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RECENT ADVANCES IN ASYMMETRIC SYNTHESIS—II†

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† This report extends the coverage of the original report by J. W. ApSimon and R. P. Seguin, "Recent Advances in Asymmetric Synthesis", *Tetrahedron* **35**, 2797 (1979).

INTRODUCTION

The total synthesis of structurally and sterically complex molecules has always been an important area of study, if only to check the assigned structure of isolated material. In the past it was acceptable to leave the isolation of the correct isomer (diastereomer) to the last step. However, in recent years it seems that the new challenge is to produce the desired stereochemistry at the earliest possible step in the sequence and then use the stereochemistry of that site to control the stereochemistry of subsequent reactions.

It is the intent of this report to extend the literature coverage to the end of 1985 highlighting recent advances (the reader is referred to Ref. 245 for a recent monograph on asymmetric synthesis and also Ref. 260). For convenience and clarity the material is arranged according to reaction type.

REDUCTIONS

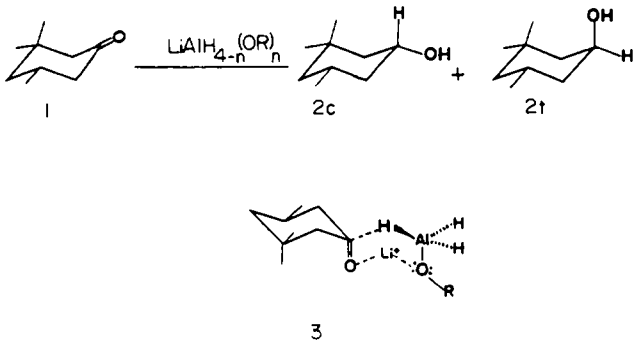
Chiral metal hydride complexes

Aluminium. Chiral lithium aluminium alkoxy hydrides have been in use since 1951 when Bothner-By utilized an LAH/CAMPHOR complex.[1] Since that first reaction many studies have been made to determine methods of increasing the stereoselectivity of the reductions. It has been found that the stereoselectivity is dependent on the temperature, solvents, substrate, the LAH : ligand ratio and the ligands used.

Early work gave poor results since the chiral groups used were alkoxy ligands which were susceptible to disproportionation in solution. This disproportionation gave rise to more than one hydride species in solution

$$2LiAl(OR)H_3 \rightarrow LiAl(OR)_2H_2 + LiAlH_4.$$

In the work by McMohon *et al.*, they stated that in the reduction of 3,3,5-trimethylcyclohexanone **1** with t-butoxyaluminohydride, mono-t-butoxyaluminohydride is most likely the species responsible for the observed stereoselectivity. The presence of a single oxygen atom in the alkoxide moiety permits the formation of a cyclic 6-membered transition state **3** (Fig. 1).

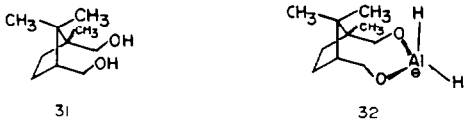


1 2c 2t

3

Fig. 1.

In the presence of di- and tri-t-butoxyaluminohydride, the lithium cation is associated with more than one O atom and is therefore less selective as to its side of attack. In the presence of chiral, rigid ligands the optical yield increases as each hydride is replaced. The use of chiral alkoxy ligands,[14] namely the tris(alkoxy)aluminium hydrides (Fig. 2) of primary alcohols was due to their stability to disproportionation. When (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane **31** is reacted with LAH, two hydrides remain, one hindered (*syn*) and one unhindered (*anti*) hydride. The effect

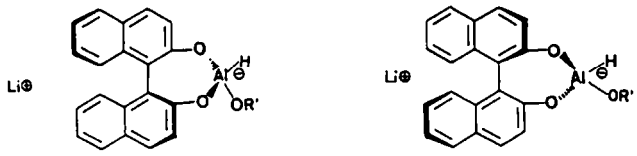


31 32

Fig. 2.

of replacing the less hindered hydride with an achiral hydride, in the reduction of acetophenone, was studied by Johnson and Klein.[14] The usual co-solvents, methanol and ethanol, in the reaction (acetophenone, LAH, **31**, alcohol 1 : 1 :1 :1) gave only a slight increase in the optical yield. There was an increase of two and three times when t-butanol and 2-propanol, respectively, were used as the co-solvent. The addition of the achiral alcohol did increase the optical yield but it also reduced the chemical yield of the reaction. The best solvent system for the reduction of acetophenone was found to be ether–THF (3 : 1).

The use of binal-H[4,5] **4** and **5** in the reduction of aryl alkyl ketones and α,β-acetylenic ketones has increased because of its stability over time and since both enantiomers of binaphthol are available in optically pure forms (Fig. 3). Noyori[4] stated that the observed enantioface differentiation is



4 5

Fig. 3.

kinetically controlled (the optical yield increases linearly as the temperature is lowered to −100°) by the relative stability of the two diastereomeric transition states in the reaction of binal-H and a carbonyl compound. The extent of the asymmetric induction is dependent upon the alkoxide unit (OR′) on the aluminium. The sense of differentiation changes as the alkoxide unit is changed from a simple alkoxide to a β,β,β-trifluoroethoxyl or a 2,6-di-t-butylphenoxy group. The reagents with alkoxy groups such as OMe or OEt exhibit high enantio-selectivity. The transition state with the simple alkoxide is a chair conformation with the most basic alkoxide and the carbonyl oxygen chelated by the lithium cation (Fig. 4). The optical yields from binal-H are at least 60%

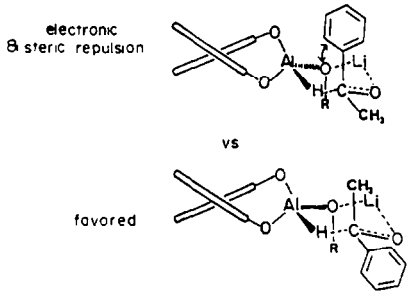


Fig. 4.

and are up to 100%. The use of biphenols as ligands usually resulted in lower optical yields (20–50% e.e.).

There was an increase in the use of LAH reductions when it was found that amine carbinols show less tendency to diproportionate in solution and the lone pair on the nitrogen is able to coordinate, leading to a 5- or 6-membered cyclic transition state, affording a rigid conformation and higher stereoselectivity.

French workers have obtained optical yields of up to 89%[2,3] in the reduction of aryl alkyl ketones with reagents of the type $LiAlH(OR)(OR')_2$ where R = (−)-N-methylephedrine and R′ = 3,5-dimethylphenol.

The reduction of α,β-acetylenic ketones to their corresponding propargylic alcohols has been of major interest in the synthesis of insect phermones, since propargylic alcohols are major intermediates in such syntheses.

Seebach and co-workers[12] found that the N- and O-substituted chiral diols **23a–i** (Fig. 5) prepared from tartaric acid and maleic acid were effective as chiral ligands in the reduction of aryl

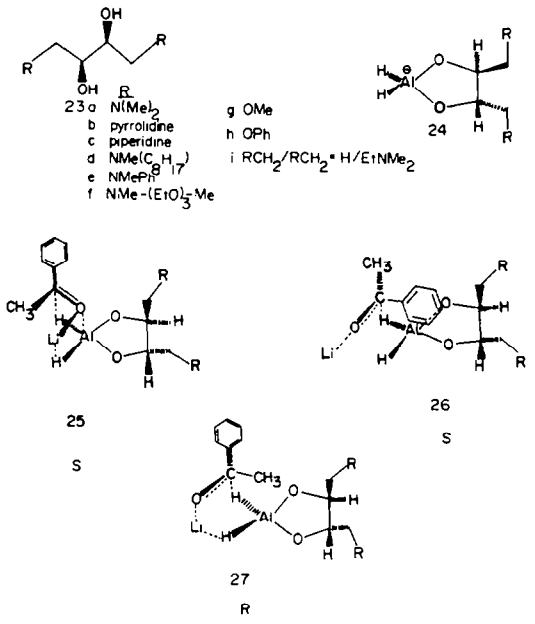
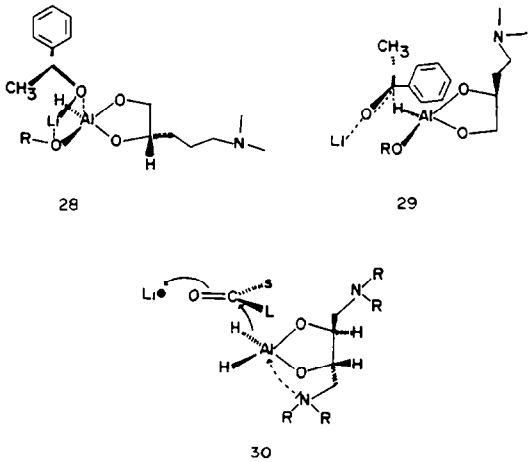


Fig. 5.

alkyl ketones. The diols react with LAH to give complexes, for which a cyclic structure **24** is proposed. The optical yields were in the range of 0.8–45% e.e. with the exception of 1-(2,4,6-trimethylphenyl)-1-ethanone which gave 87% e.e. using complex **24b**. The authors formulated a mechanism to explain the preference of the (*S*)-enantiomer without the participation of the lithium cation, the boat intermediate **25**. If *re*-attack occurs as shown in intermediate **26**, the (*S*)-enantiomer is also formed. If the ketone approaches the hydride from the more favoured *si*-side, as shown in **27**, which has the more favoured chair configuration, this type of attack gives the (*R*)-enantiomer. Also, using the alcohol modified hydride complex **24i**, the (*S*)-alcohol is obtained. This result can be explained by assuming that the reaction proceeds via the boat configuration in intermediate **28**, which contains a pentacoordinated aluminium and also be direct attack of the carbonyl C-atom to the hydride complex **29**. The poor ability of complexes **24** to produce (*R*)-enantiomers as products, can be explained by the large nitrogen substituents in ligands **23e–i** and by the rotation (caused by the methylene group in the ligand) which blocked and differentiated between the two hydrides. The relative basicity and donor abilities of the heteroatoms in a 1,4-position also plays an important role in the relative ease of attack by one of the available hydrides **30**. The mechanisms of the reactions are shown in Scheme 1. The reduction of α,β-unsaturated ketones using a LAH/(−)-N-



Scheme 1.

methylephedrine and N-ethylaniline gave their corresponding allylic alcohols in high optical (78–98% e.e.) and chemical (92–100%) yields.[13] The proposed transition state for the reduction is shown in Fig. 6. The reason for the high stereoselectivity can be seen from the single hydride being delivered from a rigid transition state.

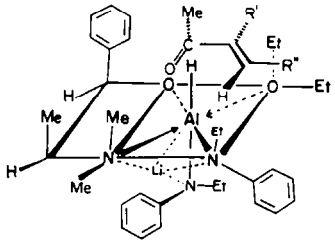
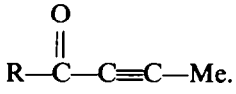


Fig. 6.

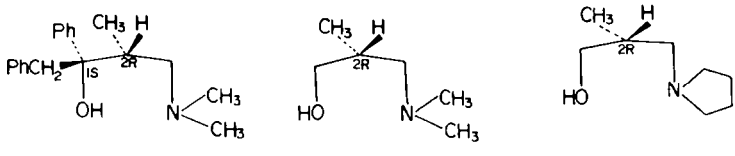
The use of aminols as ligands gives high asymmetric induction, because of their stability and rigidity in solution. An example of this is the reduction of α,β-acteylenic ketones with the chiral complex $LiAlH_4$: N-methylephedrine : 3,5-dimethylphenol[7] to give propargylic alcohols with optical purities in the order of 75–90% e.e.

The use of carbinolamines has been extensively studied and it has been found that under most conditions the optical purities are between 64 and 90%.[8] If the β-position relative to the ketone moiety is chiral there is the possibility of double asymmetric induction. If the carbinolamine is removed, the reduction proceeds with only low asymmetry.



When R is aliphatic, the yield is usually greater than 80% e.e. If the chain extends past seven carbons the optical purity drops to between 60 and 70%. The following generalizations can be made with respect to the Darvon alcohol and its derivatives.

(1) α,β-Acetylenic ketones can be reduced with the Mosher–Yamaguchi ($LiAlH_4$–Darvon alcohol) complex, **7** (Fig. 7), in generally good chemical and optical yields, giving product mixtures in which the (*R*)-carbinol configuration predominates.



7 8 9

Fig. 7.

(2) The enantiomeric ratios appear to be determined by a subtle combination of structural factors present in the substrate as well as the chiral ligand. In certain cases a double induction effect can be observed, leading to either increased or diminished stereoselectivity.

(3) The Darvon alcohol analogues **8** and **9** are able to effect substantial asymmetric induction (34–70% e.e.) which is opposite to that of the Darvon alcohol complex **7**. It is therefore apparent that the chiral secondary methyl centre in **7** is capable of exerting a substantial effect on the asymmetric induction. The results are shown in Table 1.

This effect of removed chiral centres was studied by Morrison *et al.*[9] using the substituted 1,2-aminodiols **10**–**13** (Fig. 8(a)) with different chirality α to the nitrogen.

The authors found that all chiral centres have an additive effect and centres as far away as those in **10** can induce a small (about 10% e.e.) excess of one enantiomer. As can be seen from Table 1, aminodiol **12** shows an additive effect giving the highest optical yield. The authors reported that the

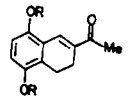
Table 1. Optical yield (reference)/chemical yield (configuration)

				Acetylenic Ketones R'-C≡C-C(O)-R"			
				R'=H		R'=n-Bu	
Reducing agent	A	B	C	D	R"=n-C_5H_{11}	R"=C_8H_{17}	R"=Me	R"=n-C_5H_{11}
LAH:4	95(5) 61(R)			91(4) 62(R)			84(4) 79(R)	
LAH:5		98(5) 62(S)	100(5) 78(S)		84(4) 87(S)	96(4) 80(S)		90(4) 85(S)
LAH:N-methylephedrine: dimethylphenol					84(7) NA(R)	82(7) NA(R)		
LAH:8	60(8) 83(S)							
LAH:9	48(8) 86(S)							
LAH:10	10(9) 87(S)	10(9) 97(S)						
LAH:11	35(9) 90(R)	19(9) 88(R)						
LAH:12	82(9) 98(R)	77(9) 98(R)						
LAH:13	44(9) 85(R)	57(9) 85(R)						
LAH:19	92(38) 93(S)							
LAH:20	93(39) 87(S)	96(39) 90(S)		86(39) 85(S)				
LAH:23a	37(12) S							
LAH:23b	30(12) S							
LAH:23c	17(12) S							
LAH:23d	25(12) S							

Substrate

	E		F	G		H	I	J
Reducing agent	R=Me	R=H		R=H	R=Me			
LAH:(-)-N-methyl ephedrine	92(13) 94(S)	≥90(13) 100(S)	78(13) 92(S)	≥90(13) 100(ND)	98(13) 98(S)			
Tris(S)-2-methyl-butyl Aluminum						7(16) 100(S)	7(16) 100(R)	14.3(16) 100(R)
LAH:94				100(35) 95(S)				
LAH:95				13(37) 35(R)				

A=Acetophenone
B=Propiophenone
C=Butanophenone
D=*alpha*-Tetralone
E=



F=

I=cyclohexenone

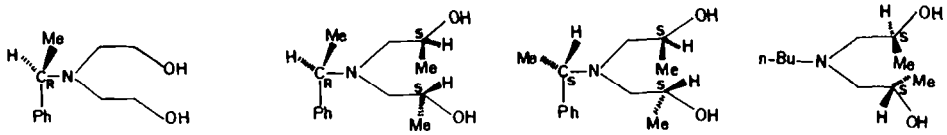
G=

H=methyl vinyl ketone

J=

Table of ligands

4:(R)-Binaphthol
5:(S)-Binaphthol
7:(2S,3R)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol
8:(R)-(-)-3-(dimethylamino)-2-methyl-1-propanol
9:(2R)-3-pyrrolidino-2-methylpropanol
10:(R)-*alpha*-methylbenzyldiethanolamine
11:(R)-*alpha*-methylbenzyl-di-((2S)-propanol) amine
12:(S)-*alpha*-methylbenzyl-di-((2S)-propanol) amine
13:n-butyl-di-((2S)-propanol) amine
19:(S)-2-(anilinomethyl) pyrrolidine
20:(S)-2-(2,6-xylidinomethyl) pyrrolidine
23a:(S,S)-(-)-1,4-bis(methylamino)-2,3-butandiol
23b:(S,S)-(-)-1,4-dipyrrolidino-2,3-butandiol
23c:(S,S)-(-)-1,4-dipiperidino-2,3-butandiol
23d:(S,S)-(-)-1,4-bis(methyloctylamino)-2,3-butandiol
94:(S)-4-anilino-3-methylamino-1-butanol
95:(S)-4-(2,6-xylidino)-3-methylamino-1-butanol



10 11 12 13

Fig. 8(a).

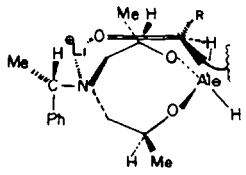
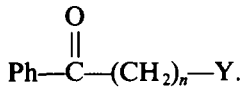


Fig. 8(b).

tertiary nitrogen coordinates with the Li^+ cation which is also coordinated to the carbonyl oxygen (Fig. 8(b)).

The effect of the substituents and the number of methylene groups in the reduction of aryl alkyl ketones **14** with lithium tri-1-menthoxyaluminium hydride was studied by Yamaguchi and Kabuto[10]



They found that when the Y group was alkyl or hydrogen, preferential attack of the hydride is from the *si*-face of the carbonyl group. In most cases the presence of the functional group does not alter the sense of the asymmetric induction. When $n = 2$ or 3 (with Y = OMe) and when $n = 2$ (with $Y = NMe_2$) the stereoselectivity of the reduction increased while with Y = SH the induction decreased. This can be reasoned by oxygen and nitrogen both being hard bases, able to chelate with the lithium cation and sulfur being a soft base, unable to chelate. As the ability to chelate increases the rigidity of the transition state increases. The value of n can be rationalized by the stability of the transition state, when $n = 2$ or 3, a 5- or 6-membered ring is formed (Fig. 9). Since the asymmetric

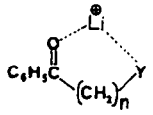
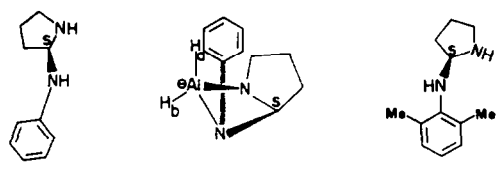


Fig. 9.

induction increases as the rigidity of the transition state increases, bidentate pyrrolidine ligands were found to give excellent results. The complexation of (*S*)-2-(anilinomethyl)pyrrolidine **19** with LAH gives two *cis*-fused 5-membered rings with one of the hydrides (H_a) hindered by the pyrrolidine and phenyl rings **19b**. The optical yields on the reduction of the ketones were in the range of 13–92% e.e.[58] An improved version of this complex was (*S*-2-(2,6-xylidinomethyl)pyrrolidine **20**[59] (Fig. 10).

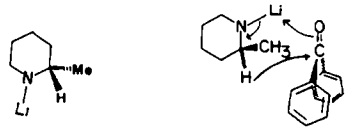


19 19b 20

Fig. 10.

The yield of the reductions, using pyrrolidine **20** as a ligand, were in the range of 11–92% e.e., in most cases the optical and chemical yields were higher than those for **19**. The increased selectivity was reasoned to be due to the two methyl groups which hinder H_a more than the phenyl group alone in **19b**.

The reduction of diaryl ketones was performed by Cervinka *et al.*[11] using an asymmetric Meerwein–Pondorf–Verley reduction. The reaction is based upon the transfer of a hydride anion from the lithium salts of secondary amines to ketones.[12] The mechanism of the transfer using the lithium salt of (*S*)-(+)-2-methyl piperidine **21** is shown in Fig. 11.



21 22

Fig. 11.

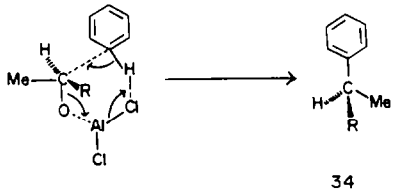
Trialkylaluminium. The reaction of β-branched alkylaluminium dichloride with some aliphatic ketones was studied by Giacomelli and Lardicci.[15] The reactions between alkyl methyl ketones and optically active (*S*)-(2-methylbutyl)aluminium dichloride occurs with defined asymmetric induction, all carbinol recovered was optically active and had the *S* configuration. The stereoselectivity of the reduction depends upon the steric hindrance to the carbonyl C atom, the hindrances increase in the following order Et < i-Pr < t-Bu. The optical yields were in the range of 6–11% e.e.

The mechanism of the reaction is shown in Fig. 12.

33

Fig. 12.

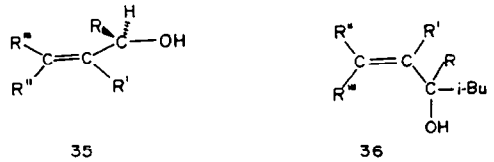
If the reaction is left for 34 h the formation of phenylalkane **34** (Fig. 13) is noted, which is derived from the direct alkylation of benzene. The phenylalkanes observed have the *R* configuration. The lower stereospecificity of the i-Pr and t-Bu is probably due to the steric hindrance of the asymmetric C atom.



34

Fig. 13.

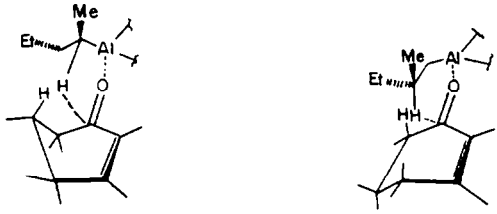
The reduction of a series of α,β-unsaturated ketones using β-branched trialkylalanes was studied by Giacomelli *et al.*[16] In all the cases investigated, no significant amounts of conjugate addition or reduction of the α,β-unsaturated system were detected. However, significant amounts of 1,2-addition products were detected (depends on the nature of the enone and the solvent used). In diethylether only the secondary allyl carbinol **35** was recovered. If the solvent used was pentane, the 1,2-addition **36** of the isobutyl group bound to the Al atom is competitive with the reduction (Fig. 14).



35 36

Fig. 14.

In the reduction of prochiral ketones by tris(*S*)-2-methylbutyl-aluminium dithyletherate, it was predicted that the products (allyl carbinols) should have the *S* configuration (Fig. 15). For linear molecules this is true but for cyclic molecules the major product was of the *R* configuration. The reversal of stereochemistry is due to the steric hindrance of the alkyl groups of the complexed organoaluminium compounds, in the 6-membered transition states **37** and **38**, with the hydrogens or the substituents in the 5- or 6-position of the cyclohexanone ring. This favours **38** which produces the (*R*)-carbinols.

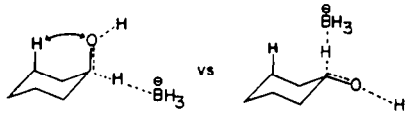


37 38

Fig. 15.

Borane reagents. The asymmetric reductions using trialkyl borohydrides have not seen much success. The optical yields obtained for the reduction of a variety of ketones are in the range of 25–55%. The reagent $NaBH_4$ has received a large amount of use in the simple reduction of aldehydes.

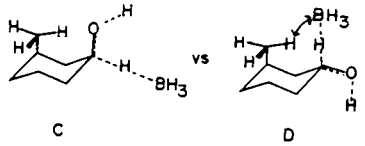
The mechanism of the reduction has been the subject of much controversy and discussion.[17,18] Wigfield[17] gave a very detailed study of all the experimental data and developed the following theory on the reduction of ketones by $NaBH_4$. To a large degree, unhindered cyclohexanones give axial alcohols and hindered cyclohexanones give equatorial alcohols. The reason for these results may be rationalized by looking at structures A–D (Figs 16 and 17). Structure B is favoured over A because of the steric hindrance in A of the oxygen with the C_3 and C_5 hydrogens (Fig. 16.) Structure C is



A B

Fig. 16.

favoured over D because of the steric hindrance in D between the BH_3 and the axial methyl group (Fig. 17). Therefore, sodium borohydride reductions are rationalized by steric interactions involved in the product-like transition state.

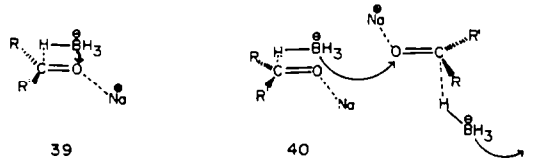


C D

Fig. 17.

There seems to be two distinct mechanisms for the reduction of ketones. In the absence of a protic solvent (e.g. THF) the mechanism originally proposed by Brown,[19] which involves the formation of a tetraalkoxyborate salt, is the mechanism observed. Two routes to this borate salt are proposed by Kayser and Eliev[18] (Fig. 18):

(a) the intramolecular transfer of the BH_3 moiety **39** or,
(b) the intermolecular transfer of the BH_3 moiety **40**.



39 40

Fig. 18.

Kayser and Eliev stated that for statistical and proximity reasons the intramolecular transfer **39** is more likely to occur. In the presence of protic solvents (alcohols), the alkoxyborate anion contains the solvent alkoxide not the alkoxide of the product and the ketone is reduced to the free alcohol.[17]

Much work has been done on the use of alkoxy groups to increase the asymmetric induction of ketones. The use of 1,2 : 5,6-di-O-isopropylidene-α-D-glucofuranose (DIPGF) **41** alone,[20] and in the presence of Lewis acids has been studied by Hiroa *et al.*[21,22]

Morrison *et al.*[23] described a chiral borohydride using sodium borohydride, a carboxylic acid and 1,2 : 5,6-di-O-cyclohexylidene-D-glucofuranose (DCHGF) **42** (Fig. 19) which in THF solutions gave optical yields in the range of 35–50% for the reduction of acetophenone and propiophenone.

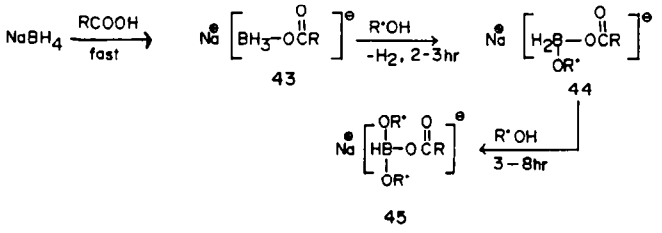
41 42

Fig. 19.

The values are 2–3 times those obtained when the carboxylic acid is omitted and are comparable to those of DIPGF and Lewis acids. It is suggested that the reaction follows the mechanism shown in Scheme 2:

(a) there is the formation of an (acyloxy)borohydride species **43** which is soluble in THF;

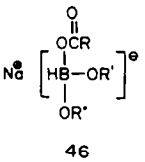
(b) the addition of DCHGF or DIPGF (2 equivs), results in the formation of a mono-alkoxy(acyloxy)borohydride species **44** (indicated by the release of 1 equiv of hydrogen gas in 2–3 h) then slowly the release of the second equivalent of hydrogen as the bis(alkoxy(acyloxy)) intermediate **45** is formed.



43 44 45

Scheme 2.

When complex **44** was formed the authors added the ketone under study. The authors believe that the reduction by complex **44** is faster than by **43**. When complex **44** reduces the ketone, a new species Na^+ $(BH(OR^*)(OR')^-$ **46** (Fig. 20) is formed. This new complex contains one sugar unit and one

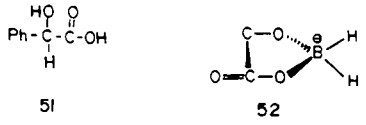


46

Fig. 20.

from the reduced ketone. The competition of the ketone and R*OH for **44** means that some, but not all of the ketone will be reduced by **43**, the rest will be reduced by either **45** or **46**. Complex **44** reduces faster than **45** or **46** but gives lower optical yields than **46**. The authors found that if they waited 8–45 h before adding the ketone, the reaction gave higher optical yields but lower conversion. Hirao *et al.*[24] studied the effect of stereoselectivity vs the carboxylic acid used. They found that the best system for the reduction of acetophenone and propiophenone was using the (*rac*)-PhCH-(Et)COOH/DCHGF (2 equiv). The system had the added feature that when acyl chlorides were present there was no hydrogenolysis detected. Propiophenone could be reduced using the reagent formed by $NaBH_4/(CH_3)_2COOH$ (or /EtCH(Ph)COOH)/DIPGF (1 : 1 : 2) giving optical yields in the range of 39–53% e.e.; if the ratio was changed to 1 : 1 : 4 the optical yield increased to 63%.

Nasipuri *et al.*[26] studied the use of (*S*)-(+)-mandelic acid **51** which forms the tentatively assigned **52** (Fig. 21). The reduction occurs slower than with $NaBH_4$ and is able to reduce saturated ketones



51 52

Fig. 21.

in quantitative yields in 2-propanol; the reduction of unhindered ketones gives equatorial alcohols and the reduction of hindered ketones gives axial alcohols. The reduction of acetophenone required excess reagent and refluxing conditions to give the (*R*)-(+)-enantiomer predominately (in 11.5% e.e.). The reason suggested for the poor asymmetric induction is that in the transition states **53** and **54**, these is no major steric interaction (Fig. 22), but the selectivity is caused by the repulsive dipole–dipole interactions between the ester carbonyl and the phenyl group.

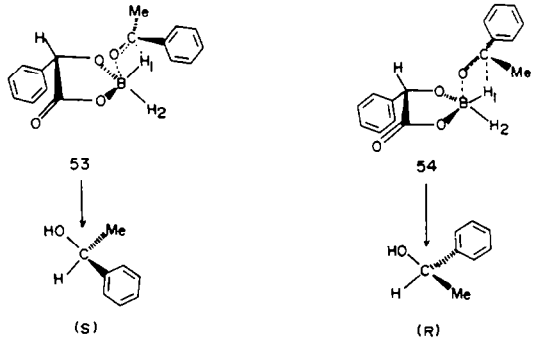
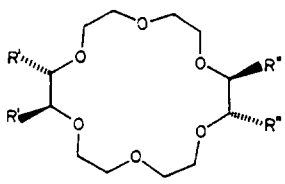
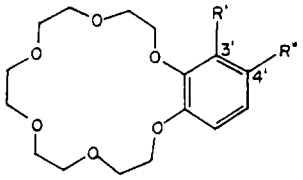


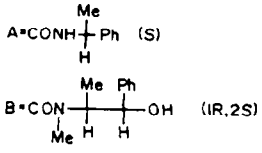
Fig. 22.

Yamamoto and co-workers[27,28] have reported the use of chiral phase transfer catalysts (PTC) (crown ethers, ammonium and phosphonium salts) as a means of inducing chirality in the reduction of carbonyls with sodium borohydride under solid–liquid conditions. The induction using chiral crown ethers was found to be small (0–8.1% e.e.) on the aryl alkyl ketones. The nine ethers tried (**55–63**) are shown in Fig. 23. In the reduction of 1-acetonaphthone, 2-acetonaphthone, acetophenone and ethyl benzoylformate, it was found that using crown ethers[28] **55–57**, the crown ether bearing four chiral centres seemed to furnish more congestion and therefore was a better asymmetric catalyst than that possessing two chiral centres **57**. In most cases of **58–63** the chirality resides on the side chain and it was found that 3-substituted derivatives afforded higher optical yields than the 4-substituted crown ethers. This suggests that the more spatially congested the reaction site above the crown ring, the more significant the chirality induction effect. using **62** and **63** the enantiomeric yields were up to 8% and using crown ethers as catalysts, in general, gave chemical yields in the range of 27–80%.

The use of chiral onium salts in a two-phase system was found to show a dependence on the presence (or absence) of OH groups and the kind of alkyl chain on the heteroatom.







55 $R' = R'' = CON(Me)_2$

56 $R' = R'' = CH_2N(Me)_2$

57 $R' = H$ $R'' = CH_2OCH_2Ph$

58 $R' = H$ $R'' = A$

59 $R' = H$ $R'' = B$

60 $R' = H$ $R'' = C$

61 $R' = H$ $R'' = D$

62 $R' = C$ $R'' = H$

63 $R' = D$ $R'' = H$

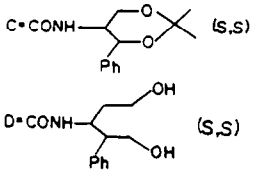
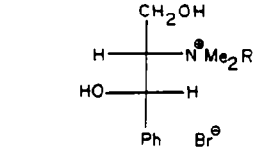
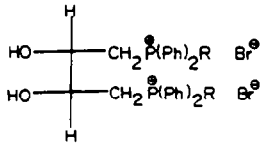


Fig. 23.

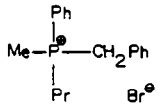
The authors found that the catalyst R = benzylmethylphenylpropylphosphonium bromide **66** which contains a chiral centre on the heteroatom gave no optically active products. The presence of OH groups in the catalyst as well as the bulkiness of the substituents in the substrate may play an important role in the stereochemical course of the reaction. Figure 24 shows the catalysts



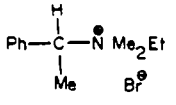
64a R = Et
b R = Bn
c R = dodecyl



65a R = Et
b R = Bn



66



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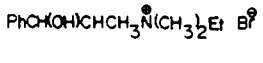

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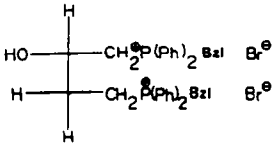

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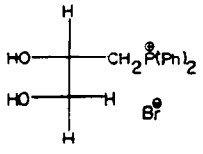


70

Fig. 24.

used in the work reported. When onium salts **64a–c** were used as chiral catalysts (0.4 equiv) in tetrachloroethane–water or chloroform–water, (*R*)-(+)-alcohols were obtained (from 1-acetonaphthone) in 3.8, 8.6 and 8.7% e.e., respectively. With phosphonium salt **65a**, the extent of asymmetric induction was about twice as large as the others (22.2% e.e.) in the reduction of 1-acetonaphthone **71** (Fig. 25). The authors found that water molecules dissolved in the chloroform layer contributed to the asymmetric induction. They found that monoaryl-substituted ketones tend to give low asymmetric yields, poly-substituted ketones give higher yields and the asymmetric bias increased with the concentration of catalyst.

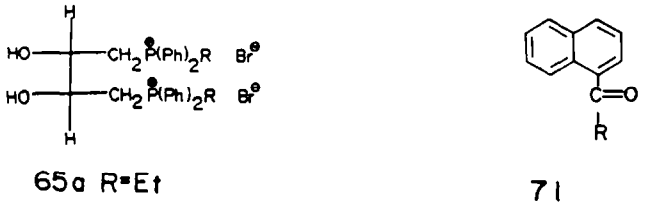


Fig. 25.

Umino *et al.*[29] utilized the chiral Na salts of α-amino acid–borane complexes **72**, which can be prepared from equimolar amounts of sodium borohydride and optically active α-amino aids at room temperature. Sodium prolinate–borane complexes **73** (Fig. 26) were found to be the best reagents,

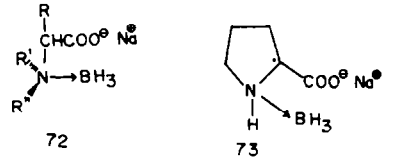


Fig. 26.

giving optical yields as high as 63% with chemical yields of 66–92%. The asymmetric reduction of cyclic imines with complexes of this type were studied by Iwahuma *et al.*,[30,31] concerning the reduction of 3,4-dehydropapaverine **74** to (*S*)-norlaudonosine hydrochloride **75** (Fig. 27). The

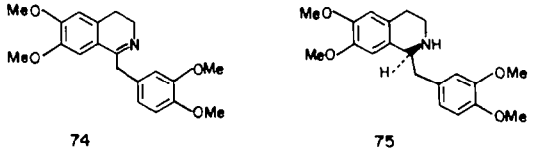


Fig. 27.

triacyloxyborohydrides derived from $NaBh_4$ (1 equiv) and (*S*)-N-acylproline (3 equiv) provided good optical yields (55–60% e.e.) of **75**. The reducing agent tris((*S*)-N-benzoxycarbonylprolyoxy)-hydroborate **76** (Fig. 28) which is isolated as a colourless powder in high yield, was studied as to the

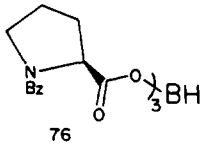


Fig. 28.

effect of solvents on the reduction. Halogenated solvents such as dichloromethane or 1,1-dichloroethane afforded higher optical yields (about 70% e.e.). 3,4-Dehydroisoquinoline derivatives were reduced to give the corresponding (*S*)-amines in high yields (88–90%) and with excellent enantioselectivity (70–86% e.e.). Another important feature is that (*S*)-N-benzyloxycarbonylproline can be recovered in almost quantitative yield after the reduction.

