Metal-Mediated Oxidation of Tertiary Alcohols and Related Fragmentations

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Keywords: Tertiary alcohols / Oxidation / Fragmentation reactions / Metal salts / Acid catalysis / Basic catalysis / Reaction mechanisms

In contrast to the abundant literature available on the oxidation of primary and secondary alcohols, examples of oxidation of tertiary alcohols are rather rare and a general review on this topic does not exist. Therefore, this microreview will briefly describe the different existing methods, mainly metal-mediated, which consist of one or two-electron oxidations and usually lead to rearrangement, cyclization or fragmentation products. Some related data is also given for fragmentation reactions observed in basic or acid medium, or catalyzed by metal complexes without a real oxidation step.

Introduction

Primary and secondary alcohols can be easily oxidized, as exemplified by the abundant literature available on this subject.[1–6] In contrast, examples of tertiary alcohol oxidations are rather rare, and often related to a structural specificity of the substrate. In this review, we describe the different existing methods to oxidize tertiary alcohols. These reactions consist of one- or two-electron oxidation processes leading to rearrangement, cyclization or fragmentation products.

The first Part deals with 2-electron oxidations of tertiary alcohols and concerns transpositions, cyclizations and fragmentations by chromium(VI) oxides or vanadium(IV) complexes. The latter type of reaction leads to the formation of a ketone and a carbocation. The second Part is dedicated to one-electron oxidations observed with cerium(IV) and cobalt(III) derivatives. They result in fragmentation reactions yielding a ketone and a carbon radical. The third Part describes tertiary alcohols fragmentations in basic or acid

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Karine Wietzerbin was born in France in 1971, and studied chemistry at the "Ecole Nationale Supérieure de Chimie" in Montpellier. In 1995 she joined the group of Bernard Meunier at the "Laboratoire de Chimie de Coordination du CNRS" in Toulouse, where she studied the mechanism of the oxidation of tertiary alcohols catalyzed by metalloporphyrins. She received a PhD for this research work in 1998. She is currently working at Eurofins Scientific (Nantes, France), where she works on food analysis using isotopic techniques.

Jean Bernadou was born in Villefranche-de-Rouergue (France) in 1947, and studied Chemistry, Pharmacy (Doctorate in Pharmaceutical Sciences in 1975) and Medicine (Doctorate in 1985) at the University Paul Sabatier of Toulouse, where he was appointed Professor of Medicinal Chemistry in 1987. His collaboration with the group of Bernard Meunier started in 1980 with his research interests in the mechanism of the action of antitumor drugs. He is currently working on biological applications of metalloporphyrins, in particular, oxidative DNA cleavage, biomimetic oxidation of drugs and characterization of reactive metal-oxo intermediates.

Bernard Meunier was born in 1947 and educated at the Universities of Poitiers (B.Sc.), Montpellier (with R. J. P. Corriu) and Orsay (with H. Felkin, ICSN-CNRS). After a period of post-doctoral study at the University of Oxford, he joined the "Laboratoire de Chimie de Coordination du CNRS" in Toulouse in 1979. His current research interests include catalytic oxidations, oxidative DNA cleavage, oxidation of pollutants, and the mechanism of action of artemisinin derivatives. He is the author of more than 230 publications and patents.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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media or catalyzed by ruthenium(II) complexes, i.e. without the need of an external oxidant. These reactions cannot be considered as genuine oxidations but they help in understanding the reactivity of tertiary alcohols under diverse conditions. The three sections are summarized in Figure 1.

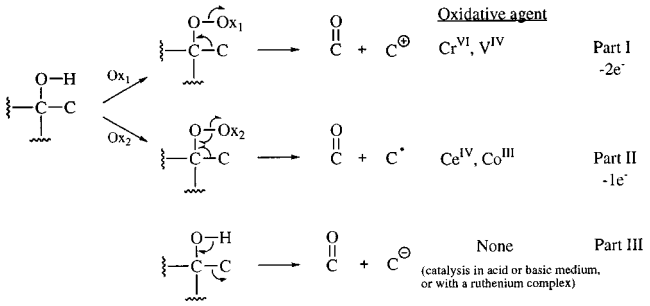


Figure 1. Modes of tertiary alcohol oxidations and fragmentations in non-oxidative media

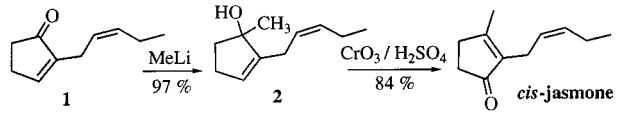
Finally, Part 4 is focused on oxidations with heme compounds. The complexity of these reactions does not allow us to classify them in one of the first three sections.

I. Two-Electron Oxidations

I.1. Oxidations Leading to Rearrangements

I.1.a. Allylic Alcohols

The ability to efficiently transpose a functional group from one carbon atom to another offers a wide degree of latitude in synthetic design of many naturally occurring compounds. For example, in 1972, the 1,3-alkylative carbonyl transposition of an α,β-unsaturated ketone *via* the oxidation of an intermediate tertiary allylic alcohol allowed Grieco[7] to prepare *cis*-jasmone (found in the essential oil of several varieties of *Jasminium*) with a reduced number of steps. The last steps of this synthesis are described in Scheme 1: The tertiary alcohol **2**, obtained by addition of methyllithium to dienone **1**, is oxidized to its transposed equivalent *cis*-jasmone using chromium trioxide in sulfuric acid (Jones reagent).[8]



Scheme 1. Last steps of formation of *cis*-jasmone

During the same period, other procedures were developed to convert tertiary allylic alcohols to α,β-unsaturated ketones. However, most of them are multi-step and indirect processes which include an initial rearrangement to a secondary alcohol, followed by oxidation to the ketone.[9,10] Moreover, the reagents used lead to a poor selectivity and low yields.

In 1976 and 1977, Babler and Coghlan,[11] and Dauben and Michno,[12] respectively, discovered a new method for 1,3-alkylative carbonyl transposition using pyridinium chlorochromate [$(ClCrO_3)^-PyH^+$] (PCC) as oxidant, which is less acidic than the Jones reagent and had been already used by Corey and Suggs[13] for oxidation of primary and secondary alcohols. The PCC oxidation of tertiary allylic alcohols (either cyclic or noncyclic), generated by 1,2-addition of organometallic reagents to α,β-unsaturated ketones, affords transposed 3-alkyl α,β-unsaturated ketones (Scheme 2). Several examples of such transpositions are reported in Table 1.[12]

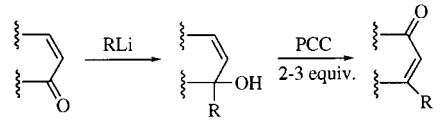
Table 1. Examples of 1,3-alkylative carbonyl transpositions by PCC (case of a starting α,β-unsaturated ketone)

Enone substrate	RLi	Allylic alcohol	Transposed enone	Yield (%)
	MeLi			94
	PhLi			90
	MeLi	 **3**	 **4**	88
	*n*BuLi	 **5**		50[a]
	PhLi	 **6**		51[b]

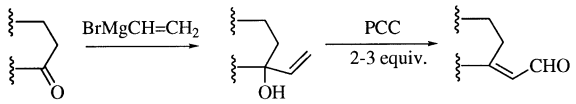
[a] 4:3 mixture of *E* and *Z* isomers, respectively. – [b] 4:1 mixture of *E* and *Z* isomers, respectively; in addition, 35% of acetophenone was also isolated.

With this method, oxidation of 1-methylcyclooct-2-en-1-ol (**3**) gives 3-methylcyclooct-2-en-1-one (**4**) in 88% yield, while the use of Jones reagent with the same compound gives a mixture of α,β- and β,γ-enones (4:3, respectively) in 48% yield. However, when the acyclic allylic alcohols **5** and **6** are oxidized, the yield is lowered due to the formation of side products generated by fragmentation reactions. For example, oxidation of 2-phenylbut-3-en-2-ol (**6**) affords acetophenone in 35% yield in addition to the transposed aldehyde.

When the initial ketone is not α,β-unsaturated, the unsaturation is conveniently introduced by reaction with an α,β-



Scheme 2. 1,3-Alkylative carbonyl transposition with PCC (case of a starting α,β-unsaturated ketone)

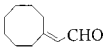
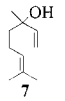
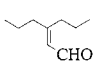


Scheme 3. 1,3-Carbonyl transposition with PCC (case of a starting saturated ketone)

unsaturated organometallic compound, e.g. vinylmagnesium bromide. Treatment of the corresponding allylic alcohol with PCC leads to an α,β-unsaturated aldehyde (Scheme 3). Such a process involves a two-carbon homologation of the starting ketone, and is equivalent to a directed aldol condensation between the latter compound and acetaldehyde. Furthermore, this is the first method described in the literature of a direct rearrangement of a tertiary allylic alcohol to an α,β-unsaturated aldehyde.

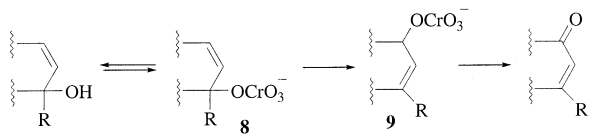
The results obtained by Dauben[12] and Babler[11] using this procedure are reported in Table 2. It is interesting to note that the 6,7-unsaturation of linalol **7** remains untouched during the oxidation process.

