Enantioselective Reactions of Some Optically Active Phosphines

by

G. F. Jay

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STATEMENT

The work described in this thesis was carried out by the author in the Organic Chemistry Research Laboratory of the Department of Chemistry, Leicester University, during the period October 1979 to October 1982.

All work recorded herein is original unless otherwise acknowledged in the text or by references.

No part of this thesis is concurrently being submitted for another degree in this or any other University.

Date: 16-6-87 ..... Signed: G F Jay .....

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LIST OF ABBREVIATIONS AND SYMBOLS

i.r = Infrared Spectroscopy
n.m.r. = Nuclear Magnetic Resonance Spectroscopy
g.l.c. = Gas-Liquid Chromatography
t.l.c. = Thin-Layer Chromatography
^{1}H n.m.r. = n.m.r. Studying the Hydrogen 1 isotope
^{31}P n.m.r. = n.m.r. Studying the Phosphorus 31 isotope
M.p. = Melting Point
m/z = Mass Divided by Charge
g = grams
p.p.m. = Parts per Million
Hz = Hertz
MHz = Mega Hertz
s = Singlet
d = Doublet
t = Triplet
q = Quartet
m = Multiplet
h = Hours
Min = Minutes
°C = Degrees Centigrade
mmHg = Pressure Measured in Millimeters of Mercury
p.s.i. = Pounds per Square Inch
Rf = Distance travelled by component divided by distance travelled by solvent on the t.l.c. plate
Rt = Time substance retained on g.l.c. Column measured from point of injection
%ee = Percentage Enantiomeric Excess
%op = Percentage Optically Pure
B.p. = Boiling Point
Me = Methyl
Et = Ethyl
Pr = Propyl
Bu = Butyl
Ph = Phenyl
THF = Tetrahydrofuran
$Eu(hfbc)_3$ = Europium Tris[D-3-Heptafluorobutylcamphorate]
$Eu(tfc)_3$ = Europium Tris[3-(trifluoromethylhydroxymethylene)-d-Camphorate]
$Eu(DPM)_3$ = Tris(dipivalomethanato)europium III

INTRODUCTION

INTRODUCTION

The object of this study was to explore the enantioselective reactions of optically active phosphine/carbon tetrachloride reagents, with a view to their possible use in the synthesis of optically active compounds.

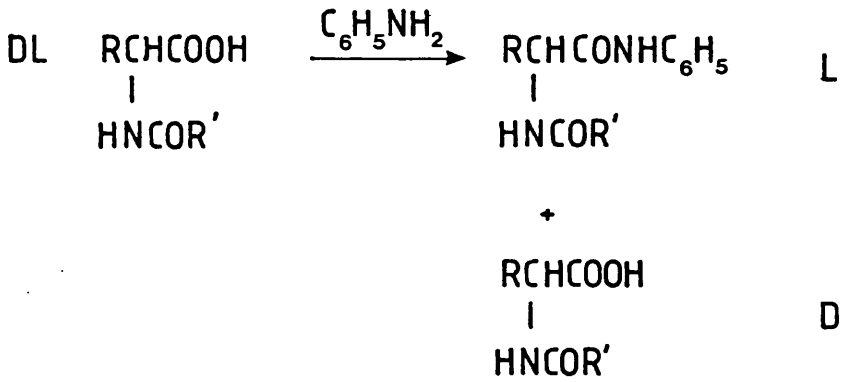
Enantioselective chlorination of alcohols with (-) menthyldiphenylphosphine [1]/carbon tetrachloride,[1] was the first example of the use of this type of reagent. (-) Menthyldiphenylphosphine [1] gave good yields of optically active alkyl chlorides of rather low optical purity;[1] however the chlorides racemised to a significant extent during the purification procedures used. The enantioselectivity of this reaction arises from a kinetic resolution which occurs between the excess chiral but racemic alcohol used, and a reactive intermediate of the reagent.[1] Chlorination of alcohols and other enantioselective reactions of optically active phosphine reagents were studied.

In the synthesis of optically active compounds, kinetic resolution has generally been regarded as a poor method compared with asymmetric synthesis. Kinetic resolution techniques suffer the obvious disadvantage that at least half the starting material is lost, and quite frequently the compounds produced are of low optical purity.

Enzymatic kinetic resolutions however, are an outstanding exception. They display excellent enantioselectivity for a wide range of compounds, while at the same time being extremely powerful and efficient catalysts. Pasteur[2,3] subjected the diammonium salt of (±) tartaric acid to fermenting yeast, and found that the originally optically inactive material, develops a 'left handed' rotation which gradually increases during the course of the fermentation to a maximum value. At this

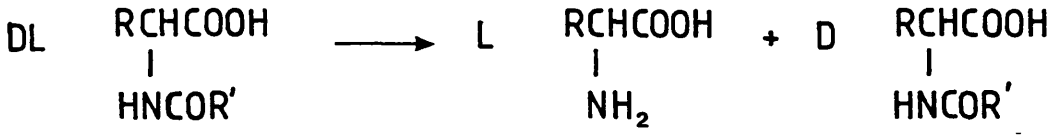
point the fermentation was stopped, and pure 'left handed' diammonium tartrate was obtained. The action of the yeast enzymes was responsible for the enantioselectivity displayed. Ehrlich used fermenting yeast to resolve a number of amino acids such as alanine,[4] alloisoleucine,[5] serine,[6] and histidine.[7] In each case the L enantiomer was decarboxylated but the D enantiomer was left unchanged in solution.[3] The decarboxylation of the L enantiomers to the amines was a result of the action of the yeast decarboxylase.[3]

More recently, purified enzyme preparations have been used to resolve large amounts of amino acids.[8] Papain is used to catalyse the synthesis of a peptide bond,[9] usually with aniline. The amine group of the amino acid is protected with an acyl group, and the enzyme catalyses the enantiomer differentiating amidation of the protected L amino acid, the D amino acid being left unchanged in solution (Scheme 1).



SCHEME 1

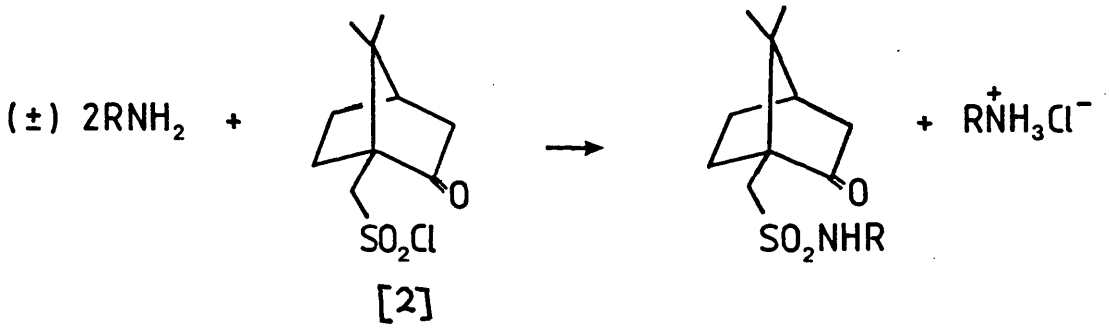
Another enzymatic enantioselective reaction is illustrated by hog kidney acylase. This has been used to selectively hydrolyse L acylaminoacids,[10] (Scheme 2).



SCHEME 2

Attempts to mimic enzymes in their enantioselective reactions have generally been unsuccessful, the optical purity of the products tending to be only low to moderate.

Read and Storey[11] discovered that (+) camphor-10-sulphonyl chloride [2] effects some degree of kinetic resolution with menthylamine, isomenthylamine and neomenthylamine. Using a 2:1 ratio of racemic menthylamine to (+) camphor-10-sulphonyl chloride [2] allows only half the menthylamine to react. The excess menthylamine was recovered and had approximately twice as much (+) isomer as the (-) isomer, (Scheme 3).

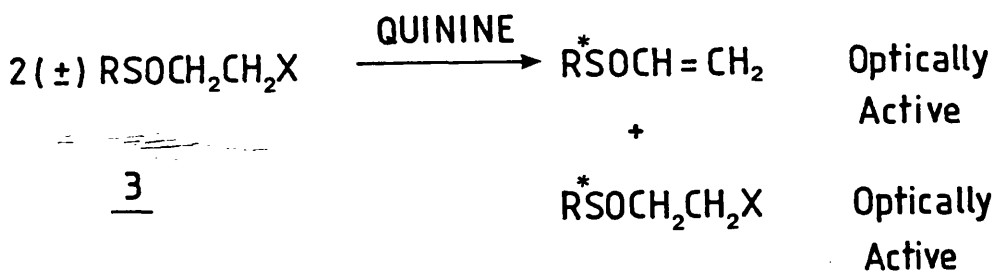


SCHEME 3

When other primary amines were used,[12] the results were not nearly as good. The best result was with α-(β-naphthyl)ethylamine with an optical purity of only 3%. Other workers[13] showed that the kinetic resolution was the result of reaction between the amine and the sulphene

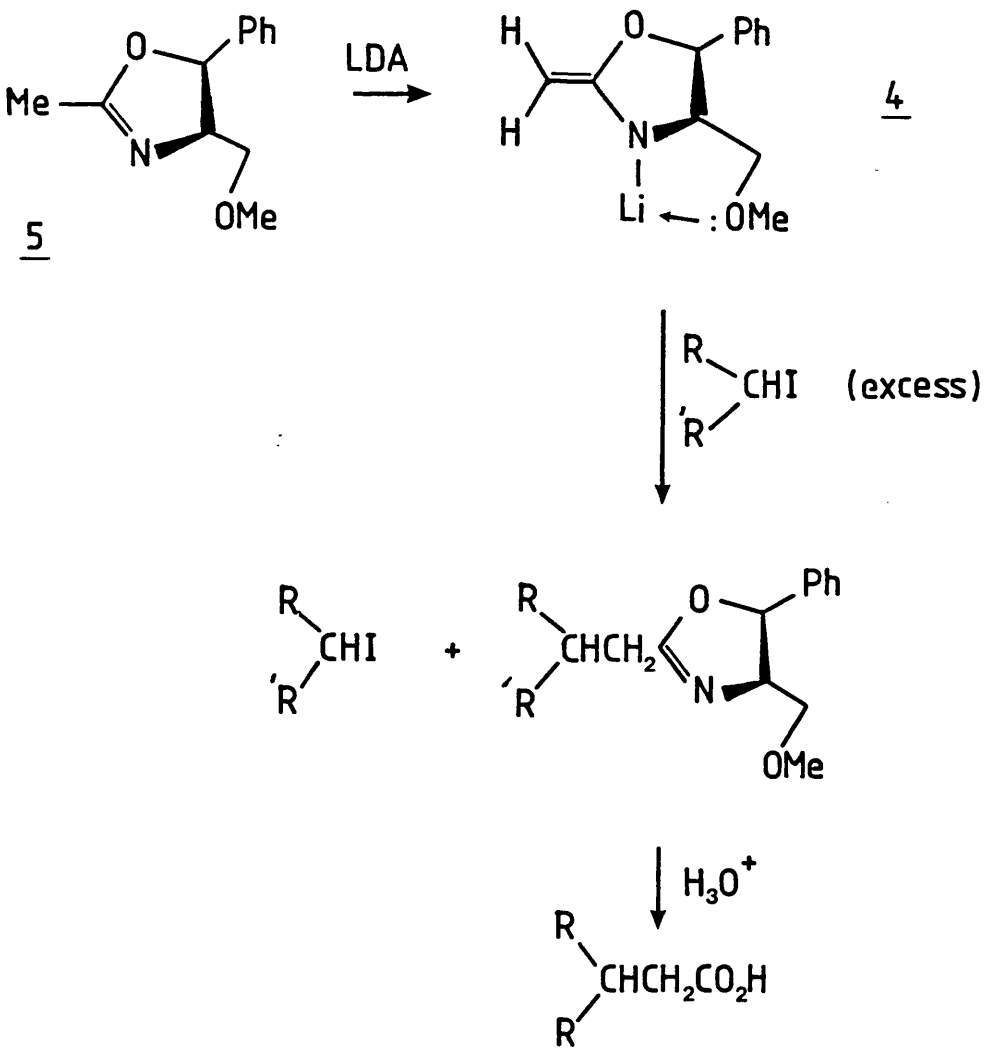
derived from [2] and not between the two starting materials as was first thought.[11,12] Direct attack of the amine on the sulphonylchloride [2] does take place, but this route apparently only accounts for approximately 10% of the product.[13] A kinetic resolution does not take place in the direct attack route, and so any product made in this way does not contribute to the enantiomeric enrichment of the unreacted amine.[13]

Naso[14] has reported a novel route to partially resolved sulphoxides from chiral but racemic β-halogenoethylarylsulphoxides [3] and optically active bases such as quinine. This involves elimination of a molecule of hydrogenhalide faster from one enantiomer than the other. The optical purity of the products tended to be rather low. They ranged from 7.5% to 24.3% optically pure (Scheme 4).



SCHEME 4

A kinetic resolution of secondary alkyl halides with simultaneous asymmetric synthesis of 3-alkylalkanoic acids has been reported by Meyers.[15] An optically active lithiooxazoline [4] is reacted with an excess of a chiral but racemic alkyl halide, the alkylated oxazoline is hydrolysed to give the acid and the excess halide is recovered with an enantiomeric enrichment (Scheme 5). When the oxazoline [5] has both of its chiral centres of the S configuration, the acid and

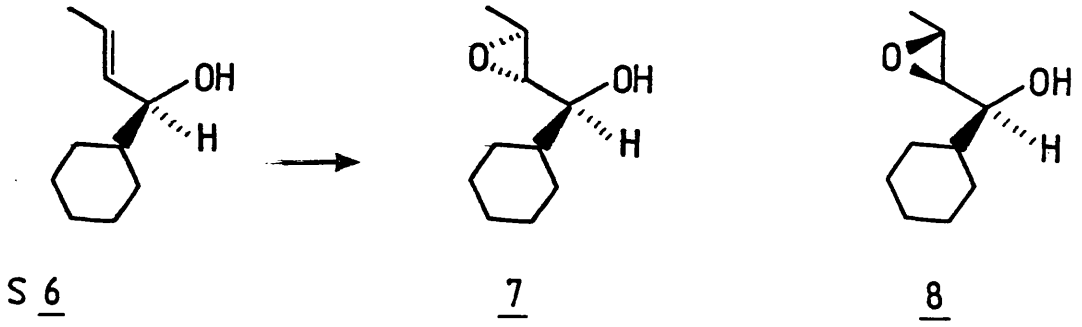


SCHEME 5

the unreacted halide have enantiomeric enrichment of the R configuration.[15] In Scheme 5 when R=Me and R=nBu the optical purity of the acid obtained was 47% and the optical purity of the recovered unreacted iodide was 49%

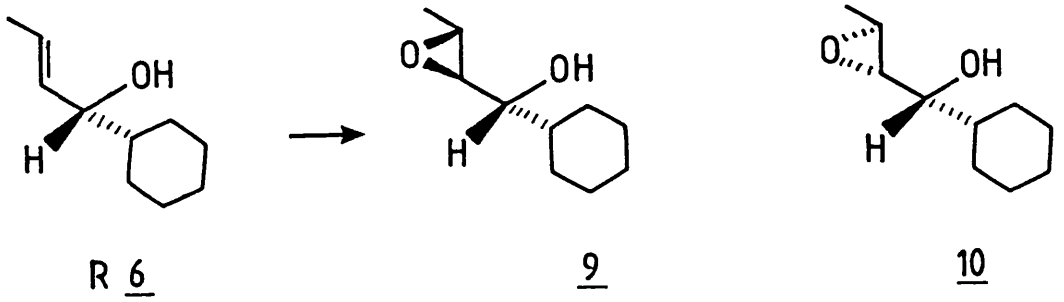
An example of a kinetic resolution with enantioselectivity approaching that displayed by enzymes has been recently reported. Sharpless,[16] showed that a titanium alkoxide tartrate epoxidation catalyst can react with racemic allylic alcohols to yield epoxy alcohols with high enantioselectivity and, moreover, high selectivity for the

erythro epoxide.[17,18] The recovered excess unreacted allylic alcohols had exceptionally high optical purities which are unprecedented in the literature for non enzymatic kinetic resolutions. In for example, the epoxidation of (±)-(E)-cyclohexylpropenylcarbinol [6] with a L-(+)-diisopropyl tartrate catalyst, the S enantiomer of [6] is the faster reacting enantiomer and reacts to give the erythro [7] and threo [8] epoxides in the ratio of 98:2 (Scheme 6). In comparison, the R



SCHEME 6

enantiomer is slower reacting and gives an erythro [9] to threo [10] epoxide ratio of 38:62 (Scheme 7). The threo/erythro ratio for both



SCHEME 7

enantiomers was obtained from the reactions of enantiomerically pure [6]. The relative rate of reaction of the two enantiomers of [6] in this case[16] was found to be Ks/Kr = 104. When racemic [6] is reacted

with the (+)-diisopropyl tartrate catalyst and only 0.6 mole equivalents of peroxide, a kinetic resolution takes place. The unreacted excess [6] recovered from the reaction mixture after 52% conversion had taken place, had the R configuration and had an enantiomeric excess of at least 96%; in addition the erythro epoxy alcohol [7] was obtained in 49% yield with an enantiomeric excess of the S enantiomer of at least 96%. Four other examples of allylic alcohols which had been prepared in this way each had enantiomeric excess values of at least 96%, three more cases had enantiomeric excess values of 80-91%. This work is significant because of the unusually high enantioselectivity of this catalysed reaction.

Kinetic resolution methods have found limited application in the determination of the absolute configuration of alcohols[19,20,21] and amines.[22] This use arises from the fact that one particular enantiomer of an alcohol or amine generally reacts faster with some optically active substrate. Hence the absolute configuration of the faster reacting enantiomer can be determined.

CHAPTER 1

The Chlorination of Alcohols

CHLORINATION OF ALCOHOLS

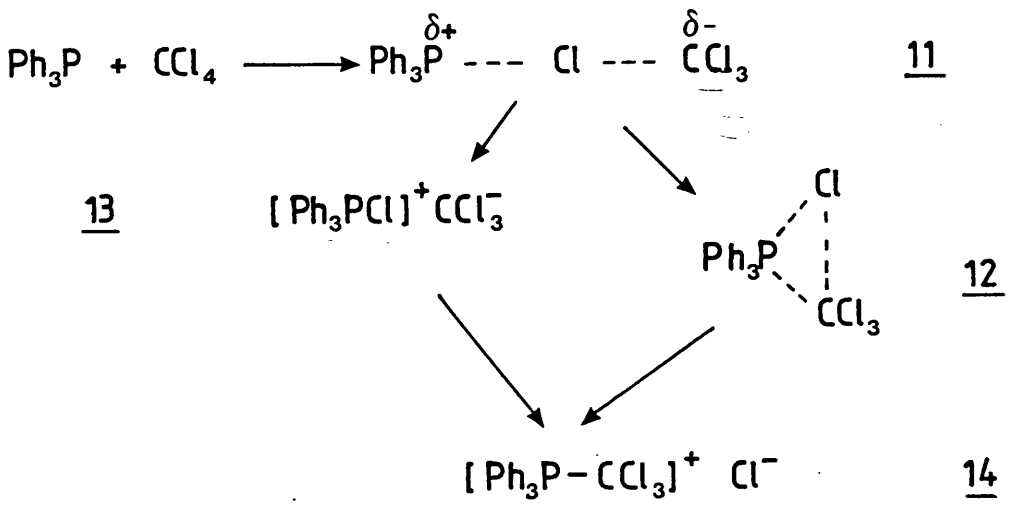
1.1 Introduction

The fact that carbon tetrachloride reacts with trivalent phosphorus compounds has been known for a long time.[23,24] However, until relatively recently,[25-27] the potential of phosphine/carbon tetrachloride reagents in organic synthesis had not been realised. These reagents are gradually finding more applications as chlorinating or dehydration agents,[27] which under very mild conditions give clean reaction products. Triphenylphosphine/carbon tetrachloride mixtures are the most widely known and used reagent of this type,[27] and as a result of this, the mechanism of the reactions of this reagent have been investigated in some depth.

1.2 The Mechanism of the Reaction Between Triphenylphosphine and Carbon Tetrachloride

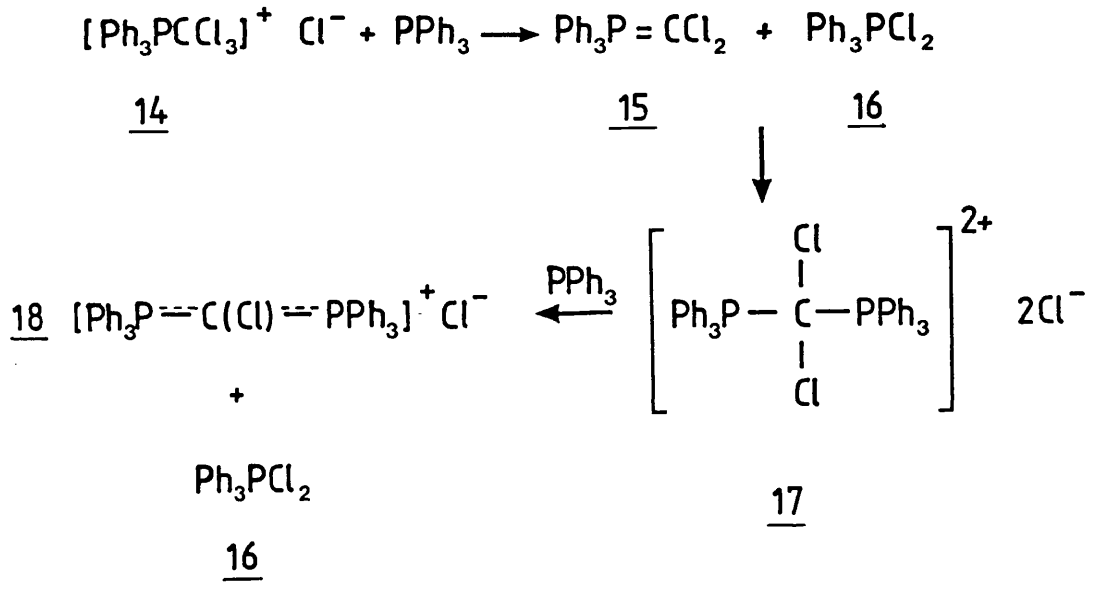
Triphenylphosphine reacts with carbon tetrachloride *via* an ionic route.[28] The polarising action of the triphenylphosphine on the symmetrical but easily polarisable carbon tetrachloride, causes a carbon chlorine bond to break,[27] (Scheme 8). For triphenylphosphine, the charge transfer in the dipolar associate [11] is not thought to be very pronounced and the reaction seems to go mainly through [12] to the ion pair [14],[29,30] rather than *via* the ion pair [13], which has not been detected in this system.

The phosphonium chloride [14] has, however, been isolated from triphenylphosphine/carbon tetrachloride mixtures,[29,31] but it is regarded as a highly reactive short-lived intermediate that reacts rapidly with more triphenylphosphine[27] in accordance with Scheme 9 to give eventually chlorotriphenylphosphonium chloride [16] and the phosphonium salt [18].



SCHEME 8

The overall reaction goes via [15] which reacts with more triphenylphosphine under the autocatalytic influence of [16][32-34] to give the intermediate [17]. The latter then reacts with further triphenylphosphine to give the stable phosphonium chloride end products [16] and [18].[27] The existence of the intermediate bisphosphonium cation [17] was demonstrated by conversion into the corresponding hexachloroantimonate salt.[33]



SCHEME 9

The rate of reaction is very dependent on the solvent used.[29] It is fastest in acetonitrile and slowest in excess carbon tetrachloride.[29] This is thought to be consistent with the charge separation step being the rate limiting process.[27,29] The solvation properties of the solvent used would be expected to have a great effect on the charge separation step, and so this appears to be a reasonable assumption.

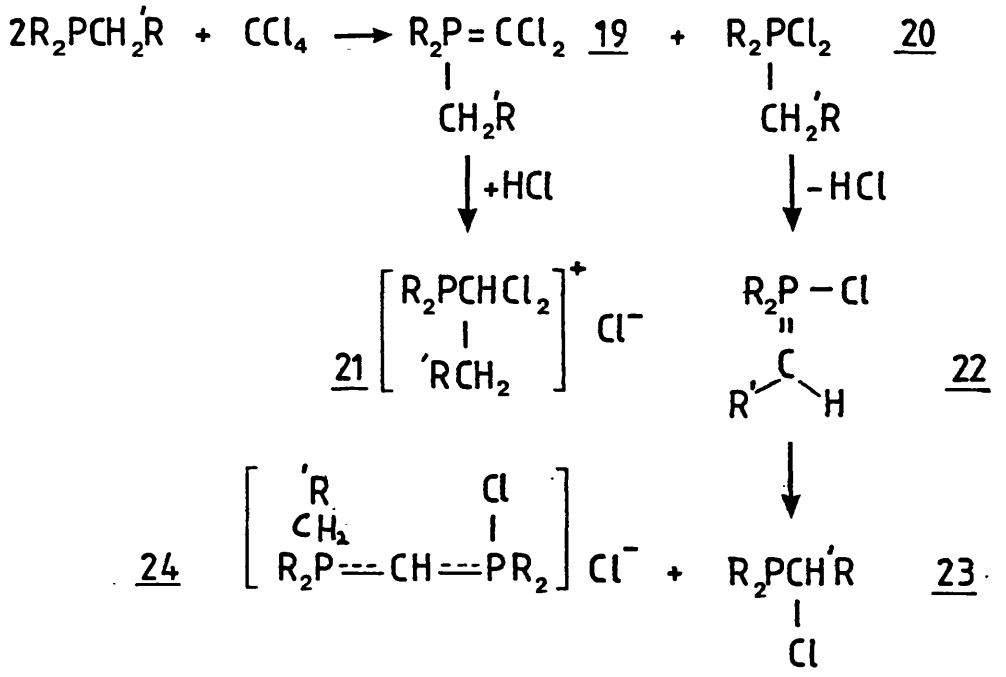
In apolar inert solvents such as benzene, the first step of the mechanism shown in Scheme 9 appears to be reversible.[34] It has also been suggested that the phosphonium chloride [14] may decompose to give triphenylphosphine and carbon tetrachloride.[27]

1.3 The Mechanism of the Reaction Between Trialkylphosphines Dialkylphenylphosphines and Alkyldiphenylphosphines and Carbon Tetrachloride

The reactions of a range of trialkylphosphines,[27,35] dialkylphenylphosphines[27,36] and alkyldiphenylphosphines,[36] with carbon tetrachloride have been studied. In certain solvents such as acetonitrile and dichloromethane under dilute conditions, these phosphines react in a similar manner to triphenylphosphine and yield the appropriate chlorophosphonium chloride [20] and phosphonium chloride [21]. This latter salt [21] is formed[27] by abstraction of a proton by [19] from the solvent.

