Chapter 15

Asymmetric synthesis

Asymmetric synthesis is undoubtedly the single area of organic synthesis which has undergone the greatest development during the 1980s and 1990s. An asymmetric synthesis may be defined as the conversion of an achiral unit, in an ensemble of substrate molecules, into a chiral unit in such a way that the possible stereoisomeric products are formed in unequal amounts. The importance of this is that, for many biologically active compounds, the desired activity is possessed by only one of the possible stereoisomers; the other isomer(s) may be inactive or possess different (perhaps undesirable) activity. For example, in the case of *thalidomide* both enantiomers have the desired sedative activity; it has been claimed, on the basis of some animal experiments, that it is only the (−)-enantiomer (**1**) which has teratogenic properties (i.e. produces foetal abnormalities). The situation is complicated, however, by the fact that the two enantiomers may interconvert in the body. Similarly the sweetness of *aspartame* is a property confined to the *S,S*-diastereomer (**2**); the other three isomers (*R,S; S,R; R,R*) have a bitter taste and must be avoided in the manufacturing process.

1

2
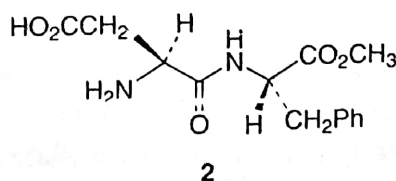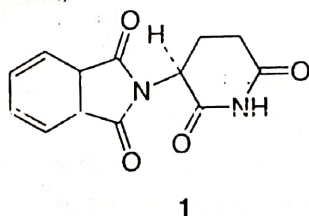
15.1   Terminology and analytical methods

For most chiral molecules, the chirality may be attributed to the presence of one or more *stereogenic centres* (Buxton and Roberts, pp. 20–21), but the primary criterion for chirality is that *the molecule cannot be superimposed on its mirror image*. For a chiral molecule with a single stereogenic centre (most commonly a carbon atom attached to four different atoms or groups) the two stereoisomeric mirror-image forms (*enantiomers*) may be designated (+) and (–), according to the direction in which the plane of plane-polarized light is rotated, and also *R*- and *S*- (according to the Cahn–Ingold–Prelog rules[42]), which specify the absolute configuration.

Since the aim of asymmetric synthesis is usually the selective formation of one enantiomer of the product, the *enantiomeric excess* (*e.e.*), which provides a measure of the selectivity achieved, is an important parameter. This is defined as *the proportion of the major enantiomer produced, less that of the minor enantiomer*, and is commonly expressed as a percentage. For example, a 3:1 mixture of enantiomers (75%:25%) has an e.e. of 50%, and an e.e. of 70% means an enantiomeric ratio of 85:15. An e.e. of zero corresponds to a racemic mixture, as an e.e. of 100% refers to an enantiomerically pure compound, sometimes also described as *homochiral*.

If the product of an asymmetric synthesis is already known in enantiomerically pure form, the e.e. from the reaction may be obtained directly from the observed specific (optical) rotation:

$$\text{e.e.} = \frac{\text{observed specific rotation}}{\text{specific rotation of major enantiomer}}$$

However, if enantiomerically pure product has not previously been obtained, the optical rotation may be of little value in determining the selectivity of the reaction. To overcome this problem, analytical methods have been developed which rely on differentiating the isomers by means of an external chiral influence: for example, chromatography (GLC or HPLC) on a chiral stationary phase, NMR in the presence of a chiral lanthanide shift reagent or a chiral solvating agent, and conversion into mixtures of diastereomeric derivatives (see below) for conventional analysis (e.g. NMR or HPLC).[43]

For molecules containing more than one stereogenic centre, there are more than two possible stereoisomers. In comparing any two of these isomers, two possibilities arise: the isomers are either mirror images of each other, i.e. enantiomers, or they are not, in which case they are *diastereomers* (or *diastereoisomers*). The reader is reminded that a synthetic step which introduces a new stereogenic centre into a molecule that already contains one or more stereogenic centres will produce a mixture of two diastereomers (cf. section 2.1.2).

The proportion of products formed may be measured by the *diastereomeric excess* (*d.e.*). This is defined, like the enantiomeric excess, as *the proportion of the major diastereomer produced, less that of the minor*. It bears no simple relationship to the observed optical rotation of the mixture, but is of course

determined relatively easily since diastereomers have different spectroscopic and chromatographic properties. As mentioned above, the conversion of an enantiomeric mixture into a diastereomeric mixture (by reaction with an enantiomerically pure compound) permits indirect determination of the e.e. of the former by means of measuring the d.e. of the latter.

15.2 Strategy and classification of methods

The ultimate source of all chirality is nature. Most naturally occurring chiral compounds are not found as racemic mixtures and many are obtainable in enantiomerically pure form. The basic strategy underlying all asymmetric synthesis therefore involves using a naturally occurring, enantiomerically pure compound to influence the stereochemical outcome of the reaction (or reaction sequence).

The main classes of natural product which have been so used[44] are:

(i) amino acids (and their reduction products, e.g. amino alcohols);
(ii) other amines and amino alcohols, including alkaloids;
(iii) hydroxy acids (lactic, tartaric, mandelic, etc.);
(iv) terpenes, such as α-pinene, camphor, etc.;
(v) carbohydrates;
(vi) enzymes and other proteins.

The known methods of asymmetric synthesis may be conveniently classified into four types [reactions (15.1)–(15.4)] according to how the enantiomerically pure compound is used.

(i) *'First-generation' or substrate-controlled methods.* These involve the formation of a new stereogenic centre in a substrate (S) under the influence of an adjacent stereogenic group (X*) already present. If the reagent is denoted by R, the product by P and chirality by an asterisk, the whole reaction may be represented as

$$S-X^* \xrightarrow{R} P^*-X^* \tag{15.1}$$

This type of reaction requires an enantiomerically pure substrate; many of the simple reactions of carbohydrates, for example, belong to this class.

(ii) *'Second-generation' or auxiliary-controlled methods.* Here an achiral substrate is made chiral by attachment of a 'chiral auxiliary' (A*), which then directs subsequent reaction and is finally removed to give the chiral product [reaction (15.2)].

$$S \xrightarrow{A^*} S-A^* \xrightarrow{R} P^*-A^* \xrightarrow{-A^*} P^* \tag{15.2}$$
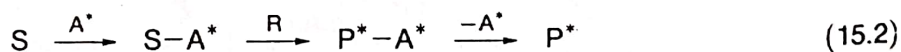
This method has one important advantage, viz. that the auxiliary can be recovered and recycled, but it also suffers from the disadvantage that two extra synthetic steps are required, one to introduce the auxiliary and another to remove it. A useful feature of the process is that P*–A* is a mixture of

diastereomers, which can be separated chromatographically if the selectivity of the reaction is poor.

(iii) *'Third-generation' or reagent-controlled methods.* The attractiveness of the auxiliary approach may be enhanced by the use of a chiral reagent, which converts the achiral substrate directly into a chiral product.

$$S \xrightarrow{R^*} P^* \qquad (15.3)$$

The method, however, has the same disadvantage as the first-generation method in that an enantiomerically pure material is required in stoichiometric amounts.

(iv) *'Fourth-generation' or catalyst-controlled methods.* A further advantage may be gained if the stoichiometric chiral reagent of the 'third-generation' method is replaced by an *achiral* reagent and a *chiral catalyst.*

$$S \xrightarrow[\text{cat.}^*]{R} P^* \qquad (15.4)$$

Included in this class are enzyme-catalysed reactions. Overall, this method is the most attractive since it is the most economical in its use of enantiomerically pure starting materials.

In all of the above methods, it is of course important to ensure that the configuration of a stereogenic centre is not destroyed in a subsequent step, or even in an isolation or purification procedure.

## 15.3   First-generation methods: the use of chiral substrates

It should be obvious that a *practicable* asymmetric synthesis of this type requires that the starting material be readily available from natural sources in an enantiomerically pure form. For this reason, first-generation methods are generally confined to a limited range of substrates, such as simple sugars, amino acids, terpenes, steroids or alkaloids.

The following first-generation processes serve to illustrate some of the general principles of asymmetric synthesis.

(a) Cholestan-3-one (3) is reduced by lithium aluminium hydride (section 8.4.3.1) to give, mainly, the alcohol (4) in which the hydroxyl group occupies the equatorial position. This is, of course, the more stable of the two possible diastereomers, but it is also the isomer formed by *attack of the reagent from the less hindered face of the molecule* (the methyl groups producing steric hindrance on the opposite face).

3

4   (95% yield; 83% d.e.)
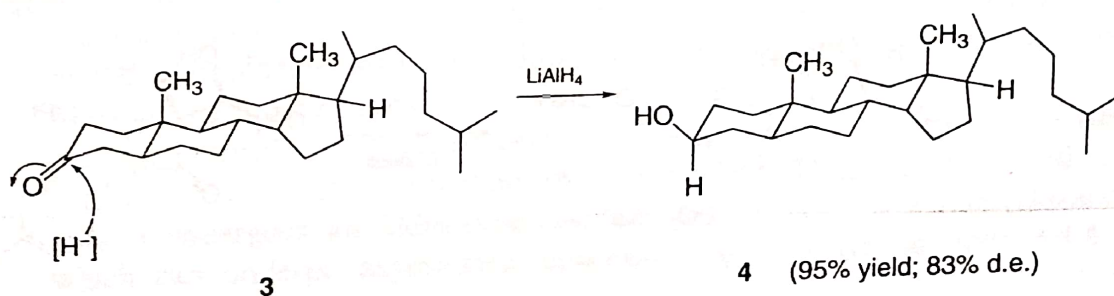
(b) in the hydroboration of (−)-isopulegol (5) (cf. section 11.1), the new stereogenic centre is formed under the influence of those already present, especially that bearing the hydroxyl group. Interaction of this nucleophilic group with the electron-deficient borane ensures that the hydroboration occurs from the rear of the molecule (as represented below):

(94% yield; 90% d.e.)
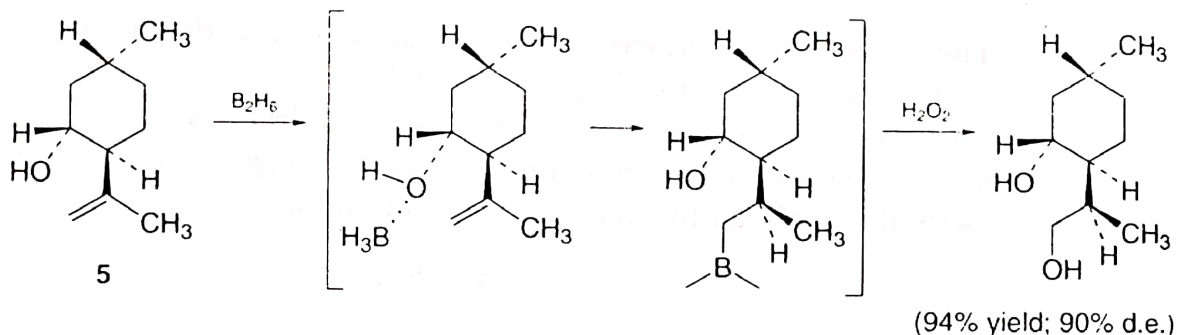
(c) Multi-stage synthetic routes to biologically active compounds may also involve first-generation processes. Two will be described in full in section 16.3 and a third is given in outline below. This involves the conversion, in 15 steps, of (−)-threonine (6), a naturally occurring amino acid with two adjacent stereogenic centres, into a *penem* antibiotic (7), which has three.[45] The first and third steps, shown here. are highly stereoselective, the first being controlled by neighbouring group participation of the carboxyl group (Sykes, pp. 93–96) and

(71%)