Table 2. Examples of 1,3-carbonyl transpositions with PCC (case of a starting saturated ketone)

Starting ketone	Allylic alcohol	Aldehyde formed	Selectivity (%)	Reference
			89	12
			83	12
			73	12
			90[a]	12
			85	11
	 **7**		80-86[a]	11 + 12
			87	11

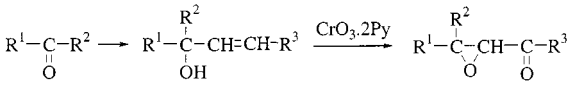
[a] 2:1 Mixture of *E* and *Z* isomers, respectively.

The mechanism proposed by Dauben and Michno[12] involves the oxidation of the substrate through its chromate ester **9**, which results from the rearrangement of the initial chromate ester **8** (Scheme 4).[12] This is consistent with the fact that formation of chromate esters from primary, secondary or tertiary alcohols is a very fast process.[14]



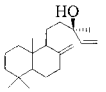
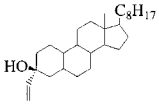
Scheme 4. Proposed mechanism for oxidation of tertiary allylic alcohols by PCC

Other chromium(VI)-oxo reagents were tested for the oxidative rearrangement of tertiary allylic alcohols and compared to PCC. Surprisingly, the use of Collins reagent ($CrO_3 \cdot 2Py$)[16] resulted in oxidative rearrangement to α-epoxy aldehydes or ketones (Scheme 5).[15]



Scheme 5. Tertiary allylic alcohol oxidation with Collins reagent

Table 3. Examples of oxidation of tertiary allylic alcohols with Collins reagent or PCC

Substrate	Oxidant	Epoxy-aldehyde[a] (% yield)	α,β-unsaturated aldehyde[b] (% yield)
			
	Collins	69	21
	PCC	–	98
			
	Collins	81	15
	PCC	–	98
			
	Collins	50	10
	PCC	–	80
			
	Collins	50	traces
	PCC	–	79
			
	Collins	70	traces
	PCC	–	72

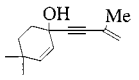
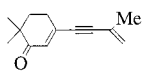
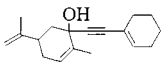
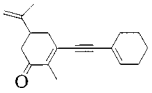
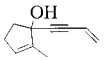
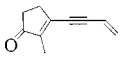
[a] 1:1 mixture of both epimers. – [b] 1:1 mixture of *E* and *Z* isomers.

The results of Table 3[15] show that for the same substrate, oxidation with Collins reagent yields mainly the α-epoxy aldehyde together with a small amount of the transposed α,β-unsaturated aldehyde, while the latter is the only product obtained with PCC as oxidant.

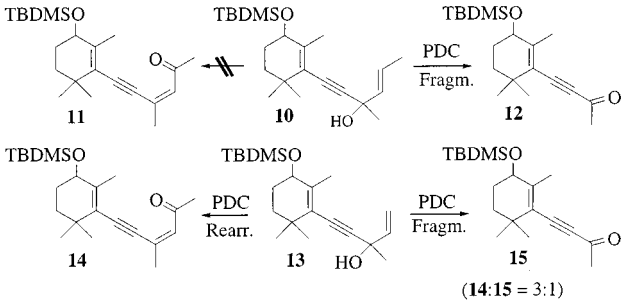
This interesting oxidative rearrangement with Collins reagent appears to be an excellent method for converting a ketone to the bis(homologous) epoxy aldehyde via a tertiary allylic alcohol.

Another chromium(VI)-amine oxidant, pyridinium dichromate [$(Cr_2O_7)^{2-}(PyH)_2^+$] (PDC),[17] was successfully used to oxidize various allylic acetylenic alcohols.[18] Prepared by addition of a lithium acetylide to an enone, the

Table 4. Examples of oxidation of enynols with PDC

Enynol substrate	Oxidation product	Yield (%)
		88
		78
		62
		90

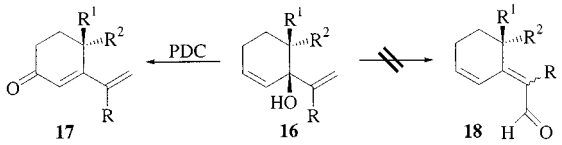
resulting enynols gave upon oxidation with PDC the transposed ketone with good to excellent yields (Table 4).[18] This PDC-induced oxidative rearrangement proceeded with complete regiospecificity since it occurred only at the olefinic site. The reaction seems to be more selective with *Z*-substituted enynols. Indeed, exposure of compound **10**, containing an *E*-double bond, to the action of PDC did not give the expected transposed product **11** (Scheme 6). Instead, ketone **12** was quantitatively produced. This product is probably the result of a vinyl hydrogen abstraction from **11**, followed by a carbon−carbon bond scission. PDC treatment of the demethylated alcohol **13** afforded a 3:1 mixture of the transposed product **14** and the fragmentation product **15**. These observations suggest that in situations where both *E*- and *Z*-vinyl hydrogen atoms are available, the rearrangement and fragmentation processes are competitive. This assumption is also consistent with the poor yields obtained by Dauben and Michno[12] for the PCC-induced oxidative rearrangement of allylic alcohols **5** and **6** (see Table 1), where the *E*-double bond could favor fragmentation reactions.



Scheme 6. Oxidation of compounds **10** and **13** with PDC

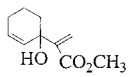
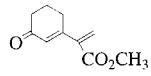
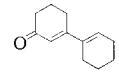
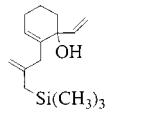
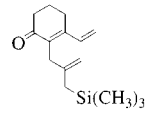
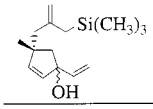
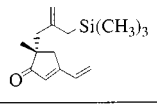
I.1.b. Bis(allylic) Alcohols

Pyridinium dichromate (PDC) was also used by Majetich et al. to oxidize dienols to dienones.[19] Their experiments established that the PDC-induced oxidative rearrangement of bis(allylic) tertiary alcohols such as **16** is regiospecific since the conjugated enone **17** is exclusively formed (Scheme 7). Several examples of these oxidations are reported in Table 5.[19]

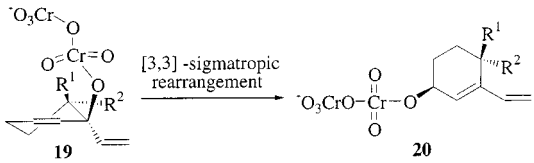


Scheme 7. Oxidation of bis-allylic alcohols with pyridinium dichromate

Table 5. Examples of oxidations of bis(allylic) tertiary alcohols with PDC

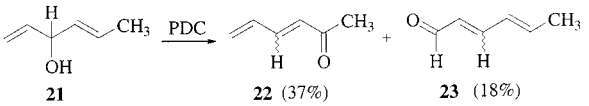
Substrate	Dienone formed	Yield (%)
		57
		62
		58
		57
		70

The regiospecificity of the [3,3]-sigmatropic rearrangement may be explained by examining the conformer **19** of the initially formed chromate ester (Scheme 8), where the Cr=O bond is above the rigid C=C double bond of the cyclohexene ring (while the exocyclic double bond is free to rotate). The rearrangement then affords the transposed chromate ester **20**, whose subsequent oxidation produces the corresponding enone.



Scheme 8. Rearrangement of the chromate ester **19** derived from **16**

This hypothesis has been supported by the oxidation of dienol **21**, in which both vinyl groups are free to rotate (Scheme 9). Treatment of **21** with PDC gave a 2:1 mixture of dienone **22** and dienal **23**, showing that the regiospecificity was lost.

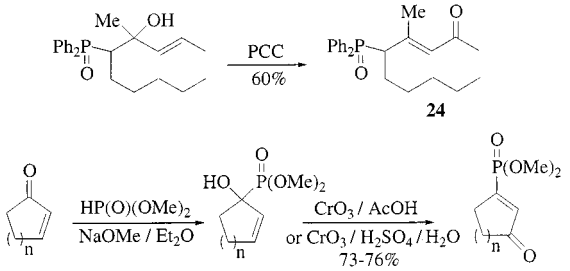


Scheme 9. Oxidation of hexan-1,4-dien-3-ol **21** with pyridinium dichromate

I.1.c. Allylic Alcohols Containing Heteroatoms

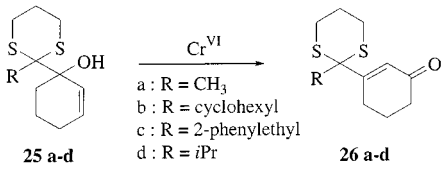
In order to extend the synthetic possibilities offered by these rearrangements, several authors attempted to use more complex substrates that would lead to attractive synthetic intermediates. They particularly focused on tertiary allylic alcohols containing heteroatoms.

