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RECENT ADVANCES IN ASYMMETRIC SYNTHESIS

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INTRODUCTION

The total synthesis of structurally and sterically complex molecules is an important and challenging area of endeavour. Most syntheses reported in the literature to date have entailed reactions carried out stereoselectively in the racemic series with an optical reolution performed at the end of the sequence. Preparatively, this is a wasteful procedure since if only one optical antipode is of use or interest, half of the synthetic product is often discarded. The other antipode may as suggested,[18] be gainfully used to perfect reaction conditions without waste of valuable material. It is economically and esthetically appealing however to exclude unwanted optical isomers at the earliest possible stage through asymmetric creation of chiral centres.

Morrison and Mosher[1] in the most comprehensive treatment of the subject to date define asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts. This is to say an asymmetric synthesis is a process which converts a prochiral† unit into a chiral unit so that unequal amounts of stereoisomeric products result". (For a review of prochirality see ref. 2). The reactant mentioned can be a chemical reagent, solvent, catalyst or a physical force such as circularily polarised light.

The concept of asymmetric synthesis has been known for over eighty years. In 1894 Emil Fischer proposed that chlorophyll acting as an asymmetric catalyst was responsible for the production of optically active sugars from carbon dioxide and water in plants.[4] In the early part of the twentieth century asymmetric induction was thought of as some mysterious unsymmetrical force acting on molecules. It was not until the late forties when the first asymmetric Meerwein–Pondorf–Verley and Grignard[6] reactions were reported that asymmetric induction was rationalised in terms of steric interactions in the transition state.

Prelog[7] examined such interactions among various conformations available to reactants and similar work by Cram and Elhafez[8] established steric control as a major factor in asymmetric induction.

A wide variety of reactions can exhibit asymmetry, but only a few match the selectivity provided by enzymes. Non-racemic chiral products have been obtained from Grignard and Meerwein–Pondorf–Verley reactions, hydride reductions, additions to carbonyls and olefins, cyclisation reactions, α alkylation of carbonyls, amino-acid syntheses, Diels–Alder cycloadditions, hetero and homogeneous hydrogenations as well as elimination reactions and rearrangements to name a few.

Many reviews have been published on asymmetric synthesis in general,[9–12] covering the literature to 1974. It is the intent of this report to extend literature coverage to mid 1978 highlighting recent advances. (The reader is referred to ref. 13 for a recent monograph on asymmetric synthesis.) For convenience and clarity the material is arranged according to reaction type excepting the synthesis of amino acids and related topics which will be considered separately.

The extent of asymmetric synthesis is easily determined in the case of diastereomeric products which are, in most cases easily separated and the ratio determined. Polarimetry is the method most commonly used to determine enantiomeric ratios.

Optical purity is determined by dividing the rotation of the product mixture by that of the pure enantiomer determined under identical conditions of temperature, concentration and wavelength. Assuming a linear plot of rotation *vs* composition;

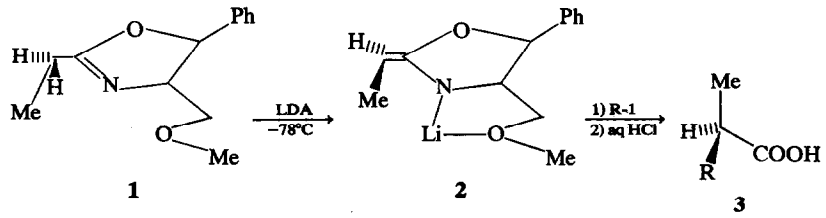
$$\%\ OPTICAL\ PURITY = \frac{[\alpha]OBS}{[\alpha]MAX} \times 100$$

percent optical purity is identical to the percent enantiomeric excess, and a direct measure of asymmetric induction.

It must be noted that the above assumption is not always valid as in the case of α-methyl-α-ethylsuccinic acid where the plot deviated appreciably from linearity;[14] thus other methods such as NMR with chiral shift reagents[15] must be used to substantiate polarimetric data in some cases.

Most asymmetry is created upon conversion of trigonal carbons to tetragonal ones at the site of functionality such as carbonyl, enamine, enol, imine

† A prochiral molecule is most easily envisaged as an achiral one of structure $CABL_2$ having a mirror plane where substitution or modification of one of the ligands L leads to a compound chiral at C. (i.e. the compound has enantiotopic or diastereotopic groups on faces[3]).



1 2 3

Scheme 1

and olefin.[11] This asymmetry at carbon is the major area of interest to the synthetic organic chemist as well as induction by, and creation of asymmetry at sulphur.

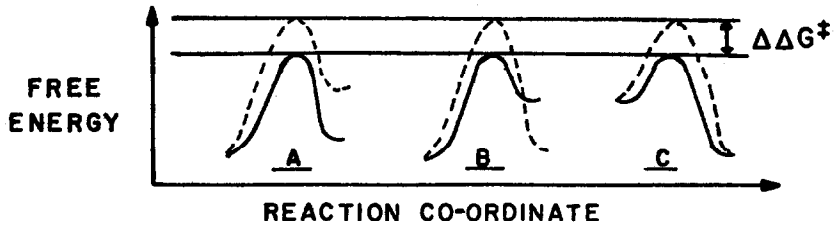
In an asymmetric reaction substrate and reagent combine to form diastereomeric transition states. One of the two reactants must have a chiral centre, which can be carbon or configurationally stable tetraco-ordinate silicon, arsenic, antimony, arsenic, sulphur or phosphorus ("onium" salts in many cases); or tri-coordinate antimony, arsenic, sulphur or phosphorus where the electron pair is formally regarded as the fourth substituent. In each case the chiral centre induces asymmetry at the reaction site.

The diastereomeric transition states so formed may be solvates[16] or other electrostatic complexes in addition to bonded compounds. The difference in free energy between them ($\Delta\Delta G^{\neq}$) determines the excess of one antipode over the other, hence it is desirable to maximise $\Delta\Delta G^{\neq}$. This is accomplished by introducing steric hindrance in the undesirable diastereomer or enhancing the lower energy pathway by some favorable interaction. The "glove-hand fit" analogy of Mislow is appropriate here, where the excellence of fit of reagent and substrate is reflected ultimately in transition state energy, but is manipulated or predicted by consideration of the steric/torsional factors described later.

The methods for the most part, are empirical however, and must be used with caution as the enthalpy ($\Delta\Delta H^{\neq}$) and entropy ($\Delta\Delta S^{\neq}$) terms of the $\Delta\Delta G^{\neq}$ function can change drastically with small changes in reaction parameters.

These concepts are practically exemplified in the use of lithiooxazolines in asymmetric synthesis.[17] Thus, treatment of the chiral oxazoline (**1**) with lithium di-isopropylamide results in the selective removal of one of the enantiotopic methylene protons. Due to hindrance of the β face by the ph. substituent and chelation of R—X to Li on the α face, the lithio salt (**2**) is preferentially alkylated via bottomside attack to give a 60–67% enantiomeric excess (e.e.) of the (*S*)α-methyl carboxylic acid (**3**) with a new chiral centre.

In kinetically controlled reactions the free energies of the reactants for competing pathways are identical ($\Delta\hat{G} = 0$) since the substrate is either achiral or a racemate reacting with a chiral reagent. A diagram representing an idealised energy profile for such reactions is shown below



showing differing energies of diastereomeric pathways leading to products. Note that the most stable product need not result from the lowest energy pathway. (For a complete discussion see ref. 25 p. 123).

Of these kinetic processes there are *kinetic resolutions*, where one enantiomer reacts preferentially with the reagent (usually an enzyme), *absolute decompositions* where one enantiomer is preferentially destroyed by a chiral physical force (circularily polarised light) and finally *asymmetric synthesis*, generally referring to an achiral but prochiral centre in a chiral or achiral substrate reacting with a chiral reagent. In all three cases $\Delta G^{0} = 0$ and $\Delta\Delta G^{\neq} \neq 0$.

The attribution of stereoselectivity to free energy differences in the competing transition states only, is a result of the Curtin-Hammett[19] principle. This rationalisation has been a subject of much controversy. Dauben *et al.*[20] found that additions to cyclic hindered ketones were subject to steric approach control, whereas unhindered cyclic ketones yield the thermodynamically favoured isomer due to product development control. Marshall[21] has proposed that for carbonyl additions, depending on the size of the nucleophile the C—Nu bond distance in the transition state may vary in length, with hindrance arising from different groupings in the substrate molecule leading to varied stereoselectivity. Torsional interactions between the developing C—Nu bond and β-hydrogens during equatorial attack have been implicated[22] and depending on the nature of the transition state, rate factors can have a varied effect.

Even though a sound knowledge of transition state geometry may be lacking an approximate analysis is possible by considering maximal orbital overlap of reacting orbitals and minimising

torsional strain from steric or polar interactions.[23,26]

It is evident that in the asymmetric creation of a chiral centre several factors must be considered *viz* initial conformation, ease of approach of reagents, energy of reaction products and their stability. Ignoring the last two factors Wipke and Gund[24] devised and evaluated a computer simulated approximation of steric congestion which they define as the steric environment of the isolated substrate in its ground state, independent of reaction partner and transition state structure. A correction for torsional strain effects[22] greatly improved the correlation to observed results.

In cases with higher steric demand (i.e. crowded substrate, large nucleophile) excellent steric congestion/stereoselectivity correlations were obtained. The torsion corrected congestion gave better results in cases of low steric demand. Such approximations offer a semiquantitative guide to the prediction of reaction stereoselectivity.

In the interest of yields it is wise to choose an early step in the synthetic sequence for asymmetric operations and to consider carefully the principles of convergent synthesis.[27] The asymmetric step should be, if possible, a reaction of known mechanism with an ordered transition state devoid of accessible symmetry elements and which is already known to proceed in a stereoselective manner.[9]

It is important to use chiral reagents efficiently for both esthetic and economic reasons. This would seem to require that the chiral reagent be recoverable or at least conserved. The most efficient use of a chiral reagent is in a catalytic sense. This has been a most successful and intense area of research in recent years, encompassing homogeneous hydrogenation, hydrosilylation and hydroformylation of olefins, enzyme catalysis of cyclisations and phase transfer catalysis.

CATALYTIC PROCESSES

Homogeneous asymmetric hydrogenation using well defined transition metal complexes has been accomplished with optical yields of 85–90% or more. The most successful catalysts are Rh(I) complexes with ligands chiral at phosphorus (Horner phosphanes),[28] phosphoranes chiral at carbon, optically active amides or ferrocenes as ligands.

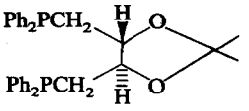
Early results with Rh(I) complexes with chiral ligands were mixed, in that optical yields were low and small changes in substrate structure resulted in large changes in optical yields and in some cases a reversal of enantioselectivity.

In many cases unidentate ligands were used and the conformational lability of these when complexed to rhodium results in rather low chiral preference generally. More recently bi and tri-dentate

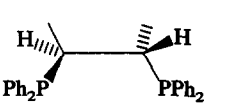
Table A. Optically active ligands for asymmetric homogeneous hydrogenation

Ligands chiral at carbon

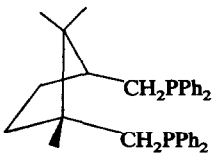
DIOP



CHIRAPHOS

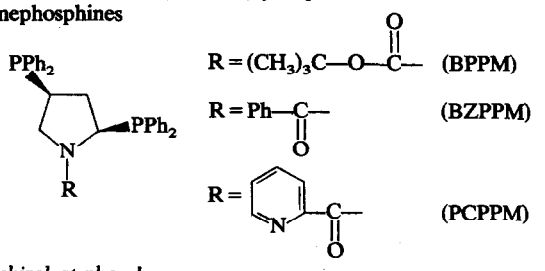


CAMPOS



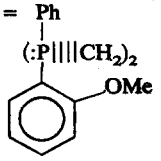
MDPP[a] = (−)-menthyldiphenylphosphine
NMDPP[a] = (+)-neomenthyldiphenylphosphine

Pyrollidinephosphines



Ligands chiral at phosphorus

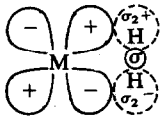
BMPP = benzylmethylphenylphosphine
ACMP = 0-anisylcyclohexyl methylphosphine
DIPAMP =



[a] for synthesis and properties see ref. 40.

phosphite and bisphosphine ligands have been developed which are much more rigid in the complex lending enhanced enantioselectivity. Other group VIII metals studied include Fe, Ru, Ni, Pd, Pt, Co, Os and Ir. A variety of structural species have been used such as $Rh(PR_3)_3X$, (X = halogen), RhL_3Cl_3 (L = optically active phosphane), Rh(L)ClS (S = optically active solvent). Several good reviews have been published on asymmetric homogeneous hydrogenation.[29-31,39,40]

The catalyst serves to activate molecular hydrogen which, having a dissociation energy of 104 Kcal/mol is rather inert. This process occurs via donor acceptor bonds where low-lying vacant d orbitals in the metal can accept electrons to form MH_2^+ species,[32] or a transfer of an electron from metal to an antibonding orbital of hydrogen (dative bonding) may occur[33] (i.e. MH_2^-). This latter process is facilitated by electron donating ligands and a low oxidation state of the metal.



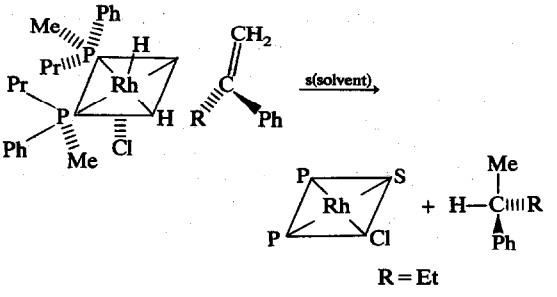
Activation of the substrate has been studied in detail[32] for hydrogenation of alkenes and alkynes. The olefin is inserted between the metal and hydrogen in a concerted four centre reaction. The catalyst is then restored by hydrogenolysis or homolysis. The stability of M—H and M-olefin bonds and the effects of other ligands on these are all important factors.

In the transition state, metal and olefin can form a double bond, σ density passing from alkene to metal while π density passes from metal to a π^* orbital of the alkene. Both factors destabilise and activate the olefin[30] which foreshadows hydrogen transfer.

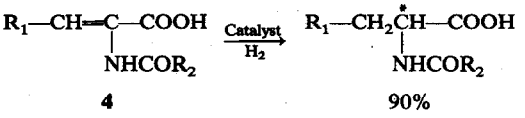
Various proposals as to the effect of metal ligands on catalytic activity and stereochemistry have been made encompassing basicity (σ donor ability),[33] the inductive effect,[35] the resonance effect,[36] the trans effect[32] and electron density on metal.[34] Nevertheless, development is yet at an early stage and success lies largely in trial and error.

Horner *et al.*,[37] in one of the first known asymmetric homogeneous hydrogenations obtained 8% e.e. ((S)-(+)-2-phenylbutane from α-ethylstyrene) using a complex derived *in situ* from Rh(1,5 cyclohexadiene)Cl_2 and (S)-(+)-methylphenyl-n-propylphosphine. The ground state model constructed to explain the effect is shown in Fig. 2. A Japanese group[42] has since performed the same hydrogenation with 77% e.e. using phosphinite ligands derived from cellulose.

In 1972 Knowles *et al.*, reported an efficient route to chiral amino acids by catalytic asymmetric reduction of α-acylamino acrylic acids (**4**) using a Rh[1,5 cyclohexadiene) (Cl)L] catalyst (L = O-anisyl methylphenyl phosphine of 95% optical purity). The catalyst achieves almost complete stereospecificity.

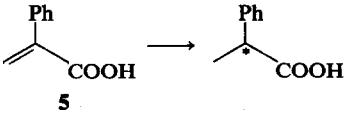


Scheme 2



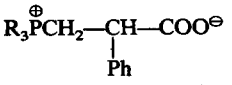
Scheme 3

The same group, in attempting to hydrogenate atropic acid (**5**)[41] noticed that % of α-phenyl propionic acid increase as the ligand/metal ratio was increased to a value of 8:1. They had presumed



Scheme 4

that the excess ligand would compete with olefin substrate for coordination at metal. Evidence suggested phospho-betaine formation (**6**), which

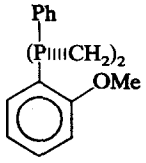


converts the acid to carboxylate; an excellent moiety for rapid complexation to metal, leaving the olefin in excellent position for hydrogen transfer. Accordingly, acrylic and other olefinic acids are preferred substrates for catalytic hydrogenation. α-acetamidoacrylic, cinnamic and *p*-hydroxycinnamic acids (amino acid precursors) have been hydrogenated with 79, 69 and 48.5% e.e. respectively using a chiral diphosphinite [(+)-*trans*-1,2-bis diphenylphosphinoxy) cyclohexane] (i.e. (+)-BDCPH) rhodium complex derived[43] from [Rh(1,5-cyclohexadiene) Cl]$_2$. Since evidence indicates[44] that steric factors as opposed to O atom effects play a major role in DIOP ligand activity, it is presumed that the high steric demand of the cyclohexane ring is responsible for the high optical yields using (+)-BDPCH ligands.

Using $[Rh(nbd)(DIOP)]^+ClO^-$ prepared from [Rh(nbd)(acac)]... (nbd = norborna-2,5-diene), (Z)-α-acetamidocinnamic acid has been hydrogenated with 78–85% optical[45] yields. The asymmetry here is solvent dependent, suggesting that solvent is present in the transition state coordination sphere of rhodium. A similar catalyst

$[Rh(COD)(DIOP)]^+ClO_4^-$ COD = cyclo-octa 1,5 diene) achieves almost identical results on these substrates.[46]

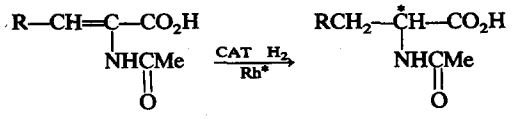
Using Rh(I) complexes with bidentate DIPAMP ligands 7 catalytic hydrogenation of α-acylamidoacrylic acids proceeds with 96% enantioselectivity[47] DIPAMP forms a rigid 5-membered



DIPAMP

7

ring with the metal preventing any rotation about the *p*-Rh bond. H-bonding between anisole methoxyl and amide substrate is also highly likely.



8

Scheme 5

The substrate is also tridentate with the olefin and two electronegative polar functions. Not surprisingly, bidentate substrates gave inferior results especially when amide functionality was absent (50% e.e. for (*Z*) isomer).

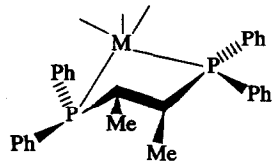
The (*Z*) isomers of **8** (R *cis* to amide function) are hydrogenated 15–100 times faster and with greater optical yields regardless of the catalyst system, however the same product is obtained in both cases. Incomplete isomerisation of *E* to *Z* in the transition state may explain this.[48]

A separate study[49] has revealed that with acid esters optical yields increase with increasing steric bulk of the ester moiety up to t-butyl. Adamantyl esters however, are reduced with lower optical yields and appreciable (*E*/*Z*) isomerism.

Conversely, increasing the steric bulk of the amide alkyl substituent lowers optical yields drastically (Me 69% e.e., i-pr−15%, t-Bu−0%) suggesting that amide is the primary site for catalyst binding in these substrates.

Rhodium complexes with bidentate CHIRAPHOS ligands hydrogenate a variety of substituted α-acylamino acrylic and cinnamic acids with excellent chiral preference.[50]

The preferred conformation of the chelate ring with diequatorial methyls is shown in **9**. The active species is probably the [Rh(S,S-CHIRAPHOS)(H_2)(solvent)$_2$]$^+$ ionic species.



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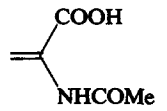
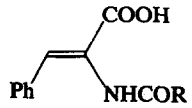
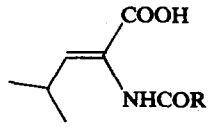
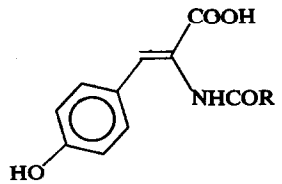
One face of the olefin is preferentially coordinated due to interaction of the carboxyl and amide groups with the phenyl groups of the rigid puckered chelate ring. Optical yields are given in Table B.

Note that entries 2 and 4 in Table B have increased optical yields with more bulky amide

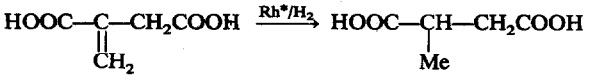
Table B. Optical yields in catalytic hydrogenations using Rh(I) chiraphos complexes

Substrate		% Optical yield (R-isomer) THF	ETOH
(1)		88	91
(2)		R = CH_3 (74) R = Ph (83)	89
(3)		R = CH_3 (100) R = Ph (87)	93 72
(4)		R = CH_3 (80) R = Ph (92)	88

substituent in contrast to ref. 49 which used a Rh DIOP complex.

A recent study by Brown *et al.*,[51] using P^{31} NMR reports that DIPAMP complexes bind *E* isomers well without isomerisation whereas DIOP complexes bind *E* isomers weakly with rapid isomerisation in many cases. This may explain the discrepancy.

Recently Rh(I) complexes of the pyrrolidinephosphine ligands outlined at the beginning of this section have been used to catalyse hydrogenation of itaconic acid (**10**) in up to 83% enan-



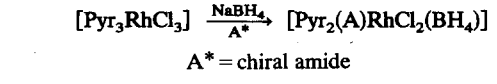
10

Scheme 6

tiomeric excess[52] (obtained with BZPPM). Best results are obtained in methanol solvent where one would suspect the N atoms of the ligand to be heavily solvated leading to reduced interaction with substrate carboxyl and reduced asymmetric induction. Optical yields are severely reduced using 2:1 benzene/methanol as solvent where there is undoubtedly more N—CO_2H interaction. The reason for this is unclear.

It is certain though that for most substrates, especially polydentate ones it is stereoselectivity in the binding step rather than relative rates of hydrogenation or diastereomeric complex formation that affords chiral preference.

Amide complexes of rhodium have been used as highly asymmetric hydrogenation catalysts.[53] Complex formation is shown in Scheme 7. The amides



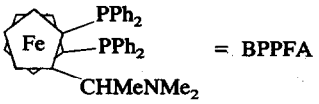
A* = chiral amide

Scheme 7

are definitely involved since, even when used in a catalytic sense, their configuration affects reaction asymmetry profoundly.

Russian workers[54] have hydrogenated α-acetamidocinnamic acid in 74% e.e. using a Py_3RhCl_3—$NaBH_4$—(S)φCHNH—CHO catalyst of this type. |
CH3

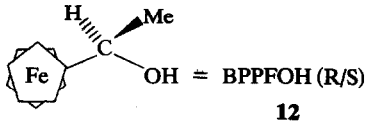
Rhodium complexes with the chiral ferrocenyl phosphine ligand BPPFA(S)—(R) prepared from a 1:2.4 ratio of [Rh(1,5 hexadiene)Cl]$_2$ and BPPFA, have been used to catalyse hydrogenation of the α-acetamidoacrylic acid series with 86–94% e.e.[55] The catalyst gives better chemical yields in aqueous solution though stereoselectivity was not solvent dependent. Ammonium-carboxylate interactions



= BPPFA

between the BPPFA amine and the substrate carboxy group are suppressed by the addition of triethylamine which severely reduces optical yields (23%).

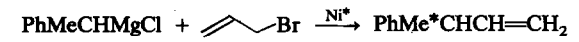
Using a cationic rhodium complex [Rh(COD)(R)—(S)BPPFOH]$^+ClO_4^-$ the same authors have achieved the highest known % e.e. for



12

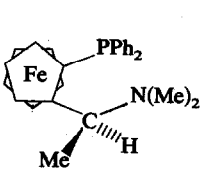
asymmetric hydrogenation of carbonyls.[59] A series of ketones and α-keto-acids were reduced in up to 83% e.e. Interestingly enough the addition of triethylamine increased optical yields by 15% in the case of pyruvic acid. The high asymmetry obtained with BPPFOH was ascribed to the H-bonding possible between the substrate CO and the ligand OH; increasing conformational rigidity in the transition state leading to hydrogen transfer.