Midland *et al.*[32] found that B-β-pinanyl-9-borabicyclo[3,3,1]nonane **77** (Fig. 29 and Table 3) reduced acetylenic ketones to their corresponding propargylic alcohols of the same absolute configuration ((*R*)-alcohols with (+)-pinene and (*S*)-alcohols with (−)-pinene). In most cases the chemical yields are good and the enantiomeric purities are in the range of 73–100%. The limiting factor in obtaining high optical yields is in the purity of the α-pinene used to form the reducing agent. Brown *et al.*[32b] have reported a method which is able to produce α-pinene of high enantiomeric purity (99.1%) from the commercially available α-pinene of lower enantiomeric purity (92%). The extent of asymmetric induction is sensitive to the size of the size of the substituents on the ketones

Table 2. Reduction of ketones by $NaBH_4$ (optical yield (reference)/chemical yield (configuration))

Reducing agent	Substrates							
	MeC(O)Ph	EtC(O)Ph	nPrC(O)Ph	iPrC(O)Ph	1-aceto-napthone	EtC(O)Me	iPrC(O)Me	tBuC(O)Me
$NaBH_4$:DIPGF	1.9(22) 100(R)	15.8(21) 100(R)	88(22) 100(R)	5.7(22) 98(R)				
" " +1/2 $ZnCl_2$	22.8(21) 99(S)	55.4(21) 66(S)	28.4(21) 100(S)	3.2(21) 99(S)				
" " +1/3 $ZnCl_2$	31.2(22) 100(S)	42.8(22) 100(S)	36.8(22) 100(S)	17.6(22) 98(S)				
" " :iPrCOOH (1:4:1)	64(24) 77(R)	63(24) 56(R)	33(24) 66(R)	18(24) 88(R)				
$NaBH_4$:DCHGF		15.8(22) 97(R)						
" " +1/3 $ZnCl_2$		3.7(22) 97(S)						
$NaBH_4$:DCHGF:iPrCH_2COOH (1:2:1)	46(23) 100(R)	39(23) 100(R)						
" "*trans*-PhCH(Et)COOH (1:2:1)		51(23) 100(R)						
$NaBH_4$:65a					22.2(28) 38.3(R)			
$NaBH_4$:L-Proline	32(29) 92(S)	90(29) 92(S)						
$NaBH_4$:D-Proline	33(29) 66(R)							
IPC_2BH	9(33) NR(R)					13(33) NR(S)	37(33) NR(S)	20(33) NR(S)
$IPCBH_2$	15(33) NR(S)					22(33) NR(S)	46(33) NR(S)	21(33) NR(S)
B-*δ*-Pinanyl-9-BBN	17(33) 100(R)					29(33) 100(R)	36(33) 100(R)	3(33) 100(R)
BH_3:96:Aniline	75(36) 39(R)	48(36) 45(R)		51(36) 42(R)				
BH_3:96:3-nitro aniline	84(36) 98(R)							
BH_3:97:aniline	43(36) 95(S)							
BH_3:98	94(37) 100(R)	94(37) 100(R)	96(37) 100(R)					
BH_3:99			97(37) 100(S)					

NR=not reported in the reference cited

Table of ligands

DIPGF 41 : 1,2:5,6-di-O-isopropylidene-*alpha*-D-glucofuranose
DCHGF 42 : 1,2:5,6-di-O-cyclohexylidene-*alpha*-D-glucofuranose
65a : 2,3-dihydroxytetramethylenebis(dibenzylphenylphosphonium) dibromide
$IPCBH_2$: monoisopinocampheylborane
IPC_2BH : diisopinocampheylborane
B-*δ*-pinanyl-9-BBN : B-*beta*-pinanyl-9-borabicyclo(3.3.1) nonane
96 : (R)-2,2'-dihydroxy-6,6'-dimethylbiphenyl
97 : (S)-2,2'-dihydroxy-6,6'-dimethylbiphenyl
98 : (S)-(-)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol
99 : (R)-(+)-2-amino-3-methyl-1,1'-diphenylbutan-1-ol

but is independent of the presence of other chiral centres in the corresponding propargylic alcohol. The reduction of chromans with (+)- or (−)-α-pinene reagents gave essentially the same degree of asymmetric induction.

The asymmetric induction observed using diisopinocampheylborane IPC_2BH **78** to reduce ketones is lower, since the hydride transfer takes place one atom away from the chiral centre. The reduction of alkyl methyl ketones gave alcohols with enantiomeric purities in the range of 9–37% e.e. Another reagent available in both isomers is monoisopinocampheylborane $IPCBH_2$ **79** which

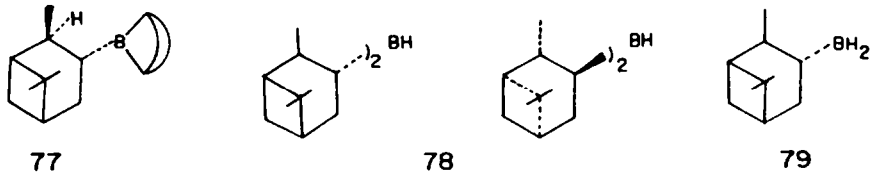


Fig. 29.

Table 3. Reduction of various acetylenic ketones by B-3-α-pinanyl-BBN (optical yield (reference)/chemical yield (configuration))

Substrates										
RC(O)C≡CR'										
		R=Ph			R=Me			R=n-C_5H_{11}		
Reducing agent	R'=	Bu	:	CO_2Et	Ph	: CO_2Et :	t-Bu	H	:	CO_2Et
B-3-*s*-Pinanyl-9-BBN		89(32) 72(R)	:	92(32) 64(R)	72(32) 98(R)	: 71(32) : : 59(R) :	73(32) 62(R)	92(32) 65(R)	:	85(32) 72(R)

reduces aliphatic and aryl alkyl ketones to their corresponding alcohols with optical yields in the range of 15–46%.

Hydroboration. The majority of work done on asymmetric hydroboration is by Brown *et al.*[38,39] One of the most versatile hydroborating reagents, diisopinocampheylborane (ICP_2BH) which is easily prepared in high enantiomeric purity (>99% e.e.) from the commercially available borane–methylsulfide complex and commercially available α-pinene (93% e.e.). It has been applied to the synthesis of alcohols, amines, ketones, alkanes, halides, and α-amino acids. The major synthetic use is in the hydroboration of double bonds to the corresponding alcohols.

The reactivity of ICP_2BH toward *cis*-disubstituted olefins decreases with the increasing steric requirements of the olefins. High asymmetric inductions (80–98% e.e) are achieved in the case of unhindered *cis*-olefins (*cis*-2-butene, *cis*-3-hexene, *cis*-2-pentene, Fig. 30). A remarkable result was

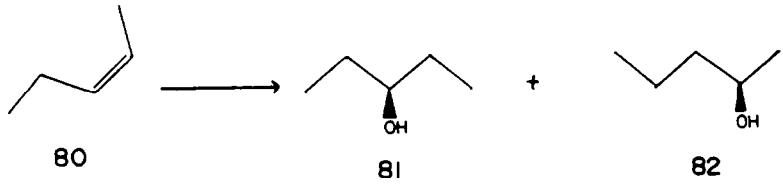
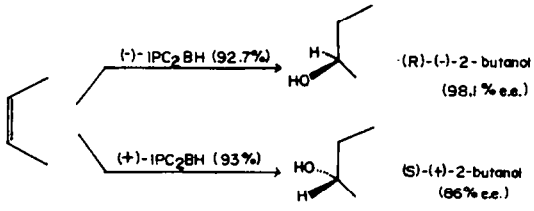


Fig. 30.

that the products 2-butanol and 3-hexanol gave optical purities of 98.1 and 93.1% e.e., respectively which is higher than that of the ICP_2BH (made from 92% α-pinene). Therefore, the optical purity of the products are higher than that of the chiral auxiliary used in the reaction. In the case of *cis*-2-pentene **80** there were two products isolated, 3-pentanol **81** and 2-pentanol **82** (59:41), which is a result of the low regioselectivity of the attack on simple alkenes.

Both symmetrical and unsymmetrical unhindered *cis*-olefins are hydroborated with equally high degrees of asymmetric induction as can be achieved for hindered olefins (60–70% e.e.). The absolute configuration of the new chiral centre at the alcohol position is consistently the same. Since both (+)- and (−)-ICP_2B are available it is possible to produce both alcohols (as in the production of 2-butanol from *cis*-2-butene shown in Scheme 3).

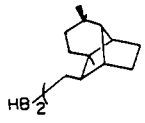


Scheme 3.

It is also possible to perform hydroboration–amination with retention of configuration,[40] asymmetric hydroboration–iodination with inversion of configuration,[41] and the synthesis of *cis*- and *trans*-olefins from 1-bromo-1-acetylenes and 1-acetylenes.[42,47,48] This procedure was recently used to stereospecifically form the *Z*-disubstituted alkene bond in the synthesis of racemic dispalure.[44]

Monoisopinocampheylborane ($ICPBH_2$), is a useful hydroborating reagent for hindered olefins and is available in an optical purity of about 100% e.e. It is capable of hydroborating *trans*-disubstituted and trisubstituted olefins to provide the alcohols in high optical purities (50–100% e.e.) and is effective for olefins with a broad range of steric and structural requirements. The new asymmetric centre at the alcohol position consistently contains the same sense of absolute configuration.[43]

Dilongifolylborane (Lgf_2BH) **83** (Fig. 31), is a hydroborating reagent of intermediate steric



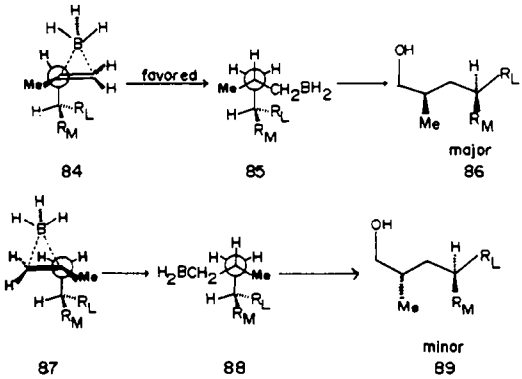
83

Fig. 31.

requirements and was discovered by Jadhav and Brown.[45] Lgf_2BH has the advantage of being able to be stored for long periods and is not susceptible to disproportionation or isomerization. The agent is able to hydroborate tertiary and *cis*-olefins to give alcohols with optical yields in the range of 60–75% e.e. The reagent is readily available in the (+)-form but the (−)-form of longifolene is not readily available.

Good levels of 1,3-asymmetric induction have been observed in the hydroboration of terminal olefins using thexylborane, diisiamylborane and (+)- or (−)-$IPCBH_2$.

Evans *et al.* proposed a transition state model to account for the observed selectivity.[46] In the two transition states shown in Scheme 4, it can be rationalized that the attack of the borane would be from the least sterically hindered conformation.



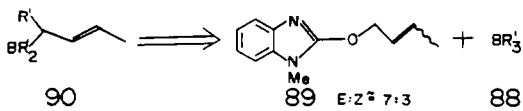
84 85 86

87 88 89

Scheme 4.

The regio- and stereoselective synthesis of γ,δ-unsaturated alcohols has been reported by Yamaguchi and Mukaiyama.[49] The reaction was based upon the following observations.

(1) Allyldialkylboranes **90** are generated by the reaction of trialkylboranes **88** and lithiated 2-(2-butenyloxy)benzimidazole **89** (Fig. 32).



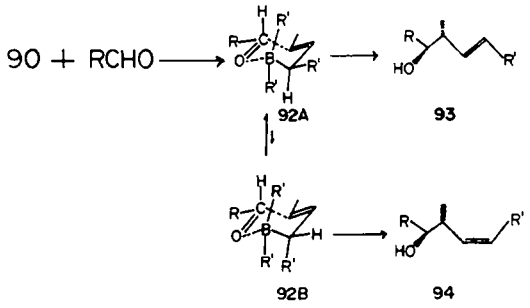
90 89 E:Z = 7:3 88

Fig. 32.

(2) Allyl transposition of allylboranes **90** does not occur at $-100°$, stirring at $-78°$ causes the isomerization. When the allylboranes **90** were treated with aldehydes and ketones γ,δ-unsaturated alcohols **91** were formed regioselectively (Fig. 33).

Fig. 33.

The chemical yields were in the range of 52–91% and the ratios of *erythro*: *threo* were >95: <5 in all reported reactions. The *E*: *Z* ratio of the double bonds were greater than 90: 10 respectively, in all reported cases. The reasons for the high selectivities were given as the fact that the reaction of the allylborane **90** and the aldehydes gives rise to two 6-membered transition states **92A** and **92B** with a chair form Scheme 5).



Scheme 5.

1,3-Diaxial interactions between the hydrogen and the alkyl group in **92B** causes **92A** to be more favourable and hence the preference in the formation of *E*-adduct **93**.

Other asymmetric reductions recently reported include those achieved by actively fermenting yeast.[50–54] The reduction of cyclohexyl-, phenyl-, α-naphthyl- and β-naphthyltrifluoro ketones using actively fermenting yeasts gave the corresponding (*R*)-alcohols in good chemical (70–80%) and high optical yields (44–>99% e.e.). Kitazume and Ishikawa[53] found that in the reduction of perfluoroalkylated ketones, ketoesters and vinyl compounds with bakers yeast, methyl ketones or β-ketoesters carrying bulky perfluoroalkyl groups are reduced by the yeast to their corresponding optically active carbinols in good chemical yields (68–87%) and high optical yields (87–96% e.e.) when the reactions worked. There has recently been an increase in the microbial reduction of carbonyls because of the resulting high optical purities (79–100% e.e.) of the corresponding carbinols obtained.[55–57]

CATALYTIC PROCESSES

Homogeneous asymmetric hydrogenation

Homogeneous asymmetric hydrogenation using transition metal complexes which possess chiral ligands has been accomplished to give high optical yields (77–99% e.e.). Many reviews have been written on this subject.[60–64] The chiral phosphine ligands may be divided into seven classes.

Table of ligand classes. Table 4 shows most of the ligands which have been tested with the various transition metals.

Chiral phosphines may be divided into seven classes of chiral phosphines.

(I) $R'(R^2)(R^3)P^*$
(II) $R^*—PR_2$
(III) $PPh_2—R^*—PR_2$
(IV) $P^*(R')(R'')—(CH_2)_n—P^*(R')(R'')$
(V) $PR''_2—R^*—PR'_2$
(VI) $PR_2—R^*—P(R')(R'')$
(VII) $P^*(R')(R'')—R^*—P^*(R')(R'')$

Table 4. Ligands chiral at carbon

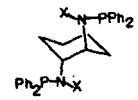
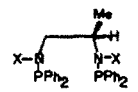
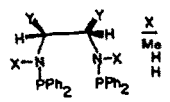
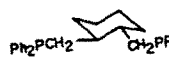
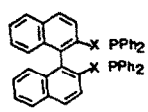
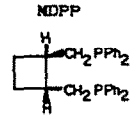
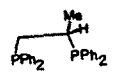
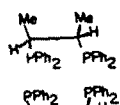
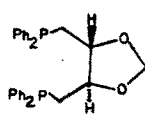
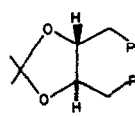
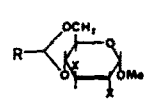
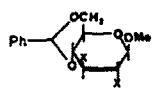
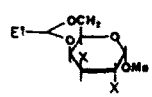
	100 101 101	X=Me (R,R)-1,2-bis[N-methyl(diphenylphosphino)amino]-cyclohexane X=H (R,R)-1,2-bis[(diphenylphosphino)amino]-cyclohexane X=H (S,S)-1,2-bis[(diphenylphosphino)amino]-cyclohexane
	102 103	X=Me (R)-1,2-bis[N-methyl(diphenylphosphino)amino]-propane X=H (R)-1,2-bis[(diphenylphosphino)amino]-propane
	104 105 106	(S,S)-1,2-bis[N-methyl(diphenylphosphino)amino] ethane (S,S)-1,2-bis[(diphenylphosphino)amino] ethane (S,S)-1,2-bis[(diphenylphosphino)amino]-2,3-butane
	107	(1S,2S)-*trans*-1,2-bis(diphenylphosphinomethyl)cyclohexane
	108 109 110	X= $-CH_2-$ (S)-(-)-NAPHOS -O- -NH-
R+S		
NMDPP NDPP 	111 112 114 115	(+)-normenthyldiphenylphosphine (-)-menthyldiphenylphosphine (-)-*trans*-1,2-bis[(diphenylphosphino)methyl]-cyclobutane (+)-*trans*-1,2-bis[(diphenylphosphino)methyl]-cyclobutane
	116	(S)-2,3-bis(diphenylphosphino)-propane (S)-PROPHOS
	117 144	(S,S)-*trans*-2,3-bis(diphenylphosphino)-butane (S,S)-CHIRAPHOS (R,R)-*trans*-2,3-bis(diphenylphosphino)-butane (R,R)-CHIRAPHOS
	118	(R,R)-*trans*-4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyldioxolan (R,R)-(-)-DIOP
	143	(S,S)-*trans*-4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyldioxolan (S,S)-(-)-DIOP
X=OPPh$_2$		
	123 124	R=Et Methyl-4,6-O-propylidene-2,3-bis-O-(diphenylphosphino)-*alpha*-D-glucopyranoside R=Phenyl Methyl-4,6-O-benxylidene-2,3-bis-O-(diphenylphosphino)-*alpha*-D-glucopyranoside
	125	Methyl-4,6-O-benzylidene-2,3-bis-O-(diphenylphosphino)-*beta*-D-glucopyranoside
	126	Methyl-4,6-O-propylidene-2,3-bis-O-(diphenylphosphino)-*alpha*-D-galactopyranoside

Table 4—(*contd.*)

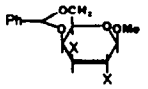
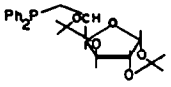
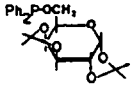
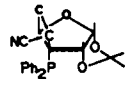
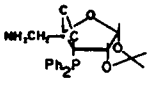
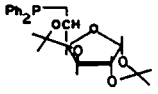
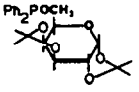
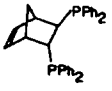
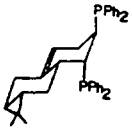
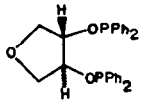
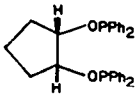
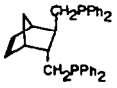
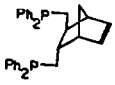
	127 Methyl-4,6-O-benzylidene-2,3-bis-O-(diphenylphosphino)-*beta*-D-galactopyranoside
	128 1,2-O-isopropylidene-3,5-O-(diphenylphosphino)-D-xylofuranoside
	129 6-deoxy-6-C-(diphenylphosphino)-1,2:3,5-di-O-isopropylidene-*alpha*-D-glucofuranose
	130 6-O-(diphenylphosphino)-1,2:3,4-di-isopropylidene-*alpha*-D-galactopyranoside
	131 (6S)-cyano-(5R)-diphenylphosphino-(3R,4S)-O-isopropylidene-2-oxo-bicyclo[3.2.0] heptane
	132 (6S)-(methylamine)-(5R)-diphenylphosphino-(3R,4S)-O-isopropylidene-2-oxo-bicyclo[3.2.0] heptane
	133 6-deoxy-6-C-(diphenylphosphino)-1,2:3,5-di-O-isopropylidene-*alpha*-D-glucofuranose
	134 6-O-(diphenylphosphino)-1,2:3,4-di-O-isopropylidene-*alpha*-D- galactopyranose
	135 (5S,6S,8R)-*trans*-5,6-bis(diphenylphosphino)-8-isopropyl-2-methyl-bicyclo[2.2.2] oct-2-ene (S,S)-PHELLANPHOS
	136 (2R,3R)-bicyclo[2.2.1] hept-5-en-2,3-bis(diphenylphosphine) (-)-NORPHOS
	137 (2S,3S)-bicyclo[2.2.1] hept-5-en-2,3-bis(diphenylphosphine) (+)-NORPHOS
	138 (R,R)-NOPAPHOS
	141 (3S,4S)-tetrahydrofuran-3,4-diyl-bis(diphenylphosphinite) (+)-DIPHIN
	142 (1S,2S)-cyclopentane-1,2-bis(diphenylphosphinite)

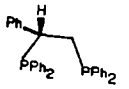
Table 4—(*contd.*)



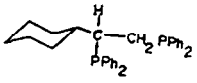
145 (-)-(2R,3R)-*trans*-2,3-bis(diphenylphosphinomethyl)-bicyclo[2.2.1]-hept-5-ene



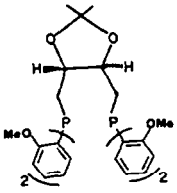
146 (+)-(2S,3S)-*trans*-2,3-bis(diphenylphosphinomethyl)-bicyclo[2.2.1]-hept-5-ene



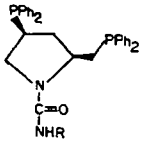
148 (S)-(+)-1,2-bis(diphenylphosphino)-1-phenylethane



149 (R)-1,2-bis(diphenylphosphino)-1-cyclohexylethane R-CYCPHOS



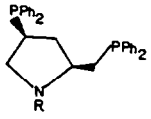
150 (R,R)-4,5-bis(diphenylphosphinomethyl)-2,2-dioxolan



(2S,4S) N-(N'-R-carbamoyl)-4-diphenylphosphino-2- diphenylphosphinomethyl pyrrolidine

151 R=Phenyl Phenyl-CAPP
152 R=p-ClC_6H_4 p-chlorophenyl-CAPP
153 R=p-BrC_6H_4 p-brosophenyl-CAPP
154 R=3,4-$Cl_2C_6H_3$ 3,4-dichlorophenyl-CAPP

155 R=p-$NO_2C_6H_4$ p-nitrophenyl-CAPP
156 R=Me methyl-CAPP
157 R=CH_2=$CHCH_2$ allyl-CAPP
158 R=c-C_6H_{11} cyclohexyl-CAPP



159 R=H (-)-(2S,4S)-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine PPM

160 R=COOtBu
(-)-N-*t*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine BPPM

161 R=$COOC_{27}H_{45}$
(-)-(2S,4S)-N-cholesteryloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine CPPM

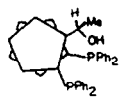
162 R=Me (-)-(2S,4S)-N-methyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine MPPM

163 R=CHO (-)-(2S,4S)-N-formyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine FPPM

164 R=COtBu (-)-(2S,4S)-N-pivalyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine PPPM

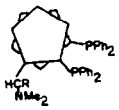
165 R=COMe (-)-(2S,4S)-N-acetyl-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine APPM

166 R=$CONH_2$
(-)-(2S,4S)-N-formamido-4-diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine CAPPM



168 (R)-*alpha*-[(S)-1',2-bis(diphenylphosphino)ferrocenyl] ethyl alcohol
(R)-(S)-BPPFOH

Table 4—(*contd.*)



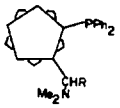
169 R=Me (S)-N,N-dimethyl-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]-ethylamine BPPFA

170 R=i-Pr (R)-N,N-dimethyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]-2-methylpropylamine BPPFA-IP (ANTIPODE)

171 R=Phenyl (S)-N,N-dimethyl-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]benzylamine BPPFA-Ph

172 R=Me (S)-N,N-dimethyl-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]-ethylamine (S)-(R)-PPFA

172a R=Me (R)-N,N-dimethyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl] ethylamine (R)-(S)-PPFA



173 R=i-Pr (R)-N,N-dimethyl-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]-2-methylpropylamine PPFA-IP (ANTIPODE)

174 R=Ph (S)-N,N-dimethyl-1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl] benzylamine (S)-(R)-PPFA-Ph

181 (S,S)-2,4-bis(diphenylphosphino)pentane (S,S)-SKEWPHOS

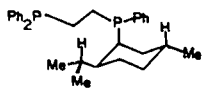
181a (R,R)-2,4-bis(diphenylphosphino)pentane (R,R)-SKEWPHOS

182 R=H (3S)-[N,N'-bis(diphenylphosphino)]-3-aminopiperidine

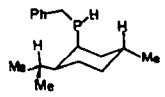
183 R=Me (3S)-[N,N'-bis(diphenylphosphino)-3-(methylamino)-piperidine

257 (S)-2-diphenylphosphinopropyldimethylamine

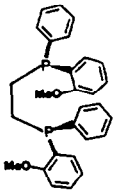
Chiral at Phosphorous



120 (+)-neomenthylphenylphosphine-2-(diphenylphosphino)-ethane
121 (-)-neomenthylphenylphosphino-2-(diphenylphosphino)-ethane



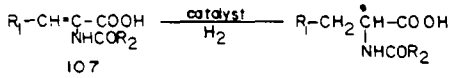
122 neomenthylphenylphosphine



175 DIPAMP

Rhodium catalysts. The most commonly used and successful catalysts are the Rh complexes with chiral ligands. Most complexes utilize bi- and tridendate phosphine or phosphite ligands to lend increased rigidity to the structure which leads to enhanced enantioselectivity.

An efficient route to chiral amino acids by the catalytic asymmetric hydrogenation of α-acylamino acrylic acids **107** (Fig. 34) using a Rh(*R*,*R*)-1,2-bis(N-methyl(diphenylphosphino)amino)-



107

Fig. 34.

cyclohexane 1,5-cyclohexadiene) hexafluorophosphate complex has been studied by Kashibaia *et al.*[65] and Onuma *et al.*[77] The complex gave N-benzoyl-(*S*)-leucine, N-benzoyl-(*S*)-phenylalanine and N-acetyl-(*S*)-phenylalanine in 94, 92 and 98% e.e., respectively.[65,77]

The authors reported that the aminophosphine complexes studied with methyl groups on the N atom always gave (*S*)-amino acids while the aminophosphine complexes without methyl groups gave (*R*)-amino acids. The results of the reaction are summarized below.

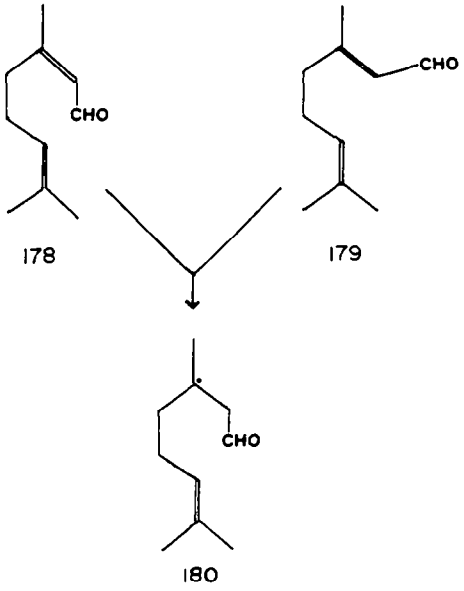
(1) The catalysts of (*R*,*R*)-aminophosphines with secondary amino groups, e.g. **101**, **103**, **105** and **106** show the selectivity to afford (*S*)-amino acid derivatives.

(2) The optical purity of the products depends on the bulkiness of the substituents in a chelate ring. The order, under this test, was **100** > **105** > **104** > **102** > **101** > **106** > **103**.

(3) The products from a substrate with different catalysts, can show a large difference in optical purity, indicating the importance of matching the substrate to the catalyst.

(4) The isolated catalysts gave products of higher optical purity than those catalysts formed *in situ*. This suggests that the chloride ions have a strong co-ordinating ability to the rhodium(I) ion which reduces the selectivity.

Hayaski *et al.*[94] reported that when the diphenylphosphine groups on the ligands were replaced by 5H-dibenzophosphol-5-yl groups (DHP) the rates of hydrogenation increased but the optical yields were much lower. This is due to the loss of steric bulk by the diphenyl groups in the transition state. The asymmetric hydrogenation of α,β-ethylenic aldehydes in the presence of simple olefins to the corresponding saturated aldehydes was accomplished using (+)-1,2-bis(diphenylphosphinomethyl)cyclobutane **145**.[95] The hydrogenation of neral **178** and geraneal **179** gave (+)- and (−)-citronellal **180** in optical yields of 70–79% and 56–60%, respectively (Fig. 35).



178 179 180

Fig. 35.

Some recent work has been performed on the use of carbohydrates **123–128** as the chiral backbone of the ligands, in which all but two of the free OH groups have been selectively protected by standard methods and the two remaining groups are converted to diphenylphosphinate.[70–72] In some cases, the hydrogenation using the rhodium catalysts were conducted in the presence of chiral auxiliary ligands.[73] The hydrogenations of N-acetamidoacrylic acid derivatives were carried out by Jackson and Thompson[70] utilizing the rhodium complex $[Rh(1,4\text{-COD})Cl]_2$ in the presence of two equivalents of the appropriate ligand (Table 5).

The results (Table 5) show that not only was moderate stereochemical control achieved but also that small variations in the stereochemistry of the sugar backbone greatly affects the optical yields (5–75% e.a.). It can be seen that the most readily available D-sugars give the naturally occurring L-amino aids. The asymmetric hydrogenation of *Z*-α-acetamidocinnamic acid and its methyl ester, using the chiral ligand **131**, gave N-acetylphenylalanine and its methyl ester in optical purities of 91 and 70% e.e. (51–100% chemical yield), respectively. When the amine derivative **132** was used as the chiral ligand, the asymmetric induction dropped to 39 and 15% e.e. (100% chemical yield), respectively. The configuration of the amino acid produced was *S* using the nitrile **131** and *R* using the amine **132** ligands. The use of *in situ* formed catalysts, using $[Rh(I)(COD)Cl]_2$ and the phosphinated sugars **133** and **134**, gave good chemical yields (78–100%) however the optical yields were low to moderate (2–67% e.e.) depending upon the substrate tested.

Table 5. Hydrogenation of various olefins with chiral rhodium catalysts (optical yield (reference)/chemical yield (configuration))

Substrates used in Table V

1) (Z)-*alpha*-acetamidocinnamic acid 2) (Z)-*alpha*-benzamidocinnamic acid 3) (Z)-*alpha*-acetamidocinnamic acid
4) (Z)-*alpha*-benzamidocinnamide 5) *alpha*-acetamidoacrylic acid 6) Methyl (Z)-*alpha*-acetamidocinnamate
7) Methyl (Z)-*alpha*-acetamidocinnamate 8) Itaconic acid

Ligand	Substrates 1	2	3	4	5	6	7	8
100	92(77) NR(S)	92(77) NR(S)	-----	-----	-----	-----	-----	-----
(R)-101	70(77) NR(R)	70(77) NR(R)	92(77) NR(S)	70(77) NR(S)	-----	-----	-----	-----
(S)-101	72(77) NR(S)	70(77) NR(S)	-----	-----	-----	-----	-----	-----
	94(77) NR(S)	93(77) NR(S)	94(77) NR(S)	80(77) NR(S)	-----	-----	-----	-----
102	70(65) 90-8(S)	48(65) 90-8(S)	-----	-----	-----	-----	-----	-----
103	28(65) 90-8(R)	21(65) 90-8(R)	-----	-----	-----	-----	-----	-----
104	68(65) 90-8(R)	-----	-----	-----	-----	-----	-----	-----
105	93(65) 90-8(S)	-----	-----	-----	-----	-----	-----	-----
106	45(65) 90-8(S)	32(65) 90-8(S)	-----	-----	-----	-----	-----	-----
107	35(66) 100(S)	8(66) 100(S)	-----	-----	35(66) 100(S)	1(66) 100(R)	35(66) 100(R)	-----
(R)-110	-----	95(89) NR(R)	-----	-----	86(89) NR(R)	69(89) NR(R)	89(89) NR(R)	-----
(S)-110	-----	-----	-----	-----	88(89) NR(S)	-----	-----	-----
(R)-116a	85(82) 100(S)	89(82) 100(S)	-----	-----	87(82) 100(S)	-----	-----	-----
118	81(84) 100(R)	70(84) 100(R)	-----	-----	73(84) 100(R)	55(84) 100(R)	38(84) 100(R)	-----
120	66(69) 100(R)	49(69) 100(R)	-----	-----	-----	66(69) 100(R)	58(69)* 100(R)	-----
121	60(69) 100(S)	85(69) 100(S)	-----	-----	-----	58(69) 100(S)	31(69)* 100(S)	-----
122	0(69) 100	13(69) 100(R)	-----	-----	-----	2(69) 100(R)	12(69)* 100(R)	-----

Table 5—(*contd.*)

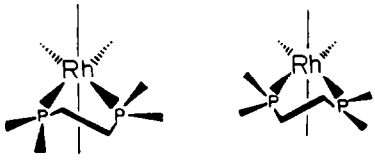
123	36(70) NR(S)		-----		-----		-----		-----		10(70) NR(S)		-----		-----					
124	71(71) 99(S)		-----		-----		-----		-----		60(71) 99(S)		-----		-----					
125	80(70) NR(S)		-----		-----		-----		-----		10(70) NR(S)		-----		-----					
126	5(71) 99(S)		-----		-----		-----		-----		10(71) 99(S)		-----		-----					
127	0(70) NR		-----		-----		-----		-----		20(70) NR(S)		-----		-----					
128	62(70) NR(R)		-----		-----		-----		-----		48(70) NR(R)		-----		-----					
129	9(73) 99(R)		2(73) 72(S)		-----		-----		-----		2(73) 99(R)		-----		14(73) 96(R)					
131	91.6(72) 83.7(S)		-----		-----		-----		-----		70.6(72) 51.4(S)		-----		-----					
132	39(72) 100(R)		-----		-----		-----		-----		15.5(72) 100(R)		-----		-----					
134	67(73) 99(R)		32(73) 85(S)		-----		-----		-----		29(73) 99(R)		-----		49(73) 99(S)					
135	95(75) 100(R)		-----		-----		-----		95(75) 100(R)		-----		-----		-----					
136	93(74) 100(S)		-----		-----		-----		90(74) 100(S)		-----		-----		-----					
137	97(74) 100(R)		-----		-----		-----		-----		-----		-----		-----					
138	80(75) NR(S)		-----		-----		-----		81(75) 100(S)		-----		-----		-----					
141	0(76) NR		-----		-----		-----		-----		20(76) NR(S)		-----		-----					
142	10(76) NR(S)		-----		-----		-----		-----		43(76) NR(S)		-----		-----					
144	88(79) 95-100(S)		94(79) 95-100(S)		-----		-----		91(79) 95-100(S)		-----		-----		-----					
143	82(90) 100(S)		70(90) 100(S)		-----		-----		-----		74(90) 100(S)		38(90) 100(S)		-----					
145	53(78) 100(S)		-----		-----		-----		-----		-----		-----		-----					
146	30(78) 100(R)		-----		-----		-----		-----		-----		-----		-----					
148	82(81) 100(R)		84(81) 100(R)		-----		-----		-----		83(81) 100(R)		-----		-----					
149	84(82) 100(S)		94(82) 100(S)		-----		-----		96(82) 100(S)		-----		-----		-----					
150	31(84) 100(S)		66(84) 100(S)		-----		-----		8(84) 100(S)		71(84) 100(S)		88(84) 100(S)		-----					
151	96.1(88) 100(S)		-----		-----		-----		-----		93(88) 100(S)		-----		92(88) 100(R)					
152	95.6(88) 100(S)		-----		-----		-----		-----		96.1(88) 100(S)		-----		95.3(88) 100(R)					
153	95.2(88) 100(S)		-----		-----		-----		-----		97.4(88) 100(S)		-----		93.7(88) 100(R)					
154	91.9(88) 100(S)		-----		-----		-----		-----		97.9(88) 100(S)		-----		94.0(88) 100(R)					
155	95.3(88) 100(S)		-----		-----		-----		-----		95.7(88) 100(S)		-----		95.4(88) 100(R)					
156	92.5(88) 100(S)		-----		-----		-----		-----		94.3(88) 100(S)		-----		94.3(88) 100(R)					
157	91.3(88) 100(S)		-----		-----		-----		-----		92.5(88) 100(S)		-----		93.2(88) 100(R)					
158	90.7(88) 100(S)		-----		-----		-----		-----		93.2(88) 100(S)		-----		94.2(88) 100(R)					

Table 5—(*contd.*)

160	-----	-----	-----	-----	-----	-----	-----	-----	92(87) 100(S)
169	93(92) 100(S)	37(90) 100(S)	-----	-----	35(90) 100(S)	69(90) 100(S)	35(90) 100(S)	32(87) 100(R)
170	82(90) 100(R)	-----	-----	-----	42(90) 100(R)	-----	-----	21(90) 100(S)
171	52(90) 100(S)	-----	-----	-----	42(90) 100(S)	-----	-----	34(90) 100(R)
172	67(90) 100(R)	-----	-----	-----	-----	-----	-----	-----
174	34(90) 100(R)	-----	-----	-----	-----	-----	-----	-----
175	94(106) NR(S)	96(106) NR(S)	-----	-----	93(106) NR(S)	-----	-----	77(90) 100(R)
181	93(96) 100(R)	76(96) 100(R)	-----	-----	98(96) 100(R)	-----	76(96)* 100(S)	-----
181b /THF	1(96) 100(S)	12(96) 100(R)	-----	-----	9(96) 100(R)	-----	4(96)* 100(R)	-----
181b /EtOH	20(96) 100(S)	10(96) 100(S)	-----	-----	5(96) 100(R)	-----	10(96)* 100(S)	-----
182	73(97) 100(S)	39(97) 100(S)	-----	-----	80(97) 100(S)	-----	-----	-----
183	79(97) 100(S)	73(97) 100(S)	-----	-----	84(97) 100(S)	-----	-----	-----
184	86(98) 100(R)	-----	-----	-----	60(98) 100(R)	-----	-----	-----
186	64(100) 100(R)	-----	-----	-----	-----	-----	-----	-----
187	91(100) 100(R)	-----	-----	-----	-----	-----	-----	-----

* note in this case the ethyl ester was used instead

PHELLANPHOS **135**,[75] NOPAPHOS **138**,[75] and NORPHOS **136** and **137**[74,78] are easily available chiral 1,2-diphosphines. PHELLANPHOS and NORPHOS were found to be more selective than NOPAPHOS, by chelation (*S,S*)-PHELLANPHOS **135** gave rise to a rigid 5-membered ring of D-absolute configuration **139**. (*R,R*)-NOPAPHOS must adopt an alternate conformation because the 1,3-diplanar conformation is not suitable for chelation on a rhodium ion. The most likely conformation is the half-chair. Therefore (*R,R*)-NOPAPHOS would produce a rigid 5-membered ring of L-conformation **140** (Fig. 36).

