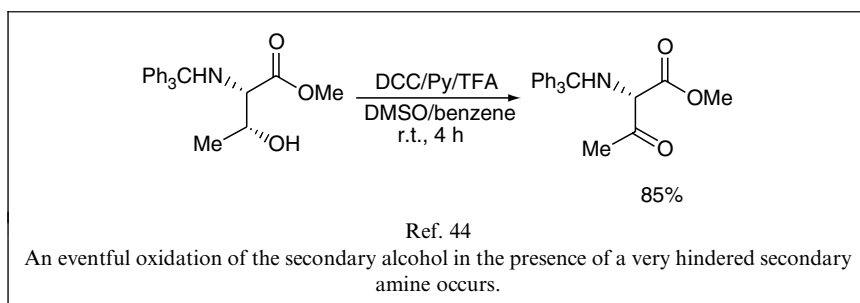
2.2.2. Functional Group and Protecting Group Sensitivity to Pfitzner–Moffatt Oxidation

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} amines⁴⁰ and amides.^{23c,d}

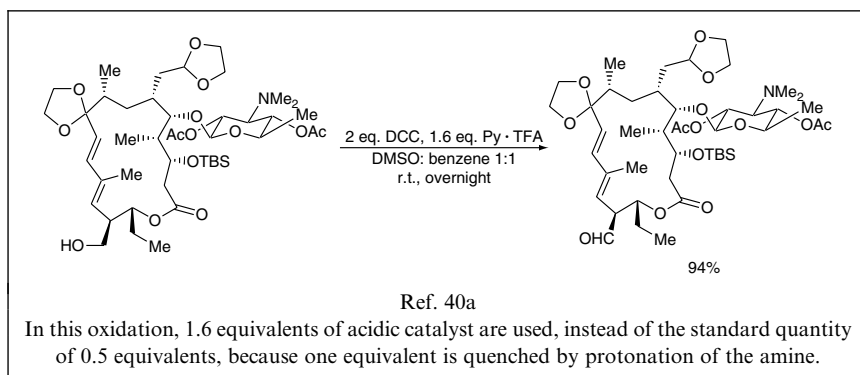
Carboxylic acids react under Pfitzner–Moffatt conditions, resulting in the formation of methylthiomethyl esters and *N*-acylureas.⁴¹ Nevertheless, although the authors are not aware of any report involving the selective oxidation of alcohols in the presence of a carboxylic acid, such outcome would be 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 puzzlingly, 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}

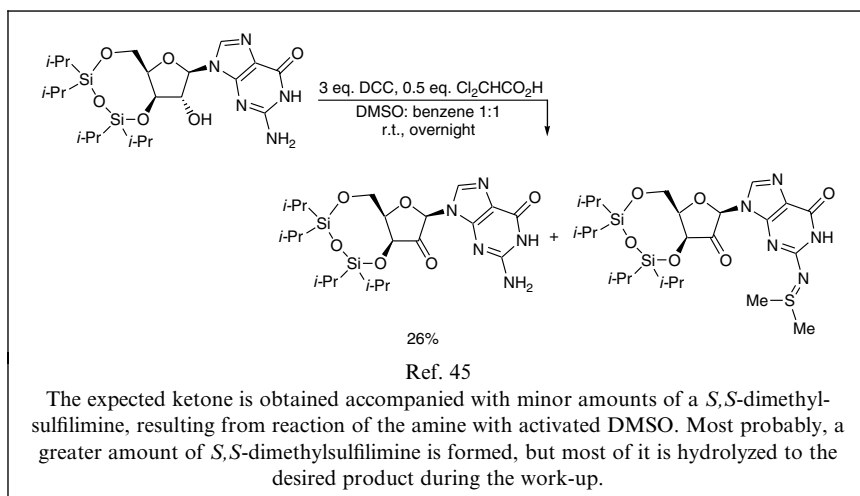
Some amines react under Pfitzner–Moffatt conditions, yielding an adduct with the carbodiimide or a *S,S*-dimethylsulfilimine, resulting from attack of the amine on activated DMSO. The reactivity of different amines is very diverse, and observed in amines, which are not substantially protonated under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



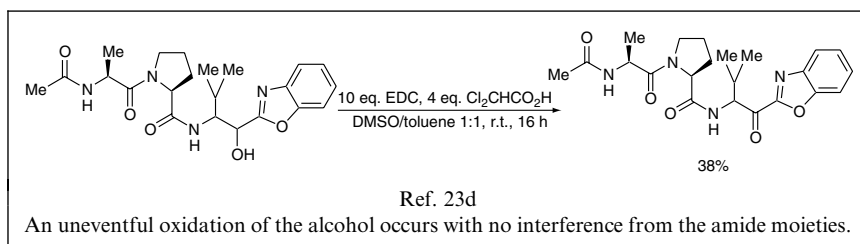
In fact, the interference of amines in Pfitzner–Moffatt oxidations very often results from the trivial fact that basic sites in a molecule can quench the acidic catalyst. In such cases, the oxidations must be carried out by adding an excess of one equivalent of acidic catalyst.



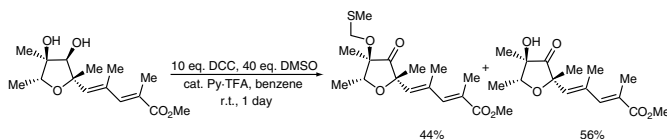
It must be mentioned that the *S,S*-dimethylsulfilimines, resulting from attack of amines on activated DMSO, are very often hydrolyzed back to the free amine during the work-up and thus, their formation may not be detected.



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}



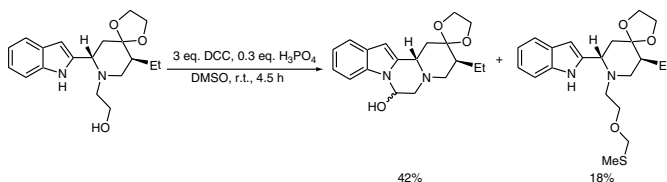
Normally, tertiary alcohols do not interfere with the oxidation of primary or secondary alcohols, although the use of a liberal quantity of reagent can lead to the formation of the methylthiomethyl ether of the tertiary alcohol, accompanying a normal oxidation of a primary or secondary alcohol.⁴⁷



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 $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$, 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

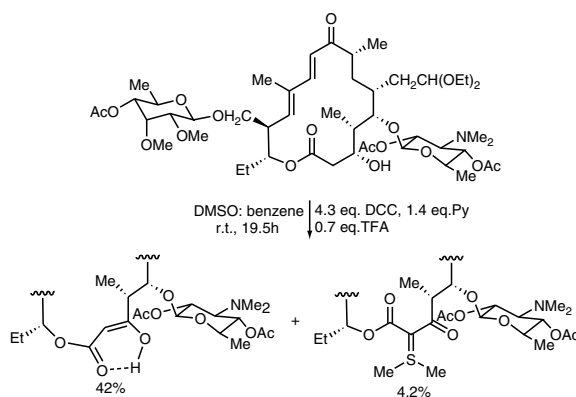


Ref. 48

The oxidation of the primary alcohol leads to an aldehyde that is isolated as an aminor. Minor amounts of a methylthiomethyl ether are isolated, resulting from the reaction of the alcohol with $\text{CH}_2=\text{S}(+)\text{-Me}$ that is formed by thermal decomposition of activated DMSO.

Interestingly, a Swern oxidation fails to deliver the desired 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}



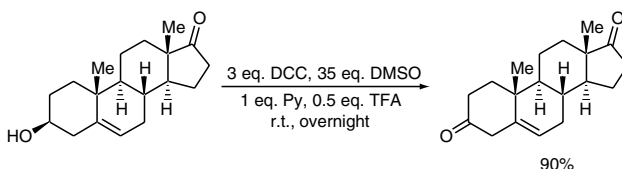
Ref. 40c

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 amines⁴⁹ and *t*-butyl esters,⁵⁰ as well as glycosides⁵¹ and acetals,⁵² remain unchanged under Pfitzner–Moffatt conditions.

2.2.3. Side Reactions

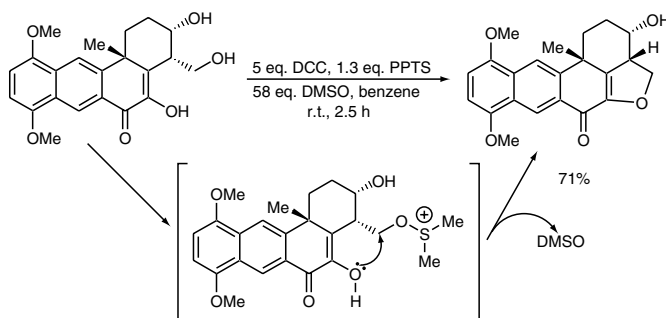
Homoallylic alcohols are oxidized, in the presence of pyridinium trifluoroacetate, with no migration of the alkene into conjugation with the carbonyl, even in cases in which such migration can occur under very mild acidic catalyses. On the other hand, the stronger acid H_3PO_4 is able to produce such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

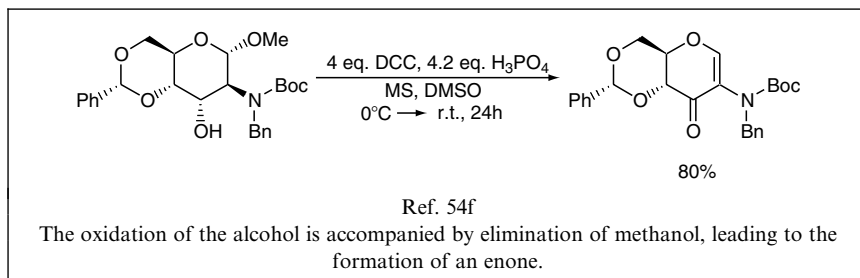
Sometimes, when intramolecular processes are favoured, the intermediate alkoxydysulfonium salt suffers displacement from a nucleophile, instead of the expected evolution to an aldehyde or ketone.⁵³



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



Section 2.2. References

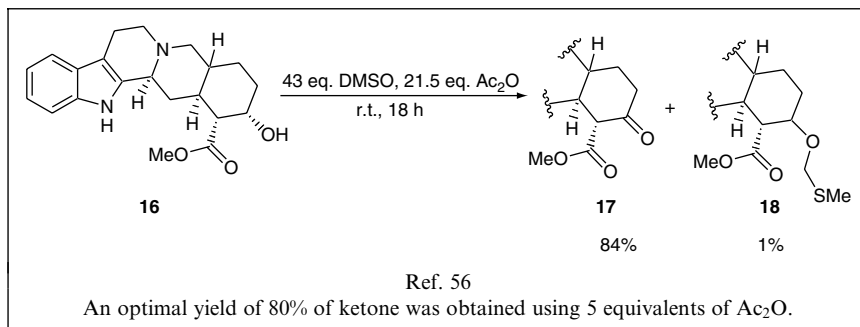
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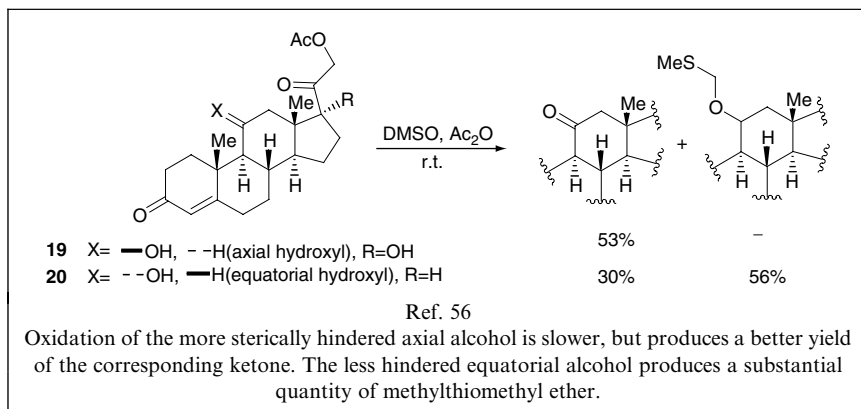
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2.3. Albright–Goldman Oxidation (Acetic Anhydride-Mediated Moffatt Oxidation)

In 1965, Albright and Goldman³ 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 Ac₂O produces the desired oxidation to yohimbine (**17**), accompanied by formation of the methylthiomethyl ether **18**.



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.



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 multi-gram 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:

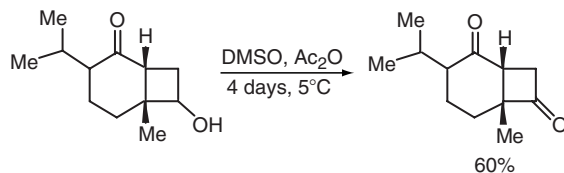
The reaction mixture is mixed with water or ice.^d This may result in the precipitation of the product that can be separated by filtration. If no precipitation occurs, the product can be extracted with an organic solvent, such as CH_2Cl_2 , CHCl_3 , Et_2O or EtOAc . The organic phase is washed with an 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 .

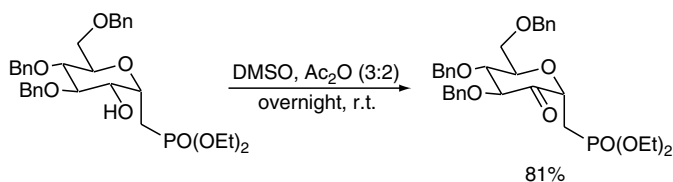
^c Normally, it takes between 2 and 40 h. If heating is applied, the reaction time can be decreased to as little as 10 min.

^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.



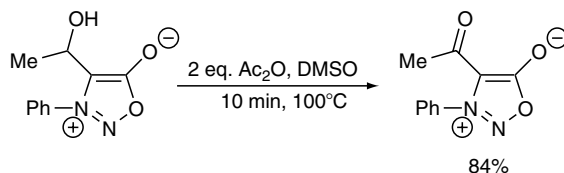
Ref. 57

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.