Amino alkyl ferrocenyl phosphine ligands of this type have been used in the nickel complex catalysed asymmetric Grignard cross-coupling reaction[60]

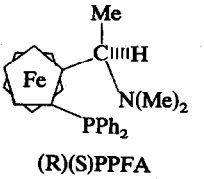


Scheme 8

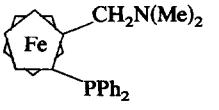
with considerable success. The catalyst was inoperative without the amino substituent which is likely to co-ordinate to the Mg atom. The (S)-FCPN ligand (**15**) has only ferrocene planar chirality yet is still highly active, indicating C-chirality is not a major factor in these ligands.



(S)(R)PPFA
(R products)
13

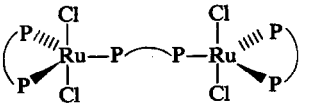


(R)(S)PPFA
(S Products)
14



(S)FCPN
(S Products)
15

James[56] *et al.*, have studied the ruthenium(II) analogues $[Ru_2X_4(+)DIOP]_3$(X = Cl, Br) where DIOP is the bridging bidentate phosphine ligand. It was found that the mononuclear compound was inactive whereas the binuclear bridged compound (**16**) hydrogenated α-acetamidoacrylic acid to N-acetyl (*S*)-alanine in 60% e.e. Use of (−)-DIOP



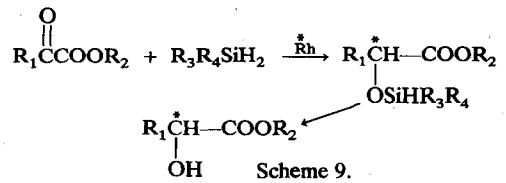
P—P = (+)DIOP

16

gave the (*R*)-enantiomer. The optical activity is similar to that using $[HRh(DIOP)_2]_2$.[57]

Due to difficulties in separating chiral products from the catalysts, polymer supports have been developed. These render the catalyst insoluble yet its reactivity is not inhibited. Using a polymer supported [RhDIOP(S)Cl](S = solvent) complex, amino acids have been synthesised from acetamidoacrylic acids in 100% chemical yield and 50–80% e.e. The configurations of products are the same as those obtained from homogeneous hydrogenations and the swelled gelatinous polymer/catalyst is easily filtered from alcoholic solvents.

Homogeneous rhodium(I) chiral tertiary phosphine catalysts have been used to hydrosilylate olefins, ketones and imines which, upon hydrolysis, accomplishes indirect hydrogenation. Optical yields are, in general, very low but good results have been obtained in some cases. A typical scheme for hydrosilylation and hydrolysis of α-keto-esters is outlined below:



Scheme 9.

Propyl pyruvate and ethyl phenyl glyoxylate have been hydrosilylated[61] using a catalyst prepared from [Rh(1,5-cyclooctadiene)Cl]$_2$ and DIOP or BMPP (benzyl methyl phenyl phosphine) ligands. The former gave 81.5% e.e. when hydrosilylated with α-napthylphenylsilane in the presence of DIOP catalyst, one of the highest known optical yields for this reaction. Unfortunately the glyoxylate was troublesome affording 10% e.e. at best for reasons unknown.

Hydrosilylation of ethyl phenyl ketone with α-napthylphenylsilane using a $[(Bu)_2RhCl]_2$/(+) DIOP catalyst followed by addition of a grignard reagent to hydrolyse the alkoxysilane yields 56% e.e. of the (*S*)-alcohol.[62] Cationic rhodium complexes are excellent catalysts for activating carbonyls towards hydrosilylation.[63] Optical yields of 31, 43, 56 and 62% are obtained in the hydrosilylation of acetophenone, propiophenone, isobutyrophenone and pivalophenone in the presence of $[Rh((R)—PhCH_2, Me, Ph^*P)_2H_2S_2]^+ClO_4^-$ (S = solvent). These results are better than those reported with Pt(II)/chiral phosphine catalysts[64] and comparable to those using stoichiometric amounts of chiral Grignard or chiral metal hydride complexes.[65] Most remarkable is the fact that trimethylsilane addition gave the (*R*)-alcohol from pivalophenone whereas phenyl dimethyl silane gave the (*S*)-antipode. The authors have suggested that the following sequence gives rise to the marked effect of silane structure:

Since step (I) results in an insertion of the activated carbonyl into the silicon-rhodium bond to form diastereomeric α-silyloxy rhodium intermediates **17** (the asymmetry inducing step) it is reasonable to assume that the steric demands of silicon play a key role. In ketone substrated bearing no phenyl groups the reaction leads to racemic products.

The same cationic complex has been used to catalyse 1,4 addition of hydrosilanes to $\alpha\beta$-enones which, upon hydrolysis, yields (*R*)-chiral ketones in ≃85% chemical yields and up to 15% e.e. The use of (−)-DIOP rather than the (*R*)-benzylmethylphenylphosphine ligand lowers optical yields in most cases.

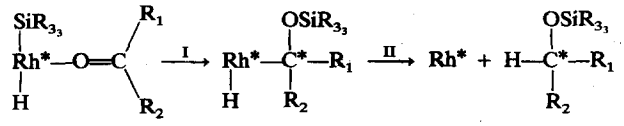
The key step in the hydrosilylation of olefins is the formation of the alkyl metal intermediate (**18**) from the insertion of the co-ordinated olefin into a hydrido moiety. The silyl group which is bound to the metal throughout this process has a much less pronounced effect on reaction asymmetry in this case.[63]

The olefins (**19**) have been hydrosilylated in the presence of a Pt catalyst $(L^*PtCl_2)_2$ ($L^* = (R)$-benzylmethylphenylphosphine BMPP or (*R*)-methylphenyl-n-propylphosphine (MPPP) in optical yields ranging from 0.5 to 6%. The silanes exert only electronic and not steric effects with trichlorosilane so activating as to cause olefin dimersisation whereas trialkyl silanes fail to add to the olefin.

Using the nickel complex $Ni(BMPP)_2Cl_2$ and $HSiMeCl_2$ higher optical yields are obtained[67] (21% R = Ph, 6.2% R = i-pr 2.5% R = Et). Rhodium complexes $[Rh(R)—PhCH_2, MePhP^*)_2H_2S_2]^+ClO_4^-$ and [(−)-DIOP)-Rh(S)Cl] give similar results.

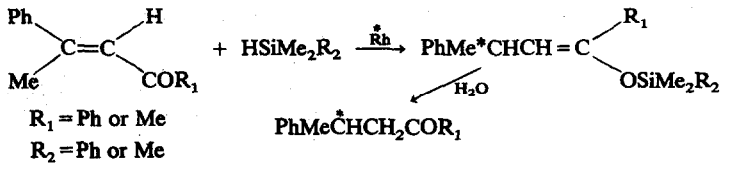
It may be seen then that many factors influence the outcome of a catalytic asymmetric hydrogenations and hydrosilylation *viz* ligands used, ligand to metal ratio, solvent, temperature, added base and hydrogen pressure to name a few. This suggests a rather complex set of equilibria which must be manipulated to optimise enantio-selectivity. Selection and synthesis of the proper ligand (catalyst tailoring) for the reaction substrate is of prime importance. Hopefully a sound knowledge of the transition states involved will aid in this approach.

Trost and Strege have applied the concept of asymmetric catalysis to the formation of C–C bonds, hitherto a much less successful area of study. They report optical yields in the range 35–45% in a catalytic alkylation[68] of *cis*-3-acetoxy-5-carbomethoxycyclohexane. Treatment of racemic **20** with 0.75 mol % of tetrakis Ph_3P and 10 mol % DIOP in DME with the sodium salt of methylphenylsulphonyl acetate gave alkylated product (**21**) which was desulphonylated and its enantiomeric purity determined with a chiral europium shift reagent. The CAMPHOS reagent ligand gave lower yields in this case but doubled optical yields

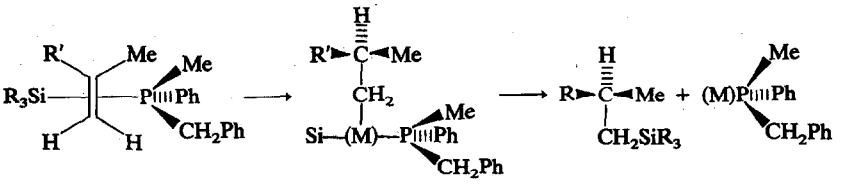


17

Scheme 10

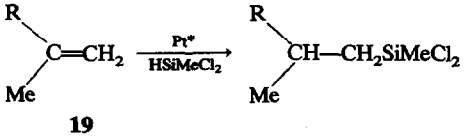


Scheme 11



18

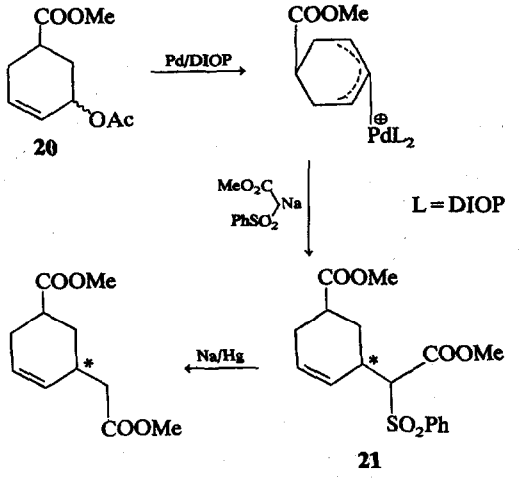
Scheme 12



19

R = Ph, i-pr, Et

Scheme 13



20

21

Scheme 14

when the malonate anion was used to alkylate. These are among the highest optical yields seen for catalytic alkylation at normal temperatures.

Very recently a Dutch group reported optical yields of up to 50% in the Michael addition of mercaptans to 2-cyclo-hexene-1-one systems catalysed by (−) quinine. A later communication[70] reports that optical yields are inversely proportional to solvent dielectric constant. It is supposed that a solvent of high ε reduces the magnitude of molecular interactions leading to reduced asymmetric induction. Formation of a chiral enamine or hemiketal with the quinine would lead to diastereomeric alkylation products in unequal amounts. Ketalisation of **22** with (*R*)-(−)-butane-2,3-diol allowed calculation of the enantiomeric excess using ^{13}C spectroscopy. ^{13}C signal intensities are not usually proportional to the number of nucleii present, however in the case of diastereomers, when corresponding carbons are compared the differences in relaxation time and nuclear Overhauser effects (NOe) leading to non-correspondence are negligible.[71]

Hydrogenation

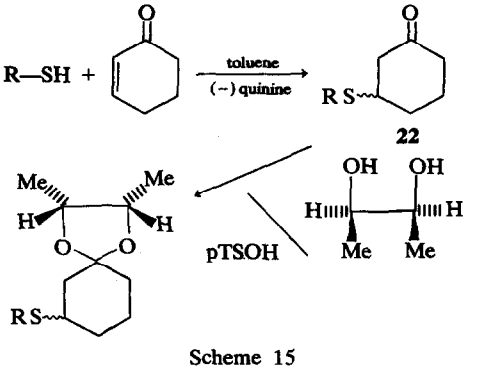
Asymmetric hydrogenation using heterogeneous catalysts modified with optically active substances has been well studied. Optical yields are, in general, very low. This is not unexpected since the active sites of the catalyst are not of uniform structure; a prime prerequisite for high stereoselectivity.

Optical yields of 35–36% have been achieved on oxime and oxazoline substrates using silkfibroin/palladium or[72] Rani nickel modified with amino-acids[73] but 10% or less is a typical figure.

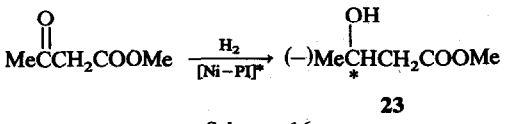
α-acetamidoacrylic acid has been hydrogenated using a Pd catalyst on a silica gel support which had been precipitated in the presence of optically active alkaloids and also on several polyaminoacid supports. A maximum of 6% e.e. was achieved.

It has been shown[76] that the catalyst modifying reagent should be optically active and that the centre of chirality should bear a carboxyl group, a proton and an amine or hydroxyl group. Consequently α-amino and α-hydroxy acids are preferred modifiers.

Recently methyl acetoacetate has been hydrogenated[77] using Ni—Pt metal Kieselguhr catalysts modified with tartaric acid to obtain 87% e.e. of the (−)-alcohol (**23**). The results are extremely



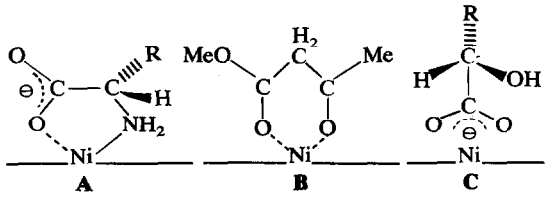
Scheme 15



23

Scheme 16

promising. Investigations of the structures of adsorption complexes of amino acid modifiers and methylacetoacetate complexes using IR techniques[78] have shown that they are similar to those of corresponding metal chelates known in coordination chemistry. It is assumed that the chelate

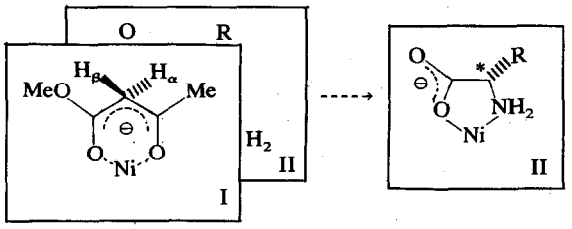


A **B** **C**

α-Amino acids Methylacetoacetate (S)-α-Hydroxy acids

Scheme 17

ring is perpendicular to the catalyst surface. α-hydroxy acids form carboxylates (**c**) with the OH group available for H-bonding in contrast to the amino acid chelate (**A**). It has been suggested that the substrate and amino acid modifier (Case **A**) are adsorbed on two adjacent Ni atoms:

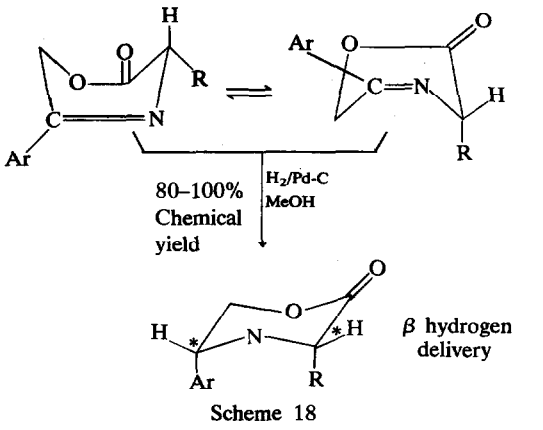


Of the four possible configurations the most stable is that in which the methyl acetoacetate molecule coordinates parallel to the modifier on the side opposite the bulky R substituent with the ester OMe oriented away from R as shown. The Me group on the β carbon of methylacetoacetate is in the plane of the chelate upon delivery of hydrogen. If the Me is pressed towards the modifier (β attack of hydrogen) severe steric hindrance arises, hence hydrogen is preferentially delivered from the modifier side. Predictions are in agreement with experimental data however the theory has yet to be generalised.

Recently, 1,3 asymmetric induction has been reported in the heterogeneous hydrogenation of a cyclic azomethine bond.[79]

Two quasi-boat conformations are of lowest energy and in both the R-substituent hinders the α face.

Diastereoselectivity is almost 100% as determined by $Eu(fod)_3$ shift studies for R = i-pr, BZ, Me and Ar = Ph, *p*F-Ph, 2,5-dimethoxy-Ph and others. It is evident that the conformational rigidity of the heterocycle as opposed to the exact spatial requirements of R is responsible for the induced asymmetry.

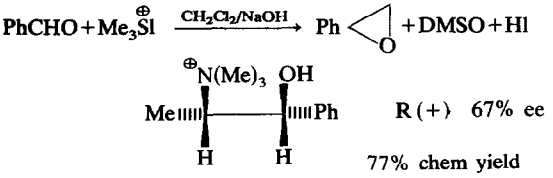


Scheme 18

Phase transfer catalysis

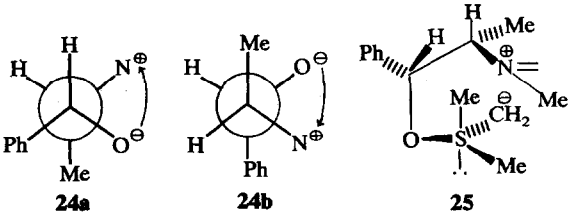
Preparative organic reactions using phase transfer catalysts have recently been reviewed.[80,81] Subsequently, several publications have appeared reporting asymmetric induction using chiral catalysts. The synthetic utility of such processes is immense.

(−)-N, N-dimethylephedrinium bromide has been used to catalyse the phase transfer synthesis of 2-phenyloxirane from benzaldehyde and chiral dimethylsulfoniummethylide (Corey's ylide) in 67%



Scheme 19

e.e.[82] Ephedrinium catalysts not bearing the OH group give racemic products and water miscible solvents (THF, Me—CN) which favour OH protonation reduce % e.e. drastically. It has been suggested that induction arises from dipole-dipole interactions of the zwitterionic species and the achiral catalyst in the organic phase as in **25**. The

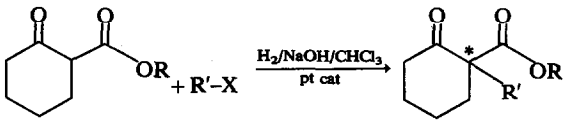


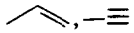
24a **24b** **25**

ylide attack occurs on one of the enantiotopic faces of benzaldehyde. The (+)-ephedrinium enantiomer gives preferentially the *S*(−)-oxirane.

The same catalyst has been used to effect dihalocyclopropanation of *trans*-propenylbenzene in 0.6% e.e.[83] A loose association of carbene to catalyst OH is suspected leading to reduced reactivity and enhanced selectivity is then possible.

An asymmetric alkylation of β-keto-esters has been reported using (−)-N-benzyl, N-methylephedrinium bromide as phase transfer catalyst.[84] This is the first report of asymmetric alkylation



R = Me, OMe, OEt
R' = Me, 

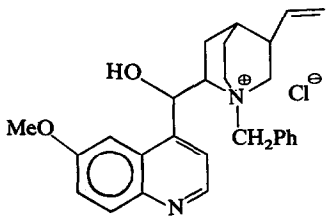
Scheme 20

under phase transfer conditions. Optical yields were estimated at 5–6% using chiral shift reagents, however the mode of induction was not rationalised.

A maximum optical yield of 14% (for t-butylphenylketone) was reported in phase transfer sodium borohydride reductions of a series of hindered ketones[85] catalysed by (−)-N-dodecyl-N-methyl ephedrinium bromide in benzene and dichloromethane. The OH group may H-bond with the CO, favouring one of the two possible diastereomeric transition states leading to hydride transfer.

In the reduction of racemic $\phi CH(Me)\overset{O}{\overset{\|}{C}}Me$ the recovered ketone was racemic when the reaction was quenched at 50% conversion, indicating that for this case the process is not a kinetic resolution.

Using benzylquininium chloride catalyst (**24**), phenyl-t-butyl ketone was reduced with optical and



24

chemical yields of 32% and 95% respectively.[86] It is the rigidity of **24** in addition to the fact that the OH is β to the cation function which makes this catalyst so effective.

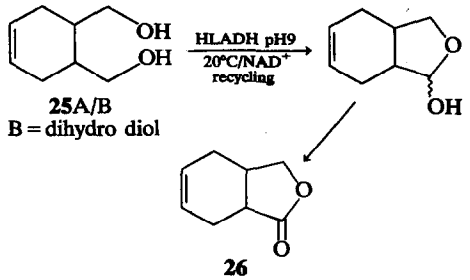
An identical phase transfer system substituting 1,2-dichoroethane for methylene chloride as solvent achieved 39% optical yields in the reduction of acetophenone using 0.4 molar equivalents of catalyst[87] whereas the previously reported system[85] failed to induce asymmetry on this substrate using 0.05 molar equivalents of catalyst. This would seem to suggest that the diastereomeric transition states may be in equilibrium with free catalyst and substrate.

Enzymatic processes

The most effective catalysts by far, are nature's enzymes. The ability of these to distinguish enantiotopic groups in molecules and to effect stereoselective transformations on them has been well documented.[88,89]

Such a discrimination occurs between enzymes and enantiomeric disubstituted cyclohexane conformers that are racemic due to interconversion at room temperature.

In the case of *cis*-diols[88] (**25A/B**) one diastereomeric enzyme-substrate complex is energetically preferred leading to high optical yields of lactones (**26A/B**) using horse liver alcohol dehydrogenase.



25A/B
B = dihydro diol

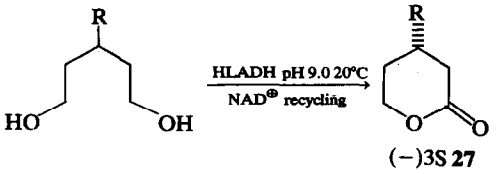
26

A (1S,2R) 79% yield 100% ee
B (1S,6R) 80% yield 85% ee

Scheme 21

The *cis*-diol is not meso in the classical sense since inversion of the chair is necessary for superimposition of enantiomers.

Jones and Irwin[91] report excellent optical yields in the horse liver alcohol dehydrogenase (HLADH) catalysed oxidation of substituted pentane 1,5-diols with a C-3 prochiral centre by NAD^+ coenzyme. The catalyst exhibited stereoselectivity for the pro-*S*-hydroxyl group in each case to produce the valerolactones (**27**).



(−)3S **27**

R = Me 90% ee,
R = i-Pr 25% ee,
R = Ph 21% ee

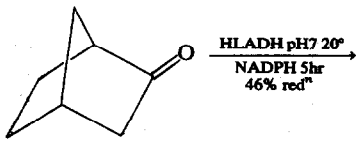
Scheme 22

The process is a "true asymmetric induction" in that it can be allowed to proceed to completion whereas a kinetic resolution is usually terminated at 50% conversion since optically pure compounds will be obtained at this point if the stereoselectivity is absolute.†

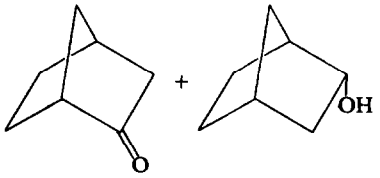
HLADH catalyses just such a kinetic resolution in the reduction of ketones with the reduced form of the nicotinamide coenzyme NAD(P)H.[93] The process is outlined below for 2-norbornanone and bicyclo[3.2.1] octanone (Schemes 23 and 24 respectively). The extent of enantiomeric enrichment of either product can be manipulated by varying the extent of overall reduction. The examples shown maximise optical yield of the alcohol.

This stereoselectivity in reduction of norbornanone is far superior to that of lithium aluminum hydride and equal to or greater than that of the

† HLADH is an NAD^+ (oxidised nicotinamide adenine dinucleotide) dependent oxido reductase.[92]



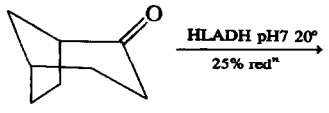
(±) 2 norbornanone



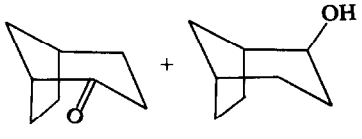
(−)(1R,4S)-**10** 31% (46% ee)

(+) (1S,2R,4R) 39% (64% ee) (*endo*)

Scheme 23



(±) bicyclo[3,2,1] octanone



(−) (1R,5R) 58% (17% ee)

(−) (1S,2S,5S) 36% (83% ee) (*exo*)

Scheme 24

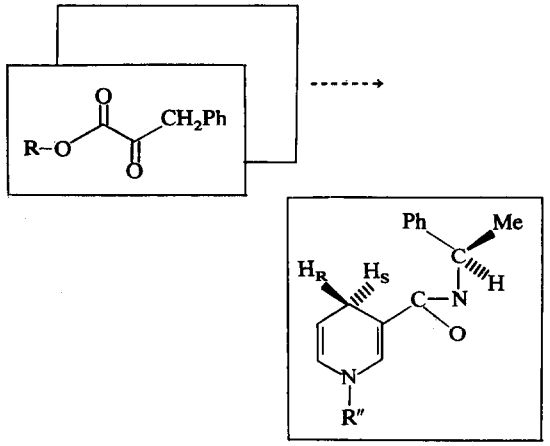
hindered trimethoxy aluminum hydrides and tri-sec-butyl (selectride) reagents.