Brown et al[20] and Öhler and Zbiral[21] showed that phosphorus-containing tertiary allylic alcohols could be efficiently oxidized with PCC or chromic acid (Scheme 10).[20,21]

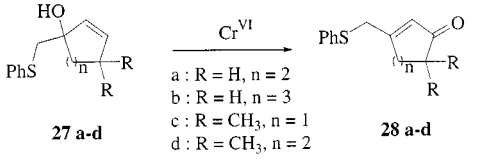


Scheme 10. Oxidations of phosphorus-containing tertiary allylic alcohols (n = 1 or 2)

Since the oxidation of sulfides to sulfoxides and sulfones with oxochromium(VI)-amine reagents is slower than the oxidation of alcohols to carbonyl compounds under the same conditions, Luzzio and Moore[22] examined the oxidative rearrangement of tertiary allylic alcohols bearing a dithianyl protecting group (general structure **25**, Scheme 11) or a (phenylthio)methyl substituent (general structure **27**, Scheme 12). This work was the continuation of early studies realized by Corey and Crouse,[23] who reported in 1968 the oxidative transposition of compounds such as **25**.



Scheme 11. Oxidation of tertiary allylic alcohols bearing a dithianyl substituent



Scheme 12. Oxidation of tertiary allylic alcohols bearing a (phenylthio)methyl substituent

In order to achieve optimal conversion, compounds **25d** and **27a** have been oxidized with different oxochromium(VI) reagents: Jones reagent, PCC, PDC, Collins reagent and 2,2′-bipyridinium chlorochromate (BPCC). The results reported in Table 6[22] established that the efficiency of conversion follows the order PCC > PDC > Collins > BPCC. The Jones reagent, which is less selective and more acidic than the oxochromium(VI)-amine complexes, led only to decomposition products.

Table 6. Oxidation of **25d** and **27a** with a series of oxochromium(VI)-amine reagents

Oxidant		Conversion (%)	
		25d	**27a**
$(ClCrO_3)^-PyH^+$	PCC	53	74
$(Cr_2O_7)^{2-}(PyH)^+$	PDC	31	62
 $ClCrO_3^-$	BPCC	<1	13
$CrO_3.2Py$	Collins	37	37

Yields could be improved by adding silica gel to the reaction medium in order to absorb the reduced chromium tars. Table 7[22] indicates the results obtained for oxidation of compounds **25a−d** to **26a−d** and of **27a−d** to **28a−d** with PCC in the presence of silica gel.

Table 7. Oxidation of **25a−d** and **27a−d** with PCC

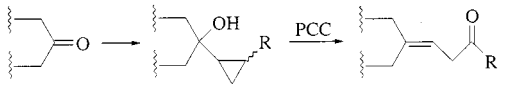
Substrate	Product	Yield(%)
25a	**26a**	28
25b	**26b**	56
25c	**26c**	62
25d	**26d**	74
27a	**28a**	75
27b	**28b**	82
27c	**28c**	83
27d	**28d**	92

In the case of the dithiane series (compounds **25a−d**), it appears that the yield increases with increasing steric hindrance of the R substituent. A possible explanation could be that as R becomes more bulky, the binding of the dithiane moiety to the unchanged reagent or reduced chromium species is disfavored, and the yields are thus increased. The ability of the dithiane moiety to bind the reduced chromium species may also explain why better yields are obtained with the (phenylthio)methyl series.

I.1.d. α-Cyclopropyl Alcohols

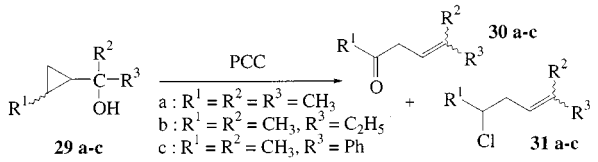
Like allylic tertiary alcohols, 2-alkylcyclopropyl carbinols are able to undergo PCC-oxidative rearrangement to give the corresponding β,γ-unsaturated ketones. The overall process is a synthetically useful method of effecting 1,4-carbonyl transposition (Scheme 13).[24] Moreover, when the tertiary alcohols used as substrates are prepared by addition of cyclopropyl organometallic reagents to ketones (as in Scheme 13), the oxidative rearrangement is also an excellent

method for converting ketones to the tris(homologous) β,γ-enones.



Scheme 13. 1,4-carbonyl transposition with PCC

The PCC-induced oxidation of tertiary 2-alkylcyclopropyl carbinols of general structure **29** (Scheme 14) yields the expected β,γ-enones **30** but also the chloro olefins **31** (48% and 15% for **30a** and **31a**, respectively). This result indicates that both the desired oxidation and the nucleophilic attack by the chloride ion take place at the homoallylic carbon atom.



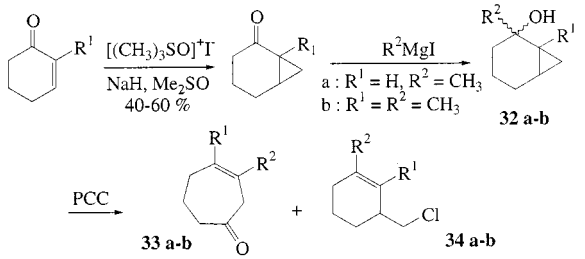
Scheme 14. Oxidation of alcohols **29a−c** with PCC

However, when the chloride ligand of the chromium complex is replaced by a tetrafluoroborate, only the desired β,γ-enone is obtained (50% for **30a**). Additionally, the use of a small amount of water together with PCC not only improved the yield of **30**, but also considerably reduced the formation of **31**. The yields obtained under these conditions are reported in Table 8.[24]

Table 8. Results of the oxidation of **29a−c** and **32a−b** with PCC in the presence of water

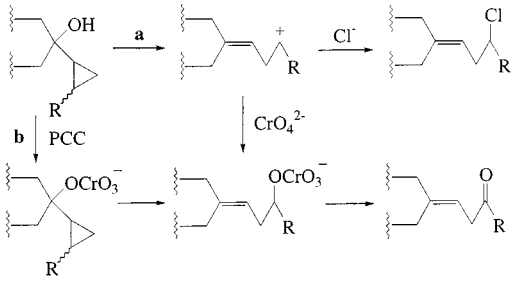
Substrate	β,γ-Enone	Yield (%)	Other products (yield, %)
29a	**30a**	60	**31a** (5)
29b	**30b**	62	**31b** (3)
29c	**30c**	57	**31c** (3)
32a	**33a**	28	**34a** (10)
32b	**33b**	30	**34b** (6)

The availability of tertiary cyclopropyl carbinols via cyclopropanation of cyclic α,β-enones followed by organometallic addition enables 1,4-carbonyl transpositions on starting ketones that already contain a cyclopropyl moiety to be performed, as depicted in Scheme 15. However, in such a process, yields are lower than above, probably because of the steric hindrance developed in these systems (Table 8, substrates **32a** and **b**).



Scheme 15. 1,4-Carbonyl transposition on α-cyclopropyl ketones

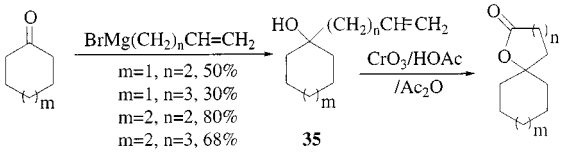
Two mechanisms have been proposed by the authors for the oxidative rearrangement of α-cyclopropyl alcohols (Scheme 16).[24] Path **a** involves a prior solvolysis of the tertiary alcohol to give a homoallylic carbocation, which then collapses in the presence of a nucleophilic species such as chloride to give a chloro olefin, or the chromate ion to give a chromate ester and then the β,γ-enone. Path **b** requires chromate ester formation prior to the rearrangement. However, path **a** appears to be more favorable for the present oxidative rearrangement since it explains the formation of chlorinated compounds.



Scheme 16. Mechanism proposed for the oxidation of 2-alkylcyclopropyl carbinols with PCC

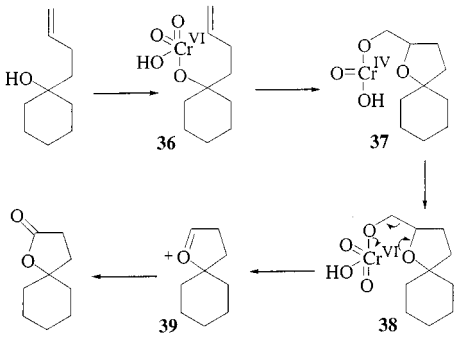
I.2. Oxidations Leading to Cyclizations

Some γ- and δ-unsaturated tertiary alcohols are able to undergo oxidative cyclizations. Treatment of tertiary alcohols of general structure **35** with the Fieser reagent CrO_3/AcOH/acetic anhydride easily gives lactones with the loss of one carbon atom (Scheme 17).[25]



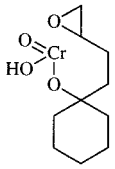
Scheme 17. Oxidative cyclization of γ- and δ-unsaturated tertiary alcohols with the Fieser reagent

The role played by the hydroxy group during the process appeared to be essential (when replaced by a methoxy or an acetoxy group, no reaction was observed). Additionally, oxidation of simple alkenes such as 1-dodecene gives only a mixture of the starting product with epoxides and acids. In an attempt to explain the cyclization process, Schlecht and Kim[25] proposed the mechanism depicted in Scheme 18. It involves the formation of the chromate ester **36**, followed by intramolecular oxidation of the double bond, which leads to the chromium(IV) ester **37**. The latter is then reoxidized to **38** by excess reagent. The oxidative fragmentation of **38** produces **39**, and then the lactone with another equivalent of oxidant.