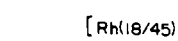


139 140

Fig. 36.

The chelate ring inversion of **139** and **140** is not possible because of the constraints introduced by the fusion with the other rings. The general rule that (*R,R*)-configuration of the phosphine ligand gives rise to (*S*)-amino acids also holds for these ligands.[75] The hydrogenation of α-(acetylamino)cinnamic acid, α-(acetylamino)acrylic acid using NOPAPHOS, NORPHOS and PHELLANPHOS gave optical yields in the range of 79–97% e.e. It was found that DIPHIN **141** displays similar trends to the closely related BDPCP **142**. The optical yields, for both ligands, increased in the order amide < ester amide < α-ethylstyrene, although the magnitude of induction was lower for DIPHIN **141**, about half that of the same reaction using (−)-DIOP **118**, the products were of

opposite configuration. NORPHOS **136** and **137**[78] forms a 5-membered chelate ring in a very rigid conformation and induces the asymmetric hydrogenation of α-acetamidocinnamic acid, with an optical yield of 96% e.e., if the NORPHOS is modified by adding a CH_2 group between the phosphorus and the chiral C atom, ligands **143** and **144** result. The asymmetric hydrogenations using ligands **145** and **146** gave high chemical yields but only moderate optical yields (43–53% e.e.).[78] The lower optical yields are probably due to the loss in rigidity because a 7-membered ring is formed in the reaction, as compared to the 5-membered ring using **136** and **137**. The use of (*S,S*)- and (*R,R*)-CHIRAPHOS **117** and **144**[79] in the asymmetric hydrogenations formed a rigid 5-membered ring and followed the general rule to give (*R*)- and (*S*)-amino acids, respectively. The norboradiene complex **147** gave amino aids in high chemical (95–100%) and optical yields (80–99% e.e.) (Fig. 37).



147

Fig. 37.

Bosnich and co-workers[96] found that (*S,S*)- and (*R,R*)-SKEWPHOS **181** and **181a** followed the general rule to give (*R*)- and (*S*)-amino acids, respectively, with optical yields greater than 90% e.e. The authors also found that the ligand, (*S*)-CHAIRPHOS **181b** gave poor results (<24% e.e.) and the sense of the induction was not consistent, it was dependent on both the substrate and the solvent used, unlike the SKEWPHOS ligands. The low induction can be explained if the ring is in a chair conformation because the phenyl groups will be in an achiral array.[96]

The asymmetric hydrogenation of *Z*-benzamido(acetamido)-3-(2-thienyl)-2-propionic acids using Rh–DIOP systems ((*R,R*)- and (*S,S*)-DIOP **118** and **143**) gave virtually quantitative conversion and optical yields upto 78%, and it was found that the Rh–DIOP catalysts were insensitive to sulfur poisoning.[80] Pinto *et al.*[93] reported that under their conditions the best ligand for the hydrogenation of N-acetyldehydrophenylalanyl-(*S*)-phenylalanine (methyl ester, Fig. 38) to give a mixture of

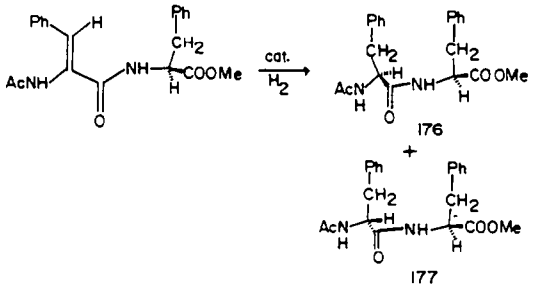


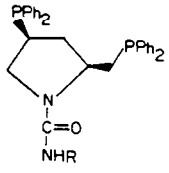
Fig. 38.

Ac-(*S*)-phe-(*S*)-pheOMe **176** and Ac-(*R*)-phe-(*S*)-pheOMe **177** were DiPAMP **175** or BPPM **160**. DiPAMP favoured the production of the (*S*)-product **176** (optical yield >90% e.e.) and BPPM favoured the (*R*)-product **177** (optical yield >80% e.e.).

King *et al.*[81] reported the synthesis of a chiral ditertiary phosphine ligand derived from mandelic acid, 1,2-bis(diphenylphosphino)-1-phenylethane **148**. The rhodium complex was tested as the preformed complex and as prepared *in situ*. It was found that the preformed cationic catalyst (ClO_4) gave better results than that of the catalyst formed *in situ*. Both methods gave complete hydrogenation and optical yields in the range of 76–88% e.e. which is lower than those using the closely related ligand PROPHOS **116**. Another bidentate phosphine (*R*)-CYCPHOS **149** has been prepared by Riley and co-workers.[82,83] The asymmetric hydrogenation of *Z*-α-amidoacrylic acids, at ambient temperature and pressure, with the Rh(I)–(*R*)-CYPHOS cationic complex gave the corresponding (*S*)-α-amino acid derivatives in high chemical yields and with optical yields in the range of 80–98% e.e. When compared with PHENPHOS and PROPHOS the order of optical yield is CYCPHOS > PHENPHOS > PROPHOS. The CYCPHOS based catalyst has a relatively poor ability to reduce ketones and did not function as a hydrogenation catalyst unless a base (e.g. triethyl amine) was present.

Brown and Murrer[84] found that when *o*-anisyl groups were substituted for the phenyl groups in (*R*,*R*)-DIOP **118**, the ligand (*R*)-PAMPOP **150** was obtained. The authors found that PAMPOP hydrogenated *Z*-dehydroamino acid esters in higher optical yields than their corresponding acids, and in the opposite optical sense to the DIOP ligand.

A series of 4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine ligands **151–166** were produced and studied by Achiwa and co-workers[85–87] and Ojima and co-workers.[87,88] They found that a rigid structure of the chiral ligand is not necessarily a crucial factor, but some flexibility plays an important role which enables "*induced-fit*" of the chiral metal complex molecules corresponding to the shape of the substrate.[88] The asymmetric hydrogenation of α-acetamidocinnamic acid, methyl α-acetamidocinnamate and itaconic acid using *in situ* formed CAPP–rh complexes (CAPP = carbomyl-4-diphenylphosphino-2-diphenylphosphinopyrrolidines). Complexes using ligands **151–158** (Fig. 39) gave products with optical purities in excess of 90% e.e. It was shown that the enantioselec-



167

Fig. 39.

tivity exhibited in these reactions are dependent upon the stereoelectronic nature of the substituent R in the CAPP ligand, **167** and the addition of triethyl amine causes only a slight change (change depends on the ligand and the substrate used) in the enantioselectivity of the production of N-acetyl-(*S*)-amino acids, their methyl esters and (*R*)-methylsuccinic acid. The asymmetric hydrogenation of itaconic acid with Rh(I)–BPPM **160** gave the (*S*)-methylsuccinic acid in optical yields upto 92% e.e., depending on the amount of base used and the nature of the catalyst. If the catalyst was preformed (the cationic catalyst. $((BPPM)Rh(I)(COD))^+ ClO_4^-$) the best results were obtained using a triethylamine : itaconic acid ratio of 1 : 1, if the catalyst was produced *in situ* (the neutral catalyst BPPM + $(Rh(I)(COD)Cl)_2$) the best results were obtained using a ratio of 2 : 1, respectively. The experimental results indicate that triethylamine acts as an "activating agent" for a carboxylic acid moiety, generating the carboxylate anion of the acid, which is able to coordinate with the rhodium metal. The proposed mechanisms[86] for the asymmetric hydrogenation of di- and trifunctional acids are shown in Figs 40 and 41.

The asymmetric hydrogenation of α-acylaminoacrylic acids and esters with axially dissymmetric bisaminophosphine–rhodium complexes **110**[89] which are available in both *R* and *S* configurations, gives the corresponding amino acids in moderate to high optical yields (up to 95% e.e.). The catalyst

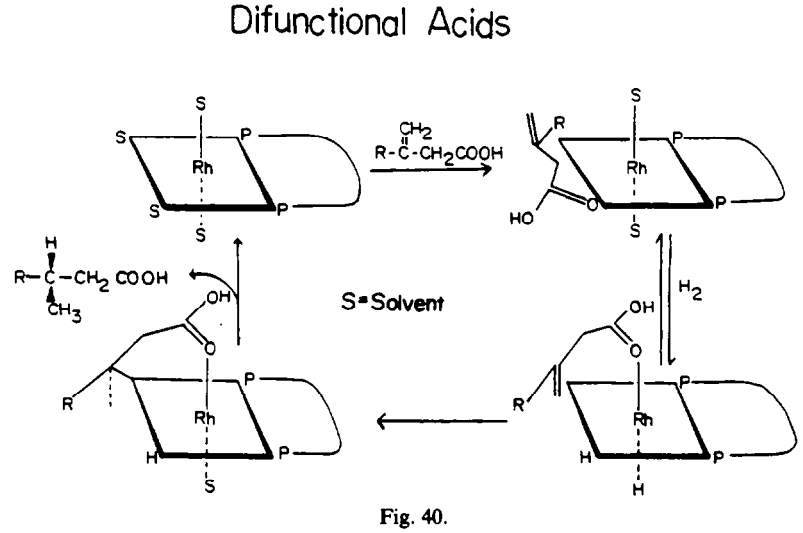


Fig. 40.

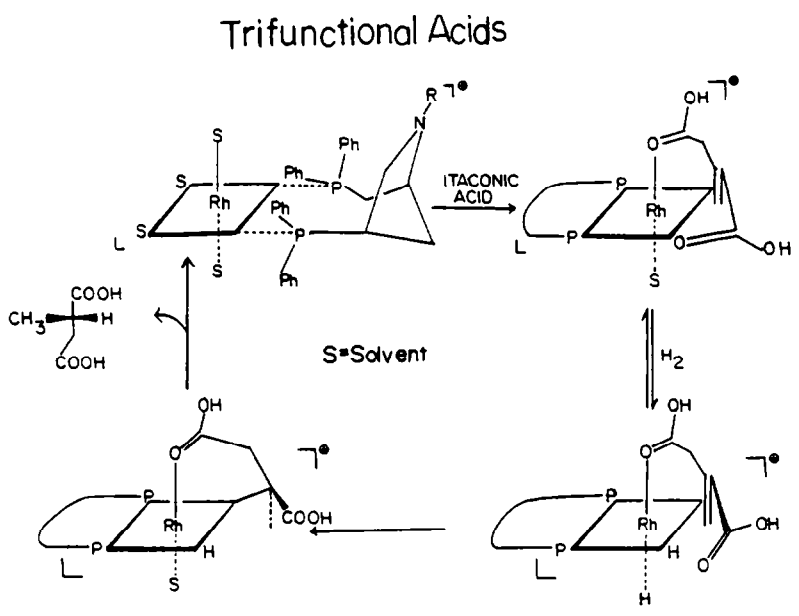


Fig. 41.

is formed by mixing $[Rh(COD)Cl]_2$ with either of the (*R*)-antipodes. The choice of solvent is important for obtaining high optical yields. The authors found that the free acids tended to give higher optical yields than the corresponding esters which indicates the necessity of the complexation of the CO group to the catalyst in the transition state.

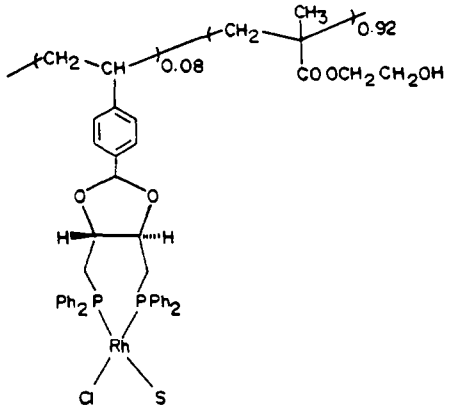
The asymmetric hydrogenation of (*Z*)-α-acetamido- and (*Z*)- and (*E*)-α-benzamidocinnamic acids and their methyl esters using Rh–RPPFA **169** and its derivatives **170–174** was studied by Yamamoto *et al.*[90] The optical yields varied according to the substrate used and the order of optical induction for the hydrogenation using Rh(I)–BPPFA was $Z > E$, acetamido > benzamido. The induction using the acids was larger than that with the esters. The order followed that of (+)-DIOP as the ligand except the yields were slightly lower in all cases. The parent BPPFA **169** is much superior in the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic and acrylic acids than the other analogues **170** and **171**. The chirality of the products using the bisphosphines **169–171** were opposite to the chirality of ferrocene (i.e. if the configuration of the ferrocene is *R* the product amino acid was *S*). The monophosphines **172–174** gave predominately the (*R*)-products. The fact that inverse selectivity was observed between the mono- and biphosphines may be explained by the different conformations of the bisphosphine chelate of **169** and **171** from that of P–N chelate of **172** and **174**, respectively.

Kumada and co-workers[91] reported that secondary alkyl alcohols of high optical purity could be obtained by the asymmetric hydrogenation of enol phosphinates, which are capable of coordinating to rhodium with P=O instead of C=O.

The rhodium cationic complex with (*R*)-1-((*S*)-1′,2-bis(diphenylphosphino)ferrocenyl)ethanol ((*R*)-(*S*)-BPPOH) **168** was the best catalyst, exhibiting high enantioselectivity (78% R) and high catalytic activity (100% conversion in 40 h). For the other catalysts used, the order of enantioselectivity was BPPOH **168** > (−)-DIOP **118** > BPPM **160** > BPPFA **169**. The ligand (*S*)-PROPHOS **116** gave no reaction under the conditions reported. When rhodium complexes of (3*S*)-(N,N′-bis(diphenylphosphino))-3-amino- and methyl aminopiperidine **182** and **183** were used to hydrogenate N-acyl-α-aminoacrylic acids, only (*S*)-amino acids were obtained. This indicates that N-methylation of the ligand does not cause any difference in the conformation of the ligand. It was found that the N-methylated ligands induced greater selectivity, up to 84% e.e.

One of the biggest problems of asymmetric hydrogenations is that in most cases neither the rhodium nor the phosphine is readily recoverable. Therefore, attempts are being made to attach the ligand to a polymer which will allow for the easy removal of the catalyst. A DIOP-type ligand was attached to a cross-linked polystyrene polymer to give the ligand **184**[98] (Fig. 42).

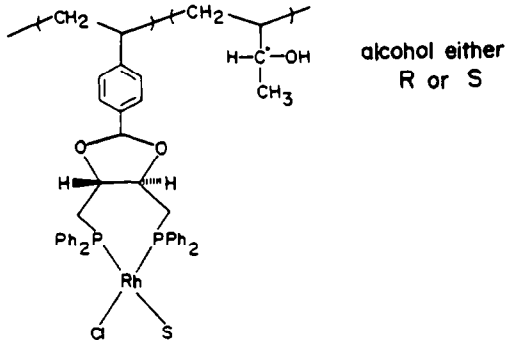
This catalyst was reported to give yields comparable to that of the homogeneous catalyst but took slightly longer to reach completion. The polymer has one drawback, that it can be expected



184

Fig. 42.

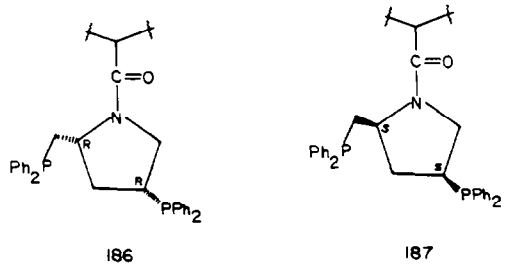
to undergo hydrolysis and/or alcoholysis under continued use. An improved version of the catalyst was **185** (Fig. 43) which gave, in alcohol solvents, optical yields similar to that of the homogeneous DIOP catalyst. The configuration of the pendant alcohol plays an important role in the transition state. This catalyst was easily removed by filtration without loss of optical purity.



185

Fig. 43.

Since the diphenylphosphino-diphenylphosphinomethylpyrrolidine ligands are excellent ligands for asymmetric hydrogenation, other polymer bound catalysts have been produced which possess the 4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine group as a pendant function, **186** and **187** (Fig. 44). The optical yields using these catalysts were as high as 93% in the production of amino acids.



186 187

Fig. 44.

Brown and Murrer[84] found that when *o*-anisyl groups were substituted for the phenyl groups in (*R*,*R*)-DIOP **118** a new ligand (*R*)-PAMPOP **150** was obtained. The authors found that (*R*)-PAMPOP was able to hydrogenate *Z*-dehydroamino acids in the opposite stereochemical sense to

(*R,R*)-DIOP. The ligand gave higher optical yields with the esters, rather than the acids of the dehydroamino acids.

Ruthenium, iridium, nickel and platinum. Other metals, such as ruthenium, iridium, nickel and platinum have been used, with moderate results, in asymmetric hydrogenation.

An excellent review on the use of ruthenium was written by Matteoli *et al.*[101] They reported that the ruthenium complexes gave lower induction than the corresponding rhodium complexes, however, the investigation of ruthenium complexes in asymmetric work is merited by the advantages given below.

(1) Ruthenium is more readily available and is cheaper than rhodium.

(2) Higher or comparable optical yields, with respect to rhodium catalysts, have been obtained in the reduction of α,β-unsaturated acids.

(3) Cluster ruthenium complexes such as $H_4Ru_4(CO)_8$(−)-DIOP) showed unusual selectivity, i.e. in the ability to reduce a carboxylic group in the presence of an olefinic double bond.

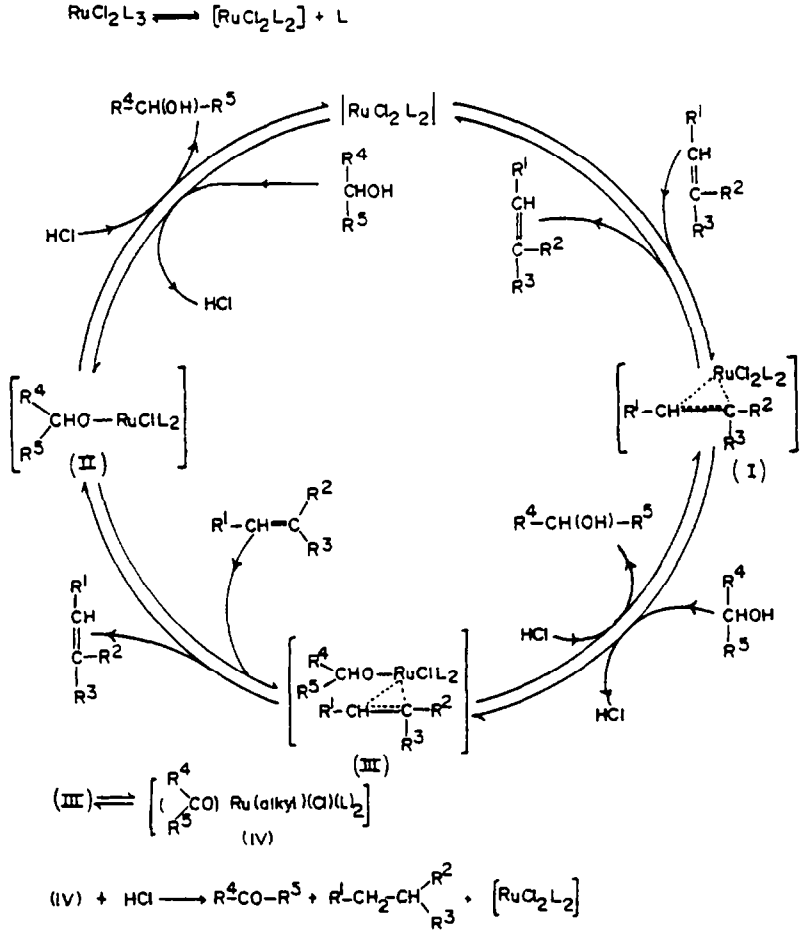
(4) Ruthenium derivatives are efficient at asymmetric transfer hydrogenation but the optical yields are still low (<10% e.e.). The mechanism of the transfer was postulated by Ohkuba, the ruthenium catalyzed transfer is more efficient than those of rhodium (Scheme 6).

The asymmetric reduction of prochiral ketones has been reviewed by James.[105] The asymmetric reduction of prochiral carbonyls can be catalytically accomplished using two methods.

(1) Direct hydrogenation across the C=O bond.

(2) Hydrosilylation of the carbonyl and subsequent hydrolysis of the silyl ether.

(1) The mechanism of the hydrogenations of ketones is not understood, but there seems to be two different types of substrates, the first are simple aryl alkyl ketones (i.e. acetophenone or



Scheme 6.[101]

propiophenone) where the optical yields are low and the second, using functionalized ketones or CO-containing substrates (compounds containing esters, amines, etc.) where the optical yields are high (75–90% e.e.). The higher enantioselectivity of functionalized carbonyls is due to their ability to generate a secondary interaction with the rhodium, which produces a chelating effect similar to that seen for olefins (Fig. 45).

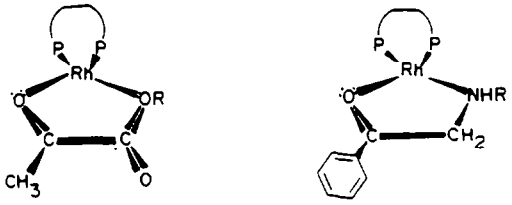
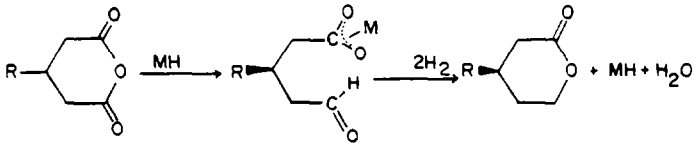


Fig. 45.

The asymmetric hydrogenation of simple ketones with phosphine–rhodium complexes (Rh–DIOP) usually occur with low efficiency. Toros *et al.*[102] reported that the addition of triethylamine to the *in situ* formed catalysts show higher catalytic activity and optical yields up to 53% using acetophenone as the substrate. The authors also reported that the solvent plays an important role in the hydrogenation, they found that when benzene was used as the solvent, the optical yield of the hydrogenation of acetophenone was 80% e.e. The mechanism of the reaction seems to be; first, the nucleophilic attack of the rhodium hydride complex on the CO group, and second, that an interaction between the aromatic rings of the ketone and those of the chiral DIOP ligand. Ikariya and co-workers[103] reported that optically active γ- and δ-lactones are obtained by the hydrogenation of 5- and 6-membered cyclic anhydrides using the Rh(II)–DIOP complex as a catalyst.

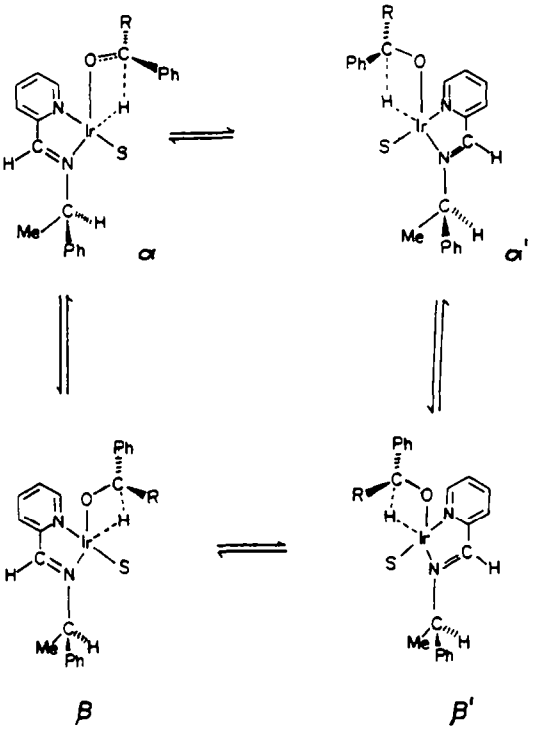
It is supposed that the reaction proceeds via ruthenium aldo-carboxylate complexes, formed by the cleavage of the C—O bond of cyclic anhydrides, followed by the formation of the aldehyde group from a CO group and a hydride ligand[103] (Fig. 46). The optical yields obtained for the reactions were in the range of 5–20% e.e.



M = Ru-DIOP

Fig. 46.

The advantage of the use of transfer hydrogenation of ketones with ruthenium complexes is that the source of chirality may be located in either the phosphine ligand or in the hydrogen donor itself. The reduction of ketones, α,β-unsaturated ketones and Schiff bases can be accomplished better by the use of iridium(I) complexes containing nitrogen donor ligands, such as 2,2′-bipyridine and 1,10-phenanthroline, iridium(I) complexes with Schiff bases as ligands are effective species for transfer hydrogenation from alcohols to ketones.[104] Zassinovich *et al.*[104] reported the use of two cationic species of the type $(Ir(I)(COD)L)^+ CLO_4^-$ (L = (+)- or (−)-2-pyridinalphenylethylimine (PPEI); L = (+)- or (−)-2-pyridinal-3(iminomethyl)pinane (PIMP)) in the reductions of prochiral ketones. Both catalysts gave good chemical yields (about 80%) but the iridium PPEI complex is more selective than the iridium PIMP complex. The substrate seems to determine the configuration of the product. Aryl alkyl ketones are reduced with a higher selectivity (up to 14% e.e.) than the alkyl methyl ketones. The configuration of the reduction products are determined by the substrates, aryl alkyl ketones are always reduced to the (*R*)-alcohols and the alkyl methyl ketones are reduced to the (*S*)-alcohols. The enantioselectivity observed can be explained by taking acount of the equilibria between the diastereomeric forms of the catalytically active species. Each has two chiral centres, the penta-coordinated iridium(I) and the asymmetric C atom in the ligand (Scheme 7).



Scheme 7.

Table 6. Hydrogenation of ketones (optical yield (reference)/chemical yield (configuration))

Ligands	Substrates A	B	C	D	E	F	G	H	I
Rhodium									
143	80(92) 64(R)	------	------	------	------	------	------	------	------
160	------	------	------	------	------	------	65.3(85) 100(R)	------	80(92) 100(R)
161	------	------	------	------	------	------	67.3(85) 99(R)	62.8(85) 98(R)	------
168	43(92) 100(R)	43(92) 100(R)	83(92) 100(R)	93(92) 100(R)	77(92) 100(R)	69(92) 100(R)	92(92) 100(R)	------	------
Ruthenium									
118	8(101) 40(S)	0.6(101) 100&62(R&S)	11.2(101) 95.3(S)	------	------	------	------	------	------
118'	4.3(101) 34.9(S)	1.9(101) 21.5(S)	0(101) 58.0	------	------	------	------	------	------
Iridium									
PIMP	1.3(104) 84(R)	------	------	------	------	------	------	------	------
PPEI	13.6(104) 91(R)	------	------	------	------	------	------	------	------

' reaction performed in the presence of propan-2-ol

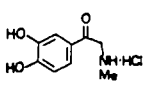
Table of Substrates

A) PhC(O)Me

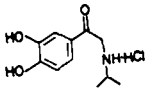
B) t-BuC(O)Me

C) MeC(O)C(O)OH

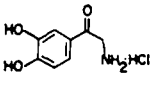
D)



E)



F)



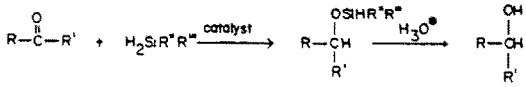
G) MeC(O)C(O)OEt

H) MeC(O)C(O)O-n-Bu

I)

The optical yield will depend on both the equilibrium ratios for the diastereoisomers and the orientation of the ketone itself in the transition state, in which a new chiral centre is created by hydride transfer. If the orientation is specific, the optical yield must depend on the equilibrium between α and α' or between β and β'. A significant variation in the optical yield is observed on varying the nature of the chiral ligand, and this is related to the equilibrium ratio between α and α' or β and β'.

(2) The hydrosilylation of ketones follows the basic mechanism shown in Scheme 8.



Scheme 8.

Kagan and co-workers[107] reported that the data they collected, on their work with *p*-substituted acetophenones, indicated that electronic effects are important suggesting some intervention of charge transfer interactions.[108] Introduction of electron-donating and withdrawing groups into the aromatic groups of the silane or the ketone substrate does not lead to any decisive conclusion regarding the electronic or steric influences of these substituents on the asymmetric induction.[107] Hydrosilylation of *p*-substituted acetophenones was shown to depend markedly upon the substitution of the substrate and not upon the silane substituents. Using RhCl((−)-DIOP)-catalysed hydrosilylations gave yields between 12 and 63% e.e. Brunner and Riepl[109] reported that rhodium complexes of optically active Schiff bases gave the best yields when the active species were formed *in situ* (see Fig. 47). The

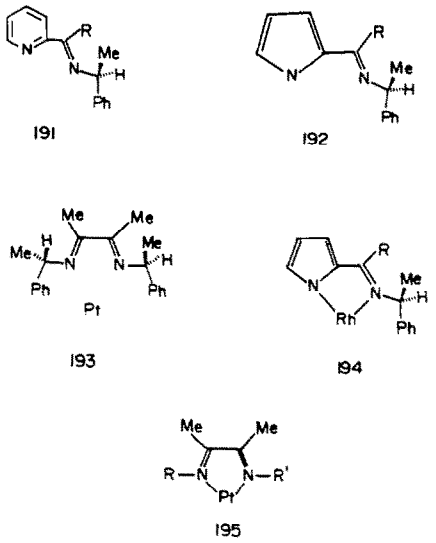
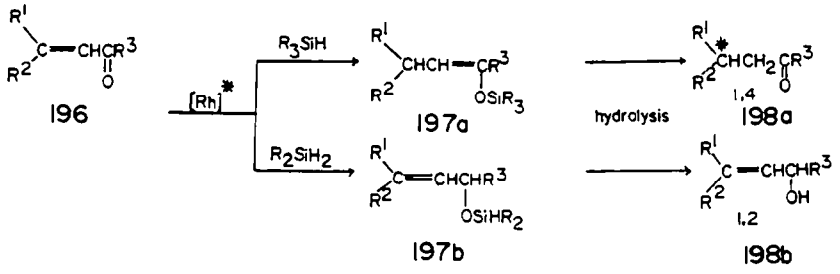


Fig. 47.

preformed catalysts (Rh(COD)LL) PF_6 or $K(PtCl_2(ethylene)LL)$ gave poor to moderate hydrosilylation (10–70%) and only slight optical induction (0–1.8% e.e.). If, however, the catalyst was formed *in situ* from $[(COD)RhCl]_2$ or $K[PtCl_3(ethylene)]$ with a large excess of the chiral ligand (10–18 times for the rhodium catalyst and 36 times for the platinum catalyst) the optical yields were increased up to 57% e.e. and the chemical yields were between 66 and 95%.

The synthesis of allylic alcohols via regioselective asymmetric hydrosilylation of prochiral α,β-unsaturated ketones using the rhodium(I) complexes with (+)-BMPP, (+)-DIOP and (−)-DIOP has been studied by Brunner and Riepl.[109] There are two kinds of regioselective asymmetric reductions of prochiral α,β-unsaturated ketones; the first is the 1,2-addition of hydrosilanes, the second is the 1,4-addition (Scheme 9). The extent of asymmetric induction was found (for 1,2-addition) to be sensitive to the structure of the substrate and the hydrosilane when DIOP is used.

The Pd(II) complexes of menthyldiphenylphosphine MDPP **199** and neomenthyldiphenylphosphine NMDPP **200**[110] were found to be effective as chiral catalysts for the asymmetric hydrosilylation of styrene and some cyclic conjugated dienes (Fig. 48).



Scheme 9.

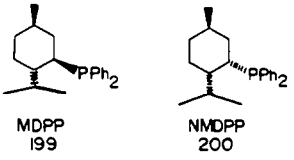


Fig. 48.

The two ligands, **199** and **200**, differ only at the chiral C-3 centre adjacent to the diphenylphosphino group and gave enantiomeric (*R*)-(+)- and (*S*)-(−)-1-phenylethyltrichlorosilane, in 34 and 22% e.e., respectively, by the hydrosilylation of styrene with trichlorosilane. The mechanism suggested for the formation of the 1-phenylethyltrichlorosilane is the migration of a silyl group bound to the palladium into a benzylic position of a π-α-methylbenzyl–palladium complex.

In the hydrosilylation of 1,3- and 1,4-cyclohexadiene, using the above conditions, only the *S* configuration was obtained (Fig. 49). The intervention of a π-allylic palladium is suggested to account for the observed enantioselectivity (Fig. 50).

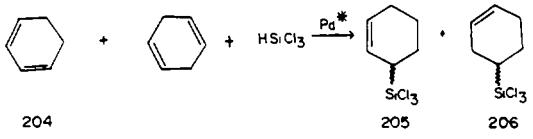


Fig. 49.

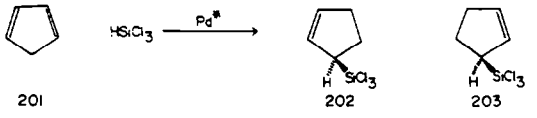


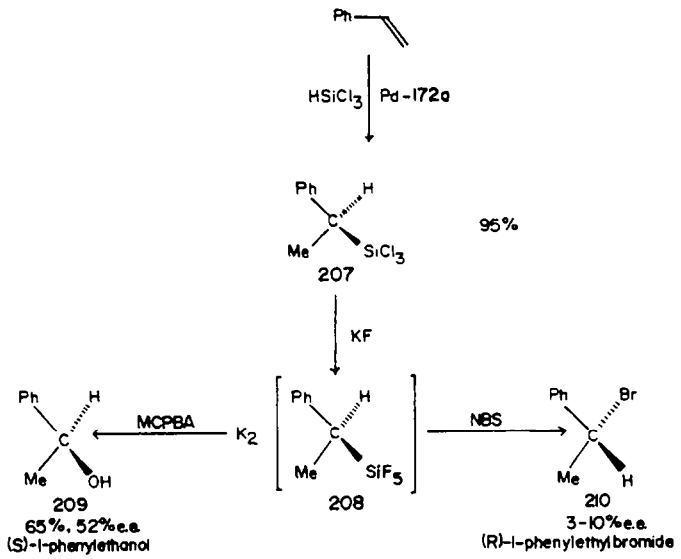
Fig. 50.