A Japanese group has synthesised and studied a biomimimetic model system of the NAD(P)H coenzyme.[94] 1-benzyl-1,4-dihydronicotinamide (BNAH) in the presence of magnesium perchlorate reduces ethyl:benzoyl formate quantitatively to racemic ethyl mandelate. 4-deutero BNAH reduction of the same substrate revealed that 70% of the available deuterium was transferred to CO carbon indicating direct hydrogen transfer here parallels enzymatic hydrogen transport.[95]

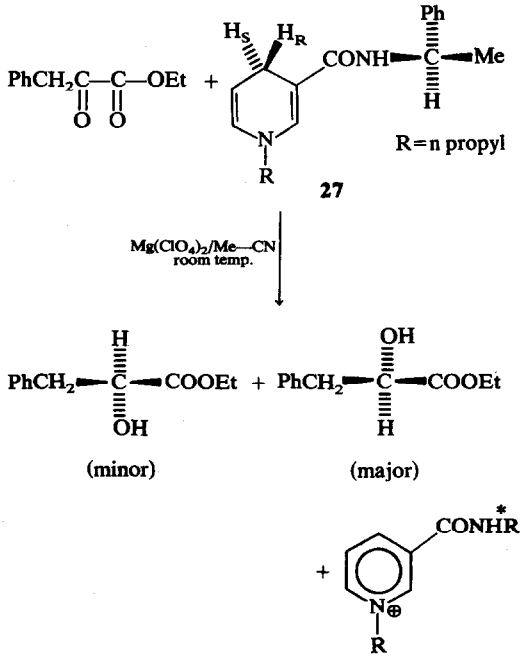
The chiral NAD(P)H models (*R*)(−)N-α-methylbenzyl-1,4-dihydronicotinamide (**27**) reduced ethyl benzoyl formate to the (*R*)-(−)-mandelate in 19% e.e. The nicotinamide's **C** chiral centre must induce asymmetry 5 carbons away at the hydride transfer centre. The metal ion is presumed to co-ordinate with the CO oxygen of the substrate reducing electron density on carbon as is known in other NAD(P)H dependent biological reactions.

A more basic CO would co-ordinate more strongly to magnesium as in the arylketoester series where greater enantioselectivity is evident. Physicochemical results suggest[96] that co-ordination is occurring primarily between the Mg ion and the 1,4-dihydropyridine ring and that interaction with the CO is more precisely, an induced polarisation.

The molecular arrangement proposed by the authors predicts a transfer of pro-*R*-hydride and steric prevention of pro-S hydrogen participation. A *trans* conformation for the two CO groups leading to the Cram model for least hindered transition state is assumed.



Scheme 26

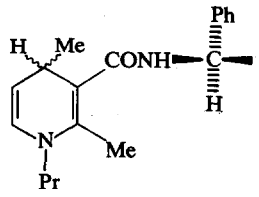


Scheme 25

A subsequent publication[97] reports that the optical purity of the product depends absolutely on the molar ratio of metal ion to coenzyme model and may be maximised by varying this ratio. 2-acetylpyridine has been reduced in 39% e.e. and 72% chemical yield via this approach.

Using N-(*R*)-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (**29**) 97% optical and quantitative chemical yields were realised in the reduction of methylbenzoylformate.[98] The two diastereomers of **29** are enantiomeric at C_4, the chiral site of hydride delivery and afford equal and opposite stereochemical results.

The fact that the chirality of the α-methylbenzyl group does not affect the enantiospecificity of the reaction is no doubt due to steric repulsion between



29

C_2 Me and amide CO twisting the latter of the plane of the dihydropyridine ring. Chirality at C_4 then, is entirely responsible for the induced asymmetry.

It is hoped that these model systems will afford an understanding of the mechanism of biochemical enzyme substrate interaction so that the efficiency of natural processes may be mimicked with greater dependability.†

Catalytic processes with acceptable chemical and optical yields as well as efficient catalyst recycling are regarded as the most efficient means of inducing asymmetry. Many of the preceding examples do not fulfil these requirements, however the field remains an area of intense study. The prospects are excellent.

REDUCTIONS AND RELATED REACTIONS

Chiral metal hydride complexes

Chiral lithium aluminum alkoxy hydrides were first used by Bothner-By[99] in 1951 when he utilised an LAH/CAMPHOR complex to reduce methyl ethyl and t-butyl ketones to obtain products of low optical activity. Subsequently (−)-menthol, (+)-borneol, (−)-isoborneol and a host of chiral carbinol amines (quinidine, quinine, ephedrine etc) as well as a variety of monohydroxy dihydroxy and other monosaccharide derivatives have been complexed with LAH to perform asymmetric reductions.

Initial results were poor presumably due to disproportionation of chiral alkoxy LAH compounds (Scheme **27**) to produce LAH itself which is more

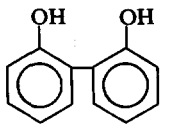
$$2LiAlH_3OR^* \rightleftharpoons LiAlH_2(OR^*)_2 + LiAlH_4$$

Scheme 27

active, giving achiral reduction. Amine carbinols show less tendency to dissociate[100] and their basicity allows for extraction from acidic solution ensuring that the reduction product is uncontaminated with chiral ligand impurities. The nitrogen lone pair is able to co-ordinate leading to a 5- or 6-membered cyclic transition state affording a more rigid conformation and higher stereoselectivity in the hydride transfer step.

The stereochemical balance of these reactions is very delicate however. In several cases stereochemistry was reversed in going from ether to THF solvent or in elevating the temperature[101] or in changing the LAH/ligand ratio.[102] the steric bulk of ketone substituents is definitely a controlling factor but no definite correlation with stereoselectivity, of any generality, has come to light.

In recent years, many of these methods and yields have been improved substantially. French workers[103,104] have obtained optical yields of up to 89% in reduction of aryl alkyl ketones with reagents of the type LiAlH (OR*) $(OR')_2$ where R* = (−)-N-methylephedrine (**30**) and R′ = 3,5 dimethyl phenol and other related phenols.



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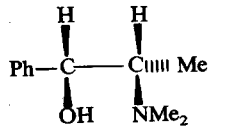
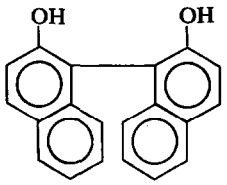


(−) N-methylephedrin

30



32

This reagent is capable of delivering only one hydride per molecule facilitating interpretation of the results and control of steric geometry. Optical yields increase as each hydride is replaced with chiral alkoxyl groups, best results being obtained with LiAlH $(OR^*)_3$. Small variations in the achiral phenol ligands used give large variations in optical yields (ex O-methylphenol 9.5% e.e., O-methoxyphenol 43% e.e.).

In each case the reaction products are of the (*R*)-configuration except when biphenols (**31**) or binaphthols (**32**) are used where (S)-isomers predominate. The atropisomeric properties of these are presumed to give rise to a mixture of diastereomers in the reaction complex.

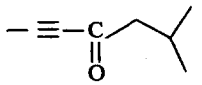
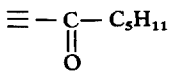
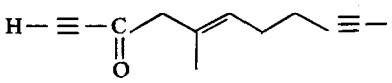
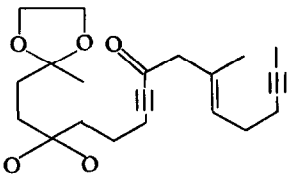
Optical yields vary drastically with temperature, optimum results being obtained at −15°. This is in all probability a result of the temperature dependency of reagent association and disproportionation. Long linear alkyl aryl detones give the best optical yields.

Reagents of the type $LiAlH_{4-n}$ (OR*)n (where R* = (+)(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol) accomplish reduction of a variety of ketones in excellent chemical and moderate optical yields.[105] A complete reversal in chiral preference when the reagent has aged somewhat leaves mechanistic interpretation difficult. The reagent may be a mixture of complexes with different n values, each existing as monomer, dimer or polymer and each having a different reduction rate. At least two distinct complexes exist if one is to explain reversal of selectivity.

The same reagent reduces acetylenic ketones with better optical yields.[106] The π electron system of the acetylenic bond appears to have a similar effect to that of the aryl system in arylalkyl ketones.

† see also Ohnishi Karami *et al.*, *Chem. Lett.* 915 (1976) for a study of biomimetic reduction of olefins with chiral NAD(P)H models in $Mg(ClO_4)_2$.

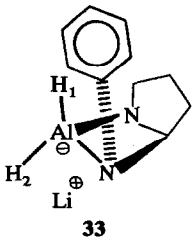
Table C. Asymmetric reduction of acetylenic ketones with $LiAlH_{4-n}(OR^a)_n$

Substrate	Synthetic yield (%)	Optical yield (%)	Product configuration
	94	82	R
	96	72	R
	70	82	R
	95	84	R

[a] R = (+)-(2*S*,3*R*)4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol.

The effect of aminic nitrogen as a substituent of the ketone substrate in these reactions has been well studied.[108,109] A 5-membered cyclic model in which the reagent metal atom is linked both to carbonyl O and N has been used to interpret the stereochemistry of nucleophilic attack on substrates of type **36**. Predominant attack occurs from the less hindered side of the CO. Three models have been proposed[110] for the case of a β-asymmetric ketone bearing amine or OH on the chiral centre.

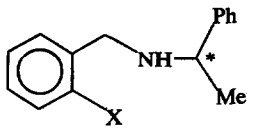
The ligand amine or OH can complex to the Li cation resulting in a tight cyclic complex.



33

Bindentate pyrrolidine ligands furnish excellent results as well. The complex **33** is extremely rigid with two *cis*-fused 5-membered rings due to complexation of (*S*)-2-(anilinomethyl) pyrrolidine with LAH. H_1 is hindered by the pyrrolidine and phenyl rings and it may be that only H_2 is delivered. This complex reduces acetophenone with 93% and 92% chemical and optical yields respectively.[107]

The co-ordinating ability of the hetero atom X in LAH complexes with (*S*)(−)N-(O-substituted benzyl)-α-phenethylamine ligands (**34**) has been studied. Of the complexes used (with X = —OCH_3—, $N(CH_3)_2$, —SCH_3) the diethylamine ligand afforded the highest chiral preference with a ligand to aluminate ratio of 3:1 (43% e.e.).



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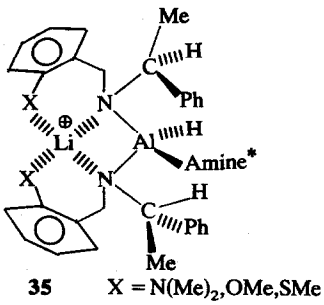
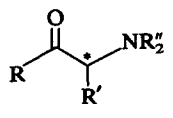


35 X = $N(Me)_2$,OMe,SMe

The stability constant of chelate formation in the complex of suspected structure **35** would decrease in the order $OCH_3 > N(CH_3)_2 > SCH_3$ consequently the steric bulk as well as co-ordinating ability of X must be taken into account.

The effect of aminic N as a substituent of the ketone substrate in these reactions has been well studied.[108,109] A 5-membered cyclic model in which the reagent metal atom is linked both to carbonyl O and N has been used to interpret the stereochemistry of nucleophilic attack on substrates of type **36**. Predominant attack occurs from the less hindered side of the CO.



36

Three models have been proposed[110] for the case of a β-asymmetric ketone bearing amine or OH on the chiral centre. Of the open chain, polar and cyclic models postulated, the latter seems to predict stereoselectivity with greater accuracy in experiments varying substrate (steric hindrance of substituents, nature of amino group and distance of

nitrogen from ketone i.e. ring size) and reagent (LAH, organolithiums and Grignards).

A recent study[111] varied the substituent Y and its distance from the ketone in **37** comparing enantioselectivity with Y = Et which has a steric bulk

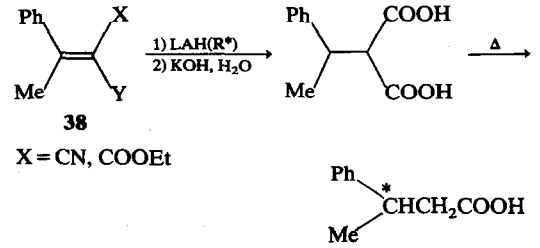
37

R* = (L)menthoxy
n = 1–4
Y = O-Me, $N(Me)_2$, S—Me

Scheme 28

similar to the other Y functions. This assures that electronic effects only, are being compared. The highest chiral selectivity was obtained for Y = OCH_3 and n = 2 (35% e.e.) and n = 3 (38% e.e.) followed by Y = $N(CH_3)_2$ then S—CH_3 in keeping with the base strength and co-ordinating ability of the heteroatom. These facts suggest a cyclic transition state.

Asymmetric induction has also been noted in the 1,4 reduction of alkylidene malononitriles (8.3% e.e.) and alkylidene cyanoacetic esters **18** (12.3% e.e.)[112] using LAH complexes of aminoalcohols (quinine quinidine and cinchonidine). The ester of cyano functions are not reduced. Reduction of the *E*- and *Z*-isomers of the alkylidene cyanoacetates



38

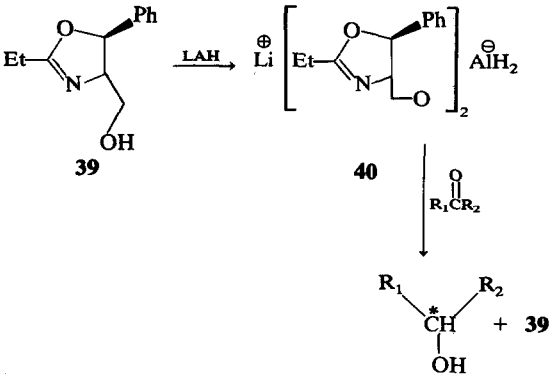
X = CN, COOEt

Scheme 29

gives products of opposite configuration in different optical yields. Quinidine affords the best optical yields in all cases and as expected quinine and quinidine induce asymmetry in the opposite sense.

These facts indicate an intermediate complex, very likely of cyclic nature is formed between substrate, metal-hydride reagent and amino alcohol. Such an intermediate has been suggested by Cervinka *et al.*, for simple ketones and the empirical rule they devised for prediction of product configuration[113] applies here.

Meyers *et al.*,[114] have used chiral non-racemic oxazolines (**39**) as ligands in asymmetric reduction of simple ketones with LAH complexes. Optical yields of up to 65% are obtained on acetophenone at −78° however other substrates (α-tetralone, 2-octanone 3-phenyl-2-propanone) are less amenable.



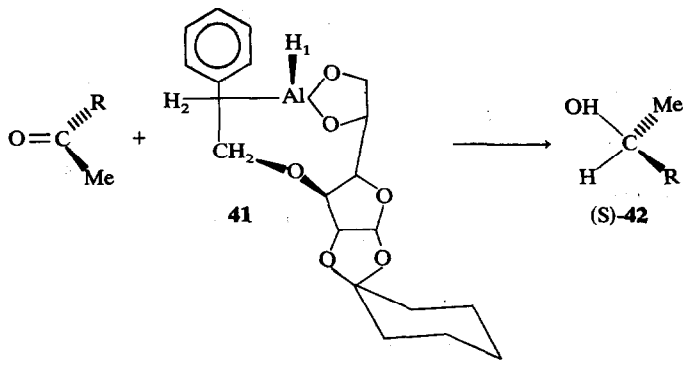
39 **40**

Scheme 30

Two moles of oxazoline per mole of LAH gives optimum induction and yield. A 3:1 ratio renders the hydride complex inactive and addition of 2 moles of ketone to **40** gives one a 50% yield of product suggesting that the fourth hydride is heavily hindered. As indicated, the oxazoline is recoverable.

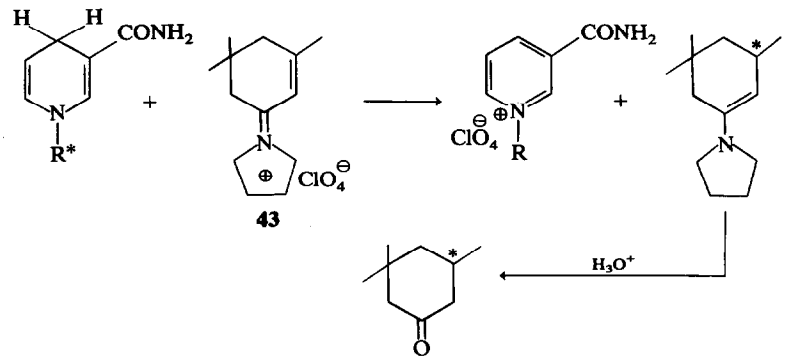
LAH complexes with monosaccharide ligands have been used successfully in the asymmetric reduction of aryl-alkyl and dialkyl ketones.[115] Best results are obtained with 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose in a 1:1 molar ratio with LAH which consistently gives product alcohols of (*S*)-configuration in optical yields up to 40%.

This suggests that the cyclic complex (**41**) between LAH and the sugar presumably at C_5 and C_6 is formed. Of the two available hydrides H_1 is severely hindered therefore if the ketone orients itself with minimum repulsion between CO and ether oxygens as shown in **41** and with the bulky group of the ketone away from the O-benzyl group, the (*S*)-alcohol (**42**) would invariably result. 3-O-Me and O-Et sugars afford only low selectivity and inconsistent results.



41 (S)-**42**

Scheme 31



Scheme 32

Surprisingly, t-butyl methyl ketone is reduced with low selectivity. It seems then that the alkyl group's bulk must be at some distance from the reaction centre to affect transition state energies for the competing pathways.

The glucofuranose/LAH complex is the only one studied that is appreciably soluble in ether and filtered solutions must be used. Reduction using unfiltered solutions of other complexes occur primarily on the solid surface of the complex giving minimal selectivity.

Addition of enough ethanol or benzyl alcohol to the complex to replace the more active H_2 increases selectivity markedly due to reduction by the more hindered H_1 only.[116] Addition of more alcohol renders the complex inactive. Optical yields of up to 70% have been attained using this method in the reduction of acetophenone. As expected the product configuration is reversed (i.e. *R*). It is clear that the mechanism is a kinetically controlled hydride transfer with the least sterically hindered transition state predominating. The delivery of the more sterically hindered hydride leads to a greater difference in free energies of activation and enhanced stereoselectivity.

Ketone oximes have been reduced to optically active amines in a similar fashion with up to 56% e.e.[117] (*S*)-amines are obtained while the ethanol modified complex yields (*R*)-products indicating a similar transition state geometry to that previously mentioned.†

Monosaccharides also act as chiral directors in dihydronicotinamide reduction of α,β-unsaturated iminium salts (**43**).[119] Optical yields are very low however (14–27%). Free OH groups on the glucopyranose substituent generally led to higher optical yields and it has been suggested that these interact with the dihydropyridine N atom providing enhanced reactivity and a more rigid topology in the activated complex.

In contrast to these kinetic processes the asymmetric reduction of alk-2-en-4yn-1-ols (**44**) with lithium bismenthyloxy aluminum hydride is a thermodynamically controlled process.[120] The intermediate anion (**50**) is achiral and exhibits chirality only after complexation with trivalent aluminum to form **46** and **47** which are hydrolysed to the respective allenic alcohols.

Reduction with LAH and subsequent addition of menthol to the aluminohydride allene complex gives the same product in the same optical yield thus precluding any possibility of kinetic hydride addition. Optical yields of 10–15% are obtained. In this case the thermodynamically preferred allene complex predominates whichever way it is formed.

Asymmetric alkylation of aldehydes and ketones to give secondary and tertiary alcohols has been reported recently[122] using a lithium alkoxy-tributylaluminate. Alkylation of carbonyls had previously been reported using "ate" complexes $LiAl(nBu)_4$ and $NaAlEt_4$.[121] The chiral organometallic reagent (**51**) is prepared by combining equimolar amounts of (−)N-methylephedrin and $LiAl(nBu)_4$. Up to 31% e.e. was obtained in the alkylation of acetophenone to give 2-phenyl-2-hexanol whereas similar alkylations using organocuprates had resulted in only 16% e.e.[123]

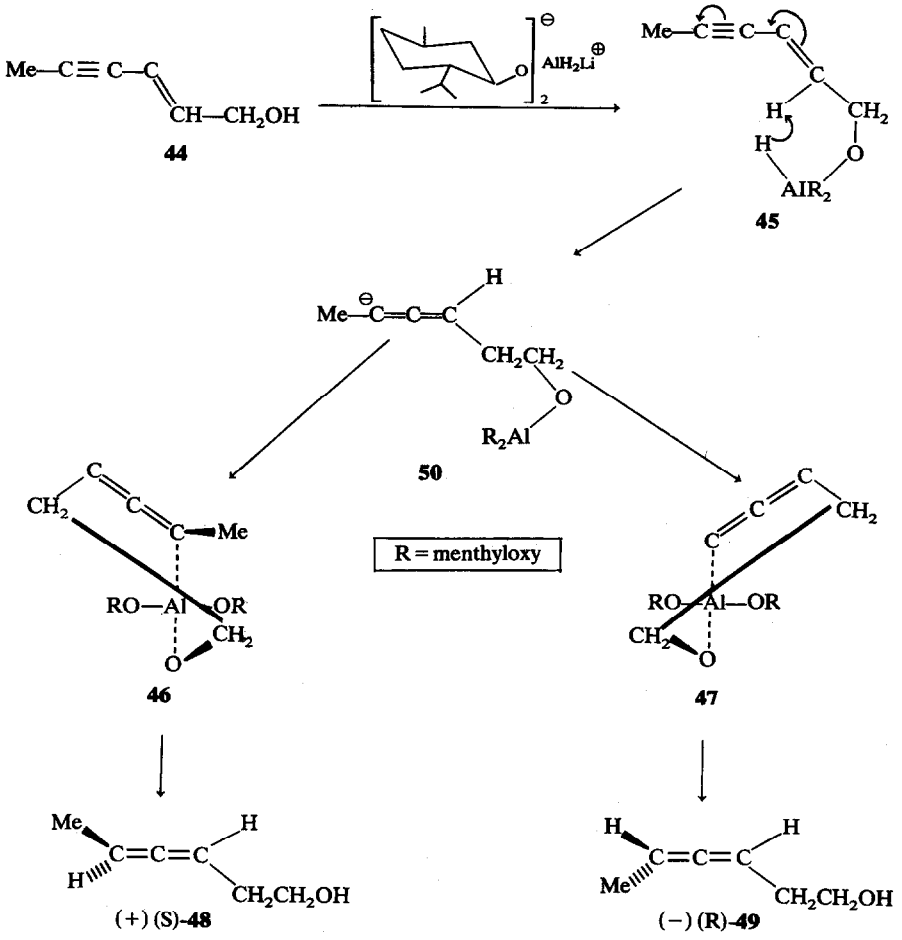
Organoaluminum reagents

Asymmetric reduction of carbonyls is also possible using organoaluminum compounds R_3Al; a reaction that had been studied more for its mechanistic aspects than stereochemistry.

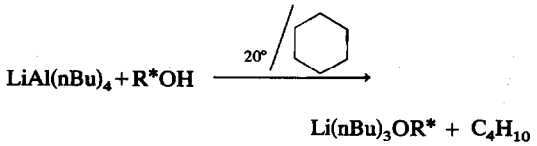
Organoaluminum compounds with chiral β-branched ligands (ex (*S*)-2-methylbutyl) or chiral solvates of triisobutylaluminum have been used.[124] The generally accepted mechanism involves complexation of reagent and substrate followed by intramolecular hydride transfer from ligand β-C atom to CO (Scheme 35). Based on the assumption of the cyclic 6-membered transition state (**52**) only four reacting conformations are favourable as shown, (**A–D**) (viewed along C . . . H_x − *C axis). **A** and **B** lead to (*S*)-carbinol with **A** more stable regarding steric and electronic requirements. Structures **C** and **D** lead to (*R*)-carbinol with **D** more stable for electronic reasons only ($CH_2-Al^{\delta+}$ between C—$O^{\delta-}$ and C—$Ph^{\delta-}$), steric factors are identical. Hence **A** is the favoured transition state geometry leading predominantly to (*S*)-products as observed for (*S*)-2-methylbutyl ligands.

The extent of asymmetric reduction varies with the R group of the ketone; following the series Me < Et < t-Bu < i-pr. Increasing the size of R prevents the free rotation of phenyl groups in **D** more

† For a detailed discussion of the reduction mechanism see ref. 118.