(75%)
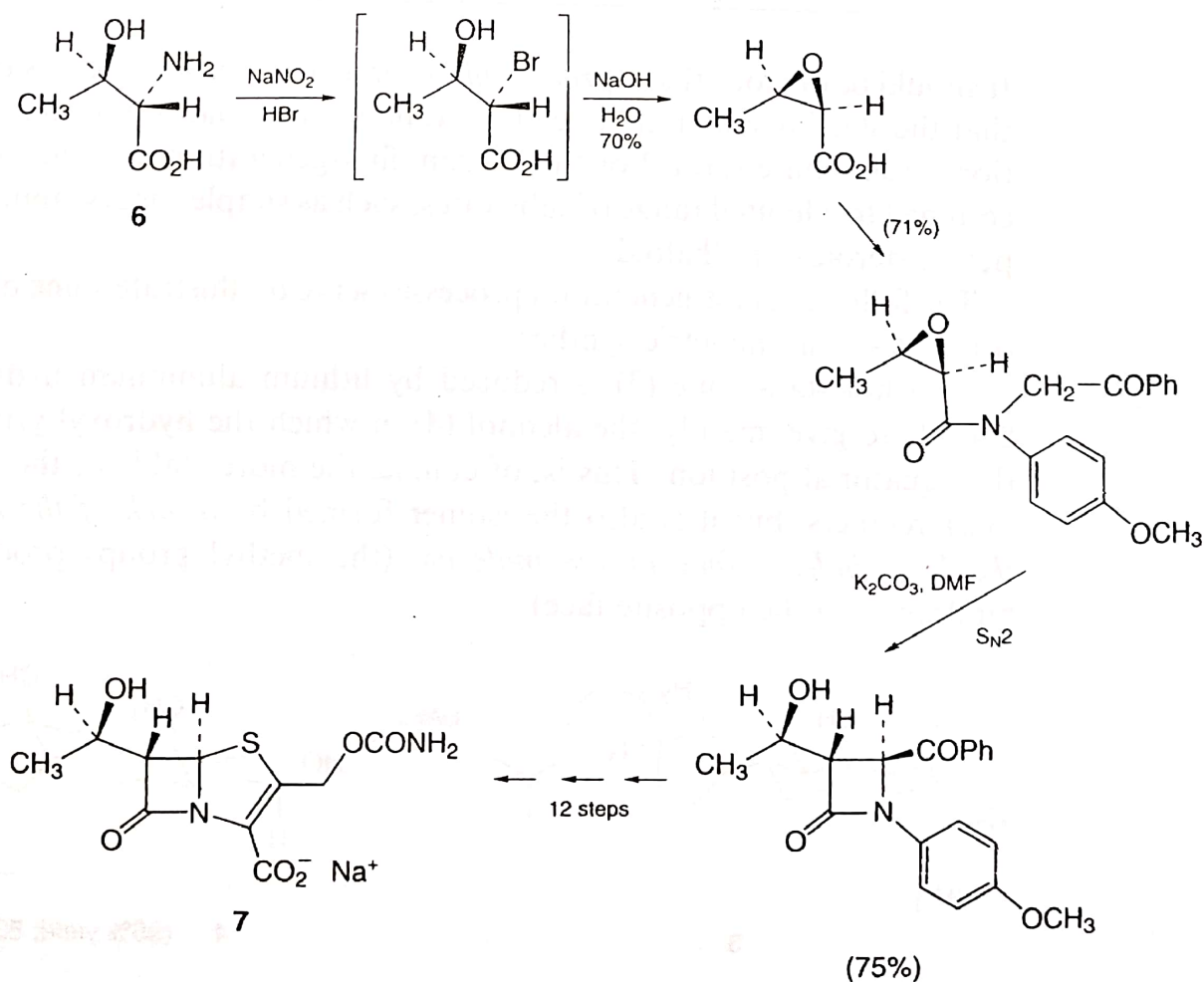
the third by the configuration and conformation of the enolate anion (covered in more detail in section 15.4.1).

15.4 Second-generation methods: the use of chiral auxiliaries

15.4.1 Alkylation of chiral enolates

Perhaps the most widely used method for the asymmetric α-substitution of a carboxylic acid involves the initial formation of a chiral N-acylpyrrolidine or N-acyloxazolidine. The auxiliaries are readily prepared from amino acids. In the first example, the chiral pyrrolidine unit is derived from S-(−)-proline. The carboxylic acid substrate (propanoic acid) is converted, via the anhydride, into (S)-N-propanoylprolinol (8), deprotonation of which gives the chiral enolate 9. The latter exists almost entirely as the Z-isomer (possibly in the conformation shown, with the two OLi units well apart); alkylation of the enolate therefore occurs *on the lower face* of the molecule (the less hindered direction of approach). On the other hand, the corresponding alkylation of the methyl ether of 8 is much less enantiospecific and actually gives *a preponderance of the other enantiomer* (56% e.e.). In this case, chelation of the ether oxygen to the lithium produces a completely different conformation for the enolate, viz. 10, and the less hindered approach for the alkylating agent is on the opposite face of the enolate:
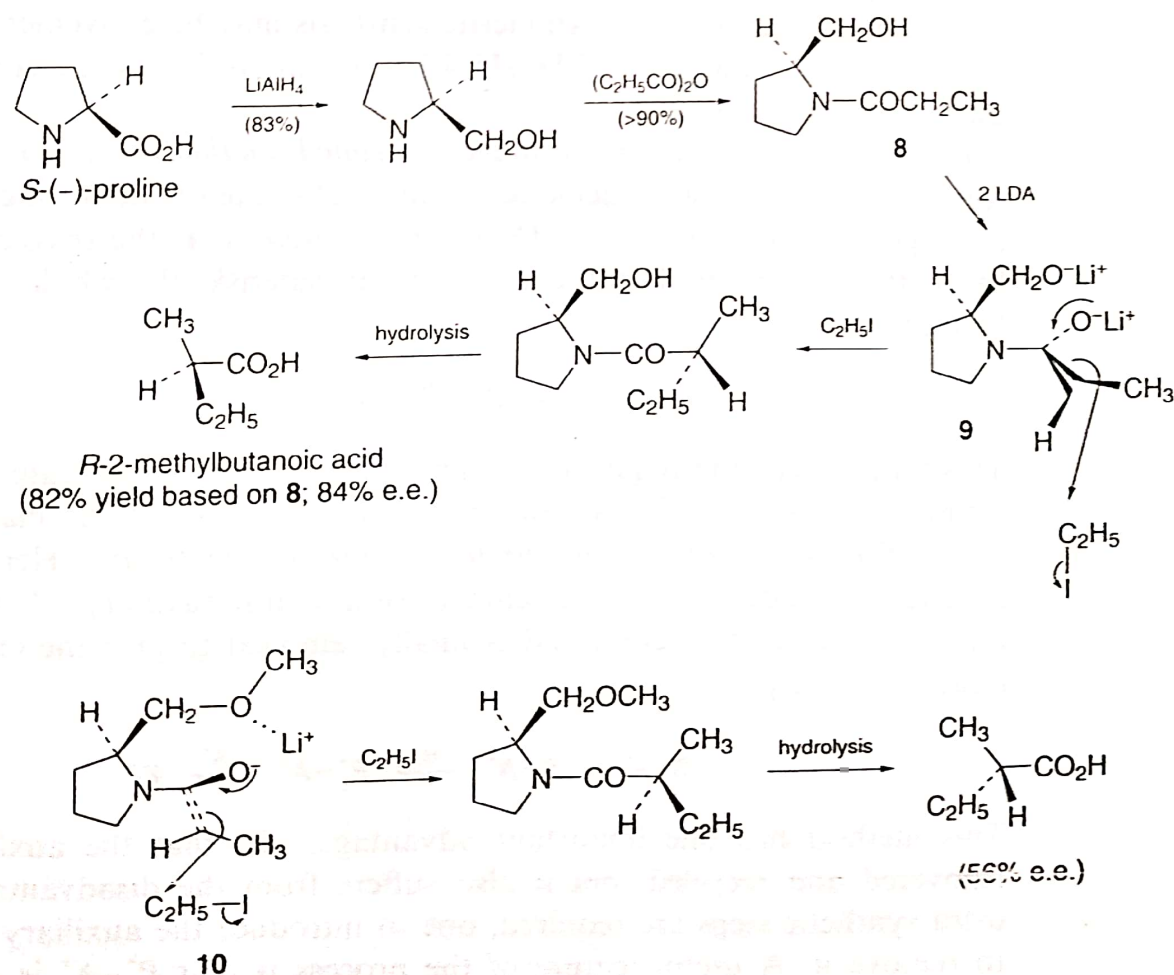
The above examples illustrate a general problem in asymmetric synthesis, viz. that it is difficult to predict the configuration at the new stereogenic centre by a simple set of rules or a visual inspection of the molecule. In the present case, the configuration of the product depends critically not only on the *configuration* (*E* or *Z*) of the enolate but also on its *conformation* in relation to the remainder of the molecule. Determination of the preferred conformation may require the use of sophisticated models (and may even then be difficult!)

Reaction of a chiral enolate with an aldehyde (other than formaldehyde) or ketone constitutes an *asymmetric aldol reaction*, and there are currently several well-established methods for bringing about such reactions. In the example below, in which a valine-derived oxazolidine serves as the chiral auxiliary, it is beneficial to exchange the lithium of the enolate for the (much bulkier) complex zirconium group. This ensures that the enolate adopts the conformation shown (**11**), and reaction with the benzaldehyde therefore gives the adduct **12**.

12a

(71% over three stages)

11 (Cp = cyclopentadienyl)
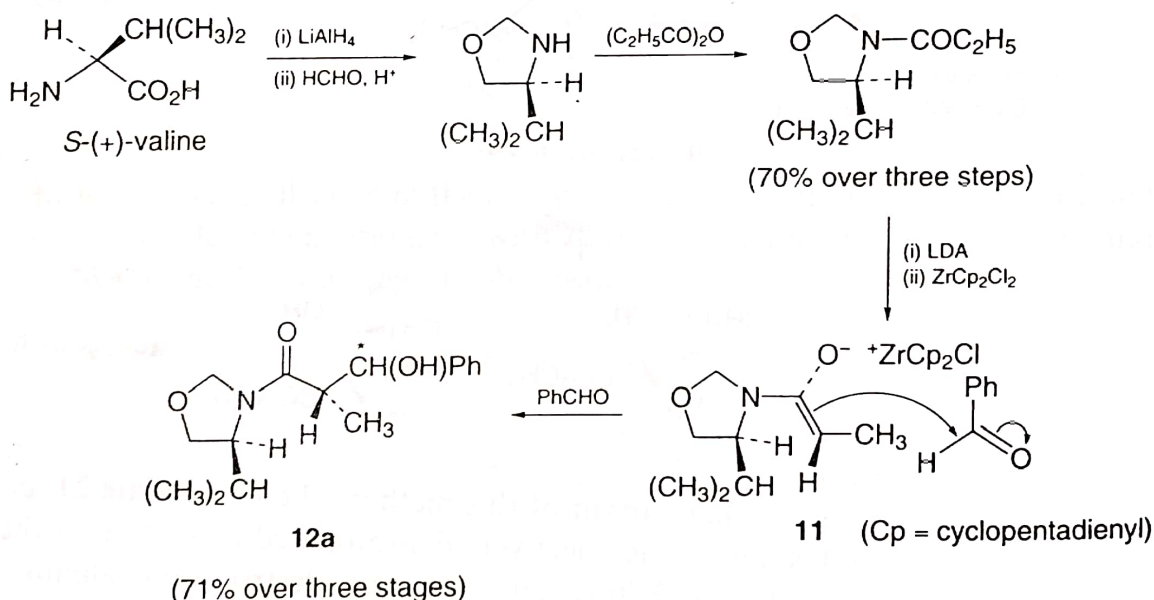
This adduct, however, has *two* new stereogenic centres, the second being denoted by an asterisk in structure **12a**. The enolate adds to the carbonyl group on the face which gives rise to the less hindered transition state (**13**),[46] and the configuration of the second stereogenic centre is thus as shown in


13
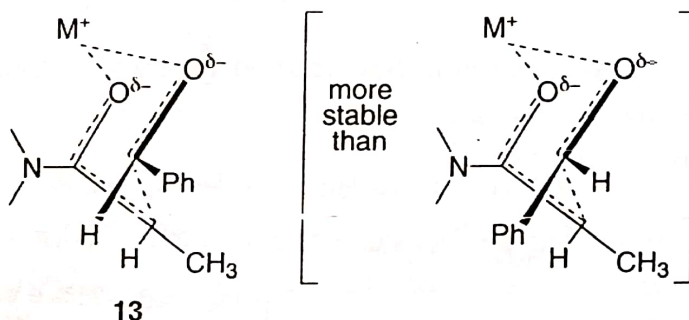
12b. Removal of the auxiliary by hydrolysis gives the hydroxy acid (**14**) (94.5% of the isomer mixture having the configuration shown).
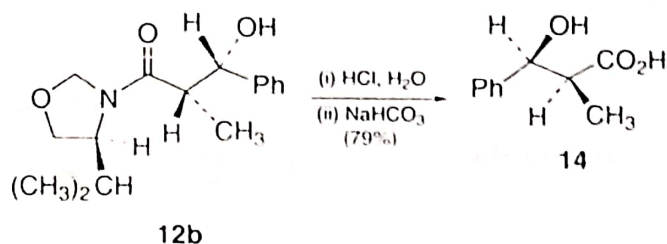
15.4.2   Chiral aza-enolates

Chiral oxazolines (4,5-dihydrooxazoles) were among the first auxiliaries found to promote carbon–carbon bond formation with very high e.e. Some of these oxazolines may be derived from the natural amino acids, but probably the most useful are derived from the S,S-(+)-aminodiol (**15**), which is a by-product in the manufacture of the antibacterial agent chloramphenicol. The primary alcohol in **15** is selectively methylated by first protecting the secondary alcohol and amino group (as an oxazoline).
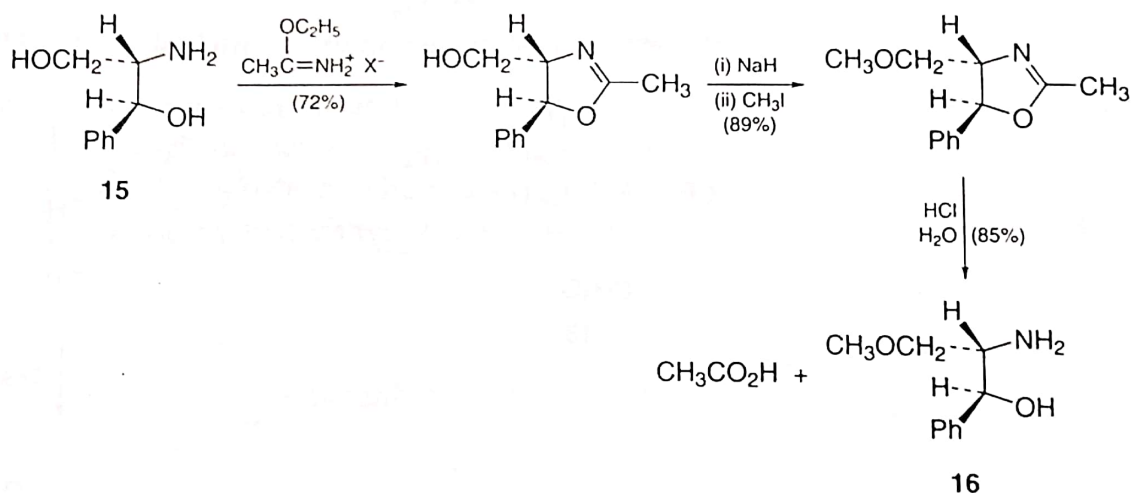
C-2 of an oxazoline is, in effect, a masked carboxyl group[47] and so asymmetric alkylation of a substituent at C-2 provides a route to asymmetrically alkylated carboxylic acids, as illustrated below.

