Directed Hydrogenation of Sulphoxides and Sulphones

Thesis submitted in partial

fulfilment of the requirements for

the degree of Doctor of Philosophy

by

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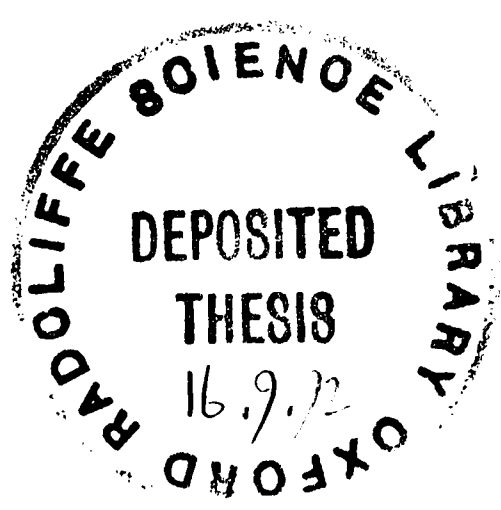
Hilary 1992



To Mom, Dad

Wayne and Tim.

Don´t place your trust in foolish promises sworn,
Nor cryptic message scrawled on every wall.
Street corner justice beware.
The spirit will find you always be fair.
The shallow verse once read means nothing at all,
Nor fearful gestures made for instant recall.
In lies your heart will not share,
The spirit inside you used without care.

The spirit that guides you, follow it through.
To the spirit inside you, always be true.
You know you´ll despair
If the spirit inside you is used without care.

The battlefield of glory pales into rust.
The river flows much thicker, fed by each thrust.
No beast alive does compare.
The spirit beside you everywhere.
Let not your head be turned by tainted reward,
Nor dreams of fortune won, forever to hoard.
Your conscience could not repair
The spirit inside you, used without care.

´Cause it will be your shelter, help you how to decide.
And it will be your helper, should your loyalties divide.

The spirit that guides you follow it through.
To the spirit inside you, always be true.
You know you´ll despair
If the spirit inside you is used without care.

The ash of pages swept before the cruel wind.
The loss of choices, praises no one will sing.
No clues to how you will fare.
The spirit implores you, tread where you dare.
The dust lies thick on casket rich or quite poor.
Distinction disappears the worm both deplore.
The candle burns out once more,
But the spirit inside you won´t be ignored.

The spirit that guides you follow it through.
To the spirit inside you, always be true.
You know you´ll despair
If the spirit inside you is used without care.

THE SPIRIT

Tony Clarkin

Acknowledgements

Firstly, I should like to thank my idiosyncratic supervisor to whom I will be eternally grateful for teaching me attention to detail, the importance of mechanism in organic chemistry, the importance of computer literacy and more. In my Part II I thanked him for his "enthusiasm, knowledge and faith in my ability". These I further tested to their limit and they were not found wanting.

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MP(Bignose) and Miss VS (The Gin Queen).

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ASLIB ABSTRACT

Directed Hydrogenation of Sulphoxides and Sulphones

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D. Phil.

Hilary, 1992

This thesis describes the synthesis of a number of hydroxy vinylsulphoxides and sulphones by a high pressure modification of the Baylis-Hillman reaction, together with their directed hydrogenation catalysed by rhodium catalysts. A detailed kinetic analysis of a number of the hydrogenation reactions carried out by numerical analysis is also presented.

Chapter 1 serves as an introduction to directed hydrogenation and the chemistry of sulphur containing compounds.

Chapter 2 details the synthesis of catalysts and substrates used in hydrogenation reactions. The use of high pressures to improve the performance of the Baylis-Hillman reaction is included.

Chapter 3 details the products and the selectivity obtained in the hydrogenation of hydroxy vinylsulphoxides and sulphones. The kinetic resolution of 3-phenyl-2-(phenyl-sulphonyl)-propene-3-ol using a DiPAMP rhodium catalyst is described.

Chapter 4 details the numerical analysis of the kinetics of the hydrogenation reactions of a number of hydroxy vinylsulphoxides and sulphones.

Abbreviations

The following abbreviations are used throughout the text, Tables, Figures and Schemes :

Ac	:	acetyl group
An	:	methoxyphenyl
Ar	:	aryl group
ASCII	:	American Standard Code for Information Interchange
b.p.	:	boiling point
BINAP	:	2,2´-bis-(diphenylphosphino)-1,1´-binapthyl
$Bu^{n,s,t}$	:	primary, secondary, and tertiary butyl group, respectively
Cy	:	cyclohexyl
DABCO	:	Diazabicyclo-[2,2,2]-octane
DIOP	:	(+)-2,3-Diisopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane
DiPAMP	:	1,2-bis-((2-methoxyphenyl)phenylphosphino)ethane
Et	:	ethyl
GCMS	:	gas chromatographic mass spectroscopy
Hx	:	hexyl group
I.R.	:	infra red
LDA	:	lithium di-*iso*propylamide
Me	:	methyl group
Mn	:	menthyl
m.p.	:	melting point
NMR	:	nuclear magnetic resonance
P.C.	:	personal computer

Ph	:	phenyl group
Pr	:	propyl
R	:	general alkyl or aryl group
S	:	solvating molecule
THF	:	tetrahydrofuran
t.l.c.	:	thin layer chromatography
TMEDA	:	*N,N,N,N*-tetramethylethylenediamine
Tol	:	tolyl
U.V.	:	ultra violet
dppe	:	1,2-Bis-(diphenylphosphino)ethane
dppb	:	1,2-Bis-(diphenylphosphino)butane
dppf	:	1,1'-Bis-(diphenylphosphino)ferrocene
nbd	:	Norbornadiene

d.e. : diastereomeric excess

e.e. : enantiomeric excess

Contents

INTRODUCTION

Introduction

1.01 General Introduction

The hydrogenation of double bonds is conceptually one of the simplest organic transformations. However, it invariably requires a catalyst and this usually takes the form of a transition metal in one state or another. Hydrogenations carried out under heterogeneous conditions suffer from the same shortcomings as other heterogeneous reactions - variable control of the chemoselectivity and stereoselectivity[1] and of course few examples of good control of the enantioselectivity.[2,3] The homogeneous counterpart has the potential to be much more selective in all three senses and in many cases it lives up to expectations.

Palladium and nickel are most often chosen for their catalytic activity in heterogeneous hydrogenation. The method of preparation of the catalyst and its support is of great importance to the results obtained.[4] This is in stark contrast to the homogeneous catalyst precursors, which are characterisable organometallic complexes,[5] usually of rhodium, ruthenium or, to a lesser extent, iridium.

The work in this thesis is mainly concerned with rhodium catalysed hydrogenation of olefins, so it will be discussed to the exclusion of other metals and substrates.

A number of points concerning rhodium catalysed homogeneous hydrogenation must be considered in order to be able to evaluate its worth :

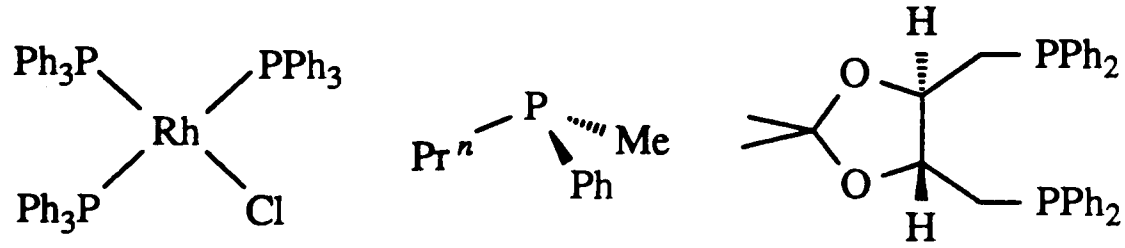
1) The range and development of useful catalysts.
2) The range of substrates which successfully undergo hydrogenation.
3) The structural characteristics of successful substrates.
4) The mechanism and its implications for each of the above.

Each of these shall be dealt with briefly.

1.02 Catalyst Development in Directed Hydrogenation

In 1965, Wilkinson[6] revolutionised the world of homogeneous catalysis with the advent of a rhodium catalyst which showed unprecedented chemoselectivity for carbon-carbon multiple bonds. Wilkinson's catalyst, (**1**), has a number of features which are still present in the catalyst precursors of today : a metal centre in a low oxidation state; phosphine ligands; a vacant coordination site or easily displaceable ligands such as olefins, which can create one; and the most obvious distinguishing feature in comparison with heterogeneous catalysts, solubility in organic solvents. It also has the most desirable properties of ease of preparation and long shelf-life, such that its use has found its way into undergraduate laboratories worldwide.

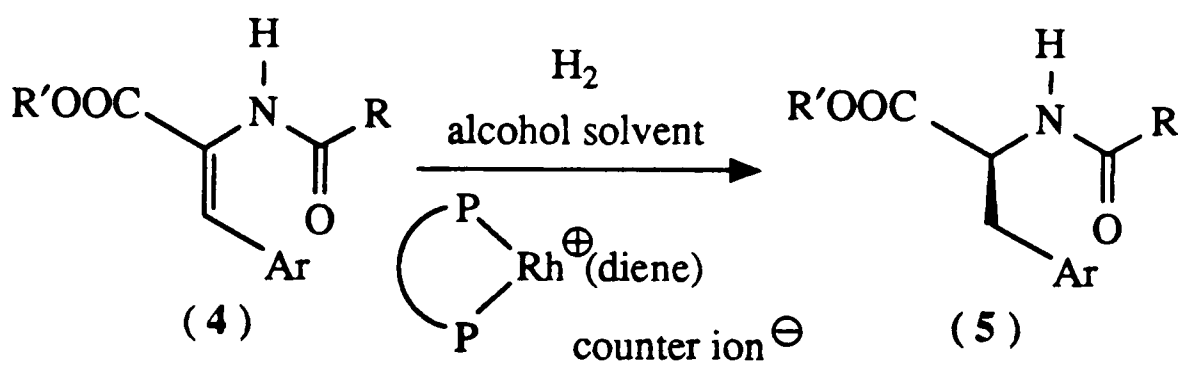
Elaboration of Wilkinson's catalyst led first to the replacement of triphenyl-phosphine by chiral monophosphines such as (**2**)[7] and then chiral chelating phosphines such as DIOP,[8] (**3**), in order to achieve asymmetric hydrogenation. This signalled a major increase in interest in the preparation of chiral phosphines, which has persisted to this day.[9]



(**1**) (**2**) (*R*,*R*)- (**3**)

Figure 1.01

Chelating biphosphines as ligands have been found to deliver the best results in the hydrogenation of olefins and, to date, several hundred have been examined as ligands in the asymmetric hydrogenation of dehydroamino acid derivatives, (**4**).



(**4**) (**5**)

Figure 1.02 - The asymmetric hydrogenation of dehydroamino acid derivatives.

A selection of e.e.'s obtained in these hydrogenations is presented in Table 1.01.

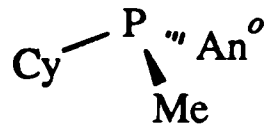
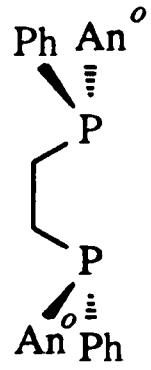
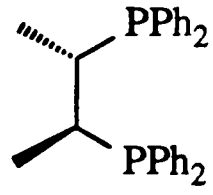
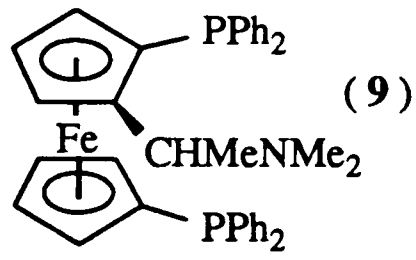
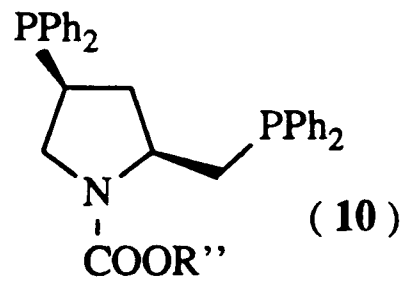
ACRONYM	PHOSPHINE	e.e. %
(*R*) - CAMP	 (6)	**80- 88** [10]
(*R*, *R*) - DIOP	(3)	**83** [8]
(*R*, *R*) - DiPAMP	 (7)	**> 95** [11]
(*S*, *S*) - Chiraphos	 (8)	**> 95** [12]
(*S*,*R*) - BPPFA	 (9)	**93** [13]
(*S*,*S*) - BPPM	 (10)	**91** [14]

Table 1.01 [10] - Hydrogenation of (**4**) R'=H, R=Me with cationic phosphine rhodium complexes, as in Figure 1.02.

Modification of existing ligand designs has led to the introduction of a new set of phosphine acronyms each year. In most cases, the "new" phosphine exhibits excellent results with at least one specific variant on the dehydroamino acid theme, e.g. BICHEP,[15] (**11**), MOD-DIOP,[16] (**12**), Me-DuPHOS,[17] (**13**), and MOC-BIMOP,[18] (**14**).

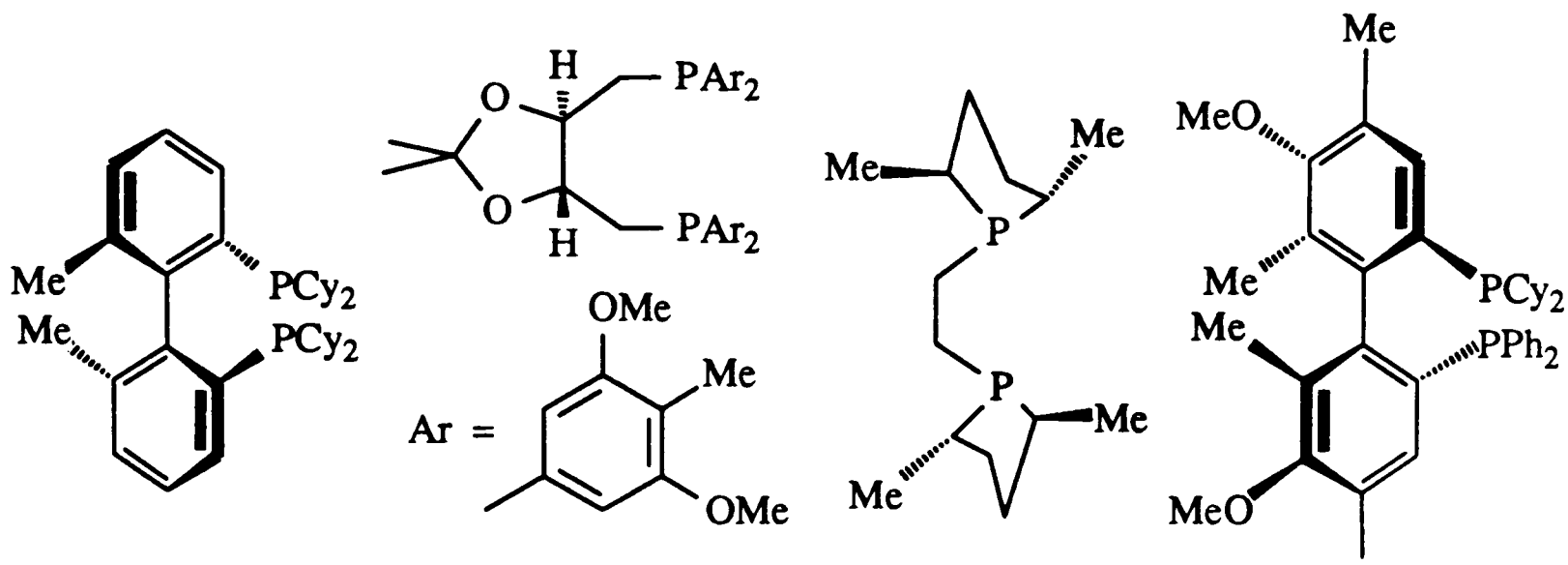
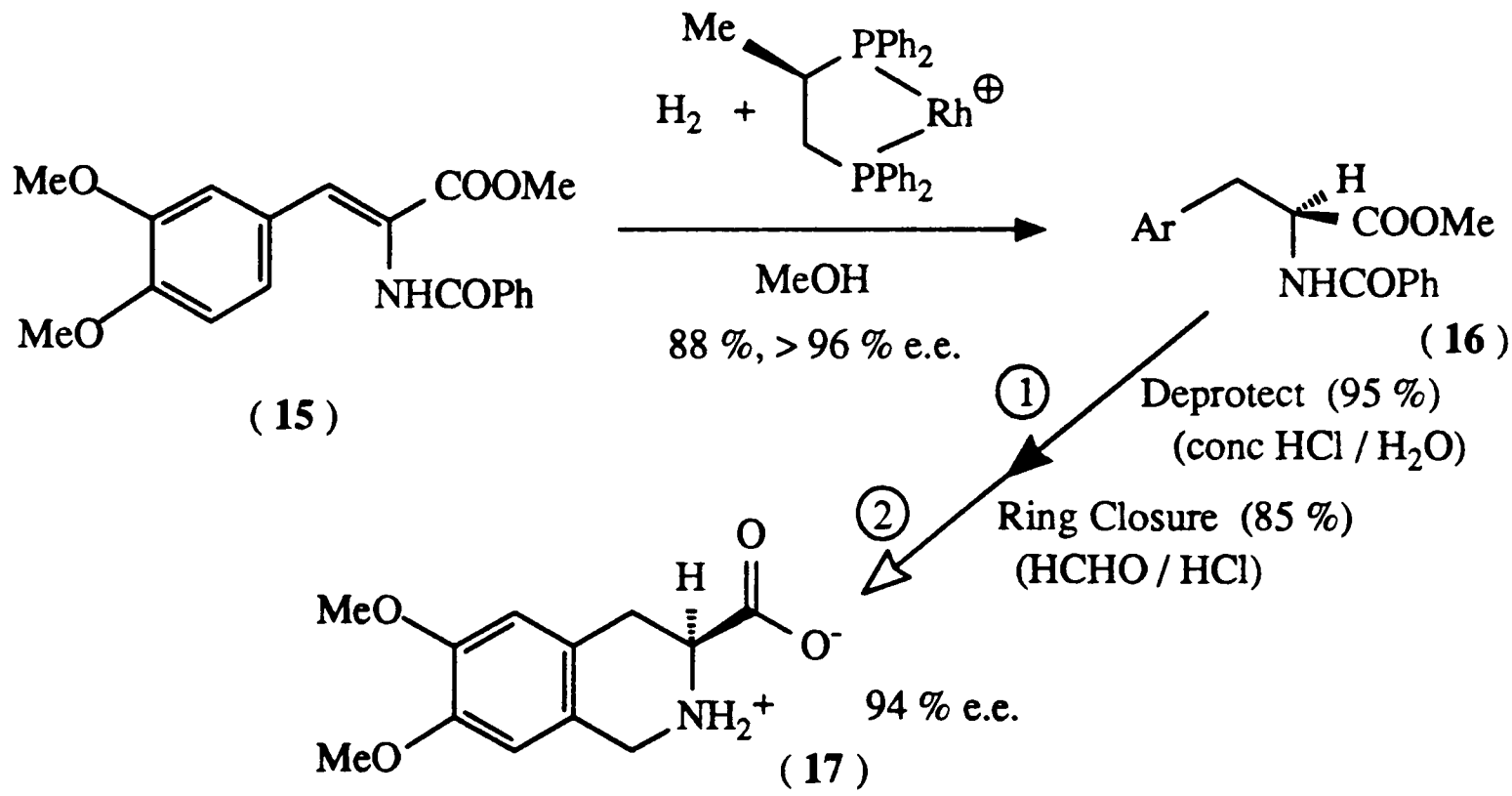


Figure 1.03 - Some recently reported biphosphines.

1.03 The Range of Substrates for Directed Hydrogenation

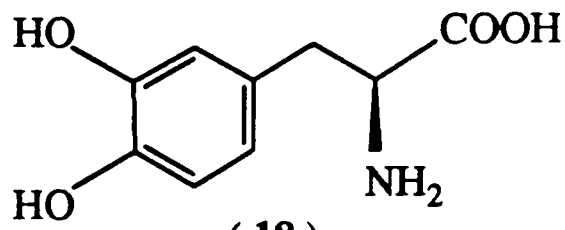
After examining the variety of catalysts for directed hydrogenation, a natural progression is to discuss the set of substrates which have been shown to give good results. One group of substrates, namely, the dehydroamino acid derivatives, (**4**), has already been mentioned in the discussion of catalyst development. The vast majority of work in the field of directed hydrogenation has concentrated on these substrates and, as can be seen from Table 1.01, it has been very fruitful in the sense that high e.e.'s can be achieved.



Scheme 1.01 - O'Reilly synthesis of a tetrahydro-3-isoquinoline carboxylic acid.[19]

The success of these hydrogenations is exemplified in the preparation of (*S*)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, (**17**), which has been used in drug synthesis (Scheme 1.01),[19] and in the industrial manufacture of *L*-DOPA, (**18**),[20]

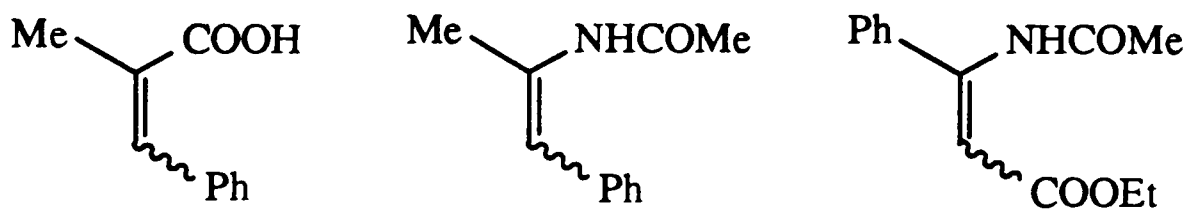
which is used in the treatment of Parkinson's disease.



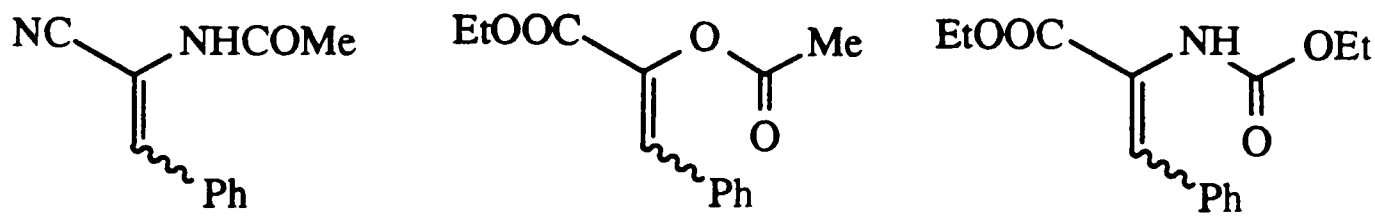
(**18**)

Figure 1.04 - *L*-DOPA.

Simple unsaturated acids, e.g. (**19**), and N-carbonyl enamines, e.g. (**20**) are not good substrates. Both *E*- and *Z*-(**19**) hydrogenate very slowly and non-enantioselectively with DiPAMP rhodium cationic complexes.[10a] Under the same conditions, *E*- and *Z*-(**20**) hydrogenate with moderate enantioselectivity, but at markedly different rates, *E* slowly and *Z* quickly.[10a] Surprisingly perhaps, *E*- and *Z*-(**21**) both hydrogenate to give the same enantiomer of product but only in 30 % e.e.[21] If one replaces the ester functionality in (**4**) with a nitrile group, as in (**22**), a slow but reasonably enantioselective hydrogenation is effectable (89 % e.e.).[10a]



(**19**) (**20**) (**21**)



(**22**) (**23**) (**24**)

Figure 1.05

Rationalising this in terms of the structural requirements of a good substrate, one finds -

i) The amido group must be *Z* to the substituent on the other terminus of the double bond.

ii) The amido group is important in the binding of the substrate since all crystal structures of catalyst substrate complexes have shown it to be bound to the metal.[23]

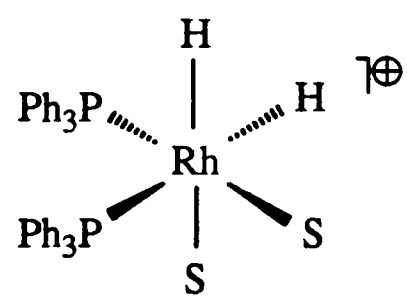
iii) An electron withdrawing group is required on the same terminus of the double bond as the amido group, since when the substitution pattern is α,β the e.e.'s are much lower.

One can then make small changes to this optimum dehydroamino acid template. Replacing the nitrogen atom with an oxygen gives an enol ester, (**23**), that, under identical conditions to above, hydrogenates well but with slightly lower e.e.'s (90 %).[22] Replacing the acetamido group with a carbamoyl group, as in (**24**), reduces the e.e. obtained slightly (89 %),[11] whereas replacing it with a thio-carbamoyl cuts it by a third to 59 %.[11]

1.04 The Mechanism of Rhodium Catalysed Directed Hydrogenation

As it is generally accepted,[24] the mechanism of rhodium catalysed homogeneous hydrogenation is an ordered sequence of well-defined steps, for which simplified prototypes exist. The mechanism seems to depend on the number of phosphine ligands and whether or not they are linked to form a chelating unit. Since the best results to date have been obtained with chelating biphosphines, it would seem best to concentrate on this case. A simplified picture of the mechanism, considering only an achiral catalyst and prochiral olefin, is presented in Scheme 1.02.

The first step, (**A**), involves the removal of the di-olefin ligand from the catalyst precursor to give the catalyst in its resting state. This change consumes two mole equivalents of hydrogen, as confirmed by spectral titration.[5] This is in stark contrast with the non-chelating biphosphine rhodium complex, which takes up three mole equivalents of hydrogen to give a biphosphine rhodium dihydride complex such as (**25**).[5]

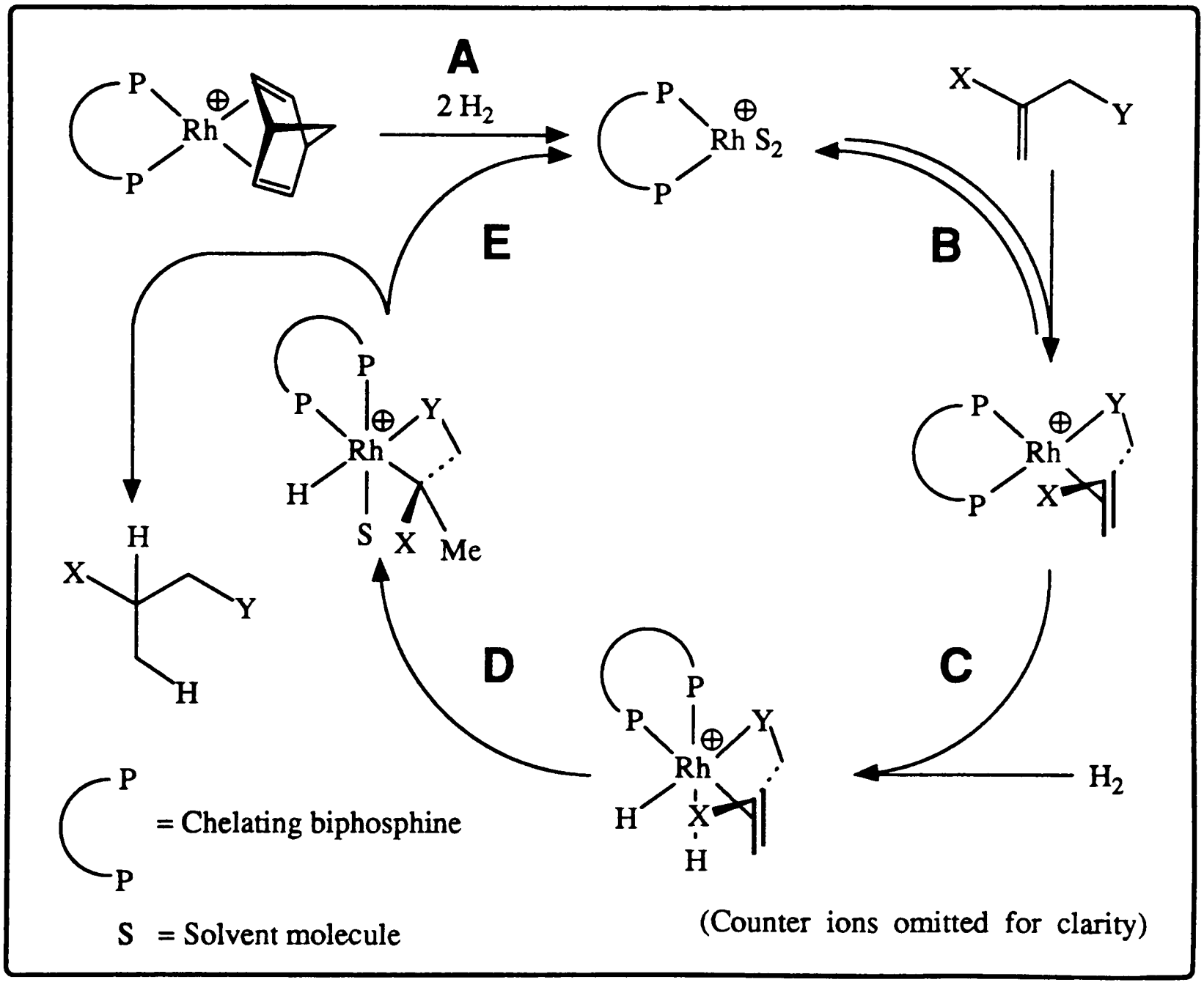


(**25**)

Figure 1.06

The second step, (**B**), is an equilibrium between the catalyst in its resting state and a catalyst-substrate complex. Since the olefin possesses two faces with which to bind to the metal centre, two complexes can result from substrate addition. With an achiral

catalyst these two complexes are enantiomeric and so are of equal energy, resulting in no preference for either enantiomer of product. This will not be the case when the catalyst contains a chiral chelating biphosphine, since the two complexes are then diastereomers. In order to take this fact into account a second catalytic cycle has to be invoked, also centred on the catalyst's resting state. All the steps of the first catalytic cycle are mirrored in the second, however, they may have wildly different rate constants. Indeed, the difference in rate constants in the two catalytic cycles is the basis for the enantioselectivity.



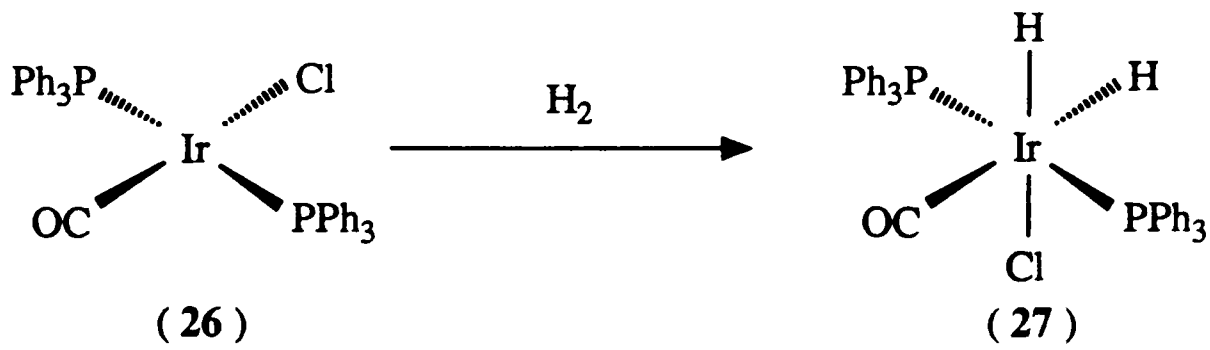
Scheme 1.02 - A proposed mechanism for rhodium catalysed hydrogenation.

If the side chain containing the binding group, Y, contains a chiral element or elements then this will be a factor determining the stereochemistry of the product. Here, the stereochemistry around the binding group can influence that of the new centre generated, and a preference for one diastereomer of product is observed. This shall be

examined further in a later chapter.

Since the second step, (**B**), takes the form of an equilibrium, an equilibrium constant may be defined for it. Halpern[5] has attempted to measure such binding constants, K_{BIND}, spectroscopically using stopped flow methods, but it is unclear what species is being observed. This shall also be revisited in later chapters.

The third step, (**C**), is simply the oxidative addition of dihydrogen to the bound substrate complex to give a rhodium (III) species. A prototype for this step is the addition of dihydrogen to Vaska's complex, (**26**), reported in 1962.[25]

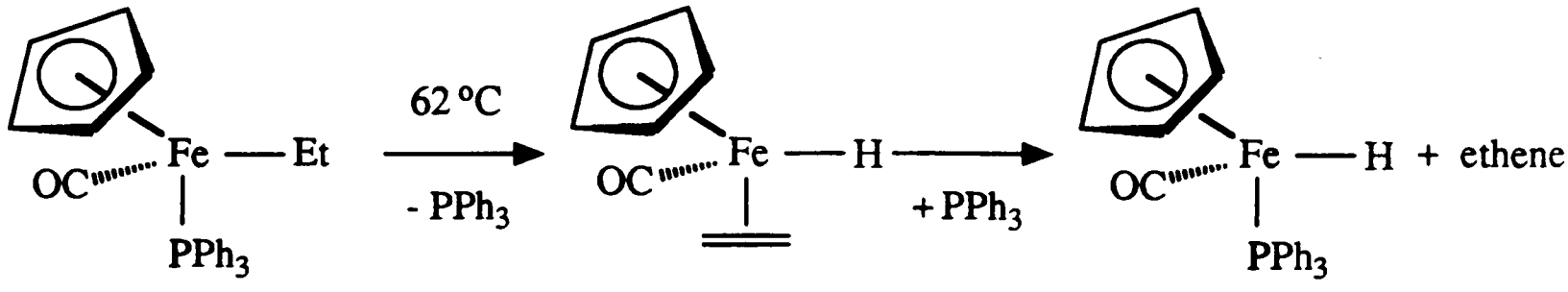


(**26**) (**27**)

Figure 1.07 - Dihydrogen addition to Vaska's complex.

It is generally accepted that dihydrogen addition to phosphine-containing low valent transition metal complexes goes through a relatively non-polar transition state and is invariably *cis*.[26] It is known that this step does not take the form of an equilibrium due to work done by Brown and co-workers [27] using para-enriched hydrogen.

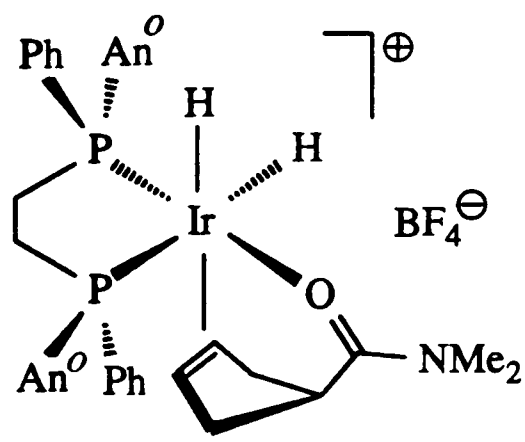
Moving on to the fourth step, (**D**), it is obvious that this is where the first hydrogen atom is transferred to the olefin *via* a migration. This is the formal reverse of β-elimination in transition metal alkyls such as the extensively studied iron alkyls e.g. (**28**).[28] In this case, for the reaction to proceed, a ligand such as triphenylphosphine must be lost reversibly to accommodate the formation of the intermediate metal η^2-olefin hydride complex, (**29**) (Scheme 1.03).



(**28**) (**29**) (**30**)

Scheme 1.03 - Loss of ethene from an iron alkyl.

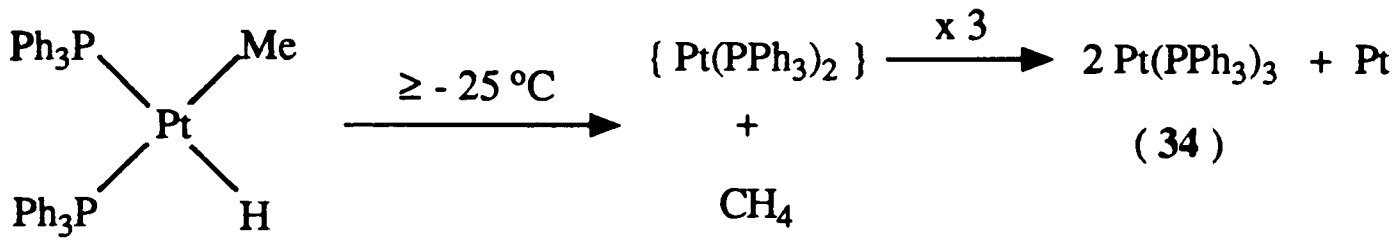
This step of the hydrogenation mechanism is exceedingly fast both in comparison with other steps in the catalytic cycle and also in an absolute sense. This is highlighted by the fact that the rhodium η^2-olefin dihydride intermediate has not been observed, even by low temperature NMR techniques. Brown and co-workers [29] have, however, been able to observe an iridium olefin dihydride complex (**31**), albeit at - 70°C.



(**31**)

Figure 1.08 - Dihydride- olefin complex observed by ^{31}P NMR.[29]

The final step, (**E**), completes the catalytic cycle by expelling the product and regenerating the catalyst in its resting state. Mechanistically, the step involves a reductive elimination, which has many parallels in organometallic chemistry,[30] e.g. platinum alkyl hydrides such as (**32**).[31]



(**32**) (**33**) (**34**)

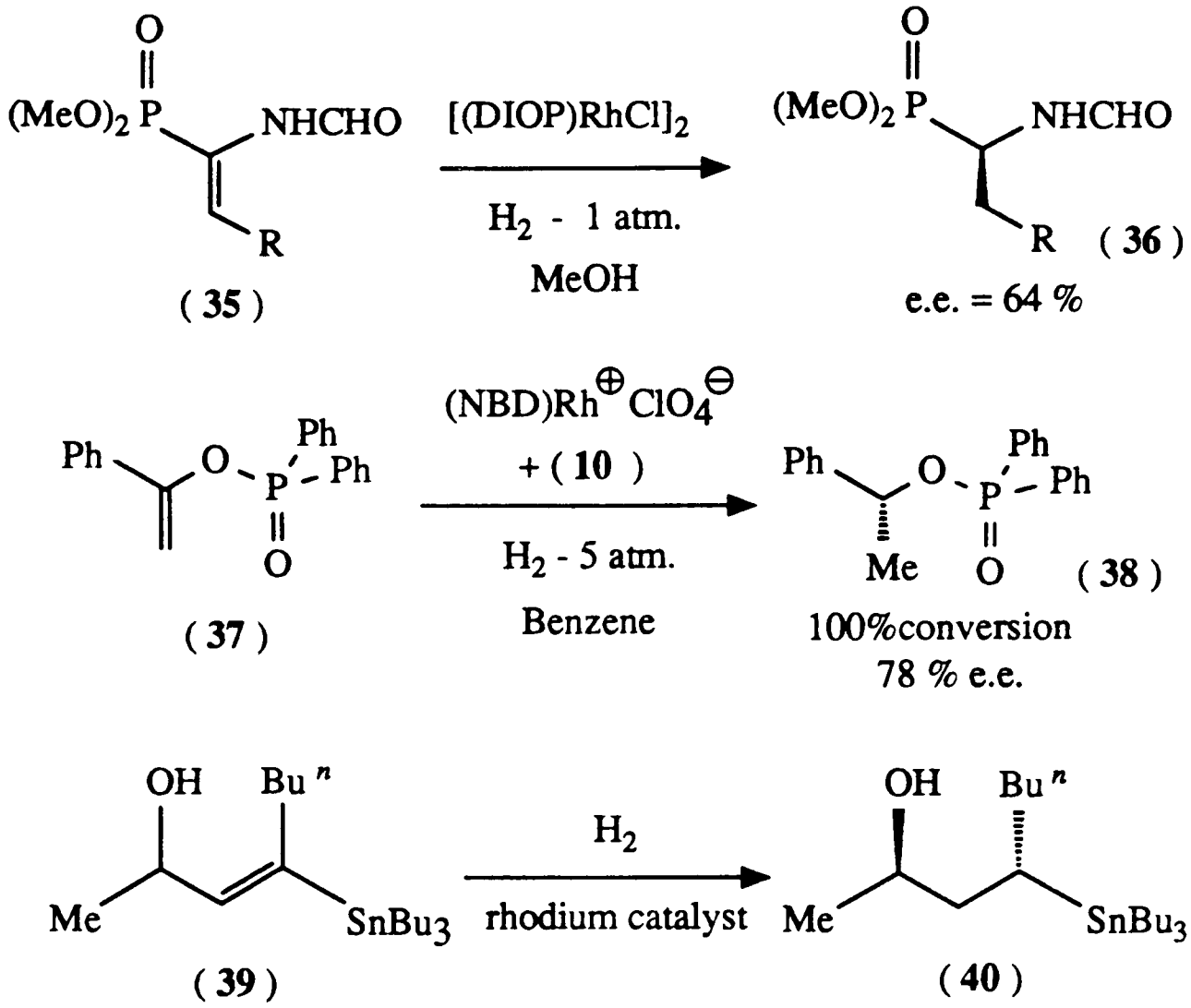
Scheme 1.04 - Reductive elimination from a platinum alkyl hydride.

1.05 Conclusions

In conclusion, it can be seen from the preceding sections that although catalytic homogeneous hydrogenation has been with us for over 25 years, and has come a long way in that time, it still suffers from a number of shortcomings :

i) A second binding group is required in the substrate in order to get good results. This is commonplace in homogeneous catalysis;[32]

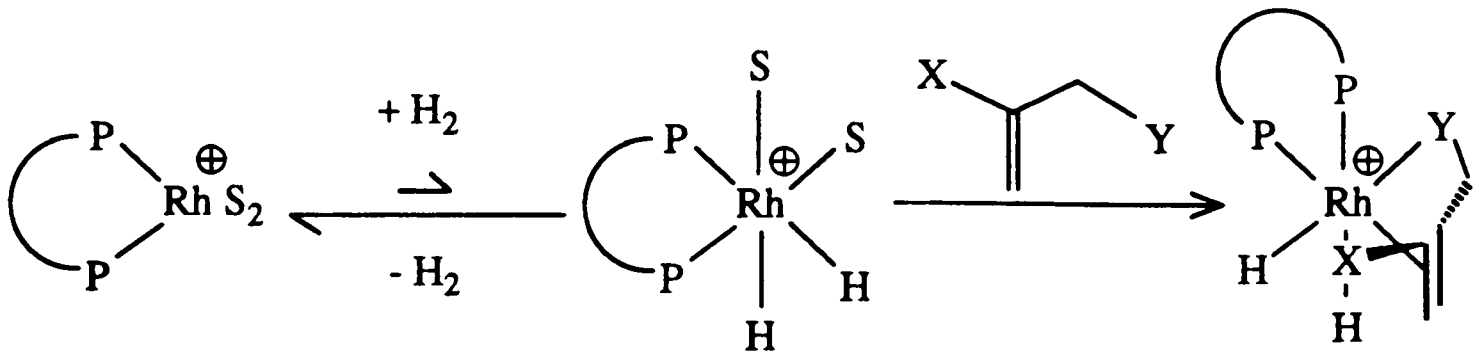
ii) A rather limited range of substrates have been reported to undergo catalysis.[33] This is especially true of compounds containing elements beyond the 2nd row, with a few notable exceptions[34, 35, 36] (Scheme 1.05).



Scheme 1.05 - The rhodium catalysed hydrogenation of heavy atom substituted olefins.[34, 35, 36]

iii) Excellent results are obtainable with dehydroamino acids as substrates,[10] and this is reflected in the fact that almost all of the mechanistic studies have concentrated on them, to the exclusion of almost all others.

iv) Although the mechanism seemed quite well understood for a while, at least one ambiguity persists. Brown's para-hydrogen experiment[27] proves only that once both dihydrogen and the substrate are in the coordination sphere of the metal they do not leave it. It does not prove that the olefin is in place when dihydrogen oxidatively adds to the metal. Thus, there may be a pre-equilibrium between a metal solvate complex and a metal dihydride (Scheme 1.06).



Scheme 1.06 - Alternative sequence of steps in the hydrogenation mechanism.

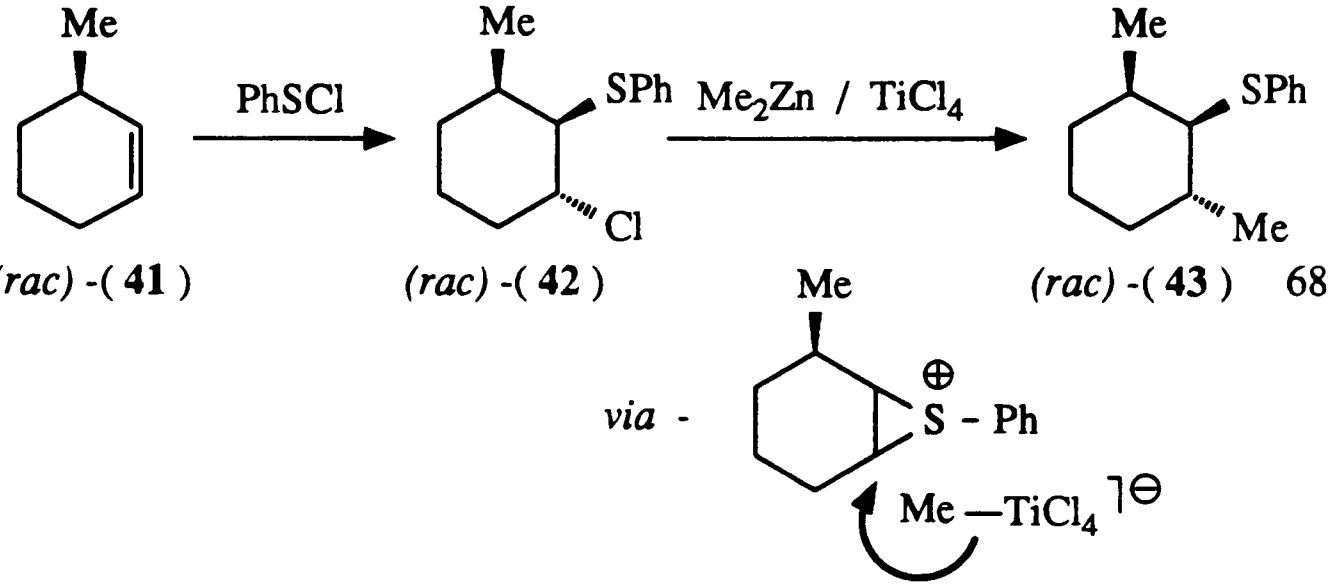
This dihydride could then bind the substrate irreversibly and go on to complete the

catalytic cycle. This shall be examined further in later chapters.

1.06 An Introduction to Sulphur Chemistry

The synthetic utility of sulphur containing compounds is undoubtable, as is highlighted by the number of sulphur containing synthetic equivalents. Indeed the organic chemist today is faced by a plethora of such reagents, just a few of which are shown in Table 1.02.[37, 38]

Sulphur compounds can exhibit excellent properties with regard to the control of the stereochemical course of a reaction. Sometimes these properties can be unique to sulphur and sometimes they can manifest themselves in extremely simple reactions such as Reetz's synthesis of diastereomerically pure sulphides (Scheme 1.07).[39]



Scheme 1.07 - Addition of PhSCl to olefins.[39]

Endeavouring to concentrate on stereocontrol in sulphur chemistry, it is possible to pinpoint five areas of particular interest and importance in this field :

i) The control of the absolute stereochemistry of sulphoxides including the asymmetric oxidation of sulphides;

ii) The use of S=O containing compounds in cycloadditions;

iii) The use of sulphinyl chiral auxiliaries to control stereochemistry in addition reactions;

iv) The use of sulphur stabilised anions in additions to gain stereochemical control;

v) The factors which make sulphoxides different from other chiral moieties.

As before, each of these shall be dealt with briefly.

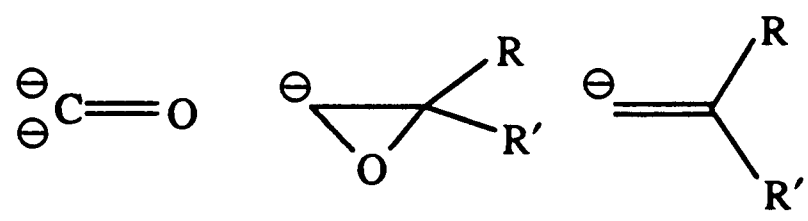
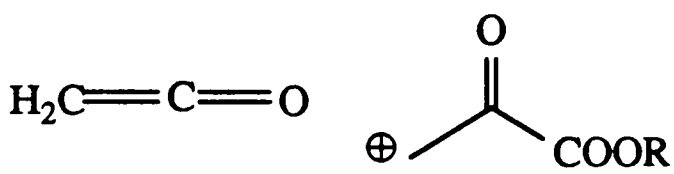
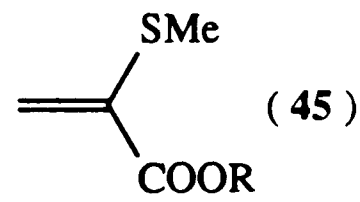
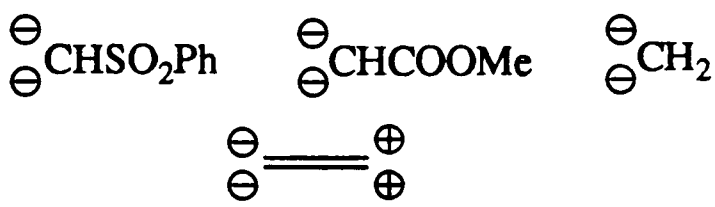
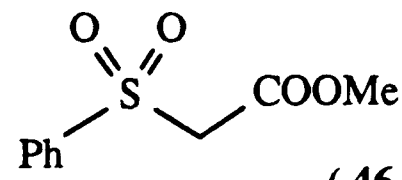
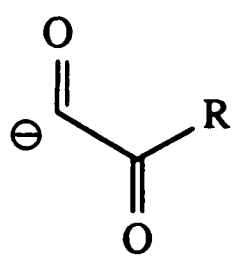
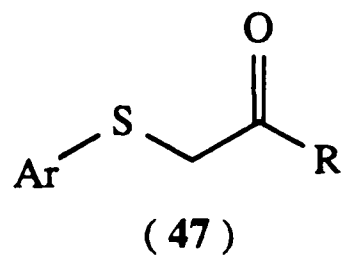
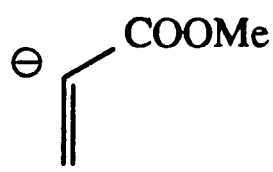
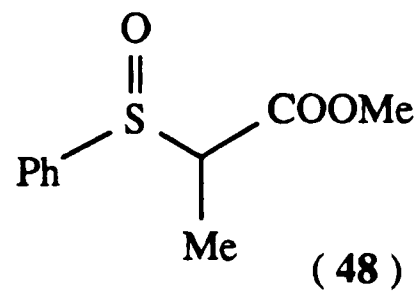
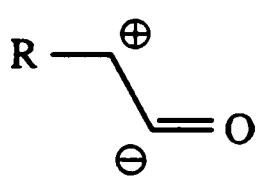
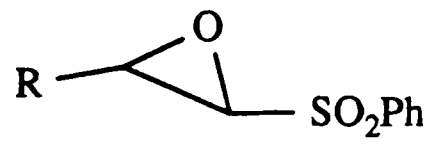
SYNTHON	SYNTHETC EQUIVALENT
	 (**44**)
	 (**45**)
	 (**46**)
	 (**47**)
	 (**48**)
	 (**49**)

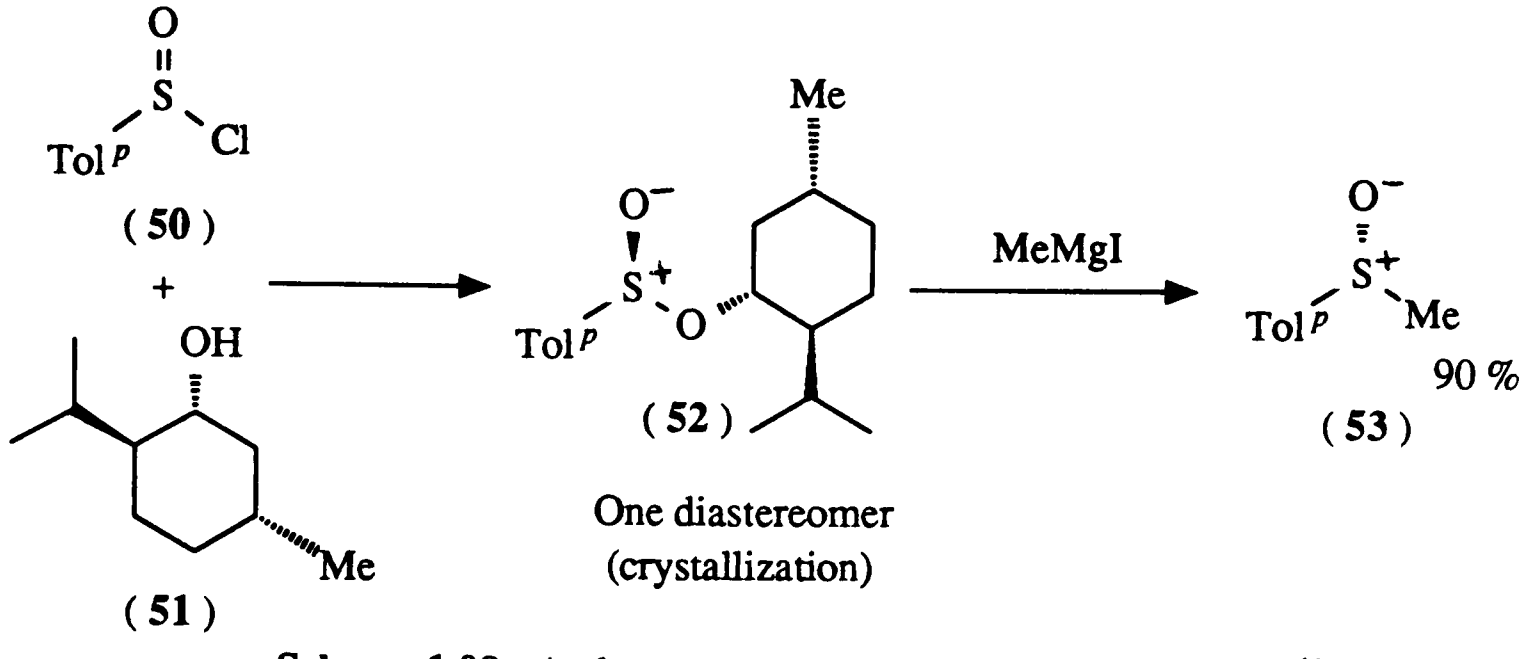
Table 1.02 - Synthons and synthetic equivalents.[37, 38]

1.07 The Control of the Absolute Stereochemistry of Sulphoxides

The classic methodology for generating chirality at sulphur involves the general principles of introducing a chiral auxiliary, resolution, then displacement of the auxiliary. There are two major variants on this theme :

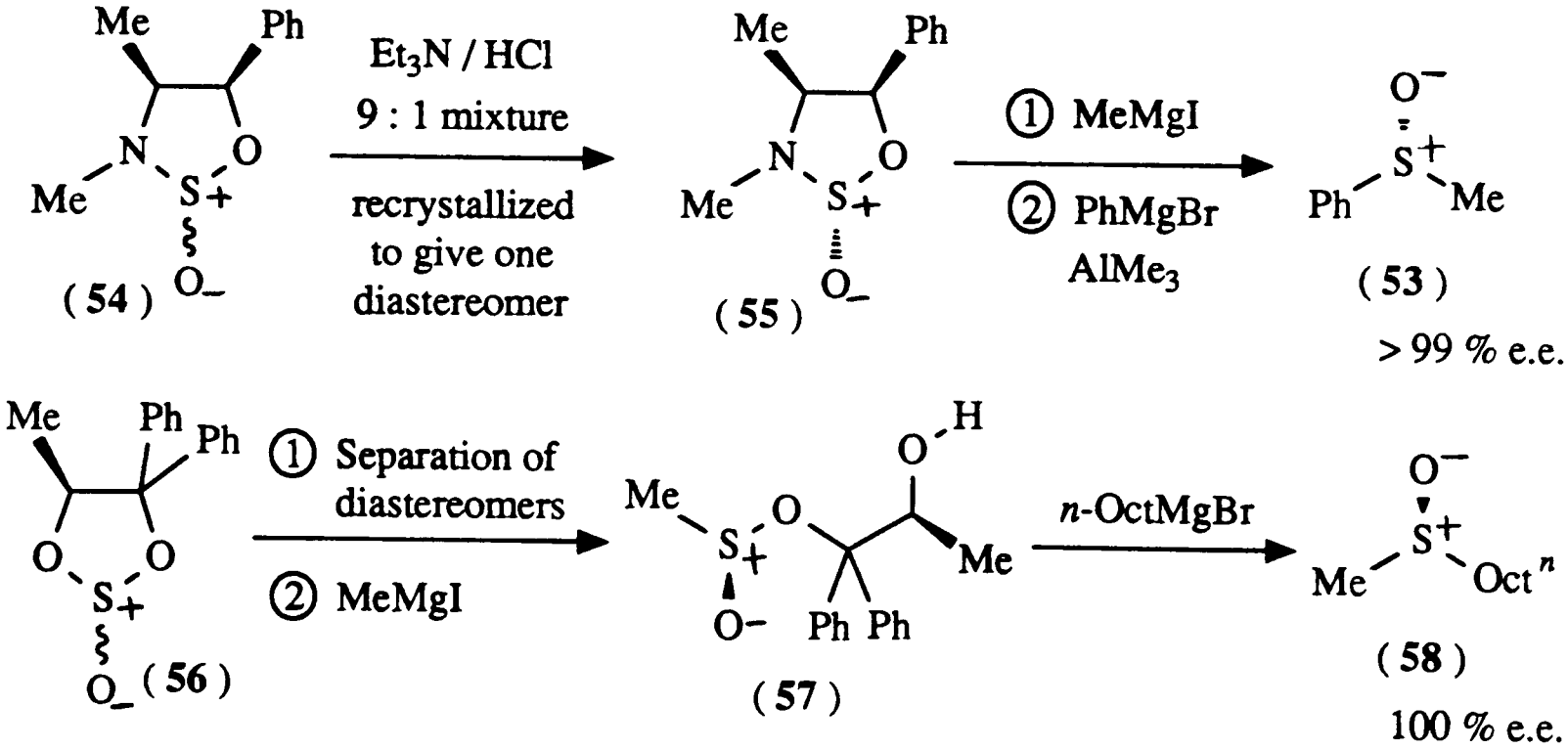
- the Andersen method,[40] which is the most prevalent technique, shown in

Scheme 1.08.[41]



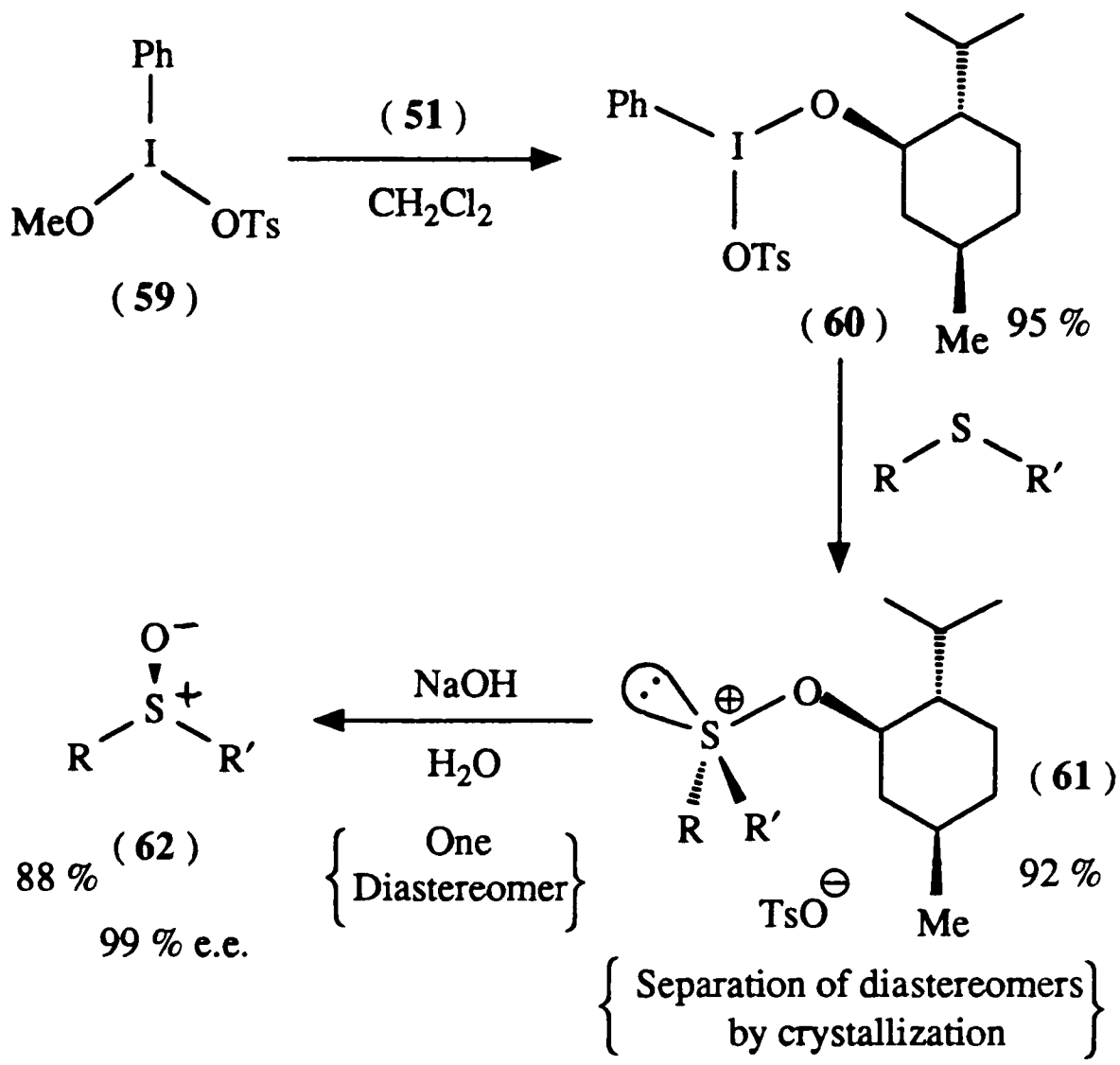
Scheme 1.08 - Andersen method of sulphoxide preparation.[41]

- and the cyclic sulphinamadite[42] / sulphinate[43] system shown in Scheme 1.09. This method has also found favour recently[9b] in the preparation of chiral phosphines, although the idea dates back to 1973.[44]



Scheme 1.09 - Preparation of homochiral sulphoxides.[42, 43]

A novel variation on the theme of replacement of a chiral auxiliary recently reported by Koser[45] involves an iodonium mentholate, (**60**), as a starting material (Scheme 1.10).



Scheme 1.10 - Koser's homochiral sulphoxide synthesis.[45]

A newer method of generating homochiral sulphoxides involves asymmetric oxidation. This subject can be broken down into two main sections - chemical and biochemical oxidation. Undoubtably the best system for chemical asymmetric oxidation is a modification of Sharpless epoxidation conditions (Figure 1.09).[46] The key difference between the two protocols is the addition of one mole equivalent of water, which increases the e.e.'s obtained quite dramatically.[47]

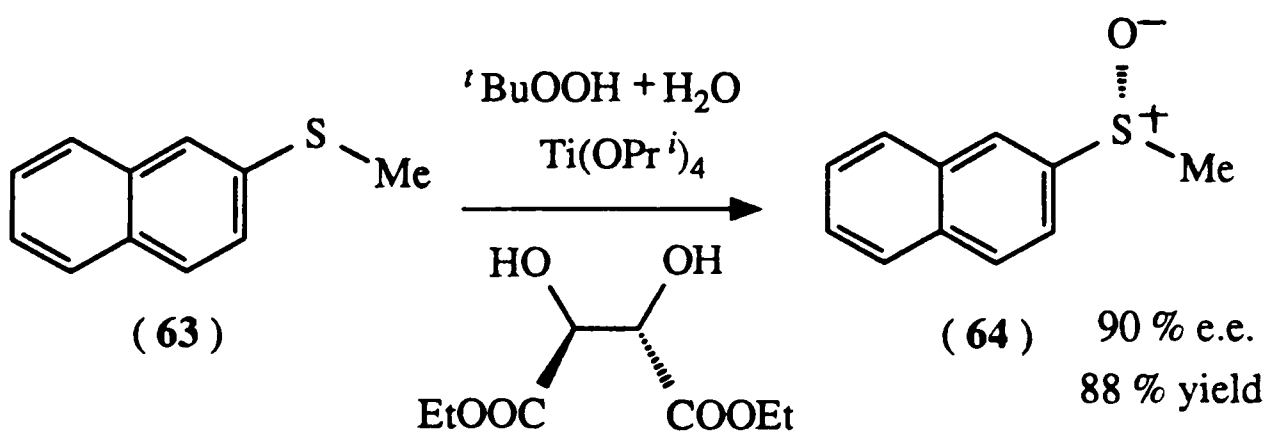


Figure 1.09 - An enantioselective sulphoxide preparation.

The area of biochemical asymmetric oxidation to synthesise homochiral sulphoxides can in turn be split into two subdivisions - the asymmetric oxidation of

sulphides and the oxidation of racemic sulphoxides effecting a kinetic resolution. A review by Holland[48] highlighted the number of excellent results obtained, two examples of which are shown in Figure 1.10, but failed to highlight any drawbacks, e.g. low yields in some cases.

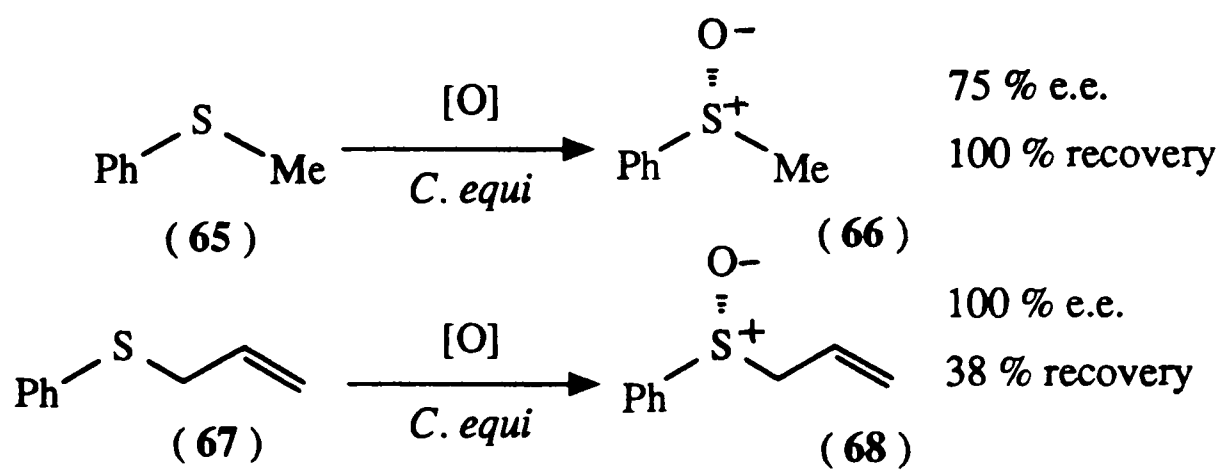
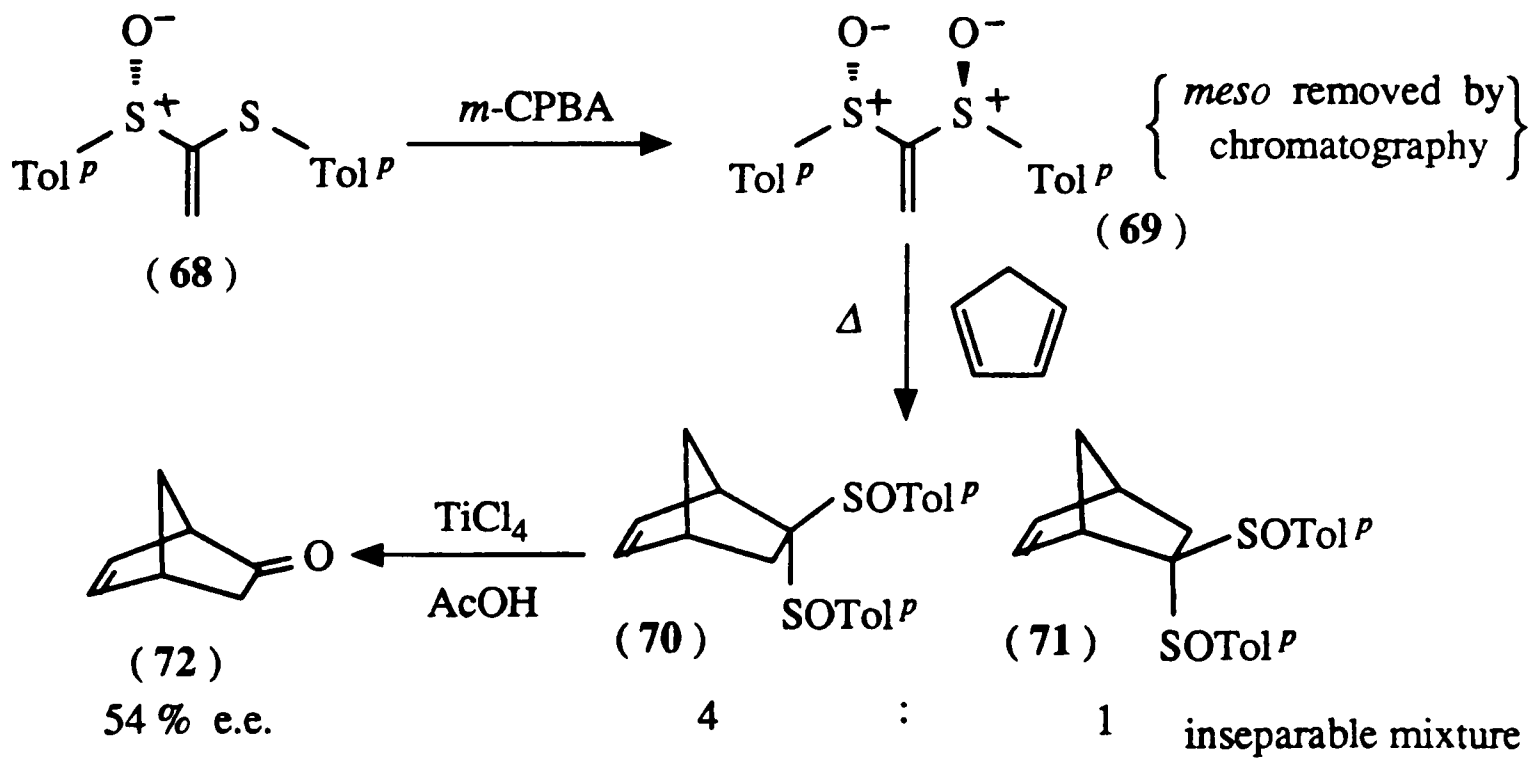


Figure 1.10 - Examples of bacterial oxidation of sulphides.

Turning to the kinetic resolution of sulphoxides, only a few examples of this have come to light in the literature[49] and it is debatable how important it will become.

1.08 Cycloadditions Involving Compounds Containing S=O Fragments

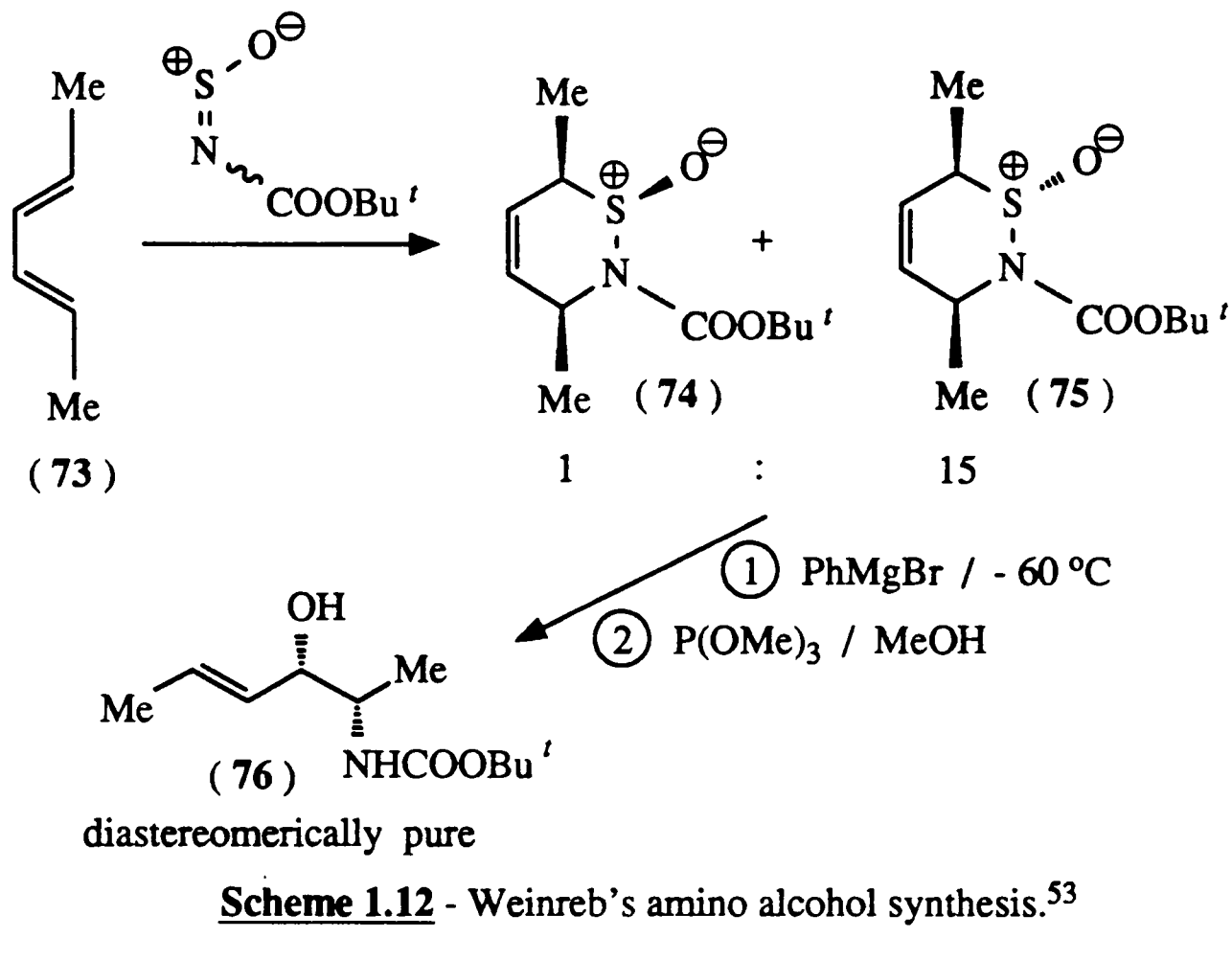
Since cycloadditions have been used to form the skeleton of many natural products,[50] it is not surprising that attempts have been made to facilitate an asymmetric version. In a number of cases this has made use of chirality at sulphur and the ease of preparation of the homochiral starting materials. One such asymmetric Diels - Alder reaction by Koizumi[51] to give norcamphor, (72), is outlined in Scheme 1.11.



Scheme 1.11 - An enantioselective synthesis of norcamphor.

Earlier work by Koizumi and co-workers[52] with α-sulphinyl esters led to a mixture of four products due to the absence of a C_2- axis of symmetry in this case.

The hetero Diels - Alder, or Danishefsky reaction has received the same attention and in at least one case has benefited from the chirality generated by an S=O group[53] (Scheme 1.12).



Scheme 1.12 - Weinreb's amino alcohol synthesis.[53]

1.09 The Control of Addition Reactions

A related field of investigation is the Michael style addition to unsaturated sulphur compounds.[55, 56] Here, much research has been done into the origin of the selectivity[56] and the difference between the sulphinyl and sulphonyl cases.[57] Some interesting parallels have been drawn between the transition state for Michael additions to α,β-unsaturated sulphoxides and that of a lithium enolate addition to carbonyl compounds.[56] For comparison two such structures are shown below (Figure 1.11).[56]

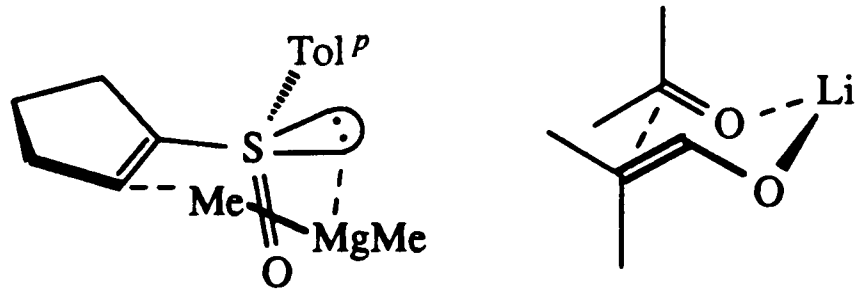
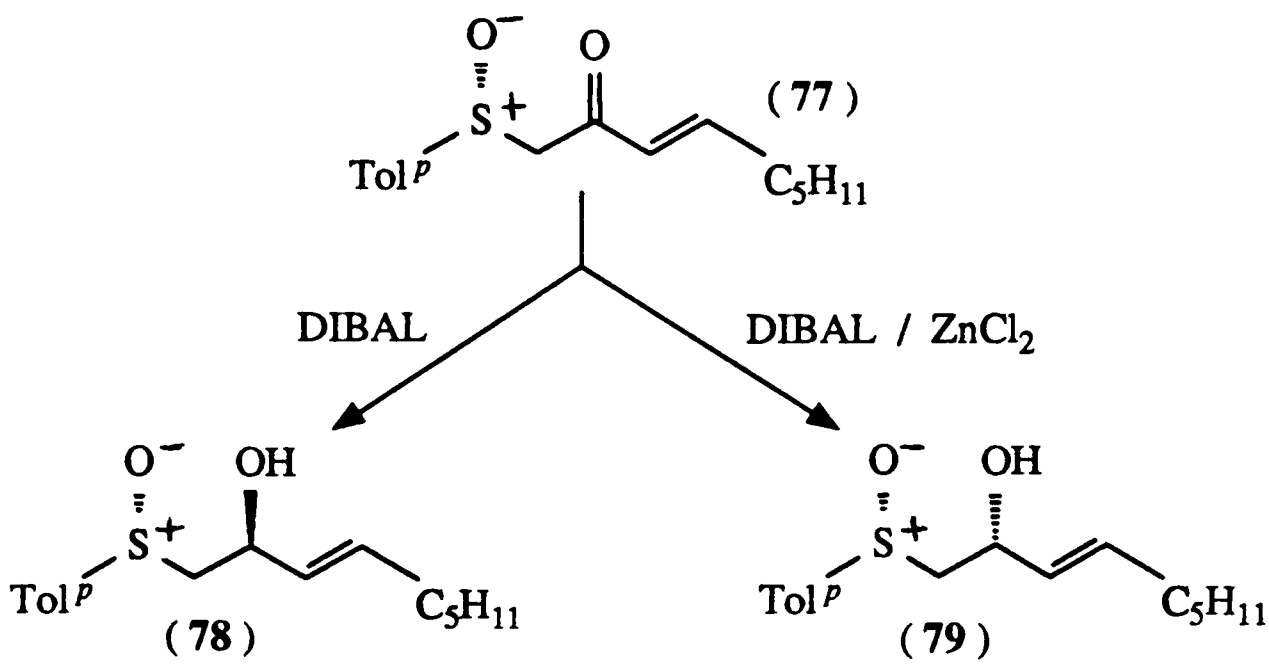


Figure 1.11 - Two transition states compared.

The reduction of functional groups in the vicinity of a sulphur containing moiety has received much attention, especially from Solladié and co-workers.[58] Among the commonest examples is the reduction of β-keto sulphoxides, the stereochemistry of which can be reversed by the use of zinc chloride as an additive (Scheme 1.13).[58e]



Scheme 1.13 - Solladié's reduction of β - keto sulphoxides.[58]

The rationale given by Solladié is simple - without a Lewis acid present the substrate adopts conformation **I** (Figure 1.12), and nucleophilic attack takes place from the least hindered face of the carbonyl; whereas with zinc chloride present to coordinate to the sulphoxide and carbonyl group, the substrate is forced into conformer **II** and the other face of the carbonyl group becomes the least hindered. This is a modification of Cram's rule.[59]

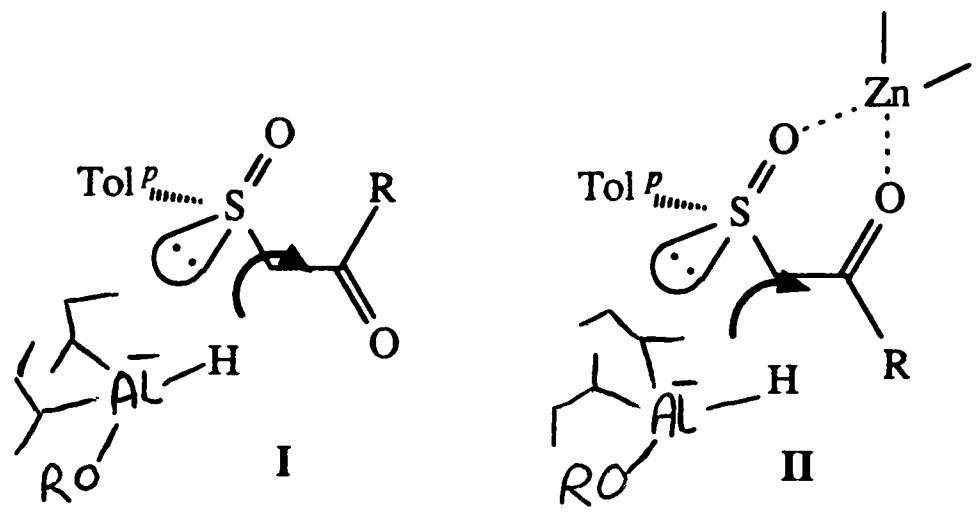
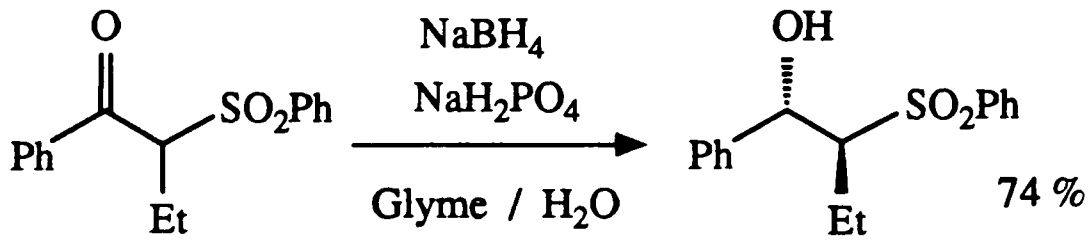


Figure 1.12 - Open chain (**I**) and cyclic (**II**) reactive conformations.

The sulphone group has also been used to dictate the stereochemistry in reductions of ketones.[60, 61] But here the chirality lies in the carbon α to the sulphur and the sulphone acts merely as a blocking group. Nonetheless, impressive diastereoselectivities can be obtained[61] (Figure 1.13).



(**80**)

(rac) - threo - (**81**)
(only detectable isomer)

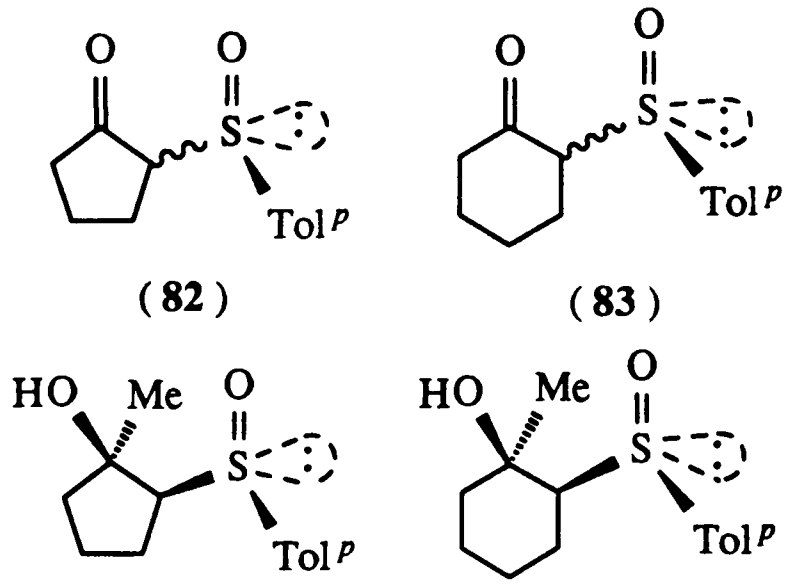
Figure 1.13 - Reduction of β-keto sulphones.

The addition of trimethyl aluminium to cyclic α-sulphinyl ketones has been examined in some depth by Carreño and Ruano recently.[62] The products of the reaction of the five and six ring ketones, (**82**) and (**83**), with trimethyl aluminium, in the presence or absence of zinc chloride, were analysed and three points came to light :

i) With the six membered ring in the absence of the zinc chloride additive, a 4:1 mixture of two diastereomers is formed differing only in their configuration at the addition site. This is found even if a mixture of diastereomeric ketones is used. This means that the α-centre must be epimerising.

ii) If the additive is used with the six ring no change is seen in the configuration of the α-centre and a good yield of (**85**) is obtained (94 %).

iii) When the five ring compound is treated similarly the situation is reversed - one product, (**84**), is isolated in excellent yield in the absence of the additive (98%), but a mixture of all four diastereomeric products is obtained with the additive.