Scheme 33

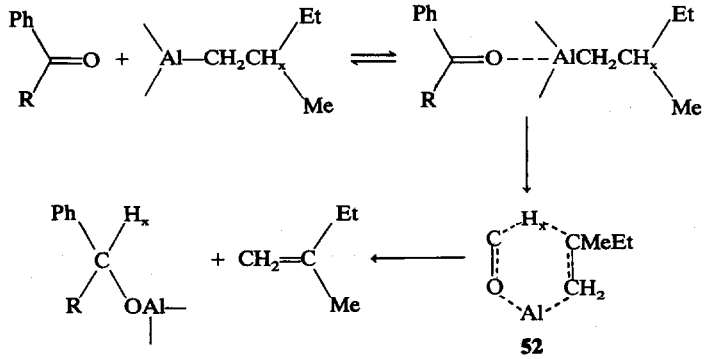


Scheme 34

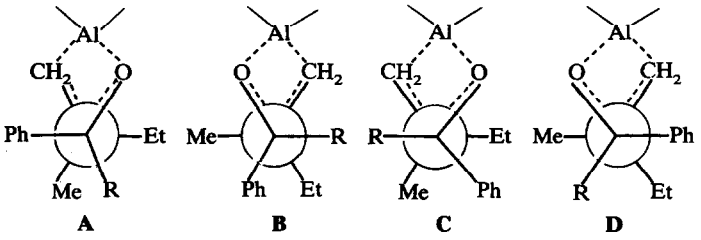
than **A** increasing the tendency for the transition state to assume the latter conformation. The anomaly in the case of R = t-Bu is assumed to result from severe crowding in **A** and **D** reducing the free energy difference between them and hence the optical yield. An enantomeric excess of 44% was obtained in the reduction of isopropyl phenyl ketone with tris [(*S*)-2-methyl butyl] aluminum at 0° in pentane. Results with donor complexes of the above reagent and triisobutylaluminum are inferior and the mechanism is yet obscure.

A later study reports up to 57% e.e. in the reduction of dialkyl ketones with the tris((*S*)2-methyl butyl) aluminum reagent.[125,126]

A similar study[127] published recently regarding the asymmetric reduction of phenyltrifluoromethyl

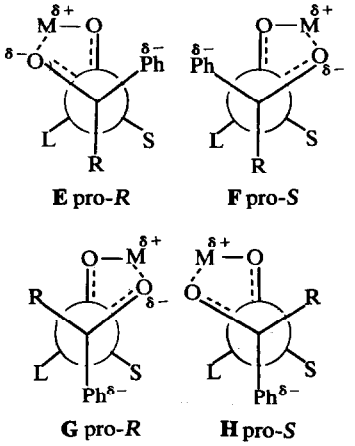


Scheme 35



ketone with optically active alkoxy aluminum dichlorides (R^*OAlCl_2) and alkoxymagnesium bromides (R^*OMgBr) reports stereochemical results anomalous to the organoaluminum reductions of alkylphenyl ketones just mentioned. The chiral ligands used include (−)-borneol, (−)-isoborneol, (−)-*p*-menthan-3-ol and (+)-1-phenylethanol all having (*R*)-configuration at carbinol carbon. Optical yields are highest with [(−)borneloxy] $AlCl_2$ (68%) and [menthyloxy]$AlCl_2$ (77%).

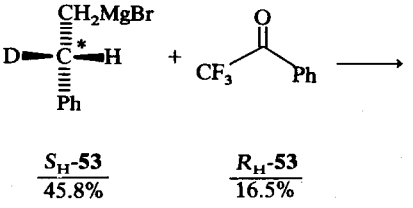
The reaction is postulated to proceed via hydride transfer from the carbinol carbon with again four competing transition state conformations (viewed along C . . . H—C* axis once more) (**E–H**).

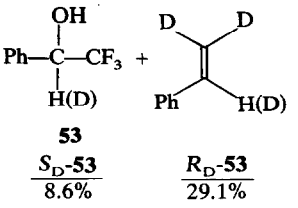


In the alkyl phenyl series electronic factors favour C—$Ph^{\delta-}$ next to O—$M^{\delta+}$ favouring **E** and **F**. **E** is more favourable sterically, hence the (*R*)-alcohol that it leads to predominates.†

However regarding the reduction of phenyl trifluromethyl ketone (R = CF_3); CF_3 is a stronger negative dipole than C—Ph and its placement next to O—$M^{\delta+}$ is favoured as in **G** and **H**. Since **H** is favoured sterically the resulting (*S*)-alcohol predominates. With cyclic chiral alcohols (L and *S* joined to form a ring) steric factors destabilise **G** and **H** and the resultant stereochemistry is in keeping with the alkyl phenyl ketone series. The role of electronic effects in asymmetric induction is well exhibited here.

Morrison Mosher *et al.*[128] have studied the Grignard reduction of the same ketone using a reagent derived from (*S*)-2-phenyl-1-bromoethane 1,1,2-d_3 that is chiral by virtue of a H *vs* D disparity at the β-carbon.





Scheme 36

There is less overall D transfer but greater asymmetric induction for this process. This has been rationalised as a result of rate of transfer differences of H *vs* D and non-bonded interactions of H *vs* D with —CF_3 and —Ph. The steric requirements of H and D do not differ by enough to have an effect.

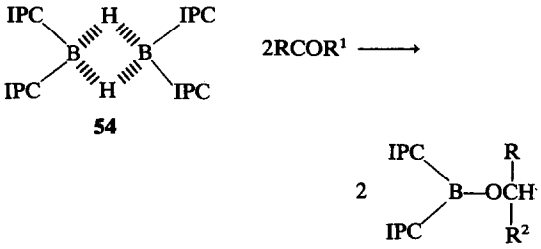
The average C—H bond distance is 0.008 Å longer than C—D and has a larger De Broglie wavelength than D, hence H may be able to transfer from reagent to substrate at a greater distance. Consequently, the closer proximity of the two reacting centres in the case of D transfer produces more steric compression and more stereoselectivity.

Borane reagents

The scope of functionality available through hydroboration and subsequent modification of organic compounds is extensive. This coupled with the capability of asymmetric creation of chiral centres in many cases using highly hindered trialkylboranes or boranes with chiral ligands makes this reaction a most valuable one in synthetic strategy and design.

(−)-Diisopinocampheylborane (IPC_2BH) prepared from (+)α-pinene and borane-THF or borane-methylsulfide reduces dialkyl ketones in good chemical yields with optical yields of 16–37%.[129] The reagent exists as a dimer (**54**) with a

† Note that ligands with (*S*)-configuration at the hydride were used in the previous study whereas the (*R*)-ligand is used here leading naturally to a preponderance of opposite isomers in the alkyl phenyl ketone series considering identical transition states.

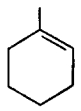


Scheme 37

small equilibrium amount of triisopinocampheyldiborane present due to dissociation. The mechanism is much the same as that for reduction using trialkylaluminums involving delivery of a β-hydrogen to the CO.

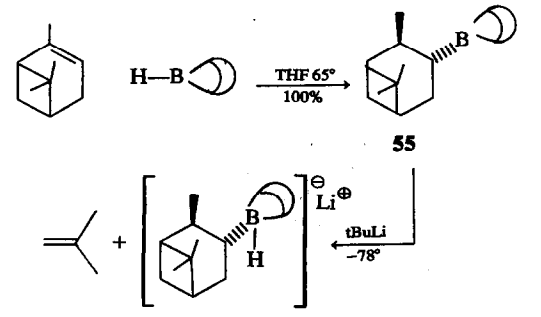
The same reagent is excellent for hydroboration of *cis*-olefins as in the conversion of *cis*-2-butene to 2-butanol with 98.4% enantiomeric excess. More hindered olefins react more slowly, with dissociation of reagent and reduced optical yields (17–22%).[130] For these monoisopinocampheylborane is more effective as is evident in Table D. The reagent

Table D. Hydroboration of trisubstituted olefins with $R^*_nBH_{2-n}$

Olefin	IPC_2BH	$IPCHB_2$
	14% e.e.	53.4% e.e.
	22%	55.4%
	—	72.4%

is prepared by reaction of α-pinene with thexyl borane-triethylamine to give $IPCBH_2 \cdot NEt_3$ which undergoes rapid reaction with borane-THF liberating $IPCBH_2$.

Hydroboration of (+)-α-pinene with 9-borabicyclononane (9-BBN) affords the highly hindered trialkylborane (**55**) which readily converted into lithium B-isopinocampheyl-9-borabicyclo-[3.3.1] nonyl hydride (**56**) which reduces dialkyl ketones in 3–37% (*R*)-e.e.[131] (See Table E) via direct transfer of hydride from boron to carbon.



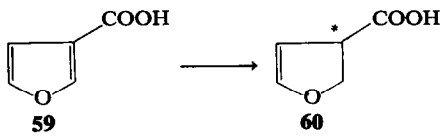
Scheme 38

Other asymmetric reductions recently reported include those achieved by actively fermenting yeast. Several functionalised ketones ($PhCOCH_2OH$, PhCOCOOH, $PhCOCH_2Cl$ and $MeCOCH_2$-COOEt) are reduced in fair chemical yields and excellent optical yields merely by addition to a fermenting yeast/sucrose suspension for one or two days followed extraction with ether or ethyl acetate.[132] *Saccharomyces cerevisiae* yeast was used. These reductions are well known in biological media but reports of *in vitro* studies are scarce.

In a later study[133] the same yeast produced optically pure (RsSc) (+)-1-phenylsulphinyl-propan-2-ol (**58**) in 50% chemical yield from 1-phenylsulphinyl acetone (**57**).

Scheme 39

In the first known asymmetric Birch reduction Japanese workers using a 1,2:5,6 di-O-isopropylidene-α-D-glucofuranose as proton donor obtained 3% e.e. in the synthesis of 2,3-dihydro-3-furoate (**60**) from 3-furoic acid[134] (**59**). In spite of low



Scheme 40

optical yields the application of asymmetric Birch reduction to natural product synthesis has interesting possibilities. The absolute configuration of **60** has not yet been determined.

ALKYLATIONS AND CYCLISATIONS

Alkylations

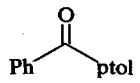
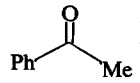
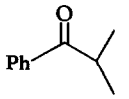
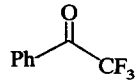
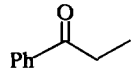
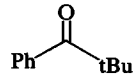
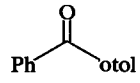
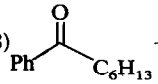
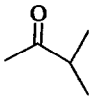
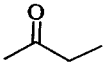
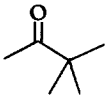
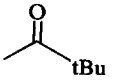
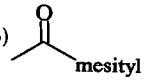
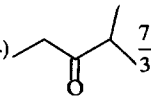
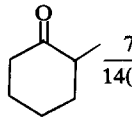
Asymmetric control in the formation of C—C bonds is an extremely advantageous tool in organic synthesis. Several excellent methods are known but advances have been slow, rendering the field a major challenge to synthetic chemists.

One of the most successful approaches has been alkylation of enamines. In 1968 Horeau reported 72% e.e. in methylation of the enamine formed from cyclohexanone and (−)-isobornylamine. Since then a variety of chiral amines and hydrazines have been used.

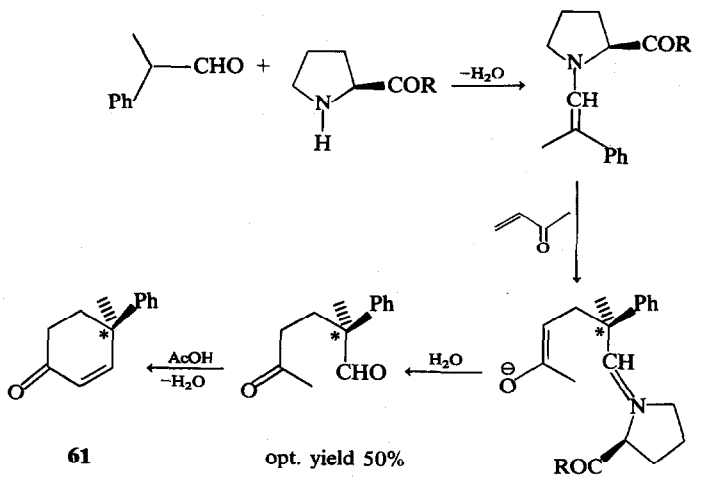
(+)-4-methyl-4-phenyl-2-cyclohexanone (**61**) has been synthesized by alkylation of the enamine derived from L-proline and 2-phenylpropanol with methyl vinyl ketone followed by hydrolysis and cyclisation.[136] The extent of induction is directly dependent on the bulk of the proline substituent R. A pyrrolidine ring in this position gives best results. Optical yields increase with a decrease in temperature to 0°.

The fact that optical yields increase after chemical yield becomes constant suggests a thermodynamic control here. Since the quaternary

Table E. Asymmetric reduction of carbonyls with various reagents (chem yield/opt. yield-configuration)

	A	B	C	D	E	F	G	H	I	J	K	L	M
(1) 	—	—	—	—	—	—	—	88 46(*R*)	—	—	100 63.2(*R*)	—	—
(2) 	70–80 17(*R*)	65 9(*R*)	—	75 4.75(*S*)	69 9.8(*S*)	—	93 92(*S*)	81 20(*R*)	100 75(*S* or *R*)	—	100 83.8(*R*)	95 58	—
(3) 	—	—	—	—	—	—	—	—	—	100 57(*R*)	100 17(*R*)	98 44.4	/46.2
(4) 	—	—	50 77(*S*)	—	—	—	—	—	96 30(*R*)	—	—	100 6.1	—
(5) 	—	—	—	77 37(*S*)	62 56(*S*)	90 52(*R*)	—	—	100 60(*R*)	100 23(*R*)	100 85(*R*)	98 13.2	/14.8
(6) 	—	—	—	65 19.2	—	90 47(*R*)	—	—	100 36(*R*)	100 25(*R*)	100 31(*S*)	96 38.4	/30.8
(7) 	—	—	—	—	—	—	—	73 56(*R*)	—	—	—	—	—
(8) 	—	—	—	—	—	95 14(*R*)	—	—	—	—	—	—	—
(9) 	70–80 36(*R*)	72 37(*S*)	—	—	—	—	—	—	—	—	100 41(*S*)	—	—
(10) 	70–80 29(*R*)	73 77(*S*)	—	—	—	—	—	—	—	—	100 14(*S*)	—	—
(11) 	70–80 3(*R*)	—	—	41 2.5(*S*)	39 3.8(*R*)	—	—	—	—	—	—	—	—
(12) 	—	78 19.8(*S*)	—	40 1.6(*S*)	—	—	—	—	100 28(*R*)	—	—	—	—
(13) 	—	—	—	—	—	28 20(*R*)	—	—	—	—	—	—	—
(14) 	70–80 37(*R*)	—	—	—	—	—	—	—	—	—	—	—	—
(15) 	70–80 14(1*R*, 2*S*)	—	—	—	—	—	—	—	—	—	—	—	—

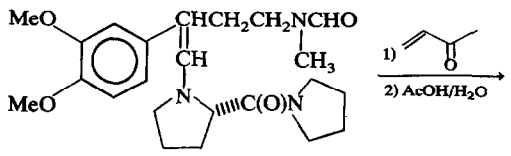
A Using β-isopinocampheyl-9-BBN Hydride, (ref. 131).
B Diisopinocampheyl Borane (ref. 129).
C (−) Menthyl-$OAlCl_2$, (ref. 127).
D 1,4:3,6-Dianhydro-D-Mannitolatodihydroaluminate, (refs. 115, 116).
E 1,3:4,6-Di-O-Benzylidene-D-Manitolatodianhydroaluminate, (refs. 115, 116).
F $LiAlR^*_3$ H R* = (*S*)(−)-N(O-dimethylaminobenzyl)α-phenethylamine (ref. 232).
G $LiAlR^*$ H_2 R* = (S)-2-(anilinomethyl)pyrrolidine, (compound **33**) (ref. 107).
H LAH/Quinine 1:1, (ref. 233).
I LAH/Darvon Alcohol, (ref. 105).
J AlR^*_3 R = (*S*)-2-methylbutyl, (ref. 126).
K $LiAlH(OR')_2$ (N-methylephedrine), (ref. 104).
L $Al(R^*_3)L$ L = solvent, R* = 2 methylbutyl (ref. 124).
M BeR_3 R = 2-methylbutyl



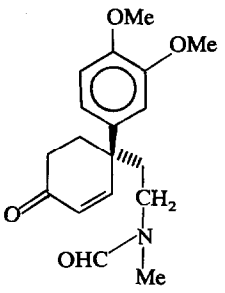
61 opt. yield 50%

Scheme 41

centre cannot racemise it is reasonable to assume an equilibrium with reactants is present, allowing inversion to occur. Asymmetric alkylation of the L-proline pyrrolidide enamine (**62**) with MVK is the key step in a total synthesis of alkaloid mesembrine[137] (**63**).



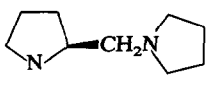
62



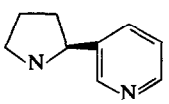
63

Scheme 42

Several other chiral amines with large steric requirements have been studied.[138,139] Of these (+)-2-(1-pyrrolidino) methyl proline (**64**) and (−)-nornicotine (**65**) afford the best results in the alkylation of the enamine formed with 2-phenylpropanol (51% and 54% e.e. respectively) although **65** gave low chemical yields.

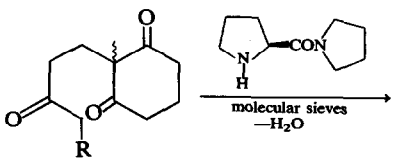


64

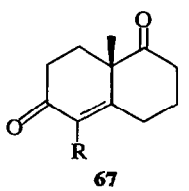


65

The enamine of triketone (**66**) cyclises regiospecifically therefore asymmetrically in 49% optical yields to afford **67** an important intermediate in diterpene synthesis. Better results are obtained in aprotic solvents at low temperatures.



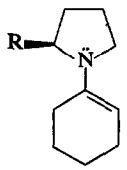
66



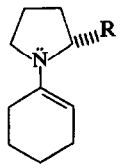
67

Scheme 43

Enamine rotamers such as **68** and **69** offer four avenues of attack by the alkylating agent and offer hindrance in only one case (backside attack on **69**).

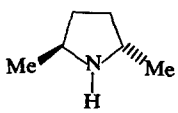


68



69

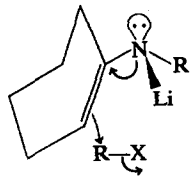
The extent of induction possible is thus severely limited. The enamine derived from (+)-*trans*-2,5-dimethyl pyrrolidine (**70**) offers the same hindrance



70

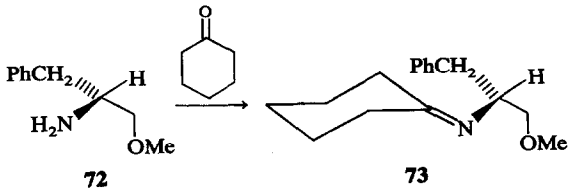
in both rotameric forms however, and alkylation of its cyclohexanone enamine proceeds in 93% e.e. with n-propyl iodide.

Yamada[141] was the first to report chiral lithio chelated enamines as substrates for asymmetric alkylation. The optically active 2-alkylcyclohexanones were obtained in 26–37% optical yield from **71**.



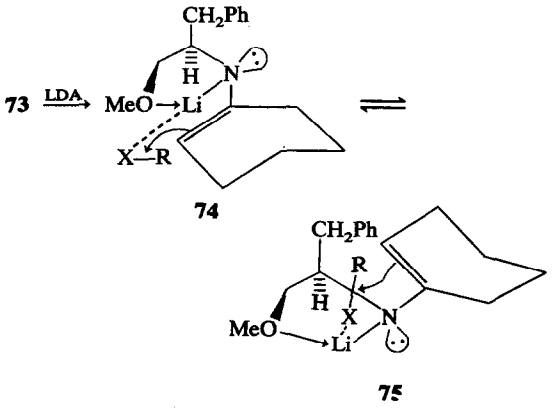
71

Subsequently more rigid[142] metalloenamines (**74** and **75**) have been developed from oxazoline derived amines (**72**). The OMe group plays a key role



72 73

Scheme 44



74 75

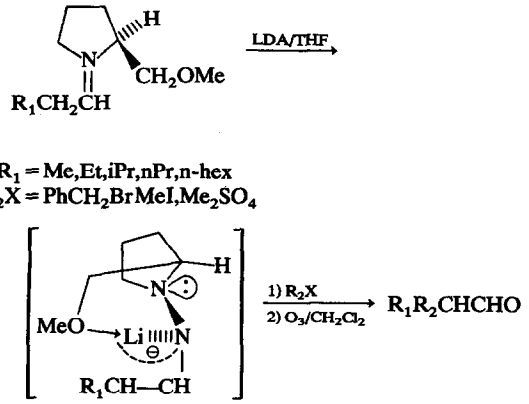
Scheme 45

here, co-ordinating with lithium to form a 5-membered ring with **74** and **75** related by inversion of the lone pair and cyclohexyl substituents on nitrogen.

Earlier studies[143] show that the halogen of the alkylating agent co-ordinates to lithium. As can be seen R—X is sterically encumbered in **75** leaving **74** the highly favoured transition state. Optical yields of 90% or greater have been realized (R = nPrI EtI, ≈Br).

A similar study[144] reports 81% optical yields using the enamine derived from (*S*)-2-amino-1-butanol and isopropyl magnesium bromide as chelating agent in the alkylation of cyclohexanone at −78°.

Metalated chiral hydrazones have been successfully used[145] as substrates for enantioselective alkylation to produce α-chiral aldehydes in moderate chemical yields and high optical purity (60–87% e.e.) using (*S*)-1-amino-2-methoxymethyl pyrrolidine as amine (Scheme 46). Optically active α-substituted ketones have been reported[146] by the same authors using a similar approach.

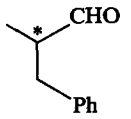
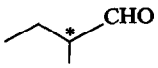
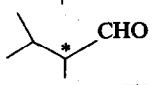
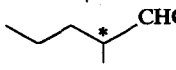
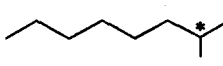
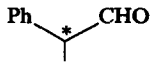


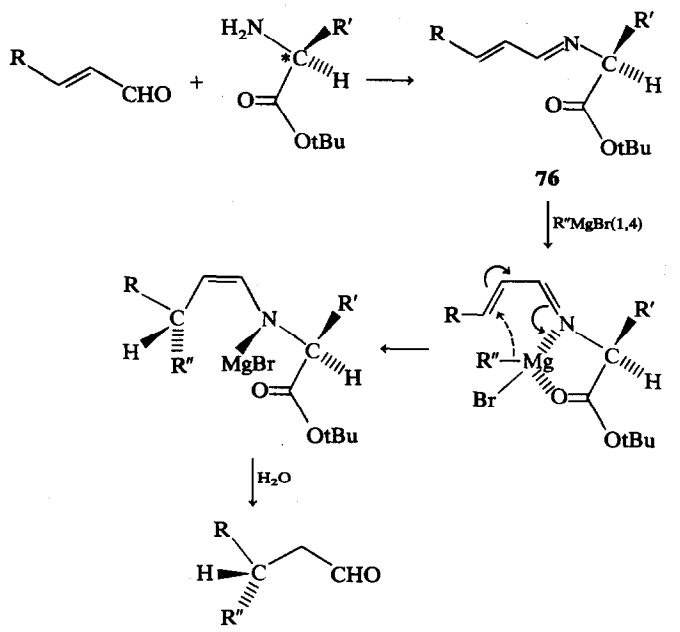
Topside Alkylation

Scheme 46

Asymmetric synthesis of β-substituted aldehydes has been achieved by[147] 1,4 addition of Grignard reagents to aldimines (**76**). Optical yields of up to 98% have been reported with most reactions proceeding in over 90% e.e. Side reactions such as

Table F. Alkylation of metalated chiral hydrazones

Product	R_2X	Chem Yield (%)	Opt yield (%)
	$PhCH_2Br$	62	82(*S*)
	MeI	65	62(*R*)
	MeI	60	57(R)
	MeI	67	not reported (*R*)
	MeI	61	87(*R*)
	Me_2SO_4	80	31(*R*)

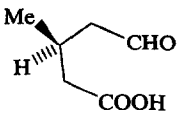


Scheme 47

proton abstraction 1,2 addition and attack of the ester CO are eliminated if t-leucine (R′ = tBu) t-butyl ester is used. Either (*R*)- or (*S*)-aldehyde can be obtained by choosing the (*R*)- or (*S*)-enantiomer of t-leucine or interchanging R and R″ in the reactants.