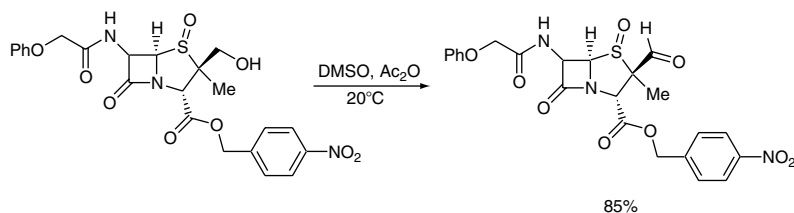
Ref. 58

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 MnO₂ cause no reaction. The use of a 1:1 mixture of DMSO and Ac₂O, 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, isopropylidene⁶¹ and benzylidene acetals,⁶² as well as glycosides⁶³ and dioxolanes⁶⁴ are known to resist the Albright–Goldman oxidation, probably because no water is present and a small amount of acetic acid is generated.

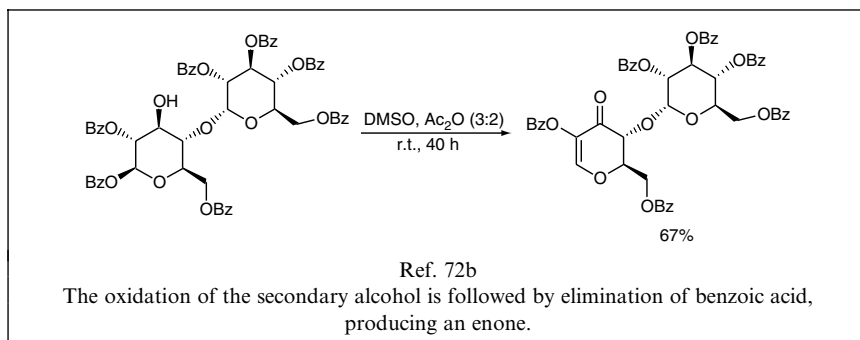
Tertiary amines,⁶⁵ dithioacetals⁶⁶ and thioethers⁶⁷ resist the action of the Albright–Goldman oxidation. Primary amines are acetylated⁶⁸ because of the presence of Ac_2O , although cases are known in which a primary amine remains unaffected,^{67c} while a secondary alcohol is oxidized.

Tertiary alcohols react slowly at room temperature with $\text{DMSO-Ac}_2\text{O}$, resulting in the formation of a methylthiomethyl ether. In fact, this is one of the standard procedures⁶⁹ 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 equivalents⁵⁶ 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



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

In 1965, Albright and Goldman in a communication⁷³ 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 P₂O₅ at room temperature. In 1987, an important improvement on this oxidation protocol was published by Taber *et al.*,⁷⁶ whereby 1.8 equivalents of P₂O₅ are added in a solution of alcohol, 2 equivalents of DMSO and 3.5 equivalents of Et₃N in dry CH₂Cl₂, 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 $\frac{1}{2}$ 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.

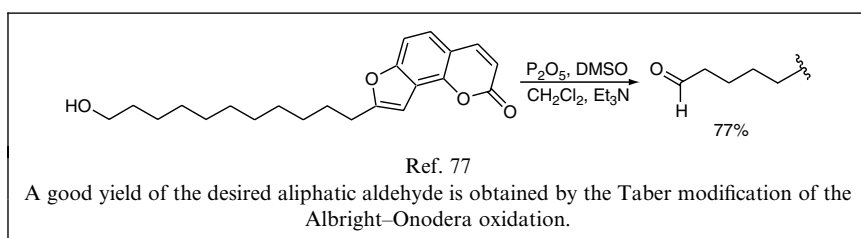
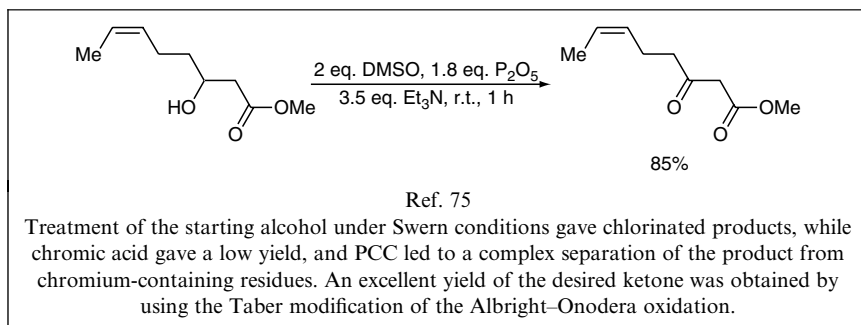
^b As phosphorous pentoxide is extremely hygroscopic, it must be promptly transferred in order to minimize hydration produced by atmospheric moisture. Phosphorous pentoxide reacts very violently with water producing a copious evolution of heat.

^c It normally takes between $\frac{1}{2}$ h and 2 h.



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.



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

It is known that acetals,⁷⁸ β -lactams,⁷⁹ TBS ethers⁷⁶ and alkenes⁷⁵ resist the action of the Albright–Onodera oxidation.

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

Parikh and Doering in 1967 described⁸⁰ 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 THF⁸² 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°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 phenols⁸⁶ and other nucleophiles, like amides⁸⁷ and amines,⁸⁸ resulting in the introduction of a $-\text{SO}_3\text{H}$ group. That is why, $\text{SO}_3 \cdot \text{Py}$ 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 $\text{SO}_3 \cdot \text{Py}$ with DMSO ca. 5–15 min before the addition to the alcohol may guarantee a good yield.⁸⁹
- Some authors reported⁸⁹ 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 base⁹¹— $\text{EtN}(i\text{-Pr})_2$ —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 ₃ N (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—SO₃·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

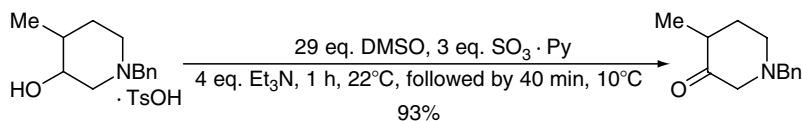
Between 2 and 9—typically 2.9–3.3—equivalents of the complex SO₃·Py (MW=159.2) in a ca. 190–400 mg/mL solution^a in dry DMSO are slowly added over ca. 0.2–0.6 M solution of 1 equivalent of alcohol in dry DMSO, containing ca. 7–17 equivalents of Et₃N (MW = 101.2, *d* = 0.726).^b When most of the starting 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 CH₂Cl₂, EtOAc or Et₂O, 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 $\text{SO}_3 \cdot \text{Py}$ is added as a solid rather than in a DMSO solution. Apparently, this is not generally deleterious for the oxidation yield, although the $\text{SO}_3 \cdot \text{Py}$ complex must be consumed by activating DMSO, before it is able to react directly with the alcohol. Adding the $\text{SO}_3 \cdot \text{Py}$ solution in DMSO from 5 to 15 min after its preparation may prevent the transformation of the alcohol into the $\text{R-OSO}_3\text{H}$ species.

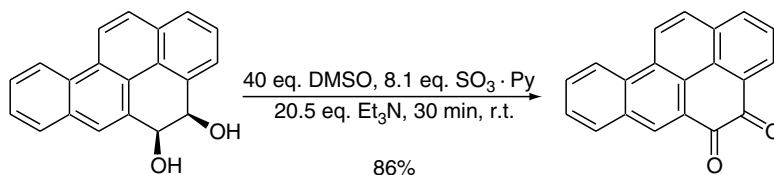
^b The reaction can be carried out at room temperature. Very often, it is done at a lower temperature, typically over an ice-water bath. Temperatures as low as -12°C have been employed. It is also common to mix the reactants at low temperature, and let the reaction be run at room temperature. This is 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.



Ref. 90

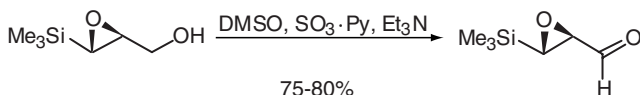
A Parikh–Doering oxidation on 40.9 Kg of starting compound in a 640 L vessel is described. A current of nitrogen is run through the reaction, in order to divert the dimethyl sulfide—generated during the oxidation—to a scrubber containing 13–15% bleach. A Parikh–Doering oxidation is preferred over a Swern 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.



Ref. 89

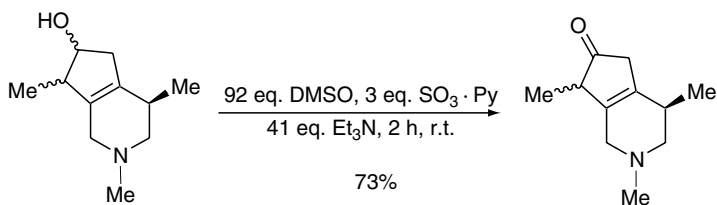
This oxidation presented a serious challenge, because of the tendency of the substrate to suffer dehydration, or oxidative breakage at the benzylic positions. It succeeded under

Parikh–Doering conditions, provided that scrupulously dry conditions are used, and the reaction of $\text{SO}_3 \cdot \text{Py}$ with DMSO precedes the interaction with the diol, in order to avoid the formation of a sulfate ester. Thus, the solution of $\text{SO}_3 \cdot \text{Py}$ 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.



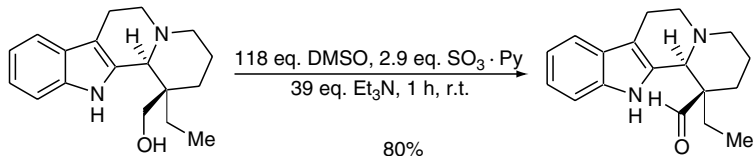
Ref. 94

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.



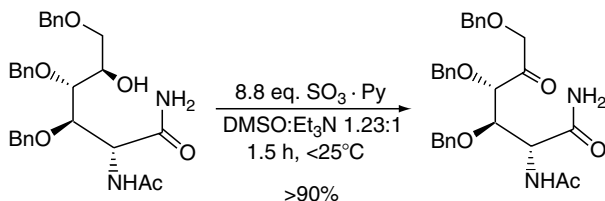
Ref. 95

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.



Ref. 96

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



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 amides⁸⁷ and phenols,⁸⁶ producing the introduction of a $-\text{SO}_3\text{H}$ 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 alcohols⁹⁸ 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

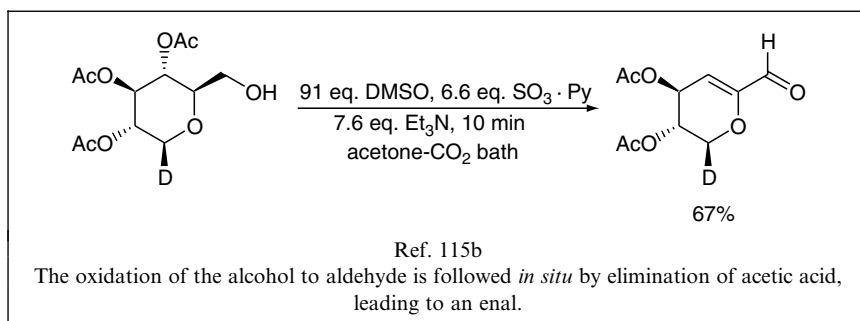
Not surprisingly, acid sensitive functionalities and protecting groups are not modified under Parikh–Doering conditions. Such groups include: acetals,¹⁰¹ glycosides,^{102a} amines protected with Boc¹⁰³ and alcohols protected with TMS,¹⁰⁵ TBS,¹⁰² MOM,¹⁰⁶ Tr¹⁰⁷ and *t*-Bu.¹⁰⁸ In spite of the presence of 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 PMB¹⁰⁴ and dimethoxybenzyl ethers^{109b}, do not react.

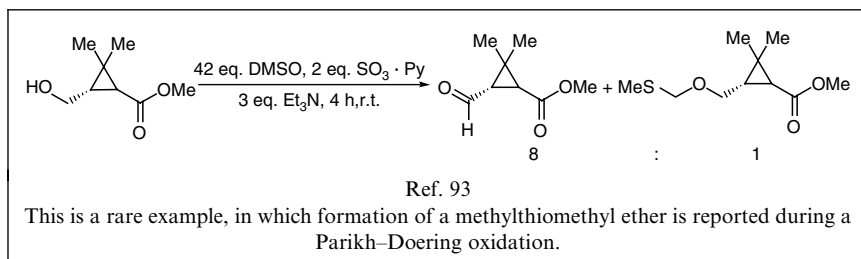
It must be mentioned that sensitive compounds, like alkyl silanes,¹¹² alkyl stannanes¹¹³ and vinyl stannanes,¹¹⁴ are not affected under the conditions of the Parikh–Doering oxidation.

2.5.3. Side Reactions

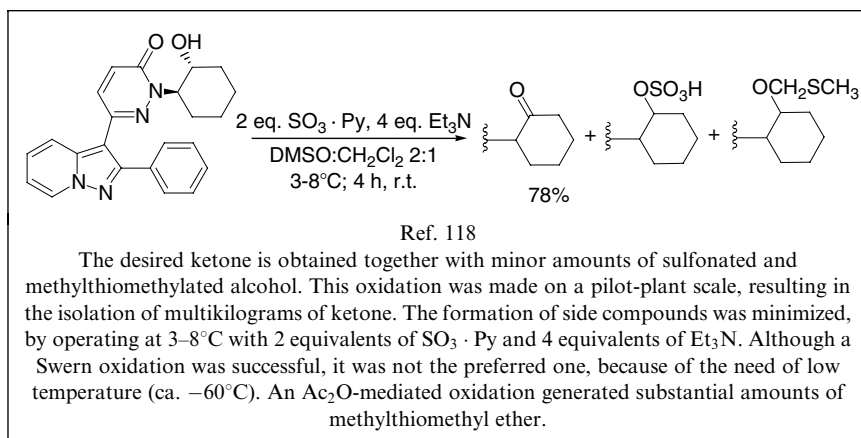
When an aldehyde or ketone, possessing a good-leaving group at the β -position, is obtained during a Parikh–Doering oxidation, very often an elimination occurs, leading to an enal or an enone. Leaving-groups suffering such elimination include acetate¹¹⁵ and sulfinyl.¹¹⁶



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



In a properly performed Parikh–Doering oxidation, the complex $\text{SO}_3 \cdot \text{Py}$ 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 $\text{SO}_3 \cdot \text{Py}$, that can react with nucleophilic sites in the molecule, including alcohols.



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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**.