All the phosphines in question have at least one α-hydrogen atom. In the chlorophosphonium chloride [20] this can be removed and the ylide effects hydrogen chloride transfer to give [22] which can then react further to give either [23] or [24] or, in some cases, both,[27,36] (Scheme 10). Apparently [23] and [24] are only formed in solvents such as ether and toluene and not in acetonitrile or dichloromethane.[27,36-38]

Section 2.7 contains a more detailed discussion of the mechanism of



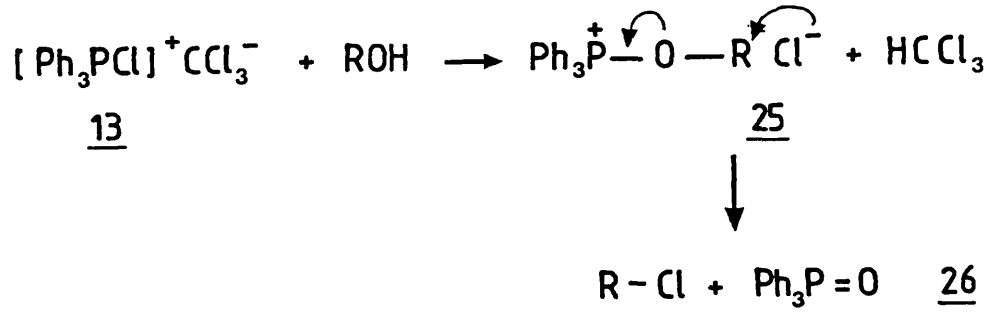
SCHEME 10

the reaction between an alkyldiphenylphosphine and carbon tetrachloride. Also covered in Section 2.7 is the probable mechanism of reaction of the optically active phosphines used in this thesis.

1.4 The Mechanism of the Reaction Between Triphenylphosphine Carbon Tetrachloride and an Alkyl Alcohol

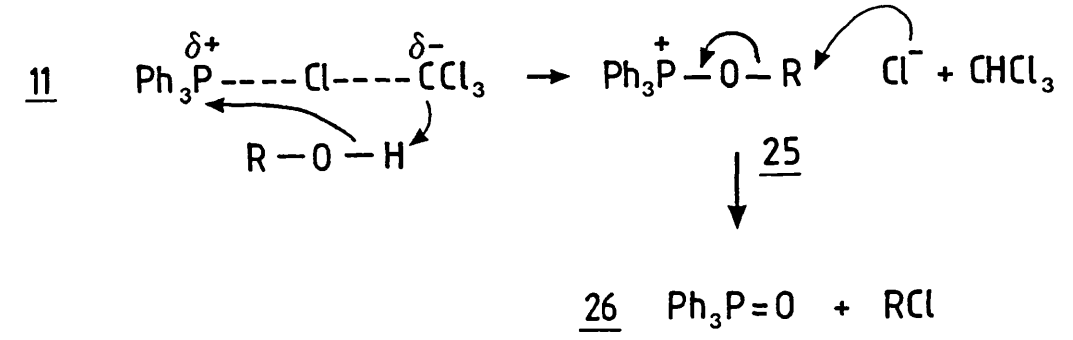
In preparatively useful reactions of triphenylphosphine/carbon tetrachloride, the reagent is treated with a 'proton active' substrate to effect chlorination or dehydration reactions.[27] In this case, the alcohol is the 'proton active' substrate and the product is a chloride. Early workers in the field[39,40] thought that species [13] was responsible for the chlorination and this rationalised the chloroform detected in the reaction mixtures (Scheme 11).

Kinetic studies,[29,30] indicate that in fact more than one mechanism is operating in this complex mixture. This is supported by the appearance of large amounts of (chloromethyl)triphenylphosphonium chloride



SCHEME 11

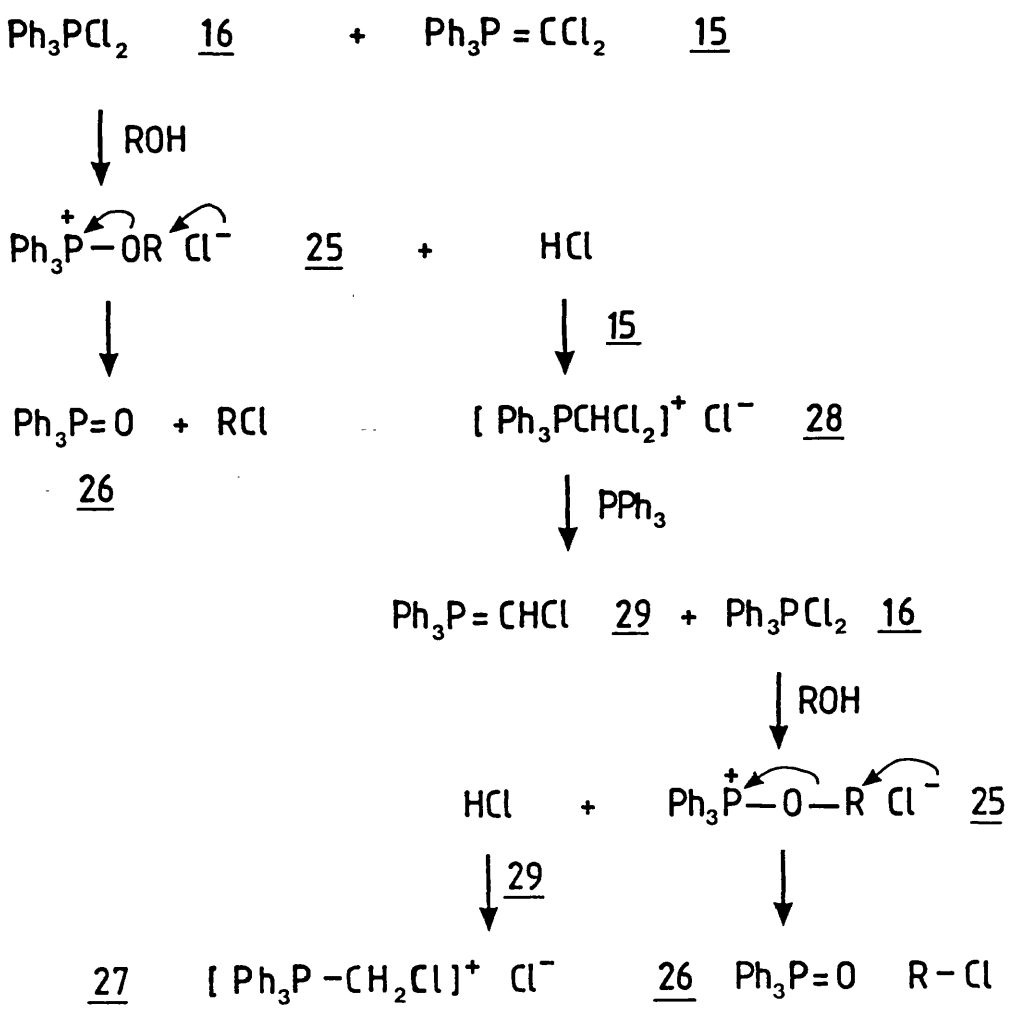
[27] in most preparative reactions of triphenylphosphine/carbon tetrachloride reagents.[27] This could not be explained by the mechanism shown in Scheme 11. Recent work[41] based on the quantity of carbon tetrachloride consumed during the reaction, has shown that less than 5% of the expected amount of chloroform for total reaction via Scheme 11, was actually produced. In addition, no evidence for the existence of chlorotriphenylphosphonium trichloromethanide [13] in triphenylphosphine/carbon tetrachloride mixtures could be found. This led to the suggestion[27] that the chloroform might be made by reacting the proton active substrate with the dipolar associate [11], (Scheme 12).



SCHEME 12

The majority of the reaction, however, is thought to go *via* species [16].[27] When [16] has been independently made by reaction of triphenyl-

phosphine with chlorine, the reactions with various nucleophiles have yielded the same end products as the triphenylphosphine/carbon tetrachloride reagent.[42] Scheme 13 shows the proposed mechanism of reaction of [16] with an alcohol. Species [15] and [16] are produced as shown in Scheme 8 and the first step of Scheme 9. The main advantage of the mechanism shown in Scheme 13 is that it can account for the formation of [27] and it does explain the observed stoichiometry of the reaction, (Equation 1). Most of the intermediates in Scheme 13 are known to be present in triphenylphosphine/carbon tetrachloride mixtures or have precedent in the literature.[27]



SCHEME 13

$$3Ph_3P + CCl_4 + 2ROH \longrightarrow \underset{\underline{26}}{2Ph_3P{=}O} + 2R{-}Cl + \underset{\underline{27}}{[Ph_3PCH_2Cl]^+\ Cl^-}$$

EQUATION 1

The reaction mechanism overall is extremely complex. It remains to be proved whether Scheme 11 or Scheme 12 accounts for the relatively small amount of chloroform produced in these reactions, if indeed either of the two schemes provides the answer. What is certain is that the dominant pathway is that shown in Scheme 13 and any other pathway plays only an insignificant role in the overall mechanism.

In Schemes 11, 12 and 13 the reaction goes via species [25]. This will decompose via a rapid Arbusov rearrangement to give the alkyl chloride and triphenylphosphine oxide [26]. When hexamethyl phosphorus triamide is used in place of triphenylphosphine, the analogue of [25] may be isolated as a stable salt [31].[26,43] If this salt [31] is then treated with a nucleophile, the alkyl derivative of the nucleophile is obtained[44] (Scheme 14).

$$\underset{\underline{30}}{[(Me_2N)_3P{-}O{-}R]^+\ Cl^-} \xrightarrow{NaBF_4} \underset{\underline{31}}{[(Me_2N)_3P{-}O{-}R]^+\ BF_4^-}$$

$$\downarrow NaCN$$

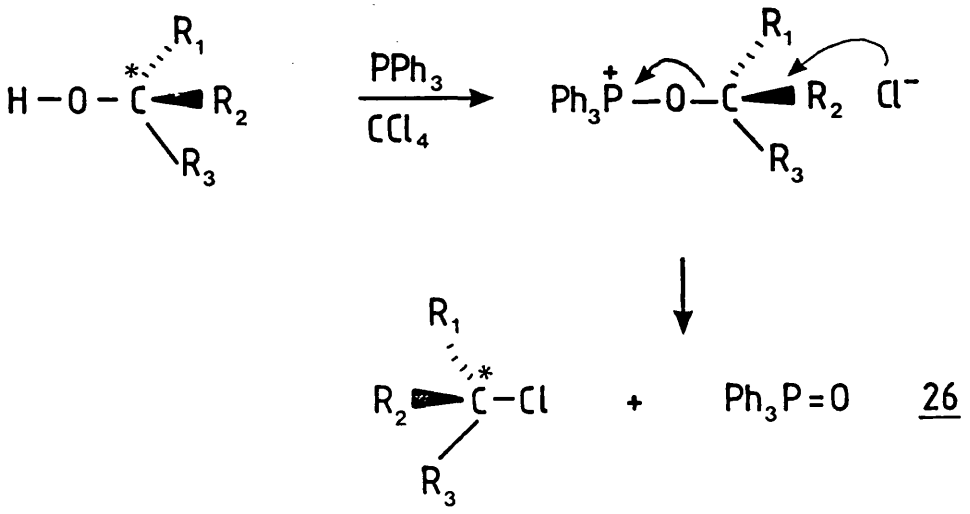
$$(Me_2N)_3P{=}O + RCN + NaBF_4$$

SCHEME 14

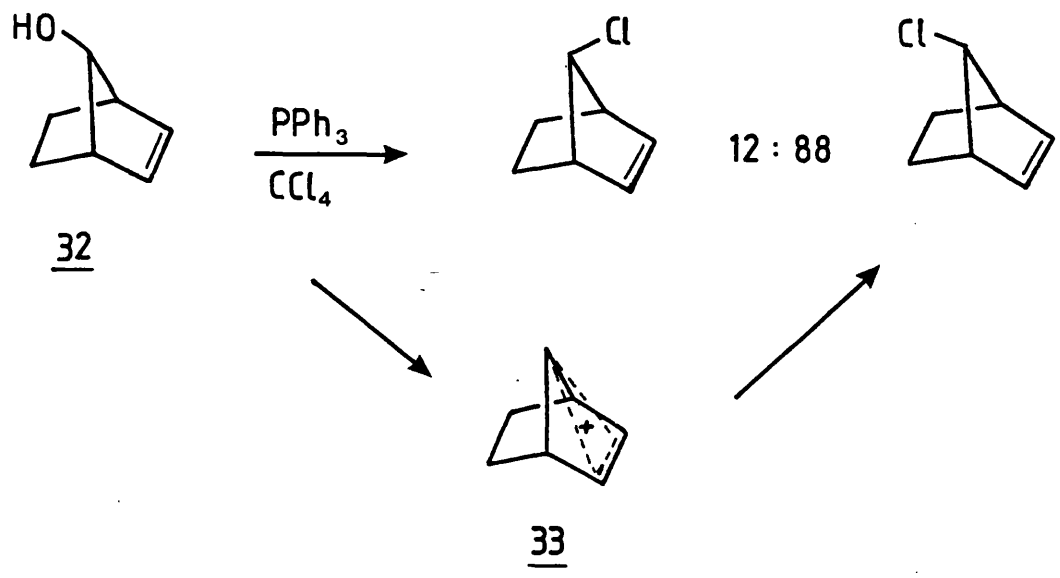
Studies on the reaction of triphenylphosphine/carbon tetrachloride with optically active alcohols have shown that the reaction goes with inversion of configuration with no observable racemisation.[38,45-48] One example of total retention of configuration has been reported[49] but more evidence is required to prove that retention, and not inversion, of configuration is occurring in this case.

Detailed studies[46,47] have shown that the carbon atom C* in Scheme 15 has little or no cationic character at any stage of the reaction under normal circumstances. This was shown by the fact that skeletal rearrangements of the alkyl group containing C* are rare, even when the system favours rearrangement.[46] Where the carbonium ion had exceptional stabilisation, the products from reaction via the carbonium ion could be seen.[46] One example of this is shown in Scheme 16. The fact that the normal inversion route can compete with the energetically more favourable carbonium ion route (which results in retention of configuration) is remarkable.

When the reaction is carried out with the analogue of [32] without the double bond, total inversion of configuration is observed.[47] This



SCHEME 15

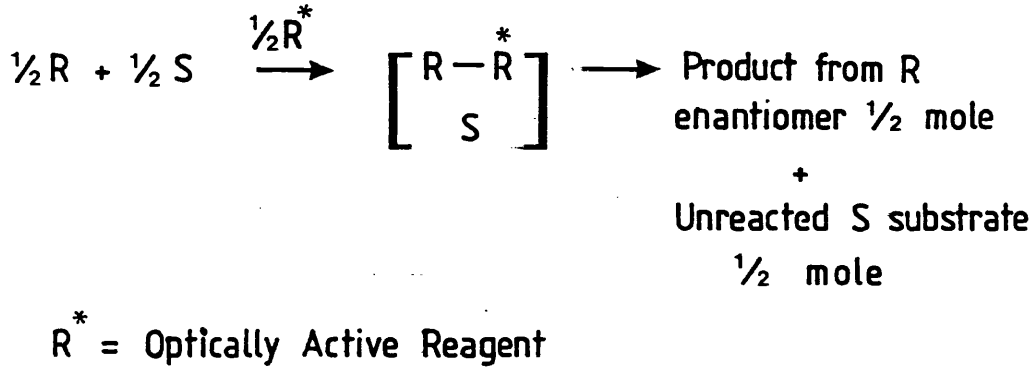


SCHEME 16

was determined by deuterium labelling experiments and illustrates the effect of the stable carbonium ion [33] in Scheme 16.

1.5 Kinetic Resolution

The rates of reaction of the two enantiomers of a racemic substrate with an optically active reagent will be different.[50] It is quite possible that the difference in the rates of reaction may be so small that it is experimentally insignificant. If the difference in the rates is significant, and a limited amount of optically active reagent is used or the reaction is quenched before it has gone to completion, the reaction mixture will consist of a product enriched in the more reactive enantiomer, and unreacted starting material enriched in the less reactive enantiomer. In the ideal case, the difference in the rates of reaction of the two enantiomers with an optically active reagent R* would be so large that only one enantiomer would react. Scheme 17 shows this for the case when the R enantiomer reacts and the S enantiomer does not. Usually this degree of selectivity is



SCHEME 17

only approached by enzyme systems.[50,51]

Figure 1 shows the case where the S enantiomer of a racemic substrate reacts faster than the R enantiomer with an optically active reagent.[51] The optically active reagent is in excess and so all the racemic substrate can react. From Figure 1 it can clearly be seen that the extent of differentiation between the two enantiomers varies with time. At the end point of the reaction there is no differentiation and there is a point at which the extent of differentiation is at a maximum (Figure 1).

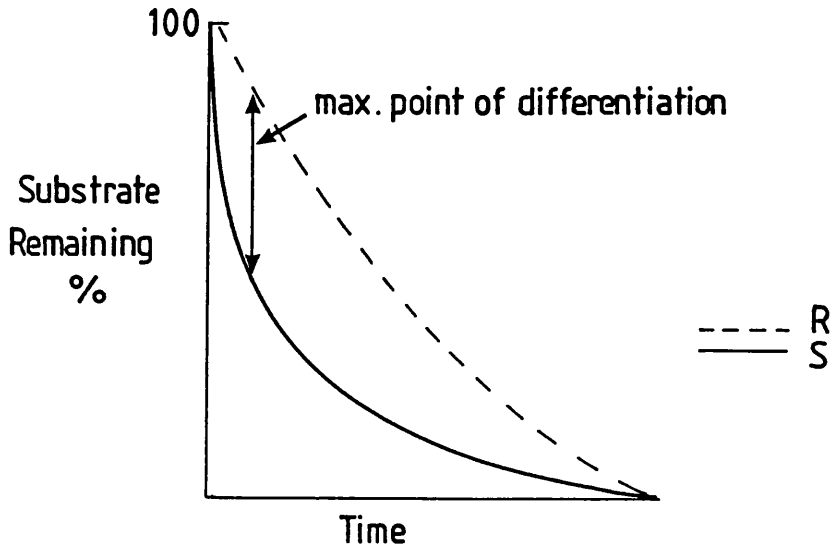


FIGURE 1

The reason for the enantiomer differentiation observed in kinetic resolutions lies with the difference in the free energies of activation $\Delta\Delta G^{\ddagger}$ of the two enantiomers.[50,51] In Scheme 18 the two enantiomers of a substrate R and S are reacting with an optically active reagent R* with retention of configuration <u>via</u> the two diastereoisomeric transition states [34] and [35] to give the enantiomeric products R' and S'.

$$R + R^{*} \longrightarrow \underset{\underline{34}}{[RR^{*}]} \longrightarrow R'$$

$$S + R^{*} \longrightarrow \underset{\underline{35}}{[SR^{*}]} \longrightarrow S'$$

SCHEME 18

As the two products are enantiomers and the two starting materials are enantiomers, the ground state free energy of both starting materials and both products must be the same.[51] The free energy of activation of the two processes shown in Scheme 18, however, will be different.[51] This is shown in Figure 2.

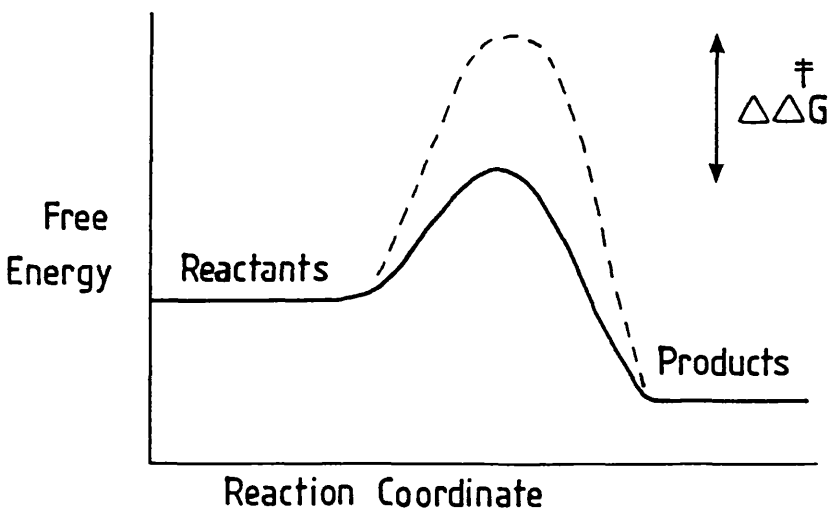


FIGURE 2

As $\Delta\Delta G^{\ddagger}$ increases it becomes increasingly favourable for the optically active reagent R* in Scheme 18 to react via the pathway of the lower free energy of activation and hence increased enantioselectivity is observed. Figure 3 shows a plot of $\Delta\Delta G^{\ddagger}$ against optical purity.[51]

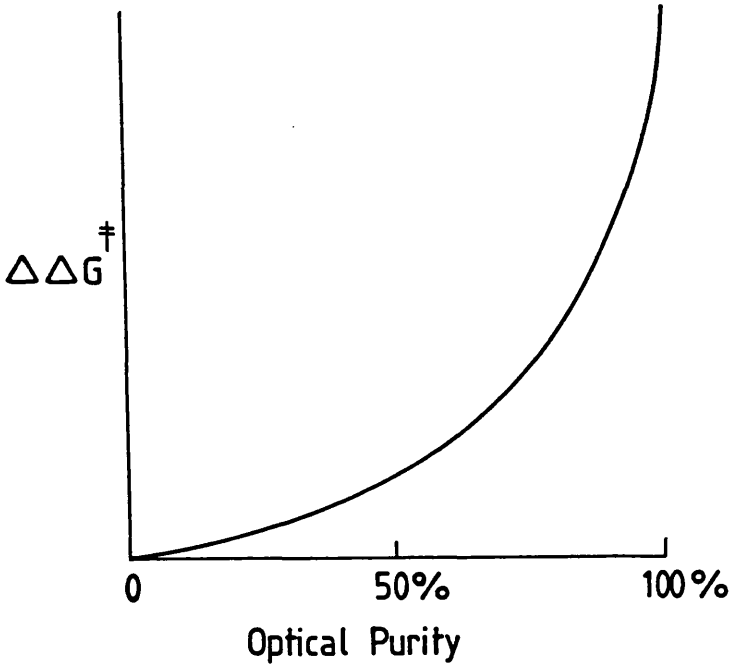


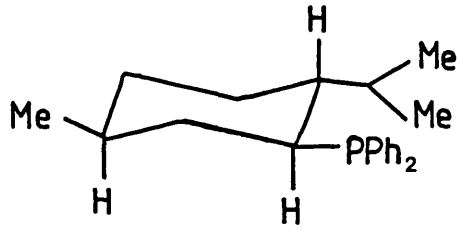
FIGURE 3

1.6 Kinetic Resolution in the Chlorination of Racemic Alcohols using Optically Active Phosphine/Carbon Tetrachloride Reagents

1.6.1 Introduction

It has been shown that an optically active phosphine/carbon tetrachloride reagent will react with an excess of a chiral but racemic alcohol to give, as a result of kinetic resolution, an optically active chloride and optically active recovered excess alcohol. The phosphine used in this study[1] was (-) menthyldiphenylphosphine [1], the structure of which is shown in Scheme 19.[52-54]

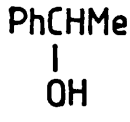
When racemic 1-phenylethan-1-ol [36] was completely converted into



1

SCHEME 19

1-chloro-1-phenylethane [37] using [1] and carbon tetrachloride, the chloride [37] displayed little or no optical activity.[1] When the reaction was carried out to only 30% conversion, the alcohol [36] and chloride [37] were found to be 12.4% and 11.5% optically pure respectively.[1] Both the recovered [36] and [37] were found to have enrichment of the R enantiomer;[1] however, this is compatible with the occurrence of a kinetic resolution since the reaction is expected to go with inversion of configuration (see Section 1.4).



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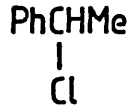


37

When the racemic alcohol [36] was reacted with chloromenthyldiphenylphosphonium chloride [38], the alcohol [36] and chloride [37] were recovered 11.8% and 20.5% optically pure, respectively, after 21% conversion.[1] The chloromenthyldiphenylphosphonium chloride [38] was made by reacting [1] with chlorine.

The major problem with this early work[1] was that the products [36] and [37] could not be purified without significant racemisation taking place. This is thought to occur <u>via</u> the formation of the stable benzylic carbonium ion [39] that may be formed from [36] or [37] during the chromatographic separation. Authentic optically active samples of

[36] and [37] were found to racemise under similar conditions to those employed for the separation from the reaction mixture.[1] The full effectiveness of the kinetic resolution could not be determined from this early work[1] because of the problem of racemisation.

1.6.2 Partial Chlorination of Chiral but Racemic Alcohols with (-) Menthyldiphenylphosphine [1] and Carbon Tetrachloride

It is essential to use chromatography in one form or another to separate the alcohol and chloride mixtures produced in reactions of this type. This is the result of the similar physical properties of the alcohol and chloride and the small scale on which it was necessary to work. To overcome the racemisation problems, there appeared to be three possible solutions:

(1) Find alcohols and chlorides that were known optically active and were stable to chromatographic separation.

(2) Convert the alcohol in the alcohol/chloride mixture into a known optically active derivative that could be separated from the chloride by physical means.

(3) Find a method of determining the extent of kinetic resolution without having to physically separate the alcohol and chloride.

Chlorination of octan-2-ol [40] was studied as the derived carbonium ion would be secondary and was therefore less stable than the benzylic carbonium ion [39].[55] The products from the chlorination of [40] would therefore be expected to be more stable to chromatography than the products from [36].

Octan-2-ol [40] was chlorinated at room temperature with half a mole equivalent of [1]. The percentage conversion was shown to be 26% by g.l.c. After separation by column chromatography on basic alumina, the

alcohol [40] and 2-chlorooctane [41] were distilled and found to be 13% and 29% optically pure, respectively. If the g.l.c. detector response is taken to be the same for [40] and [41], the optical purity of [41], calculated from the percentage conversion and the optical purity of [40], was 37%. It appeared therefore, that some racemisation had occurred during the purification procedures (see Appendix One).

When authentic optically active samples of [40] and [41] were separately subjected to chromatography conditions that were similar to those used for the separation of the mixture of [40] and [41] from the reaction mixture, the chloride [41] suffered an 85% loss of optical activity but the alcohol [40] was unaffected. The alcohol [40] suffered a 27% loss of optical activity on chromatography on silica and a small loss on chromatography on neutral alumina.

Macpherson[1] attempted to separate a mixture of optically active [36] and [37] by preparative g.l.c. but found that either racemisation occurred, or the chloride [37] eliminated hydrogen chloride to give the styrene derivative.