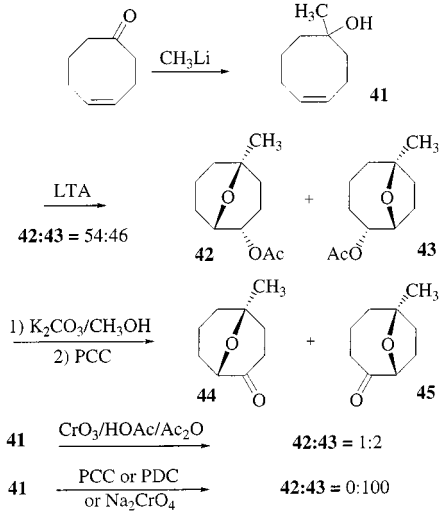


Scheme 18. Mechanism proposed for the oxidative cyclization of γ- and δ-unsaturated tertiary alcohols with the Fieser reagent

However, an alternative pathway for the transformation of **36** to **37** could proceed through the epoxy intermediate **40**, the opening of which would lead to **37**.



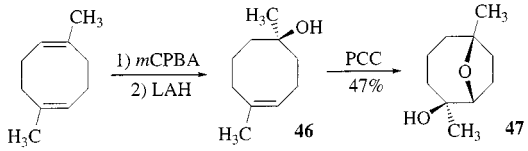
When cycloalkenols are used as the substrate, the oxidative cyclization becomes a transannular oxidative cyclization and gives β-functionalized bicyclic ethers.[26] This method is particularly convenient for preparing the oxygen-bridged bicyclic skeleton which appears in a number of biologically active natural products. Schlecht and Kim[27] observed that the oxidation of 1-methylcyclooct-4-en-1-ol (prepared from cyclooct-4-en-1-one) with lead tetraacetate (LTA) provides both acetates **42** and **43** in a ratio of 54:46, which are then converted into oxo ethers **44** and **45** by hydrolysis and oxidation (Scheme 19).



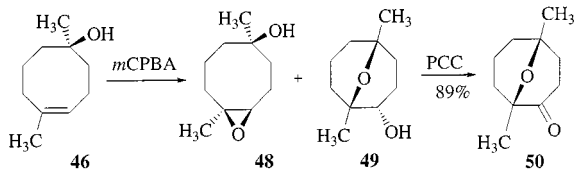
Scheme 19. Transannular cyclization of tertiary cycloalkenol

The nature of the oxidant has a great influence on the regioselectivity of the reaction since the use of the Fieser reagent instead of LTA leads to the same oxo ethers in a 1:2 ratio, while treatment with PCC, sodium chromate or PDC produces only oxo ether **45**. The cyclization process is also catalyzed by acids: the reaction rate is inhibited by addition of sodium acetate but increased in the presence of acetic acid. Additionally, no reaction occurs with the Collins reagent. These observations suggest that two different mechanisms operate depending on the nature of the oxidant. One possible mechanism involves an intermediate epoxide which undergoes internal opening by attack of the hydroxy group on one of the two carbon atoms to form two cyclic β-hydroxy ethers, subsequently oxidized to **44** and **45**. However, this mechanism does not explain the observed regioselectivity with chromium(VI) reagents. Treatment of **41** with *m*CPBA yields both the *cis*-epoxy alcohol, and a 3:2 mixture ratio of two β-hydroxy ethers corresponding to the hydrolysis products of **42** and **43** (and probably derived from the *trans*-epoxy alcohol). With either PCC or the Fieser reagent, these β-hydroxy ethers are converted into **44** and **45**, while the *cis*-epoxide gives only a complicated mixture of products under the same conditions. Consequently, the involvement of an epoxide in the course of oxidation with PCC, PDC or Na_2CrO_4 can be ruled out since it does not explain the observed regioselectivity. It seems more reasonable to postulate the formation of a chromate ester of the hydroxy group, which would be acid-catalyzed, followed by an intramolecular attack on the double bond by the tethered chromate ester moiety. In the oxidation with LTA, which occurs without selectivity, epoxide opening is likely to be involved in the mechanism. In the case of the Fieser reagent, which is a stronger oxidant than PCC, PDC and Na_2CrO_4, a contribution of both mechanisms is a reasonable assumption.

In order to obtain further information about the reaction mechanism, Schlecht and Kim studied the transannular oxidative cyclization of cyclooctenol **46**, where the methyl substituent on position 5 does not permit the further oxidation to the carbonyl, thus allowing the authors to follow the stereochemistry of the reaction.[28] The oxidation of **46** with PCC provides the β-hydroxy cyclic ether **47** exclusively (Scheme 20). The cyclization process is then not only regiospecific but also stereospecific.



Scheme 20. PCC-induced oxidative cyclization of cyclooctenol **46**



Scheme 21. Oxidation of **46** with *m*CPBA followed by PCC

As in the previous case, the action of *m*CPBA on compound **46** gives the *cis* hydroxy epoxide **48** and the cyclic

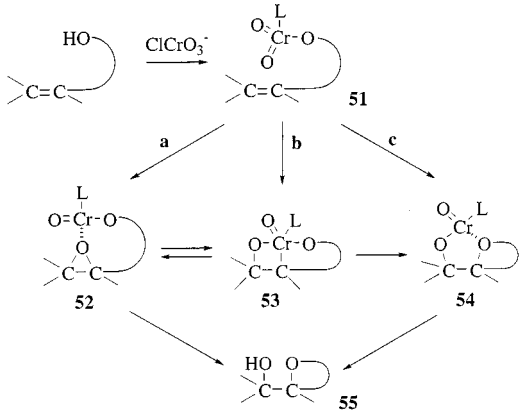
endo-β-hydroxy ether **49**, whose oxidation with PCC yields **50** (Scheme 21).

These observations are in accordance with the involvement of a chromate ester rather than an epoxide in the reaction pathway. On the basis of the *syn* configuration of the resulting product, Schlecht[28] proposed three possible mechanistic pathways after the initial step of chromate ester formation (Scheme 22):

− Pathway **a**: formation of an epoxide by an intramolecular attack of the tethered oxidant (**51** → **52** → **55** or **51** → **52** → **53** → **54** → **55**);

− Pathway **b**: formation of a metalloxetane (**51** → **53** → **54** → **55** or **51** → **53** → **52** → **55**);

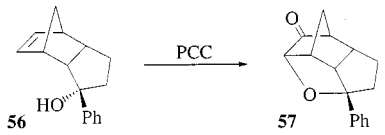
− Pathway **c**: [3+2] cycloaddition and fragmentation (**51** → **54** → **55**).



Scheme 22. Mechanism proposed for the transannular oxidative cyclization of tertiary cycloalkenols; L = Cl, O

However, the failure to convert the epoxide **52** into cyclization products upon treatment with PCC appears to rule out pathway **a** as the mechanism for the transannular oxidative cyclization.

Working with more complex substrates, where the tertiary hydroxy group was positioned in a conformationally fixed orientation with respect to the alkene group, Waddell et al.[29] obtained results which parallel those reported by Schlecht, since PCC treatment of compound **56** leads to the β-oxo ether **57** in 70% yield (Scheme 23). The process is a transannular cyclization similar to the one described by Schlecht, which probably follows the same mechanism.



Scheme 23. Oxidative cyclization of **56** with PCC

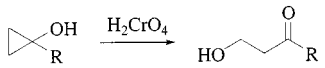
However, the strained double bond of **56** might be more reactive toward PCC than the same group in **46**. Therefore, considering a possible intermolecular attack of the double bond by the oxidant, the dicyclopentadiene was submitted to the action of PCC under the same conditions. The products proved to be only α-chloro ketones obtained in 25% yield. Consequently, the intermolecular mechanism is unlikely, and the pathway demonstrated by Schlecht may also explain the transformation of **56** to **57**.

I.3. Oxidations Leading to Fragmentations

I.3.a. Fragmentations with Chromium Oxides

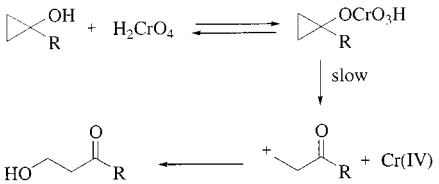
One of the first oxidative tertiary alcohol fragmentations described in the literature was reported by Barbier and Locquin in 1913.[30] They observed at that time the formation of carboxylic acids R−COOH and acetone while heating in sulfuric acid alcohols of general structure $R-CH_2-C(CH_3)_2OH$ in the presence of chromic acid. However, the reaction mechanism has been shown to involve prior dehydration of the alcohol, so that the products were in fact the result of oxidation of the intermediate olefin. This was demonstrated by Sager in 1955 by conducting kinetic studies during the oxidation of 3-ethylpentan-3-ol with chromic acid.[31]

The first example of a direct oxidation of a tertiary alcohol with chromic acid was reported by Rocek and Radkowsky in 1968.[32] They studied the oxidation of 1-methylcyclobutyl alcohol, a compound which is very reluctant to undergo dehydration[33] and whose large ring strain should favor fragmentation reactions. Although they did not identify the oxidation products, they performed kinetic measurements which revealed a first order dependence on the chromic acid concentration, thus excluding any prior dehydration. Further investigations then showed that chromic acid-induced oxidation of tertiary cyclopropanols provided β-hydroxylated ketones through ring opening (Scheme 24).[34]



Scheme 24. Oxidation of tertiary cyclopropanols with chromic acid

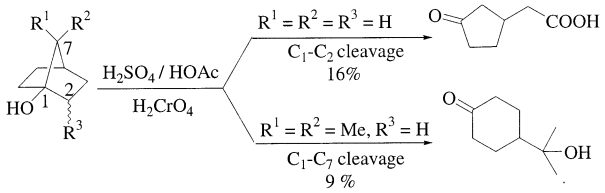
For example, 1-phenylcyclopropanol is oxidized with 43% conversion and 73% selectivity to 3-hydroxy-1-phenylpropan-1-one. Tertiary cyclopropanols are even more reactive than the corresponding secondary cyclopropanols, and the reactivity is greatly increased by alkyl substitution on the ring. This is consistent with the mechanism depicted in Scheme 25,[34] where the rate-limiting step is the formation of a carbocation by oxidative decomposition of a chromate ester of the alcohol. The reaction is then accelerated by substituents stabilizing the incipient carbocation.