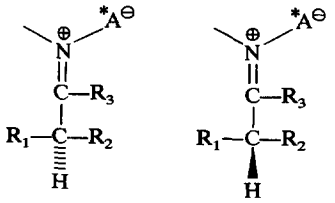
The mechanism proposed as shown, (Scheme 47) involves chelation of Mg with unshared electron pairs on N and O and subsequent attack by R″ at the β-C atom from the less hindered side. The amino acid ester chiral reagent is recoverable in good yield.

Asymmetric addition of diethyl malonate to the same substrate in a 1,4-sense followed by ester saponification, decarboxylation and imine hydrolysis generates **77** in 50% chemical and up to 86% optical yields.[148]



77

α-Chiral ketones can be obtained by a reaction sequence not involving alkylation.[149] Racemic α-disubstituted ketones are converted to enamines and these treated with optically active acids to form diastereomeric immonium salts (**78** and **79**). Subsequent hydrolysis affords the optically active ketone.



78 **79**

Equilibration of the immonium salts is thought to occur through the neutral enamine and is thus a thermodynamic process.

Oxazolines

In recent years the use of oxazolines as asymmetric induction reagents in alkylation reactions has been a fruitful area of study leading to a variety of optically active substituted carboxylic acids and lactones. The use of oxazolines as chiral ligands in LAH and grignard reactions at the CO group has been detailed earlier in this paper.

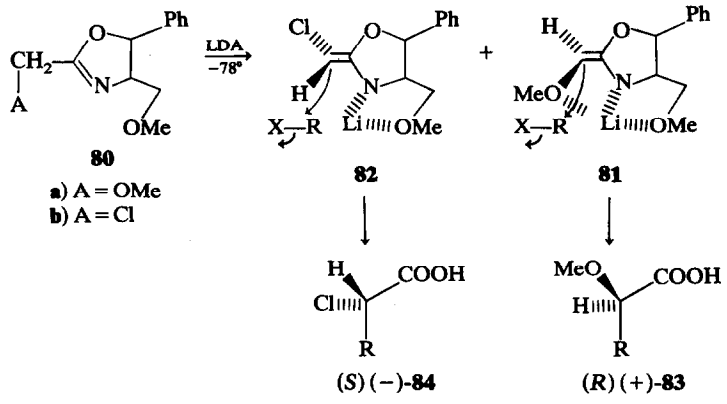
2-Methoxymethyl and 2-chloromethyl oxazolines (**80a/b**) are alkylated to produce 2-methoxy- and 2-chloralkanoic acids (**83/84**) in 42% and 28% e.e. respectively.[150] The oxazolines are converted to their lithio salts and alkylated at −78°. With small alkyl groups (R = Me) the better leaving group (X = OTs) gives best optical yields. With large alkyl groups the leaving group has little effect.

The partial complexation of the 2-OMe group with lithium in the cisoid fashion shown (**81**) is responsible for the reversal in stereochemistry of products here. Chemical yields of products approximate 60%.

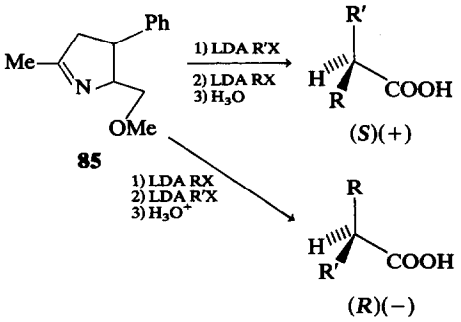
Sequential alkylation of 2-methyloxazoline substrates allows for synthesis of either (*R*)- or (*S*)-enantiomer from a single oxazoline[151] (**85**).

Initially it was found that alkylation with the smallest alkyl halide must precede the larger for good optical yields. The opposite case gives low (<20%) optical yields. Using methyl tosylate or dimethylsulfate for the second alkylation however, allows methylation of the 2-monoalkylated species in 70% e.e.

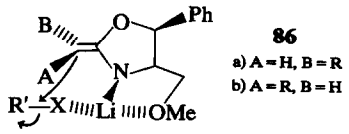
Lithio salts (**86a** and **86b**) are in thermodynamic equilibrium, with **86a** predominating.[152] If R′ is small the $\Delta\Delta G^{\neq}$ between **86a** and **86b** is small leading to low induction. Bulky tosylates and sulfates as mentioned, widen this energy difference by



Scheme 48



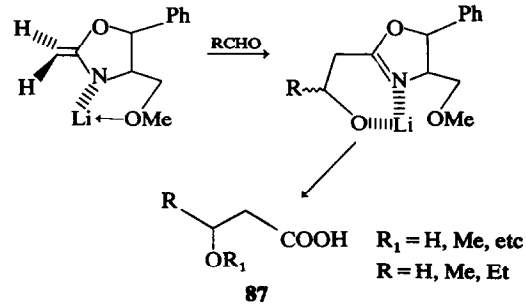
Scheme 49



complexation to lithium via their oxygen lone pairs, leading to better optical yields. Compound **86a**, having fewer non-bonded interactions in the transition state, is alkylated at a faster rate.

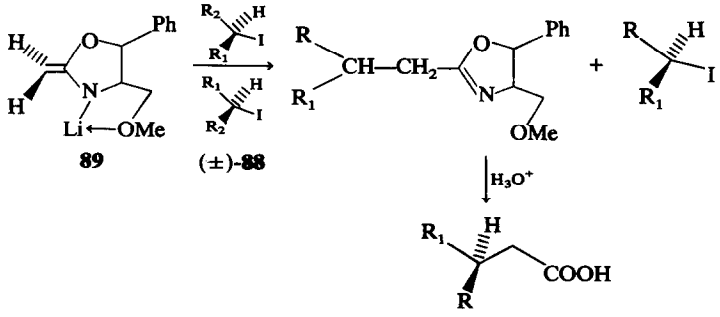
If the group of lower priority (CAHN–INGOLD–PRELOG rule) is introduced first, the (*S*)-acid results. Initial introduction of the high priority group yields (*R*)-acid. These results, the dependence of optical yields of temperature and independence on temperature of metalation indicate it is not the formation of a metalated species (**86**), but the alkylation step which leads to asymmetry. Oxazolines without the phenyl substituent afford much lower optical yields due to competitive β-alkylation.

Condensation of lithio-oxazolines[153] with alkylaldehydes leads to β-alkoxy or hydroxy acids (**67**) in moderate optical yields (20–25).[154] Benzaldehydes are not suitable since the product dehydrates readily to achiral cinnamic acid derivatives.

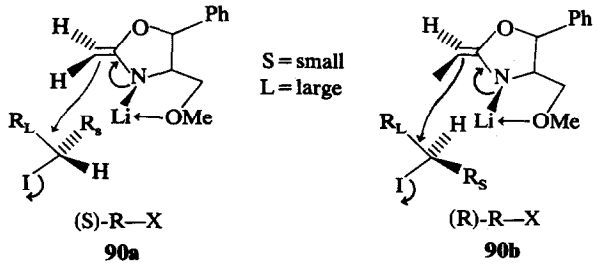


Scheme 50

Chiral oxazolines (**89**) exhibit chiral recognition in the alkylation reaction with racemic alkyl halides (**88**).[155] This is what has been termed a kinetic resolution since the rate of formation of diastereomeric transition states involving each enantiomer of the racemate is different and depending on when the reaction is quenched the antipodal products are formed in unequal amounts. Transition states (**90a** and **90b**) are postulated for (*S*)-halide and (*R*)-halide respectively. Assuming bottomside attack and an alignment of the iodide for backside attack as required for S_N displacements it can be seen that (*S*)-halide can approach the oxazoline with its two smallest groups forward and the smallest (H) towards the two fused 5-membered rings. Compound **90b** has a much less

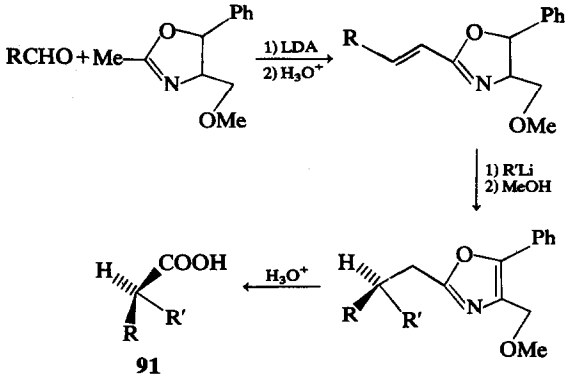


Scheme 51



favourable geometry hence the reaction is slower. The resultant 3-alkanoic acids are produced in up to 90% chemical and 58% optical yields.

Substantially higher optical yields (90–98%) have been realised in the synthesis of 3-alkylalkanoic acids (**91**) via conjugate addition organolithium

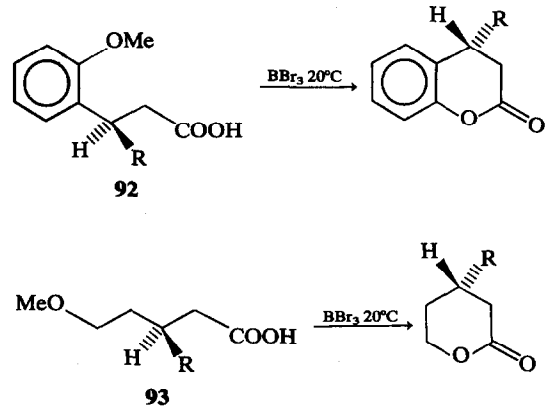


Scheme 52

reagents to oxazolines.[156] Either enantiomer of the acid can be synthesised by interchange of R' and R in the reagents selected for reaction. Chemical yields unfortunately are rather low here falling in the range 30–50%.

By using β-methoxyaldehydes, β-chiral-ω-methoxy acids (ex **92** and **93** may be synthesised.[157] Treatment of these with boron tribromide furnishes the corresponding valerolactones in 80–90% optical yields.

Optically active butyrolactones are readily available from chiral oxazolines as well.[158] Condensation of a lithio-oxazoline (**89**) with ethylene oxide produces lithio salt **94** which is converted to its trimethylsilyl ether, alkylated and hydrolysed to produce **95** in 60–90% chemical and 70% optical yields.



Scheme 53

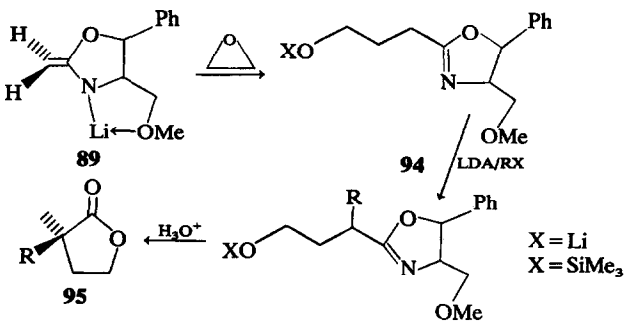
Organolithium addition to achiral aldehydes can be performed asymmetrically by addition of the chiral catalyst[159] (**96**). Optical yields are maintained even when dialkyl carbinols are synthesised in contrast to hydride reduction of ketones. The chiral preference increases with increasing steric bulk of the alkyllithium. The methyl ether of **96** is totally ineffective suggesting that the two pyrrolidine nitrogens plus lithiated hydroxyls are necessary for induction to occur.

Biomimetic cyclisations

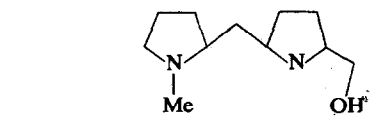
Asymmetric C–C cyclisation reactions are of crucial importance in the synthesis of a wide variety of compounds.

By far the most elegant of these are the biomimetic polyene cyclisations reported by Johnson *et al.*[160]

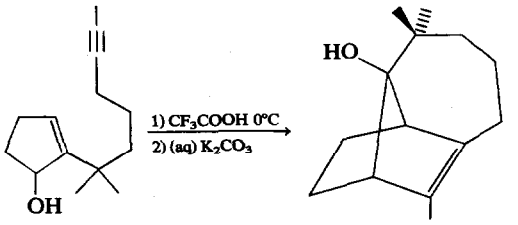
An interesting example involves cyclisation of enynol (**97**) in the synthetic route to longifolene. Chemical yields of **98** are 75%. the cyclisation may



Scheme 54



96



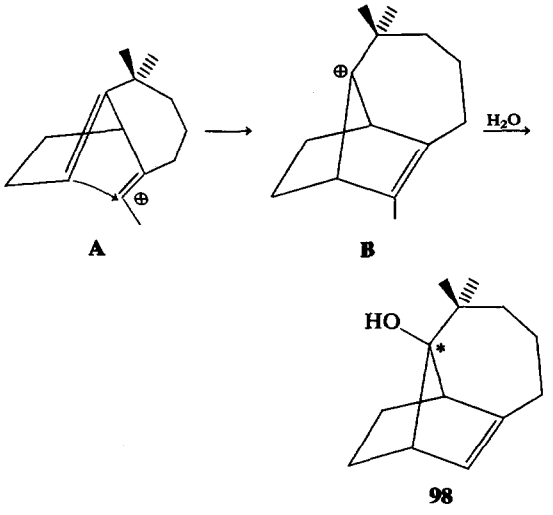
97 98

Scheme 55

Table G. Yields for $2R_1Li + R_2CHO \xrightarrow{96} R_1CHR_2$

R_1	R_2	Chemical yield (%)	Optical yield (%)
CH_3	Ph	82	21(*R*)
CH_2CH_3	Ph	32	39(*R*)
n-Pt	Ph	55	55(*S*)
n-Bu	Ph	60	72(*S*)
n-Bu	i-pr	47	56(*S*)
Ph	n-Bu	46	11(*R*)

be rationalised as follows:

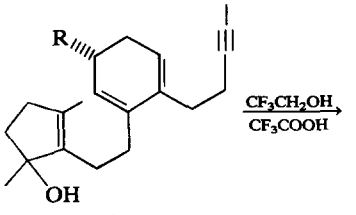


A B 98

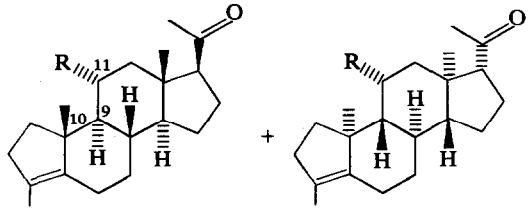
Scheme 56

allylic alcohol (**97**) cyclises to cation **A** followed by intramolecular nucleophilic attack on the vinyl cation by the olefinic bond to render bridged cation **B**. This is an apparent violation of Bredt's rule for orbital overlaps at bridgehead carbon. The authors propose that this destablisation is countered by the stability of the 7-*anti*-norbornenyl system in cation **B**. The same configuration results at the chiral centre irregardless of hydroxyl stereochemistry in **97**. The product formed is 100% optically pure (other than by products) and several minor modifications afford longifolene.

In a study pertaining to the total synthesis of 11-substituted steroids[161] Johnson *et al.*, have reported polyene cyclisation with the stereospecific formation of 6 asymmetric centres in the steroid backbone. Cyclisation of **99** (R = H) is stereospecific giving a racemic mixture of products (**100** and **101**) with a chiral centre at C-11 ($R = Me_3$) two



99



100 101

Scheme 57

tetracyclic C-11 diastereomeric pairs are possible by frontside and backside attack in the cyclisation of C-11 pro-*R* and pro-*S* polyenes.

It was found however that only the 11 α-methyl diastereomer (**100**) plus its enantiomer were formed in 66% yield. The activation energy for the formation of **101** must be significantly higher due to non-bonded interactions of Me groups at pro C-10 and pro C-11 which are diaxial in that transition state.

Polyene **99** is known to undergo facile dehydration prior to cyclisation therefore chirality of the carbinol C atom in **99** does not influence the stereochemistry of alkylation (cyclisation).

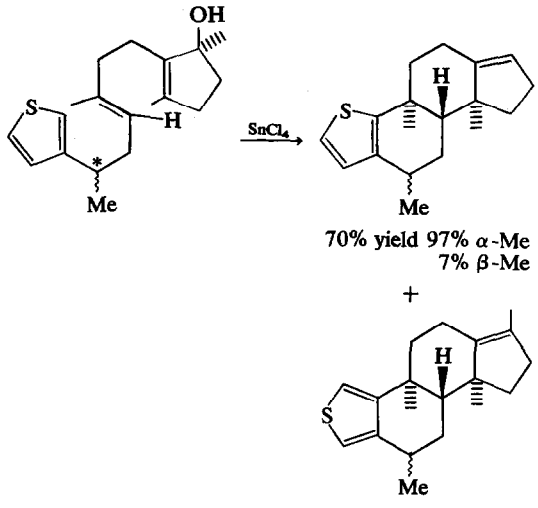
Since a racemic polyene (**94**) leads to a single diastereomeric pair (**100**)† it follows that enantiomerically pure **99** would lead to enantiomerically pure **100** and a total asymmetric synthesis induced by the C-11 centre. The sterospecificity of this reaction was the key to a total synthesis of 11-α-hydroxyprogesterone.[162]

Similar analogues incorporating a thiophene ring as cyclisation initiator cyclise stereospecifically as shown[168] (Scheme 58), to furnish only diastereomeric pair due to interaction of the pro-C_5 methyl with pro-C_7 and C_9 protons which allows only one mode of precyclisation coiling.

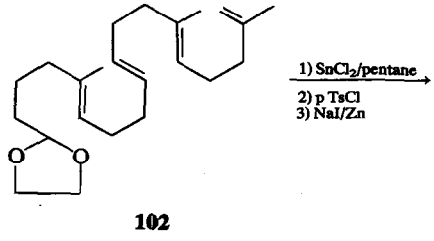
In studies on acyclic polyterpenes Johnson *et al.*,[164] achieved cyclisation of tetraenic acetal (**102**) to 4α- and 4β-hydroxy tetracycles (**103**) having the D-homosteroid nucleus configuration (*trans, anti, trans, anti, trans*). Again six asymmetric centres are stereospecifically formed in one step with 24% yields.

Similarily trienol (**104**) cyclises with total stereospecificity to furnish natural configuration products

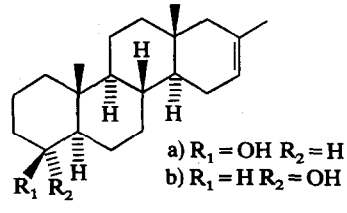
† Only one enantioner of a racemic pair is shown.



Scheme 58

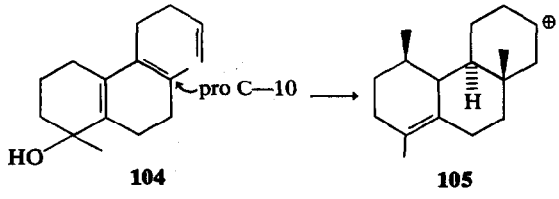


102



103

Scheme 59

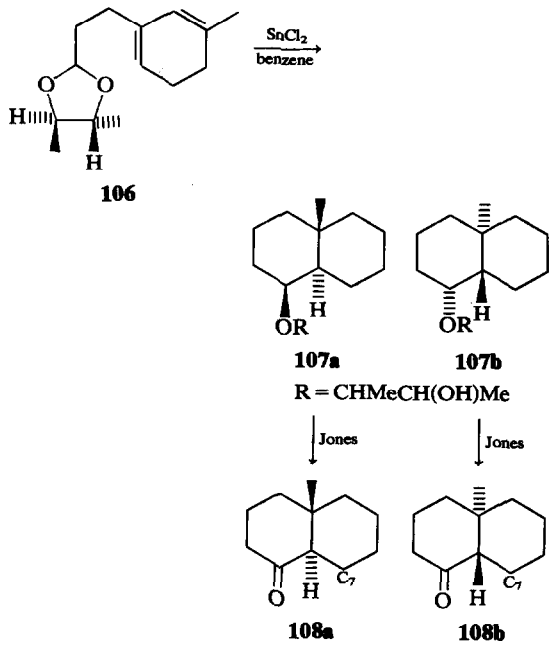


104 **105**

Scheme 60

derived from cation **105** only. It was anticipated here that again the 1,3 diaxial Me interaction might suppress stereospecificity of the cyclisation but such is not the case. Yields (66%) are lower than those for the cyclisation of a polyene not bearing the pro-C_{10} Me (93%) presumably due to this interaction. These products are stereospecific with respect to the relative configurations of asymmetric ring junctions, however the products are racemic.

In an attempt to simulate[166] enzymatic processes in the production of enantiomerically pure substances the optically pure acetal (**106**) derived from (−)2,3-butanediol was cyclised to afford hydroxy



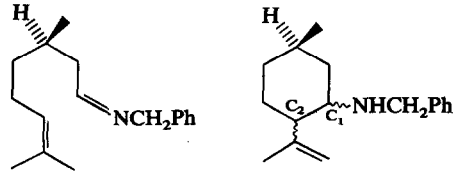
Scheme 61

ethers (**107a** and **107b**). Side chain cleavage and subsequent oxidation yielded epimeric **108a** and **108b** in 92% and 8% yields respectively (84% optical yield).

The exact nature of the transition state is not certain but it is probable that the acetal retains its cyclic nature here. One of the chiral centres may interact (non-bonded) with at least one proton on C_7.

For a review of the principles and techniques of these and other biomimetic cyclisations see ref. 167.

In addition to acetals and allylic alcohols the imines function is capable of inducing cationic polyene cyclisation.[168] β-Asymmetric induction can occur at the imine carbon via a chiral centre in the hydrocarbon skeleton (Scheme 62A) or a chiral substituent on nitrogen. The higher optical yields in Scheme 62A may be due to the position of the chiral centre or the fact that two chiral centres are created simultaneously.

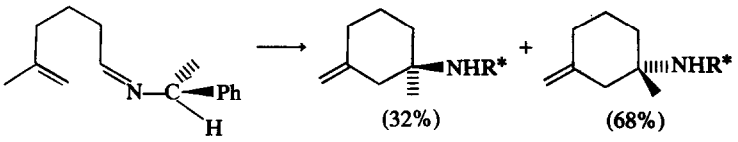


	% α	% β	% e.e.
C_1	82%	18%	64%
C_2	91%	9%	82%

Scheme 62A

Aldol reactions

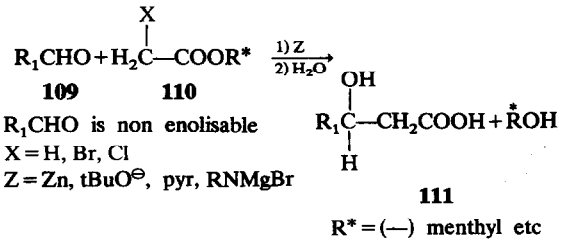
The aldol condensation is perhaps the most important cyclisation reaction in the field of organic synthesis and natural product chemistry, however



Scheme 62B

there are relatively few cases where the inducing chiral centre can be removed from the molecule. Consequently asymmetric aldol reactions have not been extensively studied.

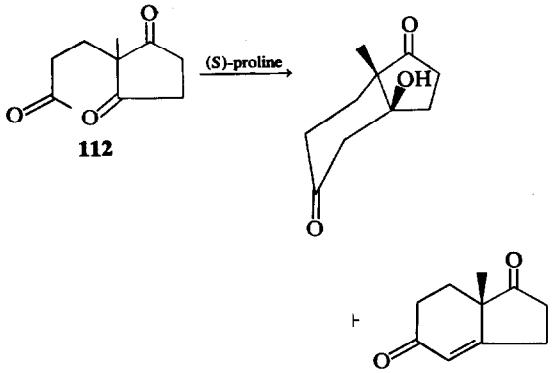
Several reactions of acyclic species represented by the sequence **109**+**110**→**111** have been



Scheme 63

studied for their asymmetric properties (See ref. 1, p. 142). Included are malonic ester, aldol, Reformatskii and Darzens reactions. Optical yields as high as 90% have been obtained but typical values lie in the range 20–30%.

Catalytic amounts of (*S*)-(−)-proline effect aldol cyclisations in 100% chemical and 93% optical yields on **112** with a reflective symmetry axis.[169]

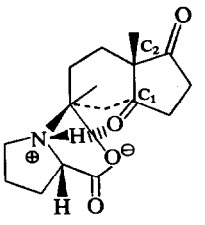


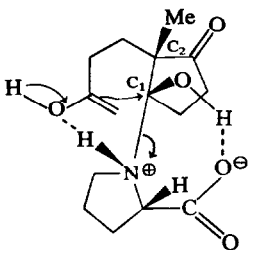
Scheme 64

The quaternary meso C is converted to an asymmetric C upon cyclisation.