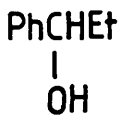
Possible separation of the alcohol [40] and chloride [41] by conversion of the alcohol in the mixture into a derivative with very different physical properties to the chloride was considered. However, problems were encountered in finding suitable derivatives that were known in optically active form. There was no guarantee that either the alcohol [40] its derivative or chloride [41] would not racemise under the conditions required to make the derivative: control experiments, using alcohol and chloride and alcohol derivative of known optical purities, would be necessary to demonstrate that this was the case. This option was not pursued as it appeared to be fraught with areas of possible errors, in addition to being extremely time-consuming.

Using alcohols with electron withdrawing groups in the molecule to retard any possible carbonium ion formation was also considered, but very few suitable examples could be found.

The solution to the problem involved the use of chiral lanthanide shift reagents. Chiral lanthanide shift reagents have been extensively used for the determination of enantiomeric purity by ^{1}H n.m.r. spectroscopy.[56] For the lanthanide shift reagent to work effectively the molecule generally must contain an oxygen or nitrogen atom.[56] If a chiral lanthanide shift reagent is used on a mixture of an alcohol and chloride, only the signals of the alcohol in the ^{1}H n.m.r. spectrum should be affected.

It is relatively easy to separate alcohol/chloride mixtures from the reaction mixture by bulb-to-bulb distillation under high vacuum and trapping the distillate in a dry ice acetone cooled bulb. As this distillation can be done at moderate to low temperatures, the risk of racemisation should be small. The percentage conversion of the alcohol to the chloride can be determined by g.l.c. on the reaction mixture provided that the detector response for the alcohol and chloride is standardised. In addition, the percentage conversion may be determined by ^{1}H n.m.r. on the distilled alcohol/chloride mixture. From the shift reagent experiments on the alcohol/chloride mixture, the enantiomeric excess of the alcohol may be found and, from this and the percentage conversion, the enantiomeric excess of the chloride may be calculated. This method removed many of the sources of possible errors and opportunities for racemisation involved in the methods discussed previously, and could easily be used on compounds that were not reported in the optically pure state in the literature.

Three alcohols [36], [42] and [43] were chlorinated with half a mole



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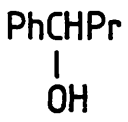


43

equivalent of [1] and carbon tetrachloride at 0°C under similar conditions. These three alcohols were chosen because all of them had been successfully studied with chiral lanthanide shift reagents.[57-59] They also formed a series where only one group in the molecule was different from any other member of the series. Table 1 shows the results from the chlorination reactions at 0°C with [1] and carbon tetrachloride.

TABLE 1

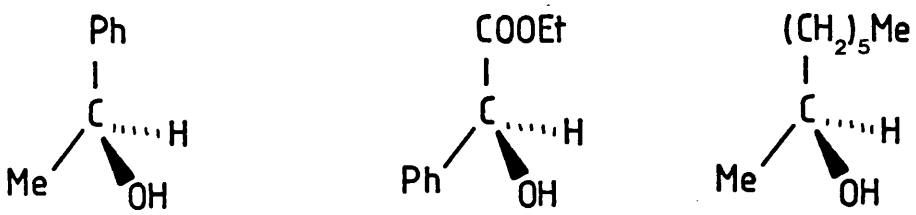
Alcohol	Conversion[a] %	Shift Reagent	Molar[c] Ratio	ee% Alcohol	ee%[d] Chloride
[36]	28	$Eu(hfbc)_3$[57]	0.28	16	41
[42]	33	$Eu(tfc)_3$[b]	0.11	10	20
[43]	30	$Eu(hfbc)_3$[59]	0.25	6	14

[a] This was determined by g.l.c. and ^1H n.m.r. The g.l.c. detector response for [36] and [37] was checked and found to be identical.
[b] $Eu(tfc)_3$ was used as $Eu(facam)_3$[58] was not available.
[c] Molar ratio of shift reagent to alcohol.
[d] Calculated value.

From Table 1 it can be seen that as the methyl group on [36] is replaced by an ethyl group and then a propyl group, the enantiomeric excesses of the alcohols and chlorides fall. The enantiomeric excess values obtained for [36] and [37] are considerably better than those previously reported,[1] and illustrate the extent of racemisation that was occurring during the chromatographic separation.

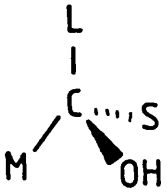
Unfortunately it is difficult to determine which enantiomer is in excess for the alcohols [36], [42] and [43] from the shift reagent

experiments. Under certain conditions, the signals from the two enantiomers have been observed to change places in the ^{1}H n.m.r. spectrum during chiral shift reagent studies.[56] This makes the identification of any enantiomer from chiral shift reagent studies unreliable. Naturally this does not affect the ability of these reagents to allow determination of the actual value of the enantiomeric excess. It is known that S-1-phenylethan-1-ol [36A],[1] S-mandelic acid ethyl ester [44],[60] and S-octan-2-ol [40A] all react faster than the R



36A 44 40A

enantiomers with [1]/carbon tetrachloride. The alcohols [36A], [40A] and [44] all appear to have the configuration shown in Scheme 20.



S = small group
M = medium group
L = large group

SCHEME 20

It would be very valuable to be able to interpret the faster rate of chlorination of [36A], [40A] and [44] than the corresponding R enantiomers in terms of the differences in the steric interactions of the two enantiomers with the active species in the mixture of [1] and carbon tetrachloride. Most workers in the field[27] believe that for the triphenylphosphine/carbon tetrachloride system, chlorotriphenylphosphonium chloride [16] is the active chlorinating agent. No detailed

studies have been undertaken for the (-) menthyldiphenylphosphine [1]/ carbon tetrachloride system, but studies (Chapter Two) indicate that [38] which is the analogue of [16] (Scheme 9), is present in large amounts. The observed stoichiometry of the reaction of [1]/carbon tetrachloride also suggests the mechanism of action is similar to that of triphenylphosphine/carbon tetrachloride (Scheme 13). Detailed molecular model studies by the author did not find a reasonable explanation why [38] should react faster with the S enantiomer of an alcohol than the R enantiomer. The steric interactions between [38] and the alcohol configuration shown in Scheme 20, appear to be equally as bad as the interactions between [38] and the mirror image of the configuration shown in Scheme 20.

It would appear that the interpretation of the results by use of molecular models of this complex system is likely to be difficult. Simpler systems need to be studied for valid conclusions to be drawn.

1.6.3 Summary and Conclusions

Chlorination of a racemic mixture of an alcohol with [1]/carbon tetrachloride, when stopped short of completion, brings about a kinetic resolution. S-octan-2-ol [40A] has been observed to react faster than the R enantiomer with [1]/carbon tetrachloride. This agrees with the observations of other workers,[1,60] using different alcohols. The extent of the kinetic resolution for three alcohols was determined and these results showed that compounds of moderate optical purities could be made in this way. Isolation difficulties make the use of these types of reagents impractical unless the products are optically stable to chromatographic conditions. If stable products can be obtained in chlorination or other reactions,[27] these reagents could find use in synthesis. One further use could be the determination of absolute con-

figuration of alcohols if it can be proved that the S-enantiomer of an alcohol generally reacts faster than the R, as indicated by this and other studies.[1,60]

CHAPTER 2

The Synthesis of Aziridines

THE SYNTHESIS OF AZIRIDINES

2.1 Introduction

Aziridines have been prepared[61] from β-amino alcohols [46] by the Gabriel[61,62] or Wenker[61,63] methods. Recently, more direct routes to aziridines from β-amino alcohols [46] have been reported using triphenylphosphine/carbon tetrachloride,[64] or triphenylphosphine/bromine.[65] The advantages of these direct routes[64,65] are that only one step is required to transform a β-amino alcohol [46] into an aziridine, and the reaction goes under very mild conditions in high yield.

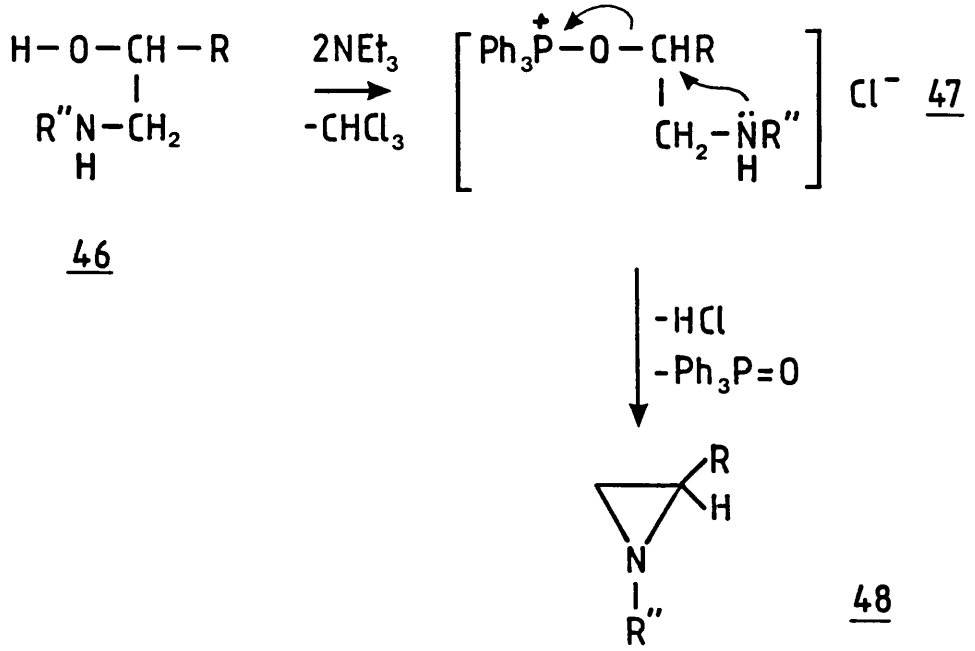
The aziridine formed from a β-amino alcohol [46] and triphenylphosphine/carbon tetrachloride can be easily isolated from the reaction mixture. Consequently this reaction was considered to be a good example to study using optically active phosphine/carbon tetrachloride reagents.

2.2 The Mechanism of the Reaction Between Triphenylphosphine Carbon Tetrachloride and a β-Amino Alcohol [46]

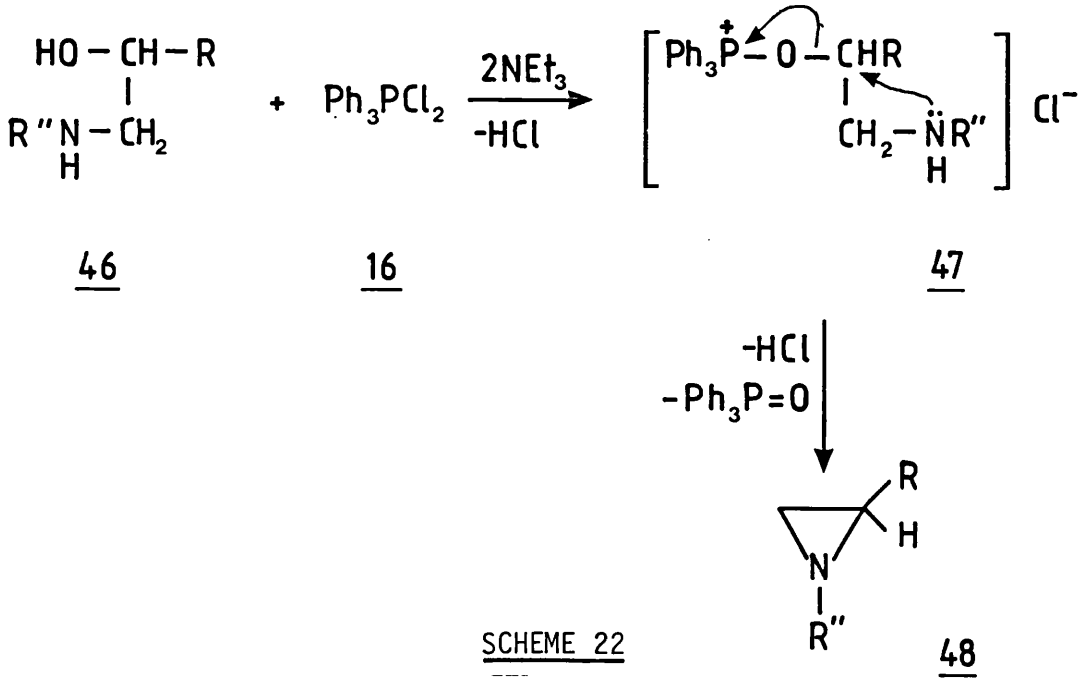
The exact details of the reaction mechanism are not known. Some possible mechanisms have been suggested[64,65] and it is probable that, as for the chlorination of alcohols, more than one mechanism is operating at the same time. Appel,[64] found that a considerable amount of chloroform was produced in these reactions; however, insufficient chloroform was found to explain the production of all the aziridine. When bromotriphenylphosphonium bromide [45] was used[65] instead of the triphenylphosphine/carbon tetrachloride mixture,[65] aziridines were obtained in moderate yields. This suggests that chlorotriphenylphosphonium chloride [16] could account for at least some of the aziridine isolated from triphenylphosphine/carbon tetrachloride reactions, and also explains the presence of (chloromethyl) triphenylphosphonium

chloride [27][64] in such reaction mixtures. Phosphonium chloride [27] could be formed <u>via</u> species [16] in an analogous manner to that shown in Scheme 13 for the chlorination of alcohols.

Two of the proposed mechanisms[64,65] are shown in Schemes 21 and 22.



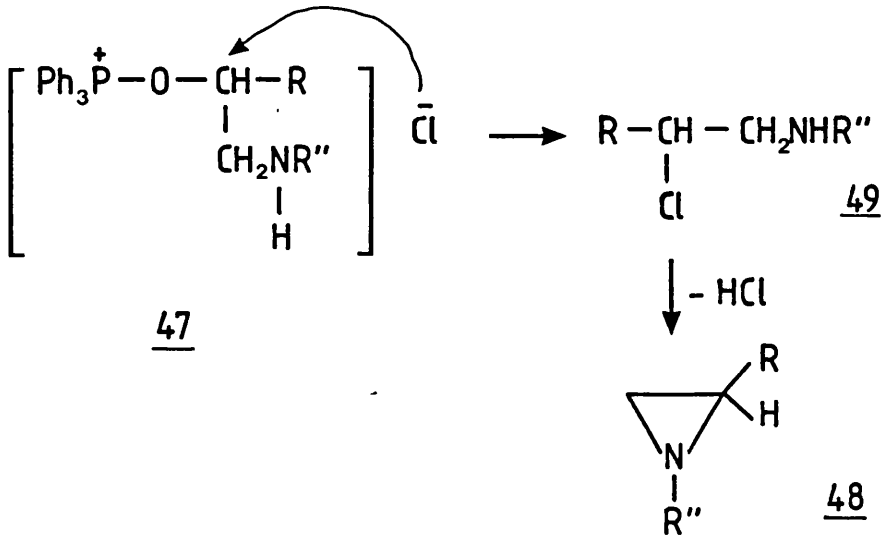
SCHEME 21



SCHEME 22

It is not known what species reacts with the β-amino alcohol [46] in Scheme 21 to eliminate chloroform, or if indeed this is the process that accounts for the production of chloroform; however, if this is the case, two possible candidates must be chlorotriphenylphosphonium trichloromethanide [13] and the dipolar associate [11], (Scheme 8).

Another suggested mechanism,[64] was that species [47] did not give the aziridine [48] directly, but gave the β-chloroamine [49] which eliminated hydrogen chloride to give the aziridine [48] (Scheme 23).



SCHEME 23

It has been suggested[65] that the ring closure step of the aziridine synthesis with triphenylphosphine/bromine goes with inversion of configuration, and this is said to give support to the mechanism shown in Scheme 22. However, as one diastereoisomer of the aziridine used in this study[65] polymerizes and the other does not, these results must be treated with caution.

When 1-t-butyl-2-phenylaziridine [50] was made from optically active 2-t-butylamino-1-phenylethan-1-ol [51] using triphenylphosphine/carbon tetrachloride and triethylamine, the aziridine [50] had at least 92%

of the original optical purity of [51]. It was not possible, however, to determine whether the reaction had proceeded with predominant inversion or retention of configuration at the chiral centre. This experiment illustrates the very high stereospecificity of the reaction.

2.3 Synthesis of Aziridines using Optically Active Phosphine/Carbon Tetrachloride Reagents

2.3.1 Introduction

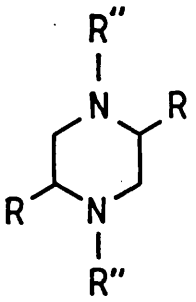
Before this study, the only phosphine/carbon tetrachloride reagent to have been used to synthesize aziridines by ring closure of β-amino alcohols was triphenylphosphine/carbon tetrachloride.[64] It was thought however, that a kinetic resolution might occur in reaction of an optically active phosphine carbon tetrachloride reagent with the racemic β-amino alcohol [46] substrate. To test this theory, a number of aziridines were prepared using a limiting amount of optically active phosphine in each case and the relevant racemic β-amino alcohol [46] in excess. In each case the phosphine, to β-amino alcohol [46], to carbon tetrachloride, to triethylamine ratio was 1:2:2:2 and the amount of solvent used was in the same proportion to the starting materials. Four different optically active phosphines were used. They were (-) menthyldiphenylphosphine [1], (+) menthyldi(2-methoxyphenyl)phosphine [52], (-) menthyldi(3-methoxyphenyl)phosphine [53] and (-) neomenthyldiphenylphosphine [54]. A maximum of four different aziridines were made with each of these optically active phosphines. They were 1-benzyl-2-methylaziridine [55], 1-benzyl-2-ethylaziridine [56], 1-benzyl-2-phenylaziridine [57] and 1-t-butyl-2-phenylaziridine [50].

2.3.2 Synthesis of 1-Benzyl-2-Methylaziridine [55], 1-Benzyl-2-Ethylaziridine [56], 1-Benzyl-2-Phenylaziridine [57] and 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1]

Table 2 shows the results for the synthesis of the four aziridines [50], [55], [56] and [57] with half a mole equivalent of (-) menthyldiphenylphosphine [1]. The preparations were carried out in two different solvents - dichloromethane and acetonitrile. As the extent of differentiation depends on the percentage conversion[50,51] (Figure 1), this makes any comparison of the results in Table 2 extremely difficult because each case has a different percentage conversion. Experimentally, the percentage conversion of these reactions were difficult to work out accurately. When the ^{1}H n.m.r. of the crude reaction mixture was run, the envelope of the menthyl group of the phosphine [1] concealed any signals from the aziridine ring. Conditions for the g.l.c. analysis of the reaction mixtures were difficult to find. The β-amino alcohols [46] used in this study tended to have extremely long retention times except on non-polar g.l.c. columns at high temperatures, whereas the aziridines [48] had relatively short retention times on non-polar columns especially at high temperatures. The separation of the aziridine [48] and β-amino alcohols [46] could be achieved relatively easily by temperature-programmed g.l.c. One of the problems that could not be solved was the determination of how much β-chloroamine [49] was formed. The salts of the β-chloroamine [49] tended to have g.l.c. retention times indistinguishable from the β-amino alcohols [46], and under the high temperature conditions required to make them come off the column, they decomposed into the corresponding aziridine [48], presumably by elimination of hydrogen chloride. This made any determination of percentage conversion in the reaction by g.l.c. unreliable. The yields quoted in Table 2 are the yields of aziridine that were obtained after

purification and, due to experimental error, cannot be absolutely compared.

In most of the aziridine preparations, two unknown compounds could be detected by t.l.c. One compound appeared to be close in chromatographic character to the aziridine [48] and one close in chromatographic character to the β-amino alcohol [46]. These were assumed to be the piperazine [58] and β-chloroamine [49] respectively. Both [49] and [58] have been reported as by-products in these types of reactions.[64,65]



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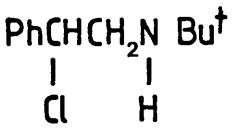
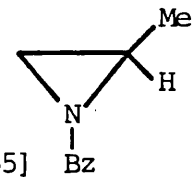
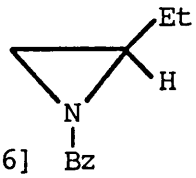
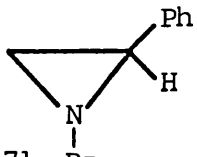
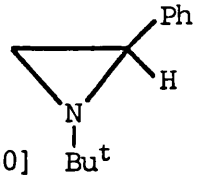


59

Other workers,[64] found that only a trace of piperazine [58] was observed in reactions with triphenylphosphine/carbon tetrachloride in the synthesis of similar aziridines but, in certain cases, up to 20% of the β-chloroamine [49] was discovered. In contrast, when triphenylphosphine/bromine was used,[65] up to 50% of the piperazine [58] could be obtained under certain conditions. In both cases,[64,65] the crude reaction mixtures could be easily studied by ^{1}H n.m.r. and this is how the relative amounts of piperazine [58] and β-chloroamine [49] were determined. All the syntheses of aziridines undertaken in this study yielded only small amounts of the piperazines [58] and β-chloroamines e.g. [49] and neither of these two compounds were ever isolated due to lack of material or isolation difficulties. The results in Table 2 show that optically active phosphine/carbon tetrachloride reagents can

TABLE 2

Synthesis of Aziridines with (-) Menthyldiphenylphosphine [1]

AZIRIDINE	TEMP °C	SOLVENT USED			
		CH_2Cl_2		CH_3CN	
		OP[a] %	YIELD[b] %	OP[a] %	YIELD[b] %
 [55]	5	-	-	32±2[c]	21[c]
 [56]	40	0	37	-	-
	5	-	-	8	26
 [57]	40	38	39	-	-
	20	-	-	52[c]	53[c]
 [50]	40	19	66	-	-
	20	-	-	51	34
	5	-	-	59	45
	2	27	55	-	-

[a] Optical purity.
[b] Isolated chemical yield based on phosphine.
[c] Twice the normal amount of solvent was required.

be used to prepare aziridines with relatively high enantiomeric excess in moderate yields. β-Amino alcohols yielding aziridines with a phenyl group on a carbon atom in the ring, seemed to give higher isolated yields and larger enantiomeric excesses of those aziridines. In addition, the reactions appeared to go better in acetonitrile than in dichloromethane. Naturally more results are needed to confirm these trends.

2.3.3 Synthesis of 1-Benzyl-2-Methylaziridine [55], 1-Benzyl-2-Ethylaziridine [56], 1-Benzyl-2-Phenylaziridine [57] and 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52]

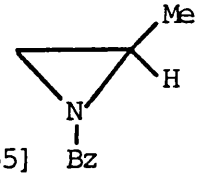
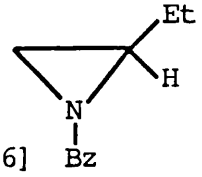
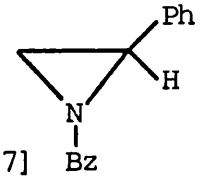
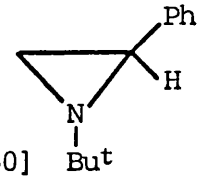
Table 3 shows the results for the synthesis of the four aziridines [50], [55], [56] and [57] with half a mole equivalent of (+) menthyldi-(2-methoxyphenyl)phosphine [52]. This phosphine was chosen to test the effect of a substituent in the phenyl rings of the phosphine, on the optical purity of the aziridines made. The resulting aziridines had only moderate optical purities.

2.3.4 Synthesis of 1-Benzyl-2-Methylaziridine [55], 1-Benzyl-2-Ethylaziridine [56], 1-Benzyl-2-Phenylaziridine [57] and 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldi(3-methoxyphenyl)phosphine [53]

(-) Menthyldi(3-methoxyphenyl)phosphine [53] was chosen as it illustrates the effect of moving the substituent in the phenyl ring one carbon atom further away from the phosphorus atom by comparison with [52]. The optical purities of the aziridines made with [53] were higher than those obtained with [52]. The results of these experiments are shown in Table 4.

TABLE 3

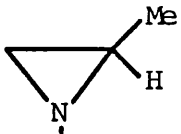
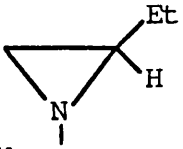
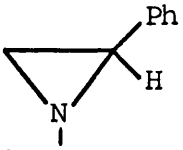
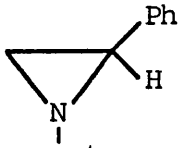
Synthesis of Aziridines using (+) Menthyldi(2-methoxyphenyl)phosphine [52]

AZIRIDINE	TEMP °C	SOLVENT USED			
		CH_2Cl_2		CH_3CN	
		OP[a] %	YIELD[b] %	OP[a] %	YIELD[b] %
 [55]	40	0	66	-	-
 [56]	40	22±2	22	-	-
 [57]	82 40 20	- 22 33	- 76 24	20 - 25	56 - 61
 [50]	20	2.5±0.2	88	17	37

[a] Optical purity.
[b] Isolated chemical yield based on phosphine.

TABLE 4

Synthesis of Aziridines using (-) Menthyldi(3-methoxyphenyl)phosphine [53]

AZIRIDINE	TEMP °C	SOLVENT USED CH_3CN	
		OP[a] %	YIELD[b] %
 [55]	20	4.5±0.5	50
 [56]	20	3.4±0.7	61
 [57]	20	35	45
 [50]	20	59	60

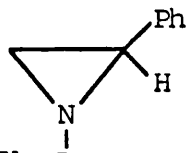
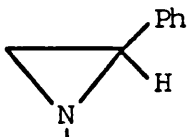
[a] Optical purity.
[b] Isolated chemical yield based on phosphine.

2.3.5 Synthesis of 1-Benzyl-2-Phenylaziridine [57] and 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Neomenthyldiphenylphosphine [54]

(-) Neomenthyldiphenylphosphine [54] was used to synthesize 1-t-butyl-2-phenylaziridine [50] and 1-benzyl-2-phenylaziridine [57]. The results are shown in Table 5. Although the isolated yields of the aziridines [50] and [57] were good the optical purity values were only moderate.

TABLE 5

Synthesis of Aziridines using (-) Neomenthyldiphenylphosphine [54] in acetonitrile

AZIRIDINE	TEMP °C	OP[a] %	YIELD[b] %
 [57]	20	19	67
 [50]	20	31	77

[a] Optical purity.
[b] Isolated yield based on phosphine.

