CHIRAL β-KETOPHOSPHONATE COMPLEXES IN THE EPOXIDATION OF ALKENES.

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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September 1993.

DECLARATION.

I, Russell Clarke, 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 or professional qualification.

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TO MY FAMILY.

Acknowledgements.

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Finally, I would like to thank my wife, Tricia, for her support over the past three years and for not complaining too much about living in what is probably the coldest house in Scotland.

List of abbreviations.

acac	acetylacetonate
bipy	2,2'-bipyridine
Bu	butyl
DMF	N,N-dimethyl formamide
Et	ethyl
$Fe(dmp)_3$	tris[1,3-bis(*p*-methoxyphenyl)-1,3-propanedionato]iron(III)
$[(Br_8TPP)Fe^{III}(Cl)]$	-[*meso*-tetrakis(2,6-dibromophenylporphinato)]iron(III) chloride
LDA	lithium diisopropylamine
Me	methyl
oxine	8-hydroxyquinoline
Ph	phenyl
Pr	propyl
salen	N,N-bis(salicylidene)ethylenediamino
t-BuOOH	*tert*-butyl hydroperoxide
(TDCPP)Cl	5,10,15,20-tetrakis(2',6'-dichlorophenyl)porphyrin
THF	tetrahydrofuran
TPP	*meso*-tetraphenylporphinato
Tritox	tri-*tert* - butylmethoxide

Summary.

From previous work carried out in this laboratory it has been shown that the transition metal complex dichloro{(1R-*endo*)-(+)-3-(diethoxyphosphoryl) camphor} dioxomolybdenum(VI) (1) displays high initial activity for the conversion of a range of alkenes to their respective epoxides. This is readily illustrated in the epoxidation of 1-methyl-1-cyclohexene where the conversion rate is approximately 80% in the first few minutes.

With this in mind a number of analogues of metal complex (1) have been synthesised, based around the chiral molecule camphor.which differ either in the nature of the chirality present in camphor, or in the nature of the alkyl groups present which are attached to the phosphorus atom. These alkyl groups range from ethyl and secondary butyl to phenyl and bi-napthyl.

It has been shown that these complexes are extremely active and in the case of limonene, selective, catalysts for the epoxidation of a range of different alkenes. In addition, it has been observed that in the presence of molecular sieves the reactivity and active lifetime of the catalyst is prolonged. The most startling effect is observed during the epoxidation of styrene. In the absence of molecular sieves 25% conversion to styrene oxide is observed in the first few minutes of the reaction when transition metal complex (1) is used as catalyst. However, over the next 2 hours this oxide subsequently degrades to a mixture of predominantly benzaldehyde with traces of phenylacetaldehyde. In the presence of sieves however, 97% conversion of styrene is observed in 24 hours with 94% selectivity to styrene oxide. This catalytic activity is heterogeneous in nature since the catalyst has been shown to bind to the sieves, most probably *via* the 'OH' groups at the surface of the sieves, and the asymmetric ligand is in turn cleaved from the metal.

In addition, it has been shown that in the presence of complex (1), there appears to be a selective ring opening reaction of limonene oxide, where, in the absence of sieves, the *cis* isomer of the epoxide hydrolyses to the diol more quickly than the *trans* isomer. The reason for this effect is most likely related to the steric crowding around the epoxide in each isomer, which can influence the ease of interaction between the metal centre in the catalyst and the oxide ring.

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Chapter 2.

Synthesis of asymmetric β-ketophosphonate ligands and complexation to transition metals.

CHAPTER ONE

EPOXIDATION AND THE USE OF TRANSITION METAL COMPLEXES AS CATALYSTS-

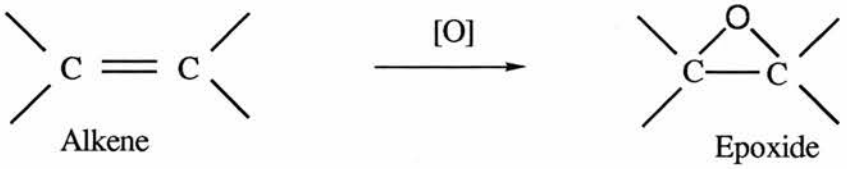
INTRODUCTION AND LITERATURE REVIEW.

1.1.1. Introduction.

The development of inexpensive systems for the direct epoxidation of alkenes is one of the most important themes for the industrial and academic fields of synthetic chemistry.[1] Epoxides are important intermediates for a variety of useful products, and the design of convenient catalytic systems using simple metal complexes with inexpensive oxygen donors such as H_2O_2, t-BuOOH and NaOCl as the oxygen source (which will now be known as the terminal oxidant) is of current interest.[2]

Homogeneous catalysts are widely used in many branches of chemistry and play a vital role in many living systems.[3] They have many 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 milder conditions than heterogeneous systems and in general display a much greater degree of selectivity. In today's fiercely economically orientated climate this is particularly important for the chemical industry, where the aim must be to keep the costs of producing and researching new and innovative materials to a minimum, but also to society itself where the conservation of energy and preservation of surroundings is becoming increasingly important.

During recent times interest in various transition-metal complexes for the epoxidation of alkenes (Equation 1.1) has been attributed to the need for functionalising lower alkenes formed as by-products in the manufacture of gasoline by 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.



Equation 1.1

Sheldon and Kochi[4] divided homogeneous metal catalysed oxidations into two types, which have been labelled homolytic and heterolytic.

In heterolytic oxidation catalysts the organic substrate or the oxygen containing reactant or both, are coordinated to the metal and so become activated. Normally 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. In this type of system free radicals are not intermediates and the metal remains closely involved with the substrate/reactant system during most or all of the reactions involved.

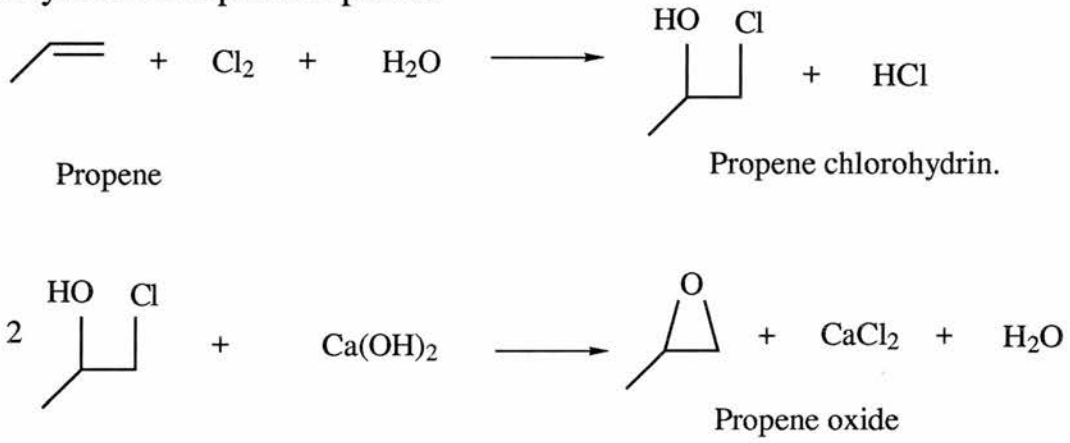
Homolytic systems involve free radicals as intermediates and in the catalytic cycle, the metal is involved in a series of one electron reduction or oxidation steps. Some typical homogeneous catalysts involving the homolytic system are the soluble transition metal salts such as napthenates of Co, Mn, and Cu.

It is generally found that the distinction between homolytic and heterolytic systems is not always clear, and this is especially true with metals which are potentially able to participate in both types of catalysis.

The most important epoxide commercially is ethene oxide (oxirane); of which 2.4 million tonnes was produced in the United States alone in 1988.[5] Of this nearly 60% is hydrolysed to ethylene glycol, a high proportion of which is used as the basis for antifreeze. Figures for the production of oxirane in Europe are over 1 million tonnes.

Propene oxide, the production of which in the United States is 1.4 million tonnes[5] and in Europe is over 0.8 million tonnes, was originally synthesised using the chlorohydrin route (Equation 1.2) which itself was developed for oxirane production.

There are several disadvatages with this process, one of which is the fact that chlorine is a relatively expensive reactant, which does not appear in the product so the reaction can be considered wasteful. In addition, the corrosive nature of chlorine also considerably shortens the lifespan of many chemical process plants.



Equation 1.2

A relatively new process, first used in 1969[7] is based upon the fact that in the presence of homogeneous catalysts, especially molybdenum complexes, organic hydroperoxides react with alkenes to give high yields of epoxides. This is now the most important process for the manufacture of propene oxide. During this process propene is reacted with tert-butyl hydroperoxide (t-BuOOH) 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.[8]

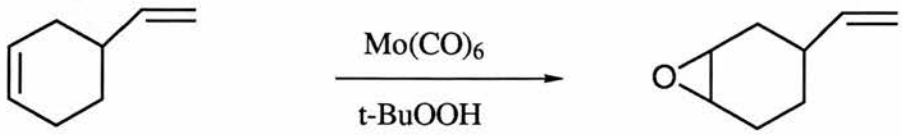
1.1.2. The Catalyst.

The properties of a metal complex which make it an effective catalyst for the epoxidation of an alkene by a hydroperoxide have been heavily investigated.[1,9] Normally the metal in such a complex has a high charge, a relatively small size and 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. It is generally agreed that the most important duty of the catalyst is to withdraw electrons from the peroxidic oxygens, hence the complex must be a good Lewis acid to act as an active catalyst.

The complex must not take part in one electron transfer reactions under strongly oxidising conditions, and 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 following order CrO_3, $MoO_3 >> WO_3 > TiO_2$, V_2O_5.

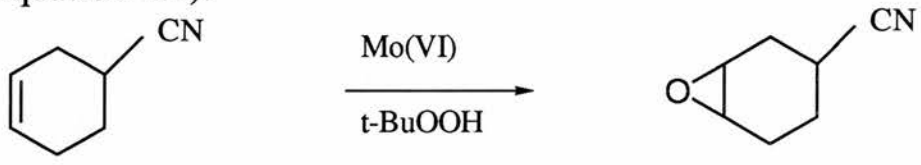
1.1.3. The Substrate Alkene.

The reactivity of double bonds is enhanced by increasing alkyl substitution following the order of tetrasubstituted > trisubstituted > disubstituted > monosubstituted. This difference in reactivity is readily shown by the regiospecific monoepoxidation of non-conjugated dienes. (Equation 1.3). Therefore by increasing the electron density at the double bond, the reactivity of the alkene is increased and this is an indication that the mechanism of epoxidation involves a nucleophilic attack of the alkene on one of the oxygens of the peroxide.



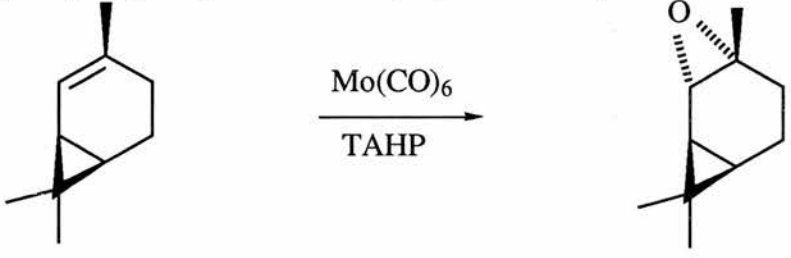
Equation 1.3

Electron withdrawing groups on the alkene seriously impede the epoxidation, for example acrylic esters are not reactive. However it is important to note that epoxidation is not seriously retarted when the electron withdrawing group is suffieciently removed from the double bond. For example, 4-cyanohexene gave the epoxide in 88% yield.[10] (Equation 1.4).



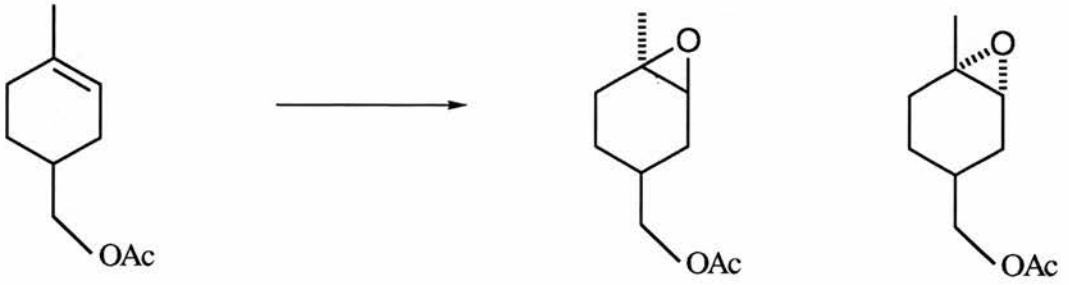
Equation 1.4

The epoxidation of alkenes by heterolytic processes is completely stereoselective and *cis* - alkenes are exclusively transformed into *cis* - epoxides and *trans* - alkenes into *trans* - epoxides. In these cases oxygen addition to the double bond preferentially occurs from the less shielded faces of the substrate, e.g in the selective epoxidation of terpenes by tert-pentyl hydroperoxide.[10] (Equation 1.5)



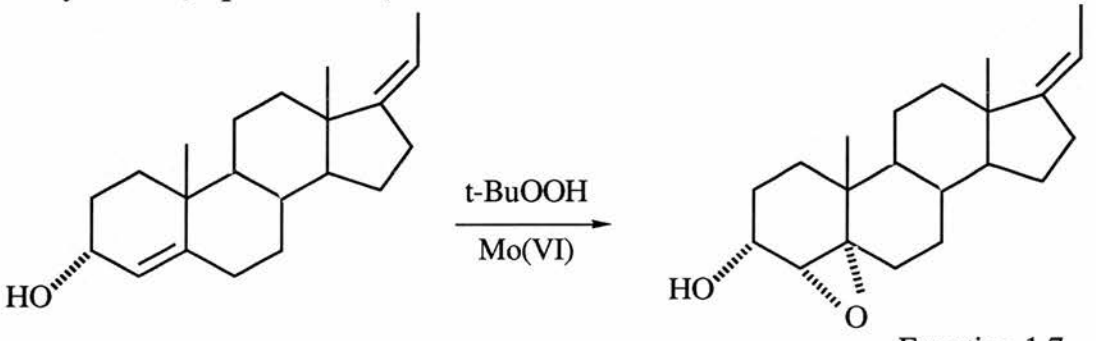
Equation 1.5

Functional groups present on the substrate which are capable of interacting with the metal can direct the stereoselectivity of the epoxidation as shown by a comparison of the reactivity of TAHP/$Mo(CO)_6$ and peroxybenzoic acid.[11] (Equation 1.6).



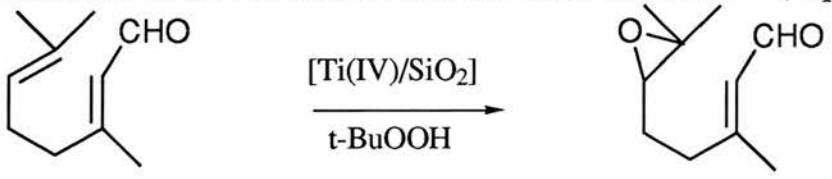
TAHP/$Mo(CO)_6$	100%	0%
PBA	50%	50%

Breslow and co - workers[12,13] have researched the template - directed remote epoxidation of double bonds which make use of the coordinating ability of the hydroxy group to the metal complex catalyst in this type of system. (Equation 1.7)



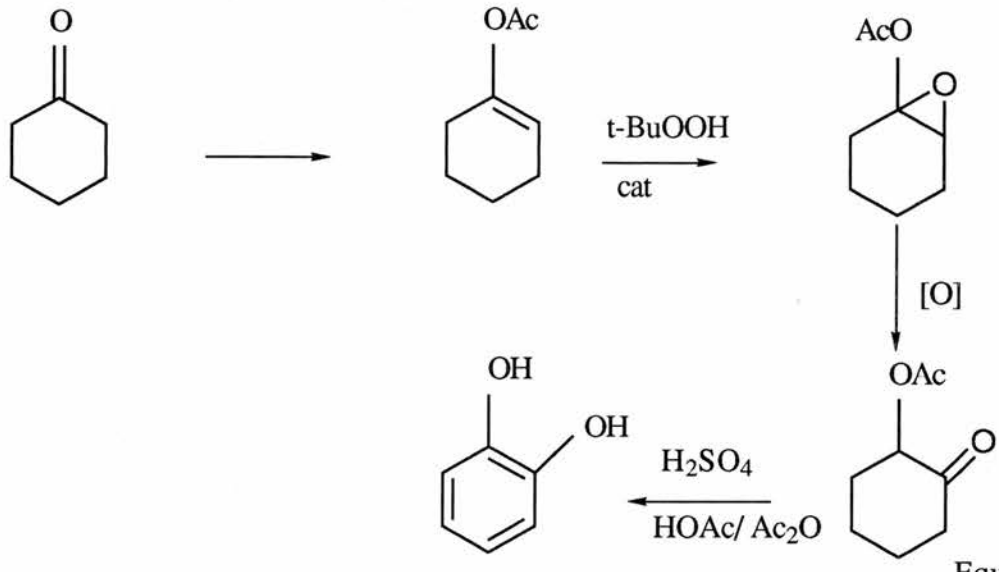
Equation 1.7

It can be seen therefore that catalytic systems offer advantages in terms of selectivity over the peracid technique, but they can also be used in the epoxidation of acid sensitive alkenes such as citral.[14] (Equation 1.8)



Equation 1.8

Steroidal enol acetates were similarly epoxidised,[15] and the metal-cataysed epoxidation of 1-acetoxycyclohexene is a key step in the synthesis of catechol from cyclohexanone. (Equation 1.9)



Equation 1.9

1.1.4. Effect of Solvent and Co-product Alcohol.

Anhydrous conditions are required for the d^0 metal catalysed epoxidations of alkenes due to the inhibitory effect of water. This effect is more pronounced for V and Ti than for Mo and W.

In addition aromatic (eg benzene or toluene) or chlorinated solvents (eg CH_2Cl_2 or $C_2H_4Cl_2$) are required for good catalyst activity, since alcohol or basic solvents such as DMF, THF or dioxane strongly retard or completely inhibit the oxidation. The co-product alcohol derived from the hydroperoxide also produces an inhibitory effect[8] in the order W < Mo < Ti < V and competes with the alkyl peroxide by forming metal alkoxides so preventing the formation of metal-alkyl peroxides.

1.1.5. Ligand Effect.

The Lewis acidity of the catalyst is influenced by the nature of the coordinating ligands. As a rule a ligand effect may only be observable in the early stages of the reaction due to the rapid replacement of the original ligands during the reaction.

The rates of molybdenum catalysed epoxidations of alkenes vary only in the initial stages of the reaction,[16] which suggests that all of the additives were subsequently changed to the same catalytic species. This was confirmed by the isolation of the catalysts at the end of the reaction as Mo(VI) - 1,2 - diolate complexes.[16] This seems to suggest that it is adventitious water present during the reaction which is responsible for the presence of this species.

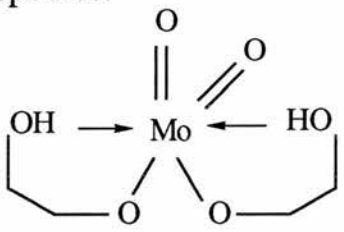


Figure 1.1

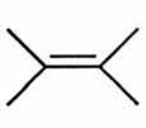
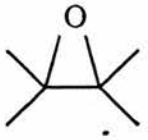
Independent experiments showed that the *cis* - dioxomolybdenum(VI) diolates were formed in situ during molybdenum - catalysed epoxidations via reaction of the catalyst with the epoxide in the presence of the hydroperoxide. The composition of the catalyst is therefore determined by the structure of the alkene being epoxidised. However, 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. In fact, $MoO_2(acac)_2$ generally showed a higher initial activity which decreased with time due to the formation of the less active 1,2 - diol complex.[16]

From work carried out on the effect of different ligands on molybdenum complex catalysed epoxidations[17] 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, whereas catalysts with very loosely bound ligands, such as $MoO_2(acac)_2$ were active but less selective than those ligands of intermediate stability, such as $MoO_2(oxine)_2$. It was suggested that the latter formed a complex with the hydroperoxide by opening only one of the bonds of the chelating ligand to molybdenum. Therefore in summary, for a catalyst to be active and selective, it should contain molybdenum - ligand bonds of intermediate strength, or it should have one strong and one weak bond for a bidentate ligand.

1.1.6. Mechanistic Considerations for d^0 Systems.

Generally it is thought that the most important step in the epoxidation reaction is the non - dissociative coordination of the hydroperoxide. According to Sharpless,[18] in such a complex the hydroperoxide is activated by this coordination because the metal centre reduces the electron density at the peroxide oxygens hence rendering them more susceptible to nucleophilic attack by the alkene. (Equations 1.10 and 1.11).

1.10 $M^{n+} + RO_2H \underset{-K_c}{\overset{K_c}{\rightleftharpoons}} [M^{n+}RO_2H]$

1.11 $[M^{n+}RO_2H] +$  $\xrightarrow{K_e}$  $+ ROH + M^{n+}$

Metal catalysed homolytic decomposition of the peroxide could also occur by the following mechanism :-

1.12 $[M^{n+}RO_2H] \xrightarrow{K_d} M^{(n-1)+} + RO_2^{\cdot} + H^+$

1.13 $M^{(n-1)+} + RO_2H \xrightarrow{Fast} M^{n+} + RO^{\cdot} + OH^-$

The relative rates of the homolytic or heterolytic pathways determine the selectivity to the epoxide, and these competing processes have been thoroughly investigated.[16,19,20] If there is no radical - induced chain decomposition of the hydroperoxide and small amounts of epoxides formed are neglected, the selectivity is given by equation 1.14.

$$\text{Epoxide Selectivity} = \frac{K_e[\text{alkene}]}{K_d + K_e[\text{alkene}]} \times 100\%$$

Equation 1.14

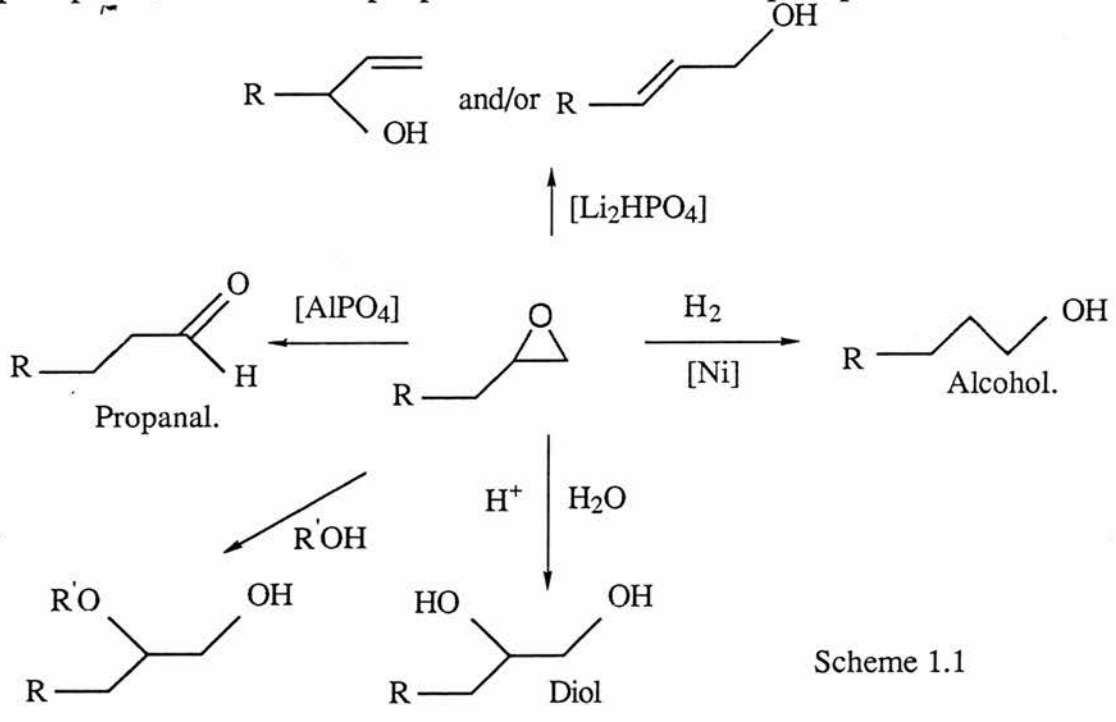
Kd and Ke are determined by the oxidation potential of the catalyst and it's Lewis-acidity respectively. In most cases the ease with which transition metal complexes catalyse the decomposition of hydroperoxides is related to their redox potentials. Hydroperoxides are strong oxidants but weak reducing agents so reaction 1.12 is the slower rate determining step and occurs most easily with strong oxidants such as Co(III) and Mn(III) which have redox potentials to the divalent ion of 1.82v and 1.51v respectively. This therefore favours the homolytic decomposition route and gives rise to poor epoxide selectivity.

However, very weak oxidants such as Mo(VI), W(VI) and Ti(IV) with one electron redox potentials of ~0.2v, -0.3v and -0.37v respectively are poor catalysts for the homolytic hydroperoxide decomposition and favour reaction 1.11.

Since V(V) is not a weak oxidant, vanadium catalysts generally give lower epoxide selectivities compared with molybdenum catalysts.[16]

1.1.7. Uses of Epoxides.

Epoxides are extremely useful intermediates due to their synthetic utility, since they can be converted to a variety of products.[1] A demonstration of their utility is shown in Scheme 1.1, where a number of typical epoxide conversions are illustrated. An epoxide can be hydrolysed to a diol in the presence of dilute acid solution, or to an alcohol by reduction with Raney nickel. In addition it has been shown that propene oxide can be rearranged to allyl alcohol over basic lithium phosphate, [21,22] and to propanal over aluminium phosphate.[22]



Scheme 1.1

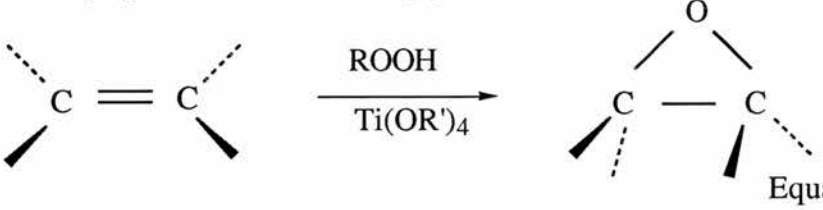
1.2 Transition Metal Mediated Epoxidation Review.

In recent times epoxidation catalysis by transition metal complexes has been the subject of a tremendous amount of both academic and industrial research,[23] and so it is for this reason that the following section is dedicated to an overview of the differing properties shown by the transition metals in a variety of complexes synthesised for the aim of carrying out epoxidation catalysis.

1.2.1 Group (IV) Transition metals.

1.2.1.1. Titanium.

The use of titanium (IV) as a catalyst for epoxidation is not more than 20 years old, although the reaction of titanium (IV) with the oxidation reagent, hydrogen peroxide, has been known for more than 100 years.[24]
Titanium (IV) catalysts, as with other well known epoxidation catalysts eg W(VI), V(V), are characterised as Lewis acids in their highest oxidation state ie d^0, and have a low redox potential,[25,26] as well as being labile with regard to ligand substitution.[27-29]
Titanium (IV) alkoxides catalyse the epoxidation of a variety of alkenes with an alkyl peroxide as the oxygen donor.[25,26, 30-33]



Equation 1.15.

However by - products formed by the addition of peroxide radicals to the substrate are often observed.[31]

By using a titanium (IV) - silicon dioxide catalyst, prepared by impregnating silica with $TiCl_4$, followed by calcination, these problems can be overcome. The combination of titanium (IV) with silicon dioxide appears to give the necessary stereochemical and electronic environment for co - ordination of the hydroperoxide and subsequent oxygen transfer.[31, 32]

The structure of the active site has been suggested to be that shown in figure (1.2).[26,31,32]

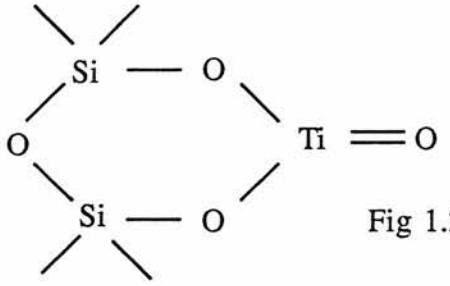


Fig 1.2.

The function of the silicate ligands is to increase the Lewis acidity of titanium (IV).

Jørgensen has used results from other d^0 transition - metal - catalysed epoxidations to predict a reaction pathway.[34] In this pathway for titanium (IV) alkoxides the first step is an interaction with the peroxide to produce a peroxo - metal intermediate. (Equation 1.16).

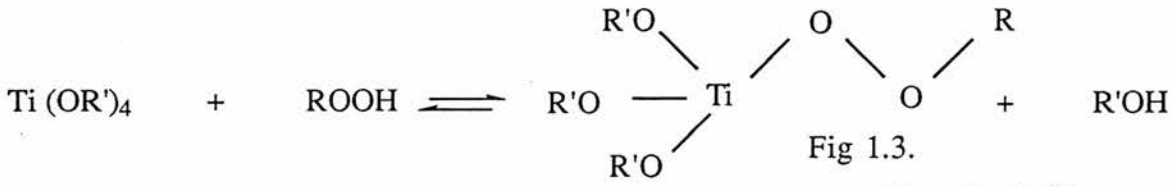


Fig 1.3.

Equation 1.16

Alternatively the titanyl complex may form via the following scheme :-

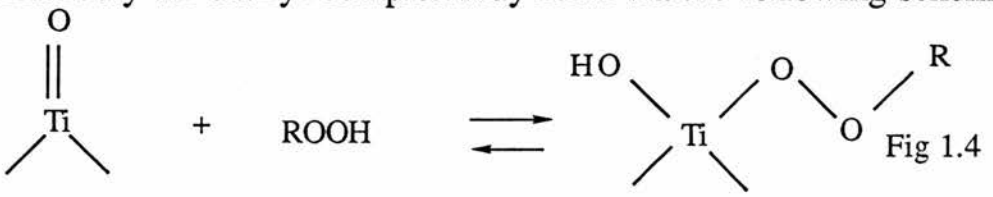


Fig 1.4

Equation 1.17

The exact structures of Fig (1.3) and Fig (1.4) are not known, but from epoxidations using vanadium and molybdenum where ^{18}O studies were carried out,[34] one might expect that the alkyl peroxide would behave in a similar fashion with titanium (IV). In (1.3) and (1.4) the binding of the alkyl or hydrogen peroxide to titanium (IV) takes place via the terminal oxygen, but in addition the other oxygen may also take part in coordination to titanium leading to a bidentate coordinated titanium peroxide. Fig (1.5).

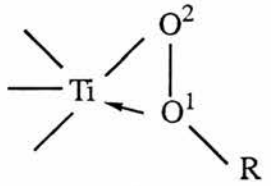


Fig 1.5.

This coordination leads to an activation of the peroxide for oxygen transfer.

Detailed *ab initio* calculations have been performed for the oxygen transfer from LiOOH, used as a model for Fig (1.5), to ethene. It has been shown from frontier orbital theory,[35-38] that the frontier orbitals of Fig (1.5) lead to the following interaction possibilities with an alkene,[35-39]

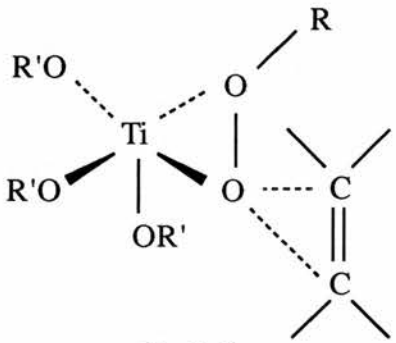


Fig 1.6

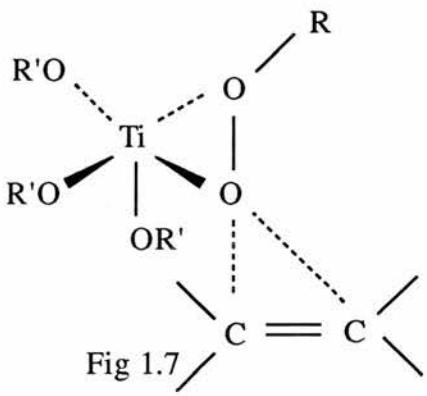
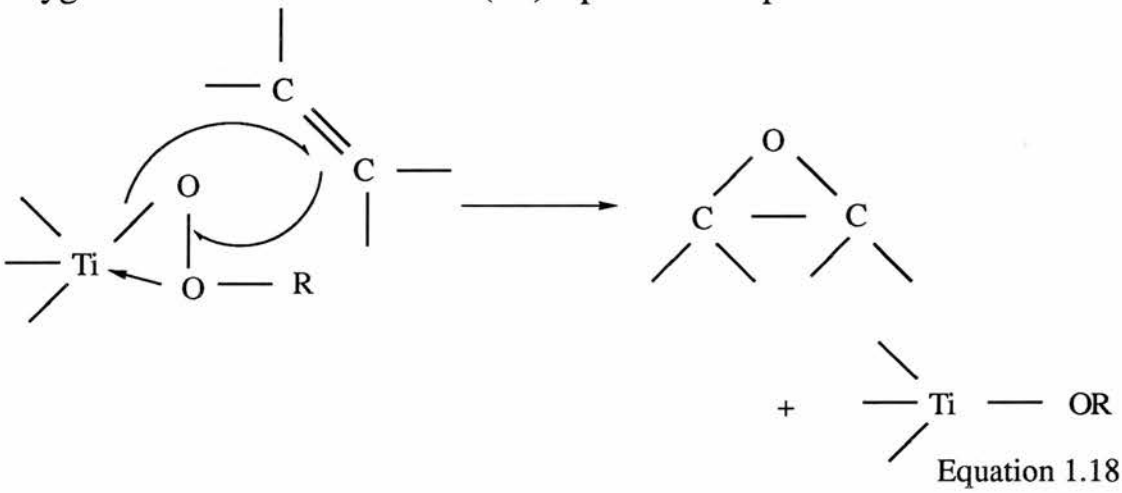


Fig 1.7

where the orientation of the alkene in Fig (1.6) corresponds to a spiro orientation relative to the titanium - peroxide plane as opposed to the planar orientation shown in Fig (1.7).

Theoretical calculations seem to support the following mechanism for oxygen transfer from titanium (IV) - peroxo complexes to alkenes :-



Equation 1.18

Other catalyst systems such as titanium dioxide,[31] oxotitanium diacetylacetonate,[31] and oxotitaniumporphyrin,[40] have been used with TBHP as the oxygen donor, but have been found less reactive than those of the silicon dioxide supported derivatives.[30-32] For example, when oxotitanium porphyrin [Fig (1.8)] was used as a catalyst the peroxotitanium porphyrin [Fig (1.9)] was formed during the reaction,[40,41] but was found to be unreactive toward alkenes.[42]

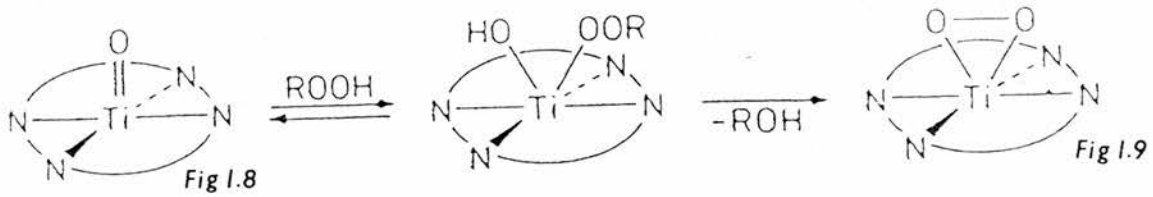


Fig 1.8 Fig 1.9

Equation 1.19

It is thought that the reason for this inactivity might be that it is not possible for the alkene to interact with one of the peroxygens because of repulsion between the porphyrin ring and the alkene.

The epoxidation of allylic alcohols with TBHP using titanium (IV) tetraisopropoxide gives syn - epoxy alcohols whereas oxidation of the same allylic alcohols with MCPBA leads largely to the anti - epoxy alcohols.

The best known epoxidation reaction of group (IV) transition metals is Sharpless epoxidation. Due to its significance, this reaction will be described in greater detail later in this chapter.

1.2.1.2. Zirconium and Hafnium.

As one would imagine a great deal of the work done in the area of zirconium (IV) and hafnium (IV) catalysed epoxidation reactions is similar to that performed with titanium (IV). In general it is found that when TBHP is used as the oxygen donor, lower yields of epoxide are detected than for titanium complexes.

Both zirconium and hafnium complexes are able to use molecular oxygen as the oxygen donor for epoxidation.[43,44] For example treatment of $(tritox)_2M(Me)$ (allylic alcohol) (M = Zr, Hf),(Fig 1.10) with molecular oxygen leads to epoxidation.[44]

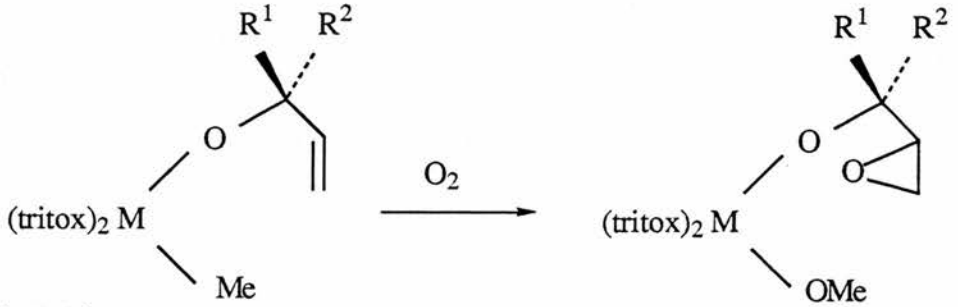


Fig 1.10 M = Zr, Hf

Equation 1.20

It is possible that the molecular oxygen is activated by the metal and inserted into the transition metal - methyl bond giving a bidentate coordinated methyl peroxide. (Fig 1.11)

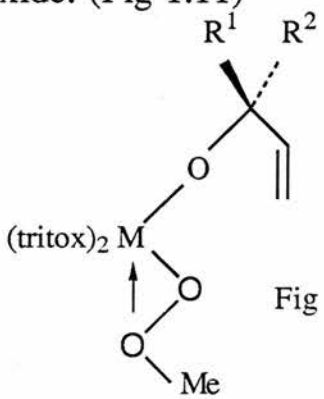


Fig 1.11.

This complex can then epoxidise the attached alkene in similar fashion to eg TBHP coordinated to a d^0 transition metal.[44] The connection between molecular oxygen activation and insertion into the metal - methyl bond in Fig (1.10) and the epoxidation was established by the observation that $(tritox)_2ZrCl(OCMe_2CH{=}CH_2)$ reacts with sodium tert - butyl peroxide, which prompts the epoxidation of the attached alkene.[44]

1.2.2. Group (V) Transition Metals.

1.2.2.1. Vanadium.

Several oxo - vanadium - ligand complexes have been studied for alkene epoxidation.[25,26,30-33,45-50]

Vanadium (V) had been found to be a relatively poor catalyst for alkene epoxidation compared with molybdenum catalysts,[25,26,32,33,47] although with allylic alcohols vanadium (V) gives higher rates and better yields than molybdenum (VI).[51]

The catalytic activity of heterogeneous oxovanadium catalysts for alkene epoxidation using TBHP as the oxygen donor is better than that of the homogeneous complexes. eg $VO(acac)_2$, a homogeneous catalyst gives yields of cyclohexene oxide in the range of 10 - 12%, whereas a vanadyl ion, bound to a polystyrene support through acetylacetonate or ethylenediamine ligands, gives yields of up to 26%.[52]

However, with the vanadyl ion immobilized on a sulphonate ion - exchange resin, yields of up to 74% of cyclohexene oxide were obtained.[53] By using ^{18}O - labelling studies, it is thought that a vanadium(V) - alkylperoxo complex is the reactive species,[34,54] when TBHP is used as the oxygen donor with the alkyl peroxide ligand coordinated in a mono Fig (1.12) or in a bidentate manner Fig (1.13).[31-33,34,35,46-50,54,55,56]

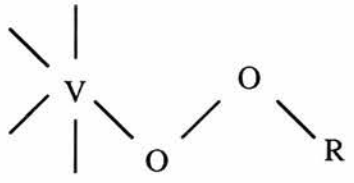


Fig 1.12

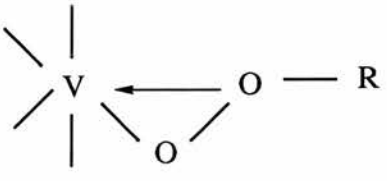
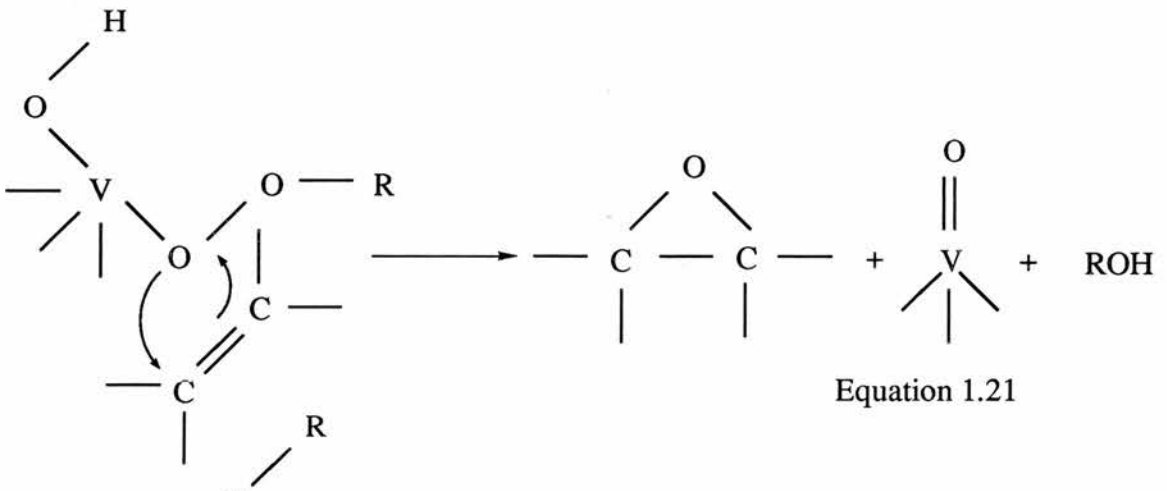
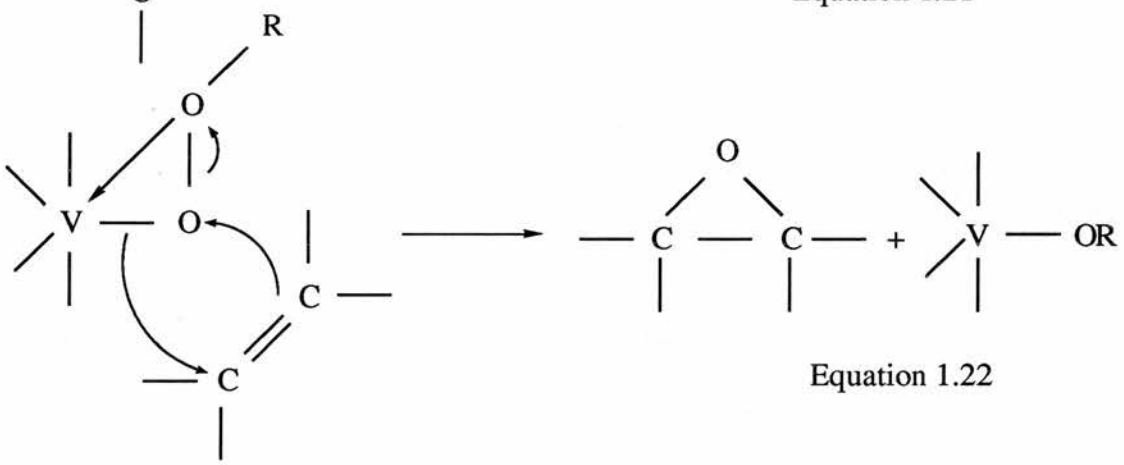


Fig 1.13

The electronic structure of Fig (1.13) has been investigated by using extended-Huckel calculations,[35] which suggest the following mechanisms:-



Equation 1.21



Equation 1.22

However, given the acceptor d orbitals at vanadium, a coordination of donors as, eg., of an alkene to vanadium might be possible, although this interaction will be very weak due to the absence of back bonding. Kinetic studies have shown that the alkene coordinates to vanadium prior to the decomposition of the vanadium - alkene complex in the rate - determining step, which may suggest the following mechanism :-

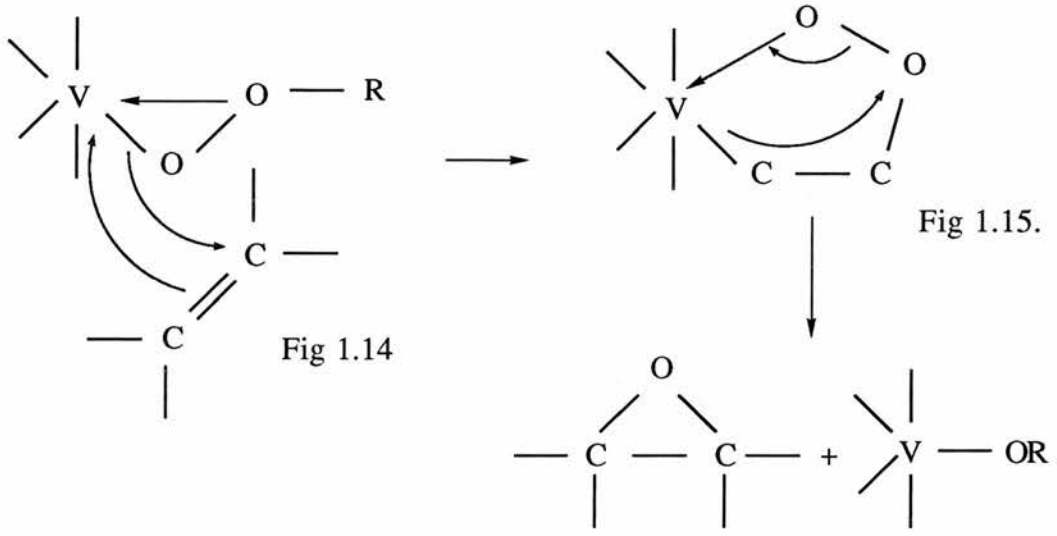
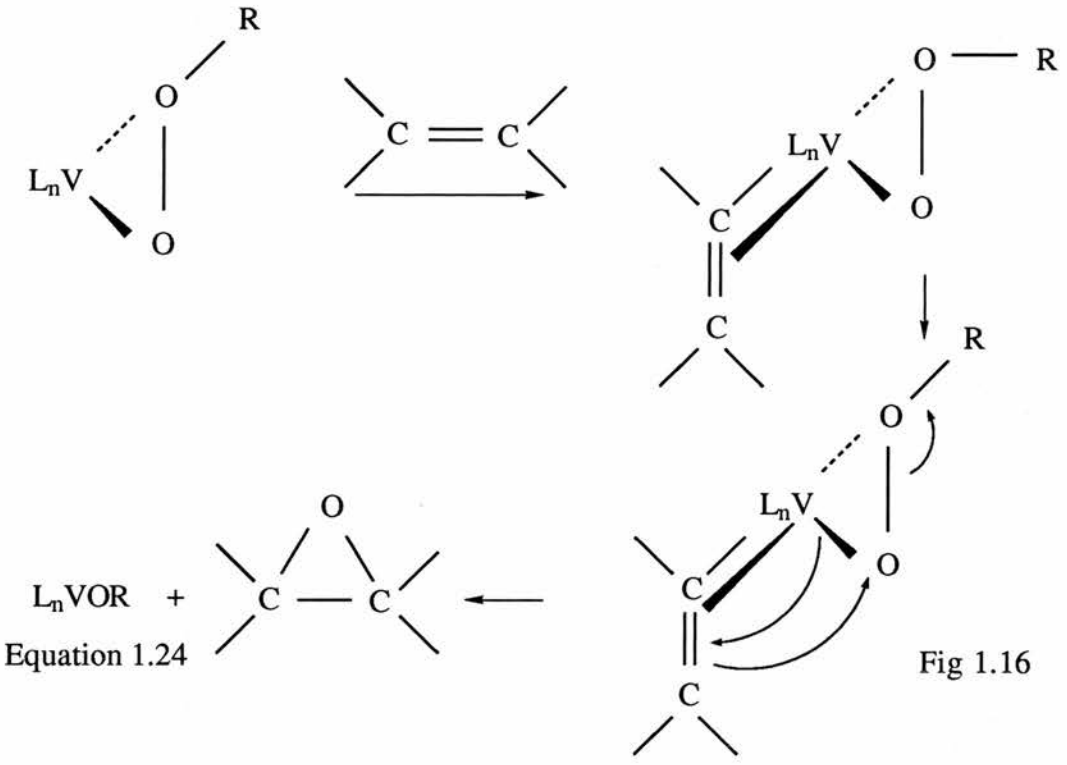


Fig 1.14

Fig 1.15.

Equation 1.23

During this reaction a five membered peroxometallacyclic intermediate is formed Fig (1.15).[48,49,54,56,57] In this mechanism the first step is coordination of the alkene to vanadium Fig (1.14), followed by insertion of the coordinated alkene into the vanadium - peroxygen bond giving Fig (1.15), from which the epoxide is formed by decomposition. No examples of the peroxometallacycle are known for vanadium although this type of species has been characterised from reactions of platinum - and rhodium - peroxo complexes with cyano - substituted alkenes.[58,59] The insertion step above should be well suited for electron - deficient alkenes, but these have not been shown to react in transition - metal catalysed epoxidations.[58] Therefore, to account for the kinetic results which indicate a coordination of the alkene to vanadium, Jørgensen has suggested a new mechanism which produces epoxides in a similar way as shown in equations 1.22 and 1.23.[60]



Equation 1.24

Fig 1.16

The first step of this reaction is the coordination of the alkene to vanadium followed by a slipping motion of the alkene toward the peroxygen giving intermediate Fig 1.16 followed by the epoxide.

A number of vanadium - peroxo complexes are known.[61,62,63] eg

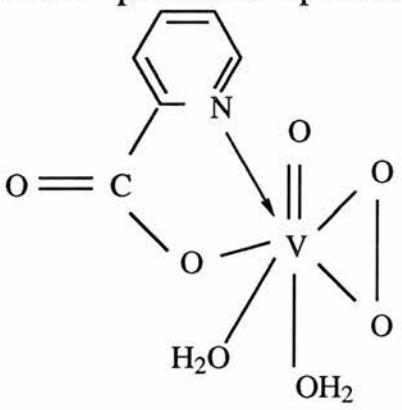


Fig 1.17.