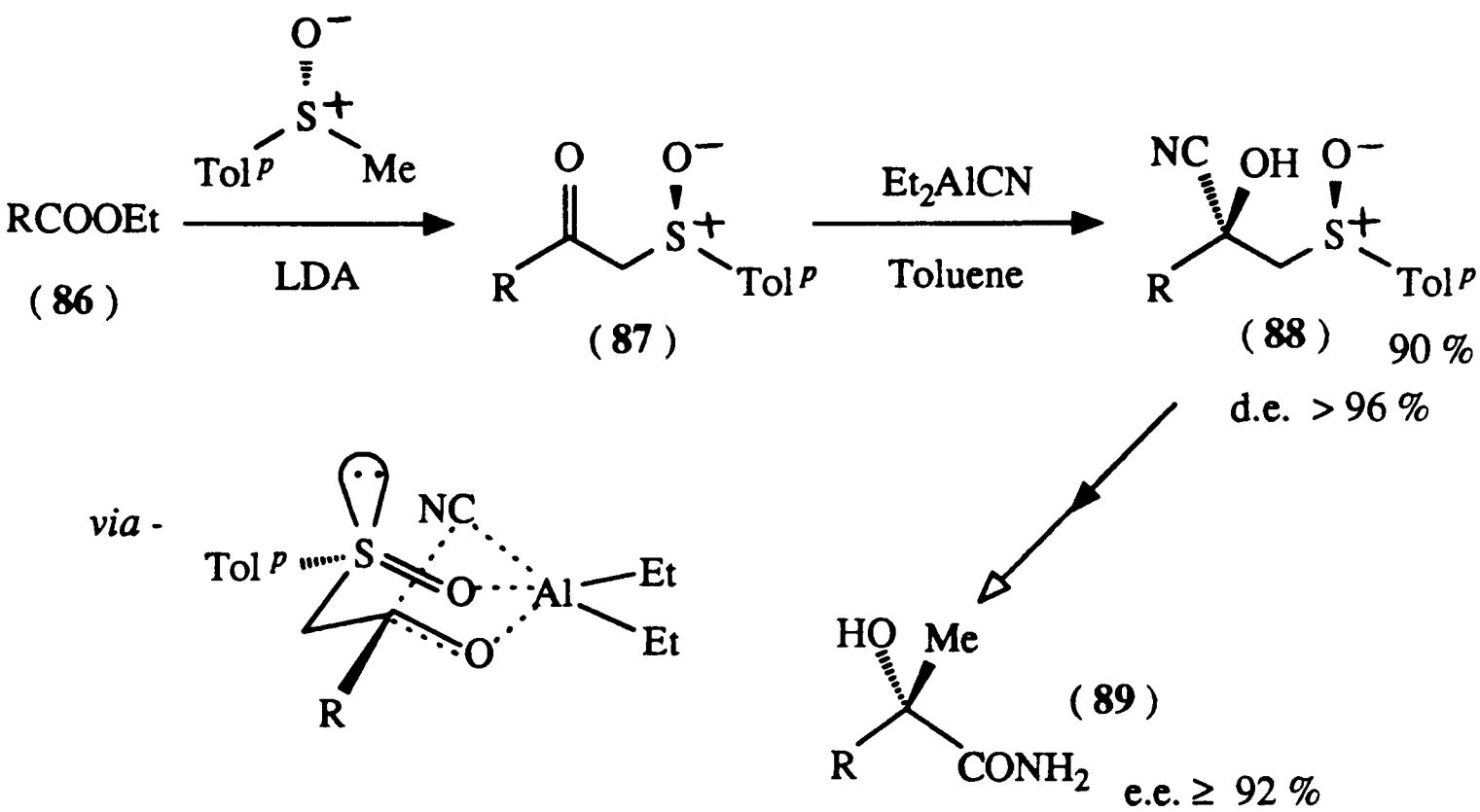
(**82**) (**83**)

(**84**) (**85**)

Figure 1.14

Hydrocyanation of ketones has been modified by the introduction of a sulphoxide moiety into the starting material. This allows the asymmetric synthesis of α-hydroxy

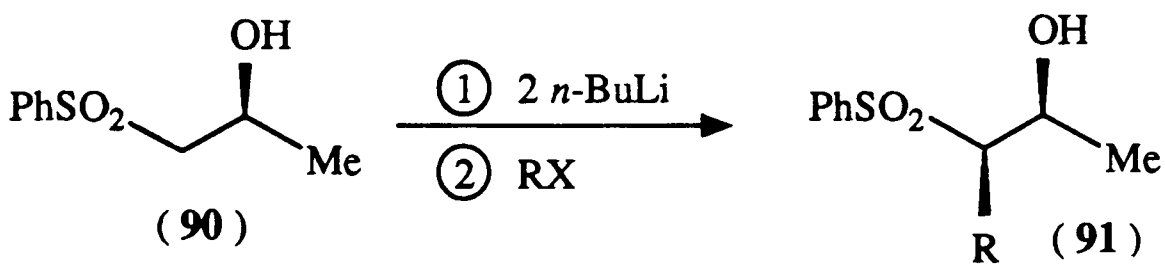
carboxylic acids and amides in high e.e.'s from, amongst other things, esters. An example by Rodriguez[63] involves the chelation effect previously observed. This time, however, it is believed that the metal binds the two sites and delivers the nucleophile to the carbonyl.



Scheme 1.14 - A homochiral cyanohydrin synthesis and use.

1.10 The Use of Sulphur Stabilised Anions in Additions

The stabilisation of carbanions α to sulphur is a major feature of sulphur chemistry and has received much attention as a consequence of this.[64] Work by Tanikaga and co-workers[65] with β-hydroxy sulphone anions and electrophiles has shown only poor selectivity. The selectivity can be enhanced somewhat by the addition of cation solvating agents such as TMEDA or HMPA[65] (Figure 1.15).



Major diastereomer

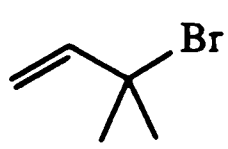
	Additive	*erythro* : *threo*
RX = MeI	none	51 : 49
RX = 	none	73 : 27
	DABCO	84 : 16
	TMEDA	85 : 15
	HMPA	58 : 42

Figure 1.15 - Addition to sulphone stabilised anion.

The sulphoxide equivalent in the above reaction, however, has the capacity to form a chelate through the sulphoxide oxygen.[65b] The asymmetry of the sulphoxide and the alcohol group then makes the two faces of the molecule inequivalent for electrophile attack. In practice, Tanikaga and co-workers [65b] found that the selectivity was improved upon compared to the sulphone and reversed in favour of the *threo*-diastereomer in the case of the *syn*-β-hydroxy sulphoxide, (**92**) (Figure 1.16).

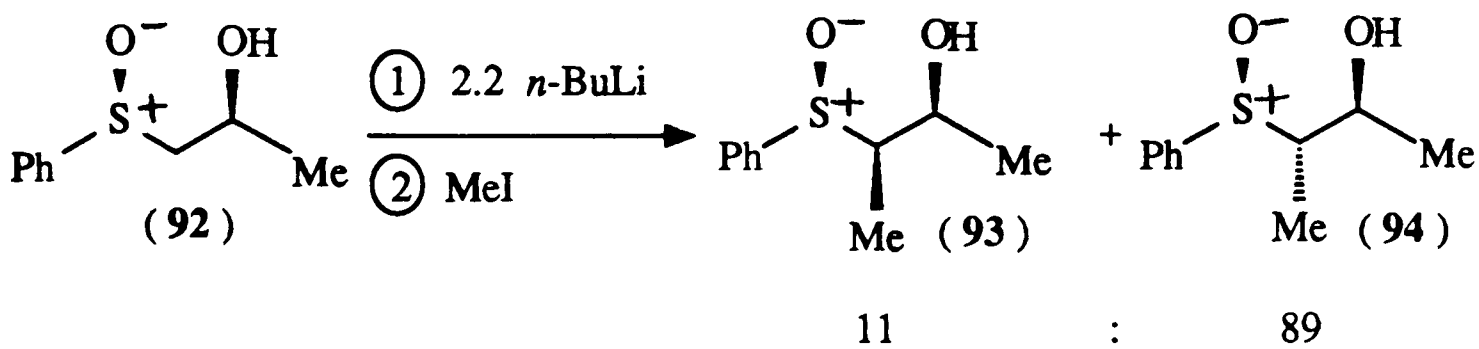


Figure 1.16 - Electrophilic addition to a sulphinyl stabilised anion.

Tanikaga[65] explains the observed preference for the *erythro*-diastereomer of the sulphone by assuming the carbanion is sp^2 hybridised, and that the *anti* conformer of the dianion is the most stable. The approach of the electrophile is then controlled by the different steric hindrance at each face. In the sulphoxide case he invokes a lithium chelate which controls the mode of approach of the electrophile. This is shown in Figure 1.17, where path B is lower in energy and hence gives rise to the major product in each case.

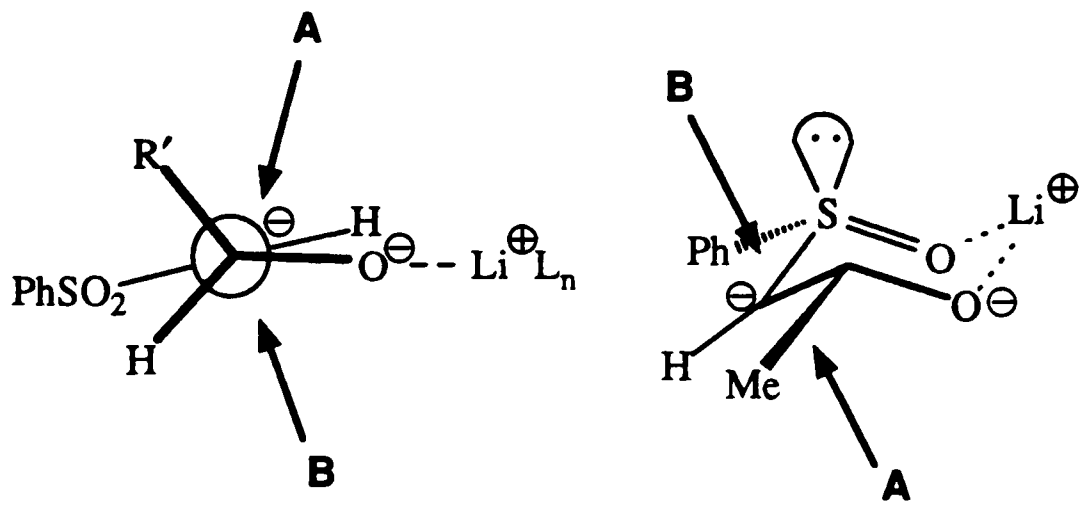


Figure 1.17 - Comparison of the reactive conformers of sulphinyl and sulphonyl stabilised anions.

Casey and co-workers[66] have recently reported similar selectivities with *p*-tolyl and *t*-butyl sulphoxide anion additions to aldehydes. They propose that the selectivity arises from the boat conformation of a six membered transition state as shown in Figure 1.18.

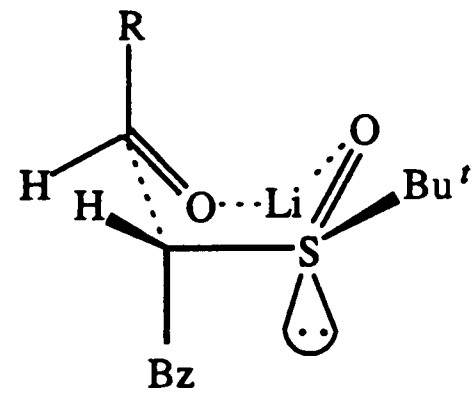


Figure 1.18 - Boat conformer in an aldehyde reaction with a sulphinyl stabilised anion.

1.11 Conclusions

i) The acidity of CH protons α to sulphur in a molecule and the electron withdrawing effect[67] of sulphur containing functional groups play a major part in the chemistry of sulphur compounds.

ii) It is not uncommon to find the rôle of a sulphone group in controlling stereochemistry to be almost purely steric in nature. Whereas the oxygen atoms of a sulphone group are not very basic,[68] the oxygen atom of a sulphoxide is quite basic and a host site for strong metal and hydrogen bonding.[68] This difference manifests itself in the preference of sulphones to form open chain transition states in addition reactions, and of sulphoxides to form transition states bound in a chelate.[65]

iii) The sulphoxide group is uniquely characterised with respect to any other chiral group by the presence of at least three different kinds of ligands from a stereoelectronic point of view - a lone pair of electrons; an oxygen atom; and two alkyl or aryl ligands.[41]

iv) The synthesis of chiral sulphoxides as starting materials is made relatively easy by a number of quite elegant routes.[69]

RESULTS AND DISCUSSION

Results and Discussion

Synthesis of Catalysts and Substrates

2.01 Introduction and Aims

Acyclic diastereocontrol is a key problem in the total synthesis of many natural products[70] and has been tackled successfully from many angles. One approach, directed homogeneous hydrogenation, has been shown to be very selective in some cases[71] and has the added advantage of relative ease of extension to asymmetric synthesis. However, the reaction suffers from a severe dearth of substrates that give good results[33] and this somewhat limits its usefulness. The work in this thesis is concerned with extending the range of substrates suitable for homogeneous hydrogenation to sulphur containing compounds, particularly those shown in Figure 2.01.

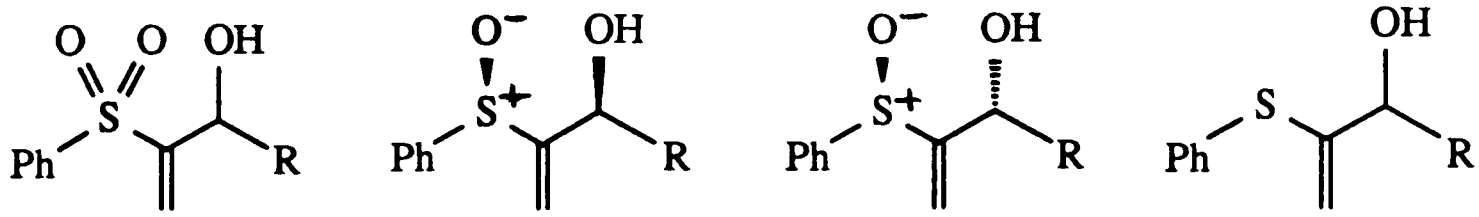
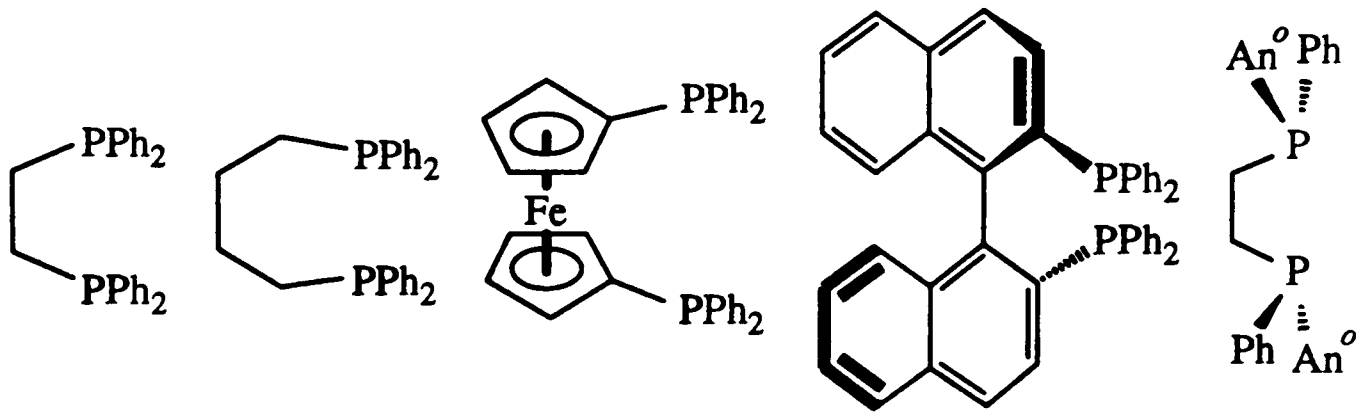


Figure 2.01 - Possible hydrogenation substrates.

The work in later Chapters will also deal with a kinetic analysis of their rate of hydrogenation. A specially designed hydrogenator will be described along with numerical analysis of the rate data on a personal computer based system.

2.02 The Synthesis of Catalysts

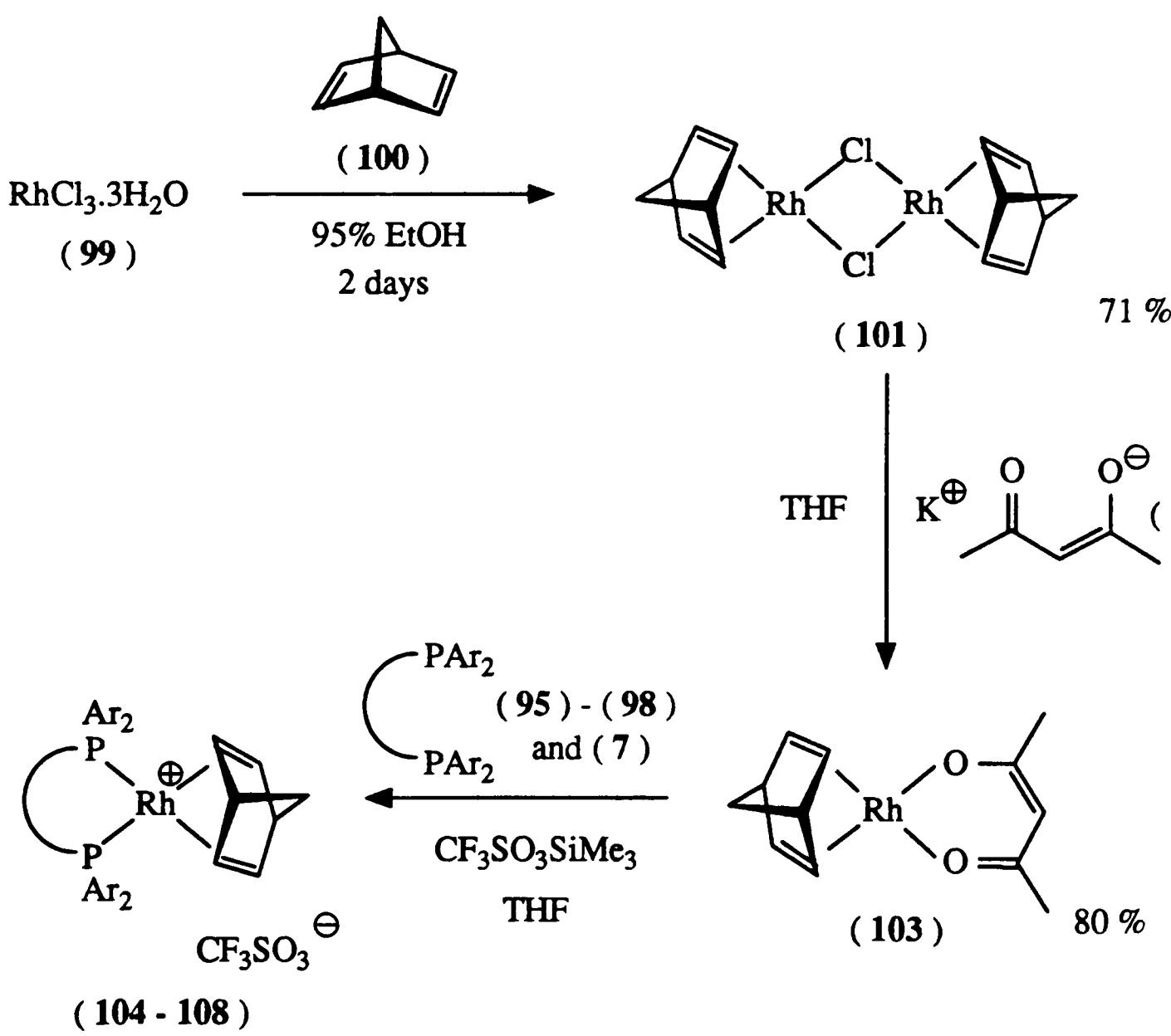
Five rhodium catalyst precursors were chosen for this investigation in the hydrogenation of sulphur compounds - three prepared from achiral phosphines and two from homochiral phosphines. The five phosphines chosen are shown in Figure 2.02.



(**95**) (**96**) (**97**) (*R*)- (**98**) (*S*,*S*)- (**7**)

Figure 2.02 - Phosphines used in catalyst preparation.

Each catalyst precursor was prepared in three steps from $RhCl_3.3H_2O$, (**99**), by literature methods[72, 73] as shown in Scheme 2.01. The yields accompanying the final reaction step are shown in Table 2.01.



Scheme 2.01 - The synthesis of catalyst precursors.

LIGAND	CATALYST PRECURSOR	YIELD
(**95**)	(**104**)	82 %
(**96**)	(**105**)	78 %
(**97**)	(**106**)	75 %
(*R*)- (**98**)	(**107**)	90 %
(*S*,*S*)- (**7**)	(**108**)	89 %

Table 2.01 - The yields of the catalyst precursors (**104**)- (**108**).

1,2-Bis-(diphenylphosphino)ethane (**95**) (dppe), 1,4-bis-(diphenylphosphino)-butane (**96**) (dppb), 1,1'-bis-(diphenylphosphino)ferrocene (**97**) (dppf), and (*S*)-1,1'-binapthyl-2,2'-bis-(diphenylphosphine) (**98**) (BINAP) are all commercially available. (*S*,*S*)-1,2-Bis-(*o*-anisylphenylphosphino)ethane (**7**) (DiPAMP), however, was synthesised in collaboration with Mr. A.D. Conn.[74]

2.03 The Synthesis of (*S*,*S*)-DiPAMP (**7**)

The two chiral catalyst precursors, (**107**) and (**108**), were chosen since they have been shown to be amongst the best asymmetric hydrogenation catalysts for dehydroamino acid derivatives (**4**). Noyori and coworkers[75] first reported the use of a BINAP rhodium cationic complex (in this case as the perchlorate salt) for this purpose. Although hydrogenation was slow, impressive selectivity was reported.[75]

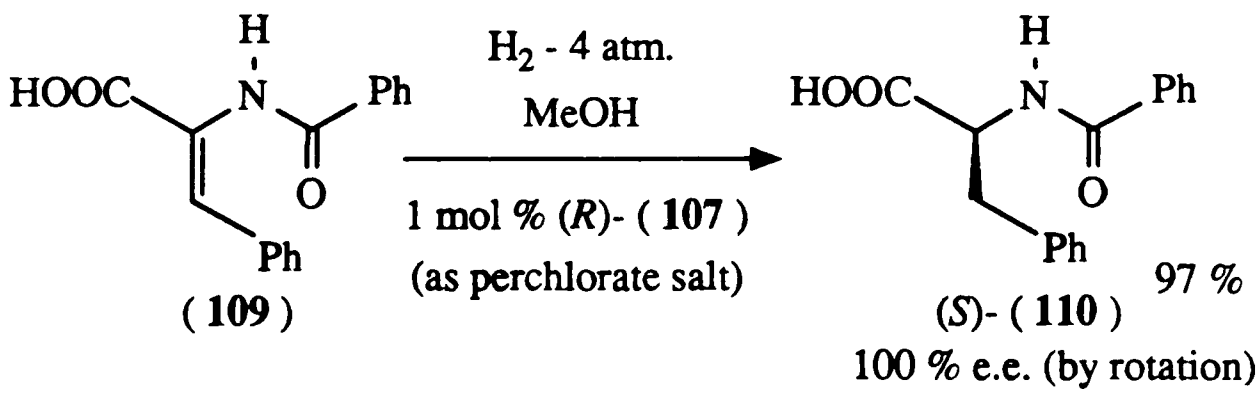


Figure 2.03 - BINAP rhodium$^{\oplus}$ catalysed hydrogenation of (*Z*)- N-benzoylamino cinnamic acid.

DiPAMP rhodium cationic complexes have also been shown to be effective in the enantioselective hydrogenation of (**4**)[10, 11] and also in the kinetic resolution[76] of hydroxy and N-substituted amino acrylates amongst others (Figure 2.04).[77]

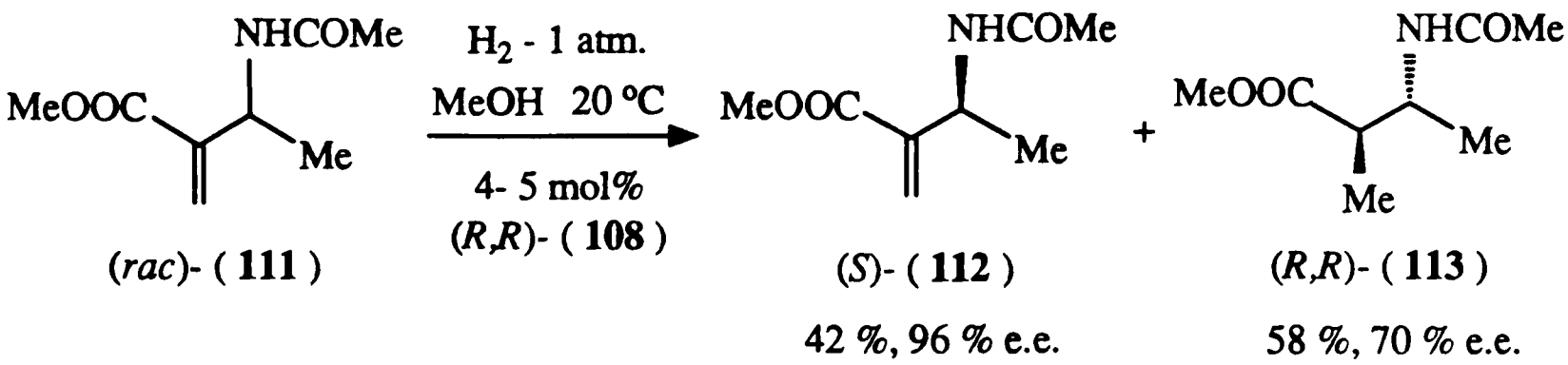
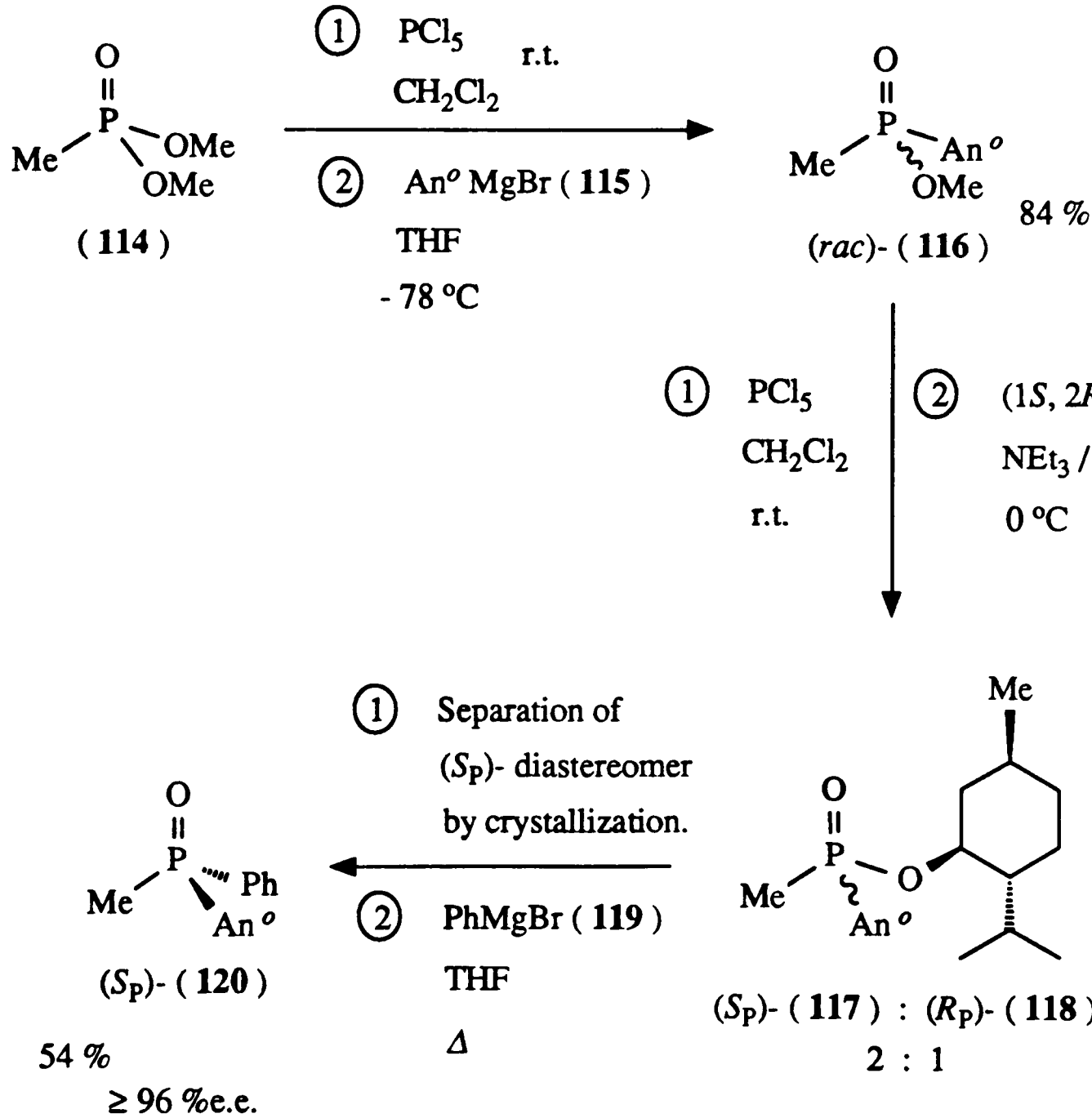


Figure 2.04 - The kinetic resolution of an acrylate derivative.[77]

It was decided to embark upon a route which encompassed four steps - i) the synthesis of a menthol phosphinate; ii) separation of the diastereomers of the menthol phosphinate; iii) displacement of menthol by an aryl Grignard reagent; and iv) homocoupling the chiral phosphine oxide to give the target molecule (*S*,*S*)-(**7**). The first three parts of this synthesis are summarised in Scheme 2.02.



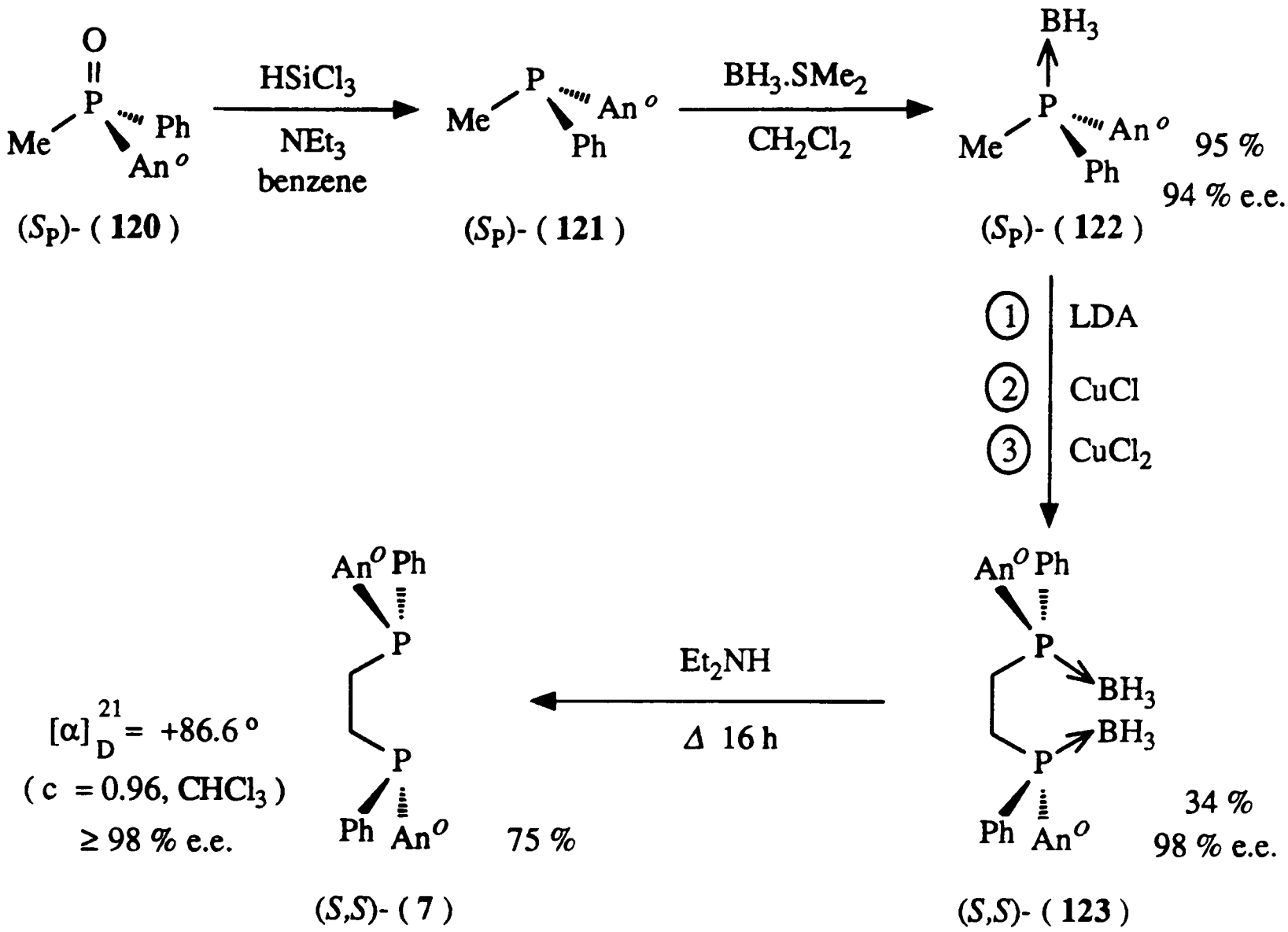
Scheme 2.02 - The synthesis of (S_P)- PAMP (**121**).

Treating dimethoxy methylphosphonate, (**114**), with phosphorus pentachloride in dichloromethane at room temperature gave a chlorophosphonate which was not isolated.[78] The chlorophosphonate was reacted immediately on preparation with *o*-anisyl magnesium bromide, (**115**). The reaction was adjudged by ^{31}P NMR to be over after 5 hours at -78°C. Work up followed by recrystallization from light petroleum ether gave almost 60 g of (**116**) in a yield of 84 %.

The next three steps involving the synthesis of a menthol phosphinate as a pair of diastereomers, (**117**) and (**118**), and their separation were carried out by Mr. A.D. Conn.[78] The phosphinate, (**116**), was converted to the corresponding phosphino chloride, which was not isolated, and then immediately reacted with menthol, (**51**), in toluene in the presence of triethylamine.[78] This produced a disappointing 2:1 ratio of diastereomers of the mentholate, which differed only in the configuration at phosphorus. These were fractionally recrystallized several times to give a total of 18 g of diastereomerically pure (S_P)-(**117**). This represented a recovery of approximately 50 % of the total quantity of (S_P)-(**117**) from the original mixture. The remaining 1:1 mixture of diastereomers proved to be inseparable.[78]

Diastereomerically pure (S_P)-(**117**) was converted to (S_P)-phenyl-*o*-anisyl-methylphosphine oxide (PAMPO), (**120**), by treatment with phenyl magnesium bromide, (**119**), in refluxing tetrahydrofuran (Figure 2.05). Liberated menthol, (**51**), was removed by Kugelröhr distillation and the resulting oil crystallized from toluene at -20°C to give the product in a moderate yield of 54 %. The optical purity of (**120**) was found by ^{1}H NMR to be greater than 96 % using a chiral shift reagent.

The next three reactions involving the conversion of PAMPO, (**120**), to the corresponding phosphine borane complex and coupling of the phosphine borane complex, (**122**), to give the DiPAMP diborane complex, (**123**), were carried out by Mr. A.D. Conn[78] and are contained in Scheme 2.03.



Scheme 2.03 - The second stage of the DiPAMP synthesis.

The synthesis was completed by the decomplexation of the DiPAMP-diborane complex, (**123**), with diethylamine yielding (*S,S*)-DiPAMP, (**7**), as shown in Scheme 2.03. The final step, performed according to Imamoto,[79] gave only a moderate yield of 75 %. After recrystallization from methanol the optical purity of the (*S,S*)-DiPAMP, (**7**), was found to be greater than 98 % by comparison with literature rotations.[11, 79]

The catalyst precursor, (1,2-bis-(*o*-anisylphenylphosphino)ethane) rhodium(I) bicyclo-[2,2,1]-heptadiene trifluoromethane sulphonate, (**108**), was prepared as indicated in Scheme 2.01 and stored at -20°C.

2.04 Synthesis of α,β-Unsaturated Sulphones

Although several studies[10a, 11, 77] concerned with the stereoselectivity of homogeneous hydrogenation have dealt with changes in the auxiliary binding group of the substrates, few have dealt with changes in the so-called activating substituent of the double bond. Most studies that have examined such changes have concentrated on

carboxylic acid derived functionalities. With this in mind, it was decided to synthesise a number of sulphur substituted allylic alcohols to investigate their suitability as substrates.

The hydroxy-acrylates such as (**127**), which are structurally similar to the target substrates, have been successfully prepared from acrylate esters, such as (**124**), and aldehydes using the Baylis-Hillman reaction[80] as in Figure 2.05.[81]

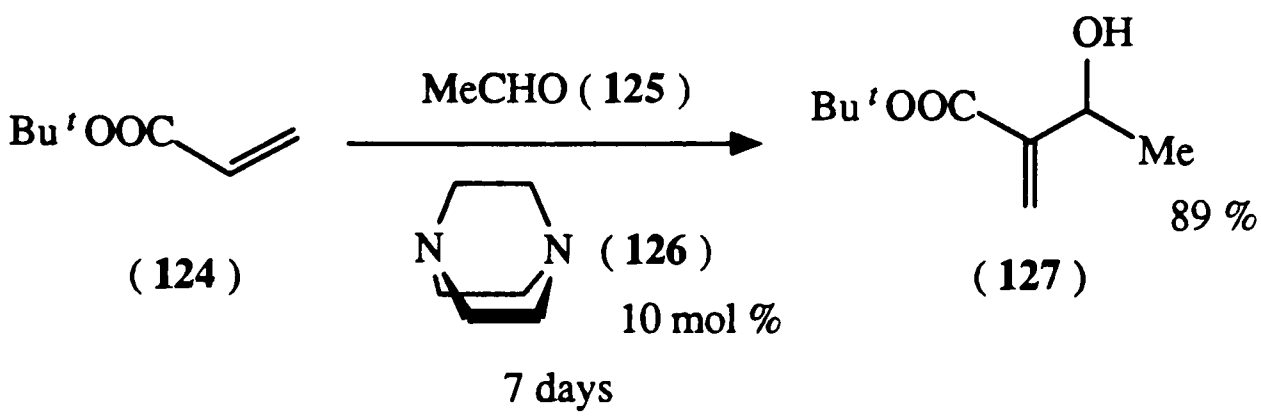
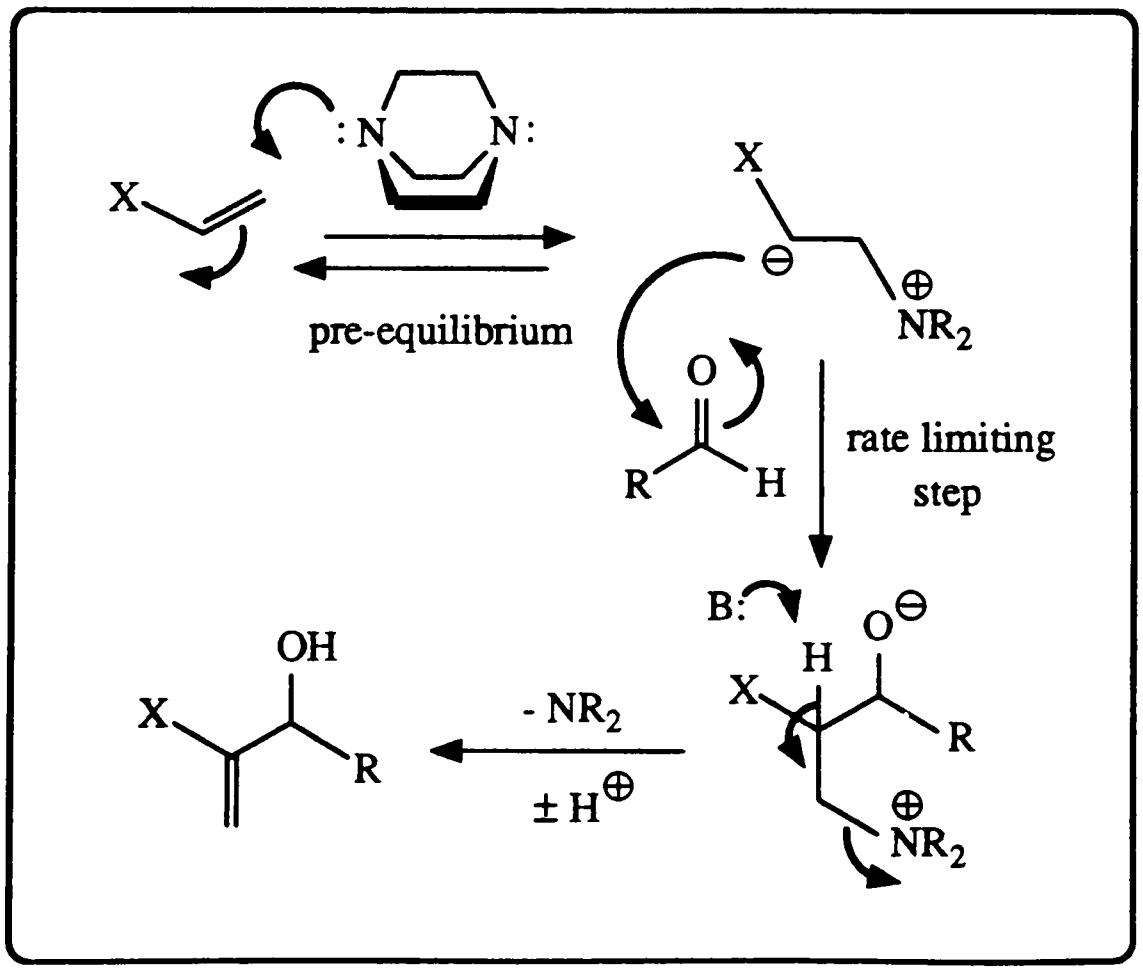


Figure 2.05 - The Baylis-Hillman reaction of ᵗbutyl acrylate (**124**).[81]

The mechanism of the Baylis-Hillman reaction is believed to involve sequential Michael-type addition of the tertiary amine to the carbon-carbon double bond, trapping of the intermediate zwitterion by the electrophile and loss of the tertiary amine. This is detailed in Scheme 2.04.[81, 82]



Scheme 2.04 - The mechanism of the Baylis-Hillman reaction.[81, 82]

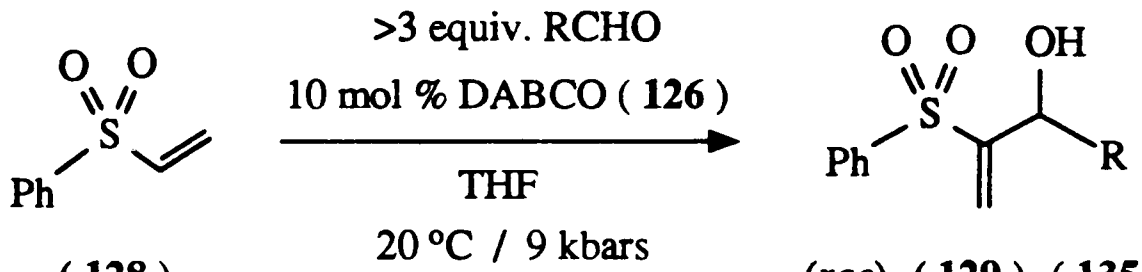
The rate of reaction exhibits a large pressure dependence[82] as a consequence of the

pseudo-termolecular mechanism and this has been used to accelerate the reaction.[82]

α-Sulphonylallyl alcohols have also been made by this method,[83, 84, 85] but rather surprisingly it has been reported that no advantage could be gained by the use of high pressures.[85]

In a trial reaction, phenyl vinylsulphone, (**128**), acetaldehyde, (**125**), and 10 mol % DABCO, (**126**), in tetrahydrofuran were put under a pressure of 12 kbar overnight. ^{1}H NMR of the crude reaction mixture showed that all the sulphone starting material, (**128**), had been consumed. This is in contrast with the ambient pressure reaction which is reported to take 7 to 10 days.[84, 85]

After a number of trial reactions, the success of which were judged by the ratio of product to starting material in the ^{1}H NMR, it was found that optimum reaction conditions depended on the aldehyde used. The optimum temperature and pressure were found to be 20°C and 9-10 kbars irrespective of aldehyde (Figure 2.10). The reaction time, however, depended on the reactivity of the aldehyde and the concentrations of the three components.



(**128**) (*rac*)- (**129**)- (**135**)

Figure 2.06 - The preparation of unsaturated sulphone substrates.

Typically, 6 mmol of phenyl vinylsulphone, (**128**), was mixed with 30 mmol of acetaldehyde, (**125**), and 0.5 mmol of 1,4- diazobicyclo[2,2,2]octane (DABCO), (**126**), in 5 ml of tetrahydrofuran and sealed in a teflon® high pressure pot. The stoppered pot was placed in a Psika hydraulic press and subjected to a pressure of 9 kbar for a period of approximately 45 minutes. After releasing the pressure, the reaction mixture was pipetted from the opened pressure pot and the solvent removed *in vacuo*. The resulting viscous oil was chromatographed on silica gel eluting with hexanes/ethyl acetate (4:1) to give the product, (**129**), as a colourless, odourless oil in a yield of 82%.

Table 2.02 summarises the products obtained by this method and the conditions employed in each case. An asterisk beside the entry number indicates a new compound.

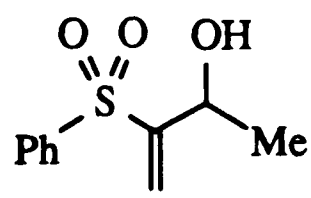
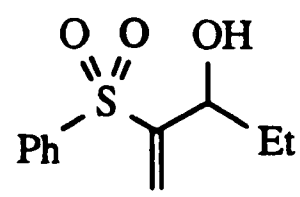
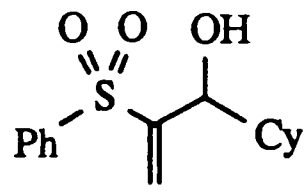
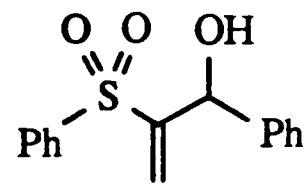
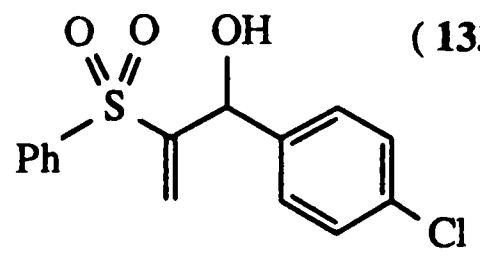
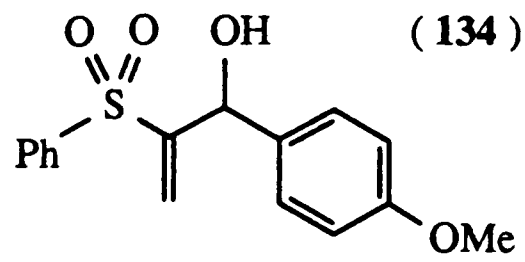
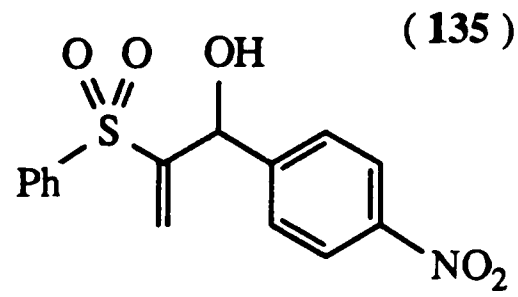
ENTRY	PRODUCT	M.P. (°C)	REACTION TIME	YIELD (%)
1	 **(129)**	OIL	45 min	82
2	 **(130)**	OIL	1 ½ h	88
3	 **(131)**	73- 74	3 h	74
4	 **(132)**	95- 96	2 ¾ h	95
5*	 **(133)**	69- 70	2 ½ h	94
6*	 **(134)**	71- 72	3 ¾ h	80
7*	 **(135)**	105- 8	2 ½ h	90

Table 2.02 - A summary of the sulphone products made by high pressure reactions.

Each hydroxy sulphone, (**129**)- (**135**), was characterised by M.P. (where appropriate), ^{1}H and ^{13}C NMR and I.R. spectroscopy. The new compounds, (**133**), (**134**),

and (**135**), were additionally characterised by elemental analysis and mass spectroscopy.

All of the unsaturated hydroxysulphones displayed O-H stretching frequencies around 3490 cm^{-1} in their respective I.R. spectra taken as neat oils or potassium bromide discs. This indicated that in all cases the hydroxy group is hydrogen-bonded.

MMX[86] molecular mechanics studies of the sulphone products, carried out on a personal computer, indicated that they contain an intramolecular hydrogen-bond in the ground-state conformation (Figure 2.07).

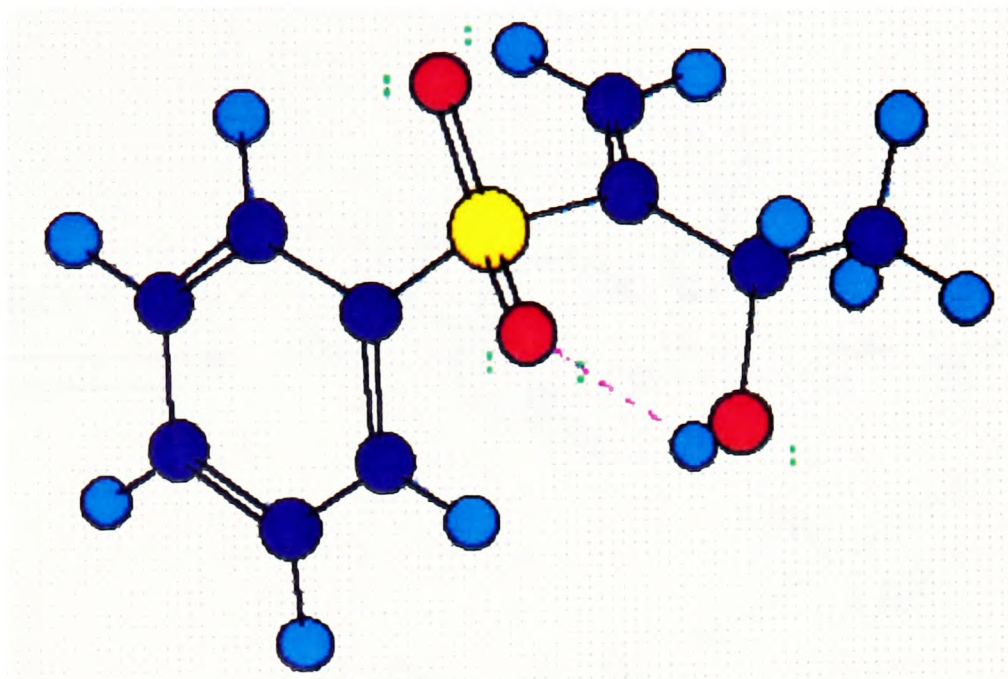


Figure 2.07 - The MMX predicted ground state conformer of (**129**)

Hydrogen-bonds to sulphone oxygen atoms are not common[87] but evidence for their existence has been reported.[88] The close proximity of the hydroxy group and one of the sulphone oxygens in this case, by virtue of the 1,3- substitution pattern, is an important factor in the hydrogen-bond formation.

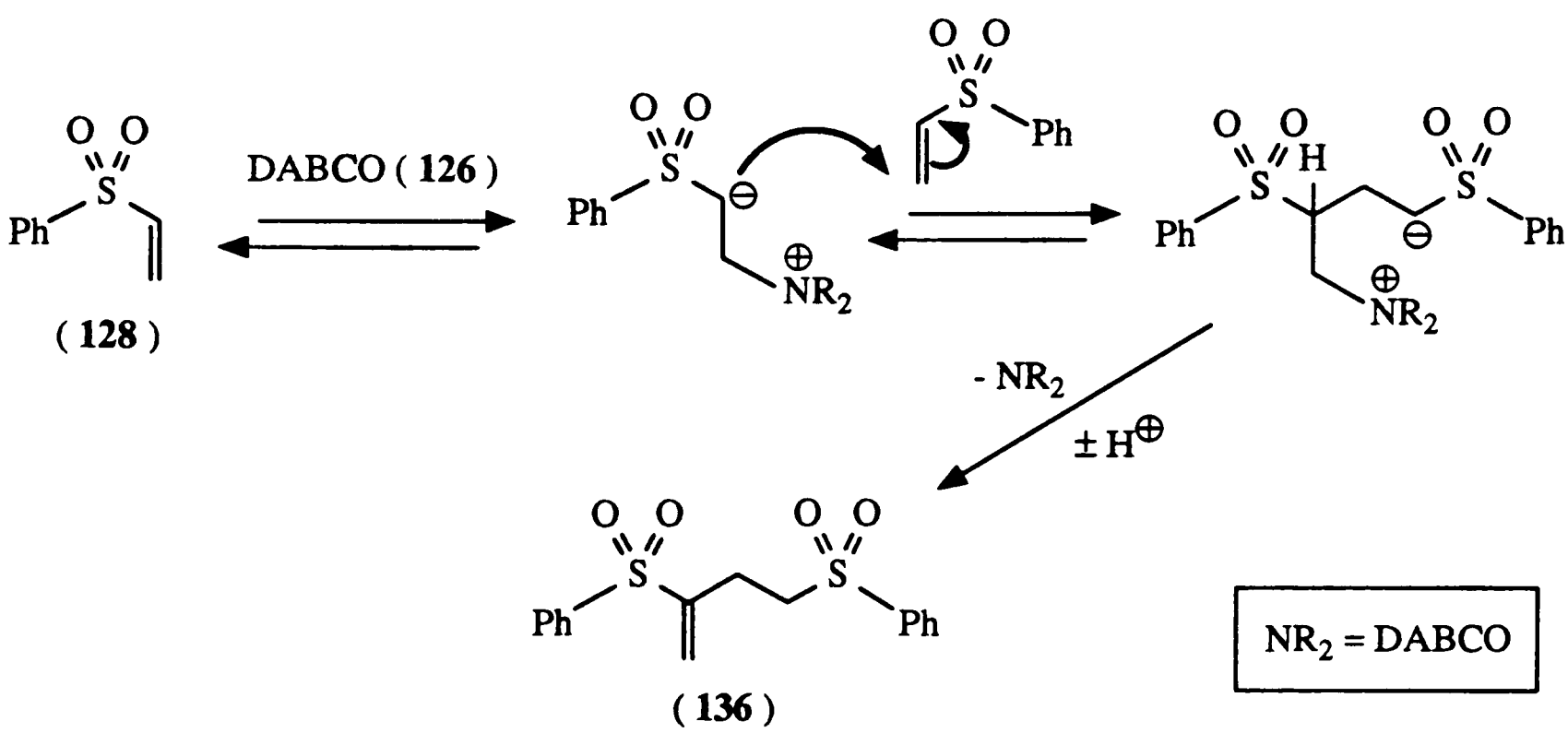
A number of points concerning the high pressure reaction deserve comment :

i) The reaction times are cut dramatically, e.g. in the case of the phenyl substituted hydroxysulphone, (**132**), from 3 weeks at ambient pressure[83] to just under 3 hours (Entry 4, Table 2.02).

ii) The high pressure reaction is high yielding. In most cases this is more so than the ambient pressure case e.g. 88 % compared to 66 % with only 50 % conversion reported by Hoffmann[84] for the preparation of (**130**) (Entry 2, Table 2.02).

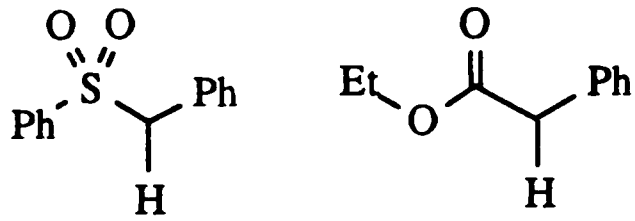
iii) The reaction time depended heavily on the reactivity of the aldehyde in use, with the longest time required for *p*-anisaldehyde in the formation of (**134**) (Entry 6, Table 2.02).

iv) A large excess of aldehyde was required, at least 5 equivalents in most cases, to obtain good yields. If less aldehyde was used then side product formation became a problem. This was especially true of less reactive aldehydes such as *p*-anisaldehyde when a side product, tentatively assigned as (**136**), was observed as a large component of the product mixture. This is believed to arise from the dimerisation of (**128**) (Scheme 2.05).



Scheme 2.05 - Possible side product formation in the high pressure preparation.

v) The reactivity of phenyl vinylsulphone (**128**) in the Baylis-Hillman reaction is much less than simple acrylates such as (**124**). This must, in part, be due to the differing abilities of the two activating groups to stabilise the intermediate carbanion in the α-position. This can be seen in the differing pK_a values of the α-protons in (**137**) and (**138**) (Figure 2.08).[89] Another contributing factor to the difference in reactivities is almost certainly the increased steric bulk of the intermediate anion in the case of the sulphone.



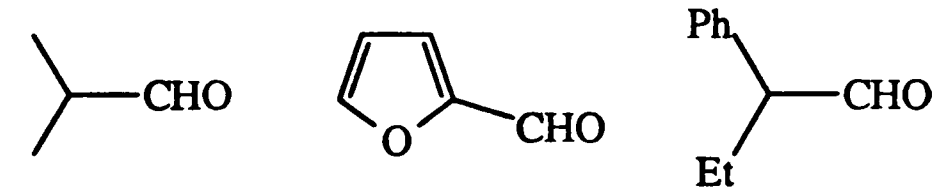
(**137**) (**138**)

Solvent = Me_2SO

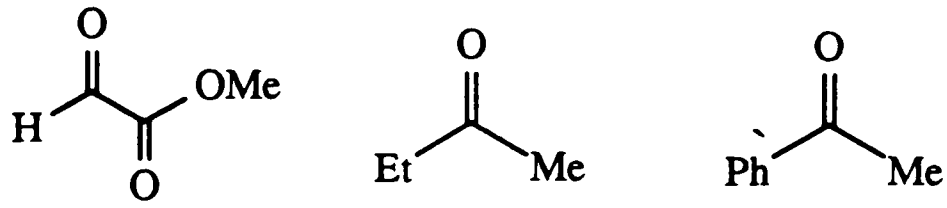
pK_a = 23.4 22.6

Figure 2.08 - A comparison of the pK_a 's of α-protons in sulphones and esters.[89]

In an attempt to extend the scope of the high pressure reaction, a number of other aldehydes, (**139**)- (**142**), and ketones, (**143**) and (**144**), were examined as starting materials (Figure 2.09). The results obtained, however, were disappointing.



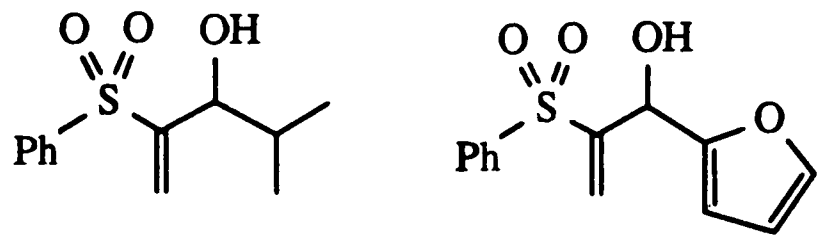
(**139**) (**140**) (*rac*)- (**141**)



(**142**) (**143**) (**144**)

Figure 2.09 - Additional aldehydes and ketones examined as starting materials for sulphone substrates.

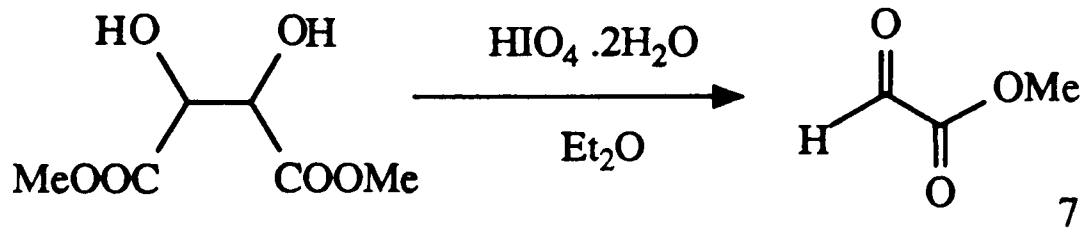
i-Butyraldehyde, (**139**), did react as expected but the reaction also produced a side product that proved inseparable from the desired product, (**145**). 2-Furfuraldehyde, (**140**), failed to give any of the desired product, (**146**), as only starting materials were isolated after 2 weeks at ambient pressure and only polymeric material formed after 1 h at 9 kbar. 2-Phenyl butyraldehyde, (**141**), gave a complex mixture of products by NMR, which contained mainly aldol-condensation products.



(**145**) (**146**)

Figure 2.10 - Inaccessible hydroxysulphones.

Methyl glyoxaldehyde, (**142**), had to prepared from tartaric acid, (**147**), in an oxidative cleavage of the central carbon-bond according to the literature[90] (Figure 2.11). Both the ambient pressure Baylis-Hillman reaction and the high pressure modification failed to give any of the desired product. It is possible that this is due to the fact that (**142**) exists in a polymeric form[90] even at ambient pressure and, as one would expect, this form is much less reactive.



(**147**) (**142**)

Figure 2.11 - The preparation of methyl glyoxaldehyde.[90]

The two ketones, (**143**) and (**144**), failed to react and only what was tentatively assigned as the sulphone dimer, (**136**), was observed by ^{1}H NMR after work-up.

2.05 Synthesis of Hydroxy Vinylsulphoxides

Since the high pressure synthesis of the sulphone substrates had been reasonably successful, it was decided to try to extend the method to the analogous sulphoxides and sulphides.

The reactivities of phenyl vinylsulphoxide, (**148**), and phenyl vinylsulphide, (**149**), it was realised, would be much less than the corresponding sulphone, (**128**), due to the lesser abilities of the sulphinyl and sulphenyl to stabilise α-carbanions. This is reflected in the pK_a's of the α-protons in (**150**) and (**151**).[89]

Figure 2.12 - Starting materials and comparison of pK_a values.[89]

A trial reaction was set up with approximately 1.5 mmol of (**148**), 4.5 mmol of benzaldehyde and 0.53 mmol of DABCO, (**126**), made up to 2 ml in volume with tetrahydrofuran to test the feasibility of the high pressure reaction with (**148**). ^1H NMR of the crude reaction mixture showed 40 % of the desired product formed after a period of 16 hours at 12 kbar. This was improved upon by increasing the time (22 h), temperature (30°C) and pressure (15 kbars) of the reaction as shown in Figure 2.14.

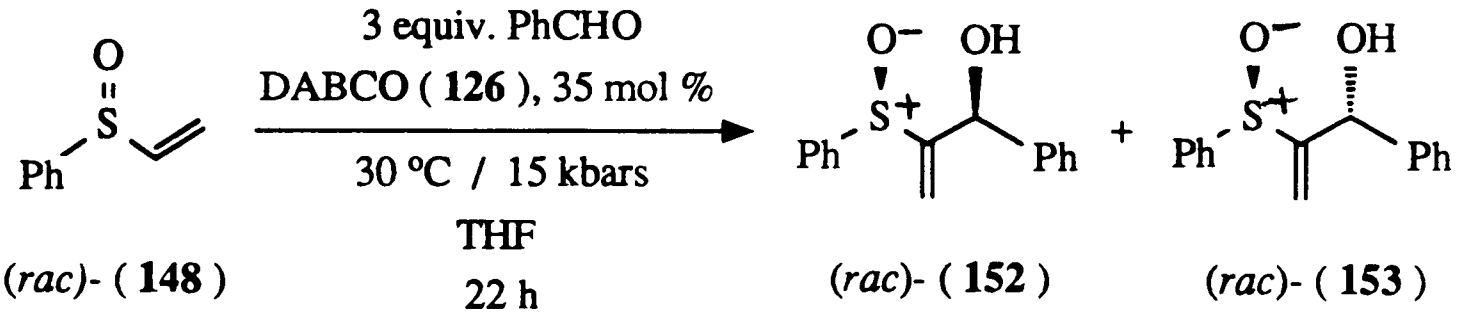
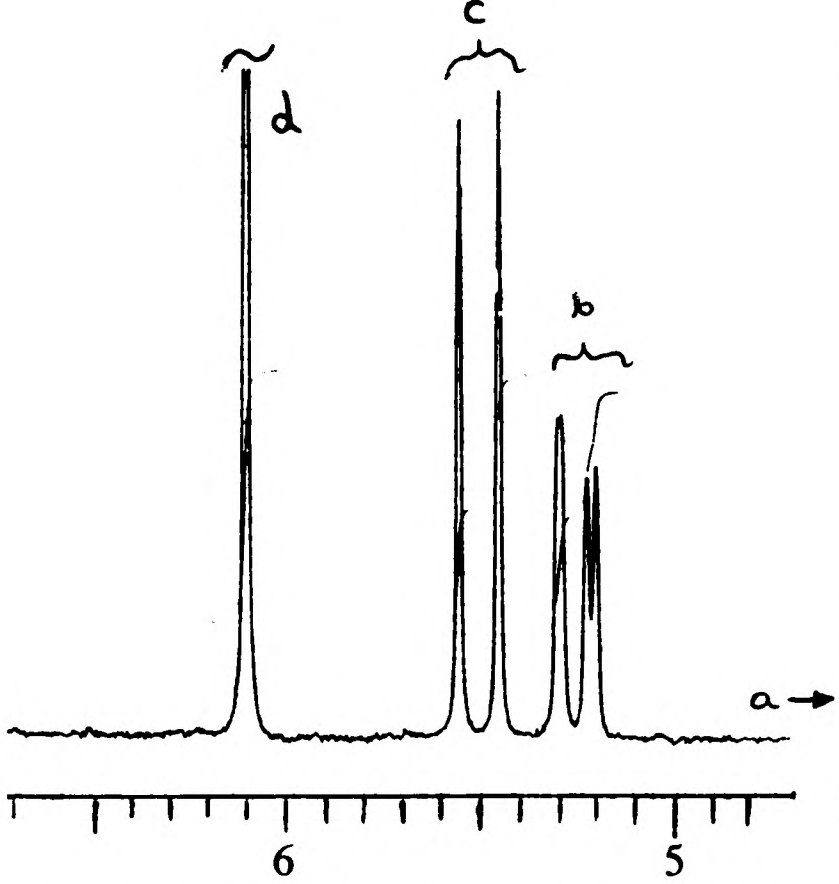
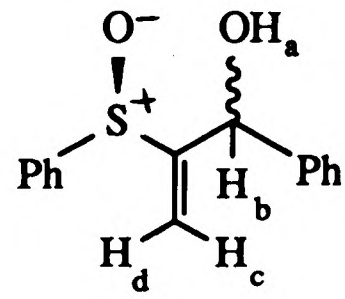


Figure 2.13 - The high pressure preparation of (**152**) and (**153**).

Optimum reaction conditions gave a 1:1 mixture of the two diastereomeric compounds, (**152**) and (**153**), in a combined yield of 80 %, after work-up involving column chromatography on silica gel (eluent system: hexanes/ethyl acetate - 7:3).

The two diastereomeric hydroxy vinylsulphoxides, (**152**) and (**153**), proved to be inseparable by both t.l.c. and column chromatography with a variety of solvent systems. A small sample of one of the diastereomers was obtained by repeated low temperature recrystallization from toluene. Although the benzylic proton and one of the vinylic protons of each of the diastereomers was distinct (Figure 2.14), it was not possible to say with any certainty which diastereomer was which.





(*rac*)-(**152**) + (*rac*)-(**153**)

Figure 2.14 - Part of the ^{1}H NMR(200 MHz, $CDCl_3$) of a mixture of (**152**) and (**153**).

MMX[86] molecular mechanics calculations were performed to model the ground state conformer of the (*R*,S**) diastereomer, hereinafter referred to as the *syn* isomer, and the (*R*,R**), or *anti*, diastereomer.

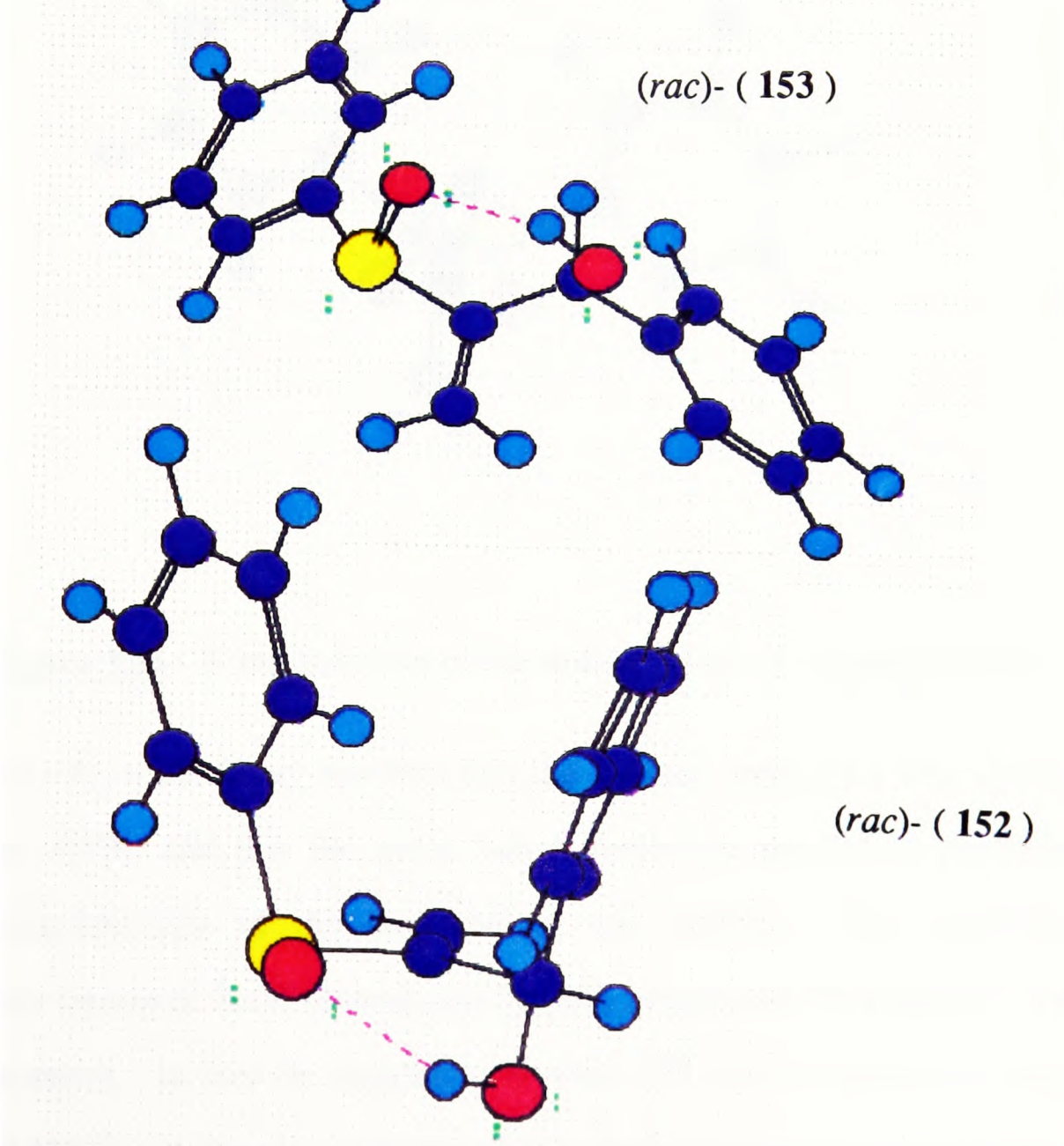


Figure 2.15 - The MMX[86] ground state conformers of the two diastereomers.

These calculations suggested that the *syn* diastereomer would show a larger proton coupling constant between the hydroxy proton, (H_a), and benzylic proton, (H_b), than the *anti* diastereomer. In the former case the hydroxy O-H and the benzylic C-H bonds are almost antiperiplanar (178°), while in the latter case the same two bonds form a dihedral angle of 55.5° (Figure 2.15). The isolated diastereomer displayed a coupling constant, J_{ab}, of 2.6 Hz compared to 5.5 Hz in the second isomer. This led to the conclusion that the diastereomer that had preferentially crystallized out was the *anti* - diastereomer.

The structure of the isolated diastereomer was determined by X-ray crystallography (courtesy of D. Ando, S.E.R.C. Crystallographic Service) and a representation of the result is shown in Figure 2.16. A full summary of the crystal structure can be found in Appendix A.

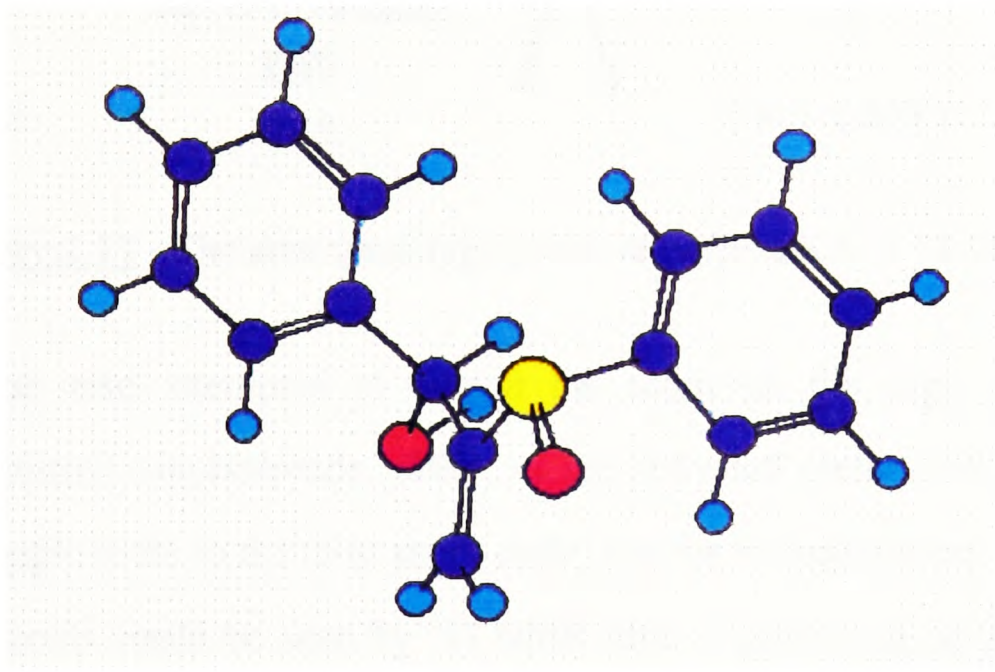


Figure 2.16 - X-ray Structure of the isolated hydroxy vinylsulphoxide.

It clear from the X-ray structure that the isolated compound was indeed the *anti* diastereomer, **(153)**, and that the initial MMX molecular mechanics prediction of the relative stereochemistry of the two centres was correct. The prediction of an intramolecular hydrogen bond between the hydroxy proton and the sulphinyl oxygen was, however, incorrect. In fact the separation between OH and SO groups in neighbouring molecules, 1.823 Å, is indicative of intermolecular hydrogen bonding in the solid state.

The bulk of the two diastereomers was finally separated using the HPLC facilities

of GLAXO, in Greenford. A 1 g sample of a 1:1 mixture of (**152**) and (**153**) was chromatographed in 50 mg portions on a LiChrosorb Diol packed column eluting with heptane/ethanol (9:1). Three fractions were collected, since baseline separation was not obtainable. The first fraction proved to be pure *anti*-diastereomer, (**153**), as isolated by crystallization. The second fraction isolated was a mixture of the two diastereomers, while the third fraction collected was a 10:1 mixture of *syn*, (**152**), to *anti*, (**153**), as determined by 300 MHz ^{1}H NMR.

Attempts to replace the aldehyde in the high pressure reaction of phenyl vinylsulphoxide with acetaldehyde proved fruitless (Figure 2.17). Only starting materials were recovered after observing the same protocol as for the reaction with benzaldehyde.

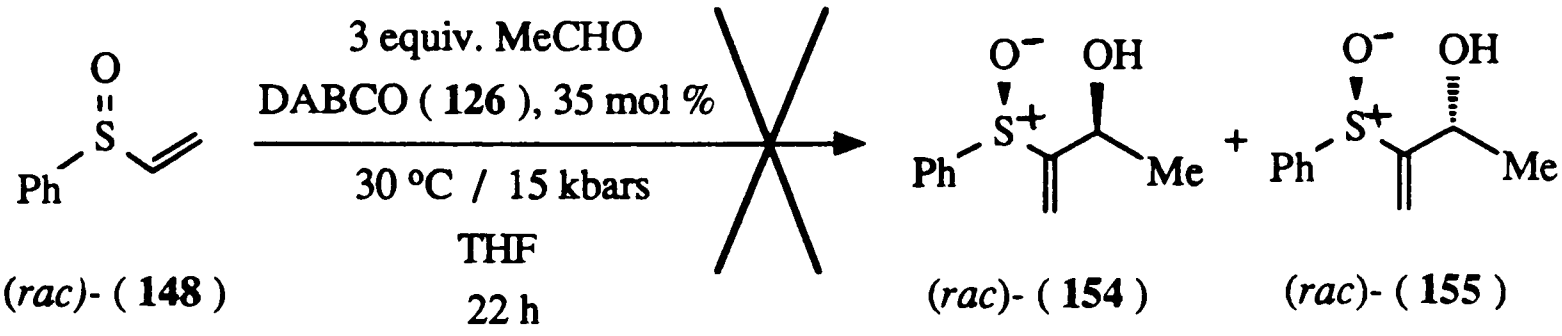


Figure 2.17 - The attempted high pressure preparation of (**154**) and (**155**).

It was also attempted to extend the scope of the high pressure reaction to encompass phenyl vinylsulphide, (**160**), as the activated olefin component. This would provide a simple route to the third set of substrates for hydrogenation. Unfortunately, only starting materials could be seen by ^{1}H NMR after a prolonged period of time under 12 kbars of pressure.

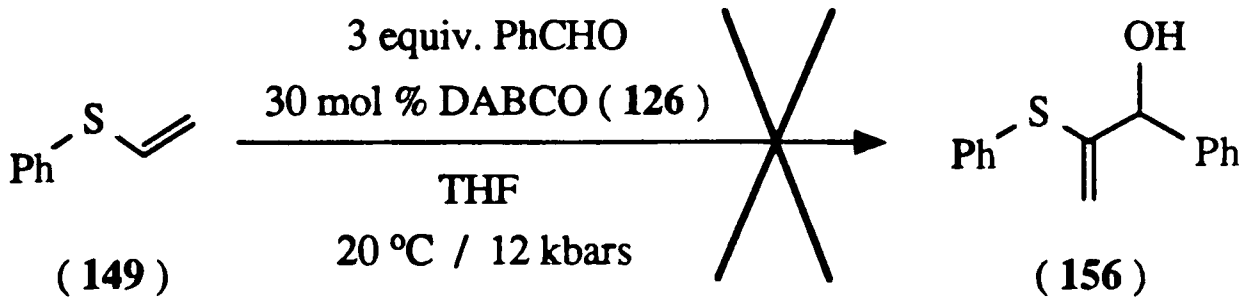
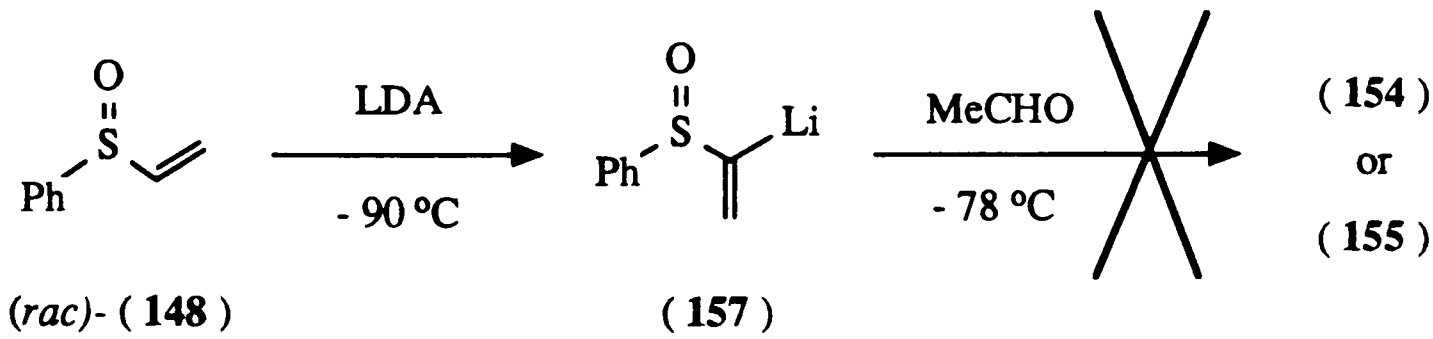


Figure 2.18 - An attempted preparation of sulphide substrate (**156**).

Since it had proved impossible to synthesise the methyl substituted hydroxy vinylsulphoxides, (**154**) and (**155**), or the hydroxy vinylsulphide, (**156**), by the high pressure modification of the Baylis-Hillman reaction, an alternate route was sought.

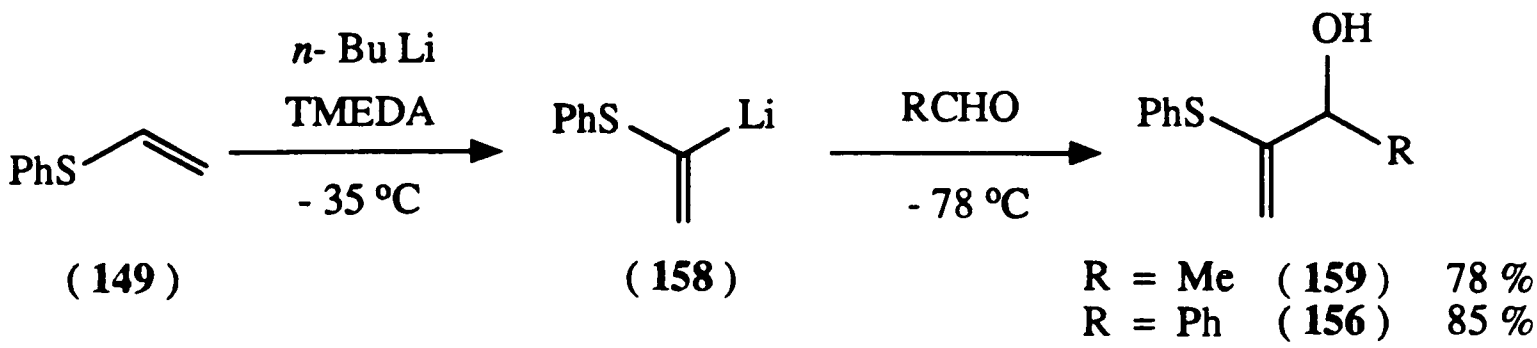
One route to (**154**) and (**155**) which was investigated, involved lithiation of phenyl vinylsulphoxide, (**148**), with lithium di-*iso*propylamide (LDA) in tetrahydrofuran[91] followed by the quenching of the lithio-compound with an aldehyde (Scheme 2.06). Although this gave acceptable yields with benzaldehyde, showing that formation of the anion was not a problem, it proved completely ineffective with acetaldehyde and only starting material was recovered after several attempts.



Scheme 2.06 - A failed synthesis of (**154**) and (**155**).

The route of choice was one which involved the synthesis of a hydroxy vinylsulphide *via* trapping of the lithiated (**149**) with an aldehyde, followed by selective oxidation to the desired compound. This synthesis had the added virtue of preparing the hydroxy vinylsulphides *en route*.

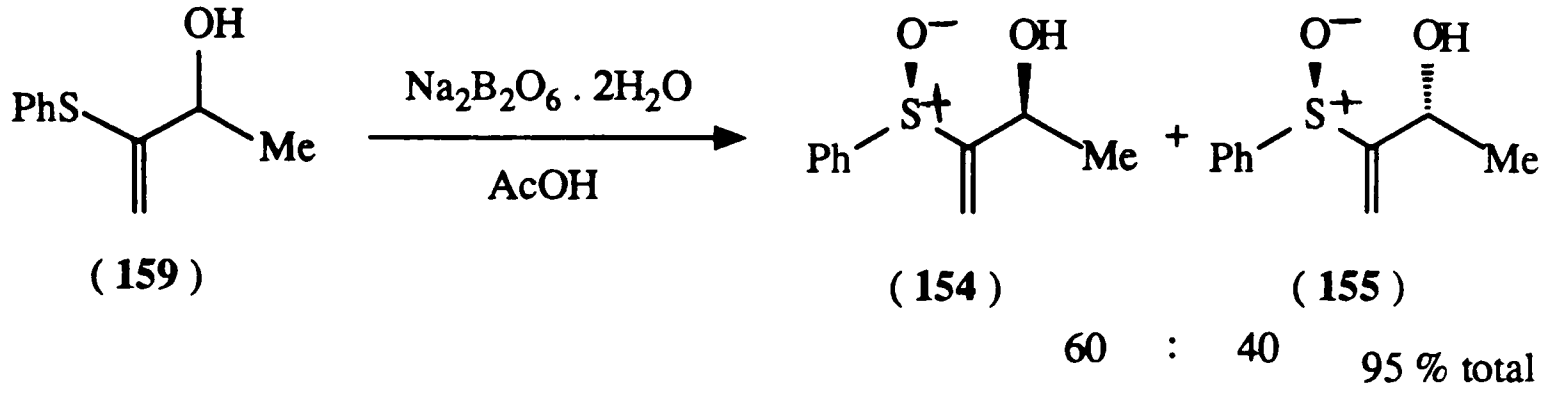
Two sulphide substrates were synthesised from phenyl vinylsulphide, (**149**), by lithiation[92] and subsequent trapping of the vinyl lithium with an aldehyde[92] in good overall yield as detailed in Scheme 2.07. Both products, which were viscous oils, were characterised by I.R. and ^{1}H NMR spectroscopy.



Scheme 2.07 - The preparation of (**159**) and (**156**).

Trial oxidations of (**159**) with *m*-chloroperbenzoic acid (*m*CPBA) in chloroform[93] were discouraging, giving low yields and a large amount side products. The reasons for this were not investigated since another simpler procedure was found. Excellent results were obtained when the method of McKillop[94] was employed. This involved stirring the

sulphide, (**159**), with 1 equivalent of sodium perborate in glacial acetic acid at 50°C for 6 hours (Figure 2.19). The products were recovered by removal of the solvent *in vacuo* and column chromatography on silica gel with hexanes/ethyl acetate (7:3) as eluent. The product mixture, isolated in a combined yield of 95 %, contained two diastereomeric sulphoxides, (**154**) and (**155**), in a 3:2 ratio as determined by ^{1}H NMR.



(**159**) (**154**) (**155**)

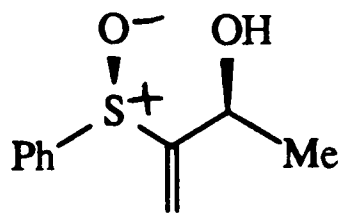
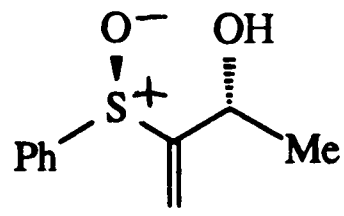
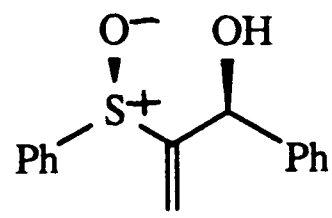
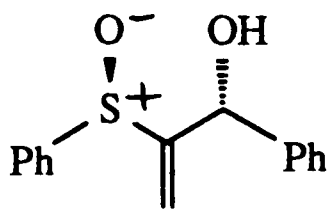
60 : 40 95 % total

Figure 2.19 - The oxidation of (**159**) to give (**154**) and (**155**).

As with diastereomeric (**152**) and (**153**), these two diastereomers, (**154**) and (**155**) proved inseparable by normal chromatographic methods and HPLC had to be used. A 1 g mixture of (**154**) and (**155**) was separated in 50 mg portions at GLAXO, Greenford, using a 9:1 heptane/methanol solvent mixture. Again, baseline separation was not obtainable under all the HPLC conditions examined, so three fractions were collected on each run. Fortunately, the first and last fraction contained pure (**154**) and pure (**155**) respectively, while the middle fraction contained a mixture of the two. The relative configuration of the two chiral centres of (**154**) and (**155**) was assigned by comparison of the ^{1}H NMR spectra, and coupling constants therein, with those of (**152**) and (**153**).

Unlike the mixture of diastereomers, which was a colourless oil, the two hydroxyvinyl methylsulphoxides, (**154**) and (**155**), were both white crystalline solids. Both (**154**) and (**155**) were fully characterised including M.P., I.R., ^{1}H and ^{13}C NMR, elemental analysis and mass spectroscopy. A summary of some of the properties and yields of the hydroxy vinylsulphoxides prepared is shown in Table 2.03.

In summary, the high pressure modification of the Baylis-Hillman reaction of sulphur substituted olefins with aldehydes can be very successful, giving good yields in acceptable time periods. The reaction is, however, only useful as a preparative tool with phenyl vinylsulphone as the activated diene component. The products in this case were generally easily separated from the side products formed during reaction.