2.3.6 Synthesis of 1-t-Butyl-2-Phenylaziridine [50] with a 4:3 and a 40:3 Ratio of Racemic 2-t-Butyl-1-Phenylethan-1-ol [51] to (-) Menthyldiphenylphosphine [1]

The rate of reaction of an enantiomer in a kinetic resolution will depend on the concentration of that enantiomer,[51] (Figure 1). In the

case where a racemic substrate is in the presence of half a mole equivalent of a kinetic resolution reagent, the rate of reaction of the 'overall faster' reacting enantiomer as the reaction nears the end point may be much less than the rate of reaction of the 'overall slower' reacting enantiomer, due to the lower concentration of the starting material of the 'overall faster' reacting enantiomer. Because of this effect, the extent of differentiation will differ with time. If this effect is cancelled out by using a large excess of starting material a greater extent of differentiation should be achieved. If a large enough excess of starting material is used, the change in concentration of the 'overall faster' reacting enantiomer should be negligible. To investigate if the amount of racemic starting material used has any effect on the optical purity of the product, two experiments were undertaken. For one experiment a 40:3 substrate to phosphine [1] ratio was used and for the other a 4:3 ratio. Both experiments were undertaken using similar conditions except for the fact that ten times more acetonitrile had to be used for the 40:3 ratio experiment in order to get all the substrate into solution. The 40:3 ratio experiment yielded 36% of [50] with an optical purity of 68% whereas the 4:3 ratio experiment yielded 36% of [50] with an optical purity of 58%. In both cases the starting concentration of substrate was the same but the phosphine was ten times more dilute in the 40:3 ratio experiment. When the 4:3 ratio experiment was repeated using the same amount of solvent as was used in the 40:3 case 36% of [50] was obtained and this had an optical purity of 67%.

A reasonable explanation for the difference in differentiation between the 4:3 and the 40:3 (substrate to phosphine ratio) cases has been already given, but the author could not find a clear-cut explanation

for the observed difference between the optical purities for the higher dilution 4:3 case and the 4:3 case. The shape of the curves in Figure 1 would not be expected to be the same for any two different kinetic resolutions. Depending on the shape of the curves and at what point the reaction is stopped, it is quite possible for an increase in the excess racemic substrate to have little or no effect on the optical purity of the product. Naturally the way to check this would be to carry out the reactions for a range of percentage conversions; however, this was not done. The two most likely explanations for the increased optical purity of the products with increased dilution are (1) a change in the reaction mechanism induced by the dilution factor and (2) experimental error in the determination of the isolated yields. As discussed in Section 2.3.2 these figures will not be very accurate due to practical difficulties. It is probable that one or both of the above explanations will account for the differences in the optical purities of the products.

When the 4:3 ratio experiment above was repeated with ten times as much triethylamine, 43% of [50] was obtained and the optical purity was seen to be 57%. This result was very similar to the result obtained from the normal 4:3 experiment. Consequently the concentration of triethylamine does not appear to have a dramatic effect on the optical purity of the product.

2.4 Preparation of 1-t-Butyl-2-Phenylaziridine [50] from Racemic 2-t-Butylamino-1-Phenylethan-1-ol [51] with an Excess of (-) Menthyldiphenylphosphine [1]/Carbon Tetrachloride

When 2-t-butylamino-1-phenylethan-1-ol [51] was completely reacted with (-) menthyldiphenylphosphine [1]/carbon tetrachloride and excess triethylamine, 1-t-butyl-2-phenylaziridine [50] was isolated in 56% yield and the optical purity of the aziridine was found to be 7.4% ± 0.2%.

In a kinetic resolution, if all the racemic starting material is reacted, the product would be expected to be racemic. In this case, the observed optical activity in the product can be explained by the conversion of a small amount of the starting material [51] into the β-chloroamine [59]. If this occurs via a kinetic resolution in a similar manner to the chlorination of alcohols described in Chapter One, the starting material will become enriched in one enantiomer, and hence the aziridine made will be optically active.

Since the optical purity of the aziridine [50] made using excess [1] is so low, this route is unlikely to be the only source of optical activity in aziridines made with a limiting amount of [1].

2.5 Preparation of 1-t-Butyl-2-Phenylaziridine [50] from Racemic 1-t-Butylamino-1-Phenylethan-2-ol [60] with Half a Mole Equivalent of (-) Menthyldiphenylphosphine [1]/Carbon Tetrachloride

The object of this experiment was to test the effect of moving the chiral centre in the starting material from the carbon atom bearing the hydroxyl group to the carbon atom bearing the amine group. In Section 2.3.2 the kinetic resolution effects for the preparation of [50] from [51] have been reported; the conversion of [60] into [50] used exactly the same conditions at the two temperatures at which it was done. The results for production of both [51] and [60] are shown in Table 6.

The primary reaction site of phosphine/carbon tetrachloride reagents in [51] and [60] is thought[64,65] to be the hydroxyl group. It is probable that the nearer the chiral centre in the starting material to the hydroxyl group, the more different the two diastereoisomeric transition states for the reaction with [1] are likely to be, and hence the more effective the kinetic resolution. In dichloromethane at 40°C the results for [51] and [60] are very similar indeed. This is quite

TABLE 6

Synthesis of Aziridine [50] using (-) Menthyldiphenylphosphine [1]

STARTING MATERIAL	TEMP °C	SOLVENT USED			
		CH_2Cl_2		CH_3CN	
		OP[a] [50] %	YIELD[b] [50] %	OP[a] [50] %	YIELD[b] [50] %
$PhCH(OH)CH_2NHBu^t$ [51]	40	19	66		
	20			51	34
$PhCH(Bu^tNH)CH_2OH$ [60]	40	19	65		
	20			3	67

[a] Optical purity.
[b] Isolated chemical yield based on phosphine.

surprising as the chiral centre is one carbon atom further away in [60] than it is in [51]. At 20°C in acetonitrile [60] gives [50] with much lower optical purity than does [51], however, the isolated yield is also much higher and this makes any comparison with the result obtained for [51] difficult.

2.6 Preparation of 1-t-Butyl-2-Phenylaziridine [50] with Half a Mole Equivalent of (-) Menthyldiphenylphosphine [1] and Chlorine

When 1-t-butyl-2-phenylaziridine [50] was prepared with half a mole equivalent of (-) menthyldiphenylphosphine [1] and chlorine, the aziridine [50] was obtained in 64% yield with 50% optical purity.

The combination of high isolated yield and high optical purity for this preparation suggest that the best results for optically active phosphine reagents could be obtained using chlorine rather than carbon tetrachloride. Naturally more studies are required to investigate if

this is a general observation or is limited to this one case. One advantage of halogens over carbon tetrachloride is that fewer reactive species will be present and it is more likely that the reactive species responsible for the reaction will be identified. When triphenylphosphine/bromine[65] was used to synthesise a range of aziridines, the yields obtained were lower than those obtained with triphenylphosphine/carbon tetrachloride, and considerable quantities of the piperazines [58] were obtained as by-products. Correct control of the amount of solvent used should eliminate these problems.

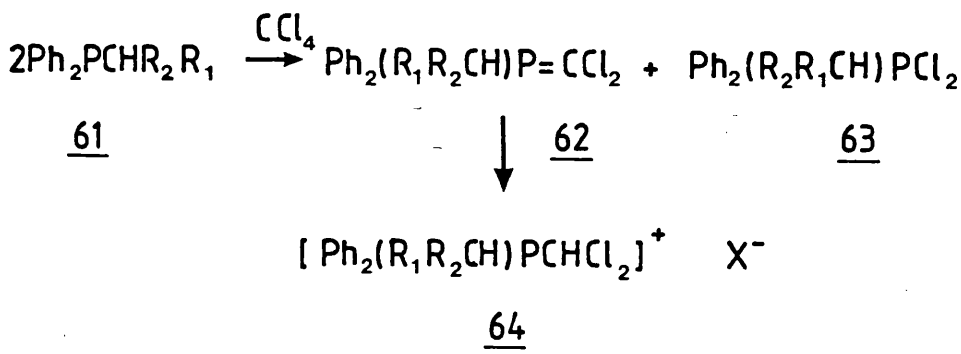
2.7 ^{31}P NMR Studies on the (-) Menthyldiphenylphosphine [1]/ Carbon Tetrachloride or Chlorine Reagents

2.7.1 Introduction

In Section 1.3 the anomalous reactions of phosphines containing an alkyl group with a hydrogen atom α to the phosphorus atom, and carbon tetrachloride were discussed. Appel[36] has investigated the reactions of alkyldiphenylphosphines [61] and carbon tetrachloride. This work[36] is particularly relevant to this study, as all the optically active phosphines used were of this type. Kolodyazhnyi[35] has studied the reactions of sterically hindered phosphines with carbon tetrachloride. He found that bulky groups on the phosphines tended to direct the reaction to go *via* the route outlined in Scheme 10; however, the role of the solvent was not considered in this study.[35] As the reactions[35] were undertaken in solvents that have been reported,[27,36-38] to favour this latter route, the conclusions drawn by Kolodyazhnyi[35] should be treated with caution until further studies have investigated the role of the solvent.

Appel[36-38] found that alkyldiphenylphosphines [61] would react with carbon tetrachloride in an analogous manner to that described in Chapter

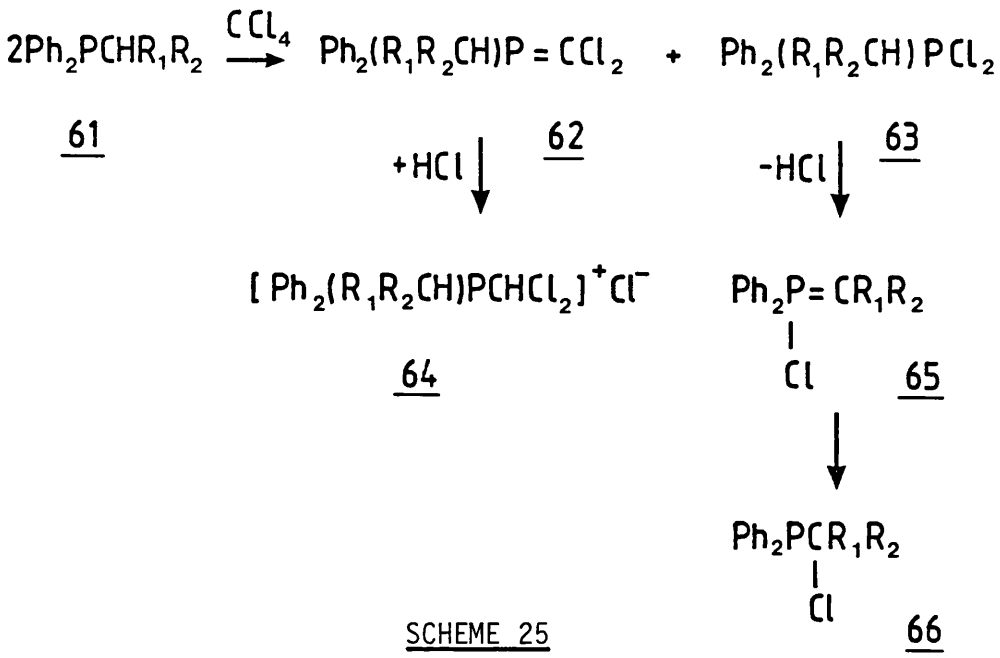
One for triphenylphosphine. This only occurred if the reactions were undertaken in solvents such as dichloromethane or acetonitrile in reasonably dilute solutions. Scheme 24 shows the result of the reaction of an alkyldiphenylphosphine with carbon tetrachloride in acetonitrile or dichloromethane. Appel claims that the reaction forms a ylide [62] and the dichlorophosphorane [63] in a similar manner to triphenylphosphine, (Schemes 8 and 9). In solvents that are able to donate a proton, the ylide [62] then abstracts a proton to form [64] and the dichlorophosphorane [63] remains unchanged, (Scheme 24). In



SCHEME 24

solvents that cannot donate a proton, the ylide [62] is said[36] to eliminate hydrogen chloride from the dichlorophosphorane [63] to give the phosphonium salt [64] and a new phosphine [66] *via* the ylide [65], (Scheme 25).

In preparative reactions of alkyldiphenylphosphines [61] the situation is much more complex than described above. The ylide [62] and dichlorophosphorane [63] might not get the chance to form, the reaction going *via* a dipolar associate as shown in Scheme 12, or *via* the chlorophosphonium trichloromethanide [67], (Scheme 11). It is possible that even in solvents that favour the reactions shown in Scheme 25 that the substrate could compete effectively for the dichlorophosphorane [63].



SCHEME 25

2.7.2 Reaction of (-) Menthyldiphenylphosphine [1] with Chlorine

(-) Menthyldiphenylphosphine [1] was dissolved in three different dry deoxygenated solvents and then dry chlorine gas was bubbled through the solutions. The ^{31}P n.m.r. spectra of the three solutions was then recorded and the results obtained are shown in Table 7. In each case two sharp singlets were obtained.

TABLE 7

^{31}P NMR Signals from (-) Menthyldiphenylphosphine [1]/ Chlorine Mixtures in Various Solvents

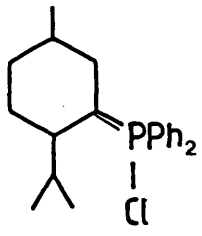
Solvent	^{31}P Chemical Shift p.p.m.
Acetonitrile	+81.1[a] +56.3[b]
Dichloromethane	+82.9[a] +54.9[b]
Toluene	+81.7[a] +60.7[b]

a = Major Peak; b = Minor Peak

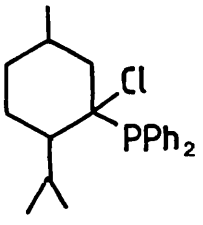
The major signal in each solvent was at approximately +82 p.p.m. and was about four times the intensity of the minor peak at approximately +54 p.p.m. Unfortunately, due to the inherent inaccuracy of ^{31}P n.m.r. integration, the exact ratio cannot be determined by this method. The positions of the signals in the ^{31}P n.m.r. spectrum varied quite considerably. This could be a solvent effect, or alternatively due to a variation in the amount of excess chlorine present in solution. Variation of ^{31}P chemical shift with amount of chlorine added is well known for solutions of chlorotriphenylphosphonium chloride [16],[66] and it is not surprising that the same occurs for chloromenthyldiphenylphosphonium chloride [38]. Chlorotriphenylphosphonium chloride [16] and chlorotri(n-butyl)phosphonium chloride [68] have been reported[67] to have ^{31}P chemical shifts of +66 p.p.m. and +106 p.p.m. in acetonitrile respectively. This makes the assumption that the signal at +82 p.p.m. in (-) menthyldiphenylphosphine [1]/chlorine is due to chloromenthyldiphenylphosphonium chloride [38] quite reasonable. The signal at approximately +54 p.p.m. was not expected. This is not due to menthyldiphenylphosphine oxide [69] as this has a ^{31}P chemical shift of +32.1 p.p.m. in acetonitrile.[1] On addition of chlorine to an acetonitrile solution of [69] the ^{31}P chemical shift does move to low field, however the effect is smaller than that required to make [69] account for the signal at +54 p.p.m. In addition, chlorine broadens the ^{31}P n.m.r. signal from [69] to a large extent, but the signals from the chlorine/[1] solutions were always sharp singlets. Addition of approximately one molar equivalent of aluminium trichloride to an acetonitrile solution of [1]/chlorine caused the chloromenthyldiphenylphosphonium chloride [38] signal to shift to +80.1 p.p.m. and the signal that was originally at +56.3 p.p.m. shifted to +57.7 p.p.m. and broadened significantly.

On addition of an excess of aluminium trichloride the sharp signal due to [38] was still observed but at +80.7 p.p.m., and two other reasonably sharp signals were observed at 57.7 p.p.m. and a minor peak at +54.5 p.p.m. When excess water was added, all three signals in the ^{31}P spectrum disappeared and were replaced by a fairly sharp singlet at +39.1 p.p.m. This was probably menthyldiphenylphosphine oxide [69], the chemical shift of which had been affected by the chlorine present.

The identity of the compound responsible for the signal in the ^{31}P n.m.r. spectrum of [1]/chlorine in acetonitrile at +56.3 p.p.m. could not be conclusively proved. As discussed in Section 2.7.1, one likely reaction of the chloromenthyldiphenylphosphonium chloride [38] is elimination of hydrogen chloride to give the ylide [70].



70



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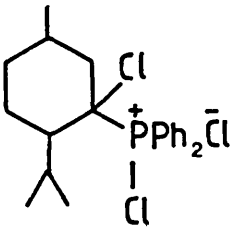
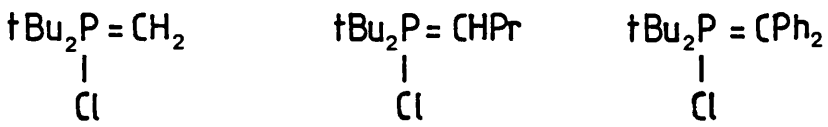


72

Ylides containing a halogen atom on phosphorus are not very stable.[27,35] Some ylides of this type that have been isolated[35] have bulky groups attached to the phosphorus atom, but even these compounds decompose at room temperature. Three phosphorus halogen ylides that have been isolated[35] are [73], [74] and [75]; the ^{31}P n.m.r. chemical shifts are +116.7 p.p.m., +101.5 p.p.m. and +92.5 p.p.m. respectively.

It seems unlikely that [70] could account for any of the ^{31}P n.m.r. signals observed for [1]/chlorine solutions in acetonitrile, as the unexplained signal is at a rather higher field than that reported for [73], [74] and [75]. In addition, the ^{31}P n.m.r. of [1]/chlorine in



73 74 75

acetonitrile was unchanged after storage for a week at room temperature, provided that air and moisture were rigorously excluded.

It is possible that any ylide [70] formed, rapidly rearranges to the β-chlorophosphine [71] which would then react with excess chlorine to give [72]; however, the ^{31}P n.m.r. spectrum of [72] would not be expected to be very different from that of [38].

From the preparative experiment described in Section 2.6, either the unknown species must be a minor component, or this species must react in a similar way to [38], otherwise the isolated yield of aziridine would not be as high as it was observed to be. This is assuming that this unknown species is formed at all in the competitive preparative reaction.

2.7.3 Reaction of (-) Menthyldiphenylphosphine [1] with Carbon Tetrachloride

(-) Menthyldiphenylphosphine [1] was dissolved in either dry deoxygenated dichloromethane or acetonitrile and the ^{31}P n.m.r. spectrum was run. Dry deoxygenated carbon tetrachloride was then added and a second ^{31}P n.m.r. spectrum recorded. The results are shown in Table 8. As expected, the ^{31}P chemical shift values of the phosphine before addition of carbon tetrachloride agree well with the literature.[1] After the carbon tetrachloride had been added the signal from the phosphine disappeared and three signals appeared.

A trace of the phosphine oxide [69] appeared at +32 p.p.m. in aceto-

TABLE 8

^{31}P NMR Signals from (-) Menthyldiphenylphosphine [1]/ Carbon Tetrachloride in Dichloromethane and Acetonitrile

Solvent	^{31}P Chemical Shift/p.p.m.	
	Before Addition of CCl_4	After Addition of CCl_4
Dichloromethane	-5.2	+84.5 +44.0 +34.1[a]
Acetonitrile	-5.4	+82.1 +44.2 +32.0[a]

a = Trace only present

nitrile and +34.1 p.p.m. in dichloromethane. The phosphine oxide [69] is presumably formed by hydrolysis of [38] or oxidation of the phosphine [1] by trace amounts of oxygen introduced into the n.m.r. tube during the addition of the carbon tetrachloride. Chloromenthyldiphenylphosphonium chloride [38] was seen in both cases, the signals occurring at +84.5 p.p.m. in dichloromethane and +82.1 p.p.m. in acetonitrile. Although these values were not exactly the same as those observed in the reaction of [1] with chlorine, (Table 7), they were reasonable assignments considering the changes chlorine can induce on the chemical shift of chlorophosphonium chlorides [76].[66] Only one signal in each solvent could not be assigned to a known compound. This signal was at

$$[R_3PCl]^+ Cl^- \qquad \underline{76}$$

+44 p.p.m. in dichloromethane and +44.2 p.p.m. in acetonitrile. This was probably [77] which is an analogue of [64], the formation of which is explained in Scheme 24.

Alternatively it is possible that the signal at +44 p.p.m. could be

$[Ph_2(Menthyl)PCHCl_2]^+ \; X^-$ **77**

$[Ph_2(Menthyl)P{=}C(Cl){=}P(Menthyl)Ph_2]^+ \; Cl^-$ **78**

due to [78] which is an analogue of [18] and could be formed by a mechanism similar to that shown in Scheme 9. The work of Appel[36] tends to support the proposal that [77] is the other compound besides [38] produced in reactions of [1] with carbon tetrachloride. As the signals of [38] and the unknown compound at +44 p.p.m. in the ^{31}P n.m.r. spectrum are of the same intensity in Table 8, it would be tempting to present this as supporting evidence for the formation of [77] rather than [78]. However, as previously mentioned, the inherent inaccuracies in ^{31}P integration make any comparison unreliable.

The most encouraging part of this particular study is that only two phosphorus-containing compounds resulted from reaction of [1] with carbon tetrachloride. This does suggest that the mechanism of reaction of [1] and carbon tetrachloride is as Appel[36-38] has proposed for alkyldiphenylphosphines [61], or as proposed in Schemes 8 and 9 for triphenylphosphine. Which mechanism is operating will, of course, have a great effect on the amount of product obtained. In this study, all the yields of reactions based on the amount of phosphine in a phosphine/carbon tetrachloride reagent assume that all the phosphine reacts as shown in Schemes 8 and 9. This was done to ensure that the yields quoted were the 'minimum' yield. Any probable variation in the stoichiometry would result in an improved yield.

2.7.4 Reaction of (-) Menthyldiphenylphosphine [1]/Carbon Tetrachloride with 2-t-Butylamino-1-phenylethan-1-ol [51] in the Presence of Triethylamine

The purpose of this experiment was to follow one of the preparations

of aziridines already described in Section 2.3.2 by ^{31}P n.m.r. spectroscopy. At room temperature the reaction apparently occurred so rapidly that the chloromenthyldiphenylphosphonium chloride [38] was not observed in the ^{31}P n.m.r. spectrum. The signal due to the phosphine [1] was seen to slowly reduce in intensity and to be replaced by three other signals at +32.9 p.p.m. (major), +34.9 p.p.m. (small) and +43.8 p.p.m. (minor). The signal at +32.9 p.p.m. was due to the phosphine oxide [69], and the signal at +43.8 p.p.m. could well be the same compound that gives rise to the signal at +44 p.p.m. in the reaction of [1] and carbon tetrachloride. In this case it is probably [77]. The identity of the compound that was responsible for the signal at +34.9 p.p.m. was not known, but it could well be due to [78], and would be formed in a similar manner to [18], (Scheme 9).

When the experiment was repeated at low temperature a small peak in the ^{31}P n.m.r. spectrum was observed at +83.5 p.p.m. at -10°C. This was probably due to the presence of [38]. On warming to room temperature again three similar signals were obtained at +33.3 p.p.m., +35.1 p.p.m. and +43.6 p.p.m.

The evidence from these experiments shows that [1]/carbon tetrachloride probably reacts in the manner which might be predicted with proton active substrates from the work of Appel;[36-38] that is, the ylide [70] and phosphonium chloride [38] are produced in a similar manner to triphenylphosphine (Schemes 8 and 9), and then the ylide abstracts hydrogen chloride to give [77] while [38] reacts with the substrate as shown in Scheme 22 for [16].

2.7.5 Reaction of (-) Menthyldiphenylphosphine [1]/Chlorine with 2-t-Butylamino-1-Phenylethan-1-ol [51] in the Presence of Triethylamine

This reaction was studied at low temperature because the reaction occurred too quickly at room temperature for any intermediates to be identified. The reactants were mixed together and then the chlorine was added to the mixture frozen in liquid nitrogen. At -95°C two peaks were visible, one at -5 p.p.m. and one at +38 p.p.m. (trace). When the temperature was allowed to rise to -80°C two further peaks were visible at +79.7 p.p.m. (major), and +88.3 p.p.m. (minor). The temperature was slowly allowed to rise to -5°C in stages. As the temperature was allowed to rise the signal at -5 p.p.m. due to the phosphine gradually disappeared, to be replaced by three other signals at +38 p.p.m., +79.7 p.p.m. and 88.3 p.p.m. The temperature was allowed to rise to room temperature and the signals at +79.7 p.p.m. and 88.3 p.p.m. gradually disappeared to be replaced by the increased signal at +38 p.p.m. As the temperature rose this signal moved to higher field and ended up at 32.3 p.p.m. at room temperature. This was clearly the phosphine oxide [69].

No evidence could be found for the signal at +56 p.p.m. that was seen in the reaction of [1] and chlorine alone (Section 2.7.2), however this could be a result of the temperature at which the experiment was done.

The signal at +88.3 p.p.m. which had only a small intensity compared with that of the chloromenthyldiphenylphosphonium chloride [38] could be due to formation of [72]. The probable mechanism of this has already been discussed in Section 2.7.1.

2.7.6 Conclusion to the ^{31}P n.m.r. Studies

The ^{31}P n.m.r. studies on the reaction of (-) menthyldiphenylphosphine [1] with carbon tetrachloride support the findings of Appel,[36-38] for alkyldiphenylphosphines [61], (Scheme 24). It does appear as if chloromenthyldiphenylphosphonium chloride [38] is formed in large amounts in the reaction of [1] and carbon tetrachloride, whether in the presence of a β-amino alcohol [46] or not. This does support the mechanism proposed in Scheme 22 for the formation of the aziridine, however it remains to be proved how much [38] itself is responsible for the formation of the aziridine [48]. Appel[64] suggests that for triphenylphosphine/carbon tetrachloride, most of the reaction in the synthesis of aziridines goes via Scheme 21. This conclusion was based on the amount of chloroform produced in these reactions and the relatively small amount of the (chloromethyl)phosphonium chloride [27] found in the reaction mixture. This does not seem to be the case for [1]/carbon tetrachloride reagents. These reagents do produce large amounts of phosphonium salts in the syntheses of aziridines undertaken in this study. The likely mechanisms for Scheme 21 cannot explain this. This does not mean that none of the reaction is going via Scheme 21. Some of it probably is; however, the results in this study tend to indicate that this proportion is smaller than that suggested by Appel.[64] The most likely mechanism for the formation of aziridine [48] from a β-amino alcohol [46] and [1]/carbon tetrachloride would be very similar to that shown in Scheme 13 for the chlorination of alcohols, where the main reactive species is proposed to be [38].

The menthyldiphenylphosphine [1]/chlorine reagent gave a good yield of a reasonably optically pure aziridine [48]; however, the reaction of [1] with chlorine did not give only the expected [38]. This is

probably a result of the phosphine having a hydrogen atom α to the phosphorus atom. This hydrogen atom could be removed to give [70] which could react further. The obvious solution to this problem is to use optically active phosphines with no α hydrogen atoms.

2.8 General Conclusion

It has been shown that an optically active phosphine/carbon tetrachloride reagent can be used to make optically active compounds in reasonable yields with high enantiomeric excess. It would be very unlikely for the menthyl group to be the most efficient for this purpose and so other more effective phosphines will probably be found.

The future of this kind of reagent lies with the optically active phosphine/chlorine reagent. When these reagents react, the phosphorus-containing product is exclusively the phosphine oxide; this can be regenerated to a dichlorophosphorane by phosgene[26,68] and hence the optically active phosphine recycled. This process will make these reagents practicable as more product can be obtained from the expensive phosphine. (-) Menthyldiphenylphosphine [1] is not suitable for this process as the reaction of [1] with chlorine does not give [38] alone; however, the author is confident that optically active phosphines that do react cleanly with chlorine can be found and that these reagents will find considerable use in synthesis.