Kumada and co-workers[112] reported the asymmetric hydrosilylation of a prochiral olefin was performed in the presence of the chiral phosphine–transition metal complex Pd–PPFA **172a**, and the conversion of the resulting allylsilane to the corresponding alkylpentafluorosilicate and the cleavage of the C–Si bond to an optically active alcohol (by treatment with MCPBA, in 65% chemical and 52% e.e.) with retention of configuration or to the corresponding bromide (by treatment with NBS, in 3–10% e.e.) with inversion of configuration (Scheme 10). The lower optical purity of the bromide may be accounted for by a partial racemization under the reaction conditions.

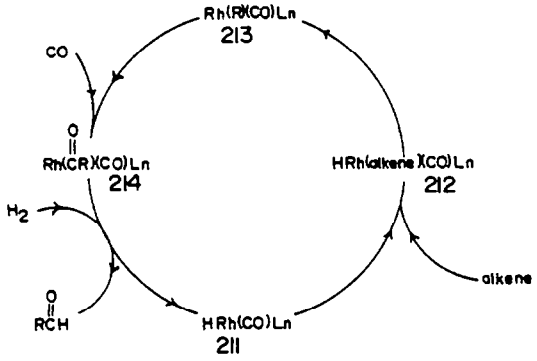
Hydroformylation

The hydroformylation reaction converts an olefin to a saturated aldehyde using carbon monoxide and hydrogen in the presence of a homogeneous transition metal catalyst. Rhodium has been found to be 10^3–10^4 times more active than cobalt. Many reviews have been written on asymmetric hydroformylation.[106,113,114] The mechanism for the rhodium-catalyzed hydroformylation reaction has been well studied and the proposed catalytic cycle is shown in Scheme 11.

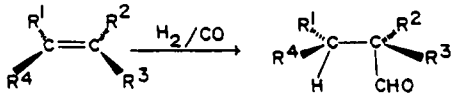
In the asymmetric hydroformylation of prochiral alkenes, there are four possible products which are produced from four independent transition states (Scheme 12).

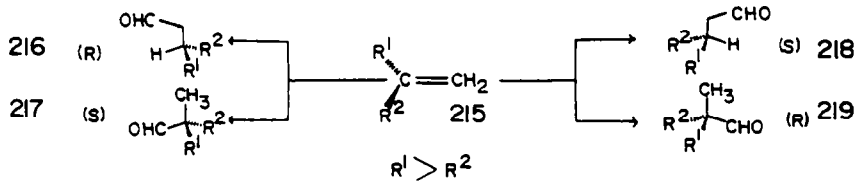


Scheme 10.



Scheme 11.





Scheme 12.

Consiglio and Pino[113] produced a model which gives the correct qualitative site of formylation. To correlate the results of asymmetric hydroformylation the following assumptions have been made.

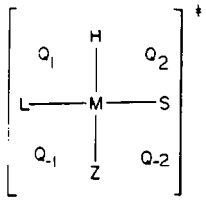
(1) The activated complex leading to the intermediate metal–alkyl complex has the highest free energy.

(2) The metal atom approached by the substrate in the transition state is a chiral centre.

(3) The double bond of the substrate in the transition state is approximately coplanar to the bond between metal and hydrogen.

The simplest way to represent such a transition state is to project it onto the plane perpendicular to the approach direction of the substrate. The groups bonded to the metal are conceived as spheres centered along the metal–ligand bonds.

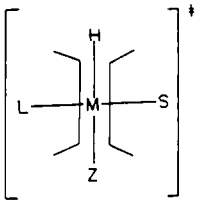
In Fig. 51, L and S represent two ligands of different size, L being larger than S, and Z is a third



229

Fig. 51.

ligand which is not hydrogen or L but larger than hydrogen. The space above the plane of the projection is divided into four quadrants (Fig. 52), containing the approach line and the L–M–Z axes, respectively. The space available to accommodate the groups bound to an unsaturated C atom of the substrate in which the double bond is superimposed and parallel to the M—H bond decreases in the order of $Q_2 > Q_1 > Q_{-2} > Q_{-1}$.



239

Fig. 52.

If the free energy differences between the transition states controlling asymmetric induction depends predominately on the repulsive steric interactions between substrate and the face of the catalyst approached by the substrate, the group(s) bound to the unsaturated C atoms of the substrate will prefer the quadrant in which more space is available. If the relative positions of the ligands L and S with respect to the M—H bond and the relative positions of H and Z with respect to the L–M–S axis are known, the face of the prochiral olefin preferentially reacting with the catalyst and the prevailing enantiomer (in the chiral reaction product) can be predicted. The same model indicates also the position of the substrate in which the formyl group will be preferentially bound in the hydroformylation product.

The authors reported that the predictions were wrong in about 20% of the test cases and of these about 60% concern substrates containing an aromatic conjugated with the olefin, and 14% concern substrates in which a heteroatom is directly bound to the double bond.[113] The optical yields for rhodium ranged between 1 and 27% e.e.[94,98,113,114] and between 1 and 22.2% e.e. for Platinum.

The asymmetric hydroformylation of 1,3-dienes was studied by Botteghi *et al.*[115] The authors found that optically active aldehydes were obtained by hydroformylation of simple aliphatic conjugated dienes under the standard conditions, using $HRh(CO)(PPh_3)_3$/(−)-DIOP as the catalyst. The products of the reactions were complex mixtures; in which mono-saturated, unsaturated aldehydes and di-aldehydes were identified. The authors found that:

(a) the regioselectivity of the hydroformylation for the branched mono-aldehydes from butadiene is low, less than 25% e.e.;

(b) the hydroformylation of isoprene to 3-methylpental takes place with a relatively high optical yield (32% e.e.).

The formation of the reaction products can be explained by the fact that the intermediary alkylrhodium complex attempts to remove as much steric hindrance in the complex as is possible, depending on the catalyst and the substrate used, the selectivities are as high as 85%.[114]

The polymer bound catalysts of the type **240** and **241** (Fig. 53) gave low optical yields (about 2% e.e.) in the hydroformylation of styrene.

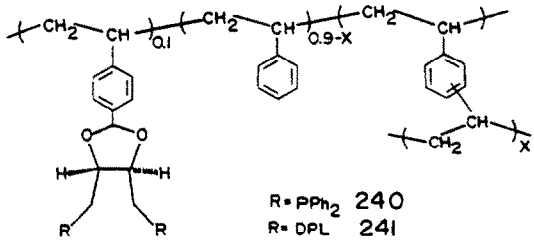
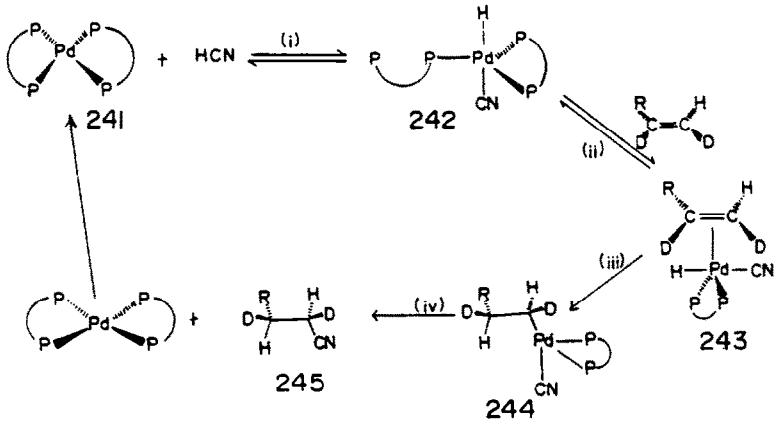


Fig. 53.

$HRh(PPh_3)_3$ and **240** produced a catalyst which catalyzed the hydroformylation of *cis*-2-butene to give 2-methylbutanal in an optical yield of 28.4% e.e. which is slightly higher than that obtained using the homogeneous analogues (only 27% e.e.).

The metal-catalyzed addition of hydrogen cyanide to alkenes has been studied by Jackson and co-workers[116–119] (Scheme 13). The most common metals used for such additions are Ni and Pd



Scheme 13.

and the ligands commonly used are (+)- and (−)-DIOP. The mechanistic proposals for this reaction are very similar for both nickel- and palladium-catalyzed reactions.[119] The organometallic species which reacts with the olefin are very bulky and the steric demands are probably greater when a bidentate rather than a monodentate phosphorus-based ligand is used. Equilibrium (ii) favours the uncomplexed alkene with the catalyst $Pd(DIOP)_2$ more than with the $Ni(P(OPh)_3)_4$ catalyst. The steric requirements of the complexed metal atom are also demonstrated by the exclusive formation of an equatorial nitrile in steps (iii) and (iv) when cyclohexene is reacted and the exclusive formation of terminal cyanides when an alk-1-ene reacts. The heavily coordinated Pd atom has a greater steric requirement than hydrogen. The asymmetric hydrocyanation is generally in the range of 9–35% e.e. depending upon the conditions. The omission of the free ligand from the reaction mixture (i.e. no excess chiral ligand) leads to a decrease in the yield as does the lowering of the amount of metal catalyst and free ligand to HCN, probably for the same reason as the low yields incurred in hydroformylation reactions. The addition of Lewis acids, also lowered the optical yields probably by allowing some rearrangement since step (iii) must be reversible, allowing rearrangements to occur.[119] Also, the temperature has a great effect on the reaction; high temperatures (100–150°) allow for chemical yields of 70–80% with optical yields in the range of 25% e.e., lowering the temperature decreases the chemical yields but increases the optical yields.

Table 7. Hydroformulation (optical yield (reference)/chemical yield (configuration))

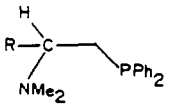
Ligand / Rhodium	Substrate A	B	C	D	E
107	15.1(94) NR(S)	-----	3.9(94) NR(R)	9.4(94) NR(S)	-----
111	1.9(113) NR(R)	-----	-----	-----	-----
114	4.2(94) NR(R)	-----	95(94) NR(S)	1.5(94) NR(R)	-----
117	26.2(113) NR(R)	21.4(113) 100(R)	-----	-----	-----
118	22.7(106) NR(R)	-----	27.0(106) NR(S)	18.8(106) NR(R)	4.2(113) 100(R)
Ruthenium					
118	0(101) 88	-----	0.5(101) 10(R)	-----	1.2(101) 51(R)
Cobalt					
118	-----	0.6(113) 100(R)	2.7(113) NR(R)	-----	4.2(113) 100(R)
Platinum					
118	28.6(113) 15(S)	-----	14.5(113) 24.3(S)	46.7(113) 1.4(R)	-----

Substrates used in Hydroformylation

A) Styrene B) 3-Phenylpropene C) *cis*-2-Butene
D) 1-Butene E) Bicyclooct[2.2.2]-2-ene

Asymmetric cross-coupling reactions

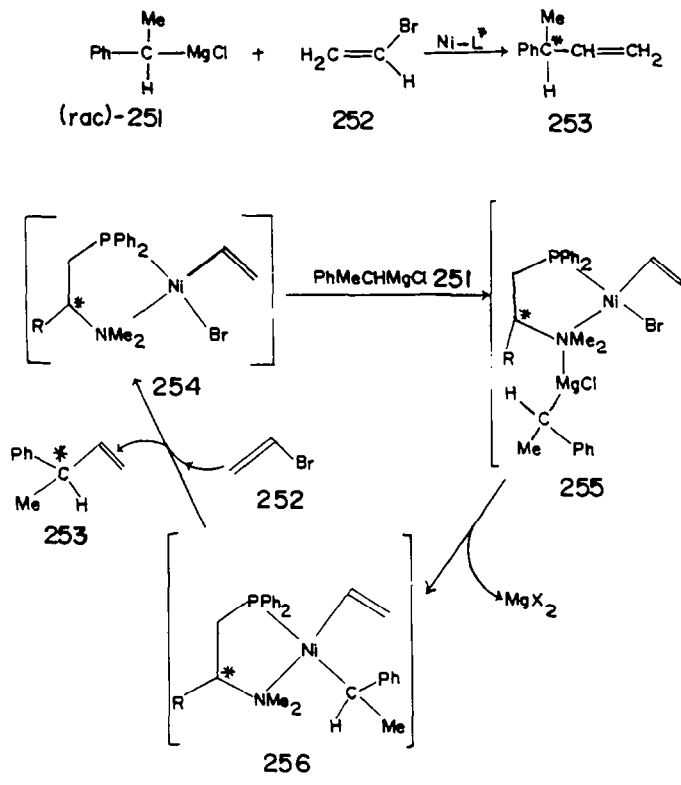
In the asymmetric cross-coupling reactions the two major metals studied are Ni and Pd. Nickel-catalyzed reactions were found to give higher selectivity by using β-aminoalkylphosphines, obtained from the corresponding amino acids (Fig. 54).[120–126]



R=Me (S)-Alaphos 246
R=Bn (S)-Phenphos 247
R=Ph (R)-Phglyphos 248
R=i-Pr (S)-Valphos 249
R=t-Bu (R)-t-Leuphos 250

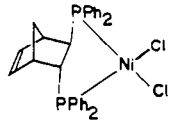
Fig. 54.

Using these chiral phosphines as ligands, the nikel-catalyzed cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide gave both (*R*)- and (*S*)-3-phenyl-1-butene. The mechanism for the reaction is shown in Scheme 14. Product **253** was obtained in high optical purity (>70% e.e.) when (*S*)-AlaPHOS **246**, (*S*)-PHENPHOS **247**, (*R*)-PhGLYPHOS **248**, (*S*)-ValPHOS **249** or (*R*)-t-LeuPHOS **250** were used as ligands. t-LeuPHOS **250** was able to induce asymmetric coupling in optical yields of up to 94% e.e. The order of efficiency for asymmetric induction is **250** > **249** > **247** and **248** > **246**. When (*S*)-2-diphenylphosphinopropyldimethylamine **257** was used as the ligand, the optical yield was found to be lower than that found for **246**, which indicates that the ligands with chiral centres at the dimethylamino group are more effective than those with a chiral carbon at the diphenylphosphino group. When the Grignard reagent approaches the organonickel intermediate **254**, the diphenylamino group in the aminophosphine ligand dissociates from the Ni and coordinates with the Mg atom in the Grignard reagent to form the diastereomeric transition state **255**. The coordination must occur selectively with one of the enantiomers of the Grignard reagent and the selectivity is affected by the steric bulkiness of the alkyl group on the Ni which leads to the di-organonickel intermediate **256**. Reductive elimination of the optically active coupling product **253** from **256** and the oxidative addition of **252** reforms **254**.[120] The optically active ligand



Scheme 14.

in the reaction of racemic Grignard reagent must bring about the kinetic resolution of it to make the reaction rate of the enantiomers different. The Grignard reagents in which the Mg atom attaches to a chiral carbon centre undergoes racemization because of the instability of the Mg—C bond. Another ligand which has been used with Ni is (−)-NORPHOS **257** (Fig. 55) to give (*S*)-3-phenyl-1-butene in 95% chemical yield and 67% optical yield from the cross-coupling of racemic 1-phenylethyl Grignard with vinyl bromide.[121]

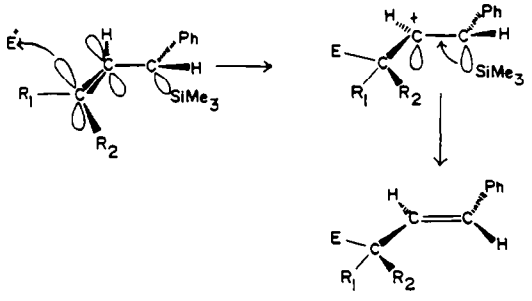


257

Fig. 55.

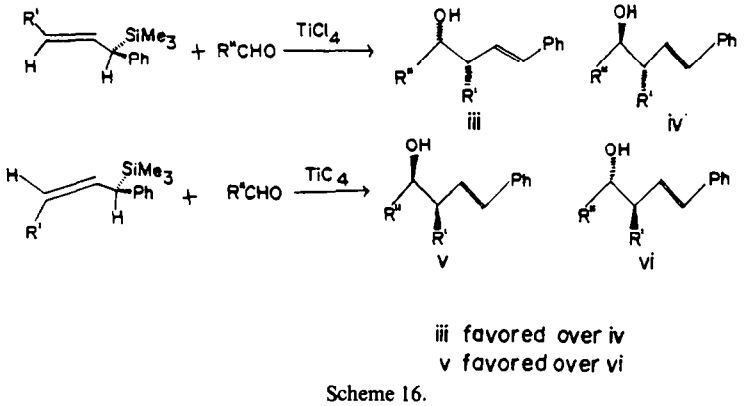
Kumada and co-workers[122] studied various chiral ferrocenylphosphines as ligands for nickel or palladium complex catalyzed asymmetric cross-coupling of some secondary alkyl Grignard reagents with organic halides, such as vinyl bromide, (*E*)-β-bromostyrene, 2-bromopropene and bromobenzene. The authors found that the (*S*)-(*R*)-PPFA **172** complex gave higher selectivity than the corresponding DIOP, PROPHOS or NAPHAS complexes and gave optical yields as high as 68% e.e. It was found that the ferrocene planar chirality is more important than the C centre chirality and the dimethylamino group on the side is a requirement for high optical yields. The stereoselectivity is independent of additional substituents on the ferrocenyl phosphine side chain. This lends aditional proof to the existence of intermediate **255**, where the Grignard associates with the amino group. Kumada and co-workers[123] found $PdCl_2$((*R*)-(*S*)-PPFA)) to be an effective catalyst for the cross-coupling of α-(trimethylsilyl)benzylmagnesium bromide with vinyl bromide, (*E*)- and (*Z*)-1-bromopropene and (*E*)- and (*Z*)-β-bromostyrene to give the corresponding allylsilanes **258** (with optical yields in the range of 13–95% e.e.) with the *R* isomer formed predominately in every case. The addition of an electrophile to an (*R*)-(*E*)-allylsilane gave products with the *S* configuration while the (*R*)-(*Z*)-allylsilane gave the *R* isomer. The optical yields of the *S* and *R* products were in the

range of 53–93% e.e. and 15–27% e.e., respectively. The *anti* stereochemistry was explained by the mechanism shown in Scheme 15.



Scheme 15.

The other possible conformation, may be excluded because of the increased steric repulsion between the olefin moiety and the phenyl group on the α-carbon. The electrophile attacks the allylsilane from the side opposite to the trimethylsilyl group (*anti* attack). The (*R*)-(*E*)- and (*Z*)-allylsilanes were reacted with a series of aldehydes (acetaldehydes, pivaldehydes and 2-methylpropanal) in the presence of titanium(IV) chloride and both enantio- and diastereoselectivities can be clearly interpreted by simple steric interaction in the transition states, shown in Scheme 16. The



iii favored over iv
v favored over vi

Scheme 16.

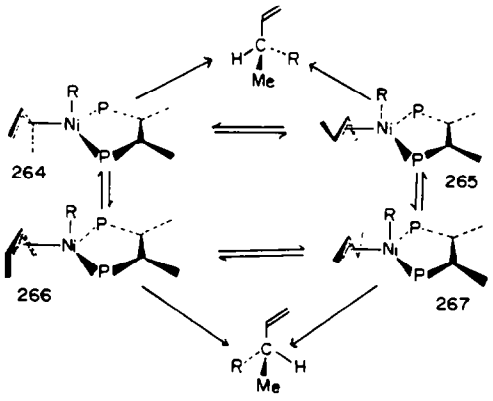
asymmetric reaction is stereospecific and within experimental error, the optical purity is the same as the starting allylsilane. The *threo* isomers are predominant in most reactions (the ratio varies from 1 : 1 to >99 : <1) depending on the steric encumberance of the aldehyde on its *re*-face over the *si*-face. The mode of attack reduces the steric repulsion between the allyl group, R″ on the aldehyde and the phenyl group on the allylsilane. When R″ is t-Bu the *threo* alcohols are produced almost exclusively, and when R″ is i-Pr or Me, the steric repulsions between R′ and R″ and the phenyl group on the allylsilane compete for the maximum steric repulsion the *threo* : *erythro* ratio approaches 1 : 1 for the *Z*-allylsilanes but still favours the *threo* product (>92%) for the *E*-allylsilanes.

The asymmetric allylation of Grignard reagents by allylphenyl ethers in the presence of ((−)-(*S*,*S*)-2,3-bis(diphenylphosphino)butane) Nickel(II) chloride to give optically active olefins with optical yields as high as 97% and chemical yields in the range of 75–99% was studied by Consiglio *et al.*[125] The authors found that both 2-butene phenyl ether **259** and 3-(1-butene) phenyl ether **260** gave the same chiral products 3-methylpent-1-ene **261** or 3-phenylbut-1-ene **262** when the Grignard reagent is ethyl- or phenylmagnesium bromide, respectively. The reaction of **259** and **260** to give the same product is rationalized on the basis of an allyl mechanism which gives rise to four different intermediates **264–267** (Scheme 17). The highest optical yields were obtained in the asymmetric coupling of 3-(cyclohex-1-ene) phenyl ether with ethylmagnesium bromide to give (*R*)-3-ethylcyclohex-1-ene **263** in 85% chemical yield and 99.7% optical yield.

Table 8. Cross-coupling (optical yield (reference)/chemical yield (configuration))

Ligand	Organic Halide	Organometal Ph-CH-MgCl Me	Ph-CH-MgBr SiMe$_3$	Ph-CH-ZnBr Me	Ph-CH-ZnBr Et	Ph-CH-MgCl Et
Palladium						
169	vinylbromide	61(122) 93(R)	-----	-----	-----	-----
172	vinylbromide	-----	-----	-----	-----	61(122) 93(R)
	allylbromide	46(122) 78(R)	-----	-----	-----	-----
	beta-bromostyrene	5(122) 48(S)	-----	-----	-----	12(122) 65(R)
	phenylbromide	-----	-----	-----	-----	22(122) 60(R)
172a	vinylbromide	86(126) >95(S)	95(92) NR(R)	85(92) NR(S)	61(126) 57(S)	-----
	allylbromide	-----	85(92) NR(R)	-----	-----	-----
	beta-bromostyrene	-----	95(92) NR(R)	-----	-----	-----
Nickel						
136	vinylbromide	-----	-----	-----	-----	67(121) 95(S)
169	vinylbromide	63(122) 73(R)	-----	-----	-----	-----
172	vinylbromide	63(122) >95(R)	-----	-----	-----	-----
172a		68(122) >95(S)	-----	-----	-----	-----
246		-----	-----	-----	-----	38(120) 98(S)
247	vinylbromide	-----	-----	-----	-----	71(120) 98(S)
248		-----	-----	-----	-----	70(120) 97(R)
249		-----	-----	-----	-----	81(120) 96(S)
250		-----	-----	-----	-----	94(120) 96(R)

NR: yield not reported in paper



Scheme 17.

ALKYLATIONS

Enamines

Two of the most successful methods of producing alkylated cyclohexanones has been the alkylation of enamines and hydrazones. There has been a review written by Hickmott on the "Recent Advances in the Synthetic, Spectroscopic, Mechanistic and Stereochemical Aspects of Enamines".[127,128] The first examples of the alkylation of enamines gave only moderate asymmetric induction (26–37% e.e.). Meyers *et al.*[129a] and Whitesell and Whitesell[130] solved the low optical

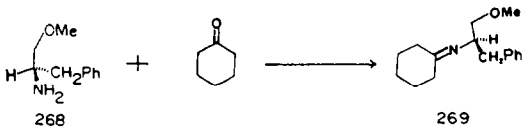
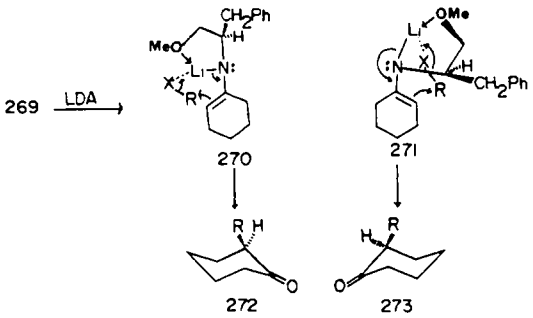


Fig. 56.

induction by adding an alkoxy substituent on the chiral amine which is able to complex to the metal cation (e.g. Li^+, Fig. 56). This additional complexation induces rigidity into the metalloenamine and inhibits rotation about the C—N bond which reduces the number of conformations available for the alkylations. Using amine **268**, the configuration of the 2-substituted cyclohexanones were *R* (except for allyl and phenyl, when the priority changes), the other enantiomer of **268** gave *S*.[128] Meyers *et al.*[129a] explained the selectivity by the following mehanism; imine **269**, formed by the reaction of amine **127** with cyclohexanone, was treated with LDA to give lithioenamines **270** and **271** (which are interconvertible by nitrogen inversion, see Scheme 18). Since **270** is a *trans*-1,2-



Scheme 18.

disubstituted chelate ring, it is favoured over the corresponding *cis*-enamine **271**. If the alkyl(allyl) halide is coordinated to the lithium, the *cis* transition state is more sterically hindered than the *trans* transition state therefore, the major (or only) product is the (*R*)-alkylcyclohexanone **272** with optical yields in the range of 87–100% e.e.[129a,132] Hashimoto and Koga[131a,b] utilized t-leucine and valine t-butyl ester, **274** and **275**, respectively (Fig. 57), as the amine and oxygen function, to give alkylated

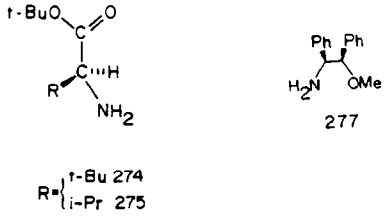
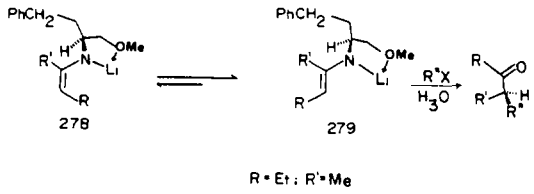


Fig. 57.

cycloalkanes with optical yields in the range of 84–98% e.e. When the reaction was applied to 2-phenylcyclohexanone or 2-phenylcyclopentanone, the more substituted (and therefore more stable) form of the enamine was obtained. The alkylation procedure resulted in the formation of the corresponding (*S*)-2,2-disubstituted ketones, with optical yields of 96 and 94% e.e., respectively, using the t-leucine t-butyl ester. Saigo *et al.*[133] found that the optical purity and the chemical yield of 2-alkylcyclohexanones were strongly influenced by the metal in the metallo-enamine when (+)- or (−)-*erythro*-2-methoxy-1,2-diphenylethylamine **276** was used as the optically active amino alcohol. The optimum purity and yield was obtained when the enaminozinc bromide was allowed to react with the alkyl halide at 0° (not at −78°) to give the 2-alkylcyclohexanone in 79–92% e.e.

When this enantioselective alkylation was applied to acyclic ketones an additional problem was the formation of *E*- and *Z*-metalloenamines[136,137] and as a result low optical yields (< 10% e.e.) were obtained.

If however, the lithioenamine was heated, to allow equilibration to the thermodynamically more stable *E*-lithioenamine **279** (Fig. 58), then alkylated the optical yield was increased to about 76% e.e.[134]

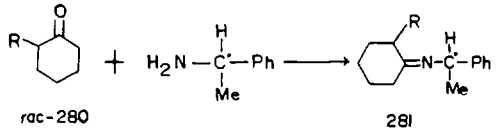


278 279

R = Et; R' = Me

Fig. 58.

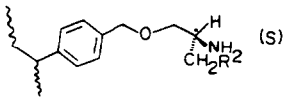
Frahm and Knupp[135] found that racemic 2-substituted ketones could be transformed into optically active *cis*-2-substituted cyclohexanenamines, by reacting the racemic cyclohexanone **280** with optically active (*R*)-(+)- or (*S*)-(−)-1-phenyl-ethylamine to give the corresponding azomethine **281** (Fig. 59). The two diastereomers are resolved and the azomethine hydrolyzed to give the optically pure cyclohexanone. McArthur *et al.*[136] have performed some work on the use of polymer supported reagents which were found to give yields as good (or better) in the methylation of lithioenamines



rac-280 281

Fig. 59.

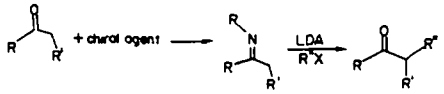
derived from cyclohexanone and **282** (Fig. 60). The authors also found that the degree of resolution depended upon the substitution on **282**. (*S*)-2-Aminopropoxymethylated polystyrene, **282a**, gave no apparent resolution while the 3-phenyl derivative, **282b**, gave 2-methylcyclohexanones with 50% e.e. of the (*S*)-enantiomer.[136]



282a R=H
282b R=Ph

Fig. 60.

Table 9. Alkylation of prochiral ketones (optical yield (reference)/chemical yield (configuration))



R	R'	R"X	268	283	284
Et	Me	EtI	76(134) 48(S)		
n-Pr	Et	MeI	98(134) 84(R)		
n-Bu	Et	MeI	88(134) 75(R)		
Ph	Me	EtI	53(134) 80(S)		
Ph	Et	MeI	35(134) 77(R)		
Ph	Ph	MeI	20(134) 88(S)		
Bz	Ph	MeI	41(134) 90(R)		
H	n-hept	MeI		55.2(138) 71(S)	75.2(138) 60(S)

Aldimines

The metallation and alkylation of chiral imines via their lithio anions to give α-substituted ketones and aldehydes in 60–100% e.e. has advanced in the past few years by studying the necessary conditions and structures of the reactions which gave favourable (and those which gave poor) optical yields. The reaction depended upon the chelated metalloenamine to provide a rigid nucleophile, and the geometry about the metalloenamine C=C bond (*E* vs *Z*) and the nature of the amino group (R_3CNH_2 or R_2CHNH_2) is critical to the asymmetric alkylation but the skeletal structure of the chiral alkoxyamines or the alkyl group on the ether has little effect.[138] Meyers *et al.*[138] found that the secondary carbinamines **283**, **284**, and **287** were more efficient chiral auxiliary groups than the tertiary carbinamines **285** or **286** (Fig. 61). Carbamines **283**, **284** and **287** gave (*S*)-2-methyl octanol

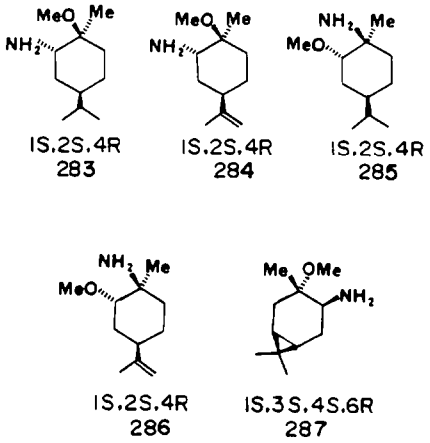


Fig. 61.

from octanal in the enantiomeric excesses of 54–75% while **285** and **286** gave only 25 and 10% e.e., respectively. The reason that the tertiary carbamines are less effective than the secondary carbamines can be rationalized by the two conformations **288** and **289** (Fig. 62) which allow the N-lone pair

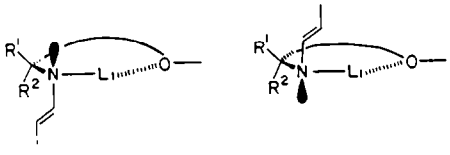


Fig. 62.

and N-vinyl group to lose their preference when R^2 is methyl. The ground state energies for **288** and **289** become similar, resulting in alkylation through both species and subsequent loss of stereoselectivity.

Koga and co-workers[139,140,165] have studied the 1,4-addition of Grignard reagents to optically active α,β-unsaturated aldimines to give β-substituted aldehydes. The authors studied the aldimines formed by the reaction of optically active α-amino acid t-butyl esters with cycloalkene-carboxaldehydes. The 1,4-addition of Grignard reagents to the enamines gave, after acidic hydrolysis, 2-substituted cyclic aldehydes. Higher chemical and optical yields were obtained for the enamines derived from t-leucine t-butyl ester (91–95% e.e.) than from most cases. The chiral reagents were bidentate amines in order to chelate with the Grignard reagent and produce rigid 5-membered transition states. Besides the 1,4-addition there are several competitive reactions as shown in Fig. 63.

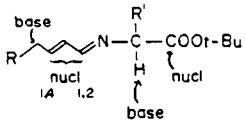


Fig. 63.

The Grignard reagent can act as a base to the hydrogen α to the olefin and the ester function, and as a nucleophile to the ester carbonyl, as well as simple 1,2-addition to the aldimine. The (*R*)- or (*S*)-aldehyde can be produced by the correct choice of the amino ester chirality. The stereochemical course of the present 1,4-addition reaction can be predicted by the previously proposed mechanism, shown in Fig. 64, with the carbon nucleophile attacking from the less hindered side of the complex.

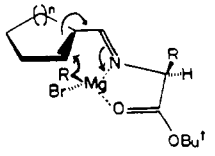


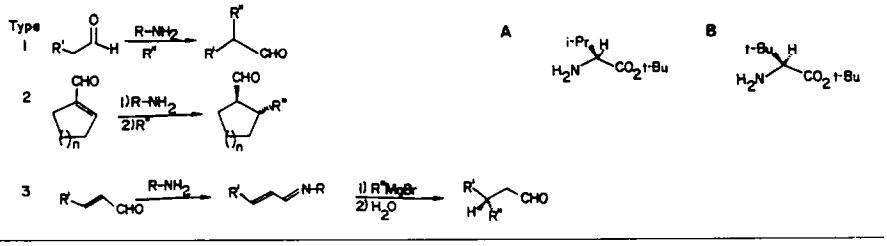
Fig. 64.

Hydrazones

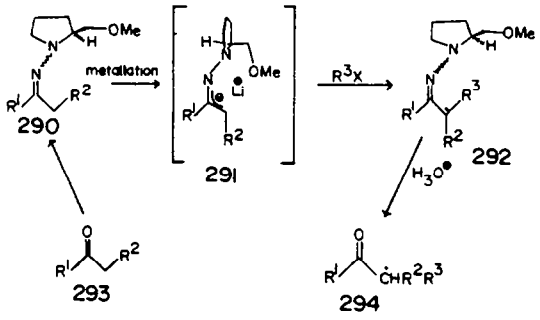
Another method of producing α-substituted ketones is by metallation and subsequent alkylation of chiral hydrazones.[141-143] Enders and Eichenauer[141] studied the enantioselectivity by utilizing their corresponding chiral SAMP-hydrazones (SAMP = (*S*)-1-amino-2-methoxymethyl pyrrolidine,

Table 10. Alkylation of aldimines (optical yield (reference)/chemical yield (configuration))

R'	R"	Chiral agent R* 283	284	285	286	287	A	B	type[1]
n-nex	LiTMP	55.2(139):	73.2(139):	29.6(139):	10.7(139):	54.3(139):			1
	MeI	71(S)	60(S)	80(S)	76(S)				
n=1	PhMgBr						61(139)	82(139)	2
							72(1R,2S)	82(1R,2S)	
	vinyl-MgBr						71(139)	92(139)	2
							36(1R,2S)	69(1R,2S)	
n=2	PhMgBr						49(139)	91(139)	2
							52(1R,2S)	54(1R,2S)	
	vinyl-MgBr						69(139)	93(139)	2
							31(1R,2S)	68(1R,2S)	
							trans:80	trans:87	
							cis :20	cis :13	
Me	PhMgBr						65(140)	91(140)	3
							42(R)	52(R)	
	cy-hex-MgBr						71(140)	91(140)	3
							6(R)	53(R)	
	n-Bu MgBr							98(140)	3
								40(S)	
Ph	EtMgBr							95(140)	3
								56(S)	



Scheme 19). They also found that the hydrazones formed from cyclic ketones existed in conformation **295** and the aldehydrazones existed in conformation **296** (Fig. 65). The metallation is best performed at temperatures in the range of −10 to 0° and in most cases gave chemical yields in excess of 90%. The optical purity of the alkylated product is very dependent upon the temperature at which the alkylation is performed. Optimum optical purity is obtained at −98° and can drop to about 20–



Scheme 19.

