APPLICATIONS OF SOME CHIRAL β-KETOPHOSPHONATE TRANSITION METAL COMPLEXES IN EPOXIDATION CATALYSIS

THESIS SUBMITTED IN ACCORDANCE
WITH THE REQUIREMENTS OF THE
UNIVERSITY OF ST ANDREWS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

by

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October 1989

Ibergekumene tsores iz gut tsu dertseylin

Troubles overcome are good to tell.

Yiddish Proverb

DECLARATION

I Michael Gahagan hereby certify that this thesis has been composed by myself, that it is a record of my own work, and that it has not been accepted in partial or complete fulfilment of any other degree of professional qualification.

Signed Date 17/10/89

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No.12 on the 1st October 1986 and as a candidate for the degree of Ph.D. on the 1st October 1986.

Signature of Supervisor Date 17.10.89

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To My Family

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List of Abbreviations

Ph	phenyl
bipy	2,2′-bipyridine
Et	ethyl
Me	methyl
Pr	propyl
Bu	butyl
LDA	lithium diisopropylamide
THF	tetrahydrofuran
av.	average
r.t.	room temperature
tritox	tritert-butylmethoxide
acac	acetylacetonate
cyclam	1,4,8,11-tetraazacyclotetradecane
CMP	carbamylmethylenephosphonate
dmso	dimethylsulphoxide
R	alkyl
salen	N,N-bis(salicylidene)ethylenediamino
X	anionic ligand (usually halide)
MCPBA	*meta*-chloroperbenzoic acid
DET	diethyl tartrate
DIPT	diisopropyl tartrate

Summary

Several β-carbonyl phosphoryl compounds have been synthesised by a variety of methods including the use of the Michaelis-Becker reaction and lithio alkanephosphonates. The optically pure β-ketophosphonate compound [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was synthesised by a lithium induced rearrangement of the corresponding vinyl phosphate. With a view to the synthesis of future non-demetallating catalysts and applications to asymmetric epoxidation, the novel organophosphorus compound 3-bromocamphor-3-phosphonic acid monoethyl ester was synthesised by the α-bromination of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor where it was discovered that a concomitant mono de-esterification had occurred. Several related compounds have been prepared and their stereochemistry determined by spectroscopic means. [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor has been found to act as both a bidentate and unidentate ligand, with complexes of molybdenum(VI) and titanium(IV) having been isolated and characterised. The X-ray diffraction results on MoO_2Cl_2[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor show that the molybdenyl unit has the two oxygen atoms *cis* at 102.8(5)° to each other, the chlorine atoms are mutually *trans* at 158.0(1)°. The β-ketophosphonate is coordinated *via* both the phosphoryl and carbonyl oxygen atoms, with bond distances of 2.183(7)Å and 2.402(7)Å respectively. The unequal bond distances from the donor atoms to the metal imply that such a complex should be a reactive and yet selective epoxidation catalyst. A very high activity has been demonstrated with the more nucleophilic alkenes such as 1-methylcyclohex-1-ene where 80% conversion to the epoxide is observed in under 30 seconds.

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CHAPTER ONE

TRANSITION-METAL CATALYSED EPOXIDATIONS

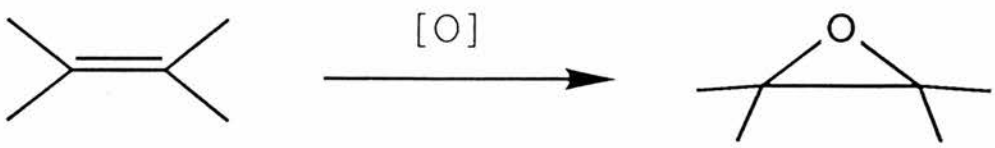
BACKGROUND AND LITERATURE REVIEW

Transition - Metal-Catalysed Epoxidations

1.1 Introduction

Homogeneous catalysts are widely used in the many branches of chemistry[1] and play a vital role in many living sytems[2]. They have extensive applications in the chemical industry as well as the laboratory. The advantages offered by such homogeneous systems, especially those incorporating transition metals, are that in general they function well under much milder conditions than heterogeneous systems and in general display a much greater degree of selectivity. This is particularly important for the chemical industry where the aim must be to keep the running costs of processes to a minimum but also to society itself where the conservation of energy is becoming increasingly important.

During the last 20 years interest in various transition-metal complexes for the epoxidation of alkenes (Equation 1.1) has been increasing. This can be attributed to the need for functionalising lower alkenes formed as by-products in the manufacture of gasoline by gas oil cracking, the need to understand biological chemical reactions, the requirement for partial selective oxidation not often offered by peracid or other methods, and the preparation of compounds of high enantiomeric purity.



alkene epoxide

Equation 1.1

Homogeneous metal catalysed oxidations can be divided into two types which have been labelled as homolytic and heterolytic by Sheldon and Kochi[3]. Homolytic systems involve free radicals as intermediates and in the catalytic cycle, the metal is involved in a series of one electron oxidation or reduction steps. An example of liquid phase homolytic oxidation is autoxidation, which occurs *via* a radical chain mechanism. The metal centre is not necessarily involved in all the stages of the reaction which is common with many metal-catalysed autoxidations where most of the chemical reaction occurs outside the co-ordination sphere of the metal. Some typical homogeneous catalysts involving the homolytic mechanism are the soluble transition metal salts such as for example naphthenates of Co, Mn and Cu. Examples of heterogeneous catalysts are the metal oxides.

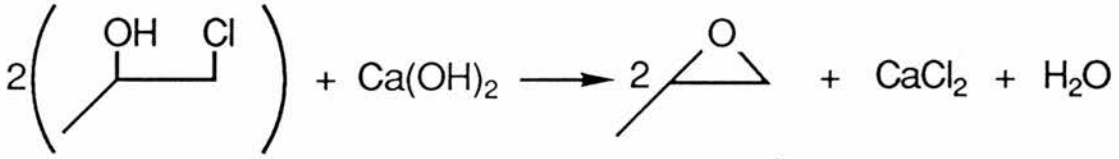
In heterolytic homogeneous oxidation catalysis the organic substrate or the oxygen containing reactant or both, are coordinated to the metal and so become activated. Characteristically the metal complex acts as a Lewis acid or if the metal undergoes a change in oxidation state it does so *via* a series of two electron steps. Free radicals are not intermediates and the metal remains closely involved with the substrate/reactant system during most or all of the reactions involved in the catalytic system.

It is found that the distinction between homolytic and heterolytic systems is not always clear especially with metals potentially being able to participate in both types of catalysis. It is notable that in propene epoxidation by heterolytic oxidation, radical chain decomposition of the hydroperoxide can occur with resulting loss of selectivity and yield of the epoxide. The most important epoxide commercially is ethene oxide(oxirane); the US production alone in 1988 was 2.4 million tonnes[4]. Of this nearly 60% is hydrolysed to ethylene

glycol. Half of the glycol is used in the production of polyethylene terephthalate and a high proportion of the remainder is the basis for antifreeze. European figures for oxirane are over 1 million tonnes[5]. Almost all of the oxirane produced is made by the direct air oxidation of ethene using a heterogeneous silver based catalyst.

Propene oxide, the production of which in the US is 1.4 million tonnes[4] and in Europe is over 0.8 million tonnes was originally synthesized using the chlorohydrin route which itself was developed for oxirane production.

propene propene chlorohydrin

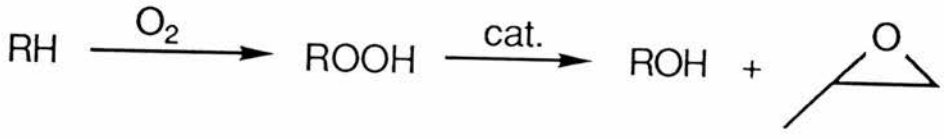


propene oxide

Equation 1.2

Among the several disadvantages with this process is the fact that chlorine is a relatively expensive reactant, which does not appear in the product so the reaction can be considered to be wasteful. The corrosive nature of chlorine also considerably shortens the lifespan of many chemical process plants.

A relatively recent process, first commercialised in 1969[6] is based on the finding that, in the presence of homogeneous catalysts especially molybdenum, organic hydroperoxides react with alkenes to give high yields of epoxides. This is now the most important industrial process for the manufacture of propene oxide. In it, propene is reacted with tert-butyl hydroperoxide in the presence of a Mo(VI) catalyst. The Mo(VI) catalysed epoxidation of propene using 1 phenylethylhydroperoxide forms the basis of the Halcon Epoxidation Process[7].



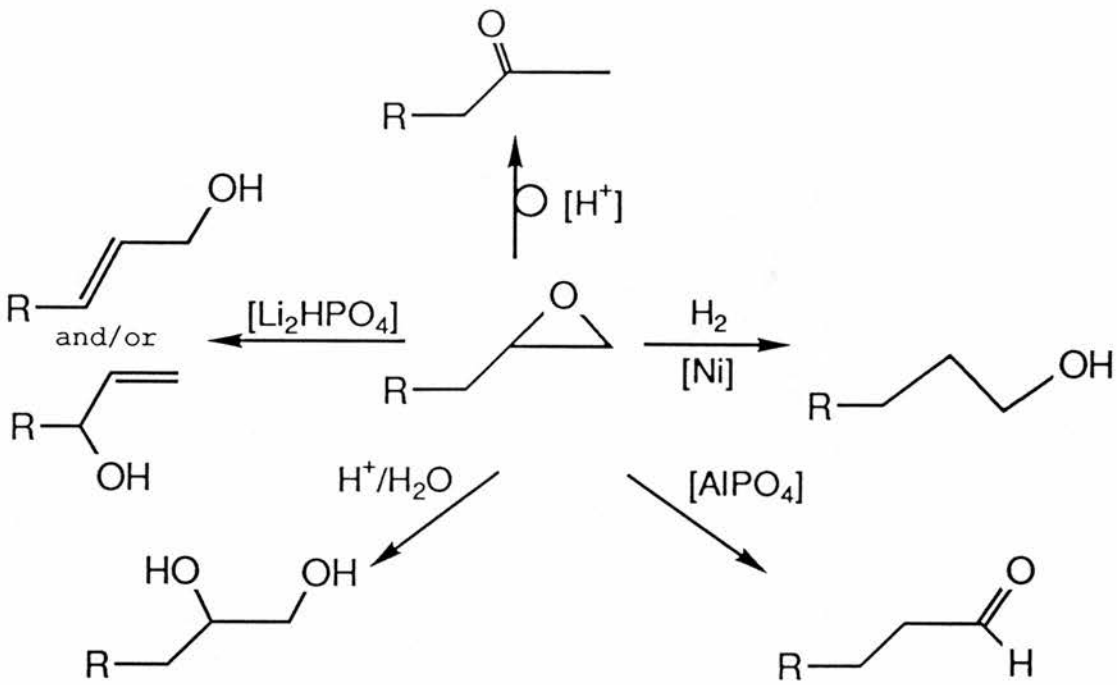
Equation 1.3

1.2 Epoxide Utility

The cardinal importance of epoxides is their synthetic utility, they are versatile chemical intermediates, and can be converted to a variety of products[8] (Scheme 1.1).

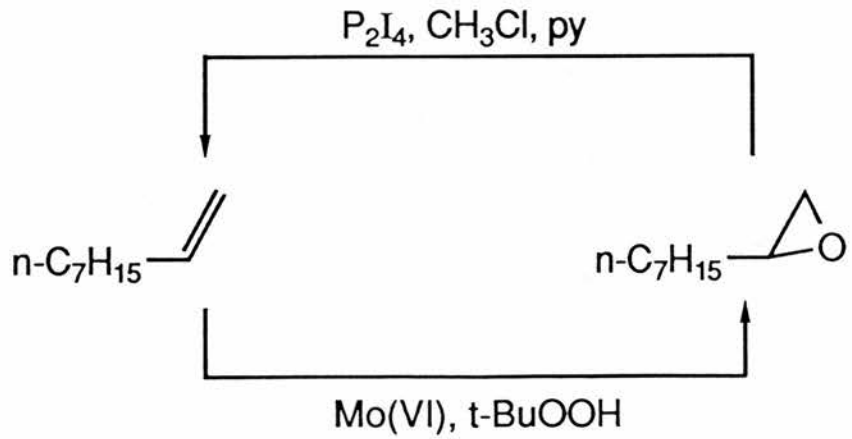
Propene oxide for example, is rearranged to allyl alcohol over basic lithium phosphate[9],[10] and to propanal over aluminium phosphate[10].

Epoxides are selectively rearranged to allylic alcohols in the presence of aluminium alkoxide catalysts[11].



Scheme 1.1

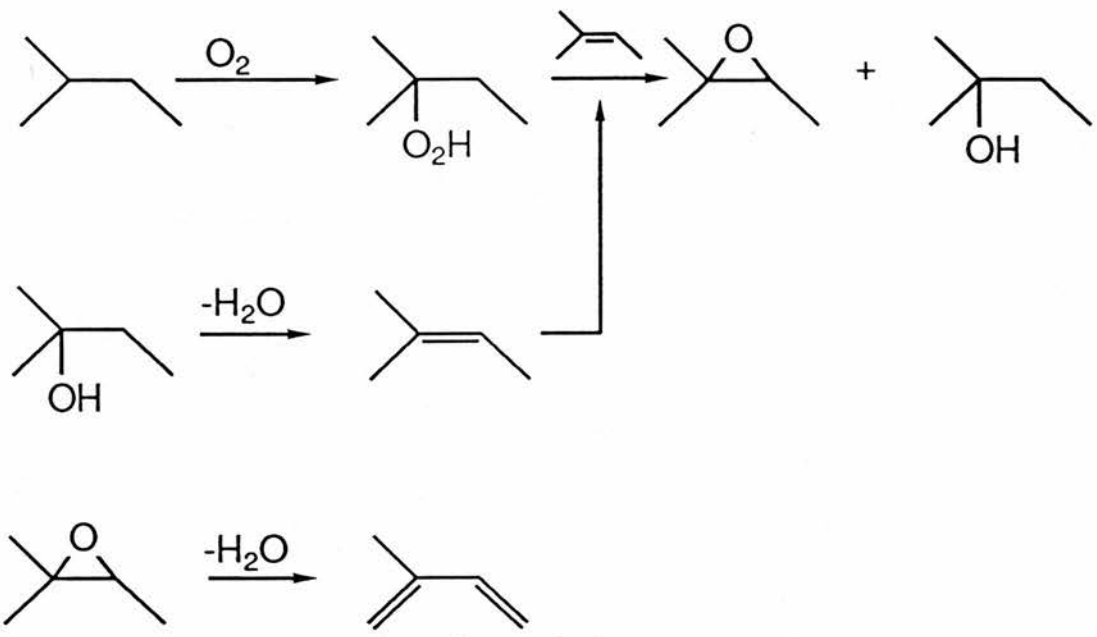
Of undoubted significance is the process whereby an epoxide can be converted back into the parent alkene. This extends the usefulness of epoxides because they can be regarded as a protecting group for alkenes. Most of the techniques involve long reaction times or expensive reagents, however diphosphorus tetraiodide (P_2I_4) affords the alkenes from the epoxides in two hours under mild conditions in 42-95% yield[12].



Equation 1.4

Many industrial applications have been envisaged such as the hydroperoxide process for the epoxidation of long chain α-olefins. Hydrogenation over a nickel catalyst would give the long chain primary alcohol product[13].

An industrial application envisaged by Farberov[14] is the conversion of isopentane to isoprene (Scheme 1.2).

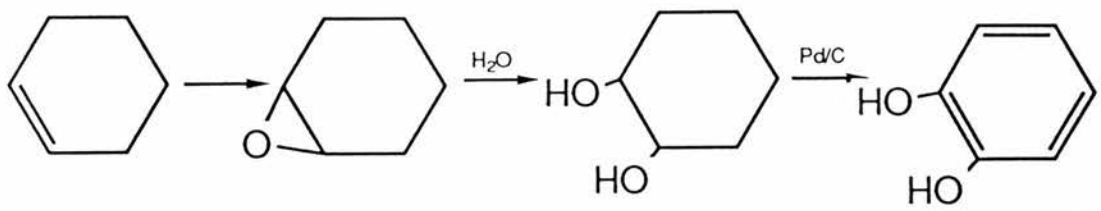


Scheme 1.2

Net Reaction:

Equation 1.5

The epoxidation of cyclohexenes can be utilized for the production of phenols and catechols[15].



Equation 1.6

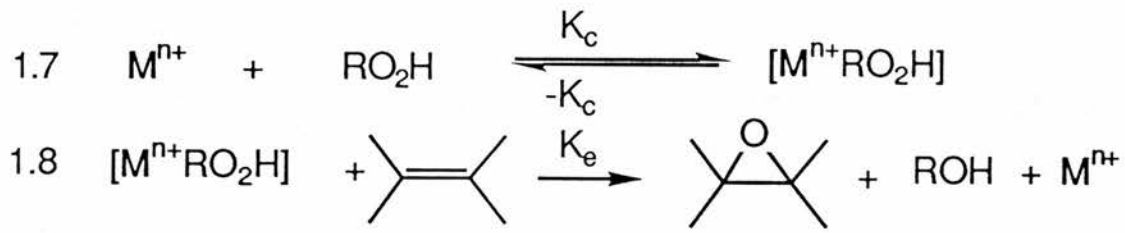
1.3 The Catalyst

The properties of a metal complex which make it an efficient catalyst for the epoxidation of an olefin by a hydroperoxide have been thoroughly investigated[8,16]. In such a metal complex the metal has a high charge, a relatively small size and has low lying d-orbitals which are at least partially unoccupied. The most active catalysts are those of Mo, W, V and Ti in their highest oxidation states. Complexes of metals in their low oxidation states eg. $Mo(CO)_6$, $W(CO)_6$ are rapidly oxidised by hydroperoxides to their highest oxidation states. The most important function of the catalyst is to withdraw electrons from the peroxidic oxygens, so that an active catalyst must be a good Lewis acid. The complex must not participate in one electron transfer reactions under strongly oxidising conditions. For the catalyst to be active at all it must form complexes which are substitutionally labile.

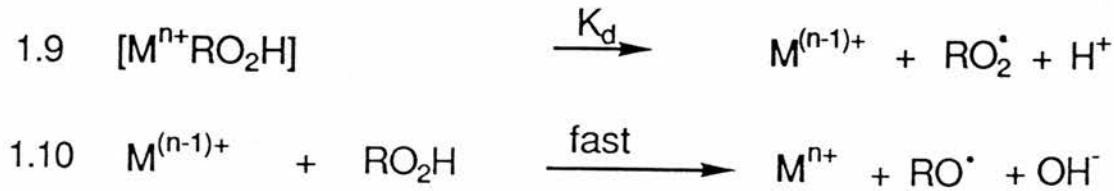
The Lewis-acidity of the transition metal oxides increases in the order CrO_3, $MoO_3 >> WO_3 > TiO_2, V_2O_5$. It is for this reason that Mo(VI) is the most effective epoxidation catalyst.

1.4 General Mechanistic Considerations for d^0 Systems

It is generally thought that the essential step in the epoxidation reaction is the non-dissociative co-ordination of the hydroperoxide. In such a complex, according to Sharpless[17] the hydroperoxide is activated by the coordination because the metal centre reduces the electron density at the peroxide oxygens thus rendering them more susceptible to nucleophilic attack by the substrate alkene. The process can be summarised in Equations 1.7 and 1.8.



The possibility of metal catalysed homolytic decomposition of the epoxide can occur.



The relative rates of the homolytic or heterolytic pathways determine the selectivity to epoxide. These are competing processes and have been widely investigated[18,19,20].

If there is no radical-induced chain decomposition of the hydroperoxide and small amounts of epoxides which may be formed *via* a radical pathway are neglected, the selectivity is given by

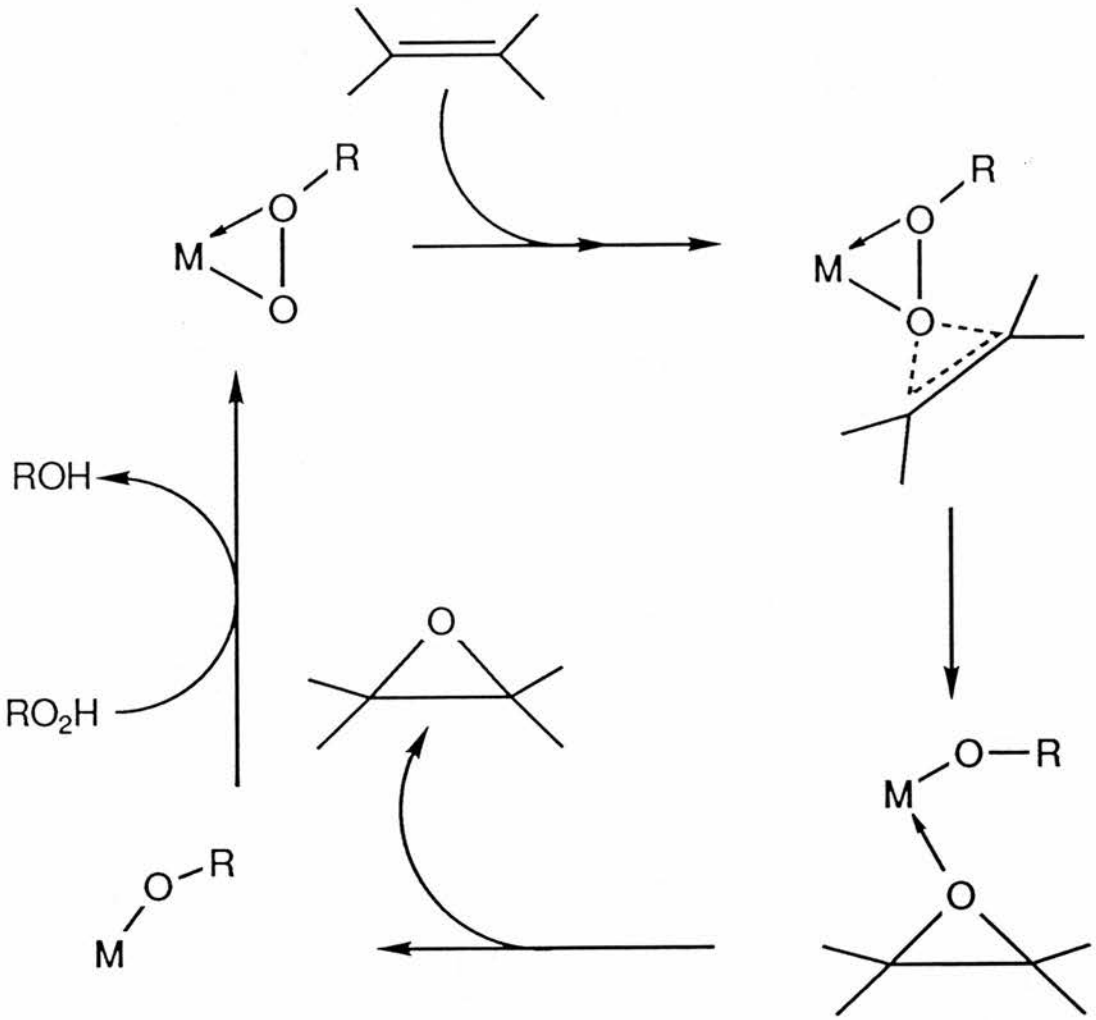
$$1.11 \quad \text{epoxide selectivity} = \frac{K_e[\text{alkene}]}{K_d + K_e[\text{alkene}]} \times 100\,\%$$

K_d and K_e are determined by oxidation potential of the catalyst and its Lewis-acidity respectively. In general, the ease with which transition metal complexes catalyse the decomposition of hydroperoxides is related to their redox potentials. Hydroperoxides are strong oxidants but weak reducing agents so reaction 1.9 is the slower rate determining step and occurs most easily with strong oxidants such as Co(III) and Mn(III), with redox potentials to the divalent ion of 1.82V and 1.51V respectively. This favours the homolytic decompositon route and gives rise to poor epoxide selectivity.

Very weak oxidants such as Mo(VI), W(VI), and Ti(IV) with one electron redox potentials of ~0.2V, -0.03V and -0.37V respectively are poor catalysts for homolytic hydroperoxide decomposition and favour reaction 1.8. V(V) is not a weak oxidant, which explains why vanadium catalysts generally give lower epoxide selectivities compared with the molybdenum catalysts[19].

Bartlett's Butterfly Mechanism

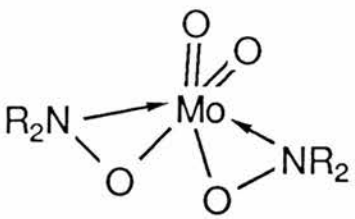
The most widely accepted mechanism for the epoxidation of alkenes is that a nucleophilic attack of the alkene on the "electrophilic" oxygen occurs which is reminiscent of Bartlett's butterfly mechanism for the epoxidation of alkenes by percarboxylic acids[21].



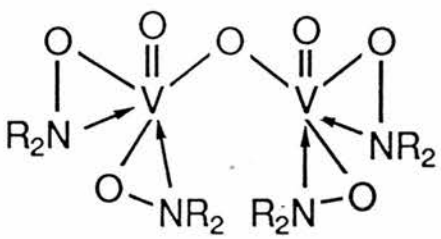
Equation 1.12

Sharpless has proposed the arrangement where in the metal-hydroperoxide complex, the hydroperoxide is bound covalently to the metal through the oxygen atom distal to the alkyl group. The proximal oxygen atom is then thought to interact with the metal in the transition state further activating the hydroperoxide toward nucleophilic attack.

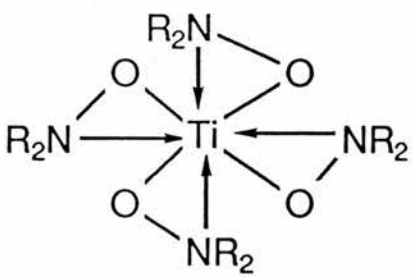
^{18}O labelling studies have clearly shown that the active catalyst is not a peroxo compound but an alkyl peroxide in which the alkyl peroxide is probably O,O-triangularly bonded to the metal[21,22] as illustrated by the X-ray crystal structure of various vanadium complexes[22]. The well characterised d^0 metal O,N-bonded N,N-dialkylhydroxylamino complexes[23,24,25] are reminiscent of the alkyl peroxide complexes of Mo(VI), V(V) and Ti(IV) which are difficult to isolate and are involved as reactive intermediates.



Structure 1.1



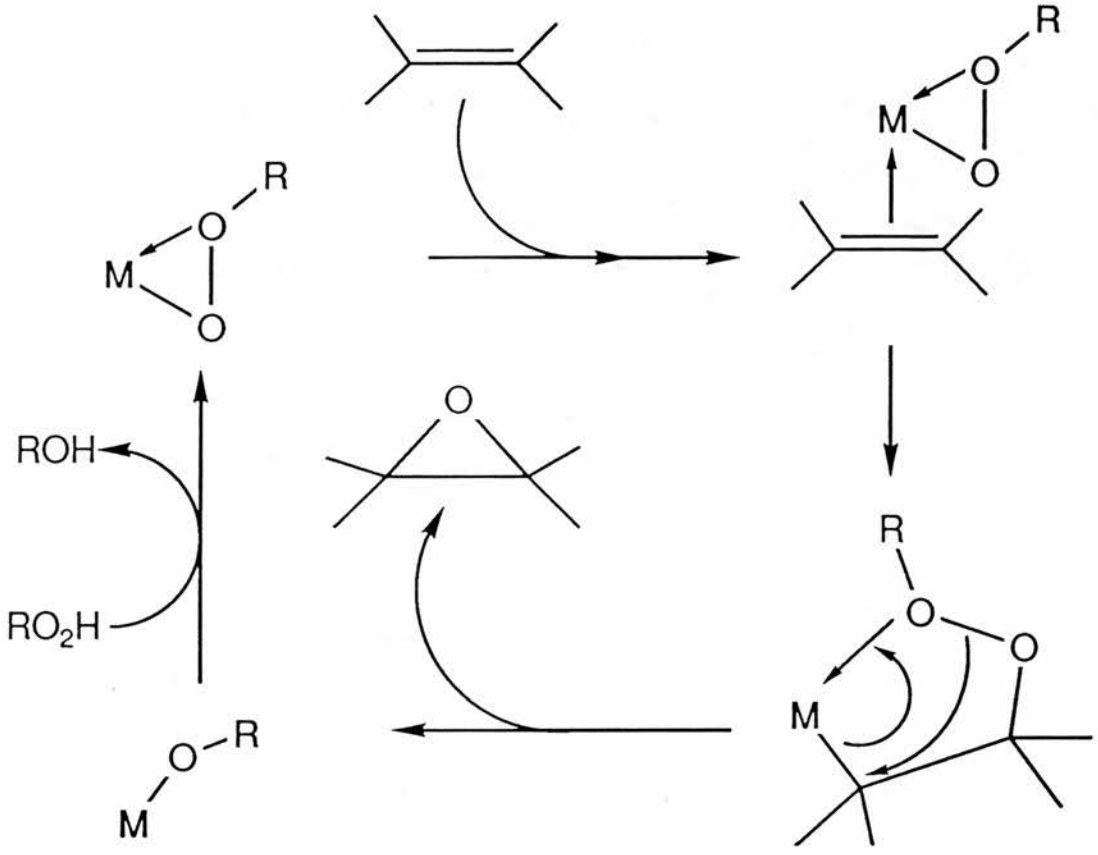
Structure 1.2



Structure 1.3

Mimoun's Peroxymetallation Mechanism

Mimoun and colleagues[24] have proposed a different mechanism to Sharpless for the epoxidation by peroxidic reagents.

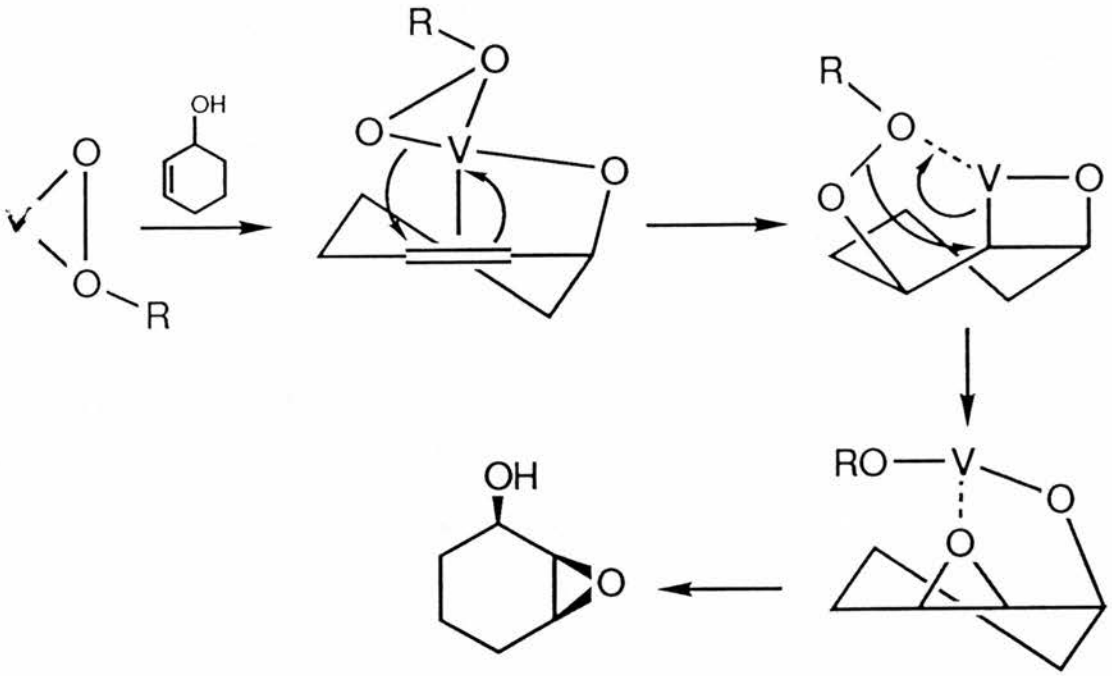


Equation 1.13

The alkene is believed to coordinate to the metal followed by its insertion between the metal oxygen bond by an intramolecular 1,3-dipolar mechanism in which a five membered peroxymetallacycle decomposes by a 1,3 dipolar cycloreversion to give an epoxide and the metal akoxide. The nature of the interaction between the alkene and the metal atom would have to be a purely Lewis base - Lewis acid one because there are no d electrons available for back bonding to the alkene.

Although peroxymetallation is well supported with platinum[26] and rhodium[27] the mechanism seems unlikely for the d^o early transition metals. There are several reasons. The formation of the

peroxymetallocycle should be easiest for alkenes suited to 1,3-dipolar additions as observed with Pt-peroxides. However, such electron-deficient olefins do not react in these metal-catalysed epoxidations with alkyl hydroperoxides. With allylic alcohols, peroxymetallation demands the formation of a strained bicyclic intermediate which is unfavourable[24].

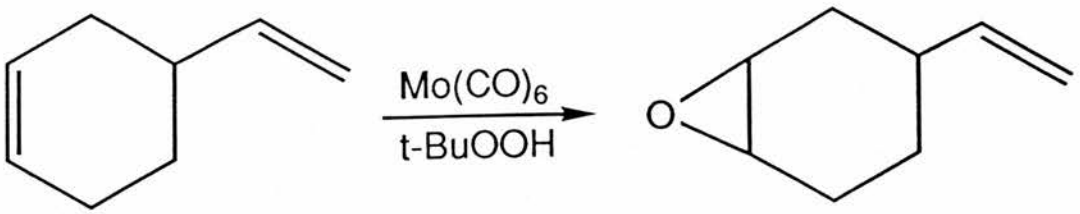


Equation 1.14

Molybdenum porphyrin complexes have been shown to catalyse the epoxidation of alkenes by hydroperoxide[28]. In such a case, the steric constraints imposed by the macrocycle makes it difficult for both the alkene and hydroperoxide to be bound to the metal at the same time.

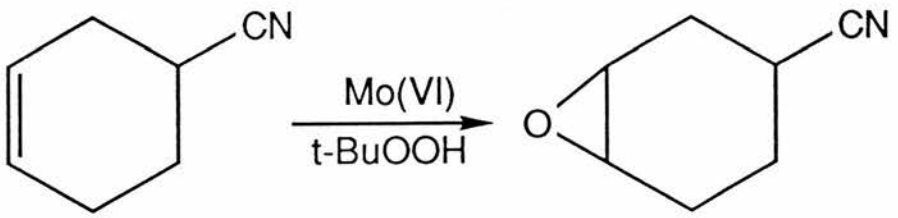
1.5 The Substrate Alkenes

The reactivity of double bonds is enhanced by increasing alkyl substitution following the order tetrasubstituted > trisubstituted > disubstituted > monosubstituted. This is illustrated by the regio-specific monoepoxidation of non-conjugated dienes.



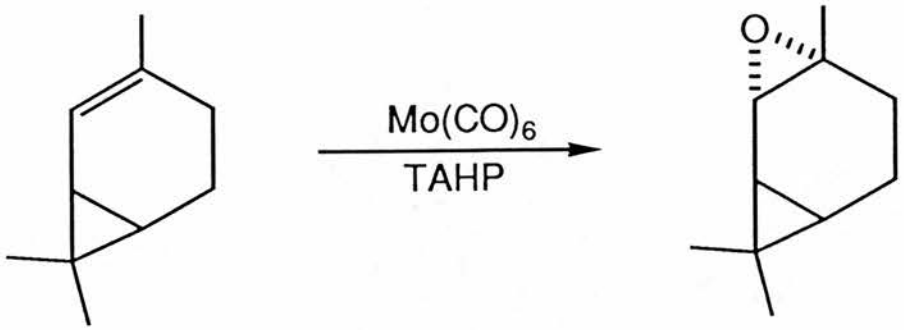
Equation 1.15

Electron withdrawing groups on the alkene considerably retard the epoxidation, for example acrylic esters are not reactive. However, epoxidation is not seriously impeded when the electron-withdrawing group is sufficiently removed from the double bond. For example 4-cyanohexene, gave the epoxide in 88% yield[15].

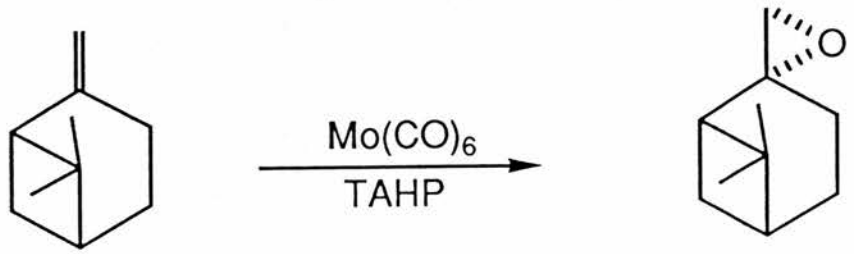


Equation 1.16

The epoxidation of alkenes by heterolytic processes is completely stereoselective: *cis*-alkenes are exclusively transformed into *cis*-epoxides and *trans*-alkenes into *trans*-epoxides. Oxygen addition to the double bond preferentially occurs from the less shielded face of the substrate, eg. in the selective epoxidation of terpenes by tert-pentyl hydroperoxide (t-amyl hydroperoxide)[15].

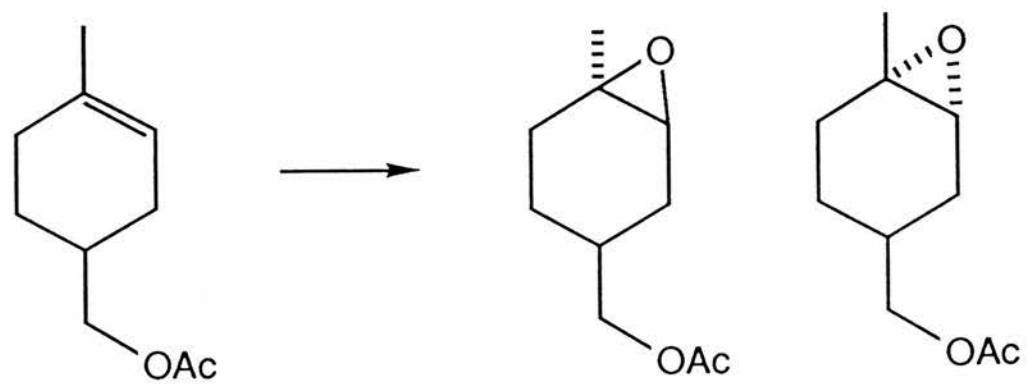


Equation 1.17



Equation 1.18

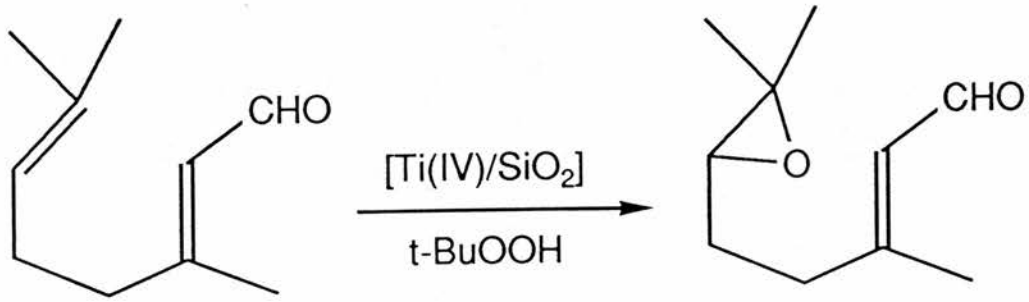
The presence on the substrate of functional groups capable of interacting with the metal directs the stereoselectivity of epoxidation, as shown by the comparative reactivity[29] towards TAHP/$Mo(CO)_6$ and peroxybenzoic acid (PBA).



TAHP/$Mo(CO)_6$ 100% 0%
PBA 50% 50%

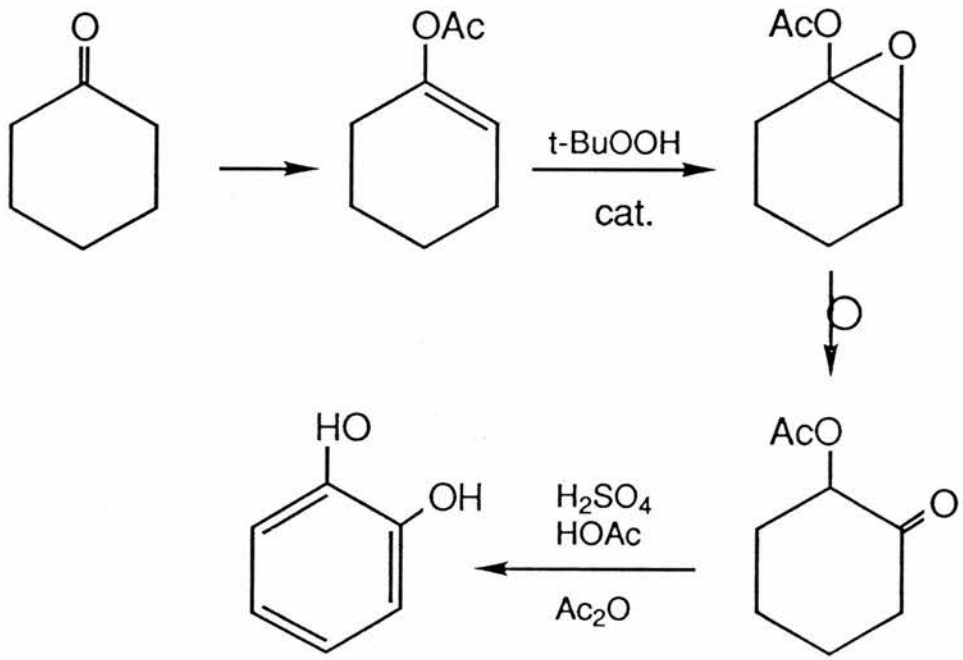
Equation 1.19

It is obvious that the catalytic systems offer advantages over the peracid technique. This can be taken advantage of in the epoxidation of acid sensitive alkenes such as in the epoxidation of citral[30].



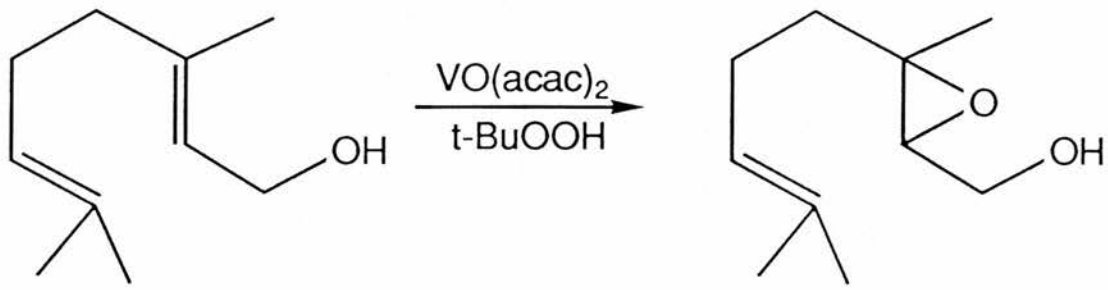
Equation 1.20

Steroidal enol acetates were similarly epoxidised[31]. The metal-catalysed epoxidation of 1-acetoxycyclohexene is a key step in a synthesis of catechol from cyclohexanone.



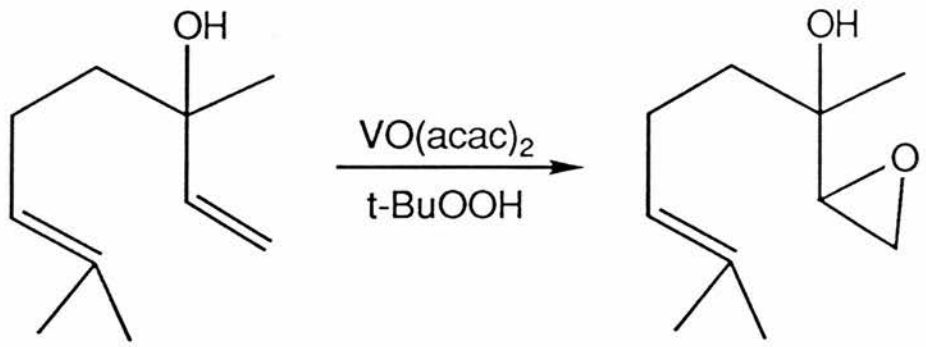
Equation 1.21

The exceptionally facile epoxidation of allylic alcohols by tert-butyl hydroperoxide in the presence of vanadium catalysts[32,33] has been used for the synthesis of complex molecules (t-BuOOH/Mo(VI) catalysts were inferior in activity and selectivity). Geraniol and linalool were selectively epoxidised to the previously unknown monoepoxides.



geraniol

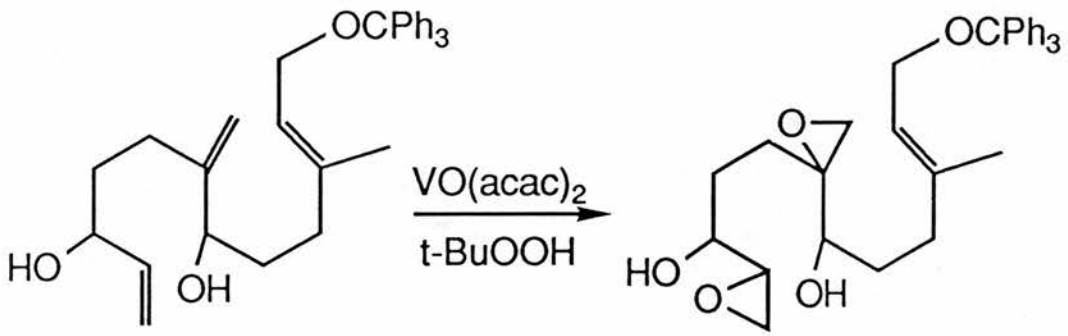
Equation 1.22



linalool

Equation 1.23

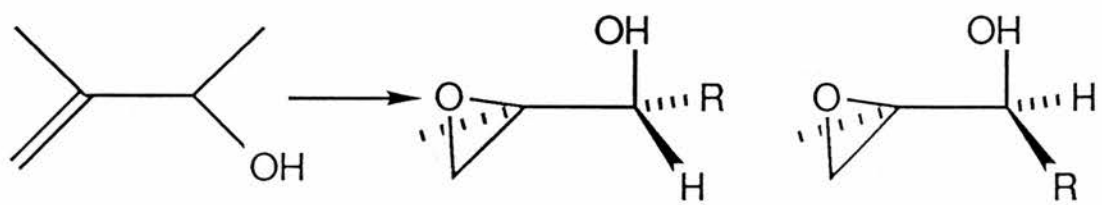
Notice the reverse in selectivity from that normally observed for the epoxidation of compounds containing more highly substituted double bonds. Similarly, the selective epoxidation of the bisallyclic alcohol to the bis epoxy alcohol with t-BuOOH-$VO(acac)_2$, is a crucial step in the synthesis of juvenile hormone from farnesol[33].



Equation 1.24

Such regioselectivities are not possible with other epoxidising agents. Orientation of the alkene by coordination to the metal catalyst through a functional group can result in the preferential transfer of oxygen to a particular double bond in a diene (regioselectivity) or to a particular face of the substrate (stereoselectivity).

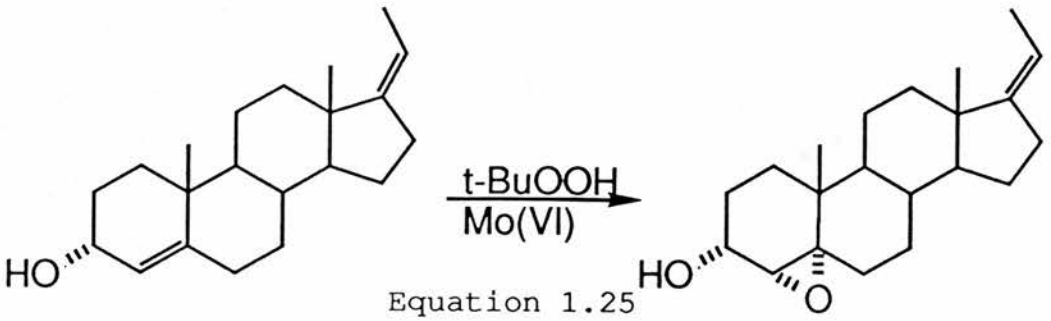
Sharpless and co-workers[34] investigated the stereoselectivity of epoxidation of acyclic allylic alcohols. The *erythro*-epoxide was formed almost exclusively with t-BuOOH/$VO(acac)_2$. The corresponding reactions with *m*-chloroperbenzoic acid, were virtually non-selective.



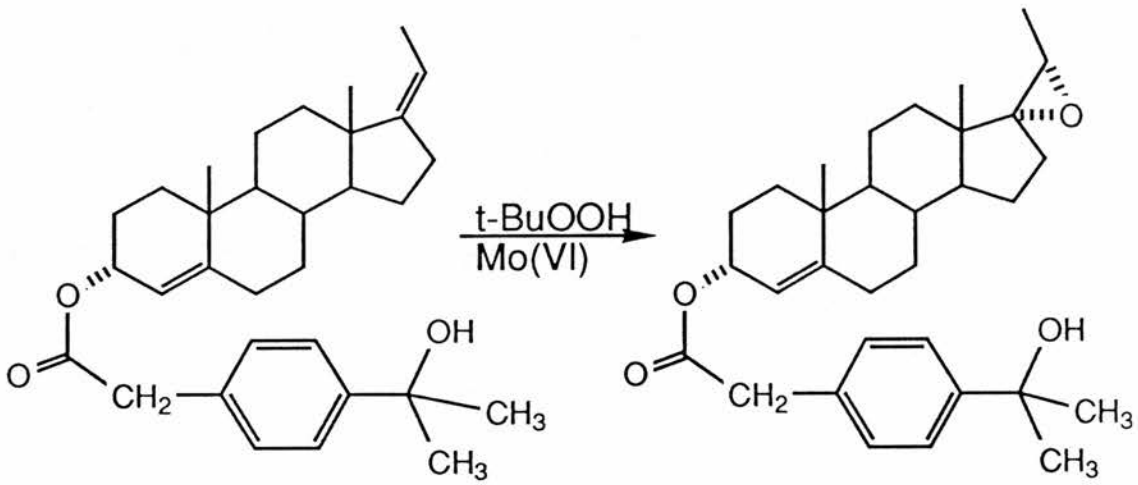
	threo	erythro
t-BuOOH-V(V)	5%	95%
t-BuOOH-Mo(VI)	16%	84%
MCPBA	45%	55%

Figure 1.1

Breslow and co-workers[35,36] have investigated the template-directed remote epoxidation of double bonds which exploit the coordinating ability of the hydroxyl group to the metal catalyst in these systems.



Equation 1.25



Equation 1.26

1.6 Effect of Solvent and Co-product Alcohol

Anhydrous conditions are required for the d^o metal-catalysed epoxidations of alkenes due to the inhibitory effect of water. This is more pronounced for V and Ti than for Mo and W. Aromatic (e.g. benzene or toluene) or chlorinated solvents (e.g. CH_2Cl_2, $C_2H_4Cl_2$) are needed for good catalyst activity. Alcohols or basic solvents like DMF, THF or dioxane, however strongly retard or completely inhibit the oxidation.

The co-product alcohol derived from the hydroperoxide also exerts an inhibitory effect in the order W < Mo < Ti < V[8] and competes with the alkyl hydroperoxide by forming metal alkoxides, preventing the formation of metal-alkyl peroxides.

1.7 Ligand Effect

The Lewis acidity of the catalyst is influenced by the nature of the co-ordinating ligands. In general a ligand effect may be observable only in the initial stages of the reaction due to rapid replacement of the original ligands during the reaction. The rates of the molybdenum-catalysed epoxidation of alkenes varied only in the initial phases of the reaction[19]. This suggests that all the additives were eventually modified to the same catalytic species. This conclusion was confirmed by the isolation of the catalysts at the end of the reaction as Mo(VI)-1,2-diolate complexes[19].

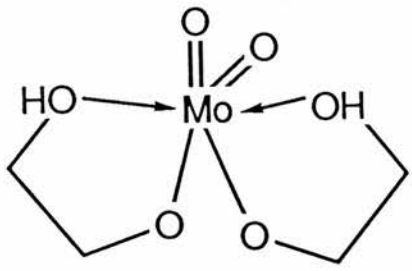


Figure 1.2

Independent experiments showed that the *cis*-dioxomolybdenum(VI) diolates were formed *in situ* during molybdenum-catalysed epoxidations *via* reaction of the catalyst with the epoxide in the presence of the hydroperoxide. The structure of the catalyst therefore is ultimately determined by the structure of the alkene being epoxidised. It should be stressed however, that the Mo(VI)-1,2 diol complexes are not the only

active Mo(VI) compounds, nor are they necessarily more active than other Mo(VI) compounds. Thus, $MoO_2(acac)_2$ generally gave a higher rate of epoxidation initially, but the rate decreased with time due to the formation of the less active 1,2-diol complex[19]. From work on the effect of different ligands on molybdenum catalysed epoxidations[37] it can be concluded that complexes with very strongly bound ligands show low activity due to the hindrance of complex formation between the catalyst and the hydroperoxide. Catalysts with very loosely bound ligands, such as $MoO_2(acac)_2$, were active but less selective than those with ligands of intermediate stability, such as $MoO_2(oxine)_2$. It was proposed that the latter formed a complex with the hydroperoxide by opening only one of the bonds of the chelating ligand to molybdenum. To be active and selective, catalysts should contain molybdenum-ligand bonds of intermediate strength.

1.8 Non-Demetallation

Of significance are the reports in the literature of non-demetallating catalyst systems. Ledon and co-workers have reported that O=Mo(TPP)OMe (d^1) is a stable catalyst for epoxidation with cumene hydroperoxide and that demetallation does not occur[28]. This result supports the mechanism proposed by Sharpless described earlier i.e. direct attack of the alkene on the electrophilic oxygen of the activated hydroperoxide, without requiring coordination of the alkene to the metal centre. Owing to the steric hindrance of the macrocyclic ligand, the mechanism for coordination of the alkene and the hydroperoxide to the metal centre as proposed by Mimoun seems unlikely. Agarwal[38] has synthesised several *cis*-dioxomolybdenum complexes using the ligands 2-aminobenzoic acid-acetylacetone and aminophenyl salicaldehyde among others. This non-porphyrin system is claimed to be an effective epoxidation catalyst and

it is claimed that no demetallation reaction occurs. It is clear that if decomplexation were not to occur then it ought to give better stereocontrol of any reaction.

1.9 Catalyst Review

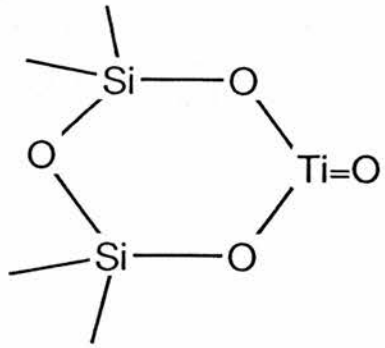
In the following sections the activity of various transition metals relative to epoxidation catalysis will be described. The mechanisms for the oxygen transfer steps will also be discussed to gain more insight into the processes involved in epoxidation catalysis. The discussion will concentrate mainly on Ti, V and Mo due to their extreme importance.

1.9.1 Group IVa Titanium, Zirconium and Hafnium

Titanium

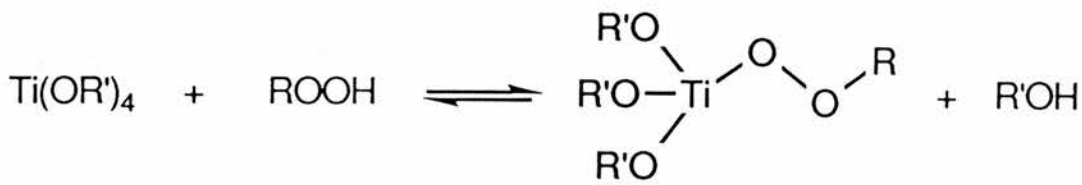
Titanium(IV) alkoxides catalyse the epoxidation of a variety of alkenes with an alkyl hydroperoxide as the oxygen donor[7,18,30]. The reaction is slow and often by-products resulting from the addition of tert-butyl peroxide radicals to the substrate have been observed[18].

Although a truly heterogeneous system the importance industrially for the epoxidation of propene warrants the inclusion of the titanium(IV)-silicon dioxide catalyst[7]. The catalyst is prepared by impregnating silica with $TiCl_4$ followed by calcination. Propene oxide yields from propene are typically >90% with ethyl hydroperoxide as the oxygen carrier. The structure of the active site is probably:



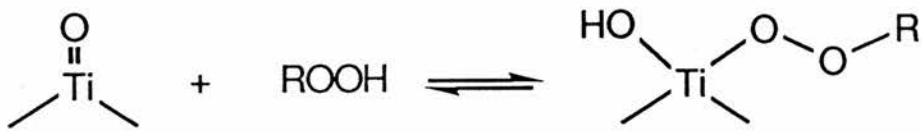
Structure 1.4

The function of the silicate ligands is to increase the Lewis-acidity of titanium(IV), and it is likely that they prevent the polymerisation which is common for titanyl complexes. Jørgensen[39] has proposed the following mechanistic explanation of Ti(IV) catalysed epoxidation. In the titanium(IV) alkoxides, one of the alkoxide ligands is exchanged for the peroxide[7,21].



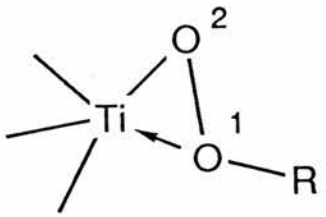
Equation 1.27

For the titanyl complex in structure 1.4 the reaction may proceed as follows:



Equation 1.28

^{18}O labelling studies on V(V) and Mo(VI) suggest that the alkyl hydroperoxide remains coordinated to the metal during the reaction and so it is thought that in the case of Ti(VI) the peroxide binds to titanium(IV) *via* the terminal oxygen, although the other oxygen may also be involved in coordination to the titanium.



