Guidebook to Organic Synthesis

2nd Edition

R K MACKIE, D M SMITH & R A AITKEN

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Second Edition

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Foreword

> "For they are not given to idleness, nor go in a proud habit, or plush and velvet garments, often showing their rings upon their fingers, or wearing swords with silver hilts by their sides, or fine and gay gloves upon their hands, but diligently following their labours, sweating whole days and nights by their furnaces. They do not spend their time abroad for recreation, but take delight in their laboratory. They wear leather garments with a pouch, and an apron where with they wipe their hands. They put their fingers 'mongst coals, into clay, and filth, not into gold rings. They are sooty and black, like smiths and colliers, and do not pride themselves upon clean and beautiful faces."

We have come a long way since Paracelsus wrote this about chemists around 1520. Indeed, that the precise molecular structure of a complex molecule such as a penicillin could be determined some forty years ago, with the help of no more physical equipment than a balance and a thermometer, must rank as one of the greatest intellectual feats of mankind. Since then, the seemingly exponential progress of spectroscopy and computing have allowed the determination of organic structures to become much simpler. Whereas cracking the basic structure of the penicillins took about 800 man years in the forties, we now confidently expect an undergraduate with access to suitable spectroscopy to do it in a day.

But we still have to be able to synthesise pure organic compounds. Here too, the pace of advance has quickened enormously. An increasing multitude of synthetic methods, routes, approaches, concepts, scenarios are there to bemuse the student. Hence this Guidebook: it is for their benefit.

I said in the foreword to the First Edition that the authors had been guided by their long experience of university teaching. That Edition turned out to be very well received. So, knowing that their readers had found it valuable, the original authors, joined now by Dr Alan Aitken, are on even stronger ground in producing their new Edition. They have operated on the principle of reinforcement of success. Thus they have continued to combine the traditional with the new to give a readable and undaunting summary of the essentials of organic synthesis which will be even more valuable than its predecessor to students and their teachers alike.

J. I. G. CADOGAN

Preface to the Second Edition

This book, like its predecessor, is intended for students who are beginning a serious and detailed study of organic synthesis. It is assumed that they will already have completed a course in elementary organic chemistry which includes the reactions of simple functional groups and the basic concepts of reaction mechanism and stereochemistry. We have particularly in mind students in the third and fourth years of a Scottish Honours Chemistry course, and their counterparts elsewhere in the world.

When, ten years ago, two of us (R.K.M. and D.M.S.) were invited by our former Head of Department, Professor John Cadogan, to write the original Guidebook, we were all aware that many of our students experienced difficulty in tutorials and examinations when confronted by synthetic problems. We required very little persuasion – and neither did Messrs Longman – that such a Guidebook was timely, especially in view of the (then) new synthetic methodology described by Warren[1] as the 'synthon–disconnection' approach and by others as 'retrosynthetic analysis'.

Now, a decade later, we are convinced that this new Edition is equally timely. Seven years of student use, and the many helpful comments which have resulted, have enabled us to refine the original version by correcting minor errors and clarifying points of difficulty. We have also been glad of the opportunity to bring the whole text up to date: this has involved a major expansion of Chapter 12 (phosphorus reagents) and Chapter 13 (silicon reagents), as well as a revised section on the Wittig reaction (section 5.3.1).

Two chapters in this Second Edition are completely new. Asymmetric synthesis (Ch. 15) is, almost certainly, the largest growth area of organic synthesis during the 1980s, and R.A.A. has been recruited to the team of authors with this chapter particularly in mind. We hope that it provides a readable introduction to this fascinating topic and the demands it makes on the synthetic chemist's ingenuity. The other new chapter, dealing with selenium reagents (Ch. 14), reflects the recent growth of interest in such reagents and the selective transformations which they bring about.

As in the First Edition, the final chapter is devoted to the detailed dis-

cussion of several multi-step syntheses taken directly from the original literature. Some of these appeared in the First Edition, while others are new. The volume ends with a list of 'Further Reading' which has been updated to the end of 1988.

We have again resisted the temptation – or recoiled at the prospect! – of producing a chapter, or chapters, on the use of transition metals in organic synthesis. We acknowledge the importance of, and the current interest in, such processes, and we apologise to any who may be offended by the omission; but the choice of material for a book of this size is not an easy one, and transition metal-mediated organic reactions are worthy of a textbook by themselves.[2]

With regard to reaction mechanisms, we have made extensive cross-reference throughout the text to Dr Peter Sykes' *A Guidebook to Mechanism in Organic Chemistry*, the page numbers referring to the Sixth Edition (Longman, 1986). In all the illustrated examples throughout the text, we have quoted product yields where these have been recorded in the literature; in the chapter on asymmetric synthesis, the enantiomeric or diastereomeric excess has also been recorded where appropriate.

We thank our students here, and our colleagues in St Andrews and elsewhere, for their comments and criticisms, and for their continuing helpful suggestions. We also thank Mrs Ruth Black for typing the new sections of the book.

R.K.M.
St Andrews D.M.S.
February 1989 R.A.A.

Notes

1. S. Warren, *Designing Organic Syntheses: A Programmed Introduction to the Synthon Approach*, Wiley, 1978; *Organic Synthesis: The Disconnection Approach*, Wiley, 1982.
2. For example, S. G. Davies, *Organotransition Metal Chemistry: Applications to Organic Synthesis*, Pergamon Press, 1982.

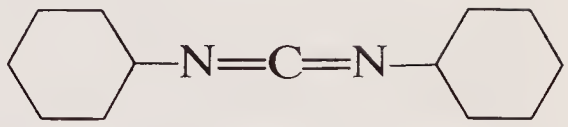
Important notice

This book is not intended to be a 'recipe book' for the experimentalist. The reactions cited here should be regarded merely as an illustration of the general principles; readers seeking to use these reactions in practice are *strongly advised* to refer first to the original literature for experimental details.

Readers are also reminded of the various hazards entailed in organic chemical reactions, and of the consequent need for proper safety precautions. The fire hazard associated with many common solvents is well known, but particular care must also be taken where a compound is liable to be explosive (e.g. azides, diazo-compounds): corrosive (e.g. phenols), skin-irritant, toxic (e.g. methylating agents) or carcinogenic (e.g. benzene, *N*-nitroso compounds, and certain arylamines). Further details of such hazards, and safety precautions, are to be found in practical handbooks, e.g. in Vogel's *Textbook of Practical Organic Chemistry* (Fifth Edition, Longman, 1989).

Abbreviations and other trivial names

DCC — *N*,*N*′-Dicyclohexylcarbodi-imide,



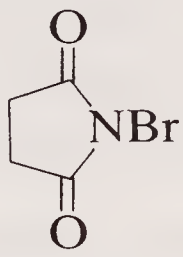
Diglyme — Diethyleneglycol dimethyl ether, $CH_3O(CH_2)_2O(CH_2)_2OCH_3$

Digol — Diethylene glycol, $HO(CH_2)_2O(CH_2)_2OH$

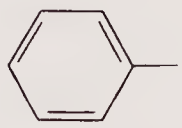
DMF — *N*,*N*-Dimethylformamide, $(CH_3)_2NCHO$

LDA — Lithium di-isopropylamide, $[(CH_3)_2CH]_2N^-Li^+$

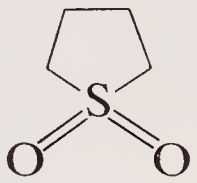
NBS — *N*-Bromosuccinimide,



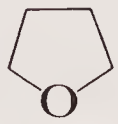
Ph — Phenyl,



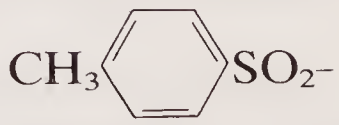
Sulpholan — Tetramethylene sulphone,



THF — Tetrahydrofuran,



Ts (also tosyl) — Toluene-*p*-sulphonyl,



1 Introduction

Of the principal constituent parts of present-day organic chemistry, synthesis is the one with perhaps the longest history. The ideas of functionality and stereochemistry, for example, have their origins in the second half of the nineteenth century, and the concepts of bonding and reaction mechanism, as we know them today, undoubtedly belong to the present century. Synthesis, however, has constituted an important part of organic chemistry from the very beginning of the subject, and thus has a history stretching back over many centuries. It has to be admitted, however, that most of the early work was fragmentary in character, depending as it did on starting materials isolated from natural sources in doubtful states of purity; the *development* of organic synthesis on a systematic basis belongs to the nineteenth century, even if its *origins* are much earlier.

In more recent times, the growth of organic synthesis has kept pace with the growth of organic chemistry as a whole. As understanding of structural and theoretical chemistry has increased, and as experimental methods have been developed and refined, the chemist has been able to set himself more and more ambitious synthetic objectives. These lead in turn to the discovery of new reactions and to the perfection of new experimental methods, and thence to new synthetic targets; and so on. Thus present-day organic synthesis often appears to the student as a vast assembly of factual information without much by way of structure or rationale.

During the 1950s and 1960s, the teaching of functional group chemistry was revolutionised, and in most cases greatly simplified, by the use of reaction mechanism. The corresponding revolution in the teaching of synthesis has, unaccountably, taken somewhat longer, but is now becoming better established.

The fundamental ideas which lie behind this revolution are neither complicated nor new. They consist in recognising that a covalent bond is formed in the vast majority of synthetically useful processes, by the interaction of an electrophilic and a nucleophilic atom: and in recognising the various structural units (called **synthons**) which go to make up a given synthetic target molecule. The ideas have been familiar to synthetic chemists for decades, but are only now being included in undergraduate textbooks or lecture courses.

In 1835, the German chemist, Friedrich Wöhler, who was one of the pioneers of organic synthesis, wrote a letter to his mentor, the great Jöns Jacob Berzelius, which included the following often-quoted remarks:[1]

> Organic chemistry just now is enough to drive one mad. It gives me the impression of a primeval tropical forest, full of the most remarkable things; a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter.

If any reader of this Introduction feels like that about organic *synthesis*, let him read on. This Guidebook has been written especially for him and those who share his view. It may not lead him right through the forest, but we hope that it will at least provide a reliable pathway, over solid ground, as far as the first clearing.

Note

1. A. Findlay, *A Hundred Years of Chemistry*, Second Edition, Duckworth, 1947, p. 21.

2 Functionalisation and interconversion of functional groups

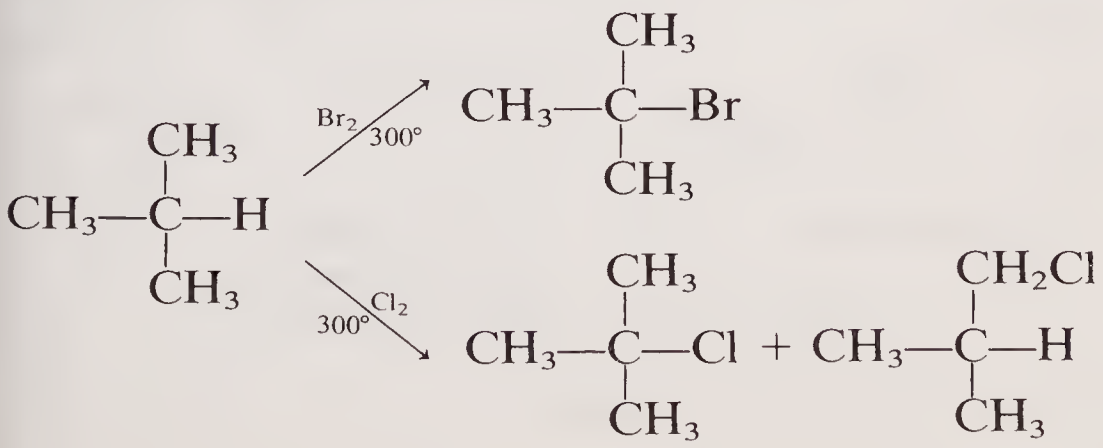
Important aspects of synthesis are the introduction of functional groups into a molecule and interconversion of functional groups. We shall show that in some instances it is relatively easy to functionalise certain positions whereas in other situations functionalisation is impossible and the desired product can only be obtained by a series of interconversions of functional groups.

In this chapter, we shall attempt to bring together, in outline only, a variety of reactions which the successful synthetic chemist will require to have at his command. Further details of the reactions mentioned in this chapter will be found in standard works on organic chemistry and Sykes describes the mechanisms of many of the reactions.

2.1 Functionalisation of alkanes

The unreactivity of alkanes towards electrophilic and nucleophilic reagents will be familiar to the reader. Alkanes are, however, reactive in radical reactions, particularly halogenation. Such reactions are nevertheless of limited synthetic use, due to the difficulties encountered in attempts to control them.

Because of the higher reactivity of $Cl^{\bullet}$ than $Br^{\bullet}$, chlorination tends to be less selective than bromination and, indeed, 2-bromo-2-methylpropane is almost exclusively formed when isobutane reacts with bromine at 300° whereas chlorination results in a 2:1 mixture of 1-chloro- and 2-chloro-2-methylpropane.



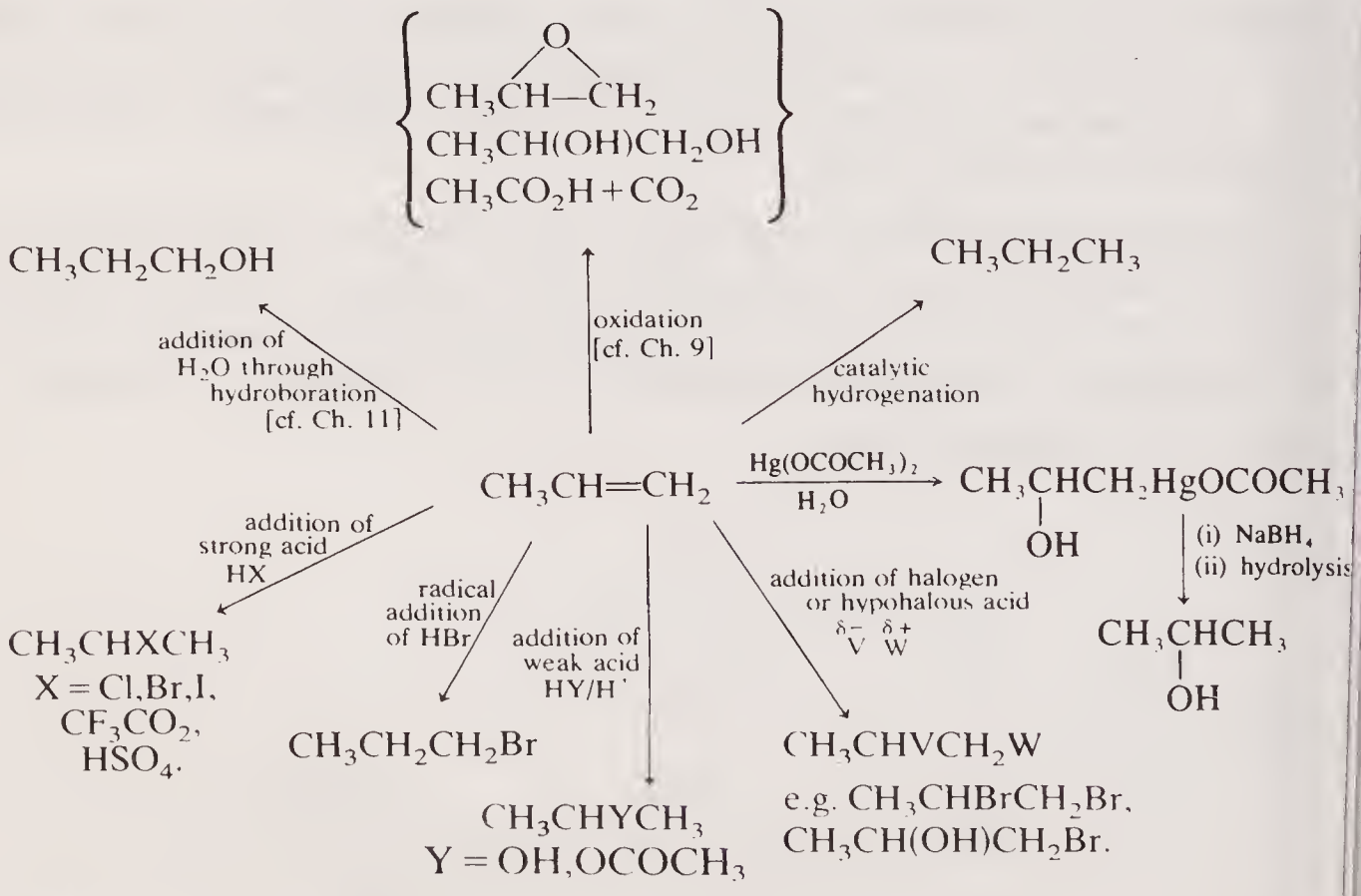
On the other hand, rearrangements are encountered in the intermediate radicals with less frequency than in the corresponding carbocations. Thus, only 1-chloro-2,2-dimethylpropane results when 2,2-dimethylpropane is chlorinated:

$$(CH_3)_4C \xrightarrow[\text{u.v.}]{Cl_2} (CH_3)_3CCH_2Cl \text{ [not } (CH_3)_2CClCH_2CH_3\text{]}$$

2.2 Functionalisation of alkenes

Unlike alkanes, alkenes contain two sites at which functionalisation can be carried out with a high degree of specificity. These are (a) at the C=C double bond and (b) at the carbon adjacent to the double bond – the *allylic* position.

The chemistry of alkenes is largely concerned with reactions of electrophiles with the double bond. The mechanism of these reactions is discussed by Sykes (pp. 178–94) and will not be discussed in detail in this chapter. It is, however, necessary to recall that addition of electrophiles to unsymmetrical alkenes proceeds through the more stable carbocation,[1] resulting in the product in which the more positive moiety of the reagent has become attached to the **less** substituted alkene carbon (the 'Markownikoff' product). Scheme 2.1 summarises addition reactions involving propene. Strong acids, e.g. HCl, HBr, HI, H_2SO_4 and CF_3CO_2H add to alkenes directly but weaker acids, e.g. CH_3CO_2H and H_2O, require catalysis by a stronger acid (e.g. H_2SO_4). An alternative to the last of these, *viz.* acid-catalysed addition of water, is provided by *oxy-*



Scheme 2.1

mercuration, using mercury (II) acetate (Hg^{II} being a Lewis acid and thus an electrophile), followed by reaction with sodium borohydride and hydrolysis. This method avoids the use of a strong protic acid.

In all of these cases, and also for the hypohalous acids, 'Markownikoff addition' is observed. The more positive (electrophilic) end of the dipolar molecule becomes attached to the less substituted carbon.

$$CH_3CH{=}CH_2 + \overset{\delta-}{V}{-}\overset{\delta+}{W} \longrightarrow CH_3\overset{+}{C}H{-}CH_2W$$

(secondary carbocation: more stable than $CH_3CHW{-}CH_2^+$)

$$\downarrow$$

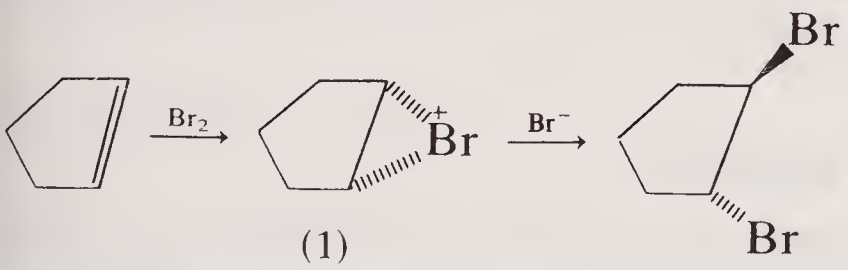
$$CH_3CHV{-}CH_2W$$

$$CH_3CH(OH)CH_2Br \xleftarrow{HOBr} CH_3CH{=}CH_2 \xrightarrow{ICl} CH_3CHClCH_2I$$

In the case of addition of water through hydroboration, although the 'anti-Markownikoff' product is eventually formed, the addition step itself (of a borane) actually follows Markownikoff's rule (cf. section 11.1).

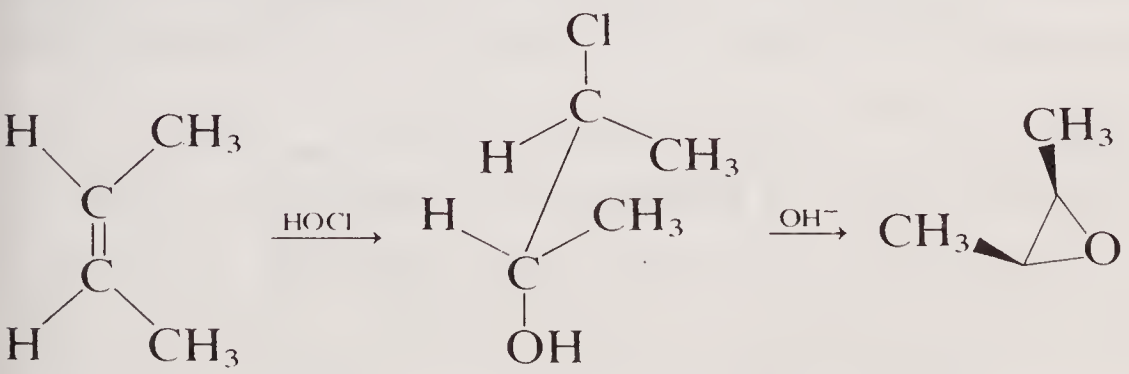
In the case of addition of HBr, however, 'Markownikoff addition' is observed only if the alkene is rigorously purified so that peroxide impurities are excluded. Otherwise, 'anti-Markowikoff addition' occurs. This is because, in presence of peroxide, a radical mechanism is followed (Sykes, pp. 316–319); the attacking radical ($Br^{\bullet}$) becomes attached to the less substituted carbon [less hindered; conditions of *kinetic control* (Sykes, p. 42)]. The fact that the more stable of the possible radical intermediates is usually produced (secondary usually more stable than primary) is merely a bonus.

The intermediate in reactions involving halogens and hypohalous acids is a halonium ion (1), reaction of which with a nucleophile leads to

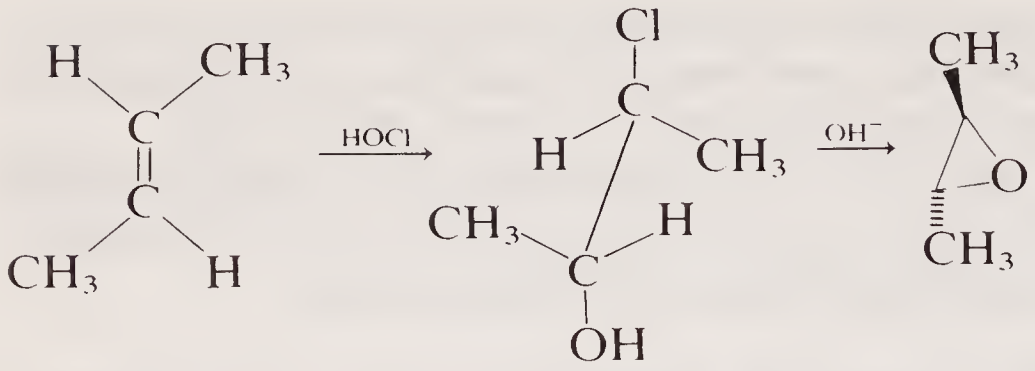


(1)

a *trans* addition product. In the case of addition of hypohalous acid, the *trans* halogeno-alcohol formed can be converted, by treatment with base, in an oxiran (epoxide):



(Z) or *cis* *threo* *cis*



(*E*) or *trans* *erythro* *trans*

An alternative means by which alkenes may be functionalised is reaction at the allylic position. Carbon–hydrogen bonds adjacent to the carbon–carbon double bond, the *allylic hydrogens*, are susceptible to oxidation and to halogenation. Although the majority of these halogenation reactions are free-radical processes, ionic reactions can also take place.

The most commonly used reagent for bromination is *N*-bromosuccinimide (NBS) and, since the reaction involves an intermediate allyl radical, a mixture of bromides can be expected:

$$RCH_2CH{=}CH_2 \xrightarrow[(PhCO_2)_2]{NBS} R\dot{C}HCH{=}CH_2 \longleftrightarrow RCH{=}CH\dot{C}H_2$$

$$\downarrow NBS$$

$$RCHBrCH{=}CH_2 + RCH{=}CHCH_2Br$$

(Z and E isomers)

However, in simple cases such as cyclohexene, a good yield of the bromoalkene is obtained.

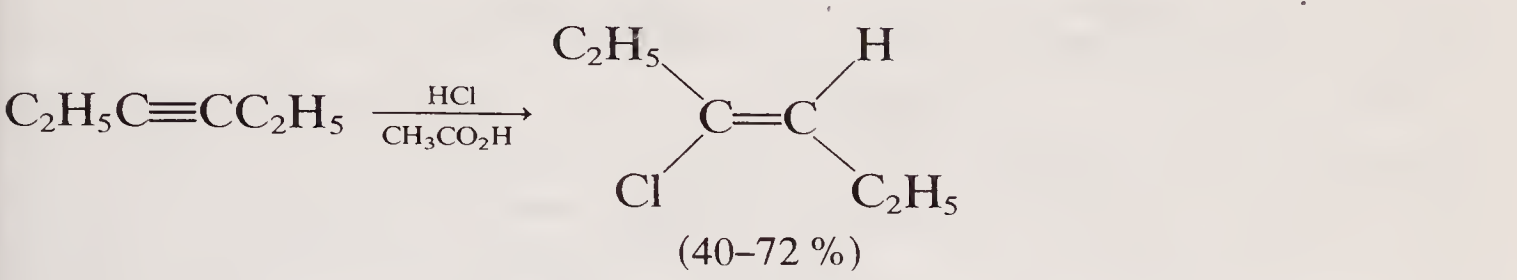
The introduction of oxygenated functional groups at allylic positions will be discussed in Chapter 9 (section 9.2.2).

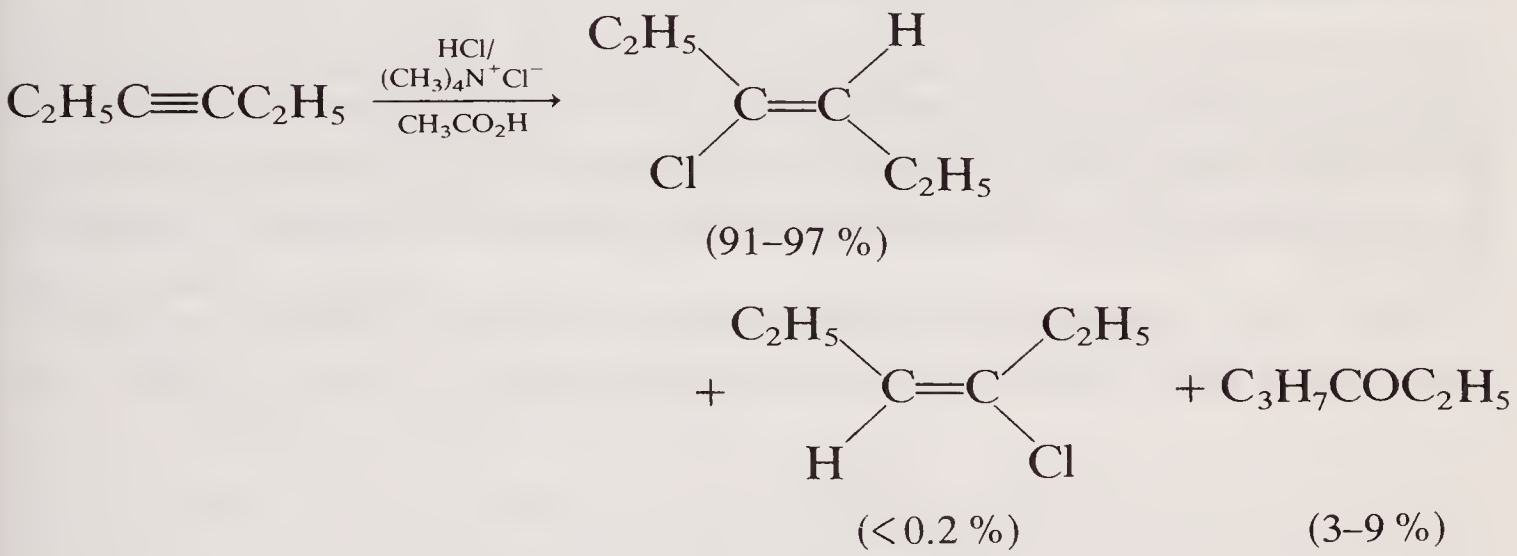
2.3 Functionalisation of alkynes

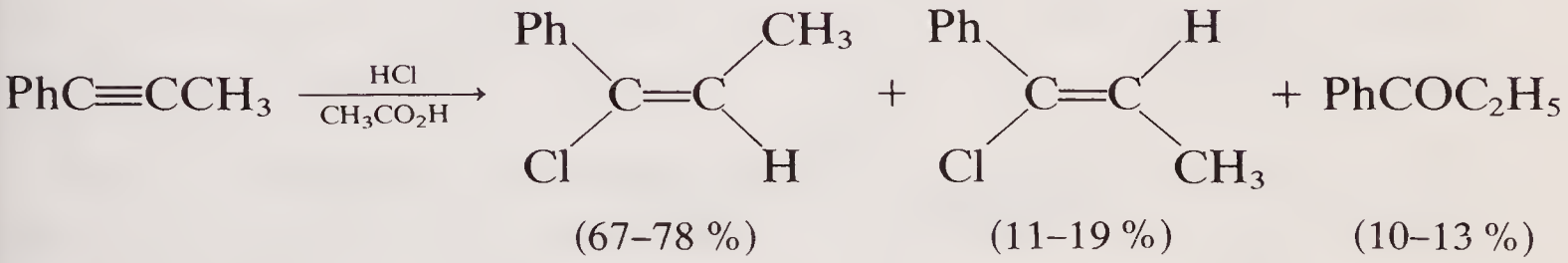
Most of the chemistry of alkynes is concerned with their reactivity towards electrophiles. As in the case of alkenes considered in the previous section, reactions with halogens, hydrogen halides and acids are synthetically useful. Hydrogenation of alkynes is also of considerable significance and will be discussed in Chapter 8. In addition, a terminal acetylene is a weak acid and the anion derived from it is of importance in carbon–carbon bond forming reactions (cf. sections 3.4.2.iii and 4.3).

Reaction of bromine with an alkyne results in the formation of a *trans*-dibromide and addition of lithium bromide to the reaction mixture increases the yield of the product. Reaction with hydrogen halide is of greater complexity, often following a *cis* stereochemistry. However, when the triple bond is not conjugated with an aromatic ring, the *trans* isomer predominates. Also, the addition of solvent may be a competing reaction,

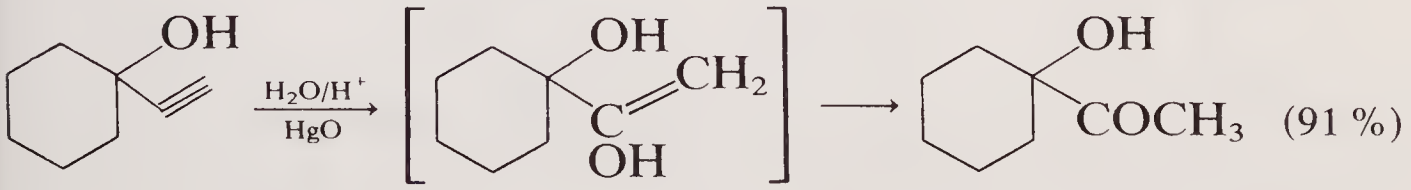
but this can be suppressed by carrying out the reaction in the presence of a quaternary ammonium halide. These complications reduce the synthetic utility of the reaction:

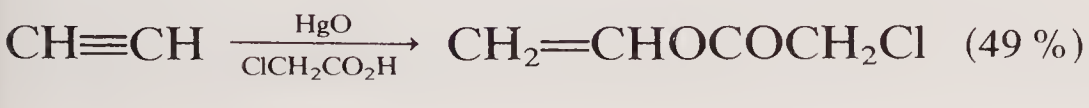




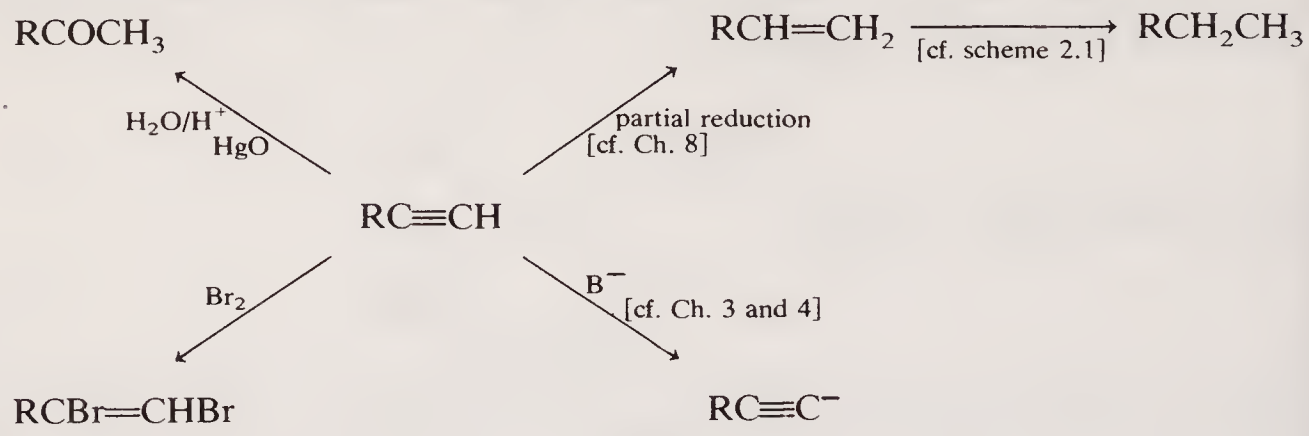


Addition of water and of carboxylic acids to alkynes is catalysed by mercuric oxide. In the former case the product from a terminal alkyne is a methyl ketone and in the latter an enol ester:





The commonly used synthetic procedures are shown in scheme 2.2.



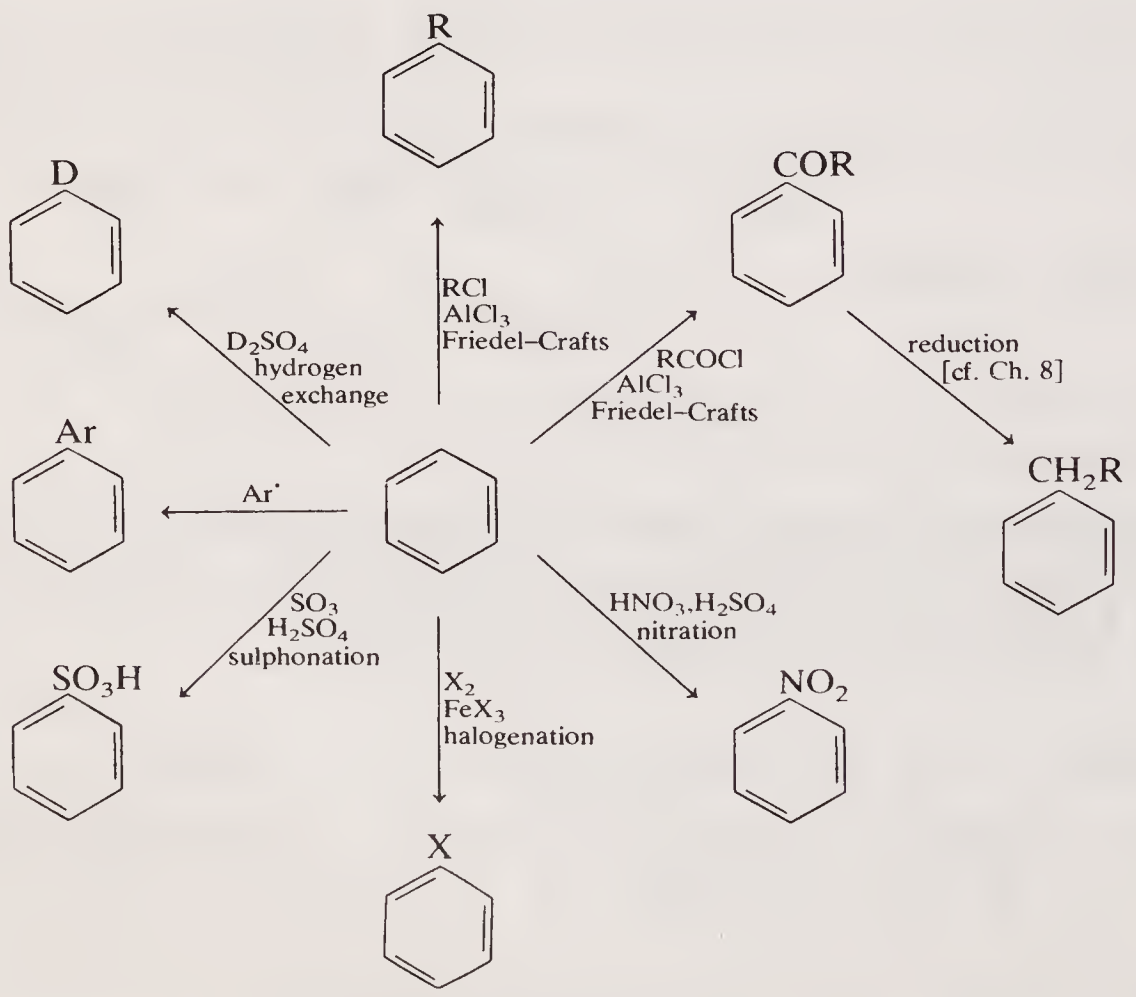
Scheme 2.2

2.4 Functionalisation of aromatic hydrocarbons

2.4.1 Substitution at a ring position

The characteristic reaction of benzene is an electrophilic addition–elimination reaction, the overall effect of which is substitution. This is the most widely used procedure for the introduction of functional groups on to the benzene ring. Scheme 2.3 outlines some of the more important reactions.

Some brief comments on the synthetic utility of these reactions is appropriate here but for a more detailed account of electrophilic aro-



Scheme 2.3

matic substitution the reader is directed to one of the monographs on the topic and to Sykes, pp. 130–49.

Friedel–Crafts **alkylation** leads to polyalkylation in most cases, since the product alkylbenzene is more reactive towards electrophiles than is benzene. Hence an indirect synthesis, *via* acylation and reduction, is often desirable. Cyclopropane, alkenes, and alcohols may be used in place of alkyl halides in the alkylation reaction. The Vilsmeier and Gattermann aldehyde syntheses may be regarded as extensions of the Friedel–Crafts acylation reaction (cf. also section 5.4.2).

Direct **halogenation** of benzene by molecular halogen catalysed by a Lewis acid is restricted to chlorination and bromination. Iodine is not sufficiently reactive to iodinate benzene, but toluene can be iodinated using iodine monochloride and zinc chloride. Fluorination is carried out by indirect methods, e.g. from diazonium salts, to be described later in this chapter.

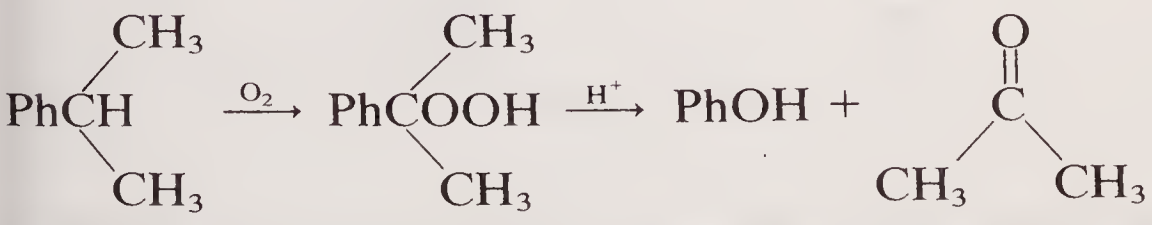
Sulphonation is an easily reversible reaction and this makes the sulphonic acid group a useful blocking group in synthesis.

Arylation of benzene can be carried out by free radical reactions involving diaroyl peroxides or *N*-nitrosoacetanilides, by the Gomberg reaction involving the alkaline decomposition of arenediazonium salts in benzene, or, perhaps most simply, by reaction with a primary arylamine and an alkyl nitrite.

2.4.2 Reaction in the side chain

Alkylbenzenes can be functionalised either in the side chain or in the ring. The latter will be discussed shortly. The side chain is susceptible to attack by radicals and also to oxidation at the position adjacent to the ring (the *benzylic* position). The oxidation of a methyl group involves three levels of oxidation: $—CH_2OH$, —CHO, and $—CO_2H$ (cf. sections 9.2.2 and 9.2.3).

The benzylic position is also susceptible to autoxidation and the commercially valuable synthesis of phenol and acetone from cumene makes use of this (Sykes, p. 127):



Halogenation at benzylic positions normally proceeds by a free radical mechanism and, in the absence of other reactive functional groups, is normally carried out using molecular chlorine or bromine. Chlorination may also be carried out using t-butyl hypochlorite or sulphuryl chloride, and bromination using *N*-bromosuccinimide. In all cases, the reaction is

stepwise and the steps become slower with increased halogen substitution. It is, therefore, feasible to prepare benzyl chloride, α,α-dichlorotoluene and α,α,α-trichlorotoluene by varying the reaction conditions:

$$PhCH_3 \rightarrow PhCH_2Cl \rightarrow PhCHCl_2 \rightarrow PhCCl_3$$

2.5 Functionalisation of substituted benzene derivatives

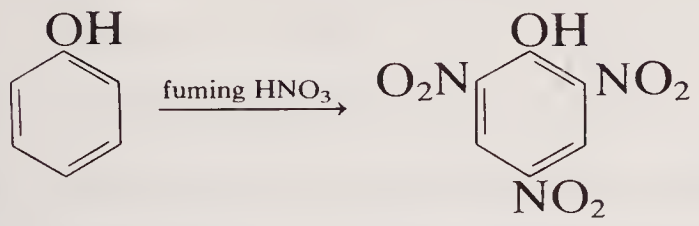
Substituted benzene derivatives undergo electrophilic and free radical substitution reactions analogous to those described previously for benzene. However, in **electrophilic substitution**, the substituents already present in the ring direct an incoming electrophile into certain position(s) and affect the rate of substitution to such an extent that certain reactions (e.g. alkylation of nitrobenzene) cannot be carried out and others not possible with benzene can take place (e.g. reactions of sodium phenoxide with diazonium salts). The mechanism of electrophilic substitution and the effect of various functional groups on orientation and rate of substitution is described by Sykes (pp. 150–64). A simplified general guide to these effects is given in table 2.1.

Table 2.1 Orientation and rate of electrophilic substitution of substituted benzenes

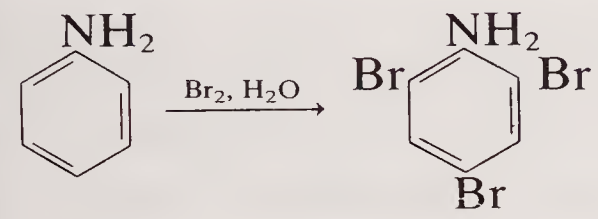
Substituent	**Orientation of electrophilic substitution**	**Rate of substitution relative to that of benzene**
alkyl or aryl	*o*-, *p*-	faster
—OH, —OR	*o*-, *p*-	faster
$-NH_2$, —NHR, $-NR_2$	*o*-, *p*-	faster
halogen	*o*-, *p*-	similar or slower
$\diagdown C{=}O$	*m*-	slower
$-C{\equiv}N$	*m*-	slower
$-NO_2$	*m*-	slower
$-SO_3H$	*m*-	slower
$-CF_3$	*m*-	slower

Two points are worth noting at this stage. Firstly, when more than one substituent is already on the benzene ring, the most strongly electron-donating group controls the position of further substitution. Secondly, in order to minimise possible substitution at nitrogen, aromatic amines are usually converted into acetanilides before substitution is carried out. This also serves to reduce the reactivity of the ring towards electrophile

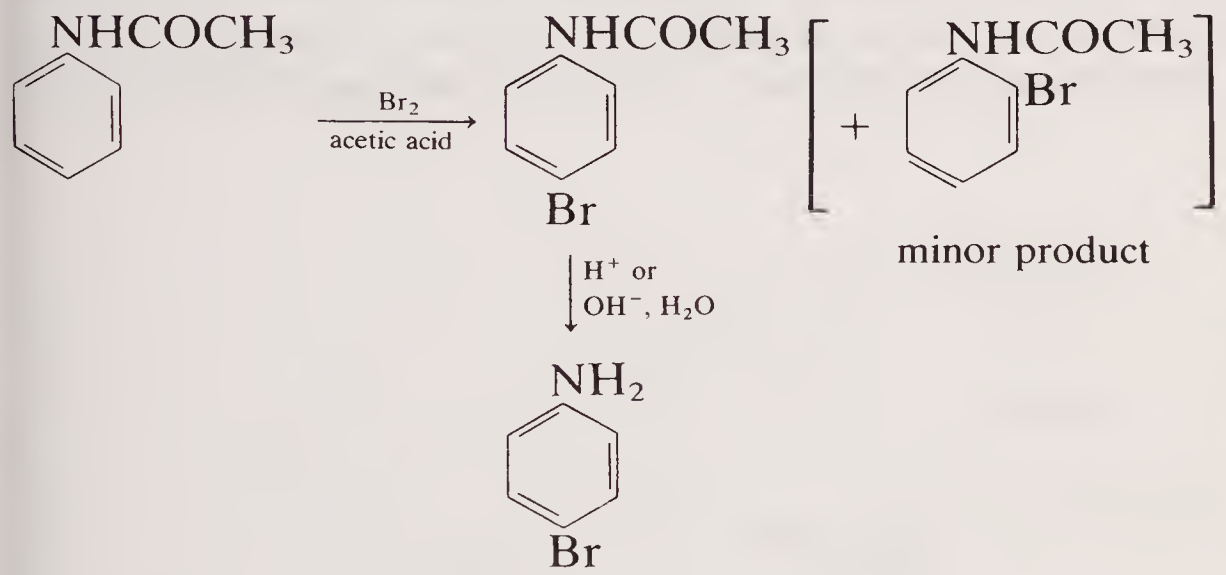
substitution. Below are given some examples which may help the reader to understand the application of the rules:

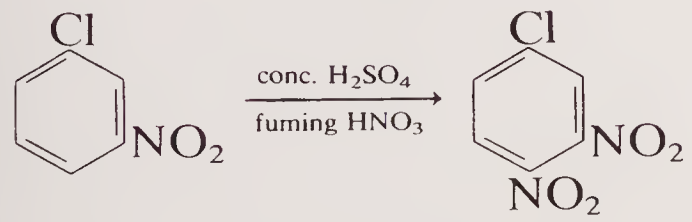
(a) 

Mononitration takes place with dilute nitric acid, indicating that phenol is much more reactive than benzene. The hydroxyl group is *o*-/*p*-directing.

(b) 

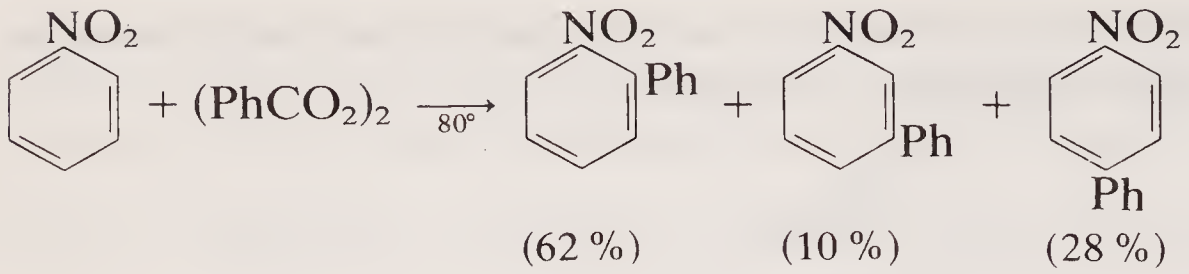
No Lewis acid catalyst is required and the reaction cannot be stopped at the mono- or the di-bromo stage. The amino group is *o*-/*p*- directing and controls the orientation of addition rather than the more weakly *o*-/*p*-directing bromine. Monobromination can be effected by way of acetanilide:



(c) 

Much more vigorous conditions are required for this reaction since both substituents retard nitration. The orientation is governed by the *o*-/*p*-directing chlorine.

The directional effects in **free radical substitution** reactions are much less pronounced, and it is normal to expect all three isomers from, for example, phenylation of a monosubstituted benzene:

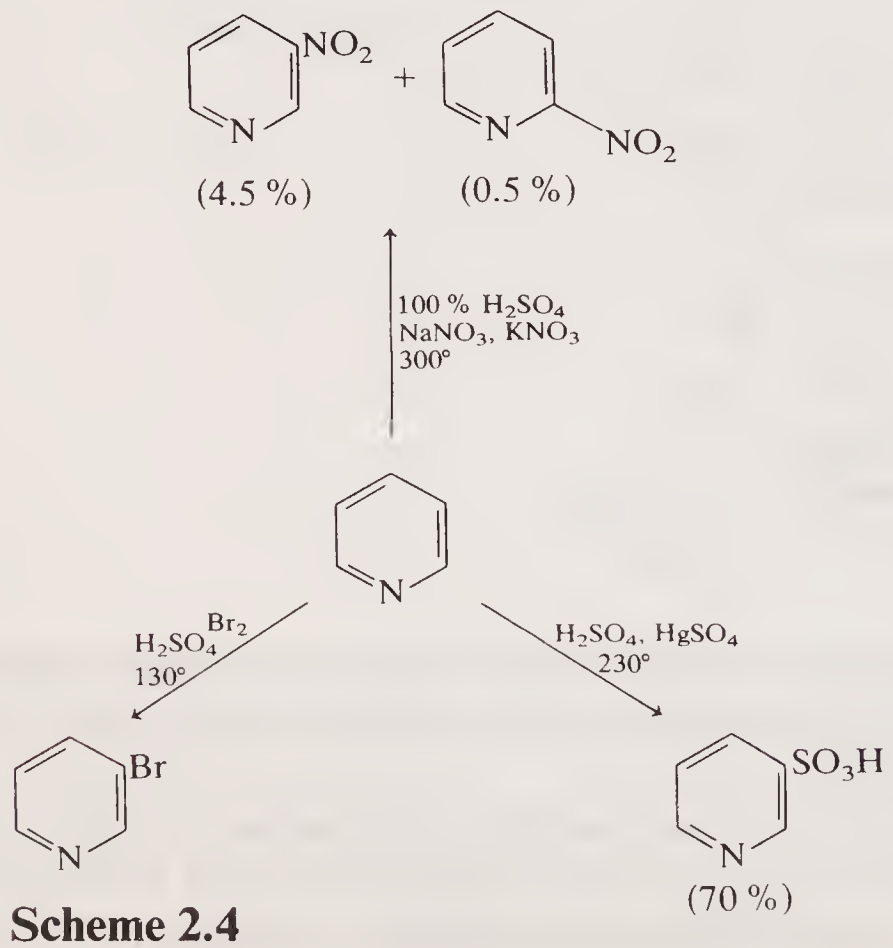


Nucleophilic substitution is accelerated by electron-withdrawing substituents, e.g. NO_2. However, a leaving group such as halogen is also required and the reaction is not considered at this point.

2.6 Functionalisation of simple heterocyclic compounds

In the space available, it is only possible to deal in outline with some of the more important reactions of simple heterocyclic compounds and, for further detail on them and on reactions of more complex heterocyclic compounds, the reader is directed to more comprehensive texts.

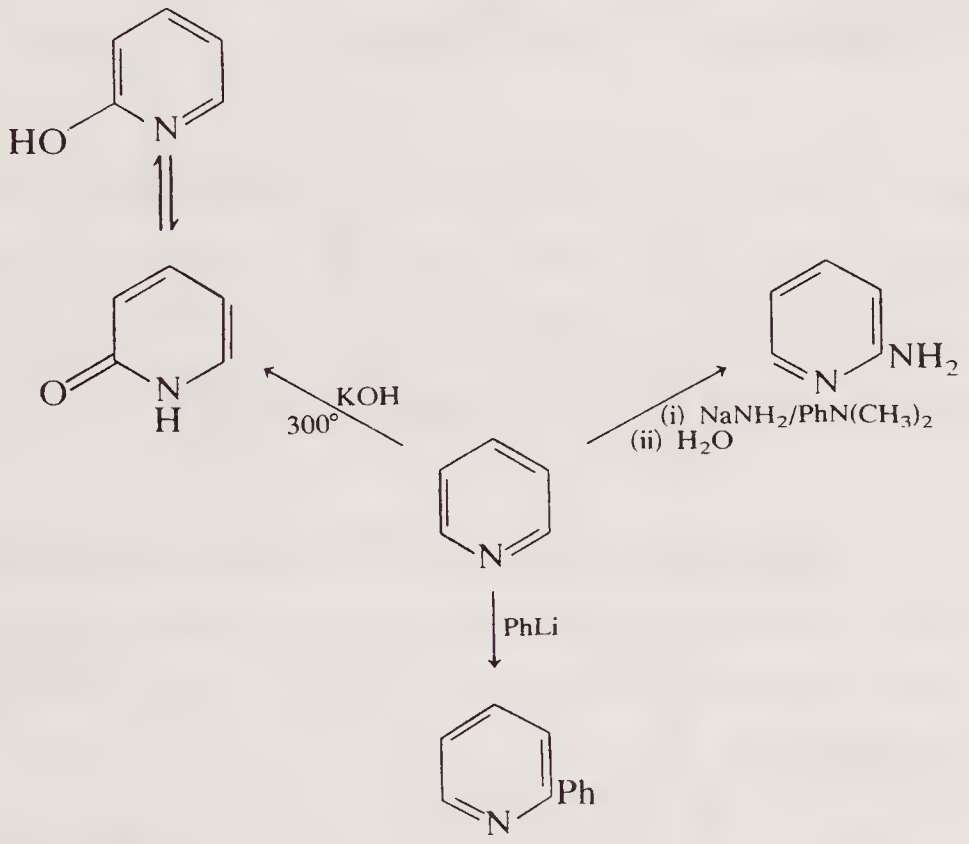
Pyridine is a weak mono-acidic base which possesses a considerable degree of aromatic character. It reacts, for example, with methyl iodide to form quaternary salts which on heating rearrange to 2- and 4-methylpyridines. Molecular orbital calculations indicate that C-3 is the carbon having the highest electron density but, even at this position, the electron density is much lower than that of benzene. Electrophilic substitution, therefore, requires forcing conditions and the reactions which may be useful are summarised in scheme 2.4. Free radical phenylation results in the formation of a mixture of all three monophenylpyridines.



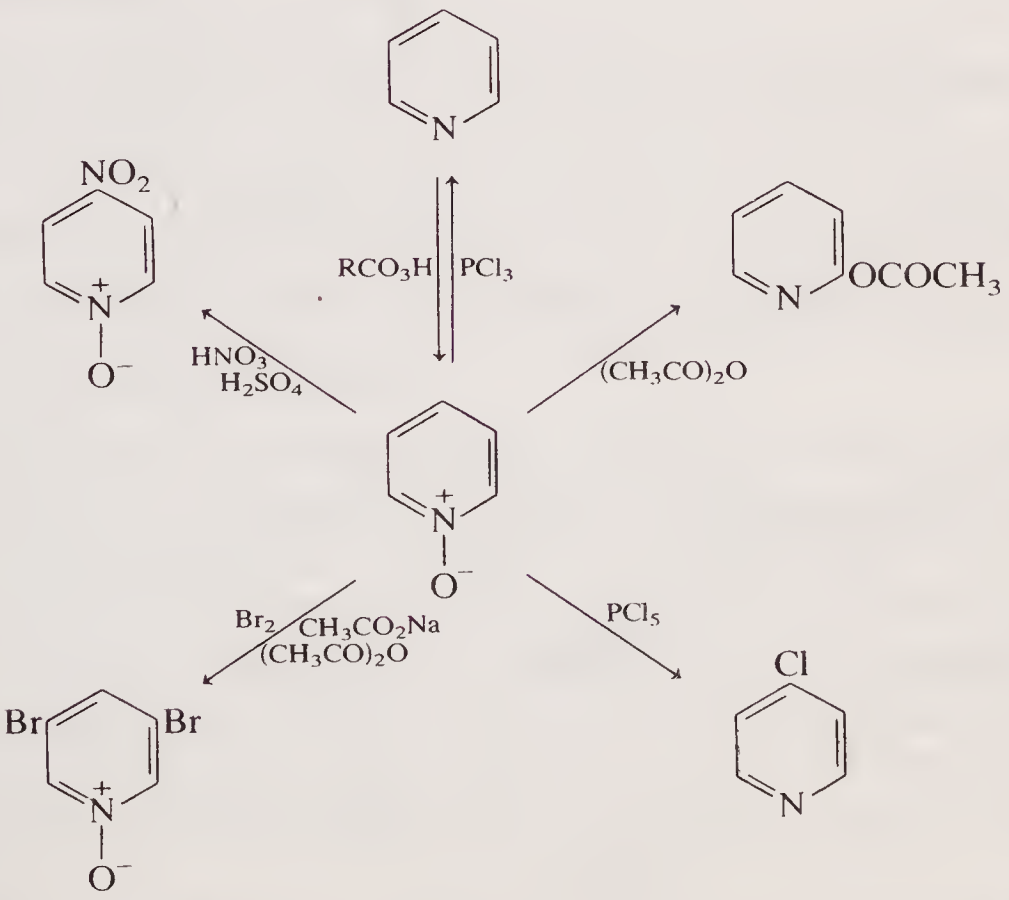
Scheme 2.4

Nucleophilic substitution results in substitution mainly at the 2-position and these reactions are summarised in scheme 2.5.

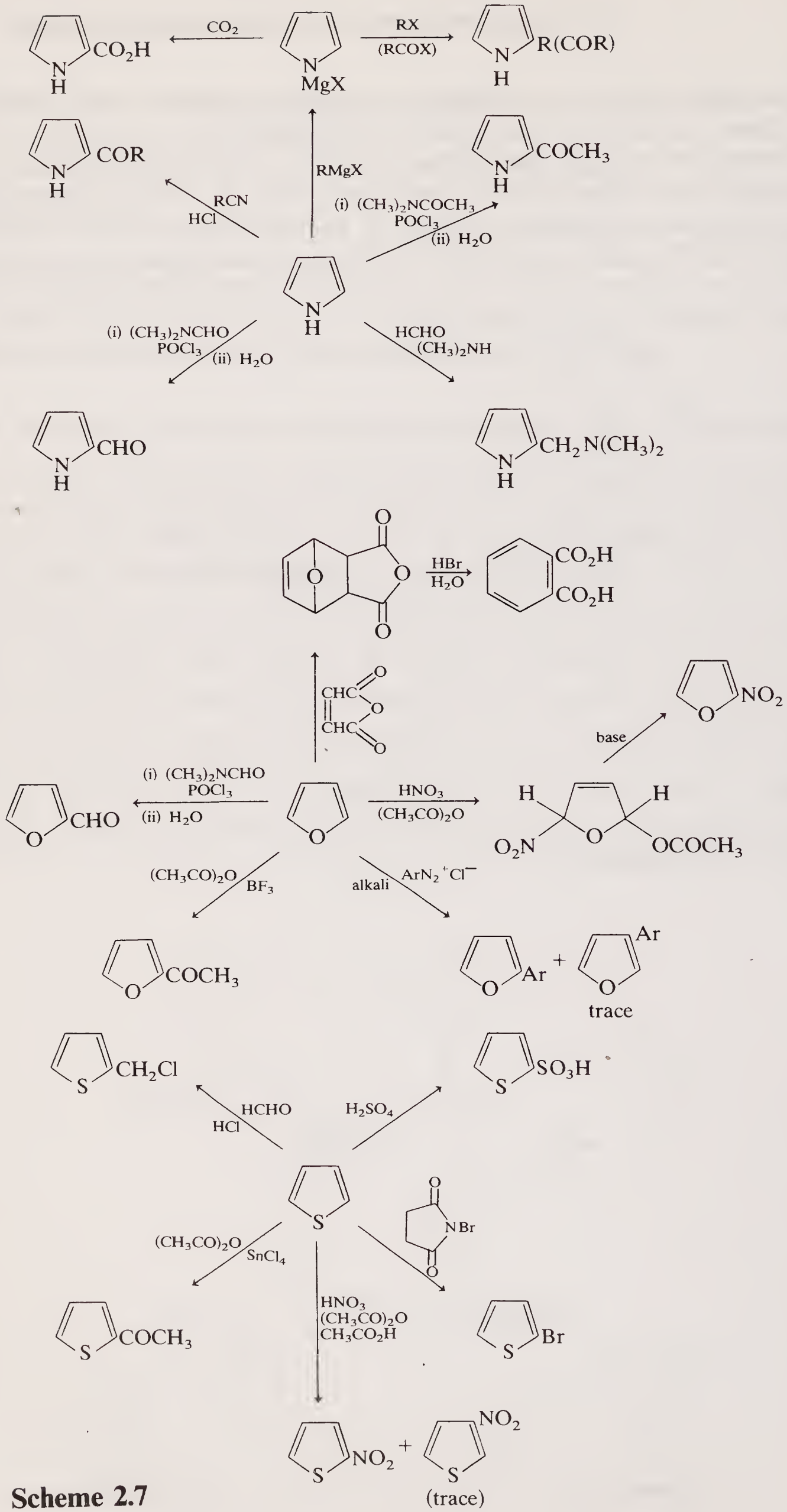
Pyridine-*N*-oxide, prepared most readily by treatment of pyridine with a peracid such as peracetic or perbenzoic acid, is a much weaker base than pyridine. It is readily nitrated in the 4-position and the directive effect of the *N*-oxide is such that 4-substitution takes place in most cases



Scheme 2.5



Scheme 2.6


CO2H
CO2
RX
(RCOX)
R(COR)
MgX
COR
RMgX
COCH3
RCN
HCl
(i) (CH3)2NCOCH3
POCl3
(ii) H2O
(i) (CH3)2NCHO
POCl3
(ii) H2O
HCHO
(CH3)2NH
CHO
CH2N(CH3)2
HBr
H2O
CO2H
CO2H
CHC
CHC
NO2
base
(i) (CH3)2NCHO
POCl3
(ii) H2O
CHO
HNO3
(CH3CO)2O
H
H
O2N
OCOCH3
(CH3CO)2O
BF3
alkali
ArN2+Cl−
COCH3
Ar
Ar
trace
CH2Cl
SO3H
HCHO
HCl
H2SO4
(CH3CO)2O
SnCl4
NBr
HNO3
(CH3CO)2O
CH3CO2H
COCH3
Br
NO2
NO2
(trace)

Scheme 2.7

except those with a hydroxy or dimethylamino group in the 2-position. If the 4-position is blocked, nitration usually fails. Direct halogenation and sulphonation do not proceed readily and, as with pyridine itself, the Friedel–Crafts reaction fails. Pyridine-*N*-oxide is converted into 2-acetoxypyridine by acetic anhydride, and on heating with bromine and acetic anhydride-sodium acetate 3,5-dibromopyridine-*N*-oxide is formed. Chlorination at the 4-position with deoxygenation can be carried out using phosphorus pentachloride. Deoxygenation of *N*-oxides is readily carried out using, for example, phosphorus trichloride. These reactions are summarised in scheme 2.6.

In contrast to pyridine, furan, pyrrole and thiophen are electron-rich molecules which react with electrophiles mainly in the 2- and 5-positions. However, under acidic conditions furan, and to a lesser extent pyrrole, are polymerised. Direct halogenation of furan, pyrrole and thiophen usually results in the formation of polyhalogenated products. Scheme 2.7 summarises some useful synthetic reactions of these compounds.

2.7 Interconversion of functional groups

As we have seen in the preceding sections, certain functional groups are readily introduced in a specific manner whilst others are not. It is now the job of the synthetic chemist to be able to interconvert functional groups in such a manner that the remainder of the molecule remains unaffected. This section will attempt to show, in outline only, how specific functional groups can be interconverted.

2.7.1 Transformation of the hydroxyl group

Alcohols are weak bases which are capable of reacting as nucleophiles. Reaction of alcohols with acid chlorides or anhydrides results in the formation of *esters*. In most cases the reaction is promoted by the addition of a tertiary base. The alkoxide ion is a stronger nucleophile which can react with alkyl halides, sulphonates and sulphates to form *ethers*. However, elimination competes with substitution in reactions involving secondary and tertiary halides.

Alkyl halides may be prepared from alcohols using reagents such as thionyl chloride for chlorides, constant boiling hydrobromic acid or phosphorus tribromide for bromides, and iodine with red phosphorus for iodides. Mild conditions must be employed for the preparation of tertiary halides to prevent elimination taking place, e.g. t-butanol shaken with concentrated hydrochloric acid gives t-butyl chloride. Some additional reagents which are useful when the more common reagents induce rearrangement, racemisation or decomposition will be discussed in Chapter 12.

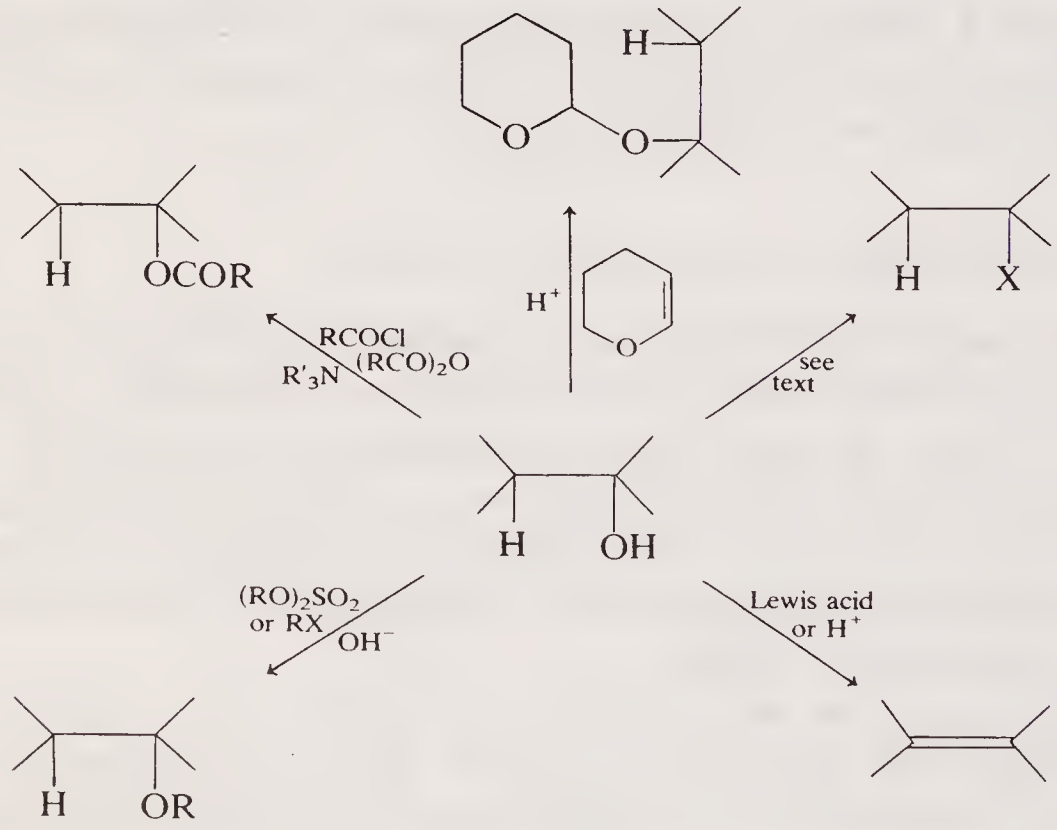
Dehydration of alcohols to form *alkenes* can be carried out using a

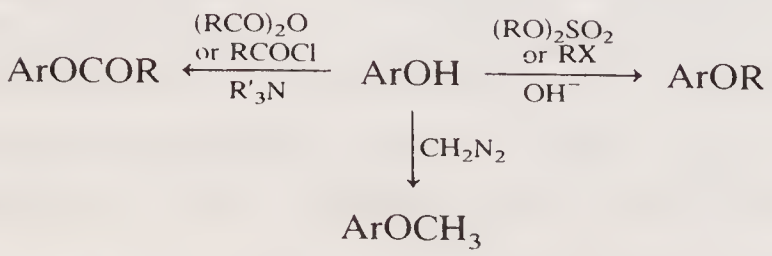
wide variety of Brønsted and Lewis acids. With strong acids, acyclic alcohols appear to be dehydrated largely by an E1 mechanism, and the products derived are usually of the Saytzeff type (i.e. the most stable alkene predominating; Sykes, p. 249) perhaps with skeletal rearrangement of the intermediate carbocation. Some reagents, e.g. phosphorus oxychloride, are regarded as inducing dehydrations which are highly stereospecifically *trans*, consistent with an E2 mechanism. Since E1 elimination may be less stereospecific than E2, choice of reagent may be an important factor in determining product distribution in dehydration of alcohols. Attempted preparation of tertiary alcohols by, for example, the Grignard reaction (cf. section 4.1.2) often results in spontaneous dehydration to the alkene.

Alcohols add to 2,3-dihydropyran under acidic conditions to give mixed *acetals* which are used to protect hydroxyl groups (cf. section 10.2.1). The reactions of alcohols with carbonyl and carboxyl groups are discussed later (cf. sections 2.7.5 and 2.7.6).

Phenols can be alkylated and acylated by ways similar to those used for alcohols. Aryl methyl ethers are often prepared by reaction of the phenol with diazomethane. The preparation of aryl halides from phenols is of little preparative significance.

The main transformations using alcohols and phenols are shown in scheme 2.8.





Scheme 2.8

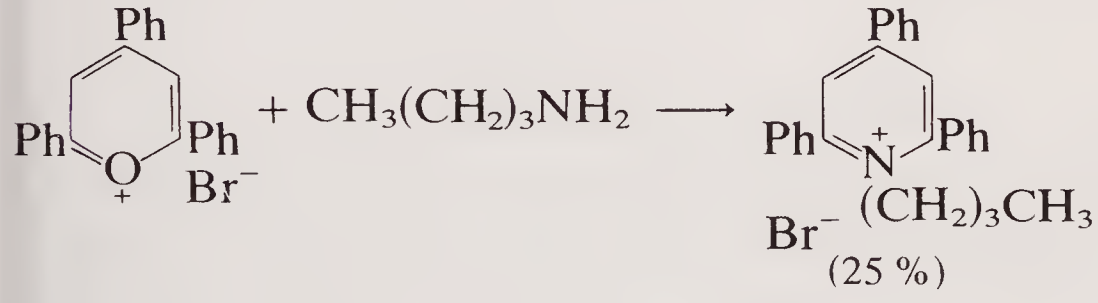
2.7.2 Transformation of the amino group

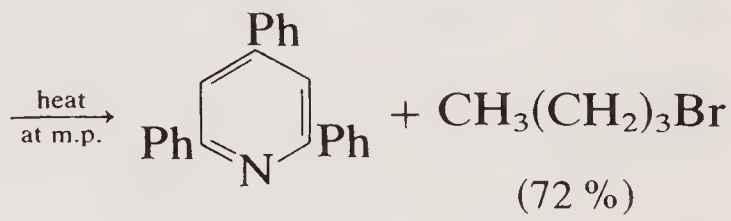
The amino group is basic and reacts as a nucleophile with alkyl halides, giving rise to secondary and tertiary amines and to quaternary ammonium salts. Acid chlorides and anhydrides give *amides* (section 2.7.6). The sulphonamide derived from reaction of a primary amine with a sulphonyl chloride has an acidic hydrogen which may be removed to produce a strongly nucleophilic species:

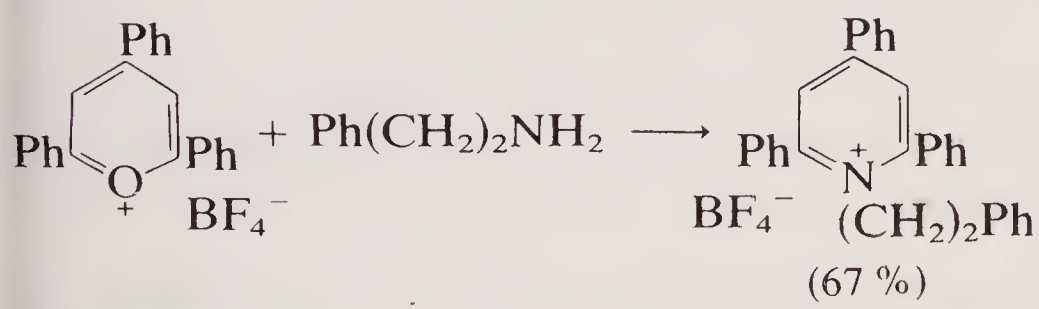
$$ArNH_2 + TsCl \longrightarrow ArNHTs \xrightarrow{NaOH} Ar\bar{N}Ts \xrightarrow{RCl} ArN(R)Ts$$

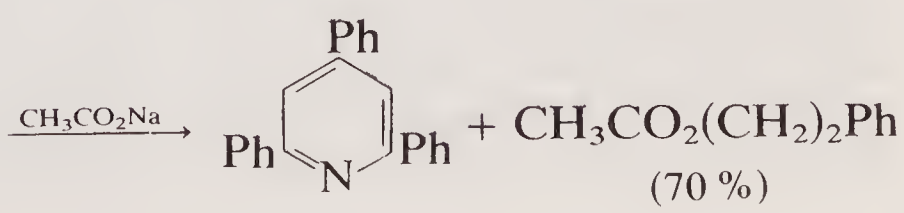
[Ts = *p*-$CH_3C_6H_4SO_2$]

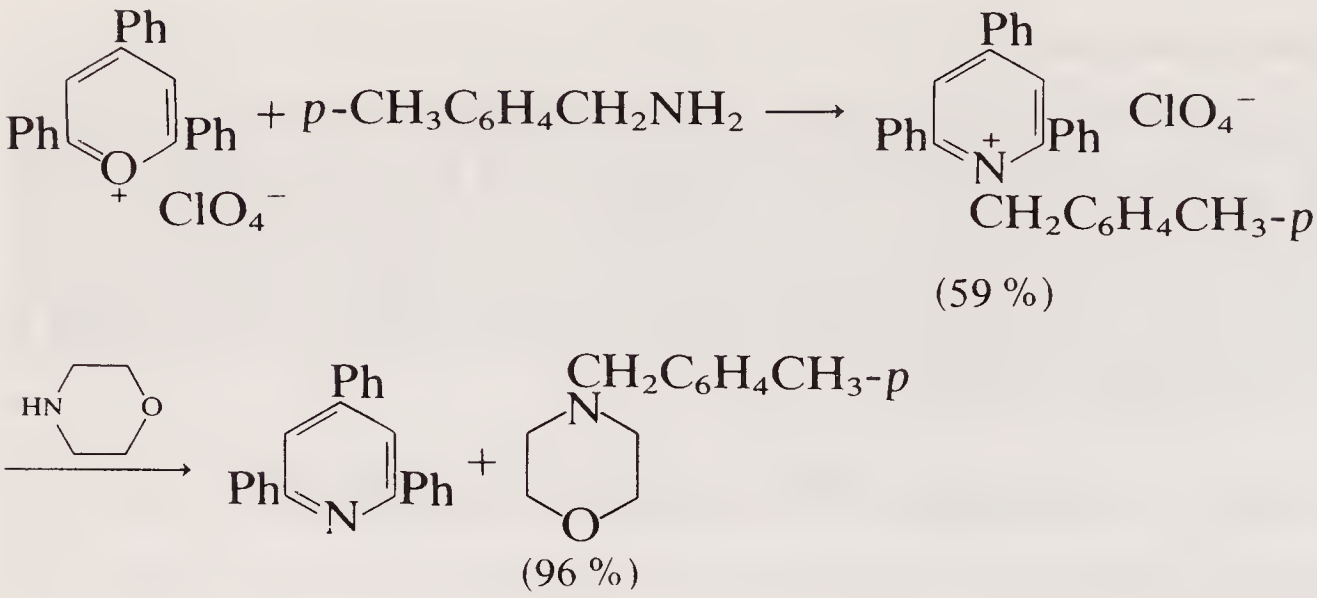
For aliphatic amines, reaction of a primary amine with nitrous acid is of little preparative significance due to the formation of a complex mixture of products, except in cases where elimination reactions cannot take place. However, it has recently been shown that primary aliphatic amines can be transformed into a wide variety of products by converting the amino group into a better leaving group such as 2,4,6-triphenylpyridine which can be displaced by a range of nucleophiles. Examples of these transformations include the following:











Treatment of secondary amines with nitrous acid results in the formation of *N*-nitroso compounds which can be reduced to *N*,*N*-disubstituted hydrazines. The reaction of tertiary aliphatic amines is complex and of no preparative importance.

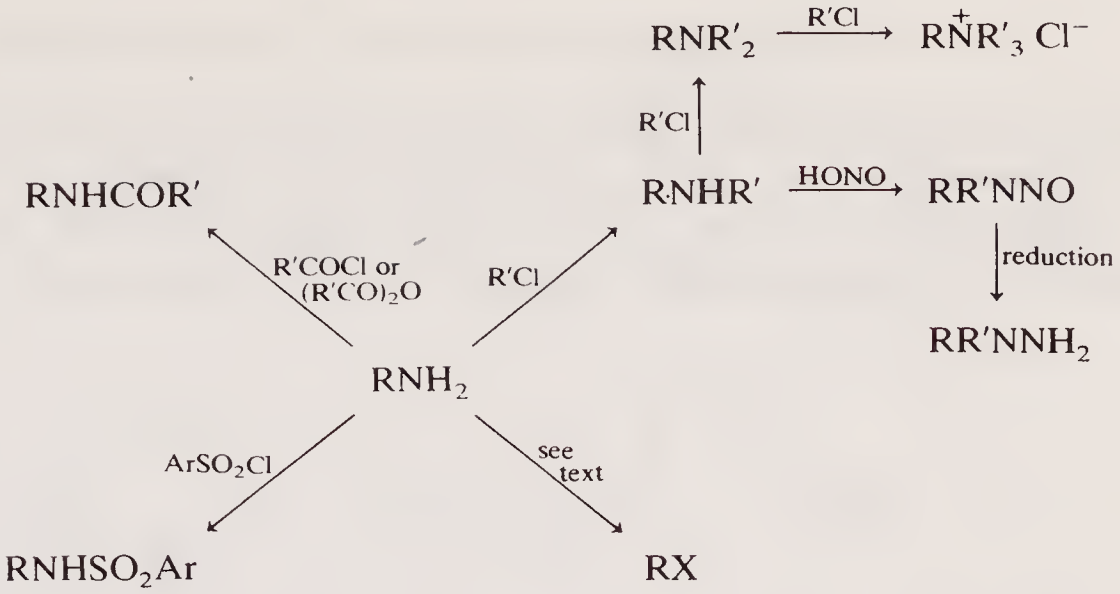
The reaction of primary aromatic amines with nitrous acid is of considerable significance. The *diazonium salts* so formed can undergo a wide variety of transformations which are of preparative use. These together with other reactions involving the amino group are collected in scheme 2.9. The reactions of amino groups with carbonyl compounds will be considered later (Ch. 6 and 7).

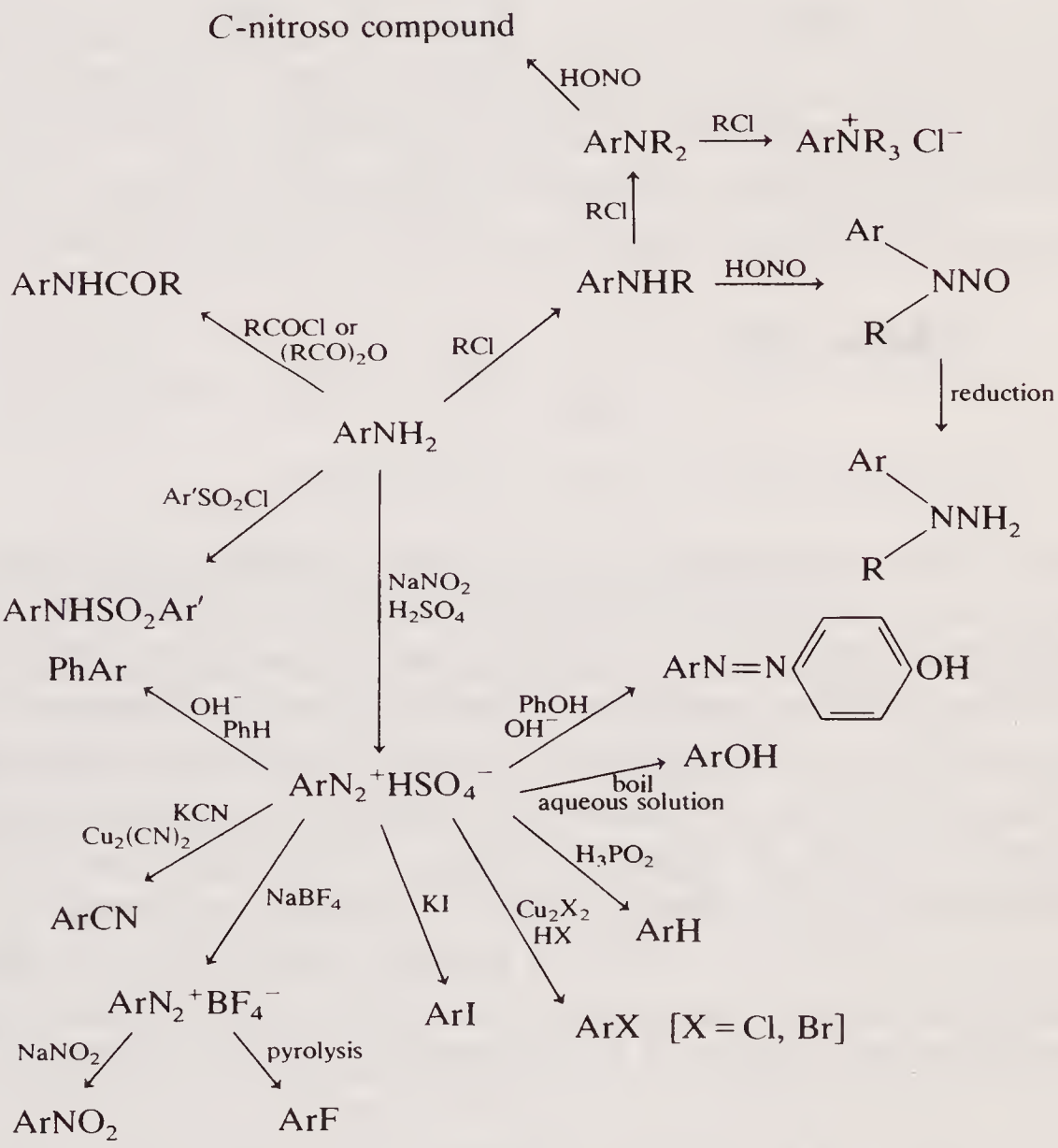
2.7.3 Transformation of halogeno-compounds

A halogen, in addition to providing a good leaving group, withdraws electrons from the adjacent carbon atom. Hence, alkyl halides participate in a wide variety of nucleophilic substitution reactions. Reactions with alcohols and with amines have already been mentioned and reactions with thiolate anions, cyanide ions, anions derived from acetylenes, and other carbanions are all valuable (cf. section 3.3.1 and Ch. 4 and 5). Elimination reactions, may, however, complicate the situation, especially in the case of secondary halides, and for many tertiary halides only elimination products are obtained.

Alkyl halides may be hydrolysed using sodium hydroxide, but in the case of most secondary and tertiary halides elimination is a competitive reaction. Elimination is favoured in the case of a strong base reacting in a non-polar solvent at high temperature. Base-catalysed elimination from secondary and tertiary halides normally obeys the Saytzeff Rule (Sykes, pp. 256–60).

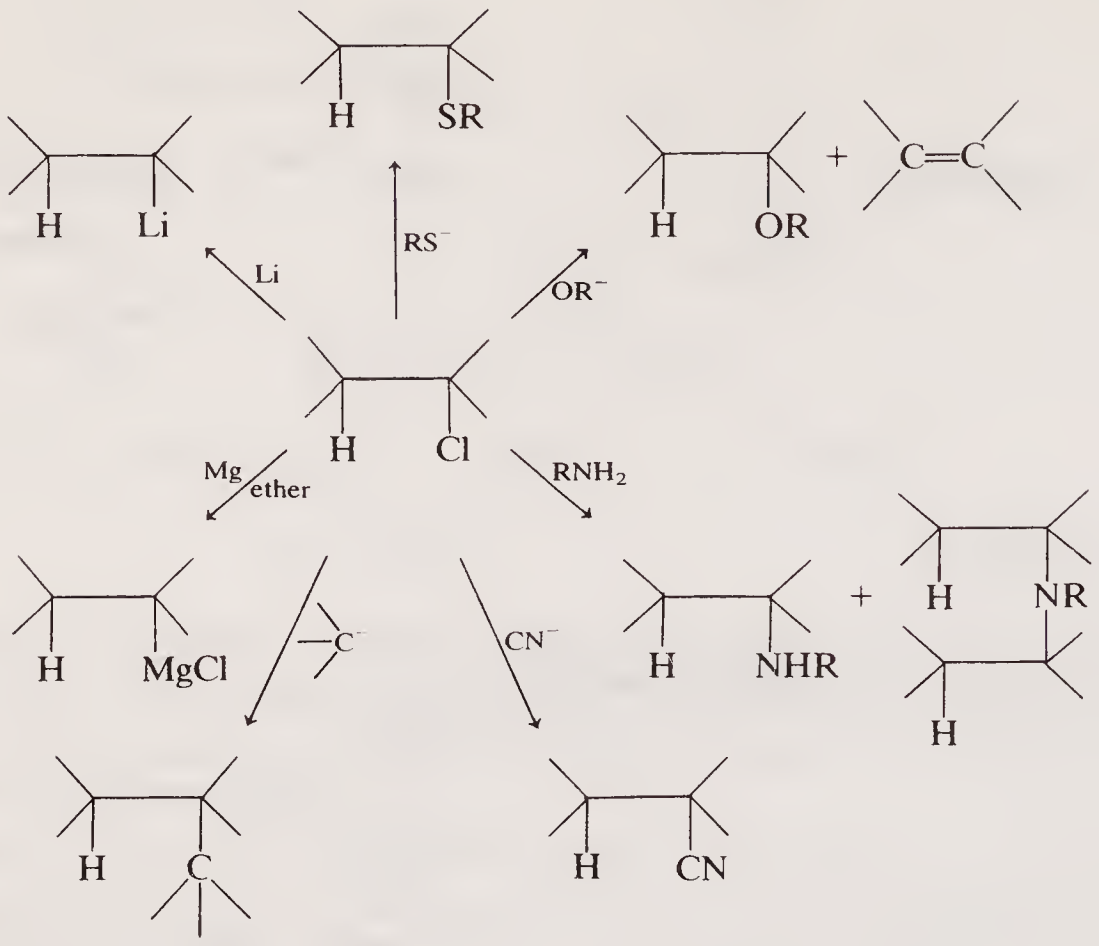
Alkyl halides react with certain metals to form metal alkyls. Of particular synthetic importance are alkyl-lithium derivatives and Grignard reagents, RMgX. These reagents are strong bases and their synthetic utility will be discussed in Chapter 4. A summary of the reactions of alkyl halides is given in scheme 2.10.





Scheme 2.9

Aryl halides are less reactive towards nucleophiles than alkyl halides, except in cases where there are sufficient electron-withdrawing substituents in positions *ortho*- and/or *para*- to the halogen. Also susceptible to nucleophilic attack are 2- and 4-halogenopyridines. Aryl halides form aryl-lithiums and Grignard reagents.

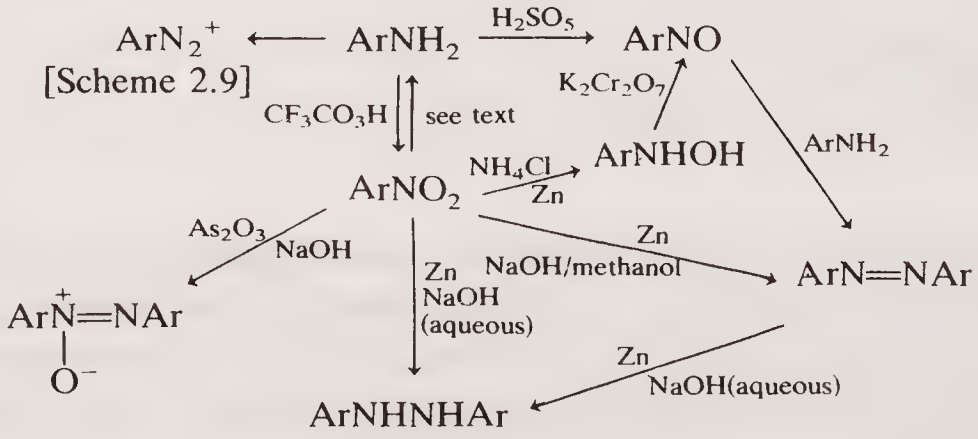


Scheme 2.10

2.7.4 Transformation of nitro-compounds

Aliphatic nitro-compounds are of lesser synthetic importance than are aromatic nitro-compounds. However, a stable carbanion can be formed on the carbon adjacent to the nitro-group and such carbanions can be used in many of the reactions to be described in Chapters 3 and 5.

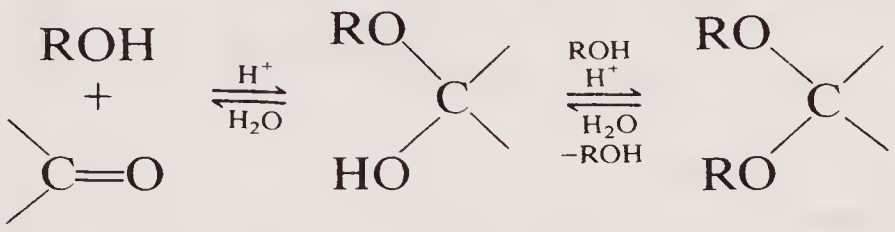
Due to the ease of formation of aryl nitro-compounds, they are of great importance for introducing a nitrogen-containing function on to the aromatic ring. Reduction with a wide variety of reagents (e.g. Sn/HCl, Raney Ni/H_2, Raney Ni/N_2H_4) causes conversion to the amino group whose synthetic versatility has just been discussed. Reduction to hydroxylamines, azo compounds, and *N*,*N*′-disubstituted hydrazines is also possible (see scheme 2.11) depending on the reagent chosen.



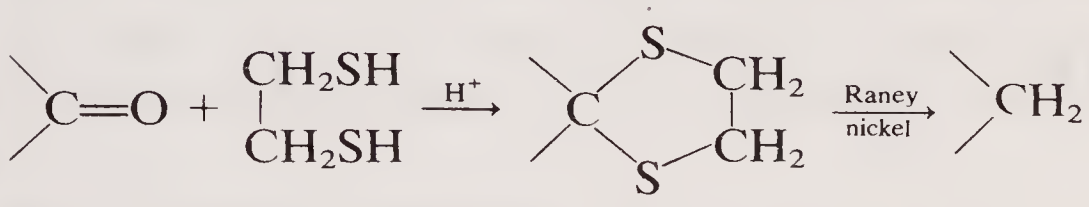
Scheme 2.11

2.7.5 Transformation of aldehydes and ketones

Oxidation (Ch. 9) and reduction (Ch. 8) of these compounds will be dealt with later, as will their reactions with carbon nucleophiles (Ch. 3 and 5). Aldehydes and ketones react reversibly under acidic conditions with alcohols to give firstly hemi-acetals and hemi-ketals and then acetals and ketals:



The acetals and ketals derived by reaction of aldehydes and ketones with ethylene glycol are used to protect the carbonyl group during reactions carried out under neutral or alkaline conditions. The analogous dithioketals are used in a conversion of carbonyl groups into methylene groups. The reaction requires, however, a large excess of Raney nickel:

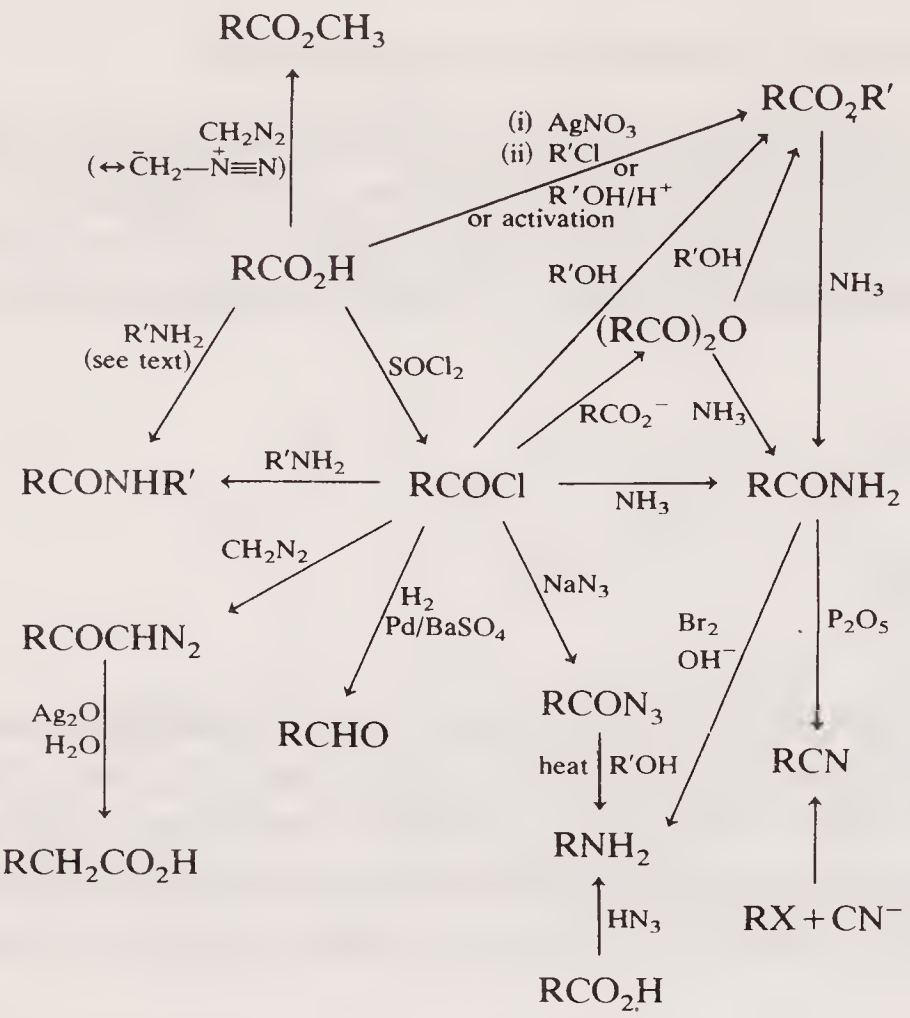


2.7.6 Transformation of acids and acid derivatives

Carboxylic acids are converted by acid-catalysed reaction with alcohols into *esters*. For methyl esters another convenient method is the use of diazomethane. For more complex esters, reaction of the alcohol with the acid chloride or with the anhydride may be more satisfactory. Many of the procedures used for amide formation will also serve in esterification. Another method of ester formation is the reaction of an alkyl halide with the silver salt of the carboxylic acid.

Acid chlorides are usually prepared by reaction of the acid with thionyl chloride. They are converted into *anhydrides* by reaction with the sodium salt of the acid. Reaction of acid chlorides with diazomethane results in the formation of diazoketones which are converted by treatment with moist silver oxide into the carboxylic acids containing an additional methylene group. Reduction of acid chlorides is considered in section 8.4.4.

Amides can be prepared by reaction of ammonia or the appropriate amine with anhydrides, esters or acid chlorides. Alternative methods of amide formation, used widely in peptide syntheses, will be discussed in Chapter 16. Primary amides can be dehydrated to nitriles which can also be prepared by reaction of alkyl halides with potassium cyanide. A useful synthetic reaction of amides is their conversion into *amines* on treatment



Scheme 2.12

with bromine and alkali (the Hofmann reaction). Alternative procedures for converting acids and their derivatives into amines are the thermal degradation of acid azides in alcoholic solvents (the Curtius reaction) and the treatment of carboxylic acids with hydrazoic acid (the Schmidt reaction).

The interconversions described in this section are summarised in scheme 2.12. Carbon–carbon bond forming reactions involving acid derivatives will be discussed in Chapters 3–5.

Note

1. The systematic name for a trico-ordinate carbocation, R_3C^+, is *carbenium* ion. This nomenclature distinguishes such a species from a pentaco-ordinate ion, R_5C^+, which is correctly named a *carbonium* ion. Traditionally, however, 'carbonium ion' has been used to denote the ion R_3C^+, and 'carbenium ion' is a term which has not yet achieved general acceptance. This book, in common with Sykes' latest edition and most other present-day textbooks, uses 'carbocation' for all positively charged trico-ordinate carbon species.

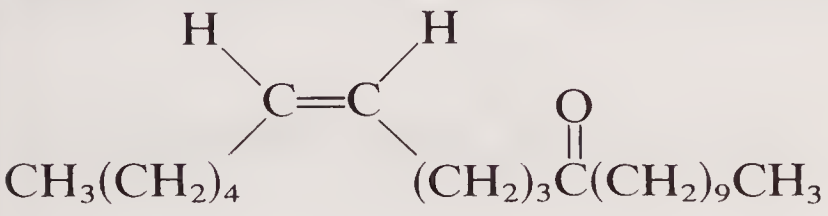
3 Formation of carbon–carbon bonds: the principles

It is surely obvious that an essential part of most organic syntheses is the construction of the carbon skeleton of the desired end-product. It is true that for some small molecules containing, say, up to six or seven carbon atoms, it may be possible to achieve their synthesis from readily available starting materials merely by functionalisation and/or group interconversions. This also holds for derivatives of simple ring systems, e.g. benzene, cyclohexane, pyridine, etc., and for molecules which are simply related to abundant naturally occurring compounds like glucose or cholesterol or penicillins. These, however, represent exceptions to the general rule.

3.1 General strategy

The construction of the molecular framework for any given target compound is, however, not merely a matter of joining together the requisite number of carbon atoms in the right way: attention must be paid to the position of functional groups in the end-product.

For example, suppose one were asked to devise a synthesis for compound A (1), below.[1] It has a straight chain of twenty-one carbon atoms, with a *Z*- (or *cis*-) double bond between C-6 and C-7 and a ketonic carbonyl group on C-11.



(1)

Compound A

How, then, does one set about such a synthesis? Straight-chain C_{21} compounds are not readily available, and so the chain has to be built up from smaller units. But which smaller units? a C_{10} and a C_{11} compound? or three C_7 compounds? or seven C_3 compounds? Does it matter?

The answer to this last question is quite clear: of course it matters. And it matters for two main reasons:

(i) Firstly, as a rule, **the fewer the number of steps in a synthesis the**

better. Few organic reactions proceed in anything approaching quantitative yield, 70–80% being normally regarded as highly satisfactory. So even with a 70% yield at each stage, a three-stage synthesis gives an overall yield of only 34%, and a five-stage synthesis gives only 17%.

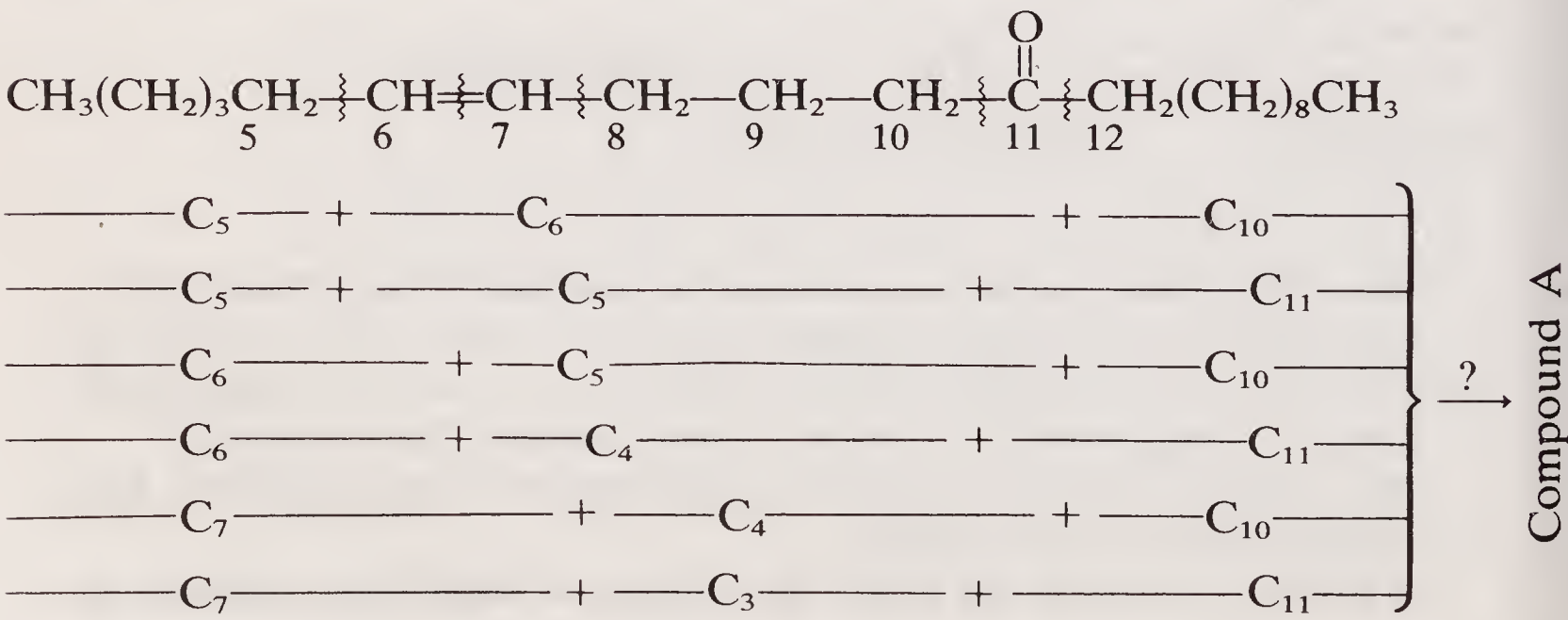
(ii) Secondly, it matters because of the functional groups in the end-product. If the end-product had been the C_{21} alkane (2), it might have been equally satisfactory to use a C_{10} and a C_{11} compound, or a C_{12} and a C_9 compound, or a C_{16} and a C_5 compound, or any other suitable pair. But the alkane is no good at all as an intermediate on the way to compound A, because there is no obvious way of inserting the functional groups into the alkane at the appropriate positions. So (and this is another general rule) **the necessary functionality must be built into the carbon skeleton as the latter is being assembled**.

$$CH_3(CH_2)_{19}CH_3$$

(2)

This need to build in functionality imposes severe restrictions on the number of ways in which one can construct the C_{21} chain in the synthesis of compound A. In the course of this chapter and the chapters which follow, it will become clear that the principal reactions leading to carbon–carbon bond formation are those in which either (i) both of the carbons to be joined initially bear functional groups, or (ii) one of the carbons initially bears a functional group and the other is directly adjacent to a functional group. Very often, as we shall see, the result of such a reaction is to leave a functional group in the product either at the point of joining of the fragments, or one carbon atom away from the joint.

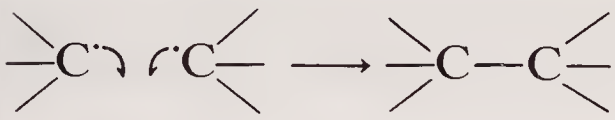
So one now has a few clues about possible synthetic approaches to compound A. With regard to the left-hand 'end', one might consider using a C_5 compound and try to form the 5,6-bond, or a C_7 compound and try to form the 7,8-bond. One might even try to use a C_6 compound to make the double bond directly. At the other 'end', the 10,11- or 11,12-bond, flanking the functionalised carbon, ought to be the easiest to form.



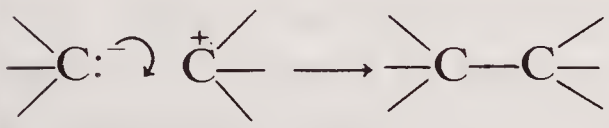
Compound A may thus be 'dissected' in a number of ways, as indicated in the diagram above. Whether any of these can be developed into a practical synthetic method, we shall see in due course.

3.2 Disconnections and synthons

In its simplest terms, a carbon-carbon bond may be defined as the sharing of a pair of electrons between the carbon atoms. There are two ways in which such a bond may be formed: in the first, each carbon atom contributes one electron to the shared pair, and in the second, one of the carbons provides both electrons for the shared pair. These possibilities may be represented schematically as follows:



(3.1)

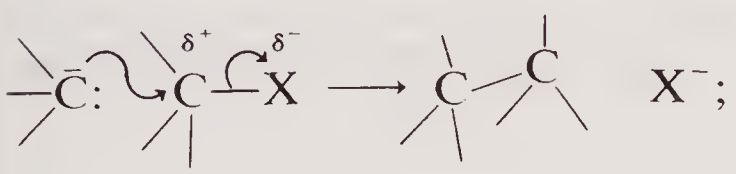


(3.2)

The first of these processes (3.1) is, of course, a radical reaction. In the simplified form above, the combination of two radicals is shown, but other variants are possible, such as (3.3), the addition of a radical to a double bond:

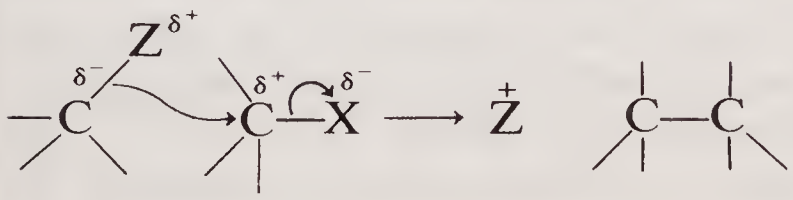
(3.3)

(This is, of course, an important step in the polymerisation of alkenes.) The second process is the more familiar type of laboratory reaction in which a nucleophile reacts with an electrophile. These are represented above by a carbanion and a carbocation respectively, but such a reaction is an extreme case, and more usual variants include the following (3.4–3.6):



(3.4)

(3.5)

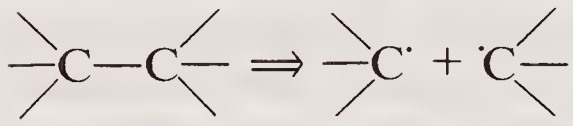


(3.6)

In summary, therefore:

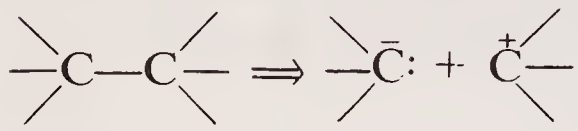
The formation of a carbon–carbon single bond implies the interaction of two carbon radicals, or the reaction of a nucleophilic carbon species with an electrophilic carbon species.

We may put this statement into a 'shorthand' form, using the mathematical symbol ⇒ in place of the word 'implies':



(3.7)

or



(3.8)

It is important to remember the distinction between the 'implies' symbol, ⇒, and the reaction arrow, →. The processes (3.7) and (3.8) do not represent synthetic reactions: in fact they are the precise opposites of such reactions, (3.7) being the opposite of reaction (3.1), and (3.8) being the opposite of reaction (3.2). Processes such as (3.7) and (3.8) are called **disconnections**, and the products of disconnections [e.g. the fragments on the right-hand side of (3.7) and (3.8)] are called **synthons**. The usefulness of the disconnection/synthon approach will become clearer in due course (cf. sections 4.4 and 5.5).

3.3 Electrophilic carbon species

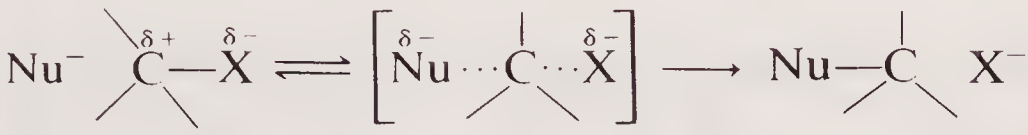
Although there are several important radical reactions which lead to carbon–carbon bond formation (e.g. arylation: section 2.4.1), the vast majority of useful laboratory methods for joining two carbon atoms are electrophile–nucleophile interactions, as expressed in reaction (3.2) or one of its variants such as (3.4–3.6). So far in this chapter we have dealt with these processes only in very general terms; we now consider in detail the functional groups and other features in a molecule which confer electrophilic or nucleophilic character on one (or more) of its carbon atoms.

3.3.1 Alkylating agents

One of the first general reactions learned by most students of organic chemistry is the nucleophilic substitution of alkyl halides (section 2.7.3, scheme 2.10), and the reader of this book should hardly need reminding that alkyl halides react with nucleophiles because the electron-withdrawing inductive ($-I$) effect of the halogen renders the halogen-bearing carbon electron-deficient, i.e. electrophilic (cf. Sykes, pp. 21–2). The mechanistic and stereochemical aspects of these reactions, especially the

distinction between the unimolecular, stepwise S_N1 process (3.9) and the bimolecular, concerted S_N2 process (3.10), should be familiar to most readers (cf. Sykes, Ch. 4).

(3.9)



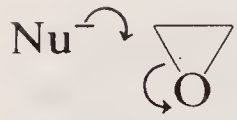
(3.10)

For the purposes of this book, however, it will not normally be necessary to distinguish between S_N1 and S_N2 mechanisms, and we shall represent the reaction of an alkyl halide with a nucleophile simply as

irrespective of the detailed mechanism. Since the nucleophile becomes attached to the alkyl group, it is said to have been **alkylated** and the process is known as **alkylation**.

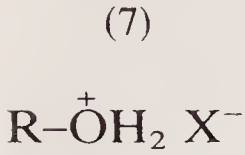
In the examples above, X has been used to represent a halogen. However, alkyl halides are not the only useful alkylating agents: as long as the C–X bond is sufficiently polarised, and as long as X^- is a stable anion which is neither a strong nucleophile nor a strong base [2] (i.e. the anion of a strong acid), nucleophilic substitution may occur. The most common alternatives to alkyl halides are the alkyl esters of sulphonic acids, especially methanesulphonates ('mesylates', 3) and toluene-*p*-sulphonates ('tosylates', 4). For methylations, dimethyl sulphate (5) is also frequently used, and one of the most powerful methylating agents available is methyl fluorosulphonate ('magic methyl', 6), although it has the disadvantage of being extremely toxic.

Carboxylic esters (R—OCOR′) are not effective alkylating agents because reactions with nucleophiles occur preferentially at the carbonyl group (cf. section 3.3.2). Alcohols and ethers (and their sulphur-containing counterparts) are also ineffective alkylating agents, because —OH, —OR, —SH, and —SR are poor **leaving groups** (i.e. they do not meet the criteria of the previous paragraph). Oxirans (epoxides), e.g. (7), can function as alkylating agents despite having no good leaving group, because the reaction with the nucleophile involves ring-opening and hence relief of strain (3.11).

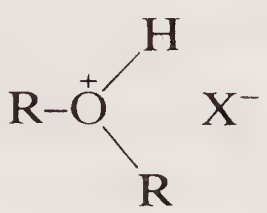


$$\longrightarrow \mathrm{NuCH_2CH_2O^-} \longrightarrow \mathrm{NuCH_2CH_2OH} \qquad (3.11)$$

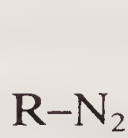
(7)



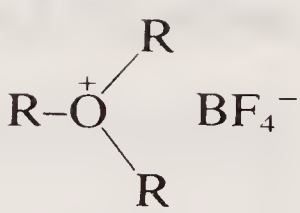
(8)



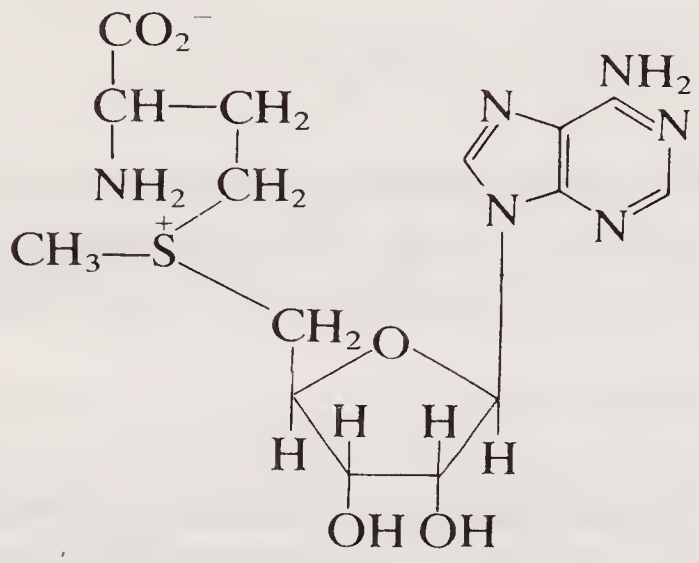
(9)



(10)



(11)

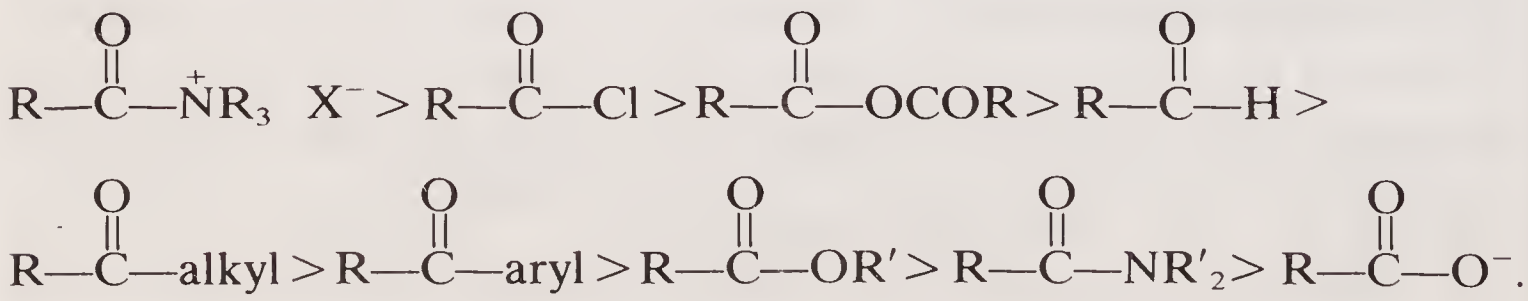


(12)

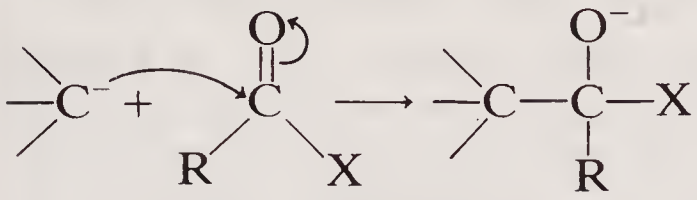
Protonated alcohols (8) and ethers (9), and also diazonium salts (10), are possible sources of carbocations and should thus be potential alkylating agents, but their formation normally requires acidic conditions under which carbon nucleophiles would be protonated and hence be rendered inactive. However, trialkyloxonium salts (11), e.g. trimethyl- and triethyloxonium fluoroborates, are powerful alkylating agents, and it is of interest to note that a trialkylsulphonium compound, *S*-adenosylmethionine (12), is one of nature's principal methylating agents.

3.3.2 Carbonyl compounds

The reader should already be familiar with the electrophilic nature of carbonyl compounds, and the consequent reactivity of such molecules towards nucleophiles (cf. Sykes, Ch. 8). The electrophilicity of the carbonyl carbon atom is due principally to the electron-accepting **mesomeric** ($-M$) effect of the oxygen, although it also depends on the electron-donating or -withdrawing ability of other attached atoms or groups. The order of reactivity in carbonyl compounds is as follows:



The general reaction of carbonyl compounds, R—C(=O)—X, with carbon nucleophiles may be represented schematically as follows (3.12):

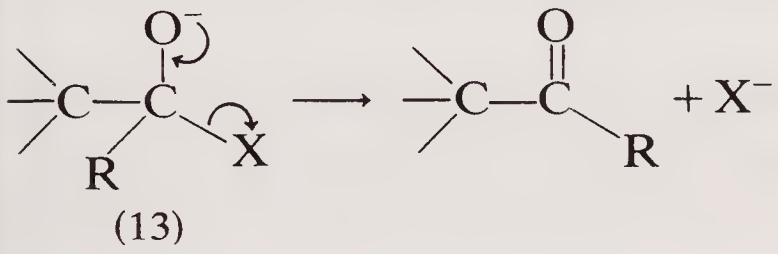


(3.12)

(13)

The initially formed anion (13) may then undergo further reaction in one of three ways.

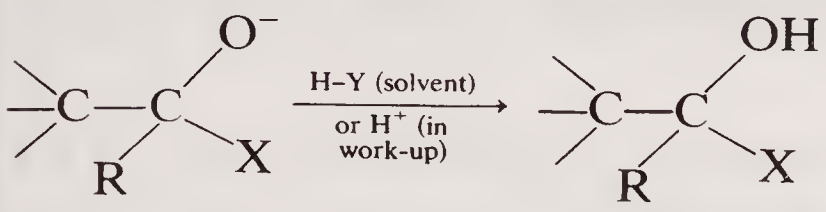
(i) If X is a leaving group (i.e. forms a stable anion), it may be eliminated as X^-. The net result (3.13) is substitution of the group X by the carbon nucleophile; the nucleophile becomes attached to an acyl group, and is thus said to have undergone **acylation**.



(3.13)

(13)

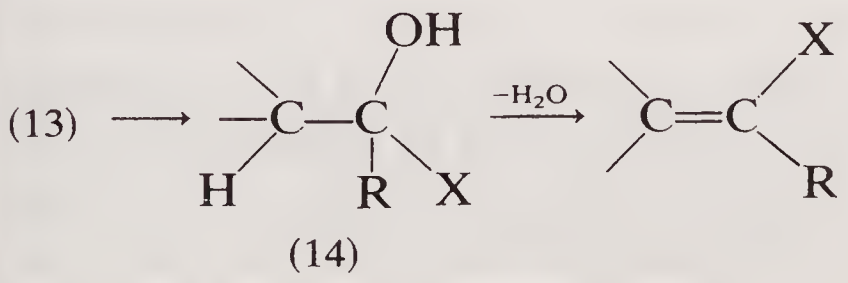
(ii) If X is not a leaving group, the anion (13) is likely to pick up a proton from the reaction medium, either immediately (if the reaction is conducted in a protic solvent) or during the isolation procedure (the 'work-up'). In such cases the net result is **addition** to the carbonyl group (3.14).



(3.14)

(13) (14)

(iii) If X is not a leaving group, and the adduct (14) also contains an acidic hydrogen adjacent to the hydroxyl group, elimination of water may follow the nucleophilic addition (3.15). This addition–elimination sequence is called a **condensation** reaction.[3]



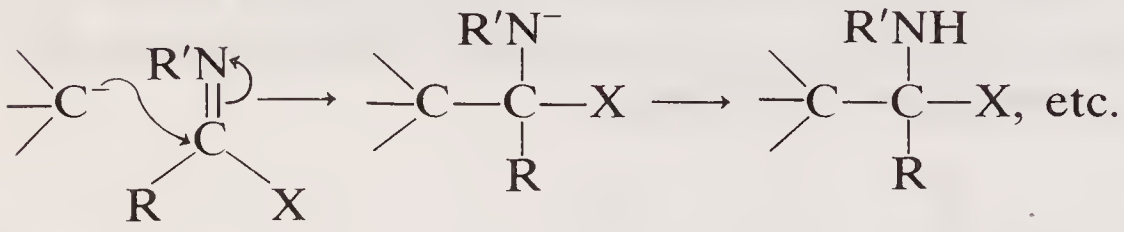
(3.15)

(14)

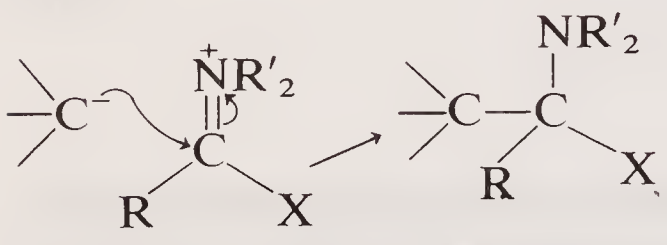
All of these reactions will be considered in more detail in Chapters 4, 5 and 7.

3.3.3 Electrophilic carbon–nitrogen reagents

One would expect compounds containing carbon–nitrogen double bonds to resemble carbonyl compounds in their reactions with nucleophiles. Imino-compounds do indeed react with nucleophiles (3.16) in accord with this expectation, although such reactions are in general much less useful than the corresponding processes involving carbonyl compounds. On the other hand, if the nitrogen is positively charged the carbon becomes highly electrophilic, and nucleophilic addition to iminium salts (3.17) is the key to important synthetic procedures such as the Mannich and Vilsmeier–Haack–Arnold reactions (sections 5.4.3 and 5.4.2).

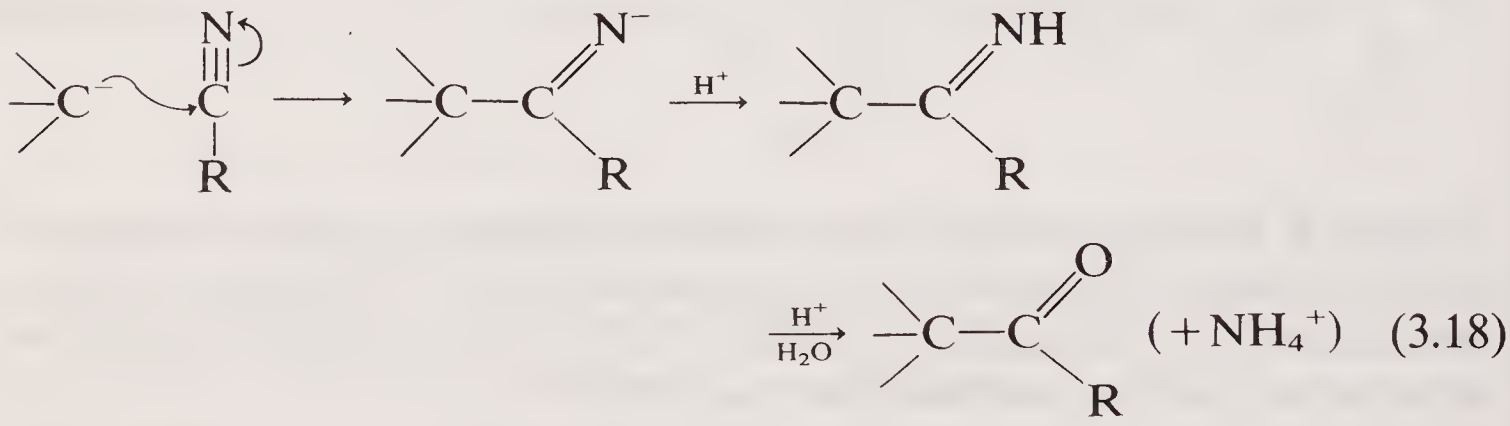


(3.16)



(3.17)

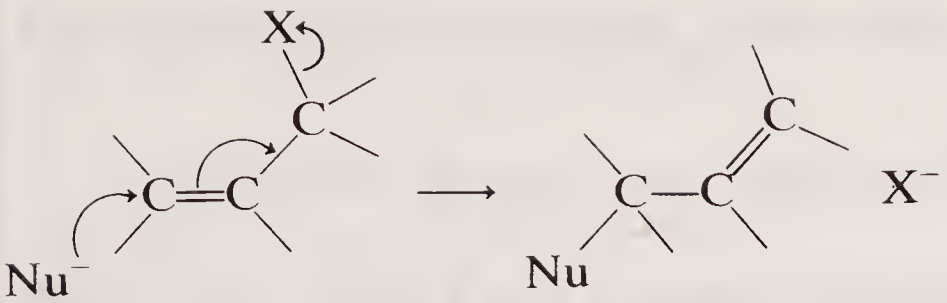
Cyano-compounds also behave as electrophiles (3.18), nucleophilic addition to such compounds giving anions of imines. The imines themselves are frequently not stable, and undergo hydrolysis to carbonyl compounds (cf. Sykes, pp. 244–5):



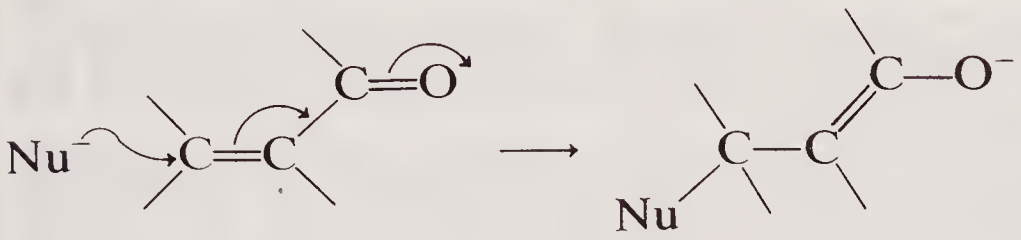
(3.18)

3.3.4 Electrophilic alkenes

One does not expect an alkene, which is an electron-rich species, to function as an electrophile: indeed, one is accustomed to alkenes being *nucleophilic* and reacting with electrophiles. However, if the carbon atom, one position removed from the double bond, is electrophilic, then nucleophilic attack may occur not only at the electrophilic carbon but at the 'far' end of the double bond as in (3.19) and (3.20) (cf. Sykes, pp. 109–10 and 198–202).

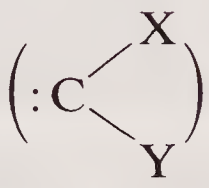


(3.19)



(3.20)

3.3.5 Carbenes

These neutral, electron-deficient species  which are highly reactive electrophiles (cf. Sykes, pp. 266–7), are of synthetic interest principally for their reactions with alkenes (section 7.2.3) and with electron-rich aromatic molecules (section 5.4.2).

3.4 Nucleophilic carbon species

In our original schematic representation of the electrophile–nucleophile interaction [section 3.2: reaction (3.2)], the nucleophile was represented by a carbanion, and so we now consider the molecular features which promote the formation of these and related nucleophilic species.

3.4.1 Grignard and related organometallic reagents

Most readers will already be familiar with Grignard reagents, RMgX, where R is an alkyl (or aryl) group and X is a halogen (usually bromine or iodine). These are undoubtedly the most widely used of the organometallic reagents in nucleophile–electrophile reactions: they are simply made from alkyl (or even aryl) halides and magnesium in a dry ether solvent, and are stable in this solution, although they are rapidly decomposed by oxygen and by water and other protic solvents (cf. below). The exact structure of Grignard reagents and the exact mechanisms by which they react with electrophiles, are matters of some dispute (cf. Sykes, pp 221–3), but these need not concern us here, since we are primarily concerned in this book with the *products* of their reactions. For synthetic purposes, they may be regarded as having the structure RMgX, which is polarised $\overset{\delta-}{R}—\overset{\delta+}{M}gX$ or even $\overset{-}{R}\ \overset{+}{M}gX$: they behave as carbanions and are adequately represented by the synthon R^-. They suffer from the disadvantage, however, of being very strong bases, and will abstract even

feebly acidic protons, e.g. from water, alcohols, or even primary and secondary amines:

$$R—MgX + H—Y \longrightarrow R—H + YMgX \quad (Y = OH, OR', NHR', NR'_2)$$

The corresponding organozinc reagents are very seldom used nowadays: they are less reactive than Grignard reagents, and are allegedly more difficult to handle. The lower reactivity, however, is utilised in the **Reformatsky reaction** (section 4.2.2).

Dialkylcadmium reagents (R_2Cd), which are preparable from Grignard reagents and cadmium chloride, are also less reactive than Grignard reagents (the metal is less electropositive than magnesium), but are sometimes used by virtue of their greater selectivity towards electrophiles. Alkyl-lithium and aryl-lithium compounds, on the other hand, are more reactive, and even less selective, than the corresponding Grignard reagents.

One group of organometallic reagents which may function as useful carbon nucleophiles and which exhibit an unusual degree of selectivity are organocopper reagents. These are of two types, both derived from copper(I) halides and alkyl-lithium compounds (3.21–3.22).

$$2RLi + Cu_2X_2 \rightarrow 2RCu + 2LiX \qquad (3.21)$$

$$4RLi + Cu_2I_2 \rightarrow 2R_2CuLi + 2LiI \qquad (3.22)$$

Of these, the first (the simple alkylcopper) is sparingly soluble in organic solvents unless it is complexed using ligands such as trialkylphosphines, but the second (called a **lithium dialkylcuprate**) is soluble in ethers and is hence of immediate use as a reagent.

The synthetic uses of all these organometallic reagents are described in Chapter 4.

3.4.2 Stabilised carbanions

The vast majority of stabilised carbanions are produced by heterolysis of a C–H bond (3.23):

(3.23)

In most cases, however, this type of ionisation does not occur spontaneously to any significant extent, since it is rare for a hydrogen bonded to carbon to be strongly acidic. A base is therefore used in order to promote the heterolysis (3.24–3.25):

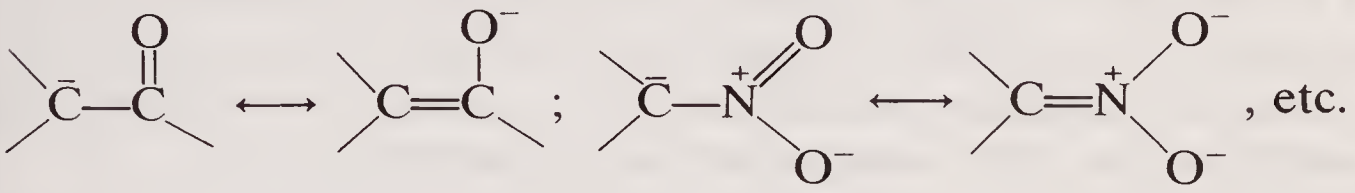
(3.24)

(3.25)

It is important to remember, of course, that reactions (3.24) and (3.25) are equilibria, since carbanions are themselves basic and can recapture protons. It follows, therefore, that if deprotonation of the $\geq$C—H compound is to be complete (or effectively complete), B^- or $\ddot{B}$ must be a much stronger base than the carbanion. Or, to put it another way, the more strongly acidic the $\geq$C—H compound, the weaker the base required for complete deprotonation. Also it must be remembered that **for complete deprotonation a molecular equivalent of base is required**. These points may at first sight appear trivial, but they are in fact very important in determining the outcome of some carbanion reactions (sections 5.1 and 5.2).

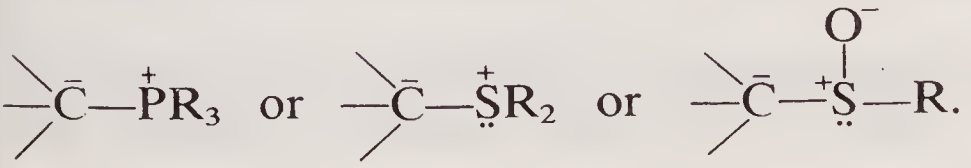
The structural features which enhance the acidity of $\geq$C—H compounds and which stabilise carbanions are described by Sykes (pp. 271–5), and so only a summary is given here.

(i) The best stabilisation of the carbanion is achieved when the anionic centre is adjacent to an electron-accepting ($-M$) group, such as carbonyl, cyano, nitro or sulphonyl. Stabilisation results from the delocalisation of the negative charge:



Of these $-M$ groups, the order of stabilising effect is $NO_2 > CO > SO_2 \simeq CN$; among carbonyl groups, the order is as expected, e.g. aldehyde > ketone > ester. If the anionic centre is flanked by two $-M$ groups, additional delocalisation of the charge is possible, the stability of the anion is considerably increased, and its basicity is correspondingly decreased; if three $-M$ groups flank the anion, it is scarcely basic at all.

(ii) When the anionic centre is adjacent to an inductive electron-withdrawing ($-I$) group, stabilisation of the carbanion results, although not surprisingly this type of stabilisation is less effective than that involving a $-M$ group. Two or more $-I$ substituents make a moderately stable carbanion, e.g. $^-CF_3$ or $\bar{C}H(SR)_2$, as do $-I$ groups carrying a positive charge, e.g.



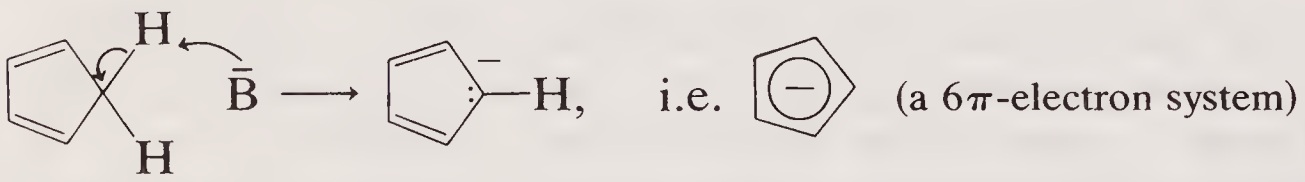
For this type of stabilisation, it is noteworthy that (fluorine apart) the most effective stabilising groups are those in which the atom next to the anionic centre is one from the second row of the periodic table (in particular phosphorus or sulphur). These atoms have unoccupied 3*d* orbitals which, in principle, may overlap with the 2*p* orbital of carbon which contains the lone pair and hence exert a type of mesomeric stabilisation of the negative charge. The extent of such overlap, and hence the degree of mesomeric stabilisation of such carbanions, is a matter of current debate, but such arguments need not concern us in this book, where reaction products take precedence over the finer points of mechanism.

(iii) When the anionic centre resides on a triply bonded carbon atom, a degree of stabilisation is conferred on the carbanion. Alk-1-ynes, although by no means strong acids, are nevertheless much stronger acids than alkanes, and are thus deprotonated easily by alkyl carbanions (Grignard and similar reagents) and also by amide ion:

$$R'C{\equiv}C{-}H \; {}^{\curvearrowleft}\bar{N}H_2 \longrightarrow R'C{\equiv}C^- + NH_3$$

The alkynyl carbanion is stabilised, relative to an alkyl carbanion, by virtue of the high *s* character of the orbital containing the unshared electron pair. Hydrogen cyanide is considerably more acidic than alkynes, and cyanide ion is much more stabilised than alkynyl ions: this enhanced stability presumably results from the polarisation of the π-bond system, which depletes the carbon of electrons, and thus reduces the availability of the lone pair for bonding.

(iv) A carbanion is greatly stabilised if the lone pair of electrons which is responsible for the negative charge forms part of an aromatic system. This is a relatively uncommon situation, but it explains, for example, the high stability of the anion derived from cyclopentadiene:



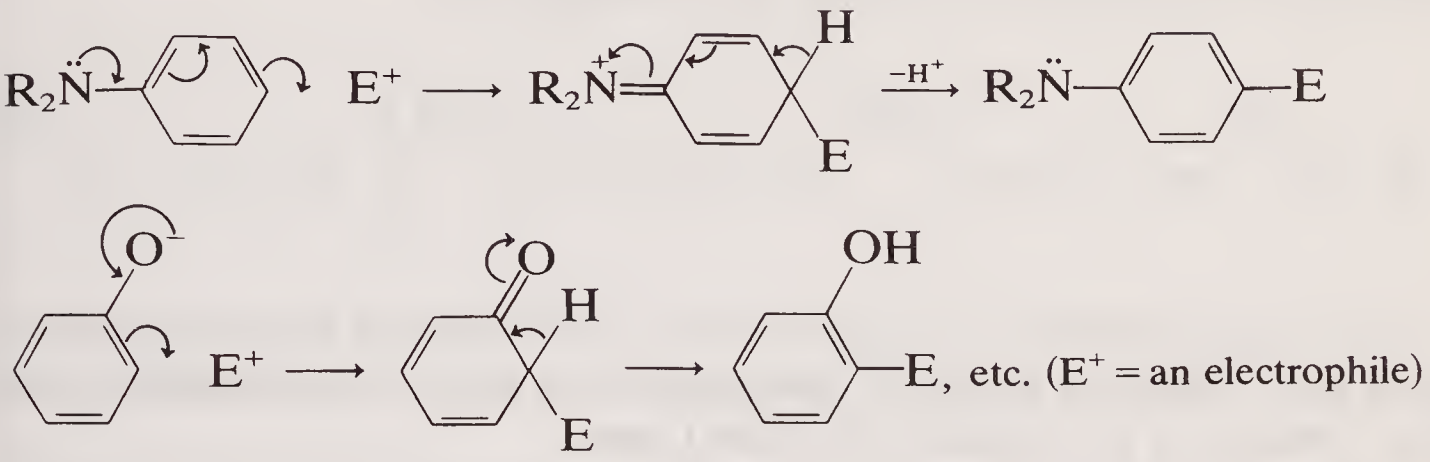
3.4.3 Alkenes, arenes and heteroarenes

The student of organic chemistry learns at a very early stage that alkenes react with electrophiles (by an addition process); that arenes (benzene, naphthalene, etc.) do likewise (by addition–elimination); and, at a later stage perhaps, that heteroaromatic compounds (furan, thiophen, pyridine, indole, etc.) react more or less in the same way as arenes. So alkenes, arenes and heteroarenes must be considered as nucleophilic carbon species.

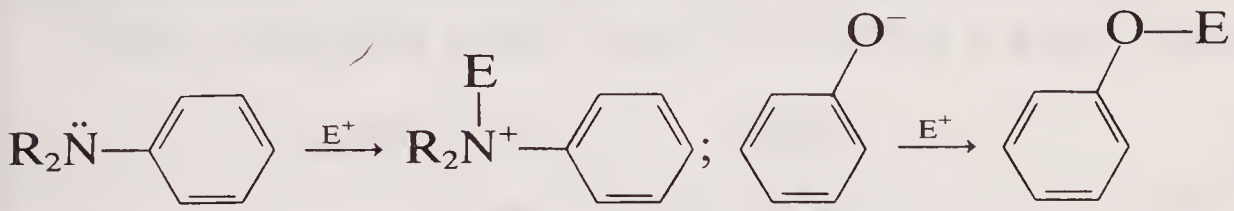
The principal reactions of these classes of compound are summarised in Chapter 2 (sections 2.2 and 2.4–2.6), and it must be obvious that

among these are very few which involve carbon–carbon bond formation. For alkenes, none at all are listed. For benzene and its heterocyclic analogues, only the Friedel–Crafts reaction has wide generality, and even that does not apply to ring systems with reduced nucleophilicity, such as nitrobenzene and pyridine.

The reader who has studied the chemistry of simple benzene derivatives will recall that an electron-donating ($+M$) substituent greatly enhances the reactivity of a benzene ring towards electrophiles (cf. Sykes, pp. 153–5). The effect is pronounced in arylamines and phenols, and even more so in phenoxide ions; reaction occurs *o*- and *p*- to the substituent, e.g.

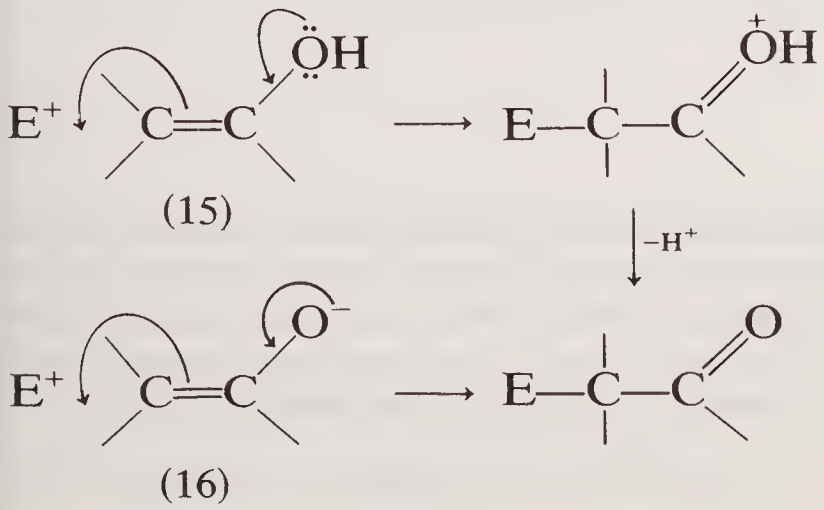


Reaction may also occur, of course, at the substituent and not on the ring:



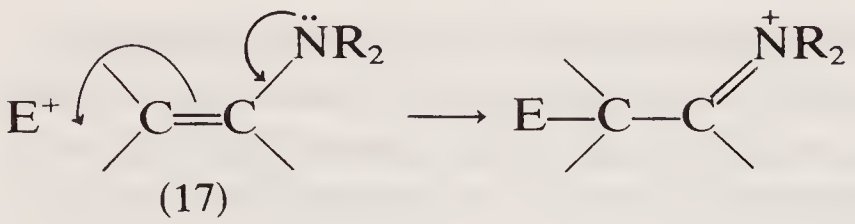
The reactions of phenols and arylamines with electrophiles include several useful carbon–carbon bond-forming reactions (cf. sections 5.4.2 and 5.4.3).