As with titanium epoxidations, molecular oxygen can be applied as the oxygen source with vanadium catalysed epoxidations,[64-67] eg $CpV(CO)_4$, $VO(acac)_2$ and V_2O_5 have been shown to be able to catalyse the stereoselective oxidation of cyclohexene to cis - 1,2 - epoxycyclohexan - 3 - ol (17) as the major product.[65,66]

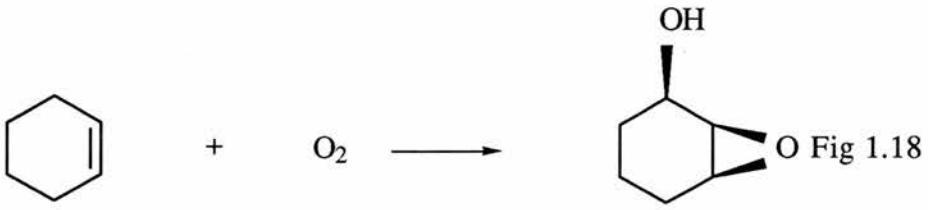


Fig 1.18

Equation 1.25.

As with titanium, vanadium has been found to be a very efficient catalyst for the epoxidation of allylic alcohols[33,51,68,69,70-77] and these reactions will be discussed more fully later in this chapter.

1.2.2.2. Nb and Ta.

Although the alkoxides of both Nb(V) and Ta(V) catalyse the epoxidation of cyclohexene with TBHP as the oxidant, the reaction times are slow and the yield is relatively low.[31] However, free and polymer - supported Cp_2NbCl_2 show low and no catalytic activity.[78,79]

In contrast the tri - μ - oxo dimer of $Nb^{v}(p$ - CH_3 - TPP) Fig (1.19) epoxidises alkenes under photochemical conditions with molecular oxygen as the oxidant.[80]

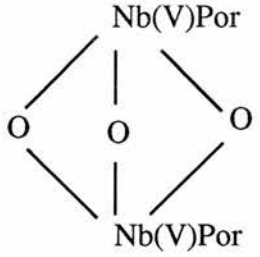


Fig 1.19.

1.2.3 Group VI Transition Metals.

1.2.3.1 Cr.

Surprisingly it has been found that although chromium(VI) is a strong Lewis acid and therefore should be expected to be a good catalyst, it is relatively poor for the epoxidation of cyclohexene using TBHP as the oxidant.[31] This is thought to be due to the fact that as a strong oxidant, Cr(VI) promotes the decomposition of TBHP.[31] Chromium oxide complexes can oxidise allylic alcohols to various epoxy derivatives,[81,82] but epoxides are not found to be the major products from unfunctionalised alkenes.[83-86] Chromyl chloride reacts with most alkenes, but complex mixtures of products are found in many instances and further studies have shown that although epoxides are formed in large amounts, they undergo further oxidation.[87-90] Chromyl nitrate has been found to be the best epoxidation reagent among chromyl complexes and epoxidises a range of alkenes.[91] ESR studies of chromyl nitrate in solution indicated that chromium(V) is formed in significant amounts by a one - electron oxidation of the solvent.[91] Therefore the epoxidation of alkenes by chromyl nitrate has been described as involving a chromium(V) species [Fig (1.20)]as opposed to chromium(VI).[91]

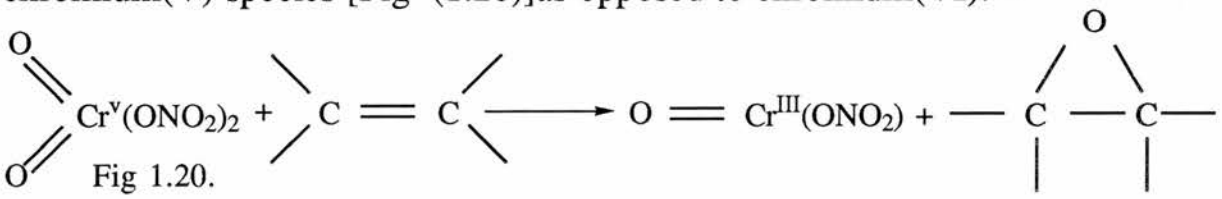
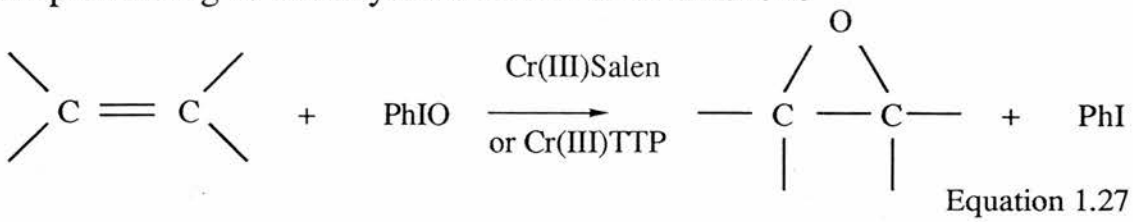


Fig 1.20.

Equation 1.26.

Oxochromium(V) complexes formed from chromium(III) - salen or - TPP complexes with iodosylbenzene have also been found to promote the conversion of an alkene to its epoxide.[92-94]

During this reaction the oxygen atom is successfully transferred from the terminal oxidant eg iodosylbenzene, to the chromium(III) - ligand complex acting as a catalyst and hence to the alkene ie



Equation 1.27

The catalytic cycle of the chromium(III) - catalysed epoxidation of alkenes with the oxochromium(V), Fig (1.21), as the intermediate is as follows :-

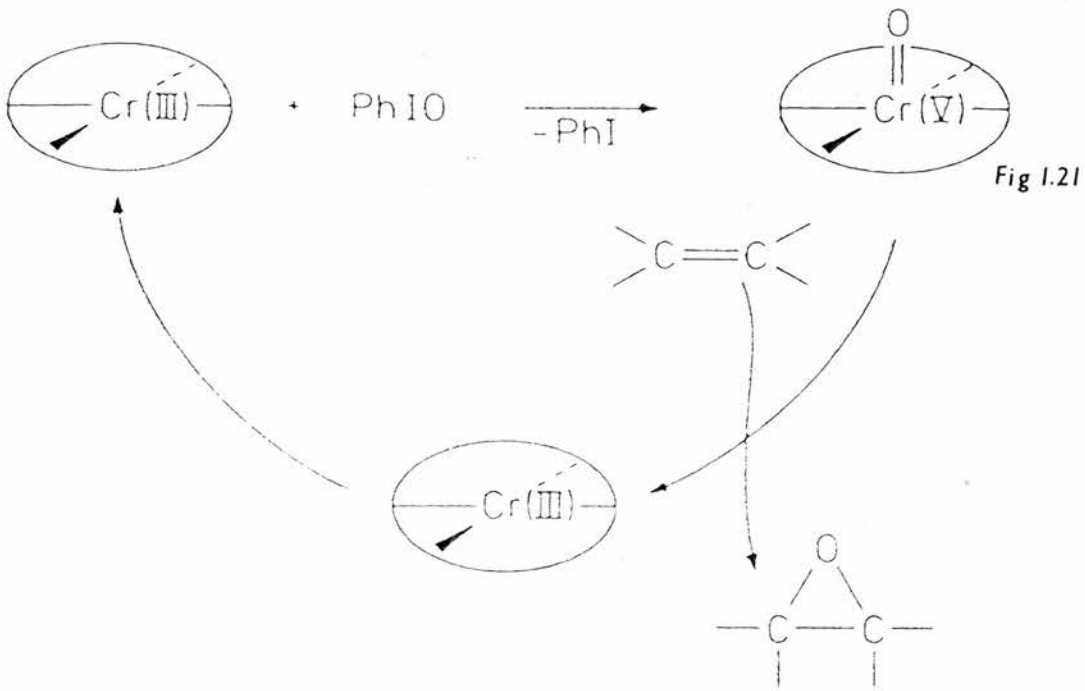
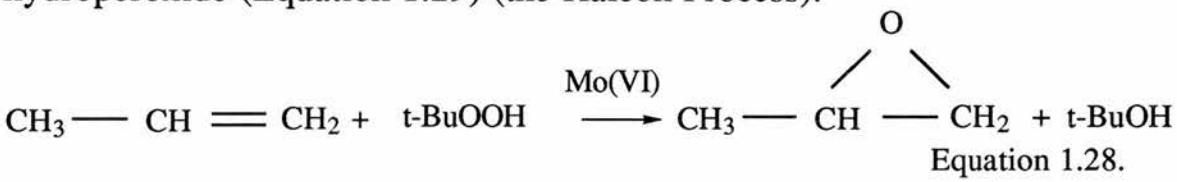


Fig 1.21

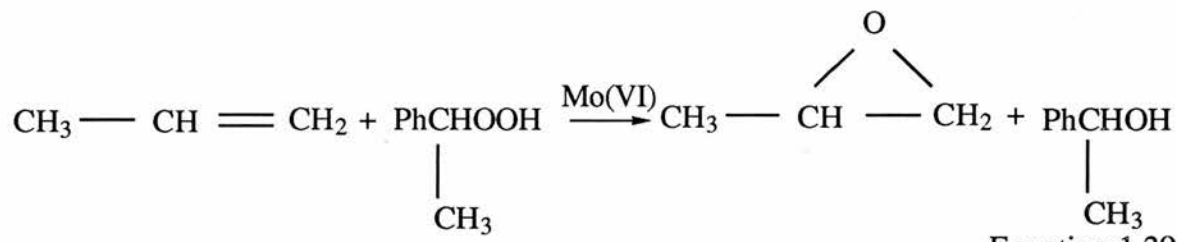
1.2.3.2 Mo.

By using alkyl hydroperoxides as the oxidant molybdenum(VI) complexes are probably the best catalysts for epoxidations and molybdenum - catalysed epoxidations have been studied in great detail.[25,26,30-33,50,95]

This type of catalyst is also widely used in industry where for example propene oxide is produced in large scale by molybdenum catalysed epoxidation of propene with TBHP (Equation 1.28) or 1 - phenylethyl hydroperoxide (Equation 1.29) (the Halcon Process).[96]



Equation 1.28.



Equation 1.29.

An advantageous feature about these reactions is that in (Equation 1.28) the tert - butyl alcohol co - product can be recycled or converted to methyl tert - butyl ether, a high - octane component for gasoline,[26] and in (Equation 1.29) the by product 1 - phenylethanol, can be dehydrated to styrene or recycled.[26]

A variety of molybdenum complexes ranging from monomeric compounds[97] such as $Mo(CO)_6$ to clusters such as $[MoO(O_2CR)_6(H_2O)_3]^{n+}$,have been synthesised and tested for catalytic activity.[98-106] It has been shown that the catalytic properties of molybdenum complexes depend to a certain extent upon the nature of the ligands attached to the metal,[32,106] eg previous work has shown that a higher rate of epoxidation can be achieved by using relatively stable molybdenum complexes,[106] eg $MoO_2(oxine)_2$.

In general molybdenum complexes can be used to catalyse the epoxidation of a wide range of alkenes from ethene to large molecules of biological interest.

Some molybdenum(V) complexes have also shown catalytic epoxidation activity with alkyl peroxides as the oxygen source, but the conversion to epoxide is often lower compared with Mo(VI) complexes such as $MoO_2(acac)_2$.[107-110]

A number of heterogeous molybdenum catalysts have been prepared and the yields of epoxide production varies considerably from one catalyst to another, but eg $MoHY_n$ zeolites with different Mo loadings give up to 100% selective epoxidation.[111]

It is interesting to note that epoxidations catalysed by $MoO_2(acac)_2$ proceed approximately 10^2 times more rapidly than the corresponding vanadium complexes,[47] and mechanistic investigations with peroxides as the oxidant have shown that the mechanism is similar to those discussed previously for both titanium(IV) and vanadium(V) catalysed epoxidations.

Similarly as with titanium(IV) and vanadium(V), molybdenum(VI) is also an effective catalyst for the epoxidation of allylic alcohols,[26,33] and these reactions will be discussed in more detail later in this chapter.

A number of monoperoxo - molybdenum complexes, $MoO(O_2)L_n$, [Fig (1.22)] and diperoxo - molybdenum complexes, $MoO(O_2)_2L_1L_2$, [Fig (1.23) have been synthesised and found to epoxidise many types of alkenes.[112]

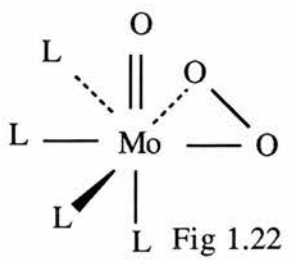


Fig 1.22

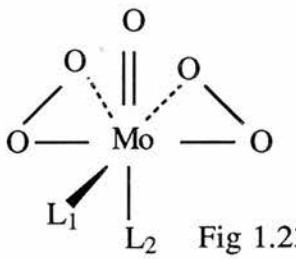


Fig 1.23

The diperoxo - molybdenum complexes, [Fig (1.23)] have been prepared with a great variety of basic ligands[112] from addition of the ligands to a solution of molybdenum trioxide in hydrogen peroxide.[113]
One example of this type of complex is $MoO(O_2)_2HMPA$ which along with other diperoxo - molybdenum - ligand complexes has been found stoichiometrically to oxidise alkenes to epoxides in good yields at room temperature in aprotic solvents.[113,114,115-119] In addition the epoxidation of alkenes is stereoselective ie *cis* - alkenes are oxidised to *cis* - epoxides and *trans* - alkenes to *trans* - epoxides,[112,115] and the coordination of a chiral bidentate ligand such as (S) - N,N - dimethylacetamide to $MoO(O_2)_2$ gives a complex which can induce asymmetric epoxidation of low - molecular weight alkenes in up to 35% ee.[120,121]

1.2.3.3. Tungsten.

Although tungsten(VI) complexes are probably the best transition - metal catalysts for epoxidation reactions of alkenes with hydrogen peroxide, they do not have the same synthetic utility as the alkyl hydroperoxide system.[25,26,122] One major drawback of course in using hydrogen peroxide as the oxidant is the production of water which can retard the reaction eg epoxides have been observed to hydrolyse in the presence of water to the corresponding glycols.
The reactive intermediate in the tungsten hydrogen - peroxide catalysed epoxidation reactions is most likely a mono - or bidentate peroxide - tungsten complex which achieves the oxygen transfer step in a similar way to the other aforementioned transtion metal d^0 - peroxide complexes.

Experimental results indicate that the mechanism for the oxygen - transfer step from the tungsten - peroxo complex to the alkene involves attack on one of the peroxygens of the complex,[123] ie one similar to that suggested for the molybdenum - peroxo system.[119,36]

The metallacycle has also been suggested in relation to oxygen transfer from some tungsten complexes, and the first example of a transition metal complex containing both a terminal oxo ligand and an alkene, [Fig (1.24)] has been characterised.[124] In this case, the metal is in oxidation state 4+.

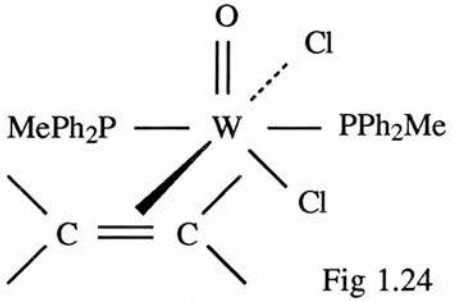
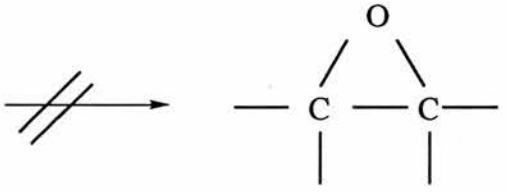


Fig 1.24



Equation 1.30.

It is possible that this type of complex could be involved in alkene epoxidations via metallacycles,[90,124] but the complex does not rearrange to give an epoxide.[125,126] However, the reverse reaction does take place leading to complex, [Fig (1.24)] when epoxides react with $WCl_2(PMePh_2)_4$.[125]

1.2.4. Group VII Transition Metals.

1.2.4.1 Manganese

Manganese complexes are used as catalysts for epoxidation reactions mainly because of the relationship of these systems to the biologically relevant manganese porphyrins. Mn(TPP)Cl, [Fig (1.25)], catalyses the epoxidation of alkenes with iodosylbenzene as the oxidant. The first step in the reaction is the formation of an unstable and reactive oxo - Mn(TPP)Cl complex, [Fig (1.26)], which then epoxides the alkene.[127]

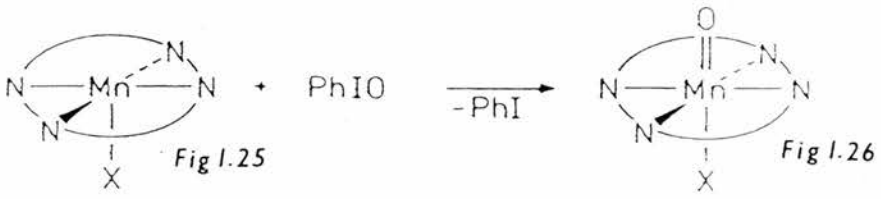


Fig 1.25 Fig 1.26

Equation 1.31

The oxygen transfer process from Fig (1.26) to the alkene takes place, as in the case of manganese(II) triflate, in a non - stereospecific manner since the epoxidation of *cis* - stilbene gives both *cis* and *trans* - stilbene oxide in the ratio of 35 : 65 respectively.[127]

When hypochlorite is used as the oxygen source during epoxidation reactions, the reaction rate, selectivity of epoxide formation and stereoselectivity can be increased dramatically by the addition of small quantites of nitrogen bases.[128-138] For example, in the presence of pyridine the *cis* - *trans* ratio for the epoxidation of *cis* - stilbene changes from 35 : 65 to 94 :6.[131]

Cationic manganese(III) - salen complexes are also effective for the epoxidation of various alkenes with iodosylbenzene as the terminal oxidant[139] and recent advances have been of great interest concerning the using of these complexes in the asymmetric epoxidation of unfuctionalised alkenes, which will be discussed more fully later in this chapter.

Tc and Re.

Both of these metals have proved to be very poor when used as part of an epoxidation catalytic system and therefore no background literature will be reported here.[140]

1.2.5 Group VIII Transition Metals.

1.2.5.1 Fe.

There are many similarities between iron and manganese complex catalysed epoxidations and the same oxygens donors can be used as for manganese complex reactions. An example of stereoselective behavior is when $Fe(acac)_3$ is used with hydrogen peroxide as the oxidant.

It is observed that *trans* - epoxides are obtained as the major product when *cis* - alkenes are used as substrates.[141] Conversely, the iron(III) chloride - hydrogen peroxide system for the epoxidation of a *cis* - alkene gave mainly the corresponding *cis* - epoxide.[142]

By using (μ_3 - oxo) triiron cluster complexes $[Fe_3O - (OCOR)_6L_3]^+$ alkenes can be epoxidised using molecular oxygen.[143] Treatment of geranyl acetate, [Fig (1.27)] with $[Fe_3O(piv)_6(MeOH)_3]Cl$, [Fig (1.28)] under molecular oxygen produced only 6,7 - epoxygeranyl acetate, [Fig (1.29)] and no isomeric 2,3 - epoxide [Fig (1.30)] could be detected.[143]

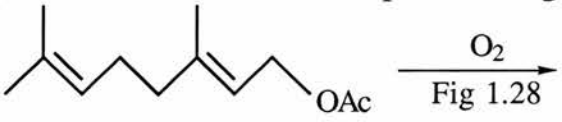


Fig 1.27

O_2

Fig 1.28

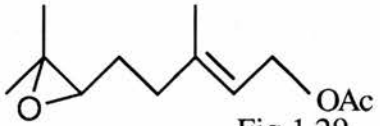


Fig 1.29

Equation 1.32.

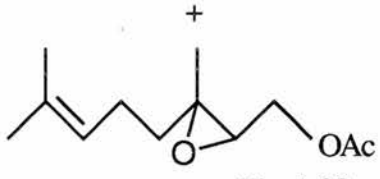


Fig 1.30

The iron porphyrin catalysts for alkene epoxidation have attracted much interest due to their relationship to oxidation reactions in biological systems.[144]

The epoxidation of alkenes catalysed by Fe(TPP)Cl using iodosylbenzene as the oxidant can be carried out in a stereospecific manner ie *cis* - alkenes yield only the corresponding *cis* - epoxides.[145,146]

Chiral "basket handle" iron porphyrins, [Fig (1.31)] which utilise iodosylmesitylene as the terminal oxidant achieve probably the highest asymmetric induction,[147,148] where up to 51% ee has been achieved in the epoxidation of *p* - chlorostyrene when iron(III) [(bi - napthylcarboxamide) phenyl] porphyrin chloride [Fig (1.31)] was used as the chiral auxilliary.[146]

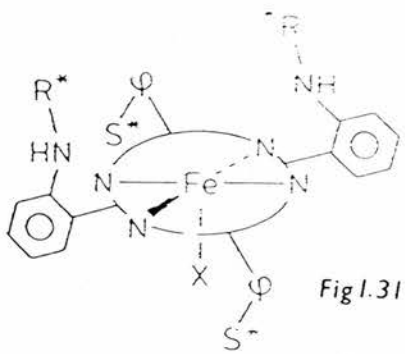


Fig 1.31

In this case the steric environment of the alkene has a pronounced effect on the asymmetric induction.[146]

1.2.5.2 Ru and Os.

Ruthenium(II) complexes such as $RuCl_2(PPh_3)_3$ using molecular oxygen or TBHP epoxidise alkenes in relatively low yield[106,149,150] but in addition using a ruthenium(III) bipyridyl complex as the catalyst with sodium periodate as oxidant, with the exception of substrates with terminal double bonds, alkenes can be oxidised to epoxides in a stereospecific manner, rather than to ketones or carboxylic acids.[151]

Although several osmium(III) porphyrins have been prepared and found to possess catalytic activity, compared to the iron porphyrins the reaction time is longer and the yield of epoxides lower.[152]

1.2.6 Co, Rh, and Ir.

1.2.6.1 Co.

$Co(acac)_2$ and $Co(acac)_3$ catalyse the epoxidation of alkenes with TBHP as oxidant, however the yields prove to be low accompanied by long reaction times.[148]

The use of cobalt(II) triflate or nitrate as catalysts and iodosylbenzene as the terminal oxidant allows the epoxidation of a variety of alkenes.[149] However, the yields of epoxide are <77% and the reaction is non - stereoselective,[149] eg in the epoxidation of *cis* - stilbene, *trans* - stilbene oxide was found to be the major product.[149]

Cobalt porphyrins have also been used as catalysts for alkene epoxidation, eg propene has been epoxidised with perbenzoic acid generated in situ in the presence of Co^{II} (p - CH_3TPP) as the catalyst and molecular oxygen as the terminal oxidant.[150]

In addition, styrene has been converted to styrene oxide with sodium hypochlorite using Co^{III}(TPP)Br as the catalyst, although the catalytic activity of the cobalt complex is lower than that of the corresponding manganese complex.[124]

Cobalt(II)bis(salicylamide), [Fig (1.32)] and related complexes have been found capable of epoxidising alkenes by one of two reaction pathways.[151]

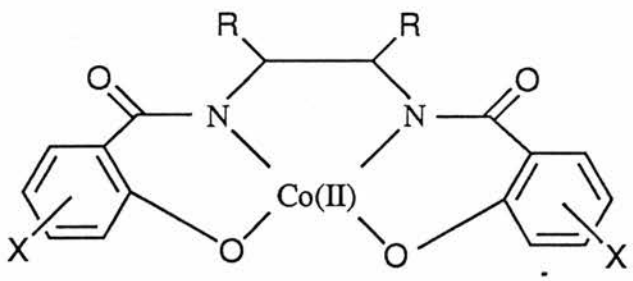
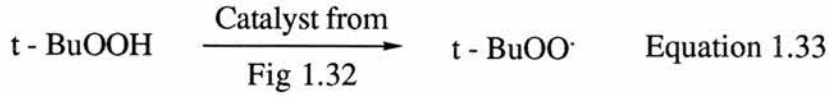
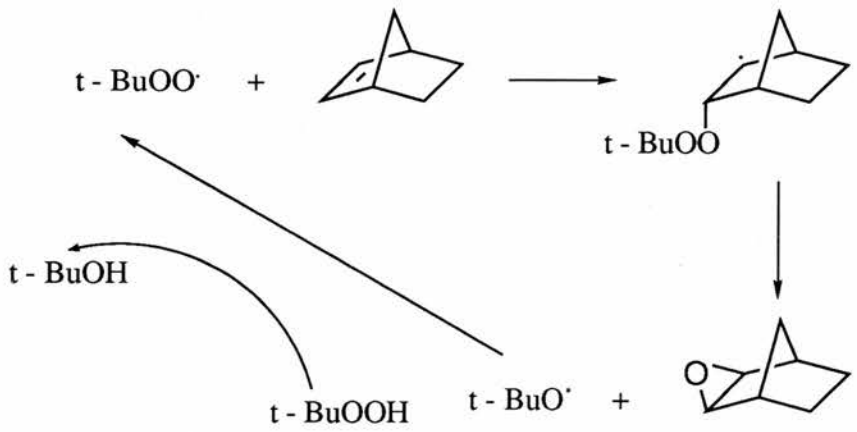


Fig 1.32.

The first of these is a radical chain mechanism by which a tert - butyl hydroperoxy radical adds homolytically to the C=C double bond of systems in which the allylic hydrogen is less reactive than the C=C double bond.[156]



Equation 1.33



Equation 1.34.

This reaction scheme is associated with the Co(II) / Co(III) interconversion in the one - electron redox process by which the tert - butylperoxy radical is formed [Equation 1.33].

The second mechanism is a two - electron oxidation by iodosylbenzene, forming an oxocobalt(IV) species that can epoxidise a variety of alkenes.[156]

1.2.6.2 Rh and Ir.

Both Rhodium(I) and Iridium complexes can utilise molecular oxygen to oxidise cyclohexenes to give a variety of products with the epoxide being one of them.[106,157-161]

1.2.7 Ni, Pd, and Pt.

1.2.7.1 Ni.

Only a limited amount of research has concentrated on nickel catalysts for alkene epoxidation, and although it has been shown that nickel(II) salts are, unlike their Fe(II), Mn(II), Co(II) and Cu(II) counterparts, completely ineffective in the catalytic epoxidation of alkenes using iodosylbenzene as the terminal oxidant, complexation of nickel(II) to tetraazamacrocycles as well as to other ligands affords systems which can act as catalysts for alkene epoxidation.[106,162]

1.2.7.2 Pd.

Palladium(II) - nitro complexes have been found able to epoxidise cyclic alkenes, although low yields of the epoxides are obtained. [Equation 1.35][163-165]

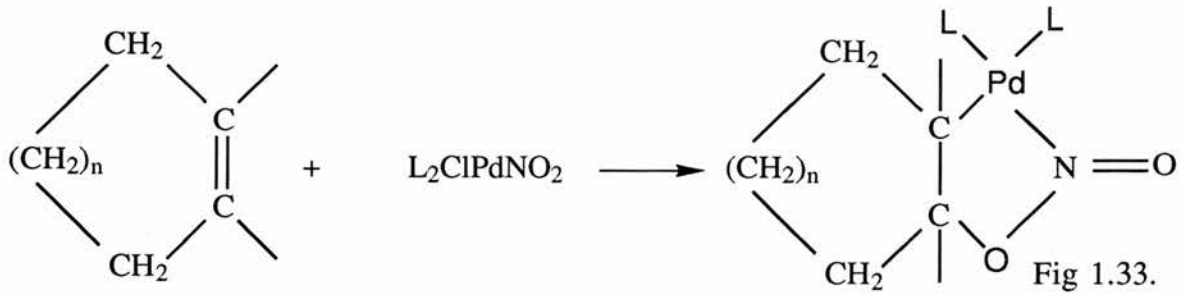
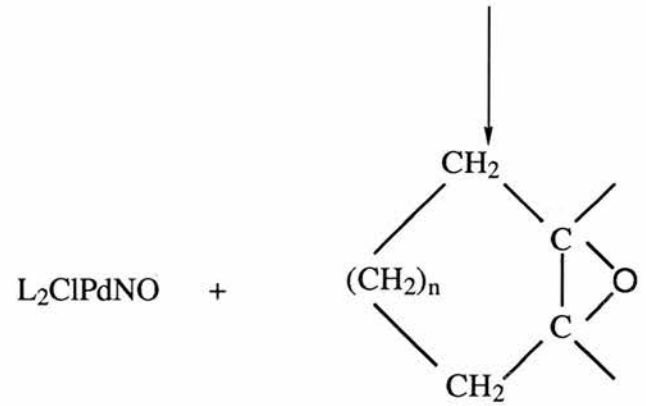


Fig 1.33.

Equation 1.35.



It is likely that the epoxide is formed by fragmentation of a palladacycle intermediate,[Fig (1.33)] formed by the addition of the alkene to one of the oxygens in the nitro group and to palladium.[163-165]

1.2.7.3 Pt.

While platinum(II) - dioxygen complexes do not react with alkenes, diluted hydrogen peroxide and hydroxyl - platinum(II) complexes are effective systems for the selective epoxidation of terminal alkenes.[166,167] Asymmetric induction has been observed by the introduction of chiral phosphines such as (-) - 2(S), 3(S) - bis (diphenylphosphino) butane [Fig (1.34)] or (+) - 2(R) - bis (diphenylphosphino) propane [Fig (1.35)] into the hydroxy - platinum(II) complex.

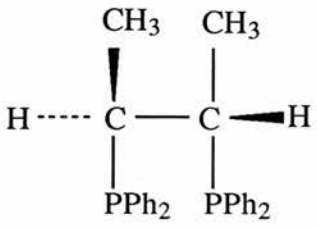


Fig 1.34

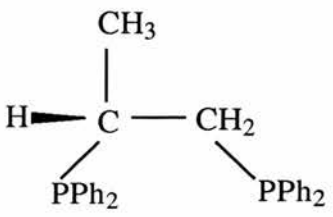


Fig 1.35

Using Fig (1.34) as the chiral ligand 41% ee of the - (S) - enantiomer was obtained in the epoxidation of propene,[168] whereas under similar conditions using Fig (1.35), 35% ee of the - (R) - enantiomer was observed.[168]

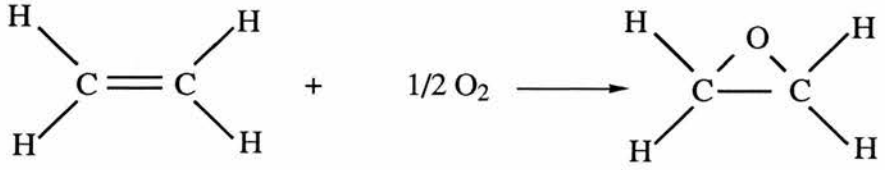
1.2.8. Cu, Au and Ag.

1.2.8.1 Cu and Au.

Copper and gold complexes have not been studied in great detail as epoxidation catalysts, but it has been shown that copper(II) nitrate and triflate can catalyse the epoxidation of alkenes using iodosylbenzene as the terminal oxidant.[154,169] However, this reaction was found to be nonstereospecific since the only oxidised product obtained from *cis* - stilbene was *trans* - stilbene oxide together with *trans* - stilbene.[154,169] Gold complexes such as $Au(PPh_3)_3Cl$ can achieve the epoxidation of cyclohexene, albeit in low yield with molecular oxygen as the oxidant.[157]

1.2.8.2. Ag.

In contrast to copper and gold, silver has been extensively studied and silver catalysts are used in industry for the selective oxidation of ethene to ethene oxide,[170-172]



Equation 1.36.

which is an important process from both a fundamental and practical point of view. The epoxidation of other alkenes by this system however results in low yields.

The epoxidation of ethene catalysed by a silver surface with molecular oxygen is not stereoselective, since the epoxidation of *cis* - 1,2 - dideuterioethene leads to a substantial amount of the *trans* - epoxide, and the corresponding *trans* - alkene produces some *cis* - epoxide.[173-175]

1.3. Summary of the Enantioselective Epoxidation of Unfuctionalised Alkenes.

Asymmetric oxidation is of great importance for the synthesis of optically active organic compounds and chiral unfunctionalised aliphatic epoxides are reactive synthons for the manufacture of optically active natural, pharmaceutical, and synthetic products.[171]

The epoxidation of functionalised allyl alcohols in an enantioselective manner is well known since Sharpless and Katzuki introduced in 1980, an extremely efficient transition metal - catalysed oxygen transfer, by means of which 2,3 - epoxyalcohols can be synthesised in good yields and with very high enantiomeric excess.[58,172] The titanium tartrate catalyst employed tolerates a high degree of structural variation in the prochiral substrate. By covalent bonding of the allyl alcohol to the chirally modified metal centre, conformational freedom is restricted and generally enantioselectivities of over 90% are achieved.

However, a great deal of importance has been placed upon the development of catalysts for the enantioselective oxidations of unfunctionalised alkenes. These alkenes cannot form conformationally restricting chelate complexes, and consequently differentiation of the enantiotropic sides of the substrate is rendered considerably more difficult.Therefore in the absence of secondary chelation, asymmetric induction must rely entirely upon nonbonded interactions.

1.3.1 Catalytic Asymmetric Epoxidation Employing Chiral (porphyrinato) Metal(III) Compounds.

Following the reports of Groves et al[173] and Chang et al[174] that iron(III) porphyrin catalysts are model compounds for cytochrome P-450 for the epoxidation of alkenes, the asymmetric epoxidation of unfunctionalised aromatic alkenes with iodosylarenes, catalysed by iron and manganese complexes of chiral (nonracemic) porphyrins has been investigated by a number of groups.

The αβαβ "basket - handle" porphyrin [Fig (1.37)] containing two rigid axially chiral binaphthyl bridges was used by Groves et al as iron(III) chloride or manganese(III) chloride porphyrin catalyst (1 equiv) with iodosylbenzene (100 eqiuv) as oxidant for the asymmetric epoxidation of alkenes (1000 equiv) yielding ee = 30% for phenyloxirane and 32% for *trans* - 2- ethyl - 3 - methyloxirane.[175]

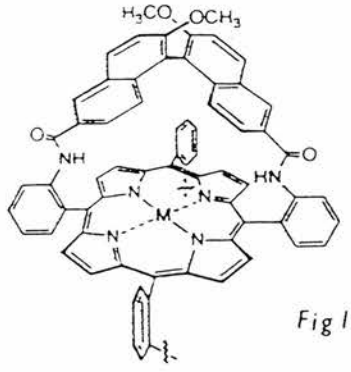


Fig 1.37

The iron(III) - chloro complexes of the "twin coronet" porphyrins [Fig (1.38)] catalysed the asymmetric epoxidation of styrene and derivatives with iodosylbenzene as oxidant.[176,177] The best enantiomeric yields were obtained in the oxidation of electron - deficient alkenes and the highest ee =89% was recorded in the case of 2 - nitrostyrene. This is the highest value reported so far in the epoxidation with chiral porphyrin catalysts.

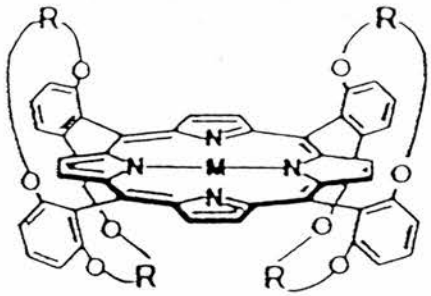


Fig 1.38

However, the problem with the previous porphyrin catalysts is that due to the presence of electron - donating substituents on the phenyl groups, the catalyst becomes more sensitive toward oxidative dehydration. The highest turnover number of 500 was achieved by catalyst shown in Fig (1.37).

Conversely, certain manganese(III) complexes proved more robust and showed in the asymmetric epoxidation of styrene or (Z) - 1 - phenylpropene ee = 20% and 40% respectively, using hypochlorite as the oxidant in a two phase system.[178] In addition, regeneration of the catalyst after 250 turnover numbers did not change the ee and after 2800 catalytic cycles the catalyst still showed 86% of the UV abdsoption band at 479nm.[178]

1.3.2 Catalytic Asymmetric Epoxidation Employing Chiral (Salen) Manganese(III) Complexes.

In this type of system it is mainly phenyl - substituted alkenes which are involved in the metal - mediated asymmetric epoxidation.

Subsequent to a report from Kochi et al which stated that the cationic (salen)manganese(III) complex [Fig (1.39)] was an efficient catalyst for the epoxidation of alkenes,[179] the asymmetric epoxidation of unfunctionalised aromatic alkenes with iodosylbenzene, iodosylmesitylene or sodium hypochlorite, catalysed by chiral C_2 - symmetric manganese(III) Schiff's base derivatives of Fig (1.39)[173-179] have been investigated by Katsuki et al[180-183] and Jacobsen et al.[184-188]

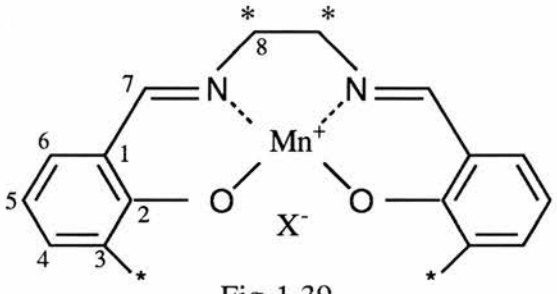


Fig 1.39.

These salen - based catalysts offer an important advantage over known chiral porphyrin systems because the asymmetric centres are located closer to the metal centre than those in the porphyrin complexes, resulting therefore in better stereochemical control in the epoxidation step.

The catalysts of Katsuki et al, [ie Figs (1.40 - 1.43)] contain four pairwise homochiral (SS and RR) stereogenic centres in various diastereomeric combinations (ie SS/SS, RR/RR, SS/RR, and RR/SS).

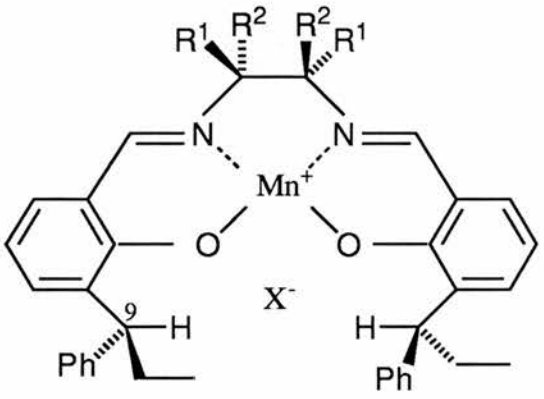


Fig 1.40: R^1=Ph, R^2=H, X=AcO
Fig 1.41: R^1=H, R^2=Ph, X=AcO

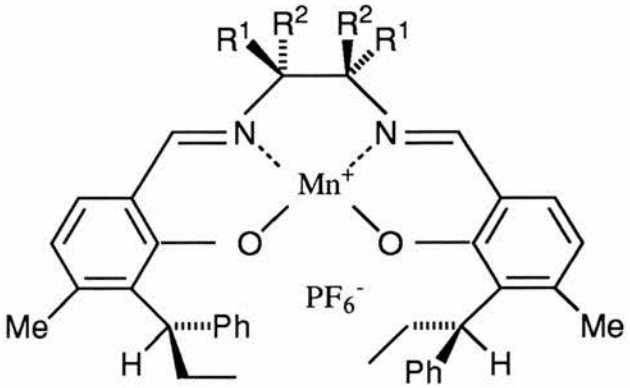


Fig 1.42: R^1=Ph, R^2=H.
Fig 1.43: R^1=H, R^2=Ph.

In the catalysts of Jacobsen et al however, [ie Figs (1.44 - 1.46)] the homochiral stereogenic centres at C(9) and C(9') are replaced by (achiral) hydrogens [Fig (1.44)] or by bulky *tert* - butyl groups [Figs (1.45, 1.46)] respectively.

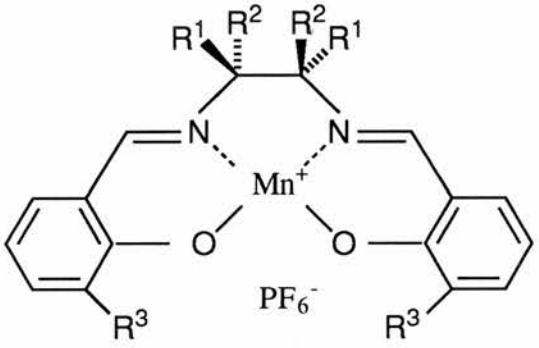


Fig 1.44: R^1=Ph, R^2=H, R^3=H.
Fig 1.45: R^1=H, R^2=Ph, R^3=t-Bu.

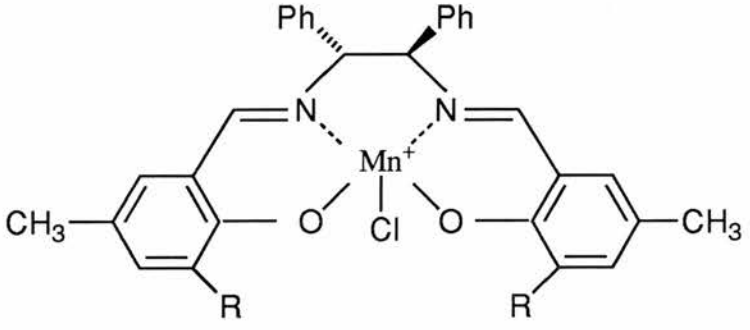
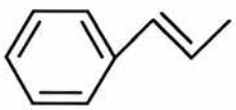
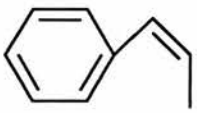


Fig 1.46: R=t-Bu.

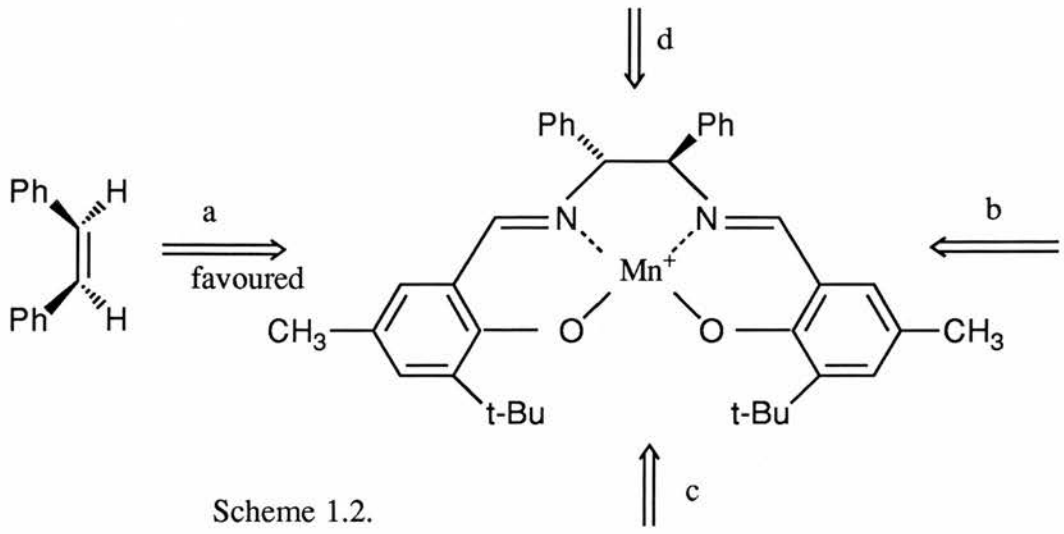
Typical results for the epoxidation of (E) - and (Z) - 1 - phenylpropene are summarised in Table 1.1 below.

Olefin.	Catalyst.	ee(%)	abs config.	yield(%)
	Fig 1.40	3	1S,2S	59
	1.41	32	1R,2R	61
	1.42	7	1R,2R	32
	1.43	17	1R,2R	25
	1.44	20	1S,2S	93
	Fig 1.41	44	1R,2S	26
	1.42	68	1S,2R	12
	1.45	84	1R,2S	88
	1.46	82	1R,2S	87

As can be seen from Table 1.1, the highest asymmetric bias is observed for the Z - alkene.

The addition of donor ligands such as 2 - methylimidazole and pyridine N - oxide alters the enantioselectivity and the chemical yield of the reaction.[181] In addition another advantage of added donor ligands is that the decomposition of the epoxides formed is suppressed.[183]

The sign and magnitude of asymmetric induction displayed by Fig (1.45) with Z - alkenes has been rationalised by a side - on perpendicular approach of the alkene to an oxomanganese(V) intermediate. (Scheme 1.2)[184,185] In addition, two structural features of Fig (1.45) are vital to its selectivity. The bulky tert - butyl groups prevent the alkene approach from (C) away from the chiral diimine bridge while the C_2 symmetry of the chiral diimine bridge discriminates approach (A) (favourable) from approach (B) (unfavourable). Approach (D) is believed to be disfavoured due to steric reasons.[186]



Scheme 1.2.

This model suggests that Z - disubstituted alkenes or bulky terminal alkenes should give the highest ee's with Fig (1.45) and this is proved by experiment. Therefore it seems that the alkene can approach most readily from the direction which is least hindered by steric crowding, which in turn induces significant stereoselectivity.

1.4 The Epoxidation of Allylic Alcohols.

This section will attempt to summarise the most widely known transition metal catalysed epoxidation of allyl alcohols due to its importance in synthetic chemistry.

1.4.1 Titanium.

One of the best known group (IV) transition metal - catalysed reactions is the treatment of titanium(IV) tetraisopropoxide, with TBHP and (+) or (-) diethyl tartrate with allylic alcohols to give epoxy alcohols with high ee.[172]

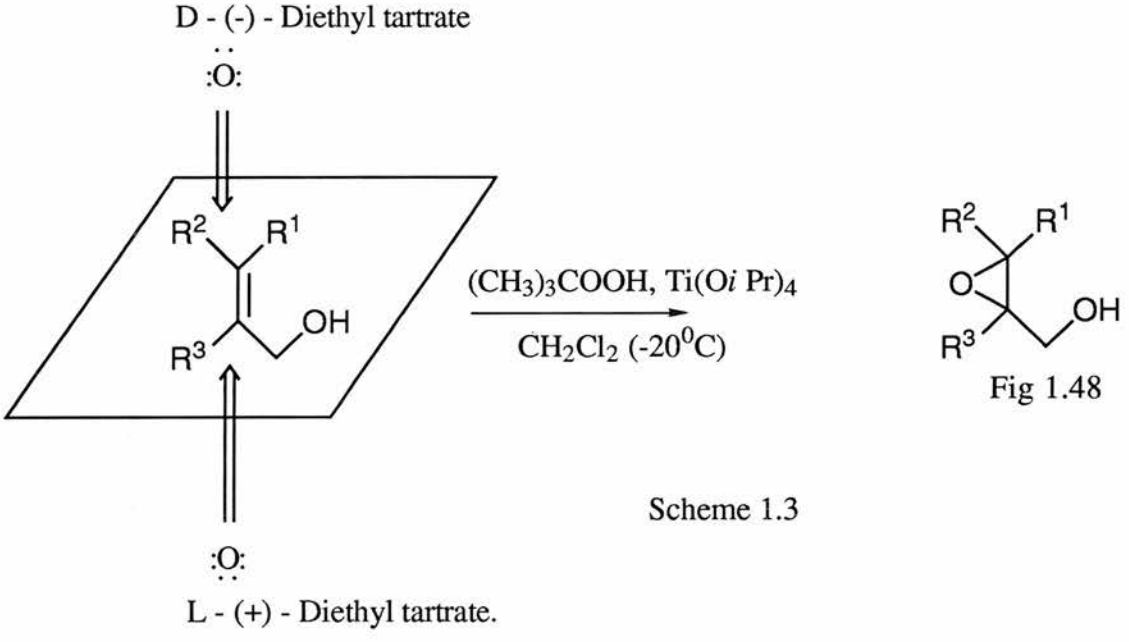


Fig 1.48

Scheme 1.3

This asymmetric epoxidation is now commonly known as the Sharpless epoxidation and it has demonstrated its usefulness in synthetic terms eg natural products.[189]

As can be seen from the above reaction,with (-) - diethyl tartrate the oxidant approaches from the top plane shown, whereas the bottom side is accessible to the (+) - diethyl tartrate reagent, resulting in the corresponding optically active epoxy alcohols [Fig (1.48)].

It has been shown that hydroperoxides other than TBHP can be used in the asymmetric epoxidation reaction[197] and a variety of allylic alcohols has been oxidised successfully under asymmetric conditions to the corresponding epoxy alcohols.[197-207] In practise the allylic alcohols which react most slowly and with poor enantiomeric excess are, eg some *cis* allylic alcohols and a few severely hindered molecules of other substituted types.It has also been found that other poor substrates are those which are epoxidised at a rapid rate and with high selectivity, but yield epoxy alcohols which are unstable under reaction conditions.[197] For substrates which have electron withdrawing groups attached the rate of epoxidation decreases whereas conversely an increase in the rate of epoxidation is observed in the presence of electron donating groups on the alkene.

1.4.2 Vanadium.

As was mentioned earlier in this chapter, vanadium complexes are very efficient catalysts for the epoxidation of allylic alcohols with TBHP as the oxidant,[208-219] and it has been found that the epoxidation of allylic alcohols is of the order of 10^3 times faster than that of the parent alkene.[208]

Using a vandium complex as the catalyst in the epoxidation of allylic alcohols favours the formation of the erythro - epoxy alcohols [Fig (1.49)], which is opposite to the stereoselectivity shown when MCPBA is used as the oxidant.

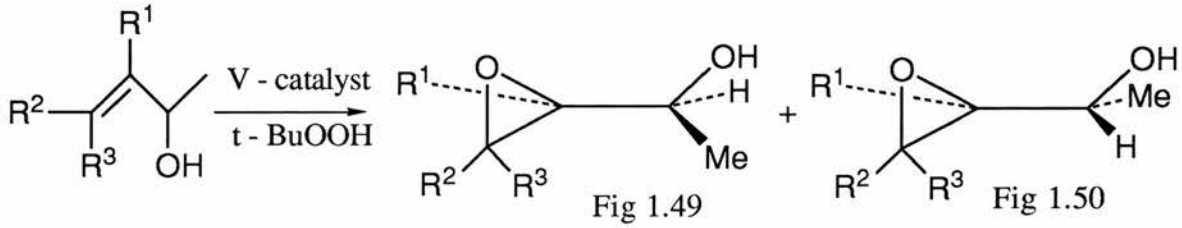


Fig 1.49 Fig 1.50

Equation 1.37

The proposed mechanism for the vanadium complex - catalysed epoxidation of allylic alcohols is shown in scheme (1.4).[15]

It is thought that the exceptional reactivity of allylic alcohols toward vanadium - alkyl hydroperoxides can be attributed to the fast and strong coordination of alcohol ligands to vanadium,[87] followed by an intramolecular oxygen transfer from the coordinated alkyl peroxide to the double bond of the allylic alcohol.

Scheme 1.4.