Structure 1.5

Such a coordination leads to an activation of the peroxide for oxygen transfer. Of the mechanisms suggested, the most appealing is that proposed by Sharpless.

Theoretical calculations[40] have led to the following interaction possibilities of an alkene with the titanium peroxide complex:

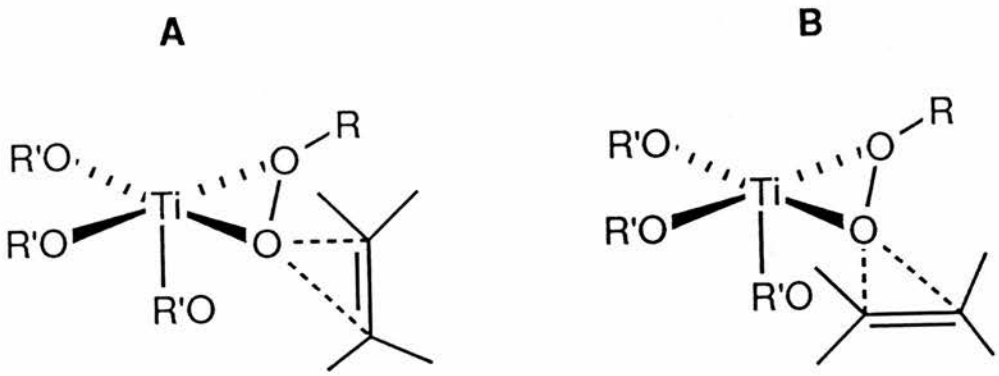
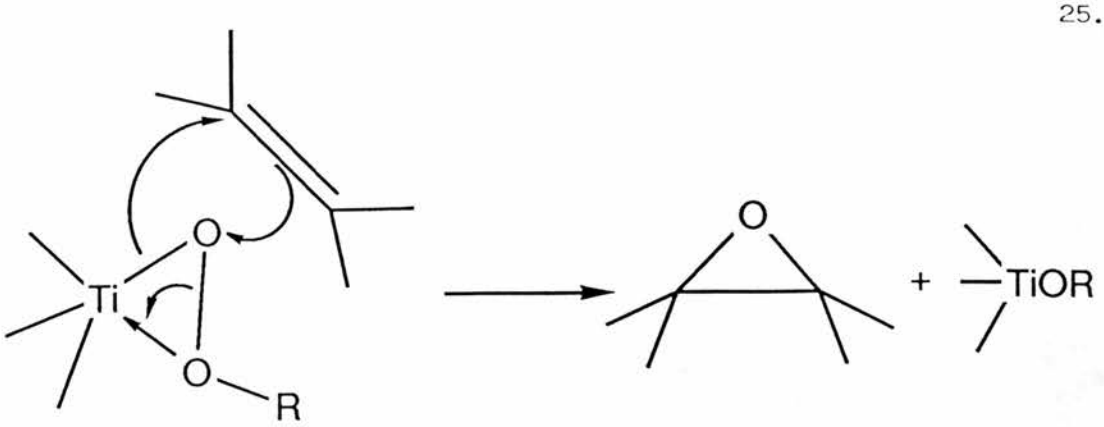


Figure 1.3

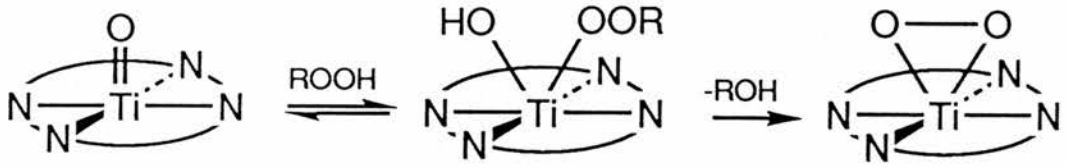
The orientation of the alkene in (A) corresponds to a spiro orientation relative to the titanium-peroxide plane whereas the orientation in (B) is planar.

Detailed *ab initio* calculations on model compounds have been performed to elucidate the mechanism of oxygen transfer from an epoxide to an alkene for titanium(IV) systems[40]. From that it is suggested that the alkene performs a "nucleophilic attack" on the electrophilic oxygen.



Equation 1.29

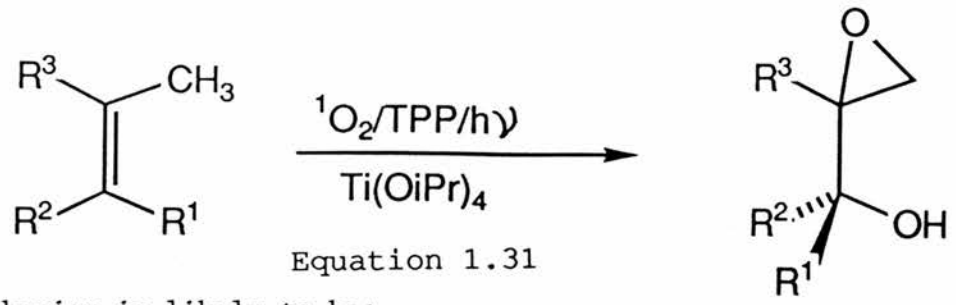
TiO_2, $TiO(acac)_2$[18] and oxotitanium porphyrin[41] have catalytic epoxidation activity, although it is not very high compared with the Ti(IV)/SiO_2 systems. It is interesting that during the epoxidation by an oxotitanium porphyrin a peroxotitanium compound was formed which was unreactive towards alkenes.



Equation 1.30

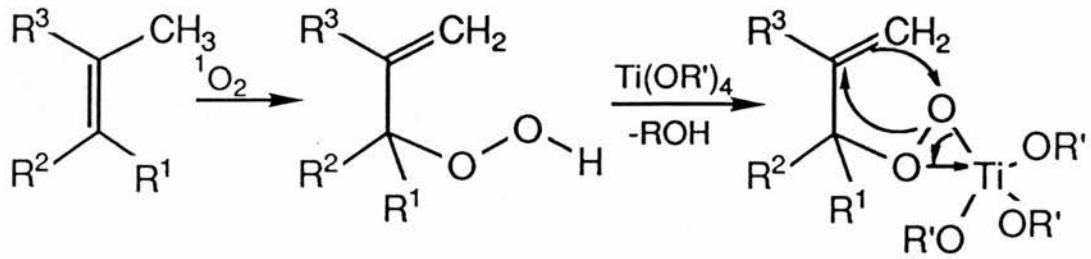
The reason given for this lack of reactivity is that steric repulsion between the porphyrin ring and the alkene prevents interaction with the peroxo-oxygen. It has been suggested[41], in this case, that it is the *cis*-hydroxy(alkylperoxo)titanium porphyrin which is the active catalyst.

Molecular oxygen has been used as an oxygen source for Ti(IV)-catalysed epoxidations of alkenes[42,43]. The ene reaction of singlet oxygen with alkenes has been used to prepare epoxy alcohols with high diastereo selectivity.



Equation 1.31

The mechanism is likely to be:



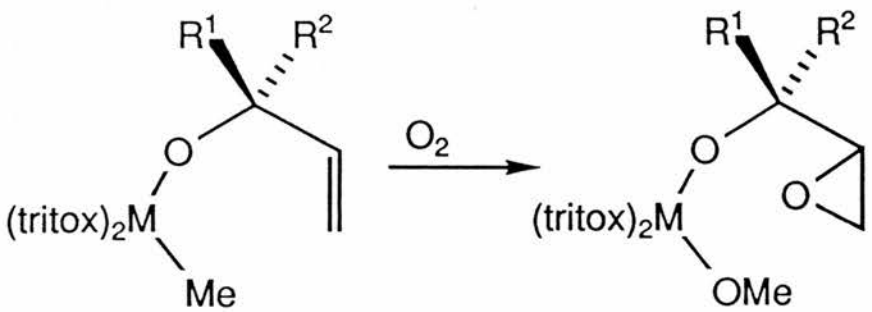
Equation 1.32

Titanium carbide and boride (TiC and TiB_2) can catalyse the epoxidation of styrene with molecular oxygen as the oxygen donor[44]. Sharpless[45] has successfully used Ti-catalysts in the asymmetric epoxidation of allylic alcohols. Due to its importance this subject is covered in greater length in Section 1.10.

Zirconium and Hafnium

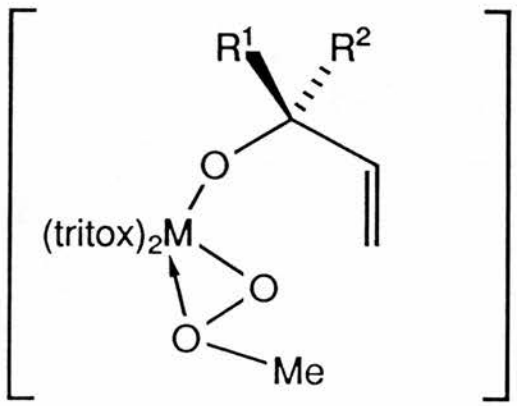
Zr(IV) and Hf(IV) are not as active catalysts as the corresponding Ti(IV) species[18].

Zirconium and Hafnium complexes can use molecular oxygen as the oxygen donor for epoxidation[46]. Treatment of the $(tritox)_2M(Me)$(allylic alcohol), (M=Zr, Hf) complex with molecular oxygen leads to stoichiometric epoxidation.



Equation 1.33

The molecular oxygen is activated by the metal and is inserted into the transition metal-methyl bond giving a bidentate coordinated methyl peroxide complex which then epoxidises the attached alkene.



Structure 1.6

1.9.2 Group Va

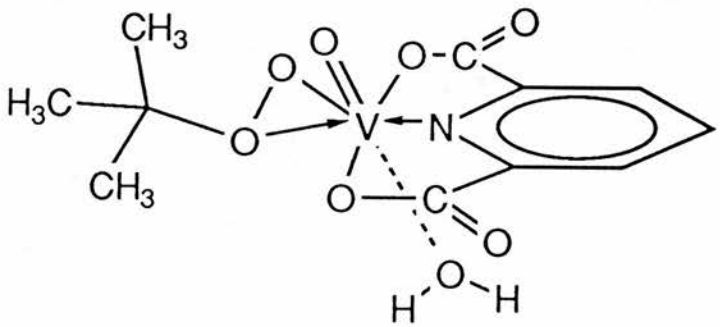
Vanadium, Niobium and Tantalum

Vanadium

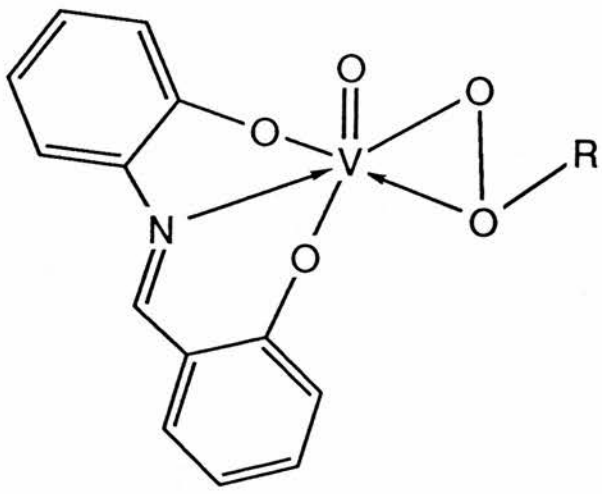
Compared with molybdenum catalysts vanadium(V) complexes[7,18,39] are relatively poor catalysts for alkene epoxidation. $VO(acac)_2$ promoted yields of cyclohexene oxide from the alkene are only 10-12% and the reaction is slow. Mo(VI)-catalysed epoxidations are about 10^2 times faster. For V(V) catalysis the stereochemistry of the epoxidation reactions is dependent on the ligand present in the complex[22]. If 2,6-pyridine dicarboxylate is the ligand *cis*-2-butene gives an approximately 3:1 mixture of the *cis* and *trans*-epoxides[47], whereas with certain tridentate Schiff base ligands[48] only *cis*-2,3-epoxybutane is obtained.

Mimoun and co-workers have obtained a crystal structure of a complex of tert-butyl hydroperoxide with vanadium(V) that clearly shows bonding of the oxygen proximal to the tert-butyl group with the metal, and that this oxygen centre displays a nearly tetrahedral geometry. The fact that the nature of the ligands exerts a dramatic influence on both the yields and selectivity of the epoxidation of cyclohexene is indicated

by the fact that the dipicolinato complex (Structure 1.7) was inactive for the epoxidation[23]. It was found however that vanadium(V) alkylperoxidic complexes containing tridentate N-(2-oxidophenyl)-salicylidenaminato Schiff base ligands (Structure 1.8) epoxidised alkenes stoichiometrically with high yields and selectivity[48].



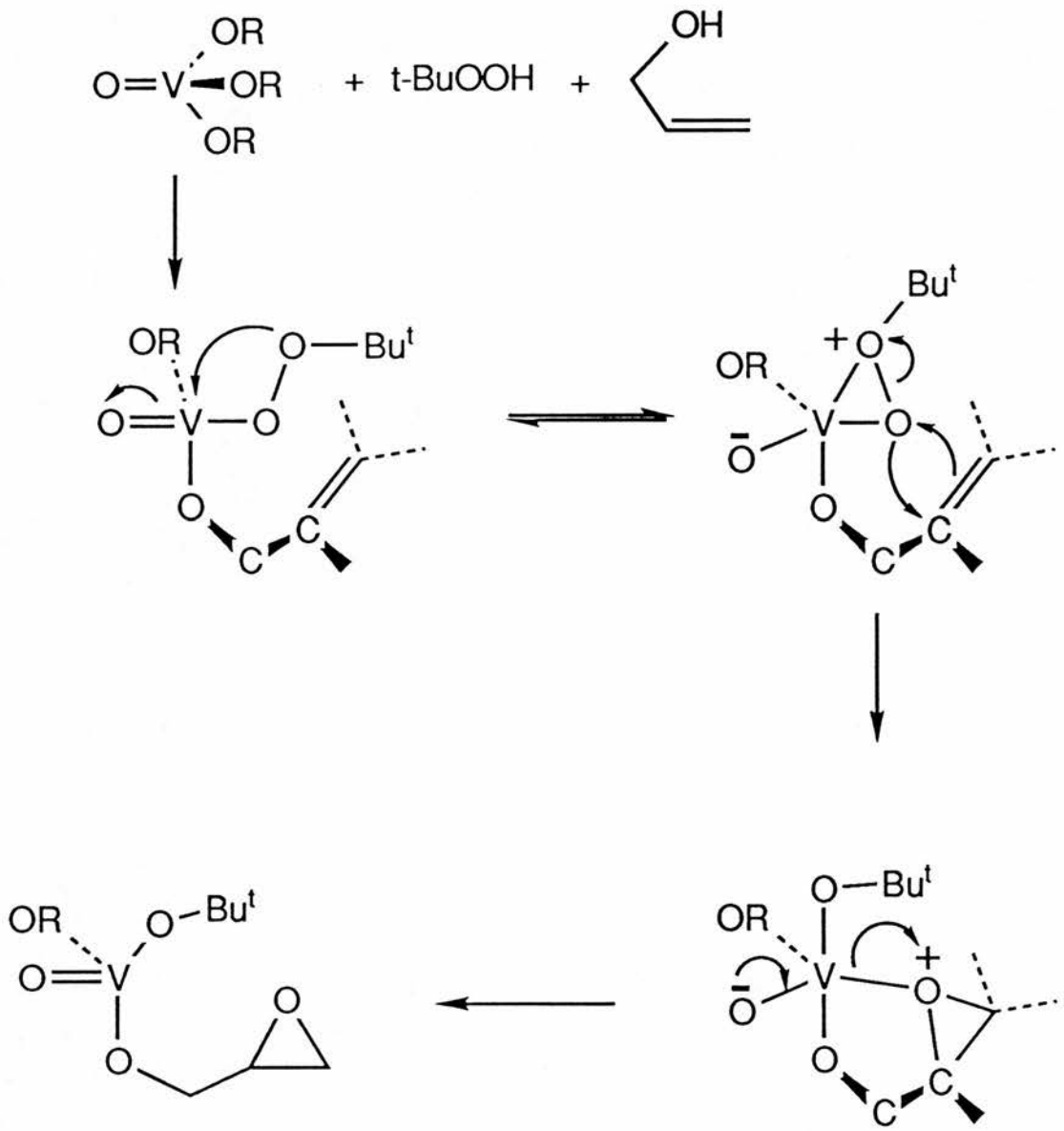
Structure 1.7



Structure 1.8

Allylic Alcohols

The epoxidation of allylic alcohols with V(V) is 10^3 times faster than that of the parent alkene[8,39]. The proposed mechanism is shown:



Equation 1.34

The exceptional reactivity of the allylic alcohols towards V(V)-alkyl hydroperoxides is attributed to the fast and strong coordination of alcohol ligands to vanadium[48], followed by an intramolecular oxygen transfer from the coordinated alkyl peroxide to the double bond of the allylic alcohol. The first step is the exchange of two alkoxide groups by the peroxide and the allylic alcohol, the next step is a bidentate coordination of the peroxide moiety. The alkene part of the allylic alcohol is lined up perpendicularly to the V(V)-alkylperoxo plane, making the interaction between the alkene and the ROO possible. The step A-B is the step in which the stereoselectivity is determined. The stereoselectivity for the formation of the *erythro*-epoxy alcohol can be explained from the formation of the intermediate.

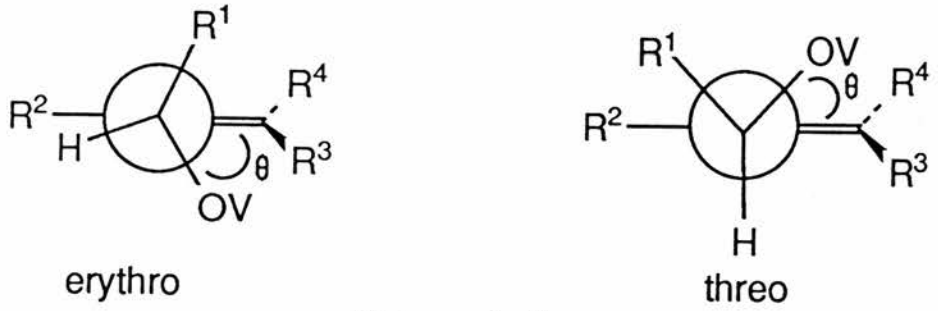


Figure 1.4

The O-C-C=C dihedral angle θ in Figure 1.4 is about 50° whereas a rotation of the O-C-C=C dihedral angle about 50° above the $R^2R^3R^4$ plane will lead to the *threo* product (Figure 1.4).

Alkyl substitution in R^1 and R^2 will cause steric repulsion and thus explains the vanadium catalyst favouring the formation of erythro epoxy alcohols. The corresponding methyl ethers of allylic alcohols are 1000 times slower to epoxidise under vanadium catalysis[39,49].

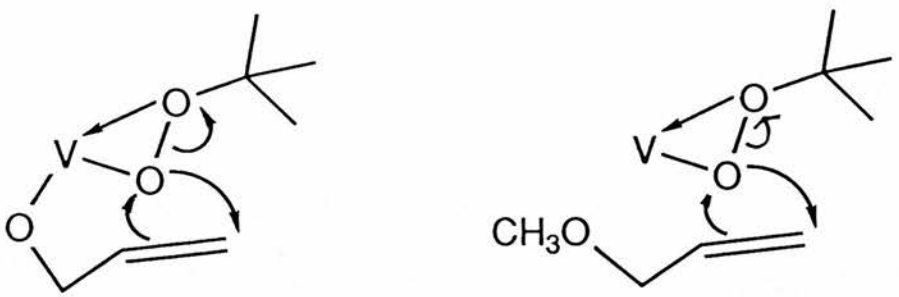
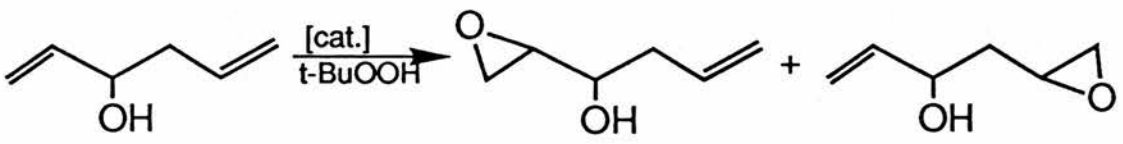


Figure 1.5

It can be seen that prior coordination is required, the rate of epoxidation of isolated alkenes is so slow that the reaction is not synthetically important[4].

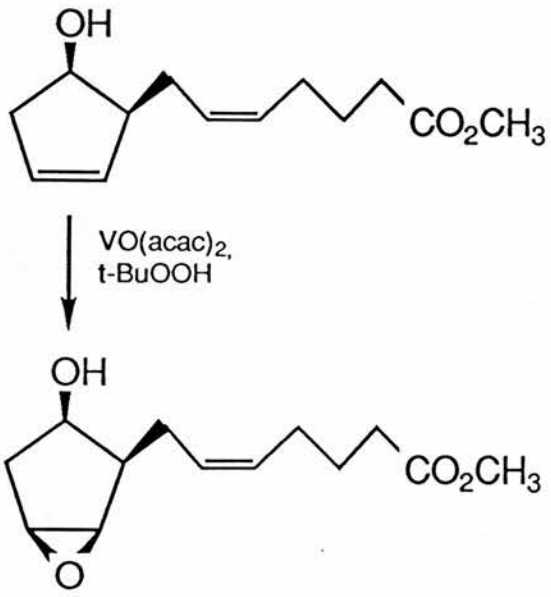
The differences between V(V) and Mo(VI) are reflected in the different regioselectivities observed in the epoxidation of the dienol shown[8]:



$VO(acac)_2$	4	:	1
$Mo(CO)_6$	1	:	1

Equation 1.35

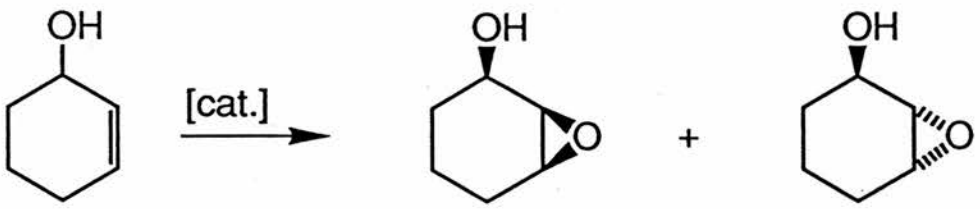
High regioselectives are observed with homoallylic alcohols as in the synthesis of the prostaglandin intermediate[50].



91%

Equation 1.36

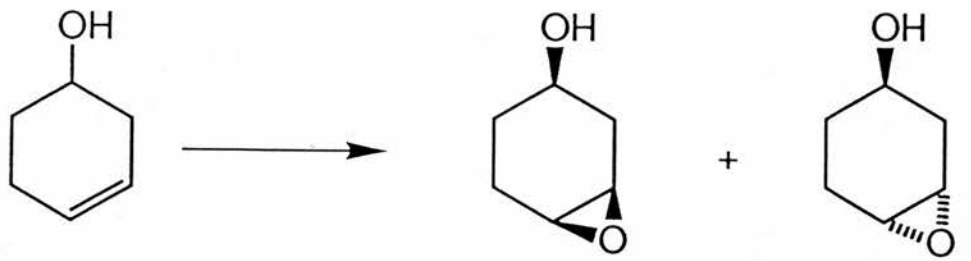
The V(V)-hydroperoxide system exhibits striking stereoselectivities resulting from the preferential *syn* transfer of oxygen within the metal-hydroperoxide-substrate complex. For example with 2-cyclohexen-1-ol, the reaction is virtually stereospecific[32,51].



t-BuOOH-VO(acac)$_2$	98%	2%
PBA	92%	8%

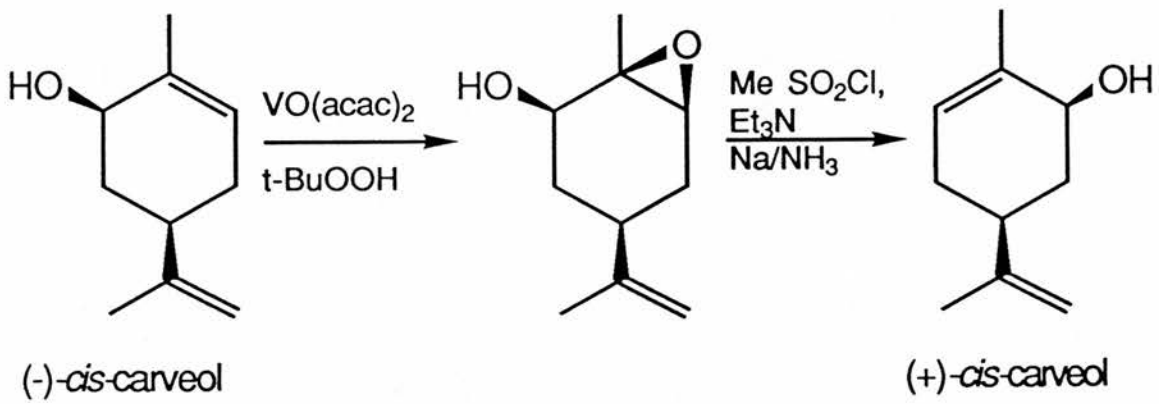
Equation 1.37

This difference in stereoselectivity is more pronounced for the homoallylic alcohol:



Equation 1.38

One of the more remarkable uses of $VO(acac)_2$ is in its exploitation for the stereoselective transposition of allylic alcohols[8].



Equation 1.39

Niobium and Tantalum

Nb(V) and Ta(V) alkoxides are poor epoxidants of alkenes with tert-butyl hydroperoxide[18]. Epoxidation of cyclohexene gave (tert-butylperoxo) cyclohexene as the major product.

1.9.3 Group VIa

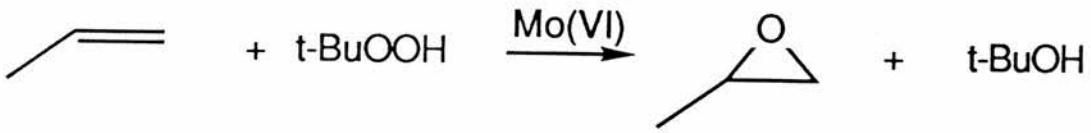
Chromium, Molybdenum and Tungsten

Chromium

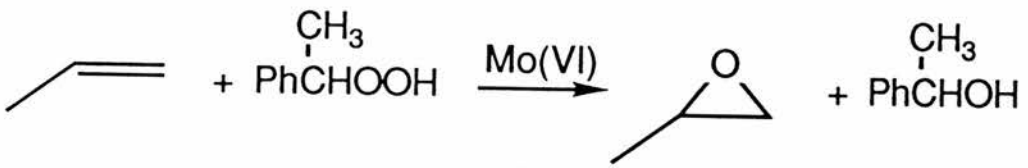
Chromium complexes eg. $Cr(acac)_3$ as discussed previously are poor catalysts for epoxidations. The main reaction is the breakdown of tert-butyl hydroperoxide giving molecular oxygen[18]. The high Lewis acidity of Cr(VI) is not mitigated by the fact that Cr(VI) is a strong oxidant which promotes the decomposition of t-BuOOH.

Molybdenum

Molybdenum(VI) complexes are considered to be the best catalysts for the epoxidation of alkenes with alkyl hydroperoxides as oxidants. This topic is well covered in the literature[8,18,39,51]. Molybdenum catalysts are commercially important because of the large scale production of propene oxide from propene with t-BuOOH or 1-phenylethyl hydroperoxide (the Halcon Process).



Equation 1.40



Equation 1.41

The tert-butyl alcohol co-product can be recycled by dehydration followed by hydrogenation and then the isobutane autoxidised to the hydroperoxide by molecular oxygen or converted to methyl tert-butyl ether, a gasoline additive with good anti-knock properties and an octane improver for petrol[8]. The co-product 1-phenylethanol obtained when 1-phenylethyl hydroperoxide is used as the oxidant, can be dehydrated to styrene or recycled[7,8]. Propene is epoxidised in 85% yield with H_2O_2 in the presence of molybdenum catalysts[8], but the water present must be continuously removed by azeotropic distillation.

A wide range of molybdenum complexes can be used for epoxidations, the more commonly used are $Mo(CO)_6$ and $MoO_2(acac)_2$[18]. Phosphine oxide complexes of molybdenum(VI) have also been used[52]. Various clusters[53] and even metallic molybdenum[54] catalyse the epoxidation of many different alkenes with different peroxides as oxygen donors. The advantage in using $Mo(CO)_6$ or $MoO_2(acac)_2$ is that they catalyse the epoxidation of alkenes in high yield with low yields of byproducts like alkylperoxo compounds[8]. The catalytic properties are dependent on the ligands attached to molybdenum[55,56].

By way of contrast to oxochromium-porphyrins which can epoxidise alkenes directly, oxomolybdenum-porphyrin requires t-BuOOH for epoxidation[37]. Molybdenum catalysed epoxidations have been used with alkenes such as ethene[56] ($MoO_2(oxinate)_2$ catalyst gives 69% oxirane) up to larger molecules of biological interest[17] and polymers[57]. Several different heterogeneous Mo(VI) catalysts have been prepared[58] molybdenum zeolites being particularly effective. Some of the catalysts use molecular oxygen as the oxygen source[59].

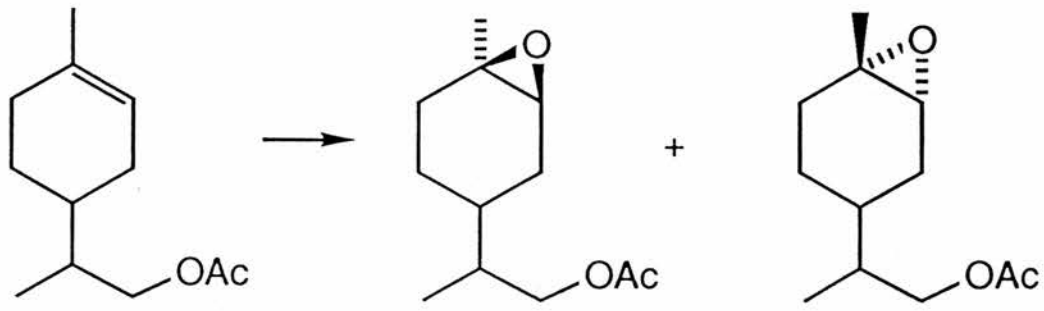
Epoxidations catalysed by $MoO_2(acac)_2$ are approximately 10^2 times faster than those catalysed by vanadium catalysts under similar conditions[60].

The mechanism for Mo(VI) catalysed epoxidations is similar to that discussed for the Ti(IV) and V(V)-catalysed epoxidations.

Although an effective catalyst for the epoxidation of 2-cyclohexenols, the stereoselectivity of $Mo(CO)_6$ is identical to that for $VO(acac)_2$ as catalysts. The molybdenum catalyst however reacted 50 times slower[61]. With the homoallylic alcohol 3-cyclohexen-1-ol a similarly high stereoselectivity was observed but the rates were very similar between $Mo(CO)_6$ and $VO(acac)_2$ as catalyst[32]. For non-cyclic allylic alcohols such as 1-butene-3-ol the *erythro*-selectivity was much poorer for $Mo(CO)_6$ as catalyst than for V(V)[34].

The mechanism is believed to be similar to that proposed for V(V) catalysis.

As described in Section 1.5, functional-group-mediated stereoselective epoxidations need not involve hydroxyl as the functional group. Tolstikov described stereospecific epoxidations of unsaturated acetates[29]. Surprisingly high selectivities were found for the acetates shown:



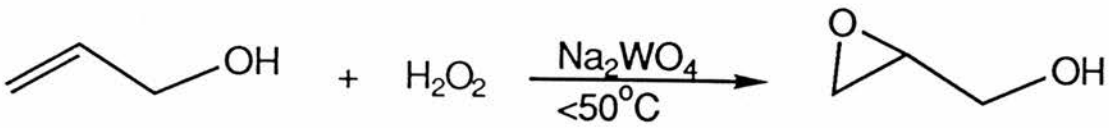
TAHP/$Mo(CO)_6$	100%	0%
PBA	50%	50%

Equation 1.42

and similarly for steroidal acetates[61]. These results are remarkable when it is considered that acetate groups are much less co-ordinating than alcohol groups. It should also be contrasted with the lack of stereoselectivity observed in the molybdenum-catalysed epoxidation of 1-cyclohexenyl acetate[32] found by Sharpless.

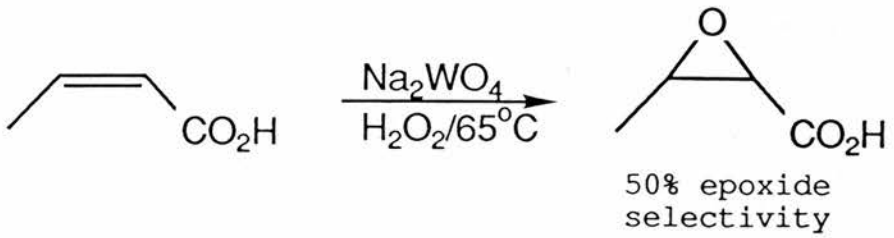
Tungsten

Tungsten(VI) complexes are probably the best transition-metal catalysts for epoxidations of alkenes with *hydrogen* peroxide. They do not however have the same broad synthetic utility as the *alkyl hydro*peroxide-metal reagents[8]. When hydrogen peroxide is used as oxidant, the presence of water can retard the reaction. Moreover, once formed the epoxide is readily hydrolysed to the corresponding glycol. The H_2O_2-metal catalyst reagents are useful for the epoxidation of water soluble alkenes such as allyl alcohol and the salts of α,β-unsaturated acids. The epoxidation of allyl alcohol to glycidol using H_2O_2-Na_2WO_4 is applied industrially as an alternative to the traditional route using epichlorohydrin[8].



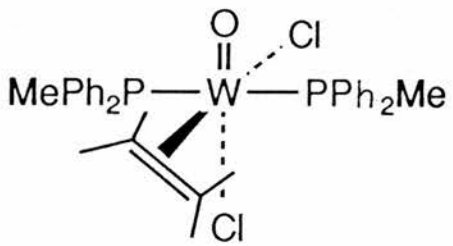
Equation 1.43

H_2O_2-metal combinations are the reagents of choice for the epoxidation of α,β-unsaturated acids which are[62] inert to alkyl hydroperoxide-metal reagents.



Equation 1.44

A fascinating tungsten complex, although d^2, which is the first ever example of a transition-metal complex containing both a terminal oxo ligand and an alkene has been characterised[63].



Structure 1.9

This type of complex could be involved in alkene epoxidations *via* metallacycles[63,64] but the complex does not rearrange to an epoxide[65]. Interestingly, the reverse reaction, an oxidative addition, leading to the complex, takes place when epoxides react with $WCl_2(PMePh_2)_4$[65].

1.9.4 Group VIIa

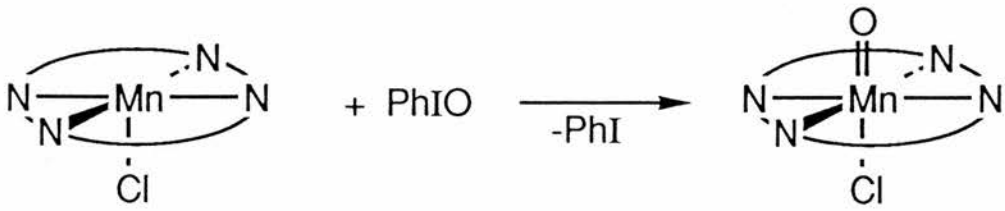
Manganese, Technetium and Rhenium

So far the catalytic properties of the metals in group IV and VI (except Cr) with peroxides as oxidant are mainly attributed to the coordinative properties of the transition metal by which the peroxide is activated toward nucleophilic attack by the alkene. The catalytic properties of

the metals in this section are mainly due to what Jørgensen[39] likens to an oxygen-rebound reaction in which the transition-metal serves as a relay for the oxygen atom transfer from the terminal oxidant to the alkene *via* an oxotransition-metal reactive intermediate. These transition-metal complexes can readily undergo one-electron changes eg. Mn(II) → Mn(III). However, a formal 2-electron oxidation state change of the catalyst has also been proposed for these systems by the reaction with an oxygen donor Mn(III) → O=Mn(V).

The interest in manganese complexes as catalysts arises from the relationship of these catalyst systems to the biologically relevant manganese porphyrins. Several different oxygen sources for Mn-porphyrin epoxidation catalysis have been used, including molecular oxygen and alkyl hydroperoxides[66]. These reactions are often non stereospecific with eg. the epoxidation of *cis*-stilbene giving both *cis* and *trans* stilbene oxide[67].

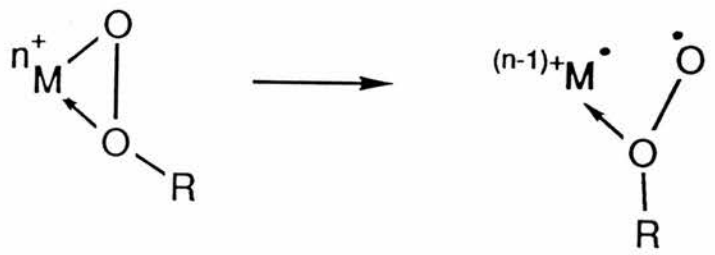
Mn(TPP)Cl catalyses the epoxidation of alkenes with iodosylbenzene as oxygen donor.



Equation 1.45

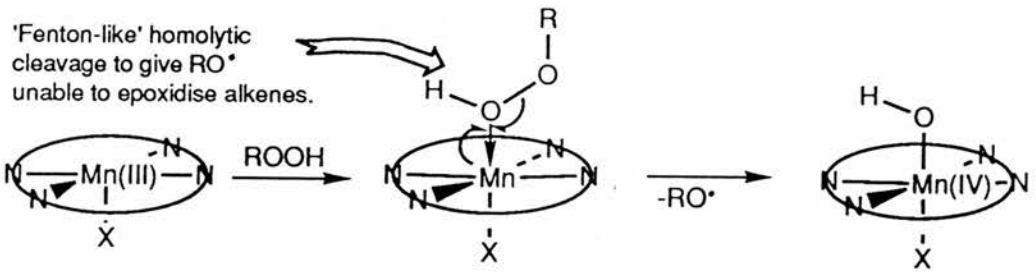
The first step is the formation of an unstable and reactive oxo-Mn(TPP)Cl complex which then epoxidises the alkene[67].

Problems often arise when alkyl hydroperoxides are used as oxygen sources since homolytic cleavage of the metal-oxygen bond occurs leading to the formation of a radical.

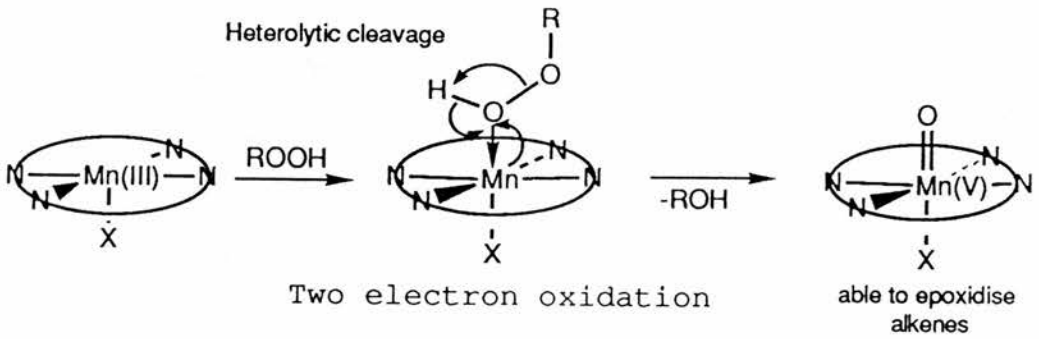


Equation 1.46

Nitrogen bases such as pyridine act as axial ligands of the catalyst and can increase the reaction rate, and hence the selectivity for epoxide formation. The stereoselectivity is also improved. The homolytic oxidation, corresponding to a one-electron transfer, and the heterolytic oxidation (2-electron transfer) of Mn-porphyrins by an alkyl peroxide is shown:



One electron oxidation



Two electron oxidation

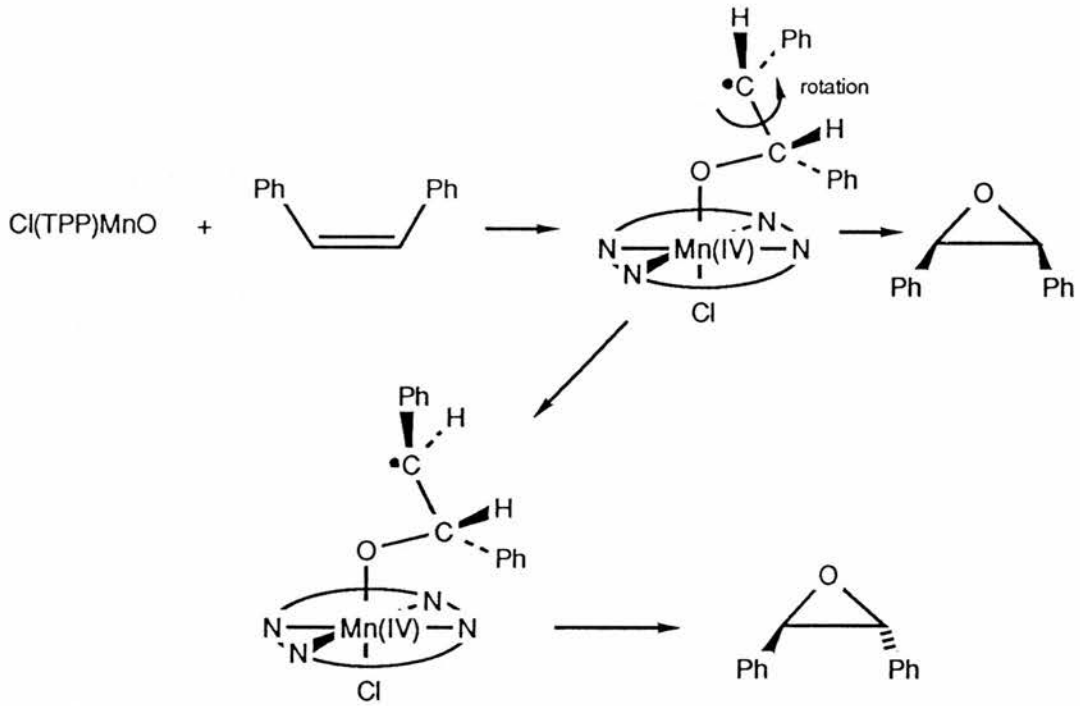
able to epoxidise alkenes

Equation 1.47

In the absence of the nitrogen base only traces of epoxides are observed when alkyl peroxides are used as oxidant. However, in the presence of imidazole epoxidation occurs with yields comparable to those obtained with PhIO as terminal oxidant[68].

It is still found however that electron-rich alkenes react faster than electron poor ones[69].

The loss of stereochemistry can be explained by the formation of a radical intermediate with a long enough lifetime to allow isomerisation by rotation around the C-C bond.



Equation 1.48

Cationic manganese(III)-salen complexes with electron-withdrawing groups on the salen ligand have greater catalytic activity[69]. Epoxidations of *cis*-alkenes produce high yields of the *cis*-epoxide with very little *trans* isomer. This is compatible with the radical intermediate proposal, if the rate of ring closure relative to that of

bond rotation is controlled by the electron-deficient Mn-centre. Two pathways were observed for the epoxidation of alkenes using alkyl hydroperoxides[70]. With t-BuOOH as terminal oxidant and cyclohexene as substrate both (tert-butylperoxo)cyclohexene and cyclohexene oxide were identified[70]. The pathway leading to the peroxycyclohexene involved a free radical chain mechanism, which is completely inhibited by the radical scavenger, ionol. The presence of ionol during the reaction does not affect the epoxidation when alkenes are treated with t-BuOOH/pyridine and a catalytic amount of Mn(III)-salen. The epoxide is formed *via* an oxo-manganese(V) complex[70].

The catalytic activity of the long lived ^{99}Tc isotope, and rhenium in complexes are similar to each other but low[39].

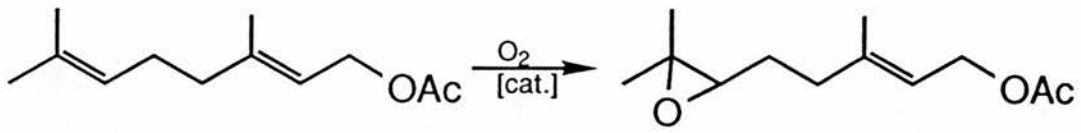
1.9.5 Group VIII

Iron, Ruthenium and Osmium

Iron

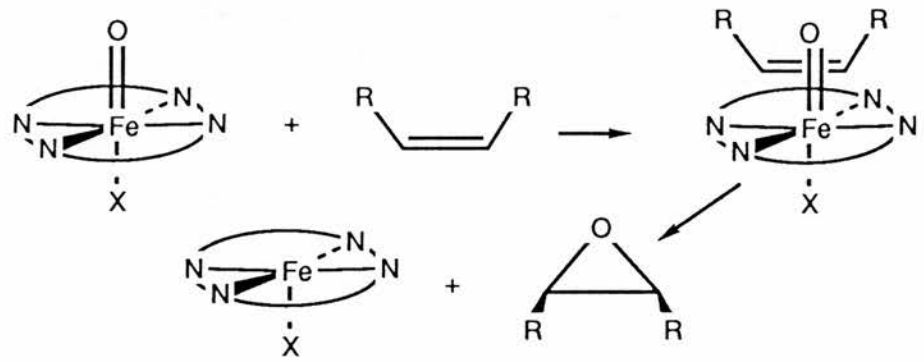
Although in many respects similar to Mn-epoxidation catalysis, the iron porphyrin catalysed epoxidations for example show different properties[60]. $Fe(acac)_3$-H_2O_2 produced *trans*-epoxides as the major products when *cis*-alkenes were used as substrates[39]. However, $Fe(III)Cl_3$-H_2O_2 gave the corresponding *cis*-epoxides[71]. The spereospecificity is in many cases terminal oxidant dependent[72].

Interestingly, treatment of geranyl acetate with $[Fe_3O(piv)_6(MeOH)_3]Cl$ and molecular oxygen produced only the 6,7 epoxy geranyl acetate[73].



Equation 1.49

In porphyrin systems it is probably the oxoiron porphyrin intermediate, which is a very unstable and reactive intermediate, that promotes the epoxidation. The ferryl complex shown is the most likely structure[66]. The suggested mechanism explains also the stereoselective epoxidation of *cis*-alkenes catalysed by Fe-porphyrins. This explains why there is a preference for reaction of *cis*-alkenes,



Equation 1.50

trans-alkenes will interact repulsively with the porphyrin ring[74].

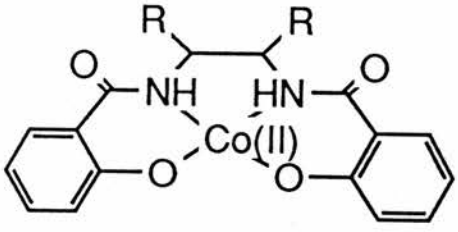
Ruthenium and Osmium

Ru(II) complexes like $RuCl_2(PPh_3)_3$ with O_2 or t-BuOOH are poor epoxidation catalysts[55]. However, dioxo(tetramesitylporphyrinato) ruthenium(VI) can epoxidise akenes with molecular oxygen[75] or PhIO[76] as oxidant.

The mechanism for the epoxidation step may be similar to that of iron because it has been observed that the epoxidation is nearly stereospecific[75] and that *cis*-alkenes are more reactive than *trans*-alkenes. A few osmium(III) complexes have catalytic epoxidation activity, however reaction times are long and epoxide yields low[78].

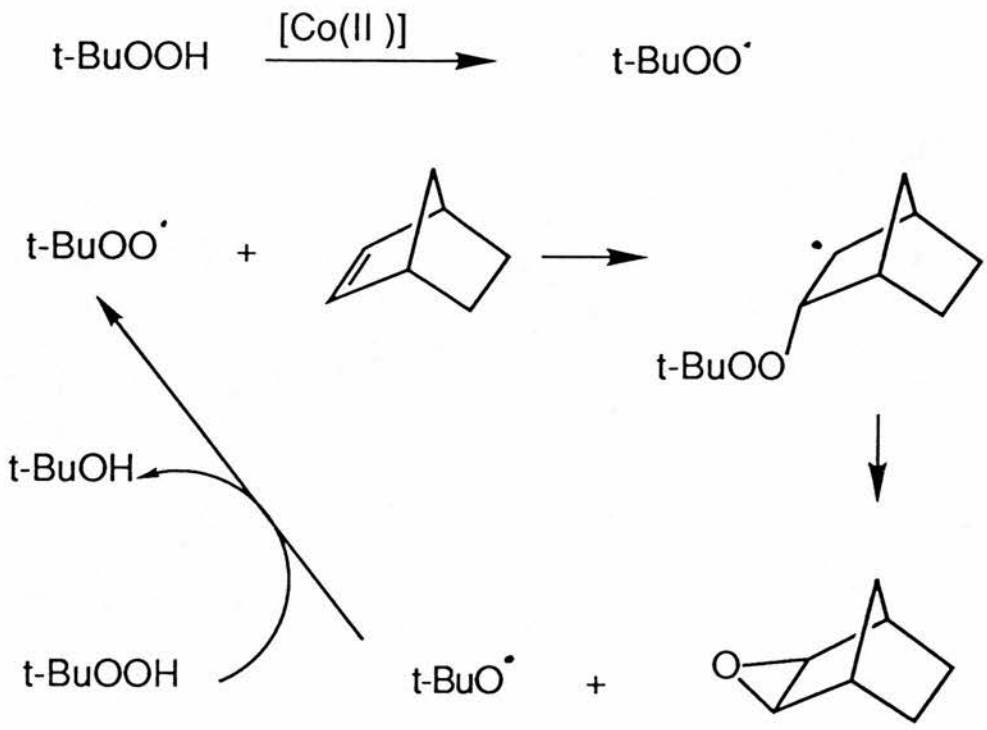
Cobalt, Rhodium and Iridium

$Co(acac)_2$ and $Co(acac)_3$ catalyse the epoxidation of alkenes with t-BuOOH as oxygen donor but again yields are low and long reaction times are required[78]. With t-BuOOH as terminal oxidant, a radical chain mechanism occurs, when Co(II) bis(salicylamide) is the catalyst. The formed tert-butylhydroperoxy radical adds homolytically to the C=C double bonds of systems in which the allylic hydrogen is less reactive than the C=C double bond[79].



Structure 1.10

Cobalt(II) bis(salicylamide) catalyst species



Equation 1.51

The reaction is associated with the Co(II)/Co(III) interconversion in the one-electron redox process by which the tert-butyl peroxy radical is formed.

$$RO_2H + Co(II) \rightarrow RO^{\bullet} + Co(III)OH$$

Equation 1.52

$$RO_2H + Co(III) \rightarrow RO_2^{\bullet} + Co(II) + H^+$$

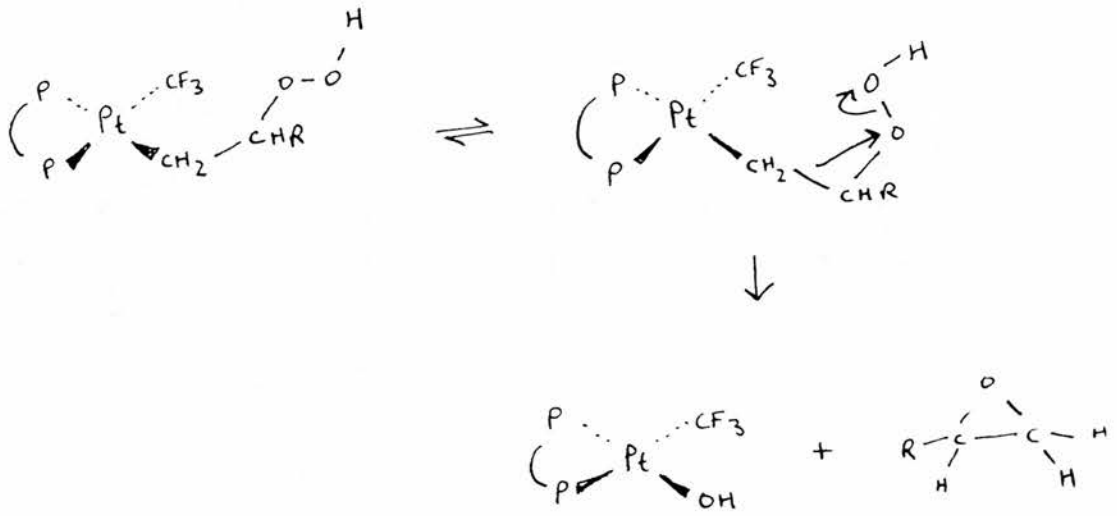
Equation 1.53

When the metal has two oxidation states of almost equal stability, reactions 1.52 and 1.53 occur concurrently. This is why Co compounds are among the most effective catalysts for autoxidation since they can induce the efficient catalytic decomposition of alkyl hydroperoxides.

Oxocobalt(IV) species can epoxidise a variety of alkenes[80], the oxygen transfer step shows high stereospecificity. The mechanism however seems to have more similarity to the chromium/oxomanganese oxidations than to the oxoiron transfers[79]. Several rhodium and iridium complexes are epoxidation catalysts however the formation of other oxidation products such as alcohols and ketones is common[80,81,82].

Nickel, Palladium and Platinum

Most Ni(II) complexes are completely ineffective epoxidation catalysts. However, complexation of Ni(II) to tetraaza macrocycles such as cyclam does give catalysts for alkene epoxidation[83]. Many Palladium(II) complexes are unreactive also but Pd(II) catalysts with α-(silyloxy)alkyl peroxobenzoates as terminal oxidants give epoxides[84].
Interestingly dilute H_2O_2 and hydroxy-platinum(II) complexes are effective systems for the epoxidation of terminal alkenes[85]. Cyclohexene and *cis*-2-hexene do not react. The hydroxy-platinum(II) complex is in equilibrium with the Pt-cation and the hydroxide anion, which abstracts a proton from hydrogen peroxide. The alkene coordinates to the platinum cation, and the hydrogen peroxide anion performs a nucleophilic attack on the coordinated alkene[86] the following mechanism for the formation of the epoxide seems reasonable[87].



Equation 1.54

1.9.6 Group Ib

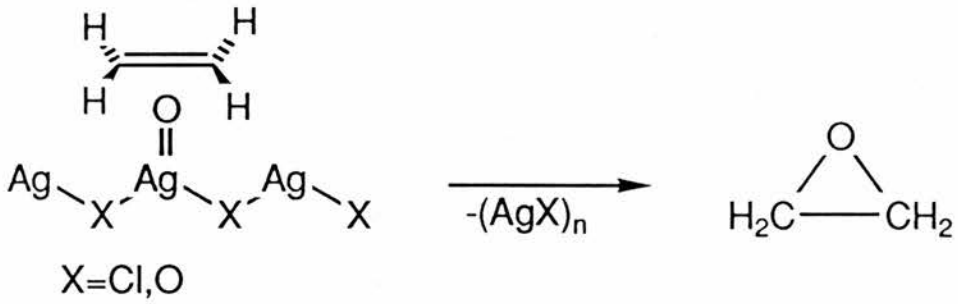
Copper, Silver and Gold

Copper(II) nitrate can catalyse the epoxidation of alkenes with PhIO as terminal oxidant[88]. The reaction is non stereospecific giving *trans*-stilbene oxide from *cis*-stilbene[89]. Gold complexes such as $Au(PPh_3)Cl$, (d^{10}), can achieve epoxidation of cyclohexene in low yield with molecular oxygen[89].

Although strictly a heterogeneous process, the supreme industrial importance of silver catalysts for the epoxidation of ethene warrants at least a brief discussion.

Oxirane is prepared commercially by the gas-phase oxidation of ethene with air or oxygen over a supported silver catalyst, which is uniquely effective, at elevated temperatures (*ca.* 250°C)[90]. Unfortunately, the oxidation of propene and higher alkenes under these conditions leads to low yields of epoxides. The Ag-catalysed autoxidation is successful

only with ethene for the following reasons: (1) the absence of labile C-H bonds renders the radical chain propagation steps *via* hydrogen abstraction unfavourable; (2) Polyperoxide formation by homolytic addition is slow, such that the low stability of the intermediate adduct $ROOCH_2\dot{C}H_2$ makes unimolecular cleavage to epoxide formation more favourable than the polyperoxide formation[8] *via* the bimolecular reaction with dioxygen. The mechanism for the epoxidation may involve a silver-oxo species[39]



Equation 1.55

and is similar to the oxo transfer involved with manganese epoxidation catalysts.

1.9.7 Conclusion

In transition-metal-catalysed epoxidations several types of mechanisms are operating. Three types of complex are involved in the transfer of an oxygen atom from the reactive intermediate to an alkene.
(1) transition-metal-peroxide complexes; (2) oxotransition metal complexes and (3) the peroxo radical.