COMPOUND	M.P. (°C)	I.R. (cm^{-1}) (O-H stretch)	YIELD[†] (%)
 (**154**)	44-7	3367	30[‡]
 (**155**)	45-50	3373	26[‡]
 (**152**)	67-70 *	3309 *	26[*‡‡]
 (**153**)	106-8	3400	24[‡‡]

Notes :

[†]indicates overall yield after prep. HPLC.

[*]indicates 9:1 mixture of diasteromers

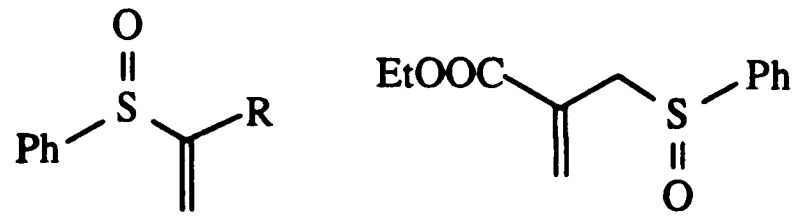
[‡]yield from phenyl vinylsulphide

[‡‡]yield from phenyl vinylsulphoxide

Table 2.03 - A summary of some of the properties of the hydroxy vinylsulphoxides.

2.06 Synthesis of Simple Unsaturated Sulphoxides

Three additional sulphoxide substrates were chosen for preparation : two vinylic, (**160**) and (**161**), and one allylic sulphoxide, (**162**), as shown in Figure 2.16. These additional potential substrates were chosen for their simplicity and the consequent ease of preparation.

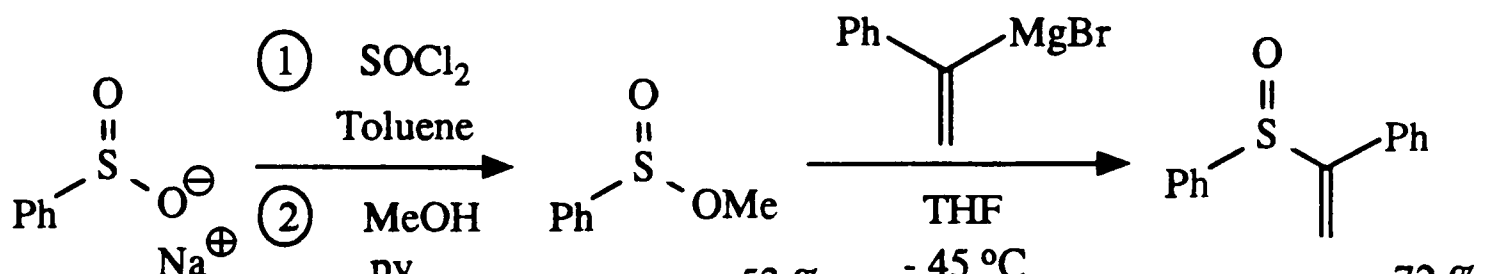


R = Ph (**160**)
R = Hx^n (**161**)

(**162**)

Figure 2.20 - Additional sulphoxide substrates.

α-Phenylsulphinyl styrene, (**160**), was prepared by the action of α-styryl magnesium bromide on (**164**) in a protocol similar to those reported for other vinylsulphoxides[41, 95] The methodology involved, which gave α-phenylsulphinyl styrene, (**160**), in an overall yield of 72 %, is outlined in Scheme 2.08. Although it was once reported that copper reagents could give better results in these reactions,[96] it has also since been reported that no advantage can be gained by their use.[95]



(**163**) (**164**) (**160**)

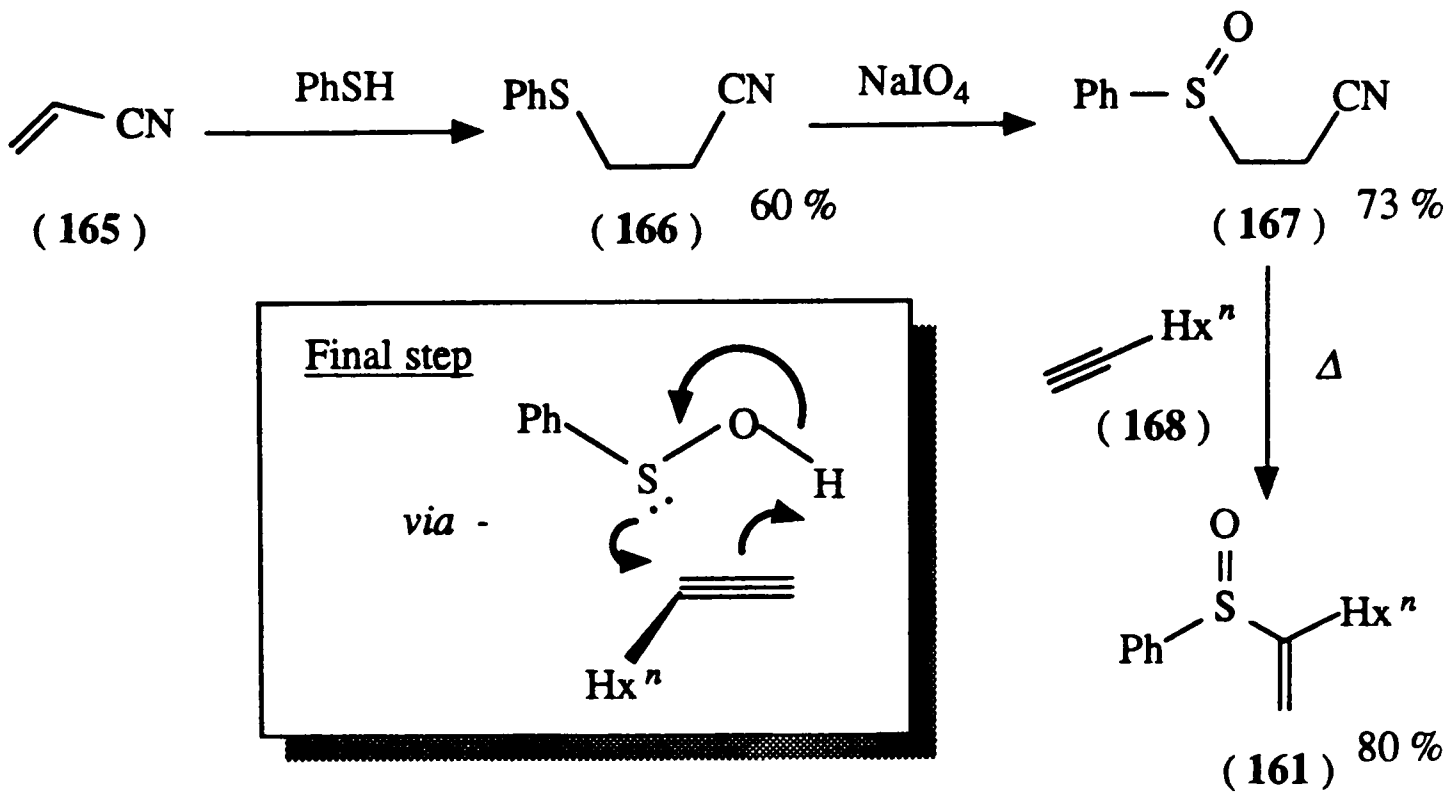
Scheme 2.08 - The synthesis of sulphoxide substrate (**160**).

The second vinyl sulphoxide, (**161**), was prepared according to Bell and co-workers[97] as shown in Scheme 2.09. The synthesis took the form of three steps -

1) The addition of thiophenol to acrylonitrile, (**165**), to give 1-cyano-2-phenylsulphenyl ethane, (**166**), in a yield of only 60 % after distillation under reduced pressure.

2) The oxidation of the addition compound, (**166**), afforded 1-cyano-2-phenyl-sulphinyl ethane, (**167**), as a white crystalline material in a yield of 73 %.

3) Finally, the pyrolysis of (**167**) in refluxing 1-octyne, (**169**), to give the final product, (**161**), in an overall yield of 35 %, after chromatography on silica gel eluting with a 3:2 mixture of light petroleum/ethyl acetate. This final step occurs *via* a [2,3] cycloaddition of phenylsulphenic acid, liberated from (**167**), to the alkyne.



Scheme 2.09 - The synthesis of 2-sulphinyl octene (**161**).

The synthesis of the allylic sulphoxide, (**162**), required the preparation of two starting materials, which were not commercially available, phenylsulphenyl chloride, (**169**), and 2-carboxyethyl propen-3-ol, (**170**). These two starting materials were each prepared in good yield by simple one step literature procedures[98, 99] as shown in Figure 2.17.

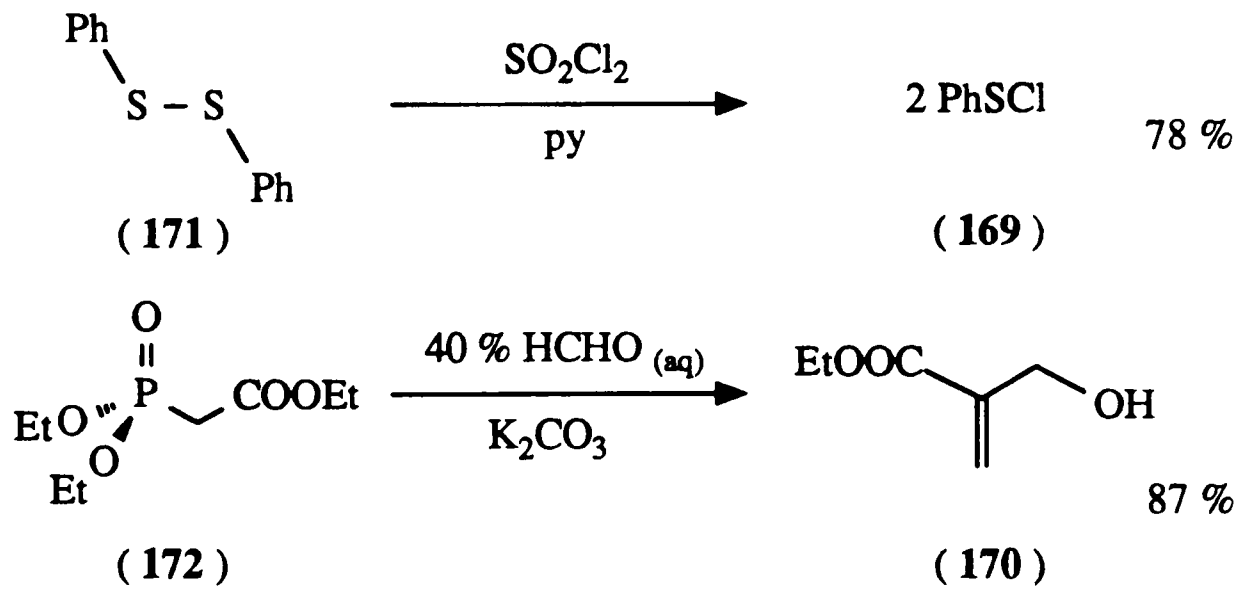
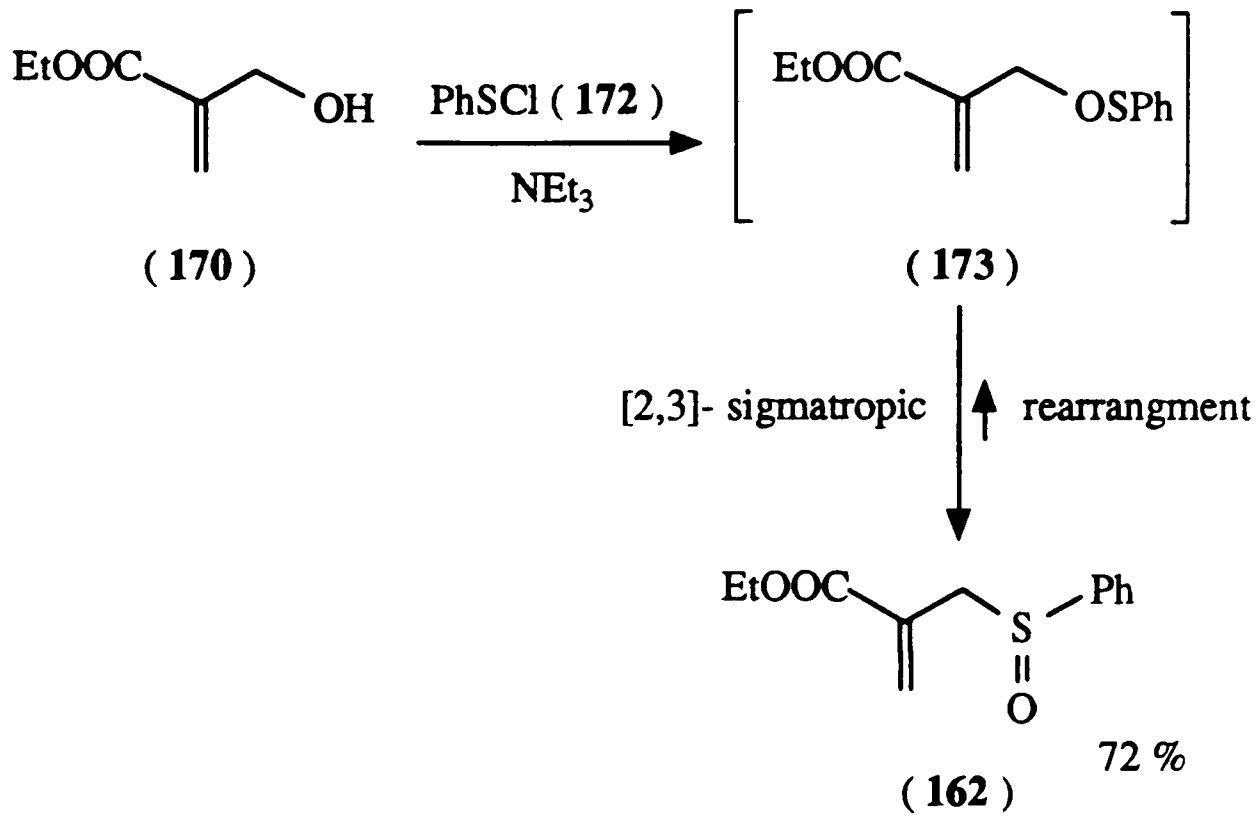


Figure 2.21 - The preparation of two starting materials.

The synthesis of the allylic sulphoxide, (**162**), then proceeded with the preparation of sulphenate of (**170**), (**173**), and its *in situ* [2,3]-sigmatropic rearrangement.[100] This gave the final product, (**162**), in a yield of 72 % after column chromatography on silica gel with hexanes/ethyl acetate (1:1) as eluent (Scheme 2.10).



Scheme 2.10 - The synthesis of allylic sulphoxide (**162**).

This final step takes the form of an equilibrium, the position of which is dependent on the solvent.[101] In polar solvents and solvents capable of forming hydrogen bonds, the predominant constitutional isomer of the compound is that shown for (**162**). This is due to the fact that these solvents can interact with the S=O (sulphoxide) dipole more favourably than with the S-O (sulphenate) dipole and thus stabilise the former over the latter.

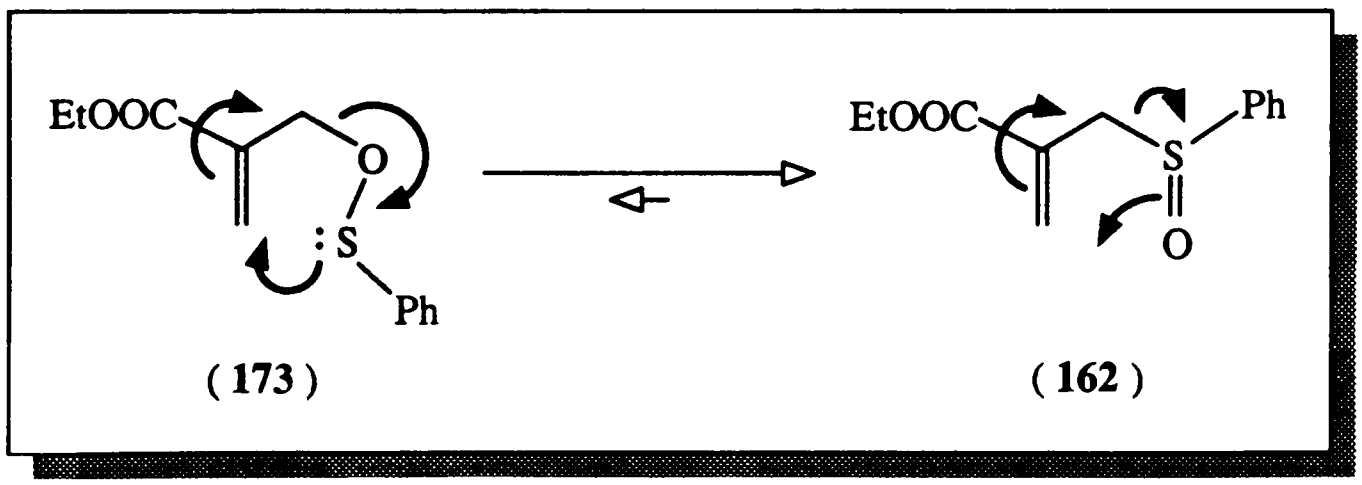


Figure 2.22 - The proposed mechanism for the sulphenate - sulphoxide, (**174**) - (**162**), equilibrium.[100, 101]

The allylic sulphoxide, (**162**), was purified by column chromatography on silica gel with hexanes/ethyl acetate (1:1) as eluent. It was characterised by I.R., ^{1}H and ^{13}C NMR spectroscopy, all of which were in agreement with the proposed structure.

2.07 Synthesis of Additional Substrates

Two hydroxyacrylates, (**175**) and (**176**), were synthesised for use in kinetic analysis presented in Chapter 4. These substrates were used for both comparison with the substrates synthesised earlier and for calibration experiments.

The two additional substrates, (**175**) and (**176**), were prepared in good yield under standard Baylis-Hillman conditions,[81] as indicated in Figure 2.23. Purification involved distillation under reduced pressure for (**175**) and recystallization from hexanes/diethyl ether for (**176**).

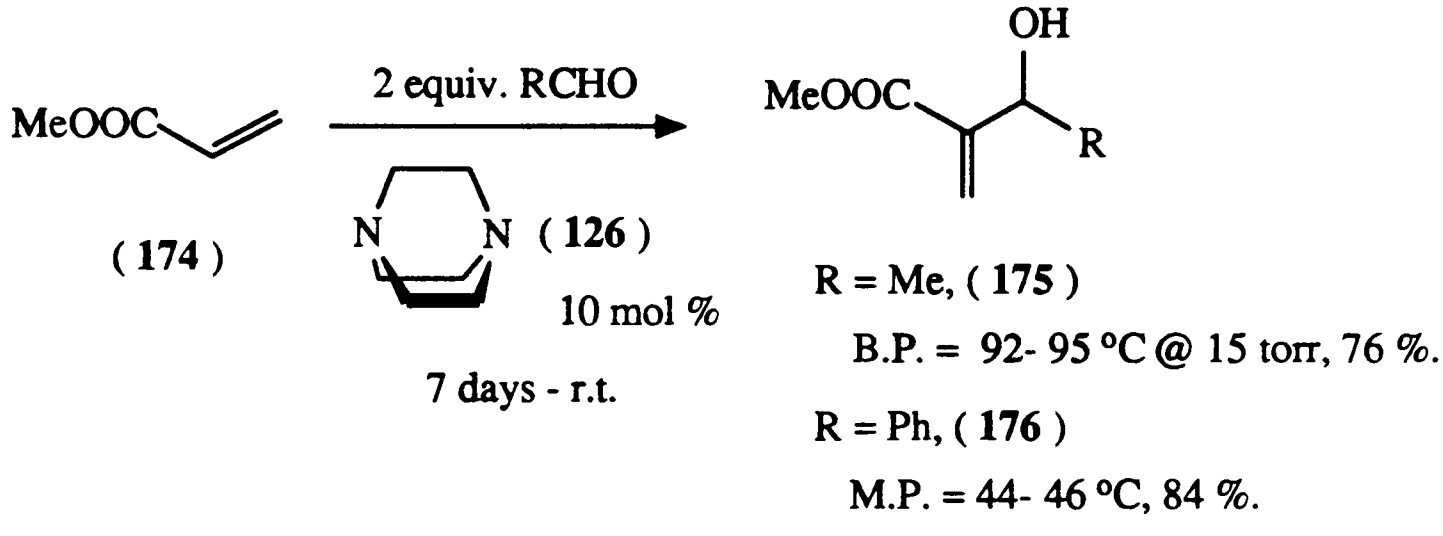


Figure 2.23 - Preparation of additional substrates, (**175**) and (**176**).

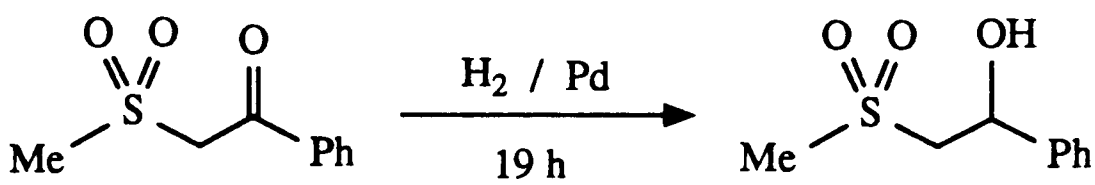
Results and Discussion

Hydrogenation of Substrates

3.01 Introduction

The use of sulphur chemistry in organic synthesis has for the major part excluded hydrogenation. This may be due to two facts: 1) sulphur compounds are known to poison heterogeneous hydrogenation catalysts[102]; and 2) carbon-sulphur bonds are labile towards transition metals, for example the desulphurization of thiols, thioacetals, sulphides, sulphoxides, etc. occurs readily with Raney nickel.[103]

Surprisingly, perhaps, sulphones and sulphoxides can be reduced to the corresponding sulphides with hydrogen and a palladium-on-carbon catalyst.[104] This may have caused problems for Field and co-workers[105] in the reduction of the β-keto sulphone, (**177**), as shown in Figure 3.01. It was reported that the catalyst was poisoned during the course of the reaction and had to be replenished.[105]



(**177**) (*rac*)- (**178**)

Figure 3.01 - Field's hydrogenation of a β-keto sulphone.[105]

Homogeneous catalysts, in contrast, have been reported to be much less susceptible to poisoning by sulphur compounds[102] and thus should give better results in the hydrogenation of the latter.

3.02 Heterogeneous Hydrogenation of Unsaturated Sulphones

The catalyst with which to investigate the heterogeneous hydrogenation chemistry of the previously prepared unsaturated sulphones was chosen to be 10 % palladium on carbon. A 50 mg sample of the phenyl substituted hydroxy vinylsulphone, (**132**), was

dissolved in dry degassed methanol and added to 5 mg of a 10 % palladium on carbon catalyst in a Schlenk tube and the suspension was degassed with three freeze-pump-thaw cycles. The argon atmosphere inside the Schlenk tube was replaced with hydrogen of greater than 99.97% purity at ambient pressure and the Schlenk tube was connected to a gas burette. Reaction, as monitored by gas uptake, was very fast, taking only 10 minutes. Work-up involving filtration through a celite plug to remove the catalyst residue, and removal of the solvent *in vacuo* gave a mixture of products with a recovery of 98 % in total. Three major products were observed : the two diastereomeric β-hydroxy sulphones, (**179**) and (**180**), and what was tentatively assigned as the dehydroxylated sulphone, (**181**) (Figure 3.02).

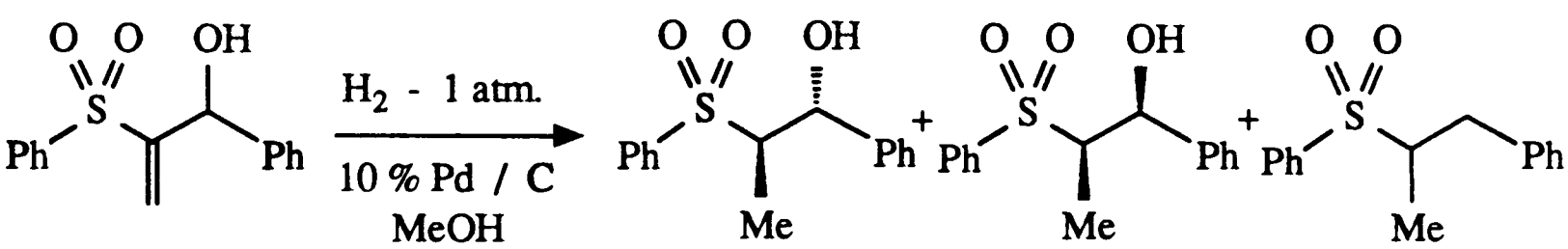
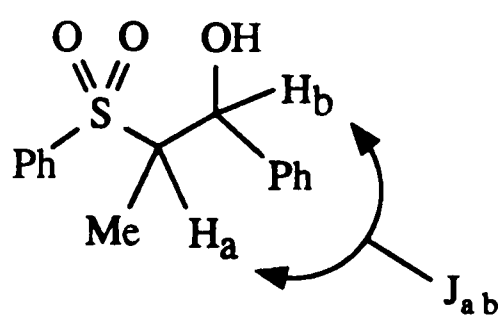


Figure 3.02 - The heterogeneous hydrogenation of hydroxy sulphone (**132**).

The two diastereomeric β-hydroxy sulphones, (**179**) and (**180**), were readily distinguishable in their ^{1}H NMR spectra. The positions of the benzylic proton, H_b differed by over 0.5 p.p.m. (δ 4.96 and 5.53 p.p.m.) and characteristically the coupling constants between H_b and the hydrogen α to the sulphonyl group H_a were 9.2 Hz and 1.8 Hz respectively, (Figure 3.03).

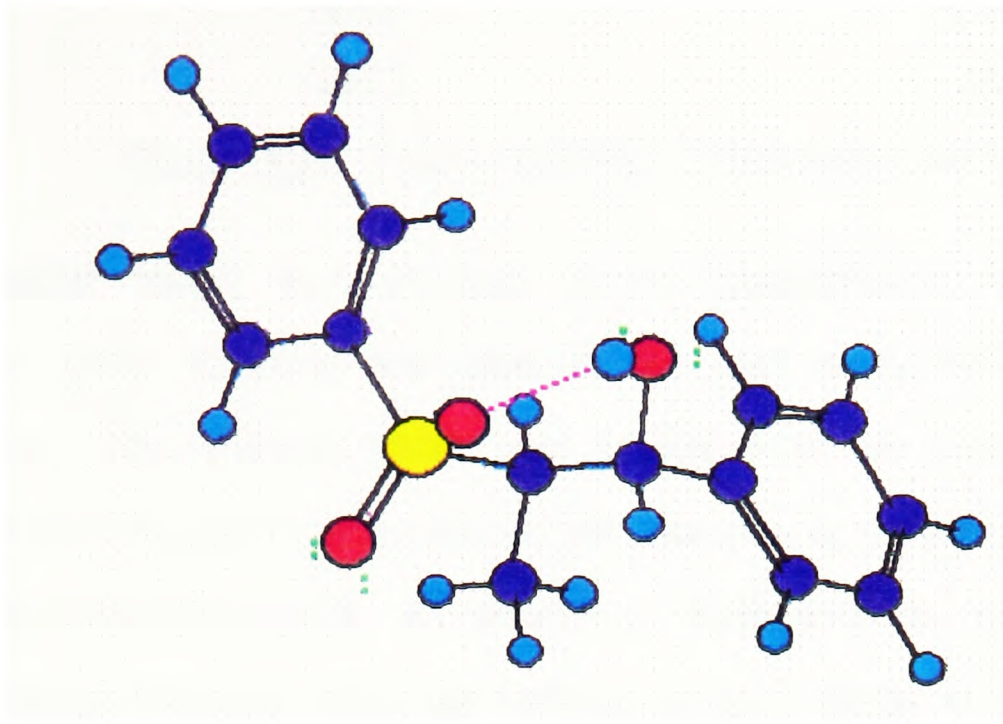


(**179**) J_{ab} = 9.2 Hz

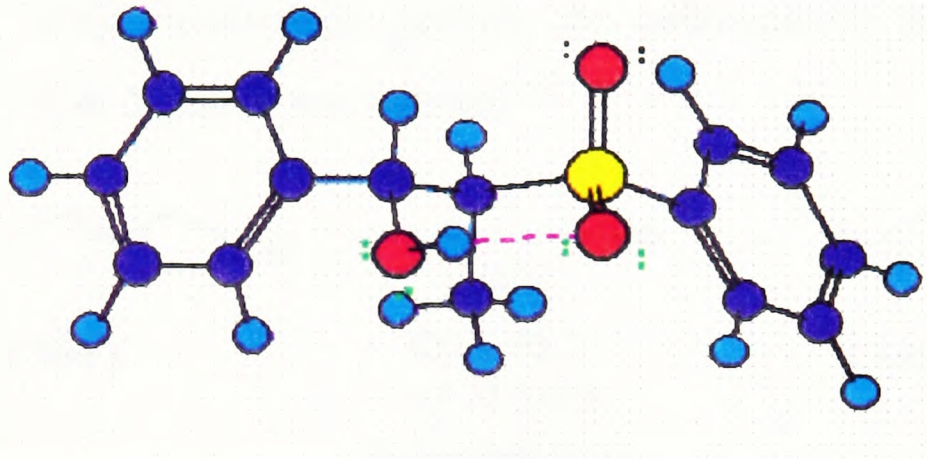
(**180**) J_{ab} = 1.8 Hz

Figure 3.03 - Selected coupling constants in (**179**) and (**180**).

MMX[86] molecular mechanics calculations on both diastereomers were carried out on a P.C.. These predicted that the two protons H_a and H_b would be almost antiperiplanar in the most stable conformer of **(179)**, whereas in the most stable conformer of **(180)** the two carbon-hydrogen bonds would form a dihedral angle of around 60° (Figure 3.04).



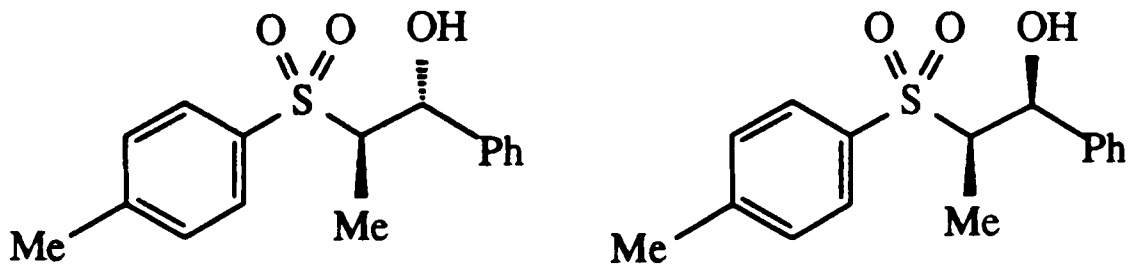
(179)



(180)

Figure 3.04 - MMX[86] modelling results with **(179)** and **(180)**.

The calculations predicted that the *threo*-diastereomer, **(179)**, would have the larger coupling constant. This is in accordance with the coupling constants of 9.0 Hz and 1.5 Hz for the similar compounds, **(182)** and **(183)**, reported by Truce and Klinger[106] (Figure 3.05).

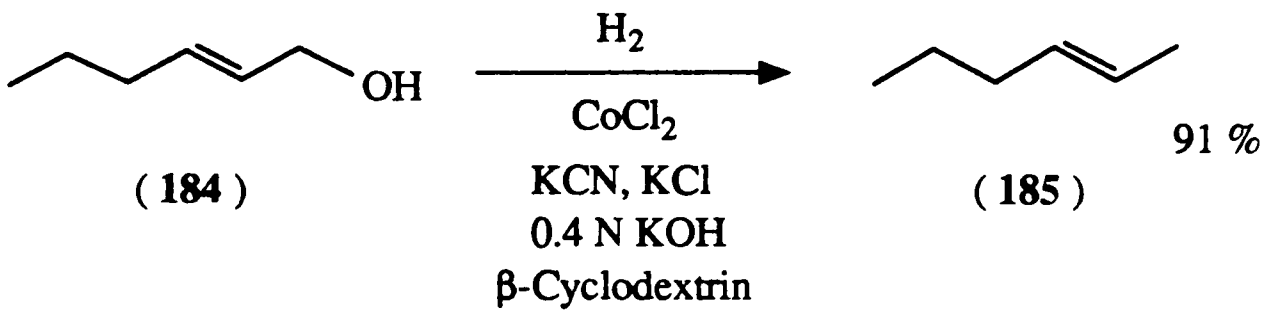


threo (**182**) *erythro* (**183**)

Figure 3.05 - Truce and Klinger's β-hydroxy sulphones.[106]

Similar results were obtained in the hydrogenation of 2-(phenylsulphonyl)-buten-3-ol, (**129**). Reaction was faster in this case taking only 5 minutes to go to completion. The products, which were analogous to the products from (**132**), were recovered in 97 % yield in approximately the same ratio as those from (**132**).

The dehydroxylation accompanying hydrogenation is not uncommon in organometallic chemistry where the hydroxy group is allylic or benzylic. Alper[107] has demonstrated that a cobalt catalyst can efficiently dehydroxylate allylic alcohols as shown in Figure 3.06. Rather surprisingly perhaps, the carbon-carbon double bond remains intact, although 4 % of 1-hexene was isolated.[107]



(**184**) (**185**)

Figure 3.06 - The dehydroxylation of (*E*)-2-hexen-1-ol.[107]

3.03 Hydrogenation of Unsaturated Sulphones with Achiral Rhodium Catalysts

It was hoped to obtain better selectivity than was observed with the heterogeneous system by progressing to homogeneous catalysts. It was also hoped that this would avoid the problem of dehydroxylation of the product.

Samples of 40 mg of the seven unsaturated sulphones were examined under identical hydrogenation conditions. Each sample was dissolved in 1 ml of dry degassed methanol together with 2 mol % of the (dppb)rhodium(I) catalyst precursor, (**105**), in a Schlenk tube under an argon atmosphere. The solution, which was completely

homogeneous, was then subjected to four freeze-pump-thaw cycles and finally the atmosphere in the Schlenk tube replaced with hydrogen. A clean, moderately fast hydrogenation of all the sulphone substrates, (**129**)- (**135**), as judged by gas uptake, ensued at ambient temperature and pressure. Hydrogenation of the substrates was complete in under two hours in all cases.

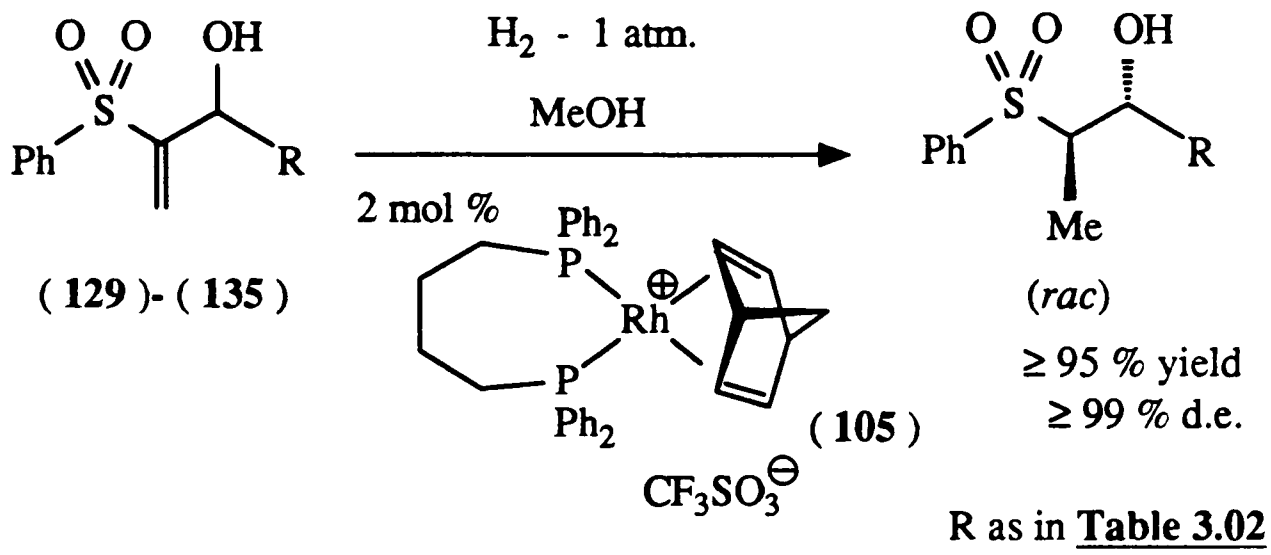


Figure 3.07 - Homogeneous hydrogenation of hydroxy sulphones (**129**)- (**135**).

The hydrogenation of the hydroxy vinyl sulphones was also carried out using dry degassed dichloromethane as solvent. The reaction conditions were otherwise identical to the hydrogenations carried out in methanol.

Work-up involving removal of the solvent *in vacuo*, trituration with hot diethyl ether followed by evaporation of the ether, gave near quantitative recovery of product in each case, except two, (**189**) and (**191**). In both the latter cases a quantity of the product precipitated from solution and the rest was recovered by reducing the volume of solution and cooling to -20°C.

Analytically pure samples of the products were obtained by recrystallization from warm diethyl ether.

All of the products were characterised by M.P. (where applicable) ^{1}H and ^{13}C NMR and I.R. spectroscopy. The new compounds, as indicated by an asterisk in Table 3.01, prepared by this method were additionally characterised by elemental analysis and mass spectroscopy.

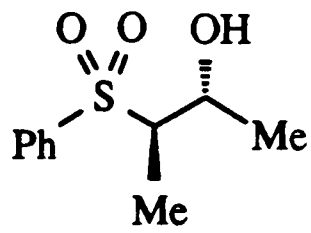
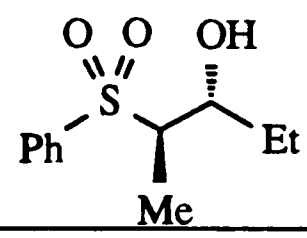
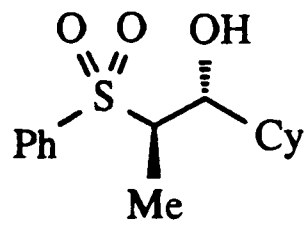
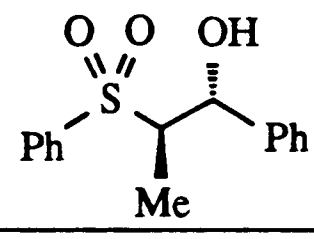
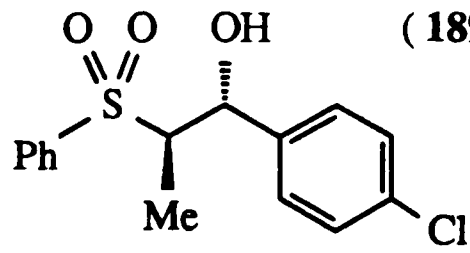
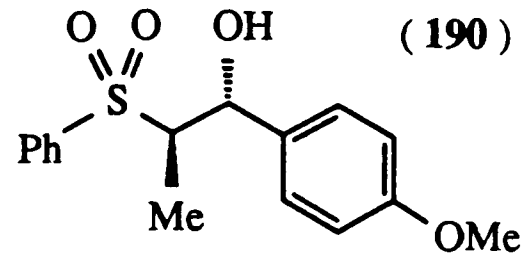
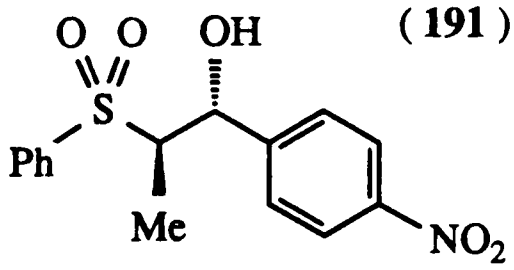
ENTRY	PRODUCT	M.P. (°C)	I.R. (cm^{-1}) (O-H stretch)	YIELD (%)
1	 (**186**)	OIL	3503	98
2*	 (**187**)	OIL	3505	98
3*	 (**188**)	101- 3	3515	97
4	 (**179**)	121	3482	98
5*	 (**189**)	176- 7	3481	97
6*	 (**190**)	86- 9	3490	98
7*	 (**191**)	175- 8	3479	95

Table 3.01 - Summary of products from homogeneous hydrogenation of hydroxy sulphones (**129**)- (**135**).

All of the β-hydroxy sulphone products showed evidence of hydrogen bonding of the hydroxyl group in their I.R. spectra, taken as neat films or potassium bromide discs. The O-H bond stretching frequencies ranged from 3515 cm^{-1} in the case of (**188**) to 3479 cm^{-1} in the case of (**191**). This is in accord with the results of molecular mechanics calculations performed on the unsaturated precursors presented in Chapter 2, and with the results of similar calculations with (**177**) and (**178**) presented earlier in this Chapter.

Measurement of the diastereoselectivity for each substrate involved dissolving a 10 mg sample of the product to be examined in 1 ml of deuterochloroform ($CDCl_3$) and taking the ^1H NMR spectrum at 500 MHz. Acquisition was continued until a sufficient signal to noise ratio was obtained. This was generally achieved after 200 to 300 scans had be acquired. A ^{13}C satellite peak of the newly formed methyl group of the major diastereomer was then integrated against the newly formed methyl group of the minor diastereomer. This protocol was necessary to allow integration of peaks of similar intensity from the respective isomers.

The diastereomeric excesses (d.e.'s) of the hydrogenation of the unsaturated sulphones in methanol were high in all seven cases. All the d.e.'s were found to be greater than 99 % as determined by the method outlined above. Individually, however, the selectivity obtained with the methyl and ethyl substituted hydroxy vinylsulphones, (**129**) and (**130**), was slightly lower than that of the other substrates.

Using dichloromethane as solvent the reaction was found to be slightly more stereoselective. In each case the d.e.'s were found to be greater than 99.5 %. This trend towards greater stereoselectivity in non-coordinating solvents has been reported for the homogeneous hydrogenation of other allylic alcohols.[71]

The selectivities obtained in the hydrogenation of the vinylsulphones in the two solvent systems are summarised in Table 3.02.

ENTRY	R	PRODUCT	D.E. (%) MeOH	D.E. (%) CH_2Cl_2
1	Me	(**186**)	99	99.7
2	Et	(**187**)	99	> 99.5
3	Cy	(**188**)	99.5	> 99.5
4	Ph	(**179**)	99.5	99.7
5	4-ClC_6H_4	(**189**)	99.5	99.7
6	4-$MeOC_6H_4$	(**190**)	99.5	99.7
7	4-$NO_2C_6H_4$	(**191**)	99.3	99.5

Table 3.02 - Summary of diastereoselectivities of homogeneous hydrogenation of hydroxy sulphones (**129**)- (**135**).

This preference for the *threo*-diastereomer in the hydrogenation of unsaturated sulphones (**129**)-(**135**) can be rationalised in the same manner as that of the hydroxy acrylates and similar substrates have been previously.[71]

Firstly, the substrate is thought to chelate to the metal centre through the carbon-carbon double bond and the oxygen of the hydroxy group,[71] in an analogous manner to the binding of the dehydroamino acids and similar compounds to rhodium[23] and iridium complexes.[23] The two faces of the carbon-carbon double bond are then made inequivalent by the presence of the secondary alcohol chiral centre. This inequivalence translates into a preference for binding to one of the faces due to the energy difference between the two complexes.

For binding of the substrate to the metal to occur successfully the C=C-C-O dihedral angle in the substrate must be in the region of +60° or -60°.[71] This forces one of the groups bonded to the carbon in the α-position to be almost coplanar with the α′-substituent, in this case the sulphonyl group. This is shown in Figure 3.08, where **I** gives rise to the *threo* product and **II**, which suffers more from this unfavourable interaction and is consequently higher in energy, gives the *erythro* product.

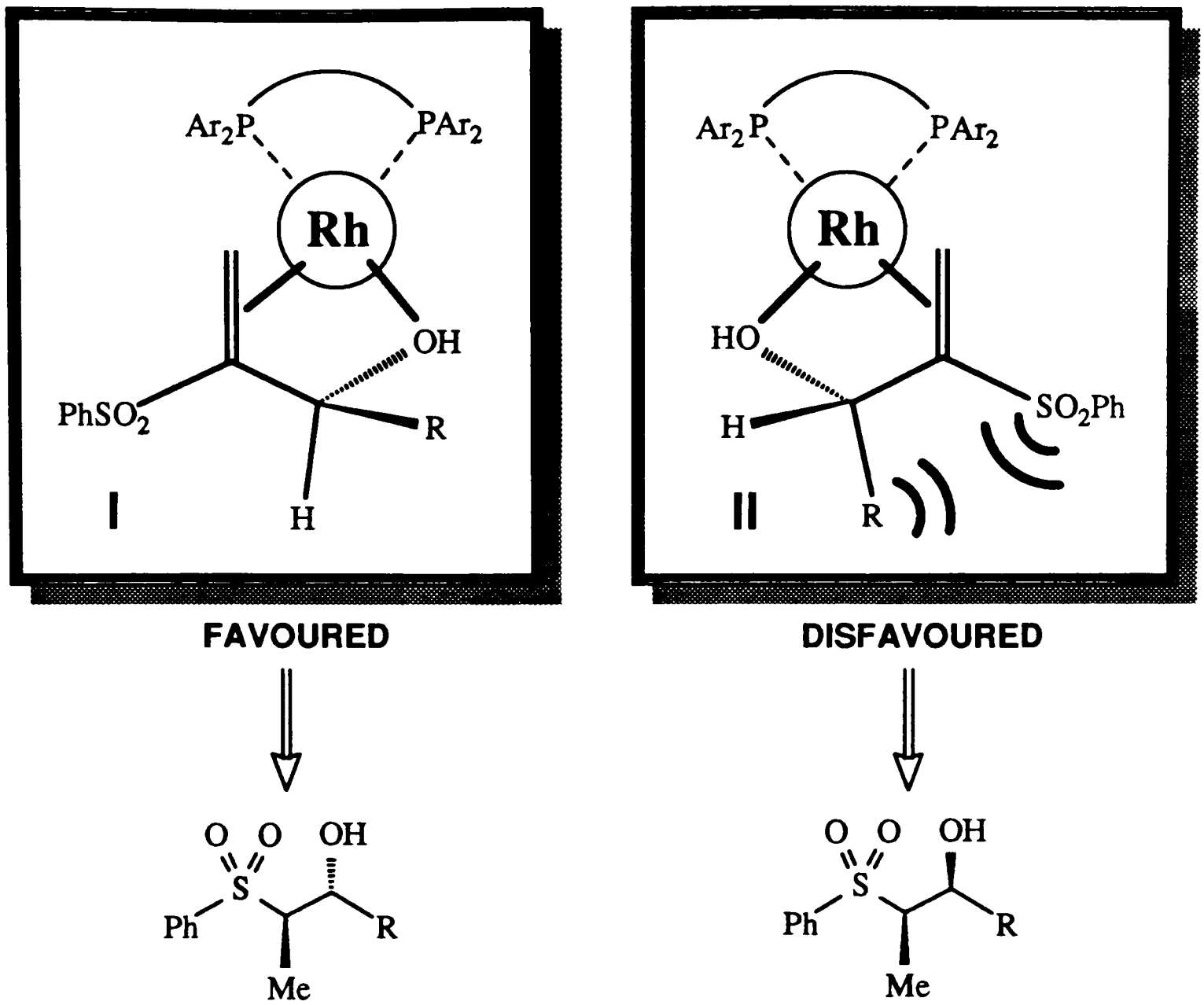
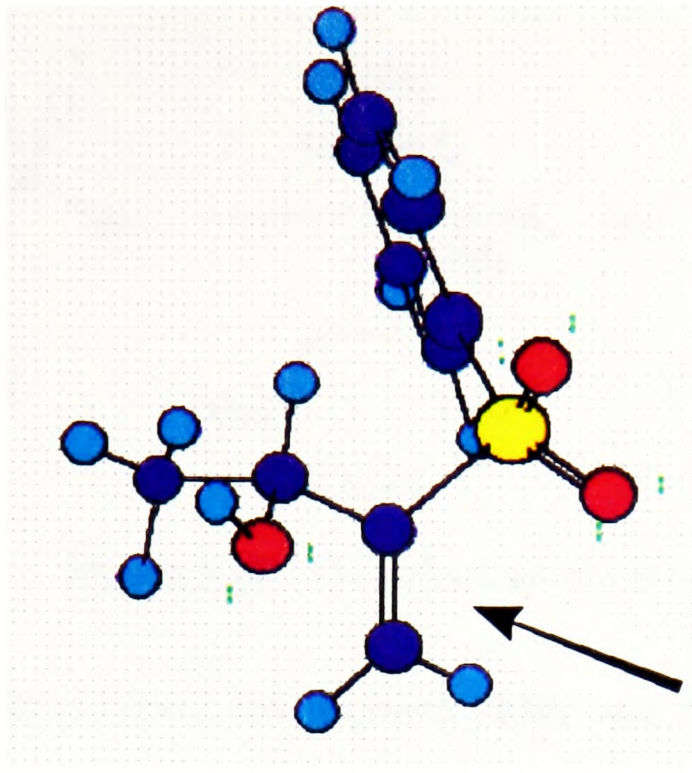


Figure 3.08 - The origin of the diastereoselectivity of directed hydrogenation.

Molecular mechanics using an MMX[86] force field was used to try to quantify the energy difference between the two structures in one case. The C=C-C-O angle was fixed at +60° and -60°, for the reasons stated previously, and these two conformations were energy minimised. The energies of the two conformations, shown in Figure 3.10, were found to be 16.84 $kJmol^{-1}$ and 25.28 $kJmol^{-1}$ above the energy of the ground state conformation. This equates to an energy difference of 8.44 $kJmol^{-1}$ for the two structures. This difference primarily arises from the aforementioned 1,4-interaction, since a proton is much less sterically demanding than a methyl group. The two energy minimised structures and the ground state conformer are shown in Figure 3.09.



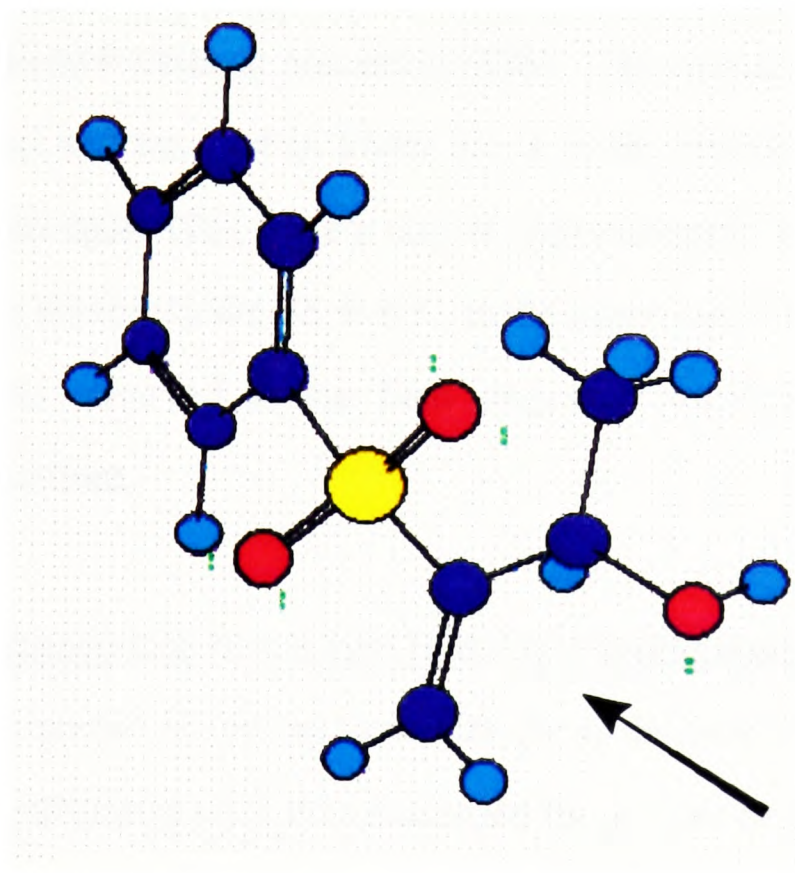
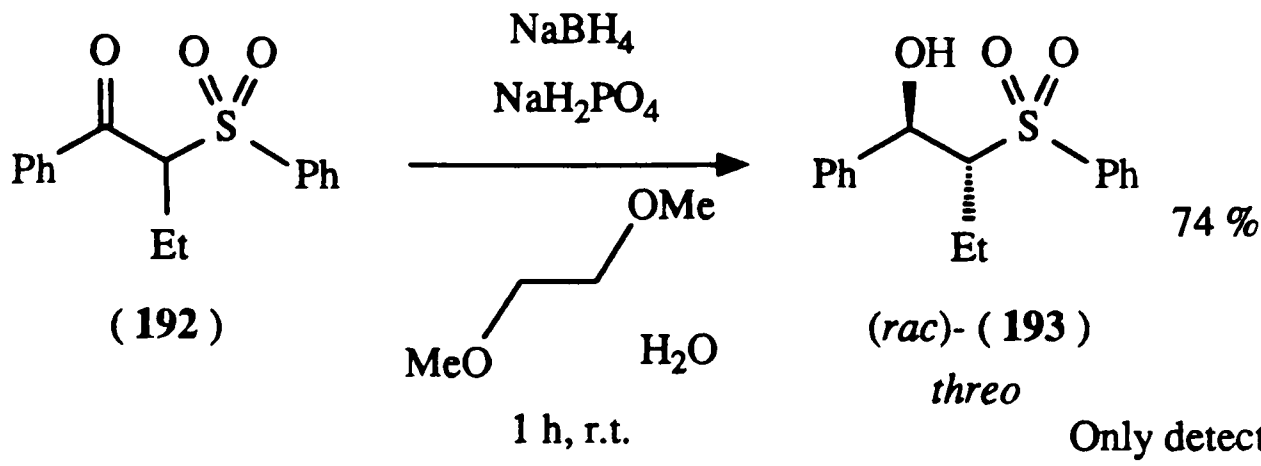


Figure 3.09 - Energy minimised conformers of (**129**).

The selectivity of the homogeneous hydrogenation of the hydroxy sulphones is of particular interest due to the difference between the sulphonyl group and ester groups of previously examined substrates. An increase in the bulk of the activating group on the double bond should aid the stereoselectivity since it is the interaction between this and the secondary alcohol substituent that gives rise to the selectivity.

The yields and d.e.'s of the hydrogenation reactions of the sulphones compare most favourably both with the directed hydrogenation of hydroxy acrylates.[76, 77] They are also very good in comparison with other routes to β-hydroxy sulphones, e.g. reduction of β-keto sulphones[108, 109] (Figure 3.10).



(**192**) (*rac*)- (**193**)

Figure 3.10 - The reduction of a β-keto sulphone.[108]

The phenyl substituted sulphone, (**132**), was also hydrogenated with the other two achiral catalyst precursors, (**104**) and (**106**), under similar conditions to those for the (dppb)rhodium(I) catalyst precursor, (**105**). The reaction in these cases took two to three times longer and resulted in lower d.e.'s in the product. The catalyst precursor, (**104**), derived from dppe, (**95**), gave a d.e. of approximately 99 % but (**106**) derived from dppf, (**97**), gave a disappointing 95 % d.e. In the latter case some discoloration of the catalyst in solution was observed in the final stages of reaction, possibly due to deposition of colloidal rhodium.

3.04 Hydrogenation of the *Syn*- Hydroxy Vinylsulphoxides

Encouraged by the success with the hydrogenation of the sulphone substrates, the sulphoxide substrates were then examined for activity as hydrogenation substrates.

The *syn* diastereomers of the two hydroxy vinylsulphoxides, (**152**) and (**154**), were exposed to identical hydrogenation conditions to the sulphones, i.e. hydrogen at 1 atm., dry degassed methanol as solvent, and 2 mol % of the (dppb)rhodium catalyst precursor, (**105**). The reactions in these cases took much longer than the corresponding sulphones, typically taking 16 hours or more and did not go to completion as judged by ^{1}H NMR. For this reason, it was deemed necessary to employ a relative catalyst concentration of 5 mol %, in which case the reaction was judged by hydrogen uptake to be over after 10 hours. Work-up, carried out in an identical manner to the hydroxy vinylsulphone hydrogenations, led to a recovery of the products in 97 % yield (Figure 3.11).

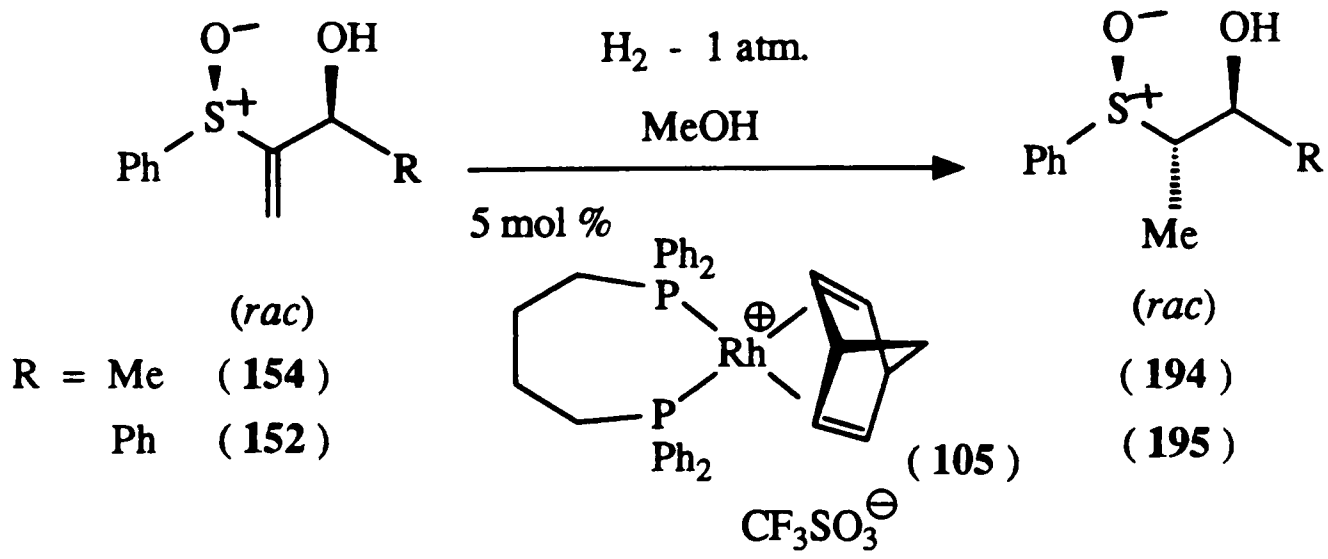


Figure 3.11 - The homogeneous hydrogenation of hydroxy sulphoxides (**154**) and (**152**).

Preparative t.l.c. of the saturated products from the hydrogenations led to the recovery of analytically pure samples of the products in an overall yield of 95%. In each case the products were characterised by M.P., ^{1}H and ^{13}C NMR, I.R., elemental analysis and mass spectroscopy, all of which were in complete agreement with the proposed structures.

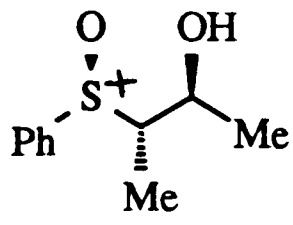
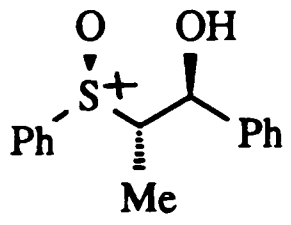
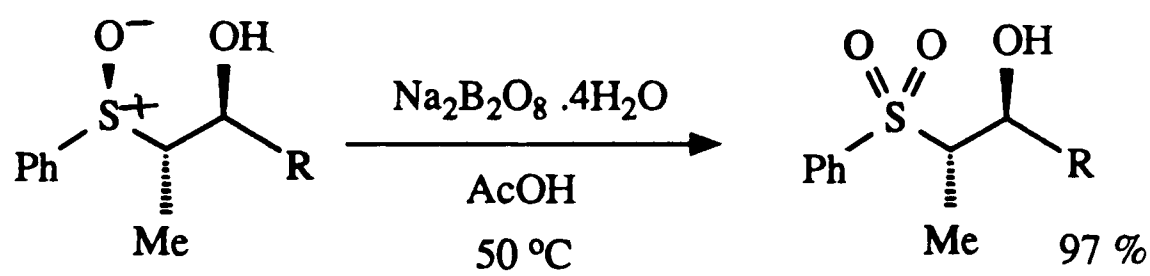
STARTING MATERIAL	PRODUCT	M.P. (°C)	I.R. (cm^{-1}) (O-H stretch)	YIELD (%)
(**154**)	 (**194**)	108- 110	3370	95
(**152**)	 (**195**)	145- 6	3246	95

Table 3.03 - A summary of hydrogenation results of the *syn*-sulphoxides (**154**) and (**152**).

In both cases there was evidence of hydrogen bonding of the hydroxy group in the I.R. spectra of the products. The O-H stretching frequency was shifted to lower wavenumbers than the analogous sulphones highlighting the fact that sulphoxides form stronger hydrogen bonds than sulphones.[87]

The diastereomeric excesses obtained with methanol as solvent, determined as before, proved to be 95 % and 85 % for (**154**) and (**152**), respectively. This rose to 99 % in both cases when, under otherwise identical conditions, 1,2-dichloroethane was used as solvent. A correction was made for the fact that the sample of (**152**) was a 9:1 mixture of diastereomers.

The relative configurations of the products and sense of the selectivity were determined to be the same as the sulphone case by comparison of vicinal proton couplings constants with those reported for similar substrates.[65b] Further proof of the structure of the products was provided by oxidation to the corresponding sulphone with sodium perborate,[94] and comparison of the ^{1}H NMR with those of (**186**) and (**179**) (Figure 3.12).



(*rac*)

R = Me (**194**) (**186**)

Ph (**195**) (**179**)

Figure 3.12 - The oxidation of the sulphoxide hydrogenation products for structure confirmation.

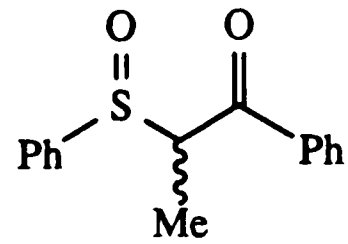
A summary of the selectivities obtained with the hydroxy vinylsulphoxides, (**154**) and (**152**), appears in Table 3.04.

STARTING MATERIAL	PRODUCT	D.E (%) MeOH	D.E (%) $ClCH_2CH_2Cl$	YIELD (%)
(**154**)	(**194**)	95	99	95
(**152**)	(**195**)	85	99	95

Table 3.04 - A summary of the selectivities obtained with the *syn*-sulphoxides (**154**) and (**152**).

Examination of the ^{1}H NMR of the crude reaction mixture from hydrogenation of (**152**) before work-up revealed the presence of a small amount, *circa* 2- 4 %, of the α-sulphinyl ketone, (**196**). A small amount of (**196**) was isolated and characterised by

I.R., ^{1}H and ^{13}C NMR spectroscopy.



(196)

Figure 3.13 - A side product from the hydrogenation of the hydroxy sulphoxides.

This ketonic side-product, (**196**), primarily responsible for the comparatively low yields, arose from rhodium catalysed olefin isomerisation. This was noted by Brown and co-workers[110] in early work with the directed hydrogenation of allylic alcohols (Figure 3.14). The olefin is initially isomerised to the enol, (**201**), which then tautomerises to the thermodynamically more stable ketone.

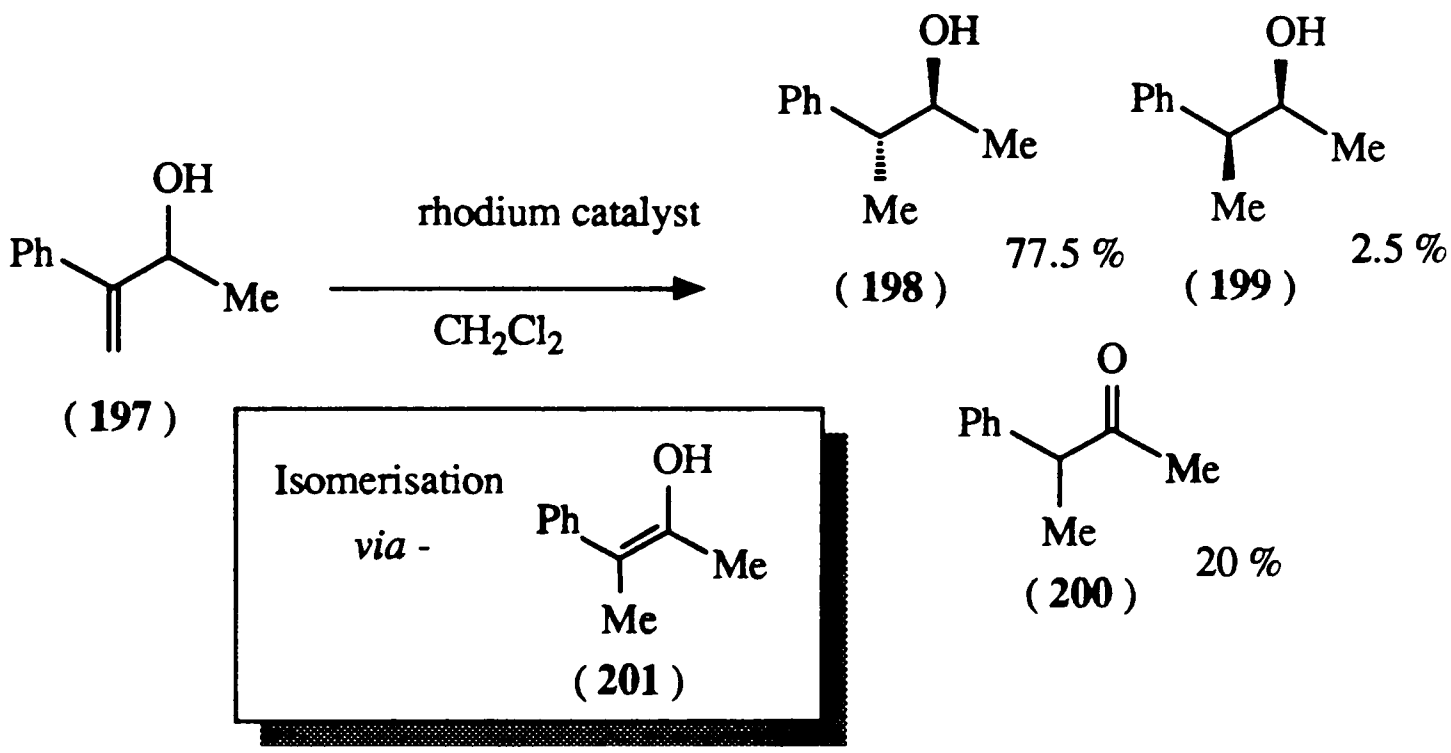


Figure 3.14 - An early hydrogenation by Brown[110] giving a ketonic side product.

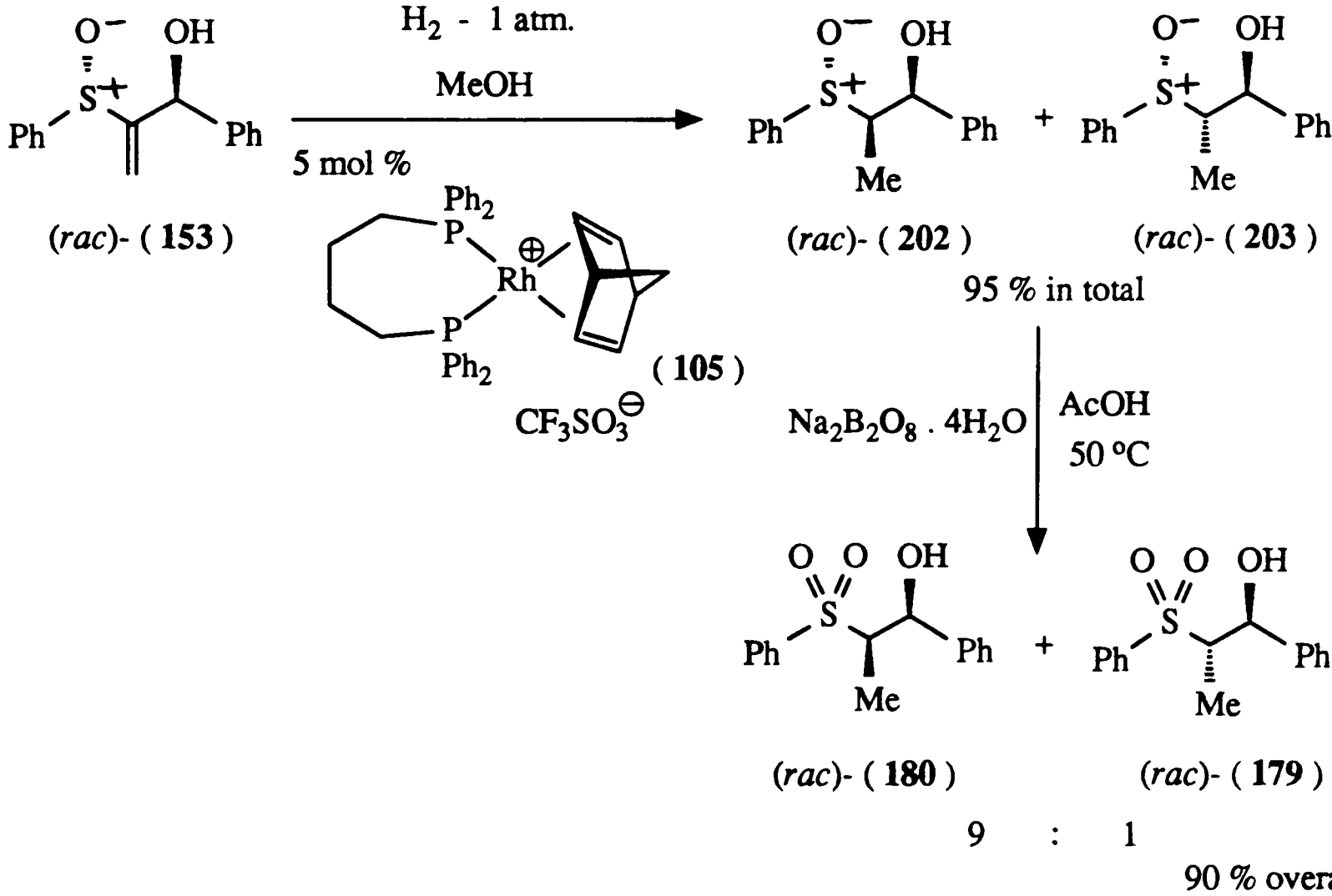
3.05 Hydrogenation of the *Anti*- Hydroxy Vinylsulphoxides

The hydrogenation of the *anti*- hydroxy vinylsulphoxides, (**153**) and (**155**), was investigated following the same protocols as established with the *syn*- hydroxy vinylsulphoxides.

When the *anti*- hydroxy vinylsulphoxides, (**153**) and (**155**), were exposed to hydrogen at 1 atm. in dry degassed methanol with 5 mol % of the (dppb)rhodium catalyst

precursor, (**105**), relatively fast hydrogenation was observed to occur. Reaction was observed to be over in under two hours as judged by hydrogen uptake. This, in itself, was surprising since it means that the reactivity of these substrates is five times that of the analogous *syn*-diastereomers.

Standard work-up procedures, including preparative t.l.c. on silica gel with hexane/ethyl acetate (7:3), were followed and a mixture of products was isolated in greater than 95 % yield. These products were determined to be a 9:1 mixture of two diastereomers by ^{1}H NMR. The selectivity in this case, however, was found to be reversed in favour of the *erythro* product as confirmed by oxidation to the corresponding β-hydroxy sulphones, (**179**) and (**180**) (Scheme 3.01).



Scheme 3.01 - The hydrogenation of *syn*- hydoxy vinylsulphoxide (**153**).

The methyl substituted *anti*-hydroxy vinylsulphoxide, (**155**), was examined under identical conditions to the phenyl analogue and the selectivity was found to be only 4:1. Again the stereoselection was in favour of the *erythro* diastereomer. Changing the reaction solvent to 1,2-dichloroethane improved the stereoselectivity markedly in both cases. The diastereomeric excess of the hydrogenation of (**155**) increased to 98 %, and

that of (**153**) increased to 97 %, while in both cases retaining the same sense of selectivity.

The products from the hydrogenations carried out in dichloromethane were purified by preparative t.l.c. on silica gel with hexanes/ethyl acetate (7:3) as eluent, and fully characterised. A summary of the products from the hydrogenations of (**155**) and (**153**), together with the diastereoselectivities obtained, appear below in Table 3.05.

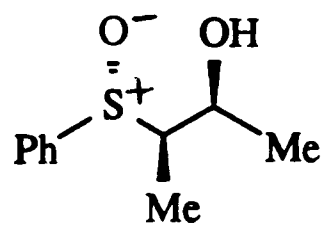
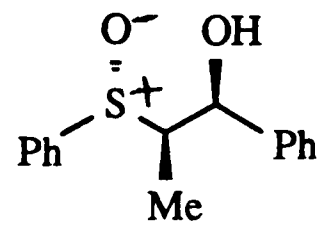
STARTING MATERIAL	MAJOR PRODUCT	M.P. (°C)	D.E. (%) MeOH	D.E. (%) $ClCH_2CH_2Cl$
(155)	 (204)	105- 8	60	98
(153)	 (202)	151- 4	81	97

Table 3.05 - A summary of the results of, and products from the hydrogenation of (**155**) and (**153**).

Overall, the results obtained with the hydroxy vinylsulphoxide substrates are not in agreement with the model proposed for the stereoselectivity obtained with hydroxy vinylsulphones. Another model involving the sulphoxide moiety must be used to account for this switch in selectivity. This obvious difference in reaction pathway, however, can be explained inside the same model if coordination of the sulphinyl oxygen atom is invoked. If the sulphinyl group is bound to the metal centre in the substrate-catalyst complex then the selectivity is reversed with respect to the sulphone with the *anti*-hydroxy vinylsulphoxides, but retained with the *syn*-hydroxy vinylsulphoxides (Figure 3.15).

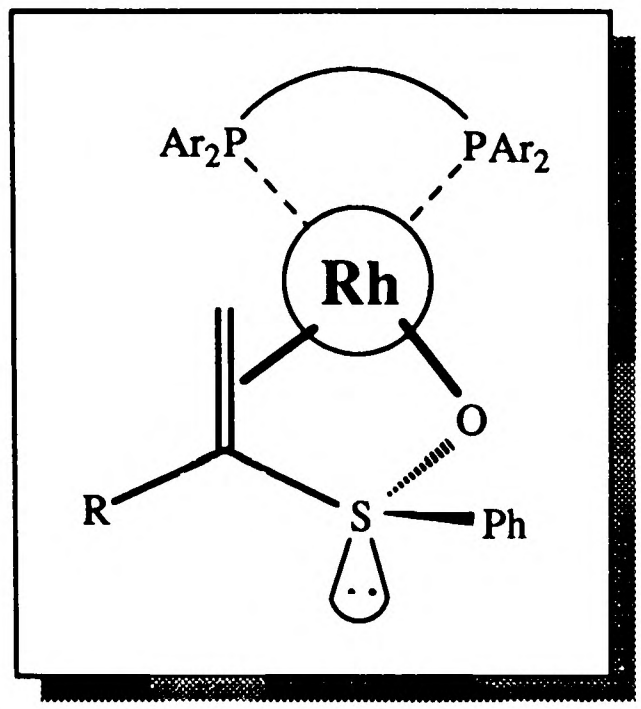


Figure 3.15 - The favoured binding mode of sulphinyl substrates to rhodium catalysts.

In an attempt to quantify the difference between the two catalyst-substrate complexes MMX[86] molecular mechanics calculations were carried out. In an analogous manner to the sulphone calculations, the energies of the two "binding conformations" of the methyl substituted vinylsulphoxide, (**155**), were computed and compared to the energy of the ground state conformation. The two energy minimised conformers are represented in Figure 3.16 below.

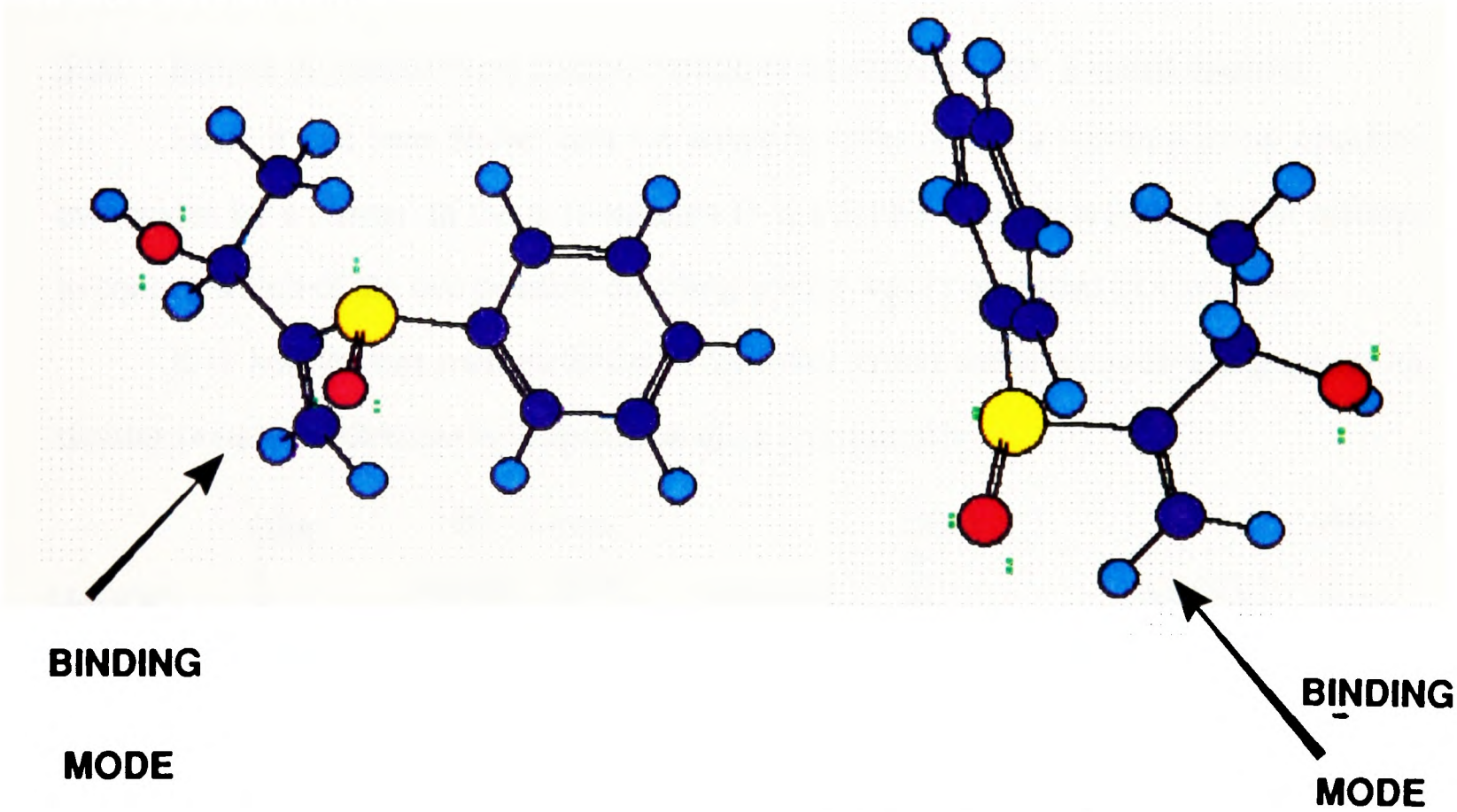


Figure 3.16 - Energy minimised conformers of (**155**).

In this case the C=C-S=O dihedral angle instead of the C=C-C-O dihedral angle

was fixed at +60° and -60°. This revealed that the favoured and disfavoured modes of binding differed in energy by 6.20 $kJmol^{-1}$. This was arrived at by discarding rotamers of the allylic carbon-bond which precluded binding of the metal centre to the double bond.

The energy difference between the "favoured" and "disfavoured"- "binding conformers" does not change significantly as the structure is changed from the hydroxy vinylsulphones to the hydroxy vinylsulphoxides. A weakness in this approach, however, lies in the fact that the difference in the strengths of the metal-oxygen bond in hydroxy and sulphinyl complexes cannot be computed. Consequently there may be a contribution from the hydroxy group as an auxiliary binding group which will tend to favour the *threo*-diastereomer. The fact that the selectivity is reversed with respect to the sulphone hydrogenations does imply that the sulphinyl oxygen forms a stronger bond to the metal centre than the hydroxy group.

Taken together, the hydrogenation of the hydroxy vinylsulphones and vinylsulphoxides provide simple routes to either of the diastereoisomers of simple β-hydroxy sulphones of high d.e. in good overall yields.

3.06 Effects of Additives on Hydrogenation of an *anti*-Hydroxy Vinylsulphoxide

Since it had been shown that the directing influence of a hydroxy group could be overridden by a change in the α-substituent of the double bond, it was decided to attempt to control which of the two possible directing groups was in operation in a reaction.

It is known that methylation of a hydroxy group reduces its directing power in rhodium catalysed directed hydrogenation quite considerably.

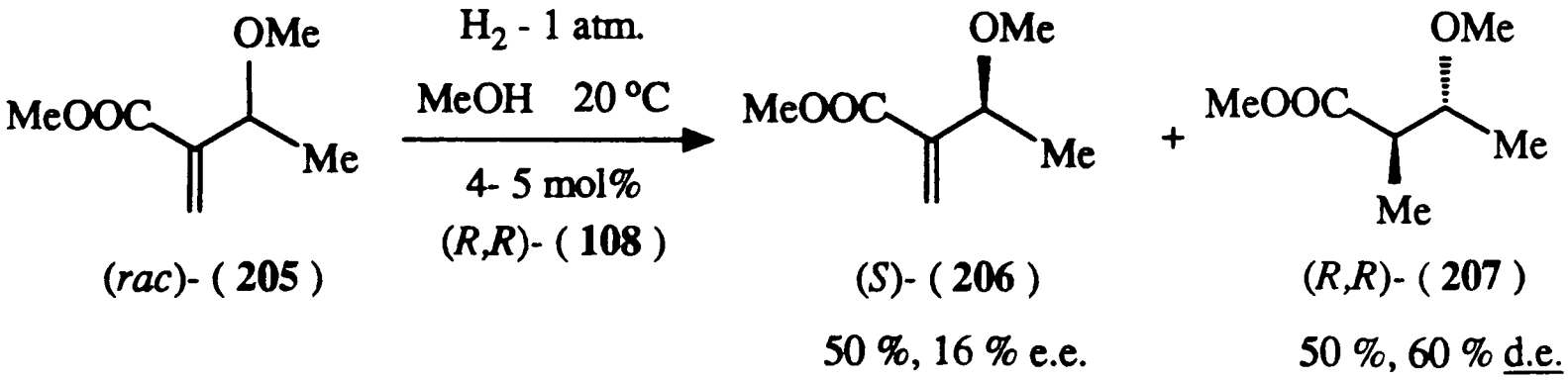


Figure 3.17 - The kinetic resolution of a methoxy acrylate derivative.[77]

It can be seen from Figure 3.17 that the effectiveness of the hydroxy directing group is reduced by methylation, since the product from the kinetic resolution of (**205**) had only 60 % d.e.[77]

This form of alteration of directing influence of a functional group requires an additional chemical step and thus increases the complexity of a synthesis. It would be far better to use an additive in the hydrogenation reaction that would disable one or other of the directing groups *in situ.*

The hydrogenation of (**153**) was carried out as detailed earlier, but in this case with the addition of one of two substrate modifiers, in 1,2-dichloroethane and at a hydrogen pressure of 1.5 atm. It was hoped that the addition of triethylamine to the hydrogenation mixture would generate the alkoxide anion of the substrate and thus increase its directing ability with respect to the sulphinyl group. As a counterpoint, it was hoped that the addition of boron trifluoride etherate would mask one or other of the directing groups by binding to it.

One equivalent, based on the substrate, of freshly distilled triethylamine was added to the hydrogenation of (**153**) as outlined in Figure 3.18. After a period of 4 hours the ^1H NMR spectrum of the crude reaction mixture was taken. This revealed that the hydrogenation of (**153**) had been completely inhibited and only starting material was present.

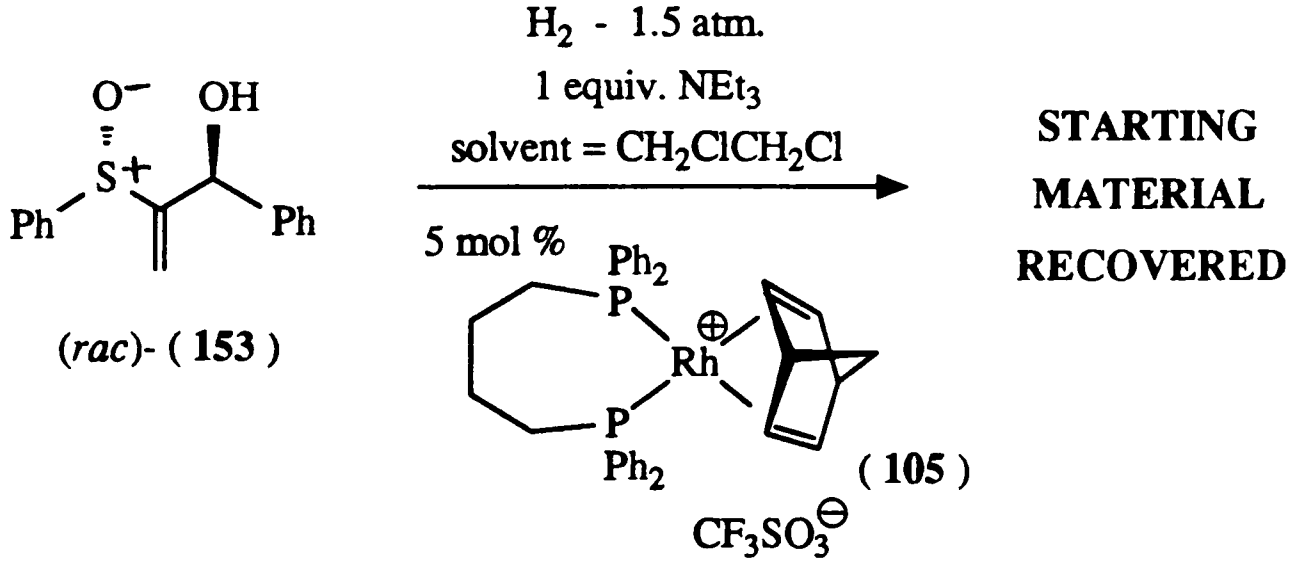


Figure 3.18 - The attempted hydrogenation of (**153**) with added triethylamine.

In a similar protocol to that observed with the triethylamine additive, (**153**) was exposed to hydrogenation conditions with one equivalent of boron trifluoride etherate

added, as outlined in Figure 3.19. In this case ^1H NMR of the crude reaction mixture after 4 hours indicated that all the starting material was consumed. Unfortunately, no recognisable product could be isolated and the ^1H NMR appeared to indicate that some form of polymerisation of the starting material had occurred. The mechanism by which the starting material had been destroyed was unknown and was not explored further.