As for the enolates in the preceding section, the Z-configuration is preferred for the aza-enolate **17**. The observed selectivity of the alkylation step in this case is consistent with the incoming electrophile being guided to the lower face of **17** by the lithium. Here again, chelation of the ether oxygen to the lithium is crucial for high enantioselectivity.

Asymmetrically β-alkylated carboxylic acids may be obtained by a similar method. The 2-methyloxazoline **18** (a chiral synthetic equivalent of acetic acid[47]) undergoes an aldol-type condensation to give a 2-alkenyloxazoline which can undergo asymmetric conjugate addition (cf. sections 3.3.4 and

4.1.4). Hydrolysis of the adduct gives the β-alkyl-carboxylic acid in excellent e.e.

(39% over three stages; 86% e.e.)

(44% over three stages)

(79% over two stages; 99% e.e.)
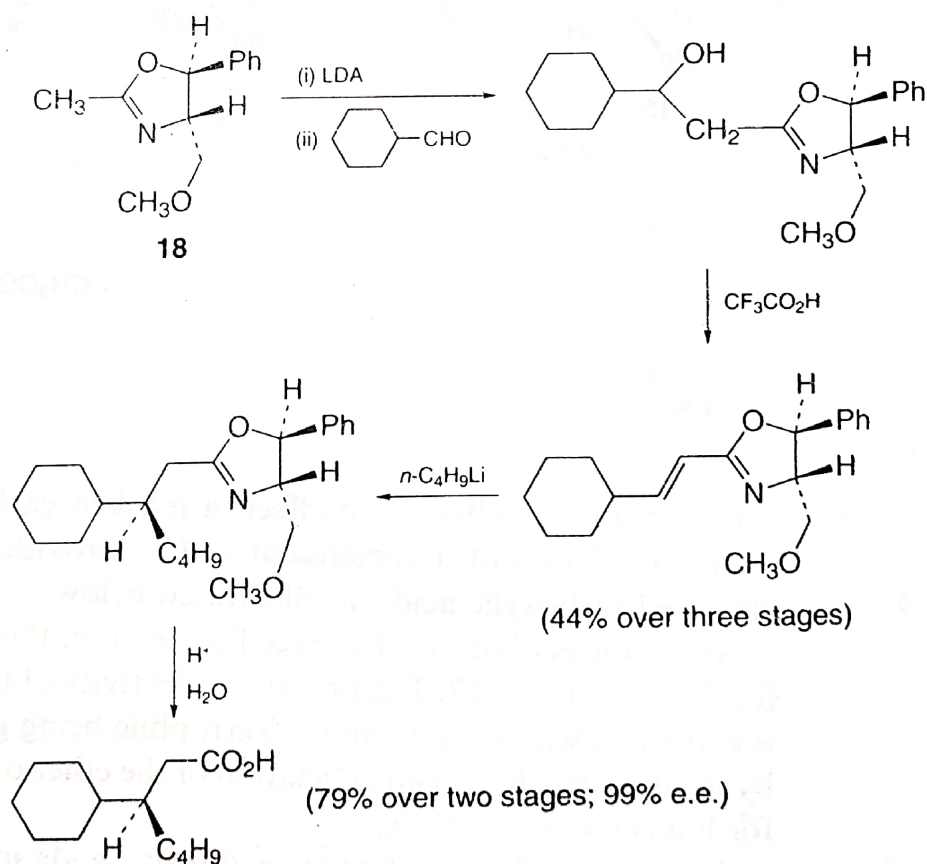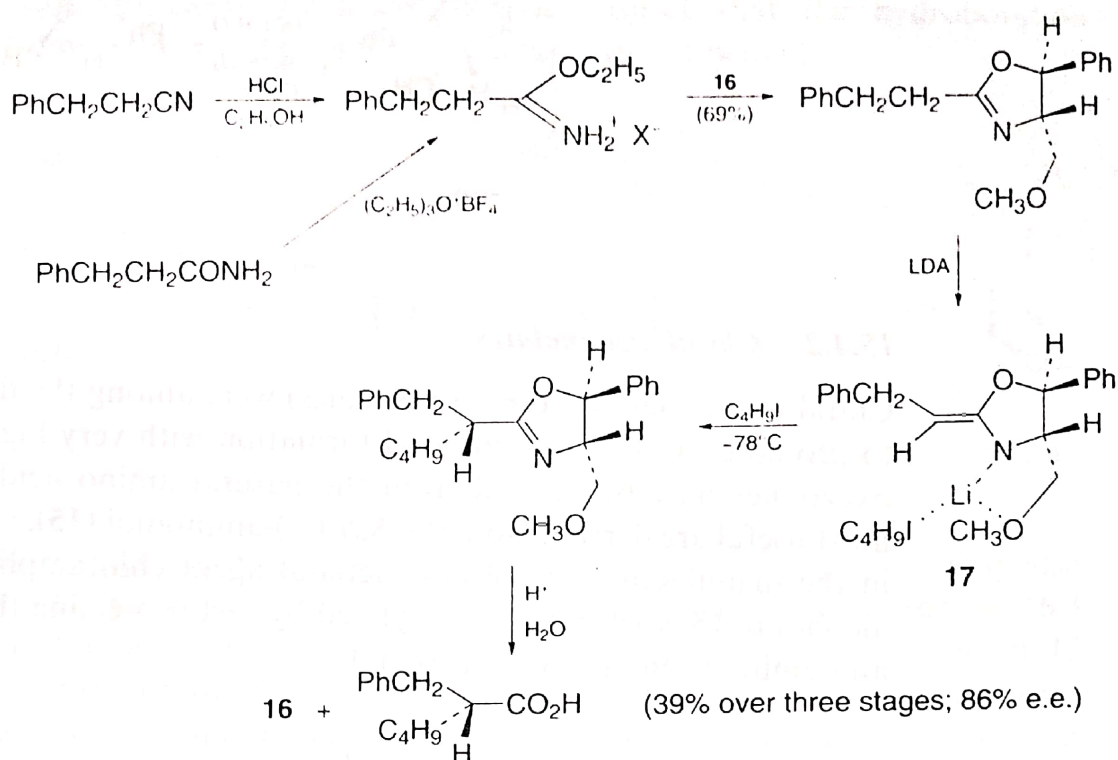
A second type of asymmetric synthesis using chiral aza-enolates utilizes as starting materials chiral 3-alkylpiperazine-2,5-diones, e.g. **19**. These are, in effect, cyclic dipeptides, and may be obtained by cyclization of an acyclic

dipeptide or two amino acids; for example, **19** is derived from S-leucine and gly-cine. O-Methylation of **19** gives a chiral bisimidate ester (**20**), which is deproto-nated selectively at C-6. (This is not only the less hindered position, but the carbanion produced is secondary rather than tertiary.[48]) Electrophilic attack then occurs on the side of the molecule remote from the bulky isobutyl group, e.g.

19

2(CH₃)₃O⁺ BF₄⁻
(93%)

20

n-C₄H₉Li

(95% based on 20)

CH₃COCH₃

HCl

(49% yield; 85% e.e.)
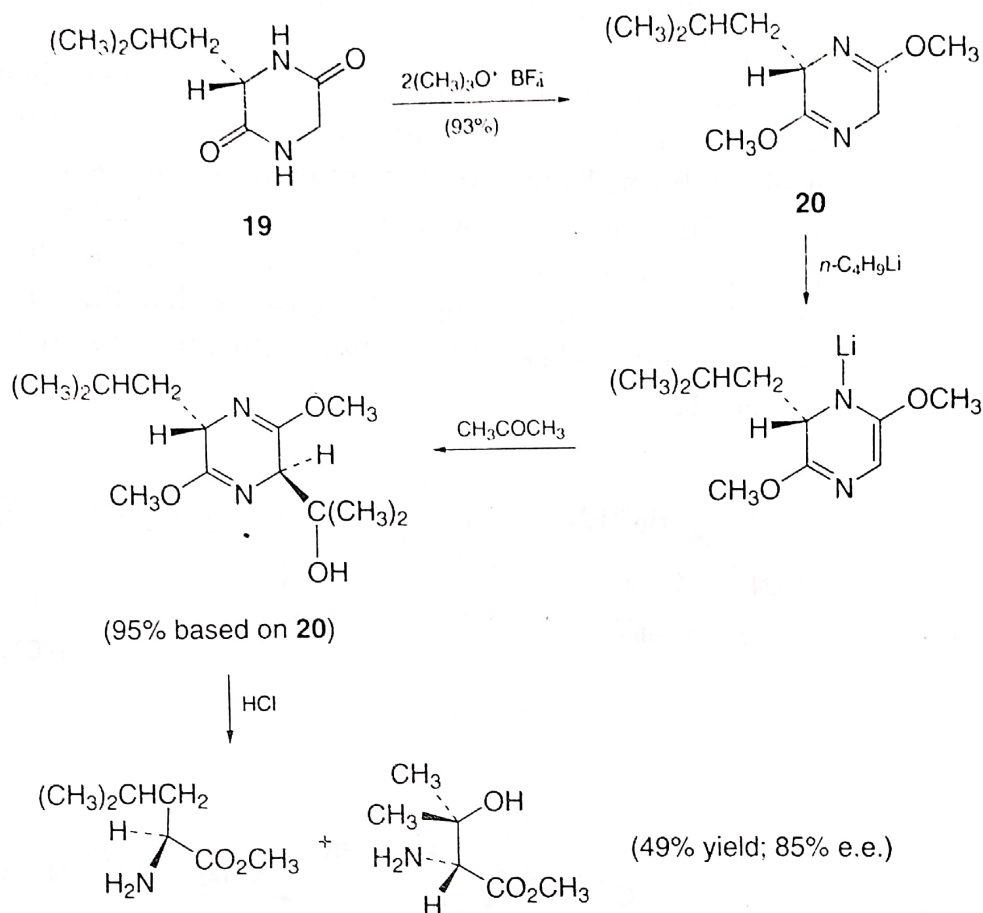
In another variant of this method, the bis-imidate **21**, derived from S-valine and S-alanine, is selectively deprotonated as shown, at the less hindered posi-tion. Although this deprotonation destroys the alanine-derived stereogenic centre, it is regenerated under the influence of the valine-derived centre. This feature will be noted again in section 15.4.6.

21

n-C₄H₉Li

CD₃I   (91%)

H⁺, H₂O

(51% yield; >95% e.e.)
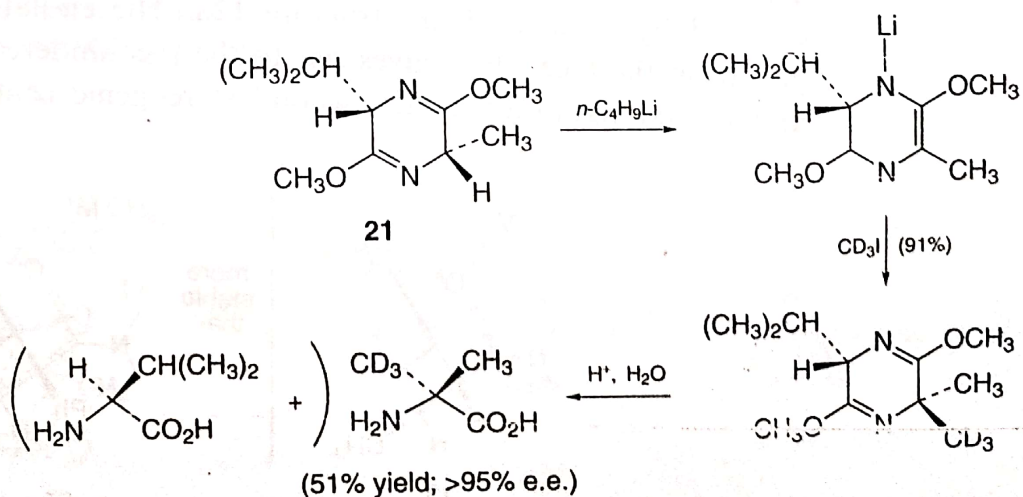
15.4.3   Alkylation of chiral imines and hydrazones

One of the easiest ways of carrying out asymmetric alkylation α to a carbonyl group is to convert the latter to a chiral imine or hydrazone, and deprotonate this using a strong base. [The achiral equivalent of this reaction was described in section 5.2.3.1, reaction (5.17).] The most useful chiral amines and hydrazines for this process are again derived from amino acids, and two of the best, viz. **22** and 'SAMP' (**23**), additionally bear a chelating methoxy group.