The transition-metal-peroxide complexes are those of the early transition-metal series, where the transition metal is d^o, the highest oxidation state, making peroxide coordination possible. The oxo

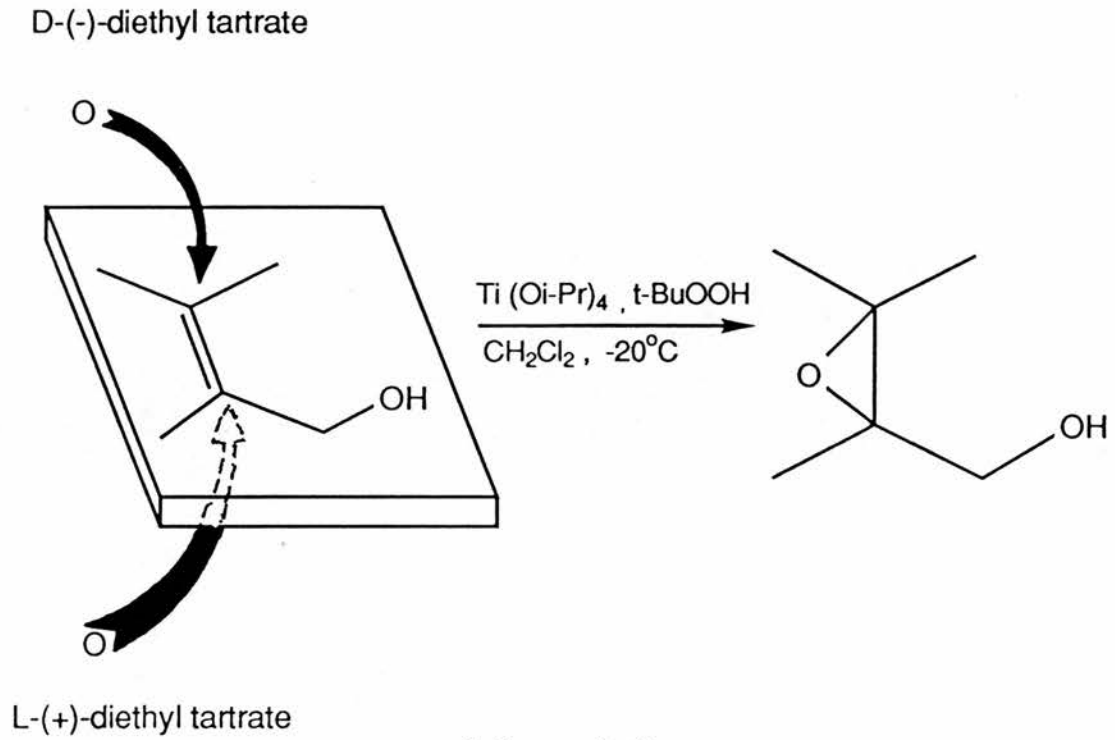
transition-metal complexes act as catalysts from the middle towards the late transition-metal series. Type (1) transfer of oxygen to an alkene is thought to be by interaction of the alkene either with one of the electrophilic peroxygens or *via* a peroxymetallocycle as proposed by Mimoun. The former being similar to the peracid mechanism. The existence of the peroxymetallocycle intermediate however cannot be ruled out. Type (2) complexes transfer the oxygen to an alkene by interaction of both the oxygen and the metal forming a metallocycle. Some data however indicate an interaction between the oxygen and either or both of the carbons in (3) operating in systems which can undergo electron transfer processes and the epoxidation takes place for alkenes in which abstraction of the allylic hydrogen is disfavoured compared to the addition to the C=C bond.

1.10 Asymmetric Epoxidation/Kinetic Resolution

Since much of the work described in this thesis is concerned with asymmetric epoxidation, it is necessary to discuss one of the most important developments in asymmetric synthesis to date, that of asymmetric epoxidation catalysis[7,49].

1.10.1 Introduction

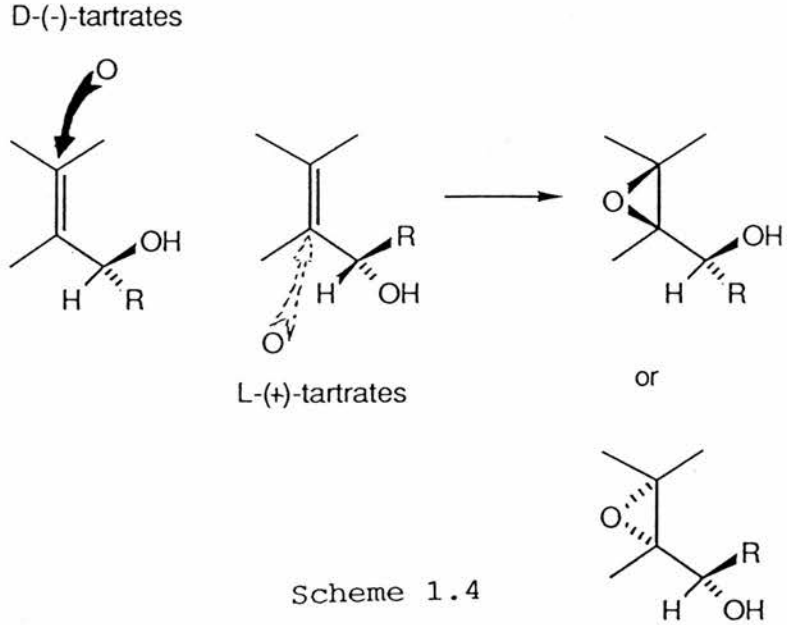
In 1980 after a decade of work Sharpless and co-worker Katsuki reported the titanium-catalysed asymmetric epoxidation. By such means it became possible to synthesise the epoxides of allylic alcohols in typically 70-90% yield and in greater than 90% ee.



Scheme 1.3

It was later shown that the same system could be used in the kinetic resolution of secondary allylic alcohols.

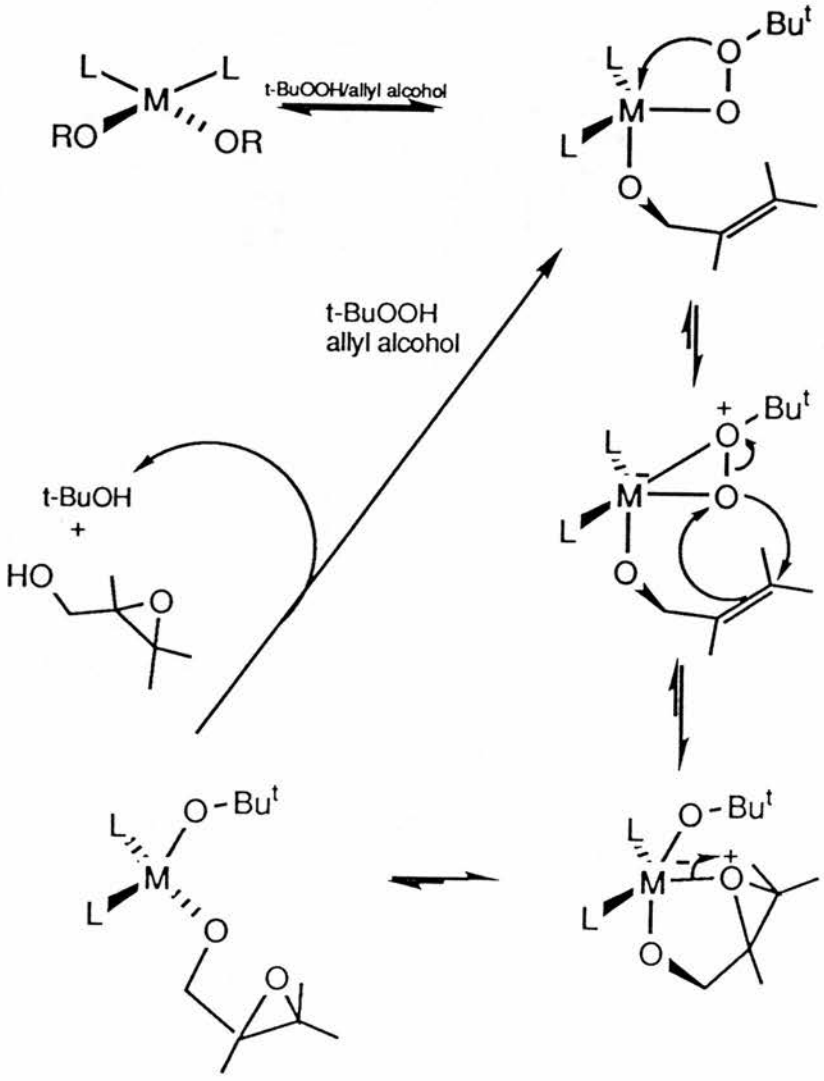
It was found in the epoxidation of isopropyl vinyl carbinol that compared with eg. an *erythro*:*threo* ratio of around 3:1, with various titanium alkoxides, when L-(+)-diethyl tartrate was used as chiral auxiliary it was found that the epoxidation had ceased at about 50% conversion with an *erythro*:*threo* ratio of 97:3. Only one enantiomer had been epoxidised and the unreacted enantiomer was recovered in an optically pure form.



Scheme 1.4

1.10.2 Mechanism

The mechanism provided by Sharpless is similar to that of other early transition-metal catalysed epoxidations.



Equation 1.55

The metal-catalyst $ML_n(OR)_m$, has 0,1, or 2 oxo ligands L and 2 to 4 alkoxide ligands (OR) depending on the metal.

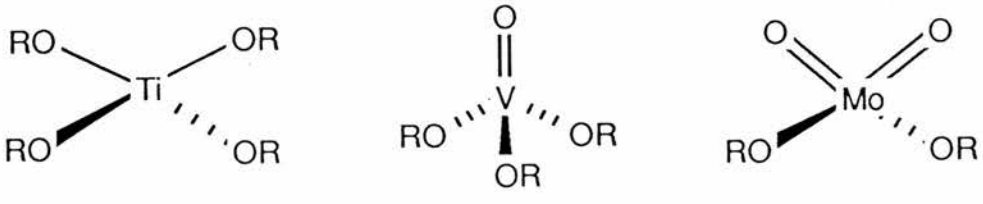
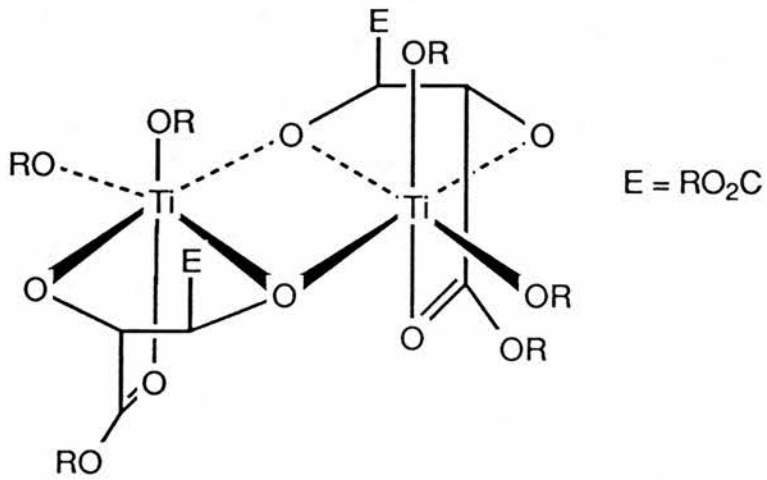


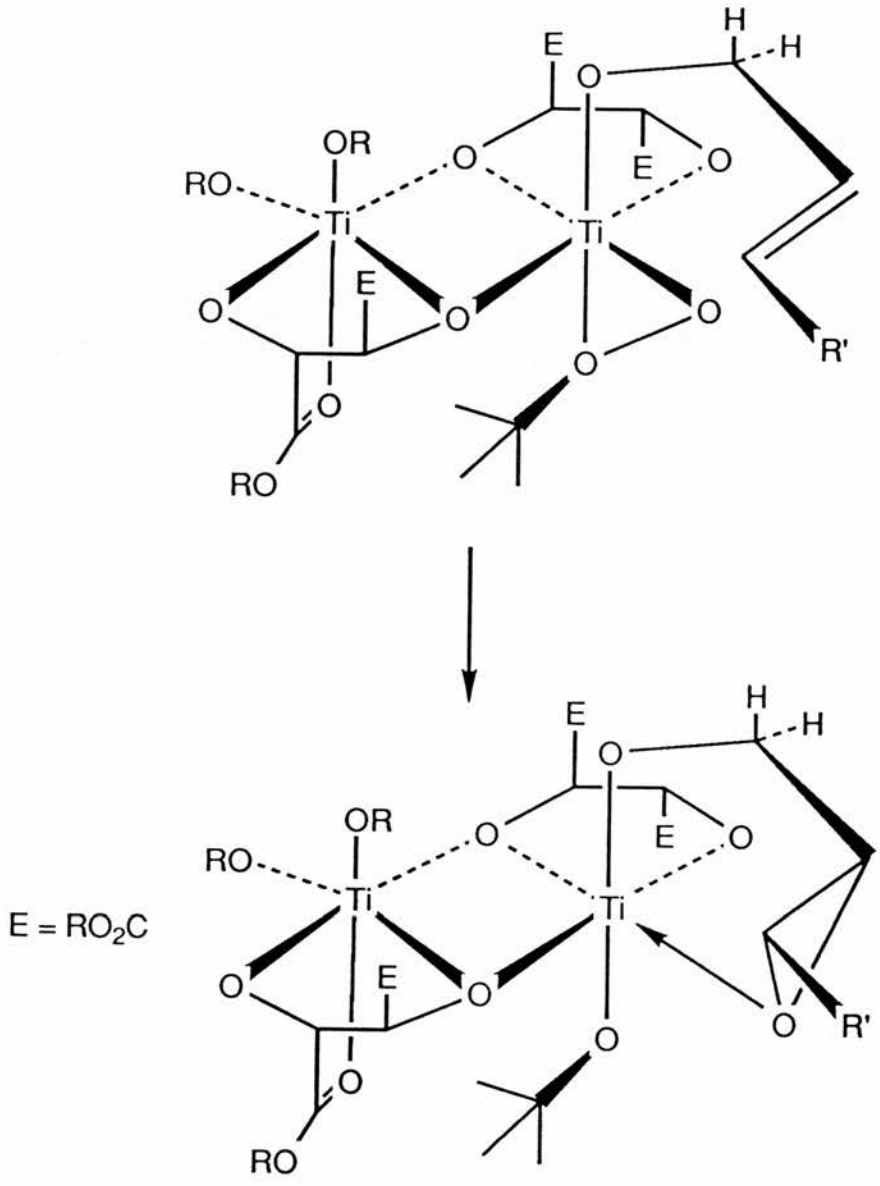
Figure 1.6

The structures of several catalytically active titanium-tartrate complexes have been determined by X-ray crystallographic investigations[7, 91]. The titanium-tartrate complexes are at least dimeric, and the structure of one is shown:



Structure 1.7

The mechanism of asymmetric epoxidation can be explained from both an experimental[17] and theoretical[40] viewpoint. It is likely that the axial and equatorial ligands undergo exchange with a coordinated peroxide and that the axially coordinated ester group is released from the titanium centre in which the peroxide bond is nearly perpendicular to the equatorial plane. This results in a linear alignment of allylic atoms and a roughly octahedral titanium coordination geometry as shown[17].



Equation 1.57

What is important about the titanium(IV) alkoxides is that the titanium has four covalently bound alkoxide ligands whereas other active catalysts do not.

Titanium does not form the Ti=O species easily unlike vanadium(V), molybdenum(VI) and tungsten(VI) for which stable oxo complexes are well known. These metal-oxo species therefore are only able to covalently bond to three alkoxide ligands for V(V) and two for Mo(VI) and W(VI), as such they cannot coordinate simultaneously with both oxygens of the hydroperoxide allylic alcohol and a bidentate ligand; this is

consistent with the often disappointing results with these catalyst systems[92].

Table 1.1 shows the results of asymmetric epoxidation with various metal alkoxides[17].

Table 1.1

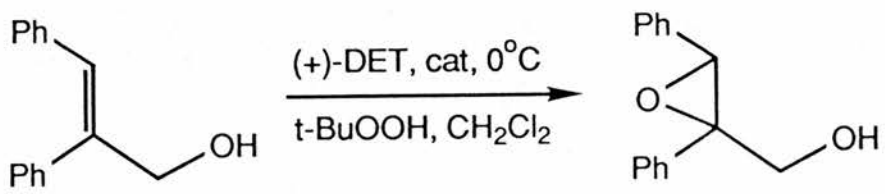
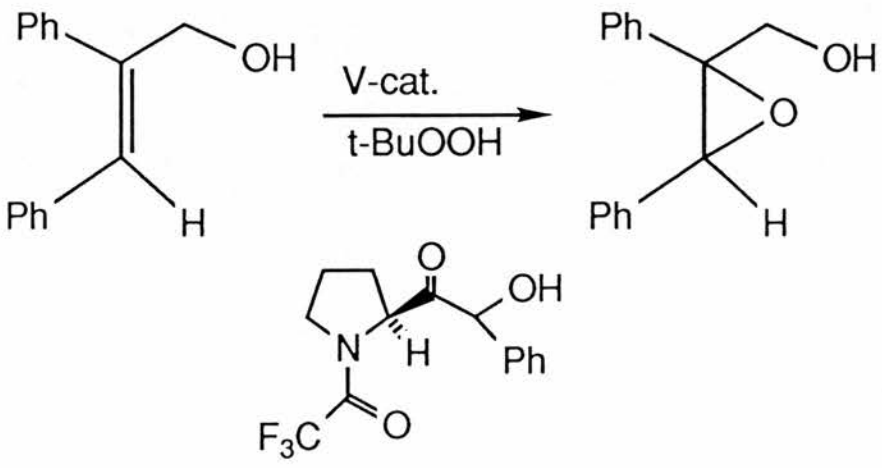


Table 1.1

$M(OR)_n$	%ee	Configuration at C2
$MoO_2(acac)_2$(40°C) ((+)-DiPT)	15	R
$VO(Oi\text{-}Pr)_3$	17	R
$Zr(Oi\text{-}Pr)_4$	10	R
$Ti(Oi\text{-}Pr)_4$(<2h;20°C)	95	S

From the table it can be seen that the metal alkoxides give reversed asymmetric induction from that observed with titanium, and also the reactions were much slower than that observed for titanium. It seems that Ti(IV) posesses the unique property that not only is it an active epoxidation catalyst for allylic alcohols but also that it can induce asymmetry effectively in the presence of tartrate-like ligands.

It is worth noting that vanadium(V) in the presence of hydroxamate ligands as chiral auxiliaries induces asymmetric epoxidations of allylic alcohols[93]. The chiral hydroxamate ligands shown gives up to 80% ee in the epoxidation of (E)-α-phenylcinnamyl alcohol.



Equation 1.58

1.10.3 Ligands

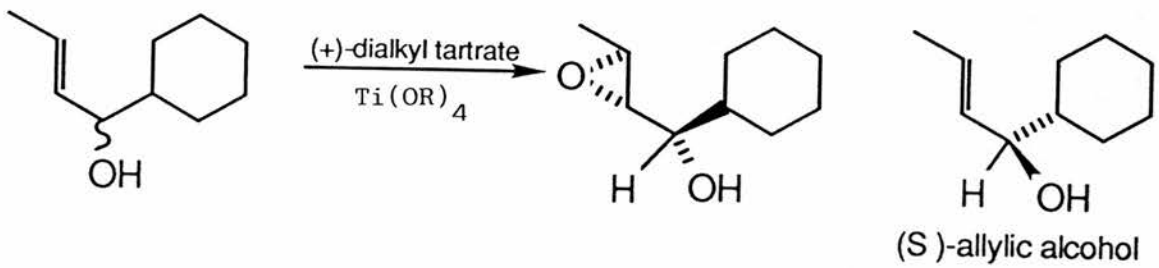
The most generally used ligands are dimethyl, diethyl and diisopropyl tartrates. These are readily available and in enantiomerically pure form and are inexpensive.

The steric bulk of the ester is important in modifying the catalyst properties, so that for diadamantyl and di-tert-butyl tartrates the reaction is slow and enantiomeric excesses are low[17].

The steric bulk is also important in determining the efficiency of the kinetic resolutions. In this reaction, one enantiomer reacts faster than the other, the efficiency being related to the relative rates of reaction of the fast and slow-reacting enantiomers K_f/K_s[94]. If one enantiomer reacts infinitely faster than the other then enantiomerically pure allyl alcohol can be produced by running the reaction to 50% conversion, when all of the fast reacting isomer has

reacted and none of the slow. For relative reaction rates less than infinity, the reaction must be carried to some degree of conversion beyond 50% to convert all of the fast acting isomer, leaving less than 50% of the slow.

For the allylic alcohol below it can be observed[96] that the relative rate K_{rel} for DMT, DET, and DiPT are 19, 36, and 104 respectively



Equation 1.59

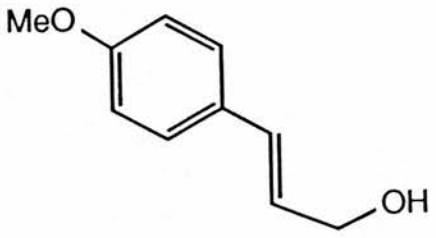
and so it can be deduced from this and studies on other allylic alcohols[95] that the relative rate values increase markedly with the size of the tartrate ester group. The use of (+)-DIPT results in a more efficient resolution.

A large range of ligands has been screened by Sharpless and co-workers[96] but none are as effective as the tartrate ligands.

1.10.4 Substrate Reactivity

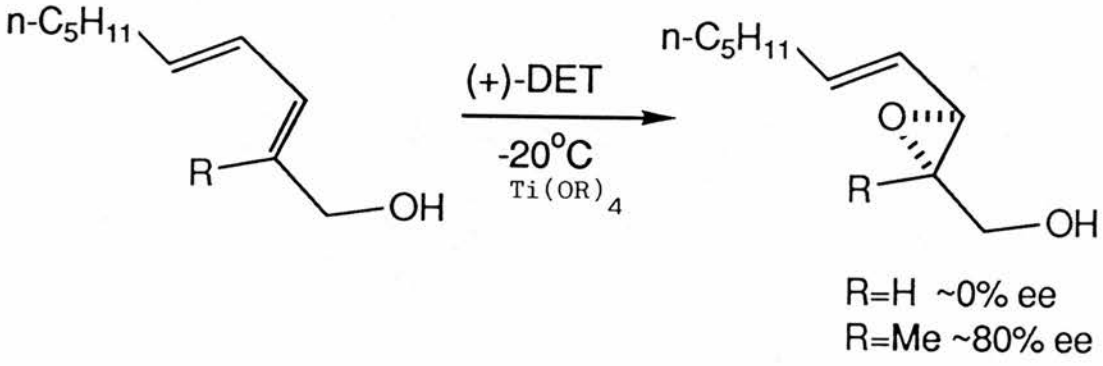
The titanium-tartrate catalyst reacts most efficiently with allylic alcohols. Similarly β-amino alcohols react more efficiently than other amino alcohols to yield products with high enantioselectivity. Like the epoxidations with other metals and peracids, the rate of reaction increases with electron density on the alkene[96]. The drawback to working with the highly reactive allylic alcohols is their high sensitivity to

decomposition, thus the highly reactive *p*-methoxyphenyl substituted allylic alcohol is susceptible to further reaction



Structure 1.8

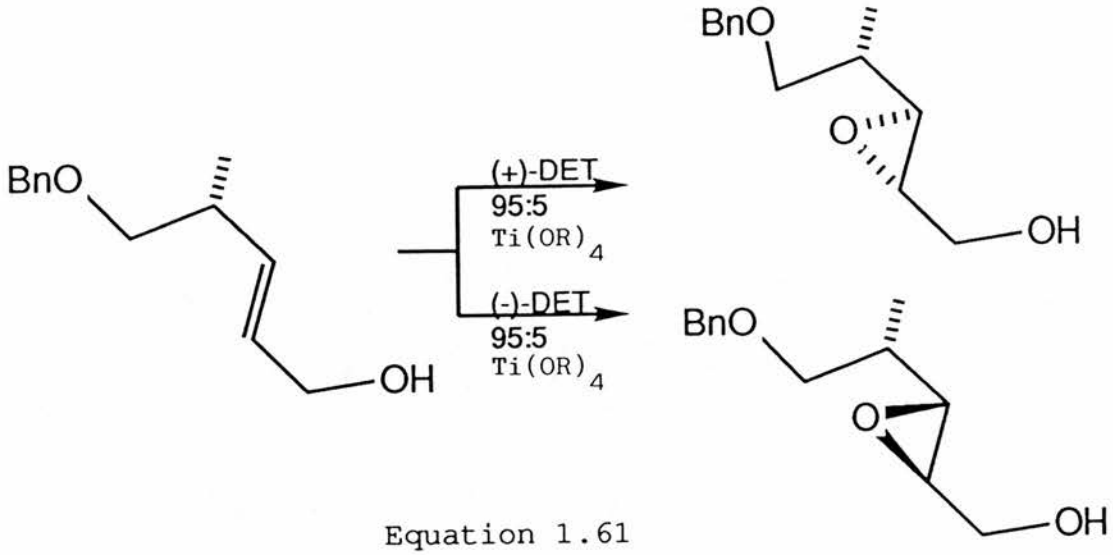
although alkyl substituents stabilise the epoxides to decomposition.



Equation 1.60

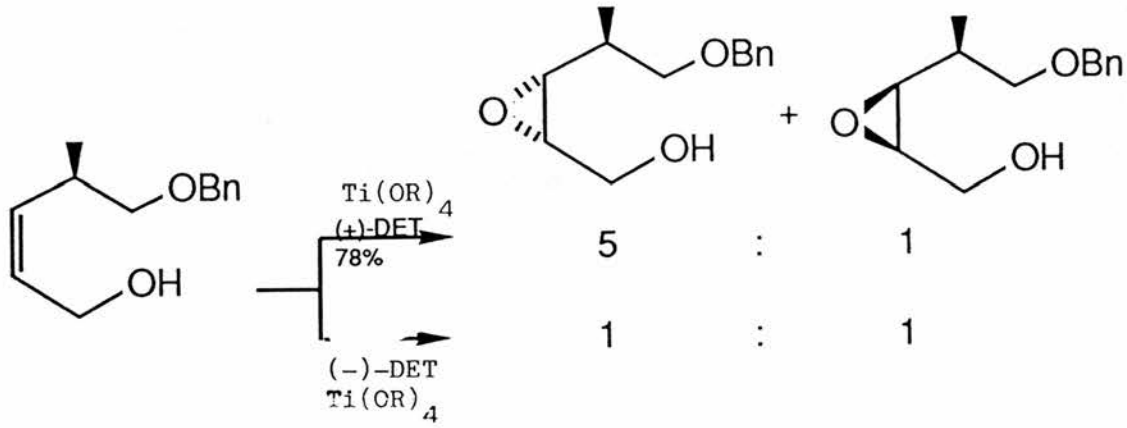
The rate of the reaction is sensitive to the steric nature of the allylic alcohol. Particularly with bulky groups at C-3 there is a noticeable rate retardation.

In two similar reactions the highly substituted (*E*)-allylic alcohol is epoxidised rapidly with high selectivity using either (+)-or(-)-DET.



Equation 1.61

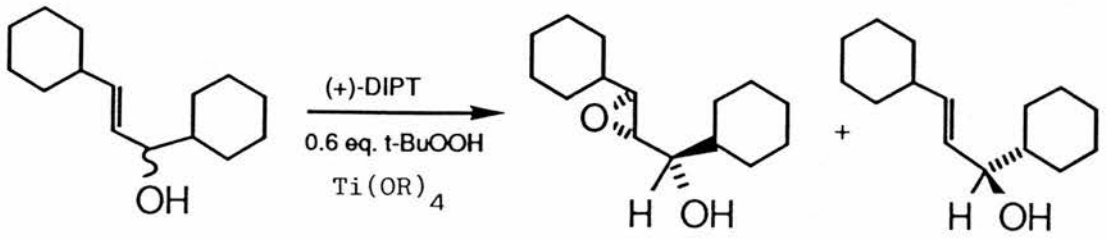
whereas the (*Z*)- isomer reacts slowly with modest to no selectivity[97].



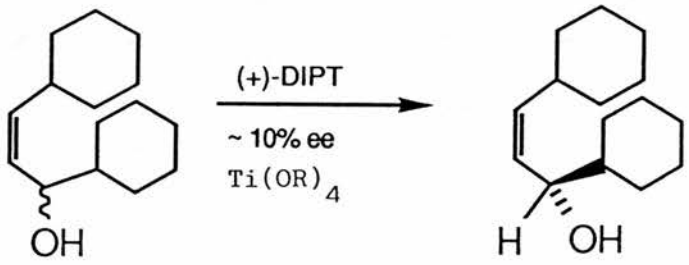
Equation 1.62

Similar observations are found with other *cis* and *trans* allylic alcohols[99].

Clearly then it can be seen that epoxidations of (*Z*)-allylic alcohols are sluggish with diminished selectivity. This is similar for the kinetic resolutions of secondary (*Z*)-allylic alcohols[17,95] as shown by the comparison of the following.



Equation 1.63

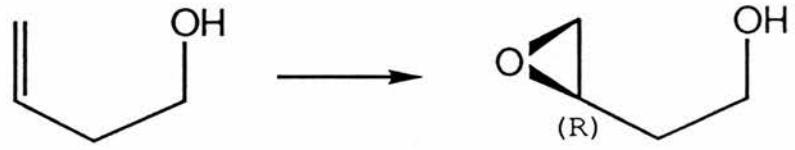


Equation 1.64

The resolution in Equation 1.63 is accomplished in 15 hours giving the epoxide and allylic alcohol both with high ee. The (*Z*) analog however, was poorly resolved. Secondary alkyl or aryl groups on C-4 of a (*Z*)-allylic alcohol results in low rates and selectivity.

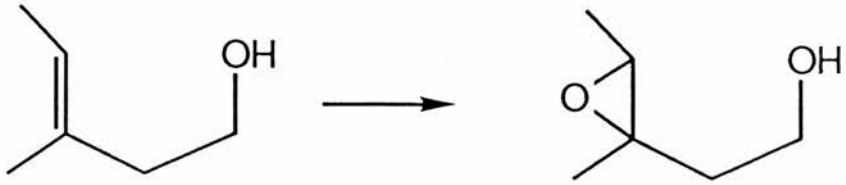
Homoallylic Alcohols

Homoallylic alcohols react sluggishly with poor yields and enantioselectivity compared with the corresponding allylic alcohols[17].



11-25% yield 55% ee

Equation 1.65

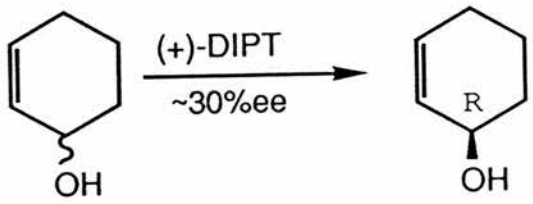


15% yield 0% ee

Equation 1.66

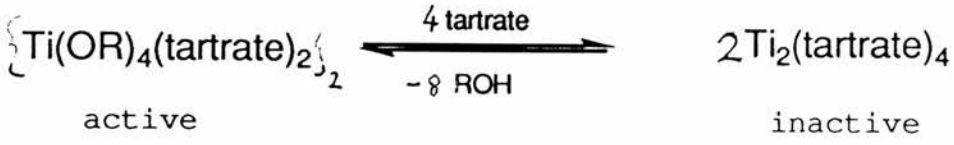
1.10.5 Reaction Conditions

The asymmetric epoxidations and kinetic resolutions are best optimised by using a titanium:ligand ratio of 1:≥1.2. Ratios of 1:<1 result in lower enantioselectivity. The kinetic resolution of 2-cyclohexenol failed when a 1:1 ratio of Ti:tartrate was used. However, an ee of 30% was obtained with a 1:1.5 ratio.



Equation 1.67

The use of an excess of tartrate retards the reaction by occupying the catalytic sites on the metal previously occupied by the alkoxides.



Equation 1.68

Tert-butyl hydroperoxide

To obtain reasonable rates, 1.5 to 2.0 equiv. of hydroperoxide are used for asymmetric epoxidations and 0-6 equiv. for kinetic resolutions so that only the fast reacting isomer is epoxidised.

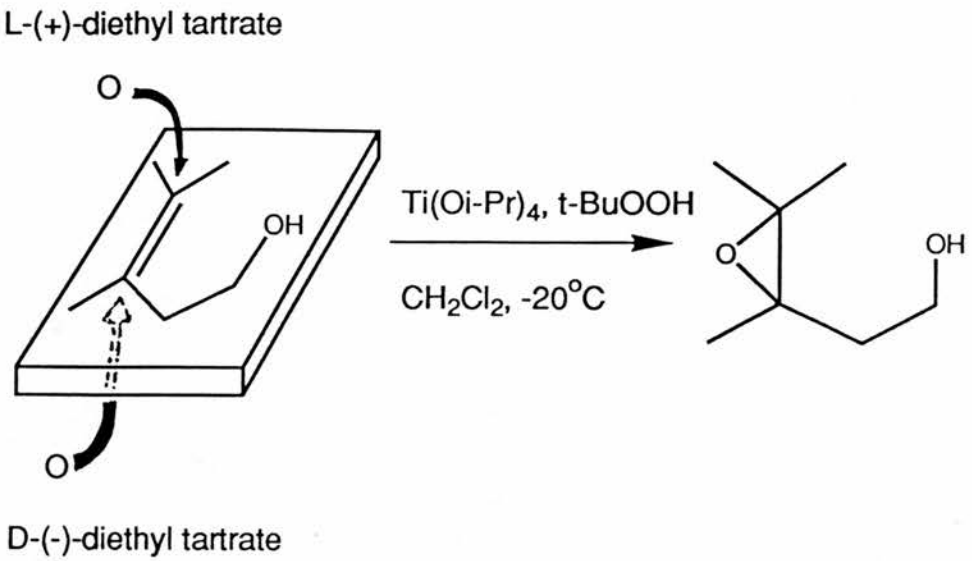
Catalyst Quantity

For most asymmetric epoxidations stoichiometric amounts of the titanium(VI) tartrate reagent are used, it was discovered however the presence of activated 3-or 4-Å molecular sieves caused the reaction to be catalytic and that most of the allylic alcohol substrates could be epoxidised with as little as 5 mol% of the titanium-tartrate catalyst with ee's as high as 95%. It is thought that it is the presence of adventitious moisture which poisons the catalytic sites by forming titanium hydroxides and oxo-bridged Ti-O-Ti units. For example the presence of 1 mol. equivalent of water in the stoichiometric epoxidation of (*E*)-α-phenylcinnamyl alcohol results in a drop of enantioselectivity from 98 to 48% ee.

1.10.6 Stereoselectivity

It is possible to predict the stereochemical outcome of asymmetric epoxidations with most substrates. The stereochemical rule for primary allylic alcohols is shown in Scheme 1.3. For a given tartrate ligand, the system delivers the epoxide oxygen from the same enantioface of the alkene regardless of the alkene substitution pattern. When the alkene unit is in the plane as indicated the use of (+)-tartrates leads to epoxidations from the underside. The use of (-)-tartrates leads to epoxidation from the topside.

For homoallylic alcohols, this stereochemical rule is reversed and that the use of L-(+)-DET delivers the oxygen primarily to the top side of the alkene as shown. It should be noted however that in general the % ee is significantly lower than for the corresponding allylic alcohols.



Scheme 1.5

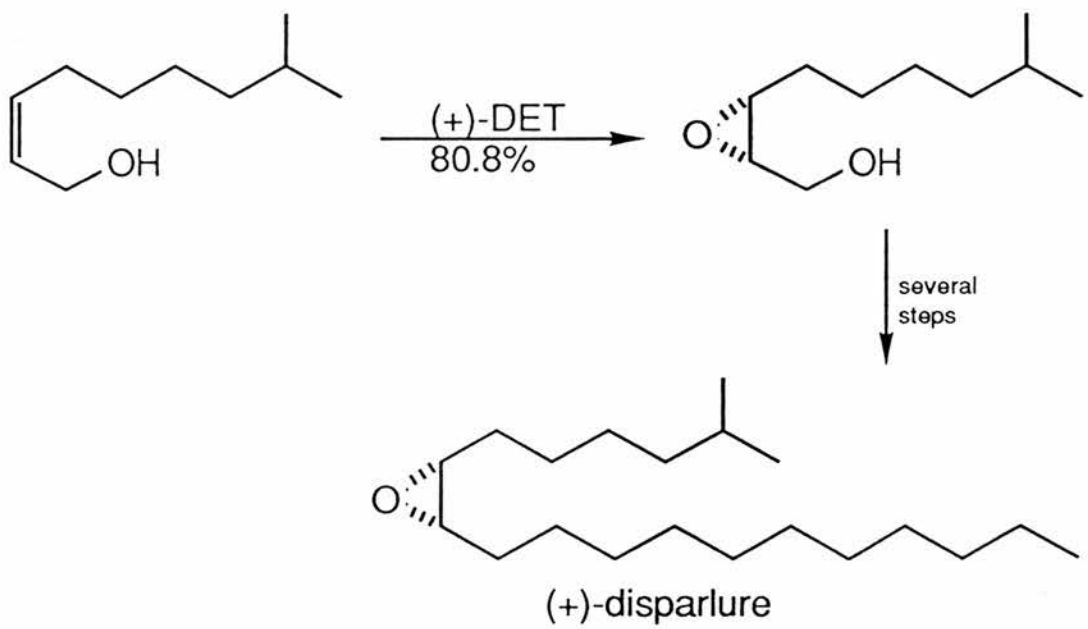
The selectivity rules for kinetic resolutions are detailed by Rossiter[17].

1.10.7 Synthetic Utility

Asymmetric epoxidation is now commonly used as a key step in the synthesis of many chiral compounds.

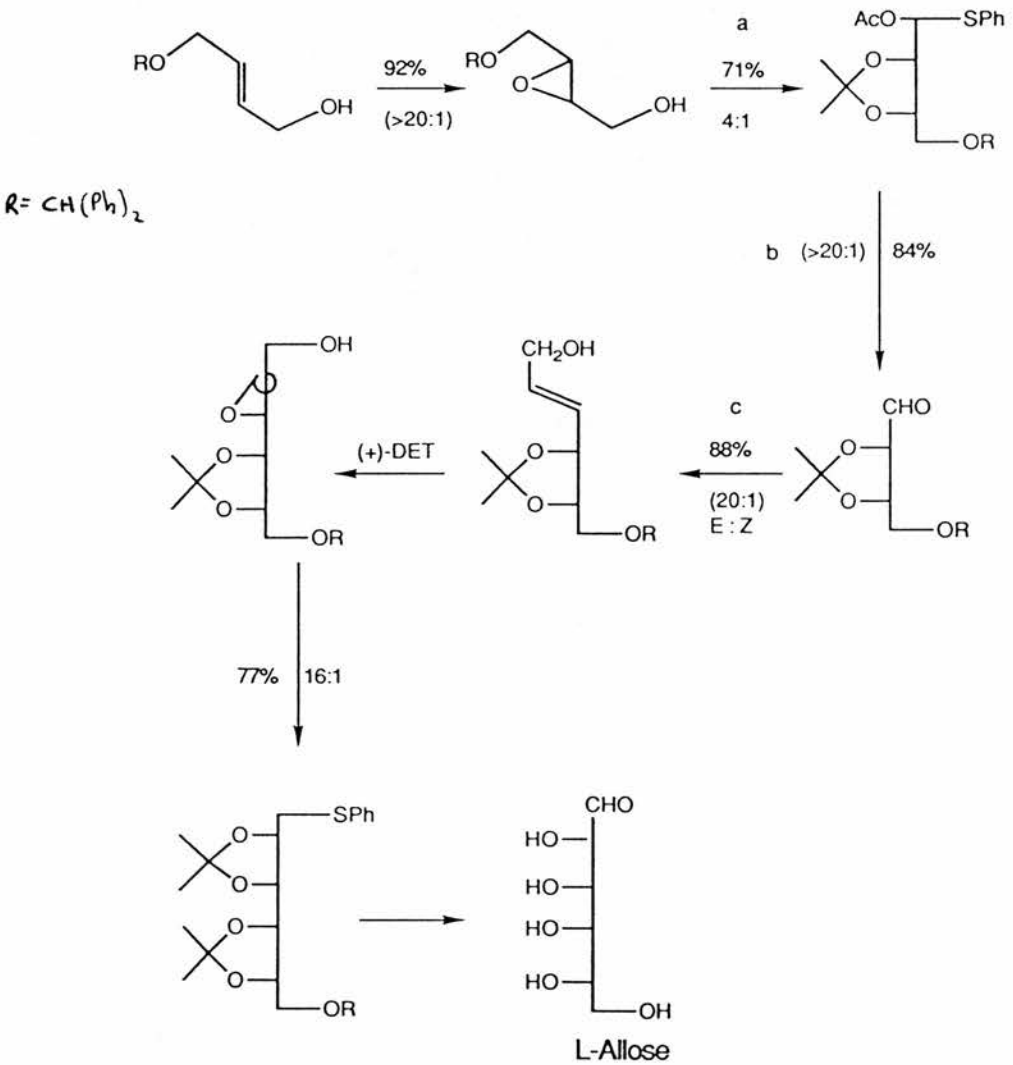
(+)-Disparlure

The first natural product containing the epoxide functionality to be synthesised by asymmetric epoxidation was (+)-disparlure, the gipsy moth sex attractant[99,100].



Equation 1.69

Since then there have been many uses of asymmetric epoxidation for the synthesis[17]. Perhaps the area of synthesis most affected by asymmetric epoxidation is that of polyhydroxylated compounds such as carbohydrates. Asymmetric epoxidation has greatly simplified the synthesis of such compounds. Previous attempts at asymmetric synthesis from achiral starting materials had been rare. One of the most sophisticated applications was the total synthesis of the hexose sugars. Sugars such as L-Allose, L-Glucose and L-Idose have been successfully snthesised from achiral starting materials by asymmetric epoxidation with a reiterative procedure involving further epoxidation[17].



a PhSH;0.5 M NaOH; $(CH_3)_2C(OMe)_2$; MCPBA; Ac_2O b DIBAL; K_2CO_3, CH_3OH

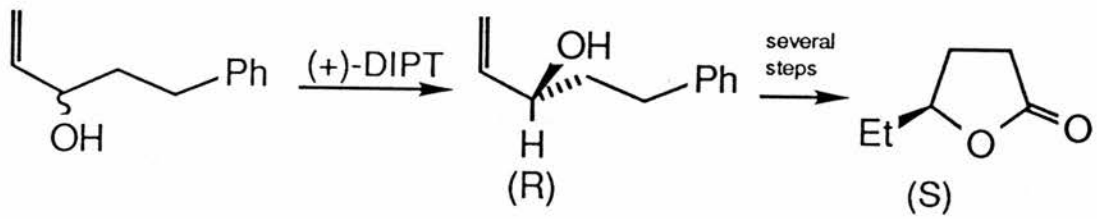
Equation 1.70

c $Ph_3P=CH-CHO$

1.9.8 The Use of Kinetic Resolution in Organic Synthesis

Kinetic resolution is widely used in organic synthesis. The advantage of kinetic resolution is that the starting substrate can be resolved to very high enantiomeric purity. This is of vital importance for example in pharmaceuticals where two enaniomers are formed, and if the unwanted enantiomer is harmful, it has to be separated.

Such a method has been used[101] in the preparation of several bioactive compounds. Kinetic resolution was used for example in the preparation of (-)-α-caprolactone.



Equation 1.71

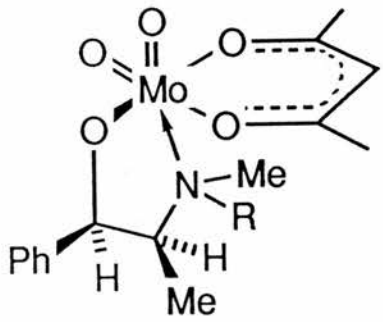
The allylic alcohol is kinetically resolved to give the R-allylic alcohol which is transformed to the desired product.

1.10.9 Other Systems

While nearly enantiomerically pure α-hydroxyalkyloxiranes can be prepared by asymmetric Sharpless epoxidation of allylic alcohols no such versatile procedure has been available for the metal-mediated epoxidation of unfunctionalised alkenes so simple methods for this are discussed in the following section.

Molybdenum

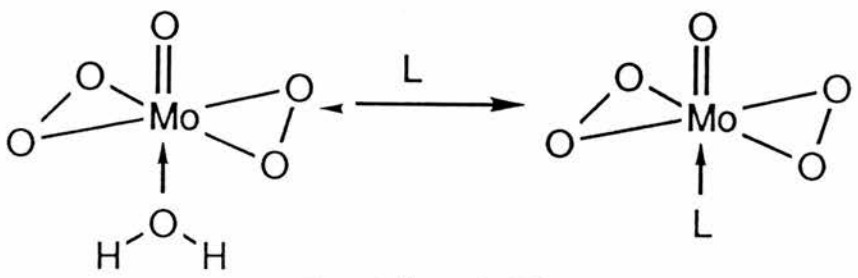
Although chiral molybdenum catalysts such as the dioxomolybdenum complex of N-methyl ephedrine (Structure 1.13) with cumene hydroperoxide gave up to 33% ee of the epoxides of allylic alcohols[102], the use of chiral molybdenum catalysts for the asymmetric epoxidation of isolated alkenes gives disappointing results. For example the use of $MoO_2(acac)_2$/t-BuOOH in the presence of optically active sugar derivatives and tartrate esters as catalysts gave only 10.2% ee[102].



Structure 1.13

Molybdenum(VI)(oxo-diperoxo) complexes

Molybdenum(VI)(oxo-diperoxo) complexes can be prepared by reaction of MoO_3 with H_2O_2. The coordination of a chiral bidentate ligand such as (S)-dimethylacetamide to the $MoO(O_2)_2$ leads to a complex that can induce asymmetric epoxidation, stoichiometrically, of low-molecular-weight alkenes such as 1-butene of around 35% ee[104,105].



Equation 1.72

Di Furia[106] has investigated peroxomolybdenum(VI) complexes bearing monodentate chiral phosphoryl ligands

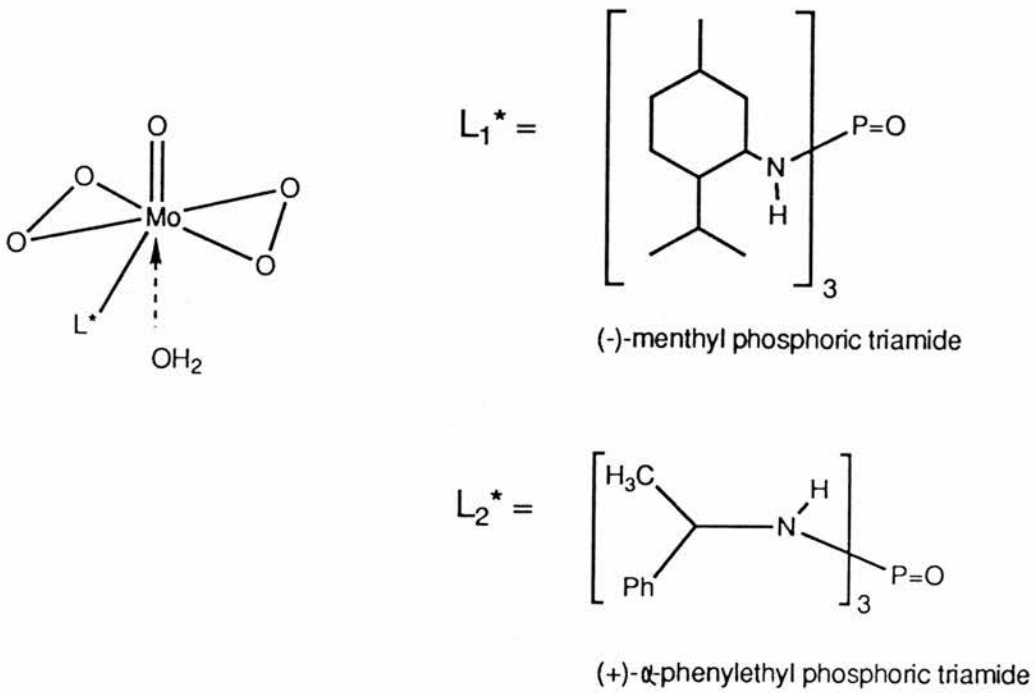
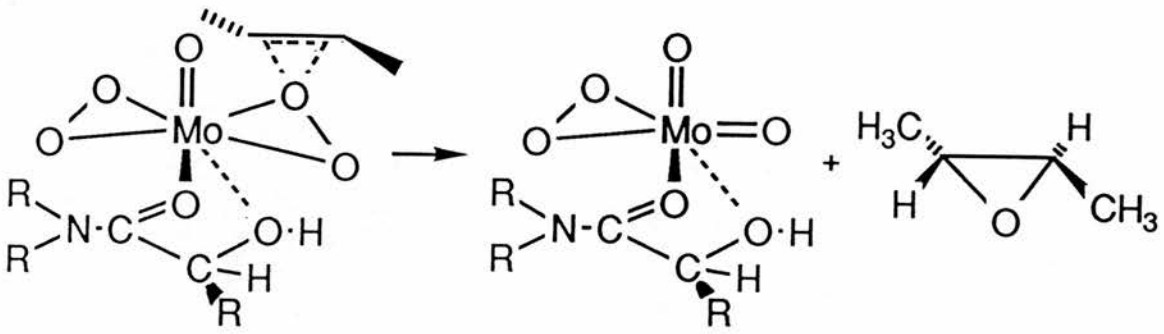


Figure 1.7

and obtained enantiomeric excesses of 8.5% for L, and 0.7% for L_2 in the epoxidation of the prochiral alkene *trans*-2-octene.

With the piperidine amide of lactic acid (PLA) as ligand the enantiomeric excess of (2R,3R)-*trans*-2,3-dimethyloxirane formed in the stoichiometric asymmetric epoxidation of *trans*-2-butene with the $MoO(O_2)_2$ system was as high as 48.6%[107].

According to the Modena[108] mechanism the olefin is directly oxidised by electrophilic attack of the peroxo group, analogous with peracid epoxidations.

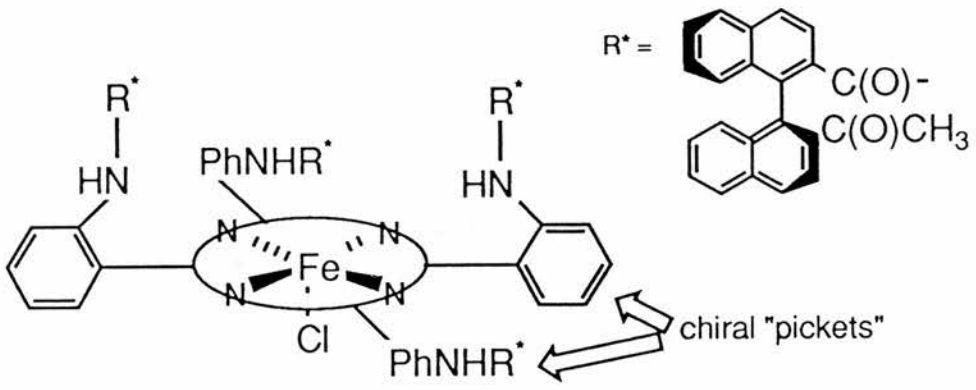


Equation 1.73

A bidentate chiral group is thought necessary, because it has been found that monodentate chiral ligands exert low prochiral recognition of alkenes.

Iron

Chiral "basket handle" iron porphyrins with iodosylmesitylene as terminal oxidant achieve probably the highest asymmetric induction in isolated alkenes[109]. Up to 51% ee in the epoxidation of *p*-chlorostyrene has been achieved when Fe(III)[(binapthylcarboxamido)phenyl]porphyrin chloride was used as chiral auxiliary[110].



Structure 1.14

The binapthyl group is a useful porphyrin appendage because it has the property of creating a large and possibly rigid chiral cavity around the iron porphyrin core of the catalyst.

The steric environment of the alkene has a pronounced effect on the asymmetric induction[111]. Substitution of the double bond decreases the ee and attempts to oxidise 1-methylcyclohexene with chiral induction failed[111].

Platinum

Hydroxy-platinum(II) complexes of chiral bidentate phosphines eg. (-)-2(S),3(S)-*bis*(diphenylphosphino)propane can catalyse the asymmetric epoxidation of simple alkenes[112]. The highest asymmetric induction was obtained with the (-)-2(S),3(S)-BDPPP complex in the epoxidation of propene, where 41% ee of the (S)-enantiomer was obtained.

1.10.10 Conclusion

While disparlure is an epoxide, chiral epoxides are more likely to be intermediates than end products. Many vitamins and over half the drugs on the market are chiral. The availability and cost of enantiomerically pure drugs may be greatly affected by the inexpensive and simple to use asymmetric epoxidation process.

Several pharmaceutical companies are investigating bioactive compounds made *via* the method. Upjohn for example has made a C_8 epoxy alcohol on a multikilo scale in a 500 gallon reactor[49].

Sharpless believes that investigations by chemists should yield more highly selective non-enzymatic catalysts in the years ahead.

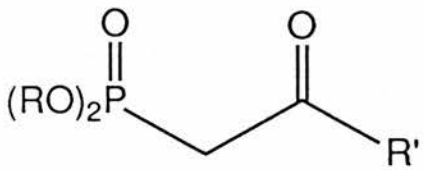
CHAPTER TWO

THE SYNTHESIS OF β-CARBONYL PHOSPHORYL COMPOUNDS

2.1 Background and Literature Review

2.1.1 Introduction

Much of the impetus for the research into β-ketophosphonates (Structure 2.1) was due to the fact that since the discovery in 1961 the Wadsworth-Horner-Emmons condensation had become an important method for the synthesis of α,β-unsaturated carbonyl compounds from carbonyl compounds and β-ketophosphonates[113]. As the demand for newer types of β-ketophosphonates increased, it became clear that the standard Arbusov approaches were not sufficient[114] so that routes to novel β-ketophosphonates have recently been developed.



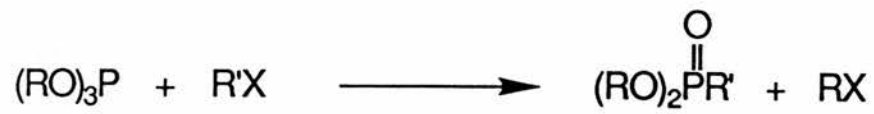
β-ketophosphonate

Structure 2.1

Since catalysts described in Chapter 4 employ β-ketophosphonates as ligands, the more important general routes to β-ketophosphonates are reviewed in the following sections.

2.1.2 Michaelis-Arbusov Reaction

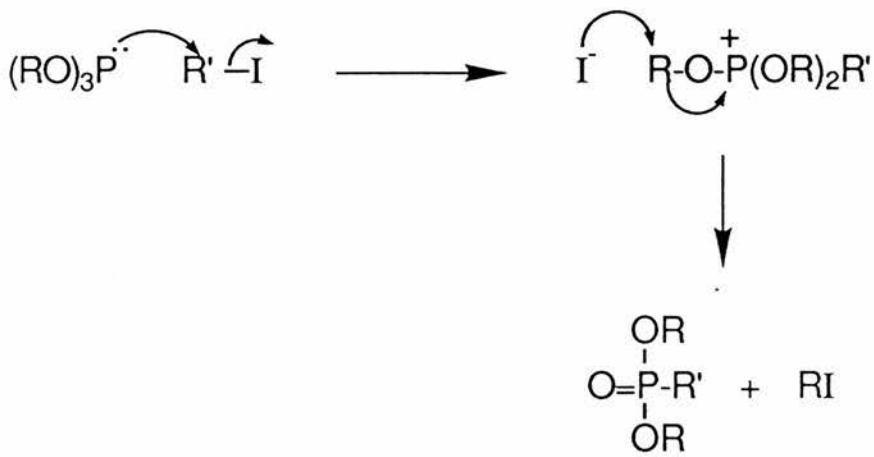
Since its discovery in 1898, the Michaelis-Arbusov reaction[115] has been the main synthetic route to phosphonate compounds. The main feature of the reaction is the reaction of an alkyl halide with a trivalent phosphorus ester.



Equation 2.1

The alkyl halide can be used catalytically when the alkyl groups R and R^1 are identical. There is in many cases a competition between the by-product alkyl halide and the starting halide. This is overcome by the removal of the by-product by distillation or the use of the desired halide in excess[116].

The reaction has been widely used in the synthesis of phosphonates, phosphinates, and phosphine oxides[116,117]. The mechanism involves the formation of an alkoxy-phosphonium salt.

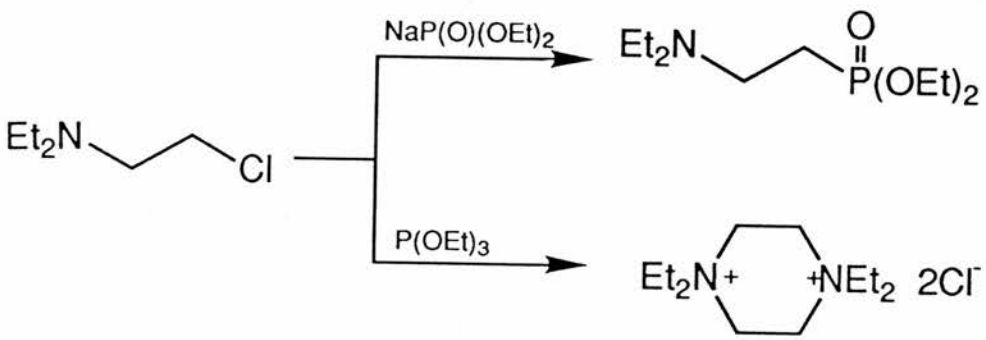


Equation 2.2

This is followed by nucleophilic displacement of an alkyl group by the displaced halide ion to generate the phosphoryl bond. The reaction represents a valency expansion common to phosphorus chemistry. The valence shell expansion of phosphorus from 8 to 10 is made possible by the availability of low energy 3d-orbitals on phosphorus. It is the strength of the P=O bond which dictates the course of this and an enormous number of reactions throughout phosphorus chemistry[118].

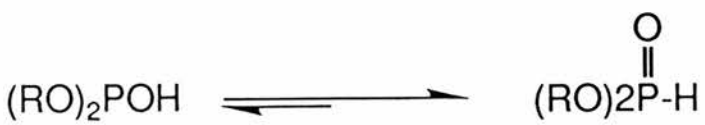
2.1.3 Michaelis-Becker Reaction

Closely related to the Michaelis-Arbusov reaction is the Michaelis-Becker reaction[119] which involves the use of the salts of dialkyl hydrogen phosphonates. For example, diethyl 2-diethylaminoethylphosphonate was obtained by this method despite the failure of the Michaelis-Arbuzov reaction with the same halide yields only a diammonium salt[120] (Equation 2.3).