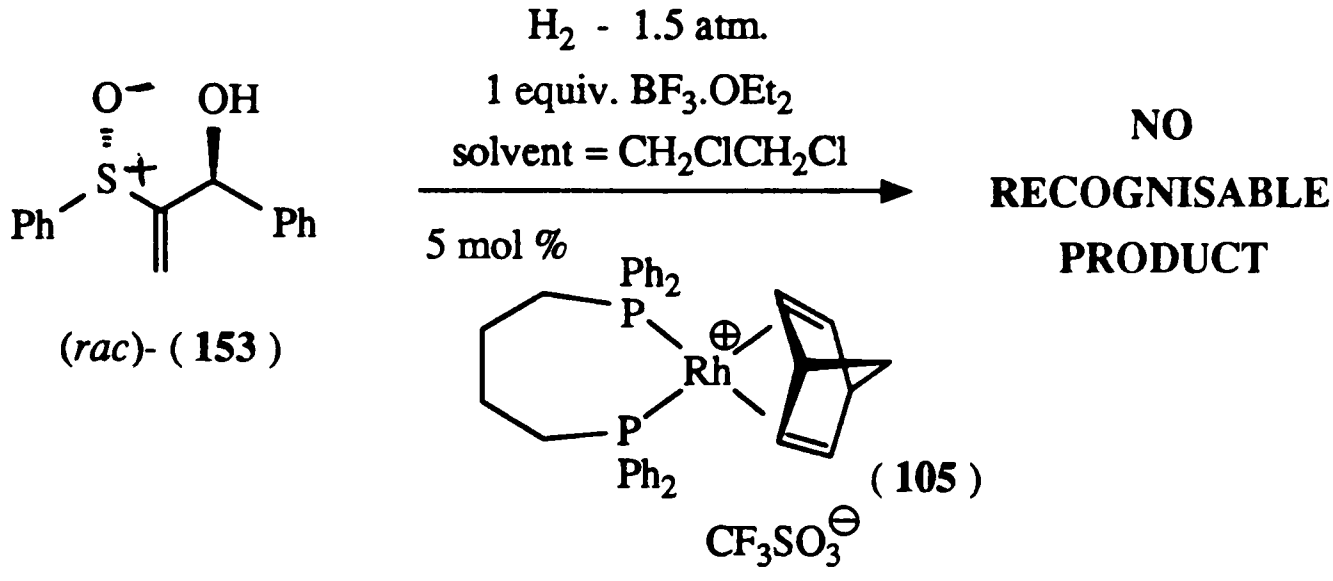


Figure 3.19 - The attempted hydrogenation of (**153**) with added $BF_3.OEt_3$.

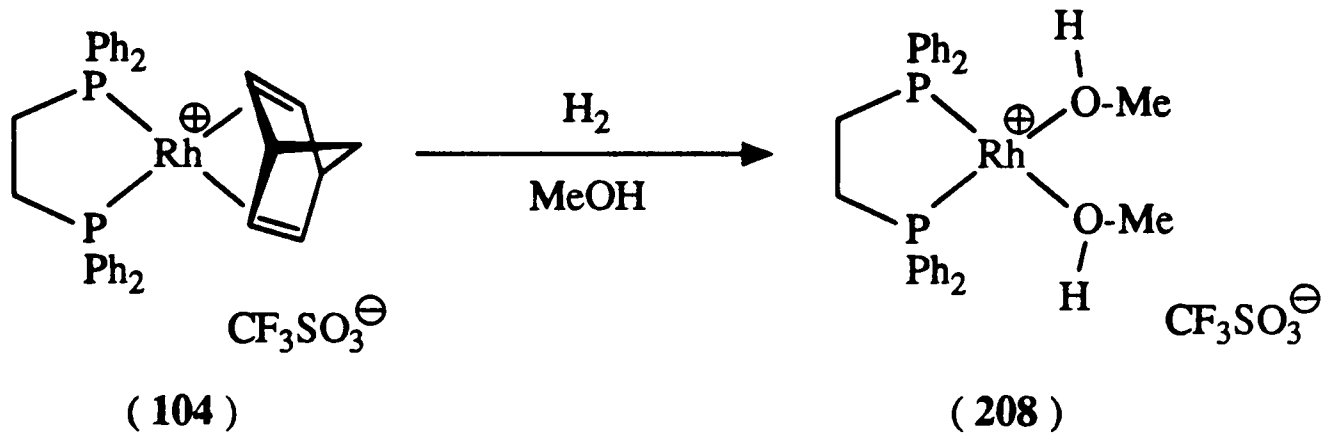
Control hydrogenations were performed under identical conditions to the two additive reactions i.e. in 1,2-dichloroethane, hydrogen at 1.5 atm. and 5 mol % of catalyst precursor, (**105**). These showed no deviation from the results presented earlier and products were recovered as normal.

3.07 Low Temperature ^{31}P NMR Investigations

The hydrogenation results obtained with the *anti*-hydroxy vinylsulphoxides pointed to the sulphinyl group being bound to the metal centre at some point in the catalytic cycle. It therefore seemed prudent to investigate the interactions between the catalyst and the substrate, under controlled conditions, in the absence of hydrogen. The structure of the catalysts, containing a chelating bis-phosphine, lends itself well to an investigation involving ^{31}P NMR and so this approach was taken. The (dppe)rhodium catalyst precursor was chosen for this investigation since substrates are known to bind more strongly to complexes containing a five membered phosphine-rhodium chelate than to complexes containing a seven membered ring chelate.[111]

Solutions of the (dppe)rhodium solvate complex, (**208**), in methanol were prepared

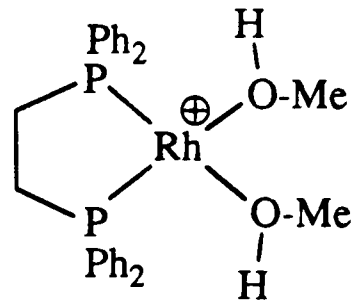
in situ by taking the 40 mg samples of the catalyst precursor, (**104**), dissolved in methanol and exposing them to hydrogen. The formation of the solvate complex was indicated by an almost instantaneous colour change of the solution from deep red to golden yellow, and confirmed by ^{31}P NMR of the solution. The hydrogen was removed from the solution and NMR tube by four freeze-pump-thaw cycles and replaced with argon.



(**104**) (**208**)

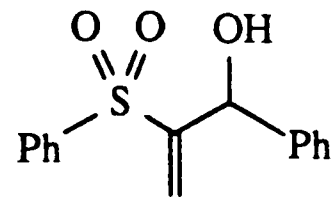
Figure 3.20 - Formation of the rhodium solvate complex for ^{31}P NMR investigations.

Five separate experiments were performed with freshly prepared solutions of the (dppe)rhodium (I) solvate complex, (**208**). Firstly one equivalent, approximately 15 mg, of the phenyl substituted hydroxy vinylsulphone, (**132**), as a solution in methanol was added to the solvate in an 8 mm NMR tube *via* a syringe. The sample was cooled to 0°C and the ^{31}P NMR was taken. This, however, showed only the solvate complex (doublet centred on 77.2 p.p.m., J_{RhP}= 205.6 Hz), albeit broadened slightly by exchange. Reducing the temperature of the sample to -40°C sharpened the appearance of the spectrum but did not affect the species observed. An increase in the concentration of the vinyl sulphone to twice its original value led to the emergence of a second set of solvate-like peaks, which amounted to only 5 % of the intensity of the true solvate. Two sets of very weak peaks centred on 50 and 65 p.p.m. were also observed. The identity of these could not be determined, however, due to exchange broadening and the consequent loss of peak height, even at -40°C.



(**208**) $CF_3SO_3^{\ominus}$

+ 2 equiv.



(**132**)

Solvent = methanol
Temperature = -40 °C
No. of scans = 1000

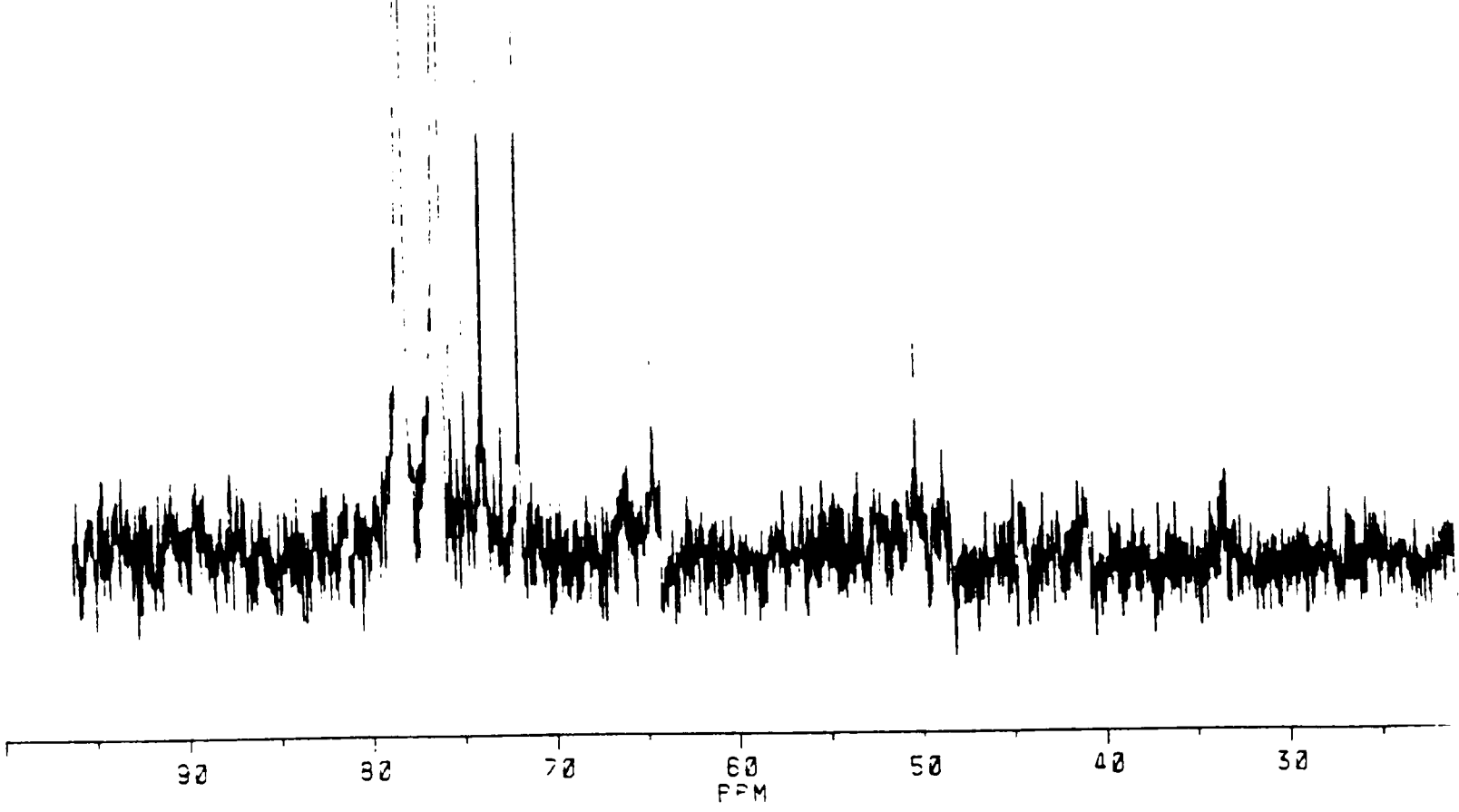
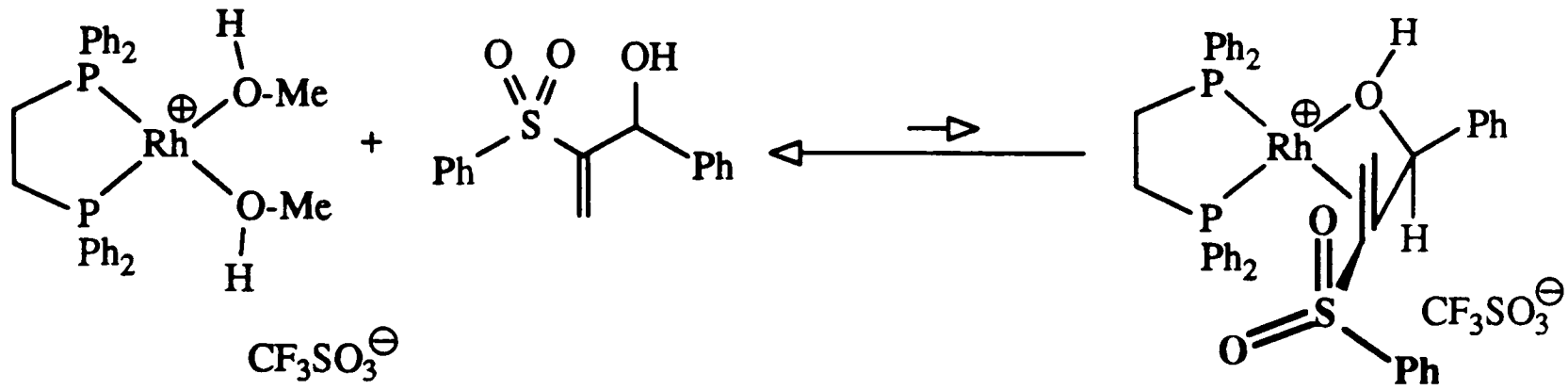


Figure 3.21 - ^{31}P NMR spectrum of solvate/sulphone mixture at -40°C.

The results obtained with (**132**) and the solvate complex, (**208**), suggest that the vinyl sulphones are in rapid equilibrium with the solvate complex, and that the position of the equilibrium is well over to the left (Figure 3.22).



(**208**) (**132**) (**209**)

Figure 3.22 - Equilibrium between the solvate complex, (**208**), and substrate complex, (**209**).

Although disappointing results were obtained with the vinylsulphone-(dppe)rhodium(I) system, it was hoped that investigations with the sulphoxide substrates, (**152**) and (**153**), would be more fruitful.

To a sample of the solvate in methanol was added 1 equivalent of the *anti*-hydroxy vinylsulphoxide, (**153**), and the ^{31}P NMR was taken at room temperature. The spectrum consisted of the severely broadened peaks of the solvate complex, (**208**), but this sharpened considerably as the temperature was reduced to -40°C, to reveal a pair of double doublets (J_{RhP}= 181 Hz, J_{PP}= 35.3 Hz). These peaks, centred on 59.6 and 70.5 p.p.m., grew in intensity at the expense of the solvate and also began to sharpen at a higher temperature as the concentration of substrate was first doubled, then trebled.

Interestingly, the doublet of doublets centred on 60 p.p.m. increased in multiplicity to a double doublet of doublets (J_1= 161.1 Hz, J_2= 48.9 Hz, J_3= 35.0 Hz) at -40°C, with three equivalents of the vinyl sulphoxide present (Figure 3.23).

The *syn*-hydroxy vinyl sulphoxide, (**152**),was examined in a similar manner. In this case, a sample of the solvate together with two equivalents of the *syn*-hydroxy vinylsulphoxide, (**152**), exhibited a pair of double doublets (J_{RhP}= 163.2 Hz, J_{PP}= 38.4 Hz) in the ^{31}P NMR taken at -40°C (Figure 3.23). This pair of signals was shifted by 5 p.p.m. to lower field relative to the *anti*-hydroxy vinylsulphoxide complex. The spectrum displayed an enhanced signal to noise ratio compared to the equivalent spectrum taken with (**153**), suggesting that the rate of exchange is slower in this case.

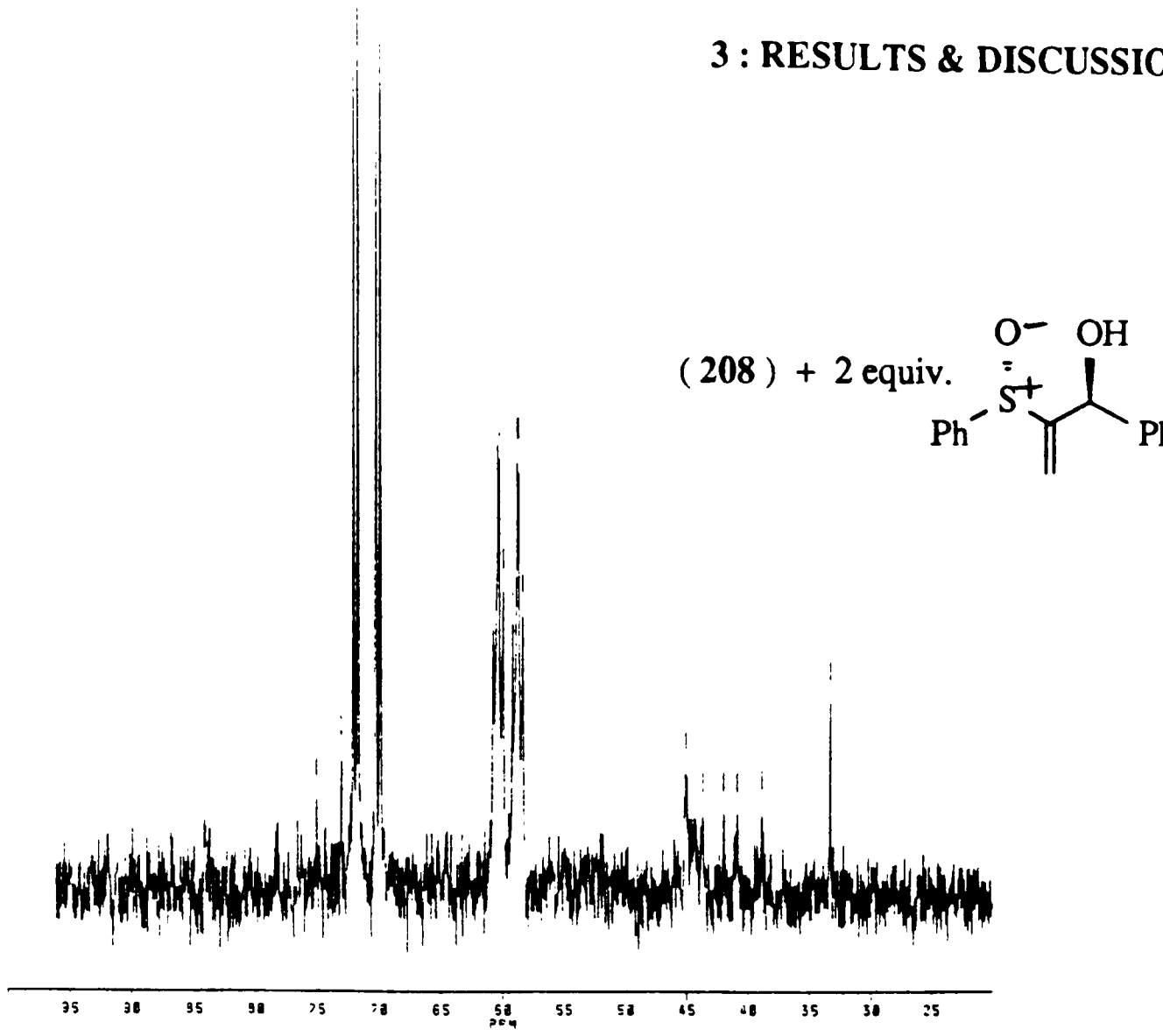


Figure 3.23 - ^{31}P NMR spectrum of solvate/vinylsulphoxide mixtures at -40°C.

Initial interpretation of the spectra led to the conclusion that the species observed with both the vinylsulphoxides was either a bis-sulphoxide complex of some sort or a sulphoxide olefin chelate. It was unclear why the two sets of peaks were so far apart (10 p.p.m.), however, and why the peaks centred on 60 p.p.m. were of such high multiplicity, if it was indeed the bis sulphoxide complex being observed.

In order to test this a sample of the solvate with one equivalent of methyl phenylsulphoxide, (**210**), was examined with low temperature ^{31}P NMR. At -30°C, only the broadened solvate complex was visible even after 600 scans. As the concentration of (**210**) was increased stepwise to ten times its original value, the signal to noise ratio decreased dramatically. At this point, at -70°C, two sets of peaks around 60 and 75 p.p.m. were just distinguishable above the baseline, but it was unclear what multiplicity if any they possessed. This pointed to the species observed with (**152**) and (**153**) being 1:1 chelates between the metal fragment and adduct rather than 1:2 complexes.

In order to check whether the olefin was bound to the metal in the complexes observed with (**152**) and (**153**), a simple β-hydroxysulphoxide, (**212**), was prepared as shown in Figure 3.24 and its interaction with the solvate complex (**208**) examined.

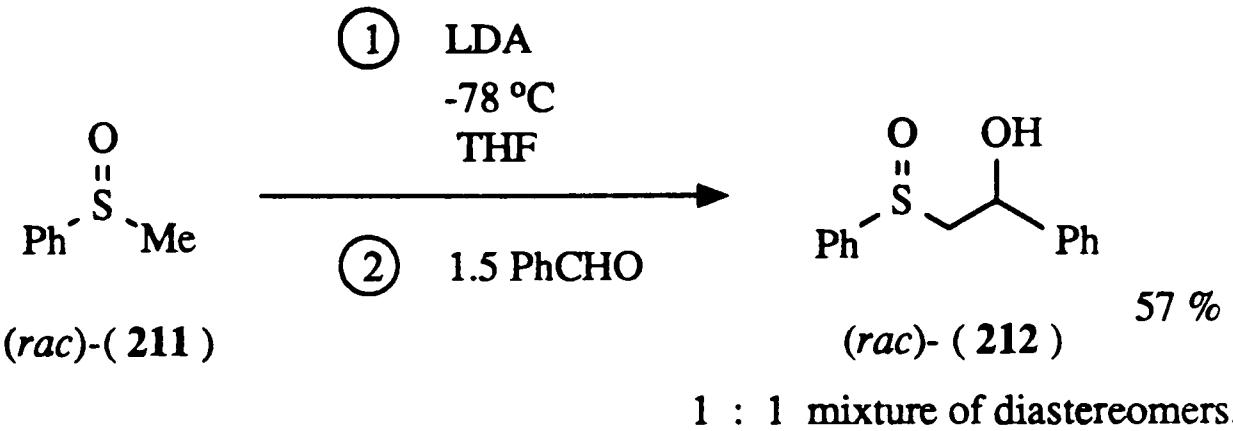


Figure 3.24 - Synthesis of β-hydroxysulphoxide (**212**).

A pure sample of (**212**), melting at 112-115°C, was obtained in 57 % yield by column chromatography of the crude product on silica gel, eluting with 1:1 hexanes/ethyl acetate. The product was characterised by ^{1}H NMR and I.R. spectroscopy each of which was in accord with the literature.[112] The product was produced as a 1:1 mixture of two diastereomers and was used as such.

A solution of the solvate complex, (**208**), together with two equivalents of the β-hydroxysulphoxide, (**212**), in methanol was cooled to -40°C and the ^{31}P NMR taken. The spectrum, which was well resolved, was almost identical in appearance to that of the solvate, (**208**), and *syn*-hydroxy vinylsulphoxide, (**152**), mixture. The coupling constants were also similar to the aforementioned spectrum, being J_{RhP}= 162.9 Hz and J_{PP}= 37.1 Hz.

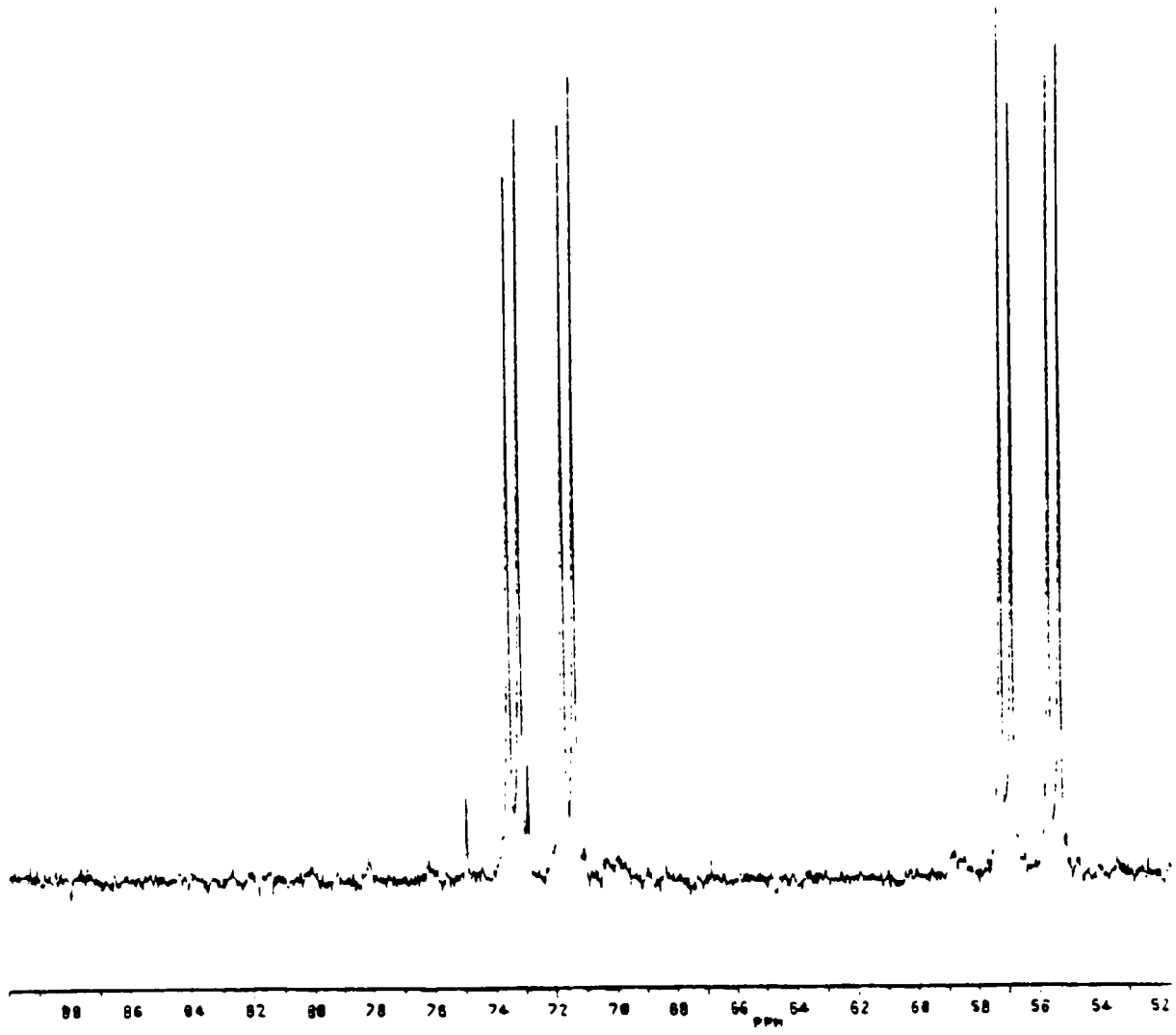
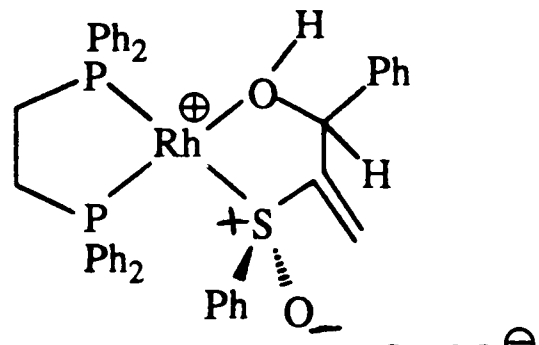


Figure 3.25 - ^{31}P NMR of solvate/β-hydroxy sulphoxide mixture at -40°C.

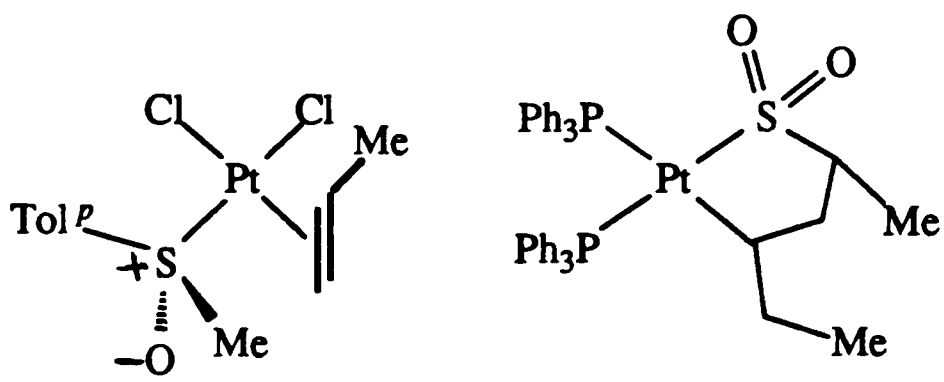
This spectrum, shown in Figure 3.25, leads to the conclusion that the species observed in all the hydroxy sulphoxide cases, (**152**), (**153**) and (**212**), contains an S, O chelate. The proposed structure for the vinylsulphoxide-rhodium complex containing (**152**), labelled (**213**), is shown in Figure 3.26.



(**213**)

Figure 2.26 - A proposed structure for the vinylsulphoxide-rhodium complexes.

Although surprising, S-bound sulphinyl complexes are not uncommon, the platinum complex (**214**) reported by Bosnich[113] being a good example of one such complex (Figure 3.27). S-bound sulphinate platinum complexes such as (**215**) have also been reported by Collum[114] amongst others.



(214) **(215)**

Figure 3.27 - An S-bound sulphoxide[113] and sulphinate.[114]

Taken as a whole, the low temperature NMR studies with the sulphoxides and sulphones showed -

i) that the sulphone, (**132**), does not bind strongly to the metal in the (dppe)rhodium system and the catalyst ground or resting state is probably the solvate complex, (**208**).

ii) that the two hydroxy vinylsulphoxides examined, (**152**) and (**153**), bind to the metal quite strongly, but that this mode of binding is non-productive in a hydrogenation sense. This means that the catalyst ground state in this case is most probably an S, O chelate such as (**213**).

These points will be dealt with further in the next Chapter, which deals with a kinetic analysis of the hydrogenation rates of the sulphoxides and sulphone.

3.08 Hydrogenation of Simple Vinylsulphoxides and Allylsulphoxides

Since the results obtained with the *anti*-hydroxy vinylsulphones were in accord with sulphoxide-directed hydrogenation, the two remaining vinyl sulphoxides, (**160**) and (**161**), were examined as substrates. Based on the aforementioned results, it was expected that the selectivity of these hydrogenations would be both high, and in favour of the *anti*-product.

The hydrogenation of 1-phenyl-1-phenylsulphinylethene, (**160**), and 2-phenyl-sulphinyloctene, (**161**), was carried out in both methanol and 1,2-dichloroethane using standard procedures.

A 0.1 M solution of the vinyl sulphoxide, (**160**) or (**161**), together with 2 mol % of

the (dppb)rhodium catalyst precursor, (**105**), in either solvent, was thoroughly degassed by three freeze-pump-thaw cycles. The atmosphere in the reaction vessel was replaced with hydrogen, and the extent of reaction judged by gas uptake. Hydrogenation was fast compared to both the *syn*- and *anti*-hydroxy vinylsulphones examined earlier.

Work-up by removal of the solvent *in vacuo* and trituration of the residue with diethyl ether gave the products in near quantitative yields.

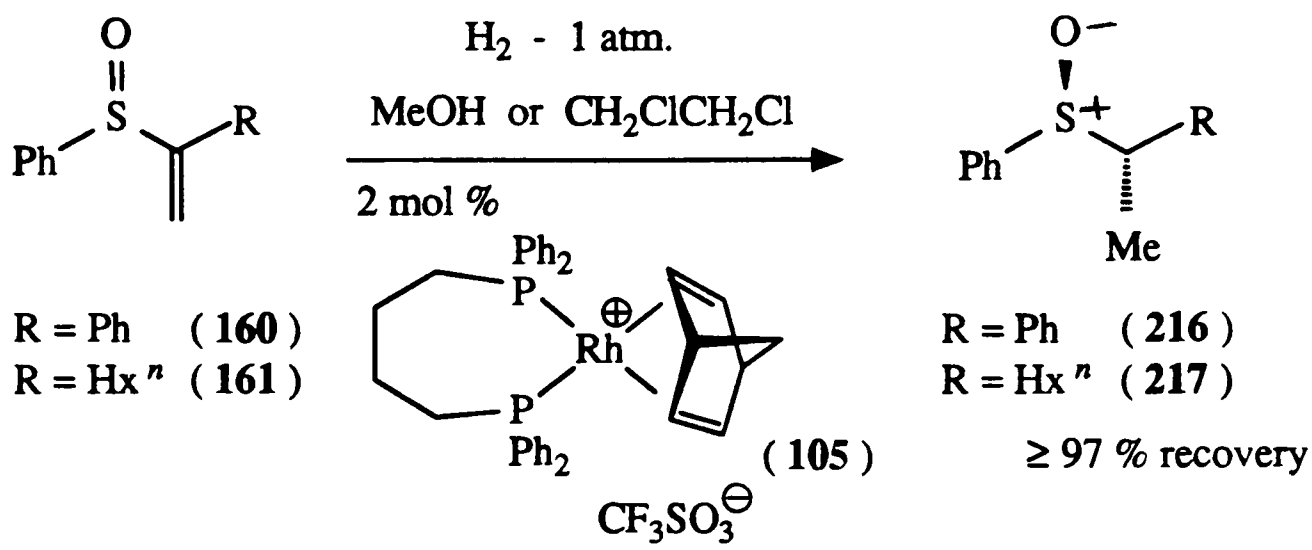


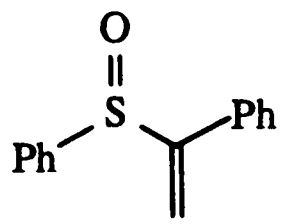
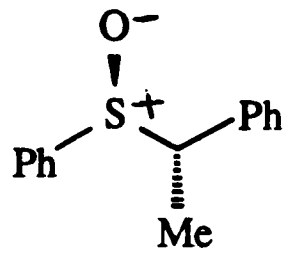
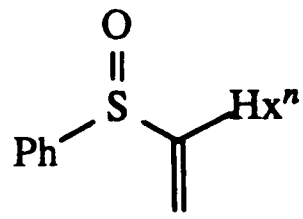
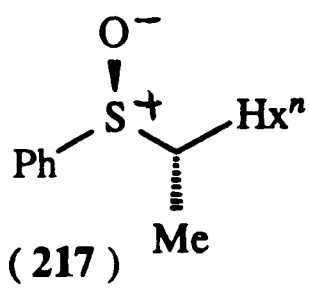
Figure 3.28 - Hydrogenation of the simple vinylsulphoxides, (**160**) and (**161**).

The major products from these two hydrogenations, which are both known compounds,[115, 116] were characterised by M.P. (in the case of (**216**)), I.R. and ^{1}H NMR spectroscopy.

The diastereomeric excess of each hydrogenation was determined by the method outlined earlier in this Chapter.

The results obtained with the *n*-hexyl substituted vinyl sulphoxide, (**161**), were not as high as expected, with the hydrogenation in methanol giving only 86 % d.e. and that in 1,2-dichloroethane giving 93 %. The results with (**160**) were much better, being 96 % d.e. in methanol 99.7 % in 1,2-dichloroethane. In all, these results represent quite impressive selectivity and excellent yields for such unfunctionalised substrates when compared with other literature reactions of sulphoxides.[41, 58a, 62, 117]

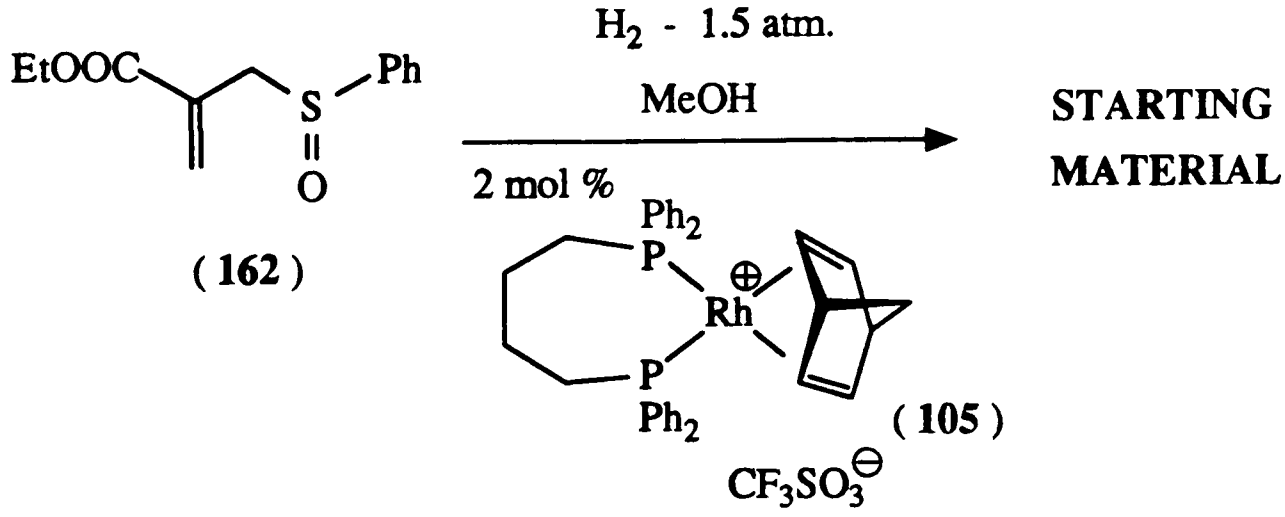
The d.e.'s obtained with the two solvent systems are summarised in Table 3.06.

STARTING MATERIAL	MAJOR PRODUCT	M.P. (%)	D.E. (%) MeOH	D.E. (%) $ClCH_2CH_2Cl$	YIELD
 (**160**)	 (**216**)	88- 92	96	99.7	98†
 (**161**)	 (**217**)	OIL	86	93	97†

†The yield was independant of solvent system.

Table 3.06 - A summary of the hydrogenation results of (**160**) and(**161**).

The allylsulphoxide, (**162**), was examined under similar hydrogenation conditions to those used with the hydroxy vinylsulphoxides. This involved 2 mol % of the (dppb)rhodium catalyst precursor, (**105**), in methanol with a hydrogen pressure of 1.5 atm. After several trial reactions in which the reaction mixture changed colour from orange to gold, however, (**162**) resisted attempts to hydrogenate it. In each case only starting material, (**162**), was observed by ^1H NMR of the reaction mixture.



(**162**) (**105**)

Figure 3.29 - Attempted hydrogenation of (**162**).

The starting material, (**162**), was repurified by column chromatography on silica gel eluting with 7:3, hexanes/ethyl acetate, to ensure that it was not contaminated with small amounts of sulphide impurities. This did not, however, change the result obtained in

attempted hydrogenations. In all cases only impure starting material was recovered.

3.09 Attempted Hydrogenation of Hydroxy Vinylsulphides

Since the hydroxy vinyl sulphoxides and vinylsulphones had given such interesting results, the hydrogenation of the analogous sulphides, it was hoped, would be straightforward and show some selectivity.

Samples of 50 mg of the two hydroxy vinylsulphides, (**156**) and (**159**), were dissolved in dry, degassed methanol together with 3 mol % of the (dppb)rhodium catalyst precursor, (**105**), in a Schlenk tube. The solutions were then degassed by four freeze-pump-thaw cycles and the atmosphere in the Schlenk tube replaced with hydrogen. The reaction mixtures were left to stir under hydrogen for a period of 15 hours and then worked-up in a similar way to all other hydrogenations described herein.

Examination of the ^1H NMR of the products from the two reactions revealed that no starting materials remained in either case. The presence of an intense singlet at δ 2.28 p.p.m. in the major product from the reaction of (**159**) indicated that isomerisation of the starting material to the α-sulphenyl ketone had taken place. This was confirmed by the I.R. spectrum of the major product, showing C=O stretches of 1713 and 1685 cm^{-1} for (**218**) and (**219**), respectively.

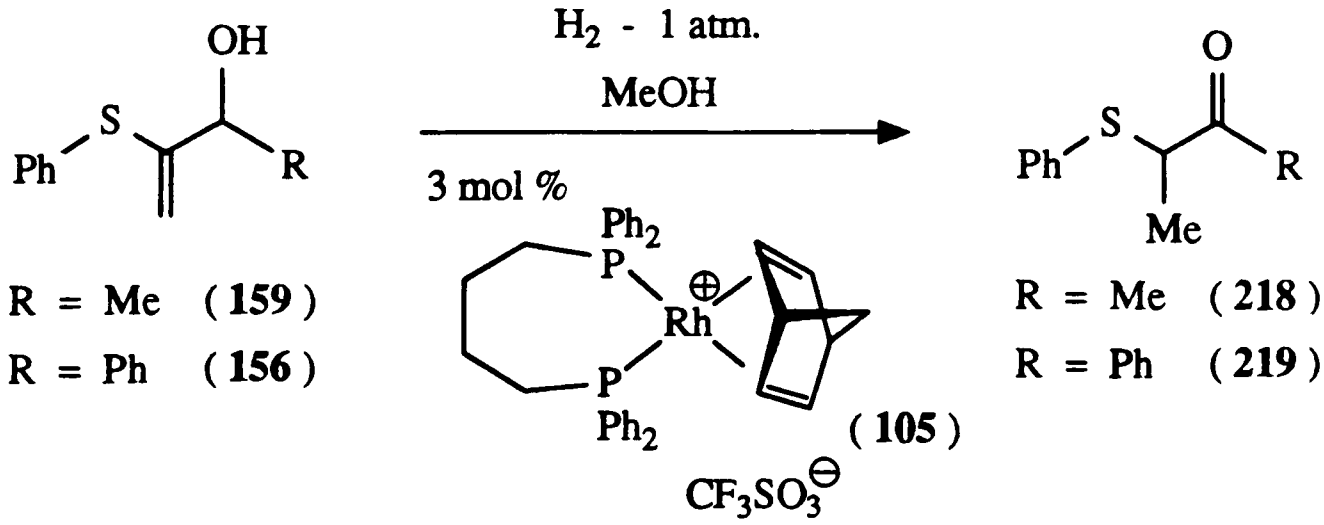
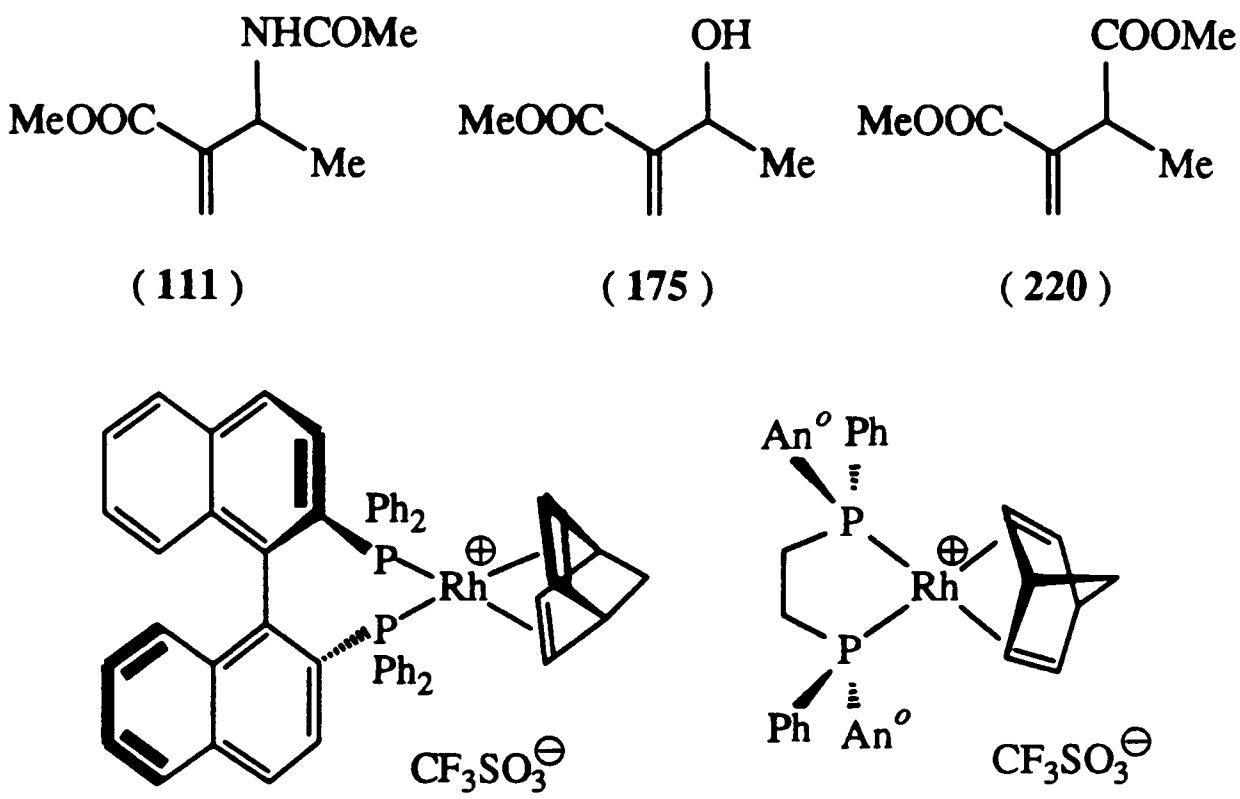


Figure 3.30 - Attempted hydrogenation of the hydroxy vinylsulphides, (**156**) and(**159**).

The formation of the α-sulphenyl ketones in these reactions can be explained in the same way as earlier by 1,3-shift of the allylic proton to the terminus of the carbon-carbon double bond, and then tautomerisation of the enol formed.

3.10 Kinetic Resolution of 3-Phenyl-2-(phenylsulphonyl)propen-3-ol

The kinetic resolution of acetamido and hydroxy acrylates such as (**111**) and (**175**) have been performed with a good degree of success using (DiPAMP)rhodium catalyst precursors.[71, 77] It was thus hoped to achieve kinetic resolution of a hydroxy vinylsulphone with the two chosen chiral catalyst precursors, (**107**) and (**108**).



(**111**) (**175**) (**220**)

(*R*)- (**107**) (*S,S*)- (**108**)

Figure 3.31

Trial reactions were carried out with both chiral catalyst precursors, (**107**) and (**108**), with the phenyl substituted hydroxy vinylsulphone, (**132**), as a substrate. A 30 mg sample of the substrate, (**132**), together with 2 mol % of freshly prepared catalyst precursor, either (**107**) or (**108**), was dissolved in dry, degassed methanol in a water-jacketed Schlenk tube. The solution was thoroughly degassed by five freeze-pump-thaw cycles and the atmosphere in the reaction vessel replaced with hydrogen at 1.5 atm. The rate of reaction was monitored by the hydrogen pressure change using a specially designed hydrogenator, the details of which are presented in the following Chapter (4).

Hydrogenation with the (DiPAMP)rhodium catalyst precursor, (**108**), proceeded at a moderate rate. No reaction, as judged by gas uptake and ^{1}H NMR of the reaction mixture, was observed, however, with the (BINAP)rhodium system. Two further attempts

to hydrogenate (**132**) with the BINAP catalyst under identical conditions were made, but both of these were unsuccessful. The efficacy of the (BINAP)rhodium catalyst precursor, (**107**), was tested in the hydrogenation of 3-methyl dimethylitaconate, (**220**), and found to be good.

The reason for the effective inactivity of the BINAP catalyst in the hydrogenation of (**132**) was not investigated, and efforts were concentrated on the more promising DiPAMP system.

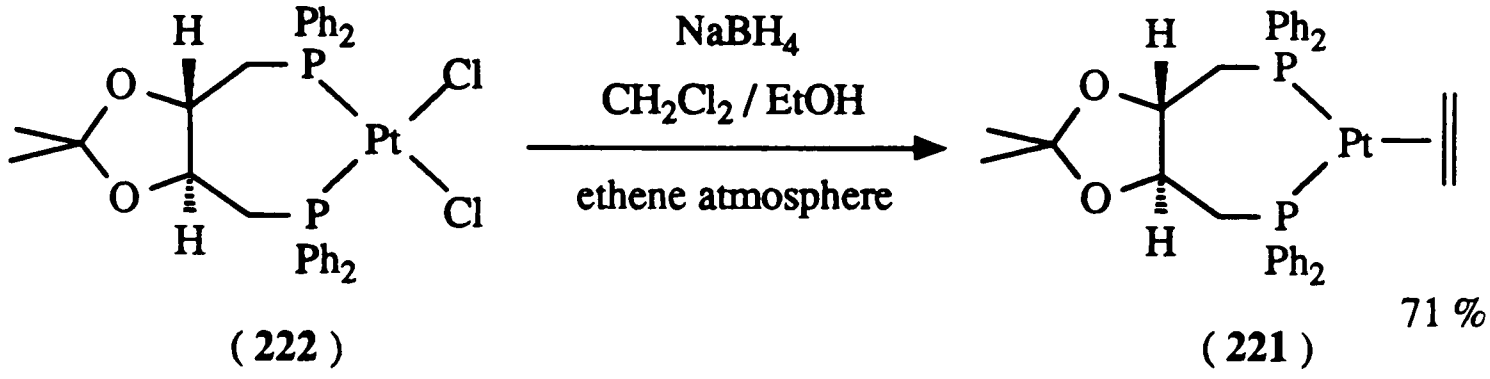
The kinetic resolution of (**132**) was carried out on a preparative scale with two samples, 300 mg and 200 mg (run 1 and 2). A gas burette was used to monitor the rate of hydrogen uptake. These hydrogenations were monitored using a gas burette due to the limits imposed by the size of the hydrogenator (described fully in Chapter 4). The extent of reaction in these two cases, determined by ^{1}H NMR, was found to be 50 % for run 1, and 57 % for run 2. Work-up involving trituration with hot diethyl ether gave a mixture of the starting material and product, in a combined yield of 96 % and 90 % for the respective runs.

Attempts to separate the starting material and product by preparative t.l.c. failed on silica gel and alumina, with a variety of solvent systems. Fortunately, a 100 mg sample of the starting material/product mixture from run 2 (57 % completion) was separated by Dr. C. Bevan at GLAXO, in Greenford. The conditions employed were identical to those used with the separation of the hydroxy vinylsulphoxides : a LiChrosorb diol packed column, eluting with 9:1 heptane/ethanol.

The enantiomerically enriched samples of starting material, (**132**), and product, (**179**), from run 2 gave optical rotations of $[\alpha]_D$ of +58.07 and +13.7, respectively in chloroform (c=1) at 20°C.

The enantiomeric excess of the starting material in the two runs was determined by two NMR methods. Method 1 involved the chiral derivatisation of the starting material mixture with a (DIOP)platinum complex,[118] (**221**), while method 2 involved the use of a chiral europium shift reagent.[119] Neither of these two methods relied on the separation of the starting material and product, and so both were carried out on samples of the mixture of the two.

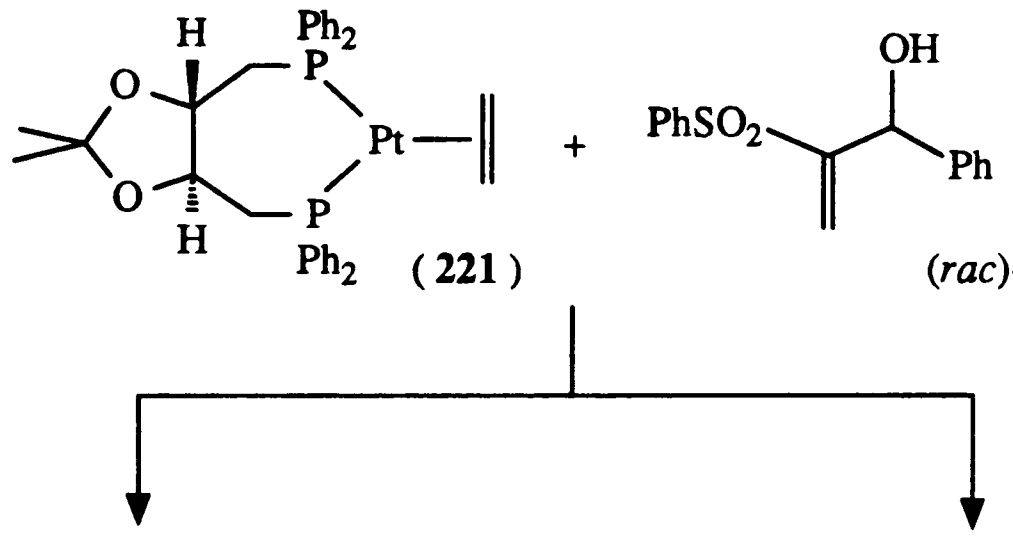
Method 1 required prior synthesis of the platinum complex, (**221**), by a reported method[120] from (*S*,*S*)-(DIOP)platinum dichloride,[121] (**222**) (Figure 3.32).



(**222**) (**221**)

Figure 3.32 - Preparation of (*S*,*S*)- (DIOP)platinum ethene complex, (**220**).

Initially the mixture of the racemate of (**132**) and the platinum complex must be considered.



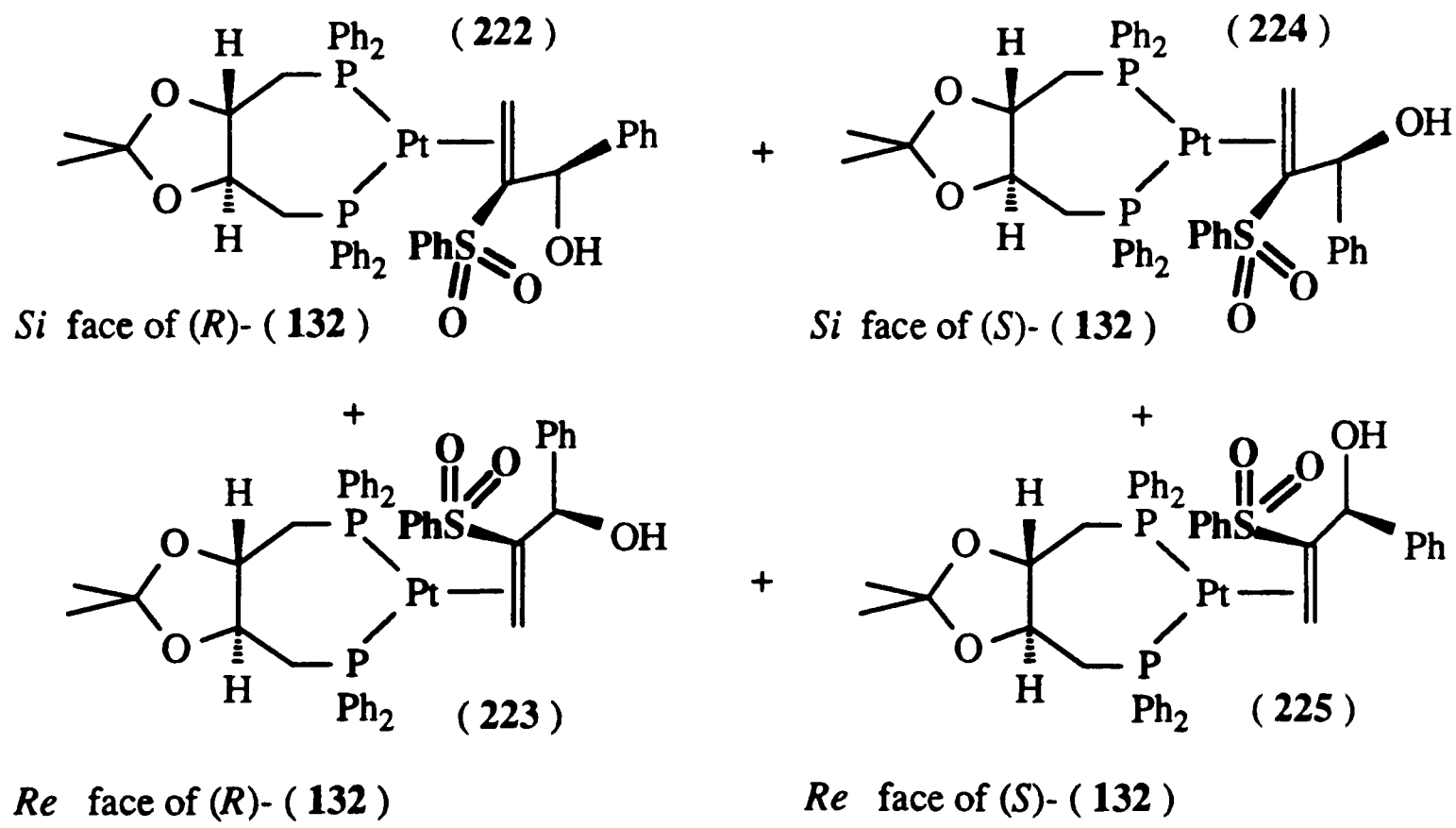


Figure 3.33 - Formation of the four platinum vinylsulphone complexes.

The analysis was carried out by stirring a 60 mg sample of the mixture of starting material and product with 20 mg of (*S*,*S*)-(DIOP)platinum ethene, (**221**), for 30 minutes in tetrahydrofuran. The solvent was removed *in vacuo*, and the residue taken up into d^6-benzene, which is known to maximise the chemical shift anisochronicity between the diastereomers.[122] The ^{31}P NMR was then taken at 202.46 MHz.

The two enantiomers of the starting material each possess two faces of a carbon-carbon double bond with which to bind to the platinum metal centre. This means that there are four possible complexes formed, (**222**)- (**225**), although not necessarily in equal proportions (Figure 3.33). In practice, the spectrum of the racemate and the (DIOP)platinum complex, (**221**), contains only three sets of peaks (each being a doublet of doublets) plus their attendant ^{195}Pt satellites.

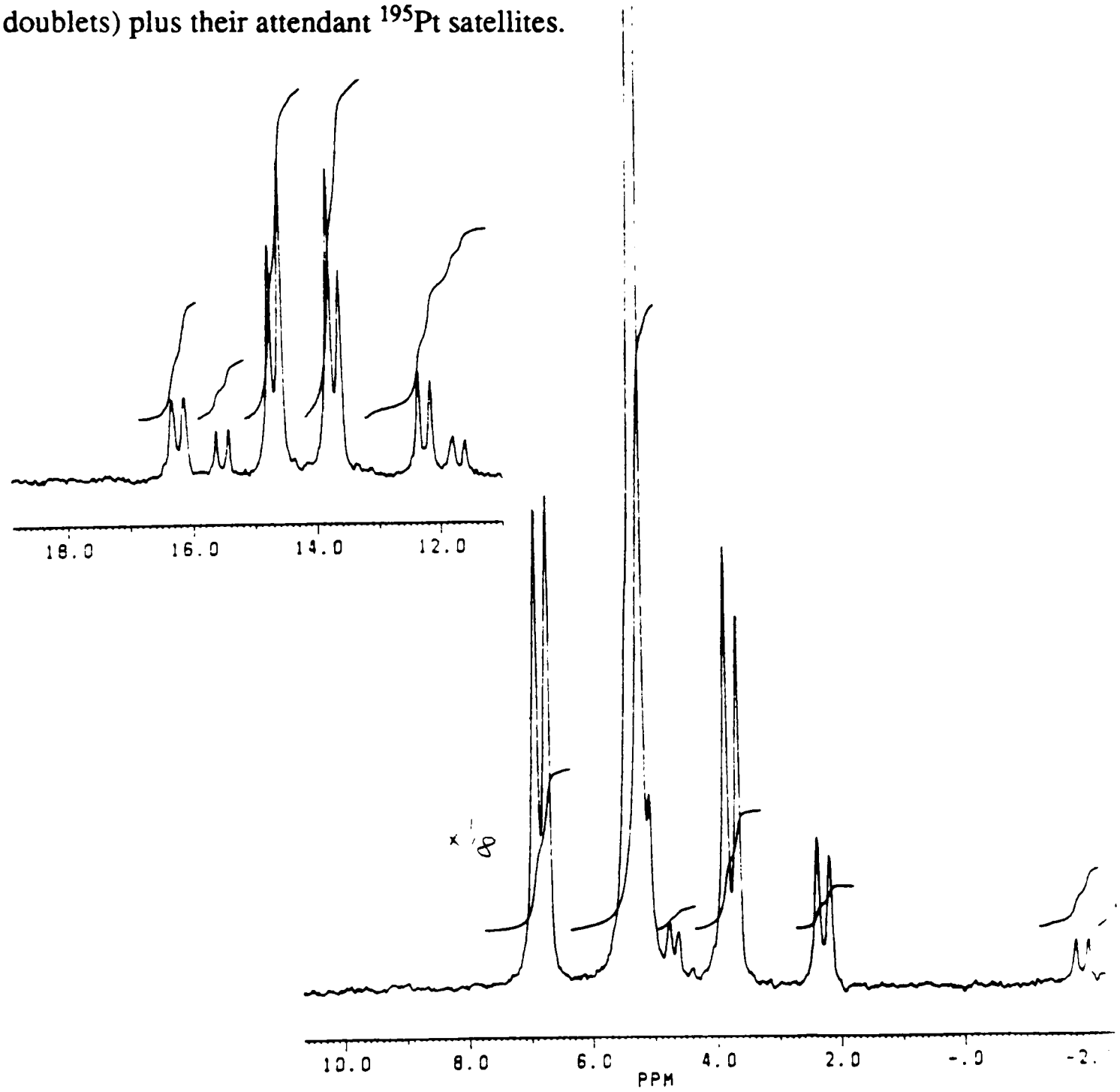


Figure 3.34 - ^{31}P NMR of (*rac*)-(**132**) and (*S*,*S*)-(**221**)

Examination of the spectra of the mixtures of starting material and product from the kinetic resolutions of (**132**) indicated that the e.e. of the starting material was 76 % for run 1, and 89 % for run 2. E.e.'s were determined by comparing the integrals of two pairs of peaks, arising from different enantiomers of the starting material, in the racemate spectrum with the equivalent peaks in the spectrum, of the enantiomerically enriched materials. The spectrum obtained for run 2, which went to 57 % completion, is shown in Figure 3.35.

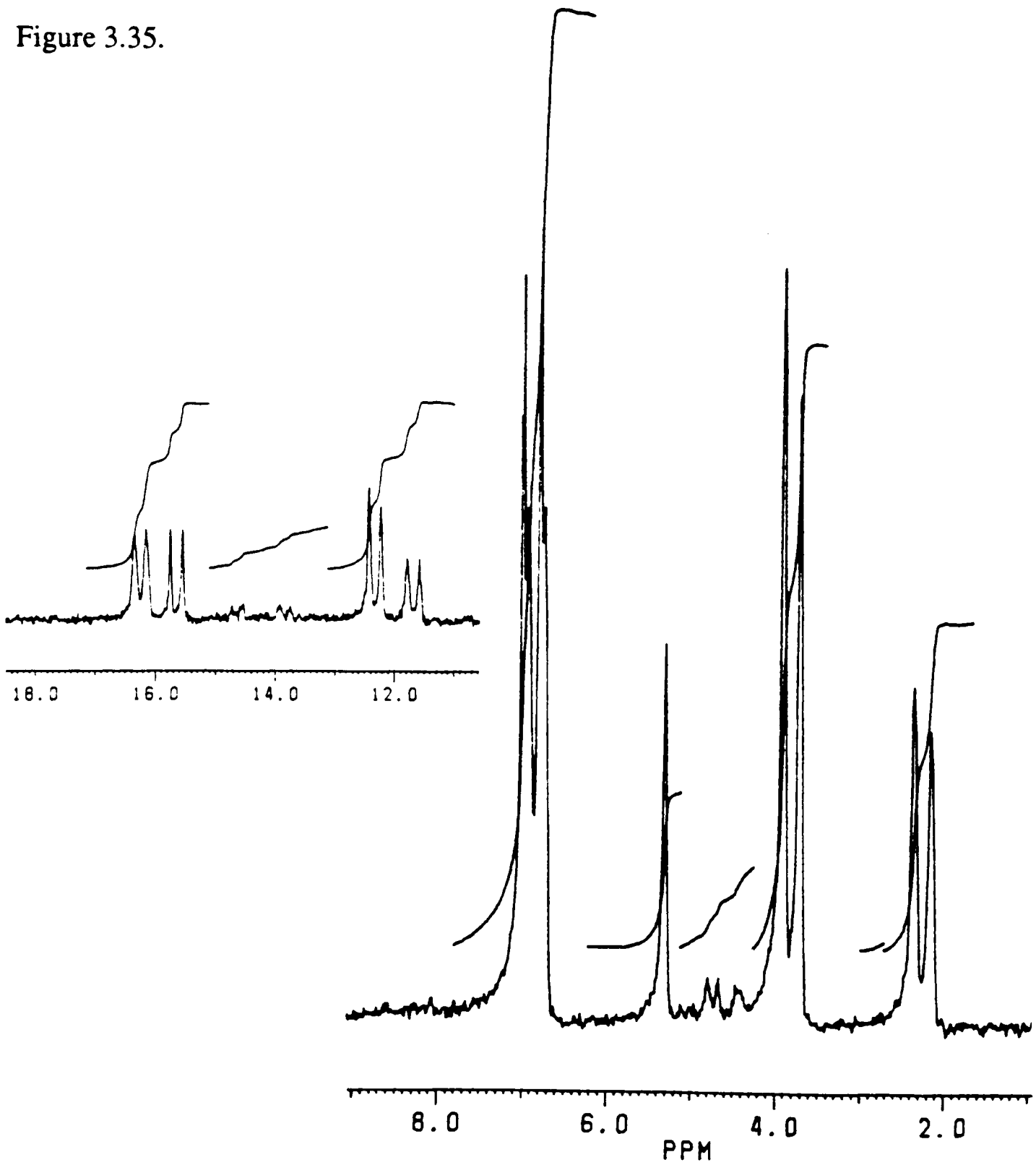
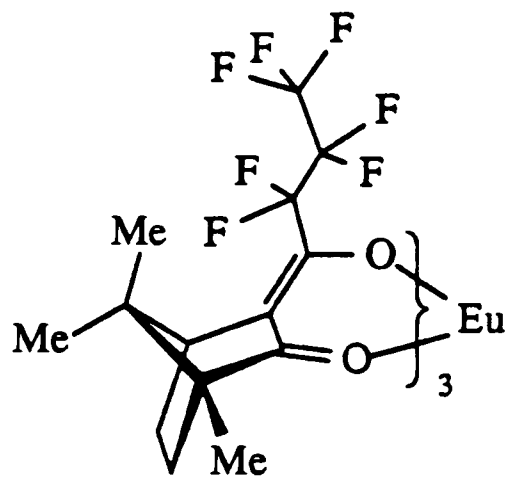


Figure 3.35 - ^{31}P NMR of (**221**) and products from run 2.

The e.e. of the starting material in run 1 was confirmed by a separate NMR shift experiment. In strictly anhydrous conditions, 3 mg of the mixture of starting material and product from run 1 in d^8-toluene was examined by ^1H NMR at 500 MHz. An aliquot of a

pre-prepared solution of the europium paramagnetic shift reagent, (**226**), was added to the NMR sample, to give a 10 mol% ratio of (**226**) to the starting material.



(**226**)

The ^{1}H NMR spectrum was taken, examined for paramagnetic splitting of the starting material or product peaks, and the amount of shift reagent increased in steps. With 26 mol% of (**226**) present in the NMR sample almost baseline separation was observed for one of the starting material vinyl peaks. This was improved upon by a twofold dilution of the sample to give the separation shown in Figure 3.36.

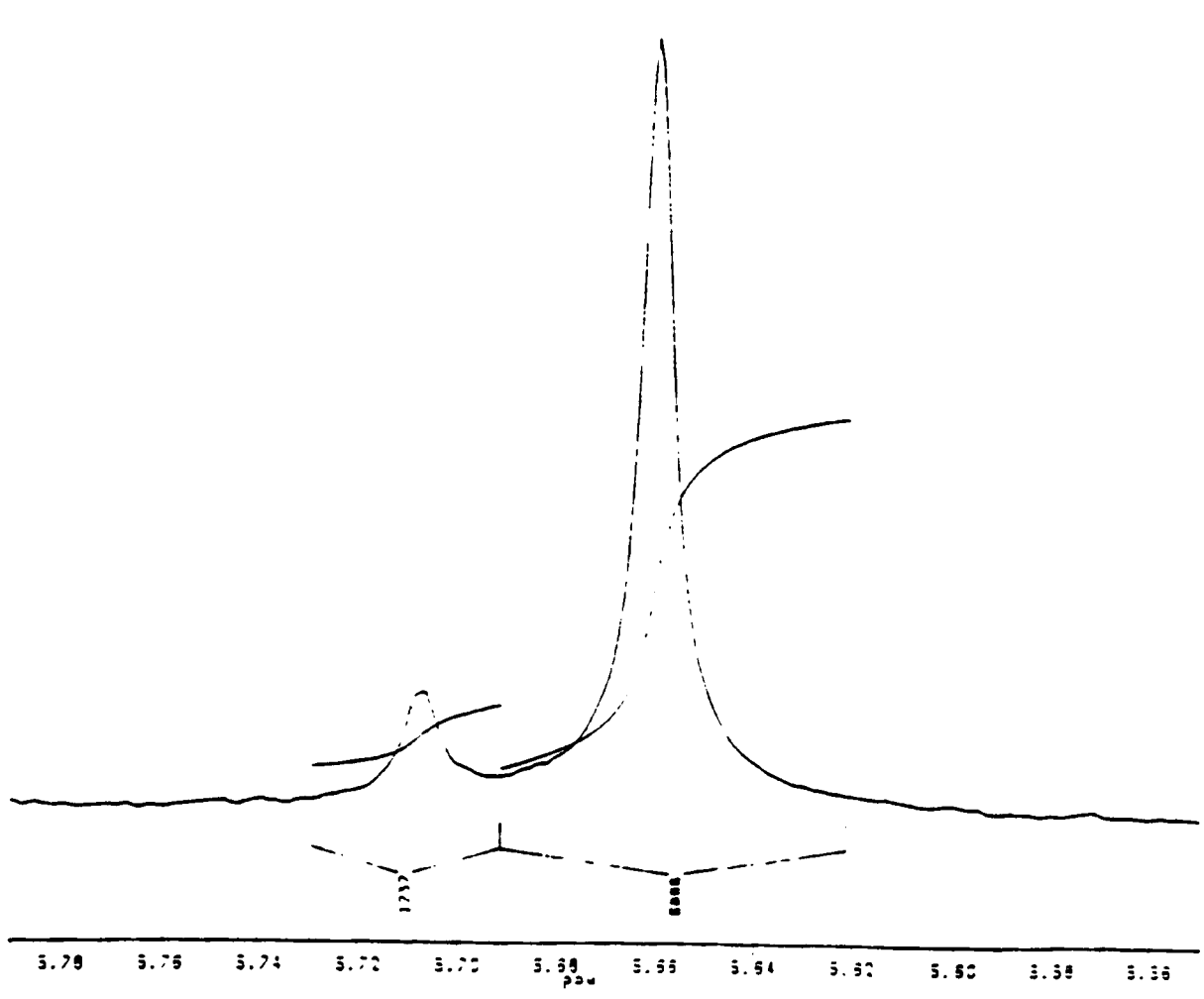


Figure 3.36 - A section from the ^{1}H NMR europium shift experiment

By cutting out and weighing the two peaks, the starting material from run 1 was found to be 77 % e.e. This is in agreement with the result obtained earlier with the chiral

derivatising agent, (DIOP)platinum ethene.

The spectrum of the racemic starting material, (**132**), was taken with the same concentrations of (**132**) and (**223**), to confirm that the vinylic signal was indeed split. In this spectrum the vinyl peak was split into two signals of equal intensity as expected.

The results obtained in the kinetic resolution of (**132**) by (DiPAMP)rhodium(I) hydrogenation are summarised in Figure 3.37.

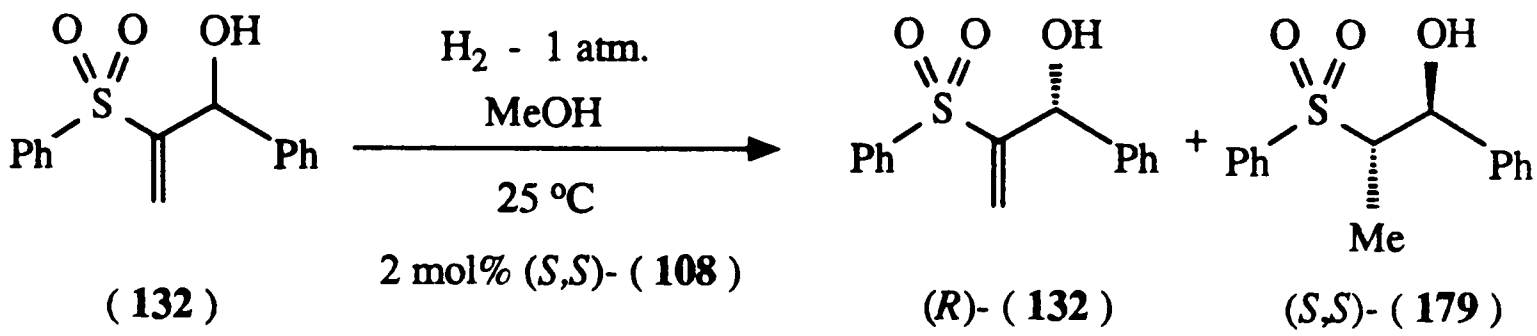
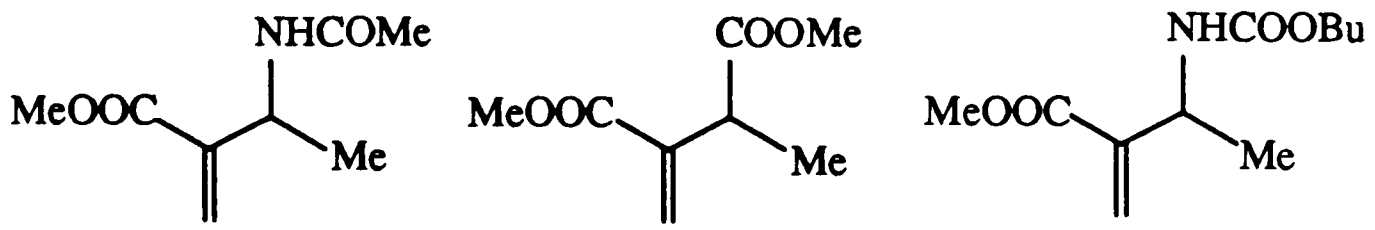


Figure 3.37 - Summary of kinetic resolution results with (**132**).

The absolute configurations of the enantiomerically enriched starting material and product, (*R*) and (*S*,*S*) respectively, were assigned by analogy with the kinetic resolution of substituted acrylates with (DiPAMP)rhodium(I) catalysed hydrogenations.[71, 77, 123]

The Selectivity Factor, S, for the (DiPAMP)rhodium(I) catalysed hydrogenation of hydroxysulphone, (**132**), is 17. This value is much higher than those obtained with similar hydrogenations of hydroxyacrylates,[71, 77, 123] which are typically 5-10. It is comparable with values obtained with acetamido acrylates,[77] and itaconate derivatives,[123] which are generally between 10 and 20.

Selected values for comparable selectivity factors for (DiPAMP)rhodium catalysed hydrogenations are shown in Figure 3.38. Note that in these cases the hydrogenations were carried out at 0°C and that reducing reaction temperature in homogeneous hydrogenation is known to increase the selectivity.



	(**111**)	(**220**)	(**227**)
Selectivity Factor, S	15	10	22

Figure 3.38 - Selected selectivity factors for (DiPAMP)rhodium kinetic resolutions.[71, 77, 123]

The kinetic resolution of hydroxy vinylsulphones by (DiPAMP)rhodium hydrogenation compares very favourably with other methods of resolving sulphur compounds. Other methods include the recently reported enzymatic kinetic resolution of hydroxy sulphones[124] and sulphoxides.[125] An example of the lipase catalysed esterification of β-hydroxy sulphones is shown in Figure 3.39.

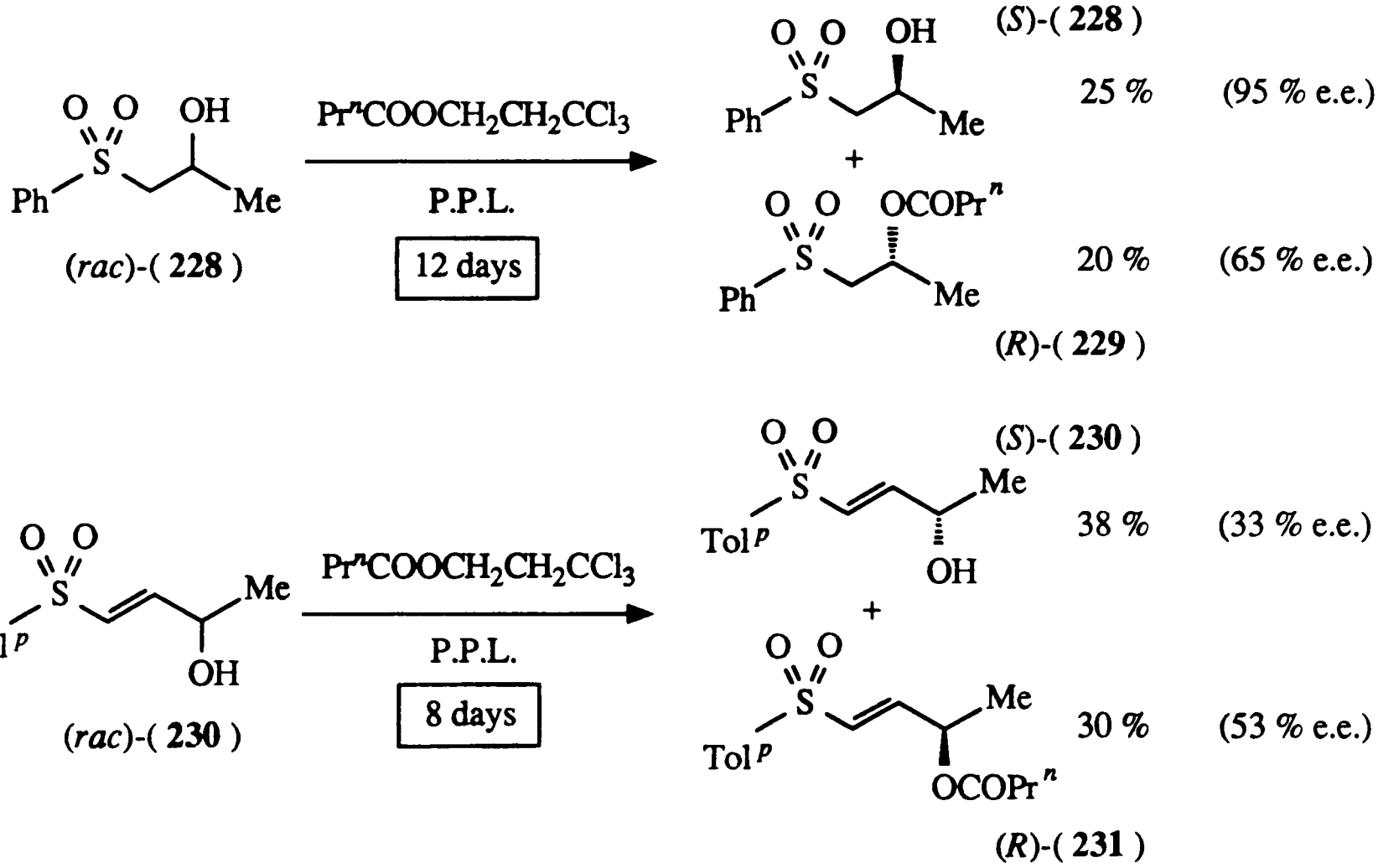


Figure 3.39 - Examples of lipase catalysed esterification.

In conclusion, it has been shown that the hydrogenation of hydroxy vinylsulphones and sulphoxides can be easily accomplished under mild conditions using a rhodium

catalyst. The yields are excellent, as are the stereoselectivities obtained when a non-hydrogen bonding solvent is used. In addition to this, it has been demonstrated that it is possible to effect a kinetic resolution of a hydroxy vinylsulphone, using a chiral rhodium catalyst prepared from (*S*,*S*)-DiPAMP. The sulphoxide has been shown to follow a different mechanistic pathway. This is believed to involve an intermediate containing a sulphinyloxygen-rhodium bond, which, in effect, directs hydrogen addition to one face of the olefinic bond.

Results and Discussion

Analysis of Reaction Kinetics

4.01 Introduction

Understanding the mechanism of a chemical reaction is crucial to the improvement of its performance. To this end, excellent work has been done with homogeneous hydrogenation by Brown,[27, 29] Halpern[5, 24, 26] and others leading to a set of results that define two possible mechanisms, discussed briefly in Chapter 1. These studies have relied upon, for the major part, determining the kinetics of notional reaction steps in isolation, or studies of putative intermediates.

In this Chapter it is intended to present an apparatus for monitoring gas uptake at constant volume, together with results obtained with the apparatus in the hydrogenation of a number of substrates. It is also intended to detail a numerical analysis of these results, which was performed to determine kinetic parameters for a simplified reaction model. This differs from the common approach in as much as the reaction is treated as an ensemble rather than single steps in isolation from each other.

4.02 Instrumentation

The simplest way to obtain information about the progression of a hydrogenation reaction is to use a gas burette at constant pressure. Monitoring the course of hydrogenation with the aid of a burette over a prolonged time period, however, can be tedious at best, and inaccurate at worst. Small fluctuations in ambient temperature and pressure will affect the volume of gas in the apparatus, and consequently the readings taken. To overcome this problem, the whole apparatus, including burette, must be insulated from temperature changes. Such an approach to the problem has been taken by Marks and coworkers.[126] The measurement of the rate of organolanthanide catalysed hydrogenation in this case, was achieved with the aid of an elaborate reaction vessel and

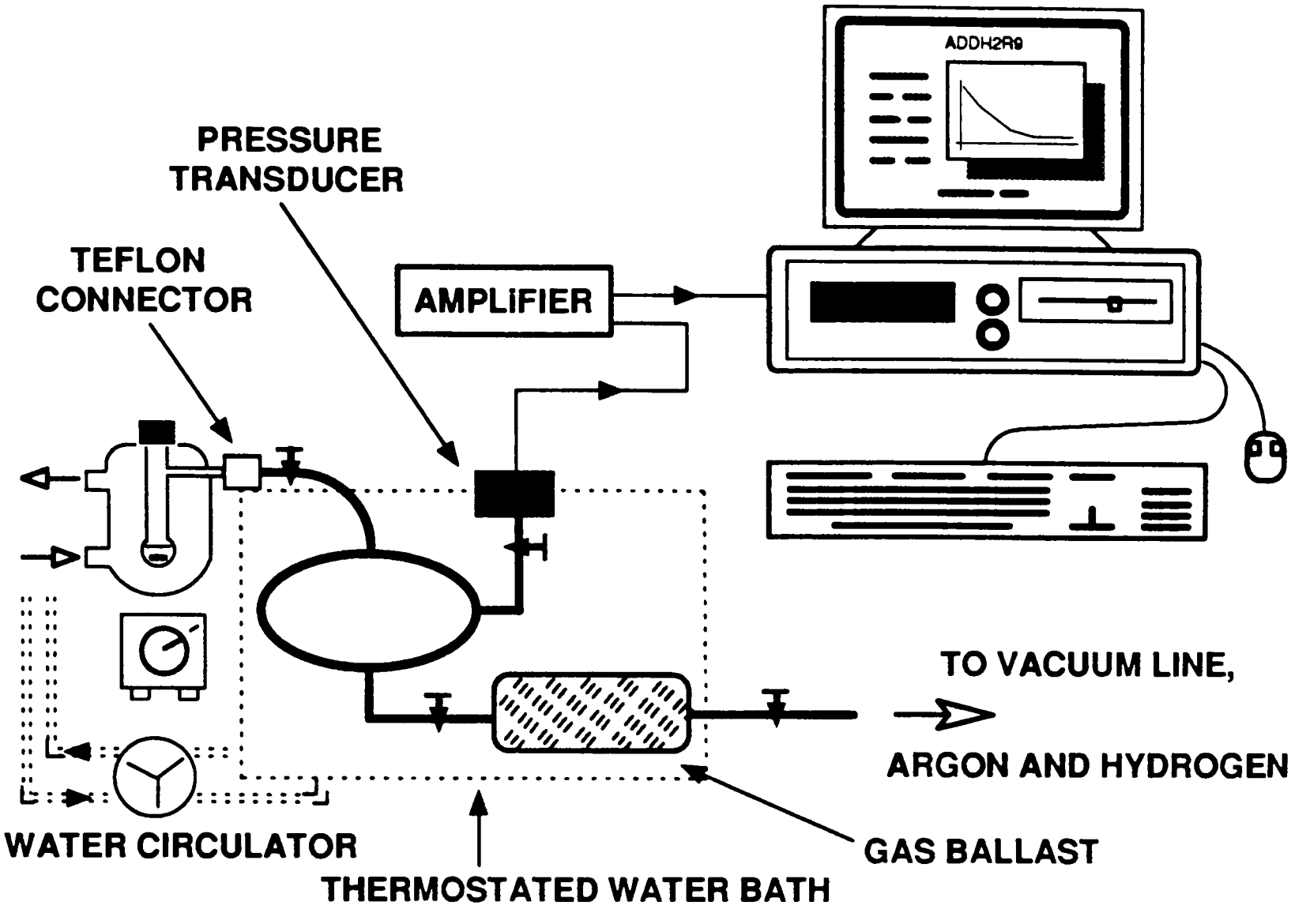
electronic differential manometer.[126] Since the pressure decrease was less than 2 % the system was regarded as pseudo constant pressure.

True constant pressure measurement of reaction rates involving changes in gas volumes has been reported by Jorden.[127] The change in pressure during evolution of nitrogen from the decomposition of 1-azido-1-phenylethene was corrected using a stepper motor connected to a personal computer. The activity of the stepper motor, controlled with a program written in BASIC, was then stored in the computer and converted to an increase in gas volume.

The limitations of the constant pressure apparatus described by Jordan[127] are twofold - 1) rather viscous movement of the plunger of the gas syringe, used to release the increase in pressure, can lead to sluggish response to even moderate rates of gas evolution; and 2) the complexity of the arrangement with two separate inputs to be monitored, which depend on each other, means that errors in measurements taken are compounded rather than negated.

These instrumentation problems can be overcome to a large extent by operating at constant volume. A closed system, thermostated appropriately, is effectively isolated from its surroundings and hence not subject to the constraints of the constant pressure equivalents. With this in mind, a constant volume hydrogenation apparatus was assembled in collaboration with Mr. A.D. Conn.[74] This apparatus was modified by simplifying the reaction vessel and introducing a custom-written computer program. A schematic representation of the set-up is shown in Scheme 4.01.

A full description of the hydrogenation apparatus appears in the Experimental section. Briefly, the apparatus consists of six parts - a water-jacketed reaction vessel, a frame of 1/8" metal tubing contained in a thermostated water bath, a pressure transducer, a voltage amplifier and a personal computer fitted with an analogue to digital converter (ADC). The reaction vessel is linked to the metal frame, which also contains a gas ballast, with the aid of a teflon® tubing-connector. The pressure of the system is determined from the voltage output of the pressure transducer, which is taken into the digital domain by the ADC expansion card.