Electron-donating substituents have a similar activating effect on simple alkenes. So **enols** (15), **enolate** ions (16), and **enamines** (17) react with electrophiles as follows (although, as above, reaction may also occur at oxygen or nitrogen):

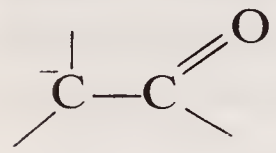


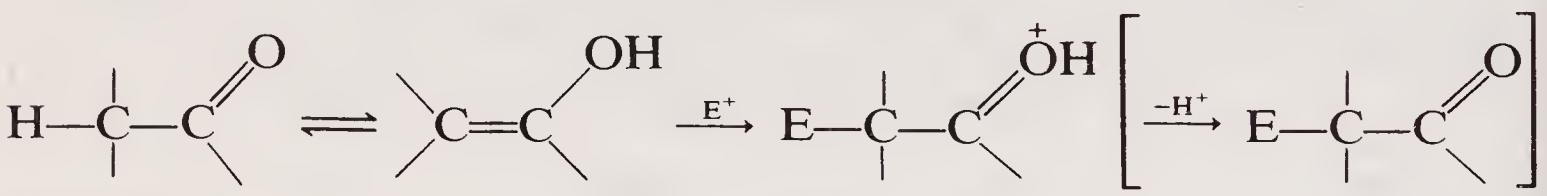
(3.26)

(3.27)



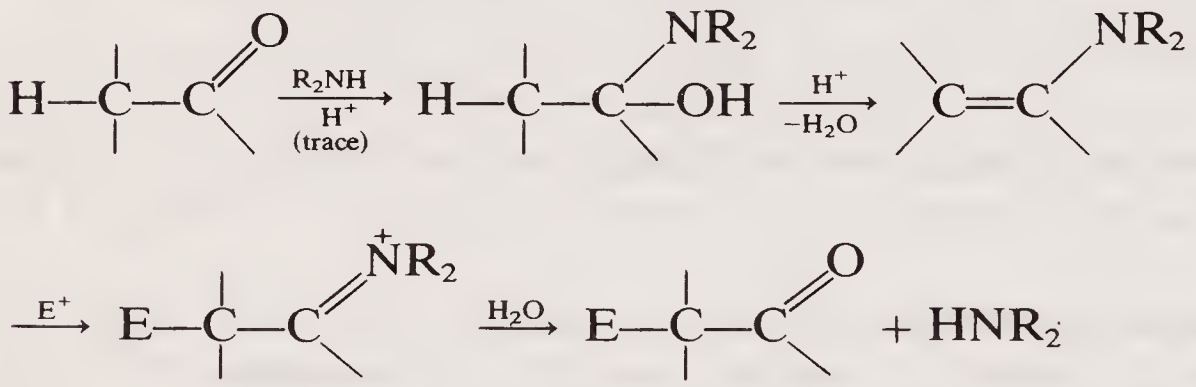
(17) (3.28)

These are three very important reactions, as will be seen later (in Ch. 5). Reaction (3.27) should already be familiar, because (16) is nothing more than the alternative canonical form for the carbanion  . Compound (15) is tautomeric with a carbonyl compound, and (3.26) should perhaps be rewritten as:



In this expanded form, the importance of the reaction becomes clear: it shows that **enolisable carbonyl compounds can react as nucleophiles even in the absence of a (carbanion-forming) base.**

A similar expansion of reaction (3.28) shows that the enamine reaction is no more than a variant of (3.26), at least from the synthetic viewpoint: it permits electrophile substitution at the α-position of an enolisable carbonyl compound using a base no stronger than a secondary amine:



The reactions of enols, enolates, and enamines will be considered further in Chapter 5.

Notes

1. Compound A is an example of a class of compounds known as *insect pheromones*. This particular compound (*Z*-heneicos-6-en-11-one) is produced by the female of the Douglas fir tussock moth in order to attract a mate, and the synthetic material is thus of value as a lure to trap male moths and hence limit the breeding process of what is regarded by the forester as a pest.

2. For the distinction between nucleophilicity and basicity, see Sykes, p. 96.

3. The term *condensation* is one for which few present day textbooks of organic chemistry seem prepared to offer a definition. In common practice the term is used loosely to describe reactions of various kinds: thus, for example, the Claisen ester 'condensation' and Dieckmann 'condensation' are in reality acylations of esters (sections 5.2.2 and 7.1.1); the aldol 'condensation', the benzoin 'condensation', and the Michael 'condensation' are three different types of addition reaction (sections 5.2.4.1; 5.6.2, Note 10; and 5.1.5) leading to three very different types of product; and the Claisen–Schmidt and Knoevenagel–Doebner 'condensations' are addition–eliminations of the general type (3.15). For the purposes of this book, where product types are the main concern, we have chosen to avoid possible confusion by using the term *condensation* to refer only to reactions of this last type. Such reactions will be considered further in sections 5.1.4; 5.2.4; and 7.1.

4 Formation of carbon–carbon bonds: reactions of organometallic compounds

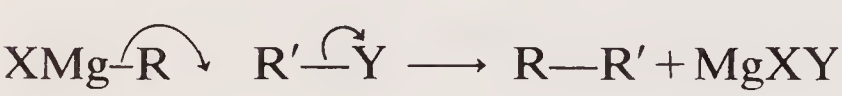
So far we have dealt with carbon–carbon bond-forming reactions only in general terms. We now turn to consider some of the most important of these processes, and we begin in this chapter with what, on paper at least, are the simplest: the reactions involving organometallic species.

4.1 Grignard reagents and electrophiles

As already noted (section 3.4.1) a Grignard reagent, RMgX, in ethereal solution (usually diethyl ether or tetrahydrofuran) acts as a source of unstabilised carbanions, i.e. R^-. R is commonly alkyl or aryl, but may also be alkenyl or alkynyl (see section 4.1.5).

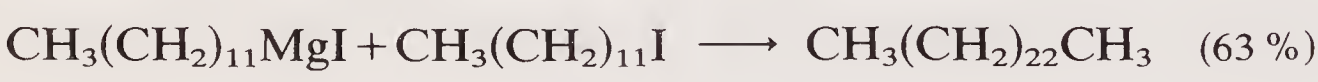
4.1.1 Alkylation

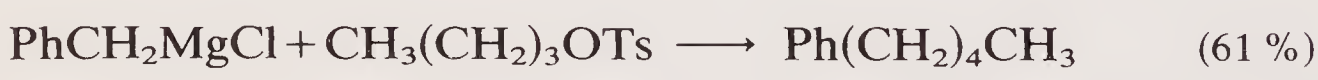
Grignard reagents undergo alkylation to give alkanes:

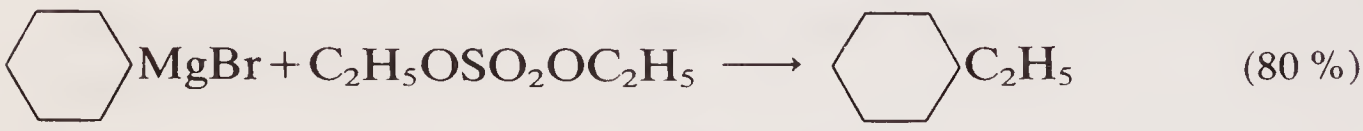


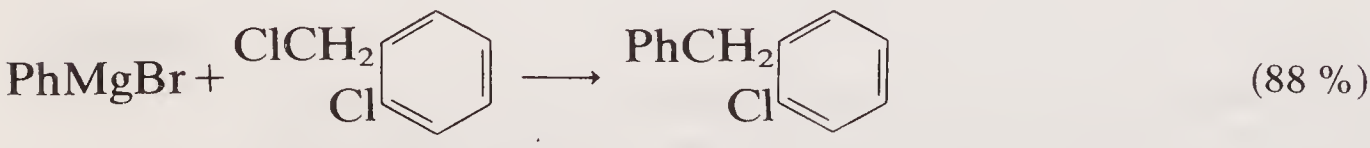
(4.1)

Thus, for example,





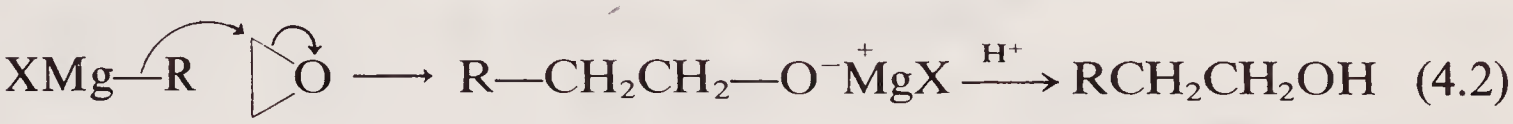




[Ts = toluene-*p*-sulphonyl]

Although good yields are obtained in the above cases, these are exceptions to the general rule: alkylations of Grignard reagents frequently pro-

ceed in very low yield (especially when the leaving group Y is a halogen), because of the intervention of side-reactions (e.g. elimination of hydrogen halide, or redox processes giving radicals). One generally useful alkylation, however, is the reaction with oxiran (ethylene oxide):

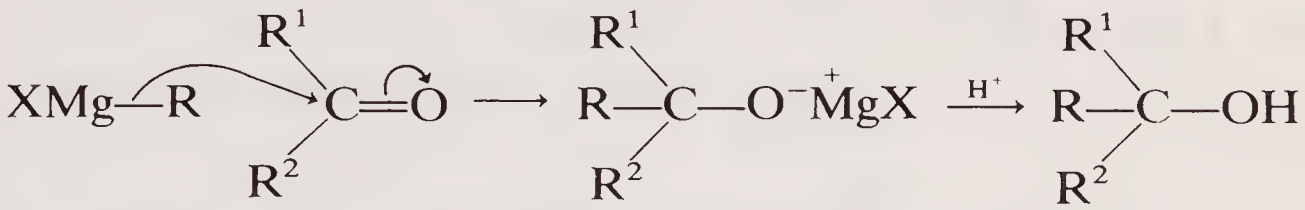


(4.2)

For example,

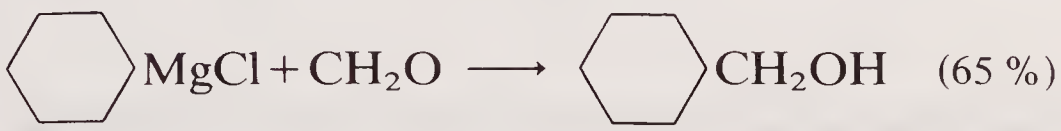
4.1.2 Reactions with carbonyl compounds

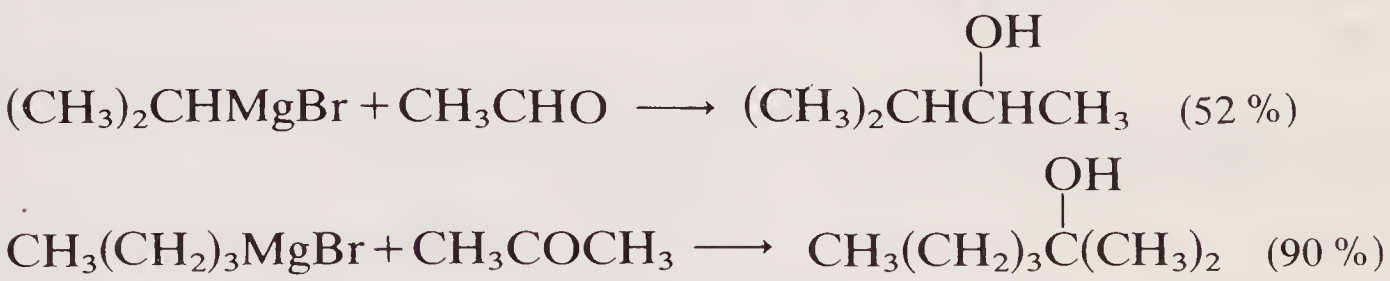
These are by far the most useful reactions of Grignard compounds. With aldehydes and ketones, the reaction is addition: formaldehyde is converted into primary alcohols, other aldehydes into secondary alcohols, and ketones into tertiary alcohols:



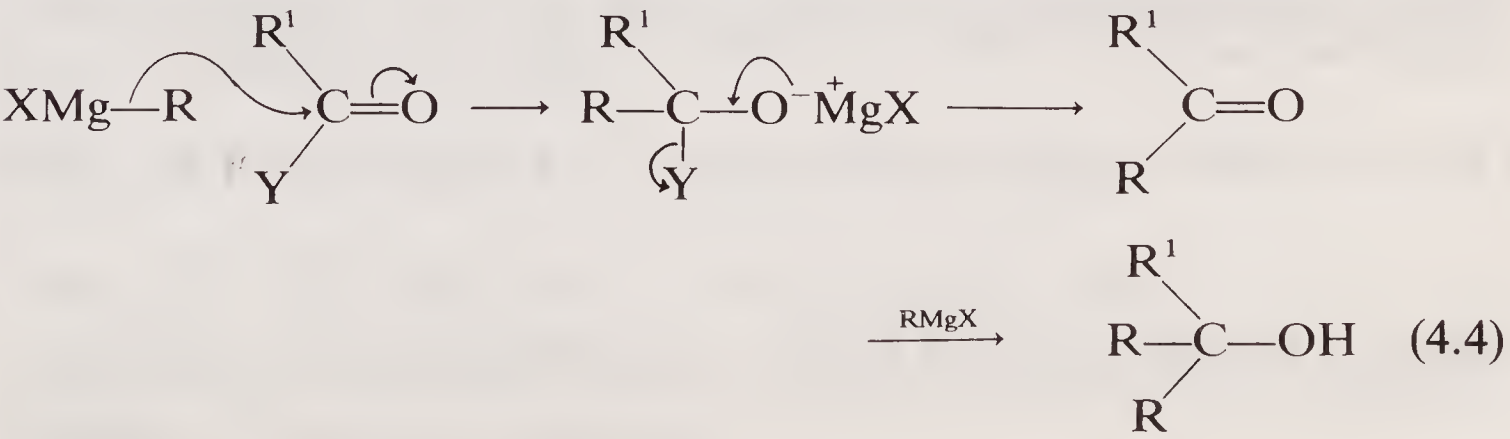
(4.3)

Thus,



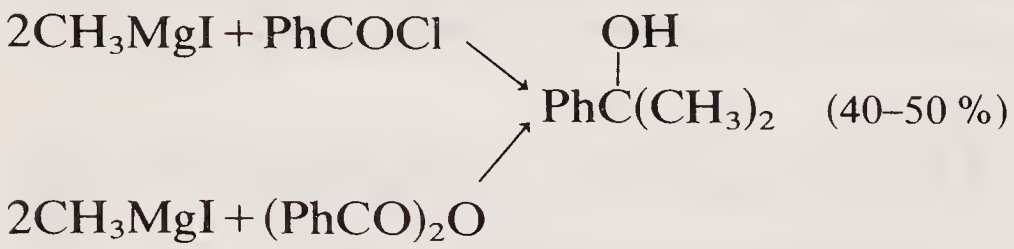


With acyl halides, anhydrides and esters, the first stage of the reaction is acylation, giving a ketone. This may then react with a second molecule of the Grignard reagent, the final product being a tertiary alcohol:



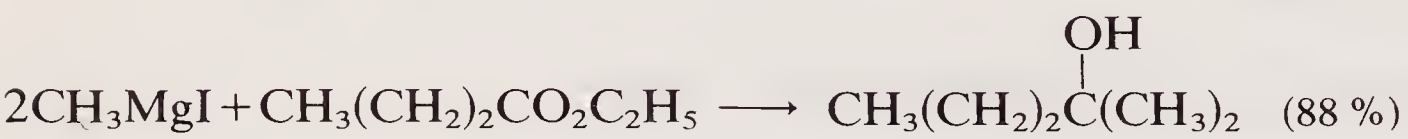
(4.4)

Of these reactions, those with esters are the most reliable and give the best yields:

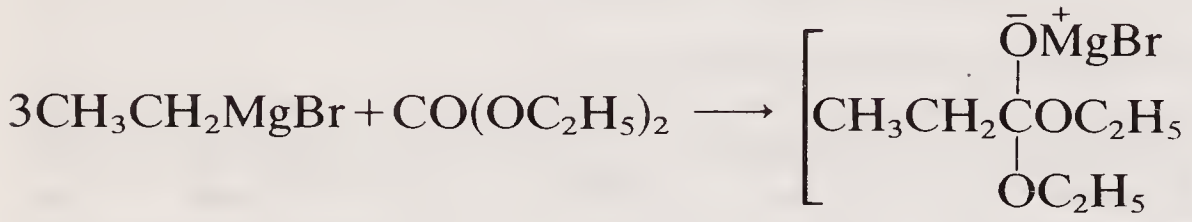


$$2CH_3MgI + PhCOCl \longrightarrow PhC(OH)(CH_3)_2 \quad (40\text{–}50\ \%)$$

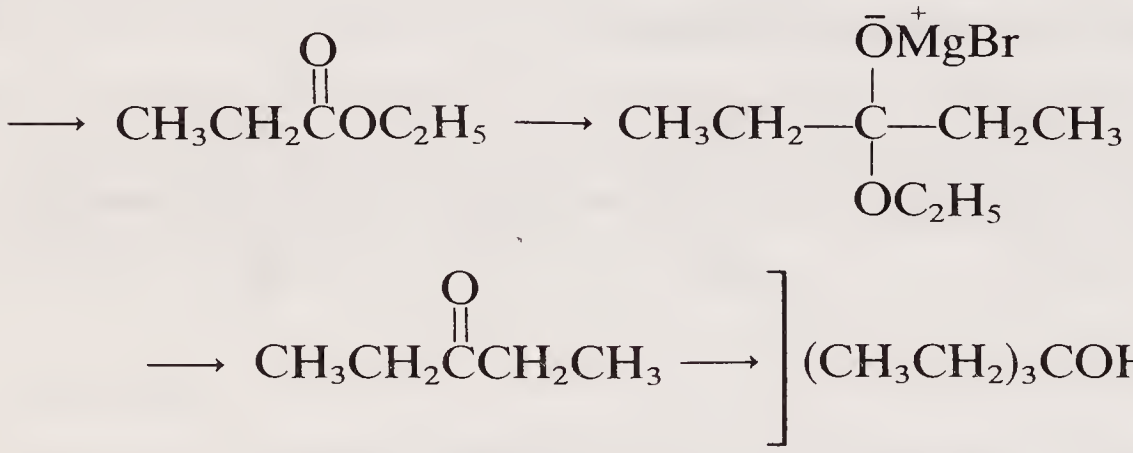
$$2CH_3MgI + (PhCO)_2O \longrightarrow PhC(OH)(CH_3)_2 \quad (40\text{–}50\ \%)$$



$$2CH_3MgI + CH_3(CH_2)_2CO_2C_2H_5 \longrightarrow CH_3(CH_2)_2C(OH)(CH_3)_2 \quad (88\ \%)$$



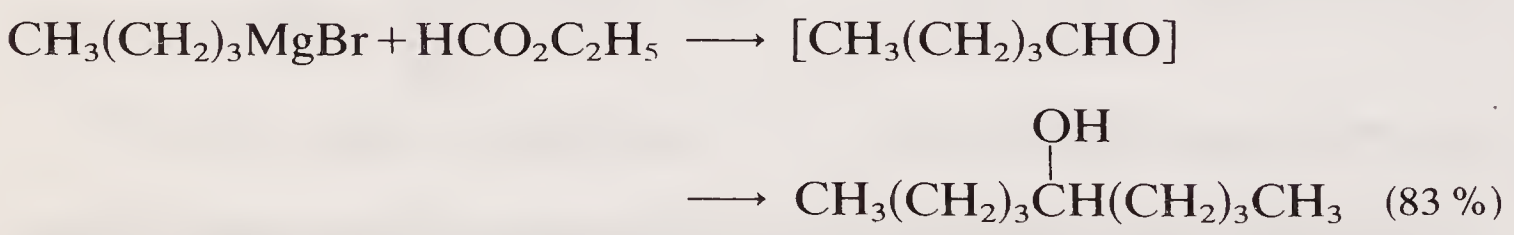
$$3CH_3CH_2MgBr + CO(OC_2H_5)_2 \longrightarrow \left[CH_3CH_2C(\bar{O}\overset{+}{M}gBr)(OC_2H_5)COC_2H_5\right]$$



$$\longrightarrow CH_3CH_2C(=O)OC_2H_5 \longrightarrow CH_3CH_2C(\bar{O}\overset{+}{M}gBr)(OC_2H_5)CH_2CH_3$$

$$\longrightarrow CH_3CH_2C(=O)CH_2CH_3 \longrightarrow (CH_3CH_2)_3COH \quad (86\ \%)$$

Formate esters, of course, give secondary alcohols [$R^1 = H$ in reaction (4.4)], e.g.

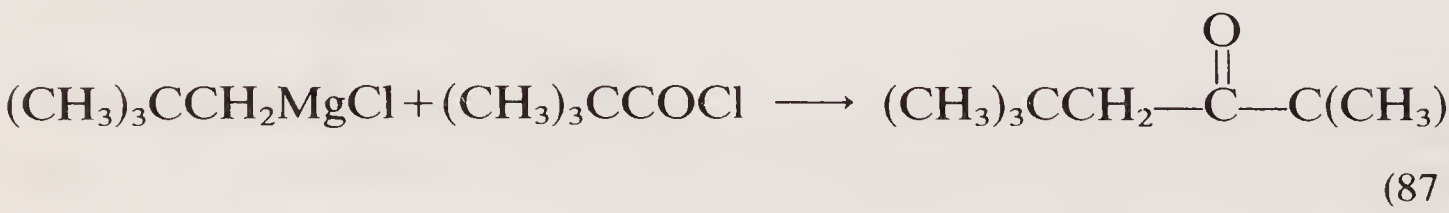


$$CH_3(CH_2)_3MgBr + HCO_2C_2H_5 \longrightarrow [CH_3(CH_2)_3CHO]$$

$$\longrightarrow CH_3(CH_2)_3CH(OH)(CH_2)_3CH_3 \quad (83\ \%)$$

It is seldom possible to stop these reactions at the half-way stage, but carbonyl compounds have occasionally been isolated under special conditions, e.g. when the acyl compound is used in excess, when the reaction temperature is low, or when the product is sterically hindered:

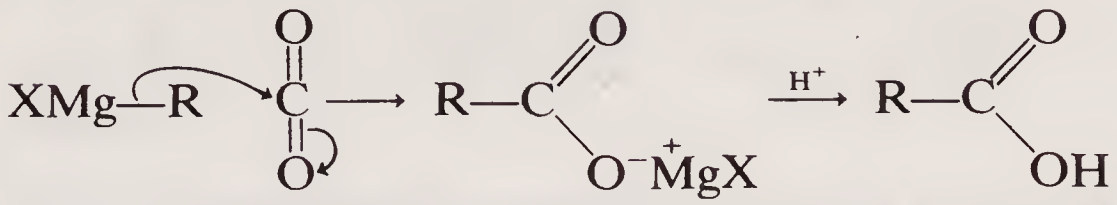
$$CH_3(CH_2)_3MgCl + (CH_3CO)_2O \text{ (excess)} \xrightarrow{-80^\circ} CH_3(CH_2)_3COCH_3 \quad (80\ \%)$$



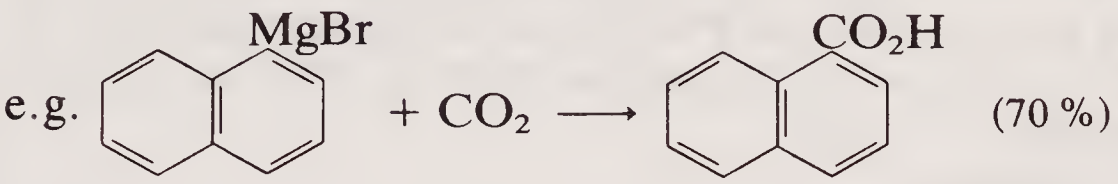
$$(CH_3)_3CCH_2MgCl + (CH_3)_3CCOCl \longrightarrow (CH_3)_3CCH_2C(=O)C(CH_3)_3$$

(87 %)

With carbon dioxide, Grignard reagents undergo carboxylation, giving carboxylate ions:



(4.5)



(70 %)

The reader may well wonder why, in this case, the carbonyl compound does not apparently react with a second molecule of the Grignard reagent. Carboxylate ions, contrary to popular belief, are not entirely unreactive towards Grignard reagents. Indeed, formate ions react very readily, giving aldehydes, e.g.

$$C_2H_5MgBr + HCO_2H \xrightarrow[0°]{THF} HCO_2^-\overset{+}{M}gBr + C_2H_6$$

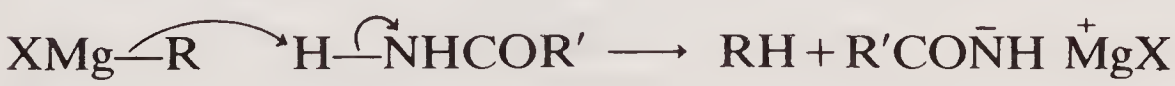
$$CH_3(CH_2)_5MgBr + HCO_2^-\overset{+}{M}gBr \xrightarrow[0°–20°,\ 40\ min]{THF} CH_3(CH_2)_5\underset{H}{\overset{\bar{O}\overset{+}{M}gBr}{\overset{|}{C}}}—\bar{O}\overset{+}{M}gBr \xrightarrow[H_2O]{H^+} CH_3(CH_2)_5CHO \quad (75\ \%)$$

and other carboxylates also react, although more slowly, e.g.

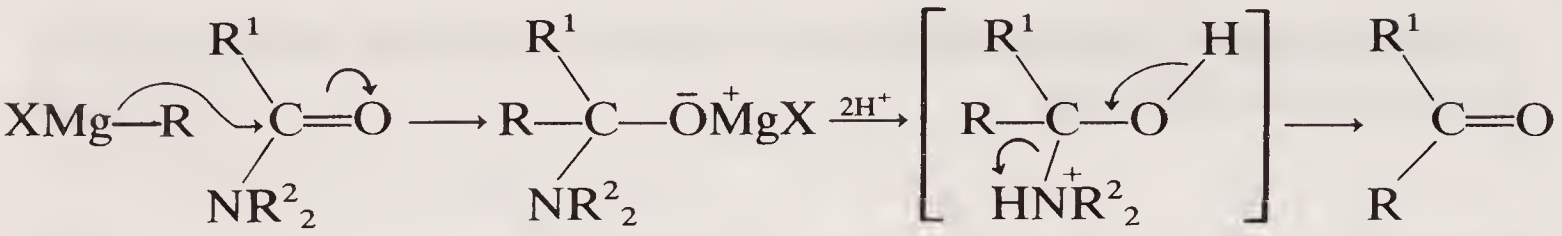
$$(CH_3)_2CHCH_2MgBr + CH_3CO_2^-Na^+ \xrightarrow[\text{room temperature, 24 hours}]{\text{ether}} (CH_3)_2CHCH_2COCH_3 \quad (\text{ca. } 25\ \%)$$

Carboxylation, however, is normally carried out using a large excess of carbon dioxide, and is much faster than addition to the carboxylate ion in any case; thus the latter is not normally an important side-reaction.

With primary and secondary amides, as with carboxylic acids, the principal action of the Grignard reagent is to remove the (acidic) proton from the nitrogen or oxygen:



The reaction with tertiary amides, however, constitutes an interesting synthesis of carbonyl compounds:

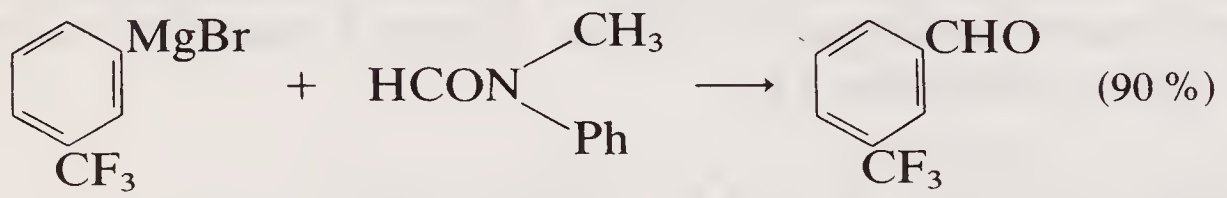


(1) (4.6)

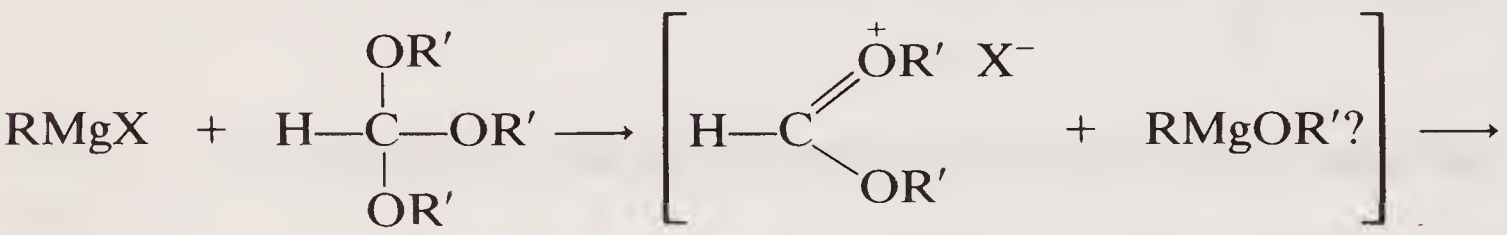
[In this reaction the initial adduct (1) does not collapse directly to the carbonyl compound because NR^2_2 is a very poor leaving group. NHR^2_2, however, produced by protonation during the work-up, is by contrast an excellent leaving group.]

Examples of this include:

(51 %)



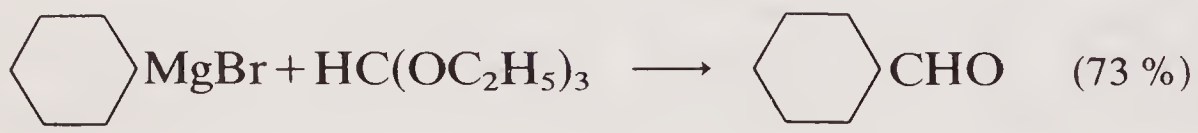
The above has not been developed extensively as a route to aldehydes, despite the ready availability of reagents such as dimethyl formamide. The other classical Grignard synthesis of aldehydes, using orthoformate esters (trialkoxymethanes), is equally simple and often gives better yields:



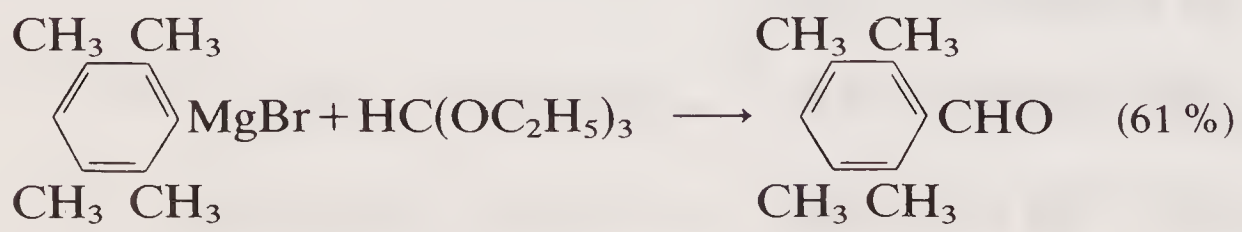
$(R' = CH_3$ or $C_2H_5)$

(4.7)

e.g.



(73 %)

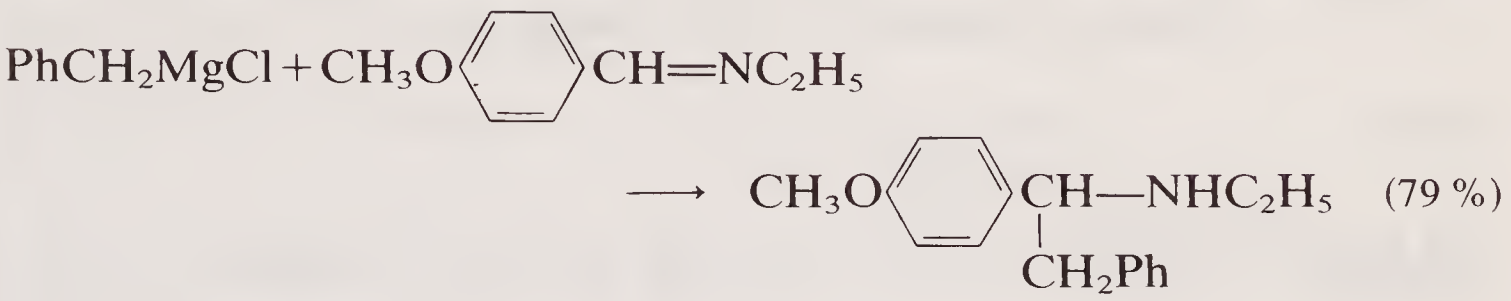


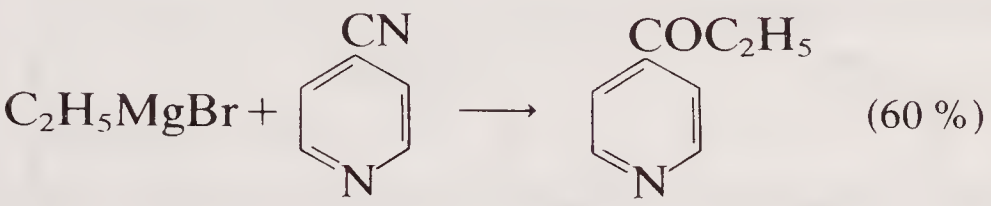
(61 %)

The recent method using formate ions (cf. p. 41) also provides a simple alternative.

4.1.3 Reactions with compounds containing >C=N— and —C≡N groups

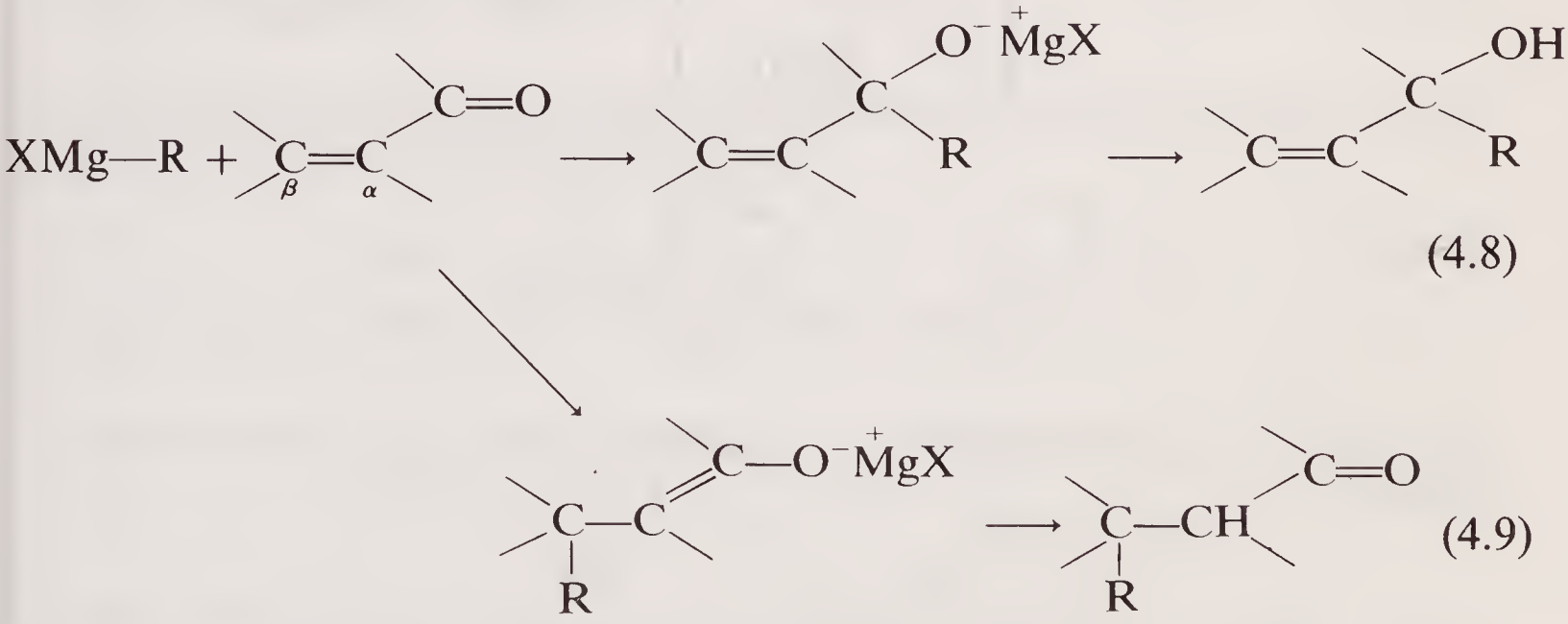
These follow the expected pathways, as the undernoted examples show. The reaction with cyano-compounds constitutes a useful general route to ketones:



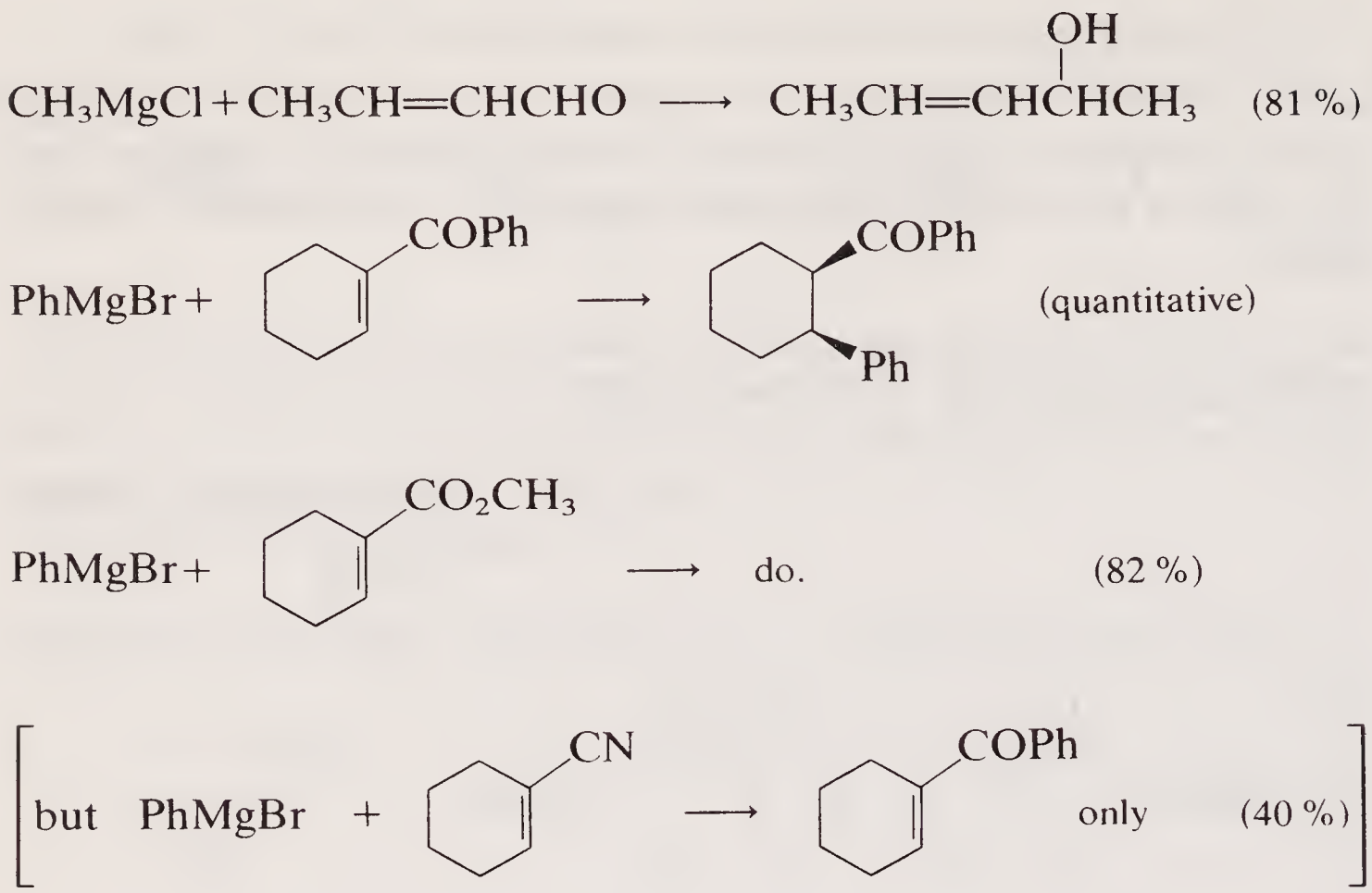


4.1.4 Reactions with >C=C—C=O and related systems

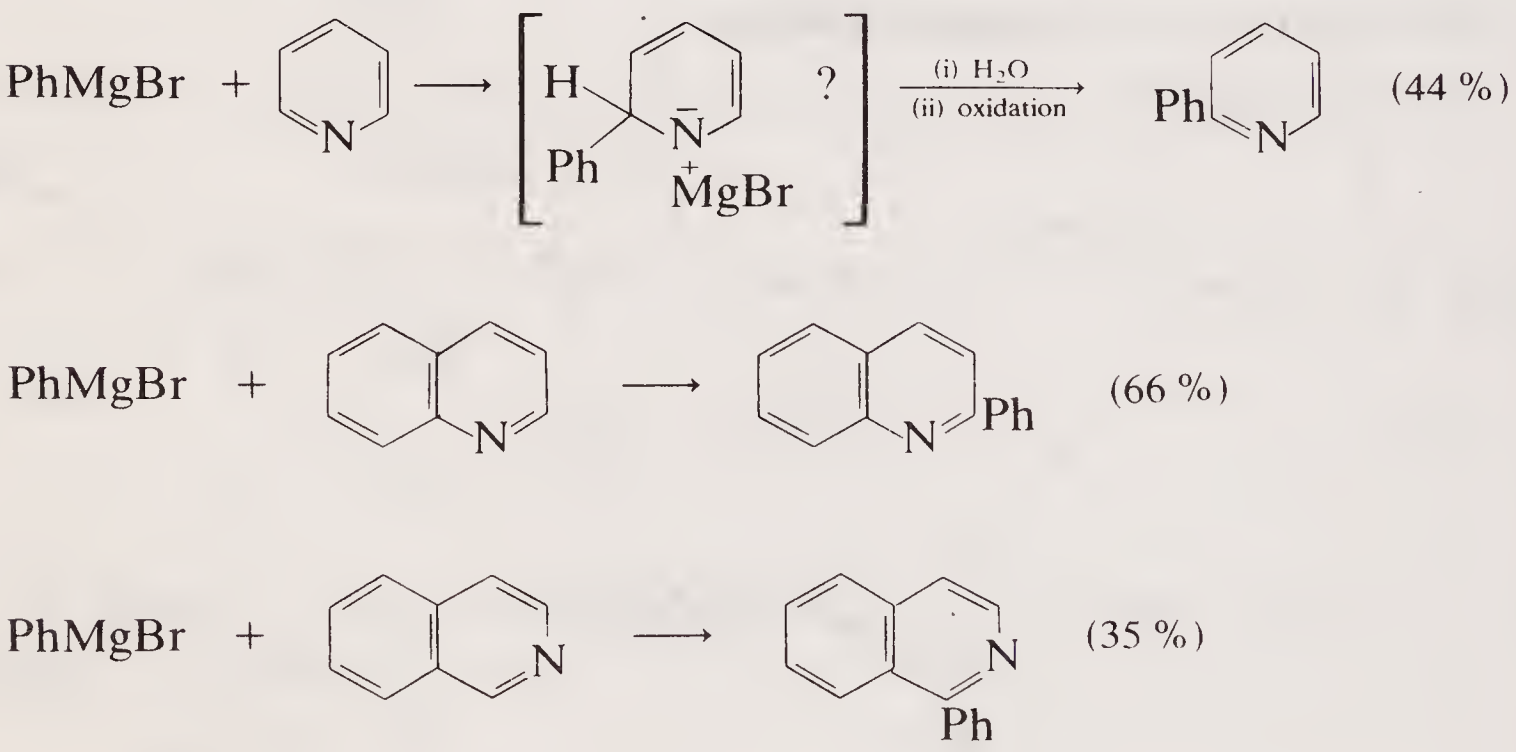
Grignard reagents may undergo reactions with α,β-unsaturated carbonyl compounds either at the carbonyl carbon or at the β-carbon. The latter is often referred to as **conjugate addition**.



Where there is no steric interference, and an alkyl Grignard reagent is used, reaction (4.8) predominates; otherwise, conjugate addition may also occur, and this is not therefore a reliable general method. Conjugate addition is the principal mechanism in presence of a copper(I) salt (cf. section 4.2.3, p. 49).



Reaction of Grignard reagents with 'π-deficient' heterocycles such as pyridine, quinoline and isoquinoline generally occur at a position adjacent to the heteroatom:



4.1.5 Alkenyl and alkynyl Grignard reagents

Halogenoalkenes, in which the halogen is attached directly to one of the doubly bonded carbons, are unreactive halides (cf. Sykes, p. 85), and they form Grignard reagents only with difficulty. Longer times and higher

temperatures are required than for alkyl and aryl halides: e.g. tetrahydrofuran (b.p. 65°) is normally used as solvent in place of diethyl ether, and several hours may be necessary for complete reaction with magnesium.

Alkynyl Grignard reagents ($RC{\equiv}CMgX$), however, are relatively easy to prepare, and are not prepared from halogenoalkynes at all. As we have noted in an earlier section (3.4.2, iii), alk-1-ynes are weak acids, and are deprotonated by strong bases – such as Grignard reagents:

$$RC{\equiv}C{-}H \;\; R'{-}MgX \longrightarrow RC{\equiv}CMgX + R'H \qquad (4.10)$$

If R′ is a lower alkyl group, such as $-CH_3$ or $-C_2H_5$, R′H is a gas (methane or ethane), and boils off, leaving behind a solution of the alkynyl Grignard reagent.

The uses of alkynyl Grignard reagents are considered in section 4.3.1.

4.2 Other organometallic reagents and electrophiles

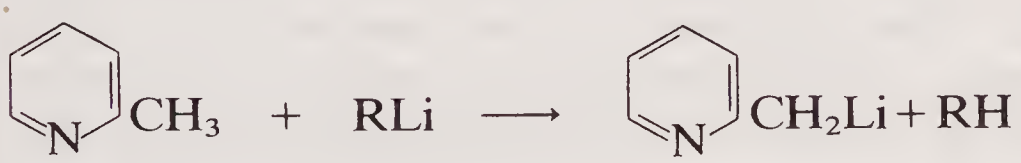
4.2.1 Organolithium reagents

These are usually prepared either from the appropriate halide and metallic lithium, or (especially for the less reactive halides) by halogen–metal exchange, i.e. reaction of the halide with a pre-formed alkyl-lithium:

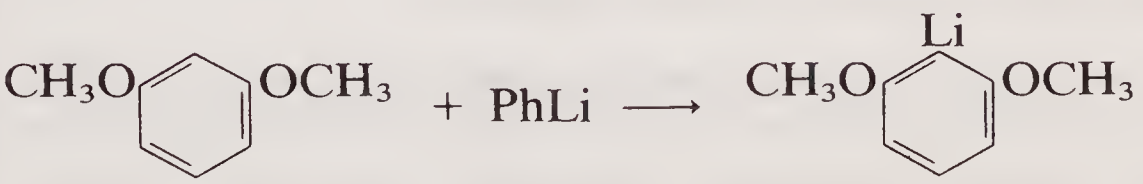
$$RBr + 2Li \rightarrow RLi + LiBr \qquad (4.11)$$

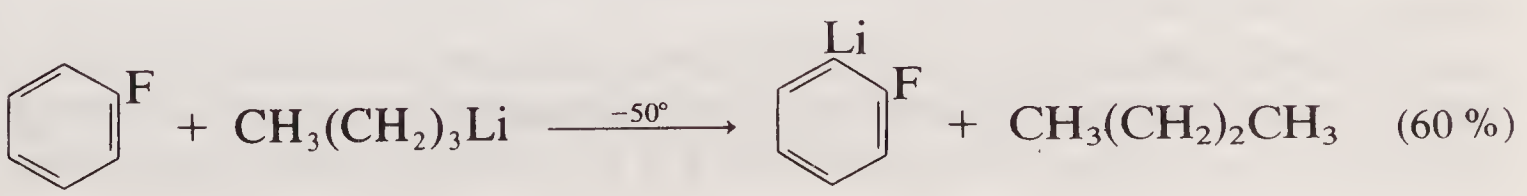
$$RBr + R'Li \rightarrow RLi + R'Br \qquad (4.12)^{[1]}$$

The lithium derivatives of acidic compounds are prepared as for alkynyl Grignard reagents (section 4.1.5), e.g.



Even benzene derivatives containing $-I$ substituents may be lithiated, e.g.



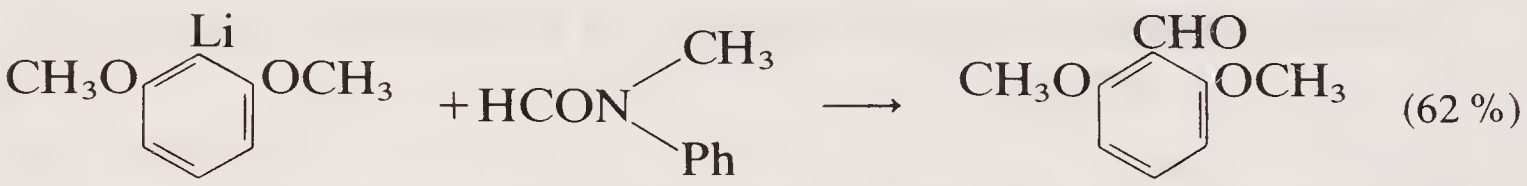


[The *o*-halogenophenyl-lithiums decompose at higher temperatures giving benzyne (cf. section 7.2.1)].

Organolithium reagents are more strongly nucleophilic than the corresponding Grignard reagents. They undergo all the addition reactions of the latter, in certain cases more efficiently: for example, the conversion of carboxylate ions into ketones, the conversion of tertiary amides into aldehydes and ketones, and addition to $\rangle C{=}N-$bonds:

$$PhLi + PhCO_2^-Li^+ \xrightarrow[5\text{–}6\,h]{\text{ether}} PhCOPh \quad (70\,\%)$$

$$CH_3Li + PhCH{=}CHCO_2^-Li^+ \xrightarrow[2\,h]{\text{ether}} PhCH{=}CHCOCH_3 \quad (69\,\%)$$



(62 %)

$$CH_3(CH_2)_9Li + HCON(CH_3)_2 \longrightarrow CH_3(CH_2)_9CHO \quad (60\,\%)$$

$$CH_3(CH_2)_9Li + CH_3CON(CH_3)_2 \longrightarrow CH_3(CH_2)_9COCH_3 \quad (88\,\%)$$

$$CH_3(CH_2)_2Li + Ph_2C{=}NPh \longrightarrow Ph_2C(CH_2)_2CH_3{-}NHPh \quad (77\,\%)$$

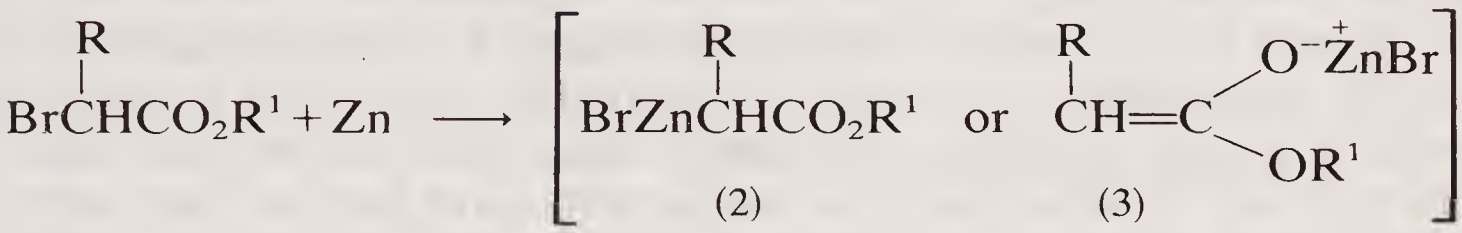
The second of the above examples illustrates the preference for addition at the carbonyl group rather than conjugate addition to the $\rangle C{=}C{-}C{=}O$ system. This preference is more marked than in the case of Grignard reagents, probably because the organolithium compound is less bulky than the Grignard reagent and its reactions are thus less subject to steric hindrance.

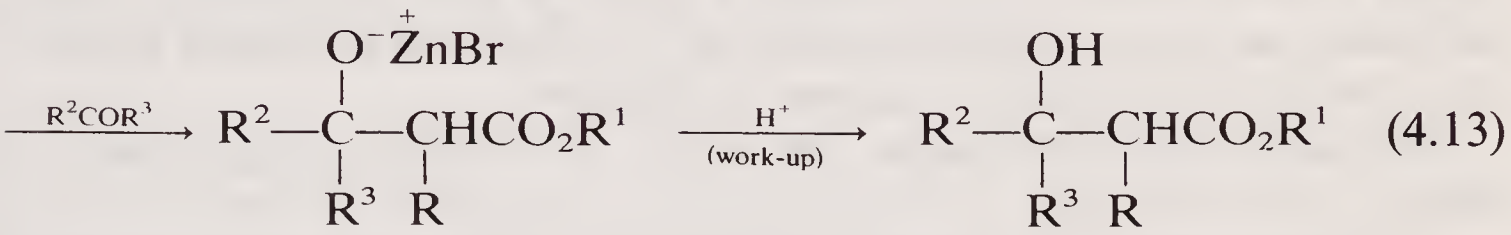
4.2.2 Organozinc and organocadmium reagents

Neither of these classes of compound is widely used nowadays, except for a few specific reactions. Both classes are less reactive nucleophiles than the corresponding Grignard reagents, and thus are more selective reagents than the latter.

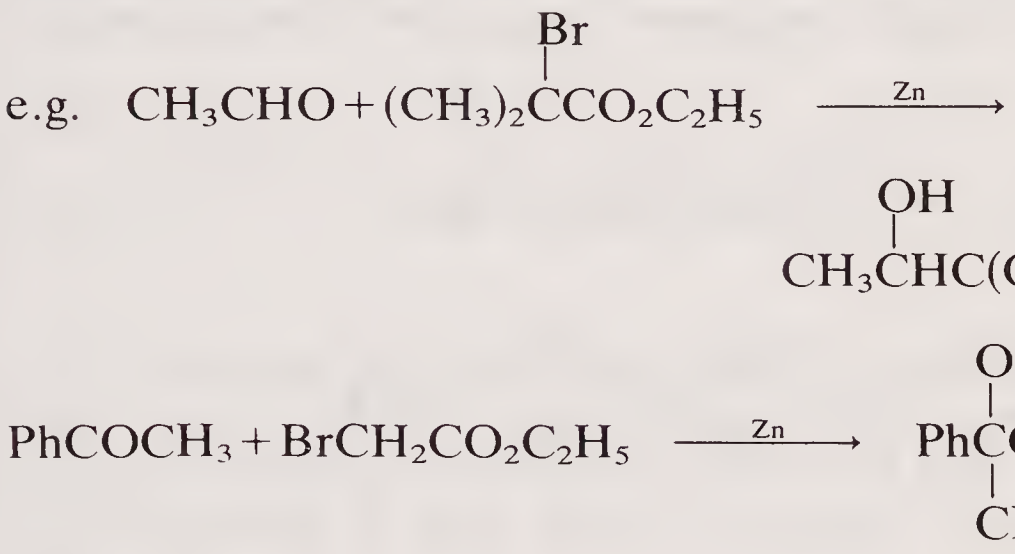
(i) α-Bromoesters react with aldehydes or ketones and metallic zinc to give β-hydroxyesters. Whether this (the **Reformatsky** reaction) is the zinc analogue of a Grignard reaction, with (2) as the nucleophilic species, or

whether it is better regarded as the addition of an enolate ion (3) to the carbonyl group, is an interesting mechanistic point but is not strictly relevant in the synthetic context. In practical terms, it is a 'one-pot' reaction, in which the zinc is normally added directly to a mixture of the other reactants. There is no need for the organometallic intermediate to be preformed, as in the case of Grignard reagents:





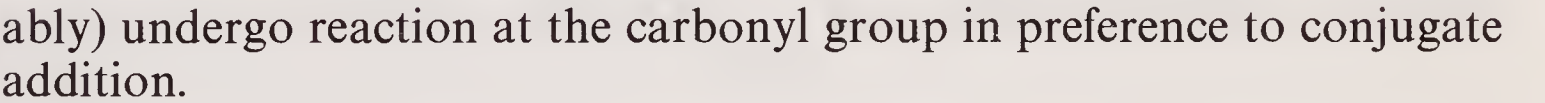
(4.13)

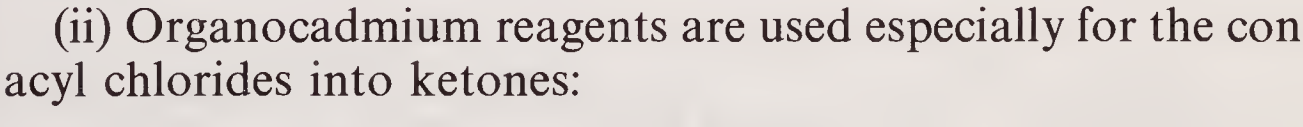


α,β-Unsaturated carbonyl compounds usually (although not invariably) undergo reaction at the carbonyl group in preference to conjugate addition.

(ii) Organocadmium reagents are used especially for the conversion of acyl chlorides into ketones:

(4.14)





These reactions demonstrate the selectivity of the dialkylcadmium reagents: the acyl chloride reacts in each case in preference to the alkyl halide, ester or ketone.[2]

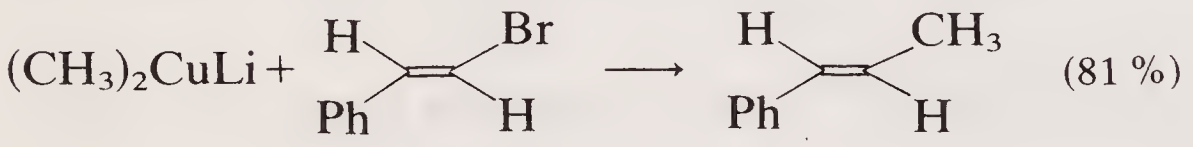
4.2.3 Organocopper(I) reagents

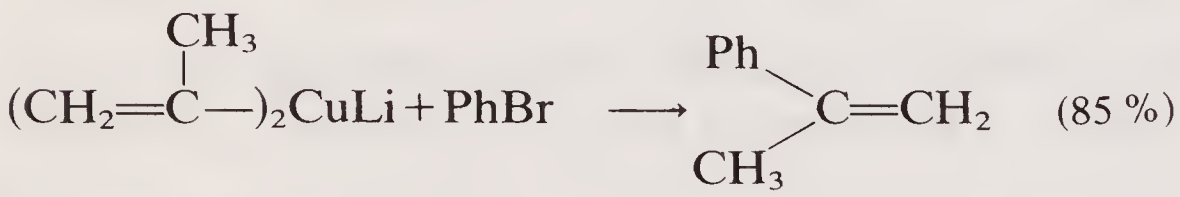
The reaction of an organolithium compound with a copper(I) halide gives organocopper species, which, depending on the proportions of reagents used, correspond to the empirical formulae RCu and R_2CuLi (cf. section 3.4.1).[3] (As in the case of the other organometallic species, the exact structures are not relevant to this book.) These reagents are formally nucleophilic, and like the other organometallic derivatives in this chapter may be represented by the synthon R^-; but their selectivity towards electrophiles is of such a remarkable nature that it must be doubtful if their reactions are simple electrophile–nucleophile interactions at all. In most cases the mechanisms have not yet been established beyond doubt, but complex formation and one-electron redox processes are such common features of the chemistry of copper derivatives that their involvement cannot be ignored.

Whatever the mechanisms, the points of synthetic importance are these:

(i) Displacement of halogens is particularly facile, even when the halogen is in a position normally considered 'unreactive' towards nucleophiles:

$$CH_3Cu + CH_3(CH_2)_9I \longrightarrow CH_3(CH_2)_9CH_3 \quad (68\,\%)$$





These reactions are most successful with the lithium dialkyl- (or dialkenyl-) cuprates and aryl copper compounds. Displacement of other leaving groups (e.g. toluene-*p*-sulphonate) and the ring-opening of oxirans also occur with lithium dialkylcuprates.

(ii) As expected from (i), displacement of halogen from an acyl halide occurs very easily (often at $-78°$), but acyl halides are the only class of carbonyl compound to show appreciable reactivity towards organocopper reagents. Thus the reaction with acyl halides does not proceed

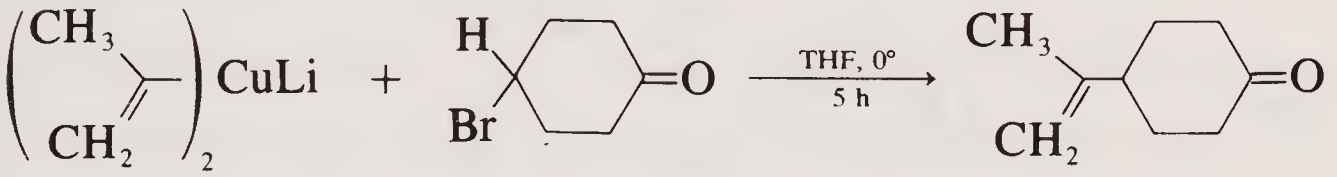
beyond the ketone stage, and other carbonyl groups in the molecule are unaffected, e.g.

$$[CH_3(CH_2)_3]_2CuLi + CH_3(CH_2)_4COCl \xrightarrow[15\ min]{-78^\circ} CH_3(CH_2)_4CO(CH_2)_3CH_3 \quad (79\ \%)$$

$$(CH_3)_2CuLi + CH_3(CH_2)_4CO(CH_2)_4COCl \xrightarrow[15\ min]{-78^\circ} CH_3(CH_2)_4CO(CH_2)_4COCH_3 \quad (95\ \%)$$

$$\underset{\text{(excess)}}{(CH_3)_2CuLi} + I(CH_2)_{10}COCl \xrightarrow[15\ min]{-78^\circ} I(CH_2)_{10}COCH_3 \quad (91\ \%)$$

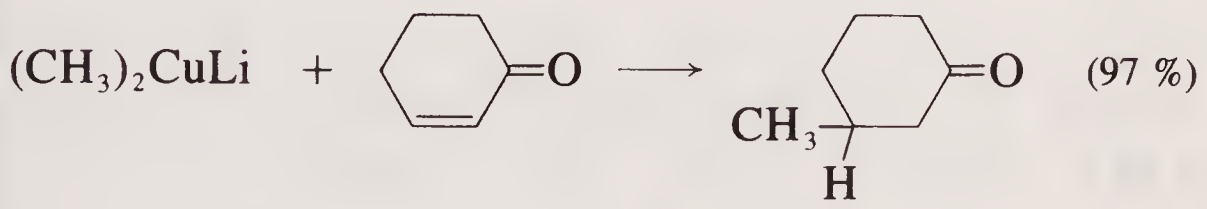
The unreactivity of ketonic carbonyl groups is also illustrated in the following example:



(65 %)

(iii) Although they do not act readily with carbonyl groups (or, perhaps, *because* they do not react readily), organocopper reagents, especially the lithium dialkylcuprates, react with α,β-unsaturated carbonyl compounds to give, almost invariably, the products of conjugate addition, e.g.

$$CH_3Cu + (E)\text{-}CH_3CH{=}CHCOCH_3 \rightarrow (CH_3)_2CHCH_2COCH_3 \quad (85\ \%)$$



(97 %)

The reaction of Grignard reagents with α,β-unsaturated carbonyl compounds may occur at either of the two electrophilic centres, as already noted (section 4.1.4), but in presence of a small proportion (< 10 mole %) of a copper(I) salt the addition is almost exclusively at the β-carbon. Organocopper species are the presumed intermediates in such reactions.

$$PhCH_2MgCl + CH_2{=}CHCO_2C_2H_5 \xrightarrow[-25^\circ]{Cu_2Cl_2} Ph(CH_2)_3CO_2C_2H_5 \quad (69\ \%)$$

(iv) Coupling reactions occur when organocopper(I) reagents are heated (sometimes they even occur at room temperature) and when lithium dialkylcuprates are exposed to oxidising agents (including atmospheric oxygen). These coupling processes are most simply rationalised in terms of a one-electron transfer followed by radical coupling:

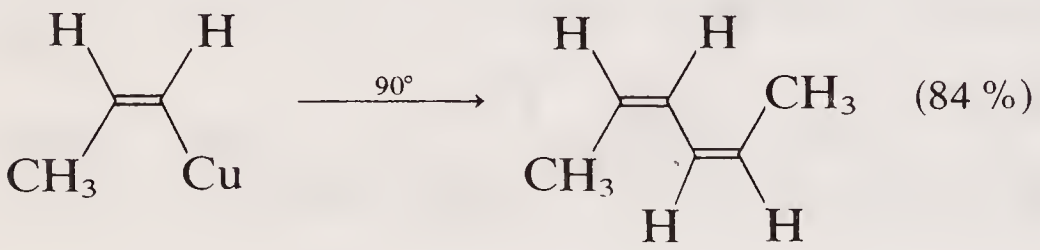
$$R{-}Cu^{I}[\rightleftharpoons R^{-} + (Cu^{I})^{+}] \rightarrow R^{\cdot} + Cu^{0};\ R^{\cdot} + R^{\cdot} \rightarrow R{-}R \qquad (4.15)$$

$$R{-}\underset{\displaystyle R}{\underset{|}{(Cu^{I})}}{}^{-} \xrightarrow{\text{oxidation}} R{-}(Cu^{II}){-}R[\rightleftharpoons R^{-} + (\overset{+}{C}u^{II}){-}R] \rightarrow R^{\cdot} + Cu^{I}{-}R;$$

$$R^{\cdot} + R^{\cdot} \rightarrow R{-}R \qquad (4.16)$$

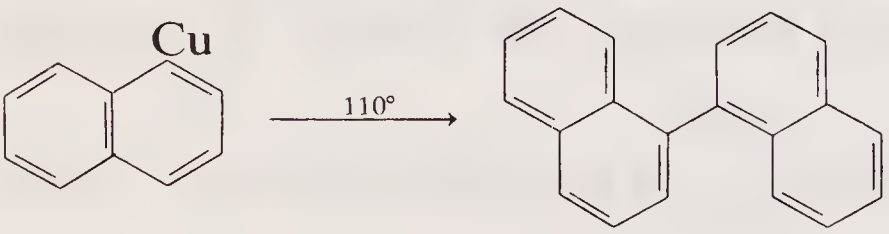
(It is, however, by no means certain that 'free' radicals are actually produced in such reactions.)

Examples of this coupling include:

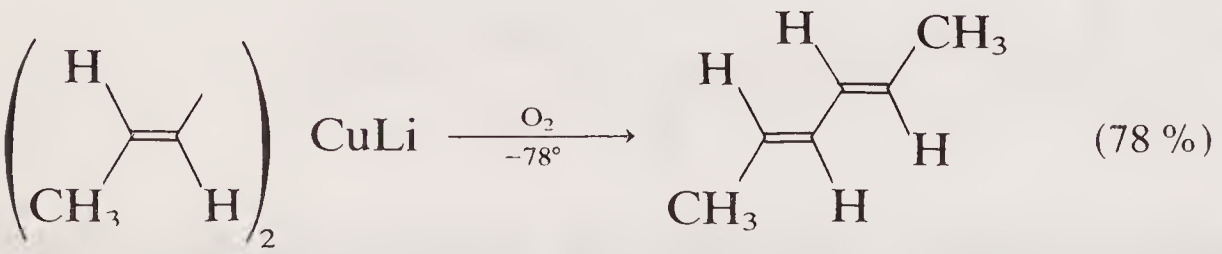


(84 %)

$$PhCH_2Cu \xrightarrow{25^\circ} PhCH_2CH_2Ph \quad (88\ \%)$$

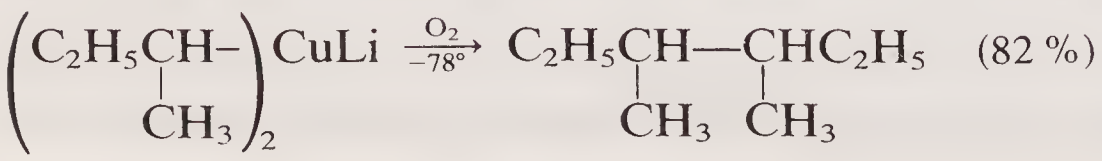


(high yield)



(78 %)

$$Ph_2CuLi \xrightarrow[-78^\circ]{O_2} Ph{-}Ph \quad (75\ \%)$$

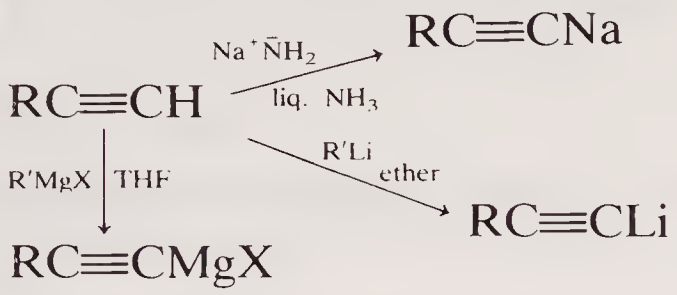


(82 %)

4.3 Reactions of nucleophiles derived from alk-1-ynes

4.3.1 Sodium, lithium and magnesium derivatives

Attention has already been drawn (sections 3.4.2.iii and 4.1.5) to the acidity of alk-1-ynes, and to the consequent formation of carbanionic species from alk-1-ynes and strong bases:



These are less powerful nucleophiles than alkyl- or aryl-lithium compounds, or alkyl or aryl Grignard reagents; nevertheless they undergo the usual range of reactions with electrophiles, as shown below.

(i) **Alkylation:** $RC{\equiv}C^-M^+ + R'{-}Y \longrightarrow RC{\equiv}CR'$ (4.17)

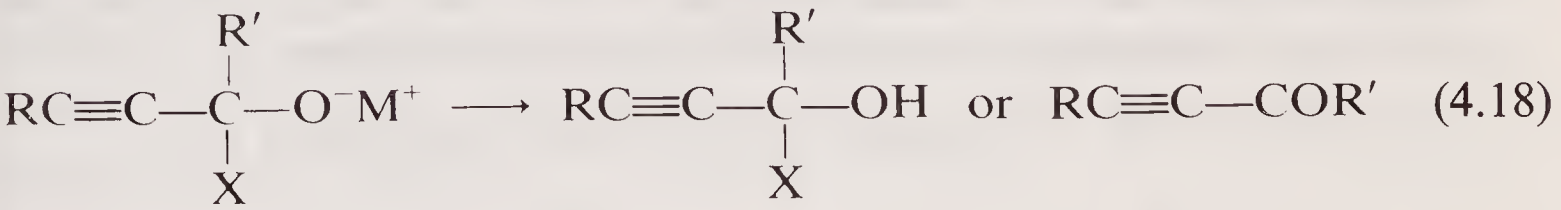
e.g. $CH_3(CH_2)_2C{\equiv}C^-Na^+ + CH_3Br \xrightarrow{NH_3} CH_3(CH_2)_2C{\equiv}CCH_3$ (58 %)

$2HC{\equiv}C^-Na^+ + BrCH_2CH_2Br \xrightarrow{THF} HC{\equiv}CCH_2CH_2C{\equiv}CH$ (81 %)

$HC{\equiv}C^-Na^+ + CH_3(CH_2)_3Br \longrightarrow [CH_3(CH_2)_3C{\equiv}CH] \xrightarrow{NaNH_2}$
not isolated

$[CH_3(CH_2)_3C{\equiv}C^-Na^+] \xrightarrow{CH_3CH_2Br} CH_3(CH_2)_3C{\equiv}C{-}CH_2CH_3$
(64 % overall)

(ii) **Reactions with carbonyl compounds:** $RC{\equiv}C^-M^+ +$  $\longrightarrow$



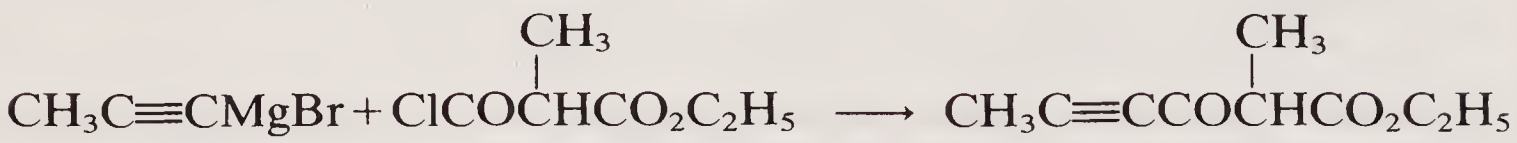
(4.18)

e.g. $CH_3(CH_2)_3C{\equiv}CLi + HCHO \longrightarrow CH_3(CH_2)_3C{\equiv}CCH_2OH$ (80 %)

$PhC{\equiv}CMgBr + CH_2{=}CH{-}CHO \longrightarrow PhC{\equiv}C{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH{=}CH_2$ (52 %)

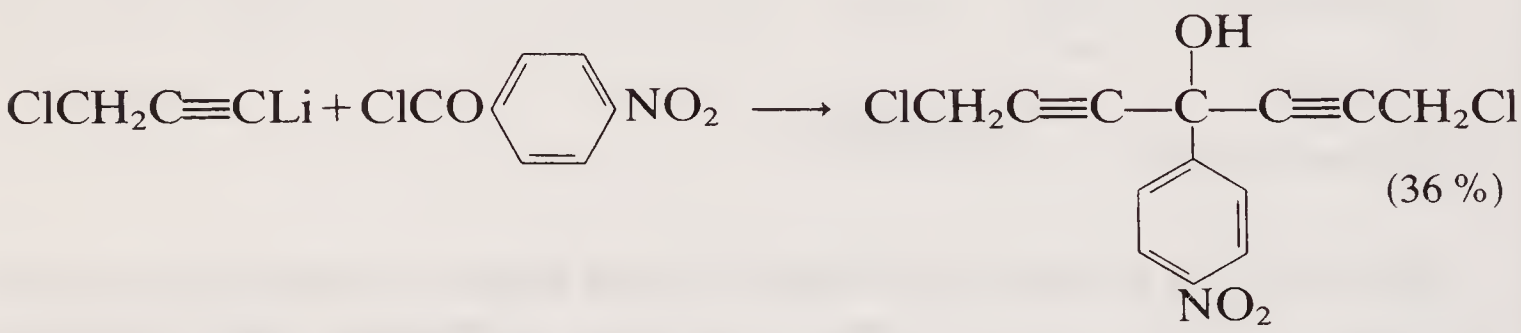
$ClCH_2C{\equiv}CLi + CH_3COCH_3 \longrightarrow ClCH_2C{\equiv}C{-}\overset{\displaystyle OH}{\overset{|}{C}}(CH_3)_2$ (67 %)

Acylation does occur in certain cases, e.g.



(65 %)

but such reactions do not often give good yields, and may not stop at the ketone stage, e.g.



(36 %)

Thus acylations are better carried out *via* the copper(I) derivatives (cf. below).

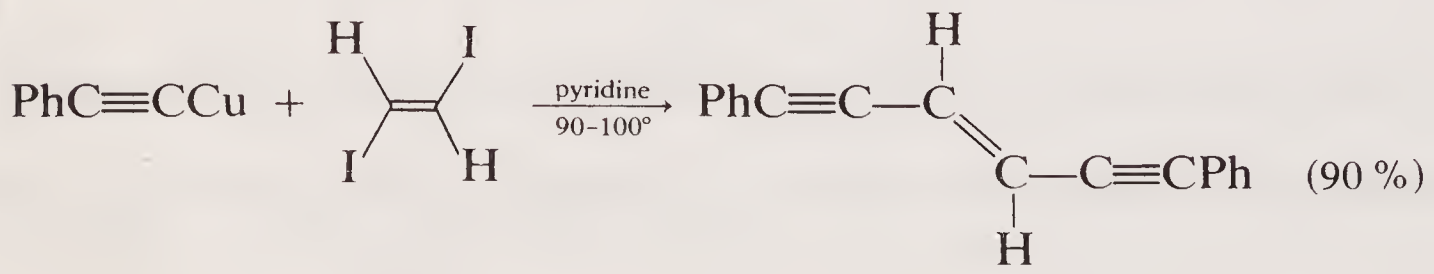
4.3.2 Alkynylcopper(I) compounds

These are much easier to prepare, and with a few exceptions are much more stable, than alkyl- or aryl-copper(I) compounds. They are produced simply by the reaction of the appropriate alk-1-yne with copper(I) chloride, either in aqueous ammonia or in a polar (non-protic) organic solvent such as dimethylformamide.

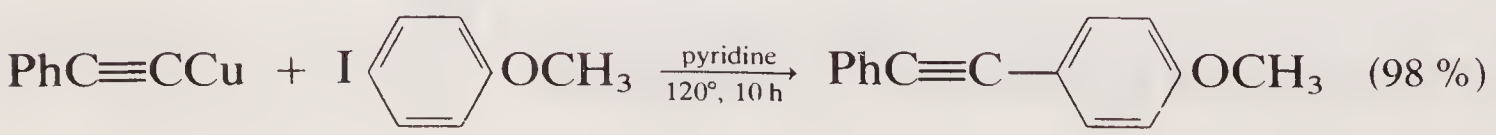
$$2R{-}C{\equiv}CH + Cu_2Cl_2 \rightarrow 2R{-}C{\equiv}CCu + 2HCl$$

The reactions of these copper derivatives parallel those of the other organocopper(I) reagents discussed earlier (section 4.2.3). The alkynylcopper reagents are thus used in preference to the sodium, lithium or magnesium analogues for the following types of reactions:

(i) Displacement of halogens from 'unreactive' positions, e.g.



(90 %)



(98 %)

(ii) Conversion of acyl chlorides into ketones, e.g.

$$CH_3(CH_2)_4C{\equiv}CCu + CH_3COCl \xrightarrow[\text{(catalyst)}]{LiI} CH_3(CH_2)_4C{\equiv}CCOCH_3$$

(81 %)

(iii) Coupling reactions giving conjugated diynes. For symmetrical diynes, oxidative coupling is used: the alkyne is either converted into its copper(I) derivative and oxidised *in situ*, usually by oxygen itself (**Glaser coupling**), or else it is treated with copper(II) acetate in pyridine (**Eglinton–Galbraith coupling**): in both cases the copper(II) ion is apparently the effective oxidant.

$$RC{\equiv}C^- + Cu^{2+} \longrightarrow RC{\equiv}C^{\cdot} + Cu^+;\ 2RC{\equiv}C^{\cdot} \longrightarrow RC{\equiv}C{-}C{\equiv}CR$$

$[Cu^+ + \text{oxidant}]$ (4.19)

For example:

$$HO_2CC{\equiv}CCu \xrightarrow{K_3Fe(CN)_6} HO_2CC{\equiv}C{-}C{\equiv}CCO_2H \quad (60\ \%)$$

$$PhC{\equiv}CCu \xrightarrow{O_2} PhC{\equiv}C{-}C{\equiv}CPh \quad (90\ \%)$$

$$(CH_3)_2C(OH){-}C{\equiv}CH \xrightarrow[O_2]{Cu_2Cl_2} (CH_3)_2C(OH){-}C{\equiv}C{-}C{\equiv}C{-}C(OH)(CH_3)_2 \quad \text{(quantitative)}$$

$$HC{\equiv}CC(CH_3)_2CH_2CO_2CH_3 \xrightarrow[\text{pyridine}]{Cu(OCOCH_3)_2} [CH_3O_2CCH_2C(CH_3)_2C{\equiv}C{-}]_2$$

(98 %)

In the case of unsymmetrical diynes, coupling of an alkynylcopper(I) with a 1-halogenoalk-1-yne is generally used (**Cadiot–Chodkiewicz coupling**); the organocopper derivative is usually generated *in situ*:

$$RC{\equiv}CCu + X{-}C{\equiv}CR' \longrightarrow RC{\equiv}C{-}C{\equiv}CR' \qquad (4.20)$$

e.g.

$$HO_2CC{\equiv}CH + BrC{\equiv}C{-}C_6H_4{-}Br \xrightarrow[C_2H_5NH_2]{Cu_2Cl_2} HO_2CC{\equiv}C{-}C{\equiv}C{-}C_6H_4{-}Br$$

(92 %)

$$PhC{\equiv}CH + BrC{\equiv}CCHO \xrightarrow[C_2H_5NH_2]{Cu_2Cl_2} PhC{\equiv}C{-}C{\equiv}CCHO \quad (71\%)$$

4.4 Review

The reactions described in this chapter lead to products of diverse structural types, but all except the oxidative coupling processes [reactions (4.15), (4.16) and 4.19)] conform to a general pattern, *viz.* that they involve the formation of a carbon–carbon single bond, with the organometallic reagent contributing both the electrons of this new bond. In each case, no matter whether the organometallic species is RMgX, RLi, R_2Cd, R_2CuLi, etc., the R-group appears in the product, singly bonded to another carbon.

4.4.1 More about disconnections and synthons

In Chapter 3 we introduced the concept of a *disconnection*, as the (imaginary) opposite of a real reaction, and we also introduced the term *synthon* to describe a 'product' (again imaginary) of a disconnection. We now focus attention on the application of these ideas to the reactions described in the present chapter.

As stated above, the general form of these products is R—C<, and they are formed from a nucleophilic R and an electrophilic C species. So the general disconnection for these products will be

$$R{-}C< \Longrightarrow R^- + {}^+C< \qquad (4.21)$$

It is worth reiterating that this means, in words,

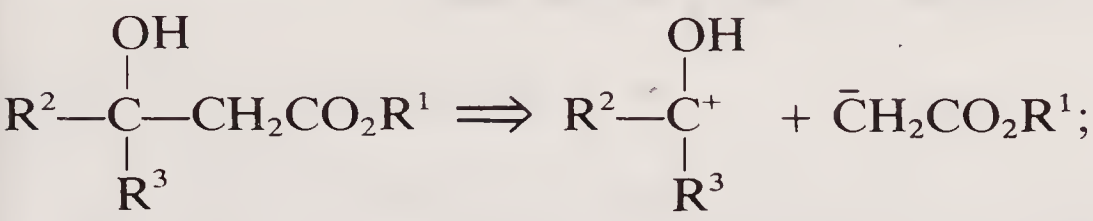
'The formation of R—C< implies the reaction of a nucleophilic R-species (which *may be* but *need not be* a carbanion) with an electrophilic C< -species (which *may be* but *need not be* a carbocation).'

We may now write down specific disconnections for the products of some of the numbered reactions in the chapter. These are listed in table 4.1.

There are three significant omissions from this table. The disconnections of the oxidative coupling products give radical synthons, e.g.

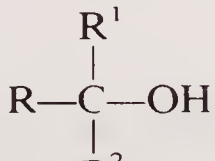
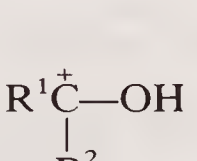
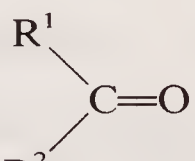
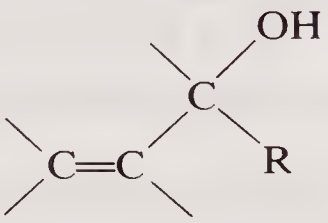
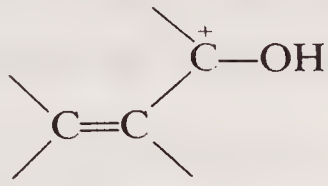
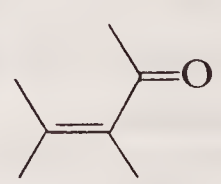
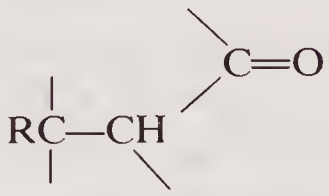
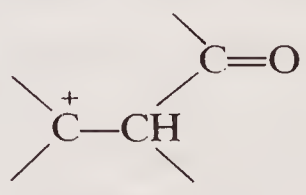
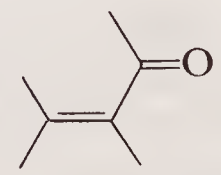
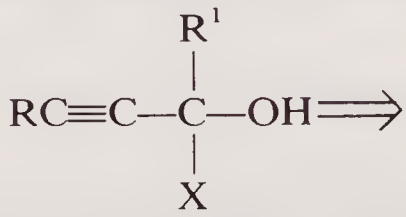
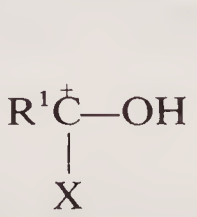
$$R{-}R \Rightarrow R^{\cdot} + {}^{\cdot}R; \quad RC{\equiv}C{-}C{\equiv}CR \Rightarrow RC{\equiv}C^{\cdot} + {}^{\cdot}C{\equiv}CR \qquad (4.22)$$

The disconnection for the product of the Reformatsky reaction (4.13) is as follows:

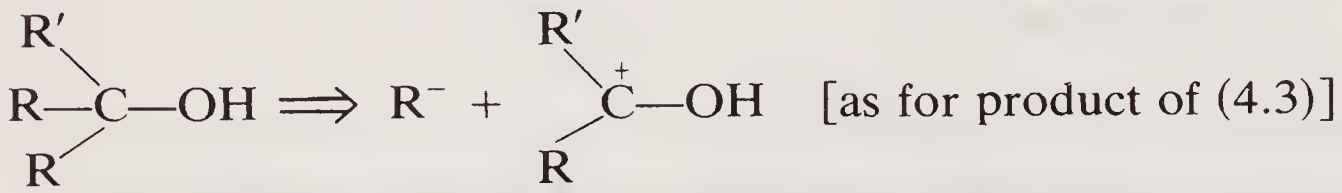


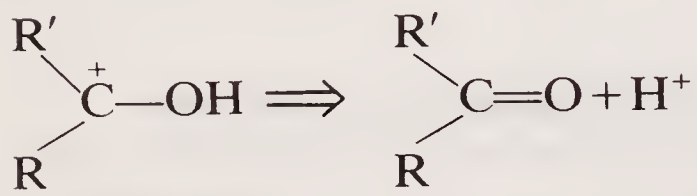
but this will not be further considered until Chapter 5 (section 5.5).

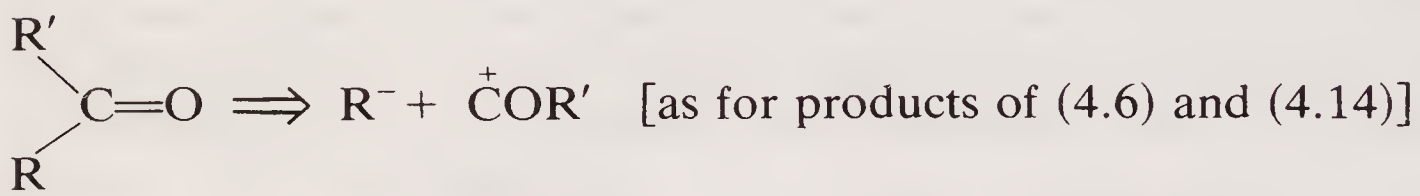
Table 4.1 Disconnections for products of organometallic reactions

Reaction number	Product		Synthons		Electrophile
4.1	$R—R^1$	$\Longrightarrow$	R^-	R^{1+}	R^1—Y (halide, sulphonate)
4.2	RCH_2CH_2OH	$\Longrightarrow$	R^-	$\overset{+}{C}H_2CH_2OH$	
4.3		$\Longrightarrow$	R^-		
4.5	RCO_2H	$\Longrightarrow$	R^-	$\overset{+}{C}O_2H$	CO_2
4.6	$RCOR^1$	$\Longrightarrow$	R^-	$\overset{+}{C}OR^1$	$R^1CONR^2_2$
4.7	RCHO	$\Longrightarrow$	R^-	$\overset{+}{C}HO$	$HC(OR^1)_3$
4.8		$\Longrightarrow$	R^-		
4.9		$\Longrightarrow$	R^-		
4.14	$RCOR^1$	$\Longrightarrow$	R^-	$\overset{+}{C}OR^1$	R^1COCl
4.17	$RC\equiv CR^1$	$\Longrightarrow$	$RC\equiv C^-$	R^{1+}	R^1—Y (halide)
4.18		$\Longrightarrow$	$RC\equiv C^-$		R^1COX
	$RC\equiv C—COR^1$	$\Longrightarrow$	$RC\equiv C^-$	$\overset{+}{C}OR^1$	R^1COX
4.20	$RC\equiv C—C\equiv CR^1$	$\Longrightarrow$	$RC\equiv C^-$	$\overset{+}{C}\equiv CR^1$	$R^1C\equiv CBr$

Reaction (4.4) is somewhat more complicated, since the formation of the product requires two successive attacks by the nucleophile. A series of disconnections is therefore necessary in this case:







4.4.2 Synthetic equivalents

In table 4.1, the synthon representing the nucleophile is shown as R^- or $RC{\equiv}C^-$. The actual nucleophile used, however, may vary: for example, in reactions (4.1)–(4.9) it is RMgX, whereas in (4.14) it is R_2Cd. In (4.1)–(4.9), however, it could equally well have been RLi, and in (4.1) and (4.14) it might also have been R_2CuLi. So RMgX, RLi, R_2Cd, and R_2CuLi are all **synthetic equivalents** of the synthon R^-, i.e. they are actual reagents which carry out the function of the synthon R^-. It is important to remember that **there may be more than one synthetic equivalent of any given synthon**.

This is also obvious in the case of the electrophilic synthons. If these are compared with their synthetic equivalents (shown in the last column of table 4.1), it may be seen that R^{1+} is the synthon corresponding to an alkylating agent (an alkyl halide or a sulphonate ester); R^1CO^+ corresponds to an acylating agent (acyl halide, tertiary amide, and also anhydride or ester or nitrile: sections 4.1.2 and 4.1.3); and so on.

Table 4.2 lists the synthons relating to the reactions in this chapter, and their common synthetic equivalents. (Page references are given for the use of each synthetic equivalent.)

4.5 Problems

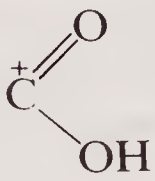
We conclude this chapter by considering the application of the disconnection/synthon approach to the solution of a few simple synthetic problems. Suppose one were asked to devise a synthesis of the following:

$PhCH_2CHOHCH_2CH_3$; $CH_3(CH_2)_{10}CO(CH_2)_2CH_3$; $PhCH(CH_3)CH_2CO_2CH_3$;
(4) (5) (6)

$CH_3C{\equiv}C{-}CH_2CH_2OH$.
(7)

One good way of tackling such problems is to write down possible disconnections for the required end-product, and to try to relate the result-

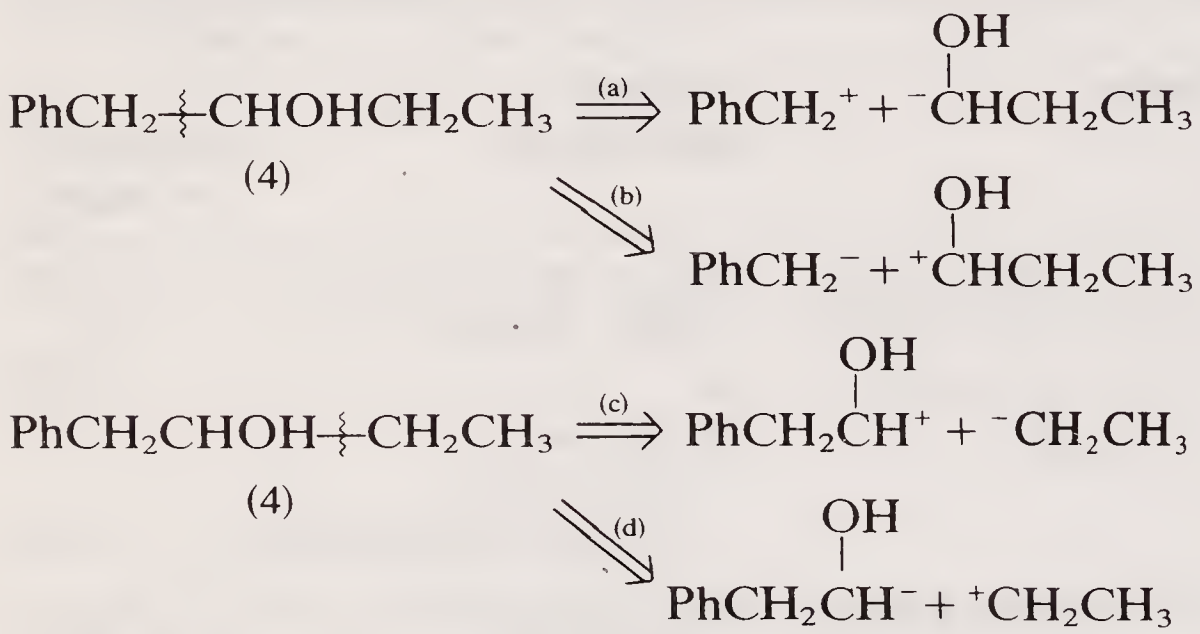
Table 4.2 Some common synthons and their synthetic equivalents (part 1)

	Synthon	Synthetic equivalents(s)	For example(s) see page(s)
(*a*) *Nucleophilic synthons*	1. R^- (alkyl group)	RMgX; RLi; R_2Cd; RCu; R_2CuLi	39–50
	2. R^- (aryl group)	do.	38–50
	3. $RC{\equiv}C^-$	$RC{\equiv}C^-Na^+$; $RC{\equiv}CMgX$; $RC{\equiv}CLi$; $RC{\equiv}CCu$	51–3
(*b*) *Electrophilic synthons*	1. R^+ (alkyl group)	RCl, RBr, RI, $ROSO_2R^1$	38, 39, 48, 51
	2. R^+ (aryl group)	RBr, RI, $RN_2^+X^-$	48, 52, 53
	3. $RCH{=}CH^+$	$RCH{=}CHBr$	48–52
	4. $RC{\equiv}C^+$	$RC{\equiv}CBr$	53
	5. $R\overset{+}{C}{=}O$	RCOCl, $(RCO)_2O$, RCO_2R^1, $RCONR^1{}_2$, RCN, (RCO_2H)	39–42, 46–49, 52–3
	6. $H\overset{+}{C}{=}O$	HCO_2R, $HCONR_2$, $CH(OR)_3$	41–2, 46
	7. 	CO_2	41
	8. $\overset{+}{C}H_2OH$	HCHO	39, 51
	9. $\overset{+}{C}HOH{\cdot}R$	RCHO	39, 51
	10. $^+CR_2OH$	R_2CO	39, 51
	11. $^+CH_2CH_2OH$		39
	12. $^+CH_2CH_2COR$ (CO_2R, CN)	$CH_2{=}CHCOR$ (CO_2R, CN)	43–4, 49

ing synthons to recognisable synthetic equivalents. With several possible disconnections for each target molecule, are there any general guidelines to assist in choosing the best one?

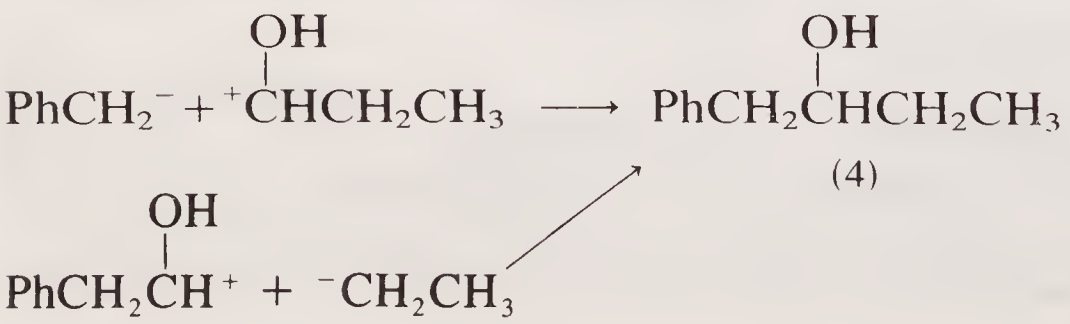
Table 4.1 indicates that the bond which is disconnected is frequently one joining two carbons of which one or both carries a functional group. So **it is worth considering a disconnection adjacent to a functional group**. The first two examples illustrate this point.

1-Phenylbutan-2-ol (compound 4). Disconnection of the 1,2-bond or of the 2,3-bond (i.e. those flanking the functional group) gives *four* pairs of synthons, as follows:



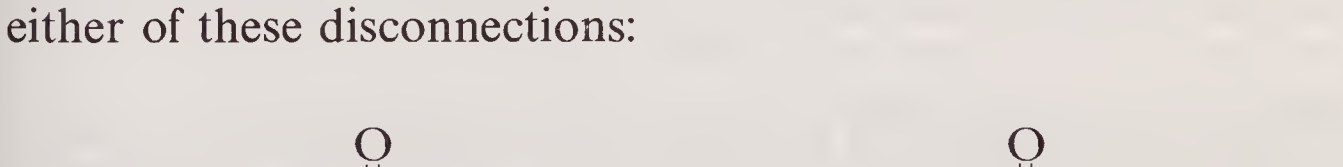
Each of these disconnections gives one synthon which is immediately recognisable, *viz.* $PhCH_2^+$, $PhCH_2^-$, $^-CH_2CH_3$, and $^+CH_2CH_3$, and synthetic equivalents are readily available for all of these (e.g. $PhCH_2Br$, $PhCH_2MgBr$, CH_3CH_2MgBr, and CH_3CH_2Br respectively). However, only two of the four disconnections, *viz.* (b) and (c), give a *pair* of recognisable synthons: $^+CHCH_2CH_3$ (OH) is, very simply, propanal $+ H^+$, and propanal is the synthetic equivalent (cf. entry 9 in table 4.2b). Similarly $PhCH_2CH^+$ (OH) has phenylethanal, $PhCH_2CHO$, as its synthetic equivalent. There are no obvious synthetic equivalents for the synthons $^-CHCH_2CH_3$ (OH) and $PhCH_2CH^+$ (OH).

This means that 1-phenylbutan-2-ol should be preparable by the reverse of disconnections (b) and (c):



All that remains is to insert the synthetic equivalent in place of each synthon. If there is a choice of synthetic equivalent, some care may be necessary in making that choice, since the synthon approach takes no account of the selectivity of reagents. If there are several suitable equivalents, however, the final choice may well depend on relative cost, and ease of handling. In the present case, the nucleophilic synthons may represent a variety of species (entry 1 in table 4.2a), but since the Grignard reagent is the easiest to make and it reacts satisfactorily with an aldehyde, it would normally be preferred to, say, the lithium derivative.

So two synthetic routes have emerged to compound (4), *viz.*



Pentadecan-4-one (compound 5). Again, disconnection on either side of the functional group gives four pairs of synthons:

(5)

As in the last example, only two of these disconnections, (b) and (c), give a pair of synthons with recognisable synthetic equivalents, since we have as yet no synthetic equivalent for a synthon of the type $RC^{-}(=O)$. So the synthesis of compound (5) should be based on the reverse of either of these disconnections:

In this example there is a choice of synthetic equivalent for all four synthons, and so there is a wide choice of possible routes to the product. There are, however, some restrictions: if the acylating agent is an acyl halide, the nucleophilic species must be a dialkyl-cadmium or an alkyl-copper reagent: if the nucleophile is an alkyl-lithium compound, the acylating agent should be a nitrile, a tertiary amide, or a lithium carboxylate, and so on. The following are two possible routes:

$$CH_3(CH_2)_{10}COCl + (CH_3CH_2CH_2)_2CuLi \longrightarrow \text{compound (5)}$$

$$CH_3(CH_2)_{10}CN + CH_3CH_2CH_2MgBr \nearrow$$

[Both of these involve a C_{12} acylating agent and a C_3 nucleophile; in practice these are preferable to reactions of C_4 acylating agents with C_{11} nucleophiles, because C_{11} halides are relatively expensive while the C_{12} acid (lauric acid) is not.]

Methyl 3-phenylbutanoate (compound 6). Disconnection of this molecule adjacent to the functional group gives only one reasonable pair of synthons, *viz.*

$$\underset{\text{(6)}}{PhCH(CH_3)CH_2CO_2CH_3} \Longrightarrow PhCH(CH_3)CH_2^- + {}^+C(=O)-OCH_3$$

which in turn might suggest the following synthetic route:

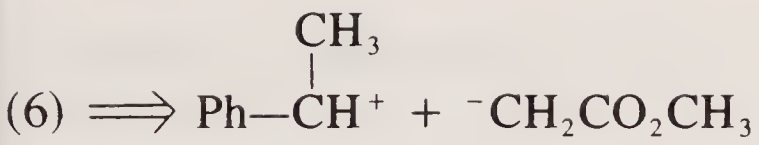
$$(PhCH(CH_3)CH_2)_2CuLi + ClC(=O)-OCH_3 \longrightarrow \text{compound (6)}$$

(highly selective) methyl chloroformate

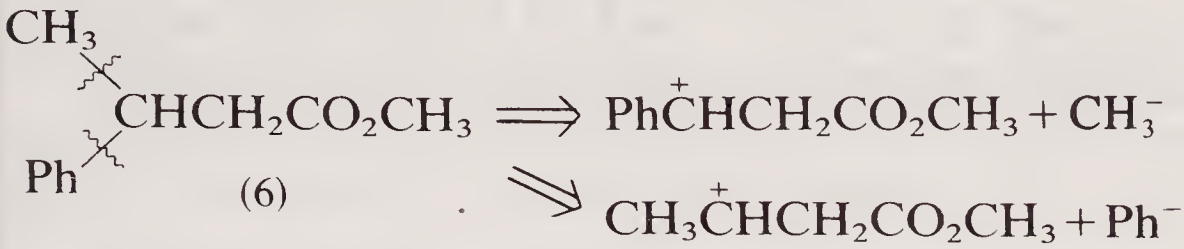
However, esters are often more easily obtained *via* the corresponding acids; even although an extra step is involved, this is counterbalanced by the simplicity of the operation. So another route to compound (6) might be:

$$PhCH(CH_3)CH_2MgBr + CO_2 \longrightarrow \underset{\text{(6a)}}{PhCH(CH_3)CH_2CO_2H} \xrightarrow[H^+]{CH_3OH} \text{compound (6)}$$

Both of the above routes suffer from the disadvantage that the nucleophile is prepared from $PhCH(CH_3)CH_2Br$, which would itself require to be prepared. So it is perhaps worth trying other disconnections of the end-product (6) [or the acid (6a)]. We shall see in the next chapter that $^-CH_2CO_2R$ is a synthon which has a number of synthetic equivalents, and so the disconnection



appears promising. Two other disconnections, still further removed from the functional group, are worthy of consideration: these involve the carbon bearing the substituent on the chain:



The synthetic equivalents of the electrophilic synthons are α,β-unsaturated esters (cf. entry 12 in table 4.2b). So the formation of compound (6) is possible by conjugative addition to such an ester, i.e. CH_3^- + $PhCH{=}CHCO_2CH_3$ (methyl cinnamate) or Ph^- + $CH_3CH{=}CHCO_2CH_3$ (methyl crotonate).

In order to ensure that the nucleophile adds conjugatively and not directly to the carbonyl group, the nucleophile of choice is a Grignard reagent containing a small (non-stoicheiometric) amount of a copper(I) salt (cf. section 4.2.3.iii).

Pent-3-yn-1ol (compound 7). The reader is invited to try this example for him(her)self. Try disconnections of the 1,2- and the 2,3-bond (next to the functional groups). Are the synthetic equivalents of the synthons easily recognisable? Which of the possible routes appears to be the simpler?

We shall present some more problems at the end of Chapter 5.

Notes

1. If RBr is (even moderately) reactive towards nucleophiles, it may react with R′Li to give R—R′ and LiBr [cf. reaction (4.1) for Grignard reagents]. Even if RBr is relatively unreactive towards nucleophiles, the product R′Br may react faster than RBr with R′Li; in this case an excess of R′Li is required:

   $$RBr + 2R'Li \rightarrow RLi + R'{-}R' + LiBr \qquad (4.12a)$$

2. This also helps to minimise interaction of RLi and R′Br to give R—R′.
   It is commonly supposed (and stated in textbooks) that dialkylcadmium reagents do not react with ketones. While it is true that a *purified* (i.e. redistilled or resublimed) dialkylcadmium shows negligible reaction with ketones, its reaction with acyl chlorides is also very slow and poor yields of ketones result. In presence of a magnesium halide (which is the case when it is generated from $RMgX + CdX_2$ and used *in situ*) a dialkylcadmium will react quite readily, in the manner of a Grignard reagent, with ketones and most other carbonyl groups. It is only its *selectivity* which is the key to reaction (4.4).
3. Other species such as R_3Cu_2Li, R_3CuLi_2, and $R_5Cu_3Li_2$ have also been recognised; the second of these is claimed to be superior to R_2CuLi in reactions with alkyl, alkenyl and aryl halides.

5 Formation of carbon–carbon bonds: the use of stabilised carbanions and related nucleophiles

The factors which contribute to carbanion stabilisation, and the different types of stabilised carbanion, have already been described in Chapter 3 (section 3.4.2), and the uses of alkynyl ions in synthesis have been included in Chapter 4 (section 4.3), because of the obvious similarities between the reactions of these ions and those of other organometallic reagents. Now we must consider in detail the reactions of the other groups of stabilised carbanions, in particular those in which the stabilisation is provided by electron-accepting ($-M$) substituents. Since carbanions stabilised by a carbonyl group may also be written as enolate ions, and indeed are frequently referred to as **enolates** [cf. formula (16) in section 3.4.3], it is convenient to consider the reactions of enols (and enamines) in the same chapter as the reactions of the anions.

We shall divide the reactions into several classes, according to the nature and number of the groups stabilising the carbanion. For each category of carbanion we shall consider reactions under three headings, *viz.* alkylation, acylation and condensation. (These terms have already been defined in sections 3.3.1 and 3.3.2.) Finally, we shall discuss the reactions of enols and enamines, and their aromatic counterparts.

5.1 Carbanions stabilised by two — *M* groups

When a —CH_2— or —CHR— group in a molecule is flanked by two $-M$ groups, such a molecule is readily deprotonated by the action of a base, and the resulting anion is stabilised by delocalisation (cf. section 3.4.2.i). The compounds in question are thus relatively strong acids: thus for example, dinitromethane (1: $pK_a \simeq 4$) is slightly more acidic than acetic acid, and pentane-2,4-dione (2: $pK_a \simeq 9$) is a slightly stronger acid than phenol. The members of this class of compound which are most useful in synthesis, such as diethyl malonate (3) and ethyl acetoacetate (4), have pK_a values of ca. 13 or less.

$CH_2(NO_2)_2$ (1) $CH_3COCH_2COCH_3$ (2) $CH_2(CO_2C_2H_5)_2$ (3)

$CH_3COCH_2CO_2C_2H_5$ (4)

From a synthetic point of view there are two important consequences of this.

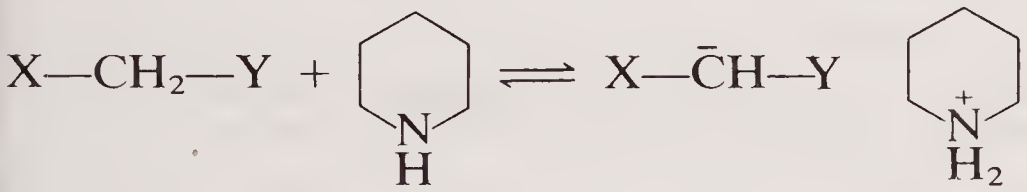
(i) These compounds are deprotonated, essentially completely, by bases such as sodium ethoxide (the pK_a of ethanol being ca. 18). Or, to express this in another way, the equilibrium (5.1) lies far over to the right:

$$X—CH_2—Y + Na^+\bar{O}R \rightleftharpoons X—\bar{C}H—Y\ Na^+ + ROH \qquad (5.1)$$

(X and Y = COR', CO_2R', CN, NO_2, etc.)

[It is of course, important to remember that the electron-accepting substituents (X and Y in reaction 5.1) may themselves be attacked by the base if the latter is also a good nucleophile. It is thus inadvisable to use, for example, hydroxide ion to deprotonate diethyl malonate, because hydrolysis of the ester would almost certainly ensue.]

(ii) These compounds are also deprotonated, if not completely then at least to a significant extent, by organic bases such as piperidine (p$K_a \simeq$ 11):



(5.2)

5.1.1 Alkylation

This is effected, relatively simply, by reaction of the (pre-formed) anions with the usual range of alkylating agents, halides being the most commonly used. Thus, for example,

$$[CH_2(CO_2C_2H_5)_2 \xrightarrow[C_2H_5OH]{NaOC_2H_5}] Na^+\bar{C}H(CO_2C_2H_5)_2 + CH_3(CH_2)_3Br \rightarrow$$

$$CH_3(CH_2)_3CH(CO_2C_2H_5)_2 \quad (88\ \%)$$

(5)

$$\left[CH_3COCH_2CO_2C_2H_5 \xrightarrow[C_2H_5OH]{NaOC_2H_5}\right] \quad Na^+\bar{C}H\begin{matrix}\diagup\ COCH_3\\ \diagdown\ CO_2C_2H_5\end{matrix}$$

$$+\ CH_3(CH_2)_2Br \longrightarrow CH_3(CH_2)_2CH\begin{matrix}\diagup\ COCH_3\\ \diagdown\ CO_2C_2H_5\end{matrix} \quad (71\ \%)$$

(6)

$$\left[CH_3COCH_2COCH_3 \xrightarrow[CH_3COCH_3]{K_2CO_3}\right] \quad K^+\bar{C}H(COCH_3)_2 + CH_3I$$

$$\longrightarrow \quad CH_3COCH(CH_3)COCH_3 \quad (75\ \%)$$

(7)

(Note the use of the weaker base, in view of the greater acidity of the diketone.)

The products of these reactions, (5)–(7), still contain an acidic hydrogen, and the alkylation process may thus be repeated, giving a dialkyl derivative. The second alkylation may be more difficult than the first, because the first alkyl substituent introduced, being electron-repelling, will diminish the acidity of the adjacent hydrogen; and the monoalkylated carbanion will in any case be more sterically hindered than its non-alkylated analogue.

If the two alkyl groups to be introduced are identical, the dialkylation may be carried out as a 'one-pot' reaction, e.g.

$$CH_2(CO_2C_2H_5)_2 \xrightarrow[(ii)\ 2C_2H_5I]{(i)\ 2NaOC_2H_5} (C_2H_5)_2C(CO_2C_2H_5)_2 \quad (83\ \%)$$

$$CH_2(CN)_2 \xrightarrow[(ii)\ 2PhCH_2Br]{(i)\ 2NaH} (PhCH_2)_2C(CN)_2 \quad (75\ \%)$$

$$CH_3COCH_2COCH_3 \xrightarrow[(ii)\ CH_3I]{(i)\ NaH} \text{compound 7 (not isolated)} \xrightarrow[(ii)\ CH_3I]{(i)\ NaH}$$

$$CH_3COC(CH_3)_2COCH_3 \quad (63\ \%).$$

If the two alkyl groups are different, they may be introduced in a stepwise manner, e.g.

$$CH_2(CO_2C_2H_5)_2 \xrightarrow[(ii)\ C_2H_5Br]{(i)\ NaOC_2H_5} C_2H_5CH(CO_2C_2H_5)_2 \xrightarrow[(ii)\ (CH_3)_2CHI]{(i)\ NaOC_2H_5}$$

(90 %)

$$(CH_3)_2CHC(C_2H_5)(CO_2C_2H_5)_2 \quad (41\ \%\ \text{overall})$$

(45 %)

The above four examples are instructive in themselves, and so it is worth examining them in greater detail.

(a) The first two may be considered together, since the only important respect in which they differ is the nature of the base required. (Sodium hydride in dimethyl sulphoxide[1] is used in the second case because ethoxide ion is liable to attack cyano-groups.) The procedure consists of addition of the carbanion source (diethyl malonate or malononitrile) to *two* molar equivalents of the appropriate base, and subsequent (gradual) addition of the alkylating agent.

It must be emphasised that the addition of, say, the diethyl malonate to two molar equivalents of sodium ethoxide does not result in the formation of a di-anion: it is an equimolar mixture of the mono-carbanion and ethoxide to which the alkylating agent (ethyl iodide) is initially added. The reader may wonder why, in that case, the ethoxide does not react with the halide to any appreciable extent: the answer lies in the fact that although ethoxide is a stronger *base* than the carbanion under these conditions, the carbanion is a much stronger *nucleophile*. As the alkylation proceeds, with the formation of the mono-alkylated malonate, so this compound is deprotonated by the ethoxide and is thus able to undergo the second alkylation step.

(b) In the third example (dimethylation of pentane-2,4-dione), the choice of base is again noteworthy. Potassium carbonate is sufficiently basic to deprotonate pentane-2,4-dione, as was shown in an earlier example, but not to deprotonate the 3-methyl derivative (7). Sodium ethoxide is basic enough for the latter operation, but is liable to react as a nucleophile at the carbonyl group (cf. section 5.1.2). Hence sodium hydride is again the reagent of choice.

In this reaction, unlike the first two, the two alkyl groups are introduced in separate operations, even although the intermediate mono-alkyl compound is not isolated. It is interesting to speculate on the possible significance of this difference in procedure. It may be, in this particular case, that the stepwise method simply give better yields, or that the alternative procedure has not been tried. However, it may also be (and this is the important point) that diketones like pentane-2,4-dione, and β-keto-esters like ethyl acetoacetate, react with two molar equivalents of base, provided that the base is sufficiently strong, to give dianions of the type (8) or (9). There are then alkylated preferentially at the 'wrong' carbon:

$$R^1R^2CHCOCH_2COR \xrightarrow[NH_3(l.)]{2NaNH_2} R^1R^2\bar{C}CO\bar{C}HCOR \xrightarrow{R^3X}$$

(8)

$$R^1R^2\overset{R^3}{\overset{|}{C}}CO\bar{C}HCOR \quad (5.3)$$

$$R^1CH_2COCH_2CO_2R \xrightarrow[(ii)\ n\text{-}C_4H_9Li]{(i)\ NaH} R^1\bar{C}HCO\bar{C}HCO_2R \xrightarrow{R^2X}$$

(9)

$$R^1\underset{\displaystyle R^2}{\underset{|}{C}}H{-}CO\bar{C}HCO_2R \quad (5.3a)$$

e.g. $$CH_3COCH_2COCH_3 \xrightarrow[(ii)\ PhCH_2Cl]{(i)\ 2NaNH_2} CH_3COCH_2COCH_2CH_2Ph \quad (69\ \%)$$

$$CH_3COCH_2CO_2C_2H_5 \xrightarrow[(ii)\ C_2H_5Br]{(i)\ NaH+C_4H_9Li} C_2H_5CH_2COCH_2CO_2C_2H_5 \quad (84\ \%)$$

(c) The final example on p. 64 illustrates the introduction of two different alkyl groups into diethyl malonate, and raises the question of the order in which the groups are inserted. In some cases the order is unimportant. However, if the two alkyl groups are very different in bulk, it is advisable to introduce the smaller group first; if the bulky group is put in first, steric hindrance may then inhibit the second alkylation. Also, if the two alkyl groups are very different in their electron-repelling ($+I$) effect, it is advisable to introduce first the group which has the lesser effect, since deprotonation of the alkyl-malonic ester for the second alkylation is made more difficult if the alkyl group is strongly electron-repelling.

Stabilised carbanions are **ambident nucleophiles** (cf. Sykes, p. 97), as implied in the canonical forms (10) and (11) or the delocalised ion (12):

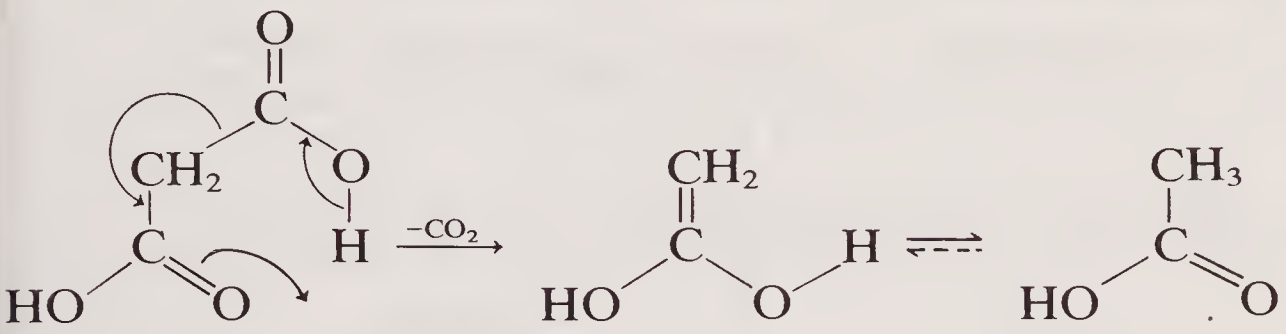
$$\rangle\bar{C}{-}X{=}Y \longleftrightarrow \rangle C{=}X{-}\bar{Y} \qquad [\rangle C{\cdots}X{\cdots}Y]^-$$

(10) (11) (12)

Such ions might therefore have been expected to undergo *O*-alkylation (since oxygen is the more electronegative 'end' of the delocalised system) rather than the exclusive *C*-alkylation indicated above. The fact is that *O*-alkylation of enolates can (and frequently does) occur along with *C*-alkylation. The proportion of *O*-alkylated product depends, apparently, on a considerable number of factors: the nature of the alkylating agent, the choice of cation, the solvent, whether the reaction is homogeneous or heterogeneous, whether either of the possible sites for alkylation is sterically hindered, etc. It is not always easy, therefore, to predict the course of a particular alkylation; but in general the use of an alkyl *halide* as the alkylating agent, a *sodium* salt as the nucleophile, and an *alcohol* as solvent (i.e. a solvent which may solvate, and hence deactivate, the oxygen of the enolate) is likely to give mainly *C*-alkylation.

5.1.2 Hydrolysis of the alkylated products: a route to carboxylic acids and ketones

The chemistry of malonic acid, $CH_2(CO_2H)_2$, and β-keto-acids such as acetoacetic acid, $CH_3COCH_2CO_2H$, is dominated by the ease with which these acids undergo decarboxylation (i.e. lose carbon dioxide) on being heated (cf. Sykes, pp. 285–7):



Similarly, $CH_3COCH_2CO_2H \xrightarrow{-CO_2} CH_3COCH_3$

The mono- and di-alkylated analogues are similarly decarboxylated, e.g.

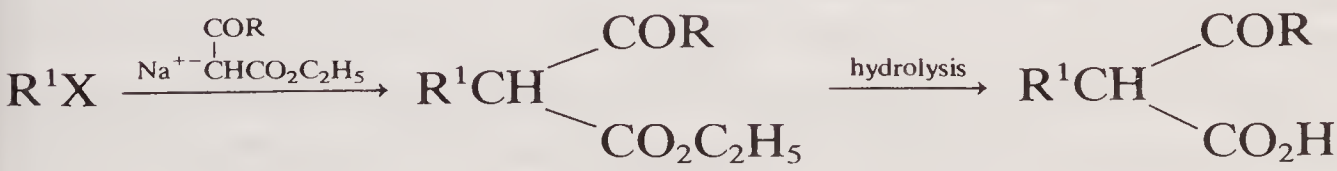
$R_2C(CO_2H)_2 \rightarrow R_2CHCO_2H;$

$CH_3COCHRCO_2H \rightarrow CH_3COCH_2R.$

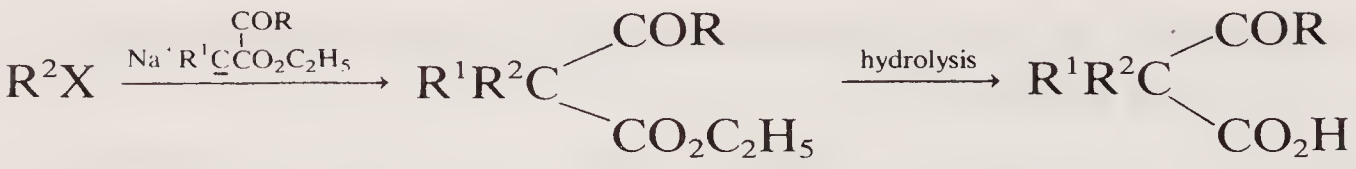
These mono- and di-alkylated acids are of course obtained by hydrolysis of the corresponding esters, the preparation of which has been described in the previous section. Since the alkyl groups are introduced by means of alkyl halides, reaction with the appropriate carbanions followed by hydrolysis and decarboxylation constitutes a method for the conversion of halides into carboxylic acids or ketones:

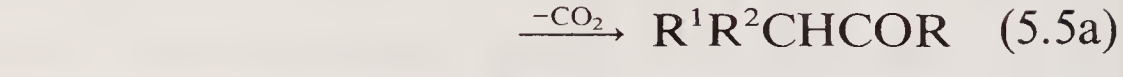
$$RX \xrightarrow{Na^+\bar{C}H(CO_2C_2H_5)_2} RCH(CO_2C_2H_5)_2 \xrightarrow{\text{hydrolysis}} RCH(CO_2H)_2 \xrightarrow{-CO_2} RCH_2CO_2H \quad (5.4)$$

$$R^1X \xrightarrow{Na^+R\bar{C}(CO_2C_2H_5)_2} RR^1C(CO_2C_2H_5)_2 \xrightarrow{\text{hydrolysis}} RR^1C(CO_2H)_2 \xrightarrow{-CO_2} RR^1CHCO_2H \quad (5.4a)$$



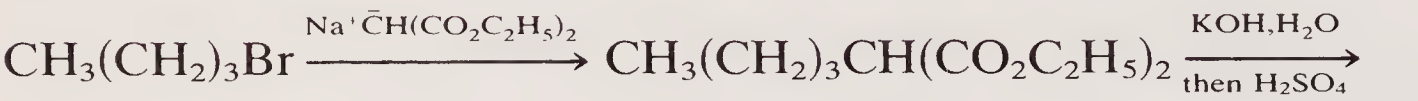
$$\xrightarrow{-CO_2} R^1CH_2COR \quad (5.5)$$





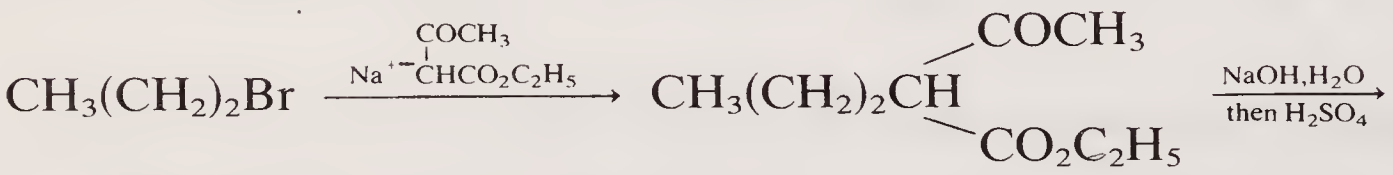
(5.5a)

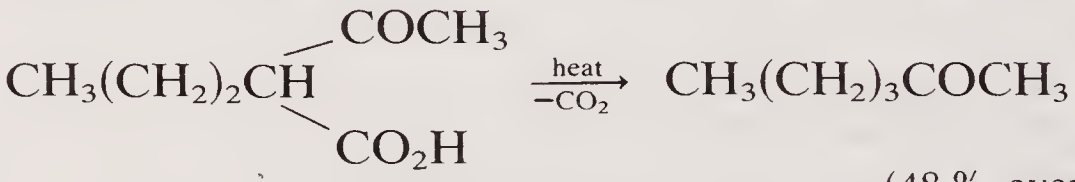
Thus, for example,



(5)

(66 % overall)





(48 % overall)

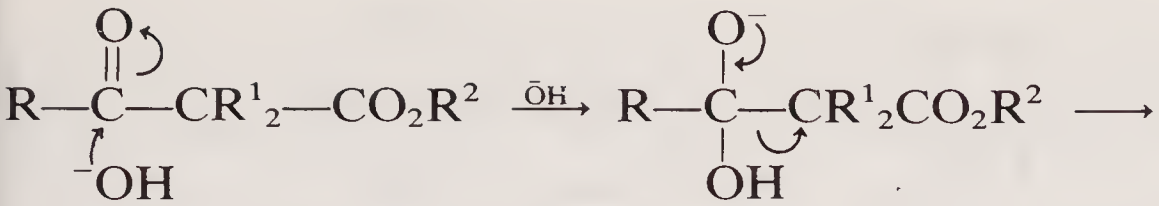
So we now have a method for replacing halogen in a molecule by CH_2CO_2H or CH_2COR. To express this in another way, we have another possible disconnection for carboxylic acids and ketones:

$$RCH_2CO_2H \Rightarrow R^+ \bar{C}H_2CO_2H \qquad (5.6)$$

$$RCH_2COR^1 \Rightarrow R^+ \bar{C}H_2COR^1 \qquad (5.7)$$

The synthetic equivalent of R^+ is, of course, the alkylating agent RX, as we have seen before. So **the synthetic equivalent of the synthon $\bar{C}H_2CO_2H$ is diethyl malonate,** and **the synthetic equivalent of $\bar{C}H_2COCH_3$** (for example) **is ethyl acetoacetate.** Similarly the synthetic equivalents of $\bar{C}HRCO_2H$ and $\bar{C}HRCOCH_3$ are the appropriately alkylated derivatives of malonic and acetoacetic esters, respectively.

There is one remaining practical point. Hydrolysis of an ester may be carried out under both basic and acidic conditions (Sykes, pp. 238–42), and although the illustrations we have used in this section both involve basic hydrolysis there is no reason why acidic hydrolysis should not be equally effective. Indeed, in some cases basic hydrolysis of β-keto-esters is unsatisfactory, since hydroxide ion may attack the ketonic carbonyl group as well as (or instead of) the ester carbonyl; in such cases hydrolysis under acidic conditions is preferable:



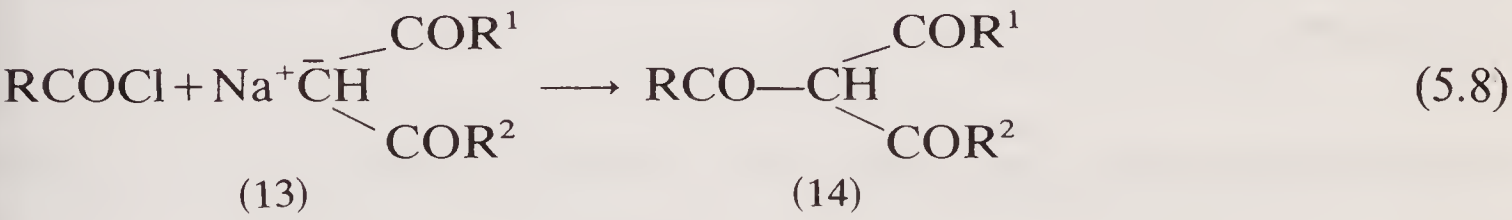
$$RCO_2H + \bar{C}R^1{}_2CO_2R^2 \rightleftharpoons RCO_2^- + R^1{}_2CHCO_2R^2$$

Although this cleavage (deacylation of the β-keto-ester) may occasionally be used to advantage (for example, to bring about a ring-opening: section 7.4.1), it is more often an unwanted side-reaction. It is not usually a serious problem in hydrolysis of mono-alkylated β-keto-esters, since these still contain an acidic hydrogen and are converted by base into delocalised enolate ions; the ketonic carbonyl group is thereby deactivated towards nucleophilic attack. Dialkylated β-keto-esters, on the other hand, contain no such acidic hydrogens, and the keto-group is then particularly prone to attack by hydroxide ion, since it contains the most electrophilic carbon in the molecule.

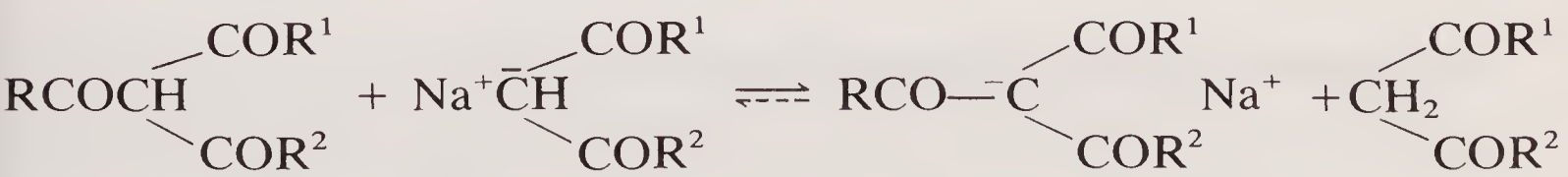
5.1.3 Acylation

Much of what has been said of alkylation in the two previous sections is equally applicable to acylation. The reactions occur readily, and usually in good yield; and hydrolysis or base-induced cleavage of the product frequently constitutes a useful synthetic procedure.

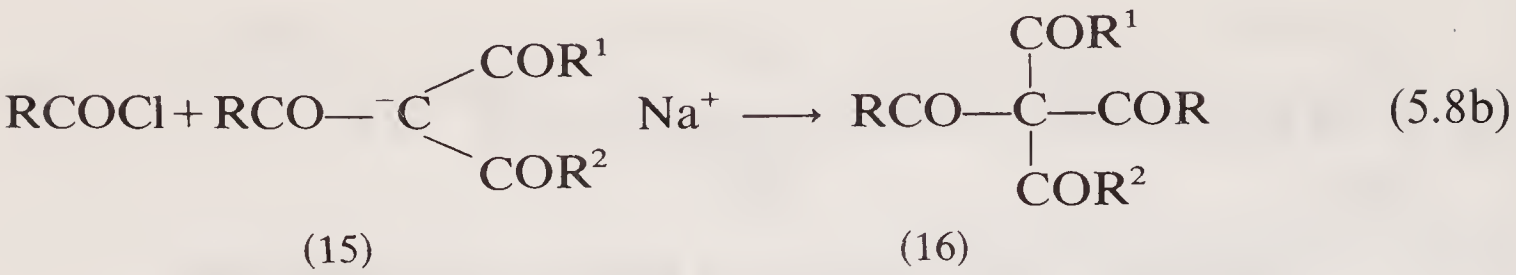
There are several important differences, however, between alkylation and acylation. Some of these are merely procedural: for example, alcoholic solvents cannot be used for acylations, since alcohols are themselves easily acylated. Also, acylation products of the type $RCOCH\begin{smallmatrix}COR^1\\COR^2\end{smallmatrix}$ are strongly acidic, the anion being stabilised by three $-M$ groups: this means that such a product may be deprotonated by carbanions of the type $\bar{C}H\begin{smallmatrix}COR^1\\COR^2\end{smallmatrix}$, and thus in the acylation of these carbanions the following reactions may be in competition:



(13) (14) (5.8)

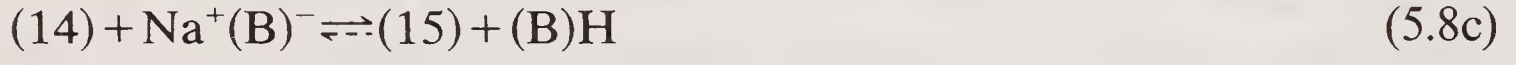


(14) (13) (15) (5.8a)



(15) (16) (5.8b)

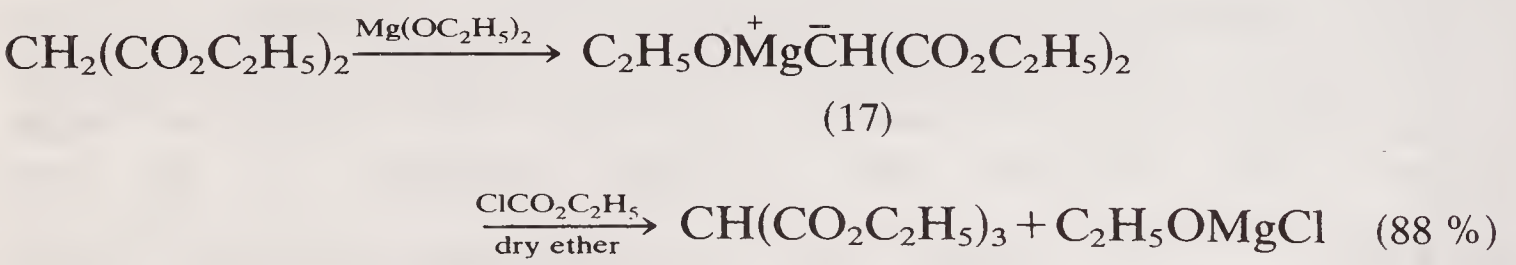
Both the main reaction, (5.8), and the first side-reaction, (5.8a), consume the carbanion (13), and so for a good yield of the monoacylated compound (14) either (5.8) must be considerably faster than (5.8a), or else (5.8a) must be suppressed in some way. Fortunately suppression of (5.8a) is straightforward: addition of a second molar equivalent of a strong base [stronger than (13)] replaces (5.8a) by (5.8c):



(5.8c)

Admittedly (5.8b) is still in principle a possible side-reaction, but (15) is much less nucleophilic than (13), and so the diacylated compound (16) is seldom an important by-product.

One neat method, which both overcomes the solvent problem and also provides the additional mole of base, is shown below. The use of magnesium ethoxide to form the initial carbanion gives a species (17) which, unlike the sodium salt, is ether-soluble, and also is capable of releasing an equivalent of ethoxide at a subsequent stage (corresponding to 5.8c):



(17) (88 %)

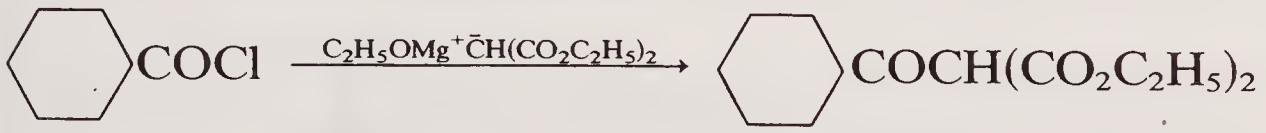
$[\rightleftharpoons ClMgC(CO_2C_2H_5)_3 + C_2H_5OH]$.

Basic hydrolysis of diethyl acylmalonates is of no value as a synthetic method, since it is accompanied by cleavage [deacylation: (5.9)]. Hydrolysis in aqueous acid gives acylmalonic acids and hence, by decarboxylation, methyl ketones (5.10):

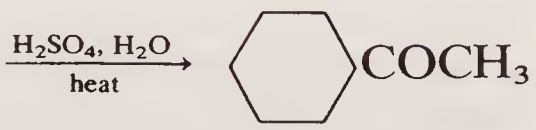
(5.9)

(5.10)

This last reaction, in conjunction with (5.8), provides another method for the conversion of RCOCl into $RCOCH_3$. Although on paper it is more complicated than the reaction with dimethylcadmium (section 4.2.2) or with lithium dimethylcuprate (section 4.2.3.ii), in practice it presents no difficulties, and the overall yields are high, e.g.

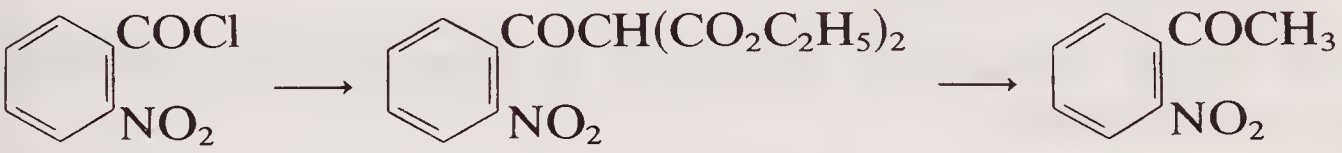


(not isolated)



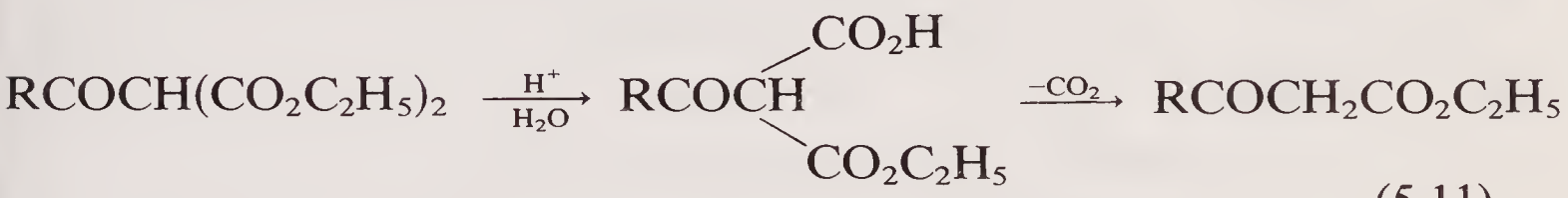
(70 % overall)

Similarly



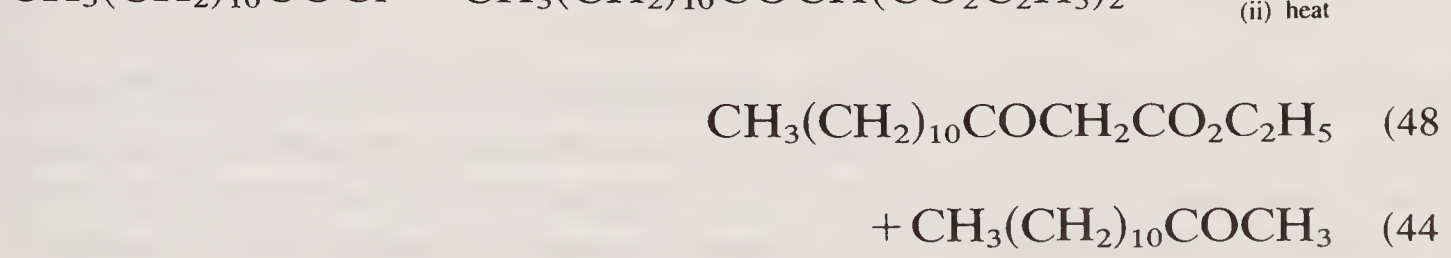
(85 % overall)

It is sometimes possible to arrest the hydrolysis of the acylmalonic ester at the half-way stage (5.11), and decarboxylation then yields a β-keto-ester; but yields in this reaction are seldom better then 50 %:



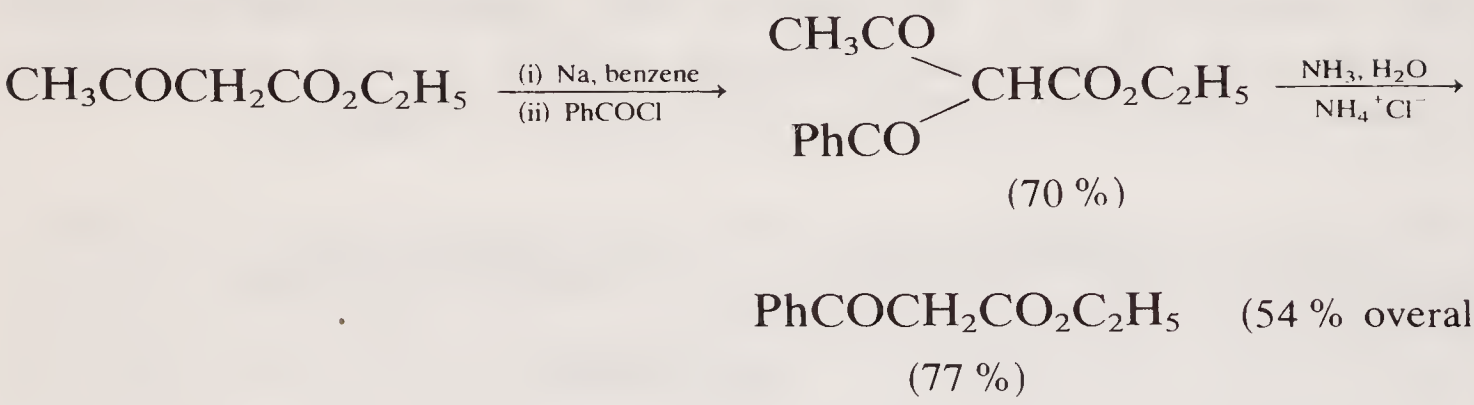
(5.11)

Thus,



Acylation of β-keto-esters followed by base-catalysed cleavage is sometimes a useful synthetic procedure. The acylation product, a diketo-ester, undergoes nucleophilic attack at the most electrophilic carbonyl group (one of the keto-functions), and the product, like the starting

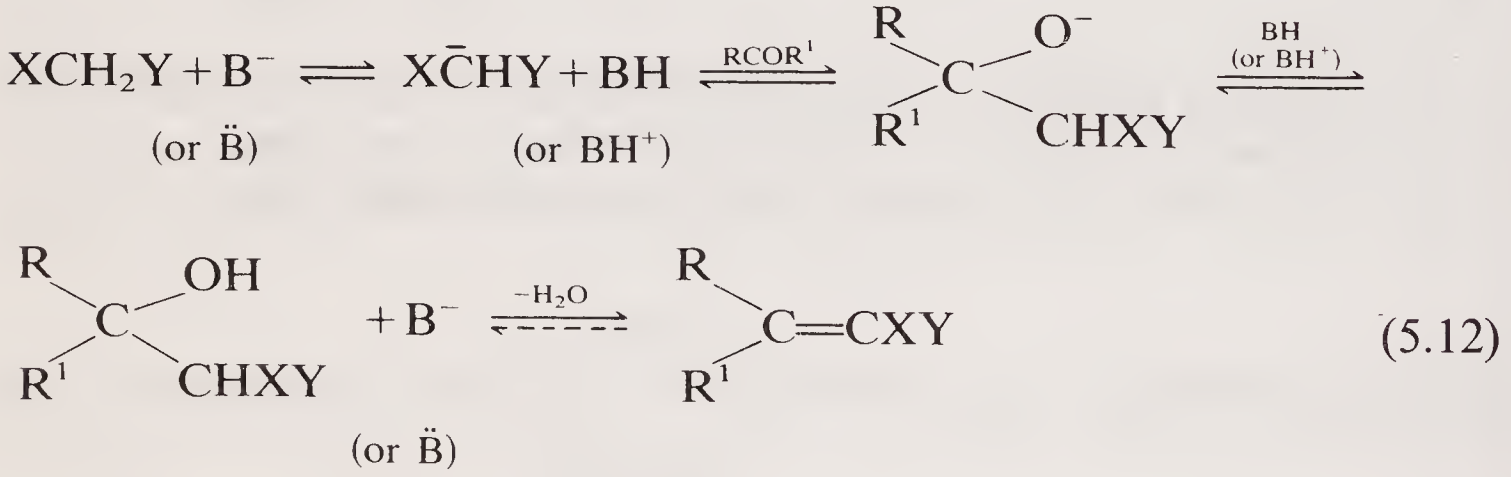
material, is a β-keto-ester, e.g.