Equation 2.3

Since dialkyl phosphites exist mainly in the phosphoryl form they are unreactive in the Michaelis-Arbusov reaction (Equation 2.4).



Equation 2.4

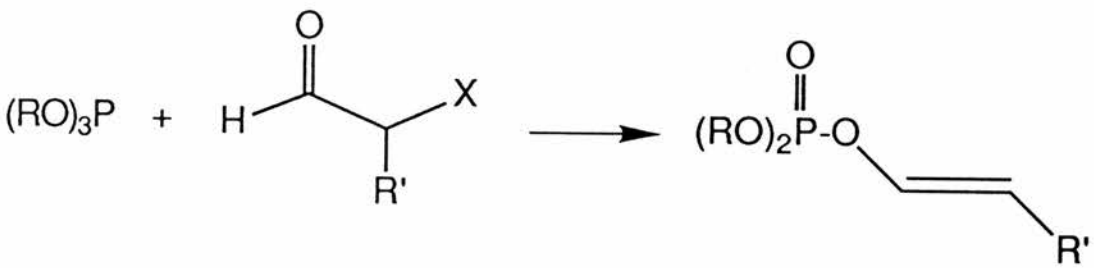
The anions however are readily available as the sodium salts, which may be generated *in situ* from the neutral compounds and tertiary amines. These react readily with alkyl halides to give high yields of phosphonates[121] (Equation 2.5).

Equation 2.5

In contrast to the Michaelis-Arbusov reaction which often requires temperatures of 120-160° for several hours, the Michaelis-Becker reaction often takes place at room temperature.

2.1.4 The Perkow Reaction

In 1952 Perkow[122] discovered that α-haloaldehydes did not react with trialkyl phosphites according to the Michaelis-Arbusov reaction but that a new type of rearrangement had occurred giving dialkyl vinyl phosphates which are isomeric with the phosphonates (Equation 2.6).



Equation 2.6

The requirement of this reaction is that the halogen atom must be attached to an α-carbon atom in an aldehyde, keto or in some cases an ester group.

Several factors including solvent, temperature and the nature of the halogen influence the product ratio of the β-ketophosphonates to vinyl phosphate[123]. Vinyl phosphate production is favoured by more electronegative halogens and low reaction temperatures.

The ratio of vinyl phosphate to β-ketophosphonate in the reaction of haloacetones with triethyl phosphite[123] is presented in Table 2.1.

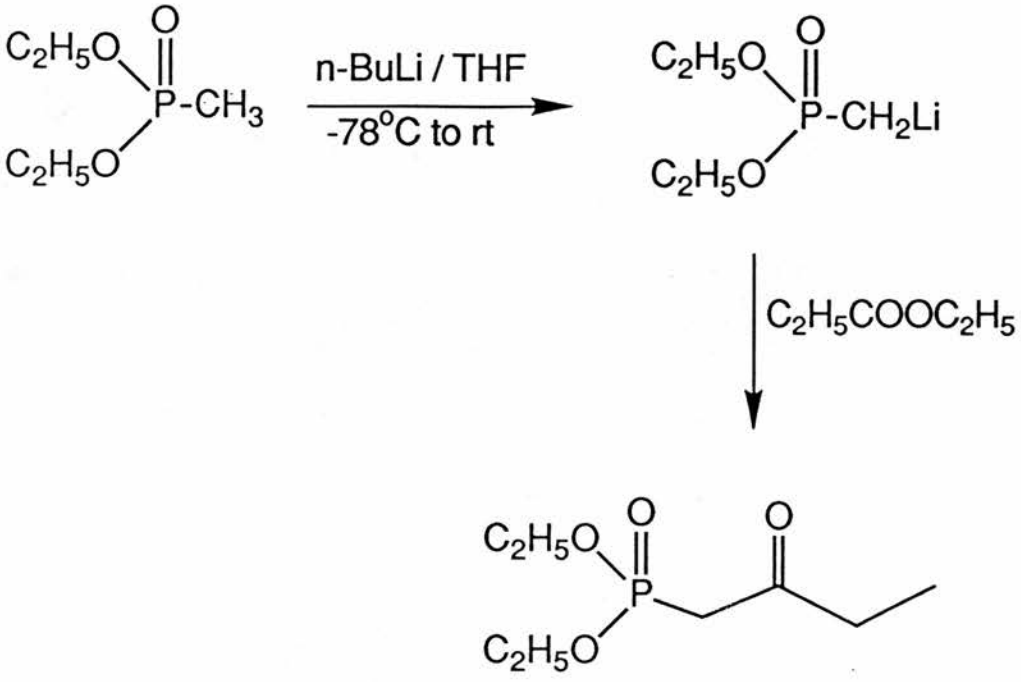
Table 2.1

Haloacetone	VP:KP at 150°C	VP:KP at 36°C
$ClCH_2COCH_3$	90:10	-
$BrCH_2COCH_3$	20:80	80:20
ICH_2COCH_3	-	10:90

For cyclic α-halo ketones, independent of the halide atom, it is the Perkow reaction which predominates.

2.1.5 Synthesis from phosphoryl stabilised carbanions

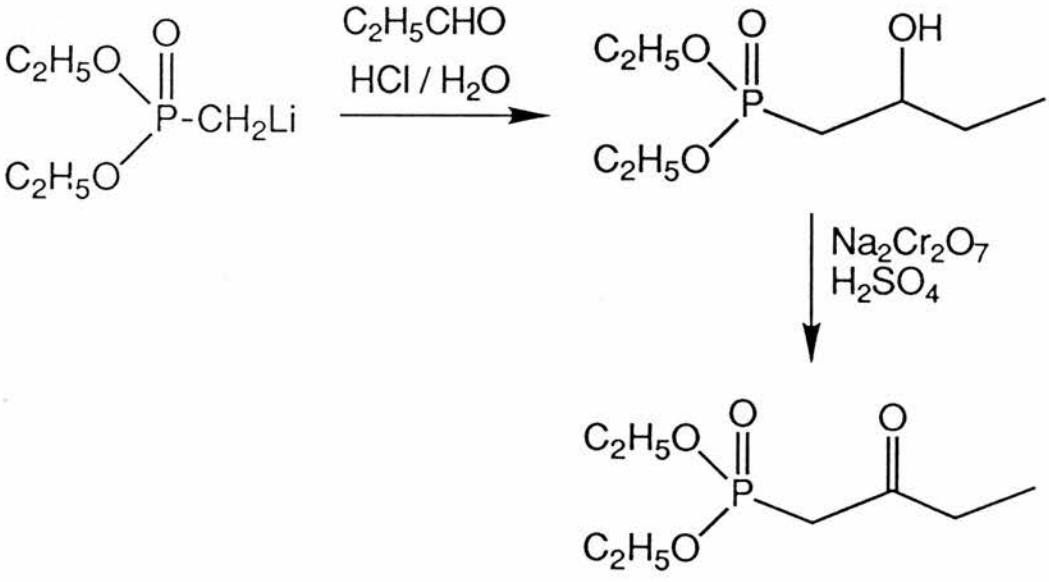
An improved synthesis of β-ketophosphonates is by the reaction of the lithio derivative of a dialkyl alkanephosphonate with either an aldehyde followed by oxidation of the β-hydroxyphosphonate product or by reaction with a carboxylic ester[124]. For example the lithio derivative of diethyl methanephosphonate can be reacted with ethylpropanoate to give diethyl butanephosphonate in ~44% yield following acidic workup.



Equation 2.7

The moderate yield is due to a fast proton exchange between the lithio derivative and the more acidic β-ketophosphonate.

The synthesis of the β-ketophosphonate by reaction of - diethyl 1-lithiomethanephosphonate with for example propanal gives the diethyl 2-hydroxybutanephosphonate almost quantitatively.

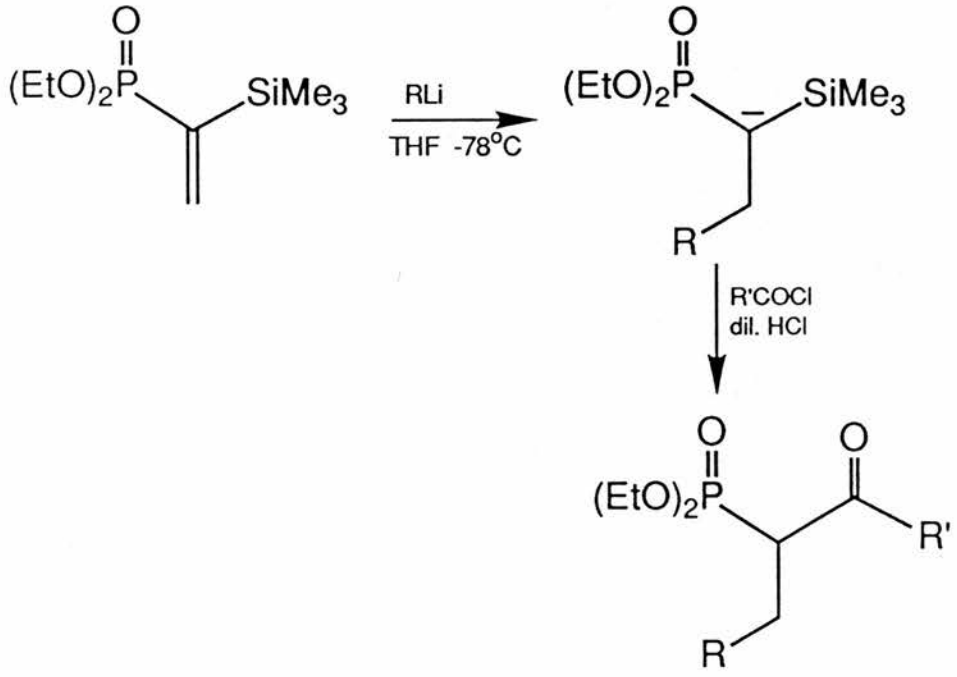


Equation 2.8

The following dichromate oxidation reaction is less efficient and gives the β-ketophosphonate in 50% yield[124].

2.1.6 Synthesis from Dialkyl 1-(trimethylsilyl)vinyl phosphonates[125]

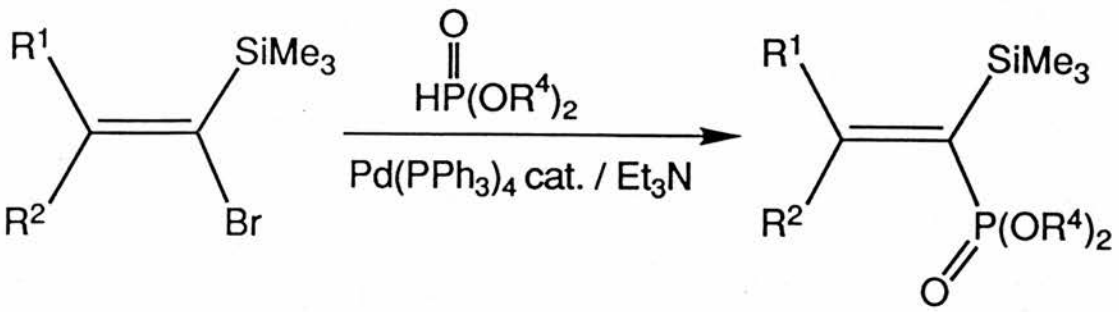
Vinyl phosphonates with a trimethylsilyl group at the α-position are sufficiently activated toward nucleophilic addition of organolithium due to the stabilising effect of the trimethylsilyl group.



Equation 2.9

Treatment of the phosphoryl stabilised anion with various acid chlorides and acidic workup gave the desired β-ketophosphonates in typically greater than 70% yield, and as such represents an improvement in yields over the synthesis presented in section 2.1.5.

The dialkyl 1-(trimethylsilyl)vinyl phosphate was prepared by a modification of the Pd catalysed phosphonation of substituted vinyl bromides[125].

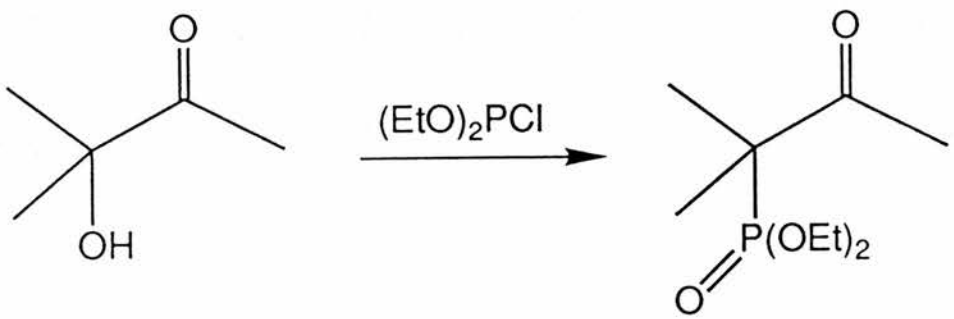


Equation 2.10

2.1.7 Synthesis from α-hydroxyketones

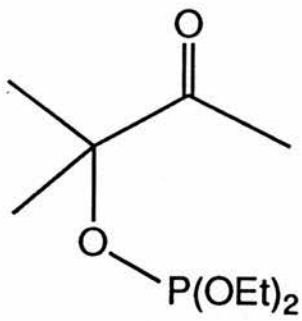
Diethyl (1,1-dimethyl-2-oxopropyl)phosphonate was prepared by Wiemer[125] by reaction of the 3-hydroxy-3-methyl-butan-2-one with diethyl phosphorochloridite in the presence of ferric chloride.

The reaction is believed to occur *via* a Lewis acid catalysed rearrangement of an intermediate phosphite (Structure 2.2).



Equation 2.11

This type of reaction constitutes a synthesis of β-ketophosphonates that is complementary to traditional approaches. It is of special value in the preparation of β-ketophosphonates where the α-carbon is fully substituted, for the Arbuzov reaction cannot be used to prepare such compounds[127].



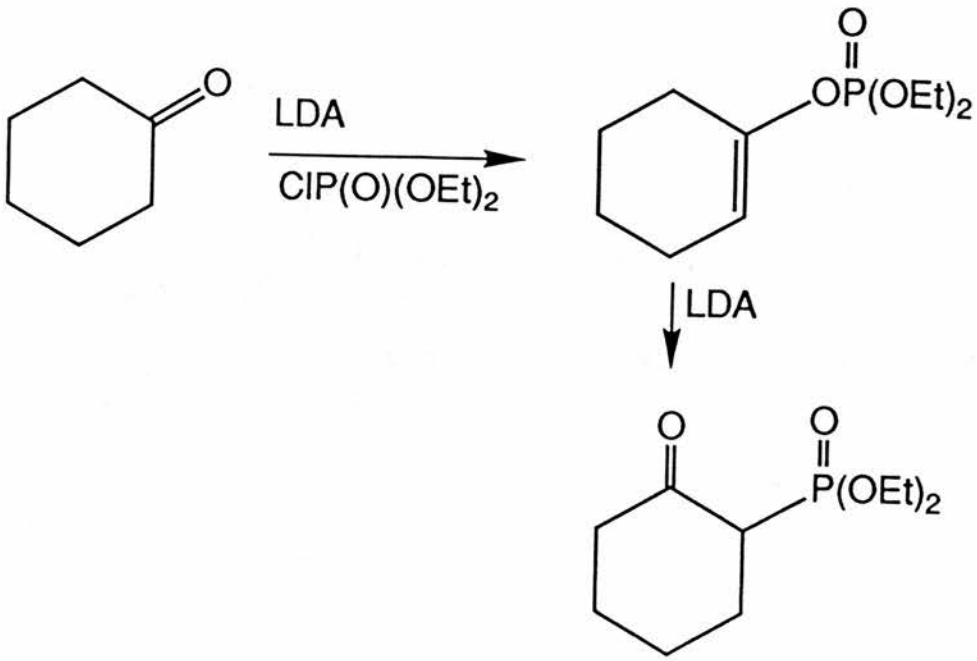
Structure 2.2

The intermediate phosphite

2.1.8 Synthesis *via* an O→C phosphorus migration

Wiemer and co-workers[114] investigated new routes to β-ketophosphonates because the existing methodologies for novel β-ketophosphonates were not sufficient.

The reaction of dialkyl chlorophosphates with enolates is well known and results in the formation of the vinyl phosphate rather than the β-ketophosphonate[128]. For example sequential treatment of cyclohexanone with LDA and diethyl chlorophosphate results in the almost quantitative formation of the vinyl phosphate which can be isolated and characterised. When it is converted to its own anion, however a rearrangement takes place to give the β-ketophosphonate from the much less stable phosphate species. This was achieved by treatment of the phosphate with further LDA.



Equation 2.12

It has been found that this methodology works best with cyclic ketones, giving precisely those β-ketophosphonates which are least accessible by other methods. For instance, the α,β-unsaturated 3-methyl-2-cyclohexenone is converted to its phosphonate analogue.

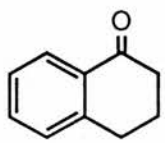
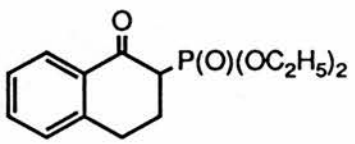
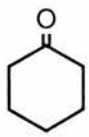
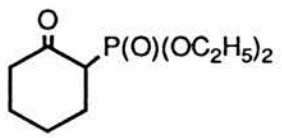
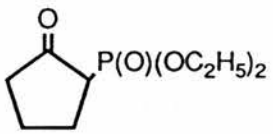
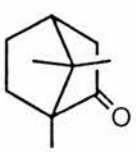
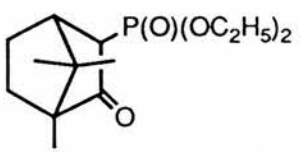
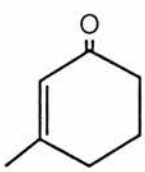
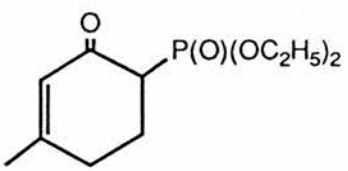
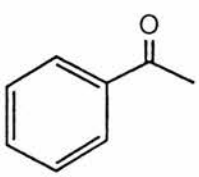
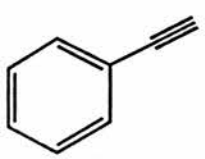
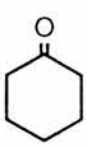
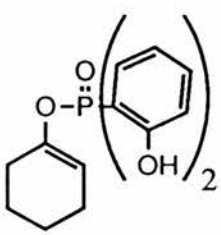
Enolates which were derived from acyclic ketones when treated under similar conditions gave more complex results. The methyl ketone, acetophenone, gave the alkyne derivative as the product resulting from a phosphate elimination reaction. It is noticeable that when the diphenyl vinyl phosphate of cyclohexanone was treated with LDA, the phosphorus migration which was observed was to the *ortho*-position of the aromatic ring rather than the vinylic position. This was discussed by Wiemer[114] as a preference for rearrangements to aryl positions.

The results obtained by Wiemer[129] are summarised in Table 2.2.

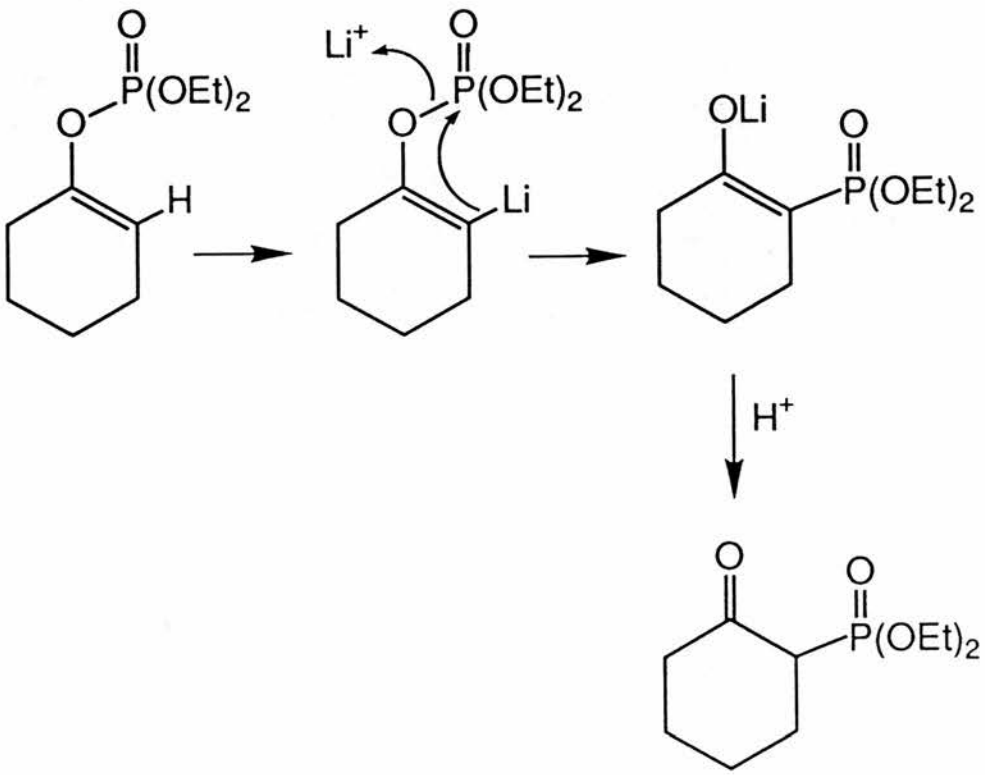
Given the importance and usefulness of this reaction it is necessary to investigate further the mechanism which Wiemer found to be operating in such a reaction.

Table 2.2

Synthesis of β-ketophosphonates

Ketone	Product	Yield
		78%
		72%
		55%
		71%
		75%
		75%
		

There is little doubt that a mechanism similar to that for hydroxyarylphosphonates[130] is in operation.



Equation 2.13

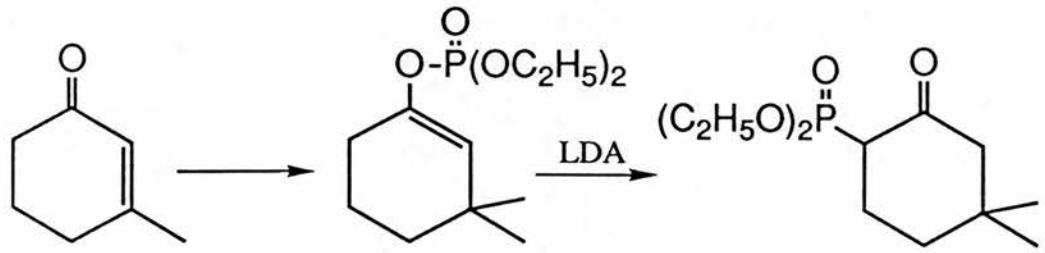
Crossover Experiment

It was shown by a crossover experiment[114] that the products of the rearrangement can only occur by an intramolecular migration. The diisopropyl vinyl phosphate of norcamphor and the diethyl vinyl phosphate of camphor together were treated with LDA in THF. Only those products resulting from an intramolecular migration were observed, eg. there was no norcamphor diethyl phosphonate formed.

Site of Hydrogen Atom Abstraction

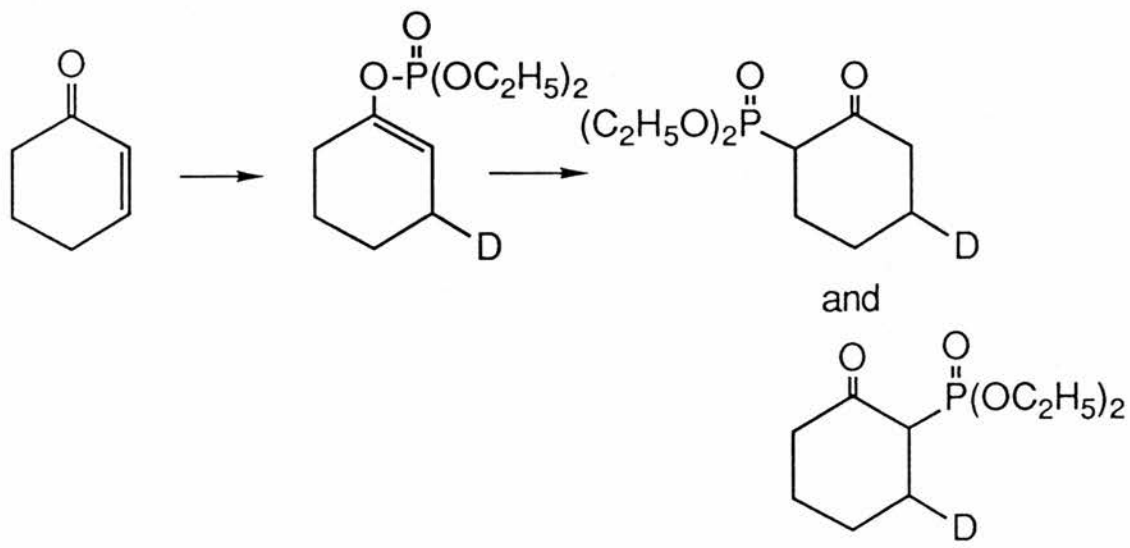
With the vinyl phosphate of cyclohexane, the O→C phosphorus migration might occur *via* abstraction of the vinylic hydrogen or *via* abstraction of hydrogen from the α′ position forming an intermediate

allyl anion. To answer this question the vinyl phosphate shown in Equation 2.14 was prepared. It can be seen that rearrangement has occurred to the position of a former allylic hydrogen.



Equation 2.14

In a similar experiment, treatment of the vinyl phosphate in Equation 2.15 with LDA gave two β-ketophosphonates in equal amounts.



Equation 2.15

These results showed that the rearrangement can occur *via* abstraction of an allylic hydrogen where one is available and that phosphorus migration can occur to any terminus of an allyl anion. In addition, it was observed that phosphorus migration to a vinylic position can occur when allyl anion formation is precluded.

Based on the work of Dhawan and Redmore[130], and Wiemer[129] on the apparently anomalous rearrangement of the diphenyl vinyl phosphate of cyclohexanone shown in Table 2.2; it was concluded that rearrangement of phosphorus to the *ortho* position of a phenyl ring takes precedence over rearrangement to either a vinylic or allylic position.

THE SYNTHESIS OF β-CARBONYL PHOSPHORUS COMPOUNDS

RESULTS AND DISCUSSION

Introduction

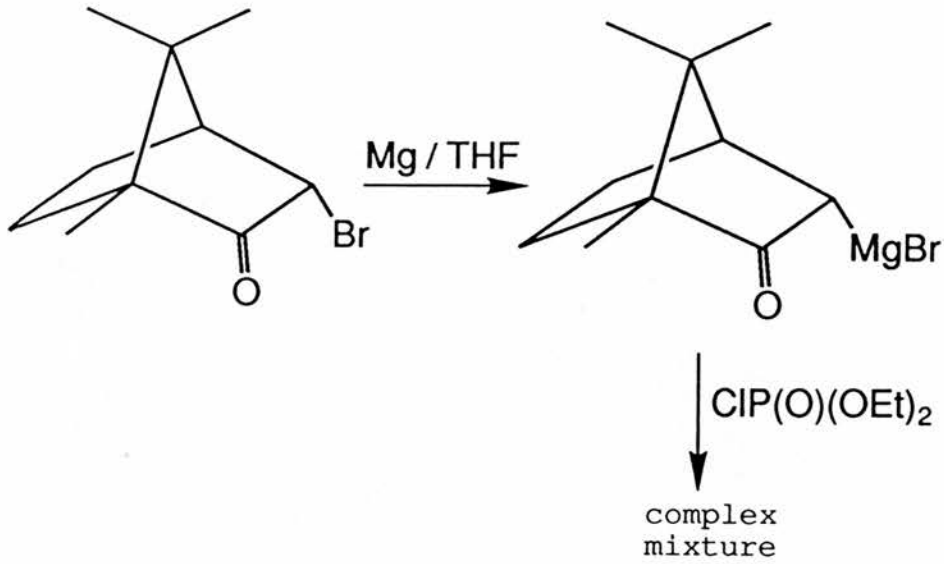
Some of the methods described in 2.1 were used for the synthesis of several β-ketophosphonates, including the optically pure [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor ligand. A range of derivatives of this compound were also synthesised, including phosphonic and bromophosphonic acids with a view to their potential as more strongly binding ligands.

The stereochemistry of these compounds has been determined spectroscopically, with particular use being made of ^{13}C-^{31}P coupling constants. The mechanistic considerations leading to their formation are discussed in detail.

2.2 β-Ketophosphonates

2.2.1 [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

The results in Chapter Three show that this compound has been the most interesting one because of its ligand behaviour. Several approaches to the synthesis of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor have been taken. Methods include preparation of the organomagnesium derivative of [(1R)-(+)-*endo*]-3-bromocamphor and attempted reaction with diethyl chlorophosphate.

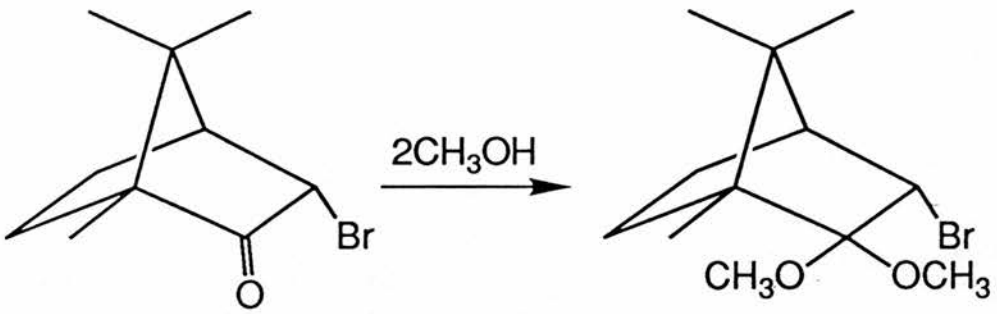


Equation 2.16

A complex mixture of products were obtained, which could not easily be identified or isolated, along with large amounts of (1R)-(+)-camphor.

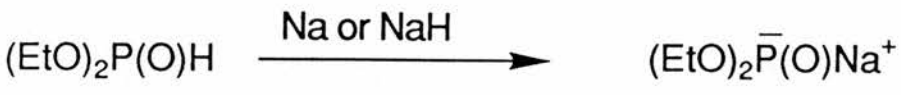
Other workers[131] have investigated reactions of phosphorus mucleophiles with protected carbonyl groups to form the Arbusov product β-ketophosphonates.

A similar methodology whereby the carbonyl function of [(1R)-(+)-*endo*]-bromocamphor could be ketalised with anhydrous methanol and sequential treatment with triethyl phosphite to give the Arbusov product seemed reasonable. Only [(1R)-(+)-*endo*]-bromocamphor was obtained. The difficulty of an S_N2 type of nucleophilic attack on ring systems has been discussed[132,114,133]. In S_N2 reactions a change of coordination number from 4 to 5 is required. The intermediate requires bond angles of 120° i.e. greater than the normal tetrahedral angle. S_N2 reactions of nucleophilic phosphorus compounds should therefore be difficult with bridged bicyclic compounds because of their stereochemical rigidity.

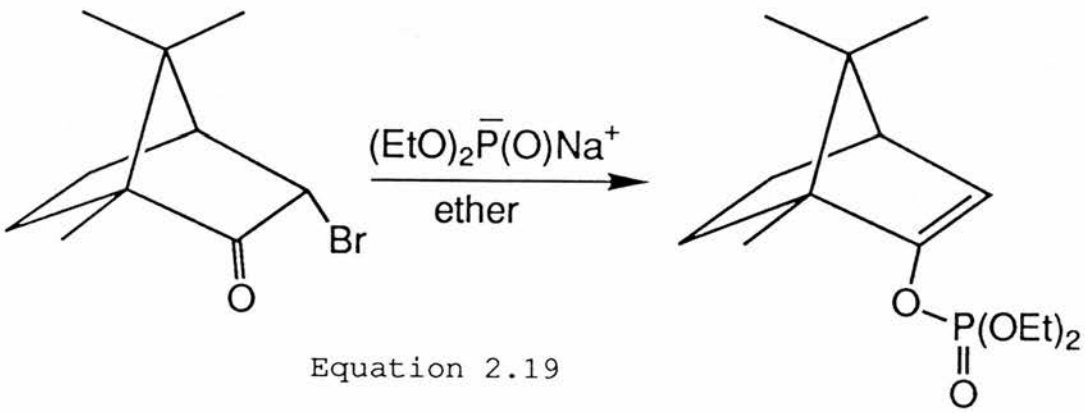


Equation 2.17

The Michaelis-Becker[123] reaction of [(1R)-*endo*]-(+)-3-bromocamphor with the sodium salt of diethyl phosphite gave the cleanly separable vinyl phosphate derivative of camphor in good yield.



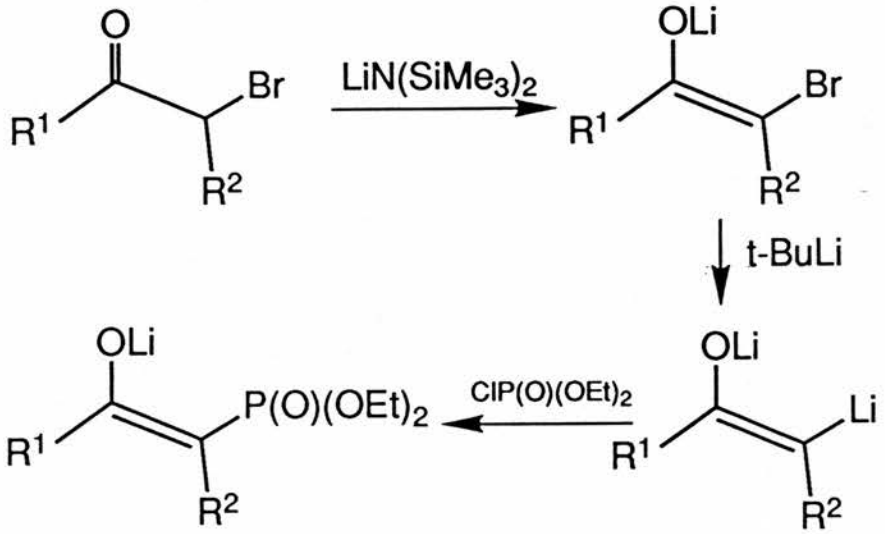
Equation 2.18



Equation 2.19

This proved a useful way of producing large amounts of vinyl phosphate for use in rearrangement reactions[132].

A report[132] that the α-keto dianion derived from [(1R)-*endo*]-(+)-3-bromocamphor by treatment with lithium hexamethyldisilazide and t-BuLi could then be treated with diethyl chlorophosphate to give the β-ketophosphonate was successfully repeated but the low yield was in accordance with the literature value of 20%[132]. Also the authors were unclear as to the configuration of the phosphorus atom at C-3.



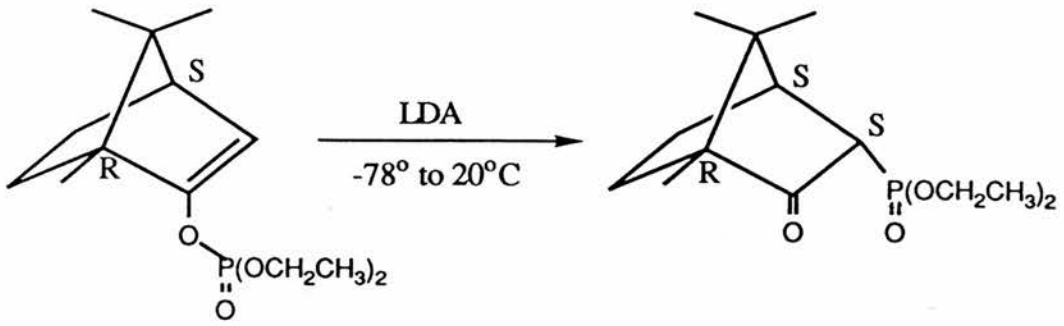
Equation 2.20

This synthesis is interesting from the point of view that the lithium hexamethyldisilazide allows the formation of the lithium enolate and the t-butyllithium is used to induce a halogen-metal exchange. The authors did not state what the other 80% of the product was. In our hands distillation of the mixture afforded camphor (*ca.*30%) and the vinyl phosphate (*ca.*50%). The latter could not be separated easily from the β-ketophosphonate.

2.2.2 O→C Migration of Phosphorus

The method of Wiemer[114,129] was extended to produce optically pure [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor. The configuration of the phosphorus atom at C-3 has been determined unequivocally by nmr of the free ligand (Section 2.2.6) and by X-ray crystallography of the molybdenum complex (Chapter 3).

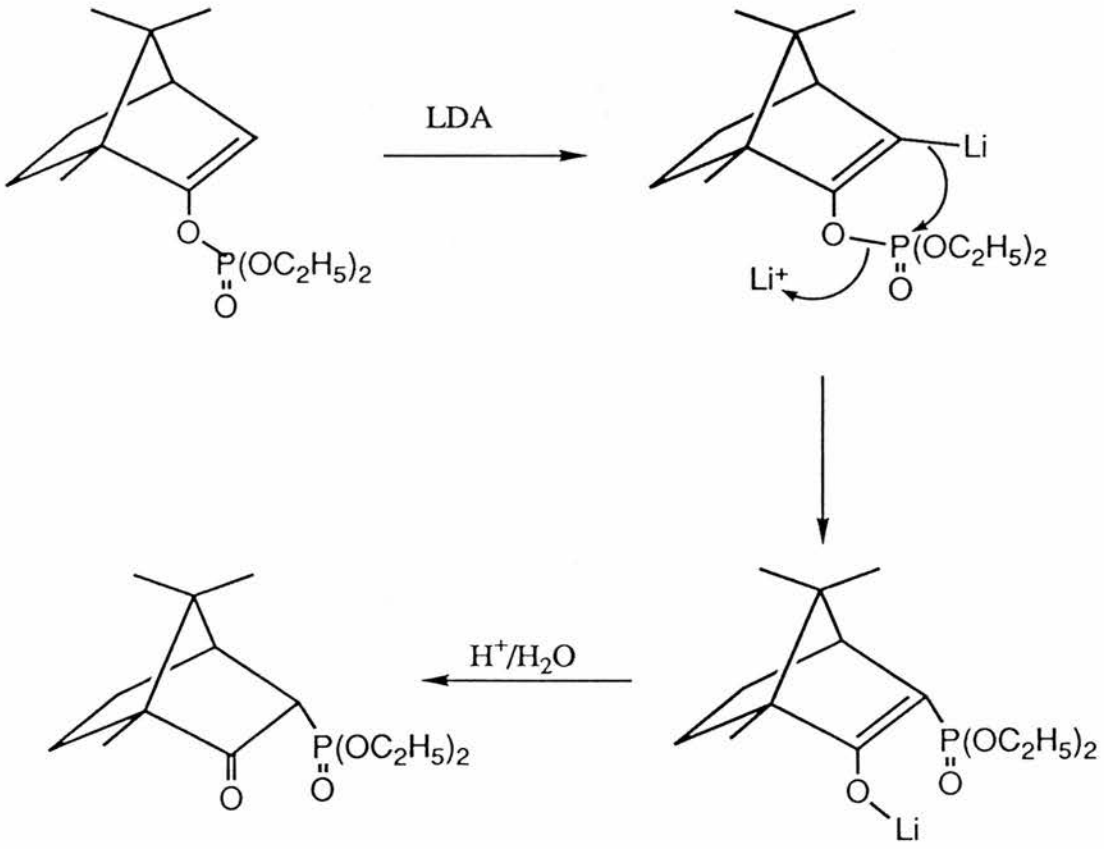
The vinyl phosphate of camphor (i.e. 2-[(diethoxyphosphinyl) oxy]-1,7,7-trimethylbicyclo[2.2.1]-2-heptene) was treated with a three molar excess of lithium diisopropylamide (LDA) at -78°C to induce an O→C(3) migration of the phosphorus moiety.



Equation 2.21

2.2.3 Mechanism for the β-Ketophosphonate Formation

The mechanism whereby the vinyl carbon C-3 is first lithiated seems likely and is analogous to lithiations of aryl phosphate compounds[130,134,135]. Where lithiation at other positions is possible such as at an allylic or aromatic site this will take precedence which suggests that vinylic metalation is difficult and so explains the requirement for such a powerful lithiating agent as LDA. An analogous mechanism can be applied to the rearrangement in aliphatic systems (Equation 2.22).

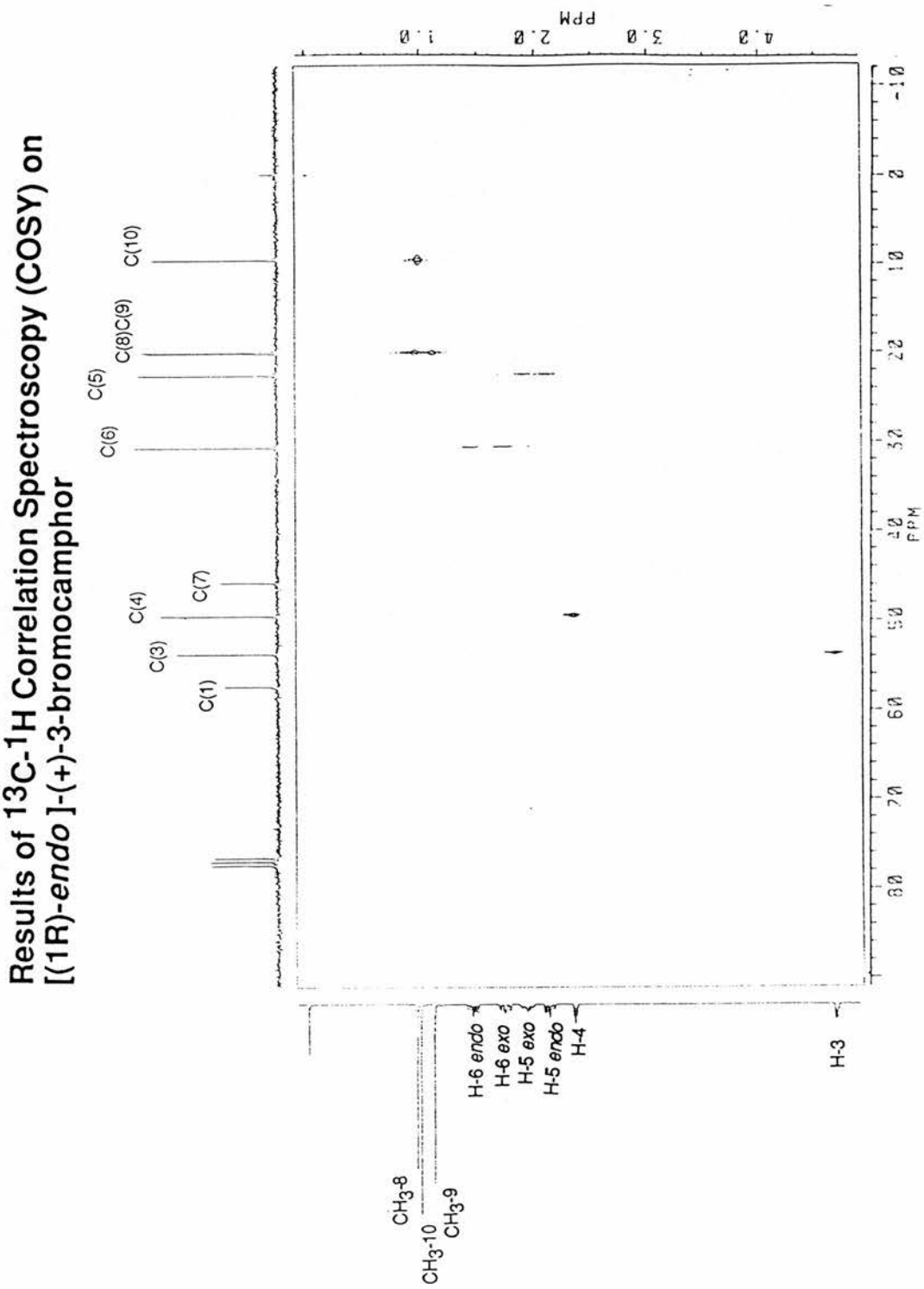


Equation 2.22

2.2.4 The use of NOE and Correlation Spectroscopy in the Assignments of the Proton Resonances of Bromocamphor as a Model Compound

Since it is proposed that the configuration of the phosphorus atom is *endo* it is useful to consider for comparison some other derivative of (+)-camphor with an *endo* substituent. [(1R)-*endo*]-(+)-3-bromocamphor is a good model compound for spectroscopic study because of its similarity to [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor. The ^{13}C chemical shifts of [(1R)-*endo*]-(+)-3-bromocamphor[135] are known and the resonances are labelled on the ^{13}C-^{1}H correlation spectrum (Figure 2.1). The resonances for H-3 and H-4 can be assigned from chemical shift and multiplicity arguments alone and show the expected correlation to the respective carbon atoms. The two signals for the two 5-H protons as well as 6-H protons show up clearly as adjacent multiplets. Of the three methyl groups the CH_3-10 resonance is the central most intense one. Because the C(9) and C(8) resonances are coincident the assignment of the remaining methyl group resonance is equivocal; however it is likely on chemical shift grounds that the CH_3-8 is the most shielded resonance because of the anisotropy of the carbonyl group (Figure 2.2).

Figure 2.1


Results of ^{13}C-^{1}H Correlation Spectroscopy (COSY) on [(1R)-*endo*]-(+)-3-bromocamphor
C(1)
C(3)
C(4)
C(7)
C(6)
C(5)
C(8)C(9)
C(10)
H-6 *endo*
H-6 *exo*
H-5 *exo*
H-5 *endo*
H-4
H-3
CH_3-8
CH_3-10
CH_3-9
PPM

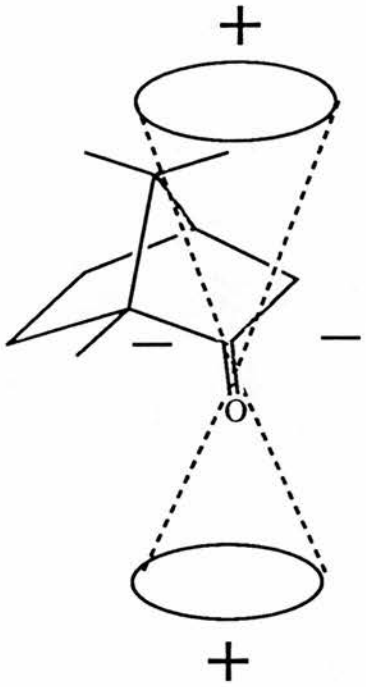
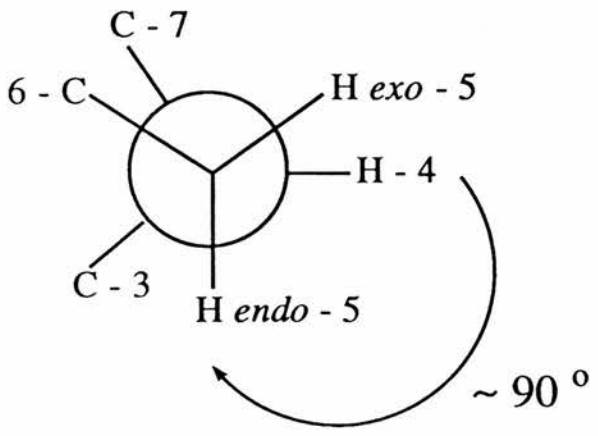


Figure 2.2

<u>^{1}H-^{1}H correlation (COSY)</u>

The basis of the COSY experiment is the process of coherence transfer in which magnetisation is transferred between coupled spins. The 2D COSY spectrum of a spin coupled system consists of diagonal and also off-diagonal (or cross) peaks. These off-diagonal peaks indicate that protons are indeed spin coupled.

An important factor influencing vicinal couplings is the dihedral angle between the CH bonds.



$J_{4,5\ endo}$ ~ O Hz

$J_{4,5\ exo}$ ~ $J_{4,3\ exo}$ ~ 3 Hz
- triplet

Figure 2.3

These theoretical predictions which can be approximately written in the form of the Karplus equation

$$J_{(CH.CH)} = 10 \cos^2\phi$$

which predicts that for $\phi = 90^o$ the coupling should be zero. The angle between H-4 and H-5 *endo* is approximately 90^o and so no coupling is observed. The angle between H-4 and H-5 *exo* is closer to 45^o. Similarly the angle between H-4 and H-3 is approximately 45^o which explains why the H-4 signal is a triplet.

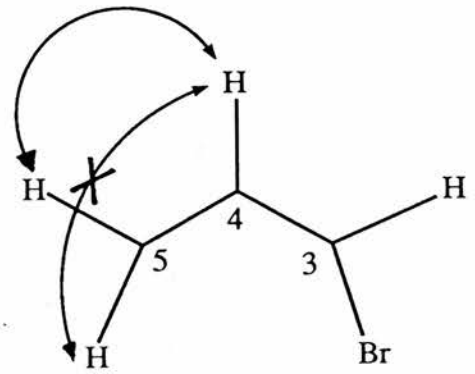
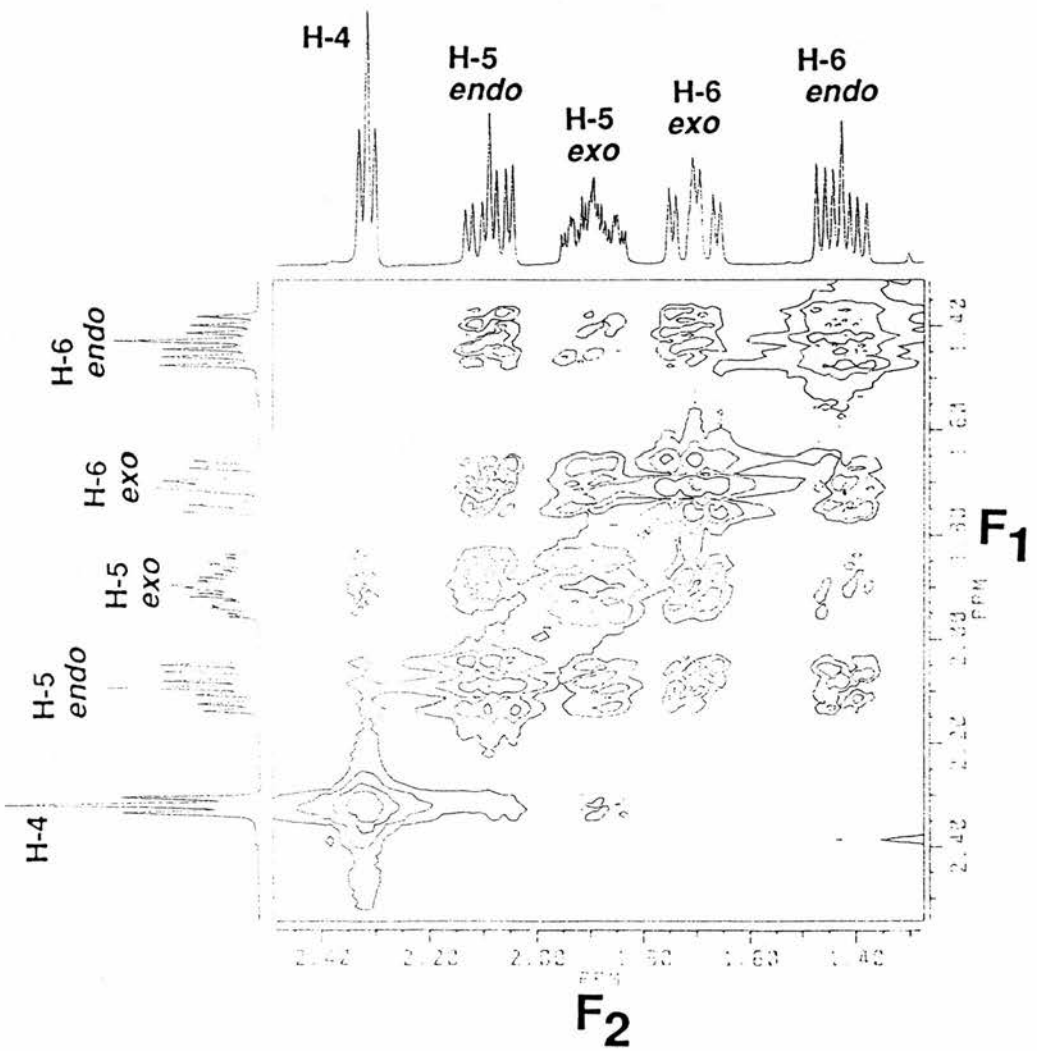


Figure 2.4

Figure 2.5

Results of ^{1}H-^{1}H Correlation Spectroscopy (COSY) on [(1R)-*endo*]-(+)-3-bromocamphor



The COSY contour plot for [(1R)-*endo*]-(+)-3-bromocamphor is shown in Figure 2.5 which also gives the 1D proton spectrum along the F_1 and F_2 axes. The diagonal and cross-peaks can be distinguished easily by inspection.

The COSY spectrum confirms the ^{13}C-^{1}H correlation results for [(1R)-*endo*]-(+)-3-bromocamphor but provides some extra information: there should be some interaction between the triplet for H-4 and the multiplets for H-5 protons which is indeed observed at the cross-peak (2.40 ppm, 1.92 ppm).

Nuclear Overhauser Enhancement

When two nuclei are close in space (2-4 Å), but not coupling:- NOE is an effect in which one spin state of a nucleus becomes more populated with respect to the other. This effect falls off rapidly with distance ($1/r^6$). Due to the rate of tumbling, molecules of mass 100 with a tumbling frequency of $10^{11}s^{-1}$ give rise to strong positive NOE's; those with mass greater than 1000 with tumbling frequency $10^{8}s^{-1}$ have negative NOE's. Molecules with intermediate molecular weight show weak or zero NOE's. In ^{1}H spectra the maximum enhancement can only be 50% of the usual intensity of the signal but the usual range is 1-20 per cent[136,137].

NOE Difference Spectra

NOE's are more easily detected by subtracting in the computer the normal spectrum from a spectrum measured while irradiating selected neighbouring nuclei and printing the difference between the two spectra. All the unaffected signals are removed and all that is shown is the enhancement itself, together with an intense signal at the irradiating frequency.

The use of the NOE Difference Spectrum in the Determination of the Configuration of the Bromine Atom [(1R)-*endo*]-(+)-3-bromocamphor

Since the phosphorus atom is thought to be *endo* which is the same for the bromine atom in [(1R)-*endo*]-(+)-3-bromocamphor it is necessary to confirm the *endo* configuration in [(1R)-*endo*]-(+)-3-bromocamphor which is known through X-ray studies[138] as a comparison for the phosphoryl compound.

The proton nmr spectrum of [(1R)-*endo*]-(+)-3-bromocamphor is reproduced in Figure 2.6 along with the stacked NOE difference spectra.

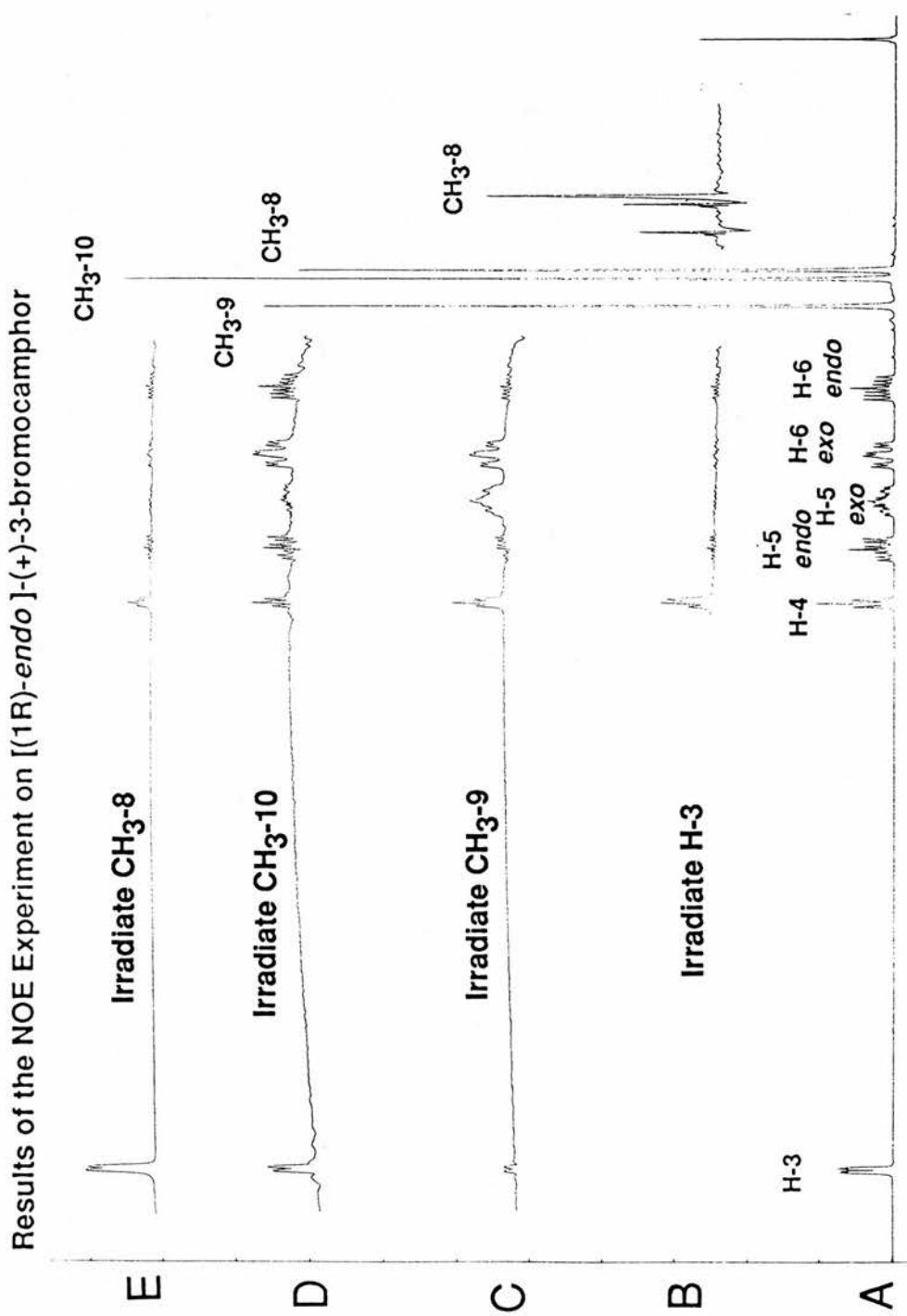
Spectrum **A** shows the normal proton nmr from zero to 4.90 ppm with the assignments labelled at the peaks. It is now possible to tell that the resonances at 1.84 ppm and 1.65 ppm are *exo* because irradiation of CH_3-9 in **C** causes significant enhancement of those signals with no effect upon the more distant 5-H *exo* and 6-H *exo* protons. There is also an interaction with H-4 which is approximately the same distance away.