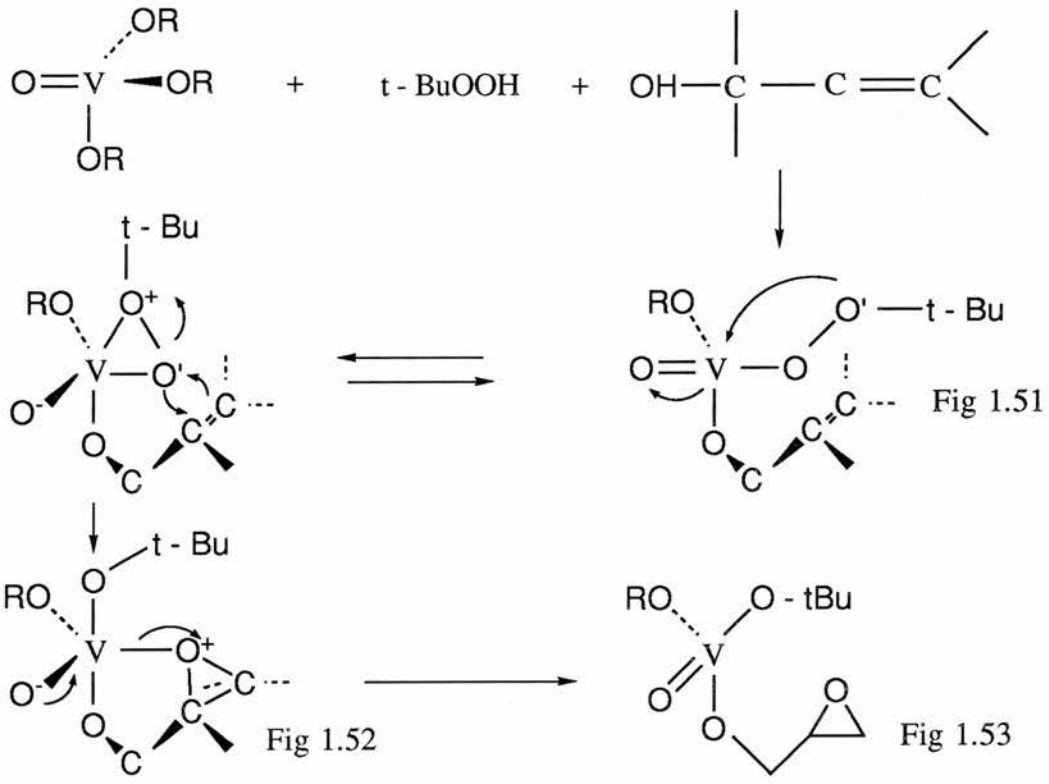
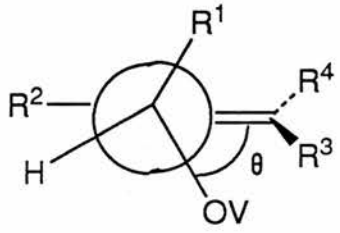


Fig 1.51 Fig 1.52 Fig 1.53

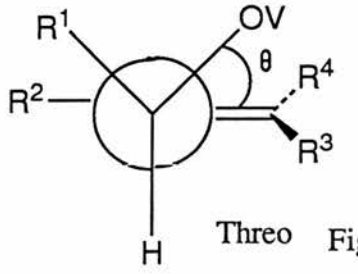
The first step is the exchange of the two alkoxide groups by the peroxide and the allylic alcohol, followed by a bidentate coordination of the peroxide moiety [leading to Fig (1.51)]. In intermediate Fig (1.51) the alkene part of the allylic alcohol is lined up perpendicular to the vanadium - alkylperoxo plane, making an interaction between the alkene and the peroxygen possible.

The conversion step from Fig (1.51) to Fig (1.52) determines the stereoselectivity and for the mechanism outlined in scheme (1.4) the formation of the *erythro* - epoxy alcohol can be explained using the conformation of the intermediate Fig (1.54).



Erythreo Fig 1.54

In this intermediate the O-C-C=C dihedral angle is approximately 50^0. A rotation of the O-C-C=C dihedral angle about 50^0 above the $R^2R^3R^4$ plane shown in Fig (1.55) will lead to the *threo* product.

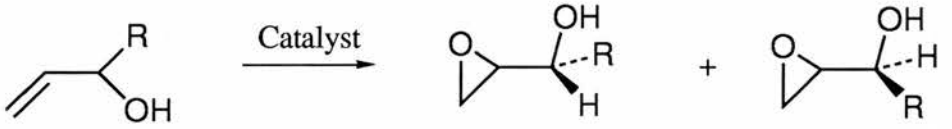


Threo Fig 1.55

The substitution pattern supports the suggested conformations since alkyl substitution in R^1R^2 will cause steric repulsion in Fig (1.55) whereas this is not the case in Fig (1.54).

1.4.3 Molybdenum.

Molybdenum(VI) has been found to be an effective catalyst for the epoxidation of allylic alcohols.[15] Comparitive studies have been carried out on a range of allylic alcohols (see table 1.2) and it has been shown that a $VO(acac)_2$ - TBHP system gave a higher yield of the erythro - epoxide compared with using $Mo(CO)_6$ - TBHP as the catalyst.[85]



Threo Erythreo

Equation 1.38.

Table 1.2

R	System	*%threo*	*%erythro*
CH_3	$VO(acac)_2$/t-BuOOH	20	80
	$Mo(CO)_6$/t-BuOOH	44	56
C_2H_5	$VO(acac)_2$/t-BuOOH	20	80
	$Mo(CO)_6$/t-BuOOH	42	58
i-C_3H_5	$VO(acac)_2$/t-BuOOH	15	85
	$Mo(CO)_6$/t-BuOOH	35	65

It is thought that the mechanism of the molybdenum(VI) catalysed system is very similar to that of the vanadium(V) system.

1.4.4 Summary

Over the last two decades it is clear that great advaces have been made in the field of asymmetric epoxidation, and this has been made possible by the immense amount of research which has been put into this area, due to its synthetic significance. It seems certain that this level of research will continue well into the future, where it is likely that increasing numbers of catalytic systems (and most likely transition metal catalysed systems) will be developed which will display improving catalytic and selective properties.

CHAPTER TWO

SYNTHESIS OF ASYMMETRIC β-KETOPHOSPHONATE LIGANDS AND COMPLEXATION TO TRANSITION METALS

2.1.1. Review of the synthesis of β-ketophosphonates.

In recent times, β-ketophosphonates (Fig 2.1) have become valuable intermediates in organic synthesis and one of the significant uses of these compounds has been the Wadsworth-Horner-Emmons condensation,[190] which is a commonly used method for the synthesis of α, β - unsaturated carbonyl compounds.

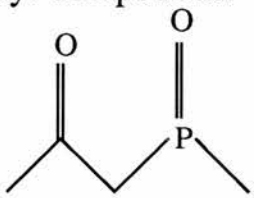
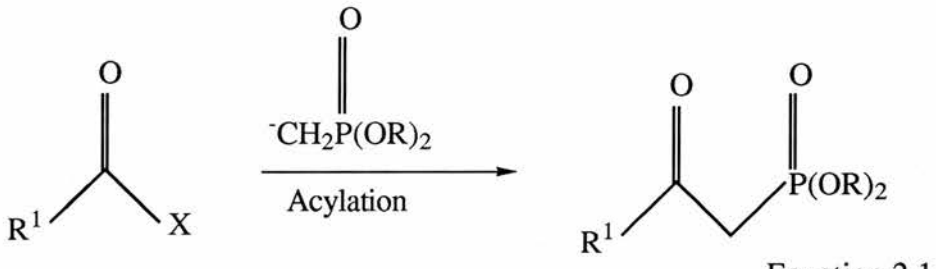


Fig 2.1

However, in contrast to the considerable amount of work which has expanded the original scope of the Wadsworth-Horner-Emmons condensation,[190] relatively little work has appeared on new methods for the synthesis of β-ketophosphonates.

One common route is the acylation of alkyl phosphonate anions,[191] (Equation 2.1) which is restricted by the limited availability of alkyl phosphonates.

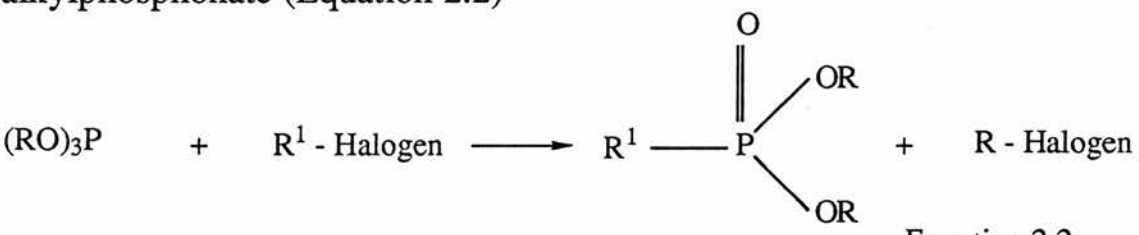


Equation 2.1

Another classical synthesis of phosphonate compounds is the Arbuzov reaction,[192] also known as the Michaelis - Arbuzov rearrangement, the Arbuzov rearrangement and the Arbuzov transformation.

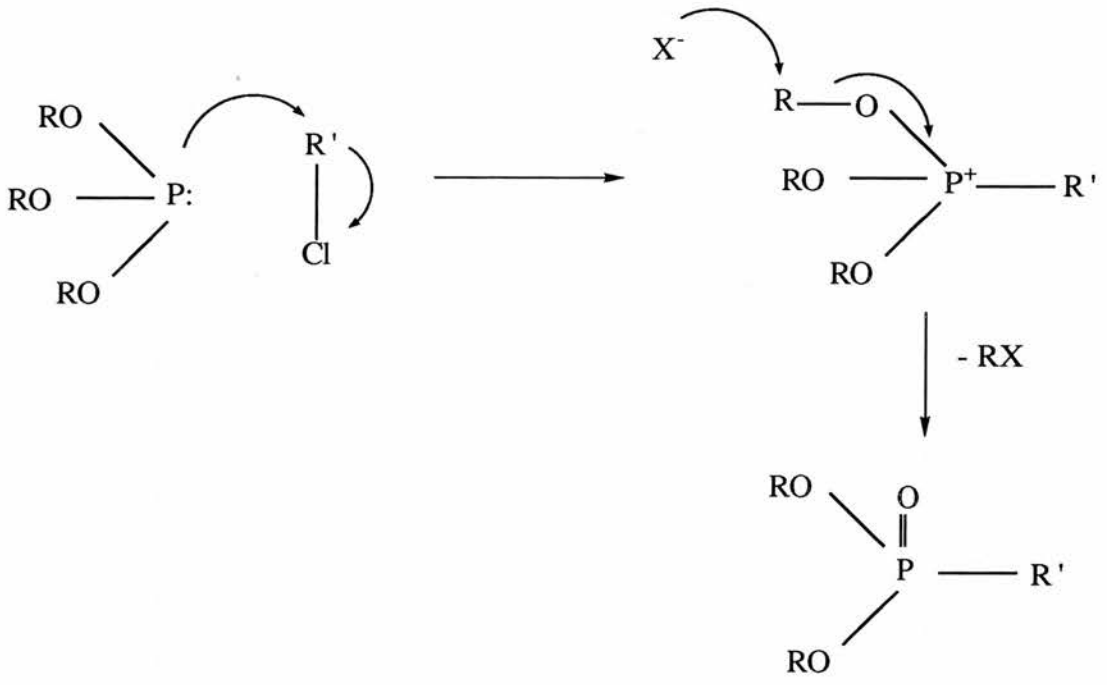
This is one of the most versatile pathways for the formation of carbon - phosphorus bonds and involves the reaction of an ester of trivalent phosphorus with alkyl halides. It is employed for the synthesis of phosphonates, phosphonic acid esters, and phosphine oxides.

In its simplest form the Arbuzov rearrangement is the reaction of an alkyl halide with a trialkyl phosphite, yielding a dialkyl alkylphosphonate (Equation 2.2)



Equation 2.2

Therefore, during the transformation a trivalent phosphorus (P^{III}) is converted into a pentavalent phosphorus (P^{V}). In general, the alkyl group of the halide gets attatched to the phosphorus, and one alkyl from the phosphorus combines with the halogen to form the new alkyl halide. On the basis of numerous investigations[193-196] the following mechanism may be written for the rearrangement.

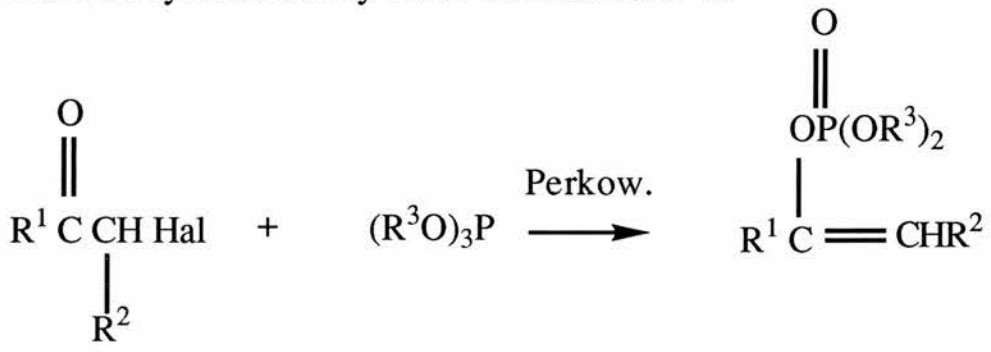


Equation 2.3

It is thought that the lone pair of electrons of the phosphite attacks the alkyl group of the alkyl halide to form the addition compound in which the alkyl group of the alkyl halide becomes attatched to the phosphorus. In the next step, an alkyl group of the phosphite leaves, resulting in the formation of the P=O bond, and the alkyl group is eliminated as the new alkyl halide. The overall result of the two steps is the conversion of trivalent phosphorus into pentavalent. When the alkyl groups of the phosphite and alkyl halides are identical ie R=R', the process amounts to an isomersization of the phosphite.

The Arbuzov rearrangement works best for primary α-iodo ketones and nucleophilic trialkyl phosphites. Primary α-bromo or α-chloro ketones often undergo a competitive Perkow process to afford enol phosphates,[197] (Equation 2.4) and substitution reactions are often difficult for secondary halides, limiting the usefulness of Arbuzov reactions with any secondary α-halo ketones.[198]

In addition, the employment of weakly nucleophilic trialkyl phosphites is problematic, for example, tris (2,2,2-trifluoroethyl) phosphite reacts with methyl iodide only when heated at 170^0C.[199]



Equation 2.4.

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

Several factors influence the product ratio of the β-ketophosphonates to vinyl phosphate,[200] including solvent, temperature and the nature of the halogen. For example, vinyl phosphate production is favoured by more electronegative halogens and low reaction temperatures

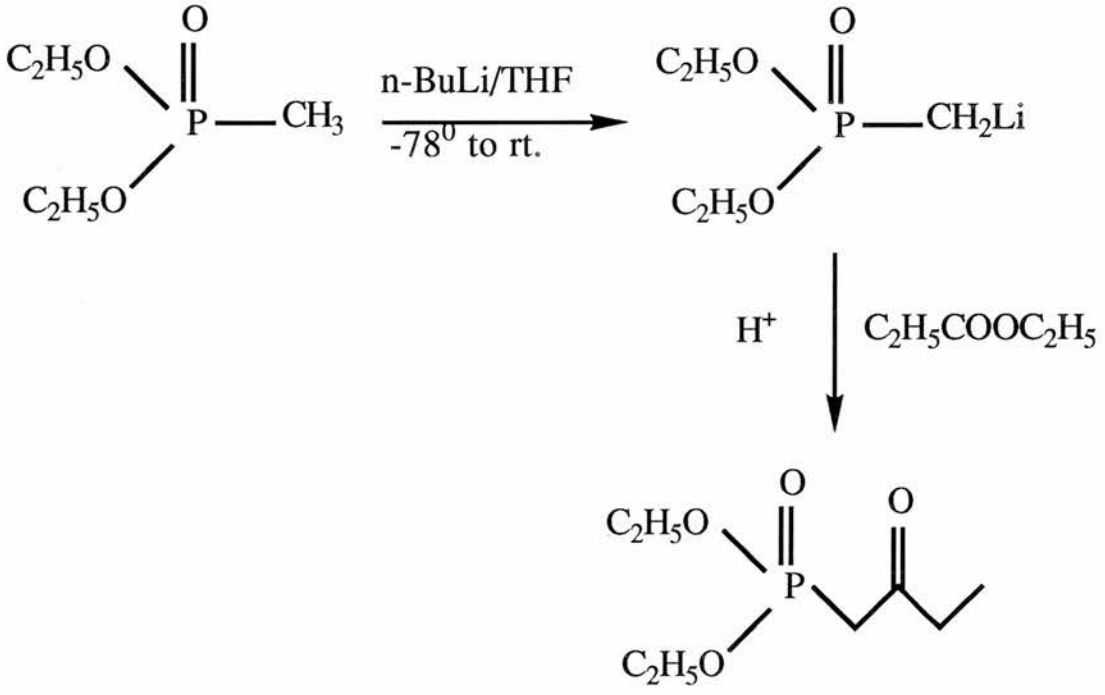
The ratio of vinyl phosphate to β-ketophosphonate in the reaction of haloacetones with triethyl phosphites is presented in table 2.1.[200]

Table 2.1.

Haloacetone.	Vinyl:β-keto. (at 150^0C)	Vinyl:β-keto. (at 36^0C).
$ClCH_2COCH_3$	90:10	-
$BrCH_2COCH_3$	20:80	80:20
ICH_2COCH_3	-	10:90

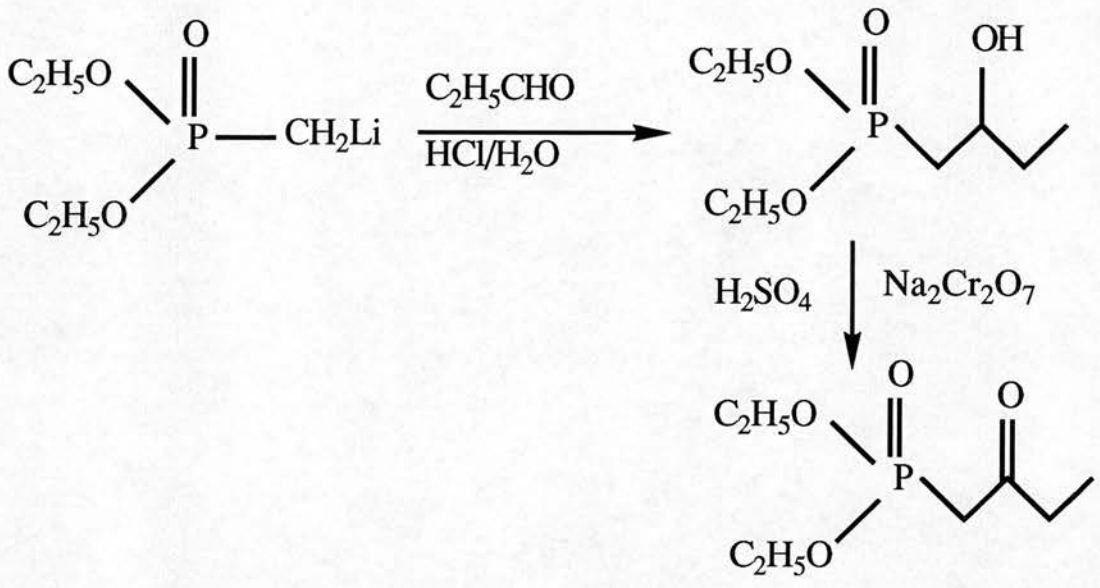
2.1.2 Synthesis of β-ketophosphonates from stabilised carbanions.

A recent synthesis of β-ketophosphonates is by the reaction of the lithio derivative of a dialkyl alkylphosphonate with either an aldehyde followed by oxidation of the β-hydroxy phosphonate product or with a carboxylic ester.[201] An example of this is the reaction of the lithio derivative of diethyl methanephosphonate with ethyl propanoate to give the diethyl butanephosphonate after acidic workup.



Equation 2 5.

Reaction of diethyl 1-lithiomethanephosphonate with for example propanal gives the diethyl 2-hydroxybutanephosphonate almost exclusively. (Equation 2.6)



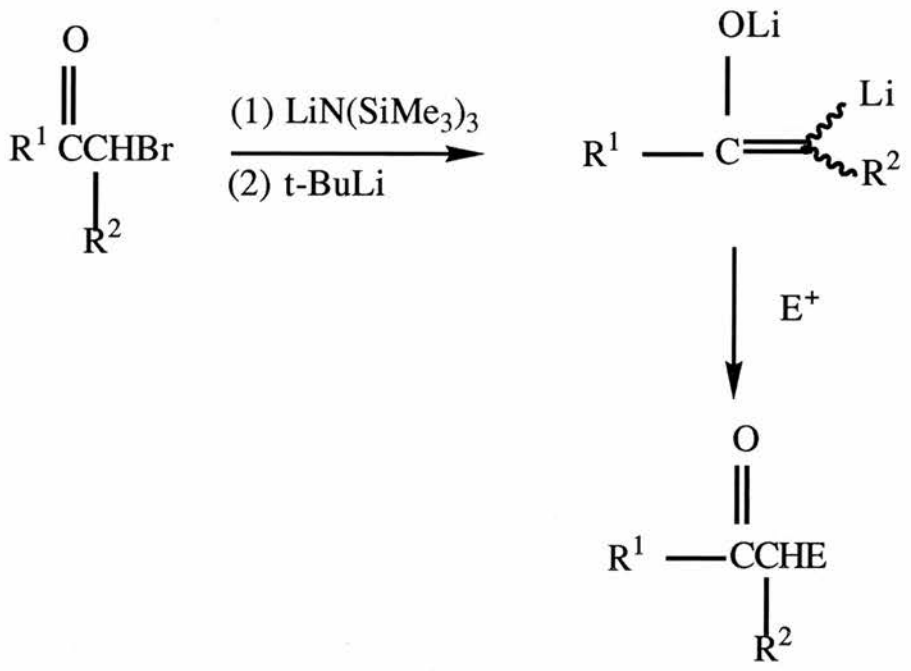
Equation 2.6.

However, the dichromate reaction which follows is less efficient and gives the β-ketophosphonate in only 50% yield.[201]

2.1.3 Synthesis of β-ketophosphonates from dilithiated species of α-bromo ketones.

A useful recent technique for the synthesis of β-ketophosphonates has come from Wiemer *et al*,[202] who set about finding a method which in contrast to the Arbuzov reaction, could utilize electrophilic phosphorus reagents.

This process is a development of work by Kowalski[203] who studied the conversion of α-bromo ketones into dilithiated species which can be viewed as both enolates and vinyl lithium reagents. (Equation 2.7).



Equation 2.7.

Kowalski's investigations have shown that reaction of such species with a number of electrophiles (trimethyl siliyl chloride, deuterium oxide,[203] and representative aldehydes and ketones[204]) occurs exclusively at carbon to produce α-substituted products.

Wiemer *et al* concluded that by employing a phosphorus electrophile (eg a dialkyl chlorophosphate), this approach might be expected to afford β-ketophosphonates. Such an umpolung approach would reverse the problems of electron demand at the phosphorus which are apparent in the Arbuzov reaction, making electron-deficient phosphorus moieties particularly reactive. The ready availability of α-bromo ketones makes this method appealing while the change in mechanism enabled the conversion of secondary α-bromo ketones into analogous β-ketophosphonates.

Wiemer *et al* generated several vinyl lithium reagents by the method of Kowalski,[203] employing lithium hexamethyldisilazide to form the α-bromo enolate and then an excess of tert-butyllithium to invoke halogen-metal exchange. The use of low temperatures in this reaction is important, (ie -110^{0}C after the addition of tert-butyllithium) for even at -78^{0}C it was found that the yields were significantly lower.The results of this work are shown in table 2.2

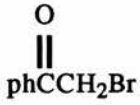
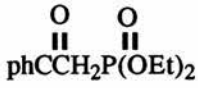
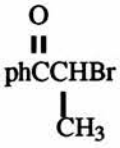
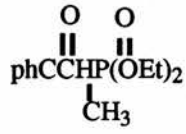
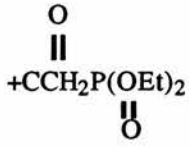
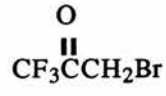
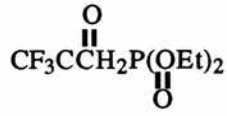
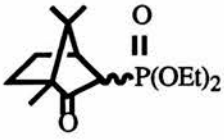
With dialkyl chlorophosphate as the electrophile, only a modest yield of the β-ketophosphonate product was obtained from α-bromoacetophenone (entry 1), however, higher yields were obtained with bromopropiophenone (entry 2), yielding a β-ketophosphonate not readily available via the classical Arbuzov approach. Under the same reaction conditions, α-bromocamphor gave only the corresponding enol phosphate, but by utilizing more forceful conditions for the halogen-metal exchange, the β-ketophosphonate was obtained in low yield.

2.1.4 Synthesis of β-ketophosphonates from vinyl phosphates via a 1,3 - phosphorus migration.

More recently Wiemer and co-workers have developed a route incorporating a 1,3 - phosphorus migration that provides β-ketophosphonates from readily available vinyl phosphates.[205]

The reaction of dialkyl phosphorochloridates with enolates is well known, and results in the formation of the enol phosphate rather than the ketophosphonate.[206] For example, sequential treatment of cyclopentanone with LDA and diethyl phosphorochloridate at -78^{0}C in THF, results in the near quantitative formation of the enol phosphate, which if desired can be isolated and characterized.

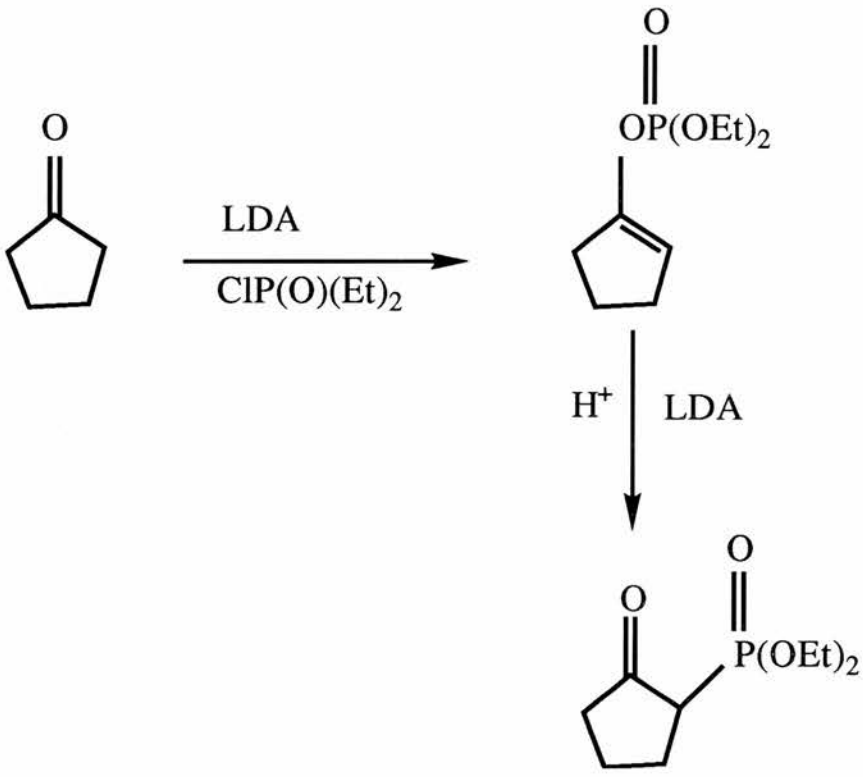
Table 2.2

α-bromo ketone.	Dialkyl chlorophosphate.	β-ketophosphate.	% yield[a]
			74(24)
			72(62)
			48(31)
			54
			31(20)

[a]Yield by gas chromatography. (Isolated yield).

However, when converted to its own anion a rearrangement takes place to give the highly stabilized β-ketophosphonate from a much less stable species.

This effect can be achieved by further treatment with LDA (Equation 2.8).

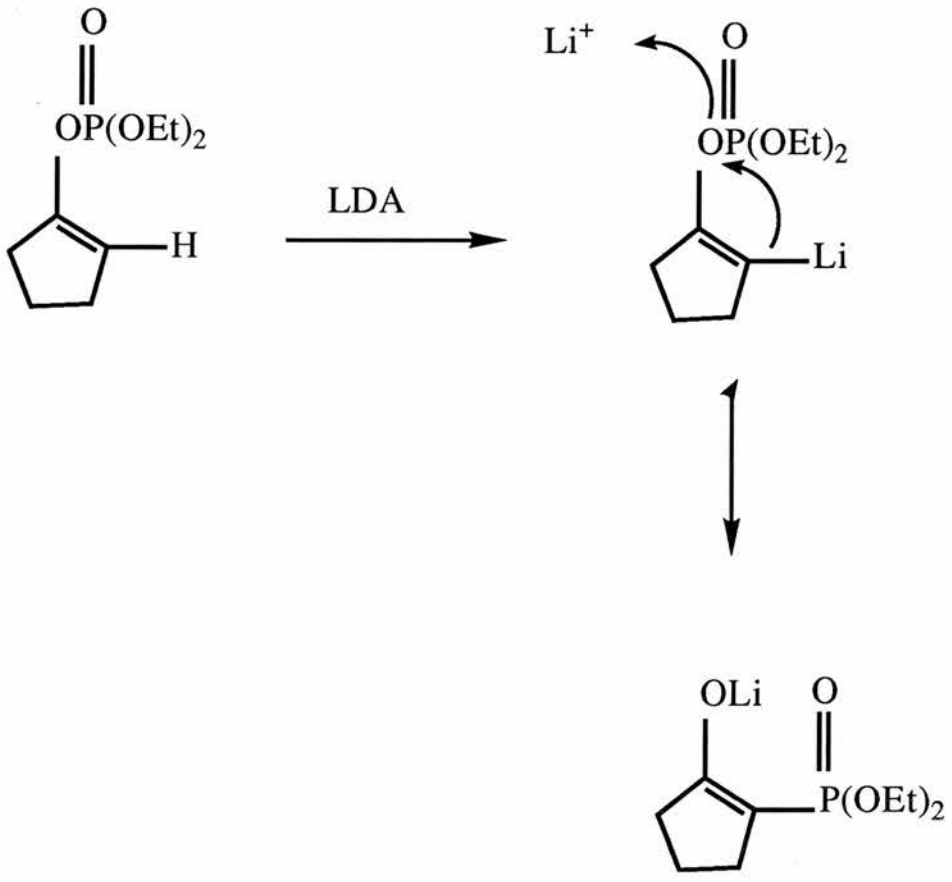


Equation 2.8

This method works best for cyclic ketones giving precisely those β-ketophosphonates which are least accessible via other methods.The results given by Wiemer *et al* are shown in table 2.3.

It is noticable that when enolates derived from acyclic ketones are treated under similar conditions, the results are more complex.With methyl ketones such as acetophenone, a phosphate elimination resulting in alkyne formation predominates.[207]

The mechanism for this reaction is thought to be:-



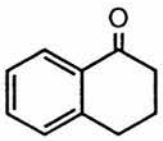
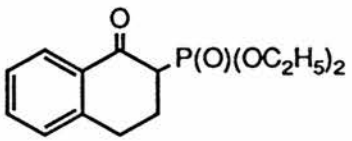
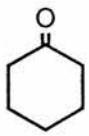
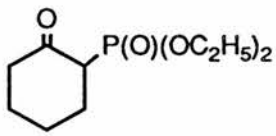
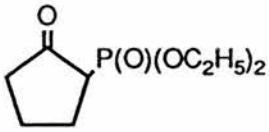
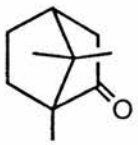
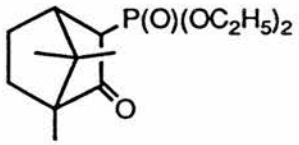
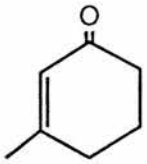
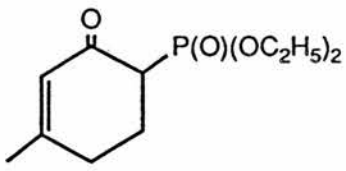
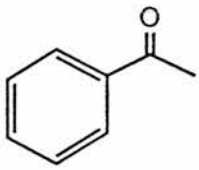
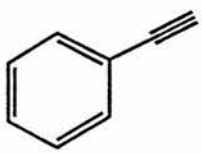
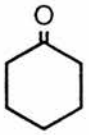
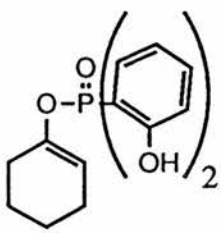
Equation 2.9.

2.1.5 Crossover experiments.

To gain an insight into the mechanism of this rearrangement, Wiemer *et al* carried out a series of experiments.[208] The first of these was a simple crossover experiment, wherein a mixture of equimolar amounts of the diethyl vinyl phosphate of camphor, and the diisopropyl vinyl phosphate of norcamphor were treated with LDA in THF. Careful analysis of the resulting mixture revealed only the products of intramolecular migration, suggesting that in this case at least the rearrangement is an intramolecular process.

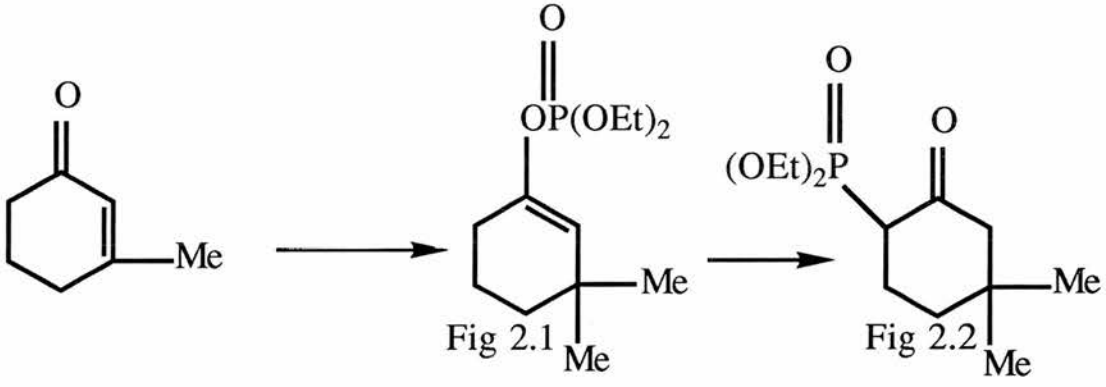
Table 2.3

Synthesis of β-ketophosphonates

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

2.1.6 Proton Abstraction experiments.

Wiemer *et al* conducted a second series of experiments to establish the site of proton abstraction.[208] With the vinyl phosphates of camphor and tetralone, an intramolecular rearrangement can occur by abstraction of the vinyl hydrogen. However, with ketones such as cyclohexanone, the migration might occur via abtraction of the vinylic hydrogen of the vinyl phosphate of via abstraction of a proton from the α-position forming an intermediate allyl anion. To attempt to discover which was occuring, the vinyl phosphate (Fig 2.1) shown in Equation 2.10 was treated with LDA to give a single product (Fig 2.2).[Where Fig (2.1) was prepared by methyl cuprate addition to 3-methyl-2-cyclohexenone and trapping of the resulting enolate with $(EtO)_2P(O)Cl$].



Equation 2 10.

In a similar experiment, vinyl phosphate (Fig 2.3) treated with LDA gives phosphonates (Figs 2.4, 2.5) in equal amounts (Equation 2.11). These results suggest that this rearrangement can occur via abstraction of an allyl hydrogen when one is available and that migration can occur to either terminus of an allyl anion. However, phosphorus migration to the vinylic position can occur when formation of an allyl anion is precluded.

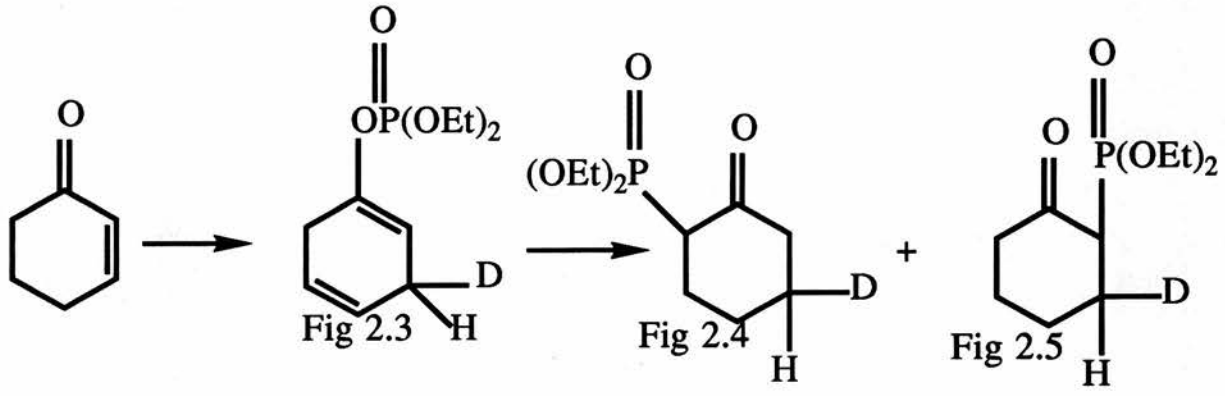


Fig 2.3 Fig 2.4 Fig 2.5

Equation 2.11.

2.2 Synthesis of β-ketophosphonates.

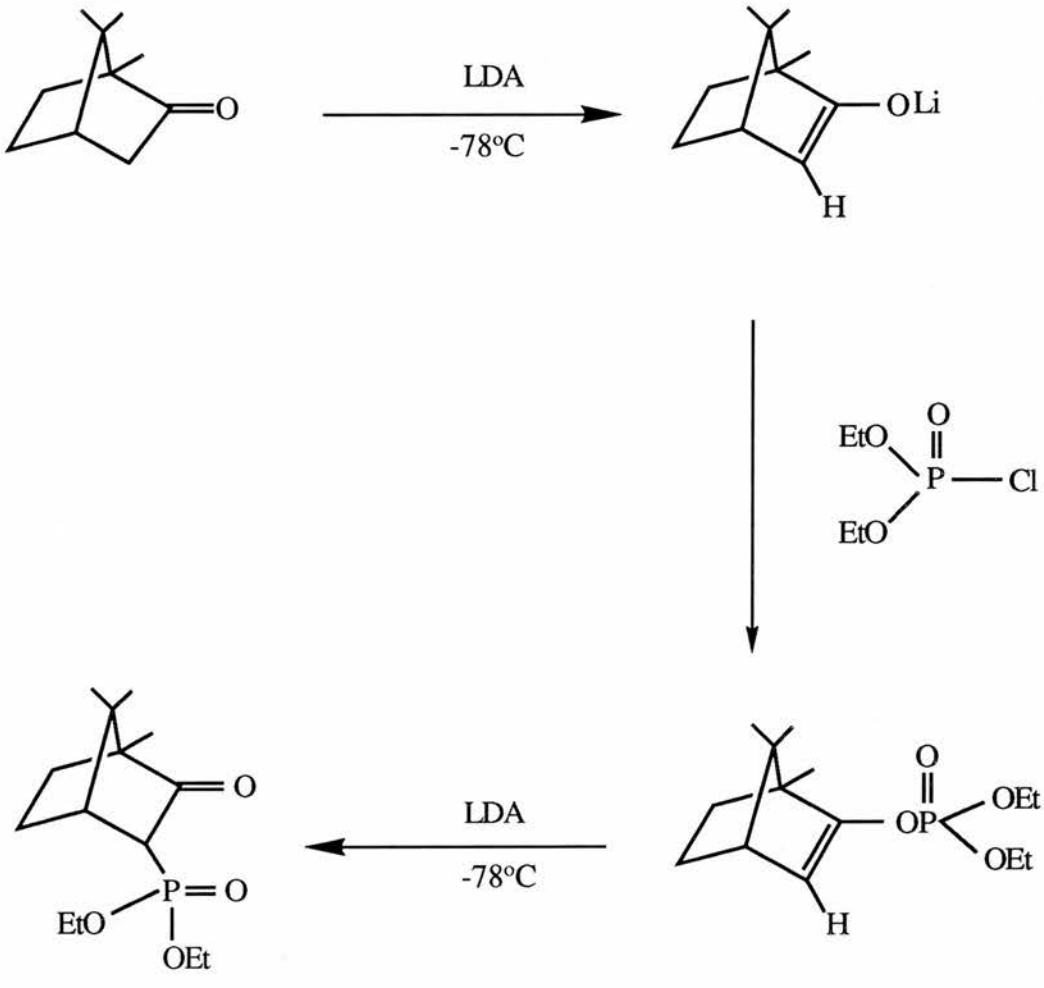
From the outset of this research it was the intention to attempt to synthesise a range of β-ketophosphonate ligands incorporating the chiral, naturally occuring asymmetric molecule camphor, which differed from one another not only in stereochemistry, but also in steric bulk.

From previous work it had been shown that the transition metal complex [(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor displayed excellent activity for the epoxidation of a range of different alkenes eg during the epoxidation of 1-methyl-1-cyclohexene at room temperature, 80% conversion to the epoxide had been observed in the first few minutes. However, no stereoselectivity had been observed. It therefore seemed logical to attempt to synthesise a range of compounds which, as well as changing the nature of the chirality previously observed at camphor, would also introduce additional optically active centres within these molecules in the hope that stereoselectivity might be observed in the epoxidation of various alkenes.

The synthesis of β-ketophosphonates using a 1,3 - phosphorus migration initiated by Wiemer *et al* was discussed at some length[208], in the previous section. It was decided that this would be the method which would be used as the cornerstone for the attempted synthesis of a range of different molecules. The reasons for using this method are the fact that it is specifically designed for electrophilic phosphorus species, and that the preparation and work-up seemed reasonably simple.

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

It was decided to attempt to synthesise this compound so that previous epoxidations using the transition metal complex of this ligand could be repeated and the kinetics studied in more detail. (Equation 2.12).



Equation 2.12.

On addition of the dialkyl phosphorochloridate an electrophilic substitution takes places due to the electrophilic nature of the phosphorus moiety and the vinyl phosphate is cleanly formed. This is a well known reaction and proceeds smoothly to the intented product. This vinyl phosphate species can if required be isolated and characterised or the next step of the reaction can take place in the same reaction vessel. From results observed in similar systems, various 1,3 - silicon migrations suggested that the vinyl phosphate itself could serve as a precursor to a β-ketophosphonate. Although this rearrangement would require the breaking of a P-O bond, it would result in the formation of a very stable ketophosphonate anion from a much less stable species.

Any remaining camphor was removed by sublimation, (since camphor sublimes between 80^0C and 120^0C under vacuo) to give a pale yellow oil of the product which gave three singlet peaks in the ^{1}H nmr at 0.8, 0.9, 1.0 ppm due to the different methyl environments present in camphor, and a doublet of multiplets at 3.0 ppm due to the hydrogen on C3 of camphor.

The complexation chemistry and epoxidation activity of the resulting transition metal complex will be discussed at greater length in the chapter of this thesis which reports on catalytic work carried out during this research.

2.2.2 [(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl) camphor.

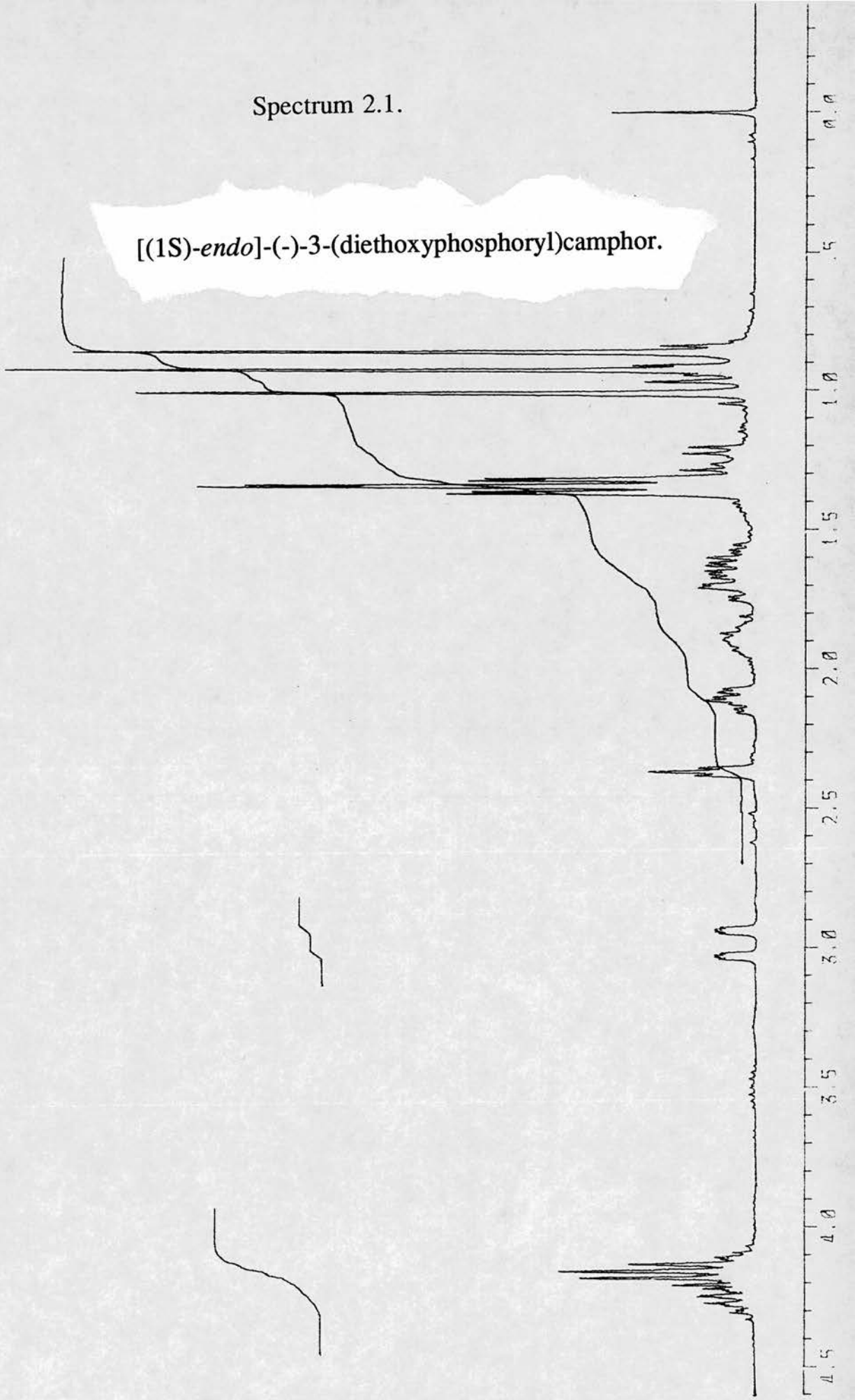
Following the successful synthesis of [(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor, it was decided that an interesting comparison could be drawn by the examination of the stereoselectivity of its enantiomer [(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl) camphor. If the transition metal complex of this ligand could be made it would be useful to observe if the change in chirality at camphor would make any significant difference in the selectivity displayed during epoxidation reactions.

The β-ketophosphonate ligand was successfully synthesised using the method previously outlined to give after sublimation, a pale yellow liquid.

Since this ligand is an enantiomer of [(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor, it is natural to expect that the physical properties and analytical data collected should be the same for both molecules. This indeed proved to be the case and the identity of this ligand was verified from ^{1}H nmr which showed the characteristic singlet peaks for the three methyl groups of camphor at 0.8, 0.9, and 1.0 ppm and the doublet of multiplets at 3.0 ppm due to the hydrogen present on C3 of camphor. This complex coupling pattern is due in part to coupling to the phosphorus atom, as well as neighbouring hydrogen atoms. (see spectrum 2.1)

Spectrum 2.1.

[(1S)-*endo*]-(-)-3-(diethoxyphosphoryl)camphor.



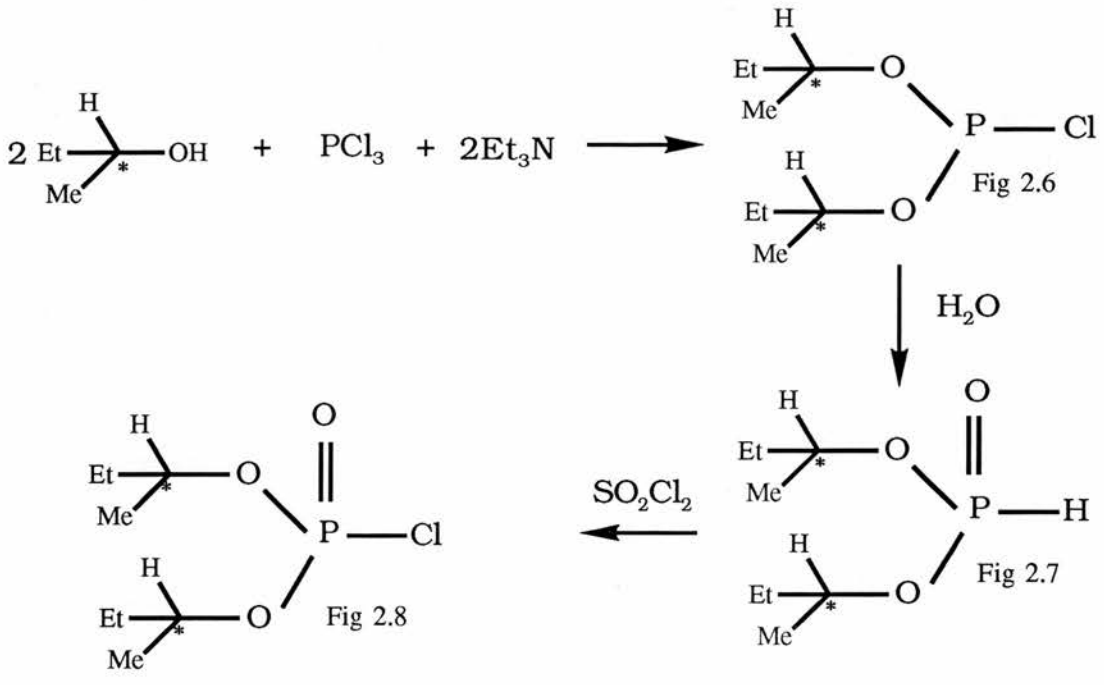
2.2.3 [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor.

Since a method for the synthesis of β-ketophosphonates had been found from a phosphorochloridate precursor, which had proved to be successful, it was decided to attempt to make a range of different ligands all of which incorporated the chirality of camphor, but which varied in the nature of the alkoxy groups attatched to the phosphorus atom, not only in their bulk, but also in their optical activity. It was for this reason that the synthesis of [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor was undertaken.

This type of ligand would not only incorporate increased size over the diethoxy analogue, due to the presence of secondary butyl groups attatched to the phosphorus atom, but would also include two new chiral centres, which it was hoped may have a stereoselective influence during the epoxidation of various alkenes.