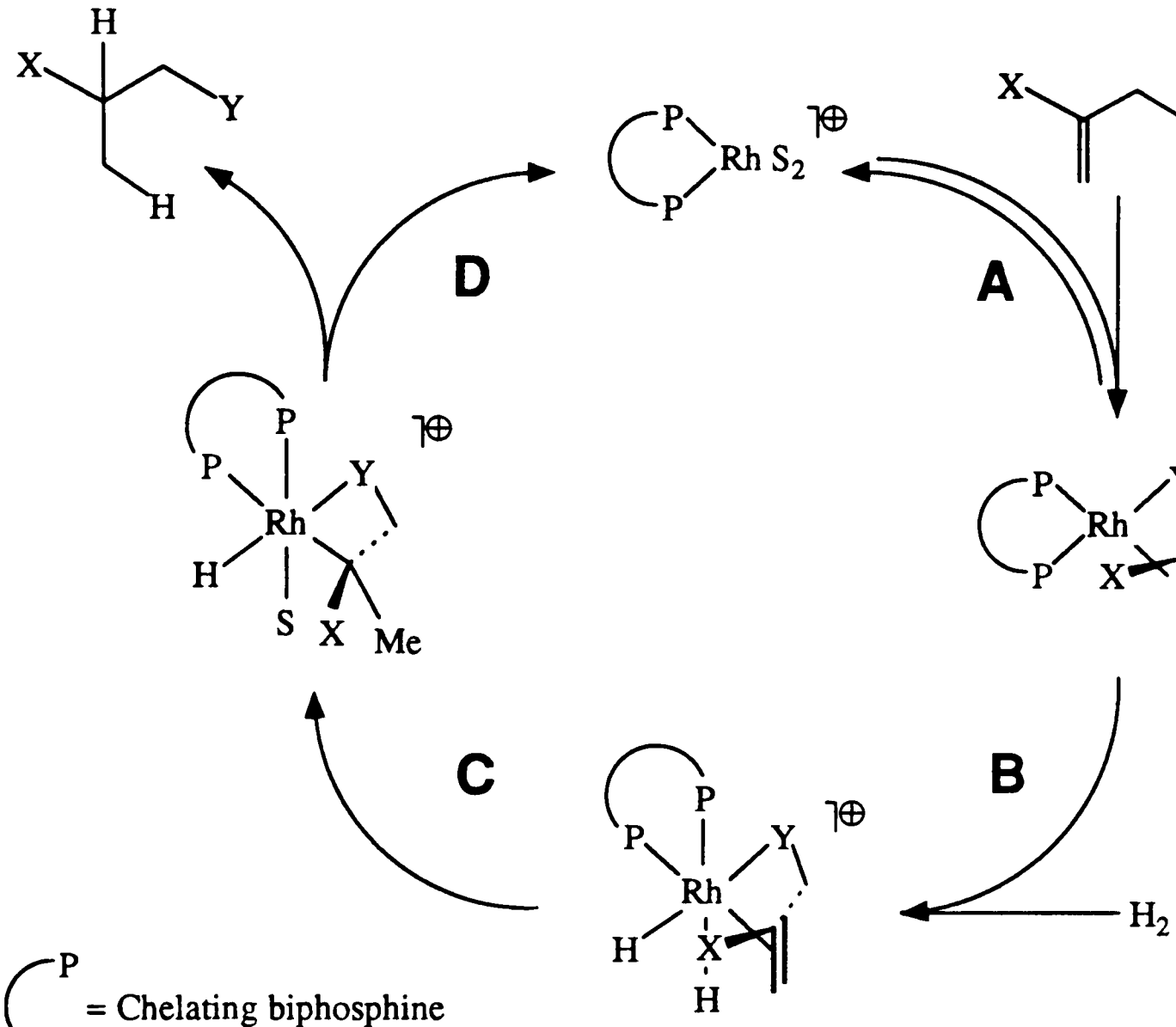
Scheme 4.01 - The constant volume hydrogenation apparatus.

The program, used to calibrate the pressure readings, monitor the pressure transducer and display the data as accumulated, is to be found in full in Appendix B. A description of how it works is also included in the Experimental section. Briefly, the program is built around an interrupt driven routine, the frequency of which can be altered from within the program. This routine takes a reading of the amplified voltage output of the pressure transducer and converts it to a pressure by the use of a calibration factor. It then saves the pressure and time into the experiment to a fixed disk, and updates the graphical display of the pressure versus time on the P.C. monitor. The limitations imposed by the C.P.U. and fixed disk speed mean that sampling rates of up to 1 Hz are achievable.

4.03 Numerical Analysis

A drawback with the constant volume apparatus is the complexity of the overall rate law for the hydrogenation reaction. Based on even the simplest mechanism as shown

in Scheme 4.02, the rate equation is not amenable to full analytical solution. Since the hydrogen pressure changes during the course of the reaction, the steady state approximation is not applicable.



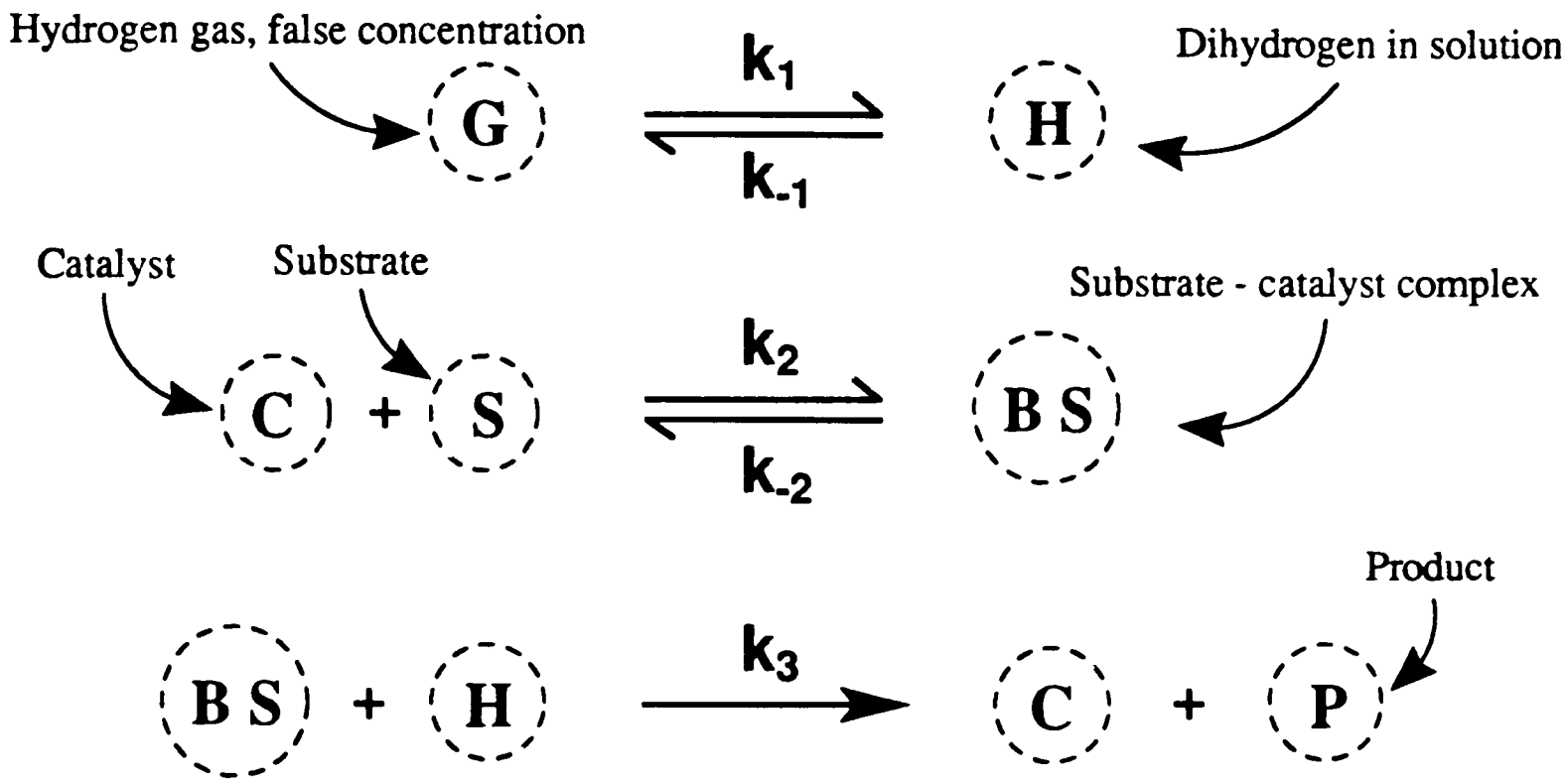
Scheme 4.02 - A simple mechanism for rhomogeneous hydrogenation.

This problem can be circumvented by turning to numerical methods of solving the equations. The growth in computing power over the past decade has enabled this to be accomplished in a matter of minutes, on a desktop personal computer.

In practice, two programs were used to analyse the data obtained in hydrogenations carried out in the constant volume hydrogenator : 1) GEAR[128] - a simulation program that integrates a given set of equations to give species concentrations as a function of time; and 2) GIT[129] - a program to fit a reaction model to a set, or sets of data.

4.04 Model used in Analysis of Results

For the purpose of modelling hydrogenation reactions with achiral catalyst precursors a set of simple equations was set up. It can be seen from the model (Scheme 4.03) that it directly parallels the mechanism as it is understood[24] in all but one respect- the hydrogen transfer step is condensed into one step. The reason for this will be explained later in this Chapter.



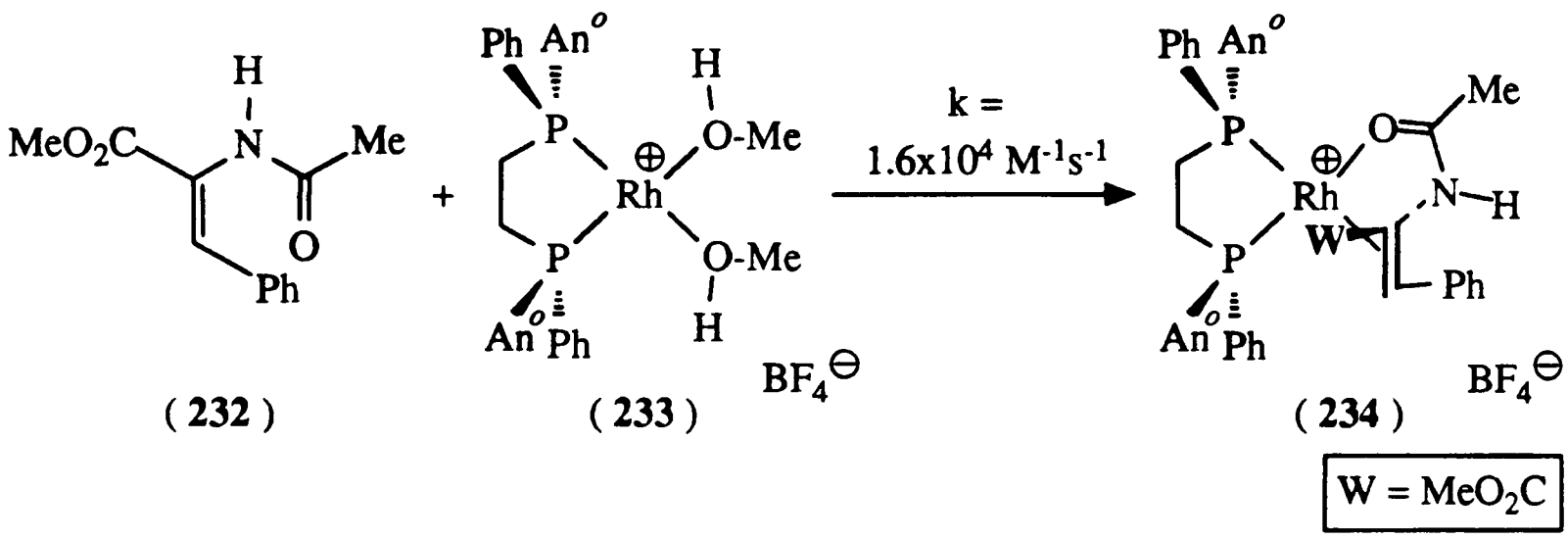
MECHANISM 1.

Scheme 4.03 - Kinetic model used in numerical analysis of hydrogenation reactions.

The first equilibrium, between a notional species, **G**, and dihydrogen in solution, **H**, is formally the transport of hydrogen into solution. It takes into account the change in pressure that occurs during the course of a reaction since **G** diminishes accordingly. In practice, **G** is equal to the concentration of hydrogen in solution if all the hydrogen gas in the apparatus was dissolved in the volume of the solvent. The two rate constants, k_1 and k_{-1}, were determined by diffusion rate experiments, described later.

The second equilibrium is between the catalyst, as its solvate, **C**, the substrate, **S**, and the bound-substrate complex, **BS**. The forward rate constant, k_2, was assumed to be 27000 $M^{-1}s^{-1}$. This Figure was used because Halpern[24] obtained a value of this order of magnitude for the rate constant of complexation of methyl acetamidocinnamic acid, (**232**), to a (DiPAMP)rhodium(I) methanol solvate complex, (**233**). In practice, reducing this value whilst maintaining the same equilibrium constant made no difference to the results

obtained. The absolute value of this rate constant is not important as long as it is much larger than the others in the cycle. This prevents the complexation step becoming rate determining in the model.



(232) (233) (234)

Figure 4.01 - A complexation reaction used in kinetic studies by Halpern.[24]

The value of the reverse rate constant, k_{-2}, was varied in order to produce the "best fit" to the model for a given data set. Hence this gave an equilibrium constant, K_{BIND}, for the binding step in the catalytic cycle.

The third equation represents the substrate-catalyst complex, **BS**, reacts with dihydrogen in solution to give the product. This represents three steps in the catalytic cycle and thus simplifies the model significantly. Neglecting to add two steps is valid for two reasons :

1) The substrate-rhodium-dihydride complex has proved impossible to observe even at low temperatures.[29] This means that as soon as the dihydride complex is formed, it rearranges to form the alkyl hydride complex.

2) The rate of collapse of the rhodium alkylhydride complex to the product is, in turn, extremely fast at 25°C. This is demonstrated by the fact that these intermediates are observable, by ^{31}P NMR, only at temperatures below -40°C.[130]

The rate constant for the third equation, k_3, was varied in conjunction with k_{-2} in the kinetic analysis. This produced the "best fit" to the model for a given data set.

4.05 Diffusion Rate Experiments

In order to be able to fit a data set to the kinetic model, both the forward and reverse rate constants, k_1 and k_{-1}, needed to be found. This was achieved by diffusion rate

experiments, in which the rate of hydrogenation was mass-transport-limited.[131]

The hydroxyacrylate, (**175**), a reasonably fast reacting substrate, was chosen for diffusion rate experiments. Hydrogenations were carried out, in the constant volume hydrogenator, with an initial substrate concentration of 0.1 M and with different concentrations of the catalyst precursor, (**105**) (Figure 4.02). The experiments were repeated for two solvents- methanol and 1,2-dichloroethane.

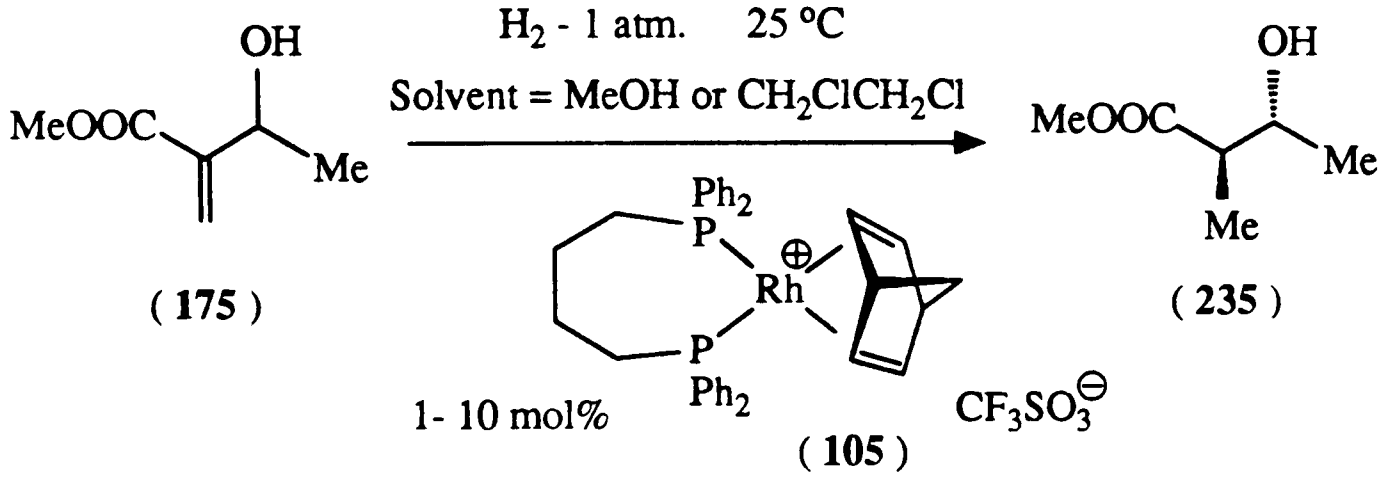


Figure 4.02 - Experiments used to determine the rate of hydrogen diffusion into solution.

The initial rate of hydrogenation was determined for each experiment, by a least squares regression analysis of the pressure change in the apparatus, in the first 2 minutes of each experiment. A simple formula, shown in Figure 4.03 and derived in Appendix C, was used to convert the pressure change from mbar s^{-1} to mol l^{-1} s^{-1}

$$\rho_{\text{mol l}^{-1}\text{ s}^{-1}} = \rho_{\text{mbar s}^{-1}} \times \frac{V_A}{RTV_S}$$

ρ_z = rate expressed in z units
R = Gas constant, 83.140 mbar l mol^{-1} K^{-1}
V_A = volume of apparatus excluding solvent, 0.01679 l
T = tempertaure of apparatus, K
V_S = volume of solvent, 0.001 l

Figure 4.03 - Equation used to convert rate of hydrogenation expressed in mbr s^{-1} to mol l^{-1} s^{-1}.

The variation of rate of initial rate of hydrogenation in methanol is displayed graphically in Figure 4.04. By increasing the initial concentration of the catalyst precursor, (**105**), the initial rate of hydrogenation increased towards an asymptotic value,

which corresponds to the rate of transfer of hydrogen across the gas/liquid interface. It can be seen from the graph that the rate of hydrogenation is diffusion controlled at relative catalyst concentrations of greater than approximately 6 mol% in methanol. Similar results were obtained for 1,2-dichloroethane as solvent.

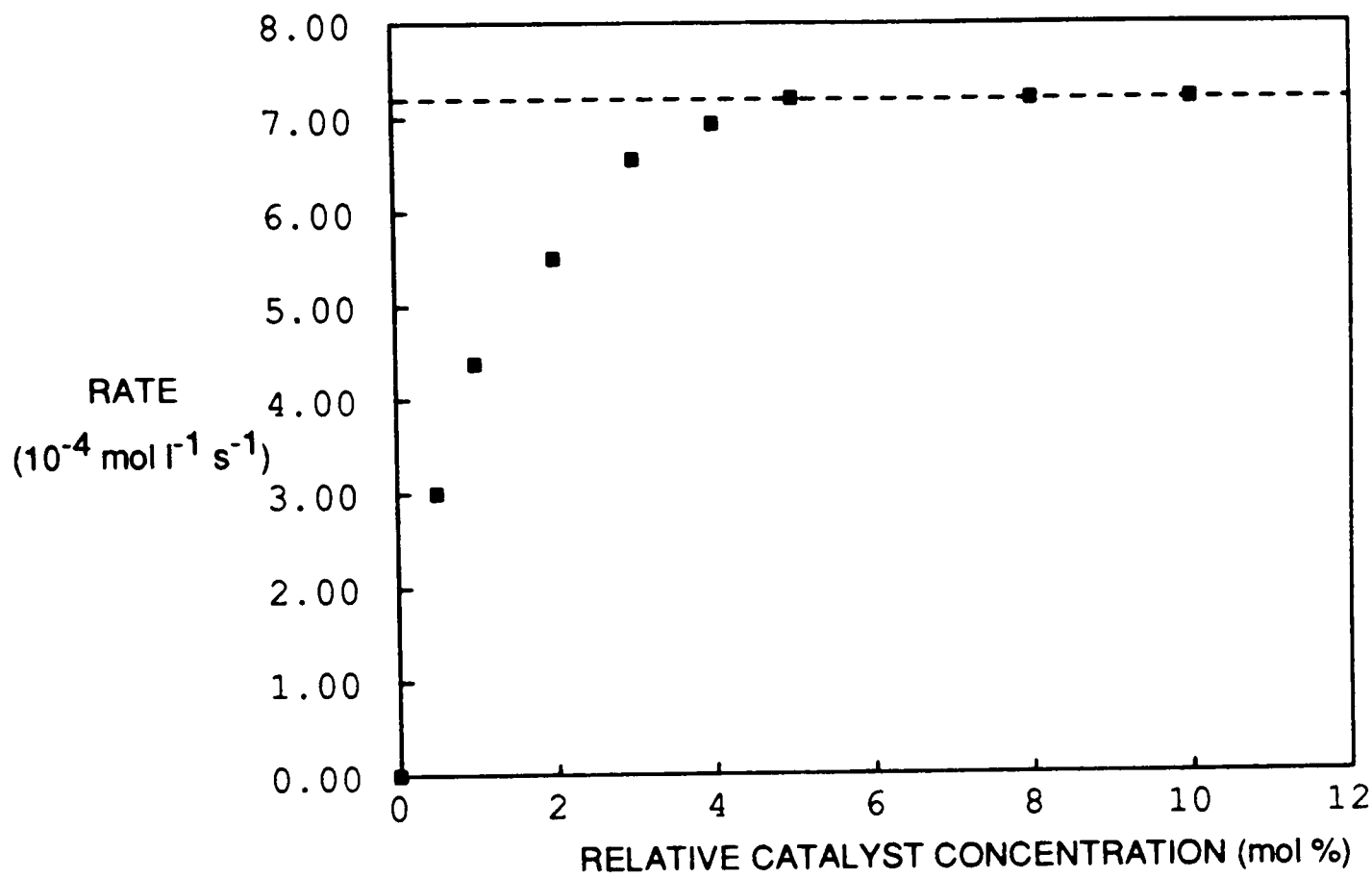


Figure 4.04 - The initial rate of hydrogenation of (**175**) as a function of catalyst precursor loading, with an initial hydrogen pressure of 1.5 atm.

Since it was known that experiments were diffusion controlled with greater than 6 mol% relative catalyst concentration, a set of five experiments were performed in methanol at different initial pressures varying from 600 to 1500 mbar.

The variation of the initial rates of hydrogenation are represented graphically in Figure 4.05. The dashed line on this graph represents a linear regression fit to the five datapoints, which are indicated by a square. It can be seen from the graph has a non-zero pressure-axis intercept. In practice, this means that the rate of hydrogenation is zero at an apparatus pressure that is appreciably greater than zero.

This phenomenon is a direct consequence of the vapour pressure of the solvent in the apparatus. The intercept on the pressure-axis and consequently the vapour pressure of methanol predicted from these measurements is 174 mbar. The literature value for this, 169.58 mbar,[132] is in surprisingly good agreement with this.

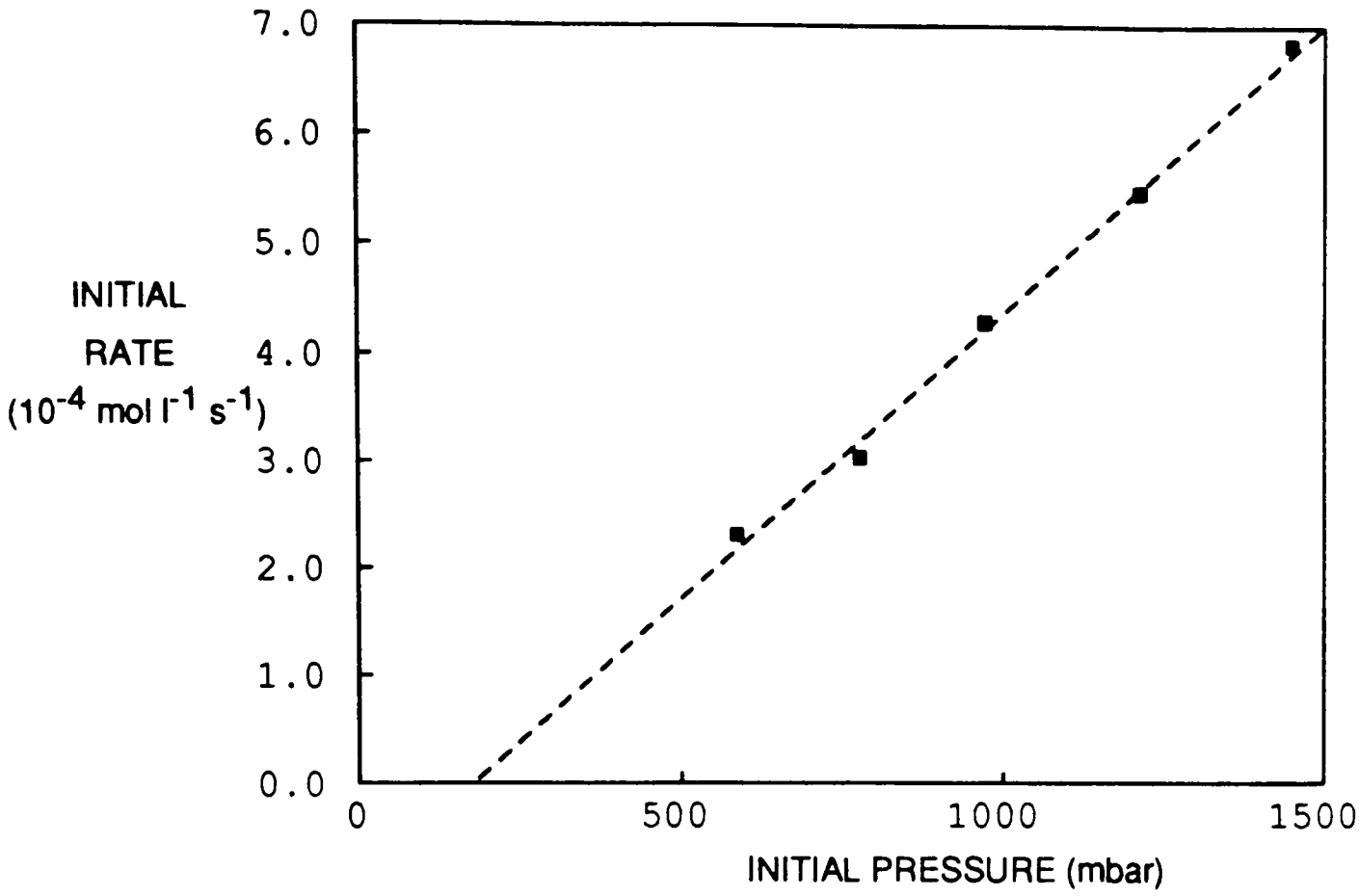


Figure 4.05 - Variation of initial rates of hydrogenation of (**175**) with pressure.

The diffusion data sets were converted to the format used by the numerical iterator, GIT,[129] by a custom written BASIC program, MAKEITR, which appears in Appendix D. This program performed two additional tasks- 1) set the initial concentrations of the species (**G**, **H**, **C**, **S**, **BS**, and **P**), correcting for any pre-hydrogenation; and 2) corrected for the vapour pressure of the solvent in the apparatus in the value of **G**, which was calculated from the initial pressure in the apparatus. The details of how values for **G** were arrived at appear in the Experimental Section.

The concentration of hydrogen gas in methanol[133, 134] and 1,2-dichloroethane[133, 135] is known to be 4.01×10^{-3} mol l^{-1} and 2.24×10^{-3} mol l^{-1}, respectively, under a hydrogen partial pressure of 1 atm. at 25°C. Since **G** is 0.6822 mol l^{-1}, at equilibrium the ratio of reverse and forward rate constants, k_{-1} and k_1, will be given by -

$$k_{-1}/k_1 = G/H_{MeOH} = 180.68 \text{ for methanol}$$

$$\text{and } k_{-1}/k_1 = G/H_{CH_2ClCH_2Cl} = 306.65 \text{ for 1,2-dichloroethane}$$

This was used to fix the ratio of the two aforementioned rate constants, while varying the forward rate constant to obtain the best fit to the relevant data sets. The binding constant, K_{BIND}, for the substrate was set to 100 M^{-1} and the final rate constant,

k_3, was set to 300 s^{-1}. This ensured that the hydrogen diffusion step, G ⇌ H, was rate limiting in the model, as it was known to be in practice.

The results of modelling the diffusion data sets, for both methanol and 1,2-dichloroethane, are summarised in Table 4.01.

SOLVENT	No. OF DATA SETS	k_1 (s^{-1})	k_{-1} (s^{-1})	OVERALL FIT
MeOH	5	7.80×10^{-4}	0.133	9.95×10^{-4}
CH_2ClCH_2Cl	3	4.40×10^{-4}	0.135	2.23×10^{-3}

Table 4.01 - Summary of results from modelling diffusion rate experiments.

The "overall fit" is the average deviation of the data points from the data generated from the model, for all the data sets examined simultaneously. Each data set can be modelled separately to give better individual fits to the model, but the average values for k_1 and k_{-1} generated by a collective analysis are more useful.

4.06 General Modelling of Hydrogenation Results

Values for the binding constant, K_{BIND}, and the rate constant, k_3, as defined by the model presented in Scheme 4.03, were arrived at, for a given substrate, in three steps :

1) The substrate and catalyst precursor were dissolved in the dried, degassed solvent and transferred into the reaction vessel of the constant volume hydrogenator *via* a syringe. The reaction vessel was cooled to -78°C and the entire apparatus evacuated to ≤ 0.1 mbar, then filled with argon to a pressure of 1100 mbar. This was repeated six times then a further four times with hydrogen gas in place of argon. After allowing the apparatus to warm to 25°C, a magnetic stirrer was started to agitate the solvent. The pressure change was then sampled by the P.C. running the custom written program, ADDH2R9, listed in Appendix B. The data was saved as a standard ASCII file. This was repeated for substrate concentration of 0.05- 1.5 M, and relative catalyst concentration of 0.5- 3 mol% in methanol and 1,2-dichloroethane.

2) Since the modelling program, GIT[129], can only handle a maximum of 60 data points and a typical data set contained 200 points, the data files had to be reduced in size. Thus, files were slimmed down using an ASCII editor[136] by removing data points at regular intervals. No weighting was applied to the distribution of data points. These data files were then converted to files, which contained product concentration and time information by the custom written program, MAKEITR, listed in Appendix D. The initial concentration of the model components, **G**, **H**, etc., required by the modelling program were also calculated in the program and added to the individual data files.

3) The final step involved running the modelling program, GIT[129], with a file containing the model rate constants, two of which were marked as variable, and a number of data sets taken with the same substrate, catalyst and solvent combination. This led to a global fit to the data sets, which was used to find individual fits for the data sets. Finally, the individual data sets were modelled and the best values for the two rate constants, k_{-2} and k_3 were found. The full modelling procedure is detailed in the Experimental Section.

4.07 Modelling of Hydroxy vinylsulphone Hydrogenations

The hydrogenation of six hydroxy vinylsulphones was carried out as outlined in the previous section using the (dppb)rhodium catalyst precursor, (**105**). The optimum values for the two variable rate constants, k_{-2} and k_3, for each data set, were then determined by fitting the model to the data set in question as described in full in the Experimental section.

Figure 4.06 shows fit of the data set generated by the hydrogenation of (**132**) with 1.2 mol% of the (dppb)rhodium catalyst precursor, (**105**), in methanol. The solid line represents the data generated from the model by GIT,[129] while filled squares represent experimental points. The "FIT" for this experiment, as outputed by the modelling program, was 8.2×10^{-4}.

Two further data sets for this substrate were obtained with different initial starting material and catalyst concentrations, and different initial hydrogen pressures. These were then modelled both in isolation from each other and together.

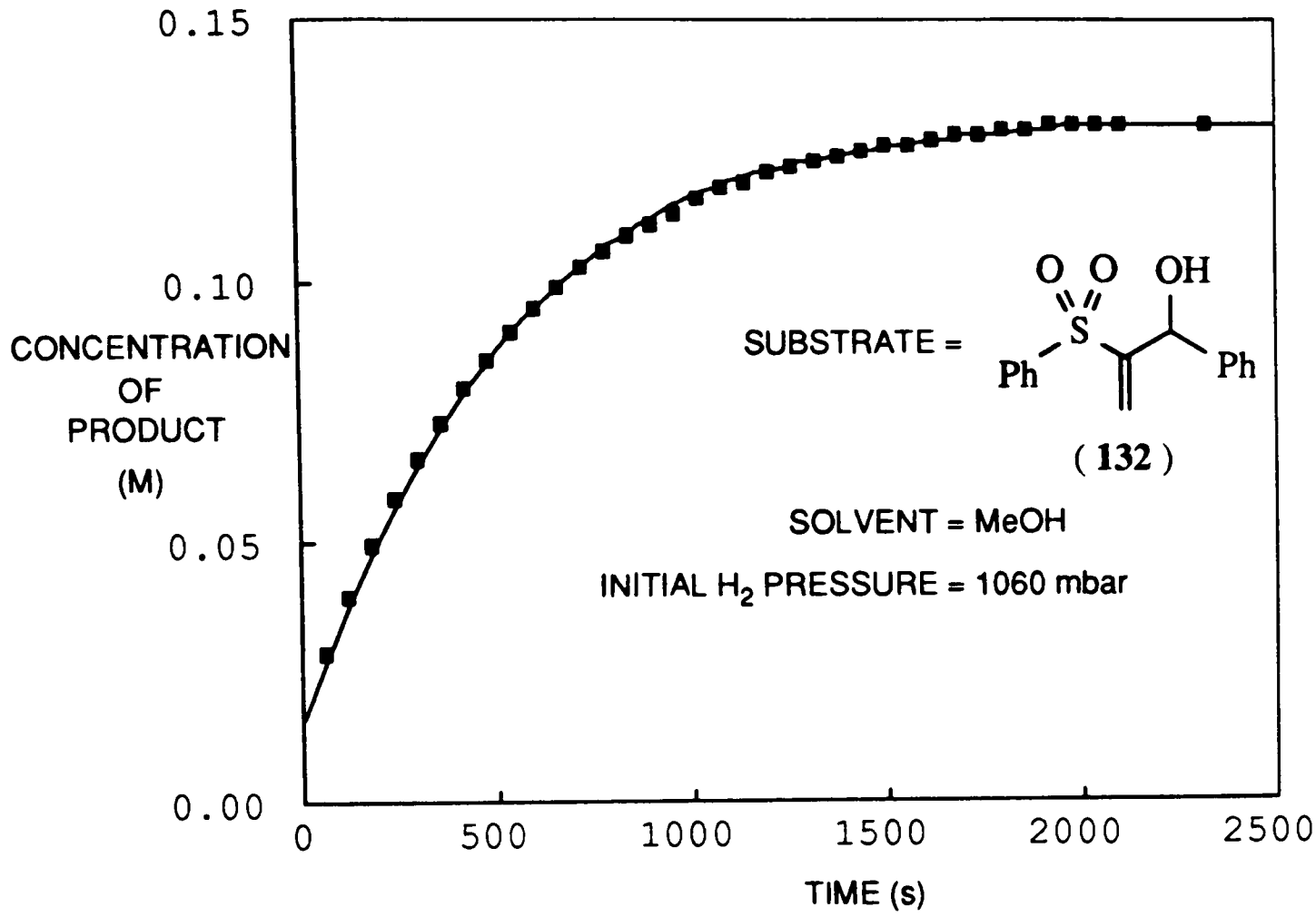
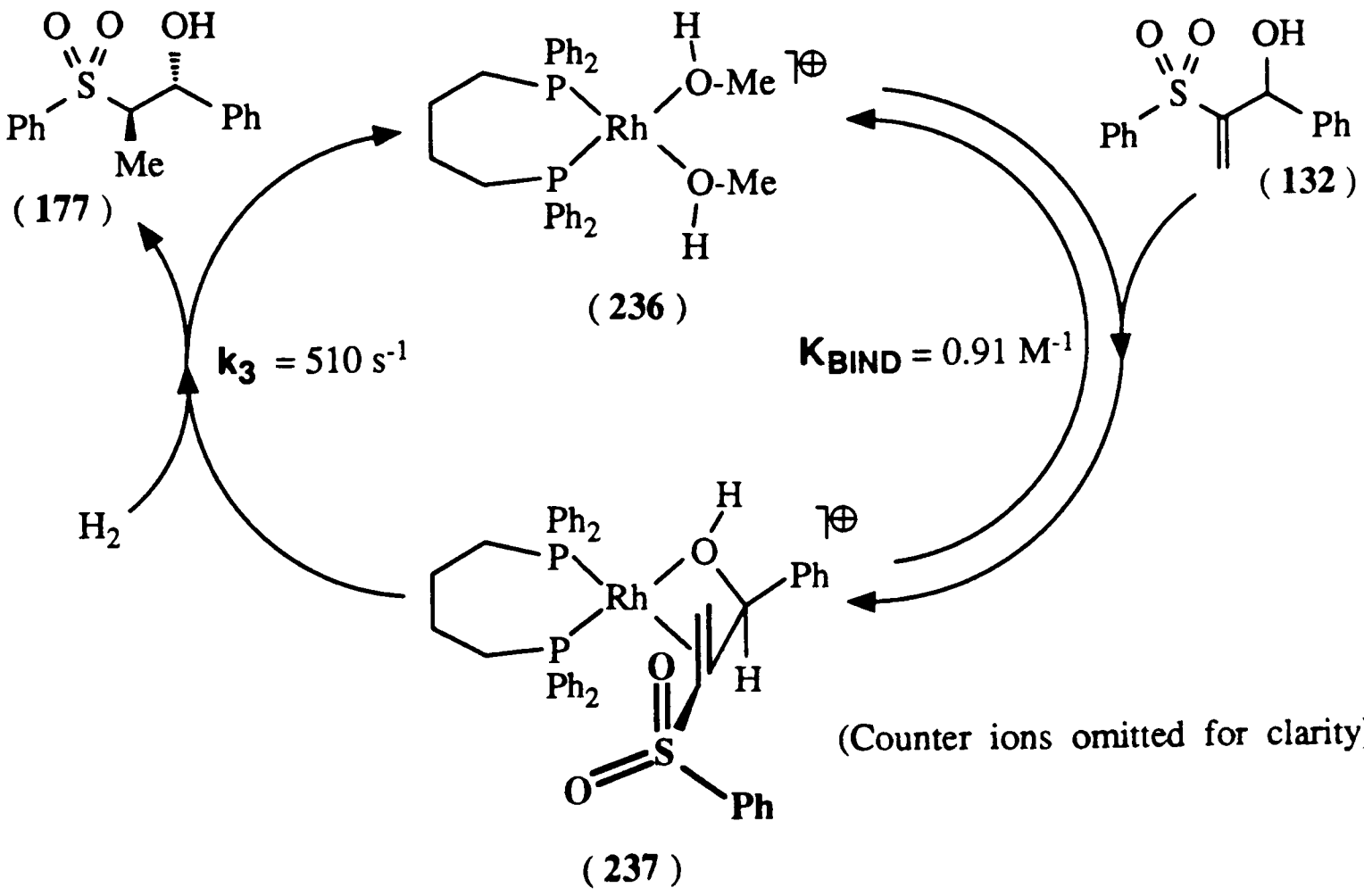


Figure 4.06 - Model fitted to experimental data obtained for (**132**).

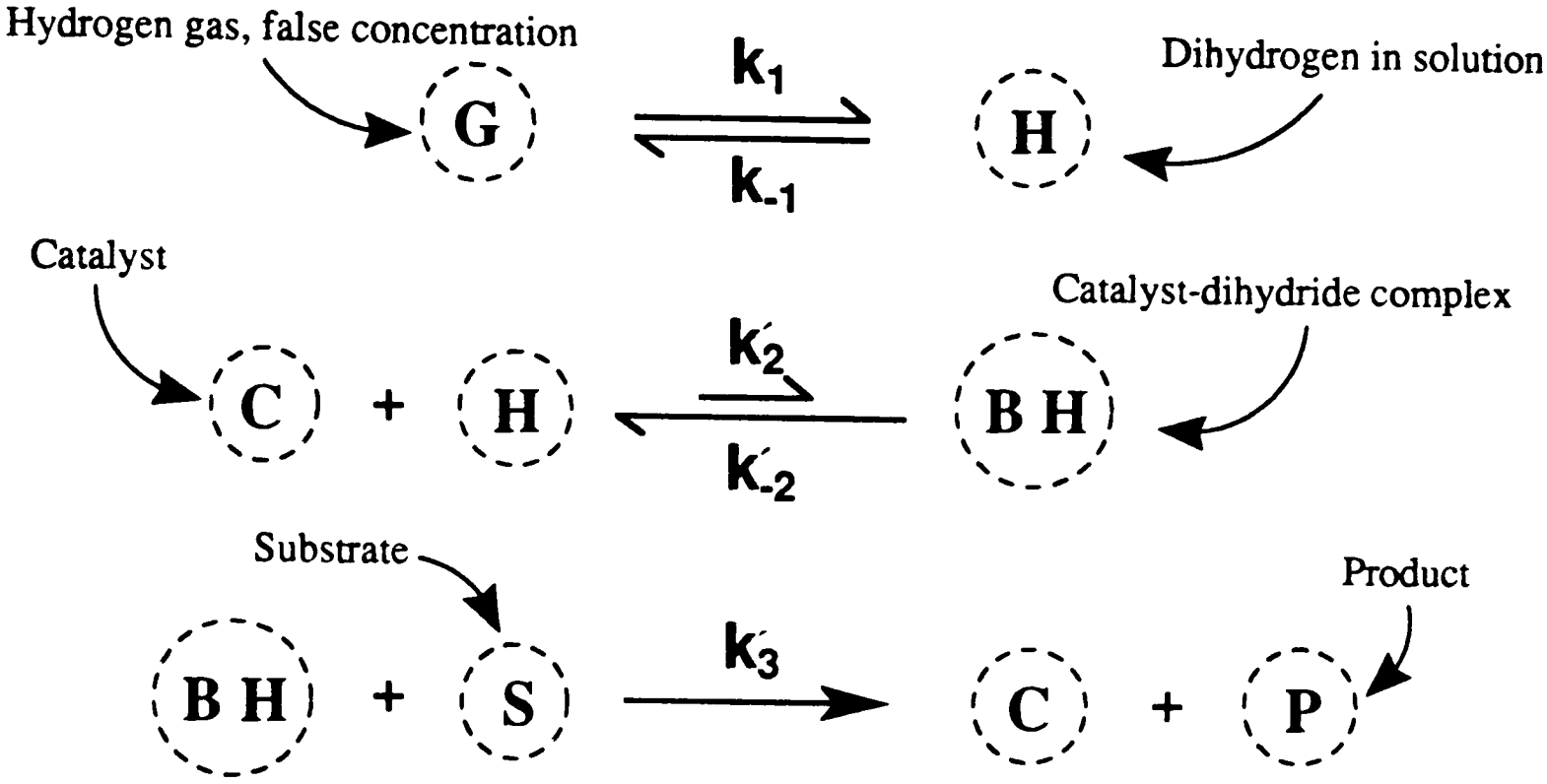
The values generated for the model by fitting the above data set and two further data sets, were 0.91 M^{-1} and 510 s^{-1}, for K_{BIND} and k_3 respectively. The model complete with these values is shown in Scheme 4.04.



Scheme 4.04 - Simplified mechanism including rate parameters.

The catalytic cycle shown in Figure 4.04 only takes into account the substrate-catalyst complex, which gives rise to the *threo*-product. The second substrate-catalyst complex, which gives rise to the *erythro*-product, has been neglected since it produces less than 0.5 % of the product.

An alternative mechanism, highlighted in first Chapter 1 and shown in Figure 4.07, involving an initial equilibrium between the catalyst and hydrogen in solution was also examined with a number of data sets.



Scheme 4.05 - MECHANISM 2.

It is known that rhodium catalysts containing chelating biphosphines do not form stable dihydride complexes in methanolic solution,[5] so the ratio of k'_2 to k'_{-2} must be small. During modelling, k'_3 was fitted to the model with ratios of k'_2/k'_{-2} from 0.0001 to 0.1. In each case the ratio of k'_2/k'_{-2} was found to be 0.033 M^{-1}, though different values for k'_3 were found for each substrate, e.g. 1.4×10^4 s^{-1} for (**132**).

Overall, the two mechanisms were found to be kinetically equivalent and consequently indistinguishable by kinetic analysis. However, comparison between the values obtained for the key equilibrium constants in each mechanism with values obtained for the equilibria by independent experiments could, perhaps, be used to distinguish between the two mechanisms.

In view of these problems it was decided to concentrate on the more generally accepted mechanism, Mechanism 1.

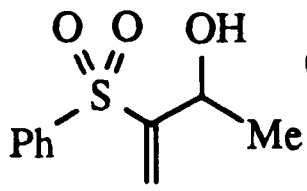
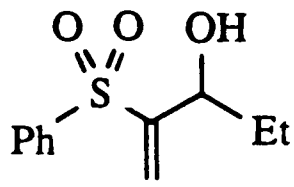
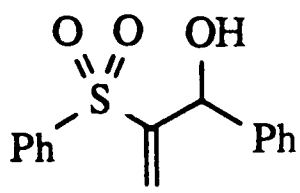
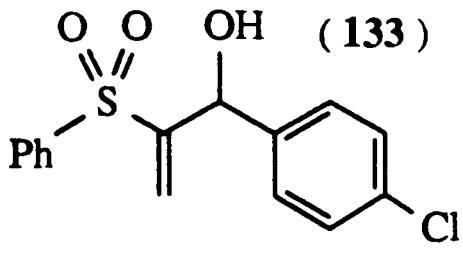
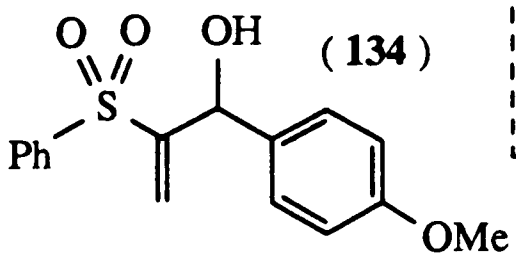
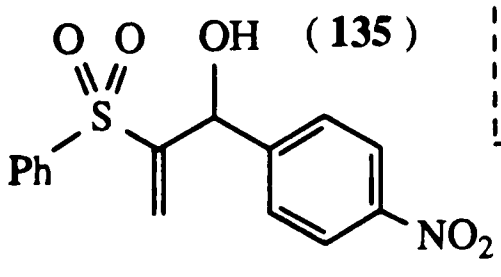
ENTRY	SUBSTRATE	INITIAL SUB. CONC. (mM)	INITIAL CAT. CONC. (mM)	K_{BIND} (M^{-1})	k_3 (s^{-1})	FIT (10^{-4})
1	 (**129**)	96	1.5	1.2	550	5.52
2		150	1.5	0.96	620	6.97
3		48	1.3	1.4	520	2.17
		GLOBAL VALUES		1.3	530	8.29
4	 (**130**)	150	1.5	0.86	550	11.5
5		75	1.5	0.93	590	3.97
		GLOBAL VALUES		0.95	537	14.0
6	 (**132**)	83	1.5	0.82	570	4.68
7		130	1.5	0.84	560	8.21
8		163	1.5	0.88	520	5.16
		GLOBAL VALUES		0.91	510	6.53
9	 (**133**)	100	2.0	0.2	580	11.4
10		150	2.0	0.35	620	9.5
		GLOBAL VALUES		0.33	580	44.3
11	 (**134**)	100	1.2	0.49	660	6.52
12		150	2.0	0.70	660	10.8
		GLOBAL VALUES		0.61	640	18.8
13	 (**135**)	100	1.5	0.23	520	11.5
14		60	1.5	0.23	510	2.81
		GLOBAL VALUES		0.21	550	6.88

Table 4.02 - A summary of kinetic modelling results for the hydroxy vinylsulphones.

The results from modelling the hydroxy vinylsulphone hydrogenations are summarised in Table 4.02, where each entry corresponds to a separate hydrogenation experiment.

It can be seen from Table 4.02 that there is a variation in K_{BIND} and k_3 as the allylic substituent is changed. The trends in these two constants are summarised in Figure 4.07.

	Allylic substituent
K_{BIND}	Me > Et ≈ Ph > $MeOC_6H_4$ > ClC_6H_4 > $NO_2C_6H_4$
k_3	$MeOC_6H_4$ > ClC_6H_4 > $NO_2C_6H_4$ ≈ Et ≈ Me > Ph

Figure 4.07 - Trends in K_{BIND} and k_3 with allylic substitution.

Generally, an increase in the bulk of the allylic substituent decreases the binding constant of the substrate. Electron withdrawing substituents in the allylic phenyl ring also appear to reduce K_{BIND}, though it is unclear why methoxyphenyl substituted (**134**) has a lower value for this than phenyl substituted (**132**).

The trend in k_3 is by no means as marked as that of K_{BIND}. The lowest value of k_3, 510 s^{-1}, is only 20 % below the highest value, 640 s^{-1}. The only correlation between the substrate and k_3 seems to be in the electron withdrawing power of the allylic substituent. In this case the value of k_3 for the phenyl substituted sulphone, (**132**), seems to be anomalous. However, it can be seen that the trend in K_{BIND} with the methoxy-, chloro- and nitrophenyl substituted is paralleled in k_3.

In order to put in perspective the values obtained for the hydroxy vinylsulphones in the first model, the two previously prepared hydroxyacrylates were investigated. Samples of (**175**) and (**176**) were hydrogenated under similar conditions as the hydroxy vinylsulphones and the rate of reaction monitored with the constant volume apparatus. Three data sets each for (**175**) and (**176**) were then fitted to the same model as the hydroxy vinylsulphones, both as an ensemble for each substrate and individually. The global values of K_{BIND} and k_3 for these two substrates are shown in Figure 4.07.

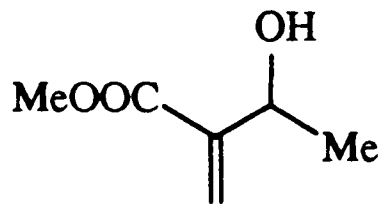
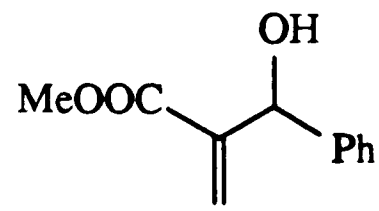
SUBSTRATE	 (175)	 (176)
K_{BIND} (M^{-1})	4.6	4.1
k_3 (s^{-1})	670	370
OVERALL FIT	7×10^{-4}	7.92×10^{-4}

Table 4.03 - Hydroxyacrylates used for kinetic analysis, and some results obtained.

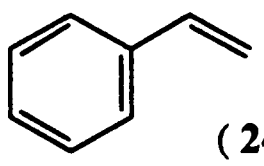
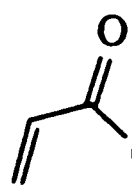
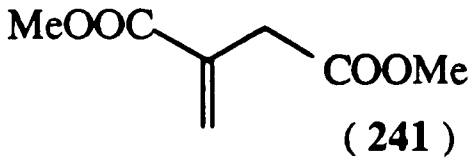
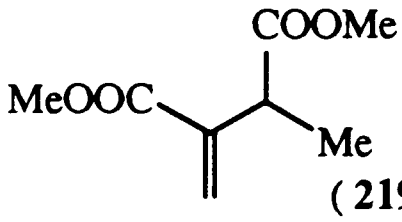
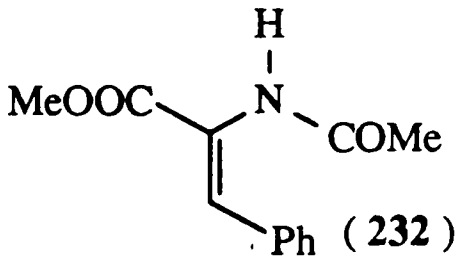
Comparing the values of K_{BIND} and k_3 for the hydroxy vinylsulphones and the hydroxyacrylates, (**175**) and (**176**), two points deserve comment -

1) The binding constant for the substrate-catalyst complex, K_{BIND}, is much smaller in the case of the vinylsulphones. This is due to two main factors- i) It must, in part, be due to the increased steric demand of the phenylsulphonyl group compared to that of the carboxymethyl group. Increasing the steric requirements of the activating group, which is very close to the ligands of the metal centre, will tend to destabilise the substrate-catalyst complex and therefore reduce the binding constant. ii) The binding constant will also be influenced by the electronic properties of the olefin-activating group, since electron withdrawing α-substituents enhance the binding of olefins to rhodium.[71] Thus, K_{BIND} for the hydroxy vinylsulphones may be smaller than the corresponding hydroxyacrylates because the olefinic bond in the former is less electron deficient. (The carbomethoxy group is judged to be more electron withdrawing than the phenylsulphonyl group by their relative abilities to stabilise α-carbanions.[89])

2) The rate of hydrogenation of the substrate once it is bound to the catalyst, determined by k_3, is the same order of magnitude in all of these cases. However, the difference between the methyl and phenyl hydroxyacrylates is much greater than with the hydroxy vinylsulphones, the former being twice the latter.

Overall the values of K_{BIND} obtained for both sets of substrates are lower than

those reported for other substrates, but those of k_3 are comparable. A selection of substrates and values of K_{BIND} and k_3 reported for them is presented in Figure 4.08.

"SUBSTRATE"	K_{BIND} (M^{-1})	k_3 (s^{-1})	METAL COMPLEX	METHOD OF ANALYSIS	Ref.
 (**238**)	1.6	0.18	**A**	Analysis of rate of constant pressure hydrogenation. + Spectral titration. (25 °C)	5
 (**239**)	18	-	**A**		
 (**240**)	20	-	**A**		
 (**174**)	3	-	**A**		
 (**241**)	31.5	151	**A**	Numerical analysis of constant volume hydrogenation. (0 °C)	74
 (**219**)	11	603	**A**		
 (**232**)	35000† + 3300‡	1.1† + 630‡	**B**	Combined methods. (25 °C)	24

Key : **A** = $(dppe)Rh^{\oplus}$; **B** = $(DiPAMP)Rh^{\oplus}$

† indicates major diastereomeric complex.

‡ indicates minor diastereomeric complex.

Table 4.04 - A selection of reported values for binding constants and hydrogenation rate constants.

It should be noted that the binding constant for benzene to (dppe)rhodium(I), (**208**), is quite large at 18 M^{-1}, but that of styrene, is not much higher at 20 M^{-1}. This suggests that the binding constant measured for styrene mainly arises from binding of the ring and not the olefinic bond. A further caveat must be added to the results obtained by U.V. spectroscopic examination- the identity of the species observed in these experiments is unknown.

4.08 Consequences of the Parameters Generated for the Hydroxysulphones

It is instructive to examine the variation of species concentrations, generated by the GEAR[128] program, during the course of reaction. The model equations with the parameters generated for the hydroxy vinylsulphone, (**132**), were integrated with respect to time. The simulations were run with initial substrate and catalyst precursor concentrations of 0.1 M and 0.001 M, respectively. The initial hydrogen partial pressure fixed at 1 atm. by setting **G** to 0.6822 M. The other two initial species concentrations, those of **H** and **BS**, were set to zero and allowed to find their own equilibrium values.

The concentrations of some of the model species, generated with the aid of the GEAR[128] computer program, are shown in Figure 4.08 and Figure 4.09.

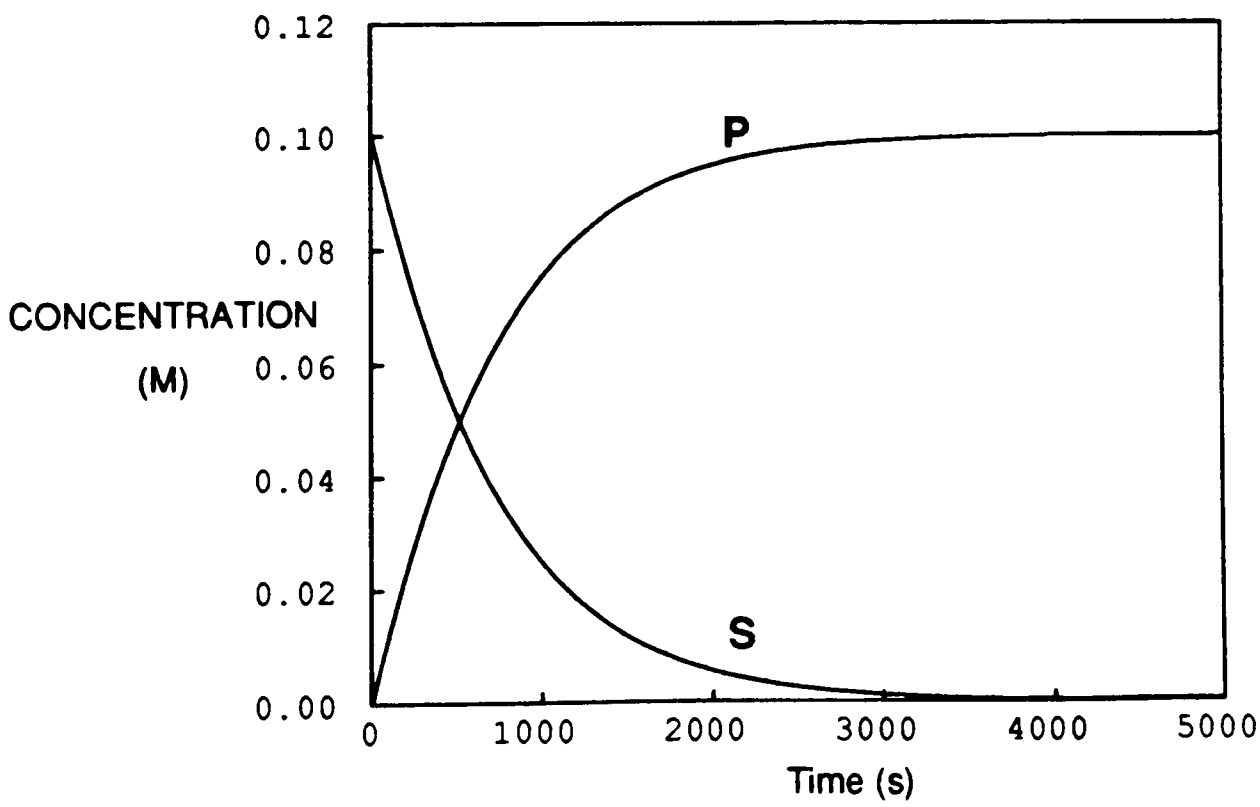
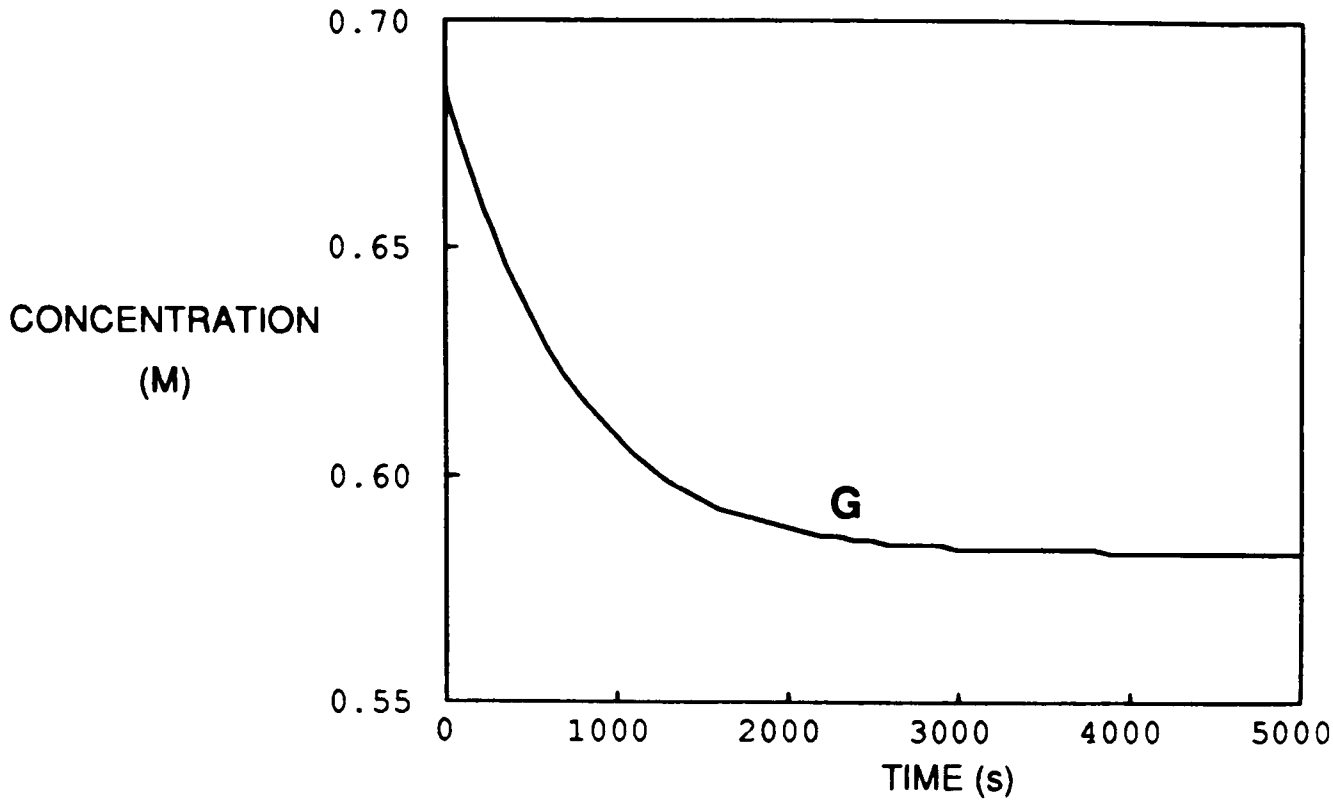


Figure 4.08 - Variation of catalyst and bound-substrate concentrations as calculated by GEAR.[ref3]



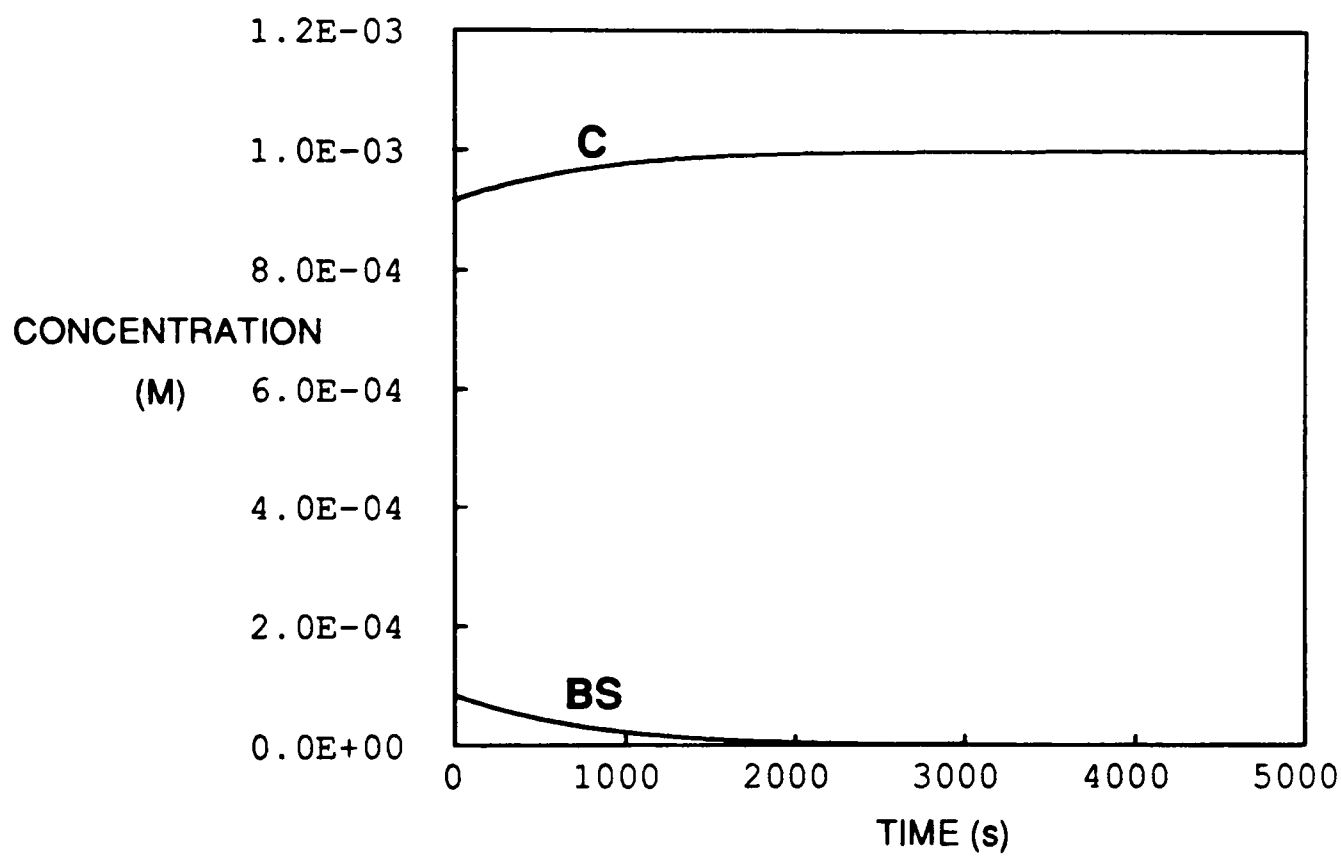


Figure 4.08 - Variations of model species conc. with time as calculated by GEAR.[ref3]

It is clear from Figure 4.08 and the first graph in Figure 4.09 that the rate of hydrogenation is not constant with time, when the substrate has such a low binding constant (0.90 M^{-1}). This is in agreement with the pressure changes observed during the course of the hydrogenation of (**132**).

It can be seen from the graph showing the variations of **C** and **BS** with time, shown in Figure 4.08, that over the time span of the reaction most of the catalyst is present as the solvate complex. Only 10 % of the catalyst is found as the bound-substrate complex initially, and this decreases with conversion of the starting material.

4.09 Testing the Model with a Mixture of Substrates

In order to check the values for K_{BIND} and k_3 for the acrylates and sulphones, and the model with which they were obtained, it was decided to perform mixed substrate hydrogenations. If the two catalytic cycles for the substrates share a common intermediate, the (dppb)rhodium(I) solvate complex, then the ratios of the starting materials and products at any point during the reaction, should be predictable from the model. To this end, two separate hydrogenations were carried out for predefined time periods, each not allowed to react to completion.

Two samples of an equimolar mixture of (**176**) and (**132**) were hydrogenated for periods of 300 and 500 seconds respectively, and the reactions quenched by exposure to air. The ratio of the four components of the reaction, the two starting materials and two products, were then determined by the ^1H NMR of the mixture taken at 500 MHz (Figure 4.09).

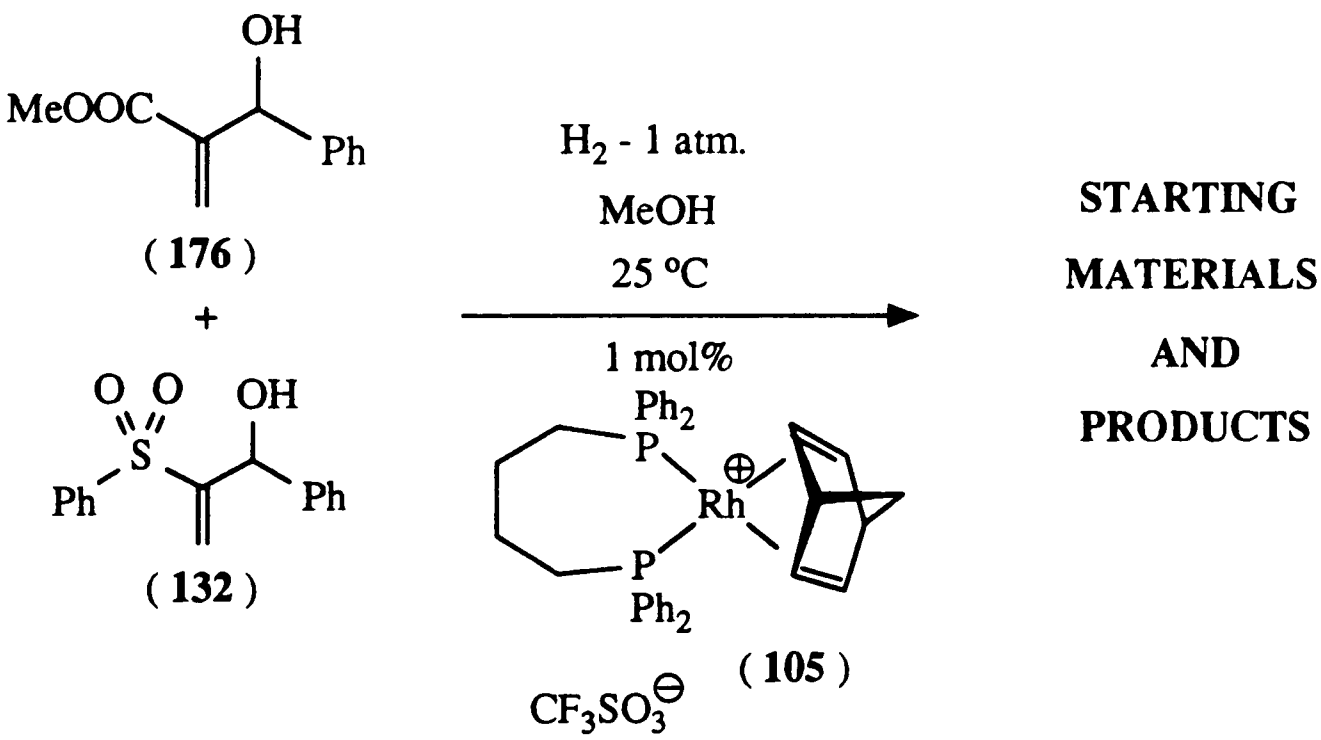
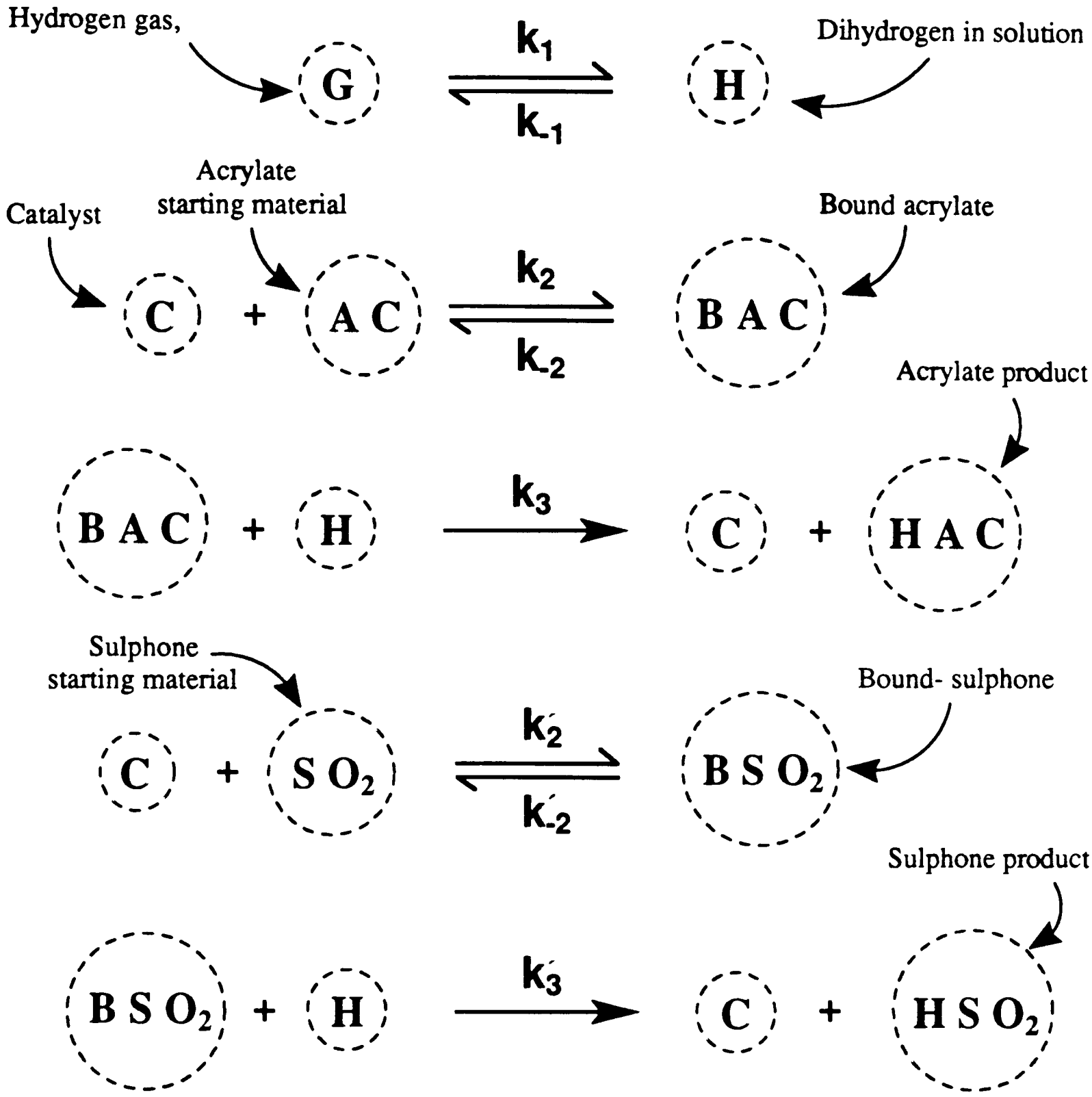


Figure 4.09 - Mixed substrate hydrogenations.

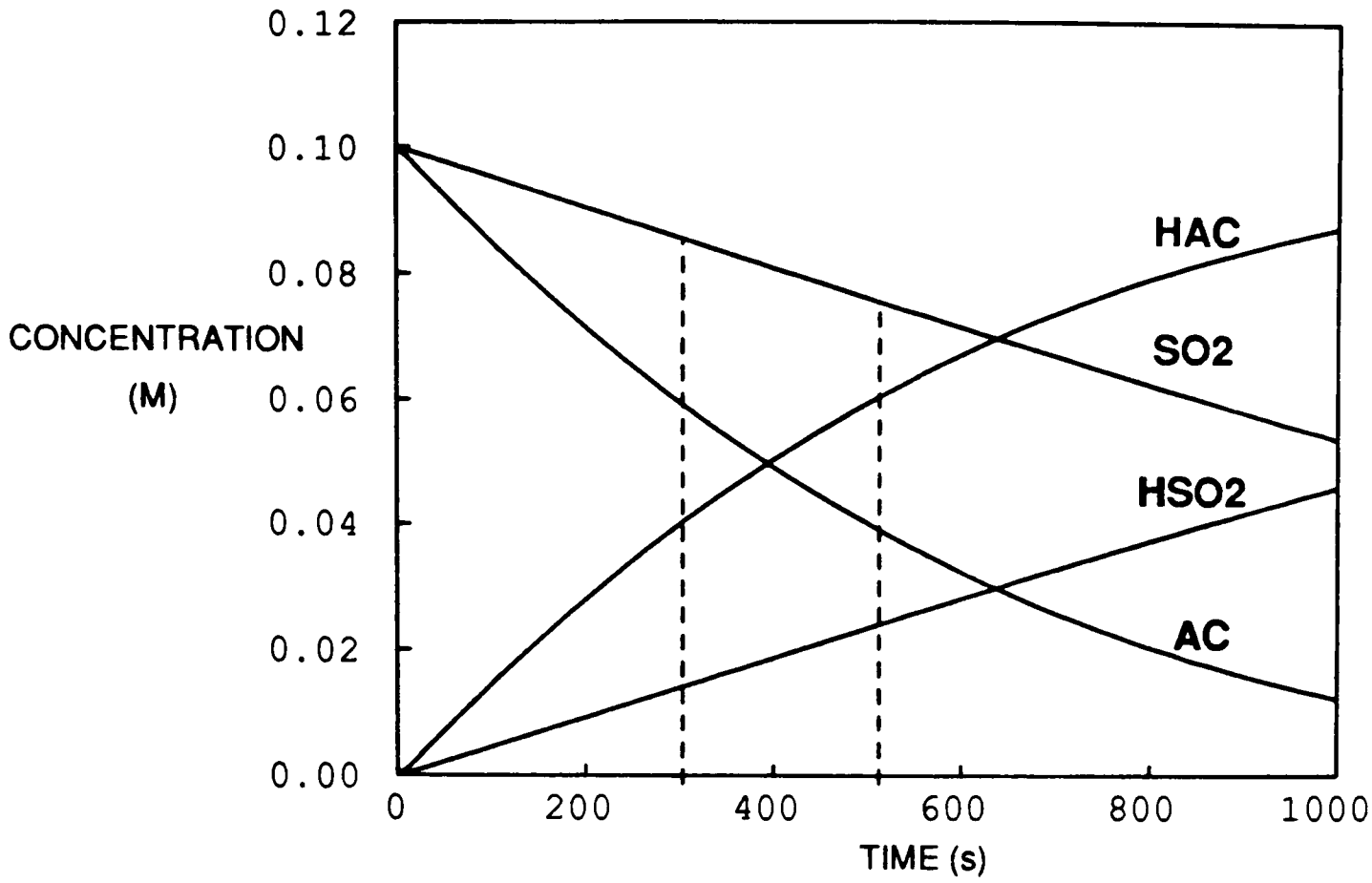
In parallel to the hydrogenation reactions, a model was set up to include both substrates and their respective values for K_{BIND} and k_3. This model was identical to the original one except that a second catalytic cycle was added. The two catalytic cycles both proceed through a common intermediate, the solvate complex. Scheme 4.06 shows the model used for the simulation.



Scheme 4.06 - Kinetic model used in mixed hydrogenation simulation.

The equations were then integrated with respect to time over a period of 1000 seconds using the GEAR[128] program. The results of the computer simulation are shown in Figure 4.10. The dashed lines represent the points in time, at which the two experiments were stopped.

The ratios of starting materials and products from the reaction mixtures were converted into concentrations. This allowed comparison with the model prediction, which was outputed as a file of concentrations of components at different times through the reaction.



Key : **AC** = acrylate substrate, (**176**)
HAC = acrylate product, (**242**)
SO2 = sulphone substrate, (**132**)
HSO2 = sulphone product, (**179**)

Figure 4.10 - Results of simulation of mixed substrate hydrogenations.

The results of the hydrogenations predicted by the model, together with the results obtained by ^1H NMR of the reaction mixtures, are tabulated below-

COMPONENT	PREDICTED		OBSERVED	
	300 s	500 s	300 s	500 s
AC	0.06	0.04	0.049	0.035
HAC	0.039	0.059	0.051	0.065
SO_2	0.087	0.078	0.085	0.079
HSO_2	0.013	0.022	0.015	0.021

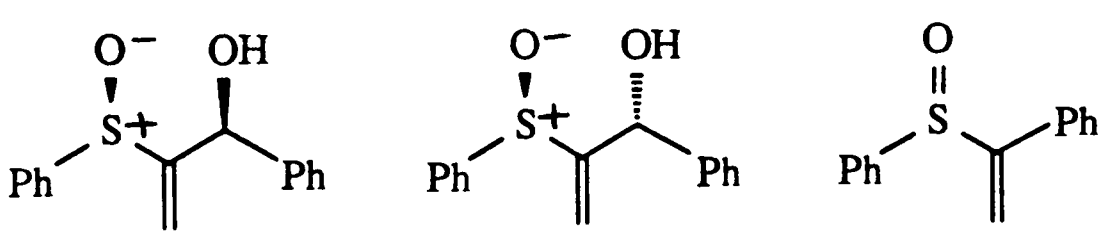
Note : All values are concentrations in mol l^{-1}

Table 4.05 - Comparison of predicted concentrations of components of mixed hydrogenations with the experimental results.

It can be seen from Table 4.05 that the simulation values are in good agreement with the results of the hydrogenations. However, the values predicted for the acrylate substrate are a little higher than those observed due to pre-hydrogenation. This occurred while allowing the apparatus to equilibrate at 25°C under hydrogen. Overall these results substantiate the system of equations used to model the hydrogenation of the two substrates.

4.10 Modelling of Sulphoxide Hydrogenations

The two previously prepared hydroxy vinylsulphoxides, (**152**) and (**153**), and the simple vinyl sulphoxide, (**160**), were chosen as substrates for kinetic analysis. It was initially intended to use the same simple model that was used with the hydroxy vinylsulphones and hydroxyacrylates and to generate rate constants for it as before.



(**152**) (**153**) (**160**)

Figure 4.11 - Sulphoxide substrates for kinetic analysis.

Hydrogenation of the three sulphoxide substrates in the constant volume hydrogenator and collect data sets as before. This proved impossible, however, in the case of the *syn*-hydroxy vinylsulphoxide, (**152**), due to the extremely slow speed at which this substrate reacted. The rate of pressure drop in the apparatus due to the hydrogenation of (**152**) was close to the leak rate of the apparatus, which was approximately 1 mbar/hour.

Data sets were collected for (**153**) and (**160**) in two solvents, methanol and 1,2-dichloroethane, using the 1,4-bis-(diphenylphosphino)butane based catalyst precursor, (**105**), and the model fitted to them using the GIT[129] computer program. It was found necessary to use 5 mol% of the catalyst precursor in hydrogenations with the *anti*-hydroxy vinylsulphoxide, (**153**), as substrate, since the rate was too slow at lower relative catalyst concentrations.

The results of the numerical analysis of the hydrogenations carried out in methanol

with (**153**) and (**160**) as substrates are summarised in Table 4.06.

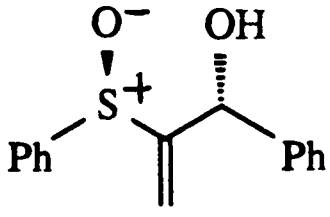
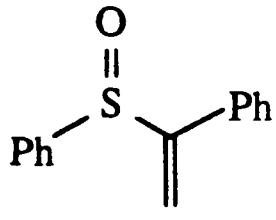
ENTRY	SUBSTRATE	INITIAL SUB. CONC. (mM)	INITIAL CAT. CONC. (mM)	K_{BIND} (M^{-1})	k_3 (s^{-1})	FIT (10^{-4})
1		100	5.0	0.068	785	5.42
2		102	5.0	0.086	743	5.55
	(153)	GLOBAL VALUES		0.084	750	13.7
3		100	2.0	0.315	700	10.5
4		60	0.6	0. 303	630	3.53
	(160)	GLOBAL VALUES		0.317	696	8.62

Table 4.06 - Summary of results of numerical analysis of sulphoxide hydrogenations carried out in methanol.

It can be seen from Table 4.06 that the binding constant, K_{BIND}, for the *anti*-hydroxy vinylsulphoxide is very small compared to the values obtained for both the hydroxyacrylates and hydroxy vinylsulphones. The value for the rate constant associated with the hydrogenation of the bound substrate complex, k_3, on the other hand, is slightly larger than the values found for the other substrates examined. The model in this case is, however, flawed since it is known that the hydroxy vinylsulphoxides form a chelate complex with the (dppe)rhodium(I) cation. Furthermore, these complexes are catalytically non-productive and thus it would seem that the substrate, and probably the product, would act as inhibitors to hydrogenation. This will be examined in the next section.

The values obtained for K_{BIND} and k_3 for the simple sulphoxide, (**160**), are similar to the values obtained for the hydroxy vinylsulphones. The value for K_{BIND} is slightly lower for the simple sulphoxide. This is consistent with the increased steric hindrance around the olefinic bond, which is phenyl substituted in the sulphoxide rather than benzylic in the sulphone.

The values obtained for k_3 with the simple sulphoxide are approximately 50% higher than the average value of k_3 obtained for the sulphones. This may also reflect the increased steric hindrance at the position α to sulphur. In this case, however, this steric demand destabilises the rhodium-alkyl-hydride complex and so increases its rate of collapse to form the product.

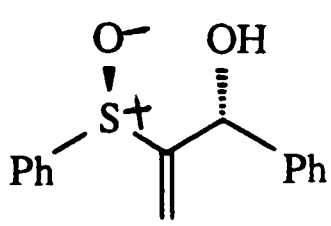
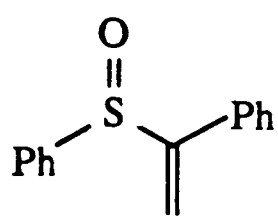
ENTRY	SUBSTRATE	INITIAL SUB. CONC. (mM)	INITIAL CAT. CONC. (mM)	K_{BIND} (M^{-1})	k_3 (s^{-1})	FIT (10^{-4})
1		100	5.0	32	11	4.59
2		122	4.0	35	10	8.34
	(**153**)	GLOBAL VALUES		33	11	13.7
3		90	1.0	110	88	1.56
4		110	1.2	80	97	2.41
5		130	1.4	95.4	75	4.23
	(**160**)	GLOBAL VALUES		117	83	16.9

Table 4.07 - Summary of results of numerical analysis of sulphoxide hydrogenations carried out in 1,2-dichloroethane.

The results obtained when 1,2-dichloro. .ethane was used as solvent for the hydrogenation of the two sulphoxides, (**153**) and (**160**), are summarised in Table 4.07. 1,2-Dichloro ethane was chosen as a non-polar solvent instead of dichloromethane because of the large vapour pressure of dichloromethane at 25°C (613 mbar @ 26.4°C)[137].

It can be seen from Table 4.07 that the values obtained for K_{BIND} and k_3 are very different with 1,2-dichloroethane as solvent. The binding constant, K_{BIND}, is greatly enhanced by two orders of magnitude in both cases. This was to be expected since a coordinating solvent such as methanol will stab ilise the metal cation with respect to the bound-substrate complex, but a non-coordinating solvent cannot do this to the same

degree. This is illustrated in Figure 4.12.

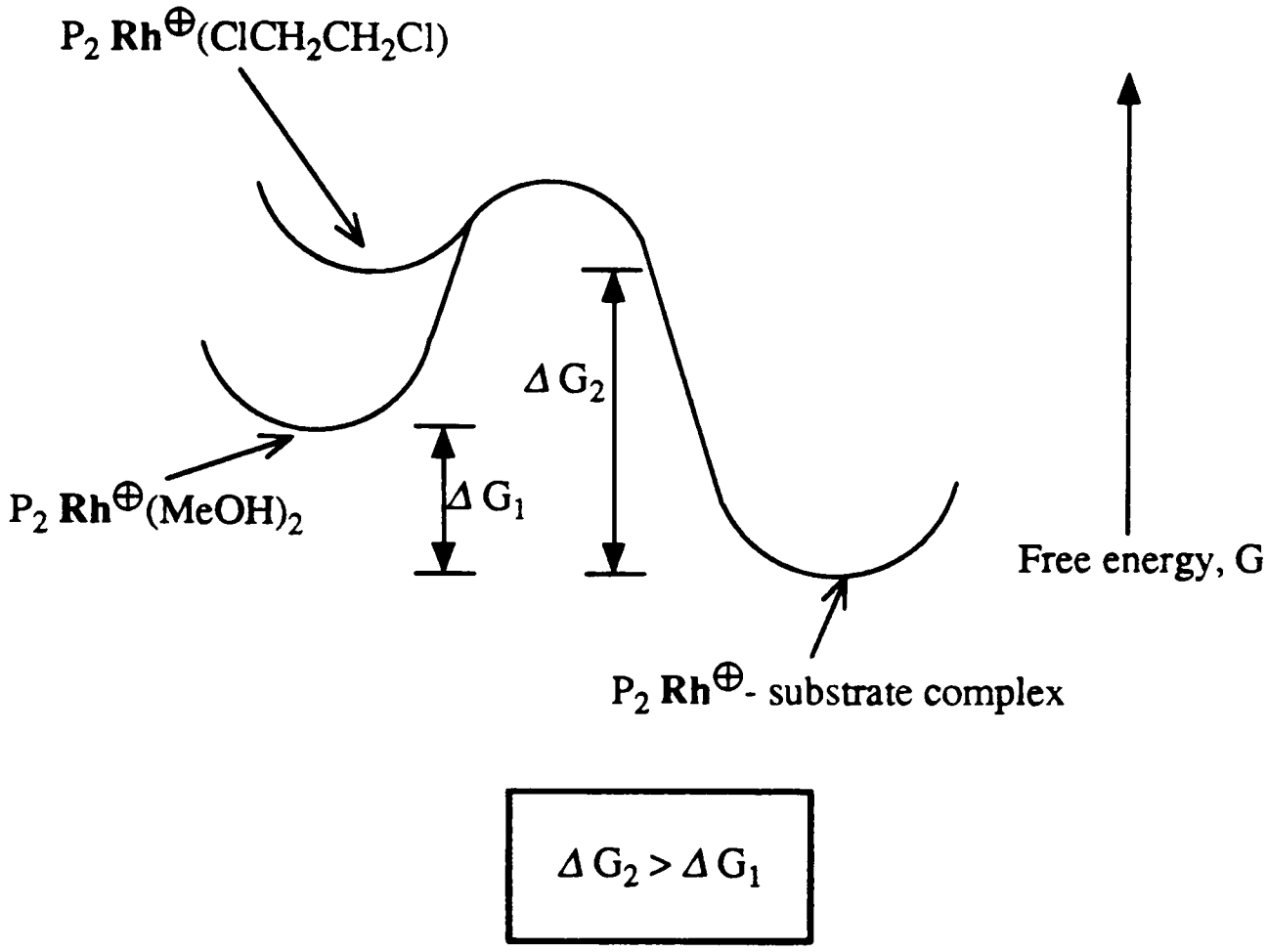
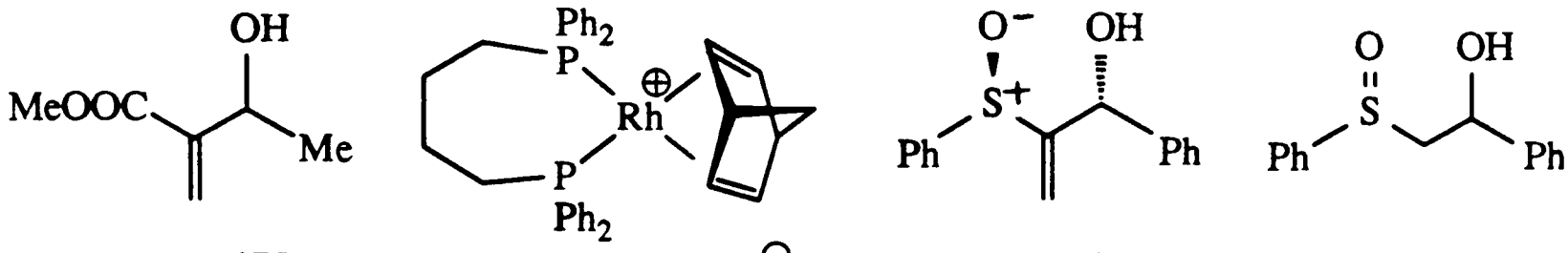


Figure 4.12 - Difference in binding constants in coordinating and non-coordinating solvents.