An interesting 'one-pot' variant of this reaction, which gives better yields (ca. 70 % overall) involves a simple Schotten–Baumann benzoylation (with benzoyl chloride and aqueous sodium hydroxide) of ethyl acetoacetate; the benzoylated product is then hydrolysed *in situ*.

5.1.4 Condensation reactions[2]

In general terms, carbanions participate in condensation reactions according to the scheme:



(5.12)

Several important points emerge from this general reaction.

(i) The overall stoicheiometry of the reaction is simply

$$XCH_2Y + RCOR^1 \rightarrow RR^1C{=}CXY + H_2O.$$

Thus, even although the base may be concerned in the rate-determining step (i.e. although its concentration may determine the **rate** of reaction), it is **not consumed** in the reaction, but is regenerated in a subsequent step. It is therefore unnecessary to use a stoicheiometric quantity of the base, and a catalytic amount may indeed be sufficient.

(ii) Since the compound XCH_2Y does not require to be converted completely into the carbanion prior to the introduction of the carbonyl compound, it is possible to use a weaker base for a condensation than that required for alkylation or acylation.

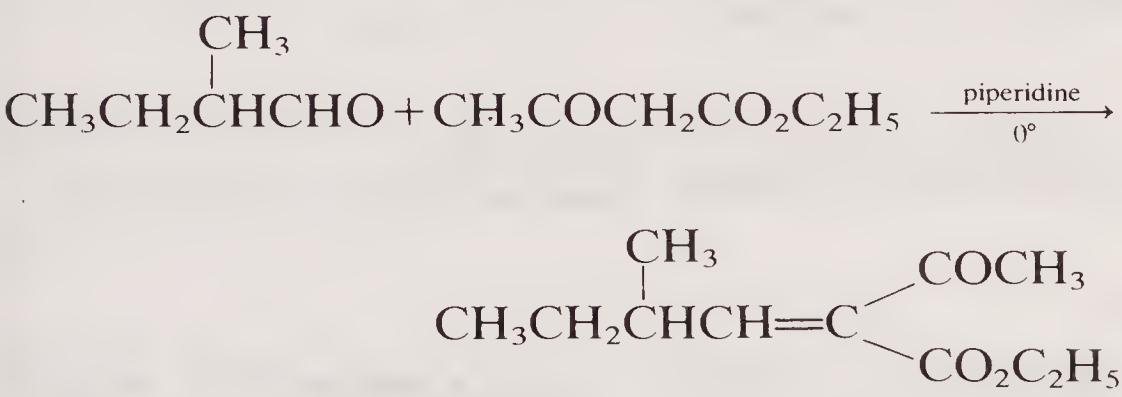
(iii) Since all the steps are, in theory, reversible, it may be advantageous to force the reaction to completion by removing the water formed in the last step.

(iv) If the system contains more then one carbanion source, and/or more than one carbonyl group, the condensation occurs preferentially *via* attack of the most stabilised carbanion on the most electrophilic carbonyl carbon atom.

It follows from the above that, if X and Y in reaction (5.12) are both $-M$ groups, condensation reactions with aldehydes and ketones should occur in presence of relatively weak bases. We have already pointed out [reaction (5.2)] that amines such as piperidine can deprotonate diethyl malonate, ethyl acetoacetate, etc., to an appreciable extent, and as a result piperidine and other amines successfully bring about condensations involving these highly stabilised carbanions and aldehydes or ketones (generally known as **Knoevenagel condensations**). Thus, for example,

$$PhCHO + CH_2(CO_2C_2H_5)_2 \xrightarrow[0°]{\text{piperidine (0.05 mol)}} PhCH{=}C(CO_2C_2H_5)_2 \quad (75\ \%)$$

(97 %)



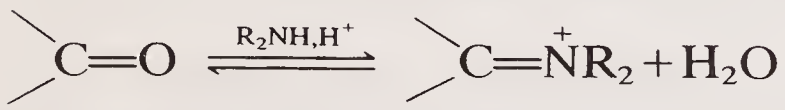
(83 %)

In these three cases there is no ambiguity regarding the most acidic hydrogen, and the aldehyde group provides a highly electrophilic carbon: the yields are therefore high. Even when the aldehyde is of the type RCH_2CHO, and can in theory undergo self-condensation (section 5.2.4.1), amines are not sufficiently basic to produce a significant equilibrium concentration of the carbanion $R\bar{C}HCHO$, and so self-condensation is rarely an important side-reaction.

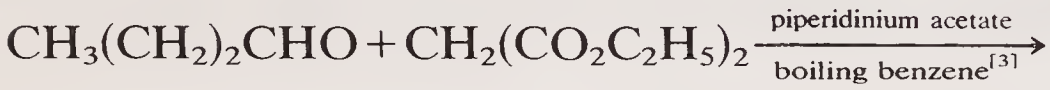
Whereas aldehydes undergo Knoevenagel condensations with a wide variety of carbanion sources (or **active methylene compounds**, as they are often called), the same is not true of ketones. Simple ketones undergo Knoevenagel reactions with malononitrile [$CH_2(CN)_2$] and ethyl cyanoacetate, but rarely with diethyl malonate (except in presence of titanium tetrachloride) or ethyl acetoacetate. Whether this selectivity is due

to decreased electrophilicity or increased steric hindrance in the ketone, or to increased nucleophilicity or smaller steric demand in the cyano-stabilised nucleophile (or to any combination of these) is not clear.

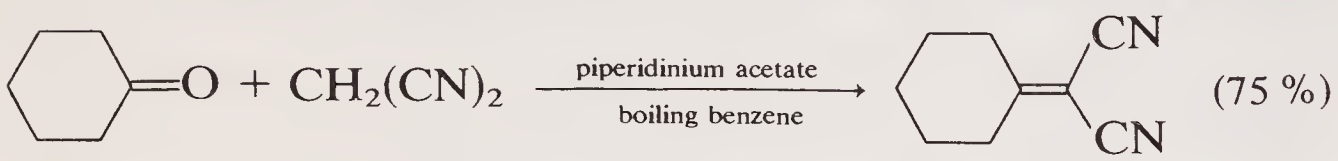
A remarkable feature of Knoevenagel condensations is the increase in yield which often results from the addition of a catalytic amount of an organic *acid* to the reaction mixture, or alternatively when an ammonium salt (usually the acetate) is used as catalyst in place of the free amine. The exact function of the acid is not fully understood. It may serve to catalyse the formation of a (highly electrophilic) **iminium salt** from the carbonyl compound and the amine [reaction (5.13)]. Alternatively (or additionally) it may serve to promote the dehydration which is the final step in the condensation process (5.12). Its function may well be different in different cases. But its effectiveness is not in doubt, as the following examples show:



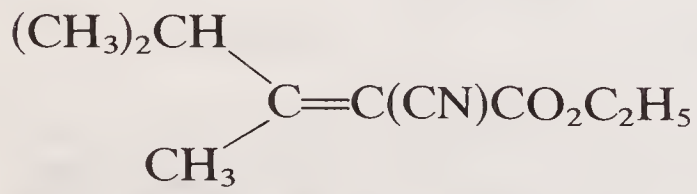
(5.13)



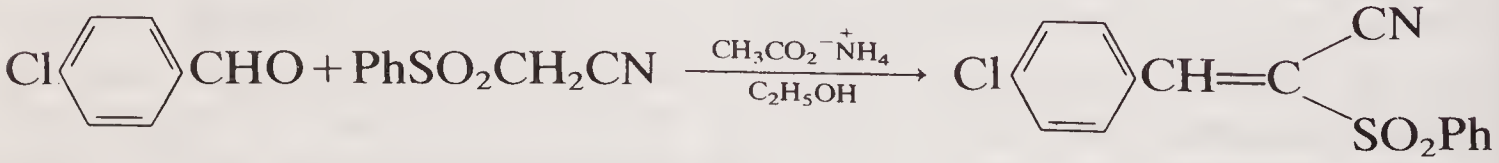
(59 %)



(75 %)



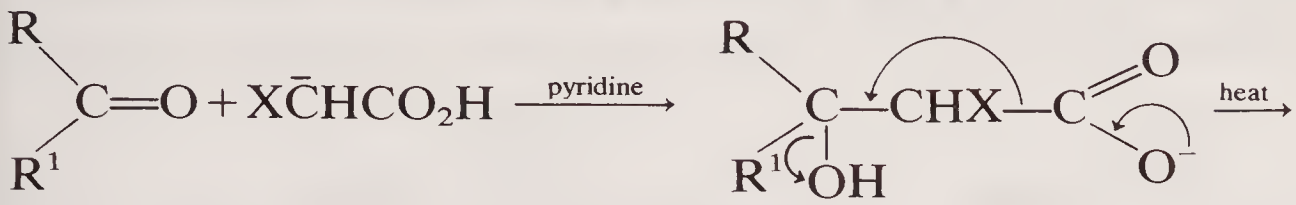
(64 %: possibly a mixture of *E*- and *Z*-)



(95 %)

The other most important variant of the Knoevenagel condensation is that in which one or both of the $-M$ groups stabilising the carbanion is carboxyl (CO_2H). In this process (usually known as the **Doebner condensation**) malonic or cyanoacetic acid generally furnishes the carbanion, and pyridine or quinoline is used as solvent. A small quantity of a

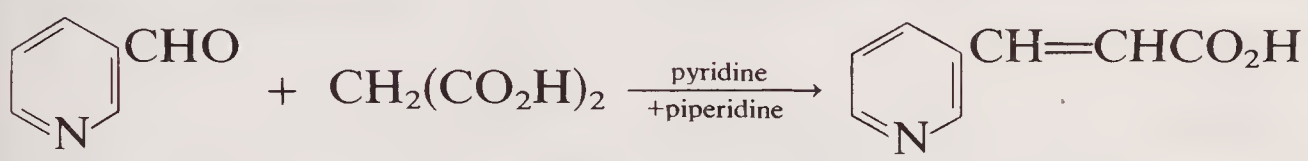
stronger base, e.g. piperidine, may be added, although this is not always necessary. In this reaction (5.14), the condensation is accompanied by decarboxylation:

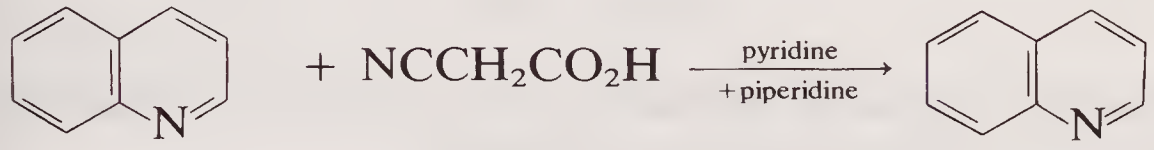


$$\begin{matrix} R \\ \diagdown \\ \quad C{=}CHX \\ \diagup \\ R^1 \end{matrix} \quad [+ CO_2 + \bar{O}H \longrightarrow HCO_3^-] \qquad (5.14)$$

For example,

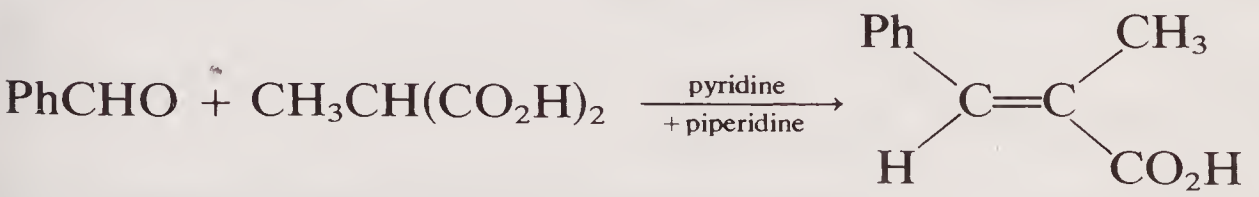
$$CH_3(CH_2)_5CHO + CH_2(CO_2H)_2 \xrightarrow{\text{pyridine}} CH_3(CH_2)_5CH{=}CHCO_2H \quad (79\ \%)$$





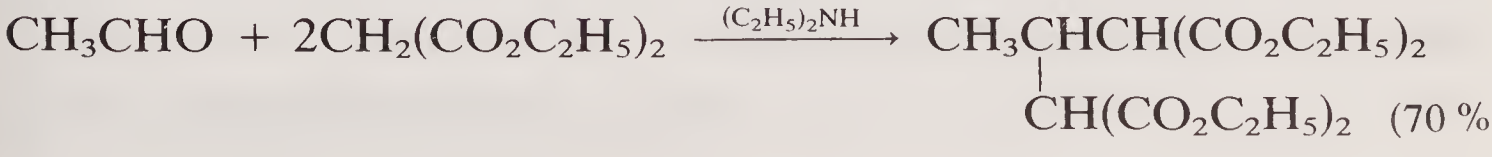
In these reactions the *E*- (i.e. *trans*)-isomer is usually formed.

Alkylmalonic acids may also be used in the Doebner condensation, e.g.

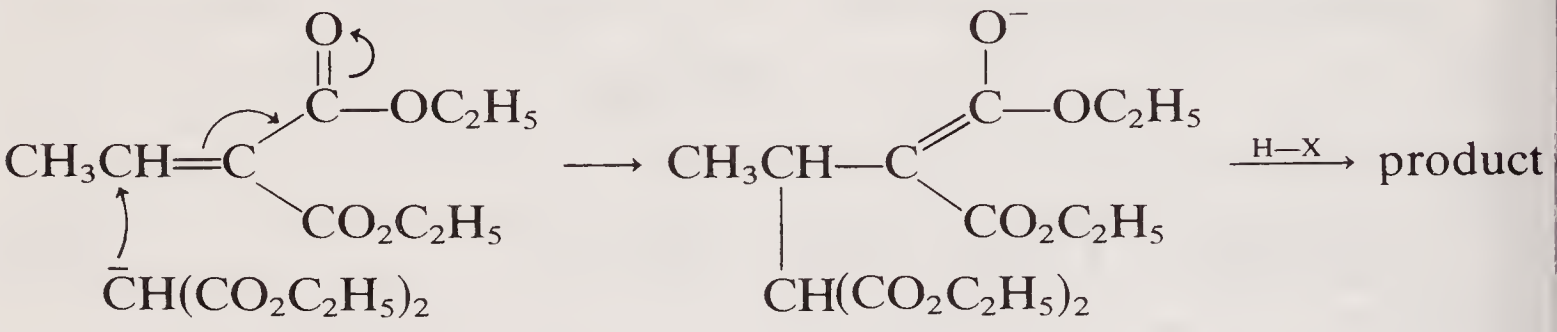


5.1.5 Reactions with $\diagdown C{=}C{-}C{=}O$ and related systems: the Michael reaction

It sometimes happens that attempts to effect a Knoevenagel condensation between a simple aldehyde and, say, diethyl malonate lead not to the simple condensation product but to one in which one mole of the aldehyde has reacted with two moles of the malonate, e.g.

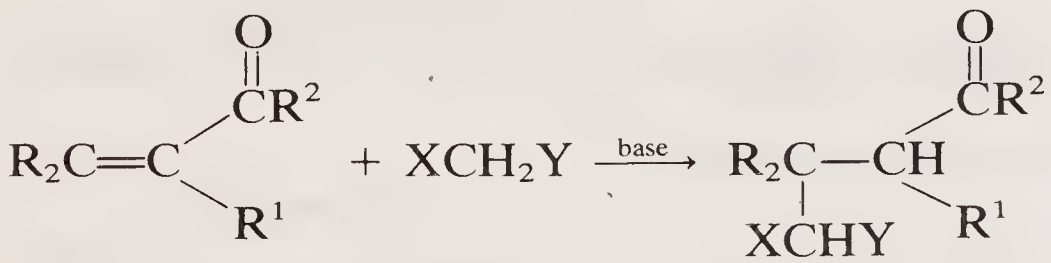


Almost certainly, Knoevenagel condensation is the first step, and the condensation product (an α,β-unsaturated ester) then undergoes **conjugate addition** (cf. section 4.1.4) of the second mole of the malonate-derived carbanion. This gives an enolate (18) which is protonated to yield the final product:



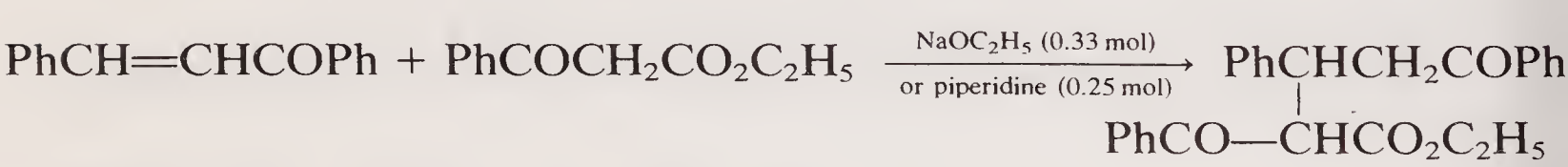
(18)

This conjugate addition of a stabilised carbanion to an α,β-unsaturated carbonyl (or cyano- or nitro-) compound has wide applicability, and is generally referred to as the **Michael reaction** (or Michael addition: reaction 5.15). The overall reaction is

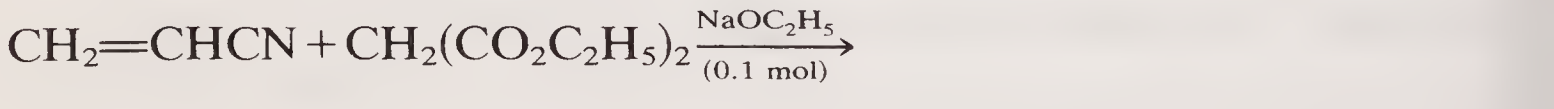


(5.15)

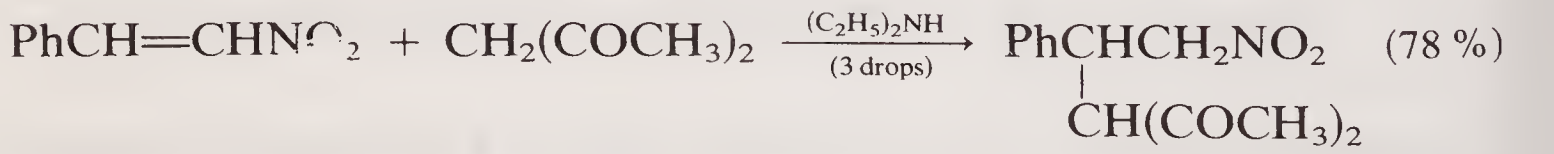
and so a stoicheiometric quantity of base is not required. The following examples illustrate the generality of the procedure:



(93 %)

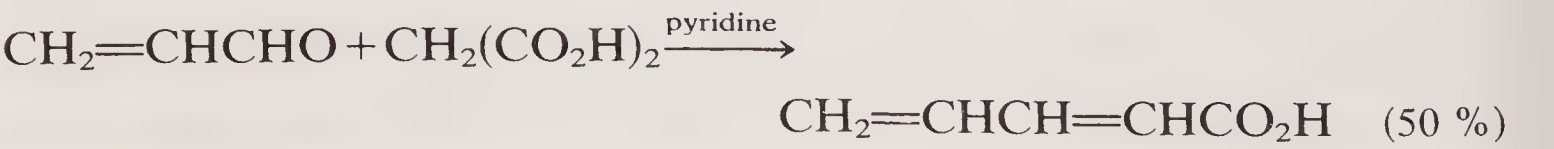


(55 %)



(78 %)

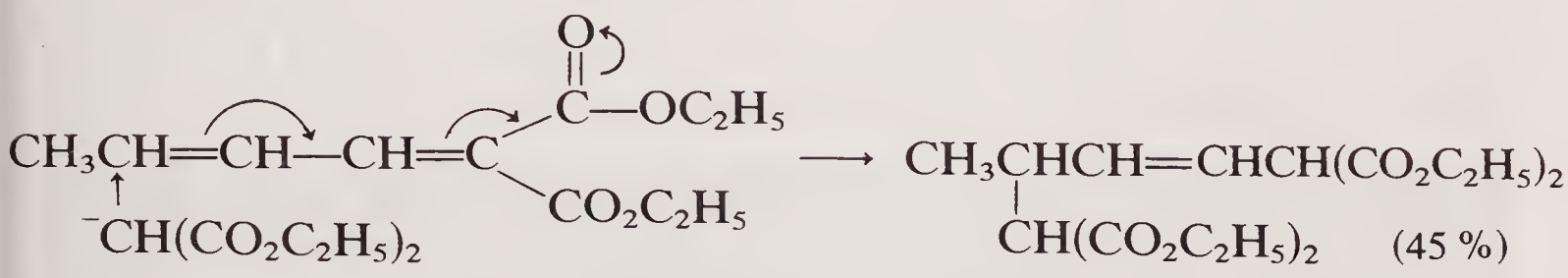
Under such conditions, α,β-unsaturated aldehydes may undergo a Knoevenagel-type condensation, or a Michael addition, or (in some cases) both, e.g.



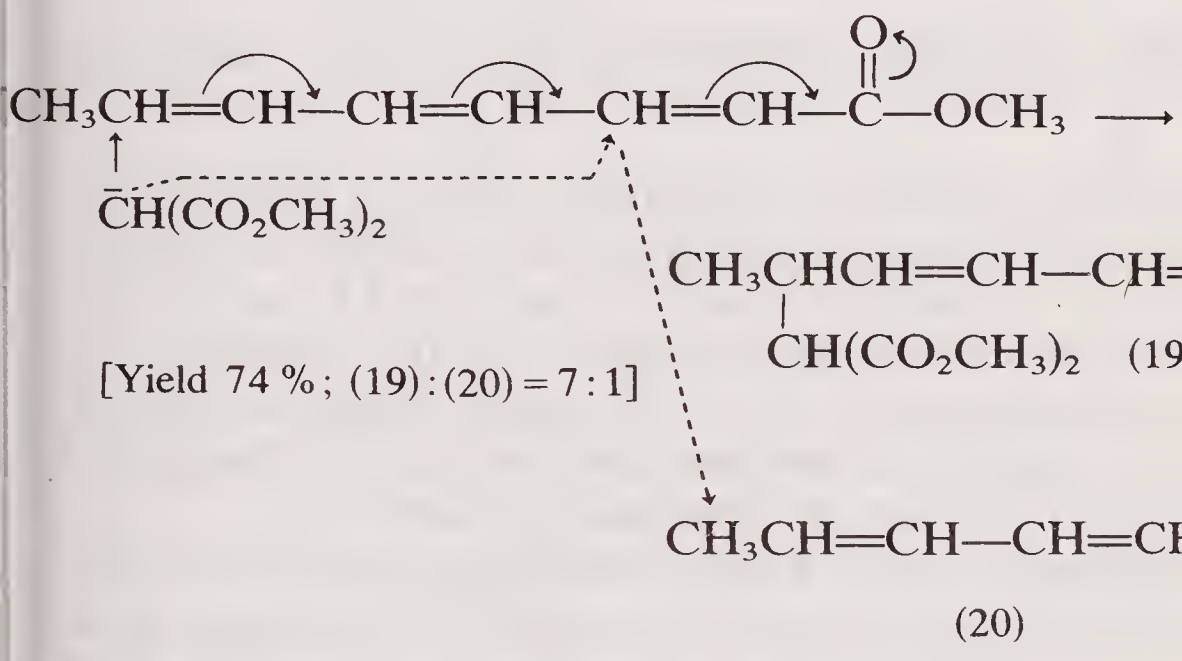
(50 %)

$$CH_2{=}CHCHO + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} (C_2H_5O_2C)_2CHCH_2CH_2CHO \quad (50\ \%)$$

$$CH_3CH{=}CHCHO + 2CH_2(CO_2C_2H_5)_2 \xrightarrow{(C_2H_5)_2NH}$$



This last example illustrates a further, apparently general, feature of the Michael reaction, namely that when the conjugated system is extended by one or more double bonds, addition occurs preferentially (although not exclusively) at the *end* of the conjugated system. Methyl octa-2,4,6-trienoate similarly undergoes Michael addition mainly at the 7-position (but also at the 3-position):



The Michael reaction is also an essential part of many procedures for ring closure, and so will be considered again in Chapter 7 (section 7.1.3).

5.2 Carbanions stabilised by one $-M$ group

The reactions in section 5.1 all involve carbanions which are formed comparatively easily by deprotonation of relatively strong carbon acids ($pK_a \leq 13$). Compounds of the type RCH_2X or R_2CHX, however (X being a $-M$ group) are in general much weaker acids: with the exception of nitroalkanes ($pK_a \simeq 9$–10), the compounds in question have pK_a values of approximately 19–27, and thus even moderately strong bases like sodium alkoxides can do no more than produce an equilibrium con-

centration of the carbanion. If complete conversion into the carbanion is required, an even stronger base must be used, e.g. an alkali metal amide. In such cases, alcohols cannot of course be used as solvents, since they are more acidic than the carbon acids, and so are deprotonated in preference to the latter.

5.2.1 Alkylation

It will be recalled (cf. section 5.1.1) that alkylation requires the use of a stoicheiometric equivalent of base, and that, for the reaction to proceed at a reasonable rate, a high initial concentration of the carbanion is desirable. Thus very strong bases are generally required. Where the stabilising $-M$ group is a cyano- or an ester group, the reactions are straightforward, e.g.

$$CH_3CN + 3CH_3(CH_2)_3Br \xrightarrow[\text{toluene, heat}]{3NaNH_2} [CH_3(CH_2)_3]_3CCN \quad (84\ \%)$$

$$CH_3CH_2CH_2CO_2CH_3 \xrightarrow[\text{(ii) } CH_3CH_2I]{\text{(i) LDA[4], THF}} (CH_3CH_2)_2CHCO_2CH_3 \quad (96\ \%)$$

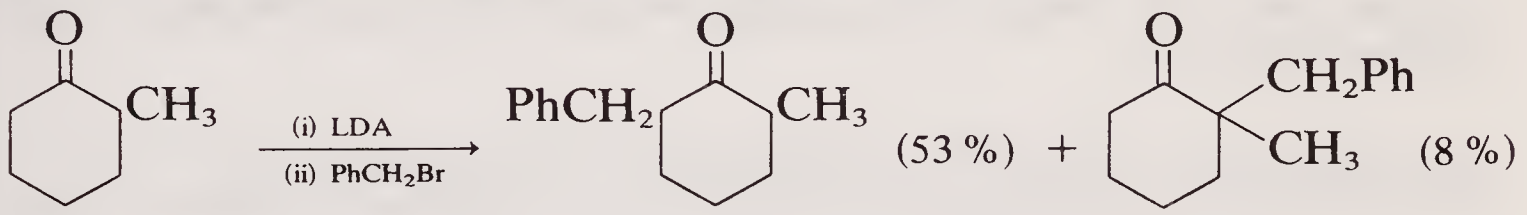
Where the $-M$ group is ketonic or aldehydic, however, serious complications may arise. Both ketones and aldehydes are liable to undergo condensation reactions in presence of base (cf. sections 3.3.2 and 5.2.4), and so self-condensation of starting material or of the product, or a 'mixed' condensation between the two, are all possible side-reactions. In addition, some unsymmetrical ketones can give rise to a mixture of two carbanions and thus to a mixture of alkylated products.

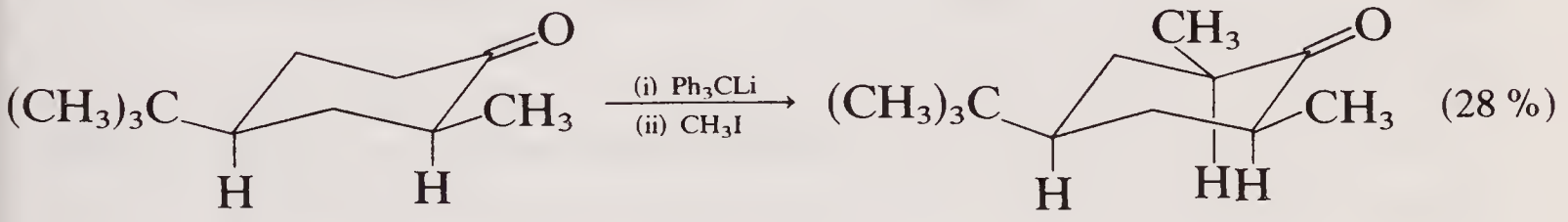
Alkylations of aldehydes, and of ketones which can give rise to only one carbanion, are (in principle at least) the simplest of this group, since the only problem is the avoidance of condensation processes. These, of course, involve attack of the carbanion on an unionised carbonyl compound, and occur especially readily in the case of aldehydes; it is therefore important to choose experimental conditions which minimise the concentration of free carbonyl compound throughout the process. The carbanions must be formed quantitatively, in an aprotic solvent, by slow addition of the ketone or aldehyde to a solution of the base (i.e. the base is always in excess), and then an excess (up to tenfold) of the alkylating agent must be added rapidly (i.e. so that alkylation is kinetically the most favoured process). Examples of such reactions include the following:

$$(CH_3)_2CHCHO \xrightarrow[\text{(ii) } BrCH_2CH{=}C(CH_3)_2]{\text{(i) KH, THF}} \underset{\displaystyle CH_2CH{=}C(CH_3)_2}{\overset{\displaystyle (CH_3)_2C(CHO)}{|}} \quad (88\ \%)$$

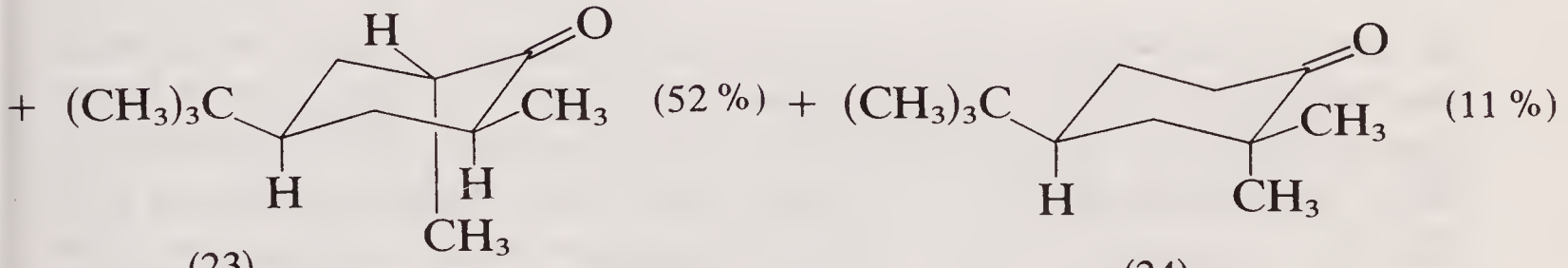
$$PhCOCH_2C_2H_5 \xrightarrow[(ii)\ C_2H_5Br]{(i)\ Ph_3CNa,\ ether} PhCOCH(C_2H_5)_2 \quad (62\ \%)$$

Ketones possessing α-hydrogens on both sides of the carbonyl group can (and generally do) give rise to a mixture of two carbanions, and alkylation of such ketones thus gives a mixture of products. Which isomer will predominate is not always easy to predict. If the deprotonation is carried out by slow addition of the ketone to a molar equivalent of the base in an aprotic solvent, the deprotonation is essentially irreversible, and the ratio of carbanions is determined by the relative rates at which the two α-protons are abstracted. This process is *kinetically controlled*, and the less hindered α-proton is generally removed more rapidly, as the following examples show:



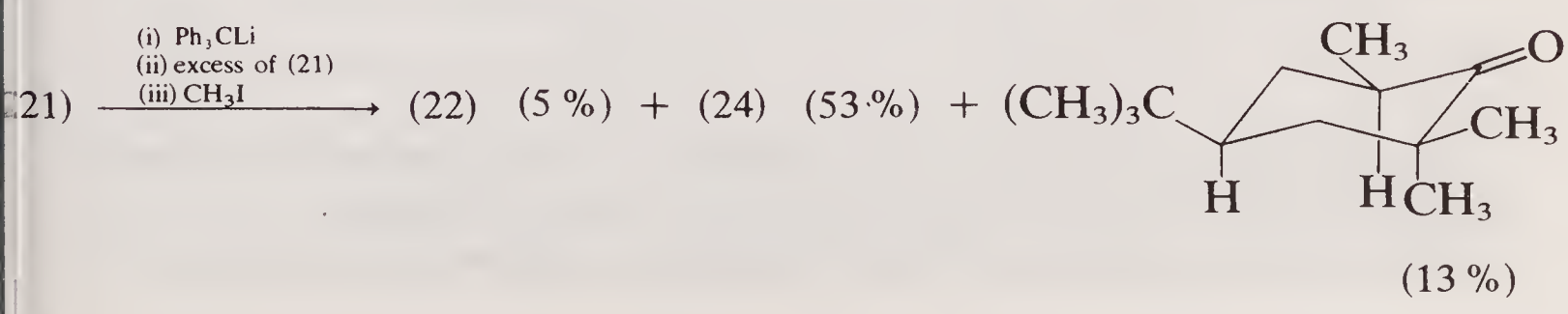


(21) (22)



(23) (24)

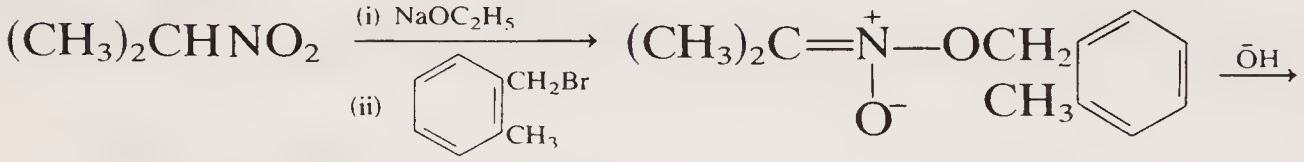
If, on the other hand, the carbanions are generated in the presence of a proton source (even if this is only a small excess of the unionised ketone) the deprotonation step is reversible, and the process is then *thermodynamically controlled*. The product ratios obtained under such conditions may differ substantially from those obtained by the kinetically controlled processes, e.g.

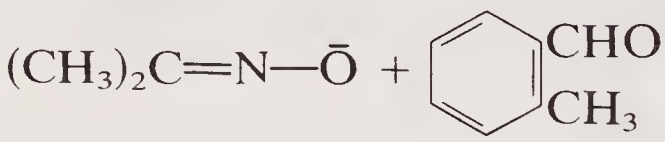


(13 %)

The above, however, is still an over simplified picture. The carbanion ratio (and hence the product ratio) depends on other factors: for example, the structure of the ketone, the steric demands of the base, the nature of the cation, and the solvent. A full discussion of all these factors is beyond the scope of this book: it is sufficient for our purposes to recognise the difficulties in such reactions, and their limited synthetic utility. In the next section but one (5.2.3) we shall explore some indirect methods for the synthesis of α-alkylated ketones which offer a means of avoiding these difficulties.

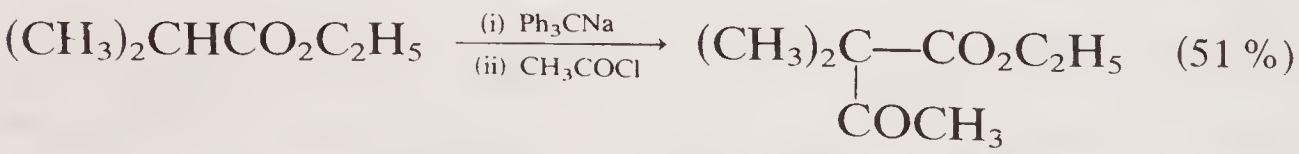
Finally, it should be noted that nitroalkanes, although alkylated under much milder conditions than the other types of compound considered above, usually (with very few exceptions) react at *oxygen* rather than at carbon, as in the following example: a new carbon–carbon bond is not formed, and the reaction has therefore no general relevance to the present chapter:





5.2.2 Acylation

In view of the problems associated with alkylation, it might be expected that acylation should present similar problems. This may indeed be the case in acylations using acyl halides and anhydrides, but these reactions have been relatively little explored, since the resulting products (1,3-dicarbonyl compounds, for example) are more easily obtained by other methods. Known examples of this type of acylation conform to the expected pattern, however, and require a molar equivalent of a very strong base per mole of acylating agent, e.g.



[It should be noted that this last product is much more easily prepared by dimethylation of ethyl acetoacetate (cf. section 5.1.1).]

The simplest acylation method, in practice at least, for simple ketones

and esters is that which uses an ester as the acylating agent. The most familiar form of this acylation (the so-called 'Claisen ester condensation'[5]) involves the formation of ethyl acetoacetate from two molecules of ethyl acetate in presence of sodium ethoxide:

$$CH_3CO_2C_2H_5 + CH_3CO_2C_2H_5 \xrightarrow[-C_2H_5OH]{NaOC_2H_5} CH_3COCH_2CO_2C_2H_5 \quad (75\ \%)$$

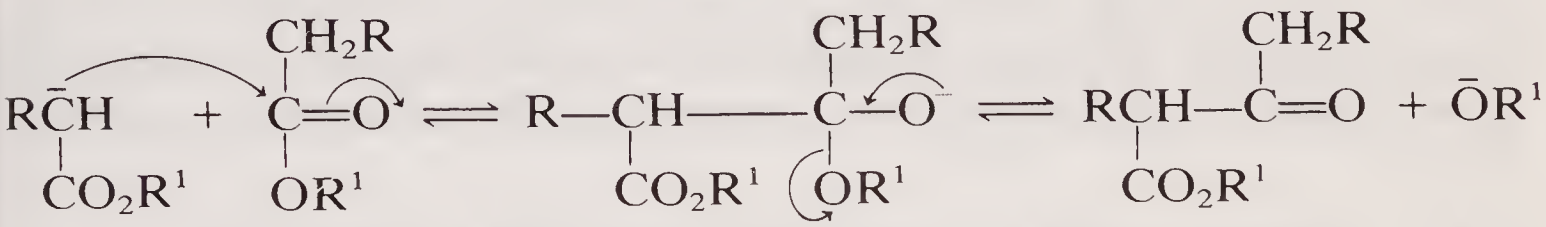
It may, however, also be applied to ketones and cyano-compounds, e.g.

$$PhCO_2C_2H_5 + CH_3COPh \xrightarrow{NaOC_2H_5} PhCOCH_2COPh \quad (62\ \%)$$

$$PhCO_2CH_3 + CH_3CN \xrightarrow{NaOCH_3} PhCOCH_2CN \quad (70\ \%)$$

These reactions appear to defy the general rules we have established in earlier sections. The sodium alkoxides are not sufficiently basic to produce more than a small equilibrium concentration of carbanion from any of these very weak acids. However, alkoxides are certainly basic enough to deprotonate the *products* (cf. section 5.1, introduction) and since all the steps in this type of acylation are reversible [reaction (5.16): cf. Sykes, p. 229–31] the quantitative conversion of the products into their anions provides the driving force for the reactions:

$$RCH_2CO_2R^1 \overset{\bar{O}R^1}{\rightleftharpoons} R\bar{C}HCO_2R^1;$$



$$\rightleftharpoons R\bar{C}(CH_2R)CO_2R^1 \quad (5.16)$$

There are two very important synthetic consequences of this.

(i) The reaction fails with esters of the type $R_2CHCO_2R^1$. The product of such an acylation, $R_2CH—CO—CR_2—CO_2R^1$, lacks the acidic hydrogen between the two carbonyl groups, and so the final deprotonation step is impossible. Successful acylation of such esters requires the use of a much stronger base, which can convert them quantitatively into

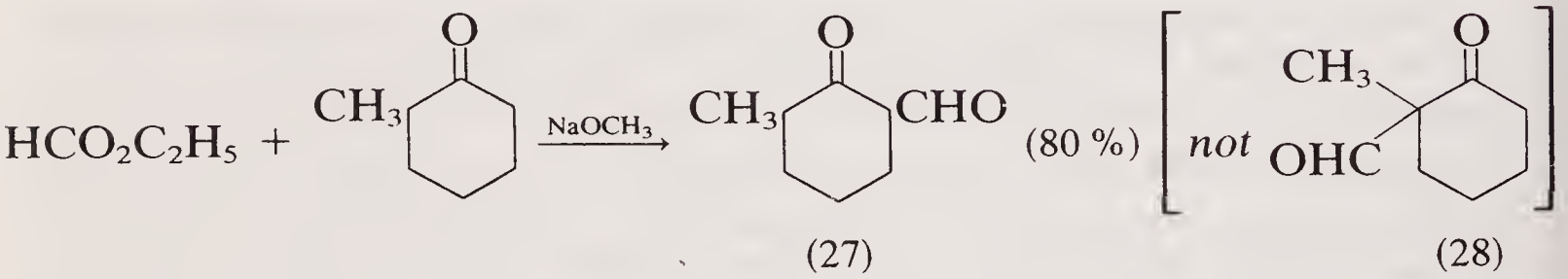
their carbanions:

$$2(CH_3)_2CHCO_2C_2H_5 \xrightarrow{Ph_3CNa} (CH_3)_2C(CO_2C_2H_5)—COCH(CH_3)_2 \quad (35\ \%)$$

(ii) Unsymmetrical ketones with α-hydrogens on both sides of the carbonyl group are acylated, almost exclusively, at the less substituted carbon, e.g.

$$CH_3CO_2C_2H_5 + CH_3CO(CH_2)_4CH_3 \xrightarrow{NaNH_2}$$

$$\underset{(25)}{CH_3COCH_2CO(CH_2)_4CH_3} \quad (61\ \%) + \underset{(26)}{CH_3COCH(COCH_3)(CH_2)_3CH_3} \quad (0.4\ \%)$$



(27) (28)

This is understandable in terms of a mechanism analogous to that of reaction (5.16). Since all the steps are reversible (the reaction is subject to thermodynamic control), the product which accumulates is the one which is the strongest acid (i.e. which forms the most weakly basic carbanion). In the latter example above, (27) is a much stronger acid than (28) (probably by about 10 pK units), because its carbanion is stabilised by both carbonyl groups. Although the difference in acidity between (25) and (26) is much less, it is still sufficient to ensure that (25) is the main product.

5.2.3 Indirect routes to α-alkylated aldehydes and ketones

In section 5.2.1, attention was drawn to the difficulties encountered in attempts to alkylate aldehydes and ketones. Both classes of compound are prone to self-condensation in presence of strong bases, and ketones which can form two carbanions generally give a mixture of alkylated products.

5.2.3.1 Routes to α-alkylated aldehydes

In order to avoid interaction of the aldehyde (either starting material or product) with strong base, the aldehyde may first be converted into a derivative which is less liable to undergo self-condensation. Imines such as (29) may be used in this way (5.17):

$$RCH_2CHO \xrightarrow{R^1NH_2} RCH_2CH{=}NR^1 \xrightarrow[\text{or LDA}]{C_2H_5MgBr^{[6]}} R\bar{C}H{-}CH{=}NR^1$$
(29)

$$\xrightarrow{R^2X} RCH(R^2){-}CH{=}NR^1 \xrightarrow{H^+,\ H_2O} RCH(R^2)CHO \quad (5.17)$$

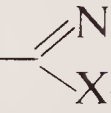
[$R^1 = (CH_3)_3C$, $(CH_3)_2N$, cyclohexyl]

e.g.

$$(CH_3)_2CHCHO \xrightarrow{\bigcirc NH_2} (CH_3)_2CHCH{=}N{-}\bigcirc \xrightarrow[(ii)\ n\text{-}C_4H_9I]{(i)\ C_2H_5MgBr}$$

$$(CH_3)_2C(CH_2)_3CH_3{-}CH{=}N{-}\bigcirc \xrightarrow[H_2O]{H^+} (CH_3)_2CCHO\ (CH_2)_3CH_3$$

(70 % overall)

The other general, indirect route to α-alkylated aldehydes involves the alkylation of a heterocyclic compound of the general type RCH_2—  .

Several such heterocyclic systems have been exploited in this way, but the best known (and possibly the most versatile) are the dihydro-1,3-oxazines (30: R = H, alkyl, aryl, $CO_2C_2H_5$, etc.). The simple preparation of these compounds, and their use in aldehyde synthesis, are outlined below [reactions (5.18)–(5.20), and the examples which follow].

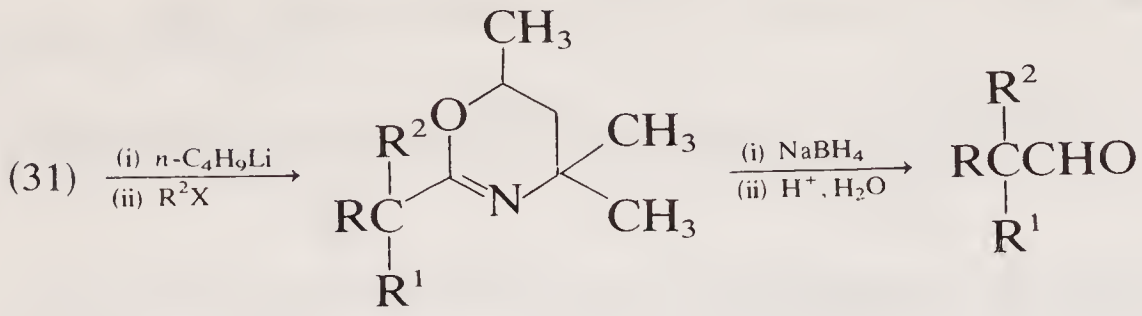
$$RCH_2CN + \text{HO}(CH_3)_2C(OH)CH_2CH(CH_3)_2 \xrightarrow{\text{c. } H_2SO_4} \text{(30)}$$

(R = H: 65 % yield; R = Ph: 50 %)

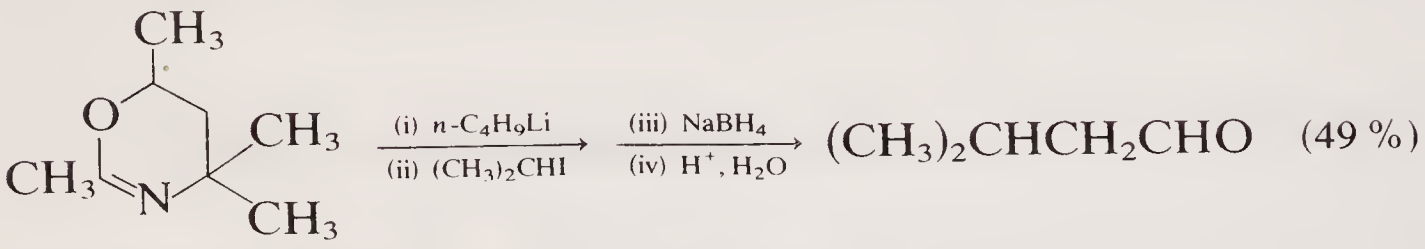
(5.18)

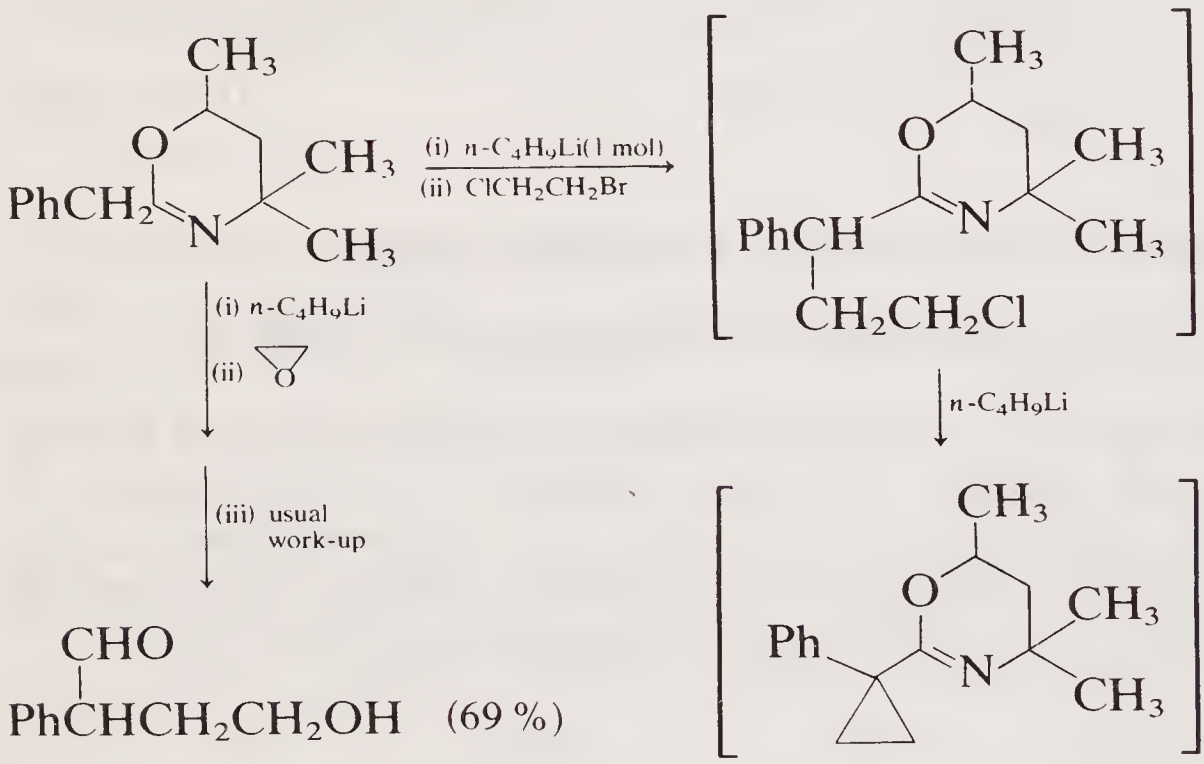
$$\text{(30)} \xrightarrow[THF,\ -78°]{n\text{-}C_4H_9Li} \xrightarrow{R^1X} \xrightarrow[\text{(cf. Section 8.4.6)}]{NaBH_4} \text{(31)}$$

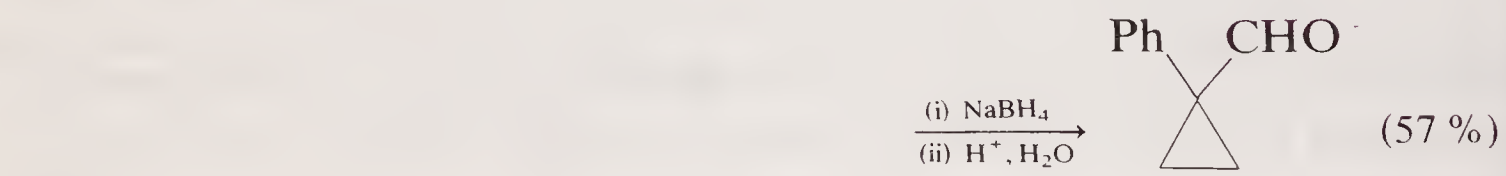
$$\xrightarrow[H_2O]{H^+} RCHCHO + \text{HO}(CH_3)_2C(NH_2)CH_2CH(CH_3)_2 \quad (5.19)$$

(31) 

(5.20)







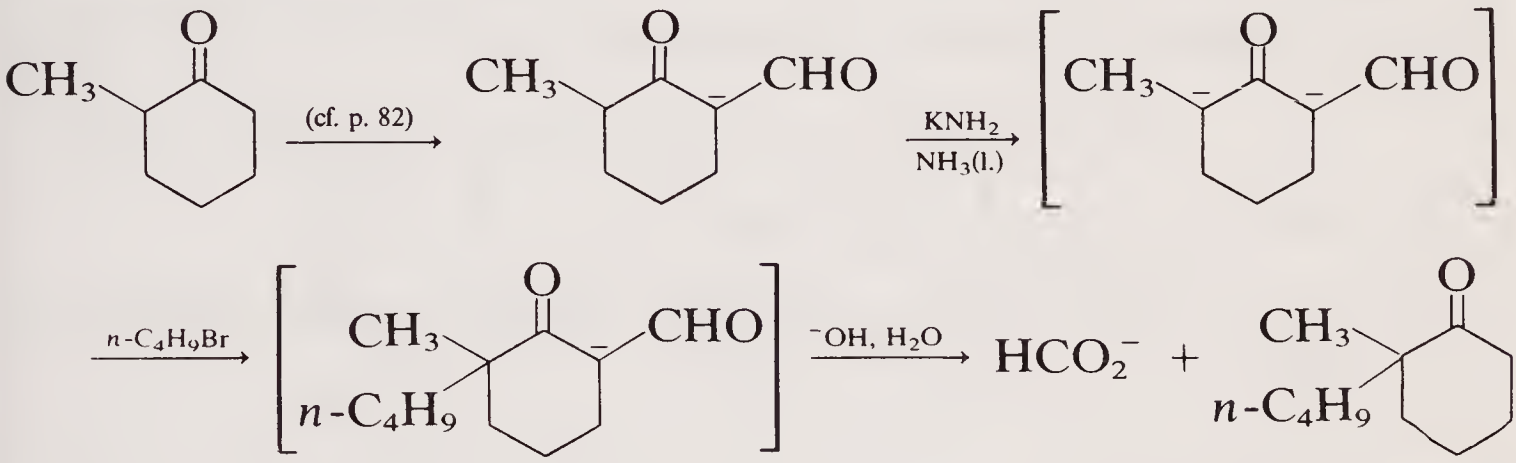
α-Alkylation of aldehydes using enamine intermediates is considered in a later section (5.4.1).

5.2.3.2 Routes to α-alkylated ketones: 'specific enolates'

The self-condensation problem encountered in the alkylation of aldehydes may also arise in connection with alkylation of ketones, although in the latter case it is considerably less important. If contact of the ketone with strong base is the only problem, it may be overcome by protection of the carbonyl group, either as an imine [cf. reaction (5.17)] or as an enamine (section 5.4.1). However, the main problem associated with ketone alkylation is that of **regiospecificity**. We have already shown (section 5.2.1) that unsymmetrical ketones which can be deprotonated at

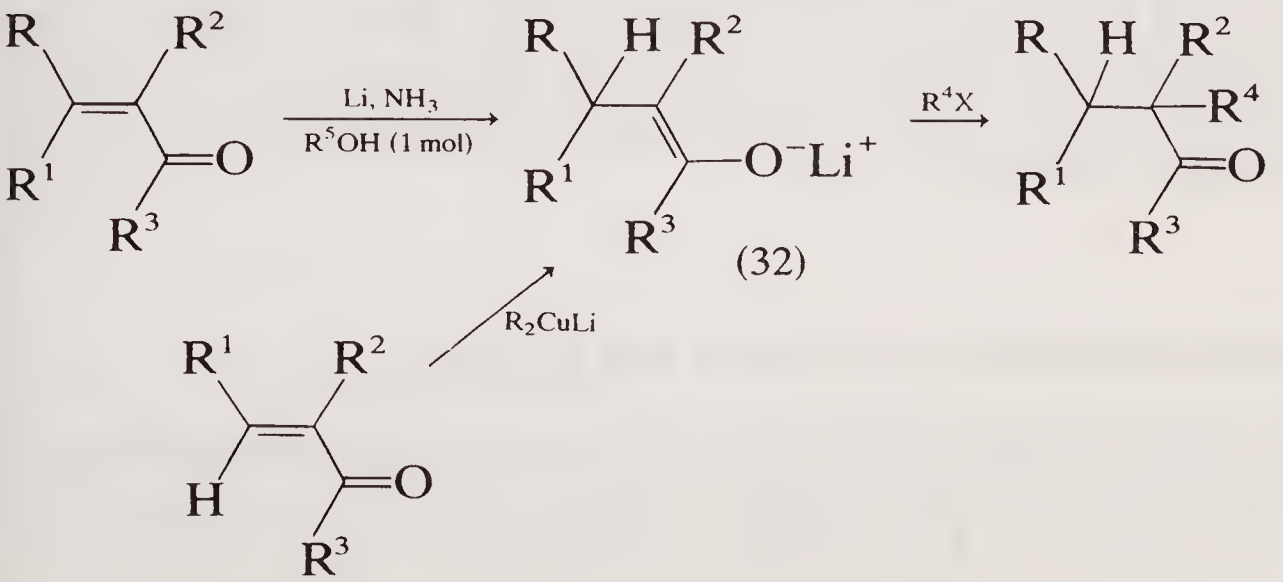
either α-carbon frequently give a mixture of alkyl derivatives, and unless the mixture of isomers is (fortuitously) easy to separate, the synthetic value of the procedure is, to say the least, doubtful. The formation of only one of the carbanions (a '**specific enolate**', as it is often called) from such ketones is thus of considerable importance, since *C*-alkylation of such a carbanion yields a single product.

If direct deprotonation of the ketone, under kinetically or thermodynamically controlled conditions, does not yield the required specific enolate, several other approaches are possible. For example, the ketone may be converted into a β-keto-aldehyde (a Claisen acylation: section 5.2.2) and the latter may then be alkylated at the γ-position [cf. reaction (5.3)] by the action of two moles of strong base and one of alkylating agent. For example,

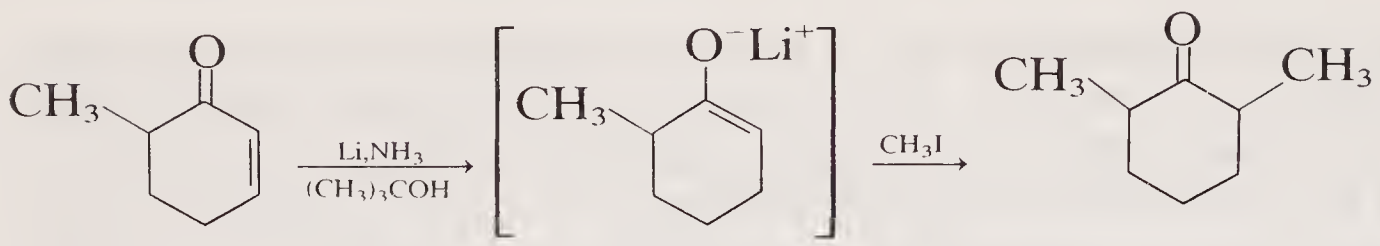


(ca. 50 % overall)

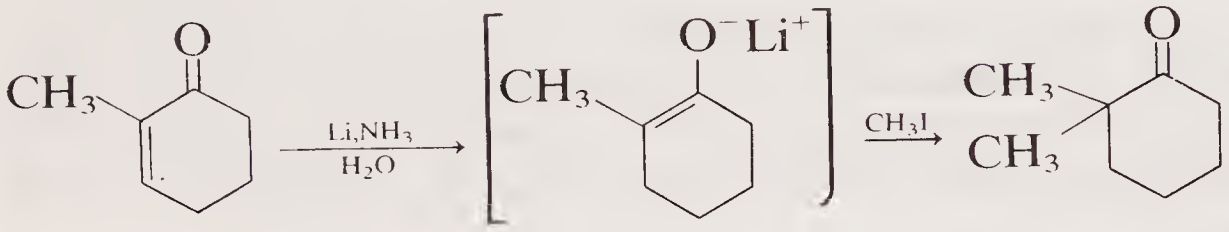
Otherwise, a β-keto-ester may be used as starting material in place of the ketone; this may then be alkylated at either the α- or γ-carbon, according to the conditions [reactions (5.3a), (5.5), and (5.5a)]. Hydrolysis and decarboxylation then yield the desired alkylated ketone. Yet another route employs an α,β-unsaturated ketone as starting material; this when subjected to dissolving metal reduction (section 8.7) yields the specific enolate (32) which may then undergo alkylation [reaction (5.21)]. Alternatively (32) may be generated by conjugate addition (e.g. of a cuprate: cf. section 4.3.2.iii) to the appropriate enone. For example,



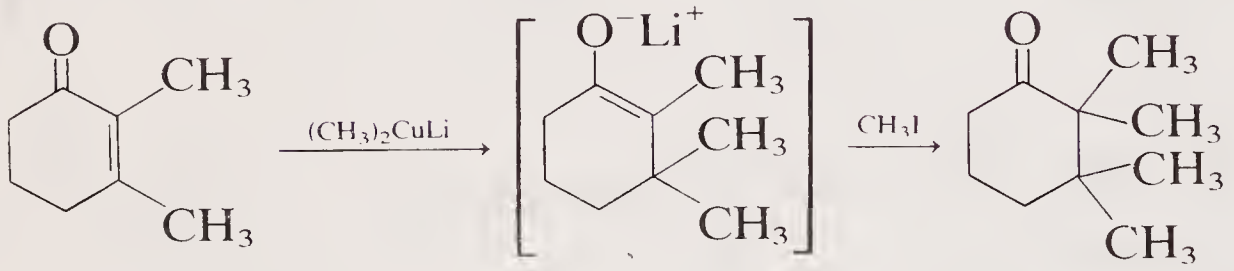
(5.21)



(37 %; no 2,2-dimethyl isomer)



(60 %; no 2,6-dimethyl isomer)



(86 %)

The regiospecificity of alkylations *via* enamines and enol trimethylsilyl ethers will be considered in later sections (5.4.1 and 13.3.4, respectively).

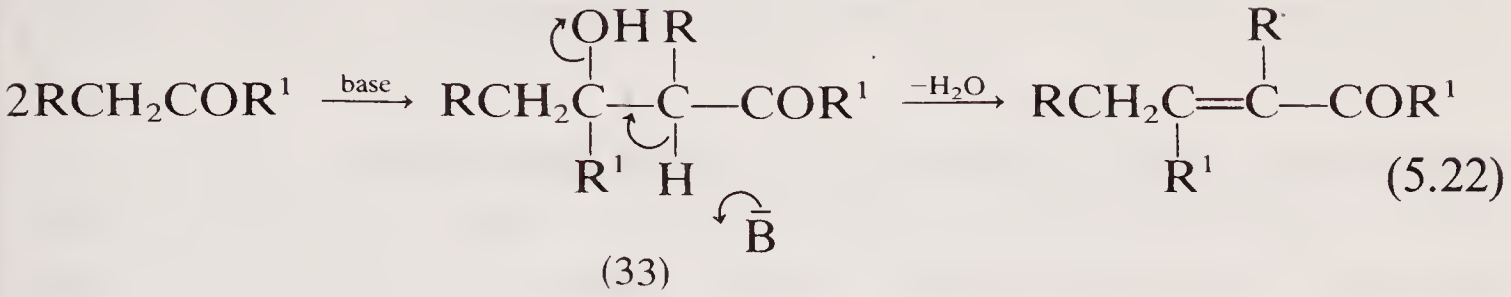
5.2.4 Condensation reactions[2]

The essential features of condensation reactions have already been set out in sections 3.3.2 and 5.1.4. It will be recalled that it is not necessary (although it may be desirable) to use a stoicheiometric quantity of base, or to use a very strong base; an equilibrium concentration of the carbanion is all that is required. It will also be recalled that in a system containing more than one carbanion source and more than one carbonyl group, the reaction occurs between the most stabilised carbanion and the most electrophilic carbonyl group.

5.2.4.1 Self-condensation of aldehydes and ketones

Most readers will already be familiar with the **aldol condensation**, in which two molecules of an aldehyde or ketone interact in presence of base (or acid: cf. section 5.4.3) to give an α,β-unsaturated aldehyde or

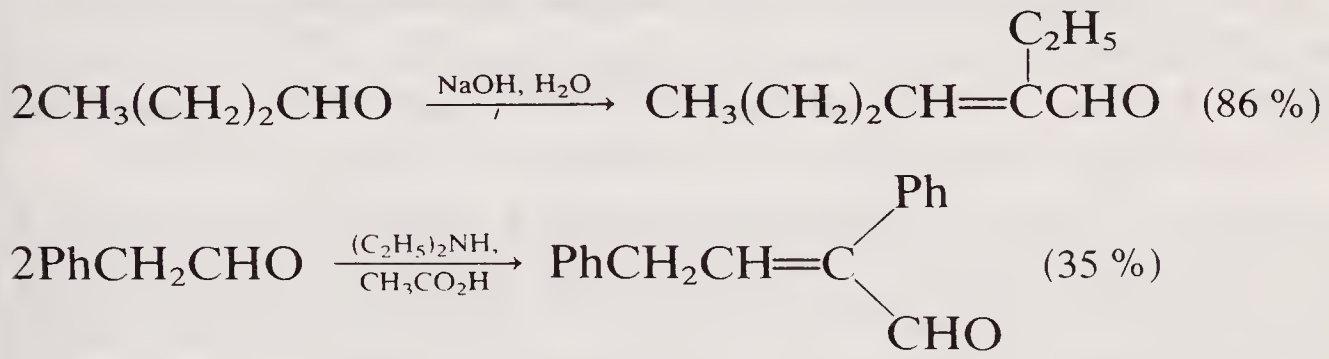
ketone [reaction (5.22)]:

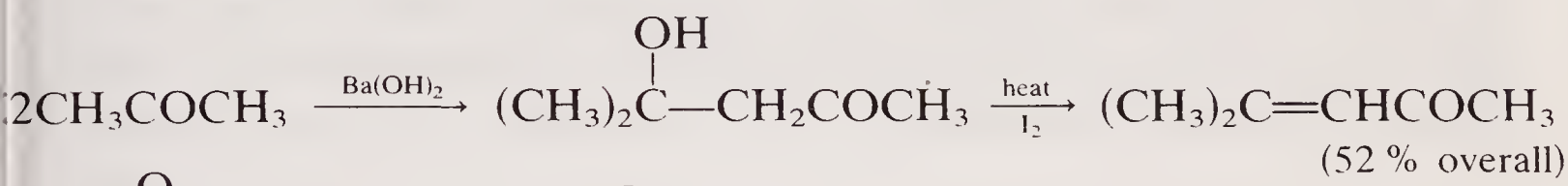


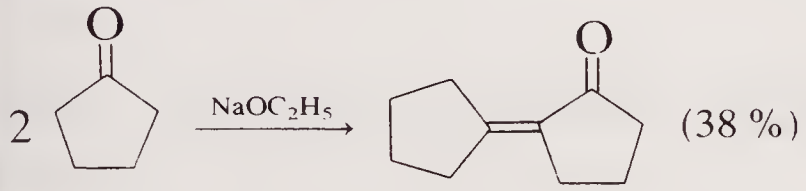
(33) (5.22)

Sometimes it is possible to isolate the intermediate addition product (33) in these reactions, and indeed it was the formation of $CH_3CH(OH)CH_2CHO$ (which is both *ald*ehyde and alcoh*ol*) from acetaldehyde which led to the first use of the term 'aldol condensation'. By our definition, however, the formation of aldols must be described as an addition, and the term **condensation** is reserved for addition *followed by loss of water.*

Some examples of self-condensation are given below:







Although a few of these reactions proceed in good yield, the majority do not. The products are prone to further reaction with the carbanion, or may themselves be deprotonated to form other carbanions, which in turn undergo further reactions. So in general, these processes lead to complex mixtures of products, and they are thus of little value in laboratory synthesis.

5.2.4.2 Mixed condensations

It follows from the previous section that attempts to condense two different aldehydes or ketones together may result in even more complex product mixtures. If both of the compounds can furnish carbanions

equally readily, and if both contain carbonyl groups of comparable reactivity, four condensation products result: two from self-condensations, e.g. (34) and (35), and two from mixed condensations, e.g. (36) and (37):

$$RCH_2CHO + R^1CH_2CHO \xrightarrow{\text{base}} RCH_2CH{=}\underset{\displaystyle R}{\overset{|}{C}}CHO$$

(34)

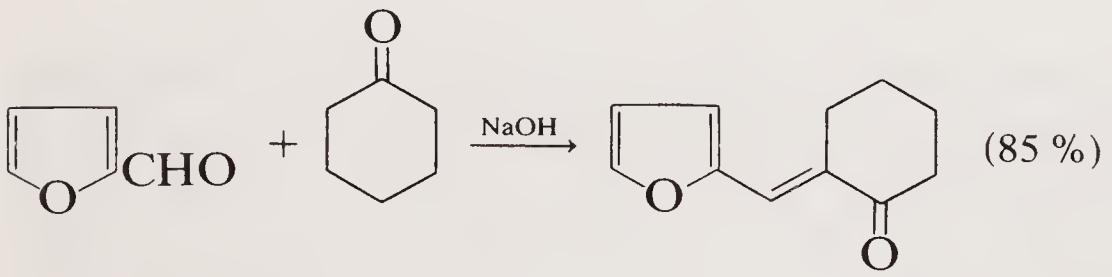
$$+ R^1CH_2CH{=}\underset{\displaystyle R^1}{\overset{|}{C}}CHO + RCH_2CH{=}\underset{\displaystyle R^1}{\overset{|}{C}}CHO + R^1CH_2CH{=}\underset{\displaystyle R}{\overset{|}{C}}CHO$$

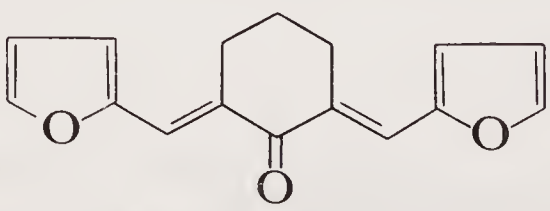
(35) (36) (37)

Mixed condensations are of synthetic value only if they lead to a single product (or, at least, to a mixture containing a preponderance of one product). This is most simply achieved when **one of the reactants contains the most acidic hydrogen and the other contains the most electrophilic carbonyl group**. It should be borne in mind that the order of electrophilicity is aldehyde > ketone > ester, and alkyl-CO— > aryl-CO—; also that acidity of α-hydrogens decreases from aldehyde to ketone to ester.

The problem of mixed condensations is also simplified, of course, if one of the reactants contains no acidic hydrogen. Aromatic (and heteroaromatic) aldehydes, which combine lack of an α-hydrogen with a highly electrophilic carbonyl group, are thus particularly useful as components of mixed condensations,[7] especially when the carbanion source is not also an aldehyde; for example,

$$PhCHO + CH_3COC(CH_3)_3 \xrightarrow[C_2H_5OH,\ H_2O]{NaOH,} PhCH{=}CHCOC(CH_3)_3 \quad (88\ \%)$$

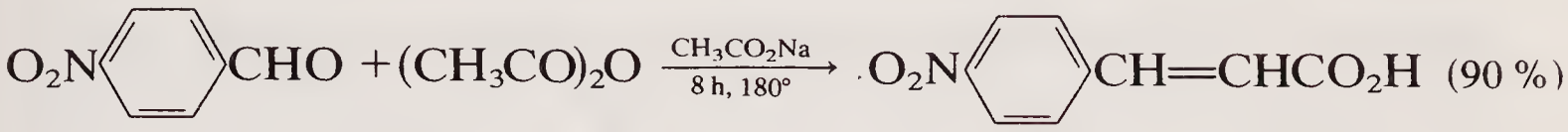




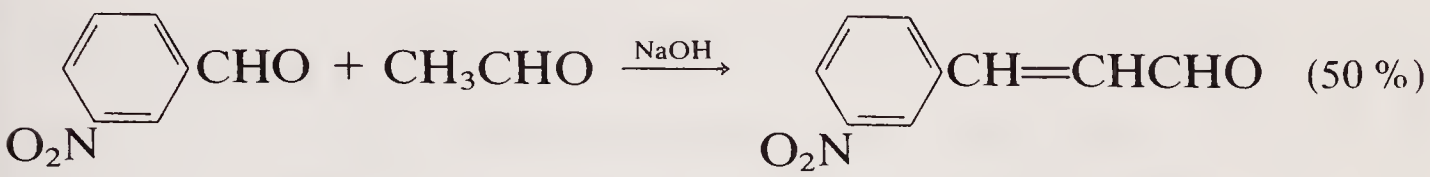
(depending on proportions of reactants)

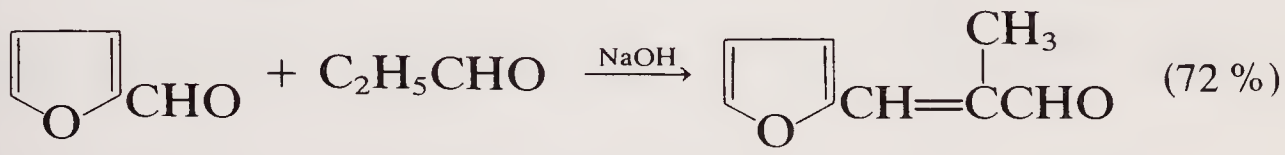
$$PhCHO + CH_3CO_2C_2H_5 \xrightarrow{NaOC_2H_5} PhCH{=}CHCO_2C_2H_5 \quad (68\ \%)$$

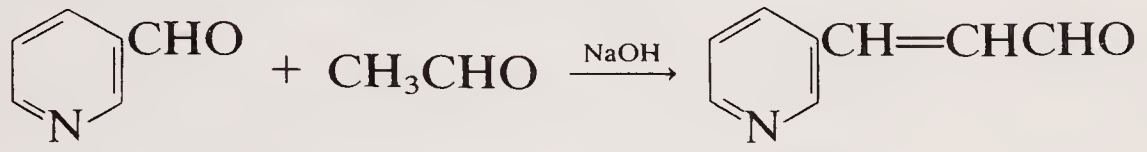
$$PhCHO + CH_3NO_2 \xrightarrow{NaOH} PhCH{=}CHNO_2 \quad (80\,\%)$$



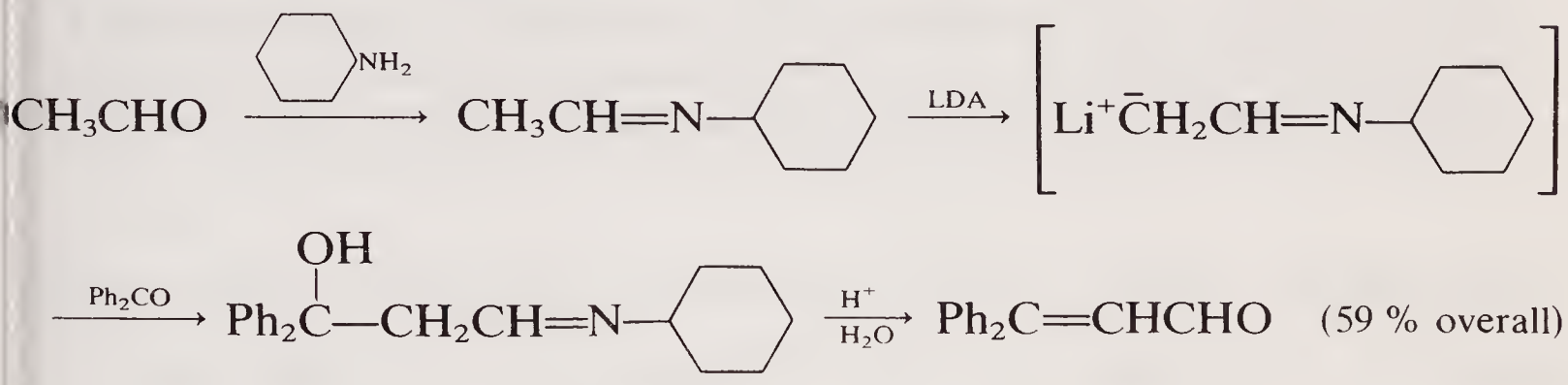
Even with other aldehydes as carbanion sources, moderate to good yields of the mixed condensation products may be obtained in some cases (cf. below). In other cases, however, self-condensation of the other aldehyde is the principal reaction:

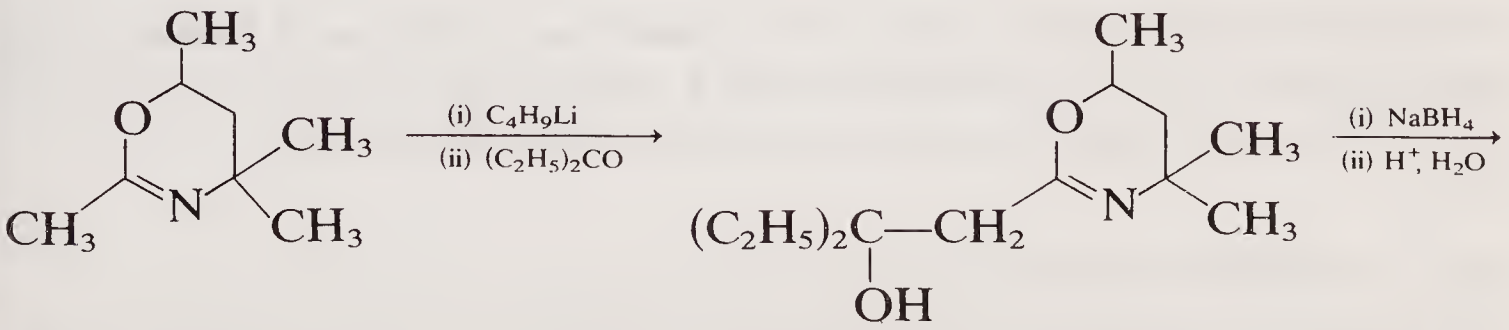




but 

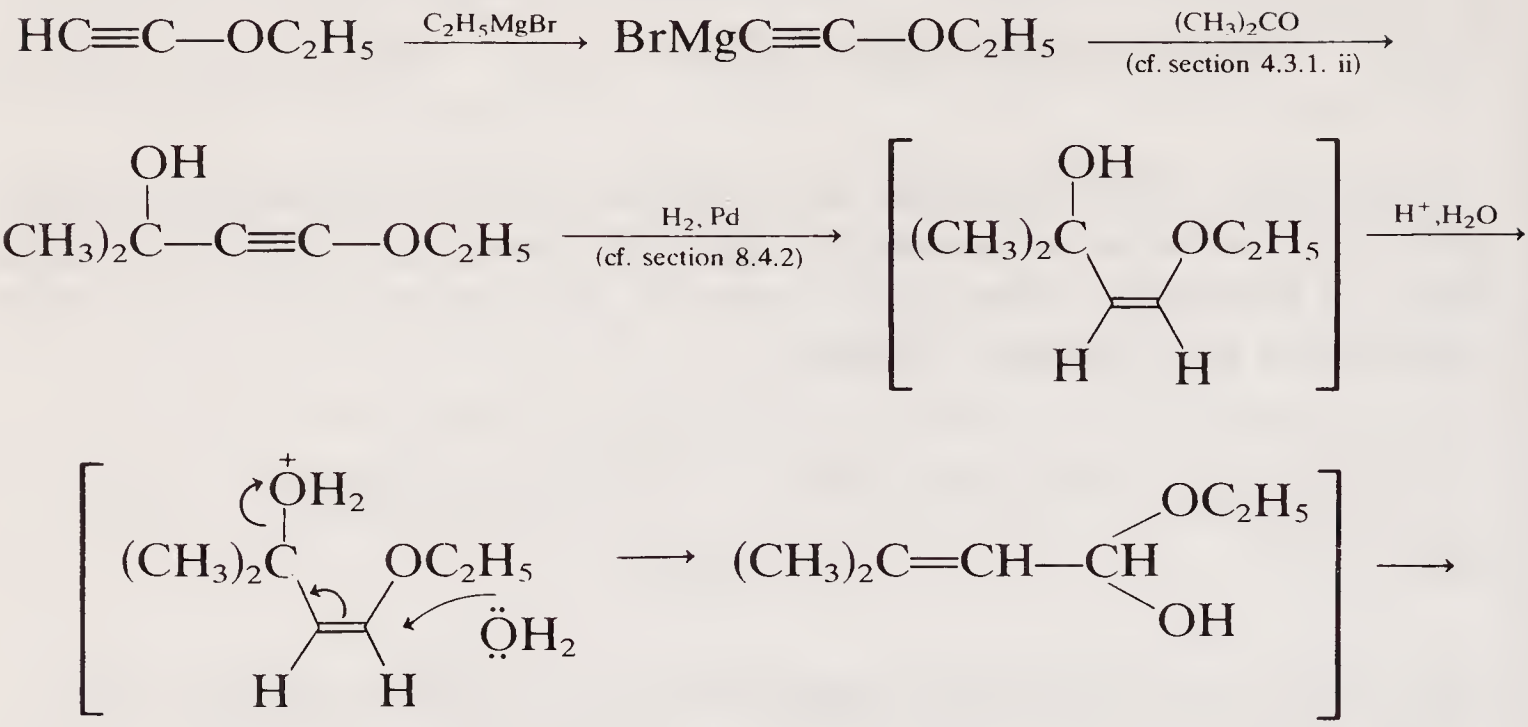
As a rule, however, aldehyde-derived carbanions do not react with ketonic carbonyl groups, but rather with unionised aldehyde to give self-condensation products. Products of the type $R_2C{=}CHCHO$ or $R_2C{=}C(R^1)CHO$ must therefore be obtained by indirect methods. Some of the methods already described (section 5.2.3.1) for the alkylation of aldehydes may be adapted for this purpose, as the following examples show:



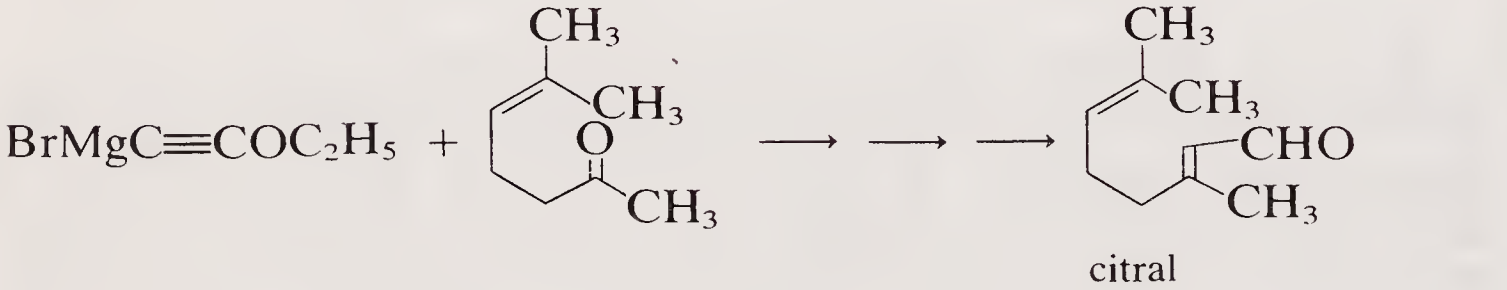


$(C_2H_5)_2C{=}CHCHO$ (62 % overall)

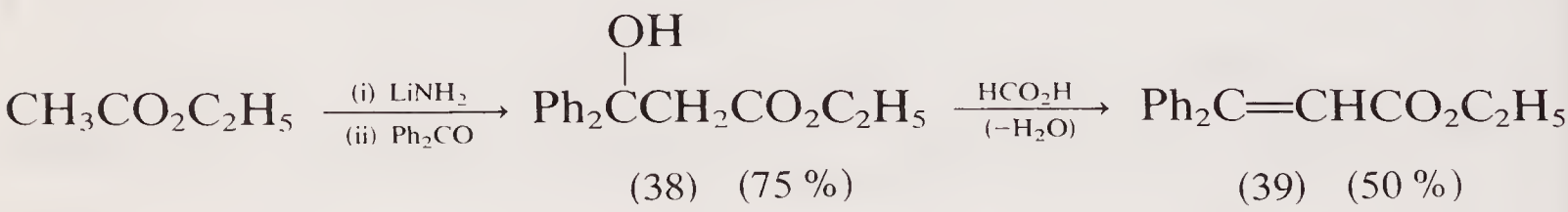
Another older method makes use of ethoxyethyne, e.g.



Similarly,



Condensations involving ester-derived carbanions and ketonic carbonyl groups may be effected by pre-forming the carbanion using a molar equivalent of strong base, but in these cases the primary product is usually the adduct, e.g. (38), and the elimination requires a separate step:

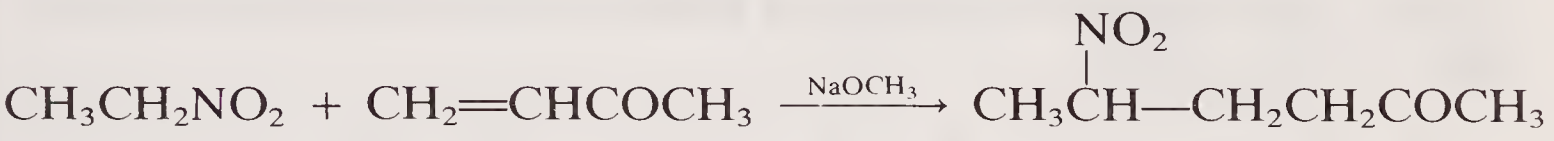


Compounds such as (38) and (39) are more easily obtained, however, by other methods: (38) by the Reformatsky reaction (section 4.2.2.i) and (39) by a Wittig or related reaction (sections 5.3.1.2 and 12.2).

5.2.5 Michael reactions

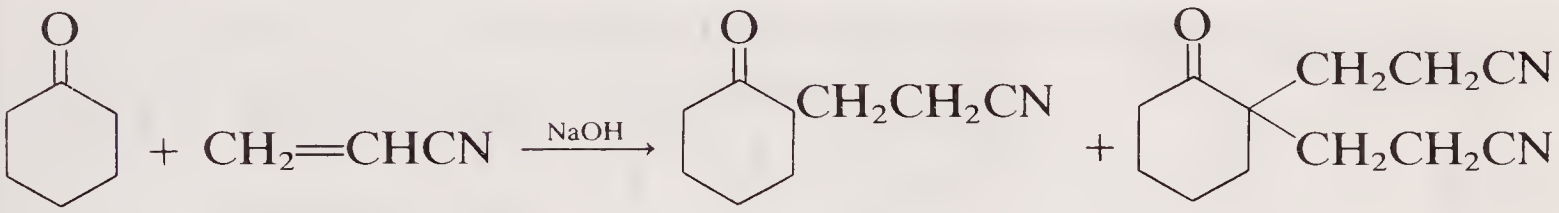
In principle, conjugate addition to $>C{=}C{-}C{=}O$ and related systems should be a characteristic of carbanions with one stabilising $-M$ group,

just as it is of their doubly stabilised analogues (section 5.1.5). In practice, however, relatively few examples are recorded of this type of Michael reaction. The only exceptions are those in which the carbanion is derived from a nitroalkane (and is therefore produced under relatively mild conditions), and those in which the electrophile is acrylonitrile, $CH_2{=}CHCN$ (which is not only highly reactive and sterically unhindered, but which affords little opportunity for side-reactions). The following examples are typical:



(51 %)

(75 %)

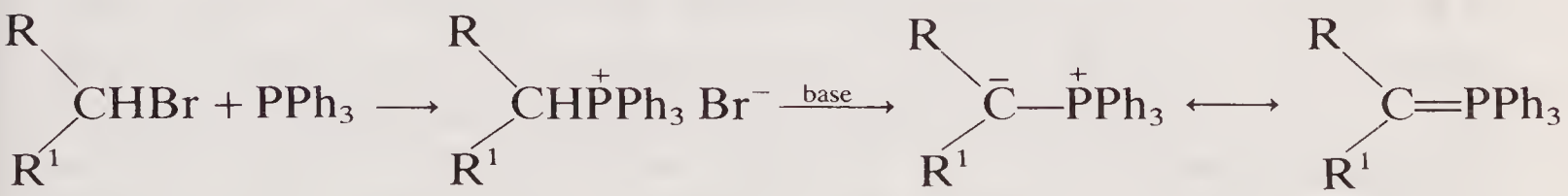


(20 %) (40 %)

5.3 Carbanions stabilised by neighbouring phosphorus or sulphur

5.3.1 The Wittig reaction

Although the uses of organophosphorus compounds are not considered in detail until Chapter 12, there is one aspect of their chemistry which belongs to the present chapter. This concerns the formation of carbanions by deprotonation of alkyltriphenylphosphonium salts [reaction (5.23a)].



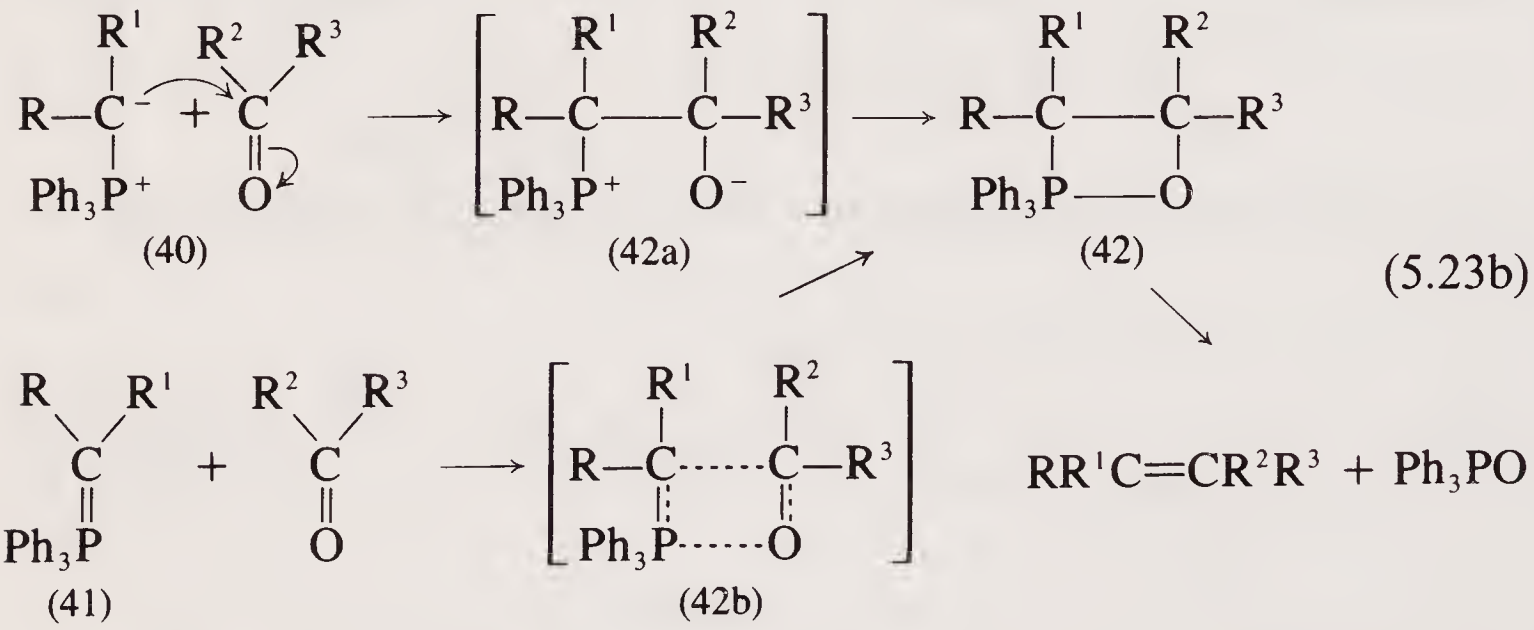
(40) (41)

(5.23a)

In the products, the negative charge on carbon is balanced by the positive charge on the adjacent phosphorus, and such zwitterions (40) are usually known as **ylides** (or ylids). The alternative **phosphorane** struc-

ture (41) implies mesomeric stabilisation of the carbanion by the phosphorus, but as already noted (section 3.4.2.ii) the extent of such stabilisation is not of major concern in this book. The ylides react as strong nucleophiles, undergoing *C*-alkylation and *C*-acylation with the normal range of reagents.

By far the most important reaction of phosphonium ylides, however, is their reaction with aldehydes and ketones (the **Wittig reaction**) to give alkenes and triphenylphosphine oxide [reaction (5.23b)]. This is an extremely valuable general synthesis of alkenes, and so it is worth considering in further detail.

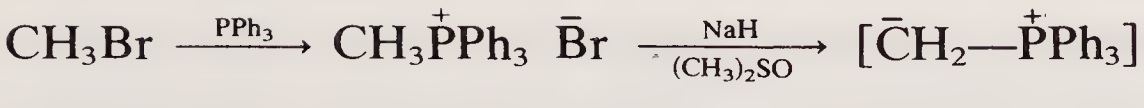


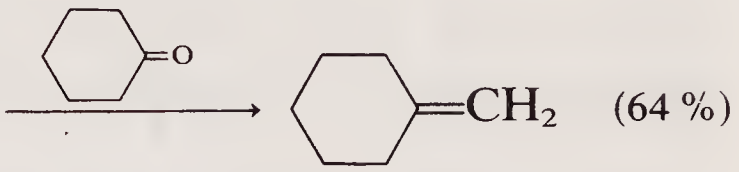
(5.23b)

Traditionally, the Wittig reaction has been depicted mechanistically in terms of nucleophilic addition to the aldehyde or ketone, giving the zwitterion (42a); cyclisation of the latter to the oxaphosphetan (42); and a final elimination of triphenylphosphine oxide. There is an increasing body of evidence which suggests, however, that (in certain cases at least) an *intermediate* (42a) may not be involved, and that the formation of the oxaphosphetan is best represented as a *cycloaddition* (cf. section 7.2) involving a *transition state* such as (42b).

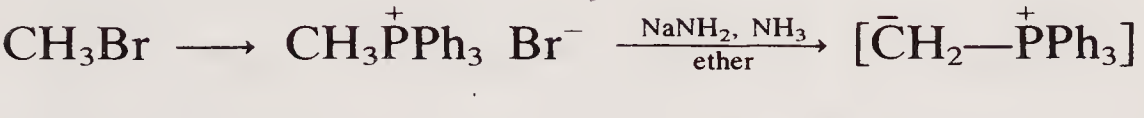
5.3.1.1 Non-stabilised ylides

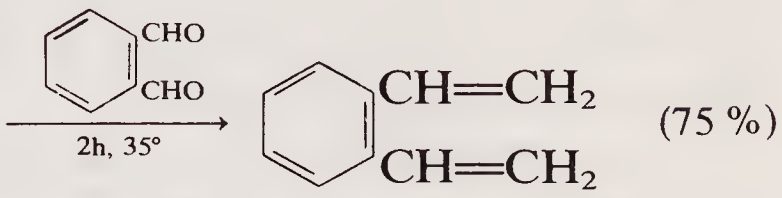
If R and R^1 in the original alkyl halide are hydrogen or simple alkyl groups, the α-hydrogen of the phosphonium salt is very weakly acidic, and a very strong base (usually butyl-lithium or phenyl-lithium) is required to produce the ylide. The ylide, once formed, is a highly reactive compound and is not generally isolable; it is not only strongly basic (deprotonating acids as weak as water), it is strongly nucleophilic in the manner of a Grignard reagent, and reacts rapidly, under mild conditions, to give the adduct (42) effectively irreversibly. This then decomposes spontaneously to give the alkene. If stereoisomerism in the product is possible, a mixture of *E*- and *Z*-isomers is generally obtained. For example,



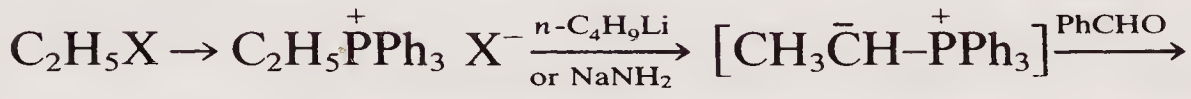


(64 %)





(75 %)

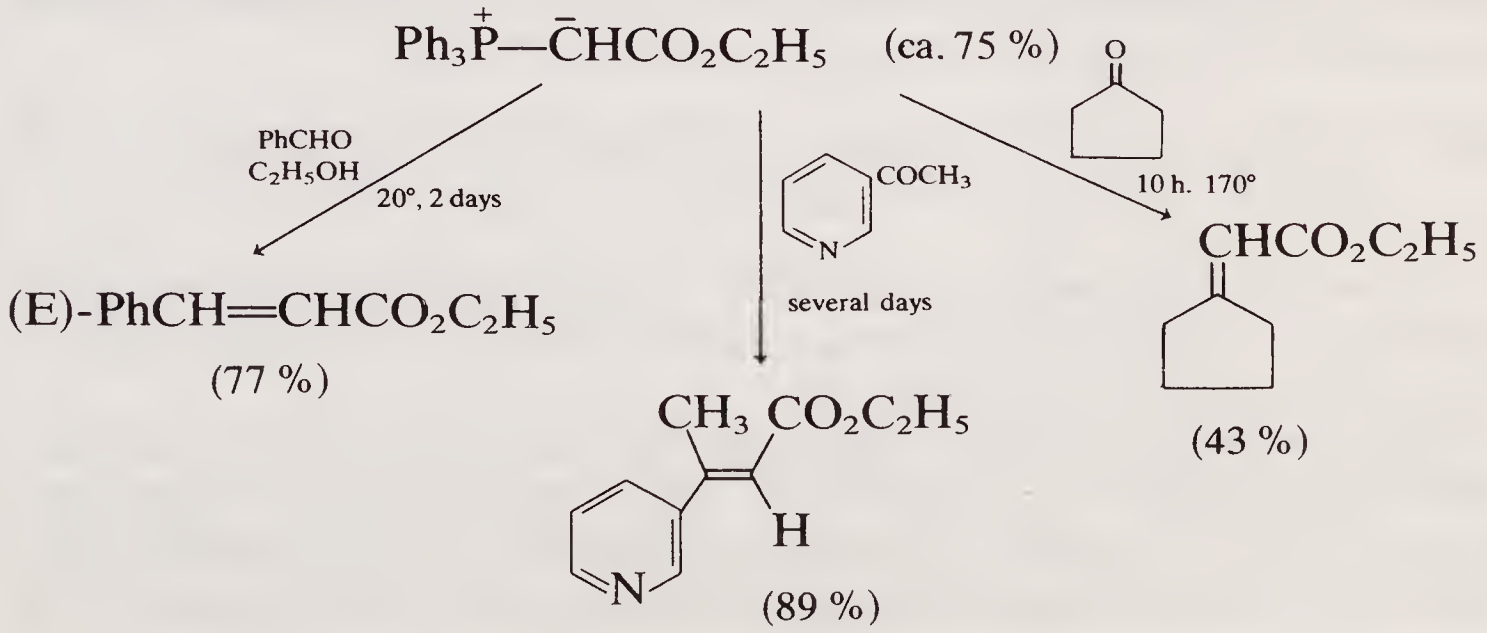


(68–98 %)

[The isomer ratio obtained in this last reaction depends on the nature of X, and of the base used (cf. section 5.3.1.3).]

5.3.1.2 Stabilised ylides

If R^1 in reaction (5.23a) is a $-M$ group (e.g. an ester), deprotonation of the phosphonium salt is achieved under much less strongly basic conditions, and the resulting ylide (40) [or phosphorane, (41)] is often sufficiently stable to be isolated. It is also sufficiently stable that it may react *reversibly* with carbonyl groups, and may not react at all readily with feebly electrophilic carbonyl groups. Where *E*- and *Z*-isomers of the final product can exist, it is the *E*-isomer which usually predominates. For example,



5.3.1.3 Steric control in the Wittig reaction

It has already been noted that some Wittig reactions involving non-stabilised ylides are not highly stereoselective, and that where the alkene structure permits it, both *E*- and *Z*-isomers are obtained. Such lack of stereoselectivity, of course, limits the synthetic usefulness of the reaction. Other Wittig reactions, however, are highly stereoselective; mention was made above of the preponderance of *E*-alkenes from stabilised ylides, and there are also circumstances in which the reactions of non-stabilised ylides can be equally selective.

If a non-stabilised ylide can be obtained [reaction (5.23a)] in a solution *free from inorganic* (*especially lithium*) *salts* (e.g. by using sodamide as the base, and filtering off the sodium halide), its reaction with an aldehyde usually gives the *Z*-alkene as the major product, e.g.

$$C_2H_5\overset{+}{P}Ph_3\ Br^- \xrightarrow{NaNH_2} [CH_3\bar{C}H{-}\overset{+}{P}Ph_3] \xrightarrow{PhCHO} \underset{(98\ \%;\ E:Z = 13:87)}{PhCH{=}CHCH_3}$$

Similarly,

$$n\text{-}C_3H_7\overset{+}{P}Ph_3\ Br^- \xrightarrow[(ii)\ n\text{-}C_3H_7CHO]{(i)\ NaNH_2} \underset{(49\ \%;\ E:\ Z = 5:95)}{n\text{-}C_3H_7CH{=}CHC_2H_5}$$

If these same reactions are carried out in presence of a lithium halide (e.g. by using an alkyl- or aryl-lithium as the base), the Wittig reaction is much less stereoselective; moreover, the *E*:*Z* ratio may vary as the halide is changed from chloride to bromide to iodide, and it may also be solvent-dependent. The mechanistic subtleties of these reactions are discussed more fully elsewhere;[8] it is, nevertheless, worthwhile to focus further attention on the reactions giving high stereoselectivity.

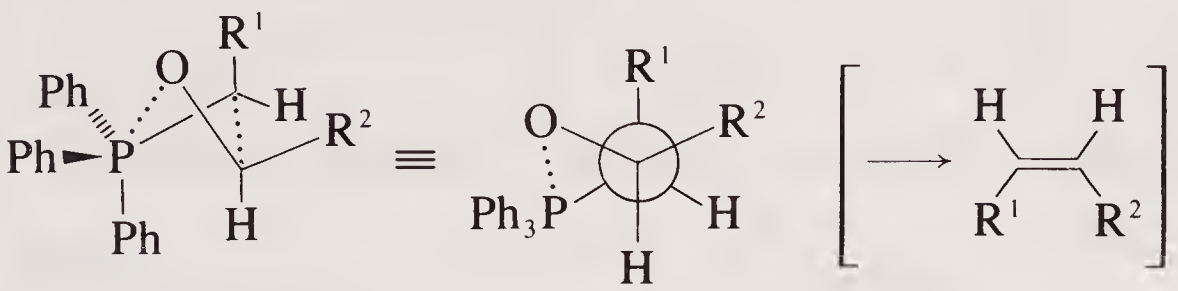
The 'salt-free' Wittig reactions have recently been subjected to considerable mechanistic scrutiny.[8b] These processes occur under kinetic control (Sykes, p. 42), so that the relative stabilities of the *E*- and *Z*-alkenes are unimportant; indeed, the proportion of *Z*-isomer actually *increases* if the aldehyde contains α-substituents, e.g.

$$Ph_3\overset{+}{P}{-}\bar{C}HCH_3 + PhCH_2CR_2CHO \longrightarrow \underset{\text{When R = H, } E:Z = 6:94\text{; when R = } CH_3,\ E:Z < 1:99}{PhCH_2CR_2CH{=}CHCH_3}$$

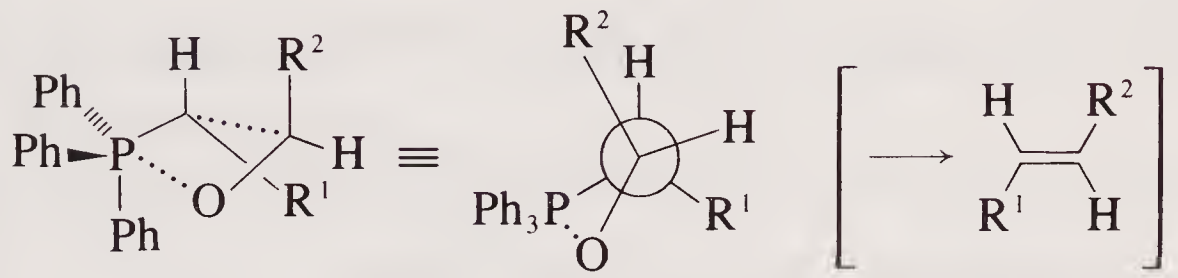
Moreover, replacement of one of the *P*-phenyl groups by, for example, isopropyl, can profoundly alter the stereoselectivity of the above reaction (when R = H, *E*:*Z* is now 82:18).

These 'salt-free' Wittig reactions of non-stabilised ylides are best represented in terms of the cycloaddition mechanism [(41) → (42b) → (42) → product in reaction (5.23b)]. In this mechanism, the stereochemical outcome of the reaction is determined by the

preferred spatial orientations adopted by the ylide and the aldehyde as they approach each other to form the transition state. For *Z*-alkene formation, these orientations are as in structure (43a) or (43b), whereas *E*-alkene formation involves the relative orientations shown in structures (44a) and (44b).



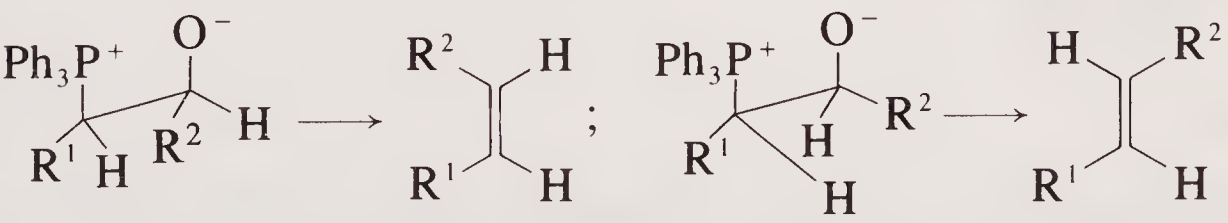
(43a) (43b)



(44a) (44b)

The puckered four-membered transition state (43) is favoured, especially if R^2 is bulky, because this group can occupy a 'pseudo-equatorial' position, and because the substituent R^1, although 'pseudo-axial', experiences no 1,3-diaxial interactions. In the alternative transition state (44), in which the four-membered ring is almost planar, there is a degree of eclipsing which is absent from (43), and there may also be an unfavourable 1,3-diaxial interaction between R^2 and one of the *P*-phenyl groups.

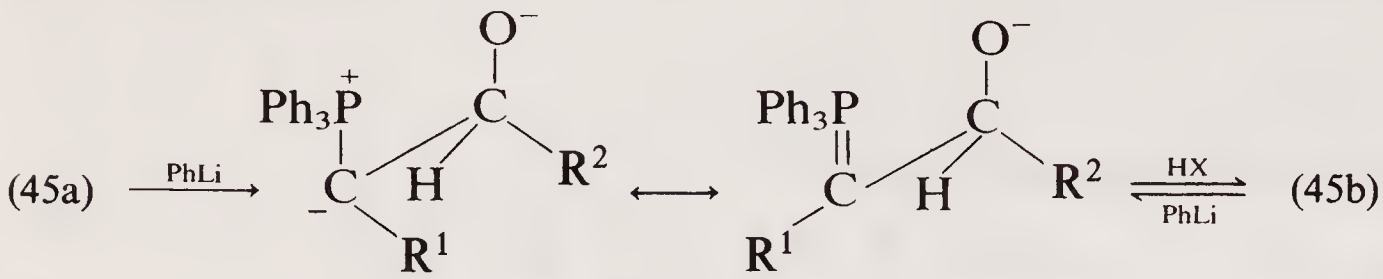
Whether or not the Wittig reactions of 'salt-free', *stabilised* ylides also follow the cycloaddition pathway remains an open question. It does appear, however, that the presence of lithium salts in the Wittig reaction, of stabilised and non-stabilised ylides alike, may favour the traditional, stepwise, mechanism at the expense of cycloaddition. By this mechanism, the primary adducts are diastereomeric zwitterions, (45a) and (45b), the former decomposing to the *Z*- and the latter to the *E*-alkene:



(45a) (45b)

Wittig reactions of non-stabilised ylides may also be modified to yield predominantly *E*-alkenes. In this modification, the ylide is prepared using phenyl-lithium, and the addition to the aldehyde is carried out at −78° so that the adducts [presumably zwitterions (45a) and (45b)] do

not undergo the elimination step. Then a second molar equivalent of phenyl-lithium is added to form the new ylide (45c), and the latter is reprotonated to give (almost exclusively) the more stable *threo*-zwitterion (45b) [reaction (5.24)]. Decomposition of this zwitterion then gives the *E*-alkene:



(5.24)

For example,

$$C_2H_5\overset{+}{P}Ph_3\ Br^- \xrightarrow{PhLi} CH_3\bar{C}H\overset{+}{P}Ph_3 \xrightarrow[(ii)\ PhLi]{(i)\ PhCHO,\ -78^\circ} \xrightarrow{(iii)\ (CH_3)_3COH} PhCH{=}CHCH_3$$

(73 %; $E:Z = 97:3$)

Similarly,

$$n\text{-}C_6H_{13}\overset{+}{P}Ph_3\ Br^- + CH_3CHO \rightarrow n\text{-}C_5H_{11}CH{=}CHCH_3$$

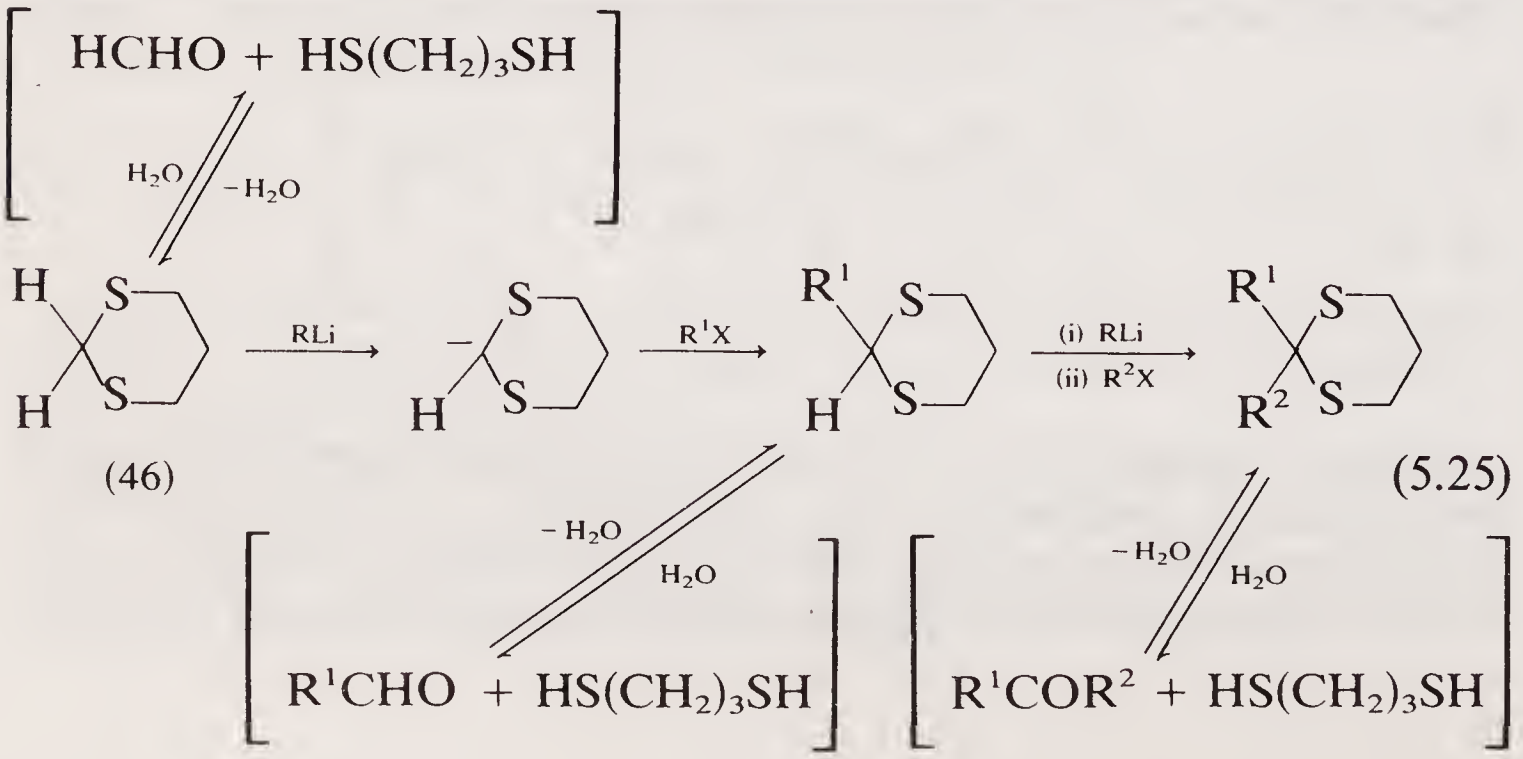
(60 %; $E:Z = 96:4$)

Other phosphorus-containing carbanions and their reactions are discussed in Chapter 12.

5.3.2 Carbanions stabilised by two sulphur atoms

The best-known and most widely used of the carbanions stabilised by divalent sulphur are those derived from 1,3-dithian (46) and its 2-alkyl derivatives. 1,3-Dithian has a pK_a value of 31, and so, although by no means a strong acid, it is converted quantitatively into its carbanion by very strong bases such as butyl-lithium.

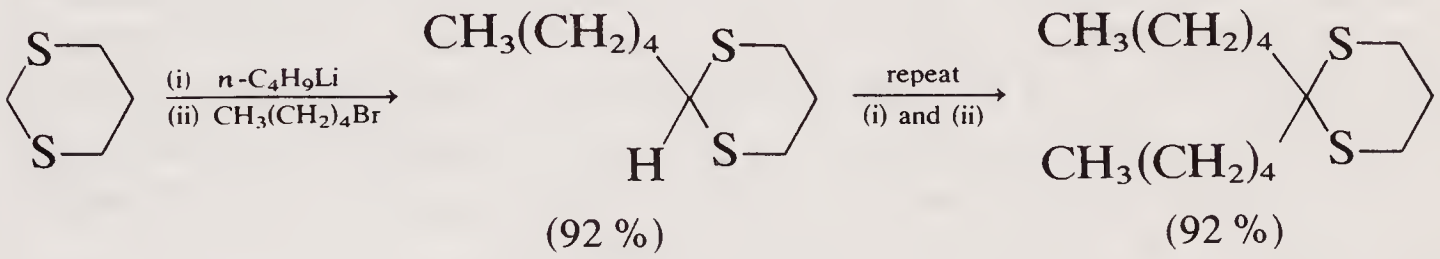
Among the reactions of these carbanions, it is alkylation which to date has proved most useful as a synthetic procedure. Mono- and di-alkylation may be carried out in a stepwise fashion [reaction (5.25)]:

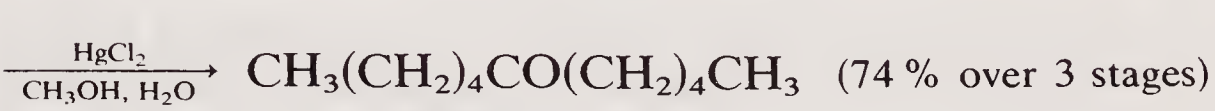


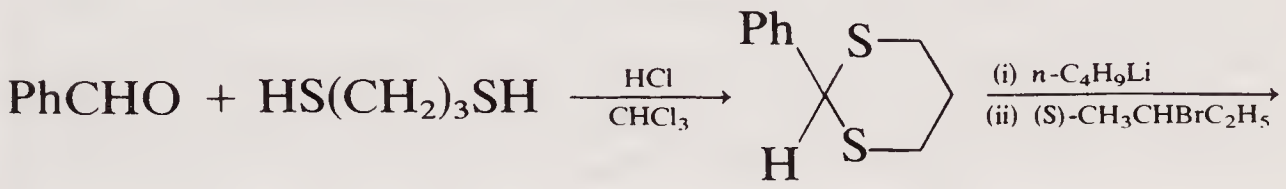
(5.25)

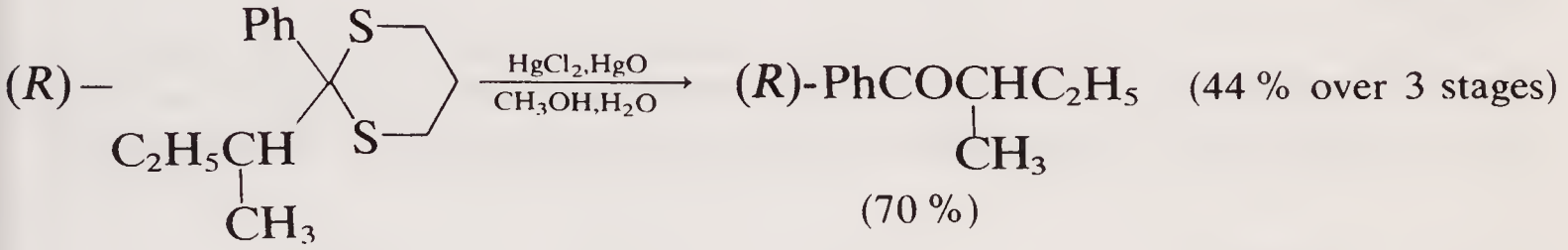
The value of this reaction lies in the fact that 1,3-dithians are dithioacetals or dithioketals, and as such are preparable from, and hydrolysable to, aldehydes or ketones. The method is therefore used to effect the **alkylation of an aldehyde on the carbonyl carbon** using an **electrophilic alkylating agent**, a process not otherwise easily accomplished. The transformation of an electrophilic carbon (>C=O) into a nucleophilic one (the deprotonated dithian), and the reverse process, are said to involve **Umpolung**.[9]

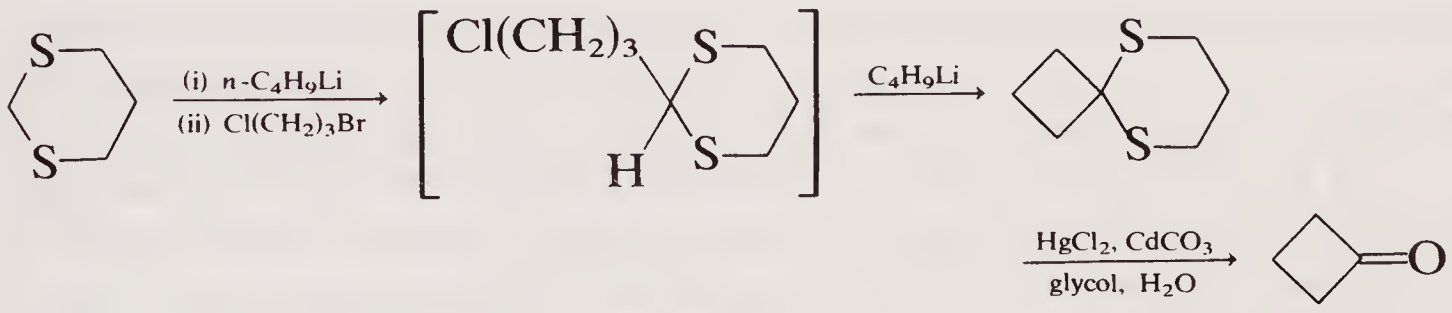
Examples of the use of 1,3-dithians include the following:



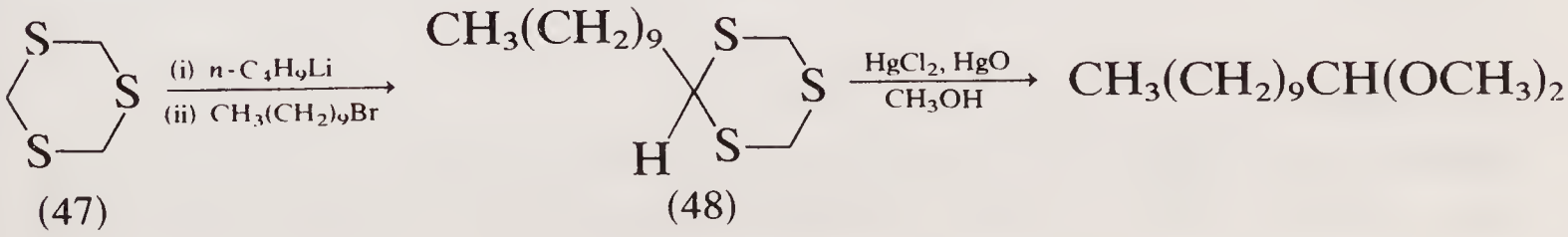








For the synthesis of aldehydes, 1,3,5-trithian (47) provides a convenient (and cheaper!) alternative to 1,3-dithian, e.g.



The trithian method cannot, however, be used to prepare ketones, since further alkylation of 2-alkyl-1,3,5-trithians [e.g. (48)] occurs at the 4-position.

5.4 Alkene, arene and heteroarene nucleophiles

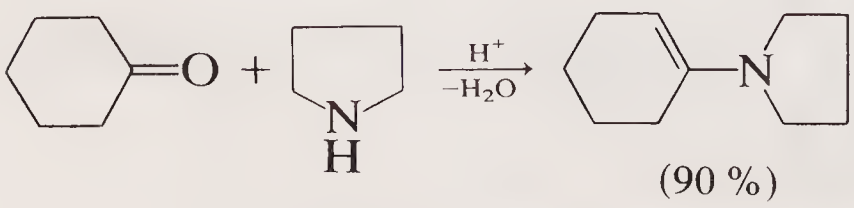
So far in this chapter we have discussed carbon–carbon bond-forming reactions in which the nucleophilic component bears a formal negative charge, i.e. is a carbanion. We now turn to consider a group of reactions in which the nucleophilic species is a neutral molecule. Simple alkenes, arenes and heteroarenes come into this category, but as we have already noted (sections 2.2, 2.4–2.6 and 3.4.3), there are relatively few synthetically useful 'laboratory' reactions (as opposed to industrial reactions) of this group which involve carbon–carbon bond formation. The Friedel–Crafts reaction, of course, is a notable exception.

We have also noted (section 3.4.3) that an electron-donating ($+M$) substituent greatly enhances the nucleophilicity of alkenes and arenes, and this 'activation' enables such compounds to react with much weaker carbon electrophiles than those involved in the Friedel–Crafts reaction (for a discussion of the latter, see Sykes, pp. 141–6). In the present section we consider the reactions of such electrophiles with enols and enamines, and their aromatic counterparts, phenols and arylamines. Comparisons are made, where appropriate, with electron-rich heteroaromatic ring systems.

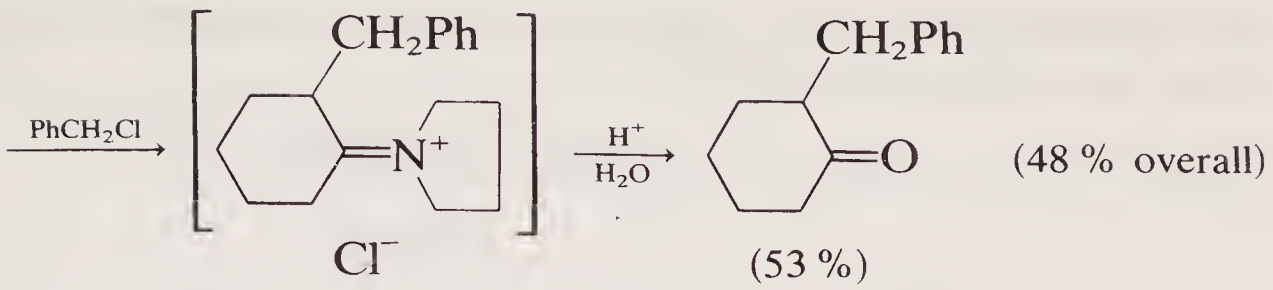
(Enols are, of course, tautomers of aldehydes and ketones, and the reactions of enols described below are more precisely described as reactions of carbonyl compounds which involve enolisation as the first step.)

5.4.1 Alkylation

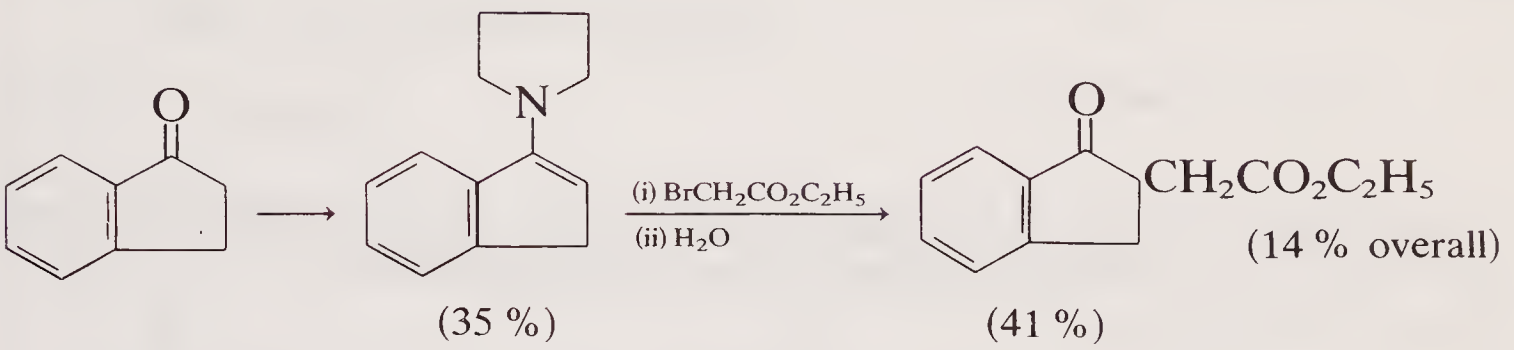
This is the least important of the C–C bond-forming reactions involving this group of nucleophiles. Alkylation of aldehydes and ketones is generally achieved *via* carbanions (*enolates*) rather than *via* enols (cf. sections 5.2.1 and 5.2.3), and alkylation of phenols, arylamines and heteroarenes generally occurs at the heteroatom rather than at carbon. The alkylation of enamines, however, is of some preparative importance, since it provides a method for the indirect α-alkylation of aldehydes and ketones in the absence of strong bases (cf. section 5.2.3). The most useful *C*-alkylations occur when a highly electrophilic alkyl halide is used (cf. the examples below); in other cases, however, *N*-alkylation may be the major reaction:



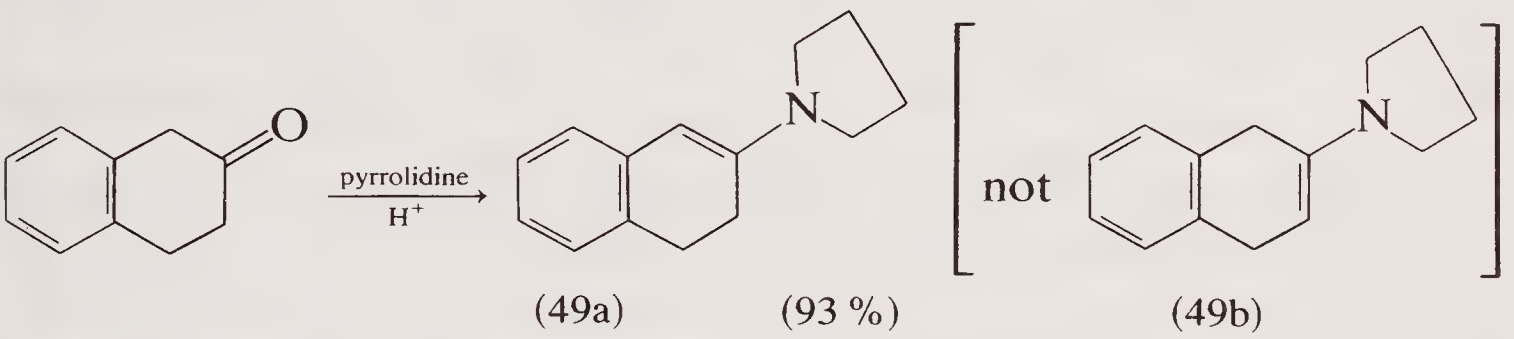
(90 %)

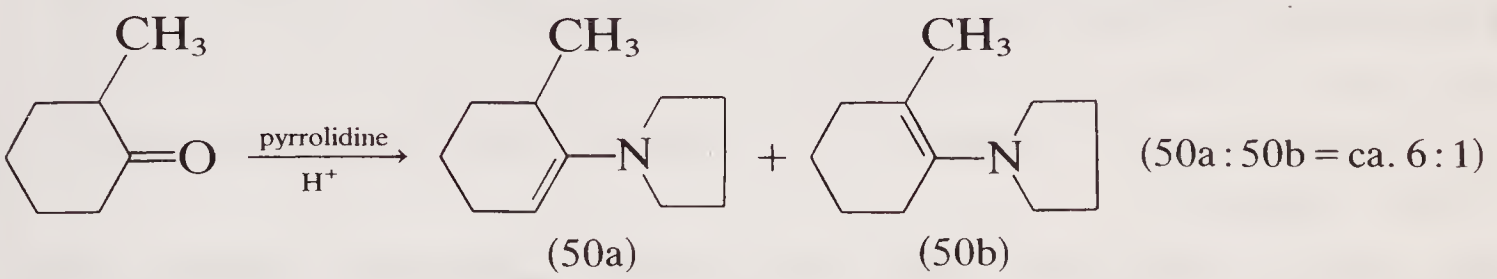


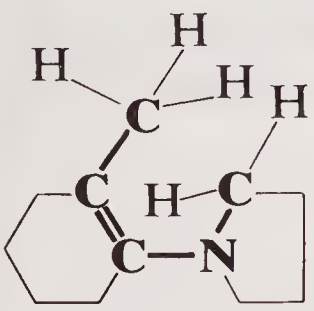
Similarly:



When an unsymmetrical ketone may give rise to two enamines, it is the more stable of the two which generally predominates. In the case of β-tetralone, the conjugated enamine (49a) is formed, apparently exclusively, at the expense of the non-conjugated isomer (49b); and in the case of 2-methylcyclohexanone the major product formed with pyrrolidine is (50a), since there is a destabilising steric repulsion in the minor isomer (50b) involving the methyl group and the α-hydrogens of the heterocyclic ring:







(the five boldface atoms are coplanar)

(50b)

α-Alkylation of aldehydes *via* enamines is of limited usefulness because of the intervention of side-reactions (*N*-alkylation of the enamine and

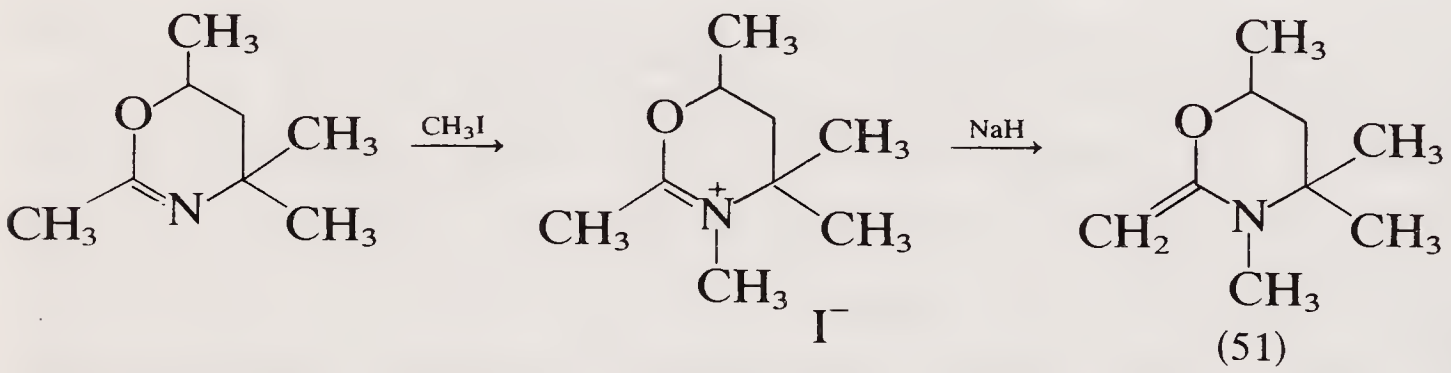
self-condensation of the aldehyde). In some instances however, alkylations have been successful, e.g.

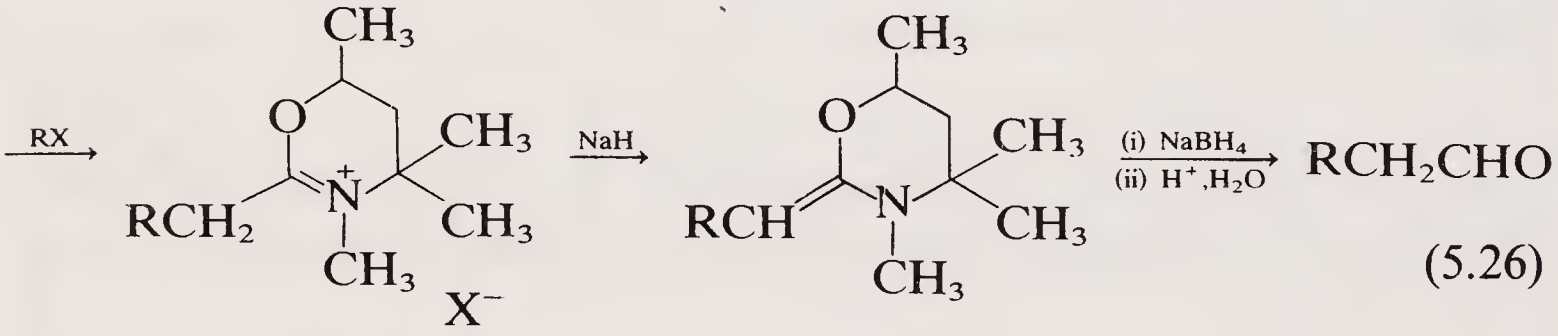
$$[CH_3CH_2CH_2CHO + n\text{-}C_4H_9NHCH_2CH(CH_3)_2 \rightarrow]$$

$$CH_3CH_2CH{=}CH{-}\underset{\displaystyle C_4H_9\text{-}n}{N}CH_2CH(CH_3)_2$$

$$\xrightarrow[\text{(ii) } H^+/H_2O]{\text{(i) } CH_3CH_2I} CH_3CH_2CH(CH_2CH_3){-}CHO \qquad (41\ \%)$$

A convenient variant of the dihydro-1,3-oxazine route to aldehydes (section 5.2.3.1) also involves an enamine intermediate (51):



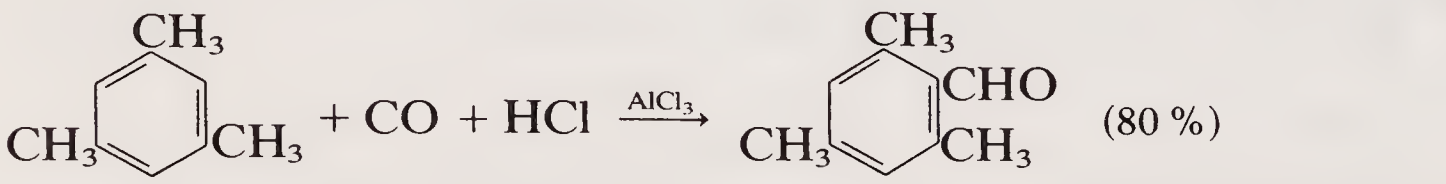


(5.26)

For example, $Ph(CH_2)_3I \xrightarrow[\text{(ii) work-up as above}]{\text{(i) (51)}} Ph(CH_2)_4CHO$ (51 %)

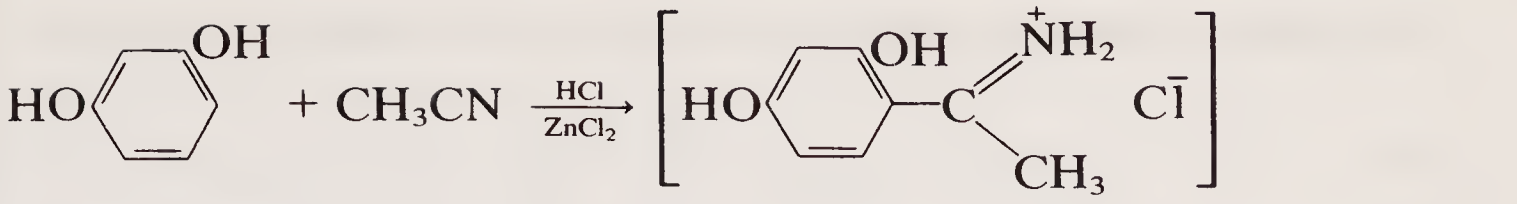
5.4.2 Acylation

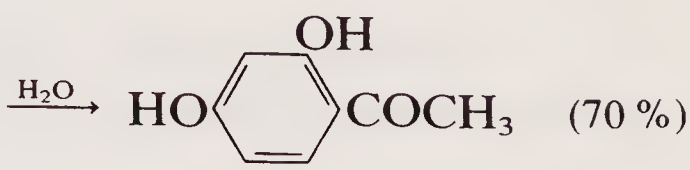
In contrast to alkylation, where the synthetic usefulness is limited, acylation of activated alkenes, arenes and heteroarenes is of considerable synthetic importance. Many of these acylations are obvious variants of the Friedel–Crafts reaction, e.g.



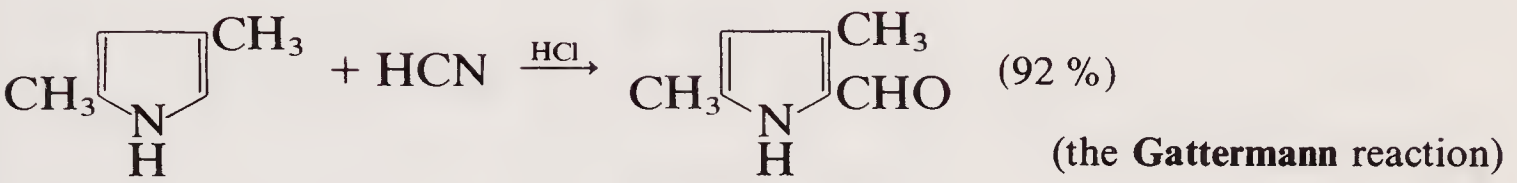
(80 %)

(the **Gattermann–Koch** reaction)

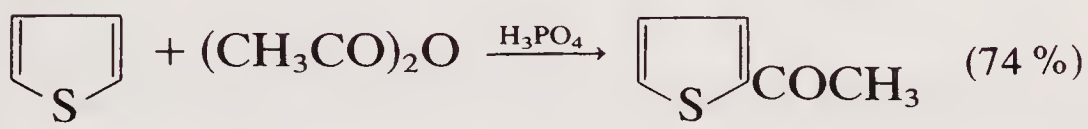


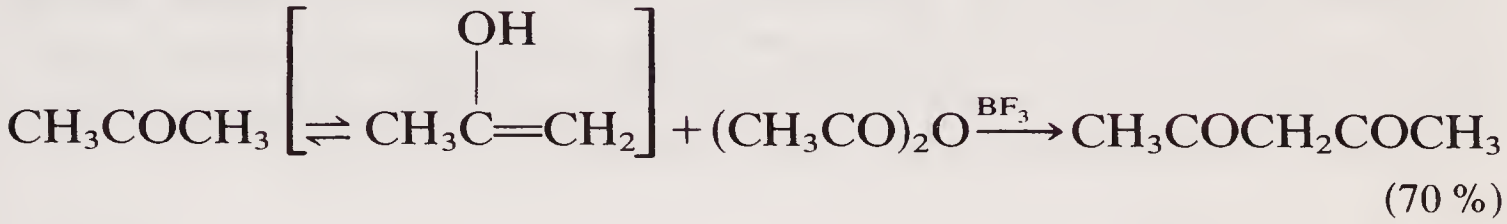


(the **Hoesch** reaction)

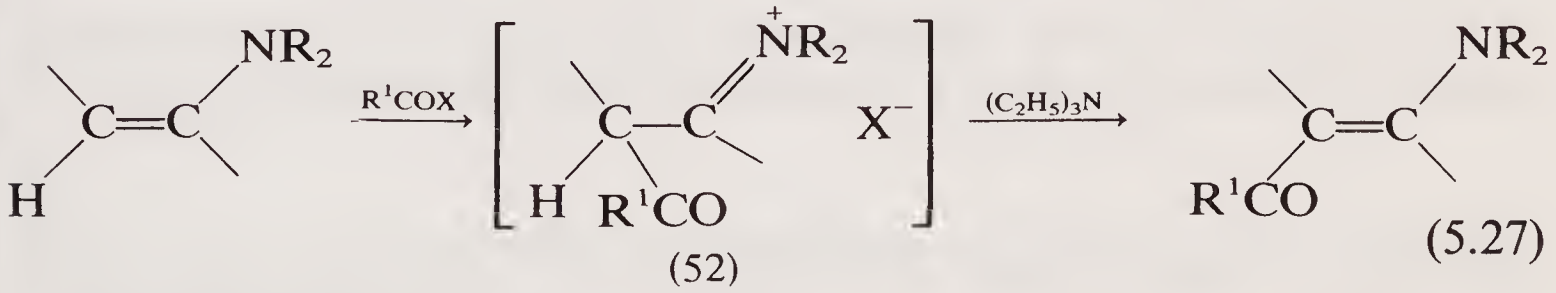


(the **Gattermann** reaction)





Acylation of enamines, like alkylation, may occur either at carbon or at nitrogen, but since the latter process is easily reversible and gives an *N*-acylammonium salt which can itself act as an acylating agent, it is usually possible to obtain high yields of *C*-acylated products. These acylations are often carried out in presence of an added base, such as triethylamine, since the initial acylation product (52) is moderately acidic and can protonate unreacted enamine in the absence of any stronger base:

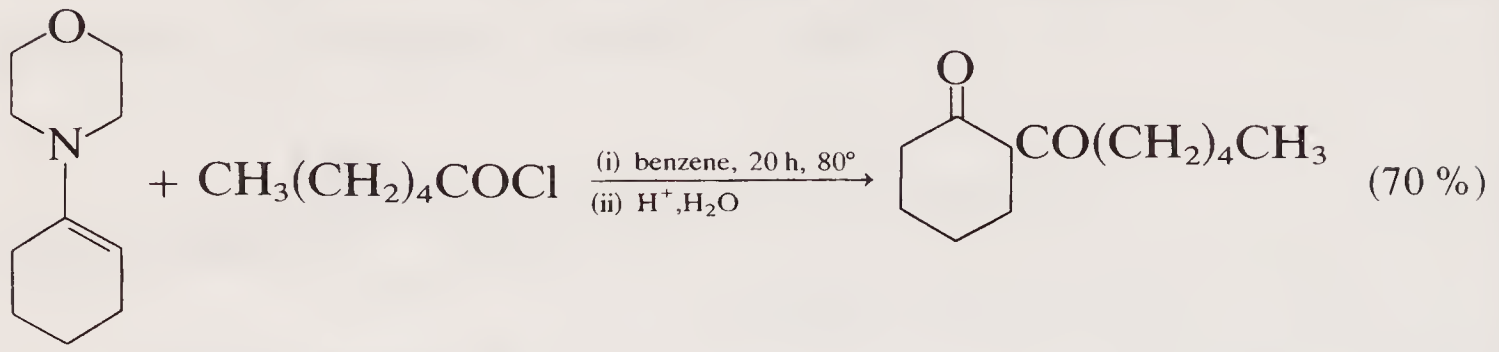


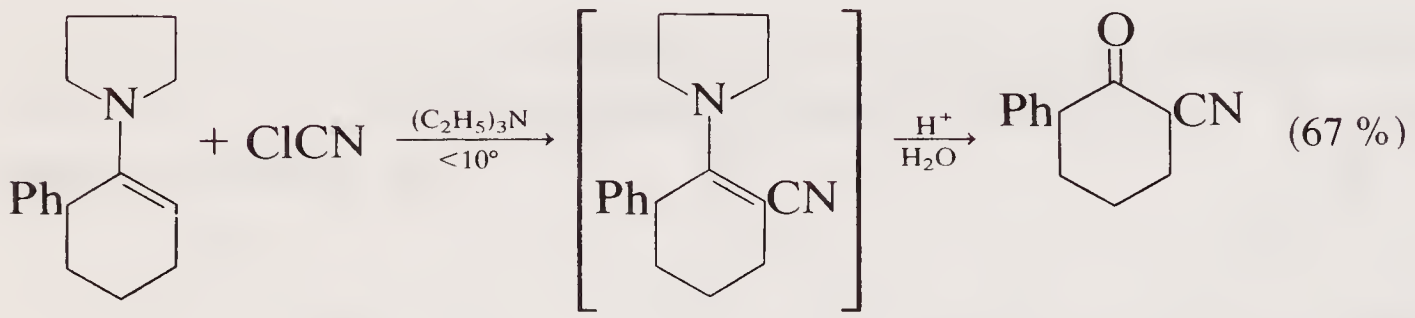
(52)

(5.27)

On the other hand, if the acylating agent contains an α-hydrogen, it may react with the added base giving a keten, which in turn undergoes cycloaddition to the enamine. In such cases, little, if any, acylation product may be obtained.