Unfortunately, di - [(S) - (+) - 2 - butyl] phosphorochloridate, which is required for the 1,3 - phosphorus migration reaction is not commercially available and so a method had to be devised for the synthesis of this molecule. It was decided to start from the optically active alcohol (S) - (+) - 2 - butanol, which is commercially available.

The first step of this process was the attempted synthesis of the chlorophosphine of (S) - (+) - 2 - butanol .[Fig (2.6)] This was achieved by a well known reaction which involves the dropwise addition of the optically pure alcohol to stirred solution containing triethylamine, phosphorus trichloride, and diethyl ether which was cooled to 0^0C. (Equation 2.13)



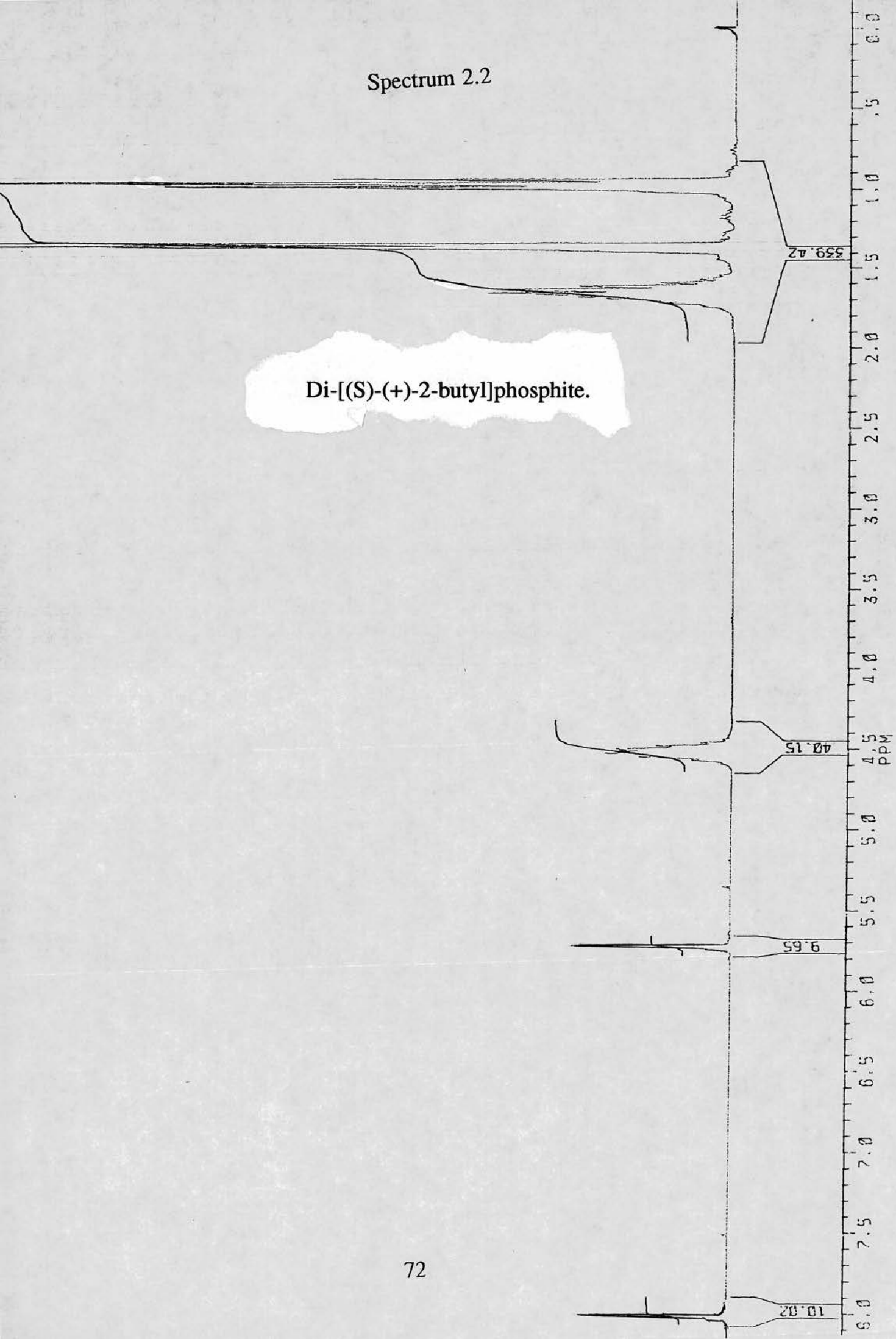
Equation 2.13

(* - indicates a chiral carbon atom)

The solution is cooled to ensure that the reaction only proceeds to the second substituted stage. The alcohol is added slowly to the stirred mixture containing phosphorus trichloride and triethylamine to ensure that there is never a local excess of alcohol, hence preventing the trisubstituted species being formed.

The chlorophosphine can then be poured straight into a crushed ice solution to effect the hydrolysis step to give di - [(S) - (+) - 2 - butyl] phosphite [Fig (2.7)]. This compound is then purified by washing with base to ensure that any acid present is removed and can be easily identified from ^{1}H nmr which shows a doublet due to phosphorous-hydrogen coupling, with a coupling constant of 688.7 Hz.(spectrum 2.2)

Spectrum 2.2



Di-[(S)-(+)-2-butyl]phosphite.

The phosphite can then be transformed to di - [(S) - (+) - (2) butyl] phosphorochloridate [Fig (2.8)] by treating the phosphite with sulphuryl chloride in anhydrous methylene chloride at room temperature. A great deal of care must be taken in the purification of this product to ensure that it does not come into contact with air since it will readily hydrolyse to the phosphonic acid species. Although the synthesis of the phosphorochloridate from the chiral alcohol is shown in Equation (2.13) as one reaction scheme it should be pointed out that the product formed at each step of this reaction can be isolated and identified by analytical methods (eg ^{1}Hnmr) if required.

Having successfully made di - [(S) - (+) - 2 - butyl] phosphorochloridate, the synthesis of the phosphonate analogue was the next target using (R) - (+) - camphor in the first instance. This reaction proved to be successful yielding the β-ketophosphonate [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl) camphor Fig 2.9 in modest yield.[Equation 2.14]. As with previous synthesis of phosphonate ligands, any remaining camphor was removed by sublimation under vacuum. An additional problem found during the purification of this molecule was that diisopropylamine, which is regenerated during the synthesis from reaction of LDA proved extremely difficult to remove from the final product. This seemed strange since it has a boiling point of approximately 78^{0}C and should therefore be easily removed along with any unreacted camphor during the sublimation process. This however proved not to be the case, and after exhaustive efforts, the only method found successful in fully removing this side product was to wash the crude mixture with concentrated hydrochloric acid. Fortunately, the ligand appeared unaffected by this procedure.

This product was readily identified from its ^{1}H nmr (spectrum 2.3) which showed a doublet of multiplets at 2.95 ppm due to the hydrogen present on C3 of camphor, and was also very interesting because it very clearly showed that the hydrogen atoms present on the two different secondary butyl groups are in different orientations (ie diastereotopic) since they can be clearly distinguished from one another. There was also only one signal in the ^{31}P nmr at + 20.8 ppm, which is in the typical region for β-ketophosphonate compounds.

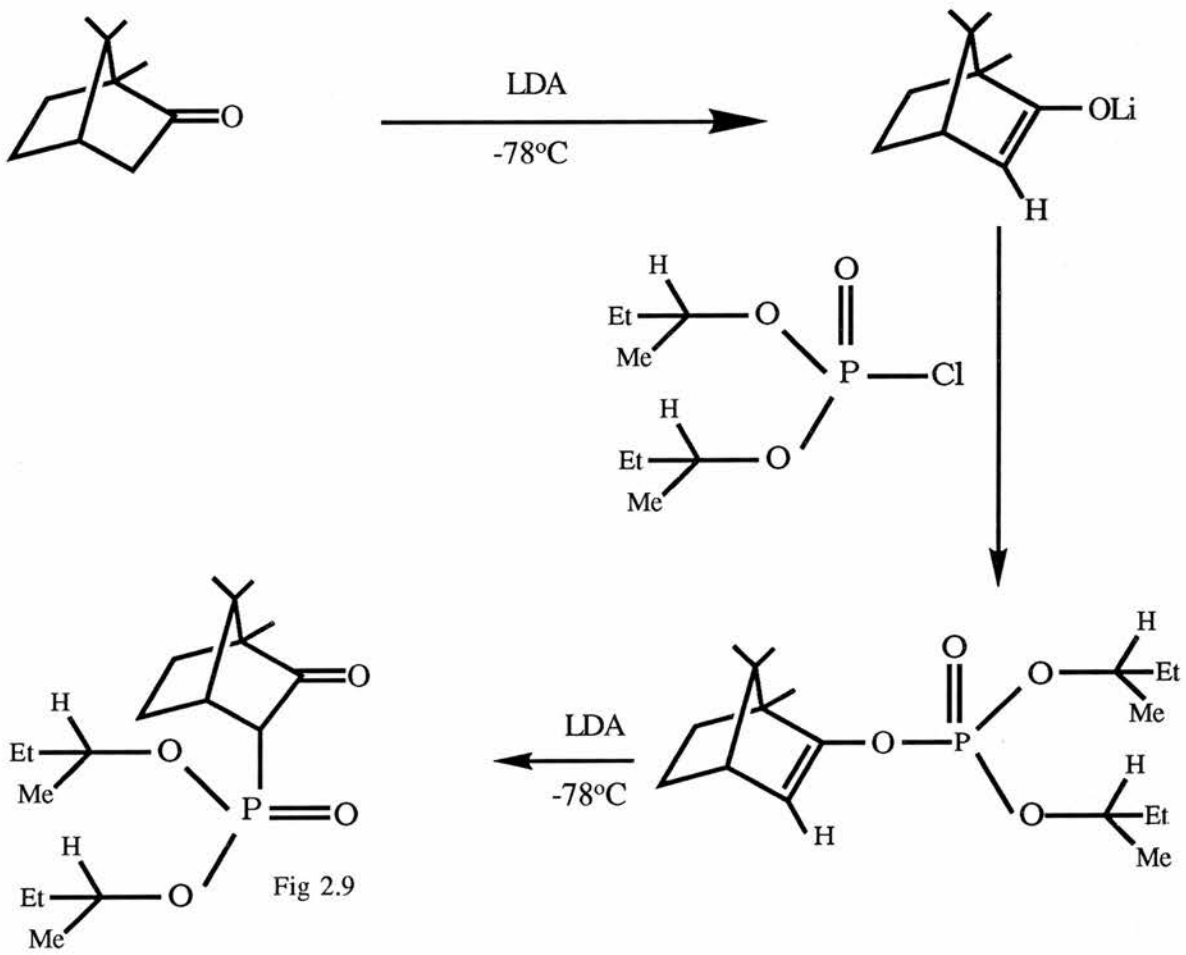
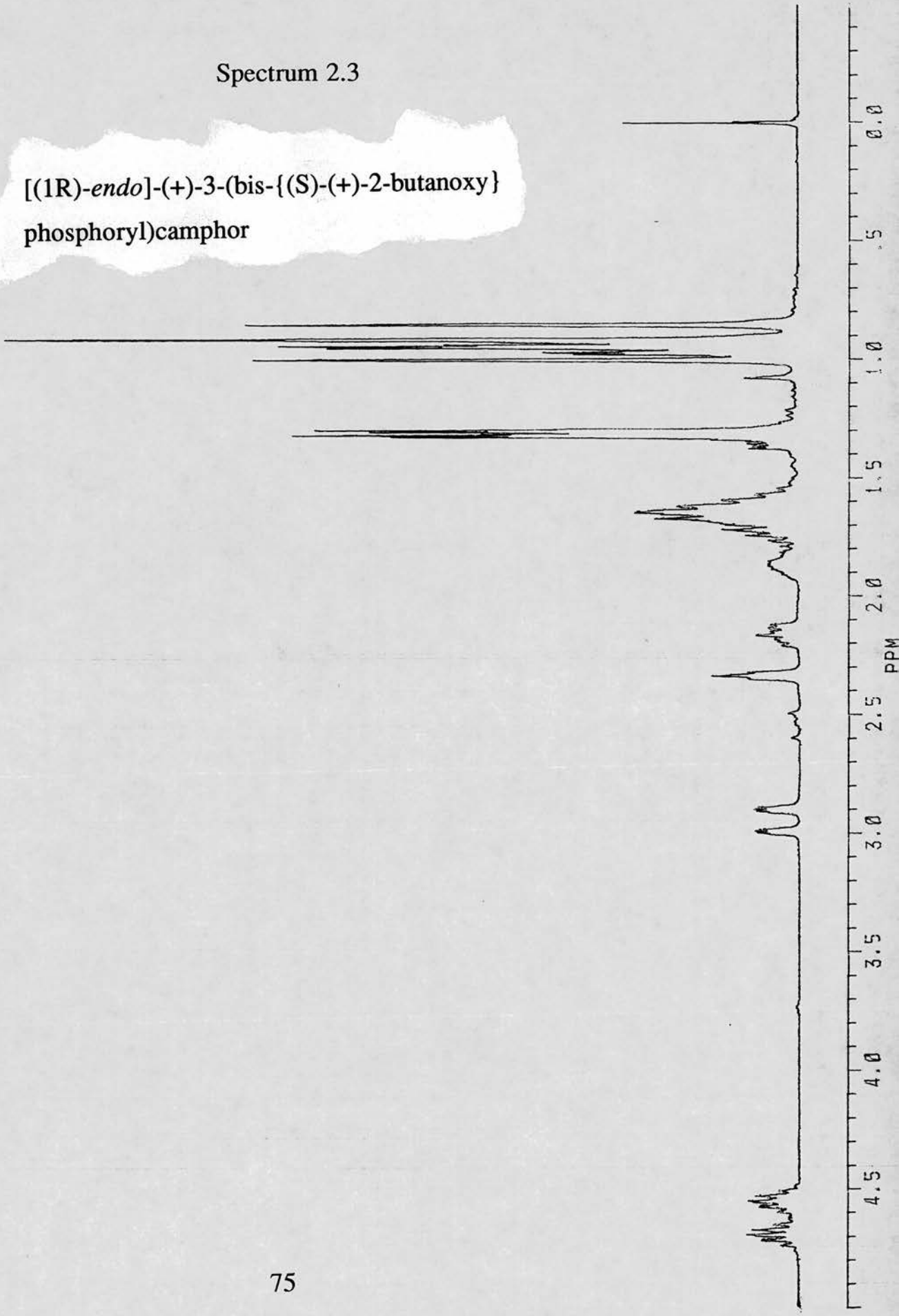


Fig 2.9

Equation 2.14

Spectrum 2.3

[(1R)-*endo*]-(+)-3-(bis-{(S)-(+)-2-butanoxy}
phosphoryl)camphor



The successful synthesis of [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 butanoxy}phosphoryl] camphor then led the way for the synthesis of a range of phosphonate compounds which differed either in the nature of the chirality present at camphor, or in that present at the secondary butyl groups which are attached to the phosphorus atom. To date all four possible diastereoisomers have been successfully synthesised, as shown on table 2.4.

Table 2.4.

	Nature of camphor chirality.	
	(R)-(+)	(S)-(-)
Nature of sec butyl chirality.		
(S)-(+)-2-butanol.	√	√
(R)-(-)-2-butanol.	√	√

Each of these isomers was synthesised using the same method outlined above, and presents the opportunity in the future for the study of the transition metal complexation chemistry of these diastereoisomers and their potential in epoxidation catalysis. It is hoped that during this study proof can be obtained as to what effects changing the chirality at differing places in the catalyst will have on the stereoselective nature of the epoxidation reaction upon different substrate alkenes, if any.

2.2.4 [(1R) - *endo*] - (+) - 3 - [(+,-) - (1,1 - bi - 2 - napthoxyphosphoryl)] camphor.

If the Bartlett butterfly mechanism operates for epoxidation reactions catalysed by Mo^{VI} complexes, it may be necessary for enantioselective reaction not only to increase the number of optically active centres around the metal centre, where the oxygen transfer is taking place, but also to develop a ligand with increased bulk around the metal. This would promote the chances of a lock and key effect during epoxidation. ie that an alkene approaching a metal centre in order to participate in nuleophilic substitution would, in a sterically crowded atmosphere, only be able to approach in one direction.

With this in mind that we have tried to develop a successful synthesis of [(1R) - *endo*] - (+) - 3 - [(+,-) - 1,1 - bi - 2 napthoxyphosphoryl)] camphor. In order to make use of 1,3 - phosphorus migration reaction it was necessary to develop a method for the production of (+,-) - 1,1 - bi - 2 - napthoxy phosphorochloridate,[Fig (2.10)] since it is not commercially available.This was achieved from reaction of (+,-) - 1,1 - bi - 2 - napthol with phosphorous oxychloride, and triethylamine in anhydrous methylene chloride.[Equation 2.15]

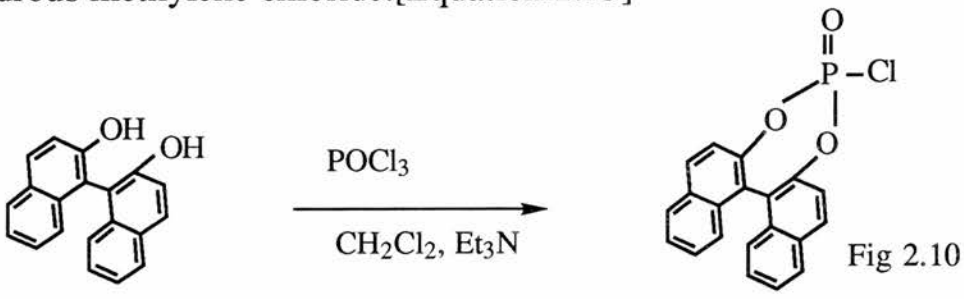


Fig 2.10

Equation 2.15

1,1 - bi - 2 - napthol is in itself asymmetric and therefore optically active, although it does contain any chiral centres. The reason for its asymmetry is due to the orientation of the nathyl ring systems, which cannot be in same plane.[Fig (2.11)] It therefore seems strange that in the attempted synthesis of optically active compounds, the starting material used should be a racemic mixture when each optical isomer is commercially available. However, the cost of each isomer was such that it was felt that if the phosphonate could be successfully synthesised in racemic form, then there was an excellent opportunity to resolve the isomers by some experimental means at that stage. This method is explained in more depth later in this section.

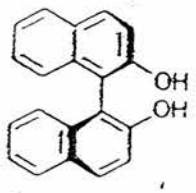


Fig 2.11

The phosphorochloridate can be transformed to the β-ketophosphonate [Fig (2.12)] using the method outlined in Equation 2.16. After the normal work-up with acetic acid is followed, a fine yellow powder of the product is obtained in very low yield.

As was stated earlier in this section, by using a racemic alcohol mixture at the start of the synthesis of the phosphonate, as expected a mixture of isomers was obtained on the purification of the product, which can be easily identified by ^{1}H nmr (spectrum 2.4), which showed six singlet peaks in the correct region, for the two sets of three methyl groups present on the two different diastereomers, and in addition, two overlapping doublet of multiplets at 3.0 ppm, representing the two different hydrogen atoms present on C3 of camphor.

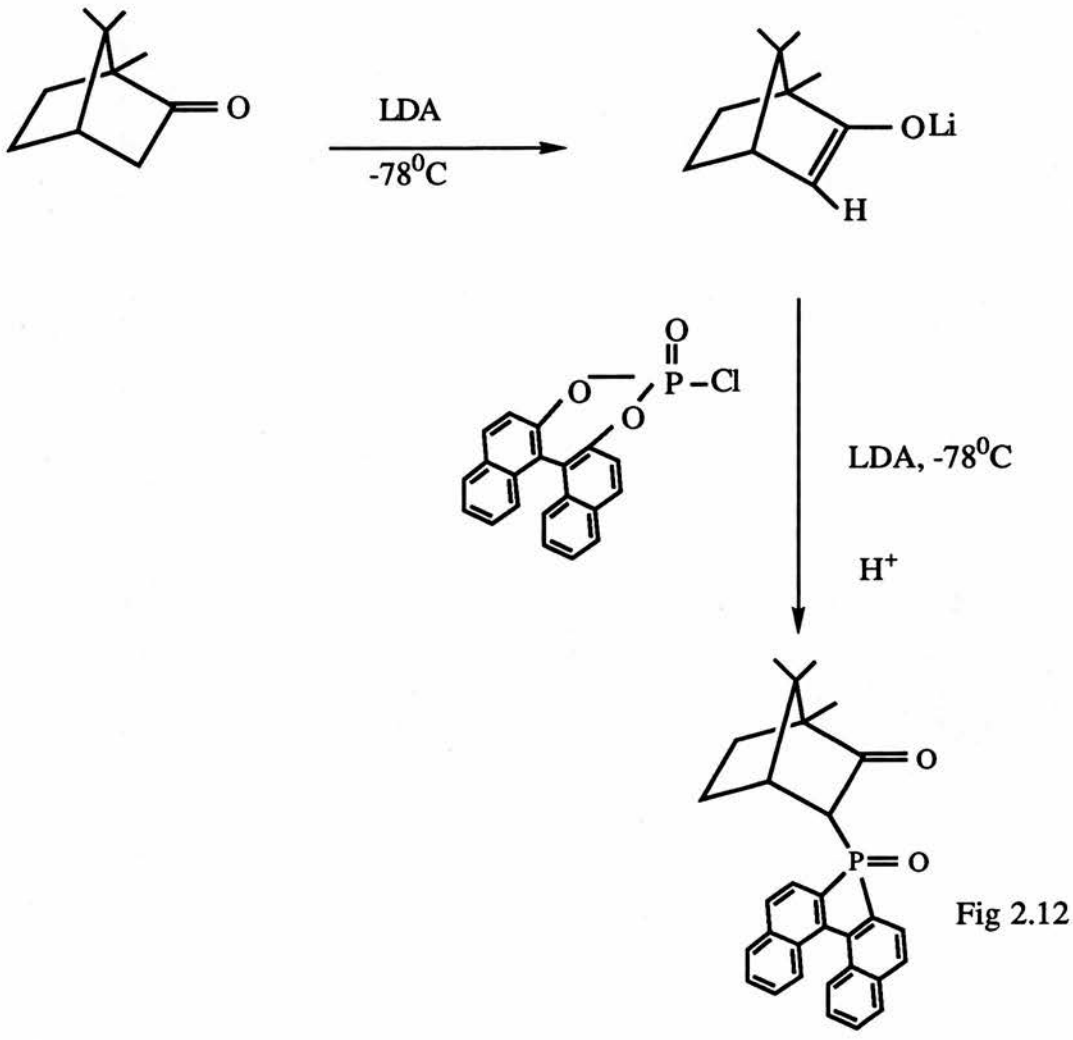


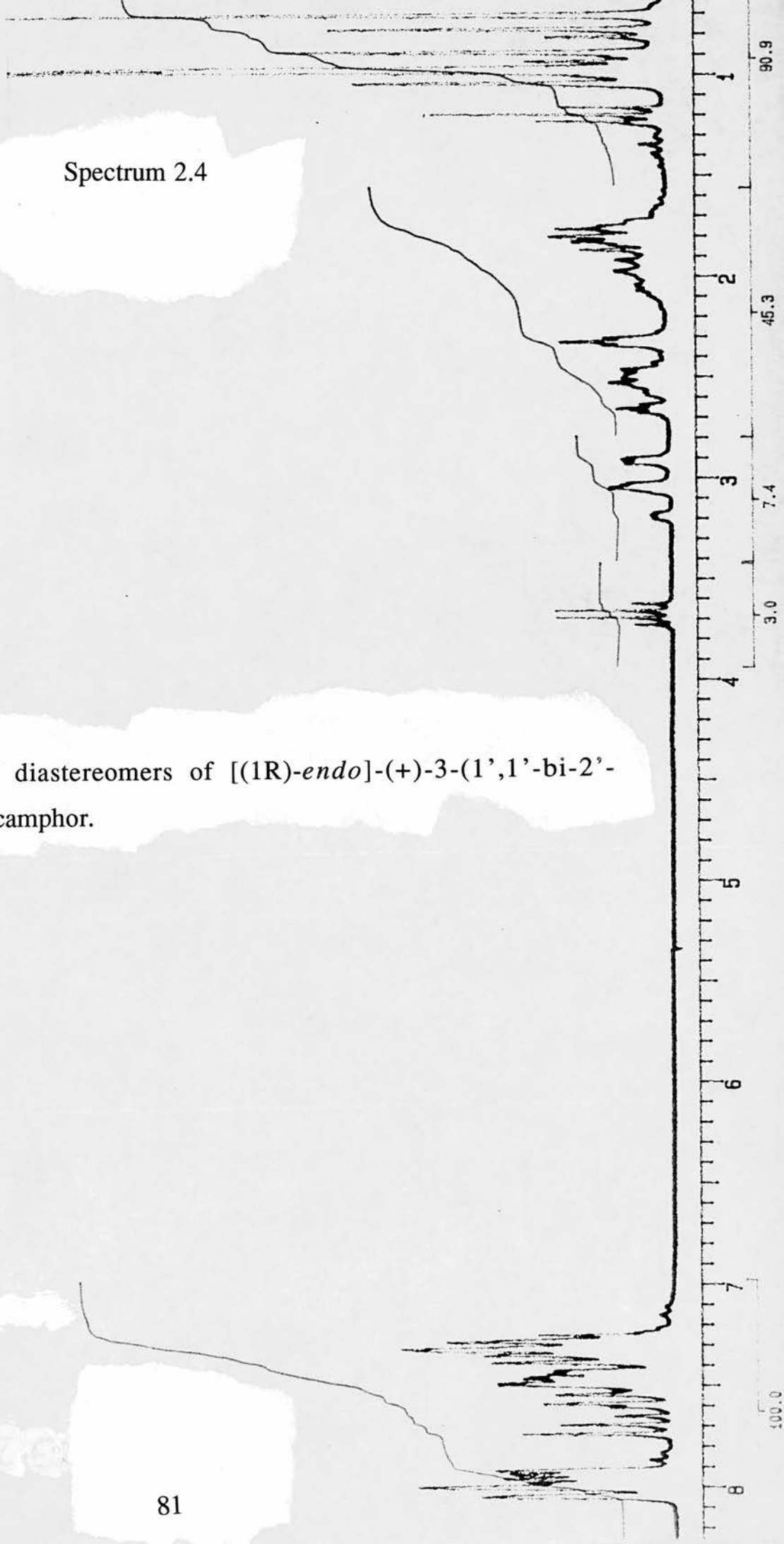
Fig 2.12

Equation 2.16

These two isomers can then be successfully separated by fractional recrystallisation from ethanol to give one diastereomerically pure isomer (spectrum 2.5), which as was hoped showed only one doublet of multiplets present at 3.0 ppm, and the corresponding three singlet peaks at approximately 1.0 ppm. These represent the three different methyl environments from the camphor starting material.

During the attempted purification of this compound, removal of the unreacted camphor proved to be more difficult since it was found that the target molecule decomposes at approximately 110^0C under vacuum. In this instance, the removal of free camphor by sublimation could only be achieved with a great deal of care, by ensuring that the temperature of the system did not rise above this decomposition temperature.

Spectrum 2.4



Racemic mixture of diastereomers of [(1R)-*endo*]-(+)-3-(1',1'-bi-2'-napthoxyphosphoryl) camphor.

Spectrum 2.5

[(1R)-*endo*]-(+)-3-(1',1'-bi-2'-napthoxyphosphoryl) camphor.

2.2.5 [(1R) - *endo*] - (+) - (3) - [(+,-) - bis-{pinacolyloxy}phosphoryl] camphor.

The synthesis of this ligand was attempted for the same reasons as those outlined in the previous sections of this chapter. ie that it would present a different opportunity to study the effect of variation of steric bulk and increased chirality upon the the reactivity and selectivity shown during the attempted catalytic epoxidation of a number of alkenes.

The synthesis of this phosphonate began in a similar manner to that of the bis-butanoxy phosphonates ie from the alcohol [Equation 2.17] However, the enantiomerically pure alcohol was not commercially available and so the racemic version was used instead. Again it was hoped that at some future stage in the synthetic proceedure the different isomers could be separated into their optically pure components. As before the alcohol was added dropwise to the mixture of phosphorus trichloride and triethylamine, in anhydrous diethyl ether solution to produce the chlorophosphine, which was then easily hydrolysed to the phosphite by addition to a large excess of ice. The phosphorochloridate [Fig (2.13)] was then obtained by reaction of the phosphite with sulphuryl chloride in anhydrous methylene chloride at room temperature. However, when the synthesis of the β-ketophosphonate was attempted, on work-up of the reaction mixture it was found that not all of the vinyl phosphate had rearranged to the phosphonate. It is possible that a greater excess of lithium diisopropylamine is required for this step of the reaction to ensure that it proceeds fully to completion.

However, it is important to note that the main product from this reaction is the β-ketophosphonate, and this was verified by ^{1}H nmr which showed the characteristic doublet of multiplets at 3.0 ppm for the hydrogen atom at C3 on camphor.

This synthesis has not been repeated since it was decided to concentrate on those β-ketophosphonates which can be derived from enantiomerically pure alcohols.

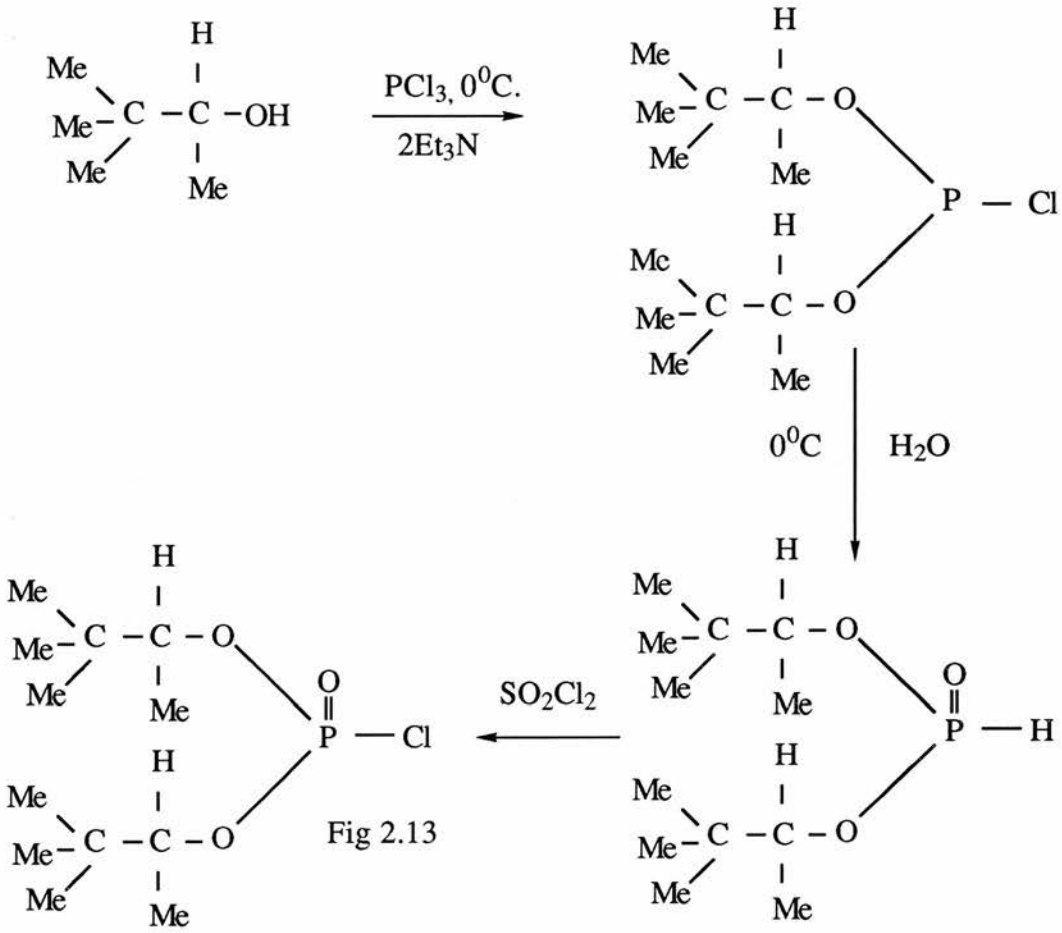


Fig 2.13

Equation 2.17

2.2.6 [(1R) - *endo*] - (+) - (3) - [(+,-) - bis-{α - methyl benzoxy}phosphoryl] camphor.

Once again the aim in trying to synthesise this ligand was that it could provide a transition metal complex which would include the bulk of the phenyl groups present and in addition optically active centres present on the alkoxy groups attatched to the phosphorous. [Equation 2.18]

Since the phosphorochloridate [Fig (2.15)] was again commercially unavailable the same method as previously outlined was attempted, starting from the racemic alcohol [Fig (2.14)].

During the first step of this reaction scheme, the intended chlorophosphine product seemed to have been successfully synthesised, since on addition of the alcohol, a great deal of white precipitate appeared indicating the formation of the triethylaminehydrochloride salt. The salt was then filtered as normal and the filtrate poured into a solution of iced water to effect the hydrolysis step. However, on treatment of the phosphite with sulphuryl chloride, decomposition seemed to take place since the solution immediately turned a lime green colour, which is unexpected since in previous reactions the phosphorochloridate gave a colourless solution. On examination of the ^1H nmr a styrene type species seemed to be present which confirmed some kind of decomposition. The presence of the styrene type species in the ^1H nmr of the decomposition products is a good indication that an elimination reaction is taking place at some stage during the reaction which would be analogous to that of an alkyl halide when treated with base to yield an alkene.

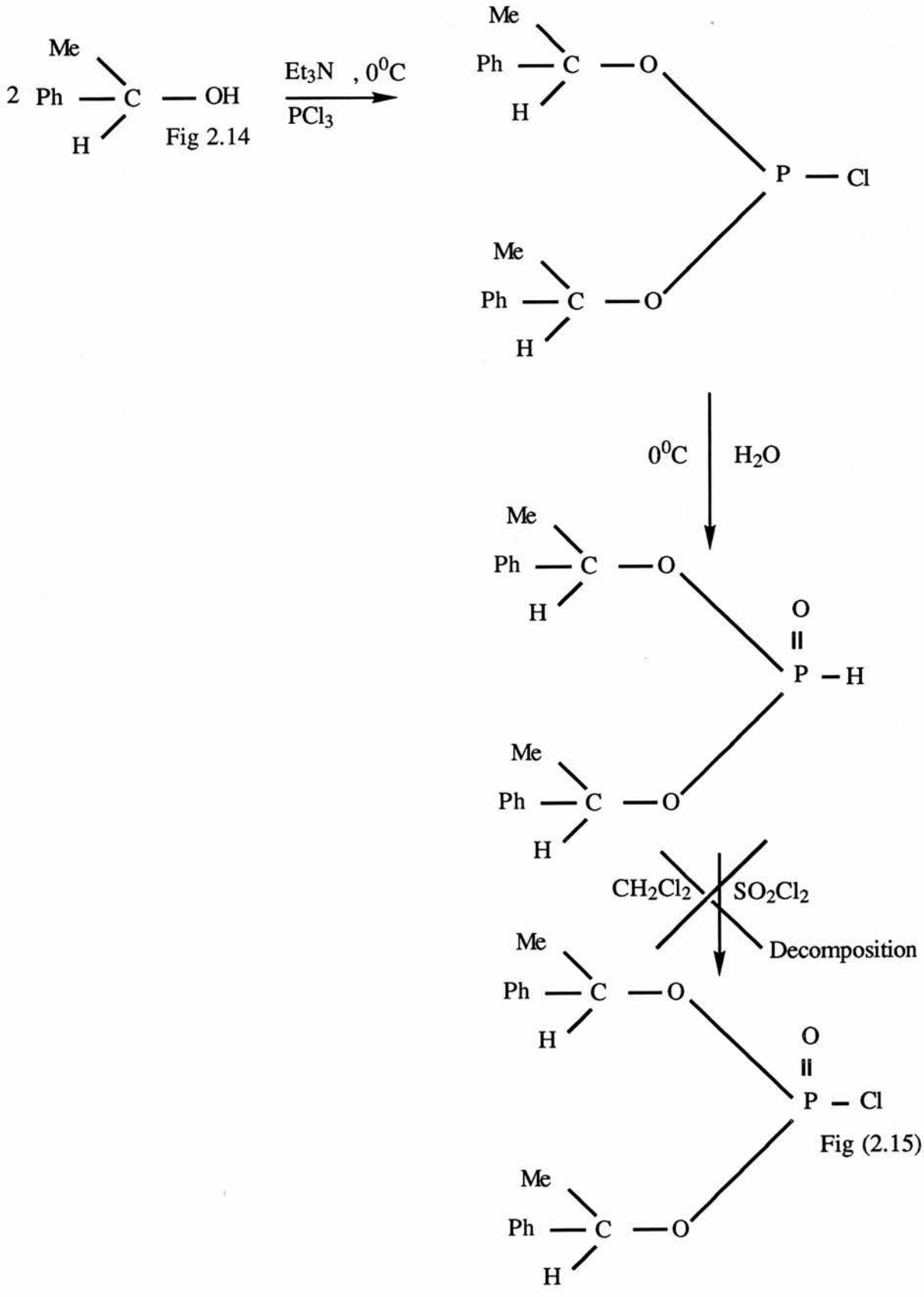


Fig 2.14

Fig (2.15)

Equation 2.18

2.2.7 [(1R) - *endo*] - (+) - (3) - [(+,-) - {ethoxynapthoxy}phosphoryl] camphor.

Since the aim of synthesising many of these ligands has been to try and introduce chirality as close to the metal centre as possible, in the hope that stereoselectivity can be observed during epoxidation catalysis, it was decided to try and synthesise a molecule which would have chirality present at the phosphorus atom. It is thought that in this system during the epoxidation mechanism, the P=O bond remains coordinated to the metal centre, whilst the C=O metal bond breaks to provide a coordination site for the oxidant during the epoxidation reaction. This is thought to be the case due to crystal structure data obtained on [(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor,[209] which indicates that the metal-oxygen bond is shorter for the phosphoryl oxygen than for the carbonyl oxygen. If a ligand can be made therefore which includes a chiral phosphorus atom, this may increase the chances of selectivity being observed.

A good starting point seemed to be from a molecule such as the commercially available ethyl dichlorophosphite [Fig (2.15)]. Using a similar method as that described above, [Equation 2.19] ethyl dichlorophosphite was added to a solution containing triethylamine and anhydrous diethyl ether. To this solution, (which had been cooled to 0^0C) was added dropwise with stirring, 2-napthol in anhydrous diethyl ether. On addition of the alcohol, a white precipitate of the triethylaminehydrochloride was seen to appear, indicating that the reaction had been successful.

The mixture was then allowed to stir overnight after which time it was poured into a large excess of ice with stirring to form the phosphite. The successful synthesis of the phosphite was verified by ^1H nmr (spectrum 2.6), where a doublet with a large J_{PH} can be easily seen. (ie approximately 700 Hz). This ^1Hnmr was obtained at 200MHz nmr, whereas the previous nmr displayed of another phosphite, (S) - (+) - dibutyl phosphite, was obtained at 300MHz nmr, hence the slight differences in the appearance of the spectrum even though the coupling constants are very similar. (This coupling constant of approximately 690 - 700 Hz, has been found from this work to be a typical and indicative value for this class of compound.)

However, when the attempted chlorination was carried out decomposition again seemed to occur, since the reaction mixture turned a green colour immediately on addition of the chlorinating agent. As with the reaction using α-methylphenyl alcohol, it seems likely that this is due to the presence of free HCl generated during the reaction.

On analysis of the reaction products it was found that there appeared to be no ethoxy groups now attached to the phosphorus atom, indicating that a nucleophilic substitution is taking place, possibly with the chloride ion generated during the reaction acting as the nucleophile. To try and investigate this reaction in a little more depth, a similar procedure was carried out as previously outlined in order to synthesise the phosphite intermediate.

However, on attempted chlorination of the phosphite in this instance, the base triethylamine was present in the reaction mixture to try and prevent any interaction between the HCl formed during the reaction and the phosphorochloridate, by formation of the triethylaminehydrochloride salt.

However, it was found that once again on addition of the chlorinating agent sulphuryl chloride, the solution turned a lime green colour again indicating decomposition of the intended product.

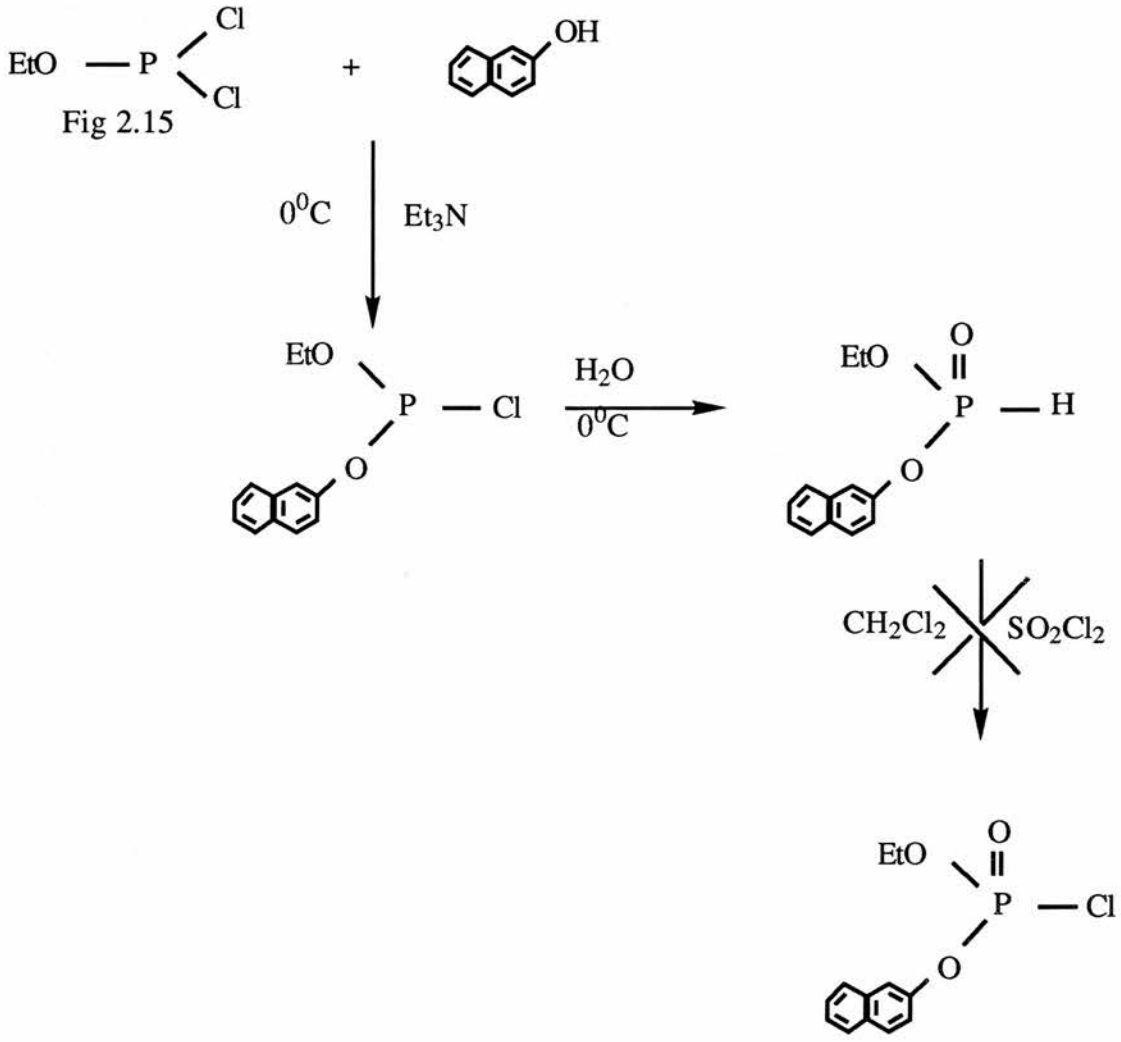
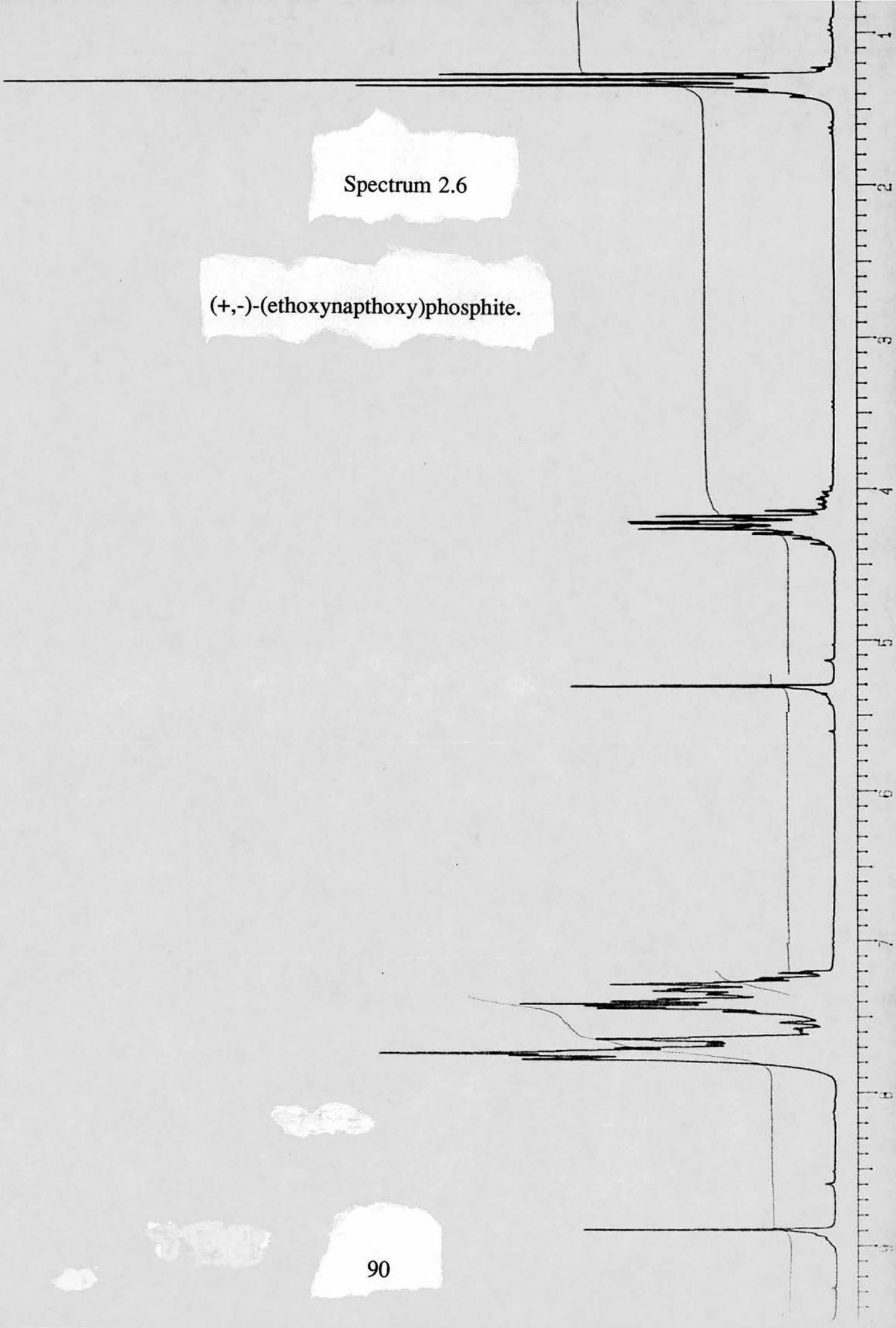


Fig 2.15

Equation 2.19

Spectrum 2.6

(+,-)-(ethoxynapthoxy)phosphite.



2.2.8 [(1R) - *endo*] - (+) - (3) - (diphenylphosphoryl) camphor.

This ligand is prepared by oxidation [(1R) - *endo*] - (+) - (3) - (diphenylphosphino) camphor with hydrogen peroxide or in air, and has been previously synthesised in this laboratory.[210] (Equation 2.20)

In the ^{1}Hnmr the compound produced also displayed the characteristic doublet of multiplets for the hydrogen attached to C3 of camphor (spectrum 2.7).

It was decided to synthesise this ligand again because the transition metal complex chemistry had never been studied or examined for epoxidation activity.