It is surprising to find that k_3 is much smaller in the non-coordinating solvent. This may arise from an increase in size in going from the rhodium-alkyl-hydride to the transition state complex. This will increase the charge diffusion in the transition state. Thus, the transition state complex will be less stabilised with respect to the rhodium-alkyl-hydride complex in polar solvents than in non-polar solvents, because the smaller cation will be stabilised by the polar solvent.

4.11 Inhibition of Hydrogenations

Since it had been shown that the hydroxy vinylsulphoxides, (**152**) and (**153**), and the β-hydroxysulphoxide, (**212**), form chelate complexes with a (dppe)rhodium(I) cation, in which the sulphinyl group is S-bound, the ability of these compounds to inhibit hydrogenation reactions was investigated. The hydroxyacrylate, (**175**), was hydrogenated in the constant volume hydrogenator at 1000 mbar with 1 mol% of the (dppb)rhodium(I) based catalyst precursor, (**105**), together with varying amounts of (**153**) or (**212**).



(*rac*)- (**175**) (**105**) (*rac*)- (**153**) (*rac*)-(**212**)

Figure 4.13 - Compounds used in inhibition studies.

Initially, (**175**) was hydrogenated in methanol with 6 different concentrations of (**153**) present, and the initial rate of hydrogenation determined by a least squares regression of the points taken in the first 100 seconds of hydrogenation. The results of these hydrogenations are represented graphically in Figure 4.14.

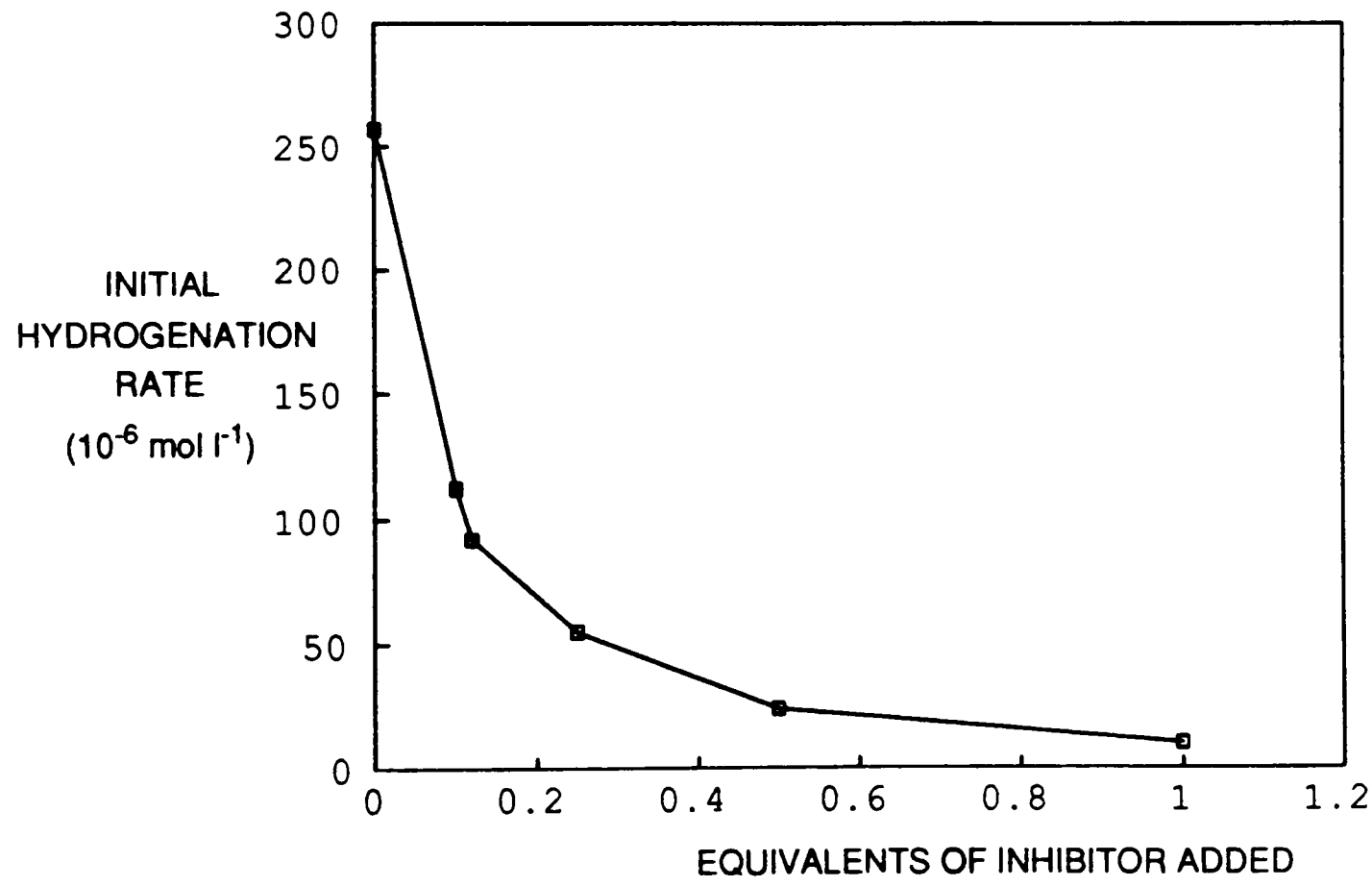


Figure 4.14 - Variation of the initial rate of hydrogenation of (**175**) with different equivalents of (**153**).

It can be seen from Figure 4.14 that the initial rate of hydrogenation is halved by the addition of only 0.1 equivalents of the *anti*-hydroxy vinylsulphoxide. Thus, the hydroxy vinylsulphoxide, (**153**), very markedly inhibits the hydrogenation of (**175**). The inhibitor achieves this by removing a large fraction of the catalyst from the catalytic cycle and keeping it as hydroxy-S-sulphinyl chelate.

The hydrogenation of (**175**) was also performed with 5 different concentrations of the β-hydroxysulphoxide, (**212**), and the initial rates of reaction computed as before. (**212**) was used as a substitute for the hydrogenation product from (**153**). The results obtained in this case are shown in Figure 4.15.

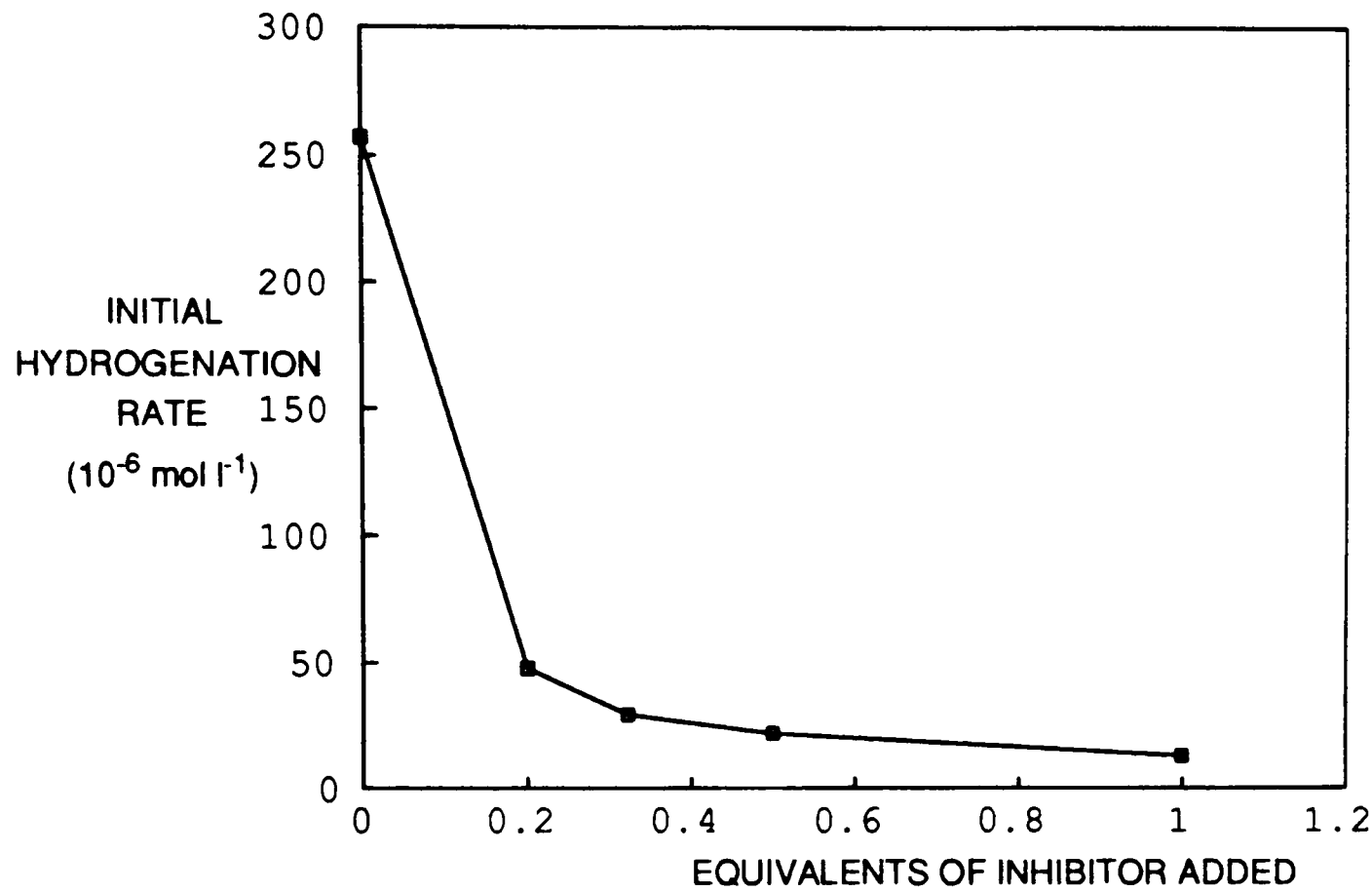
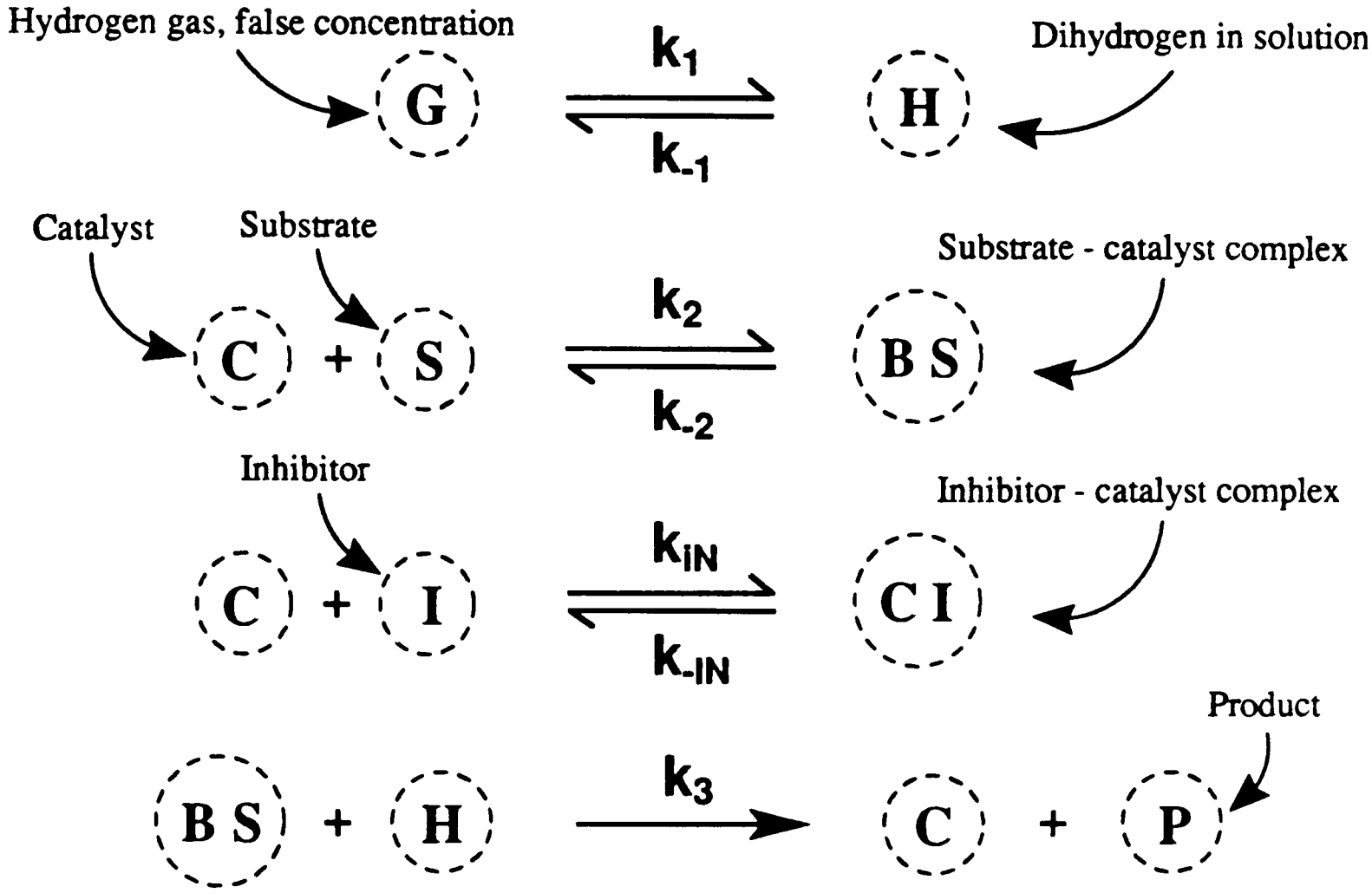


Figure 4.15 - Variation of the initial rate of hydrogenation of (**175**) with different amounts of added (**212**).

It is evident from Figure 4.15 that (**212**) inhibits the hydrogenation of (**175**) to a slightly greater extent than does (**153**). The difference in the abilities of (**153**) and (**212**) to inhibit hydrogenation is sufficiently small to allow them to be approximated as equal.

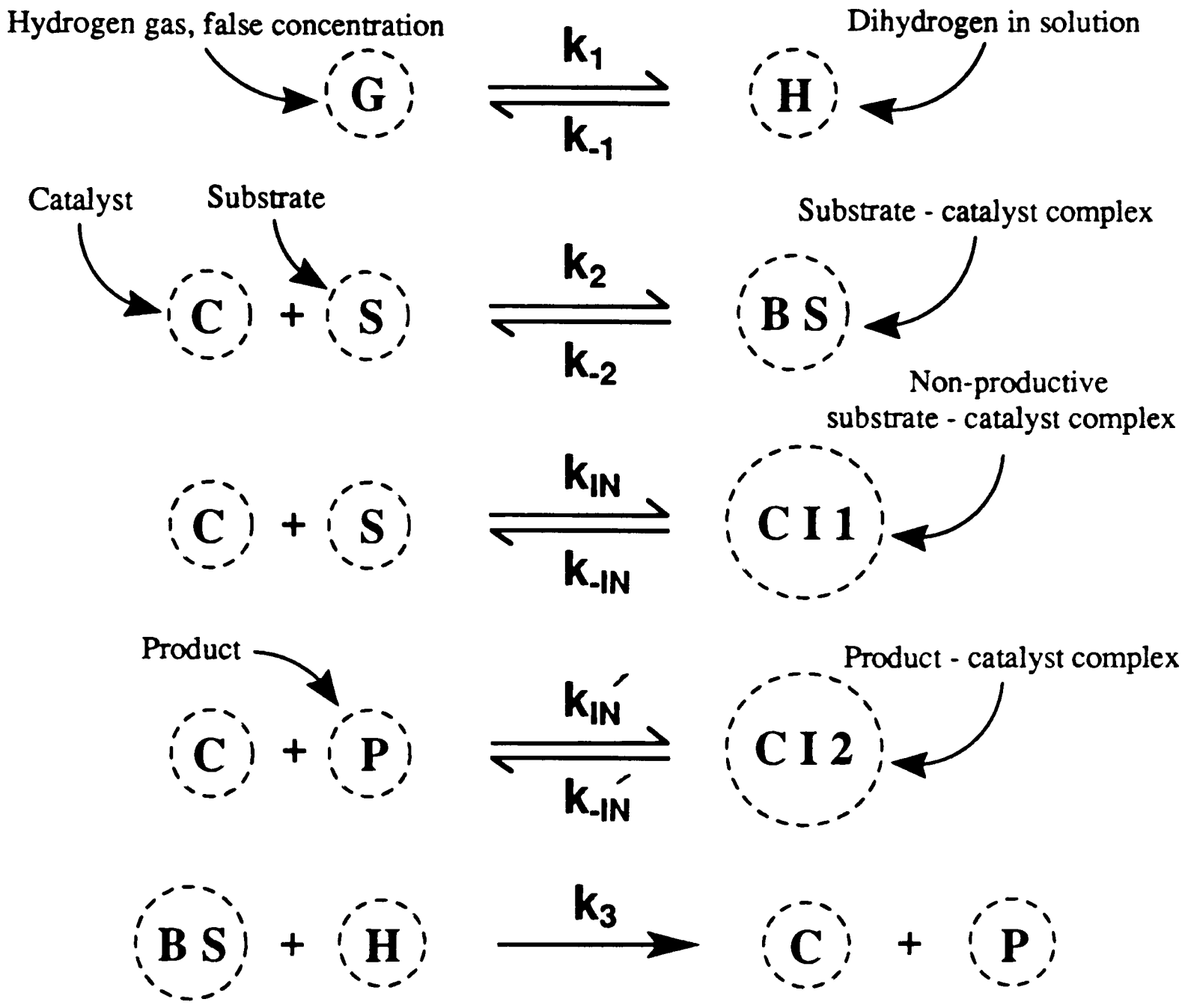
The results from the inhibition results prompted the setting up of two more models for kinetic analysis. The first model was based on the original hydrogenation model for the hydrogenation of hydroxy acrylates but also incorporated a third equilibrium. This equilibrium was between the catalyst and the inhibitor and a catalyst-inhibitor complex, CI. It was then hoped that it would be possible to use the previously described inhibition data sets to obtain values for k_{IN}/k_{-IN}.



Scheme 4.07 - Kinetic model used in modelling of inhibition reactions.

The model in Scheme 4.07 was fitted to the inhibition data sets with the previously generated values of K_{BIND} and k_3 for (**175**). This lead to a binding constant, k_{IN}/k_{-IN}, for the general inhibitor of 860 M^{-1}.

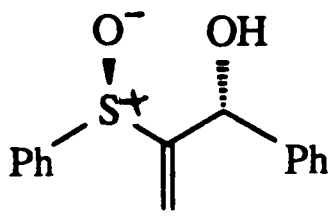
A second model, which incorporated two further equilibria to take into account inhibition by substrate and product, was set up for hydrogenation of the hydroxy vinylsulphoxide, (**153**). This model is shown in Scheme 4.08, where CI1 and CI2 are catalyst-substrate and catalyst-product complexes, respectively. CI1 differs from the bound substrate complex, BS, in the mode of binding employed by the substrate. In both CI1 and CI2 the substrate and product are bound to the metal through the sulphur atom and the hydroxy group. This mode of binding is catalytically non-productive with CI1, in contrast to the mode of binding in BS.



Scheme 4.08 - Kinetic model used in modelling of inhibition reactions.

The value for the binding constant of the general inhibitor, 860 M^{-1}, was used in the second model and new values for K_{BIND} and k_3 were then generated as before. This lead to values of 1.8 M^{-1} and 285 s^{-1} for K_{BIND} and k_3, respectively. These values for K_{BIND} and k_3 obtained for (**153**), taking into account inhibition by substrate and product, are much more in line with the values obtained for both the hydroxyacrylates and hydroxy vinylsulphones.

The results of the analysis of the hydroxy vinylsulphoxide, (**153**), are summarised in Table 4.08. These results supplant entries 1 and 2 in Table 4.06, which were obtained without inclusion of the inhibition by starting material and product.

ENTRY	SUBSTRATE	INITIAL SUB. CONC. (mM)	INITIAL CAT. CONC.	K_{BIND} (M^{-1})	k_3 (s^{-1})	FIT
1		100	5.0	1.96	290	3.49
2		122	4.0	1.67	250	19.6
	(153)	GLOBAL VALUES		1.80	285	8.3

Solvent = methanol

Table 4.08 - Summary of results of numerical analysis of sulphoxide hydrogenations after taking into account the inhibition by the starting material and product.

4.12 Modelling of Kinetic Resolution Reactions

Finally, it was hoped to extend modelling to the hydrogenation of the hydroxy vinylsulphone, (**132**), with the DiPAMP catalyst precursor, (**108**). Hydrogenations were carried out in the constant volume hydrogenator with approximately 0.1 mmol of substrate, (**132**), and a relative catalyst concentration of 3 mol%. The pressure changes in the apparatus were monitored over periods of 4-12 hours.

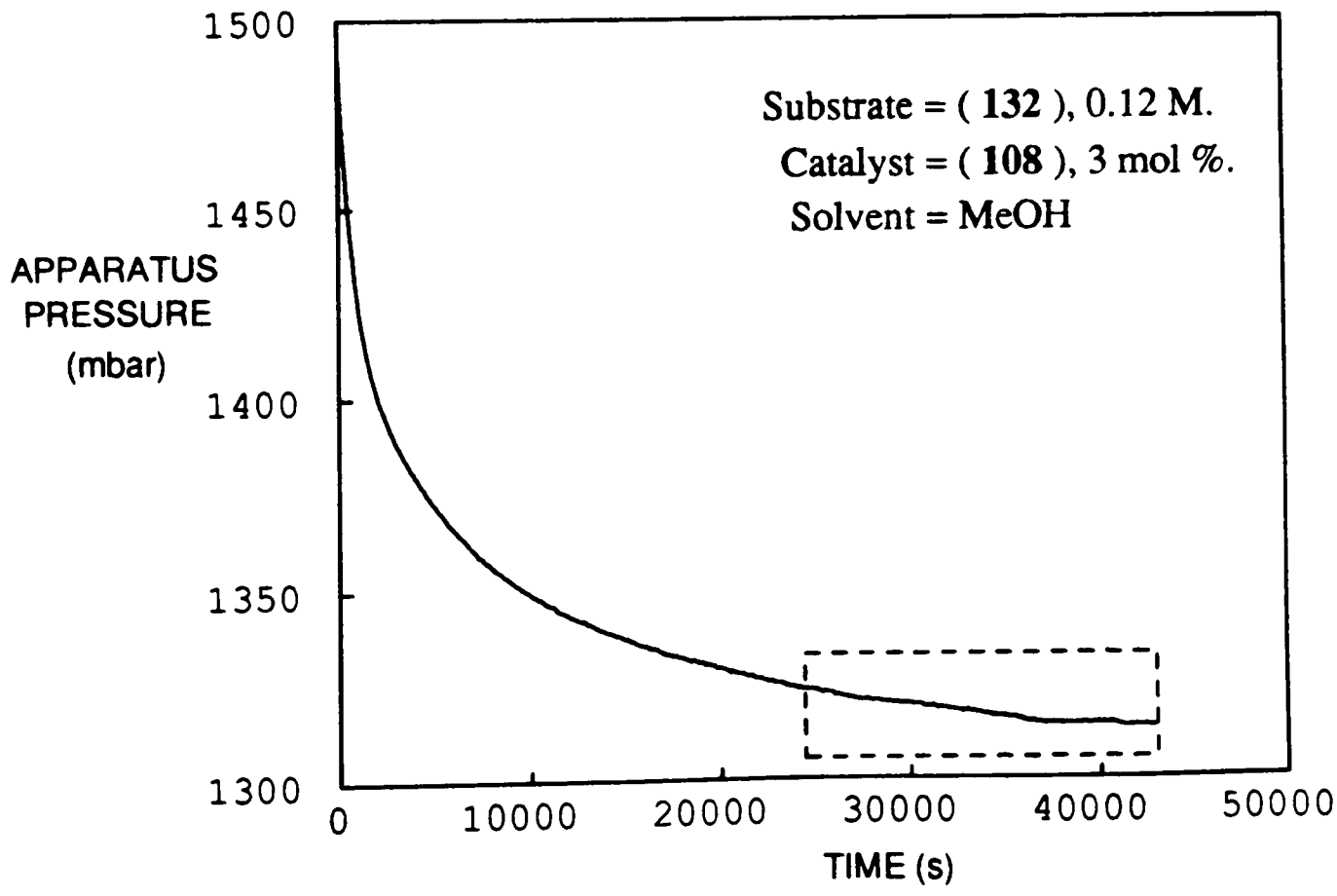


Figure 4.16 - Example of a (DiPAMP)$Rh^{\oplus}$ catalysed hydrogenation of (**132**).

As was expected, the rate of hydrogenation exhibited biphasic behaviour with markedly different reaction rates at 0 % and 50 % conversion. Figure 4.16 shows a graph of the pressure changes with time during a (DiPAMP)rhodium catalysed hydrogenation, which exemplifies this biphasic behaviour. Initially the rate of hydrogenation is 60 μmol s^{-1} but this diminishes to 6.1 μmol s^{-1} at approximately 60 % conversion (1 hour).

The rate in the latter stages of the hydrogenations proved to be exceedingly slow and approached the leak rate of the apparatus. This meant that it was not possible to obtain data sets of sufficient quality for numerical analysis. The highlighted section of the graph shown in Figure 4.16 indicates where the leak rate of the apparatus is similar to the rate of hydrogenation of the slow reacting enantiomer.

4.13 Summary and Conclusions

It has been demonstrated that kinetic parameters can readily be determined for hydroxyacrylates, hydroxy vinylsulphones, *anti*-hydroxy vinylsulphoxides and simple vinylsulphoxides using the constant volume hydrogenator to accumulate the data and numerical methods to analyse it. The binding constants obtained using this method for the (dppb)rhodium based catalyst, (**105**), suggest a correlation between the binding constant and the steric hindrance around the olefinic bond of the substrate. This would seem perfectly reasonable since increased steric hindrance in the substrate will destabilise the bound-substrate complex and relative to the catalyst-solvate complex. The trends in the catalyst-substrate complex hydrogenation rate constant are not as clearly defined, with only the value obtained for (**176**), differing significantly from the average value of 600 s^{-1}.

It has been confirmed that the two plausible rhodium catalysed hydrogenation mechanisms are kinetically indistinguishable. If reliable independent values of the binding constants for given catalyst-substrate combinations could be obtained, then it might prove possible to disprove the bound-substrate mechanism. It might also be possible to disprove the second mechanism if reliable values of the equilibrium constant for the binding of hydrogen to rhodium, in biphosphine cationic complexes were known.

Although plausible values of K_{BIND} and k_3 were found for hydroxyacrylates, hydroxy vinylsulphones, and simple vinylsulphoxides using the simple model, meaningful

values could not be obtained for the *anti*-hydroxy vinylsulphoxide examined, and a slightly more complex model had to be invoked. This model, which included equilibria to take into account substrate and product inhibition, proved to give values for K_{BIND} and k_3 that were much more in line with the values obtained for the other substrates.

EXPERIMENTAL

Experimental

7.01 Instrumentation and General Procedures

Melting points were determined on a Reichert-Köfler block and are uncorrected.

Proton NMR spectra were recorded on either a Varian Gemini 200 at 200 MHz, a Bru ker WH300 at 300 MHz or a Bru ker AM500 at 500MHz and are quoted in δ p.p.m. relative to tetramethylsilane. ^{13}C NMR spectra were recorded on either a Varian Gemini 200 at 50.38 MHz, Bru ker AM250 at 62.98 MHz or Bru ker AM500 at 125.95 MHz and are also quoted in δ p.p.m. relative to tetramethylsilane. ^{31}P NMR spectra were recorded on either a Bru ker AM250 at 101.23 MHz or a Bru ker AM500 at 202.46 MHz with an external D_2O or d^6-acetone lock and are quoted in δ p.p.m. relative to 85% aqueous phosphoric acid. Abbreviations used in spectral analysis are : J_{ab}= coupling constants between protons labelled a and b; s= singlet; d= doublet; t= triplet; qu= quartet; qi= quintet; m= multiplet; and br= broad.

IR spectra were recorded on a Perkin-Elmer 1750 Fourier Transform spectrophotometer and are quoted in wavenumbers $\bar{\nu}_{MAX}$, cm^{-1}. Abbreviations used in IR spectral analysis are : vs= very strong; s= strong; m= medium; w= weak; ben= bend; symm str = symmetric stretch; asymm str = asymmetric stretch; and str = stretch; comb= combined stretches and/or bending vibrations.

Mass spectra were recorded on a TRIO-1 GCMS spectrometer in chemical ionisation (CI+) mode. M/z values, followed by percentage abundance in parentheses, are given for the molecular ion and base peaks in Daltons.

Optical rotations were determined on a Perkin-Elmer 141 polarimeter and were performed in triplicate.

Analysis were performed by Mrs. V. Lambourn of the Dyson Perrins Laboratory.

Silica gel used for flash chromatography[138] was silica gel 60 'Merck' 230-300

mesh supplied by B.D.H..

Molecular minimisations were carried out on a Int$_e$l *i*386DX® based P.C.-clone operating at 25 MHz fitted with a Cyrix 80D387 coprocessor synchronised with the C.P.U.. PCMODEL® from Serena Software[86] was used as a graphical interface for the MMX program, also from Serena Software, which used an MMX[86] force field. A full procedure is described where appropriate.

Reagent grade solvents and aldehydes were purified according to standard procedures[139] immediately prior to use. *n*-Butyl lithium was standardised according to Gilman,[140] also immediately prior to use.

Manipulations involving potentially air sensitive compounds, particularly organometallic complexes, were carried out in Schlenk tubes under an atmosphere of dry argon. Solvents in these cases were degassed and saturated in argon before use, using standard vacuum line techniques.

Homogeneous hydrogenations, which were not the subject of a kinetic investigation, were performed using a standard protocol. This involved combining the substrate, catalyst and degassed solvent in a Schlenk tube under argon and freezing the mixture at -196°C (liquid nitrogen). The Schlenk tube was then evacuated to below 0.1 mbar and the mixture allowed to melt. When the solution had completely thawed the Schlenk tube was filled with argon. The solution was then frozen and the cycle repeated a further three times. The solution was then frozen once more and the atmosphere in the Schlenk tube replaced with hydrogen. At this point the Schlenk tube was connected to a gas burette containing hydrogen and the apparatus allowed to equilibrate at room temperature. When the volume of the gas in the system had stabilised along with the temperature of the Schlenk tube, the solution was stirred vigorously with the aid of a magnetic stirrer. A representation of the apparatus is shown in Scheme 5.1.

When the required amount of hydrogen had been taken up by the system, the reaction mixture was frozen (-196°C) and the atmosphere in the Schlenk tube replaced with argon. Standard work up procedure involved removal of the solvent *in vacuo*, followed by trituration with hot diethyl ether except where stated otherwise.

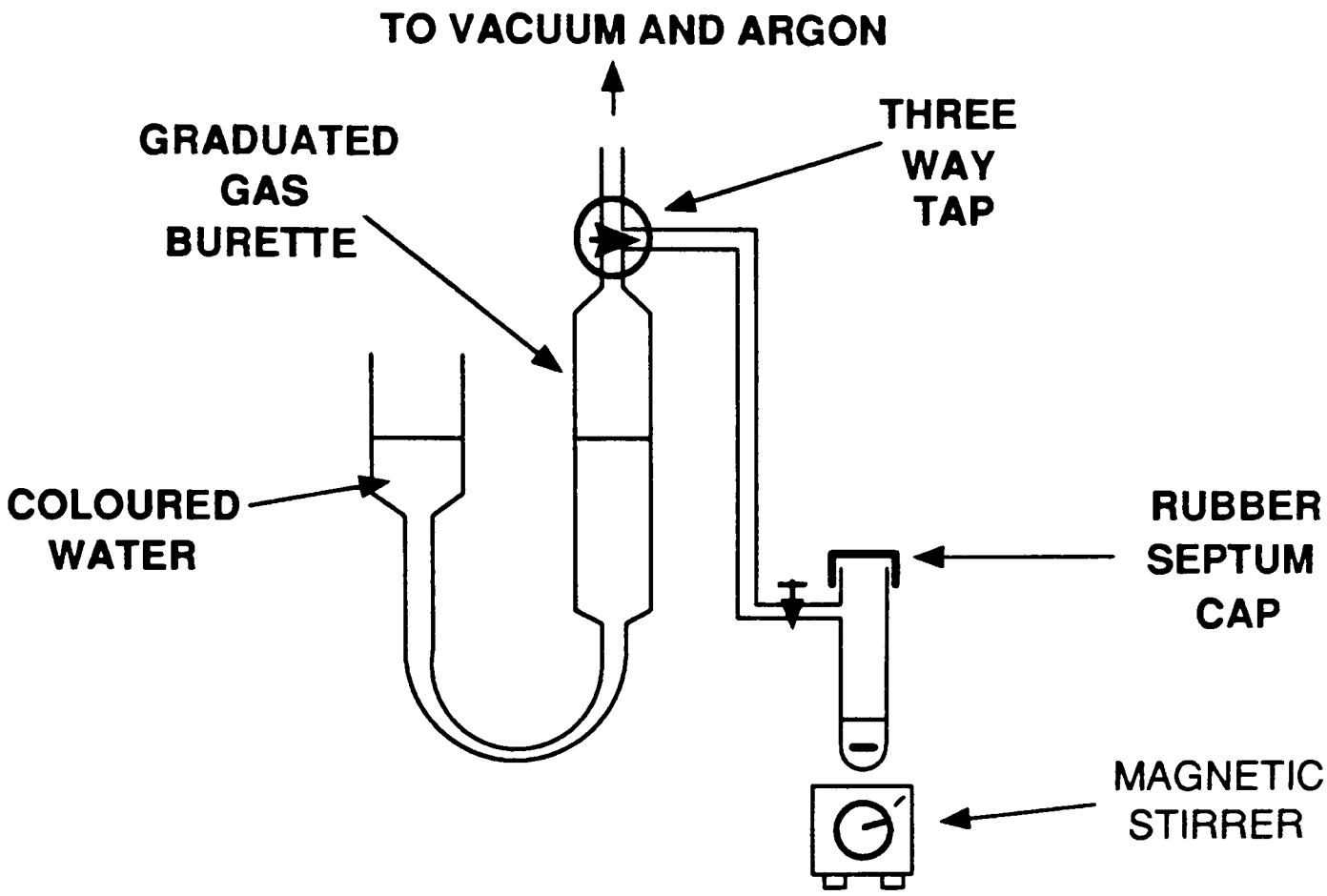


Figure 5.1 - Apparatus used in standard hydrogenations.

The protocol used for hydrogenations that were performed as part of a kinetic analysis of reaction rates, differed slightly from the standard procedure due to the design of the constant volume apparatus, which was presented in Chapter 4. The substrate, catalyst and degassed solvent were placed in the reaction vessel of the constant volume apparatus under a stream of argon and the reaction vessel was cooled to -78°C (CO_2/acetone). The entire apparatus was evacuated to below 0.1 mbar, then the reaction mixture was allowed to thaw. The entire apparatus was then filled with argon to a pressure of approximately 1100 mbar. This freeze-pump-thaw procedure was repeated a further five times before the entire apparatus was filled with hydrogen to a pressure of approximately 1000 mbar.

The reaction mixture was then subjected to two freeze-pump-thaw degas cycles filling with hydrogen rather than argon at the end of each cycle. Care was taken not to disturb the surface of the solvent in order to prevent hydrogenation. At the end of the final freeze-pump-thaw cycle the hydrogen atmosphere was set to approximately 150 mbar below the required pressure and the apparatus sealed.

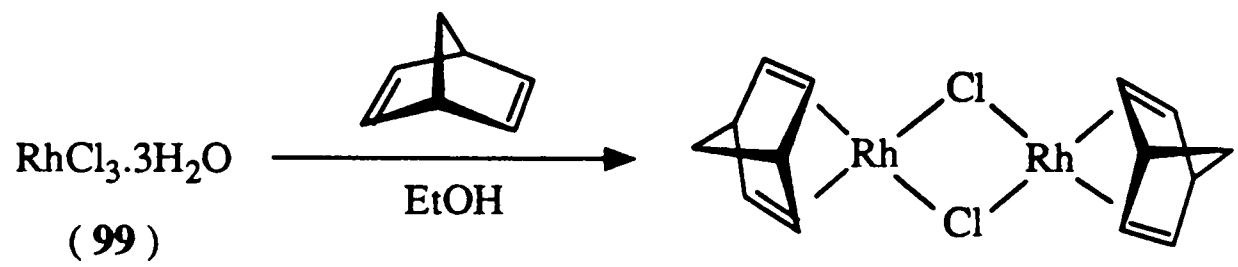
The reaction vessel was warmed to 25°C and kept at that temperature with the aid of a water circulator fitted with a thermostat. When the pressure in the apparatus had

stabilised to within 0.5 mbar over a period of 2 minutes, the magnetic stirrer, which was preset to a constant speed, was placed under the reaction vessel and sampling of the reaction vessel pressure commenced with the computer program (Appendix B). Sampling was continued until the pressure in the reaction vessel had stabilised to within 0.5 mbar over a period of 15 minutes.

Diastereomeric excesses in the products from hydrogenation reactions were determined by ^{1}H NMR analysis at 500 MHz. A 10 mg sample of the reaction products was dissolved in $CDCl_3$ (0.75 ml) and the ^{1}H NMR spectrum taken. One of the ^{13}C satellite peaks of the newly formed methyl group in the product was integrated against the peak due to the minor diastereomer. The chemical shift of the minor diastereomer's methyl group was determined by less selective or non-selective hydrogenation or by comparison with literature values.

7.02 Synthesis of Organometallic Complexes

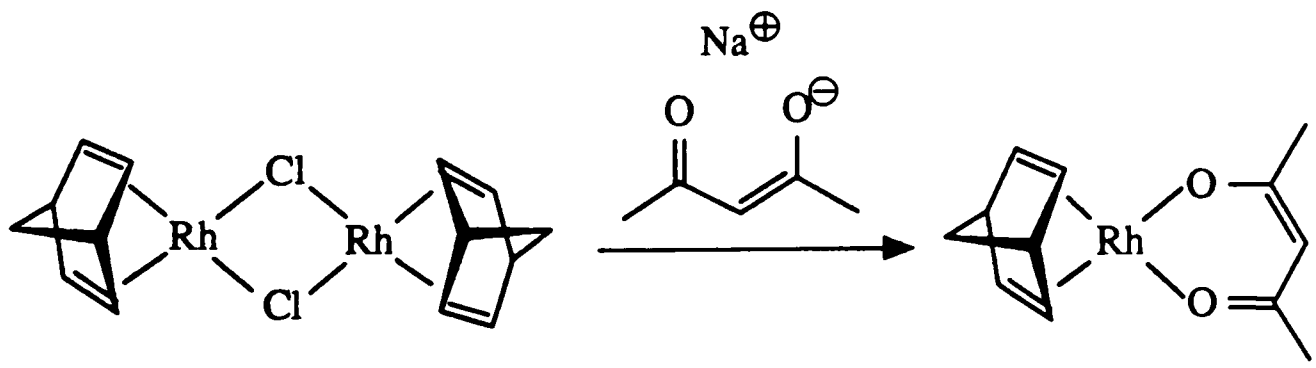
Bis-(bicyclo-[2,2,1]-hepta-2,5-diene rhodium-μ^2-chloride) (**101**)



(**99**) (**101**)

The title complex was prepared according to Abel[72] by stirring rhodium trichloride (5.0 g, 23.9 mmol), (**99**), together with bicyclo-[2,2,1]-hepta-2,5-diene (15 ml, 0.139 mol) in ethanol (70 ml) for a period of two days. The product, collected by suction filtration, was recrystallized (hexanes/chloroform, 3:1) to give bis-(bicyclo-[2,2,1]-hepta-2,5-diene rhodium-μ^2-chloride) as pale yellow microcrystals (3.899 g, 71 %). m.p. 232-239°C (dec) (lit.[72] 240°C(dec)). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.197 (2H, t, $J_{CH\text{-}CH2}$= 1.53 Hz, C$\underline{H}_2$CH), 3.834 (2H, bs, C$\underline{H}$CH=CH), 3.936 (4H, dd, $J_{Rh\text{-}CH}$= 2.54 Hz, $J_{CH\text{-}CH}$= 4.66 Hz, CHC$\underline{H}$=C$\underline{H}$) p.p.m..

Bicyclo-[2,2,1]-hepta-2,5-diene rhodium 2,5-pentadionate (**103**)

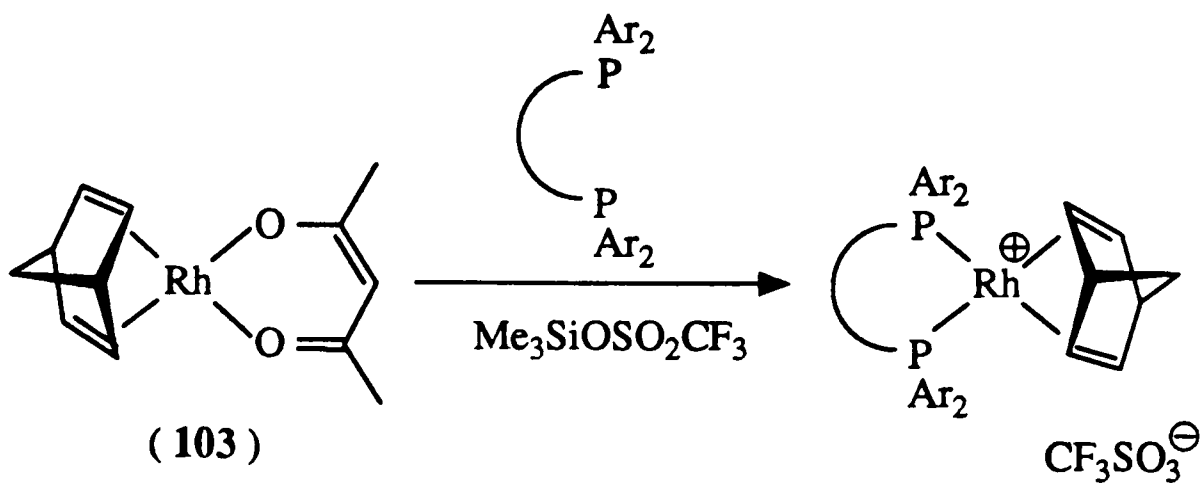


(**101**) (**103**)

The title compound was prepared according to Evans[73] by stirring a solution of bicyclo-[2,2,1]-hepta-2,5-diene rhodium chloride dimer (1.87 g, 4.1 mmol), (**101**), with sodium 2,5-pentadionate (1.0 g, 18.2 mmol) in tetrahydrofuran (50 ml) for a period of 4 h. The solution was filtered and the solvent removed *in vacuo*. The resulting off-yellow solid was then vacuum sublimed (oil bath temperature 125°C @ 0.1 mbar) to give the title compound as bright yellow needles (1.92 g, 80 %). m.p. 182-184°C (lit.[141] 176-177°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.239 (2H, t, J= 1.64 Hz, C$\underline{H}_2$), 1.919 (6H, s, C$\underline{H}_3$), 3.796 (2H, bs, $CH_2C\underline{H}CH$=C), 3.952 (4H, dd, $J_{Rh\text{-}CH}$= 4.734 Hz, $J_{CH\text{-}CH=C}$= 2.55 Hz,

CHCH=CHCH), 5.312 (1H, s, COCHCO) p.p.m..

Biphosphine Rhodium Catalyst Precursors



(**103**) (**104 - 108**)

1,4-Bis-(diphenylphosphino)butane rhodium(I) (bicyclo-[2,2,1]-hepta-2,5-diene) trifluoromethane sulphonate (**105**)

The title compound together with all other biphosphine catalyst precursors* was prepared as followed. To a stirred solution of bicyclo-[2,2,1]-hepta-2,5-diene rhodium 2,5-pentadionate (0.51 g, 1.73 mmol), (**103**), in tetrahydrofuran (5 ml) under argon was added trimethylsilyl trifluoromethanesulphonate (334 µl, 0.384 g, 1.73 mmol) via microsyringe. The resulting orange solution was stirred for 10 min then 1,4-bis-(diphenyl-phosphino)-butane (0.736 g, 1.74 mmol) was added in one portion under a stream of argon. After stirring the deep red solution for a further 15 min, diethyl ether (20 ml) was added and an orange precipitate collected by suction filtration. Recrystallization under argon (dichloromethane-hexanes, 1:4) gave the title compound as orange crystals (1.01 g, 78 %). m.p. 180-190°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.551 (2H, s, $C\underline{H}_2CHCH{=}C$), 1.704 (4H, bs, $C\underline{H}_2CH_2P$), 2.52 (4H, bs, $CH_2C\underline{H}_2P$), 3.961 (2H, bs, $CH_2C\underline{H}CH{=}C$), 4.491 (4H, dd, $J_{Rh\text{-}CH}$= 4.395 Hz, $J_{CH\text{-}CH=C}$= 1.98 Hz, $CHC\underline{H}{=}C\underline{H}CH$), 7.537 (20H, m, Ar) p.p.m.. ^{31}P NMR (101.23 MHz, Me_2SO) δ = 24.271 (d, $J_{Rh\text{-}P}$= 147.7 Hz) p.p.m..

*Except (*S*,*S*)-DiPAMP(7) derived catalyst precursor.

1,2-Bis-(diphenylphosphino)ethane rhodium(I) (bicyclo-[2,2,1]-hepta-2,5-diene) trifluoromethane sulphonate (**104**)

Prepared as above. (0.706 g, 82 %). m.p. 195-200°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.821 (2H, s, $C\underline{H}_2CHCH=C$), 2.389 (4H, d, J_{CH-P}= 19.60Hz, $C\underline{H}_2P$), 4.240 (2H, bs, $CH_2C\underline{H}CH=C$), 5.333 (4H, m, $CHC\underline{H}=C$), 7.519 (20H, m, Ar) p.p.m.. ^{31}P NMR (101.23 MHz, THF) δ = 53.478 (d, J_{Rh-P}= 157.2 Hz) p.p.m..

1,1'-Bis-(diphenylphosphino)ferrocene rhodium(I) (bicyclo-[2,2,1]hepta2,5-diene) trifluoromethane sulphonate (**106**)

Prepared as above. (0.320 g, 75 %). m.p. 190-200°C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.588 (2H, s, $C\underline{H}_2CHCH=C$), 3.992 (2H, bs, $CH_2C\underline{H}CH=C$), 4.400 (8H, m, C<u>H</u>- ferrocenyl), 4.329 (4H, m, $CHC\underline{H}=C$), 7.601 (12H, m, Ar), 7.707 (8H, m, Ar) p.p.m.. ^{31}P NMR (101.23 MHz, THF) δ = 24.502 (d, J_{Rh-P}= 160.9 Hz) p.p.m..

1,1'-Bis-(diphenylphosphino)-binapthyl rhodium (I) bicyclo-[2,2,1]-hepta-2,5diene trifluoromethane sulphonate (**107**)

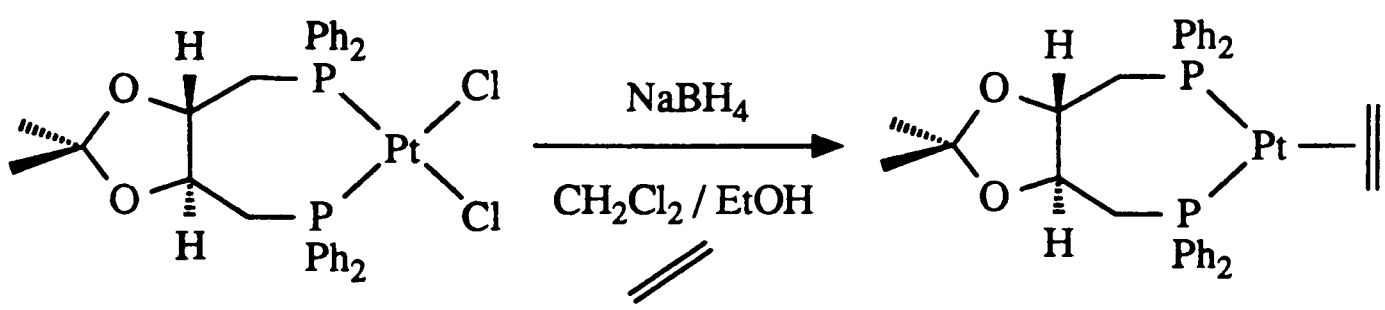
Prepared as above. (0.160 g, 90 %). m.p. 170-182°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.70 (2H, s, $C\underline{H}_2CHCH=C$), 4.137 (2H, bs, $CH_2C\underline{H}CH=C$), 4.93 (4H, m, $CHC\underline{H}=C$), 6.48 (2H, d, J= 8.5 Hz, Ar), 6.65-6.9 (5H, m, Ar), 7.00 (2H, t, J= 7.3 Hz, Ar), 7.3-7.73 (23H, m, Ar) p.p.m..

1,2-Bis-((2-methoxylphenyl)phenylphosphino)ethane rhodium(I) (bicyclo -[2,2,1]-hepta-2,5-diene) trifluoromethanesulphonate (**108**)

Prepared according to Conn[74] on the day of use and stored at -20°C between manipulations. To a stirred solution of bicyclo-[2,2,1]-hepta-2,5-diene rhodium 2,5-pentadionate (19.25 mg, 65.4 μmol), (**103**), in tetrahydrofuran (0.4 ml) under argon was added trimethylsilyl trifluoromethanesulphonate (15 μl, 17.45 mg, 1.2 equivalents) via microsyringe. The resulting solution was stirred for 2 min after which time, 1,2-Bis-(2-methoxylphenyl phenylphosphino)-ethane (30.0 mg, 65.4 μmol) was added in one portion under a stream of argon. The solution was left to stir for 10 min and then was

transferred *via* cannula into pre-cooled (0°C) hexane (7 ml) under argon. The pale orange precipitate was centrifuged and the mother liquor removed. The product was dried under a stream of argon to give the title compound together with 14 %, (by ^{31}P NMR), bis(1,2-bis-((2-methoxyphenyl)lphenylphosphino)ethane) rhodium (I) (bicyclo-[2,2,1]-hepta-2,5-diene) trifluoromethanesulphonate (47.2 mg, 89.9 %). ^{31}P NMR (101.23 MHz, THF) δ = 47.49 (d, $J_{Rh\text{-}P}$= 158.14 Hz), 52.45 (d, $J_{Rh\text{-}P}$= 157.0 Hz, {bis biphosphine Rh (I) impurity}) p.p.m..

(+)-2,3-Diisopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane platinum (O) ethene (**221**)



(**222**) (**221**)

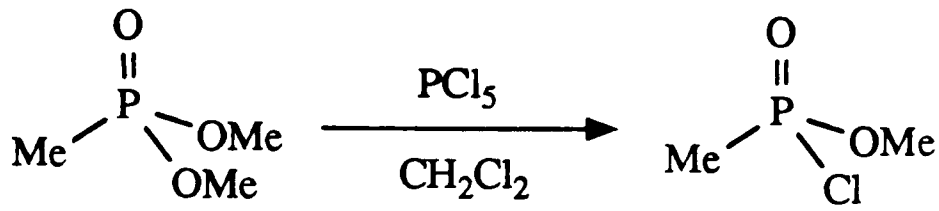
The title compound was prepared as reported[120] from (+)-2,3-Diisopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane platinum dichloride.[121] (+)-DIOP platinum dichloride (0.20 g, 0.244 mmol) was dissolved in 50:50 ethanol-dichloromethane (5 ml) at -78°C under an atmosphere of ethene. The solution was saturated in ethene then sodium borohydride (0.024 g, 0.63 mmol) was added to the stirred solution in one portion under a stream of ethene. The solution was allowed to stir for 10 min then allowed to warm to room temperature over a period of 10 min. Ethanol (20 ml) was added and the precipitate collected under suction filtration. The precipitate was washed in quick succession with water (5 ml), ethanol (2 ml) and hexane (10 ml) then dried *in vacuo* to give the title compound as a white powder (0.120 g, 71 %). m.p. 165-168°C (dec) (lit.[120] 168-173°C (dec)). ^{1}H NMR (200 MHz, d^6-benzene) δ = 1.24 (6H, s, $C\underline{H}_3C(O)_2$), 2.42 (4H, m, $C\underline{H}_2$-PPh_2), 2.56 (2H, m, O-$C\underline{H}CH_2$), 3.65 (2H, m, platinum-bound ethene including Pt satellites), 4.12 (2H, bm,), 6.97 (12H, m, Ph), 7.50 (4H, bm, Ph), 7.83 (4H, bm, Ph) p.p.m.. ^{31}P NMR (202.46 MHz, d^6-benzene) δ = 2.490 ($\frac{1}{6}$P, s, ^{195}Pt satellite, $J_{Pt\text{-}P}$= 3588.5 Hz), 11.351 ($\frac{2}{3}$P, s), 20.214 ($\frac{1}{6}$P, s, ^{195}Pt satellite, $J_{Pt\text{-}P}$=

3588.5 Hz) p.p.m..

7.03 Synthesis of 1,2-Bis-((2-methoxyphenyl)phenylphosphino)ethane (**7**)

This synthesis was carried out in collaboration with Mr. A.D. Conn.[74, 78]

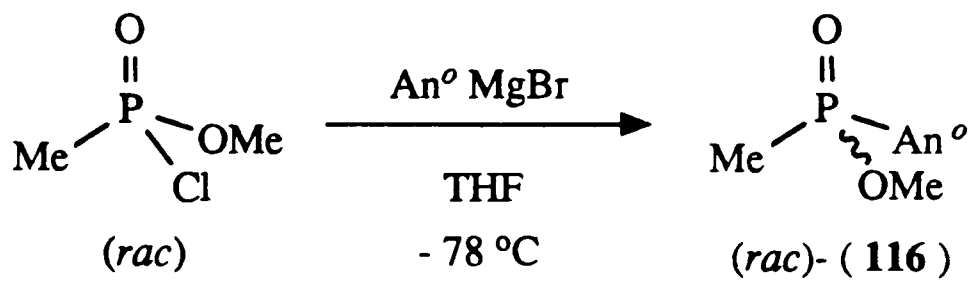
Methoxy methylphosphonyl chloride



(*rac*)

This was prepared by Mr. A.D. Conn[78] and used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.97 (3H, d, $J_{P\text{-}CMe}$= 17.6 Hz, PC$\underline{H}_3$), 3.86 (3H, d, $J_{P\text{-}OMe}$= 13.7 Hz, P-OMe) p.p.m..

(2-Methoxyphenyl)methoxy methylphosphonate (**116**)



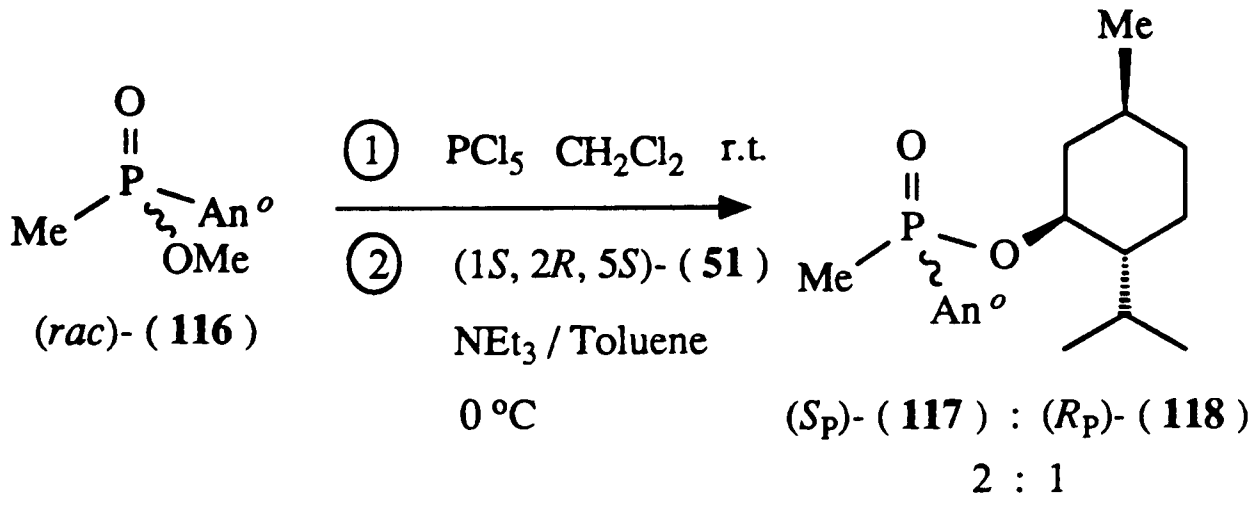
(*rac*) (*rac*)- (**116**)

The reaction required the preparation of a ethereal solution of anisyl magnesium bromide. Magnesium turnings (20 g, 0.823 mol) were stirred under argon in a 1.0 l round bottom flask for three days. Dry degassed diethyl ether (500 ml) was added and the reaction flask cooled to 0°C in an ice-bath. A solution of *o*-bromoanisole (150 g, 0.823 mol) in diethyl ether (100 ml) was then added dropwise over a period of 1½ h. The reaction was allowed to warm to room temperature and stirred for a further 2 h. The molarity of the Grignard reagent solution was determined by the method of Gilman[140] and found to be 0.805 M.

To a mechanically stirred solution of methoxy methylphosphonyl chloride (45 g, 0.35 mol) in tetrahydrofuran (600 ml) cooled to -78°C was added the pre-cooled (-15°C) solution of the Grignard reagent (450 ml, 0.36 mol) over a period of 45 min. The reaction mixture was then left to stir at -70°C for 5½ h. Saturated aqueous ammonium chloride solution (200 ml) was added with vigorous stirring to the reaction mixture and the mixture

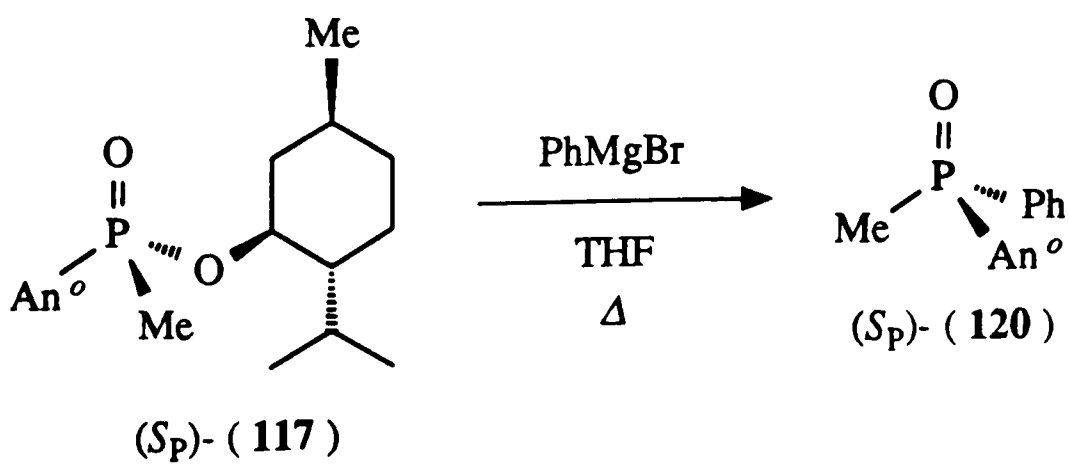
allowed to warm to room temperature. The layers were separated and the aqueous layer extracted three times with dichloromethane (400 ml). The organic layers were then combined and the solvent removed *in vacuo* to give a pale yellow oil. Light petroleum ether (50 ml) was added and a solid collected. The product was recrystallized from hexanes to give (2-methoxyphenyl)methoxy methylphosphonate as a white solid (59.123 g, 84.4 %). m.p. 65-69°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.59 (3H, d, $J_{P\text{-}Me}$= 15.6 Hz, P-C$\underline{H}_3$), 3.40 (3H, d, $J_{P\text{-}OMe}$= 11.7 Hz, OC$\underline{H}_3$), 3.74 (3H, s, Ar-OC$\underline{H}_3$), 6.75-6.95 (2H, m, Ar), 7.39 (1H, t, J= 7.5 Hz, Ar), 7.80 (1H, ddd, J_1= 13.1 Hz, J_2= 7.4 , J_3= 1.8 Hz, Ar) p.p.m.. ^{31}P NMR (101.23 MHz, $CDCl_3$) δ = 36.21 (s) p.p.m.. GCMS (CI+) m/z = 201(100) $M+H^{\oplus}$.

<u>(S_p)-(2-Methoxyphenyl)methyl-(+)-menthyl phosphonate</u> (**117**)



The title compound was prepared as, and separated from, a 2:1 ratio of diastereomers (S_p:R_p) by Mr. A.D. Conn[78]. m.p. 94-96°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.1-2.4 (19H, m, menthyl), 1.80 (3H, d, $J_{P\text{-}Me}$= 15.3 Hz, P-C$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 6.88-8.09 (4H, m, Ar) p.p.m.. ^{31}P NMR (101.23 MHz, $CHCl_3$) δ = 36.54 (s) p.p.m..

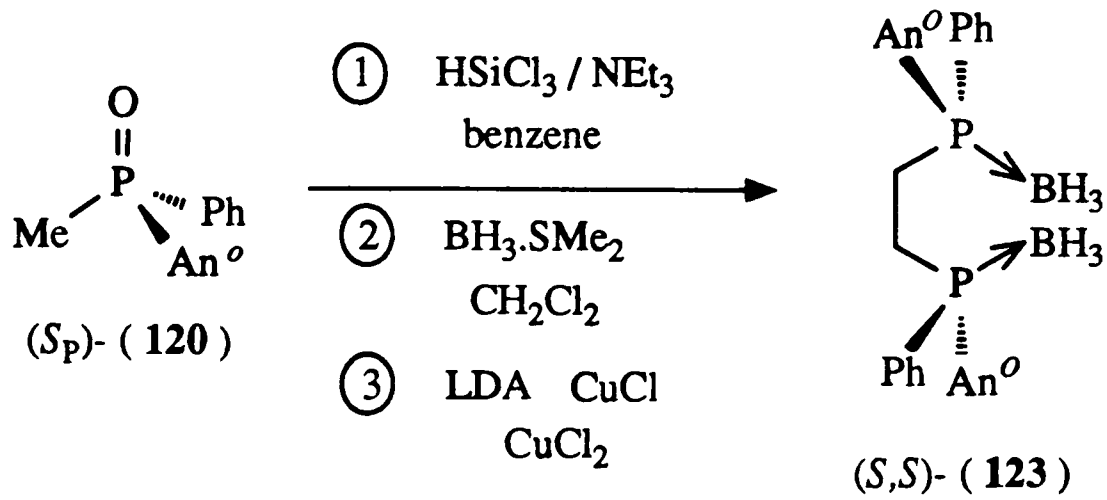
<u>(S_p)-(2-Methoxyphenyl)methylphenyl phosphine oxide</u> (**120**)



The reaction required the preparation of an ethereal solution of phenyl magnesium bromide. Magnesium turnings (24.5 g, 1.0 mol) were stirred in a 1.0 l round bottom flask under nitrogen for 3 days. Dry degassed diethyl ether (500 ml) was added and the reaction flask cooled to 0°C in an ice-bath. A solution of freshly distilled bromobenzene (157 g, 1.0 mol) in diethyl ether (200 ml) was then added dropwise over a period of 1½ h. The reaction was allowed to warm to room temperature and stirred for a further 2 h. The molarity of the Grignard reagent solution was determined by the method of Gilman[140] and found to be 1.3 M.

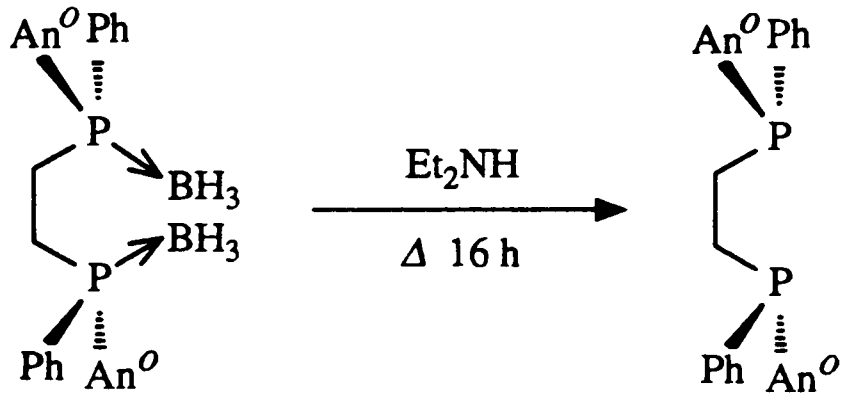
The diethyl ether solvent from a sample of the Grignard solution (140 ml) was removed *in vacuo* and replaced with dry degassed tetrahydrofuran (100 ml). To a stirred solution of (S_p)-(+)-menthyl-(2-methoxyphenyl)methyl phosphonate (10 g, 30.9 mmol) in tetrahydrofuran (100 ml) was added the Grignard solution in tetrahydrofuran. The reaction mixture was then refluxed for 16 h under argon. After allowing the mixture to cool to room temperature, saturated aqueous ammonium chloride solution (50 ml) was added with stirring and the layers were separated. The aqueous layer was then extracted three times with dichloromethane (100 ml) and the organic layers combined and reduced in volume *in vacuo*. The menthol component of the product mixture was removed by kugelrohr distillation (123°C @ 15 mmHg). The resulting yellow oil was then crystallized from the minimum volume of toluene at -30°C to give (S_p)-(2-methoxyphenyl)methylphenyl phosphine oxide (7.39 g, 54 %). m.p. 73-76°C (lit.[11] 70-76°C). $[\alpha]^{25}_{D=}$ +24.9° (c=1, MeOH) (96 % e.e.) (lit.[11] $[\alpha]^{25}_{D=}$ -25.9° (c=1, MeOH)). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.07 (3H, d, $J_{P\text{-}Me}$= 14.0 Hz, P-C$\underline{H}_3$), 3.71 (3H, s, -OC$\underline{H}_3$), 6.87 (1H, dd, J_1= 8.2 Hz, J_2= 5.8 , Ar), 7.08 (1H, t, J= 6.4 Hz, Ar), 7.35-7.5 (4H, m, Ph), 7.70-7.76 (2H, m, Ar + Ph), 7.95 (1H, dd, J_1= 13.1 Hz, J_2= 7.5 Hz,) p.p.m.. ^{31}P NMR (101.23 MHz, THF) δ = 19.63 (s) p.p.m.. GCMS (CI+) m/z = 247(100) $M+H^{\oplus}$.

(*S*,*S*)-1,2-Bis-(boronato(2-methoxyphenyl)phenylphosphino)ethane (**123**)



The title compound was prepared from (S_P)-(2-methoxyphenyl)methylphenyl phosphine oxide by Mr. A.D. Conn.[78] m.p. 161-162°C. $[\alpha]^{20}_D$= -70.2° (c=1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ = 2.54 (4H, s, $C\underline{H}_2$-$C\underline{H}_2$), 3.59 (6H, s, O-$C\underline{H}_3$), 6.8-7.9 (18H, m, Ar) p.p.m..

(*S*,*S*)-1,2-Bis-((2-methoxyphenyl)phenylphosphino)ethane (**7**)



The title compound was prepared from its diborane complex by the method of Imamoto.[79] (*S*,*S*)-1,2-Bis-(boronato(2-methoxyphenyl)phenylphosphino)ethane (0.53 g, 1.17 mmol) was refluxed in diethylamine (10 ml) under argon for 15 h. The solvent was removed *in vacuo* and the residue dissolved in benzene. The solution was passed through a column of celite and then the solvent removed *in vacuo*. The white solid was recrystallized from hot methanol to give (*S*,*S*)-1,2-Bis-(*o*-anisylphenylphosphino)ethane (0.345 g, 75 %). m.p. 102-103°C (lit.[11] 102-104°C). $[\alpha]^{25}_D$= +86.6° (c=0.96, $CHCl_3$) (lit.[79] $[\alpha]^{25}_D$= -87.0° (c=1.0, $CHCl_3$)). ^1H NMR (200 MHz, $CDCl_3$) δ = 1.85-2.3 (4H, m, -$C\underline{H}_2$-), 3.74 (6H,s, -O$C\underline{H}_3$), 6.7-7.0 (6H, m, Ar), 7.2-7.45 (12H, m, Ar) p.p.m..

7.04 Synthesis of Hydroxy Vinylsulphones

i) Optimum conditions.

Phenyl vinylsulphone (0.10 g, 0.595 mmol), diazobicyclo-[2,2,2]-octane (7.0 mg, 0.06 mmol) and ethanal (0.5 ml, 8.8 mmol) was mixed in a 1 ml Teflon® high pressure reaction pot and the volume made up to 0.75 ml with tetrahydrofuran. The reaction pot was sealed with a rubber flanged teflon® stopper. The vessel was placed in a 19 kbar Psika high pressure machine and the pressure increased to 5 kbar. This pressure was maintained for 2 h then the vessel was removed from the machine and the solvent removed *in vacuo*. ^{1}H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture showed clean conversion of approximately 25 % of the starting material. This process was repeated at 7 kbar, 9 kbar, 11 kbar and 13 kbar. It was found that the proportion of side products as judged by multiplets in the δ 0.8-2.0 region of the ^{1}H NMR spectrum increased with the pressure applied. Optimum conditions were judged to be 9 kbar, which gave complete conversion and a small amount of side products.

ii) Trial preparation of 4-methyl-2-(Phenylsulphonyl)-pentene-3-ol (**145**).

Phenyl vinylsulphone (0.10 g, 0.595 mmol), diazobicyclo-[2,2,2]-octane (7.0 mg, 0.06 mmol) and 2-methylpropanal (0.5 ml, 8.0 mmol) was mixed in a 1 ml Teflon® high pressure reaction pot and the volume made up to 0.75 ml with tetrahydrofuran. The procedure then followed that of the initial trial reactions with the pressure being kept at 9 kbar for 2h. Excess aldehyde was removed *in vacuo* and the residue chromatographed on flash silica eluting with hexanes/ethyl acetate (60:40). The product was obtained with contaminants evident between δ 0.8-2.4 p.p.m. in the ^{1}H NMR spectrum (200 MHz, $CDCl_3$). Further attempts to purify the product by chromatography on flash silica eluting with hexanes/diethyl ether (60:40) did not give the product of sufficient purity for hydrogenation studies.

iii) Trial preparation of 3-(2-furanyl)-2-(Phenylsulphonyl)-propene-3-ol (**146**).

Phenyl vinylsulphone (0.10 g, 0.595 mmol), diazobicyclo-[2,2,2]-octane (7.0 mg, 0.06 mmol) and 2-furanal (0.5 ml, 8.0 mmol) was mixed in a 1 ml Teflon® high pressure

reaction pot and the volume made up to 0.75 ml with tetrahydrofuran. The procedure then followed that of the initial trial reactions with the pressure being kept at 9 kbar for 1h. Examination of the ^1H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture showed no identifiable products.

iv) Trial preparation of 4-phenyl-2-(Phenylsulphonyl)-hexene-3-ol.

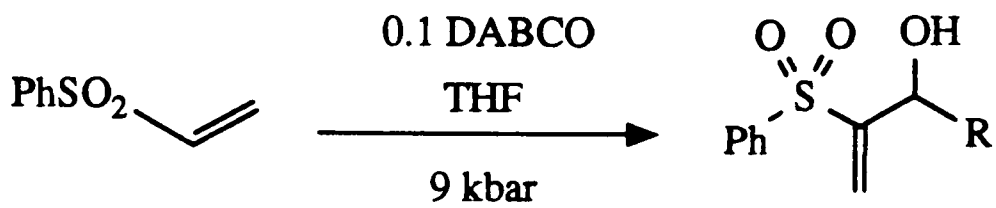
Phenyl vinylsulphone (0.10 g, 0.595 mmol), diazobicyclo-[2,2,2]-octane (7.0 mg, 0.06 mmol) and 2-phenylbutanal (0.5 ml, 7.3 mmol) was mixed in a 1 ml Teflon® high pressure reaction pot and the volume made up to 0.75 ml with tetrahydrofuran. The procedure then followed that of the initial trial reactions with the pressure being kept at 9 kbar for 2h. Examination of the ^1H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture showed a multitude of peaks between δ 0.5-3.5 p.p.m.. There was no evidence of vinylic protons between δ 5.5-6.5 p.p.m..

v) Trial preparations of 3-phenyl-2-(Phenylsulphonyl)-butene-3-ol and 3-methyl-2-(Phenylsulphonyl)-pentene-3-ol.

Phenyl vinylsulphone (0.10 g, 0.595 mmol), diazobicyclo-[2,2,2]-octane (7.0 mg, 0.06 mmol) and butan-2-one (0.5 ml, 8.3 mmol) was mixed in a 1 ml Teflon® high pressure reaction pot and the volume made up to 0.75 ml with tetrahydrofuran. The procedure then followed that of the initial trial reactions with the pressure being kept at 9 kbar for 3h. A similar procedure was applied using methyl phenyl ketone (0.5 ml, 9.0 mmol). ^1H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture exhibited two main vinylic peaks at δ 6.1 and 6.5 p.p.m. and two sets of multiplets at δ 1.82 and 3.01 p.p.m.. These peaks were tentatively asigned as belonging to 2,4-bis-(phenylsulphonyl)butene, (**136**).

vi) Preparative reactions.

Note : The ´ superscript in NMR assignments indicates protons or carbons in the allylic phenyl ring.



(**128**) (**129**)- (**135**)

2-(Phenylsulphonyl)-butene-3-ol (**129**)

R = Me

Phenyl vinyl sulphone (1.0 g, 5.95 mmol), 1,4-diazobicyclo[2,2,2]octane (0.050 g, 0.446 mmol) and ethanal (2.5 ml, 44.3 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The reaction pot was sealed with a rubber flanged teflon® stopper. The vessel was placed in a 19 kbar Psika high pressure machine and the pressure was increased to 9 kbar. The pressure was maintained at 9 kbar and 20°C for 45 min. After releasing the pressure and removing the vessel from the pressure machine, the reaction mixture was washed out of the reaction pot with dichloromethane (20 ml). The solution was then washed with 2 M aqueous hydrochloric acid solution and the organic layer separated and dried (Na_2CO_3). The solvent was removed *in vacuo* and the resulting oily residue was chromatographed on flash silica eluting with hexane-ethyl acetate (90:10) to give the title compound as a viscous colourless oil (0.980 g, 78 %). (lit.[85] m.p. 34-36°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.359 (3H, d, J= 6.4 Hz, C$\underline{H}_3$), 2.622 (1H, d, J= 3.73 Hz, O$\underline{H}$), 3.448 (1H, dq, J_1= 6.4 Hz, J_2= 3.7 Hz, C$\underline{H}$OH), 6.127 (1H, s, *E*- C$\underline{H}_2$=C), 6.429 (1H, s, *Z*-C$\underline{H}_2$=C), 7.567 (2H, t, J= 7.4 Hz, 3-Ph), 7.659 (1H, t, J= 7.4 Hz, 4-Ph), 7.910 (2H, d, J=7.4 Hz, 2-Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 22.06 (Me), 64.767 ($\underline{C}$HOH), 124.11 ($\underline{C}H_2$=C), 128.13 (3-Ph), 129.29 (2-Ph), 133.68 (4-Ph), 139.34 (1-Ph), 154.17 (CH_2=$\underline{C}$) p.p.m.. IR (KBr disc) $\bar{\nu}_{MAX}$ = 3500 s (O-H str), 1585 m-w (C=C str), 1448 m (O-H ben), 1304 s (SO_2 symm str), 1141 s (SO_2 asymm str), 1078 s (C-O str) cm^{-1}.

2-(Phenylsulphonyl)-pentene-3-ol (**130**)

R = Et

Phenyl vinyl sulphone (1.0 g, 5.95 mmol), 1,4-diazobicyclo[2,2,2]octane (0.050 g, 0.446 mmol) and propanal (2.5 ml, 33.6 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for 1½ h. The product from chromatography, as with (**129**), was collected as a viscous oil (1.15 g, 88 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.851 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 1.675 (2H, dq, J_1= 7.3 Hz, J_2= 7.2 Hz, $C\underline{H}_2$), 2.35 (1H, bs, O<u>H</u>), 4.302 (1H, t, J= 7.2 Hz, C<u>H</u>OH), 6.092 (1H, s, *E*-$C\underline{H}_2$=C), 6.452 (1H, s, <u>Z</u>-$C\underline{H}_2$=C), 7.564 (2H, t, J= 5.3 Hz, 3-Ph), 7.631 (1H, t, J= 6.3 Hz, 4-Ph), 7.907 (2H, dd, J_1= 6.9 Hz, J_2= 1.3 Hz, 2-Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3503 s (O-H str), 1448 m (O-H ben), 1306 s (SO_2 symm str), 1141 s (SO_2 asymm str), 1080 s (C-O str) cm^{-1}.

3-Cyclohexyl-2-(phenylsulphonyl)-propene-3-ol (**131**)

R = Cy

Phenyl vinyl sulphone (1.0 g, 5.95 mmol), 1,4-diazobicyclo[2,2,2]octane (0.050 g, 0.446 mmol) and cyclohexyl carboxaldehyde (3.0 ml, 22.0 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for 3 h. The product from chromatography, as with (**129**), was collected as a white crystalline solid (1.19 g, 74 %). m.p. 73-74°C (lit[142] m.p. 76°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.05 (5H, m, Cy), 1.57 (6H, m, Cy), 2.33 (1H, bs, O<u>H</u>), 4.10 (1H, d, J= 6.8 Hz, C<u>H</u>OH), 6.04 (1H, s, *E*-$C\underline{H}_2$=C), 6.46 (1H, s, *Z*-$C\underline{H}_2$=C), 7.54 (2H, t, J= 6.8 Hz, Ar), 7.64 (1H, t, J= 6.8 Hz, Ar), 7.985 (2H, d, J= 7.3 Hz, Ar) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 25.55 (Cy), 25.8 (cy), 26.02 (Cy), 26.98 (Cy), 74.00 (<u>C</u>HOH), 126.20 ($\underline{C}H_2$=C), 128.41 (3-Ph), 129.44 (2-Ph), 133.86 (4-Ph), 139.56 (1-Ph), 152.11 (CH_2=<u>C</u>) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3476 s (O-H str), 2926 s (Cy comb), 1449 s (O-H ben), 1303 s (SO_2 symm str), 1179 s (SO_2 asymm str), 1075 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 298(100) $M+NH_4^{\oplus}$, 281(10) $M+H^{\oplus}$, 263(45) $M^{\oplus}-H_2O$. Found C, 64.44; H, 7.34; S, 11.44 %.

$C_{15}H_{20}O_3S$ requires C, 64.24; H, 7.19; S, 11.44 %.

3-Phenyl-2-(phenylsulphonyl)-propene-3-ol (**132**)

R = Ph

Phenyl vinyl sulphone (1.0 g, 5.95 mmol), 1,4-diazobicyclo[2,2,2]octane (0.050 g, 0.446 mmol) and benzaldehyde(2.5 ml, 18.4 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for $2\frac{3}{4}$ h. The product from chromatography, as with (**129**), was collected as a white crystalline solid (1.52 g, 95 %). m.p. 95-96°C (lit.[142] 93°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.028 (1H, d, J= 4.0 Hz, O<u>H</u>), 5.573 (1H, d, J= 3.6 Hz, C<u>H</u>OH), 5.934 (1H, s, *E*-C<u>H</u>$_2$=C), 6.541 (1H, s, Z-C<u>H</u>$_2$=C), 7.190 (5H, m, Ph´), 7.44 (2H, t, J= 6.7 Hz, 3-Ph), 7.57 (1H, t, J= 7.0 Hz, 4-Ph), 7.735 (2H, d, J= 7.1 Hz, 2-Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 73.53 (<u>C</u>HOH), 126.71 (3-Ph´), 126.96 (<u>C</u>H$_2$=C), 128.01 (2-Ph´), 128.24 (4-Ph´), 128.42 (3-Ph), 129.00 (2-Ph), 133.35 (4-Ph), 139.00 (1-Ph´), 139.43 (1-Ph), 153.10 (CH$_2$=<u>C</u>) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3500 s (O-H str), 1584 w (C=C str), 1296 s (SO_2 symm str), 1135 s (SO_2 asymm str), 1080 s (C-O str) cm^{-1}.

3-(4-Chlorophenyl)-2-(phenylsulphonyl)-propene-3-ol (**133**)

R = 4-ClPh

Phenyl vinyl sulphone (0.5 g, 2.98 mmol), 1,4-diazobicyclo[2,2,2]octane (0.025g, 0.223 mmol) and 4-chloro-benzaldehyde (1.3 g, 9.0 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for $2\frac{1}{2}$ h. The product from chromatography, as with (**129**), was collected as a white crystalline solid (0.863 g, 94 %). m.p. 69-70°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.62 (1H, d, J= 3.0 Hz, O<u>H</u>), 5.49 (1H, d, J= 3.0 Hz, C<u>H</u>OH), 6.02 (1H, s, *E*-C<u>H</u>$_2$=C), 6.49 (1H, s, *Z*-C<u>H</u>$_2$=C), 7.00 (2H, d, J= 7.8 Hz, 2-Ph´), 7.10 (2H, d, J= 7.8 Hz, 3-Ph´), 7.37 (2H, t, J= 7.1 Hz, 3-Ph), 7.53 (1H, t, J= 6.8 Hz, 4-Ph), 7.59 (2H, d, J= 8.1 Hz, 2-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 70.67 (<u>C</u>HOH), 127.29 (<u>C</u>H$_2$=C), 128.06 (Ar), 128.52 (Ar),

128.71 (Ar), 129.26 (Ar), 133.68 (4-Ph), 134.20 (1-Ph´), 137.72 (4-Ph´), 139.23 (1-Ph), 152.74 (CH_2=C) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3500 s (O-H str), 1584 m (C=C), 1447 s(O-H ben), 1305 vs (SO_2symm str), 1142 vs (SO_2 asymm str), 1082 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 326(100) $M+NH_4^{\oplus}$, 309(25) $M+H^{\oplus}$. Found C, 58.40; H, 4.28; S, 10.39 %. $C_{15}H_{13}ClO_3S$ requires C, 58.32; H, 4.25; S, 10.39 %

3-(4-Methoxyphenyl)-2-(phenylsulphonyl)-propene-3-ol (**134**)

R = 4-MeOPh

Phenyl vinyl sulphone (0.5 g, 2.98 mmol), 1,4-diazobicyclo[2,2,2]octane (0.025 g, 0.223 mmol) and 4-methoxy-benzaldehyde (1.8 ml, 10.6 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for 3¾ h. The product from chromatography, as with (**129**), was collected as a white crystalline solid (0.726 g, 80 %). m.p. 71-72°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.99 (1H, d, J= 4.0 Hz, O<u>H</u>), 3.77 (3H, s, O-C<u>H</u>$_3$), 5.53 (1H, d, J= 3.7 Hz, C<u>H</u>OH), 6.06 (1H, s, *E*-C<u>H</u>$_2$=C), 6.54 (1H, s, *Z*-C<u>H</u>$_2$=C), 6.73 (2H, d, J= 8.8 Hz, 3-Ph´), 7.06 (2H, d, J= 8.9 Hz, 2-Ph´), 7.40 (2H, t, J= 7.6 Hz, 3-Ph), 7.56 (1H, t, J= 7.6 Hz, 4-Ph), 7.70 (2H, d, J= 7.1 Hz, 2-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 55.26 (O-<u>C</u>H$_3$), 71.02 (<u>C</u>HOH), 113.97 (3-Ph´), 126.81 (Ar), 128.13 (Ar), 128.38 (Ar), 129.14 (Ar), 131.11 (1-Ph´), 139.60 (CH_2=<u>C</u>), 153.21 (1-Ph), 159.79 (4-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3501 s (O-H str), 1583 m (C=C), 1451 s (O-H ben), 1291 vs (SO_2 symm str), 1256 vs (C-OMe), 1132 vs (SO_2 asymm str), 1080 s (C-OH str), 1029 vs (O-Me symm str) cm^{-1}. GCMS (CI+) m/z = 322(20) $M+NH_4^{\oplus}$, 286(100) $M^{\oplus}$-H_2O. Found C, 62.84; H, 5.26; S, 10.45 %. $C_{16}H_{16}O_4S$ requires C, 63.12; H, 5.30; S, 10.54 %.