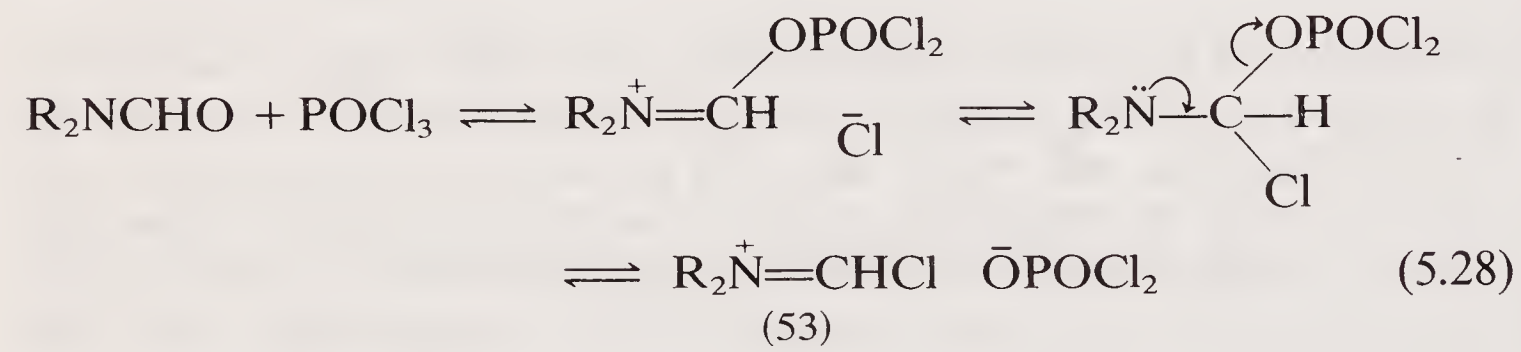
Examples of enamine acylations include the following:





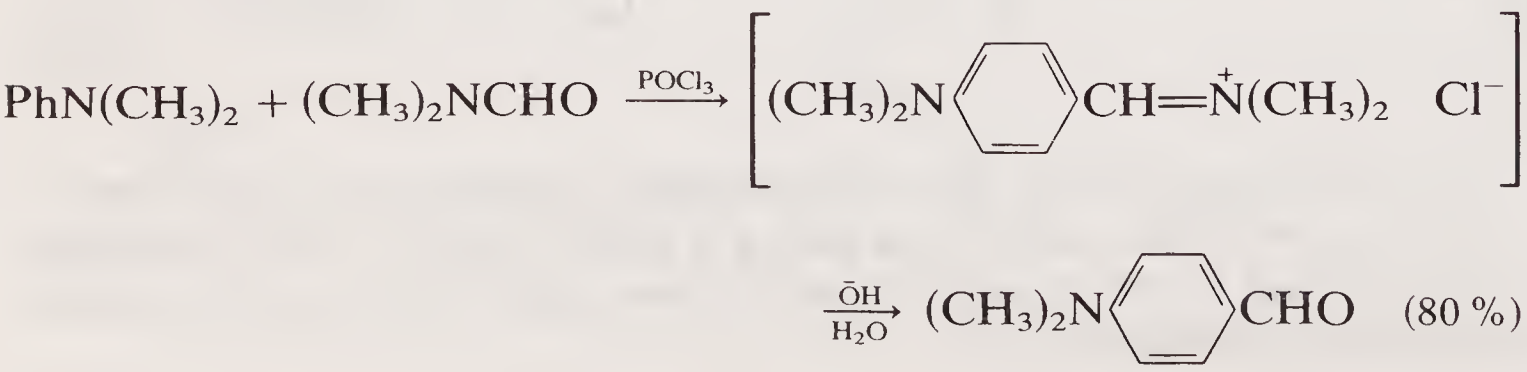
(The latter reaction, although perhaps not formally an acylation, is mechanistically similar.)

Among methods for formylation, the **Vilsmeier–Haack–Arnold** method, using an *N*,*N*-disubstituted formamide and phosphoryl chloride, is among the most useful. The effective electrophile in these reactions is the chloromethyleneiminium ion (53) [reaction (5.28)]:

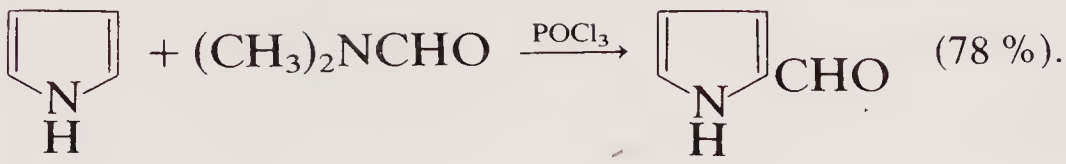


Similarly, $R_2NCHO + COCl_2 \rightarrow R_2\overset{+}{N}{=}CHCl\ Cl^- + CO_2$.

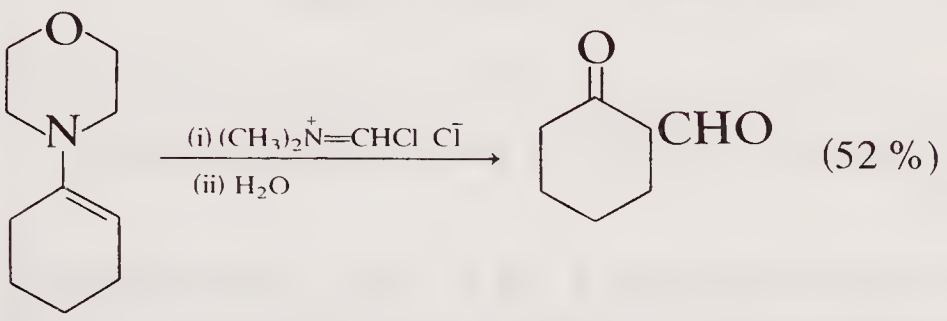
In its original version (the Vilsmeier–Haack reaction) the method is used for the formylation of activated arenes and heteroarenes, e.g.



Similarly

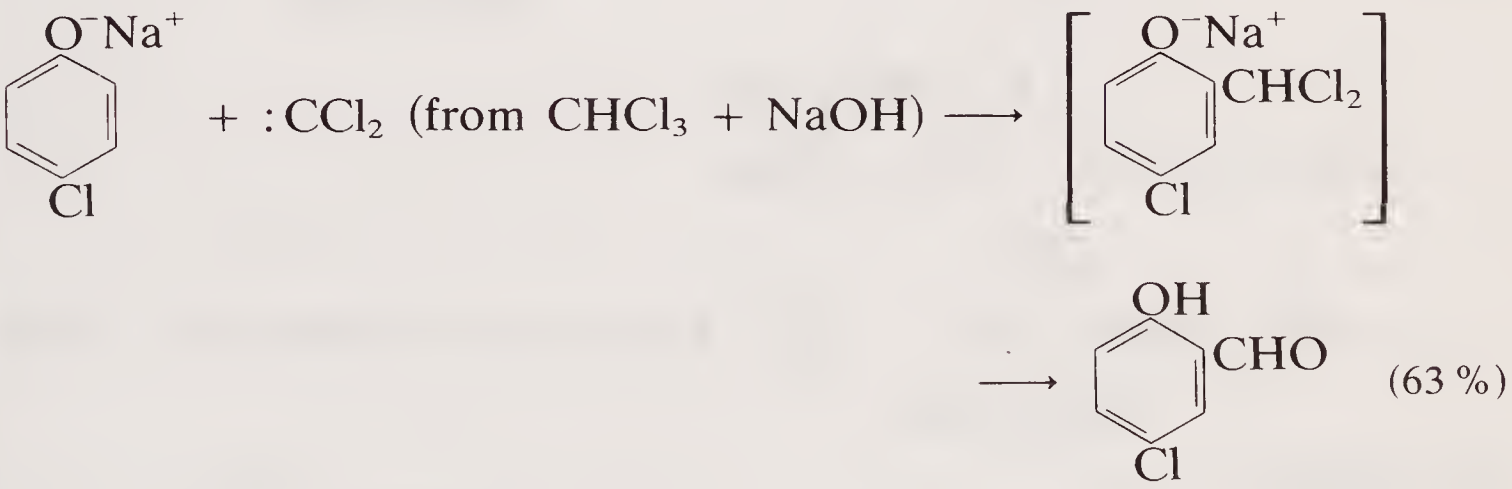


Some activated alkenes also react with these iminium salts very readily, e.g.

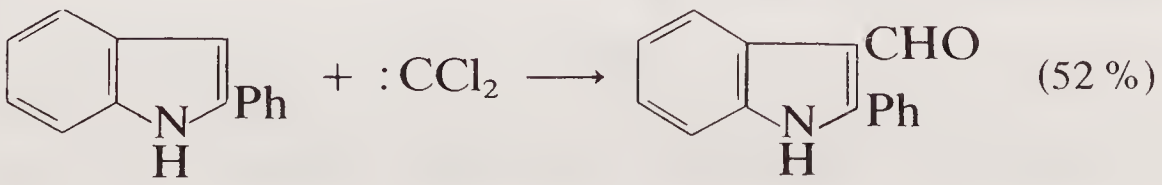


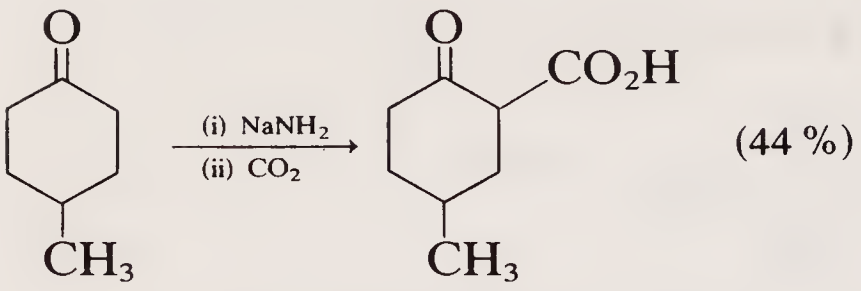
However, it appears that in the majority of cases simple formylation products are not obtained.

Two other reactions which are formally acylations are worthy of brief mention. Both are associated principally with acylation of phenols: the **Reimer–Tiemann** reaction, in which the electrophile is dichlorocarbene, and the **Kolbe–Schmitt** reaction, in which the electrophile is carbon dioxide (cf. Sykes, pp. 290–1):



Both types of reaction have been applied to nucleophiles other than phenoxide ions, e.g.



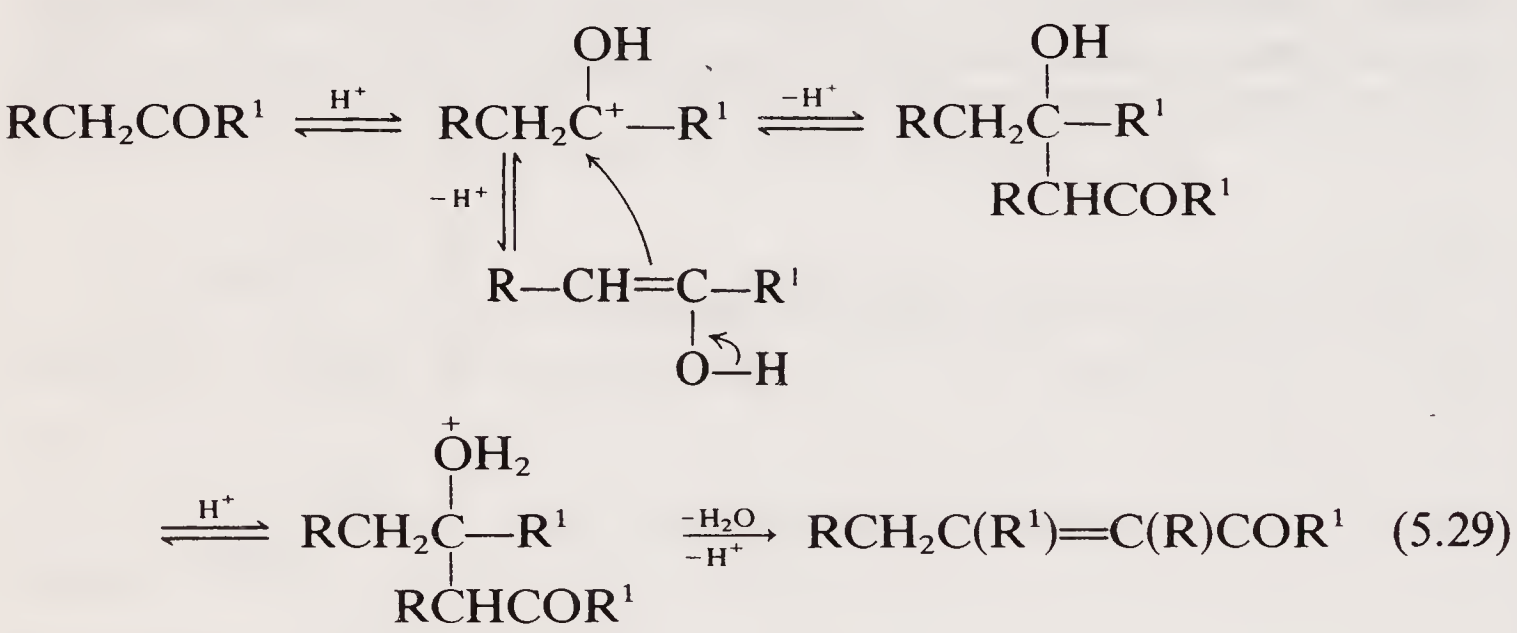


(44 %)

Yields, however are generally low, and by-products are common in the Reimer–Tiemann process. Neither process is therefore a *generally* useful method, although each may be important in specific cases.

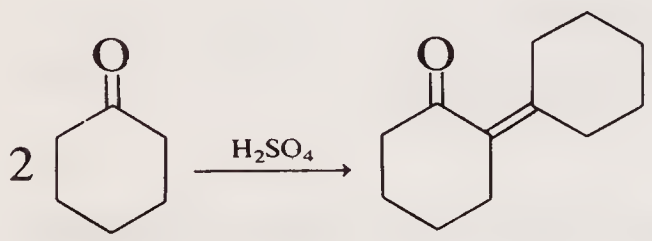
5.4.3 Addition and condensation reactions with carbonyl and related compounds

Mention has already been made (section 5.2.4.1) that aldehydes and ketones may undergo self-condensation in acidic as well as basic media. The mechanism of the condensation under acidic conditions clearly cannot involve a carbanionic nucleophile, and such reactions are envisaged as involving an enol as the nucleophile and a protonated carbonyl species as the electrophile [reaction (5.29); cf. Sykes, p. 225]:



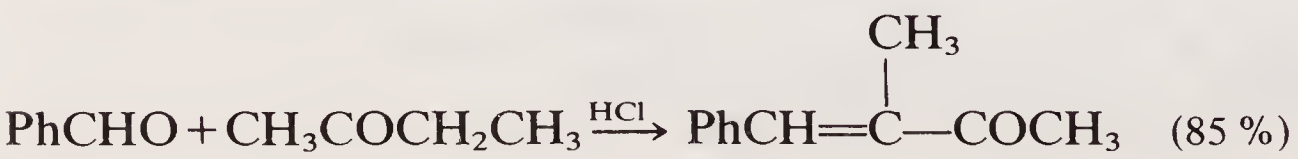
(5.29)

For example,



(83 %)

Mixed condensations may also occur, e.g.



(85 %)

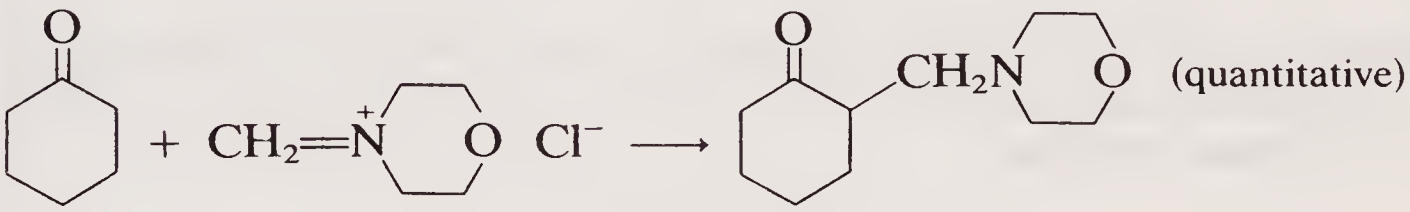
A mechanistically related reaction, of much greater importance in synthesis, is the **Mannich reaction**, in which the electrophilic component is not a protonated carbonyl group but a methyleneiminium ion [produced *in situ* from formaldehyde and a secondary amine in presence of acid: reaction (5.30)]. Unlike the acid-catalysed condensation reactions, Mannich reactions consist of a simple addition step without a final elimination (this presumably reflects the fact that $-\overset{+}{N}HR_2$ is a poorer leaving group than $-\overset{+}{O}H_2$):

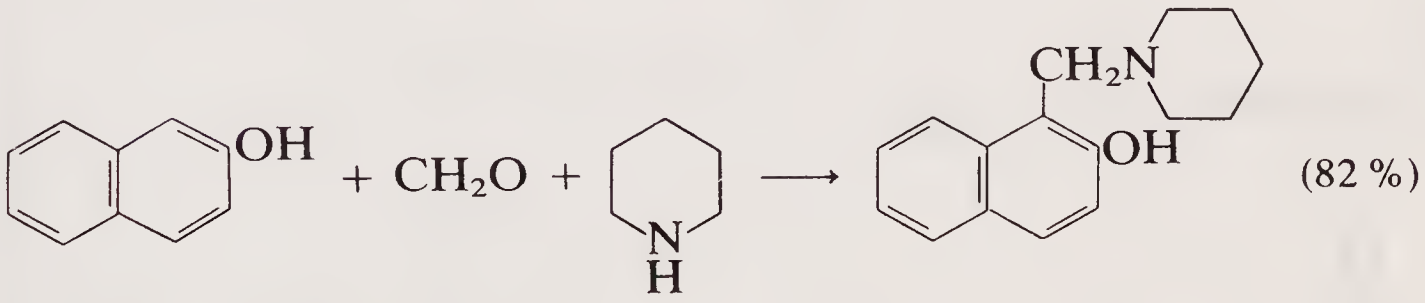
$$CH_2{=}O \overset{H^+}{\rightleftharpoons} \overset{+}{C}H_2OH \overset{R_2NH}{\rightleftharpoons} R_2\overset{+}{N}(H)-CH_2OH \rightleftharpoons R_2\ddot{N}-CH_2-\overset{+}{O}H_2 \overset{-H_2O}{\rightleftharpoons} R_2\overset{+}{N}{=}CH_2 \quad (5.30)$$

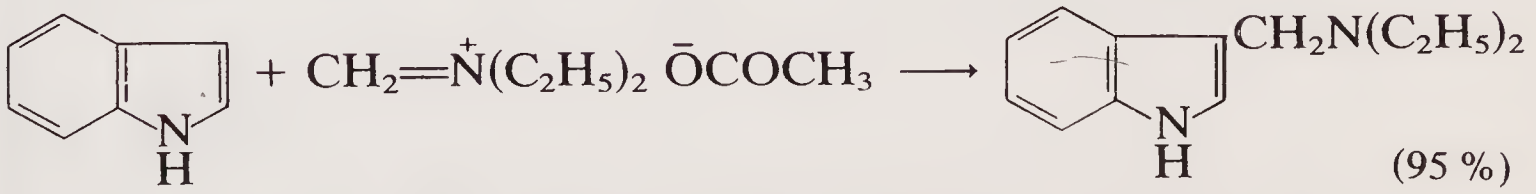
The nucleophile in the Mannich reaction may be an enol, or an activated arene, or a π-excessive heteroarene, e.g.

$$PhCOCH_3 \left[\rightleftharpoons PhC(OH){=}CH_2\right] + CH_2{=}\overset{+}{N}(CH_3)_2\ \bar{C}l \ \text{(from } CH_2O + (CH_3)_2NH + HCl) \rightarrow PhCOCH_2CH_2N(CH_3)_2 \ (60\ \%)$$

(54)







The products of many Mannich reactions (**Mannich bases**, as they are called) are themselves useful synthetic intermediates. β-(Dialkyl amino)-ketones such as (54) are readily convertible, by an elimination of the Hof-

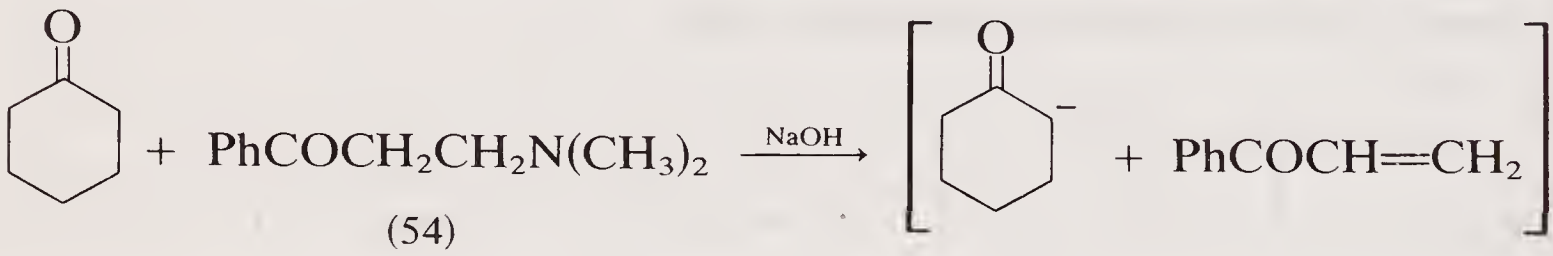
mann type (cf. Sykes, p. 256), into vinyl ketones [reactions (5.31) and (5.32)]:

$$RCOCH_2CH_2NR^1{}_2 \xrightarrow[\text{or distillation}]{\text{base (e.g. } \bar{O}H)} RCOCH{=}CH_2 + R^1{}_2NH \qquad (5.31)$$

$$RCOCH_2CH_2NR^1{}_2 \xrightarrow{CH_3I} RCOCH_2CH_2{-}{}^{+}\underset{\displaystyle CH_3}{\underset{|}{N}}R^1{}_2\,I^- \xrightarrow{\text{base}}$$

$$RCOCH{=}CH_2 + R^1{}_2NCH_3 \qquad (5.32)$$

Since vinyl ketones are valuable electrophiles in the Michael reaction (sections 5.1.5 and 5.2.5) but are themselves rather unstable (being liable to polymerisation), their generation *in situ* from Mannich bases provides a useful variant of the Michael reaction, e.g.

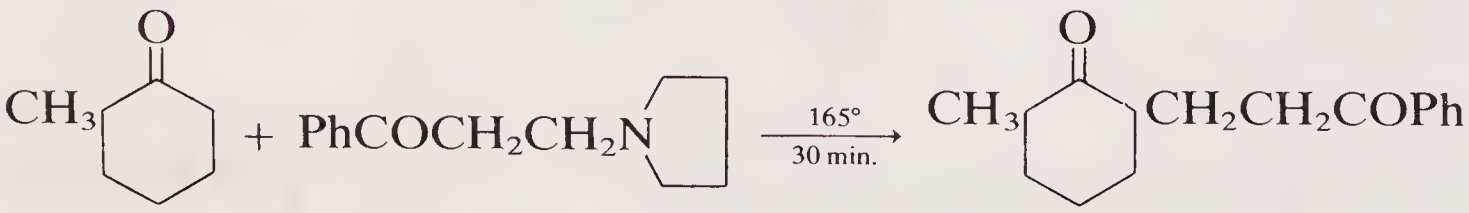


(54)

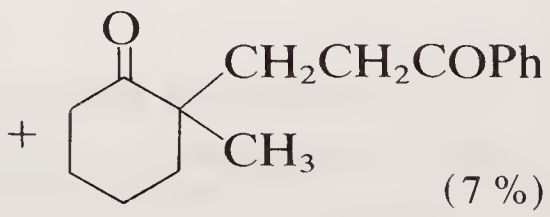
(52 %)

Added base may not even be necessary, since thermal decomposition of the Mannich base gives a secondary amine which may serve as catalyst for the Michael reaction:

(95 %)

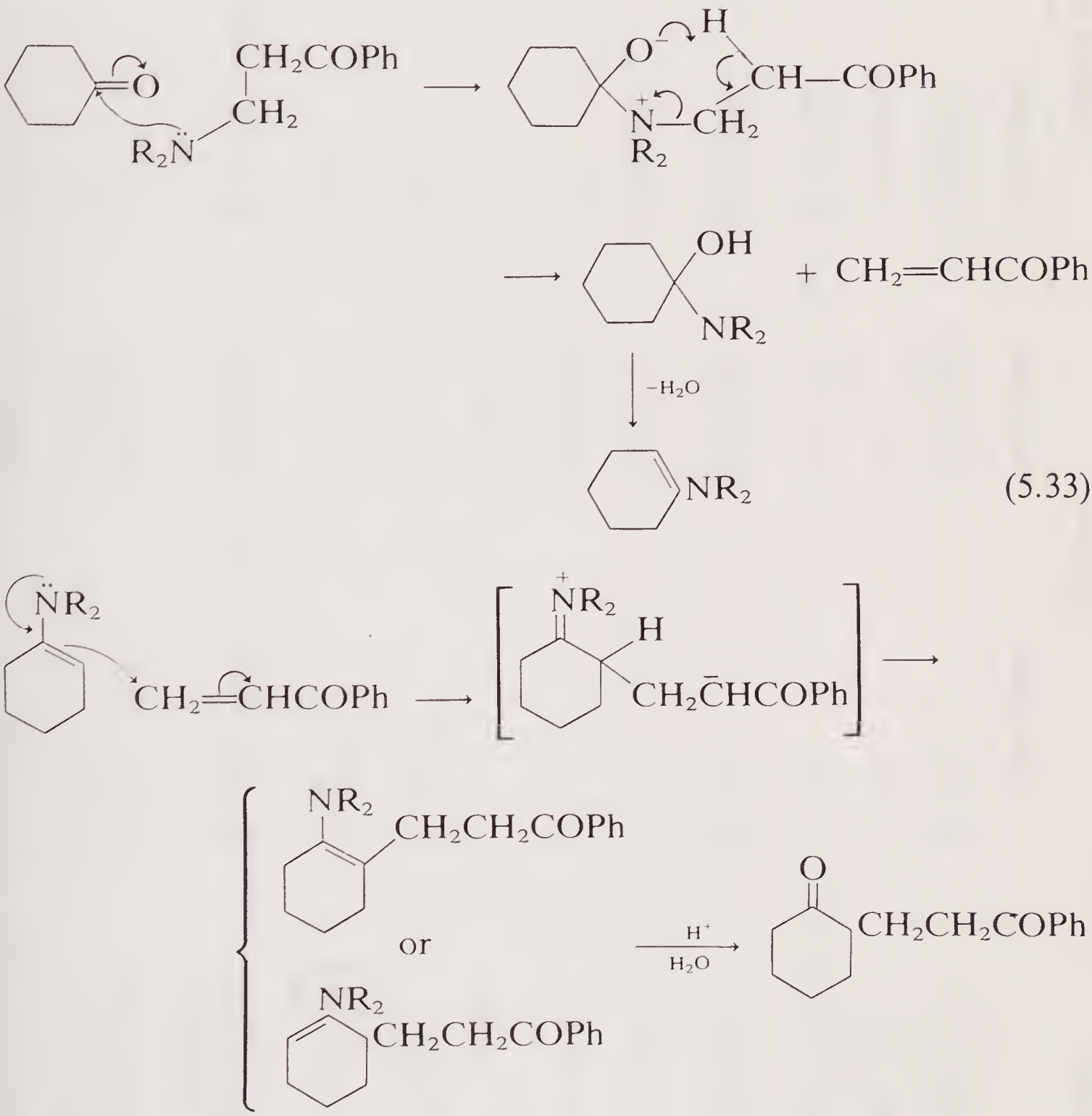


(57 %)



(7 %)

These so-called 'thermal Michael reactions' are of particular mechanistic interest: thermal decomposition of (54) at 160°, for example, produces dimethylamine (b.p. 7°) which should be lost as vapour and thus be unable to catalyse the addition. It is supposed that transamination occurs between the Mannich base and the other ketone, giving the enone and an enamine [reaction (5.33)]. The latter then functions as the nucleophile in the Michael addition:



(5.33)

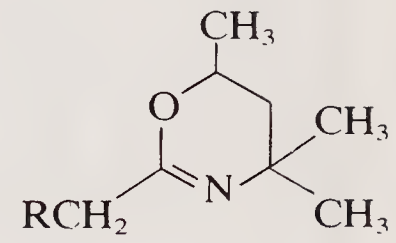
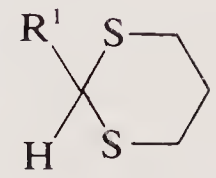
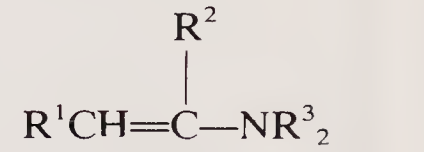
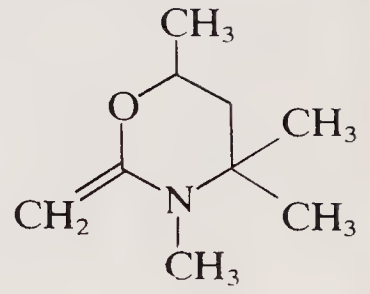
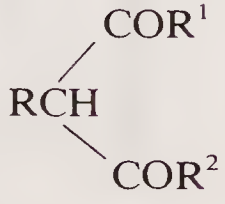
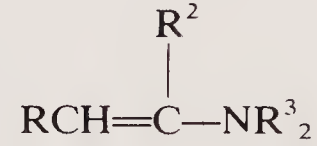
5.5 Review

The majority of the reactions contained in Chapter 4 lead to monofunctional products, and involve nucleophilic synthons which are devoid of functionality. In the present chapter, however, the majority of the products contain two or more functional groups, and (since the nucleophiles

Table 5.1 Disconnections for some products formed from stabilised carbanions and related species

Section number	Product		Synthons		Synthetic equivalents	
			Electrophilic	Nucleophilic	Electrophilic	Nucleophilic
5.1.1 (pp. 63–6)	$RCH(CO_2R^1)_2$	⇒	R^+	$\bar{C}H(CO_2R^1)_2$	RX (halide)	$CH_2(CO_2R^1)_2$
5.1.1	$RCH\begin{matrix}\diagup CO_2R^2 \\ \diagdown COR^1\end{matrix}$	⇒	R^+	$\bar{C}H\begin{matrix}\diagup CO_2R^2 \\ \diagdown COR^1\end{matrix}$	RX (halide)	$CH_2\begin{matrix}\diagup CO_2R^2 \\ \diagdown COR^1\end{matrix}$
5.1.1 (pp. 65–6)	$RCH_2COCH_2COR^1$	⇒	R^+	$\bar{C}H_2COCH_2COR^1$	RX (halide)	$CH_3COCH_2COR^1$
5.1.2, reaction (5.4)	RCH_2CO_2H	⇒	R^+	$\bar{C}H_2CO_2H$	RX (halide)	$CH_2(CO_2R^1)_2$
5.1.2 reaction (5.5)	RCH_2COR^1	⇒	R^+	$\bar{C}H_2COR^1$	RX (halide)	$CH_2\begin{matrix}\diagup CO_2R^2 \\ \diagdown COR^1\end{matrix}$
5.1.3, reaction (5.8)	$RCOCH\begin{matrix}\diagup COR^1 \\ \diagdown COR^2\end{matrix}$	⇒	RCO^+	$\bar{C}H\begin{matrix}\diagup COR^1 \\ \diagdown COR^2\end{matrix}$	RCOCl	$CH_2\begin{matrix}\diagup COR^1 \\ \diagdown COR^2\end{matrix}$
reaction (5.11)	$RCOCH_2CO_2R^1$	⇒	RCO^+	$\bar{C}H_2CO_2R^1$	RCOCl	$CH_2(CO_2R^1)_2$
5.1.5, reaction (5.15)	$R_2C(COR^2)—CH(R^1)—CH(COR^3)_2$	⇒	$R_2\dot{C}—CHR^1—COR^2$	$\bar{C}H(COR^3)_2$	$R_2C{=}CR^1—COR^2$	$CH_2(COR^3)_2$
5.2.1 (pp. 78–9) also 5.2.3.2	RR^1CHCOR^2 (CN)	⇒	R^+	$R^1\bar{C}HCOR^2$ (CN)	RX	$R^1CH_2COR^2$ (CN)
5.2.2 (pp. 80–2)	$RCOCHR^1CO_2R^2$	⇒	RCO^+	$R^1\bar{C}HCO_2R^2$	RCO_2R^2	$R^1CH_2CO_2R^2$

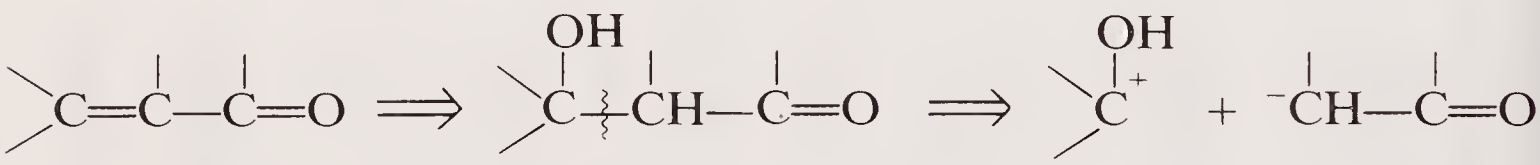
Table 5.1. (*cont.*)

5.2.3.1, reaction (5.17)	RR^2CHCHO	$\Rightarrow$	$(R^2)^+$	$R\bar{C}HCHO$	R^2X	$RCH_2CH{=}NR^1$
5.2.3.1 reaction (5.19)	RR^1CHCHO	$\Rightarrow$	$(R^1)^+$	$R\bar{C}HCHO$	R^1X	
5.3.2, reaction (5.25)	R^1COR^2	$\Rightarrow$	$(R^2)^+$	$R^1\bar{C}O$	R^2X	
5.4.1, (pp. 98–100)	RR^1CHCOR^2	$\Rightarrow$	R^+	$R^1\bar{C}HCOR^2$	RX	
5.4.1, reaction (5.26)	RCH_2CHO	$\Rightarrow$	R^+	$\bar{C}H_2CHO$	RX	
5.4.2, (pp. 101–2)		$\Rightarrow$	R^1CO^+	$R\bar{C}HCOR^2$	R^1COCl	
5.4.3, (pp. 106–7)		$\Rightarrow$	$RCOCH_2CH_2^+$	$R^1\bar{C}HCOR^2$	$RCOCH_2CH_2NR^3{}_2$	$R^1CH_2COR^2$

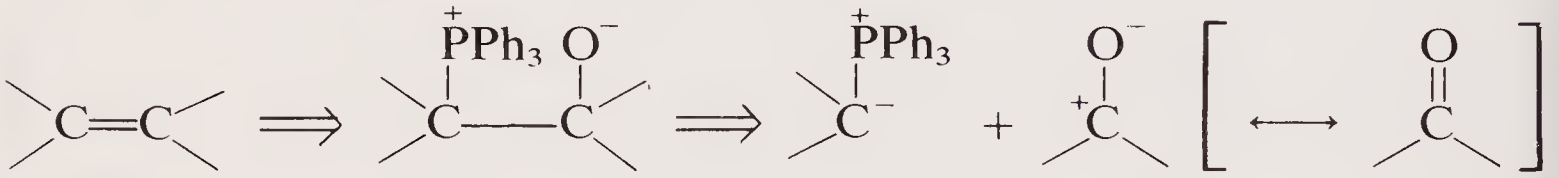
in each case are stabilised by adjacent atoms or groups) these nucleophilic synthons are all of the type $\bar{C}H_2X$ or $\bar{C}HXY$ or $\bar{C}XYZ$ (X, Y and Z being functional groups). These are shown in table 5.1; it will be noted that the electrophilic synthons are, in general, the same as in Chapter 4. The synthons and their synthetic equivalents are collected in table 5.2.

The other new development in this chapter is the description of two processes which lead to the formation of carbon–carbon double bonds, *viz.* condensations and Wittig reactions. So now we have to devise a system for the disconnection of double bonds.

Neither of these processes is, of course, a one-step reaction. Each consists of an addition step, which forms a single carbon–carbon bond, followed by an elimination step in which the second carbon–carbon bond is formed. So disconnection of a double bond is also a two-stage process: (i) addition to the double bond, i.e. the opposite of elimination, and (ii) disconnection of the resulting C—C single bond. Thus,



(5.34)



(5.35)

[There are, of course, other methods of forming double bonds, by functional group interconversion. The partial reduction of a triple bond (sections 8.4.2 and 11.5) is among the most familiar of these, and in certain cases it may be attractive to use an alkyne as the synthetic precursor of an alkene – especially since a wide variety of substituted alkynes may be easily prepared (cf. section 4.3)].

5.6 Problems

5.6.1 Strategy of disconnection

In the 'Problems' section of Chapter 4 we demonstrated that synthetic routes to monofunctional compounds could frequently be revealed by performing a disconnection on the end-product (the 'target molecule') adjacent to the functional group. Similarly we showed that another useful disconnection may be one adjacent to a point of chain branching, i.e. one adjacent to a tertiary (or quaternary) carbon.

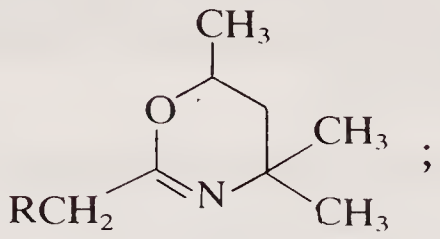
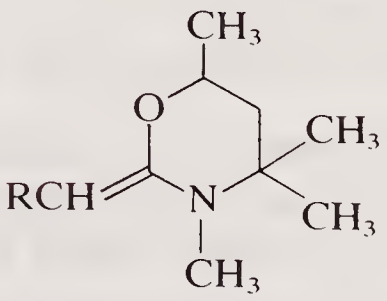
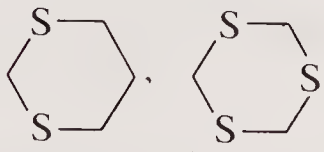
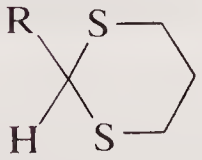
	Synthon	Synthetic equivalents	For example(s), see page(s)
(*a*) *Nucleophilic synthons*	4. $R\bar{C}HCHO$	RCH_2CHO; $RCH_2CH{=}NR^1$;  ; 	78, 82–4 86–9 99–100
	5. $R\bar{C}HCOR^1$	RCH_2COR^1; $RCH{=}C(R^1){-}NR^2{}_2$; $RCH(CO_2R^2)COR^1$	67–72, 78–82 84–8, 98–9 101–7
	6. $R\bar{C}HCO_2H$	$RCH_2CO_2R^1$; $RCH(CO_2H)_2$; $RCH(CO_2R^1)_2$	67–70, 74–5
	7. $R\bar{C}HCO_2R^1$	$RCH_2CO_2R^1$; $RCH(CO_2R^1)_2$; $RCH{=}C(\bar{O}\overset{+}{Z}nBr)(OR^1)CO_2R^1$	67–70 78, 80–2 88, 90 46–7
	8. $R\bar{C}HCN$	RCH_2CN; $RCHCN$	75, 78, 81
	9. $R\bar{C}HCOCH_2COR^1$	$RCH_2COCH_2COR^1$	65–6, 85
	10. $\bar{C}HO$		96–7
	11. $R\bar{C}O$		96–7
	12. $R\bar{C}(COR^1)_2$, $R\bar{C}(CO_2R^1)_2$, etc.	$RCH(COR^1)_2$, $RCH(CO_2R^1)_2$, etc.	62–77
(*b*) *Electrophilic synthons*	6. $\dot{H}CO$	HCO_2R; $HCONR_2$; $CH(OR)_3$; $ClCH{=}\overset{+}{N}R_2\ X^-$	82, 85, 100–3
	12. $\dot{C}H_2CH_2COR$	$CH_2{=}CHCOR$; $R^1{}_2NCH_2CH_2COR$; $R^1{}_3\overset{+}{N}CH_2CH_2COR\ X$	75–7, 91, 106–7
	13. $\dot{C}HCl_2$	$CHCl_3$ (*via* $:CCl_2$)	103

Table 5.2 Some common synthons and their synthetic equivalents (part 2) This table is a continuation of table 4.2 (p. 57), and the entries are numbered consecutively with those of that previous Table.

We are now able to extend the list of potentially useful disconnections, and to consider disconnections of difunctional compounds.

(i) **If the compound contains only carbon–carbon single bonds, try the following disconnections:**

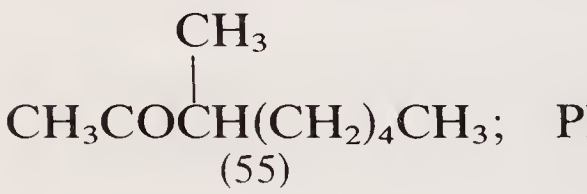
(a) adjacent to a functional group;
(b) between the carbons α- and β- to a functional group;
(c) between the carbons β- and γ- to a functional group;
(d) adjacent to a branching point in a carbon chain.

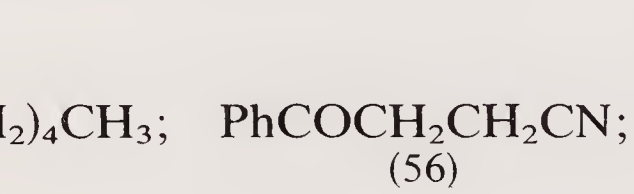
(ii) **If the compound contains only carbon–carbon single bonds, and two functionalised carbon atoms close together (separated by not more than three other carbons), it is usually worth trying one disconnection between the functional groups. If the functionalised carbons are farther apart, two disconnections of the types shown in (i) are likely to be required.**

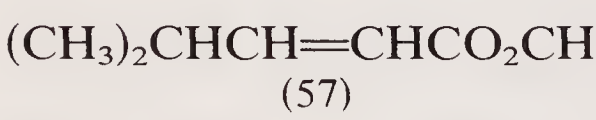
(iii) **If the compound contains a carbon–carbon double bond, it is worth considering a disconnection of this bond.** If it is an isolated (i.e. non-conjugated) double bond, it may imply a Wittig reaction; if it is conjugated to a $-M$ group, it may imply a condensation reaction or a Wittig reaction with a stabilised ylide. **If each of the doubly bonded carbons is attached to hydrogen, it may be worth considering if the corresponding alkyne is readily accessible.**

5.6.2 Examples

As in Chapter 4, we conclude with some worked examples. Once again we consider four target molecules:

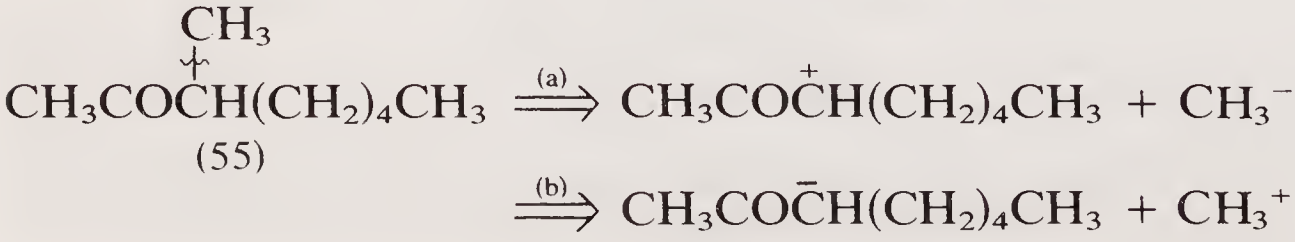

(55)

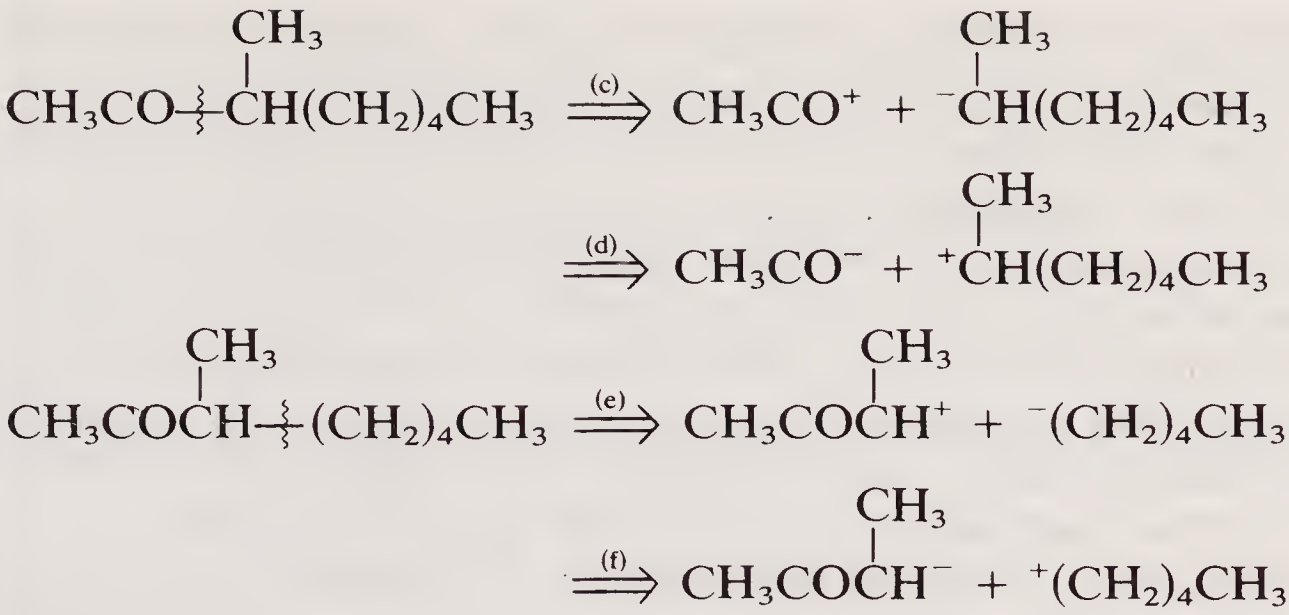

(56)


(57)


(58)

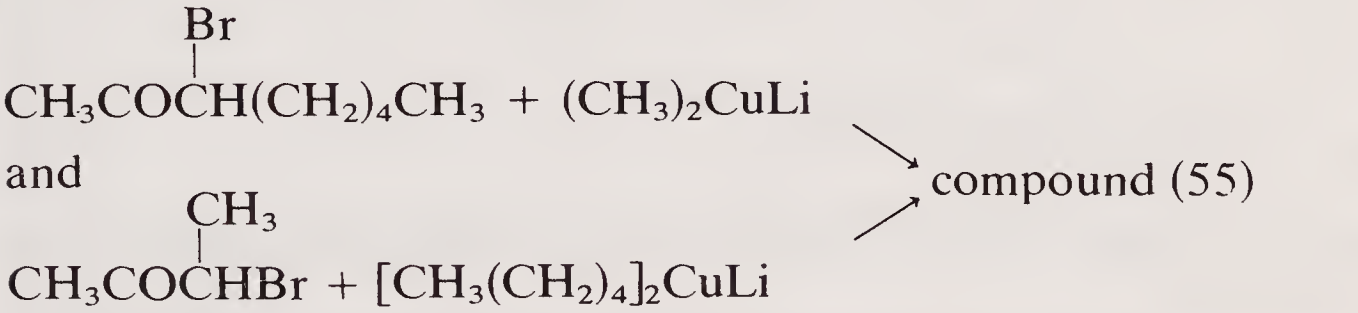
3-Methyloctan-2-one (compound 55). Of all the possible disconnections for this molecule, those adjacent to C-3 appear particularly attractive: not only is C-3 α- to the functional group, but it is also the branching point of the chain. Since C-3 is joined to three other carbons, there are six pairs of synthons to be considered, *viz.*


(55)



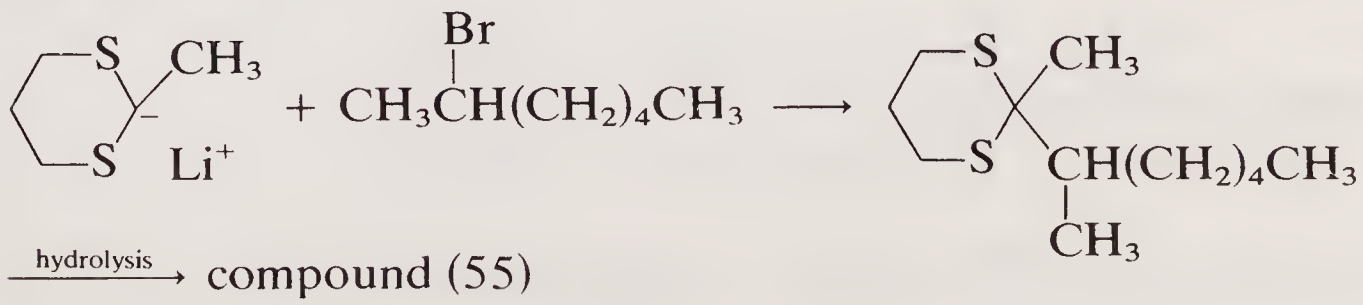
The twelve synthons all have recognisable synthetic equivalents, and so the reverse of any one of the six disconnections may form the basis of a successful synthesis.

Disconnections (a) and (e) offer the least attractive (or, in any case, the most difficult) possibilities. In each case the electrophile is an α-halogenoketone ($CH_3COCHXR$) and the nucleophile an organometallic reagent – most probably a cuprate, since Grignard and lithium derivatives would react with the ketone as well as the halide. So the two syntheses would be:



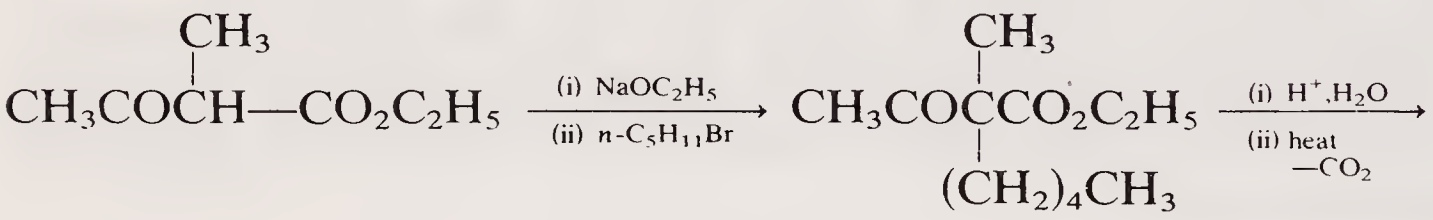
Difficulties arise, however, in the preparation of the bromoketones. Bromination of butanone and octan-2-one does indeed give the required 3-bromo-derivatives, but also the isomeric 1-bromo-compounds and di- and poly-brominated products: purification of the 3-bromo-compounds can thus be difficult.

Disconnection (c) indicates a synthesis of compound (55) from an acylating agent and an organometallic derivative of 2-bromoheptane. This is similar to the synthesis of pentadecan-4-one already discussed (section 4.5, p. 59) and is not considered further here. Disconnection (d) indicates a synthesis from an acyl anion equivalent (i.e. a dithian) and an alkylating agent:

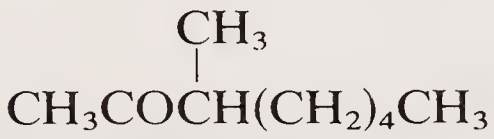


The remaining two disconnections, (b) and (f), indicate synthesis of (55) by the reactions of alkylating agents with stabilised carbanions or related species. The critical factor in each is the choice of the synthetic equivalent of the nucleophilic synthon. In case (f), for example, the most obvious synthetic equivalent is butanone, and the problem then becomes that of generating only one of the two possible carbanions (i.e. specific enolate formation: section 5.2.3.2). It is not easy to ensure that a mixture of anions, and hence a mixture of isomeric products, will not be obtained. The same difficulty arises with the enamine route, since butanone may give two isomeric enamines by reaction with any given amine.

The simplest way of ensuring reaction only at the required position is to 'activate' that position (i.e. attach another $-M$ group to C-3). So the synthetic equivalent of choice is $CH_3COCH(CH_3)—CO_2C_2H_5$, and the synthesis may be summarised as follows:



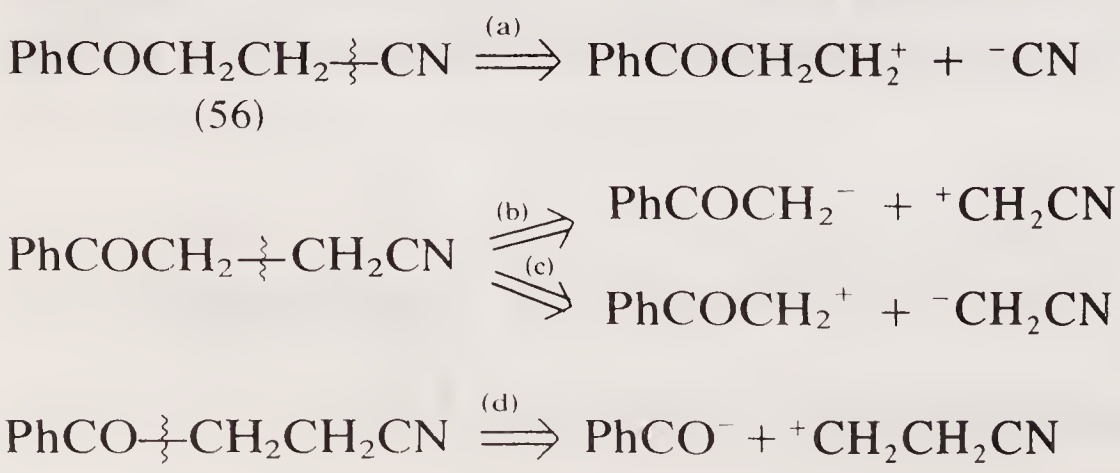
(55a)



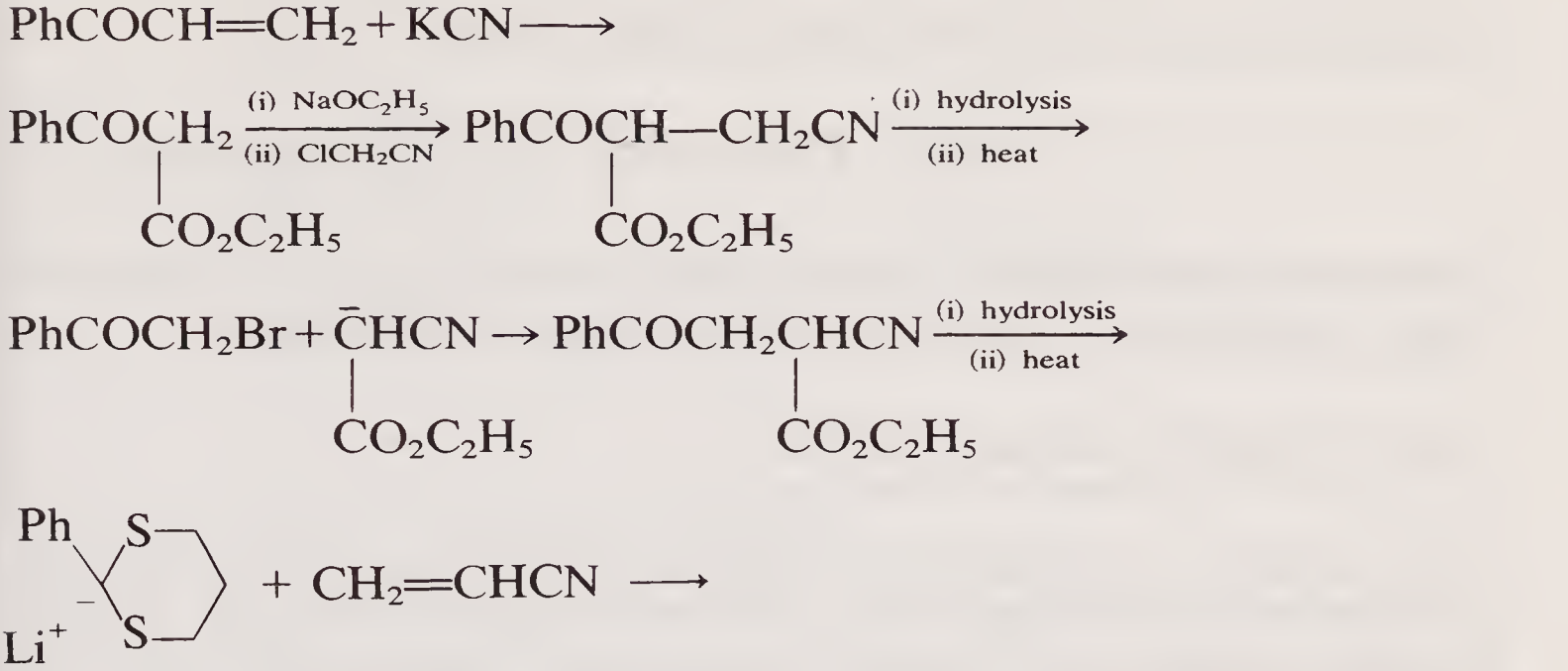
A similar argument may be used for case (a): the same intermediate, (55a), is involved.

The syntheses outlined here are not, of course, the only possible routes to 3-methyloctan-2-one. Which is the best in practice has never been determined, and such determination may well be no more than a process of trial and error.

4-Oxo-4-phenylbutanonitrile (compound 56). In this molecule the two functional groups are sufficiently close to each other to make it worth considering a single disconnection between the two. There are four such disconnections which are reasonably obvious:

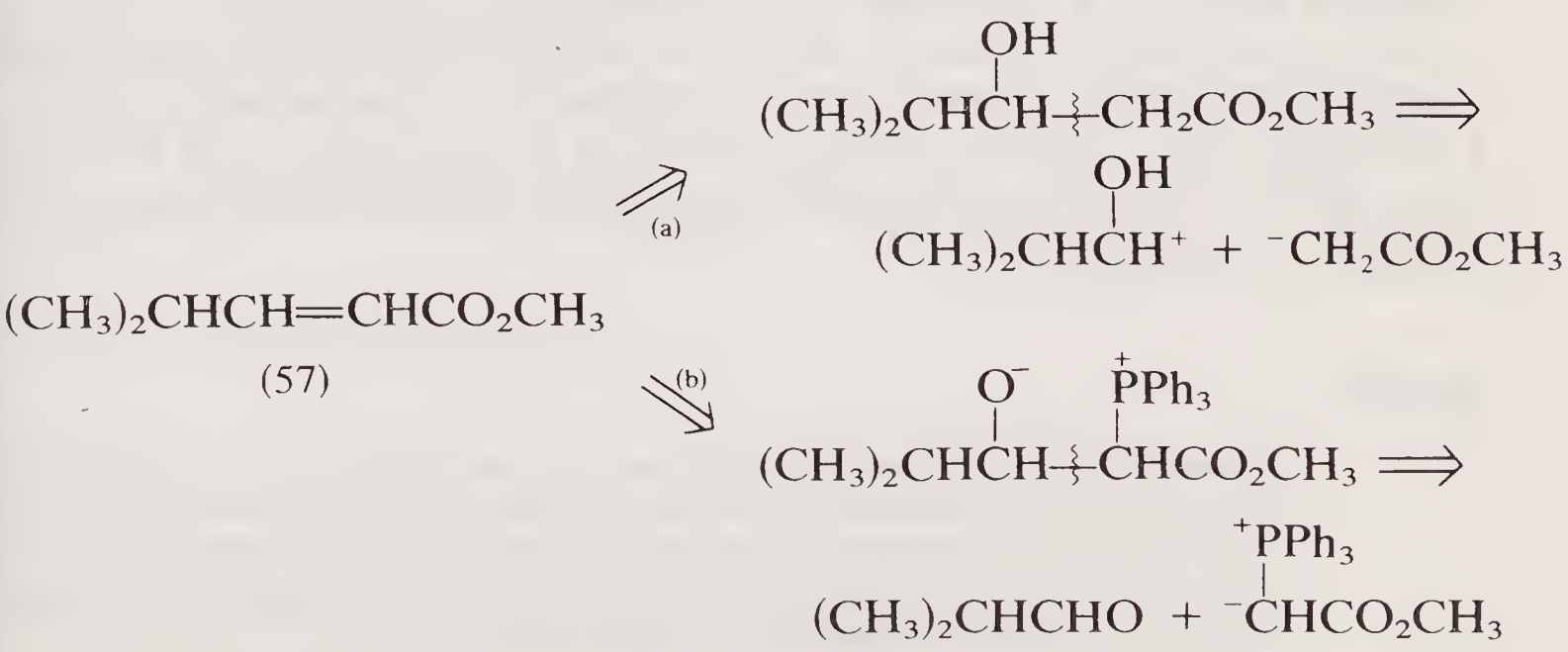


These in turn imply the following possible syntheses for compound (56):



The first possibility, involving conjugate addition of cyanide ion to an enone, is the simplest of the four. The Mannich base (54), which we have already encountered (p. 105), may be used as a substitute for the enone. The second and third possibilities are also acceptable, since they both involve the alkylation of a doubly stabilised carbanion by means of a highly reactive halide, and since esters are much more easily hydrolysed than nitriles. The final possibility, involving the dithian, is the least attractive of the four: organolithium reagents generally prefer direct attack on functional groups at the expense of conjugate addition (section 4.2.1). On the other hand, other synthetic equivalents of $PhCO^-$ [10] may be capable of successful conjugate addition and provide a useful synthesis of (56).

Methyl 4-methylpent-2-enoate (compound 57). This molecule contains a carbon–carbon double bond conjugated with an ester carbonyl group, and so is conceivably the product of a condensation or of a Wittig reaction involving a stabilised ylide. Thus,



The Wittig synthesis is therefore:

$$BrCH_2CO_2CH_3 \xrightarrow{PPh_3} Ph_3\overset{+}{P}CH_2CO_2CH_3\ Br^- \xrightarrow{NaOCH_3}$$

$$Ph_3\overset{+}{P}—\bar{C}HCO_2CH_3 \xrightarrow{(CH_3)_2CHCHO} \text{compound (57)}$$

The condensation method is less straightforward. The most obvious synthetic equivalents for the two synthons suggest the following:

$$(CH_3)_2CHCHO + CH_3CO_2CH_3 \xrightarrow{base}$$

This, however, is unsatisfactory, since the *aldehyde*, not the ester, contains the most acidic hydrogen; so the ester must be 'activated'. A satisfactory procedure uses dimethyl malonate, and another makes use of the Reformatsky reaction:

$$(CH_3)_2CHCHO + CH_2(CO_2CH_3)_2 \rightarrow (CH_3)_2CHCH{=}C(CO_2CH_3)_2, \text{ etc.}$$

$$\longrightarrow \longrightarrow \text{compound (57)}$$

$$(CH_3)_2CHCHO + BrCH_2CO_2CH_3 \xrightarrow{Zn} (CH_3)_2CH\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CO_2CH_3 \xrightarrow[-H_2O]{H^+}$$

compound (57)

The reader may be able to devise other methods.

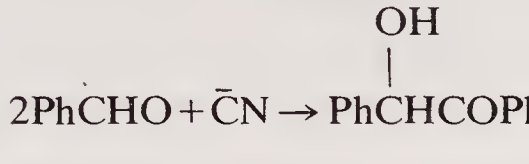
Non-7-enal (compound 58). As in the last chapter, the final problem is left unsolved as a challenge to the reader. There are several possible syntheses, and the method of choice may depend, in practice, on availability of starting materials. The principal difficulty in the synthesis of this compound is the sensitivity of the aldehyde group towards oxidation, reduction and condensation, and so it may be advantageous to introduce the aldehyde group at a late stage in the synthesis.

Compound (58) is similar in its functionality to the insect pheromone which we introduced at the beginning of Chapter 3 (compound A, p. 23). The reader is now invited to devise a route to Compound A, and to compare this route with those already published: these are summarised in Chapter 16 (section 16.2).

Notes

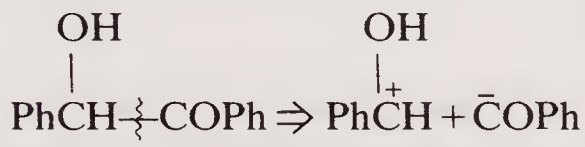
1. Sodium hydride, although a strong base, is a surprisingly poor nucleophile; if hydride is required to act as a nucleophile (for example, to react with a carbonyl group), a complex hydride, such as $\bar{A}lH_4$ or $\bar{B}H_4$, should be used (cf. section 8.2). In any case the reactive species produced by solution of sodium hydride in dimethyl sulphoxide is $CH_3SOCH_2^-Na^+$.

2. The reader is reminded that we have chosen in this book to adopt a restricted definition of the term 'condensation reaction', *viz.* a reaction in which addition of a carbanion (or other nucleophile) to a carbonyl compound (or other electrophile) is followed by elimination of water (cf. section 3.3.2, note 3).
3. The use of boiling benzene as solvent facilitates removal of water (by azeotropic distillation).
4. LDA = lithium di-isopropylamide, $Li^+\bar{N}[CH(CH_3)]_2$.
5. This does not conform to our restricted definition of a 'condensation reaction' (cf. note 2, and section 3.3.2, note 3).
6. Addition of the Grignard reagent to the double bond of (29) is not, apparently, an important side-reaction.
7. The condensation of an aromatic aldehyde with another aldehyde or ketone is generally known as the **Claisen–Schmidt condensation**, and that with an anhydride as the **Perkin condensation**.
8. For example, by (a) I. Gosney and A. G. Rowley, in *Organophosphorus Reagents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic Press, 1979, Chapter 2; (b) E. Vedejs and C. F. Marth. *J. Am. Chem. Soc.*, **110**, 3948 (1988), and references therein.
9 German: reversal of polarity.
10. So far we have made no mention of other synthetic equivalents for the synthon $R\bar{C}O$, but several others are in fact known. One such is involved in the formation of benzoin from benzaldehyde and cyanide ion:

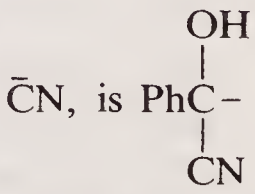


$$2PhCHO + \bar{C}N \rightarrow PhCHCOPh$$

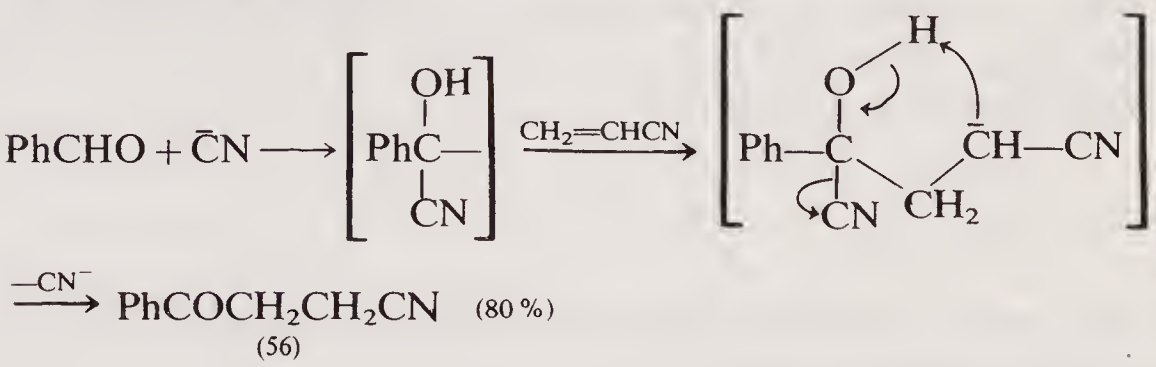
The disconnection corresponding to this reaction is



$$PhCH\text{-}COPh \Rightarrow PhC\overset{+}{H} + \bar{C}OPh$$

The actual nucleophile, formed from benzaldehyde and  $\bar{C}N$, is $PhC(OH)(CN)-$

(cf. Sykes, p. 231), and this nucleophile (a stabilised carbanion) readily participates in the Michael reaction (section 5.2.5). Thus, compound (56) may be obtained as follows:



$$PhCHO + \bar{C}N \longrightarrow \left[PhC(OH)(CN)-\right] \xrightarrow{CH_2=CHCN} \left[Ph-C(CN)(CH_2)-\bar{C}H-CN\right] \xrightarrow{-CN^-} PhCOCH_2CH_2CN \quad (80\,\%)$$

(56)

6 Formation of carbon–heteroatom bonds: the principles

In the last three chapters we have been concerned with the formation of carbon–carbon bonds, with a view to constructing the molecular framework of some particular target compound. This is all very well if the target compound has a skeleton composed entirely of carbon atoms. But there are, of course, very many organic compounds for which this is not true: in this connection one thinks particularly of *heterocyclic* compounds, which by definition have molecular skeletons containing *heteroatoms*, i.e. atoms other than carbon. Before we deal with methods of forming cyclic compounds, therefore, it is appropriate to consider a few general points in relation to carbon–heteroatom bond formation.

6.1 Carbon–halogen bonds

One does not normally think of a halogen atom in an organic molecule as constituting part of the molecular framework, but rather as a substituent attached to that framework. One may also consider that the principal methods for forming a carbon–halogen bond are simply matters of functionalisation or functional group interconversion and as such have been covered already in Chapter 2. So why return to the subject here?

The answer is simple – to recall an important mechanistic point. If one were asked to express in general terms how carbon–halogen bonds are usually formed, one would tend to think first of the reaction of an electrophilic carbon with a halide ion:

$$R\text{–}X \Rightarrow R^+ + X^- \qquad (6.1)$$

It is all too easy to ignore the reaction of a *nucleophilic* carbon with an *electrophilic* halogen species:

$$R\text{–}X \Rightarrow R^- + X^+ \qquad (6.2)$$

although there are possibly just as many useful syntheses of this latter

type as of the former [the halogenation of benzene derivatives (scheme 2.3) being one of the most familiar examples]. In addition it will be recalled that, whereas halide ions are rather weak nucleophiles and thus require strongly electrophilic carbon species for reaction, some of the positive halogen species are highly potent electrophiles.

Finally it must be remembered that there is a third possible disconnection for the R—X bond:

$$R\text{-}\!\!\!\sim\!\!\!\sim X \Rightarrow R^{\cdot} + {}^{\cdot}X \qquad (6.3)$$

and radical reactions constitute another important method for carbon–halogen bond formation (section 2.1; cf Sykes, pp. 323–8).

6.2 Carbon–oxygen and carbon–sulphur bonds

Unlike the halogens, oxygen and sulphur atoms are able to form *two* covalent bonds to carbon in an uncharged molecule, and can therefore be incorporated into the skeleton of organic compounds as well as contributing towards functional groups attached to the skeleton.

In the case of carbon–oxygen bond formation, the vast majority of the reactions are those of electrophilic carbon with nucleophilic oxygen:

$$R\text{-}\!\!\!\sim\!\!\!\sim O\text{—}R' \Rightarrow R^{+} + {}^{-}O\text{—}R' \qquad (6.4)$$

$$RCO\text{-}\!\!\!\sim\!\!\!\sim O\text{—}R' \Rightarrow R\overset{+}{C}O + {}^{-}O\text{—}R' \qquad (6.5)$$

[It must be remembered, of course, that although the synthon ^{-}O–R′ appears in the above, it is not necessary for the synthetic equivalent to bear a negative charge: alcohols (or water, if R′ = H) may be sufficiently nucleophilic to react with the electrophile.]

Those bond-forming reactions between a nucleophilic carbon and an electrophilic oxygen are much less common: from the synthetic viewpoint the most useful of this type are oxidative procedures such as the formation of oxirans from alkenes (epoxidation: cf. scheme 2.1 and section 9.2.5.1; also Sykes, p. 190) and the Baeyer–Villiger reaction (section 9.5.3; cf. Sykes, pp. 127–8). Similarly C–O bond formation *via* radical reactions is of relatively limited synthetic value (but see section 9.4).

With regard to carbon–sulphur bonds, the position is complicated by the different oxidation states in which sulphur is commonly encountered. The formation of a $\gtrless C\text{—}S\text{—}C\lessgtr$ (or $\gtrless C\text{—}S\text{—}H$) grouping is almost invariably one requiring electrophilic carbon and nucleophilic sulphur.

However, the oxides of sulphur are electrophiles [cf. the sulphonation of benzene (section 2.1)], and so the formation of a $\geq C-SO_2X$ or $\geq C-SO_2-C\leq$ grouping may well involve a carbon nucleophile and a sulphur electrophile, e.g.

$$CH_3(CH_2)_{11}MgBr + SO_2 \rightarrow CH_3(CH_2)_{11}SO_2H \quad (80\,\%)$$

$$PhSO_2Cl + PhH \xrightarrow{FeCl_3} PhSO_2Ph \quad (80\,\%)$$

6.3 Carbon–nitrogen bonds

Carbon–nitrogen bond formation is more complicated still. An uncharged nitrogen atom in an organic molecule forms three covalent bonds, and so nitrogen forming part of the molecular framework may be singly bonded to three different atoms (as in amines); or it may be doubly bonded to one atom and singly bonded to another (e.g. $>C=N-C\leq$); or it may replace —CH in an aromatic compound, so that its bonding may be represented as $>C\cdots N\cdots C<$. [Nitrogen triply bonded to a single carbon, of course, constitutes a cyano-group, and the formation of cyano-compounds is already covered in Chapter 2 (schemes 2.9, 2.10, 2.12)]. The fact that positively charged nitrogen is tetra-covalent might be regarded as a further complication, but in fact this complication is much more apparent than real.

The bond-forming reactions may conveniently be grouped under several headings, according to the reaction mechanism.

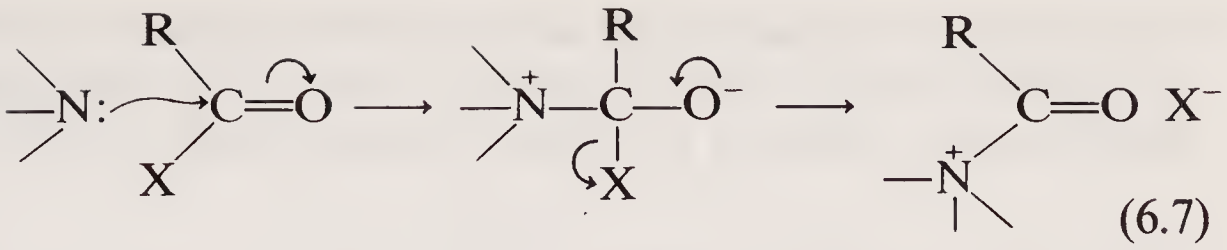
6.3.1 Nucleophilic nitrogen and electrophilic carbon

This is by far the most important process for carbon–nitrogen bond formation. Ammonia and amines are good nucleophiles, by virtue of possessing a lone pair of electrons, and they react with electrophiles in similar fashion to carbon nucleophiles:

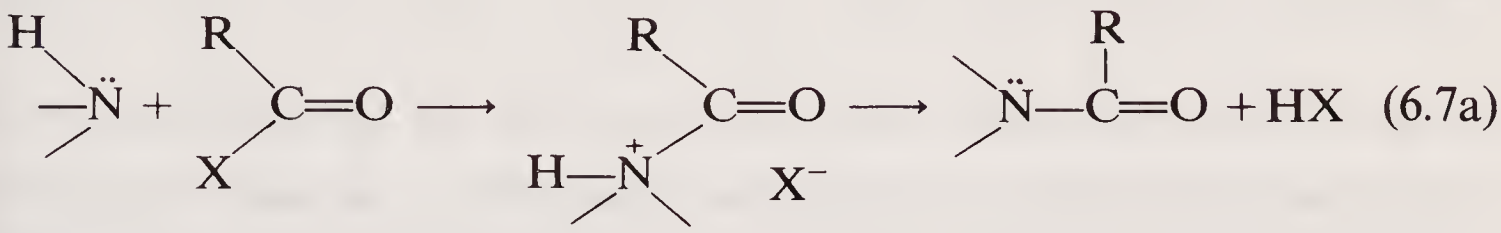
(i) Alkylation: $\geq N: \curvearrowright R-X \longrightarrow \geq \overset{+}{N}-R\ X^-$ (6.6)

$$H-N: \curvearrowright R-X \longrightarrow \overset{H}{\underset{}{}}\geq \overset{+}{N}-R\ X^- \rightleftharpoons \geq \ddot{N}-R + HX \quad (6.6a)$$

(ii) Acylation:

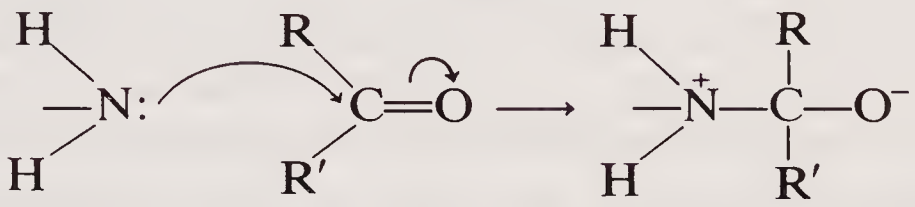


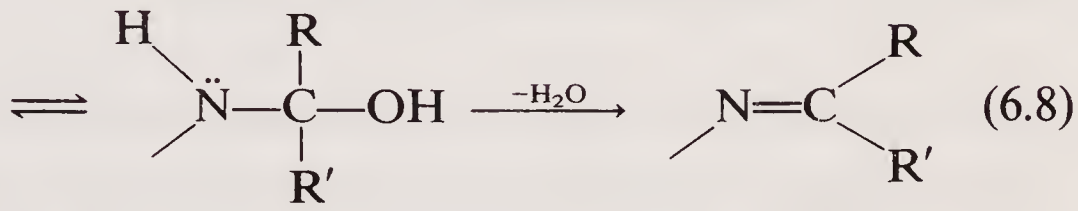
(6.7)



(6.7a)

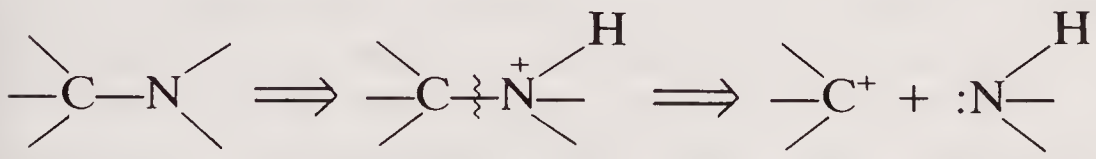
(iii) Condensation:





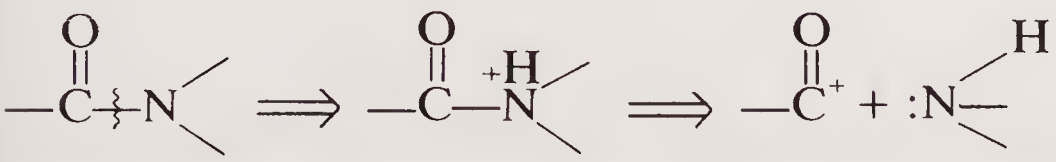
(6.8)

Thus it follows that when a molecular skeleton contains amino-nitrogen (i.e. —N< singly bonded to three different atoms) the correct disconnection is almost always:



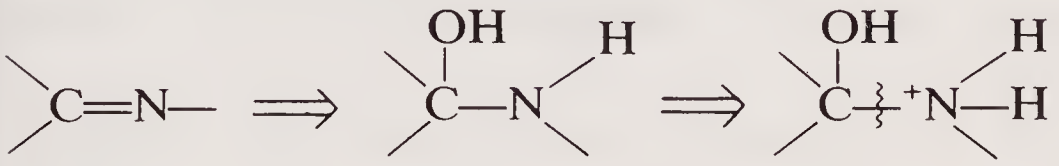
(6.9)

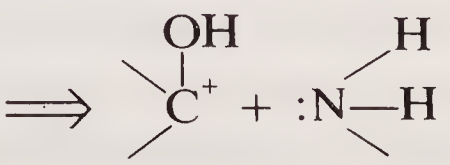
Similarly for amides,



(6.10)

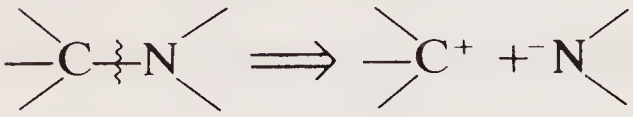
and for carbon–nitrogen double bonds, by far the most common disconnection is:





(6.11)

The reader is entitled to ask why we have chosen to write (6.9) in an extended form rather than the simpler form (6.9a) shown below, since in this latter form there is an obvious analogy with (6.1) and (6.4):



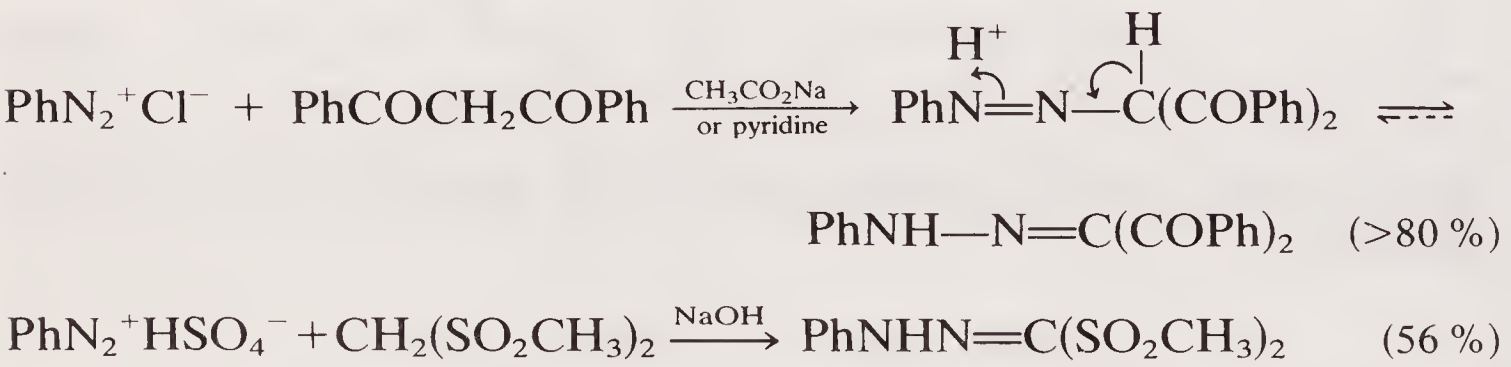
(6.9a)

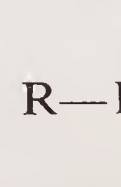
In fact, there is no reason why one should not use the simplified form (6.9a), provided that one remembers that  **is only a synthon** (representing nucleophilic nitrogen) and that **it does not represent amide ions.** Admittedly, alkali metal amides are occasionally used to form C–N single bonds [for example, in the Tschitschibabin amination of pyridine (scheme 2.5)], but they are much too strongly basic to be generally useful as nucleophiles, since they are liable to cause eliminations, rearrangements, and other unwanted side-reactions.

6.3.2 Electrophilic nitrogen and nucleophilic carbon

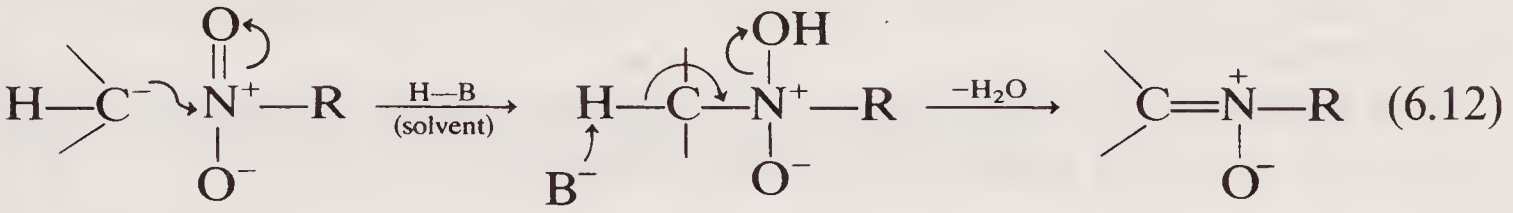
As far as amino-nitrogen is concerned, this type of interaction is rarely important. The two notable exceptions (and neither is particularly common) are the formation of aziridines from alkenes and nitrenes (cf. section 7.2.3) and the Beckmann rearrangement (Sykes, pp. 123–6).

On the other hand, nitrogen electrophiles occupy an important place in the chemistry of aromatic compounds, NO_2^+, NO^+, and ArN_2^+ being the most familiar. Of these, the first two are of value mainly for the introduction of functional groups, and need not concern us further here (but see section 6.3.3). However, arenediazonium ions may be used in skeleton-forming reactions, not only with 'electron-rich' aromatic systems like phenols (scheme 2.9) but also with enolates and other stabilised carbanions, e.g.



In principle, it should be possible for nitro-compounds,  , to function as sources of electrophilic nitrogen, and one might expect

reaction with, for example, a carbanion as follows (cf. condensation with a $>C{=}O$ group):

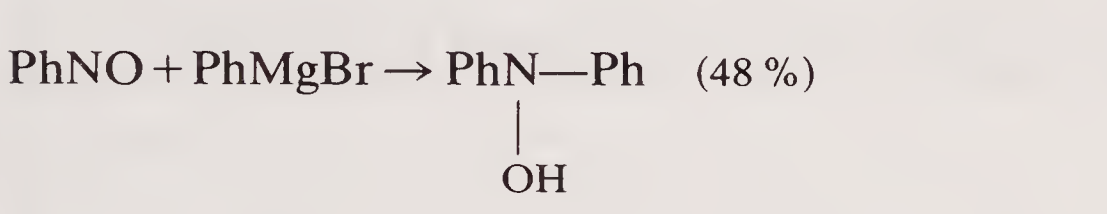


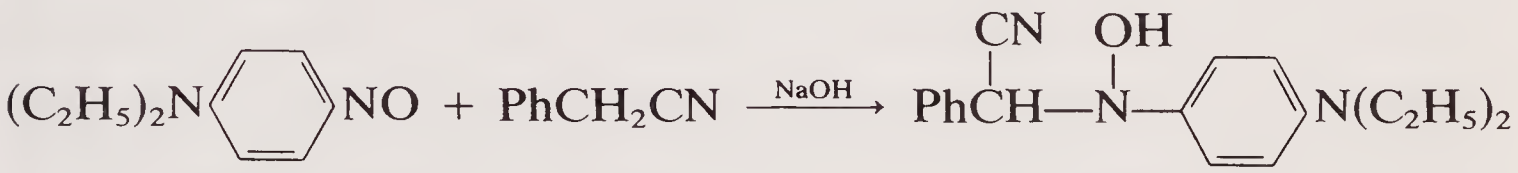
(6.12)

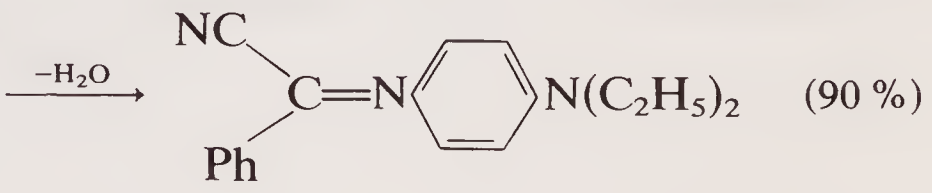
In practice, however, although the process is useful in certain areas of heterocyclic chemistry (section 7.1.4.2) the generality of the reaction is insufficient to merit further consideration here.

6.3.3 Nitroso-compounds, including nitrites

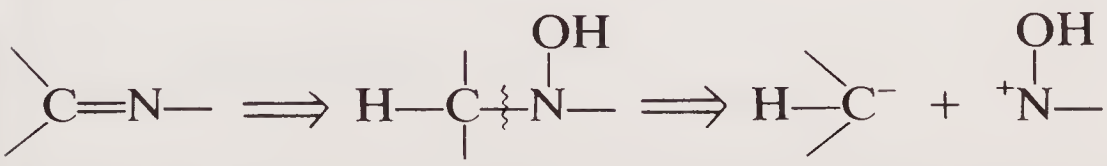
In principle, the nitroso-group may act as a source of either electrophilic or nucleophilic nitrogen; for although the N=O bond is polar, and the nitroso-group may thus be regarded as the nitrogen analogue of an aldehyde (i.e. with *electrophilic* nitrogen), the nitrogen also carries an unshared pair of electrons which may confer *nucleophilic* character upon it. In practice most of the useful synthetic procedures involve nitroso-compounds as electrophilic species, as the following examples show:







This latter reaction indicates another possible disconnection for a carbon–nitrogen double bond:



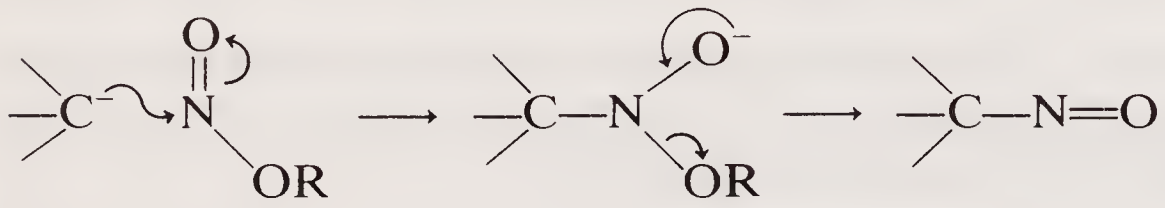
(6.13)

It must be emphasised, however, that this is relatively uncommon. Nitroso-compounds are themselves often difficult to prepare, and once

prepared they may be highly reactive and difficult to handle. In the vast majority of cases, the correct disconnection for C=N bonds is that of (6.11).

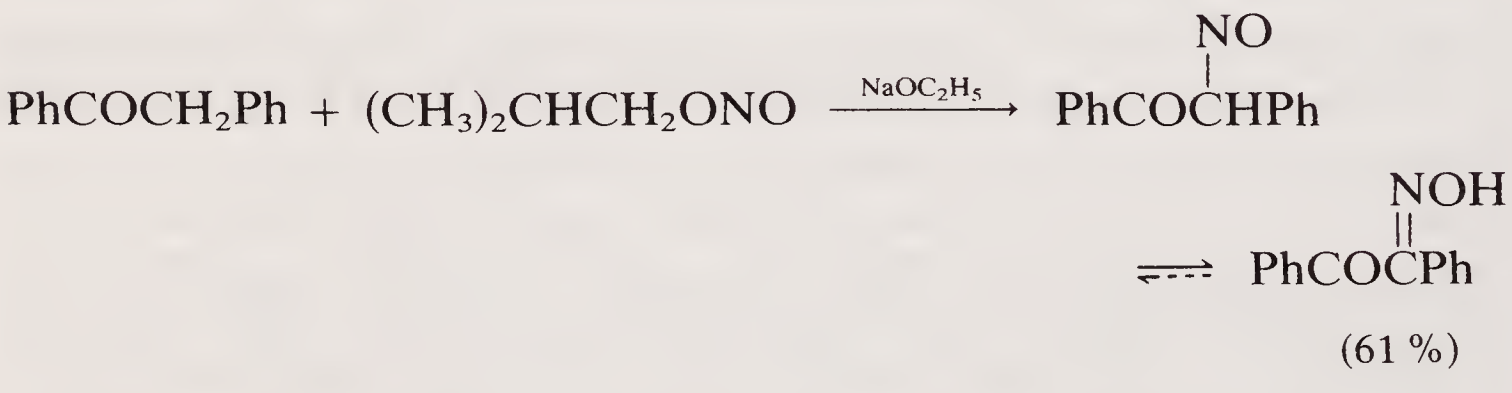
We shall return to this and related reactions in the chapter on oxidation (section 9.2.3).

Just as carboxylate esters may act as acylating agents (cf. sections 4.1.2 and 5.2.2) so nitrite esters are nitrosating agents:



(6.14)

For example,



We shall also return to this reaction in Chapter 9 (section 9.5.2).

7 Ring closure (and ring opening)

So far in this book, little attention has been paid to those bond-forming reactions which lead to the creation of a cyclic molecule, and so, in this final chapter dealing with the construction of molecular frameworks, we consider reactions resulting in ring closure.

The first (and, undoubtedly, the largest) group of ring forming reactions comprises nothing more than **intramolecular** variants of reactions described elsewhere in the book in *inter*molecular terms. In these processes, an *n*-membered ring is formed by cyclisation of a chain of *n* atoms. The second group of reactions is **intermolecular,** involving the simultaneous formation of *two* bonds between (usually) two different molecules. Such processes are usually called **cycloadditions,** the **Diels–Alder reaction** (Sykes, pp. 197–8) being the best known example. (A careful distinction should be made between these genuinely concerted, intermolecular ring closures and the large group of apparently intermolecular cyclisations which in reality consist of two separate steps, ring closure being the second.) The third group consists of **electrocyclic** reactions, which are *intra*molecular and related mechanistically to cycloadditions.

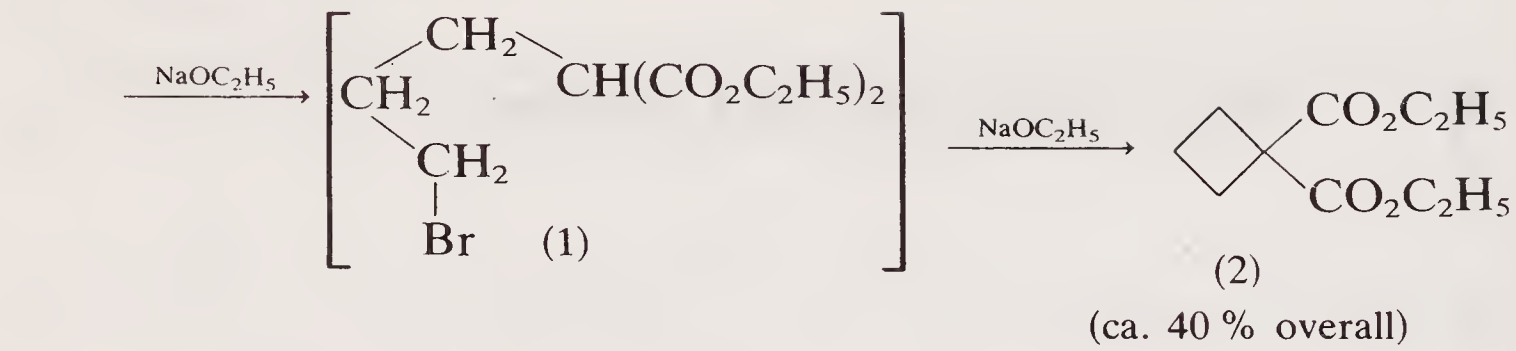
By comparison with ring closure, ring opening is a relatively little-used process in synthesis, but it is of considerable value in a few special situations, as will be seen in section 7.4.

7.1 Intramolecular cyclisation by electrophile–nucleophile interaction

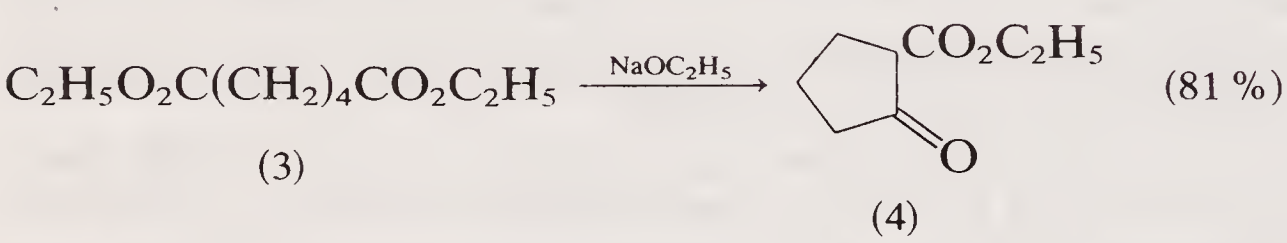
7.1.1 Introduction

Many of the bond-forming reactions which were described in earlier chapters may be adapted to produce cyclic compounds, as the following examples show:

Alkylation (cf. section 5.1.1):



Acylation (cf. section 5.2.2):

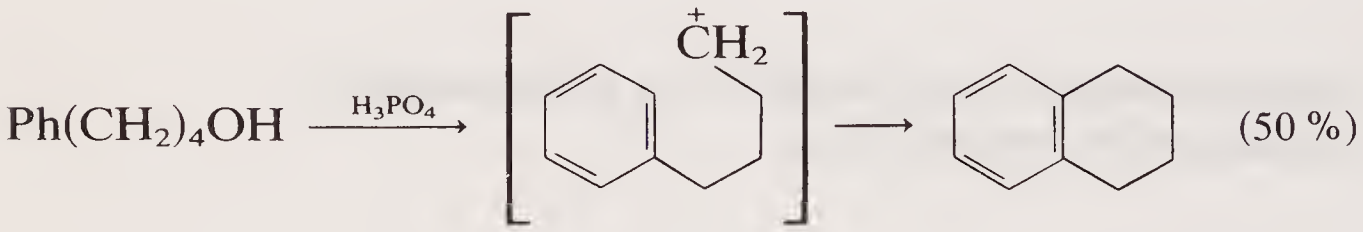


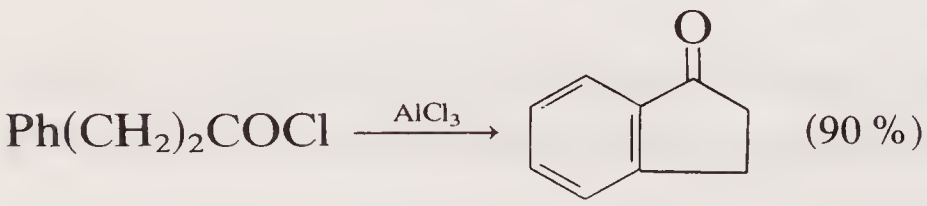
This intramolecular equivalent of the Claisen acylation is generally known as the **Dieckmann reaction** (see also Sykes, p. 230).

Condensation (cf. section 5.2.4):

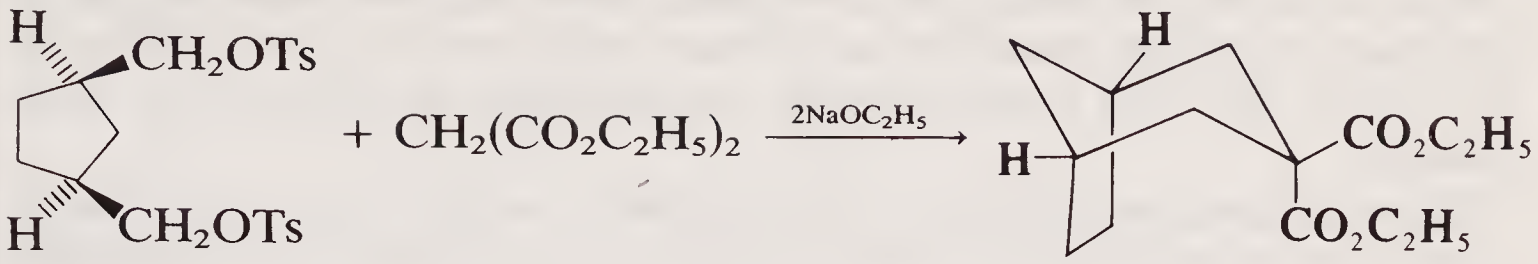
Monocyclic compounds may similarly be converted into bicyclic compounds, e.g.

Electrophilic aromatic substitution (section 2.5):



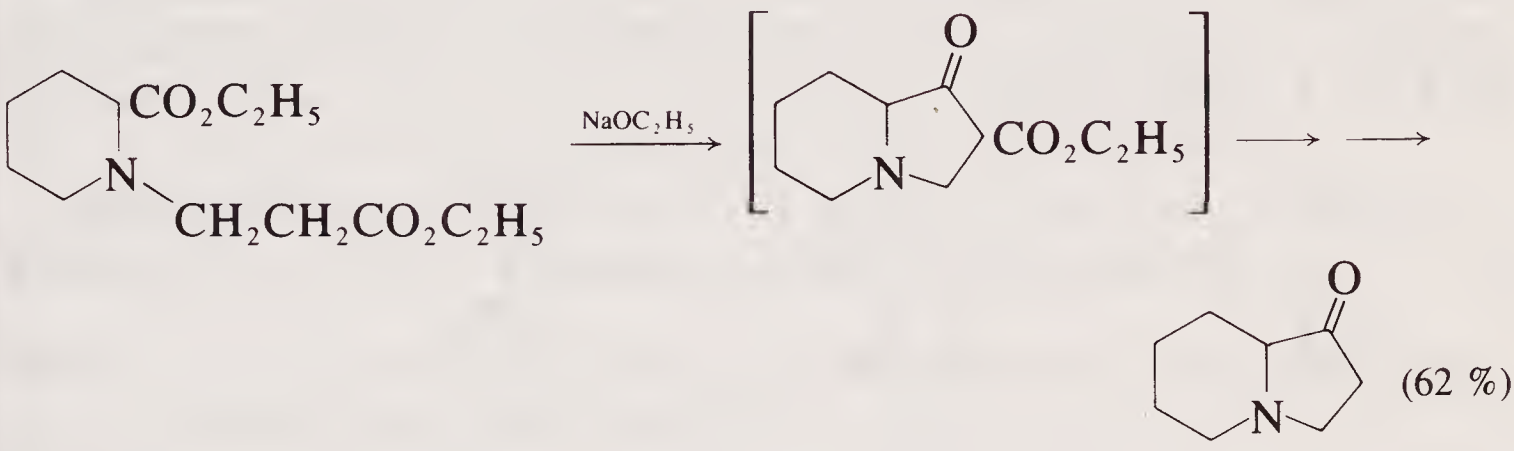


Alkylation:



(75 %)

Acylation



(62 %)

Condensation:

(85 %)

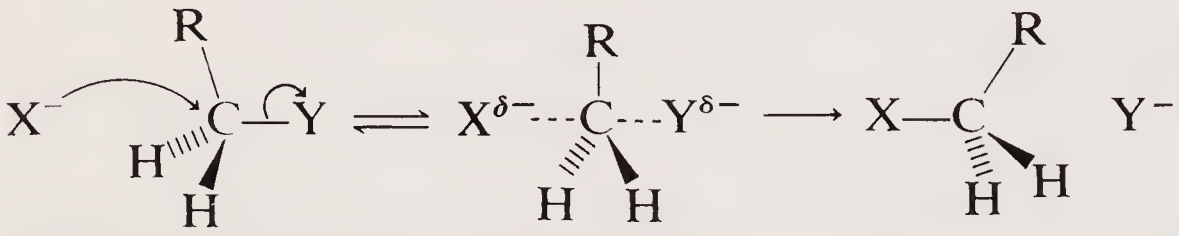
Heterocyclic compounds may be prepared by analogous methods: the majority of these involve carbon–heteroatom bond formation with the heteroatom as the nucleophilic centre.

7.1.2 Facility of intramolecular ring closure: Baldwin's rules

There are several factors which influence the ease with which intramolecular ring closure occurs. First, there is the 'distance factor'. For the formation of an *n*-membered ring, the new bond must be formed between two atoms which are separated by $(n - 2)$ other atoms, and it follows that, as *n* increases, there is a decreasing probability of the molecule adopting a conformation in which the 'reactive' atoms are sufficiently close for bond formation to occur. Second, there are various kinds of 'strain factor'. Angle strain (i.e. distortion of the normal bond angles) in the cyclised compound may destabilise it relative to its acyclic precursor, and *if the ring closure is reversible* the equilibrium may then lie in favour of the latter. Unfavourable steric interactions in the product (e.g. 1,3-diaxial repulsion between substituents[1]) may have the same effect. Angle strain and/or unfavourable steric interactions in the *transition state* for the ring closure step are of much wider significance. It is a consideration of the geometry of these transition states which has led to the

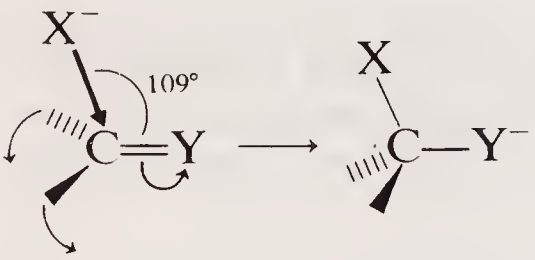
formulation of **Baldwin's rules for ring closure.**[2] If a transition state cannot be attained without a serious distortion of normal bond angles or distances, it follows that the ring closure will occur only with difficulty (or not at all), and such processes are described by Baldwin as *disfavoured.*

Most readers will already be familiar with the geometry of the transition state for nucleophilic substitution (S_N2 reaction) at a tetrahedral carbon atom. If the overall reaction is $X^- + RCH_2Y \rightarrow RCH_2X + Y^-$, for example, the optimum direction of approach of the incoming nucleophile X^- is along the C–Y axis, and the resulting transition state (5) has an X–C–Y angle of 180°.

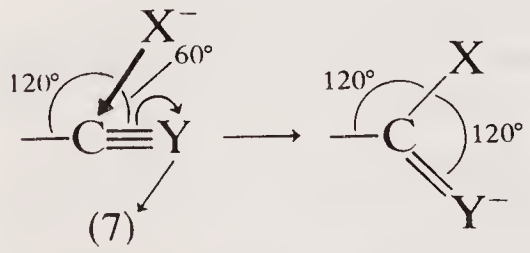


(5) (7.1)

In the corresponding reactions in which the electrophilic carbon is trigonal (as in a carbonyl group) or digonal (e.g. in an alkyne or a cyano-group), the optimum direction of approach of the nucleophile is at an angle of 109° to the C=Y bond, and 60° to the C≡Y bond respectively [structures (6) and (7)].

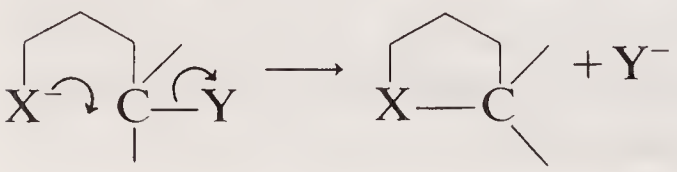


(6) (7.2)



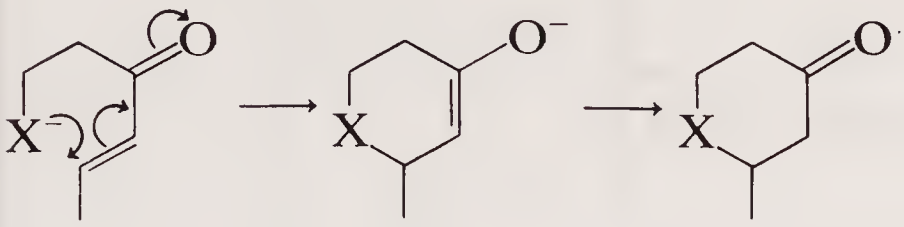
(7) (7.3)

In Baldwin's terminology, ring closures are classified according to three criteria: (i) the size of the ring being formed, (ii) whether the atom or group Y lies outside the ring being formed or else is part of the ring system, and (iii) whether the electrophilic carbon is tetrahedral, trigonal, or digonal. So a reaction of the type (7.4) would be classified as 5-*Exo-Tet* (five-membered ring, Y outside the ring being formed, tetra-



(7.4)

hedral carbon undergoing substitution). Similarly, an intramolecular Michael reaction of the type (7.5) would be classified as 6-*Endo-Trig*



(7.5)

[six-membered ring, Y (= carbon in this case) forming part of the ring, trigonal carbon undergoing addition], and reactions (1) → (2) and (3) → (4) (p. 126) are 4-*Exo-Tet* and 5-*Exo-Trig* respectively.

Baldwin's Rules are as follows. They apply to cyclisations in which the nucleophilic atom X is a first-row element (e.g. C, N or O).

Rule 1 3- to 7-*Exo-Tet* processes are all favoured; 5- and 6-*Endo-Tet* processes are disfavoured.[3]

Rule 2 3- to 7-*Exo-Trig* processes are all favoured; 3- to 5-*Endo-Trig* processes are disfavoured; 6- and 7-*Endo-Trig* processes are favoured.

Rule 3 3- and 4-*Exo-Dig* processes are disfavoured; 5- to 7-*Exo-Dig* processes are favoured; 3- to 7-*Endo-Dig* processes are favoured.

It does not follow, of course, that because a process is 'favoured' it will necessarily occur readily in every case. The other factors mentioned earlier may all exert an influence. In general, however, a 'favoured' process occurs more readily than one which is 'disfavoured', and five- and six-membered ring compounds are formed more easily than their analogues with smaller or larger rings.

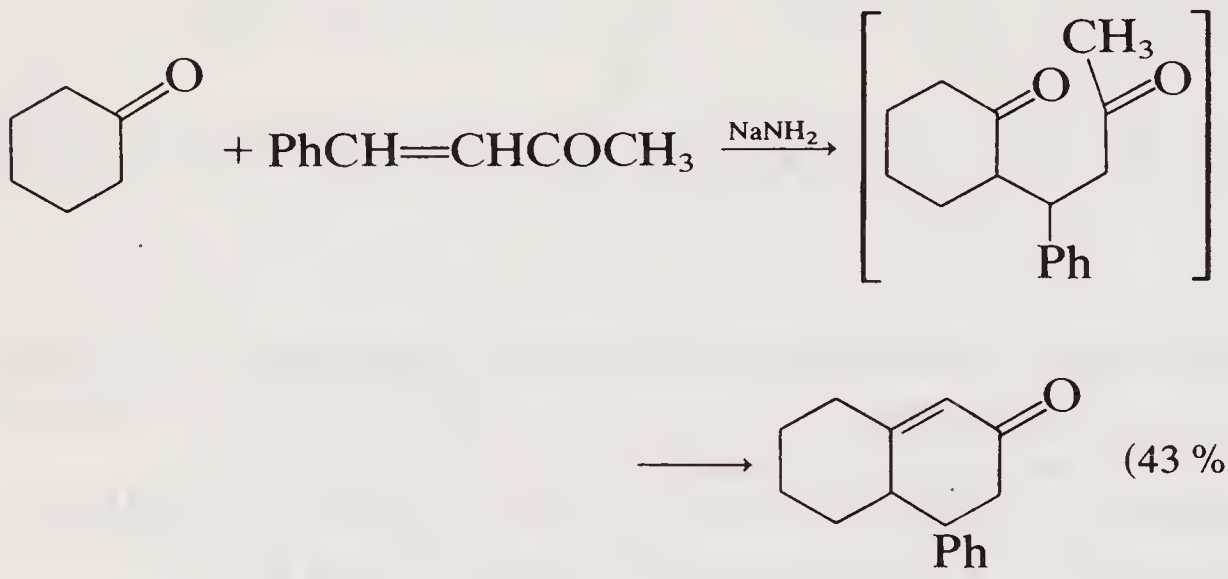
The reader is invited to describe the other cyclisations in this section using the Baldwin notation.

7.1.3 Michael addition in ring closure processes

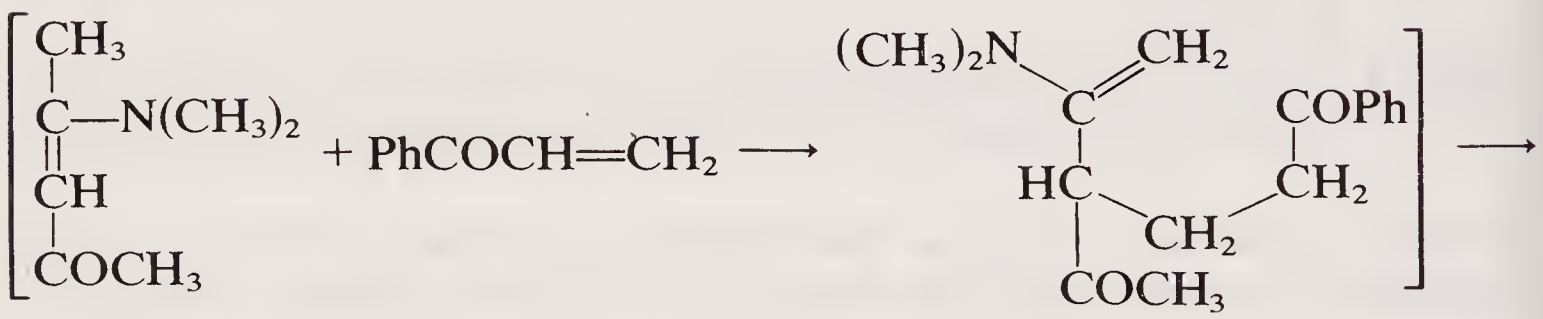
Intramolecular cyclisation of the type described above involves the interaction of an electrophilic and a nucleophilic centre which are already joined by a chain of, say, $(n - 2)$ other atoms. The electrophilic and nucleophilic properties of those centres result from the presence of adjacent functional groups, and the construction of the chain of n atoms with the functional groups correctly positioned is often the most difficult part of the synthesis.

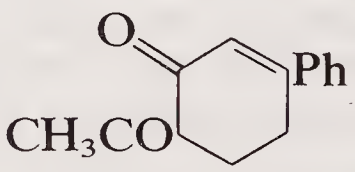
In this regard, the Michael reaction in one or other of its various forms (sections 5.1.5, 5.2.5, and 5.4.3) has proved particularly useful, since it leads to a product in which two $-M$ groups are separated by (usually) three carbon atoms. The basic conditions necessary for the Michael reac-

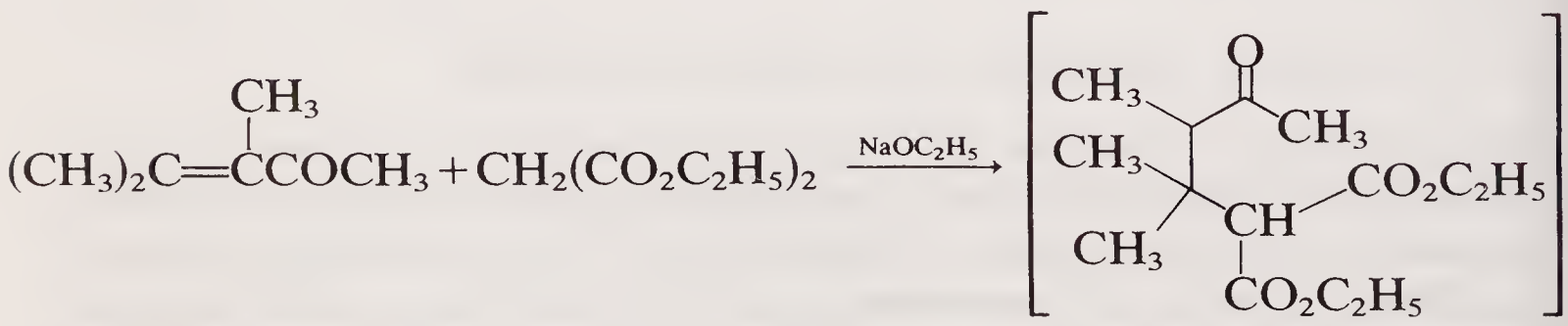
tion may also serve to promote a subsequent condensation or similar ring closure step, as the following examples show:

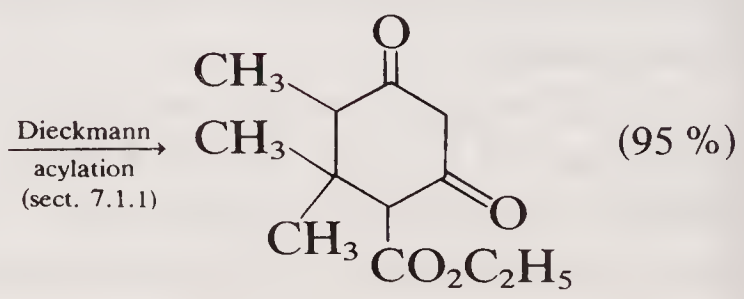


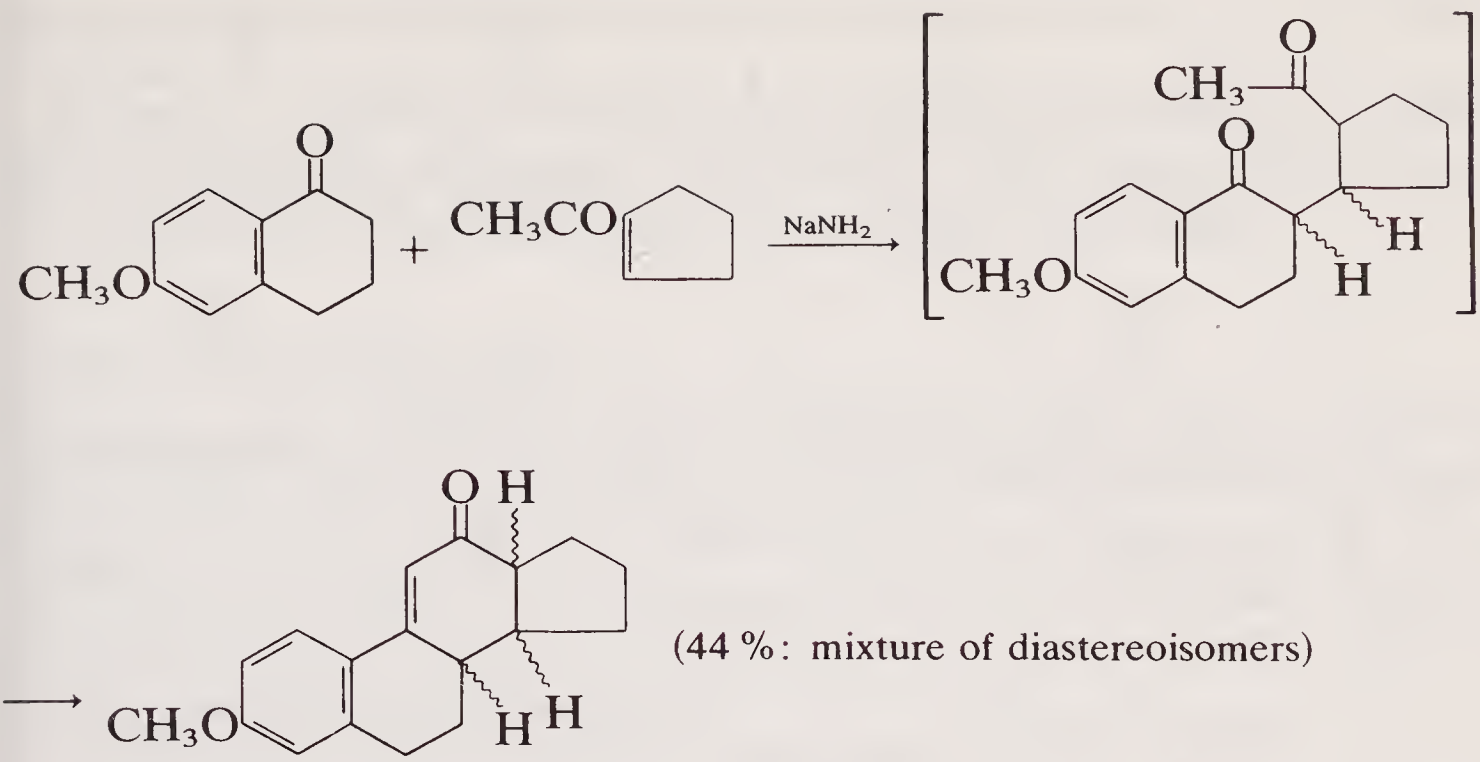
$$CH_3COCH_2COCH_3 + PhCOCH_2CH_2N(CH_3)_2 \xrightarrow[\text{[cf. reaction (5.33)]}]{\text{'thermal Michael'}}$$











(44 %: mixture of diastereoisomers)

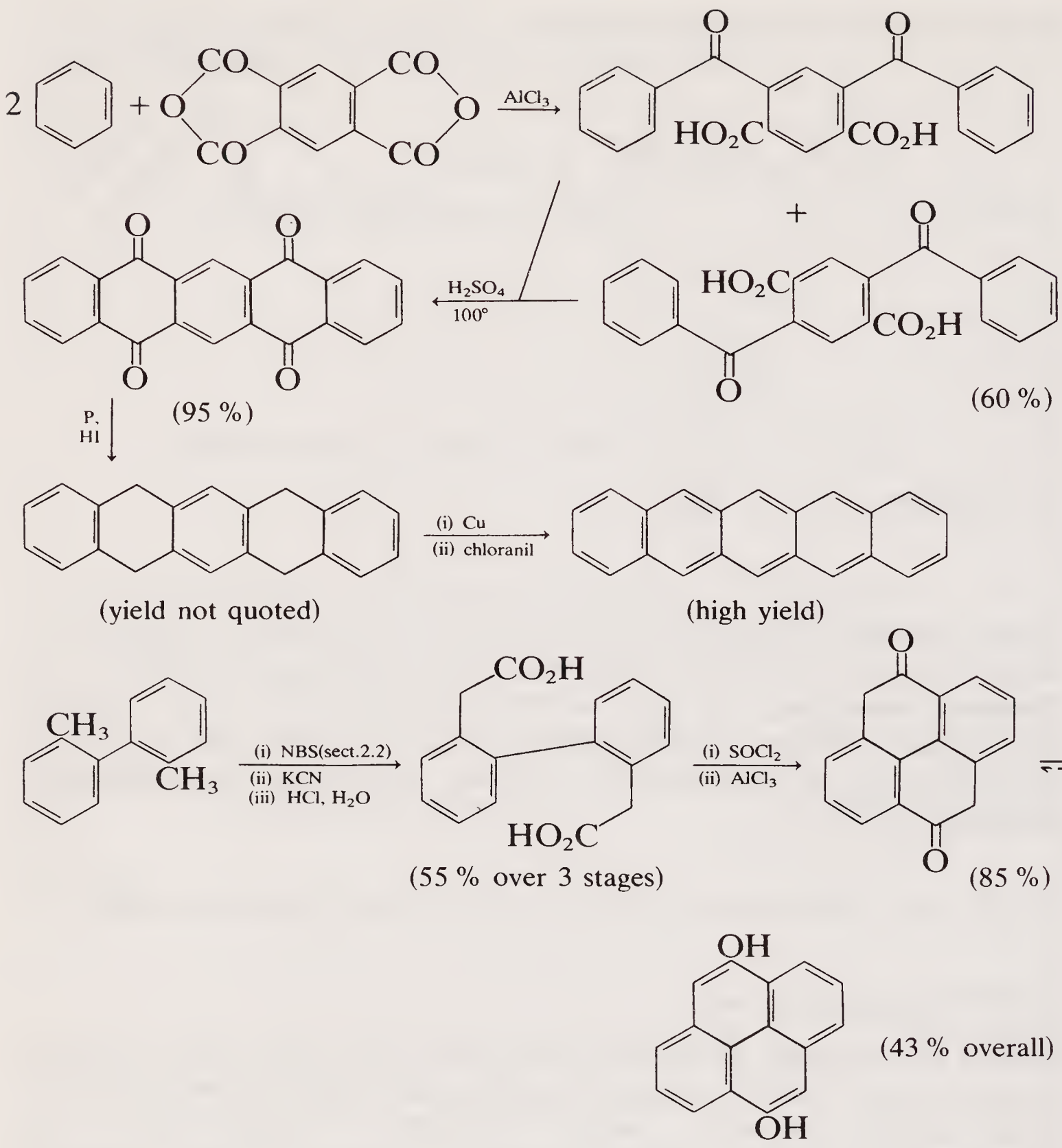
Michael addition followed by intramolecular condensation, as illustrated in the first and last of the above reactions, is sometimes referred to as **Robinson annulation.** The use of a Mannich base in place of an enone in the Michael reaction was also introduced by Robinson, and such reactions (like the second example above) are sometimes called **Michael–Robinson additions**.

7.1.4 Cyclisation leading to aromatic and heteroaromatic rings

7.1.4.1 Carbocyclic rings

Such a large number of benzene derivatives, with a wide variety of functional groups, may be obtained commercially that the preparation of other benzene derivatives usually amounts to nothing more than functionalisation and/or interconversion of functional groups. Methods for preparing benzene derivatives from acyclic precursors are seldom of practical importance, at least on a 'laboratory' scale, and are therefore not considered further in this book.

Naphthalene derivatives are also available in reasonable variety, but relatively few representatives of other polycyclic aromatic systems are obtainable other than by laboratory syntheses. Such syntheses generally involve benzene or naphthalene derivatives as starting materials, and two reactions commonly employed for the actual ring-closure step are a variant of the Friedel–Crafts reaction (cf. section 7.1.1) or an arylation (cf. section 2.5), as the following examples show. It should be noted that the Friedel–Crafts method may not lead initially to the formation of a fully conjugated molecule, and that a subsequent dehydrogenation step (or steps: section 9.2.4) may therefore be required:


2
+
CO
CO
CO
CO
AlCl3
HO2C
CO2H
H2SO4
100°
+
HO2C
CO2H
(95 %)
(60 %)
P,
HI
(i) Cu
(ii) chloranil
(yield not quoted)
(high yield)
CH3
CH3
(i) NBS(sect.2.2)
(ii) KCN
(iii) HCl, H2O
CO2H
HO2C
(55 % over 3 stages)
(i) SOCl2
(ii) AlCl3
(85 %)
OH
OH
(43 % overall)
CHO
NO2
+ PhCH2CO2−K+
(CH3CO)2O
CO2H
NO2
(50 %)
FeSO4
NH3,H2O
CO2H
NH2
(77 %)
NaNO2
H2SO4
CO2H
N2+
HSO4−
Cu
100°
CO2H
(93 %)
(36 % overall)

(Intramolecular arylation of this type is usually referred to as the **Pschorr reaction.**)

The Diels–Alder reaction may also be used in certain cases to prepare polycyclic systems (cf. section 7.2.1), and in other instances (cf. section 7.3) electrocyclic processes have been employed successfully.

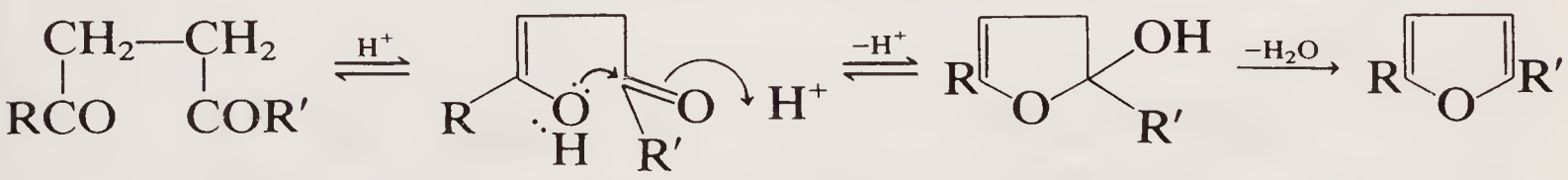
7.1.4.2 Heterocyclic rings

Methods for the synthesis of heterocyclic compounds are so numerous, and of such variety, that a separate volume would probably be required to cover the topic adequately. What follows here is an attempt to offer a few general guidelines; the coverage is restricted to the most common ring sizes and heteroatoms, *viz.* five- and six-membered rings containing oxygen, sulphur, and nitrogen.

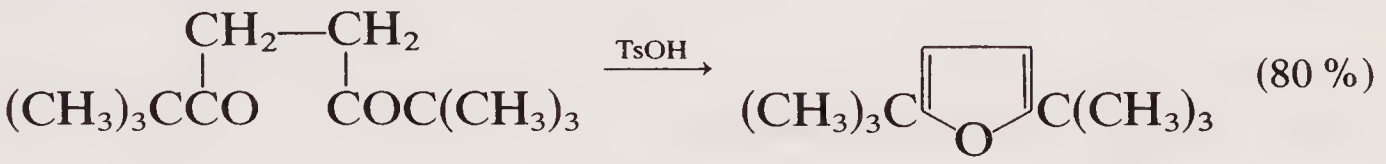
The following features of these reactions should be noted:

(i) in the synthesis of a monocyclic compound, the ring closure step very often (although by no means always) involves carbon–heteroatom bond formation;
(ii) if the system contains two adjacent heteroatoms, it is unusual for the ring closure step to involve heteroatom–heteroatom bond formation [except when the electrophilic group is nitroso- or nitro- (cf. sections 6.3.2 and 6.3.3), a nitrene (cf. section 12.4.2), or a diazonium group (cf. section 6.3.2)];
(iii) if the target molecule is bicyclic, with the heterocyclic ring fused to a benzene ring, the starting compound is almost invariably a pre-formed benzene derivative.

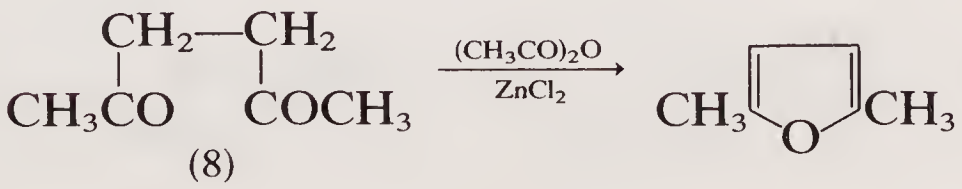
A. *Monocyclic compounds* For the formation of heterocycles containing **oxygen** or **sulphur,** the majority of ring closure procedures involve an enol or enethiol as the nucleophile, and a carbonyl group as the electrophile, e.g.



Specific examples include the following:

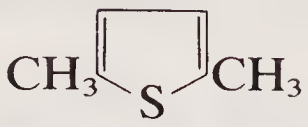
1. 

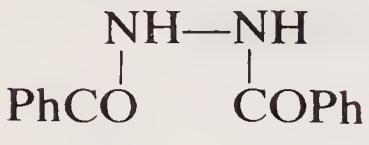
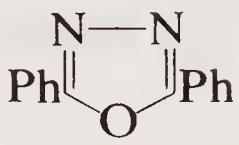
(80 %)

2. 

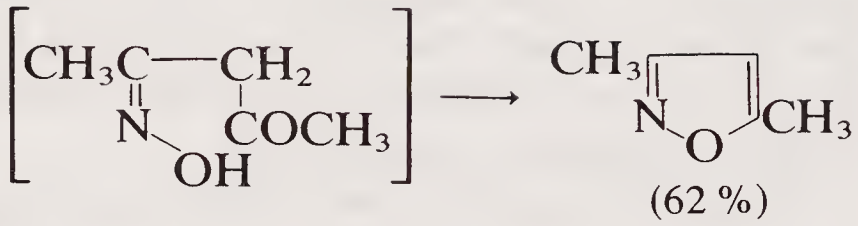
(62 %)

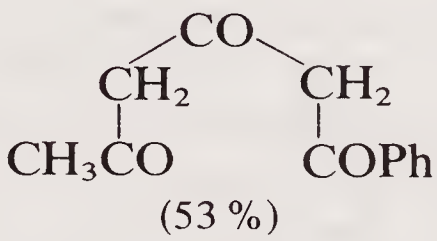
(8)

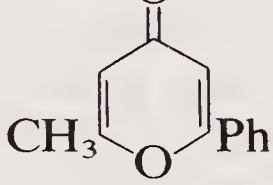
3. Compound (8) $\xrightarrow{P_2S_5}$  (50 %)

4.  $\xrightarrow{SOCl_2}$  (78 %)

5. $CH_3COCH_2COCH_3 + H_2NOH \xrightarrow{HCl}$

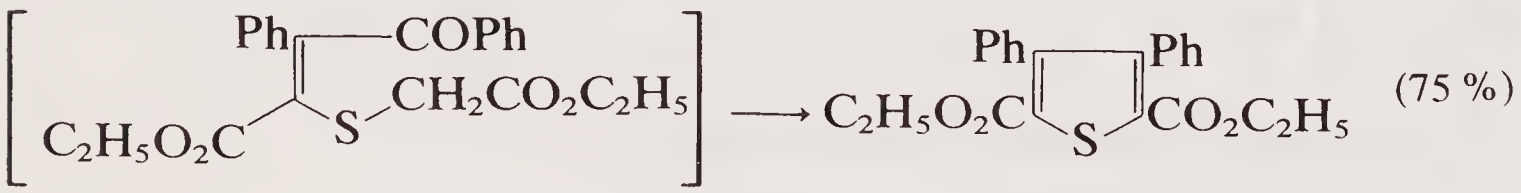

(62 %)

6. $CH_3COCH_2COCH_3$ $\xrightarrow[\text{(ii) } PhCO_2CH_3 \text{ (Claisen acylation; sect. 5.2.2)}]{\text{(i) } 2KNH_2 \text{ [cf. reaction (5.3)]}}$ 
(53 %)

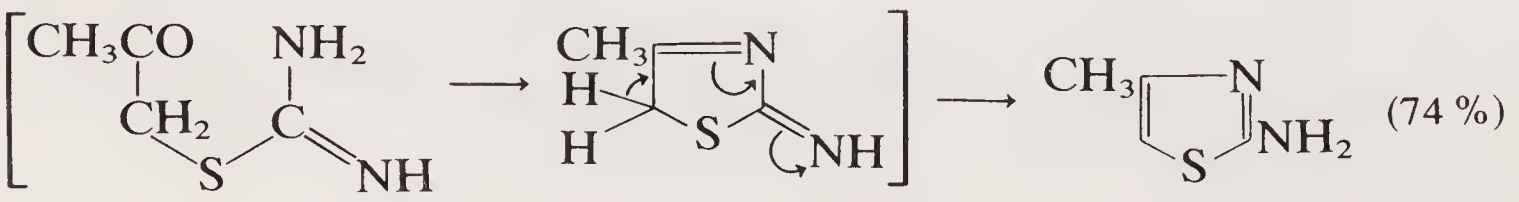
$\xrightarrow{H_2SO_4}$ 
(60 %) (32 % overall)

Exceptions to this general mode of ring closure are more common in the sulphur-containing series; in such cases intramolecular condensation usually serves as the cyclisation step, e.g.

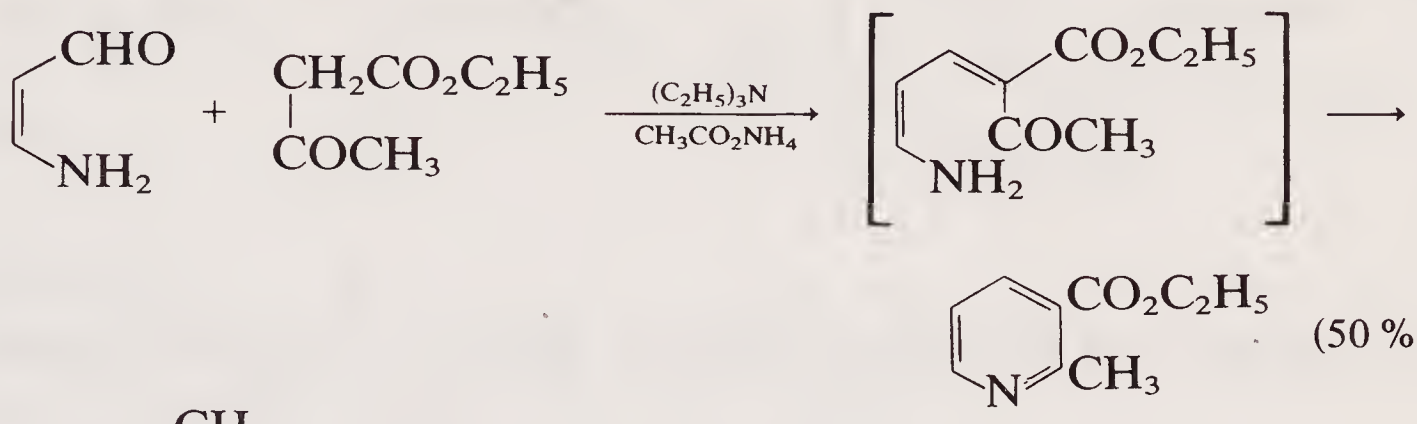
7. $PhCOCOPh + S(CH_2CO_2C_2H_5)_2 \xrightarrow{(CH_3)_3COK}$


(75 %)

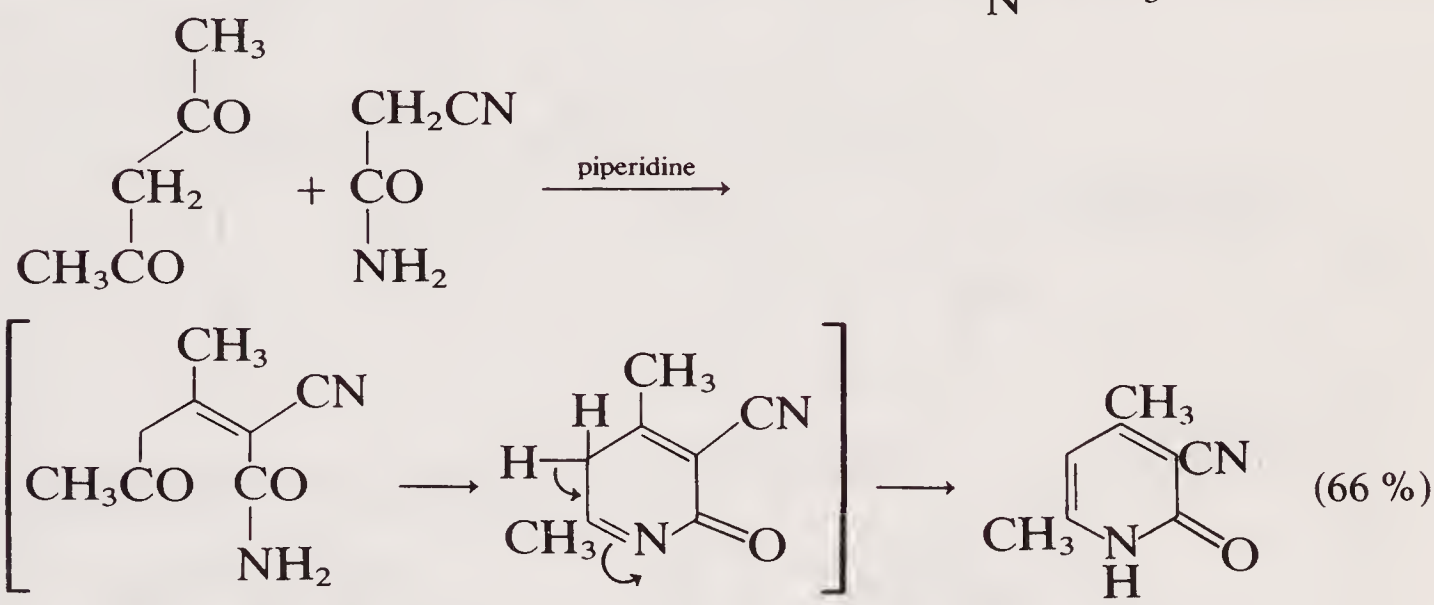
8. $CH_3COCH_2Cl + (H_2N)_2C{=}S \longrightarrow$


(74 %)

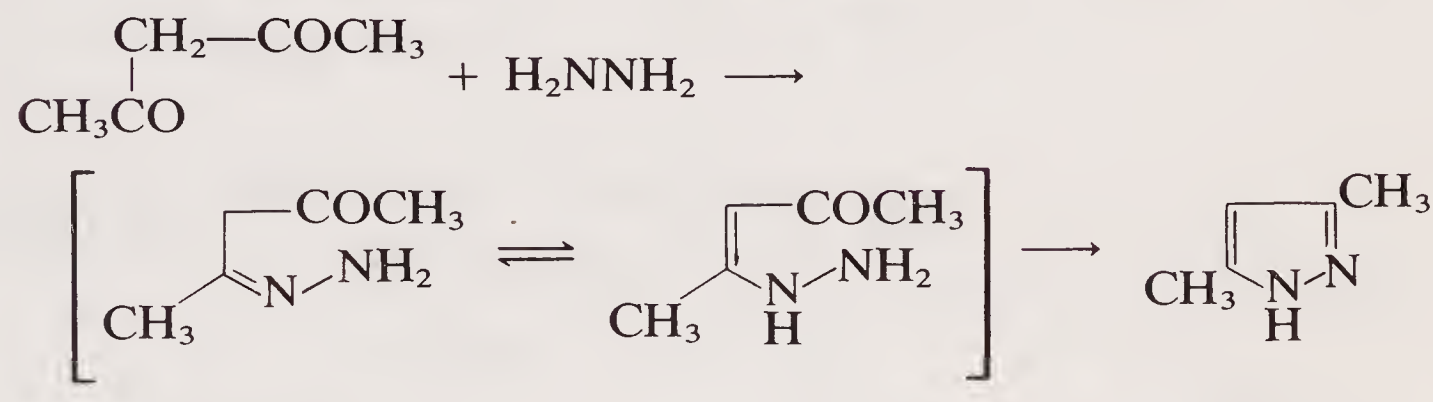
Example 8 involves carbon–nitrogen bond formation as the cyclisation step, and interactions of carbonyl and amino-groups (acylation and condensation) undoubtedly constitute the majority of cyclisations leading to **nitrogen** heterocycles, as the following examples also show:

9. 