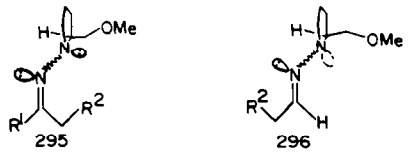
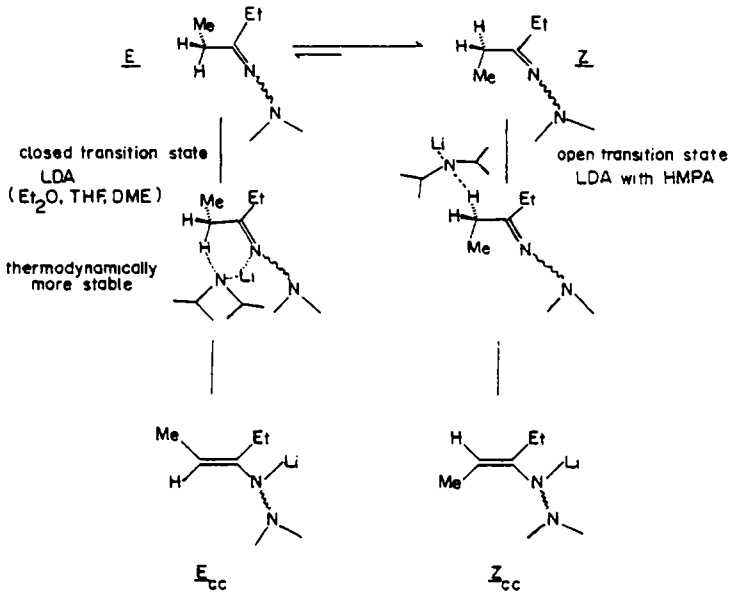


Fig. 65.

30% e.e. at $-30°$. The metallation can occur from two different transition states (Scheme 20). The thermodynamically preferred *trans*-metallated species (in the absence of HMPA) can be seen by



Scheme 20.

noting that in the open transition state there is a 1,3-allylic interaction between the methyl group and the hydrazone nitrogen (Fig. 66).

In general esters, oxazolines, thioamides, ketones, and aldehydes all give the *trans*-enolate as the major enolate. If HMPT is added the open transition state and therefore the *cis*-enolate is favoured. The exceptions to this rule are very hindered ketones and amides. There also exists two conformations

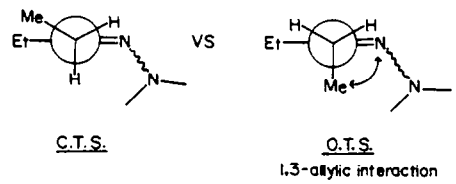


Fig. 66.

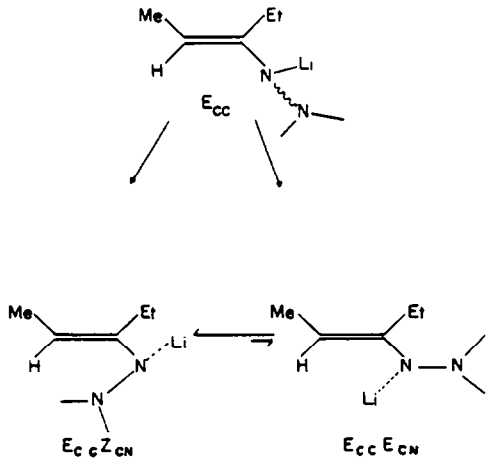


Fig. 67.

about the C—N bond (Fig. 67). The *Z*-configuration around the C—N bond is favoured by π-bond overlap. The advantages of hydrazones are:

(a) the chemical yields are in the range of 77–96%;

(b) the enolates are not sensitive to aldol type self-condensation and once formed, they are stable up to 25° in the absence of H_2O of CO_2;

(c) the hydrazones are more reactive to electrophiles such as RX, oxiranes, and carbonyls,

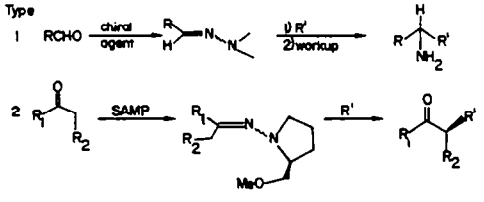
(d) the hydrazones are formed with a great deal of regiospecificity and the reaction gives only monoalkylated carbonyls;

(e) the hydrazones may be easily removed under various mild conditions.

Table 11. Alkylation of ketones by the use of hydrazones (optical yield (reference)/chemical yield (configuration))

R	R'	type 1 l-ephedrine	type 2 SAMP
Ph	BzMgCl	40(142) 60(S)	
Bz	PhLi	91(142) 70(R)	
R_1 : R_2	1)LDA 2		89(143) 26(S)

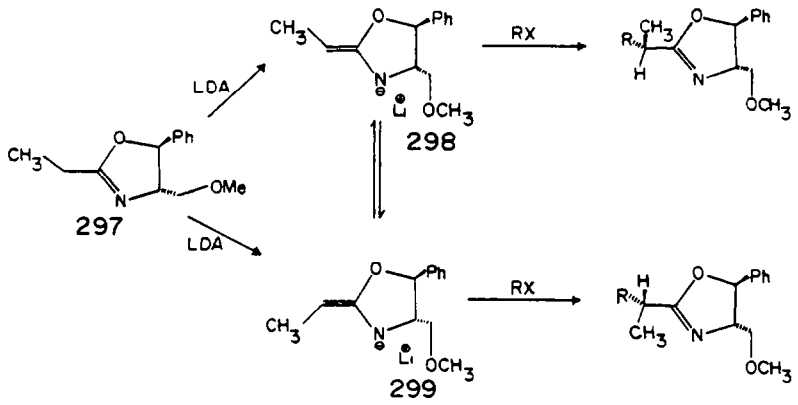
optical yield based on product further on in the synthesis



Oxazolines

In recent years the use of oxazolines has been actively studied by Meyers and co-workers[144,166] because of their ability, in the past, to produce chiral dialkylacetic acids (72–86% e.e.), 2-alkylbutyrolactones and valerolactones ((*R*)-lactones in 70–75% e.e. and (*S*)-lactones in 80–86% e.e.), β,β-dialkylpropionic acids (92–99% e.e.), in the kinetic resolution of racemic alkyl halides (30–58% e.e.) and 2-substituted alkanoic acids.[146,147]

The structures of the chiral oxazoline lithio anions have been studied, using ^{13}C-NMR, by Hoobler *et al.*[145] Their reaction scheme, which is based upon that proposed by Meyers,[144] is shown



Scheme 21.

in Scheme 21. The authors found that dimethyloxazoline lithio anions when examined by ^1H decoupled ^{13}C-NMR the ratio of the two labelled peaks did not change at $-50°$ over 2 h. This indicates that rapid rotation does not occur between **301** and **302** (Fig. 68). The ratio of *E* and *Z*

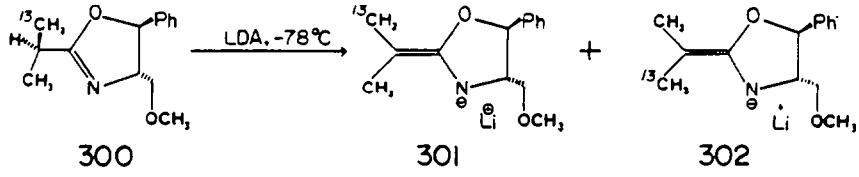


Fig. 68.

isomers (**298** and **299**) produced by the deprotonation of the oxazolines was found to vary as a function of the base used. It was found that the methoxy group and the phenyl group is required to aid in the selectivity. The phenyl group directs the base to a bottomside attack for deprotonation. LDA is a better base for deprotonation than BuLi because it is a larger base and LDA contains an N atom which may complex with the hydrogen. The optimum temperature for metallation and alkylation is about -98 to -78 and $-98°$, respectively.

Table 12. Ratio of *E* (**298**) and *Z* (**299**) isomers formed with various bases[145]

Base and solvent used	*E* (298) : *Z* (299)	
Lithium diisopropylamide–tetrahydrofuran	96	4
Lithium diisopropylamide–dimethoxyethane	96	4
n-Butyllithium–tetrahydrofuran	69	31
Lithium diisopropylamide–hexamethylphosphoric triamide–tetrahydrofuran	67	33
Lithium diphenylamide–tetrahydrofuran–tetrahydrofuran	80	20

The formation of β-alkylalkanoic acids via α,β-unsaturated oxazolines, involves the use of the oxazoline as a chiral electrophile which should undergo Michael additions. The first method of producing the α,β-unsaturated oxazoline was the aldol type addition of a lithio oxazoline anion **303** with an aldehyde to give the corresponding β-hydroxy oxazoline **304**, which with the subsequent loss of water to form the α,β-unsaturated oxazoline **305** (Fig. 69).

However, this method gives a mixture of *cis* and *trans* α,β-unsaturated oxazolines, Meyers and co-workers found that high yields of the pure *E* isomer **305** could be formed by the intermediacy of phosphonate **306** (Fig. 70). The addition of a series of alkyl and aryllithium reagents to **305** gave the alkylated oxazoline **307**. The hydrolysis gave the β,β-disubstituted propionic acid **308**.

The only anions which failed to react were MeLi, dithiane anions and stable ions (eg. lithio enolates, Fig. 71). The removal of the phenyl group resulted in no major loss of enantiomeric purity.

Shibata *et al.*[146,147] utilized chiral oxazolines to transformracemic 2-chloro- or 2-phenyl alkanoic acids to the corresponding optically active acids. The optical yields of the acids formed by the

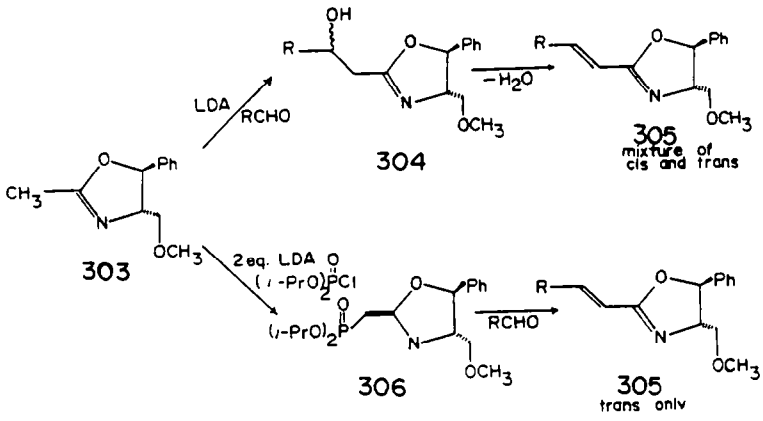


Fig. 69.

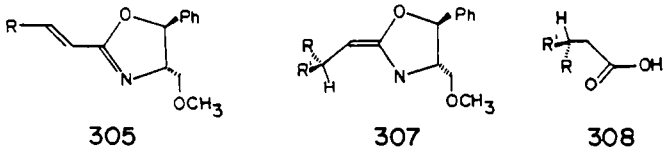


Fig. 70.

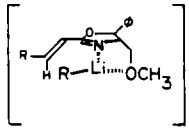
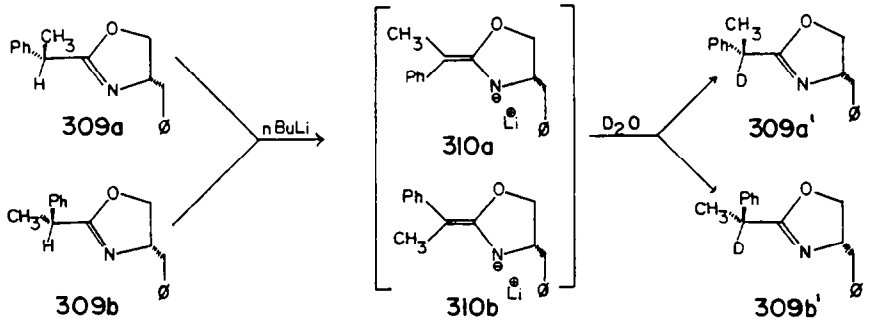


Fig. 71.

protonation of the lithiooxazolines, formed by the metallation of the oxazolines with n-BuLi, was in the range of 45–73% and 29–53%, respectively. The authors also determined the mechanism of the asymmetric transformation (Scheme 22). It was found that the ratio of products **309a′** and **309b′**

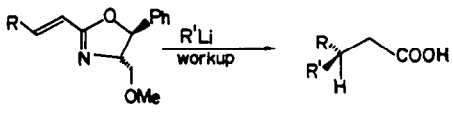


Scheme 22.

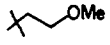
is controlled (in THF) by kinetic control under the experimental conditions studied. When the ratio **309a** : **309b** was 98 : 2 initially, the product ratio was 82–83 : 18–17, respectively; if a racemic mixture or where **309b** predominates, the ratio of the products were 62–68 : 38–32 and is practically independent of the post metallation period. If the reaction is performed in 25% HMPA/THF, the lithio oxazolines **310a** and **310b** are in equilibrium which gives rise to low optical yields (<22% e.e.).

McManus and co-workers[148] produced a polymer bound oxazoline **311** which, when alkylated, gave α- and α,α′-mono- and dialkylated acetic acids or their ethyl esters in 68–81% chemical yields, upon hydrolysis or ethanolysis. The binding of *trans*-(4*S*,5*S*)-2-ethyl-4-(hydroxymethyl)5-5phenyl-

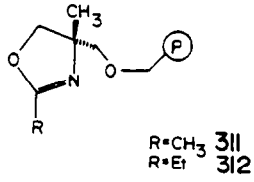
Table 13. Oxazolines, see Ref. 144 (optical yield/chemical yield (configuration))



R'Li	R				
	R"	Me	Et	Ph	cyclohexyl
EtLi	85 nr(R)	92 38(R)		97 66(R)	99 75(R)
PhLi	98 nr(R)	98 34(S)	92 31(S)		
n-BuLi	90 nr(R)		97 50(R)		>99 76(R)

R" = 

2-oxazoline **313** to the polymer, gave the polymer bound oxazoline **314** (Fig. 72). When the polymer bound oxazoline was alkylated with benzyl chloride, oxazoline **315** was obtained, which gave pure



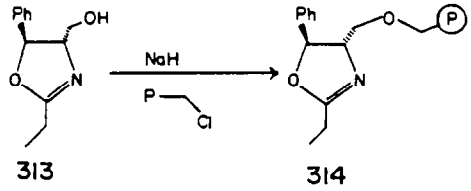


Fig. 72.

(*S*)-(+)-ethyl 2-methyl-3-phenylpropionate **316**, in 56% optical yield and 43–48% chemical yield (Fig. 73).

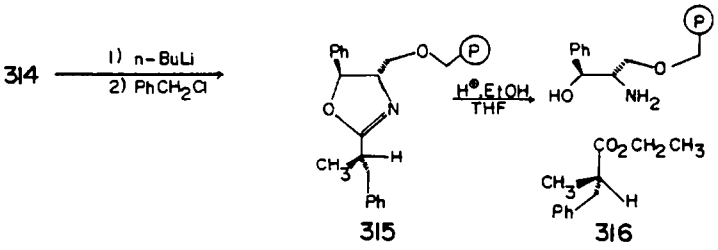


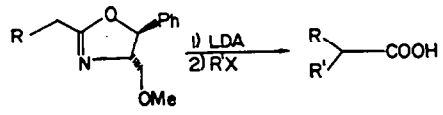
Fig. 73.

Michael addition

The Michael reaction has been studied extensively to determine the optimum conditions and the catalysts for the reaction.[167–169] There are three methods of producing chiral adducts.

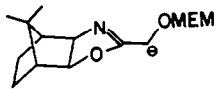
(1) Addition of chiral anions to prochiral Michael acceptors.

Table 14. Oxazoline II (optical yield (reference)/chemical yield (configuration))



R'X	R = Me	Et	n-Pr	n-Bu	Bz	A
Me_2SO_4		79(144) 83(R)	72(144) 75(R)			
EtI	78(144) 84(S)				73(144) 37(S)	77(164) 42(R)
n-PrI	72(144) 79(S)					86(164) 57(R)
n-BuI					86(144) 39(R)	
BzCl		85(144) 30(S)		82(144) 41(S)		92(164) 70(R)
t-BuI						87(164) 26(R)
sec-BuI						88(164) 72(R)

A)

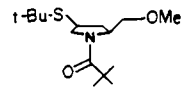


(2) Addition of achiral anions which are complexed to chiral ligands, to prochiral Michael acceptors.

(3) Addition of an achiral anion to a Michael acceptor which possesses one or more chiral centre(s).

(1) Matloubi and Solladie[149] have reported the use of a chiral α-sulfinyl ester and α,β-unsaturated ester as chiral anions in Michael aditions. The optical yield obtained was only 24% e.e. which is low when compared to some of the other methods presently available.

(2) The second method which involves the use of a chiral ligand attached to the anion, usually by a metal, has been shown to give optical yields of up to 90% e.e. Bkole and Gogte[150,151] reported the use of quinine or quinidine in the synthesis of optically active β-phenylmercaptomethyl aryl/alkyl ketones in optical yields of upto 10% e.e. Wynberg and Greijdanus[152] found that the enantiomeric purity of the products was inversely proportional to the dielectric constant of the solvent used in the rection. An improved version of the quinine/quinidine catalyst was a homogeneous catalyst prepared by the reaction of $MoO_2(acac)_2$. Gogte and co-workers[153] reported that the optical yields for the reactions under study were in the range of 19–35% e.e. and the products were obtained in good chemical yields. Gustafsson *et al.*[154] studied the use chiral lithium hetero(butyl) cuprates to add butane to 2-cyclohexanone in a Michael addition, where the hetero functionality is R'O or R'S. The optimum yield was 15.3% e.e. using (+)-neomenthylthiol as the chiral ligand, in moderate chemical yield. The reactions with 4-phenyl-3-butene-2-one were found to be very sensitive to the size of the chiral ligand and to the choice of solvent.[154] Imamoto and Mukaiyama[155] investigated the asymmetric conjugate addition of methyl Grignard reagents to 1,3-diphenyl-2-propene-1-one in the presence of (*S*)-1-methyl-2-hydroxymethylpyrrolidine and a cuprous salt. They found that the selectivity of the asymmetric reaction depended upon the nature of the Grignard reagent and the cuprous salt. The best results were obtained using a large excess of reagent prepared from methylmagnesium bromide and cuprous bromide (the reagent should be used within a short time after preparation). The best yield obtained using this method was 68% e.e. with the (*S*)-enantiomer predominating in a 71% chemical yield. Laucher and Laucher[156] found that when (2*S*)-methoxymethyl-(4*S*)-thiotertbutoxy-N-pivaloyl pyrrolidine **317** (Fig. 74) was used as a ligand in chiral cuprates, it gave up to 75% e.e. in the β-methylation of chalcone.



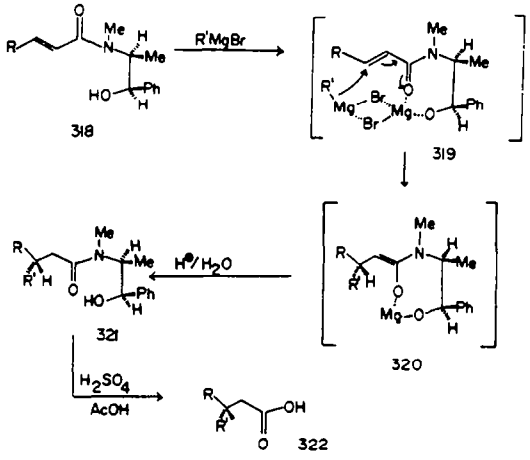
317

Fig. 74.

The authors found that in all experiments reported, the optical yields were insensitive to dilution, and they rationalize this to be a result of the thioalkyl group. All the ligands behave (probably) as at least bidentate ligands towards the Cu atom. In all cases the (*R*)-enantiomer is formed predominately, and N-alkylated ligands gave optical yields in the range of 2–7% e.e., whereas the N-carboalkoxylated and N-acylated ligands gave optical yields in the range of 33–75% e.e.

(3) In internal asymmetric induction, the Grignard reagents are reacted with substrates which are able to form rigid internal chelate complexes.

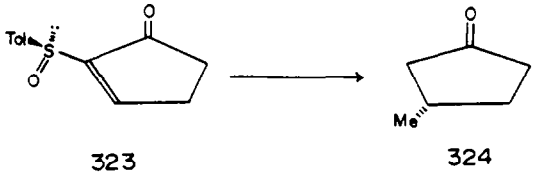
Mukaiyama and Iwasawa[157] studied the addition of Grignard reagents to α,β-unsaturated carboxylic amides **318** derived from L-ephedrine (Scheme 23). The optical yields of the β-substituted



Scheme 23.

alkanoic acids **322** varied from 79 to 99% e.e. and were also obtained in high chemical yield when R = Me, Et, n-Bu and phenyl. The differences in the optical purity of the products were explained by the strength of the coordination of the metal salts to the carbonyl oxygen. When the solvent was dimethyl ether or THF, the optical purity of the products was reduced because of the strong coordinating property of the solvents. The solvents coordinate to the metal salts and prevent the formation of the rigid chelate complex. Diethyl ether was found to be the best solvent under these conditions. When n-BuLi or n-BuMgI was used as the nucleophile, the conformation of the molecule could not be sufficiently fixed. The best results were obtained using n-BuMgBr as the nucleophile in ether.

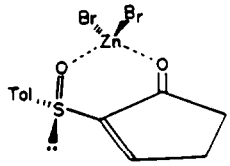
Posner *et al.*[158] found that there was virtually complete asymmetric induction achieved during the β-conjugate addition of methyl-, vinyl-, and naphthylmetallic anions to enantiomerically pure (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentanone. The authors found that both (*R*)- and (*S*)-products of the methyl addition could be prepared. A rationalization of this was proposed by the authors. They stated that the cold enone sulfoxide exists primarily in conformation **323** (having the sulfoxide and carbonyl dipoles oriented in opposite directions). The conjugate addition then occurs from the more exposed side of the enone C=C bond, leading to the (*S*)-3-methylcyclopentanone **324** (Fig. 75). If



323 324

Fig. 75.

$ZnBr_2$ is added first the (*R*)-enantiomer is produced, probably by the formation of the zinc chelate **325** (Fig. 76) before the addition of the Grignard reagent.

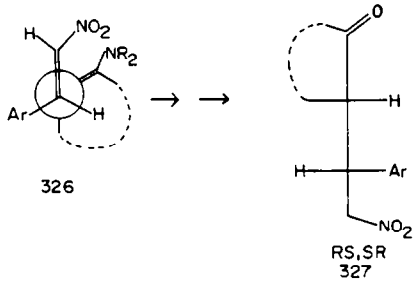


325

Fig. 76.

Michael additions to nitroolefins

The Michael addition of aliphatic, acyclic and aryl-substituted nitroolefins and enamines to give the corresponding γ-nitroketones in good chemical an excellent diastereomeric yields (>90%) has been reported by Seebach and Golinski.[159] The authors found that such a reaction follows a topological rule which is applicable to diene synthesis, cyclopropanations, carbonyl olefinations, methylenations, aldol and nitroaldol-type additions, as well as additions of Li, B and Cr derivatives to aldehydes. Risaliti *et al.* reported that the kinetically controlled Michael additions of enamines derived from cyclic ketones to nitroolefins (mainly ω-nitrostyrene) occur with (Re*—Re*) approach of the two components as shown in the Newmann projection[159] **326** (Fig. 77) and the type of reaction

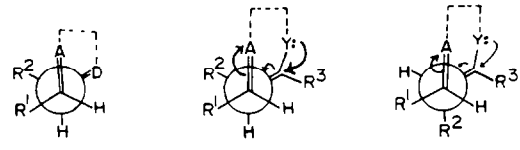


326

RS,SR
327

Fig. 77.

is proposed to be made of reaction of most enamines and nitroolefin Michael additions. When the reaction occurs in aprotic media under kinetic control, the preferred approach of the two prochiral centres RCH = X can be described by **328–330** (Fig. 78):



328
re-si-approach

329
(syn-donor)
re-si-approach
quasi-chair

330
(anti-donor)
re-re-approach
quasi-chair

Fig. 78.

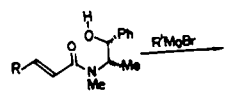
(a) with staggering of all bonds around the newly formed bond;

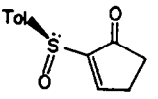
(b) in a γ-*gauche* (synclinal) arrangement of the donor C=D bond between the C—A and the C—H bonds of the acceptor;

(c) with the H atom, the smaller substituent on the donor component, in an *anti* (antiperiplanar) position with respect to the C=A bond (**328**);

(d) if the components can exist in (*E*/*Z*) (*anti*/*syn*)-isomeric forms (**329** and **330**), the actual donor and acceptor atoms are situated close to each other (A and Y in **329** and **330**, A = NO_2 and Y = NR_2).

Table 15. Internal asymmetric induction (optical yield (reference)/chemical yield (configuration))





R	R' Et	n-Bu	n-Hexyl	Ph	RM	
Me	98(157): 58(S)	85(157): 53(S)	91(157): 63(S)	95(157): 55(R)	MeMgCl	≥98(158) 76(S)
Et	———	79(157): 44(S)	———	93(157) 62(R)	MeMgI / $ZnBr_2$	87(158) 89(R)
n-Bu	99(157): 61(R)	———	———	99(157) 54(R)		
Ph	98(157): 47(S)	99(157): 63(S)				

Some examples of the reaction indicate that the above rule does not hold, when very bulky groups R^1 and R^2 and substituents on Y are present. When the solvent is protic an *anti-* rather than a *γ-gauche*-relationship, allowing for better solvation of the donor and acceptor heteroatoms, is kinetically preferred.

Instead of **328**, **329** or **330**, the Re*Re* topology A, or the Re*Si* topologies B–D may be obtained under these conditions (Fig. 79).

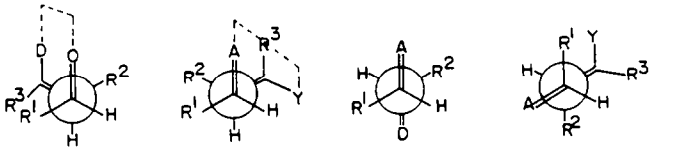


Fig. 79.

Kobayashi and Iwai[160] have studied Cinchona alkaloid assisted addition of thiols to nitroolefins. The authors found that when the thiol contains a carboxyl group (e.g. thioglycolic acid **331**) there seems to be an interaction between the carboxyl group and the active site of the catalyst (quinuclidine nitrogen). The reaction is sensitive to the order of addition, which indicates the salt formation between quinine and thioglycolic acid **331** exerts a pronounced effect in the reaction rate and stereochemistry. Figure 80 shows the reaction sequence.[160]

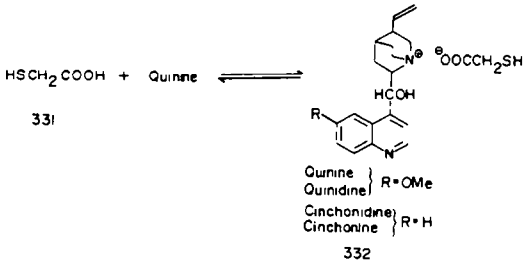


Fig. 80.

The stereochemistry of products seems to depend upon the amount of free quinine (Cinchona alkaloid) in the system relative to that of **332**. The stereochemistry is also controlled by the C_8 and C_9 carbons in the alkaloid, if quinine or chinonidine having C_8-(*S*), C_9-(*R*) *erythro* configuration gives the (*S*)-enantiomer in excess and quinindine or cinchonine with the opposite (*R*)-(*S*) *erythro* arrangement give the (*R*)-enantiomer in excess. The same authors[161,162] have also developed a

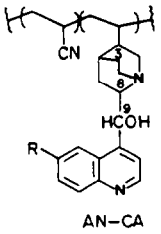


Fig. 81.

polymer version of the alkaloid (AN-CA, Fig. 81) from the polymerization of acrylonitrile with cinchona alkaloids.

They found that the C_3 carbon exerts a strong influence in the enantioface differentiating step. The products of all four cinchona alkaloids gave the same enantiomer in excess. The four asymmetric centres in the alkaloid, those at C_3 and C_4 are in all four AN-CA polymers. The most probable explanation[161,162] is that the chiral force, stemming from C_3 is greatly reinforced by the large substituent (polymer chain) to exceed the chiral force stemming from C_8 and C_9. Optical yields of upto 20% e.e. were found.

The alkylation of aldehydes and ketones can be divided into three main methods; as were the Michael additions.

(1) Addition of chiral anions to prochiral ketones.
(2) Achiral anions to prochiral ketones in presence of chiral ligands.
(3) Addition to chiral containing ketones.

(1) There are very few references to this method in the past few years.

(2) The addition of alkyllithium and dialkylmagnesium to aldehydes using (2*S*,2*S*') - 2 - hydroxymethyl - 1 - [(1 - alkylpyrrolidin - 2 - yl) - methyl] pyrrolidines as a chiral ligand, was studied by Mukaiyama *et al.*[170] The authors found that the chiral ligand (2*S*,2*S*') - 2 - hydroxymethyl - 1 - [(1 - methylpyrrolidin - 2 - yl) - methyl] pyrrolidine **333** (Fig. 82) gave the best results when the molar ratio of the aldehyde : n-butyllithium : **333a** was 1.0 : 6.7 : 4.0, respectively.

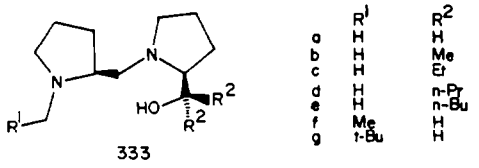


Fig. 82.

The optical purity increased as the temperature was lowered. The optimum purity for the asymmetric addition of n-butyllithium to benzaldehyde using **333** was 95% to give the (*S*)-enantiomer at −123°. The authors studied various organometallic compounds and it was found that dialkylmagnesium was more effective than Grignard reagents, dialkylzinc, alkylcopper or trialkylaluminium. All of the dialkylmagnesiums tested gave alcohols of *R*-configuration whereas in the similar reaction of alkyllithiums, the alcohols possessed the *S* or *R* configuration depending upon the size of the alkyllithiums. Methyl- and ethyllithium gave (*R*)-alcohols in the alkylation of benzaldehyde using **333** as a chiral ligand. Ethyl-, n-propyl- and n-butyllithium gave (*S*)-alcohols. The rigid complex **334** (Fig. 83) is proposed to be formed by virtue of the coordination of oxygen and two N atoms to the alkylmetal which provides an effective environment for asymmetric induction.[170]

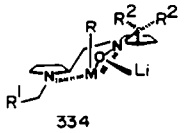
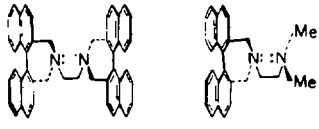


Fig. 83.

Mazaleyrat and Cram[171] studied the use of (*R*,*R*)-**335** and (*R*)-**336** Fig. 84) in the additions of alkyllithiums to aldehydes to give alcohols. The highest optical yields (95% e.e.) were obtained in the alkylation of benzaldehyde with *n*-butyllithium in the presence of (*R*,*R*)-**335**, at −120° in ether.



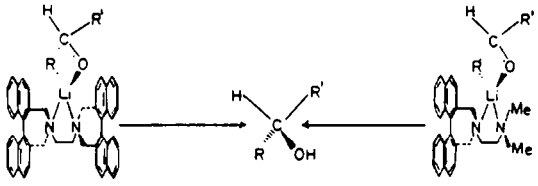
(R,R)-335 (R)-336

Fig. 84.

The lowest yields (35% e.e.) were obtained using methyllithium. The higher values are associated with three structural features:

(a) the reactants with the higher steric requirements;
(b) the more highly shaped and sterically confining catalyst;
(c) the use of benzaldehyde rather than an acyclic aldehyde.

The authors stated[171] that the configurational bias is determined by the formulations of the transition states **337** and **338** to give **339** (Fig. 85). In **337**, because of the rigid polyspirane structures

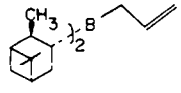


337 339 338

Fig. 85.

of the presumed transition states, the only degree of freedom is the placement of the H and R′ of the aldehyde. The H is directed toward the face of the upper left naphthalene and in **337**, R is directed alongside the face of the lower right naphthalene.[171]

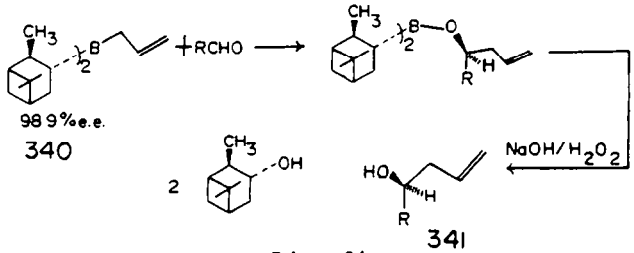
Brown and Jadhov[172] reported the simple synthesis of secondary homoallylic alcohols by the condensation of B-allyldiisopinocampheylboron ($Ipc_2BCH_2CH{=}CH_2$), **340** (Fig. 86(a)), with a variety of aldehydes in high enantiomeric purities (83–96% e.e.).



340 98.9%e.e.

Fig. 86(a).

The reaction of **340** with a variety of aldehydes (acetaldehyde, propionaldehyde, n-butyraldehyde, 2-methylpropionaldehyde, 2,2-dimethylpropionaldehyde, and benzaldehyde) gave the corresponding alcohols **341** after treatment with alkaline hydrogen peroxide, in greater than 83% e.e. and in 71–88% chemical yield following the reaction sequence shown in Scheme 24.



Scheme 24.

The authors reported that the addition of the alkyl group to the aldehyde takes place in the same stereochemical sense, but the Cahn–Ingold–Prelog notations for the products differ due to the priority assignments.[172]

Hoffmann *et al.*[172a] have also reported the synthesis of secondary homoallylic alcohol by the condensation of allylboronates (substituted with camphor glycols as the chiral inducing agent) with aldehydes. The enantiomeric purities of the alcohols produced were in the range of 70–86% e.e. Hoffmann *et al.*[172b] have reported that the Cram or *anti*-Cram diastereomers may be preferentially produced from the addition of *Z*-crotylboronates to (*S*)-(+)-α-methylbutyraldehyde by the proper selection of the chiral auxiliary, attached to the boronate.

Weidmann and Seebach recently published a review of the use of Ti and Z as selective nucleophilic reagent.[173] One section concerns the enantioselective addition of chiral organotitanium reagents $RTi(OR^*)_3$ to aldehydes. The authors stated that the auxiliaries for organolithium reagents can only bind to the metal centre via the heteroatoms with relatively weak coordinates forces, for the titanium reagents heteroatoms can be used. This means that in organic media the dissociation of ligands of this type from the metal, therefore maintaining the integrity of the chiral ligand shell during the buildup of steric strain when the "wrong" face of a CO group is approached.[173] They stated that higher optical yields were obtained with bidentate ligands, than the derivatives of simple alcohols (with the exception of menthol). This is explained by the restriction in movement (rotation) caused by the two ligands, whereas the simple alcohols may freely rotate, allowing the adoption of many different conformations (Fig. 86(b)). Optical yields of up to 90% have been obtained for

Fig. 86(b).

substrates and anions which either cannot be reacted with chiral modified organolithium compounds, or do not react nearly so well.