Scheme 25. Reaction pathway for oxidation of tertiary cyclopropanols with chromic acid

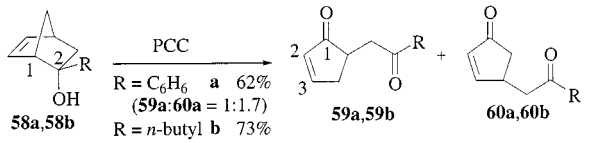
Although their conversion is low, Cawley and Spaziano showed that norbornanol derivatives are able to undergo

oxidation in a same way.[35] The C−C bond cleavage occurs on C^1-C^2 or C^1-C^7 bonds, depending on the nature of the substituents. Two kinds of product are thus obtained (Scheme 26).



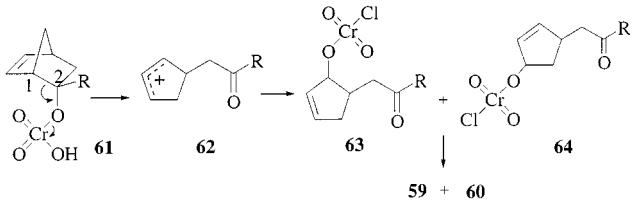
Scheme 26. Oxidation of norbornanol derivatives with chromic acid

In the same series, norbornenols of structure **58** are easily oxidized with PCC to two isomeric cyclopentenones **59** and **60** resulting from C^1-C^2 bond cleavage, the latter being the main product (Scheme 27).[29]



Scheme 27. Oxidation of **58** with PCC

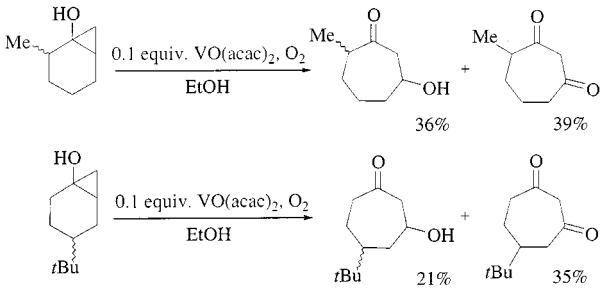
It is interesting to note that an oxidative cyclization (see section I.2) would have been reasonable given the *endo* position of the hydroxy group, but the expected highly strained 5-oxo-2,6-oxetane is not formed. The oxetane is neither a reaction intermediate, since if it were, the $O-C^2$ bond would break to give products not observed in the present case. Interestingly, PCC-induced oxidation of the *exo* isomer of **58a** leads to the same fragmentation products **59a** and **60a**. Consequently, an intramolecular oxidation of the double bond can be ruled out. The mechanism assumed for the transformation is illustrated in Scheme 28,[29] and parallels that proposed by Rocek et al.[34] in Scheme 25. It requires the formation of a chromate ester **61**, which suffers fragmentation to give the allylic carbocation **62**. Capture of **62** by a chromate species gives two new chromate esters **63** and **64**, and subsequent elimination leads to the 4- and 5-substituted cyclopentenones. It is noteworthy that this mechanism also explains the observed product ratio since **62** is not symmetric and the capture of the chromate moiety at the least hindered positive center gives **64** and the 4-substituted isomer **60** as the major product.



Scheme 28. Mechanism proposed for oxidation of **58** with PCC

I.3.b. Fragmentations with Vanadium Oxides

Bicyclic cyclopropanols undergo oxidation in the presence of catalytic amounts of vanadyl acetylacetonate $VO(acac)_2$ under oxygen to afford ring-enlarged β-hydroxy ketones and β-diketones.[36] Two examples of such reactions are represented in Scheme 29. β-Diketones are not obtained by the reaction of β-hydroxy ketones with $VO(acac)_2$, suggesting that β-diketones originate directly from the cyclopropanol systems.



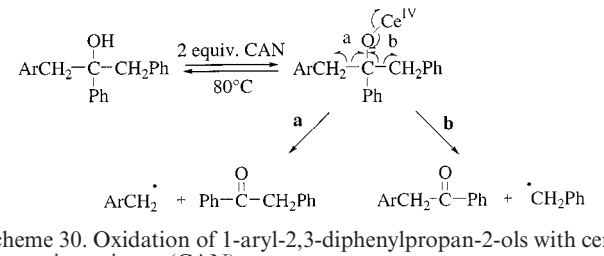
Scheme 29. Oxidation of bicyclic cyclopropanols catalyzed by vanadyl acetylacetonate

Molecular oxygen acts as the co-oxidant and reoxidizes the low valent vanadium compound formed. Nevertheless, it is possible to perform the reaction under a nitrogen atmosphere using stoichiometric amounts of $VO(acac)_2$. Although the absence of inhibition with a radical trap suggests that a radical pathway is not involved, the precise reaction mechanism is still unknown.

II. One-Electron Oxidations

II.1. Oxidative Cleavages with Ceric Ammonium Nitrate (CAN)

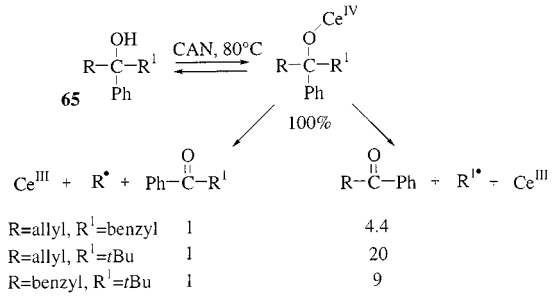
Oxidations of tertiary alcohols using ceric ammonium nitrate (CAN) as oxidant produce fragmentation products. The experiments carried out by Trahanovsky et al. on 1-aryl-2,3-diphenylpropan-2-ols showed that, in the presence of CAN, two competitive cleavages occur, producing two different ketones. The use of radical scavengers revealed the presence of aryl and benzyl radicals.[37] Therefore, the reaction likely proceeds through an intermediate $R-O-Ce^{IV}$ complex, whose homolytic cleavage affords the oxidation products (Scheme 30).



Scheme 30. Oxidation of 1-aryl-2,3-diphenylpropan-2-ols with ceric ammonium nitrate (CAN)

In order to determine whether the fragmentation regioselectivity depends on the stability of the released radicals, Trahanovsky and Macaulay investigated the oxidation of tertiary alcohols of general structure **65**, where R and R′

are allyl, *tert*-butyl or benzyl groups.[38] The relative ratios of the resulting ketones are given in Scheme 31.

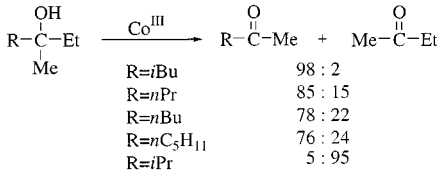


Scheme 31. Relative ratio of the ketones obtained from oxidation of **65** with CAN

It appeared that even though *tert*-butyl radical is less stable than allyl and benzyl radicals,[39] its formation was preferred. Thus, the stability of the released radicals is not the only factor controlling the selectivity of the reaction. The authors suggested that steric (release of the steric strain) or conformational factors (preventing vinyl or phenyl groups from stabilizing the incipient radicals) might play an important role during the reaction.

II.2. Cleavages with Cobalt Salts

Similarly to Ce^{IV}, Co^{III} is able to oxidize tertiary alcohols to form a ketone and a radical. Hoare and William examined the oxidation of a series of substituted tertiary alcohols in the presence of cobalt(III) perchlorate.[40,41] The results obtained and the relative ratio of the resulting ketones are indicated in Scheme 32.



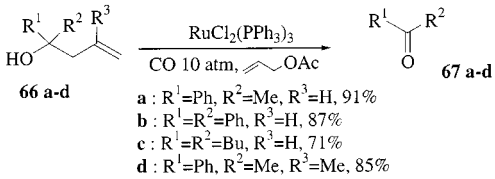
Scheme 32. Relative ratio of ketones resulting from the oxidation of alkylethylmethylcarbinols with Co^{III}

Evidence is given that the ease of elimination of the alkyl radicals increases according to the order: $Me^{\bullet} < RCH_2CH_2^{\bullet} < Et^{\bullet} < iPr^{\bullet}$. Therefore, it seems that for these simple tertiary alcohols, the fragmentation regioselectivity depends on the stability of the released radicals.