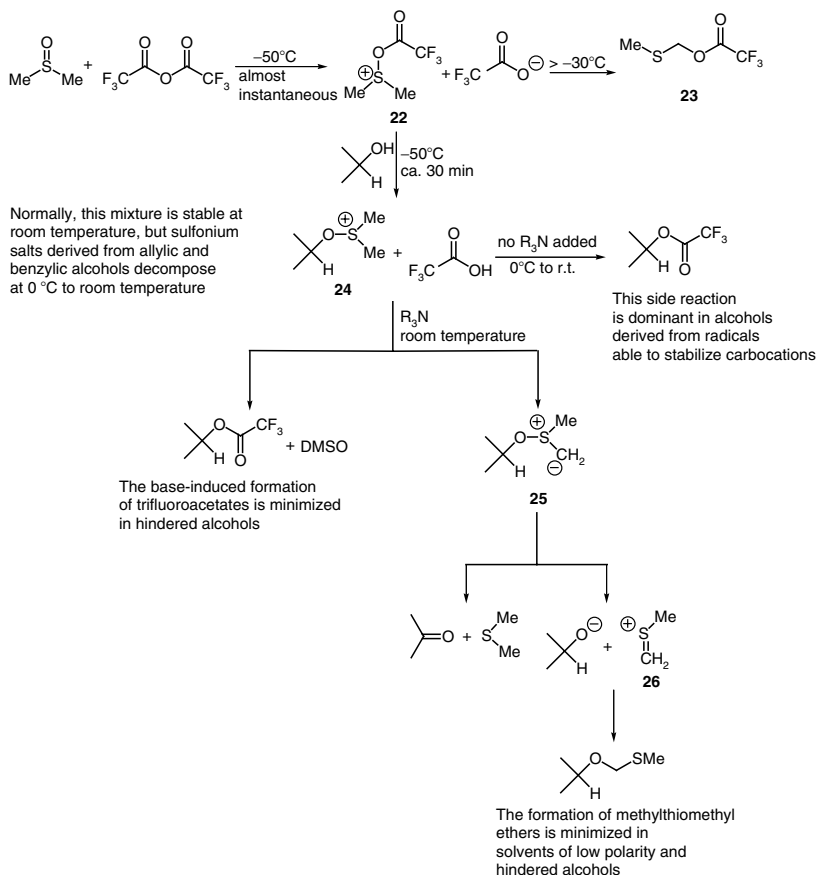
Interestingly, although trifluoroacetic anhydride reacts very quickly with alcohols, the reaction with DMSO is even quicker. Therefore, the formation of the activated DMSO species **22** can be made in the presence of the alcohol, resulting in little erosion of the oxidation yield.

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

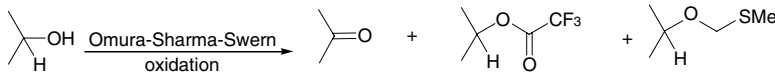
cases, the so-called *Procedure A* must be used, whereby an amine is added at low temperature to the alkoxydimethylsulfonium salt **24**, and the resulting mixture is allowed to reach slowly at room temperature. These results are exemplified in Table 2.1.

Additionally, it must be mentioned that the formation of methylthio-methyl 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 alkoxy-sulfonium salt **24** and the resulting mixture is left to reach slowly at room temperature. *Procedure C*: like *Procedure A* but the solution of the alkoxy-sulfonium 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.

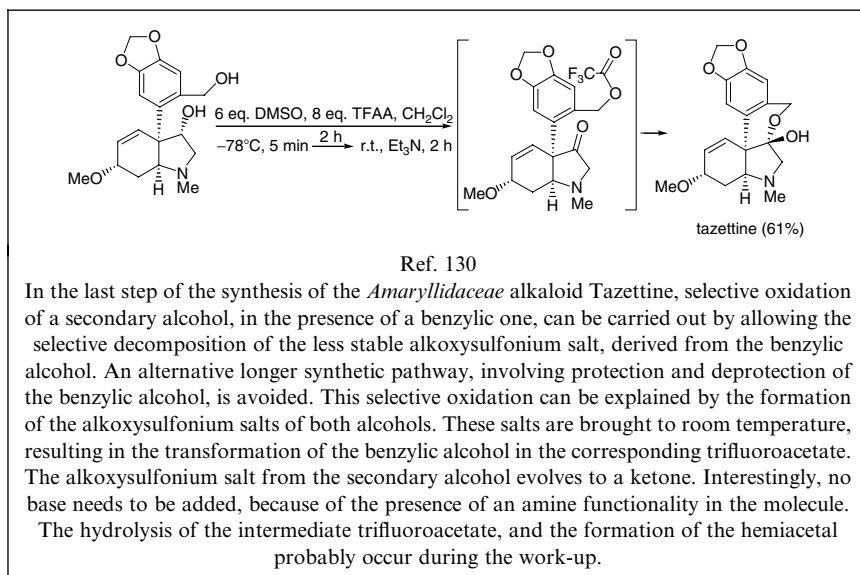
Interesting modifications of the standard *Procedure A* include, allowing a prolonged reaction—till 90 min—of activated DMSO **22** with the alcohol at low temperature, in order to make sure the complete formation of the alkoxy-sulfonium intermediate **24**,¹²⁶ and performing the final steps at ca. -78°C 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 alkoxy-sulfonium salt by attack of the alcohol.

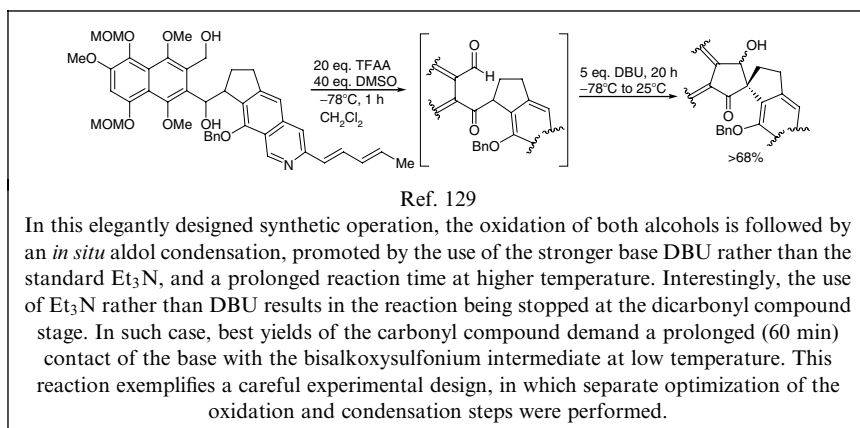
The nature of the amine, used for the decomposition of the alkoxydimethylsulfonium salt, has a great influence in the yield of the aldehyde or ketone. Swern *et al.* proved^{122c} that best yields are obtained with hindered amines, like Hünig's base ($\text{Et}_3\text{N} \cdot \text{Pr}_2$). Nevertheless, 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

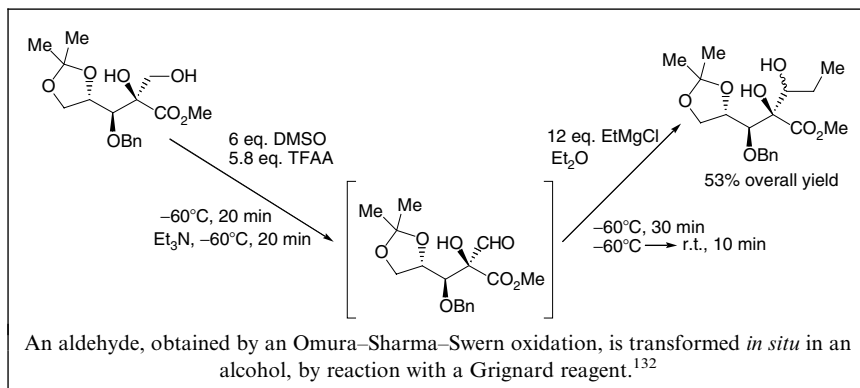
The differential stability of alkoxysulfonium salts, derived from diverse alcohols, and the lesser tendency of hindered alcohols to provide trifluoroacetate side compounds can explain some interesting selective oxidations reported in the literature.^{125,130}



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



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.



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 .^c 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 ($\text{Et}_3\text{N} \cdot \text{Pr}_2$)^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.

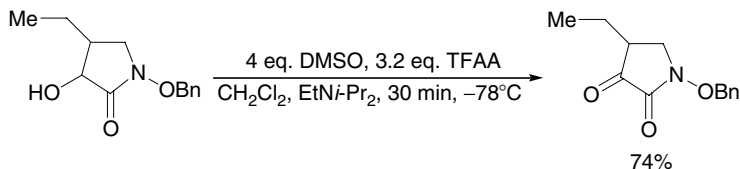
^f DMSO and TFAA are reported to react instantaneously at -60°C . The resulting activated DMSO is stable at low temperature, at least, during several days. Therefore, little change in the oxidation yield is expected, depending on the time that DMSO and TFAA are in contact at low temperature.

^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.

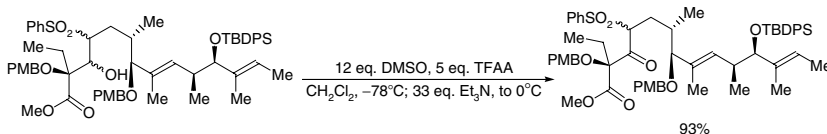
ⁱ Sometimes, the reaction mixture is left stirring at low temperature, or is left to reach 0°C rather than room temperature. In those cases, very often the reaction is quenched at low temperature with an alcohol, like MeOH or *i*-PrOH, before the work-up.

^j It takes about 1 h.



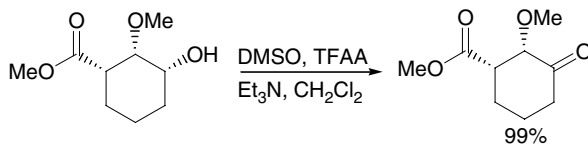
Ref. 132

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

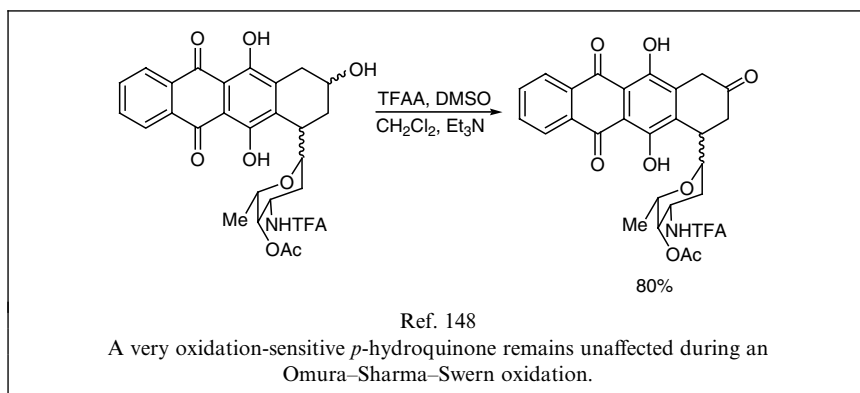
A 99% yield of ketone is obtained via an Omura–Sharma–Swern oxidation, while Dess–Martin periodinane delivers a 73% yield.

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

As expected, acid sensitive functionalities, including THP,¹³⁵ Tr,¹³⁶ TBS¹³⁷ and *t*-Bu¹³⁸ ethers, orthoesters,¹³⁹ acetals¹⁴⁰ and glycosides,^{137a,141} as well as Boc-protected¹⁴² amines, are resistant to Omura–Sharma–Swern oxidations.

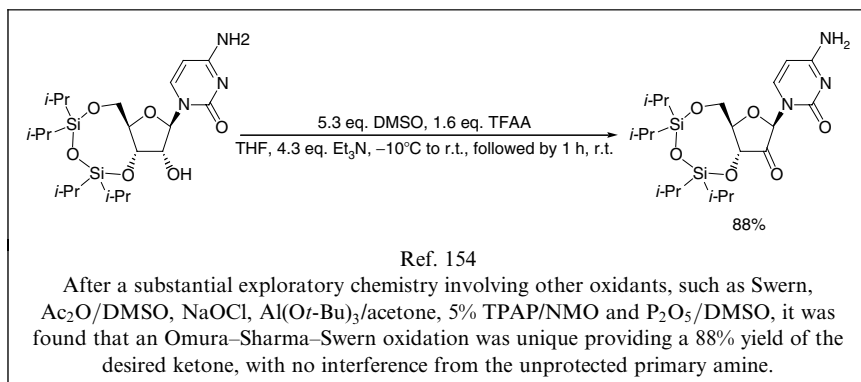
Normally, functionalities sensitive to basic hydrolyses, like esters, resist this oxidation protocol, because the added amine operates in the absence of water.

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 ethers¹³³ and esters,¹⁴³ sulfides,^{143a,144} thioacetals,¹⁴⁵ nitrogen heterocycles¹⁴⁶ and most peculiarly even selenides,¹⁴⁷ and *p*-hydroquinones.¹⁴⁸

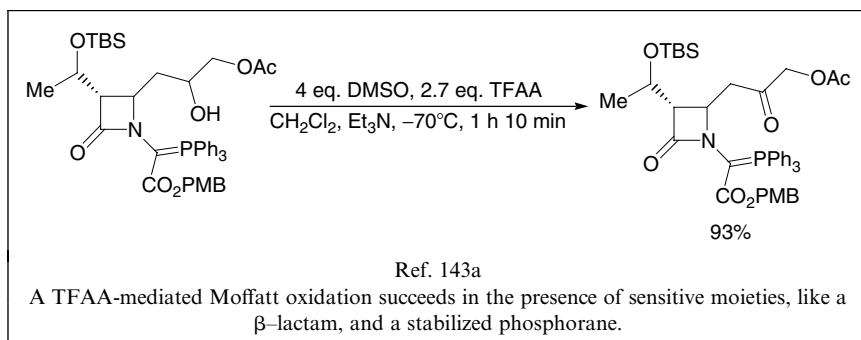


Although very often indoles are recovered unchanged,¹⁴⁹ there are evidences¹⁵⁰ showing that they do react under Omura–Sharma–Swern conditions, producing an intermediate that, in the absence of excess of oxidizing reagent, reverts to starting indole during the work-up. However, this intermediate sometimes may evolve, resulting in the generation of side compounds (see page 137).