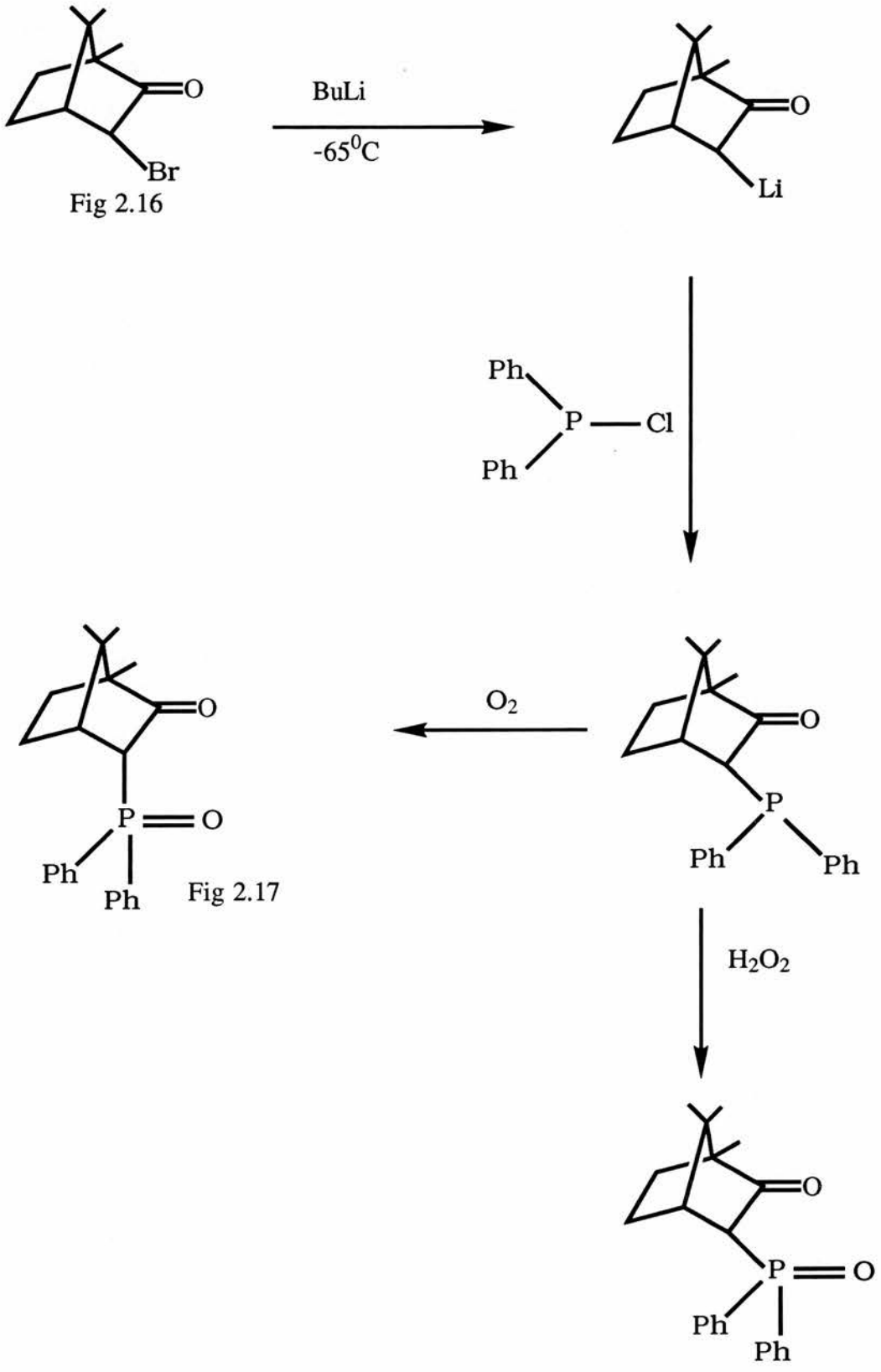


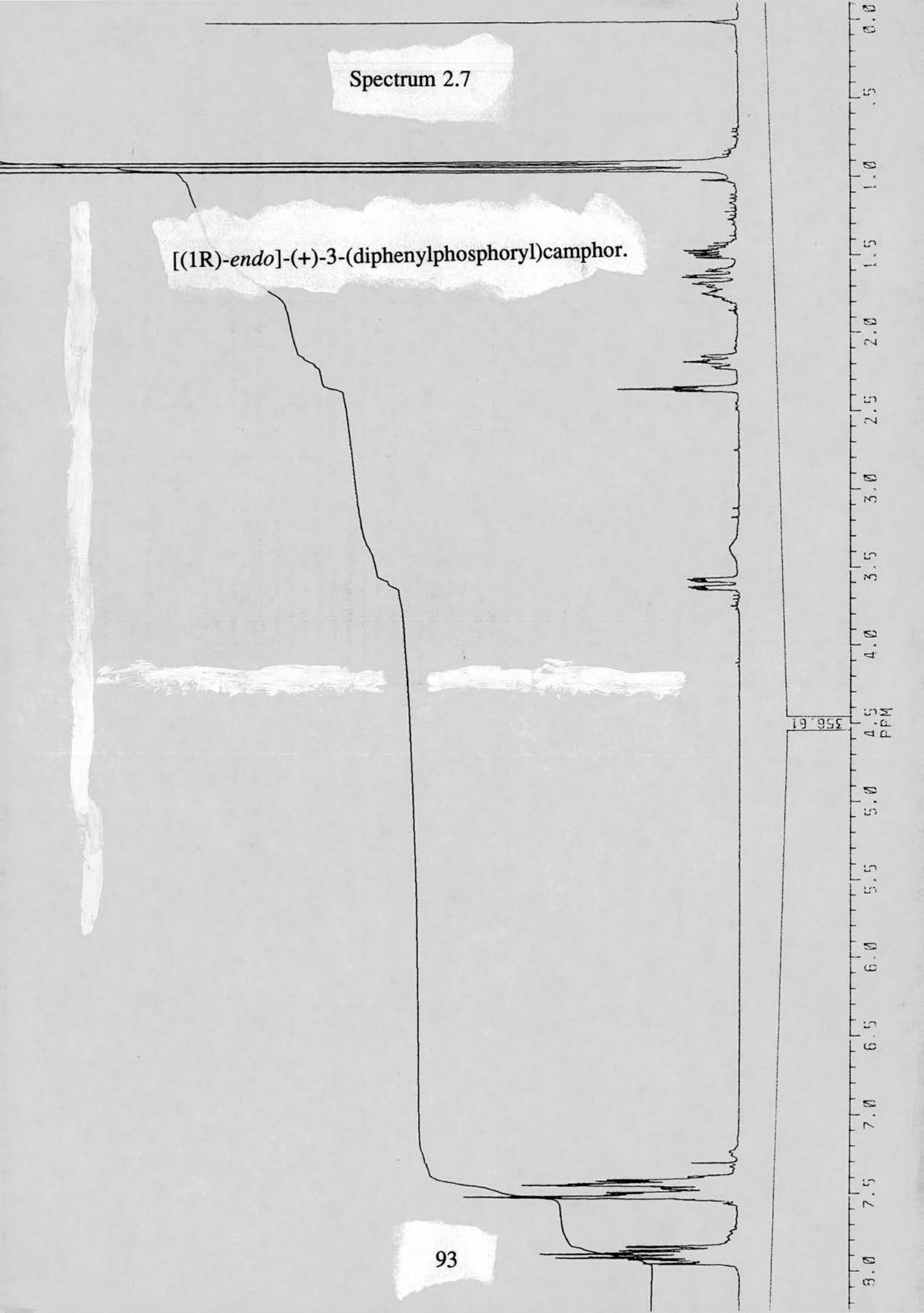
Fig 2.16

Fig 2.17

Equation 2.20

Spectrum 2.7

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



2.2.9 Summary of the Synthesis of β-ketophosphonate ligands.

As was mentioned earlier in this chapter, it was the intention of this research to attempt to synthesise a range of β-ketophosphonate ligands based around the chiral molecule camphor which varied not only in size but also nature and number of asymmetric centres.

The synthesis of a number of different ligands has been attempted, and in most cases these reactions have proved to be successful. From this synthetic work it then seemed possible to be able to investigate thoroughly how these variations in structure and stereochemistry would affect the reactivity and selectivity of these ligands when incorporated into transition metal complexes. Table 2.5 displays a full list of the ligands which have been successfully synthesised.

Table 2.5.

Nature of Group	Stereochemistry at Camphor.	
Attached to Phosphorus.	(R) - (+)	(S) -(-)
OEt	√	√
OBu (secondary) (S) - (+)	√	√
OBu (secondary) (R) - (-)	√	√
O_2BiNap	√	
Ph	√	
OPinacolyl	√	

2.3 Transition Metal Complexation Chemistry of β-ketophosphonates.

Previous work using β-ketophosphonates as ligands for complexation to transition metals have shown that [(1R) - *endo*] - (+) - (3) - (diethoxyphosphoryl) camphor will efficiently complex to molybdenum dioxide dichloride, binding in a bidentate manner, through the C=O, and P=O present in the ligand, to give the transition metal complex [Fig (2.18)].

The synthesis of this metal complex is very simple [Equation 2.21] and involves the the addition of the ligand at room temperature to a solution of molybdenum dioxide dichloride in anhydrous THF with stirring. This mixture can be left for approximately one hour after which time the reaction has normally gone to completion.

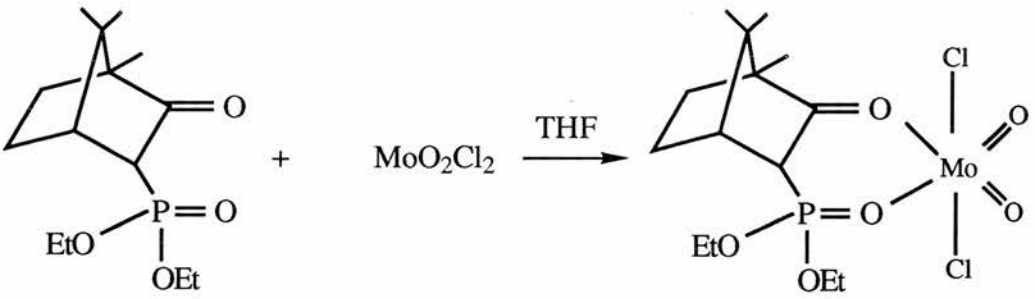


Fig 2.18

Equation 2.21

On formation of the complex a great deal of care must be exercised to ensure that they do not come into contact with air. These complexes can be easily identified by a number of methods which include elemental analysis, and also infra-red which on formation of this type of complex display a very characteristic stretching for the carbonyl group on camphor at approximately 1690 cm^{-1} - 1700 cm^{-1}. cf 1735-1745cm^{-1} for the free ligand.

In addition, on analysis of these complexes by ^{1}H nmr it has been shown that the doublet of doublets which normally resonates at 3.0 ppm for the free ligand, is shifted to approximately 3.8 ppm, most likely due to the Lewis acid nature of the metal centre. This is readily illustrated by comparison of the ^{1}H nmr of the free ligand [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor (spectrum 2.3) and that of the metal complex of this ligand dichloro {[(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum(VI) (spectrum 2.8).[Fig (2.19)]

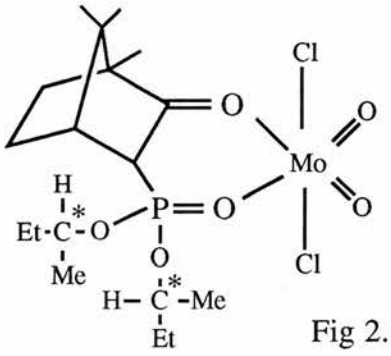


Fig 2.19

(*) - indicates the chiral carbon atom present on the alkoxide chain.

As well as the differences already outlined it is clear that the two methyl groups attached to the chiral carbon atoms on the secondary butanoxy chains have been resolved to show that in the metal complex they are in different orientations, since two distinct doublets at approximately 1.5 ppm in the metal complex spectrum can be clearly distinguished, whereas this is not the case in the spectrum of the free ligand. (spectrum 2.3).

These methyl groups are of course represented as doublets due to coupling by the neighbouring hydrogen atom which is also attached the the chiral carbon atom.

The metal instils greater rigidity into the structure which is not present in the free ligand, and so one methyl group is above the plane of the Mo-O-C-C-P-O ring whilst the other is below it.The bridgehead of the camphor is above the plane.

Only the coordination of the ligands with MoO_2Cl_2 was investigated because the major purpose of the project was to study the use of these complexes in epoxidation, and subsequently ring opening reactions.

The metal complexes which have been successfully synthesised are shown in table 2.6 below.

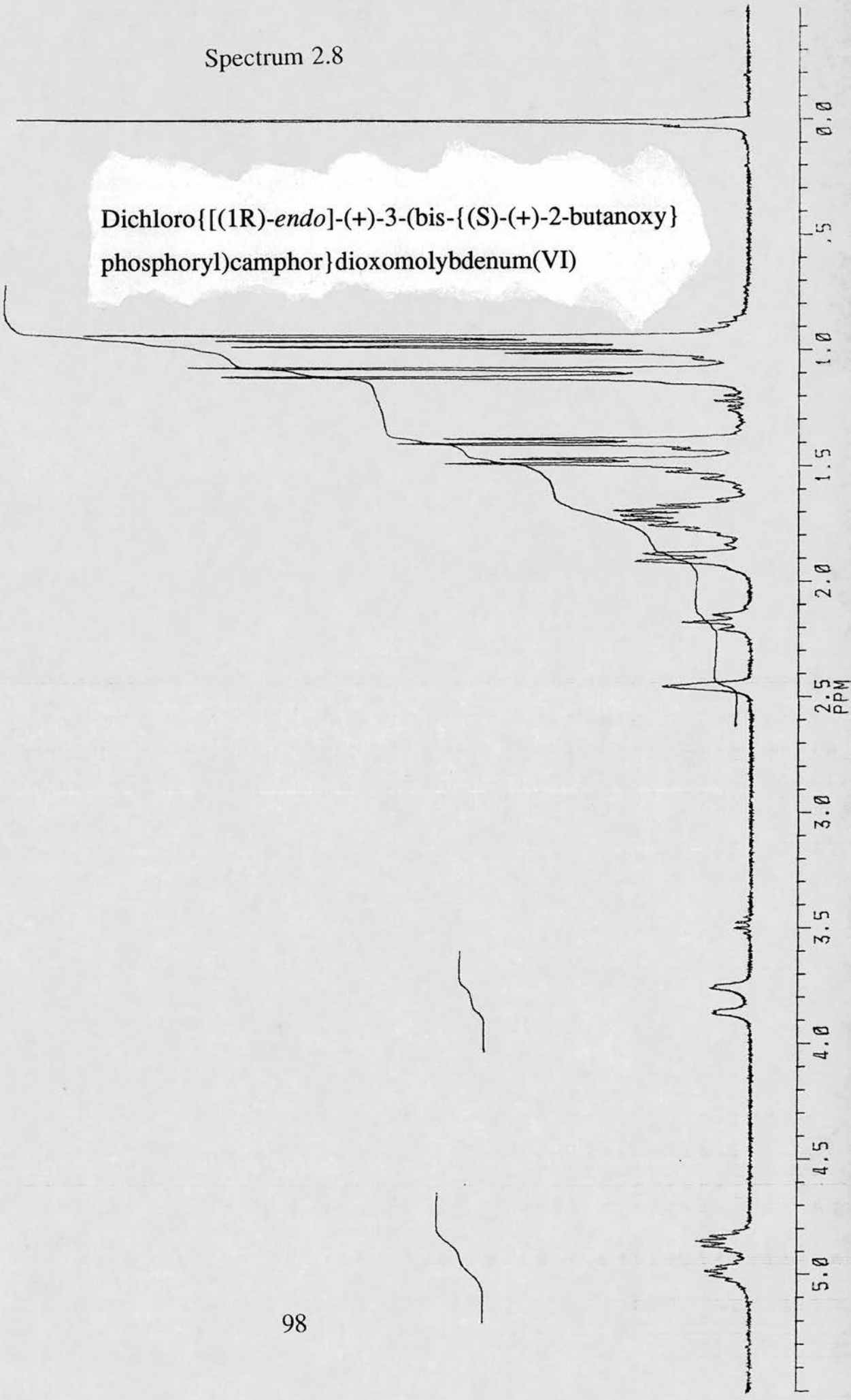
Table 2.6

Nature of the group attached to the phosphorus atom.	Nature of chirality at camphor. (R) -(+)	(S) -(-)
OEt	√	√
OBu (secondary) (S) - (+)	√	√
OBu (secondary) (R) - (-)	√	√
Ph	√	

The attempted synthesis of the metal complex using the ligand O_2BiNap was not successful.

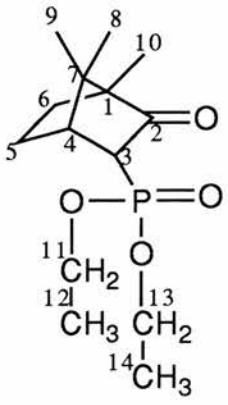
Spectrum 2.8

Dichloro{[(1R)-*endo*]-(+)-3-(bis-{(S)-(+)-2-butanoxy}phosphoryl)camphor}dioxomolybdenum(VI)

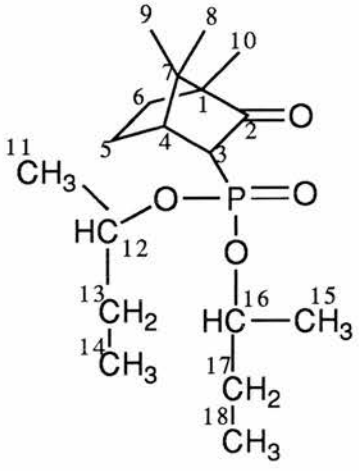


2.4 Assignment of ligands and complexes using nmr.

Assignment of ligands and complexes using ^{1}H and ^{13}C nmr.
(Each carbon atom is numbered which corresponds to the nmr data)



diethoxy ligand



Bis-butanoxy ligand

Table 2.7.

^{1}H nmr Assignments For Ligands and Complexes.(Solvent used was $CDCl_3$)

Compound Name.	Value of Chemical Shift, ppm. (Multiplicity, Integration value).										
	CH-3	CH-4	CH-5 *endo*	CH-5 *exo*	CH-6 *endo*	CH-6 *exo*	CH_3-8	CH_3-9	CH_3-10	CH_2-11/13	CH_3-12/14
[(1S)-*endo*]-(-)-3-(diethoxyphosphoryl) camphor. (L_1)	3.0 (dm,1H) (J_{P-H} : 27.4)	2.35 (t,1H)	2.1 (m,1H)	1.9 (m,1H)	1.7 (m,2H)		0.85 (s,3H)	0.9 (s,3H)	1.0 (s,3H)	4.2 (m,4H)	1.35 (t,6H)
$MoO_2Cl_2(L_1)$	3.8 (dm,1H) (J_{P-H} : 32.06)	2.5 (t,1H)	2.1 (m,1H)	1.9 (m,1H)	1.55 (m,2H)		0.9 (s,3H)	1.0 (s,3H)	1.1 (s,3H)	4.4 (m,4H)	1.4, 1.35 (t,3H),(t,3H)
										Aromatic Protons.	
[(1R)-*endo*]-(+)-3-[(+,-)-(1,1-bi-2-napthoxyphosphoryl)] camphor.	3.0 (dm,1H)	2.3 (t,1H)	2.5 (m,1H)		1.8 (m,3H)			0.7, 1.0 (s,3H),(s,6H)		7.25-8.05 (m,12H)	
										Aromatic Protons.	
$MoO_2Cl_2(L_2)$ (where L_2 is [(1R)-*endo*] -(+)-(3)-(diphenylphosphoryl) camphor.	4.55 (dm,1H)	2.7 (t,1H)		1.5-2.0 (m,4H)				1.1,1.0,0.95 (s,3H),(s,3H),(s,3H)		7.5-8.0 (m,10H)	

Table 2.8.

^{1}H nmr Assignments For Ligands and Complexes.(Solvent used was $CDCl_3$)

Compound Name.	Value of Chemical Shift, ppm. (Multiplicity, Integration value).												
	CH-3	CH-4	CH-5 *endo*	CH-5 *exo*	CH-6 *endo*	CH-6 *exo*	CH_2-13/17	CH_3-8	CH_3-9	CH_3-10	CH_3-14/18	CH_3-11/15	CH-12/16
[(1R)-*endo*]-(+)-3-[bis {(S)-(+)-2-butanoxy} phosphoryl]camphor[(A)] (=L_3)	2.9 (dm,1H) (J_{P-H} : 27.58)	2.3 (t,1H)	2.15 (m,1H)	1.90 (m,1H)		1.6 (m,6H)		0.8, 0.9, 1.0. (s,3H),(s,3H),(s,3H)			0.9 (m,6H)	1.3 (m,6H)	4.55, 4.65 (m,1H),(m,1H)
$MoO_2Cl_2(L_3)$[(A)]	3.8 (dm,1H) (J_{P-H} : 32.28)	2.45 (t,1H)	2.15 (m,1H)		1.7, 1.9 (m,5H),(m,2H)					0.95, 1.0, 1.05 (m,9H),(s,3H),(s,3H)		1.4, 1.5 (d,3H),(d,3H)	4.85, 5.0 (m,1H),(m,1H)
[(1R)-*endo*]-(+)-3-[bis {(R)-(-)-2-butanoxy} phosphoryl]camphor[(B)] (=L_4)	2.95 (dm,1H) (J_{P-H} : 27.52)	2.35 (t,1H)	2.20 (m,1H)	1.90 (m,1H)		1.65 (m,6H)				0.85, 0.95,1.0. (s,3H),(m,9H),(s,3H)		1.35, 1.40 (d,3H), (d,3H)	4.55, 4.65 (m,1H),(m,1H)
$MoO_2Cl_2(L_4)$[(B)]	3.8 (dm,1H) (J_{P-H} : 32.16)	2.45 (t,1H)	2.15 (m,1H)		1.65, 1.85 (m,5H),(m,2H)					0.9, 1.05, 1.1. (m,9H), (s,3H), (s,3H)		1.4 (m,4H)	4.85, 5.05 (m,1H),(m,1H)

(A) : Also applicable to [(1S)-*endo*]-(-)-3-[bis {(R)-(-)-2-butanoxy}phosphoryl)camphor.

(B) : Also applicable to [(1S)-*endo*]-(-)-3-[bis {(S)-(+)-2-butanoxy]phosphoryl)camphor.

Table 2.9

^{13}C nmr Assignments for β-ketophosphonate ligands.(Solvent used was $CDCl_3$)

	Value of Chemical Shift, ppm.(Coupling constant J_{P-C},Hz)													
Compound name.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11/13	C12/14		
[(1S)-*endo*]-(-)-3-	58.89	211.33	50.67	46.18	23.01	29.72	49.92	18.74	19.39	9.64	62.04/61.89	16.43		
(diethoxyphosphoryl)	(3.78)	(2.09)	(144.29)	(1.64)	(4.87)	(0.00)	(17.37)	(0.00)	(0.00)	(0.00)	(6.27/7.00)	(6.09)		
camphor.														
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11/15	C12/16	C13/17	C14/18
[(1R)-*endo*]-(+)-3-	58.93	211.39	51.37	46.36	22.92	29.68	46.79	18.75	19.43	9.68	21.13/20.93	75.10/74.83	30.62/30.43	9.46/9.33
[bis {(S)-(+)-2-butanoxy}	(3.64)	(0.00)	(145.99)	(1.87)	(5.00)	(0.00)	(17.17)	(0.00)	(0.00)	(0.00)	(3.58/10.06)	(6.95/7.19)	(4.47/6.14)	(0.00)
phosphoryl] camphor.(A)														
[(1R)-*endo*]-(+)-3-	58.86	211.32	51.19	46.34	22.94	29.63	46.76	18.74	19.40	9.67	21.46/21.00	75.29/74.74	30.71/30.39	9.34/9.29
[bis {(R)-(-)-2-butanoxy}	(3.8)	(2.66)	(145.55)	(1.67)	(4.98)	(0.00)	(17.18)	(0.00)	(0.00)	(0.00)	(1.67/3.72)	(6.95/7.22)	(3.61/5.89)	(0.00)
phosphoryl] camphor.(B)														

(A) : Also applies to [(1S)-*endo*]-(-)-3-[bis {(R)-(-)-2-butanoxy}phosphoryl] camphor.

(B) : Also applies to [(1S)-*endo*]-(-)-3-[bis {(S)-(+)-2-butanoxy}phosphoryl] camphor.

CHAPTER THREE

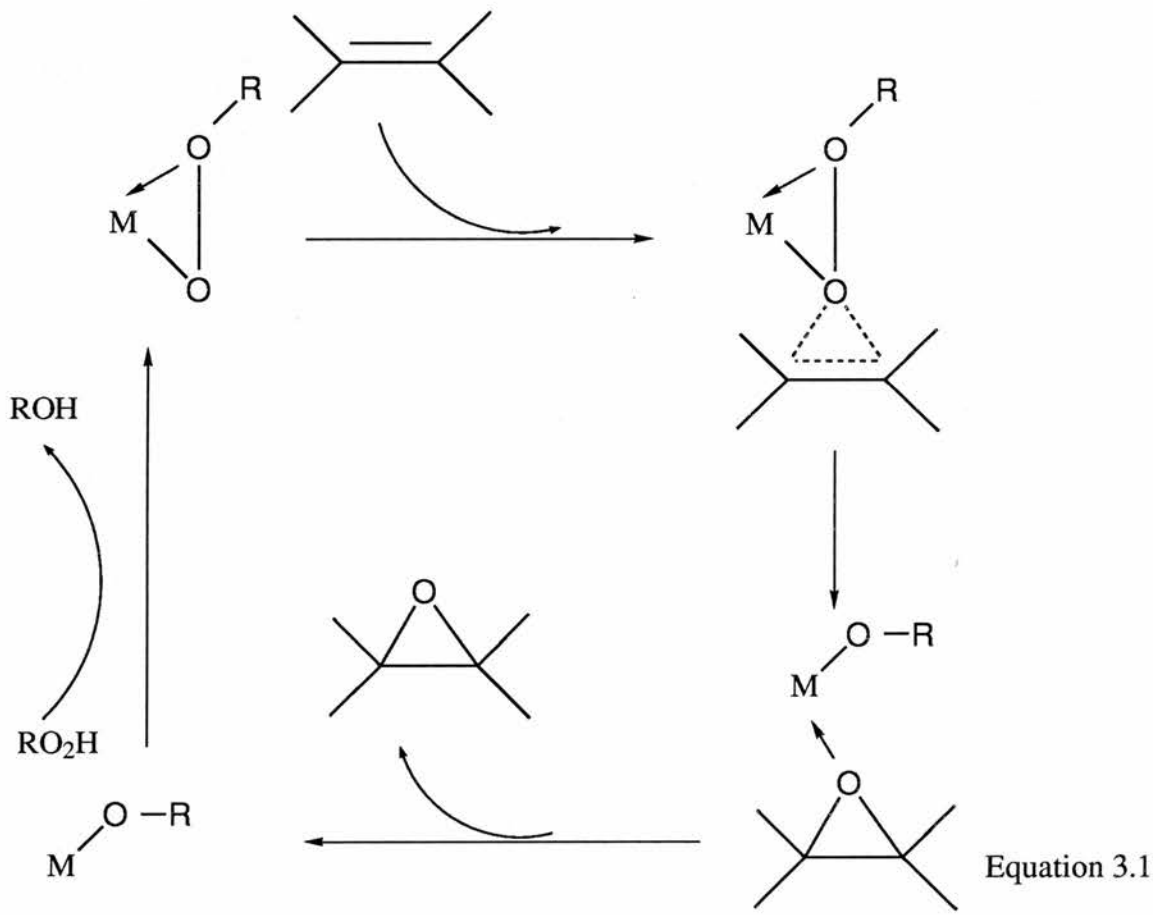
CATALYTIC STUDIES CARRIED OUT USING ASYMMETRIC β-KETOPHOSPHONATE TRANSITION METAL COMPLEXES.

Chapter 3.

Catalytic Studies Carried Out Using Asymmetric β-ketophosphonate Transition Metal Complexes.

3.1 Catalytic Mechanism.

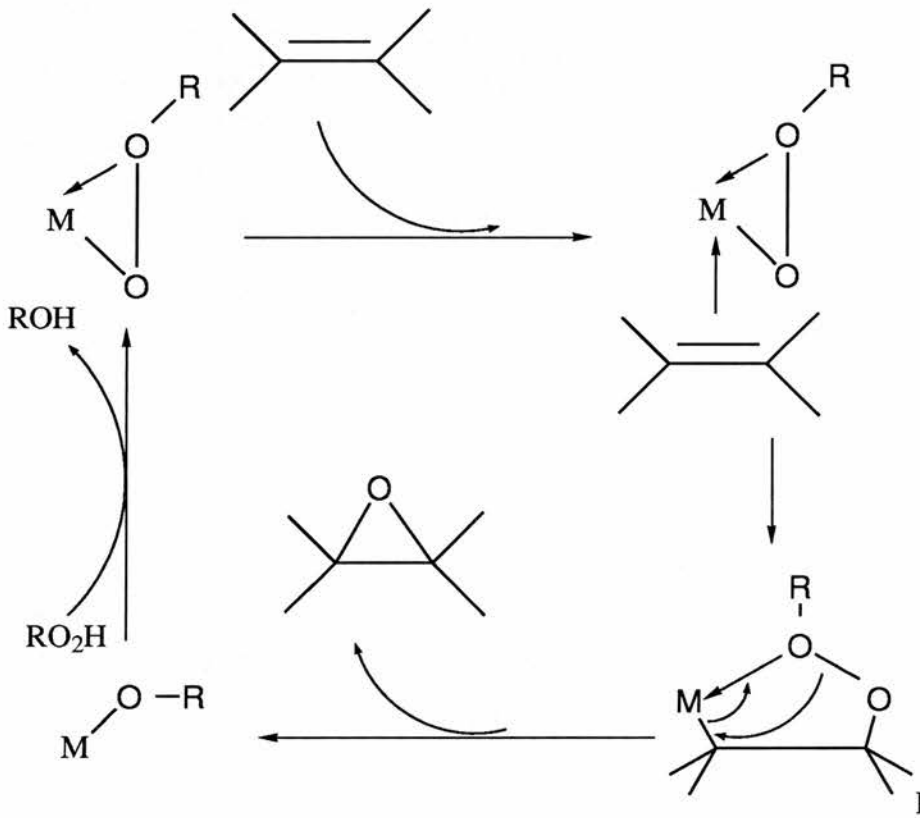
The most widely accepted mechanism for the epoxidation of alkenes using a transition metal complex is reminiscent of Bartlett's Butterfly mechanism for the epoxidation of alkenes by percarboxylic acids,[30] during which a nucleophilic attack of the alkene on the "electrophilic" oxygen of the coordinated hydroperoxide occurs. (Equation 3.1)



Equation 3.1

It is thought that when the metal-hydroperoxide complex forms, 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.

An alternative mechanism has been proposed by Mimoun and colleagues for the epoxidation of alkenes by peroxidic reagents.[211] (Equation 3.2)



Equation 3.2

During this mechanism the alkene is believed to coordinate to the metal. This is followed by insertion of the alkene into the M-O(peroxo) bond by an intramolecular 1,3 - dipolar mechanism to give a five membered peroxymetallacycle. This then decomposes by a 1,3 dipolar cycloreversion to give an epoxide and the metal alkoxide.

Since there are no d electrons available for back bonding to the alkene the nature of the interaction between the alkene and the metal atom would have to be a purely Lewis base - Lewis acid one.

This type of mechanism seems unlikely for the early d^0 transition metals for a number of reasons. First of all, the formation of the peroxymetallocycle should be easiest for electron deficient alkenes which are suited to 1,3 - dipolar additions as observed with platinum peroxides. However, such electron-deficient alkenes are unreactive towards epoxidations with alkyl peroxides catalysed by high valent early transition metals.[211] In addition, with allylic alcohols, peroxymetallation demands the formation of a strained bicyclic intermediate which is unfavourable, if there is the expected binding of the OH group to the metal. Also molybdenum porphyrin complexes have been shown to catalyse the epoxidation of alkenes by a hydroperoxide. In such a case, the steric constraints imposed by the macrocycle makes it difficult for both the alkene and the hydroperoxide to be bound to the metal at the same time.[95]

3.2 Results of Epoxidation Catalysis Using β - ketophosphonate Transition Metal Complexes.

3.2.1 Epoxidation Studies Carried Out Using Dichloro{[(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum (VI).

From previous work carried out in this laboratory it has been shown that the transition metal complex dichloro{[(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum (VI) (Fig 3.1) displayed excellent activity as a catalyst during the epoxidation of 1-methyl-1-cyclohexene.[209] (Equation 3.3) This activity was of course dependent upon the the reaction conditions and the catalyst to substrate ratio, although no stereoselectivity was observed.

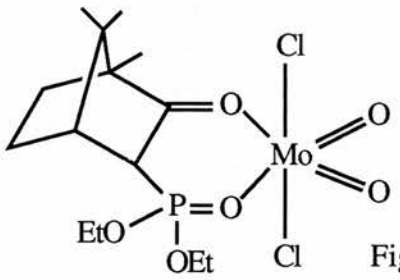
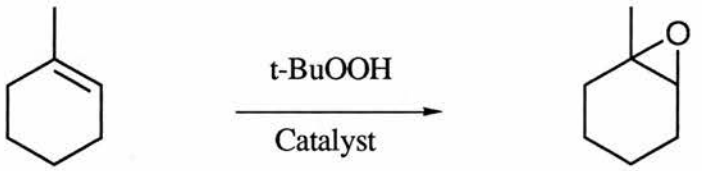


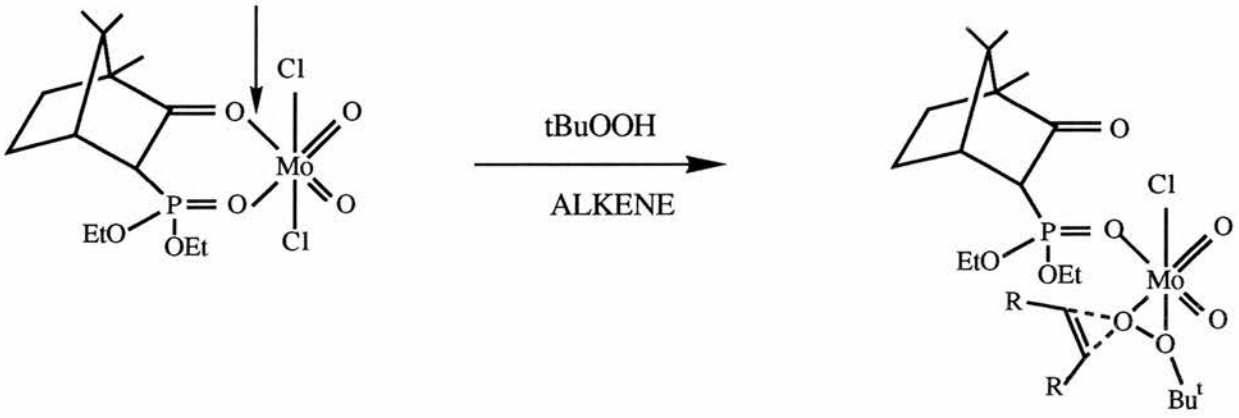
Fig 3.1



Equation 3.3

By crystal structure analysis it was shown that in this β-ketophosphonate complex the carbonyl oxygen to metal bond is longer than the corresponding phosphoryl oxygen to metal bond length and hence should be weaker.[209] This weaker bond should then break preferentially to create a site for coordination of the hydroperoxide to the metal during an epoxidation reaction. (Equation 3.4) Indeed, it was also shown that reaction of the complex with excess ligand gave $MoO_2Cl_2L_2$ in which both β-ketophosphonates were bound through the phosphoryl oxygen atom.

WEAK BOND, EASILY DECOMPLEXED.



Equation 3.4

As previously stated in chapter one, it is thought that transition metal complexes which have a bidentate ligand containing contrasting ligand to metal bond strengths display the necessary characteristics which may lead to asymmetric induction, if the necessary asymmetric environment is present.
In order to verify the reactivity previously displayed by this complex a series of epoxidation reactions were carried out on 1-methyl-1-cyclohexene. In addition it was hoped that the kinetics of the reaction could be studied after the addition of the catalyst to the reaction mixture, which contained the substrate, the solvent (normally methylene chloride) and the oxidant (normally t-BuOOH).
In an attempt to study the kinetics a stopwatch was started on addition of the catalyst to the reaction mixture and samples of approximately 0.1ml were taken from the reaction mixture at predetermined times. These samples were then added to 0.01g of triphenylphosphine in 0.5ml of CH_2Cl_2 to arrest the oxidation at that stage, and subsequently analysed for conversion to the epoxide by gas liquid chromatography. The yield of epoxide at any one time can be calculated as follows:-

$$\% \text{ Yield of Epoxide} = \frac{\{\text{Total area under alkene + epoxide peaks}\} - \{\text{Area under alkene peak}\}}{\text{Total area under alkene + epoxide peaks}} \times 100$$

Equation 3.5

The validity of this method was checked by injecting an exactly 1:1 ratio of pure alkene to epoxide for each different substrate. The results obtained from these reactions are shown in graph 3.1 and table 3.1 below.

Graph 3.1

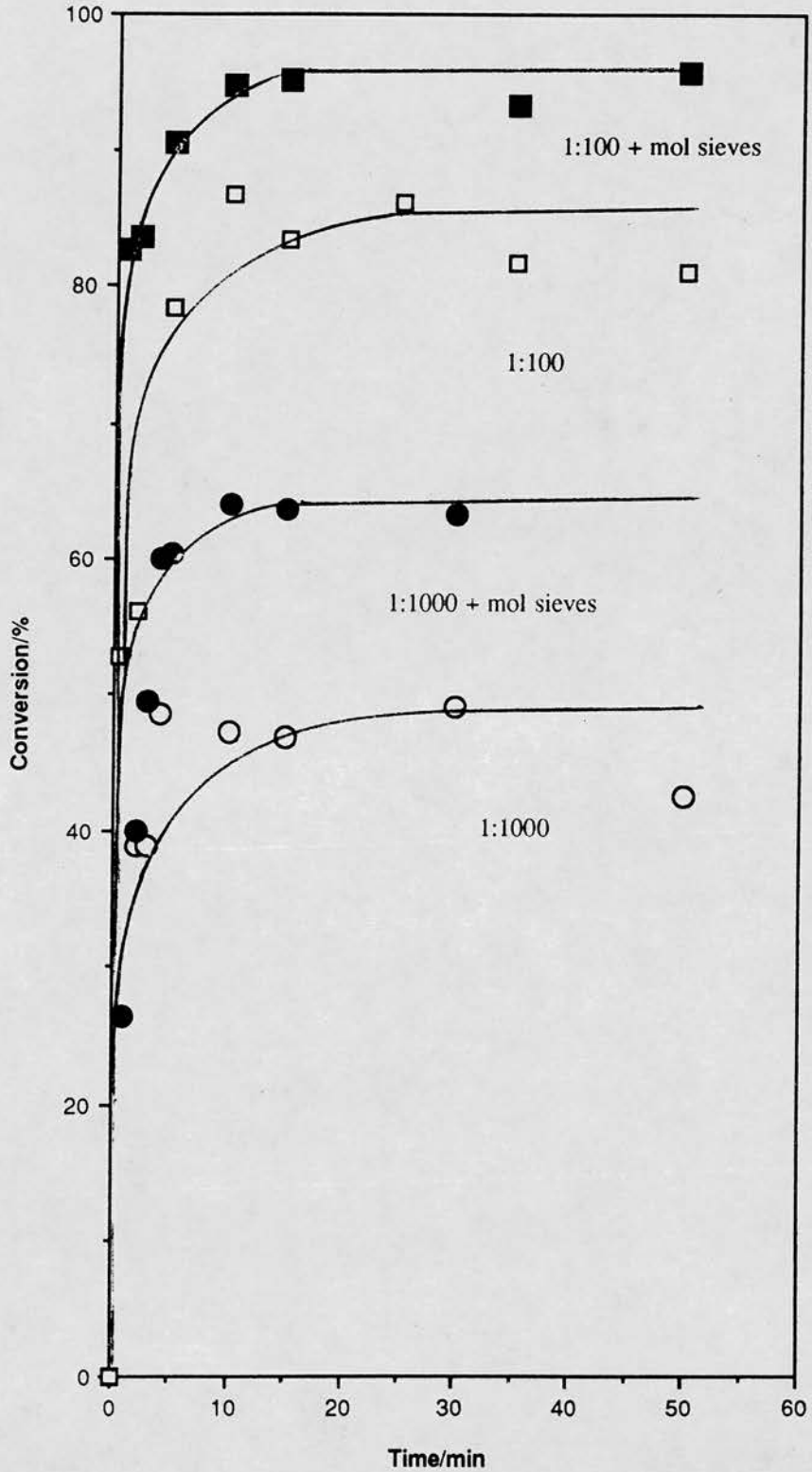

100
80
60
40
20
0
Conversion/%
0
10
20
30
40
50
60
Time/min
1:100 + mol sieves
1:100
1:1000 + mol sieves
1:1000

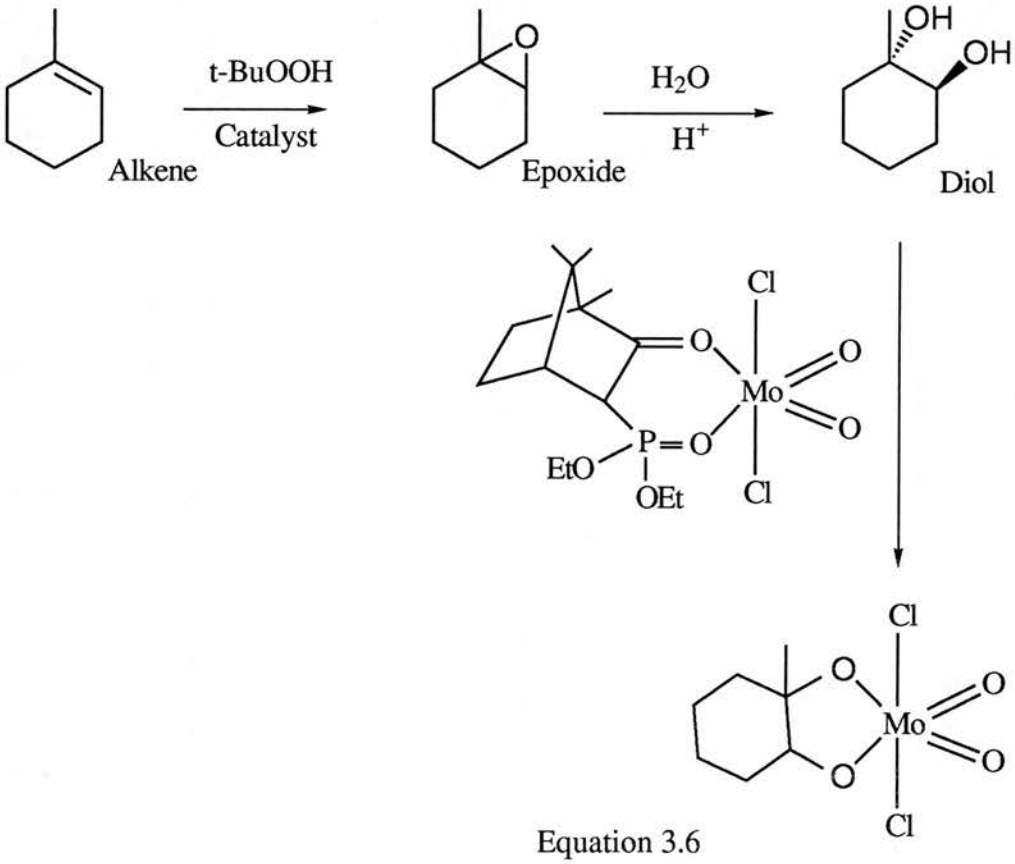
Table 3.1.

(For the epoxidation of 1-methyl-1-cyclohexene at 0^0C. Conversions quoted are after 1 hour)

Catalyst to substrate Ratio	% Conversion to Epoxide	
	(With M/Sieves)	(Without M/Sieves)
1:100	95.8	74.7
1:1000	66.0	49.1

As can be seen quite readily from these results, independant of the catalyst to substrate ratio or the presence or absence of molecular sieves (the use of which will be fully explained in the following pages) the pattern of this reaction always follows the same course ie an extremely high turnover rate is achieved in the initial stages of the reaction, but as the reaction proceeds, the reactivity appears to tail off. This is not simply a result of the decrease in substrate concentration, but appears to indicate biphasic kinetics.

It was initially thought that the apparent fall off in reactivity may be due to the presence of any adventitious water, which could subsequently take part in a hydrolysis reaction of the epoxide product to form the corresponding diol. This diol species can then interact with the catalyst to form a secondary catalytic species which may not be as active as the original β-ketophosphonate complex. (Equation 3.6)



Equation 3.6

This kind of reaction has previously been observed in the epoxidation of propene using Mo(VI) catalysts.[16,20]

It was hoped that, by addition of powdered molecular sieves, any water present in the reaction vessel would be quickly scavenged, hence removing any threat of secondary catalyst formation. From the results presented in graph 3.1 and table 3.1, it is clear that there is a significant increase in the activity of the catalytic system on the addition of molecular sieves, irrespective of the catalyst to substrate ratio. In addition, however, these reactions also displayed similar biphasic kinetic characteristics.

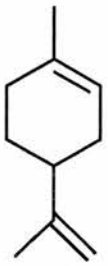
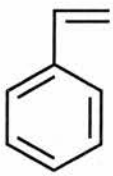
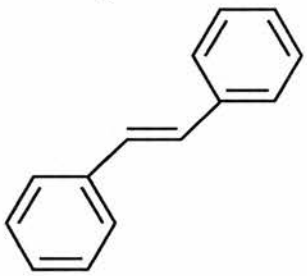
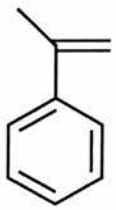
More detailed studies of the exact role of molecular sieves in these reactions has been carried out using styrene as the substrate and these are discussed in chapter 4.

These results therefore verify that this transition metal complex is an extremely active catalyst when used in the epoxidation of 1-methyl-1-cyclohexene.

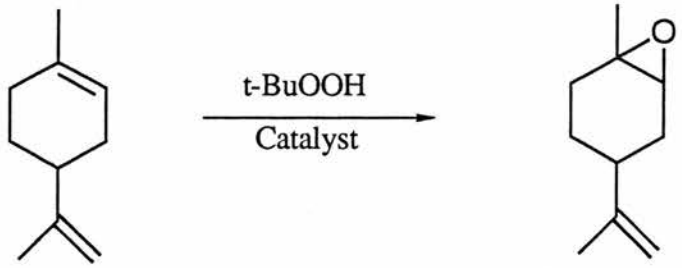
Since epoxidation involves electrophilic attack of oxygen onto the double bond, it would be expected that the epoxidation reaction would occur more favourably for double bonds such as that in 1-methyl-1-cyclohexene which bear electron donating groups and, indeed, many Mo(VI) catalysts show much higher activity for this kind of alkene than for e.g. styrene.

Accordingly, we have investigated epoxidation of a variety of alkenes with different electron densities in the double bonds, as well as limonene which has two double bonds with different electron densities. The results of these investigations are shown in table 3.2

Table 3.2.

Alkene.	% Conversion to Epoxide After 1 Hour.	
	Without Sieves.	With Sieves.
 Limonene.	68.8	87.0
 Styrene	0.0	77.0
 *Trans* - Stilbene	56.3	82.0
 ∝ - methyl styrene	11.7	55.5

It can be concluded from these results that this catalyst is reactive for a number of different alkenes. In the case of limonene it is also selective since it is the *endo* cyclic double bond which is oxidised exclusively over the *exo* cyclic double bond. This is as expected since the *endo* cyclic double bond bears three constituents but the *exo* cyclic has only two. (Equation 3.7)



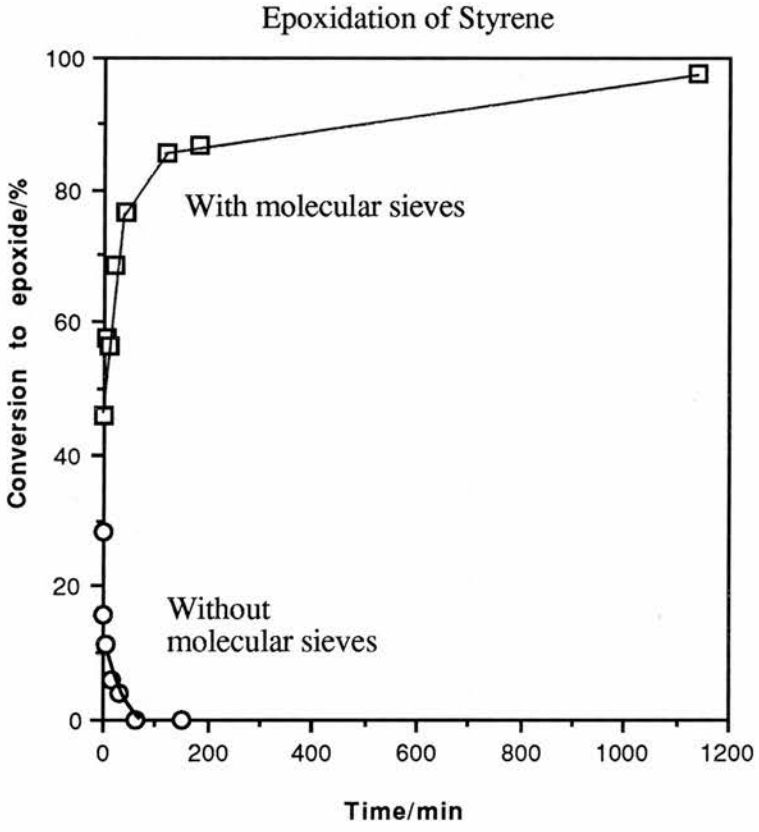
limonene limonene Oxide

Equation 3.7

In addition it has been found that during the epoxidation of most alkenes, the epoxide is formed as the only oxidised species. For styrene, in the absence of molecular sieves, the situation is quite different. Samples taken after 1hr of reaction show no styrene oxide to have been produced. However, closer examination shows that some reaction does occur. Thus approximately 25% of the styrene is converted to styrene oxide in the first few minutes of the reaction. This oxide subsequently degrades to a mixture of benzaldehyde, which is the major degradation product, and traces of phenylacetaldehyde. However, in the presence of molecular sieves approximately 77% of the styrene is successfully oxidised to the epoxide in the first hour and yields of up to 97% with 94% selectivity can be observed after 24 hrs.(Graph 3.2) This is a dramatic turnaround, especially when it is taken into account the degree of difficulty which has been encountered in the literature when this reaction has been attempted, in the hope that a high yield of epoxide would be observed.[139, 212-216]

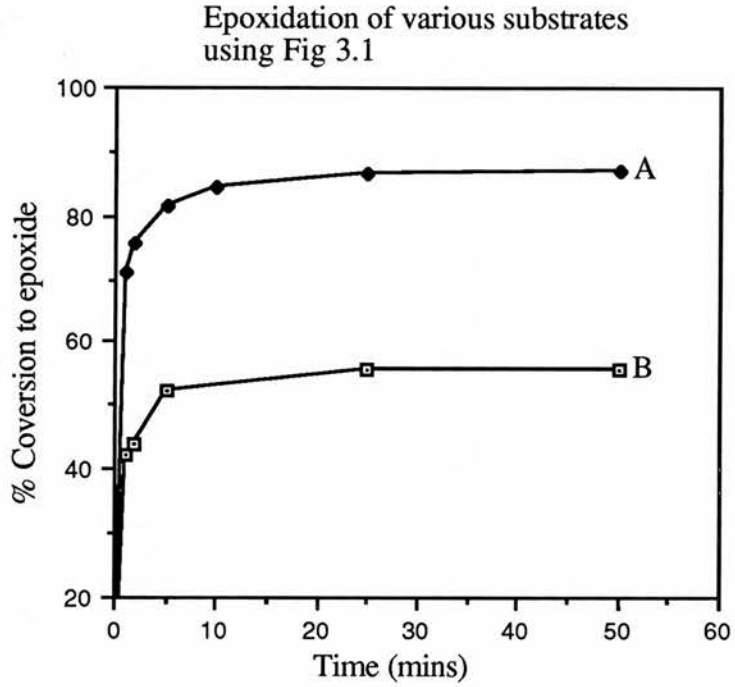
It is obvious from these results that the presence of molecular sieves in some way prevents the degradation of styrene oxide. Further investigation has been carried out during this research and it is reported in chapter 4.

Graph 3.2. (These reactions were carried out at room temperature. Catalyst to substrate ratio : 1:100).



Similar kinetic studies were carried out during the epoxidation of a range of different substrates and certain conclusions can be drawn from the results obtained. Irrespective of the alkene being oxidised, the reactivity pattern displayed like that for the epoxidation of 1-methyl-1-cyclohexene, shows a very rapid initial reaction generally leading to ~50% conversion, followed by a much slower period of the reaction in which further increases in product only occur over a period of several hours. (Graph 3.3)

Graph 3.3.