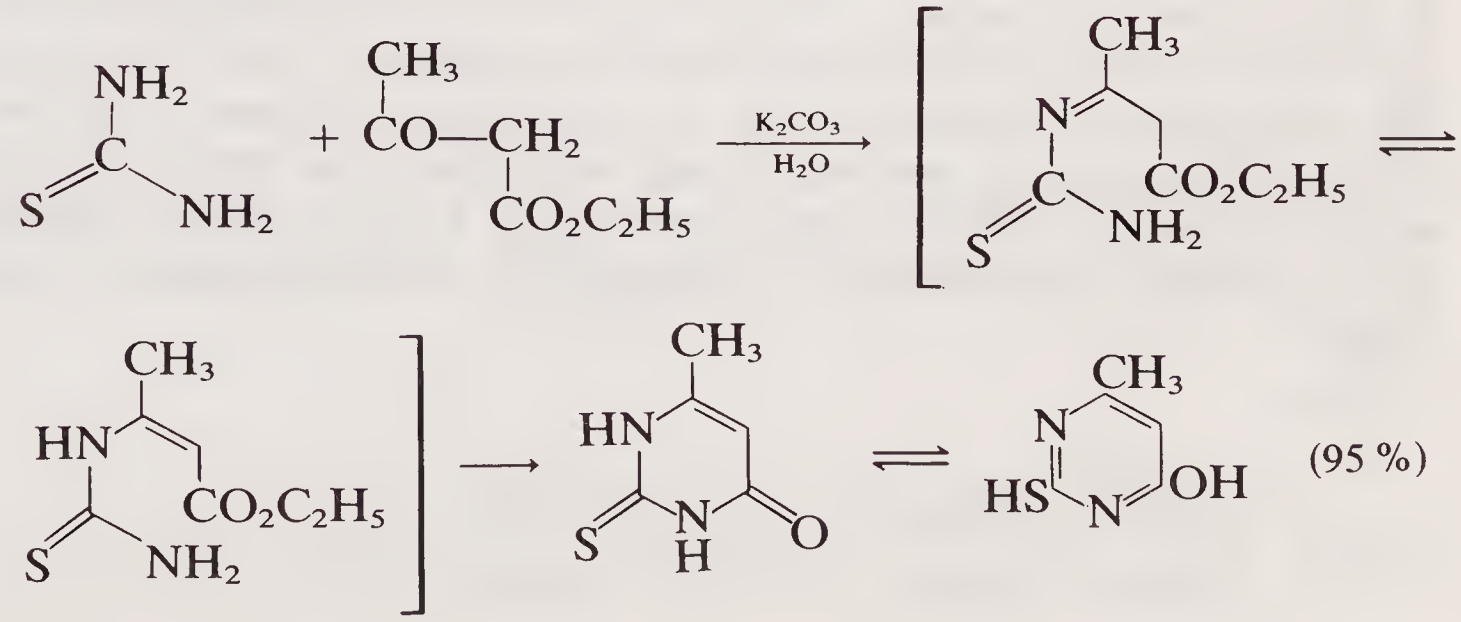
(50 %)

10. 

(66 %)

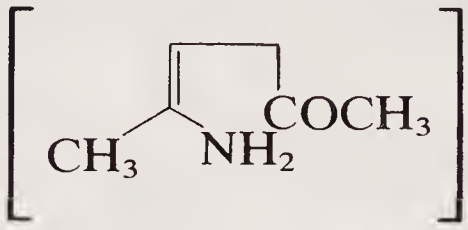
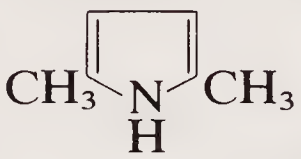
11. 

(73 %)

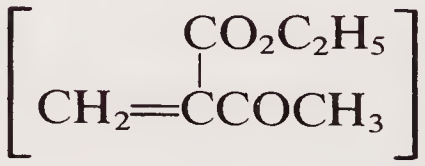
12. 

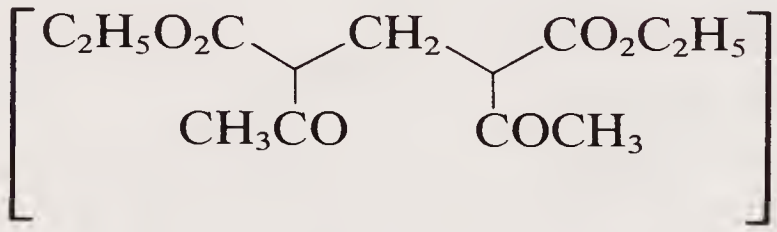
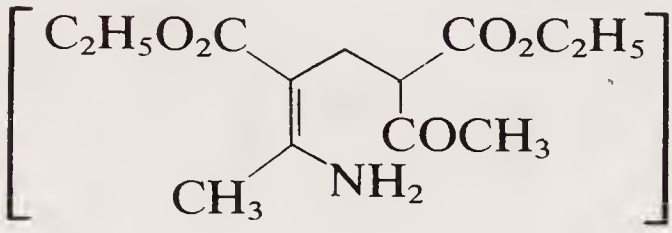
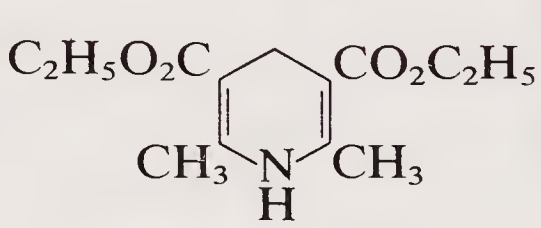
(95 %)

Nitrogen analogues of examples 1–6 involve enamines as nucleophiles in place of enols or enethiols, e.g.

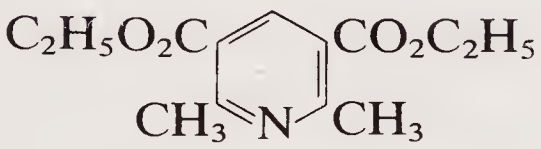
13. Compound (8) $\xrightarrow[100°]{(NH_4)_2CO_3}$  

(70 %)

14. $HCHO + CH_3COCH_2CO_2C_2H_5 \xrightarrow[\text{(cf. sect. 5.1.4)}]{(C_2H_5)_2NH}$ 

$\xrightarrow[\text{(Michael addition)}]{CH_3COCH_2CO_2C_2H_5}$  $\xrightarrow{NH_3}$  

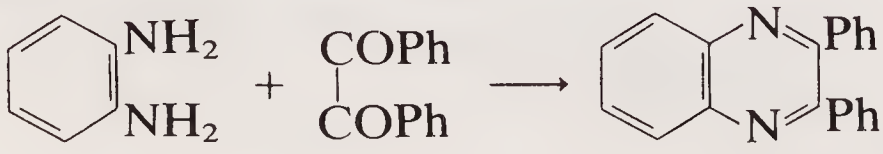
(84 %)

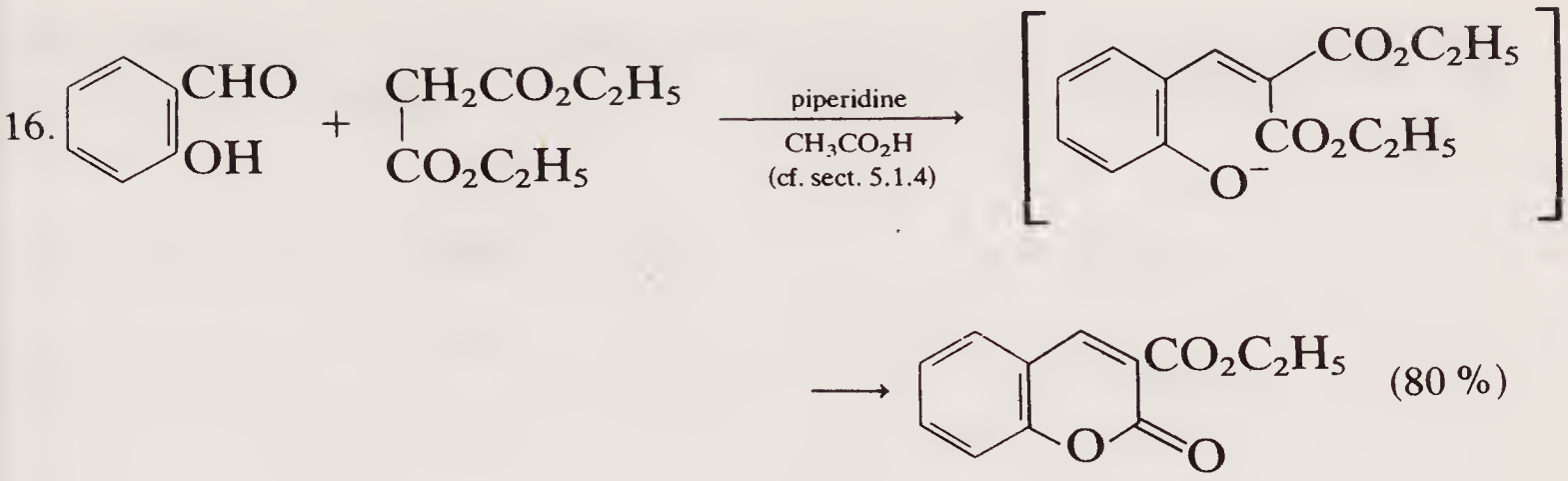
$\xrightarrow[(HNO_3)]{\text{oxidation}}$  (50 % overall)

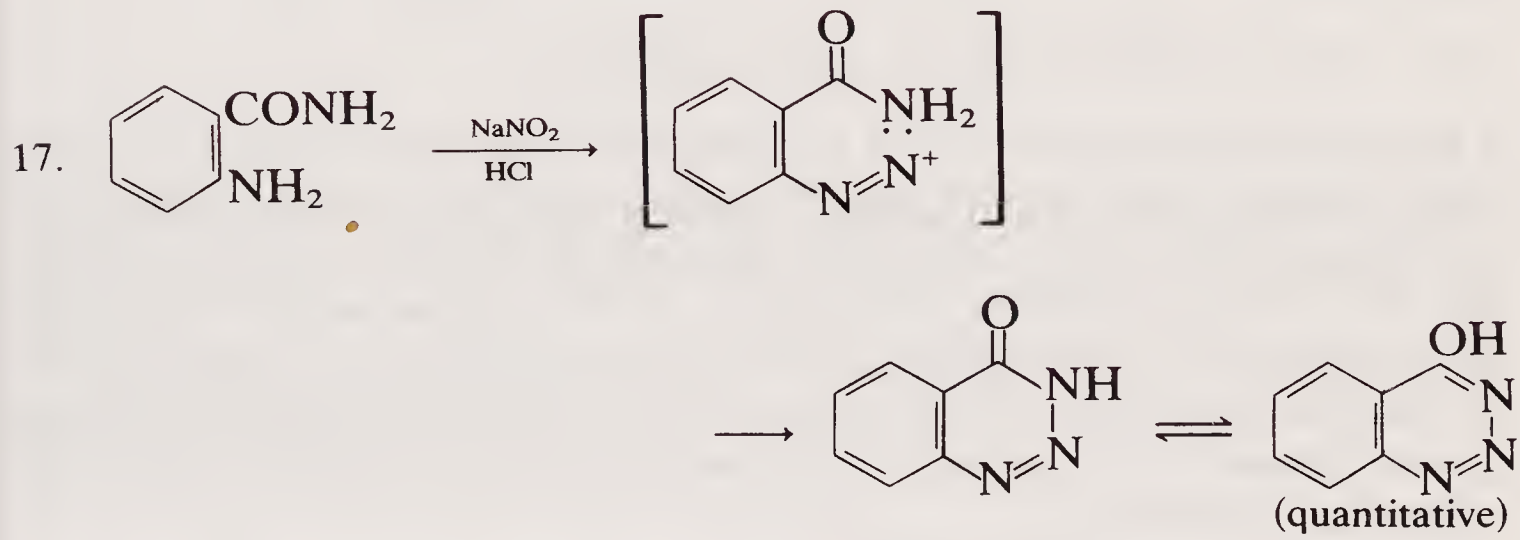
(62 %)

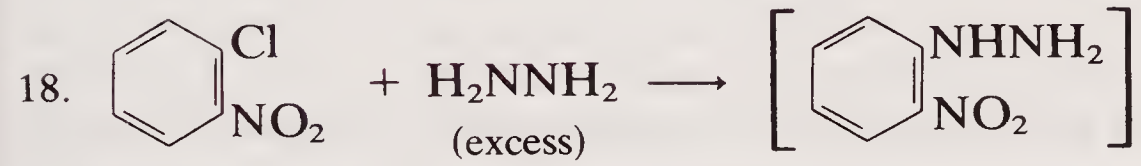
B. *Benzo-fused compounds* In these cyclisations, the starting material is generally an *ortho*-disubstituted benzene (examples 15–18), in which case the ring closure is effected by one of the methods outlined in section A above; otherwise only one substituent on the benzene ring is incorporated (examples 19–20), and ring closure is then brought about by electrophilic aromatic substitution, very often of the Friedel–Crafts or related type.

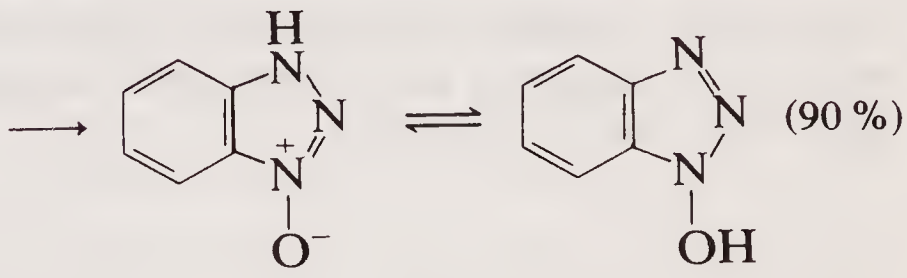
Thus,

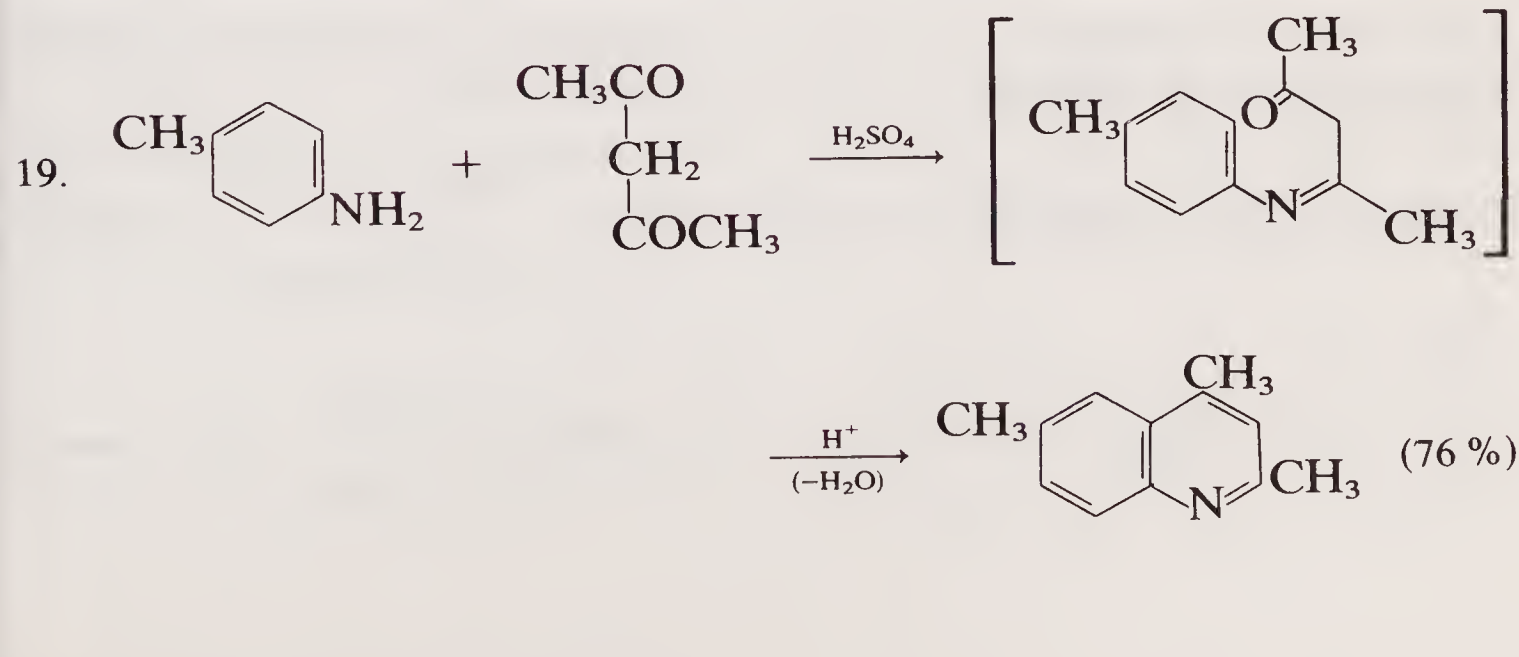
15.  (51 %)

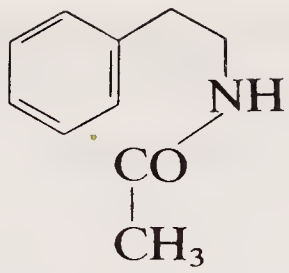
16. 
CHO
OH
+
CH2CO2C2H5
CO2C2H5
piperidine
CH3CO2H
(cf. sect. 5.1.4)
CO2C2H5
CO2C2H5
O−
CO2C2H5
O
O
(80 %)

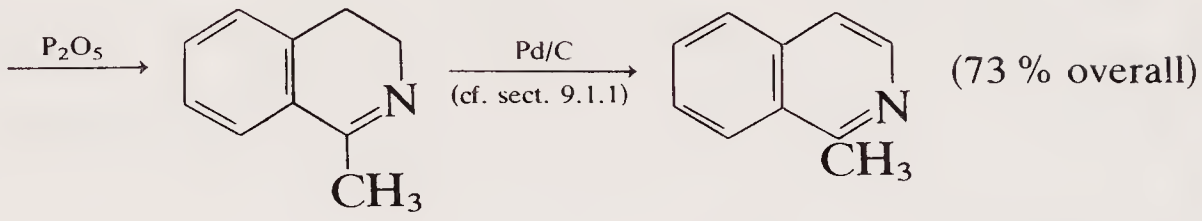
17. 
CONH2
NH2
NaNO2
HCl
O
NH2
N+
N
O
NH
N
N
OH
N
N
N
(quantitative)

18. 
Cl
NO2
+ H2NNH2
(excess)
NHNH2
NO2


H
N
N
+
N
O−
N
N
N
OH
(90 %)

19. 
CH3
NH2
+
CH3CO
CH2
COCH3
H2SO4
CH3
CH3
O
N
CH3
H+
(−H2O)
CH3
CH3
N
CH3
(76 %)

20. $PhCH_2CH_2NH_2 + CH_3COCl \longrightarrow$ 

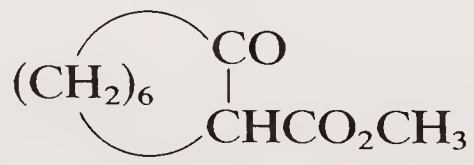


(73 % overall)

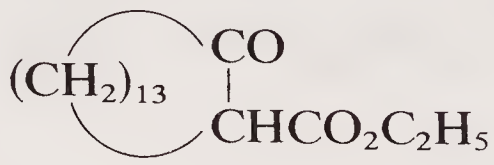
7.1.5 Formation of medium and large rings

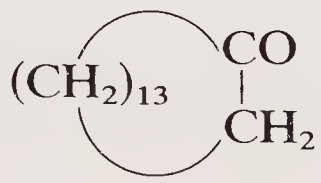
It has already been pointed out in section 7.1.2 that one of the factors on which the ease of intramolecular cyclisation depends is the so-called 'distance factor': the larger is the ring to be formed, the less is the probability that the acyclic precursor will adopt a conformation which brings the electrophilic and nucleophilic atoms sufficiently close for cyclisation to be possible. Under such circumstances, *inter* molecular reaction between two molecules of the precursor becomes much more probable than *intra*-molecular cyclisation.

For the formation of medium (eight- to eleven-membered) and large rings (twelve-membered and over), therefore, special methods may be required in order to promote cyclisation at the expense of intermolecular reactions. In the usual procedure, normally referred to as the 'high dilution' technique, the acyclic precursor is introduced very slowly into the reaction medium, so that its concentration is always very low often 10^{-3} M or less); at this concentration the probability of intermolecular reaction is greatly reduced. Under such high dilution conditions, Dieckmann and related acylation reactions lead to acceptable yields of medium- and large-ring compounds, e.g.

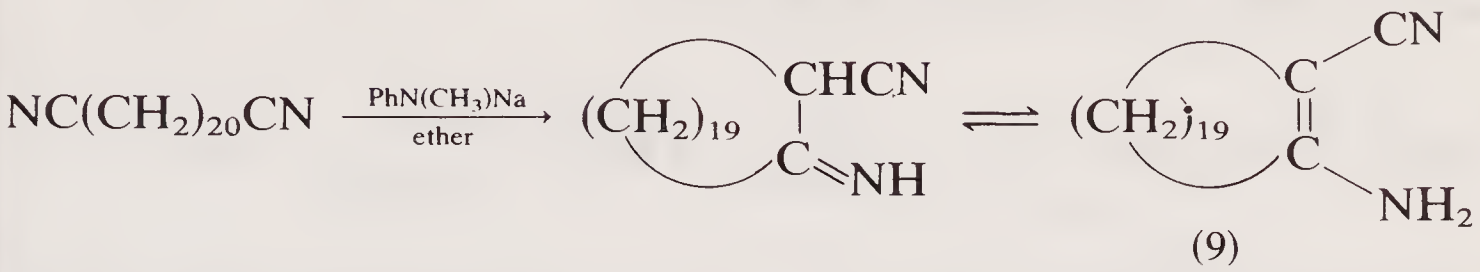
$CH_3O_2C(CH_2)_7CO_2CH_3 \xrightarrow[\text{xylene}]{\text{NaH}}$  (48 %)

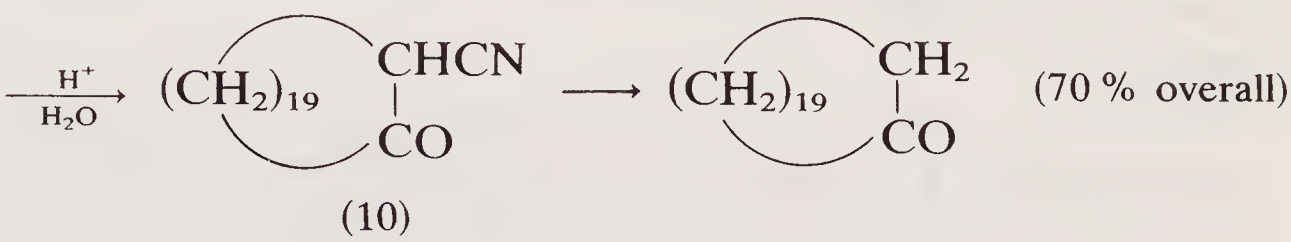
[The ester (1 M solution) is added to dropwise over 9 days to a stirred suspension of the hydride (2.5-fold excess; ca. 1 M).]

$C_2H_5O_2C(CH_2)_{14}CO_2C_2H_5 \xrightarrow[\text{xylene}]{(CH_3)_3COK}$  $\xrightarrow[\text{(cf. sect. 5.1.2)}]{H^+, H_2O}$

 (48 % overall)

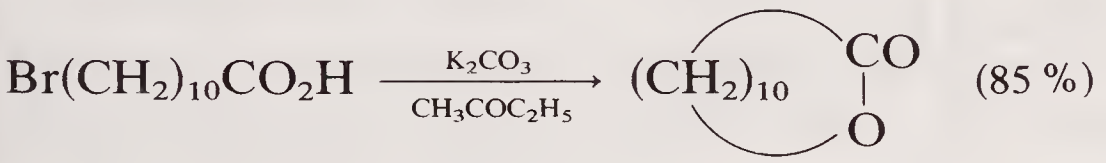
[The ester (4 M solution) is added to the base (4.8-fold excess; also ca. 4 M) dropwise over 24 h.]





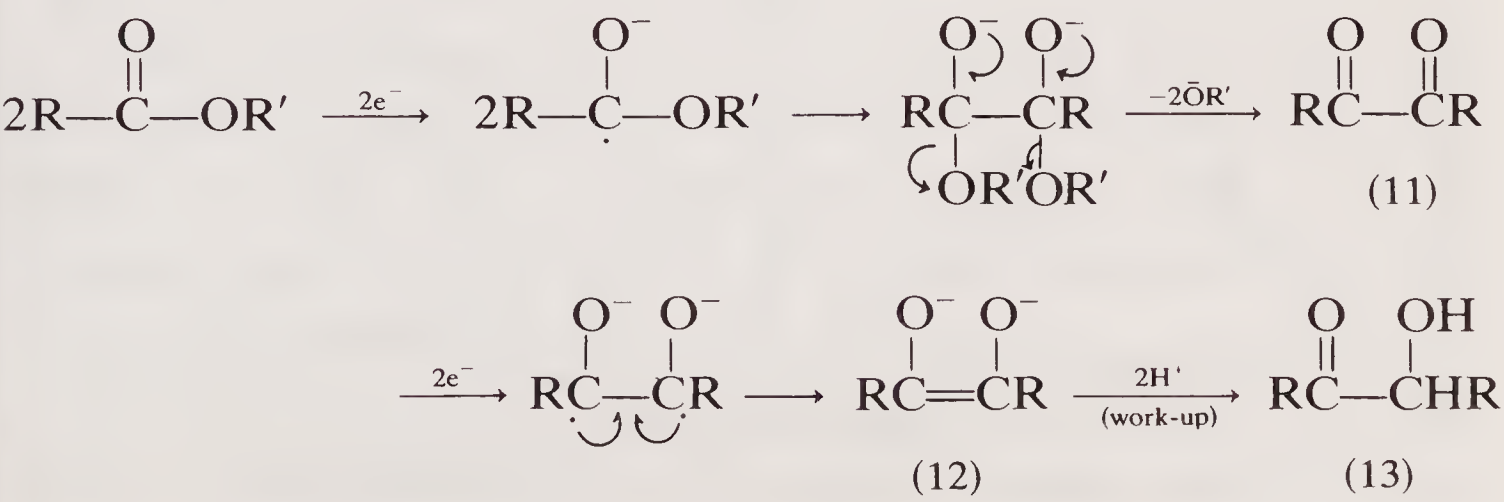
In this version (the **Thorpe–Ziegler reaction**) the intermediate cyano-enamine [such as (9)] or cyano-ketone [such as (10)] may be isolated if desired.

High dilution methods may also be applied to the preparation of macrocyclic esters (lactones), e.g.

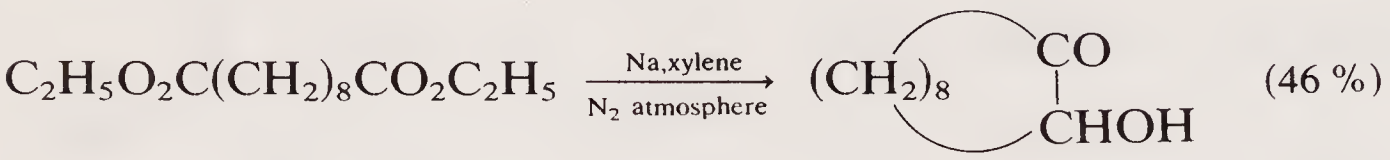


[The bromoacid (0.15 M solution) is added over 2 days to the base (large excess: ca. 0.25 M).]

One reaction which has been applied with great success to the preparation of medium and large rings is the **acyloin reaction.** This, in its simplest form, is an analogue of the bimolecular reduction of ketones (section 8.4.3.2) and is also related to the Bouveault–Blanc reduction (section 8.4.4). It involves one-electron reduction of an ester by metallic sodium, and dimerisation of the resulting radical anion. This then loses alkoxide ions, giving a diketone (11), and the latter then undergoes further reduction to the dianion (12) of the acyloin (13).

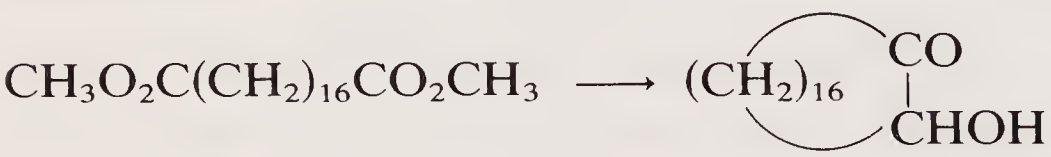


Long chain *diesters* give cyclic acyloins; since the reaction is heterogeneous, taking place on the surface of the metal, there is not the same need to employ high dilution methods, e.g.



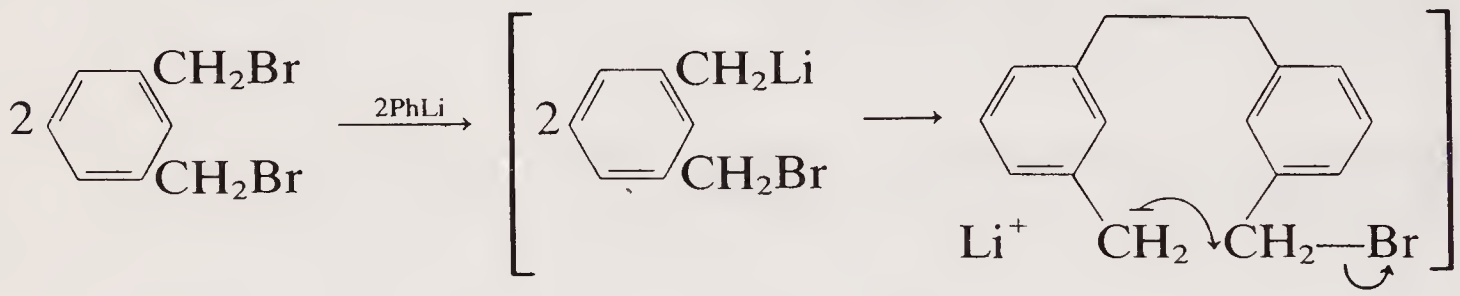
(46 %)

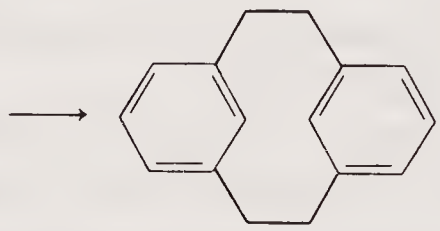
[The ester (undiluted) is added over 3 h to a suspension of sodium (4-fold excess) in xylene.]
Similarly,



(96 %)

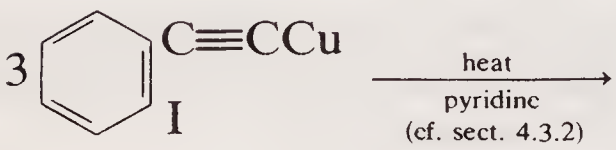
If a long chain of atoms contains one or more rigid sections, in which free rotation about bonds is not possible, there may be an increased chance of cyclisation to form a medium or large ring, e.g.

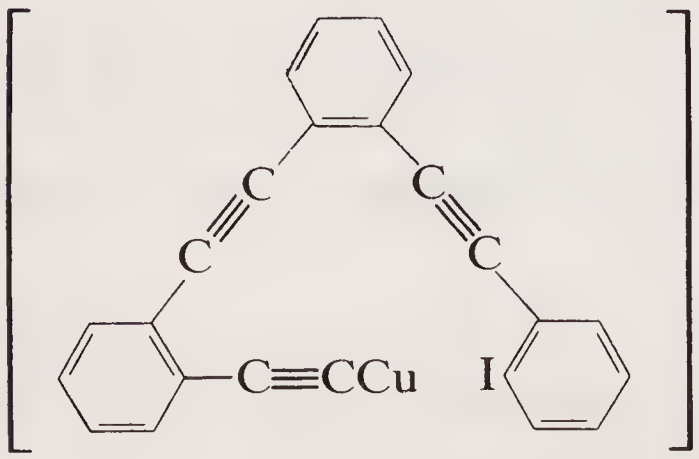


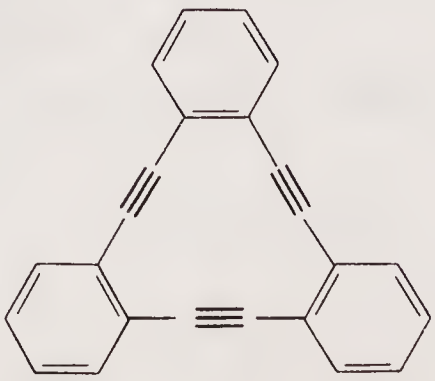


(39 %)

(10-membered ring)

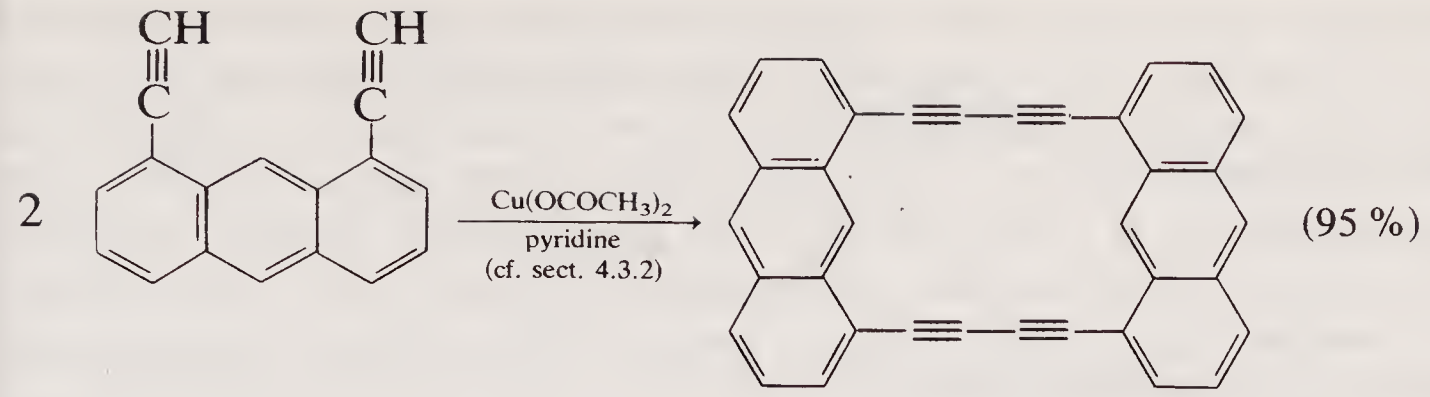






(26 %)

(12-membered ring)



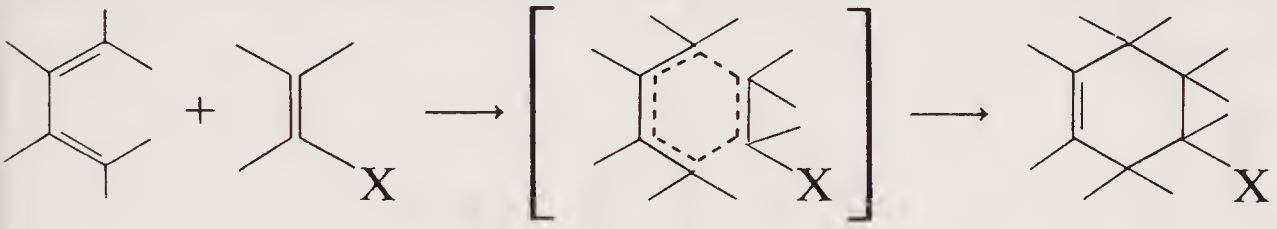
(18-membered ring)

This last process, oxidative coupling of alkynes, has been of particular value in the synthesis of **annulenes** (for an example, see Chapter 16).

Bicyclic compounds (fused or bridged systems) may also serve as precursors of medium- or large-ring monocyclic compounds. Such reactions are formally ring opening procedures, and as such are discussed in section 7.4.

7.2 Cycloaddition

Most readers will already be familiar with the Diels–Alder reaction, which in its simplest form consists of the reaction of a conjugated diene with a monoene (usually conjugated with a $-M$ group) to give a cyclohexene derivative [reaction (7.6)]:



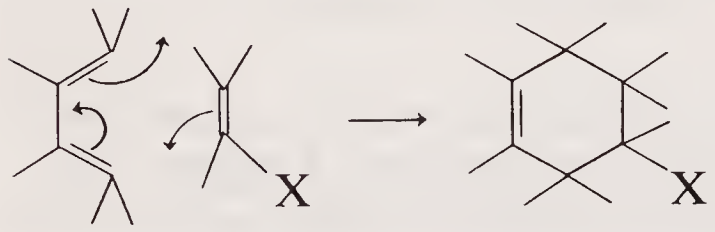
(7.6)

e.g. $CH_2{=}CHCH{=}CH_2 + CH_2{=}CHCHO \xrightarrow{100°}$  (quantitative)

Most readers will also have appreciated that reactions of this type cannot be described adequately in terms of electrophile–nucleophile interactions, and it is equally clear that they do not involve radical pathways. They are representatives of a large group of reactions which involve the interaction of π-electron systems in a concerted manner and *via* a cyclic transition state, and such reactions are generally described as **pericyclic** or **symmetry-controlled.**

The mechanisms of these reactions are considered in Sykes, Chapter 12 (pp. 340–357) in terms of **frontier orbitals.**[4] The reactions are considered to arise by interaction of the **highest occupied molecular orbital**

(**HOMO**) of one component with the **lowest unoccupied molecular orbital** (**LUMO**) of the other component. We shall adopt the same approach here when necessary, although, as we have stated before, mechanism is not the primary concern of this book. The 'curved arrow' notation may also be used [as in (7.6a)] to show the overall result of these reactions: although not strictly correct mechanistically, this is still a useful device for ensuring that all the electron pairs in the starting materials are accounted for in the products.



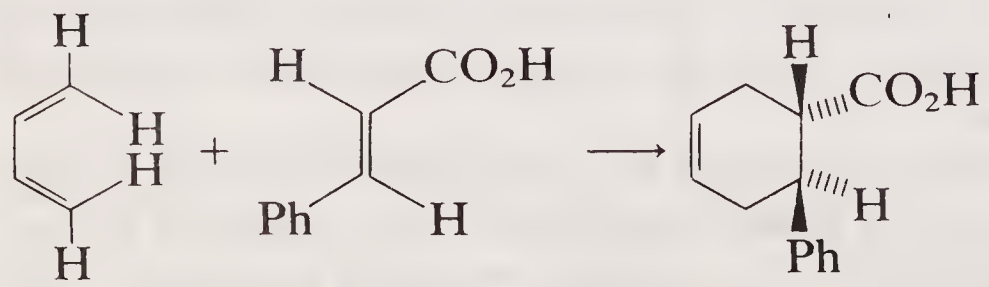
(7.6a)

In the remainder of this section, and in section 7.3, we shall consider some of the most important pericyclic reactions from the synthetic viewpoint.

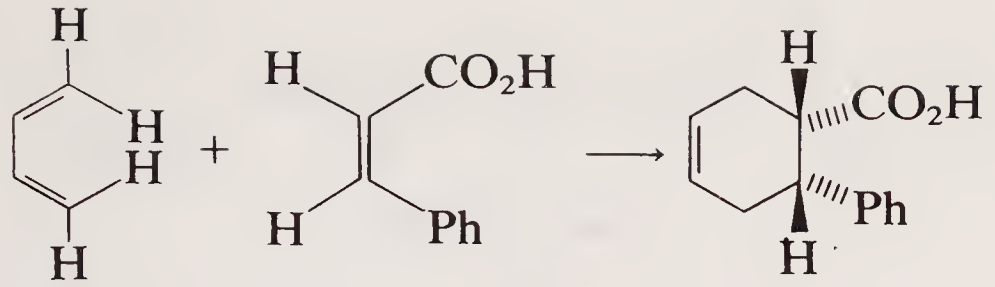
7.2.1 The Diels–Alder reaction

The main features of this reaction have already been set out by Sykes (pp. 197–8 and 349–51): the process involves the interaction of a 4π-electron system (the diene) and a 2π-electron system (the monoene or **dienophile**, as it is often called), and so the overall reaction is a [4 + 2]-cycloaddition. The reaction is stereospecifically *syn*- with respect to both diene and dienophile, as expected for a HOMO–LUMO interaction of the type (14) + (15) or (16) + (17).

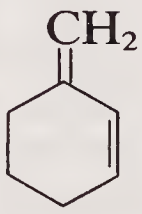
Thus, the relative configuration of the starting materials is retained in the product, e.g.

1. 

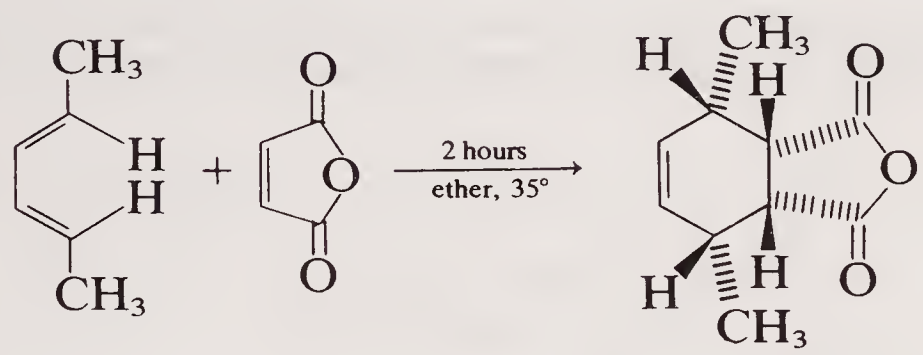
(ca. 35 %; no *cis*-isomer)

2. 
(ca. 10 %; no *trans*-isomer)

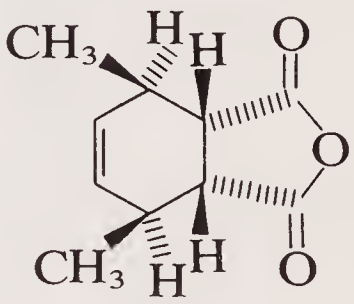
The diene must be able to adopt the *cisoid* conformation in order that reaction should occur. Dienes which are fixed in the *transoid* conformation, e.g. (18), cannot undergo the Diels–Alder reaction. If the adoption

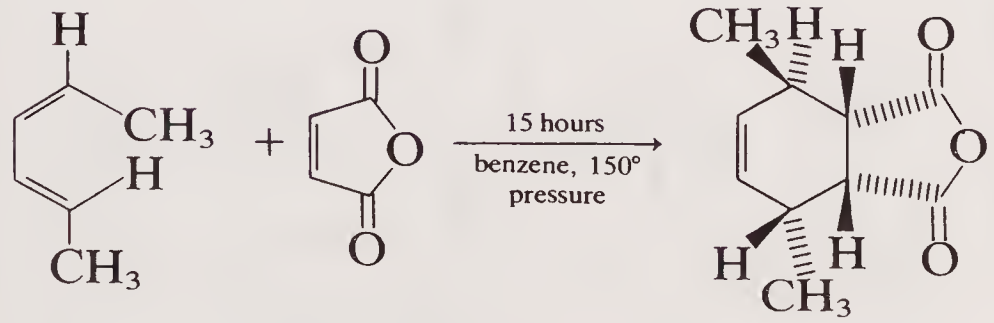

(18)

of the *cisoid* conformation leads to unfavourable steric interactions (as in example 4, between CH_3 and H) the reaction may be very slow (contrast examples 3 and 4).

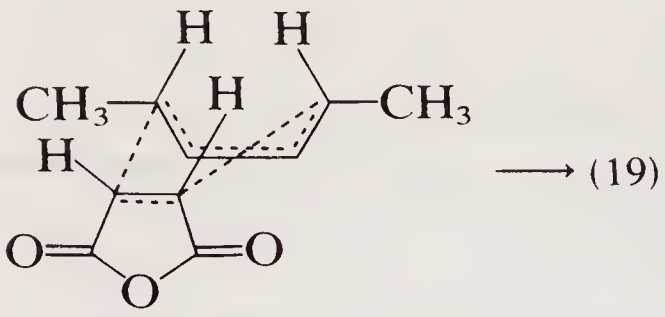
3. 
[quantitative; no. (20)]

(19)

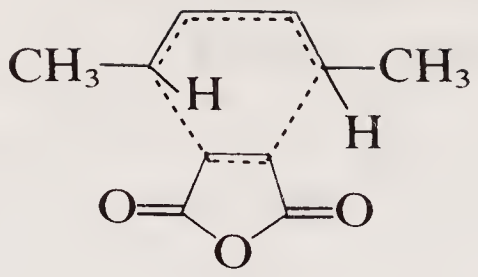

(20)

4. 
(ca. 32 %)

If the *syn*-addition of the diene and dienophile can lead to two possible adducts, as in example 3, it is usually the product of *endo*-addition [in this case, (19)] which predominates over the *exo*-addition product [in this case, (20)]. This preference for *endo*-addition is attributed to additional orbital overlap between the components in the transition state [cf. (21)] which cannot occur in the *exo*-transition state [cf. (22)]:

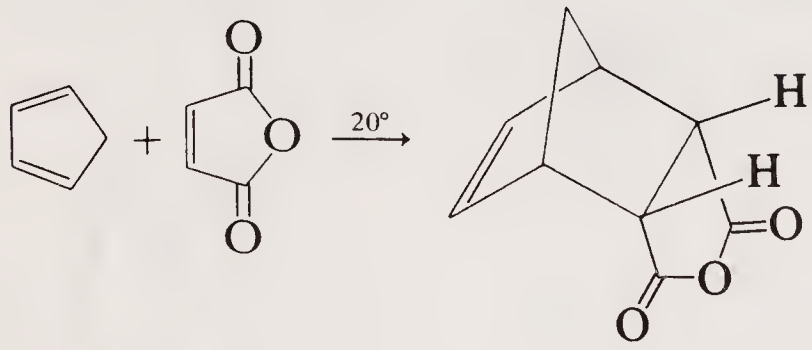


(21) ⟶ (19)

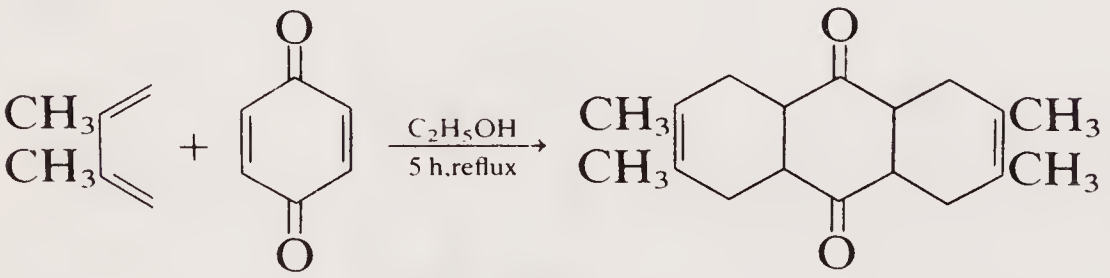


(22) ⟶ (20)

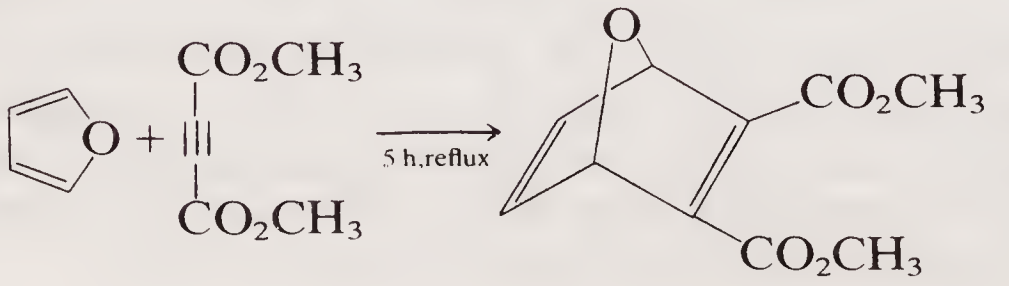
A wide variety of components may participate in the Diels–Alder reaction, and so the procedure is of considerable synthetic importance. For example, the diene may be carbocyclic (example 5) or heterocyclic (examples 7 and 8). Benzene derivatives do not participate readily in Diels–Alder reactions, since the adducts would be non-aromatic, but polycyclic compounds such as anthracene readily form adducts (examples 9 and 10) since an additional benzenoid ring is thereby formed. The dienophile component may be subject to equally wide variation: simple alkenes like ethylene require high temperature and pressure for satisfactory reaction, but alkenes conjugated to a $-M$ group are generally useful. Alkynes (example 7), including benzyne (dehydrobenzene; examples 8 and 10), may be used in place of alkenes. Heteroatoms may replace carbon in either the diene or dienophile (examples 11–13):

5. 

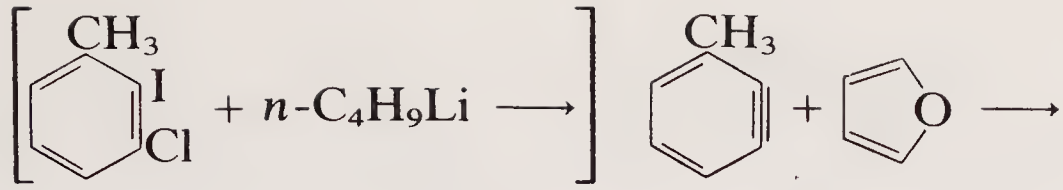
(quantitative)

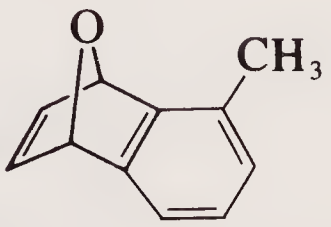
6. 

(60 %)

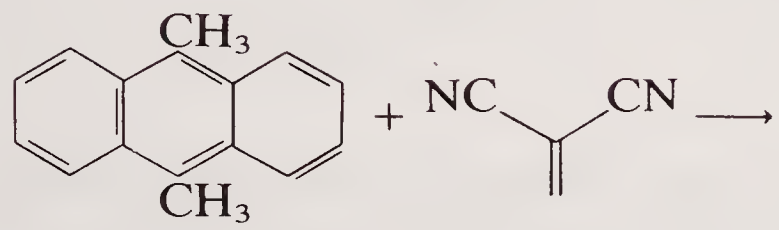
7. 

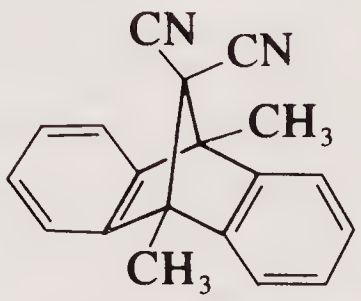
(77 %)

8. 

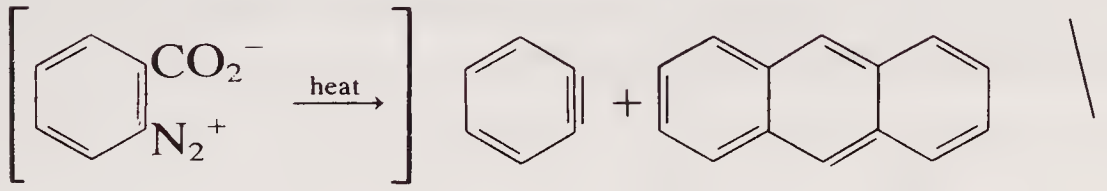


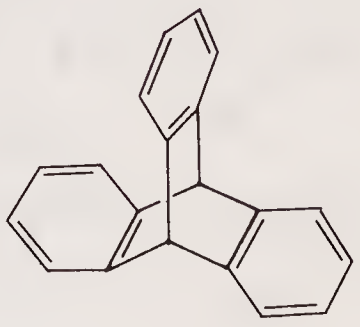
(43 %)

9. 

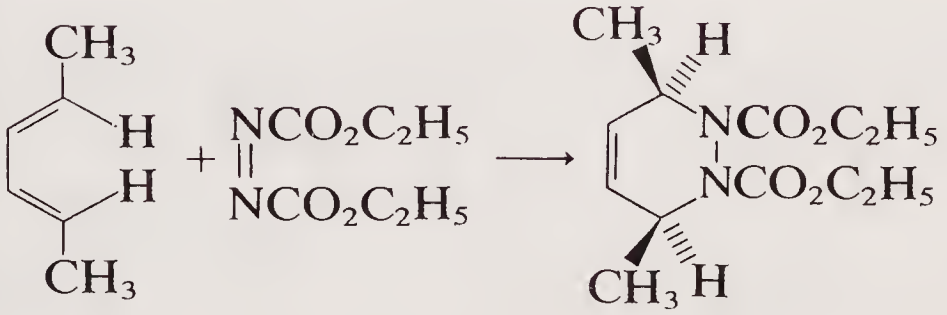


(83 %)

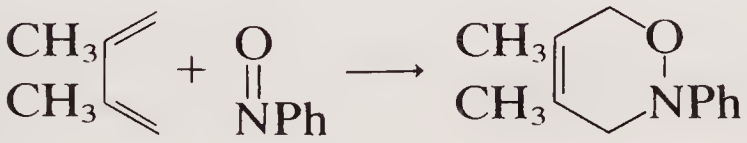
10. 



(59 %)

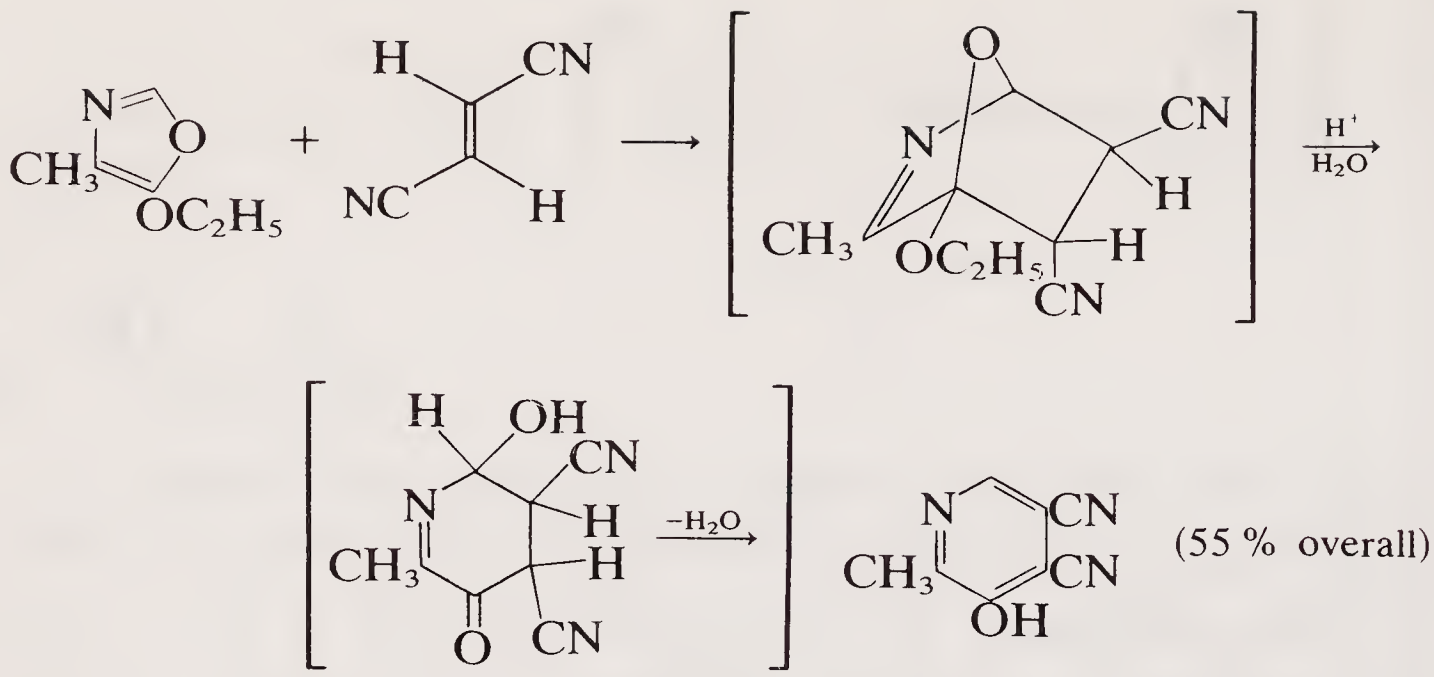
11. 

(quantitative)

12. 

(66 %)

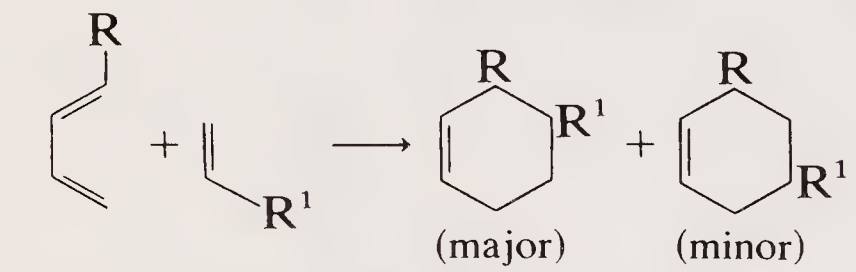
13.



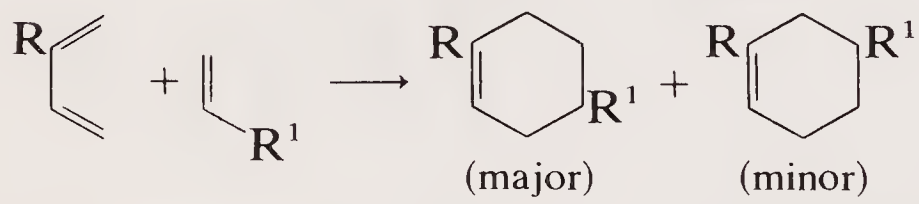
(55 % overall)

[Example 13 provides a useful route to the pyridoxine (B_6) vitamins.]

If the diene and dienophile are both unsymmetrical, the Diels–Alder addition may occur in two ways giving a mixture of isomeric adducts; in general, however, one of the two possible adducts is strongly favoured over the other. This *regioselectivity* may be explained in terms of frontier orbital theory,[5] and although discussion of the theory is beyond the scope of this book, the overall result is not. For the vast majority of substituents in diene and dienophile, the major Diels–Alder adduct is as shown in (7.7) and (7.8). It should be noted that the '*meta*-disubstituted' product is the minor isomer in both cases:

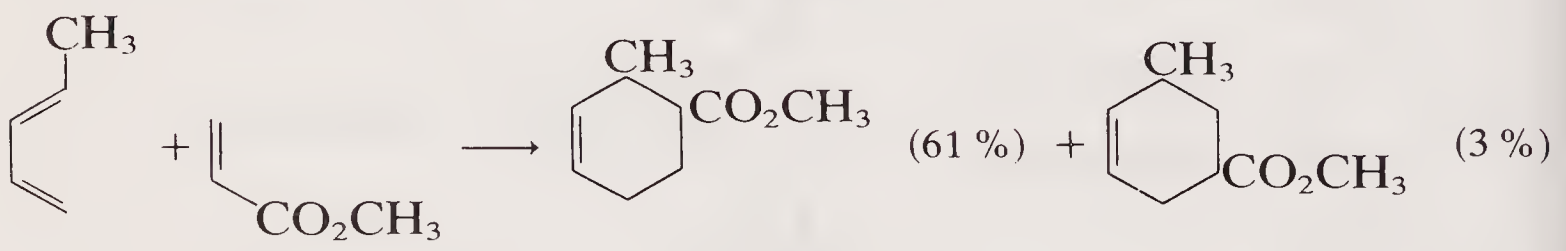


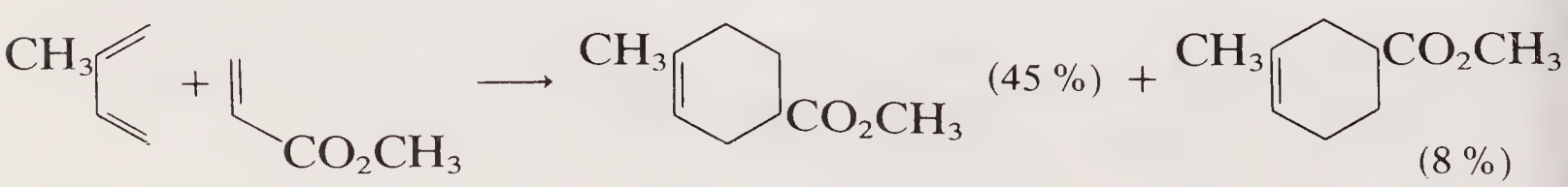
(7.7)

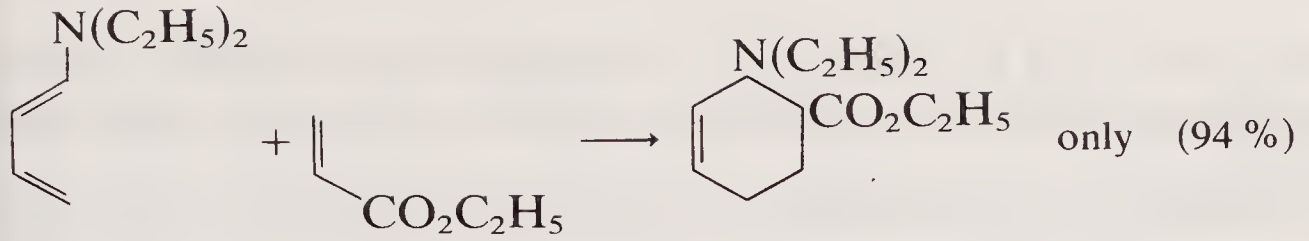


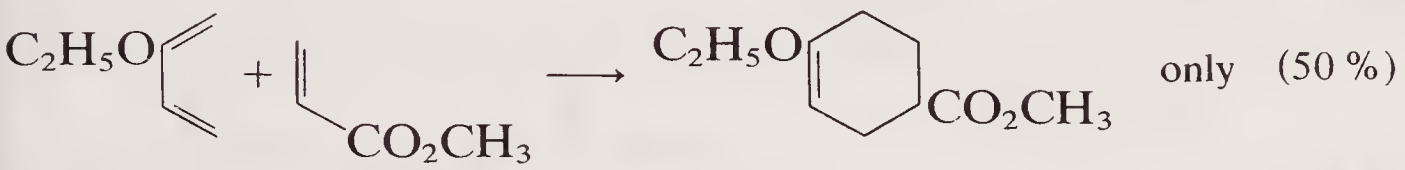
(7.8)

For example,

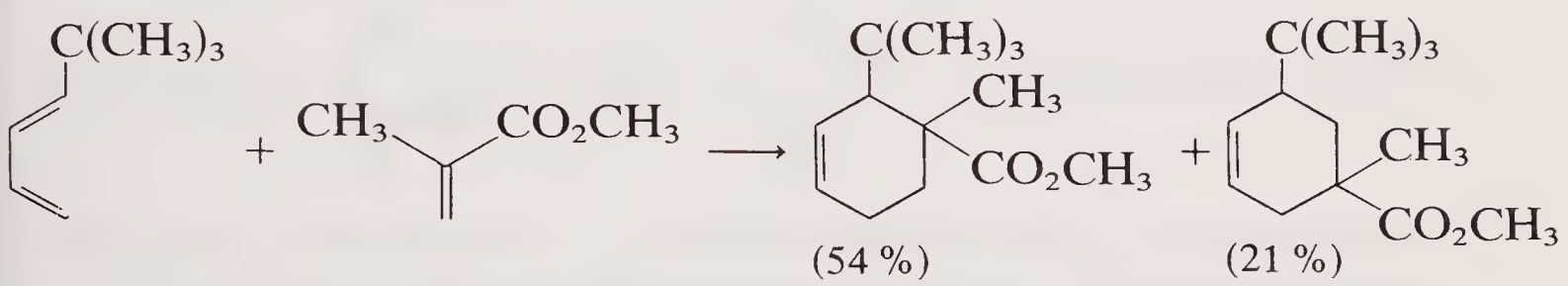






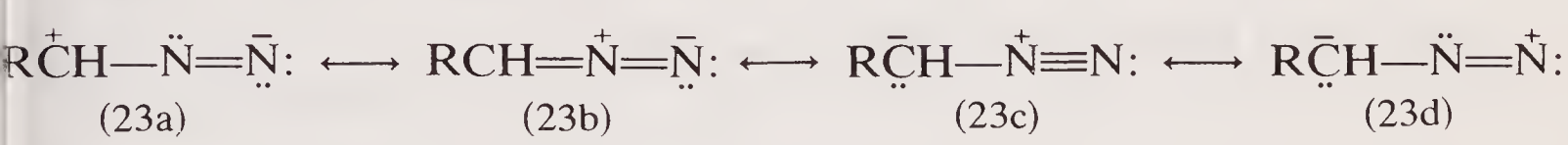


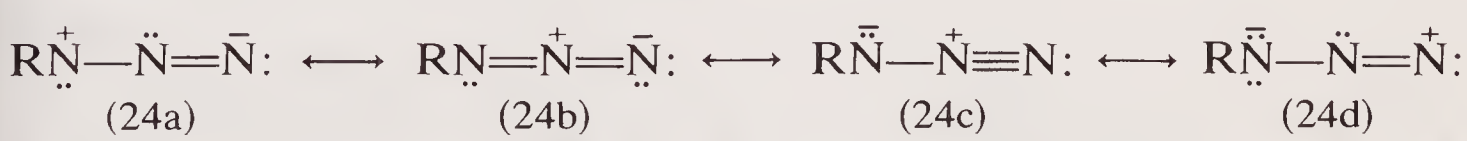
Even where steric hindrance might be expected to influence the formation of an '*ortho*-adduct', the latter may still be formed in substantial amount, e.g.



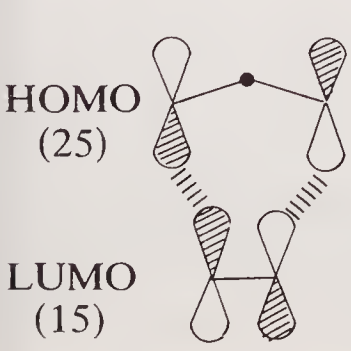
7.2.2 1,3-Dipolar cycloaddition

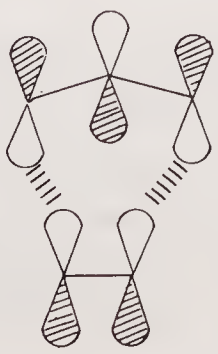
This type of cycloaddition is also a $[4\pi + 2\pi]$ process, and as such is a relative of the Diels–Alder reaction; but the 4π-electron component is not a diene but a **1,3-dipole,** in which the four π-electrons are distributed over only three atoms, and for which at least one canonical structure can be drawn in which atoms 1 and 3 bear opposite charges. The most common 1,3-dipoles are probably the diazoalkanes, e.g. (23), and the azides, e.g. (24), although the examples show several others and demonstrate the versatility of this type of cyclisation:





The HOMO (25) and LUMO (26) of such systems[6] can interact with the LUMO (15) and HOMO (17) of a monoene in the same way as in the Diels–Alder reaction (p. 142):

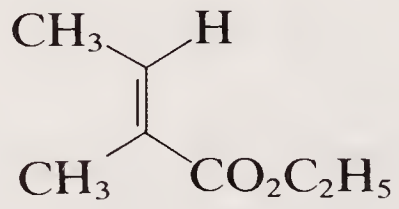
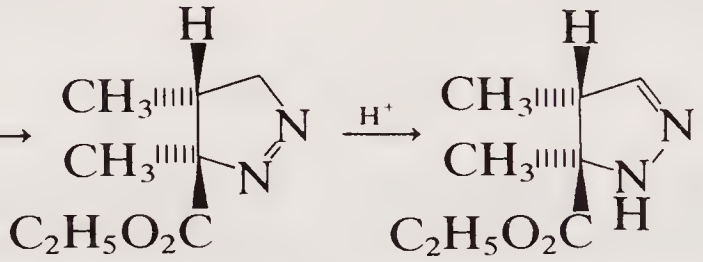


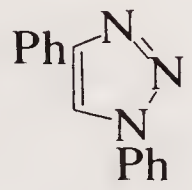
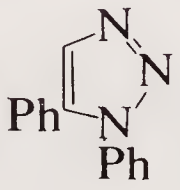


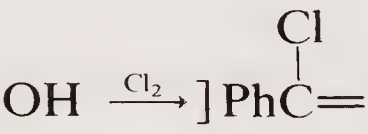
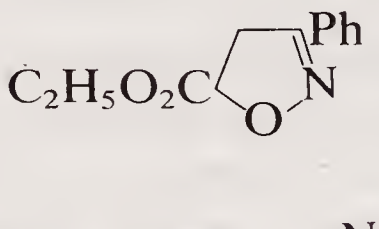
[see Note 6 for case of linear 1,3-dipoles]

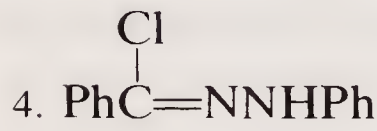
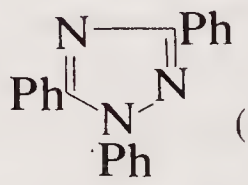
The regioselectivity of additions to unsymmetrical alkenes (or other **dipolarophiles**) is much more difficult to explain, and is not considered further here.

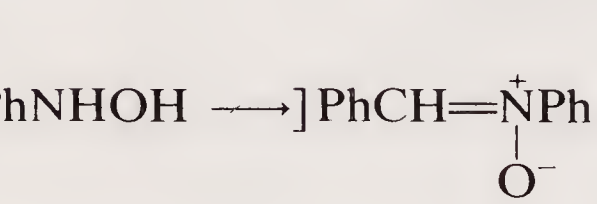
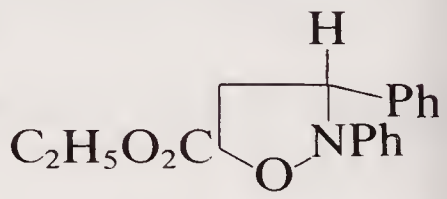
The following are representative examples of 1,3-dipolar cycloadditions:

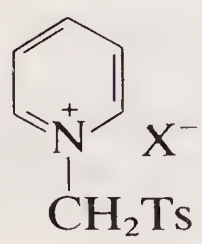
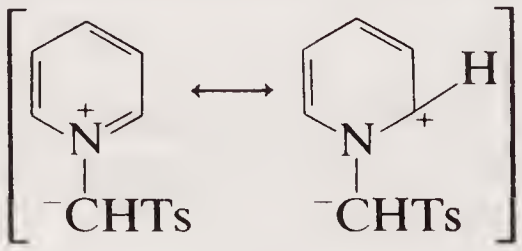
1. CH_2N_2 +   (75 %)

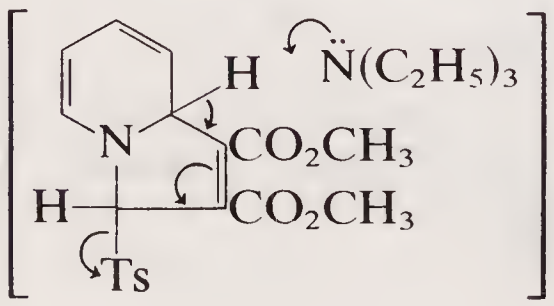
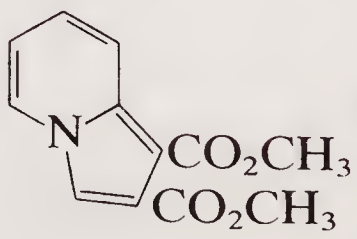
2. $PhN_3 + PhC{\equiv}CH \longrightarrow$  (43 %) +  (52 %)

3. [PhCH=NOH $\xrightarrow{Cl_2}$]  $\xrightarrow{(C_2H_5)_3N}$ [PhC≡$\overset{+}{N}$—$\bar{O}$] $\xrightarrow{CH_2{=}CHCO_2C_2H_5}$  (quantitative)

4.  $\xrightarrow{(C_2H_5)_3N}$ [PhC≡$\overset{+}{N}$—$\bar{N}$Ph] $\xrightarrow{PhC{\equiv}N}$  (72 %)

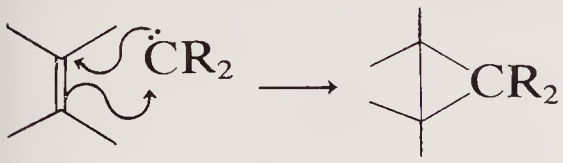
5. [PhCHO + PhNHOH ⟶]  $\xrightarrow{CH_2{=}CHCO_2C_2H_5}$  (97 %)

6.  $\xrightarrow{(C_2H_5)_3N}$  $\xrightarrow{CH_3O_2C{-}{\equiv}{-}CO_2CH_3}$

 ⟶  + $(C_2H_5)_3\overset{+}{N}HTs^-$ (72 %)

7.2.3 Addition of carbenes and nitrenes to alkenes

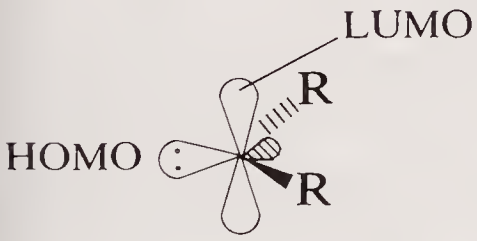
Carbenes (Sykes, pp. 266–7) are uncharged electron-deficient carbon species, R_2C:. Among their most characteristic, and synthetically useful, reactions is addition to alkenes [reaction (7.9)] to give cyclo propanes. **Nitrenes,** which are the nitrogen analogues of carbenes, similarly undergo addition to alkenes giving aziridines [reaction (7.10)].



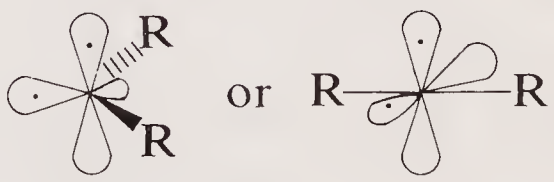
(7.9)

(7.10)

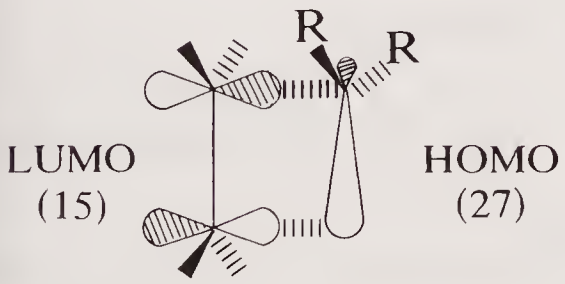
The precise mechanism of the addition depends on the arrangement of the non-bonding electrons in the carbene or nitrene. If both electrons are in one orbital and the other is empty [the so-called *singlet state*: e.g. structure (27)], the addition may be regarded as a [2 + 2] cycloaddition involving a HOMO–LUMO interaction as shown below [(27) + (15) or (27) + (17)]. If the two electrons are in different orbitals [the *triplet state*: e.g. (28)], the addition follows a radical pathway and is not concerted but stepwise.

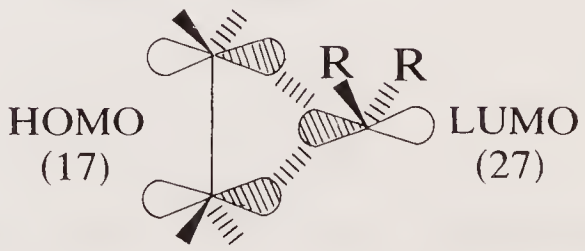


(27)



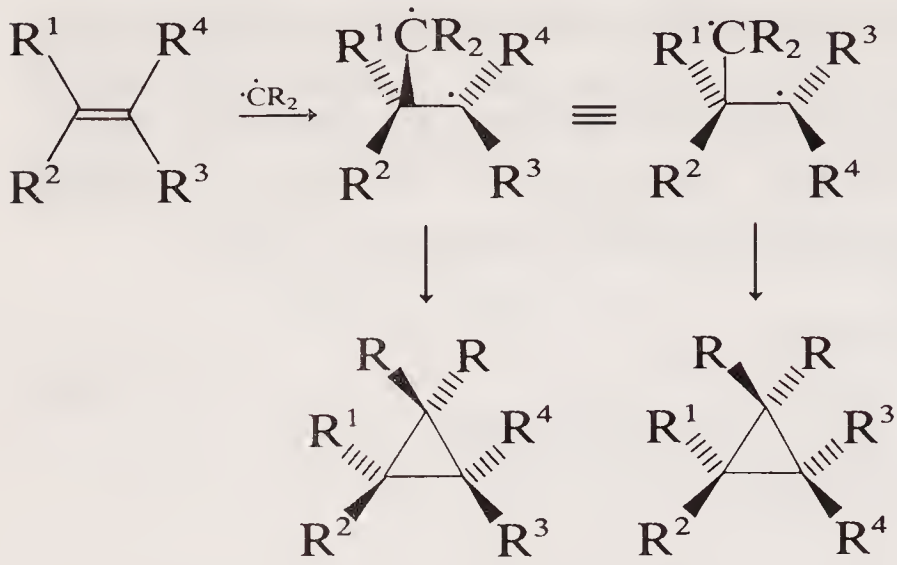
(28)





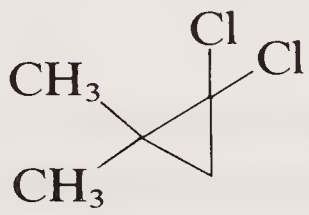
In many cases, the detailed mechanism is unimportant for our purposes; the result is the same, whichever mechanism operates. In other cases, however, the stereochemistry of the product may depend on the mechanism: the concerted addition is stereospecific, the relative configurations in the alkene being retained in the product, but the stepwise radical addition is not stereospecific and may lead to a mixture of

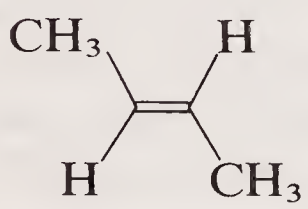
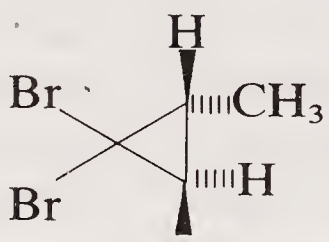
diastereoisomeric cyclopropanes [reaction (7.11)]:

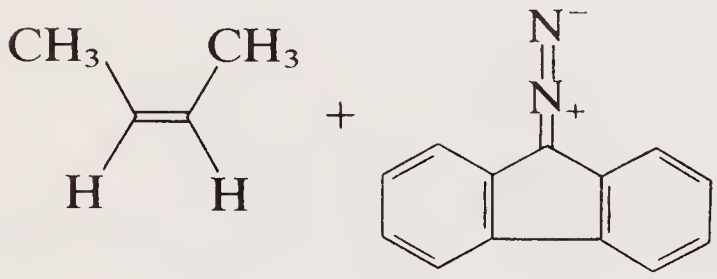
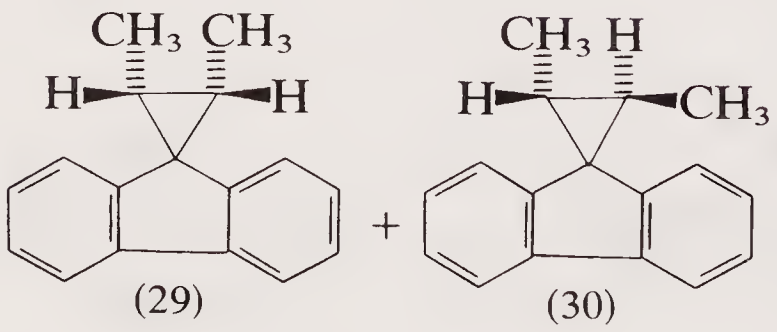


(7.11)

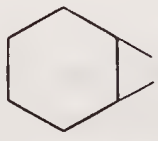
The following are representative examples:

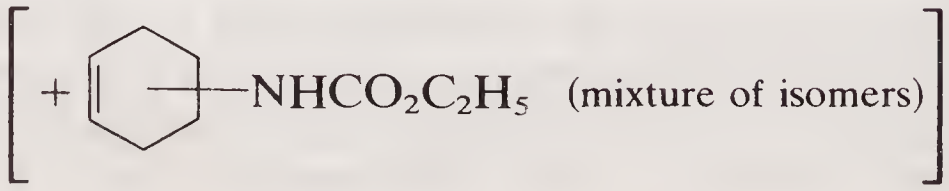
1. $(CH_3)_2C{=}CH_2 \xrightarrow[NaOCH_3]{Cl_3CCO_2C_2H_5}$  (65 %)

2.  $\xrightarrow{CHBr_3,\ (CH_3)_3COK}$  (68 %)

3.  $\xrightarrow{h\nu}$ 

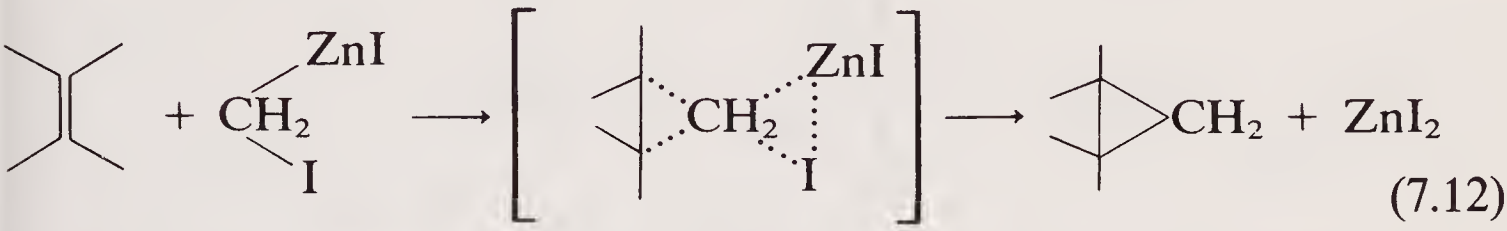
[ca. 50 %; (29) : (30) = 66 : 34]

4.  $+ N_3CO_2C_2H_5 \xrightarrow{h\nu}$  (50 %)



An alternative method for the formation of cyclopropanes from alkenes is provided by the **Simmons–Smith reaction** [reaction (7.12)], which involves reaction of the alkene with a dihalogenomethane and zinc (usually in presence of copper). This is most simply rationalised in terms of a carbene intermediate, but the available evidence suggests that the more likely intermediate is (31) and that a free carbene is not involved:

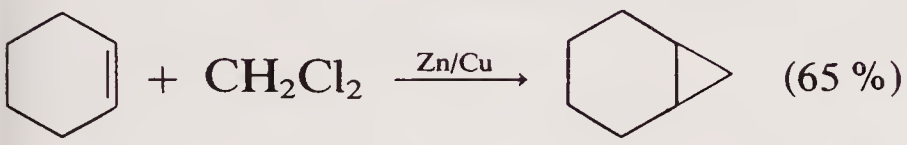
$$CH_2I_2 + Zn \longrightarrow ICH_2ZnI$$

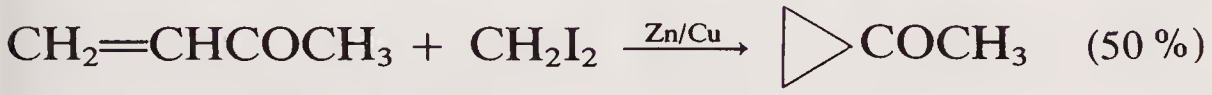


(7.12)

(31)

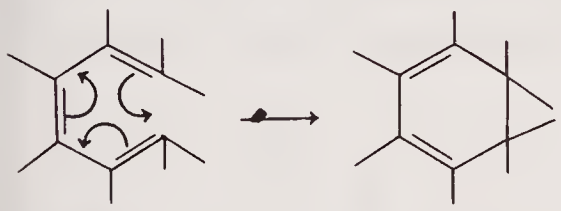
Thus, for example,





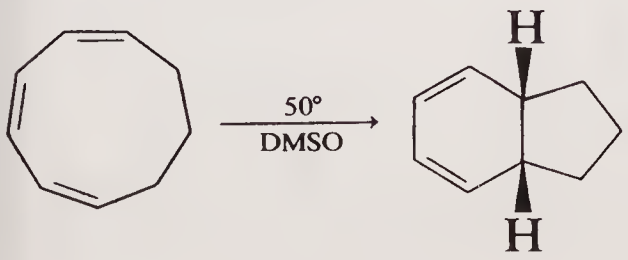
7.3 Electrocyclic ring closure

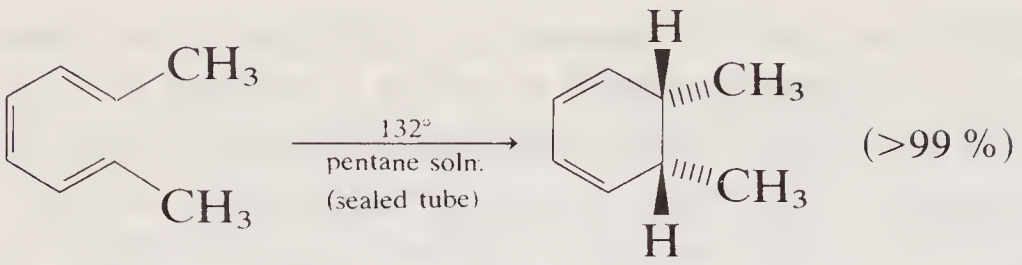
The Diels–Alder reaction and 1,3-dipolar cycloaddition, which are described in the preceding section, each involve the redistribution of six π-electrons *via* a cyclic transition state. If these six π-electrons are contained *within the same molecule*, an analogous redistribution may take place intramolecularly, and such an intramolecular pericyclic process is referred to as an **electrocyclic** reaction:



(7.13)

The reaction is stereospecific, like the Diels–Alder and 1,3-dipolar cycloadditions, e.g.

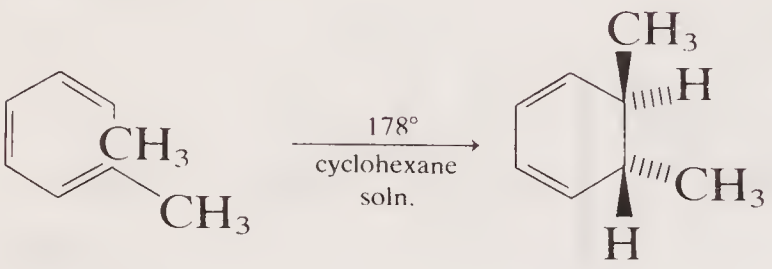




(>99 %)

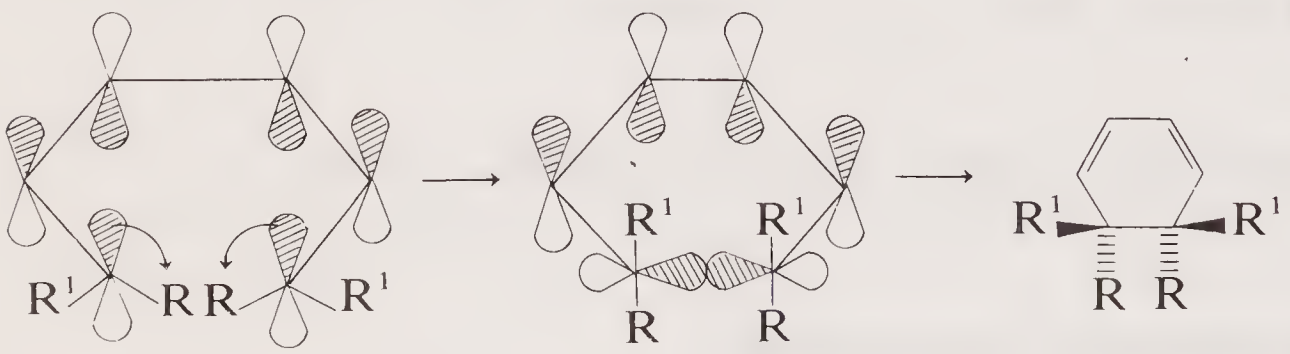
(32)

Similarly,



(high yield)

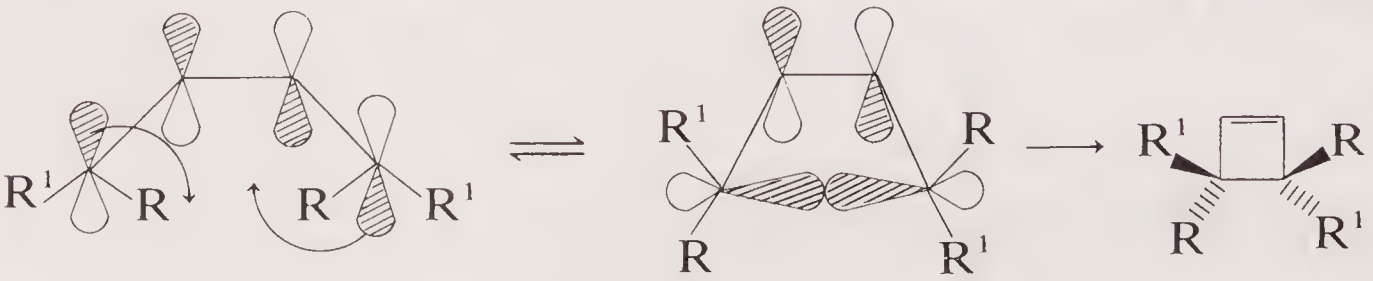
The stereochemistry of the products may be explained in terms of frontier orbital theory (cf. Sykes, pp. 344–6). The HOMO for a conjugated triene is (33), and ring closure is thus a **disrotatory** process:



(33)

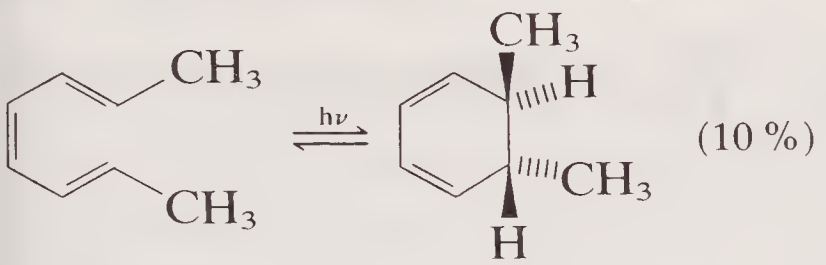
These reactions are, however, reversible (as, indeed, are the Diels–Alder and dipolar cycloaddition reactions), and the examples above are equilibria which happen to favour the cyclised isomer. In other cases the equilibrium favours the acyclic isomer, and this occasionally provides a useful method of ring *opening* (cf. section 7.4.3). One might, for example, expect a conjugated diene to be capable of cyclisation to a cyclobutene [a **conrotatory** process, the HOMO being (14)], but in such cases the equilibria generally lie on the side of the diene.

(7.14)



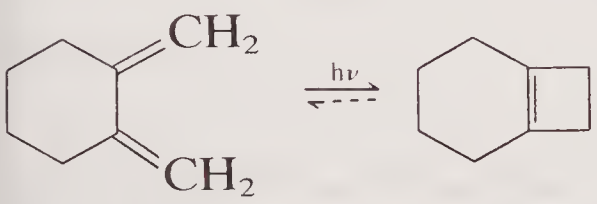
(14)

Electrocyclic ring closure may also be brought about by photochemical means. In such reactions the stereochemistry of the product is the opposite of that obtained by thermal cyclisation, e.g.

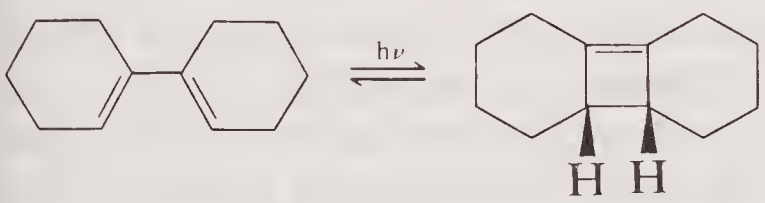


(10 %)

(32)

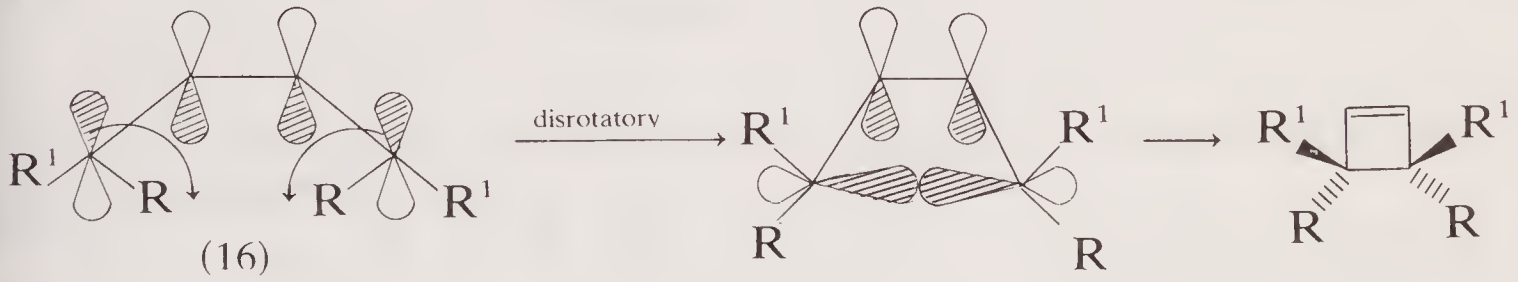


(>95 %)

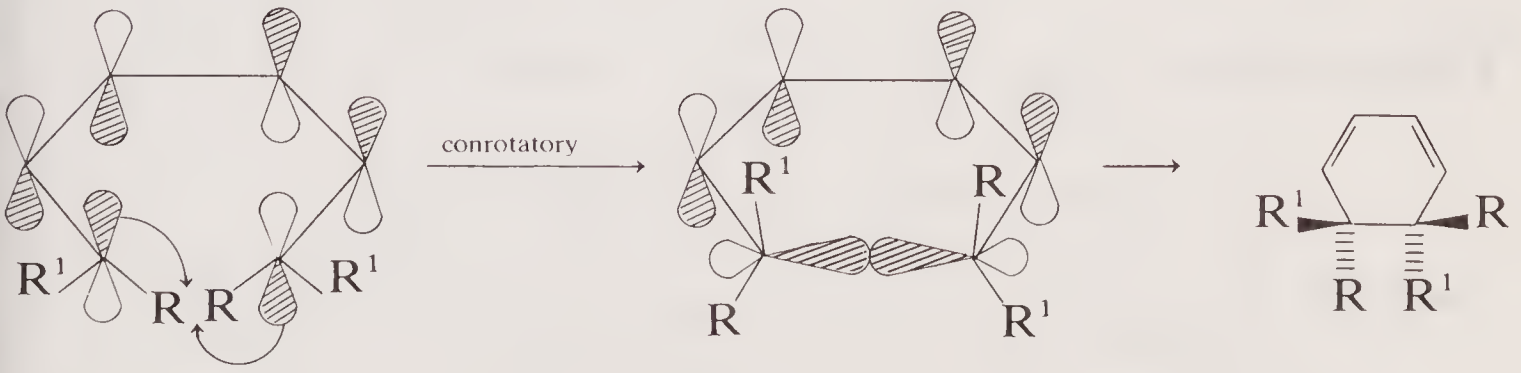


(27 %)

Irradiation of the substrate results in the promotion of an electron into the orbital of next higher energy level, i.e. the ground-state LUMO. This now becomes the HOMO for the photochemical ring closure [(16) for a diene and (34) for a triene], and the resultant ring closures are disrotatory and conrotatory respectively (cf. Sykes, pp. 346–7).



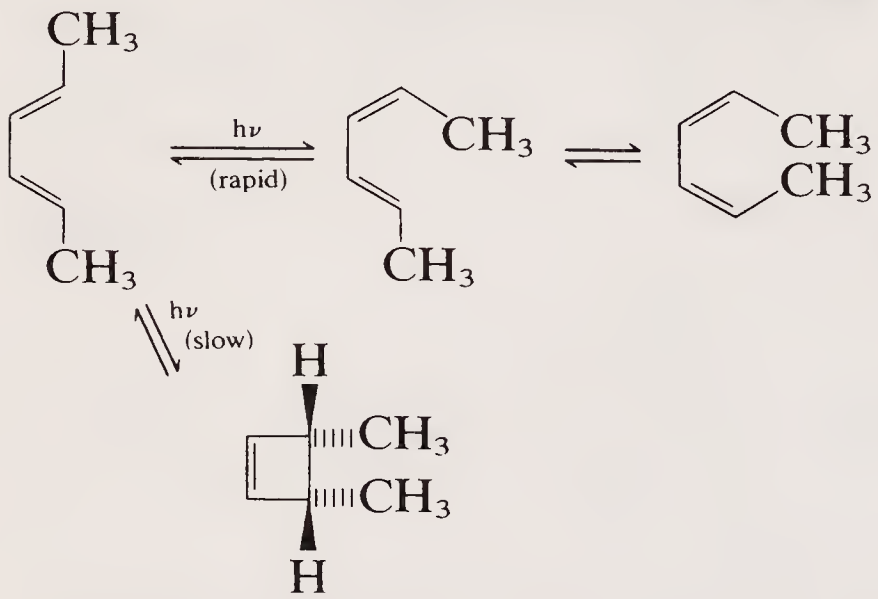
(16)



(34)

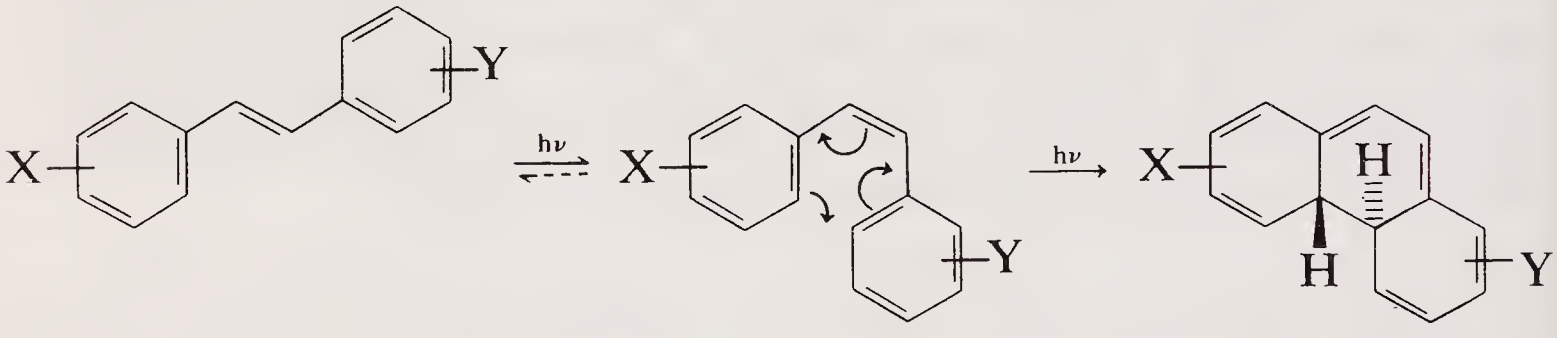
Irradiation of alkenes, however, also leads to the interconversion of *E*- and *Z*-isomers, and so a diene or triene in which the double bond con-

figurations are not fixed (e.g. in a ring system) may undergo this type of isomerisation as well as ring closure, e.g.

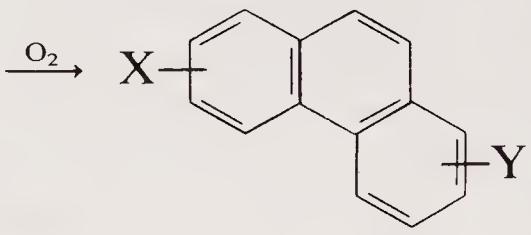


(equilibrium proportion 36:30:34)

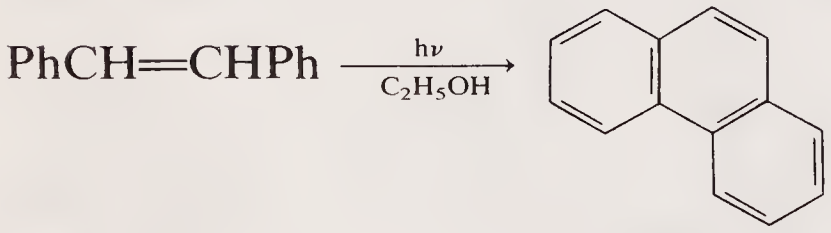
The $E \rightarrow Z$ isomerisation is used to considerable advantage in the photocyclisation of stilbenes (1,2-diarylethenes). Irradiation of either isomer, or a mixture of the two (such as might be obtained from a Wittig reaction: section 5.3.1) gives a dihydrophenanthrene (35), which in the presence of air undergoes spontaneous dehydrogenation to the phenanthrene [reaction (7.15)]. This is probably the simplest route to phenanthrene derivatives currently available.



(35)

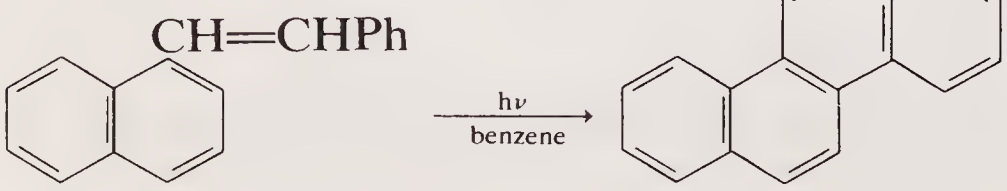


(7.15)



(73 %)

Similarly



(77 %)

The method has also been adapted with considerable success for the synthesis of **helicenes** (cf. Ch. 16).

7.4 Ring opening

The value of ring opening as a synthetic procedure is not as obvious as that of ring closure: indeed we have discussed synthesis so far only in terms of bond formation, and examples of bond cleavage (e.g. the decarboxylation of malonic or β-keto-acid derivatives, or the release of carbonyl groups from 1,3-dithians or dihydro-1,3-oxazines) have been incidental to the main theme. In Chapter 10 we shall encounter bond cleavage in connection with the removal of protective groups. In the present section, however, we consider bond cleavage in a specific context – ring opening – and as a synthetic method in its own right.

Apart from the above, the two main synthetic uses of ring opening are as follows:

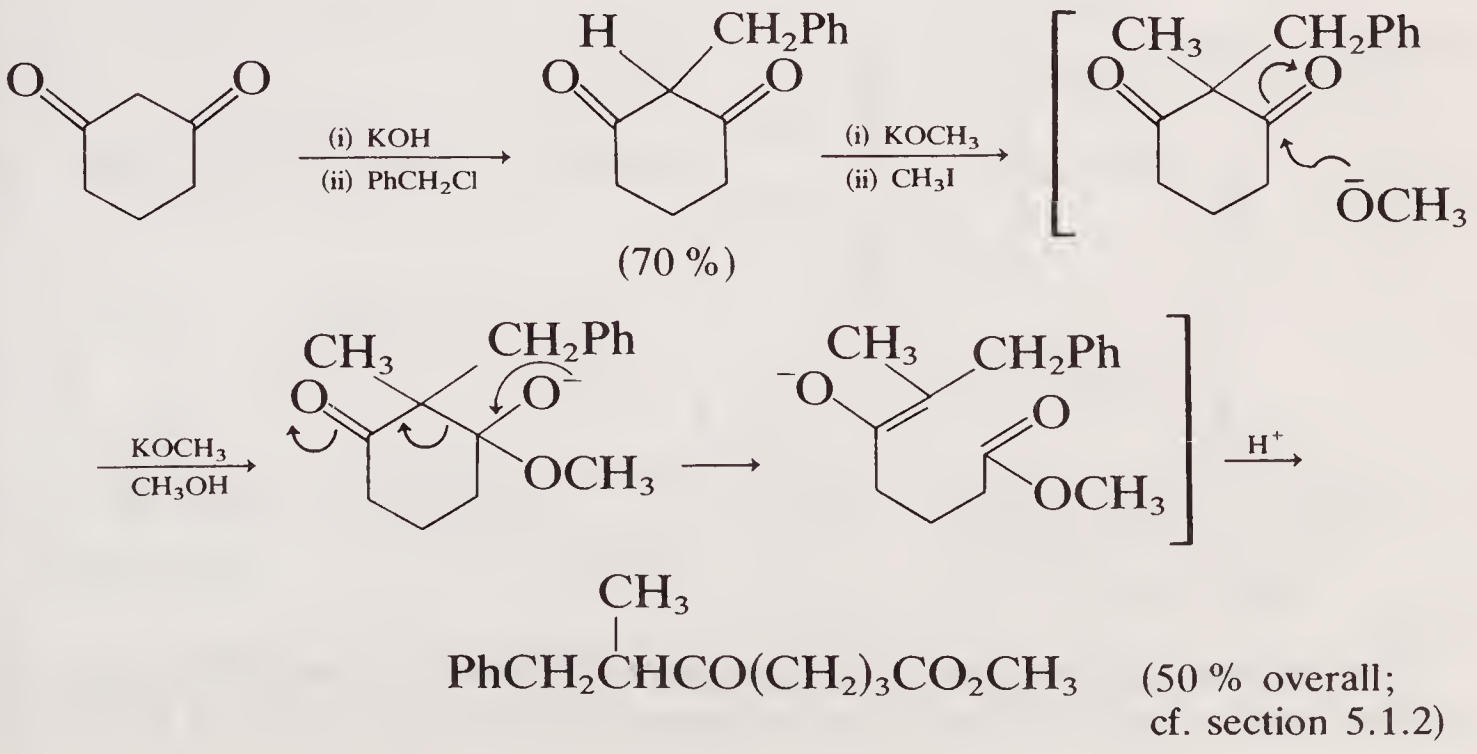
(i) the atoms at either end of the bond which is broken will bear functional groups in the ring-opened product; ring opening may thus provide a route to difunctional molecules in which the functional groups are separated by several other atoms.
(ii) in a bi- or polycyclic molecule, cleavage of a bond which is common to two rings may lead to a medium- or large-ring molecule which is otherwise difficult to prepare.

We shall classify ring opening processes according to their reaction type.

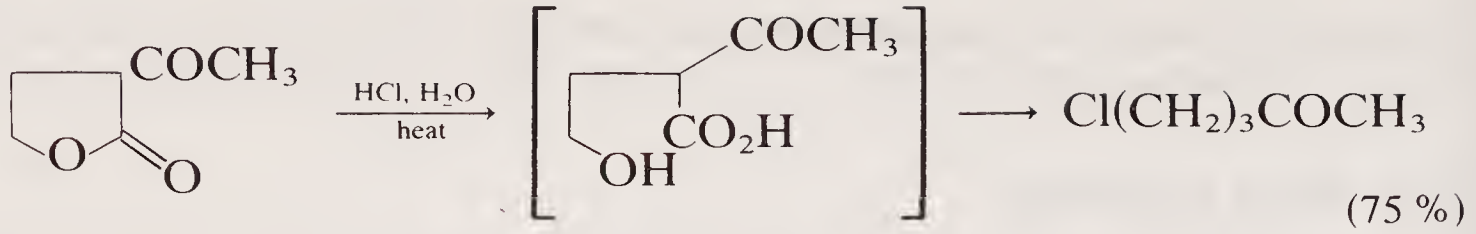
7.4.1 Hydrolysis, solvolysis and other electrophile–nucleophile interactions

This is a large and diverse group, and the examples are merely illustrative of this diversity:

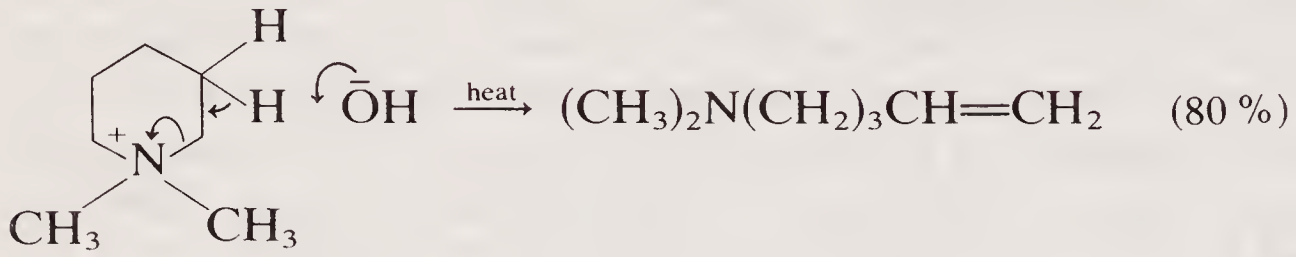
1.



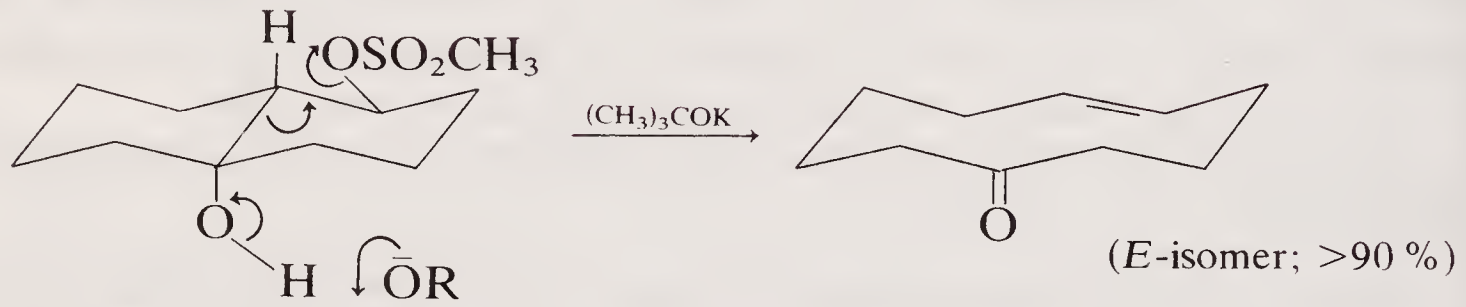
$PhCH_2CH(CH_3)CO(CH_2)_3CO_2CH_3$ (50 % overall; cf. section 5.1.2)

2. 

(75 %)

3. 

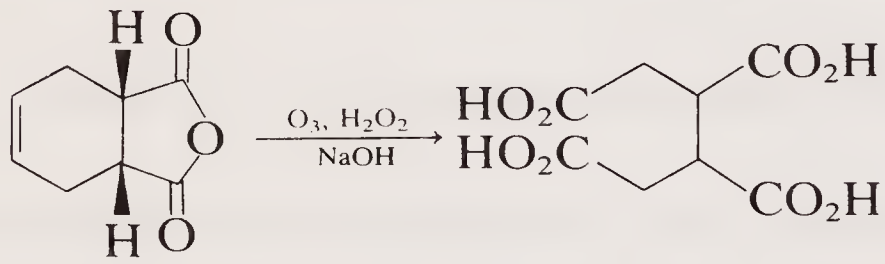
(80 %)

4. 

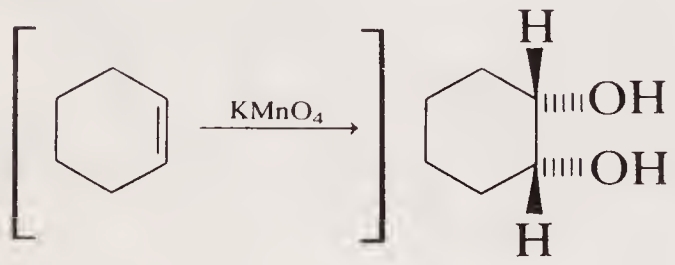
(*E*-isomer; >90 %)

7.4.2 Oxidative and reductive ring opening

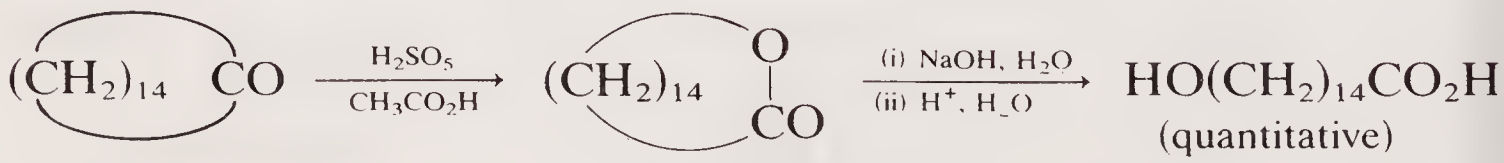
Oxidative ring opening of a synthetically useful kind is generally that of a cycloalkene or a cycloalkanone. These reactions are discussed at greater length in sections 9.2.6 and 9.5.3, but the examples below serve to illustrate the potential of the methods:

1. 

(73 %)

2. 

(67 %)

3. 

(quantitative)

Reductive ring opening is of less general value, although hydrogenolysis of some sulphur-containing compounds (cf. also section 8.4.3.3) pro-

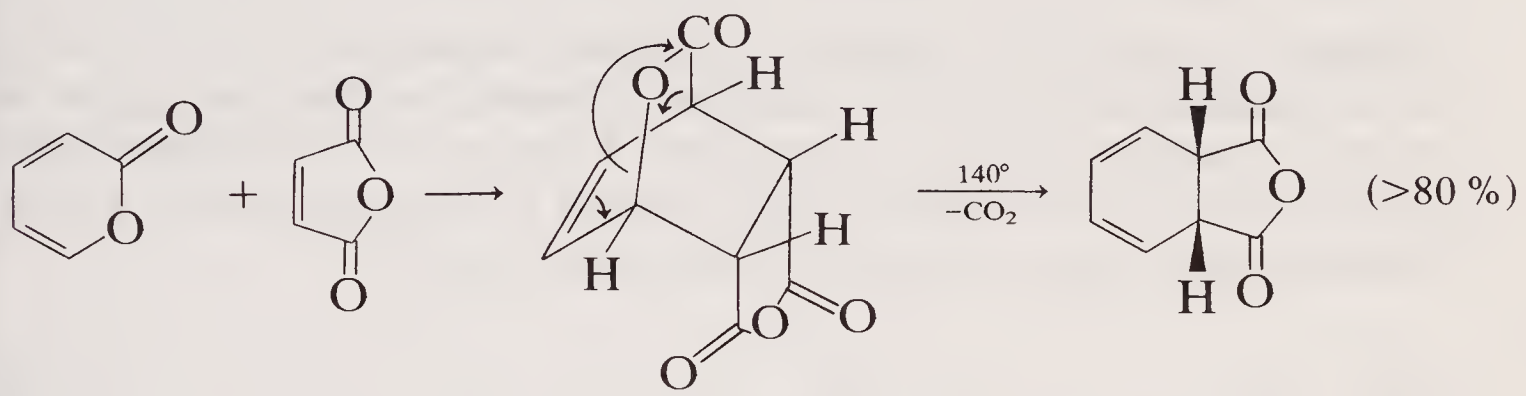
vides a notable exception, e.g.

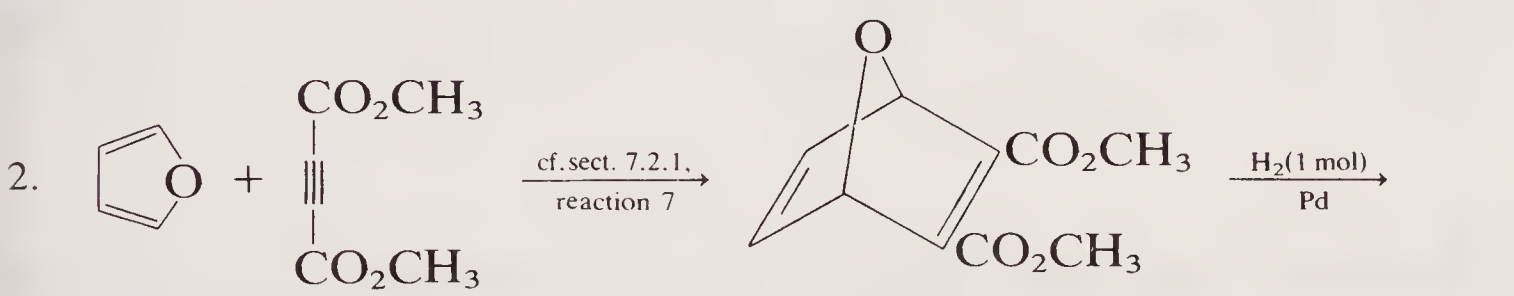
4. $(CH_3)_3C$–thiophene–$CO_2H \xrightarrow{H_2,Ni} \left[(CH_3)_3C\text{–}\underset{\text{S}}{\text{thiolane}}\text{–}CO_2H?\right] \longrightarrow$

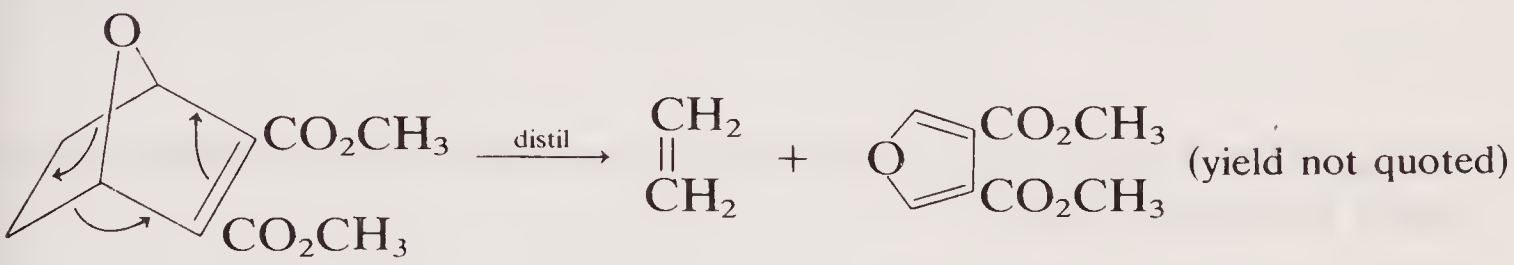
$(CH_3)_3C(CH_2)_4CO_2H$ (70 %)

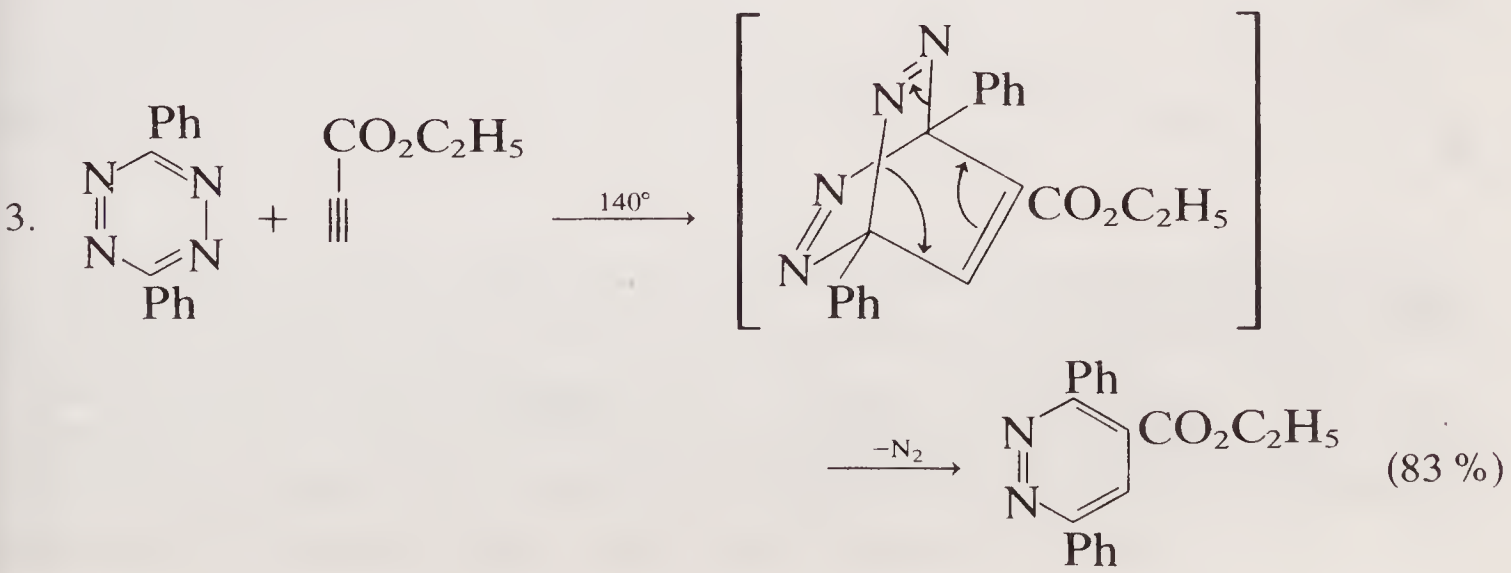
7.4.3 Pericyclic ring opening

We have already pointed out that Diels–Alder and related cycloadditions are, in principle, reversible, and the **retro-Diels–Alder reaction** has some useful synthetic applications. Many of these involve the cleavage of a bicyclic Diels–Alder adduct which has itself been formed from a cyclic diene and a dienophile. The cleavage reaction becomes effectively irreversible if one of the cleavage products is volatile. For example,

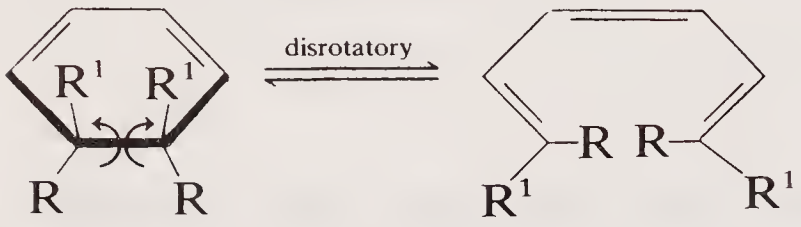
1. 

2. 

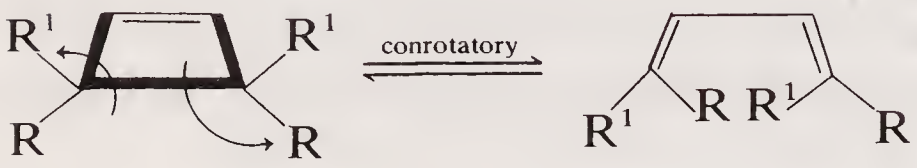


3. 

Electrocyclic ring opening is another important pericyclic reaction, and is the exact opposite of the electrocyclic ring closure described in section 7.3 [reactions (7.13) and (7.14)]. The thermal ring opening of a cyclohexadiene is thus *disrotatory* [reaction (7.16)] and that of a cyclobutene is *conrotatory* [reaction (7.17)].

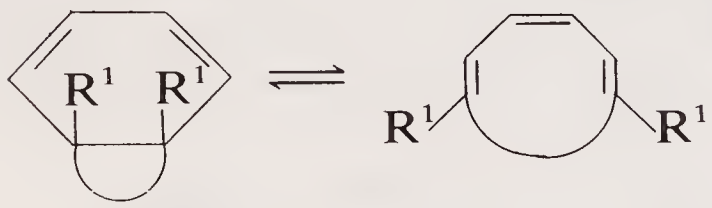


(7.16)

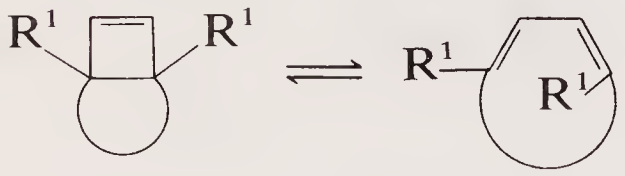


(7.17)

There is one very important synthetic consequence of the above stereospecificity. If the two R groups are part of a ring system, the disrotatory cleavage presents no problem; however the conrotatory cleavage generates a *trans*-alkene which cannot be accommodated within a 'normal-sized' ring [reactions (7.16a) and (7.17a)]:

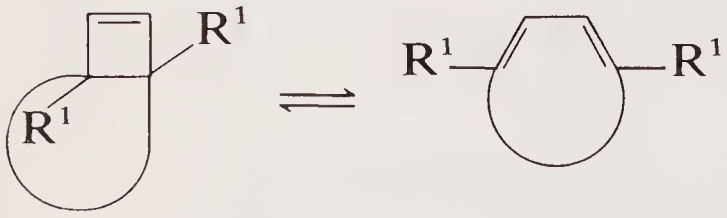


(7.16a)



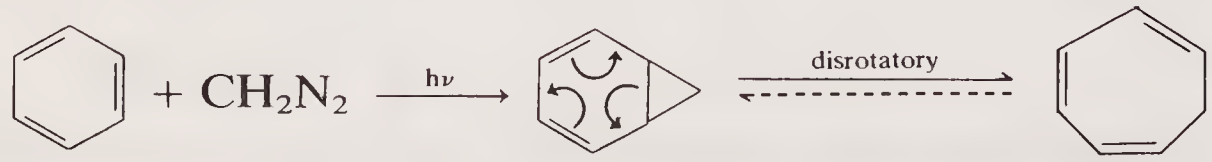
(7.17a)

On the other hand, if the cyclobutene is *trans*-fused, a *cis*, *cis*-diene is produced [reaction (7.18)]:

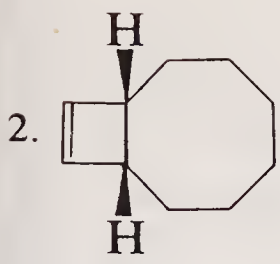


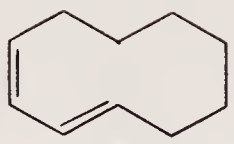
(7.18)

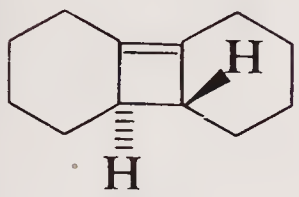
Thus, for example,

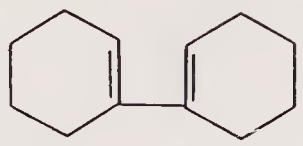
1. 

(32 %)

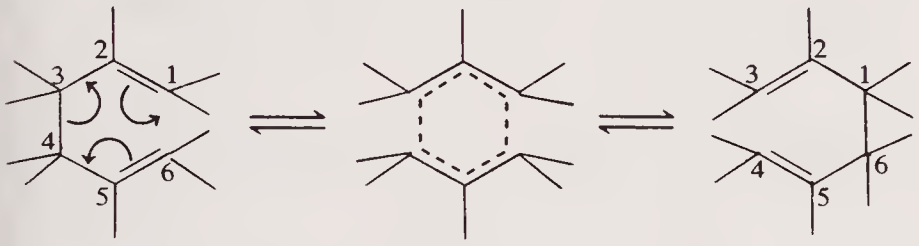
2. 

200°
(conrotatory)

(95 %)

3. 

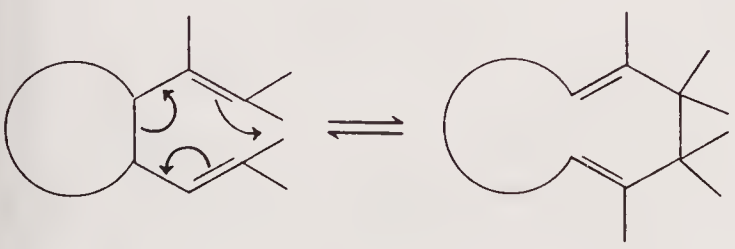
(36)
<100°
(conrotatory)

(37)
(high yield)[7]

The final type of pericyclic process to be considered in this chapter is one involving a **Cope rearrangement** (cf. Sykes, pp. 354–6). In this reaction, which also involves a six-membered cyclic transition state [reaction (7.19)], a 1,5-diene is rearranged to another 1,5-diene by concerted formation of a 1,6-bond, breaking of the 3,4-bond and migration of both double bonds:

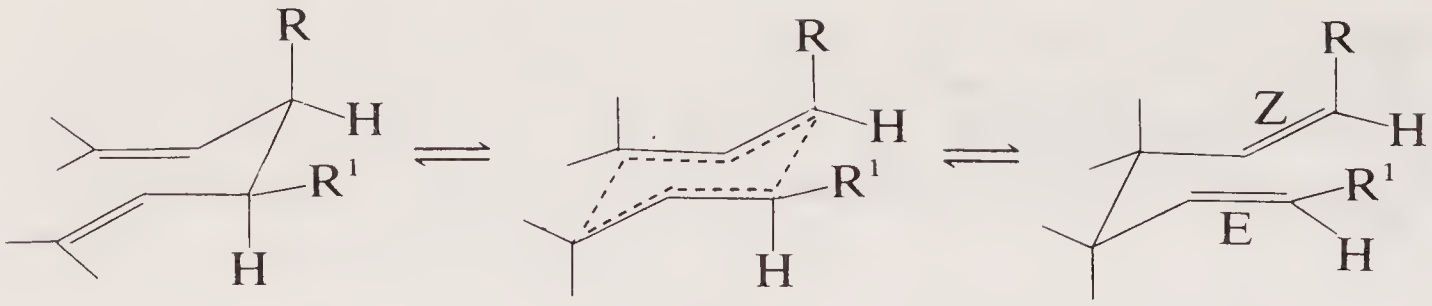


(7.19)

It follows that if the original 3,4-bond is part of a ring system the method may be used for a type of ring opening [reaction (7.19a)].


(7.19a)

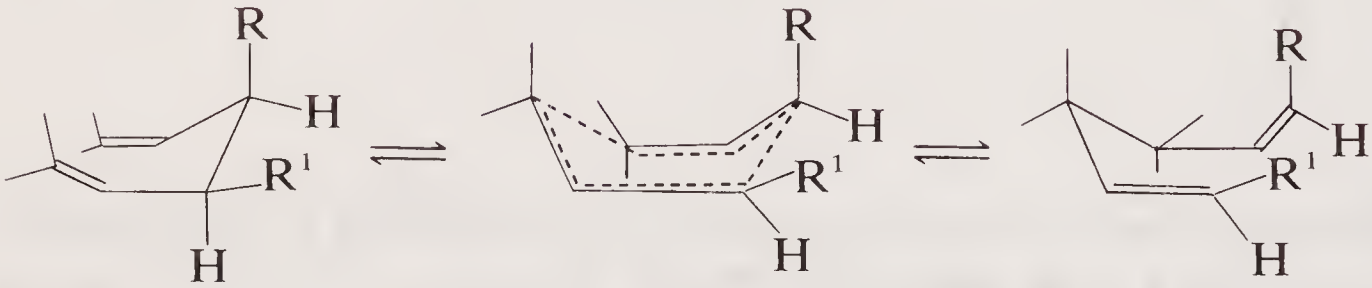
The rearrangement is generally stereospecific, although the configuration of the product is not always predictable, depending as it does on the conformation in the transition state. A chair conformation (38) is preferred to a boat [(39) or (40)] where both may reasonably be formed: thus a diene of type (41) gives (42) rather than (43) or (44), and a diene such as (45) similarly gives (44) rather than (43) or (42):



(41)
(*erythro*- or *cis*-)

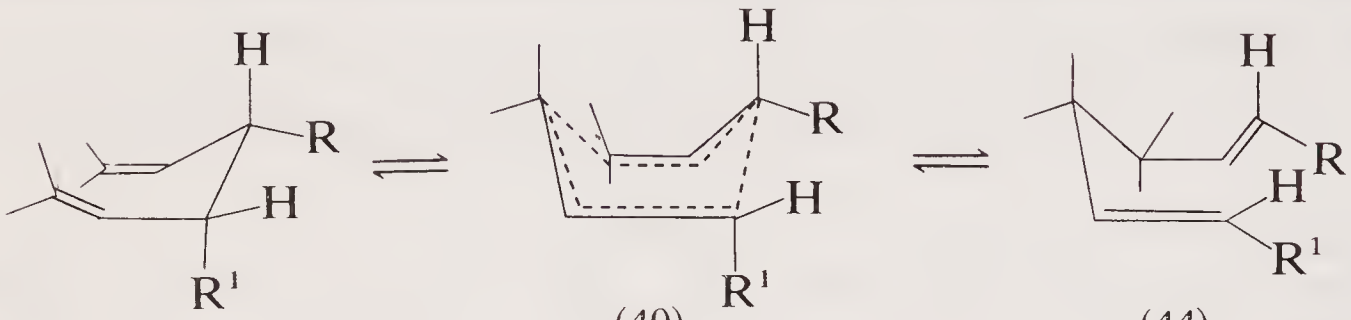
(38)

(42)
(*E*, *Z*)



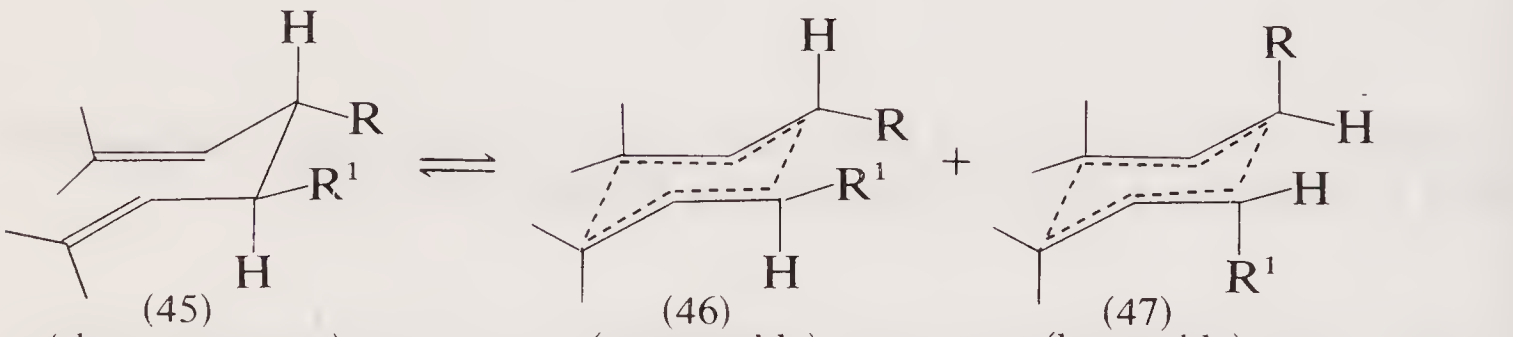
(39)

(43)
(*Z*, *Z*)



(40)

(44)
(*E*, *E*)



(45)
(*threo*- or *trans*-)

(46)
(more stable)

(47)
(less stable)

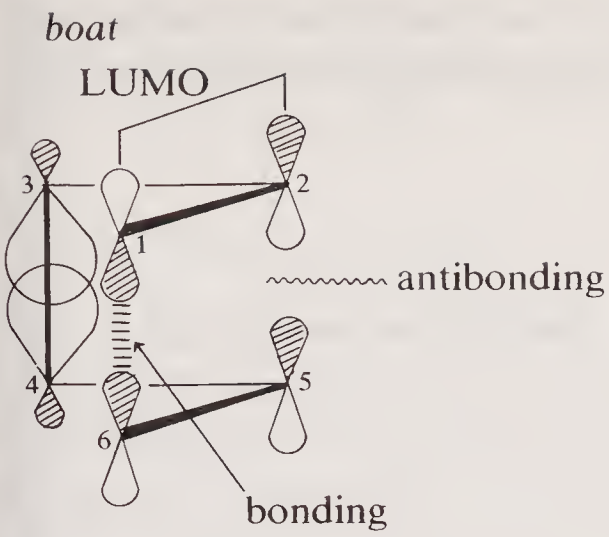
boat

(42)

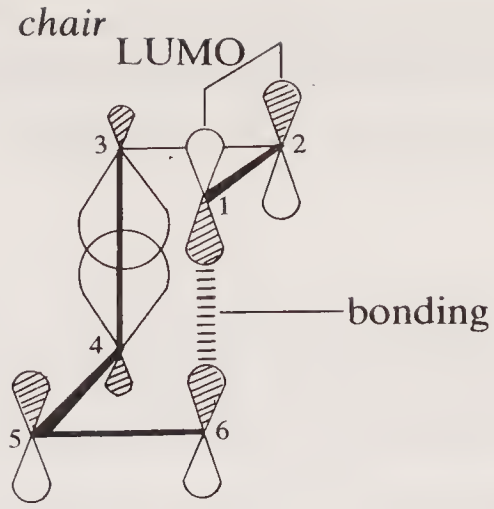
(44)
(major product)

(43)
(minor product)

The preference for the chair-like transition state is explicable in frontier–orbital terms.[8] If the formation of the new single bond is regarded as a HOMO–LUMO interaction, the formation of the *boat-like* transition state (48) requires an unfavourable orbital interaction between C-2 and C-5; such an interaction is absent in the chair-like transition state (49).

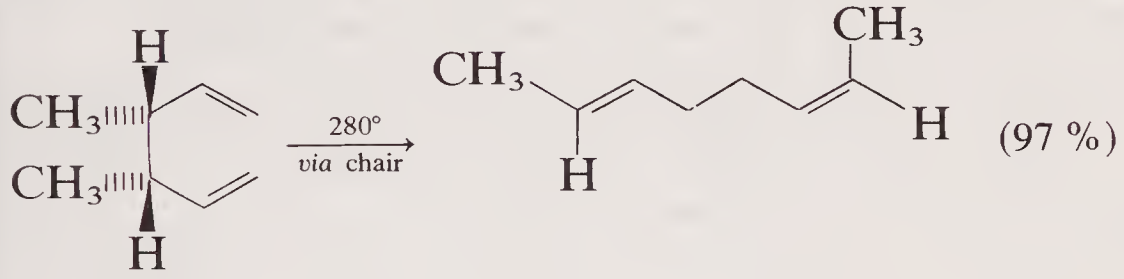


(48)



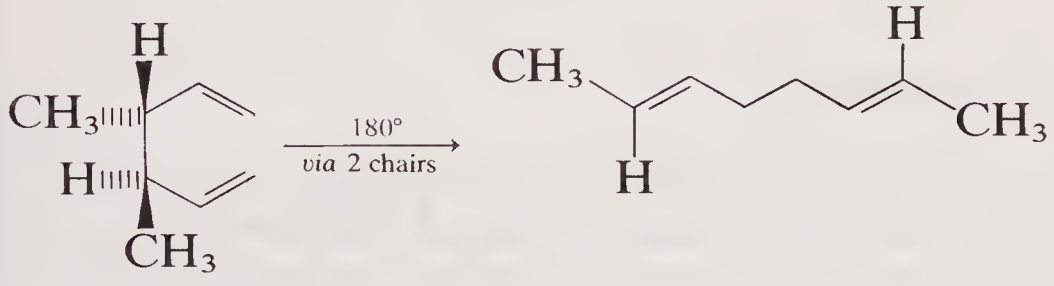
(49)

Examples of the Cope rearrangement include the following:

1. 

(97 %)

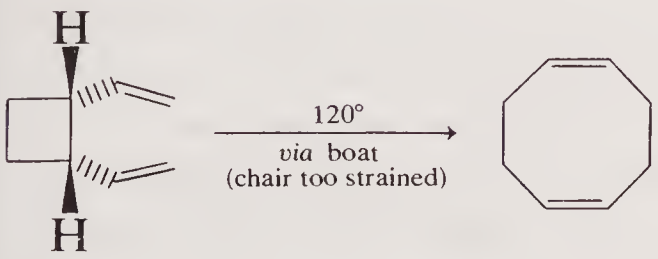
(*erythro*-)

2. 