Tertiary¹⁵¹ amines remain unaffected, and there are examples of unreactive secondary¹⁵² amines, recovered unchanged in Omura–Sharma–Swern oxidations. There is one report¹⁵³ 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



It is interesting to note that stabilized phosphoranes^{143a,b} and phosphonate¹⁵⁵ anions can resist TFAA-mediated Moffatt oxidations.



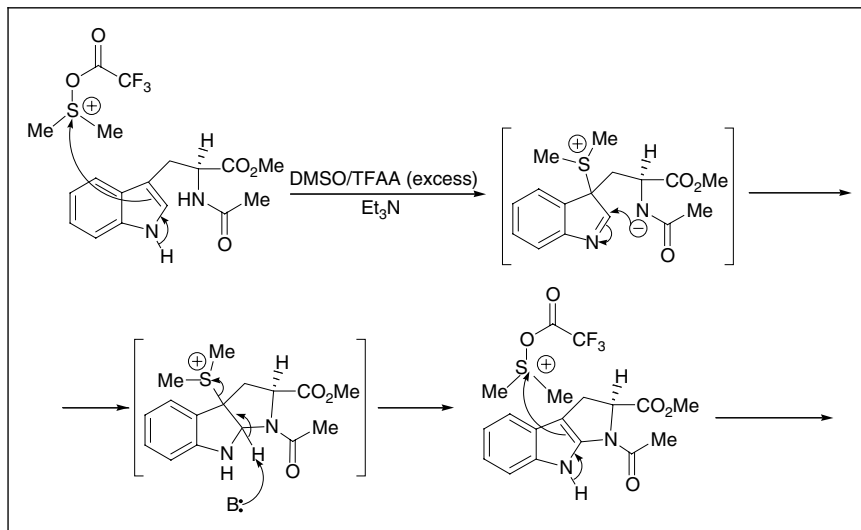
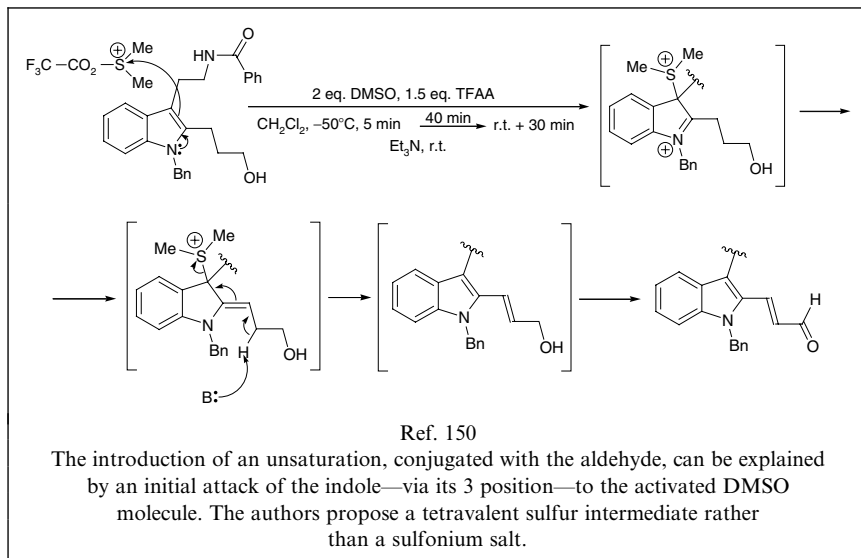
2.6.3. Side Reactions

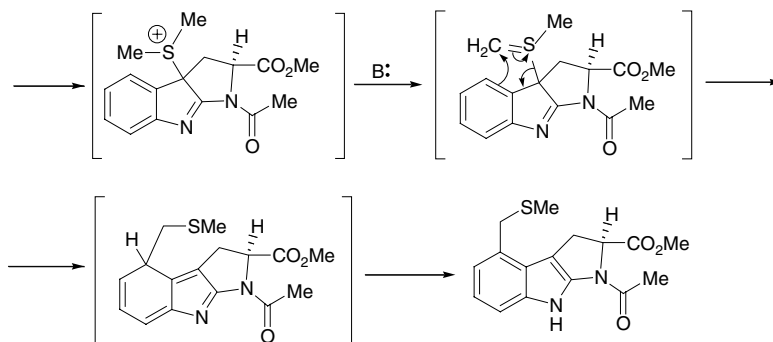
Very often, alcohols are transformed into the corresponding trifluoroacetates. This side reaction can be very substantial in alcohols possessing radicals able to stabilize carbocations, such as benzylic and allylic alcohols.^{122a,b} A proper choice of reaction conditions can result in a minimization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

The action of the amine over the alkoxy-sulfonium intermediate— $\text{ROS}(+)\text{Me}_2$ —can produce either the desired oxidation, or the generation of $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$. This compound can react with alcohols, resulting in the formation of methylthiomethyl ethers, $\text{R-O-CH}_2\text{-S-Me}$. It can also react with other nucleophilic sites, resulting in the introduction of a methylthio-methyl 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— $\text{F}_3\text{CCO}_2\text{-S}^+(\text{Me})_2$ —, indoles being particularly prone to do so.

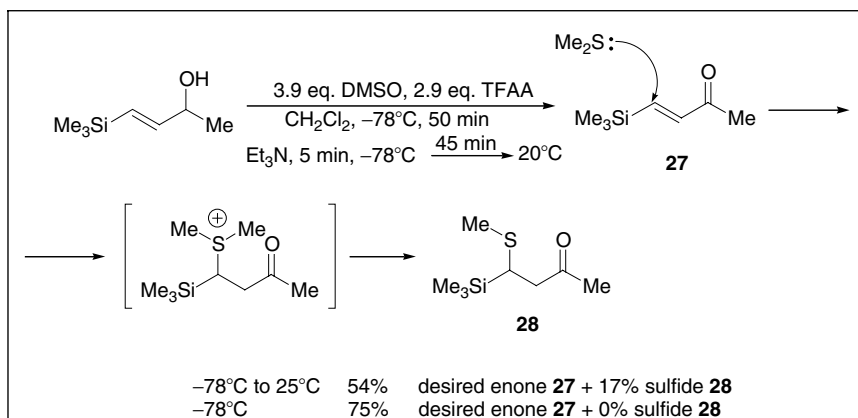




Ref. 150

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 $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$, would hardly explain the regioselectivity of the methylthiomethylation.

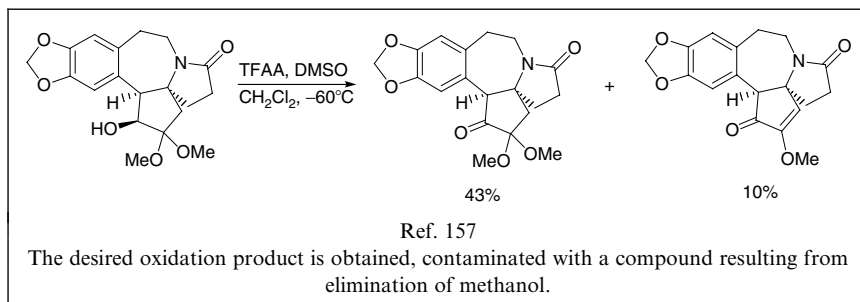
Sometimes, side products are formed, resulting from attack on electrophilic sites of dimethylsulfide generated from DMSO.



Ref. 156

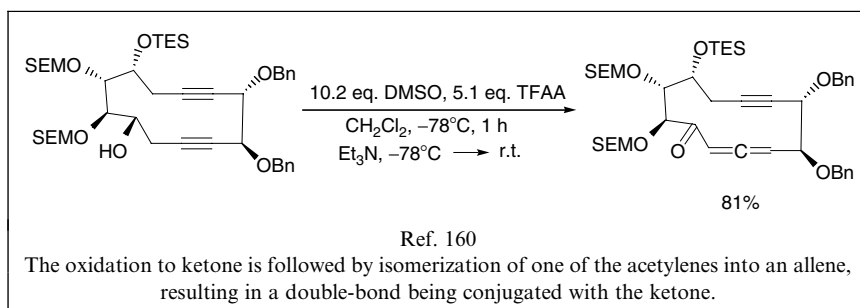
Dimethyl sulfide, generated from DMSO, attacks the enone resulting from the oxidation of the alcohol. A sulfonium salt is generated that decomposes into a sulfur-containing side-compound. Performing the oxidation entirely at -78°C , prevents the undesired attack of dimethyl sulfide.

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



It must be mentioned that such eliminations need not to occur, and examples are known in which no carboxylate,^{140c,142b} sulfone,¹⁵⁸ or hydroxy¹⁵⁹ groups suffer elimination.

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



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

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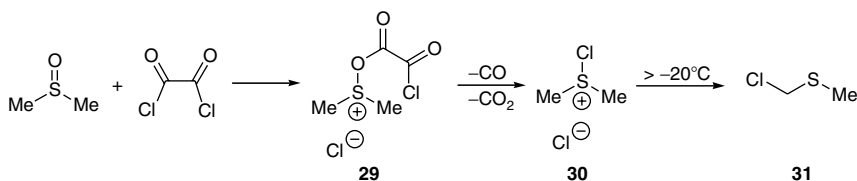
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2.7. Swern Oxidation (Oxalyl Chloride-Mediated Moffatt Oxidation)

Few oxidation methods have enjoyed the almost immediate success of the Swern procedure for the oxidation of alcohols. Since the publication of three foundational papers¹⁶¹ 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.

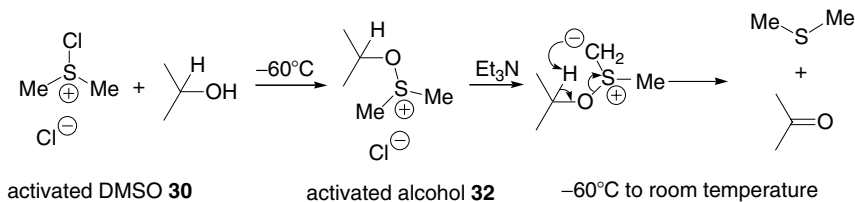
Mechanism

DMSO and oxalyl chloride react in an explosive manner at room temperature. The reaction at -60°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°C , an almost instantaneous reaction takes place, resulting in the formation of chlorodimethylsulfonium chloride (**30**).



The primary product (**29**) of the reaction of DMSO and oxalyl chloride decomposes very quickly to **30** even at -140°C .¹⁶³ However, the activated DMSO molecule **30** remains stable below -20°C , but decomposes above this temperature to chloromethyl methyl sulfide (**31**), via the reactive species $\text{H}_2\text{C}=\text{S}^+-\text{Me}$.

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**).



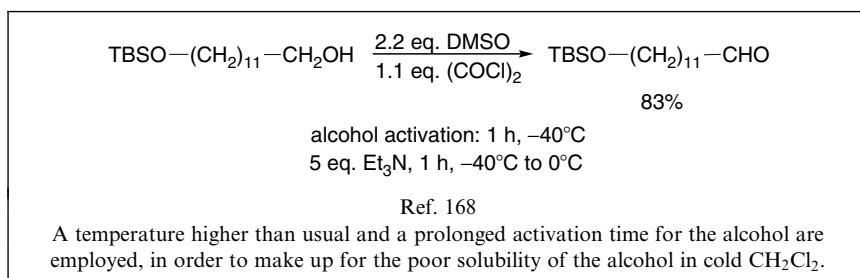
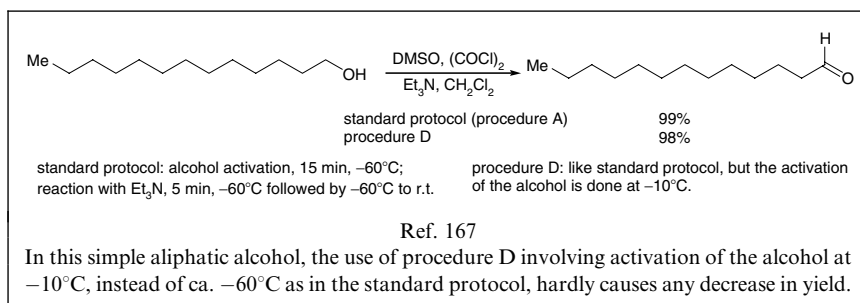
According to the standard protocol (procedure A) as described by Swern *et al.*, the alcohol is allowed to react with activated DMSO for 15 min at low temperature (normally -78 to -50°C). This is followed by the addition of triethylamine, which reacts with the activated alcohol, while the reaction is left to reach room temperature. This standard protocol, involving the generation of activated DMSO in CH_2Cl_2 at low temperature (ca. -60°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°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

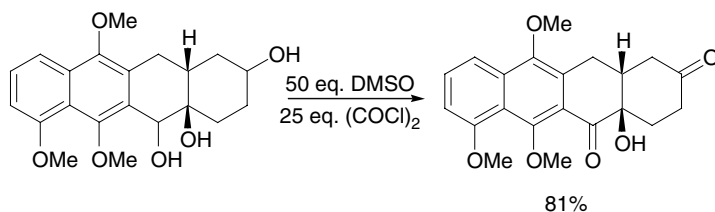
alcohol involved, dictates different experimental protocols. Thus, in the case of alcohols derived from radicals able to stabilize cations—particularly allylic, propargylic and benzylic alcohols—the corresponding activated alcohol species **32** are expected¹⁶⁵ to decompose at temperatures lower than 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°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°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°C).



Alcohol Activation

The observations performed by Marx and Tidwell,¹⁶⁹ regarding alcohol ligand interchange in alkoxy-sulfonium salts, show that the activation of normal alcohols at low temperature is extremely rapid, being possible to complete in a few minutes at -60°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



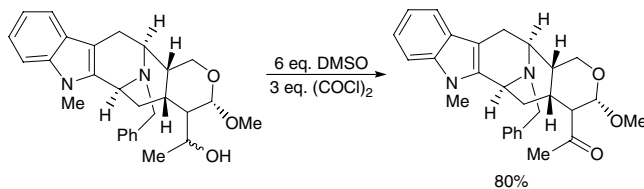
alcohol activation: 45 min at -60°C
115 eq. Et_3N , 15 min -60°C , followed by -60°C to r.t.