The reaction proceeds in alcoholic solvent with optical yields in proportion to the polarity of the alcohol alkyl portion (ETOH 27.6%, t-BuOH 83.7%) however polar aprotic solvents give better chemical yields (MeCN − 85% optical purity, 100% chemical yield, DMF 93.4% optical purity, 100% chemical yield). These are suspected to provide less interference in the H-bonded transition-state. Various other optically active amines have been used, but give poor results due to insolubility and/or unreactivity towards the ketone.

Of the two mechanisms suggested, that leading to transition state (**113**) seems less likely since no ^{18}O label was incorporated from labelled water as would be required in formation of the protonated enamine.



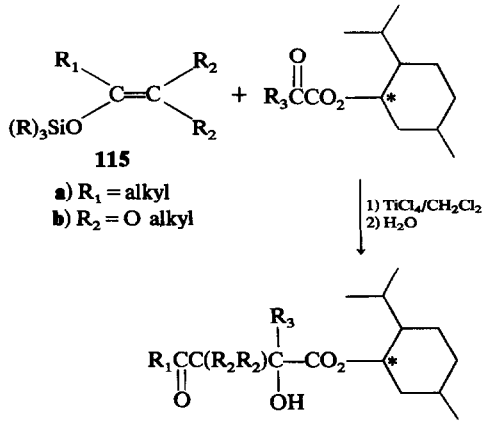


A more plausible mechanism involves addition of (*S*)-proline in its zwitterionic form to one of the ketones of the cyclopentanedione ring to form **114** in which the proline chiral centre is only 2 bonds away from C_1 and 3 from C_2 as opposed to 4 and 5 bond separations in **113**. Only catalysts having two separate functionalities capable of good H-bonding give good optical yields ((*S*)-proline 93.4% e.e., (−)-*trans*-4-hydroxyproline 73.1%, *S*(−)azetine carboxylic acid (63.9%)) again lending support to **114**.

Solladié *et al.*, have studied[170] aldol condensations between (−)-menthyl acetate and several alkyl phenyl ketones. The asymmetric inductions (R = Me 58% e.e., Et 58% e.e., i-pr 48% e.e., t-Bu 42% e.e.) vary with the nature of R. A single recrystallisation of crude product raised the optical yields by as much as 40%. Optical yields increased with a decrease in temperature down to 0° then remain constant.

Optical yields here are reasonable and might be improved substantially by varying the chiral alcohol.

Titanium tetrachloride promoted cross-aldol reactions of silyl enol ethers (**115a**) and silyl ketene acetals (**115b**) with chiral ketone substrates shows

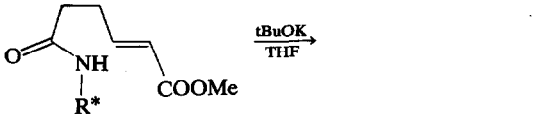


Scheme 65

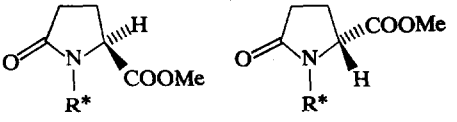
much promise for the asymmetric generation of highly functionalised carbinols.[171] Chemical yields are excellent (80–100%) and optical yields as high as 68% (average 45%) making this type of condensation a most valuable synthetic tool.

Other cyclisations

Asymmetric cyclisations in up to 56% e.e. have been reported in the intramolecular 1,4-addition of chiral amide anion to the unsaturated ester function in **116**.[172] A more polar solvent which would increase the dissociation of the $R_1R_2N^-K^+$ system



116



(favoured)

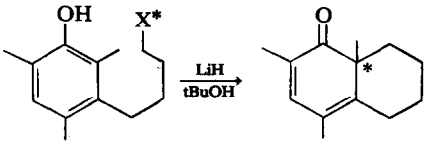
R* = S(−) phenyl ethyl

Scheme 66

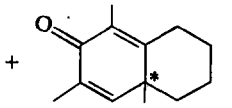
decreases the diastereoselectivity considerably hence a close association here must play a key role. Repulsion between amide carbonyl and the phenyl group may suppress free rotation about N—R* providing a rigid conformation for asymmetric induction. The cyclisation rate is very fast due to entropy factors involved in 5-membered ring formation.

Recently asymmetric induction has been noted in the intramolecular alkylation reaction of phenols (**117**)[173] which proceeds via the so called Ar_2^- 6 mechanism in which the chiral leaving group is present in the transition state. The ortho alkylated product (**118**) is predominant and exhibits a $Eu(Fdc)_3$ shift corresponding to 19% e.e. The optical purity of **119** approximates 12.5%.

Since the leaving group is still present, the transition states from attack above or below the phenox-



117 **118**



119

X* = (+)camphor-10-sulphonyloxy 8.9:1.0 ratio

Scheme 67

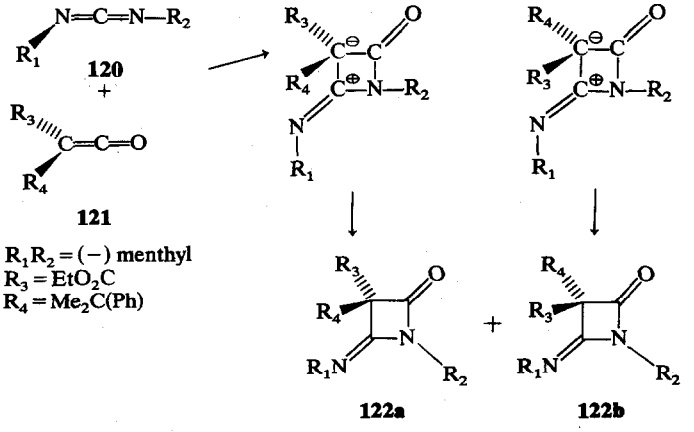
ide ring are diastereomeric in this reaction. A comparison of these demonstrates a substantial variance in the steric interaction responsible for product enantiomeric excess.

Intermolecular alkylation by allyl (+)-camphor-10-sulphonate afforded *ortho* alkylated products in 8.4% optical yields.

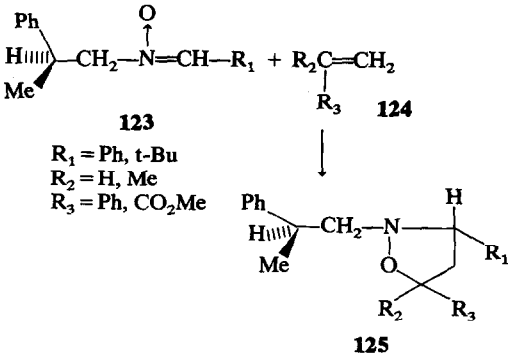
Diels–Alder and other related cycloadditions are important means of obtaining cyclic products as well. The principles of asymmetric induction have been applied to these reactions with quite some success. (See ref. 1, p. 252).

Polish workers have recently reported two cycloadditions with excellent asymmetry properties. The first involves cycloaddition of chiral carbo-diimide (**120**) with prochiral ketene (**121**) to furnish diastereomeric β-lactams (**122 a/b**).[174] The reaction proceeds via an ionic mechanism as shown, with ring closure and chiral centre formation. The slowest steps providing non-racemic (**122a**) in 75% yield. The geometry of the transition state closely resembles that of products, consequently steric interactions between R_1 and the ionic prochiral centre are responsible for the selectivity reported. Other di-imide substituents give lower yields and 3 to 30% of **122**.

The same group reported asymmetric 1,3-dipolar cycloadditions of chiral nitrones (**123**) to prochiral olefins to yield diastereomeric non-racemic 2,3,5-

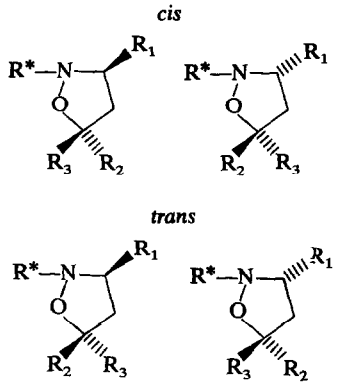


Scheme 68



Scheme 69

substituted iso-oxazolines (**125**).[175] The reaction produces two sets of diastereomers resulting from *cis* and *trans* addition with respect to the largest substituents R_1 and R_3 within each pair a maximum of 75% e.e. was obtained for *cis* and 100% e.e. for *trans* addition, however chemical yields were 75/25



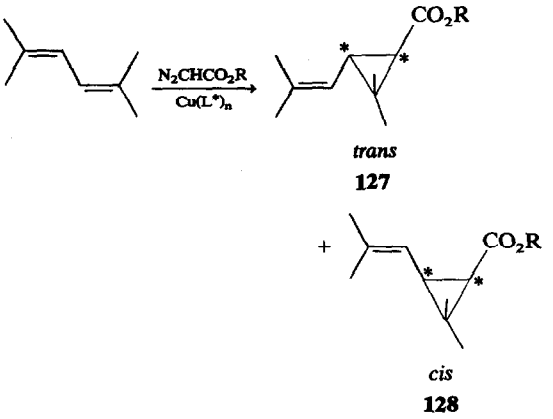
in favour of *cis* addition. Optical yields are excellent in each case nevertheless.

Various methods of asymmetric cyclopropanation have been attempted with mixed results. Chiral sulfonium ylides (maximum 30% e.e.) and Simmons–Smith reagents (9.3% e.e.) have been successfully employed but it seems that cyclopropanation via diazoalkanes in the presence of chiral copper(II) or cobalt(II) complex catalysts is more effective.

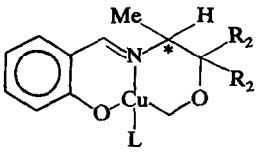
2,5-Dimethyl-2,4-hexadiene has been cyclopropanated using catalytic amounts of (*S*) **126** (1 mol %) and ethyldiazoacetate.[176] It is suspected that the diazo compound decomposes in solution, displacing the ligand (L) from the catalyst rendering the active chiral species. The process gives approximately a 50/50 mixture of *cis*/*trans* ethyl chrysanthemate with optical yields of 68% for the *trans* and 62% for the *cis*-isomer.

Higher optical yields are obtained generally, on a variety of olefinic substrates upon reaction with diazoalkanes in the presence of bis[(−)-camphorquinone-α-dioximato] cobalt[177](II). The ligands are bidentate, reducing ligand dissociation and precluding any rotation of the metal-ligand bond. Optically active cyclopropanes are obtained in good optical yields and chemical yields of 80–95%.

Hydrolysis and recrystallisation raises the optical



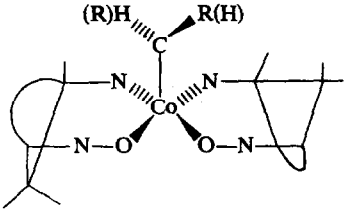
Scheme 70



S-**126** R_2 = 5-t-butyl-2-octyloxyphenyl
L = pyridine

purity to 100% in most cases. The reaction is regioselective to a terminal double bond in conjugation with an aryl, carbonyl or olefinic function but does not work with allenes or acetylenes.

The reaction rate depends on the concentrations of both the diazoalkane and catalyst and approaches first order with respect to olefin at low centration (<3 M). The fact that nitrogen is evolved in the absence of olefin suggests formation of a metal-carbene complex such as **129** via complexation of Co to C and elimination of N_2 A similar



complex has been suggested previously for reactions of ethyldiazoacetate with octaethylporphinatocobalt(II).[178]

AMINO ACIDS

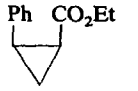
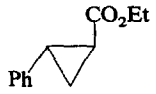
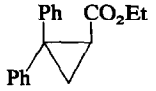
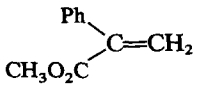
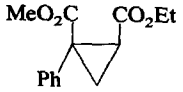
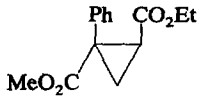
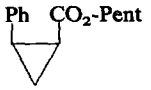
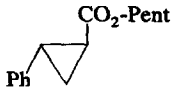
Substantial quantities of optically active amino acids are used in the drug industry and as building blocks for peptides in medical science and biochemistry. In recent years increased interest in sources of nutritional protein has made the asymmetric synthesis of amino acids an area of vital concern.

Several approaches have been successful and these are catalogued below. For reviews of amino acid synthesis see ref. 179.

(i) *Hydrogenations*

Early attempts at asymmetric hydrogenation employed heterogeneous catalysis on silk fibroin or

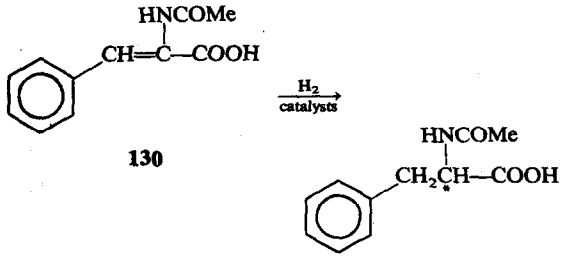
Table H. Asymmetric cyclopropanations with ethyl diazoacetate in the presence of Co(α-cqd)2·H_2O[d]

Olefin[a]	Product	Chemical[b] yield (%)	Optical yield (%) (config.)
PhCH=CH_2		92	67(1S, 2R)
			75(1S, 2S)
Ph_2C=CH_2		95	70(1S)
		92	37(1R, 2S)
			71(1S, 2S)
Ph—CH=CH_2[c]		87	81(1S, 2R)
			88(1S, 2S)

[a] reactions performed in each neat olefin.
[b] based on the diazoacetate.
[c] using N_2CO_2-neopentyl.
[d] from ref. 177.

Rani Ni in alkaline glucose solution. Stereoselectivities of up to 70% have been reported but results in general have been disappointing.

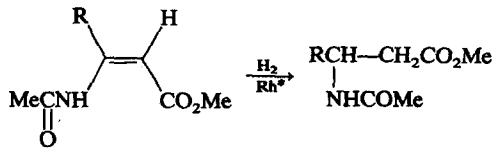
Homogeneous hydrogenation of α-acetamidocinnamic acids (**138**) with hydrogen and soluble chiral rhodium complexes furnishes 90% e.e. of N-acetyl-phenylalanine (**131**).[181]



130 **131**

Scheme 71

β-amino acids are of interest because of their occurrence as a component of peptide antibiotics and their structural similarity to the β-lactam function. These are readily available in moderate optical yields (7–55%) by catalytic hydrogenation of olefinic substrates (**136**) using chiral rhodium catalysts complexed with N-substituted bisphosphino-



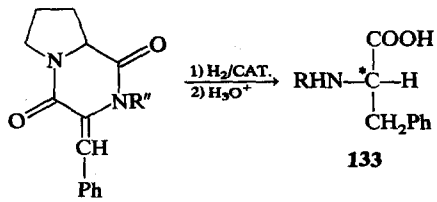
136

Scheme 72

pyrrolidine ligands.[181] Chemical yields are generally excellent (88–100%).

The hydrogenation of C=N bond in achiral substrates was studied but stereoselectivity was poor and the approach has received little attention recently.

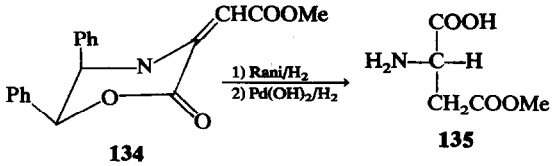
Hydrogenations of diketopiperazines (**132**) and subsequent hydrolysis furnishes 90% optically pure phenyl alanine derivatives.[182]



132 **133**

Scheme 73

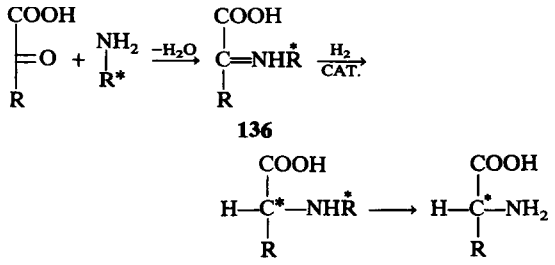
Rani nickel hydrogenation of oxazine derivatives (**134**) and subsequent hydrolysis gives [*S*]-(+)-aspartic acid monomethyl ester (**135**) of 98% optical purity in quantitative chemical yields.



134 **135**

Scheme 74

Chiral ketimines (**137**) are also good substrates for asymmetric hydrogenation. (*S*)-alanine has been synthesised in 60% optical yields via this method.[183] The auxiliary chiral amine (R*) is removed by hydrogenolysis in neutral medium without racemisation of the chiral centre.

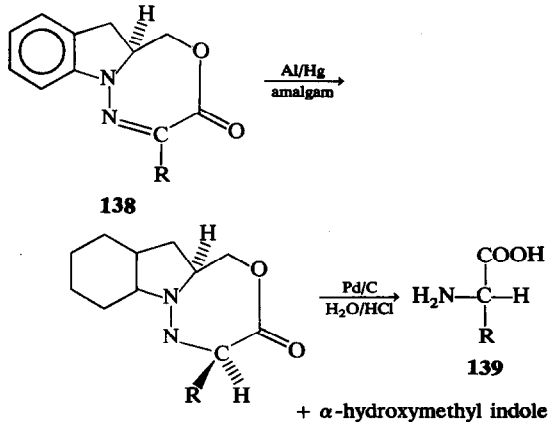


R* = α-phenylethylamine, α-phenylpropylamine

Scheme 75

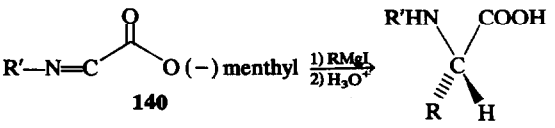
Hydrogenation of chiral menthyl esters of achiral imines leads to products of low optical purity due to the large distance between prochiral and auxiliary chiral centres.[184]

High optical yields (80–90%) have been realised by Corey *et al.*, in the hydrogenation of hydrazonolactones (**138**). Hydrogenolytic splitting of the N–N linkage affords correspondingly pure amino acids (**139**).[185] The method's drawback lies in the synthesis of **138**, a difficult preparation.



Scheme 76

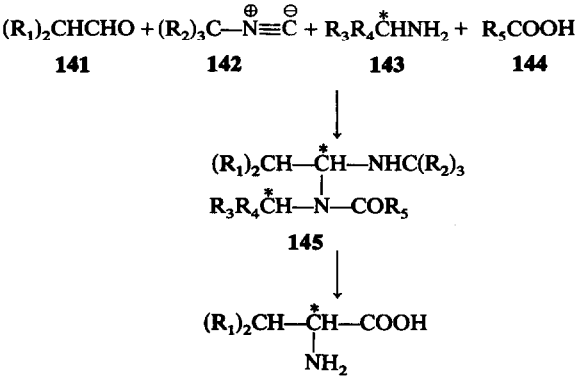
Kagan *et al.*,[186] obtained up to 63% e.e. in the synthesis of (*S*)-amino acids in the valine and alanine series by addition of Grignard reagents to (−)-menthyl esters of glyoxylic imines (**140**).



140

Scheme 77

The four component Ugi synthesis is most interesting.[187] An aldehyde (**141**), isonitrile (**142**) carboxylic acid (**144**) and chiral amine (**143**) are reacted to yield intermediate **145**. Hydrolysis and hydrogenolysis of **145** affords the desired amino acid.

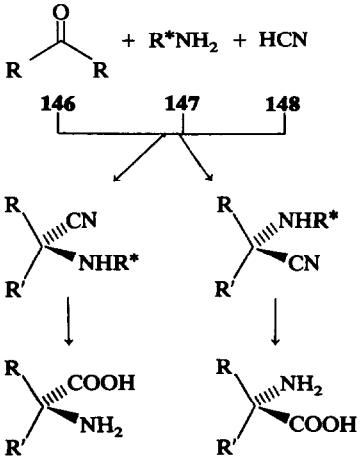


Scheme 78

Two diastereomers of **145** are formed and the configuration of the new chiral centre depends on concentration, solvent, temperature and configuration of the chiral amine used. Optical yields in the range 70–75% are typical.

The synthesis of amino acids from a carbonyl compound, an optically active amine and hydrogen cyanide is known as the Strecker synthesis.

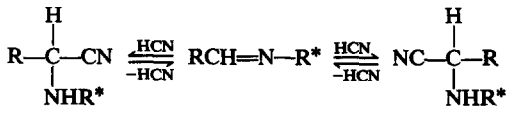
It is not certain whether **146** and **148** react to give enantiomeric cyanohydrins which then react with amine or whether **146** and **147** react to form the ketimine to which hydrogen cyanide is added asymmetrically.



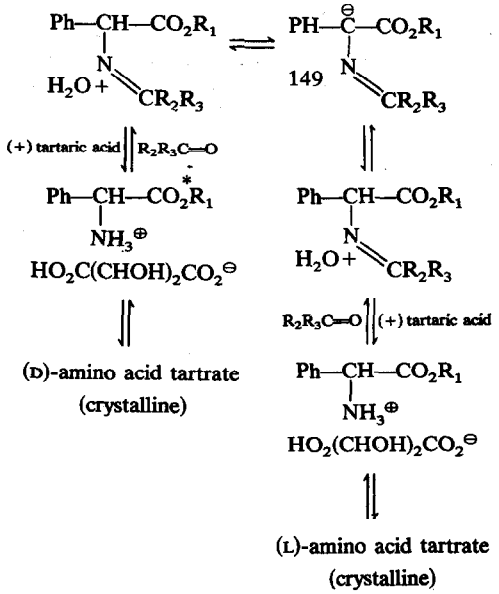
R = α-phenylpropylamine,
α-naphthylethylamine,
α-phenylglycine

Scheme 79

Optical purities of 100% have been achieved in the addition reaction of HCN to the preformed imine. A thermodynamic equilibrium may be responsible as shown (Scheme 80). Preferential crystallisation of one diastereomer shifts the equilibrium, resulting in high optical yields.



Scheme 80



Scheme 81

Such an equilibrium is apparent in the asymmetric formation of amino acid tartrates from the Schiff bases (**149**).[189] Stirring benzaldehyde, (+)-tartaric acid in an ethanolic solution of the DL-amino acid gives, for phenylglycine, an 85% yield of the optically pure amino acid salt.

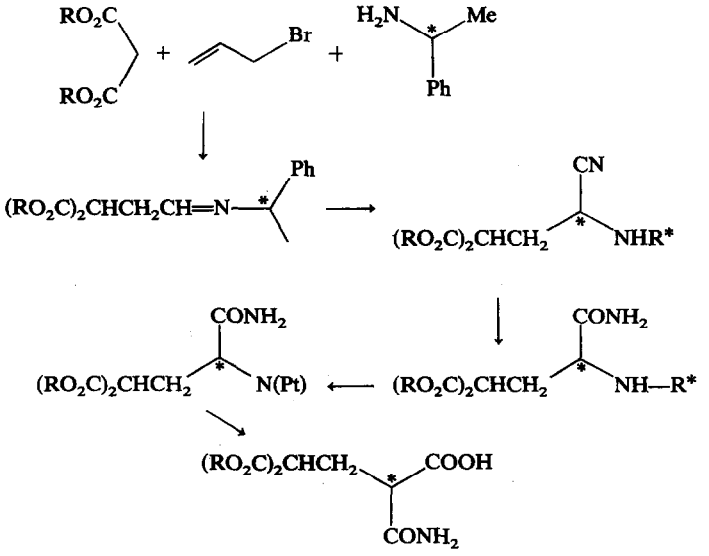
The Schiff base, present in equilibrium amounts, is easily racemised since its anion is triply stabilised. The solution equilibria do not effect asymmetry directly. It is the reprotonation step during which the thermodynamically favoured tartrate diastereomer is formed preferentially and crystallises.

Amino acids without an α-phenyl group give lower optical yields and require longer reaction times.

Recently a modified Strecker synthesis has been used to prepare $\gamma\gamma$-di-t-butyl-L(−)N-pthaloyl-γ-carboxyglutamate (**150**) with almost 100% optical purity.[190] Transamination reactions where an amino group is transferred from an α-amino acid to an α-keto-acid asymmetrically under the influence of an enzyme and pyridoxal phosphate are well known *in vivo* (ref. 1, p. 303).