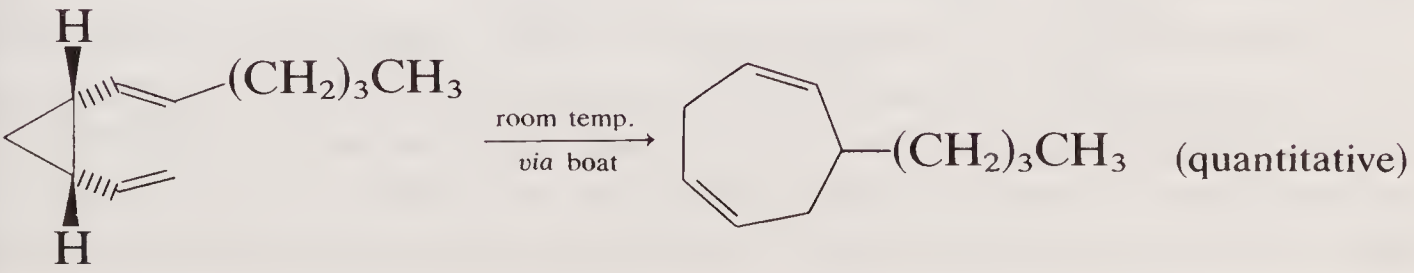
(87 %)

(10 %)

(*threo*-)

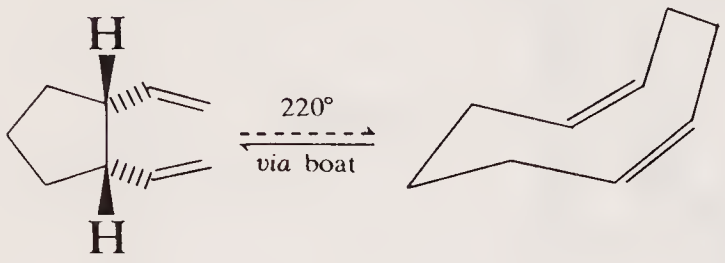
3. 

(91 %)

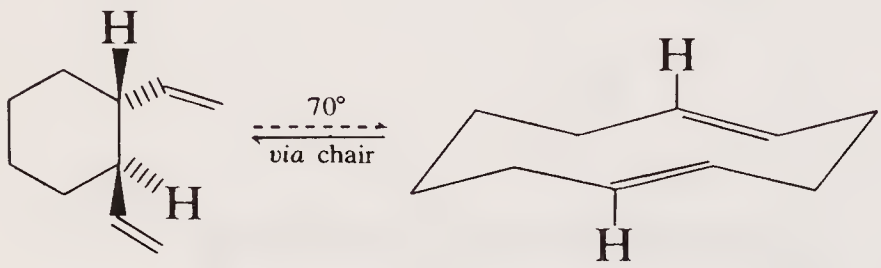
4. 

(quantitative)

The Cope rearrangement, however, like other pericyclic processes, is reversible, and the position of equilibrium depends on the relative stabilities of the isomers; thus, for example,

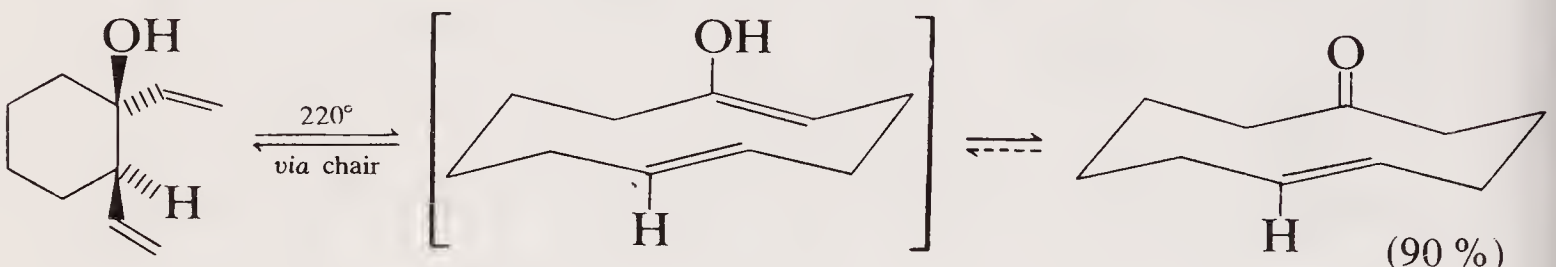
5. 

(*Z*, *Z*) [equilibrium ratio 95 : 5]

6. 

(*E*,*E*) [equilibrium ratio >99 : 1]

In such cases the forward reaction can be made to predominate only if the product reacts further, e.g. the **'oxy-Cope' rearrangement**:

7. 

(90 %)

7.5 Review and problems

The range of reactions covered in this chapter, and the diversity of products which are formed, are both so wide that a brief review can do no more than summarise a few general trends, and so suggest possible synthetic approaches for various types of target molecule.

7.5.1 Non-aromatic rings

Saturated rings of 'normal' size (five- and six-membered) are generally made by standard electrophile–nucleophile interactions; the guidelines for disconnections are the same as have already been described in section 5.6.1. Smaller rings may also be obtained in this way, although special methods are also commonly used for each ring system (e.g. cyclopropane ⇒ alkene + carbene). Medium and large rings, as we have already seen, require special methods (section 7.1.5).

The same applies to *partially saturated rings*, although for such molecules the possibility of pericyclic synthesis should be borne in mind (e.g. the Diels–Alder reaction for cyclohexenes, 1,3-dipolar cycloaddition for five-membered rings, or photocyclisation of dienes for cyclobutenes). There is also the possibility that the unsaturation may be introduced *via*

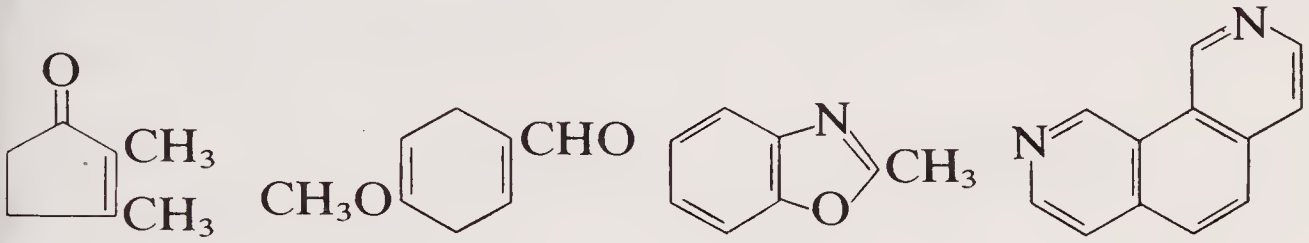
an elimination reaction (cf. section 9.2.4), or that the molecule results from partial hydrogenation of an aromatic or other fully conjugated species (cf. section 8.8).

7.5.2 Aromatic rings

We have already indicated that monocyclic benzene derivatives are usually made from simpler benzene derivatives by functionalisation and/or functional group interconversion, and that benzo-fused compounds (whether carbocyclic or heterocyclic) are usually synthesised from a mono- or (*ortho*-di)-substituted benzene; so the correct disconnection for a benzo-fused molecule is either next to a ring junction or one atom removed from a ring junction. For five-membered heteroaromatic rings the correct disconnection is usually that of a carbon–heteroatom bond.

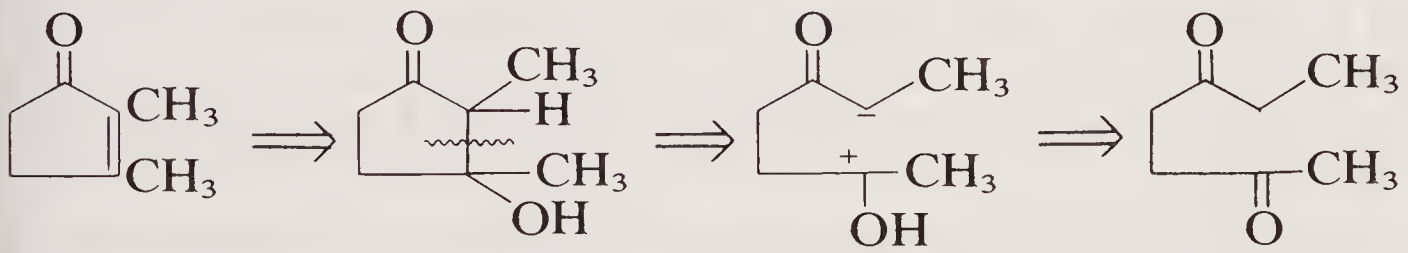
7.5.3 Problems

We conclude this chapter, like Chapters 4 and 5, with four synthetic exercises. Two of the target molecules are carbocyclic and two are heterocyclic:

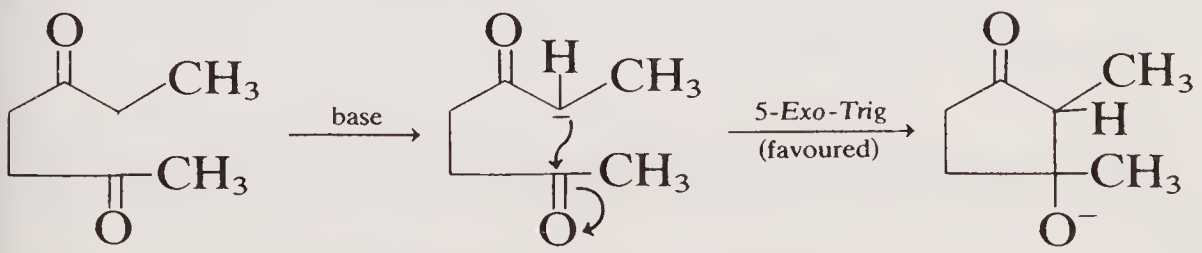


(50) (51) (52) (53)

(i) **2,3-Dimethylcyclopent-2-enone** (compound 50). An α,β-unsaturated ketone, whether cyclic or acyclic, may always be regarded as a possible condensation product. In this case, the appropriate disconnection is

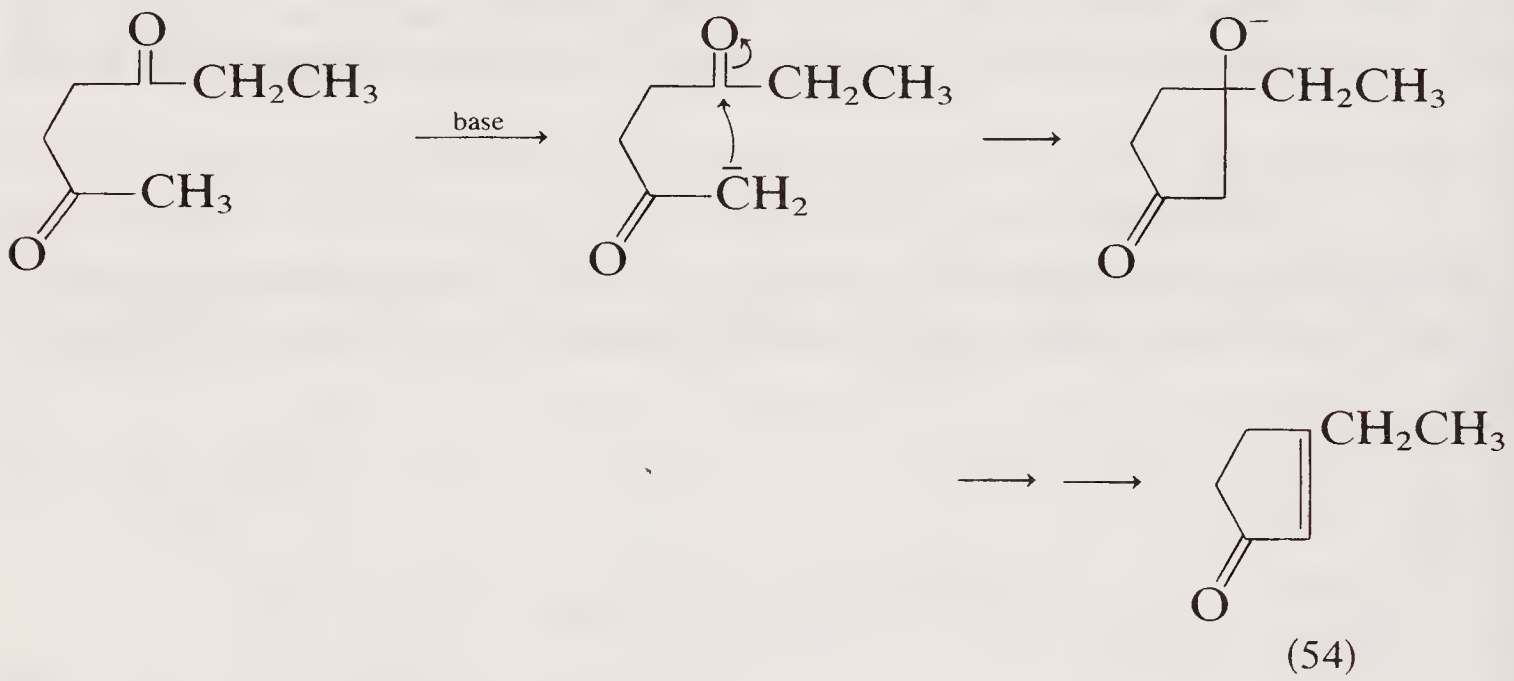


So the synthesis would be:



⟶ ⟶ compound (50)

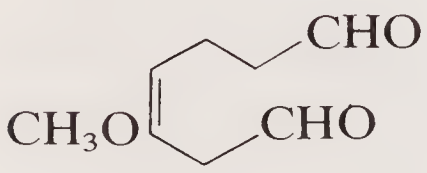
Heptane-2,5-dione is not readily available commercially, and so will require to be made: problems of this kind have already been discussed in section 5.6.1 and are not considered further here. It is of importance, however, that deprotonation of heptane-2,5-dione may occur not only at position 6, but also at positions 1, 3, and 4, and thus compound (50) may not be the sole product. Deprotonation at position 1 might lead ultimately to 3-ethylcyclopent-2-enone (54), a process which is a possible competitor with the cyclisation to (50), but in practice (50) is the main product of reaction of heptane-2,5-dione with a variety of bases. (Deprotonation at position 3 or 4 cannot lead to unstrained cyclic products – only to *inter*molecular reaction – and is of no major significance.)



(54)

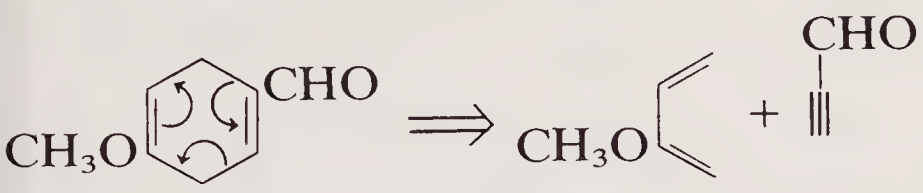
(ii) **4-Methoxycyclohexa-1,4-diene-1-carboxaldehyde** (compound 51). The relationship of this compound to the readily available *p*-methoxybenzaldehyde is so obvious that one is tempted to consider a reductive method based on the latter. However, this is by no means as simple as it initially appears: partial reduction of benzene derivatives usually requires a 'dissolving metal' method (Birch reduction: section 8.9), conditions under which the aldehyde function would not survive. If this method were to succeed, the aldehyde group would require protection (Ch. 10).

One might also consider the condensation approach. Disconnection in the usual manner gives (55) as the required acyclic precursor, and although the synthesis of this dialdehyde is not impossible, it is certainly not easy.

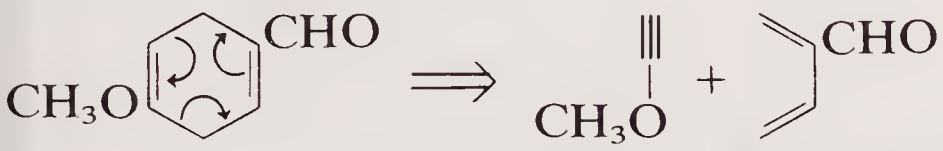


(55)

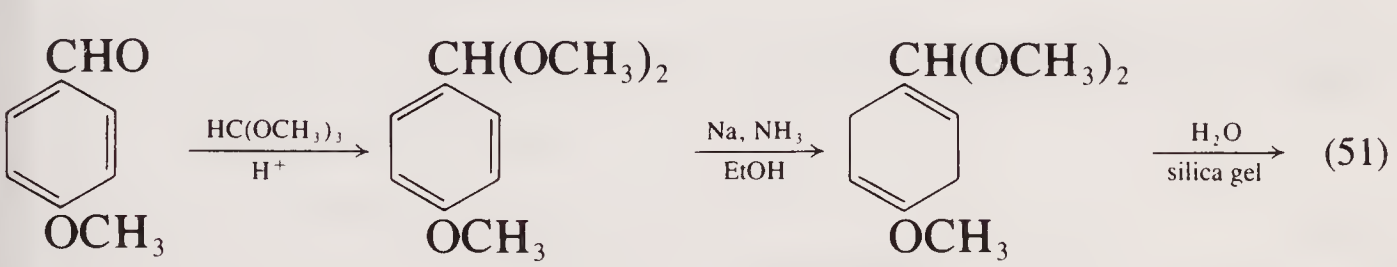
There is also the possibility of a pericyclic process, and the Diels–Alder reaction is worth considering for the formation of a partially saturated six-membered ring. Disconnection of a Diels–Alder adduct is precisely the same as performing a retro-Diels–Alder reaction (section 7.4.3), and when this is applied to (51) the results are as follows:



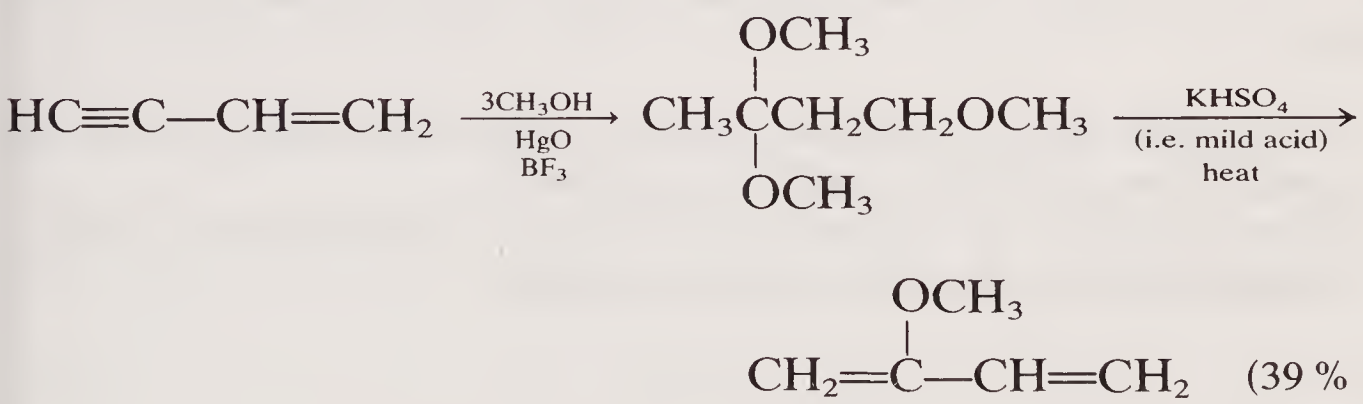
or



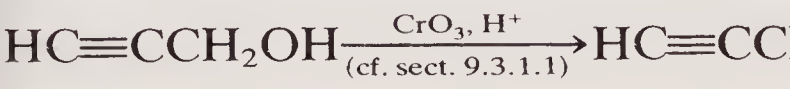
Two syntheses of compound (51) have been recorded in the literature at the time of writing (1989). One involves the conversion of *p*-methoxybenzaldehyde into its dimethyl acetal, and Birch reduction of the latter using sodium in liquid ammonia, with ethanol as the proton source. The aldehyde function is regenerated by very mild hydrolysis of the acetal (using moistened silica gel).



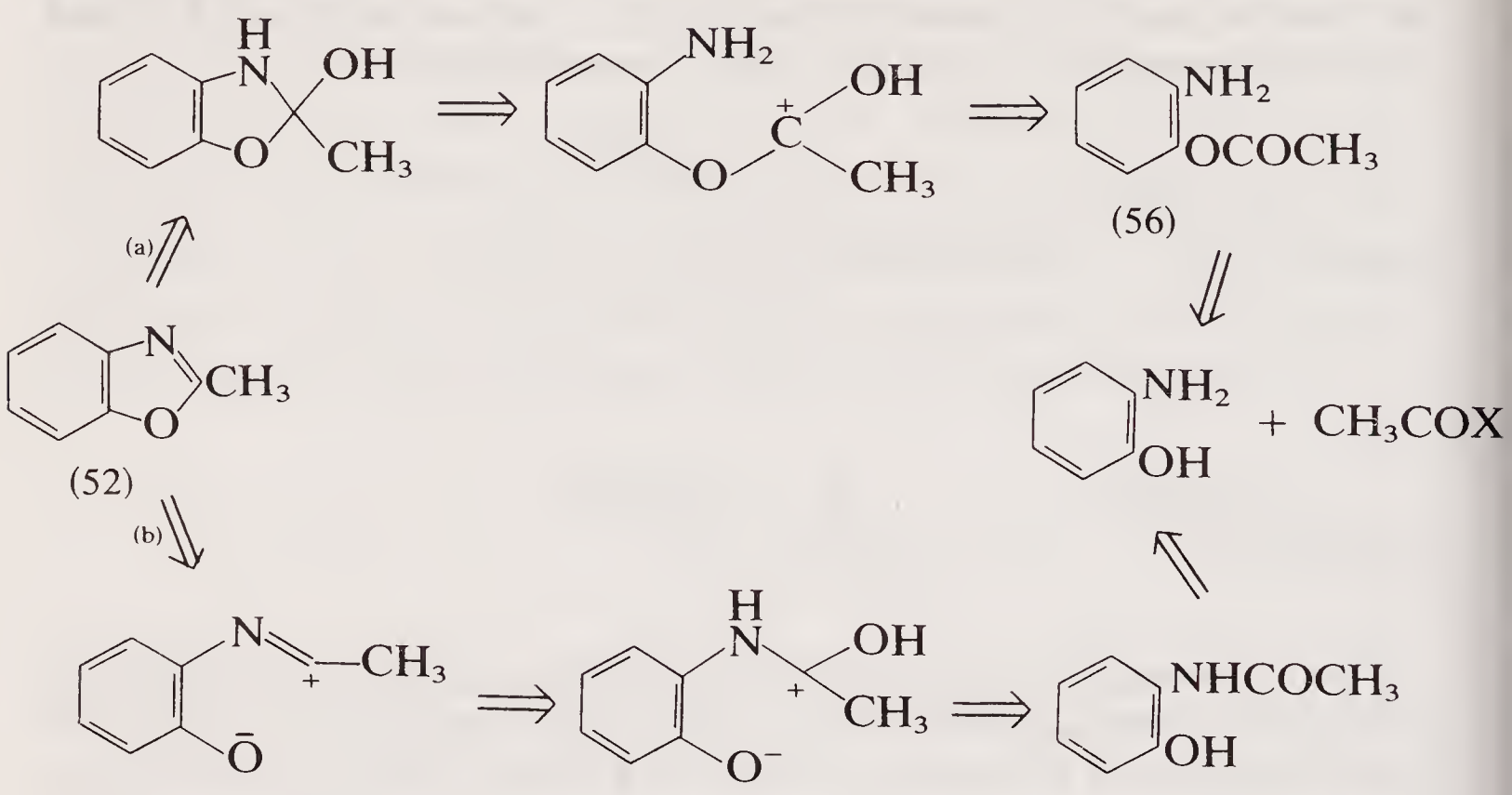
The Diels–Alder synthesis corresponding to the first of the above disconnections has also been reported. 2-Methoxybutadiene and propynal are both readily preparable from commercially available reagents, as follows:



[The intermediate, 1,3,3-trimethoxybutane, is also commercially available.]

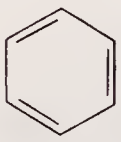


(iii) **2-Methylbenzoxazole** (compound 52). The correct disconnection for a benzo-fused heterocycle usually involves a carbon–heteroatom bond, e.g.



Possible syntheses of (52) might therefore be:

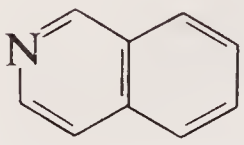
+ $(CH_3CO)_2O$ ⟶



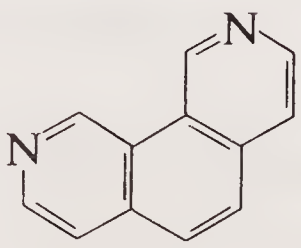
reduction → [compound 56] $\xrightarrow{-H_2O}$

(iv) **2,9-Phenanthroline** (compound 53). As in Chapters 4 and 5, the solution of the final problem is left to the reader. The symmetry of the product is noteworthy, and two synthetic approaches are worthy of consideration:

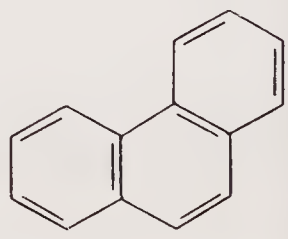
(a) the product may be regarded as an isoquinoline, and one of the standard isoquinoline syntheses applied;
(b) the product may be regarded as a phenanthrene derivative and a standard phenanthrene synthesis applied.



isoquinoline

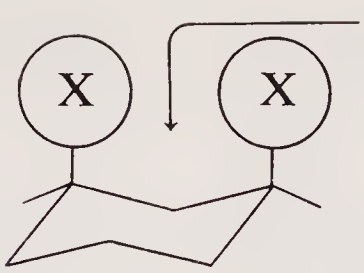


(53)



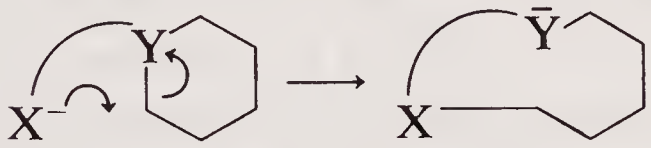
phenanthrene

Notes

1. 

2. Cf. J. E. Baldwin, *J. Chem. Soc. Chem. Comm.*, **1976**, 734.

3. An *Endo-Tet* process is not formally a ring closure at all, but the term could be used to describe a reaction such as



4. As Sykes has pointed out, of course, the **Woodward–Hoffmann rules** [R. B. Woodward and R. Hoffmann, *Angew. Chem., Internat. Edition*, **8,** 781 (1969)] provide a much more rigorous treatment of these reactions, in that the symmetry of all the orbitals of reactants and products is considered. The frontier orbital method is a simplified approach.

5. Cf. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, 1976, pp. 132–40.

6. Cf. Fleming, *op. cit.*, p. 93.

7. The *cis*-isomer of (36) is decomposed to (37) only at a much higher temperature (> 250°): this may be a radical reaction rather than an unfavourable disrotatory cleavage.

8. Cf. Fleming, *op. cit.*, pp. 102–3, 108.

8 Reduction

In this chapter we shall discuss the reduction of a number of multiply bonded functional groups and some examples of reductive cleavage of single carbon–heteroatom bonds. In addition to a number of fairly specific reactions for reduction of certain functional groups, there are three methods which may be used for the reduction of many functional groups: (a) catalytic hydrogenation, (b) metal hydride reduction, and (c) dissolving metal reactions. These three general methods are considered first.

8.1 Catalytic hydrogenation

8.1.1 Heterogeneous catalysts

In this, the most commonly used method, the reaction is carried out by stirring or shaking a solution of the compound, containing a suspension of the catalyst, under an atmosphere of hydrogen. It is convenient to discuss the catalyst and the solvent in terms of two types of reaction: (a) low-pressure and (b) high-pressure hydrogenation. The former involves the use of pressures of hydrogen usually in the range 1 to 4 atm at 0 to 100° and the latter 100 to 300 atm pressure at up to 300°.

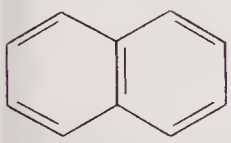
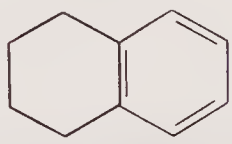
Low-pressure hydrogenation is carried out in presence of a catalyst such as Raney nickel, platinum (usually produced *in situ* by hydrogenation of PtO_2–Adams' catalyst), or palladium or rhodium on a support which can be, in order of decreasing activity, carbon, barium sulphate or calcium carbonate. Solvents can affect the activity of a catalyst, the activity increasing from neutral non-polar solvents such as cyclohexane to polar acidic solvents such as acetic acid.

Depending on the physical properties of the compound to be reduced, high-pressure hydrogenation can be carried out with or without a solvent in presence of a catalyst such as Raney nickel, copper chromite,[1] or palladium on carbon. Table 8.1 lists hydrogenation products of various functional groups in an approximate order of ease of hydrogenation, the acid chloride being the most reactive and the arene the least.

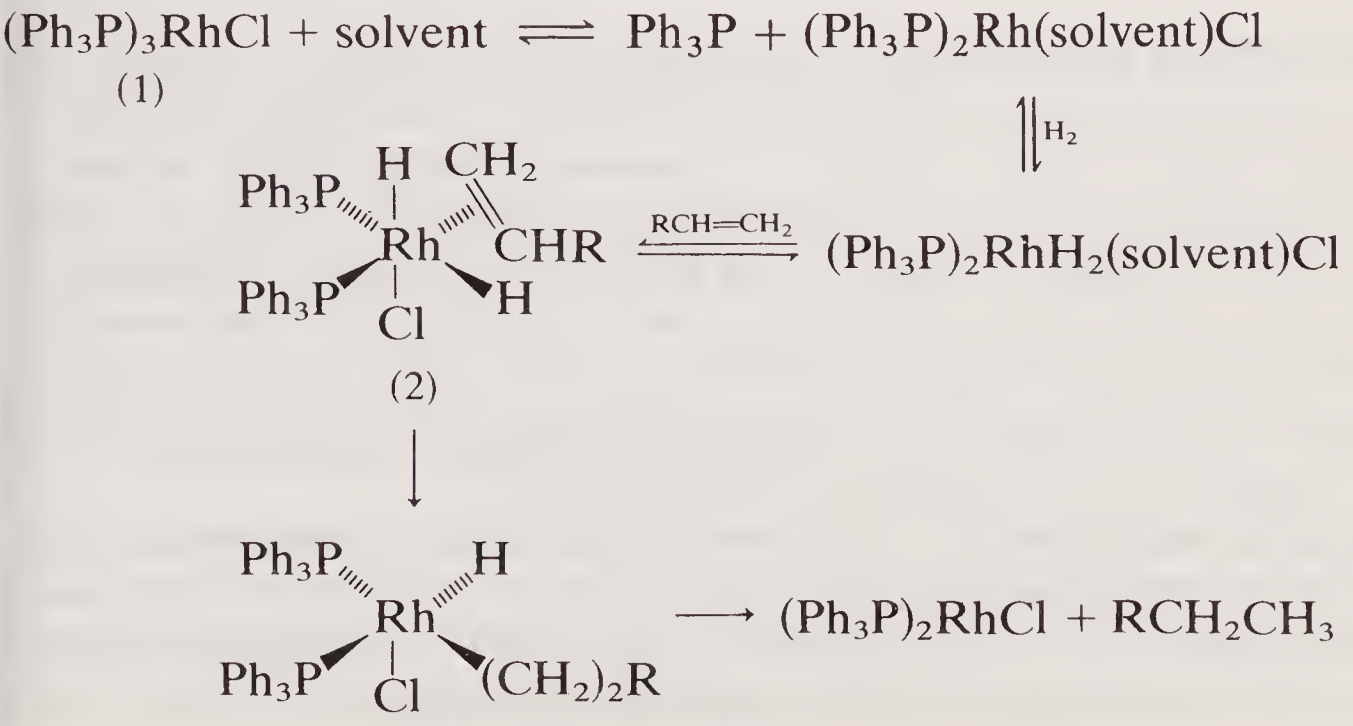
8.1.2 Homogeneous catalysts

Hydrogenation using a heterogeneous catalyst may sometimes lead to

Table 8.1 Products of catalytic hydrogenation

Functional group	Hydrogenation product(s)
$RCOCl$	$RCHO$
RNO_2	RNH_2
$RC{\equiv}CR$	$RCH{=}CHR$ (*Z*, *cis*)
$RCHO$	RCH_2OH
$RCH{=}CHR$	RCH_2CH_2R
$RCOR$	$RCH(OH)R$
$ArCH_2X$	$ArCH_3$
$RC{\equiv}N$	RCH_2NH_2
	
RCO_2R'	$RCH_2OH + R'OH$
$RCONHR$	RCH_2NHR
	

isomerisation of the substrate (cf. section 8.4.1). Isomerisation may be minimised by use of a homogeneous catalyst, e.g. tris(triphenylphosphine)–rhodium chloride (1), since the intermediate complex (2) is less susceptible to rearrangement than its counterpart in the heterogeneous reaction. This can be of considerable importance in, for example, deuteriation. The ease of separation of the catalyst from the reaction mixture is sacrificed when using a homogeneous catalyst, but polymer-bound analogues may combine ease of removal with the formation of products of high purity:



(8.1)

8.1.3 Transfer hydrogenation

In this method, the source of hydrogen is not the element itself, but a compound which may undergo *dehydrogenation* by the catalyst. Hydrogen is thus transferred from the donor to the catalyst, and thence to the substrate undergoing reduction.

The hydrogen donor may be organic (e.g. cyclohexene, propan-2-ol or formic acid) or inorganic (e.g. hydrazine or sodium borohydride), and the catalyst may be heterogeneous or homogeneous. The obvious advantage of the method over the more conventional technique is that the use of gaseous hydrogen, and its attendant hazards, are avoided.

8.2 Metal hydride reductions

Certain metal hydrides are synthetic equivalents of the hydride ion (H^-) synthon and as such are powerful reducing agents which react preferentially at electron-deficient centres. The more strongly basic hydrides (e.g. NaH and CaH_2), however, are not reducing agents. Some of the many commercially available hydride reducing agents (table 8.2) react violently with water and readily with alcohols, and so reactions must be carried out in anhydrous ethereal or hydrocarbon solvents. The most commonly used solvents for each reagents are also given in the table.

Table 8.3 lists some selected reductions which can be achieved using the reagents listed in table 8.2. Unless otherwise stated, the product(s) obtained are those indicated in the left-hand column.

As indicated in table 8.3, $LiAlH_4$, RED-AL®, and AlH_3 are non-selective reagents. Only in the case of an α,β-unsaturated carbonyl compound is AlH_3 preferred to $LiAlH_4$. In fact, the more selective reagent, DIBAL-H, is probably a better choice.

$$Ph(CH_2)_3OH \xleftarrow{LiAlH_4} PhCH{=}CHCHO \xrightarrow{AlH_3} PhCH{=}CHCH_2OH$$

RED-AL® has the following advantages over $LiAlH_4$: (i) it does not ignite in moist air and is stable in dry air, (ii) it is thermally stable up to 200°, and (iii) it is very soluble in aromatic hydrocarbon solvents. Sodium cyanoborohydride is a very selective reagent: for example, it may even be used to reduce primary alkyl halides in presence of aldehydes.

Choice of solvent may also play a part in selectivity. For example, sodium borohydride in diglyme solution is a very mild reagent, reducing aldehydes but not ketones. This selectivity can also be achieved by use of lithium triacetoxyborohydride as reducing agent.

It is, therefore, important to make a careful choice of reagent, solvent and reaction conditions to obtain the desired selectivity. New and increasingly selective hydrides are still being introduced, including some which may be used in asymmetric synthesis (cf. section 15.5.3).

Table 8.2 Solvents for metal hydride reductions

No.	Metal hydride	Solvent
1	$LiAlH_4$	ether, THF, diglyme
2	$LiAlH[OC(CH_3)_3]_3$	THF, diglyme
3	$NaAlH_2(OCH_2CH_2OCH_3)_2$ [RED-AL®]	benzene, toluene, xylene
4	$NaBH_4$	water, ethanol, diglyme
5	$NaBH_3(CN)$	water, methanol, DMSO
6	$LiBH_4$	THF, diglyme
7	AlH_3	ether, THF
8	$AlH[CH_2CH(CH_3)_2]_2$ [DIBAL-H]	toluene, $CH_3O(CH_2)_2OCH_3$

Table 8.3 Products of metal hydride reductions

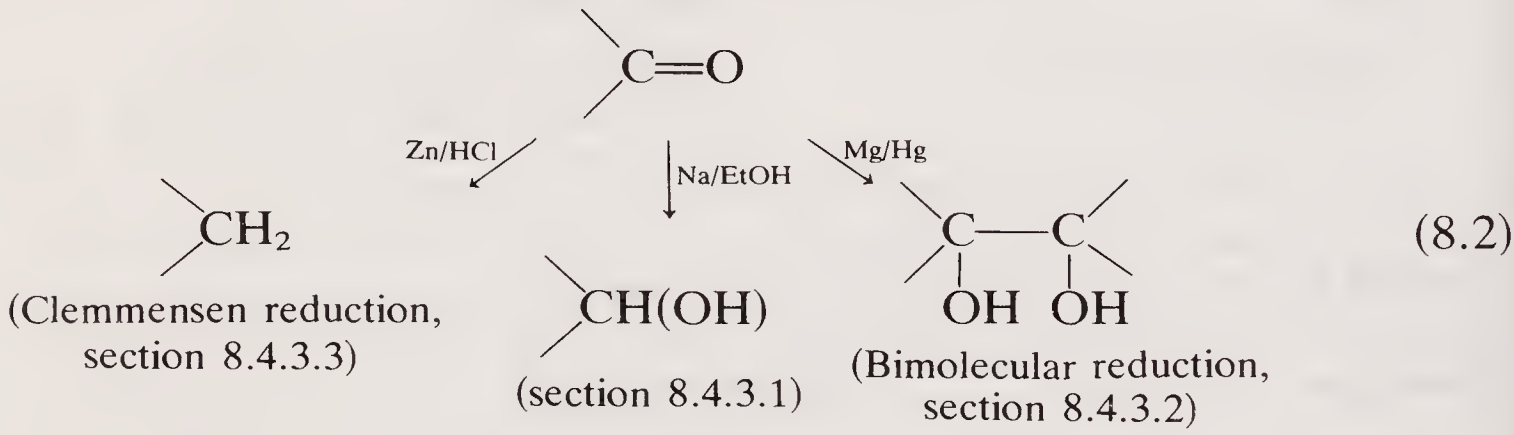
Reduction	Reducing agent							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
$RCHO \rightarrow RCH_2OH$	√	√	√	√	√	√	√	√
$RCOR \rightarrow RCH(OH)R$	√	√	√	√	√	√	√	√
$RCOCl \rightarrow RCH_2OH$	√	(a)	√	√		√	√	
lactone → diol	√	×	√	(b)	×	√	√	(c)
epoxide → 1,2-diol	√	×	√	(b)	×	√	√	
$RCO_2R' \rightarrow RCH_2OH + R'OH$	√	(d)	√	(b)	×	√	√	(a)
$RCO_2H \rightarrow RCH_2OH$	√	×	√	×	×	√	√	(a)
$RCONR_2 \rightarrow RCH_2NR_2$	(e)	×	√	×	×	×	√	×
$RC{\equiv}N \rightarrow RCH_2NH_2$	√	×	×	×	×	×	√	(a)
$RNO_2 \rightarrow RNH_2$	(f)	×		×	×	×	×	
$RX^{(g)} \rightarrow RH$	√	×	√	×	√	×	×	
$RC{\equiv}CR \rightarrow RCH{=}CHR\ (Z)$								√

(a) reduction proceeds to the aldehyde stage only
(b) very slow reaction
(c) reduction proceeds to lactol stage only
(d) phenyl esters give aldehydes
(e) some amides are reduced to aldehydes
(f) where R is aliphatic; if R is aromatic, azoarenes are formed
(g) X = halogen or OSO_2R'

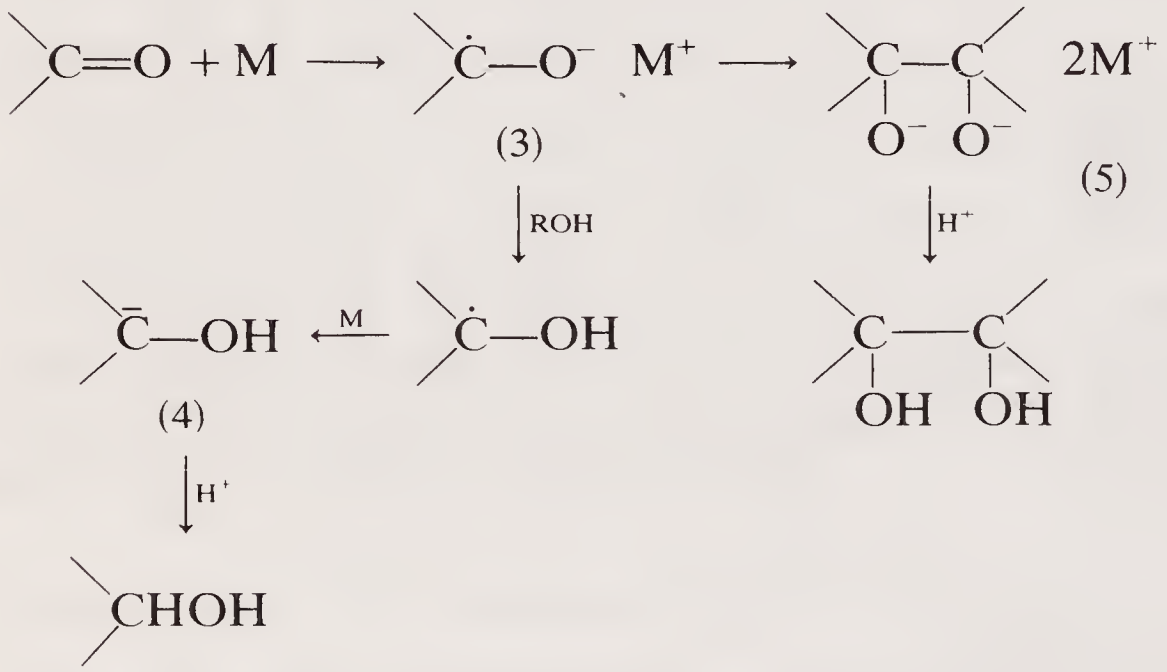
8.3 Dissolving metal reductions

This type of reaction, formerly thought to involve 'nascent' hydrogen, involves electron transfer to the substrate from a metal such as lithium, sodium, potassium, magnesium, calcium, zinc, tin or iron. A proton donor (e.g. water or ethanol) may either be present during electron

transfer or be added at a later stage. Reduction of the carbonyl group can result in the formation of three types of product depending on the reaction conditions used (8.2). Reduction to the alcohol takes place in presence of a proton donor, when the initially formed radical anion (3) is first protonated and then converted into the carbanion (4) by a second electron transfer. In the absence of a proton donor, (3) dimerises to the pinacolate dianion (5). The Clemmensen procedure involves successive electron transfers to the protonated ketone adsorbed on the surface of the metal. In this case, low concentrations of ketone at the metal surface are desirable to minimise bimolecular reduction.



(8.2)



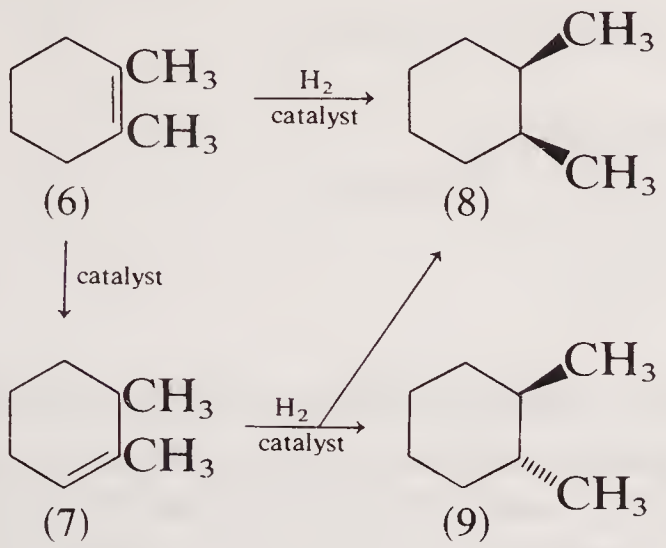
Under certain circumstances, reductions analogous to those carried out under dissolving metal conditions can be carried out electrochemically. Some examples of dissolving metal and of electrochemical reductions will be found in the later sections of this chapter.

8.4 Reduction of specific functional groups

8.4.1 Reduction of alkenes

Alkenes are rapidly hydrogenated in presence of a catalyst, usually platinum, Raney nickel, or palladium or rhodium on carbon, to the corresponding alkane. Although such reactions are normally regarded as being stereospecifically *cis* additions, rearrangements occurring on the catalyst

surface make this statement an oversimplification. For example, 1,2-dimethylcyclohexene (6) isomerises to 2,3-dimethylcyclohexene (7), and catalytic hydrogenation of (6) thus gives a mixture of *cis*-(8) and *trans*-(9) dimethylcyclohexanes. Isomerisation of this type often results in the formation of complex product mixtures when catalytic deuteriations are attempted.

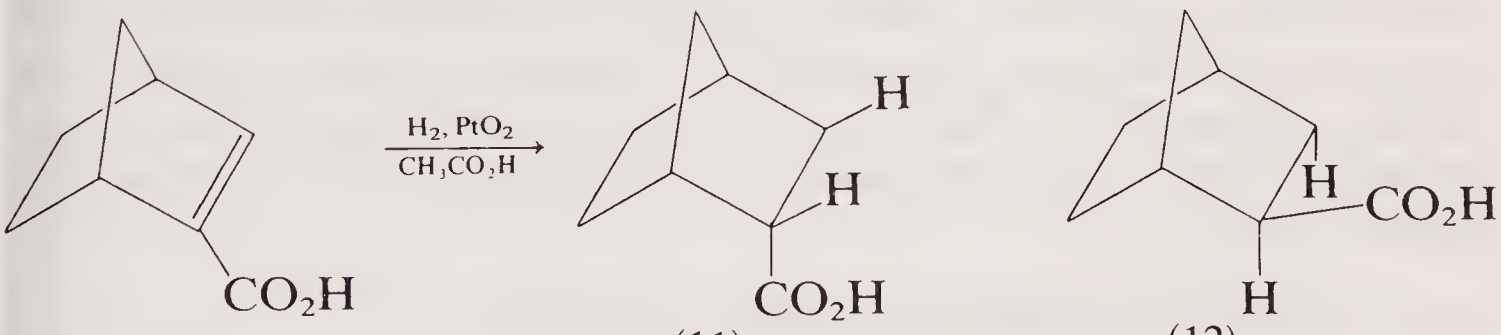


Platinum catalysts tend to cause less isomerisation than palladium, e.g.

$$(6) \xrightarrow[\text{R.T., acetic acid}]{\text{1 atm } H_2,\ PtO_2} \underset{(82\ \%)}{(8)} + \underset{(18\ \%)}{(9)} \quad (100\ \%)$$

$$(6) \xrightarrow[\text{R.T., acetic acid}]{\text{1 atm } H_2,\ Pd/Al_2O_3} \underset{(23\ \%)}{(8)} + \underset{(77\ \%)}{(9)} \quad (100\ \%)$$

In hindered alkenes, addition takes place on the less hindered side. For example, in the case of bicyclo[2.2.1]hept-2-enecarboxylic acid (10) there is less steric hindrance to adsorption on the catalyst surface on the face of the molecule *cis* to the methylene bridge. The product is then the *endo* isomer (11) rather than the *exo* isomer (12).

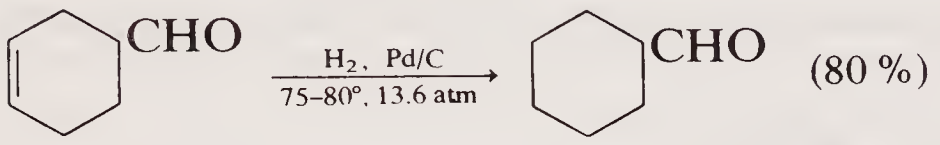


(10) (11) (83 %) (12)

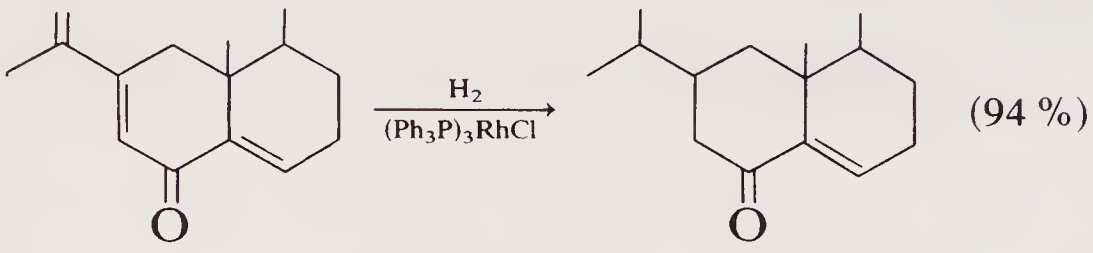
It is possible to reduce double bonds selectively in presence of esters and ketones and even, in some instances, aldehydes provided that the reaction conditions are carefully controlled. However, a greater degree of selectivity is achieved by use of the homogeneous catalyst tris(triphenyl-

phosphine)rhodium chloride:

$$PhCH{=}CHCOPh \xrightarrow[CH_3CO_2C_2H_5]{H_2,Pt} PhCH_2CH_2COPh \quad (90\ \%)$$



(80 %)



(94 %)

Non-polar and moderately polar carbon–carbon double bonds are reduced by di-imide (13) whereas polar double bonds such as carbonyl groups and the carbon–carbon double bonds in α,β-unsaturated ketones are not affected. Although the first reports of reductions involving di-imide used hydrazine in presence of an oxidising agent, a more useful source is the decomposition of azodicarboxylate salts in an acidic medium [reaction (8.3)]:

$$^{-}O_2CN{=}NCO_2^{-} + 2H^{+} \rightarrow HN{=}NH + 2CO_2 \qquad (8.3)$$

(13)

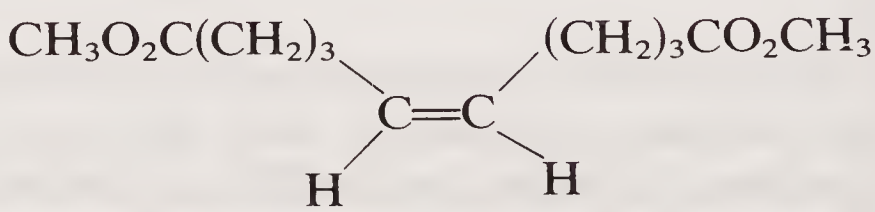
$$CH_2{=}CHCH_2OH + 2K^{+}\ {}^{-}O_2CN{=}NCO_2^{-} \xrightarrow[\text{methanol}]{CH_3CO_2H} CH_3CH_2CH_2OH + N_2 + 2CO_2$$

(room temp.; 78 %)

8.4.2 Reduction of alkynes

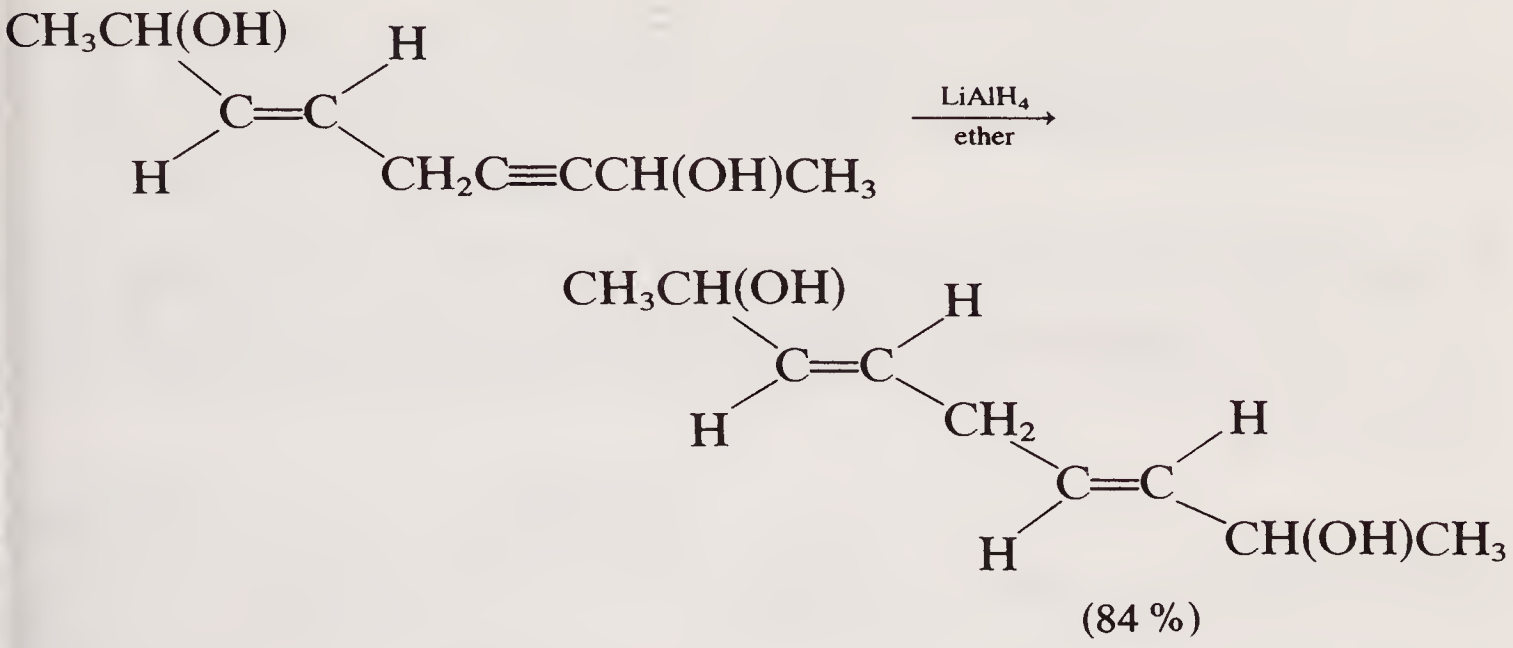
Catalytic hydrogenation of alkynes results in complete reduction to the corresponding alkanes. However, if a reduced-activity catalyst, the **Lindlar catalyst** (Pd on $BaSO_4$ partially poisoned with quinoline or lead acetate), is used, hydrogenation can be stopped at the intermediate *Z*-alkene stage.

$$CH_3O_2C(CH_2)_3C{\equiv}C(CH_2)_3CO_2CH_3 \xrightarrow[\text{quinoline}\ \text{methanol}]{H_2,Pd/BaSO_4}$$



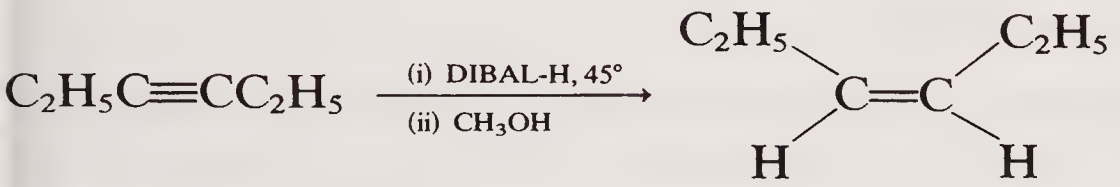
(97 %)

Lithium aluminium hydride does not readily reduce aliphatic alkynes but α-hydroxyalkynes and α,β-alkynoic acids are both reduced to (*E*-)-allylic alcohols.



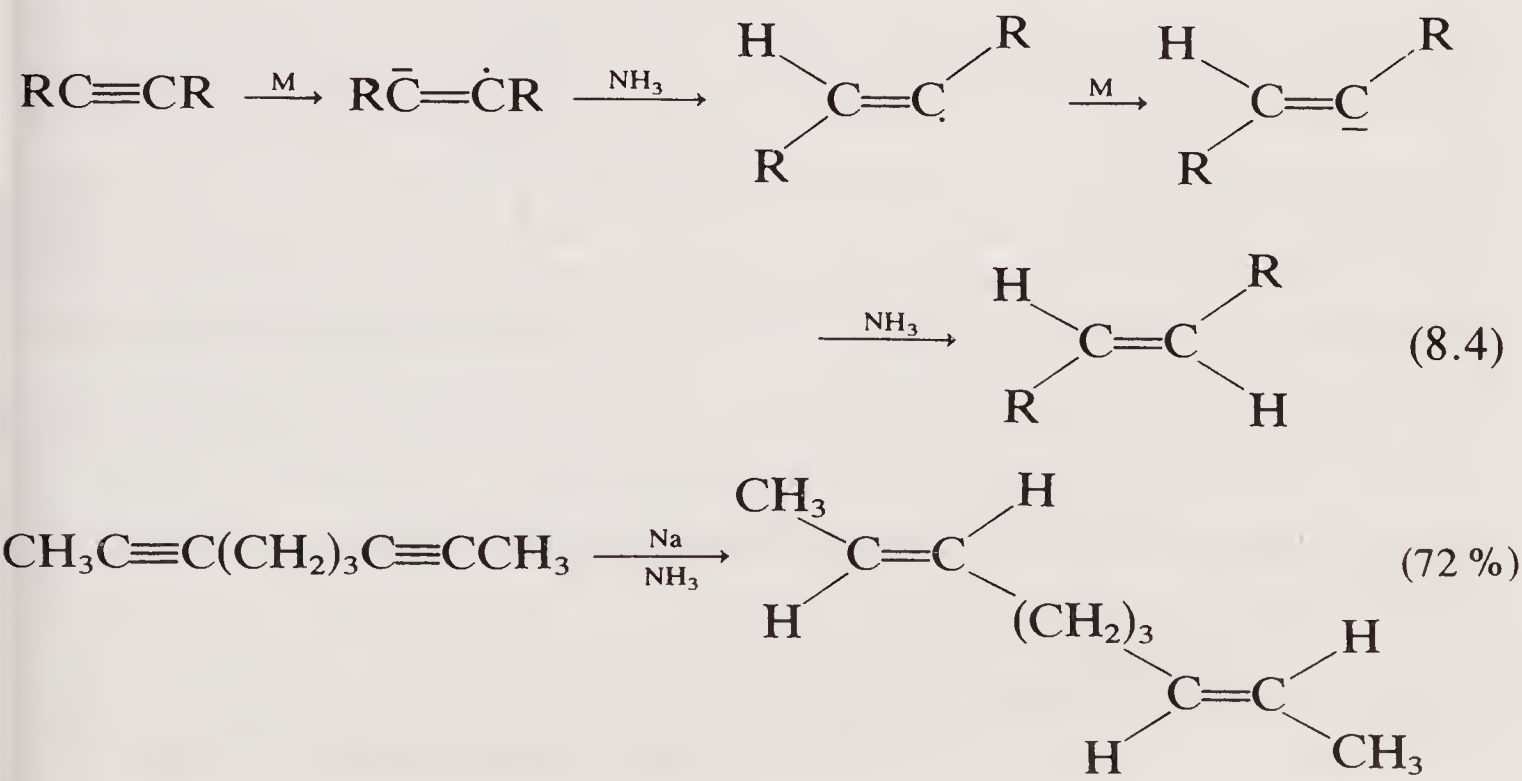
(84 %)

DIBAL-H does, however, react more readily with aliphatic alkynes, the product in this case being the *Z*-alkene:



(91 %)

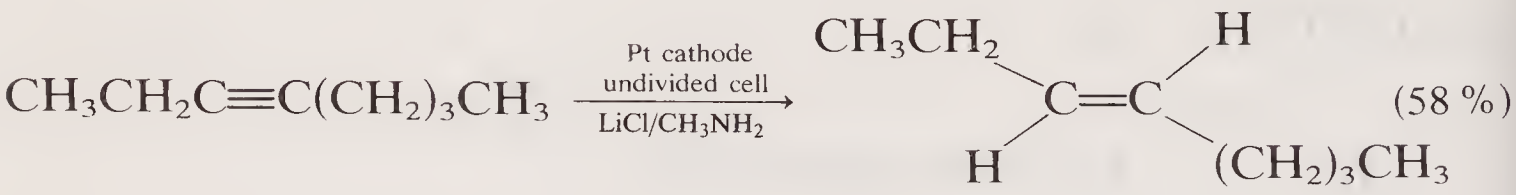
A more general method for reducing non-terminal alkynes to *E*-alkenes is the **dissolving metal procedure** using lithium or sodium in liquid ammonia followed by protonation [reaction (8.4)]. Reduction of diarylalkynes is more complex; either *E*- or *Z*-alkenes can be formed depending on the metal used.



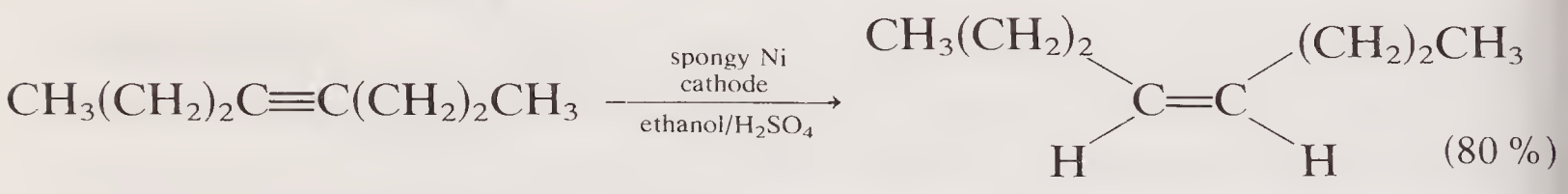
(8.4)

(72 %)

Electrochemical reduction of alkynes with lithium chloride in methylamine may involve formation of lithium atoms which reduce the alkyne by electron transfer. This results in formation of *E*-alkenes.



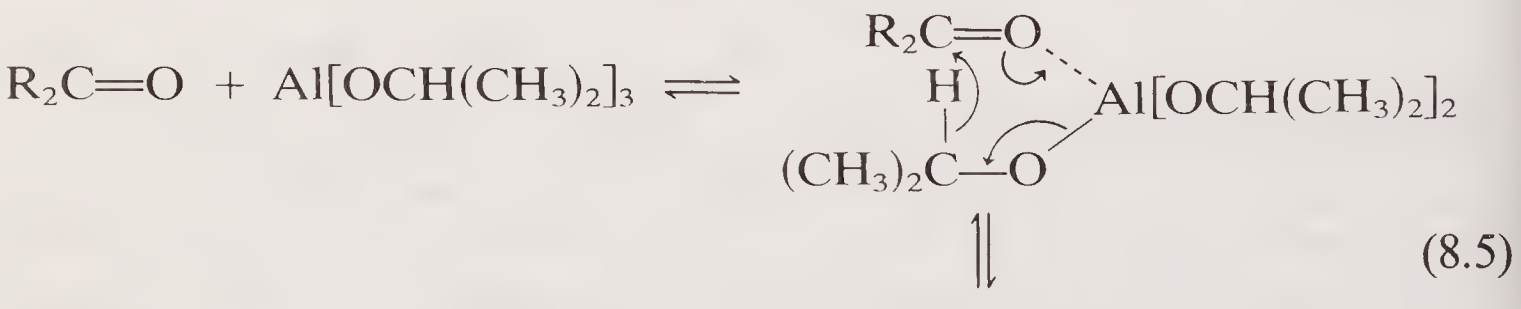
A mechanism involving electrocatalytic hydrogenation has been suggested for the formation of *Z*-alkenes at a spongy nickel cathode. Reduction to the *Z*-alkene is also brought about through hydroboration (cf. section 11.5).

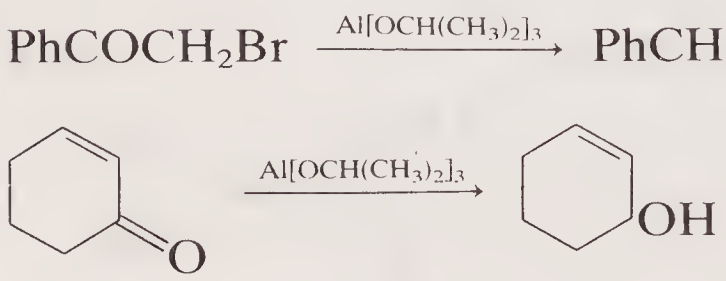


8.4.3 Reduction of aldehydes and ketones

8.4.3.1 Reduction to alcohols

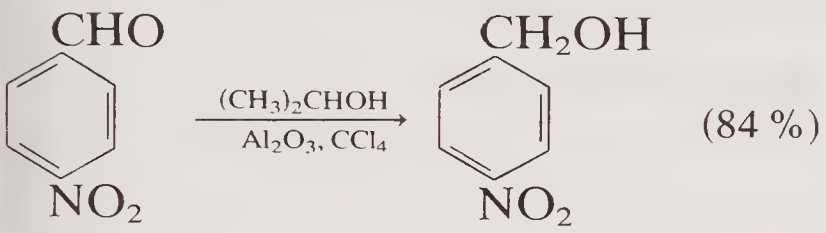
Reduction of aldehydes and ketones can be carried out by a variety of methods including catalytic hydrogenation, and use of metal hydrides, dissolving metals, and aluminium isopropoxide (the **Meerwein–Ponndorf–Verley** reaction). Unless stereochemical considerations, which will be discussed later, are important, all methods result in the same product from acyclic ketones and aldehydes. However, the Meerwein–Ponndorf–Verley reaction (8.5) is useful when the carbonyl group is to be reduced in presence of other reducible groups:





The reduction of aldehydes and ketones, dissolved in an inert solvent, by propan-2-ol catalysed by dehydrated alumina is also a general method. The advantages claimed for the method are:

(i) α,β-unsaturated aldehydes are reduced to allylic alcohols;
(ii) aldehydes can be reduced in presence of some ketones;
(iii) many labile functional groups (e.g. nitro, cyano and halogeno) survive the reaction;
(iv) the propanol/alumina reagent can be stored in a sealed vial for long periods;
(v) reagents are cheap and products are easily isolated.



(84 %)

$$(CH_3)_2C{=}CH(CH_2)_2CH{=}CHCHO \xrightarrow[Al_2O_3,\ CCl_4]{(CH_3)_2CHOH} (CH_3)_2C{=}CH(CH_2)_2CH{=}CHCH_2OH \quad (88\ \%)$$

When stereochemical factors are involved, a more complex situation is encountered. If a hydride reduction can give two diastereomeric alcohols, the outcome may depend either on (i) the relative stabilities of the two products, or (ii) on the preferred direction of approach of the incoming hydride reagent. When this is bulky, the latter is the dominant influence, and the nucleophilic attack is from the less hindered side of the molecule. If the hydride reagent is not sterically demanding, however, the reaction usually takes place so as to give a preponderance of the more stable alcohol. Electrochemical and dissolving metal reductions also follow the latter pattern.

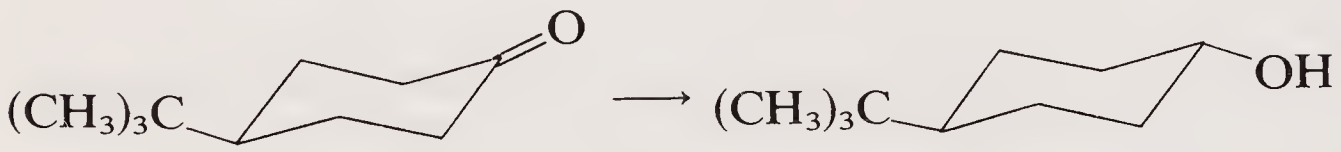
Catalytic hydrogenation results in *cis* addition from the less hindered side of the molecule. The products formed on reduction of 4-t-butylcyclohexanone (14) and of 3,3,5-trimethylcyclohexanone (17) under a variety of conditions are listed in tables 8.4 and 8.5, respectively and serve to illustrate the importance of choice of reagent when stereochemical factors have to be considered. It should be noted that the relative thermodynamic stabilities of (15) and (16) are approximately 4:1 and of (18) and (19) approximately 16:1.

Table 8.4 Products of reduction of 4-t-butylcyclohexanone

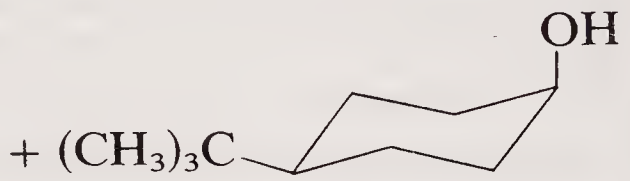
Reducing agent	**Ratio of (15) : (16)**
$LiAlH_4$	9 : 1
$LiAlH[OC(CH_3)_3]_3$/THF	9 : 1
Li/liq. NH_3 in ether/butanol	49 : 1
H_2/Raney Ni/ethanol	1 : 1
$Al[OCH(CH_3)_2]_3$	3 : 1

Table 8.5 Products of reduction of 3,3,5-trimethylcyclohexanone

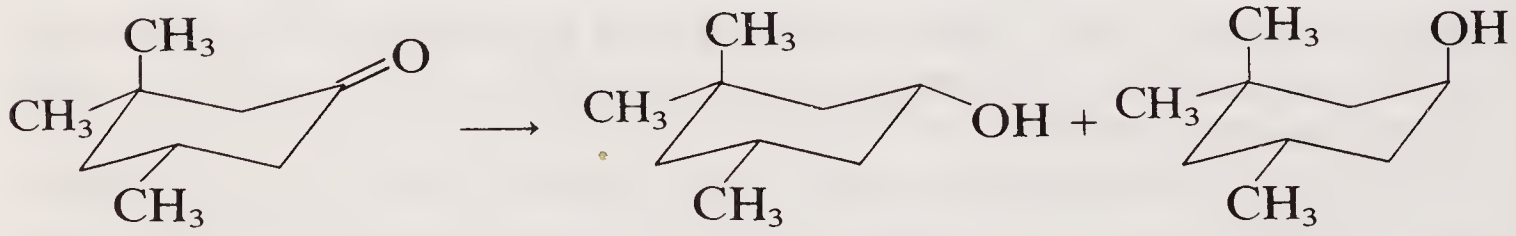
Reducing agent	**Ratio of (18) : (19)**
$LiAlH_4$/ether	1 : 1
$LiAl[OC(CH_3)_3]_3$/THF	1 : 8
H_2/Raney Ni/ethanol	1 : 9
Pt cathode/LiCl	10 : 1
Li/liq. NH_3/ethanol	99 : 1



(14) (15)



(16)

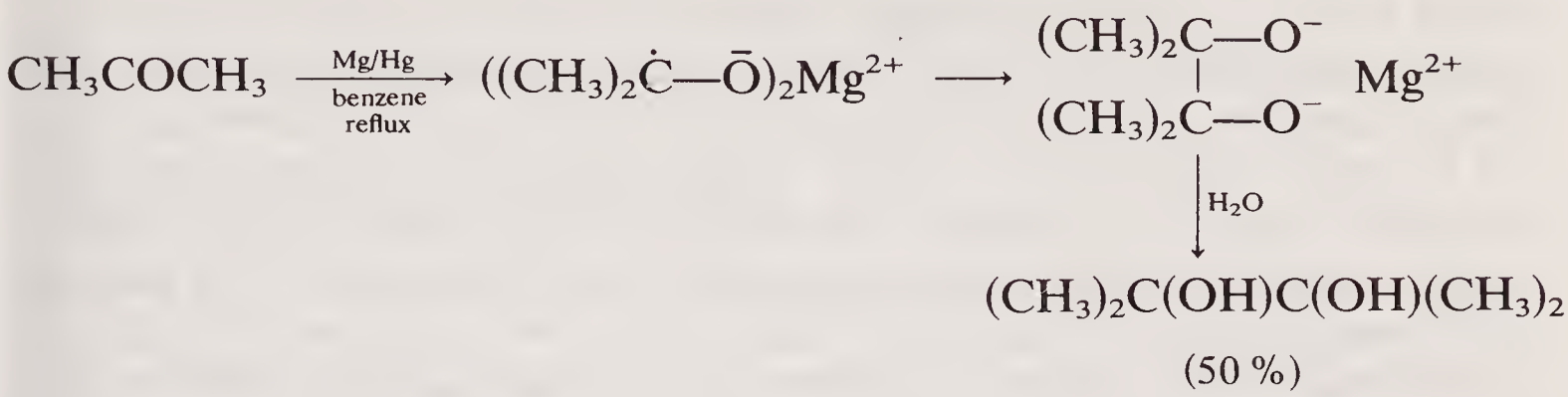


(17) (18) (19)

8.4.3.2 Bimolecular reduction

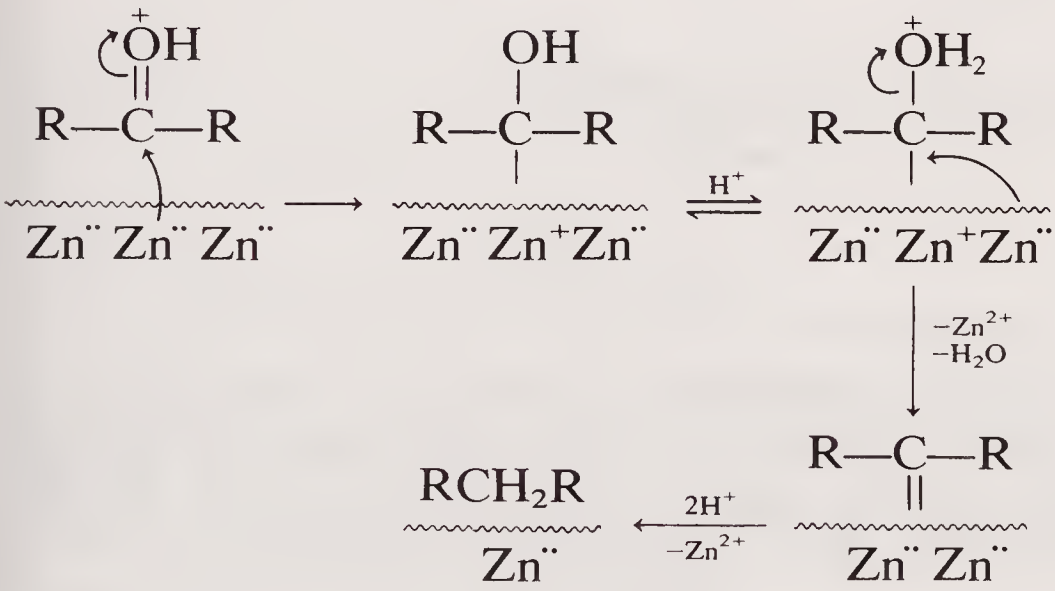
When ketones react with magnesium, zinc or aluminium (used often as amalgams) in the absence of proton donors, the initially formed radical

ions dimerise to the dianion of a 1,2-diol. Bimolecular reduction competes with other reductions such as the Clemmensen reaction:



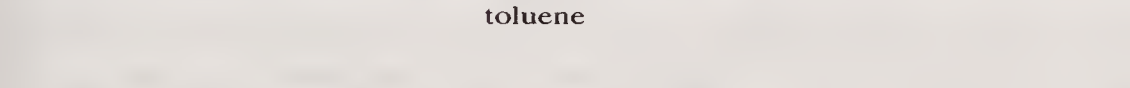
8.4.3.3 Reduction of ketones to methylene groups

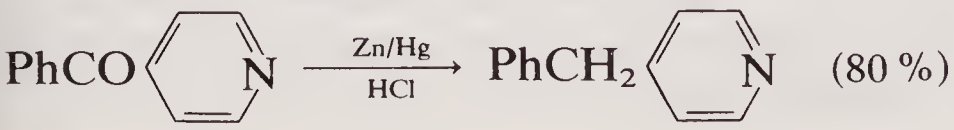
Reduction of ketones with zinc amalgam in presence of mineral acid (the **Clemmensen** reaction) reduces the carbonyl group to methylene. Often the reaction is carried out in presence of toluene to produce a three-phase system in which most of the ketone remains in the upper hydrocarbon layer, and the protonated carbonyl compound in the aqueous layer is reduced on the metal surface by the mechanism shown in reaction (8.6):



(8.6)

The purpose of carrying out the reaction in a three-phase system is to minimise bimolecular reduction by maintaining only a low concentration of protonated carbonyl compound at the metal surface. The following examples demonstrate the scope of the reaction. (The method cannot, of course, be used for the reduction of acid-sensitive compounds.)

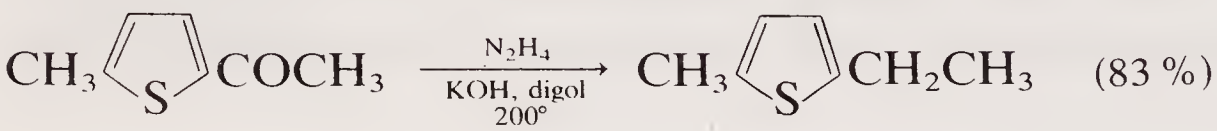


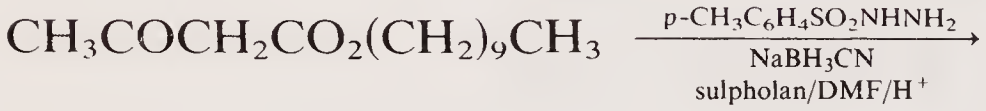


Complementary to the Clemmensen reduction is the **Wolff–Kishner** reaction (8.7) in which the ketone hydrazone is treated with a strong base. Several modifications of the reaction have been used, one of the more successful being the **Huang–Minlon** procedure. In this case, the carbonyl compound, hydrazine hydrate, and potassium hydroxide are heated together in a high boiling solvent. It has also been shown that use of dimethyl sulphoxide as solvent causes reaction to take place at substantially lower temperatures. For base-sensitive compounds an alternative procedure involves the reaction of a tosylhydrazone of the ketone with sodium cyanoborohydride. Due to the slow reduction of carbonyl compounds under these conditions, it is unnecessary to preform the hydrazone:

$$R_2C{=}O \xrightarrow{N_2H_4} R_2C{=}NNH_2 \xrightarrow{OH^-} R_2C{=}N\bar{N}H \rightleftharpoons R_2CHN{=}NH$$

$$\xrightarrow{OH^-} R_2CHN{=}N^- \longrightarrow R_2CH^- + N_2 \xrightarrow{R'OH} R_2CH_2 \qquad (8.7)$$





Hydrogenolysis of ketone dithioketals represents a very mild procedure for the conversion of carbonyl groups into methylene groups. However, since a large excess of Raney nickel is required (7 g/g of substrate), it is normally only of use in small-scale preparations.

8.4.4 Reduction of carboxylic acids and their derivatives

Acids, amides and esters are resistant to catalytic hydrogenation. Indeed, both ethyl acetate and acetic acid are commonly used solvents in low pressure hydrogenations.

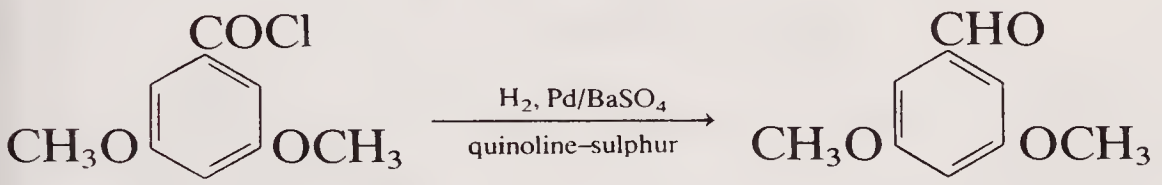
Esters are readily reduced to alcohols by lithium aluminium hydride and by dissolving metal reactions. The latter, the **Bouveault–Blanc** method, only rarely holds advantage over lithium aluminium hydride and has largely been replaced by it. Acids are also reduced to primary alcohols by lithium aluminium hydride. The acyloin reaction of esters of dibasic acids is discussed in section 7.1.5.

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2C_2H_5 \xrightarrow[\text{ethanol}]{Na} CH_3(CH_2)_7CH{=}CH(CH_2)_8OH \quad (50\,\%)$$

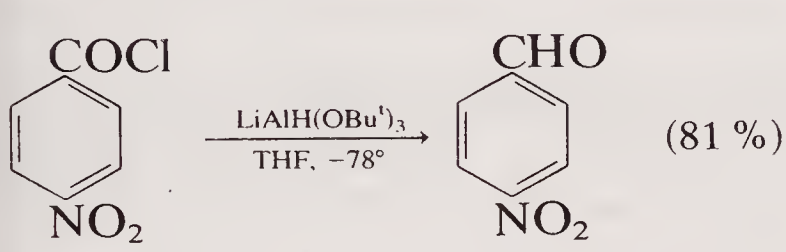
$$CH_3CH(OCH_3)CH_2CO_2CH_3 \xrightarrow[\text{ether}]{LiAlH_4} CH_3CH(OCH_3)CH_2CH_2OH \quad (70\,\%)$$

$$CH_3CH{=}CHCH{=}CHCO_2H \xrightarrow[\text{ether}]{LiAlH_4} CH_3CH{=}CHCH{=}CHCH_2OH \quad (92\,\%)$$

Acid chlorides can be hydrogenated to aldehydes in presence of the reduced activity **Rosenmund catalyst**, which consists of palladium on barium sulphate to which is added a quinoline–sulphur poison. In many cases an alternative procedure, which can be used in presence of a wide variety of functional groups (see table 8.3), is the use of lithium tri-(t-butoxy)aluminium hydride at low temperatures:

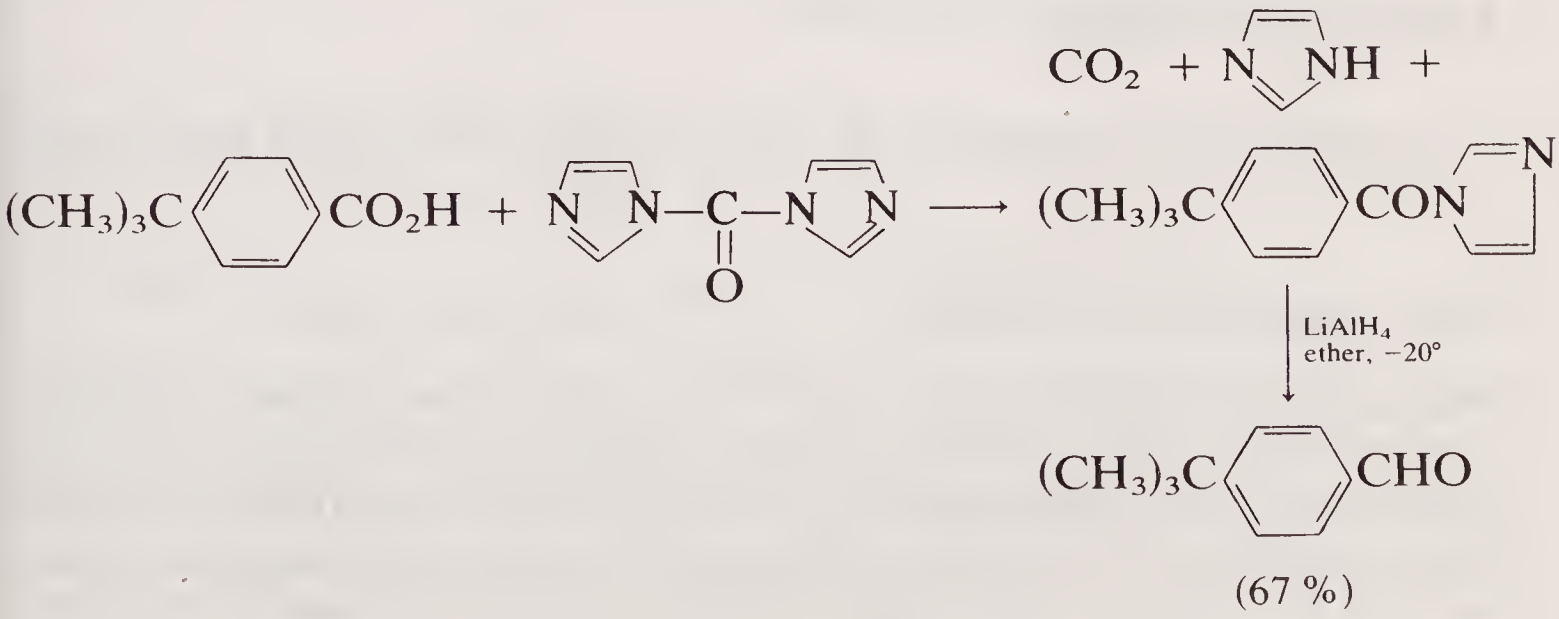


(73 %)

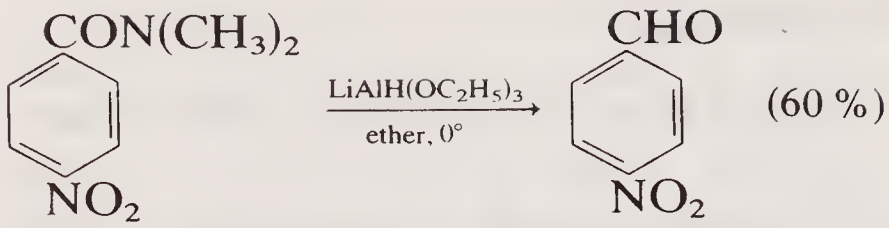


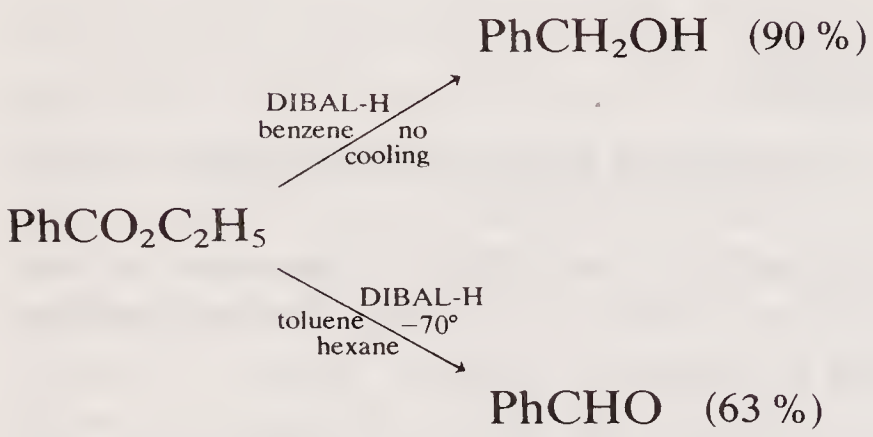
(81 %)

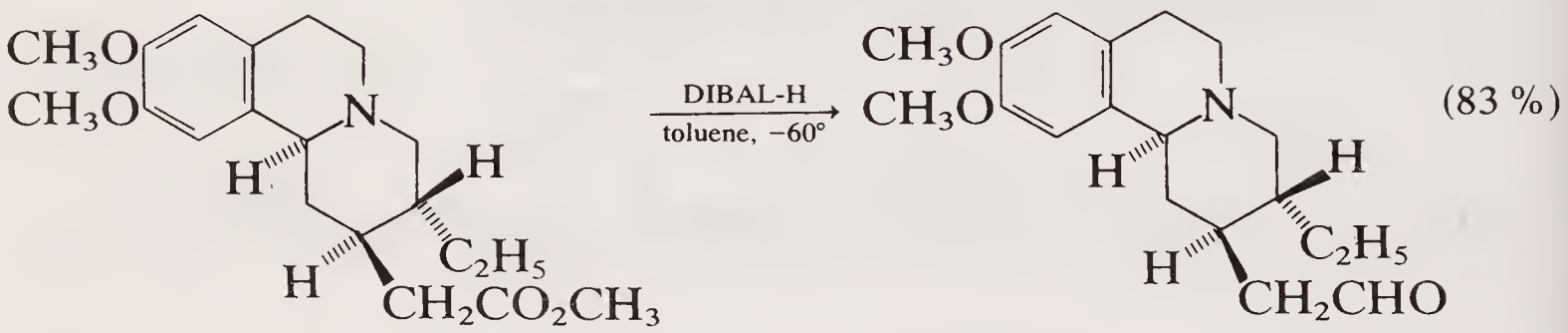
Aldehydes can also be prepared from other acid derivatives by reduction with metal hydrides: *viz.* amides derived from imidazole, carbazole or aziridine with lithium aluminium hydride; simple tertiary amides with lithium triethoxyaluminium hydride; phenyl esters with lithium tri-(t-butoxy)aluminium hydride; and ethyl esters with di-isobutylaluminium hydride at low temperatures:



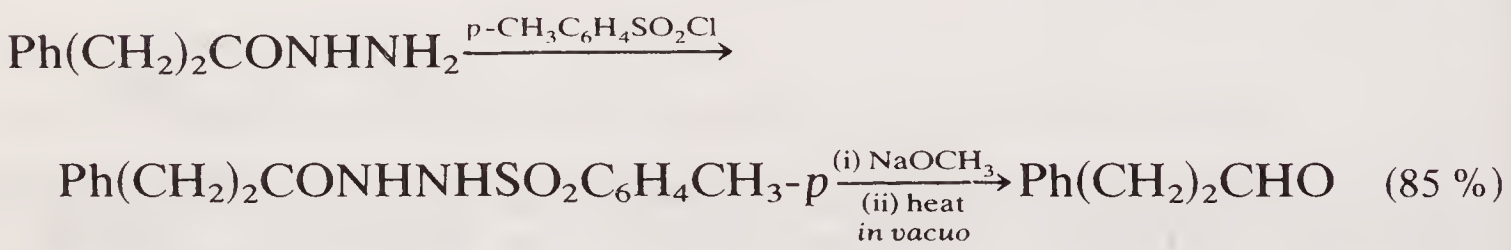
(67 %)







Finally, acids may be converted into aldehydes through a sulphonylhydrazide (the **McFadyen–Stevens** reaction), a reaction which bears certain similarities to the Wolff–Kishner reaction (section 8.4.3.3). Yields are, however, often poor.

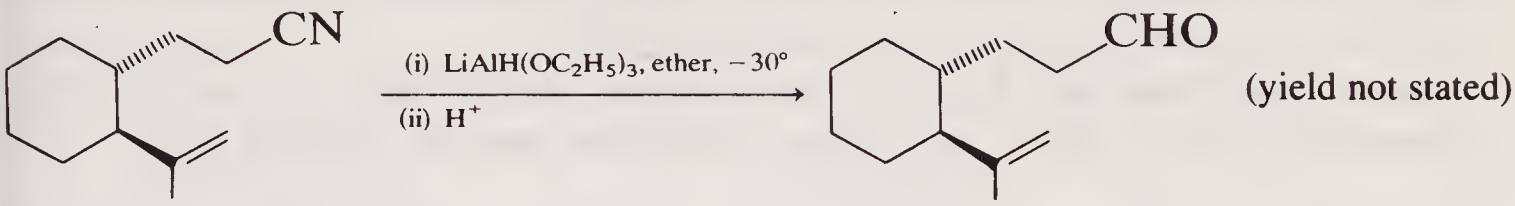


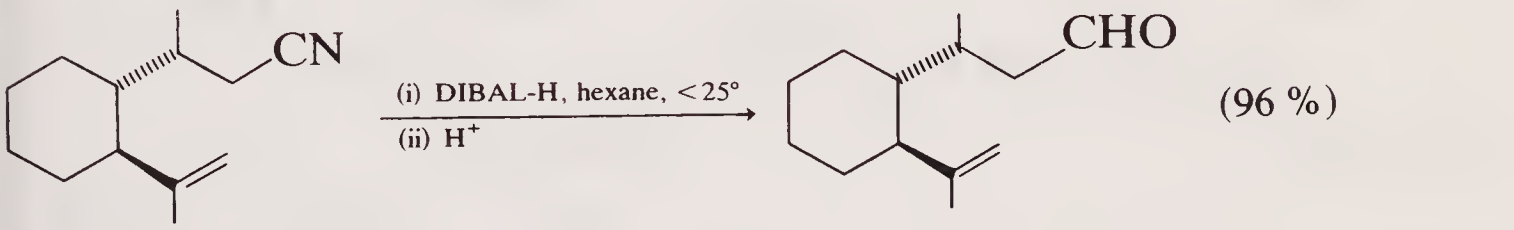
8.4.5 Reduction of nitriles

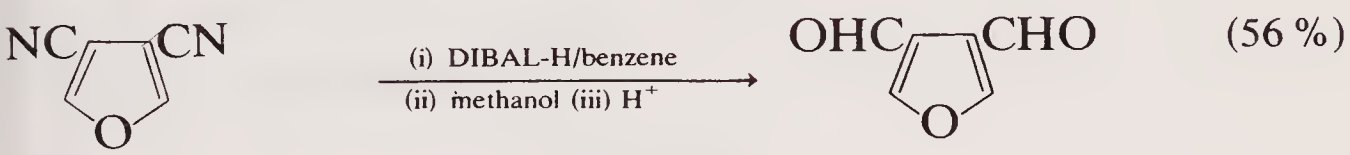
Both catalytic hydrogenation and lithium aluminium hydride reduction convert nitriles into primary amines, although in the former case the product may be contaminated by secondary amine impurities. The imine (20) is presumed to be an intermediate in these reactions and if the reduction can be stopped at this stage an aldehyde will be formed on hydroly-

sis. Examples of this are given below:

$$RC{\equiv}N \longrightarrow \underset{(20)}{[RCH{=}NH]} \longrightarrow RCH_2NH_2$$

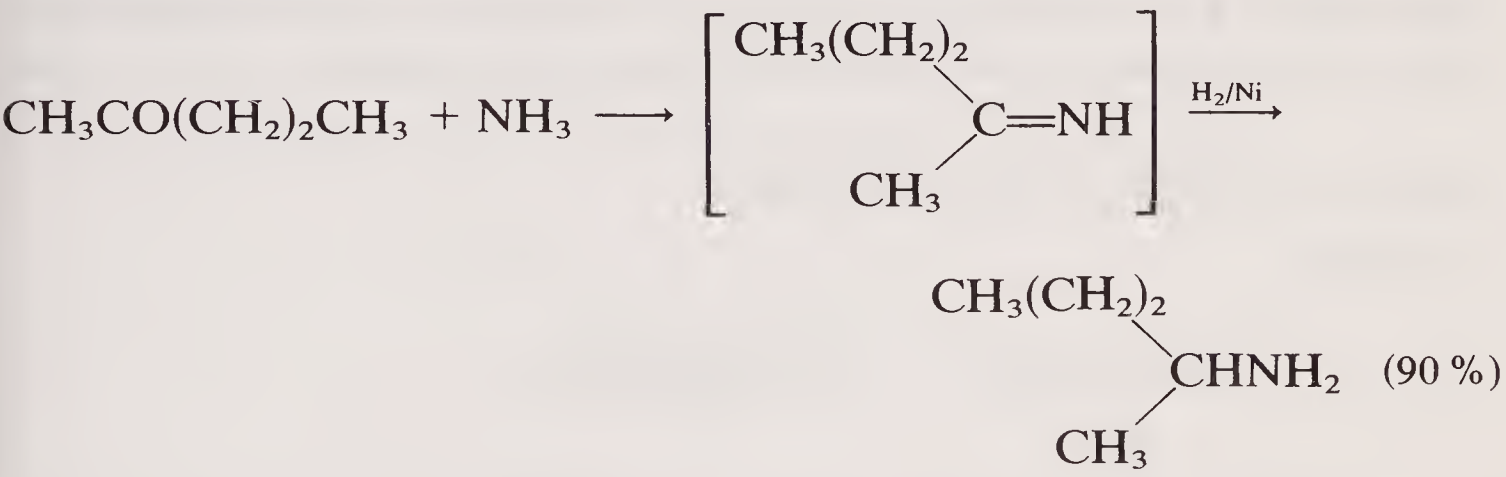


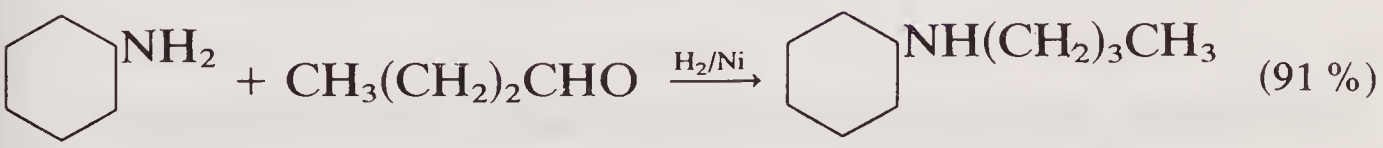




8.4.6 Reduction of imines and oximes, including reductive alkylation

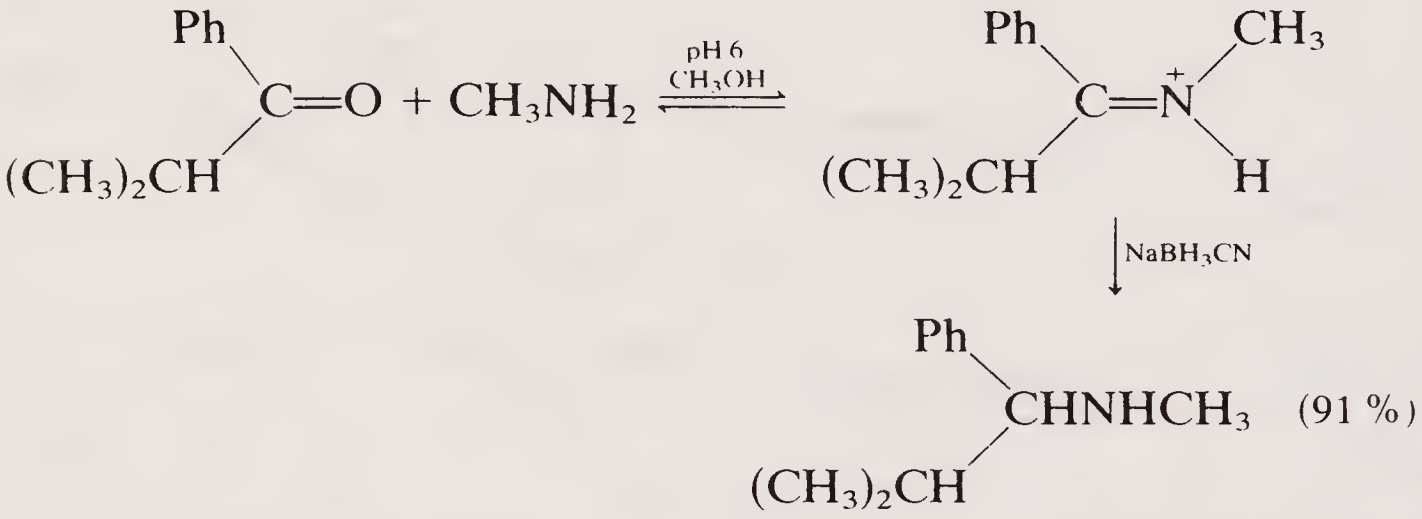
Imines are hydrogenated catalytically to amines. Closely related is the reductive alkylation of amines (including ammonia) and nitro-compounds leading to the formation of primary, secondary and tertiary amines.



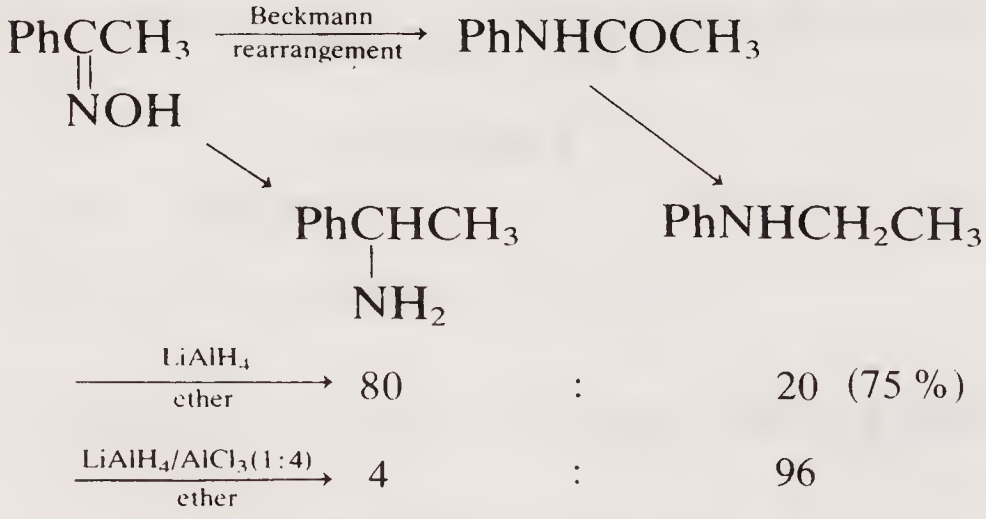


Reductions of imines and iminium salts to amines by metal hydrides such as lithium aluminium hydride and sodium borohydride require neutral or slightly acidic conditions. The greater stability of cyanoborohydrides under such conditions renders them more suitable than other complex hydrides for carrying out this transformation.

Since aldehydes and ketones are reduced only slowly by sodium cyanoborohydride at pH 6, reductive alkylation can be carried out.



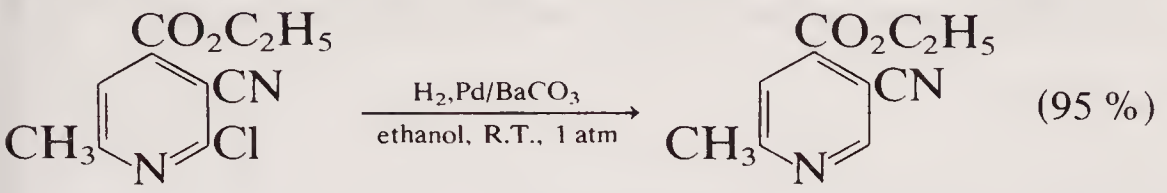
Oximes are reduced to primary amines by catalytic hydrogenation over platinum in acetic acid, or by dissolving metal reduction using, for example, sodium in ethanol. Reduction with lithium aluminium hydride gives primary amines almost exclusively from aliphatic oximes. However, the corresponding reduction of aryl ketoximes results in the formation of appreciable amounts of secondary amines. The latter can be the sole product if the reaction is carried out in presence of aluminium chloride, perhaps because of an initial Beckmann rearrangement of the oxime:



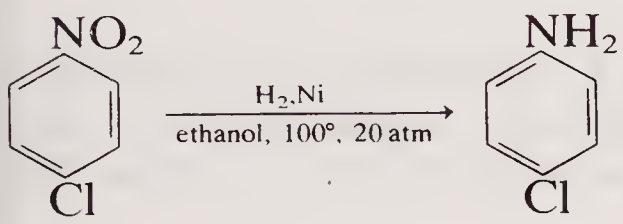
8.5 Reductive cleavage of carbon–heteroatom bonds

Reductive cleavage of single bonds by catalytic hydrogenation is usually described as hydrogenolysis. Halides undergo hydrogenolysis with an ease dependent on the type of halide (alkyl less than allyl, aryl, benzyl and vinyl), the halogen ($F \ll Cl < Br < I$), the catalyst (palladium catalysts

are more effective than Raney nickel which should be the catalyst chosen if hydrogenolysis is undesirable) and solvent (polar solvents and the presence of base favour hydrogenolysis). Halogenoanilines and halogenopyridines are thus very readily hydrogenolysed in other than acidic conditions:

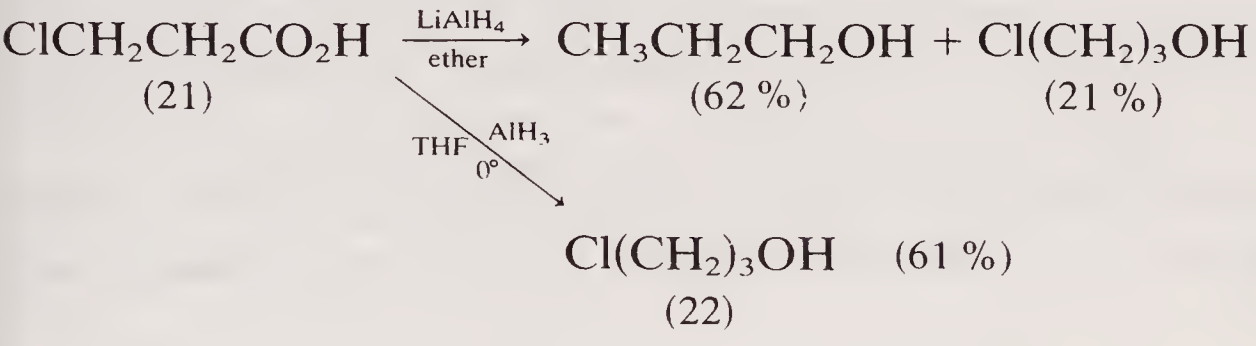


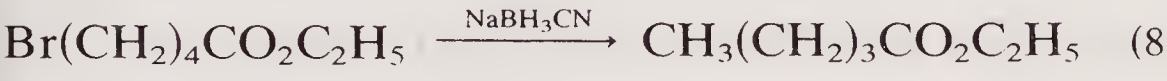
(95 %)



(90 %)

Lithium aluminium hydride and sodium borohydride both reduce primary and secondary alkyl halides to hydrocarbons. However, a wide range of other functional groups in the molecule may also be affected. The reaction appears to involve an S_N2 mechanism with inversion of configuration at the reaction centre. At approximately pH 6, sodium cyanoborohydride reduces few functional groups other than carbon–halogen bonds and is a highly specific reagent for carrying out this transformation:





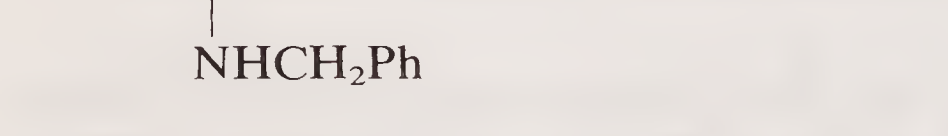
(88 %)

It is also of interest to note that alkyl halides are only slowly attacked by the electrophilic reducing agent, aluminium hydride, and therefore choice of this reagent will minimise unwanted carbon–halogen bond cleavage during reduction of other functional groups [(21) → (22)].

An extension of the cyanoborohydride method provides a method for the direct conversion of primary alcohols into hydrocarbons: no improvement in yield is achieved by isolating the intermediate iodo-compound. (Secondary and tertiary alcohols undergo elimination.)

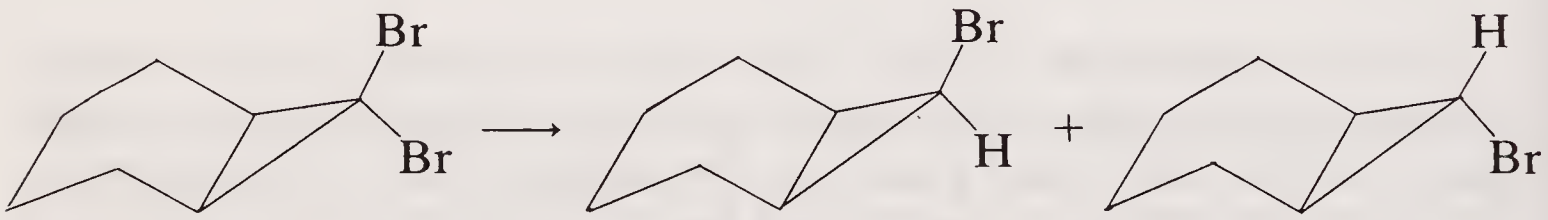
$$CH_3(CH_2)_9OH \xrightarrow{Ph_3\overset{+}{P}CH_3\ I^-} CH_3(CH_2)_9I \xrightarrow{NaBH_3CN} CH_3(CH_2)_8CH_3 \quad (100\ \%)$$

Aryl halides react only slowly with lithium aluminium hydride, but organotin hydrides, which attack halides in a free radical process, can be used to cleave aryl halides and other halides which cannot undergo S_N2 reactions:



(90 %)

Carbon–halogen bonds are also cleaved by dissolving metal and electrochemical methods. The reaction is of particular significance in partial reduction of *gem*-dihalides where similar stereospecificities are observed:

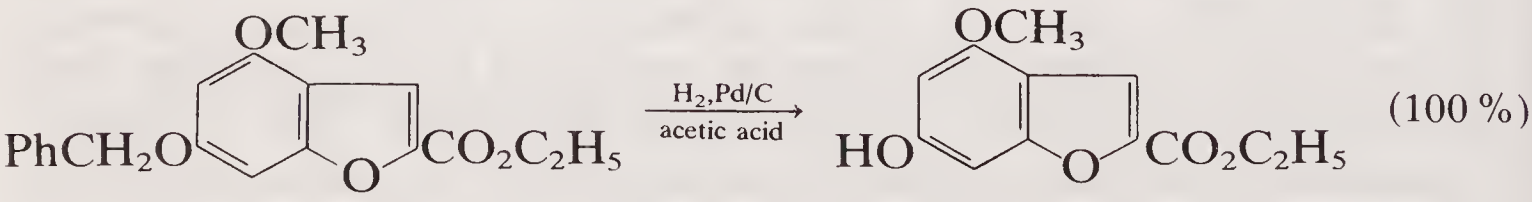


(23) (24)

Under both electrolytic and dissolving metal conditions (23) and (24) are formed in the ratio of between 1:1 and 5:1.

For heteroatoms other than halogen, the reductive cleavage of greatest synthetic importance occurs at benzylic positions. This can be achieved by catalytic hydrogenation, complex metal hydride, or electron transfer methods. Hydrogenolysis is normally the method of choice, the order of reactivity being $PhCH_2{-}\overset{+}{N}\!\!<\ >\ PhCH_2O{-}\ >\ PhCH_2N\!<$. This renders the benzyl group very useful for protecting hydroxyl and amino groups (cf. Ch. 10).

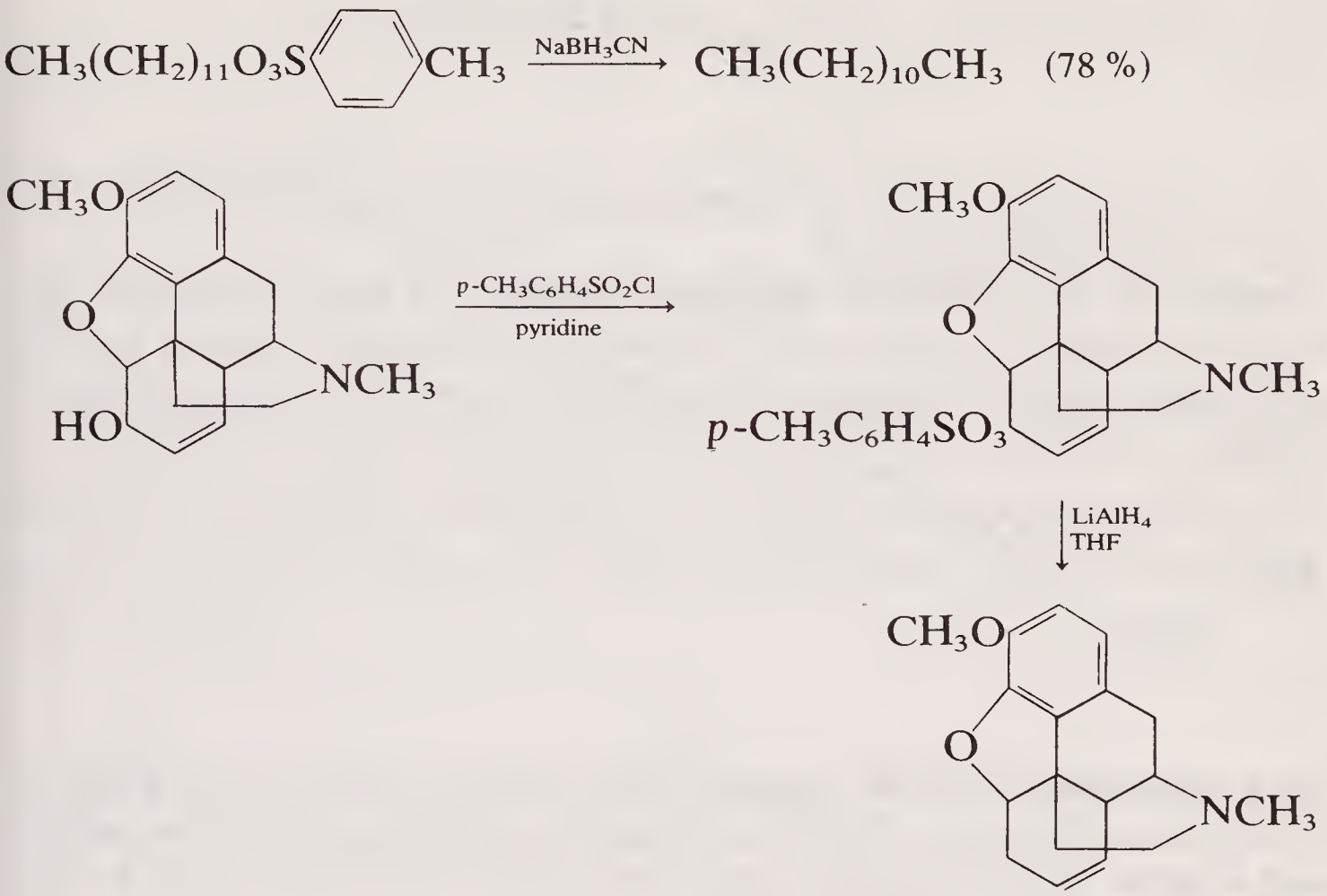
$$HOCH_2CH(NHCH_2Ph)CO_2H \xrightarrow[\text{ethanol}]{H_2,\ Pd/C} HOCH_2CH(NH_2)CO_2H \quad (90\ \%)$$



(100 %)

Other reductive cleavage reactions of importance are the Rosenmund reduction of acid chlorides (section 8.4.4) and desulphurisation using

Raney nickel (section 8.4.3) already discussed, and reduction of primary and secondary alcohols *via* sulphonate esters. Reductive ring opening of epoxides will be considered in the following section.

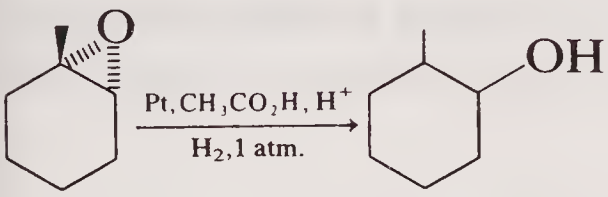


(85 %)

8.6 Reductive ring-opening of epoxides

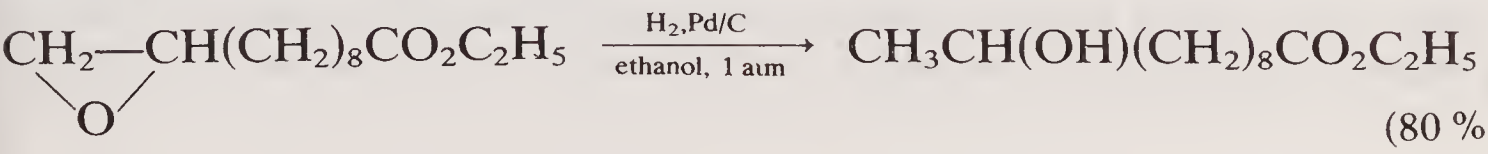
In **hydrogenolysis** of epoxides the following observations have been made:

(i) In acidic solvents hydrogenation takes place rapidly over **platinum** catalysts to give the ring-opened product(s) derived from the *more stable carbocation.*



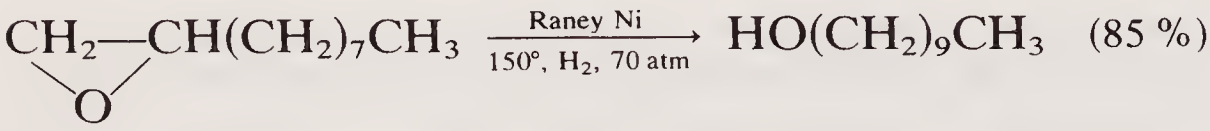
cis and *trans*

(ii) **Palladium** on carbon is the most effective catalyst. In a neutral medium hydrogenolysis occurs at the less hindered C–O bond, and *the more substituted alcohol is obtained*:



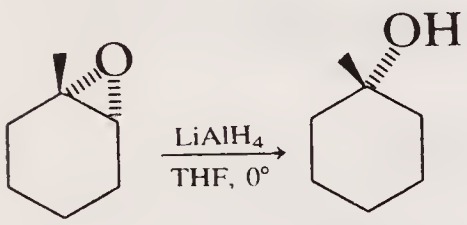
(80 %)

(iii) **Raney nickel** requires a high pressure and temperature and *the less substituted alcohol predominates* in neutral solution, but in presence of base *the more substituted alcohol is formed.*

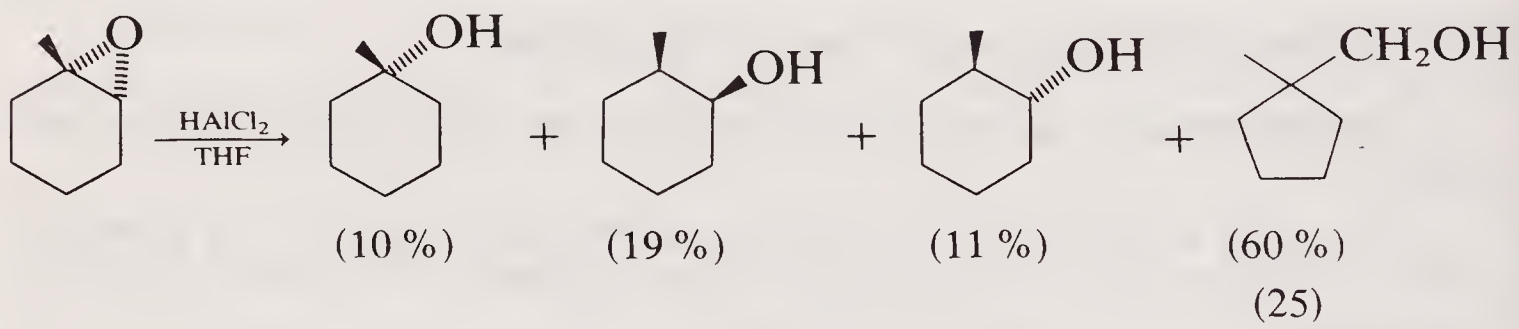


(iv) 1-Aryl-1,2-epoxides are opened under all conditions to give the 1-aryl-2-hydroxy compound.

Reduction using **lithium aluminium hydride,** as expected for an S_N2 process, normally results in the opening of the epoxide ring at the less substituted carbon (primary if possible) to give *the more substituted alcohol.*



Using **electrophilic hydride reagents** ring opening tends to take place in the direction of the more stable carbocation and thus gives *the less substituted alcohol.* Rearrangements may also occur, as can be seen by the formation of (25).



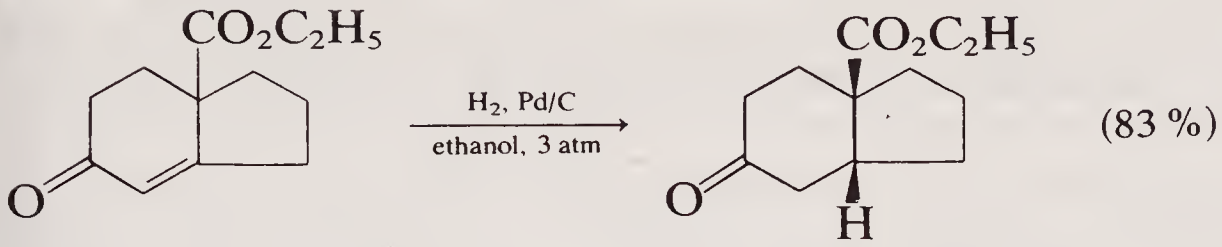
(25)

The reductive ring opening of epoxides with **lithium in ethylenediamine** also gives rise to *the more substituted alcohol* and is a superior method for hindered epoxides.

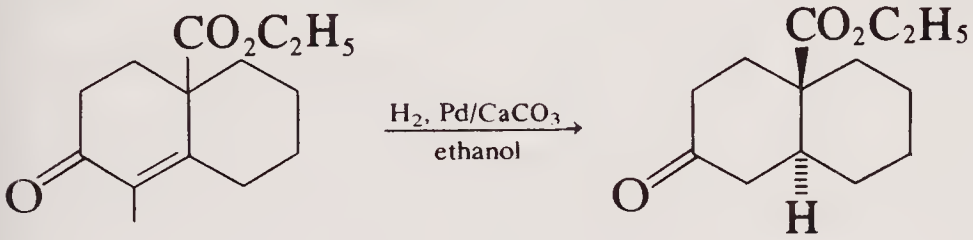
8.7 Reduction of α,β-unsaturated carbonyl compounds

Carbon–carbon double bonds are more readily hydrogenated than carbonyl double bonds or nitriles. Palladium is the preferred catalyst in this case, and in basic media carbonyl-conjugated double bonds are hydrogenated in preference to isolated double bonds. It is, however, not always

easy to predict the stereochemistry of such hydrogenations:

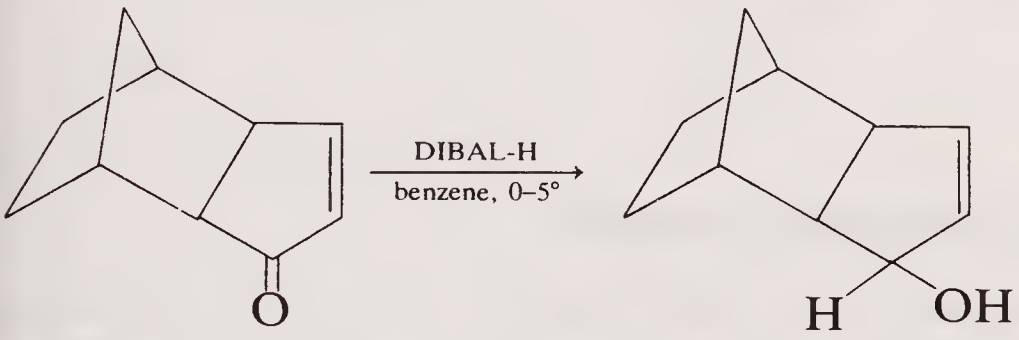


(83 %)



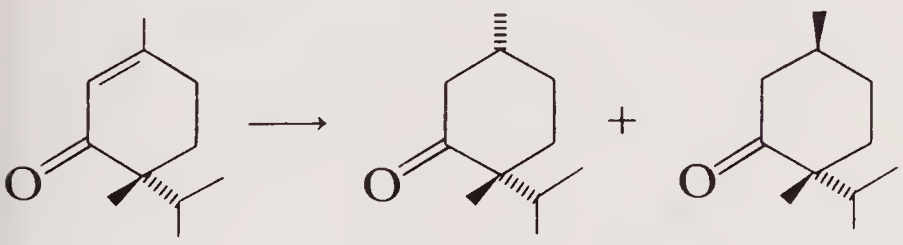
(92 %)

Although techniques such as inverse addition (i.e. addition of hydride to a solution of the α,β-unsaturated compound) at low temperatures have been successful in reducing such compounds to allylic alcohols, a more satisfactory reagent for this transformation is di-isobutylaluminium hydride:



(90 %)

Dissolving metal reduction, on the other hand, leads to reduction of the carbon–carbon double bond. The stereochemistry of the product may, however, differ from that of the product of catalytic hydrogenation:



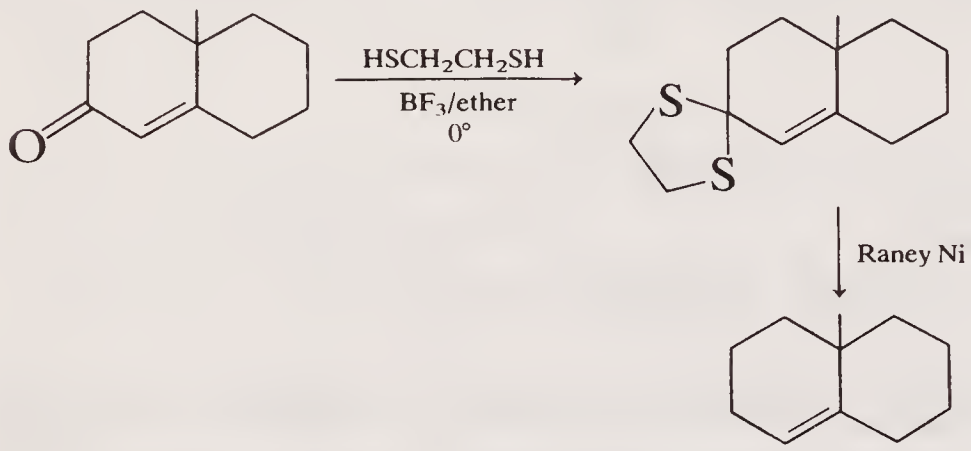
(~80 %)

(26) (27) (28)

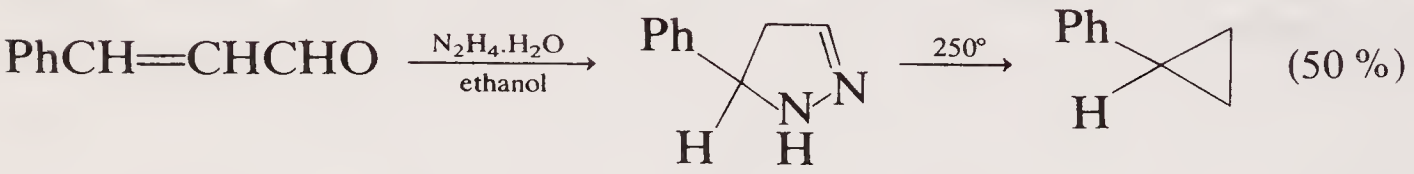
$$(26) \xrightarrow[\text{methanol}]{H_2,Pd/C,1\ atm.} \underset{(30\ \%)}{(27)} + \underset{(70\ \%)}{(28)}$$

$$(26) \xrightarrow[\text{liq. } NH_3]{Li} \underset{(75\ \%)}{(27)} + \underset{(25\ \%)}{(28)}$$

Reduction of α,β-unsaturated ketones to alkenes is usually effected by desulphurisation of the dithioketal by Raney nickel, since the Wolff–Kishner procedure results in cyclopropane formation *via* the pyrazoline (29) and the Clemmensen reduction frequently gives complex mixtures.



(60 %)

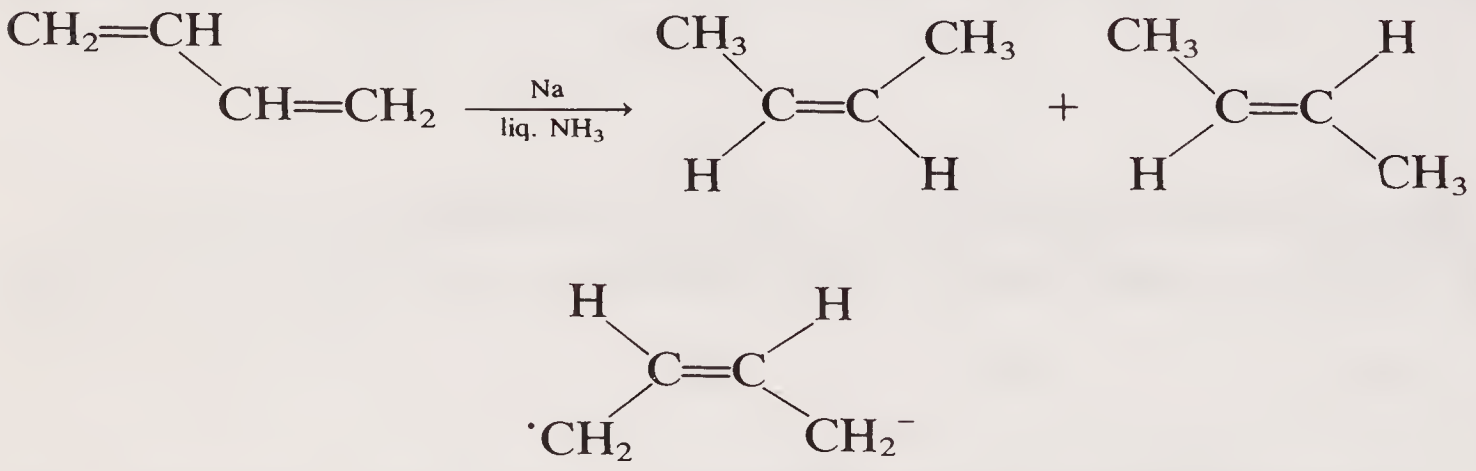


(50 %)

(29)

8.8 Reduction of conjugated dienes

Dissolving metal reduction of 1,3-dienes results in 1,4-addition giving a mixture of *E* and *Z* alkenes, the isomer ratio being temperature-dependent. Trapping experiments indicate that the initial radical anion (30) has the *Z* configuration shown:



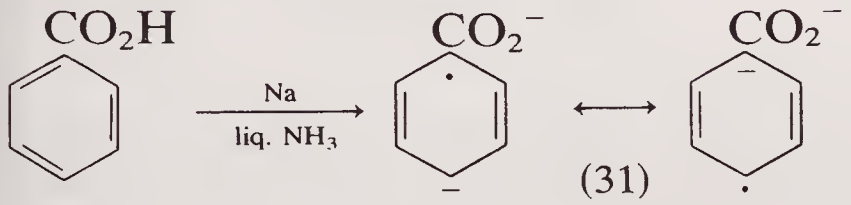
(30)

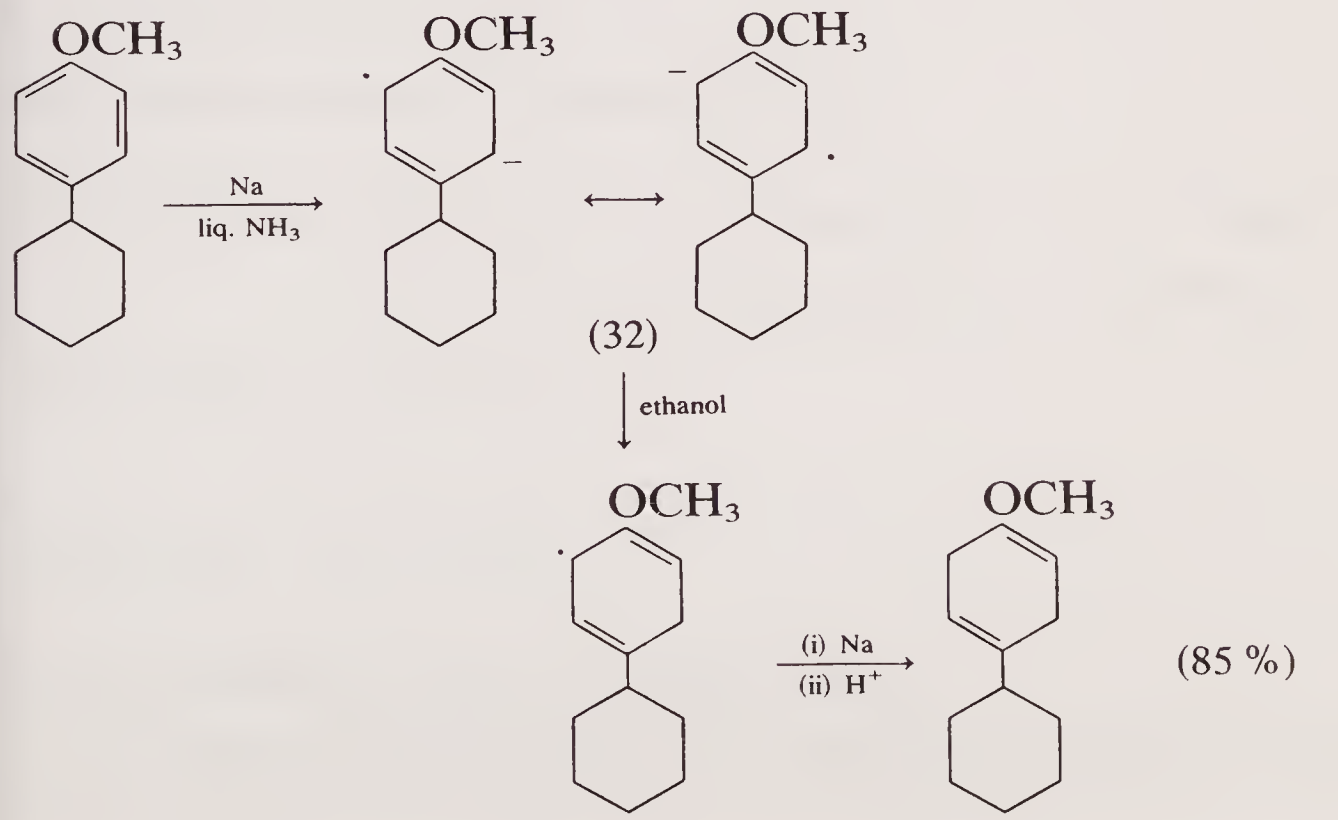
Conjugated dienes are completely hydrogenated using nickel, platinum or palladium catalysts. Analysis of partially hydrogenated butadiene reveals that but-1-ene, and *E* and *Z*-but-2-ene are present in amounts which depend on the catalyst used.

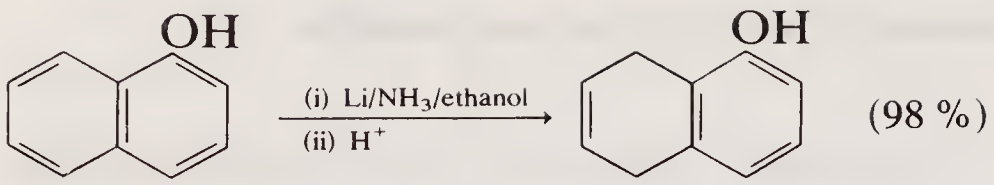
8.9 Reduction of aromatic and heteroaromatic compounds

Catalytic hydrogenation of benzenoid compounds usually requires high-pressure conditions, and in these circumstances other groups such as olefinic double bonds and carbonyl groups will also be reduced. Benzenoid compounds except those with one or more electron-withdrawing substituents are not affected by hydride reagents. The only reduction of benzenoid compounds which will be considered here is the dissolving metal reduction (**Birch reduction**) using lithium or sodium in liquid ammonia. The product of this reduction in the case of benzene is cyclohexa-1,4-diene. As expected, electron-withdrawing substituents facilitate the reaction whereas anisole is only reduced with difficulty.

In the case of compounds with electron-withdrawing substituents, reduction takes place at the carbon bearing the substituent, but with electron-donating substituents reduction occurs at an *ortho*-carbon. This can be rationalised in terms of the relative stabilities of the intermediate anion radicals (31) and (32). In bicyclic compounds the ring of lower electron density is reduced:

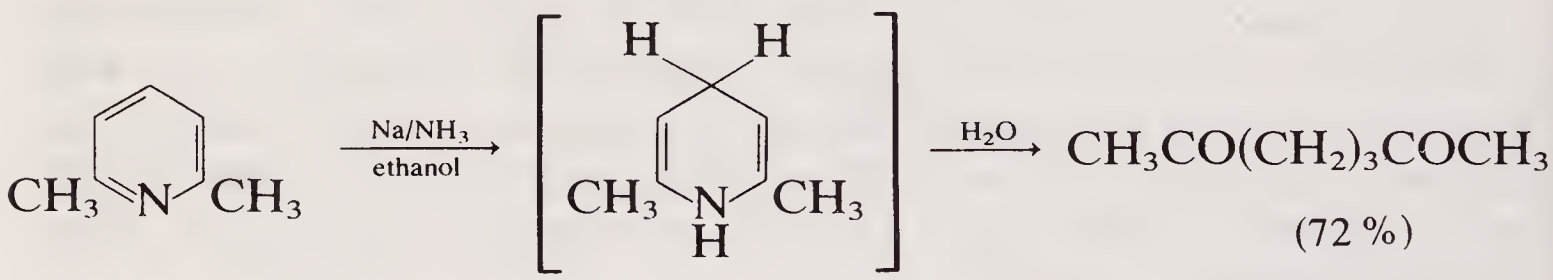






(98 %)

Pyridinium salts are reduced to piperidines using high-pressure catalytic hydrogenation, or sodium borohydride; 1,2-dihydro- and 1,2,5,6-tetrahydro-pyridines can also be isolated depending on the reaction conditions used. Dissolving metal reduction of pyridines may also give piperidines, but it is possible, using the conditions of the Birch reduction, to obtain 1,4-dihydropyridines. These are cyclic enamines, and are readily hydrolysed to 1,5-dicarbonyl compounds:



(72 %)

Notes

1. Copper chromite (copper–chromium oxide) catalyst is produced by thermal decomposition of copper(II) ammonium chromate to which barium ammonium chromate may be added. The presence of barium is reported to protect the catalyst against sulphate poisoning and to stabilise the catalyst to hydrogenation.

9 Oxidation

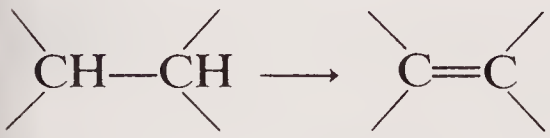
Oxidation is, of course, the opposite of reduction, and so the reactions to be described in this chapter should be, in principle at least, the reverse of those discussed in Chapter 8. Three distinct types of reduction have been described, *viz.* the addition of hydrogen to multiple bonds (using catalytic and non-catalytic methods); the substitution of a functional group by hydrogen; and one-electron addition to an electrophilic centre. The opposite of these processes should therefore constitute oxidations: elimination of hydrogen to form multiple bonds; substitution of hydrogen by a functional group such as OH or halogeno; and one-electron abstraction from a nucleophilic centre.

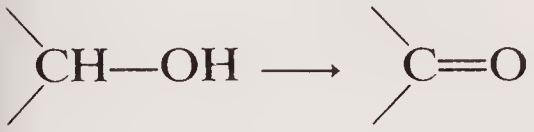
Examples of all three types are well known, as will be apparent in the sections which follow. To these three types must be added a fourth, the addition of oxygen-containing reagents to multiple bonds (the reductive counterparts of such reactions are, in general, much less common, and have not been considered in Chapter 8), and to heteroatoms such as nitrogen, phosphorus, and sulphur.

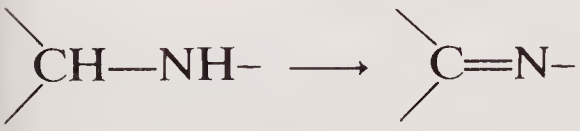
9.1 General principles

9.1.1 Dehydrogenation

This heading covers a variety of reactions:



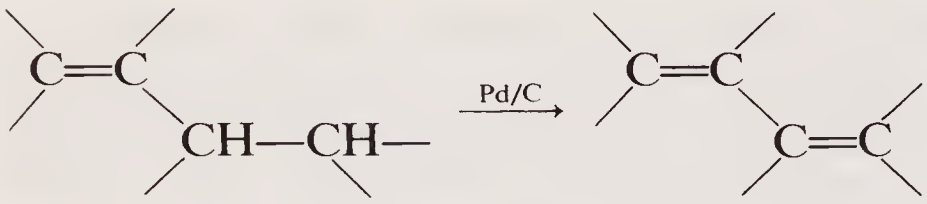




It also embraces a variety of reaction types:

(i) *Catalytic dehydrogenation.* The capacity of metals like palladium for adsorption of hydrogen and for co-ordination of alkenes is used most

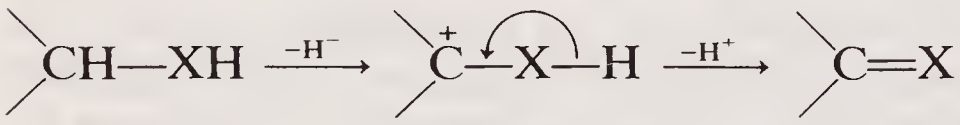
frequently to effect hydrogenation of the alkenes. But *in the absence of added hydrogen* palladium may effect the dehydrogenation of an alkylated alkene in such a way that a conjugated diene is produced [reaction (9.1)]:



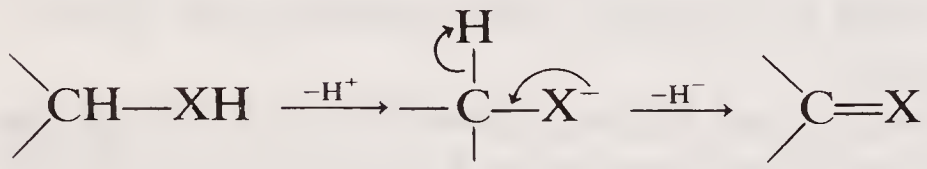
(9.1)

The reaction is particularly successful if the conjugated system produced is aromatic (cf. section 7.1.4.2, example 20; also section 9.2.4.1).

(ii) *Dehydrogenation by successive hydride and proton transfers.* These may be represented schematically by reactions (9.2) and (9.3):



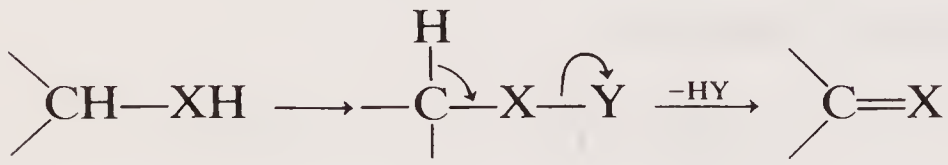
(9.2)



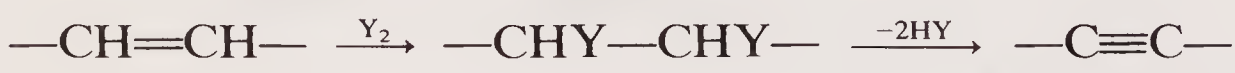
(9.3)

Clearly these processes will be most effective if the intermediate cation or anion is stabilised, and if a good hydride acceptor (a strong electrophile) is present.