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



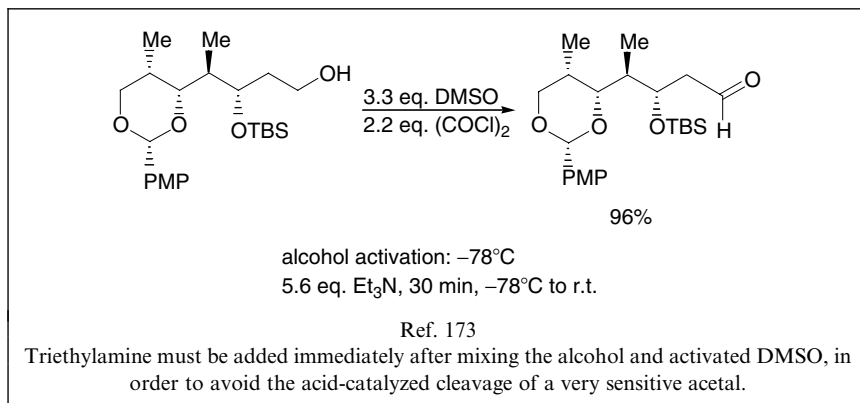
alcohol activation: 1.25 h, -78 to -10°C
14.4 eq. Et_3N , 45 min, -10°C to r.t.

Ref. 172b

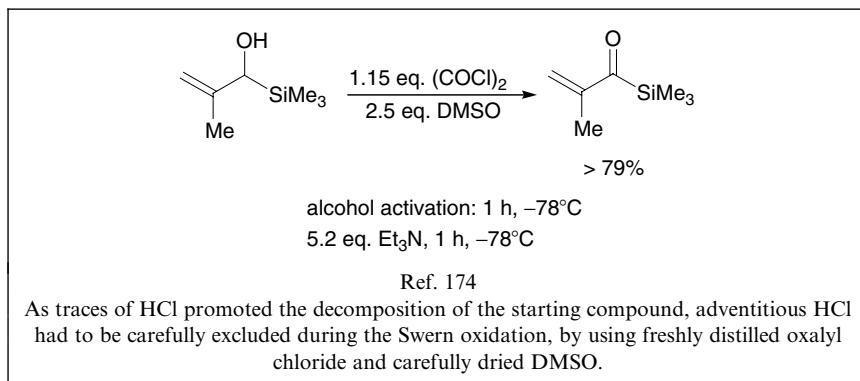
In this Swern oxidation, the activation of a very hindered alcohol demands 1.25 h, while the temperature is increased from -78 to -10°C .

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.



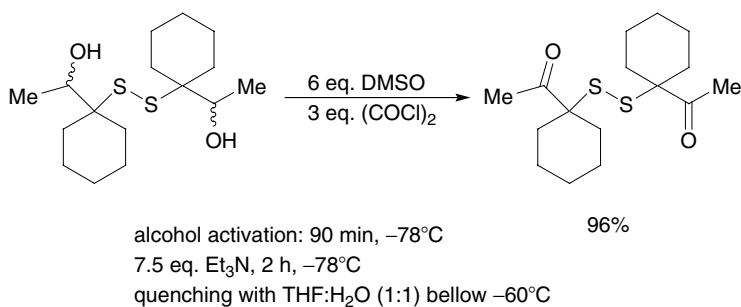
The decomposition of acid-sensitive substrates during Swern oxidations can also be explained by the presence of adventitious hydrogen chloride. This can be avoided by the use of freshly distilled oxalyl chloride and carefully dried DMSO.¹⁷⁴



Preventing Base-induced Side Reactions

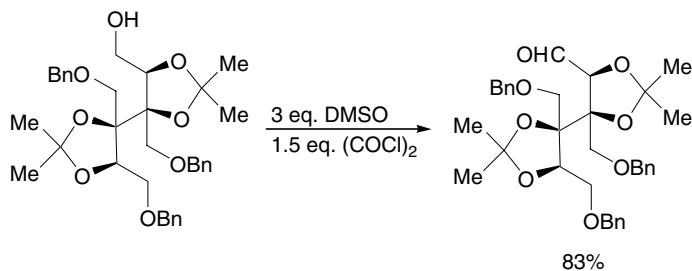
In the standard protocol the transformation of the activated alcohol into the carbonyl compound is done by the action of Et_3N for 5 min,

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 -epimerization¹⁷⁶ or a β -elimination¹⁷⁷ of the product must be avoided.



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 below -60°C . The use of the standard protocol allows the isolation of the diketone in a moderate yield (ca. 60%).

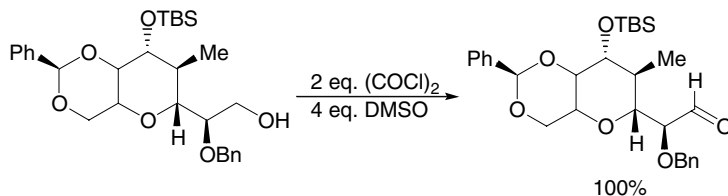


Ref. 176a

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 Et₃N, may cause a substantial decrease on the reaction speed.¹⁷⁹

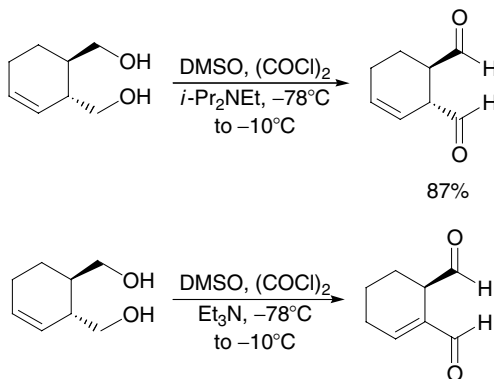


alcohol activation: 15 min, -78°C

8 eq. *i*-Pr₂NEt, 1 h, -78°C , followed by -78°C to -40°C
quenching at -40°C with a neutral phosphate buffer

Ref. 180

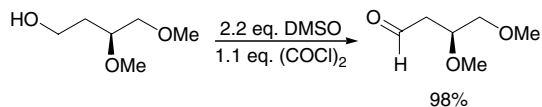
In order to avoid a very facile α -epimerization of the aldehyde, the bulky base diisopropylethylamine was used and quenching was performed at -40°C with a phosphate buffer at pH 7.



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

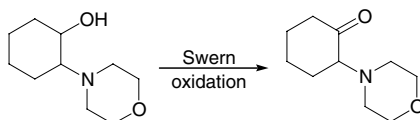


alcohol activation: 25 min, -78°C
3.3 eq. *N*-methylmorpholine, 70°C to 0°C , followed by 2 h, 0°C

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

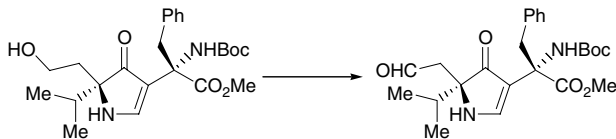


base	%
<i>i</i> -Pr ₂ NEt	65
Et ₃ N	68
<i>N</i> -ethylpiperidine	93
<i>N</i> -methylpyrrolidine	57

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 ₃ N	46%
(COCl) ₂ , DMSO, <i>i</i> -Pr ₂ NEt	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 tetrahydrofuran¹⁸⁴ 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 chains¹⁸⁸ and sulfoxides bound to polymers, such as polystyrene¹⁸⁹ 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 triethylamineⁱ (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.

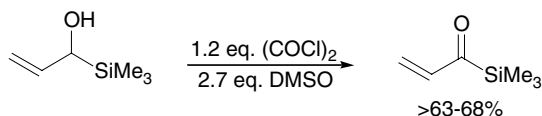
^g In the oxidation of simple aliphatic alcohols, the solution of activated DMSO may be left to reach as high as -10°C in order to increase the solubility of the alcohol. The routine use of such high temperature is not advisable for it may cause side reactions.

^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.

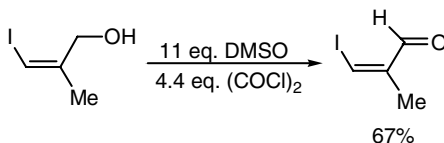


alcohol activation: 1 h, -75°C

5.4-5.8 eq. Et₃N, 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.

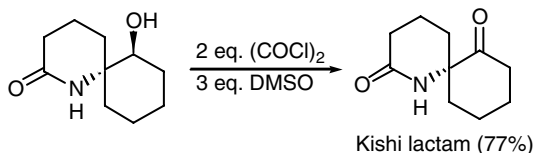


alcohol activation: 30 min, -78°C

1.2 eq. Et₃N, 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.

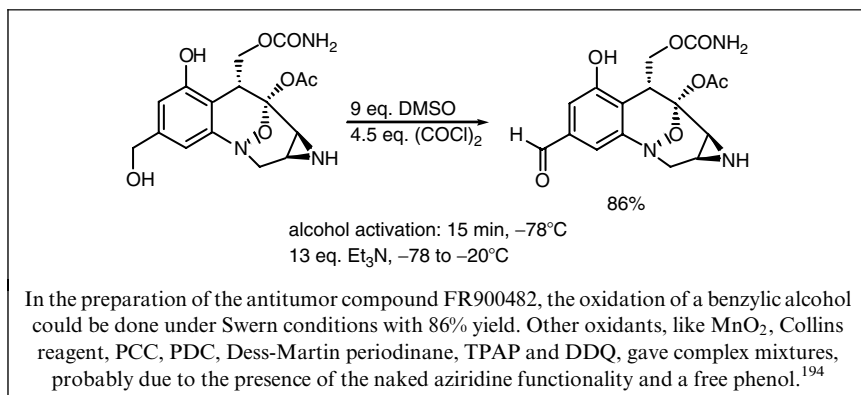


alcohol activation: 5 min, -78°C

4 eq. Et₃N, 2 h, -78°C and 12 h, 0°C

Ref. 193

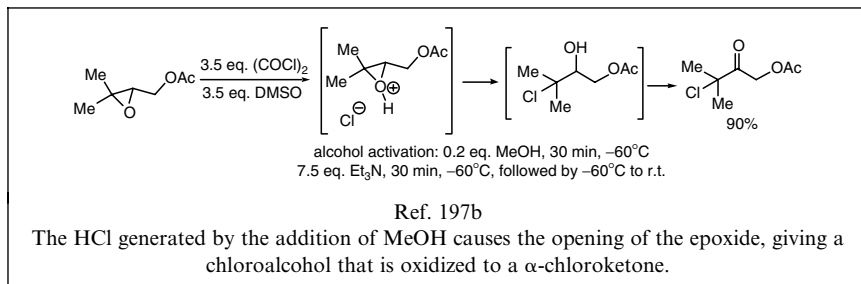
In an enantioselective synthesis of a key intermediate for the preparation of poisons from the skin of tropical frogs, a key oxidation was performed under Swern conditions with 77% yield, while PCC provided a 28% yield and Pfitzner–Moffatt oxidation 73% yield.



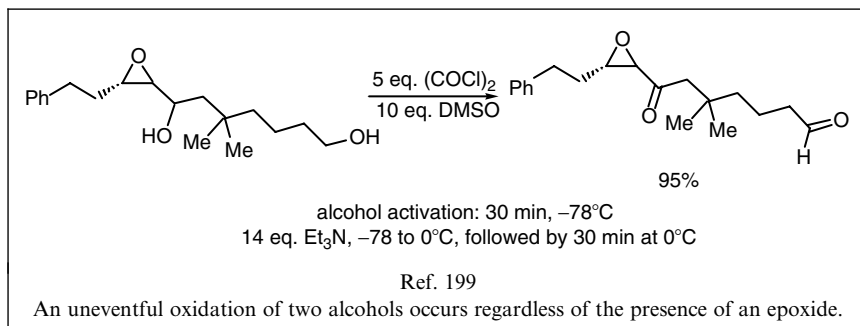
2.7.2. Functional Group and Protecting Group Sensitivity to Swern Oxidation

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 THP¹⁹⁵ or trityl¹⁹⁶ 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.



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



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 possessing a good-leaving group at the β -position

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

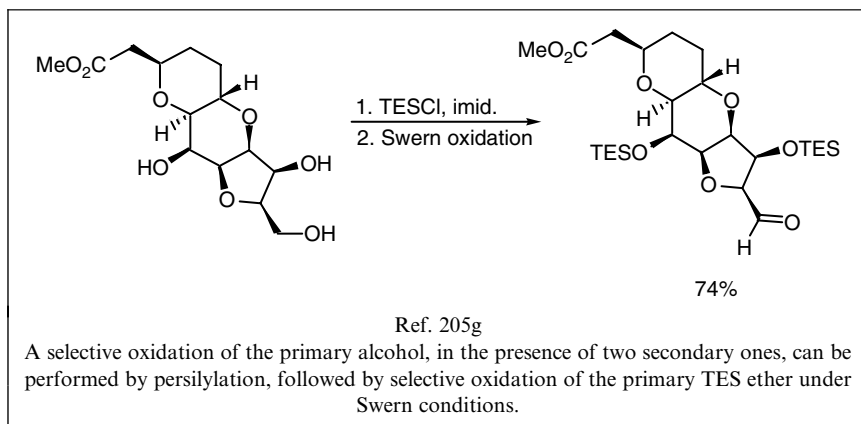
- Using bases, like Hünig's base, which are more hindered than triethylamine
- Using amines, like *N*-methylmorpholine, which are less basic than triethylamine
- Quenching the reaction at low temperature under mild conditions

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 selenides²⁰⁰ resist the action of Swern oxidation.

Protecting groups that are cleaved by an oxidant, like *p*-methoxybenzyl²⁰¹ and dimethoxybenzyl²⁰² ethers or *p*-methoxybenzylidene²⁰³ and dimethoxybenzylidene²⁰⁴ acetals, resist the action of oxalyl chloride-activated DMSO.