(3) Addition to chiral molecules utilizes the chirality inherent in the substrate to direct the aldehyde via a chelation-controlled transition state. The reader is referred to a recent review on this subject by Reetz.[174a]

Still and Schneider[174] studied the chelation-controlled additions with β-alkoxyaldehydes because the effect of an α-asymmetric centre substituted by oxygen is a powerful directing effect and should have similar control in β-alkoxy systems (Fig. 87). The authors examined the reaction of

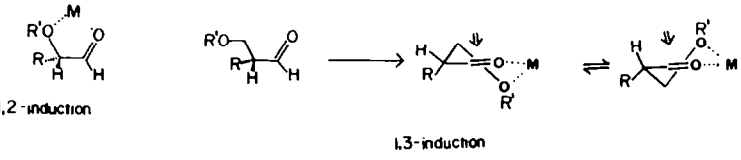


Fig. 87.

organometallics with various α-asymmetric aldehydes which also possess β-oxygen substituents, in a search for new systems showing high asymmetric induction. The authors found that the addition of a methyl anion is best done by way of a lithium dimethylcuprate. This method is not totally stereospecific but does give high chemical yields and the product of chelation-controlled (*threo*) in up to 97% diastereomeric purity. The stereoselectivity for the *threo* product occurs for saturated organic nucleophiles, but relatively stable, sp^2 organic anions (e.g. vinyl) seem to give poor asymmetric induction. It should be noted that Grignard reagents are the best reagents for α-alkoxyaldehydes, while cuprate reagents are best for β-alkoxyaldehydes.[174b]

Mulzer and Angermann[175] studied the addition of organotitanium and organozinc reagents to (*R*)-2,3-isopropylidene glyceraldehyde **345** to give the alcohols **346** an **347** (Fig. 88). The *erythro* product **346** is the Cram adduct and the *threo* product **347** is the *anti*-Cram adducts. The ratio of *erythro*:*threo* is dependent upon the organometal used. As was observed before Grignard and

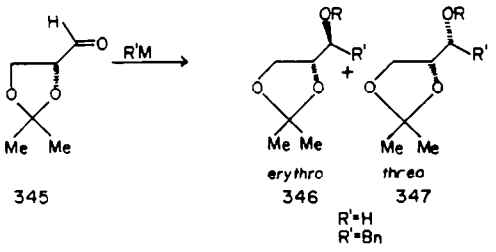


Fig. 88.

organolithium reagents gave only low to moderate selectivity. Zn and $Ti(OiPr)_3$ gave considerably higher diastereomeric excesses. The authors found that all the organometallic reagents studied (except $PhTi(OiPr)_3$) favoured the Cram process if a stereoselective addition does occur. The two arrangements are shown in Fig. 89.[175]

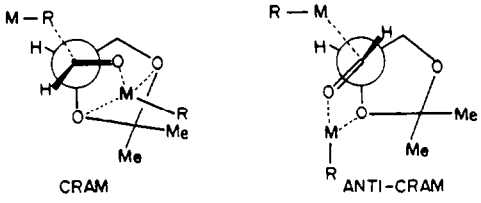
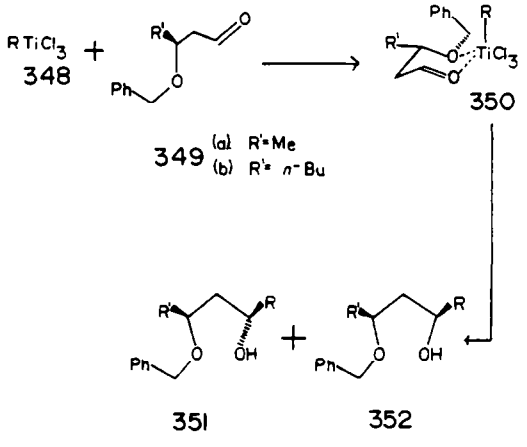


Fig. 89.

They also found that allyl anions could be added with high diastereoselectivity (in upto 91:9 but 82:18 is typical[175a]) using the allylzinc reagent.[175]

Reetz and Jung[176] studied the 1,3-asymmetric induction in the addition reactions of chiral β-alkoxyaldehydes **349** using Lewis acid Ti reagents. The authors speculated that compounds of the type $RTiCl_3$ **348** might react with chiral β-alkoxy aldehydes **349** to form the chelation-controlled products **351** and **352** via intermediate **350** in greater than 90:10, respectively, using R' = Me (Scheme 25).



Scheme 25.

The authors also observed that complexations of **349a** and **b** using $TiCl_4$ followed by additions of allylsilanes or dibutylzinc resulted in selectivities of greater than 90%. This type of reaction shows great promise in the area of 1,3-additions.

Enolate addition

The aldol condensation is perhaps the most important carbon bond forming reaction in the field of organic synthesis and natural product chemistry. As with other C—C bond forming reactions, there are three possible types of reaction.

Type i.

(1) Addition of a chiral enolate to a prochiral carbonyl.

(2) Addition of an achiral enolate to a chiral carbonyl.

(3) Addition of an achiral enolate to a prochiral carbonyl in the presence of a chiral catalyst.

(1) The term "chiral enolate" is defined as an enolate which itself contains a chiral centre or is attached to a metal which possesses a chiral ligand. Most cases encountered are of the latter type.

Sugasawa and Toyoda[177] studied the simple asymmetric aldol condensation of acetophenone and benzaldehyde was performed via chiral vinylaminodichloroborane. (*S*)-(−)-N-(α-Methylbenzyliden) isobornylamine **353**, when treated with boron trichloride (in the presence of triethylamine) gave the chiral boron intermediate **354** (Fig. 90). When intermediate **354** was treated with benzaldehyde,

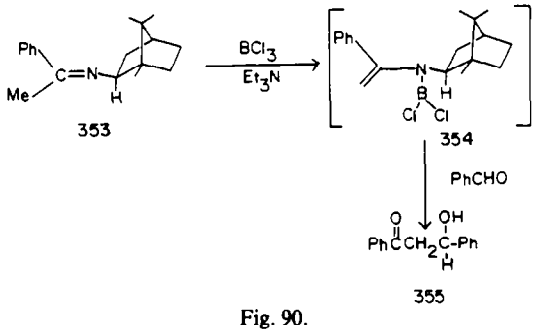


Fig. 90.

(*R*)-(+)-β-hydroxy-β-phenylpropiophenone **355** was obtained in 30.3% chemical yield and with an optical purity of 47.7%. A similar reaction of chiral imines, (*S*)-(+)-α-methyl-N-(α-methyl-benziliden) benzylamine **356** and (*R*)-(−)-(α-methylbenzyliden)-1-(1-naphthyl) ethylamine **357** reacted with *p*-nitrobenzaldehyde to give the adducts in optical yields of 34.5 and 2.5% e.e., respectively. The reaction of **356** and benzaldehyde using LDA gave poor results, only 4.6% e.e. A surprising result was obtained using ethylmagnesium bromide which gave 12.5% e.e., but the opposite enantiomer. Boron enolates produce higher yields because of the more rigid intermediates and by boron's stronger coordination to the carbonyl oxygen.[177]

Masamune *et al.*[178] studied the synthesis of 3-hydroxy-2-vinylcarbonyl intermediates (as in the synthesis of amphotericin B **362**). The authors found that the *Z*(O)-dicyclopentylboron enolate from the (*R*)-3-benzeneselenoketones **358** and **359** when reacted with propanal gave the expected 2,3-*syn*-product **360** (after further modification) in 97% chemical yield (with greater than 100:1 diastereoselection) and **361** from the *S*-*Z*(O)-enolate reagent **359** and 3-benzyloxypropanal (after further modification) with the same efficiency (Fig. 91). Note that the chirality at the carbinols in **358** and **359** directs the chirality of the aldol condensation.

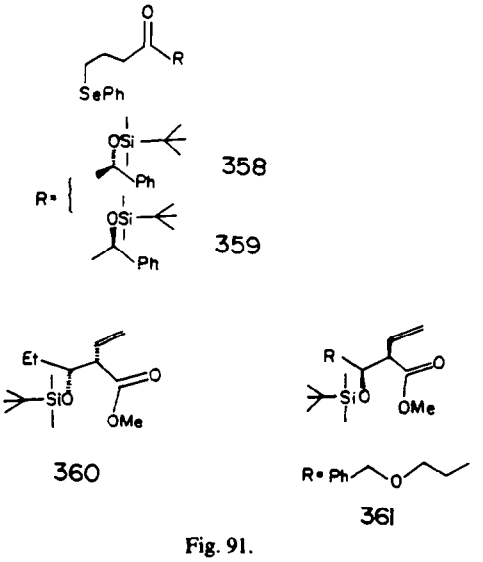
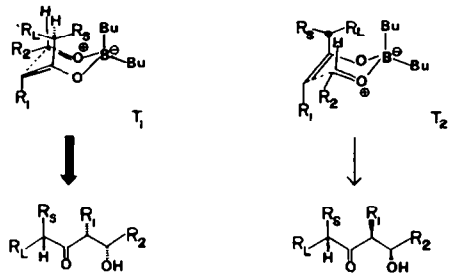


Fig. 91.

Evans and Taber[179] studied the enantioselective aldol condensations via chiral boron enolates which have been shown to be effective in stereoregulated aldol condensations. They proposed a transition state model to account for the chirality transfer. Given that aldol condensations proceed by a pericyclic process,[180] two diastereomeric transition states, T_1 and T_2, which accommodate minimal steric interactions with the aldehyde are shown in Scheme 26 for methyl ketone and *cis*-enolates (R^1 = H, Me).[179]



Scheme 26.

In the transition state with boron, where both chelation (with R_S and R_L) and aggregation phenomena are absent, T_1 is preferred over T_2 for steric reasons.[179]

d'Angelo *et al.*[181] used a hydroxyacetaldehyde equivalent **363** on ketones and aldehydes to give an efficient enantio- and diastereoselective route to vicinal polyols. As with most aldol condensations the selectivity increased with the reduction in temperature (Fig. 92). By lowering the temperature

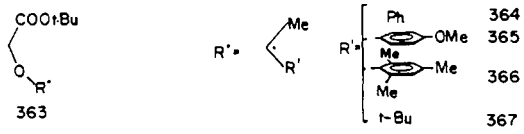


Fig. 92.

from −78 to −128°, the stereoselectivity of the aldol condensation of **366** with acetone increased from 4:1 to 17:1 *erythro*:*threo*, respectively. The optical yield was not affected by the presence of electron donors on the aromatic ring of the acetalehyde equivalent, and as with the boron enolates mentioned above the optical yields increased with the increasing steric strain on the enolate.

The utility of this hydroxyacetaldehyde equivalent is enhanced by the ease of removal of the chiral auxiliary using $H_2/Pd(OH)_2$.

The condensation of the enolate **364*R*** (Fig. 93) with acetaldehyde gave (after elimination of the α-methylbenzyl group) the diolesters **368** and **369** with isomer **368** *erythro* predominating (**368**/**369** = 10:1).

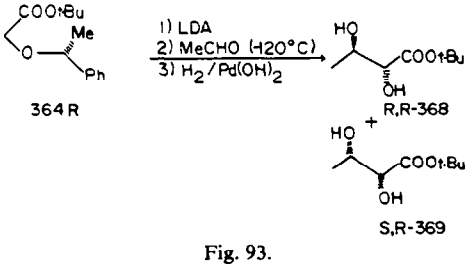


Fig. 93.

(2) Addition of an achiral enolate to a chiral carbonyl. Heathcock and co-workers[182,183] have studied the use of "double stereodifferentiation" to enhance 1,2-diastereoselection in the aldol condensations of chiral aldehydes. The authors used this method as a method of influencing "Cram's rule selectivity" in aldol condensations of chiral aldehydes. The principle of double stereodifferentiation, simply stated, is the reaction of a chiral aldehyde **370** with an achiral ketone **371**,

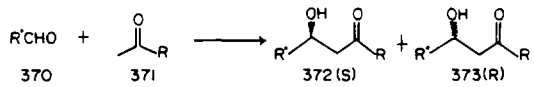


Fig. 94.

in which diastereomers **372** and **373** are produced in unequal amounts[182,183] (Fig. 94). One enantiomer of **370** will give **372** as the major product and the other enantiomer will give **373** as the major product. Similarly the reaction of an achiral aldehyde **374** with a chiral ketone **375**, one enantiomer of **374** will give diastereomer **376** and the other enantiomer will give diastereomer **377** predominately.

This indicated that there are two enantiomers, one is "(*S*)-selective" and the other is "(*R*)-selective" (Fig. 95(a)) with regard to the chirality of the carbinol centre created in an aldol con-

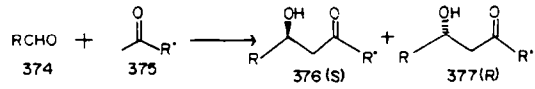


Fig. 95(a).

densation of either aldehyde **370** with the chiral ketone **375**. The *S*: *R* ratio will depend upon which pair of enantiomers are employed. The relative amount of the desired (*S*)-enantiomer at the newly created centre will be greater when two "(*S*)-selective" enantiomers are reacted. The type of 1,2-diastereoselectivity exhibited by the aldehydes is greater than 30 : 1. Masamune *et al.*[184a,b] has shown that if a sufficiently (*R*)- or (*S*)-selective reagent is employed, it is possible to overcome the small Cram/*anti*-Cram selectivity intrinsic to the chiral aldehyde. This ability allows the preparation of either the 3,4-*syn* or the 3,4-*anti* aldol adduct as the major product. An excellent example of the use of this selectivity, is in the synthesis of both the Prelog–Djerassi and the *iso*-Prelog–Djerassi lactonic acid (shown in Fig. 95(b)).

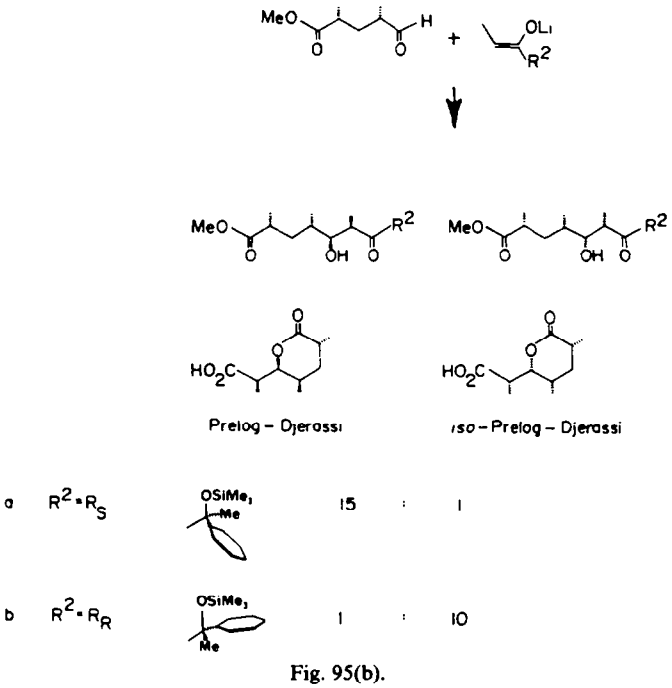


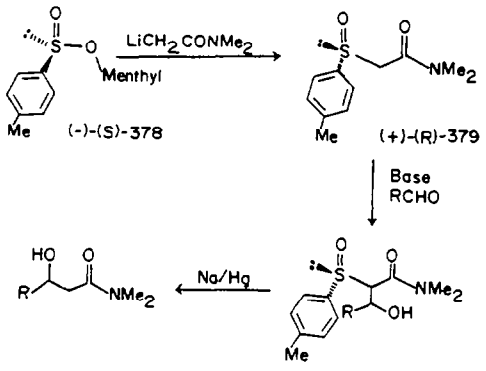
Fig. 95(b).

Lithium and magnesium enolates exhibit distinctive propensities for coordination with oxygenated functional groups present in the enolate itself or the reacting aldehyde.[184] The stereochemical consequences resulting from this coordination have been explained by Cram's cyclic (coordination) model.

In the aldol reaction of lithium *Z*(O) enolate with an aldehyde gives rise to two possible products.

The asymmetric synthesis (up to 99% e.e.) of β-hydroxy-N,N-dimethylacetamide has been

reported by reacting aldehydes with an optically active sulfoxide.[185] Treatment of α-lithio-N,N-dimethylacetamide with diastereoisomerically pure (−)-(*S*)-menthyltoluene-*p*-sulfonate **378** gives rise to the α-sulfinylamide **379** (Scheme 27). The metal enolate derived from **379** was reacted with



Scheme 27.

various aldehydes. Low to medium levels of enantioselection (up to 47% e.e.) were achieved using n-BuLi as a base. With magnesium enolates, chiral discrimination was much higher (≥90–99% e.e. under the best conditions). The addition of hexamethylphosphoramide (HMPA) to the lithium enolate reversed and lowered the enantioselectivity. The high asymmetric induction observed for the magnesium enolates is sufficiently high to suggest a rigid model for the transition state (Fig. 96).

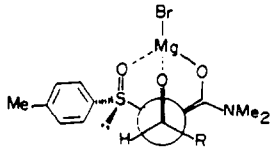
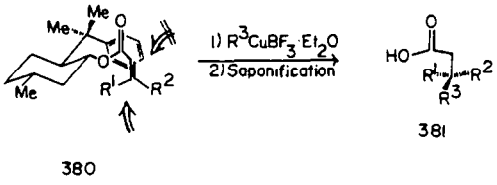


Fig. 96.

(3) Alkylation of chiral enolates. Chiral enolates have also seen much work in the area of asymmetric alkylations, a few examples are shown below.

Oppolzer and Löher[186] studied the 1,4-additions of $PhCu \cdot BF_3$, $n\text{-}BuCu \cdot BF_3$ and $MeCu \cdot BF_3$ to *trans*-8-phenylmenthyl enolate **380** (Fig. 97) with high chiral induction (in most cases >70%

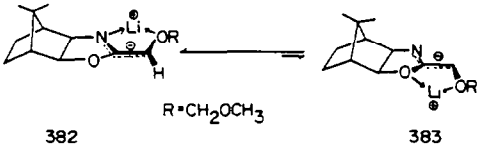


380 381

Fig. 97.

e.e.). Saponification gave the β-substituted alkanoic acids **381**. The high selectivity is probably a result of the transition state, **380**, as proposed by the authors. The conformational rigidity is enhanced by the coordination of the carbonyl with a Lewis acid.

A recent example of an oxazoline-based method to produce α-hydroxy acids in high optical purity (56–88% e.e.) was the alkylation of the glycolate anion equivalent, **382**, demonstrated by Kelley and Arvontis[187] (Fig. 98). The authors deduced that to give useful optical purities only two



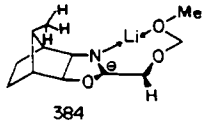
382 383

Fig. 98.

criteria need be met:

(a) anion generation must be highly stereoselective;
(b) once generated, the anion should exhibit high diastereofacial selectivity.[187]

Enolate **382** is preferred over enolate **383** by chelation effects (the basicity of the nitrogen compared to that of oxygen). The diastereofacial selectivity is achieved by the methyl group *endo* to the oxazoline ring because it effectively shields the β-face of the anion,[187] as is shown in Fig. 99, **384**.



384

Fig. 99.

CYCLOADDITION REACTIONS

Diels–Alder

Another versatile reaction is the Diels–Alder reaction for which Otto Diels and Kurt Alder received the Nobel prize in 1950. The Diels–Alder reaction is normally highly stereospecific which lends the reaction its synthetic utility.

Recently Gleiter and Böhm discussed the regio- and stereoselectivity in the Diels–Alder reaction in terms of second-order orbital interactions, which they subdivided into secondary orbital effects, substituent effects and polar group effects.[188]

There are two methods of inducing asymmetry in the Diels–Alder reaction.

(1) The use of a chiral diene, dienophile or enophile.
(2) The use of chiral Lewis acids.

Chiral dienophile or enophile. The reader is referred to a recent review by Oppolzer *et al.*[191c]

The simplest method of producing a chiral dienophile is to append a chiral functionality to it. For the reaction to be truly versatile, the functionality being appended must be readily available in both enantiomers. One of the first auxiliary groups to be used was menthol[189–196] and other naturally occurring amino acids and carbohydrates. The optical activity of the product in a Diels–Alder reaction was explained by Jurczak to be the result of a rigid transition state. The dienophile and diene approach each other in parallel planes, which results in two possible transition states of the reaction: **385**, in which the diene is situated above the dienophile plane from the side of the smaller substituent M, giving a 1*R*,2*R* configuration (using butadiene and (−)-(*R*)-menthyl fumarate) and **386**, in which the diene is situated under the dienophile plane from the side of the larger substituent L, giving an adduct of the 1*S*,2*S* configuration (Fig. 100).

The optical activity of the product is due to the difference in the steric ease of mutual approach of the reactants. The highest optical yields obtained in the Diels–Alder reaction of chiral acrylates varied between about 2–20% for uncatalyzed and 47–93% with the aid of Lewis acid catalysts.[196a]

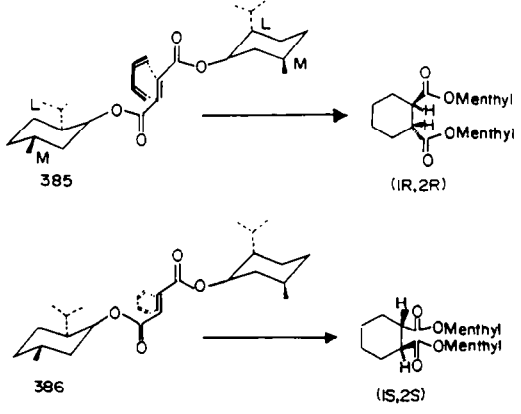


Fig. 100.

Masamune and co-workers[195] found that if the chiral centre is one atom closer to the enone unit, type i, as compared to type ii (Fig. 101), the optical yields of the products were found to be

Fig. 101.

higher. The reason was attributed to the closer proximity of the chiral centre. The authors reported that the uncatalyzed reaction of **387** with cyclopentadiene (Fig. 102) gave a ratio of >100:1 of

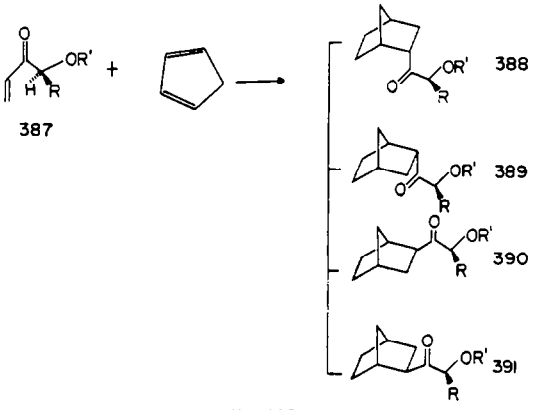


Fig. 102.

388:**389**, respectively (**390** and **391** were undetectable, R = t-Bu and R′ = H). The authors conclude that the high selection noted is attributed to the strong H-bonding between the hydrogen and the ketonic function in **387**. The formation of a 5-membered chelate effectively freezes the free rotation along the C—(=O)—C (asymmetric) axis, thus making two diastereotopic faces of the enone system highly distinguishable, **392** and **393** (Fig. 103). As R increases in steric bulk the diastereoselectivity

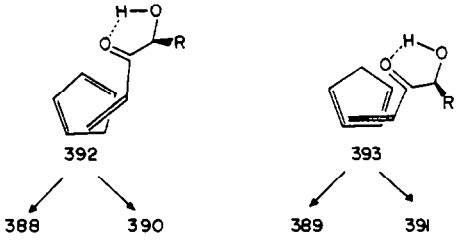
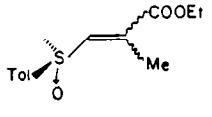


Fig. 103.

of the reaction increases correspondingly. Results using this system rival those of the catalyzed Diels–Alder reactions of type ii enones.

Koizumi *et al.*[196] also reported excellent results using a dienophile, ethyl *p*-tolylsulfinylmethylenepropionate **394** (Fig. 104), which has the chiral auxiliary directly attached to the



394

Fig. 104.

reaction centre, type iii. Because the chiral centre is directly attached, the diastereoselectivity in the asymmetric Diels–Alder reaction with **394** and cyclopentadiene was increased (Fig. 105). There were

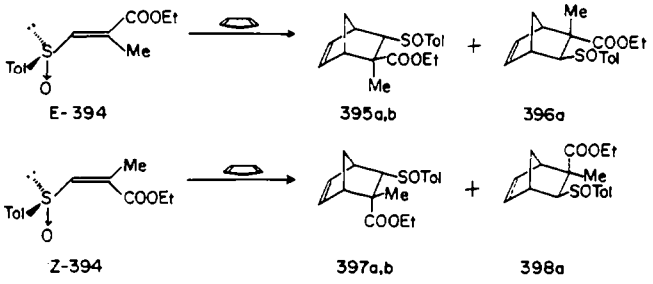


Fig. 105.

eight possible products from the reaction, only six products were obtained, from the Diels–Alder reaction of *E*- and *Z*-(R)$_S$-**394** with cyclopentadiene. The *endo*-sulfoxides **395a** and **b** and the *exo*-sulfide **396a** were obtained by heating a mixture of *E*-(R)$_S$-**394** and cyclopentadiene in 63, 15 and 22% yields, respectively. The diastereomeric *exo*-sulfide **396b** could not be detected.[189] Similarly, *Z*-(R)$_S$-**394** gave the *endo*-sulfoxides **397a** and **b** and the *exo*-sulfoxide **398a** in 63, 2, and 35% yield, respectively. The diastereoselectivity of the reaction is shown in Table 16.

Table 16.

Product	Diastereoselectivity (%)
395a and **b**	62
396a	100
397a and **b**	94
398a	100

The mechanism proposed by Koizumi *et al.*[196] is shown, in Fig. 106, for the case of *E*-(R)$_S$-**394**, assuming that, in the transition state, the α,β-unsaturated sulfoxide takes the *S-trans* conformation. This reaction leads to many possible uses due to the ease of removal of the sulfoxide.

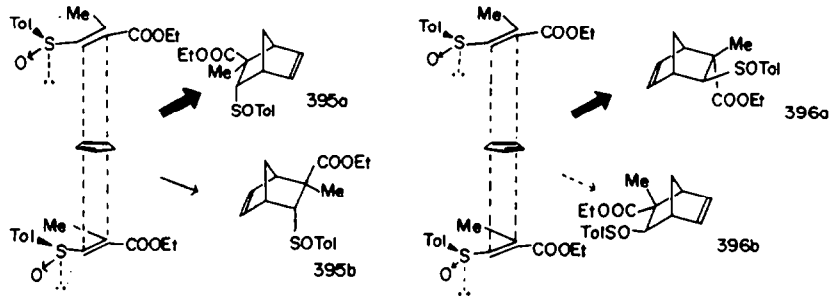
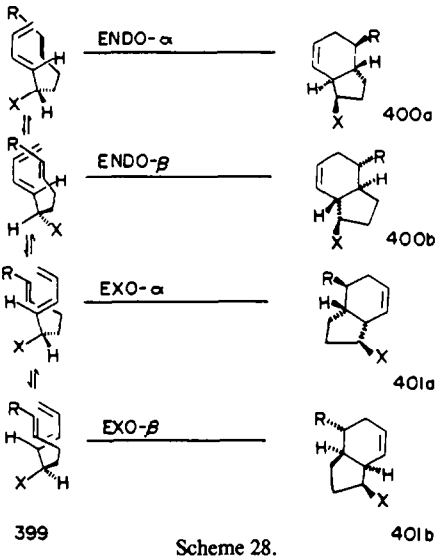


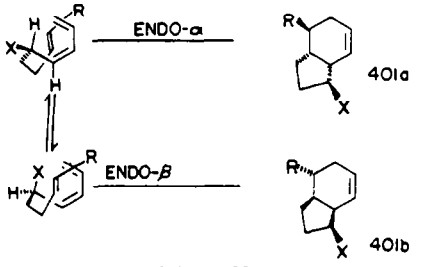
Fig. 106.

Chiral dienes. The intramolecular Diels–Alder reaction of *E*-dienes has the limitation that an *E*-diene **399** has two relatively easily accessible transition states which may afford a mixture of *cis*- and *trans*-fused products, **400** and **401**.[198] If a chiral centre is present then four possible products are possible **400a** and **b** and **401a** and **b** which are shown in Scheme 28.[197]

Z-Dienes lend themselves much more readily to predictions about product stereochemistry because a *Z*-diene can only attain a single transition state, in an intramolecular Diels–Alder reaction (Scheme 29). In the case of unsymmetrically substituted dienes, it can be easily seen that the steric interactions in the transition state *endo*-α (X being more sterically demanding than H). Fuchs and co-workers[197] found that in the cases reported chiral *Z*-dienes undergo intramolecular Diels–Alder reactions with enones to afford *cis*-fused products with complete stereo- and enantiospecificity.

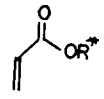
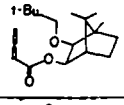


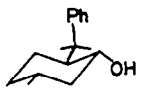
Scheme 28.

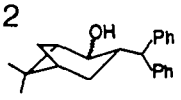


Scheme 29.

Table 17. Diels–Alder reaction of various chiral dienophiles with simple dienes (optical yield (reference)/ chemical yield configuration))

(-)-di-(R)-menthyl fumarate		12.8(189) 100(1S,2S)	12.4(189) 100(1S,2S)		
(-)-(R)-menthyl glyoxylate				20.9(190) 32(R)	
	R*				
	1				89(191) (R)
	2				85(191) (R)
	3				88(191) (S)
					>98(196) 98(S)
					>99(188) (S)

1 

2 

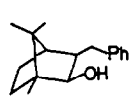
3 

Table 18. Lewis acid catalysed Diels–Alder reaction of various dienophiles with cyclopentadiene (optical yield (reference)/chemical yield (configuration))

Lewis acid catalyst	MeO$_2$C	OHC	CHO		Ph
	6(196) 65(S)	0(196) 40	72(196) 89(S)		
	0(196) 82	3(196) 73(S)	86(196) 72(R)		
	9(196) 78(R)	27(196) 55(196)	25(196) 84(S)		
$SnCl_2$				51(191a) (R)	89(191a) 95(R)
$AlCl_3$				40(191a) (R)	70(191a) 72(R)
Me_2AlCl				47(191a) 73(R)	64(191a) 95(R)
$TiCl_4$				62(191a) 65(R)	93(191a) 86(R)
$BF_3 \cdot Et_2O$					93(191a) 44(R)

Another commonly used reaction is the 1,3-dipolar, "ene"; e.g. NOC (nitrile oxide cyclization).

Ene reactions. Oppolzer and Thirring[199] used an intramolecular thermal ene reaction **402** → **403** whose stereochemistry was controlled by the carbon α to the reaction centre in **402** (Fig. 107); as a

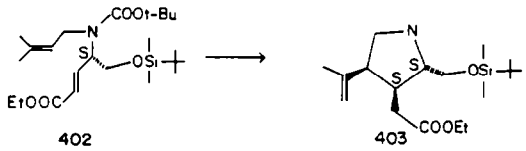


Fig. 107.

key reaction intermediate in the synthesis of (−)-α-kainic acid **404** (Fig. 108). As can be easily seen the silylated side chain directs the approach of the ene functionality. Oppolzer *et al.*[200] have also reported the enantioselective ene-type cyclization in the synthesis of (+)-α-alkanoic acid.

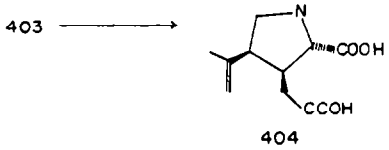
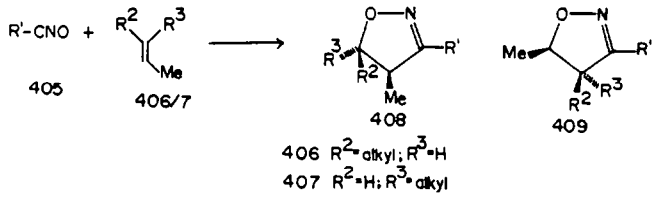


Fig. 108.

1,3-*Dipolar cycloaddition reactions*

[3+2] *Cycloadditions.* The 1,3-dipolar cycloaddition reaction of suitably functionalized 1,3-dipoles represents a novel synthesis of fused-ring heterocycles.[201] The NOC reaction involves a high degree of regioselectivity in the *Z*-disubstituted olefins **406**, Martin and Dupre[202] found that the 1,3-dipolar cyloadditions of nitrile oxides **405** (Scheme 30), gave the isoxazoline **408** whereas addition to *E*-disubstituted olefin **407** affords a mixture of isomeric **408** and **409**.



Scheme 30.

Kozikowski and Ghosh[203] studied the diastereoselection in intermolecular NOC reactions by performing the synthesis of 2-deoxy-D-ribose. It is known, in Diels–Alder reactions, that allylic positions can control the diastereofacial selection; however, such selection is normally small in the absence of a "chelatable" functionality. The authors reported that an allylic oxygen substituent can serve as a useful control element for the diastereofacial selectivity in [3 + 2] cycloaddition reactions.[203] The authors reacted optically active (+)-(*S*)-isopropylidene-3-butene-1,2-diol **410** with carboethoxy formonitrile oxide **411** which yielded an 80 : 20 mixture of diastereomeric adducts **412** and **413** (Fig.

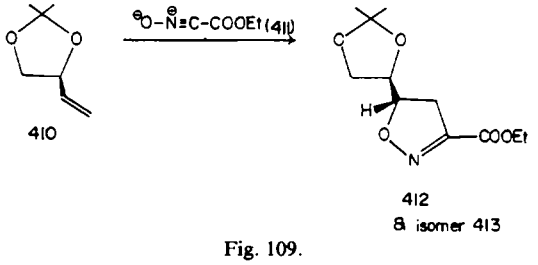


Fig. 109.

109), which can easily be converted to 2-deoxy-D-ribose. The authors rationalized the production of 2-deoxy-D-ribose by the following two factors.

(1) Cycloaddition occurs preferentially through a transition state resembling conformer **414**.
(2) Addition of the nitrile oxide occurs *anti* to the C—O bond (*anti*-periplanar, Fig. 110).

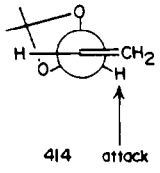


Fig. 110.

This effect is due probably to minimize the secondary antibonding orbital interactions. Koizumi *et al.* reported similar results in their work on the use of chiral sulfoxides as directing groups in the cycloaddition reactions.[204] The authors reported optical yields greater than 80% e.e.

Type ii. Asymmetric induction catalyzed by external chiral functionalities

This area has recently been receiving increased study.[206] Koga and co-workers[205] reported that moderate asymmetric induction (0–72% e.e.) can be obtained in Diels–Alder reactions catalyzed by chiral alkoxyaluminium dichlorides **415–417** (Figs 111 and 112). The authors noted that the degree of asymmetric induction is greatly affected by the structure of the reactants and the catalysts. Roush *et al.*[206] reported that in the case of the cyclization of (+) - (1*R*,2*S*,5*R*) - 2 - (1 - methyl - 1 -

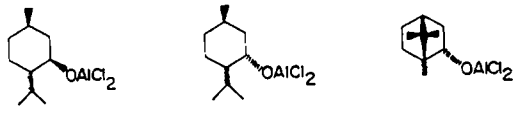


Fig. 111.

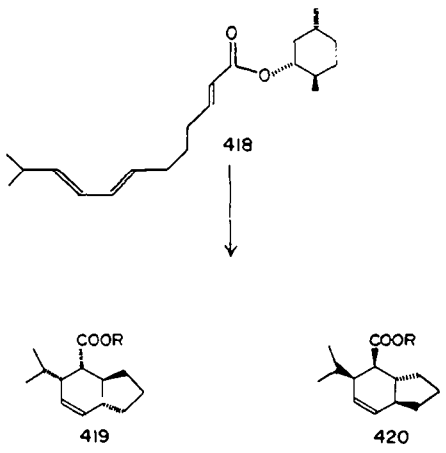
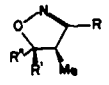
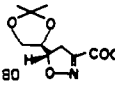
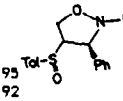
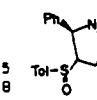
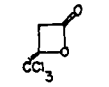


Fig. 112.

phenylethyl) - 5 - methylcyclohexyl (*E,E,E*) - 11 - methyldodeca - 2,7,9 - trienoate **418** (Fig. 112), racemic **415** gave higher diastereomeric excess (34%) of **418** than the chiral menthyloxy reagent **415**. The authors found that the chirality of the optically active Lewis acid has a negligible effect on the results and modest results are obtained using chiral dienophile esters[206] and $TiCl_4$.