(iii) *Dehydrogenation by substitution–elimination and addition–elimination processes.* These are represented by reactions (9.4) and (9.5), and almost certainly constitute the most common dehydrogenation methods: for example, the vast majority of carbonyl-forming oxidations can be represented by reaction (9.4) [X = O]:



(9.4)



(9.5)

9.1.2 Substitution of hydrogen by a functional group

The opposite of hydrogenolysis (replacement of a functional group by hydrogen) is functionalisation, a topic which has already been discussed briefly in Chapter 2. It is unusual, however, to regard functionalisation in general as an oxidative process, except when hydrogen is replaced by an oxygenated function such as OH. The mechanism of these reactions may

be either radical or ionic [reactions (9.6) and (9.7)], e.g.

$$RCH_2R' \xrightarrow{X^{\cdot}} HX + R\dot{C}HR' \xrightarrow{Y^{\cdot}\,(\text{or } Y\text{–}X)} \underset{\displaystyle Y}{\overset{|}{R}}CHR' \qquad (9.6)$$

$$RCH_2R' \xrightarrow{-H^+} R\bar{C}HR' \xrightarrow{Y^+} \underset{\displaystyle Y}{\overset{|}{R}}CHR' \qquad (9.7)$$

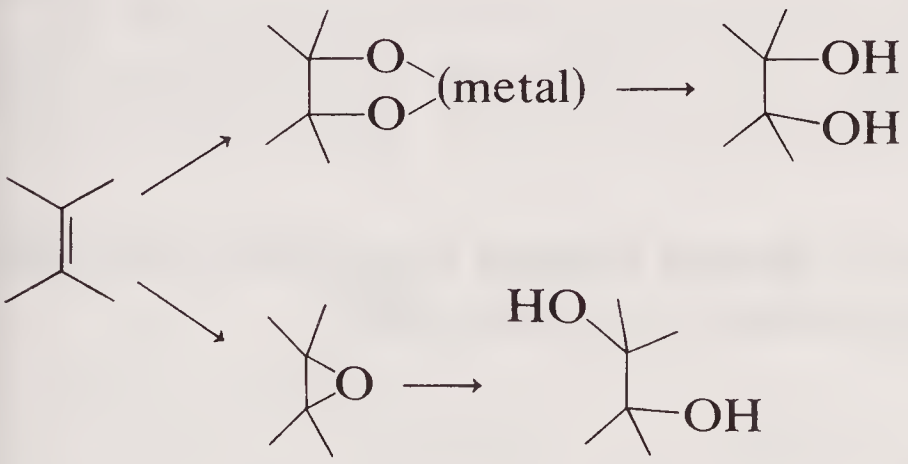
9.1.3 One-electron abstraction from a nucleophilic centre

The most common form of this reaction involves abstraction of one electron from an anion to give a radical, and subsequent dimerisation of the latter [reaction (9.8)]. Such a process has already been encountered in Chapter 4 in connection with organocopper derivatives (pp. 50 and 53). If the radical is stabilised by delocalisation, coupling may give an unsymmetrical dimer (cf. section 9.4):

$$2R\text{—}XH \xrightarrow{-2H^+} 2R\text{—}X^- \xrightarrow{-e^{\cdot}} 2R\text{—}X^{\cdot} \rightarrow R\text{—}X\text{—}X\text{—}R \qquad (9.8)$$

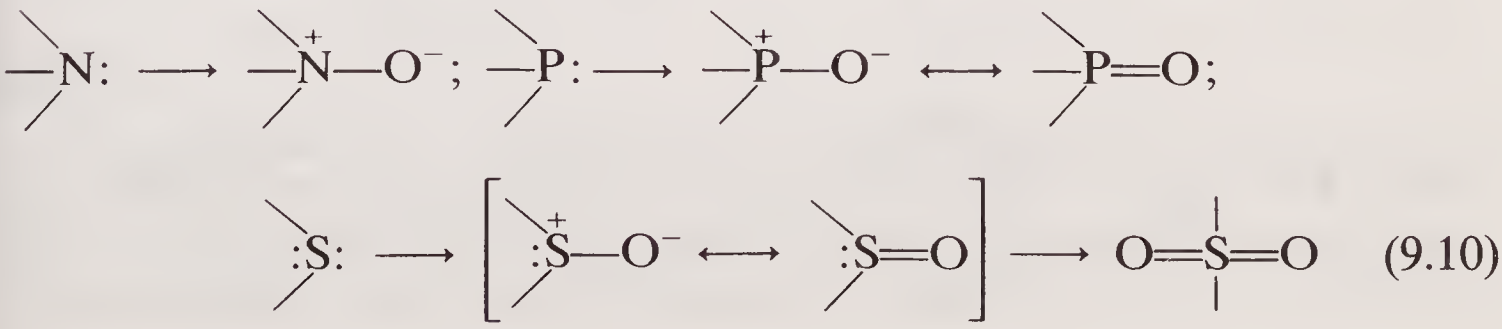
9.1.4 Addition of oxygen-containing reagents to multiple bonds and heteroatoms

Two types of reactions are included in this section: the hydroxylation of multiple bonds [e.g. reaction (9.9)] and the addition of oxygen (usually from a peracid) to a heteroatom carrying a donatable lone pair [reaction (9.10)]:



(9.9a)

(9.9b)



(9.10)

9.2 Oxidation of hydrocarbons

This is, of course, an enormously important area of industrial interest, in relation not only to fuels but also to rubber, plastics, food stuffs, etc. The purpose of this section, however, is not to discuss these but to concentrate on some synthetically useful oxidations from a 'laboratory' viewpoint.

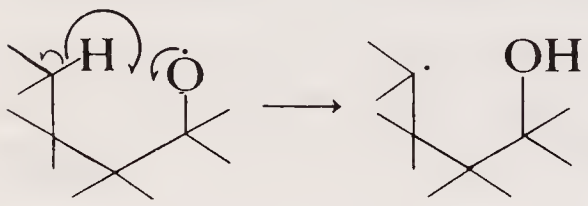
9.2.1 Alkanes and alkyl groups

Oxidation, like other reactions of alkanes, follows a radical mechanism [reaction (9.6)], in which abstraction of a hydrogen atom is the first step. This is a useful synthetic procedure only if the abstraction occurs specifically at one position. Tertiary hydrogens, for example, are more easily abstracted than secondary or primary hydrogens, and some branched-chain alkanes may be oxidised to tertiary alcohols, e.g.

$$(C_2H_5)_3CH \xrightarrow[CH_3CO_2H,\ H_2SO_4]{Na_2Cr_2O_7} (C_2H_5)_3COH \quad (41\ \%)$$

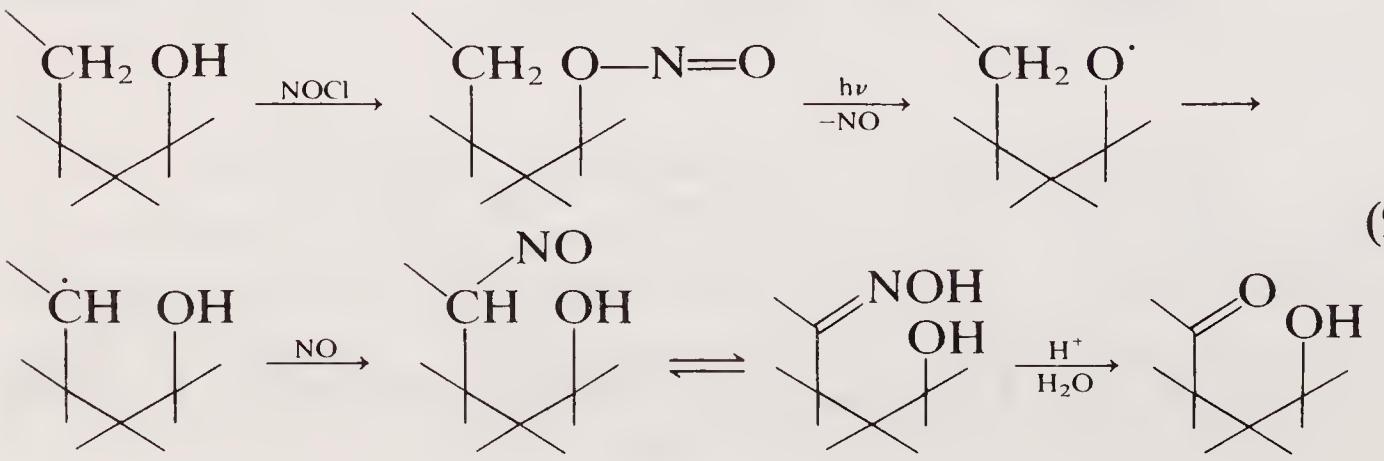
This generally compares unfavourably, however, with the Grignard method (section 4.1.2) for the preparation of tertiary alcohols.

Much more important from the synthetic standpoint is a group of oxidations in which the radical is generated by *intramolecular* hydrogen abstraction; a radical of the type (1) may rearrange, *via* a six-membered transition state, to (2) [reaction (9.11)]:



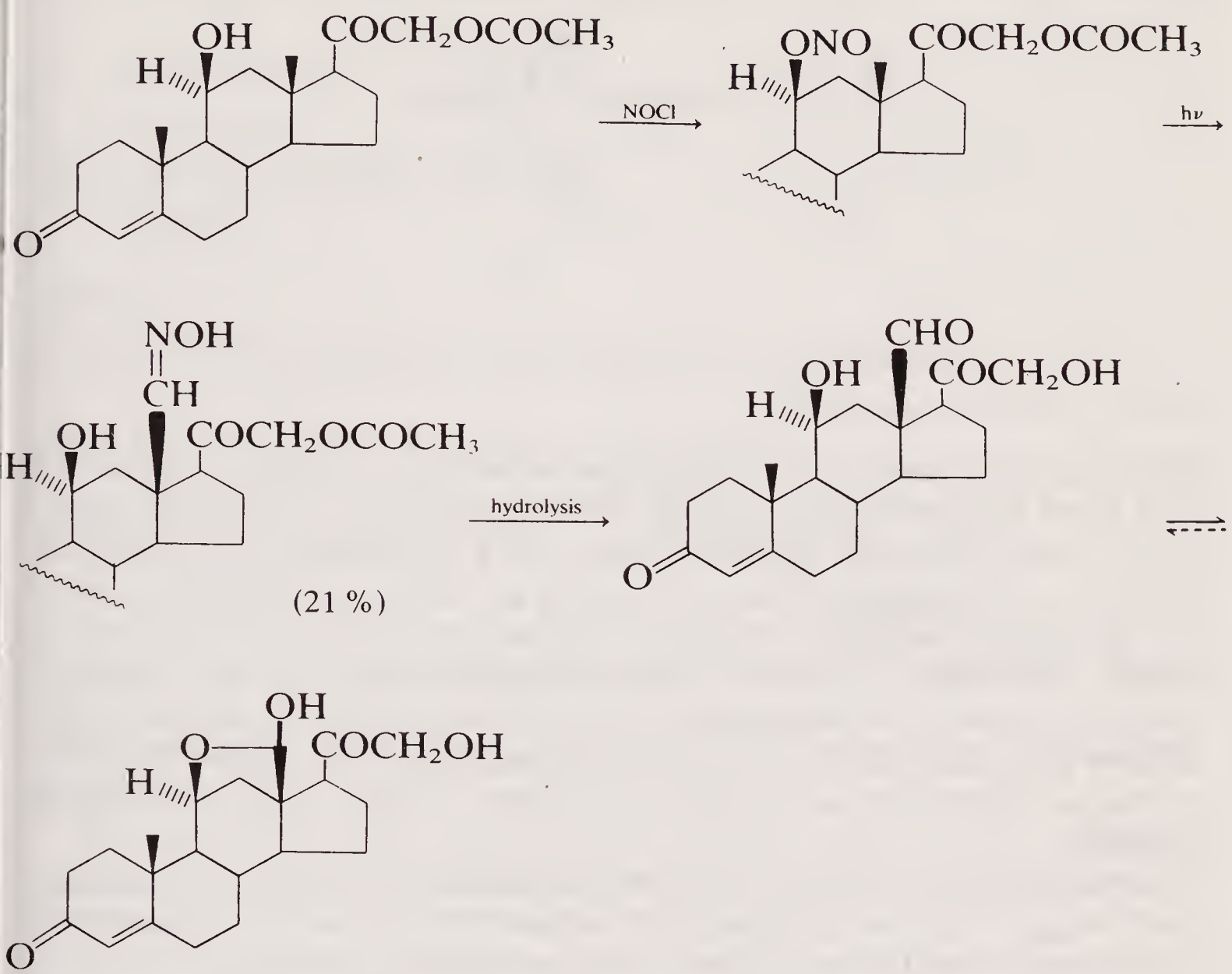
(1) (2) (9.11)

In the best-known of these, the **Barton reaction** [reaction (9.11a)], the radical is generated by the photolysis of a nitrite ester:



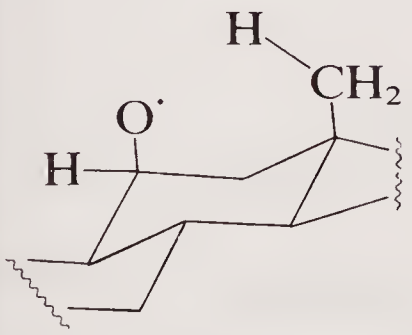
(9.11a)

The reaction has been applied with great success to selective oxidations in steroids, e.g. in the synthesis of the hormone aldosterone (3):



(3)

In the steroid field the intramolecular hydrogen transfer is, presumably, facilitated by the rigidity of the molecular skeleton and the 1,3-diaxial relationship of the interacting groups (cf. structure 4).



(4)

Oxy-radicals such as (1) can obviously undergo reactions other than intramolecular hydrogen abstraction, and it might therefore be expected that acyclic nitrites, lacking the rigidity of the steroid skeleton, might give very low yields in the Barton reaction. In practice, however, the yields in

some cases are surprisingly high, e.g.

$$CH_3(CH_2)_7ONO \xrightarrow[\text{heptane}]{h\nu} CH_3(CH_2)_3\underset{\displaystyle NO}{\underset{|}{C}}H(CH_2)_3OH$$

(isolated as the dimer)

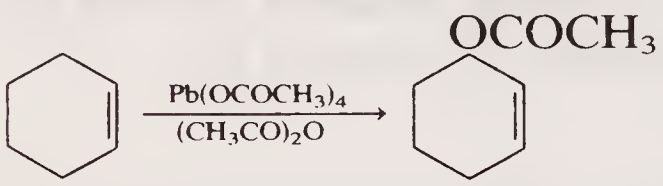
$$\xrightarrow[\text{----------}]{60^\circ,\ 2\ \text{days}} CH_3(CH_2)_3\underset{\displaystyle NOH}{\underset{\|}{C}}(CH_2)_3OH$$

(26 %)

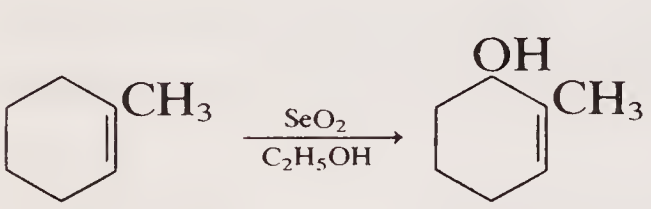
9.2.2 Allylic oxidation

Hydrogens are much more readily abstracted from an allylic position (i.e. one atom removed from a double bond) than from a completely saturated alkane, since the resultant radical may be stabilised by resonance (Sykes, p. 311). Allyl cations and anions are similarly stabilised relative to their fully saturated counterparts (Sykes, pp. 105 and 273–4), and so allylic oxidations of several different types, involving allyl radicals, cations or anions as intermediates, should be possible. Oxidation of the alkene grouping itself is, of course, a competing process, and the intermediates themselves can undergo reactions at either 'end' of the allylic system.

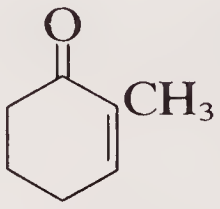
Oxidation to the alcohol is possibly achieved most simply by bromination using *N*-bromosuccinimide (cf. section 2.2) followed by hydrolysis of the bromide, but the oxygenated function may be introduced directly by the use of lead(IV) acetate, selenium(IV) oxide or a peroxyester in presence of a copper(I) salt, e.g.



(55 %)



(35 %) +



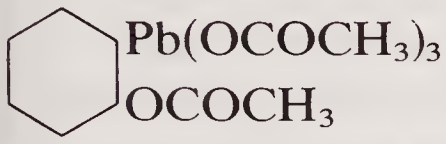
(27 %)

$$CH_3(CH_2)_5CH{=}CH_2 \xrightarrow[Cu_2Cl_2,\ 70^\circ]{CH_3CO_2OC(CH_3)_3} CH_3(CH_2)_4\underset{\displaystyle OCOCH_3}{\underset{|}{C}}HCH{=}CH_2 \quad (78\ \%)$$

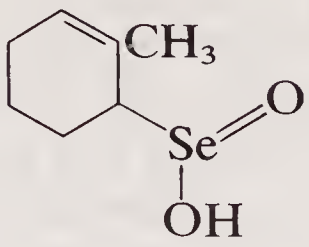
$$+\,CH_3(CH_2)_4CH{=}CHCH_2OCOCH_3 \quad (11\ \%)$$

The detailed mechanisms of these reactions need not concern us here; it is sufficient to note that the first and second probably involve initial

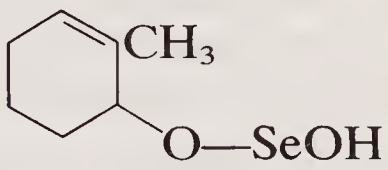
attack on the double bond and the intermediacy of species such as (5) and (6) or (7). The third example probably involves an allylic radical and then an allylic cation [reaction (9.12)]:



(5)



(6)



(7)

$$CH_3CO{-}O{-}OC(CH_3)_3 \xrightarrow{\text{heat}} CH_3CO{-}O^{\cdot} + {}^{\cdot}OC(CH_3)_3$$

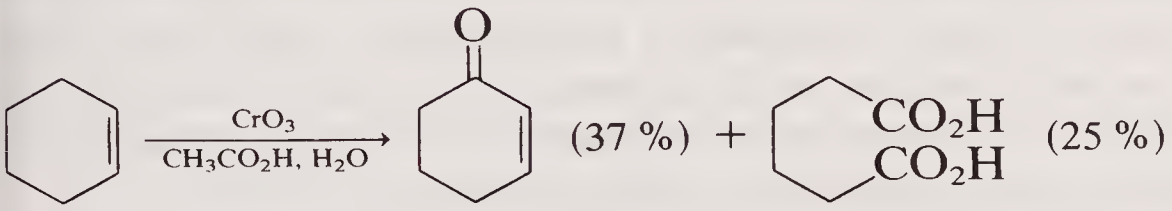
$$CH_3CO{-}O^{\cdot} + Cu(I)^{+} \rightarrow Cu(II)^{2+} + CH_3CO_2^{-}$$

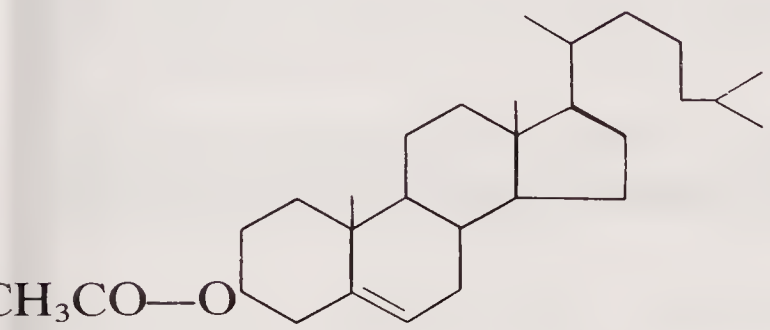
$$(CH_3)_3CO^{\cdot} + RCH_2CH{=}CH_2 \longrightarrow R\dot{C}HCH{=}CH_2 \xrightarrow{Cu(I)^{+}}$$

$$R\overset{+}{C}HCH{=}CH_2 \xrightarrow{CH_3CO_2^{-}} R\underset{\displaystyle OCOCH_3}{C}HCH{=}CH_2 \qquad (9.12)$$

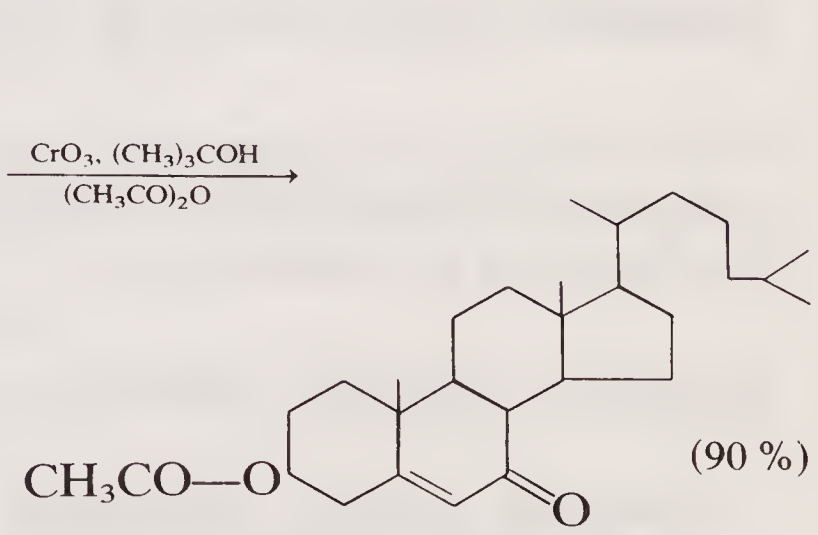
Allylic oxidation using other selenium-containing reagents is described in section 14.3.2.2.

More powerful, and less selective, oxidants carry allylic oxidation beyond the alcohol stage, and may also effect oxidation at the double bond, e.g.





(cholesteryl acetate)



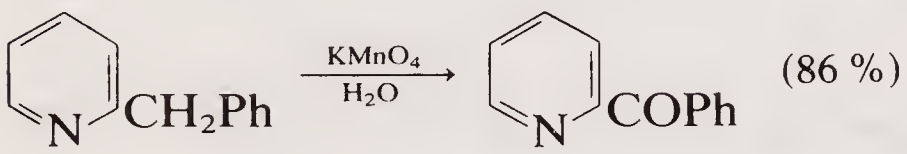
Potassium permanganate is generally unsatisfactory for allylic oxidation, since it reacts preferentially with the double bond (cf. section 9.2.5).

9.2.3 Benzylic oxidation

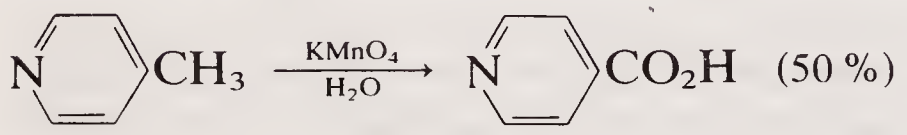
Attention was drawn in the last section to the stabilisation of a radical, a cation and an anion by an adjacent double bond, and to the consequent diversity of mechanistic routes by which allylic oxidation may occur. The same diversity exists for benzylic oxidation, since an aromatic system can serve to stabilise a radical or a charge on the benzylic carbon, and oxidations involving benzylic radicals, cations and anions are all known (see below). Oxidation elsewhere in the molecule is not usually a serious problem in these reactions, since aromatic rings are in general oxidised only with difficulty.

Strong oxidants, such as potassium permanganate or chromic acid, oxidise benzylic carbons to the highest degree possible, e.g.

$$Ph_3CH \xrightarrow[CH_3CO_2H]{CrO_3} Ph_3COH \quad (85\,\%)$$



(86 %)



(50 %)

Other alkylbenzenes, with two or more carbons in the alkyl group, are also oxidised to benzoic acid derivatives under these conditions. The initial oxidation is presumed to occur at the benzylic position, since t-butylbenzene (which lacks benzylic hydrogens) is resistant to oxidation, and since aryl ketones are occasionally isolated as by-products.

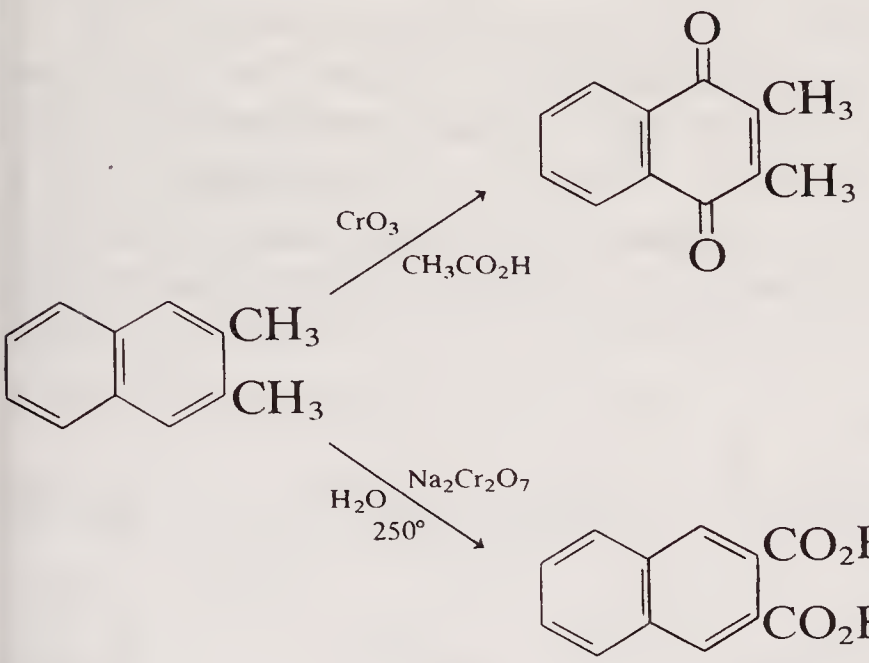
$$PhCH_2CH_3 \xrightarrow[H_2SO_4,H_2O]{CrO_3} PhCO_2H \quad (80\,\%)$$

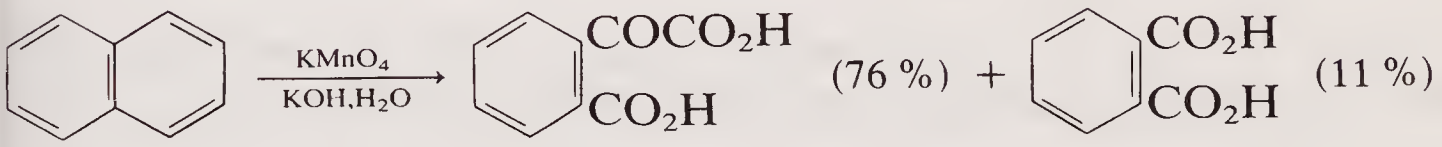
The use of aqueous sodium dichromate as oxidant *in the absence of added acid* provides slightly milder conditions, under which the cleavage of the alkyl group is not observed, e.g.

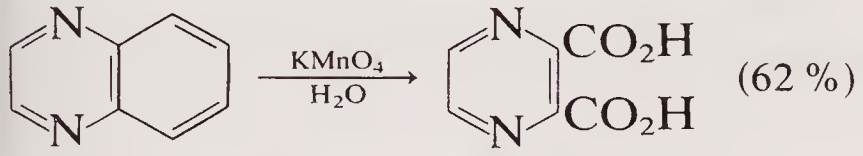
$$PhCH_2CH_3 \xrightarrow[250°,\ \text{pressure}]{Na_2Cr_2O_7,\ H_2O} PhCOCH_3 \quad (50\,\%)^{[1]}$$

Fused-ring aromatic compounds give different oxidation products according to the reagent used. For example, chromium(VI) reagents oxidise naphthalenes to **naphthoquinones** in acidic media, whereas sodium dichromate in the absence of acid oxidises only substituents.

Potassium permanganate carries the oxidation further still, with ring cleavage and the formation of monocyclic dicarboxylic acids:

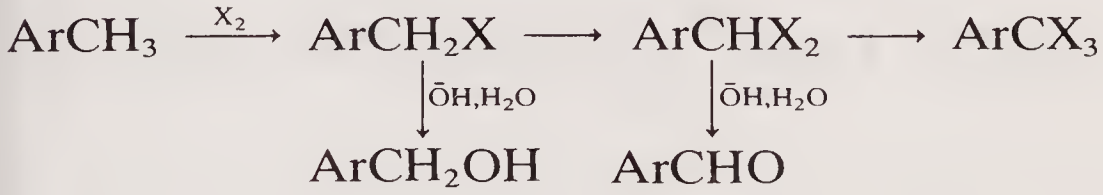






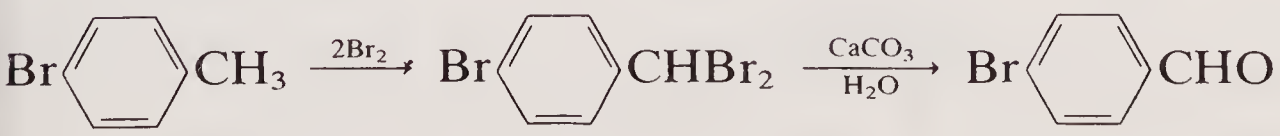
Oxidation of a benzylic centre to a level below the highest attainable presents more difficulties. $ArCH_3 \rightarrow ArCHO$ and $ArCH_2R \rightarrow ArCH(OH)R$, for example, are difficult because the products are more easily oxidised than the starting materials.

Several methods have been developed for the controlled oxidation of methyl groups to aldehydes. The simplest involves free-radical halogenation of the methyl group, and subsequent separation and hydrolysis of the dihalogeno-derivative [reaction (9.13)]:



(9.13)

e.g.



(68 % overall)

A second approach makes use of chromium(VI) reagents, under conditions which ensure that the aldehyde group is generated only in the final work-up. In the best-known of these oxidations, the **Étard reaction**, the oxidant is chromyl chloride, CrO_2Cl_2, in an inert solvent (CCl_4 or CS_2), but chromyl acetate, $CrO_2(OCOCH_3)_2$ (prepared *in situ* from chromium(VI) oxide, acetic anhydride, and sulphuric acid) may also be used successfully. In the Étard reaction (9.14a) the intermediate is a 2:1 adduct of chromyl chloride and the toluene derivative, possibly (8), and in the chromyl acetate oxidation the primary product is the diacetate (9) [reaction (9.14a)]:

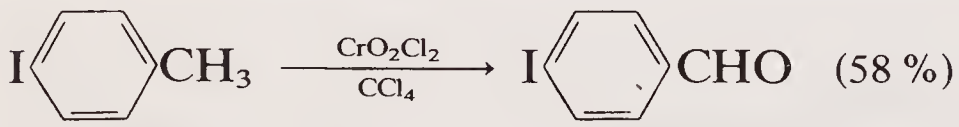
$$ArCH_3 \xrightarrow{2CrO_2Cl_2} \left[ArCH(OCrCl_2)_2?\right] \xrightarrow[(ii)\ H^+,H_2O]{(i)\ Na_2SO_3} ArCHO \qquad (9.14a)$$

(8)

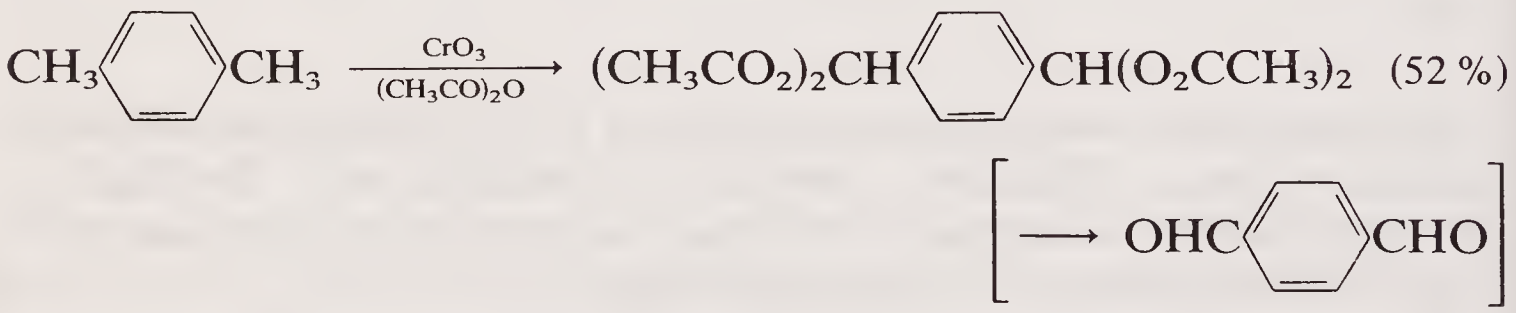
$$ArCH_3 \xrightarrow[(CH_3CO)_2O]{CrO_3} ArCH(OCOCH_3)_2 \xrightarrow{H^+,H_2O} ArCHO \qquad (9.14b)$$

(9)

Neither of these two reactions gives good yields in every case, but many synthetically valuable examples of each are known, e.g.

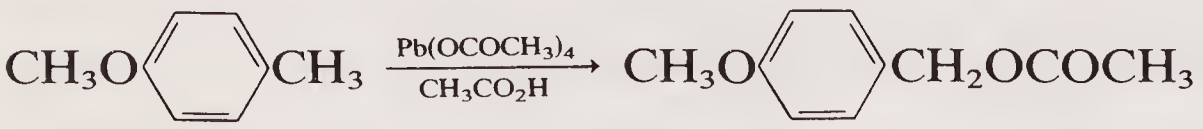


(58 %)



(52 %)

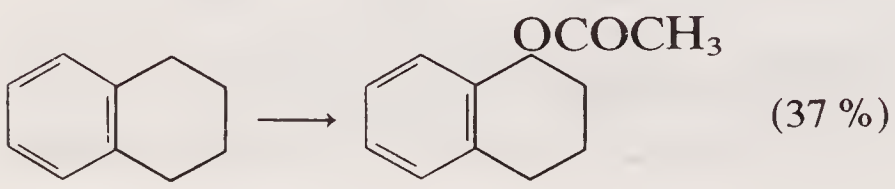
Oxidation of a benzylic centre to the alcohol may be achieved, as in reaction (9.13), by mono-halogenation followed by hydrolysis. Direct oxidation to the alcohol level is also possible using lead(IV) acetate (cf. allylic oxidation: section 9.2.2), e.g.



(60 %)

Similarly

$Ph_2CH_2 \rightarrow Ph_2CHOCOCH_3$ (71 %)

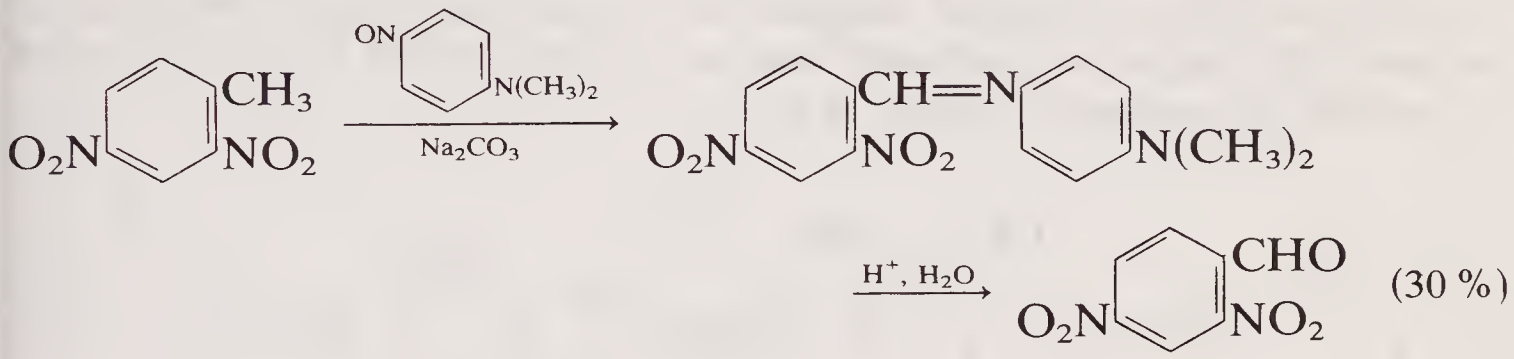


(37 %)

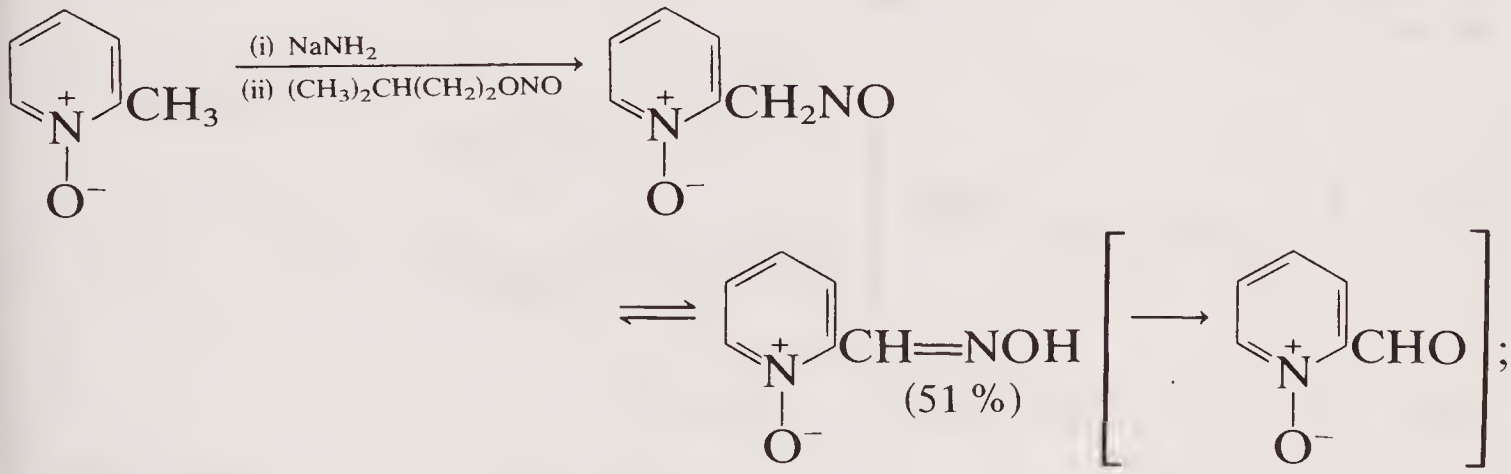
Autoxidation of benzylic compounds, although important industrially (cf. section 2.4.2), is of less value as a 'laboratory' method and is not considered further here.

The mechanisms of many of the reactions described in this section have not been established beyond doubt, but in most cases the initial step is probably abstraction of a *hydrogen radical* or *hydride ion* from the benzylic carbon.

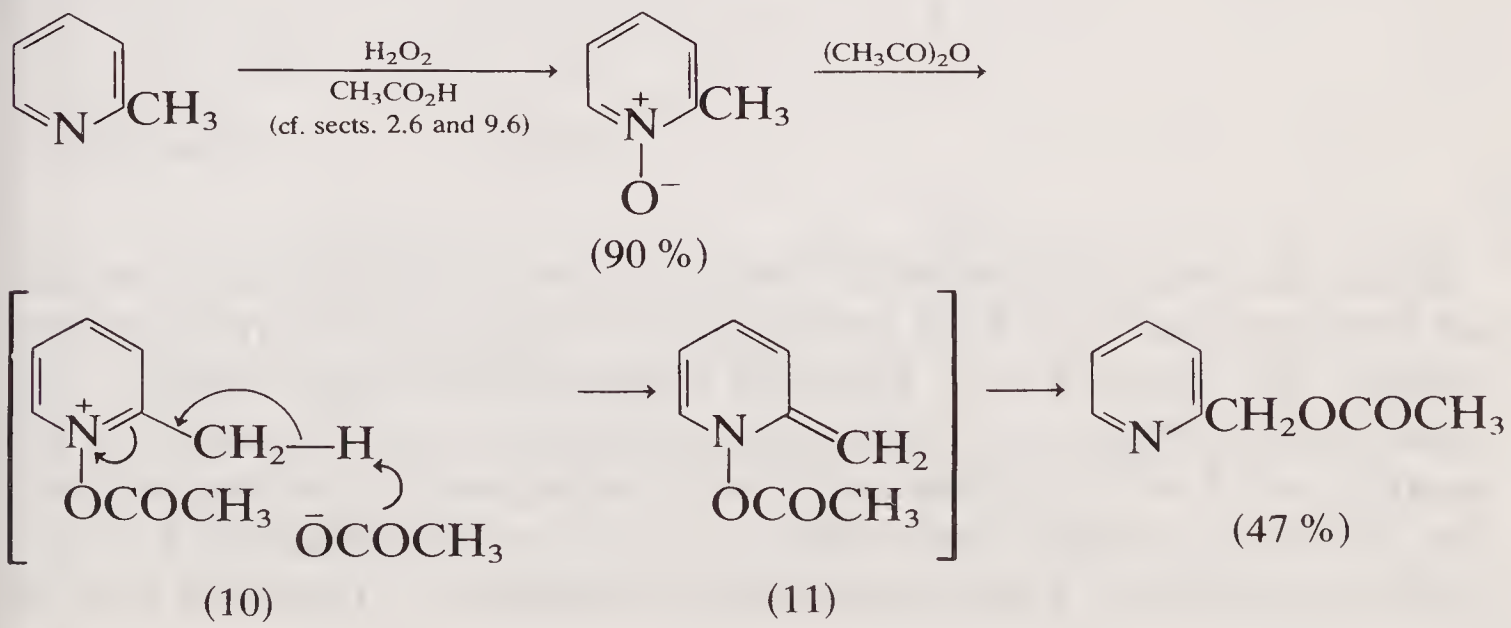
If a benzylic centre can lose a *proton* easily, i.e. if it is a potential carbanion source, it may undergo condensation with a nitrosoarene, and the resulting anil may then be hydrolysed to a carbonyl compound and an arylamine (cf. section 6.3.3), e.g.



Nitrosation of a benzylic carbanion also leads to oxidation, e.g.



and a deprotonation step, (10) → (11), is the key to the oxidation of 2-methylpyridine to 2-pyridylmethanol:[2]

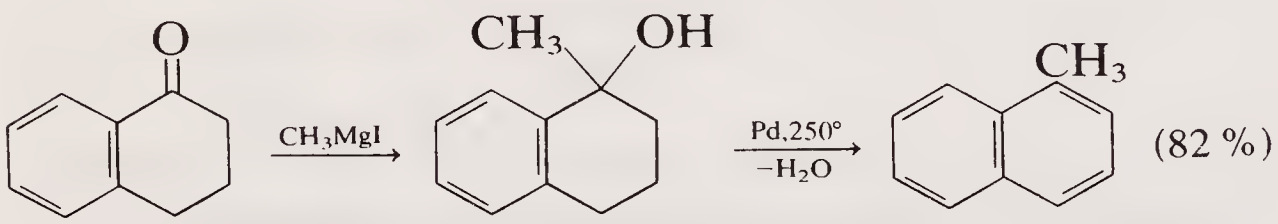


9.2.4 Dehydrogenation of alkanes, alkyl groups and alkenes

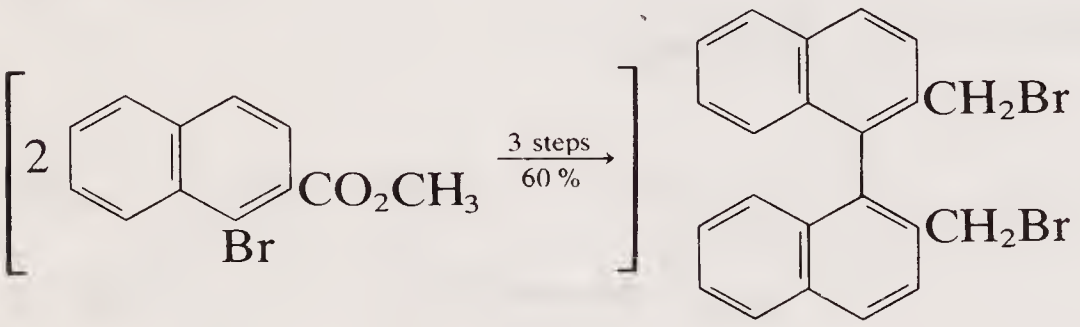
9.2.4.1 Alkanes and alkyl groups

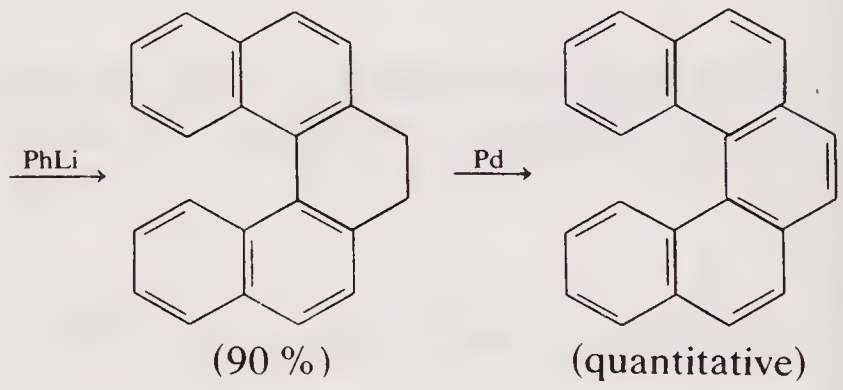
The formation of an alkene by dehydrogenation of the corresponding dihydro-compound cannot be regarded as a general reaction; it succeeds only if the double bond is introduced entirely regiospecifically, and this is possible only if the starting compound possesses the requisite structural features and/or functional groups. Nevertheless the three types of dehydrogenation outlined in section 9.1.1 are all well known and widely used methods for the introduction of carbon–carbon double bonds.

(i) As already mentioned (section 9.1.1) catalytic dehydrogenation in presence of palladium succeeds best when the double bond so formed completes an aromatic system, e.g.



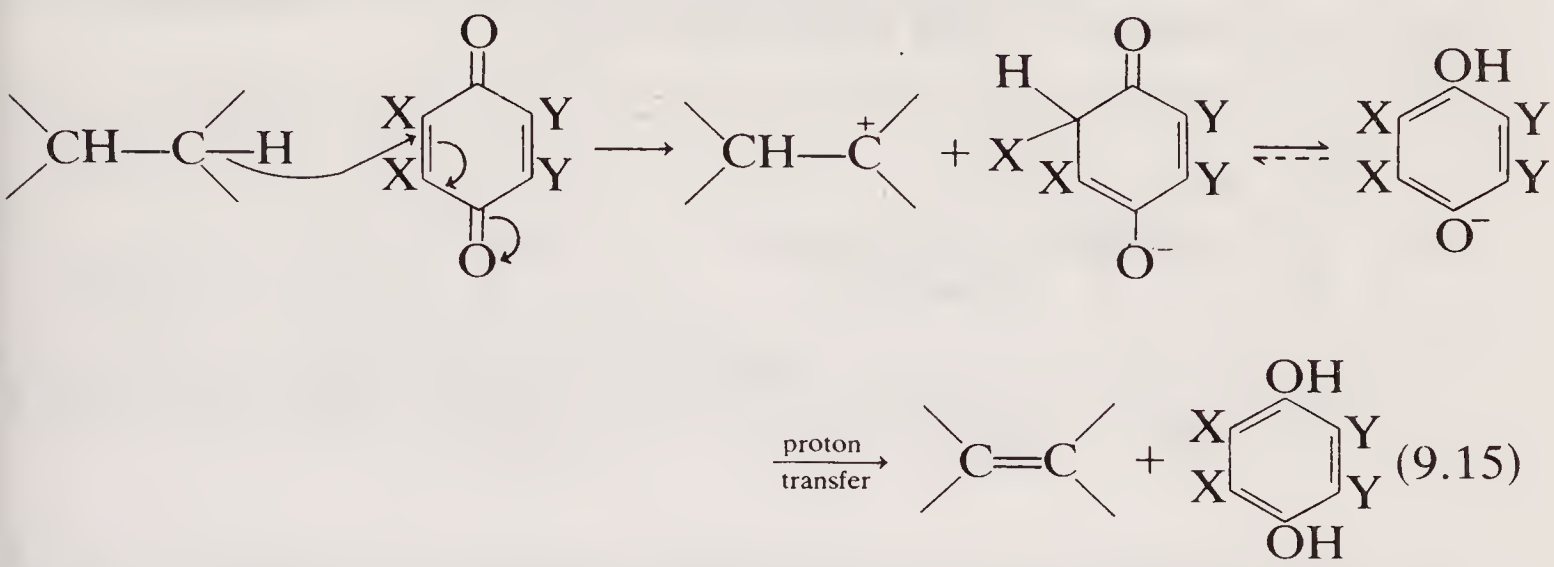
(for preparation see sect. 7.1.1)



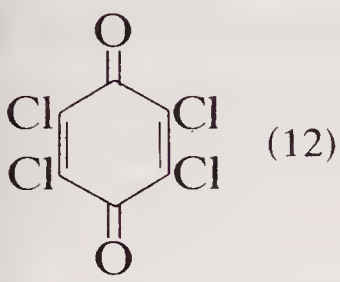


(ii) In the ionic elimination of hydrogen, loss of hydride ion is usually the first step [reaction (9.2)], and dehydrogenation of this type therefore requires the presence of a powerful hydride-abstracting reagent: quinones bearing electron-withdrawing substituents, e.g. (12) and (13), are usually used. Loss of hydride ion from the substrate produces a carbocation and occurs readily only if the carbocation is stabilised (e.g. if it is allylic or benzylic). This type of dehydrogenation is therefore used to

convert an alkyl–alkene into a conjugated diene, a diene into a triene, an alkylbenzene into a styrene derivative, and so on:

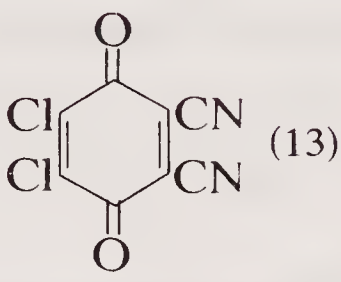


(9.15)



(12)

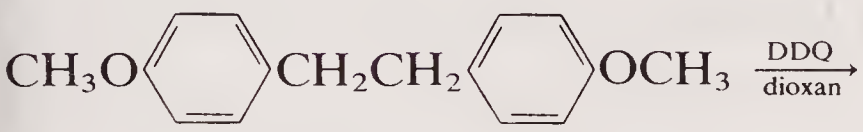
chloranil

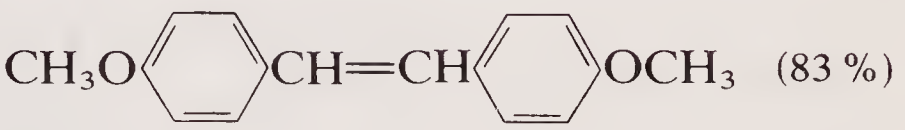


(13)

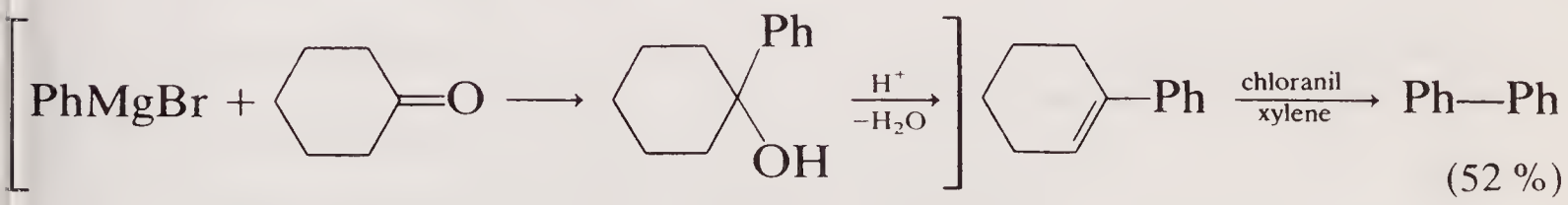
DDQ(**di**chloro**di**cyanobenzo**qu**inone)

For example,

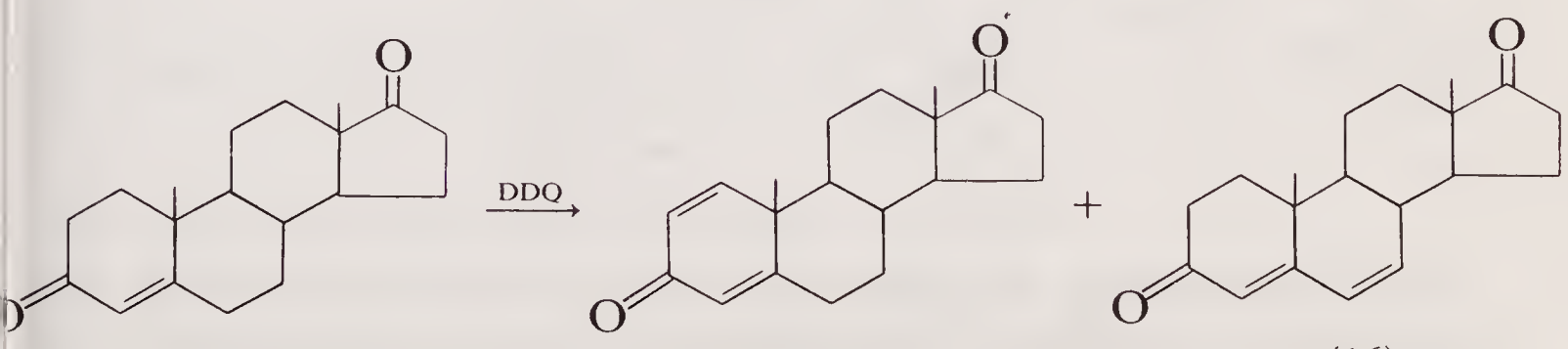




(83 %)



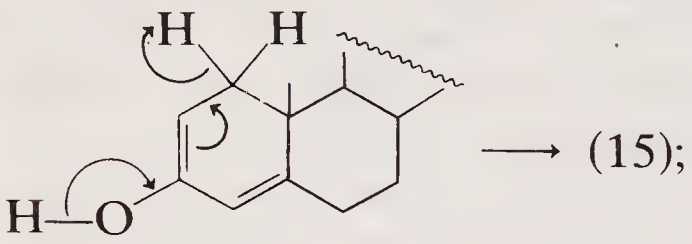
(52 %)



(14) (15) (16)

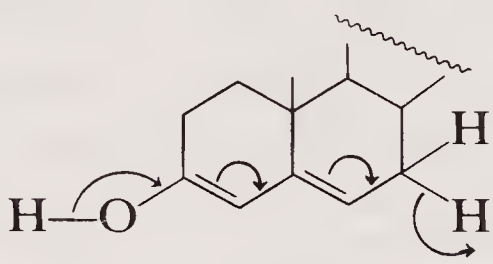
[(15) : (16) ratio depends on reaction conditions]

This last example is worthy of a little additional comment. Enolisation of (14) is the first step, and this may occur in either of two directions, giving (14a) or (14b). These then lose H^- and H^+ as shown, to give the observed products (15) and (16), respectively:



(14a)

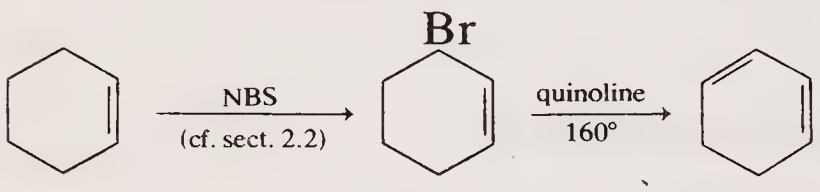
⟶ (15);



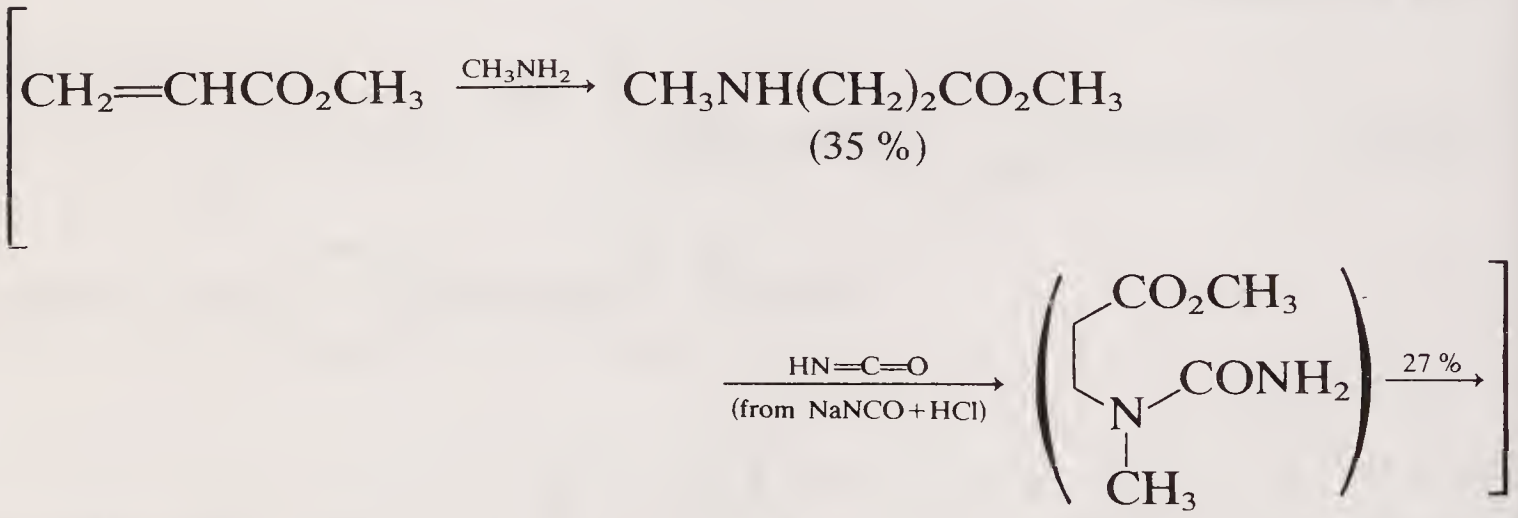
(14b)

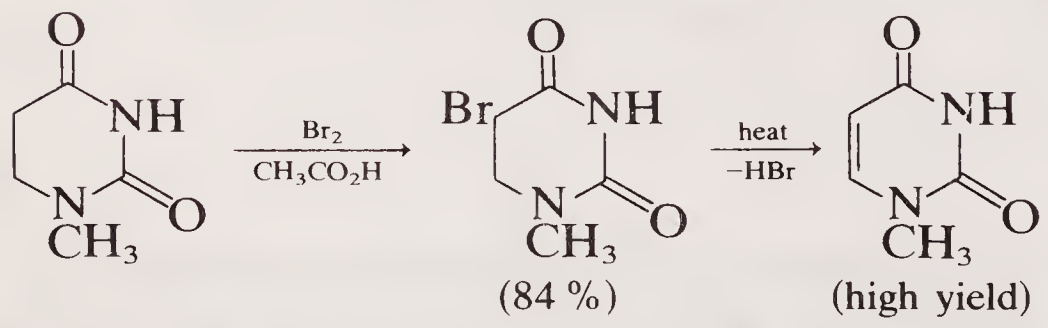
⟶ (16)

(iii) The simplest of the substitution–elimination sequences is halogenation (usually bromination) followed by elimination of hydrogen halide, e.g.



(45 %) (68 %) (31 % overall)





(84 %) (high yield)

It should be noted, of course, that in each of the above examples, the bromination and dehydrobromination steps lead to a single product, and the success of the method is limited to cases in which such regiospecificity is observed.

9.2.4.2 Alkenes

Bromination followed by dehydrobromination is the usual method for the conversion of an alkene into an alkyne, e.g.

$$CH_2{=}CH(CH_2)_2CH{=}CH_2 \xrightarrow{2Br_2} \underset{(95\ \%)}{BrCH_2CHBr(CH_2)_2CHBrCH_2Br} \xrightarrow[NH_3(l)]{NaNH_2} \underset{(56\ \%)}{HC{\equiv}C(CH_2)_2C{\equiv}CH} \quad (53\ \%\ \text{overall})$$

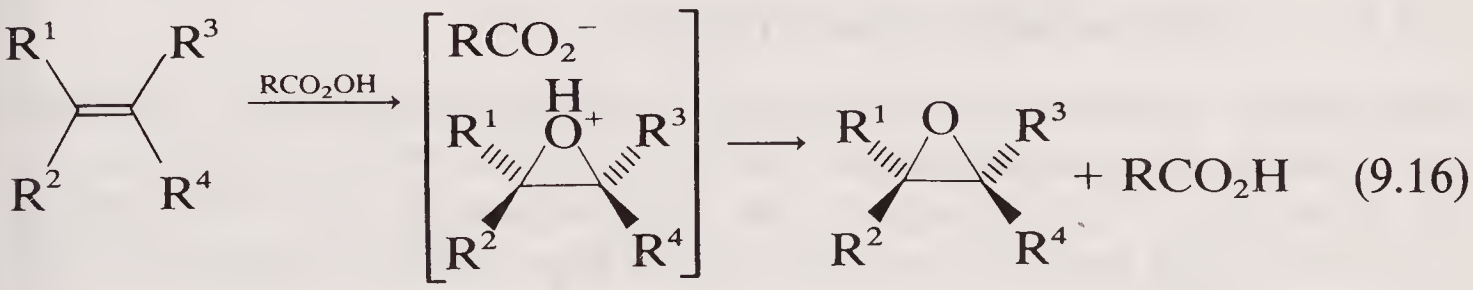
$$PhCH{=}CH_2 \xrightarrow[CCl_4]{Br_2} \underset{(97\ \%)}{PhCHBrCH_2Br} \xrightarrow[THF]{NaNH_2} \underset{(90\ \%)}{PhC{\equiv}CH} \quad (87\ \%\ \text{overall})$$

9.2.5 Oxidative addition to alkenes

In this section we shall consider two types of addition: the formation of oxirans (epoxides) by addition of an oxygen atom across the double bond, and the formation of 1,2-diols, which is effectively the addition of a hydroxyl group at each end of the double bond.

9.2.5.1 Oxiran formation (epoxidation)

Oxirans (epoxides) are formed by the direct reaction of alkenes with peroxy-acids [reaction (9.16): cf. Sykes, p. 190], the stereochemistry of the alkene being retained in the product:

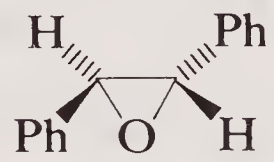


(9.16)

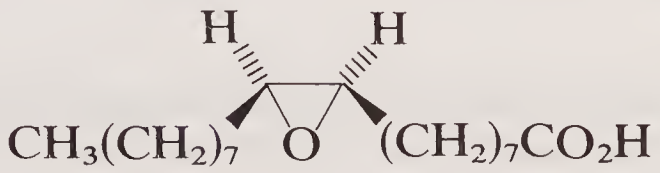
Peroxy-acids are often generated *in situ* from hydrogen peroxide and a carboxylic acid derivative, but **m-chloroperbenzoic acid** (*m*-$ClC_6H_4CO_2OH$:MCPBA) is a relatively stable solid.

Examples of epoxidation include the following:

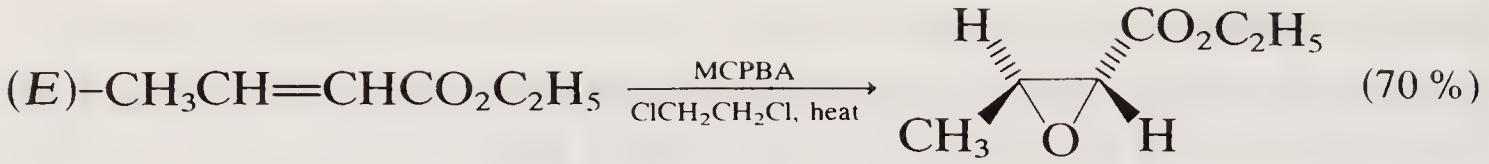
$$(E)\text{–}PhCH{=}CHPh \xrightarrow[\substack{CH_2Cl_2\\ 20\text{–}30^\circ}]{CH_3CO_2OH} \quad (70\ \%)$$



$$(Z)\text{–}CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H \xrightarrow[\text{acetone, } 0\text{–}5^\circ]{PhCO_2OH^{[31]}}$$

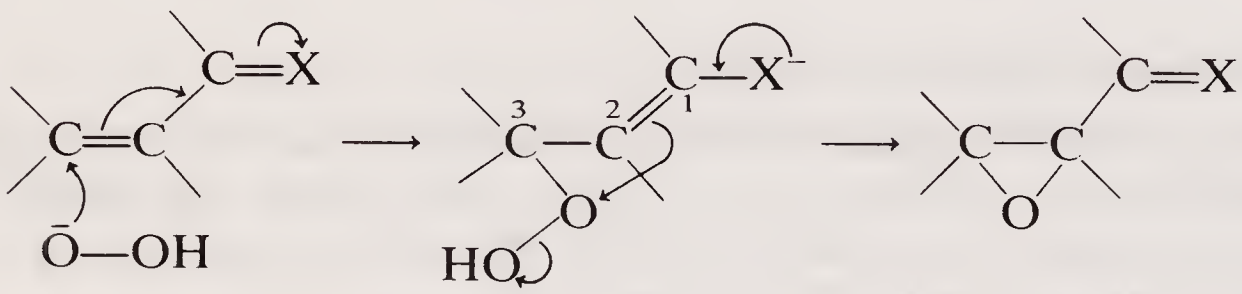


(62 %)



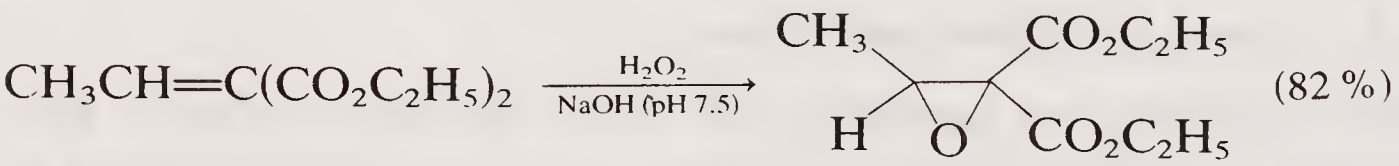
(70 %)

This last example illustrates the relative difficulty in oxidising an electron-deficient alkene using a peroxy-acid. Alkenes which are conjugated to a $-M$ group are epoxidised by reaction with *alkaline* hydrogen peroxide: this involves Michael-like addition of HO_2^- and subsequent loss of $\bar{O}H$ [reaction (9.17)]. Note that in this case the stereochemistry of the original alkene need not be retained in the product, since free rotation about the 2,3-bond in the intermediate is possible:



(9.17)

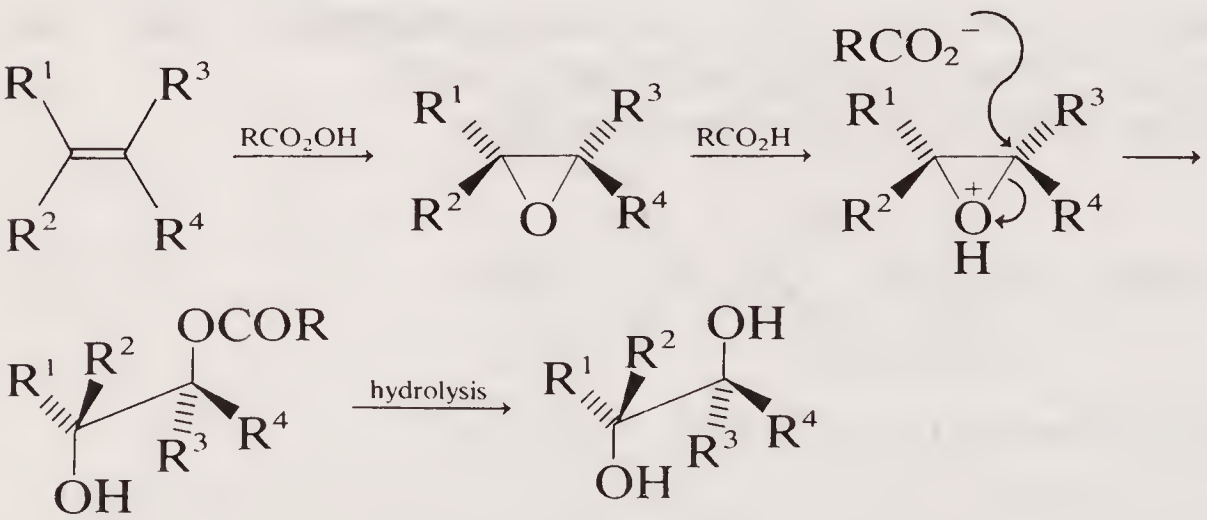
e.g.



(82 %)

9.2.5.2 1,2-Diol formation (hydroxylation)

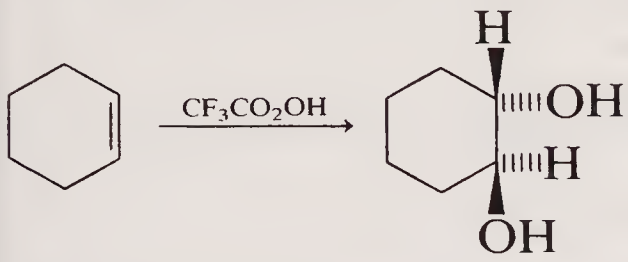
Three general methods are commonly used for the conversion of alkenes into 1,2-diols; these complement one another to a certain extent and are thus all worthy of consideration. The first proceeds by way of the oxiran (cf. the preceding section), and leads to the *trans*-adduct [reaction (9.18); cf. Sykes, p. 190].



(9.18)

The method depends on the strength of the acid RCO_2H (i.e. on its ability to protonate the oxygen of the oxiran). Formic and trifluoroacetic

acids are sufficiently strong to effect the ring-opening, and their peroxy-derivatives are thus commonly used for hydroxylation. Thus, for example,

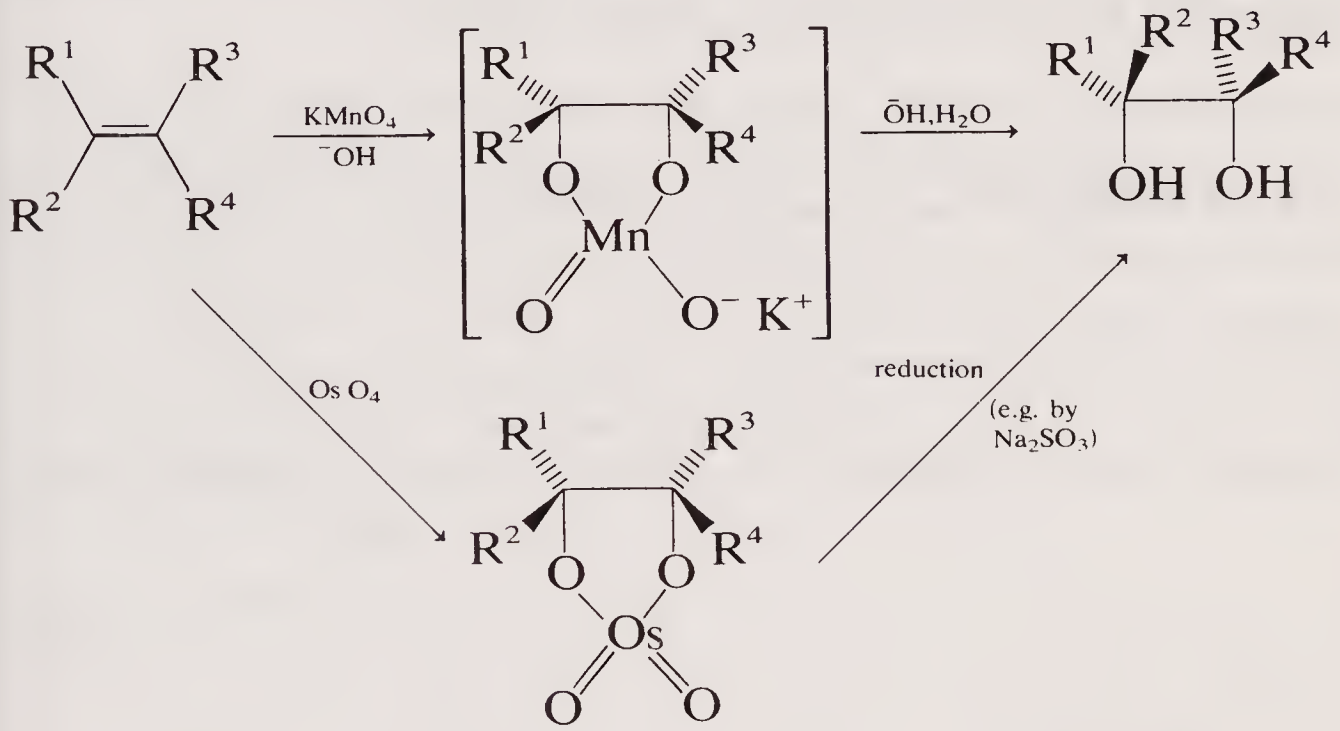


(82 %)

$$(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H \xrightarrow{HCO_2OH}$$

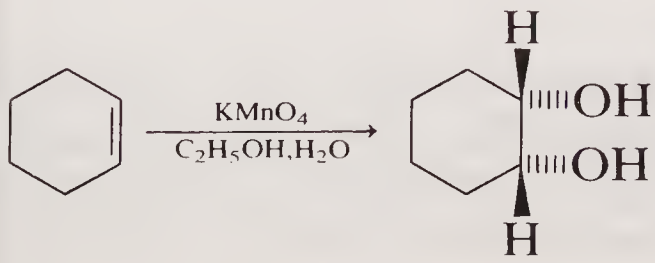
$$\textit{threo}\text{-}CH_3(CH_2)_7CHOHCHOH(CH_2)_7CO_2H \quad (80\ \%)$$

The second involves the formation of a cyclic ester, by reaction of the alkene with potassium permanganate or osmium(VIII) oxide [reaction (9.19): cf. Sykes, p. 189], and subsequent hydrolysis; this leads to the *cis*-adduct.



(9.19)

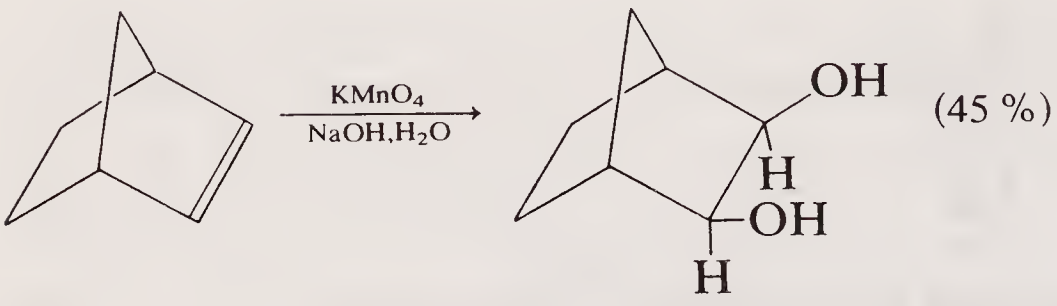
Osmium(VIII) oxide, however, is several hundred times more expensive than potassium permanganate, and is also toxic. It is therefore used only in small-scale reactions where the cost is (relatively) low and high yields are essential. Potassium permanganate, while inexpensive, may bring about further oxidation of the diol (cf. section 9.3.2), and may also oxidise other functional groups in a complex molecule; yields in permanganate hydroxylations, therefore, are not always high. Examples include:



(45 %)

$$(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H \xrightarrow[NaOH,H_2O]{KMnO_4}$$

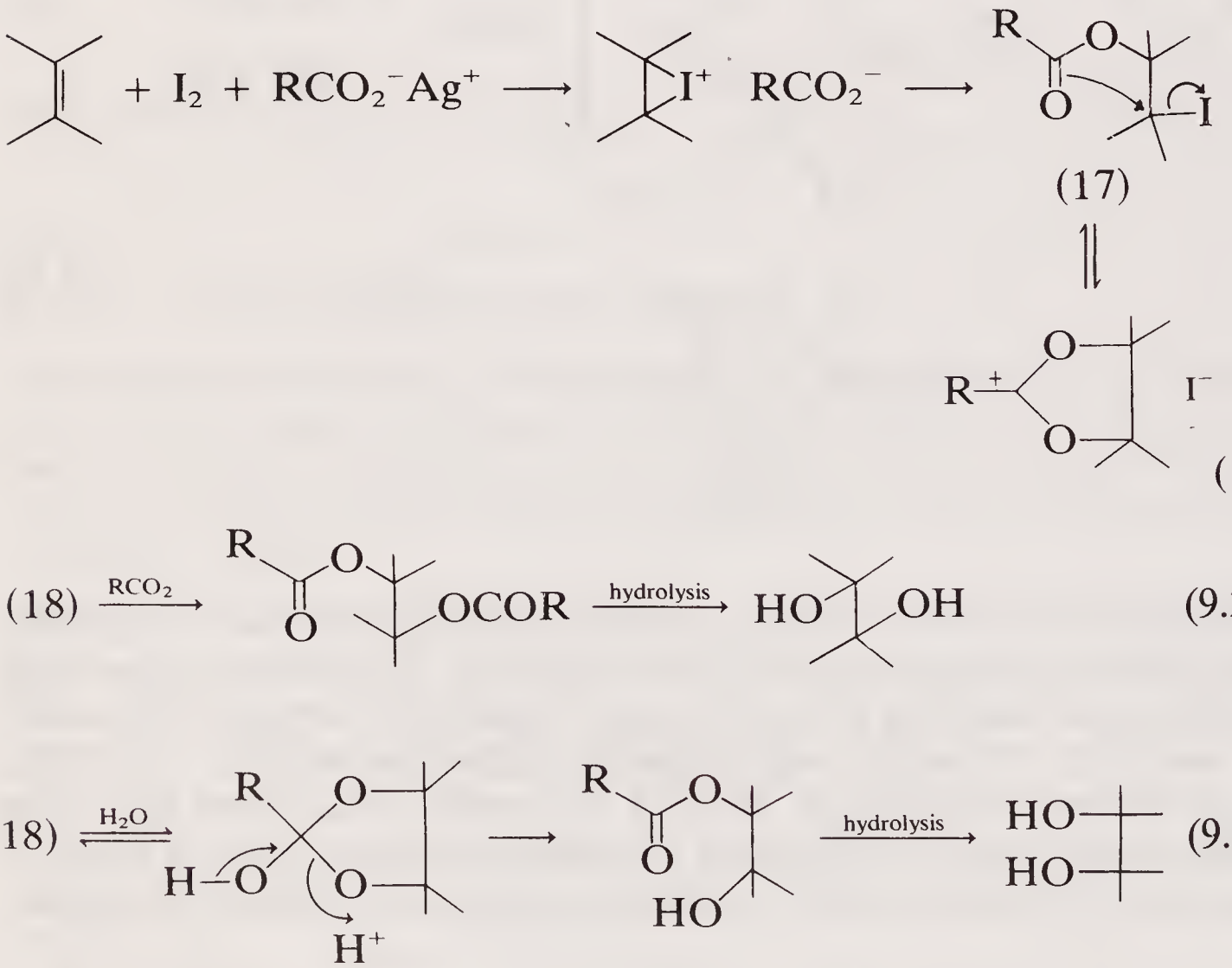
$$\textit{erythro}\text{-}CH_3(CH_2)_7CHOHCHOH(CH_2)_7CO_2H \quad (81\,\%)$$



(45 %)

Note, in this last example, that only one of the possible *cis*-diols is isolated: this arises because the permanganate attacks the alkene *on the less hindered side*.

The third hydroxylation method is the Prévost reaction, in which the alkene is heated with iodine and a silver salt (usually the benzoate or acetate). This process may lead to *cis*- or *trans*-addition to the double bond, depending on the conditions [reaction (9.20)]:



Initial *trans*-addition to the alkene gives the iodo-ester (17). This may then react, in the absence of any other nucleophile, with a second carboxylate ion [reaction (9.20a)]; note that neighbouring group participation ensures that the resulting diester (and hence the diol) retains the *trans*

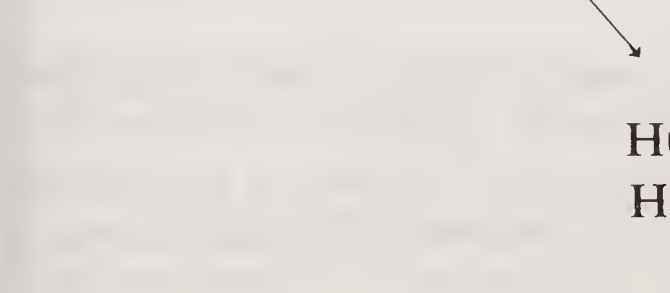
stereochemistry. In presence of water, however, the iodo-ester may be hydrolysed in a different way [reaction (9.20b)] to give the *cis*-diol.

The Prévost reaction under anhydrous conditions thus gives the same diol as the peroxy-acid reaction, e.g.

$$(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H \xrightarrow[\text{dry benzene}]{I_2,PhCO_2Ag}$$

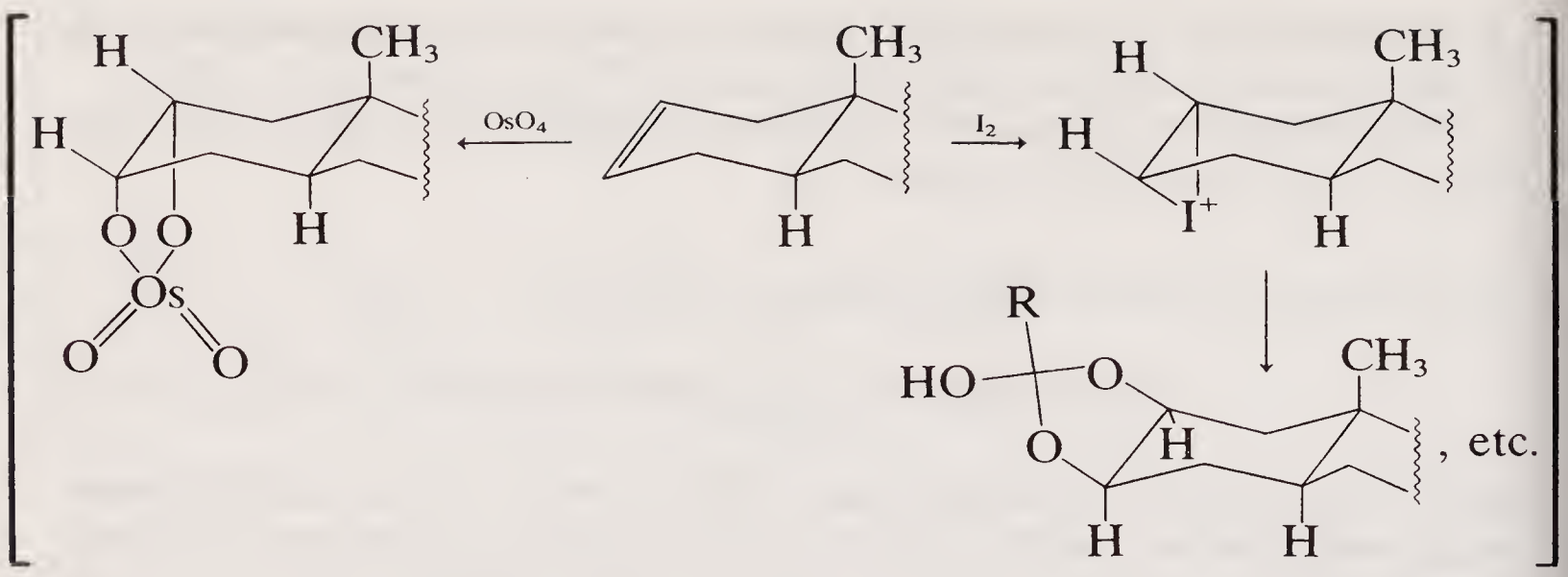
$$\textit{threo}\text{-}CH_3(CH_2)_7CHOHCHOH(CH_2)_7CO_2H \quad (75\ \%)$$

and the corresponding reaction in presence of water (the so-called **Woodward modification**) usually gives the same product as the permanganate method, e.g.



(66 %)

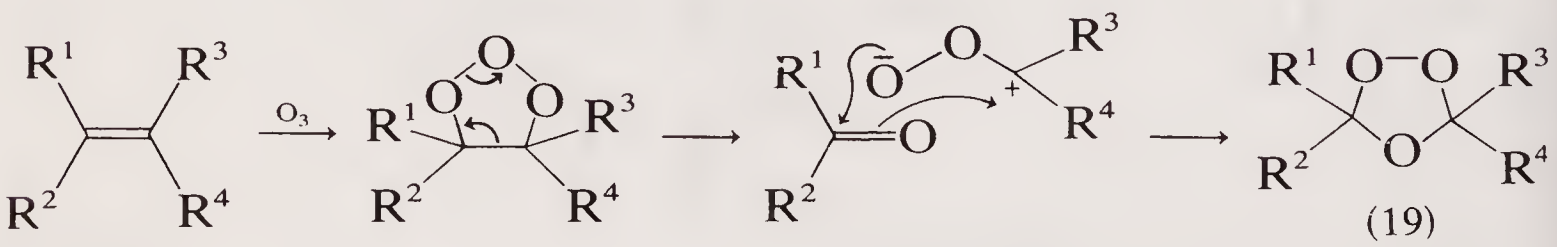
The Prévost reaction would thus appear little more than an expensive alternative to other satisfactory hydroxylation methods. However, it holds an obvious advantage over the peroxy-acid method for the *trans*-hydroxylation of acid-sensitive compounds. The Woodward modification is important in cases where a single alkene may produce two *cis*-diols; whereas permanganate oxidation produces the less hindered diol (see above), the Woodward procedure leads to the less hindered iodonium ion and thence [cf. reaction (9.20b)] to the *more hindered diol*, e.g.



9.2.6 Oxidative cleavage of alkenes

This type of reaction is of much less value in synthesis than it is (or was) in degradative structural determination. Oxidative cleavage of a carbon–carbon double bond leads generally to aldehydes, ketones, or carboxylic acids, and it is seldom that an alkene is the most convenient source of any of these. We have already drawn attention, however (section 7.4.2), to the value of oxidative cleavage as a ring opening procedure, and there are also occasions when an alkene may be used as a latent carbonyl function in a multi-stage synthesis.

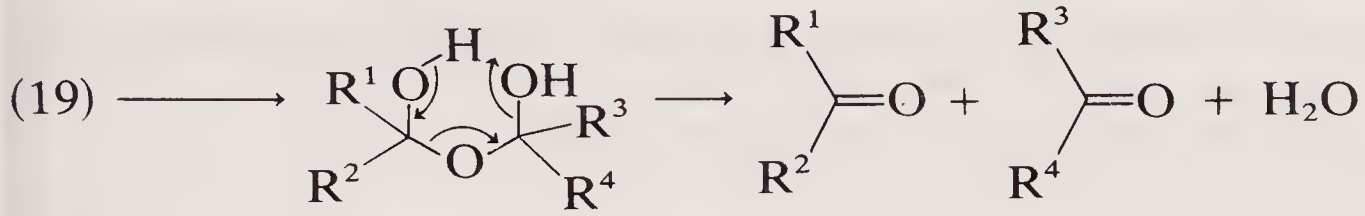
There are two principal methods for bringing about this cleavage. The first involves hydroxylation and subsequent oxidation of the diol (cf. section 9.3.2) using potassium permanganate, lead(IV) acetate, or a periodate. The second involves **ozonisation** of the alkene [reaction (9.21)], a sequence of reactions involving a 1,3-dipolar cycloaddition of ozone, a pericyclic ring opening ('retro-cycloaddition'), and a second 1,3-dipolar cycloaddition (Sykes, pp. 192–4):



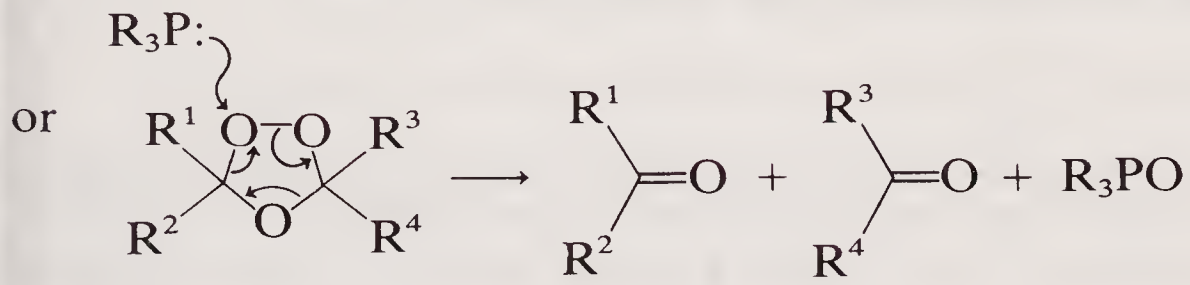
(9.21)

The primary product, the ozonide (19), is not isolated, but is converted directly into the required carbonyl compounds. *Reductive work-up* (e.g. using zinc and acetic acid, or a complex metal hydride, or a tervalent phosphorus reagent) produces aldehydes or ketones (although excess of the reducing agent may react with these: e.g. the use of lithium alumi-

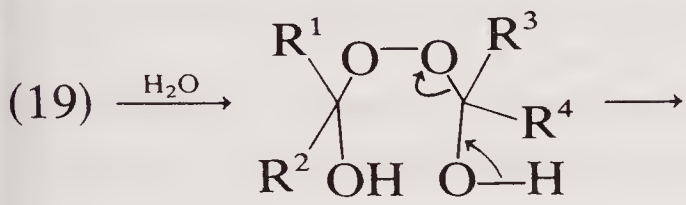
nium hydride gives alcohols):

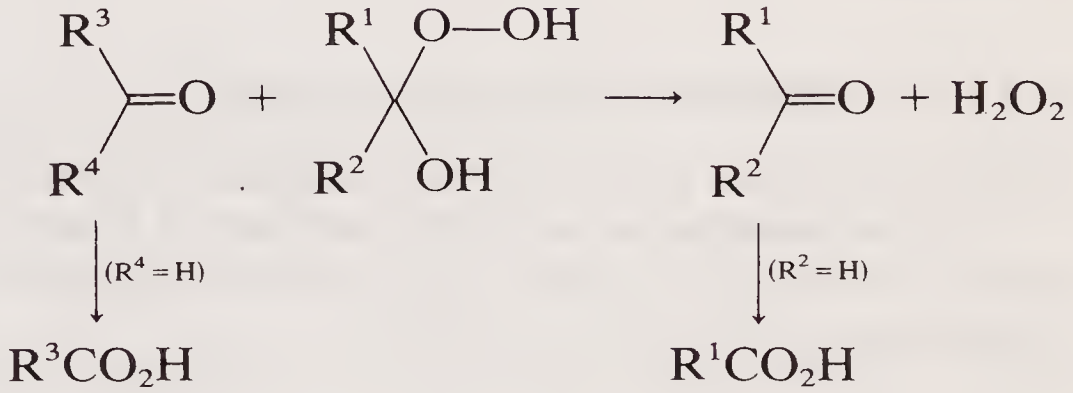


or



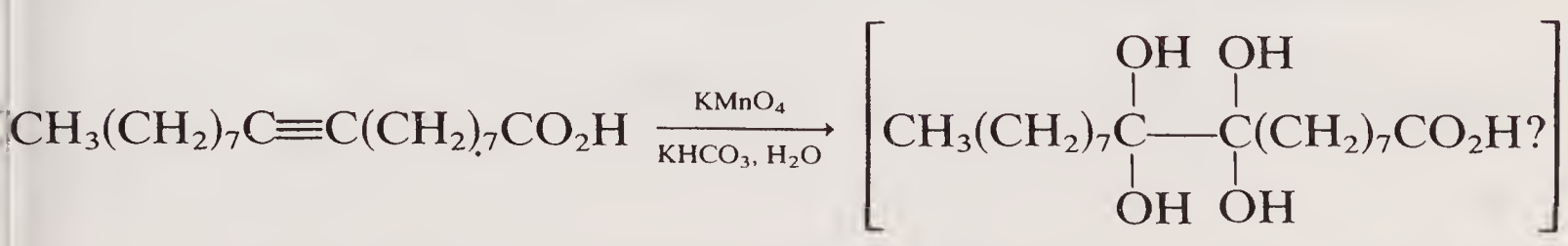
Oxidative work-up usually involves a peroxy-acid, and possibly involves hydrolysis as the first step. Under such conditions the products are carboxylic acids or ketones:





9.2.7 Oxidation of alkynes

The oxidation of a carbon–carbon triple bond is a much less-used synthetic procedure than the corresponding oxidation of an alkene. Some examples are known of the formation of 1,2-diketones by hydroxylation methods, e.g.



In many cases, however, complex mixtures result, and hydroxylation of alkenes is thus not a *general* method for diketone preparation.

Much more important as a general method is **oxidative coupling** of alk-1-ynes: this has already been discussed in detail in Chapter 4 (section 4.3.2) and is also mentioned in Chapter 7 (section 7.1.5).

9.3 Oxidation of alcohols and their derivatives

9.3.1 Formation of aldehydes or ketones (dehydrogenation)

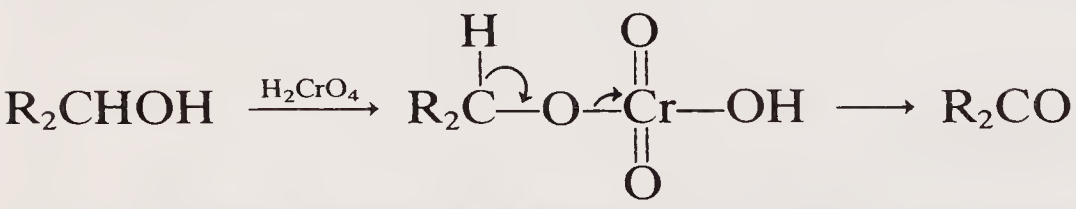
Most students of organic chemistry learn at an early stage that oxidation of primary alcohols gives aldehydes and then carboxylic acids, that oxidation of secondary alcohols gives ketones, and that tertiary alcohols are resistant to oxidation unless the conditions are sufficiently vigorous to produce C–C bond cleavage. The oxidations referred to in elementary courses are, as a rule, completely unselective, involving reagents such as hot acidified potassium permanganate or hot chromic acid, but a great deal of work has gone towards the production of methods for the *selective* oxidation of alcohols to carbonyl compounds.

The conversion of alcohols into carbonyl compounds is formally a dehydrogenation, and the three methods outlined in section 9.1.1 may all be applied.

9.3.1.1 Substitution–elimination method

This is by far the most common method, at least on a laboratory scale.

For the **oxidation of secondary alcohols to ketones**, chromium(VI) oxidants are the most popular. The reaction apparently proceeds *via* a chromium ester [e.g. reaction (9.22)]:



(9.22)

The chromium species produced by this first step [a Cr^{IV} derivative] is not the end-product. A further complicated sequence of redox steps (the details of which need not concern us here) leads eventually to a chromium(III) salt, and the overall stoicheiometry of the reaction is:

$$3R_2CHOH + 2CrO_3 \rightarrow 3R_2CO + 2Cr(OH)_3$$

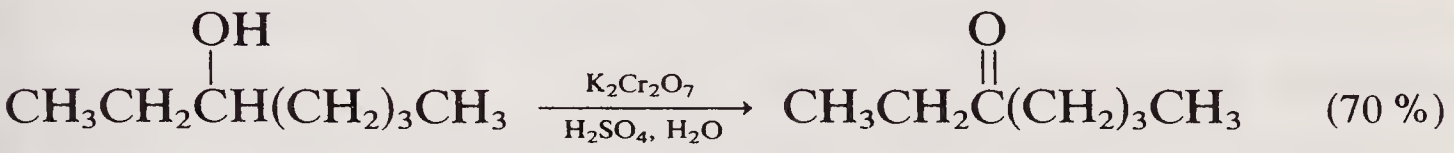
or

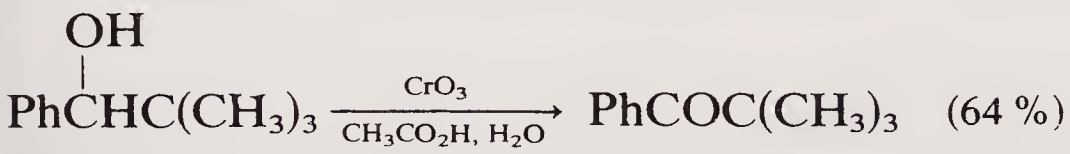
$$3R_2CHOH + 2H_2CrO_4 \rightarrow 3R_2CO + 2Cr(OH)_3 + 2H_2O$$

or

$$3R_2CHOH + 2CrO_3 + 6H^+ \rightarrow 3R_2CO + 2Cr^{3+} + 6H_2O$$

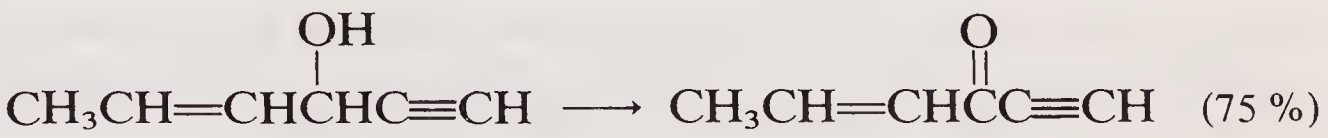
A large number of variants of this oxidation are known. If the alcohol contains no other oxidisable functional group, and is not acid-sensitive, chromic acid in aqueous sulphuric or acetic acid is the most convenient, e.g.



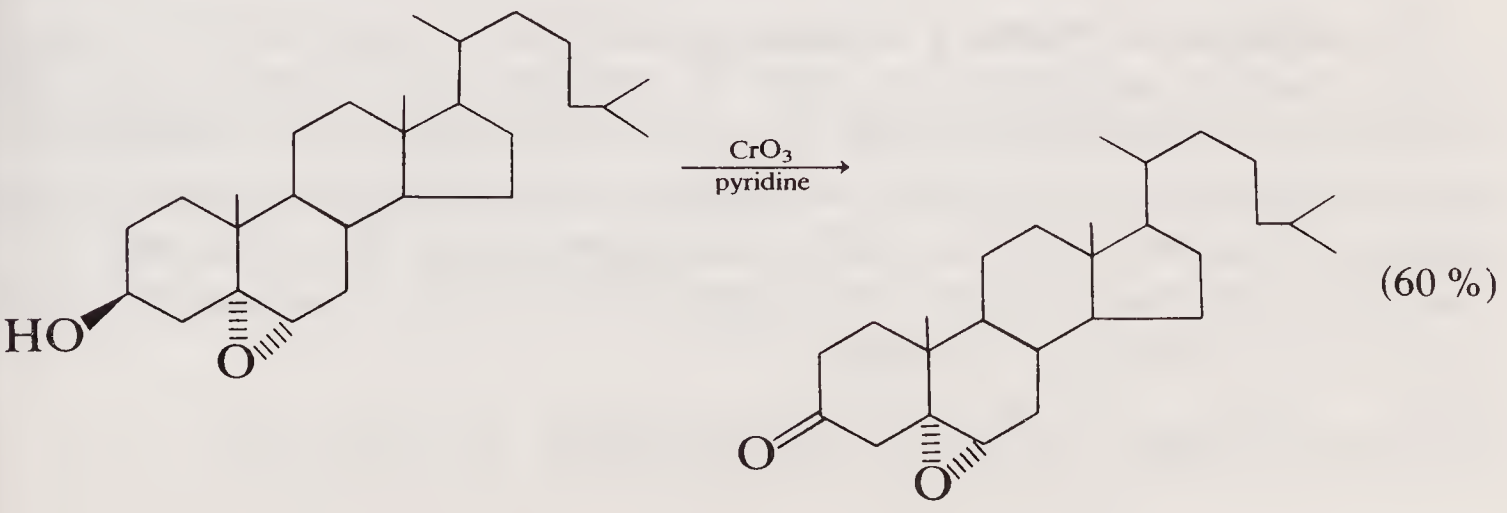


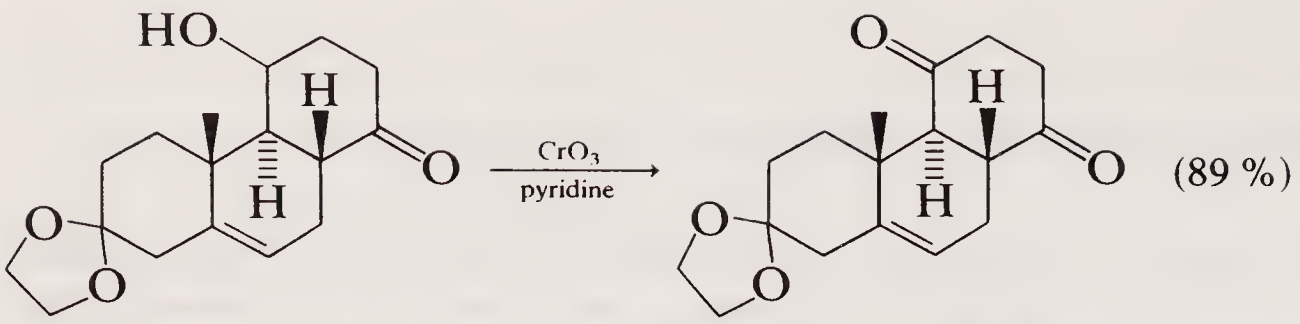
Alcohols containing double or triple bonds may be selectively oxidised using **Jones' reagent** (an aqueous solution of chromium(VI) oxide and sulphuric acid, in the correct stoicheiometric proportions); the alcohol, dissolved in acetone, is effectively titrated with the reagent at or below room temperature. Under these conditions the alcohol group is selectively oxidised, e.g.

Similarly



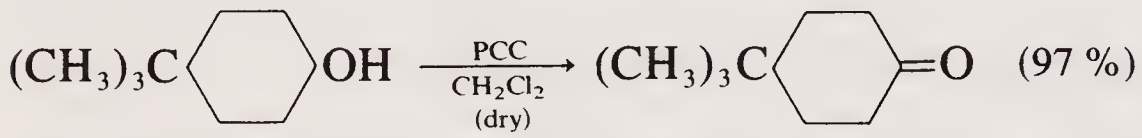
If acid-sensitivity is a problem, **chromium(VI) oxide in pyridine** may be the oxidant of choice. Alternatively the chromium oxide-pyridine complex may be isolated and used in another organic solvent such as dichloromethane. For example,



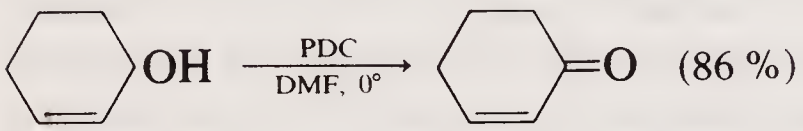


(89 %)

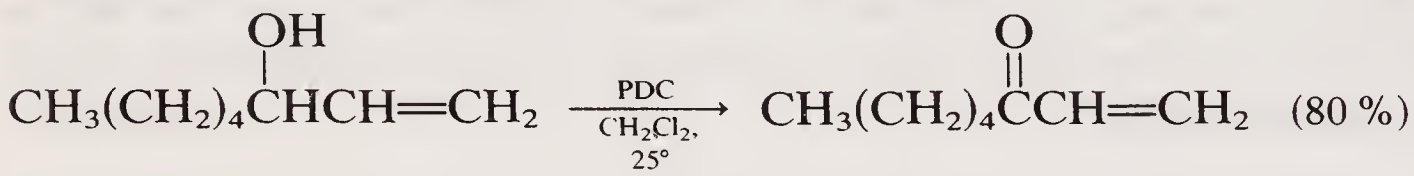
Chromium(VI) reagents which can be used for oxidations in organic solvents include **pyridinium chlorochromate**, ($C_5H_5\overset{+}{N}HCrO_3\ Cl^-$, PCC), prepared from chromium(VI) oxide, aqueous HCl, and pyridine, and **pyridinium dichromate** [$(C_5H_5NH^+)_2Cr_2O_7^{2-}$, PDC], prepared from chromium(VI) oxide, pyridine, and water. Examples of their use include the following:



(97 %)

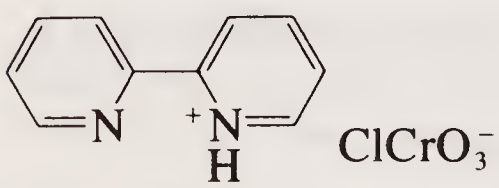


(86 %)

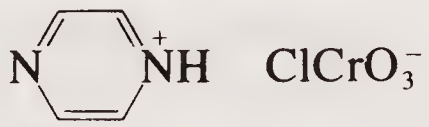


(80 %)

For alcohols containing acid-sensitive functional groups, PDC is the preferred reagent. **2,2′-Bipyridylium chlorochromate** (20) and **pyrazinium chlorochromate** (21) are some of the other oxidants which have been used for this type of reaction. The use of (20) apparently makes for a simplified work-up procedure (all the chromium-containing by-products are water-soluble), and a similar advantage is claimed for (21) (the product being isolated by simple extraction and chromatography).



(20)

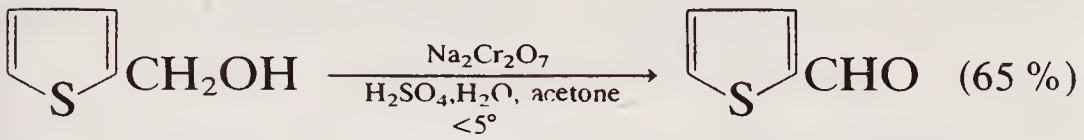


(21)

The **oxidation of primary alcohols to aldehydes** requires careful control of the reaction conditions in order to prevent over-oxidation and the production of carboxylic acids. The use of chromium(VI) reagents for such oxidations is nevertheless widespread. The classical method for preparing the lower aliphatic aldehydes makes use of their relatively low boiling points, the products being distilled out of the oxidising solution as they are formed: for example,

(b.p. 49°; 45 %)

For less volatile aldehydes, it is possible in some cases to obtain good yields by strict control of the reaction time and temperature, e.g.



In other cases (particularly those which involve allylic or benzylic oxidation) the CrO_3/pyridine reagent is satisfactory, e.g.

$$CH_3(CH_2)_5CH_2OH \xrightarrow[CH_2Cl_2,25°]{CrO_3/\text{pyridine complex}} CH_3(CH_2)_5CHO \quad (77\ \%)$$

$$PhCH{=}CHCH_2OH \xrightarrow[\text{pyridine(solvent)}]{CrO_3,\ 0°} PhCH{=}CHCHO \quad (81\ \%)$$

$$+ PhCH{=}CHCO_2H \quad (5\ \%)$$

PCC and PDC appear to be generally useful for this type of oxidation, e.g.

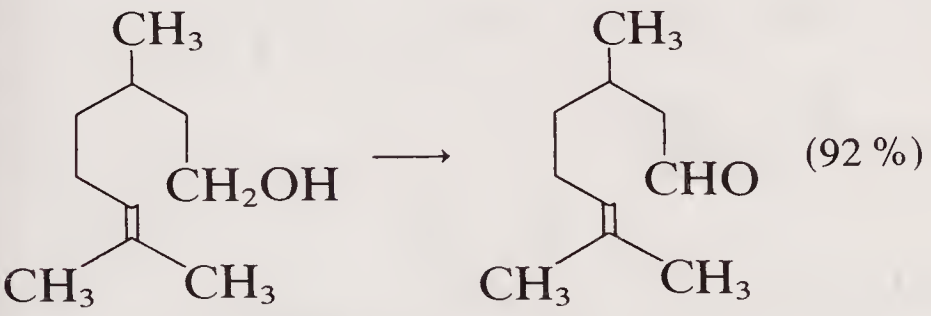
$$CH_3(CH_2)_4C{\equiv}CCH_2OH \xrightarrow[CH_2Cl_2,25°]{PCC} CH_3(CH_2)_4C{\equiv}CCHO \quad (84\ \%)$$

Similarly

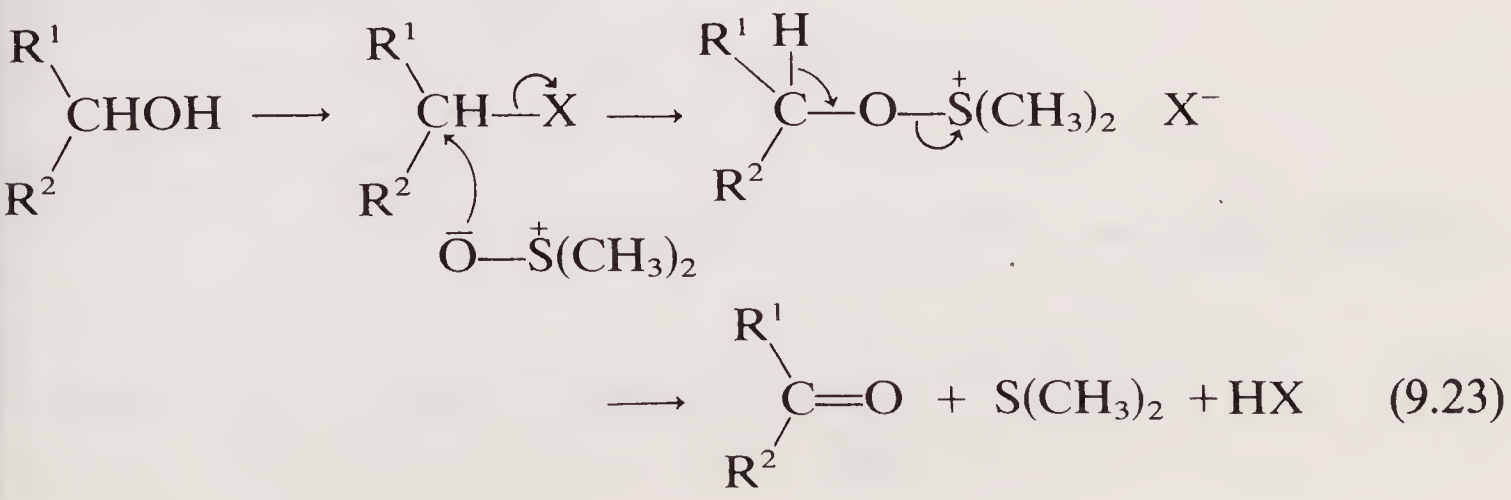
$$HO(CH_2)_6OH \rightarrow OHC(CH_2)_4CHO \quad (68\ \%)$$

$$CH_3(CH_2)_9OH \xrightarrow[CH_2Cl_2,25°]{PDC} CH_3(CH_2)_8CHO \quad (98\ \%)$$

Similarly

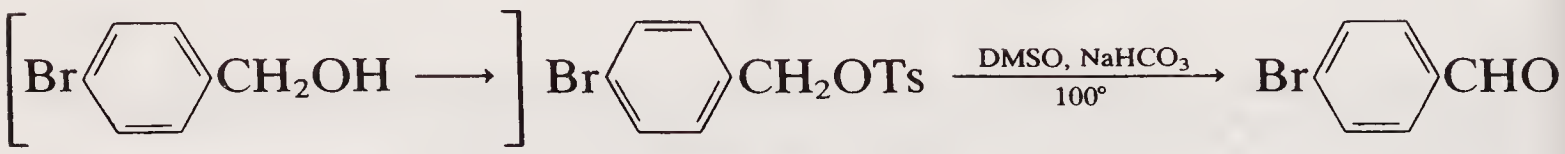


A second useful approach to the selective oxidation of alcohols to aldehydes and ketones makes use of **dimethyl sulphoxide as oxidant**. In principle the reaction is as shown below [reaction (9.23)]:



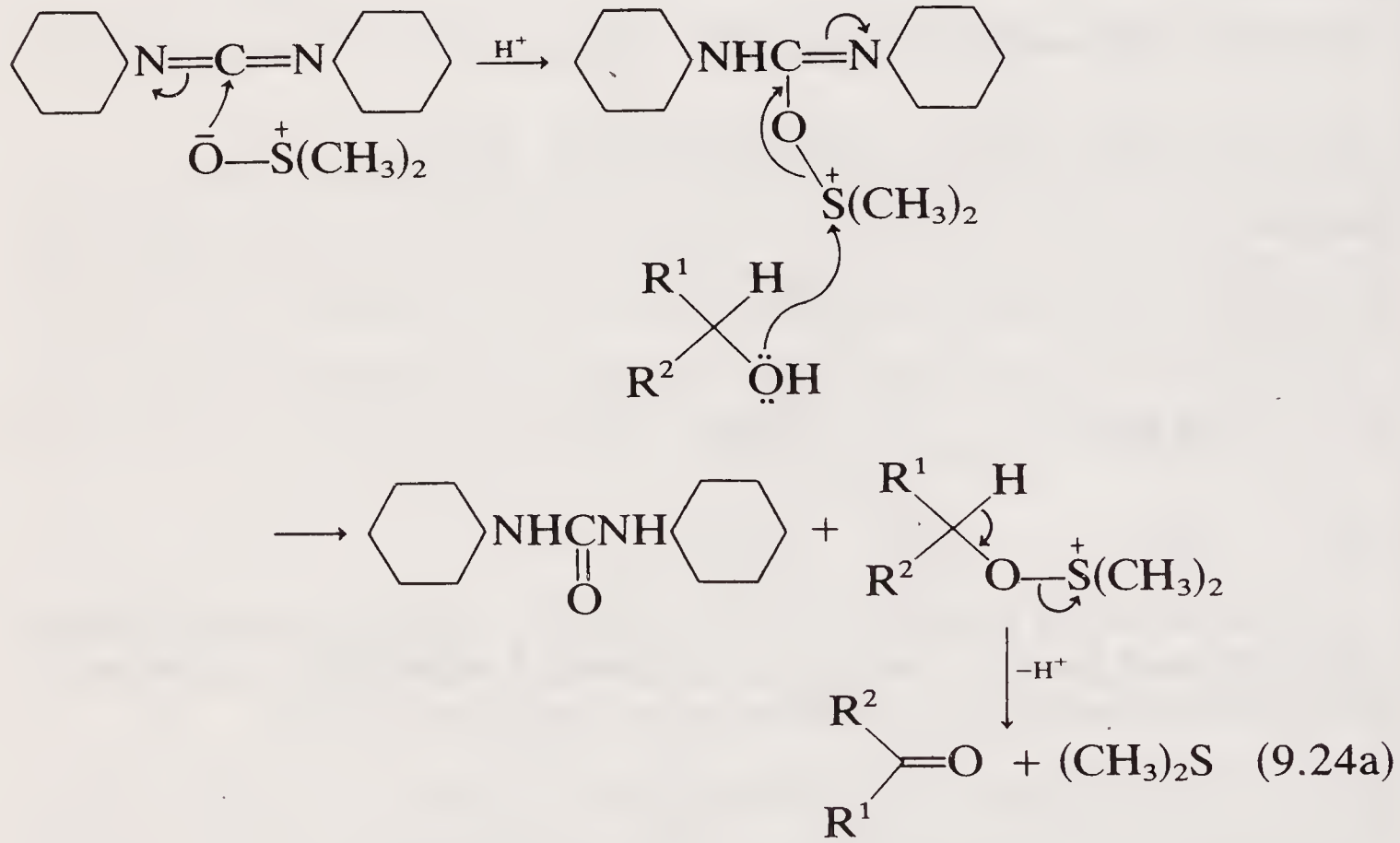
For example,

$$[CH_3(CH_2)_7OH \rightarrow]CH_3(CH_2)_7I \xrightarrow[\substack{150°,\ 4\ min\\ N_2\ atmosphere}]{DMSO,\ Na_2CO_3} CH_3(CH_2)_6CHO \quad (74\ \%)$$

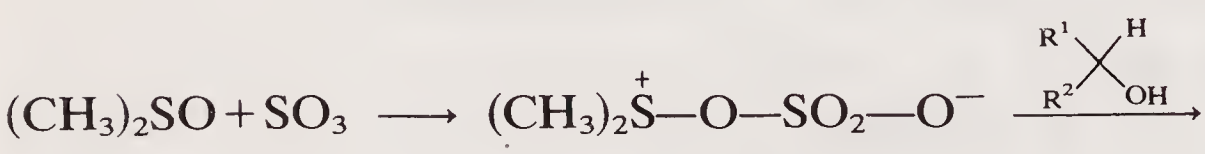


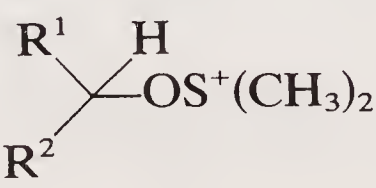
(65 %)

The conversion of the alcohol into the halide or toluene-*p*-sulphonate, however, constitutes an extra step, and the use of unselective reagents. For a multi-step synthesis, therefore, a one-step, selective oxidation is preferable; and this is achieved by converting the dimethyl sulphoxide (a weak *nucleophile*) into a strong *electrophile* which may react directly with the alcohol. Activation of the dimethyl sulphoxide is most commonly achieved using *N*,*N*′-dicyclohexylcarbodiimide [DCC: reaction (9.24a)], but sulphur trioxide (as its pyridine complex) and acetic anhydride are two other electrophiles which have been used successfully [reactions (9.24b) and (9.24c)]:

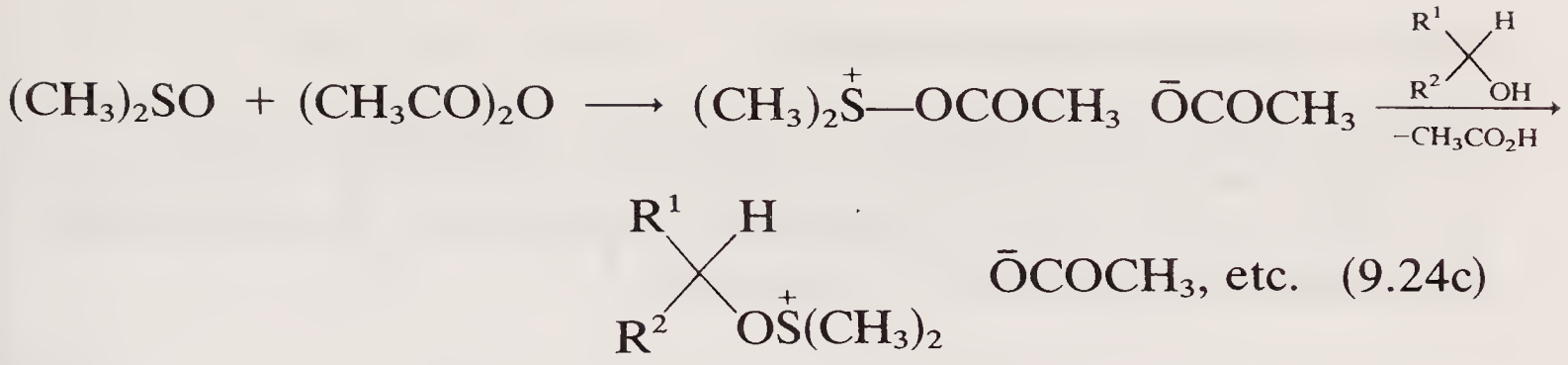


(9.24a)

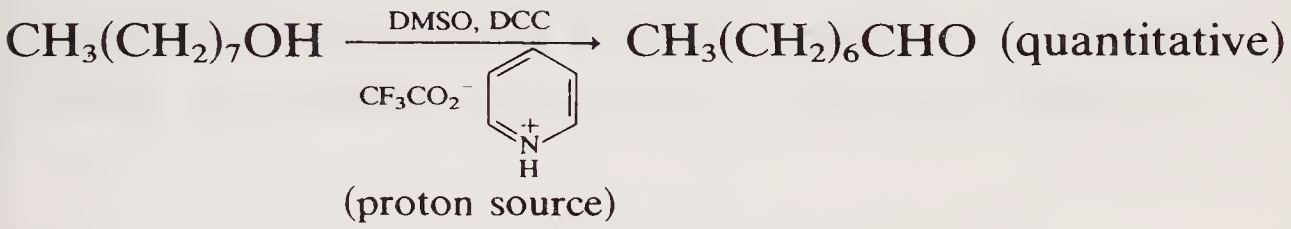




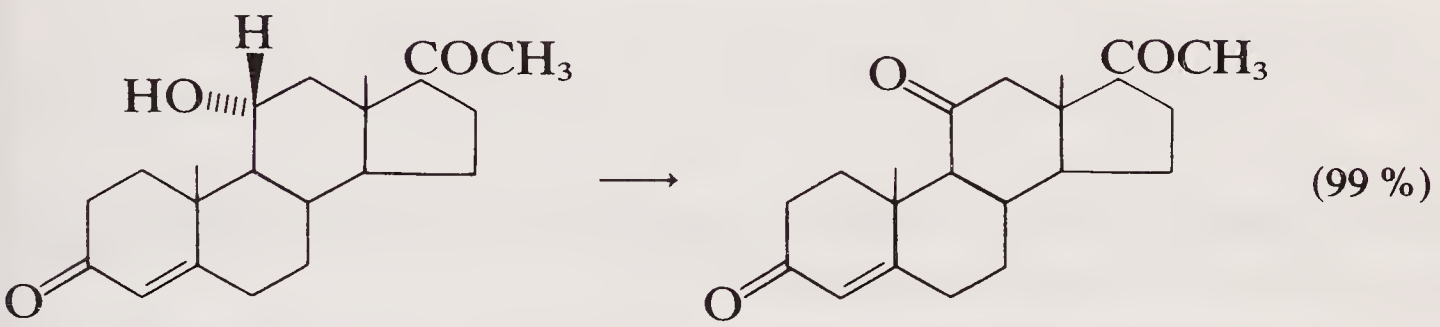
HSO_3^-, etc. (9.24b)



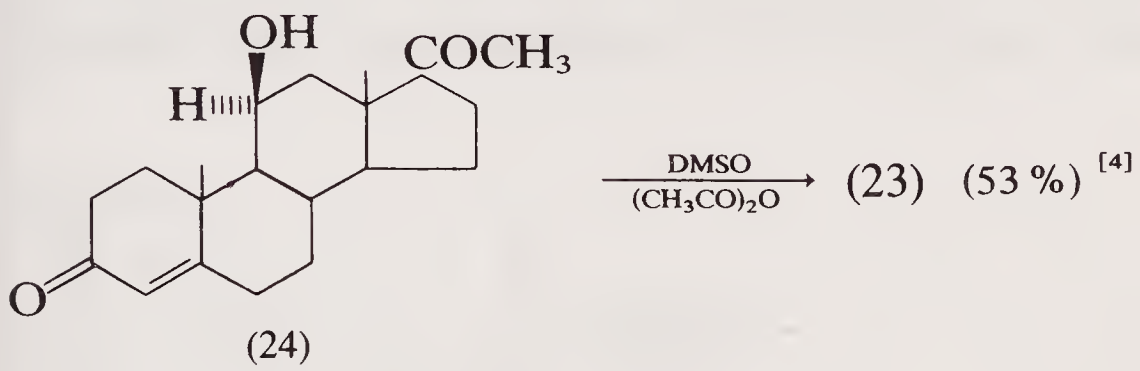
Examples of these processes include:



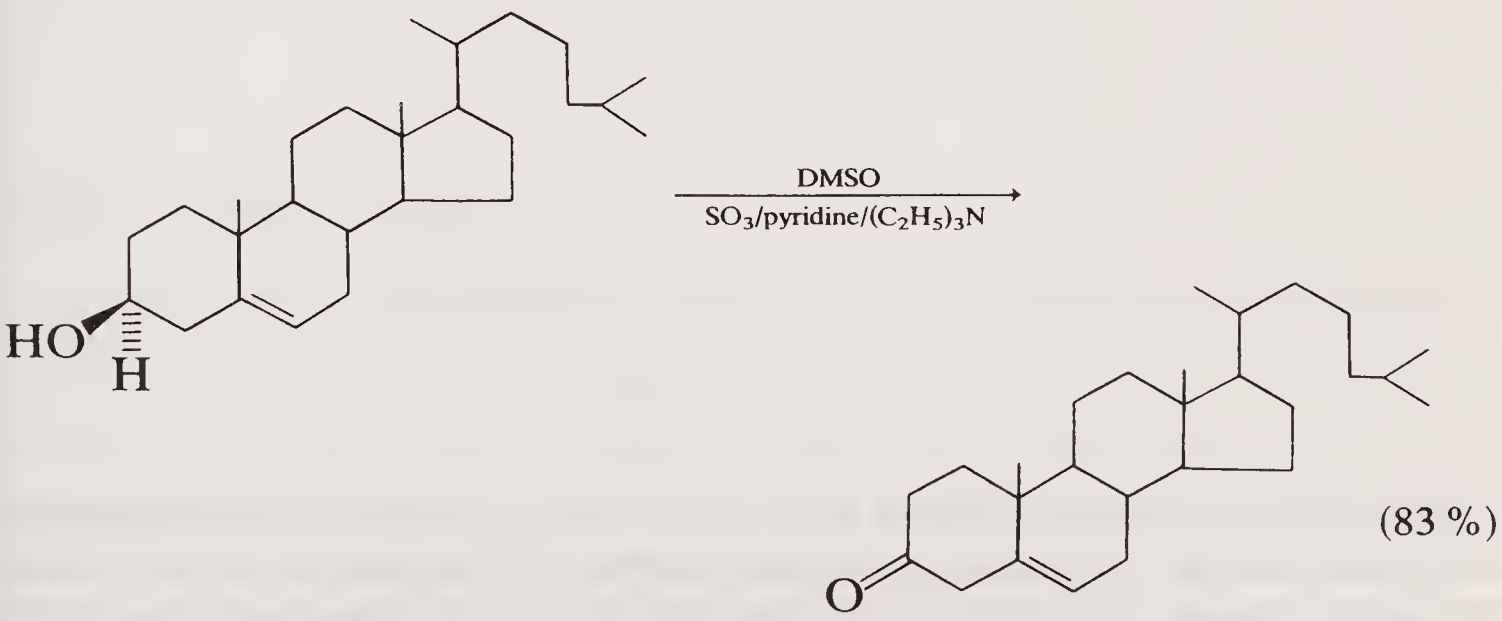
Similarly:



(22) (23)



(24)

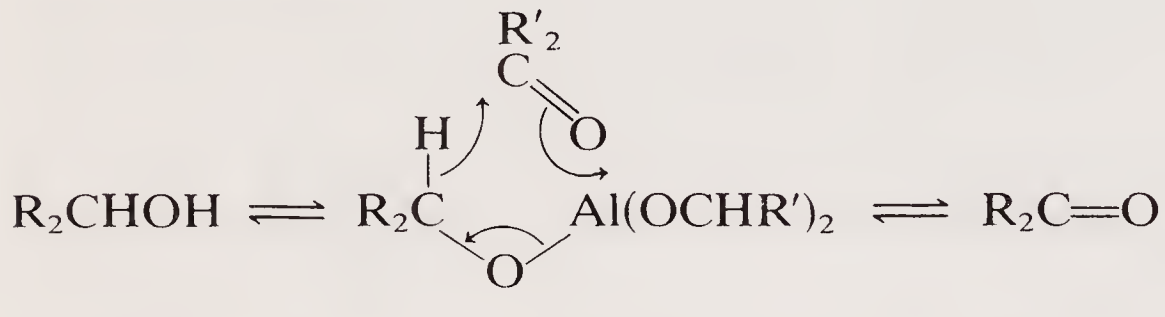


9.3.1.2 Hydride-transfer method

The most important of these is the **Oppenauer oxidation** [reaction (9.25)], in which a secondary alcohol is oxidised to a ketone by another ketone (usually acetone or cyclohexanone) in presence of an aluminium alkoxide (usually isopropoxide or t-butoxide):

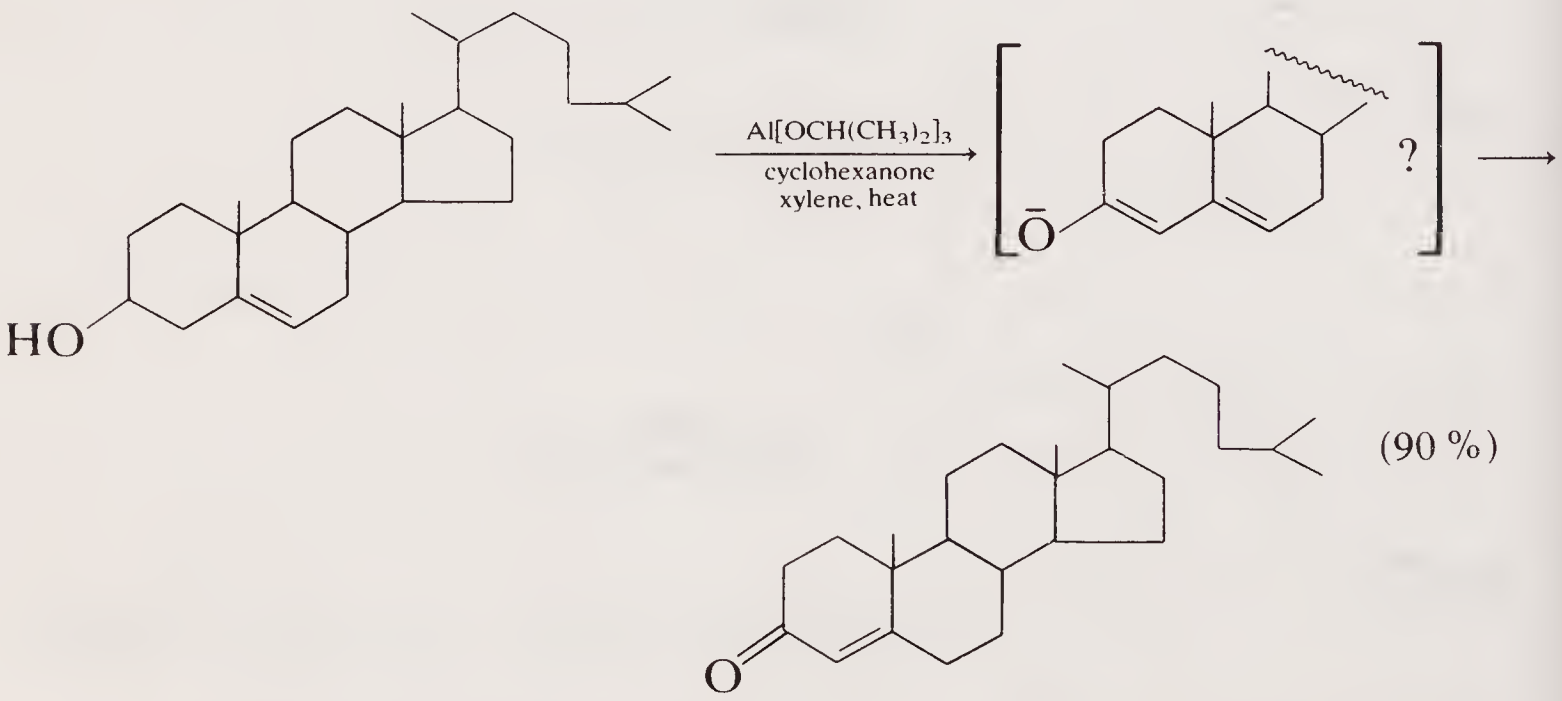
$$R_2CHOH + R'_2CO \overset{Al[OCH(CH_3)_2]_3}{\rightleftharpoons} R_2CO + R'_2CHOH \qquad (9.25)$$

This reaction is the exact opposite of the Meerwein–Ponndorf–Verley reduction [section 8.4.3.1; reaction (8.5)]. It involves deprotonation of the alcohol by equilibration with the alkoxide, followed by hydride transfer to the ketone.



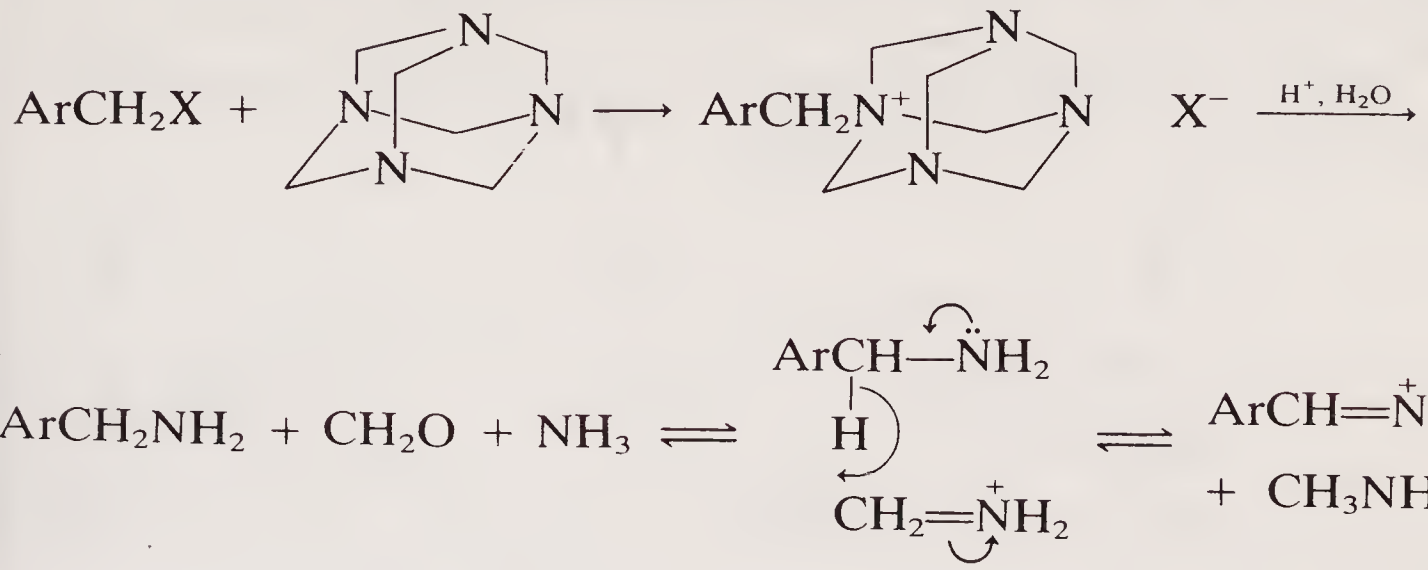
The equilibrium (9.25) is usually displaced to the right by the use of a large excess of the hydride acceptor R'_2CO.

The Oppenauer oxidation has been of particular value in steroid syntheses, in view of its high selectivity. It is, however, a reaction involving a strongly basic medium, and converts β,γ-unsaturated alcohols into α,β-unsaturated ketones, presumably *via* a conjugated enolate ion. Thus, for example,



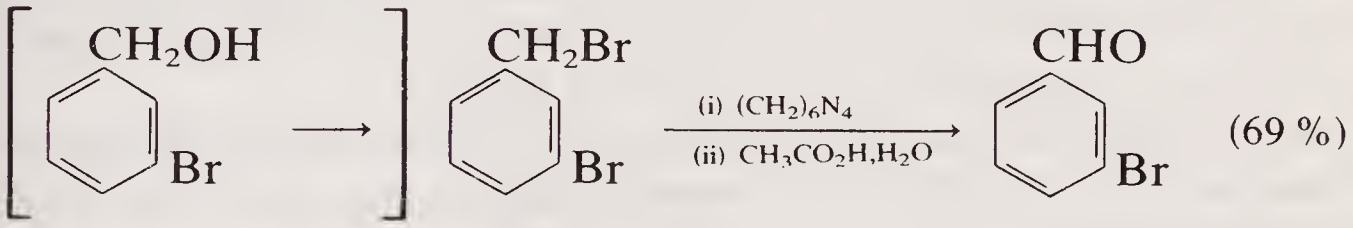
The second hydride-transfer process is usually known as the **Sommelet reaction**. In this procedure, a halide (usually benzylic) is treated with hexamethylenetetramine, and the resulting salt hydrolysed in presence of

an excess of the amine [reaction (9.26)]:

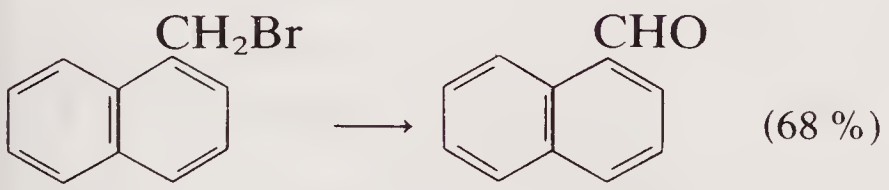


$$\xrightarrow{H_2O} ArCHO + NH_3 + CH_3NH_2 \quad (9.26)$$

As with the Oppenauer reaction, the equilibrium is displaced by adding excess of hexamethylenetetramine (i.e. an excess of $CH_2{=}\overset{+}{N}H_2$). The method gives acceptable yields of aldehydes, as the examples show, but it offers no obvious advantage over the dimethyl sulphoxide method described above (p. 217):



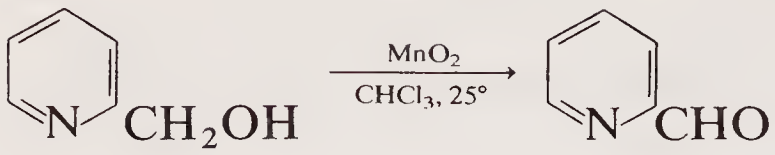
Similarly,



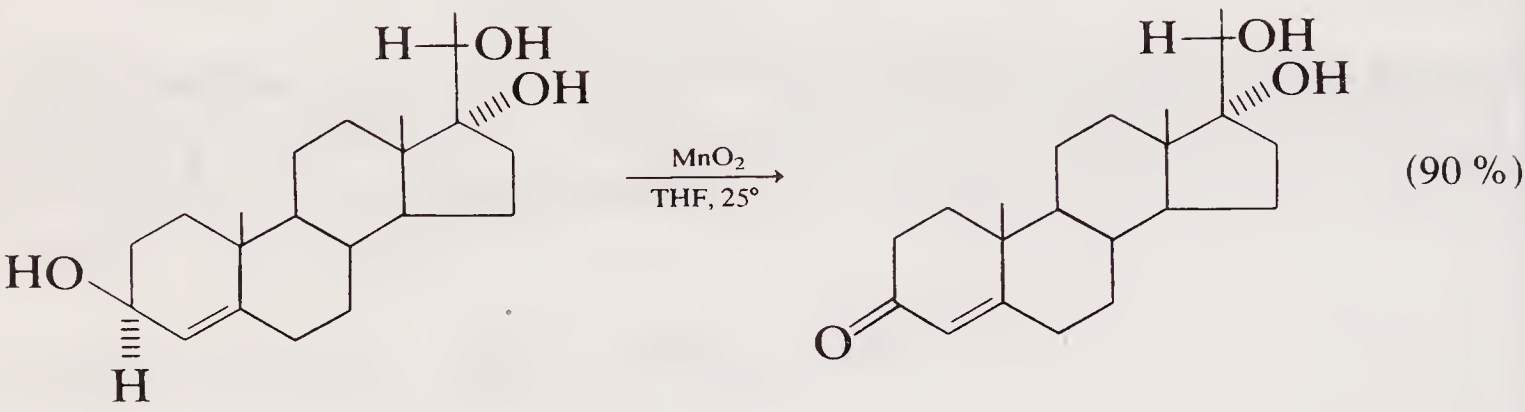
9.3.1.3 Other methods

Catalytic dehydrogenation of alcohols, although important industrially, holds no particular advantage on a 'laboratory' scale over the chemical methods described in the previous sections, and so is not considered further here. The oxidation of allylic and benzylic alcohols using manganese(IV) oxide is worthy of mention. It is a heterogeneous reaction, and the detailed mechanism is unknown; its success also depends on the freshness of the oxide used. However, with freshly prepared oxide the

yields may be high and the oxidations selective, e.g.