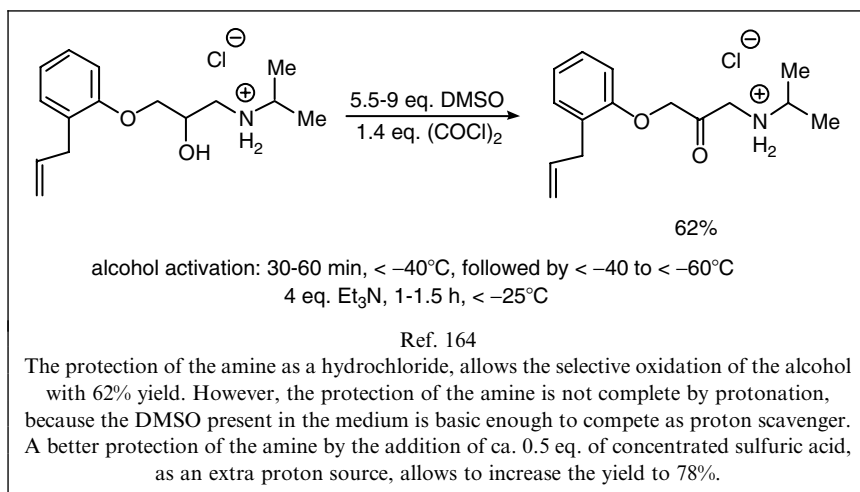
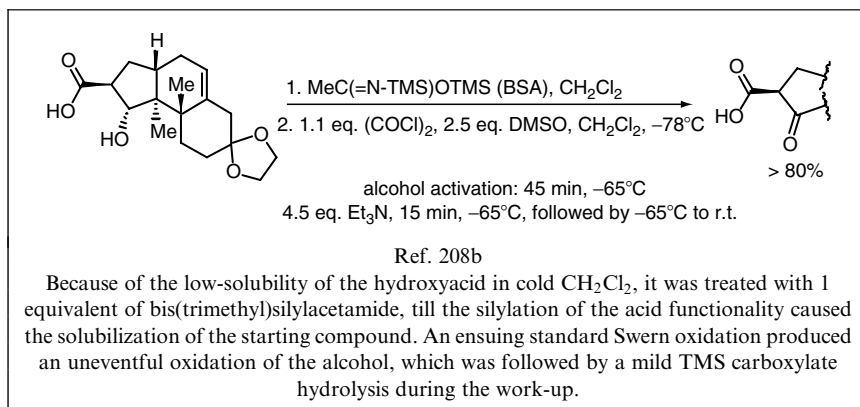
Primary TMS and TES ethers²⁰⁵ are deprotected and transformed into the corresponding aldehydes under Swern conditions. Other less labile silyl ethers—such as TBS ethers as well as secondary TMS and TES ethers—, remain unaffected. This allows to perform selective oxidations of primary alcohols in the presence of secondary ones by persilylation of polyols by TMS or TES, followed by selective oxidation of the primary silyl ethers to aldehydes 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 raises 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-phenylfluorenyl²¹¹ 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.

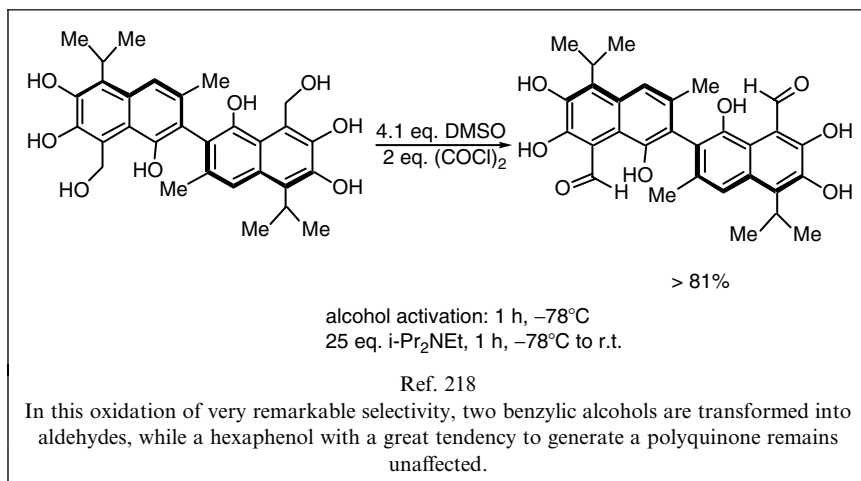


Tertiary amines normally remain unaffected under Swern conditions.

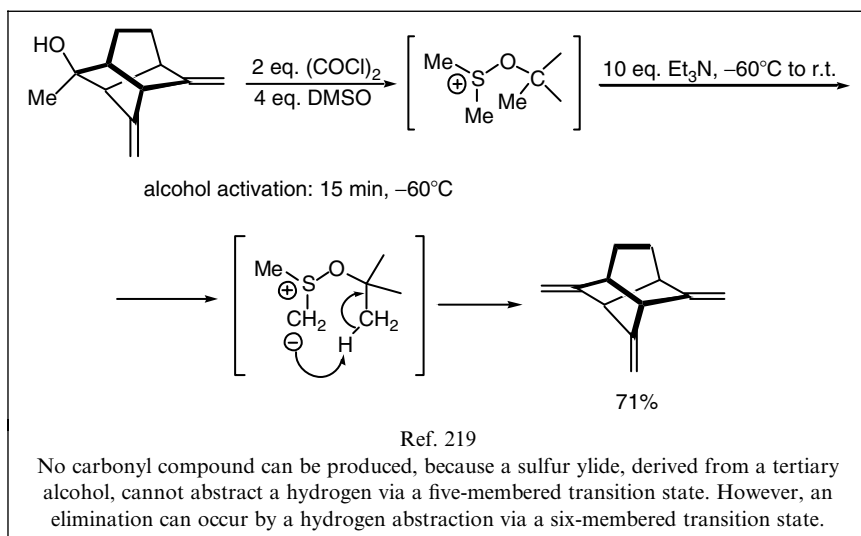
Primary amides react under Swern conditions, producing the corresponding nitriles²¹³ and minor amounts of iminosulfurans.²¹⁰ Nonetheless, there is some report depicting the selective oxidation of alcohols in the presence of primary amides.²¹⁴ Secondary and tertiary amides remain unaffected.

Nitro groups remain unaffected²¹⁵ during Swern oxidations, although there is one report in which a nitroalcohol is transformed into a lactone.²¹⁶

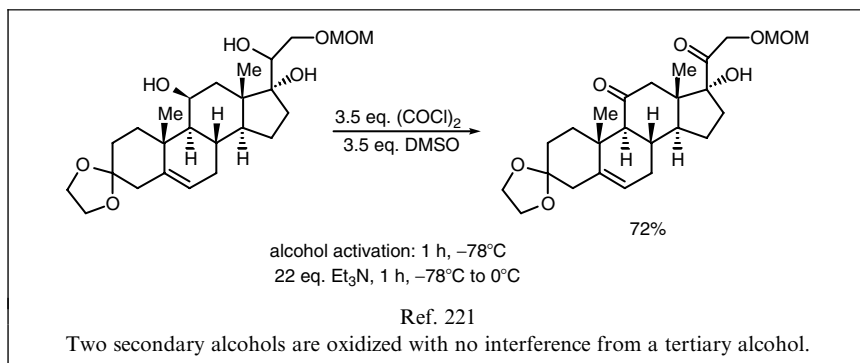
It is possible to oxidize alcohols in the presence of free phenols,²¹⁷ although many times phenols are protected for solubilizing purposes.



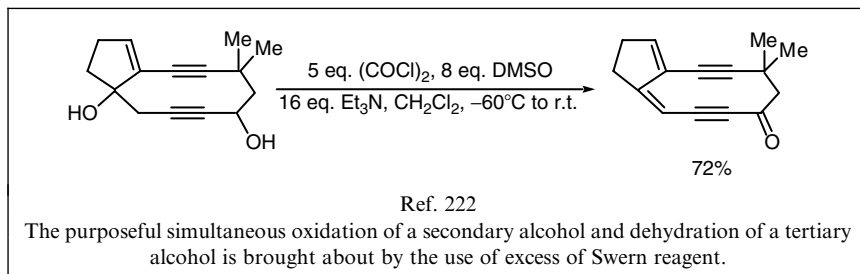
Tertiary alcohols react with activated DMSO, yielding an activated alcohol, that, as it lacks an α -hydrogen, is not able to evolve to a carbonyl compound. Nevertheless, when a β -hydrogen is present, elimination to an alkene can occur under the action of a base.²¹⁹



Because of steric constraints, 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

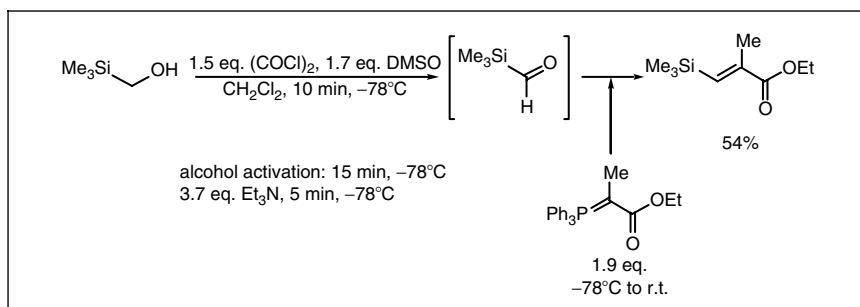


The simultaneous oxidation of a secondary or primary alcohol, and dehydration of a tertiary alcohol can be carried out by using excess of Swern reagent.²²²



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

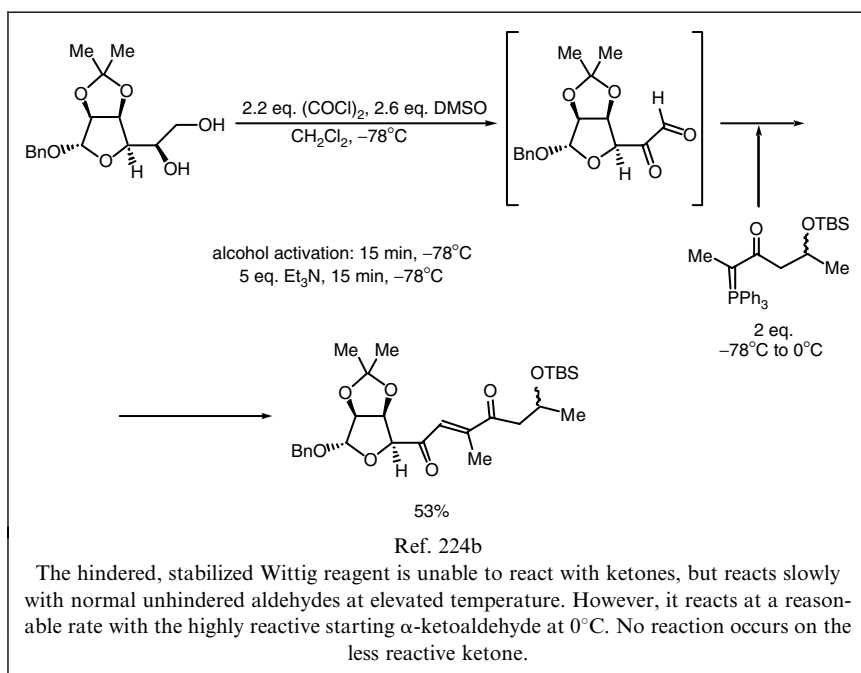
Swern oxidations produce the quite unreactive side compounds carbon monoxide, carbon dioxide, dimethyl sulfide and an amine hydrochloride. Therefore, it is very often possible to perform the *in situ* addition of a nucleophile to the aldehyde or ketone, resulting from the oxidation. This is particularly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



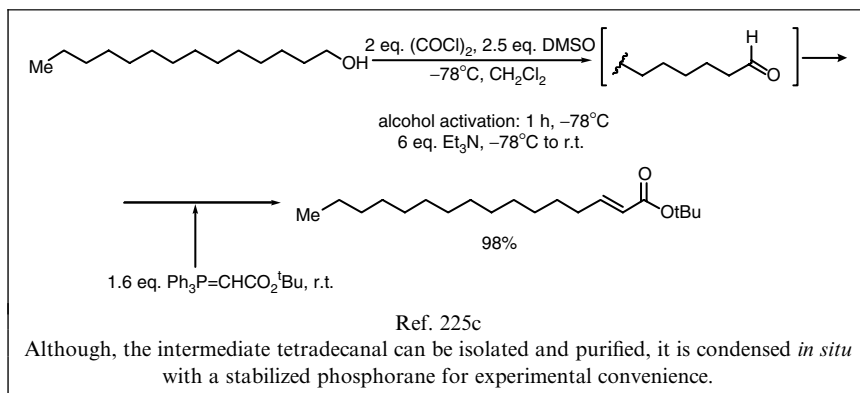
Ref. 223

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.

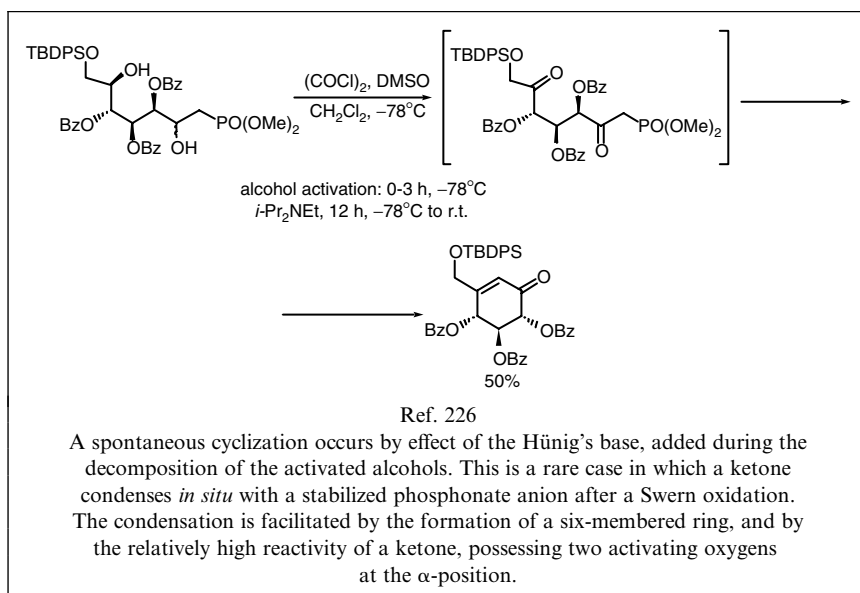
Particularly, the *in situ* condensation of highly reactive aldehydes—generated by Swern oxidation—with stabilized phosphoranes and phosphonate anions is finding ample use in organic synthesis.²²⁴ It must be mentioned that highly reactive aldehydes—for example α -ketoaldehydes, or aldehydes possessing 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.