Table 19. "NOC" cyclizations (optical yield (reference)/chemical yield (configuration))

compound and catalysts used	product 1	product 2	diastereomeric excess	chemical yield	ref.
R—CNO + 					
R=PH$_2$C, R'=i-Pr, R"=H			99	96	201
R=t-Bu, R'=H, R"=t-Bu			>99	35	201
R=2,4,6-Me$_3$C$_6$H$_2$, R'=i-Pr, R"=H			>99	92	201
 + ONC—COOEt	 80	 20	60	NR	203
 +  R=Ph R=Me	 95 92	 5 8	90 84	37 39	204 204
CH_2=C=O + CCl_3CHO (+)-quinidine			98	95	201

Danishefsky and co-workers[207] studied the use of $Eu(hfc)_3$ as the chiral inductor in the cyclocondensation of aldehydes with siloxydienes. The authors found that the cyclocondensation of the oxygenated diene **421** with benzaldehyde gave the cyclic ether **422** (Fig. 113). The authors found

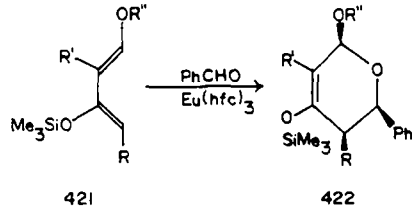
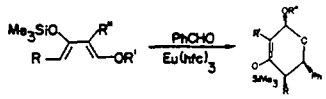


Fig. 113.

Table 20. $Eu(hfc)_3$ catalysed cycloaddition of benzaldehyde with the oxygenated diene **422**



R = H ; R" = H			R = H; R" = Me		R = Me ; R" = Me	
R' = Me	R' = i-Pr	R' = t-Bu	R' = Me	R' = t-Bu	R' = Me	R' = t-Bu
18 (R)	22 (R)	38 (R)	15 (R)	39 (R)	36 (R,R)	42 (R,R)

that optical enrichment was obtained in the cases when the size of the alkoxy substituent at C_1 of the diene was increased (R = H, R′ = H), when R″ was t-Bu the optical yield was 38% e.e. as compared to 18% when R″ was Me.

In the 1-methoxy series (R″ = Me), the 2-methyl (R′ = Me) substitutent does not appear to greatly influence the cycloaddition reaction. The addition of a 4-methyl group (R = Me) does affect a large increase in optical activity (36% e.e.). The optical purity does not seem to be influenced by increasing the concentration of $Eu(hfc)_3$. The important features in this cycloaddition are:

(a) alkoxy substituent at C_1 is larger than H increases optical purity;
(b) methyl substituent at C_4 increases the optical purity;
(c) increased amounts of $Eu(hfc)_3$ increases the rate of reaction but not optical purity.

Because of the increased need for chiral substituted cyclobutanones and β-lactones, there has been an increase in the study of methods to easily produce such valuable intermediates.

Wynberg and Staring[208] studied the synthesis of (*S*)- and (*R*)-malic acid from ketene and chloral. The authors studied the use of Chinona alkaloids as chiral catalysts in the [2+2] cycloaddition. They found that:

(a) tertiary amines with or without β-hydroxy groups give comparable induction (>60% e.e.);
(b) flexible and rigid catalysts give the same optical induction (70–77% e.e.);
(c) in most cases the chirality of the product is predictable on the basis of knowledge of the chirality of the carbon adjacent to the tertiary amine function in the catalyst.

The authors proposed the following mechanism for the reaction.[208]

The mechanism is based upon the formation of a ketene–amine complex. Using 1,2-dimethylpyrrolidine **423**, as an example, the assumption is made that 1,2-dimethylpyrrolidine at −50° is present in its more favourable *trans* conformation. Complexation of 1,2-dimethylpyrrolidine with ketene **424** can give rise to two different complexes **425** and **426** (Fig. 114). The configuration of the

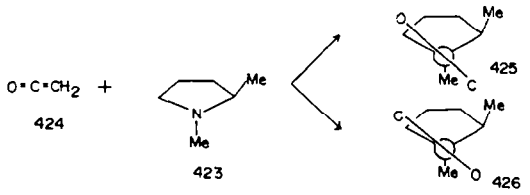
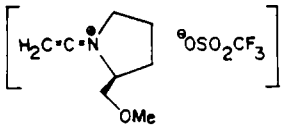


Fig. 114.

product in the reaction of the complex with chloral is then determined by the manner in which the trichloromethyl group of the chloral recognizes the chirality of the tertiary amine. The proposed mechanism suggests that the chiral centre adjacent to the tertiary nitrogen determines the chirality of the product. Ghosez and co-workers[209] examined keteneiminium salts **427** (Fig. 115) derived



427

Fig. 115.

from chiral amines (a ketene equivalent) bearing the chiral inductor on the C atom where binding is expected to be the most advanced in the transition state of the cycloaddition. The reaction of the aldoketene iminium salt **427** with cyclopentene gave, after hydrolysis adducts **428a** and **b** (Fig. 116).

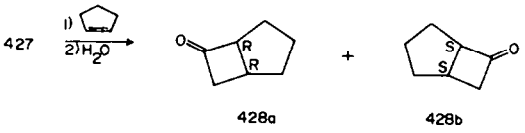


Fig. 116.

Compound **428b** was obtained in a much higher yield; the optical yield of **428b** was 55.4%. The diastereoselectivity was higher in the case of the β-disubstituted keteneiminium salt **429** (Fig. 117)

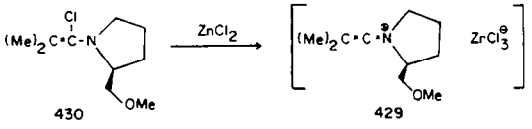


Fig. 117.

which was obtained from **430** by treatment with $ZnCl_2$, was treated *in situ* (Fig. 118) with cyclopentene to give cyclobutanone **431** with almost complete induction (>97%). The twin transition

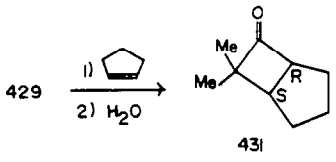


Fig. 118.

states (Fig. 119) proposed by the authors in the reaction are **432** which leads to the 1*S*,5*S* configuration and is favoured when R = H. When R = alkyl, the transition state **432** becomes hindered and the alternate transition state **433** becomes favoured and the 1*R*,5*S* configuration results.

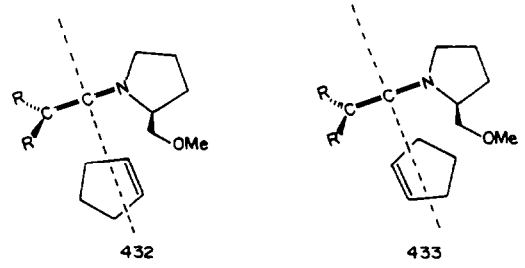
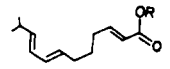
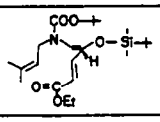
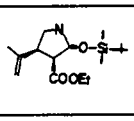
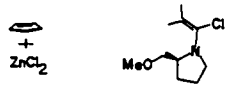


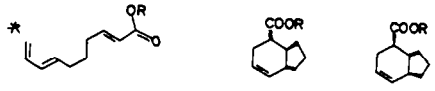
Fig. 119.

Table 21. Internal Diels–Alder (optical yield (reference)/chemical yield (configuration))

compound and catalysts used	product 1	product 2	diastereomeric excess	chemical yield	ref.
					
$TiCl_4$	86	14	72	8	206
(rac)-menthyloxy$AlCl_2$	68	32	36	75	206
(l)-menthyloxy$AlCl_2$	67	33	34	61	206
(rac)-menthyloxy$AlCl_2$*	75	25	50	40	206
(l)-menthyloxy$AlCl_2$* R=(-)-Phenylmenthoxy	86	14	72	72	206
R=Me					
(l)-bornyl-O$AlCl_2$			<1	85-7	206
(l)-menthyl-O$AlCl_2$			<1	85-7	206

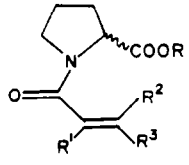
Internal "ENE" cyclization

		>83	75 : 199
		>97	:70 : 209



EPOXIDATIONS

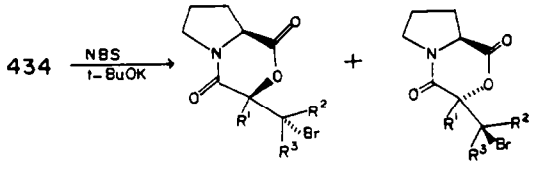
A convenient method for the stereoselective synthesis of epoxyaldehydes and epoxylactones is to utilize a bromolactone. The bromolactone may be produced stereoselectively by the bromolactonization of N-(α,β-unsaturated) acylprolines **434**[210,211] (Fig. 120). The reaction of **434** with



434

Fig. 120.

NBS and t-BuOK gives the bromolactones **435** and **436** where the ratio of **435** : **436** was greater than 92 : 8[210,211] (Fig. 121). After reaction with sodium methoxide, followed by $NaAlH_2(OEtOMe)_2$ the



435 **436**

Fig. 121.

epoxyaldehyde **437** was obtained in optical yields of 84–98% e.e. By using (*S*)-prolines, as the chiral auxiliary agent (2*R*,3*S*)-epoxyaldehydes are formed (Fig. 122). This method is able to give good

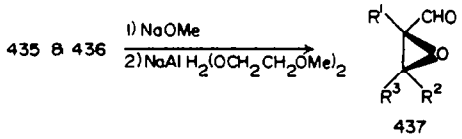
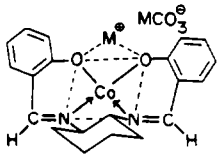


Fig. 122.

chemical and optical yields but requires a chiral centre in the molecule to direct the epoxidation. The best method would be to start with a prochiral olefin system and externally direct the epoxidation. An example of this technique was shown by Takeichi *et al.*[212] in which optically active chloromethoxirane was obtained from 1,3-dichloro-2-propanol, the highest optical yield obtained was 67% e.e. using Co(II) (3,5-Cl·Cl-Sal)$_2$ (*S*-CHXDA)[213] and K_2CO_3. The asymmetric cyclizations of racemic 2,3-dichloro-1-propanol and 2-chloro-1-propanol were found to, under the same conditions, give optically active chloromethyloxiranes and methyl oxirane by a kinetic resolution mechanism, although the optical yields were lower.

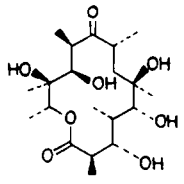
The authors found that the cobalt (Salen)-type complex forms a new complex with alkali metal carbonate **438**, which directs the approach of the halohydrin (Fig. 123). As was seen in the alkylations



438

Fig. 123.

which were ligand assisted, OsO_4 and $Vo(AcAc)_2$ utilize the molecules' inherent chirality as in the stereoselective synthesis of the chiral sequence of Erythronolide A **439**[214] (Fig. 124), or by the use



439

Fig. 124.

of dihydroquinine **440** and dihydroquinidine **441** to direct the attack of the epoxidation agent (Fig. 125), in the OsO_4 epoxidation of olefins.[215] The stereoselectivity is thought to be the result of the quinuclidine nitrogen to bind the OsO_4 and hinder the approach to the olefin. If the chiral centre is adjacent to the binding site, the optical yields were in the range of 40–80% e.e.

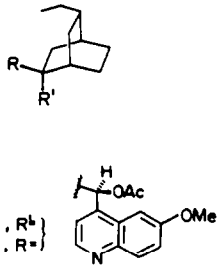
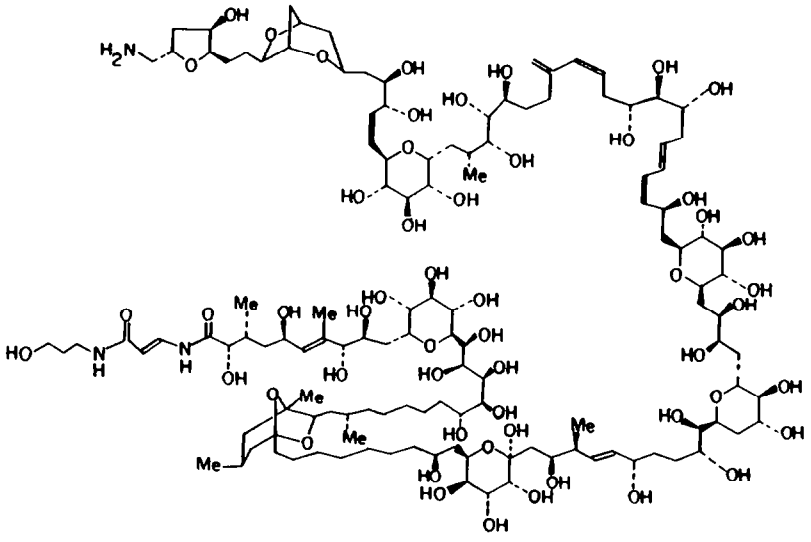


Fig. 125.

One of the most popular methods of epoxidation is the metal-catalyzed oxygenation of olefins and acetylenes. The reader is directed to a recent review of such reactions by Sharpless and Verhoeven.[216]

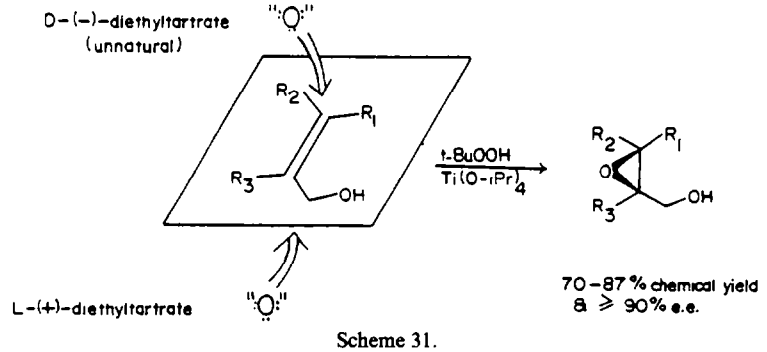
In 1980, Katsuki and Sharpless[217] reported a new metal-catalyzed asymmetric process for allylic and propargylic alcohols. The process is now known as the "Sharpless reagent" ((+)- or (−)-diethyltartrate, titanium tetraisopropoxide and t-butyl hydroperoxide).[219] The reagent has seen much use in the preparation of poly-hydroxy compounds and a recent use of it was in the synthesis of the hydroxylated portions of palytoxin **442** (Fig. 126).[219a] The direction of attack is decided by



442

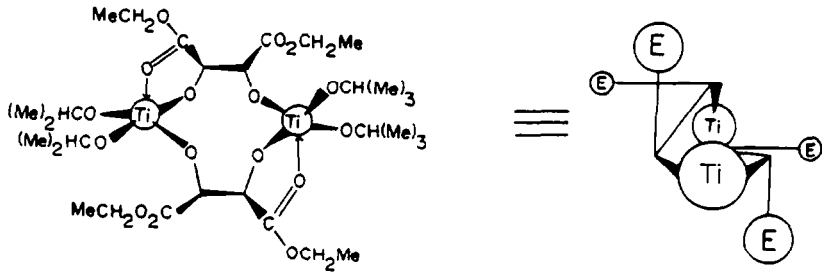
Fig. 126.

the choice of the diethyl tartrate used in the reaction[219] (Scheme 31). Sharpless has determined that the selectivity of the reaction is the result of a catalytic species in which two metal atoms are connected by two tartrate molecules to form a 10-membered ring[219] (Fig. 127). The tartrate ester groups extend outward from the ring "like the vanes of a windmill", thereby limiting the manner in which the allylic alcohol and hydroperoxide can bind to the metal.[218]



Scheme 31.

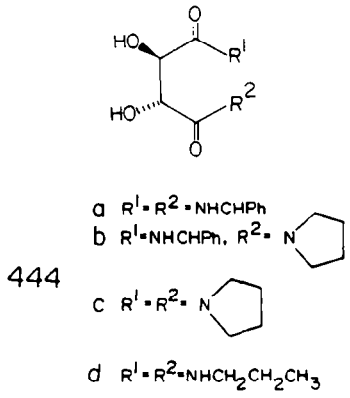
Recently, Sharpless and co-workers[220a] reported two new asymmetric epoxidation catalysts. The standard catalyst utilizes a 1:1 titanium:tartrate asymmetric catalyst. The new catalyst system depends on a titanium:tartrate ligand ratio of 2:1. The two new systems that involve epoxidation of an allylic alcohol effect the epoxidation with an enantiofacial selection that is opposite to that of the standard catalyst.



443

Fig. 127.

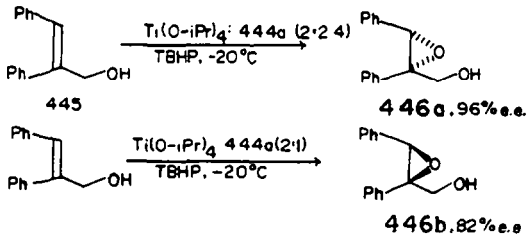
The first of the new systems utilizes amide ligands such as those of **444a–d** (Fig. 128). By carefully controlling the amount of ligand **444** to titanium, the stereoselection of the epoxidation may be



444

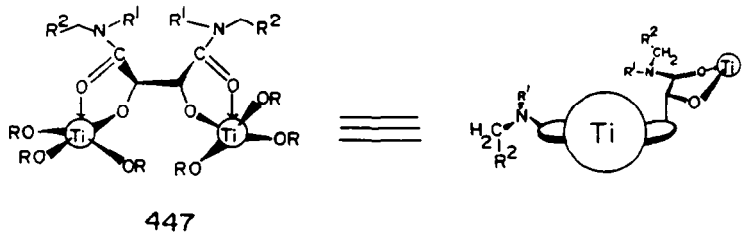
Fig. 128.

controlled as is shown in Scheme 32. The epoxidation of (*E*)-α-phenylcinnamyl alcohol with various 2:1 Ti(O—i-Pr)$_4$–tartamide complexes has been studied by the authors. The selectivity of the



Scheme 32.

tartamide complexes increased in the following order **444c** < **444d** < **444a** < **444b**, for (*E*)-α-phenylcinnamyl alcohol (2*R*,3*R* configuration) with optical yields of 53, 6, 82, and 84% e.e., respectively. This reverse selectivity is very substrate dependent, the selectivity is always opposite to the standard system but the optical yields vary. To account for the difference in selectivity the authors proposed structure **447** (Fig. 129).



447

Fig. 129.

The second of the new catalysts utilizes $TiCl_2(O—i\text{-}Pr)_2$. Certain epoxy alcohols are difficult to obtain by standard reactions, due to their sensitivity to epoxide opening under the standard reaction conditions. The problem has been traced to the titanium alkoxide catalyzed opening of the epoxide by i-PrOH, TBHP, allylic alcohol, epoxy alcohol or possibly by t-BuOH.[220a]

When the epoxidation of allylic alcohol **448** was carried out under the standard conditions (a 1:1 tartrate:titanium ratio) using $Ti(O—t\text{-}Bu)_4$ instead of the normal $Ti(O—i\text{-}Pr)_4$ the yield of epoxy alcohol **449b** increased to 51% as compared to 15% under standard conditions.[220a] When the oxidation of **448** was carried out with a 2:1 $TiCl_2(O—i\text{-}Pr)_2$:(+)-DET, the chlorodiol **450** was obtained which when treated with base closed cleanly to give epoxide **449a** in 68% e.e.[220a] (Fig.130).

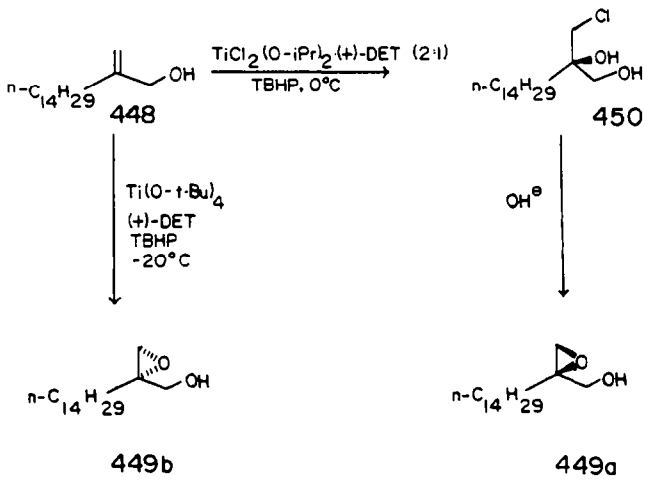


Fig. 130.

The chlorohydroxylation has been applied to other allylic alcohols and the reversed facial selectivity was observed in every case studied. The optical yields for the reactions ranged from 20 to 68%.[220a] Further study of this reaction should lead to increased optical yields in the future using the inexpensive (+)-DET ligands.

SULFUR REAGENTS

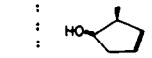
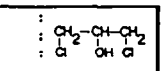
Substituted tri-coordinated sulfur compounds such as sulfinates, sulfoxides and sulfilimines are capable of exhibiting optical activity. This section will deal with recent efforts regarding the synthesis of these in optically active forms and their use as chiral inducing agents in the formation of chiral C atoms.

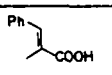
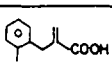
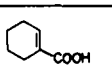
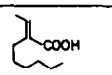
The use of microbial oxidation has been reported in the past. Sugimoto *et al.*[221] obtained optically active aromatic sulfoxides, in the presence of bovine serum albumin (BSA), of up to 81% e.e.[221,222] and the kinetic resolution of racemic sulfoxides was reported.

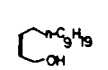
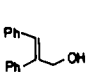
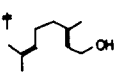
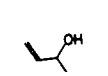
Hiroi *et al.*[223] reported this use of a recyclable chiral director for the synthesis of chiral sulfoxides (Scheme 33). The benzoxathiazine-2-oxide derivatives **452** and **453** were prepared by the reaction of the aminophenols **451** with thionyl chloride. The crude benzoxathiazine-2-oxide derivatives **452** and **453** were obtained in a 2:1 ratio, respectively. The treatment of the crude mixture of **452** and **453** with phenylmagnesium bromide flowed by alkyllithiums gave the (*R*)-(+)-alkylphenylsulfoxide with about 33% optical activity. However, **452** can be epimerized to **453** by treatment with HCl. Repeating the sequence described above gave the (*S*)-(−)-alkylphenylsulfoxide in about 80% e.e. The aminophenol **451** was recovered without racemization, in good chemical yield, thus making this method very attractive for the production of optically active alkylphenylsulfoxides.

Because of the facile generation of C—S bonds there has been reported the use of sulfur groups as chiral auxiliaries in the synthesis of oxaziridines.[224,225] The authors reported the use of 2-

Table 22. Formation of epoxides (optical yield (reference)/chemical yield (configuration))

catalyst	styrene	1-phenyl-cyclohexene	(E)-3-hexene		
OsO_4 + dihydroquinineacetate	64(215)* 90(S)	68(215) 88(1S,2S)	30(215) 69(S,S)		
OsO_4 + dihydroquinidineacetate	61(215) 62(R)	67(215) 87(1R,2R)			
$VO(AcAc)_2$ + t-BuO_2H				≥95(214) 86(1S,2S,3S,4R)	
Co(II)(3,5-Cl,Cl-Sal)$_2$(S-CHXDA)#					67(212) 59.8(S)

				
Proline halolactaonisation*	98(210) 62(2R,3S)	92(210) 52(1S,2R)	≥99(210) 35(1R,2S)	>99(210) 22(2R,3S)

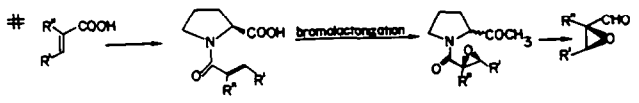
allylic alcohols				
2:2 $Ti(OiPr)_4$:1 ligand in the presence of TBHP				
ligand				
(+)-DET	90(217) 82(2S,3R)	95(217) 87(2R,3S)	95(217) 77(2S,3S)	
(-)-DET	90(217) 80(2R,3S)			91(220a) 54(2S,3R)
444a		96(220) 90(2S,3S)		

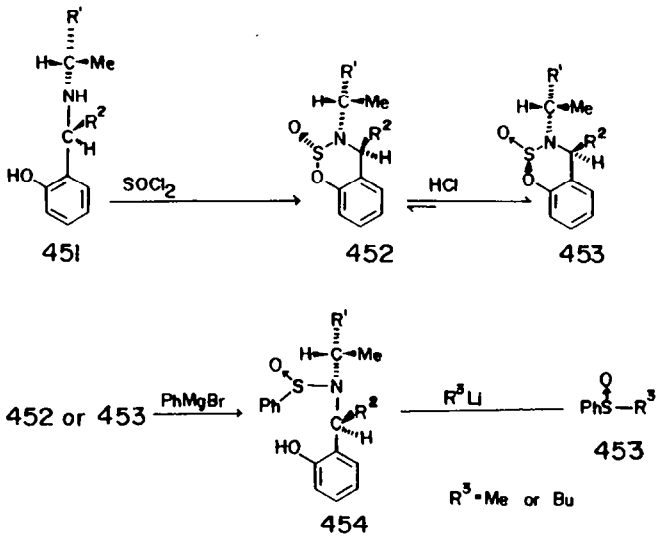
2:1 $Ti(OiPr)_4$:ligand in the presence of TBHP				
444a		82(220) (2R,3R)		
444b		94(220) (2R,3R)		
444c		93(220) (2R,3R)		
444d		16(220) (2R,3R)		

* based on diol produced by H^- reduction of epoxide

S-CHXDA = N,N'-disalicylidene-(1S,2S)-1,2-cyclohexanediaminato

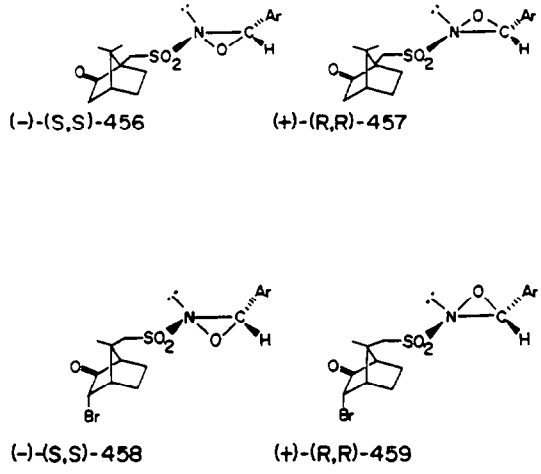
non-allylic alcohol not epoxidized





Scheme 33.

sulfonyloxaziridines **456–459** (Scheme 34), which may be obtained optically pure by fractional crystallization. The oxidation of unfunctionalized substrates (e.g. sulfides and disulfides) by 2-sulfinyloxaziridines seems to be controlled by steric hindrance alone. The selectivity of these reagents



Scheme 34.

can be explained by the authors[224] as a "chiral recognition model".[224] The aromatic functionality (in this case the 2-chloro-5-nitrophenyl group) behaves as if it was smaller than the camphorsulfonyl group. The oxaziridine 3-membered ring can be divided into large and small regions (Fig. 131).

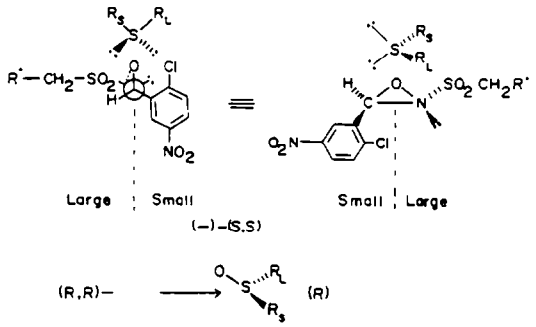


Fig. 131.

Thus the enantiomer of sulfoxide may be chosen by the careful selection of the oxaziridine used. Oxidation with (*S,S*)-(−)-**458** and (*R,R*)-(+)-**459** afforded sulfoxides of *S* and *R* configurations, respectively, and in optical yields of upto 35% but 10–20% is commonly found. The absolute configuration of the oxaziridine 3-membered rings confers the configuration of the products.

Chiral sulfoxides have been used as a chiral auxiliary in many reactions with varying results:

(a) 1,3-dipolar cycloaddition of nitrones[226] (>90% e.e.);
(b) synthesis of functionalized 5- and 6-membered lactones[227] (>80% e.e.);
(c) alkylation of α,β-unsaturated sulfoxides[228,229] (60–100% e.e.);
(d) aldol type reactions (66–100% e.e.);[230,231]
(e) formation of optically active alcohols,[230] β-oximes and β-hydroxylamino sulfoxides.[231]

REARRANGEMENTS

[3,3]- *and* [2,3]-*sigmatropic rearrangements*

The transition states of the [3,3]- and the [2,3] -sigmatropic rearrangements are usually highly ordered, which results in the effective transfer of the stereochemical relationships in the starting material being transferred to specific stereochemical relationship in the product.

Some common [3,3]-sigmatropic rearrangements are Cope and Claisen rearrangements. The Cope rearrangements of unsubstituted 1,5-hexadienes are not synthetically useful reactions (Fig. 132), if X and Y in the above reaction are the same, the product is indistinguishable from the starting

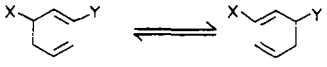
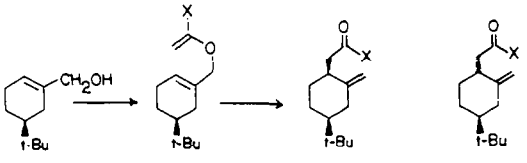


Fig. 132.

materials. The Cope rearrangement suffers as a synthetic method because the reactions are reversible and favour the production of the highest substituted olefins. However, these two are synthetically useful due to the shift in the equilibrium to the product by the formation of stable carbonyls (oxy-Cope), or enolates (alkoxy-Cope).[232]

An example of the Claisen rearrangement is the rearrangement of vinyl ether derivatives (such as **461**) of 5-*t*-butyl-1-(hydroxymethyl)-1-cyclohexene **460** by Ireland and Varney[233] (Scheme 35).



Scheme 35.

The authors found that the axial rearrangement product **462** predominated over equatorial product **463**. The Claisen rearrangement resulted in the attachment of the CH_2COX side chain predominately on the β-face of the cyclohexene ring, in the axial orientation. The rearrangement is apparently stereoelectronically controlled, steric bias can add to or subtract from this effect. The authors envisaged two limiting transition states (CHAIR T‡ and BOAT T‡) to account for the results (Fig. 133). The cases where the vinyl ether portion terminates with CH_2 favoured the CHAIR T‡

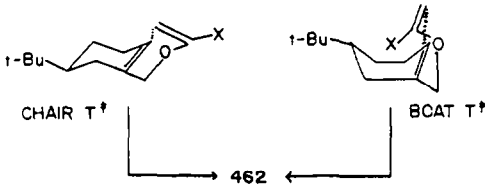
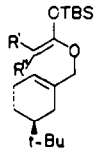


Fig. 133.

arrangement. In the case of **464** (Fig. 134), the *Z*-ketene acetal (R′ = CH_3, R″ = H) the chair (axial transition state is favoured however in the case of the *E*-ketene acetal (R′ = H, R″ = CH_3), the equatorial attachment competes with the axial attachment.[233]



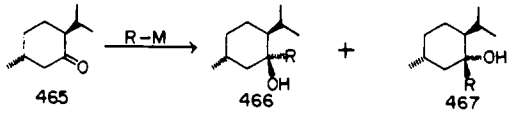
464

Fig. 134.

For either the CHAIR T‡ or the BOAT T‡ conformation for the axial approach, the *E*-ketene acetal will require that a bulky vinyl substituent be buried in the cyclohexene ring.[233]

The authors further stated that while axial attachment of the side chain by Claisen rearrangement is preferred in the cyclohexenylmethanol system, relatively minor substitution of the vinyl ether portion of the molecule can have a great effect on the amount of equatorial attachment obtained.[233]

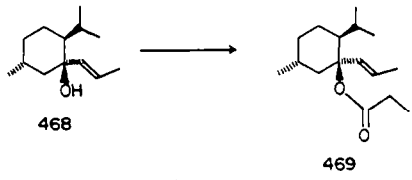
Hart and co-workers[234] studied the formation of axial tertiary alcohols of the type **466** (with high diastereoselection) which were prepared by treatment of menthone **465** with various organometallic reagents (Fig. 135). The propionate **469**, derived from *trans*-(*Z*)-**468**, undergoes an enolate Claisen



465 466 467

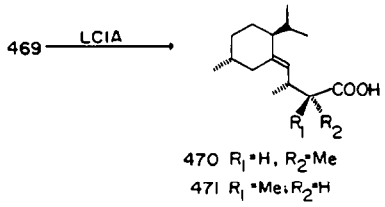
Fig. 135.

rearrangement with nearly complete transfer of chirality (Fig. 136). Treatment of **469** with lithium cyclohexylisopropylamide afforded a mixture of acids **470** and **471** in 59 and 6% yields, respectively. Enolization of **469** affords a mixture of **469***Z* and **469***E* in which **469***Z* predominates. This acounts



468 469

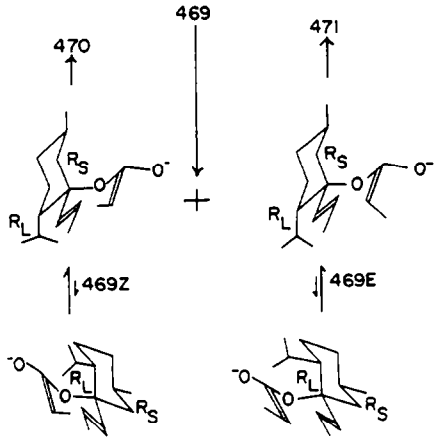
Fig. 136.



470 R_1 = H, R_2 = Me
471 R_1 = Me, R_2 = H

Fig. 137.

for the small production of acid **471**. The authors propose that the rearrangement of **469***Z* (*E* proceeds via a chair–chair transition state (Scheme 36) in which the R_L group (i-Pr) occupies a pseudoequatorial site to give **470** (**471**). The propionate **472** obtained from *cis*-**468** did not undergo



Scheme 36.

Claisen rearrangement. This was probably due to severe pseudo-1,3-diaxial interactions as shown in structure **473Z** (Fig. 138).

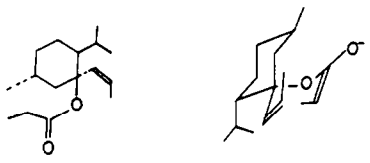
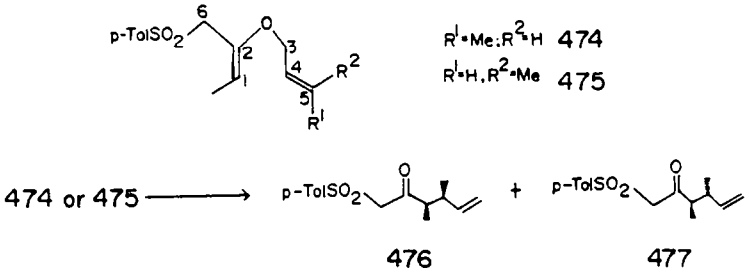


Fig. 138.

Denmark and Harmata[235] found that carbanion-accelerated Claisen rearrangements were highly stereoselective (as selective as their thermal counterparts) and were dependent upon solvent, counterion and temperature (Scheme 37). The authors found that the rearrangement of **474** and **475** to



Scheme 37.

476 and **477** proceeded smoothly and with high stereoselectivity (98 : 2 and 4 : 96, respectively). The carbanionic rearrangement (M—H/DMSO; M = K, Na or Li) of **474** to **476** and **477** (98 : 2, respectively) in dimethyl sulfoxide at room temperature (heated to 50° for 2–5 min at the end to assure completion). The carbanionic rearrangement of **475** formed 1-(*p*-tolysulfonyl)-2-butanone in large amounts but could be completely suppressed by using lithium dimsylate as the base, resulting in high selectivity. The highest selectivities and yields were obtained at slightly elevated temperatures (about 50°) and short reaction times (0.25–4 h). The outcome of the carbanionic rearrangements of **474** and **475** is in agreement of a chair-like transition state. The slower rate of thermal rearrangement of **475** vs **474** (2 times) is reasoned to be due to pseudo-1,3-diaxial interactions between CH_3C (C_5) and the sulfonylmethylene group (Fig. 139). The carbonionic rearrangement of **475** is 12 times

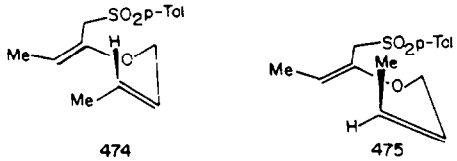
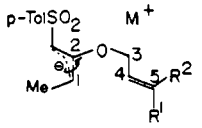


Fig. 139.