'A' : Limonene is the substrate.

'B' : ∝ - methyl styrene is the substrate.

(Ratio of catalyst to substrate : 1 : 100. These reactions were carried out at room temperature in the presence of molecular sieves.)

3.2.2 Epoxidation Studies Carried out Using Dichloro{[(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum (VI).

This catalyst (Fig 3.2) was successfully synthesised using the experimental procedure outlined in the previous chapter.

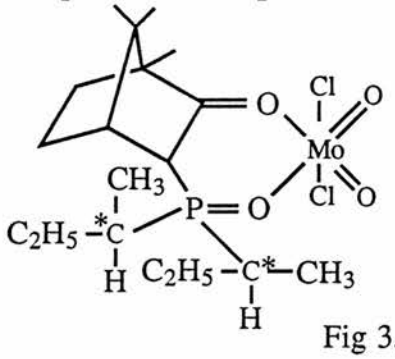


Fig 3.2

C* : indicates the presence of a chiral centre on the alkyl group attached to the phosphorus atom. (Pure diastereomers were used in the reaction).

The catalytic activity of this complex was then examined for a range of substrates. The results from these investigations are presented in table 3.3 and graph 3.4 below).

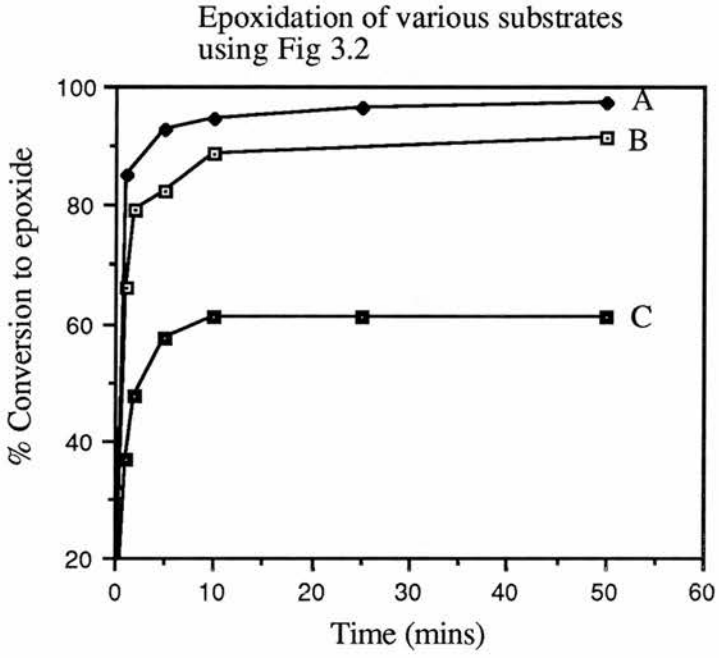
Table 3.3.(Catalyst to substrate ratio 1:100, reactions carried out at room temperature)

Substrate Alkene.	% Conversion to Epoxide.(1 Hr)	
	In the absence of sieves.	In the presence of sieves
Limonene	74.0	91.0
		75.0[a]
Styrene	0	61.0
1-methyl-1-cylohexene	61.7	97.5
	28.9[a,b]	34.2[a,b]

X[a] : Reaction carried out at 0^0C

X[b] : Ratio of catalyst to substrate 1:1000.

Graph 3.4. (Catalyst to substrate ratio 1:100; Reactions carried out in the presence of molecular sieves at room temp)



'A' : 1-methyl-1-cyclohexene is the substrate.

'B' : Limonene is the substrate.

'C' : Styrene is the substrate.

On analysis of the results obtained from these reactions it is clear that the kinetic data again indicates biphasic reaction kinetics, irrespective of the alkene which is being epoxidised.

Indeed this has proved to be the case when any of transition metal complexes which have been synthesised during this work have been used as catalysts during an epoxidation reaction.

The addition of molecular sieves once again enhances this reaction system, by prolonging the period during which high activity is observed, but does not, apparently, completely eliminate the process of deactivation of the catalyst.

The results presented in table 3.3 indicate that there appears to be no significant alteration observed in catalytic activity when the nature of the alkoxy groups attached to the phosphorus atom is altered. In addition the excellent degree of chemo and regioselectivity displayed by the diethoxy catalyst is maintained. For example, limonene is once again epoxidised at the *endo* cyclic double bond as opposed to the *exo* cyclic, and in the case of styrene epoxidation, the epoxide is observed as the sole oxidised product when molecular sieves are present in the reaction system.

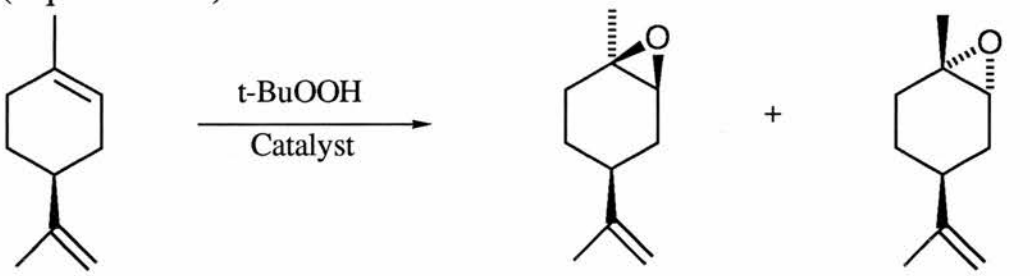
3.2.3 Epoxidation Studies Carried out Using Dichloro{[(1R) - *endo*] - (+) - 3 - [diphenylphosphoryl] camphor} dioxomolybdenum (VI).

The activity of this catalyst has been looked at only very briefly to verify that it is comparable with those described previously. It is found to convert 83.7% of limonene to the epoxide, specifically at the *endo* cyclic double bond, in one hour, in the absence of molecular sieves. This reaction is found to follow similar biphasic kinetics to those previously outlined and the level of activity compares favourably with those catalysts previously described.

From the results presented it can be concluded that these transition metal complexes are extremely active catalysts for the epoxidation of a variety of different alkenes, especially in the presence of molecular sieves. They also show very high chemoselectivity towards the production of epoxides and regioselectivity towards the epoxidation of more electron rich double bonds, when two double bonds are present in the molecule. Similar selectivity towards the epoxidation of *cis* and *trans* internal double bonds in the presence of terminal double bonds has previously been observed in the epoxidation of polybutadiene using t-BuOOH as oxidant and MoO_2Cl_2L as catalyst. [L = Dichloro{[(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum (VI).] [217]

3.3 Stereochemical Studies Carried out During the Epoxidation of Limonene.

As previously stated, excellent chemo and regioselectivity is observed during the epoxidation of limonene when this class of catalyst is used, since it is the *endo* cyclic double bond which is epoxidised in preference to the *exo* cyclic one. (Equation 3.8)



limonene | *trans* - limonene oxide. | *cis* - limonene oxide.

Equation 3.8.

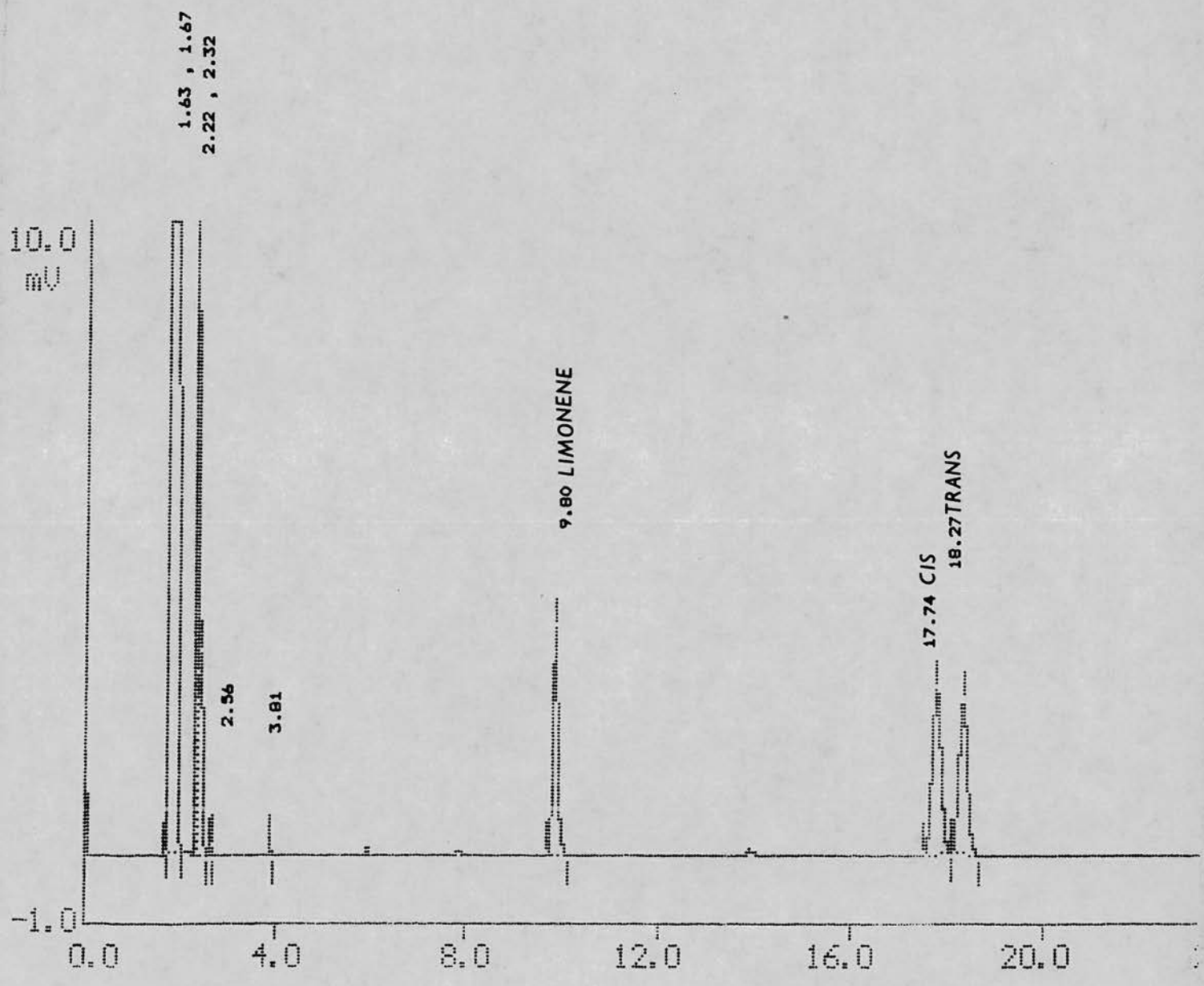
The chiral centre already present in limonene is very helpful at the point of stereoselective examination of products, since it is now diastereomeric epoxide isomers which are formed and not enantiomers, as is the case with styrene. Therefore the two possible epoxide products are diastereomers and so will be separable by either GLC or ^{1}H nmr, since they will display different chemical and physical properties.

In this case diastereomeric excess was easily calculated by GLC by comparison of the areas underneath the peaks of the two different diastereomers. (Spectrum 3.1).

It was observed that irrespective of the catalyst which was used, no significant diastereomeric excess was calculated during the epoxidation of limonene, although excellent selectivity and reactivity was displayed.

However, on leaving the reaction solutions in air (only in the cases where molecular sieves were not used) changes in the *cis* and *trans* ratios indicated that one isomer, the *cis,* was ring opening preferencially to the diol. This effect has been studied and the results are presented in chapter 5.

Spectrum 3.1


1.63 , 1.67
2.22 , 2.32
10.0
mV
2.56
3.81
9.80 LIMONENE
17.74 CIS
18.27TRANS
-1.0
0.0
4.0
8.0
12.0
16.0
20.0

3.4.1 Stereochemical Studies Carried Out On The Epoxidation of Styrene.

On finding that the transition metal complexes of chiral β-ketophosphonates do show excellent epoxidation activity for a series of alkenes, it then became important to discover if any stereoselectivity was taking place during these reactions. The most convenient method for calculating enantiomeric excesses when dealing with the oxidation of substrates which yielded epoxide isomers which were equivalent by GLC and ^1H nmr, was found to be the use of chiral solvating (shift) agents for the nuclear magnetic resonance determination of enantiomeric purity. Other methods can be used such as chiral chromatography, (which may present problems in finding a suitable system which would yield satisfactory separation of products) and optical rotation, but in this case the use of chiral solvating agents were found to be satisfactory. Previous work by Pirkle and co-workers[218-221] had shown that diastereomeric solvates result from the solvation of enantiomeric lactones by the chiral solvating agent 2,2,2 trifluoro-1-(9-anthryl) ethanol (Fig 3.3). In most cases, these solvates are of similar general structure and energy as a consequence of "two-point only" interaction. The nature of the time-averaged NMR spectral differences of these diastereomeric solvates is a reliable guide to the absolute configurations of lactone enantiomers.

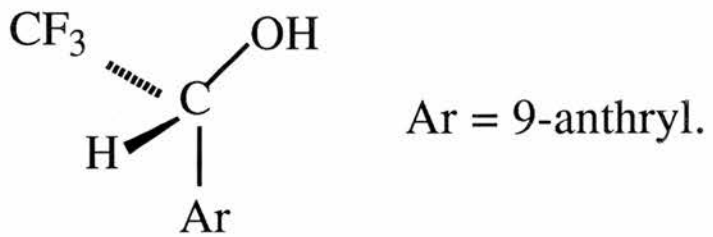


Fig 3.3.

Pirkle and Co investigated[218-221] the interaction between certain "chiral solvating agents" and a diverse series of enantiomer solutes. In many cases, both enantiomeric purity and absolute stereochemistry can be determined for the solutes on the basis of such interactions. For example, they reported that the "two-point" interaction between chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol and ϒ-lactone enantiomers, as shown in Fig 3.4, and Fig 3.5, is responsible for the non-eqiuvalence of the NMR spectra of the enantiomers.

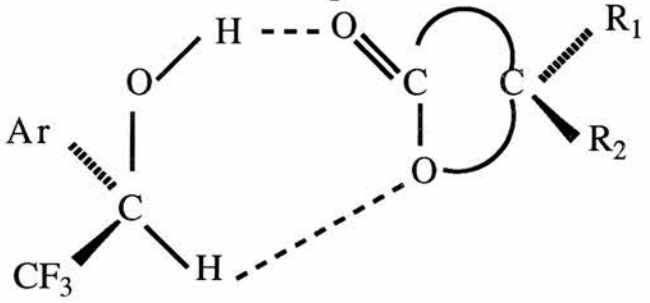


Fig 3.4

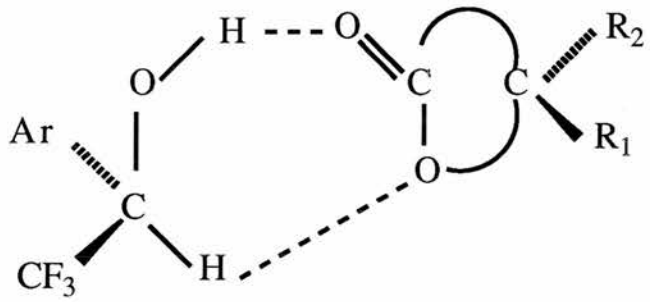
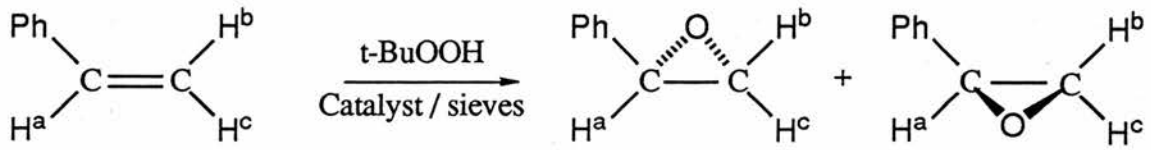


Fig 3.5

The shielding effect of the anthryl substituent causes the resonances of the R_1 substituents to occur at a higher field for the enantiomer incorporated into Fig 3.4 than for that into Fig 3.5 The converse situation holds for the resonces of R_2 substituents located on the other face of the lactone.By the use of GLC (using a non-chiral stationary phase) or ^{1}Hnmr (in the absence of shift reagents) it is not possible to determine the degree of stereoselectivity induced during the epoxidation of the substrate styrene, since the two potential products are enantiomers and therefore are equivalent on analysis by these techniques. (Equation 3.9).



Styrene Styrene oxide isomers

Equation 3.9

However, it was hoped that by the addition of the chiral solvating agent 2,2,2-trifluoro-1-(9-anthryl) ethanol to the product mixture, an interaction would take place between the solvating agent and the two styrene oxide isomers to such an extent that they would become seperable by ^1H nmr.(ie diastereomeric adducts would form between the shift reagent and the styrene oxide isomers. Since diastereomers have different chemical and physical properties, they would be seperable by an analytical technique such as ^1H nmr) By subsequent analysis of the value of the integration of each isomer it was hoped that the degree of stereoselectivity could then be calculated. On inspection of the ^1H nmr of styrene oxide it is observed that the atoms H^a, $H^b$and H^c display a doublet of doublets for each atom. This is because each proton is in an electronic environment which is unique. Atoms H^b and H^c are of course different since H^b is *cis* to the phenyl substituent whereas H^c is *trans*. If a mixture of isomers of styrene oxide were analysed by ^1H nmr the chemical equivalence of the two isomers would result in only one set of peaks, for each atom. Spectrum 3.2 shows an enlargement of the signal observed for H^a when a sample containing a mixture of isomers of styrene oxide is analysed.(note: only one set of doublet of doublets is observed).

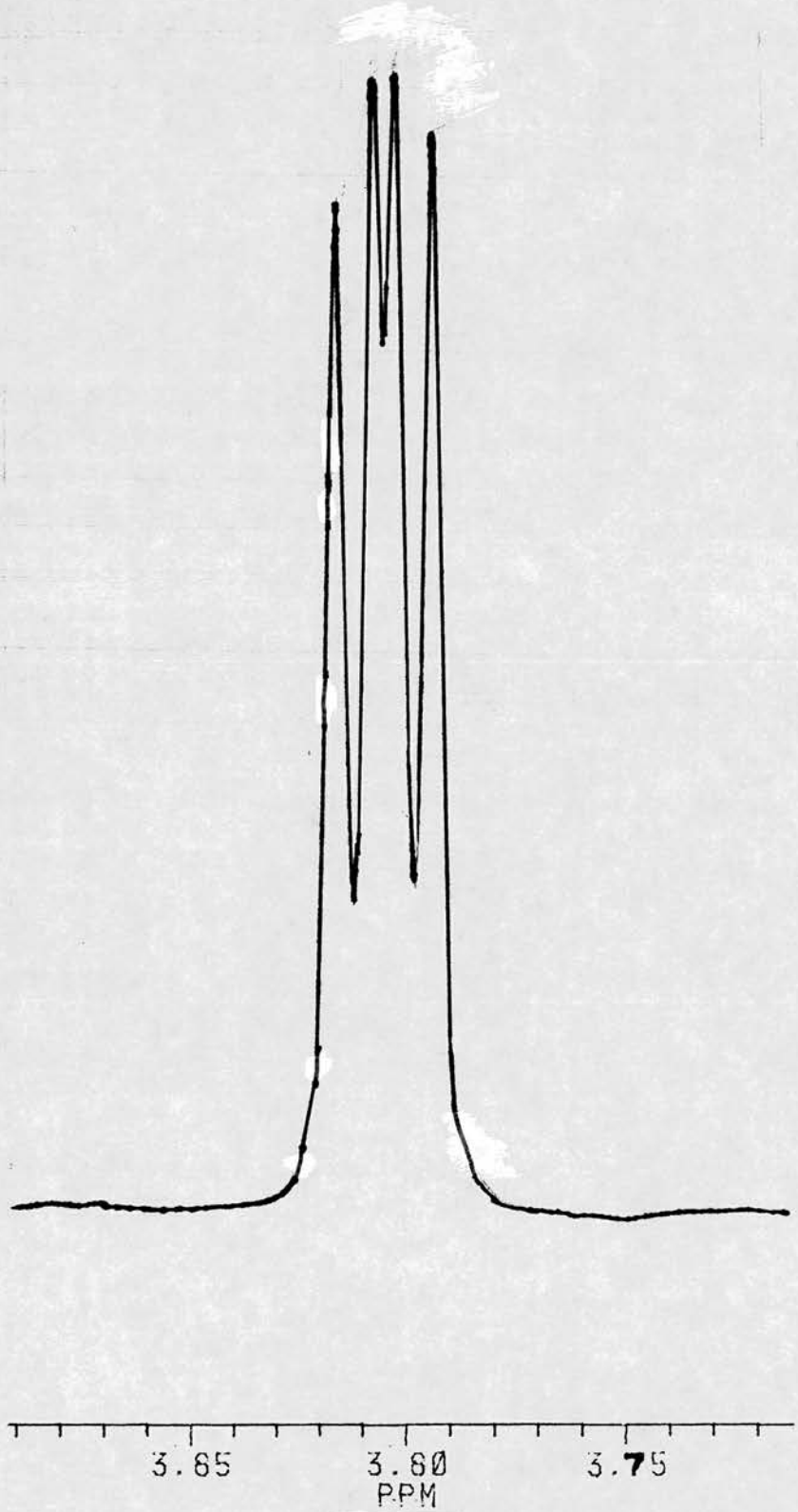
On addition of a suitable amount of shift reagent, this splitting pattern changes significantly, showing quite clearly the intended separation of the two sets of doublet of doublets representing the two different isomers of styrene oxide.(Spectrum 3.3).

The peaks which correspond to the shift reagent do not overlap in any way with the signal from these three protons in styrene oxide, which means that this shift reagent can be used without any fear of confusing results. By careful integration of the spectrum obtained from a sample from an epoxidation reaction carried out on styrene, it is possible to determine if any stereoselectivity is taking place during these reactions.

These stereochemical studies are carried out in a similar fashion to normal epoxidation reactions, except for the amounts of reagents and solvent used in the reactions which have to be significantly reduced to ensure that a large enough separation was observed in the ^{1}H nmr, on addition of the shift reagent.(see experimental chapter 6).

The amounts of each isomer produced can then be determined by measurement of the value of the integration of the outward peak of each set of doublet of doublets (peaks x and y in spectrum 3.3) for a specific hydrogen atom. In an attempt to improve the quality of the spectra obtained from these reactions, resolution enhancement was employed. Resolution enhancement incorporates a gaussian multiplication factor which applies an optimum resolution enhancement function. By using the gaussian lineshape, resolution of overlapping resonances is greatly improved. Gaussian lineshape can be brought about by optimisation of the line broadening factor and maximisation of the gaussian function. However, this enhancement also increases the degree of difficulty which is encountered when trying to integrate the spectrum obtained since the line of integration will tend to follow the base line which in some instances tends to dip when this technique is employed.Therefore, in order to attain accurate measurement of integral values a great deal of care had to be taken during measurement. These stereochemical studies were carried out at different temperatures to observe the effect of temperature variation upon the selectivity . The results from these reactions are shown in table3.4.

Spectrum 3.2



Spectrum 3.3

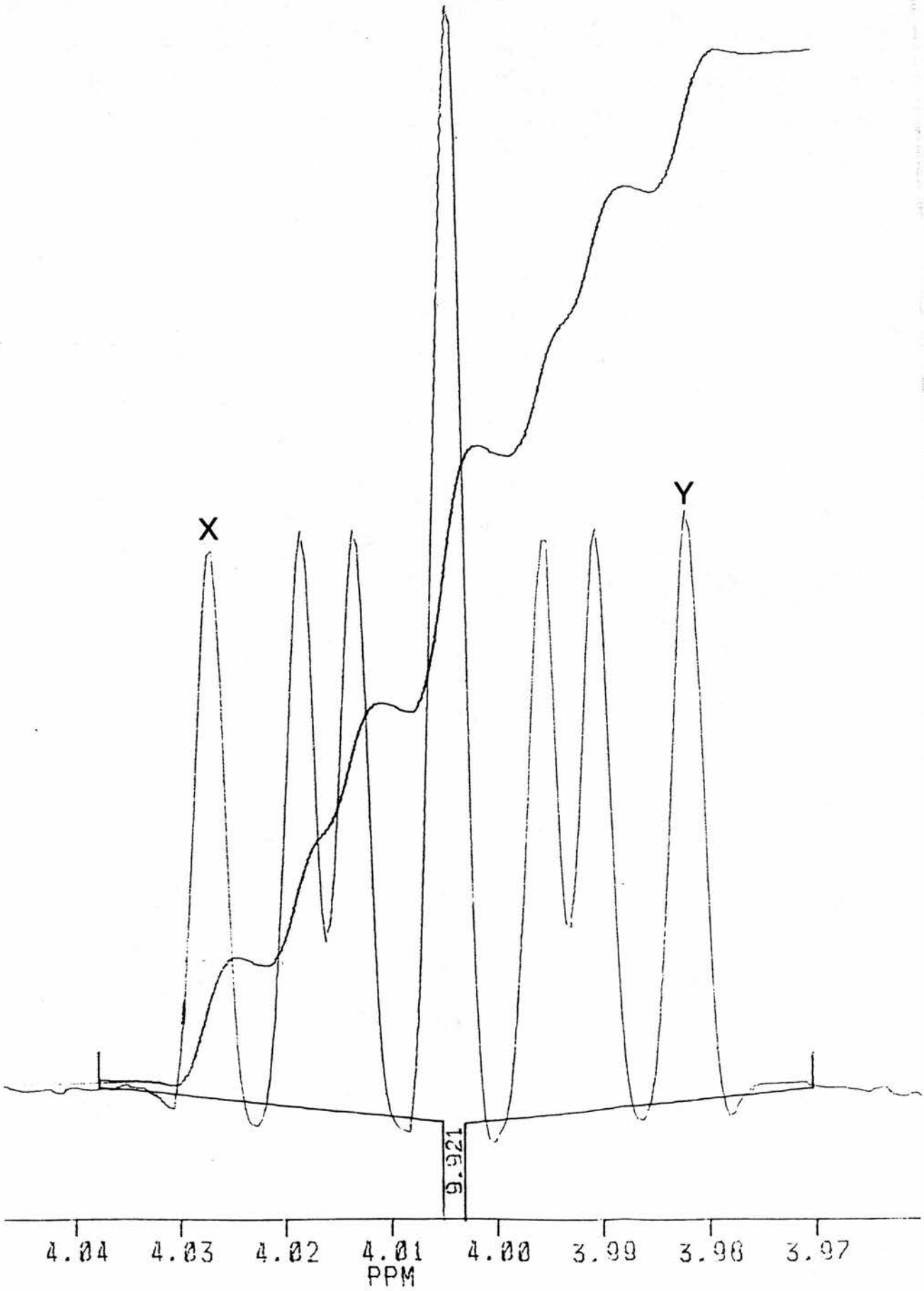


Table 3.4
Results from the Stereochemical Experiments Carried out on Styrene.

	Ratio of Epoxide Isomers Produced at Various Temperatures.{note isomer 'X' is quoted first}(enantiomeric excess)			
Catalyst.	Room Temp.	0^0C	-10^0C	-70^0C
$MoO_2Cl_2(L_A)$	49.15 : 50.85. (1.70%)	46.38 : 53.62. (7.24%)	47.25 : 52.75. (5.50%)	–
$MoO_2Cl_2(L_B)$	48.60 : 51.40. (2.80%)	51.28 : 48.72. (2.56%)	47.45 : 52.55. (5.10%)	47.06 : 52.94. (5.88%)
$MoO_2Cl_2(L_C)$	46.88 : 53.12. (6.24%)	49.18 : 50.82. (1.64%)	–	–
$MoO_2Cl_2(L_D)$	48.57 : 51.43. (2.86%)	47.71 : 52.29. (4.58%)	–	–
$MoO_2Cl_2(L_E)$	46.48 : 53.52. (7.04%)	49.44 : 50.56. (1.12%)	–	–
$MoO_2Cl_2(L_F)$	47.33 : 52.67. (5.34%)	52.14 : 47.86. (4.28%)	–	–
$MoO_2Cl_2(L_G)$	47.26 : 52.74. (5.48%)	47.62 : 52.38. (4.76%)	–	46.17 : 53.83. (7.66%)

L_A = [(1R)-*endo*]-(+)-3-(diethoxyphosphoryl) camphor.
L_B = [(1S)-*endo*]-(-)-3-(diethoxyphosphoryl) camphor.
L_C = [(1R)-*endo*]-(+)-3-[bis {(S)-(+)-2-butanoxy}phosphoryl] camphor.
L_D = [(1S)-*endo*]-(-)-3-[bis {(S)-(+)-2-butanoxy}phosphoryl] camphor.
L_E = [(1R)-*endo*]-(+)-3-[bis {(R)-(-)-2-butanoxy}phosphoryl] camphor.
L_F = [(1S)-*endo*]-(-)-3-[bis {(R)-(-)-2-butanoxy}phosphoryl] camphor.
L_G = [(1R)-*endo*]-(+)-3-(diphenylphosphoryl) camphor.

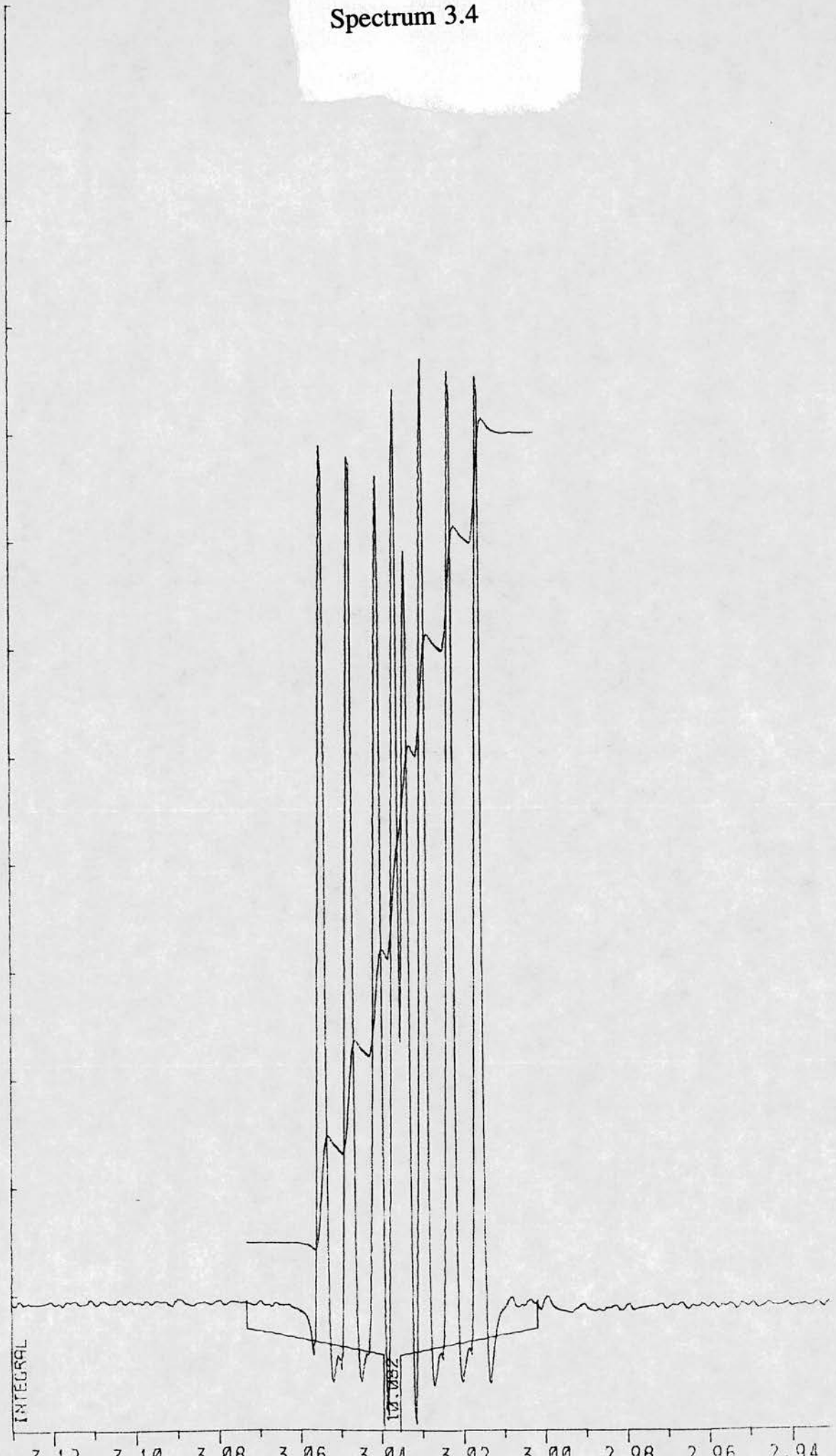
A typical splitting pattern obtained on analysis of styrene oxide products by ^{1}H nmr is shown in spectrum 3.4. This spectrum was obtained from the analysis of the products from the epoxidation of styrene by dichloro{[(1R)-*endo*]-(+)-3-(diphenylphosphoryl) camphor} dioxomolybdenum (VI) at room temperature. This spectrum illustrates the nature of the small enantiomeric excesses which were obtained in most of these reactions.

3.3.2 Summary of the Stereochemical Studies Carried out on Styrene.

The stereochemical studies which have been performed on the epoxidation of styrene with this class of catalyst have shown that very little stereoselective induction is taking place during these reactions. In most cases isomer 'X' is produced in slightly greater quantity. This is an indication that the asymmetric environment which is present is not sufficient to provoke asymmetric oxidation. It may be that the asymmetric centres are not close enough to the reaction centre, or that increased steric bulk is required.

However, from experiments carried out which examined the interaction between this range of catalysts and molecular sieves, (see chapter 4) it has been shown that in order to bind to the surface of the sieves, the ligand attached to the catalyst is cleaved. Therefore the asymmetric environment is removed from the proposed site of oxygen transfer and explains why no asymmetric induction is taking place. It should be pointed out that the stereochemical studies were carried out before this was discovered.

Spectrum 3.4



CHAPTER FOUR

AN INVESTIGATION INTO THE ROLE PLAYED BY MOLECULAR SIEVES DURING β-KETOPHOSPHONATE TRANSITION METAL COMPLEX CATALYSED EPOXIDATION REACTIONS.

Chapter IV.

An Investigation Into the Role Played By Molecular Sieves During β-Ketophosphonate Transition-Metal Complex Catalysed Epoxidation Reactions.

4.1.1 Introduction and Background.

As reported in the previous chapter, the molybdenum complexes of β-ketophosphonates are extremely active and regioselective as epoxidation catalysts for a range of different substrate alkenes.

In every case examined, irrespective of the catalyst or the substrate alkene oxidised, the rate profile always displayed similar characteristics. ie An extremely high rate of initial activity in the first few minutes of the reaction after the addition of the catalyst, followed by a levelling off of activity (ie biphasic kinetics) indicating that the initial highly active catalyst is being replaced by a less active form. This phenomenon has been observed[23] before and attributed[16,19] to the formation of a complex incorporating a bidentate diolato ligand being derived from the product alkene oxide, perhaps by reaction with water in the system. eg the complex $[MoO_2(OC_7H_{14}OH)]$ may be formed during the epoxidation of 1-methyl-1-cyclohexene.

Molecular sieves have been used to scavenge adventitious water in epoxidation[222] and other oxidation[223] systems and it has been reported that stoichiometric reactions can be rendered catalytic[222] or improvements can be obtained in enantioselectivities.[223]

In an attempt to improve still further this very active catalytic system, epoxidation reactions have been carried out in the presence of molecular sieves. (purchased from Aldrich, 4A, particle size 2-3 μm).

The results presented in the previous chapter illustrate quite clearly, that when molecular sieves are employed, the initial rapid phase of these reactions is extended so that higher yields of product are obtained in a shorter time. In the case of 1-methyl-1-cyclohexene, using catalyst to substrate ratio's of 1:100, 97% conversion is observed in 20 minutes, and using a ratio of 1:1000, up to 10 catalyst turnovers per second are initially observed, although in this case, deactivation of the catalyst again occurs. The initial catalyst is active for approximately 650 cycles, cf 480 in the absence of sieves.

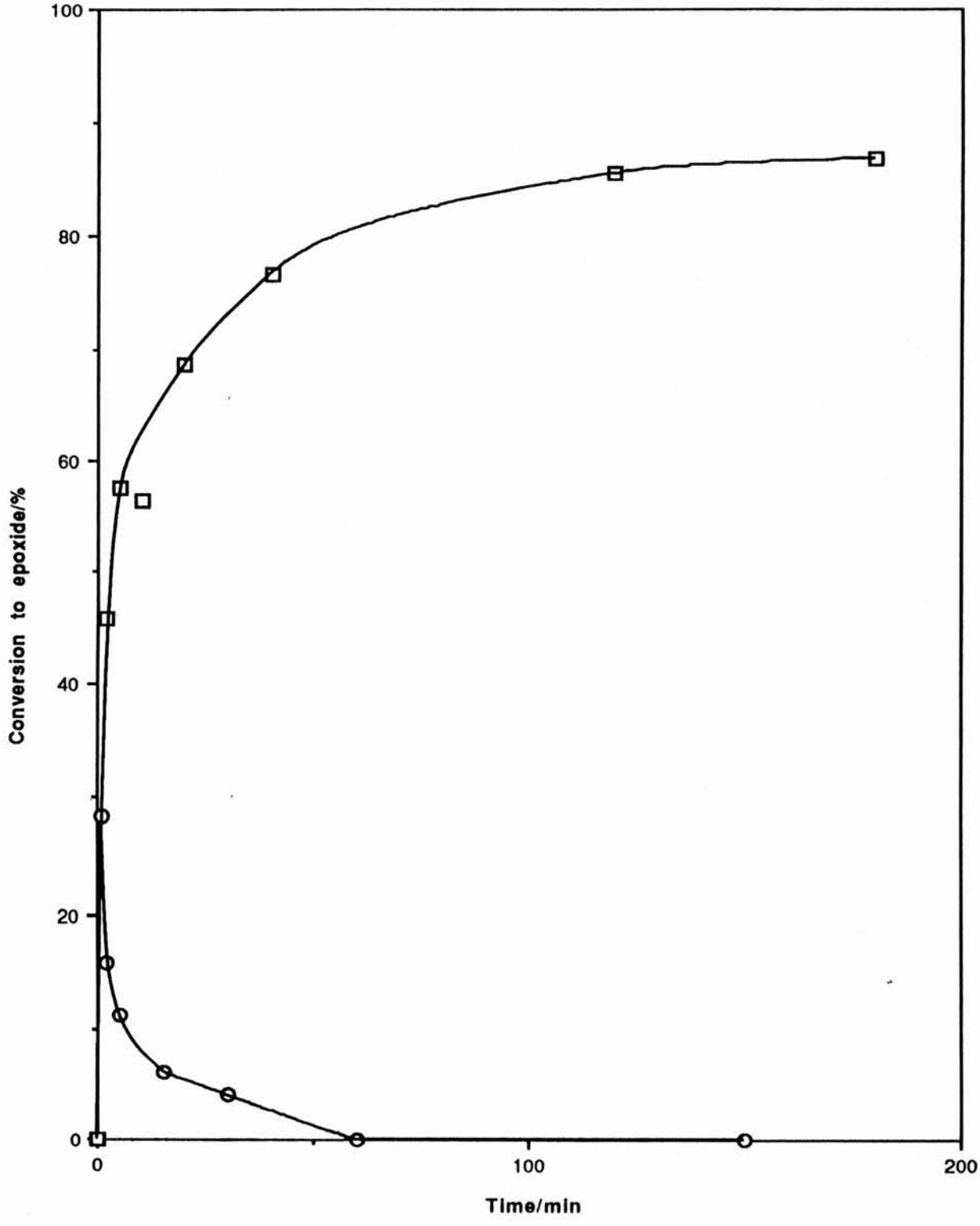
A dramatic turnaround in activity is observed on the addition of sieves during the epoxidation of styrene.[224] In the absence of sieves it has been found by analysis of reaction rate profiles, that up to 25% conversion to styrene oxide is observed in the first few minutes of the reaction. This oxide however, subsequently degrades to predominantly benzaldehyde and also traces of phenylacealdehyde. Conversely, in the presence of molecular sieves 77% conversion to styrene oxide is achieved in the first hour of the reaction after addition of the catalyst, and the styrene oxide is stabilised by the presence of the sieves.(Graph 4.1) Yields as high as 97% with 94% selectivity can be observed after 24 hours.

4.1.2 Review of Styrene Epoxidation using other transition metals.

A great deal of research has taken place in the area of epoxidation catalysis of alkenes including styrene, which has illustrated the difficulty experienced when trying to oxidise styrene specifically to styrene oxide. There are however, a number of systems incorporating transition metal complexes which have been successful in the area.

Jørgensen and co-workers[214] have achieved 19% conversion specifically to styrene oxide using Ag_2O_3 as catalyst in a reaction also yielding 3% benzaldehyde.

Graph 4.1



Nickel complexes have also been used as catalysts[212] and $Ni(bpy)_2Cl_2$ converts 99% of styrene at room temperature using NaOCl as the oxidant. The main oxidation products of this reaction were styrene oxide (74%) and benzoic acid (15%).

Manganese porphyrins have been used to good effect and Mansuy and co-workers[225] have observed 93% conversion to styrene oxide after 2 hours at room temperature when Mn(TDCPP)Cl was used as catalyst with H_2O_2 as oxidant. Benzaldehyde(1%) and phenylacedaldehyde(1%) were.also detected. A similar manganese(III) porphyrin system[226] [tetrasodium salt of 5,10,15,20-tetrakis(2,6-dichloro-3-sulphonatophenyl)porphinatomanganese(III)chloride] (Fig 4.1) bound to latex also displayed excellent catalytic activity yielding 80% styrene oxide at room temperature in 1 hour using NaOCl as oxidant.

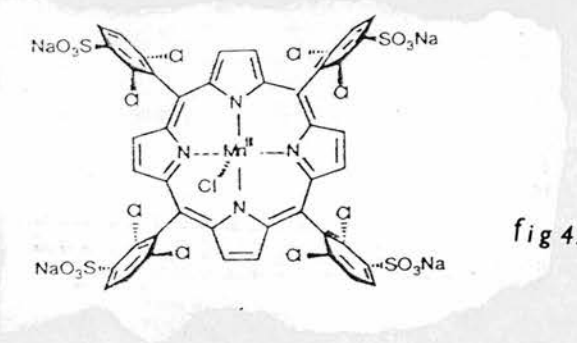


fig 4.1

However, other manganese(III) systems have not displayed the same degree of activity eg cationic manganese complexes of the salen ligand[134] (Fig 4.2) achieved only 37% conversion to styrene oxide.

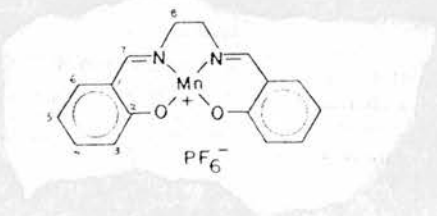
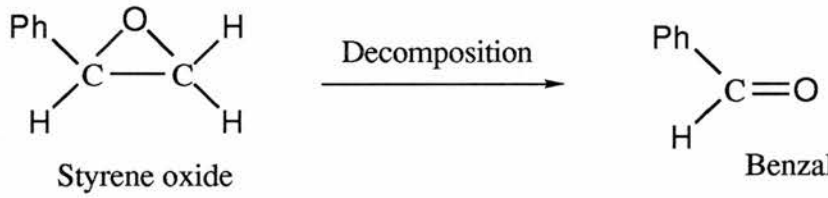


fig 4.2

Excellent activity has also been displayed by a number of iron complexes eg [(Br_8TPP)Fe(III)(Cl)] achieved 97% conversion specifically to styrene oxide at room temperature.[227]

4.2 An investigation into the role played by molecular sieves during the epoxidation of styrene.

The decomposition of styrene oxide to benzaldehyde is an interesting one since it requires the cleavage of a C-C bond. (Equation 4.1)

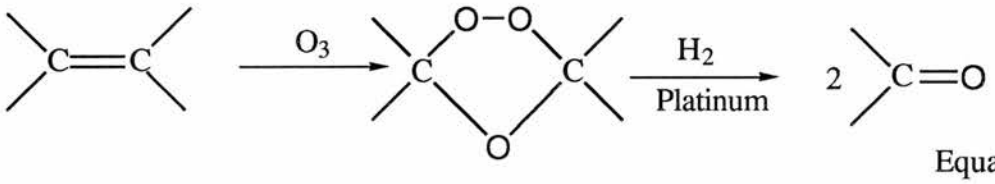


Styrene oxide

Benzaldehyde.

Equation 4.1

This is somewhat similar in nature to an ozonolysis oxidation reaction. (Equation 4.2)



Equation 4.2

In this case the substrate alkene is initially oxidised to the intermediate shown, but in order to obtain the aldehyde product, a further reduction reaction must take place.

Studies in this area by other research groups have also shown that in the presence of Mo(VI) complexes, styrene oxide will decompose and both benzaldehyde and phenylacealdehyde have been observed as degredation products.[228](Equation 4.3)

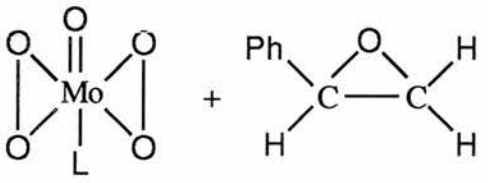


Fig 4.3
(where L is hexamethylphosphoramide)

Styrene oxide

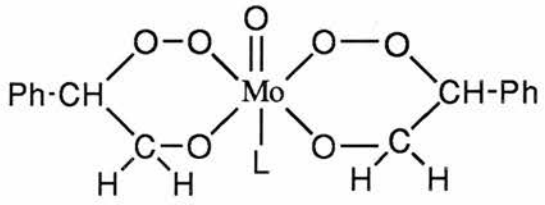


Fig 4.4

Equation 4.3

The mechanism of this reaction is unclear, although it has been proposed that prior to styrene oxide decomposition, complex Fig 4.4 may be formed.

The mechanism of decomposition of complex Fig 4.4 to the final products (Equation 4.4) {which requires the breaking of both O-O bonds and one of the C-C bonds} is unknown, as is the exact pathway for the formation of formic acid (detected as one of the products by HPLC).

The possiblity of formation of free formaldehyde and it's subsequent oxidation to formic acid is excluded since aldehydes cannot be oxidised by the starting complex (Fig 4.1) and the same oxidation by Fig 4.4 seems unlikely.

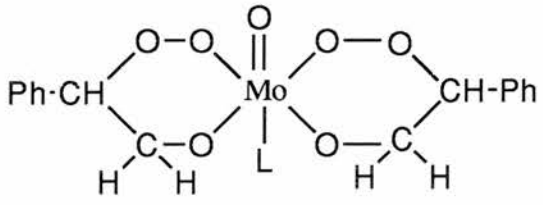
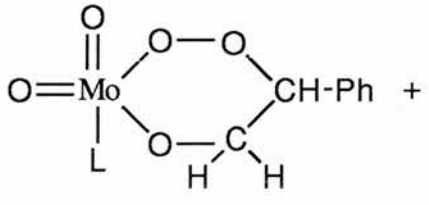
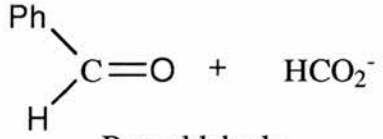


Fig 4.4



Equation 4.4



Benzaldehyde.

It is thought that formic acid may be formed in the coordination sphere of molybdenum, after benzaldehyde elimination. It is reported that attempts to isolate complex Fig 4.4 have failed, but it seems likely that decomposition would occur in the high temperatures employed when the product samples were analysed by gas chromatography. Although an intermediate such as complex fig 4.4 seems unlikely in our system a related complex may be that shown in Fig 4.5

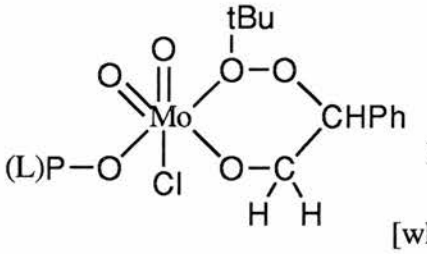


Fig 4.5

[where (L) = β-ketophosphonate ligand]

Other work[229] has shown that the decomposition of styrene oxide formed during the epoxidation of styrene by the catalyst ammonium heptamolybdate(VI)-dioctylin oxide is suppressed when salts such as Na_2SO_4 and $NaNO_3$ are added to the reaction mixture. This effect has been attributed to the coordination of the anions within these salts to the Mo(VI) ions. The anions are thought to reduce the Lewis-acidity of the catalyst and hence act as a styrene oxide stabilizer.

Our research has attempted to rationalise the role played by molecular sieves[224] and the results of this work are presented in table 4.1.

Entrics 1 and 2 illustrate the conversion rates achieved during standard epoxidation reactions either in the presence or absence of molecular sieves. Further investigation has shown that if the catalyst is stirred with molecular sieves then filtered, the filtrate shows no activity for alkene epoxidation when added to a mixture of t-BuOOH and styrene in CH_2Cl_2, (entry 3) whilst addition of the solid fraction to a similar solution does give some epoxidation activity. (entry 4).

Similarly, if the t-BuOOH is first stirred with sieves, filtered into CH_2Cl_2 containing styrene and molecular sieves, then the catalyst added, (entry 5) the activity is significantly lower than simply adding t-BuOOH.

In addition, almost no activity is observed if the catalyst adsorbed onto molecular sieves is added to a solution containing styrene, t-BuOOH and molecular sieves, (entry 6) suggesting that both the t-BuOOH and the catalyst must be adsorbed onto the same sieve particles, although whether the catalyst or the peroxide is added first does not appear to influence the conversion very much. (entries 7 and 8).There is no evidence for styrene being affected by stirring with molecular sieves (entry 9) and no reaction is observed in the absence of the catalyst.

The most logical explanation for these observations is that the catalyst binds to the sieves *via* metathesis of the Mo-Cl bonds with surface bound hydroxyl groups (the catalyst is too large to enter the pores of the 4A molecular sieves). The acidity of the suppport appears to be important since no activity is observed if the sieves are replaced with silica. (entry 10)

Interestingly, when dried magnesium sulphate is used as a direct replacement for molecular sieves, approximately 18% of the styrene is epoxidised to styrene oxide after only a few minutes, and this level of epoxide was still present after 30 minutes, indicating that the presence of this salt is stabilizing the styrene oxide. This may confirm the fact that the presence of anions reduces the Lewis-acidity of the complex and hence prolongs the lifetime of styrene oxide within this system. The stability of styrene oxide in the presence of molecular sieves may be due to the fact that the sieves are reducing the Lewis-acidity of the complex and hence preventing further oxidation of styrene oxide.