Recently Yamada *et al.*, have obtained 70% optical yields in direct chemical transamination reactions.[191] Reaction of methyl pyruvate (**151**) with L-amino acid t-butyl ester (**152**) gives the Schiff base (**153**) which was hydrogenated to give **154** with a new chiral centre at the previous carbonyl carbon via 1,3-asymmetric induction. Selective hydrolysis of the t-butyl ester and oxidative decarboxylation with t-butyl hypochlorite gives imine **155** which is hydrolysed to furnish (L)-alanine **156** and the aldehyde. Overall chemical yields are in the range 55–60%. Similar studies using optically active benzylamine derivatives have been reported.[92]

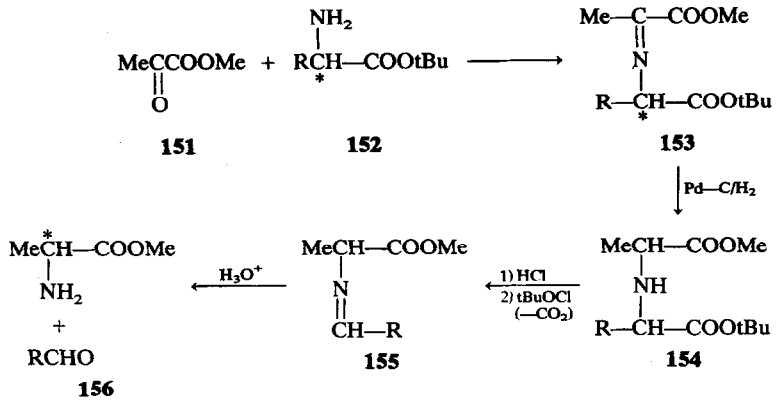
In the novel approach[193] α-keto acids (**157**) are coupled with (*S*)-proline methyl ester (**158**) to give N-α-ketoacyl derivatives (**159**). These are cyclised in the presence of dry ammonia to afford 5-α hydroxy dioxopiperazines (**160**). Dehydration and



Pt = phthaloyl

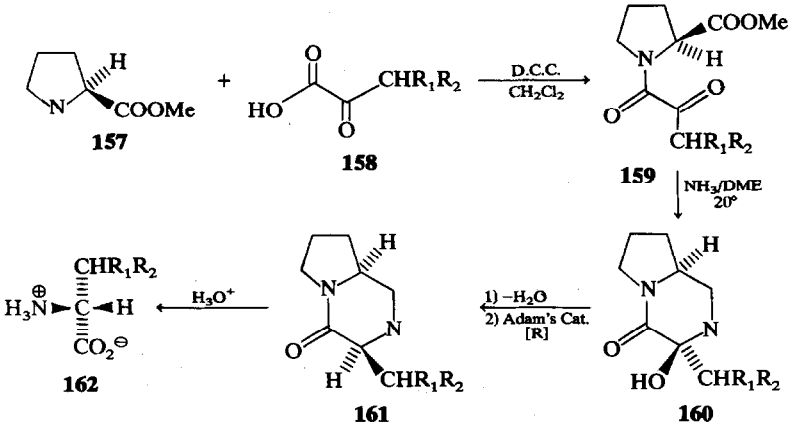
150

Scheme 82



Scheme 83

hydrogenation with Adam's catalyst gives the (*S,S*)-cyclo-dipeptide (**161**) which upon acid hydrolysis gives the amino acid zwitterion (**162**) and L-proline.

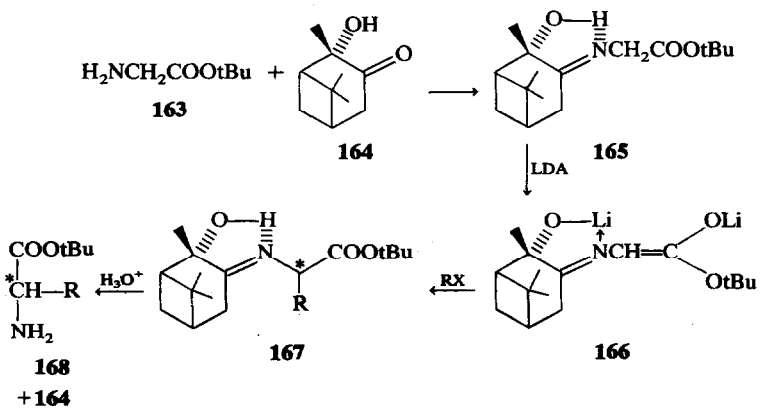


Scheme 84

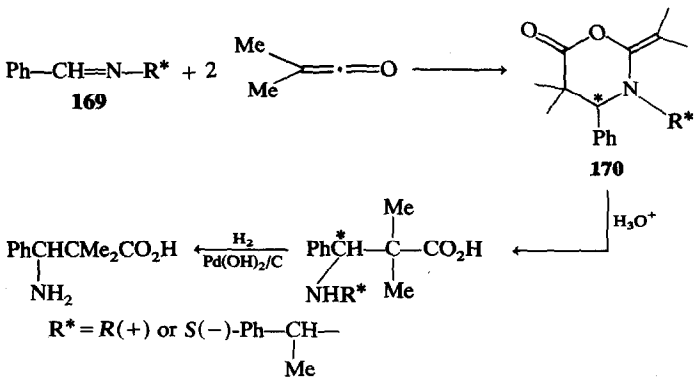
Optical yields are over 90% ($R_1 = R_2 = H$) for alanine. Several other amino acids are available by this route.

Recently alkylation of chiral Schiff's bases has been accomplished to produce α-amino acids in 75–85% e.e.[194] Condensation of glycine t-butyl ester (**163**) with 2-hydroxypivan-3-one (**164**) gave ketimine **165** which was lithiated and alkylated. Compound **167** was then hydrolysed to the amino acid t-butyl ester (**168**) and recovered chiral reagent (**164**).

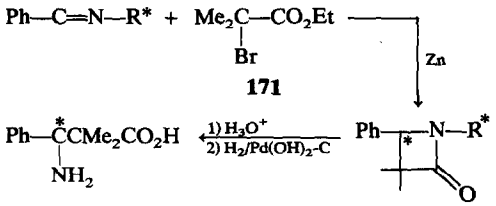
Optically active amino acids result from reaction of chiral Schiff's base (**169**) with achiral dimethyl ketene or the achiral Reformatskii reagent (**171**).[195]



Scheme 85



Scheme 86



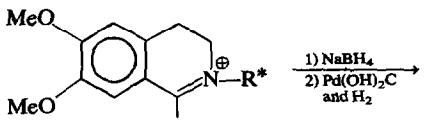
Scheme 87

In both cases the chiral nitrogen substituent induces asymmetry upon cyclisation.

In Scheme 86 the oxazinones (**170**) are isolated in 56–68% chemical yields after 0.5 hr in Me_3CN solution. Overall chemical yields are 30% with 50% e.e. Corresponding chemical and optical yields for Scheme 87 are 35% and 36% respectively.

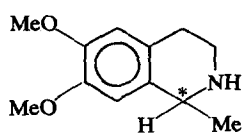
Asymmetric reactions of Schiff's bases, in addition to amino acid related syntheses have played a prominent role in several other syntheses.

Kametani *et al.*,[196] employed a sodium borohydride reduction of chiral imine (**172**) in an asymmetric synthesis of the alkaloid salsolidine. Use of (*S*)(−)R* gave (*S*)(−)-salsolidine and (*R*)-(+)-R* gave (*R*)(+)-salsolidine. Best results were obtained with **172b** (36–44% e.e.)



R* = **a**) (S)(−) -α-ethyl benzyl
b) (−)(S) -α-methyl benzyl
c) (−)(S)-1-(1-naphthyl)ethylamine

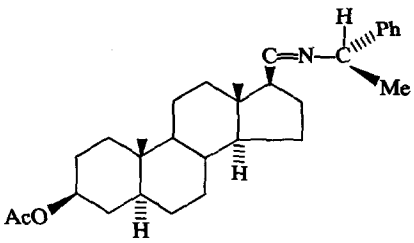
172a–c



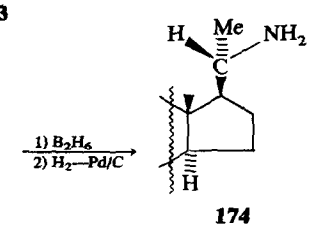
Scheme 88

Similar reduction of steroid derivative **173** afforded, after hydrogenolysis, 84% optical yields of the amino compound **174**.

Asymmetric induction has also been reported in the oxidation of Schiff's bases with chiral substituents on nitrogen by MCl—PBA.[198] Optical yields of the resultant oxaziridines are in the range 70–95%.



173



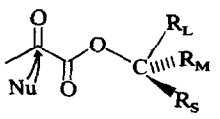
174

Scheme 89

α- AND β-HYDROXY ACIDS

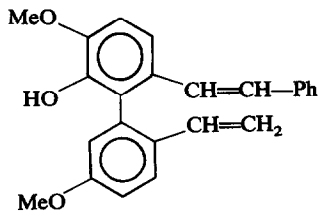
Asymmetric synthesis of α-hydroxy acids has been of interest since the work of Kipping and of Cohen and Wheatley was published in 1900.[199]

In asymmetric nucleophilic additions to chiral alcohol esters of keto-acids the aforementioned Prelog generalisation and Cram Rule of Asymmetric Induction apply as shown below and the same limitations apply. The nucleophiles commonly used are hydride or Grignard reagents.



175

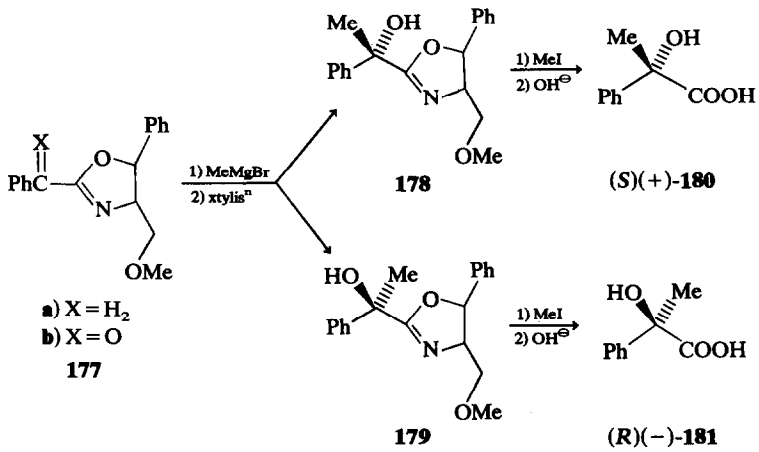
The classic case is the atrolactic acid synthesis where **175** (R = pH) is methylated with MeMgI and the ester hydrolysed under mild conditions. Several optically active alcohols have been used to induce asymmetry, such as (+)-3,3-dimethyl-2-butanol (24% e.e.) 1,2:5,6-di-O-isopropyldene-α-D-glucofuranose (33% e.e.), epi-catechin tetramethyl ether (43% e.e.), (−)-dinaphthoyl carbinol (astropisomeric



(R)-(+)-176

Recently allytrimethylsilane was reported to add to (−)-menthyl esters of pyruvic acid **182** (R = Me) and phenyl glyoxalate **182** (R = Ph) in optical yields ranging from 16 to 55%.[200] In contrast to the usual nucleophilic addition, the phenyl group causes inferior optical yields in this case. Chemical yields are excellent for all substrates.

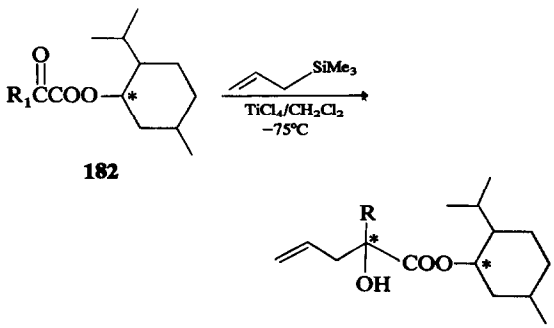
The reduction of chiral and achiral α-keto esters (**183**) with chiral and achiral Hantzsch esters (**184**) is an excellent system for obtaining α-hydroxy[201]



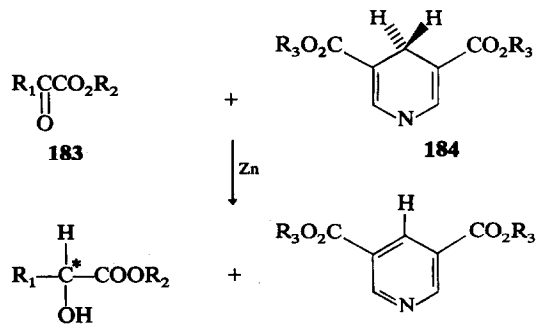
Scheme 90

chirality − 20% e.e.) and the biphenyl **176** (atropisomeric chirality − 93% e.e.). Hydride additions generally result in lower optical yields presumably due to the lower steric requirement of this nucleophile. α-keto acid amides from chiral amines have also proven to be good substrates for asymmetric addition of nucleophiles.

An excellent synthesis of chiral α-hydroxy acids from chiral 2-benzyl oxazolines (**177a**) has been outlined by Meyers and Slade.[20] Compound **177a** is oxidised with molecular oxygen and treated with MeMgBr at −78% to produce equal amounts of diastereomeric **178/179** which are easily separated by crystallisation. Alkaline hydrolysis affords the respective atrolactic acids (**180**; 93% e.e.) and (**181**; 99% e.e.). Since this is a resolution rather than an asymmetric synthesis chemical yields of each enantiomer are low but nevertheless enantiomerically pure compounds are available.



Scheme 91



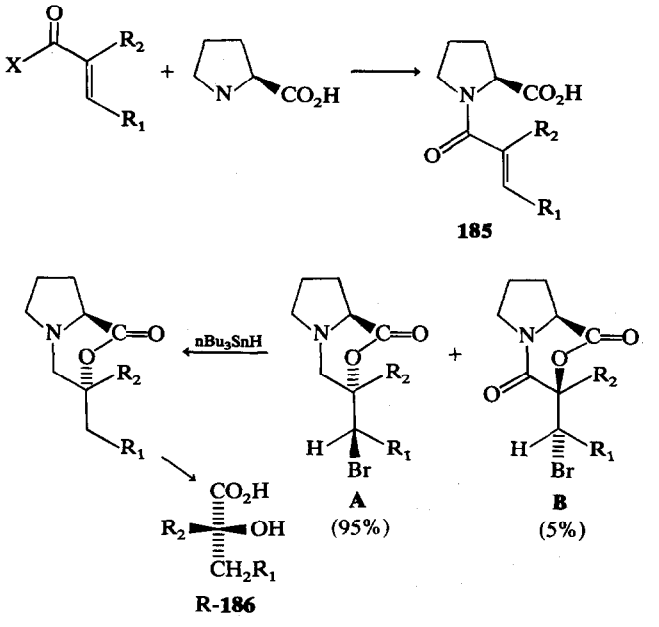
$R_1 = Me, Ph \quad R_2 = Me, (-)menthyl \quad R_3 = Et, (-)menthyl$

Scheme 92

acids in high optical yields. Best results are obtained when both moieties are chiral (70–78% e.e.) whereas chiral **184** with achiral **183** (8–21%) and *vice-versa* (15–47%) provide less induction. Chemical yields can be increased by addition of *p*-t-butylcatechol but the stereochemistry remains unaffected.

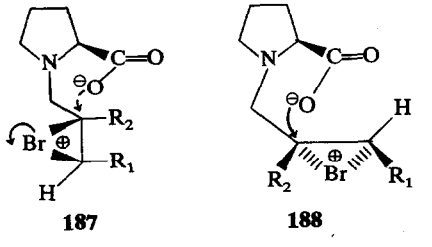
It has been proposed[170] that the Zn atom binds the Co and dihydropyridine functions, stabilising the transition state via chelation. This parallels the function of the Mg ion in the closely related NAD(P)H reducing systems found *in vitro*.

A novel approach to α-hydroxy acids takes advantage of an asymmetric intramolecular halolactonisation reaction of the N-substituted proline[202] (**185**). The halolactonisation proceeds in a trans fashion giving two diastereomers (**A** and **B**) from which optically active *R*(−)-2-hydroxy-2-methylbutyric acid (**186**) ($R_1 = R_2 = Me$) is obtained in 85% e.e.



Scheme 93

The stereospecificity is attributed to either α-attack of the carboxylate anion on the *S-cis*-bromonium species (**187**) or β-attack on the *S-trans*-conformer (**188**).

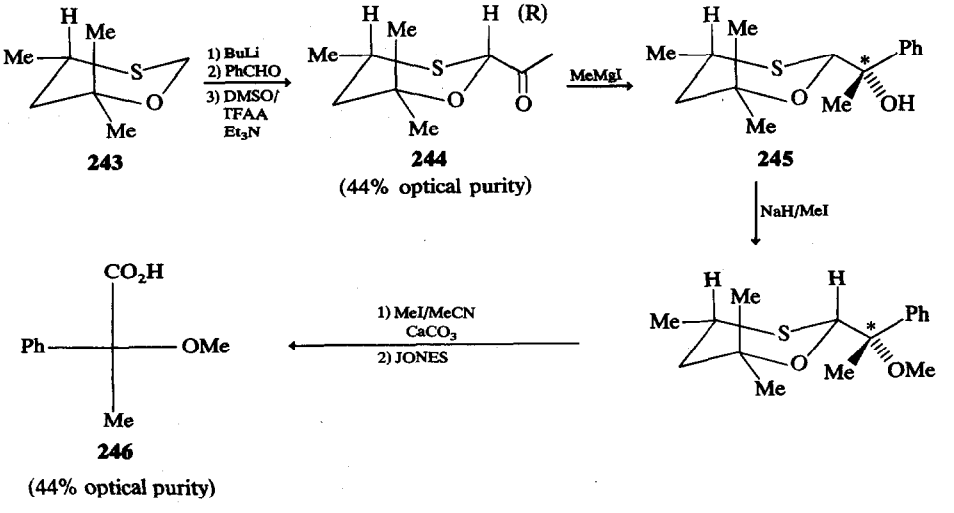


187 **188**

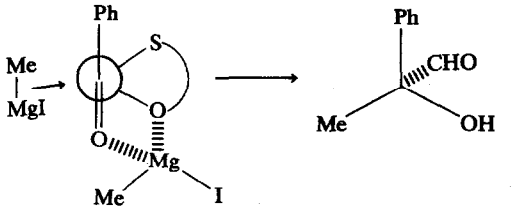
Atrolactic acid methyl ether (**246**) has been synthesised with almost 100% chiral transmission by alkylation of 1,3-oxathianes (**243**).[204] Condensation of **243** with benzaldehyde followed by Jones oxidation furnishes **244** in 44% optical yield with no trace of axially substituted product. Reaction with the methyl Grignard reagent, etherification oxathiane hydrolysis and Jones oxidation gives atrolactic acid in 44% optical purity.

The Grignard magnesium (hard acid) complexes simultaneously with the ketone oxygen and oxathiane oxygen (hard base) rather than the sulphur (soft base). The rigid complex (**247**) is alkylated from the least hindered side (Crams rule, hydrogen *vs* sulphur bulk) only. The Grignard reaction is totally stereospecific as none of the diastereomer of **245**, which is epimeric at the carbinol carbon is formed.

The chirality of the chiral oxathiane is retained in the (−)-4-mercapto-4-methyl-2-pentanol obtained upon ring hydrolysis and the reagent can in principle be regenerated.



Scheme 93a



247

SULPHUR REAGENTS

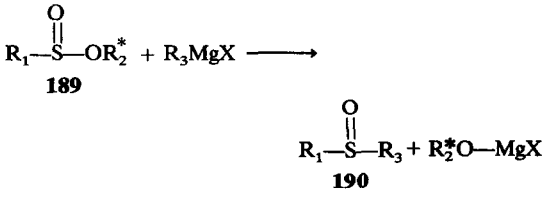
Substituted tri-coordinate sulphur compounds such as sulphinates, sulphoxides and sulphilimines are capable of exhibiting optical activity. This section will deal with recent efforts regarding the synthesis of these in optically active forms and their use as chiral inducing agents in the formation of chiral C atoms.

Original efforts to prepare chiral sulphoxides utilised chiral oxidising agents such as (+)-monopercamphoric acid or (+)-perhydroatropic acid to oxidise unsymmetrical sulfides. Optical yields in general were poor (0–10%) primarily since the oxidising centre is quite removed from the chiral centre in the peracid.

Microbial oxidation[205] provides excellent results when at least one sulphide substituent is aromatic (75–100% e.e.) and lower values for dialkyl sulphides (10–35%). A kinetic resolution of racemic sulphoxides by microbial oxidation to sulphones has also been reported[206] in 5–43% e.e.

Recently t-butylhydroperoxide oxidation of sulphides catalysed by $Vo(acac)_2$ and $(Mo(acac)_2$ in optically active alcoholic solvent has been reported to give sulphoxides in up to 10% e.e.[207] Alcohols used include (−)-2-octanol, (−)-menthol and (−)-borneol. These are proposed to enter into the co-ordination sphere of the metal catalyst to influence the nature of the transition state.

It has been known for quite some time that reaction of sulphinate esters (**189**) with Grignard reagents furnishes sulphoxides (**190**). If R_2 is chiral

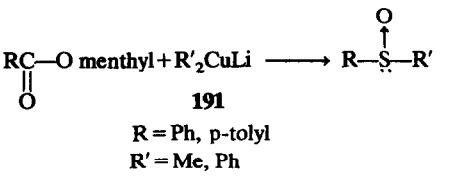


Scheme 94

then β-induction can lead to non-racemic sulphoxides, however the reaction is very unclean in most cases and troublesome separation problems reduce isolated yields drastically.

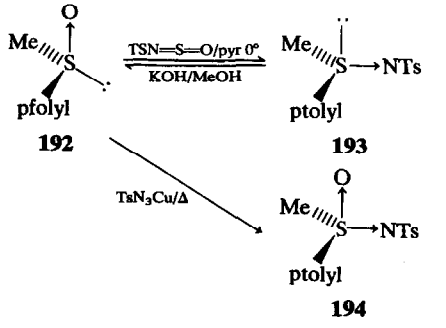
Alternately the use of organocopperlithium reagents (**191**) rather than Grignards has proven quite successful in that 60% chemical and 100% optical yields of sulphoxides have been realised.[208]

From the optically active sulphoxides (**192**) obtained via these methods sulphilimines (sulphimides, sulphinamides) **193** and sulphoximides (**194**) are readily available with excellent retention of optical activity in all cases (94% or greater).[209]



R = Ph, p-tolyl
R′ = Me, Ph

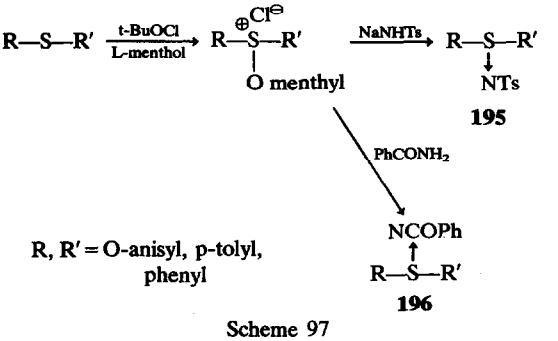
Scheme 95



Scheme 96

Nucleophilic substitution in conversion of (192 → 193) proceeds with inversion whereas the imidation reaction (192 → 194) entails retention of configuration. A trigonal bipyramid or square pyramid transition state structure is possible for these processes.

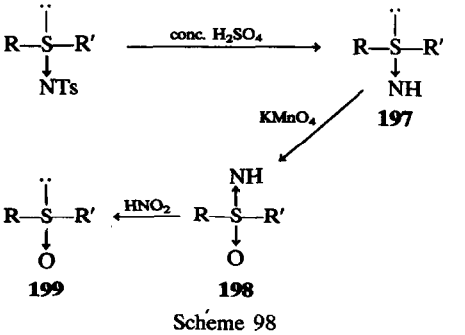
Optically active sulphilimines (**195** and **196**) have been synthesised in 20–30% e.e. by reaction of the corresponding unsymmetrical sulphide and t-butylhypochlorite in the presence of (1)-menthol and



R, R′ = O-anisyl, p-tolyl, phenyl

Scheme 97

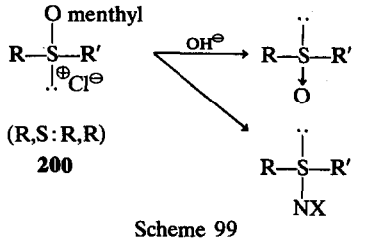
amide anions. Optically pure compounds are available by simple recrystallisation and the N-unsubstituted sulphilimine (**197**) is easily obtained without loss of optical purity from the substituted compounds by treatment with mineral acid.