Irradation of CH_3-10 had no significant effect upon the other resonances compared with **B**,**C**,**E** and the gain had to be increased by a large factor to obtain even the spectrum shown.

Irradiation of H-3 in **B** should only affect CH_3-8 if the bromine atom were *endo*. Since CH_3-8 is strongly affected, the H-3 is therefore *exo*. As a cross-check, the methyl group CH_3-8 was irradiated (spectrum **E**) and the effect upon H-3 was quite pronounced.

It is now possible to make assignments of the resonances in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor.

Figure 2.6


Results of the NOE Experiment on [(1R)-*endo*]-(+)-3-bromocamphor
E
D
C
B
A
Irradiate CH_3-8
Irradiate CH_3-10
Irradiate CH_3-9
Irradiate H-3
CH_3-10
CH_3-9
CH_3-8
CH_3-8
H-3
H-4
H-5 *endo*
H-5 *exo*
H-6 *exo*
H-6 *endo*
2.0

2.2.5 Spectroscopic Examination of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

The loss of the band in the infrared spectrum at 1626cm^{-1} and the appearance of a strong carbonyl stretch at 1742 cm^{-1} is consistent with the conversion of vinyl phosphate to β-ketophosphonate. The ^{31}P nmr resonance at +23.1 ppm is in the typical region for β-ketophosphonates[114].

^{1}H and ^{13}C nmr

It is necessary to assign the proton and ^{13}C resonances for this compound because the introduction of a phosphoryl group at C-3 creates a new chiral centre, at which it is important to determine the configuration. Also reactions carried out upon [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor to increase the steric bulk at C-3 (Section 2.4.5) give rise to sometimes complex spectra which can only be understood in the light of a completely assigned [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor spectrum.

Complete NMR Spectroscopic Assignment of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

Proton NMR

The multiplet at 4.1-4.3 ppm is due to the two sets of methylene protons bound to O-P. The doublet of multiplets at 2.95 ppm is due to H-3 and the coupling constant of 27.5Hz is in the range for P-C-H couplings[139,140]. Treatment of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor with sodium hydride and then D_2O results in the disappearance of this resonance from the spectrum which is consistent with this proton being the most acidic in the molecule,

which is reflected in its chemical shift value. Upon inspection, the multiplets at 2.40, 2.13, 1.92, 1.69 and 1.63 ppm are very similar in appearance to the multiplets in *endo*-bromocamphor although the 1.69, 1.63 ppm peaks have merged slightly.

It is unlikely that if the stereochemistry at C(3) was different the appearance of the spectrum in this region would be so similar and the triplet at 2.49 ppm would most likely be a doublet. The multiplets can therefore be assigned to 4, 5 *endo*, 5 *exo*, 5 *exo* and 6 *endo* respectively. The appearance of a slightly split triplet at 1.34 ppm is due to the two diastereotopic methyl groups O-C-CH_3 and has the typical chemical shift and couplings for compounds of this type. It is interesting to note that the spectrum of this compound with benzene-d6 as the solvent shows these peaks as completely resolved triplets. The methyl resonance at 0.92 ppm is assigned to the methyl group CH_3-10 because of its close coplanarity with the carbonyl group. The most shielded camphor skeleton methyl peak is at 0.86 ppm and is due to the methyl group lying above the shielding plane of the carbonyl π-system. The methyl resonance at 1.00 ppm therefore must be due to CH_3-9.

^{13}C NMR

The complete assignment of the carbon atoms in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was assisted by using a DEPT sequence. This permitted the identification of the CH, CH_2, CH_3, - (and quaternary carbon nuclei by default). Also comparison with spectra of camphor and bromocamphor[135] as model compounds proved to be useful.

The resonance at 210.93 ppm with a small relative intensity is in the correct region for a carbonyl sp^2 hybrid. This signal disappears in the DEPT sequence which confirms the assignment.

The resonance at 64.46 and 63.76 ppm with the coupling constants 6.2 and 6.6 Hz are consistent with the existence of two diastereotopic P-O-CH_2 groups, confirmed by DEPT.

The quaternary carbon with the high chemical shift of 59.00 ppm is typical of carbon atoms α-to the carbonyl[135]. The small coupling to P indicates that this is the C(1) atom. A similar chemical shift but large coupling constant is expected for C(3) which turns out to be the case for the tertiary carbon C(3) at 50.67 ppm and J_{CP} = 144.24Hz.

C(7) should be the most shielded of the quaternary carbon nuclei and so it has a resonance at 46.88 ppm. The chemical shifts 46.2, 29.7, 22.98, 19.36, and 18.72 ppm follow closely those of bromocamphor. By analogy with bromocamphor and study of the DEPT spectrum leads to the assignments CH-4, CH_2-5, CH_3-9, CH_3-8 respectively. It should be noted that in the proton nmr, the protons of CH_3-8 were the most shielded of the methyl groups present. Side-on projections and models show that the C(8) nucleus is tilted back away from the influence of the carbonyl π-electrons so that the shielding effect in this case is minor and that the "γ-effect" in C(10) is more important making it the most shielded methyl group at 9.62 ppm.

The diastereotopic methyl groups of the diethoxyphosphinyl function can be found at 16.47 and 16.42 ppm and the couplings to phosphorus of 4.91 and 5.74 Hz are typical for P(O)-O-C-CH_3 groups[138,139].

2.2.6 The use of the Nuclear Overhauser Effect in the Determination of the stereochemistry at C-3 in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

The NOE technique should be useful for the determination of the stereochemistry at C(3) because the two sets of protons at C(3) and C(8) should be close enough in space for their nuclei to relax each other (Figure 2.7). Irradiation of the methyl group should give an increase in the intensity of the C(3) proton signal.

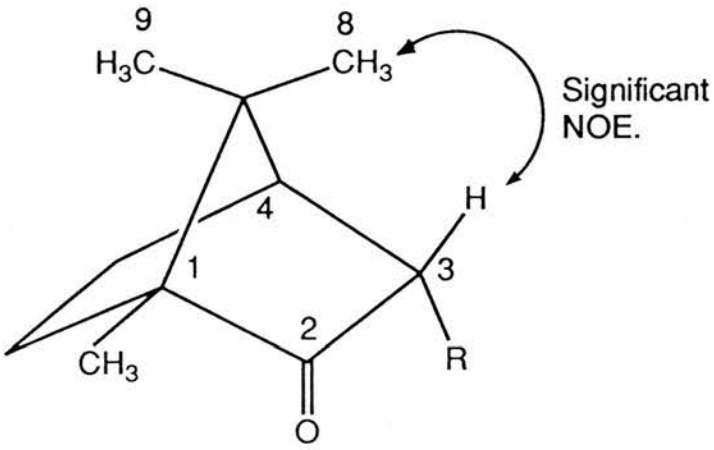
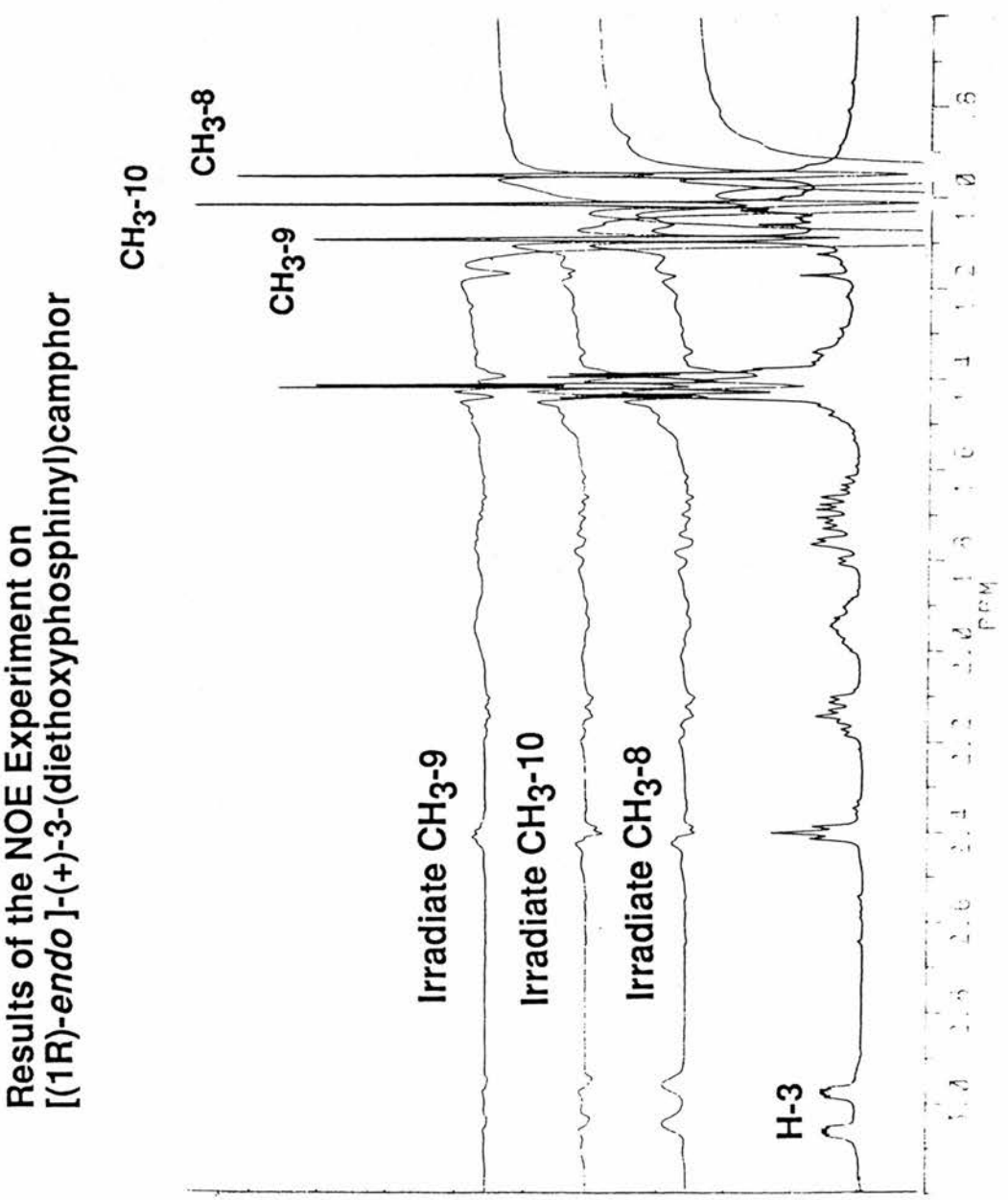


Figure 2.7

Although a single peak in the ^{31}P spectrum of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor in a range of solvents precludes the existence of both *exo* and *endo* phosphoryl isomers. The NOE difference plot in Figure 2.8 confirms that the phosphoryl group is *endo*. It can be seen that irradiation of the methyl groups CH_3-9 and CH_3-10 have no significant effect on the signal for the H-3 proton. Irradiation at the frequency of the methyl group at 0.86 ppm (CH_3-8) can be seen to have a significant effect upon H-3 and since this also has been assigned previously there is no doubt that these sets of protons must be close in space. Also since there is little interaction

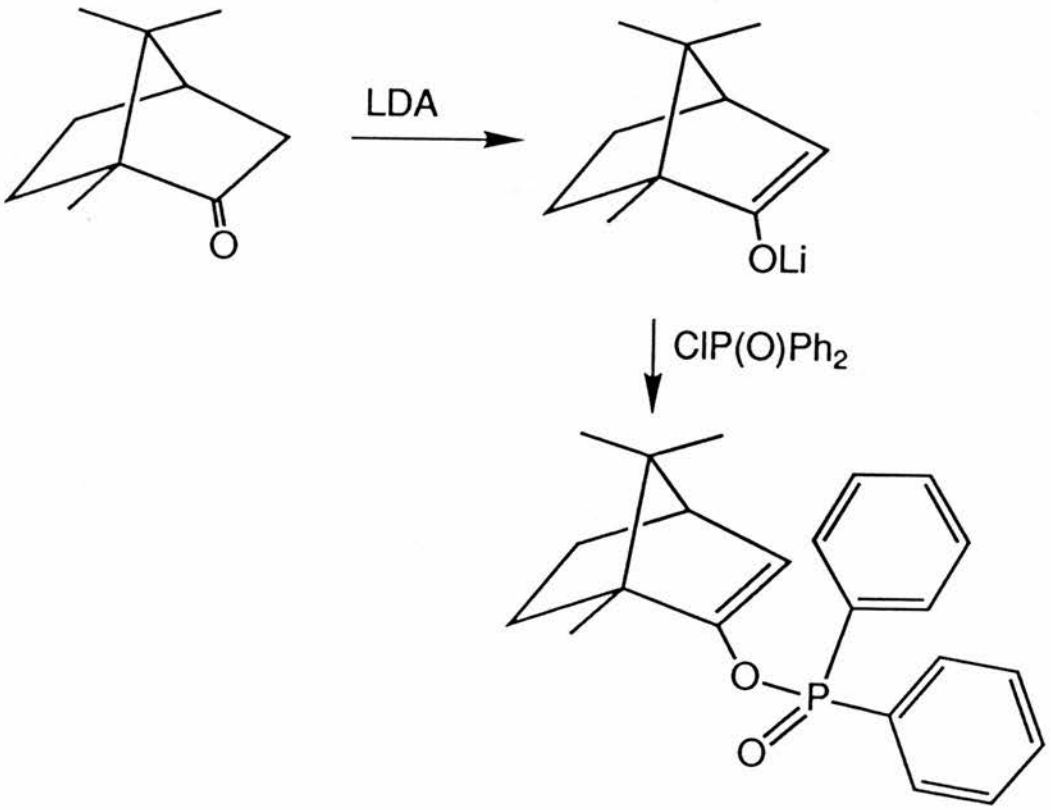
Figure 2.8


Results of the NOE Experiment on
[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor
CH_3-10
CH_3-8
CH_3-9
Irradiate CH_3-9
Irradiate CH_3-10
Irradiate CH_3-8
H-3
PPM

between the 5 and 6 *endo* protons with CH_3-9 it can be concluded that these are further apart than in the similar H-3/CH_3-8 case. This then rules out any interaction between a putative *exo* proton and CH_3-8 because the distance would be even greater still and confirms that the epimeric from of the diethoxyphosphinyl group is *endo*.

2.2.7 2-[(diphenylphosphinyl)oxy]-1,7,7-trimethylbicyclo[2.2.1]-2-heptene

In an attempt to prepare the phosphine oxide analogue of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor. (+)-camphor was treated sequentially with LDA, chlorodiphenylphosphine oxide and LDA. Work-up of the mixture gave an oil which was distilled to give as the product, not the β-ketophosphine oxide but instead 2-[(diphenylphosphinyl)oxy]-1,7,7-trimethylbicyclo[2.2.1]-2-heptene. It is obvious that this reaction is comparable to a vinyl phosphate synthesis. It is clear that the addition of the second equivalent of LDA did not induce the rearrangement of the vinyl phosphinite.



Equation 2.23

The lack of rearrangement product is most likely due to ortho-lithiation occurring at the expense of the vinyl proton-lithium exchange process. It is known from Wiemer's studies that vinyl proton-lithium exchange is less well favoured compared with allylic proton exchange or *ortho* lithiation of vinyl diaryl phosphates. It is probable that it may take several moles excess of LDA to bring about any rearrangement.

2.2.8 NMR Studies of Vinyloxyphosphoryl Compounds

^{13}C-^{31}P couplings

The similarity in the ^{13}C nmr of the phosphate 2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene and that of the phosphinite 2-[(diphenylphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene is quite noticeable. It can be seen that in both cases coupling to the ring ^{13}C atoms is not so extensive as in the case of the β-ketophosphonates so that the coupling is limited to C(1),(2) and (3) only.

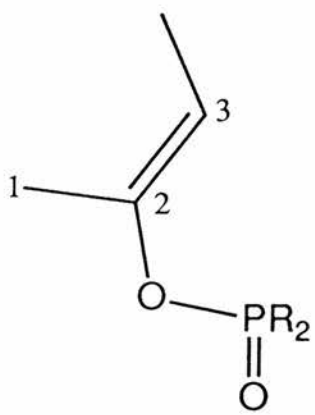


Figure 2.9

Couplings to C(2) are in the order of 10Hz with couplings to C(1) and C(3) approximately half of that value.

Chemical Shifts

The chemical shifts of comparable carbon atoms differ by 2.05 ppm at the most for C(3) and by *ca*. 1 ppm for the others.

Proton nmr

The most striking feature of the proton nmr spectra is the considerable upfield shift in the resonance for the CH_3-8 group. The CH_3-8 resonance in the phosphinite is at 0.70 ppm. The phosphate in particular has its CH_3-8 resonance at the more upfield position 0.35 ppm when compared with protons in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor. The upfield shifting can be rationalised in terms of the shielding effect caused in protons lying in a plane above the anisotropic π-system of the alkene[137].

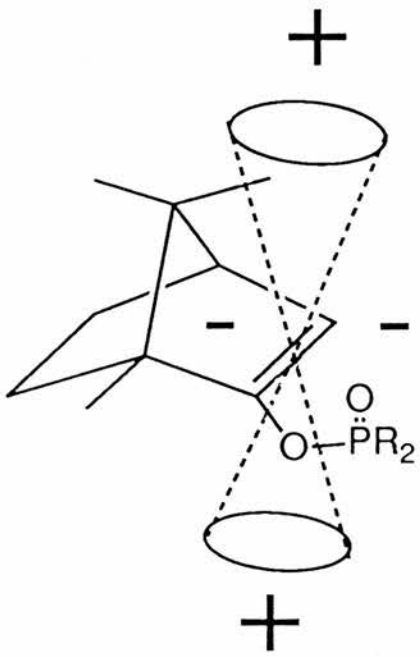
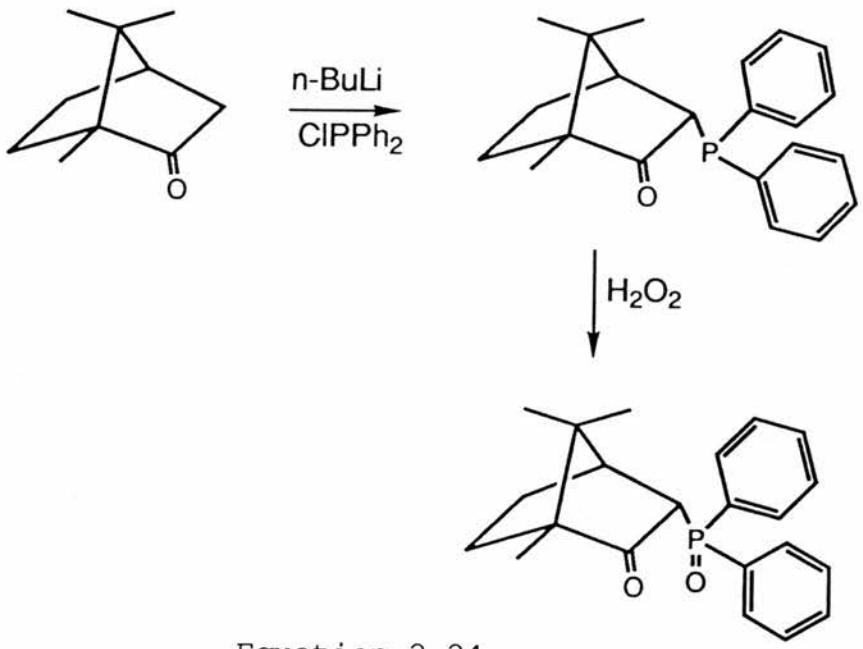


Figure 2.10

2.2.9 3-(diphenylphosphinyl)camphor

Attempts to prepare the phosphine oxide derivative of camphor by addition of chlorodiphenylphosphine to the Grignard product of [(1R)-*endo*]-(+)-3-bromocamphor and then oxidising the products gave a complex mixture which could not easily be identified.

Cole-Hamilton and Knight[141] had been investigating routes to phosphine derivates of (+)-camphor which involved reaction of the anion of camphor with chlorodiphenylphosphine.



Equation 2.24

Oxidation of the product phosphine dissolved in ethanol with hydrogen peroxide solution afforded the β-ketophosphine oxide quantitatively.

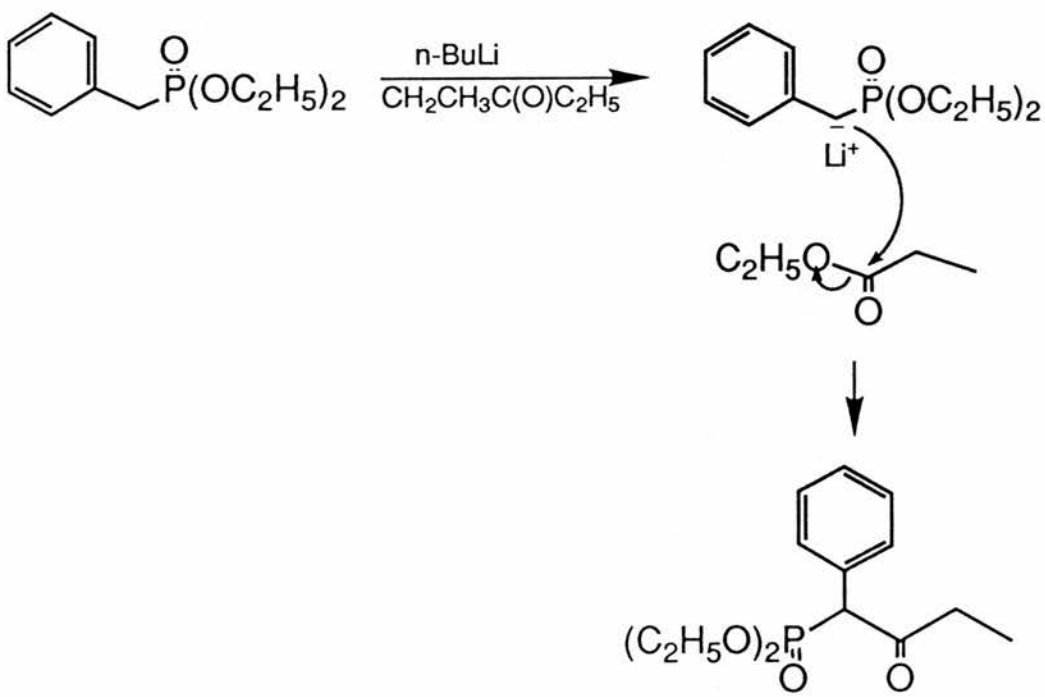
2.3 Synthesis of β-Ketophosphonates by Means of Phosphoryl Stabilised Carbanions

A potential route to chiral β-ketophosphonates is by a variation of the technique described in Chapter 2 Section 1 and would involve taking a naturally ocurring chiral ester or aldehyde and treating it with a suitable lithio-phosphonate[124]. As a first step, the synthesis of

diethyl (1-phenyl-2-oxobutane)phosphonate as a model compound was carried out.

2.3.1 Diethyl (1-phenyl-2-oxobutane)phosphonate

The reaction of diethyl benzylphosphonate with n-butyllithium in THF at -78° gave the corresponding lithio-derivative which was reacted with ethyl propionate to give the β-ketophosphonate: diethyl (1-phenyl-2-oxo butane)phosphonate.



Equation 2.25

From the ^{31}P and ^{1}H nmr results it is clear that the product β-ketophosphonate had been formed and that in accordance with the theoretical explanation[124] much of the diethyl benzylphosphonate was also recovered.

Some of the more noticeable features from the proton nmr spectrum of diethyl (1-phenyl-2-oxobutane)phosphonate are the three

triplets, one at 1.01 ppm due to CH_3-4 which is similar in chemical shift to 1.03 ppm for the α-methyl group in butan-2-one[142]. The ethoxy methyl groups have become diastereotopic due to the formation of a chiral centre at C-1. The inequivalence of these groups can be seen more clearly by consideration of the Newman projection, which is viewed along the P-C-1 bond (Figure 2.11).

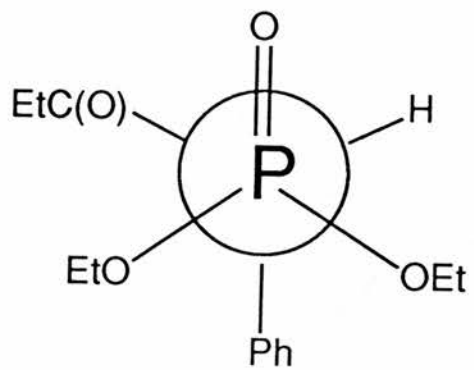
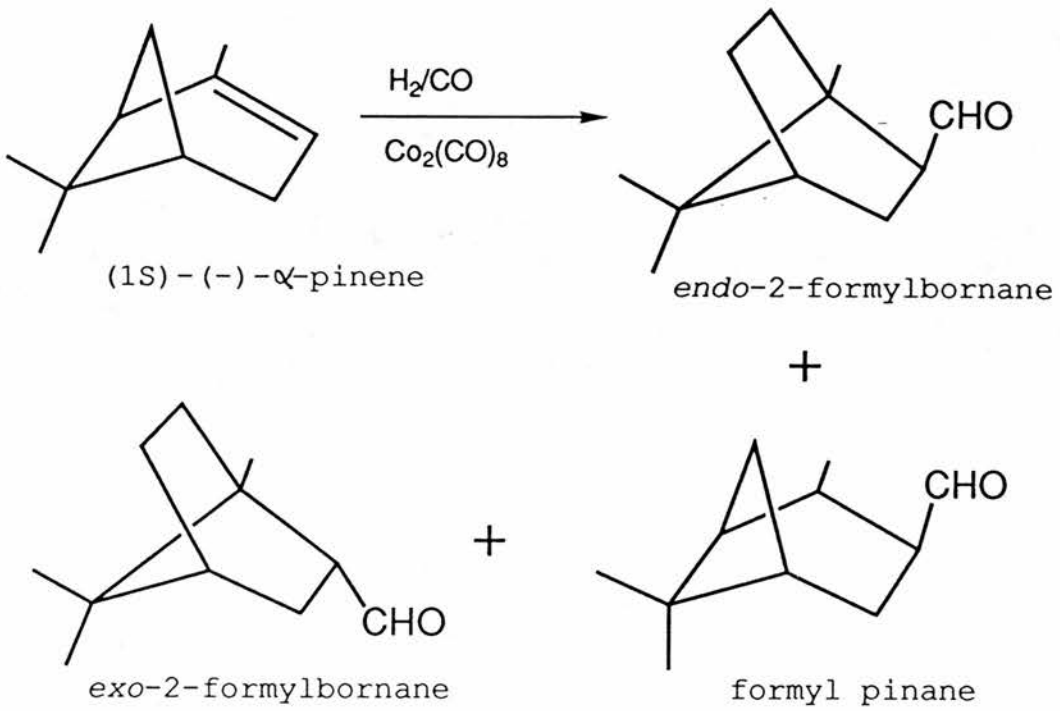


Figure 2.11

Rotation around this bond cannot place one ethoxy group in exactly the same environment as the other and so two triplets for each of the ethoxy methyl groups can be observed at 1.09 and 1.24 ppm.

2.3.2 Hydroformylation of Pinene

In an approach to the synthesis of the bornyl β-ketophosphonate the hydroformylation of (1S)-(-)-α-pinene seemed a good method for the production of the starting aldehyde[143].

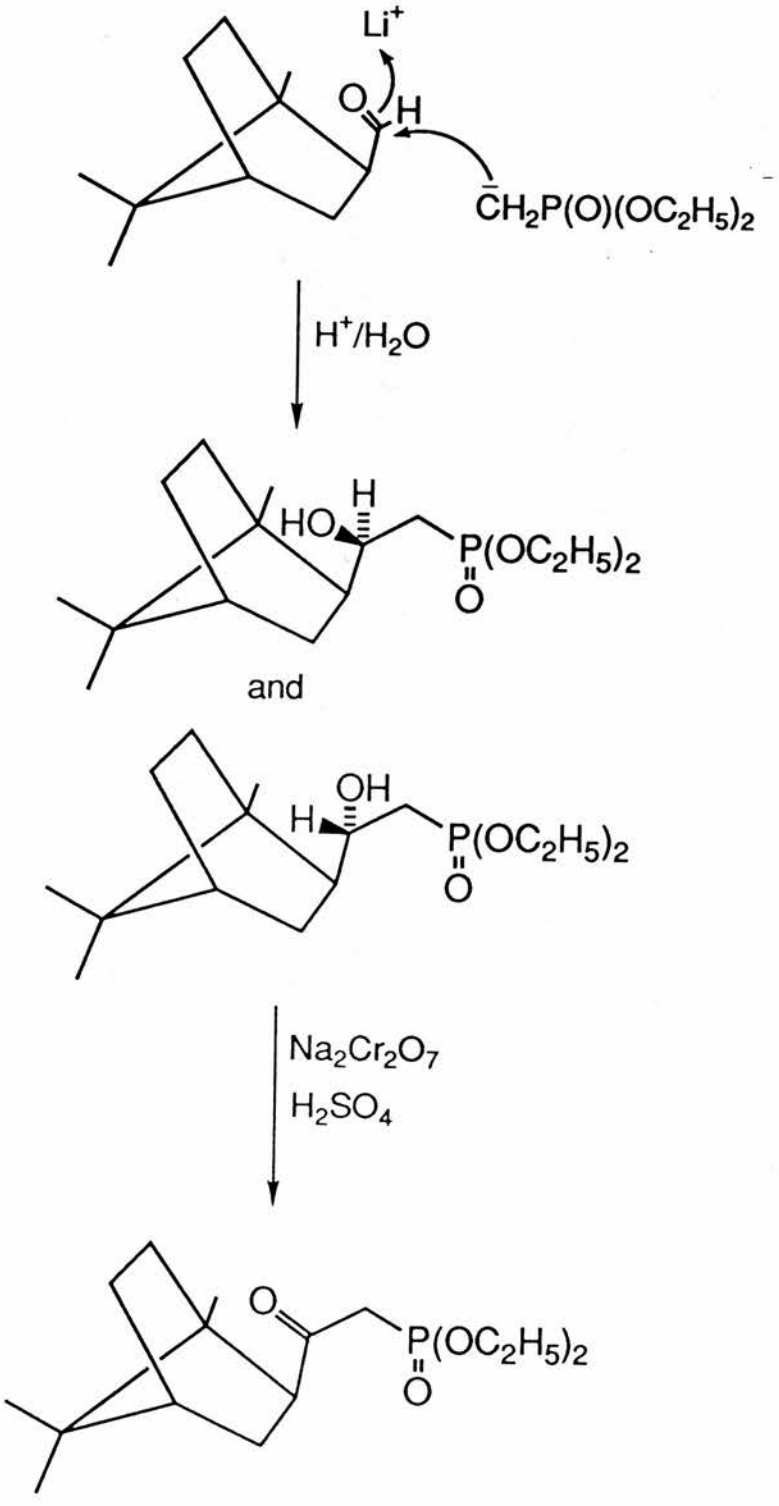


Equation 2.26

The octacarbonyldicobalt catalysed hydroformylation of pinene gave a mixture of products which could not be separated by distillation. The proton nmr resonances at 9.81, 9.76 and 9.70 ppm are consistent with the predominant formation of three aldehydes which is also confirmed by ^{13}C nmr resonances at 202.5, 202.66 and 205.45 ppm. The carbonyl stretching frequency is at 1712 cm^{-1} and there is an aldehyde peak at 2705 cm^{-1}.

Himmele[143] proposed that the main product of such a hydroformylation was 2-formylbornane. It is likely that the other two are the formylpinane and *exo*-formylbornane[143].

These results were encouraging enough to proceed with the synthesis of the ketophosphonate. The aldehyde mixture was reacted with 1-lithio-methane phosphonate according to the Equation 2.27 and



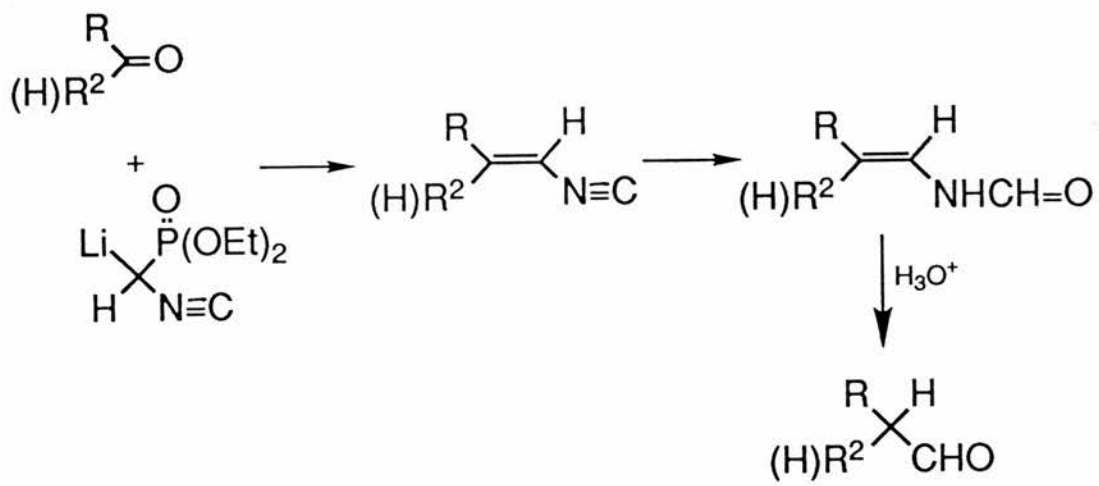
Equation 2.27

then the hydroxyphosphonate oxidised with acidic sodium dichromate to give three corresponding β-ketophosphonates with resonances at +20.03,+19.91 and +19.80 ppm in the ^{31}P nmr spectrum which are typical for ketophosphonates of that type and three doublets in the ^{13}C nmr spectrum 203.70 ppm (J=6.74Hz) 202.85 ppm (J=6.09Hz) and 200.40 (J=5.59Hz).

In the infrared spectrum the carbonyl stretching frequency occurs at 1710 cm^{-1} and phosphoryl stretch at 1260 cm^{-1}. In the ^1H nmr there are methyl group resonances at 0.95 ppm (major isomer), 0.88 and 0.76 ppm. The methyl protons of the phosphoryl group appear as a triplet at 1.3 ppm (J=7.0 Hz) and the corresponding methylene signals as a multiplet at 4.2 ppm (J_{HP}=6.0 Hz).

Mass spectroscopic analysis of the product gave the molecular ion peak at 316 (M+) and *inter alia* a subsequent peak at 298 (extrusion of ethylene from P-O-CH_2CH_3).

A report in the literature[144] that the bornyl aldehyde could be synthesisted by a one carbon homologation reaction of camphor with isocyanomethylphosphonate $(EtO)_2P(O)CH_2NC$ has been investigated[145].



Equation 2.28

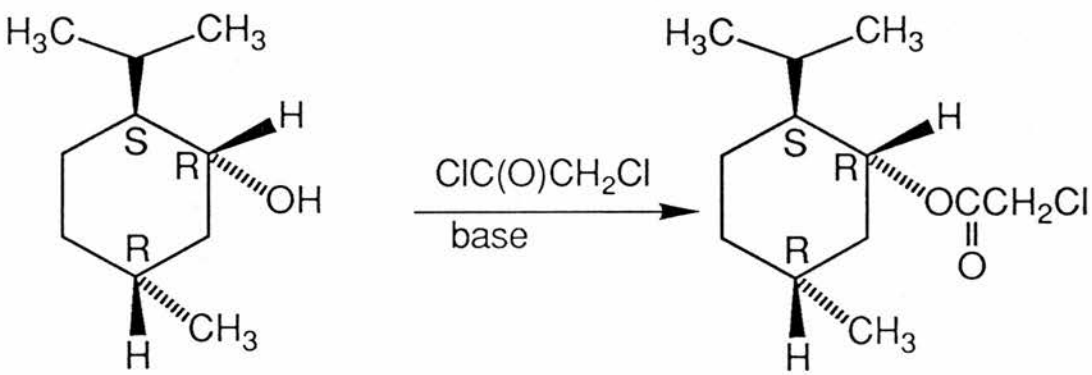
The reaction was indeed successful, however unreacted camphor was present in large amounts from which it was difficult to separate the bornyl aldehyde. The low product yield along with the knowledge that in the more successful ligands for asymmetric catalysis the chirality is closer to both chelating functions[17] led to the belief that the performance of ligands such as [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor may be better so that this approach was discontinued.

2.4 Diethyl (-)-menthyloxycarbonylmethylenephosphonate

Since many α-halo esters gave the Arbusov rather than the Perkow product the reaction of the sodium salt of diethylphosphite with the α-chloroester derived from (-)-menthol was carried out.

(-)-menthyl chloroacetate

Treatment of (-)-menthol with chloroacetyl chloride and an amine base gave (-)-menthyl chloroacetate.

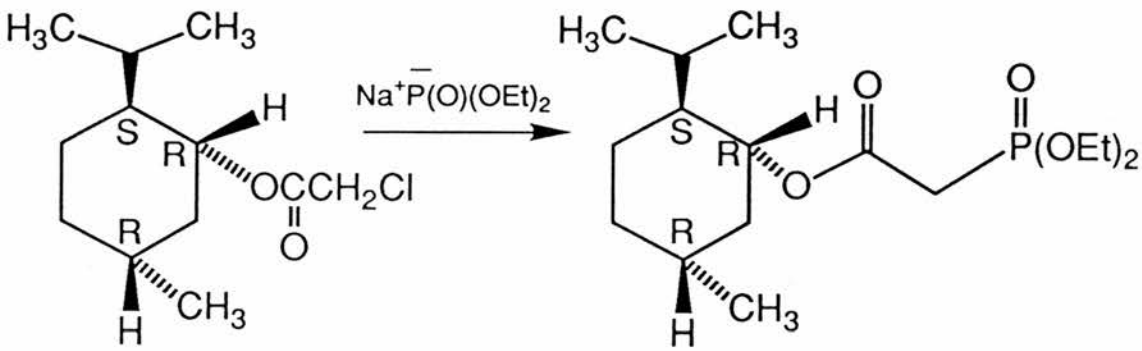


Equation 2.29

The spectra were consistent with the literature[143].

Diethyl (-)-menthyloxycarbonylmethylenephosphonate

The Michaelis-Becker reaction was the preferred methodology for the synthesis of the phosphonoacetate. Consistent with the observations of Lichtenthaler[128] and others[146] where the products of the reactions of trialkyl phosphites with α-halo esters commonly gave the phosphonate rather than the vinyl phosphate, the product of the treatment of (-)-menthyl chloroacetate with the sodium salt of diethylphosphite was diethyl (-)-menthyloxycarbonylmethylenephosphonate.



Equation 2.30

Spectroscopy

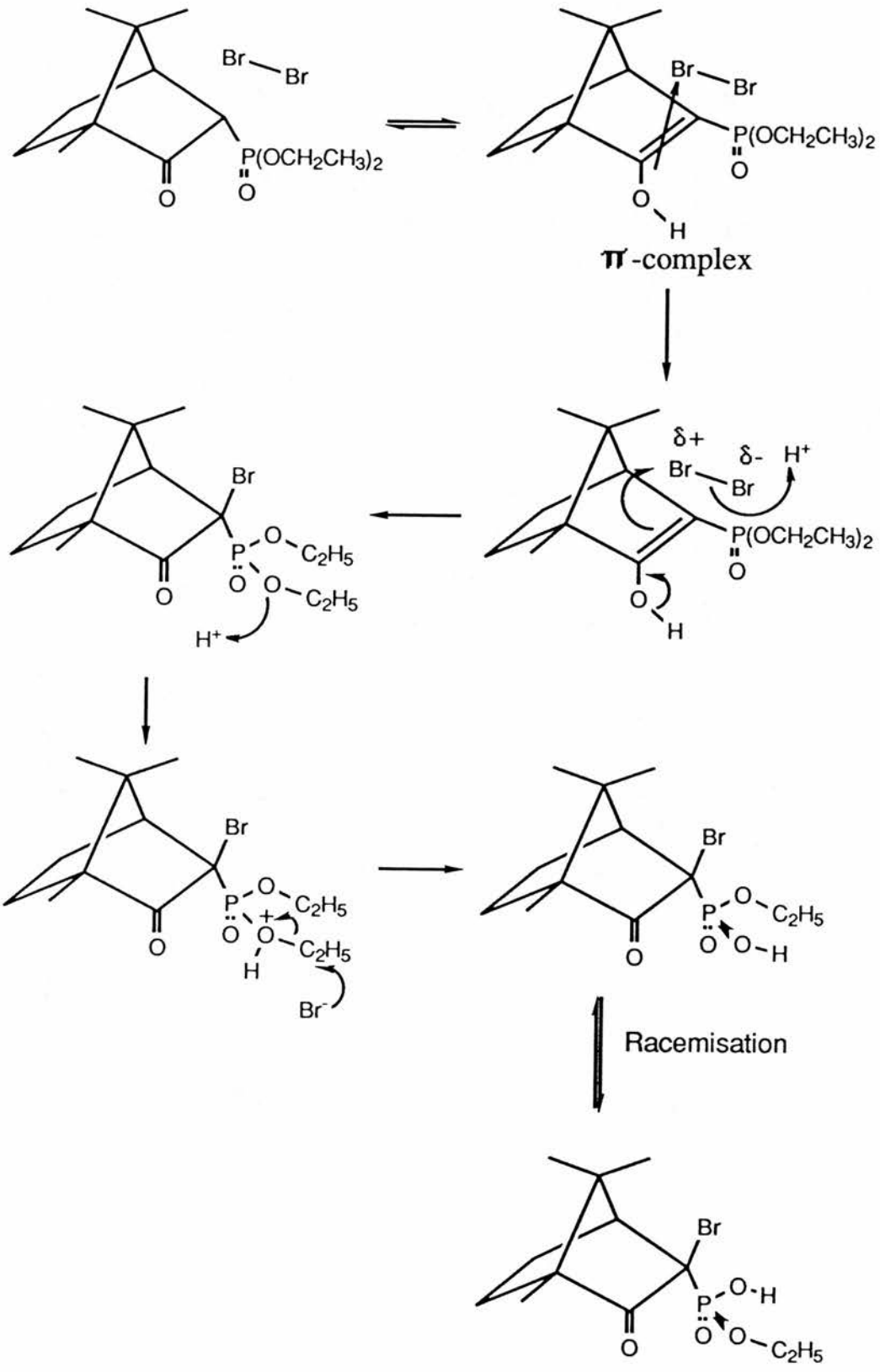
The existence of one resonance in the ^{31}P nmr spectrum at +19.21 ppm precludes the existence of both vinyl phosphate and β-ketophosphonate isomers and is typical for that of a phosphonate. It is clear also that only one diastereomer is present which must be R at C(3). The appearance of a carbonyl stretching frequency at 1730 cm^{-1} and phosphoryl stretch at 1270 cm^{-1} is confirmation that the product is indeed the ketophosphonate. The proton nmr shows no signals typical of vinylic protons.

2.5 Camphor-3-phosphonic acid Derivatives

The compound [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor has 3 chiral centres 1R, 3S, and 4R. Substitution of the proton at C(3) by the large bromine atom should increase the steric crowding around that centre and should induce some ring distortion.

2.5.1 Bromination of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor

[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor brominated cleanly at the 3 position with the corresponding loss of the C(3) proton. The colourless crystalline compound obtained had only one ethoxy group according to ^{1}H and ^{13}C nmr evidence. A hydroxyl proton was observed in the ^{1}H nmr at 10.70 ppm and the microanalysis and mass spectrometry results were consistent with a compound having the composition $C_{12}H_{21}PO_4Br$. It is clear that de-ethylation had taken place and GC-MS analysis of the products showed the presence of substantial amounts of ethyl bromide.



Equation 2.31

The most likely mechanism for the formation of the bromocamphor phosphonic acid monoester involves:

(i) The formation of a π-complex between Br_2 and the enol form of the camphor moiety (Equation 2.31).

(ii) This breaks down in a similar manner to other brominations[147] of ketones to form the brominated product plus HBr.

(iii) Since hydrobromic acid is a reagent of choice for the de-alkylation of phosphonic acid esters[148], it is likely that the HBr formed will lead to the de-ethylation.

Only one isomer is isolable from the bromination, the phosphoryl must be *endo* or *exo*. From arguments presented in Section 2.1.5, the product formed has the phosphoryl *endo* which is interesting because at first it would seem that the product has been derived from a seemingly more sterically congested π-complex intermediate, perhaps due to the effect of the gem-dimethyl bridge. This turns out not to be the case and it is likely that the H-5/H-6 *exo* protons which are held fixed under the enolic π-bond offers a greater barrier to the approach of the bromine than the protons on C(8) which can be rotated away from the π-bond.

Inspection of the arrangement of the substituents at phosphorus would suggest that the phosphorus itself is chiral with two possible enantiomeric P atoms (Figure 2.12).

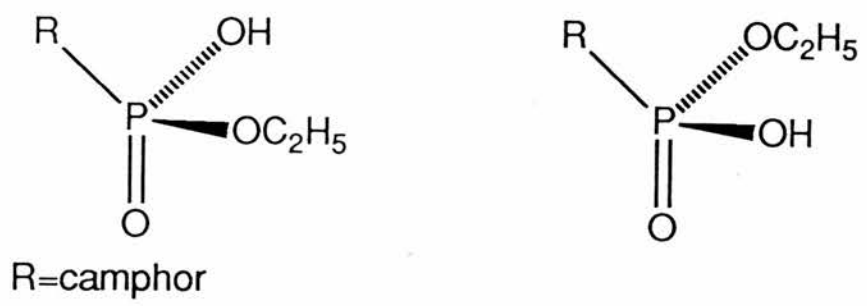


Figure 2.12

The fact that there is only one resonance in the ^{31}P nmr spectrum and that the relative simplicity of the ^{13}C and ^{1}H nmr could draw one to the conclusion that the product was enantiomerically pure at phosphorus.

Morrison however reports[149] the anions of phosphinic acids $R_2PO_2^-$ are symmetric and do not form diastereomeric salts with chiral cations. There is little doubt that the form in this compound is typical of other phosphonic acids in that a rapid equilibrium exists between the two chiral forms of phosphorus.

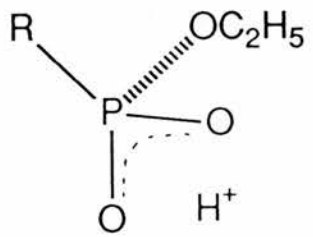


Figure 2.13

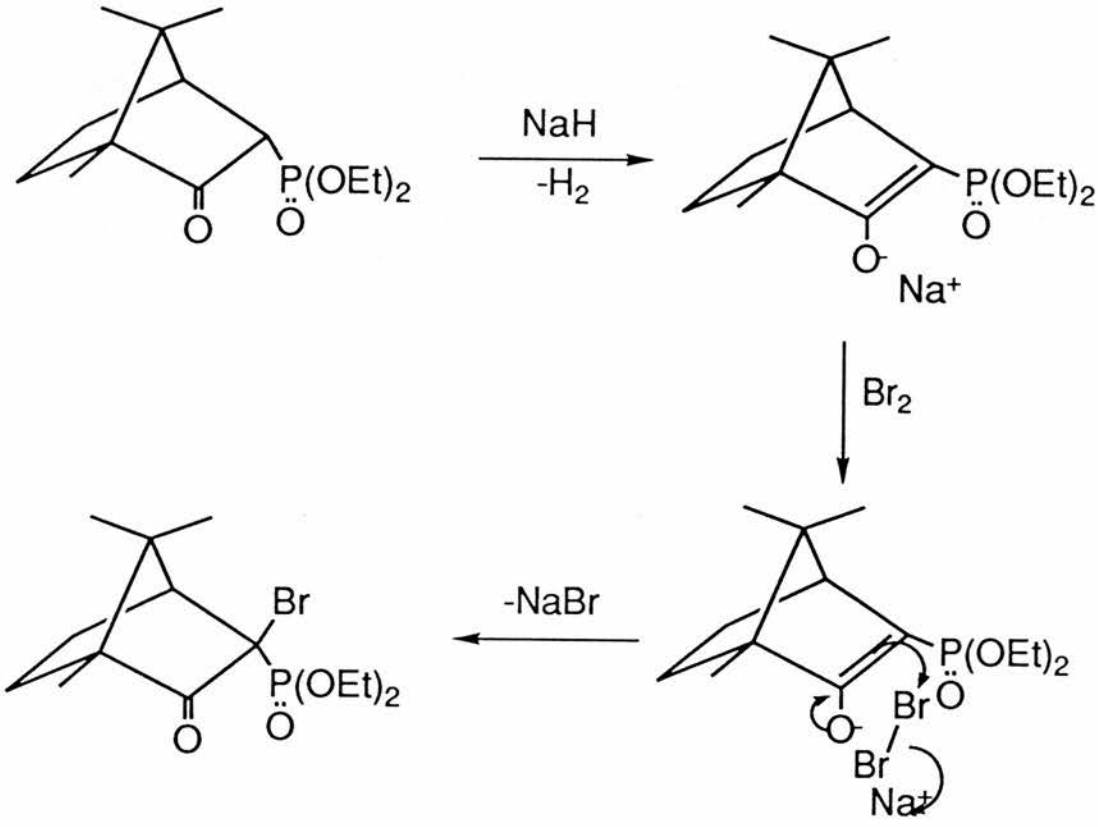
The existing chiral centres in the rest of the molecule and the alteration in the nature of the phosphoryl grouping should make this a very interesting ligand for study.

It is worth noting that de-alkylation of the corresponding thiophosphoryl compound $(RO)_2P(S)R^1$- would result in the formation of two distinct enantiomeric phosphorus atoms[149]. The anions of thiosphosphinic acids exist and acids $R^1R^2P(S)OH$ can be resolved into enantiomeric forms through separation of diastereomeric salts[149,150].

2.5.2 3-(diethoxyphosphinyl)-3-bromocamphor

Since it is likely that free HBr is responsible for the de-ethylation step a method of synthesising 3-bromocamphor-3-phosphonic acid diethyl ester was carried out.

Bromination without dealkylation was achieved by treatment of [(1R)-*endo*]-(+)-3-(diethyoxyphosphinyl)camphor with sodium hydride to produce the sodium salt of the ketophosphonate. Addition of Br_2 resulted in the formation of the crystalline bromodiester.

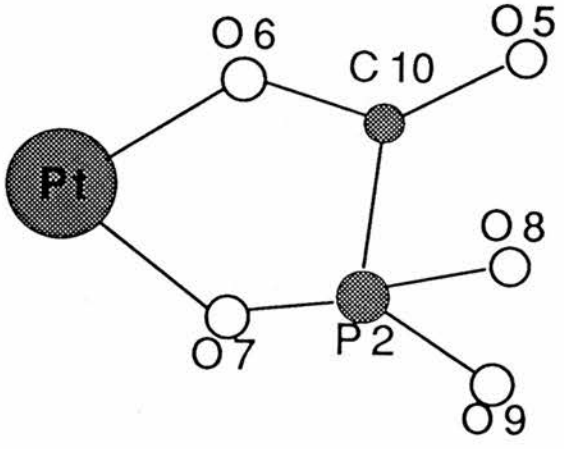


Equation 2.32

2.5.3 Camphor-3-phosphonic acid monoethyl ester

Due to viral inhibitory activity of phosphonoformic (PFA) and phosphonoacetic (PAA) acids particularly with respect to Herpes, influenza and other viruses[151,152,153], there has been interest in the

nature of the binding to an endogeneous metal of enzymes (eg. Zn^{2+}) or the exogeneous coenzymes (eg. Mg^{2+} or Mn^{2+}) required for enzymatic activity. The paucity of information about the ligand properties has led workers[154] to investigate the complexation chemistry of PFA with Pt^{2+} (Structure 2.3) as a useful preliminary model for Zn^{2+}.



[*cis*- $Pt(NH_3)_2(PFA)]^-$ anion

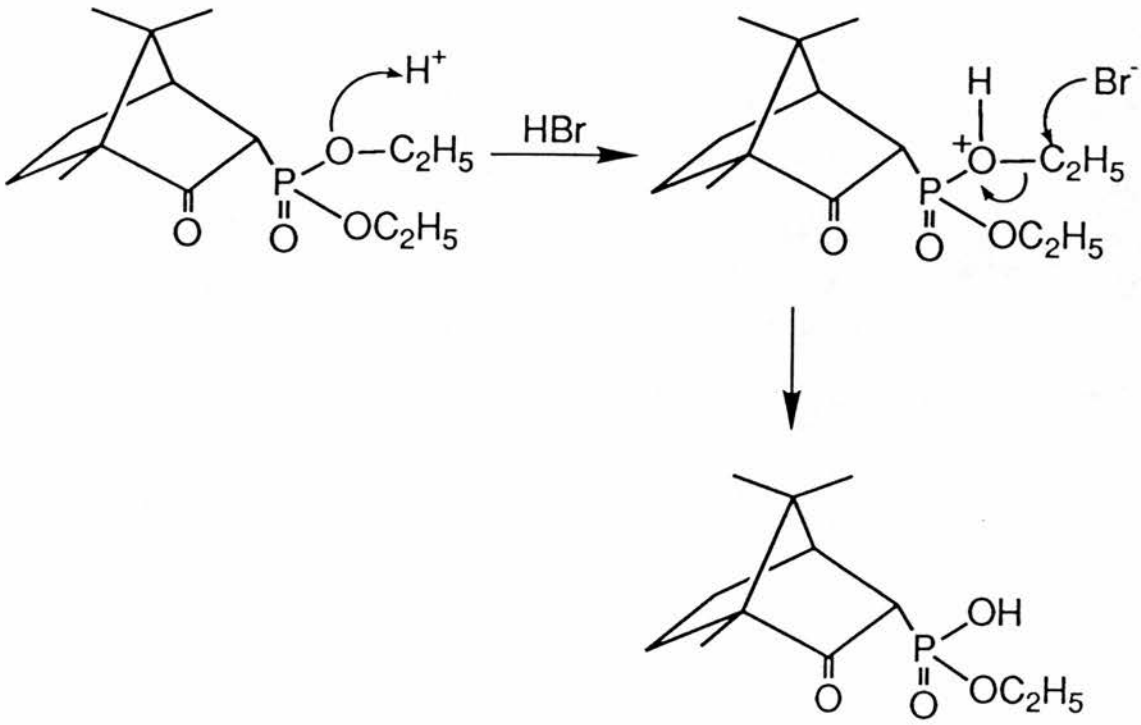
Structure 2.3

The activity of compounds such as the β-ketophosphonic acid: camphor-3-phosphonic acid monoethyl ester both biologically and in co-ordination chemistry should prove interesting indeed.

The de-alkylation of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor cannot cause recemisation at C(3) because no reasonable mechanism can be produced for reaction at that centre in this context.

The de-ethylated [(1R)-*endo*]-(+)-3-(diethoxyphopshinyl) camphor is a good comparison with the brominated phosphorus esters, particularly in terms of its stereochemistry.

Treatment with aqueous hydrobromic acid gave camphor-3-phosphonic acid monoethyl ester (Equation 2.33).



Equation 2.33

The reaction can be envisaged as the attack of the soft nucleophile Br^- upon the protonated form of the phosphorus diester.

2.5.4 NMR Spectroscopy Discussion of the Camphor-3-phosphonic acid Derivates - The Assignment of Stereochemistry at C(3)

Since the first report[140] of the utility of ^{13}C NMR as a technique for the stereochemical analysis of cyclohexyl compounds in 1966, the methods established[155] have been used to study the conformational effects among cyclohexyl phosphorus compounds containing tri- and tetravalent phosphorus atoms[156]. The influence of axial and equatorial pentavalent phosphorus atoms on the carbon shifts and ^{13}C-^{31}P couplings has also been examined for series of dialkylphosphono cyclohexanes[139].

This technique has been extended to deduce the preferred geometries of the phosphorus atom in the previously unknown phosphonic acids and esters.

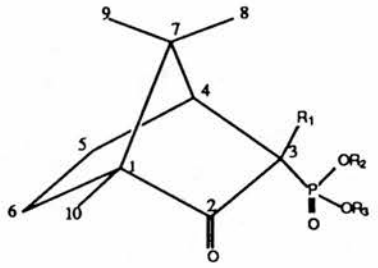
Chemical Shifts

The ^{13}C chemical shifts for the compounds (1) to (4) are presented in Table 2.3, along with the corresponding general structure and numbering scheme. Also included are the chemical shifts of camphor and *endo*-3-bromocamphor for comparison. The entries in the first column refer to the carbon atom number.

It can be seen that the effect on the chemical shifts of camphor upon bromination is to cause a deshielding effect for those carbon atoms except for the carbonyl atom - C(2), and atoms C(5), and C(7) which are shielded by 9.1, 4.1 and 0.8 ppm respectively. It should be noted that in the other bromo-derivates the halogen atom has been found to be *exo* so that although this is a valid and useful comparison, the chemical shift difference in the carbon atoms between an *exo*- and *endo*-bromocamphor will be small but significant.

Table 2.3

The Stereochemical Dependence of ^{13}C NMR Chemical Shifts in the Determination of the Structure of α-Substituted Camphor Phosphonic Acids.