CHAPTER 3

The Determination of the Enantiomeric Excess of Optically Active Aziridines with Chiral Lanthanide Shift Reagents

THE DETERMINATION OF THE ENANTIOMERIC EXCESS OF OPTICALLY ACTIVE AZIRIDINES WITH CHIRAL LANTHANIDE SHIFT REAGENTS

3.1 General Introduction

Comparatively few simple aziridines have optical rotations known for the optically pure material; of those that have, few can be made using phosphine/carbon tetrachloride reagents. To achieve reasonable yields using phosphine/carbon tetrachloride reagents in the synthesis of aziridines, the nitrogen atom of the aziridine must bear a fairly bulky alkyl group.[27,64,65] Many of the aziridines that are known optically pure do not fulfil this requirement. In order to complete the study of the enantioselective synthesis of aziridines in Chapter Two it was necessary to either make optically pure aziridines, or find a method of determining the enantiomeric excess of optically impure aziridines without the need of a sample of the optically pure material.

Optically active aziridines have been made in the past,[61,69-72] however this could prove to be an extremely time-consuming and cumbersome process. As any synthesis of optically active aziridines would involve a number of synthetic steps, any partial racemisation inherent in the steps, would have a cumulative affect on the optical rotation of the product. In addition, there was no guarantee that if the optically pure aziridine was made, the optical rotation would be sufficiently large to allow measurement of the sometimes small optical purity values encountered in kinetic resolution experiments.

The use of chiral lanthanide shift reagents provided a very convenient and accurate substitute for the lack of known optically pure aziridines.

Chiral lanthanide shift reagents have been extensively used[56,74,75] to determine the enantiomeric excess of optically active compounds. Generally the molecule being studied has either an oxygen or a nitrogen

atom in it[56] and, consequently, aziridines seem to be reasonable candidates for studies involving chiral lanthanide shift reagents. The use of these reagents to study the enantiomeric excess of the partially optically pure aziridines made in Chapter Two, could make the synthesis of optically pure samples of the aziridines unnecessary. Thus time and materials would be saved.

3.2 The Study of Optically Active Aziridines using Chiral Lanthanide Shift Reagents

3.2.1 Introduction

To the best of the author's knowledge, determination of the enantiomeric excess of an optically active aziridine using chiral lanthanide shift reagents has not been reported in the literature. Optically active amines,[56,73,76] epoxides[77] and diaziridines[78] have been successfully studied along with many other compounds.[56]

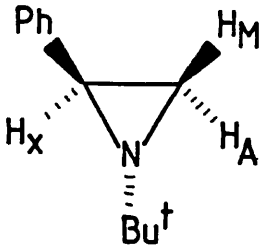
Lanthanide shift reagents have also been used to study the ratios of invertomers at nitrogen. This will be discussed in Section 3.2.4.

3.2.2 Chiral Lanthanide Shift Reagent Studies on 1-t-Butyl-2-Phenylaziridine [50]

1-t-Butyl-2-Phenylaziridine [50] $[\alpha]_D^{24} = +79°$ (c4 in $CHCl_3$) was dissolved in dry distilled carbon tetrachloride containing a small amount of tetramethylsilane. A 90 MHz ^1H n.m.r. spectrum of this solution was recorded and was identical with that already recorded for the racemic material and with that quoted in the literature.[79]

To this solution was added in small portions $Eu(tfc)_3$ under anhydrous conditions in a dry box. After addition of a trace of $Eu(tfc)_3$ there was no significant change in the spectrum apart from a slight loss of resolution due to line broadening. Addition of more $Eu(tfc)_3$ resulted in further loss of resolution due to line broadening. Two of the

protons H_A and H_M (Scheme 26) underwent a downfield shift of 0.05 p.p.m. and a small signal 0.05 p.p.m. to highfield of H_M appeared.



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SCHEME 26

More $Eu(tfc)_3$ was added. None of the signals shifted any further but a small signal appeared as a shoulder on the low field side of the signal due to H_A. The resolution was again slightly decreased and a new signal appeared at $\delta = 3.1$ p.p.m.; this was extremely broad and was due to the shift reagent. The small signal 0.05 p.p.m. to high field of H_M was still present. On addition of more shift reagent, the resolution improved slightly.

The signal from H_X now appeared as two overlapping, unequal-sized, doublet of doublets, but the splitting was not nearly large enough for integration. H_M and H_A remained the same as before but the small signal to low field of H_A had disappeared. A final amount of shift reagent was added and then the solution was filtered through a dry cotton wool plug in a dry box. The filtration removed some fine particles that had appeared. As a result of the filtration the resolution was greatly improved. The final spectrum was:

$\delta = 1.1$ p.p.m. broad singlet 9H

$\delta = 1.5$ p.p.m. broad multiplet with a small multiplet to high field 1H

$\delta = 1.85$ p.p.m. two broad signals with a small signal to high field 1H

$\delta = 2.55$ p.p.m. doublet of doublets 2H $J = 3Hz + 6Hz$ 1H

$\delta = 2.9$ p.p.m. very broad signal due to shift reagent

$\delta = 7.25$ p.p.m. multiplet slightly broadened 5H.

The ^1H n.m.r. was then studied at a variety of temperatures at 100 MHz. Spectra at 20°C, -5°C and -11.5°C are shown in Figure 4. These clearly show the signals due to H_A and H_M (Scheme 26, Figure 4) splitting into the two signals from both enantiomers as the temperature was decreased. When the 200 MHz ^1H n.m.r. spectrum was run at -15°C the H_M signals from both enantiomers could be integrated with respect to each other relatively easily. The integration gave an enantiomeric ratio of 79.3:20.7 which gives the enantiomeric excess of the aziridine [50] as 58.6%. As this sample of aziridine has a known rotation of $[\alpha]_D^{24} = +79°$ (c4 in $CHCl_3$) the rotation of the optically pure material may be calculated to be $[\alpha]_D^{24} = +135°$ (c4 in $CHCl_3$).

Racemic 1-t-butyl-2-phenylaziridine [50] was dissolved in dry distilled carbon tetrachloride containing a small amount of tetramethylsilane. To this solution was added $Eu(tfc)_3$.

This gave an aziridine [50] to $Eu(tfc)_3$ ratio of 4.8:1, and a concentration of aziridine of 0.12g cm^{-3}. For the experiment using optically active aziridine [50] described in Section 3.2.2, the aziridine [50] to $Eu(tfc)_3$ ratio was 5.3:1 and the concentration of aziridine was 0.13g cm^{-3}.

The 100 MHz ^1H n.m.r. spectrum of the racemic [50]/$Eu(tfc)_3$ solution at room temperature was very similar to that recorded for [50] in the absence of any shift reagent.[72] At -2°C the spectrum changed considerably. The doublet of doublets due to H_X (Scheme 26) shifted to 2.55 p.p.m. but was otherwise unchanged, the doublet of doublets due to H_A (Scheme 26) had shifted to 1.9 p.p.m. and had split into two overlapping equal-sized doublet of doublets, and the doublet of doublets due to H_M

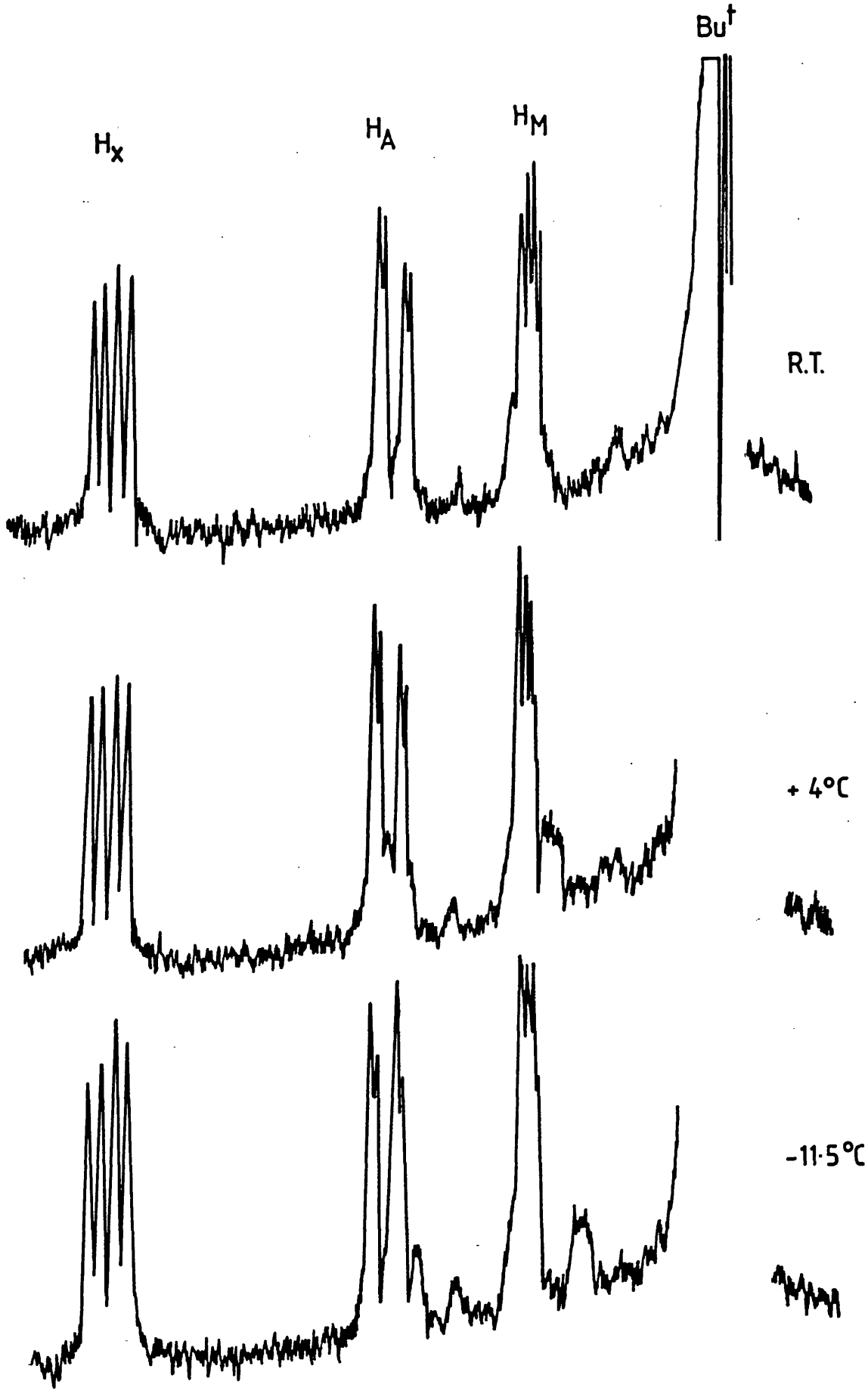


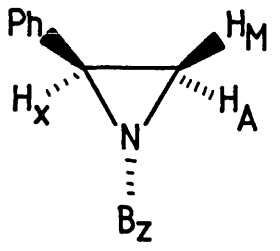
FIGURE 4

(Scheme 26) had an unchanged chemical shift but was splitting out into two equal-sized doublet of doublets. The temperature was decreased slowly in stages until at -19°C the optimum separation was achieved. Integration of the two doublet of doublets for H_M (Scheme 26) confirmed that they were of equal intensity.

3.2.3 Chiral Lanthanide Shift Reagent Studies on 1-Benzyl-2-Phenylaziridine [57]

1-Benzyl-2-Phenylaziridine [57] $[\alpha]_D^{20}$ = +69.3° (c8 in $CHCl_3$) was dissolved in dry distilled carbon tetrachloride. A 90 MHz ^1H n.m.r. spectrum of this solution was recorded and it was identical to that recorded for the racemic material (Chapter Two).

To this solution was added $Eu(hfbc)_3$ under anhydrous conditions in a dry box. After addition of the shift reagent the ^1H n.m.r. changed significantly. The aromatic protons had split into two signals at 7.25 p.p.m. and 6.75 p.p.m., a new broad signal from the shift reagent appeared at 4.25 p.p.m., and the benzylic protons split into two at 3.65 p.p.m. and 3.5 p.p.m. The doublet of doublets at 2.35 p.p.m. due to H_X (Scheme 27) had a small shoulder on it to high field. At



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SCHEME 27

2 p.p.m. the doublet due to H_M was unchanged but the doublet due to H_A at 1.75 p.p.m. had another doublet appearing to high field; however, half of the doublet was underneath the main signal from H_A.

More $Eu(hfbc)_3$ was added. The aromatic protons were split further

in a ratio of 4:6 at 7.35 p.p.m. and 6.75 p.p.m. respectively; at 4.3 p.p.m., the signal from the shift reagent and the benzylic protons merged into a multiplet; the splitting of H_X was more pronounced; the main signal was at 2.7 p.p.m. and was still seen to be a doublet of doublets and a smaller signal was seen to be merging with the signal from H_M at 2.45 p.p.m. The signal from H_A could be seen to be two doublets at 2.1 p.p.m. and 1.8 p.p.m. $J_{AX} = 7Hz$. They were in the ratio of 76:24 respectively. This gives the enantiomeric excess as 52%, and from this and the known optical rotation of the aziridine, the rotation of the optically pure material was calculated to be $[\alpha]_D^{20} = +133°$ (c8 in $CHCl_3$).

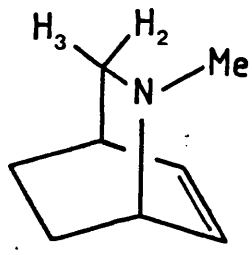
Racemic 1-benzyl-2-phenylaziridine [57] was dissolved in dry distilled carbon tetrachloride containing a small amount of tetramethylsilane. The 90 MHz ^1H n.m.r. was identical with that already reported for the racemic material (Chapter Two). $Eu(hfbc)_3$ was added under anhydrous conditions in a dry box. This made the aziridine to $Eu(hfbc)_3$ ratio 12:1 compared with 12.5:1 for the optically active aziridine (Section 3.2.4). The concentration of the aziridine was 0.11g cm^{-3} compared with 0.14g cm^{-3} for the optically active aziridine (Section 3.2.4).

The ^1H n.m.r. spectrum of the solution containing the shift reagent was very similar to that for the optically active material. The aromatic protons had split into two multiplets at 7.15 and 7.6 p.p.m. and were in a ratio of 3:2. There was a broad signal due to the shift reagent at 4.35 p.p.m. and the benzylic protons from the benzyl group attached to nitrogen had split into two singlets of equal intensity at 4 p.p.m. and 3.85 p.p.m. The doublet of doublets due to H_X was split into two equal-sized, overlapping doublet of doublets at 2.8 p.p.m.,

but the doublet due to H_M (Scheme 27) was unchanged apart from a slight loss of resolution and a downfield shift to 2.6 p.p.m. The signal due to H_A (Scheme 27) was split into two doublets of equal intensity at 2.1 p.p.m. and 2.3 p.p.m. Both of these signals had the same coupling constants of 7Hz.

3.2.4 Discussion

Lanthanide shift reagents have been used to study inversion at nitrogen.[80-83] Morishima[80,81] studied the effect of Ni(acetylacetonate)$_2$ on the ^{1}H n.m.r. of [79]. He claims that from studying the change in



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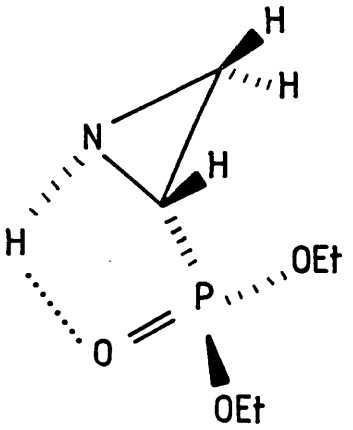
the chemical shift of protons H_2 and H_3 in [79] with increasing concentrations of Ni(acetylacetonate)$_2$, that it is possible to qualitatively predict which invertomer is present in the greater amount. The individual signals from the two invertomers were not seen by Morishima and his results have been questioned by other workers studying the same system with different methods.[82]

Berlin[84] studied the effect of Eu(dpm)$_3$ on the ^{1}H n.m.r. spectrum of diethyl-2-aziridinylphosphonate [80]. Hydrogen bonding between the hydrogen atom on the nitrogen and the oxygen atom on phosphorus in [80] was said[84] to account for the "retardation of nitrogen inversion". This is shown in Scheme 28 by the dotted line. As a result of this effect it was said to be possible to determine the actual ratio of invertomers. This does appear to be a special case, and lanthanide shift reagents are not to the best of the author's knowledge, widely



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SCHEME 28

used to measure the ratios of invertomers of aziridines.

The shift reagent studies on racemic [50] and [57] prove experimentally that the splitting observed in the ^{1}H n.m.r. spectra of optically active [50] and [57] in the presence of the shift reagent is due to the enantiomers of the carbon chiral centre and not to the existence of the nitrogen invertomers. As the splitting observed in the studies on racemic [50] and [57] revealed a 1:1 ratio of signals, this proves that the splitting is enantiomeric since it is extremely unlikely for the invertomers to be present in a 1:1 ratio under the conditions employed. It would be expected[86] for [50] and [57] to have a preferred orientation where the group on the nitrogen atom and the phenyl group on the aziridine ring are trans to each other. Only a small amount of the invertomer where the two groups are syn would be expected to be present.

3.2.5 Conclusion

Chiral lanthanide shift reagents can be used to determine the enantiomeric excess of optically active 2-substituted aziridines; however, some care needs to be taken in any extension of this work to ensure that the enantiomeric ratio is the ratio being observed rather

than any ratio involving nitrogen invertomers. The optical rotation of optically pure [50] and [57] was calculated accurately and conveniently from the result of the experiments described in Sections 3.2.2 and 3.2.3, and these results were used to calculate the optical purity values of [50] and [57] throughout Chapter Two.

EXPERIMENTAL

INTRODUCTION

Routine ^{1}H n.m.r. were recorded using a Varian EM390 90 MHz spectrometer, non-routine and variable temperature ^{1}H n.m.r. spectra were run on a Jeol JNM-PS-100 MHz or Jeol JNM-FX-200 MHz spectrometer. Unless otherwise stated, samples were dissolved in deuteriochloroform with tetramethylsilane as an internal standard. Fourier transform ^{31}P n.m.r. spectra were recorded using a Jeol JNM-FX-60 MHz spectrometer. Samples for ^{31}P n.m.r. spectra were dissolved in ether unless otherwise stated. The external standard used was tetrahydroxyphosphonium perchlorate in deuterium oxide, and chemical shifts are quoted as positive to low field of the reference. All n.m.r. chemical shifts are quoted in δ p.p.m.

Mass spectra were recorded using a VG Micromass 16B instrument. The peaks recorded were those of highest intensity and are arranged in decreasing mass. Structures were not always assigned to the peaks quoted. Infra-red spectra were recorded using Perkin-Elmer 257 or 298 spectrometers.

Analytical g.l.c. measurements were carried out using a Pye Unicam 104 instrument. Peak ratios were determined by measuring the area under the curve of the peak by cutting and weighing, and checked using a Stanley Allbrit planimeter. Preparative g.l.c. was carried out using a Pye Unicam 105 instrument. In each case, the carrier gas was nitrogen and the apparatus was equipped with a flame ionisation detector.

Optical rotations were recorded using a Perkin-Elmer 141 automatic polarimeter. Unless otherwise stated these measurements are accurate to ±1%.

Melting points were measured using a Kofler heating stage and were uncorrected.

Small scale distillations were carried out "bulb-to-bulb" using a

Kugelrohr apparatus. The temperature quoted is the oven temperature at which distillation occurred.

All starting materials were checked for purity before use by melting point, ^1H n.m.r., g.l.c. or t.l.c. Providing that the starting materials were seen to be pure by at least one of the methods outlined above they were used without purification. Unless otherwise stated below all starting materials were supplied by the Aldrich Chemical Company, (-)Menthol was supplied by BDH Chemicals Limited, (-)Neomenthyldiphenylphosphine was supplied by Fluorochem Limited. $Eu(tfc)_3$ was supplied by the Aldrich Chemical Company, $Eu(hfbc)_3$ was supplied by Fluorochem Limited. Lanthanide shift reagents were dried over P_2O_5 before use but otherwise were used as supplied.

Ether and tetrahydrofuran were dried over sodium wire, and then distilled from lithium aluminium hydride under a dry nitrogen atmosphere. Carbon tetrachloride and acetonitrile were dried by distillation from phosphorus pentoxide and dichloromethane by distillation from calcium hydride. Triethylamine and other amines were distilled from, and stored over, potassium hydroxide pellets. All solvents used for chromatography were distilled prior to use. Dried solvents were stored in sealed bottles over molecular sieves in the dark.

Organic solvents were generally removed on a rotary evaporator under reduced pressure. Unless otherwise stated, organic solutions were dried over magnesium sulphate.

The nitrogen gas used for inert atmospheres was 'white spot' grade supplied by The British Oxygen Company. It was dried by bubbling through concentrated sulphuric acid and then the gas was passed through sodium hydroxide pellets.

Unless otherwise specified chromatography was performed on UG γ type Alumina 150 mesh supplied by Laporte.

Preparation of (-) Menthyl Chloride [81]

This was prepared by the method of Smith and Wright,[88] using (-) menthol $[\alpha]_D^{20}$ = -47° (c3.9 in EtOH) (ex B.D.H. Chemicals) (lit.[93] $[\alpha]_D^{20}$ = -54.1° (EtOH)). The product was purified by distillation under reduced pressure b.p. 90-92°C (15 mmHg) (lit.[88] 101-101.5°C, 21 mmHg) to yield the product [81] (47g, 84%) $[\alpha]_D^{20}$ = -47° (neat) (lit.[89] $[\alpha]_D^{20}$ = -51° (neat)) (92% optically pure). The product [81] was shown to be pure by g.l.c. (10% E30 158°C Rt 4.8 min). When (-) menthol of lower optical purity $[\alpha]_D^{20}$ = -44° (c14 in EtOH) (ex B.D.H. Chemicals) (lit.[93] $[\alpha]_D^{20}$ = -54.1° (EtOH)) was used the product [81] was obtained in similar yield (45g, 80%) $[\alpha]_D^{20}$ = -44° (neat) and was shown to be pure by g.l.c. as described above.

Preparation of Menthylphosphorus Dichloride [82]

This was prepared by the method of Tanaka and Ogatha,[90] using (-) menthyl chloride as prepared above. The product was purified by distillation under reduced pressure b.p. 124-126°C (15 mmHg) to yield [82] (25g, 60%). The ^{31}P n.m.r. spectrum showed one peak at +210.8 p.p.m. (lit.[1] +210.8 p.p.m.) and the ^{1}H n.m.r. spectrum a broad multiplet at 0.8-3.0 p.p.m. with major peaks at 1.0, 1.1 and 1.8 p.p.m.

Preparation of (-) Menthyldiphenylphosphine [1]

This was prepared by the method of Macpherson.[1] Purification of the product by bulb-to-bulb distillation under high vacuum conditions as described by Macpherson[1] was found not to be effective. The product was recrystallised from deoxygenated ethanol to yield [1] (60%) m.p. 60-62°C (lit.[90] 57.5-58.5°C). The ^{31}P n.m.r. spectrum showed one peak at -5.2 p.p.m. (CH_2Cl_2) (lit.[1] single peak at -5.4 p.p.m.). The ^{1}H n.m.r. was consistent with that quoted in the literature and was made up of a broad multiplet δ 0.8-3.0 p.p.m. (19 H) and a broad multiplet at

7.2-7.6 p.p.m. (10 H). The optical rotation of the product depended entirely on the optical purity of the (-) menthyl chloride [81] used to make the menthylphosphorus dichloride [82]. When (-) methyl chloride $[\alpha]_D^{20}$ = -47° (neat) was initially used prepared as above [1] was obtained with $[\alpha]_D^{20}$ = -84° (c3.01 in CH_2Cl_2) (lit.[91] $[\alpha]_D^{20}$ = -93.9° (c1.7 in CH_2Cl_2)). When (-) menthyl chloride $[\alpha]_D^{20}$ = -44° (neat) was initially used prepared as above [1] was obtained with $[\alpha]_D^{20}$ = -74° (lit.[91] $[\alpha]_D^{20}$ = -93.9° (c1.7 in CH_2Cl_2)).

Experiment to Record the Optical Rotation of Octan-2-ol [40] in Chloroform

Octan-2-ol [40] $[\alpha]_D^{20}$ = +9.6° (neat) (lit.[92] $[\alpha]_D^{20}$ = +9.9° (neat)) (ex Aldrich) (hence 97% optically pure) shown to be pure by g.l.c. (10% E30, 130°C, Rt 8 min), was dissolved in chloroform and the optical rotation was recorded $[\alpha]_D^{20}$ = +8.78° (c2.86 in $CHCl_3$). Hence it was calculated that the rotation of optically pure octan-2-ol [40] in chloroform would be $[\alpha]_D^{20}$ = +9.05° (c2.86 in $CHCl_3$).

Preparation of an Authentic Sample of Optically Active 2-Chlorooctane [41]

The octan-2-ol [40] above (0.534g, 4.1×10^{-3} mol) and triphenylphosphine (1.62g, 6.2×10^{-3} mol) were dissolved in freshly dried and distilled dichloromethane (20ml). To this mixture was added carbon tetrachloride (1g, 6.2×10^{-3} mol) and the mixture was then heated under reflux and a dry nitrogen atmosphere for 4h. After this time no alcohol [40] could be detected by g.l.c. (10% E30, 130°C). The solvent was removed on a rotary evaporator and the residue distilled b.p. 90°C (bulb-to-bulb; water pump) to yield the product [41] (0.5g, 82%) (lit.[93] b.p. 75°C, 28 mmHg) $[\alpha]_D^{20}$ = +23.8° (c0.6 in $CHCl_3$). The product was shown to be pure by g.l.c. (10% E30, 130°C, Rt 2 min), ^1H n.m.r. δ 0.8-

1.4 (13H, m, $(CH_2)_5CH_3$), 1.5 (3H, d, J = 7Hz, C(2)Me), and 4.0 (1H, m, J = 7Hz, C(2)H). From the optical rotation of [41] made above the rotation of optically pure [41] was calculated to be $[\alpha]_D^{20}$ = +24.6° (c0.6 in $CHCl_3$).