S-(–)-phenylalanine

(i) SOCl₂, CH₃OH
(ii) NaBH₄
(iii) KH, CH₃I

(72%)

22

S-(–)-proline

(i) LiAlH₄
(ii) C₂H₅ONO

(83%)

(i) NaH, CH₃I
(ii) LiAlH₄

(72%)

S-1-amino-2-(methoxymethyl-pyrrolidine) (SAMP)   **23**
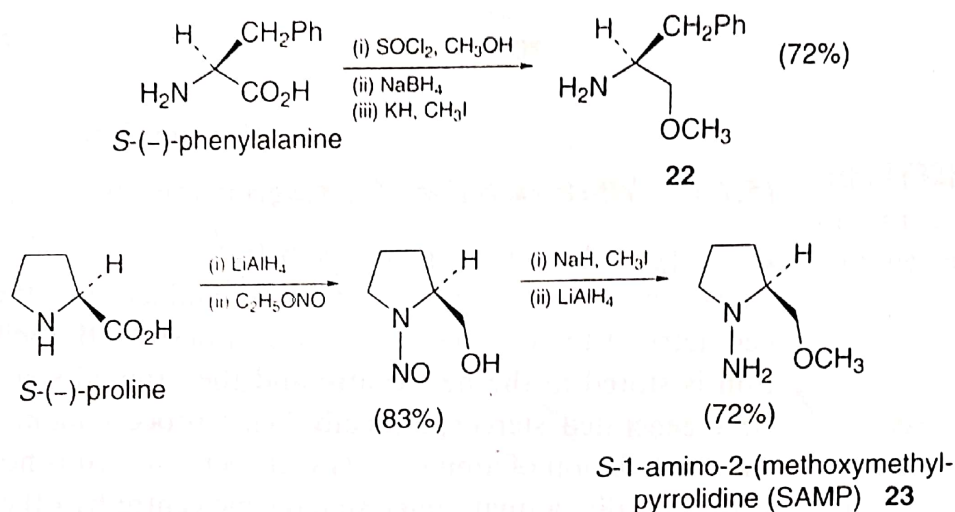
Both are highly effective in the asymmetric alkylation of cyclohexanone and give rise to different enantiomers: with **22** the product is the S-enantiomer, and with SAMP the R-enantiomer is obtained.

22
(93%)

(i) LDA
(ii) CH₃I
(iii) H⁺, H₂O

(65% overall yield; 87% e.e.)

23
(92%)

(i) LDA
(ii) (CH₃)₂SO₄
(iii) O₃

(70% overall yield; 99% e.e.)
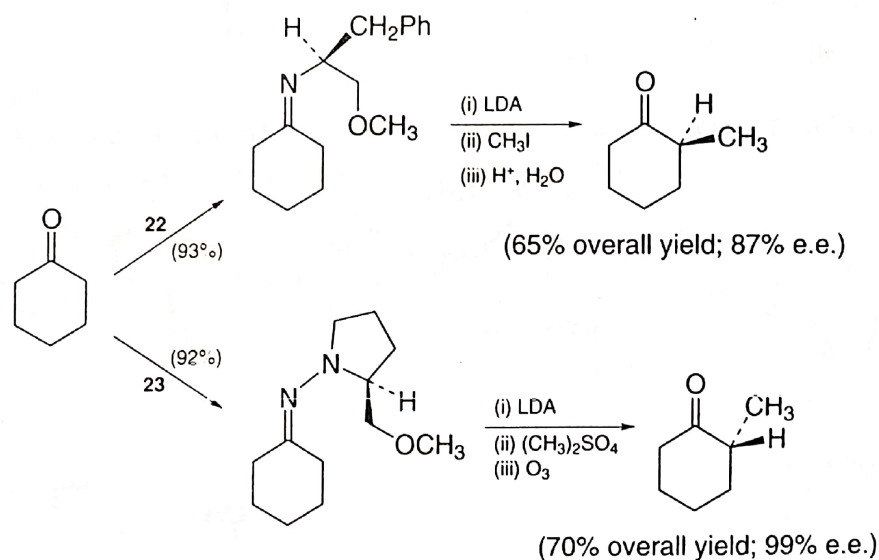
This imine or hydrazone may be removed in either case by hydrolysis, but in the latter case ozonolysis (cf. section 9.2.6) offers an attractive alternative; in this case the chiral auxiliary is recovered as the N-nitroso compound which may be reduced back to SAMP.

The enantiomer of SAMP (not unnaturally referred to as RAMP!) is also readily available; RAMP and SAMP, reacted with the same achiral carbonyl compound, permit enantioselective α-alkylation to take place in either

direction. For example, the synthesis of **24** (the defence substance of the daddy-longlegs spider) is achieved using pentan-3-one and SAMP, whereas the use of RAMP gives the opposite enantiomer — the e.e. in each case exceeding 95%.
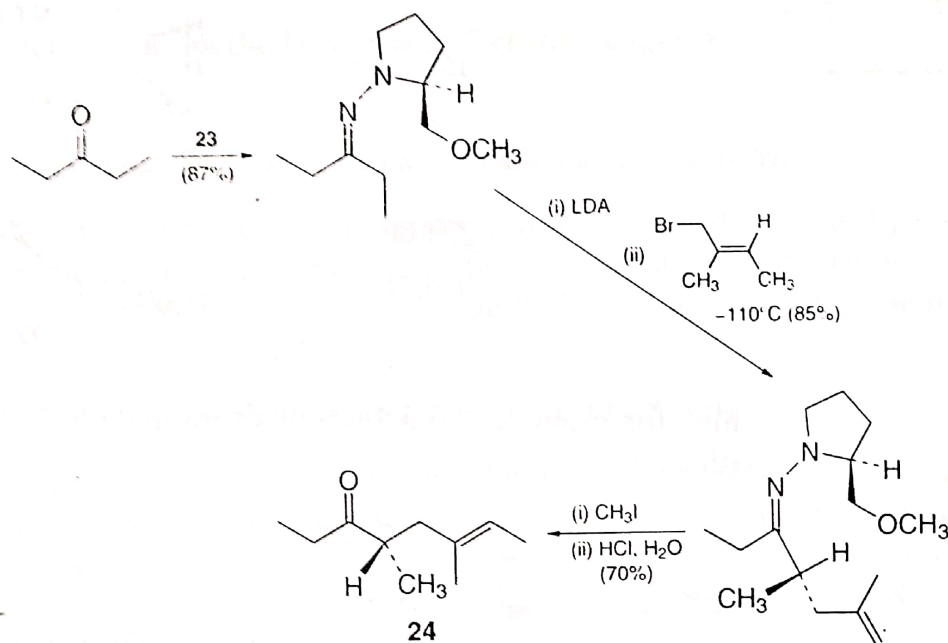

15.4.4 Alkylation α to nitrogen: chiral formamidines

Asymmetric alkylation at the α-position of an amine is of great value since many biologically active compounds, particularly alkaloids, have a stereogenic centre next to nitrogen. The α-alkylation of an amine may be achieved in an achiral sense by first converting the amine into a t-butylformamidine (**25**), as shown.
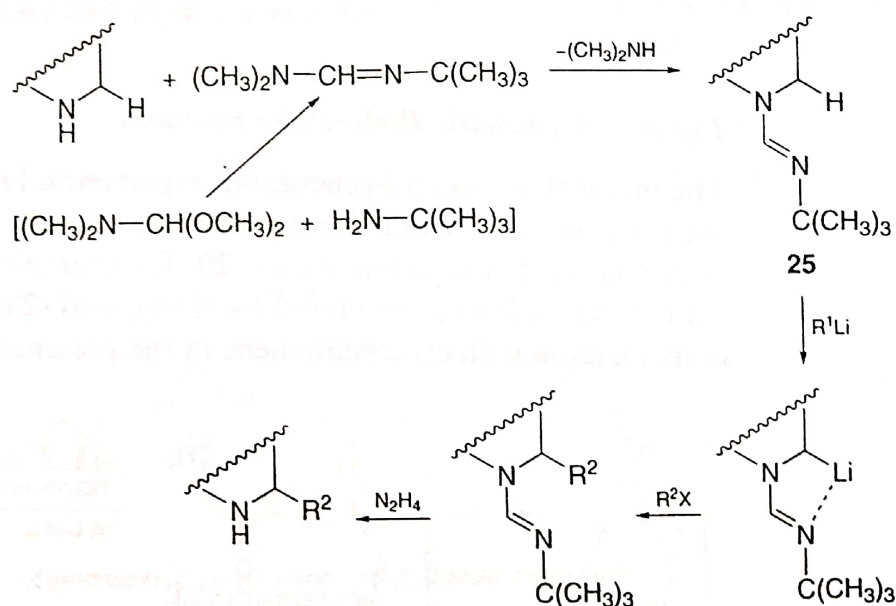
If, however, the formamidine contains a stereogenic centre, an efficient asymmetric alkylation is possible. The two auxiliary groups which give the best

results are the bis-trimethylsilyl ether **26** derived from the amino-diol **15** and the t-butyl ether **27** derived from S-valinol.
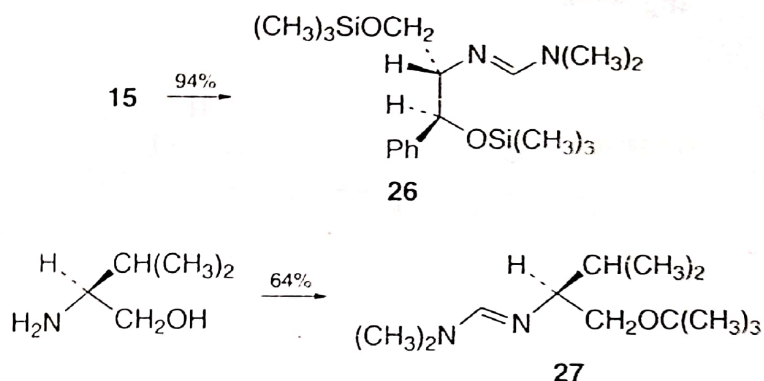
Thus, for example, 1,2,3,4-tetrahydroisoquinolines may be alkylated at C-1 with e.e. >95%:

(79% over two stages; 99% e.e.)
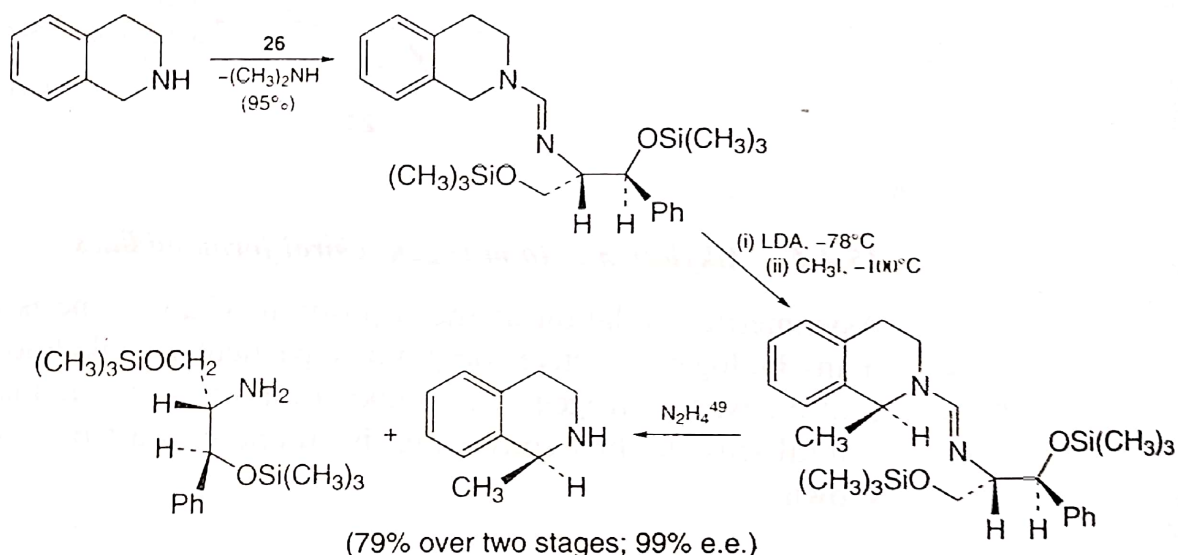
15.4.5 Asymmetric Diels–Alder reactions

The majority of 'second-generation' asymmetric Diels–Alder reactions involve the reaction of an achiral diene with a chiral dienophile, commonly a derivative of acrylic acid. The acrylate ester **29**, for example, which is derived from the readily available (+)-camphor-10-sulfonic acid (**28**), shows excellent selectivity in its reaction with cyclopentadiene in the presence of a Lewis acid:

(77% yield; 99% e.e.)
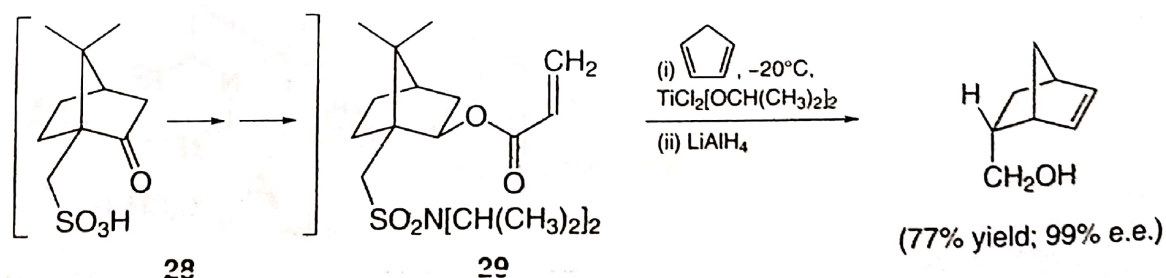
The further degree of rigidity introduced by using **30** as the dienophile allows other α,β-unsaturated acids to be used in this reaction; the use of a more

reactive Lewis acid catalyst permits lower reaction temperatures, thus further improving the e.e.