11 12 13 14

$R_2=CH_2CH_3$ $R_3=CH_2CH_3$ or H

(1): R_1=H, $R_2=R_3=C_2H_5$ (2): R_1=H, $R_2=C_2H_5$, R_3=H

(3): R_1=Br, $R_2=C_2H_5$, R_3=H (4): R_1=Br, $R_2=R_3=C_2H_5$

	Camphor	Bromocamphor	(1)	(2)	(3)	(4)
1	57.40	57.10	58.82	58.92	60.32	60.25
2	218.40	209.30	210.93	210.0	209.91	210.43
3	43.10	53.90	50.67	50.43	56.53	57.37
4	43.20	49.80	46.21	46.18	55.38	55.43
5	27.00	22.90	22.98	22.75	25.30	25.58
6	29.90	30.70	29.73	29.82	28.64	28.64
7	46.60	45.80	46.88	46.89	47.48	47.48
8	19.10	20.20	18.72	18.72	20.39	20.45
9	19.70	20.20	19.36	19.39	24.40	20.34
10	9.20	10.00	9.62	9.65	10.54	10.40
11	-	-	62.04	61.87	64.52	64.46
12	-	-	16.47	16.39	16.26	16.39
13	-	-	61.83	-	-	63.76
14	-	-	16.42	-	-	16.19

All of the ^{13}C chemical shifts display a similar trend to that of camphor and bromocamphor without transposition.

The effect on the chemical shift of compounds (1) to (4) upon bromine substitution at C(3) is to cause a significant deshielding of *ca.* 6 ppm at that carbon. This is about half the value of the downfield shift induced in the C(3) resonance of camphor itself upon bromination. The effect of having a bromine atom and a phosphoryl group is to cause a downfield shift in all of the camphor skeleton carbon resonances except for C(2) which shows no significant chemical shift difference and C(6) which shows an upfield shift of *ca.* 2 ppm. The most pronounced effect is in C(4) in which the resonance shifts upfield by 5.63 ppm. The origin of the large chemical shift difference between C(8) and C(9) (4 ppm) in the bromomonoester is unknown. The other compounds show a difference of no greater than *ca.* 0.6 ppm.

The Introduction of a Phosphoryl Substituent

Introduction of a phosphoryl substituent at position 3 is to deshield every ^{13}C nucleus except C(2), C(5), C(6) and C(9) which show increased shielding of 7.47, 4.10, 0.17 and 0.98 ppm respectively. The effect upon C(2) is the largest and perhaps the most interesting in that substitution at C(3) of camphor by an electronegative bromine atom deshields the C(2) nucleus by *ca.* 9 ppm but another substitution, by an electronegative phosphoryl group this time, causes an only very slight deshielding (*ca.* 1 ppm) when compared with bromocamphor.

In compounds (1) and (4) the O-C and O-C-C positions are diastereotopic which explains minor shift differences are observed.

The Stereochemical Dependence of ^{13}C-^{31}P Couplings in the Determination of the Structure of α-Substituted Camphor Phosphonic Acids

Selected ^{13}C-^{31}P coupling constants for the four camphor phosphonic acid esters are displayed in Table 2.4. The first row gives the couplings for [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor which is a useful comparison because its stereochemistry is known unequivocally.

Investigations by Buchanan[139] have shown that 3 bond C-P couplings are sensitive to stereochemistry.

One Bond Couplings

The direct ^{13}C-^{31}P couplings are given in the third column. Couplings for the phosphonic acids tend to be larger than the couplings for the phosphonic esters. The small variations found in J_{CP} is most likely due to the fact that the series is not truly homologous. In the case of t-butyl cyclohexylphosphonates the one-bond coupling is 5-6 Hz larger when the phosphorus atom is axial[139].

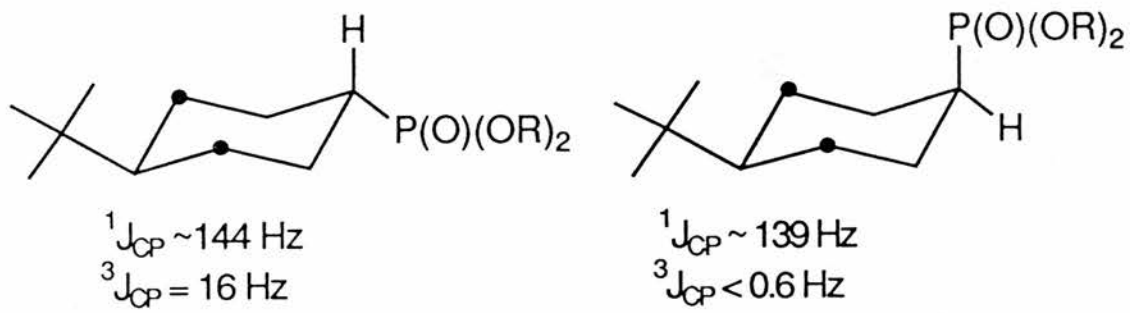


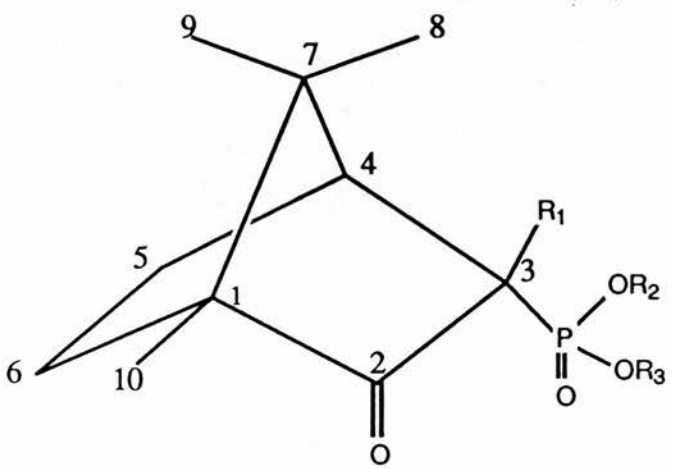
Figure 2.14

Three Bond Couplings

The magnitude of 3 bond couplings in other phosphonates[139] is extremely stereochemically dependent. It is interesting to note that for t-butylcyclohexyl phosphonates J=16Hz when the phosphorus atom is axial, whereas when it is equatorial the coupling is as little as 0.6 Hz.

Table 2.4

Carbon-Phosphorus Coupling Constants (Hz) for *endo*-Substituted Camphor Phosphonic Acid Esters.



11 12 13 14
$R_2=CH_2CH_3$ $R_3=CH_2CH_3$ or H

Carbon atom	1	2	3	5	7	11	12
$R_1=H, R_2=R_3=C_2H_5$	3.6	2.4	144.2	5.0	17.4	6.2 6.5	4.91 5.74
$R_1=H, R_2=C_2H_5, R_3=H$	-	-	148.4	4.7	17.5	6.2	6.0
$R_1=Br, R_2=C_2H_5, R_3=H$	2.2	-	154.5	5.0	15.6	7.3	6.3
$R_1=Br, R_2=R_3=C_2H_5$	2.7	-	148.2	5.3	15.6	7.9 6.7	6.0 6.4

Similarly the couplings to the carbon with which the phosphorus also has a *trans* relationship is large in the *exo* norbornyl phosphonate.

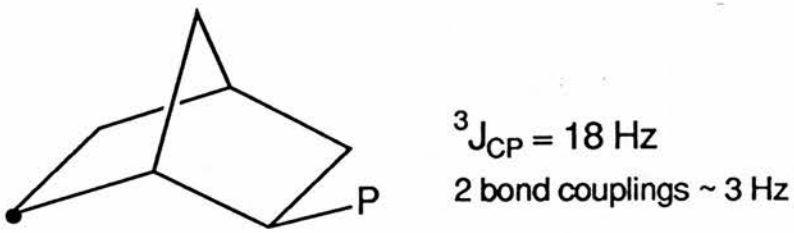


Figure 2.15

From the table it can be seen that all of the couplings to C(6) are noticeably similar. This can only be the case if they have similar geometries and since the geometry of the phosphorus atom in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor is known it can be deduced that the phosphoryl substituent in the camphor phosphonic acids is *endo*.

The phosphoryl substituent does not have this *trans*-type of arrangement in the esters thus explaining the low values for the couplings when compared to couplings of *ca*. 15-17 Hz for C(7) to which be phosphorus has this *trans* relationship.

<u>The Effect on the ^{31}P Chemical Shift of De-Alkylation and Bromination α-to the Phosphoryl Group</u>

The results show the sensitivity of ^{31}P NMR to both substitution at an α-carbon and to de-ethylation.

It can be seen that bromination of the carbon α to phosphorus has a shielding effect of 7.59 ppm in the mono and 7.08 ppm in the diesters. A deshielding effect is found when the diesters are converted to the monoesters and the values are 3.37 ppm in the bromo and 3.88 ppm in the bromomonoester.

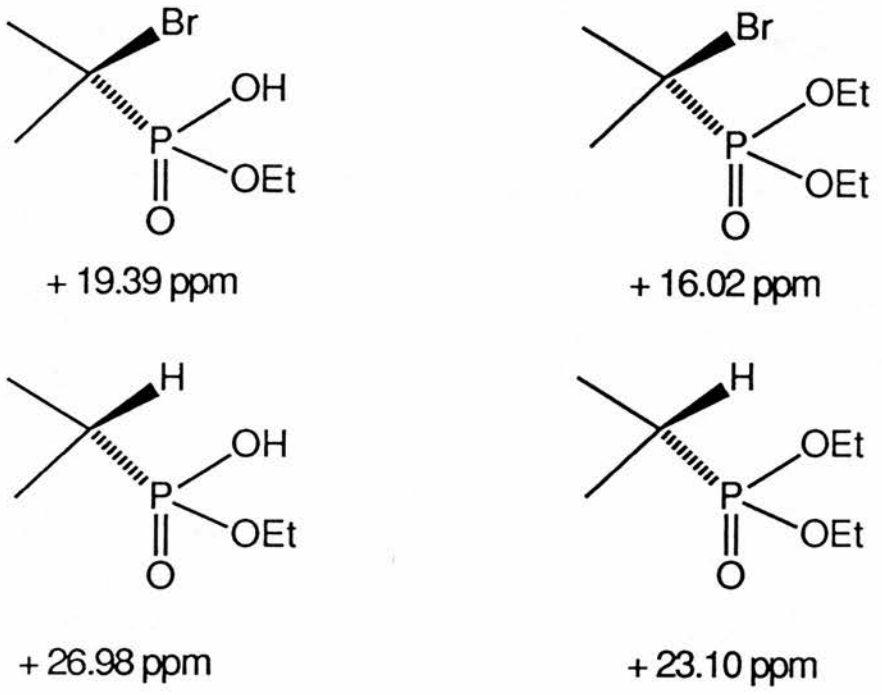


Figure 2.16

Proton NMR

All of the phosphonic acid esters (2) to (4) have much better resolved spectra than that of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor and are reminiscent of the NMR spectrum of [(1R)-*endo*]-(+)-3-bromocamphor. In all of the brominated cases however there appears to be two sets of resonances which have become transposed; two of the methyl resonances and the 6-*endo* with the 6-*exo* proton signals. The camphor phosphonic acid has an nmr spectrum virtually identical to its diester. The phosphorus no longer has the inequivalent ethyl groups so that there only appears a simpler multiplet for P-O-CH_2- at 4.19 ppm and a well resolved triplet at 1.34 ppm for P-O-C-CH_3. The only significant downfield shift is for H-3 which appears at 3.05 ppm with J_{HP}=28.23Hz. The methyl resonances are unperturbed.

Upon bromination the proton at C(3) in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor is replaced and so this explains why the dd usually at 2.98 ppm disappears from the spectrum in both the bromo esters. Also significant is the fact that the proton signals for CH-4 is shifted to *ca*. 2.6 ppm and appears to be a doublet which confirms the coupling of the CH-4 to both *exo* protons CH-5, CH-3 in the other compounds and no coupling to the CH-5 *endo* proton due to the Karplus effect as in Figure 2.3.

In the bromomonoester and bromodiester the appearance of the multiplet at 1.60 ppm is characteristic for the CH-6 *exo* proton in bromocamphor an the CH-6 *endo* proton appears shifted downfield at 1.80 ppm. It is clear then that chemical shift transposition occurs upon *exo*-bromination.

In the bromodiester the inequivalence of the phosphoryl methyl groups can be shown as two overlapping triplets at *ca*. 1.40 ppm.

2.6 Experimental

2.6.1 2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene

Sodium hydride (60% dispersion in mineral oil, 80g, 2 mol) was washed three times with diethyl ether and filtered to remove the oil. Dry diethyl ether (100 ml) was added. To this suspension with stirring was added slowly a solution of diethyl phosphite (165.6g, 1.2 mol) in diethyl ether (600 ml). After 2 hours when all hydrogen evolution had ceased, a solution of bromocamphor (277g, 1.2 mol) in ether (approx. 500 ml) was added. After 4 hours the products were filtered through a sinter funnel and 100 ml of saturated aqueous ammonium chloride was added to the filtrate and the organic phase was extracted with ether and dried over anhydrous magnesium sulphate. Flash distillation (132°C) 0.05 mmHg gave 2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene (211.2g, 0.77 mol, 61.1%) (lit. b.p. 90-92°C/0.15 mmHg).

Analysis

^{31}Pnmr -6.06 ppm

Infrared spectrum 1626 cm^{-1} $\nu C=C$

Mass spectrometry M/e (rel.int.) 90(62), 92(38), 105(100), 154(49), 258(61), 260(24), 286(51), 288(21)M^+. M/e (rel.int.) assignment 260(24) loss of ethylene.

2.6.2 [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

Lithium diisopropylamide (0.49 mol) was prepared by the slow addition of n-butyllithium (46 ml, 0.49 mol, 10 mol l^{-1}) to a solution of

diisopropylamine (68.11 ml, 0.49 mol) in THF (100 ml) at -78°C. After 1 hour 2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo [2.2.1]-2-heptene (46.45g, 0.162 mol) was added and the temperature maintained for two hours and then kept at r.t. for 24 hours. The mixture was then carefully poured into a saturated ammonium chloride/ice mixture. Solvent extraction of the organic phase with diethyl ether and drying over anhydrous magnesium sulphate gave upon distillation (128°C, 0.05 mmHg) [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (28.55 g, 61% yield).

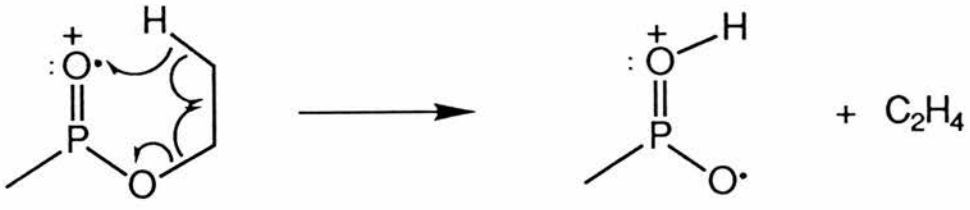
Analysis

^{31}Pnmr +23.1 ppm

Infrared spectra νP=O 1251 cm^{-1}; νC=O 1745 cm^{-1}

Mass spectrometry. M/e (rel.int.) 41(100), 44(42), 55(63), 81(36), 123(43), 152(43), 178(37), 150(34), 160(24)-extrusion of ethene by a McLafferty rearrangement., 288(9) M^+.

McLafferty rearrangement in phosphorus esters:-



Equation 2.34

2.6.3 2-[(diphenylphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene

(+)-Camphor (2.61g, 17mmol) dissolved in THF (15 ml) was added to a stirred suspension of lithium diisopropylamide (2.02g, 19 mmol) in THF (30 ml) at -78°. After 45 minutes the resulting enolate was treated with chlorodiphenylphosphine oxide (4.5g, 19 mmol) and the mixture was

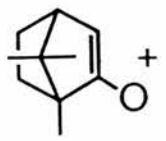
allowed to warm up to 25°C. Quenching with saturated aqueous ammonium chloride was followed by extraction with ether and drying over anhydrous magnesium sulphate. The sticky pale yellow oil which was left after the removal of the ether was distilled at 160°C/0.5 mmHg. The distillate quickly solidified and crystallization of the solid from ethanol/water gave 2-[(diphenylphosphinyl)oxy]-1,7,7-trimethyl-bicyclo [2.2.1]-2-heptene (0.52g, 8.7%) m.p.184-6°C.

Analysis

^{31}P +28.79 ppm

Infrared. $\nu C=C$ 1625 cm^{-1}, $\nu P=O$ 1230 cm^{-1}

Mass spectrometry, M/e(rel.int.). 41(43), 77(52), 106(48), 201(72), 202(94), 219(100), 324(46), 352(34)M^+, M/e(rel.int.) assignment: 151(11)*; 201(73)Ph_2PO^+

* 

Structure 2.4

2.6.4 3-(diphenylphosphinyl)camphor

To camphor-3-diphenylphosphine (0.42g, 1.25 mmol) dissolved in ethanol (10ml) was added aqueous hydrogen peroxide solution ("100 volumes", 20 ml). The solution was stirred for 24h then extracted with CH_2Cl_2 (3 x 100 ml).

After drying over anhydrous $MgSO_4$, the solvents were removed under reduced pressure and the residue was dissolved in ethanol (3 ml) and left to crystallise slowly to give 3-(diphenylphosphinyl) camphor m.p. 192-3°C. (10.40g, 1.14 mmol, 91%).

Analysis

^{31}Pnmr +28.24ppm (no other resonances were visible in crude sample)

Infrared. νC=O 1730 cm^{-1} νP=O 1174 cm^{-1}.

Mass spectrometry. M/e(rel.int.) 41(32), 77(35), 201(78), 202(40), 215(36), 216(30), 242(100), 352(84)M^+.

Microanalysis $C_{22}H_{25}PO_2$

Theoretical (Result of analysis) 74.98(74.94)%C, 7.15(7.24)%H

2.6.5 Diethyl (1-phenyl-2-oxobutane)phosphonate

To a solution of diethylbenzylphosphonate (5g, 22 mmol) in THF (30 ml) at -78°C was added tetramethylethylenediamine (6.6 ml, 0.72 mmol) followed by n-butyllithium (10.22 ml, 2.26 mol l^{-1}). After 15 min of stirring a solution of ethyl propionate (2.24g, 22 mmol) in THF (30 ml) was added. The mixture was stirred at -78°C for 30 minutes and for 2 hours at room temperature. The solvents were removed and the residue was dissolved in water (200 ml) and neutralised by the addition of conc. HCl. The aqueous solution was extracted with dichloromethane (3 x 70 ml) and the combined dichloromethane solutions were washed with water (2 x 100 ml) and dried over anhydrous $MgSO_4$, evaporated and the residue distilled to give diethyl (1-phenyl-2-oxobutane)phosphonate. Yield (2.80g, 44.8%) b.p. 150°/0.5 mmHg.

Analysis

^{31}Pnmr +19.43 ppm

Infrared 1717 cm^{-1} νC=O

1600 cm^{-1} ar. C-H

1255 cm^{-1} νP=O

Mass spectrometry

228(39) (loss of $CH_3CH=C=O$ from M); 200(9) (loss of ethene from 228); 172(26) (loss of ethene from 200); 124(11); 118(32); 91(100); 89(16); 65(29); 57(22).

2.6.6 Hydroformylation of (1S)-(-)-α-pinene

Octacarbonyldicobalt (0.2g) was added to (1S)-(-)-α-pinene (40g, 0.29 mol) in a high pressure autoclave which was then pressurised to 100 atmospheres. The contents were heated to 120°C for 24 hours and then cooled to 20°C and the pressure released. The contents were distilled to give a sweet smelling oil (4.55g, 9.5%, b.p.52°C/0.5 mmHg) which according to Himmele[143] is mainly (+)-2-formyl bornane (50% by nmr ratio). The unreacted pinene (26.6g) was recovered by distillation.

2.6.7 Addition of the lithio derivative of diethylmethane phosphonate to the hydroformylation products

To diethylmethanephosphonate (4.56 g, 29 mmol) dissolved in THF (40 ml) at -78°C was added n-butyllithium (12 ml, 29 mmol, 2.5M in hexanes). 20 minutes later the formylbornane mixture (4.8g) was injected into the solution. This was stirred for 60 mins and the temperature was allowed to rise to 20°C. 30 mins later a conc. hydrochloric acid solution was added until the pH was neutral and the solvents removed at the water pump. The organic components were taken up in dichloromethane (50 ml) and dried over anhydrous magnesium sulphate. The hydroxyphosphonate was used directly for the oxidation step.

Oxidation of the hydroxyphosphonate

The the hydroxyphosphonate at 35°C, a solution of sodium dichromate (7.1g) and concentrated sulphuric acid (4 ml) in water (20 ml) was

slowly added. 2 hours later the reaction was left at 20°C for 18 hours. After solvent extraction with dichloromethane (3 x 70 ml) and drying over anhydrous magnesium sulphate, distillation gave the ketophosphonate mixture (2.75g, b.p. 155-160°C/0.5 mmHg). Yield of product mixture 30.0%.

Analysis 2-formylbornane

A mixture was obtained so that spectroscopic identification of the products was difficult.

^{13}Cnmr (solvent $CDCl_3$)

202.5, 202.66 and 205.45 ppm. Three aldehydes.

^{1}Hnmr

9.81, 9.76, 9.70 ppm. Three aldehydes (relative integrals 2:1:1).

Infrared

1712 cm^{-1}(s) νC=O 2705 cm^{-1}(m) aldehyde band.

Ketophosphonate derivative of 2-formylbornane

^{13}Cnmr (solvent $CDCl_3$)

203.70 ppm (J=6.74Hz), 202.85 ppm (J=6.09Hz) and 200.40 (J=5.59 Hz). Ketonic group.

^{1}Hnmr

Methyl group resonances of the major isomer 0.76, 0.88 and 0.95 ppm. P-CH_2 1.3 ppm (t, J=7.0Hz). P-C-CH_3 (m, J=6.0Hz). (Isomer ratio 2:1:1).

^{31}P nmr

+20.03, +19.91, +19.80 ppm. Three singlets.

Infrared

1710cm^{-1} νC=O; 1260 cm^{-1} νP=O.

2.6.8 Diethyl (-)-menthyloxycarbonylmethylene phosphonate

(i) Synthesis of (-)-menthylchloroacetate as starting material

Chloroacetyl chloride (15.3 ml, 0.2 mol) was added to a mixture of (-)-menthol (31.3g, 0.2 mol) and dimethylaniline (25 ml, 0.2 mol) over a period of ten minutes. The reaction mixture was kept below 30°C and left stirring for 45 minutes. The product was added to iced water (200 ml) followed by diethyl ether (100 ml). The ether layer was finally washed with saturated sodium bicarbonate and dried over anhydrous sodium sulphate. The ether layer was evaporated to give (-)-menthyl chloroacetate b.p. 141-142/1.5 mmHg.

Yield 22.25g (48%). The spectrum of this compound was essentially identical to that given in the literature[142].

Analysis

Infrared: νC=O 1730 cm^{-1}; ^{1}Hnmr: singlet at 4.1 ppm ($-CH_2Cl$) multiplet at 0.6 - 2.3 ppm (menthyl).

(ii) Diethyl (-)-menthyloxycarbonylmethylenephosphonate

Sodium metal (1.5g, 0.09 mol) was dissolved in a solution of diethyl phosphite (12ml, 0.09 mol), in dry diethyl ether (100 ml). (-)-menthyl chloroacetate (20.35g, 0.09 mol) in dry diethyl ether (40ml) was then added to the mixture cooled in an ice-bath. The product was boiled for one hour and left for 12 hours whereupon the sodium chloride was filtered off. The ether was evaporated and the residue fractionally distilled to give diethyl (-)-menthyloxycarbonylmethylenephosphonate. (15.1g, 52%) b.p. 146-148°C/0.5mmHg.

^{31}Pnmr +19.21 ppm

Infrared νC=O 1730 cm^{-1}, νP=O 1270 cm^{-1}.

2.6.9 3-bromocamphor-3-phosphonic acid monoethyl ester

To [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (5g, 17 mmol) in dichloromethane (60 cm^3) in a 100 cm^3 flask fitted with a water cooled reflux condenser was rapidly added bromine (2.9g, 18 mmol). The initially dark solution became paler over five days whereupon the solvent and any excess bromine was removed under reduced pressure. The remaining orange sticky oil was treated with diethyl ether/petroleum ether (1:6, 30 cm^3) and water (30 cm^3). The two phases were treated with a concentrated solution of sodium hydroxide whereupon the orange oil completely dissolved. An ether/water mixture (100 cm^3, 1:1) was added and the layers separated and washed with ether (3 x 50 ml). The ether layer was dried over anhydrous magnesium sulphate and the solvents were removed on the rotary evaporator to give a pale brown oil from which crystallised 3-bromocamphor-3-phosphonic acid diethyl ester (0.5g, 8%). M.p. 78-79°C.

The almost colourless aqueous layer was treated with conc. hydrochloric acid until the solution became acidic. A fine white suspension of 3-bromocamphor-3-phosphonic acid, monoethyl ester formed. Following filtration and washing with cold water (3 x 10 ml) the product was dried for 12 hours in a vacuum desiccator. M.p. 163-4°C 3.1g 54% yield.

The synthesis of the monoester by addition of bromine to [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was optimised by having no solvent present. Yield of 3-bromocamphor-3-phosphonic acid monoethyl ester after 24 hours (61%). A sample of the reaction mixture after 30 mins was studied by GC-MS which detected the presence of large amounts of ethyl bromide.

Analysis

^{31}Pnmr +26.98 ppm

Infrared νC=O 1738 cm^{-1}, νP=O 1152 cm^{-1}

Microanalysis Theoretical (Results of analysis) 55.38(55.77)%C, 8.13(8.11)%H for $C_{12}H_{20}BrPO_4$

Mass spectrometry. M/e (rel.int) 39(60), 41(100), 42(74), 53(52), 55(74), 67(57), 81(93), 91(51). M^+=338/340

M^+-28=310/312 (loss of ethylene McLafferty Rearrangement).

M^+-79/81=259 (loss of bromine).

2.6.10 3-(diethoxyphosphinyl)-3-bromocamphor

[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1.07g, 3.72 mmol) was dissolved in dry diethyl ether (30 ml) and slowly added to a suspension of sodium hydride (approx. 3 molar excess) from which the mineral oil had been washed off with diethyl ether. Several hours later when hydrogen evolution had ceased, the solution was filtered and the solvents removed under reduced pressure to leave the sodium salt as a gummy residue. To this was added carbon tetrachloride (40 ml) with stirring. When all of the sodium salt had dissolved, the solution was cooled in an ice-bath and bromine liquid (0.192 ml, 3.72 mmol) was added rapidly. Several hours later the volatile components were removed on the rotary evaporator to leave a pale brown oil. After 24 hours large (0.5 cm long) colourless acicular crystals developed from the oil. Washing with cold ethanol/water left the product 3-(diethoxyphosphinyl)-3-bromocamphor (0.52g, 38% isolated yield). M.p. 78-79°C.

Analysis

^{31}Pnmr +16.02 ppm

Infrared

νC=O 1746 cm^{-1}, νP=O 1248 cm^{-1},

Microanalysis Theoretical (results of analysis) 45.79(45.94)%C

6.59(6.84)%H for $C_{14}H_{24}BrPO_4$

Mass spectrometry. M/e (rel int.) 42(100), 55(90), 121(58), 259(54), 79(46), 81(46), 91(45), 65(39). M^+ 366/368, M^+-28=338/340 (loss of ethene by McLafferty rearrangement), M^+-79/81=287 (loss of bromine).

2.6.11 Camphor-3-phosphonic acid monoethyl ester

To hydrobromic acid (20 ml, 48% aquaeous solution) was added [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1g, 3.47 mmol). After one month hydrochloric acid (conc. 10 ml) was added and the mixture left for a further week. Acetone was added and the acetone/water mixture was removed at the water pump. The residue was dissolved in dichloromethane (30 ml) whereupon water (30 ml) and saturated aqueous sodium hydroxide (30 ml) was added with cooling. The layers were separated and the dichloromethane layer was washed with aqueous sodium hydroxide (3 x 10 ml). The aqueous layer was treated with conc. hydrochloric acid until the solution was no longer alkaline. After 24 hours white needles of camphor were deposited, these were filtered and dried *in vacuo*. (0.24g, 29.8%). M.p. 163-164°C.

Analysis

^{31}Pnmr +19.39 ppm

Infrared νC=O 1740 cm^{-1} νP=O 1240 cm^{-1}

Microanalysis Theoretical (results of analysis) 42.50(42.34)%C

5.94(5.97)%H for $C_{12}H_{21}PO_4$

Mass spectrometry. M/e (rel.int) 39(61), 41(100), 42(74), (53(52), 55(71), 67(58) , 81(93), 91(52). 260(5) M^+

2.7

2-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo[2.2.1]-2-heptene

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
4.95	d	1	H-3
3.75	m	4	CH_2-11
1.54	m	1	H-4
1.45	m	1	H-5 *exo*
1.15	m	1	H-6 *exo*
0.95	t	6	CH_3-12
0.90	m	1	H-5 *endo*
0.70	m	1	H-6 *endo*
0.55	s	3	CH_3-10
0.50	s	3	CH_3-9
0.35	s	3	CH_3-8

^{13}Cnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Coupling Const.J_{PC}(Hz)	Assignment
154.66	10.09	2
109.10	3.6	3
63.27	5.91	11
54.92		4
52.36	6.05	1
48.80		7
30.18		6
25.38		5
18.93		8
18.87		9
15.22		12
9.80		10

[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
4.10	m	4	CH_2-11/CH_2-13
2.93	dd	1	H-3
2.40	t	1	H-4
2.13	m	1	H-5 *endo*
1.92	m	1	H-5 *exo*
1.69	m	1	H-6 *exo*
1.63	m	1	H-6 *endo*
1.35	t	3	
1.34	t	3	CH_3-12/14
1.00	s	3	CH_3-9
0.92	s	3	CH_3-10
0.86	s	3	CH_3-8

^{13}Cnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Coupling Const.J_{PC}(Hz)	DEPT	Assignment
210.93	2.4	quarternary	2
62.04/61.83	6.0	CH_2	11/13
58.82	3.6	quarternary	1
50.66	144.2	CH	3
46.88	17.4	quarternary	7
46.21	1.7	CH	4
29.73	0	CH_2	6
22.98	5.0	CH_2	5
19.37	0	CH_3	9
18.72	0	CH_3	8
16.42	6.1	CH_3	12/14
9.62	0	CH_3	10

[2-[(diphenylphosphinyl)oxy]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-ene.

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
7.70	dm(J_{HP}=104.9Hz)	10	phenyl rings
5.25	dd	1	H-3
2.19	t	1	H-4
1.65	m	1	6 *exo* H
1.45	m	1	5 *exo* H
1.00	s	3	CH_3-9
0.90	m	2	H-5/6 *endo*
0.71	s	3	CH_3-10
0.70	s	3	CH_3-8

^{13}Cnmr

Chemical Shift(ppm)	Coupling Const.(Hz)	Assignment
155.05	11.00	2
111.15	6.05	3
55.68		4
53.37	4.95	1
49.79		7
30.83		6
20.18		5
19.85		8
19.23		9
10.08		10
131.88	256.36	
131.83		
131.76	aromatic	
128.56		
128.48		
128.30		

3-(diphenylphosphinyl)camphor

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
7.90-7.40	m(J_{PH}≃100Hz)	10	C(ar)-H
3.59	dm(J_{PH}≃10.7Hz)	1	H-3
2.37	t	1	H-4
2.18	m	1	5-H *endo*
1.61 overlapping	m	2	5-H *exo*
1.75 slightly	m		6-H *exo*
1.44	m	1	6-H *endo*
0.99	s	3	CH_3-9
0.93	s	3	CH_3-10
0.90	s	3	CH_3-8

^{13}Cnmr

Chemical Shift(ppm)	Coupling Const.J_{PC}(Hz)	DEPT	Assignment
211.77		quaternary	2
133.42	100.90	quaternary	P-(ar)C-1
133.31	100.31	quaternary	P-(ar)C-1
131.73-128.28		CH	P-(ar)CH
59.67		quaternary	1
52.85	69.25	CH	3
47.36		quaternary	7
46.91		CH	4
29.24		CH_2	6
23.13	5.41	CH_2	5
19.48		CH_3	8/9/10
18.57		CH_3	
9.74		CH_3	

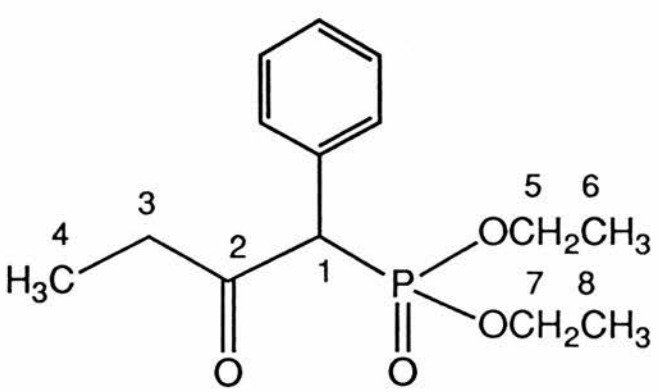
Diethyl (1-phenyl-2-oxobutane)phosphonate (Structure 2.5)

Proton nmr (Solvent $CDCl_3$)

Chemical Shift	Multiplicity	Integral	Assignment
7.36	m	5	ar-H
4.48	d (J=25.71Hz)	1	H-1
4.06	m	4	CH_2-5/7
2.66	m	2	CH_2-3
1.24	t (J=14.5Hz)	3	CH_3
	slight overlap		CH_3- 6/8
1.09	t (J=14.5Hz)	3	CH_3
1.01	t (J=14.0Hz)	3	CH_3-4

^{13}Cnmr

Chemical Shift(ppm)	Coupling Const.J_{PC}(Hz)	Assignment
203.19	4.35	C-2
130-127	complicated region	C-ar
62.48	35.23	O-CH_2
62.39	35.44	O-CH_2
58.44	132.65	C-1
36.22	2.50	C-3
15.74	5.92	O-C-CH_3 6/8
7.17	0	C-4



Structure 2.5

Analysis

3-(diethoxyphosphinyl)-3-bromocamphor

^{13}Cnmr (solvent $CDCl_3$)

Chemical Shift	Coupling Const. J_{PC}(Hz)	Assignment
210.43	0	2
64.46	7.94	11
63.76	6.71	13
57.36	148.22	3
55.430	0	4
47.50	15.55	7
28.64	0	6
25.58	5.33	5
24.34	0	8
20.45	0	9
16.39	5.95	12
16.17	6.40	14
10.41	0	10

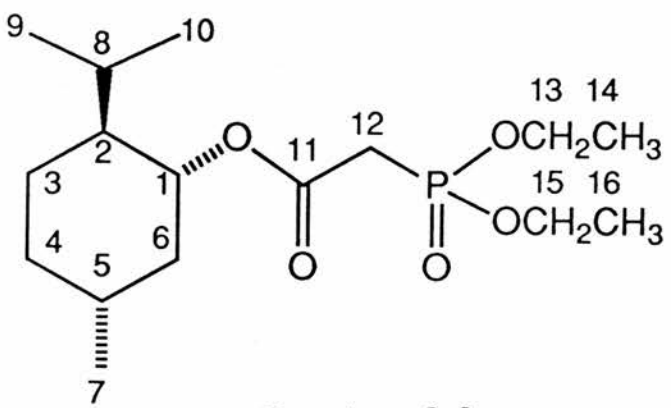
^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift	Multiplicity	Integral	Assignment
4.25	m	4	CH_2-11/13
2.55	d	1	CH-4
2.30	m	1	CH-5
2.00	m	1	CH-5
1.85	m	1	CH-6
1.60	m	1	CH-6
1.40	m(2 overlapping t)	6	CH_3-12/14
1.25	s	3	CH_3-10
1.05	s	3	CH_3-8
1.00	s	3	CH_3-9

Diethyl (-)-menthyloxycarbonylmethylenephosphonate

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
4.50-5.0	triplet split into doublets	1	H-1
3.95-4.4	m	4	CH_2-13/15
2.75-3.15	d(J_{PH}=21.7Hz)	2	CH_2-12
1.2-1.5	t	6	CH_3-14/16
0.4-1	three overlapping doublets	9	CH_3-9/10 and CH_3-7
1-2.3	m		all other remaining protons



Structure 2.6

3-bromocamphor-3-phosphonic acid monoethyl ester

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
10.70	s(br)	1	POH
4.25	m	2	CH_2-11
2.60	d	1	H-4
2.25	m	1	H-5
2.00	m	1	H-5
1.80	m	1	H-6
1.55	m	1	H-6
1.30	t	3	CH_3-12
1.20	s	3	CH_3-10
1.00	s	3	CH_3-8
0.94	s	3	CH_3-9

Analysis

^{13}Cnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Coupling Const.J_{PC}(Hz)	Dept	Assignment
209.91	0	quarternary	2
64.52	7.34	CH_2	11
60.32	2.23	quarternary	1
56.53	154.47	quarternary	3
55.38	0	CH/CH_3	4
47.48	15.57	quarternary	7
28.64	0	CH_2	6
25.30	5	CH_2	5
24.41	0	CH/CH_3	
20.39	0	CH/CH3	8,9
16.26	6.30	CH/CH_3	12
10.54	0	CH/CH_3	10

Camphor-3-phosphonic acid monoethyl ester

^{1}Hnmr (Solvent $CDCl_3$)

Chemical Shift	Multiplicity	Integral	Assignment
10.20	s	1	OH
4.19	m	2	CH_2-11
3.05	dm(J_{PH}=28.23Hz)	1	H-3
2.37	t	1	H-4
2.05	m	1	H-5
1.86	m	1	H-5
1.65	m	2	H-6 *exo/endo*
1.35	t	3	CH_3-12
1.00	s	3	CH_3
0.95	s	3	CH_3
0.85	s	3	CH_3

^{13}Cnmr (solvent $CDCl_3$)

Chemical Shift	Coupling Const.	Assignment
210.00	0	2
61.87	6.15	11
58.92	0	1
50.43	148.42	3
46.89	17.45	7
46.18	0	4
29.82	0	6
22.75	4.69	5
19.39	0	9
18.72	0	8
16.39	5.99	12
9.65	0	10

CHAPTER THREE

THE COMPLEXATION CHEMISTRY

OF

[(1R)-*ENDO*]-(+)-3-(DIETHOXYPHOSPHINYL)CAMPHOR

WITH

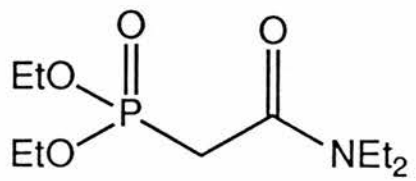
TITANIUM(IV) AND MOLYBDENUM(VI)

SPECIES

3.1 Introduction

The coordination chemistry of neutral donor β-ketophosphonate ligands $[(RO)_2P(O)CH_2C(O)R]$ has been investigated by Osipov for elements such as Ti(IV) and Sn(IV)[157] and some studies have been carried out by Lestas[158] on β-ketophosphine oxide complexes.

Much interest has developed recently into carbamylmethylene phosphonates because of their chelation properties[159-163].



diethyl (N,N-diethylcarbamyl)methylenephosphonate

Structure 3.1

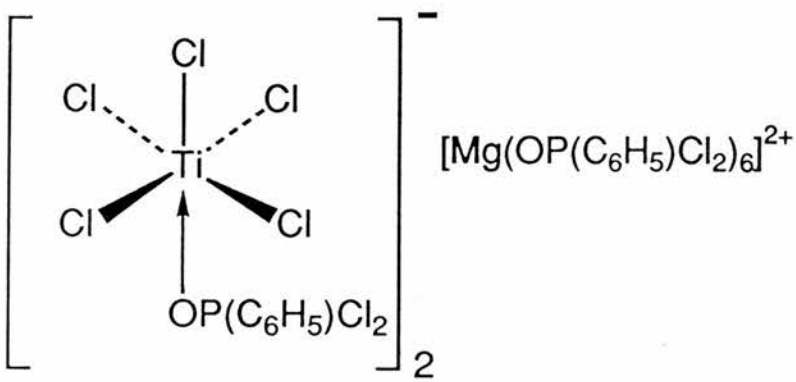
Siddall and co-workers[164,165,166] have studied the extraction chemistry of CMP ligands with lanthanides and actinides found in liquid acidic nuclear waste. Primarily on the basis of equilibrium distribution measurements, it has been concluded that trivalent lanthanide and actinide ions form tris-chelate complexes, $M(CMP)_3^{3+}$, in which the metal ion is bonded to the CMP ligands in a bidentate co-ordination mode through the carbonyl and phosphoryl atoms.

A number of CMP complexes with various lanthanide and actinide elements have been prepared and characterised by Paine[159-162].

Complexes of the deprotonated form of β-ketophosphonates $[(RO)_2P(O)CHC(O)R]^-$ with Cr(III), Co(II) and Zn(II) have been investigated by Cotton and Schunn[167]. The β-ketophosphonates are not as acidic as for example acetylacetone and so were deprotonated by sodium sand[167], sodium hydride[168] or sodium hydroxide[158].

Phosphoryl coordination compounds have found use in catalytic polymerisation processes. The complexes which were obtained by reacting $TiCl_4$, $VOCl_3$, $MoOCl_4$, $WOCl_4$, or $AlCl_3$ with beryllium, magnesium, calcium or strontium chlorides in the presence of $OPCl_3$ are able to polymerise ethylene or to copolymerise it with α-olefins when they are associated with $Al(i\text{-}C_4H_9)_3$[169]. When $PhP(O)Cl_2$, $TiCl_4$ and $MgCl_2$ were reacted the complex $(TiCl_5L)_2(MgL_6)$, $L=PhP(O)Cl_2$ was obtained[169]. This was used for low pressure ethylene-hexene copolymerisation by reacting ethylene and hexene with the complex in the presence of *iso*-Bu_3Al at 10 atm.

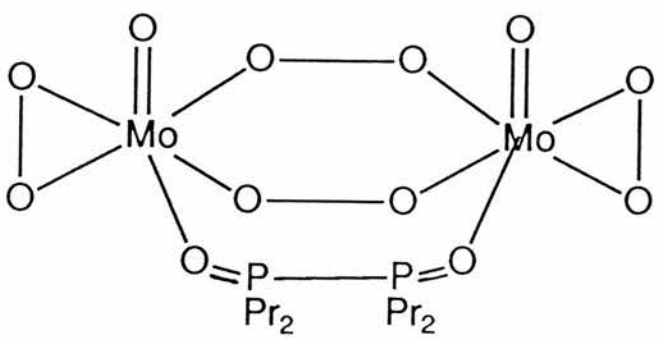
The structure of the catalyst has been determined crystallographically as:



Structure 3.2

Epoxidation

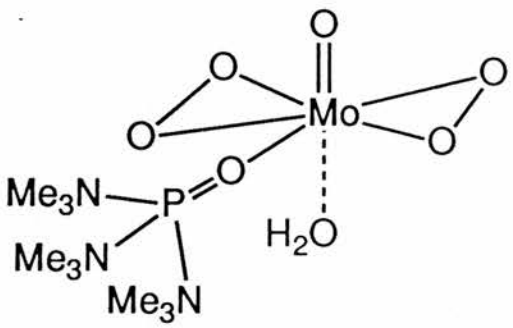
Several diperoxo complexes of molybdenum and tungsten are able to promote the epoxidation of alkenes. For example the use of a bis phosphine oxide can stabilise the species:



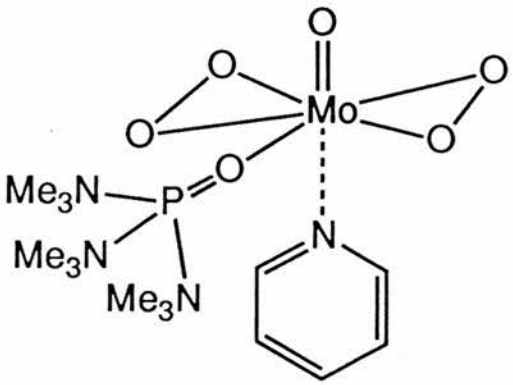
Structure 3.3

which is useful for either the stoichiometric or catalytic epoxidation of alkenes[170].

Complexes of Mo(VI)-oxodiperoxo compounds with hexamethyl phosphoric triamide as a neutral donor ligand have been widely investigated for the stoichiometric epoxidation of alkenes[171-173] (Structure 3.4). A similar compound is commercially available[174] (Structure 3.5) for various selective oxidations eg. for enolizable ketones[175].



Structure 3.4



Structure 3.5

To date no such epoxidants using chiral bidentate phosphoryl containing ligands have been tested.

Molybdenum complexes containing achiral bidentate phosphoryl ligands such as diphos dioxide $Ph_2P(O)CH_2CH_2P(O)Ph_2$ have been used successfully in homogeneous epoxidation catalysis as well as Mo(VI) complexed by polymer supported phosphine oxides[52].

Surprisingly little work has been carried out on β-ketophosphonate complexes, presumably due to the past difficulty of ligand preparation. Recently improved synthetic methods for β-ketophosphonate production has increased the potential for studies into their complexation chemistry.

It is for this reason coupled with the fact that some complexes of early transition metals show catalytic activity for epoxidation that the preparation, isolation and characterisation of complexes of Mo(VI) and Ti(IV) are reported in the Results and Discussion section of this thesis.

Nuclear Magnetic Resonance Spectroscopy in Phosphoryl Complexes

Proton NMR

Most investigations into the nmr of phosphoryl coordination compounds have utilised ^{1}Hnmr. In most cases however no special information is obtained other than the presence of a given ligand. For example the ^{1}Hnmr spectrum of $OP[N(CH_3)_2]_3$ is hardly influenced by coordination to metal ions such as Zn^{2+} [176].

^{31}P NMR

The application of ^{31}P nmr spectroscopy to phosphoryl complexes is of great interest because it gives direct information about the electronic structure of the phosphorus atom which is very close to the coordinating ion and it reflects changes induced by coordination. Results regarding ^{31}P chemical shifts of the ligand (δ_L), the complex (δ_C), and the coordination shift ($\Delta=\delta_C-\delta_L$) have been gathered by De Bolster and Groeneveld[177].

The change of the ^{31}P chemical shift upon coordination is almost invariably positive i.e. downfield. For example a rather large downfield coordination shift of +26.1 ppm is found for the ligand $OP(C_8H_{17})_3$ (δ_L=+41.0 ppm) in the complex $UO_2L_2(NO_3)_2$ (δ_C=+67.1 ppm)[178]. Coordination chemical shifts of as low as +0.7 ppm for the complex $\{OP[N(CH_3)_2]_3\}BF_3$[179], however are quite common. Negative coordination chemical shifts although rarer have been found in certain boron trifluoride complexes of phosphate ligands[180].

By considering the coordination shift of the same ligand with different metal ions there is no apparent trend.

If however the coordination shift of different ligands with respect to the same metal ion is considered, it is found for example that phosphine oxides show a far greater coordination shift than phosphonates. According to the magnitude of the coordination shift it is found that

$$OPR_3 > OP(OR)R_2 > OP(OR)_2 \sim OP(OR)_3$$

and

$$OPCl_3 > OP(NR_2)_3 > OP(OR)_3$$

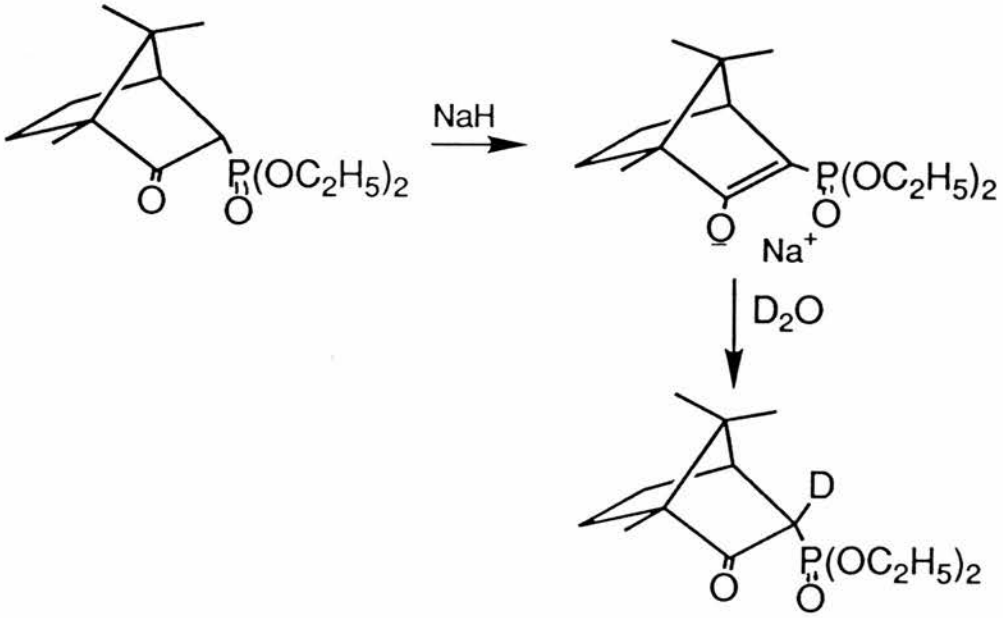
Results and Discussion

The coordination chemistry of various phosphoryl donor groups such as phosphine oxides[181] and carbamylmethylenephosphonates[163] with transition metals have been widely investigated. The ligand behaviour of [(1R)-*endo*]-(+)-3(diethoxyphosphinyl)camphor, however, was investigated with metals considered to be potential epoxidation catalysts. The mode of coordination, ease of characterisation, and overall stablity were factors influencing the choice of catalysts.

3.2 Phosphonoenolate Coordination Chemistry

3.2.1 (1R)-3-(diethoxyphosphinyl)-3-deuterocamphor

Although apparently similar to β-diketones, β-ketophosphonates are not so acidic[167] so that [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was deprotonated with sodium hydride. As deduced from its proton nmr spectrum the most acidic proton in the molecule is H-3. This acidity was confirmed when D_2O was added to the sodium salt and the doublet of doublets at 2.93 ppm which is observed in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was not observed in this case.



Equation 3.1

The triplet at 2.40 ppm due to H-4 in the undeuterated case becomes a doublet upon deuteration due to coupling to 5-H *exo* only.

3.2.2 bis[(1R)-3-(diethoxyphosphinyl)camphorato]dioxomolybdenum(VI)

Two mol. equivalents of the sodium salt of [(1R)-3-(diethoxyphosphinyl) camphor was reacted with one mol. equivalent of molybdenum dioxide dichloride which was dissolved in THF. The sodium chloride which formed was removed to give a green compound which rapidly became blue upon exposure to the atmosphere. The complex was an oil which could not be induced to crystallise by either the addition of petrol (b.p.40-60°C) or cooling to -20°C for several days at a time. From the infrared spectrum of the complex it is obvious that new strong bands occur at the frequencies 1542 cm^{-1}, 1363 cm^{-1} and 1155 cm^{-1}.

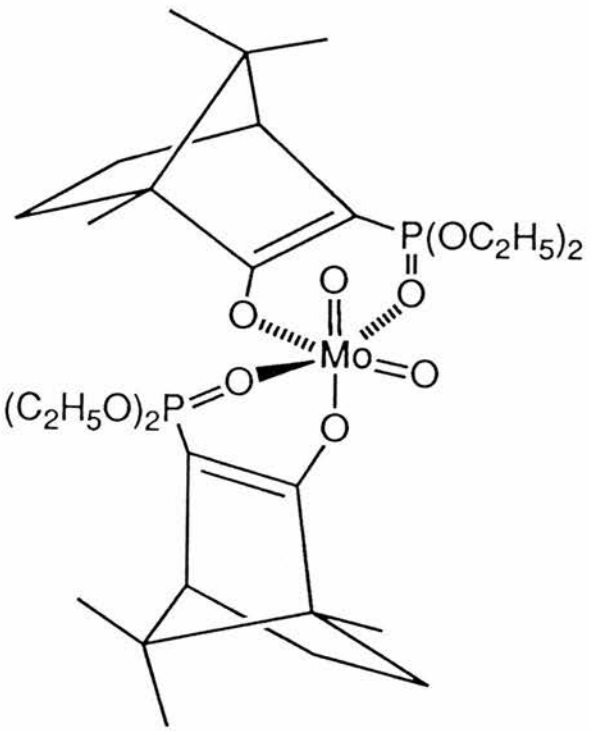
The 1555 cm^{-1} band may be assigned to the P=O stretching frequency which has dropped by 84 cm^{-1}. For comparison, simply coordinated phosphine oxide complexes of the type R_3POM show decreases in the P=O stretching frequencies of only about 50 cm^{-1} (for an average of 14 complexes[182] with the largest decrease of 70 cm^{-1}). This compares with a νP=O of 1160 cm^{-1} in the complex MoO_2Cl_2[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor where the ligand is neutral and suggests that the P=O bond is not markedly weakened in the anionic case when compared with the neutral coordinated phosphoryl ligand.

It can be concluded, though, that the greater decrease in the P=O stretching frequency in the phosphonoenolate complex suggests a further lowering of the P=O bond order over that expected for simple coordination of the P=O oxygen atom to the metal atom.

The two strong bands at 1542 cm^{-1} and 1363 cm^{-1} are remarkably similar to those found in metal acetylacetonate complexes where several (usually two) rather intense bands have been assigned to vibrations which are mixtures of CO stretching and CC stretching in the

planar six-membered chelate rings[183]. In Cotton and Shunn's investigation of complexes of dialkoxyphosphonylacetylmethanide ions[183], they found that in the complex $Zn[(EtO)_2P(O)CHC(O)CH_3]_2$ there were three new bands in the infrared spectrum at 1530, 1415 and 1170 cm^{-1}. They suggested that the 1170 cm^{-1} band was due to a coordinated phosphoryl group with the bands at 1530 and 1415 cm^{-1} being ascribed to mixtures of CO and CC stretchings.

The similarity of the 1600 - 1400 cm^{-1} region in the infrared spectrum of [(1R)-3-(diethoxyphosphinyl)camphorato]MoO_2 to that of $MoO_2(acac)_2$ where a chelate ring system has been reported as occurring in the solid state from X-ray crystal structure measurements, suggests a bidentate chelation in the camphorato complex also and that this information provides convincing evidence that the phosphoryl and carbonyl type oxygen atoms are involved in bonding with the molybdenyl unit as shown:



Structure 3.6

The appearance of strong absorptions at 945 cm^{-1} and 911 cm^{-1} is consistent with the existence of a *cis* dioxomolybdenum group[181] which can be assigned therefore to symmetrical and asymmetrical stretches respectively[184]. This can be compared with for instance $MoO_2(acac)_2$ where the corresponding absorptions occur at 935 cm^{-1} and 904 cm^{-1} respectively.

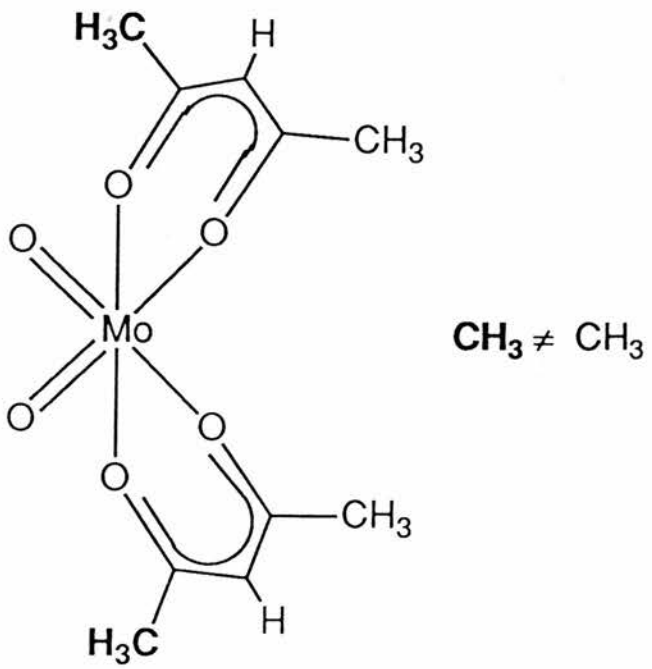
It is worth noting that the moisture sensitive nature of the camphorato complex is demonstrated by the appearance of strong free ligand bands in the infrared spectrum upon exposure to air for even a few minutes. It is likely that the camphorato ligand is not strongly bound to the metal and that its ease of reprotonation by the moisture in air may reflect this. After approximately 5 minutes exposure, the infrared spectrum bears a strong resemblance to the free 3-(diethoxyphosphinyl) camphor ligand spectrum, indicating that complete de-complexation has taken place.

The downfield chemical shift to +24.5 ppm in the ^{31}P nmr spectrum of the complex is consistent with the findings of Cotton and Schunn[167] where downfield shifts occur in anionic complexes with for example Zn^{2+} and Na^{+}, albeit of a much larger magnitude. Paine and co-workers[168] have investigated complexes of the anionic derivatives of carbamylmethylene phosphonates with mercury and they attribute the downfield shift observed to a possible electron delocalisation onto the phosphoryl oxygen atom upon deprotonation of the methylene group and the formation of a planar [P(O)CHC(O)] backbone. This is a possible explanation for what is occurring in the camphorato molybdenyl case.

The appearance of the proton nmr makes the assignment of proton resonances difficult because of significant broadening. The coupling constants cannot be measured and there is also overlapping between 0.50 and 1.50 ppm. Several features however are worthy of note; a complex multiplet at *ca.* 4.20 ppm can be assigned to the

methylene groups CH_2 12 and 14. Noticeably absent from the spectrum is the doublet of doublets normally present in the free neutral ligand at 2.93 ppm, which is consistent with the ligand being anionic in this case. The triplet which normally occurs in the free neutral ligand at 2.40 ppm for H-4 shows up in the spectrum of the anionic complex at 2.41 ppm with any fine structure broadened out. The other discernable resonances are for the three methyl groups of the camphor moiety at 0.86, 0.87 and 1.20 ppm.

In work carried out by Craven[185] the lability and stereochemistry of dioxobis(acetylacetonato)molybdenum was investigated. Spectroscopic and X-ray studies[185] reveal that the molybdenyl oxygens are *cis* as well as the acac ligands.