III. Fragmentations in Non-Oxidative Media

III.1. Fragmentations with Ruthenium Complexes

The selective cleavage of tertiary homoallylic alcohols has been recently investigated by Kondo et al.[42] They showed that treatment of such alcohols with allyl acetate in the presence of a ruthenium complex $[RuCl_2(PPh_3)_3]$ caused a β-allyl elimination to generate the corresponding ketone

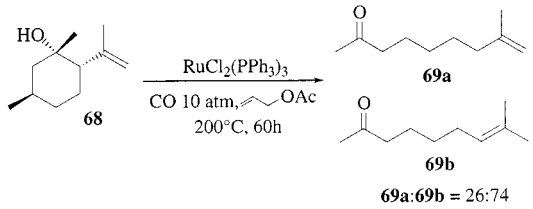


Scheme 33. Catalytic fragmentation of tertiary homoallylic alcohols with $RuCl_2(PPh_3)_3$

(Scheme 33). Thus, 2-phenylpent-4-en-2-ol (**66a**) is converted into acetophenone in 91% yield. In a same way, other derivatives bearing alkyl or aryl groups (**66b−d**) undergo a deallylation to afford various ketones **67b−d**.

Several ruthenium complexes such as $Ru_3(CO)_{12}$ or *cis*-$RuCl_2(CO)_2(PPh_3)_2$ were examined with regard to their ability to catalyze the deallylation of **66a** to **67a**. All of them show catalytic activity, and among them $RuCl_2(PPh_3)_3$ is the most efficient. In contrast, among the other transition metals examined (Pt, Pd, Ni, Rh), only the rhodium complex $[RhCl(PPh_3)_3]$ shows moderate catalytic activity (45% conversion for the deallylation of **66a** to **67a**).

A synthetic application of this procedure is illustrated in the following ring opening reaction of cyclic homoallylic alcohols (Scheme 34). Treatment of **68** with $RuCl_2(PPh_3)_3$ affords the unsaturated ketones **69a−b** in 76% yield. This catalytic system thus represents an efficient and convenient method to perform catalytic ring-opening reactions on general 2-vinylcycloalkanols.

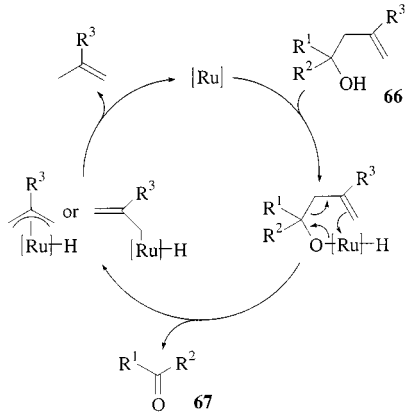


Scheme 34. Ring-opening reaction catalyzed by $RuCl_2(PPh_3)_3$

The following observations provide insight into the mechanism: (i) The treatment of a **66a** derivative bearing an acetoxy instead of the hydroxy group does not lead to **67a**. This result indicates that the first step of the reaction is the oxidative addition of a hydroxy group of **66a** to ruthenium; (ii) treatment of the saturated analogue of **66a**, i.e. 2-phenylpentan-2-ol, does not afford **67a** through propyl elimination. This suggests that the driving force of the reaction is the formation of an allylruthenium species; (iii) treatment of the secondary allylic alcohol 1-phenylbut-3-en-1-ol, which bears both a hydrogen atom and an allyl group at the β-position, yields the α,β-unsaturated ketone (1-phenylbut-2-en-1-one) from hydrogen β-elimination and not benzaldehyde from allyl elimination.

Considering all of these observations, Kondo et al. propose the mechanism depicted in Scheme 35.[42] The initial step might consist of oxidative addition of the hydroxy group of **66** to an active ruthenium center. Subsequent β-allyl elimination from the alkoxyruthenium intermediate

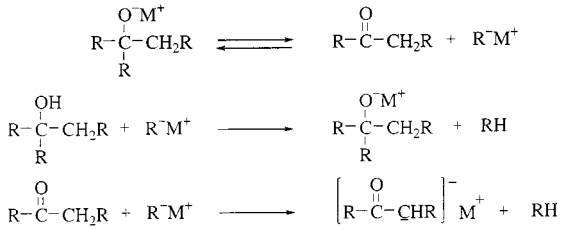
gives ketone **67** together with a (allyl)(hydrido)ruthenium species, which undergo a reductive elimination to give $R_3(CH_3)C{=}CH_2$.



Scheme 35. Proposed mechanism for the fragmentation of tertiary homoallylic alcohols with $RuCl_2(PPh_3)_3$

III.2. Alkoxide Fragmentations

Tertiary alcohols are easily cleaved in their alkoxide forms, obtained for example in the presence of metallic potassium, lithium hydride or sodium amide. At high temperatures, their oxidative fragmentation produces a ketone with elimination of a carbanion. The latter then captures a hydrogen atom from either the excess alcohol or the resulting ketone when it is an enol. The whole process is described in Scheme 36.



Scheme 36. Fragmentation of tertiary alcohols under the alkoxide form (M = metal)

In 1959, Zook et al. applied this procedure on various tertiary alcohols. The results are summarized in Table 9.[43] The experiments show that the ease of cleavage increases with the branching in the substituent R. For example, triisopropyl carbinol required a temperature of 300 °C to be cleaved to diisopropyl ketone, while 200 °C is sufficient to cleave *tert*-butyl diisopropyl carbinol, and triethyl carbinol cannot be cleaved at 335 °C (experiments 5, 6 and 8). Therefore, it seems that steric strain favors the fragmentation reaction.

Experiments 1, 2 and 3 (Table 9) carried out on diisopropylalkyl carbinols demonstrate that the ease of cleavage of primary alkyl substituents increases with increasing bulkiness of the group, the order being *n*-propyl < isobutyl < neopentyl. Additionally, primary alkyl substituents are more readily eliminated than the isopropyl group, since no trace of alkyl isopropyl ketone was detected. Phenyl and *tert*-butyl are likewise eliminated preferentially to isopropyl (experiments 4 and 5).

The nature of the metallic cation also plays an important role. The results of the experiments performed on *tert*-butyl diisopropyl carbinol showed that the temperature required for the cleavage depends on the cation used (Table 10).[43] The order of ease of cleavage is Li < Na < K, which corresponds to the order of decreasing electronegativities. This is explained by the fact that as the electronegativity of the metal decreases, the negative charge developed on the anion becomes greater and the alkoxide is then more reactive.

Table 10. Influence of the cation on the fragmentation of $(iPr)_2tBu$-COH

Cation	Temp.(°C)	Products (%)		
		$iPr_2tBuCOH$	iPr_2CO	$iPrCOtBu$
K	160−182	0	60	35
Na	199−215	7	52	32
Li	213−320	24	35	25

Other authors used milder conditions compared to those used by Zook et al.[44−46] For example, using potassium dimesylate $[(CH_3SOCH_2)^-K^+]$ in DMSO is a convenient way to readily cleave tertiary alcohols at room temperature. Thus, in addition to the metallic cation, the solvent chosen also has an influence on the reaction.

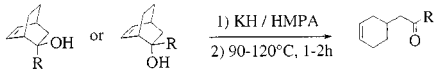
Snowden et al. have studied alkoxide cleavages, particularly with bis- and tris(homoallylic) alkoxides.[47,48] It is noteworthy that allylic homoallylic alkoxides undergo oxy-Cope rearrangement rather than fragmentation under the same conditions.[48] The authors also examined more com-

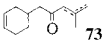
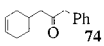
Table 9. Examples of cleavage of sodium alkoxides $R_1R_2R_3CO^-Na^+$

Exp.	Substrate			Temp.(°C)	Products (%)				
	R^1	R^2	R^3		$R^1R^2R^3COH$	R^1COR^2	R^3H	R^1COR^3	R^2H
1	*i*Pr	*i*Pr	*n*Pr	266−392	30	19	58	0	0
2	*i*Pr	*i*Pr	*i*Bu	264−362	53	37	38	0	0
3	*i*Pr	*i*Pr	*neo*P	222−240	26	35	36	0	0
4	*i*Pr	*i*Pr	Ph	242−276	13	72	70	3	3
5	*i*Pr	*i*Pr	*t*Bu	199−215	7	52	31	32	23
6	*i*Pr	*i*Pr	*i*Pr	300−312	21	20	24	−	−
7	Ph	Ph	Ph	280−320	51	23	31	−	−
8	Et	Et	Et	335	No cleavage				

plex bicyclic substrates. Thus, 2-substituted bicyclo[2.2.2]-oct-5-en-2-ols can be cleaved by heating the alkoxides at 120 °C.[49] The results obtained with such alcohols are summarized in Table 11.[49]

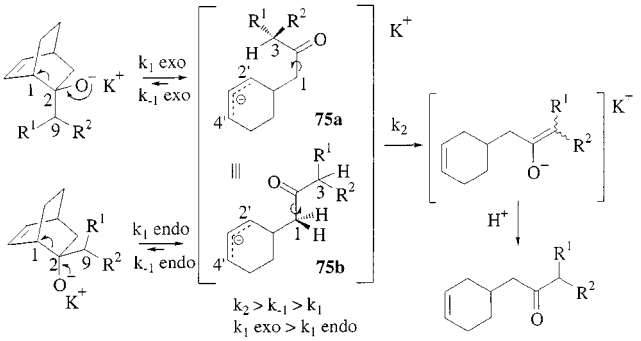
Table 11. Examples of bicyclo[2.2.2]oct-5-en-2-ols fragmentations