3-(Nitrophenyl)-2-(phenylsulphonyl)-propene-3-ol (**135**)

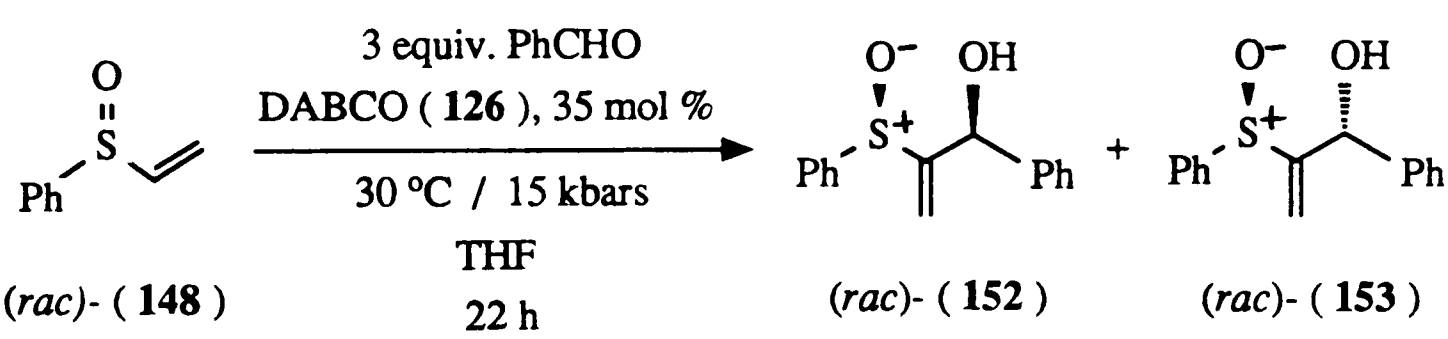
R = 4-NO_2Ph

Phenyl vinyl sulphone (0.5 g, 2.98 mmol), 1,4-diazobicyclo[2,2,2]octane (0.025 g, 0.223 mmol) and 4-nitro-benzaldehyde (1.5 g, 9.93 mmol) were mixed in a 5 ml teflon® high pressure reaction pot and the volume made up to 2 ml with tetrahydrofuran. The

procedure then followed that of (**129**) except that the reaction was kept at 9 kbar for 2½ h. The product from chromatography, as with (**129**), was collected as a pale yellow amorphous solid (0.850 g, 90 %). m.p. 105-108°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.55 (1H, s, O<u>H</u>), 5.66 (1H, s, C<u>H</u>OH), 5.97 (1H, s, *E*-C<u>H</u>$_2$=C), 6.55 (1H, s, *Z*-C<u>H</u>$_2$=C), 7.32 (2H, d, J= 8.6 Hz, Ar), 7.44 (2H, t, J= 7.8 Hz, 3-Ph), 7.59 (1H, t, J= 7.2 Hz, 4-Ph), 7.70 (2H, d, J=7.5 Hz, 2-Ph), 8.03 (2H, d, J=8.6 Hz, Ar) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 70.55 (<u>C</u>HOH), 123.71 (Ar), 127.76 (Ar), 128.08 (Ar), 128.23 (Ar), 129.47 (Ar), 134.1 (4-Ph), 138.87 (1-Ph´), 146.38 (CH_2=<u>C</u>), 147.82 (1-Ph), 152.25 (4-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3489 s (O-H str), 1527 vs (NO_2 asymm str), 1448 s (O-H ben), 1348 vs (NO_2 symm str), 1288 vs (SO_2 symm str), 1177 s (C-N str), 1134 vs (SO_2asymm str), 1076 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 337(100) M+$NH_4^{\oplus}$, 291(95) M-NO_2+$NH_4^{\oplus}$. Found C, 56.3; H, 3.90 %. $C_{15}H_{13}NO_5S$ requires C, 56.42; H, 4.10 %.

7.05 <u>Attempted High Pressure Synthesis of Hydroxy Vinylsulphoxides and Sulphides</u>

<u>3-Phenyl-2-(phenylsulphinyl)propene-3-ol</u> (**152**) and (**153**)



(*rac*)- (**148**) (*rac*)- (**152**) (*rac*)- (**153**)

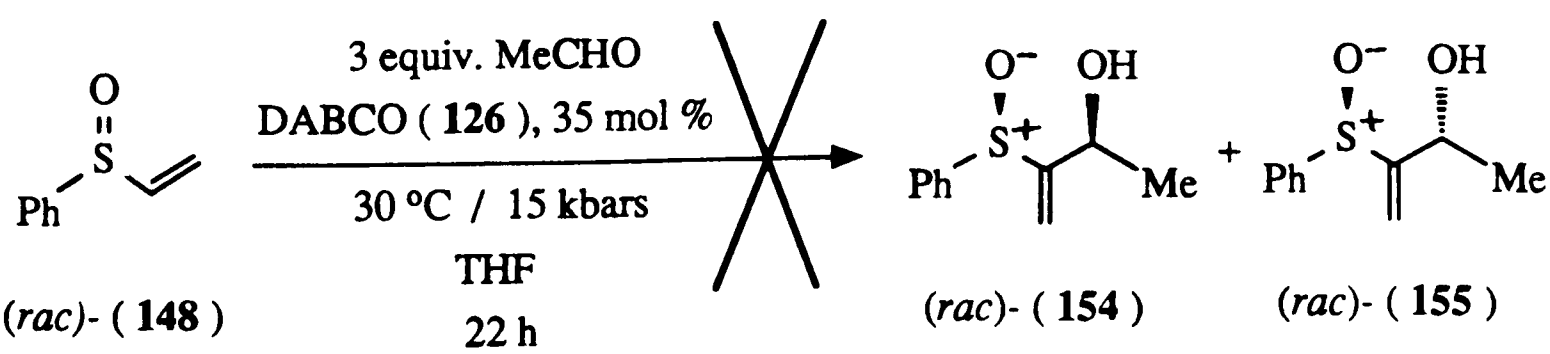
Phenyl vinylsulphoxide (2.0 g, 13.2 mmol), 1,4-diazobicyclo[2,2,2]octane (0.50 g, 0.45 mmol) and benzaldehyde (4.0 g, 37.7 mmol) were mixed in an 8 ml teflon® high pressure reaction pot and the volume made up to 7 ml with tetrahydrofuran. The procedure then followed that which was used with the hydroxy vinylsulphones except that the reaction mixture was kept at 15 kbar (rather than 9 kbar) for 22 h. ^{1}H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture indicated that almost all of the starting material had been consumed. The solvent was removed from the crude reaction mixture *in vacuo* and the residue was chromatographed on flash silica eluting with hexanes/ethyl acetate (7:3). The product was isolated as a white amorphous mixture (50:50) of the two diastereomers of the title compound (2.70 g, 80 %). The mixture was recrystallized three times from toluene at -20°C to give the *anti*-diastereomer, (**153**), (0.30 g), a sample of

which was submitted for crystallographic analysis. A 1.0g quantity of the mixture of diastereomers was separated in 50 mg portions by HPLC with a LiChrosorb diol column eluting with heptane/ethanol (90:10). Three fractions were collected across the elution profile to give a pure sample of (**153**) and a 9:1 mixture of (**154**) and (**153**) in the first and last fractions, respectively. Recovery based on the 1 g of material used in the HPLC separation was 30 % (*R*,S**) and 33 % of the (*R*,R**)/(*R*,S**) mixture.

Physical properties : (*R*,R**)/(*R*,S**) mixture. m.p. 67-70°C. Data for (*R*,R**)- ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.80 (1H, bs, O<u>H</u>), 5.24 (1H, d, J= 3.3 Hz, C<u>H</u>OH), 5.46 (1H, s, *E*-C<u>H</u>$_2$=C), 6.10 (1H, s, *Z*-C<u>H</u>$_2$=C), 7.25-7.45 (5H, m, Ar), 7.55-7.7 (5H, m, Ar) p.p.m. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 71.33 (<u>C</u>HOH), 119.01 (<u>C</u>H$_2$=C), 125.63 (Ar), 126.65 (Ar), 128.48 (Ar), 129.26 (Ar), 131.37 (4-Ph), 140.39 (CH$_2$=<u>C</u>), 143.11 (1-Ph´), 157.27 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3309 s (O-H str), 1447 m (O-H ben), 1197 m (S=O str), 1043 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 243(100) M-O+H$^{\oplus}$, 259(35) M+H$^{\oplus}$. Found C, 69.89 %; H, 5.05 %; S, 12.40 %. $C_{15}H_{14}O_2S$ requires C, 69.74 %; H, 5.46 %; S, 12.41 %.

(*R*,S**)-(**153**). m.p. 106-108°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.810 (1H, d, J= 2.6 Hz, O<u>H</u>), 5.30 (1H, d, J= 2.1 Hz, C<u>H</u>OH), 5.54 (1H, s, *E*-C<u>H</u>$_2$=C), 6.10 (1H, s, *Z*-C<u>H</u>$_2$=C), 7.1-7.3 (5H, m, Ar), 7.5-7.8 (5H, m ,Ar) p.p.m.. ^{13}C NMR (125.95, $CDCl_3$) δ = 71.32 (<u>C</u>HOH), 120.42 (<u>C</u>H$_2$=C), 125.02 (Ar), 126.80 (Ar), 128.13 (4-Ph´), 128.42 (Ar), 129.32 (Ar), 131.29 (4-Ph), 139.44 (1-Ph´), 142.63 (CH$_2$=<u>C</u>), 156.12 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3400 s (O-H str), 1442 m (O-H ben), 1180 m (S=O str), 1050 m (C-O str) cm^{-1}. GCMS (CI+) m/z = 241(90) M-H$_2$O+H$^{\oplus}$, 259(100) M+H$^{\oplus}$. Found C, 69.86 %; H, 5.64 %. $C_{15}H_{14}O_2S$ requires C, 69.72 %; H, 5.47 %.

<u>2-(Phenylsulphinyl)butene-3-ol</u> (**154**) and (**155**)

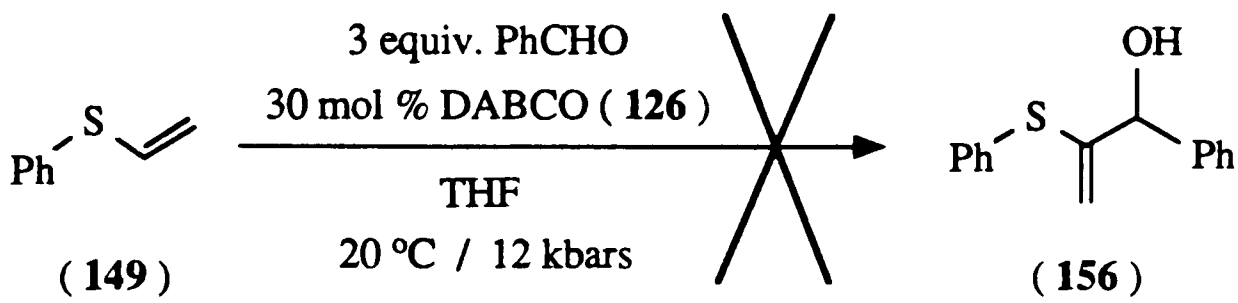


(*rac*)- (**148**) (*rac*)- (**154**) (*rac*)- (**155**)

Phenyl vinylsulphoxide (0.50 g, 3.3 mmol), 1,4-diazobicyclo[2,2,2]octane (0.10 g,

0.09 mmol) and ethanal (0.3 ml, 9.9 mmol) were mixed in an 2 ml teflon® high pressure reaction pot and the volume made up to 1.5 ml with tetrahydrofuran. The procedure then followed that which was used with the hydroxy vinylsulphones except that the reaction mixture was kept at 15 kbar (rather than 9 kbar) for 22 h. ^{1}H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture indicated that only starting materials were present.

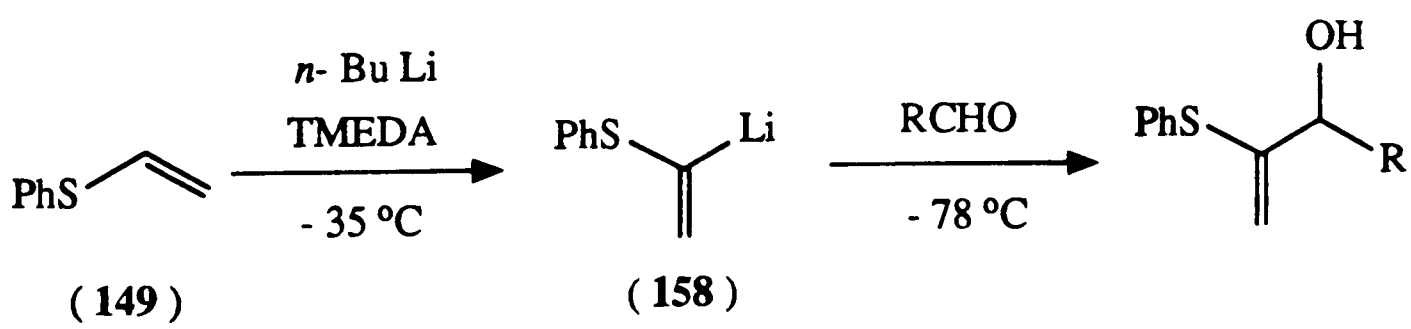
3-Phenyl-2-(phenylsulphenyl)propene-3-ol (**156**)



Phenyl vinylsulphide (0.50 g, 3.68 mmol), 1,4-diazobicyclo[2,2,2]octane (0.50 g, 0.45 mmol) and benzaldehyde (1.2 g, 11.0 mmol) were mixed in an 5 ml teflon® high pressure reaction pot and the volume made up to 4 ml with tetrahydrofuran. The procedure then followed that which was used with the hydroxy vinylsulphones except that the reaction mixture was kept at 12 kbar (rather than 9 kbar) for 48 h. ^{1}H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture indicated that only starting materials were present.

7.06 Synthesis of Hydroxy Vinylsulphoxides and Sulphides

n-Butyl lithium (TMEDA) in tetrahydrofuran was prepared by adding *N,N,N,N*-tetramethylethylene diamine (0.235 g, 2.04 mmol) to a stirred solution of *n*-butyl lithium (1.3 M, 1.6 ml, 2.03 mmol) in tetrahydrofuran (5 ml) cooled to -40°C. The solution was then left to stir for 30 min at -30°C prior to use.



2-(Phenylsulphenyl)butene-3-ol (**159**)

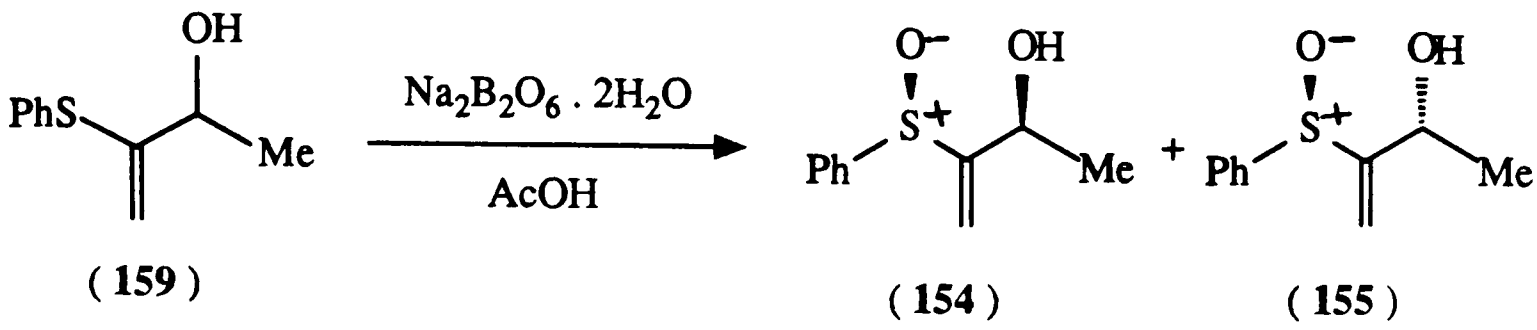
To a stirred solution of *n*-butyl lithium (TMEDA) in tetrahydrofuran (5.0 ml, 2.03

mmol) cooled to -35°C was added a solution of phenyl vinylsulphide (0.250 g, 1.84 mmol) in tetrahydrofuran (2 ml). The reaction mixture was allowed to stir at -35°C for a period of 90 min, then it was cooled to -78°C. Ethanal (0.525 ml, 10.15 mmol) was added slowly and the mixture left to stir for 1h, after which time it was allowed to warm to ambient temperature. Aqueous ammonium chloride solution was then added until the pH of the mixture was approximately 7. The mixture was extracted three times with dichloromethane (50 ml) and the organic layers combined and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue chromatographed on flash silica eluting with hexanes/ethyl acetate (70:30). The product was then distilled under reduced pressure to give the title compound as a colourless oil (2.06 g, 78 %). b.p. 95-97°C (0.2 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.44 (3H, d, J= 6.4 Hz, C<u>H</u>$_3$), 2.60 (1H, d, J=2.6 Hz, O<u>H</u>), 4.37 (1H, dq, J_1= 6.4 Hz, J_2= 2.6 , C<u>H</u>OH), 4.99 (1H, s, *E*-C<u>H</u>$_2$=C), 5.52 (1H,s, *Z*-C<u>H</u>$_2$=C), 7.2-7.49 (5H, m, Ar) p.p.m.. ^{13}C NMR (62.98 MHz, $CDCl_3$) δ = 22.86 (CH<u>C</u>H$_3$), 70.34 (<u>C</u>HOH), 112.94 (<u>C</u>H$_2$=C), 127.92 (4-Ph), 129.33 (2-Ph), 132.00 (CH$_2$=<u>C</u>), 132.99 (3-Ph), 150.22 (1-Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3369 s (O-H str), 1609 m (C=C str), 1440 s (O-H ben), 1087 vs (C-O str) cm^{-1}.

<u>3-Phenyl-2-(phenylsulphenyl)propene-3-ol</u> (**156**)

To a stirred solution of *n*-butyl lithium (TMEDA) in tetrahydrofuran (10.0 ml, 4.06 mmol) cooled to -35°C was added a solution of phenyl vinylsulphide (0.500 g, 3.68 mmol) in tetrahydrofuran (2 ml). The reaction mixture was allowed to stir at -35°C for a period of 90 min, then it was cooled to -78°C. Benzaldehyde (0.662 ml, 4.87 mmol) was added slowly and the mixture left to stir for 1h. The procedure then followed that of (**159**) and ending with kugelrohr distillation to give the title compound as a pale yellow oil (0.752 g, 85 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.78 (1H, d, J= 2.6 Hz, C<u>H</u>OH), 5.17 (1H, s, *E*-C<u>H</u>$_2$=C), 5.28 (1H, d, J= 2.6 Hz, C<u>H</u>Ph), 5.60 (1H, s, Z-C<u>H</u>$_2$=C), 7.25-7.5 (10 H,m, Ar) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3410 s (O-H str), 1612 m-w (C=C str), 1445 (O-H ben), 1080 (C-O str) cm^{-1}. bp 230-240 (0·2 mmHg).

2-(Phenylsulphinyl)butene-3-ol, (**154**) and (**155**)



(**159**) (**154**) (**155**)

2-(Phenylsulphenyl)buten-3-ol (0.10 g, 0.56 mmol) was added to a stirred solution of sodium perborate tetrahydrate (0.086 g, 0.56 mmol) in glacial acetic acid (2 ml) at 50°C. The mixture was stirred for 6 h then the solvent was removed *in vacuo*. The residue was chromatographed on flash silica eluting with hexanes/ethyl acetate (70:30) to afford the title compound as a 3:2 mixture of diastereomers (0.104 g, 95 %). A 1.0g quantity of the mixture of diastereomers was separated in 50 mg portions by HPLC with a LiChrosorb diol column eluting with heptane/ethanol (90:10). Three fractions were collected across the elution profile to give pure samples (as judged by ^{1}H NMR (500 MHz, $CDCl_3$)) of the two diastereomers in the first and last fraction. Recovery based on the 1 g of material used in the HPLC separation was 40 % (*R*,S**) and 35 % (*R*,R**).

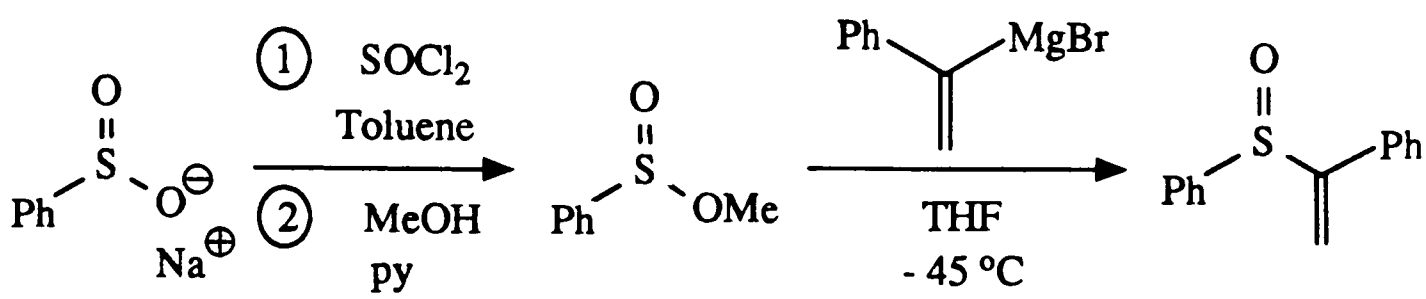
Physical properties : (*R*,S**)-(**155**) m.p. 44-47°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.359 (3H, d, J= 6.5 Hz, $C\underline{H}_3$), 2.26 (1H, d, J= 5.5 Hz, O$\underline{H}$), 4.292 (1H, m, C$\underline{H}$OH), 5.864 (1H, s, *E*C$\underline{H}_2$=C), 6.059 (1H, s, *Z*-C$\underline{H}_2$=C), 7.5-7.6 (3H, m, Ph), 7.7-7.8 (2H, m, Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 22.98 ($\underline{C}H_3$), 65.51 ($\underline{C}$HOH), 116.57 ($\underline{C}H_2$=C), 125.42 (3-Ph), 129.30 (2-Ph), 131.29 (4-Ph), 143.14 (CH_2=$\underline{C}$), 158.39 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3367 s (O-H str), 1445 m (O-H ben), 1104 s (S=O str), 1083 m (C-O str) cm^{-1}. GCMS (CI+) m/z = 181(100) M-O+H$^{\oplus}$, 197(90) M+H$^{\oplus}$. Found C, 61.27 %; H, 5.90 %; S, 16.58 %. $C_{10}H_{12}O_2S$ requires C, 61.20 %; H, 6.15 %; S, 16.34 %.

(*R*,S**)-(**154**) m.p. 45-50°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.20 (3H, d, J= 6.5 Hz, $C\underline{H}_3$), 3.51 (1H, bs, O$\underline{H}$), 4.423 (1H, m, C$\underline{H}$OH), 5.893 (1H, s, *E*-C$\underline{H}_2$=C), 6.054 (1H, s, *Z*-C$\underline{H}_2$=C), 7.5-7.6 (3H, m, Ph), 7.7-7.8 (2H, m, Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 21.74 ($\underline{C}H_3$), 65.54 ($\underline{C}$HOH), 117.591 ($\underline{C}H_2$=C), 124.93 (3-Ph), 129.29 (2-Ph), 131.23 (4-Ph), 142.29 (CH_2=$\underline{C}$), 157.10 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3373 s (O-H str), 1445 m (O-H ben), 1158 m (S=O str), 1082 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 181(100) M-O+H$^{\oplus}$, 197(85) M+H$^{\oplus}$. Found C, 61.19 %; H, 5.91 %; S, 16.34 %.

$C_{10}H_{12}O_2S$ requires C, 61.20 %; H, 6.15 %; S, 16.34 %.

7.07 Synthesis of Simple Vinylsulphoxides and Allylic Sulphoxides and β-Hydroxysulphoxides

1-Phenyl-1-(phenylsulphinyl)ethene (**160**)



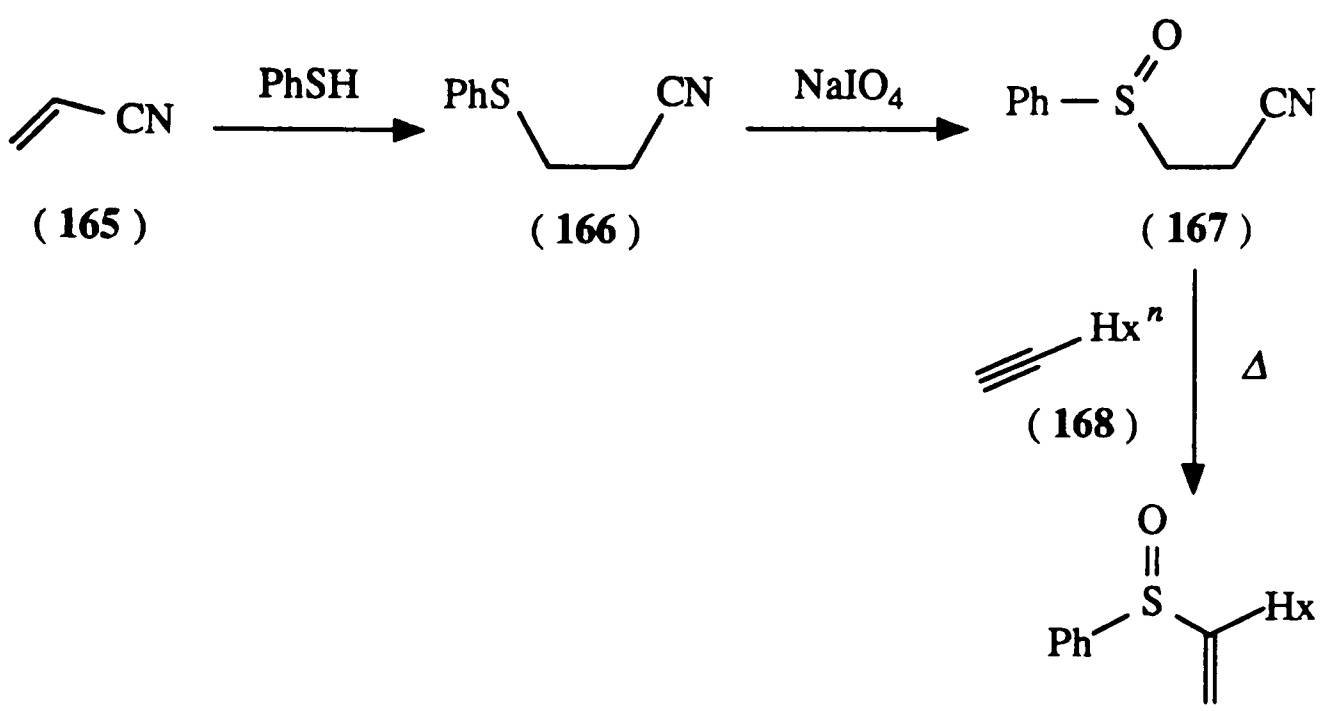
(**163**) (**164**) (**160**)

Methoxy benzenesulphinate was prepared by stirring thionyl chloride (14.5 ml, 0.182 mol) under nitrogen and adding sodium benzenesulphinate (10 g, 60.9 mmol) in small portions over a period of 1 h. After half of the salt had been added, dry toluene (10 ml) was added to aid stirring. The solution was left to stir for 1½ h, then the excess thionyl chloride was removed *in vacuo*. The resulting oil was diluted with tetrahydrofuran under argon and then a mixture of pyridine (6.0 ml, 75.0 mmol) and methanol (6.0 ml, 0.150 mol) was added dropwise with stirring. The solution was then diluted with diethyl ether (20 ml) and filtered. The solvent was removed *in vacuo* and the residue distilled under reduced pressure to give methoxy bezenesulphinate (5.0 g, 53 %). b.p. 70-75°C (0.1 mmHg) (lit.[143] 59-60°C (0.04 mmHg)). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.17 (3H, s, $OC\underline{H}_3$), 7.5-7.6 (3H, m, Ar), 7.62-7.77 (2H, m, Ar) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 1148 vs (S=O str) cm^{-1}.

A solution of 1-(1-phenylethene)-magnesium bromide was prepared by stirring a suspension of magnesium turnings (0.31 g, 12.0 mmol) in tetrahydrofuran (4 ml) under argon together with a crystal of iodine. Freshly distilled 1-bromo-1-phenylethene (1.6 ml, 12.0 mmol) was added as a solution in tetrahydrofuran (4 ml) over a period of 15 min. The solution was left to stir for 1 h then 4 ml was transferred *via* cannula into a cooled (-45°C) solution of methoxy benzenesulphinate (1.0 g, 6.0 mmol) in tetrahydrofuran (2 ml) over a period of 20 min. The solution was left to stir at -40°C for 1 h then saturated aqueous ammonium chloride solution (20 ml) was added with vigorous stirring. The organic layer was separated and the aqueous layer extracted twice with dichloromethane

(20 ml). The organic layers were then combined and dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was then chromatographed on flash silica eluting with hexanes/ethyl acetate (4:1) to give 1-Phenyl-1-(phenylsulphinyl)ethene as a colourless oil (1.98 g, 73 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.919 (1H, s, C$\underline{H_2}$=C), 6.257 (1H, s, C$\underline{H_2}$=C), 7.2-7.5 (10H, m, Ar) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 1080 vs (S=O str) cm^{-1}.

2-(Phenylsulphinyl)octene (**161**)



(**165**) (**166**) (**167**) (**168**) (**161**)

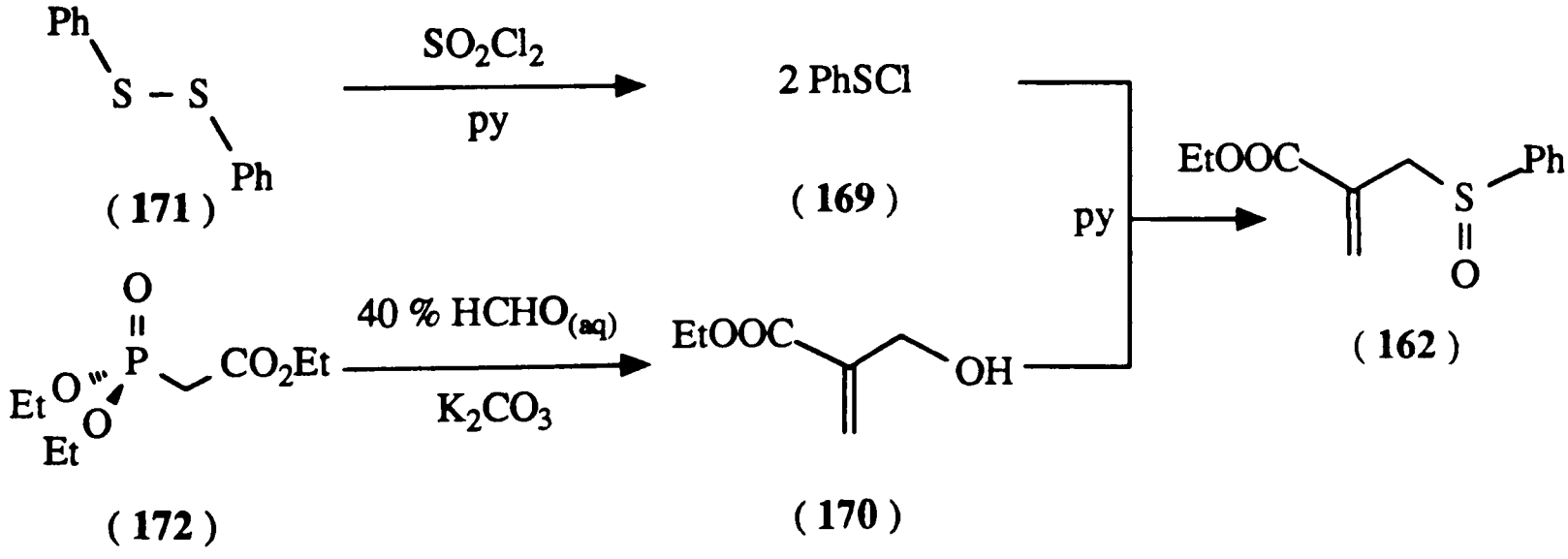
The title compound was prepared by the method of Bell.[97] 1-cyano-2-phenylsulphinylethane was prepared by slowly adding freshly distilled acrylonitrile (24.8 ml, 0.385 mol) to a stirred mixture of thiophenol (12.9 ml, 0.126 mol) and benzyltrimethylammonium hydroxide (0.5 ml, 40 % solution in H_2O) while maintaining the temperature below 45°C. The mixture was then stirred for 8 h. Dichloromethane (200 ml) and water (50 ml) was added and the layers were separated. The organic layer was then dried (Na_2SO_4) and distilled to give 1-cyano-2-phenyl-sulphenylethane (12.2 g, 60 %). b.p. 96-100°C (0.10 mmHg) (lit.[97] 116-118°C (0.3 mmHg)). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.60 (2H, t, J= 7.3 Hz, SC$\underline{H_2}$), 3.13 (3H, t, J= 7.3 Hz, NCC$\underline{H_2}$), 7.2-7.5 (5 H, m, Ar). I.R. (neat film) $\bar{\nu}_{MAX}$ = 2251 s (C≡N str) cm^{-1}.

1-Cyano-2-phenylsulphenylethane (10.0 g, 61.3 mmol) in methanol (100 ml) was added to a stirred solution of sodium metaperiodate (13.1 g, 61.3 mmol) in water (100 ml) cooled to 0°C. The mixture was stirred for 48 h then poured into dichloromethane (200

ml) and water (200 ml). The mixture was shaken then filtered through glass wool. The layers were separated and the aqueous layer extracted three times with dichloromethane (200 ml). The solvent was removed *in vacuo* to give a pale yellow oil, which was crystallized from dichloromethane/hexanes (1:5). 1-Cyano-2-phenylsulphenylethane was obtained as white crystals (8.05 g, 73 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.4-2.8 (1H, m, $SC\underline{H}_2$ diastereotopic), 2.75-3.0 (2H, m, $NCC\underline{H}_2$), 3.1-3.3 (1H, m, $SC\underline{H}_2$ diastereotopic), 7.5-7.65 (5H, m, Ar) p.p.m..

1-Cyano-2-phenylsulphenylethane (2.1 g, 11.7 mmol) was stirred under argon in refluxing oct-1-yne (11.2 g, 0.102 mol) for 30 min. The mixture was passed through a col umn of neutral alumina (100 g) eluting first with hexanes to remove the excess oct-1-yne. The product was obtained from the column by eluting with ethyl acetate. The solvent was removed *in vacuo* and the residual oil chromatographed on silica eluting with hexanes/ethyl acetate (3:2) to give 2-(phenylsulphinyl)octene (2.2 g, 80 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.822 (3H, t, J= 6.0 Hz, $CH_2C\underline{H}_3$), 1.0-1.45 (8H, m, $C\underline{H}_2$), 1.75-1.95 (1H, m, CH_2=C-$C\underline{H}_2$ diastereotopic), 2.0-2.2 (1H, m, CH_2=C-$C\underline{H}_2$ diastereotopic) 5.60 (1H, s, *E*-$C\underline{H}_2$=C), 6.06 (1H, s, *Z*-$C\underline{H}_2$=C), 7.4-7.52 (3H, m, Ar), 7.55-7.66 (2H, m, Ar) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 1629 m (C=C str), 1050 vs (S=O str) cm^{-1}.

2-Carboxyethyl-3-(phenylsulphinyl)propene (**162**)



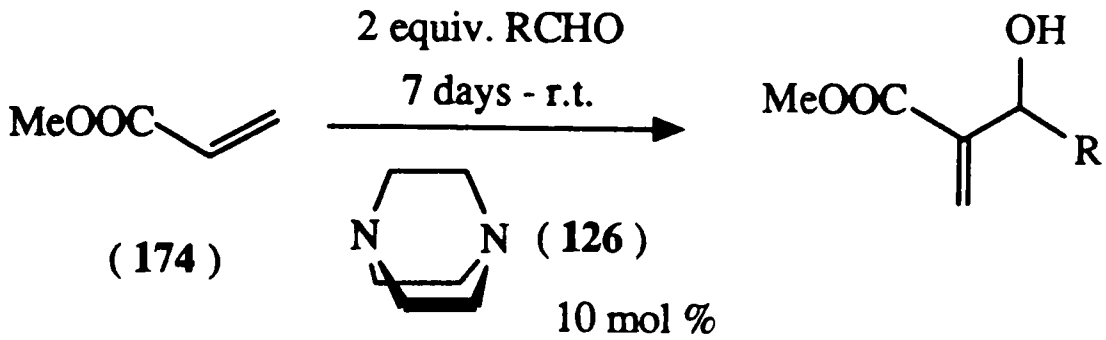
2-carboxyethyl-propene-3-ol was prepared by the method of Villiéras.[99] To a rapidly stirred mixture of triethylphosphonoacetate (5 g, 22.3 mmol) and aqueous formaldehyde (37% w/w; 10 ml, 90 mmol) was added potassium carbonate (6.25 g, 44.6

mmol) in water (20 ml) over a period of 30 min. The solution was left to stir for 1 h and then saturated aqueous ammonium chloride (20 ml) was added. The solution was then extracted three times with diethyl ether (20 ml) and the organic layer dried ($MgSO_4$). Evapo ration of the diethyl ether gave a colourless oil which was kugelrohr distilled (oven temp. 70°C, 0.04 mmHg) to give 2-carboxyethyl-propene-3-ol (2.514 g, 87 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.30 (3H, t, J= 7.1 Hz, $CH_2C\underline{H}_3$), 4.22 (2H, q, J= 7.1 Hz, $C\underline{H}_2CH_3$), 4.31 (1H, s, O<u>H</u>), 5.82 (1H, q, J= 1.3 Hz, *E*-$C\underline{H}_2$=C), 6.24 (1H, d, J= 1Hz, *Z*-$C\underline{H}_2$=C) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3457 s (O-H str), 1714 s (C=O str), 1637 m (C=C str) cm^{-1}.

Benzenesulphenyl chloride was prepared by the method of Mueller.[98] Sulphuryl chloride (4.2 g, 31.1 mmol) was added to a stirred solution of diphenyldisulphide (6.8 g, 31.1 mmol) and pyridine (1ml), in dichloromethane (30 ml) over a period of 10 min. The mixture was then stirred for a further 2 h. The solvent was removed *in vacuo* and the residue was kugelrohr distilled to give benzenesulphenylchloride as a deep red oil (6.1 g, 68 %). b.p. 88-90°C (15mmHg) (lit.[98] 49°C 4 mmHg). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.65-7.75 (m, Ph) p.p.m..

2-Carboxyethyl-3-(phenylsulphinyl)propene was prepared by adding freshly distilled benzenesulphenyl chloride (0.30 g, 2.11 mmol) to a stirred solution of 2-carboxyethyl-propene-3-ol (0.275 g, 2.11 mmol) and triethylamine (0.23 g, 2.33 mmol) in diethyl ether (1 ml) cooled to -78°C. The solution was left to stir for 1 h then allowed to warm to ambient temperature. The resulting suspension was filtered and the solvent removed from the filtrate at reduced pressure. The residue was then chromatographed on flash silica eluting with hexanes/ethyl acetate (50:50) to give the title compound as a colourless oil (0.5 g, 72 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.241 (3H, t, J= 7.1 Hz, $CH_2C\underline{H}_3$), 3.740 (1H, d, J= 12.3 Hz, diastereotopic $C\underline{H}_2SO$), 3.810 (1H, J= 12.3 Hz, diastereotopic $C\underline{H}_2SO$), 4.097 (2H, q, J= 7.1 Hz, $C\underline{H}_2CH_3$), 5.771 (1H, d, J= 0.8 Hz, $C\underline{H}_2$=C), 6.439 (1H, d, J= 0.8 Hz, $C\underline{H}_2$=C), 7.45-7.42 (3H, m, Ph), 7.6-7.64 (2H, m, Ph) p.p.m.. $\bar{\nu}_{MAX}$ = 1714 s (C=O str), 1627 m (C=C str), 1189 s (S=O str) cm^{-1}.

7.08 Synthesis of Hydroxyacrylates



2-(Carboxymethyl)butene-3-ol (**175**)

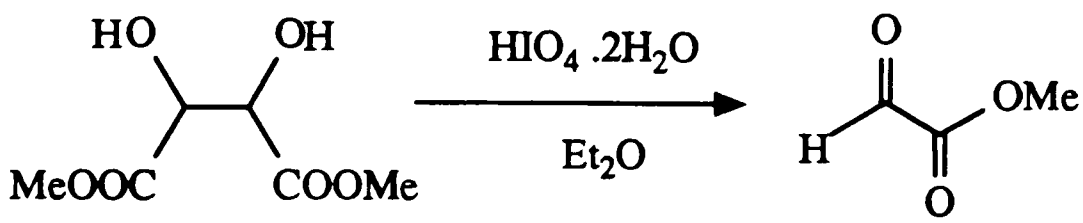
Methyl acrylate (15.0 ml, 0.167 mol), freshly distilled acetaldehyde (19.0 ml, 0.334 mol) and diazobicyclo-[2,2,2]-octane (1.9 g, 0.0167 mol) were mixed together under agron and storred at room temperature and pressure for 7 days. Distillation of the mixture under reduced pressure gave 2-Carboxymethyl-butene-3-ol (16.5 g, 76 %). b.p. 92-95°C (15 mmHg) (lit.[144] 79-80°C (9 mmHg)). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (3H, d, 6.2 Hz, CHC$\underline{H}_3$), 2.42 (1H, bs, O$\underline{H}$), 3.79 (3H, s, OC$\underline{H}_3$), 4.62 (1H, m, C$\underline{H}$Me), 5.85 (1H, s, *E*-C$\underline{H}_2$=C), 6.20 (1H, s, *Z*-C$\underline{H}_2$=C) p.p.m.. I.R. (Neat film) $\bar{\nu}_{MAX}$ = 3452 s (O-H str), 1718 vs (C=O str) cm^{-1}.

2-(Carboxymethyl)-3-phenylpropene-3-ol (**176**)

Methyl acrylate (10.0 ml, 0.111 mol), freshly distilled benzaldehyde (27.0 ml, 0.20 mol) and diazobicyclo-[2,2,2]-octane (1.10 g, 0.01 mol) were mixed together under agron and storred at room temperature and pressure for 7 days. The mixture was then diluted with dichloromethane (50 ml) and washed three times with aqueous hydrochloric acid (1M, 30 ml). The organic layer was dried ($MgSO_4$) and then the solvent removed *in vacuo*. The excess benzaldehyde was removed by warming at a pressure of 0.05 mmHg to give a viscous oil, which waxed on cooling. The wax was crystallized from hexanes/diethyl ether (1:1) to give 2-Carboxymethyl-3-phenyl-propene-3-ol (16.1 g, 84 %). m.p. 44-46°C (lit.[74] 43-45°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.10 (1H, s, O$\underline{H}$), 3.73 (3H, s, OC$\underline{H}_3$), 5.59 (1H, s, C$\underline{H}$OH), 5.85 (1H, s, *E*-C$\underline{H}_2$=C), 6.35 (1H, s, *Z*-C$\underline{H}_2$=C), 7.2-7.9 (5H, m, Ar) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3560 s (O-H str), 1710 vs (C=O str) cm^{-1}.

7.09 Synthesis of Miscellaneous Organic Compounds

Methyl glyoxaldehyde (**142**)



(**147**) (**142**)

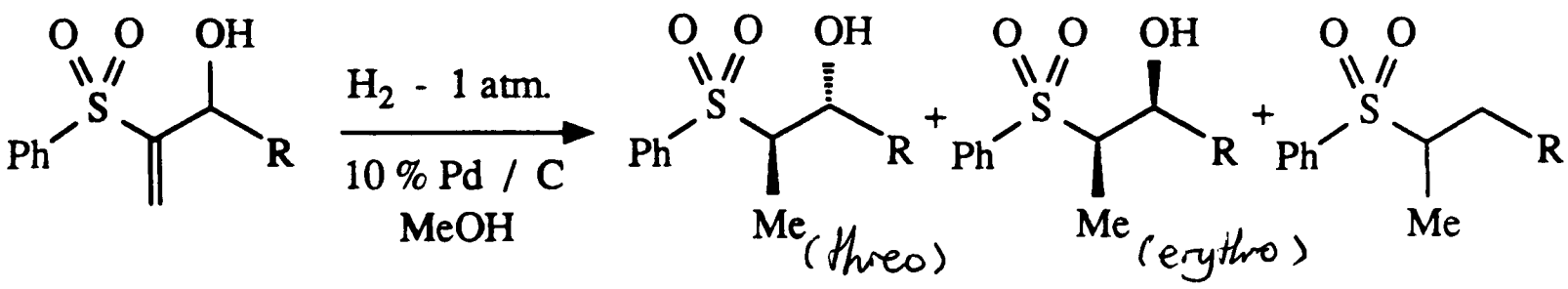
Methyl glyoxaldehyde was prepared by the method of Kelly.[90] Periodic acid (25.0 g, 0.112 mol) was added in small portions to a stirred solution of dimethyl tartrate (20.0 g, 0.112 mol) in diethyl ether (250 ml) over a period of 1 h. The mixture was then left to stir for 20 min. Magnesium sulphate (20 g) was added and the mixture was filtered. The solvent was then removed from the filtrate at 15 mmHg keeping the temperature at 0°C. The oily residue was then distilled under reduced pressure to give the title compound in a polymeric form as a colourless oil (14.0 g, 71 %). b.p. 41-42°C (15 mmHg) (lit.[90] 47°C (25 mmHg)). ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.45 (1H, s, O-CH-O), 3.72 (3H ,s, O$C\underline{H}_3$) p.p.m..

1-Phenyl-2-(phenylsulphinyl)ethanol (**212**)

Methylphenylsulphoxide (2.0 g, 14.28 mmol) was added as a solution in tetrahydrofuran (2.0 ml) to a stirred solution of LDA (10 ml; 7.14 mmol) cooled to -78°C under argon. The solution was left to stir for 2 h then freshly distilled benzaldehyde (2.29 g, 21.42 mmol) was added as a solution in tetarhydrofuran (6.0 ml) over a period of 15 min. The mixture was left to stir for a further 1 h and then allowed to warm to ambient temperature. Saturated aqueous ammonium chloride solution (20 ml), then aqueous hydrochloric acid (2.0 M) was added until the pH of the mixture was 7. The mixture was extracted three times with dichloromethane (50 ml) then the organic extracts were combined and the solvent removed *in vacuo*. The residue was chromatographed on flash silica eluting with hexanes/ethyl acetate (50:50) to give (212) as a white amorphous powder (2.0 g, 57 %). m.p. 112-115°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.85-3.05 (4H, m, $C\underline{H}_2$), 3.15-3.20 (4H, m, $C\underline{H}_2$), 3.70 (2H, s, O$\underline{H}$), 5.27 (1H, dd, J_1= 10.4 Hz, J_2= 1.9 Hz, C$\underline{H}$OH, first diastereomer), 5.39 (1H, dd, J_1= 9.8 Hz, J_2= 2.7 Hz, C$\underline{H}$OH,

second diastereomer), 7.30-7.70 (20H, m, Ar) p.p.m.. I.R. $\bar{\nu}_{MAX}$ = 3256 s (O-H str), 1016 vs (S=O str) 986 vs (C-O str) cm^{-1}. RATIO OF DIASTEREOMERS = 1 : 1

7.10 Hydrogenation of Hydroxy Vinylsulphones under Heterogeneous Conditions



Heterogeneous Hydrogenation of 2-(Phenylsulphonyl)butene-3-ol (**129**)

2-(Phenylsulphonyl)butene-3-ol (20 mg, 0.094 mmol) was dissolved in dry degassed dichloromethane (1.0 ml) in a Schlenk tube, together with 10 % Palladium on charcoal (8.1 mg, 8 mol %) under argon. The mixture was thoroughly degassed with four freeze-pump-thaw cycles, and filled with argon after each cycle. The solution was finally frozen and the atmosphere replaced with hydrogen. The Schlenk tube was then connected to a gas burrette containing hydrogen and allowed to equilibrate at ambient temperature. The mixture was then stirred vigoruosly and the uptake of hydrogen monitored at intervals of 1 min. After a period of 5 min, the uptake of hydrogen was judged to have ceased and stirring was stopped and the mixture was frozen. The atmosphere in the Schlenk tube was replaced with argon and then the reaction mixture filtered through a plug of celite. The solvent was removed *in vacuo* and the ^{1}H NMR (200 MHz, $CDCl_3$) of the product mixture taken. The ^{1}H NMR spectrum included three main sets of peaks : 1.14 (3H, d, J= 6.2 Hz, SCHC$\underline{H}_3$ *threo*) and 1.24 (3H, d, J= 6.4 Hz, CHOHC$\underline{H}_3$ *threo*); 1.20 (3H, d, J= 6.3 Hz, SCHC$\underline{H}_3$ *erythro*) and 1.31 (3H, d, J= 6.4 Hz, CHOHC$\underline{H}_3$ *erythro*) and; 0.95 (3H, t, J= 8.8 Hz, $CH_2C\underline{H}_3$ dehydroxylated material) and 1.39 (3H, d, J= 8.2 Hz, C$\underline{H}_3$ dehydroxylated material) p.p.m.. These peaks were integrated to give an approximate ratio of 5:4:1 of *threo*:*erythro*:dehydroxylated material.

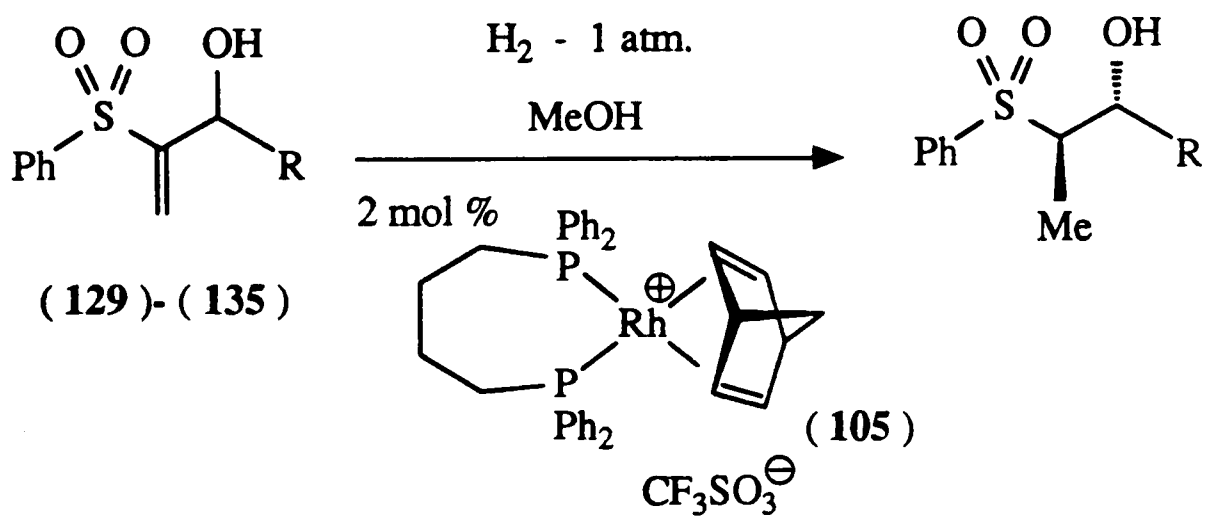
Heterogeneous Hydrogenation of 3-Phenyl-2-(Phenylsulphonyl)propene-3-ol

(**132**)

3-Phenyl-2-(Phenylsulphonyl)propene-3-ol (0.10 g, 0.365 mmol) was dissolved in

dry degassed dichloromethane (1.0 ml) in a Schlenk tube, together with 5 % Palladium on charcoal (20 mg, 3 mol %) under argon. The procedure then follwed that of 2-(Phenylsulphonyl)butene-3-ol. ^{1}H NMR (200 MHz, $CDCl_3$) of the product mixture included 3 main sets of peaks : 0.84 (3H, d, J= 7.0 Hz, $CHC\underline{H}_3$ *threo*); 1.2 (3H, d, J= 7.2 Hz, $CHC\underline{H}_3$ *erythro*), 1.03 (3H, d, $CHC\underline{H}_3$ dehydroxylated material) p.p.m.. These peaks integrated in an approximate ratio of 5:4:1 of *threo*:*erythro*:dehydroxylated material.

7.11 Hydrogenation of Hydroxy Vinylsulphones under Homogeneous Conditions



(**129**)- (**135**) (**105**)

Hydrogenation of 2-(Phenylsulphonyl)butene-3-ol (**129**)

A sample of 2-(Phenylsulphonyl)-butene-3-ol (40 mg, 0.189 mmol) and (**105**) (2.9 mg, 3.78 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 2-(Phenylsulphonyl)butane-3-ol as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.142 (3H, d, J= 3.2 Hz, $SO_2CHC\underline{H}_3$), 1.242 (3H,d , J= 6.4 Hz, $CHOHC\underline{H}_3$), 3.137 (1H, dq, J_1= 6.4 Hz, J_2= 6.2 Hz, $SO_2C\underline{H}$), 3.895 (1H, bs, O$\underline{H}$), 4.188 (1H, dq, J_1= 6.4 Hz, J_2= 6.2 Hz, C$\underline{H}$OH), 7.587 (2H, t, J= 7.5 Hz, 3-Ph), 7.684 (1H, t, J= 7.4 Hz, 4-Ph), 7.895 (2H, d, J= 7.4 Hz, 2-Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 11.42 ($CHOHC\underline{H}_3$), 20.18 ($CHC\underline{H}_3$), 66.31 ($\underline{C}$HOH), 66.36 ($\underline{C}HCH_3$), 128.94 (3-Ph), 129.22 (2-Ph), 133.96 (4-Ph), 137.29 (1-Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3503 vs (O-H str), 1304 vs (SO_2 symm str), 1147 vs (SO_2 asymm str), 1083 s (C-O str) cm^{-1}.

Hydrogenation of 2-(Phenylsulphonyl)-pentene-3-ol (**130**)

A sample of 2-(Phenylsulphonyl)-pentene-3-ol (40 mg, 0.175 mmol) and (**105**) (2.7 mg, 3.5 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 2-(Phenylsulphonyl)-pentane-3-ol as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.98 (3H, t, J= 7.2 Hz, $CH_3C\underline{H}_3$), 1.14 (3H, d, J= 6.9 Hz, $CHC\underline{H}_3$), 1.47 (1H, m, diastereotopic $C\underline{H}_2$), 1.65 (1H, m, diastereotopic $C\underline{H}_2$), 3.19 (1H, dt, J_1= J_2= 7.5 Hz, $C\underline{H}OH$), 3.90, 1H, bs, $O\underline{H}$), 3.95 (1H, m, $C\underline{H}CH_3$), 7.59 (2H, t, J= 7.0 Hz, 3-Ph), 7.70 (1H, t, J= 7.1 Hz, 4-Ph), 7.97 (2H, d, J= 7.4 Hz, 2-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 8.71 ($CH_2\underline{C}H_3$), 11.40 ($\underline{C}H_2CH_3$), 26.25 ($CH\underline{C}H_3$), 64.98 ($\underline{C}HOH$), 70.55 ($\underline{C}HCH_3$), 129.14 (3-Ph), 129.47 (2-Ph), 134.26 (4-Ph), 137.22 (1-Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 3505 s (O-H str), 1303 vs (SO_2 symm str), 1147 vs (SO_2 asymm str), 1084 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 229(30) M+H$^{\oplus}$, 246(100) M+NH$_4^{\oplus}$. Found C, 57.75 %; H, 7.23 %; S, 13.73 %. $C_{11}H_{16}O_3S$ requires C, 57.85 %; H, 7.07 %; S, 14.05 %.

Hydrogenation of 3-Cyclohexyl-2-(phenylsulphonyl)propene-3-ol (**131**)

A sample of 3-Cyclohexyl-2-(phenylsulphonyl)propene-3-ol (40 mg, 0.142 mmol) and (**105**) (2.2 mg, 2.84 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 3-Cyclohexyl-2-(phenylsulphonyl)propene-3-ol as a white solid. m.p. 101-103°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.14 (3H, d, J= 7.1 Hz, $CHC\underline{H}_3$), 1.19-1.80 (10H, m, Cy), 3.27 (1H, dq, J_1= 9.0 Hz, J_2= 7.1 Hz, $C\underline{H}CH_3$), 3.78 (1H, d, J= 9.0 Hz, $C\underline{H}OH$), 3.95 (1H, d, J= 2.1 Hz, $O\underline{H}$), 7.5-7.8 (3H, m, Ar), 7.92 (2H, d, J= 6.8 Hz, 4-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 11.87 ($\underline{C}H_3$), 24.21 (Cy), 25.94 (Cy), 26.12 (Cy), 26.47 (Cy), 30.14 (Cy), 39.86 (Cy),

63.64 (CHOH), 73.42 ($\underline{C}HCH_3$), 129.25 (3-Ph), 129.44 (2-Ph), 134.24 (4-Ph), 137.20 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3515 s (O-H str), 2926 s (Cy comb), 1276 s (SO_2 symm str), 1136 s (SO_2 asymm str), 1083 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 265(20) $M-H_2O+H^{\oplus}$, 283(30) $M+H^{\oplus}$, 300(100) $M+NH_4^{\oplus}$. Found C, 63.94 %; H, 7.98 %; S, 11.03 %. $C_{15}H_{22}O_3S$ requires C, 63.78 %; H, 7.86 %; S, 11.36 %.

Hydrogenation of 3-Phenyl-2-(phenylsulphonyl)propene-3-ol (**132**)

A sample of 3-Phenyl-2-(phenylsulphonyl)propene-3-ol (40 mg, 0.145 mmol) and (**105**) (2.2 mg, 2.90 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 3-Phenyl-2-(phenylsulphonyl)-propene-3-ol as colourless needles. m.p. 121°C. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.839 (3H, d, J= 7.0 Hz, $C\underline{H}_3$), 3.409 (1H, dq, J_1= 9.2 Hz, J_2= 7.0 Hz, $C\underline{H}CH_3$), 4.500 (1H, d, J= 1.5 Hz, O<u>H</u>), 4.960 (1H, d, J= 9.2 Hz, C<u>H</u>OH), 7.319 (5H, m, Ph´), 7.629 (2H, t, J= 7.5 Hz, 3-Ph), 7.724 (1H, t, J= 6.2 Hz, 4-Ph), 7.978 (2H, d, J= 7.4 Hz, 2-Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 12.92 ($CH\underline{C}H_3$), 66.26 ($\underline{C}HCH_3$), 73.98 (CHOH), 127.14 (Ar), 128.68 (Ar), 129.08 (Ar), 129.30 (Ar), 134.10 (4-Ph), 137.39 (1-Ph), 139.77 (1-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3482 s (O-H str), 1285 vs (SO_2 symm str), 1143 vs (SO_2 asymm str), 1083 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 259(15) $M-H_2O+H^{\oplus}$, 276(100) $M^{\oplus}$, 294(30) $M+NH_4^{\oplus}$. Found C, 65.58 %; H, 5.70 %; S, 11.57 %. $C_{15}H_{16}O_3S$ requires C, 65.22 %; H, 5.84 %; S, 11.60 %.

Hydrogenation of 3-(4-Chlorophenyl)-2-(phenylsulphonyl)propene-3-ol (**133**)

A sample of 3-(4-Chlorophenyl)-2-(phenylsulphonyl)propene-3-ol (40 mg, 0.129 mmol) and (**105**) (2.0 mg, 2.58 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction

carried out in dichloromethane led to recovery of diastereomerically pure 3-(4-Chlorophenyl)-2(phenylsulphonyl)propene-3-ol as needles. m.p. 176-177°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.840 (3H,d, J= 7.3 Hz, C<u>H</u>$_3$), 3.37 (1H, dq, J_1= 9.2 Hz, J_2= 7.4 Hz, C<u>H</u>CH$_3$), 4.59 (1H, d, J= 1.4 Hz, O<u>H</u>), 4.97 (1H, d, J= 9.2 Hz, C<u>H</u>OH), 7.26 (2H, d, J= 8.6 Hz, Ph´), 7.33 (2H, d, J= 8.6 Hz, Ph´), 7.55-7.8 (3H, m, Ph), 7.96 (2H, d, J= 7.0 Hz, 4-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 12.71 (<u>C</u>H$_3$), 65.87 (<u>C</u>HOH), 73.20 (<u>C</u>HCH$_3$), 128.67 (Ar), 129.07 (Ar), 129.23 (Ar), 129.80 (Ar), 134.53 (4-Ph), 136.99 (1-Ph), 138.23 (4-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3481 s (O-H str), 1449 m (O-H ben), 1295 s (SO_2 symm str), 1142 s (SO_2 asymm str), 1090 s (C-O str) cm^{-1}. GCMS (CI+) m/z = 293(20) M-H_2O+H$^{\oplus}$, 310(100) M$^{\oplus}$, 328(50) M+$NH_4^{\oplus}$. Found C, 58.08 %; H, 4.72 %; S, 10.07 %. $C_{15}H_{15}ClO_3S$ requires C, 57.95 %; H, 4.87 %; S, 10.32 %.

<u>Hydrogenation of 3-(4-Methoxyphenyl)-2-(phenylsulphonyl)-propene-3-ol</u> (**134**)

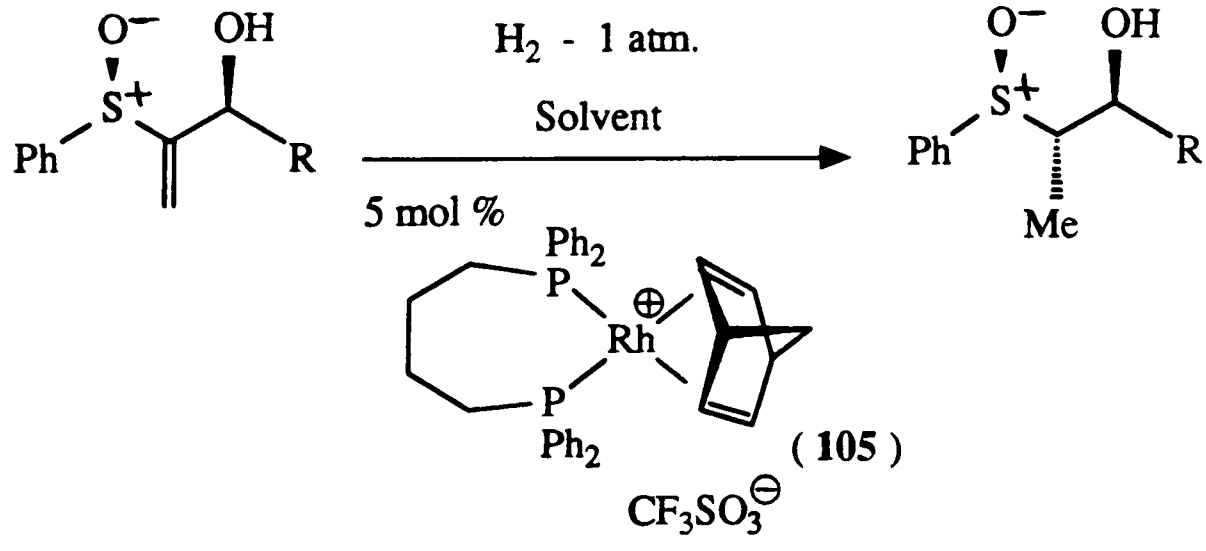
A sample of 3-(4-Methoxyphenyl)-2-(phenylsulphonyl)propene-3-ol (40 mg, 0.131 mmol) and (**105**) (2.0 mg, 2.62 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 3-(4-Methoxyphenyl)-2-(phenylsulphonyl)propene-3-ol as needles. m.p. 86-89°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.84 (3H, d, J= 7.2 Hz, CHC<u>H</u>$_3$), 3.41 (1H, dq, J_1= 9.3 Hz, J_2= 7.2 Hz, C<u>H</u>CH$_3$), 3.80 (3H, s, OC<u>H</u>$_3$), 4.48 (1H, s, O<u>H</u>), 4.93 (1H, d, J= 9.3 Hz, C<u>H</u>OH), 6.87 (2H, d, J= 8.6 Hz, Ph´), 7.23 (2H, d, J= 8.6 Hz, Ph´), 7.6-7.8 (3H, m, Ph), 7.98 (2H, d, J= 7.9 Hz, 4-Ph) p.p.m.. ^{13}C NMR (50.38 MHz, $CDCl_3$) δ = 12.80 (<u>C</u>H$_3$), 55.26 (O<u>C</u>H$_3$), 66.15 (<u>C</u>HOH), 73.42 (<u>C</u>HCH$_3$), 114.17 (3-Ph´), 128.45 (Ar), 129.25 (Ar), 129.51 (Ar), 132.03 (1-Ph´), 134.39 (4-Ph), 137.26 (1-Ph), 160.01 (4-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3490 s (O-H str), 1447 s (O-H ben), 1284 vs (SO_2 symm str), 1079 s (C-OH str), 1041 s (C-OCH$_3$ str) cm^{-1}. GCMS (CI+) m/z = 289(100) M-H_2O+H$^{\oplus}$, 306(10) M$^{\oplus}$, 324(10) M+$NH_4^{\oplus}$. Found C, 62.66 %; H, 5.94 %; S, 10.23 %. $C_{16}H_{18}O_4S$ requires C, 62.70 %; H, 5.93 %; S, 10.47 %.

Hydrogenation of 3-(4-Nitrophenyl-2-(phenylsulphonyl)propene-3-ol (**135**)

A sample of 3-(4-Nitrophenyl-2-(phenylsulphonyl)propene-3-ol (40 mg, 0.124 mmol) and (**105**) (1.9 mg, 2.48 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and dichloromethane. The diastereomeric excess in the product was determined by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in dichloromethane led to recovery of diastereomerically pure 3-(4-Nitrophenyl-2-(phenylsulphonyl)propene-3-ol as a pale yellow microcrystalline material. m.p. 175-178°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 0.86 (3H, d, J= 7.1 Hz, $C\underline{H}_3$), 3.39 (1H, dq, J_1= 9.2 Hz, J_2= 7.1 Hz, $C\underline{H}CH_3$), 4.73 (1H, s, O<u>H</u>), 5.13 (1H, d, J= 9.2 Hz, C<u>H</u>OH), 7.5-7.8 (5H, m, Ar), 7.97 (2H, d, J= 7.8 Hz, 2-Ph), 8.22 (2H, d, J= 8.3 Hz, Ph´) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 12.71 ($\underline{C}H_3$) , 65.87 ($\underline{C}$HOH), 73.10 ($\underline{C}HCH_3$), 123.77 (Ar), 128.14 (Ar), 128.46 (Ar),129.04 (Ar), 134.36 (4-Ph), 137.26 (1-Ph), 146.73 (1-Ph´), 148.29 (4-Ph´) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3479 s (O-H str), 1534 s (NO_2 asymm str), 1348 s (NO_2 symm str), 1284 vs (SO_2 symm str), 1175 s (C-N str), 1141 vs (SO_2 asymm str), 1082 s (C-O str) cm^{-1}. Found C, 56.06 %; H, 4.88 %; N, 4.08; S, 9.62 %. $C_{15}H_{15}NO_5S$ requires C, 56.07 %; H, 4.70 %; N, 4.36 %; S, 9.98 %.

7.12 Hydrogenation of Hydroxy Vinylsulphoxides

Hydrogenation of *(R_S*,S*)*-2-(Phenylsulphinyl)butene-3-ol (**154**)



A sample of *(R_S*,S*)*-2-(phenylsulphinyl)butene-3-ol (40 mg, 0.204 mmol)and (**105**) (7.9 mg, 10.75 μmol) was hydrogenated under the standard hydrogenation

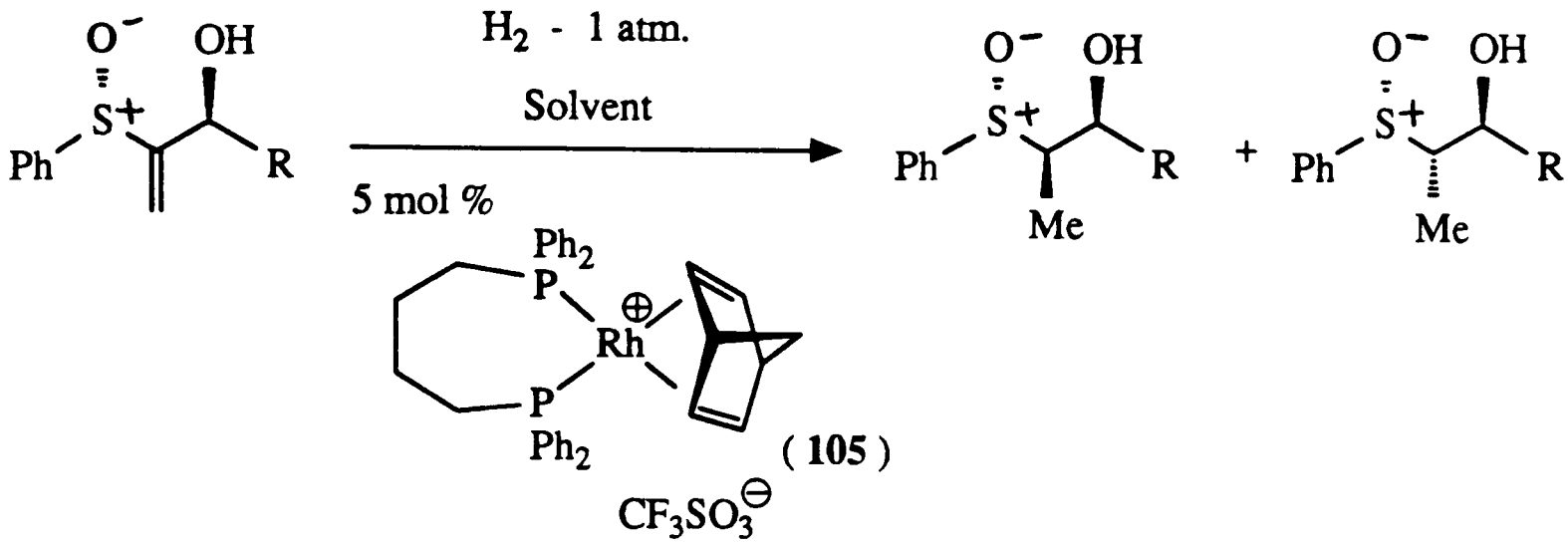
conditions detailed earlier in two solvents, methanol and 1,2-dichloroethane. The diastereomeric excesses in the products were determined to be 95% (MeOH) and 99% (CH_2ClCH_2Cl), by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in 1,2-dichloroethane led to recovery of diastereomerically pure (S_S*,*S**,*S**)-2(phenylsulphinyl)butane-3-ol as a white solid. m.p. 108-110°C. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.957 (3H,d, J= 7.1 Hz, $CHOHC\underline{H}_3$), 1.296 (3H,d, J= 6.2 Hz, $CHC\underline{H}_3$), 2.868 (1H, dq, J_1= 7.1 Hz, J_2= 1.4 Hz, C<u>H</u>OH), 4.244 (1H, dq, J_1= 7.0 Hz, J_2= 1.3 Hz, $C\underline{H}CH_3$), 7.52-7.6 (3H, m, Ph), 7.65-7.7 (2H, m, Ph) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 9.87 ($CHOHC\underline{H}_3$), 20.97 ($CHC\underline{H}_3$), 65.85 (<u>C</u>HOH), 69.78 ($\underline{C}HCH_3$), 125.39 (3-Ph), 129.26 (2-Ph), 131.86 (4-Ph), 143.25 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3370 s (O-H str), 1444 m (O-H ben), 1080 m (C-O str), 1020 s (SO_2 str) cm^{-1}. GCMS (CI+) m/z = 165(65) M-O-H_2O+$H^{\oplus}$, 181(100) M-H_2O+$H^{\oplus}$. Found C, 60.38 %; H, 6.86 %; S, 16.22 %. requires C, 60.58 %; H, 7.12 %; S, 16.17 %.

<u>Hydrogenation of (R_S*,*S**)-3-Phenyl-2-(phenylsulphinyl)propene-3-ol</u> (**152**)

A sample of (R_S*,*S**)-3-phenyl-2-(phenylsulphinyl)propene-3-ol (40 mg, 0.155 mmol) and (**105**) (6.0 mg, 7.75 µmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and 1,2-dichloroethane. Taking into account the presence of 10% of (153) in the starting material, the diastereomeric excesses in the products were determined to be 85% (MeOH) and 99% (CH_2ClCH_2Cl), by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in 1,2-dichloroethane led to recovery of almost diastereomerically pure (S_S*,*S**,*S**)-3-phenyl-2(phenylsulphinyl)propane-3-ol as a white solid. m.p. 105-106°C. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.683 (3H,d, J= 7.1 Hz, $CHC\underline{H}_3$), 3.161 (1H, dq, J_1= 9.2 Hz, J_2= 7.1 Hz, $C\underline{H}CH_3$), 4.968 (1H, d, J= 9.2 Hz, C<u>H</u>OH), 7.30-7.6 (10H, m, Ar) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 10.22 ($CH\underline{C}H_3$), 65.36 (<u>C</u>HOH), 125.75 (3-Ph´), 127.20 (2-Ph´), 128.44 (4-Ph´), 128.59 (3-Ph), 129.27 (2-Ph), 131.89 (4-Ph), 140.73 (1-Ph´), 142.36 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3246 s (O-H str), 1450 m (O-H ben), 1050 m (C-O str), 1007 s (S=O str) cm^{-1}. GCMS (CI+) m/z = 227(100)

M-O-H_2O+$H^{\oplus}$, 243(40) M-H_2O+$H^{\oplus}$. Found C, 68.89 %; H, 5.97 %; S, 12.16 %. $C_{15}H_{16}O_2S$ requires C, 69.20 %; H, 6.19 %; S, 12.31 %.

Hydrogenation of (R_S*,*R**)-2-(Phenylsulphinyl)butene-3-ol (**155**)



(**105**)

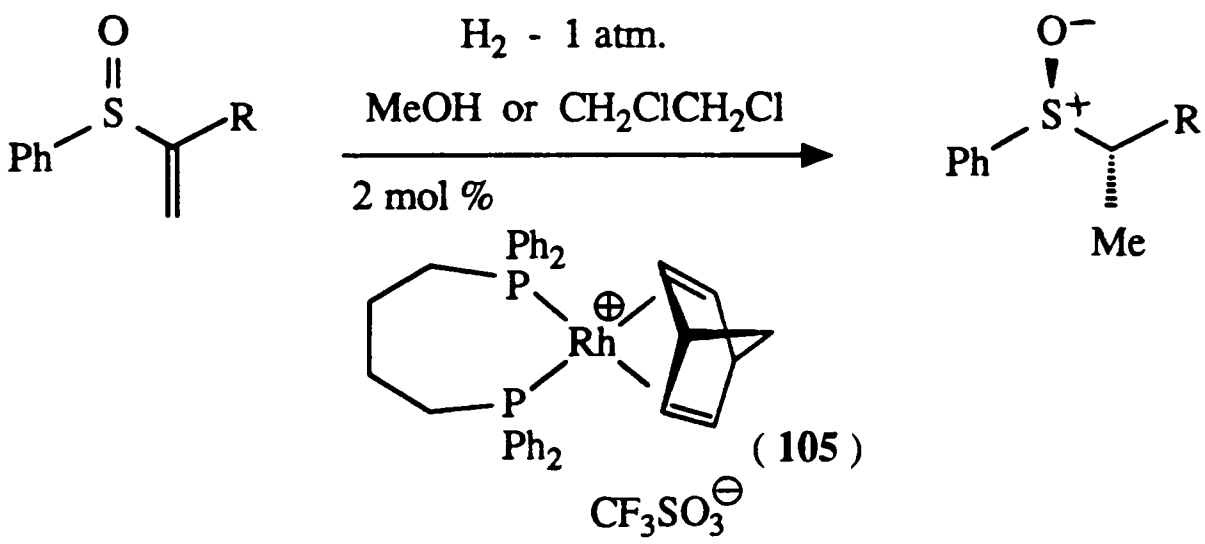
A sample of (R_S*,*R**)-2-(phenylsulphinyl)butene-3-ol (40 mg, 0.20 mmol) and (**105**) (7.9 mg, 10.2 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and 1,2-dichloroethane. The diastereomeric excesses in the products were determined to be 60% (MeOH) and 98% (CH_2ClCH_2Cl), by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in 1,2-dichloroethane led to recovery of diastereomerically pure (S_S*,*S**,*R**)-2(phenylsulphinyl)butane-3-ol as a white solid. m.p. 105-108°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.192 (3H, d, J= 6.6 Hz, CHOHC$\underline{H}_3$), 1.400 (3H, d, J= 7.2 Hz, CHC$\underline{H}_3$), 2.553 (1H, dq, J_1= 7.2 Hz, J_2= 1.7 Hz, C$\underline{H}$OH), 4.340 (1H, dq, J_1= 6.4 Hz, J_2= 1.7 Hz, C$\underline{H}$CH$_3$), 7.55-7.60 (3H, m, Ph), 7.65-7.75 (2H, m, Ph) p.p.m.. ^{13}C NMR 125.95 MHz, $CDCl_3$) δ = 8.84 (CHOH$\underline{C}$H$_3$), 20.29 (CH$\underline{C}$H$_3$), 63.09 ($\underline{C}$HOH), 66.40 ($\underline{C}$HCH$_3$), 124.88 (3-Ph), 129.32 (2-Ph), 131.36 (4-Ph), 142.14 (1-Ph) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 3309 s (O-H str), 1447 m (O-H str), 1073 m (C-O str), 1015 vs (S=O str) cm^{-1}. GCMS (CI+) m/z = 165(100) M-O-H_2O+$H^{\oplus}$, 199(80) M+$H^{\oplus}$. Found C, 60.79 %; H, 7.40 %; S, 16.37 %. requires C, 60.58 %; H, 7.12 %; S, 16.17 %.

Hydrogenation of (R_S*,*R**)-3-Phenyl-2-(phenylsulphinyl)propene-3-ol (**153**)

A sample of (R_S*,*R**)-2-(Phenylsulphinyl)propene-3-ol (40 mg, 0.155 mmol) and (**105**) (6.0 mg, 7.75 μmol) was hydrogenated under the standard hydrogenation conditions

detailed earlier in two solvents, methanol and 1,2-dichloroethane. The diastereomeric excesses in the products were determined to be 81% (MeOH) and 97% (CH_2ClCH_2Cl), by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in 1,2-dichloroethane led to recovery of diastereomerically pure (S_S*,S*,R*)-2(Phenylsulphinyl)propane-3-ol as a white solid. m.p. 151-154°C. ^1H NMR (300 MHz, $CDCl_3$) δ = 1.283 (3H, d, J= 7.3 Hz, $CHC\underline{H}_3$), 2.720 (1H, dq, J_1= 5.5 Hz, J_2= 1.8 Hz, $C\underline{H}CH_3$), 4.234 (1H, d, J= 2.6 Hz, O<u>H</u>), 5.349 (1H, s, C<u>H</u>OH), 7.177 (2H, d, J= 6.7 Hz, 2-Ph), 7.290 (3H, m, Ph´), 7.604 (3H, m, Ph), 7.737 (2H, d, J= 8.0 Hz, 2-Ph´) p.p.m.. ^{13}C NMR (125.95 MHz, $CDCl_3$) δ = 8.193 ($CH\underline{C}H_3$), 64.11 (<u>C</u>HOH), 70.80 (<u>C</u>HCH_3), 124.30 (2-Ph´), 124.80 (3-Ph´), 125.66 (2-Ph´), 127.39 (4-Ph´), 128.29 (3-Ph), 131.41 (4-Ph), 140.59 (1-Ph´), 142.18 (1-Ph) p.p.m.. I.R. $\bar{\nu}_{MAX}$ = 3263 s (O-H str), 1445, m (O-H ben), 1089 m (C-O str), 1009 vs (S=O str) cm^{-1}. GCMS (CI+) m/z = 227(100) M-O-H_2O+$H^{\oplus}$, 243(45) M-H_2O+$H^{\oplus}$. Found C, 69.43 %; H, 6.02 %; S, 12.32 %. $C_{15}H_{16}O_2S$ requires C, 69.20 %; H, 6.19 %; S, 12.31 %.

7.13 Hydrogenation of Simple Vinylsulphoxides and Allylic Sulphoxides



(**105**)

Hydrogenation of 1-Phenyl-1-(phenylsulphinyl)ethene (**160**)

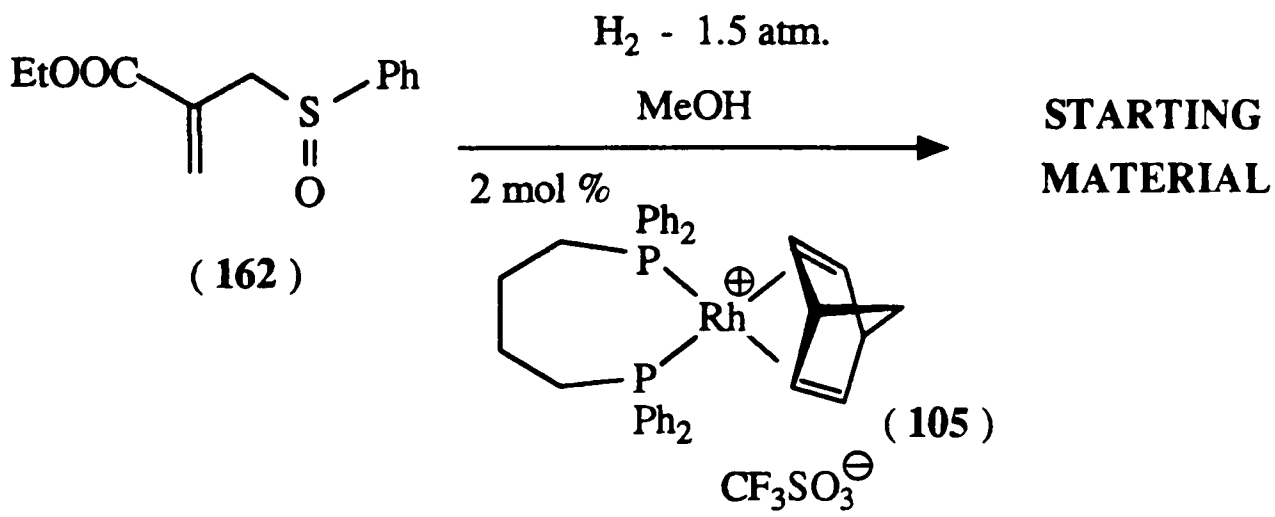
A sample of 1-phenyl-1-(phenylsulphinyl)ethene (40 mg, 0.175 mmol) and (**105**) (1.5 mg, 1.75 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and 1,2-dichloroethane. The diastereomeric excesses in the products were determined to be 96% (MeOH) and 99.7% (CH_2ClCH_2Cl), by ^1H NMR (500 MHz, $CDCl_3$) as detailed earlier. Crystallization (diethyl ether) of the product obtained from the reaction carried out in 1,2-dichloroethane led to recovery of

diastereomerically pure 1-Phenyl-1(phenylsulphinyl)ethane as a white solid. m.p. 84-87°C (lit.[115] 89-90°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.60 (3H, d, J= 7.1 Hz, $CHC\underline{H}_3$), 4.04 (1H, q, J= 7.1 Hz, $C\underline{H}CH_3$), 7.00 (2H, d, J= 7.4 Hz, Ar), 7.11 (2H, d, J= 7.2 Hz, Ar), 7.2-7.45 (6H, m, Ar) p.p.m.. I.R. (KBr disc) $\bar{\nu}_{MAX}$ = 1026 (S=O str) cm^{-1}.

Hydrogenation of 2-(Phenylsulphinyl)octene (**161**)

A sample of 2-(Phenylsulphinyl)octene (40 mg, 0.169 mmol) and (**105**) (1.3 mg, 1.69 μmol) was hydrogenated under the standard hydrogenation conditions detailed earlier in two solvents, methanol and 1,2-dichloroethane. The diastereomeric excesses in the products were determined to be 86% (MeOH) and 93% (CH_2ClCH_2Cl), by ^{1}H NMR (500 MHz, $CDCl_3$) as detailed earlier. 2-(Phenylsulphinyl)octane was obtained from these hydrogenations as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.852 (3H, t, J= 7.0 Hz, $CH_2C\underline{H}_3$), 1.08 (3H, d, J= 6.9 Hz, $CHC\underline{H}_3$), 1.15-1.4 (H, m, -$C\underline{H}_2$-), 1.62 (1H, m, $CHCH_3C\underline{H}_2$ diastereotopic), 2.8 (1H, m, $C\underline{H}CH_3$), 7.45-7.65 (5H, m, Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 2929 s (C-H str), 1045 s (S=O str) cm^{-1}.

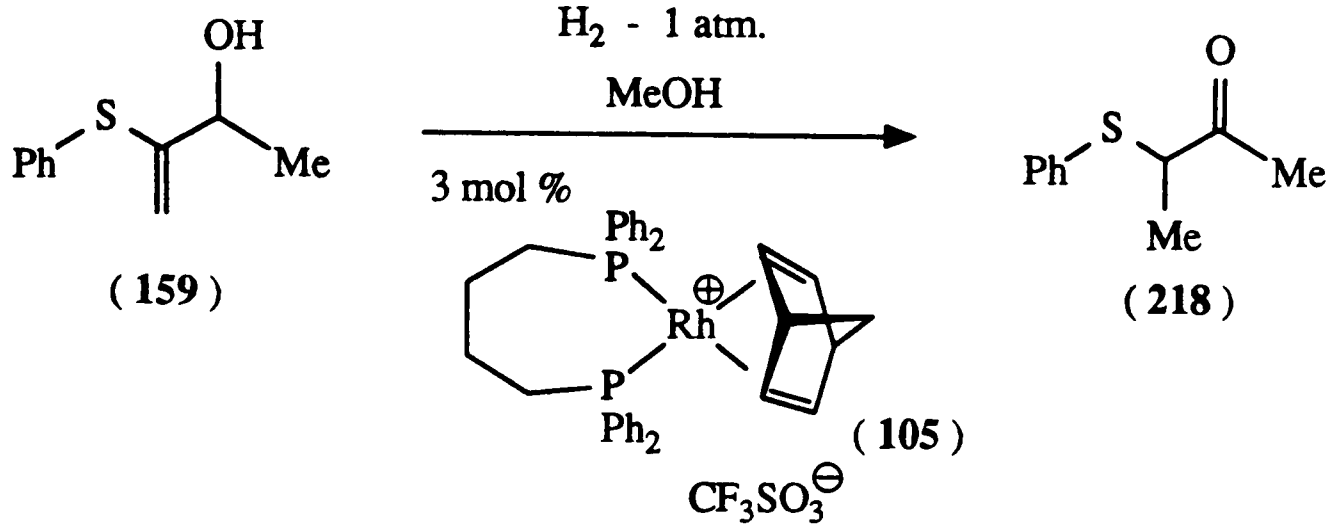
Attempted Hydrogenation of 2-Carboxyethyl-3-(phenylsulphinyl)propene (**162**)



A sample of 2-Carboxyethyl-3-(phenylsulphinyl)propene (40 mg, 0.169 mmol) and (**105**) (2.6 mg, 3.38 μmol) was exposed to hydrogen in methanol (1 ml) under the standard conditions detailed earlier. The ^{1}H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture showed only starting materials to be present. The reaction was repeated twice, but identical results were obtained each time.

7.14 Attempted Hydrogenation of Hydroxy Vinylsulphides

Attempted hydrogenation of 2-(Phenylsulphenyl)butene-3-ol (**159**)



A sample of 3-Phenyl-2-(phenylsulphenyl)propene-3-ol (40 mg, 0.222 mmol) and (**105**) (5.1 mg, 6.66 μmol) was exposed to hydrogen in methanol (1 ml) under the standard conditions detailed earlier, overnight. Preparative t.l.c. of the crude reaction mixture on silica plates with a hexanes/ethyl acetate (7:3) led to recovery of 3-(phenyl-sulphenyl)butan-2-one (27.0 mg, 70 %) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.4 (3H, d, J= 7.1 Hz, $CHC\underline{H}_3$), 2.28 (3H, s, $COC\underline{H}_3$), 3.76 (1H, q, J= 7.1 Hz, $C\underline{H}CH_3$), 7.2-7.45 (5H, m, Ph) p.p.m.. I.R. (neat film) $\bar{\nu}_{MAX}$ = 1714 vs (C=O str)

7.15 Low Temperature ^{31}P NMR Studies

Samples of the ((1,2-bis-diphenylphosphino)ethane)rhodium(I) methanol solvate complex were prepared from ((1,2-bis-diphenylphosphino)ethane)rhodium(I) (bicyclo-[2,2,1]-heptadiene) trifluoromethanesulphonate, (Dppe)rhodium(I)(nbd), (20 mg, 0.295 mmol), in the form of its triflate salt, was dissolved in dry degassed methanol (2 ml) in an 8 mm NMR tube. The solution was then degassed by 3 freeze-pump-thaw cycles and the tube finally filled with hydrogen. The solution was then agitated with the aid of a whirly mix for 2 to 3 min. Hydrogenation of the complex was signalled by a colour change from deep red to orange. The atmosphere in the NMR tube was then replaced with argon after freezing the solution. The NMR tube was then fitted with a septum cap under a stream of argon and its ^{31}P NMR taken (101.23 MHz, external D_2O lock) δ = 77.2 (d, J_{RhP}= 205.6 Hz) p.p.m.. Samples of the solvate complex were freshly prepared prior to each experiment.