30

(91% yield; 98% e.e.)
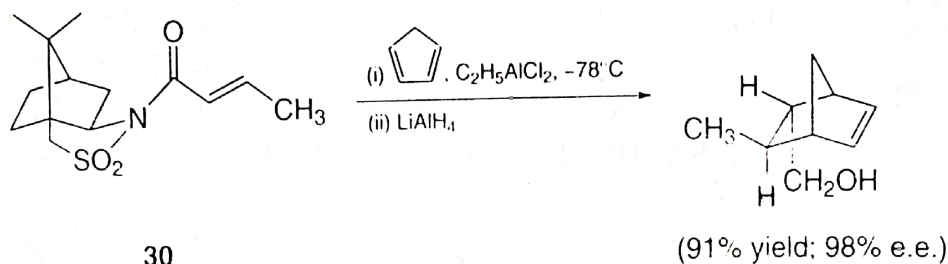
15.4.6   Self-regeneration of stereogenic centres

In this type of reaction, a chiral substrate is derivatized in such a way that a new stereogenic centre is created under the influence of the first. If the tetrahedral geometry of the original centre is then destroyed, the stereochemical information is stored in the new centre and the original stereogenic centre may then be regenerated stereospecifically. This process makes possible, for example, the α-alkylation of amino acids such as proline; it is not easy to generate, enantiospecifically, a quaternary stereogenic centre by other methods.
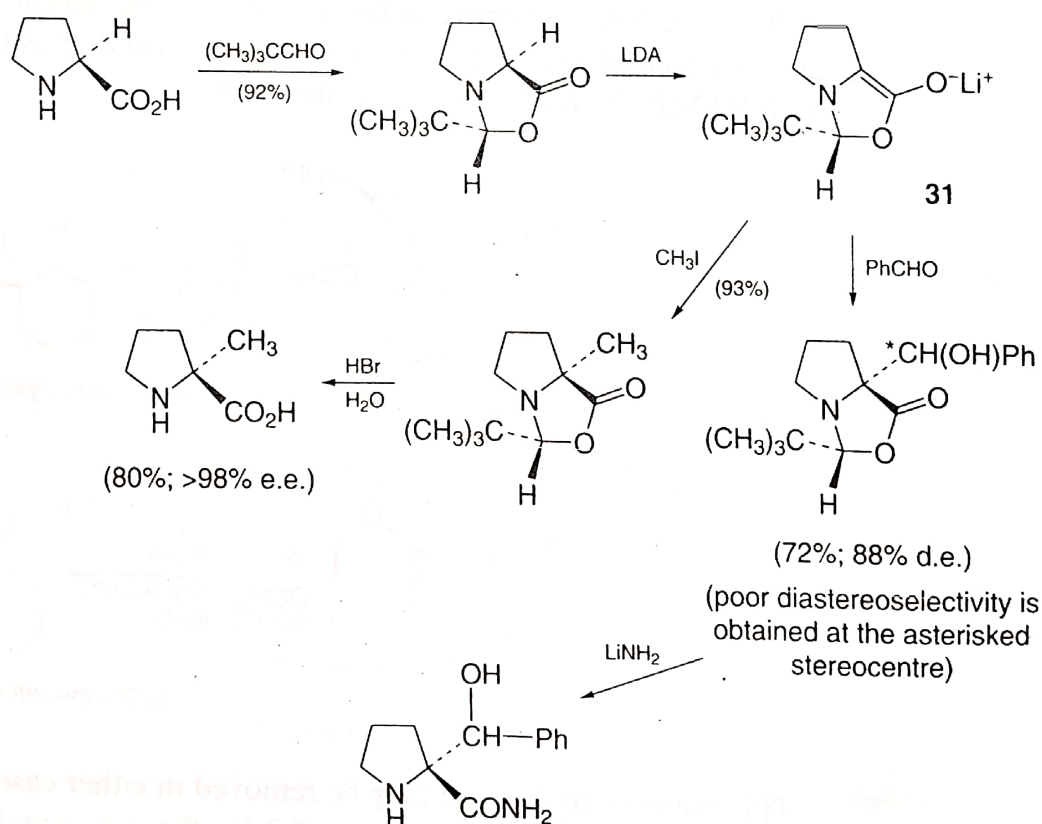
At first sight it may appear strange that the electrophile becomes attached to the lower face of the molecule, on the same side as the extremely bulky t-butyl group. In fact, however, in the enolate **31** the t-butyl group seeks to occupy a 'pseudo-equatorial' position and the resulting conformation of the molecule,

represented by **31a**, is such that the lower face of the molecule is actually less hindered than the upper.

31a
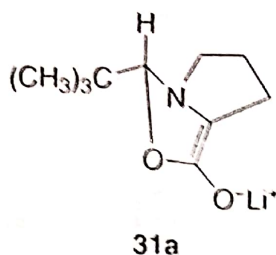
15.4.7   Chiral sulfoxides

Reaction of a sulfinyl chloride with a chiral alcohol, e.g. (−)-menthol (**32**), gives a diastereomeric mixture of sulfinate esters, **33** and **34**. Separation of these, and displacement of the menthyloxy group by an organolithium reagent, generates a pair of chiral sulfoxides [reaction (15.5)].

$(Ar = p\text{-}CH_3C_6H_4)$

32

(= Men*—OH)

(15.5)
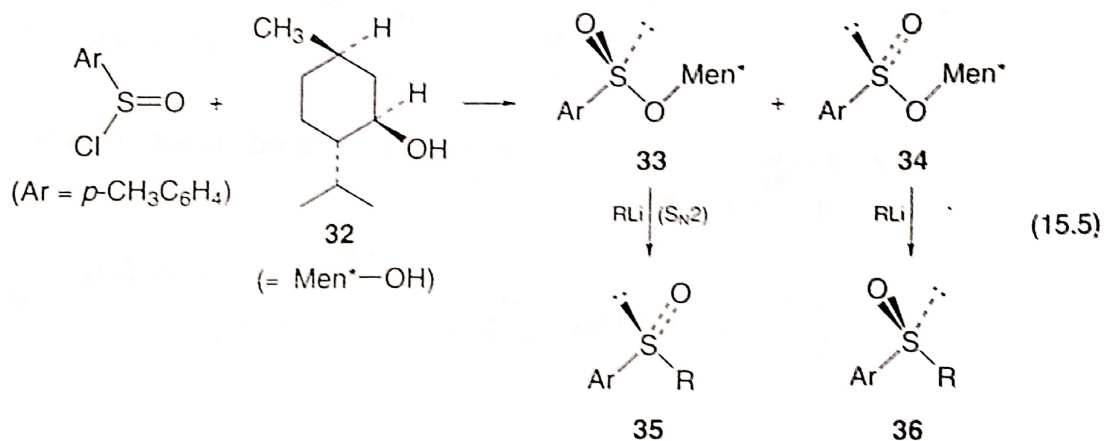
This then acts as a powerful directing group for asymmetric reactions such as the conjugate addition of Grignard reagents to enones, e.g.

(71% over two stages; 87% e.e.)
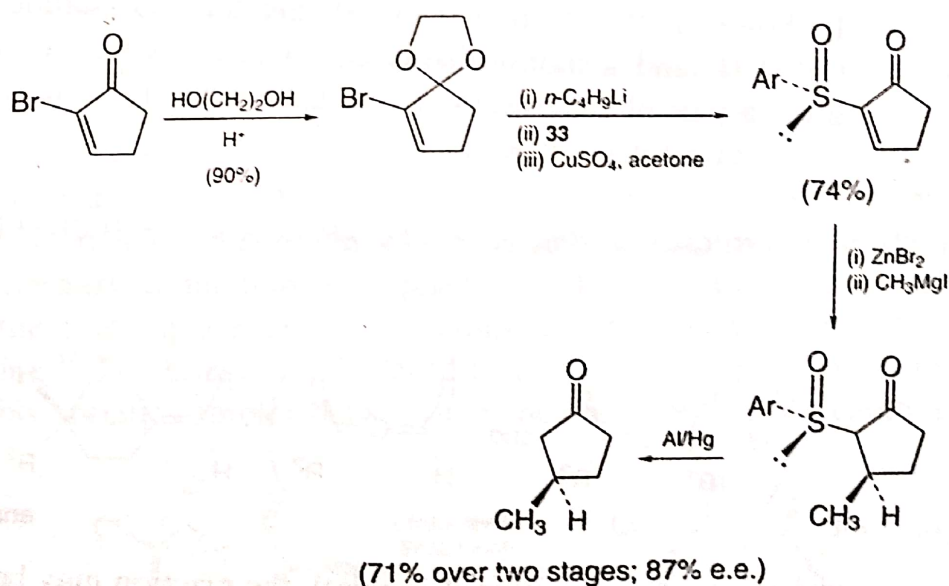
The sulfoxide substituent is readily removed by reaction with aluminium amalgam.

The use of a chiral sulfoxide in an asymmetric aldol reaction is illustrated in section 16.3.

15.5   Third-generation methods: the use of chiral reagents

15.5.1   Asymmetric reduction using lithium aluminium hydride

Lithium aluminium hydride can supply all four of its hydrogens as hydride ions for reduction, and several more selective reducing agents may be obtained by reaction of lithium aluminium hydride with a stoichiometric amount of a proton donor (cf. section 8.2), e.g.

$$LiAlH_4 + 3(CH_3)_3COH \longrightarrow LiAlH[OC(CH_3)_3]_3$$
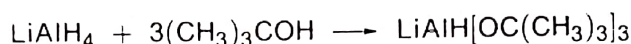
The corresponding reaction of lithium aluminium hydride with a chiral diamine or amino alcohol gives a reagent which can be used for efficient asymmetric reduction. For example, reduction of propiophenone (37) with lithium aluminium hydride in the presence of the proline-derived diamine (38) gives S-1-phenyl-propan-1-ol with high selectivity.
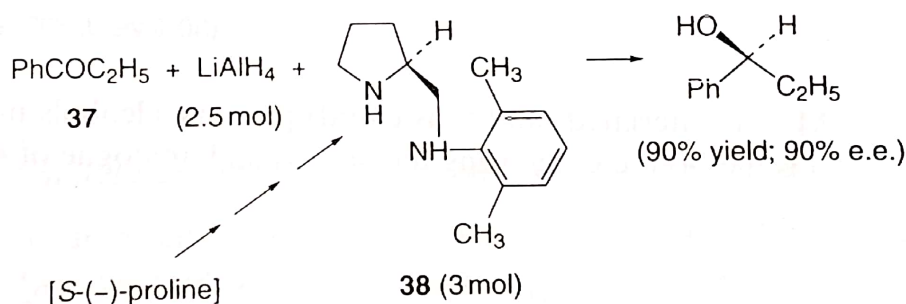
The reduction of the conjugated enone (39) in the presence of $(-)$-N-methyl-ephedrine (40) and N-ethylaniline is even more efficient.
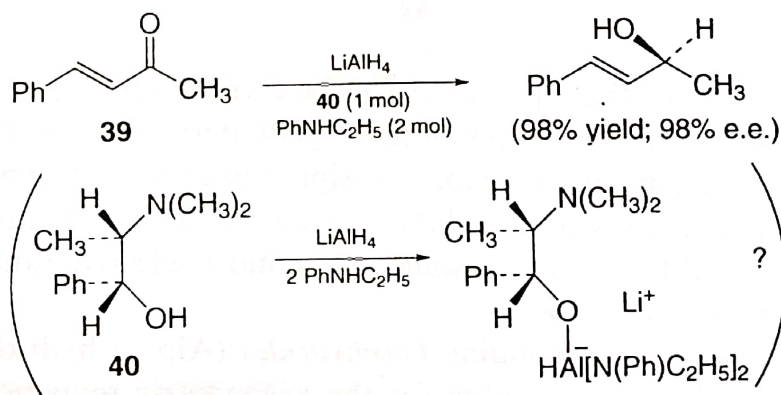

15.5.2   Asymmetric reduction using boron reagents

Reference has already been made (section 11.2.4) to the formation of chiral boranes by the hydroboration of terpenes such as α-pinene. The products are useful asymmetric reducing agents: for example, the reagent 41, formed

by reaction of (+)-α-pinene with 9-borabicyclo[3.3.1]-nonane (9-BBN), is commercially available (as R-Alpine-Borane®) and has been used to reduce a variety of ketones in high e.e. In these reactions, the hydride transferred during the reduction originates in the 9-BBN and the α-pinene, which is regenerated during the process, may be regarded as a chiral carrier of hydride.