Structure 3.7

The variable temperature nmr spectra are indicative of considerable intramolecular lability in solution and the stereochemistry of the complex permits the explanation that where the acac ligands are *cis*, they consequently have two non-equivalent sets of methyl groups which may be capable of rapid configuration changes between the non-equivalent sites.

3.3 β-Ketophosphonate Coordination Chemistry

The deprotonation of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor results in the loss of chirality at C(3). If however stable complexes of the neutral form of the ligand can be prepared, the stereochemistry at C(3) is preserved so this type of complex should find greater application for asymmetric catalysis than with the anionic form of the ligand where the chiral centres are more distant.

The hard-soft/acid-base theory[161] predicts that the hard oxygen donor ligands of C=O and P=O present in β-ketophosphonates ought to form stable complexes with the so-called hard transition metals. For this reason complexes of the neutral ligand with the early transition metals titanium(IV) and molybdenum(VI) were prepared.

3.3.1 Tetrachloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} titanium(IV)

When 1 mol. equivalent of titanium(IV) tetrachloride was added to a solution of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor in toluene, the yellow powder which was formed which analysed for a complex with the stoichiometry 1:1, ligand to $TiCl_4$.

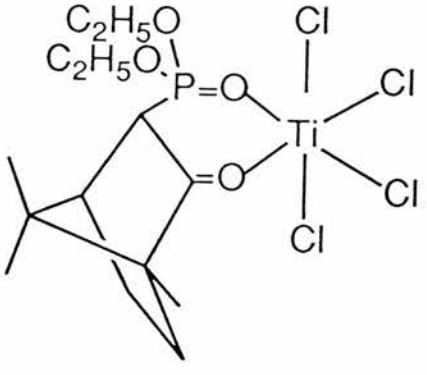
Cotton[182] and others[186] suggest that in phosphine oxide complexes of various transition metals, a downfrequency shift in the P=O stretching frequency indicates that coordination has occurred. Similarly in the case of phosphonoacetic acid triester complexes with titanium(IV), Osipov argues that the decrease in the phosphoryl and carbonyl stretching frequency is due to bidentate chelation to the metal, through the phosphoryl and carbonyl oxygen atoms.

The coordination shift in the carbonyl stretching frequency from 1742 cm^{-1} is consistent with ligation through the oxygen atom of the ketone moiety. This is consistent with the findings of Osipov[157] who observed a shift to lower frequencies in the carbonyl group of various ligands. for instance $[(i\text{-PrO})_2P(O)CH_2COOEt]TiCl_4$ has a shift of -74 cm^{-1} (av.) for the coordinated phosphoryl group. Osipov found that the heats of complex formation and the shifts in the C=O absorption band increase along the series.

$(i\text{-PrO})_2P(O)CH_2COCH_3 < (i\text{-PrO})_2P(O)COOEt < (i\text{-PrO})_2P(O)CH_2COPh$

In the light of this and information from Paine[161] who found carbonyl stretching frequency shifts of 46, 46 and 39 cm^{-1} for the (diethylcarbamoyl)methylthiophosphonate $(EtO)_2P(S)CH_2C(O)NEt_2$ which had been complexed with the other hard metal La, Nd and Er ions; the observed C=O shift for complexed [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor is large indeed. This may suggest that the carbonyl oxygen atom is more strongly bound to the metal. Related work on ethyl acetate-metal halide complexes[187], has indicated that there is a correlation between the shift in the carbonyl frequency and the Lewis acid strength of the acceptor molecule. It may be that the large shift difference between C=O in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor and the related titanium complexes studied by Osipov is due to the [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor being a better electron donor. The use of $\Delta\nu$ as an electron acceptor is only permissible if the acceptor molecules to be compared are under very similar conditions however.

The phosphoryl coordination frequency shift from 1251 cm^{-1} to 1120 cm^{-1} is in accordance with the phosphoryl coordination frequency shifts of -116 cm^{-1} (av.) for $[(i\text{-}PrO)_2P(O)CH_2C(O)CH_3]TiCl_4$ although again the magnitude of the shift may indicate a more strongly bound phosphoryl in the [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor ligand.



Structure 3.8

The decrease in the phosphoryl stretching frequency on complex formation has been discussed by Cotton[182] who considers that the decrease of $p\pi \rightarrow d\pi$ back bonding from O to P overcomes effects such as enhanced P-O σ-bonding and metal-oxygen π interaction, which would increase the bond order hence the phosphoryl stretching frequency. The main effect thus appears to be the polarisation of the P=O bond, and this must be related to the strength of the metal-oxygen bond.

The magnitude of the phosphoryl coordination frequency shift possibly reflects the better donor ability of the P=O in [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor, than in other β-ketophosphonate ligands with $TiCl_4$.

The proton nmr spectrum of tetrachloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}titanium(IV) displays a doublet of doublets corresponding to H-3 at the much more downfield position at 4.06 ppm compared to the free ligand H-3 resonance at 2.93 ppm, similarly the resonance for H-4 occurs downfield at 2.63 ppm compared with the free ligand H-4 resonance at 2.40 ppm. Such downfield shifts are common for the other resonances for the protons in the molecule, although the magnitude of the effect is much less pronounced.

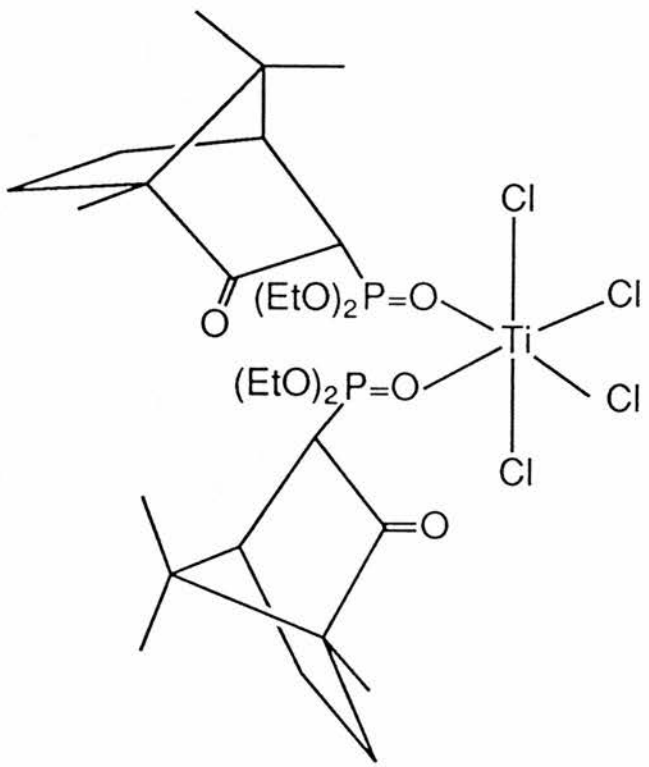
In the ^{31}P spectrum the small downfield shift to +23.9 ppm in the complex from +23.1 ppm in the free ligand is similar to carbamylmethylenephosphonate-lanthanide[186] complexes and other metal-phosphoryl ligand complexes.

3.3.2 Tetrachlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} titanium(IV)

When titanium tetrachloride was added to 2 molar equivalents of the ligand [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor dissolved in a 1:1 mixture of petrol and toluene, the solution became orange in colour

and over 18h became a much darker red. The solvents were evaporated to leave a reddish coloured glassy compound. Unlike the 1:1, titanium to ligand complex, this compound could not be induced to crystallise, it was also very soluble in organic solvents so that the small amount of free ligand still present could not easily be washed out. Nevertheless infrared spectroscopy proved useful for determining the coordination mode of the β-ketophosphonate.

The carbonyl stretching frequency was found to occur at 1742 cm^{-1} which is unchanged with respect to the free ligand stretch. The phosphoryl stretching frequency however had shifted to 1160 cm^{-1} from 1251 cm^{-1}. By a similar rationalisation to that of Osipov[157] it is proposed that the coordination to the titanium(IV) centre is through the phosphoryl oxygen only as shown:



Structure 3.9

In the proton nmr spectrum, the resonances are somewhat broad and due to the stated problems of purification the spectrum is rather more complex, the assignments therefore are tentative. The most striking feature about the spectrum of the bis complex when compared with that of the 1:1 complex is the complete disappearance of the doublet of doublets at 4.06 ppm, there is however a very broad featureless hump upfield at 3.62 ppm and it is likely that this is the resonance for H-3, although this represents a small downfield shift from 2.93 ppm in the free ligand and is similar to that found in the bis complex of $(EtO)_2P(S)CH_2C(O)NEt_2$ with Mo(VI) where the methylene protons occur at 3.31 ppm in the complex but at 2.92 ppm in the free ligand[161]. In general where the other resonances differ significantly from those in the 1:1 complex, they are shifted upfield. The ^{31}P nmr spectrum of tetrachlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}titanium(IV) displays a resonance at +23.22 ppm which is similar in trend to the ^{1}Hnmr where the chemical shifts in the bis complex occur at a more upfield position than the 1:1 complex but more downfield than in the free ligand.

3.3.3 Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

Due to the significance of molybdenum(VI) complexes in epoxidation catalysis[8], the complexation chemistry of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor with molybdenum(VI) species was investigated.

When [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor was added to 1 mol. equivalent of molybdenum dioxide dichloride dissolved in THF, the solution rapidly became greenish blue. Upon evaporation of the THF and the addition of diethyl ether a microcrystalline powder was

deposited. Microanalysis of the compound was consistent with the formation of a complex having a 1:1, ligand to metal stoichiometry. Infrared and nmr spectroscopy confirmed that the complex was dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI).

Infrared analysis of this complex shows that the carbonyl stretching frequency has shifted to 1697 cm^{-1}. This shift by -45 cm^{-1} is similar to that found in $[(i\text{-PrO})_2P(O)CH_2C(O)NEt_2]MoO_2Cl_2$ where $\Delta\nu C{=}O$ is -52 cm^{-1} and is also comparable to those shifts observed in carbamylmethylenephosphonate complexes with UO_2^{2+}[160], Th(IV)[161], and other lanthanides[162].

The phosphoryl stretching frequency occurs at 1171 cm^{-1} and 1152 cm^{-1}. This type of splitting occurs in many carbamylmethylene phosphonate[163] and phosphine oxide complexes[182]. Osipov[157] has noted that in the complexes of related ligands, the band for the P=O group is a doublet, but that since two bands are present both in the spectra of the crystalline substances and in the spectra of the dissolved compounds, the splitting cannot be due to the effect of the crystal field or the dissociation of the complexes in solution. In compounds of the type $MX_4.2L$, the presence of two bands is sometimes explained by the interaction of two groups in the *cis* position[187]. However, such *cis* splitting cannot occur in compounds of 1:1 composition, in which different donor groups are in the *cis* position. In many cases[161,166,190] split $\nu P{=}O$ and $\nu C{=}O$ bands have been observed for several metal-CMP complexes, however, a full understanding of this splitting has not been realized.

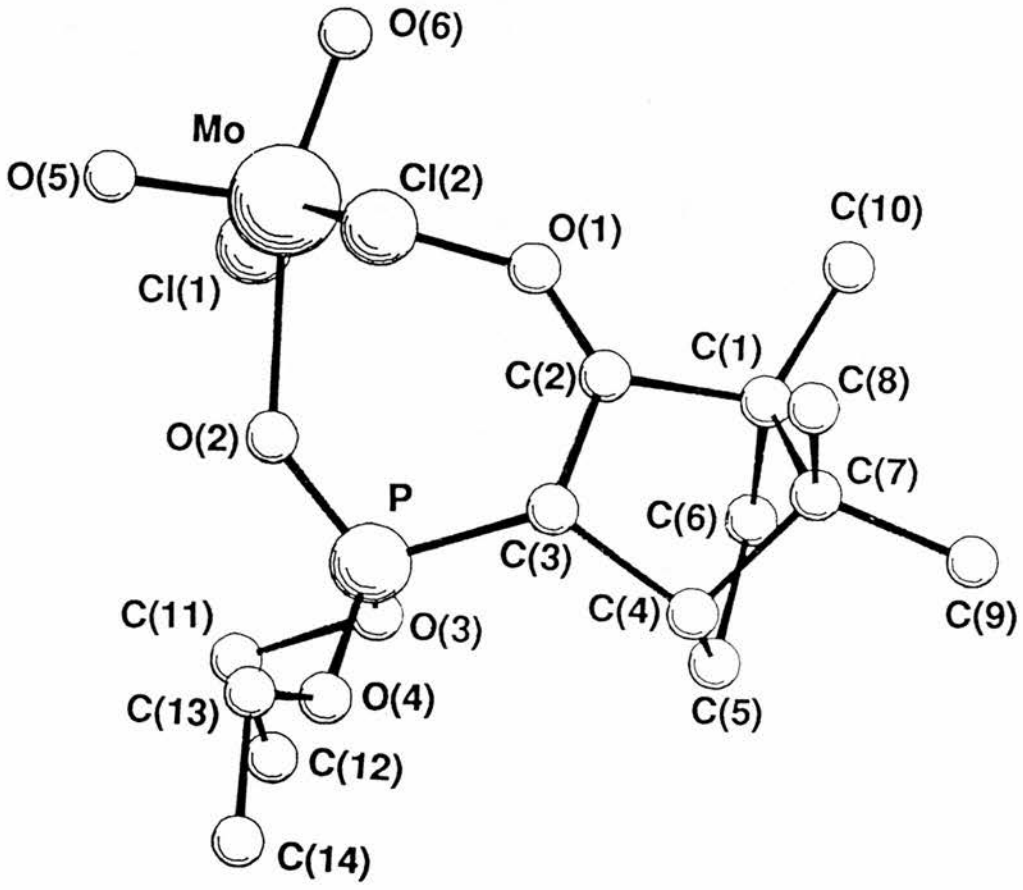
3.3.4 X-Ray Crystallographic Analysis of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI)

The main features of the solid state structure of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) are shown in Structure 3.10 and bond lengths and angles in Tables A3 and A4 in the Appendix. As can be seen from the structure the arrangement of the donor atoms about the central molybdenum(VI) is typical of oxomolybdenum(VI) complexes having a six coordinate distorted octahedral geometry[181]. Both the terminal oxygen atoms O(5) and O(6) and the ligand oxygen atoms O(1) and O(2) are *cis* to one another while the halogen ligands Cl(1) and Cl(2) are *trans* to each other. Previous workers have shown that in mixed ligand complexes of Mo(VI) the π-bonding is concentrated in bonds to terminal oxygen atoms at the expense of bonds to other atoms[163,191]. Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) is no exception to this observation which is shown up most clearly in the significant lengthening of bonds *trans* to the terminal oxygen atoms. The phosphoryl oxygen atom which is *trans* to the O(6) terminal oxygen atom, makes a Mo-O(2) bond distance of 2.183(7) Å which is comparable with 2.169(1) Å for the monodentate Ph_3PO ligand[191] in the complex $MoO_2Cl_2[Ph_3PO]_2$, and 2.220(2) Å in the related complex $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$[163].

It should be noted that in the case of the phosphine oxide complex, the two phosphoryl oxygen-molybdenum bond lengths are not identical, and that the longer of the bonds is the one which is *trans* to the shorter molybdenum - terminal oxygen bond (Mo-O(2)).

Structure 3.10

X-Ray Crystal Structure of Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI)



The molybdenum - terminal oxygen bond lengths of the [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor complex are essentially identical and the bond lengths of around 1.655 Å indicate a double bond between the molybdenum and these oxygen atoms[181,192]. In the complex $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$, Paine found that the terminal Mo-O distance of 1.677(2) Å was *trans* to the longer Mo-O (carbonyl oxygen) distance and the long terminal Mo=O distance of 1.687(2) Å was *trans* to the shorter Mo-O (phosphoryl oxygen). In the [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor complex, the carbonyl oxygen atom makes a Mo-O(1) bond distance of 2.402(7) Å which is significantly longer than the phosphoryl oxygen -molybdenum bond length of 2.183(7) Å and can be compared with the Mo-O(C) bond distance 2.246(2) Å in the related bidentate complex[163] $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ which is also consistent with weaker binding of the carbonyl oxygen than that of the harder phosphoryl oxygen. In the uranyl complex $UO_2(NO_3)_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ where the terminal oxygen atoms are *trans* to each other and *cis* to the carbonyl and phosphoryl oxygen atoms, it was found that the U-O(P) distance 2.420(4) Å, was similar to the U-O(C) distance, 2.406(5) Å. Clearly then for uranyl complexes care must be taken in assuming relative base strengths of ligand coordination sites based solely on coordination bond distances because P=O is generally considered to be a stronger Lewis base. The Mo-Cl bond lengths are the same and at 2.343(5) Å for Mo-Cl and 2.358(5) Å are comparable with the corresponding distances in the phenanthrene *ortho* quinone[193] complex 2.343(3) and 2.370(3) Å, and 2.397(1), 2.388(1) Å in the triphenylphosphine oxide complex.

The P=O(2) bond distance, 1.472(7) Å is only slightly longer than that expected for an uncoordinated P=O *ca.* 1.46 Å, but is similar to that for $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$, 1.487(2) Å and $UO_2(NO_3)_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ where the P=O bond length is 1.485(5) Å as well as for the monodentate phosphine oxide complex. $MoO_2Cl_2[Ph_3PO]_2$, 1.492(1) Å. The corresponding P=O distances for $[Cl_3PO]_2MoO_2Cl_2$[194] are 1.457(4) and 1.437(4) Å.

The carbonyl bond distance C(2)-O(1) 1.202(10) Å is much shorter than those found in $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$, 1.262(3) Å, $UO_2(NO_3)[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ 1.260(8) Å, which suggests that if the bond is perturbed less, then it will be much more weakly bound to the metal.

The expansion from the ideal angle for octahedral coordination of 90° for O(5)-Mo-O(6) which would exist in an ideal octahedral structure, to 102.8(5)° is typical when compared to those observed in the triphenylphosphine oxide complex 102.2(7)° and in $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ 102.8(1)° for the *cis* molybdenyl group. This expansion to *ca.* 103° means that the O(1)-Mo-O(2) angle of the coordinated phosphoryl-camphor group is compressed to 78.6(3)°, giving a very distorted octahedron. This bite angle for the ligand is similar to that found in $MoO_2Cl_2[(i\text{-}PrO)_2P(O)CH_2C(O)NEt_2]$ 78.9(1)° and even that found in $MoO_2Cl_2[Ph_3PO]_2$ (77.81(5)°) where the donor phosphoryl oxygen atoms are not constrained in a bidentate ligand.

The Cl-Mo-Cl bond angle is 158.0(1)° not 180° as expected for mutually *trans* Cl atoms, however, it is comparable to the related angles in $MoO_2Cl_2[Ph_3PO]_2$ of 162.2(1)° and 157.7(5)° in MoO_2Cl_2(*o*-phen)[195]. This represents quite a considerable expansion from the reported[196] Cl-Mo-Cl bond angle of 113.0° in MoO_2Cl_2 itself.

In conclusion therefore:

(i) The complex has a six-coordinate distorted octahedral mode of coordination.

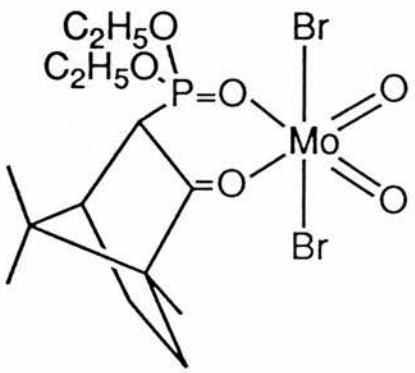
(ii) There are two short bonds to the *cis* terminal oxygen atoms with the molybdenum at the centre of the distorted octahedron being significantly displaced towards these terminal oxygen atoms.

(iii) There is significant lengthening of the bonds *trans* to terminal oxygen atoms.

(iv) The weaker π-bonding donor atoms such as phosphoryl in a mixed-ligand complex are *trans* to the terminal oxygen atoms, the strongest π-bonding donor atoms e.g. chloro will be *cis* to the terminal oxygen atoms where according to Butcher and others[181] they will not be competing with them for the available d orbitals.

3.3.5 Dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxo molybdenum(VI)

As an analogue of the dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI) complex, the complex dibromo{[(1R)-*endo*]-(+)-3(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) was prepared by dissolving molybdenum dioxide dibromide in THF by means of a Soxhlet extractor because of its lower solubility than the dichloride. To the solution was added 1 mol. equivalent of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor. The resulting complex dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) was precipitated with diethyl ether and larger (*ca*. 0.5 mm in length) cuboid crystals were grown from THF.



Structure 3.11

Microanalysis has shown that the stoichiometry is 1:1 ligand to metal, the same as in the case of the dichloro molybdenyl complex.

The coordination frequency shift in the infrared spectrum of the carbonyl group from 1742 cm^{-1} to 1698 cm^{-1} is comparable with the shift to 1697 cm^{-1} in the dichloro analogue.

In the case of the phosphoryl stretching frequency also the shift from 1251 cm^{-1} to 1159 cm^{-1} (av.) represents an almost identical coordination frequency shift compared with the dichloro complex.

The molybdenum *cis*-dioxo stretches, at 960 cm^{-1} and 919 cm^{-1}, are essentially the same as those found in dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI). It can be deduced therefore that the effect of the different halogen atoms upon the molybdenum oxygen stretching frequencies in the β-ketophosphonate complexes is minimal. In the case of $MoO_2Cl_2.2dmso$[192], the molybdenyl stretches occur at 921 (ν sym) and 892 cm^{-1} (ν asym). In the dibromo analogue, bands with the same assignment occur at 922 cm^{-1} and 890 cm^{-1}. This small effect in changing the halogens *cis* to the oxygen atoms can also be observed in the THF complexes where νsym Mo=O for $MoO_2Cl_2.2THF$ occurs at 958 cm^{-1} and ν asym is at 920 cm^{-1}. Those bands with the same assignment in $MoO_2Br_2.2THF$ occur at 958 cm^{-1} and 917 cm^{-1}.

The band at 260 cm^{-1} can be assigned to ν asym Mo-Br particularly when compared to MoO_2Br_2.phen. with ν asym Mo-Br occurring at 257 cm^{-1}. The out-of-plane mode δ $Mo(O_{terminal})_2$ in MoO_2Br_2.phen and MoO_2Br_2 was expected to have an absorption at *ca.* 257 cm^{-1} although this is unresolved in the spectrum. It is likely that this is the case also for dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI).

The similarity in the infrared spectra of dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) and dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) extends from 4000 cm^{-1} to 346 cm^{-1} whereupon, the band normally expected for νMo-Cl at ~340 cm^{-1} is completely absent from the dibromo analogue spectrum. The only significant band occurring in the region 450-200 cm^{-1} of the dibromo compound is one at 260 cm^{-1} which

is in common with the dichloro complex at 262 cm^{-1} and in the dichlorobis complex at 273 cm^{-1}. Since this band has been assigned in the complex $MoO_2Cl_2[Ph_3PO]_2$ to a δ $Mo(O(t))_2$[181] it can only be concluded that the absence of the Mo-Br stretch is due to either the Mo-Br stretch being coincident with δ $Mo(O(t))_2$ or that the stretching frequency is less than 200 cm^{-1} in which case the band will not have been recorded. In the infrared spectrum of $MoO_2Br_2[Ph_3PO]_2$ which was recorded between 4000 cm^{-1} and 140 cm^{-1}, Butcher[181] assigns a νMo-Br band at 180 cm^{-1}.

The proton nmr of the complex displays a doublet of doublets (J_{HP}=30Hz) at 3.86 ppm which can be assigned to H-3 and can be compared with 2.93 ppm in the uncomplexed ligand. This compares well with similar observations for the dichloro analogue (3.85 ppm) and is less than in the case of tetrachloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} titanium(IV), where the H-3 is shifted further downfield (4.06 ppm).

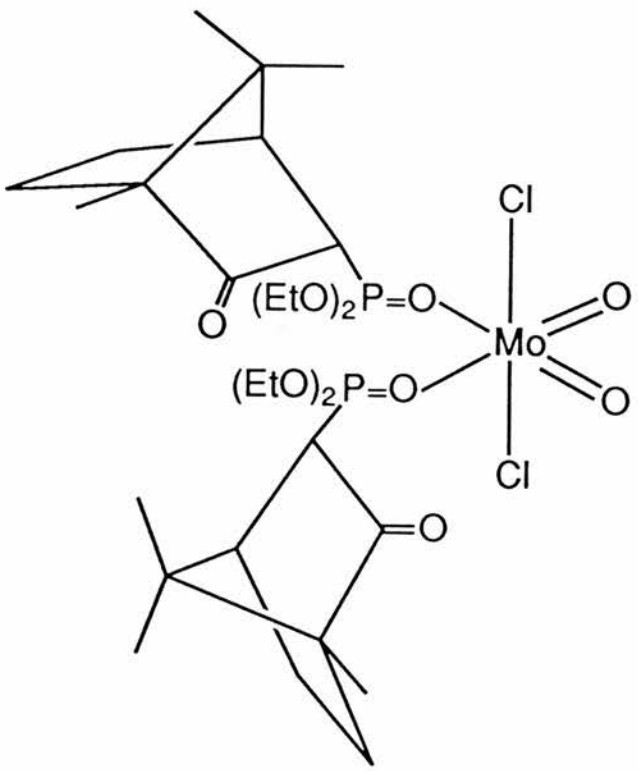
3.3.6 Dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

With the carbonyl O(1)-Mo bond length of 2.402(7) Å and the phosphoryl O(2)-Mo bond length of 2.183(7) Å in the complex dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI), it was thought likely that if two moles of the ligand were reacted with MoO_2Cl_2 then the coordination would be through the phosphoryl only.

Two mol. equivalents of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor, therefore were added to a solution of MoO_2Cl_2 in THF. A dark blue oil was left behind after the solvent was removed. When a THF/petroleum(b.p.40-60°) mixture was added to dissolve the oil and then cooled to -25°C, extremely thin very pale blue needles of dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxo-molybdenum(VI) were formed.

Partial elemental analysis of the complex was consistent with the formation of a 1:2 metal to ligand complex. The infrared spectrum displays a strong absorption at 1748 cm^{-1} and a split band at 1187, 1173 and 1205 cm^{-1} which can be assigned to $\nu C{=}O$ and the split band to $\nu P{=}O$ respectively. The small shift found in the P=S stretching frequency by Paine and co-workers[161] in the related thiophosphonate complex $MoO_2Cl_2[(EtO)_2P(S)CH_2C(O)NEt_2]_2$ led them to conclude that there was no coordination of the sulphur atom and that the low frequency coordination shift of $\nu C{=}O$ by 47-64 cm^{-1}, indicated the coordination of the carbonyl oxygens only. This they confirmed by X-ray crystallographic analysis.

By a similar rationalisation it can be concluded that for the bis(diethoxyphosphinyl)camphor complex, the phosphoryl oxygen atoms have coordinated to the molybdenum but that the small $\Delta\nu C{=}O$ of +5 cm^{-1} indicates no significant interaction between the carbonyl oxygen atom and the molybdenyl unit.



Structure 3.12

Surprisingly the coordination frequency shift for the P=O in the 3-(diethoxyphosphinyl)camphor molybdenum 1:1 complex has a much greater value which is unusual when compared with $TiCl_4[(i\text{-}PrO)_2P(O)CH_2COCH_3]$ where $\Delta\nu P{=}O$ is -127, -103 and $TiCl_4[(i\text{-}PrO)_2P(O)CH_2COCH_3]_2$ where $\Delta\nu P{=}O$ is -103, -158. A similar trend to the latter is found in other ligands with both titanium and silicon[157].

The dioxomolybdenum terminal symmetric and asymmetric stretches are assigned at 910 and 943 cm^{-1} and can be compared with 900 and 966 cm^{-1} in $MoO_2Cl_2[(RO)_2P(S)CH_2C(O)NEt_2]_2$ where R=Et and 909, 950 cm^{-1} where R=Bu.

Comparison with the related $MoO_2Cl_2[(EtO)_2P(S)CH_2C(O)NEt_2]_2$ compound in which binding of the organic ligand is unidentate through the carbonyl oxygen, occurs presumably because the Class A Mo(VI) prefers binding to the hard oxygen rather than the soft sulphur centre. The preference for binding to the phosphoryl rather than the carbonyl oxygen in the bis 3-(diethoxyphosphinyl)camphor case suggests that the phosphoryl oxygen is the harder centre.

3.3.7 N.M.R. Spectroscopy of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) and dichloro bis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

The ^{1}Hnmr spectra are complex, however the most significant shift to higher frequency compared with the ligand is at H-3 and it is greater in the bidentate complexes (~ 1 ppm) than in the bis complex (~ 0.5 ppm) where evidence from i.r. spectroscopy indicates binding solely through P=O. Differences in multiplicities of certain resonances compared with those of the free ligand may be caused by minor changes in bond lengths

and angles resulting from complexation. One of the most striking features is the non-equivalence of the CH_3 and CH_2 resonances of the ethoxy groups shown up clearly in the spectrum of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI).

3.4 Experimental

3.4.1 (1R)-3-(diethoxyphosphinyl)-3-deuterocamphor

To [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (0.1g, 0.35 mmol) dissolved in diethyl ether was added sodium hydride (4 molar excess) from which the mineral oil had been removed with diethyl ether. After hydrogen gas evolution had ceased the stoppered tube was centrifuged and the supernatant liquid was injected into another tube and the ether removed under reduced pressure. A sample of the gummy residue of [(1R)-3-(diethoxyphosphinyl)camphorato]sodium was removed for nmr and i.r. analysis. Deuterium oxide (0.5 ml) was added to the sodium salt and the organic components extracted into deuterochloroform (1 ml). The deuterochloroform layer was transferred quantitatively to a 5 mm nmr tube for proton and ^{31}P nmr analysis.

^{31}Pnmr +22.93 ppm.

3.4.2 Bis{(1R)-3-(diethoxyphosphinyl)camphorato}dioxomolybdenum(VI)

To a stirred suspension of sodium hydride (0.2g, 8.64 mmol) in diethyl ether (15 ml) which had previously been washed with diethyl ether (3 x 15 ml) and filtered, was added [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1.25g, 4.32 mmol) dissolved in diethyl ether (20 ml). After 2 hours when hydrogen evolution was complete, the sodium salt solution was filtered by means of a *canula* into a solution of molybdenum dioxide dichloride (0.43g, 2.16 mmol) in THF (20 ml). The resulting solution became dark green in colour. Evaporation

of the solvent under reduced pressure left a dark green oil to which was added petroleum (b.p. 40-60°) to precipitate the sodium chloride. The petroleum was removed under reduced pressure and diethyl ether was added to dissolve the complex which was filtered by means of a *canula* into another flask. Removal of the diethyl ether left a green oil, bis{(1R)-3-(diethoxyphosphinyl)camphorato}dioxomolybdenum(VI).

^{31}P +24.0

Infrared νC O 1542 cm^{-1} νP=O 1363, 1145 cm^{-1}

νP-O-C 1040 cm^{-1} νMo=O 911,945 cm^{-1}

3.4.3 Tetrachloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}titanium(IV)

To a solution of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1.26g, 4.38 mmol) in toluene (30 ml) was quickly added titanium tetrachloride (0.49 cm^3, 4.38 mmol). The resulting red coloured solution deposited a yellow powder upon cooling. The suspension was filtered and the remaining solid was washed with cold toluene (5 cm^3) and dried for 24 hours *in vacuo*. M.p. 98-101°C. Yield 0.84g, 40.2%. Found C 35.5, H 5.2%; $C_{14}H_{25}Cl_4O_2PTi$ requires C 35.3, H 5.3%.

$^{31}P_{nmr}$ +23.9 ppm

Infrared νTi-Cl 360 cm^{-1} s.br

νP=O 1120 cm^{-1} s, 1096 cm^{-1} s

νC=O 1675 cm^{-1} s

3.4.4 Tetrachlorobis{[(1R)-*endo*-]-(+)-3-(diethoxyphosphinyl) camphor}titanium(IV)

To [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1.93g, 6.7 mmol) dissolved in toluene (10 ml) was added titanium tetrachloride (0.37 ml,

3.4 mmol) with stirring. The solution which became red in colour was cooled to -30°C. When no solid appeared, petroleum ether was added. The solution could still not be induced to crystallise. Finally the toluene was removed under reduced pressure to leave tetrachlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}titanium(IV) as a gummy residue.

Due to the high solubility of the complex in a range of organic solvents, free β-ketophosphonate ligand could not be washed out of the complex effectively so that the proton nmr spectra were rather complicated.

^{31}Pnmr +23.33 ppm

Infrared 1742 cm^{-1} νC=O 1160 cm^{-1} νP=O

3.4.5 Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

MoO_2Cl_2 (1.5g, 7.54 mmol) was dissolved in dry THF (30 ml). [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (2.17g, 7.54 mmol) was added with stirring. One hour later, the THF was removed to leave an oily residue. Treatment with dry diethyl ether (15 ml) gave a solid which was washed with ether (2 x 5 ml portions) and was found to have m.p. 176-7°C. Yield 2.67g, 73%. Found C 34.6, H 5.2%; $C_{14}H_{24}Cl_2MoO_6P$ requires C 34.5, H 5.2%.

^{31}P nmr +24.3 ppm

Infrared

νMo-Cl	346 cm^{-1} s, 304 cm^{-1} w	νP=O	1171 cm^{-1} s, 1152 cm^{-1} s
νMo=O	967 cm^{-1} s, 923 cm^{-1} s	νC=O	1697 cm^{-1} s

3.4.6 Dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

Molybdenum dioxide dibromide (1.06g, 13.7 mmol) was dissolved in dry THF (70 ml) by means of a Soxhlet Extractor. The solution was cooled to room temperature whereupon [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (1.07g, 3.7 mmol) was added and stirred for 60 mins. The solvents were then evaporated and the additon of diethyl ether (10 ml) deposited dibromo{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) as a fine solid m.p. 176-177°C. 0.74g, 34%. Further material was obtained by subsequent evaporation and crystallisation of the mother liquors. Found C 35.5, H 5.2%. $C_{14}H_{25}Br_2O_6PMo$ requires C 35.3, H 5.3%.

^{31}P nmr +23.27 ppm

Infrared

νC=O	1698 cm^{-1}	νMo=O	960 cm^{-1}, 919 cm^{-1}
νP=O	1159 cm^{-1}	$\delta Mo(Ot)_2$	260 cm^{-1}

3.4.7 Dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

MoO_2Cl_2 (1.38g, 6.94 mmol) was dissolved in dry THF (20 cm^3) and [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (4.00g, 13.88 mmol) was added with stirring. The solution gradually became greenish blue. Two hours later the THF was removed to leave a dark blue semi-solid and petroleum (15 cm^3)/THF(4 cm^3) was added to dissolve the product. The flask was placed in a freezer at -25°C for two hours whereupon the product formed as fine pale blue needles. These were filtered cold, washed twice with 5 ml portions of petroleum and dried *in vacuo*. M.p. 103-4°C.

Yield 4.93g, 91.6%. Found C 43.2, H 6.4%; $C_{28}H_{50}Cl_2MoO_{10}P_2$ requires C 43.4, H 6.4%.

^{31}P nmr +24.5 ppm

Infrared

νMo-Cl 336 cm^{-1} s νP=O 1205 cm^{-1} s, 1187 cm^{-1} s, 1173 cm^{-1} s

νMo=O 943 cm^{-1} s, 910 cm^{-1} s νC=O 1748 cm^{-1}

$\delta Mo(O(t))_2$ 273 cm^{-1}

3.5

Tables of NMR spectra

3.5.1 [(1R)-3-(diethoxyphosphinyl)camphorato]sodium

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
3.80	m	4	CH_2-11/13
2.20	m	1	H-4
1.81	m	1	all other protons
1.35-1.00	m	8	not possible to
0.83	s	3	distinguish them
0.77	s	3	CH_3-8/9/10
0.74	s	3	

3.5.2 (1R)-3-(diethoxyphosphinyl)-3-deuterocamphor

^{1}Hnmr (solvent $CDCl_3$)

Chemical Shift(ppm)	Multiplicity	Integral	Assignment
4.16	m	4	CH_2-11/13
2.37	d	1	H-4
2.17	m	1	H-5 *exo*
1.80	m	1	H-5 *endo*
1.64	m	2	CH_2-6
1.33	two overlapping t	6	CH_3-12/14
0.99	s	3	CH_3-9
0.93	s	3	CH_3-10
0.77	s	3	CH_3-8

3.5.3 Bis{[(1R)-3-(diethoxyphosphinyl)camphorato}dioxo molybdenum(VI)

^{1}Hnmr (solvent toluene d8) all signals are broadened

Chemical Shift(ppm)	Multiplicity	Assignment
4.20	m	CH_2-11/13
2.41	m	H-4
1.90	m	CH_5-5/6
1.29	two overlapping t	CH_3-12/14
1.20	s	CH_3-8/9/10
0.87	s	
0.86	s	

3,5.4 ^{1}Hnmr spectroscopic data for complexes with $TiCl_4$ and MoO_2Cl_2
L=[(1R)-endo]-(+)-3-(diethoxyphosphinyl)camphor. Sovent $CDCl_3$

	$TiCl_4L$	$TiCl_4L_2$[a]	MoO_2Cl_2L	MoO_2Br_2L	$MoO_2Cl_2L_2$
CH_3-8	0.98(s)	0.87(s)	0.95(s)	0.92(s)	0.91(s)
CH_3-10	1.09(s)	0.90(s)	1.08(s)	1.08(s)	0.99(s)
CH_3-9	1.11(s)	0.98(s)	1.12(s)	1.10(s)	1.05(s)
CH_3-12[b]	1.46(t)		1.40(t)		1.38(t)
CH_3-14[b]	1.49(t)	1.48(m)	1.48(t)	1.40[c]	1.40(t)
H-6 endo	1.60[a](m)	1.54(m)	1.58(m)		1.58(m)
H-6 exo	2.05[a](m)	1.70(m)		1.88(m)	1.78(m)
H-5 exo	1.98(m)	1.91(m)	1.92(m)	2.03(m)	1.91(m)
H-5 endo	2.12[a](m)	2.04(m)	2.09(m)	2.45(m)	2.06(m)
H-4	2.63(t)	2.66(m)	2.45(t)	2.90(m)	2.50(m)
H-3	4.06(dm)	3.62(m)[d]	3.85(dd)	3.86(dd)	3.40br(dd)
J_{PH}	34.30Hz		30.00Hz	30.00Hz	30.01Hz
CH_2-11/13	4.54(m)	4.48(m)	4.40	4.43	4.35(m)

b assignments are arbitrary
a assignments are tentative
c two overlapping t
d not possible to measure due to broadening

CHAPTER FOUR

THE USE OF

[(1R)-*ENDO*]-(+)-3-(DIETHOXYPHOSPHINYL)CAMPHOR

DERIVED COMPLEXES OF MOLYBDENUM

AS CATALYSTS FOR THE EPOXIDATION

OF ALKENES

4.1 Introduction

The widespread importance of epoxidation catalysis has meant an ever increasing interest in the development of novel catalysts with the aim of improving their reactivity and selectivity. For this reason therefore a new type of Mo(VI) epoxidation catalyst has been developed using the β-ketophosphonate [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor as the ligand. The reactivity of the catalyst with various alkenes and its unique selectivity to a polymeric system are described in the following sections.

4.2 Epoxidation Catalysis

The complexes dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI) and dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) were screened for their activity as epoxidation catalysts with a range of alkenes. On some of the more small scale preparations of epoxides, GC-MS analysis of the product using the computer library back-up service proved to be sufficient. On larger scale preparations, the spectra of the epoxides were compared with the literature spectra or by comparison either by GC or nmr with epoxides prepared by other means.

4.2.1 Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) catalysed epoxidation

Typically in the larger scale preparations, the catalyst (1 mol% to alkene) was added to a solution of alkene, tert-butyl hydroperoxide (1.5 mol equivalent of a 3M solution in 2,2,4-trimethylpentane) and dichloromethane at 25°C.

Epoxidations

The alkene 1-methyl-1-cyclohexene could be stirred with tert-butyl hydroperoxide solution for several hours without any reaction; when 1 mol% of the catalyst was added, the reaction mixture became hot enough to self-reflux. For many of the less substituted alkenes, this effect was much less pronounced, and in the case of hex-1-ene, the reaction mixture had to be heated in order to obtain significant conversion.

Table 4.1 displays the yields of several epoxides catalysed by MoO_2Cl_2L.

Table 4.1

Epoxidation of various alkenes catalysed by MoO_2Cl_2L[a]

alkene	t/h	T/°C	yield of epoxide [b]/%
1-hexene[c]	24	35	70.6
1-dodecene	24	35	45[d]
styrene[e]	24	20	0
cyclohexene	24	20	77.8
1-methylcyclohexene	0.7	0	89
	24	20	100(52)[d,f]
R(+)-limonene	28	20	65[g]
norbornene	24	20	20[c]

a Molar ratio: alkene(100): catalyst(1): t-BuOOH(3mol l^{-1} in 2,2,4-trimethylpentane)(150): CH_2Cl_2(1466)
L=[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

b glc yield unless otherwise indicated

c 1.08 molar ratio of catalyst

d isolated yield, after work up

e 930 molar ratio CH_2Cl_2

f 378 molar ratio of CH_2Cl_2

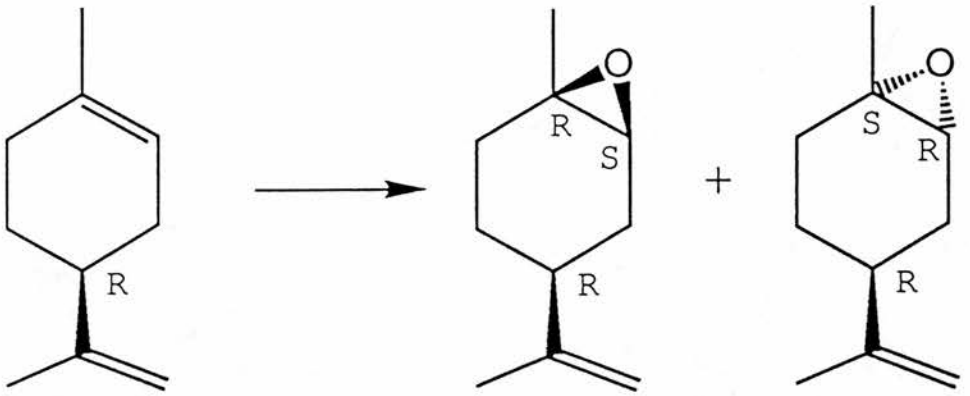
g As 1:1 mixture of diastereomers of 1-methyl-4-(1-methylethenyl)-7-oxabicyclo[4.1.0]heptane

From the table it can be seen that dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) has catalysed the epoxidation of a wide range of alkenes giving good yields of product with apparently no side reaction, although it is not active for styrene epoxidation. This is consistent with the expectation from other studies on epoxidations[100] where it has been found that electron-withdrawing

groups attached to the alkene decrease the rate of epoxidation while electron-donating groups increase the rate. This explains why the epoxidation of 1-methyl-1-cyclohexene is better than cyclohexene which does not have the methyl group available for electron donation to the alkene. The relative increase in the reactivities of the double bonds by increasing alkyl substitution is reflected in the selective monoepoxidation of nonconjugated dienes as shown for example in Equation 1.15.

It can also be seen from the table that in the monoepoxidation of limonene even with 1½ mol-equivalents of t-BuOOH only the endocyclic double bond is epoxidised. In the case of styrene the lack of reactivity is notable; it is likely that the epoxidation is seriously impeded by the electron-withdrawing phenyl ring as a substituent. Although a rather extreme example it is consistent with the observation that allyl chloride is about one tenth as reactive as propene toward t-BuOOH/Mo(VI)[19]. Also Sheng and Zajacek found acrylic esters and acrylonitrile cannot be epoxidised with such a system[197].

The GC results of the epoxidation of limonene are interesting because there are two peaks close together, each one corresponding in the mass spectrum to the endocyclic monoepoxide of limonene, this can be explained by considering that the limonene is chiral at the 1-position with the R-configuration.

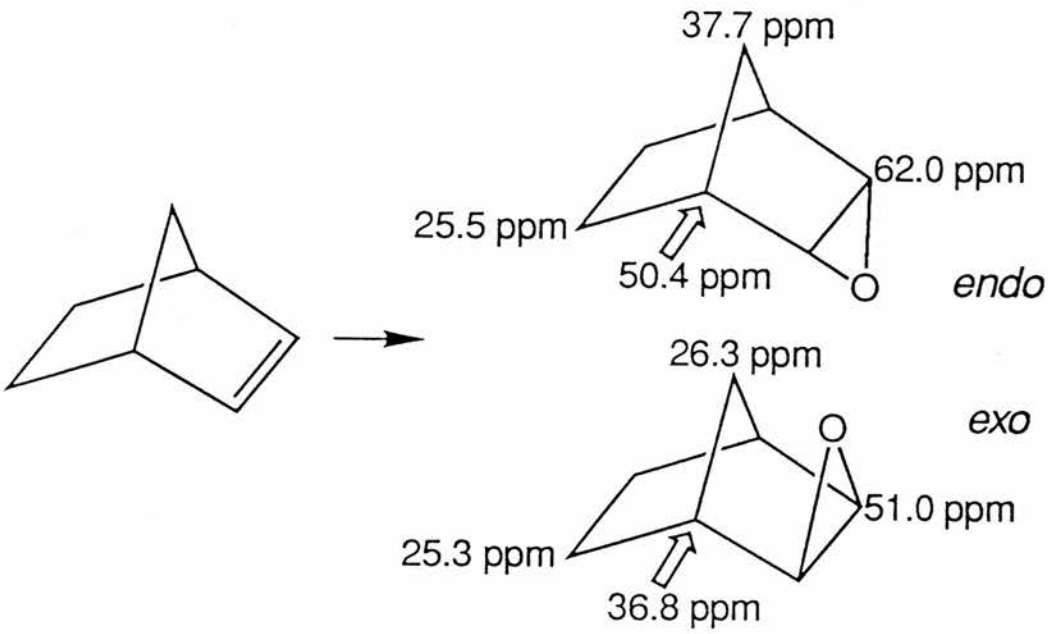


(4R)-(+)-limonene *cis* *trans*

Equation 4.1

It is clear that epoxidation of the endocyclic double bond should lead to two diastereomers and that the fact that the two isomers are present in a 1:1 ratio indicates that in this case epoxidation by the dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI)/t-BuOOH system is not diastereospecific.

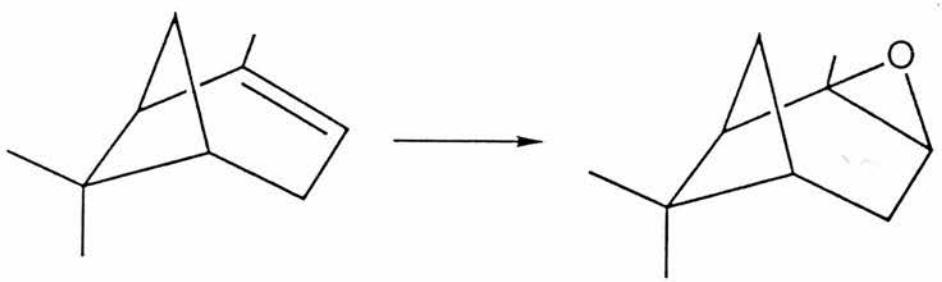
It should be noted that the epoxidation of norbornene can give two products; either the *endo* or *exo* oxa-derivative.



Equation 4.2

The isomers are shown along with the carbon atoms labelled with their ^{13}C chemical shifts in $CDCl_3$ obtained from the literature[198]. The product of the epoxidation of norbornene with dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) as catalyst had almost identical chemical shifts to that of the *exo* isomer and so it can be concluded that the epoxidation of norbornene has proceeded according to the "*exo*-addition rule" which is based on the observations that due to steric effects such additions give the least sterically hindered products.

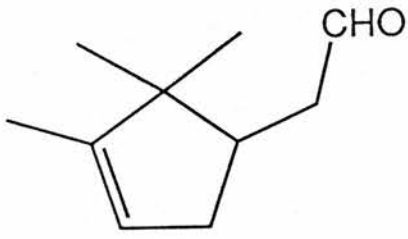
Tolstikov[199] and co-workers who used tert-amyl hydroperoxide with molybdenum catalysts for the selective epoxidation of a variety of terpenes obtained pinene oxide from 1S-(-)-α-pinene. With dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) as catalyst, however, the results were more complex. From the GC-MS results two products were observed in the ratio 10:1, the major componenent was eluted first and the mass spectrum was that expected for α-pinene oxide.



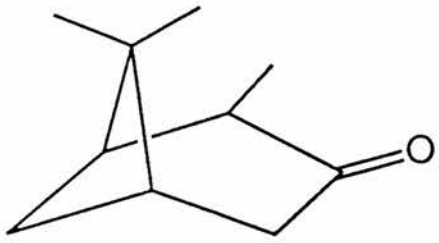
Equation 4.3

The second component could not be easily identified. The product was distilled, and GC-MS analysis of the distilled product revealed that the (1S)-(α)-pinene oxide had been converted into three main products in the ratio 1½:1:1.

Infrared analysis of the product mixture displayed absorptions characteristic of the OH group at 3420cm^{-1}, weak bands at 2835, 2715cm^{-1} corresponding to aldehydic C-H stretch and a rather broad but strong carbonyl stretch at 1725cm^{-1}. These results together with the nmr spectra add credence to the computer library assignments of the three components, namely that the first component is 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (Structure 4.1).

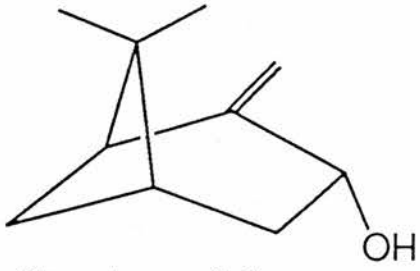


Structure 4.1



Structure 4.2

the second one being (1α,2β,5α)-2,6,6-trimethyl-bicyclo[3.1.1] heptan-3-one (Structure 4.2) with the third component as [(1S)-(1α)]-6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptan-3-ol (Structure 4.3).



Structure 4.3

^{1}H and ^{13}C nmr spectroscopy of the distilled product indicated a complex mixture of components with predominant resonances in the olefinic and aldehydic regions, which supports the GC-MS findings. It is likely that α-pinene oxide had been formed but under the conditions of distillation with the catalyst product still present, some type of rearrangement had occurred.

In the epoxidation of α-pinene with t-BuOOH and $V(acac)_3$ as catalyst, Banthorpe[200] obtained the epoxide in 44% yield, however under similar conditions with $Mo(CO)_6$ as catalyst campholenic aldehyde: 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde was also obtained. This became the sole product in the absence of solvent. The formation of the aldehyde which is a synthetically important intermediate[200,201] presumably reflects the high Lewis-acidity of $Mo(CO)_6$, as α-pinene oxide is known to be converted to the aldehyde by certain Lewis acids such as boron trifluoride[201].

4.3 Kinetics

As discussed previously, the principal function of the catalyst is to withdraw electrons from the peroxidic oxygens, making them more susceptible to attack by nucleophiles such as alkenes. In so doing the catalyst acts as a Lewis acid. However, it is known[3] that the Lewis acidity of the catalyst is also influenced by the nature of the effect of different ligands on molybdenum-catalysed epoxidations, it was concluded that those complexes with very strongly bound ligands show low activity, presumably due to hindrance of complex formation between the catalyst and the hydroperoxide. Catalysts with very loosely bound ligands such as $MoO_2(acac)_2$ were active but less selective than those with ligands of inermediate stability, such as $MoO_2(oxine)_2$. It was proposed that the latter formed a complex with the hydroperoxide by opening only one of the bonds of the chelating ligand to molybdenum. It can be suggested therefore that for catalysts to be active and selective one of the bonds can be weak or moderate and the other strong.

This allows certain rather useful predictions to be made upon the reactivity of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI) and dichlorobis{[(1R)-*endo*]-(+)-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) as catalysts. That is, that the former should be more catalytically active than the latter. As mentioned in Chapter 3, the 1:1 complex is formed by the oxygen atoms of C=O and P=O binding to the metal, with the P=O being the more strongly bound. In the 1:2 complex, both good donor P=O groups are bound.

The implication is that the lability of the carbonyl oxygen atoms should allow facile coordination of the hydroperoxide thus rendering the hydroperoxide oxygen atoms more electrophilic. This effect should be less pronounced in the 1:2 complex because the strength of phosphoryl oxygen-molybdenum bond will disfavour the decomplexation step which would allow hydroperoxide coordination.

The kinetics of the epoxidation of 1-methyl-1-cyclohexene with identical amounts of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) and the bis complex was investigated.

4.3.1 Kinetics of the Epoxidation of 1-methyl-1-cyclohexene with dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI)

The results of the epoxidation of 1-methyl-1-cyclohexene with 1 mol% of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) are shown in Graph 4.1. It is clear that from the data that the 1:1 complex is indeed a highly efficient epoxidation catalyst, as mentioned previously 80% conversion was observed before the first sample was taken for glc analysis (~30sec), when the catalyst to alkene ratio was 1:100. However, after the very rapid initial epoxidation, the rate dropped dramatically and the remaining alkene was epoxidised more slowly. As with other epoxidation catalysts[3] it is

likely that the β-ketophosphonate ligand is replaced by a small amount of diol side product and that this complex has a low activity for epoxidation. It is likely that the decrease in rate is caused by catalyst poisoning or of an alteration in the nature of the catalyst itself. This is discussed in more detail in Section 2.4.6.

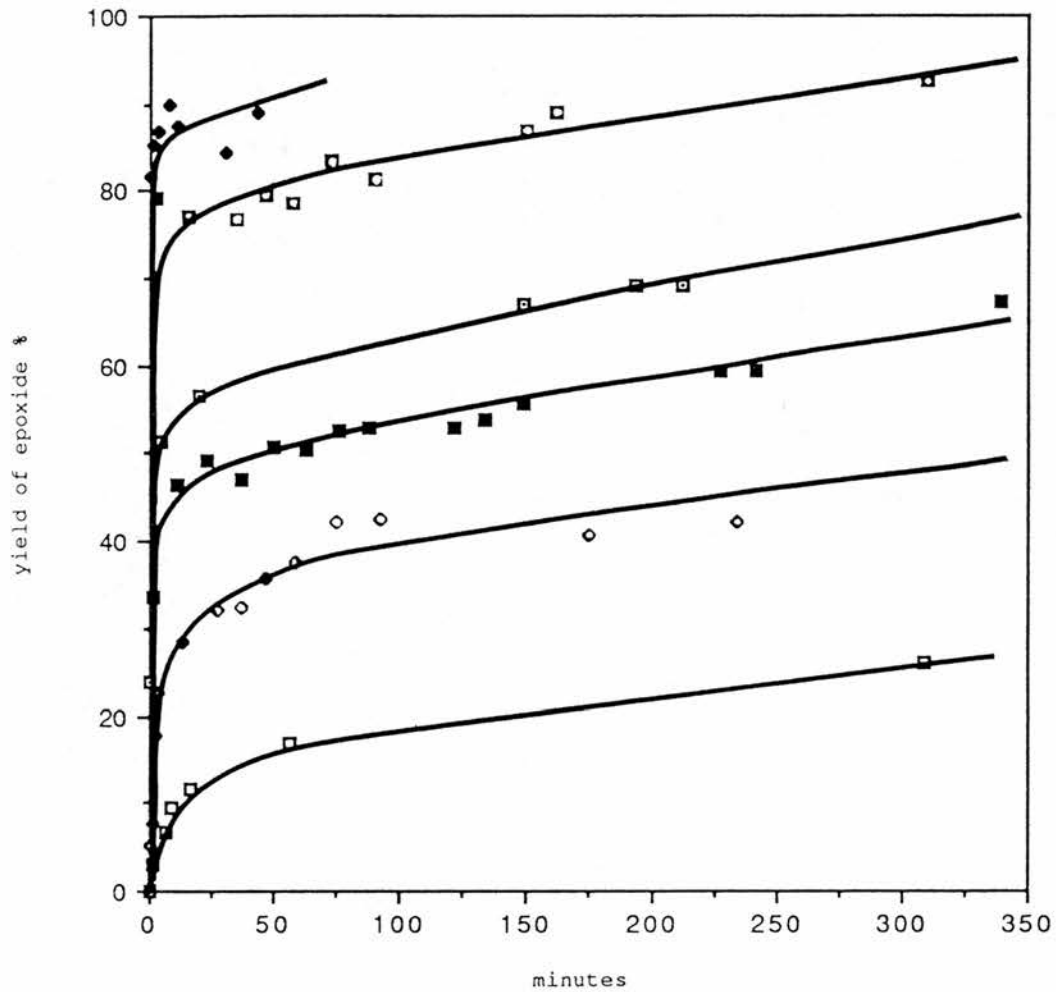
When the catalyst to alkene ratio was 1:1000 it can be seen that even when the catalyst concentration has been decreased by a factor of 10, the activity is still significantly high, having given a 50% yield of epoxide in 1 hour, the slowing down in rate becomes apparent, however, such that after 5 hours only slightly more than 60% of epoxide was formed.

4.3.2 Kinetics of the Epoxidation of 1-methyl-1-cyclohexene with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI)

Consistent with the predictions it can be seen from Graph 4.1 that although the 2:1 complex was a good epoxidation catalyst for a catalyst to alkene ratio of 1:100, it was not as effective as the 1.1 complex. In the first few seconds, the yield of epoxide had already reached approximately 80%, but to achieve a 90% yield it took around 225 minutes compared with around 50 minutes for the 1:1 catalyst. The only difference between the two systems is that the 2:1 complex, instead of having a ligating carbonyl function, it has another more strongly bound phosphoryl one.

Graph 4.1

Epoxidation of 1-methyl-1-cyclohexene catalysed by various complexes. Conditions as Table 4.1



◆ MoO_2Cl_2L.

◘ $MoO_2Cl_2L_2$.