Chlorination of Racemic Octan-2-ol [40] using a Limiting Amount of (-) Menthyldiphenylphosphine [1] and Carbon Tetrachloride

Freshly distilled racemic octan-2-ol [40] (0.8g, 6.2×10^{-3} mol) and dry carbon tetrachloride (6ml, 6×10^{-2} mol) were mixed at room temperature under a dry nitrogen atmosphere. (-) Menthyldiphenylphosphine [1] prepared as above (1g, 3.1×10^{-3} mol) $[\alpha]_D^{20}$ = -84° (c3.01 in CH_2Cl_2) (lit.[91] $[\alpha]_D^{20}$ = +93.9° (c1.7 in CH_2Cl_2)), was dissolved in dry dichloromethane (8ml). The octan-2-ol [40]/carbon tetrachloride solution was cooled down to -78°C and the phosphine [1] solution was added dropwise with stirring. The reaction mixture was stored at -15°C for 4 days, being checked by g.l.c. (10% E30, 130°C) after 1 and 4 days; this revealed that only a very small fraction of the octan-2-ol [40] had been chlorinated. Consequently the reaction mixture was stored for a further 15 days at 5°C, but still no significant conversion had taken place. After a further 8 days at room temperature g.l.c. analysis showed 26% conversion (10% E30, 130°C, Rt chloride 2 min, Rt alcohol 8 min). The solvent was taken off on a rotary evaporator and the residue put onto a basic alumina column and the column eluted. The chloride [41] was eluted with 9:1 light petroleum (b.p. 40-60°C)/ether and the alcohol [40] with a 1:1 mixture of the same solvents. Both [40] and [41] were separately distilled b.p. 50°C (bulb-to-bulb; water pump) to yield 2-chlorooctane [41] (88mg) $[\alpha]_D^{20}$ = -7.3° (c5.5 in $CHCl_3$) hence 29% optically pure and octan-2-ol [40] (270mg) $[\alpha]_D^{20}$ = -1.16° (c16 in $CHCl_3$) hence 13% optically pure (for the optical rotation of optically pure [40] and [41]

see the previous two experiments). Both the alcohol [40] and chloride [41] were checked for purity by g.l.c. (10% E30, 130°C) and were found to be pure compounds. The ^1H n.m.r. of [41] agreed with that reported above. The ^1H n.m.r. of [40] was δ 0.8-1.6 (16H, m, all H other than OH and C(2)H), 2.5 (1H, brs, exchangeable D_2O), 3.8 (1H, m, C(2)H) and agreed with that reported in the literature.[96]

Experiment to Check the Optical Stability of Octan-2-ol [40] on Basic Alumina

A sample of the optically active octan-2-ol [40] prepared above $[\alpha]_D^{20}$ = -1.16° (c16 in $CHCl_3$) was put onto a basic alumina column and eluted with light petroleum (40-60°C)/ether 7:3. The proportion of ether was gradually increased until pure ether was used. The fractions containing [40] were identified using g.l.c. (10% E30, 130°C) and combined, then the solvents were removed on a rotary evaporator and the product [40] was distilled b.p. 50°C (bulb-to-bulb; water pump). The ^1H n.m.r. agreed with that reported above. The recovered [40] had $[\alpha]_D^{20}$ = -1.2 ± 0.05° (c3.95 in $CHCl_3$).

Experiment to Check the Optical Stability of 2-Chlorooctane [41] on Basic Alumina

A sample of optically active 2-chlorooctane [41] prepared above $[\alpha]_D^{20}$ = -7.3° (c5.4 in $CHCl_3$) was put onto a basic alumina column and eluted with light petroleum (b.p. 40-60°C). The eluting solvent was made gradually more polar by addition of increasing amounts of ether until pure ether was used. The fractions containing [41] were identified using g.l.c. (10% E30, 130°C) and combined, then the solvents were removed on a rotary evaporator and the 2-chlorooctane [41] distilled (bulb-to-bulb; water pump) b.p. 50°C. The product was shown to be pure by ^1H n.m.r. and had $[\alpha]_D^{20}$ = -1.2° (c3.95 in $CHCl_3$). The optical activity was therefore reduced by 85%.

Experiment to Check the Optical Stability of Octan-2-ol [40] on Neutral Alumina

A sample of optically active octan-2-ol [40] $[\alpha]_D^{20}$ = +8.8° (c4 in $CHCl_3$) (ex Aldrich) was stirred with 2g of neutral alumina (ex Hopkins and Williams) in ether (10ml) for 10h. The mixture was filtered and the filter cake washed with ether (3 × 10ml). The ether solutions were combined and product isolated as above. The product [40] was shown to be pure by g.l.c. (10% E30, 130°C Rt 8 min) and ^1H n.m.r. and had $[\alpha]_D^{20}$ = +8.4° (c3 in $CHCl_3$). The optical activity was therefore reduced by 5%.

Experiment to Check the Optical Stability of Octan-2-ol [40] on Silica

Octan-2-ol [40] $[\alpha]_D^{20}$ = +9.6° (neat) (0.5g, ex Aldrich) was dissolved in ether (4ml) and stirred with silica (1g, ex Hopkins and Williams) for 3h. The silica was filtered off and the filter cake washed with ether. The ether layers were combined and the product [40] isolated as above. The recovered [40] (0.48g, 96%) had $[\alpha]_D^{20}$ = +6.85° (neat) and was shown to be pure by ^1H n.m.r. Thus 29% of the original optical activity had been lost.

Preparation of 1-Chloro-1-Phenylethane [37]

1-Phenylethan-1-ol [36] (10g, 0.08 mol) and triphenylphosphine (26.2g, 0.1 mol) were dissolved in dry deoxygenated dichloromethane (100ml) under a dry nitrogen atmosphere. To this stirred mixture was added dropwise carbon tetrachloride (15.4g, 0.1 mol). The mixture was heated under reflux for 2h, before the solvent was removed on a rotary evaporator. The product [37] was distilled from the reaction flask and then re-distilled b.p. 84-86° (water pump) to yield the chloride [37] (5.5g, 49%). The ^1H n.m.r. agreed with that previously reported:[1]
δ 1.75 (3H, d, J = 7Hz, Me), 5 (1H, q, J = 7Hz, C(1)H), 7.25 (5H, m, Ph).

Experiment to Test the G.L.C. Flame Ionisation Detector Response to 1-Phenylethan-1-ol [36] and 1-Chloro-1-Phenylethane [37]

A standard solution of [36] and [37] was made by dissolving 1-phenylethan-1-ol [36] (0.4783g, 3.92×10^{-3} mol) (ex Aldrich, seen to be pure by g.l.c. conditions as below) and 1-chloro-1-phenylethane [37] (0.3329g, 2.37×10^{-3} mol) (prepared as above, seen to be pure by g.l.c. conditions as below) in dry distilled ether. The percentage composition by molarity determined from the weights of [36] and [37] initially used was calculated to be 62.3% [36] and 37.7% [37]. This solution was then analysed by g.l.c. 3% NPGS, 126°C; Rt alcohol [36] 8.4 min, Rt chloride [37] 3.4 min. The percentage composition of the solution was determined by cutting and weighing the g.l.c. traces. Weight of alcohol [36] peak = 0.0780g, 61.2%. Weight of chloride [37] peak = 0.0491g, 38.8%.

A second standard solution was made up from [36] (0.267g, 2.19×10^{-3} mol) and [37] (0.1335g, 9.5×10^{-4} mol) in ether. The percentage composition by molarity calculated from the weights of [36] and [37] initially used was found to be 69.7% [36] and 30.3% [37]. The solution was analysed twice by g.l.c. (conditions as above) and the percentage conversion determined by cutting and weighing the g.l.c. traces.

Run 1

Weight of alcohol [36] peak = 0.0499g, 68.5%.

Weight of chloride [37] peak = 0.0230g, 31.5%.

Run 2

Weight of alcohol [36] peak = 0.0731g, 70.1%.

Weight of chloride [37] peak = 0.0311g, 29.9%.

Thus the detector response was found to be the same for [36] and [37] within the probable limits of experimental error.

Experiment to Determine the Enantiomeric Excess of 1-Phenylethan-1-ol [36] in a mixture of 1-Phenylethan-1-ol [36] and 1-Chloro-1-Phenylethane [37] Produced Using (-) Menthyldiphenylphosphine as a Chlorinating Agent on Racemic 1-Phenylethan-1-ol [36]

(±) 1-Phenylethan-1-ol [36] (0.5g, 4.1×10^{-3} mol) was dissolved in dry deoxygenated dichloromethane (15ml). To this mixture was added carbon tetrachloride (0.63g, 4.1×10^{-3} mol) and the mixture was then cooled in ice. To the stirred mixture under a nitrogen atmosphere was added dropwise (-) menthyldiphenylphosphine (0.66g, 2.05×10^{-3} mol) $[\alpha]_D^{20} = -74°$ (c1.2 in CH_2Cl_2) (prepared as above) in dry deoxygenated dichloromethane (5ml). The reaction mixture was stirred at 0°C for 3h and then for a further 48h at room temperature. Analysis of the reaction mixture by g.l.c. (3% NPGS, 126°C) showed that 28% conversion to the chloride had taken place. The solvent was removed from the reaction mixture on a rotary evaporator and the alcohol [36] and chloride [37] were distilled from the reaction mixture residue at 90°C (10 mmHg, bulb-to-bulb). A small amount of the chloride [37]/alcohol [36] mixture (0.0914g) was dissolved in dry carbon tetrachloride (0.626g) and a 100 MHz ^1H n.m.r. spectrum recorded. This was consistent with the expected ^1H n.m.r. spectrum of a mixture of [36],[1] and [37],[94] and was as follows: δ 1.35 (d, J = 8Hz, alcohol [36] Me), 1.8 (d, J = 7Hz, chloride [37] Me), 3.8 (bs, OH), 4.75 (q, J = 8Hz, alcohol [36] methine H), 5.0 (q, J = 7Hz, chloride [37] methine H), 7.27 (m, phenyl ring protons for [36] and [37]). $Eu(hfbc)_3$ was added in stages under anhydrous conditions in a dry box until the methine proton of [36] was split sufficiently to enable integration of the enantiomeric signals. A total of 0.179g of $Eu(hfbc)_3$ was added to the solution. The signals from the methine protons in enantiomers of the alcohol [36] were at 10.7 p.p.m. and the methyl signal from the alcohol [36] was at 1.35 p.p.m. when all the shift reagent had been added. The alcohol [36] methyl signal at 1.35 p.p.m. was irradiated

to enable more accurate integration of the enantiomeric alcohol [36] methine protons; the latter collapsed into two singlets as a result of the irradiation of the methyl signal. The decoupled spectrum was run at 90 MHz. The integration of the spectrometer was checked by cutting out and weighing the methine signals from the spectrum. The enantiomeric excess of the alcohol [36] was found by both methods to be 16%. Hence the enantiomeric excess of the chloride [37] was calculated to be 41% (see Appendix One).

Preparation of 1-Phenylbutan-1-ol [43]

n-Propylmagnesium Bromide was made in the usual way from freshly distilled n-bromopropane (43g, 0.35 mol), magnesium turnings (8.5g, 0.35 mol) in dry ether (200ml) under a dry nitrogen atmosphere. The Grignard reagent was heated under reflux for 1h after the addition of the bromide. To the Grignard reagent was added freshly distilled benzaldehyde (37g, 0.35 mol) in dry ether (100ml), and the mixture stirred for 2h. To the mixture was added ice water (100ml) and the mixture heated under reflux for ½h. After cooling the mixture was filtered and the ether layer separated and dried over magnesium sulphate. After filtration to remove the magnesium sulphate the ether was removed on a rotary evaporator and the product [43] distilled b.p. 112-114°C (water pump) (lit.[93] 115°C, 14 mmHg) to yield (30.9g, 59%). The product was purified by column chromatography on basic alumina eluting with chloroform, to yield [43] (25g, 48%). The product [43] was shown to be pure by g.l.c. (3% NPGS, 157°C) and ^{1}H n.m.r. δ 0.9 (3H, t, J = 7Hz, Me), 1-1.8 (4H, m, CH_2-CH_2), 1.9 (1H, bs, collapses with D_2O), 4.6 (1H, t, J = 6Hz, C(1)H), 7.25 (5H, m, Ph).

Preparation of 1-Chloro-1-Phenylpropane [83]

1-Phenylpropan-1-ol [42] (1g, 7.4×10^{-3} mol) was dissolved in dry

toluene (10ml). To this stirred solution under a dry nitrogen atmosphere was added dropwise freshly distilled thionyl chloride (1.75g, 1.5×10^{-2} mol) in dry toluene (5ml). After heating the mixture under reflux for 2h, the solvent was removed and the product distilled b.p. 110°C (bulb-to-bulb; water pump) (lit.[95] b.p. 80°C, 8 mmHg) to yield (0.95g, 80%) of the product [83]. The ^{1}H n.m.r. of the product in carbon tetrachloride was as follows: δ 1.0 (3H, t, J = 7.5Hz, Me), 2.0 (2H, m, $-CH_2-$), 4.65 (1H, t, J = 4.5Hz, CH), 7.25 (5H, m, Ph).

Preparation of 1-Chloro-1-Phenylbutane [84]

This was prepared in a similar manner to that reported above for 1-chloro-1-phenylpropane [83] from 1-phenylbutan-1-ol [43]. The product [84] was distilled b.p. 120°C (water pump; bulb-to-bulb) (lit.[93] b.p. 94°C 20 mmHg) to yield 75% of a clear colourless oil. The ^{1}H n.m.r. in carbon tetrachloride was δ 0.9 (3H, t, J = 9Hz, Me), 1.4 (2H, m, $CH_2C\underline{H}_2CH_3$), 2.0 (2H, m, $C\underline{H}_2CH_2CH_3$), 4.75 (1H, t, J = 7Hz, CH) and 7.25 (5H, m, Ph).

Experiment to Determine the Enantiomeric Excess of 1-Phenylpropan-1-ol [42] in a mixture with 1-Chloro-1-Phenylpropane [83] Produced using (-) Menthyldiphenylphosphine [1] as a Chlorinating Agent on Racemic 1-Phenylpropan-1-ol [42]

1-Phenylpropan-1-ol [42] (0.25g, 1.8×10^{-3} mol) was dissolved in dry dichloromethane (10ml) at room temperature under a nitrogen atmosphere. Carbon tetrachloride (0.28g, 1.8×10^{-3} mol) was then added to the mixture which was then cooled in ice. To this stirred mixture was added dropwise (-) menthyldiphenylphosphine [1] $[\alpha]_D^{20} = -74°$ (c1.2 in CH_2Cl_2) (prepared as above) in dry dichloromethane (10ml). The mixture was then stirred for 4h at 0°C and stored at room temperature for 3 days. After this time the reaction mixture was analysed by g.l.c. (13% NPGS, 155°C) and the percentage conversion to the chloride [83] was found to be 33%. The solvent was removed from the reaction mixture on a rotary evaporator, and

the alcohol [42] and chloride [83] distilled (bulb-to-bulb at 80°C 1 mmHg), the distillate being trapped in a dry ice/acetone slush-cooled trap. The result of the distillation was a clear colourless oil (0.25g). An ^1H n.m.r. of the distillate (0.0525g) dissolved in dry carbon tetrachloride (0.8069g) was consistent with the distillate being a mixture of 30% [83] and 70% [42] (see above).[96] The ^1H n.m.r. consisted of: δ 1.4-2.3 (overlapping multiplets, Et groups from [42] and [83]), 2.5 (bs, collapses with D_2O, OH), 4.4 (t, J = 6Hz, alcohol methine), 4.7 (t, J = 4.5Hz, chloride methine), 7.25 (m, Ph [from alcohol and chloride]). To the solution used to record the ^1H n.m.r. spectrum above was added, in stages, $Eu(tfc)_3$ under anhydrous conditions in a dry box. After 0.0369g of the shift reagent had been added there was a marked loss of resolution. After filtration through a dried cotton wool plug to remove some fine particles, the ^1H n.m.r. spectrum was re-run. The resolution was greatly improved by the filtration. The methine proton of the alcohol [42] had been shifted to 8.7 p.p.m. and had split into two overlapping triplets J = 3Hz. When the methylene protons of the alcohol [42] at 4.9 p.p.m. were irradiated, the two triplets at 8.7 p.p.m. collapsed into two singlets and integration of the two singlets showed that the enantiomeric excess of the alcohol [42] was 10%. Hence the enantiomeric excess of the chloride [83] was calculated to be 20% (see Appendix One).

Experiment to Determine the Enantiomeric Excess of 1-Phenylbutan-1-ol [43] in a Mixture with 1-Chloro-1-Phenylbutane [84] Produced using (-) Menthyldiphenylphosphine [1] as a Chlorinating Agent with Racemic 1-Phenylbutan-1-ol [43]

This experiment was carried out in the same manner as the previous experiment except that it was done on twice the previous scale. The percentage conversion was found to be 30% by g.l.c. analysis of the reaction mixture (3% NPGS, 180°C). The ^1H n.m.r. of the distilled

chloride [84]/alcohol [43] mixture was consistent with the mixture being a 7:3 mixture of [43]:[84] (see above). The ^1H n.m.r. of the distilled mixture (0.0936g) dissolved in dry carbon tetrachloride (0.7945g) was as follows: δ 0.9-2.2 (overlapping multiplets, Propyl groups from alcohol and chloride), 2.7 (s, collapses with D_2O), 4.45 (t, J=6Hz, alcohol methine H), 4.75 (t, J=7Hz, chloride methine H), 7.25 (m, Ph [from alcohol and chloride]). $Eu(hfbc)_3$ was added in stages under anhydrous conditions in a dry box. After 0.3051g had been added the methine proton of the alcohol [43] had split sufficiently to enable integration of the two enantiomeric signals. The signals at this stage were at 9 p.p.m. and were both triplets with the same coupling constant as the authentic racemic alcohol (6Hz, see above). To enable accurate integration of the two enantiomeric alcohol [43] methine signals, the methylene protons of the alcohol [43] adjacent to the methine proton were irradiated. The methylene protons were at 4.5 p.p.m. at this stage. The irradiation caused the two methine triplets at 9 p.p.m. to collapse into two singlets and integration of these two singlets showed the alcohol [43] enantiomeric excess to be 6%. The enantiomeric excess of the chloride [84] was therefore calculated to be 14% (see Appendix One).

CHAPTER TWO

EXPERIMENTAL SECTION

The yields of aziridines in kinetic resolution experiments in this Chapter are based on two-thirds of the phosphine reacting to give the aziridine.

Preparation of (+) Menthyldi(2-Methoxyphenyl)Phosphine [52]

This was prepared as described in the literature.[1] The (-) menthol used (ex BDH Chemicals) had $[\alpha]_D^{20} = -47°$ (c3.9 in EtOH). For the preparation of (-) menthyl chloride and menthylphosphorus dichloride, see above. Purification of the product was achieved by recrystallisation from deoxygenated light petroleum (b.p. 60-80°C) under a nitrogen atmosphere to yield [52] (87%), m.p. 115-116°C, (lit.[1] 114-116°C) $[\alpha]_D^{20} = +20°$ (c1 in EtOH), (lit.[1] $[\alpha]_D^{20} = +20.68$ (c0.9 in EtOH)) ^{31}P n.m.r. ($CDCl_3$) single peak at -31 p.p.m. (lit. ^{31}P -30.9 p.p.m.[1]).

Preparation of (-) Menthyldi(3-Methoxyphenyl)Phosphine [53]

3-Methoxyphenylmagnesium bromide was prepared in the usual way from magnesium turnings (1.26g, 5.3×10^{-2} mol) and 3-bromoanisole (9.8g, 5.3×10^{-2} mol) in dry deoxygenated ether (30ml) under a nitrogen atmosphere.

The Grignard reagent was decanted from the small amount of magnesium sludge and added dropwise, with stirring, to menthylphosphorus dichloride [82] (5g, 2.1×10^{-2} mol) (made as above from (-) menthol $[\alpha]_D^{20} = -47°$ (c3.9 in EtOH) (ex BDH Chemicals)) in dry ether (100ml). The mixture was then heated under reflux for 2h. After this time a ^{31}P n.m.r. spectrum of the reaction mixture showed a single peak at -4 p.p.m. To the reaction mixture was added dropwise with stirring under a nitrogen atmosphere 30% ammonium chloride solution (30ml). The organic layer was separated, dried and the ether removed on a rotary evaporator. A very thick yellow oil resulted. This was put under a vacuum (0.2 mmHg) for

½h whilst warming to remove all traces of ether. The oil became gradually thicker but would not crystallise out. Finally the oil was distilled b.p. 180°C (bulb-to-bulb, 7×10^{-5} mmHg) to yield the product [53] (5.63g, 70%), $[\alpha]_D^{20} = -51°$ (c0.9 in EtOH). The ^{31}P n.m.r. of the product showed only one peak at -3 p.p.m. ($CDCl_3$), and the ^1H n.m.r. δ 0.6-2.7 (19H, m, menthyl group), 3.75 (6H, s, OMe groups), 6.7-7.35 (8H, m, aromatic protons). Mass spectrum m/e M^+ 384, 341, 277, 214, 171, 139, 107, 96. As a result of the reactive nature of [53] the elemental analysis was done on the methyl iodide salt [85] (see below).

Preparation of Menthyldi(3-methoxyphenyl)Methyl Phosphonium Iodide [85]

(-) Menthyldi(3-methoxyphenyl)phosphine [53] (0.25g, 6.5×10^{-4} mol) (prepared as above) was dissolved in deoxygenated ether (20ml) under a nitrogen atmosphere. To the stirred mixture was added methyl iodide (0.185g, 1.3×10^{-3} mol) in deoxygenated ether (10ml). The mixture was heated under reflux for 2h and then allowed to cool. A white solid that had appeared during the heating was filtered off and washed well with ether (4 × 5ml) to yield [85] (0.102g, 30%). The product [85] was dried over P_2O_5 at 0.2 mmHg for 3h. The product [85] did not have a sharp melting point; it appeared to decompose at temperatures greater than 80°C. Mass spectrum m/e 399, 384, 341, 277, 214, 171, 139, 107, 96. Elemental analysis (Found: C, 57.16; H, 7.16; P, 5.53. Calc. for $C_{25}H_{36}O_3PI$: C, 57.04; H, 6.89; P, 5.88%).

Synthesis of β Amino Alcohols [46] for Aziridine [48] Synthesis

These compounds were made by the methods of Emerson,[97] Stolberg[98] and Bottini.[99] Equimolar amounts of the appropriate amine and epoxide were dissolved in methanol and heated under reflux for a number of hours. The methanol was removed on a rotary evaporator and the product was distilled or recrystallised according to its nature.

Preparation of 2-t-Butylamino-1-Phenylethan-1-ol [51]

The reaction mixture was heated under reflux for 4h. Then the product [51] was recrystallised from n-heptane to yield [51] (66%), m.p. 85-86°C (lit.[97] 86-87°C).

^{1}H n.m.r. δ 1.1 (9H, s, tBu)

2.0-3.0 (4H, m, $C\underline{H}_2$,$N\underline{H}$,$O\underline{H}$). This signal makes up the AB part of an ABX system (with the X proton at 4.6 p.p.m.) together with an extremely broad signal due to the amine and hydroxyl protons. On D_2O shake the integration is reduced from 4H to 2H, the broad signal collapsing. The centre of the AB part was at 2.75 p.p.m. with Jax = 5Hz, Jbx = 10Hz, Jab = 12Hz

4.6 (1H, dd, Jax = 5Hz, Jbx = 10Hz, $C\underline{H}OH$)

7.25 (5H, m, Ph).

Preparation of 2-Benzylamino-1-Phenylethan-1-ol [86]

The reaction mixture was heated under reflux for 40h. Recrystallisation twice from n-heptane yielded [86], (40%) m.p. 98-99°C (lit.[65] m.p. 100-102°C).

^{1}H n.m.r. δ

2.3-3.0 (4H, m, $O\underline{H}$, $N\underline{H}$, $BzNHC\underline{H}_2$)

This signal comprises the AB part of an ABX system (with the X proton at 4.7 p.p.m.) and a broad signal (that collapses on D_2O shake) due to the amine and hydroxyl protons. The integration on D_2O shake is reduced from 4H to 2H. Jax = 9Hz, Jbx = 4.5Hz, Jab = 12Hz. The centre of the AB part of the ABX system is at 2.7 p.p.m.

3.75 (2H, s, $PhC\underline{H}_2$)

4.7 (1H, dd, Jax = 9Hz, Jbx = 4.5Hz, $C\underline{H}OH$)

7.25 (10H, m, aromatic protons).

Preparation of 1-Benzylaminobutan-2-ol [87]

The reaction mixture was heated under reflux for 40h. Purification was achieved by distillation b.p. 114-117°C (0.4 mmHg), (lit.[65] 126°C (2 mmHg)) to yield [87], (51%). The product crystallised on standing m.p. 35-37°C.

^{1}H n.m.r. δ 0.9 (3H, t, J = 7Hz, CH_3)

1.4 (2H, q (with fine coupling), J = 7Hz, J = 1.5Hz, $C\underline{H}_2CH_3$)

2.3-3.0 (4H, m, N$\underline{H}$, O$\underline{H}$, $C\underline{H}_2$CHOH)

This signal comprises the AB part of an ABX system (the X proton being at 3.5 p.p.m.), with Jab = 12Hz, Jax = 9Hz, Jbx = 4.5Hz together with a very broad signal that collapses on D_2O shake to reduce the integration to 2H

3.5 (1H, m, C$\underline{H}$OH)

This is the X proton of the ABX system which is further split by the other adjacent methylene group at 1.4 p.p.m.

3.7 (2H, s, Ph$C\underline{H}_2$)

7.25 (5H, m, Ph).

Preparation of 1-Benzylaminopropan-2-ol [88]

The reaction mixture was heated under reflux for 8h. Purification was achieved by distillation b.p. 112-114°C (0.5 mmHg) (lit.[65] 117.5-119.5, 1.5 mmHg) to yield [88] (35%).

^{1}H n.m.r. δ

1.1 (3H, d, J = 6Hz, CH_3)

2.5 (2H, m, $C\underline{H}_2$)

This signal is the AB part of an ABX system (the X proton being at 3.7 p.p.m.) with Jab = 12Hz, Jax = 7.5Hz, Jbx = 4.5Hz

2.7 (2H, bs, O$\underline{H}$, N$\underline{H}$) (this signal collapses on D_2O shake)

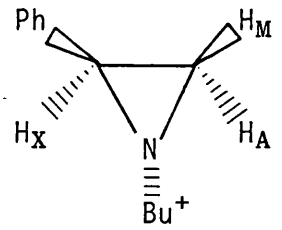
3.7 (3H, m, $PhC\underline{H}_2$ $C\underline{H}OH$)

This signal comprises the X proton of the ABX system which is further split into by the methyl group at 1.1 p.p.m. and the methylene protons of the benzyl group. On irradiation of this signal the AB part of the ABX system collapses to two overlapping doublets

7.25 (5H, m, Ph).

Preparation of Racemic 1-t-Butyl-2-Phenylaziridine [50]

This was made by the method of Appel.[64] The product [50] was distilled b.p. 60°C (0.1 mmHg, bulb-to-bulb) to yield 44%. The t.l.c. on alumina of the product showed one spot Rf 0.63 (80% light petroleum (b.p. 40-60°C) 20% ether) and the ^1H n.m.r. (CCl_4) was consistent with that quoted in the literature,[101] and was as follows:
δ 1.0 (9H, s, tBu), 1.45 (1H, dd, Jam = 1.5Hz, Jmx = 3Hz, Hm), 1.8 (1H, dd, Jam = 1.5Hz, Jax = 6Hz, Ha), 2.5 (1H, dd, Jmx = 3Hz, Jax = 6Hz, Hx), 7.25 (5H, m, Ph).