(+)-α-pinene   9-BBN   **41**

$$CH_3(CH_2)_4COC\equiv CH \xrightarrow{\textbf{41}}$$

HO   H
    \/
CH_3(CH_2)_4   C≡CH

(90% e.e.; no yield given)

$$CH_3COCO_2C_2H_5 \xrightarrow{\textbf{41}}$$

HO   H
    \/
CH_3   CO_2C_2H_5

(50% yield; 89% e.e.)
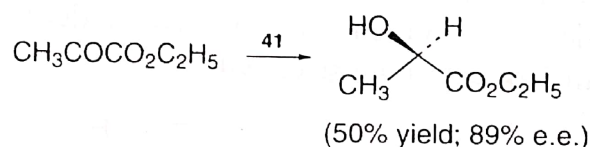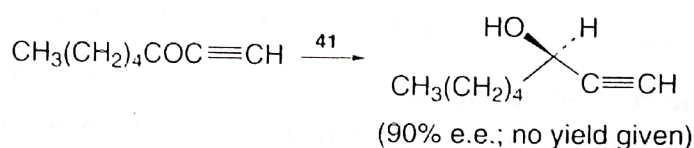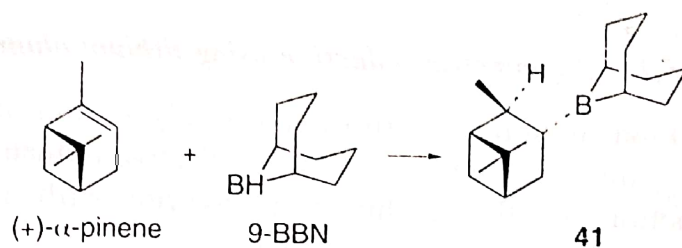
Monodeuteriated (and thus chiral) primary alcohols may also be obtained by this method, e.g. by using the deuteriated analogue of **41**, viz. **42**:

+ PhCHO ⟶

D   H
  \/
Ph   OH

(82% yield; 90% e.e.)

42
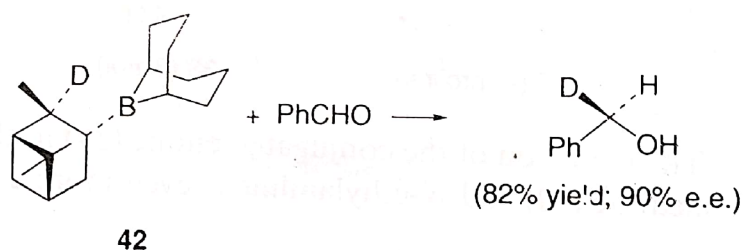
All of these processes can be carried out to give the opposite enantiomer by using the corresponding reagent derived from (−)-α-pinene, which is also commercially available (S-Alpine-Borane®]. The natural pinenes are not enantiomerically pure and the derived reagents are not of 100% e.e.; nevertheless the chiral boranes give some of the most selective (and high-yielding) asymmetric reactions known.

The corresponding *borohydrides* (Alpine hydrides®) are also commercially available and usable for the asymmetric reduction of carbonyl compounds. With simple ketones, however, these reactions generally proceed with relatively low e.e. (*c.* 30%).

15.5.3 *Asymmetric hydroboration*

Hydroboration is one of the most useful methods for functionalization of a double bond (cf. section 11.1–11.3) and the reagents formed from borane and
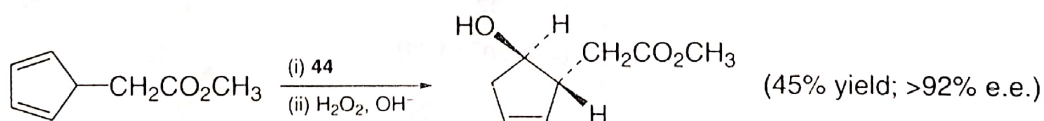
one or two equivalents of α-pinene, viz. **43** and **44**, can be used to achieve this process asymmetrically.
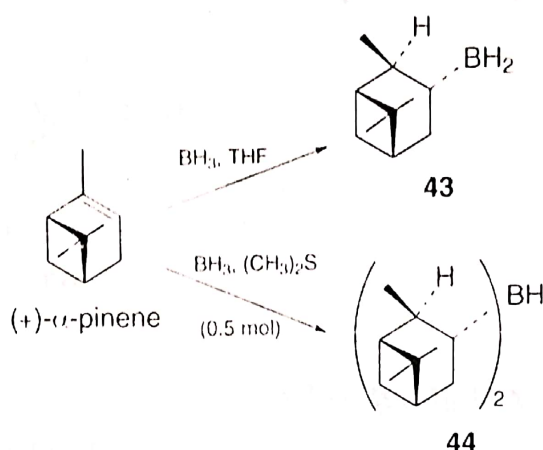
The former is the more reactive (and the less hindered) and it is the reagent of choice for hydroboration of trisubstituted alkenes, e.g.


(71% yield; >99% e.e.)
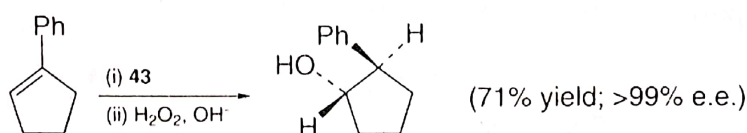
Z-Disubstituted alkenes, on the other hand, react smoothly with the disubstituted borane (**44**).

(45% yield; >92% e.e.)

15.5.4 Asymmetric Wittig-type reactions

At first sight, the formation of an alkene by a Wittig or related process (cf. sections 5.3.1 and 12.2.1) should not of itself constitute an asymmetric synthesis. If, however, the starting materials are an alkyl halide of the type R^1CH_2X ($R^1 \neq H$) and a monosubstituted, achiral cyclic ketone, the Wittig reaction gives a pair of stereoisomers which are enantiomeric (in the same manner as 1,3-disubstituted allenes):

enantiomers
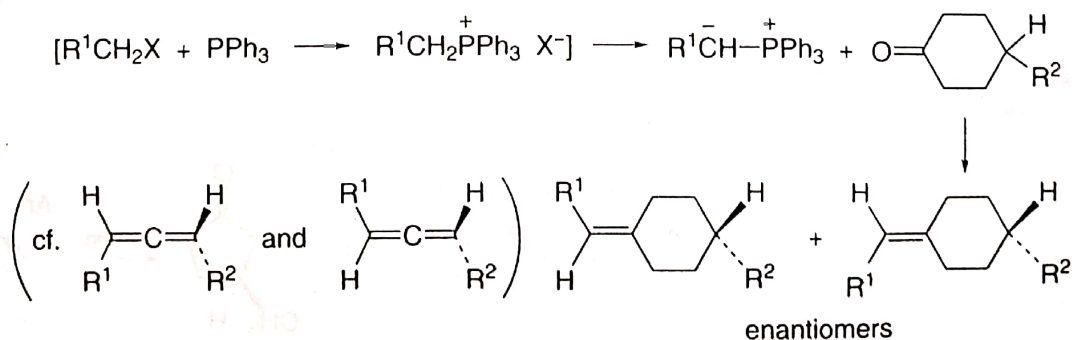
If the Wittig reagent itself is chiral, the reaction may become acceptably enantioselective. For example, the chiral Wittig-type reagent **46** [preparable from tris(dimethylamino)phosphine and the chiral diamine **45** in a sequence involving

a Michaelis–Arbusov reaction (section 12.1)] brings about the asymmetric Wittig reaction (48) ⟶ (49).
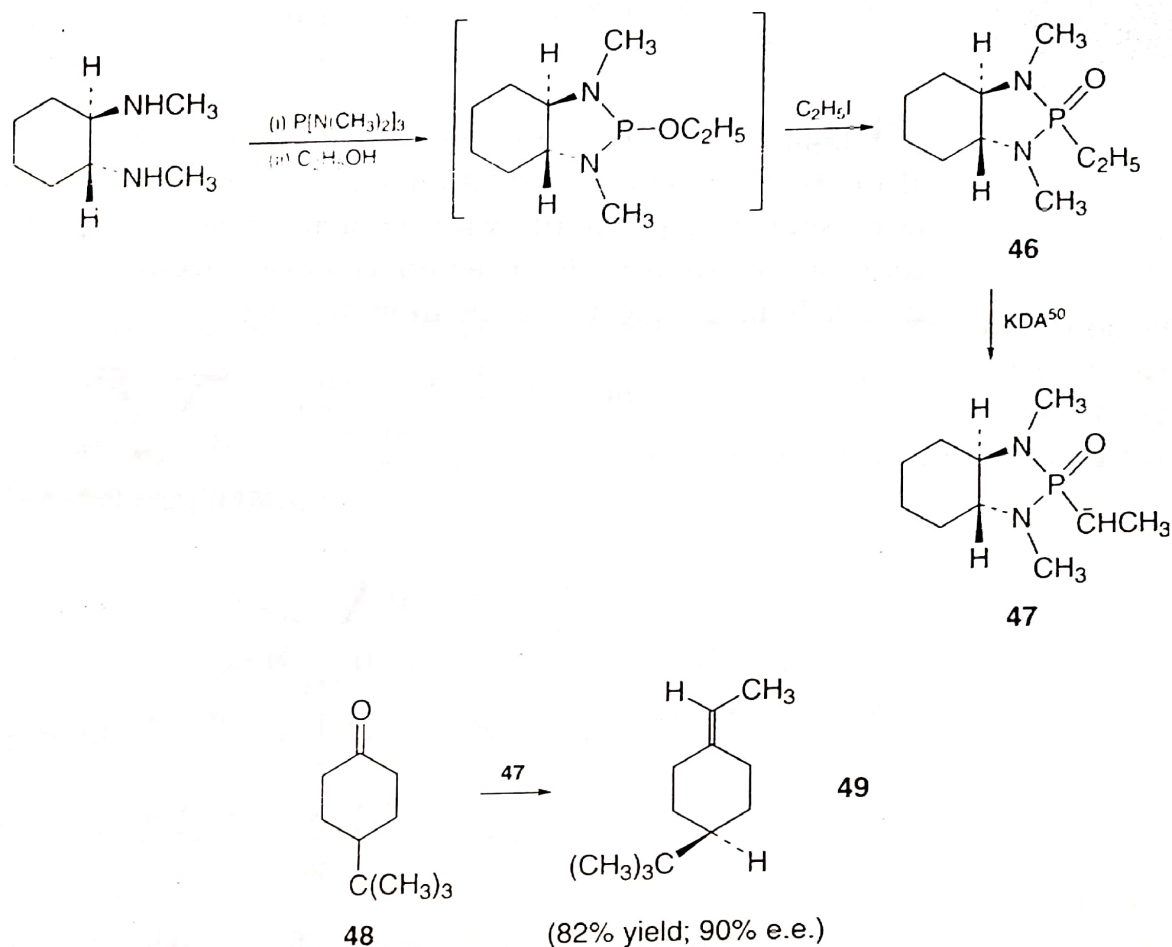

15.6   Fourth-generation methods: asymmetric catalysis

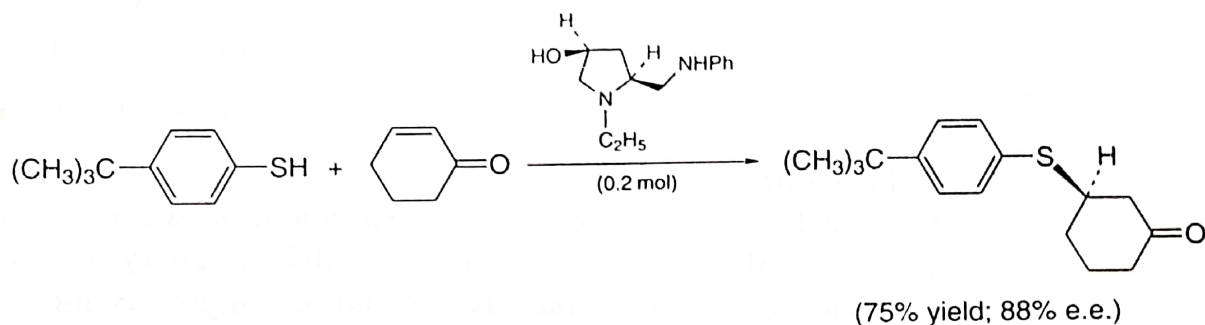### 15.6.1   Catalytic asymmetric alkylation

This type of reaction has been carried out successfully in some cases, although extensive optimization of the reaction conditions may be required in order to obtain a high e.e. In the following example, α-methylation of the 2-phenyl-indan-1-one derivative **50** gives, almost exclusively, the S-enantiomer. The reaction is carried out in a two-phase system (toluene–water) in the presence of a quaternary ammonium salt (phase-transfer conditions[51]); the salt in this case is the chiral quaternary ammonium salt (**51**) derived from the alkaloid cinchonine.[52] The high e.e. is believed to be the result of the initial formation of a highly specific complex between the enolate of **50** and the catalyst.

51
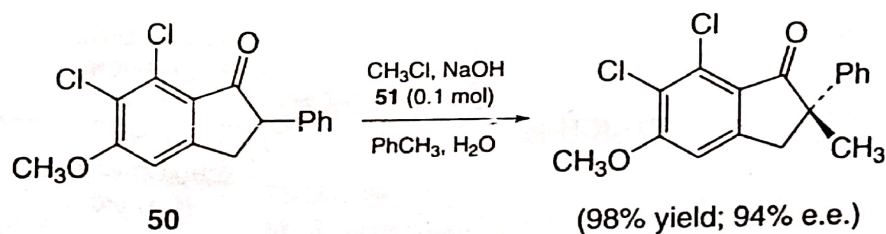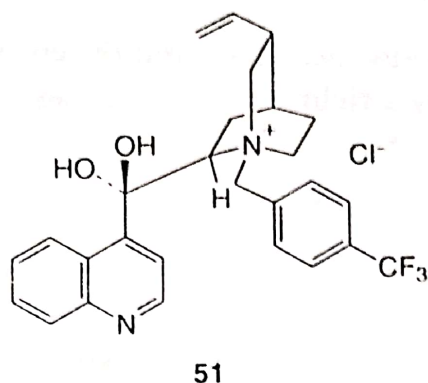
15.6.2 Catalytic asymmetric conjugate addition

Alkaloids and other chiral amines gives good selectivity in the addition of nucleophiles, particularly thiophenols, to α,β-unsaturated ketones; thus, for example,

(75% yield; 88% e.e.)