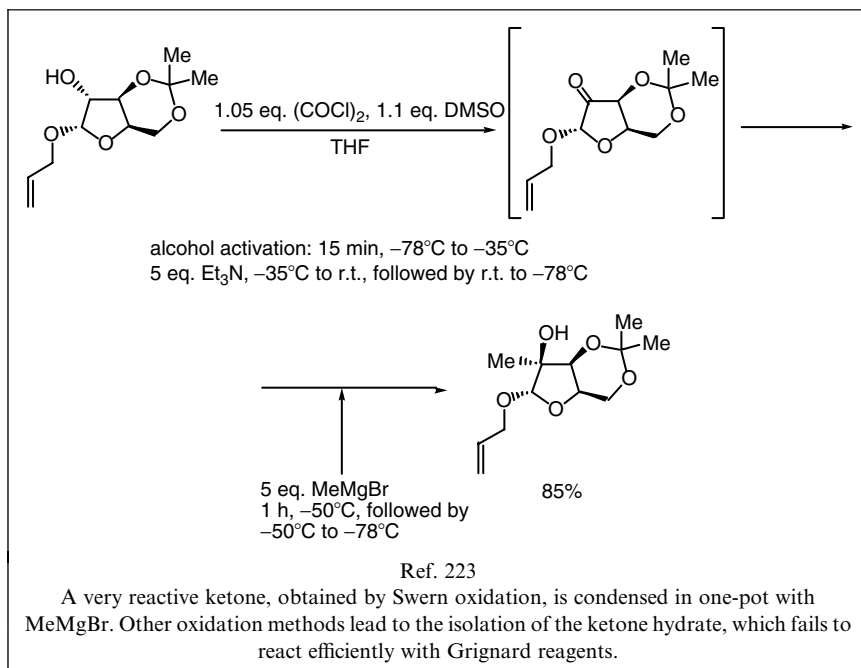
Although many aldehydes with lesser reactivity can be isolated and purified before condensation with phosphorous compounds, often an *in situ* condensation is performed for experimental convenience.²²⁵



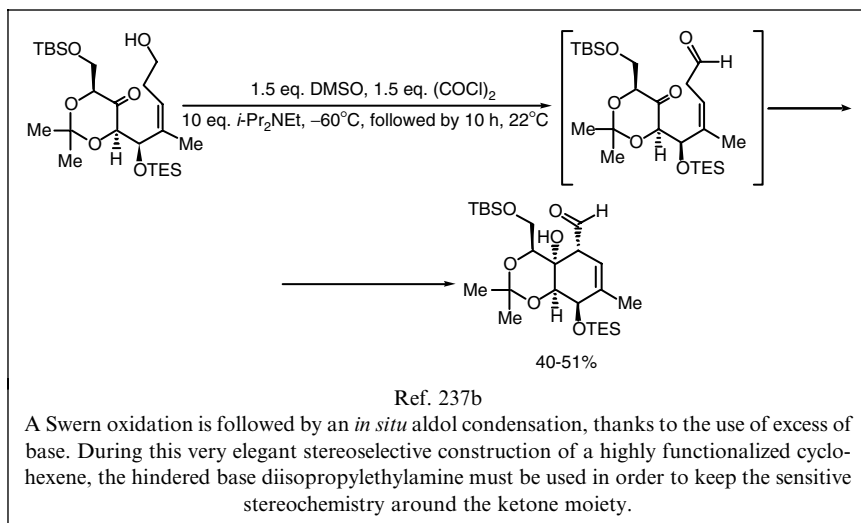
These *in situ* oxidations, followed by condensation with a phosphorous reagent, are normally not possible on ketones, because of their lack of reactivity with stabilized phosphoranes and phosphonate anions. Nevertheless, one-pot condensation with ketones can occur in very favourable cases.²²⁶



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



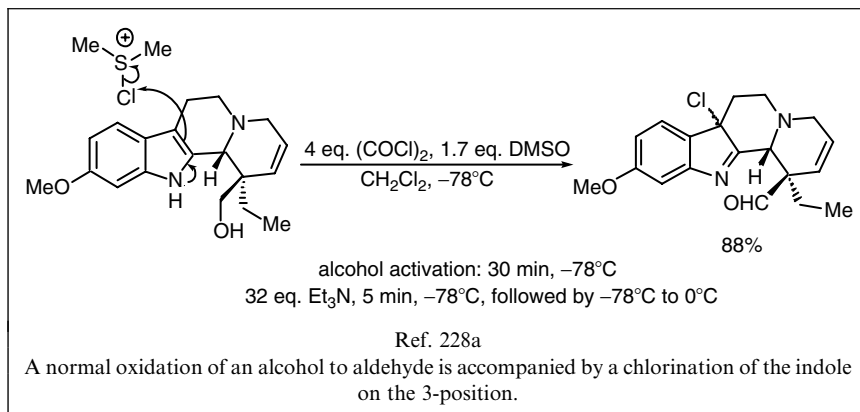
Aldehydes and ketones, obtained by Swern oxidation, may suffer *in situ* intramolecular aldol condensations, resulting in very elegant construction of cycles.^{237b}



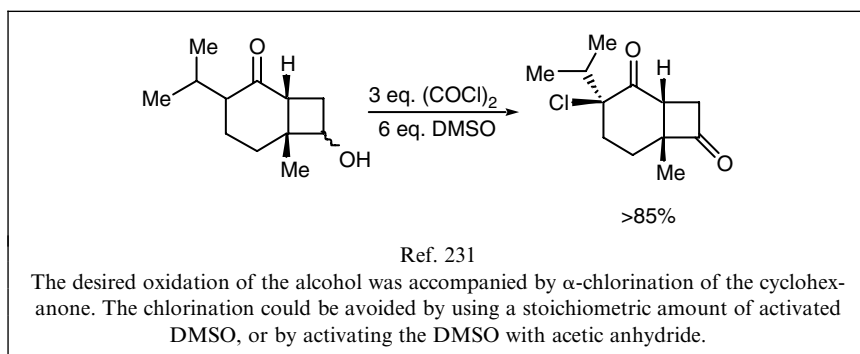
2.7.4. Side Reactions

2.7.4.1. Activated DMSO as Source of Electrophilic Chlorine

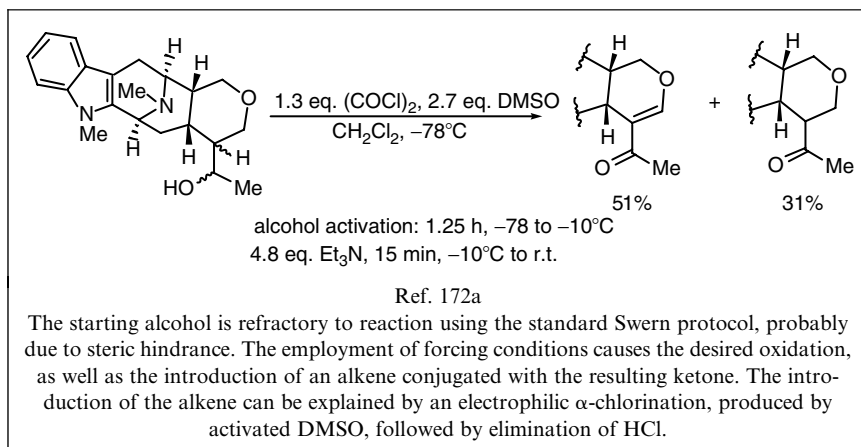
Nucleophilic sites in a molecule can be chlorinated by attack on the electrophilic chlorine atom, present in activated DMSO. Indoles are particularly prone to suffer this kind of chlorination on the 3-position.²²⁸



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

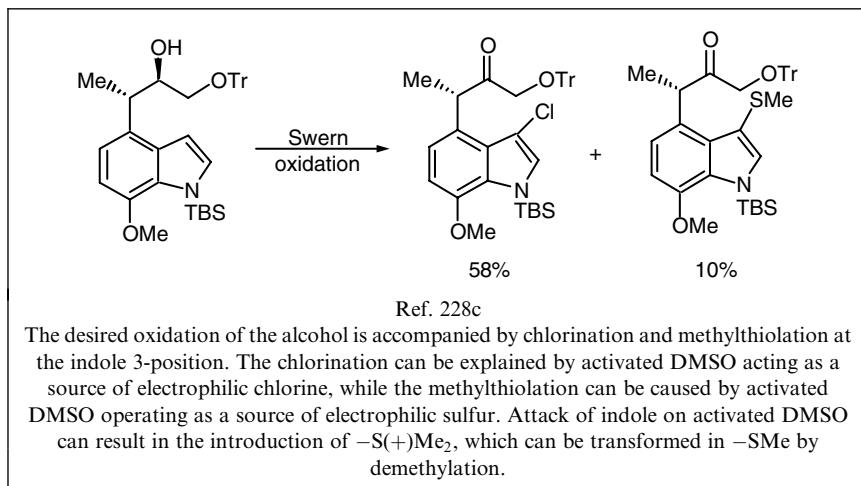


Sometimes, an alkene conjugated with a ketone is introduced during a Swern oxidation.^{172a,232} This can be explained by an α -chlorination followed by elimination of HCl .



2.7.4.2. Activated DMSO as Source of Electrophilic Sulfur

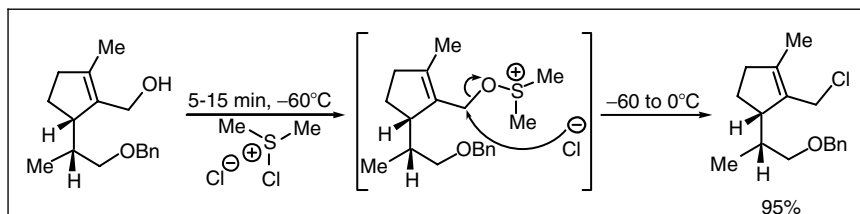
A methylthio group can be introduced in a nucleophilic site of a molecule by a reaction, in which activated DMSO can operate as a source of electrophilic sulfur.^{228c}



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

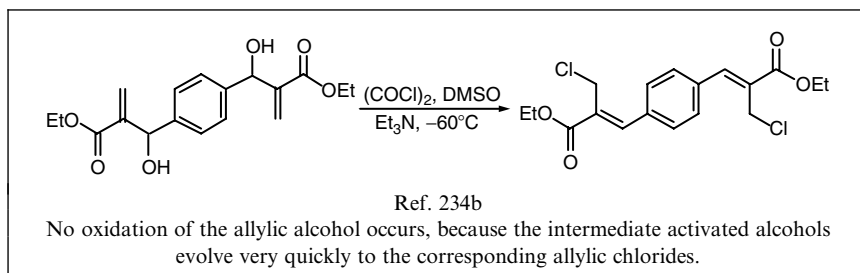
purposefully be brought about, by letting the activated alcohol to heat up with no base added.²³³



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

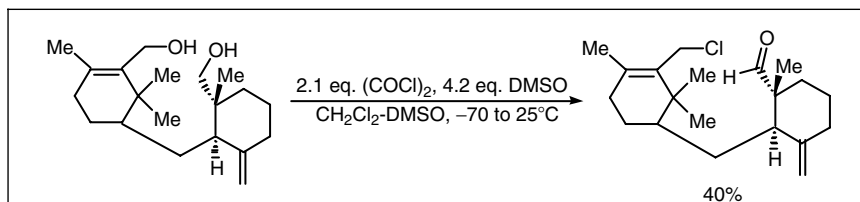


Ref. 234b

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

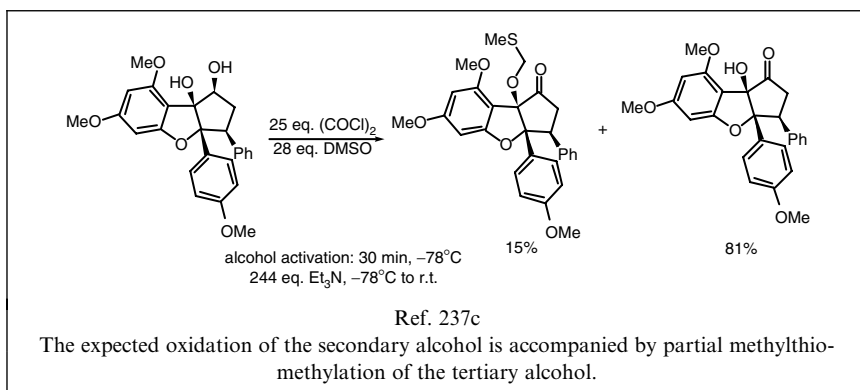


Ref. 236

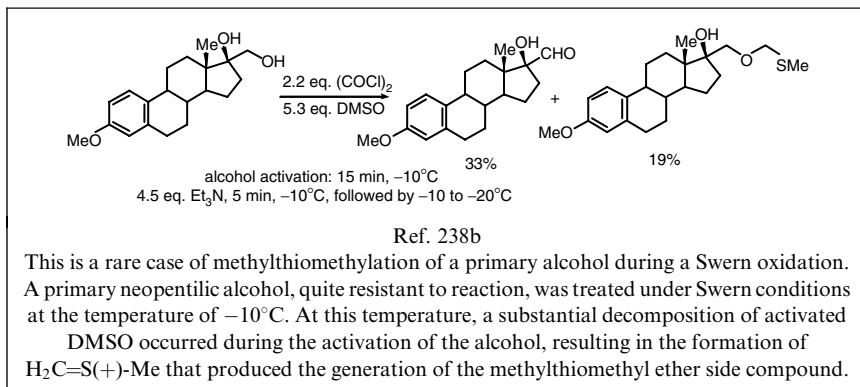
The use of moist DMSO causes the generation of adventitious HCl, that produces the transformation of the allylic alcohol into an allylic chloride. A properly performed Swern oxidation, under anhydrous conditions, allows the obtention of the desired dialdehyde in 95% yield.