478

Fig. 140.

slower than that of **471** which suggests a more serious interaction with the metal ion **478** and its attendant solvent molecules (Fig. 140). Rotation about the C—C_2 bond is stereochemically important and the authors concluded either:

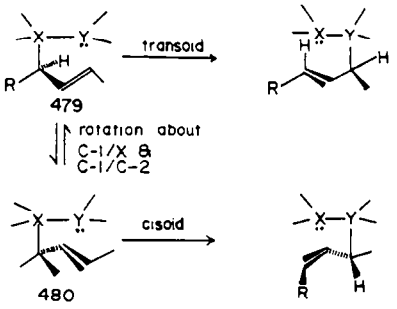
(a) the barrier is extremely high or
(b) the *E* geometry is strongly favoured at equilibrium.

[2,3]-*Sigmatropic rearrangements*

[2,3]-Sigmatropic rearrangements have seen an increase in study due to the 5-membered rings' greater "flexibility" compared to the 6-membered transition state of the [3,3]-sigmatropic rearrangements.

Hoffmann[236] has written a review as to the "stereochemistry of [2,3]-sigmatropic rearrangements". In the review Hoffmann made several observations.

(1) In the case of 1,2-disubstituted double bond rearrangements starting from **479** and **480** can proceed via two transition states, designated as transoid and cisoid by Mislow[236] (Scheme 38).



Scheme 38.

(2) In most cases rearrangement yields an *E* olefin. In the case of trisubstituted double bonds, the *E*:*Z* stereoselectivity depends upon the relative sizes of the substitutents attached to C-1 (Fig. 141), if R′ > R^2 R′ should prefer a pseudo-equatorial position leading to *E* olefins.

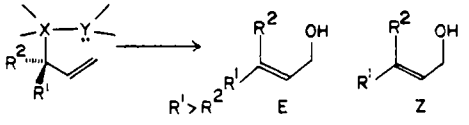


Fig. 141.

(3) Transfer of chirality has been described as a "self-immolative" asymmetric synthesis because the chirality at C-1 is lost to produce the chirality at C-3. There are three types of transfer:

(a) Transfer of chirality from C-1 to C-3. The configuration about C-2/C-3 must be all-*Z* or all-*E* in order to obtain the highest possible yield since the transfer will follow from a suprafacial course of rearrangement.

(b) Transfer of chirality from a chiral group on C-1 to C-3. A commonly used version of this reaction is the allyl sulfoxide/allyl sulfenate rearrangement.[237-242] A good example of this reaction is the rearrangement of 17-vinyl-17-hydroxy steroids.[242] The authors reported a "one-pot" epimerization procedure of 17*a*-vinyl-17*b*-hydroxy steroids **481** and **482**, the rather inaccessible 17-epimers **483** and **484** can be assembled by the use of the sulfoxide sulfenate [2,3]-sigmatropic rearrangement

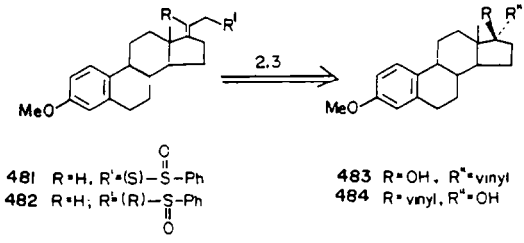
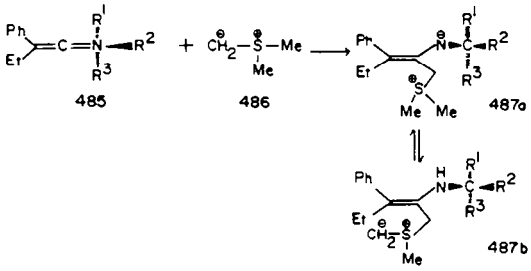


Fig. 142.

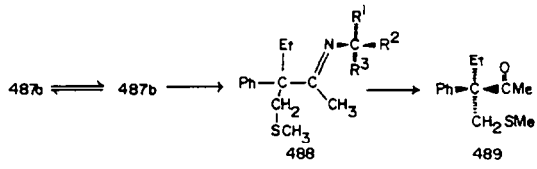
(Fig. 142). Sulfoxides **481** and **482** were obtained from **483** and **484**, respectively, by treatment with n-butyllithium and phenylsulfenyl chloride. The rearrangement and cleavage of **481** (trimethyl phosphite in methanol at reflux for 40 h) gave a mixture of **483** and **484**, 65 and 23%, respectively. The rearrangement of **482**, under similar conditions gave almost exclusively **484** (only trace amounts, about 1%, of **483** were detected). This method should allow for the preparation of "unnatural" stereochemistries in materials which are otherwise biased.

(c) Transfer of chirality *X* to *Y*. Most accounts of this type of reaction are for the rearrangements of sulfur ylides. An example of this type of reaction was the [2,3]-sigmatropic rearrangement of 2-alkylamino-3-phenyl-2-pentenylmethylsulfonium methylide, **487a** and **b**, which was obtained by the reaction of ethylphenylketenimines **485** having chirality next to the N atoms with trimethylsulfonium ylide **486**[243] (Scheme 39). The actual species which undergoes the rearrangement is **487b** to give



Scheme 39.

imines **488** (Scheme 40). Hydrolysis of **488** yields 3-methylthiomethyl-3-phenyl-2-pentane **489**. After proton transfer from the C-1 carbon to the N atom in **487a**, approach of the sulfur ylide group to



Scheme 40.

the π-bond in **487b** would occur from the less hindered side. Because of the steric interference between the small (S) or medium (M) group and the sulfur ylide moiety in the most preferred conformation **490**, in which the large group (L) should be in the same plane as the C=C bond nitrogen line (Fig. 143). This method, although optical yields were low to moderate (4–55% e.e.),

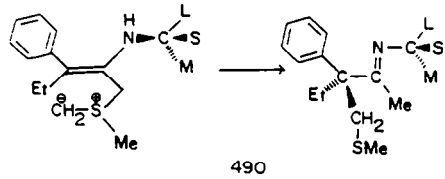


Fig. 143.

could be a valuable tool to the preparation of optically active α′-substituted methyl ketones. Rearrangements of moderate to high optical purity (56–90% e.e.) have been reported via chiral ammonium ylides.[244]

The asymmetric [2,3]-sigmatropic rearrangements of chiral ammonium chlorides (*E*)- and (*Z*)-**491a** and **b** were achieved by treatment with t-BuOK followed by acidic hydrolysis of the aminonitriles **493a** and **b** obtained to give (*R*)-(+)- and (*S*)-(−)-2-methyl-2-phenyl-3-butenal **494a** and **b**, respectively[244] (Fig. 144). The highest optical purity (90% e.e.) was obtained by performing the

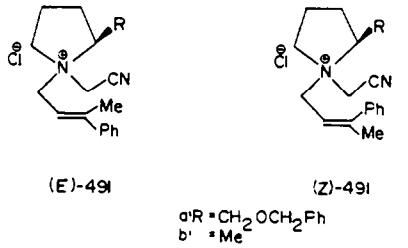


Fig. 144.

reaction at −98°. The author proposed the following mechanistic pathway for the asymmetric induction (Fig. 145). Conformation **495** is favoured over **496** by the steric strain between the R′ group and the R group (Fig. 146).

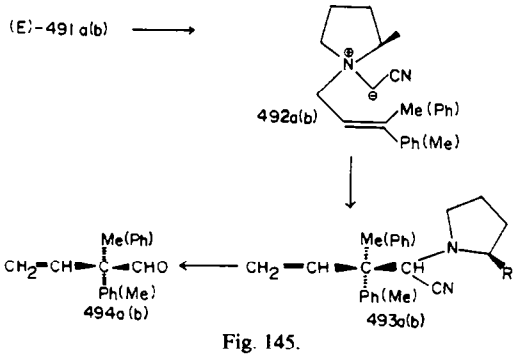


Fig. 145.

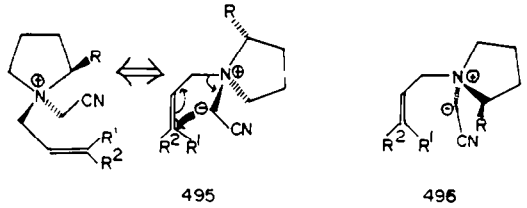


Fig. 146.

ADDENDUM

The area of asymmetric synthesis continues to expand rapidly as evidenced by the many publications which appeared since the completion of the original manuscript. There have been some reports which should be included for completeness.

Reductions

Mukaiyama *et al.*[246] reported the asymmetric reduction of prochiral ketoesters (Fig. 147) with a reagent generated by the treatment of a mixture of tin(II) chloride and a chiral diamine (derived

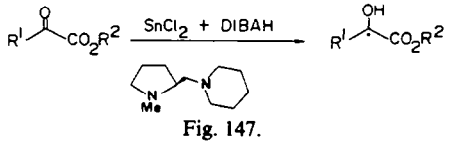
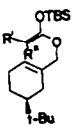
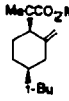
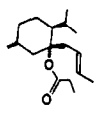
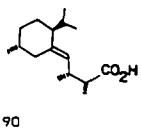
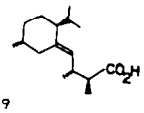
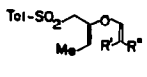
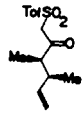
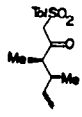
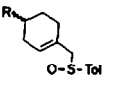
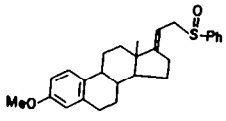
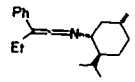
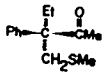
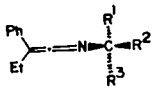
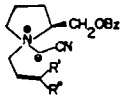
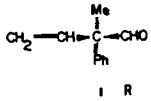


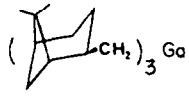
Fig. 147.

Table 23. Rearrangements (optical yield (reference)/chemical yield (configuration))

compound and catalysts used	product 1	product 2	diastereomeric excess	chemical yield	ref.
					
R'=H, R"=Me	71	29	42	67	233
R'=Me, R"=H	87	13	74	62	233
					
	90	9	81	65	234
					
R'=Me, R"=H	96	4	92	97	235
R'=H, R"=Me	4	96	92	89	235
					
R=i-Pr	76	25	51	62	240
R=t-Bu	70	25	45	62	240
					
chirality at sulphur					
(R)	>99	trace	>99	63	242
(S)	74	26	48	88	242
	 R		55.8	36	243
					
R' R² R³	Reactant config.	Product config	optical yield	chemical yield	ref.
Me Et H	S	S	14.1	40	243
i-Pr CH_2OMe H	S	R	15.3	20	243
					
R'=Me, R"=Ph	S	R	90	44	244
R'=Ph, R"=Me	S	S	36	35	244

from (*S*)-proline) with Dibal-H. In these reductions, the authors reported that the efficient coordination of the bidentate chiral diamine to the divalent tin hydride (formed from tin(II) chloride and Dibal-H) plays an important role. The authors stated that the reduction of benzoyl esters gave the corresponding hydroxy esters with optical yields in the range of 68–89% e.e. and with the *S* absolute configuration. Alkyl and vinyl-α-ketoesters gave lower optical yields (40–48% e.e.) with the same absolute configuration (except for ketoesters which possess an α-branched alkyl group).

Giacomelli *et al.*[247] recently reported that the reactivity of tris(*cis*-myrtanyl) gallium **498** (Fig. 148) is similar to that of alkylaluminium reagents. The authors stated that, in the absence of solvents,



498

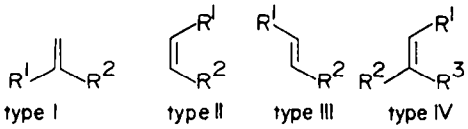
Fig. 148.

the organogallium gave, after hydrolysis, the corresponding carbinols in moderate chemical yield. In all of the cases studied the absolute configuration, of the carbinol, was *R* and the optical purity ranged from 21 to 75% e.e.

Hydroboration

Masamune *et al.*[248] reported that the borolanes **499a** and **b** are superior to the existing hydroborating agents (PC_2BH, Lgf_2BH, LimBH, and $IpcBH_2$) and are able to induce >98% e.e. (Fig. 149) in reactions with all types of representative achiral alkenes except for type I. The use of **499a**

499a (R,R) 499b (S,S)



type I type II type III type IV

Fig. 149.

(*R*,*R*) resulted in the formation of the (*S*)-enantiomer (or (*S*,*S*)-enantiomer), in all the cases studied. The results indicate that all hydroborations (with the exception of type I) proceeded with excellent stereoselection.[248] Brown[248] has indicated that in general monoboranes rather than the diboranes are the reacting species in the hydroboration transition state. With this observation, the authors proposed the following transition-state model for the reactions of olefins with **499a** (Fig. 150).

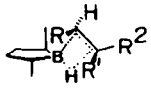
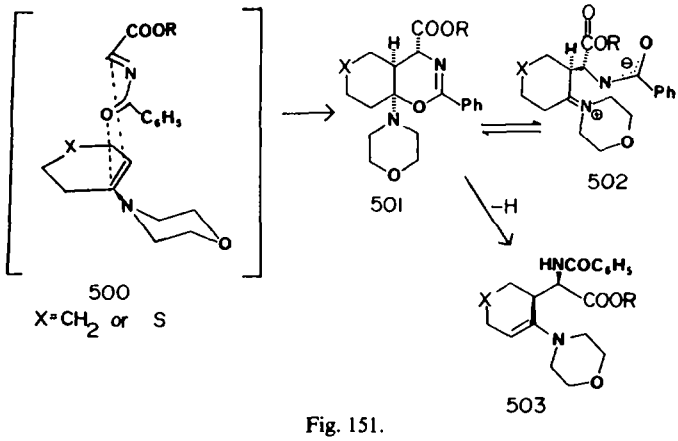


Fig. 150.

Alkylation

Enders and co-workers[249] reported the synthesis of α-amino-γ-oxo acid esters by the reaction of acyliminoacetates with enamines (Fig. 151). The authors found that by employing double stereo-



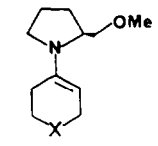
500

X=CH_2 or S

501 502 503

Fig. 151.

differentiation complete asymmetric induction ≥99.9% d.e. or e.e.) for the C—C bond formation. The authors stated that the high stereoselectivity of the reaction by assuming a Diels–Alder-like transition state (Fig. 151). The introduction of a chiral auxiliary ((−)- and (+)-menthyl esters and (−)-8-phenylmenthyl ester) into the ester and the use of an optically active enamine (*S*)-**503a** (X = S or Ch_2, Fig. 152), the reaction proceeded with complete diastereo- and stereoselectivity (≥99.9%

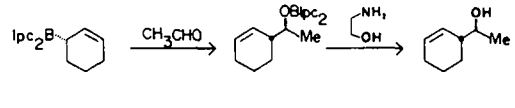


(S)-503a

Fig. 152.

d.e. = e.e.) and in quantitative yield. The use of the (−)-menthyl ester, a mismatched case, exhibited the reverse effect and lead to only 45% e.e.

Brown *et al.* recently reported the synthesis of the diastereomeric 1-(2-cyclohexenyl)-1-alkanols **506** in high optical purity via B-2-cyclohexen-1-yldiisocampheylboranes **504a** and **b**. The two reagents **504a** and **b** (from (+)- and (−)-α-pinene, respectively) react with acetaldehyde to give, after workup, (1*R*,1′*R*)-(+)-1-(2-cyclohexenyl)-1-ethanol **506a** (using **504a**) in 94% e.e. and 100% erythro selectivity (Fig. 153). The other isomer (1*S*,1′*S*)-(−)-1-(2-cyclohexen)-1-ethanol **506b** was obtained from **504b** in similar optical yield.



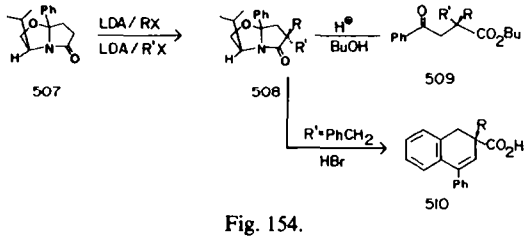
504
a) Ipc from (+)-pinene
b) Ipc from (−)-pinene

505

506a,b
a) R,R
b) S,S

Fig. 153.

Meyers *et al.*[251] reported the novel synthesis of 2,2-dialkyl-4-ketocarboxylic acids **509** and 3,3-dialkyl-3,4-dihydronaphthalenes **510** from the bicyclic lactam **507** (Fig. 154). The authors stated



507

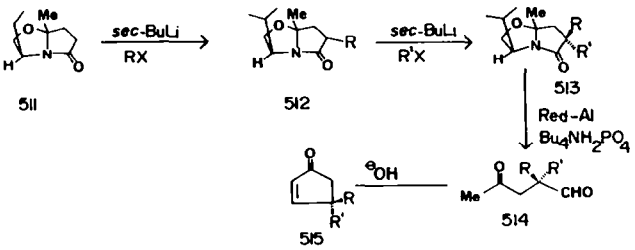
508

509

510

Fig. 154.

that the sequential alkylation, leading to **508**, occurred with R′X adding from the *endo* face. The selectivity ranged from 10–40 : 1 and the hydrolysis gave either the chiral keto ester **509** or the dihydronaphthalenes **510** in >99% e.e. The authors[252] recently reported that if the phenyl group at the ring junction in **508** was replaced by a methyl group, 4,4-dialkyl-2-cyclopentenones **515** may be produced in either *R* or *S* configuration (Fig. 155). The authors stated that were able to obtain



511

512

513

514

515

Fig. 155.

good yields of the 4,4-dialkylcyclopentenones and in high enantiomeric purity (>99%). Either antipode could be produced by the sequence of alkylation.

Colombo and co-workers[253] studied the reaction of (*R*)-(4-methylphenylsulfinyl)-ethyl-N-methoxy acetamide **516** with various aldehydes. The adducts, after desulfurization, were converted into optically active β-hydroxyesters (Fig. 156). The esters were obtained in up to 80% e.e. The

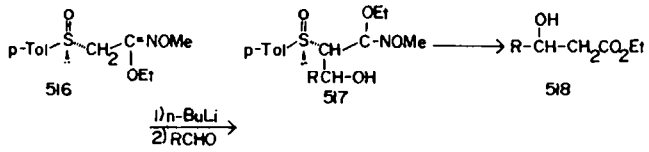


Fig. 156.

authors stated that higher diastereoselectivity was achieved by changing the counterion from Li to Zn. The increased chelation of Zn leads to tighter intermediates; such as **519** and **520** (Fig. 157),

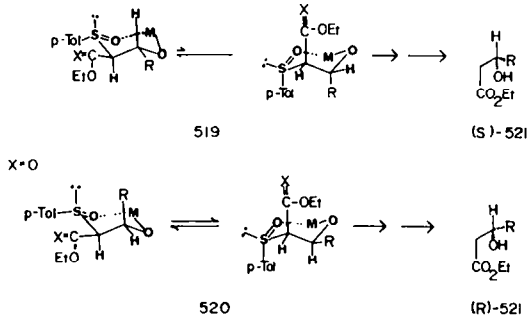


Fig. 157.

which favour **519**. In order to obtain diastereoselection, under kinetic control, the authors found that the zirconium enolate gave the *syn* isomer **520** and consequently the (*R*)-β-hydroxy ester **521** was favoured due to the tighter transition state.

Cozzi and co-workers[254] stated that good to excellent enantio- and diastereoselectivity (40–100%) was obtained in the condensation of chiral racemic aldehydes with chiral α-sulfinyl hydrazones. The selectivity of the attack upon the aldehyde is based upon steric selectivity (Fig. 158).

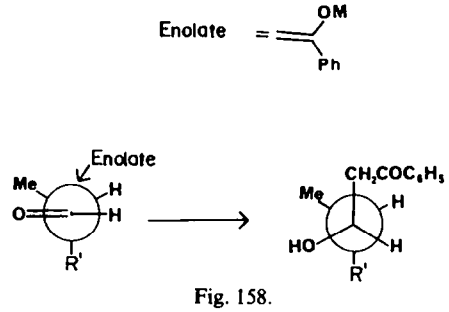
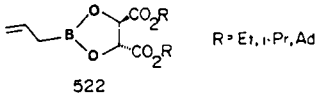


Fig. 158.

Roush and co-workers[255,256] reported that when 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylic esters **522** (tartarate ester modified allylboronates, Fig. 159(a) are reacted with achiral aldehydes they yield homoallylic alcohols in good chemical yield and high enantioselectivity (71–87% e.e.). The authors noted that the solvent played an important role in the stereoselectivity of the reaction.



522

Fig. 159(a).

Methylene chloride favours the formation of the *erythro* alcohols in matched cases whereas toluene favours *threo* alcohols in mismatched reactions. The authors stated that the stereoselectivity cannot be explained by simple steric interaction with the tartrate ester alone. The authors propose that a more likely explanation is that transition state A is favoured because of the n–n electronic repulsive interactions involving the aldehydic oxygen atom and the β-face ester group (Fig. 159(b)).

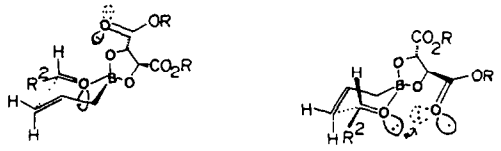
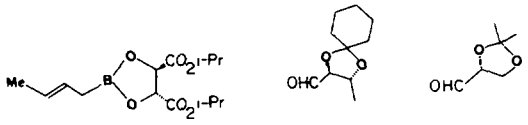


Fig. 159(b).

In similar work, Roush and Haltermann[256] discovered that diisopropyl tartrate modified *E*-crotylboronates (+)- and (−)-**523** (Fig. 160) were highly enantioselective when reacted with alde-



(-)-523 524 525

Fig. 160.

hydes. The reaction of **523** with chiral aldehydes **524** and **525** (Fig. 161) gave three adducts in which (+)-**523** was highly selective for **526** (22 : 1 diastereoselectivity) whereas for the antipodal (−)-**523**, the facial selectivity was reversed and favours **527** over **526** by a factor of 23 : 1[256] when reacted

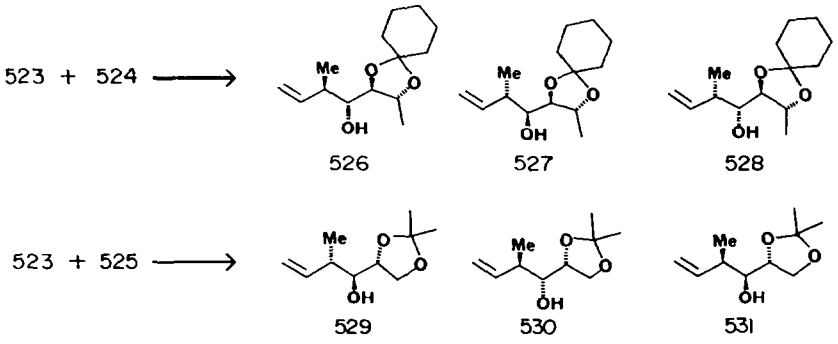


Fig. 161.

with **524**. The authors stated that reagent **523** is highly enantioselective since the stereochemistry at C(3) amnd C(4) of **526, 527, 529**, and **530** is controlled simply by selecting the appropriate enantiomer of **523**. The selectivity in the reactions is consistent with the stereoelectronic model proposed above (Fig. 159(b)).

Diels–Alder

Oppolzer and Dupuis[257] reported that the intramolecular [4+2] cycloaddition of **532a** and **b** afforded adducts **533–536** in which **533** was the major product isolated ($n = 1$, 97%, $n = 2$, 94%; Fig. 162). Adduct **533** was easily purified by either crystallization or flash chromatography to provide

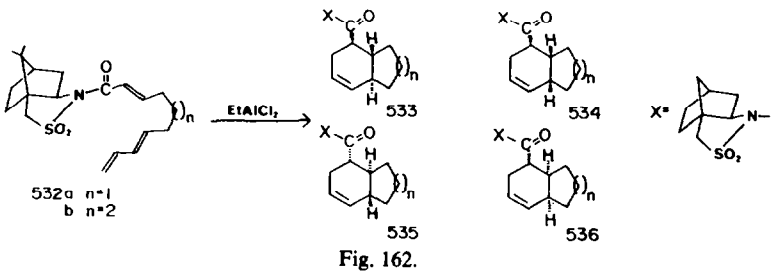
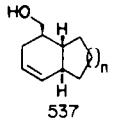


Fig. 162.

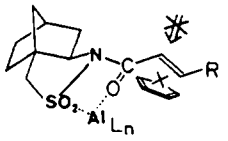
pure **533** (>97% d.e. chemical yields: $n = 1$, 75–8%; $n = 2$, 53%). The authors reported that the treatment of triene-imides **532** with $EtAlCl_2$ at $-20°$ provided, after reduction with $LiAlH_4$, enantiomerically pure bicyclic alcohol **537** (Fig. 163). The chiral auxiliary was also recovered. The



537

Fig. 163.

authors rationalized the rate acceleration and topological control observed to the chelation of the SO_2 and C=O groups by the metal which directs the approach of the diene to the less hindered *re*-face of intermediate **538** proposed in a similar intermolecular reaction (Fig. 164).

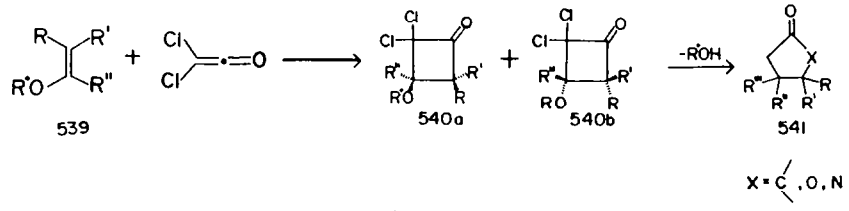


538

Fig. 164.

[2+2]-*Cycloadditions*

Greene and Charbonnier[258] observed significant asymmetric induction in the cycloaddition reaction of dichloroketene with chiral enol ethers **539** (Fig. 165). The authors reported that the



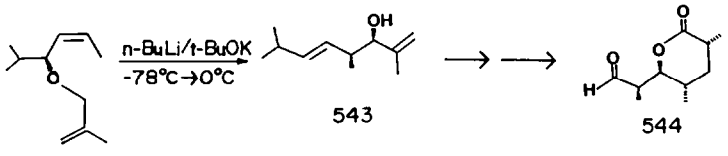
539 540a 540b 541

Fig. 165.

selectivity of **540a** and **b** could be controlled by the choice of the chiral auxiliary attached to the enol ether **539**. The resulting diastereometric cyclobutanones may be easily converted into synthetically useful α-chlorocyclopentenones **541**. The diastereoselectivity was commonly 75:25 (the choice of diastereoisomer depends upon the choice of chiral auxiliary) but in some cases was found to be as high as 90:10.

[2,3]-*Sigmatropic rearrangements*

Midland and co-workers[259] reported the use of a [2,3]-sigmatropic (Wittig) rearrangement as a key step in the synthesis of the (+)-Prelog–Djerrasi lactonic aldehyde **544** which is a key intermediate in the syntheses of the macrolide antibiotics, 6-deoxyerthronolide B and narbomycin. The authors treated (−) - (2*Z*,4*S*) - 5 - methyl - 2 - hexen - 4 - yl - 2 - methyl - 2 - propen - 1 - yl - ether **542** with n-BuLi/t-BuOK to give the alcohol (−) - (3*R*,4*S*,5*E*) - 2,4,7 - trimethyl - 1,5 - octadien - 3 - ol **543** which possesses the correct geometry for two of the four chiral centres necessary (Fig. 166).



542 543 544

Fig. 166.

Dienol **543** could easily be converted by a stereoselective hydroboration and an asymmetric alkylation to give the lactonic aldehyde **544** in essentially 100% epimeric and optical purity. The desired *syn* isomer **543** was obtained in a 97 : 3 ratio which could be easily purified via flash chromatography and possessed an optical purity of 91% e.e.

NOTE ADDED IN PROOF

Brown and co-workers[261] have investigated the hydroboration of heterocycles, which possess an endocyclic double bond, with diisoampheylborane (Ipc_2BH). The authors reported that the hydroboration of 2,3-dihydrofurans and thiophene with (+)- and (−)-Ipc_2BH gave the corresponding 3-hydroxyheterocycle **545** (after treatment with acetylaldehyde and oxidation with alkaline hydrogen peroxide) in 100% e.e. The hydroboration of 2,5-dihydrofuran was accomplished with a similar yield to give the same alcohol but with the opposite chirality (Fig. 167).

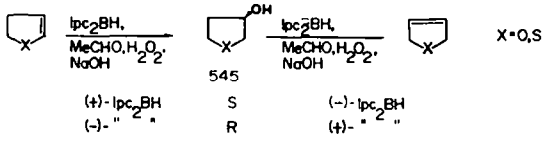


Fig. 167.

The treatment of 3-pyrroline with (−)-Ipc_2BH failed to hydroborate, the only product isolated was an amine-borane complex **546**. However, the N-carbobenzyloxy derivative **547** underwent successful hydroboration to give the corresponding alcohol in 89% e.e. (Fig. 168).

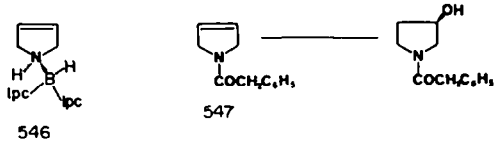


Fig. 168.

The hydroboration of six-membered heterocycles gave the corresponding alcohols in lower optical yields than the five-membered heterocycles (68–81% e.e.).

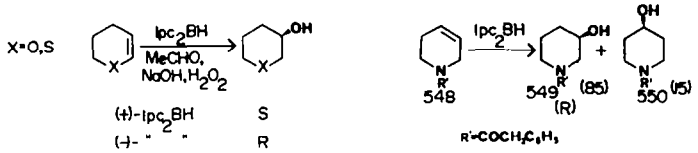


Fig. 169.

The hydroboration of N-(carbobenzyloxy)-1,2,3,6-tetrahydropyridine **548** produced a mixture of N-(carbobenzyloxy)-3-piperidinol **549** (70% e.e.) and N-carbobenzyloxy)-4-piperoidinol **550** in a ratio of 85 : 15 (Fig. 169). Keinan *et al.*[262] reported that the asymmetric reduction of aliphatic acyclic ketones (C_4-C_{10} substrates) was efficiently achieved by the use of the alcohol dehydrogenase from *Thermoanerobium brockii*.

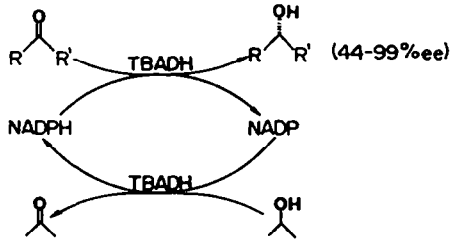


Fig. 170.

The authors noted that the stereoselectivity was dependent upon the size of the alkyl group i.e. for methyl ethyl, methyl isopropyl or methyl cyclopropyl ketones the product obtained was the R alcohol. The higher ketones form the S enantiomers.

ALKYLATION

Michael addition

Koga *et al.*[263] reported that (S)-γ-trityloxymethyl-γ-butyrolactam **551** serves as an efficient chiral auxiliary in the asymmetric conjugate addition to the corresponding imide **552** by reaction of the α,β-unsaturated carboxylic acid. The attack by the nucleophile is from the α-face (Fig. 171).

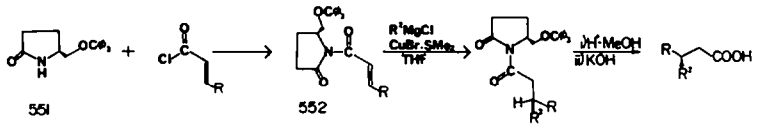


Fig. 171.

The optical purity of the β,β-disubstituted carboxylic acids produced by this method were in the range of 77–97% e.e. Meyers *et al.*[264-5] reported two methods of asymmetric alkylation. The alkylation of the formamidine **554**, obtained from the treatment of octahydroisoquinoline **553** with the isocyanide derived from valinol *tert*-butyl ether **555a** in the presence of cuprous oxide or the dimethyl formamidine **55b** by heating, with a benzyl chloride gave the 1-benzyl derivative **556** in > 98% e.e. (Fig. 172).

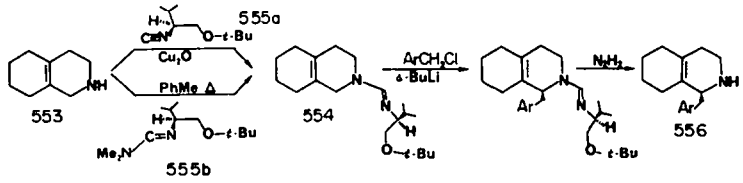


Fig. 172.

The asymmetric additions to chiral naphthalenes was reported by Meyers *et al.*[266] The authors reported that organolithium addition to (1-naphthalyl) oxazolines followed by proton quench gives 84–97% diastereofacial selectivity and in high optical purity. The authors reported that addition of organolithium to (+)-**557** in THF followed by quenching with TFA to give the adduct **558** (Fig. 173).

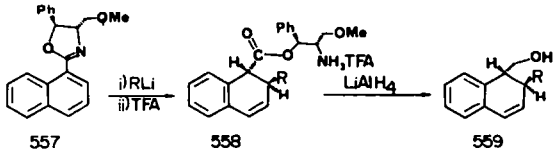


Fig. 173.

The reduction of **558** by $LiAlH_4$ gave the single diastereomer **559** in yields of 42–85%. Chiral boronic esters[267] and boranes[268] have been shown to alkylate aldehydes in high optical yields.

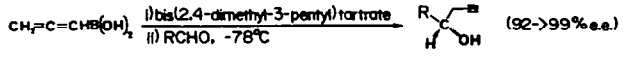
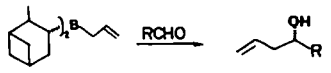


Fig. 174.

Yamamoto *et al.*[267] reported the asymmetric addition of allylic nucleophiles to carbonyl compounds to give the corresponding homopropargylic alcohols. The authors found that the condensation with aromatic aldehydes is not as efficient as the reaction with saturated aldehydes (92–99% e.e.) and the yields with unsaturated aldehydes (< 50%) allows this method to complement

existing methods (Fig. 174). Brown *et al.*[268] reported that the condensation of allyl diisopinocampheylborane with aldehydes proceeds with high enantioselectivity. The authors noted that the enantioselectivity does not vary appreciably with the structure of the aldehyde and the absolute stereochemistry was the same in all cases studied.



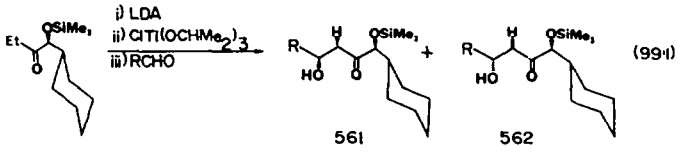
560

Fig. 175.

Also the authors reported that allyl diisocaranylborane **560** achieved < 99% asymmetric induction in the condensation of aldehydes. In most cases, the optical purity obtained by the use of allyl diisocaranylborane, however only the (+)-form is readily available.

ALDOL

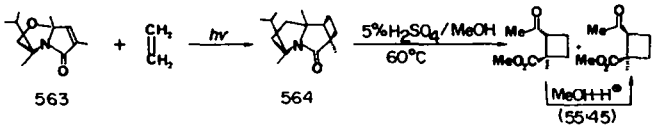
Thornton *et al.*[269] reported the first example of diastereofacial selectivity using a chiral titanium enolates, in the aldol reaction.



561 562

Fig. 176.

The authors reported that in all cases studied none of the corresponding *anti* isomer was observed and the ratio of the *syn* isomers **561** : **562** (99 : 1) and indicates the high diastereoselectivity of the titanium intermediate (Fig. 176). Meyers and Fleming[270] reported an efficient asymmetric [2+2] photocycloaddition using a "chiral enone". The authors reported that when the chiral enone **563** was subjected to photocycloaddition, in the presence of ethylene, the major product obtained was the *exo*-cyclobutane fused product **564** (Fig. 177).



563 564

Fig. 177.

This method allows the production of a "chiral enone" where the auxiliary directing the cycloaddition may be easily removed to leave the chiral cyclobutane following the addition.

CONCLUSION

As can be seen from the preceding pages, the area of asymmetric synthesis is continuing to grow at an explosive rate. There exists much which remains to be discovered in the area of asymmetric induction.

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