15.6.3 Catalytic asymmetric hydrogenation

Catalytic hydrogenation over transition metal catalysts with chiral ligands is a process of considerable importance and has been particularly successful for the synthesis of aromatic amino acids. In the example shown, a rhodium complex of the enantiomerically pure phosphine **52**, prepared by resolution, is used to produce the important pharmaceutical L-DOPA [S-3-(3,4-dihydroxyphenyl)-alanine, **53**].


52

53
(88% e.e.)
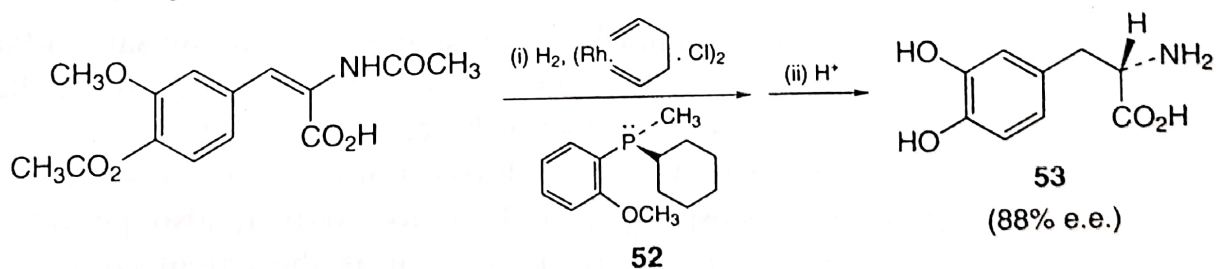
15.6.4 Asymmetric oxidations

The asymmetric epoxidation of the double bond in allylic alcohols is an important and versatile synthetic procedure. The reaction, usually known as Sharpless oxidation, is brought about by hydroperoxides, in the presence of (+) or (−)-diethyl tartrate (DET) and a titanium(IV) salt [reaction (15.6)]. The reaction creates two contiguous stereogenic centres, with predictable stereochemistry according to which enantiomer of DET is used (both are

commercially available), and the epoxides are versatile synthetic intermediates in their own right.


(15.6)
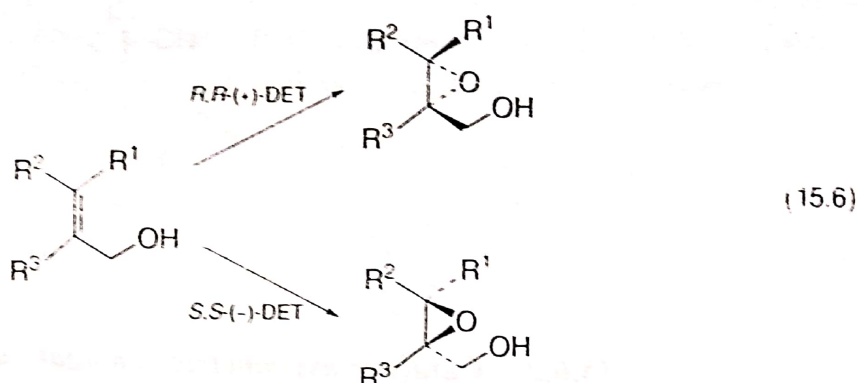
For example,

(79% yield; >95% e.e.)
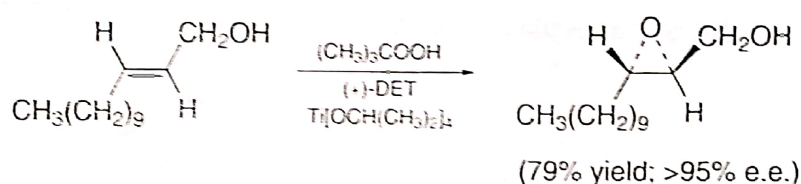
The major catalytic species in this reaction is the binuclear titanium complex (54), which undergoes successive displacement of isopropoxy groups from one titanium by the hydroperoxide and the allylic hydroxy function. The epoxidation then occurs between these two ligands in a highly asymmetric environment.
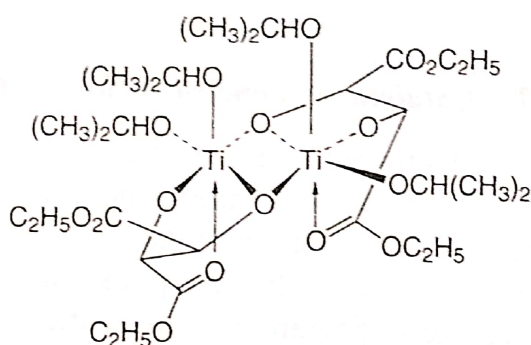

54

The reaction is genuinely catalytic, both in titanium salt and in DET, provided that water is excluded from the system (i.e. hydrolysis of the complex is prevented): this may be achieved by carrying out the reaction in the presence of molecular sieves. This procedure is not only cost-effective [especially when the relatively expensive (−)-DET is involved], it also permits the synthesis of highly reactive epoxy-alcohols, such as the parent compound, glycidol (55), and their conversion into isolable derivatives, e.g. toluene-p-sulfonates:
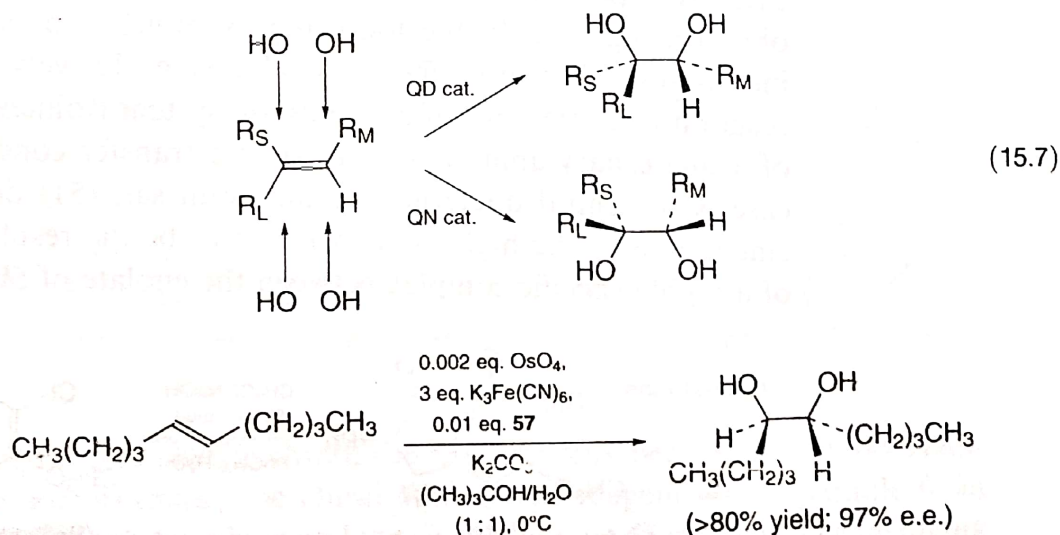

(40% overall; 94% e.e.)
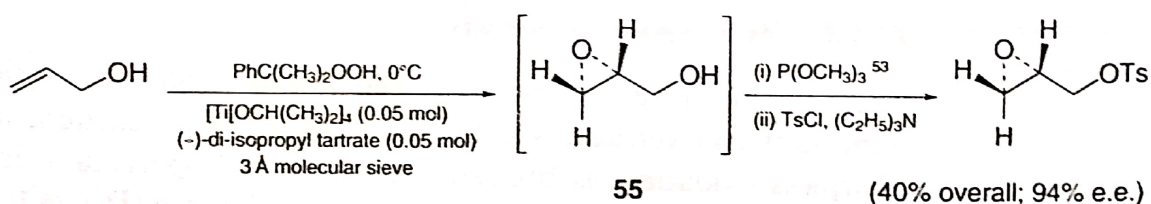
The same reagent system may also be used for the asymmetric oxidation of sulfides and sulfoxides. In this case, water is actually required in order to achieve good selectivity.

$$(CH_3)_3COOH$$
$$(+)\text{-DET (2 mol)}$$
$$\overrightarrow{}$$
$$Ti[OCH(CH_3)_2]_4$$
$$CH_2Cl_2,\ H_2O$$
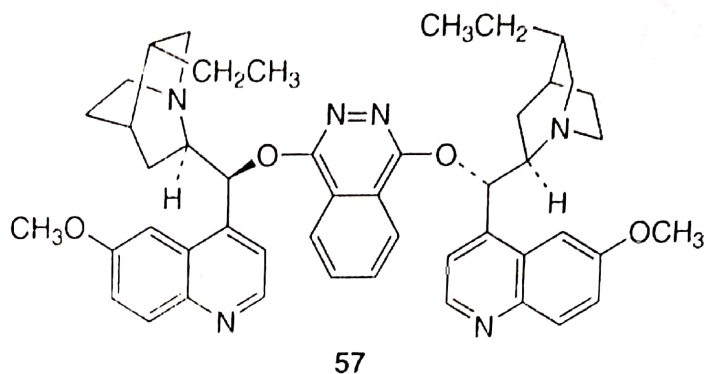
(90% yield; 90% e.e.)
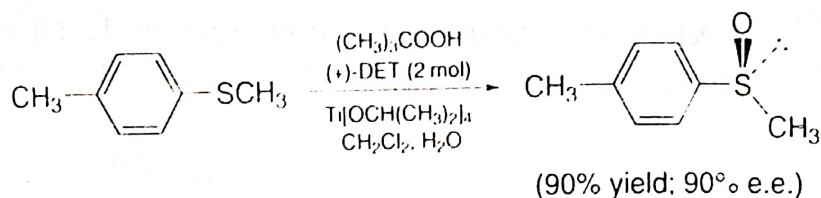
A limitation of the aforementioned method is that it is restricted to allylic alcohols. Asymmetric epoxidation of unfunctionalized alkenes may be achieved using sodium hypochlorite with the manganese–salen complex **56** as a chiral catalyst. As shown, the reaction is most effective for Z-alkenes with the double bond conjugated to an aromatic ring.

NaOCl, H₂O

0.04 eq. **56**,
CH₂Cl₂

(81% yield; 92% e.e.)

56
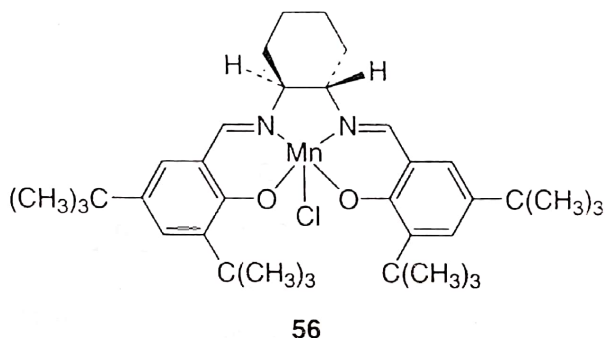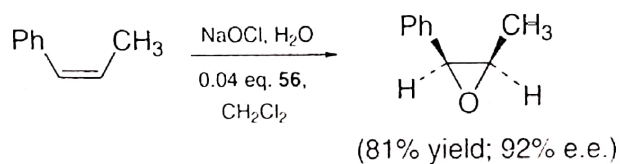
The 1.2-dihydroxylation of alkenes (cf. section 9.2.5.2) can also be carried out asymmetrically with predictable enantioselectivity [reaction (15.7)] using osmium(VIII) oxide in the presence of bidentate catalysts derived from quinine (QN) or quinidine (QD). Because of the toxicity of osmium(VIII) oxide it is used in a catalytic quantity with a reoxidant such as potassium ferricyanide. In the example shown, the dihydroxylation of dec-5-ene is directed by the catalyst **57**, termed (DHQD)₂PHAL, which is derived from dihydroquinidine. The corresponding catalyst derived from dihydroquinine would give the opposite enantiomer.

(15.7)

0.002 eq. OsO₄,
3 eq. K₃Fe(CN)₆,
0.01 eq. **57**

K₂CO₃

(CH₃)₃COH/H₂O
(1 : 1), 0°C

(>80% yield; 97% e.e.)

57

In a more recent extension of this approach, 1,2-aminohydroxylation of alkenes has also been possible. In this case, the less volatile, and therefore safer, potassium osmate is used instead of osmium(VIII) oxide and the amino function is provided by the readily available sodium salt of N-chloro-p-toluene-sulfonamide (Chloramine-T).

(66% yield; 71% e.e.)
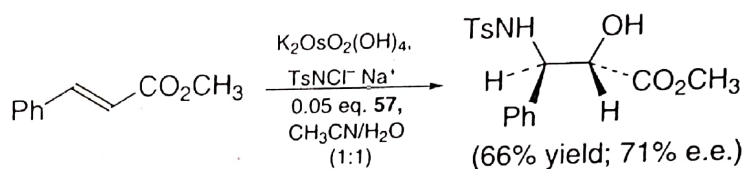
### 15.6.5 Asymmetric aziridination and cyclopropanation

As described in the previous section, the asymmetric oxidation of an alkene, either to the epoxide or to the 1,2-diol, results directly in the formation of two new adjacent stereogenic centres. Catalytic procedures for the asymmetric conversion of alkenes into both aziridines and cyclopropanes (cf. section 7.2.3) are also available and these also give excellent enantioselectivity.