Exp.	Substrate	Cyclohexene formed	Yield (%)	Other products (Yield, %)
1		**70** 	68	
2		**70**	52	
3			70	
4		 **71**	67	
5		**71**	51	
6		 **72** α-β:β-γ = 1:4	74	
7		**72**	<10	 + PhOH (65) 3:1
8		 **73** α-β:β-γ = 1:4	76	
9		**73**	<10	 + PhOH (61) 3:1
10		 **74**	54	
11		**74**	<5	 + PhOH (70) 3:1

Experiments 1 to 5, in which substituents are saturated alkyl groups, demonstrate that epimeric alcohols give the same product, i.e. 1-(cyclohex-3′-enyl)alkan-2-one resulting from C^1-C^2 bond cleavage (in each case only 10% of the 2′-enyl isomer is formed). However, the *exo*-alkoxide reacts noticeably faster than its *endo* epimer. On the other hand, no epimerization of the substrate is observed during the reaction. These results are consistent with a reaction mechanism in which the rate determining step is the heterolytic cleavage of the allylic C^1-C^2 bond to form a transient allylic anion which is then irreversibly quenched by intramolecular capture of a proton on C^3 adjacent to the carbonyl group. The resulting enolate subsequently affords the ketone by external protonation (Scheme 37).[49]

The high regioselectivity with respect to the position of the cyclohexenyl double bond may be rationalized by the strong preference for intramolecular proton transfer from the C^3-position to the $C^{2'}$-position of the allylic anion (rather than the $C^{4'}$-position) via a six-membered transition state (see conformation **75a**, Scheme 36). Additionally, an intermolecular protonation would not be expected to be regioselective. The observed rate difference between the *exo*- and *endo*-epimeric alkoxides is possibly the result of stabilization of the C^1-C^2 bond in the *endo*-alkoxide by electron donation from the O-anion to the cyclic double bond.



Scheme 37. Mechanism proposed for the cleavage of bicyclo[2.2.2]-oct-5-en-2-ols in the presence of potassium hydride

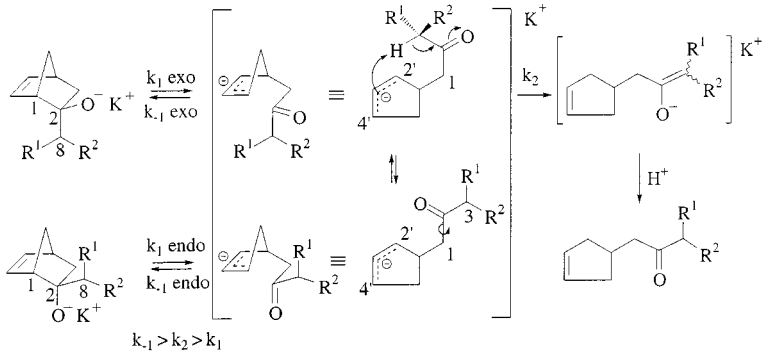
Experiments 6−11 (Table 11) were performed on substrates bearing an unsaturated C^2-substituent. In contrast with 2-alkyl-substituted alkoxides, the reaction products from these epimeric alkoxides are dependent on the substrate stereochemistry: The *exo*-alkoxides afford (4:1)-mixtures of β,γ- and α,β-unsaturated ketones via C^1-C^2 bond cleavage while the *endo*-alkoxides yield mostly the ketone resulting from C^2-C^9 bond cleavage. This marked difference between the epimeric alkoxides may be due to a strengthening of the C^1-C^2 bond in the *endo*-alkoxide caused by selective electron donation from the O-anion to the structurally rigid, cyclic double bond. In the *exo*-alkoxide, the C^2-C^9 bond may be stabilized by a similar electron donation from the O-anion to the double bond of the C^2-substituent.

Alkoxides derived from C^2-substituted norbornenols react similarly to the above compounds, producing 1-(cyclopent-3′-enyl)alkan-2-ones resulting from C^1-C^2 bond cleavage.[50] Nevertheless, an important epimerization of the substrate is observed during the reaction, suggesting that the rate determining step is the intramolecular protonation step which follows reversible C^1-C^2 bond cleavage to give the allylic anion (Scheme 38).[50]

When the substituents are unsaturated, the selectivity with regard to the cyclopentenyl double bond is decreased, indicating that an intermolecular protonation by reaction with the substrate also occurs. This is consistent with the reversibility of the first step which ensures an appreciable concentration of alkoxide during the reaction.

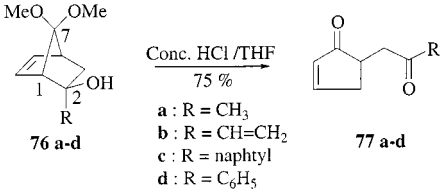
III.3. Fragmentations in Acidic Media

Norbornenols are able to undergo fragmentation, not only under basic conditions as described above, but also in acidic media. Thus, Palani et al. showed that several 7,7-dimethoxynorbornenols derivatives afford the corresponding substituted cyclopentenones through C^1-C^2 bond



Scheme 38. Mechanism proposed for the cleavage of norbornenols in the presence of potassium hydride

cleavage upon treatment with hydrochloric acid in THF (Scheme 39).[51]



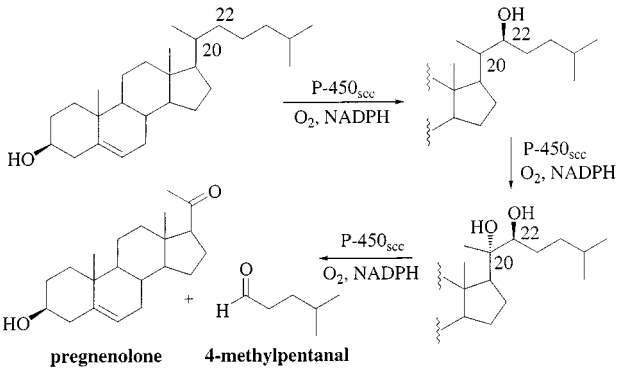
Scheme 39. Fragmentation of 7,7-dimethoxynorbornenols in acidic media

The behavior of compounds **76b** and **76c** is in remarkable contrast to that observed in basic media, since in the presence of sodium hydride the oxy Cope rearrangement products are obtained.[52] The use of hydrochloric acid is then an interesting option when the fragmentation process competes with the oxy Cope rearrangement under basic conditions.

IV. Oxidations Catalyzed by Heme-Containing Systems

IV.1. Catalysis with Cytochrome P-450

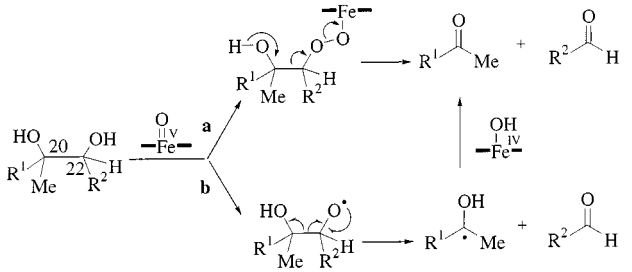
Cytochromes P-450 belong to the monooxygenase family and are able to catalyze several oxidation reactions in the presence of molecular oxygen and NADPH. Among them, alkane hydroxylations and alkene epoxidations have been widely studied.[53,54] Some of these heme-enzymes play an important role in steroids biosynthesis by catalyzing two or three successive oxidation steps, where the last one can be



Scheme 40. Cholesterol side chain cleavage catalyzed by P-450 scc/O_2/NADPH

C−C bond cleavage. These cleavages sometimes occur at carbon atoms bearing a tertiary alcohol functionality. For example, P-450$_{scc}$ (cholesterol **s**ide **c**hain **c**leavage P-450) catalyses the side chain degradation of cholesterol via two hydroxylations at C^{20} and C^{22}, followed by an oxidative cleavage of the $C^{20}-C^{22}$ bond. The whole process leads to the formation of pregnenolone and 4-methylpentanal (Scheme 40).[54−56]

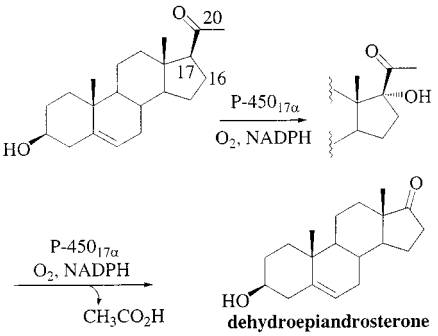
Although the first two steps are classical, the last one, where the enzyme acts as a lyase, is more original and interesting from a mechanistic point of view. The proposed mechanism is represented in Scheme 41. The active species of the catalyst is a high valent oxo-iron complex Fe=O. In the first hypothesis, the reaction pathway proceeds through the addition of the hydroxy group at C^{22} to the activated oxygen atom to form an iron-peroxo species. Deprotonation of the adjacent hydroxy group then induces the C−C bond cleavage (Scheme 41, path **a**). However, this hypothesis requires the formation of a peroxo complex with a poorly stable O−O bond, which is a thermodynamically unfavorable process. A second hypothesis involves the formation of an alkoxyl radical resulting from the abstraction of a proton and an electron at one of the hydroxy groups by the oxo-iron species. The subsequent β-fragmentation affords the oxidation products (Scheme 41, path **b**).[55,56]



Scheme 41. Mechanism of the side chain cleavage of cholesterol by P-450$_{scc}$

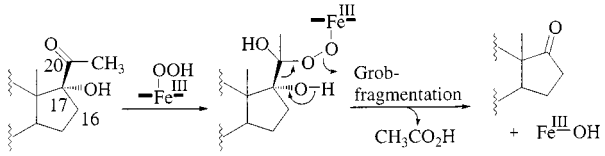
Another type of cytochrome P-450, 17α-hydroxylase-17,20-lyase or P-450$_{17\alpha}$, catalyses the pregnenolone deacetylation to form mainly dehydroepiandrosterone via an intermediate tertiary alcohol (Scheme 42).