Attempted Observation of the Bound Hydroxy Vinylsulphone Complex.

To a sample of the (dppe)rhodium(I) methanol solvate under argon was added 3-phenyl-2-(phenylsulphonyl)propene-3-ol (16.2 mg, 0.06 mmol) as a solution in methanol (50 µl). The ^{31}P NMR (101.23 MHz) at -40°C contained only the signals arising from the solvate complex as discernable peaks.

Observation of the Bound *Anti*-Hydroxy Vinylsulphoxide Complex

To a sample of the (dppe)rhodium(I) methanol solvate under argon was added (R_S*,*R**)-3-Phenyl-2-(phenylsulphinyl)propene-3-ol (20.9 mg, 0.09 mmol) as a solution in methanol (100 µl). The ^{31}P NMR (101.23 MHz) at -40°C contained two sets of peaks centred on 70.96 (dd, J_{Rh-P}= 181 Hz, J_{P-P}= 35.3 Hz) and 59.57 (ddd, J_{Rh-P}= 160 Hz,J_{P-P}= 35.0 Hz, J_3= 48.9 Hz).

Observation of the Bound *Syn*-Hydroxy Vinylsulphoxide Complex

To a sample of the (dppe)rhodium(I) methanol solvate (0.06 g, 0.082mmol of starting complex) under argon was added (R_S*,*S**)-3-Phenyl-2-(phenylsulphinyl)-propene-3-ol (0.042 g, 0.163 mmol) as a solution in methanol (100 µl). The ^{31}P NMR (101.23 MHz) at -40°C contained two sets of peaks centred on 73.33 (dd, J_{Rh-P}= 183.1 Hz, J_{P-P}= 37.3 Hz) and 57.67 (dd, J_{Rh-P}= 161.7 Hz,J_{P-P}= 38.4 Hz).

Attempted Observation of the Methylphenylsulphoxide Rhodium Complex

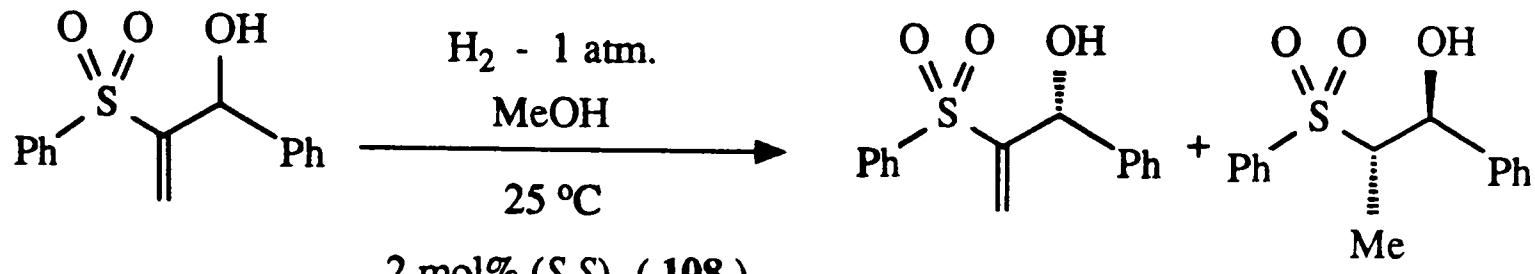
To a sample of the (dppe)rhodium(I) methanol solvate under argon was added methylphenylsulphoxide (41.0 mg, 0.295 mmol) as a solution in methanol (100 µl) in portions of 10 µl. Only the broadened signals arising from the solvate were observed by ^{31}P NMR (101.23 MHz) at -40°C. As the amount of methylphenylsulphoxide was increased the broadness of the solvate signals increased rather than decreased.

Observation of the Bound β-Hydroxysulphoxide Complex

To a sample of the (dppe)rhodium(I) methanol solvate (0.032 g, 0.431 mmol of starting complex) under argon was added 1-phenyl-2-(phenylsulphinyl)ethanol (0.0212 g, 86.2 µmol) as a solution in methanol (100 µl). The ^{31}P NMR (101.23 MHz) at -40°C

contained two sets of peaks centred on 72.44 (dd, J_{Rh-P}= 181.1 Hz, J_{P-P}= 37.1 Hz) and 56.29 (dd, J_{Rh-P}= 162.5 Hz,J_{P-P}= 37.2 Hz).

7.16 Kinetic Resolution of Hydroxy Vinylsulphone (132)



Conversion :

50 %	77 % e.e.	73 % e.e.
57 %	89 % e.e.	63 % e.e.
	$[\alpha]_D^{20}$ = +57.07°	$[\alpha]_D^{20}$ = +13.7°

Two separate experiments were conducted using the same protocol for kinetic resolution of the sulphone, (**132**).

A sample of 3-phenyl-2-(phenylsulphonyl)propene-3-ol (0.30 mg, 1.094 mmol) together with a freshly prepared sample of (*S,S*)-(**108**) (20 mg, 2.28 mol%) was dissolved in dry degassed methanol (10 ml) and the standard procedure for hydrogenation experiments detailed earlier was then followed. The reaction was stopped by exposure to air when hydrogen uptake, as judged by a gas burette, was 55 % of the estimated total. Standard work-up procedure gave a mixture of starting material and product (0.29 g, 96 %). ^{1}H NMR (300 MHz, $CDCl_3$) indicated that the extent of reaction was only 50 %. Separation of the starting material and product by t.l.c. under a variety of solvent systems proved impossible. The e.e. in the starting material was determined by NMR methods to be 77 %.

A second sample of (**132**) (0.185 g, 0.674 mmol) together with a freshly prepared sample of (*S,S*)-(**108**) (10.8 mg, 2.0 mol%) in methanol (5 ml) was treated in the same manner as above to give a mixture of starting material and product (0.166 g, 90 %). The extent of reaction as judged by ^{1}H NMR (200 MHz, $CDCl_3$) was 57 %. The e.e. in the starting material was determined by NMR methods to be 89 %.

A 100 mg sample of the starting material and product from this experiment were

separated by Dr. C. Bevan at GLAXO, Greenford, using a LiChrosorb diol packed column eluting with heptane/ethanol (9:1). Starting material - $[\alpha]^{20}_D$= +57° (c=1, $CHCl_3$). Product - $[\alpha]^{20}_D$= +13.7°(c=1, $CHCl_3$).

The e.e. in the starting materials of the above two hydrogenations were measured by two separate sets of NMR experiments.

i) 3 mg of the substrate/product mixture was dissolved in freshly distilled d^8-toluene (0.4 ml) and the ^1H NMR (500 MHz) was taken. 10 µl of a solution of europium(III) (3-heptafluorobutyrylcamphorate) (26 mg, 22.0 µmol) in d^8-toluene (0.22 ml) was added and the NMR was retaken. A further 9 µl, in 3 µl portions was added and one of the vinylic signals was observed to split into two almost baseline separate signals. The ratio of the areas of the two peaks was measured by integration and by cutting out the trace and weighing them separately. The identity of the peaks was confirmed by a control experiment with a sample of the racemic starting material.

ii) 65 mg of the substrate/product mixture together with (+)-(*S*,*S*)-(DIOP)platinum ethene (20 mg, 28 µmol) was dissolved in dry degassed tetrahydrofuran (3 ml) under argon and left to stir for 30 min. The solvent was removed *in vacuo* and the residue taken up in d^6-benzene. The ^{31}P NMR was then taken at 202.46 MHz and the signals due to the two enantiomers of the starting material were intergrated. The entire procedure was repeated for a racemic sample of the starting material. The e.e. in the substrate from the kinetic resolution reactions was then calculated from the ratios of the species containing the two enantiomers, after a correction was made for diasteroselective binding of the substrate to the platinum complex.

7.17 Molecular Modelling Studies

Minimisation of the energy of molecules was performed by the computer program MMX.[86] These initial structures were then examined for more stable rotamers of the central bonds by a procedure in PCMODEL.[86] The more stable rotamers were then reminimised to determine the true ground state conformation.

The energy difference between the favoured and disfavoured binding mode conformations for the hydroxy vinylsulphones, hydroxy vinylsulphoxides and simple vinyl

sulphoxides was determined with the MMX[86] program. The energy minimised ground state conformations of the molecules to be examined were manipulated to give two structures each, in which the auxiliary binding group was orientated to allow binding to the two faces of the olefinic bond. In practice, this meant fixing the torsion angle between the olefinic bond and the bond to the auxiliary binding group to +60° and -60°. Sterically demanding groups were orientated away from the face, to which the metal would bind, and the structures were energy minimised.

7.18 Kinetic Analysis of Hydrogenation Reactions

Sets of data from hydrogenations carried out in the constant volume apparatus, stored as ASCII computer files, were reduced in size to approximately 50 points. This was achieved by removing points at regular intervals using an ASCII editor. The data file was then converted to an ITR file, that used by the modelling program, by the custom written computer program MAKEITR (Appendix D). This file contained initial concentrations of the model species together with the experimental data, which was converted to a concentration of product with time.

The model, which was in the form of a set of equations in an ASCII computer file, was changed to include initial guesses at the rate constants for the final two equations **4, 5**. These guesses were deliberately set high. This was done because the iterating program, GIT, altered rates constants by a percentage of their value, and thus a larger change in these constants could be achieved. This allowed the program to "escape" from local minima.

	G		→		**H**				**1**
	H		→		**G**				**2**
C	**+**	**S**	→		**BS**				**3**
	BS		→	**C**	**+**	**S**			**4**
BS	**+**	**H**	→	**C**	**+**	**P**			**5**

The iterating program, GIT, was allowed to optimize the two variable rate constant to produce a best fit and the figure for the average deviation noted. The process was then

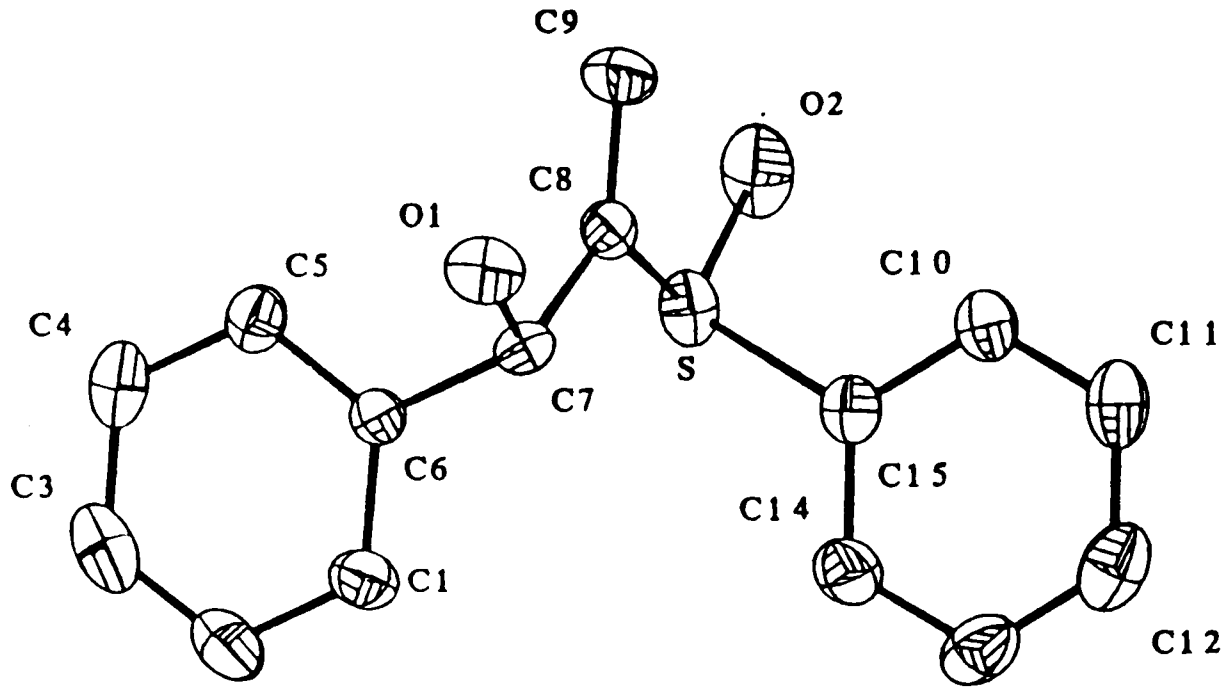
repeated with lower initial values for the two variable rate constants, until the lowest value for the average deviation was obtained.

The values quoted in the Results and Discussion Chapters for the **GLOBAL VALUES** of the kinetic parameters refer to the values obtained when the data sets were modelled as an ensemble. The **FIT** quoted refers to the average deviation of the data points from the model.

APPENDICES

APPENDIX A

X-Ray Cystal Structure Data for (R*,S*)-3-Phenyl-2-Phenylsulphinyl-Propen-3-ol



Crystal Data, Intensity Data, Collection Parameters and Details of Refinement for 91DA46

Crystal Data:

Stoichiometry	C(15)H(14)O(2)S
M.Wt.	258.34
a, Å	7.266(1)
b, Å	12.200(1)
c, Å	29.593(6)
alpha, o	90
beta, o	90
gamma, o	90
V, $Å^3$	2623.33
System	Orthorhombic
Space group	Pcab
Dc, g/cm^{-3}	1.31
Z	8
F(OOO)	1088
Radiation	Mo k alpha
lambda	0.71069
MU 1/cm	2.26

Data Collection

Temperature	293 K
total data measured	8675
total data unique	2029
total data observed	1403
significance test	F(o) >4sigmaF(o)

Refinement

No. of parameters	157
g* (weighting scheme)	0.0001
Absorption correction	None
Fi: l R	0.055
Final RW	0.057
Final RG	0.065
R{merg}	0.060

*$1/[\sigma^2(Fo) + gFo^2]$

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$) for 91DA46{C15 H14 O2 S}

	x	y	z
C(1)	6657(2)	6355(4)	6799(1)
C(2)	7270(2)	6479(4)	7196(1)
C(3)	6826(2)	5874(4)	7604(1)
C(4)	5769(2)	5144(4)	7615(1)
C(5)	5156(2)	5020(4)	7218(1)
C(6)	5600(2)	5625(4)	6810(1)
C(7)	4939(3)	5546(5)	6379(1)
O(1)	4035(2)	6779(4)	6387(1)
C(8)	4495(3)	3646(5)	6287(1)
C(9)	3461(4)	3147(8)	6292(2)
S	5514(1)	1903(1)	6200
O(2)	4910(3)	138(4)	6139(1)
C(10)	5260(2)	2209(4)	5283(1)
C(11)	5596(2)	2712(4)	4849(1)
C(12)	6591(2)	3623(4)	4788(1)
C(13)	7251(2)	4031(4)	5159(1)
C(14)	6916(2)	3529(4)	5593(1)
C(15)	5921(2)	2617(4)	5654(1)

TABLE 2

Anisotropic temperature factors ($\mathring{A}^2 \times 10^3$) for 91DA46{C15 H14 O2 S}

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	51(2)	54(3)	60(3)	-1(2)	-3(2)	-10(2)
C(2)	63(3)	71(3)	70(3)	-13(3)	-17(2)	-6(2)
C(3)	86(4)	64(3)	66(4)	-21(3)	-28(3)	18(2)
C(4)	93(4)	58(3)	41(3)	-3(2)	4(2)	12(2)
C(5)	61(3)	47(3)	43(3)	0(2)	6(2)	-1(2)
C(6)	42(2)	30(2)	42(2)	-4(2)	3(2)	0(1)
C(7)	37(2)	40(2)	41(2)	5(2)	5(2)	0(2)
O(1)	51(2)	45(2)	74(2)	7(1)	-4(1)	8(1)
C(8)	49(2)	39(2)	34(2)	7(2)	-3(2)	-6(2)
C(9)	55(3)	59(3)	70(3)	1(2)	1(2)	-19(2)
S	73(1)	38(1)	42(1)	3	-6	6
O(2)	138(3)	33(2)	66(2)	4(1)	7(2)	-14(2)
C(10)	61(3)	54(3)	47(3)	-1(2)	-7(2)	4(2)
C(11)	93(4)	69(3)	44(3)	1(2)	-9(2)	15(2)
C(12)	107(4)	54(3)	61(3)	9(3)	21(3)	14(3)
C(13)	82(3)	53(3)	79(4)	-2(3)	29(3)	-8(2)
C(14)	64(3)	48(3)	65(3)	-10(2)	0(2)	-6(2)
C(15)	57(3)	35(2)	47(3)	-2(2)	-1(2)	9(2)

The temperature factor exponent takes the form:

$$-2\pi^2(U_{11}.h^2.a^{*2} + \ldots + 2U_{12}.h.k.a^*.b^*)$$

TABLE 3

Hydrogen fractional atomic co-ordinates ($x10^4$) and isotropic temperature factors ($Å^2 x10^3$) for 91DA46{C15 H14 O2 S}

	x	y	z	U
H(11)	6963(2)	6772(4)	6518(1)	95(7)
H(21)	7998(2)	6982(4)	7188(1)	95(7)
H(31)	7248(2)	5960(4)	7877(1)	95(7)
H(41)	5463(2)	4728(4)	7896(1)	95(7)
H(51)	4428(2)	4517(4)	7226(1)	95(7)
H(71)	5411(23)	5831(42)	6153(11)	29(9)
H(10X)	4419(35)	7927(72)	6349(19)	104(18)
H(91)	3317(21)	1914(47)	6228(10)	26(9)
H(92)	2924(31)	4092(56)	6355(14)	68(13)
H(101)	4576(2)	1582(4)	5325(1)	88(6)
H(111)	5142(2)	2431(4)	4594(1)	88(6)
H(121)	6822(2)	3969(4)	4489(1)	88(6)
H(131)	7936(2)	4658(4)	5117(1)	88(6)
H(141)	7370(2)	3810(4)	5848(1)	88(6)

TABLE 4

Bond lengths (Å) for 91DA46{C15 H14 O2 S}

C(2)-C(1)	1.395	C(6)-C(1)	1.395
C(3)-C(2)	1.395	C(4)-C(3)	1.395
C(5)-C(4)	1.395	C(6)-C(5)	1.395
C(7)-C(6)	1.510(7)	O(1)-C(7)	1.421(5)
C(8)-C(7)	1.509(7)	C(9)-C(8)	1.312(6)
S-C(8)	1.793(6)	O(2)-S	1.491(4)
C(15)-S	1.767(5)	C(11)-C(10)	1.395
C(15)-C(10)	1.395	C(12)-C(11)	1.395
C(13)-C(12)	1.395	C(14)-C(13)	1.395
C(15)-C(14)	1.395		

TABLE 5

Hydrogen bond lengths (Å) for 91DA46{C15 H14 O2 S}

H(11)-C(1)	0.960	H(21)-C(2)	0.960
H(31)-C(3)	0.960	H(41)-C(4)	0.960
H(51)-C(5)	0.960	H(71)-C(7)	0.908(30)
H(10X)-O(1)	0.964(50)	H(91)-C(9)	0.932(33)
H(92)-C(9)	0.968(38)	H(101)-C(10)	0.960
H(111)-C(11)	0.960	H(121)-C(12)	0.960
H(131)-C(13)	0.960	H(141)-C(14)	0.960

TABLE 6

Bond angles (deg.) for 91DA46{C15 H14 O2 S}

C(6)-C(1)-C(2)	120.0	C(3)-C(2)-C(1)	120.0
C(4)-C(3)-C(2)	120.0	C(5)-C(4)-C(3)	120.0
C(6)-C(5)-C(4)	120.0	C(5)-C(6)-C(1)	120.0
C(7)-C(6)-C(1)	119.2(3)	C(7)-C(6)-C(5)	120.8(3)
O(1)-C(7)-C(6)	112.2(4)	C(8)-C(7)-C(6)	112.3(4)
C(8)-C(7)-O(1)	107.5(4)	C(9)-C(8)-C(7)	126.5(5)
S-C(8)-C(7)	115.1(3)	S-C(8)-C(9)	118.3(4)
O(2)-S-C(8)	106.4(3)	C(15)-S-C(8)	96.8(2)
C(15)-S-O(2)	106.3(3)	C(15)-C(10)-C(11)	120.0
C(12)-C(11)-C(10)	120.0	C(13)-C(12)-C(11)	120.0
C(14)-C(13)-C(12)	120.0	C(15)-C(14)-C(13)	120.0
C(10)-C(15)-S	119.7(2)	C(14)-C(15)-S	120.2(2)
C(14)-C(15)-C(10)	120.0		

TABLE 7

Hydrogen bond angles (deg.) for 91DA46{C15 H14 O2 S}

H(11)-C(1)-C(2)	120.0	H(11)-C(1)-C(6)	120.0
H(21)-C(2)-C(1)	120.0	H(21)-C(2)-C(3)	120.0
H(31)-C(3)-C(2)	120.0	H(31)-C(3)-C(4)	120.0
H(41)-C(4)-C(3)	120.0	H(41)-C(4)-C(5)	120.0
H(51)-C(5)-C(4)	120.0	H(51)-C(5)-C(6)	120.0
H(71)-C(7)-C(6)	106.0(20)	O(1)-C(7)-H(71)	111.1(21
C(8)-C(7)-H(71)	107.6(21)	H(1OX)-O(1)-C(7)	99.6(29
H(91)-C(9)-C(8)	116.4(18)	H(92)-C(9)-C(8)	117.2(26
H(92)-C(9)-H(91)	126.4(31)	H(101)-C(10)-C(11)	120.0
H(101)-C(10)-C(15)	120.0	H(111)-C(11)-C(10)	120.0
H(111)-C(11)-C(12)	120.0	H(121)-C(12)-C(11)	120.0
H(121)-C(12)-C(13)	120.0	H(131)-C(13)-C(12)	120.0
H(131)-C(13)-C(14)	120.0	H(141)-C(14)-C(13)	120.0
H(141)-C(14)-C(15)	120.0		

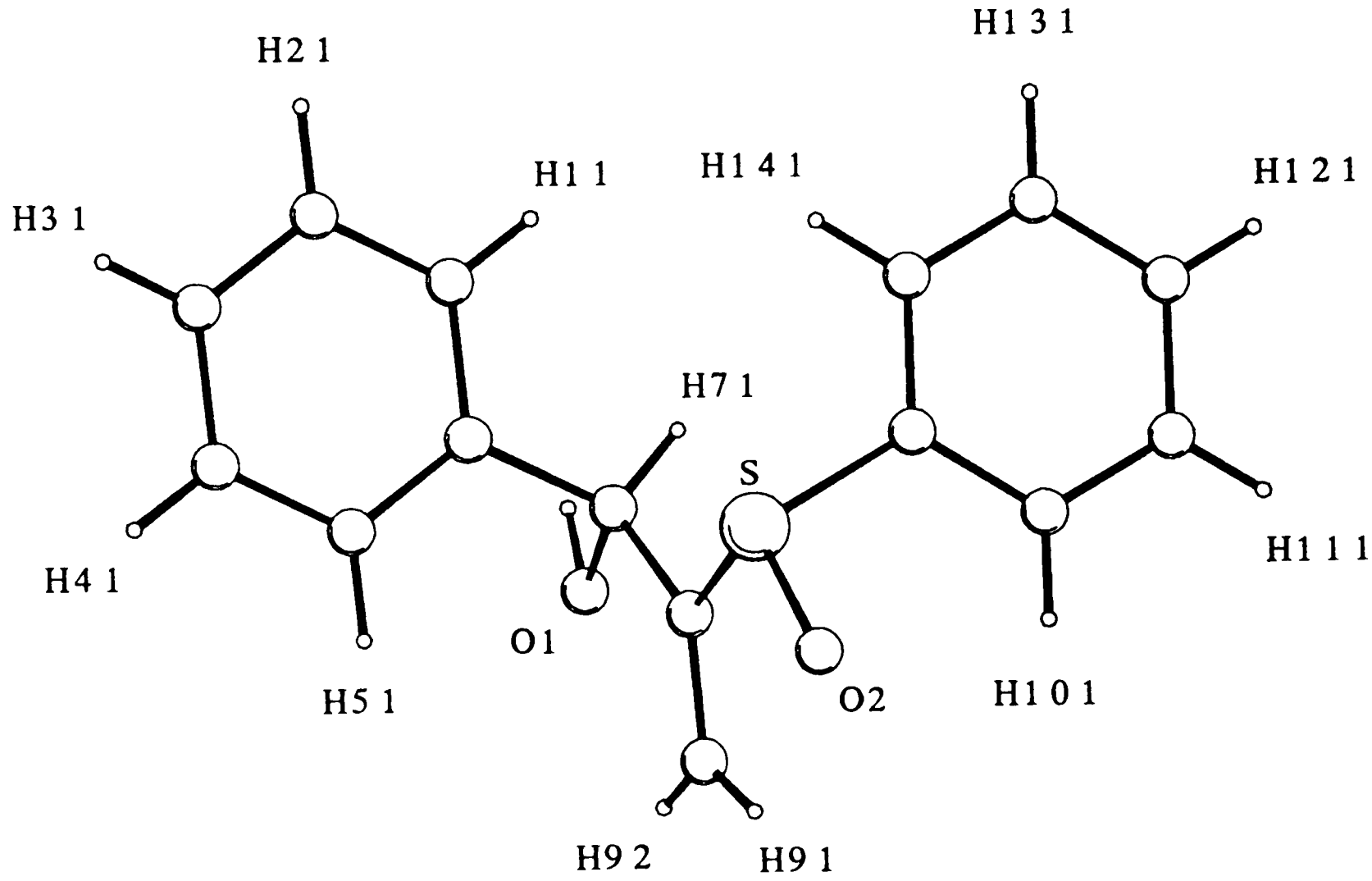
Selected non-bonded distances (Å) for 91DA46{C15 H14 O2 S}

Intramolecular:

C(3)-C(1)	2.416	C(4)-C(1)	2.790
C(5)-C(1)	2.416	H(21)-C(1)	2.051
C(7)-C(1)	2.507	H(71)-C(1)	2.473
C(4)-C(2)	2.416	C(5)-C(2)	2.790
C(6)-C(2)	2.416	H(11)-C(2)	2.051
H(31)-C(2)	2.051	C(5)-C(3)	2.416
C(6)-C(3)	2.790	H(21)-C(3)	2.051
H(41)-C(3)	2.051	C(6)-C(4)	2.416
H(31)-C(4)	2.051	H(51)-C(4)	2.051
H(41)-C(5)	2.051	C(7)-C(5)	2.526
O(1)-C(5)	3.092	C(8)-C(5)	3.041
S-C(5)	3.794	H(11)-C(6)	2.051
H(51)-C(6)	2.051	H(71)-C(6)	1.965
O(1)-C(6)	2.433	H(1OX)-C(6)	2.596
C(8)-C(6)	2.508	S-C(6)	3.253
H(21)-H(11)	2.355	C(7)-H(11)	2.657
H(71)-H(11)	2.286	H(31)-H(21)	2.355
H(41)-H(31)	2.355	H(51)-H(41)	2.355
C(7)-H(51)	2.688	C(8)-H(51)	2.853
H(1OX)-C(7)	1.845	C(9)-C(7)	2.521
H(92)-C(7)	2.677	S-C(7)	2.789
C(15)-C(7)	3.250	O(1)-H(71)	1.942
H(1OX)-H(71)	2.029	C(8)-H(71)	1.982
S-H(71)	2.860	C(14)-H(71)	2.986
C(15)-H(71)	2.831	C(8)-O(1)	2.363
C(9)-O(1)	2.744	H(92)-O(1)	2.378
H(91)-C(8)	1.918	H(92)-C(8)	1.955
O(2)-C(8)	2.635	C(10)-C(8)	3.284
C(15)-C(8)	2.661	S-C(9)	2.676
O(2)-C(9)	2.848	H(92)-H(91)	1.696
S-H(91)	2.682	O(2)-H(91)	2.348
C(10)-S	2.741	C(14)-S	2.748
H(101)-S	2.841	H(141)-S	2.851
C(10)-O(2)	2.978	C(15)-O(2)	2.612
H(101)-O(2)	2.658	C(12)-C(10)	2.416
C(13)-C(10)	2.790	C(14)-C(10)	2.416
H(111)-C(10)	2.051	C(13)-C(11)	2.416
C(14)-C(11)	2.790	C(15)-C(11)	2.416
H(101)-C(11)	2.051	H(121)-C(11)	2.051
C(14)-C(12)	2.416	C(15)-C(12)	2.790
H(111)-C(12)	2.051	H(131)-C(12)	2.051
C(15)-C(13)	2.416	H(121)-C(13)	2.051
H(141)-C(13)	2.051	H(131)-C(14)	2.051
H(101)-C(15)	2.051	H(141)-C(15)	2.051
H(111)-H(101)	2.355	H(121)-H(111)	2.355
H(131)-H(121)	2.355	H(141)-H(131)	2.355

Intermolecular:

H(21)-C(4a)	3.024	S-H(11b)	3.220
H(141)-H(11b)	2.604	C(9)-H(31c)	3.054
H(1OX)-H(41d)	2.594	S-H(41c)	3.328
O(2)-H(41c)	2.908	O(2)-C(7e)	3.411
H(111)-H(71f)	2.632	O(2)-O(1e)	2.763
H(121)-O(1f)	2.847	C(9)-O(1g)	3.215
H(91)-O(1g)	2.909	H(92)-O(1g)	2.923
S-H(1OXe)	3.213	O(2)-H(1OXe)	1.823
H(92)-H(91h)	2.577	H(111)-O(2i)	2.861
H(131)-C(10a)	2.919	H(131)-C(11a)	2.959
H(131)-C(15a)	3.017	H(131)-H(101j)	2.554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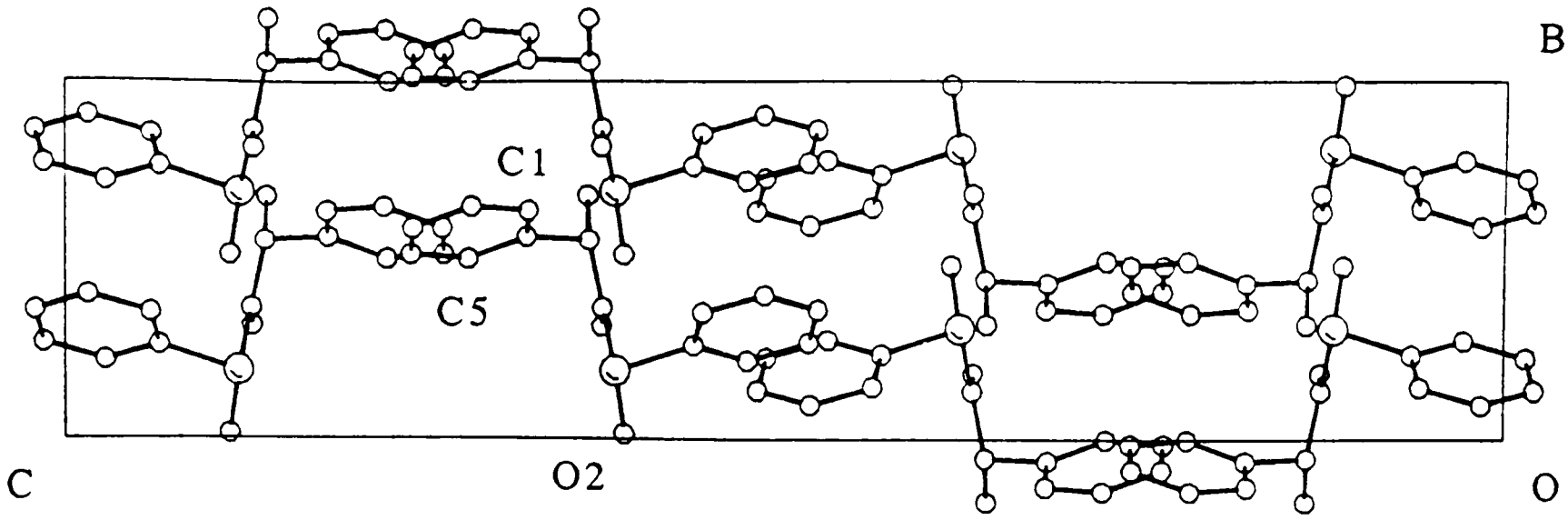
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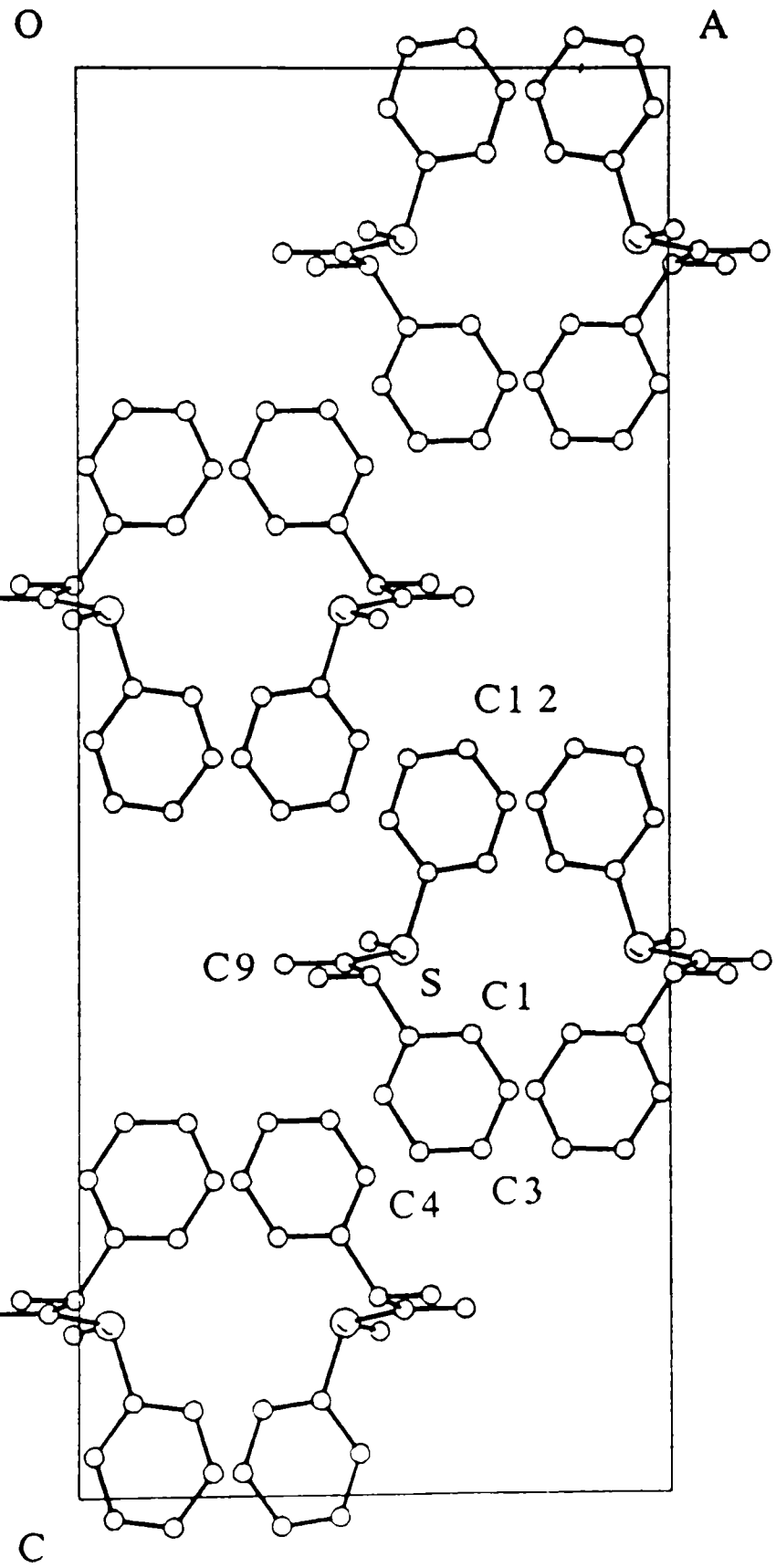
C1
C5
C
O2
O


O
A
C12
C9
S
C1
C4
C3
C

APPENDIX B

Computer Program used to Monitor hydrogenation Apparatus

ADDH2R9.BAS - Written under Microsoft QuickBASIC™

```
5  CLEAR :  ON ERROR GOTO 10000
10 DIM SAMPLE(5, 1000) AS SINGLE, time(5, 1000) AS SINGLE, C(5) AS INTEGER,
       load(5) AS STRING
20 SCREEN 10, , 1, 1: COLOR 1, 0: PALETTE 2, 1: CLS
30 OPEN "I", #2, "C:\DATA\ACQ.CFG": IF NOT erflag$ = "fnf" THEN 40
35 BEEP: LOCATE 12, 5: PRINT "Please configure and calibrate the apparatus": FOR T
       = 1 TO 2000: NEXT T: Chan% = 3: Cala! = .426: Calb! = 25: CLS : GOTO 60
40 INPUT #2, Chan%, Cala!, Calb!: CLOSE #2
60 LINE (40, 40)-(600, 310), 3, BF: LINE (46, 46)-(594, 304), 0, BF
62: LINE (50,50)-(590, 300), 3, B
65 LINE (268, 76)-(284, 176), 1, BF: LINE (316, 76)-(332, 176), 1, BF
67 LINE (344, 156)-(368, 162), 1, BF: LINE -(362, 176), 1, BF: LINE -(344, 171), 1, BF
70 LINE -(350, 191), 1, BF: LINE -(368, 185), 1, BF: LINE (268, 76)-(284, 176), 3, B:
       LINE (316, 76)-(332, 176), 3, B
72 LINE (284, 114)-(316, 130), 1, BF: LINE (284, 114)-(316, 114), 3: LINE (284,
       130)-(316, 130), 3: LINE (190, 200)-(430, 202), 3, BF
75 DRAW "C3;NM430,208;M+0,-8;M+10,+7;M430,208": PAINT (434, 201), 3, 3:
       CIRCLE (235, 272), 12, 3
77 LOCATE 8, 25: COLOR 2: PRINT "A D D"
78 LINE (145, 191)-(145, 211), 3: LINE (151, 191)-(151, 211), 3: CIRCLE (148, 187), 4,
       3: CIRCLE (148, 215), 4, 3
```

```
80 LINE (478, 191)-(478, 211), 3: CIRCLE (478, 186), 4, 3: CIRCLE (478, 216), 4, 3
85 PAINT (148, 187), 3, 3: PAINT (148, 215), 3, 3: PAINT (478, 186), 3, 3: PAINT (478,
       216), 3, 3
86 COLOR 3: LOCATE 17, 22: PRINT "Hydrogenation Data Acquisition Package   H"
87 LOCATE 13, 63: PRINT "H"
88 LINE (478, 186)-(495, 177), 3: LINE (478, 216)-(495, 226), 3
90 LOCATE 18, 23: PRINT "RELEASE 9  -  INTEGRATED & GRAPHICAL"
95 LOCATE 20, 30: PRINT "C": LOCATE 20, 34: PRINT "1991  D. W. PRICE"
100 an$ = INKEY$: IF an$ = "" THEN 100
110 CLS : COLOR 3
112 LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
115 LOCATE 1, 32: PRINT CHR$(201); STRING$(11, 205); CHR$(187)
120 LOCATE 2, 32: PRINT CHR$(186); " MAIN MENU "; CHR$(186)
125 LOCATE 3, 32: PRINT CHR$(200); STRING$(11, 205); CHR$(188)
130 COLOR 1: LOCATE 8, 24: PRINT "1   :  SETUP AND CALIBRATION CHECK"
140 LOCATE 10, 24: PRINT "2   :  CONTINUOUS MONITORING"
150 LOCATE 12, 24: PRINT "3   :  ACQUIRE DATA"
160 LOCATE 14, 24: PRINT "4   :  DISPLAY DATA"
165 LOCATE 16, 24: PRINT "5   :  FILE MANAGEMENT"
170 LOCATE 18, 24: PRINT "6   :  POSTSCRIPT PRINTING"
180 LOCATE 20, 24: PRINT "7   :  DOS SHELL"
190 LOCATE 22, 22: PRINT "[ESC] :  RETURN TO DOS": COLOR 3: LOCATE 23,
       60: PRINT CHR$(1); "  D.W.P.": COLOR 1
200 an$ = INKEY$: IF an$ = "" THEN 200
205 IF ASC(an$) = 27 THEN 230
210 IF VAL(an$) > 8 OR VAL(an$) < 1 THEN 200
220 ON VAL(an$) GOSUB 4000, 9000, 2000, 1000, 5000, 3000, 6000, 230
225 GOTO 110
230 CLS : BEEP
240 LOCATE 12, 34: COLOR 3: PRINT "END (Y/N) ?"
```

```
250 an$ = INKEY$: IF an$ = "" THEN 250
260 IF NOT an$ = "Y" AND NOT an$ = "y" THEN 110
300 SYSTEM

1000            REM **** DATA DISPLAY ****
1010 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
1015 COLOR 3: LOCATE 1, 33: PRINT CHR$(201); STRING$(14, 205); CHR$(187)
1020 LOCATE 2, 33: PRINT CHR$(186); " DATA DISPLAY "; CHR$(186)
1025 LOCATE 3, 33: PRINT CHR$(200); STRING$(14, 205); CHR$(188): COLOR 3:
        LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
1030 COLOR 1: IF NOT FLAG3$ = "LOADED" THEN 1050
1035 LOCATE 10, 5: PRINT "Same file as before ?"
1040 an$ = INKEY$: IF an$ = "" THEN 1040
1045 IF an$ = "Y" OR an$ = "y" THEN 1080
1050 IF NOT Flag2$ = "sampled" THEN 1070
1055 LOCATE 10, 5: PRINT "Use acquired data ?  "
1060 an$ = INKEY$: IF an$ = "" THEN 1060 ELSE IF ASC(an$) = 27 THEN RETURN
1065 IF an$ = "Y" OR an$ = "y" THEN 1080
1070 GOSUB 9500: IF erflag$ = "nf" THEN erflag$ = "": RETURN:  ELSE FLAG3$ =
        "LOADED"
1080 LOCATE 10, 5: PRINT SPC(39); : LOCATE 10, 30: PRINT "1"; " : LIST OF
        DATA"
1090 LOCATE 12, 30: PRINT "2"; " : GRAPH OF DATA"
1100 LOCATE 14, 30: PRINT "3"; " : RETURN TO MAIN"
1110 an$ = INKEY$: IF an$ = "" THEN 1110 ELSE IF ASC(an$) = 27 THEN RETURN
1160 IF VAL(an$) < 1 OR VAL(an$) > 3 THEN 1110 ELSE LOCATE 10, 30: PRINT
        SPC(30); : LOCATE 12, 30: PRINT SPC(30); : LOCATE 14, 30: PRINT
        SPC(30);
1170 IF VAL(an$) = 2 THEN 1400
1180 IF VAL(an$) = 3 THEN RETURN
```

```
1190 A% = (C(1) - (INT(C(1) / 15) * 15)): N% = INT(C(1) / 15)
1195 IF N% = 0 THEN 1330
1198 FOR Y% = 0 TO (N% - 1)
1200 LOCATE 5, 5: COLOR 3: PRINT "TIME"; TAB(15); "PRESSURE": COLOR 1
1210 FOR Z% = 1 TO 15
1300 LOCATE , 5: PRINT time(1, Y% * 15 + Z%); TAB(15); SAMPLE(1, Y% * 15 +
        Z%)
1305 NEXT Z%
1310 LOCATE 10, 35: COLOR 2: PRINT "Any key to continue"
1315 an$ = INKEY$: IF an$ = "" THEN 1315
1320 LINE (40, 280)-(200, 80), 0, BF: NEXT Y%
1330 IF A% = 0 THEN 1380
1340 LOCATE 5, 5: COLOR 3: PRINT "TIME"; TAB(15); "PRESSURE": COLOR 1
1360 FOR Y% = 1 TO A%
1365 LOCATE , 5: PRINT time(1, Y% + N% * 15); TAB(15); SAMPLE(1, Y% + 15 *
        N%)
1370 NEXT Y%
1380 LOCATE 10, 35: COLOR 2: PRINT " DO YOU WISH TO GRAPH THIS ?"
1385 an$ = INKEY$: IF an$ = "" THEN 1385
1387 LINE (40, 280)-(200, 80), 0, BF
1390 IF an$ = "Y" OR an$ = "y" THEN 1400
1395 CLS : COLOR 1: RETURN
1400 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
1420 COLOR 3: LOCATE 1, 33: PRINT CHR$(201); STRING$(10, 205); CHR$(187)
1430 LOCATE 2, 33: PRINT CHR$(186); " GRAPHING "; CHR$(186)
1440 LOCATE 3, 33: PRINT CHR$(200); STRING$(10, 205); CHR$(188): COLOR 3:
        LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
1445 COLOR 1: LOCATE 12, 12: PRINT "Axes selection AUTO or MANUAL (A/M) ?"
1450 an$ = INKEY$: IF an$ = "" THEN 1450 ELSE IF ASC(an$) = 27 THEN RETURN
1455 IF an$ = "m" OR an$ = "M" THEN 1600
```

```
1460 XMIN = 10 * (INT(time(1, 1) / 10)): XMAX = 10 * (INT(time(1, C(1)) / 10)) + 10
1470 IF SAMPLE(1, 1) < SAMPLE(1, C(1)) THEN 1490
1480 YMIN = SAMPLE(1, C(1)): YMAX = SAMPLE(1, 1)
1485 GOTO 1500
1490 YMIN = SAMPLE(1, 1): YMAX = SAMPLE(1, C(1))
1500 YMAX = 10 * INT(YMAX / 10) + 10: YMIN = 10 * INT(YMIN / 10) - 10
1510 XSCALE = 430 / (XMAX - XMIN): YSCALE = 360 / (YMAX - YMIN)
1520 GOTO 1640
1600 LOCATE 12, 13: PRINT "First reading = "; SAMPLE(1, 1); "   Last reading = ";
        SAMPLE(1, Count)
1610 LOCATE 10, 25: INPUT "Pressure Max : "; YMAX: LOCATE 10, 25: PRINT
        SPC(30);
1620 LOCATE 10, 25: INPUT "Pressure Min : "; YMIN: LOCATE 10, 25: PRINT
        SPC(30);
1630 XMIN = INT(time(1, 1)): XMAX = 10 * INT(time(1, Count) / 10) + 10
1640 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
1645 COLOR 3: LOCATE 1, 33: PRINT CHR$(201); STRING$(10, 205); CHR$(187)
1650 LOCATE 2, 33: PRINT CHR$(186); " GRAPHING "; CHR$(186)
1655 LOCATE 3, 33: PRINT CHR$(200); STRING$(10, 205); CHR$(188): COLOR 3:
        LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
1660 COLOR 1
1680 LINE (120, 70)-(120, 270), 3: REM LINE (117, 70)-(123, 70)
1685 LINE (120, 270)-(520, 270), 3: REM LINE (520, 267)-(520, 273)
1690 FOR A% = 120 TO 520 STEP 40: LINE (A%, 267)-(A%, 273), 3: NEXT A%
1695 FOR B% = 270 TO 70 STEP -20: LINE (117, B%)-(123, B%), 3: NEXT B%
1700 LOCATE 6, 9: PRINT YMAX: LOCATE 13, 10: PRINT "mbar"
1710 LOCATE 20, 9: PRINT YMIN: LOCATE 21, 16: PRINT "0"
1750 LOCATE 21, 38: PRINT "s": LOCATE 21, 65: PRINT XMAX
1755 FOR LP = 1 TO C(1)
1760 X = 120 + (time(1, LP) / (XMAX - XMIN)) * 400
```

```
1765 Y = 270 - ((SAMPLE(1, LP) - YMIN) / (YMAX - YMIN)) * 200
1770 LINE (X + 1, Y + 1)-(X - 1, Y - 1), 3, BF
1775 NEXT LP
1777 COLOR 3: LOCATE 5, 52: PRINT load$
1780 LOCATE 22, 29: COLOR 2: PRINT "Any Key To Continue": COLOR 1
1785 an$ = INKEY$: IF an$ = "" THEN 1785
1790 RETURN

2000        REM **** DATA ACQUISITION ****
2005 PALETTE 2, 2: CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
2010 OUT &H703, &H92: OUT &H702, 16 * Chan% + 2
2015 COLOR 3: LOCATE 1, 31: PRINT CHR$(201); STRING$(18, 205); CHR$(187)
2020 LOCATE 2, 31: PRINT CHR$(186); " DATA ACQUISITION "; CHR$(186)
2025 LOCATE 3, 31: PRINT CHR$(200); STRING$(18, 205); CHR$(188)
2030 COLOR 1: LOCATE 7, 3: PRINT "SAMPLING          : OFF"
2040 LOCATE 9, 3: PRINT "SAMPLING INTERVAL  :"
2045 LOCATE 11, 3: PRINT "SAMPLING RATE     :"
2050 LOCATE 13, 3: PRINT "TOTAL TIME        :"
2060 LOCATE 15, 3: PRINT "PERIOD THRU'      :"
2070 LOCATE 17, 3: PRINT "KEYBOARD          : ENABLED"
2080 LOCATE 19, 4: INPUT "Time interval between samples (whole seconds please) ";
        I$:
2085 IF I$ = "" THEN RETURN
2088 IF ASC(I$) = 27 THEN RETURN:  ELSE I = INT(VAL(I$))
2090 LOCATE 20, 4: INPUT "Total sampling time (again whole seconds)"; T$
2100 IF T$ = "" THEN Flag4$ = "LONGT": Flag$ = "EN": SNUM = 0: GOTO 2110
2105 IF ASC(T$) = 27 THEN RETURN:  ELSE TTOTAL! = INT(VAL(T$)): SNUM =
        (TTOTAL! / I) + 1
2110 IF SNUM > 999 THEN BEEP: PRINT "Too Many Samples": FOR DELAY = 1 TO
        5000: NEXT DELAY: LOCATE 18, 51: PRINT SPC(4); : LOCATE 19, 48:
```

```
        PRINT SPC(5); LOCATE 20,4 : PRINT SPC(17); : GOTO 2080
2120 IF Flag4$ = "LONGT" THEN 2150 ELSE LOCATE 21, 4: PRINT "DO YOU WISH
        TO BE ABLE TO TERMINATE THE SAMPLING BEFORE COMPLETTION ?"
2130 an$ = INKEY$: IF an$ = "" THEN 2130 ELSE IF ASC(an$) = 27 THEN RETURN
2140 IF an$ = "Y" OR an$ = "y" THEN Flag$ = "EN" ELSE Flag$ = "DIS"
2150 ERASE SAMPLE, time
2160 LOCATE 9, 24: PRINT I; "s    ":
2165 LOCATE 11, 25: PRINT USING "#.###"; 1 / I; : PRINT "Hz"
2170 LOCATE 13, 24: IF Flag4$ = "LONGT" THEN PRINT "LONGTERM":
        ELSE PRINT TTOTAL!; "s"
2180 COLOR 3: LOCATE 17, 24: IF Flag$ = "DIS" THEN PRINT "DISABLED": ELSE
        PRINT "ENABLED "
2190 COLOR 1: LOCATE 19, 4: PRINT SPC(68); : LOCATE 20, 4: PRINT SPC(68);
2200 LOCATE 21, 4: PRINT SPC(69); : LOCATE 22, 4: PRINT SPC(69);
2210 LOCATE 19, 4: INPUT "Filename for data set (OMIT .EXT) [RET = temp.dat]";
        name$
2215 IF name$ = "" THEN name$ = "C:\DATA\TEMP.DAT": GOTO 2218
2216 IF ASC(name$) = 27 THEN RETURN:  ELSE name$ = "C:\DATA\" + name$ +
        ".DAT"
2218 OPEN "O", #1, "C:\DATA\ACQ.DAT": OPEN "O", #2, name$
2220 IF NOT erflag$ = "bfn" THEN 2230 ELSE LOCATE 19, 4: PRINT SPC(50); :
        LOCATE 19, 20: PRINT "BAD FILE NAME RETRY"
2225 FOR T = 1 TO 3000: NEXT: erflag$ = "": GOTO 2210
2230 LOCATE 19, 4: PRINT SPC(69); : file$ = "C:\DATA\" + name$ + ".DAT"
2240 LOCATE 19, 4: INPUT "ESTIMATE OF FINAL PRESSURE (mbar) "; EST$:
        LOCATE 19, 4: PRINT SPC(68);
2250 YMIN = INT(VAL(EST$) / 10) * 10
2260 LINE (316, 60)-(316, 194): LINE (313, 60)-(319, 60)
2270 LOCATE 9, 35: PRINT "mbar"
2280 LOCATE 14, 34: PRINT YMIN: LINE (312, 190)-(605, 190): LINE (605,
```

```
        187)-(605, 193)
2290 LOCATE 15, 40: PRINT "0": LOCATE 15, 56: PRINT "s": LOCATE 15, 73:
        PRINT TTOTAL
2300 LINE (264, 50)-(615, 214), , B
2310 IF Flag4$ = "LONGT" THEN 2600
2320 ON TIMER(I) GOSUB 2925
2330 FIN$ = ""
2340 LOCATE 20, 5: PRINT "PRESS SPACE TO ENABLE SAMPLING"
2350 an$ = INKEY$: IF an$ = "" THEN 2350
2360 IF ASC(an$) = 27 THEN CLOSE #1, #2: RETURN
2370 IF an$ <> " " THEN 2350 ELSE TIMER ON: T0 = TIMER: T1 = T0: LOCATE 20,
        5: PRINT SPC(60);
2380 COLOR 2: LOCATE 7, 24: PRINT " ON ": COLOR 1: COLOR 3: LOCATE 23, 60:
PRINT CHR$(1); "  D.W.P.": COLOR 1
2390 Count = 1
2400 FOR L% = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR DELAY = 0 TO 20: NEXT
        DELAY
2405 HB% = INP(&H701): LB% = INP(&H700): OUT &H702, 16 * Chan% + 2
2410 SAMPLE(1, 1) = SAMPLE(1, 1) + ((HB% AND 15) * 256 + LB%) * Cala! - Calb!:
        NEXT L%
2415 time(1, 1) = 0: SAMPLE(1, 1) = SAMPLE(1, 1) / 5: LOCATE 15, 24: PRINT
        time(1, 1); "s   "
2420 PRINT #1, 0, SAMPLE(1, 1): PRINT #2, 0, SAMPLE(1, 1)
2425 LOCATE 21, 20: PRINT "CURRENT  PRESSURE = "; : PRINT USING
        "####.##"; SAMPLE(1, Count); : PRINT " mbar "
2430 YMAX = 10 * INT(SAMPLE(1, 1) / 10) + 10
2440 XSCALE = 289 / TTOTAL!: YSCALE = 130 / (YMAX - YMIN)
2455 LOCATE 5, 34: PRINT INT(YMAX)
2460 X = 316: Y = 190 - ((SAMPLE(1, 1) - YMIN) * YSCALE)
2465 LINE (264, 50)-(615, 214), 3, B
```

```
2480 PSET (X, Y), 3
2500 IF Flag$ = "DIS" THEN 2550
2510 an$ = INKEY$
2520 IF an$ <> "T" THEN 2550
2530 TIMER OFF: CLOSE #1: CLOSE #2
2540 COLOR 3: LOCATE 7, 24: PRINT "STOPPED": COLOR 1: GOTO 2590
2550 IF FIN$ = "FIN" THEN 2585
2555 IF TIMER - T1 < 1 THEN 2500 ELSE T1 = TIMER: LOCATE 15, 25: PRINT
        SPC(7);
2560 LOCATE 15, 24: PRINT INT(TIMER - T0); "s"
2575 GOTO 2500
2585 CLOSE #1: CLOSE #2: COLOR 3: LOCATE 7, 24: PRINT "FINISHED": COLOR
        1
2588 LOCATE 15, 24: PRINT INT(TTOTAL!); "s"
2590 Flag2$ = "sampled": C(1) = Count
2595 COLOR 2: LOCATE 19, 26: PRINT "ANY KEY TO CONTINUE": COLOR 1
2599 an$ = INKEY$: IF an$ = "" THEN 2599 ELSE RETURN


2600 ON TIMER(I) GOSUB 2925: XMAX = 10 * I: COLOR 3: LOCATE 23, 60: PRINT
        CHR$(1); "  D.W.P.": COLOR 1
2610 CLOSE #1: OPEN "O", #1, "D:ACQ1.DAT": NYMIN = YMIN
2620 LOCATE 20, 5: PRINT "PRESS SPACE TO ENABLE SAMPLING"
2630 an$ = INKEY$: IF an$ = "" THEN 2630
2640 IF ASC(an$) = 27 THEN CLOSE #1, #2: RETURN
2650 IF an$ <> " " THEN 2630 ELSE LOCATE 20, 5: PRINT SPC(49);
2660 COLOR 2: LOCATE 7, 25: PRINT "ON "; : COLOR 1
2670 Count = 1: TIMER ON
2680 SAM = 0: C = 1
2730 FOR L% = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR DELAY = 0 TO 20: NEXT
        DELAY
```

```
2740 HB% = INP(&H701): LB% = INP(&H700): OUT &H702, 16 * Chan% + 2
2750 SAM = SAM + ((HB% AND 15) * 256 + LB%) * Cala! - Calb!: NEXT L%
2760 ti = 0: SAM = SAM / 5: LOCATE 15, 24: PRINT ti; "s   "
2770 PRINT #1, 0, SAM: PRINT #2, 0, SAM
2780 LOCATE 21, 20: PRINT "CURRENT  PRESSURE = "; SAM; " mbar "
2785 YMAX = 10 * INT(SAM / 10) + 10
2790 XSCALE = 289 / XMAX: YSCALE = 130 / (YMAX - YMIN)
2792 LOCATE 5, 34: PRINT INT(YMAX): LOCATE 15, 73: PRINT XMAX
2795 X = 316: Y = 190 - ((SAM - YMIN) * YSCALE)
2797 LINE (264, 50)-(615, 214), 3, B: PSET (X, Y), 3
2800 IF ti >= XMAX THEN XMAX = INT(XMAX * 1.3):        ELSE 2870
2802 IF NYMIN < YMIN THEN YMIN = NYMIN: LOCATE 14, 34: PRINT YMIN
2805 SCREEN 10, , 1, C: LINE (317, 189)-(605, 60), 0, BF: COLOR 1: LOCATE 15, 73:
        PRINT XMAX
2810 CLOSE #1: OPEN "I", #1, "D:ACQ1.DAT"
2815 XSCALE = 289 / XMAX: YSCALE = 130 / (YMAX - YMIN)
2840 INPUT #1, ti, SAM: PSET (316, 190 - ((SAM - YMIN) * YSCALE)), 3
2845 FOR Q% = 2 TO Count: INPUT #1, ti, SAM: X = 316 + (ti * XSCALE): Y = 190 -
        ((SAM - YMIN) * YSCALE)
2850 LINE -(X, Y), 3: NEXT Q%
2855 CLOSE #1
2860 OPEN "A", #1, "D:ACQ1.DAT": GOTO 2890
2870 X = 316 + (ti * XSCALE)
2875 Y = 190 - ((SAM - YMIN) * YSCALE)
2880 LINE -(X, Y), 3
2885 LOCATE 15, 24: PRINT I * (Count - 1); "s"
2890 an$ = INKEY$
2900 IF NOT an$ = "T" AND NOT an$ = "t" THEN 2800 ELSE TIMER OFF
2905 CLOSE #1: CLOSE #2: COLOR 3: LOCATE 7, 24: PRINT "STOPPED": COLOR
        1
```

```
2910 COLOR 2: LOCATE 19, 26: PRINT "ANY KEY TO CONTINUE": COLOR 1
2915 an$ = INKEY$: IF an$ = "" THEN 2915
2920 RETURN

2925 Count = Count + 1:      REM **** INTERUPT SAMPLING ****
2930 A = POS(1): B = CSRLIN: SAM = 0
2935 FOR L% = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR DELAY = 0 TO 20: NEXT
        DELAY
2940 HB% = INP(&H701): LB% = INP(&H700): OUT &H702, 16 * Chan% + 2
2945 SAM = SAM + ((HB% AND 15) * 256 + LB%) * Cala! - Calb!: NEXT L%
2950 ti = (Count - 1) * I: SAM = SAM / 5: IF SAM < YMIN + 15 THEN NYMIN =
        YMIN - 10
2952 PRINT #1, ti, SAM: PRINT #2, ti, SAM: SCREEN 10, , 1, C: COLOR 1
2955 LOCATE 21, 20: PRINT "CURRENT  PRESSURE = "; : PRINT INT(SAM * 100) /
        100; " mbar    "
2960 IF Flag4$ = "LONGT" THEN 2995 ELSE time(1, Count) = ti: SAMPLE(1, Count) =
        SAM
2965 R = (SAMPLE(1, Count) - SAMPLE(1, Count - 1)) / I
2970 LOCATE 23, 20: PRINT "CURRENT  RATE     = "; : PRINT INT(R * 100) / 100;
        " mbar/s     "
2975 X = 316 + (time(1, Count) * XSCALE)
2980 Y = 190 - ((SAMPLE(1, Count) - YMIN) * YSCALE)
2985 LINE -(X, Y), 3
2990 IF Count = SNUM THEN TIMER OFF: FIN$ = "FIN"
2995 LOCATE B, A: RETURN

3000 COLOR 3: CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
3005 LOCATE 1, 28: PRINT CHR$(201); STRING$(21, CHR$(205)); CHR$(187):
        COLOR 3: LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
3010 LOCATE 2, 28: PRINT CHR$(186); : PRINT " PostScript PRINTING "; : PRINT
```

```
        CHR$(186): LOCATE 3, 28: PRINT CHR$(200); STRING$(21, CHR$(205));
        CHR$(188)
3012 COLOR 1: LOCATE 10, 10: INPUT "FULL name of PRINT-FILE to be generated
        "; PS$
3014 page = 0: OPEN "O", #6, PS$: LOCATE 10, 10: PRINT SPC(60);
3015 IF NOT FLAG3$ = "LOADED" THEN 3030 ELSE LOCATE 10, 5: PRINT "Same
        file as before ?"
3020 an$ = INKEY$: IF an$ = "" THEN 3020
3025 IF an$ = "Y" OR an$ = "y" THEN 3065
3030 LOCATE 10, 10: PRINT "Number of data sets to be printed as graphs ?"
3035 an$ = INKEY$: IF an$ = "" THEN 3035
3040 IF ASC(an$) = 27 THEN CLOSE #6: RETURN
3045 IF VAL(an$) < 1 OR VAL(an$) > 5 THEN 3035 ELSE N = VAL(an$)
3050 LOCATE 10, 10: PRINT SPC(60);
3055 GOSUB 9500: IF erflag$ = "nf" THEN erflag$ = "": RETURN
3065 IF SAMPLE(1, 1) < SAMPLE(1, C(1)) THEN 3100
3070 XMIN = time(1, 1): XMAX = time(1, C(1)): YMIN = SAMPLE(1, C(1)): YMAX =
        SAMPLE(1, 1)
3075 IF N = 1 THEN 3150
3080 FOR T = 2 TO N: IF time(T, 1) < XMIN THEN XMIN = time(T, 1)
3085 IF time(T, C(T)) > XMAX THEN XMAX = time(T, C(T))
3090 IF SAMPLE(T, 1) > YMAX THEN YMAX = SAMPLE(T, 1)
3095 IF SAMPLE(T, C(T)) < YMIN THEN YMIN = SAMPLE(T, C(T))
3097 NEXT T
3098 GOTO 3150
3100 XMIN = time(1, 1): XMAX = time(1, C(1)): YMIN = SAMPLE(1, 1): YMAX =
SAMPLE(1, C(1))
3105 IF N = 1 THEN 3150
3110 FOR T = 2 TO N
3115 IF time(T, 1) < XMIN THEN XMIN = time(T, 1)
```

```
3120 IF time(T, C(T)) > XMAX THEN XMAX = time(T, C(T))
3125 IF SAMPLE(T, C(T)) > YMAX THEN YMAX = SAMPLE(T, C(T))
3130 IF SAMPLE(T, 1) < YMIN THEN YMIN = SAMPLE(T, 1)
3140 NEXT T
3150 SY = 1: F$ = "##": IF YMAX - YMIN > 100 THEN SY = 100: F$ = "####": GOTO
        3165
3155 IF YMAX - YMIN > 10 THEN SY = 10: F$ = "###": GOTO 3165
3160 IF YMAX - YMIN > 1 THEN SY = 1: F$ = "##"
3165 IF (YMAX - YMIN) / SY < 6 THEN SY = SY / 2: F$ = F$ + ".#"
3170 IF (YMAX - YMIN) / SY < 6 THEN SY = SY / 2
3175 IF (YMAX - YMIN) / SY < 6 THEN SY = SY / 2
3180 YMAX = 10 * INT(YMAX / 10) + SY / 10: YMIN = 10 * INT(YMIN / 10) - SY /
        10
3185 XSCALE = 430 / (XMAX - XMIN): YSCALE = 360 / (YMAX - YMIN)
3200 SX = 10: IF XMAX - XMIN > 10000 THEN SX = 10000: GOTO 3215
3205 IF XMAX - XMIN > 1000 THEN SX = 1000: GOTO 3215
3210 IF XMAX - XMIN > 100 THEN SX = 100
3215 IF (XMAX - XMIN) / SX < 5 THEN SX = SX / 2
3220 IF (XMAX - XMIN) / SX < 5 THEN SX = SX / 2
3225 XMAX = 10 * INT(XMAX / 10) + SX / 10: XMIN = 10 * INT(XMIN / 10)
3305 PRINT #6, "newpath 1 setlinewidth "
3310 PRINT #6, "576 0 translate 90 rotate 210 120 translate "; xs; " "; ys; " scale"
3315 PRINT #6, "/Helvetica findfont 10 scalefont setfont"
3320 PRINT #6, "-5 0 moveto "
3325 FOR X = (INT(XMIN / SX)) * SX TO (INT(XMAX / SX)) * SX STEP SX * 2
3330 IF X + SX < XMIN THEN 3345 ELSE IF X < XMIN THEN 3340
3335 PRINT #6, INT((X - XMIN) * XSCALE); " 0 lineto 0 -8 rlineto -12 -10 rmoveto (";
        X; ") show "; INT((X - XMIN) * XSCALE); " 0 moveto"
3340 PRINT #6, INT((X - XMIN + SX) * XSCALE); " 0 lineto 0 -8 rlineto -12 -10
        rmoveto ("; X + SX; ") show stroke "; INT((X - XMIN + SX) * XSCALE); " 0
```

```
        moveto "
3345 NEXT X
3350 PRINT #6, "0 -5 moveto "
3355 FOR Y = (INT(YMIN / SY)) * SY TO (INT(YMAX / SY)) * SY STEP SY * 2
3360 IF Y + SY < YMIN THEN 3385 ELSE IF Y < YMIN THEN 3375
3365 PRINT #6, "0 "; INT((Y - YMIN) * YSCALE); " lineto -8 0 rlineto -35 -4 rmoveto
        (";
3370 PRINT #6, USING F$; Y; : PRINT #6, ") show 0 "; INT((Y - YMIN) * YSCALE); "
        moveto "
3375 PRINT #6, "0 "; INT((Y - YMIN + SY) * YSCALE); " lineto -8 0 rlineto -35 -4
        rmoveto (";
3380 PRINT #6, USING F$; Y + SY; : PRINT #6, ") show  stroke 0 "; INT((Y - YMIN +
        SY) * YSCALE); " moveto "
3385 NEXT Y
3390 PRINT #6, "200 -48 moveto (time/s) show"
3395 PRINT #6, "-90 180 moveto (p/mbar) show"
3405 FOR U% = 1 TO N
3410 PRINT #6, (N * .2) - .2; " setgray"
3415 PRINT #6, INT(XSCALE * (time(N, 1) - XMIN)); " "; INT(YSCALE *
        (SAMPLE(N, 1) - YMIN)); " moveto"
3420 FOR T = 1 TO C(U%)
3425 PRINT #6, INT(XSCALE * (time(U%, T) - XMIN)); " "; INT(YSCALE *
        (SAMPLE(U%, T) - YMIN)); " 2 0 360 arc fill"
3430 NEXT T
3435 PRINT #6, (N * .2) - .2; " setgray "; 450; " "; 350 - (U% - 1) * 14; " moveto "; 450; "
        "; 350 - (U% - 1) * 14; " 2 0 360 arc fill"
3440 PRINT #6, 460; " "; 346 - (U% - 1) * 14; " moveto (= "; load(U%); ") show"
3445 NEXT U%
3450 PRINT #6, "showpage": page = page + 1
3455 LOCATE 20, 14: PRINT "Do you want to produce another set of graphs (Y/N) ?"
```

```
3460 an$ = INKEY$: IF an$ = "" THEN 3460 ELSE LOCATE 20, 14: PRINT SPC(60);
3465 IF ASC(an$) = 27 THEN CLOSE #6: GOTO 3500
3470 IF NOT an$ = "Y" AND NOT an$ = "y" THEN CLOSE #6: GOTO 3500
3475 GOTO 3030
3500 LOCATE 15, 22: IF page = 1 THEN PRINT "ONE PAGE PRINTED - Any key to
        continue": GOTO 3520
3510 PRINT page; " PAGES PRINTED - Any key to continue"; ""
3520 an$ = INKEY$: IF an$ = "" THEN 3520 ELSE RETURN

4000 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
4010 COLOR 3: LOCATE 1, 32: PRINT CHR$(201); STRING$(13, 205); CHR$(187)
4020 LOCATE 2, 32: PRINT CHR$(186); " CALIBRATION "; CHR$(186): COLOR 3:
        LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
4025 LOCATE 3, 32: PRINT CHR$(200); STRING$(13, 205); CHR$(188)
4030 COLOR 1: : LOCATE 5, 25: PRINT "Channel [" + STR$(Chan%) + "]       "
4040 LOCATE 5, 38: INPUT Chan$: IF Chan$ = "" THEN 4105
4050 Chan% = VAL(Chan$): IF Chan% < 0 OR Chan% > 15 THEN LOCATE 5, 5:
        PRINT SPC(20); : GOTO 4030
4105 OUT &H703, &H92: OUT &H702, 16 * Chan% + 2
4110 COLOR 3: LOCATE 10, 7: PRINT "CONNECT THE APPARATUS TO
        VACUUM AND TYPE IN THE PRESSURE READING"
4120 COLOR 1: LOCATE 12, 25: INPUT VAL0!: RED0% = 0
4125 FOR T = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR DELAY = 0 TO 50: NEXT
        DELAY
4127 RED0% = RED0% + INP(&H700) + (INP(&H701) AND 15) * 256: OUT &H702,
        16 * Chan% + 2
4130 NEXT T: RED0% = RED0% / 5
4140 LOCATE , 22: PRINT "(ADC CONVERTER OUTPUT WAS "; RED0%; ")"
4150 COLOR 3: LOCATE 15, 5: PRINT "NOW BRING THE APPARATUS UP TO
        NORMAL PRESSURE AND TYPE IN THE PRESSURE"
```

```
4160 COLOR 1: LOCATE 17, 25: INPUT VAL1!: RED1% = 0: IF VAL1! = 0 THEN
     RETURN
4165 FOR T = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR DELAY = 0 TO 50: NEXT
     DELAY
4167 RED1% = RED1% + INP(&H700) + (INP(&H701) AND 15) * 256: OUT &H702,
     16 * Chan% + 2
4170 NEXT T: RED1% = RED1% / 5
4175 LOCATE , 22: PRINT "(ADC CONVERTER OUTPUT WAS "; RED1%; ")"
4177 IF RED1% = RE0% THEN RETURN
4180 Cala! = (VAL1! - VAL0!) / (RED1% - RED0%)
4190 Calb! = Cala! * RED1% - VAL1!
4195 LOCATE 20, 23: PRINT "GAIN = "; Cala!; "    OFFSET = "; Calb!
4200 LOCATE 22, 22: PRINT "DO YOU WANT TO SAVE THIS CALIBRATION [N]
     ?"
4210 an$ = INKEY$: IF an$ = "" THEN 4210
4220 IF an$ = "Y" OR an$ = "y" THEN 4240
4230 RETURN
4240 OPEN "O", #3, "C:\DATA\ACQ.CFG"
4250 PRINT #3, Chan%, Cala!, Calb!: CLOSE #3
4260 LOCATE 23, 20: PRINT "OK, CONFIGURATION CHANGED AND SAVED ON
     DISK"
4270 FOR X% = 0 TO 10000: NEXT X%: RETURN
5000 dir$ = "C:\DATA\"
5005 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
5010 COLOR 3: LOCATE 1, 30: PRINT CHR$(201); STRING$(17, 205); CHR$(187)
5020 LOCATE 2, 30: PRINT CHR$(186); " FILE MANAGEMENT "; CHR$(186)
5030 LOCATE 3, 30: PRINT CHR$(200); STRING$(17, 205); CHR$(188): COLOR 1
5040 LOCATE 8, 24: PRINT "1    : SHOW DATA-DIRECTORY CONTENTS"
5050 LOCATE 10, 24: PRINT "2    : RENAME A FILE"
5060 LOCATE 12, 24: PRINT "3    : DELETE A FILE"
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```
5070 LOCATE 14, 24: PRINT "4    : BACKUP DATA TO FLOPPY": COLOR 3:
        LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
5080 LOCATE 16, 24: REM PRINT "5   : "
5090 LOCATE 18, 24: REM PRINT "6   :"
5100 LOCATE 20, 22: PRINT "[ESC]  : RETURN TO MAIN MENU"
5110 an$ = INKEY$: IF an$ = "" THEN 5110
5120 IF ASC(an$) = 27 THEN RETURN
5130 IF VAL(an$) > 6 OR VAL(an$) < 1 THEN 5110
5140 ON VAL(an$) GOTO 5200, 5300, 5400, 5800
5200 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
5215 LOCATE 10, 25: PRINT "Which directory do you wish to"
5220 LOCATE 12, 25: INPUT "operate from (C:\DATA) "; D$
5225 IF D$ = "" THEN dir$ = "C:\DATA\" ELSE dir$ = D$ + "\"
5230 IF LEFT$(D$, 2) = "A:" OR LEFT$(D$, 2) = "a:" THEN d2$ = RIGHT$(D$,
        LEN(D$) - 2):    ELSE GOTO 5260
5235 SHELL "A:": SHELL "CD\" + d2$
5240 IF LEFT$(D$, 2) = "C:" OR LEFT$(D$, 2) = "c:" THEN d2$ = RIGHT$(D$,
        LEN(D$) - 2):    ELSE GOTO 5260
5245 SHELL "C:": SHELL "CD\" + d2$
5260 CLS : FILES dir$ + "*.*": LOCATE CSRLIN + 2, 25: PRINT "Any key to
        continue"
5265 an$ = INKEY$: IF an$ = "" THEN 5265
5270 GOTO 5005
5300 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B: FILES dir$ +
        "*.*"
5310 PRINT : LOCATE , 10: INPUT "Which file do you wish to rename "; N$
5315 PRINT : LOCATE , 10: INPUT "New name of file "; n2$
5320 NAME "C:\DATA\" + N$ AS "C:\DATA\" + n2$
5325 LOCATE CSRLIN + 1, 25: PRINT "Any key to continue"
5330 an$ = INKEY$: IF an$ = "" THEN 5330
```

```
5335 GOTO 5005
5400 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B: FILES dir$ +
     "*.*"
5410 LOCATE CSRLIN + 1, 10: INPUT "Which file do you wish to delete (omit .ext) ";
     N$
5420 KILL "C:\DATA\" + N$ + ".DAT"
5425 LOCATE CSRLIN + 1, 25: PRINT "Any key to continue"
5430 an$ = INKEY$: IF an$ = "" THEN 5430
5435 GOTO 5005
5800 CLS : FILES dir$ + "*.*"
5810 PRINT : LOCATE , 20: INPUT "Name of file you wish to backup "; N$
5820 IF N$ = "ALL" THEN N$ = "*"
5830 BU$ = "COPY " + dir$ + N$ + ".DAT A:": SHELL BU$
5840 GOTO 5005
5900 RETURN

6000 CLS : SHELL "C:": PRINT TAB(9); "You must type EXIT and return to ADDH2
     when finished !": SHELL: RETURN


9000 OUT &H703, &H92: OUT &H702, 16 * Chan% + 2: ON TIMER(1) GOSUB 9200
9005 CLS : LINE (6, 18)-(634, 344), 1, B: LINE (10, 22)-(630, 340), 1, B
9010 COLOR 3: LOCATE 1, 28: PRINT CHR$(201); STRING$(23, 205); CHR$(187)
9020 LOCATE 2, 28: PRINT CHR$(186); " CONTINUOUS MONITORING ";
     CHR$(186)
9030 LOCATE 3, 28: PRINT CHR$(200); STRING$(23, 205); CHR$(188): COLOR 1:
     COLOR 3: LOCATE 23, 60: PRINT CHR$(1); "  D.W.P.": COLOR 1
9040 LOCATE 8, 22: PRINT "GAIN = "; Cala!; "   OFFSET = "; Calb!
9050 LOCATE 12, 27: PRINT "PRESSURE  =":
9060 LOCATE 14, 20: PRINT "RATE OF CHANGE   ="
9070 LOCATE 18, 28: PRINT "[ESC] : RETURN TO MAIN"
```

```
9080 LOCATE 20, 28: PRINT "[SPC] : GO ON TO ACQUIRE": TIMER ON
9130 an$ = INKEY$: IF an$ = "" THEN 9130
9140 IF an$ = " " THEN TIMER OFF: GOTO 2000
9150 IF ASC(an$) = 27 THEN TIMER OFF: RETURN ELSE GOTO 9130
9200 Y = CSRLIN: X = POS(1): TEMP1 = TEMP2: TEMP2 = TEMP3: TEMP3 = 0
9210 FOR W = 1 TO 5: OUT &H702, 16 * Chan% + 3: FOR T% = 0 TO 20: NEXT T%
9220 HB% = INP(&H701): LB% = INP(&H700): OUT &H702, 16 * Chan% + 2
9230 TEMP3 = ((HB% AND 15) * 256 + LB%) * Cala! - Calb! + TEMP3: NEXT W
9240 TEMP3 = TEMP3 / 5: R = (TEMP3 - TEMP1) / 3
9245 LOCATE 14, 38: PRINT SPC(30);
9250 LOCATE 14, 41: IF R > 1 THEN PRINT "LARGE +ve": GOTO 9260:  ELSE IF R
        < -1 THEN PRINT "LARGE -ve": GOTO 9260
9255 PRINT USING "+#.##"; R; : PRINT " mbar/s        "
9260 LOCATE 12, 41: PRINT SPC(25); : LOCATE 12, 41: PRINT TEMP3; " mbar       "
9270 LOCATE Y, X: RETURN
```

```
9500 ERASE time, SAMPLE: IF N > 1 THEN 9650: REM  ****  LOAD FILES  ****
9520 LOCATE 10, 8: INPUT "Name of the file that you require "; load$
9530 load(1) = load$: IF load$ = "" THEN erfleg$ = "nf": RETURN
9535 LOCATE 10, 8: PRINT SPC(55); : erflag$ = ""
9540 OPEN "I", #1, "C:\DATA\" + load$ + ".DAT": Count = 1
9545 IF NOT erflag$ = "bfn" AND NOT erflag$ = "fnf" THEN 9620
9550 LOCATE 10, 8: PRINT SPC(50);
9560 LOCATE 10, 8: PRINT "BAD FILE NAME OR FILE NOT FOUND, TRY
        AGAIN": erflag$ = ""
9570 FOR T = 1 TO 20000: NEXT T: LOCATE 10, 5: PRINT SPC(50); : GOTO 9520
9620 INPUT #1, time(1, Count), SAMPLE(1, Count): IF erflag$ = "de" THEN 9650
9630 IF EOF(1) THEN CLOSE #1: C(1) = Count: RETURN
9640 Count = Count + 1: GOTO 9620
9650 T% = 1:
```

```
9655 Count = 1: LOCATE 10, 8: PRINT SPC(55);
9660 LOCATE 10, 8: INPUT "Name of the file that you require "; load(N)
9670 OPEN "I", #1, "C:\DATA\" + load(N) + ".DAT": Count = 1
9680 IF errflag$ = "fnf" THEN N = T% - 1: RETURN
9690 INPUT #1, time(1, Count), SAMPLE(1, Count): IF erflag$ = "de" THEN N = T% -
        1: RETURN
9700 IF EOF(1) THEN CLOSE #1: C(T%) = Count: T% = T% + 1: IF T% = N + 1 THEN
        RETURN:  ELSE 9655
9710 Count = Count + 1: GOTO 9690
9850 erflag$ = "": CLOSE #1: LOCATE 10, 5: PRINT "THERE HAS BEEN AN ERROR
        (IN LINE "; Count; " ) IN READING IN THIS FILE"
9860 PRINT "          PLEASE CHECK THE FILE WITH AN ASCII EDITOR FOR
        OUTSIDE ADDH2"
9870 FOR T = 1 TO 20000: NEXT: RETURN


10000 WIW% = ERR: REM **** ERROR HANDLING ****
10010 TIMER OFF
10020 IF WIW% = 6 THEN PRINT "Numbers Too BIG, sorry !": FOR DELAY = 0 TO
        2000: NEXT DELAY: RESUME 110
10100 IF WIW% = 64 THEN erflag$ = "bfn": RESUME NEXT
10200 IF WIW% = 70 THEN PRINT "Access Denied :-  File Locked": FOR DELAY = 0
        TO 2000: NEXT DELAY: RESUME 110
10300 IF WIW% = 55 THEN PRINT "THAT FILE IS ALREADY OPEN":
10310 IF WIW% = 53 THEN erflag$ = "fnf": RESUME NEXT
10320 IF WIW% = 62 THEN erflag$ = "de": RESUME NEXT
10400 IF WIW% = 58 THEN PRINT "File already exists I'm affraid, sorry !": FOR
        DELAY = 0 TO 2000: NEXT DELAY: RESUME 110
10500 IF WIW% = 72 THEN erflag$ = "dnid": RESUME NEXT
10600 CLS
10610 LOCATE 10, 3: PRINT "AN ERROR OCURRED ("; ERR; ") IN LINE ("; ERL; ")
```

```
        BUT THERE IS NO ERROR TRAPING "
10620 PRINT "       FOR THIS, SUGGEST YOU CONSULT THE SOURCE CODE
        OR RING ME "
10630 PRINT "                    D.W.PRICE (1991) ": BEEP: BEEP: BEEP: FOR T = 1
        TO 2000: NEXT: RESUME 110
```

APPENDIX C

Derivation of the Rate of Hydrogenation in $moll^{-1}s^{-1}$

$$pV = nRT$$

so - $\Delta p_A V_A = \Delta nRT$

and rearranging - $\Delta p_A = \Delta nRT / V_A$

by definition - $\rho_p = \Delta p_A / \Delta t$

and - $\rho_n = \Delta n / \Delta t$

so - $\rho_p = \Delta nRT / V_A \Delta t$

using - $\rho_c = \rho_n / V_s$ it follows - $\rho_c = \rho_p \ V_A / V_s RT$

p_A = hydrogen pressure in apparatus

V_A = volume of apparatus

t = time

ρ_x = rate of hydrogenation in units of x

V_s = volume of solvent

APPENDIX D

Computer Program used to Generate Files for Modelling

MAKEITR.BAS - Written under Microsoft QuickBASIC™

```
0 ON ERROR GOTO 1100
10 DIM SAMPLE(1, 3000) AS SINGLE, time(1, 3000) AS SINGLE: N = 0
20 SCREEN 9: COLOR 15, 1: : LINE (4, 346)-(636, 4), 15, B: LINE (8, 342)-(632, 8), 15,
        B
30 LOCATE 1, 34: PRINT " MAKEITR "
40 GOSUB 1000
50 LOCATE 10, 5: INPUT "Name of output file (return for same with .itr) "; n2$
60 LOCATE 10, 5: PRINT SPC(59); : REM  GOTO 6625
70 IF n2$ = "" THEN n2$ = LEFT$(load$, LEN(load$) - 4)

80 LOCATE 10, 5: INPUT "Number of mili-moles of SUBSTRATE "; M: LOCATE 10,
        5: PRINT SPC(59);
90 LOCATE 10, 5: INPUT "Number of micro-moles of  catalyst ";
        cat: LOCATE 10, 5: PRINT SPC(59);
100 LOCATE 10, 5: INPUT "Small loop used [Y] ?"; an$: LOCATE 10, 5: PRINT
        SPC(59);
110 IF an$ = "y" OR an$ = "Y" THEN Vapp = 16.79:       ELSE Vapp = 103.3

120 cat = cat / 1000:       REM **** Convert cat conc to mol ****

130 LOCATE 10, 5: INPUT "Temperature experiment conducted at (degree C) "; t:
```

```
        LOCATE 10, 5: PRINT SPC(70);
140 LOCATE 10, 5: INPUT "Solvent (D=DCE, M=MeOH) "; SOLV$: LOCATE 10, 5:
        PRINT SPC(59);
150 IF SOLV$ = "D" OR SOLV$ = "d" THEN Ps = 10 ^ (7.1628 - 1278.323 / (t +
        223.694)): GOTO 180
160 IF SOLV$ = "M" OR SOLV$ = "m" THEN Ps = 10 ^ (8.2303 - 1595.61 / (t +
        240.905)): GOTO 180

170 GOTO 140: REM **** Wrong letter entered ****

180 DropPress = ((t + 273) * M * 83.1402) / Vapp
190 FinalPress = SAMPLE(1, Count): InitPress = SAMPLE(1, 1)
200 ExInitPress = DropPress + FinalPress: IC = M * (ExInitPress - InitPress) / DropPress
210 FOR Q = 1 TO Count
220 SAMPLE(1, Q) = ((ExInitPress - SAMPLE(1, Q)) * M) / DropPress
230 NEXT Q
240 G = 1000 * ((InitPress - Ps) / 1013.25) * Vapp / ((t + 273.15) * 82.053): REM R in
        atm K-1 cm3
250 TMAX = 100 + (INT(time(1, Count) / 100)) * 100
260 OPEN "O", #5, "C:\DATA\" + n2$ + ".ITR"
270 PRINT #5, USING "######"; TMAX
280 PRINT #5, USING ".###^^^^_ _ "; G; 0; cat; M - IC; 0; IC
290 IF time(1, 1) = 0 THEN P = 2 ELSE P = 1
300 FOR Q = P TO Count
310 PRINT #5, time(1, Q), SAMPLE(1, Q)
320 NEXT Q
330 CLOSE #5
340 LOCATE 10, 5: PRINT "FINISHED !"
350 FOR t = 1 TO 5000: NEXT t
```

```
400 LOCATE 10, 5: PRINT SPC(59);
410 LOCATE 10, 5: PRINT "MAKE ANOTHER ITR FILE ?"
420 an$ = INKEY$: IF an$ = "" THEN 420 ELSE LOCATE 10, 5: PRINT SPC(59);
430 IF an$ <> "y" AND an$ <> "Y" THEN CLS : SYSTEM
440 LOCATE 17 + N, 60: PRINT load$
450 N = N + 1: GOTO 20

1000 REM *** LOAD DATA ***
1010 Count = 1: ERASE time, SAMPLE
1020 LOCATE 10, 10: INPUT "Name of data set to be processed (+ .ext) "; load$:
        LOCATE 10, 10: PRINT SPC(59);
1030 OPEN "I", #1, "C:\DATA\" + load$: REM  "A:\" + load$
1040 IF erflag$ = "fnf" THEN erflag$ = "": LOCATE 20, 20: PRINT "FILE NOT
        FOUND": GOTO 1020
1050 INPUT #1, time(1, Count), SAMPLE(1, Count)
1060 IF EOF(1) THEN CLOSE #1: GOTO 1080
1070 Count = Count + 1: GOTO 1050
1080 LOCATE 20, 20: PRINT SPC(49); : RETURN

1100 IF ERR = 53 THEN erflag$ = "fnf": RESUME
1110 PRINT "AN ERROR HAS OCCURED IN LINE "; ERL; ", TERMINATING"
        :STOP
```

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