Scheme 98

The intermediate aminosulphinium salt does not racemise under the reaction conditions. Optically active sulphoximines (**198**) and sulphoxides (**199**) are acquired from **197** with little or no loss of optical purity and complete retention of configuration in both cases.

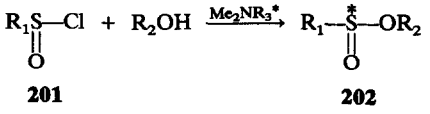
This substitution reactions at sulphur in these cases are highly stereospecific. Asymmetric synthesis from optically sulphides proceeds via diastereomeric menthoxysulphonium chlorides (**211**). When



Scheme 99

the steric requirement of R is large as in the case of O-substituted phenyls a large excess of one diastereomer is formed due to favourable steric interactions with the isopropyl group of menthol leading to enantiomeric excess upon menthol cleavage.

Sulphinite esters (**212**) are key compounds in the synthesis of other classes of sulphur compounds. These are available in up to 45% e.e. by the condensation of sulphinyl chlorides (**201**) with alcohols in the presence of a chiral amine catalyst.[211]



Scheme 100

The optical yields are highly dependent on reaction temperatures with best results at −60°. Sulphinates may also be prepared with comparable optical yields by condensation of sulphinyl chlorides with chiral alcohols.

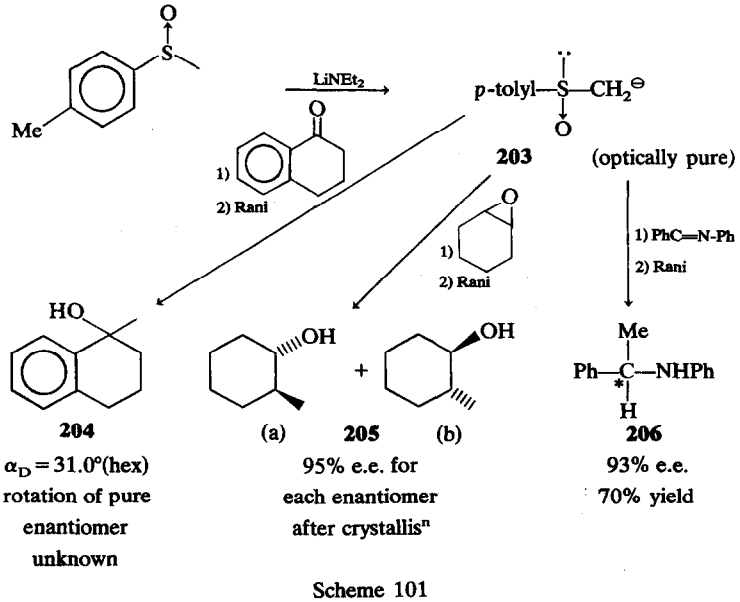
Thiosulphinates have been prepared in low optical yield (<11%) by the same chiral amine catalysis in the condensation of thiols and sulphinyl chlorides.[212] These are generally, optically unstable (excepting the case of —S—t-Bu) due to their susceptibility to nucleophilic displacement. An improvement in the optical yields would make thiosulphinates excellent sources of sulphoxides and sulphinamides to which they may be converted with good retention of configuration.

One can appreciate from these examples that a wide variety of chiral sulphur functionality is available with good optical purity. This is of interest in that these compounds can be used as vehicles for asymmetric synthesis since transfer of chirality from sulphur to carbon is possible and S—C bond cleavage is often a facile procedure.

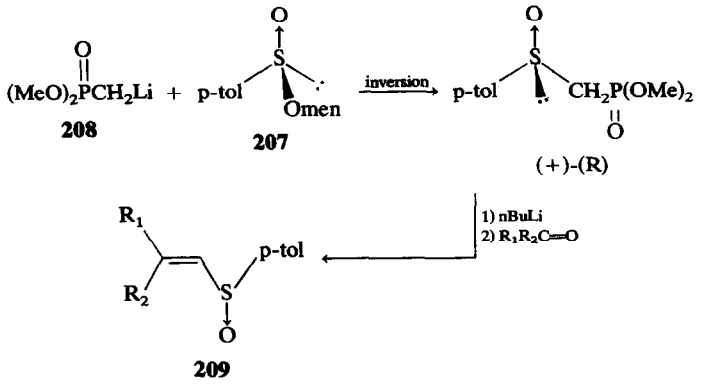
The optically active *p*-tolyl sulphinyl carbanion (**203**) is a versatile reagent for asymmetric synthesis of chiral alcohols and amines as shown.[213] This is the first known asymmetric synthesis of **204** and its optical rotation is unknown as is the optical yield of the reaction. Alcohols (**205a** and **205b**) (from specific trans opening of the epoxide) are each available in 95% e.e. by fractional crystallisation of the condensation product followed by desulphurisation.

In the reaction with N-benzylidene aniline it was found that only one diastereomer (Rs,Sc) was obtained. Recrystallisation and desulphurisation provided amine (**206**) in excellent optical and chemical yields.

Optically active α,β-unsaturated sulphoxides are available by first treating the (−)-(*S*)-menthyl-*p*-toyl sulphinate (**207**) with dimethylphosphoryl-methyllithium (**208**) giving the (*R*)(+)-sulphoxide in 70% yield with full retention of enantiomeric purity but with complete inversion. These sulphoxides undergo Wittig-Horner reaction with retention of S-chirality to furnish the α,β-unsaturated sulphoxides (**209**) in good yields.[214] These can racemise, however, via [2,3] sigmatropic processes to give the sulfenate ester.

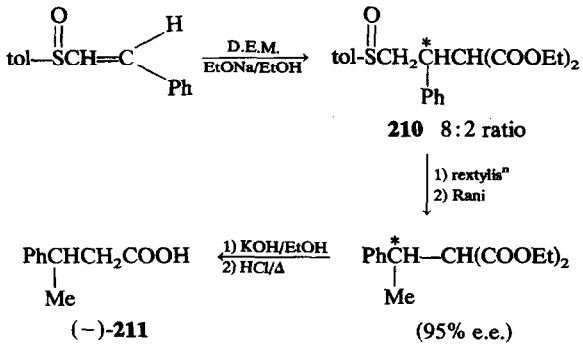


Scheme 101



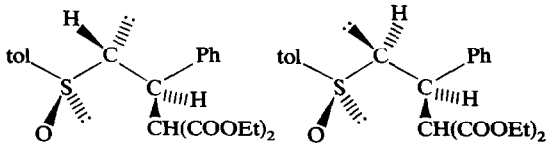
Scheme 102

The Michael addition of diethylmalonate to optically active α,β-unsaturated sulphoxides has been reported to proceed diastereoselectively. Recrystallisation, desulphurisation and decarboxylation furnishes (−)-3-phenyl butyric acid (**211**) in excellent optical yields.



Scheme 103

The reaction is kinetically controlled and irreversible with formation of carbanions (**212a/b**) the rate limiting step, hence the transition state should bear resemblance to these. Compound **212a** where the

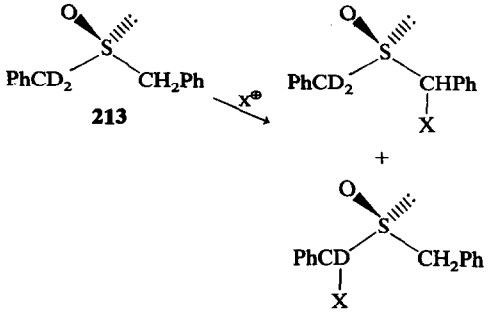


carbon lone pair is *trans* to the sulphinyl oxygen is generally accepted as the most stable situation for the α-sulphinyl carbanion in polar protic solvents and the reaction must proceed preferentially via this diastereomer.

The ratio of **212a/212b** was found to decrease with the ionic radius of the counter cation ($K^+ > Na^+ > Li^+$) and in THF solvent with Li^+ cation (**212b**) was predominant therefore both enantiomers of **211** may be obtained from a single chiral sulphoxide[216] in good chemical and optical yields.

Optical yields of 74% have been realised in the Michael addition of piperidine to β-methylvinyl-*p*-tolylsulphoxide (β-induction) and 32% in the addition of bromine to vinyl-*p*-tolylsulphoxide (α-induction).[217]

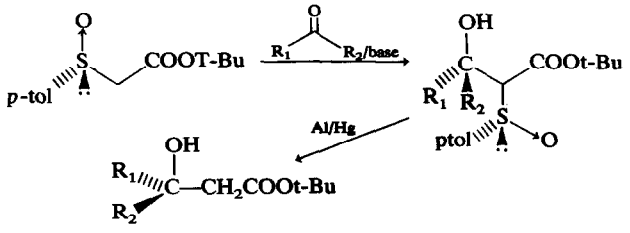
α-Induction in the chlorination of di-deutero compound (**213**), chiral by virtue of isotopic disymmetry, affords a single diastereomer from hydrogen



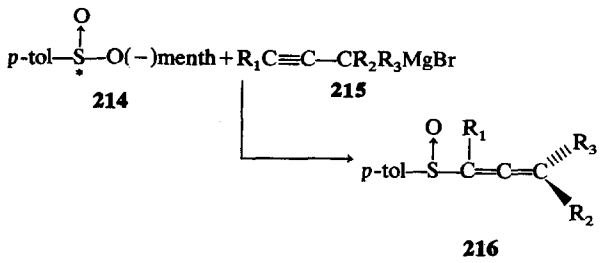
Scheme 104

displacement along with a single diastereomer from displacement of deuterium in a 9:1 ratio respectively and 60% chemical yields. The reaction is highly regioselective due to isotope effects and almost totally stereoselective. This is the first known example of asymmetric induction by isotopic dissymmetry.[218]

A β-induction process in the condensation of chiral α-sulphinyl ester enolate ions with prochiral ketones leads β-hydroxy acids in excellent (95%) optical yields[219] as determined by NMR spectroscopy using chiral europium shift reagents.



Scheme 105



Scheme 106

Finally, asymmetric induction to the extent of up to 60% e.e. has been reported by Stirling *et al.*, in[220] the synthesis of allenic sulphoxides (**216**) from mentyl sulphinates (**214**) and prop-2-ynyl Grignard reagents (**215**).

The ready availability of a variety of optically pure sulphur compounds and their excellent asymmetry inducing properties in C–C bond forming reactions has drawn much attention to this area of study.

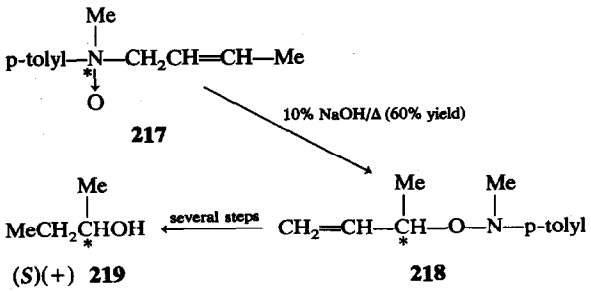
REARRANGEMENTS

Rearrangements are highly useful processes in synthetic chemistry. The Wittig, Stevens, Meisenheimer and Sommelet rearrangements are prime examples.

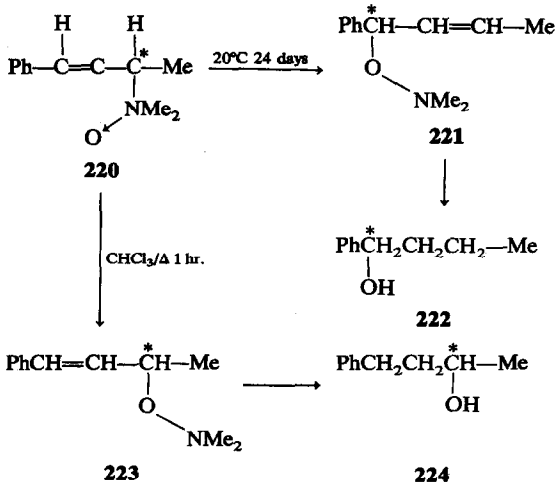
These processes are termed [2,3] sigmatropic shifts and generally proceed via a radical dissociation-recombination process in nonallylic systems in contrast to the concerted shift in allylic systems.

Such an allylic rearrangement has recently been reported with (*R*)-(+)-N-*trans*-Crotyl-N-methyl-*p*-toluidine oxide (**217**).[221] The transfer of chirality from *N* in **217** to *C* in **218** occurs with 83% conservation of asymmetry. The optical purity of **217** was established by the Pirkle method of magnetic non-equivalence of chemical shifts in chiral solvents[222] and that of **218** by conversion to (*S*)-(+)-2-butanol (**219**). This is categorised as a self-immolative asymmetric process since chirality is lost at nitrogen.

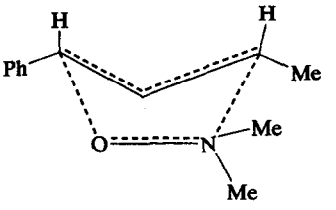
A related study reports transfer of chirality from tetrahedral to trigonal carbon via the same self-immolative process.[223] Amine oxide (**220**) rearranges via the [2,3] sigmatropic process to the O-alkyl-N,N-dimethyl hydroxyl amine (**221**) with 85% retention of chirality as assessed from the degradation product (**222**). The benzylic alcohol is known to racemise to some extent during the degradative process (Zn dust) hence optical yields of **221** are assumed to be somewhat higher.



Scheme 107



Scheme 108



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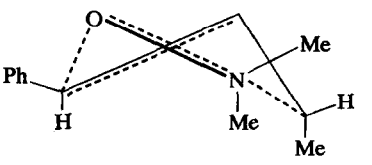
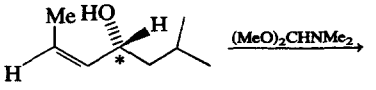


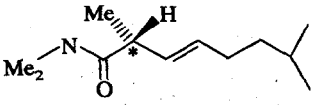
226

Refluxing in chloroform for one hour affords the [1,2] shift product (**223**) with no trace of **221**. Conservation here was only to the extent of 20% and the Meisenheimer radical mechanism is suspected. Intermediate (**225** and **226**) have been suggested with **225** most probable since the *trans*-amine-oxide leads to *trans*-hydroxylamine. There are also steric interactions between H and $-CH_3$ in **226** which would destablise it substantially.

A highly efficient 1,3-transfer, of chirality is evident in the [2,3]-sigmatropic rearrangement of allylic alcohols (**227**) to β,γ-unsaturated amides (**228**). The reaction is postulated to proceed via a



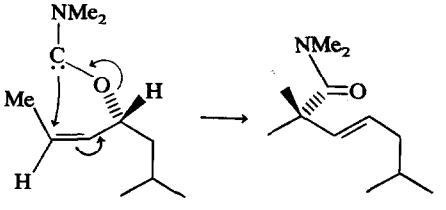
(*R*)-(*Z*) **227**



(2*R*)-(*E*) **228**

Scheme 109

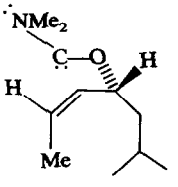
carbene intermediate (**229**) which undergoes a concerted [2,3]-sigmatropic process through a cyclic 5-membered transition state (**229**) with almost 100% transmission of chirality.



229

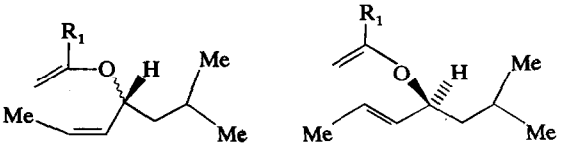
Scheme 110

The alternate rotational intermediate (**230**) is not favoured due to severe interactions between allylic and isopropyl methyls. The (*S*)-(*E*) alcohol affords a separable mixture of the (2*R*)-(*E*) and (2*S*)-(*Z*) α,β-unsaturated amides.

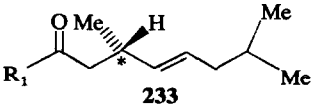


230

Certain [3,3]-sigmatropic shift processes with a high rate of intramolecular transfer of asymmetry have been used in successful asymmetric syntheses. One excellent example is the use of a Claisen rearrangement of isomeric allylic alcohols (**231** and **232**).[225]



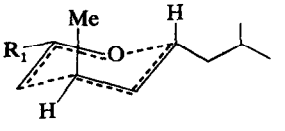
(*R*) *Z*-**231** (*S*) *E*-**232**



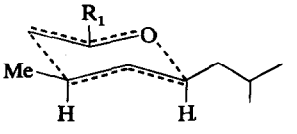
233

Scheme 111

The rearrangement of **231** is presumed to proceed via transition state **A** and that of **232** via **B** since these cyclic species have the least number of nonbonded (i.e. pseudoaxial) interactions. Both lead to the same product (**233**) having (*S*)-(*E*)

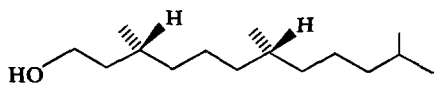


A



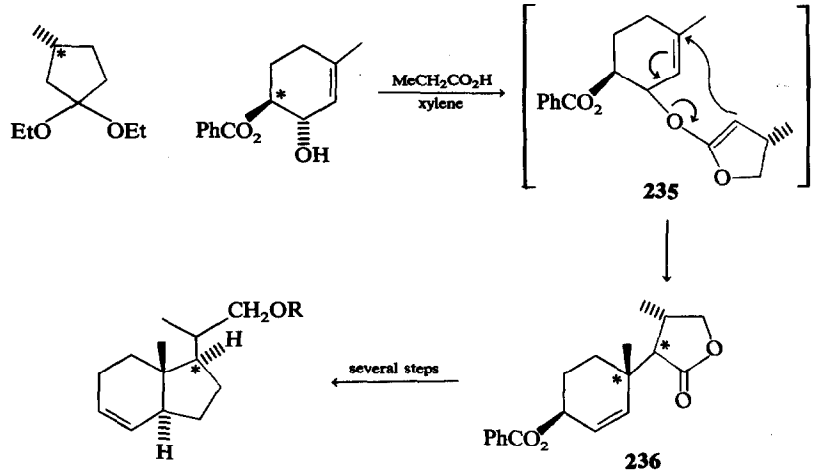
B

stereochemistry. The allyl vinyl ethers were prepared in racemic form, then resolved and rearranged in refluxing benzene. High pressure liquid chromatographic analysis of the (*R*)-α-methyl-*p*-nitrobenzylamide derivatives of the products ascertained no less than 98% transfer of chirality for the sequence. Repetition of the sequence on the aldehyde obtained from **233** furnished the 15 carbon intermediate (**234**) possessing both chiral centres of the tocopherol series and is thus a direct route to Vitamins E and K.



234

The asymmetric ortho-ester Claisen rearrangement of intermediate (**235**) allows the totally stereospecific creation of two C atoms in **237**.[225] Reaction of optically pure starting materials affords a single crystalline lactone (**236**) from which **237** an important intermediate in the synthesis of vitamin D_2 is derived in several steps. The benzoyl ester hinders the β-face forcing backside alkylation of the cyclohexane ring in **235**.



Scheme 112

Hydroboration is yet another highly useful reaction in preparative organic chemistry. The asymmetric properties of this reaction have been heavily studied, and are reviewed in previous works (refs. 1 and 227), hence it is not touched upon here.

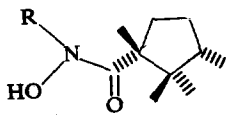
PEROXIDATIONS

The epoxide function plays an extremely important role in metabolic processes therefore its asymmetric creation is of quite some interest in bioorganic and medicinal chemistry. Epoxidations using optically active per-acids generally proceed with low optical yields. This mode of epoxide preparation has been reviewed.[228]

Quaternary ammonium salts derived from alkaloids such as quinine and quinidine have been used to mediate the peroxide epoxidation of electron poor olefins under phase transfer conditions[229] in optical yields of up to 25%.

Transition metal catalysed epoxidation of olefins by alkyl hydroperoxides has also been quite successful.[230] Best results are obtained with allylic alcohols and it is strongly suspected that the alcohol function co-ordinates to the metal atom during the oxygen transfer step.

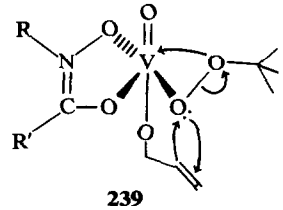
The most efficient catalyst ligands are hydroxamic acids (**238**). They are resistant to oxidation and bind well to the metal. Complexes of molybdenum have given poor results (<2% e.e.) however vanadium hydroxamates are much more effective furnishing optical yields generally in the range 20–30% with a maximum of 50%. As expected induction increases at lower temperatures but unfortunately chemical yields drop off drastically. Optimum inductions are realised with a 5:1 ratio of ligand to VO $(acac)_2$ catalyst.



238

R = Me, Ph 2,6Me_2Ph

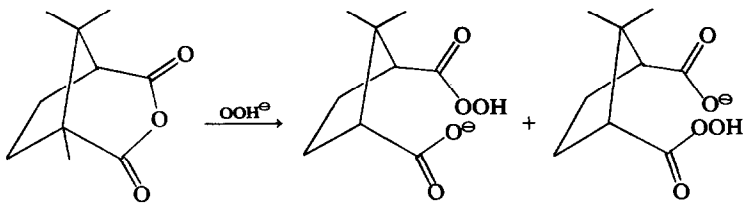
Although other mechanisms have been proposed the authors tentatively propose a new mechanism via transition state (**239**).



239

Pirkle *et al.*, have recently devised a new method for the preparation of monoperoxycamphoric acid which increases the optical yields substantially.[231] The preparation of the peracid by peroxide opening of the anhydride (**240**) might logically be expected to lead to both **241** and **242** which would each lead to induction in the opposite sense lowering overall optical yields. By concentrating the ethereal extract of the monoperacids and dilution with CH_2Cl_2 colorless crystals were obtained which ^{13}C NMR shows to be a 15:1 mixture of **241** and **242**. An additional recrystallisation afforded pure **241**.

Under crystalline peracid has resulted in far superior optical yields to those obtained by use of



240 241 242

Scheme 113

the crude non-crystalline extract as is the usual procedure. For example asymmetric synthesis of 2-t-butyl-3-*p*-(bromophenyl) oxaziridine proceeds with 40% e.e. using crystalline per-acid whereas the crude extract affords only 24% e.e. Other substrates do not produce such a striking difference but the crystalline per-acid is superior in each case.

CONCLUSION

From the preceding pages the importance and scope of asymmetric synthesis is evident.

The number of reaction types being studied for their asymmetric properties and the number of publications in the field are constantly increasing. The asymmetric creation of the carbon-hydrogen bond is well in hand, while the more important area of asymmetric C–C bond formation is not so laden with success. There are, however, several sound approaches (i.e. alkylation of enamines, Schiff bases and oxazolines).

Optically active centres can be synthesised in several ways; in achiral compounds by reaction with chiral reagents or in chiral solvents or in molecules which already contain one or more asymmetric centres.

The most successful cases generally involve a highly rigid (usually cyclic) conformation in the transition state as a result of chelation or H-bonding. It is the difference in free energy ($\Delta\Delta G^{\neq}$) between the competing diastereomeric pathways that is responsible for the extent of asymmetric induction. A knowledge and control of the steric and electronic factors in the rate limiting step of the mechanism is the most direct means of manipulating this factor. Thus a knowledge of transition state geometry and reaction kinetics is very helpful. In most cases a slower rate (lower temperature) leads to larger optical yields.

The use of chiral reagents in a catalytic sense is most desirable in contrast to self-immolative processes where the chiral reagent is not recoverable and equimolar quantities must be used. In this regard, attempts to mimic enzymatic processes in vitro holds prospects for extremely fruitful results.

Any asymmetric reaction affording less than 50% optical yield is not useful synthetically, except in special cases. Any such reactions described in this report are in the interests of scope and completeness.

Note added in proof. The area of asymmetric synthesis continues to expand rapidly as evidenced by the many publications appearing in the literature. Since submission of this manuscript two excellent reviews complimentary to the present article have appeared.[234,235]

Because of the explosion of publications in this area much has appeared since submission of this Report. Omission of these articles in no way detracts from the work of the authors but simply reflects the cut-off point for final preparation of this work.

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