For the aziridination reaction, phenyliodonium N-p-toluenesulfonylimide, $PhI = NTs$, proves to be a suitable nitrene equivalent and the reaction is catalysed by a Cu(I) derivative of the bis-oxazoline ligands **58** or **59** formed *in situ*. The most effective catalyst depends upon the substrate as shown and **59**, which gives the best results for hydrocarbons, gives only 16% yield and 19% e.e. with methyl cinnamate.


(63% yield; 94% e.e.)

58 R = Ph
59 R = C(CH₃)₃

(89% yield; 63% e.e.)
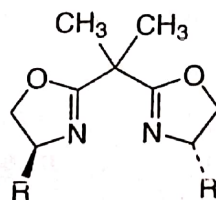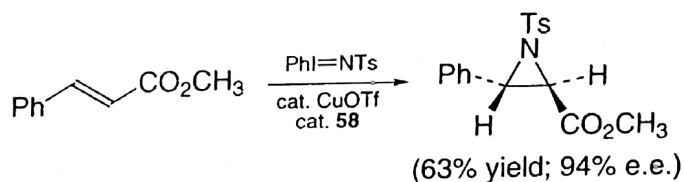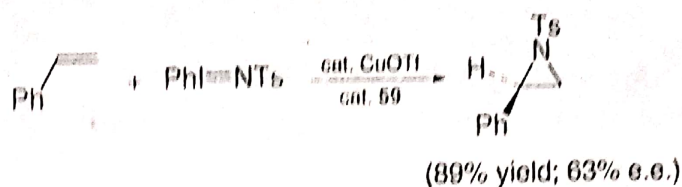
A similar approach has also proved effective for asymmetric cyclopropanation of alkenes by diazo esters. The same catalysts may be used and, although initial studies focused on very bulky diazo esters to obtain the best selectivity, the method also works well for simpler diazo esters in some cases.

(85% yield; 94:6 *trans/cis*; 99% e.e. for *trans*)

(91% yield; >99% e.e.)
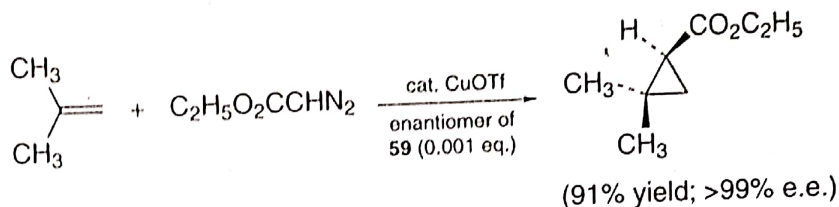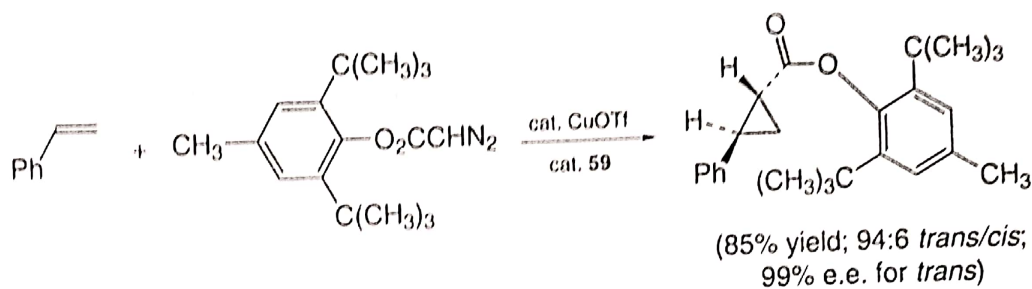
Another approach to cyclopropanation which has been successfully developed into a catalytic asymmetric method is the Simmons–Smith reaction (cf. section 7.2.3). Like the titanium tartrate-mediated epoxidation of the previous section, this reaction is confined to allylic alcohols and the selectivity can be predicted [reaction (15.8)] according to which of the enantiomeric dioxaborolane Lewis acid catalysts, 60 or 61, is used.


(15.8)
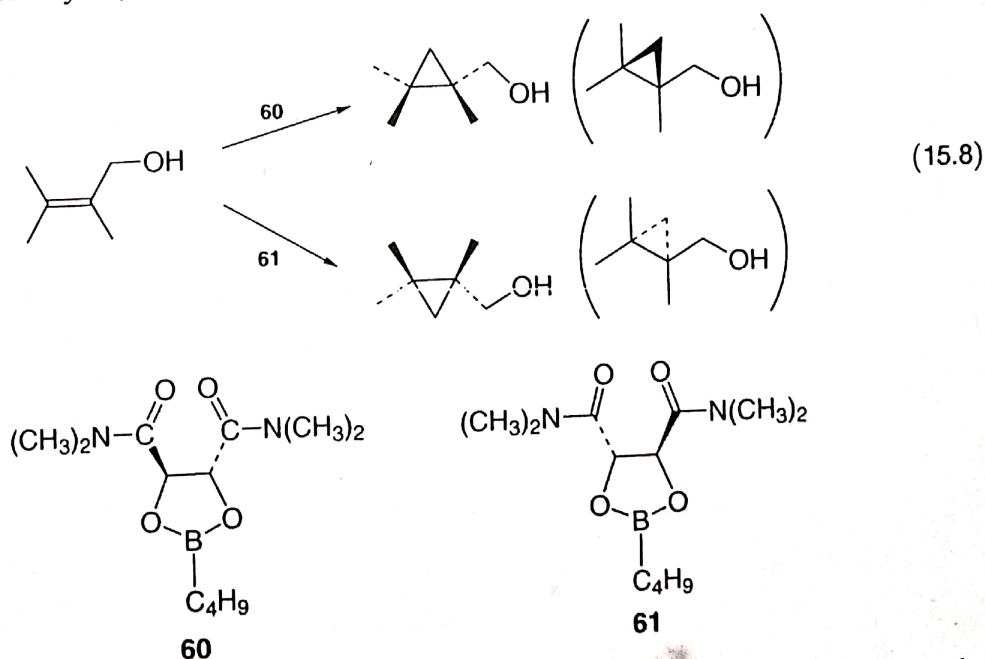
The safest and most convenient procedure involves preforming the dimethoxyethane complex of $Zn(CH_2I)_2$ (62) as shown and then adding an excess of

this to the alkene and the catalyst at −10°C. An elegant application of this method to total synthesis is illustrated in section 16.5.

62

(>98% yield; 93% e.e.)


(>98% yield; 93% e.e.)
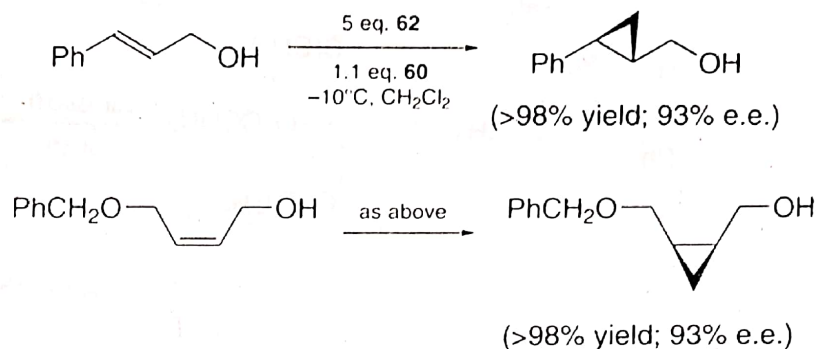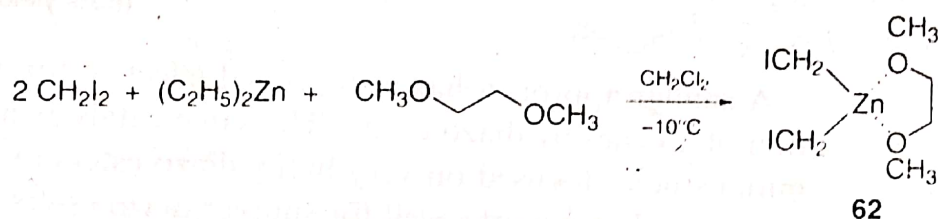
15.6.6 Reactions catalysed by enzymes and other proteins

A wide variety of asymmetric reactions, including oxidation, reduction and hydrolysis, have been successfully performed using either isolated enzymes or intact organisms such as yeast. Although such methods are generally considered expensive, and substrate specificity may limit their general use, they are of increasing importance and often provide access to chiral compounds which are otherwise not available. As examples of substrate specificity, ethyl aceto-acetate (63) can be reduced to the S-hydroxy-ester using baker's yeast (60% yield, 97% e.e.), whereas the homologue (64) gives very poor selectivity under the same conditions. The bacterium *Thermoanaerobium brockii*, however, effects the reduction of compound (64) to the S-hydroxy-ester (93% e.e.) in 40% yield.


63: R = CH₃
64: R = C₂H₅
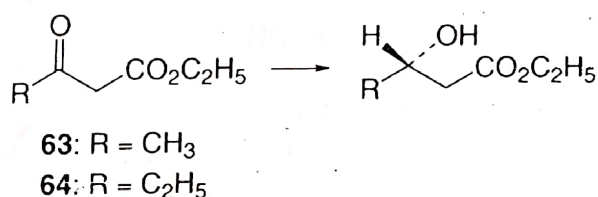
Enantioselective reactions of meso-compounds have, until recently, only been possible using enzymes. For example, horse liver alcohol dehydrogenase (HLADH) selectively oxidizes the diol 65 to the lactone 66 and pig liver esterase (PLE) brings about selective hydrolysis of the ester 67.

(>97% e.e.)

65   **66**

67
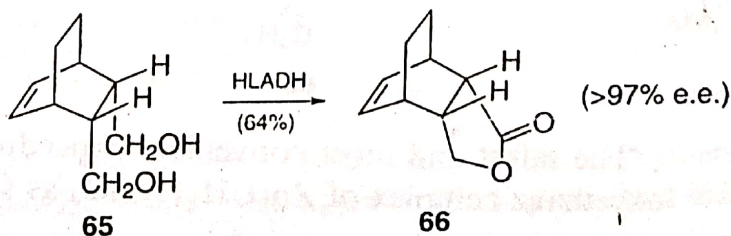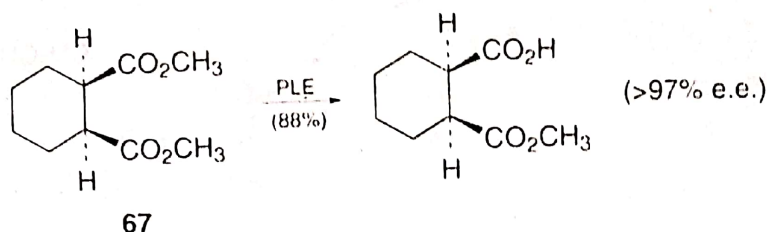
Proteins other than enzymes have been used as catalysts in a few asymmetric syntheses. The *Darzens reaction*, for example, is a variant of the aldol reaction (section 5.2.4) which, in an achiral sense, is brought about by strong bases, such as potassium t-butoxide:
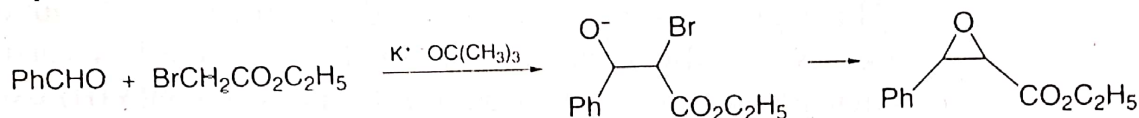
In aqueous base, however, in the presence of the readily available protein, bovine serum albumin, an asymmetric Darzens reaction becomes possible, e.g.

(100% d.s.; 62% e.e.)
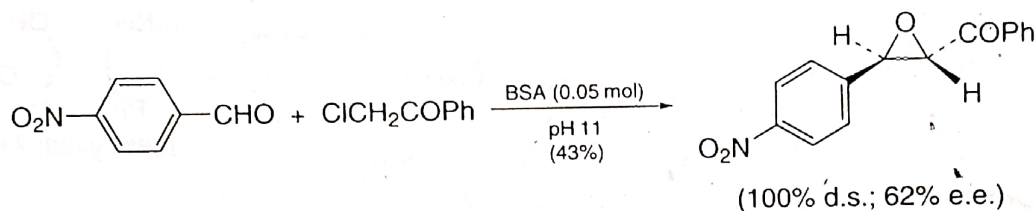
Summary
- Stereochemical vocabulary is revised and definitions provided for *enantiomeric excess* and *diastereomeric excess*.

- Asymmetric syntheses are classified into four types:

  (i) substrate-controlled methods, in which the starting compound is available (often from natural sources) in enantiomerically pure form and new stereogenic centres are formed under the influence of those already present;

  (ii) auxiliary-controlled methods, in which chirality is introduced by the attachment of a so-called 'chiral auxiliary': this directs the subsequent reaction and is finally removed;

  (iii) reagent-controlled methods, in which a chiral product is formed directly by treating an achiral starting compound with a chiral reagent;

  (iv) catalyst-controlled methods, an extension of (iii) in which the reaction is brought about using an achiral reagent in the presence of a chiral catalyst; enzyme-catalysed reactions belong to this class.

- Numerous examples are provided, especially of reactions belonging to categories (ii), (iii) and (iv). The synthetic principles already established (in an achiral sense) in Chapters 5, 7, 8, 9 and 11 are thereby extended into the asymmetric field.