This peculiar reaction has been widely studied by Akhtar et al.[57−59] Labeling experiments performed with $^{18}O_2$ and deuterium led to the proposal of a reaction mechanism for



Scheme 42. Deacetylation of pregnenolone by P-450$_{17\alpha}$

the last step, which is depicted in Scheme 43. Its originality lies in the nature of the active species of the catalyst, which is a Fe^{III}-hydroperoxo species. After its addition to the carbonyl group, the $C^{17}-C^{20}$ bond breaks according to a Grob-type fragmentation, releasing acetic acid. The results of the labeling experiments are in accordance with this mechanism: when hydroxypregnenolone bears a trideuteriated methyl at position 21 and reaction is performed under $^{18}O_2$, the acetic acid produced contains three deuteriums and one ^{18}O atom, whereas no labelled oxygen is incorporated into dehydroepiandrosterone.

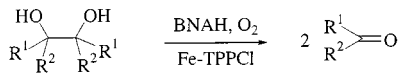


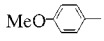
Scheme 43. Mechanism of the oxidation of hydroxypregnenolone with P-450$_{17\alpha}$

IV.2. Catalysis by Synthetic Metalloporphyrins

Synthetic metalloporphyrins are excellent biomimetic oxidation catalysts mimicking cytochrome P-450. They have been widely studied for hydroxylation and epoxidation reactions,[60] but only very few examples of tertiary alcohol oxidation have been reported in the literature up to now.

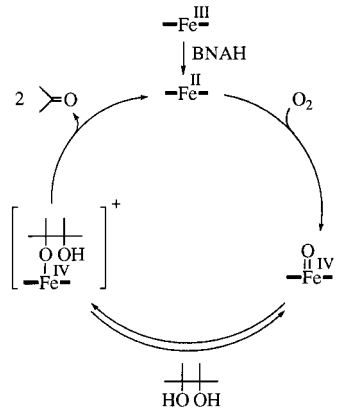
One of them concerns the oxidation of ditertiary 1,2-diols catalyzed by an iron porphyrin in the presence of molecular oxygen and 1-benzyl-3-carbamoyl-1,4-dihydropyridine (BNAH, which acts as the reducer).[61] The reaction simulates the final step of the side chain cleavage of cholesterol catalyzed by P-450$_{scc}$ (vide supra). The products formed are two ketones resulting from the cleavage of dihydroxylated C−C bond (Scheme 44).



R^1	R^2	Conv (%)	Yield (%)
	CH_3	100	95
	CH_3	100	86
		80	48
		95	91

Scheme 44. Examples of fragmentations of ditertiary 1,2-diols with the system (TPP)FeCl/BNAH/O_2

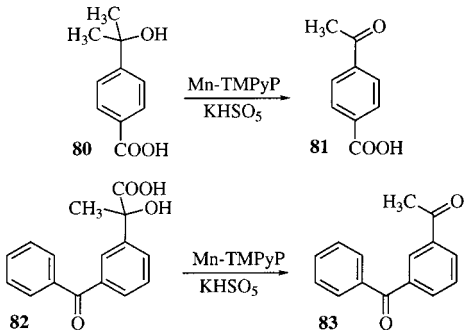
Kinetic studies enabled the authors to propose a reaction mechanism (Scheme 45) in which the active species $Fe^{IV}=O$ reacts reversibly with the diol to form a Fe^{IV}-alkoxo complex before the fragmentation. This mechanism represents an alternative to the one proposed with P-450$_{scc}$ in Scheme 41.



Scheme 45. Mechanism of the oxidation of ditertiary 1,2-diols with the system Fe−TPPCl/BNAH/O_2

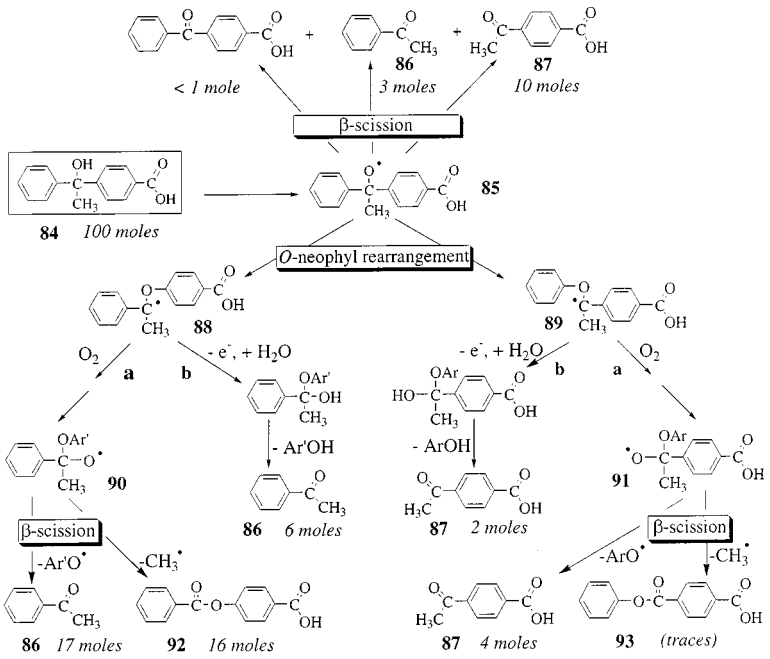
The fragmentation of ditertiary 1,2-diols can also be performed photocatalytically in the presence of a water soluble iron porphyrin and dioxygen.[62]

Recently, a catalytic system able to oxidize tertiary alcohols has been developed in our laboratory.[63] It consists of a water soluble manganese porphyrin (Mn−TMPyP) together with an oxygen atom donor, potassium monopersulfate ($KHSO_5$). The latter avoids the use of a reductant to form the active species of the catalyst. The tertiary alcohols used as substrates are the compounds **80** and **82**, whose oxidation leads respectively to the ketones **81** and **83** corresponding to the loss of a methyl or a carboxyl group (Scheme 46).



Scheme 46. Tertiary alcohols oxidation by the system Mn−TMPyP/$KHSO_5$

Labeling experiments performed with $H_2{}^{18}O$ revealed that no oxygen atom coming from water is incorporated in compound **83** (this study cannot be performed with compound **81** owing to the rapid exchange of the carbonyl oxygen atom with water). This observation suggests that **83** is formed through β-fragmentation of the alkoxyl radical of **82** resulting from the abstraction of a proton and an electron by the active species of the catalyst.



Scheme 47. Mechanism and diverse reaction pathways in oxidation of the tertiary alcohol **84** with the system Mn−TMPyP/$KHSO_5$; the number of mol is the amount of each product formed if the initial amount of **84** is 100 mol

Such a β-fragmentation of an alkoxyl radical may in fact compete with a *O*-neophyl rearrangement as has been shown in the catalytic oxidation of the tertiary alcohol **84** by the Mn−TMPyP/$KHSO_5$ system (Scheme 47).[64] Labeling experiments using $^{18}O_2$ or $H_2{}^{18}O$ under different reaction conditions demonstrate that the carbonyl oxygen atoms of acetophenone **86** and acetylbenzoic acid **87** originate either from substrate, water or dioxygen. The direct β-scission of the alkoxyl radical **85** leads to unlabelled compounds **86** and **87**. In a competitive reaction pathway, the *O*-neophyl rearrangement of **85** affords the carbon-based radicals **88** and **89** which then react with dioxygen (path **a**) or Mn^{IV}−OH/water (path **b**) to give in several steps labelled compounds **86** and **87** (the label comes either from water or dioxygen) and the unexpected esters **92** and **93** (from β-scission of the intermediate alkoxyl radicals **90** and **91**).

Conclusion

Metal-mediated oxidations of tertiary alcohols are mainly based on the use of stoichiometric or an excess of environmentally unfriendly metal oxides or metal oxy compounds (chromium oxide, ...). Consequently, this domain of tertiary alcohol oxidation is open to new catalytic methods using " green oxidants " (dioxygen, hydrogen peroxide, ...). In addition, the fragmentation reactions observed during the tertiary alcohol oxidations should be controlled by the metal center in order to ensure the product selectivity and avoid the formation of several products resulting from free-radical chemistry. Metal-controlled radical chemistry will be the future for metal-catalyzed oxidation of tertiary alcohols.

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Received December 16, 1999
[I99386]