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 $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$ (page 97). This species can react with tertiary alcohols present in the molecule, resulting in the formation of a methylthiomethyl ether.²³⁷



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 alcohols²³⁸ with $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$. 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 $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$ during a properly performed Swern oxidation.



2.7.4.5. Base-Induced Reactions

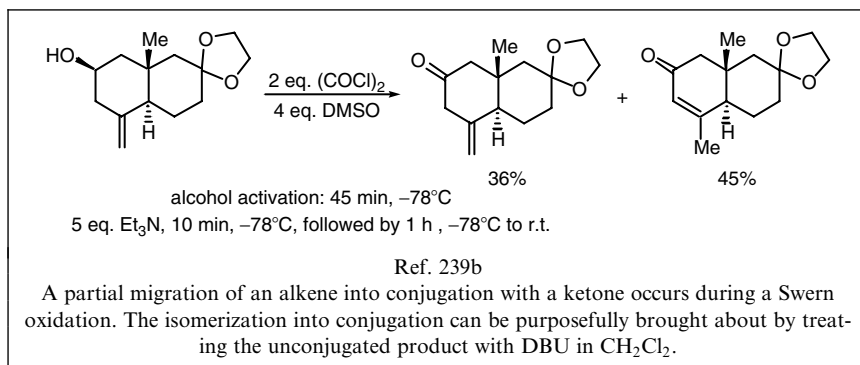
Addition of triethylamine to the activated alcohol, during a Swern oxidation, may produce side reactions, beginning with a deprotonation step. As triethylamine operates at very low temperature, only substrates very sensitive to deprotonation suffer these side reactions. No base-catalyzed hydrolyses are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

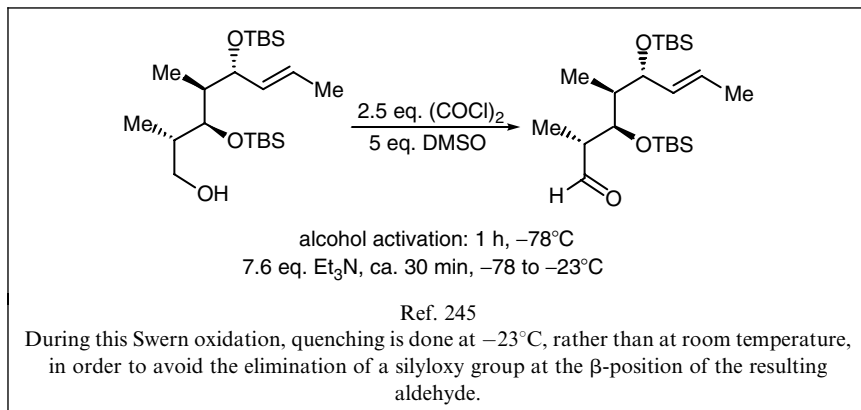
The Swern oxidation of homoallylic alcohols leads to a β,γ -unsaturated carbonyl compound, which sometimes suffers an *in situ* base-induced isomerization of the alkene into conjugation with the carbonyl group.²³⁹



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).

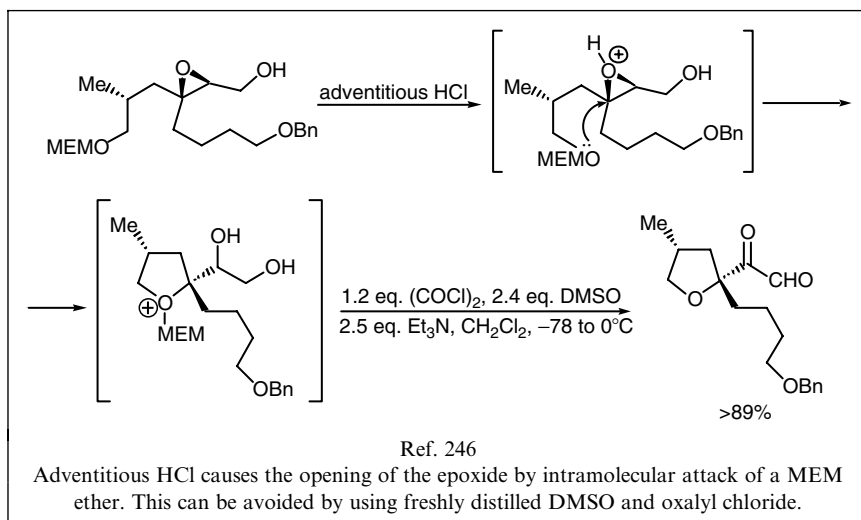
Sometimes, when a Swern oxidation produces a carbonyl compound possessing a good-leaving group at the β -position, an *in situ* elimination occurs, resulting in the generation of a conjugated enone or enal.

Aldehydes and ketones, possessing tertiary alcohols,²⁴¹ halides,^{209d} epoxides,^{242, 243} and sulfonates²⁴⁴ 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 quenching²⁴⁵ can help to avoid these eliminations.



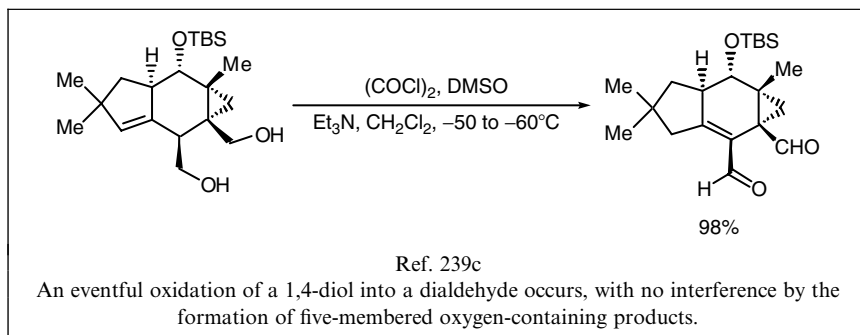
2.7.4.6. Acid-Induced Reactions

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}

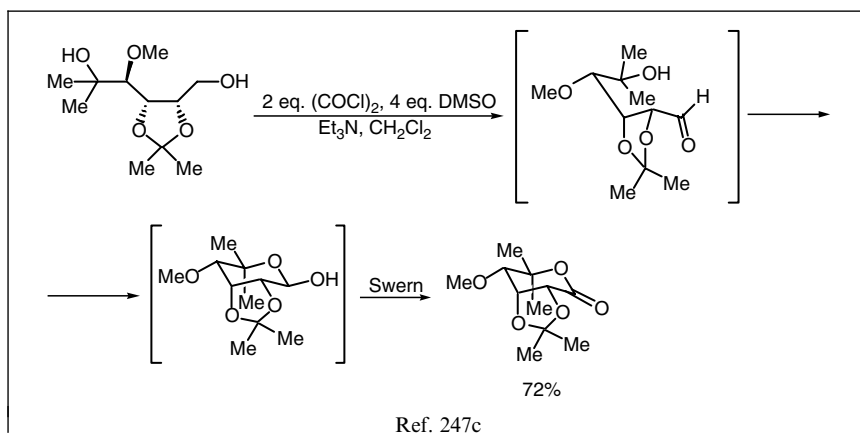


2.7.4.7. Formation of Lactones from Diols

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.



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



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.

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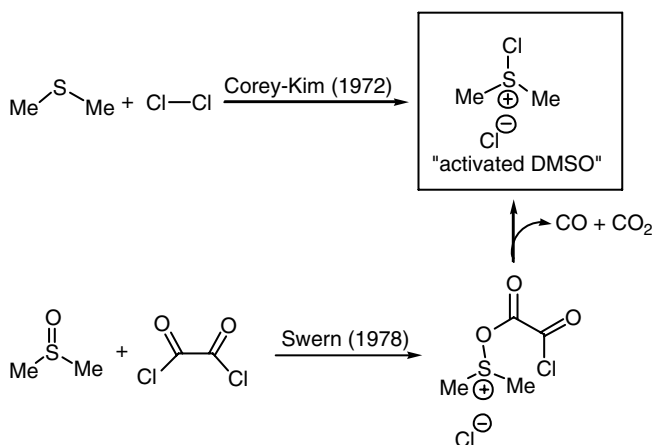
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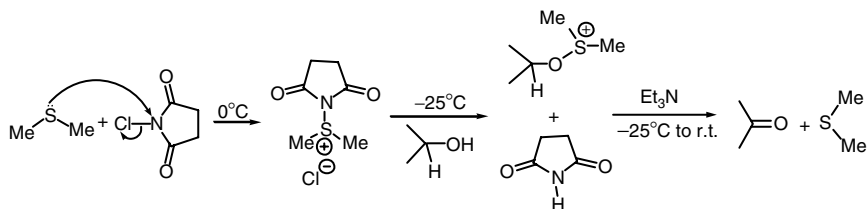
2.8. Corey–Kim Oxidation

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 1972²⁴⁸ that reaction of dimethyl sulfide with chlorine yields chlorodimethylsulfonium chloride, which is precisely the same species described later²⁴⁹ 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°C . Typically, NCS (*N*-chlorosuccinimide) and Me_2S are mixed in toluene at 0°C , resulting in the formation of a precipitate of activated DMSO. The reaction mixture is cooled to ca. -25°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 benzylic 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

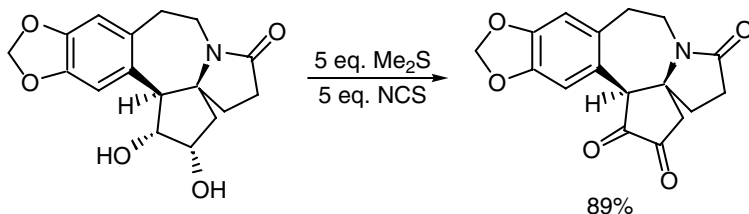
The Corey–Kim procedure is the oxidation method of choice for the transformation of β -hydroxycarbonyl compounds into 1,3-dicarbonyl compounds. Treatment of β -hydroxycarbonyl compounds under Corey–Kim conditions leads to an intermediate 1,3-dicarbonyl compound **33** that reacts *in situ* with activated 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



alcohol activation: 1.5 h, -25°C
1.8 eq. Et_3N , 10 min

Ref. 256

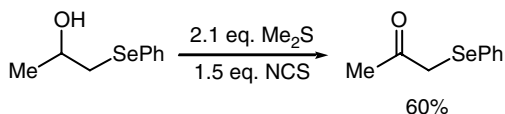
This difficult substrate can be oxidized under Corey–Kim conditions with 62% yield, while other methods such as PCC, PDC, Swern or Jones provide less than 27% yield.



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.



alcohol activation: 6 h, -20°C
1.5 eq. Et_3N , 5 min

Ref. 258

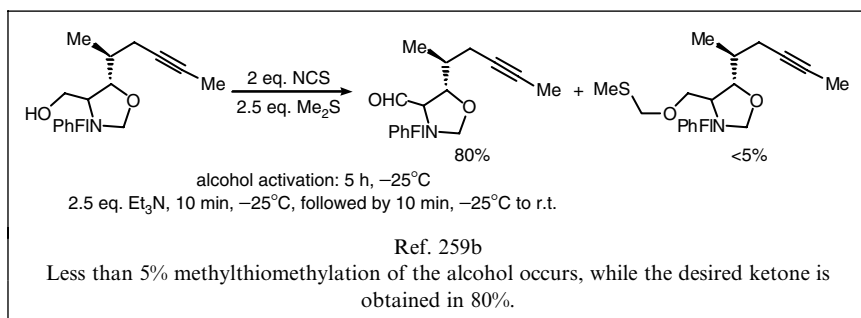
This oxidation on an apparently very simple substrate fails with PCC, PDC, DCC–DMSO and $(\text{F}_3\text{C-CO})_2\text{O}$ –DMSO, because of the high sensitivity of the selenium atom to suffer oxidation. On the other hand, a Corey–Kim oxidation delivers a 60% of the desired ketone.

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 $\text{H}_2\text{C}=\text{S}(+)\text{-Me}$, resulting from decomposition of activated DMSO.²⁵⁹



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 groups²⁶¹ are occasionally found.

Section 2.8. References

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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 ₂ O	Briefly mentioned by Albright ²⁶⁸ as an efficient substitute of Ac ₂ O
Methanesulfonic anhydride	Ms ₂ O	Briefly mentioned by Swern ²⁶⁹ and Albright, ²⁶⁸ it delivers from good to excellent yields at –20°C
<i>p</i> -Toluenesulfonic anhydride	Ts ₂ O	Briefly mentioned by Albright ²⁶⁸ who reports high yields at –20°C
Trifluoromethane sulfonic anhydride	Tf ₂ O	Briefly mentioned by Hendrickson and Schwartzman ²⁷⁰
Methyl chloroglyoxylate	CH ₃ OC(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°C
Diphosgene, trichloromethyl chloroformate	Cl ₃ COC(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	$(\text{Cl}_3\text{CO})_2\text{CO}$	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
<i>p</i> -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	$\text{Cl}_3\text{C}-\text{C}\equiv\text{N}$	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	$\text{Ph}_3\text{P}\cdot\text{Cl}_2$	Reported as an alternative to oxalyl chloride, providing from good to excellent yields at -78°C ²⁶⁶
Triphenylphosphine dibromide	$\text{Ph}_3\text{P}\cdot\text{Br}_2$	Reported as an alternative to oxalyl chloride with properties closely resembling $\text{Ph}_3\text{P}\cdot\text{Cl}_2$ 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	$\text{PhOP}(\text{O})\text{Cl}_2$	It provides from good to excellent yields in oxidations performed from -10°C to room temperature ²⁶⁷
Diphenyl chlorophosphate	$(\text{PhO})_2\text{P}(\text{O})\text{Cl}$	Briefly mentioned by Liu and Nyangulu ^{267a} as a less satisfactory activator than phenyl dichlorophosphate

Diethyl chlorophosphate	$(\text{EtO})_2\text{P}(\text{O})\text{Cl}$	Briefly mentioned by Liu and Nyangulu ^{267a} as a less satisfactory activator than phenyl dichlorophosphate
Ethoxyacetylene	$\text{EtO}-\text{C} \equiv \text{C}-\text{H}$	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.

Section 2.9. References

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