A further series of experiments were carried out to investigate this effect. On stirring the catalyst with sieves, examination of the filtrate by ^1H nmr shows quite clearly that the ligand has cleaved from the metal since a very clean spectrum of the free ligand is obtained. It now seems clear that for the metal to bind to the sieves, it is the ligand-metal bonds which are broken and not the Mo-Cl bonds as originally thought. The catalytic activity must then be a result of MoO_2Cl_2 bound to the surface of the zeolite. However, when a normal epoxidation reaction was carried using styrene as the substrate and MoO_2Cl_2 as catalyst it was found that only 29.1% of styrene was converted to styrene oxide in the first hour, and that this conversion did not increase in the following hour. This difference in activity may be due to the lack of solubility of MoO_2Cl_2 in the solvent mixture, hence reducing its ability to act effectively as a catalyst, whereas in the case of the other catalysts, the organic ligand may have helped overcome any potential solubility problems up to the point where the metal binds to the surface of the sieves, at which point the asymmetric ligand is cleaved. It should be pointed out that the previous effect was only observed after the stereochemical studies, (the results of which are presented in chapter 3) were carried out, and rationalises why no asymmetric induction was observed in these studies.

Styrene is generally rather a difficult alkene to epoxidise and high yields with high selectivities are unusual. The best results using molybdenum catalysts (93% selectivity at 98% conversion) have been obtained using molybdeum octanoate in the presence of $B(OPr^i)_3$ and using cumene hydroperoxide as oxidant, but forcing conditions, 100-125^{0}C, are required.[230] The results which we have obtained with styrene are almost as good as these but are obtained at room temperature.

Table 4.1

Effect of different reaction protocols on the epoxidation of styrene catalysed by [MoO_2Cl_2L]

	Protocol [a]	time/h	Conversion to epoxide
1	S + St + O + C	0.02	25
		1.0	0
2	Sv + S + St + O + C	0.02	45
		24	97.7
3	Sv + S + St + O + [C + S + Sv]F	18	0
4	S + St + O + CSv	18	20
5	Sv + S + St + [Sv + S + O]F + C	1.0	22
		48	44
6	Sv + S + St + O + CSv	18	0
7	Sv + S + C + St + O	24	43.4
		144	69.5
8	Sv + S + St + [Sv + S + O]F + C	24	54.5
		144	81.3
9	Sv + S + O + [Sv + S + St +]F + C	0.02	47
		24.0	98
10	Si + S + St + O + C	0.02	0
		1.0	0

[a] S = CH_2Cl_2, St = styrene, O = ^tBuOOH, C = catalyst, Si = silica, Sv = molecular sieves; [ ]F = the filtrate from stirring together the components shown in brackets; CSv means the solid obtained from filtering a solution of sieves, solvent and catalyst. The reagents were added in the order shown in each case.

[where L = dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl) camphor} dioxomolybdenum(VI)

CHAPTER FIVE

KINETIC RESOLUTION OF EPOXIDES BY RING OPENING REACTIONS.

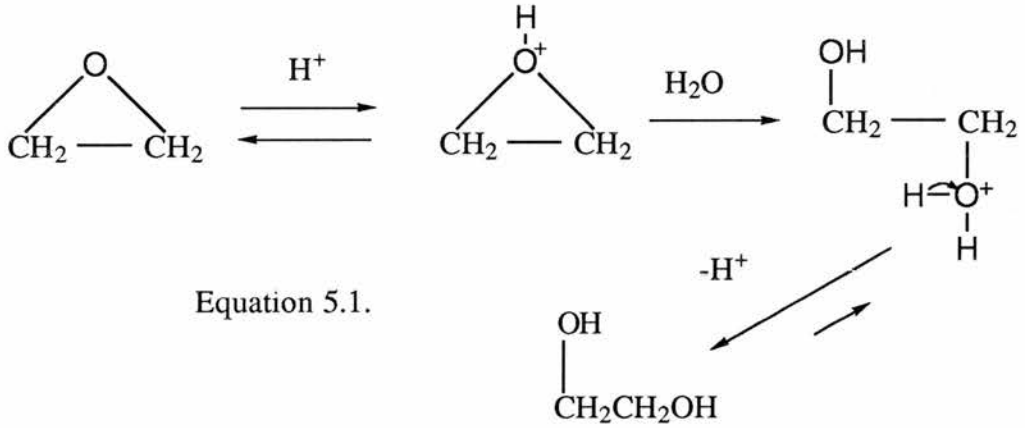
Kinetic Resolution of Epoxides by Ring Opening Reactions.

5.1 Introduction and Background.

During studies aimed at the synthesis of chiral epoxides, it has been discovered that MoO_2Cl_2L {where L = [(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} catalyses the ring opening of limonene oxide by water, such that one isomer, the *cis*, opens much more rapidly than the *trans*.

As discussed in chapter 1, the essential importance of epoxides is their synthetic utility, they are versatile intermediates, and can be converted to a variety of different products,[1] including diols.

The hydration of epoxides has been studied many times. The ring opening by water is acid or base catalysed. During the catalytic action of different acids on the scission of the oxide ring, a proton adds coordinatively to the oxygen atom of the oxide ring, water then acts as a nucleophile to attack the most positively polarised carbon atom in a nucleophilic substitution, the leaving group being the 'OH' derived from the original epoxide.(Equation 5.1)



Equation 5.1.

In view of the fact that the reactions of the opening of the oxide ring involve a nucleophilic substitution at the carbon atom, an inversion in configuration at the attacked carbon atom usually occurs.

In other words, when the alpha-oxide ring is split, as in the formation of alpha-diols, the new substituents appear in mutually anti positions.(*trans* attack)

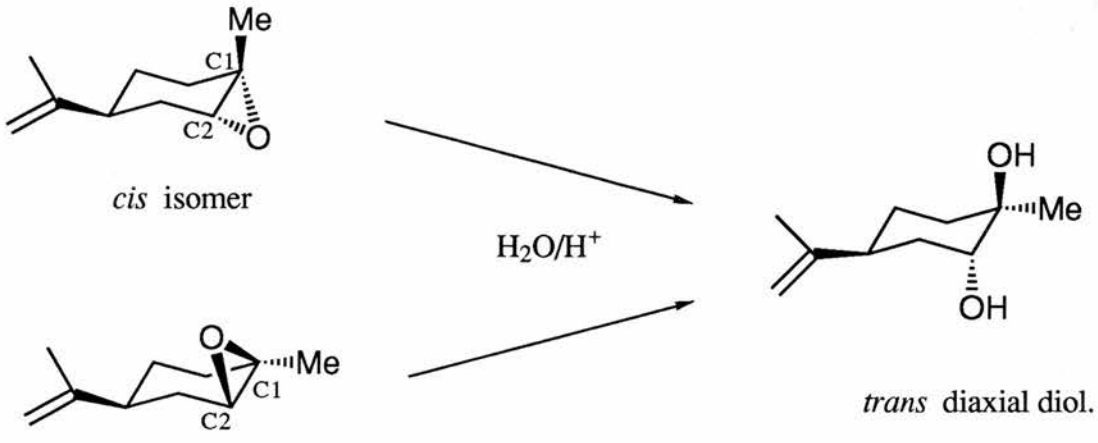
With this in mind, chiral epoxides have enormous potential in asymmetric synthesis, but they are difficult to prepare enantiomerically pure.

5.2 Results and Discussion of Ring Opening Studies.

During the epoxidation of limonene with t-BuOOH catalysed by MoO_2Cl_2L {where L = [(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor}, it was noted that changes occured in the relative ratios of the *cis* and *trans* epoxide products if catalytic solutions were allowed to stand for several days in air in the absence of molecular sieves. One possible explanation was that water from air was dissolving in the CH_2Cl_2 and a ring opening reaction catalysed by MoO_2Cl_2L was occuring. Water was added deliberately to mixtures of MoO_2Cl_2L and preformed limonene oxides to investigate whether or not this was the reason for the observed changes in the *cis/trans* ratios and to investigate whether diastereoselective ring opening might occur.

Limonene oxide undergoes a number of ring opening reactions as do most epoxides.[1] (see chapter 1, section 1.17). As well as hydration to the diol, the mono alcohol can be obtained from limonene oxide, by reduction with lithium aluminium hydride.[231] The hydroxy acetate derivative can be obtained by treatment of limonene oxide with an acetic acid/sodium acetate solution.[232]

Previous work on the ring opening reactions of limonene oxide has shown that both *cis* and *trans* limonene oxide yield the same *trans* diaxial diol.[231,232] (Scheme 5.1)

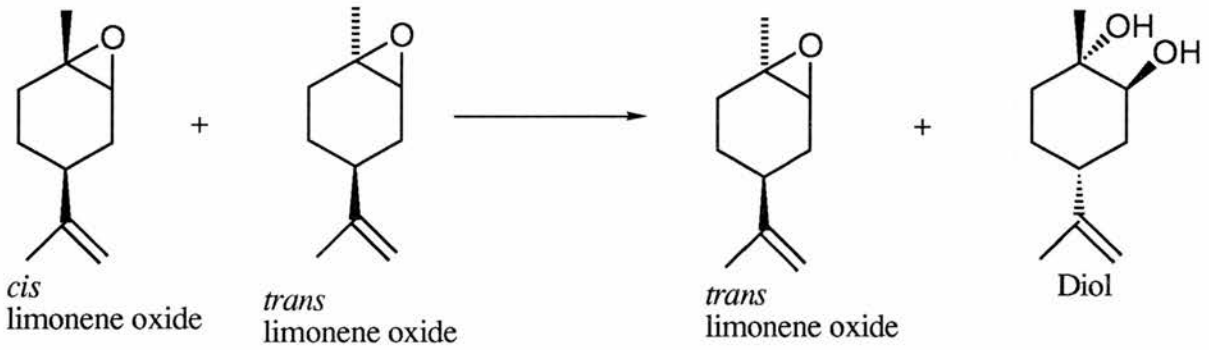


Scheme 5.1

In the case of the *cis* isomer, attack of the 'OH' from water occurs at the C1 position and inversion of configuration at C1 is observed. This is a curious reaction since one would expect the attack to take place at C2 for both steric (ie the presence of the methyl group) and electronic reasons. (ie the methyl group will donate electron density into C1 and therefore make it less positively charged). However, it is thought[231,232] that the transition states which lead to the product influence the position of this attack, and that because attack at C1 of the *trans* isomer leads to a chair-like transition state, the C1 position is attacked, hence the *trans* diaxial product is formed. Conversely, attack of the *trans* isomer takes place at the expected C2 position and therefore the *trans* diaxial molecule is once again produced. In this case, the chair like transition state is formed from attack at C2 so all influences direct the attack to this carbon atom. There is no evidence from the literature that the ring opening of the two isomers occurs at significantly different rates.

5.2.1 Ring Opening Reactions of (+) and (-) Limonene Oxide by Water Using Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) Catalyst.

This catalyst was first used to verify the original finding that in the presence of water, this catalyst aided the preferential ring opening of limonene oxide, such that the *cis* isomer opened more favourably to the diol than the *trans* isomer.(Equation 5.2)



cis limonene oxide + *trans* limonene oxide → *trans* limonene oxide + Diol

Equation 5.2

Using a 1:100 molar ration of catalyst to limonene oxide and one drop of water to initiate the ring opening in dichloromethane solvent, samples were taken and injected into the GC after different time intervals The results show the relative proportions of *cis* to *trans* isomers remaining after the time elapsed. Since the diol being formed was not observed under the conditions of the GC experiment, the actual conversions of the two diastereomers have not been estimated, although in a separate experiment it was shown by nmr that after two weeks in air the relative ratios of *cis* epoxide : *trans* epoxide : diol were 2.99% : 29.85% :67.16%. ie 92.8% of the original *cis* isomer was transformed to the diol and 48.8% of the original *trans* isomer was transformed to the diol.

(+)-Limonene Oxide.			(-)-Limonene Oxide		
0 mins	*cis*	43%	0 mins	*cis*	44%
	trans	57%		*trans*	56%
10 mins	*cis*	37%	35 mins	*cis*	36%
	trans	63%		*trans*	64%
1hr 5mins	*cis*	24%	1hr 15 mins	*cis*	33%
	trans	76%		*trans*	67%
24hrs	*cis*	20%	3hr 25 mins	*cis*	33%
	trans	80%		*trans*	67%
98hrs	*cis*	1%	46hrs	*cis*	30%
	trans	99%		*trans*	70%
			148hrs	*cis*	26%
				trans	74%
			503hrs	*cis*	0%
				trans	100%

It can be seen that for both enantiomers the *cis* isomer almost completely disappears regardless of whether the limonene oxide is (+) or (-). The (-) limonene oxide does take longer for all the *cis* isomer to react.

5.2.2 Ring Opening reactions of (+) and (-) limonene oxide by water using Dichloro { [(1S) - *endo*] - (-)- 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum(VI) Catalyst.

The other enantiomer of the diethoxy catalyst was then used in the same way to investigate whether the *cis* isomer would ring open preferentially or whether the different enantiomer would effect the selectivity.

(+)-Limonene Oxide.			(-)-Limonene Oxide		
0 mins	*cis*	43%	0 mins	*cis*	44%
	trans	57%		*trans*	56%
10 mins	*cis*	35%	10 mins	*cis*	40%
	trans	65%		*trans*	60%
36 mins	*cis*	26%	1hr	*cis*	33%
	trans	74%		*trans*	67%
1hr 5 mins	*cis*	28%	1hr 40 mins	*cis*	31%
	trans	72%		*trans*	69%
71hrs	*cis*	15%	27hrs	*cis*	13%
	trans	85%		*trans*	87%

It can be seen that the enantiomeric forms of this catalyst do not alter the preferential ring opening of the epoxide and the reaction almost goes to completion. For the (+)-limonene oxide the resolution occurs at a similar rate to that for the enantiomeric catalyst, whereas for the (-)-limonene oxide it is perhaps somewhat faster.

5.2.3 Ring Opening reactions of (+) and (-) limonene oxide by water using Dichloro{[(1R)-*endo*] -(+)-3-[bis - {(S)-(+)-butanoxy} phosphoryl]camphor} dioxomolybdenum(VI) Catalyst.

Again the same method was used in the ring opening reactions to those described previously. The object was to investigate the effect of the ligand upon the ring openings.

	(+)-Limonene Oxide.			(-)-Limonene Oxide	
0 mins	*cis*	43%	0 mins	*cis*	44%
	trans	57%		*trans*	56%
10 mins	*cis*	40%	10 mins	*cis*	38%
	trans	60%		*trans*	62%
35 mins	*cis*	35%	1hr	*cis*	35%
	trans	65%		*trans*	65%
264hrs	*cis*	3%	47 hrs	*cis*	35%
	trans	97%		*trans*	65%
			648 hrs	*cis*	0%
				trans	100%

It can be seen that the same selectivity again occurs and the *cis* isomer ring opens to completion in both cases.

5.2.4 Ring Opening reactions of (+) and (-) limonene oxide by water using Dichloro{[(1R)-*endo*]-(+)-3-(diphenylphosphoryl)camphor} dioxomolybdenum(VI) Catalyst.

For these reactions, the electron density at the phosphoryl phosphorus atom was altered by replacing the alkoxy groups of the previous catalysts by phenyl. This catalyst was used in the ring opening reactions in an identical way as before.

(+)-Limonene Oxide.			(-)-Limonene Oxide		
0 mins	*cis*	43%	0 mins	*cis*	44%
	trans	57%		*trans*	56%
40 mins	*cis*	30%	10 mins	*cis*	37%
	trans	70%		*trans*	63%
2 hrs	*cis*	27%	1hr	*cis*	33%
	trans	73%		*trans*	67%
72 hrs	*cis*	20%	24 hrs	*cis*	33%
	trans	80%		*trans*	67%
768 hrs	*cis*	20%	72 hrs	*cis*	31%
	trans	80%		*trans*	69%
			600 hrs	*cis*	25%
				trans	75%
			672hrs	*cis*	24%
				trans	76%

Once again the same selectivity was shown. However, since the reaction appears to stop in each case before completion it is possible that some catalyst decomposition is occuring, although this effect does not seem to have been observed in the case of other catalysts. Another theory is that this effect is due to the steric bulk of the ligand or some electronic effects from the diphenyl group.

5.2.5 Ring Opening of (+) and (-) limonene oxide by water using dichlorodioxomolybdenum (VI).

Finally, the molybdenum complex MoO_2Cl_2 was used in order to investigate whether or not the β-ketophosphonate ligands have an effect.

(+)-Limonene Oxide.			(-)-Limonene Oxide		
0 mins	*cis*	43%	0 mins	*cis*	44%
	trans	57%		*trans*	56%
40 mins	*cis*	38%	10 mins	*cis*	40%
	trans	62%		*trans*	60%
1 hr 5 mins	*cis*	37%	42 mins	*cis*	42%
	trans	63%		*trans*	58%
23.5 hrs	*cis*	42%	1 hr 5 mins	*cis*	37%
	trans	58%		*trans*	63%
70 hrs	*cis*	36%	24.5 hrs	*cis*	35%
	trans	64%		*trans*	65%
96.5 hrs	*cis*	36%	96 hrs	*cis*	32%
	trans	64%		*trans*	68%

The selectivity for the *cis* isomer is still the same but the reaction occurs very slowly and does not approach completion. This illustrates that molydenum dioxide dichloride is not a good catalyst and highlights the effect of the ligand. Finally, an experiment was carried out where no catalyst was added to the reaction flask with limonene oxide and water. The result was that there was no effect on the ratio of *cis* to *trans* isomers in either (+) or (-) limonene oxide proving that it is the catalyst which is inducing selectivity.

5.2.6 Summary and possible conclusions to ring opening reactions.

From the GC results it can be seen that the opening of the *cis* isomer is preferred over the *trans* isomer in all cases regardless of the catalyst and the ligand present.

However, the nature of the ligand is important, with both activity and selectivity following the order: OEt~OBu>Ph>no ligand for the substituents on phosphorus in the camphor derived β-ketophosphonate.

No definite conclusions can be drawn from this data as to why the *cis* isomer is reacting, but one possible reason is that the stereochemistry of the *cis* isomer is vulnerable to react with the Mo catalyst which acts as a Lewis acid and withdraws electrons from the epoxide.

There may be a chelate bonding effect between the catalyst and the double bond of the methylethenyl group at the same time as the catalyst is interacting with the epoxide. This however seems unlikely since the epoxide and the methylethenyl group are on opposite faces of the ring in the *cis* isomer. In addition Mo^{VI} is d^0 and so an interaction with the alkene will not be stabilised by back-bonding and should be weak.The possibility of this effect is further investigated.(see section 5.4 on studies carried out on hydrogenated limonene oxide)

Another theory is that the catalyst can easily bind to the epoxide in the *cis* isomer without steric hindrance from either the methyl group at C1 or the methylethenyl group at C_4 since they are both on the opposite face of the ring to the epoxide group in the *cis* isomer. (see scheme 5.2) Whereas, in the *trans* isomer the methylethenyl group may sterically hinder any interaction between the catalyst and the epoxide group since the oxide ring and the 4-substituent are both on the same face of the ring in this case, thus reducing the Lewis-acid action of the catalyst on the epoxide group.(see scheme 5.2)

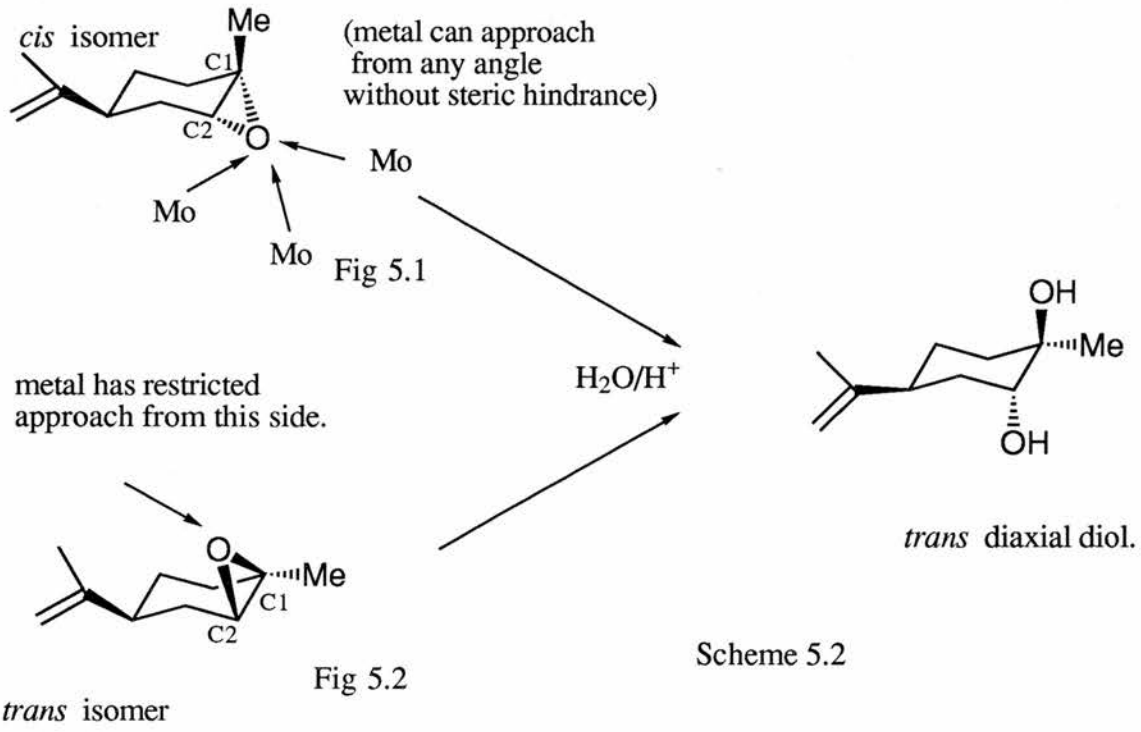
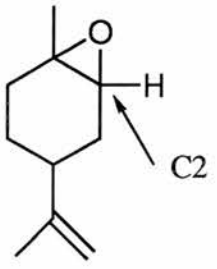


Fig 5.2

Scheme 5.2

5.3 ^{1}H NMR Analysis.

In an attempt to understand further, the bonding between limonene oxide and the catalyst, a series of experiments analysed by ^{1}H nmr were carried out. Firstly, the ^{1}H nmr of limonene oxide had to be understood. (Spectrum 5.1)



Limonene oxide.

It can be seen from spectrum 5.1, that the proton in the C2 position of limonene oxide results in a doublet from the *trans* isomer at 2.95 ppm, and a triplet as a result of the *cis* isomer at 3.05 ppm.[231]

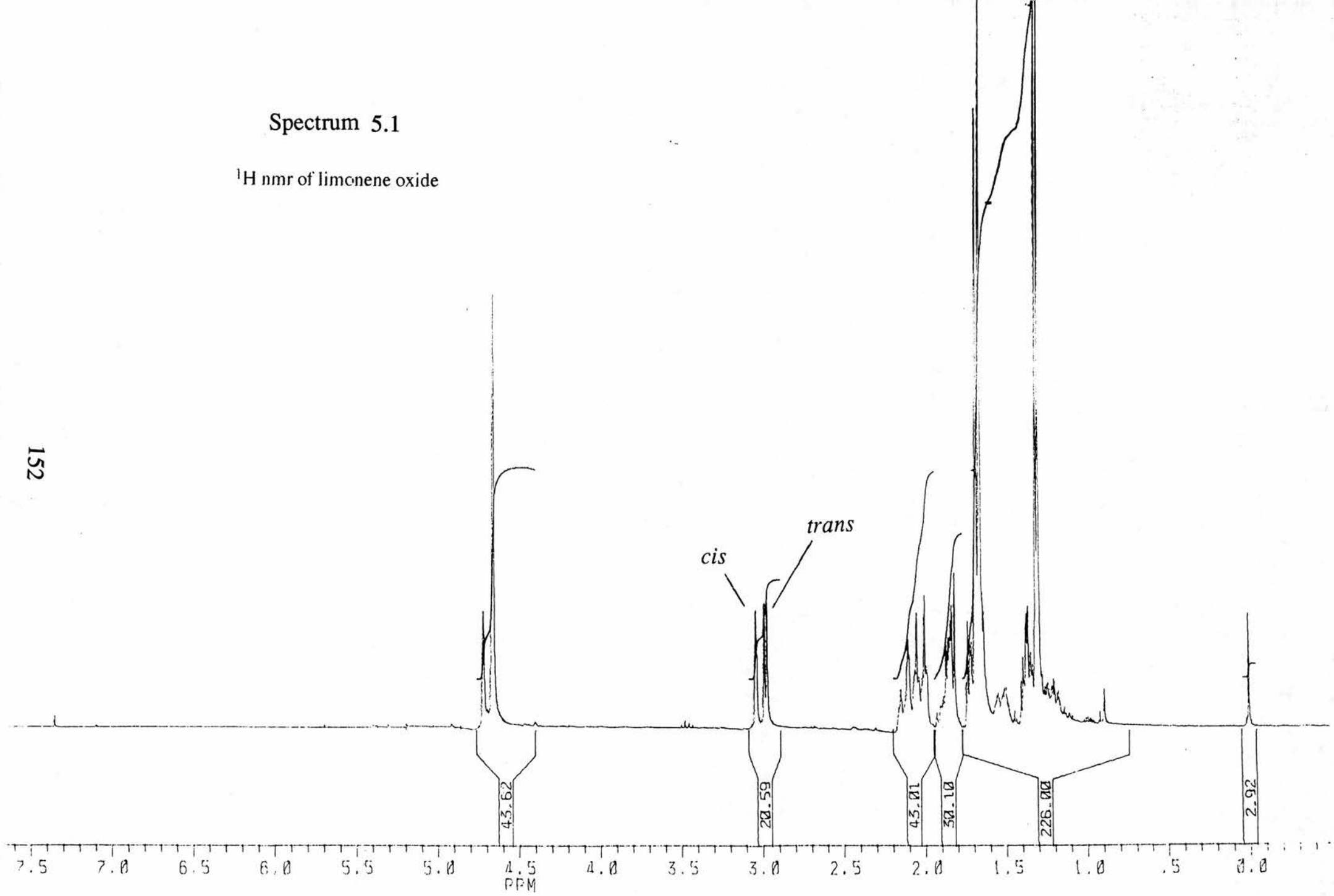
The reason for the different splitting patterns for the two isomers is due to differing dihedral angles between the proton at C2 and those at C3 in the different diastereomers. From the Karplus equation it has been shown that as the dihedral angle between two neighbouring atoms approaches 90^0, the coupling constant between these atoms tends to zero. Conversely, the coupling constant is largest when the dihedral angle approaches either 0^0 or 180^0.Therefore, since the *trans* isomer gives only a doublet for the proton at C2 instead of the expected triplet, this is an indication that the dihedral angle between one of the protons at C3 and the proton at C2 is very close to 90^0. This is indeed the case between the proton at C2 and the equatorial hydrogen atom at C3.

Spectrum 5.2 is a result of a ring opening reaction whereby the catalyst dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) had been reacted with (+) limonene oxide in air.

The sample was taken after approximately 2 weeks and it can be seen that the *cis* triplet has almost completely disappeared leaving the *trans* doublet at 2.95 ppm. The peak at 3.6 ppm arises from the diol. It has been calculated that after 5 minutes in air the *cis : trans* ratio was 41.7% : 58.3%. After 2 weeks in air the *cis : trans :* diol ratio was 2.99% :29.85% : 67.16%. Therefore it has been calculated that % of *cis* transformed to diol = 92.8% and the % of *trans* transformed to diol = 48.8%. Thus, both isomers of the epoxide ring open to the same diol, as has previously been observed, but the *cis* opens much more rapidly than the *trans*. (Equation 5.3)

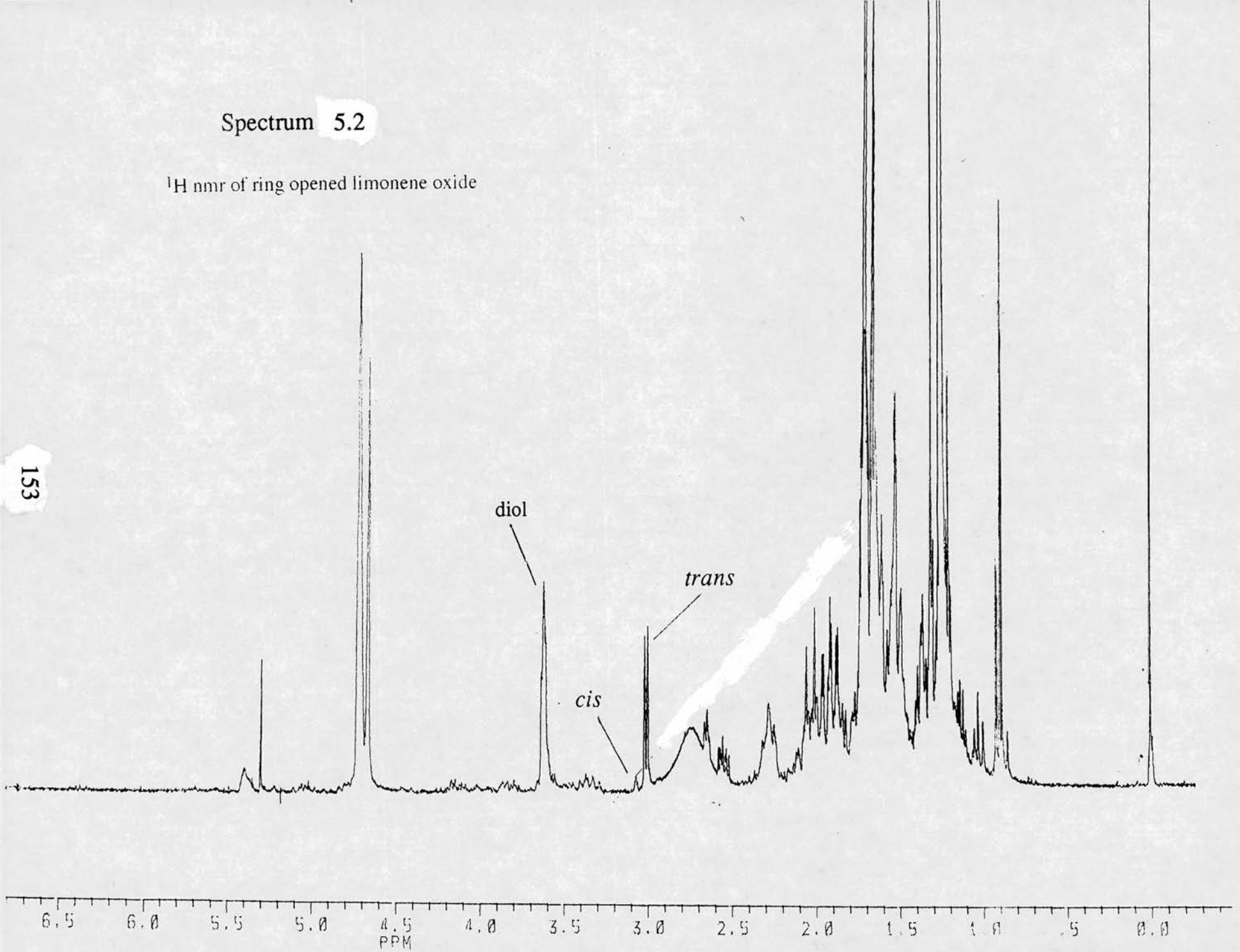
Spectrum 5.1

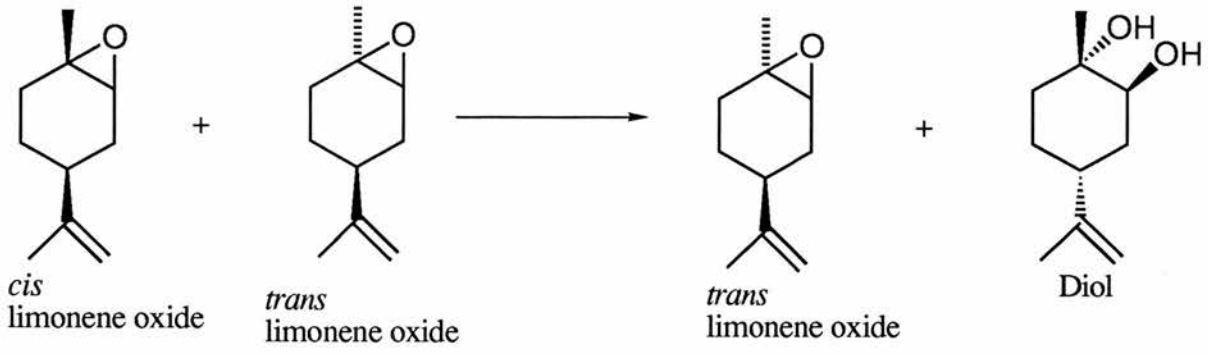
^{1}H nmr of limonene oxide



Spectrum 5.2

^{1}H nmr of ring opened limonene oxide





cis limonene oxide

trans limonene oxide

trans limonene oxide

Diol

Equation 5.3.

5.3.1Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) catalyst with (+) limonene oxide in a 1 : 2 molar ratio.

In an attempt to study whether preferential binding was responsible for the diastereoselectivity observed during ring opening reactions of limonene oxide, a ^1H nmr spectrum of a mixture of (+)-limonene oxide (*cis : trans* 1:1) was taken (in solution) in the presence of MoO_2Cl_2L (L=[(1R-*endo*) - (+) - 3 - (diethoxyphosphoryl) camphor]) with an epoxide : catalyst ratio of 1 : 2. (Spectrum 5.3)

It can be seen that the *trans* doublet is unmoved at 2.95 ppm, but the *cis* triplet has been shifted to a position at 4.05 ppm, which is probably due to the Lewis acid effect of the Mo atom binding to the epoxide. This suggests that the catalyst binds preferentially to the *cis* isomer.

Interestingly, when a 1:1 ratio of catalyst to substrate is used it is observed that the triplet from the *cis* isomer has been shifted as expected, whereas the *trans* isomer seems largely unaffected. However, it is almost certain that there must be some limited interaction since it has already been shown that the *trans* isomer does ring open, albeit over a very long time period.(see 5.3).

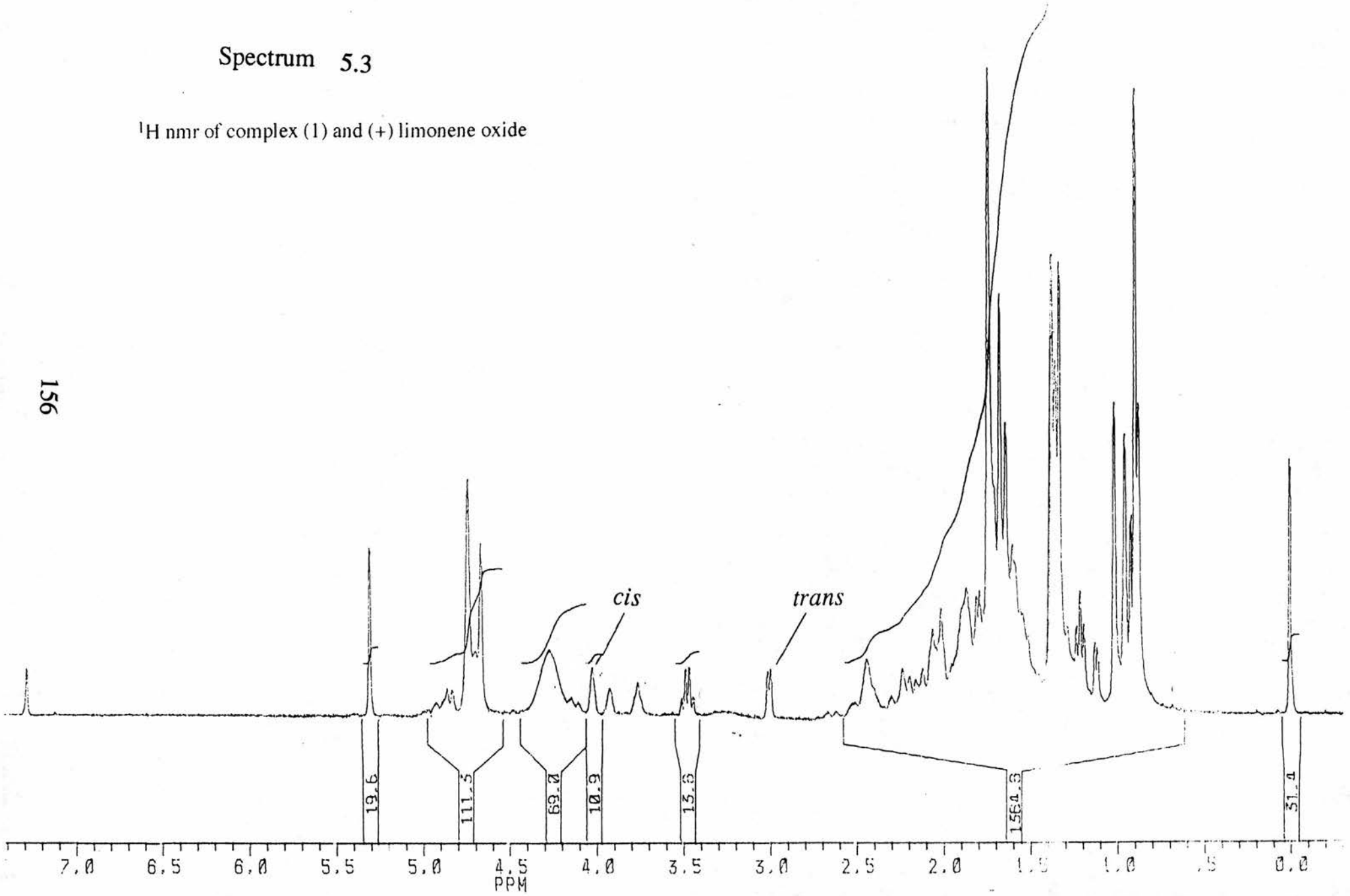
5.3.2 Formation of complex using Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) catalyst with (+) limonene oxide in a 1 : 2 molar ratio.

In a similar experiment to the last, an attempt was made to precipitate out the adduct of the catalyst with the *cis* isomer and to remove the unreated *trans* isomer in solution, by filtration, in the hope that the *trans* isomer will have disappeared and to prove that it is not reacting with the catalyst.

The result, Spectrum 5.4, shows that the *trans* doublet has been removed and the *cis* triplet has been shifted as in Spectrum 5.3, to 4.05 ppm. This confirms that only the *cis* isomer binds to the molybdenum if there is insufficient complex present to bind to both isomers. It is also clear from spectra 5.3 and 5.4 that the resonances from the hydrogen atom attached to the methylethenyl group remain essentially unaffected by the binding of the Mo complex, thus confirming that interaction of the molybdenum with the double bond is not occuring.

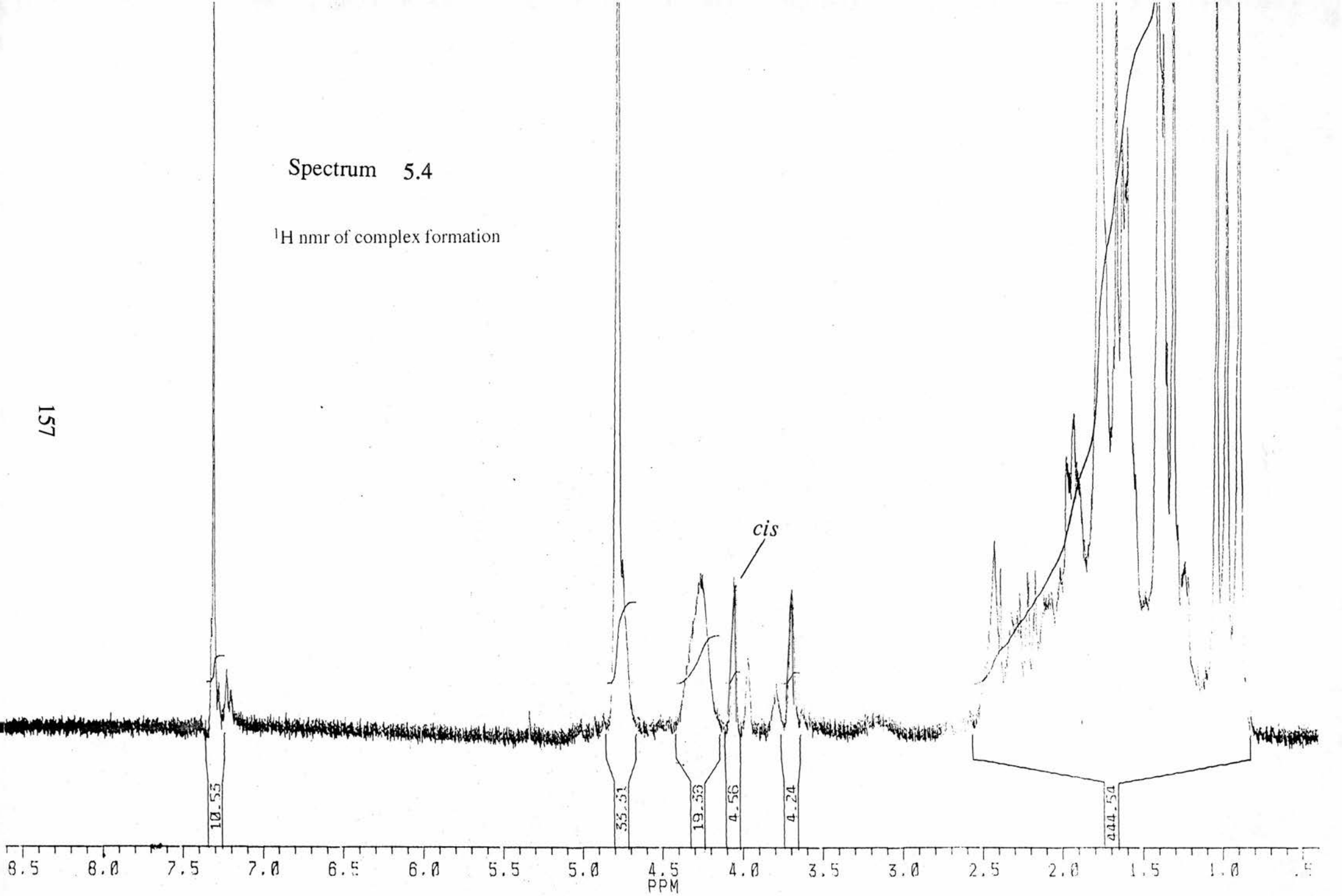
Spectrum 5.3

^{1}H nmr of complex (1) and (+) limonene oxide



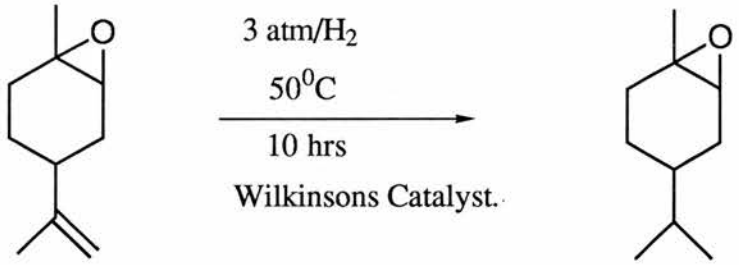
Spectrum 5.4

^{1}H nmr of complex formation



5.4 Hydrogenation of (+)-limonene Oxide.

In an attempt to clarify the interaction of the catalyst with the *cis* isomer and to verify whether it is the double bond of limonene oxide which is having a chelate effect with the catalyst, or whether it is the steric effect that causes the diastereoselective ring opening, the following reaction was performed to remove the double bond from limonene oxide. (Equation 5.4).



Equation 5.4

The reaction was carried out in THF solvent which was removed under vacuum and the decomposed catalyst was removed by fractional distillation. GC-mass spec. confirmed that hydrogenated (+)-limonene oxide had been produced. ^{1}H nmr also showed a triplet at 3.05 ppm from the *cis* isomer and a doublet at 2.95 ppm from the *trans* isomer as in the unhydrogenated species. Resonances from the double bond near 5 ppm were absent.

5.4.1.Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) catalyst with hydrogenated (+)-limonene oxide in a 1:2 molar ratio.

In an almost identical experiment to that with the unhydrogenated species, the hydrogenated (+)-limonene oxide was analysed in solution by ^{1}H nmr with the diethoxy catalyst present in the same 1 : 2 molar ratio.

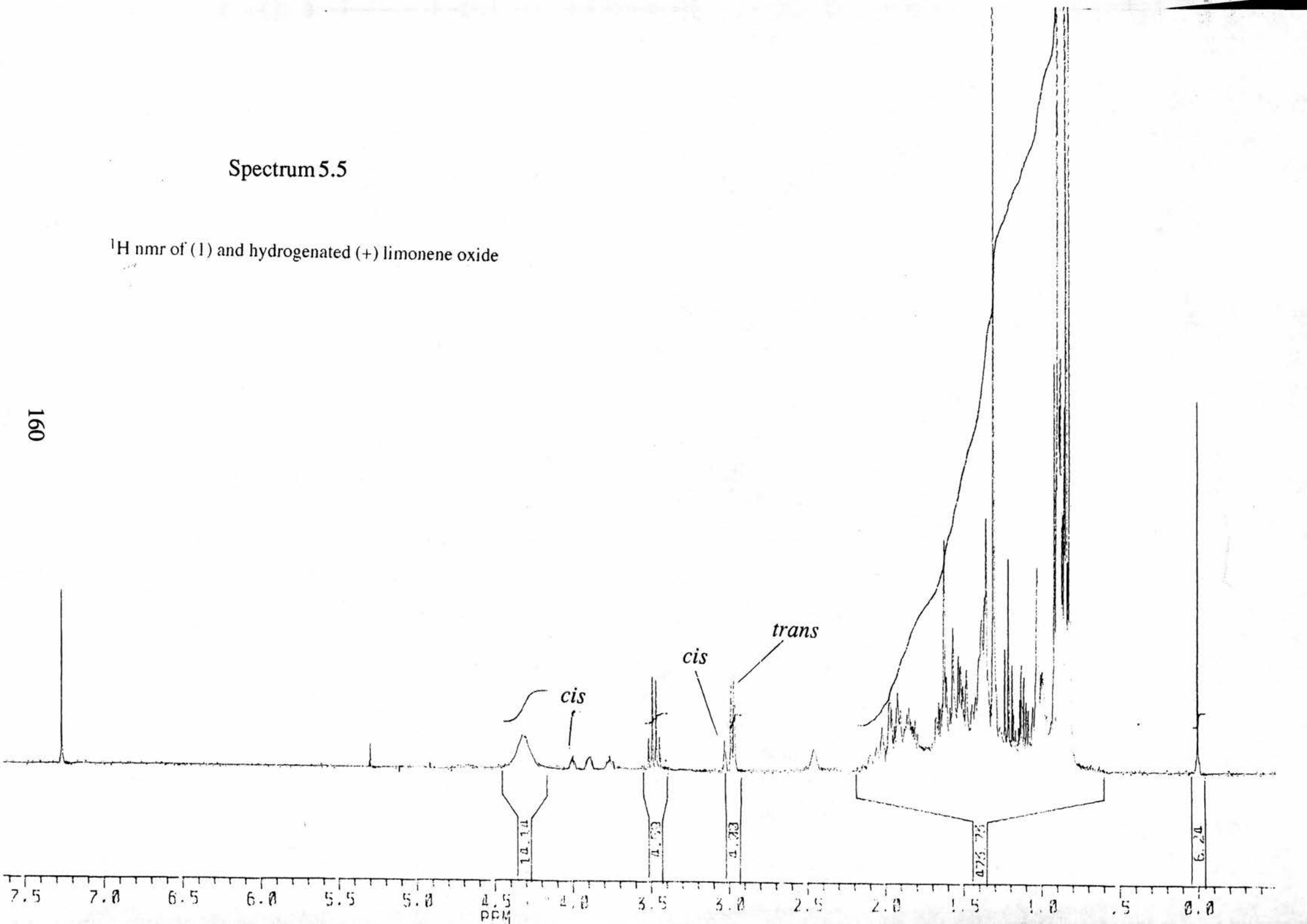
Spectrum 5.5 shows the ^1H nmr spectrum. As with the unhydrogenated species, the *trans* doublet is unmoved at 2.95 ppm. Some of the *cis* triplet however, is unreacted as there is still a trace at 3.05 ppm.

5.4.2 Formation of complex using Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum(VI) catalyst with hydrogenated (+)-limonene oxide in a 1:2 molar ratio.

Also in an identical experiment to that of the unhydrogenated species, the hydrogenated (+)-limonene oxide was added to the catalyst and the resulting complex precipitated out of solution. Following filtration of the solvent, in which the *trans* isomer was expected to remain, the solid was dried under vacuum and a proton nmr was obtained. The result, Spectrum 5.6, shows no peaks in the region of 2.95 to 3.05 ppm indicating the *trans* isomer has remained unreacted in solution. The *cis* isomer has shifted in the same way as has been observed previously, and is thought to lie below the doublet of doublets at 3.8 ppm, which arises from the diethoxy catalyst, although from measurement of the intergral values this is difficult to confirm, since measurement indicates that the doublet of multiplets at 3.8ppm (which is equivalent to CH-3) is approximately one quarter of the value measured for the multiplet peak at 4.5ppm. (which is equivalent to CH_2-11/13), which is consistant if no other peaks were present in this area of the spectrum. However, it is clear that one multiplet from the set of peaks at 3.8ppm is noticably larger than the other, which is not observed in the free complex, and in addition the intergral value for these peaks is greater than that measured for triplet at 2.5ppm, which is also equivalent to one proton. In addition, from ring opening experiments outlined in section 5.4.3 it has been shown that the *cis* isomer does open preferentially, although in this case both isomers open much more quickly than observed in the unhydrogenated species.