◇ $MoO_2Cl_2L_2$ + 10 mol. equiv. of L. Catalyst to alkene ratio = 1:1000.

■ $MoO_2Cl_2L_2$ to alkene ratio = 1:1000.

□ $MoO_2Cl_2L_2$ with 2 mol. equiv. of $AgBF_4$.

⊡ MoO_2Cl_2.

L = [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor.

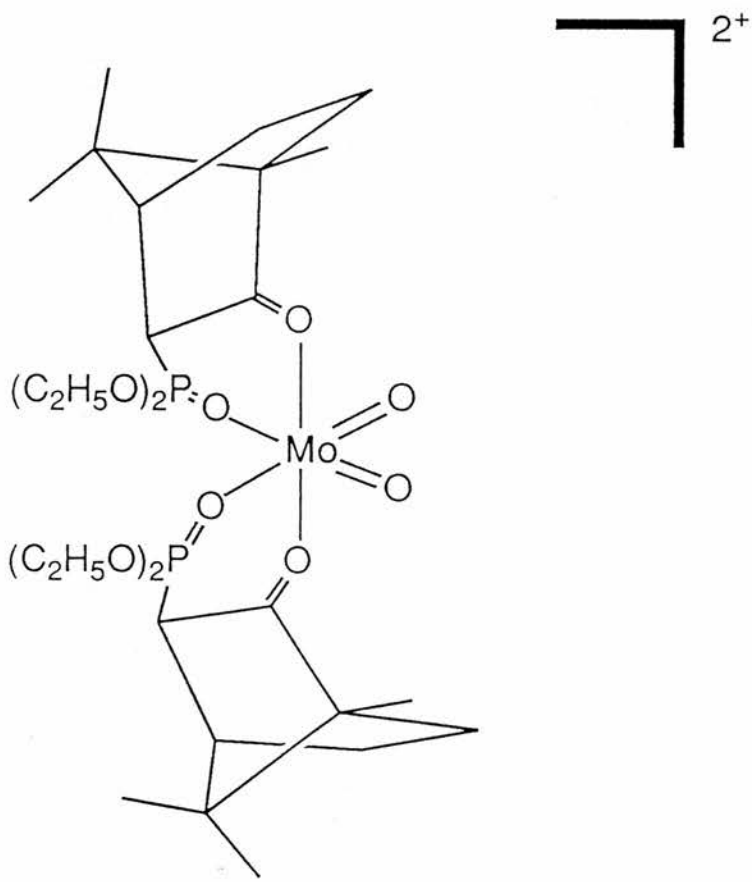
4.3.3 Epoxidation of 1-methyl-1-cyclohexene with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) in the presence of 10 molar equivalents of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

Addition of 1 mol% of dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) to 1-methyl-1-cyclohexene, t-BuOOH (in 2,2,4-trimethylpentane), and dichloromethane also containing a large excess of the free ligand (10 molar equivalents) resulted in a much reduced epoxidation rate when compared with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) with no excess of ligand. From Graph 4.1 the much lower activity became very apparent after 1 hour where approximately 38% of epoxide was formed compared with the 80% yield when the dichlorobis complex was used without excess free ligand. It is clear that suppression of the dissociation of the β-ketophosphonate by the addition of excess free ligand must be occurring such that tert-butyl hydroperoxide coordination therefore becomes less favoured and hence the much slower rate of epoxidation. When compared with the complex bis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) bis tetrafluoroborate as catalyst, it can be deduced that suppression of β-ketophosphonate dechelation by creating a more positive metal centre is much more effective than suppresssion by having excess of ligand present.

4.3.4 Epoxidation of 1-methyl-1-cyclohexene with bis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) bis tetrafluoroborate

Two molar equivalents of silver tetrafluoroborate dissolved in dichloromethane were reacted with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI). The silver chloride

which formed was removed by filtration and the product was used to catalyse the epoxidation of 1-methyl-1-cyclohexene. A scaling up of the amounts used in the synthesis of the catalyst is required for a full determination of the structure of the compound formed, however, the mode of action of silver tetrafluoroborate on metal halide complexes[202] is well known. The aim was to replace the halogen atoms with non-coordinating BF_4^- units. To satisfy an overall six-coordinate geometry for the molybdenum atom it is necessary for the carbonyl functions to coordinate to the metal also. The effect of halide removal was to form a very Lewis-acidic $[MoO_2]^{2+}$ unit in which the phosphoryl and carbonyl functions coordinate more strongly to the metal centre than in the uncharged complex.



Structure 4.4

The effect upon the activity of the catalyst is quite striking since it displays the poorest performance for any of the catalysts for 1-methyl-1-cyclohexene epoxidation (Graph 4.1). Less than 20% of the epoxide was formed after 1 hour compared with a yield of approximately 80% in the same time when compared with its parent dichlorobis complex. It seems likely that the reason for the low activity of this catalyst is that the high Lewis-acidity of the molybdenum atom in the dication favours the bidentate coordination of the [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor ligand and that decomplexation of a C=O group to give the vacant site for coordination of the t-BuOOH does not readily occur.

4.3.5 Molybdenum Dioxode Dichloride as an Epoxidation Catalyst

The high Lewis-acidity of molybdenum dioxide dichloride should make this compound itself a good epoxidation catalyst. Under identical conditions to the epoxidations with dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) discussed previously and dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI), molybdenum dioxide dichloride was added to a solution of 1-methyl-1-cyclohexene, t-BuOOH (in 2,2,4-trimethylpentane) and dichloromethane. As can be seen in Graph 4.1, the activity of this compound is much lower than would have been predicted from straightforward Lewis-acidity considerations. Concurrent examination of the contents of the reaction vessel showed that the complex was very slow to dissolve in that particular solvent system. It is likely that the poor solubility of MoO_2Cl_2 is one of the factors which makes it a poor catalyst.

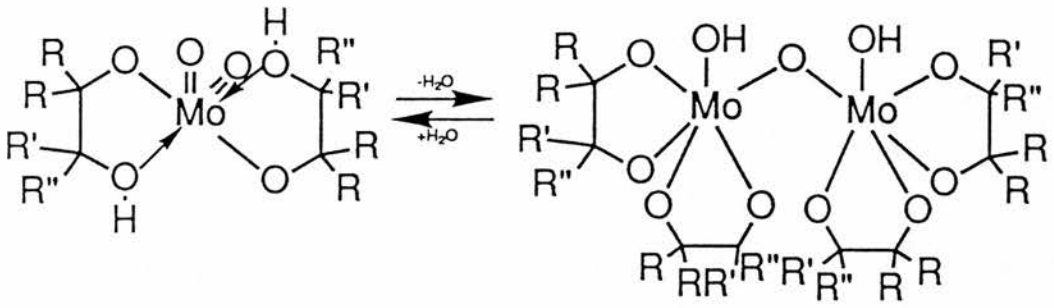
4.3.6 Recovery of Catalyst Product after Epoxidation of 1-methyl-1-cyclohexene with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI) as catalyst

It can be seen from Graph 4.1 that all of the catalysts studied follow a similar trend in the epoxidation reactions namely a relatively fast rate of epoxidation occurs at first which is followed by a much slower rate where the alkene is epoxidised slowly. As with other epoxidation catalysts[3] it is likely that the β-ketophosphonate ligand is replaced by a small amount of diol side product and that it is the diol complex which has the low activity for epoxidation. Also the fact that the gradients are all approximately the same suggests that the catalysts are all modified to the same species. The epoxidation of 1-methyl-1-cyclohexene with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) was scaled up to allow isolation of any catalyst products after epoxidation. For this reason the epoxidation was carried out in the normal manner except that the volatile components were removed *in vacuo* to leave behind a pale yellow oil. ^{31}P analysis of the oil indicated that there was [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor present as the only phosphorus containing component and that it was completely uncomplexed. Diethyl ether was used to dissolve the free ligand whereupon a fine white microcrystalline solid was precipitated. Some of the solid was taken up into deuterochloroform and the ^{13}C and ^{1}Hnmr spectra were recorded. The ^{13}Cnmr spectrum showed that there were seven resonances and the sample was pure. Since there are seven carbon atoms either in 1-methyl-1-cyclohexene oxide or in the derived diol which was the only organic material in the sample it is reasonable to suppose that the original ligands have been replaced, either by a diol or epoxide ligand. The existence of two downfield shifted resonances at 77.23 and 73.92 ppm are consistent with the observed chemical shift of 70.0 ppm[135]

for the C-OH in cyclohexanol. Coordination by the epoxide can be ruled out by the consideration that the most downfield ^{13}C resonance for 1-methyl-1-cyclohexene oxide occurs at only 58.86 ppm. The ^{1}Hnmr spectrum displays the characteristic broad peak at 2.19 ppm which can be assigned to a hydroxyl proton. The microanalysis results however offer little in the way of clarification; MoO_2(1-methylcyclohexane-1,2-diolate) ought to have the theoretical composition 43.53 %C and 6.78 %H, instead of which the sample analyses for 60.13 %C and 10.01 %H. The infrared spectrum displays a strong broad band at 3300cm^{-1} which can be assigned to νO-H and another strong band at 760cm^{-1} which is normally characteristic for oxo bridged dimers of metal complexes. There are apparently no Mo=O stretches in the spectrum.

Sheldon and Van Doorn[18,19] have successfully isolated molybdenum(VI)-1,2-diolate complexes as the catalyst product from epoxidations with other species.

A known reaction[203] of Mo(VI)-1,2-diol complexes is their reversible dimerisation with loss of one molecule of water.



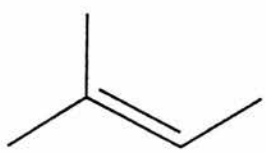
Equation 4.4

(a) $R=R'=R''=CH_3$

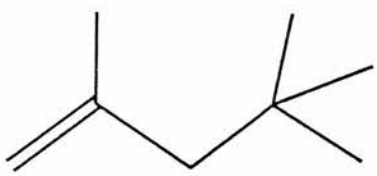
(b) $R=H;\ R'=CH_3;\ R''=(CH_3)_3CCH_2$

The ease of this reaction is known to increase with increasing substitution of the α-carbon atoms of the diol complex. If the diol contains at least one tertiary hydroxyl group a dimeric complex is formed directly by reaction of the diol with $MoO_2(acac)_2$[203].

It was not surprising that catalysts isolated from molybdenum-catalysed epoxidations of the highly substituted alkenes 2,3-dimethyl-2-butene and 2,4,4-trimethyl-1-pentene were found to be the dimeric Mo(VI)-1,2-diol complexes (a) and (b) respectively.



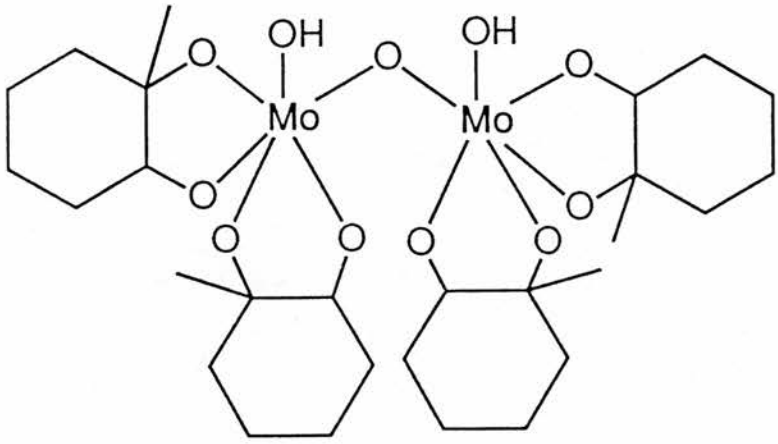
2,3-dimethyl-2-butene



2,4,4-trimethyl-1-pentene

Figure 4.1

Since the alkene 1-methyl-1-cyclohexene has one carbon atom of the double bond fully substituted, the catalyst product may in fact also be dimeric.



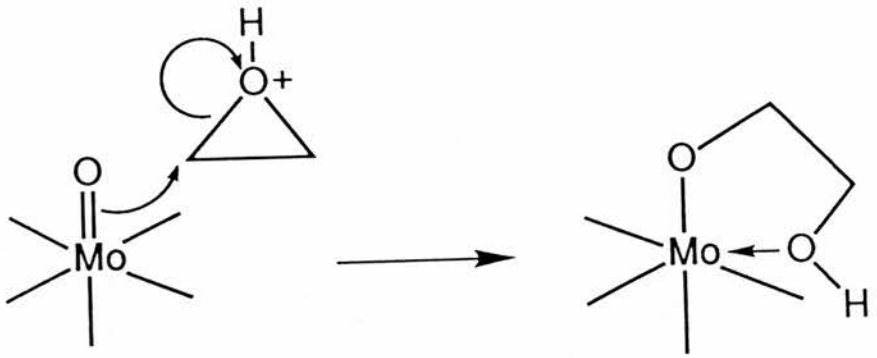
Structure 4.5

Such a compound however would microanalyse as 44.57%C and 6.68%H.

In work carried out by Butcher[181] into the Mo(VI)-1,2-diol complex bis(butane-2,3-diolato)dioxomolybdenum(VI), the X-ray crystal structure was solved it was found that the crystal structure consisted of molecules of MoO_2L_2 (L=butane-1,2-diolate) each surrounded by two molecules of HL (HL=butane-1,2-diol) which were attached by hydrogen bonds to the molybdenum complex and also linked by hydrogen bonds to neighbouring HL molecules. The overall effect was that of a layered structure. Although the diolate complex studied by Butcher was prepared by the reaction of molybdenum trioxide with refluxing diol, it is possible that it is the presence of similarly bound 1-methyl-1-cyclohexane-1,2-diol which is the cause of the rather high C,H percentage in analysis in the catalyst product. Future work should concentrate on the isolation and full characterisation of the catalyst products.

Mechanism of diolate complex formation

A likely rationale for the formation of the diolate complex is that the hydroperoxide acts as an acid catalyst for the ring opening of the epoxide. The fact that acetic acid could be used in the place of the hydroperoxide in other studies confirms this[19].



Equation 4.5

4.3.7 Epoxidation of Hex-1-ene with Dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) as Catalyst

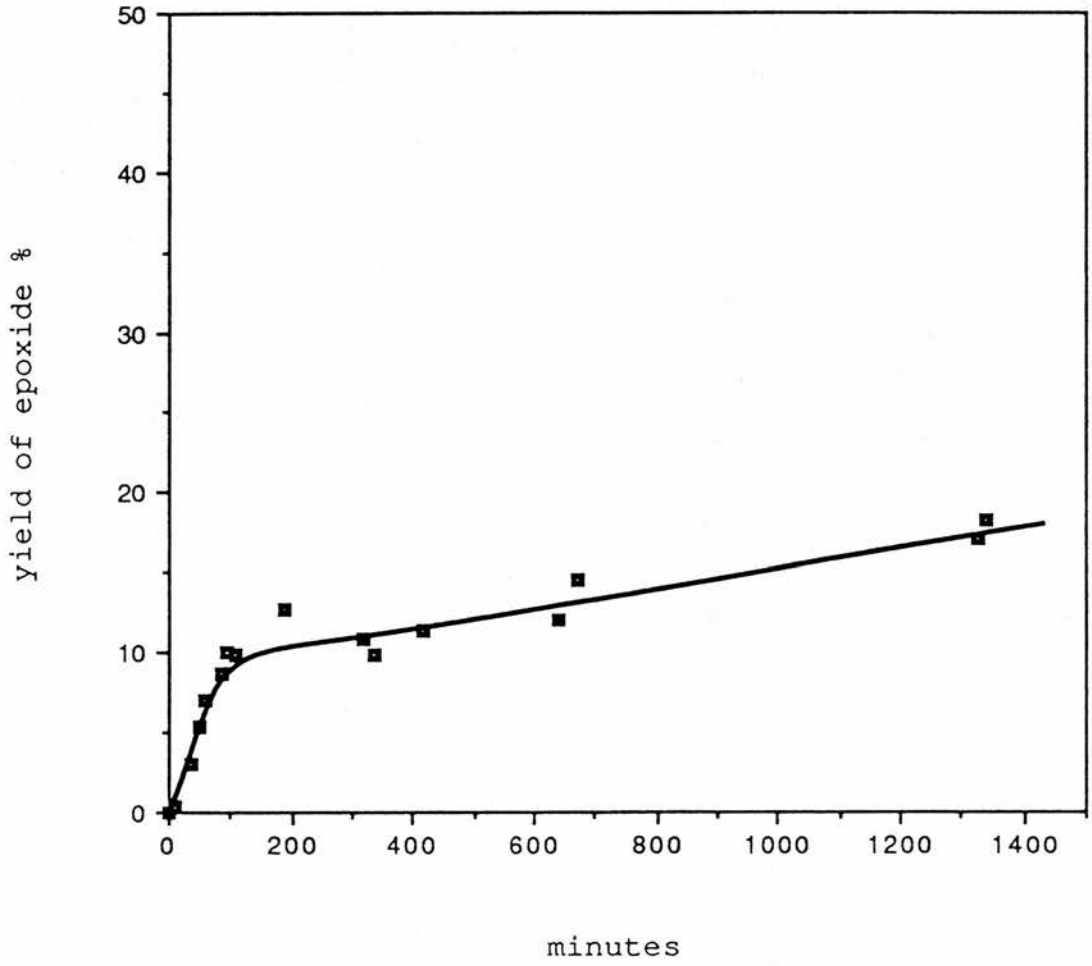
The substrate-dependency of the epoxidation rate of dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) as catalyst for the production of 1,2-epoxyhexane from hexene was demonstrated by epoxidising hexene under the same conditions as the epoxidation of 1-methyl-1-cyclohexene. From Graph 4.2 it can be seen that at 0°C, even after 17 hours, the yield of epoxide had not exceeded 20%. The curve is of a similar type to those in Graph 4.1 and others with the initially rather fast epoxidation slowing down as the β-ketophosphonate ligands are replaced by some other, most likely to be a hexene-1,2-diolate ligand. The comparative rates of reaction are entirely consistent with the observation that alkenes possessing a high degree of alkyl substitution such as 1-methyl-1-cyclohexene ought to be epoxidised much faster than the less nucleophilic, less substituted hex-1-ene.

4.4 Attempted Asymmetric Epoxidation of 1-methyl-1-cyclohexene and Geraniol

Many catalysts for asymmetric synthesis employ ligands derived from the chiral carbon pool. For instance typical chiral ligands for catalytic asymmetric cross coupling reactions[17] are derived from α-amino acids whereas many of those such as menthyldiphenylphosphine and CAMPHOS are

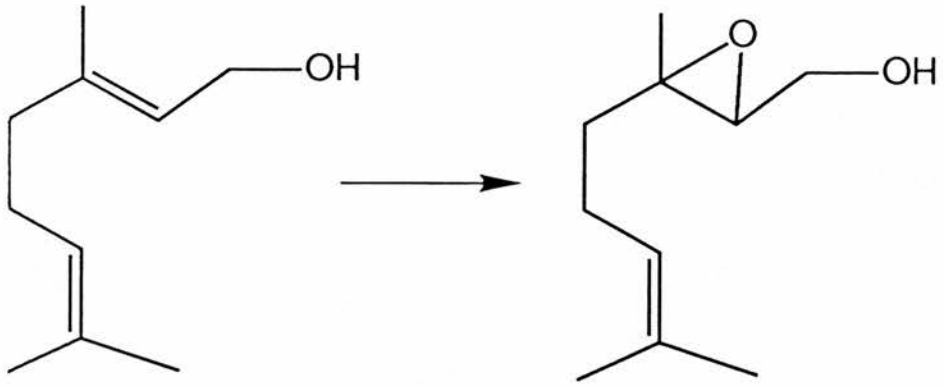
Graph 4.2

Epoxidation of hex-1-ene catalysed by dichlorobis-{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}-dioxomolybdenum(VI). Conditions as Table 4.1



derived from naturally occurring terpenes, CAMPHOS in particular being derived from camphor[17]. Similarly, the ligand [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor is derived from (+)-camphor. The coordination properties which make [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor an interesting ligand also seems to confer activity to the molybdenum(VI) in the catalytic systems discussed in the previous sections. It would be of further use to determine if the ligand could confer any chiral catalytic properties to the molybdenum(VI) system. If the degree of asymmetric epoxidation of 1-methyl-1-cyclohexene was significant, such an enantiomeric excess would be easily detected by polarimetry. However, the specific rotation of the isolated 1-methyl-1-cyclohexene oxide was close to zero. 1-methyl-1-cyclohexene ought to be one of the better unfunctionalised alkenes for epoxidation due to its more sterically bulky nature compared with for example hex-1-ene. The problems associated with the asymmetric epoxidation of unfunctionalised alkenes are well known[108] and are described in Chapter 1.

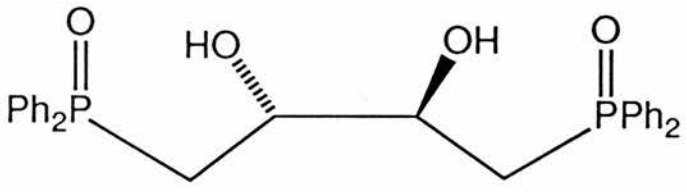
If the ligand [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor is to be a successful one for asymmetric epoxidations then catalysts derived from it should epoxidise an allylic alcohol such as geraniol giving significant ee. This is because the existence of the alcohol group will allow binding to the metal and present one face of the alkene preferentially to the coordinated hydroperoxide. The epoxidation of geraniol was carried out under identical conditions to the Sharpless epoxidation using titanium tetraisopropoxide, except that instead of diisopropyl tartrate as ligand, the β-ketophosphonate was used. Work-up of the products and distillation afforded an oil which was found to be 2,3-epoxygeraniol in good yield (66%).



Equation 4.6

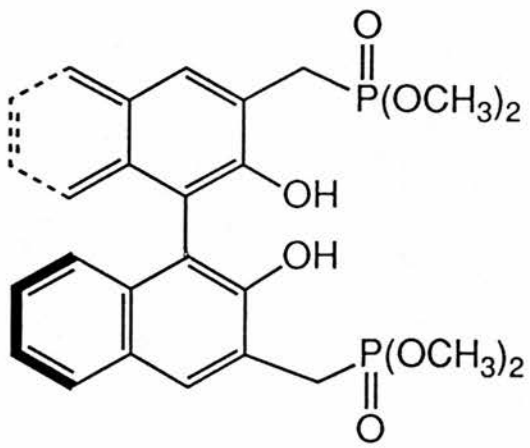
The epoxidation had been selective towards the allylic double bond, however the epoxide posessed no net optical rotation. A later fraction obtained by high temperature distillation did have a significant $[\alpha]_D$ but it was found by ^{1}Hnmr to be due to the presence of some [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor which had distilled over at the much higher temperature. Nevertheless, the fact that the catalytic activity of the Ti/β-ketophosphonate system does not seem to suffer any form of auto-retardation means that there is a good deal of scope for asymmetric epoxidation of certain allylic alcohols using this type of system.

In experiments carried out concurrently by Sharpless[97] it was found that the epoxidation of (*E*)-2,3-diphenyl-2-propenol by $Ti(Oi\text{-}Pr)_4$ and t-BuOOH at 0°C in CH_2Cl_2 with the chiral ligand shown in Structure 4.6.



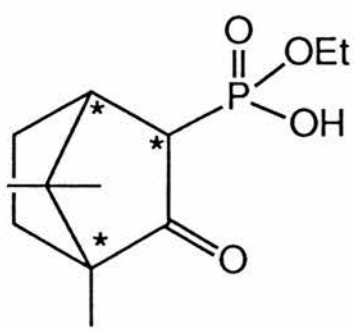
Structure 4.6

gave 0% ee. It was found that epoxidation of (*E*)-α-phenylcinnamyl alcohol with the binap-type ligand[17]



Structure 4.7

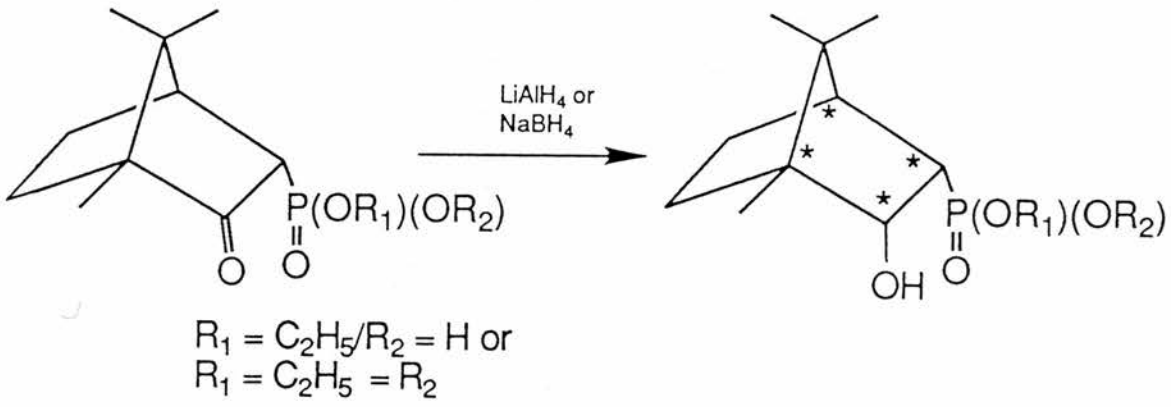
gave an ee of only 2% compared with >96% with other, especially tartrate-like, ligands. Clearly then, Sharpless has come across the same problem. The ligand [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor however represents a potential improvement of many of the Sharpless ligands because of the β-ketophosphonate's ease of derivatisation. The problem with the hydroxyphosphine oxide is most likely due to the fact that the very good donor phosphine oxides will compete strongly with the hydroxyl oxygen for coordination to the titanium(IV) centre. Where this is the case ligands such as the camphor-3-phosphonic acid class



Structure 4.8

would be interesting because there would be "backbone chirality" α to the phosphorus atom with chelate binding involving the POH oxygen and the carbonyl group. This is not the case with the Sharpless β-hydroxy-phosphine oxide where the chirality exists at the carbinol carbon atom which is β to the phosphorus atom.

The β-hydroxyphosphonate in principle derivable from [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor by treatment with sodium borohydride or lithium aluminium hydride represents an extension of the β-ketophosphonate chemistry in this work and that of Sharpless because there will be chiral centres both α and β to the phosphoryl group.



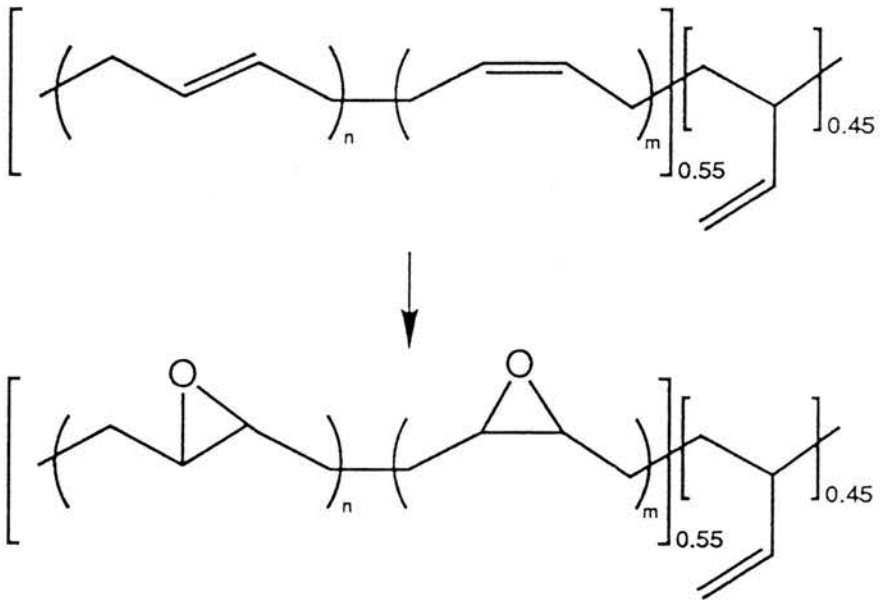
Equation 4.7

4.5 The Regioselective Epoxidation of Polybutadiene

The catalyst dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI) was used, as an extension of this work, for the epoxidation of polybutadiene. Much of the work was carried out by a co-worker A.Iraqi, who successfully prepared the epoxy-polymer using the catalyst. For the sake of completeness it is relevant to include the results, which are significant indeed, in this section. The reader is referred to the literature, however for the more detailed experimental information[57].

The functionalisation of polybutadiene by, for example, hydroformylation results in the pendant vinyl groups being hydroformylated with the backbone double bonds being unreacted. This type of derivative is of interest because attachment of a terphenyl unit to the functionalised moiety ought to confer liquid-crystalline behaviour to the polymer[204], and hence this and other transformations of the polymer has many potential applications in materials science.

The polybutadiene used consisted of 55% backbone double bonds (n+m) and 45% of terminal vinylic groups. The epoxidation product displayed no proton resonances due to those on the backbone whereas the pendant vinyl groups were left intact.



Equation 4.8

Previous attempts to epoxidise similar polybutadienes either using organic[205,206] or catalytic[207] epoxidising systems have shown a preference for the backbone double bonds (*cis*1,4>*trans* 1,4>>1,2) but in no cases have very high selectivities been observed; the terminal double bonds are epoxidised before all of the backbone double bonds have reacted, or some of the backbone double bonds are left unreacted. When dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}molybdenum(VI) was used as the catalyst, all of the backbone double bonds were

epoxidised within three hours at room temperature. There was no further change in the next 70 hours. The terminal double bonds remained unreacted. Using eg. $MoO_2(acac)_2$ as an epoxidation catalyst required refluxing the polymer with t-BuOOH for 24h and even then a much less selective reaction was observed and substantial amounts of other products, possibly diols, were formed.

Part of the reason for this selectivity observed with MoO_2Cl_2L is almost certainly due to the fact that the backbone double bonds have more electron-releasing groups on them. This can be compared with the epoxidation of R-(+)-limonene, discussed in 4.2.1, where it was found that only the endocyclic double bond was epoxidised because it had the greater degree of alkyl substituation. The catalyst however is less reactive towards (R)-(+)-limonene than the polymer. It is clear that the reasons behind the particular reactivity and selectivity in the reaction with polybutadiene requires further investigation.

4.6 Experimental

4.6.1 Epoxidation of various alkenes

tert-butyl hydroperoxide

The tert-butyl hydroperoxide used was stored below -5°C in the refrigerator and the container was allowed to warm to room temperature over the space of one hour before use. The volume of hydroperoxide to be used was determined by measuring cylinder as the use of syringes is strongly discouraged. This is because traces of transition metals from the needle inserted into the solution can contaminate the stock solution and will cause the facile decomposition of the hydroperoxide over a short period of time. The tert-butyl hydroperoxide was purchased as an anhydrous 3 molar solution in 2,2,4-trimethylpentane (iso-octane) and contained in a high density polyethylene bottle. When properly capped, these polyethylene bottles develop a negative pressure in the

refrigerator and compress. Water from the air will be absorbed if the bottles were to be opened immediately upon removal from the refrigerator. Sharpless has found that if these conditions are adhered to such a solution can be stored for months without losing effectiveness. Only 5-10% of the sample decomposes even after constant use and warming when these recommendations are followed.

Although no problems have been encountered with the tert-butyl hydroperoxide it is safer to follow some rules: Never add even a drop of strong acid to high strength tert-butyl hydroperoxide solutions. Never add transition-metal salts (notably Mn, Fe, Ru and Co) known to be good autoxidation catalysts, to high strength tert-butyl hydroperoxide solutions. Tert-butyl hydroperoxide is prone to metal-catalysed radical-chain decomposition which gives oxygen as one of the products. Never work with pure tert-butyl hydroperoxide and try to avoid the use of high strength solutions. Tert-butyl hydroperoxide ought not to be stored in glass bottles due to the possibility of gas evolution. Low density polyethylene bottles should not be used because they are permeable to many of the solvents for tert-butyl hydroperoxide[208].

Work-up of epoxidations involves fractional distillation over molecular sieves (4Å) with the epoxide distilling last. Although caution is advisable during distillation because of the likely presence of excess peroxides, it should be noted that tert-butyl hydroperoxide is one of the most stable members of the peroxide class, and that dilute tert-butyl hydroperoxide solutions used in these syntheses are thermally very stable and are safe as long as no autoxidation catalysts or strong acids are present.

Epoxidation Procedure

The typical procedure for the epoxidation of the various alkenes, summarised in Table 4.1 involved adding 1 mol% of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) to a stirred solution of anhydrous tert-BuOOH (1.5 molar equivalents) in 2,2,4 trimethylpentane also containing the alkene (1 molar equivalent) and dichloromethane 14.66 molar equivalents. For the epoxidations of 1-methylcyclohexene and cyclohexene at 20°C a water-cooled reflux condenser was required due to the exothermic nature of the epoxidation.

Chromatography

Where the epoxides were not isolated, comparison by co-chromatography with the identical epoxide prepared by peracetic acid epoxidation of the alkene proved to be useful. In the cases of (R)-(+)-limonene and 1-dodecene, norbornene, pinene oxides co-chromatography was not carried out but satisfactory GC-MS with computer library back-up was sufficient for identification.

The kinetics of the epoxidation of hex-1-ene and 1-methyl-1-cyclohexene were followed by GC. The samples (0.05ml) were quenched into approximately 0.01g of the reducing agent triphenyl phosphine which prevents further epoxidation and then the desired amount of the solution was injected into the chromatograph. The quantitation was based on the amount of epoxide formed compared with the amount of alkene left unreacted at that injection time. The validity of this method was checked by injecting an exactly 1:1 ratio of pure alkene/epoxide and 1-methyl-1-cyclohexene/epoxide GC-traces a 1:1 ratio in areas was found. The yield of epoxide at any one time could be calculated as follows:

$$\text{yield of epoxide \%} = \frac{\left[\begin{array}{l}\text{total area under} \\ \underline{\text{alkene+epoxide peaks}}\end{array}\right] - \left[\begin{array}{l}\text{area under} \\ \text{alkene peak}\end{array}\right]}{\text{total area under alkene + epoxide peaks}} \times 100$$

4.6.2 Epoxidation of 1-methyl-1-cyclohexene with 1mol% of dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) previously treated with 2mol-equivalents of silver tetrafluoroborate

To silver tetrafluoroborate (13.6mg, $7x10^{-5}$mol) in dichloromethane (50 ml) with stirring was added dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) (21.4mg, $3.5x10^{-1}$mol). The white precipitate of silver chloride which formed was removed by filtration and the dichloromethane was removed under reduced pressure to leave a pale blue glassy residue. This was kept under dry nitrogen for two days whereupon dichloromethane (3.3ml) and tert-butyl hydroperoxide (1.74ml, $5.2x10^{-3}$mol) were added and 1-methyl-1-cyclohexene (0.41ml, $3.5x10^{-3}$ mol) was added to the mixture at 0°C.

The course of the reaction was monitored by Gas-Liquid Chromatography of approx. 0.05ml portions of reaction mixture quenched into triphenylphosphine (approx. 0.01g) in dichloromethane (0.5ml). The injection volume was typically 1μl.

4.6.3 1-methyl-1-cyclohexene oxide (As a comparison for the epoxide produced by Mo(VI) catalysts)

To a stirred suspension of anhydrous sodium carbonate (approx. 25g) in dichloromethane (70 ml) at 0°C was added 1-methyl-1-cyclohexene (6g, 62.4 mmol) followed by peracetic acid (19.5g of a 35 wt% solution in acetic acid). When the addition of the peracid was complete the mixture was allowed to warm to room temperature. 24 hours later the solution was filtered through a sinter funnel and the solvents removed by distillation to give 1-methyl-1-cyclohexene oxide (5.45g, 77% yield) b.p. 136-138°C.

Analysis

^{1}Hnmr (Solvent $CDCl_3$)

Chemical shift ppm, mulitiplicity, integral

2.7,d,1; 1.7,m,3; 1.4,m,1; 1.2,m,2; 1.1,complex,5.

^{13}Cnmr

Chemical shift ppm (assignment)

58.86(2); 56.75(1); 29.48(7); 24.37; 23.46; 19.63; 19.24.

Mass Spectrometry M/e (rel.int.)

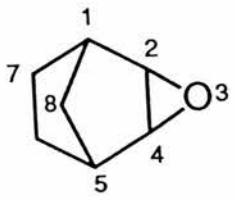
39(84), 41(100), 42(51), 43(61), 55(49), 67(8), 69(11), 97(34)

No M^+ - loss of $^{\bullet}CH_3$ from 112 gives stable oxonium ion M/e=97.

4.6.4 3-oxatricyclo[2.2.1.$0^{2,4}$]octane

(*exo*-epoxynorbornane)

To dichloromethane (20 ml) containing bicyclo[2.2.1]hept-2-ene (2.43g, 26 mmol) was added t-butyl hydroperoxide (16.97 ml, 52 mmol of a 3M solution in 2,2,4-trimethylpentane) at 25°C. To the mixture was added dichloro{[(1R)-*endo*]-3-(diethoxyphosphinyl)camphor} dioxomolybdenum(VI) (0.13g, 0.26 mmol). The solution was allowed to self-reflux. 24 hours later when GLC analysis showed an epoxide trace with no starting alkene, the mixture was worked-up by removal of the volatiles on the rotary evaporator and distillation of the residue gave 3-oxatricyclo[2.2.1.$0^{2,4}$]octane 1.52g. 53.3% yield, M.p. 120-122°C.



Structure 4.9

Analysis

^{1}Hnmr (Solvent $CDCl_3$)

Chemical shift ppm, multiplicity, integral.

3.11,s,1; 2.49,s,1; 1.7-1.05, complex, 7; 0.72,d,1.

^{13}Cnmr

Chemical shift ppm (Assignment)

24.63(8), 25.72(6), 36.19(1), 50.79(2).

4.6.5 Epoxidation of (1S)-(-)-α-pinene

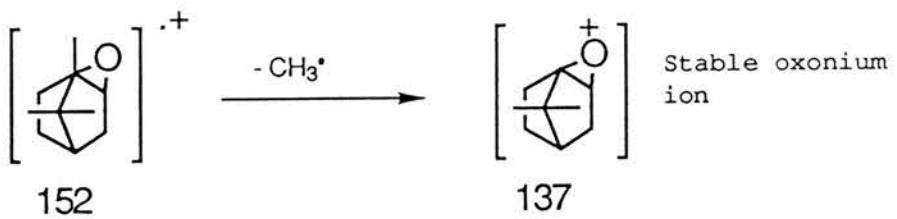
To (1S)-(-)-α-pinene (4g, 29 mmol) in dichloromethane (25 ml) at 25°C was added tert-butyl hydroperoxide (14.7 ml, 43.5 mmol), 3M in 2,2,4-trimethylpentane). To this was added dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) (0.29g, 0.58 mmol). The solvents were prevented from distilling by means of a water-cooled reflux condenser. 18 hours later GC-MS analysis showed that approximately 45% of the alkene had been converted to (-)-α-pinene oxide 1.27g isolated (28%) b.p. 70-85° (0.1mmHg).

Analysis

Prior to distillation:- Mass spectrometry: M/e (rel.int.)

41(54), 43(62), 62(100), 81(36), 82(40), 83(38), 109(68), 137(32).

152(1)



152 137

Equation 4.9

After distillation:-

^{1}Hnmr (solvent $CDCl_3$)

Chemical shift ppm, multiplicity, (assignment)

9.70, t, (CHO); 5.10,br,s,(OH); 4.90,t,(C=CH); 4.75,s,(C=CH)

0.55-2.6 complex region

^{13}Cnmr

Complex. Significant resonances are 203ppm(C=O); 216ppm(C=O); 112ppm C=C; 121ppm C=C; 67ppm CH-OH

Infrared spectrum, thin film

3420cm^{-1} νOH 1725cm^{-1} νC=O 1672cm^{-1} νC=C 2722cm^{-1} νC-H(aldehydic)

GC-MS

Oven temp. 100°C

3 components, relative proportions 3:2:2

(1) 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde

Mass spectrometry: M/e(rel.int.)

27(25), 29(26), 39(27), 41(37), 67(28), 93(68), 95(25), 108(100).

(2) [(1S)-(1α,3α,5α)]-6,6-dimethyl-2-methylene-bicyclo[3.1.1]heptan-3-ol

(*trans*-(-)-pinocarveol)

Mass spectrometry: M/e(rel.int.)

27(55), 29(40), 39(59), 41(100), 55(74), 70(42), 91(58), 92(56)

(3) (1α,2β,5α)-2,6,6-trimethyl-bicyclo[3.3.1]heptan-3-one

(isopinocamphone)

Mass spectrometry: M/e(rel.int.)

27(37), 29(26), 39(42), 41(91), 55(99), 69(66), 81(16), 83(100), 152(7) M^{+}

4.6.6 Recovery of catalyst product after epoxidation of 1-methyl-1-cyclohexene with dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl) camphor}dioxomolybdenum(VI)

To a stirred solution of tert-butyl hydroperoxide (30 mmol, 10 ml of a 3M solution in 2,2,4 trimethylpentane), 1-methyl-1-cyclohexene (3.55 ml, 30 mmol) in dichloromethane (15ml) was added dichlorobis{[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI) (0.23g, 0.3 mmol). After 24 hours, the volatile components were removed under reduced pressure with gentle heating to leave behind a yellow oil. A white solid was deposited upon the addition of a diethyl ether/petrol mixture (1 ml,1:1) and cooling to -25°C. The microcrystalline molybdenum-diolate compound was filtered and dried *in vacuo* for 3 hours.

Yield 0.05g M.p. 72°C.

Microanalysis: 60.13%C, 10.01%H

^{1}Hnmr (Solvent $CDCl_3$)

Chemical Shift ppm	Multiciplicty	Integral	Assignment
3.51	dd	1	H-2
2.19	br	1-2*	OH
1.84	m	1	
1.67	m	2	other
1.60	m	1	ring
1.32	m	4	protons
1.19	s	3	CH_3

* not accurately measured.

^{13}Cnmr

Chemical Shift ppm	Assignment
77.23	2
73.92	1
38.61	
31.03	
24.00	3/4/5/6
23.26	
19.68	7

Infrared (Nujol mull)

3300cm^{-1} νO-H 760cm^{-1} νMo-O-Mo

4.6.7 2,3-epoxygeraniol

(*trans*-3-methyl-3-(4-methyl-3-pentenyl)oxiranemethanol)

To dichloromethane (40 ml) was added titanium tetra-isoproproxide (0.44g, 1.6 mmol) followed by molecular sieves 4Å (0.97g), [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor (0.69g, 2.4 mmol) and (*E*)-3,7-dimethyl-2,6-octadiene-1-ol (geraniol) (4.45g, 32.5 mmol). The mixture was kept at -40°C by means of an ethylene glycol/water (2:1) bath and dry-ice. One hour later tert-butyl hydroperoxide (21.3 ml, 63 mmol of a 3M solution in 2,2,4 trimethylpentane) was added. The mixture was allowed to warm to room temperature over 60 minutes. The catalyst solution was hydrolysed by adding 6 ml of a 30% aqueous solution of sodium hydroxide saturated with sodium chloride. After 35 minutes of vigorous stirring the dichloromethane layer was separated, combined with 2x50 ml extracts of the aqueous phase, dried with sodium sulphate and distilled, bp 100-105°C at approx. 1mmHg, 3.64g.

Yield 66% $[\alpha]^{25}=0^{o}$.

The spectra were identical to those given in the literature[208].

Concluding Remarks

The ligand dependency of the effectiveness many epoxidation catalysts requires that novel complexes between various transition metals eg. Mo, Ti and the ligand systems described in Chapter 2 should be tested for their catalytic activity with many types of substrate. As far as asymmetric synthesis is concerned although tartrate-catalysed asymmetric epoxidation of allylic alcohols is well established, the same cannot be said of homoallylic alcohols and unfunctionalised alkenes which can only be epoxidised with much lower enantioselectivity. Not only do certain (*Z*)-allylic alcohols epoxidise slowly but they also do so with significantly lower enantiomeric excesses. That investigations into asymmetric epoxidation catalysis of these systems be carried further, particularly with new chiral ligands is of paramount importance.

Further work on the allylic alcohol-type of substrate for epoxidation should be initially with the Ti(IV) alkoxides which offer the greatest chance of success. The presence of the oxo-groupings in Mo(VI) and V(V) catalysts means a loss of potential binding sites and so these metals may not be as suitable.

It is likely that further experiments in the asymmetric epoxidation of simple unfunctionalised alkenes will proceed with Mo(VI) (oxo-diperoxo) systems which offers a good deal of promise of success for the stiochiometric epoxidations.

Chiral iron porphyrin and platinum phosphine complexes are moderately successful for catalytic asymmetric epoxidation so that the study of analogues will be interesting indeed.

Finally, the recent observations[38] that certain *cis*-dioxomolybdenum(VI) complexes of various multidentate ligands do not undergo demetallation adds impetus to the investigations into their chiral equivalents. Much of the lack of enantioselectivity in the molybdenum case may be due in part to decomplexation of the chiral ligand giving rise to diol complexes[8]. Complexes with multidentate chiral ligands in which some of the functions can de-coordinate to allow peroxide complexation, while other functions remain firmly attached and so still produce a chiral environment for the epoxidation, are likely to have useful and interesting catalytic properties. As Sharpless has stated[49] "Asymmetric epoxidation is at the tip of a new iceberg that has selective abiological catalysis as its foundation".

APPENDICES

1) Structural determination of

MoO_2Cl_2[[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor

2) Experimental Methods and Starting Materials

Appendix 1

Introduction

In recent years structure determination by X-ray crystallography has become a commonly used technique in chemistry, largely as a result of the development of automatic diffractometers, powerful computers and efficient programs.

The following chapter presents the results obtained from the determination* of the single crystal molecular structure of dichloro {[(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor}dioxomolybdenum(VI).

Crystallography

Cubic crystals were obtained from THF-diethyl ether at -5°.
Crystal data. $C_{14}H_{25}PMoO_6Cl_2$, M=487.168 orthorhombic a=15.528(2); b=13.721(2), c=9.777(1) Å, $\alpha=\beta=\gamma=90°$; U=2083.03 $Å^3$, space group $P2_12_12_1$, D_m=1.56 gcm^{-3}, Z=4, D_c=1.55 gcm^{-3}, Mo-Kα radiation, λ=0.71069Å, μ=8.89 cm^{-1}, F(000)=992.

2101 unique reflections were recorded on a CAD4 diffractometer measuring to $\theta_{max}=25°$. Psi-scan absorption corrections were made (min 0.9559, max 0.9993). The structure was solved by Patterson and Fourier methods. The positions and anisotropic vibrational parameters of all non-hydrogen atoms were refined.

The final R factor was 0.043 and R_g ($=\{1/[(F_o)+0.000326F_o]\}$) 0.054 for 1664 reflections having $F>3\sigma(F)$. The R value for the enantiomorphic structure was 0.048. The largest peaks in the final difference map were 0.5e in the vicinity of the carbon atoms.

* The data was collected and the structure solved by M.B Hursthouse and M. Harman, Queen Mary College, London.

Table A.1
Fractional Atomic Coordinates ($x10^4$) of Atoms

	x	y	z
Mo	3950.3(5)	2797.8(6)	1227.4(7)
P	6031(2)	2400(2)	2222(2)
Cl(1)	4516(2)	4359(2)	862(3)
Cl(2)	3805(2)	1242(2)	2225(3)
O(1)	4345(4)	3188(4)	3539(5)
O(2)	5307(3)	2382(5)	1250(6)
O(3)	6524(5)	3389(6)	2234(7)
O(4)	6735(5)	1647(6)	1912(8)
O(5)	3810(5)	2490(6)	-397(6)
O(6)	2977(4)	3157(6)	1697(8)
C(1)	5072(7)	3227(8)	5752(9)
C(2)	4922(5)	2911(7)	4262(8)
C(3)	5606(5)	2177(7)	3886(8)
C(4)	6191(8)	2180(12)	5223(9)
C(5)	6658(8)	3162(13)	5385(13)
C(6)	5898(9)	3895(12)	5624(13)
C(7)	5442(7)	2219(12)	6328(9)
C(8)	4767(9)	1396(9)	6321(13)
C(9)	5821(9)	2367(13)	7800(10)
C(10)	4317(8)	3697(8)	6438(9)
C(11)	6903(11)	3762(15)	900(24)
C(12)	7436(17)	4269(17)	1205(28)
C(13)	6563(10)	750(9)	1273(19)
C(14)	7382(10)	136(11)	1281(20)

Table A.2
Anisotropic Temperature Factors ($Å^2x10^4$)

	U 11	U 22	U 33	U 23	U 13	U 12
Mo	50.4(4)	58.6(5)	51.6(4)	-1.7(4)	-3.5(4)	-8.3(4)
P	52(1)	64(2)	56(10	1(1)	9(1)	14(1)
Cl(1)	100(2)	49(2)	101(2)	21(2)	-11(2)	-3(1)
Cl(2)	124(3)	60(2)	102(2)	5(2)	4(2)	-39(2)
O(1)	63(3)	48(3)	45(3)	0(3)	0(3)	14(3)
O(2)	56(3)	64(4)	48(3)	-1(3)	9(3)	5(3)
O(3)	78(5)	73(5)	84(5)	-3(4)	6(4)	-19(4)
O(4)	76(5)	90(5)	89(5)	-6(5)	5(4)	31(5)
O(5)	84(5)	117(6)	54(3)	-6(4)	-13(3)	-33(4)
O(6)	51(4)	116(7)	91(5)	-8(5)	-1(3)	1(4)
C(1)	92(7)	67(7)	46(4)	-7(5)	0(5)	5(6)
C(2)	62(5)	38(5)	43(4)	3(4)	-2(4)	-2(5)
C(3)	69(7)	183(17)	84(8)	-25(10)	-10(6)	-23(10)
C(4)	78(7)	156(12)	47(4)	20(7)	8(5)	71(9)
C(5)	93(7)	141(11)	42(4)	6(8)	-2(5)	56(9)
C(6)	100(10)	152(13)	78(7)	-14(8)	-19(7)	-36(10)
C(7)	60(4)	60(5)	49(4)	12(6)	1(4)	17(5)
C(8)	135(11)	71(8)	84(7)	30(7)	16(8)	7(8)
C(9)	125(10)	190(16)	42(4)	19(7)	-2(5)	62(11)
C(10)	119(9)	83(8)	52(6)	-24(6)	5(5)	38(7)
C(11)	99(11)	145(16)	190(19)	-11(15)	18(12)	-65(11)
C(12)	191(21)	171(23)	231(25)	-69(22)	67(24)	60(18)
C(13)	122(11)	62(7)	155(12)	-13(10)	-4(11)	10(8)
C(14)	94(9)	80(9)	182(14)	7(11)	33(12)	12(7)

The temperature factor exponent takes the form:
$-2\pi^2(U_{11}.h^2.a^{*2}+ \ldots +2U_{12}.h.k.a^*.b^*)$

Table A.3
Bond lengths (Å)

Cl(1)-Mo	2.343(5)	Cl(2)-Mo	2.358(5)
O(1)-Mo	2.402(7)	O(2)-Mo	2.183(7)
O(5)-Mo	1.658(8)	O(6)-Mo	1.655(9)
O(2)-P	1.472(7)	O(3)-P	1.558(10)
O(4)-P	1.533(9)	C(3)-P	1.783(10)
C(2)-O(1)	1.202(10)	C(11)-O(3)	1.519(24)
C(13)-O(4)	1.406(15)	C(2)-C(1)	1.538(14)
C(6)-C(1)	1.580(19)	C(7)-C(1)	1.538(14)
C(10)-C(1)	1.497(15)	C(3)-C(2)	1.509(14)
C(4)-C(3)	1.592(15)	C(5)-C(4)	1.538(22)
C(7)-C(4)	1.589(16)	C(6)-C(5)	1.567(23)
C(8)-C(7)	1.540(20)	C(9)-C(7)	1.568(16)
C(12)-C(11)	1.121(29)	C(14)-C(13)	1.525(21)

Table A.4
Bond angles (deg.)

Cl(2)-Mo-Cl(1)	158.0(1)	O(1)-Mo-Cl(1)	81.0(3)
O(1)-Mo-Cl(2)	80.6(3)	O(2)-Mo-Cl(1)	83.0(3)
O(2)-Mo-Cl(2)	81.5(3)	O(2)-Mo-O(1)	78.6(3)
O(5)-Mo-Cl(1)	97.8(4)	O(5)-Mo-Cl(2)	98.8(4)
O(5)-Mo-O(1)	172.6(3)	O(5)-Mo-O(2)	94.0(4)
O(6)-Mo-Cl(1)	96.4(4)	O(6)-Mo-Cl(2)	93.9(4)
O(6)-Mo-O(1)	84.6(4)	O(6)-Mo-O(2)	163.1(3)
O(6)-Mo-O(5)	102.8(5)	O(3)-P-O(2)	113.3(5)
O(4)-P-O(2)	113.9(5)	O(4)-P-O(3)	103.8(6)
C(3)-P-O(2)	107.6	C(3)-P-O(3)	108.9(6)
C(3)-P-O(4)	109.2(5)	C(2)-O(1)-Mo	132.3(5)
P-O(2)-Mo	137.7(4)	C(11)-O(3)-P	118.5(9)
C(13)-O(4)-P	122.9(9)	C(6)-C(1)-C(2)	102.3(9)
C(7)-C(1)-C(2)	98.3(8)	C(7)-C(1)-C(6)	103.8(11)
C(10)-C(1)-C(2)	115.2(10)	C(10)-C(1)-C(6)	114.9(11)
C(10)-C(1)-C(7)	119.7(10)	C(1)-C(2)-O(1)	125.5(9)
C(3)-C(2)-O(1)	126.3(8)	C(3)-C(2)-C(1)	108.2(8)
C(2)-C(3)-P	111.6(7)	C(4)-C(3)-P	122.5(8)
C(4)-C(3)-C(2)	101.6(8)	C(5)-C(4)-C(3)	110.9(11)
C(7)-C(4)-C(3)	98.1(9)	C(7)-C(4)-C(5)	104.3(13)
C(6)-C(5)-C(4)	102.9(11)	C(5)-C(6)-C(1)	104.5(13)
C(4)-C(7)-C(1)	92.9(10)	C(8)-C(7)-C(1)	112.9(10)
C(8)-C(7)-C(4)	118.1(13)	C(9)-C(7)-C(1)	110.2(12)
C(9)-C(7)-C(4)	110.7(11)	C(9)-C(7)-C(8)	110.8(12)
C(12)-C(11)-O(3)	105.4(27)	C(14)-C(13)-O(4)	108.9(13)

Appendix 2

Experimental Techniques and Starting Materials

N.M.R. Spectroscopy

^{1}Hnmr spectra were recorded on a Bruker AM300 spectrometer (300 MHz) or on a Bruker WP80 (80 MHz). ^{13}C(75.4 MHz) and ^{31}P nmr (121.4 MHz) were recorded on the Bruker AM300 instrument operating in the pulse Fourier Transform mode. ^{31}P nmr specra were also recorded on a Varian CFT-20 at 32.2 MHz. The chemical shifts quoted in this thesis are relative to internal tetramethylsilane (TMS) for ^{1}H and ^{13}C spectra and external 85% D_3PO_4 for ^{31}P spectra.

Infrared Spectroscopy

Infrared spectra of organic compounds were recorded on Perkin Elmer 1420 (Dispersion), and Perkin Elmer 1710 (Fourier Transform) spectrometers as Nujol mulls for solids and thin films for liquids between NaCl plates. Spectra of complexes were recorded as Nujol mulls between CsI plates on a Perkin Elmer 1710 (dispersion infrared spectrometer).

Gas-Liquid Chromatography

The detection and quantitative determination of the various epoxides was effected using a Pye-Unicam PU4500 chromatograph using a column with 3% OV 101 packing. The injector and detector were held at 40°C above the column temperature, and detection was by flame ionization.

Identification of the epoxides and other organic compounds was assisted by Gas Chromatography - Mass Spectrometry. The capillary column packing was cross-linked methylsilicone on a Hewlett Packard 5890 instrument coupled to a Finnigan-MAT INCOS 50 quadripole mass spectrometer. An eight peak index of fragment ions from the sample was compared with the results obtained from the National Bureau of Standards by use of a Data General computer library back up facility. This substantiated the data obtained by the aforementioned techniques.

Mass Spectrometry

Spectra were recorded on a AEI MS902 high resolution mass spectrometer where samples were introduced *via* probe inlet for solids. for low resolution spectra the Finnigan-MAT mass spectrometer was used with the sample being introduced by direct insertion probe.

Microanalysis

Microanalyses were performed by the University of St Andrews microanalytical service.

Solvents

Tetrahydrofuran, light petroleum (40-60° boiling range), diethyl ether and toluene were dried by distillation over sodium benzophenone ketyl. Dichloromethane was dried by treatment with P_2O_5, decanted and distilled from CaH_2. All distillations were carried out under N_2 and all solvents were thoroughly degassed before use.

Vacuum Lines

The majority of the work previously described was carried out under nitrogen using standard Schlenk line and catheter techniques. The nitrogen was further purified by passing through a Cr^{2+} on silica column. The vacuum line used was a standard poly(tetrafluoroethylene) greaseless tap line with ball and socket compression joints.

Melting Points

Melting points were determined on a Gallenkamp melting point apparatus in air and are uncorrected.

Polarimetry

The optical activity of [(1R)-*endo*]-(+)-3-(diethoxyphosphinyl)camphor and (1R)-3-[(diethoxyphosphinyl)oxy]-1,7,7-trimethyl-bicyclo-[2.2.1]-2-heptene were measured on an Optical Activity AA-100 polarimeter using a 1 dm cell.

Starting Materials

Diethyl benzylphosphonate and diethyl methanephosphonate were obtained from Lancaster. Titanium tetrachloride, chloroacetyl chloride, and ethyl propanoate were obtained from BDH. Octacarbonyl dicobalt, molybdenum dioxide dichloride and molybdenum dioxide dibromide were obtained from Alfa. The sodium metal was obtained from Fluka. All other starting materials used were purchased from Aldrich and, unless otherwise specified, were used as obtained.

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