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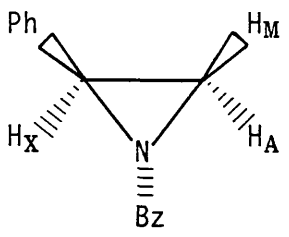
Preparation of Racemic 1-Benzyl-2-Phenylaziridine [57]

This was prepared by the method of Appel.[64] The product [57] was distilled b.p. 120° (0.1 mmHg, bulb-to-bulb) to yield 75% . The t.l.c. of the product had one spot Rf 0.48 (alumina, 80% light petroleum (b.p. 40-60°C), 20% ether). ^1H n.m.r. (CCl_4) δ 1.65 (1H, d, Jam ≃ 0, Jax = 7Hz, Ha), 1.8 (1H, d, Jam ≃ 0, Jmx = 3Hz, Hm), 2.35 (1H, dd, Jax = 7Hz, Jmx = 3Hz, Hx), 3.5 (2H, s, $C\underline{H}_2Ph$), 7.25 (10H, m, Ph).



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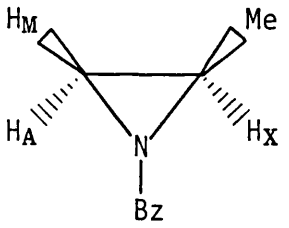
Preparation of Racemic 1-Benzyl-2-Methylaziridine [55]

This was made by the method of Appel.[64] The product [55] was distilled b.p. 100°C (0.3 mmHg, bulb-to-bulb) to yield 22% of a clear colourless oil. The t.l.c. of the product showed one spot Rf 0.33 (alumina, 80% light petroleum (b.p. 40-60°C) 20% ether). ^{1}H n.m.r. (CCl_4, 220MHz) δ 1.15 (3H, d, J = 5Hz, Me), 1.2 (1H, d, Jax = 7.5Hz, Ha), 1.35 (1H, m, Hx), 1.45 (1H, d, Jmx = 2.5Hz, Hm), 3.33 (2H, AB system, J = 15Hz, $C\underline{H}_2Ph$), 7.25 (5H, m, Ph).



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^{1}H n.m.r. ($CDCl_3$, 100MHz) δ 1.25 (d, J = 5Hz, Me), 1.45 (d, J = 7.5Hz, Ha), 1.5 (m), 1.6 (d, J = 2.5Hz, Hm). The signals from 1.25-1.6 p.p.m. collectively integrated to 6H. 3.45 (2H, AB system, J = 15Hz, $C\underline{H}_2Ph$), 7.25 (5H, m, Ph).

Preparation of Racemic 1-Benzyl-2-Methylaziridine [55] Using an excess of (-) Menthyldiphenylphosphine [1]

(-) Menthyldiphenylphosphine [1] (2g, 6.17×10^{-3} mol) $[\alpha]_D^{20}$ = -74° (c1.2 in CH_2Cl_2) prepared as above, 1-benzylaminopropan-2-ol [88] (0.7g, 4.1×10^{-3} mol) prepared as above and triethylamine (0.63g, 6.2×10^{-3} mol) were dissolved in dry deoxygenated dichloromethane (30ml). Carbon tetrachloride (1g, 6.2×10^{-3} mol) in dichloromethane (10ml) was then added dropwise to the stirred mixture. The mixture was then heated under reflux

for 7h and then allowed to stand for 12h at room temperature. The reaction mixture was then studied by t.l.c. (alumina, 80% light petroleum (b.p. 40-60°C), ether 20%). This yielded no sign of the starting β amino alcohol [88]. Purification of the product was achieved using column chromatography on alumina eluting with a 1:1 mixture of light petroleum (b.p. 40-60°C) and ether. Finally the product was distilled b.p. 100°C (0.3 mmHg, bulb-to-bulb) to yield [55] (51%) $[\alpha]_D^{20} = 0°$ (c1.3 in $CHCl_3$). The 100 MHz ^1H n.m.r. spectrum was identical with that reported above.

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 5°C in Acetonitrile

(-) Menthyldiphenylphosphine [1] (1.62g, 5×10^{-3} mol) $[\alpha]_D^{20} = -84°$ (c3 in CH_2Cl_2) prepared as above and 2-t-butylamino-1-phenylethan-1-ol [51] (1.93g, 1×10^{-3} mol) prepared as above were placed into a clean, flame-dried, three-necked flask fitted with a dropping funnel and nitrogen bubbler. The flask was flushed through with nitrogen and then dry deoxygenated acetonitrile (60ml) was added by syringe through a septum cap. To the stirred solution was added dry deoxygenated triethylamine (1.01g, 1×10^{-2} mol) and the mixture was cooled down to 0°C. Carbon tetrachloride (1.54g, 1×10^{-2} mol) in dry deoxygenated acetonitrile (10ml) was then placed into the dropping funnel by syringe through a septum cap and added to the stirred mixture dropwise over ½h. The mixture was then stored at 5°C for 30 days. After this time the solvent was removed on a rotary evaporator and the reaction mixture adsorbed onto basic alumina (5g), which was then put dry onto the top of a basic alumina column (250g) and the column eluted with 80% light petroleum (b.p. 40-60°C) 20% ether. The fractions containing the product were identified using t.l.c. (alumina, 80% light petroleum (b.p. 40-60°C) 20% ether, Rf 0.63). The fractions containing only the product were combined and the solvents removed on a rotary evaporator. Finally the

product was distilled b.p. 80°C (0.1 mmHg, bulb-to-bulb) to yield [50] (0.26g, 45%). The purity of the product was confirmed by t.l.c. (conditions as above) and ^1H n.m.r. which was exactly the same as reported above for the racemic material and as reported in the literature.[101] The product had $[\alpha]_D^{24} = +79°$ (c4 in $CHCl_3$) and the enantiomeric excess was found to be 59% (see Chapter Three).

The experiment described above is a typical case for the preparation of aziridines by kinetic resolution undertaken in this study. Unless otherwise stated the following preparations were done in a similar manner with identical proportions of reagents and solvent. Identification of the products was achieved by ^1H n.m.r. and the purity was always checked by t.l.c. (for authentic ^1H n.m.r. spectra and t.l.c. conditions, see preparation of racemic aziridines above).

The phosphines used were as follows:

(-) Menthyldiphenylphosphine [1] $[\alpha]_D^{20} = -84°$ (c3 in CH_2Cl_2) (prepared as above).

(-) Neomenthyldiphenylphosphine [54] $[\alpha]_D^{20} = -87.4°$ (c1.6 in CH_2Cl_2) (lit.[91] $[\alpha]_D^{20} = +94.4°$ (c1.3 in CH_2Cl_2)) (ex Fluorochem).

(+) Menthyldi(2-methoxyphenyl)phosphine [52] $[\alpha]_D^{20} = +20$ (c1 in EtOH) (prepared as above).

(-) Menthyldi(3-methoxyphenyl)phosphine [53] $[\alpha]_D^{20} = -51°$ (c0.9 in EtOH) (prepared as above).

<u>Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 20°C in Acetonitrile</u>

During the addition of the carbon tetrachloride solution the reaction flask was cooled to 0°C, and was then allowed to warm to room temperature and stirred for 12 days. Yield of [50] (35%) $[\alpha]_D^{20} = +72°$ (c1.3 in $CHCl_3$) optical purity 51% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 40°C in Dichloromethane

The carbon tetrachloride solution was added dropwise to the refluxing mixture over ½h and then refluxed for a further 7h. Yield of [50] (67%) $[\alpha]_D^{21}$ = +26° (c4.7 in $CHCl_3$) optical purity 19% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 2°C in Dichloromethane

The reaction flask was cooled to 0°C during the addition of the carbon tetrachloride solution and then stored at 2°C for 11 days. Yield of [50] (56%) $[\alpha]_D^{23}$ = +37° (c2.2 in $CHCl_3$) optical purity 27% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 20°C in Acetonitrile

Twice as much acetonitrile was required to fully dissolve the starting materials compared with the typical case, however the amount of acetonitrile in the carbon tetrachloride solution was the same. The carbon tetrachloride solution was added over ½h at room temperature and then the reaction mixture was stored at room temperature for 20h. Yield of [57] (54%) $[\alpha]_D^{20}$ = +69° (c8 in $CHCl_3$) enantiomeric excess 52% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 40°C in Dichloromethane

The carbon tetrachloride solution was added dropwise to the refluxing mixture and then the mixture was refluxed for 3h. Yield of [57] (39%) $[\alpha]_D^{20}$ = +50° (c1 in $CHCl_3$) optical purity 38% (see Chapter Three).

Preparation of 1-Benzyl-2-Methylaziridine [55] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 5°C in Acetonitrile

Twice as much acetonitrile was required to completely dissolve the starting materials, however the amount of acetonitrile in the carbon

tetrachloride solution was still the same. The carbon tetrachloride solution was added over ½h at 0°C and the reaction mixture was stored at 5°C for 80h. Yield of [55] (21%) $[\alpha]_D^{19}$ = +3.1 ± 0.2° (c0.9 in EtOH) (lit.[102] $[\alpha]_D$ = +9.71 (EtOH)). Hence optical purity 32 ± 2%.

Preparation of 1-Benzyl-2-Ethylaziridine [56] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 40°C in Dichloromethane

The carbon tetrachloride solution was added dropwise to the refluxing reaction mixture over ½h and the mixture heated under reflux for a further 7h. The product was isolated in the usual way to yield [56] (38%) $[\alpha]_D^{20}$ = 0° (c3 in benzene) (lit.[102] $[\alpha]_D^{20}$ = 22.6° (benzene)). The ^{1}H n.m.r. was as follows: (CCl_4) δ 0.9 (3H, t, J = 7Hz, Me), 1.25-1.4 (5H, dq with some signals underneath, J = 7Hz, 2Hz, CH_2CH_3, $-CH_2$-CHEt and -CHEt), 3.25 (2H, AB system, J_{AB} = 14Hz, $-CH_2Ph$), 7.25 (5H, m, Ph). Mass spectrum m/e M^+ 161, 146, 132, 91, 70, 42. The t.l.c. of the product showed only one spot Rf = 0.47 (alumina, 80% light petroleum (b.p. 40-60°C) 20% ether).

Preparation of 1-Benzyl-2-Ethylaziridine [56] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 5°C in Acetonitrile

Due to the poor solubility of the starting materials in acetonitrile at 5°C, twice the normal amount of solvent had to be used. The amount of acetonitrile in the carbon tetrachloride solution was normal. During the addition of the carbon tetrachloride solution the reaction mixture was cooled down to 0°C. After the addition was complete the reaction mixture was stored at 5°C for 36h. Yield of [56] (27%) $[\alpha]_D^{20}$ = +1.82° (c4.5 in C_6H_6) (lit.[102] $[\alpha]_D^{20}$ = +22.6° (benzene)). Hence optical purity 8%. The ^{1}H n.m.r. and t.l.c. were similar to that recorded above.

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 20°C in Dichloromethane

To the reaction mixture at room temperature was added dropwise the carbon tetrachloride solution over ½h and then the reaction mixture was stored at room temperature for 65h. Yield of [50] (88%) $[\alpha]_D^{20}$ = +3.4 ± 0.2° (c2 in $CHCl_3$). Optical purity 2.5 ± 0.2% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 20°C in Acetonitrile

The addition took place at room temperature and the reaction mixture was then stored for 20h at room temperature. Yield of [50] (38%) $[\alpha]_D^{20}$ = +23.5° (c2 in $CHCl_3$). Optical purity 17% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 40°C in Dichloromethane

The carbon tetrachloride solution was added dropwise to the refluxing reaction mixture over ½h and the mixture was then refluxed for 20h. Yield of [57] (76%) $[\alpha]_D^{20}$ = +29° (c4.8 in $CHCl_3$). Optical purity 22% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 20°C in Dichloromethane

To the reaction mixture at room temperature was added dropwise the carbon tetrachloride solution over ½h and the reaction mixture was stored for 48h at room temperature. Yield of [57] (24%) $[\alpha]_D^{19}$ = +44° (c1.1 in $CHCl_3$). Optical purity 33% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 20°C in Acetonitrile

The addition took place at room temperature and then the reaction mixture was stored for 80h at room temperature. Yield of [57] (62%) $[\alpha]_D^{18}$ = +33° (c2.3 in $CHCl_3$). Optical purity 25% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 82°C in Acetonitrile

To the refluxing reaction mixture was added dropwise the carbon tetrachloride solution. To allow for loss of triethylamine during the reflux a two-fold excess compared to normal was used. The mixture was refluxed for 44h. Yield of [57] (56%) $[\alpha]_D^{18}$ = +27° (c0.8 in $CHCl_3$). Optical purity 20% (see Chapter Three).

Preparation of 1-Benzyl-2-Methylaziridine [55] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 40°C in Dichloromethane

The carbon tetrachloride solution was added dropwise over ½h to the refluxing reaction mixture and then refluxed for a further 8h. Yield of [55] (22%) $[\alpha]_D^{20}$ = +2.1 ± 0.2° (c1 in EtOH) (lit.[102] $[\alpha]_D$ = +9.71° (EtOH)). Optical purity 22 ± 2%.

Preparation of 1-Benzyl-2-Ethylaziridine [56] with a Limiting Amount of (+) Menthyldi(2-methoxyphenyl)phosphine [52] at 40°C in Dichloromethane

The addition took place at 40°C and the reaction mixture was then refluxed for a further 8h. Yield of [56] (66%) $[\alpha]_D^{20}$ = 0° (c2.4 in benzene)(lit.[102] $[\alpha]_D^{20}$ = +22.6° (benzene)). Optical purity therefore 0%.

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldi(3-methoxyphenyl)phosphine [53] at 20°C in Acetonitrile

After the addition of the carbon tetrachloride solution at room temperature the reaction mixture was allowed to stand at room temperature for 80h. Yield of [50] (60%) $[\alpha]_D$ = +78° (c1 in $CHCl_3$). Optical purity 58% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (-) Menthyldi(3-methoxyphenyl)phosphine [53] at 20°C in Acetonitrile

The addition was made at room temperature and then the reaction mixture was stored at room temperature for 80h. Yield of [57] (45%) $[\alpha]_D^{21}$ =

+46° (c2 in $CHCl_3$). Optical purity 35% (see Chapter Three).

Preparation of 1-Benzyl-2-Methylaziridine [55] with a Limiting Amount of (-) Menthyldi(3-methoxyphenyl)phosphine [53] at 20°C in Acetonitrile

After the addition of the carbon tetrachloride solution at room temperature the reaction mixture was stored for 100h at room temperature. Yield of [55] (61%) $[\alpha]_D^{20}$ = +0.33 ± 0.15° (c1.5 EtOH) (lit.[102] $[\alpha]_D$ = +9.71 (EtOH)). Optical purity therefore 3.4 ± 1.4%.

Preparation of 1-Benzyl-2-Ethylaziridine [56] with a Limiting Amount of (-) Methyldi(3-methoxyphenyl)phosphine [53] at 20°C in Acetonitrile

The addition was made at room temperature and then the reaction mixture stored for 80h at room temperature. Yield of [56] (50%) $[\alpha]_D^{20}$ = -1.0 ± 0.2° (c1 in benzene)(lit.[102] $[\alpha]_D^{20}$ = +22.6° (benzene)). Optical purity therefore 4.5 ± 0.9%.

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Neomenthyldiphenylphosphine [54] at 20°C in Acetonitrile

The addition was made at room temperature and then the reaction mixture was stirred for 80h. One hour after the addition had been completed a large amount of a white solid crystallised out, and this was still present after 80h. The solid was filtered off, washed well with water and was then dried over P_2O_5 at 0.8 mm for 5h. Yield 63% based on (-) neomenthyldiphenylphosphine [54]. A ^{31}P n.m.r. spectrum of the solid in chloroform had a single peak at +33 p.p.m. The melting point of the sample was found to be 215.5-217°C and the sample appeared to sublime before melting. (Lit.[91] m.p. neomenthyldiphenylphosphine oxide [90] 216-217°C). The aziridine [50] was purified from the mother liquor in the normal way. Yield of [50] (77%) $[\alpha]^{21}$ = +42° (c3.5 in $CHCl_3$). Optical purity 31% (see Chapter Three).

Preparation of 1-Benzyl-2-Phenylaziridine [57] with a Limiting Amount of (-) Neomenthyldiphenylphosphine [54] at 20°C in Acetonitrile

This was carried out exactly the same as reported above and again a large quantity of white solid was obtained. Once more the solid was identified as neomenthyldiphenylphosphine oxide [90] by its melting point and ^{31}P n.m.r. spectrum. The yield of aziridine [57] achieved after normal work up was (67%) $[\alpha]_D^{21} = -25°$ (c4 in $CHCl_3$). Optical purity 19% (see Chapter Three).

Preparation of Optically Active 2-t-Butylamino-1-Phenylethan-1-ol [51]

This was attempted by a classical resolution method using 2-t-butylamino-1-phenylethan-1-ol [51] and (+) tartaric acid. This preparation has been described in the literature,[103] however it was not found to be possible to dissolve the quantity of (+) tartaric acid required in the same volume of water as described in the literature.[103] It was assumed that there had been a printing mistake. Ten times the quantity of water used in the literature was the minimum amount required to dissolve the stated amount of tartaric acid and so this was the quantity used.

Racemic 2-t-Butylamino-1-phenylethan-1-ol (3g, 1.55×10^{-2} mol) [51] was dissolved with some heating in methanol (12ml). This solution was added very slowly to a hot solution of D (+) tartaric acid (2.33g, 1.55×10^{-2} mol) in water (4ml). During this addition a large amount of heat was evolved. The mixture was allowed to stand at room temperature overnight but no crystals were obtained, the mixture was then stored at 5°C for two days but still no crystals were obtained. On storing the mixture at 0°C overnight all the salt crystallised out. The solution was warmed until all the solid had dissolved and was then allowed to stand at room temperature for two days after which time all the salt had crystallised out. Water (1ml) and methanol (3ml) was then

added to the mixture and the mixture was warmed until all the solid had dissolved. After two days at room temperature again all the salt crystallised out. A further amount of water (1ml) and methanol (2ml) was added and the solution warmed until everything had dissolved. Again all the solid came out on standing. Methanol (5ml) was added and the solution was cooled down to 5°C for three days. A small amount of crystals were formed. These were filtered off and recrystallised from methanol/water 9:1 to yield (0.6g) of the tartrate salt of [51], $[\alpha]_D^{20}$ = +41.4° (c0.8 in MeOH), lit.[103] $[\alpha]_D^{20}$ = +47.6° (methanol), m.p. 65-75°C (lit.[103] m.p. 98°C). The tartrate salt of [51] was dissolved in water (10ml) and made basic (pH 11) with 2M sodium hydroxide solution, the white crystals formed were filtered off, washed with water, dried, and recrystallised twice from ethyl acetate to yield the product [51] (0.2g), m.p. 103-105°C (lit.[103] m.p. 106-107°C), $[\alpha]_D^{20}$ = -64° (c0.5 in $CHCl_3$) (lit.[103] $[\alpha]_D^{20}$ = +80.5° ($CHCl_3$)). Hence the product [51] was determined to be 79.5% optically pure. The ^1H n.m.r. of the product [51] was similar to that reported above for the racemic material.

<u>Preparation of an Authentic Sample of 1-t-Butyl-2-Phenylaziridine [50]</u>
2-t-Butylamino-1-phenylethan-1-ol (0.25g, 1.3×10^{-3} mol) [51] $[\alpha]_D^{18}$ = -64° (c0.5 in $CHCl_3$) prepared as above, was dissolved in dry acetonitrile (25ml) under a nitrogen atmosphere. To this was added triphenylphosphine (0.5g, 2×10^{-3} mol) and triethylamine (0.15g, 1.3×10^{-3} mol). The mixture was warmed to 50°C with stirring and carbon tetrachloride (0.3g, 2×10^{-3} mol) in dry acetonitrile (5ml) was added dropwise. Then the mixture was stirred at 50°C for 2h. After allowing the reaction mixture to cool the solvent was removed and the product extracted into light petroleum (b.p. 40-60°C) (2 × 25ml). The solution was then filtered and the solvent removed on a rotary evaporator. Finally the product was distilled bulb-to-bulb to yield [50] (0.138g,

61%) of a clear colourless oil. The ^1H n.m.r. agreed with that already quoted above and the product was seen to be pure by g.l.c. and t.l.c. $[\alpha]_D^{21}$ = +98° (c1.8 $CHCl_3$) hence 73% optically pure (see Chapter Three).

Preparation of the Ethyl Ester of 2-Bromo-2-Phenylacetic Acid [89]

This was prepared as described in the literature,[104] to yield the product [89] (80%). The ^1H n.m.r. of the product was δ 1.1 (3H, t, J = 8Hz, Me), 4.05 (2H, q, J = 8Hz, $C\underline{H}_2$), 5.15 (1H, s, $C\underline{H}Br$), 7.25 (5H, m, Ph).

Preparation of Ethyl 2-(t-Butylamino)-2-Phenylethanoate [90]

Ethyl 2-Bromo-2-Phenylethanoate [89] (24g, 9.9×10^{-2} mol) prepared above was mixed with t-Butylamine (30g, 0.45 mol) and the mixture heated under reflux for 24h under a calcium chloride guard tube. The excess t-Butylamine was removed on a rotary evaporator and then 2M sodium hydroxide solution (20ml) was added to the residue. This water mixture was then extracted with ether (3 × 50ml). The ether solutions were combined, dried over magnesium sulphate, filtered and the ether removed on a rotary evaporator. Finally the product was distilled at 148-150°C (water pump) to yield [90] (9.9g, 43%) as a clear colourless oil. ^1H n.m.r. δ 1.2 (12H, overlapping triplet J = 7Hz and singlet, CH_3 and tBu), 2.2 (1H, bs, collapses on D_2O shake, $N\underline{H}$), 4.1 (2H, m, CH_2), 4.4 (1H, s, $C\underline{H}Ph$), 7.25 (5H, m, Ph), ν (thin film neat liquid) 2950, 1725 (C=O), 1600, 1480, 1440, 1380 and 1355 (tBu), 1200, 1020, 720 and 690 (5 adjacent aromatic C-H) cm^{-1}. m/e M^+ 235, 220, 163, 162, 146, 135, 106, 90, 57. (Found: C, 71.4, H, 8.94, N, 5.83. Calc. for $C_{14}H_{21}NO_2$: C, 71.45, H, 9.0, N, 5.95%).

Preparation of 1-t-Butylamino-1-phenylethan-2-ol [60]

To a stirred mixture of lithium aluminium hydride (2.4g, 6.4×10^{-2} mol) in dry ether (50ml) at 0°C was added ethyl 2-(t-butylamino)-2-phenyl-

ethanoate [90] (5g, 2.13×10^{-2} mol) prepared as above in ether (50ml). The mixture was stirred for 1h and then heated under reflux for a further 3.5h. After allowing the mixture to cool, water (30ml) was added and the mixture stirred for 30 min. The reaction mixture was then filtered and the ether layer separated. The water layer was extracted with ether (2×20ml) and then the ether layers combined, dried, filtered, and finally the ether was removed on a rotary evaporator. The resulting oil was distilled 150°C (15 mmHg, bulb-to-bulb) to yield [60] (3.3g, 80%). The product was a clear colourless oil that crystallised out on standing m.p. 59-61°C. ^{1}H n.m.r. δ 1.0 (9H, s, tBu), 2.8 (2H, bs, collapses on D_2O shake, N$\underline{H}$, O$\underline{H}$), 3.35 (2H, AB part of an ABC system $J_{ab} = 10.5$Hz, $J_{ac} = 4.5$Hz, $J_{bc} = 9$Hz, C$\underline{H}_2$), 3.8 (1H, C part of ABC system, $J_{ac} = 4.5$Hz, $J_{bc} = 9$Hz, C$\underline{H}$Ph), 7.25 (5H, m, Ph). ν(thin film neat liquid) 3350 broad (OH), 2950, 1600, 1450, 1380 and 1360 (tBu), 1220, 1060, 1030, 750 and 700 (5 adjacent aromatic C-H) cm^{-1}. m/e M^+ 193, 178, 163, 162, 146, 105, 90. (Found: C, 74.79, H, 9.77, N, 7.10. Calc. for $C_{12}H_{19}NO$: C, 74.57, H, 9.91, N, 7.25%).

<u>Preparation of 1-t-Butyl-2-Phenylaziridine [50] from 1-t-Butylamino-1-Phenylethan-2-ol [60] Using a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 40°C in Dichloromethane</u>

The carbon tetrachloride solution was added to the refluxing mixture over ½h and the mixture was refluxed for a further 7h. Yield of [50] (65%) $[\alpha]_D^{21} = +26°$ (c5 in $CHCl_3$). Optical purity 19% (see Chapter Three).