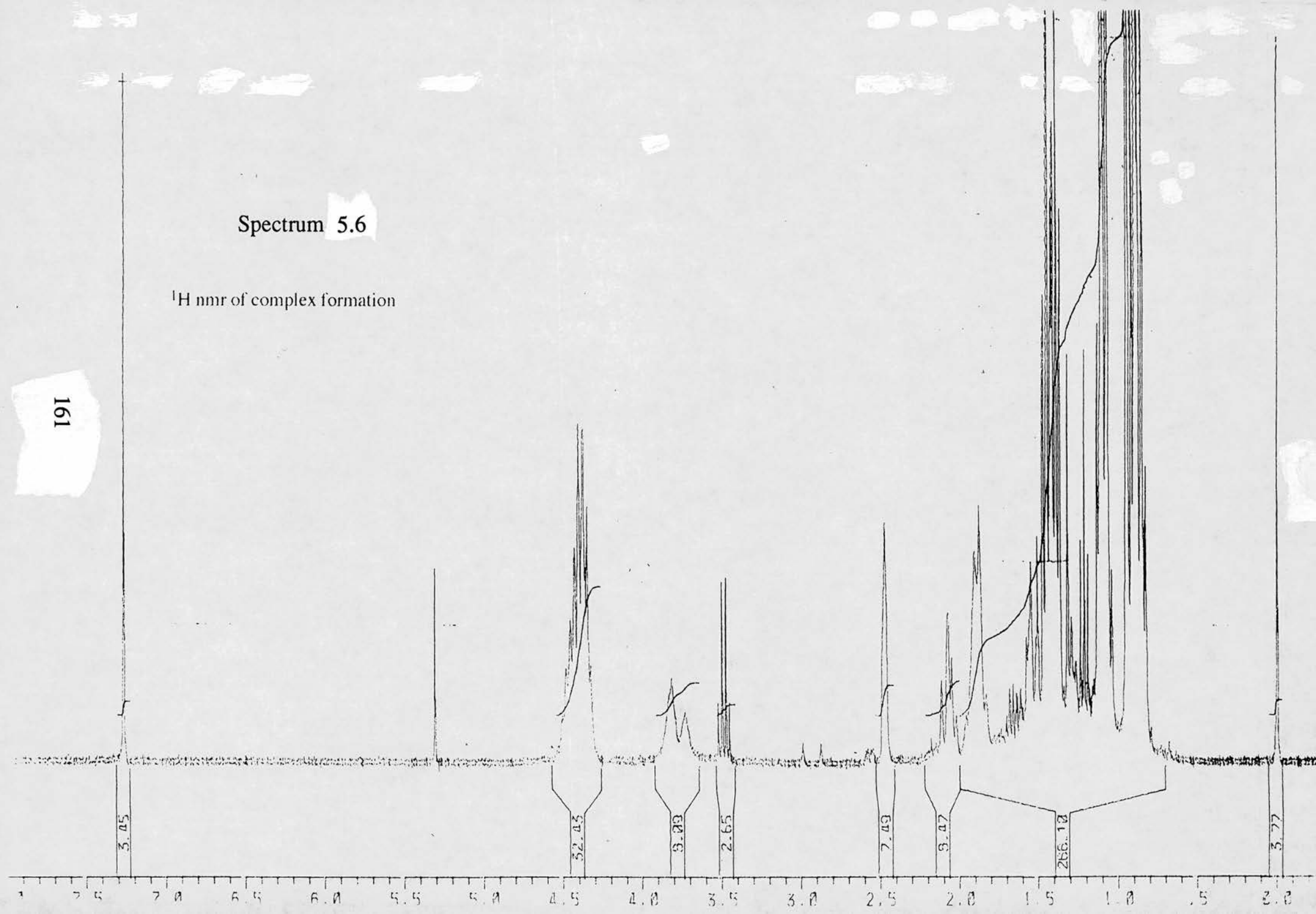
Spectrum 5.5

^{1}H nmr of (1) and hydrogenated (+) limonene oxide



Spectrum 5.6

^{1}H nmr of complex formation



5.4.3 Ring Opening of Hydrogenated (+)-limonene Oxide.

Hydrogenated (+)-limonene oxide could not be separated on the GC column as efficiently as (+) or (-)-limonene oxide. In an attempt to rationalise the results so far, ring opening reactions were performed on the hydrated species and analysed by ^{1}H nmr.The reactions were performed in the same way as the previous ring opening reactions and samples were taken for ^{1}H nmr after 3 hours (Spectrum 5.7) and 74 hours (Spectrum 5.8).

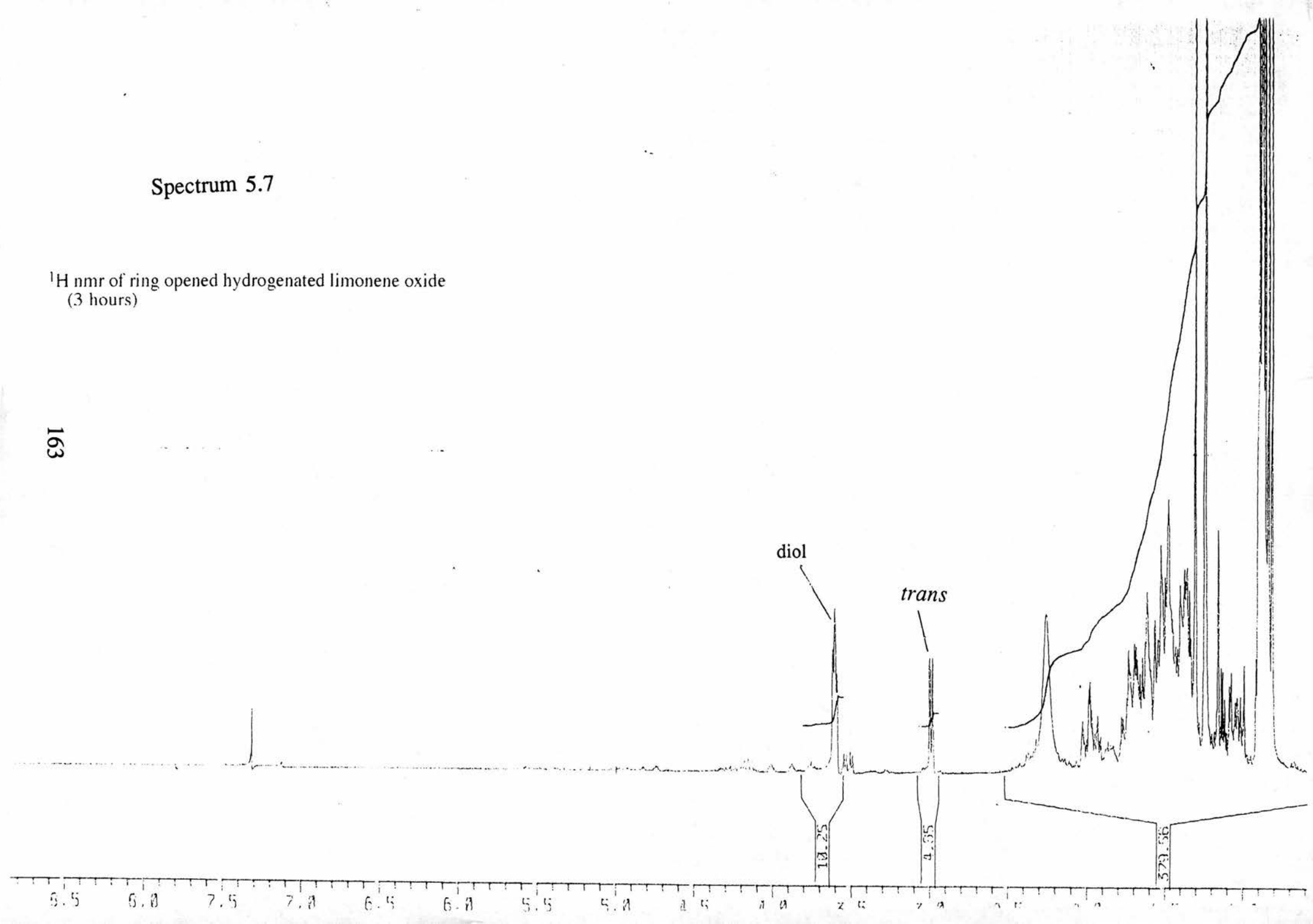
Spectrum 5.7 shows that all of the *cis* isomer, has reacted to form the diol (peak at 3.65 ppm). The *trans* isomer appears to be partially unreacted as a doublet remains at 2.95 ppm. From measurement of integral values it has been calculated that after 3 hours only 43.54% of the *trans* isomer has been hydrated to the diol. After 74 hours however, Spectrum 5.8 shows no apparent signs of either *cis* or *trans* limonene oxide and both isomers appear to have ring opened to the diol, shown at 3.6 ppm.The most interesting point to note here is that the *cis* isomer of the hydrogenated species has completely reacted after only 3 hours; ie much more quickly than that of the unhydrogenated species (see above). After a slightly longer period (74 hours) the *trans* has also completely ring opened, again this was not the case with normal limonene oxide.

5.5 Rationalisation of ^{1}H nmr data.

Having already discussed possible theories as to the selectivity that we are achieving in ring opening reactions, we are now in a better position to explain these results, but cannot yet make firm conclusions. However, with this nmr data from the stoichiometric reactions and bearing the previous results in mind we can make some probable suggestion as to why we achieve such selectivity in these ring opening reactions.

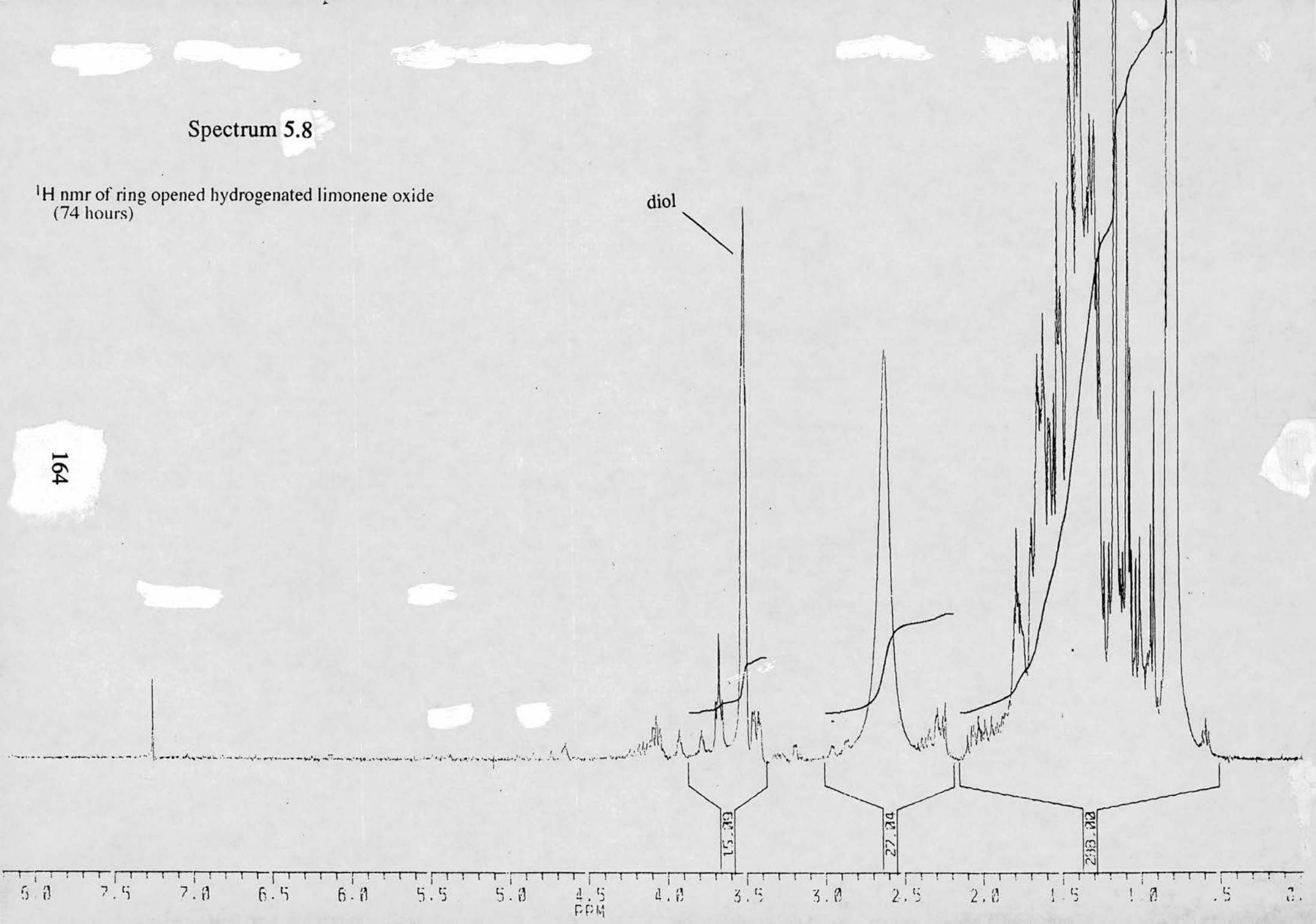
Spectrum 5.7

^{1}H nmr of ring opened hydrogenated limonene oxide
(3 hours)



Spectrum 5.8

^{1}H nmr of ring opened hydrogenated limonene oxide
(74 hours)



It is clear from the nmr data collected that there is a preferential interaction between the catalyst and the *cis* isomer, and since this preference is still observed in the case of hydrogenated limonene oxide, it is unlikely that this effect is due to secondary chelation of the catalyst with the methylethenyl double bond. As discussed in section 5.2.6 this would be very unlikely in any case since the epoxide and the methylethenyl double bond are on opposite faces of the ring in the *cis* isomer.

It is interesting to note that this effect decreases as the steric bulk of the catalyst increases, except in the case of MoO_2Cl_2. This would appear to indicate some kind of steric interaction effect. It is possible that as the steric bulk of the catalyst is increased so the ability of the catalyst to interact with the epoxide, either *cis* or *trans* is decreased. One would expect however, that MoO_2Cl_2 would show the greatest preference of all, but it may be that an organic ligand is required on the metal to enable the catalyst to dissolve efficiently in organic solvents, before this preferential effect is observed.

This preferencial ring opening is maintained in the reactions with hydrogenated limonene oxide, although is not clear as to why both isomers should open faster in this case, since it is difficult to imagine any significant change in steric crowding in comparison to the unhydrogenated species.

CHAPTER SIX

EXPERIMENTAL.

EXPERIMENTAL.

6.1 Synthesis of β-ketophosphonate ligands.

6.1.1 [(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor.

A solution of [(1R) - (+) - *endo*] camphor (0.37g, 2.43 mmol) in anhydrous THF (4 cm^3) was added dropwise via a catheter to a stirred solution of lithium diisopropylamine [LDA, 1.1 equiv, prepared in situ from diisopropylamine (0.38 cm^3) and *n* - BuLi (1.7 cm^3, 1.6 mol dm^{-3})] in THF (1.5 cm^3) at -65^0C. After 45 min, the resulting enolate was treated with diethyl phosphorochloridate (0.4 cm^3, 2.67 mmol) and the mixture was allowed to warm to 0^0C over the course of 50 min. After this mixture was cooled to -75^0C, it was transferred dropwise via a catheter to a solution of LDA (2.2 equiv in 3 cm^3 of THF). The resulting solution was allowed to warm to 10^0C over 2 hr, and then left to stir for 48 hr.

Standard workup then followed whereby a solution of glacial acetic acid in diethyl ether (1 mol dm^{-3}, 4 equiv) was added slowly via a catheter to the cooled reaction mixture, and the resulting solution was filtered through hyflosupercel to remove the precipitate. The filtrate was then washed thoroughly with distilled water (3 x 25 ml) to remove any remaining salt, and concentrated on a rotavapour before purification using kuglerorh distillation. Yield 246 mg, 34.9%.

Analysis.

^{31}P : + 22.42 ppm.

^1H : dm 2.95 ppm.

$[\alpha_D]$: $+144.68^0$

This data is consistent with literature values.[208]

6.1.2 [(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl) camphor.

This compound was prepared similarly to above using [(1S) - *endo*]-(-)-camphor. Yield 212mg, 30.08%.

Analysis.

^{31}P : +23.25 ppm.

^{1}H : dm 2.95 ppm.

$[\alpha_D]$: -136.04^0

(Please refer to chapter 2, tables 2.7 and 2.9 for detailed nmr data.)

6.1.3 [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor.

6.1.3.1 Di - [(S) - (+) - 2 - butyl]chlorophosphine.

(S) - (+) - 2 - Butanol (2.2 cm^3, 0.026 mols) was added dropwise via a catheter to a cooled solution of phosphorus trichloride (1.1 cm^3, 0.013 mols), triethylamine (3.7 cm^3, 0.026 mols) and diethyl ether (20 cm^3) with stirring. This solution was allowed to stir for 24 hr after which time the triethyl-ammonium salt was removed by filtration through hyflosupercel. The filtrate was concentrated on a rotavapour, to give a colourless oil. Yield 1.7g, 59%.

Normally, this compound was not isolated, but instead immediately hydrolysed to the corresponding phosphite. Therefore no analytical data has been collected.

6.1.3.2 Di - [(S) - (+) - 2 - butyl] phosphite.

To a large excess of ice was added di - [(S) - (+) - 2 - butyl]chlorophosphine (2 g, 0.0094 mols) in anhydrous diethyl ether (20 cm^3) with stirring. After 2 hr the water was removed and the organic layer was washed with sodium carbonate (1 mol dm^{-3}, 2 x 20 cm^3). The organic layer was then dried over magnesium sulphate, filtered, evapourated on a rotavapour and purified by distillation to give a clear liquid. Yield 1.2 g, 66.7%.

Analysis.

^{31}P : + 4.71 ppm.

^{1}H : J(P - H) 688.7, 4.5 ppm (m, 2H), 1.7 ppm (m, 4H), 1.4 ppm (d, 6H), 0.95 ppm (t, 6H).

6.1.3.3 Di - [(S) - (+) - 2 - butyl] phosphorochloridate.

Sulphuryl chloride (1.8 g, 0.0134 mols) was added slowly via a catheter to a stirred solution of di - [(S) - (+) - 2 - butyl] phosphite (2.6 g, 0.0134 mols) in anhydrous dichloromethane (20 cm^3) with stirring. This solution was allowed to stir for 2 hr, after which the solvent was removed under vacuo, leaving a pale yellow oil. Yield 2.22 g, 72.6%

Analysis.

^{31}P : + 2.67 ppm.

^{1}H : No one bond phosphorus - hydrogen coupling. Other peaks: 4.6 ppm (m, 2H), 1.7 ppm (m, 4H), 1.5 ppm (d, 6H), 1.0 ppm (t, 6H).

6.1.3 [(1R) - *endo*] - (+) - 3 - [bis {(S) - (+) - 2 - butanoxy}phosphoryl] camphor.

A solution of [(1R) - *endo*] camphor (1.3 g, 0.0088 mols) in anhydrous THF (14.5 cm^3) was added dropwise via a catheter to a stirred solution of lithium diisopropylamine [LDA, 1.1 equiv, prepared in situ from diisopropylamine (1.4 cm^3) and *n* - BuLi (6.2 cm^3, 1.6 mol dm^{-3})] in THF (5.5 cm^3) at -65^{0}C. After 45 min, the resulting enolate was treated with di - [(S) - (+) - 2 - butyl] phosphorochloridate (2.2 g, 0.0097 mol) and the mixture was allowed to warm to 0^{0}C over the course of 50 min. After this mixture was cooled to -75^{0}C, it was transferred to a solution of LDA (2.2 equiv in 10.9 cm^3 of THF). The resulting solution was allowed to warm to 10^{0}C over 2 hr. Standard workup (as outlined in 6.1.1) was followed and the product was purified by washing with conc HCl (5 cm^3) then sodium carbonate solution and finally by Kuglerorh distillation. Yield 1.2g, 39.4%.

Analysis.

^{31}P nmr : + 20.8 ppm.

^{1}Hnmr : dm at 2.95 ppm.

I R : ν(C=O) 1742 cm^{-1}..

$[\alpha_D]$: +165.15^0

(Please refer to chapter 2, tables 2.8, and 2.9 for more detailed nmr data)

6.1.4 [(1S) - *endo*] - (-) - 3 - [bis {(S) - (+) - 2 - butanoxy}phosphoryl] camphor.

This compound was prepared using the method outlined in 6.1.3, using [(1S) - *endo*] camphor.
Yield 0.9g, 29.56%.

Analysis.

^{31}P nmr : + 23.14 ppm.

^{1}Hnmr : dm 2.95 ppm.

I R : ν(C=O) 1743 cm^{-1}.
$[\alpha_D]$: -93.54^0
(Please refer to chapter 2, tables 2.8, and 2.9 for more detailed nmr data)

6.1.5 [(1R) - *endo*] - (+) - 3 - [bis - {(R) - (-) - 2 - butanoxy}phosphoryl] camphor.

6.1.5.1 Di - [(R) - (-) - 2 - butyl]chlorophosphine.

This compound was prepared using the method outlined in 6.1.3.1, using (R) - (-) - 2 - butanol.

6.1.5.2 Di - [(R) - (-) - 2 - butyl] phosphite.

This compound was prepared using the method outlined in 6.1.3.2, using di - [(R) - (-) - 2 - butyl]chlorophosphine.
Yield 1.1g, 61.11%.
Analysis.

^{31}P : + 4.74 ppm.
^{1}H : J(P-H) 682.5. (Other ^{1}H nmr data is identical to that outlined in 6.1.3.2)

6.1.5.3 Di - [(R) - (-) - 2 - butyl] phosphorochloridate.

This compound was prepared using the method outlined in 6.1.3.3, using di - [(R) - (-) - 2 - butyl]phosphite.
Yield 2.1g, 68.63 %.

Analysis.

^{31}P : + 2.61 ppm.
^{1}H : No one bond phosphorus - hydrogen coupling. (Other ^{1}H nmr data is identical to that outlined in 6.1.3.3.).

6.1.5 [(1R) - *endo]* - (+) - 3 - [bis {(R) - (-) - 2 - butanoxy}phosphoryl] camphor.

This compound was prepared using the method outlined in 6.1.3, using [(1R) - *endo*] camphor, and di - [(R) - (-) - 2 - butyl] phosphorochloridate.

Yield 1.0g, 32.8%.

Analysis.

^{31}P nmr : .+ 21.23 ppm.

^{1}Hnmr : dm 2.95 ppm..

I R. ν (C=O) 1745 cm^{-1}.

$[\alpha_D]$: +107.17^0

(Please refer to chapter 2, tables 2.8, and 2.9 for more detailed nmr data).

6.1.6 [(1S) - *endo*] - (-) - 3 - [bis {(R) - (-) - 2 - butanoxy}phosphoryl] camphor.

This compound was prepared using the method outlined in 6.1.3, using [(1S) - *endo*] camphor and di - [(R) - (-) - 2 - butyl] phosphorochloridate.

Yield 1.3g, 42.7%.

Analysis.

^{31}P nmr : .+ 21.03 ppm.

^{1}Hnmr : dm 2.95 ppm.

I R : .ν(C=O) 1743 cm^{-1}.

$[\alpha_D]$: -167.20^0

(Please refer to chapter 2, tables 2.8, 2.9 for detailed nmr data).

6.1.7 [(1R) - *endo*] - (+) - 3 - (1',1' - bi - 2' - napthoxyphosphoryl) camphor.

6.1.7.1 (+,-)-(1',1')-bi-2'-napthyl phosphorochloridate

A slurry of (+,-) - 1',1' - bi - 2' napthol (5 g, 0.017 mol), phosphorus oxychloride (3.17 g, 0.021 mol), and CH_2Cl_2 (30 cm^3) was stirred under nitrogen and triethylamine (4.18 g, 0.41 mol) was added dropwise at a rate that maintained gentle reflux. After addtion was complete the solution was stirred an additional hour and extracted with 20 cm^3 of water. Removal of the solvent left a white crystalline solid of the product. Yield 7.47 g, 87.5%.

Analysis.

^{31}P nmr : + 10.55 ppm. (one peak only).
I R : Showed OH group stretching.
^{1}H nmr : 7.5 - 8.1 ppm (m, 12H)

6.1.7 [(1R) - *endo*] - (+) - 3 - (1',1' - bi - 2 - napthoxyphosphoryl) camphor.

A solution of [(1R) - *endo*] - (+) camphor (5 g, 0.033 mol) in anhydrous THF (54 cm^3) was added dropwise via a catheter to a stirred solution of lithium diisopropylamine [LDA, 1.1 equiv, prepared in situ from diisoproplyamine (5.1 cm^3) and *n* - BuLi (23.1 cm^3, 1.60 mol dm^{-3})] in THF (20.2 cm^3) at -65^{0}C. After 45 min, the resulting enolate was treated with 1',1'-bi-2'-napthyl phosphorochloridate (13.23 g, 0.036 mol) and the mixture was allowed to warm to 0^{0}C over the course of 50 min. After this mixture was cooled to -75^{0}C, it was transferred via a catheter to a solution of LDA (2.2 equiv, in 40.5 cm^3 of THF). The resulting solution was then allowed to warm to 10^{0}C over 2hr. Standard workup (as outlined in 6.1.1) was then followed using an acetic acid solution.

Pale yellow crystals of the product were then obtained by fractional crystallisation from ethanol, to give only one diastereomer in very low yield.

Analysis.

^{1}H nmr : dm 3.0 ppm; 3 eqiuvalent methyl groups due to camphor at 0.8 ppm, 0.9 ppm, and 1.0 ppm.

^{31}P nmr= 33.7ppm

(Please refer to chapter 2, table 2.7, for more detailed nmr data).

6.1.8 [(1R - *endo*) - (+) - 3 - [(+,-) - bis - (pinacolyl)phosphoryl] camphor.

6.1.8.1 Di - [(+,-) - pinacolyl]chlorophosphine.

This compound was prepared using the method outlined in 6.1.3.1, using (+,-) pinacolyl alcohol.
Yield 2.34 g, 67 %.
Analysis.

I R : No OH stretching present.

.6.1.8.2 Di - [(+,-) - pinacolyl] phosphite.

This compound was prepared using the method outlined in 6.1.3.2, using di - [(+,-) - pinacolyl]chlorophosphine.
Yield 1.304 g, 70 %.
Analysis.
^{1}H : J(P-H) 690. 4.25 ppm (m, 2H), 1.3 ppm (d, 6H), 0.95 ppm (s, 18H)
^{31}P : Three main peaks at + 6.66 ppm, +6.11 ppm, and + 4.80 ppm. Where the peak at + 6.11 ppm is approx twice the height of the other two.

6.1.8.3 Di - [(+,-) - pinacolyl] phosphorochloridate.

This compound was prepared as outlined in 6.1.3.3, using di - [(+,-) - pinacolyl]phosphite.
Yield 0.8 g, 72 %.

Analysis.

^{1}H nmr : No one bond phosphorus-hydrogen coupling. 4.2 ppm (m, 2H) 1.2 ppm (d, 6H), 1.0 ppm (s, 18H).

^{31}P nmr : 3 peaks at + 4.21 ppm, + 3.39 ppm, + 2.96 ppm. (These peaks are in the region expected for this type of species.

6.1.8 [(1R - *endo*) - (+) - 3 - [(+,-) - bis - (pinacolyloxy)phosphoryl] camphor.

A solution of [(1R) - *endo*] camphor (0.39 g, 0.00257 mol) in anhydrous THF (4.15 cm^3) was added dropwise via a catheter to a stirred solution of lithium diisopropylamine [LDA, 1.1 equiv, prepared in situ from diisopropylamine (0.4 cm^3) and *n* - BuLi (1.78 cm^3, 1.6 mol dm^{-3})] in THF (1.56 cm^3) at -65^0C. After 45 min, the resulting enolate was treated with di - [(+,-) - pinacolyl phosphorochloridate] (0.8 g, 0.0028 mol) and the mixture was allowed to warm to 0^0C over the course of 50 min. After this mixture was cooled to -75^0C, it was transferred to a solution of LDA (2.2 equiv in 3.12 cm^3 of THF). The resulting solution was allowed to warm to 10^0C over 2 hr. Standard workup (as outlined in 6.1.1) was followed, giving a mixture of products. (See chapter 2, section 2.2.5).

6.1.9 Attempted synthesis of the β-ketophosphonate [(1R - *endo*) - (+) - 3 - (+,-) - bis (α - methylbenzoxy)phosphoryl] camphor.

6.1.9.1 (+,-) - bis (α - methylbenzoxy) chlorophosphine.

This compound was prepared using the method outlined in 6.1.3.1, using (+,-) - α - methyl alcohol.

Yield 25.2 g, 75.7 %.

Analysis.

^{1}H : No OH present.

6.1.9.2 (+,-) - bis - (α - methylbenzoxy) phosphite.

This compound was prepared using the method outlined in 6.1.3.2, using (+,-) - bis (α - methylbenzoxy) chlorophosphine.

Yield 22 g, 93.6%..

Analysis.

^{31}P nmr : 3 main peaks at + 5.24 ppm, + 4.62 ppm, and + 4.24 ppm. Where the peak at + 4.62 ppm is approx twice as large as the other two.

6.1.10 Attempted synthesis of the β-ketophosphonate [(1R - *endo*) - (+) - 3 - (+,-)-(ethylnapthylphosphoryl) camphor.

6.1.10.1 Ethylnapthyl chlorophosphine.

2 - napthol (4.9 g, 0.034 mol) in anhydrous diethyl ether (20 cm^3) was added dropwise via a catheter to a cooled solution of ethyl dichlorophosphine (5 g, 0.034 mol), triethylamine (4.74 cm^3, 0.034 mols) and diethyl ether (100 cm^3) with stirring. This solution was allowed to stir for 24 hr after which time the triethyl-ammonium salt was removed by filtration through hyflosupercel, and concentrated on a rotavapour. Yield 6.2 g, 71.61%.

Analysis.

IR : No OH stretching present.

6.1.10.2 Ethylnapthyl phosphite.

Ethylnapthyl chlorophosphine (5 g, 0.020 mol) in diethyl ether (60 cm^3) was added with stirring to a large excess of ice.This was allowed to stir for 2 hours after which time the organic layer was separated and washed with sodium carbonate solution (2 x 100 cm^3).The solution was then dried over anhydrous magnesium sulphate and concentrated by rotavapour to give a white solid. Yield 3.8 g, 81.95 %.

Analysis.

^{31}P nmr : + 4.77 ppm.

^{1}H nmr: J (P-H) = 720.Other peaks : 7.2-7.9 ppm (m, 7H), 4.25 ppm (m, 2H), 1.3 ppm (t, 3H).

6.1.11 (1R) - *endo* - (+) - 3 - (diphenylphosphoryl) camphor.

To a solution of (1R) - *endo* - (+) - 3 - bromocamphor (1.16 g, 5mmol) in THF (90 cm^3) was added dropwise at -78^{0}C a solution of *n* - butyl lithium (3.44 cm^3, 1 mol dm^{-3} in hexane, 5.5 mmol). After the mixture was stirred for 1 hr at -78^{0}C, a solution of chlorodiphenyl phosphine (0.9 cm^3, 5 mmol) in THF (5 cm^3) was added dropwise via a catheter. The mixture was allowed to warm to room temperature and stirred for a further 72 hr. The solvent was then removed in vacuo and the residue extracted into diethyl ether. Removal of the solvent and recrystallisation fro ethanol in air afforded pure (1R) - *endo* - (+) - 3 - (diphenoxyphosphoryl) camphor as a white crystalline solid. Yield 1.34g, 76%.

Analysis.

^{31}P : + 28.12 ppm.

^{1}H : dm 3.55 ppm.

IR : ν(C=O) 1737 cm^{-1}.

ν(P=O) 1184 cm^{-1}.

This data is consistent with literature values.[210] (Please refer to chapter 2, table 2.7 for more detailed nmr data).

6.2 Synthesis of Transition metal complexes of β-ketophosphonate ligands.

6.2.1 Dichloro{[(1R) - *endo*] - (+) - 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum (VI).

MoO_2Cl_2 (1.5 g, 7.54 mmol) was dissolved in dry THF (30 cm^3). [(1R) - *endo* - (+) - 3 - (diethoxyphosphoryl) camphor (2.17 g, 7.54 mmol) was added via a catheter with stirring. One hour later, the THF was removed under vacuo to leave an oiley residue. Treatment with dry diethyl ether (15 cm^3) gave a solid which was washed with ether (2 x 5 cm^3 portions) and was found to have a m.p 176 - 177^{0}C. Yield 2.67 g, 73 %.

Analysis.

^1H : dm 3.8 ppm.

Microanalysis: Theoretical composition (C : 34.50%, H : 5.20%)
Actual composition (C : 34.60%, H : 5.20%)

More detailed nmr data on all transition metal complexes synthesised can be obtained from chapter 2, tables 2.7, and 2.8.

6.2.2 Dichloro{[(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl) camphor} dioxomolybdenum (VI).

This compound was prepared using the method outlined in 6.2.1, using [(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl) camphor

Analysis.

^{1}H : dm 3.85 ppm.

^{31}P : +23.69 ppm.

Microanalysis : Theoretical composition : (C : 34.50%, H : 5.20%)

Actual composition : (C : 34.25%, H : 5.02%)

6.2.3 Dichloro{[(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum(VI).

MoO_2Cl_2 (1.152 g, 0.0058 mol) was dissolved in THF (25 cm^3). [(1R) - *endo*] - (+) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor (2 g, 0.0058 mol) in THF (10 cm^3) was added dropwise via a catheter with stirring. After two hours the THF was removed under vacuo to leave an oily residue. This residue was then added slowly via a catheter to a large volume of pet ether (40 - 60)(80 cm^3) whereupon a fine powder of the product appeared. Yield 2.2 g, 69.8%.

Analysis.

^{31}P nmr : +21.13 ppm.

^{1}H nmr : dm 3.8 ppm.

IR : ν(C=O) 1697 cm^{-1}.

Microanalysis : Theoretical composition :(C : 39.80%, H : 6.12%)

Actual composition : (C : 40.40%, H : 5.99%).

6.2.4 Dichloro {(1S) - *endo*) - (-) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum (VI).

This compound was prepared using the method outlined in 6.2.3, using (1S) - *endo*) - (-) - 3 - [bis - {(S) - (+) - 2 - butanoxy}phosphoryl] camphor

Yield 2.4 g, 76.14%.

Analysis.

^{1}H nmr: dm 3.8 ppm.

IR nmr : ν(C=O) 1699 cm^{-1}.

Microanalysis : Theoretical composition : (C : 39.80 %, H : 6.12 %).

Actual composition : (C : 39.74 %, H : 6.28 %).

6.2.5 Dichloro{[(1R) - *endo*] - (+) - 3 - [bis - {(R) - (-) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum(VI).

This compound was prepared using the method outlined in 6.2.3, using [(1R) - *endo*] - (+) - 3 - [bis - {(R) - (-) - 2 - butanoxy}phosphoryl] camphor

Yield 2.5g, 79.31%.

Analysis.

^{1}H nmr : dm 3.8 ppm.

^{31}P nmr : + 21.21 ppm.

Microanalysis: Theoretical composition : (C : 39.80%, H : 6.12%)

Actual composition : (C : 39.13%, H : 5.92%)

6.2.6 Dichloro {(1S) - *endo*) - (-) - 3 - [bis - {(R) - (-) - 2 - butanoxy}phosphoryl] camphor} dioxomolybdenum (VI).

This compound was prepared using the method outlined in 6.2.3, using [(1S) - *endo*] - (-) - 3 - [bis - {(R) - (-) - 2 - butanoxy}phosphoryl] camphor

Yield 2.3 g, 72.97%.

Analysis.

^{1}H : dm 3.8 ppm.

^{31}P : +21.13 ppm.

Microanalysis: Theoretical composition : (C : 39.80%, H : 6.12%)

Actual composition : (C : 38.59%, H : 5.51%).

6.2.7 Dichloro{[(1R) - *endo*] - (+) - 3 - [diphenylphosphoryl] camphor} dioxomolybdenum(VI).

MoO_2Cl_2 (0.55g, 0.00284 mol) was dissolved in THF (25 cm^3). [(1R) - *endo*] - (+) - 3 - [diphenylphosphoryl] camphor (1g, 0.00284 mol) in THF (10 cm^3) was added dropwise via a catheter with stirring. After two hours the THF was removed under vacuo to leave an oily residue. This residue was then added slowly via a catheter to a large volume of pet ether (40 - 60)(80 cm^3) whereupon a fine powder of the product appeared. Yield .1.3g. 83.87%.

Analysis.

^{1}H : dm 4.45ppm

^{31}P : +42.78ppm.

IR : ν(CO) 1694cm^{-1}

Microanalysis.: Theoretical Composition : (C : 47.93%, H : 4.57%)

Actual Composition : (C : 47.83%, H : 4.41%)

6.3 Experimental Procedure Used During Catalytic Epoxidation Reactions.

The tert-butyl hydroperoxide used was stored below -5^{0}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 was determined by measuring cylinder as the use of syringes is strongly discouraged, since traces of transition metals from the needle inserted into the solution can contaminate the stock solution and subsequently commence facile decomposition of the hydroperoxide over a short period of time.

The tert-butyl hydroperoxide was bought as an anhydrous 3 molar solution in 2,2,4-trimethylpentane (iso-octane) and contained in a high density polythene bottle. When sealed properly, these bottles develop a negative pressure in the refrigerator and compress. Water from the air will be absorbed if the bottles were to be opened directly upon removal from the refrigerator.

A number of guide lines have been followed during this research regarding the use of tert-butyl hydroperoxide : Strong acid should never be added to high strength tert-butyl hydroperoxide solutions. Transition metals known to be good autoxidation catalysts should never be added to tert-butyl hydroperoxide solutions. It is recommended never to work with pure tert-butyl hydroperoxide, and to try and 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, and low density polyethylene bottles should not be used because they are permeable to many of the solvents used for tert-butyl hydroperoxide.

6.4 Epoxidation Procedure.

The normal procedure for the epoxidation of various alkenes involved the addition of 1 mol% of the catalyst to a stirred solution of anhydrous t-BuOOH (1.5 molar equivalents) in 2,2,4 trimethylpentane, the substrate alkene (1 molar equivalent) and dichloromethane (14.66 molar equivalents). The presence of molecular sieves was dependant on the particular reaction being carried out.

The kinetics of these epoxidation reactions were followed by GLC. Samples from the reaction vessel were taken at pre-determined times after the addition of the catalyst to the reaction mixture. These samples were quenched into approximately 0.01g of the reducing agent triphenyl phosphine to prevent further epoxidation, and then the desired amount was injected into the chromatogram. The quantitation was based upon the amount of epoxide formed against the amount of alkene left unreacted at that time. As stated in chapter 3, which presented the results of this catalytic work, this quatitative method was verified by injecting an exactly 1.1 molar ratio of pure alkene/epoxide and examining the resulting areas to ensure that they were equivalent

6.5.1 Studies carried out on the effect of molecular sieves on the epoxidation of styrene.

Various studies were carried out to examine the exact role of molecular sieves during the epoxidation of styrene. The experimental precedure for these reactions is the same as that outlined above, with the exception that the order of addition of the reaction products was varied. These variations are outlined in chapter 4.

6.5.2 Epoxidation Procedure Carried out During Styrene Stereochemical Studies.

These studies were carried out in a similar fashion to normal epoxidation reactions, except in this case the reaction products were studied approximately one hour.after the addition of the catalyst to the reaction mixture.

After this length of time had elapsed, the stirring was stopped to allow the filtrate to be removed from the molecular sieves. On transfering the filtrate into a clean flask, any volatile components within the reaction mixture such as dichloromethane were removed under vacuo, in the hope that this would enhance the quality of the NMR spectra which would be obtained.

In all cases 0.1ml (0.87×10^{-3} mol) of the substrate styrene was used and the remaining components within the reaction mixture were scaled down accordingly. eg only 0.87×10^{-5} mol of the catalyst was required in this case. This ensured that even if a high conversion of the alkene to the epoxide was achieved, 40 mg of shift reagent would be sufficient to produce the desired separation of resonances in the ^{1}H nmr spectrum.

6.6 Experimental Procedure used during Ring Opening Studies.

6.6.1 Ring opening of (+) and (-) limonene oxide by water using dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI).

Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) (0.019g, 0.039mmol) was weighed out under nitrogen and either (+) or (-) limonene oxide (0.639cm^3, 3.9mmol) was added. Dichloromethane (3.67cm^3) was then added and the solution stirred.One drop of distilled water was then added and the stop watch was started. Samples were then taken at regular time periods, 0.05cm^3 of the solution was removed and added to 0.5cm^3 of dichloromethane. These samples were then analysed by GC.

6.6.2 Ring opening of (+) and (-) limonene oxide by water using dichloro{[(1S)-*endo*]-(-)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI).

These experiments were carried out using the method outlined in 6.6.1, using dichloro{[(1S) - *endo*] - (-) - 3 - (diethoxyphosphoryl)camphor} dioxomolybdenum (VI).

6.6.3 Ring opening of (+) and (-) limonene oxide by water using dichloro{[(1R)-*endo*] - (+) - 3 - [bis - {(S) - (+) - butanoxy}phosphoryl]camphor} dioxomolybdenum (VI).

These experiments were carried out using the method outlined in 6.6.1, using Dichloro{[(1R) - *endo*] - (+) - 3 - [bis - {(S)- (+) - 2 - butanoxy}phosphoryl)] camphor} dioxomolybdenum

6.6.4 Ring opening of (+) and (-) limonene oxide by water using dichloro{[(1R)-*endo*]-(+)-3-(diphenylphosphoryl)camphor} dioxomolybdenum (VI).

These experiments were carried out using the method outlined in 6.6.1, using dichloro{[(1R) - *endo*] - (+) -3 - (diphenylphosphoryl)camphor} dioxomolybdenum (VI)

6.6.5 Ring opening of (+) and (-) limonene oxide by water using dichlorodioxomolybdenum (VI).

These experiments were carried out using the method outlined in 6.6.1, using dichlorodioxomolybdenum.

6.6.6 Examination of the interaction of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) with (+)-limonene oxide in a 1:2 molar ratio.

(+)-limonene oxide ($0.031cm^3$, 0.194mmol) was added to the Mo catalyst (0.0473g, 0.097mmol). This mixture was dissolved in anhydrous $CDCl_3$. These procedures were carried out under nitrogen and a ^1H nmr spectrum was taken.

6.6.7 Attempted formation of a complex between dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) and (+)-limonene oxide using a 1:2 molar ratio.

(+)-limonene oxide ($0.0322cm^3$, 0.196mmol) was added to the Mo catalyst (0.0478g, 0.098mmol) under nitrogen. Dry dichloromethane was then added dropwise via a syringe with stirring until in soluiton. Dry petroleum ether was then added dropwise until a precipitate formed. When precipitation was complete the solvent was removed by filtration and the solid was dried under vacuum. Anhydrous $CDCl_3$ was then added and a ^1H nmr spectrum taken.

6.6.8 Hydrogenation of (+)-limonene oxide

Wilkinson's catalyst [$(Ph_3P)_3RhCl$] (0.2g) was added to (+)-limonene oxide ($2cm^3$). Dry THF ($10cm^3$) was degassed and then added. The flask (a $100cm^3$ thick walled tube fitted with a screw top adapter to take a needle valve) was then sealed under vacuum and pressurised under hydrogen to 3 atm. The solution was stirred at 50^0C for 12 hours. The THF was then removed under vacuo and the decomposed catalyst separated by fractional distillation also under vacuum. The product was then analysed by GC-Mass Spec and ^1H nmr and was found to be pure, with a parent ion at m/e =154 equivalent to that of hydrogenated limonene oxide.

6.6.9 Examination of the interaction of dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) with hydrogenated (+)-limonene oxide in a 1:2 molar ratio.

Hydrogenated (+)-limonene oxide ($0.026cm^3$, 0.146mmol) was added to the Mo catalyst (0.038g, 0.073mmol). This mixture was then dissolved in anhydrous $CDCl_3$. These procedures were carried out under nitrogen and a ^1H nmr spectrum was taken.

6.6.10 Attempted formation of a complex between dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) and hydrogenated (+)-limonene oxide using a 1:2 molar ratio.

Hydrogenated (+)-limonene oxide ($0.023cm^3$, 0.139mmol) was added to the Mo catalyst (0.034g, 0.07mmol) under nitrogen. Dry dichloromethane was then added dropwise via a syringe with stirring until in soluiton. Dry petroleum ether was then added dropwise until a precipitate formed. When precipitation was complete the solvent was removed by filtration and the solid was dried under vacuum. Anhydrous $CDCl_3$ was then added and a ^1H nmr spectrum taken.

6.6.11 Ring opening of hydrogenated (+)-limonene oxide by water.

Dichloro{[(1R)-*endo*]-(+)-3-(diethoxyphosphoryl)camphor} dioxomolybdenum (VI) catalyst (0.01g, 0.021mmol) was weighed out under nitrogen. Hydrogenated (+)-limonene oxide ($0.34cm^3$, 2.1mmol) was then added followed by $CDCl_3$ ($2.3cm^3$). One drop of water was then added and the mixure was stirred. ^1H nmr spectra were then taken of the sample after 3 hours and 74 hours.

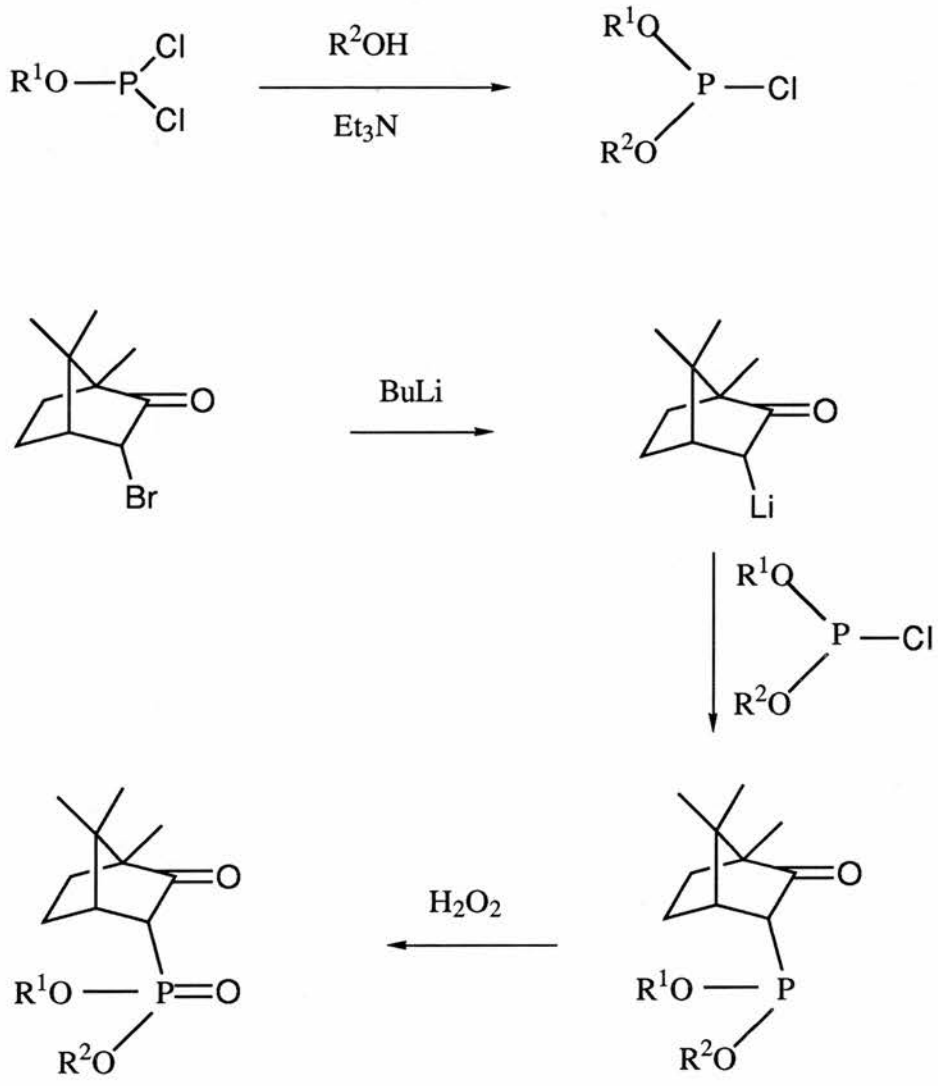
Conclusions and future work.

Over the past two decades, scientific research has provided catalytic systems which carry out asymmetric epoxidation reactions, not only of allylic alcohols, but also of unfunctionalised alkenes in high enantiomeric excesses. The challenge must now be to manufacture catalysts which can reproduce this selectivity, but in turn are inexpensive (ie industrially viable) and which increase the efficiency of the systems already present.

This work has applied a simple synthetic route to the synthesis of a range of asymmetric β-ketophosphonate transition metal complexes. These complexes have have been shown to be extremely active as catalysts during the epoxidation of a range of different substrate alkenes, although no stereoselectivity has as of yet been observed.

In an attempt to preserve this activity, but at the same time strive for selectivity, it seems likely that asymmetric centres should be placed closer to the metal centre, which is the proposed site of oxygen transfer, than those synthesised to date. One possible synthetic route may be as outlined in scheme 1, where in this case, a new centre of asymmetry is created at the phosphorus atom. This method may also prove more fruitful in the attempted synthesis of the catalyst incorporating the ligand bi-napthyl, than that outlined in chapter 2. Theoretically, it is possible to synthesise a series of optically active β-ketophosphonates which are asymmetric at the phosphorus atom, by this method.

This work has also shown that this range of complexes are potentially useful catalysts in the stereoselective ring opening of limonene oxide, where it has been observed that one isomer, the *cis* , opens much more quickly than the *trans*, in the presence of these complexes. More work is required in the future to realise the full potential of this system.



Scheme 1

In conclusion then, there are still a number of areas which can be explored in this field of epoxidation catalysis, although it should be stressed that in order to achieve high levels of stereoselectivity, any future work must concentrate on carrying out these reactions in the absence of molecular sieves to avoid catalyst degradation.

Appendices.

NMR Spectroscopy.

^{1}H nmr were recorded on a Bruker AM300 spectrometer (300MHz) and on a Varian Gemini (200MHz). ^{13}C (75.4 MHz) and ^{31}Pnmr (121.4 MHz) were recorded on the Bruker AM300 instrument operating in the pulse Fourier Transform mode. ^{31}Pnmr spectra were also recorded on a Varian CFT-20 at 32.2 MHz. Chemical shifts are relative to external TMS unless otherwise stated for ^{1}H and ^{13}C spectra, and external 85% D_3PO_4 for ^{31}P spectra. All spectra were run in $CDCl_3$ unless otherwise stated.

Infra-red Spectroscopy.

Infra-red spectra were recorded on a Perkin Elmer-1710 (Fourier Transform) spectrometer as Nujol mulls between sodium chloride plates.

Gas-liquid Chromatography.

The measurement of epoxide conversions was achieved by adding $0.05cm^3$ of the reaction mixture into $0.5cm^3$ of CH_2Cl_2. 0.2µl of this solution was then injected into a Pye Unicam 4500 chromatograph containing a Hewlett Packard CPSIL 19CB g.c column, having 60 mls per minute N_2 gas flow and a flame ionisation detector.

Microanalysis.

Microanalysis were performed by the University of St Andrews Microanalytical Service.

Solvents.

Tetrahydrofuran, light petroleum ($40\text{-}60^0$ boiling range), diethyl ether and toluene were dried by distillation over sodium benzophenone ketyl. Dichloromethane was dried by treatment with phophorus pentoxide, decanted and distilled from CaH_2. All solvents were thoroughly degassed before use.

Vacuum Lines.

The majority of the work described in this thesis was carried out under nitrogen using standard Schlenk line and catheter tubing techniques. Oxygen-free nitrogen was further purified by passing through a column containing chromium(II) adsorbed on silica.

Polarimetry.

Optical rotations were measured on an Optical Activity AA - 1000 polarimeter using a 1 dm cell.

Starting materials.

With the exception of MoO_2Cl_2, which was purchased from Lancaster, all commercial starting materials were obtained from Aldrich and were used without further purification.

GC-MS.

Sampes were tested on an Incos 50 GC-MS using an HP1 column.

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