<u>Preparation of 1-t-Butyl-2-Phenylaziridine [50] from 1-t-Butylamino-1-Phenylethan-2-ol [60] Using a Limiting Amount of (-) Menthyldiphenylphosphine [1] at 20°C in Acetonitrile</u>

The carbon tetrachloride solution was added to the refluxing mixture over ½h and the mixture was then left at room temperature for 24h. Yield of [50] (67%) $[\alpha]_D^{20} = +4.2°$ (c6 in $CHCl_3$). Optical purity 3% (see Chapter

Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] Using a (-) Menthyldiphenylphosphine [1] to 2-t-Butylamino-1-phenylethan-1-ol [51] Ratio of 3:4 in Acetonitrile at 20°C

(-) Menthyldiphenylphosphine [1] (0.4g, 1.2×10^{-3} mol) and 2-t-butylamino-1-phenylethan-1-ol [51] (0.288g, 1.6×10^{-3} mol) were placed into a clean dry two-neck flask and the system was flushed through with nitrogen. Triethylamine (0.25g, 2.4×10^{-3} mol) and dry acetonitrile (23ml) were then added by syringe through a septum cap. Carbon tetrachloride (0.189g, 1.2×10^{-3} mol) in acetonitrile (2ml) was added dropwise over ½h and then the solution was stirred for 80h. The aziridine was purified in the usual way to yield [50] (0.051g, 36%) $[\alpha]_D^{19} = +78°$ (c1 in $CHCl_3$). Optical purity 58% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] Using a (-) Menthyldiphenylphosphine [1] to 2-t-Butylamino-1-Phenylethan-1-ol [51] Ratio of 3:4 with a Ten-Fold Excess of Triethylamine

This experiment was carried out on the same scale and with the same method as the previous experiment, except for the fact that ten times as much triethylamine was used. Yield of [50] (43%) $[\alpha]_D^{20} = +77°$ (c1 in $CHCl_3$). Optical purity 57% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] Using a (-) Menthyldiphenylphosphine [1] to 2-t-Butylamino-1-Phenylethan-1-ol [51] Ratio of 3:4 under High Dilution Conditions in Acetonitrile at 20°C

This experiment was carried out on the same scale and with the same method as the previous experiment, however, ten times as much acetonitrile was used. Yield of [50] (36%) $[\alpha]_D^{20} = +90°$ (c0.8 in $CHCl_3$). Optical purity 67% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] Using a (-) Menthyldiphenylphosphine [1] to 2-t-Butylamino-1-Phenylethan-1-ol [51] Ratio of 3:40 in Acetonitrile at 20°C

This preparation was carried out exactly the same as the previous

example (ratio [1] to [51] 3:4), however ten times as much 2-t-Butyl-1-phenylethan-1-ol [51] was used (2.88g, 1.6×10^{-3} mol) and ten times as much acetonitrile (230ml) was required to fully dissolve it. Yield of [50] (36%) $[\alpha]_D^{19} = +92°$ (c1.5 in $CHCl_3$). Optical purity 68% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] Using Excess (-) Menthyldiphenylphosphine [1]

The preparation was conducted in the usual way using a phosphine [1] to substrate [51] ratio of 2:1. After the reaction mixture had been stirred for 20h at room temperature the substrate [51] could not be detected by g.l.c. (3% OV17, 240°C, Rt authentic material 6 min). The solvent was removed from the reaction mixture on a rotary evaporator and the product was extracted with light petroleum (2×20ml). The petroleum extract was filtered and the solvent removed on a rotary evaporator. The product was distilled bulb-to-bulb under reduced pressure to yield [50] (56%) $[\alpha]_D^{21} = +10 \pm 0.3°$ (c1.2 in $CHCl_3$). Hence optical purity $7.4 \pm 0.2\%$ (see Chapter Three). The ^1H n.m.r. was similar to that reported above for the racemic aziridine [50] and the t.l.c. showed one spot Rf 0.63 (alumina eluting with 8:2 light petroleum: ether).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] and Chlorine

2-t-Butylamino-1-phenylethan-1-ol [51] (0.431g, 0.0024 mol) and triethylamine (0.292g, 0.0029 mol) were dissolved in dry acetonitrile (23ml) under nitrogen. (-) Menthyldiphenylphosphine [1] (0.4g, 0.00123 mol) was dissolved in dry acetonitrile (10 ml) and dry chlorine was bubbled through the acetonitrile until the solution was saturated. Dry nitrogen gas was bubbled through this solution to remove any excess chlorine, and then the solution was added dropwise over ½h to the stirred triethylamine solution at 0°C. The reaction mixture was then

stirred for 24h at room temperature. The product was purified in the usual way to yield the aziridine [50] (0.138g, 64%) $[\alpha]_D$ = +67.5° (c3 in $CHCl_3$). Optical purity 50% (see Chapter Three).

Preparation of 1-t-Butyl-2-Phenylaziridine [50] with a Limiting Amount of (-) Menthyldiphenylphosphine [1] and Excess Chlorine

This experiment was done exactly the same as the previous example, except on half the scale, and the excess chlorine was not removed by bubbling nitrogen through the chlorine solution. The reaction mixture did not show any sign of the expected aziridine [50] from t.l.c. Half the reaction mixture was put onto an alumina column and eluted with ether, ether/methanol, and then methanol, but only the phosphine oxide [69] and 2-t-butylamino-1-phenylethan-1-ol [51] were obtained. The other half of the reaction mixture had the solvent removed and was taken up in hot chloroform and then petroleum spirit was added. Some white crystals were formed on cooling and were filtered off. These crystals proved to be triethylamine hydrochloride. The yellow oil resulting from removal of the solvent from the mother liquors was taken up in hot chloroform and petroleum spirit was added. On cooling, some white crystals formed and these were filtered off and recrystallised from chloroform/petroleum spirit to yield (30mg, 24%), m.p. 205-206°C $[\alpha]_D^{21}$ = +3.1 ± 0.3° (c0.03 in $CHCl_3$). ^1H n.m.r. δ 1.5 (9H, s, tBu), 3.1 (2H, AB portion of ABX system, J_{ax} = 3Hz, J_{bx} = 8Hz, J_{ab} = 10.5Hz, $C\underline{H}_2$), 5.4 (1H, X portion of ABX system, J_{ax} = 3Hz, J_{bx} = 8Hz), 6.5 (1H, bs, N$\underline{H}$), 7.3 (5H, m, Ph). T.l.c. on alumina eluting with chloroform one spot Rf = 0.5. m/e 176, 175, 174, 160, 144, 104, 77, 57, 58, 36. An accurate chemical analysis could not be obtained. The compound obtained was thought to be the hydrochloride salt of 2-t-butylamino-1-chloro-1-phenylethane [59] which might be expected to be rather unstable

hence the difficulties experienced with the chemical analysis.

^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] and Chlorine in Acetonitrile

(-) Menthyldiphenylphosphine [1] (0.062g) was dissolved in dry deoxygenated acetonitrile (1ml) and a ^{31}P n.m.r. spectrum of this solution recorded. This showed predominantly one peak at -5.4 p.p.m. due to the phosphine,[1] and a trace of phosphine oxide [69] at +32.1 p.p.m.[1] The solution was saturated with dry chlorine at 0°C and then allowed to warm to room temperature. A ^{31}P n.m.r. spectrum of this solution showed two peaks at +81.1 p.p.m. and a much smaller peak at +56.3 p.p.m. On addition of approximately one mole equivalent of freshly sublimed aluminium trichloride the signal at +56.3 p.p.m. broadened considerably and shifted to +57.7 p.p.m.; the other peak was still sharp but had shifted to +80.1 p.p.m. On addition of a large excess of aluminium trichloride three peaks were visible, one at 80.7 p.p.m. which was still very sharp, one quite broad signal at 57.7 p.p.m. and a minor peak at 54.5 p.p.m. On addition of excess water the signals disappeared leaving one signal at 39.1 p.p.m.

^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] and Chlorine in Dichloromethane

This experiment was conducted in the same way as described above. The solution saturated with chlorine had the following ^{31}P n.m.r. spectrum: one major peak at +82.9 p.p.m. and one minor peak at +54.9 p.p.m.

^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] and Chlorine in Toluene

This experiment was conducted in the same way as described above. The solution saturated with chlorine had the following ^{31}P n.m.r. spectrum: one major peak at +81.7 p.p.m. and one minor peak at +60.7 p.p.m.

^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] and Carbon Tetrachloride in Acetonitrile

(-) Menthyldiphenylphosphine [1] (0.045g) was placed into a clean dry ^{31}P n.m.r. tube and a tightly fitting septum cap was fitted. The tube was then thoroughly flushed out with nitrogen and dry acetonitrile (1ml) was added by syringe. The ^{31}P n.m.r. spectrum showed one peak at -5.4 p.p.m. To the solution was added dry carbon tetrachloride (0.1ml) by syringe and again the ^{31}P n.m.r. spectrum was recorded. There were three peaks present at +82.1 p.p.m., +44.2 p.p.m. and a small peak at +32.0 p.p.m. On addition of water the peak at 82.1 p.p.m. disappeared leaving two peaks at +43.6 p.p.m. and +38.1 p.p.m.

^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] and Carbon Tetrachloride in Dichloromethane

This experiment was exactly the same as the previous example except dichloromethane was used as solvent. The ^{31}P n.m.r. spectrum of the phosphine/carbon tetrachloride mixture showed three peaks: +84.5 p.p.m., +44 p.p.m. and a small peak at +34.1 p.p.m.

Low Temperature ^{31}P n.m.r. Studies on the Reaction of 2-t-Butylamino-1-Phenylethan-1-ol [51] (-) Menthyldiphenylphosphine [1] and Carbon Tetrachloride in the presence of Triethylamine

(-) Menthyldiphenylphosphine [1] (0.086g, 2.7×10^{-4} mol) and 2-t-butylamino-1-phenylethan-1-ol [51] (0.047g, 2.7×10^{-4} mol) were placed into a clean dry ^{31}P n.m.r. tube and a tightly fitting septum cap was fitted. The tube was flushed out with nitrogen and then dry dichloromethane (1 ml) and triethylamine (0.1 ml) were added by syringe. While the tube was under a slight positive pressure of nitrogen, the tube was cooled down in liquid nitrogen and carbon tetrachloride (0.04g, 2.7×10^{-4} mol) was added by syringe. The ^{31}P n.m.r. spectrum was recorded at -85°C and consisted of one peak at -7 p.p.m. No change in the ^{31}P n.m.r. spectrum was seen on warming until at -10°C a very small peak at +83.5 p.p.m. was

seen. Again no further change was seen until the temperature was increased to +5°C. The spectrum at +5°C consisted of four peaks at -7 p.p.m., +33.3 p.p.m., +35.1 p.p.m. and a peak at +43.6 p.p.m. At 5°C the phosphine could be seen to be slowly disappearing to be replaced by the phosphine oxide [69]. The tube was allowed to warm up to room temperature and stand for 1h and the ^{31}P n.m.r. spectrum again consisted of four peaks at -7 p.p.m. (trace), +33.3 p.p.m. (major peak), +35.1 p.p.m. (small peak) and +43.6 p.p.m. (minor peak).

<u>^{31}P n.m.r. Studies on the Reaction of (-) Menthyldiphenylphosphine [1] Carbon Tetrachloride and 2-t-Butylamino-1-phenylethanol-ol [51] at Room Temperature</u>

This experiment was carried out as described above except it was undertaken at room temperature. No further information was obtained. The ^{31}P n.m.r. spectrum merely showed the gradual disappearance of the phosphine and the gradual appearance of three peaks at +43.8 p.p.m. (minor peak), +34.9 p.p.m. (small peak) and +32.9 p.p.m. (major peak), which correspond to those described in the previous experiment.

<u>Studies on the Effect of Chlorine on the ^{31}P Spectrum of (-) Menthyldiphenylphosphine Oxide [69]</u>

(-) Menthyldiphenylphosphine oxide [69] (6.5mg) was dissolved in dry acetonitrile (1.5ml). The ^{31}P n.m.r. spectrum of this solution showed a sharp peak at +31.9 p.p.m. (lit.[1] +32.1 p.p.m.). When the solution had chlorine bubbled through it for a few seconds the ^{31}P n.m.r. spectrum changed. There was significant line broadening of the signal due to the (-) menthyldiphenylphosphine oxide [69] and the signal had shifted to +35.9 p.p.m. On saturating the solution with chlorine the signal was further broadened and shifted to +43.2 p.p.m.

Low Temperature ^{31}P n.m.r. Studies on the Reaction of Chlorine/(-) Menthyldiphenylphosphine [1] and 2-t-Butylamino-1-phenylethan-1-ol [51]

(-) Menthyldiphenylphosphine [1] (0.075g, 2.4×10^{-4} mol) and 2-t-butylamino-1-phenylethan-1-ol [51] (0.04g, 2.4×10^{-4} mol) were placed into a clean dry ^{31}P n.m.r. tube and then a tightly fitting septum cap was fitted and the tube was flushed out with nitrogen. To the tube was then added by syringe, dry dichloromethane (0.8ml) and triethylamine (0.4ml). While the tube was under a small positive pressure of nitrogen it was cooled in liquid nitrogen and then chlorine (20ml) at atmospheric pressure was added by syringe. The tube was allowed to warm to -95°C with facilities for releasing any pressure built up in the tube due to the warming and the ^{31}P n.m.r. spectrum was run. There were two peaks: one at -5 p.p.m. and a very small peak at +38 p.p.m. On warming to -80°C two further peaks appeared at +79.7 p.p.m. and a much smaller one at +88.3 p.p.m. and the peak at +38 p.p.m. appeared to have increased in intensity. Spectra were recorded at -70°C, -65°C, -60°C and -55°C and no change was recorded apart from the gradual disappearance of the phosphine (-5 p.p.m.), which was completed at -55°C and the gradual increase in intensity of the other three peaks. The tube was allowed to warm up gradually to room temperature and spectra were recorded at -40°C, -10°C, 0°C, 20°C. The only changes that could be seen were the gradual disappearance of the signals at +88.3 p.p.m. and +79.7 p.p.m. and the gradual increase in intensity of the signal at +38 p.p.m. which showed a gradual change in chemical shift on warming to end up at +32.3 p.p.m. at room temperature.

CHAPTER THREE
EXPERIMENTAL SECTION

Introduction

The shift reagent experiments described in this Chapter were all undertaken in carbon tetrachloride that had been freshly distilled from phosphorus pentoxide under a dry nitrogen atmosphere. A small amount of tetramethylsilane was put into the carbon tetrachloride to act as a reference. The volume of carbon tetrachloride used was calculated from the weight and the density.[93] No allowance was made for the change in density of carbon tetrachloride due to the presence of tetramethylsilane.

All manipulations were carried out in a dry box under nitrogen atmosphere. In each case the shift reagent was commercially available and was used without further purification apart from drying over P_2O_5. The preparations of the aziridines studied are reported in Chapter Two and their physical data is also recorded there.

Chiral Lanthanide Shift Reagent Studies on Optically Active 1-t-Butyl-2-Phenylaziridine [50] with $Eu(tfc)_3$

In the mixture that was used to determine the enantiomeric excess, the molar ratio of aziridine [50] to $Eu(tfc)_3$ was 5.3:1 and the concentration of the aziridine was 0.13g cm^{-3}.

Chiral Lanthanide Shift Reagent Studies on Racemic 1-t-Butyl-2-Phenylaziridine [50] with $Eu(tfc)_3$

This experiment was carried out in exactly the same way as the previous experiment. More details are given in Section 3.2.3. The molar ratio of aziridine [50] to $Eu(tfc)_3$ was 4.8:1 and the concentration of the aziridine was 0.12g cm^{-3}.

Chiral Lanthanide Shift Reagent Studies on Optically Active 1-Benzyl-2-Phenylaziridine [57] with $Eu(hfbc)_3$

In the mixture that was used to determine the enantiomeric excess, the molar ratio of aziridine [57] to $Eu(hfbc)_3$ was 12.5:1 and the concentration of the aziridine was 0.14g cm^{-3}.

Chiral Lanthanide Shift Reagent Studies on Racemic 1-Benzyl-2-Phenylaziridine [57] with $Eu(hfbc)_3$

The molar ratio of aziridine [57] to $Eu(hfbc)_3$ was 12:1 and the concentration of the aziridine was 0.11g cm^{-3}.

REFERENCES

REFERENCES AND NOTES

(1) A. J. MacPherson, Ph.D. Thesis, Leicester University, 1980.

(2) L. Pasteur 'Researches on the Molecular Asymmetry of Natural Products', 1860.

(3) R. Bentley 'Molecular Asymmetry in Biology', Academic Press, 1969, p.127.

(4) F. Ehrlich, Chem. Ber., (1904), 37, 1809.

(5) F. Ehrlich, Biochem. Z., (1906), 1, 8.

(6) F. Ehrlich and A. Wendel, Biochem. Z., (1908), 8, 438.

(7) F. Ehrlich, Biochem. Z., (1914), 63, 379.

(8) J. P. Greenstein and M. Winitz 'Chemistry of the Amino Acids', Wiley Interscience, USA, 1961, Volume 1.

(9) C. A. Dekker and J. S. Fruton, J. Biol. Chem., (1948), 173, 471.

(10) V. E. Price and J. P. Greenstein, J. Biol. Chem., (1948), 175, 969.

(11) J. Read and R. A. Storey, J. Chem. Soc., (1930), 2761.

(12) K. Okamoto, E. Minami, and H. Shingu, Bull. Chem. Soc. Jpn., (1968), 41, 1426.

(13) J. F. King, S. K. Sim, and S. K. L. Li, Can. J. Chem., (1973), 51, 3914.

(14) G. Marches, F. Naso, and L. Ronzini, J. Chem. Soc., Chem. Commun., (1974), 830.

(15) A. I. Meyers and K. Kamata, J. Am. Chem. Soc., (1978), 98, 2290.

(16) V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, J. Am. Chem. Soc., (1981), 103, 6237.

(17) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., (1980), 102, 5974.

(18) B. E. Rossiter, T. Katsuki, and K. B. Sharpless, J. Am. Chem. Soc., (1981), 103, 464.

(19) R. Weidman and A. Horeau, Bull. Soc. Chim. Fr., (1967), 117.

(20) A. Horeau, Bull. Soc. Chim. Fr., (1964), 2673.

(21) K. H. Bell, Aust. J. Chem., (1979), 32, 65.

(22) K. H. Bell, Aust. J. Chem., (1981), 34, 665.

(23) A. W. Hoffmann, Proc. Roy. Soc. Lond., (1859), 10, 189.

(24) A. W. Hoffmann, Proc. Roy. Soc. Lond., (1860), 11, 290.

(25) J. B. Lee and T. J. Nolan, Can. J. Chem., (1966), 44, 1331.

(26) R. Appel, Angew. Chem. Int. Ed. Engl., (1975), 14, 801 and references quoted therein.

(27) R. Appel and M. Haistenberg, Organophosphorus Reagents in Organic Synthesis, Academic Press, 1979 and references quoted therein.

REFERENCES AND NOTES (Continued)

(28) R. Rabinowitz and R. Marcus, J. Am. Chem. Soc., (1962), 84, 1312.

(29) R. Appel, F. Knoll, W. Michel, W. Morbach, H. D. Wihler, and H. Veltmann, Chem. Ber., (1976), 109, 58.

(30) R. Appel and K. Warning, Chem. Ber., (1975), 108, 6.

(31) R. Appel and W. Morbach, Synthesis, (1977), 699.

(32) R. Appel, F. Knoll, and H. Veltmann, Angew. Chem. Int. Ed. Engl., (1976), 15, 315.

(33) R. Appel and H. Veltmann, Tetrahedron Lett., (1977), 399.

(34) R. Appel, F. Knoll, H. F. Schoter, and H. D. Wihler, Angew. Chem. Int. Ed. Engl., (1976), 15, 702.

(35) O. I. Kolodyazhnyi, J. Gen. Chem. USSR (Engl. Transl.), (1982), 51, 2125.

(36) R. Appel, R. Milker, and I. Ruppert, Chem. Ber., (1977), 110, 2383.

(37) R. Appel and H. F. Scholer, Chem. Ber., (1978), 111, 2054.

(38) R. Appel and M. Huppertz, Z. Anorg. Allg. Chem., (1979), 459, 7.

(39) I. M. Downie, J. B. Holmes, and J. B. Lee, Chem. Ind. (London), (1966), 600.

(40) J. B. Lee and I. M. Downie, Tetrahedron, (1967), 23, 359.

(41) I. Tomoskozi, L. Gruber, and L. Radics, Tetrahedron Lett., (1975), 2473.

(42) J. I. G. Cadogan and R. K. Mackie, Chem. Soc. Rev., (1974), 3, 87 and references given therein.

(43) B. Castro and D. C. Selve, Bull. Soc. Chim. Fr., (1971), 4368.

(44) B. Castro, Y. Chapleur, B. Gross, and D. C. Selve, Tetrahedron Lett., (1972), 5001.

(45) A. W. Friederang and D. S. Tarbell, J. Org. Chem., (1968), 33, 3799.

(46) R. G. Weiss and E. I. Snyder, J. Chem. Soc., Chem. Commun., (1968), 1358.

(47) R. G. Weiss and E. I. Snyder, J. Org. Chem., (1970), 35, 1627.

(48) R. G. Weiss and E. I. Snyder, J. Org. Chem., (1971), 36, 403.

(49) J. B. Lee and T. J. Nolan, Tetrahedron, (1967), 23, 2787.

(50) J. D. Morrison and H. S. Mosher 'Asymmetric Organic Reactions', Prentice Hall, 1971.

(51) Y. Izumi and A. Tai 'Stereo Differentiating Reactions', Academic Press, 1977.

(52) J. M. Ourt and R. Parthosarathy, J. Cryst. Mol. Struct., (1975), 195, 359.

REFERENCES AND NOTES (Continued)

(53) A. Itai, Y. Iitaka, U. Nagai, and Y. Kamo, Acta Crystallogr., (1976), 32B, 1533.

(54) E. B. Fleischer, N. Axelrod, M. Green, and K. Mislow, J. Am. Chem. Soc., (1964), 86, 3395.

(55) P. von R. Schleyer, 'Carbonium Ions', Interscience, 1968, Volume 1.

(56) G. R. Sullivan, 'Topics in Stereochemistry', Volume 10, p.287 and references quoted therein.

(57) R. R. Fraser, M. A. Petit, and J. K. Saunders, J. Chem. Soc., Chem. Commun., (1971), 1450.

(58) K. Yamamoto, T. Hayashi, and M. Kumada, Bull. Chem. Soc. Jpn., (1974), 47, 1555.

(59) G. R. Sullivan, D. Ciawarella, and H. S. Mosher, J. Org. Chem., (1974), 39, 2411.

(60) D. J. H. Smith and C. Zaracostas, personal communication.

(61) P. E. Fanta, 'The Chemistry of Heterocyclic Systems', J. Wiley, 1964, Part 1, Chapter 2.

(62) S. Gabriel and J. Weiner, Chem. Ber., (1881), 21, 2669.

(63) H. Wenker, J. Am. Chem. Soc., (1935), 57, 2328.

(64) R. Appel and R. Kleinstuck, Chem. Ber., (1974), 107, 5.

(65) I. Okada, K. Ichimura, and R. Sudo, Bull. Chem. Soc. Jpn., (1970), 43, 1185.

(66) D. B. Denney, D. Z. Denney, and B. C. Chany, J. Am. Chem. Soc., (1968), 90, 6322.

(67) G. A. Wiley and W. R. Strine, Tetrahedron Letters, (1967), 2321.

(68) R. Appel and W. Heinzerlmann, GP 1,192,205.

(69) S. Tsuboyama, A. Onta, and M. Yanagita, Tetrahedron Letters, (1969), 44, 3921.

(70) S. Tsuboyama, K. Tsuboyama, S. Tanji, and M. Yanagita, Nippon Kaguku Kaishi, (1976), 3, 540.

(71) S. Tsuboyama, Bull. Chem. Soc. Jpn., (1966), 39, 698.

(72) F. H. Dickey, W. Fickett, and H. J. Lucas, J. Am. Chem. Soc., (1952), 74, 944.

(73) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, J. Am. Chem. Soc., (1974), 96, 1495.

(74) B. C. Mayo, Chem. Soc. Rev., (1973), 2, 49.

(75) A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Rackman, Chem. Soc. Rev., (1973), 73, 553.

(76) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, J. Am. Chem. Soc., (1974), 96, 1038.

REFERENCES AND NOTES (Continued)

(77) J. M. Domagala, R. D. Bach, and J. Wemple, J. Am. Chem. Soc., (1976), 98, 1975.

(78) M. Mintas, A. Mannschreck, and L. Klasino, Tetrahedron, (1981), 37, 867.

(79) S. J. Brois, Tetrahedron, (1970), 26, 227.

(80) K. Yoshikawa and I. Morishima, J. Am. Chem. Soc., (1975), 97, 2950.

(81) K. Yoshikawa, K. Bekki, M. Karatsu, K. Toyoda, T. Kamio, and I. Morishima, J. Am. Chem. Soc., (1976), 98, 3272.

(82) J. B. Grutzner, J. Am. Chem. Soc., (1976), 98, 6385.

(83) I. Morishima, K. Yoshikawa, and K. Owada, J. Am. Chem. Soc., (1976), 98, 3787.

(84) S. Rengaraju and K. D. Berlin, J. Org. Chem., (1972), 37, 3304.

(85) J. B. Lambert, Top. Stereochem., (1971), 6, 19 and references therein.

(86) A. T. Bottini and R. L. Vanetten, J. Am. Chem. Soc., (1965), 87, 855.

(87) S. J. Brois, J. Am. Chem. Soc., (1967), 89, 4242.

(88) J. G. Smith and G. F. Wright, J. Org. Chem., (1952), 17, 1116.

(89) D. Kursorov, Annu. Rev. Phys. Chem., (1901), 318, 327.

(90) M. Tanaka and I. Ogatha, Bull. Chem. Soc. Jpn., (1975), 48, 1094.

(91) J. D. Morrison and W. G. Master, J. Org. Chem., (1974), 39, 270.

(92) R. G. Weiss and E. I. Snyder, J. Chem. Soc., Chem. Commun., (1968), 1358.

(93) 'Dictionary of Organic Compounds', Eyre & Spottiswoode, 4th. Edition.

(94) 'The Aldrich Library of NMR Spectra', The Aldrich Chemical Co., 5, 1C.

(95) S. Manedov, B. M. Alieva, and M. A. Avanesyan, Obshch. Khim., (1964), 34, 2877.

(96) 'The Aldrich Library of NMR Spectra', The Aldrich Chemical Co., 5, 2B.

(97) W. S. Emerson, J. Am. Chem. Soc., (1945), 67, 516.

(98) M. A. Stolberg, J. O'Neill, and T. Wagner, J. Am. Chem. Soc., (1953), 75, 5045.

(99) A. T. Bottini and J. D. Roberts, J. Am. Chem. Soc., (1958), 80, 5203.

(100) J. A. Deyrup and C. L. Moyer, J. Org. Chem., (1969), 34, 175.

(101) S. J. Brois, Tetrahedron, (1970), 26, 227.

(102) S. Tsuboyama, K. Tsuboyama, S. Tunji, and M. Yanagita, Nippon Kaguku Kaishi, (1976), 3, 540.

REFERENCES AND NOTES (Continued)

(103) H. Wollweber, R. Hiltmann, H. Kaller, and H. G. Kroneberg, BP 1,043,510.

(104) T. Tsunerari and Y. Hirosuke, JP 7,126,930.

Appendix

APPENDIX ONE

The following formula may be used to calculate the enantiomeric excess of the product of a kinetic resolution from the enantiomeric excess of the reactant and the percentage conversion:

$$\text{ee of reactant} \frac{(100 - \text{percentage conversion})}{\text{percentage conversion}} = \text{ee of product}$$

The above formula is only applicable if the following conditions apply to the kinetic resolution:-

1) That the kinetic resolution takes place with total inversion or total retention of configuration.

2) That the enantiomers of the reactants and the enantiomers of the product are stable to the reaction conditions and take no part in any reactions other than the kinetic resolution.

ABSTRACT

ENANTIOSELECTIVE REACTIONS OF SOME OPTICALLY ACTIVE PHOSPHINES

by G.F. Jay

The enantioselective chlorination of alcohols by the menthyldiphenylphosphine/carbon tetrachloride reagent previously reported in the literature was investigated and quantified. Further examples were found.

A new enantioselective reaction of menthyldiphenylphosphine/carbon tetrachloride was discovered. This was the synthesis of aziridines by ring closure of β amino alcohols. Other optically active phosphines in conjunction with carbon tetrachloride were found to react in a similar manner to menthyldiphenylphosphine/carbon tetrachloride with a variety of β amino alcohols.

Menthyldiphenylphosphine was found to react enantioselectively with a β amino alcohol in the presence of chlorine.

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