(68 %)

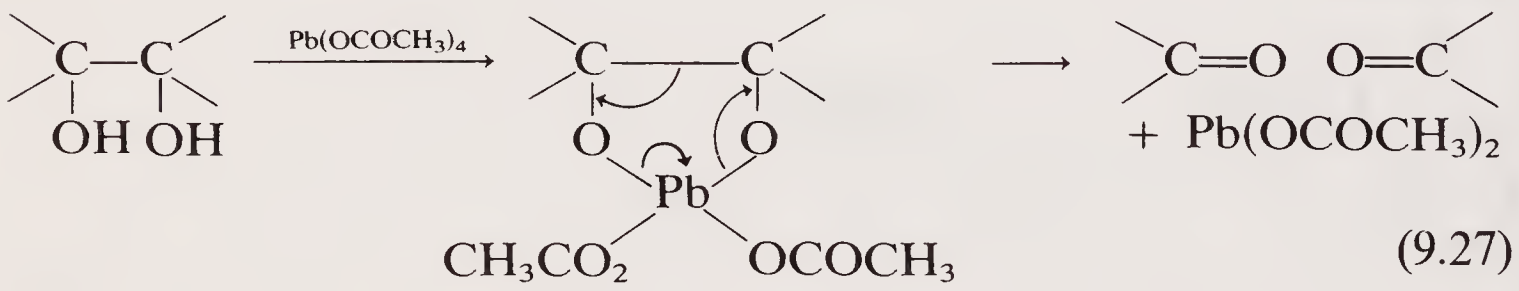


(90 %)

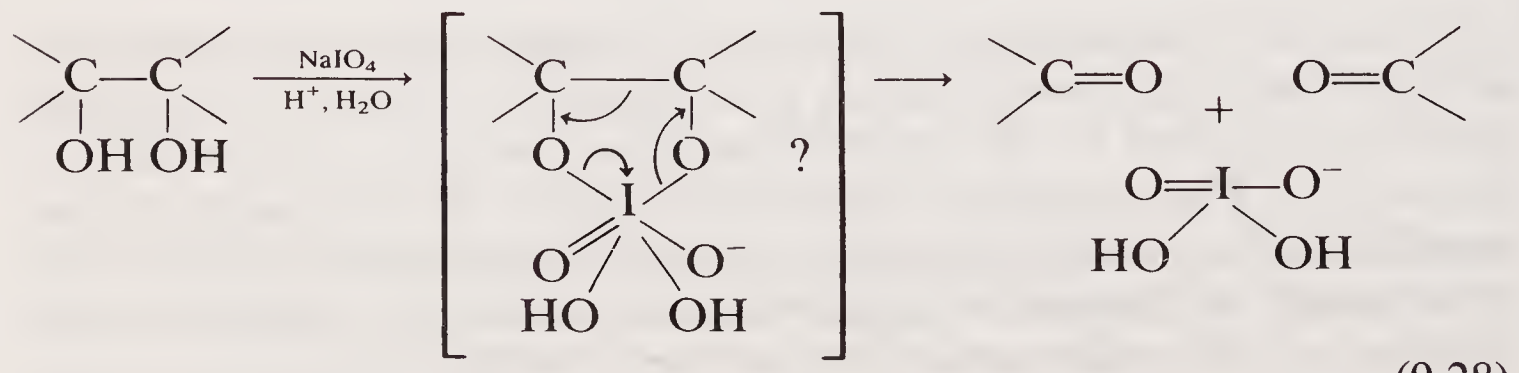
9.3.2 Oxidative cleavage of 1,2-diols

Mention has already been made (section 9.2.6) of the oxidative cleavage of alkenes by ozonisation, and of the (limited) use of this procedure in synthetic work. Alkenes may also undergo oxidative cleavage by hydroxylation to a diol and subsequent cleavage of the latter, although the usefulness of this as a synthetic tool is similarly limited.

The two classical methods for the cleavage of diols involve the use of **lead(IV) acetate** [reaction(9.27)] or **periodic acid** or one of its salts (e.g. **sodium metaperiodate**, $NaIO_4$) [reaction (9.28)]:

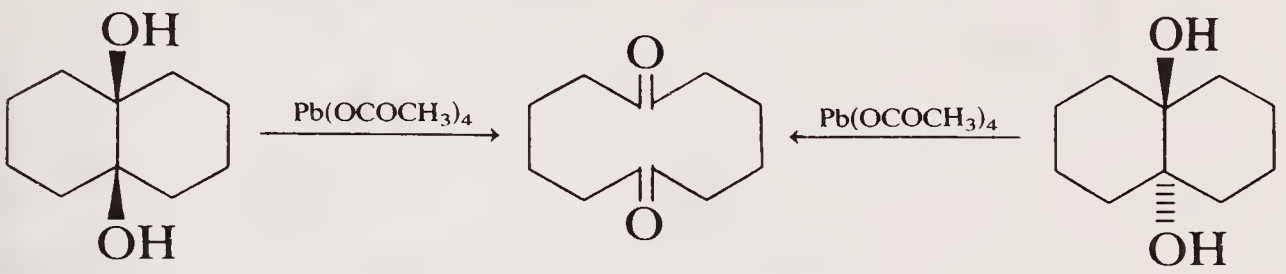


(9.27)

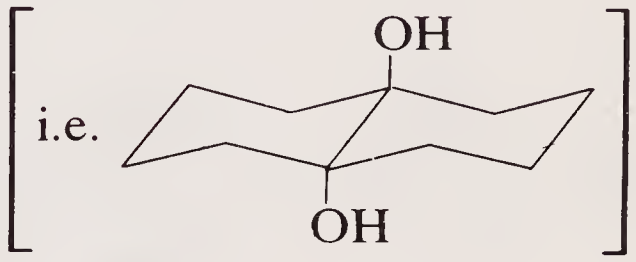


(9.28)

Both reactions involve cyclic intermediates, and thus diols in which the intermediate cannot be formed (e.g. a diaxial *trans*-diol in a ring system) are very resistant to cleavage. For example, the cleavage of (25) to cyclodecane-1,6-dione occurs 300 times faster than that of (26).



(25) (26)



Diol cleavage, like ozonisation, is used synthetically for ring opening (cf. section 7.4.2), to release a carbonyl function from a 'masked' group, and to produce synthetically useful materials from abundant natural products, e.g.

$$\textit{erythro}\text{-}CH_3(CH_2)_7CHOHCHOH(CH_2)_7CO_2H \xrightarrow[\text{ethanol}]{KIO_4,H_2SO_4}$$

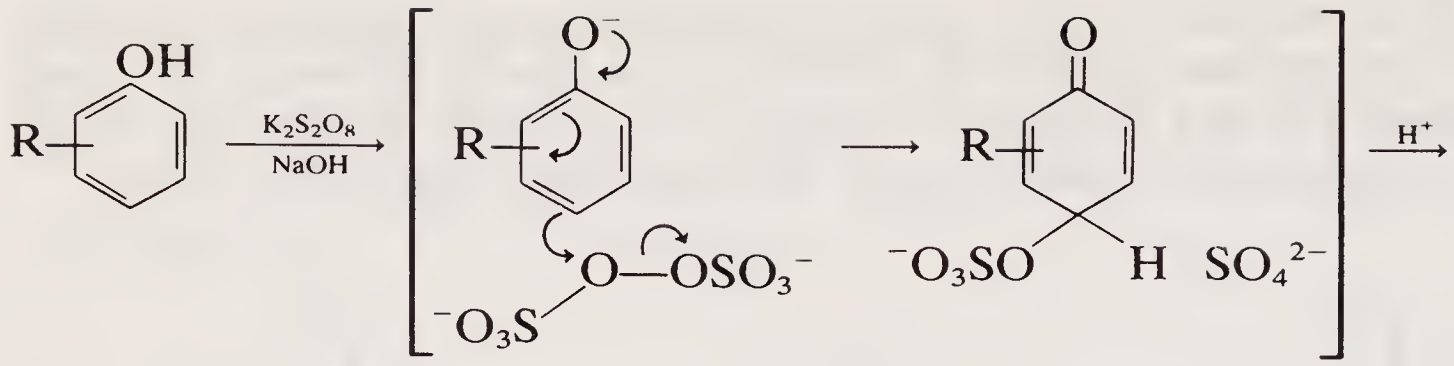
(from oleic acid: cf. p. 210)

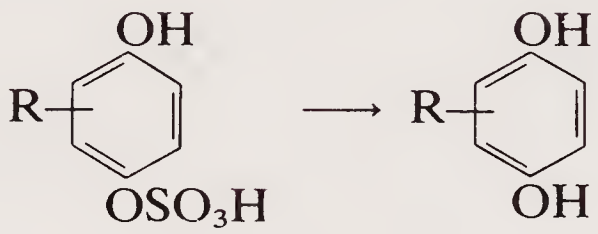
$$\underset{(89\ \%)}{CH_3(CH_2)_7CHO} + \underset{(76\ \%)}{OHC(CH_2)_7CO_2H}$$

9.4 Oxidation of phenols

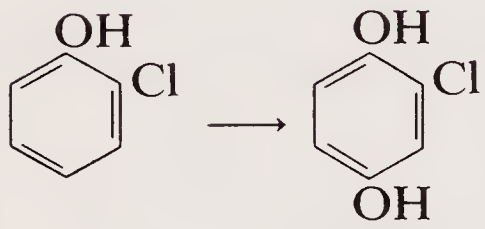
Two major features of the chemistry of phenols are the stabilisation of the phenoxide anion (and the phenoxy radical) by the adjacent aromatic ring, and the stabilisation of a positive charge on the ring by the hydroxyl group. The first of these results in the facile removal of the hydroxyl hydrogen (either as a proton or as a radical), and the second results in high reactivity (at the *ortho*- and *para*-positions) towards electrophiles (cf. section 2.5).

Both ionic and radical mechanisms are known for oxidations of phenols. The **Elbs reaction**, for example [reaction (9.29)] is probably an electrophilic substitution, and the oxidation with **Frémy's salt** (a stable free radical) is obviously a radical process [reaction (9.30)]:

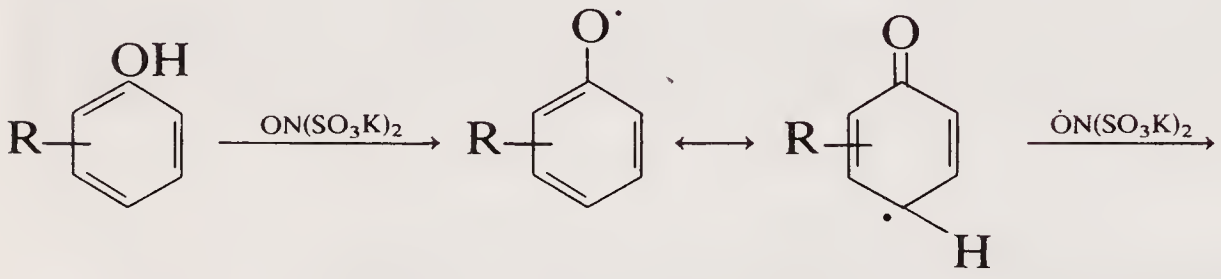


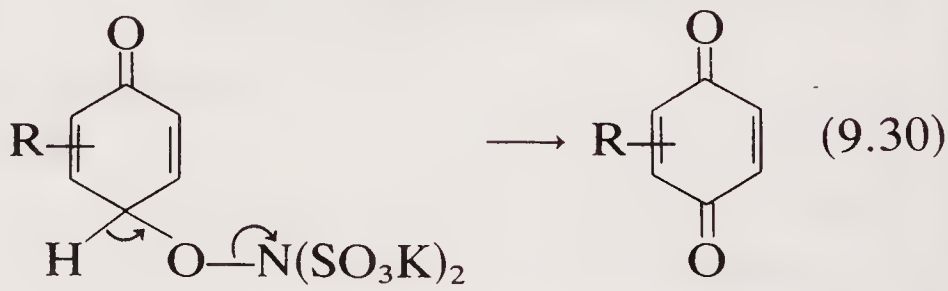


(9.29)

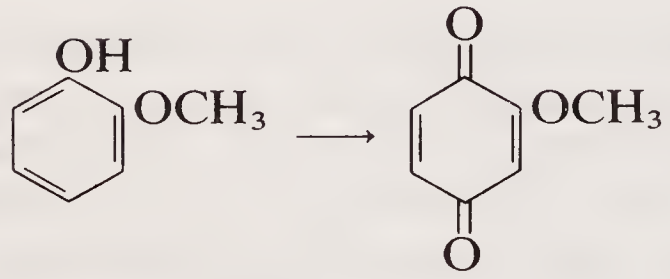
e.g. 

(50 %)

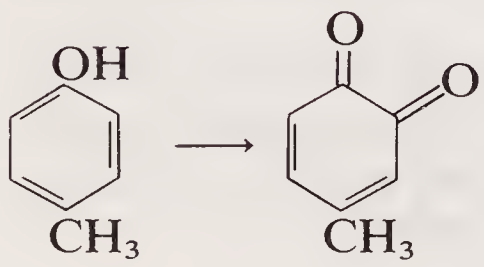




(9.30)

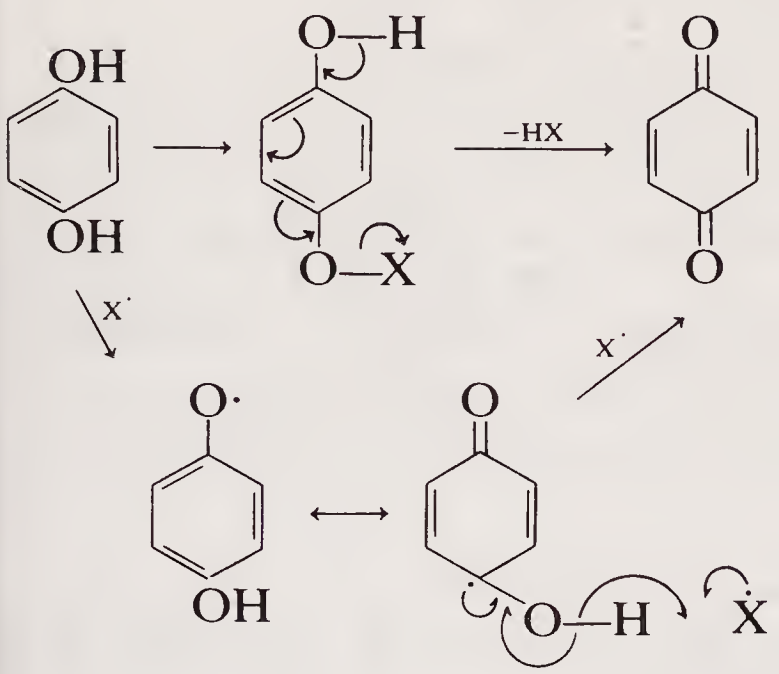
e.g. 

(90 %)



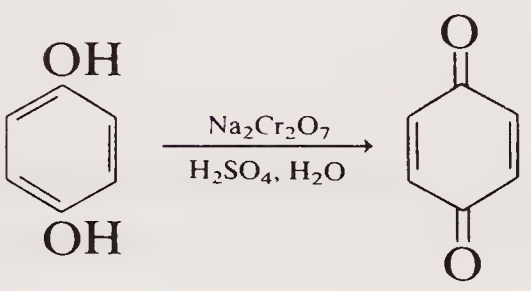
(71 %)

Oxidation of *o*- and *p*-dihydroxybenzenes to quinones is a relatively easy matter, whether by a substitution–elimination sequence or a radical process [reaction (9.31)]:



(9.31)

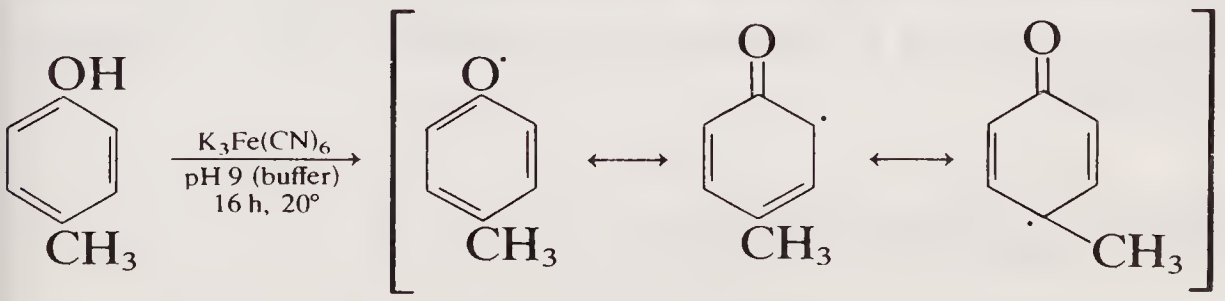
e.g.



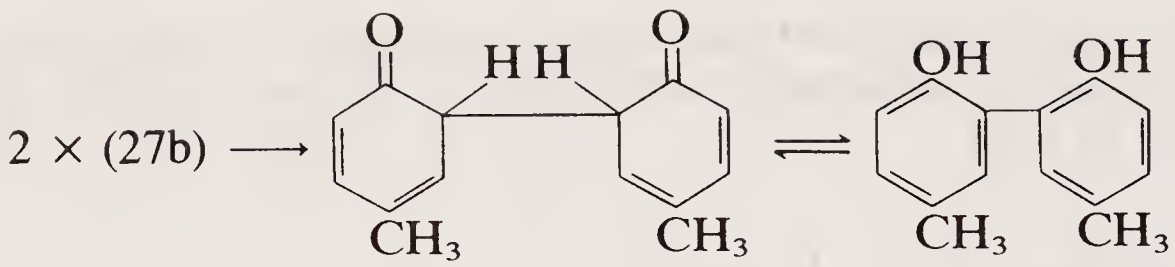
(76 %)

The corresponding oxidations of aminophenols similarly yield quinone-imines and hence quinones and ammonia.

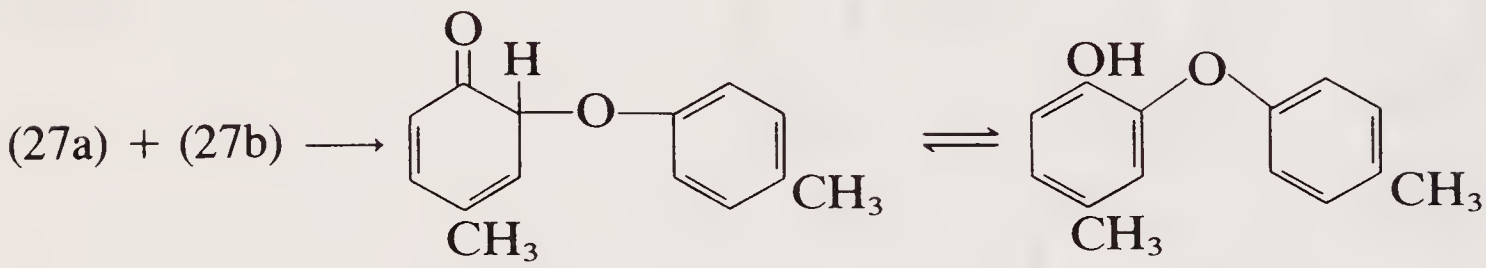
One-electron oxidation of phenoxide ions, very often using an iron(III) compound as oxidant, gives phenoxy radicals which may undergo coupling reactions. **Oxidative coupling**, as it is usually called, is an extremely important biosynthetic procedure,[5] but many *in vitro* examples are also known. It is rare for two phenoxy radicals to give a peroxide dimer; much more common is dimerisation by way of C–C bond formation. Both symmetrical and unsymmetrical dimers are obtainable, but these may themselves be highly reactive and undergo further transformations. For example,



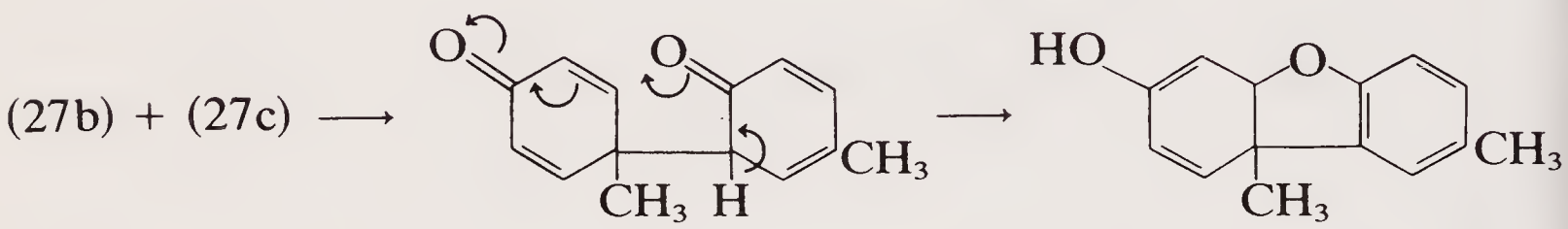
(27a) (27b) (27c)

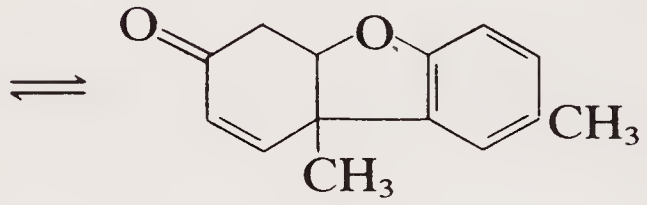


(28)



(29)





(28) : (29) : (30) = 52 : 7 : 41

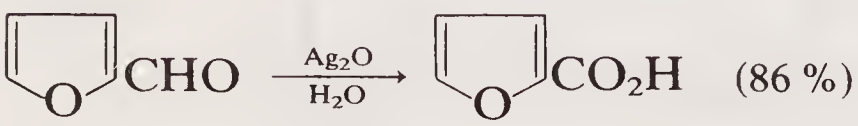
(30)

The product ratio depends on temperature, concentration, solvent and the particular oxidant used.

9.5 Oxidation of aldehydes and ketones

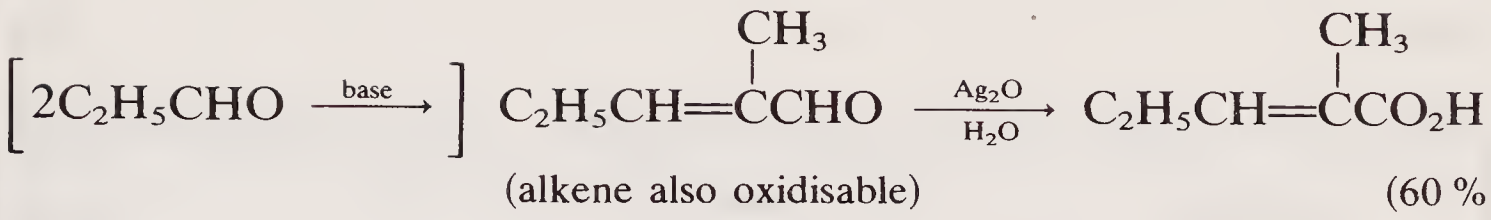
9.5.1 Oxidation to carboxylic acids

We have already referred (section 9.3.1) to the oxidation $RCH_2OH \rightarrow RCHO \rightarrow RCO_2H$ with which most students should be familiar. Aldehydes themselves are very easily oxidised, by chromic acid or potassium permanganate (with or without added acid), by molecular oxygen, or by mild oxidants such as silver oxide: this last-named is usually the reagent of choice if the molecule contains other oxidisable groups. For example,



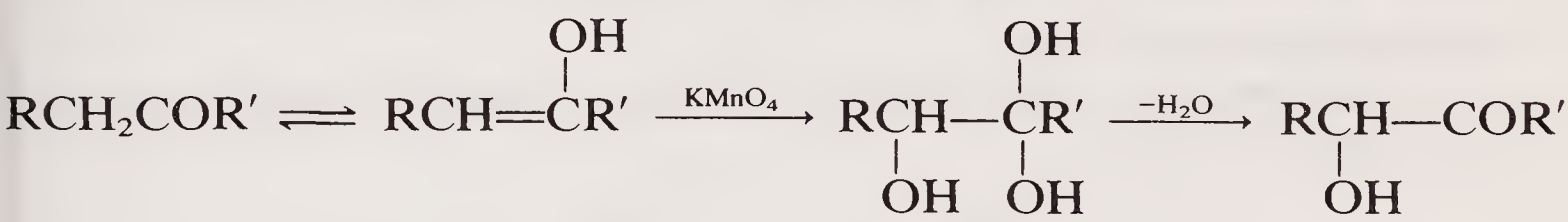
(86 %)

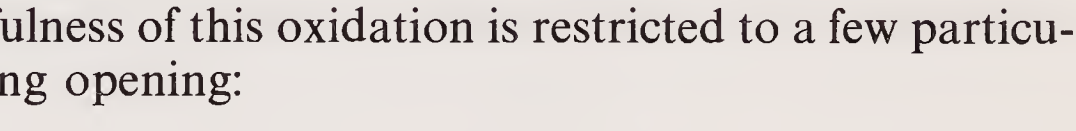
(acid-sensitive)



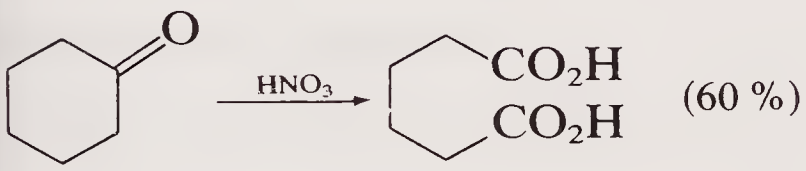
Under more vigorous oxidising conditions, side-reactions [especially cleavage: cf. reaction (9.32)] may intervene, and attempts to oxidise primary alcohols to carboxylic acids in a 'one-pot' reaction are similarly subject to side-reactions (e.g. $RCH_2OH \rightarrow RCO_2H$; $RCH_2OH + RCO_2H \rightarrow RCO_2CH_2R$).

Oxidation of ketones to carboxylic acids necessarily involves C–C bond cleavage. In many cases, the reaction apparently involves the enol (or enolate) as intermediate [e.g. reaction (9.32)]:

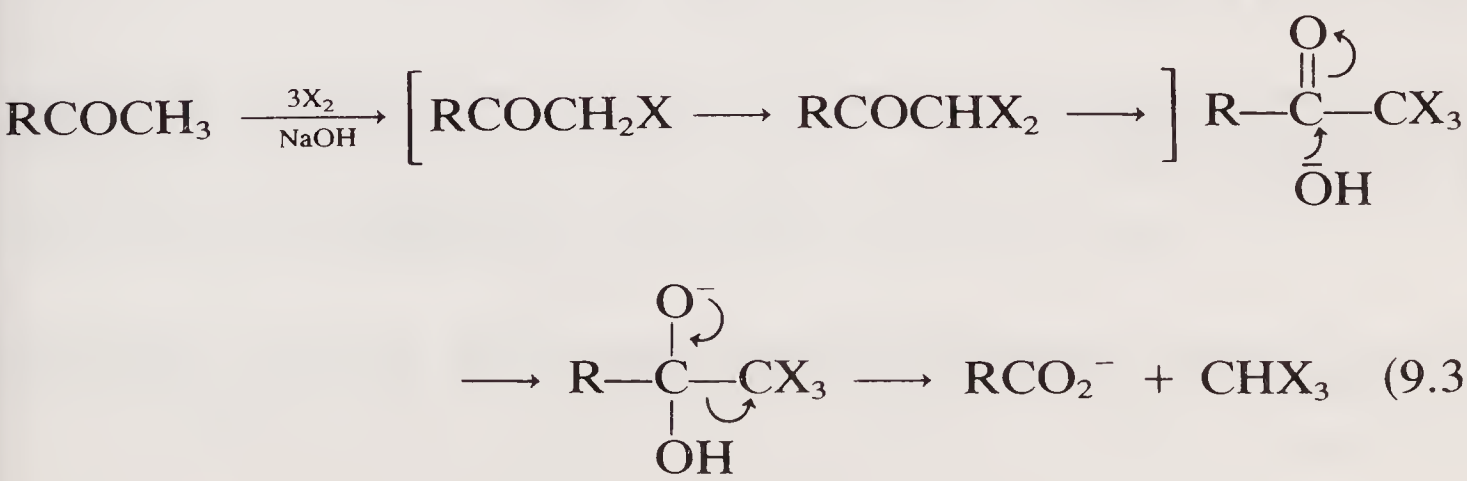




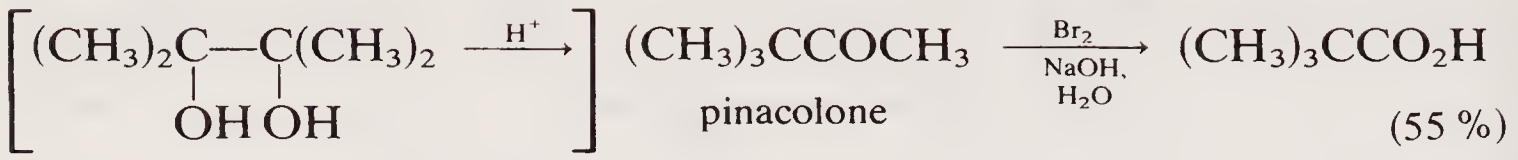
The synthetic usefulness of this oxidation is restricted to a few particular situations, e.g. ring opening:

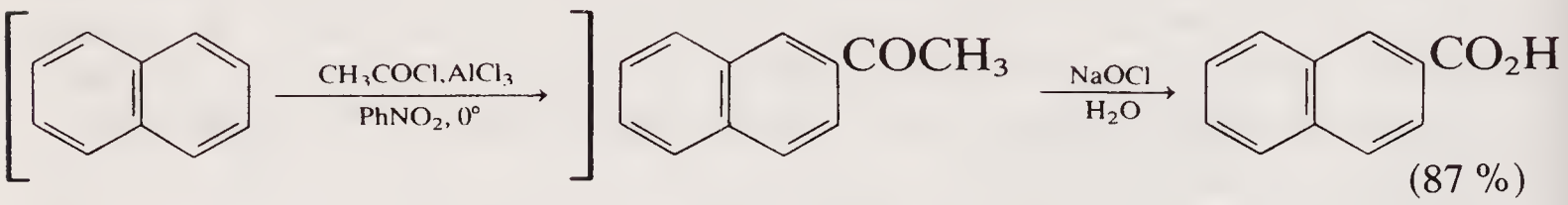


Methyl ketones, on the other hand, may be converted into carboxylic acids under mild conditions by the **haloform reaction** (Sykes, pp. 296–7). Base-catalysed halogenation is followed by an addition–elimination sequence. The reaction $RCOCH_3 \rightarrow RCO_2H$ [reaction (9.33)] succeeds only if the group R is not itself halogenated under these conditions.



e.g.

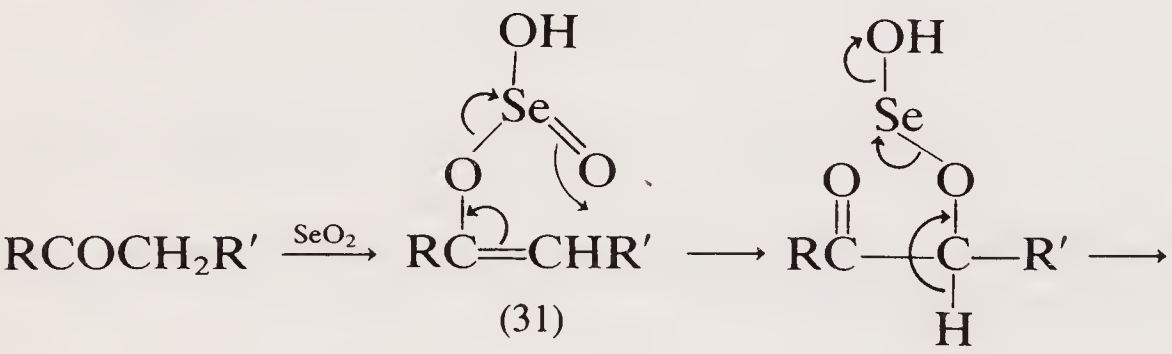




9.5.2 Oxidation to 1,2-dicarbonyl compounds

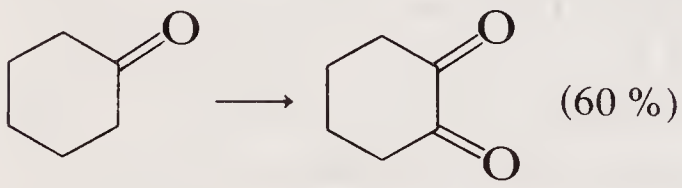
Oxidation of an 'active methylene' group to carbonyl is usually carried out by one of three routes; the enol or enolate is again involved as an intermediate in each case.

(i) *Selenium (IV) oxide oxidation* [which probably proceeds *via* the enol selenite (31)]:



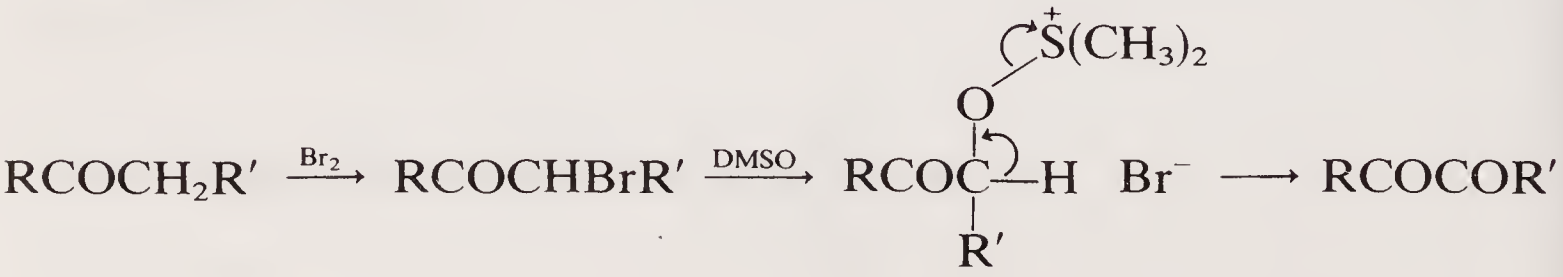
e.g.

$PhCOCH_3 \rightarrow PhCOCHO$ (72 %)

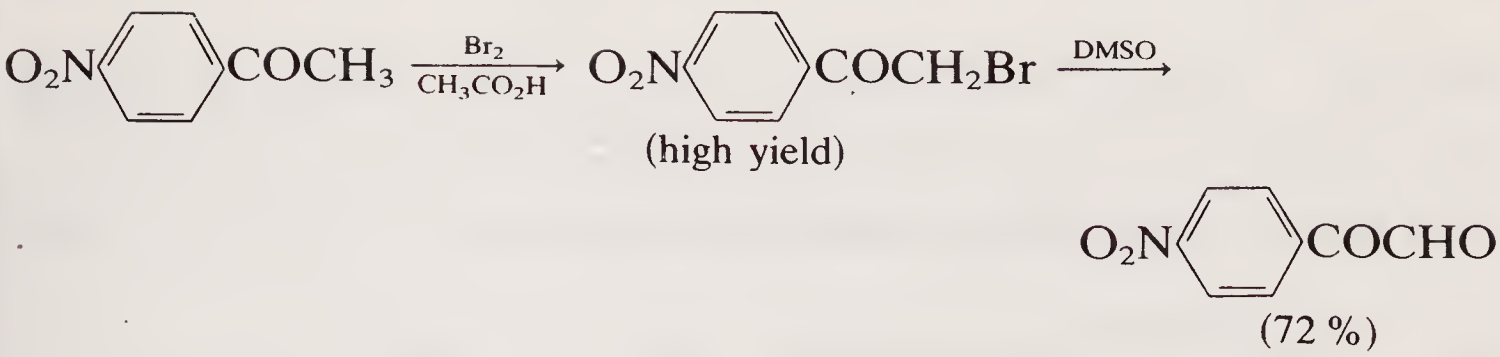


$CH_3COCH_2COCH_3 \rightarrow CH_3(CO)_3CH_3$ (29 %)

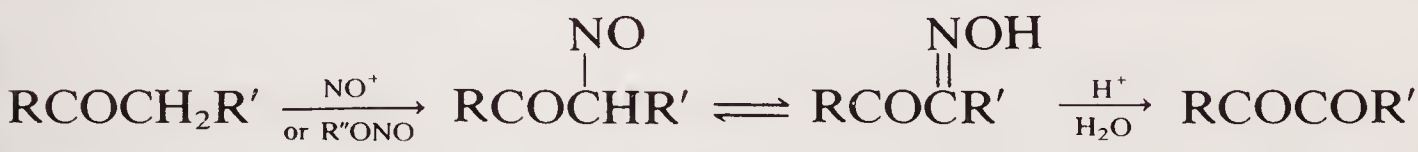
(ii) *Monohalogenation* followed by *reaction with dimethyl sulphoxide* (cf. section 9.3.1.1):



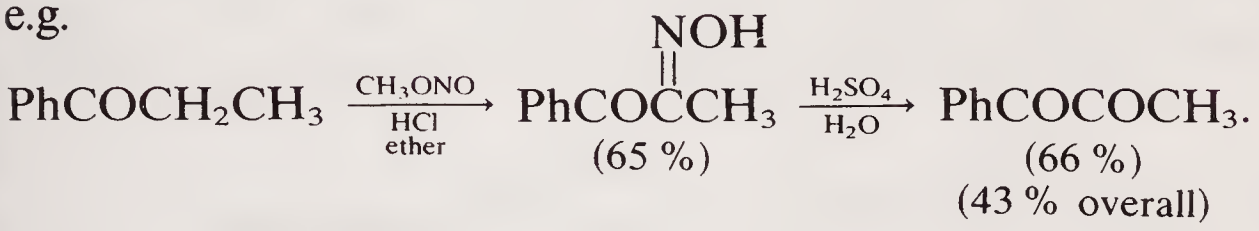
e.g.



(iii) *Nitrosation* followed by *hydrolysis* (cf. section 6.3.3):

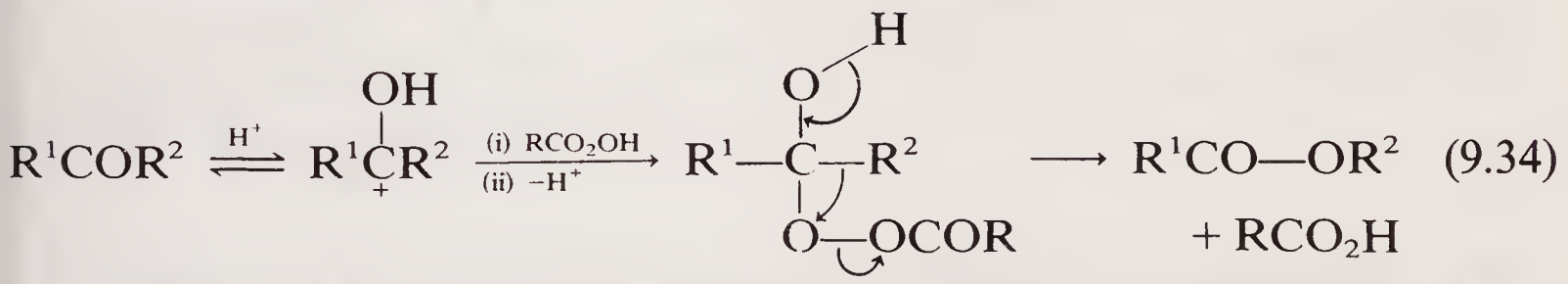


e.g.

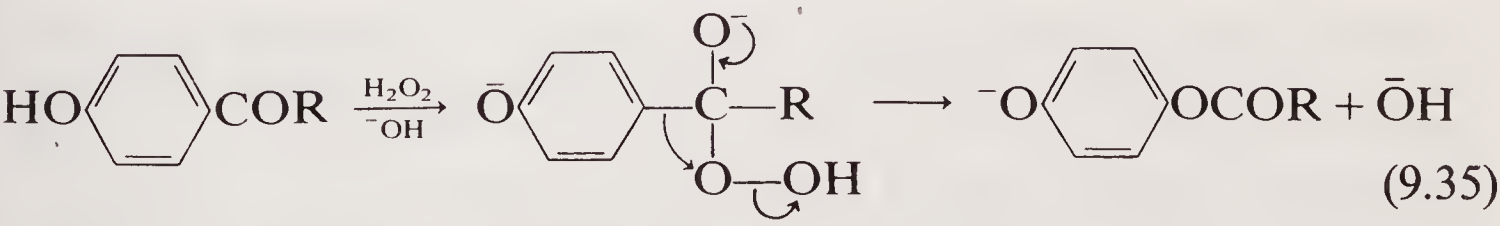


9.5.3 Oxidation to esters: the Baeyer–Villiger and Dakin reactions

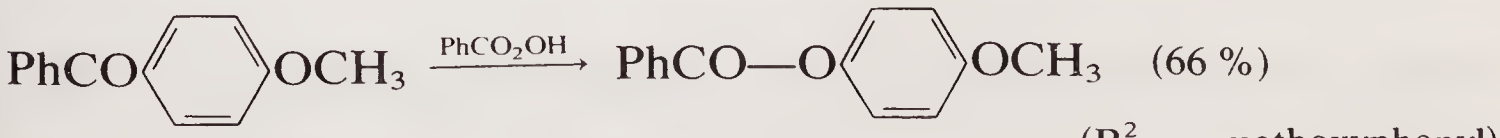
The **Baeyer–Villiger oxidation** involves the reaction of a ketone with hydrogen peroxide or a peroxy-acid [reaction (9.34): cf. Sykes, pp. 127–8] to give an ester:



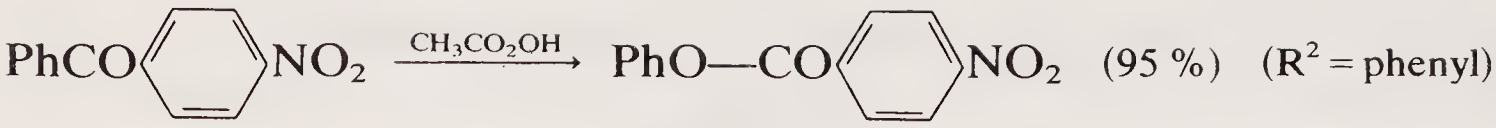
The **Dakin reaction**, although similar, is more restricted in application [reaction (9.35)]:



It should be noted that in the Baeyer–Villiger reaction, as in other molecular rearrangements of this type, the group which migrates (R^2 in the equation) is the more nucleophilic of the two; thus:



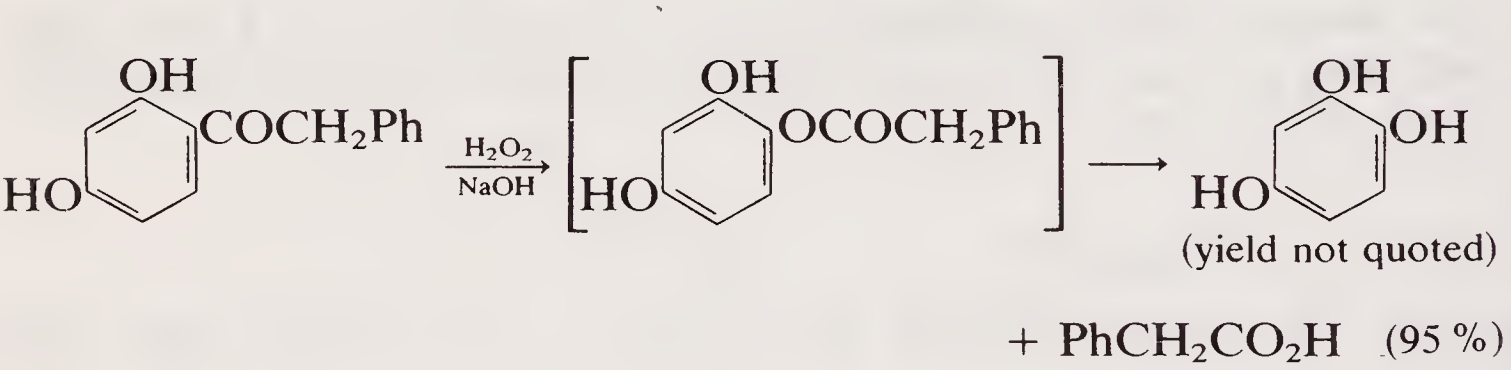
whereas



Aryl groups migrate more readily than alkyl, e.g.

and a secondary alkyl more readily than a primary alkyl, e.g.

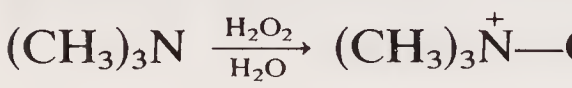
Examples of the Dakin reaction include:

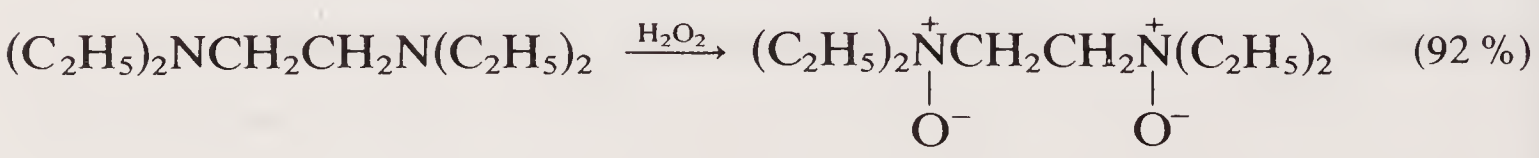


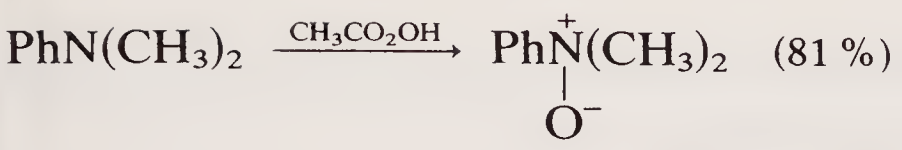
9.6 Oxidation of functional groups containing nitrogen

9.6.1 Formation of *N*-oxygenated compounds

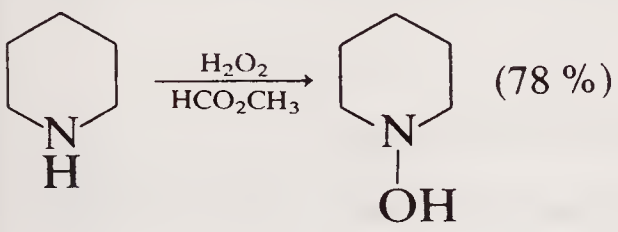
Amines, being nucleophilic, react with sources of electrophilic oxygen such as peroxy-acids to produce *N*-oxygenated compounds. The most familiar example of such reactions involve the formation of *N*-oxides from heteroaromatic tertiary amines such as pyridine (cf. section 2.6). *N*-Oxide formation, however, is a characteristic reaction of tertiary amines in general, e.g.



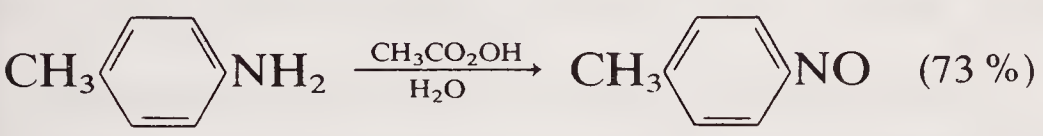




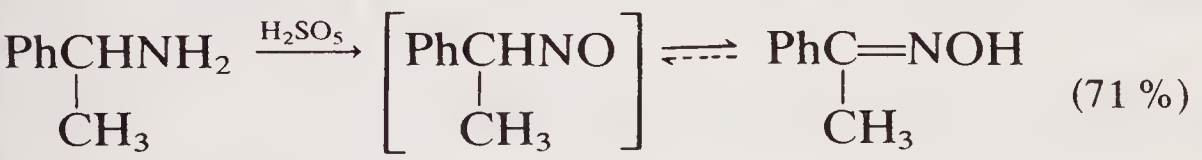
In the case of secondary amines, *N*-oxidation is followed by proton transfer, and the product is a hydroxylamine. Yields are not uniformly high, but in some cases are synthetically acceptable, e.g.

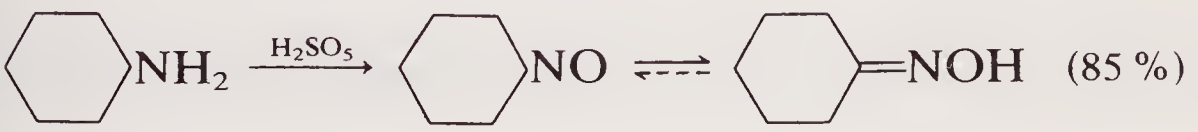


In the case of primary amines, the reaction is somewhat more complicated, since the hydroxylamine itself undergoes *N*-oxidation [$RNH_2 \rightarrow RNHOH \rightarrow RN(OH)_2 \xrightarrow{-H_2O} RNO$], e.g.

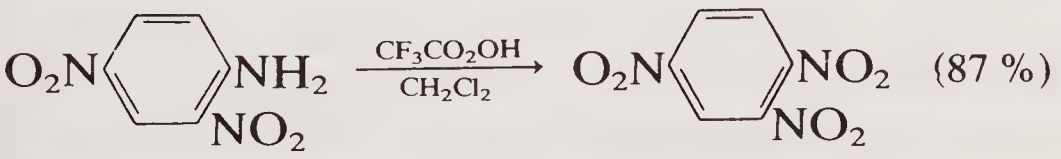


If the nitroso-compound contains an α-hydrogen it may undergo tautomerisation to an oxime, e.g.

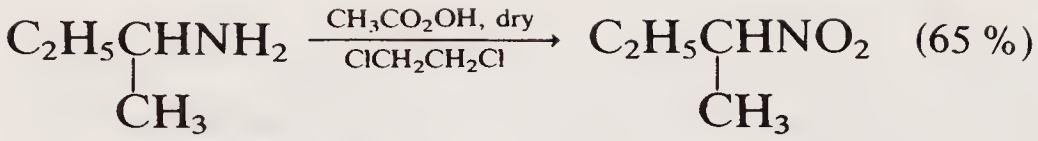




The use of peroxytrifluoroacetic acid, or *anhydrous* peroxyacetic acid, can lead to *N*-oxidation even of the nitroso-compound, and to the formation of a nitro-compound. This reaction can be useful for the preparation of unusually substituted nitroarenes, e.g.

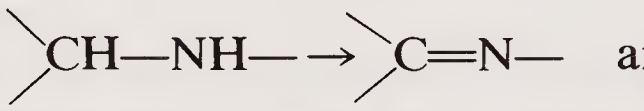
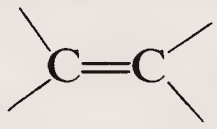
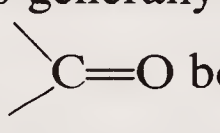


Also:

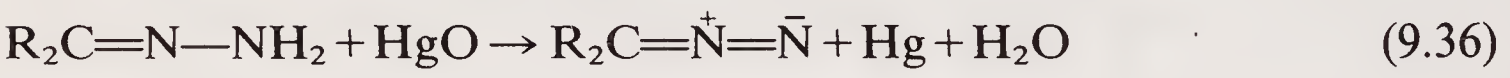


[but $CH_3(CH_2)_5NH_2 \xrightarrow{CF_3CO_2OH}$ only $CH_3(CH_2)_5NHCOCF_3$ (80 %)]

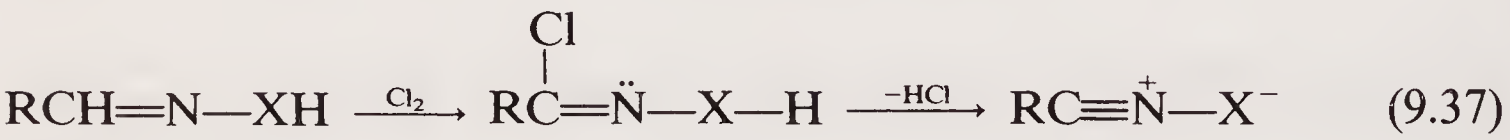
9.6.2 Dehydrogenation involving nitrogen functions

This general heading embraces a large number and wide variety of reactions. Oxidations of the type  are well known, especially if the new double bond forms part of a conjugated system, but these are much less generally used than the corresponding reactions giving  and  bonds. Dehydrogenation of the type —NH—OH → —N=O has been referred to in the preceding section. The catalytic dehydrogenation of hydrazine to nitrogen may be used to provide hydrogen for hydrogenation; the intermediate dehydrogenation product, di-imide, also serves as a reducing agent (section 8.4.1). Oxidation of 1,2-disubstituted hydrazines produces azo-compounds (RN=NR′).

Hydrazones of the type $R_2C{=}NNH_2$ are oxidised to diazoalkanes by reagents such as mercury(II) oxide [reaction (9.36)], and substitution–elimination sequences lead to the dehydrogenation of arylhydrazones and oximes to give 1,3-dipolar species [reaction (9.37): cf. section 7.2.2]:



(9.36)



(9.37)

(X = O or NAr)

9.7 Oxidation of functional groups containing sulphur

9.7.1 Thiols

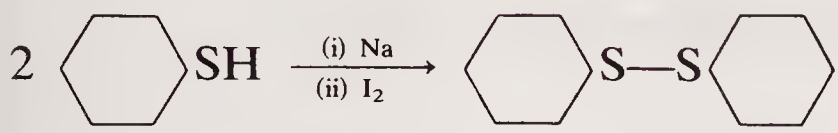
Thiols, unlike alcohols, readily undergo oxidative coupling to give disulphides, i.e. 2RSH → RS—SR. Oxidation may occur simply in air, or by the action of oxidants such as halogens, hydrogen peroxide, or iron(III)

salts. Both radical and electrophile–nucleophile interactions may be involved, e.g.

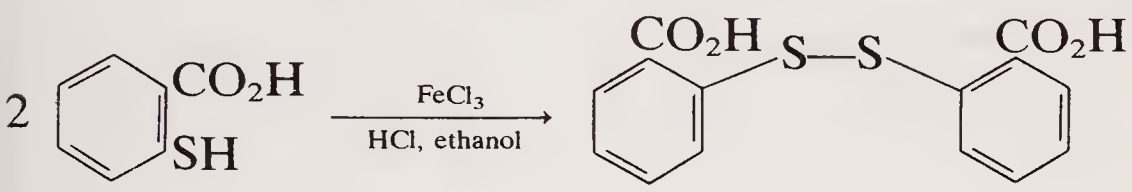
$$RSH \xrightarrow[\text{or } Fe^{3+}]{O_2} RS^{\cdot}; \quad 2RS^{\cdot} \rightarrow RS{-}SR$$

$$RSH \xrightarrow{X_2} R{-}S{-}X \longrightarrow R{-}S{-}\overset{+}{S}(H)(R)\ X^{-} \longrightarrow RS{-}SR + HX$$

Examples include:



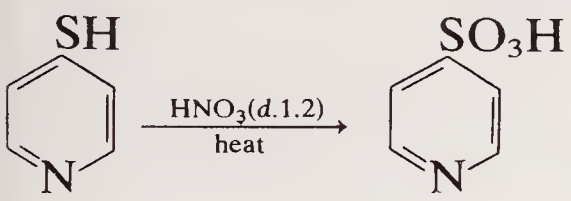
(yield not quoted)



(quantitative)

More powerful oxidising agents convert thiols directly into sulphonic acids, e.g.

$$CH_3(CH_2)_{15}SH \xrightarrow[H_2O]{KMnO_4} CH_3(CH_2)_{15}SO_3H \quad (36\ \%)$$



(60 %)

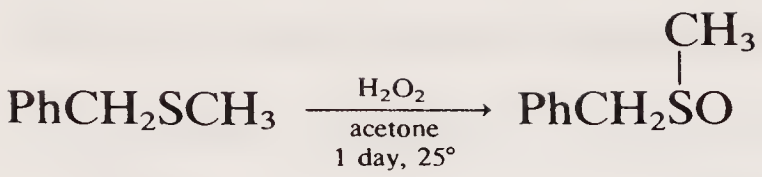
9.7.2 Sulphides

These react with sources of electrophilic oxygen, e.g. peroxyacids, in the same manner as amines, i.e.

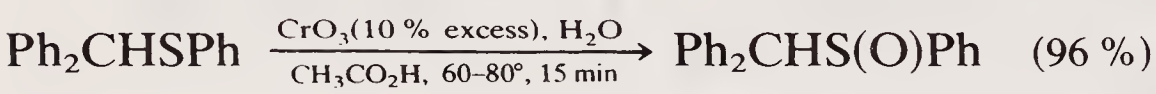
$$R_2S \rightarrow R_2\overset{+}{S}-\bar{O}(\leftrightarrow R_2S{=}O) \rightarrow R_2\overset{+}{S}(O^{-}){=}O\ (\leftrightarrow R_2S(=O){=}O).$$

The first oxidation step, giving the sulphoxide, is often considerably faster than the second, which gives the sulphone, and many sulphoxides may thus be prepared by this route, e.g.

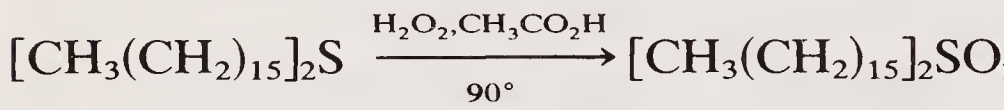
$$Ph_2S \xrightarrow[4\text{ days},25^{\circ}]{H_2O_2,CH_3CO_2H} Ph_2SO \quad \text{(quantitative)}$$

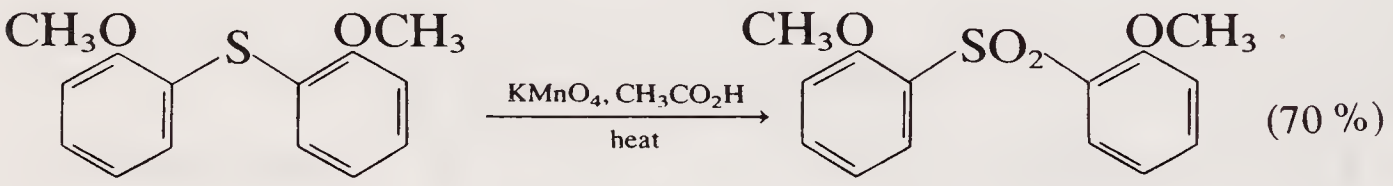


Other oxidants may also be used, provided that the reaction conditions are carefully controlled to prevent over-oxidation, e.g.



More vigorous reaction conditions lead directly to sulphones, e.g.

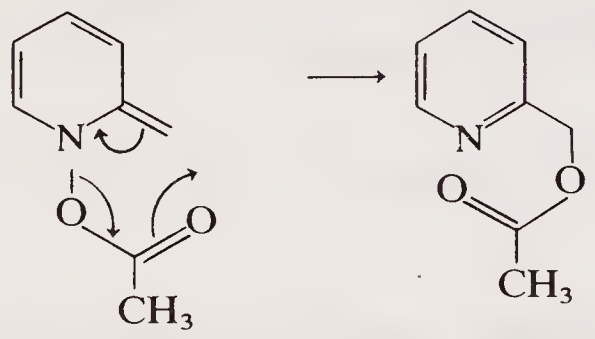




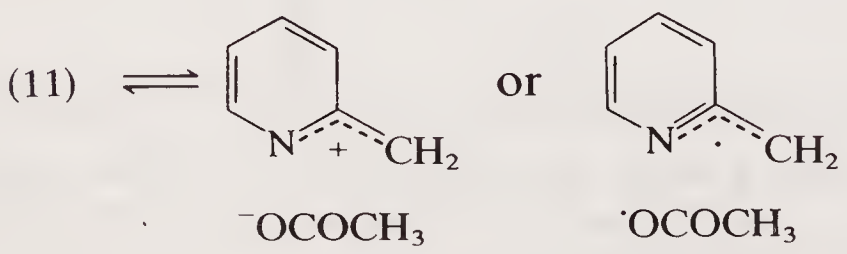
Notes

1. A literature report that oxidation of ethylbenzene under these conditions gives phenylacetic acid could not subsequently be confirmed [D. G. Lee and U. A. Spitzer, *J. Org. Chem.*, **34,** 1493 (1969)].

2. The conversion of (11) into the final product may be represented as an analogue of the Cope rearrangement (section 7.4.3):

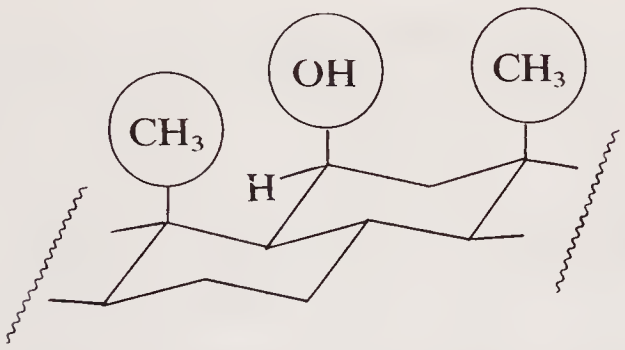


but it is more likely to involve cleavage of the N–O bond in (11) to give an ion-pair or a radical pair:



3. Peroxybenzoic acid is usually made from dibenzoyl peroxide and methanol followed by acid hydrolysis.

4. The axial alcohol (24) is sterically hindered by the two angular methyl groups: the bulkier DMSO/DCC and DMSO/SO_3 reagents do not therefore effect this oxidation.



(24)

5. See for example, J. Mann, *Secondary Metabolism*, Oxford University Press, Second Edition, 1987, pp. 60–2, 223 and 230–3.

10 Protective groups

This chapter aims to set out the principal features of the use of protective groups in synthetic sequences. It is not intended to be a comprehensive treatment of the topic but rather some illustrative examples will be considered.

10.1 The strategy

In a synthetic sequence, it is frequently necessary to carry out a transformation at one centre while another reactive site remains unchanged. Two principal techniques[1] are used to achieve this purpose. One, to which reference has been made in most, if not all, of the remaining chapters, involves the careful choice of a selective reagent and/or of reaction conditions. The other, which we shall now describe in some detail, involves the temporary modification of the site at which reaction is undesirable in such a manner that it remains intact during reaction at the other site and at the end of the reaction sequence the original group can be easily regenerated. The group modifying the functional group is known as the **protective group.**

Thus we can make the following specification for an ideal protective group:

(i) the group should be introduced under mild conditions;
(ii) the group should be stable under the reaction conditions necessary to carry out transformations at other centres in the compound;
(iii) the group should be removed under mild conditions.

In some instances, this last condition can be relaxed to allow the protected group to be converted directly into another functional group. We shall now show how these specifications can be satisfied by considering the case of protection of hydroxyl groups. Protection of the amino and carbonyl groups will also be dealt with briefly. Further examples will be found in Chapter 16.

10.2 Protection of alcohols

10.2.1 Ether formation

In general, ethers are stable under neutral and alkaline conditions and to most oxidising agents. While methyl and ethyl ethers are readily formed [e.g. scheme 10.1, (1) → (2), (3) → (4)], they are not normally easily removed. Exceptions to this do, however, occur in carbohydrate chemistry. Methyl ethers at C-1, which are in fact *acetals*, are readily hydrolysed [e.g. scheme 10.1, (4) → (5)]. Lewis acids such as boron trichloride can be used to cleave methyl ethers [e.g. scheme 10.1, (10) → (11)].

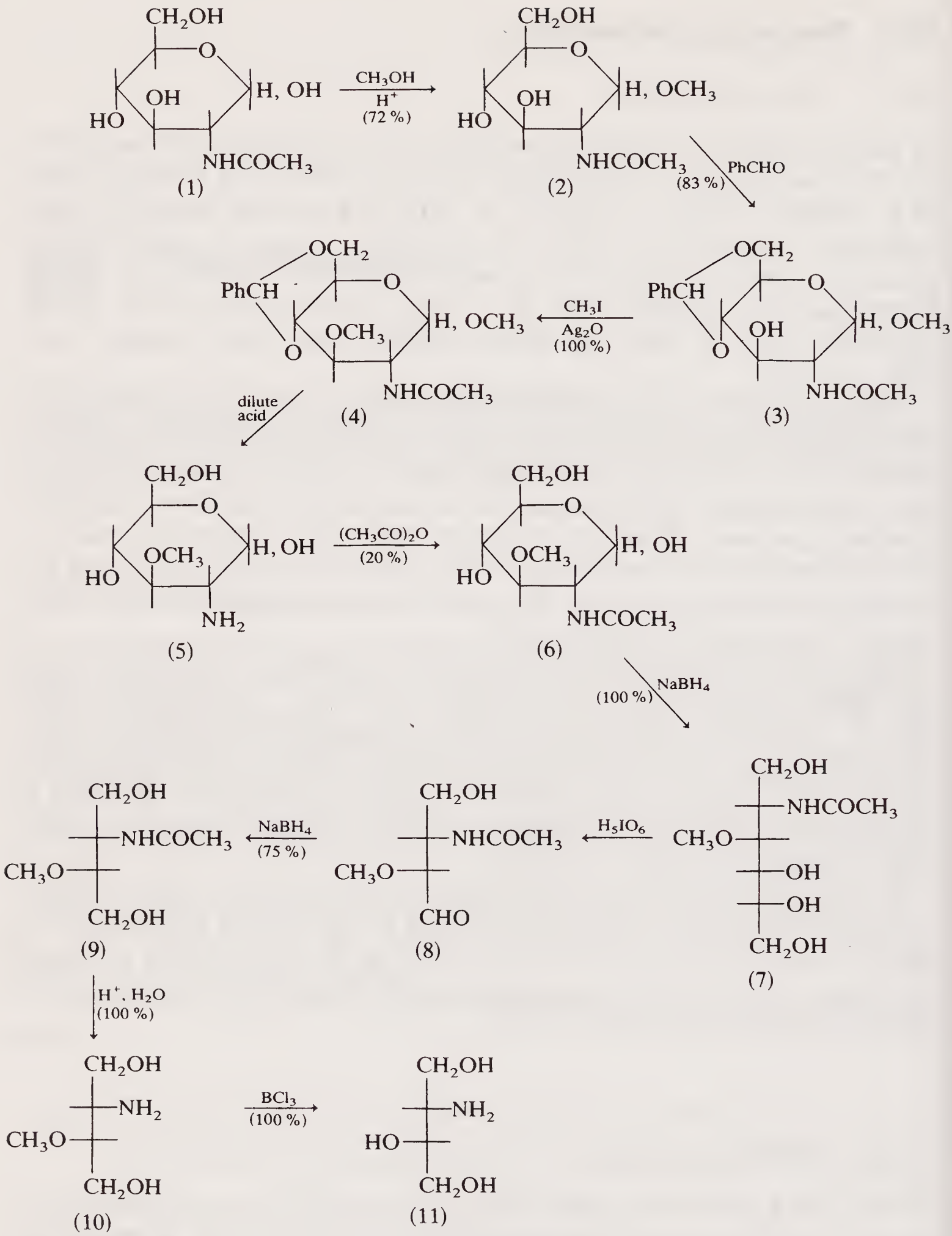
More commonly used derivatives are benzyl, trityl (triphenyl methyl), tetrahydropyranyl, and trialkylsilyl ethers. The last mentioned, as the trimethyl derivatives, have been widely used in gas chromatographic and mass spectroscopic applications but are too easily hydrolysed for most synthetic purposes. Recently, however, bulky silyl derivatives such as t-butyldimethyl have been found to be somewhat more stable than the trimethyl derivatives and can be used in situations where selective protection is desired (cf. section 13.6].

Benzyl and trityl ethers are formed by treatment of the alcohol with the appropriate halide in presence of base [e.g. scheme 10.2, (12) → (13)]. The hydroxyl group can be regenerated by hydrogenolysis or, in the case of trityl ethers, by mild acid treatment [e.g. scheme 10.2 (14) → (15), (19) → (20)]. Since tritylation of hindered alcohols is much slower than that of primary alcohols, selective protection is possible [scheme 10.2, (12) → (13)].

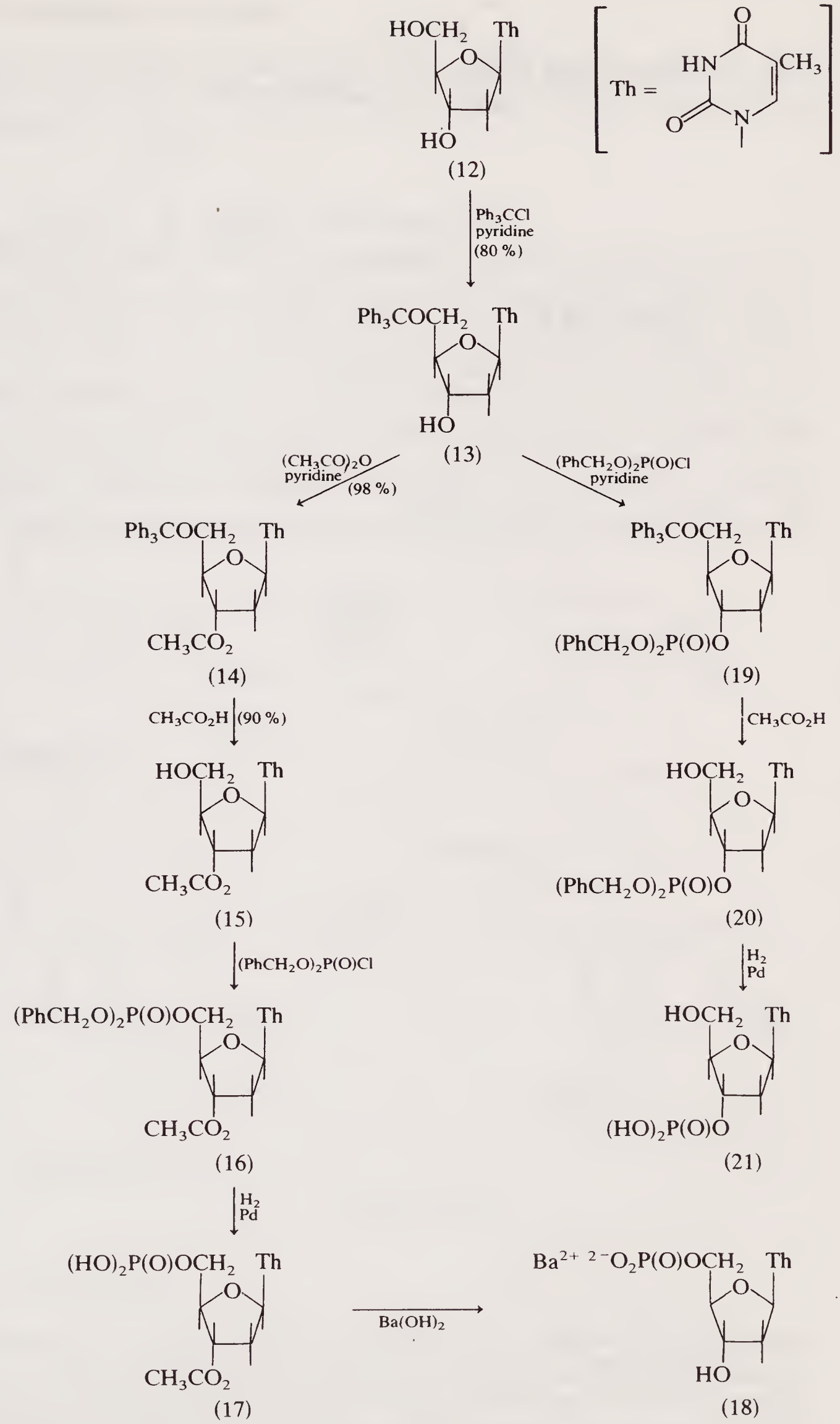
Tetrahydropyranyl ethers are formed from the alcohol and 2,3-dihydropyran under acid catalysis. The alcohol is regenerated with dilute sulphuric acid. Alcohols are often protected in this way during reactions involving organometallic compounds when the protective group is often lost in the work-up (scheme 10.3).

10.2.2 Ester formation

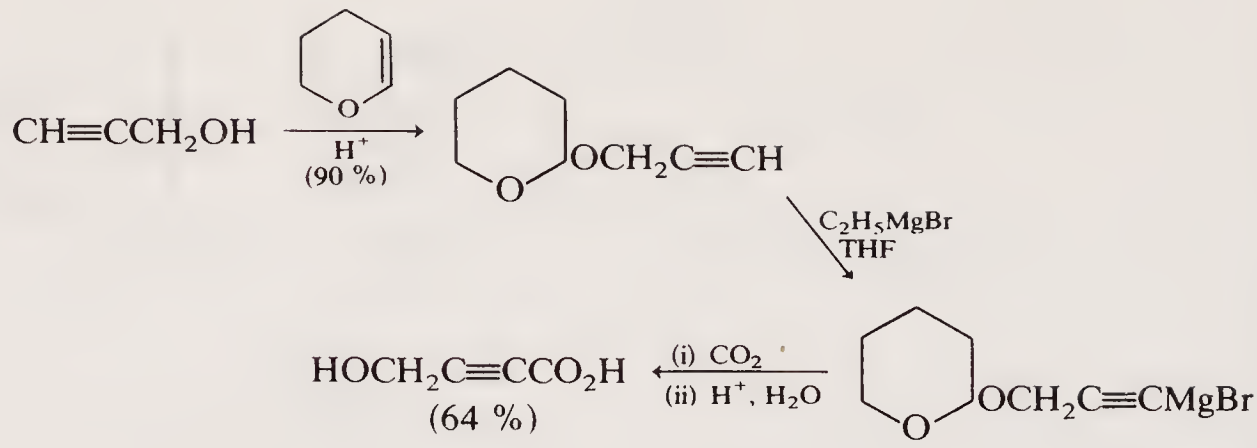
Esters, being reasonably stable under acidic conditions, are often used to protect hydroxyl groups during nitration, oxidation and formation of acid chlorides. Acetates and trifluoroacetates are usually formed by treatment of the alcohol with the appropriate anhydride or acid chloride in presence of base [scheme 10.2, (13) → (14)]. Formates are prepared by use of formic acid in presence of perchloric acid. The alcohol is regenerated by treatment with base [scheme 10.2, (17) → (18), scheme 10.4] but in the case of trifluoroacetates, water is often sufficient.


CH2OH
O
OH
HO
H, OH
NHCOCH3
(1)
CH3OH
H+
(72 %)
H, OCH3
(2)
PhCHO
(83 %)
OCH2
PhCH
(3)
CH3I
Ag2O
(100 %)
OCH3
(4)
dilute acid
NH2
(5)
(CH3CO)2O
(20 %)
(6)
NaBH4
(100 %)
(7)
(8)
(9)
H+, H2O
(100 %)
BCl3
(100 %)
(10)
(11)

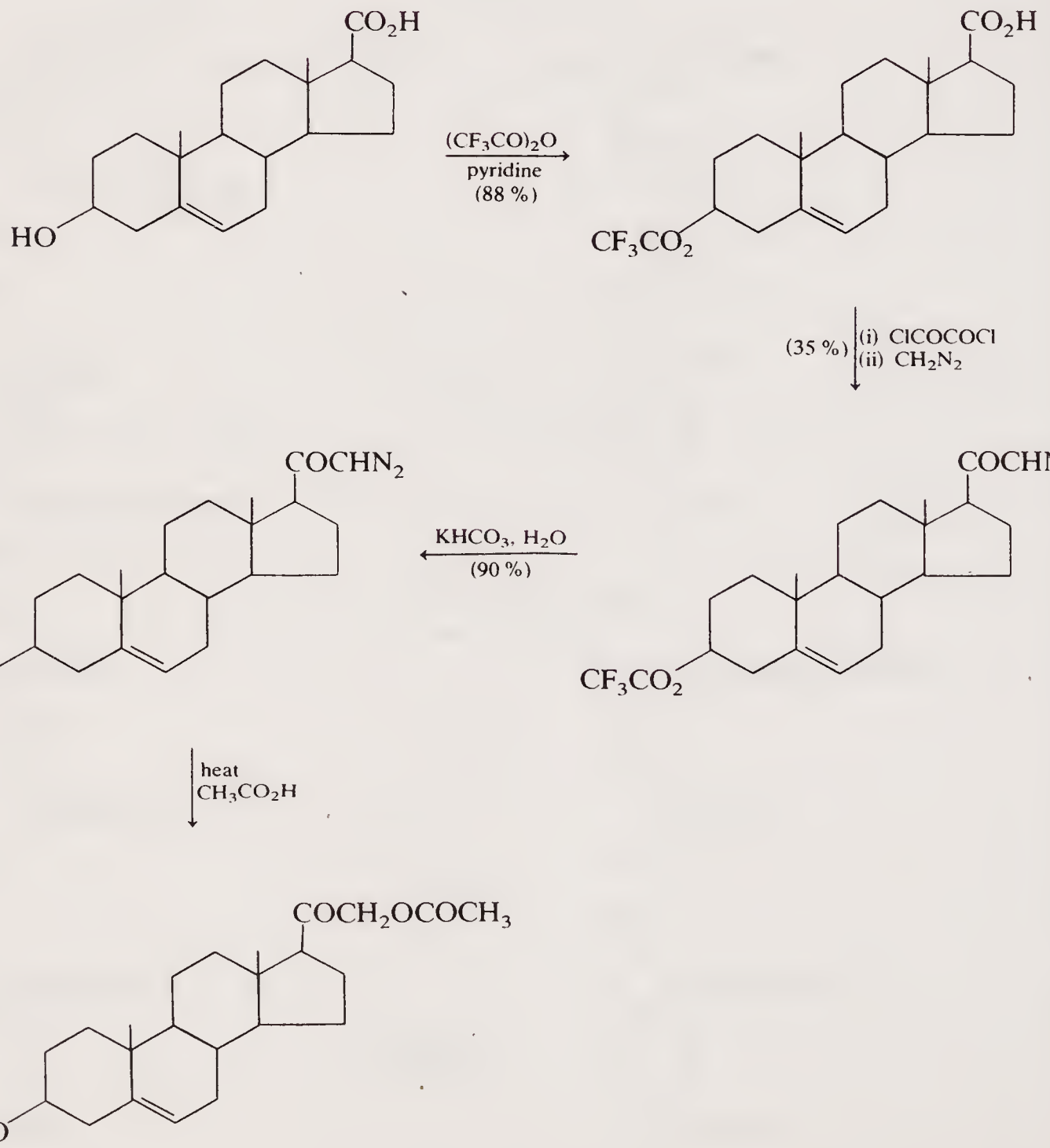
Scheme 10.1


HOCH2 Th
O
HO
(12)
Th =
HN
O
CH3
O
N
Ph3CCl
pyridine
(80 %)
Ph3COCH2 Th
O
HO
(13)
(CH3CO)2O
pyridine
(98 %)
(PhCH2O)2P(O)Cl
pyridine
Ph3COCH2 Th
O
CH3CO2
(14)
Ph3COCH2 Th
O
(PhCH2O)2P(O)O
(19)
CH3CO2H (90 %)
CH3CO2H
HOCH2 Th
O
CH3CO2
(15)
HOCH2 Th
O
(PhCH2O)2P(O)O
(20)
(PhCH2O)2P(O)Cl
H2
Pd
(PhCH2O)2P(O)OCH2 Th
O
CH3CO2
(16)
HOCH2 Th
O
(HO)2P(O)O
(21)
H2
Pd
(HO)2P(O)OCH2 Th
O
CH3CO2
(17)
Ba(OH)2
Ba2+ 2−O2P(O)OCH2 Th
O
HO
(18)

Scheme 10.2



Scheme 10.3



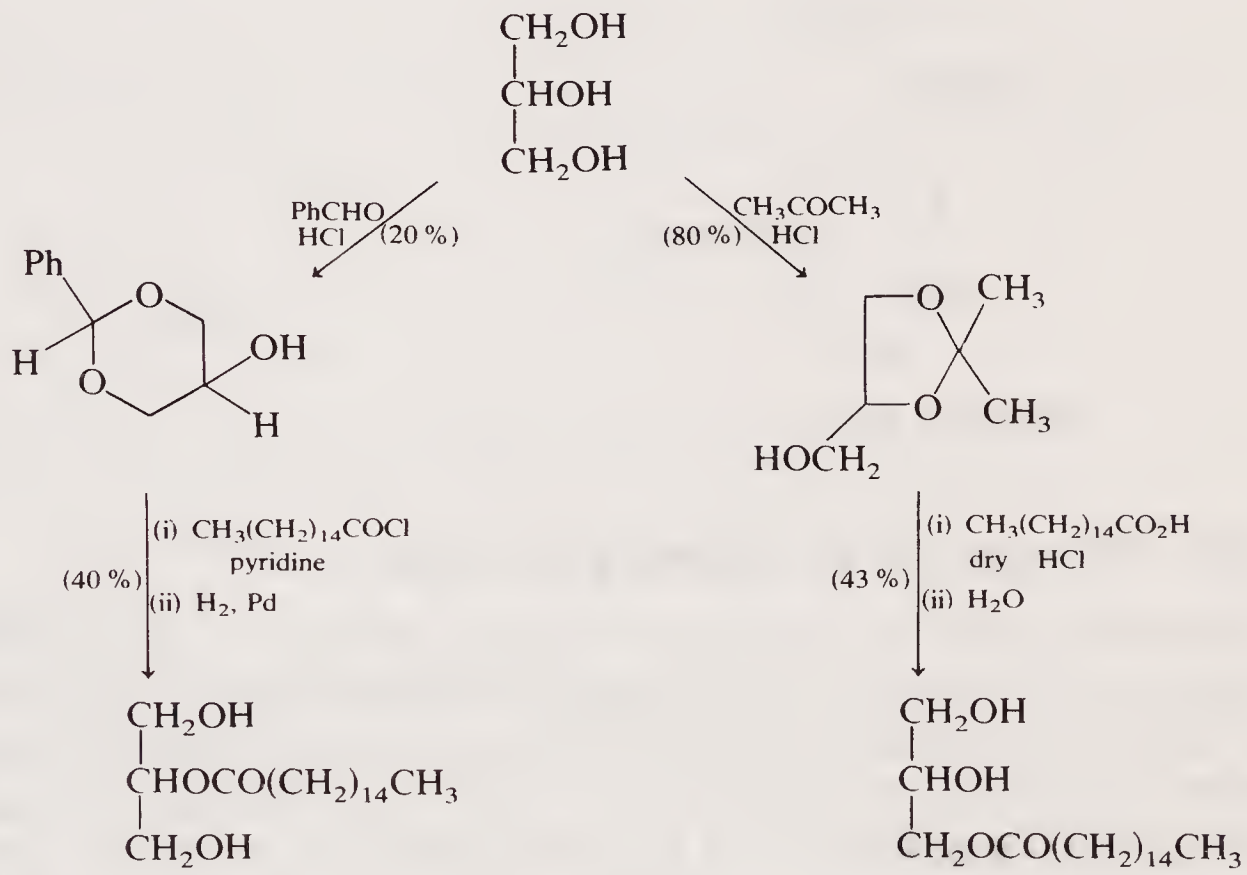
Scheme 10.4

10.3 Protection of diols

It is often convenient to protect hydroxyl groups two at a time in poly-hydroxy-compounds. The protective groups can be either acetals, ketals or carbonates.

10.3.1 Acetals and ketals

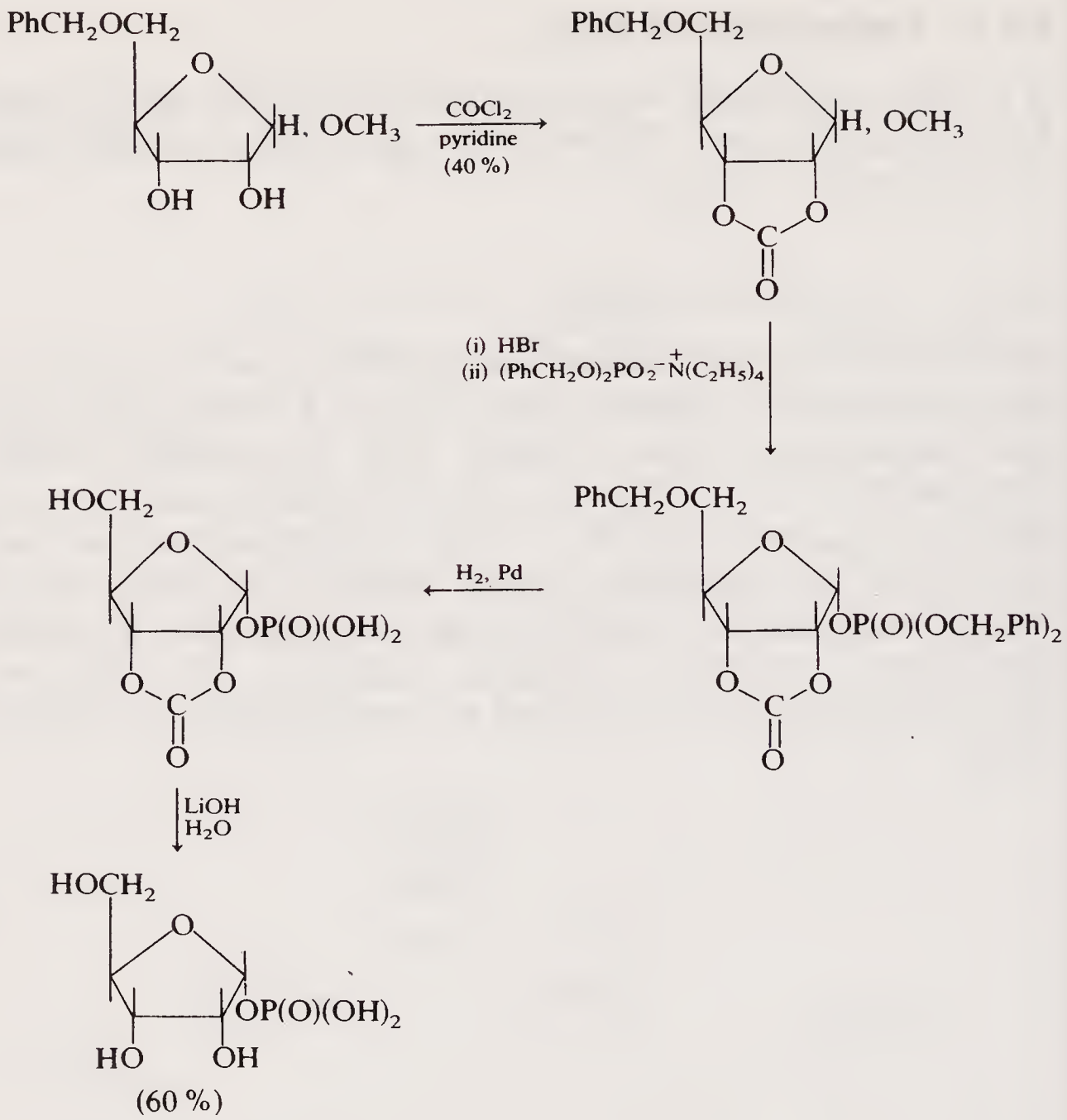
The commonly used carbonyl compounds in such reactions are acetone and benzaldehyde. Acetone reacts with *cis*-1,2-diols under acid catalysis, and benzaldehyde with 1,3-diols often in presence of zinc chloride [scheme 10.1, (2) → (3)]. The diols are regenerated by treatment with dilute acid [scheme 10.1, (4) → (5)]. Hydrogenolysis can also be used in the case of the benzylidene group. Acetals and ketals are stable under neutral and alkaline conditions and can, therefore, be used to protect diols during alkylation, acylation, oxidation, and reduction provided that the reactions can be carried out under alkaline conditions (scheme 10.5).



Scheme 10.5

10.3.2 Carbonates

Phosgene reacts with *cis*-1,2-diols in presence of pyridine to give a cyclic carbonate which is stable under neutral and mildly acidic conditions and can protect 1,2-diols during oxidations and reductions carried out under such conditions. Treatment with alkaline reagents regenerates the diol from the carbonate [scheme 10.6].

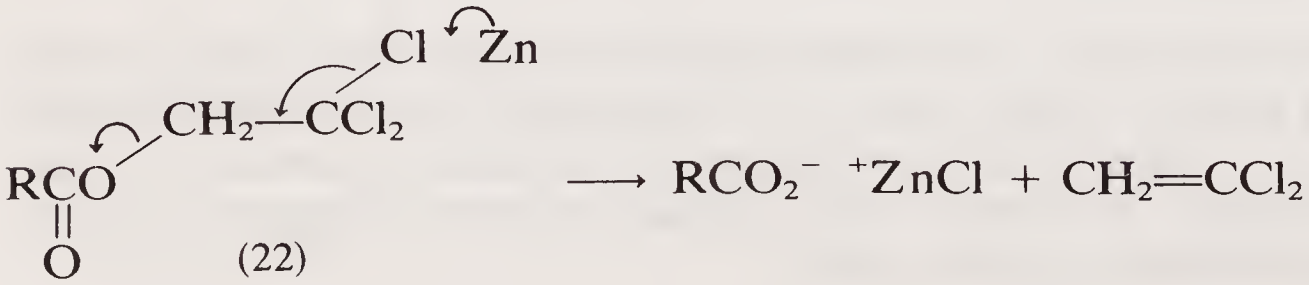


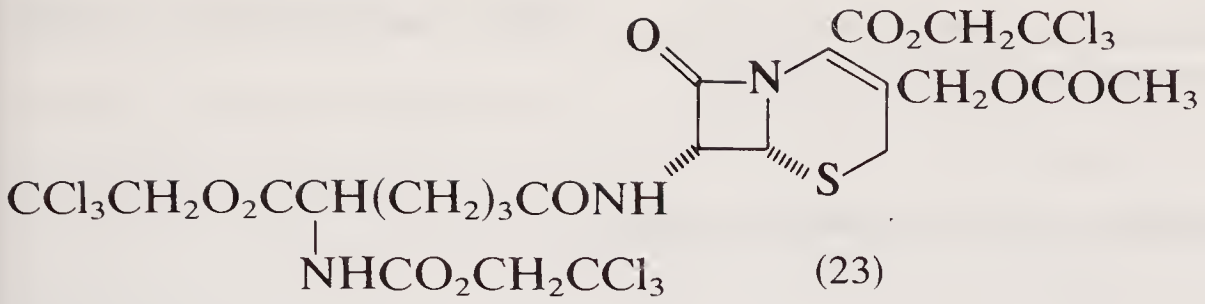
(60 %)

Scheme 10.6

10.4 Protection of carboxylic acids

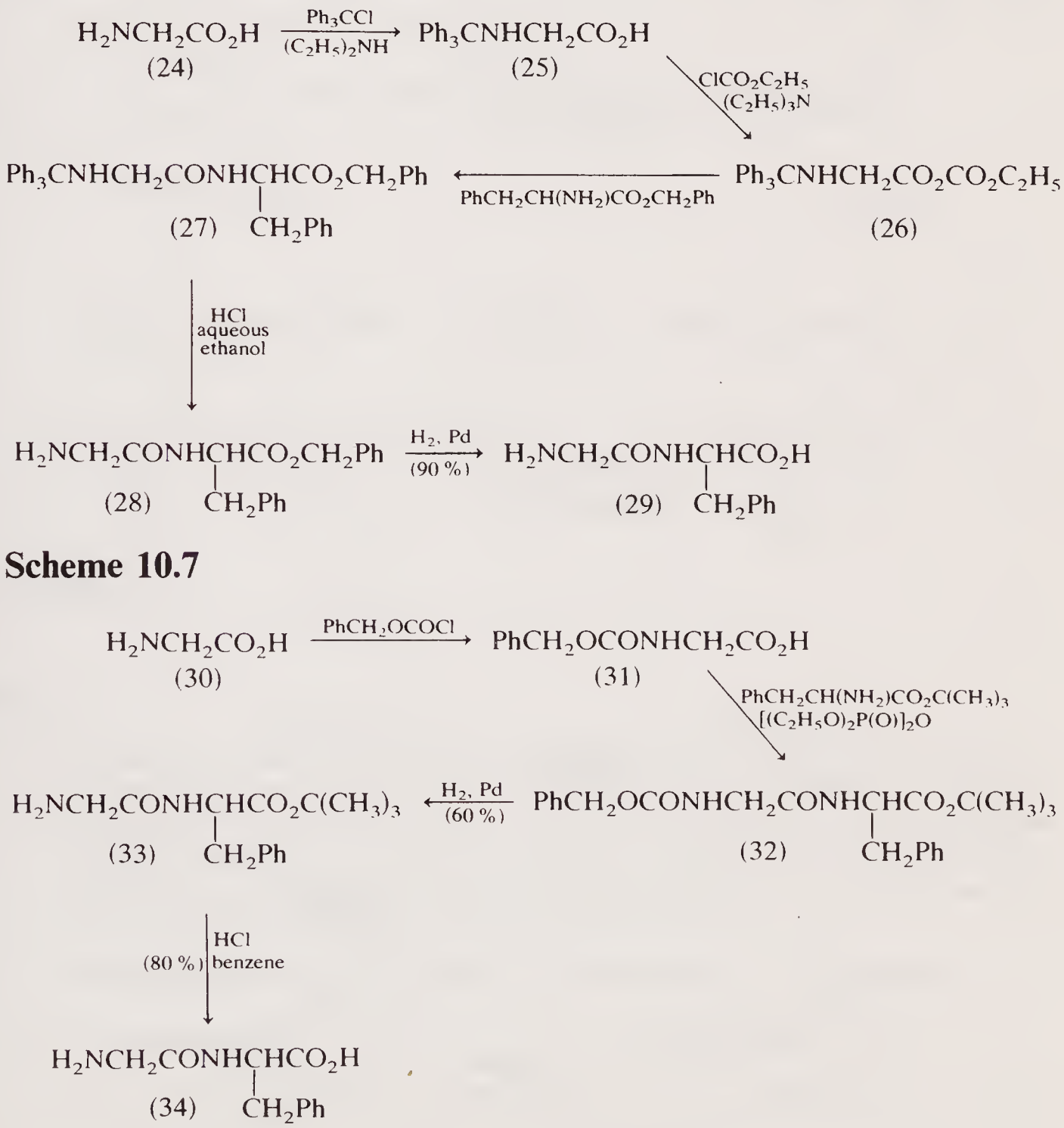
Carboxylic acids are protected as esters. Methyl or ethyl esters are frequently used. However, the strongly acidic or basic conditions required for their removal may be disadvantageous. In such circumstances, t-butyl esters (which can be removed by mild acid treatment), benzyl esters (which can be debenzylated by hydrogenolysis) or β,β,β-trichloroethyl esters (22) (for which deprotection involves a zinc-induced elimination reaction) may be more useful. Trichloroethyl esters have been used in Woodward's cephalosporin C synthesis where the β-lactam ring in (23) has to be kept intact during removal of the protective groups:





(23)

Both benzyl and t-butyl esters are widely used in peptide synthesis (schemes 10.7 and 10.8). Scheme 10.7 shows how the benzyl protective group is used to direct the reaction of the free amino-group with the activated carboxyl group ($-\overset{\|}{C}O\overset{\|}{C}OC_2H_5$), [(26) → (27)], the stability of the group to mild acid treatment [(27) → (28)], and its ease of removal by hydrogenolysis [(28) → (29)]. Scheme 10.8 shows, in addition to the protection of the acid as the t-butyl ester, the stability of the t-butyl



Scheme 10.7

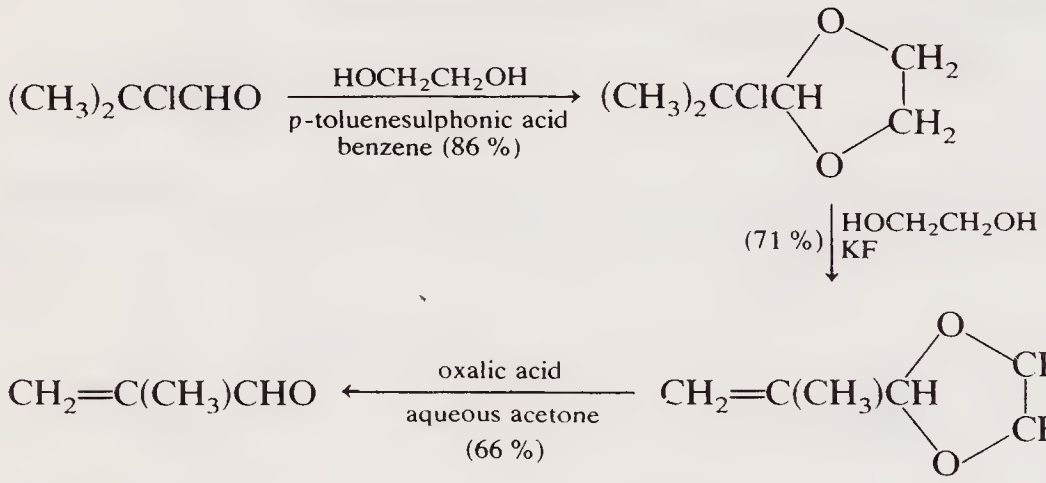
Scheme 10.8

group to catalytic hydrogenation [(32) → (33)] and its facile removal by mild acid treatment [(33) → (34)].

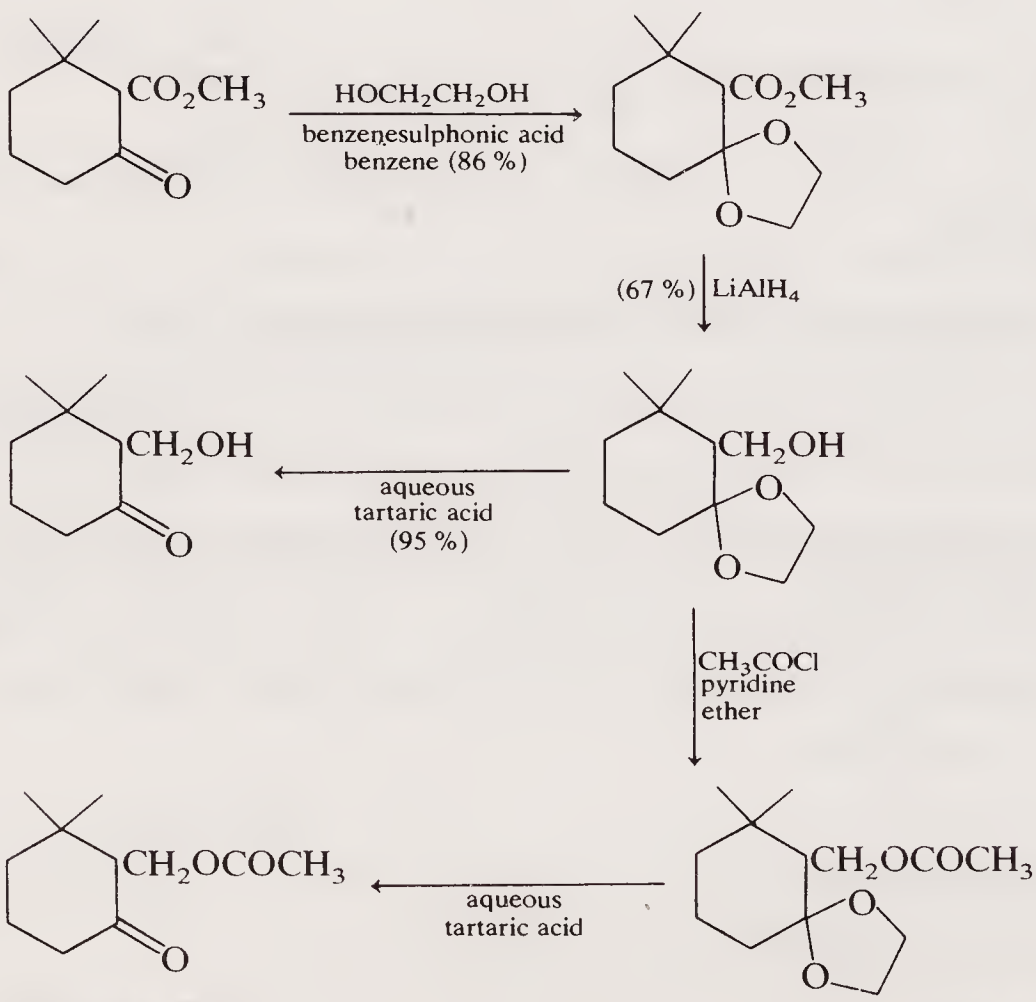
10.5 Protection of the amino group

Schemes 10.7 and 10.8 also show the use of two protective groups frequently used for amines, the benzyloxycarbonyl group and the triphenylmethyl (trityl) group. In scheme 10.8 is shown the formation of the former using benzyl chloroformate [(30) → (31)] and its removal by hydrogenolysis [(32) → (33)]. The trityl derivative is formed by base-catalysed substitution of trityl chloride by the amino group [scheme 10.7, (24) → (25)] and is removed by mild acid treatment [(27) → (28)]. Amines are also protected by acetylation when moderate stability under acidic conditions is required and when removal under strongly basic or acidic conditions can be tolerated. An example is given in scheme 10.1, (7) → (8).

(a)



(b)

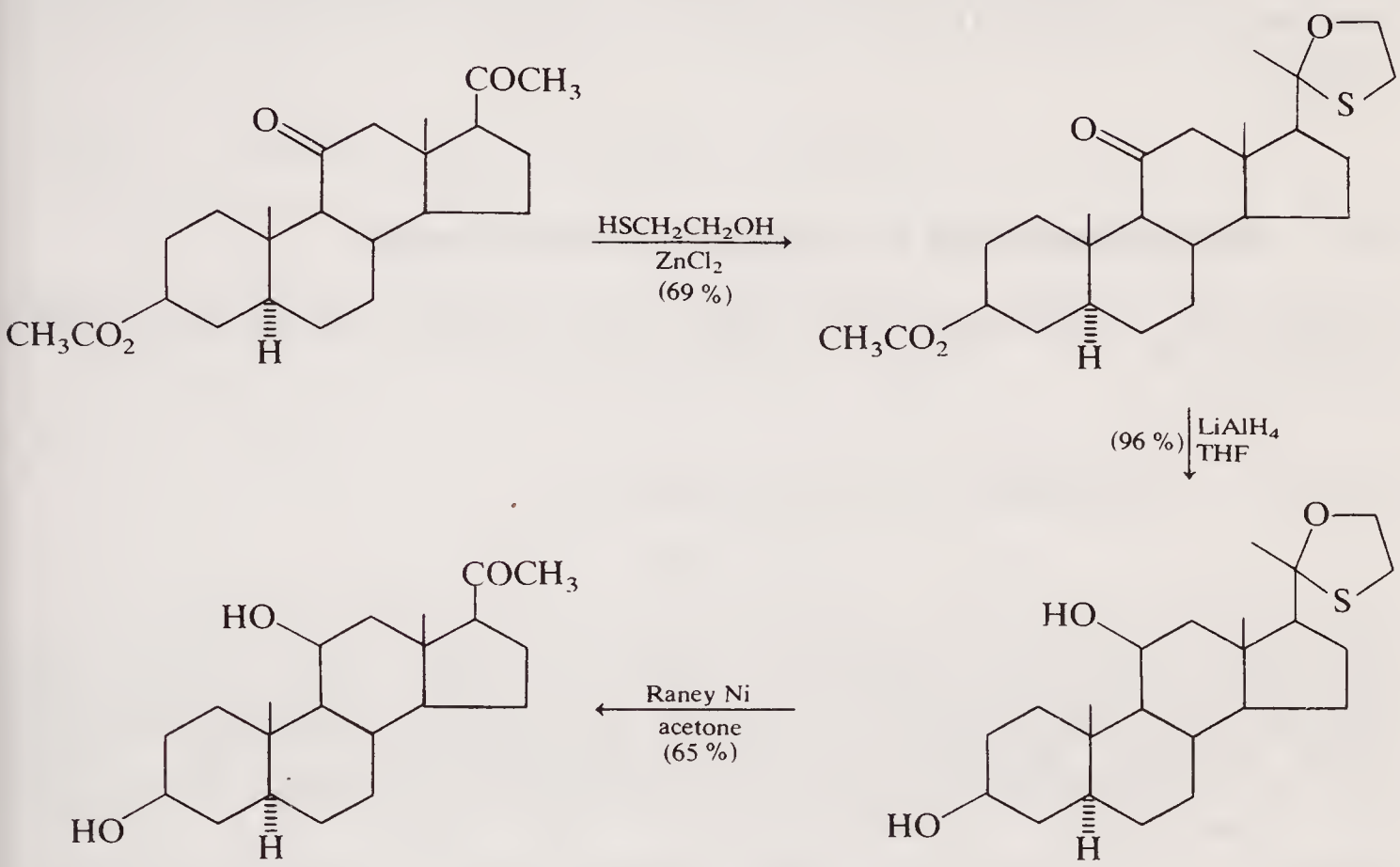


Scheme 10.9

10.6 Protection of the carbonyl group

As has been already pointed out, 1,2-diols can be protected as the ketal by reaction with acetone (cf. section 10.3.1). Aldehydes and ketones are frequently protected as the acetal or the ketal derived from ethylene glycol. Their stability under neutral and alkaline conditions is demonstrated in scheme 10.9.

When slightly greater stability to mildly acidic conditions is required, or when acid sensitive compounds are being used, the monothioketal[2] may be a better protective group, since it is introduced by zinc chloride-catalysed reaction with mercaptoethanol and removed by treatment with Raney nickel (scheme 10.10).



Scheme 10.10

Notes

1. This chapter does not attempt to discuss *latent functionality* as a method of protection. This has already been used, although not described as such, in section 5.2.3.1, where a dihydro-1,3-oxazine is used in place of an aldehyde until the final step of a synthetic sequence. Similarly, an oxazoline (section 15.4.2) may serve as a 'masked' carboxylic acid function, or an alkene may serve as a latent carbonyl function (section 9.2.6).

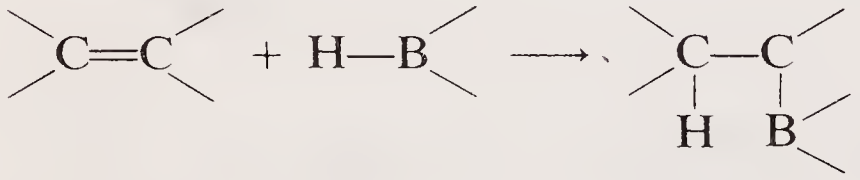
2. This derivative is also described in the literature as a hemithioketal.

11 Boron reagents

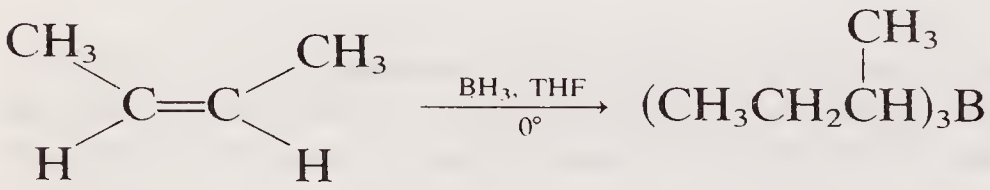
Since the discovery in the 1950s of the facile addition of borane to alkenes, many synthetic applications of boron-containing compounds have been developed. In this chapter, we summarise the more important of these.

11.1 Hydroboration of alkenes with borane

Compounds containing B–H bonds add readily to carbon–carbon double bonds.

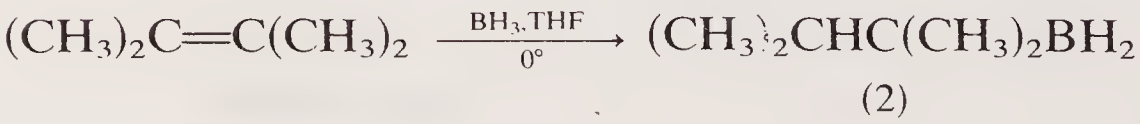


In the case of reaction of borane[1] with most alkenes, the product of the reaction is the trialkylborane, but with more highly substituted alkenes the reaction may stop at the di- or mono-alkylborane stage. Only on very rare occasions has hydroboration not been achieved [e.g. when the double bond is in a sterically hindered environment such as in (3)]. Hindered boranes, $(Sia)_2BH$ (1)[2] and thexylborane (2)[3], are in themselves useful reagents (cf. sections 11.2.1, 11.2.2, 11.3.3, 11.5):

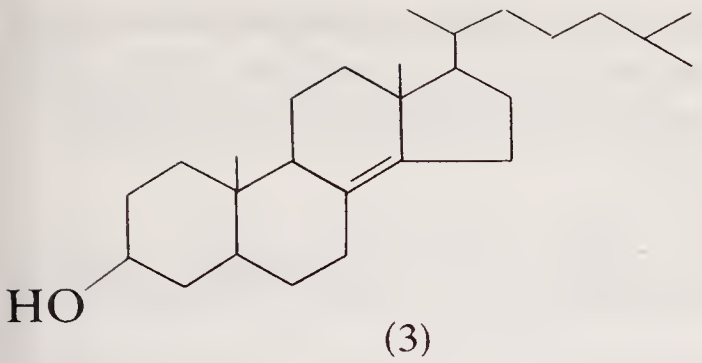


$$(CH_3)_2C{=}CHCH_3 \xrightarrow[0^\circ]{BH_3,THF} \left(\begin{matrix}CH_3\\|\\(CH_3)_2CHCH\end{matrix}\right)_2BH$$

(1)

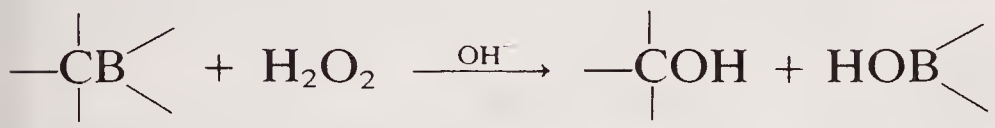


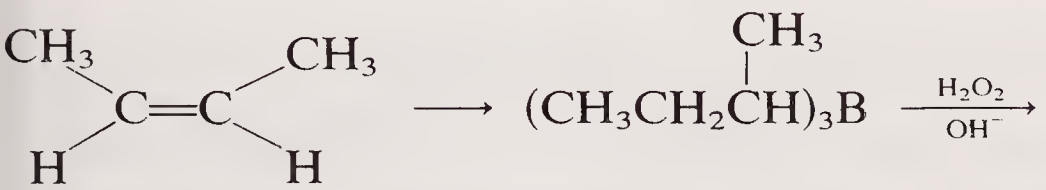
(2)



(3)

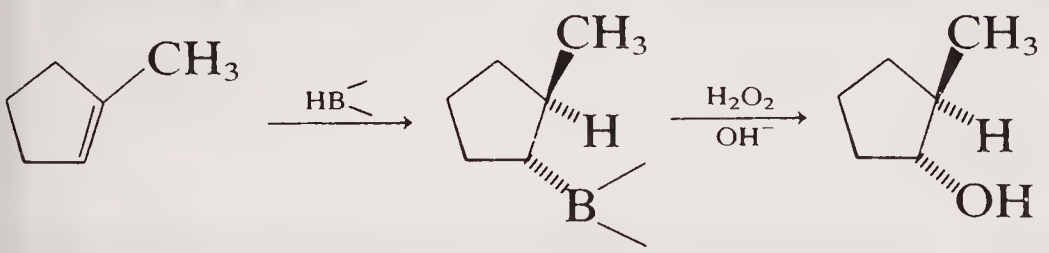
Of the reactions which will be discussed later (cf. section 11.3), one of the most important is the virtually quantitative oxidation of alkylboranes with alkaline hydrogen peroxide (11.1). The overall reaction is addition of water to the carbon–carbon double bond of an alkene:



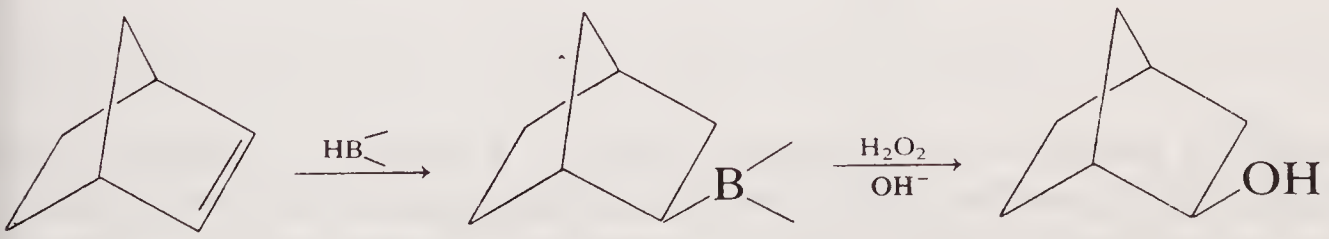


$$CH_3CH_2CH(OH)CH_3 + B(OH)_3 \qquad (11.1)$$

It should be noted that the decomposition of the borane takes place with retention of configuration, and so the stereochemistry of the product is determined by the stereochemistry of the addition of borane to the alkene. The following examples demonstrate that the addition to the double bond is *cis* on the *less hindered side* of the molecule:

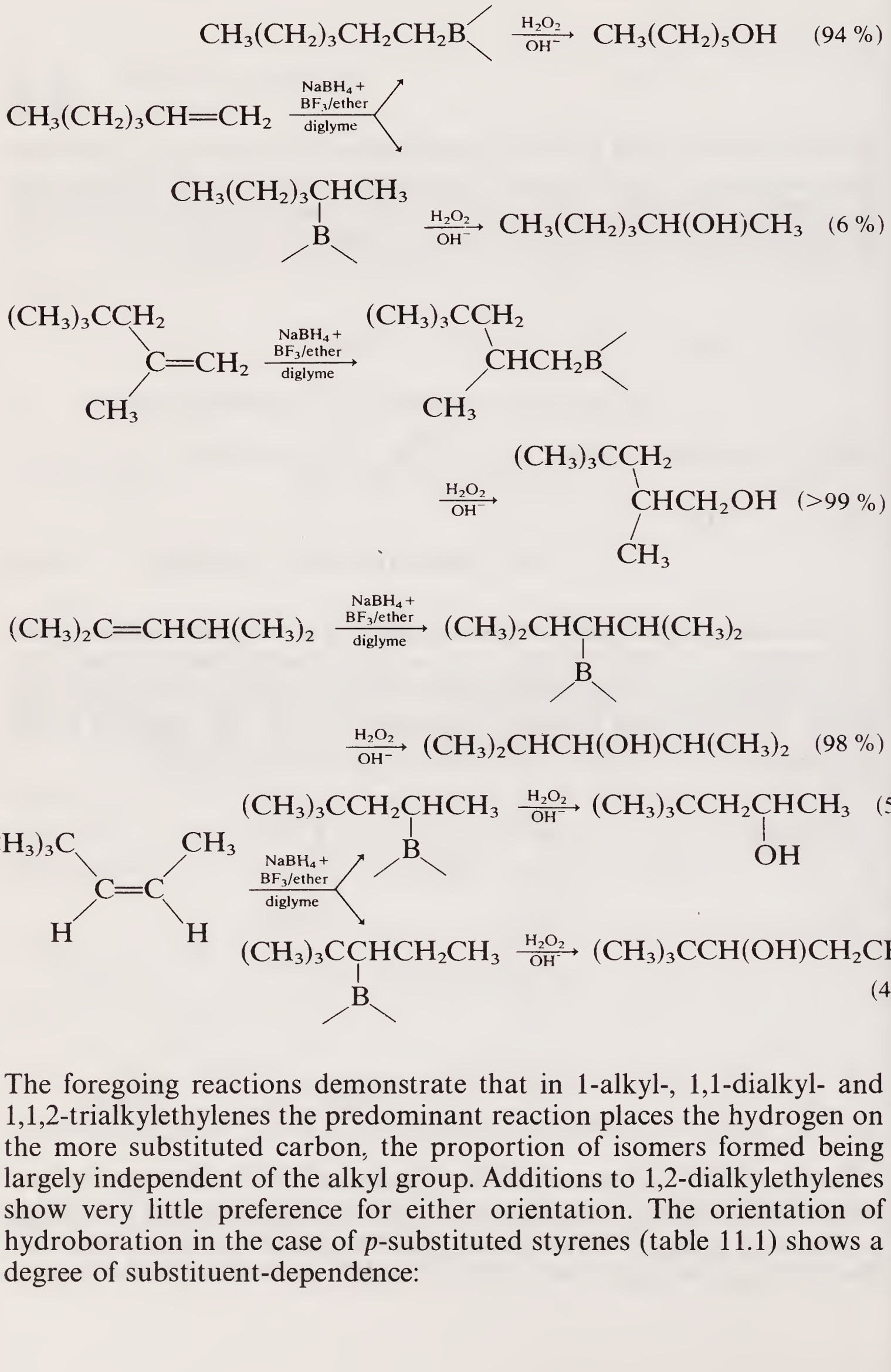


(11.2)



Reaction 11.2 indicates another feature of the hydroboration procedure. The orientation of addition is such that the hydrogen is attached to the more highly substituted carbon, giving, after treatment with alkaline hydrogen peroxide, the product formally derived by 'anti-Markow-

nikoff' addition of water. The procedure is, therefore, complementary to acid-catalysed hydration and oxymercuration (cf. section 2.2). The following examples demonstrate the degree of specificity obtainable:



The foregoing reactions demonstrate that in 1-alkyl-, 1,1-dialkyl- and 1,1,2-trialkylethylenes the predominant reaction places the hydrogen on the more substituted carbon, the proportion of isomers formed being largely independent of the alkyl group. Additions to 1,2-dialkylethylenes show very little preference for either orientation. The orientation of hydroboration in the case of *p*-substituted styrenes (table 11.1) shows a degree of substituent-dependence:

Table 11.1 Orientation of hydroboration in *p*-substituted styrenes

$p\text{-}XC_6H_4CH{=}CH_2 \rightarrow$	$p\text{-}XC_6H_4\underset{\displaystyle B}{\underset{\vert}{C}}HCH_3$	$+\ p\text{-}XC_6H_4CH_2CH_2B$
$X = OCH_3$	7 %	93 %
$X = H$	19 %	81 %
$X = Cl$	27 %	73 %

Boranes react more rapidly with carbon–carbon double bonds than with most other functional groups. So, in many cases, hydroboration can be carried out selectively, e.g.

$$CH_2{=}CH(CH_2)_8CO_2CH_3 \xrightarrow{BH_3/THF} \begin{matrix} \\ \\ B(CH_2)_{10}CO_2CH_3 \end{matrix}$$

It is, however, desirable to protect carbonyl groups as acetals or ketals, and acids as esters (cf. sections 10.4, 10.6).

Polar groups attached to the double bond exert a directive effect analogous to that noted previously in the case of *p*-substituted styrenes, e.g.

$$(CH_3)_2C{=}CHOC_2H_5 \xrightarrow{BH_3/THF} (CH_3)_2\underset{\displaystyle B}{\underset{\vert}{C}}CH_2OC_2H_5$$

($\geq$88 %) ($\leq$12 % of 1-isomer)

but:

$$(CH_3)_2C{=}CHOCOCH_3 \xrightarrow{BH_3/THF} (CH_3)_2CH\underset{\displaystyle B}{\underset{\vert}{C}}HOCOCH_3$$

($\geq$95 %) ($\leq$5 % of 2-isomer)

The effect decreases as the heteroatom is further removed from the double bond, e.g.

$$CH_3CH{=}CHCH_2Cl \xrightarrow{BH_3/THF} CH_3CH_2\underset{\displaystyle B}{\underset{\vert}{C}}HCH_2Cl + CH_3\underset{\displaystyle B}{\underset{\vert}{C}}HCH_2CH_2Cl$$

(>90 %) (<10 %)

$$CH_2{=}CHCH_2CH_2Cl \xrightarrow{BH_3/THF} \begin{matrix} \\ \\ B(CH_2)_4Cl \end{matrix} + CH_3\underset{\displaystyle B}{\underset{\vert}{C}}HCH_2CH_2Cl$$

(80 %) (20 %)

11.2 Hydroboration of alkenes with alkylboranes

A number of alkylboranes have found synthetic application and some of these with their uses will now be considered.

11.2.1 Disiamylborane[2]

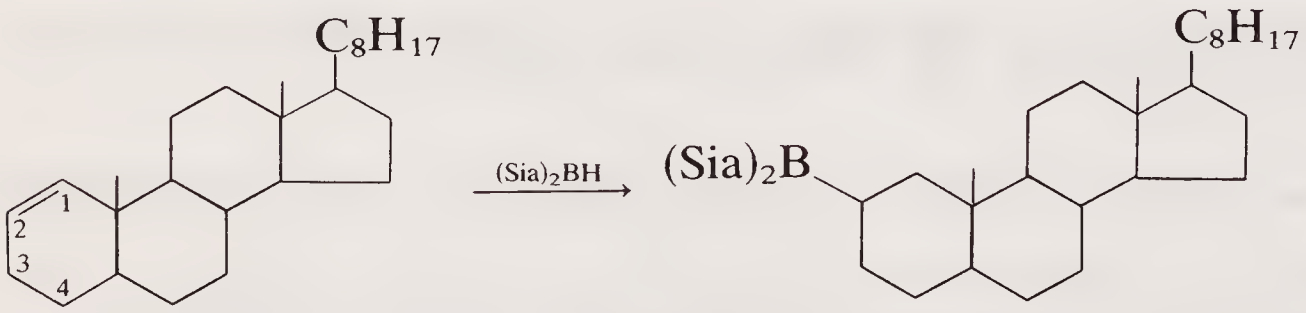
2-Methylbut-2-ene reacts with borane only slowly beyond the dialkylborane stage. The resultant dialkylborane (1), often known as 'disiamylborane' or $(Sia)_2BH$, reacts with a very high degree of selectivity with monosubstituted alkenes. In cases such as that of allyl chloride, where addition of borane itself leads to a mixture of adducts (the reverse adduct being formed as the result of the inductive effect of the halogen), the use of the bulkier disiamylborane is necessary to ensure that only 'normal' addition occurs:

$$CH_3(CH_2)_3CH{=}CH_2 + \underset{(1)}{[(CH_3)_2CHCH(CH_3)]_2BH} \rightarrow CH_3(CH_2)_5B[CH(CH_3)CH(CH_3)_2]_2$$

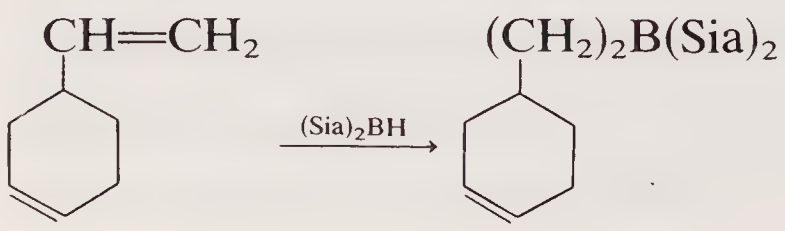
$$ClCH_2CH{=}CH_2 \xrightarrow{(Sia)_2BH} Cl(CH_2)_3B(Sia)_2$$

$$ClCH_2CH{=}CH_2 \xrightarrow{BH_3/THF} \underset{(60\,\%)}{Cl(CH_2)_3B} + \underset{(40\,\%)}{ClCH_2CH(B)CH_3}$$

The reagent also shows a high degree of selectivity towards the less hindered site in a disubstituted alkene: for example in (4), where reaction with borane produces only a slight excess of the 2-isomer. $(Sia)_2BH$ also reacts preferentially with monosubstituted alkenes:



(4) no detectable amount of 1-isomer

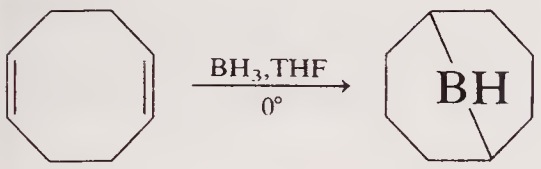


11.2.2 Thexylborane[3]

2,3-Dimethylbut-2-ene reacts with borane to give a monoalkylborane (2) which is often known as 'thexylborane'. It is used mainly when mixed alkylboranes are required (cf. section 11.3.5) and for the alkylation of dienes (cf. section 11.4).

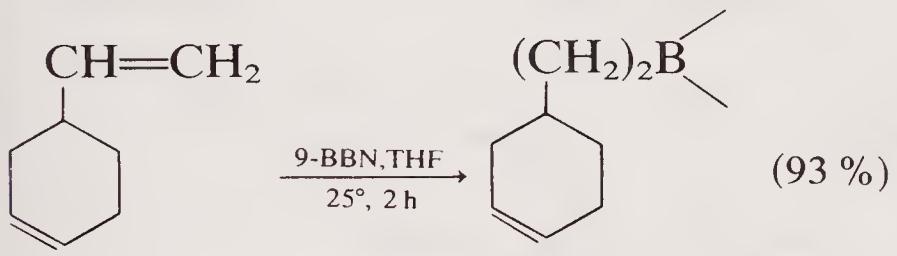
11.2.3 9-Borabicyclo[3.3.1]nonane

As will be seen later (section 11.4), 1,5-dienes react with borane: when cycloocta-1,5-diene is used, the product is 9-bora bicyclo[3.3.1]nonane (5), 9-BBN. This alkylborane reacts more slowly with alkenes than does $(Sia)_2BH$. It has, however, a much greater thermal stability than most dialkylboranes and hence reactions can be carried out in refluxing tetrahydrofuran.

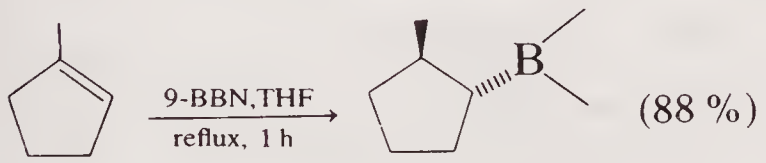


(5)

9-BBN shows a higher degree of regioselectivity than does $(Sia)_2BH$ and its greater stability to heat and towards oxidation renders it the more suitable reagent in most situations:



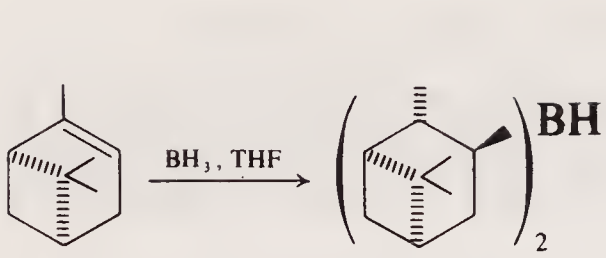
no trace of 2-isomer



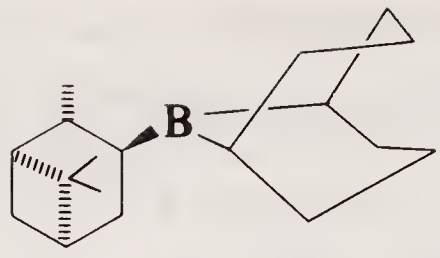
no trace of 1-isomer

11.2.4 Chiral boranes

The hydroboration of a chiral alkene produces a chiral alkylborane. Hydroboration of the terpenoid hydrocarbon, α-pinene, is of particular interest in this connection, since each enantiomer can be obtained in a pure state from natural sources, and since the double bond is sufficiently hindered that the hydroboration does not proceed beyond the dialkylborane stage even with borane itself.



(−) (+)



(6)

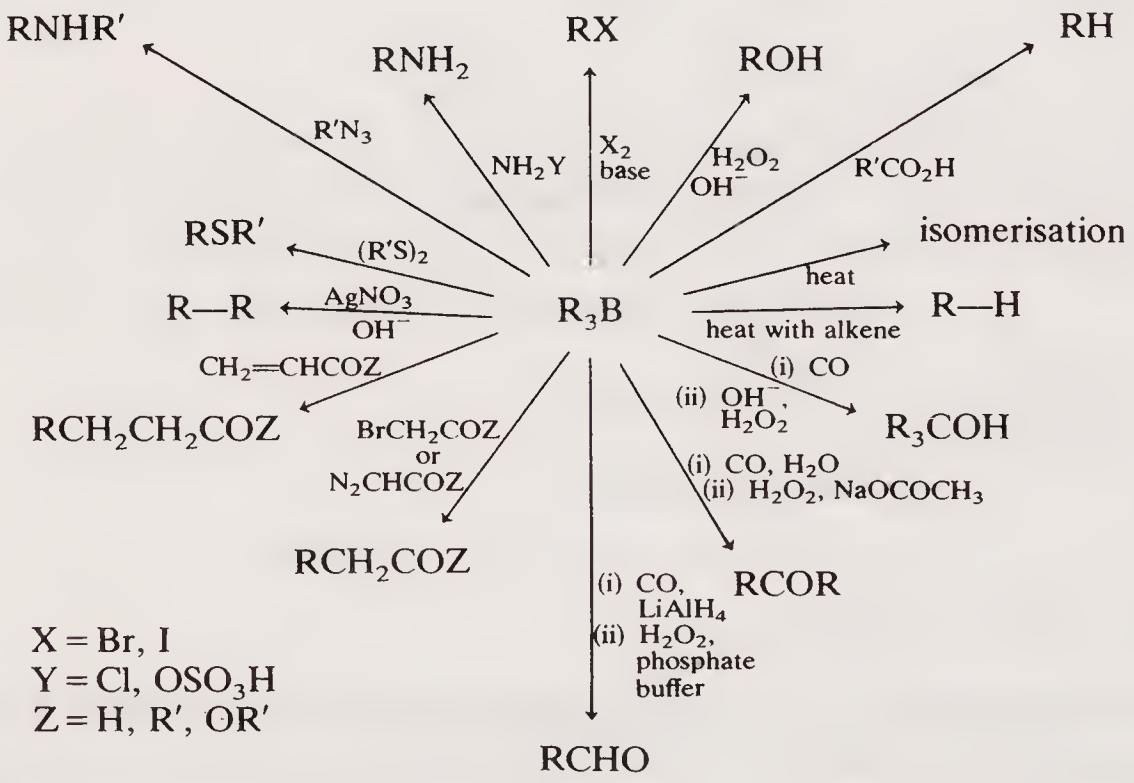
Hydroboration of α-pinene with 9-BBN gives the trisubstituted borane (6), which is available commercially as 'Alpine-borane'® (Aldrich Chemical Co. Ltd). It is used in asymmetric synthesis (see section 15.5.3) as are the related alkali metal borohydrides ('Alpine-hydrides'®) (section 15.5.3).

11.3 Reactions of organoboranes

These are summarised in scheme 11.1 and some of the more important are discussed in the following sections.

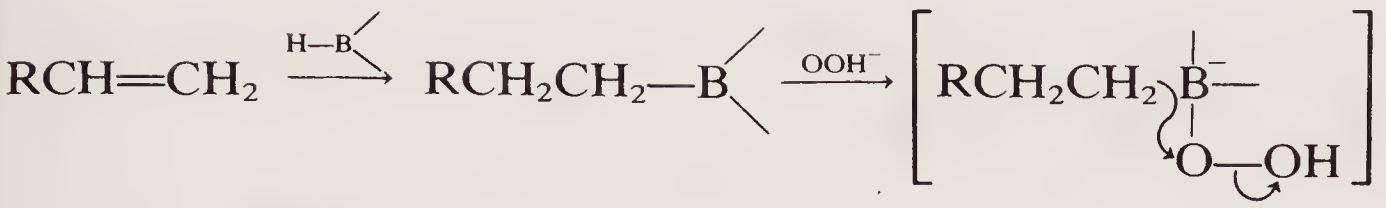
11.3.1 Reaction with alkaline hydrogen peroxide

This is probably the single most widely used reaction of organoboranes in which the borane is converted, with retention of configuration (*via* a borate ester), into the alcohol. Thus, the overall reaction of the alkene is its conversion into an alcohol by the *cis*-addition of the elements of water [reactions (11.3) and (11.4)].

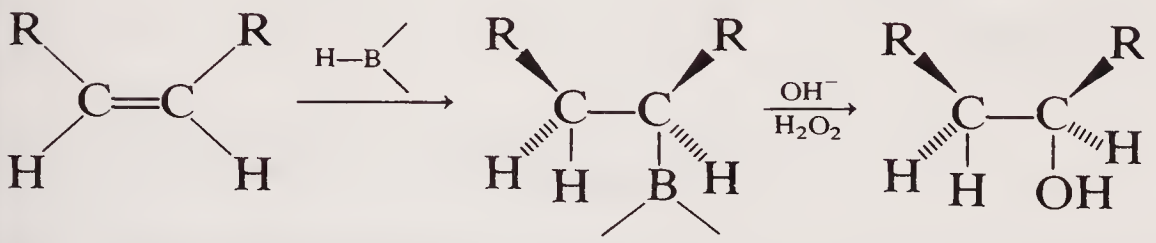


Scheme 11.1

The regiospecificity of the reaction is, of course, determined by that of the hydroboration step (sections 11.1, 11.2).

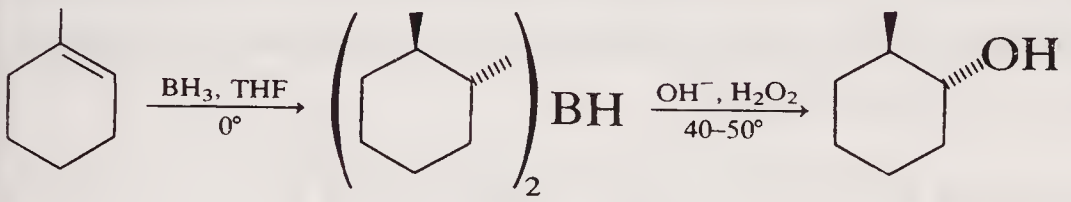


(11.3)

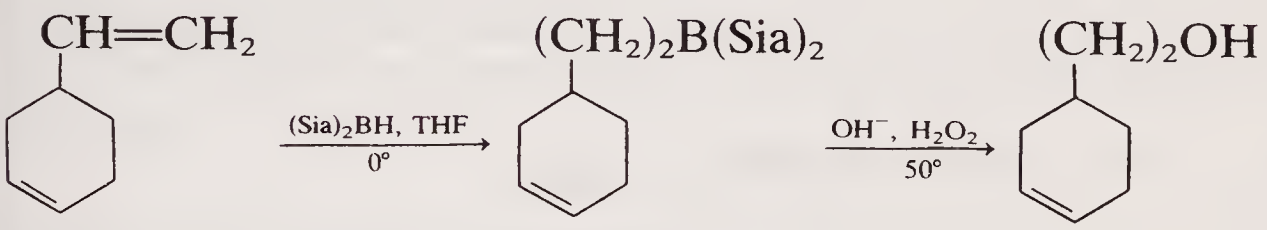


(11.4)

The reaction is thus in some respects complementary to the acid-catalysed hydration discussed in section 2.2.



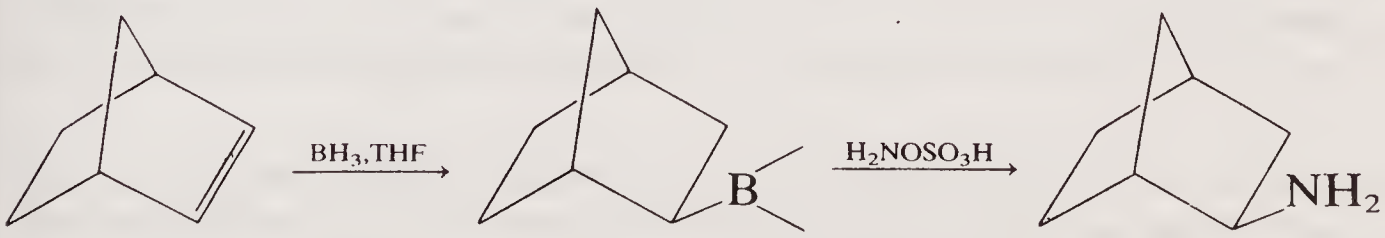
(85 %)



(72 %)

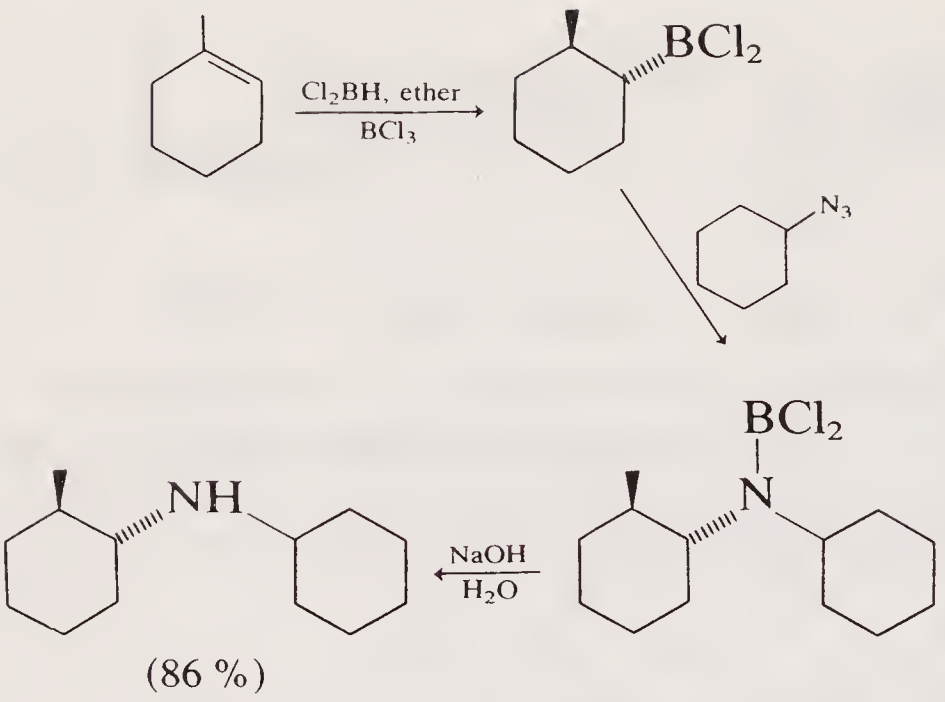
11.3.2 Conversion to amino groups

Boranes react with compounds NH_2X where X is a good leaving group. These are often unstable compounds but hydroxylamine-*O*-sulphonic acid is a reasonably stable compound which can be used in synthesis. The product is a primary amine:



(57 %)

Secondary amines can be obtained from reaction of dichloroboranes with an azide:

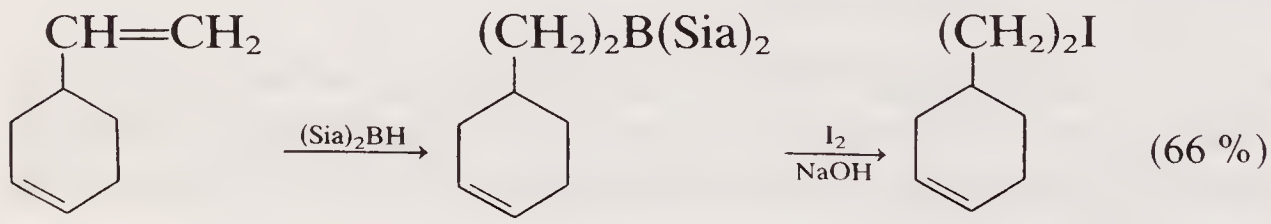


11.3.3 Conversion to halogeno-compounds

Although boranes are quite stable to halogens, rapid reaction follows the addition of alkali. In the case of tri-(primary alkyl)-boranes, only two of the three alkyl groups react; and secondary alkyl groups do not react. Thus, for conversion of terminal alkenes into primary iodides, it is preferable to use Sia_2BH for optimum yield:

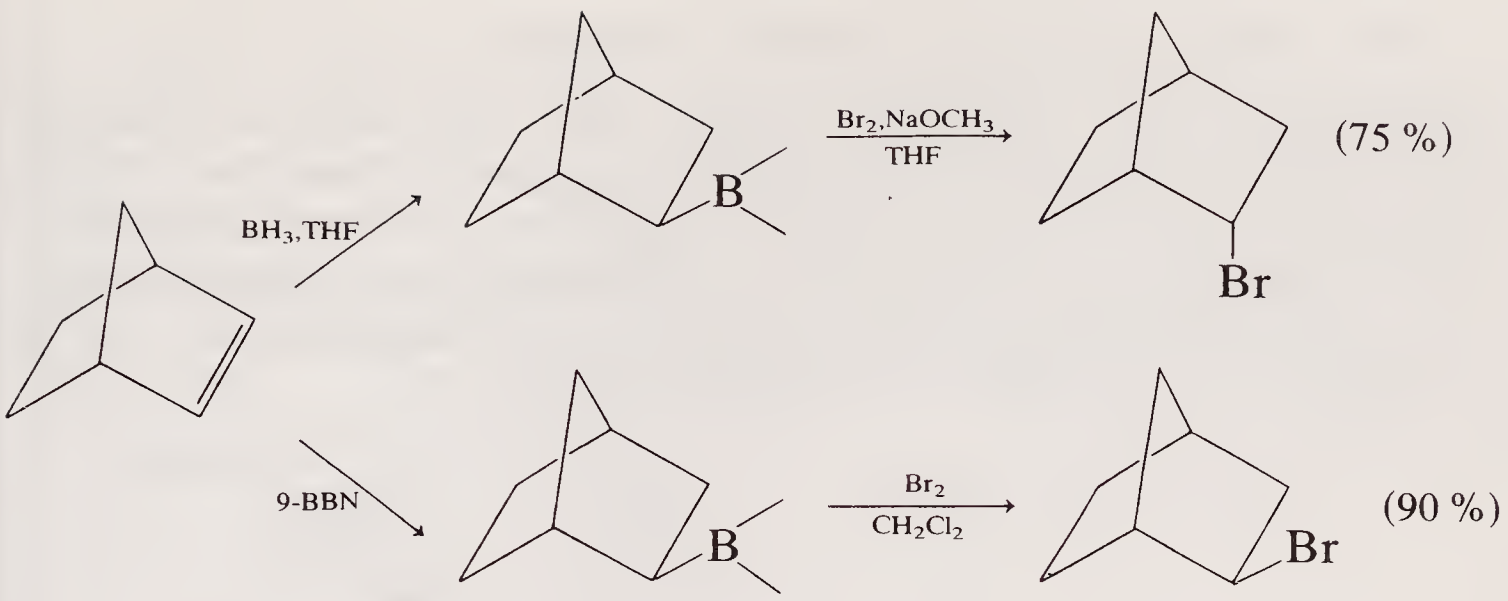
$$3RCH{=}CH_2 \xrightarrow{BH_3} (RCH_2CH_2)_3B \xrightarrow[2NaOH]{2I_2} 2RCH_2CH_2I + 2NaI + RCH_2CH_2B(OH)_2$$

$$RCH{=}CH_2 \xrightarrow{(Sia)_2BH} RCH_2CH_2B(Sia)_2 \xrightarrow[NaOH]{I_2} RCH_2CH_2I + NaI + (Sia)_2BOH$$



Conversion into bromides is also observed by use of bromine and sodium methoxide but water must be rigorously excluded (due, possibly, to the formation of hypobromous acid which hydrolyses boranes to alcohols).

It should be noted that in this case (i) secondary alkyl groups react and (ii) the *endo*-bromo-compound is produced from the *exo*-norbornyl borane. The *exo*-isomer is formed by reaction of bromine with the adduct of norbornene with 9-BBN when the reaction proceeds by radical attack of bromine on the α-hydrogen of the alkylborane:

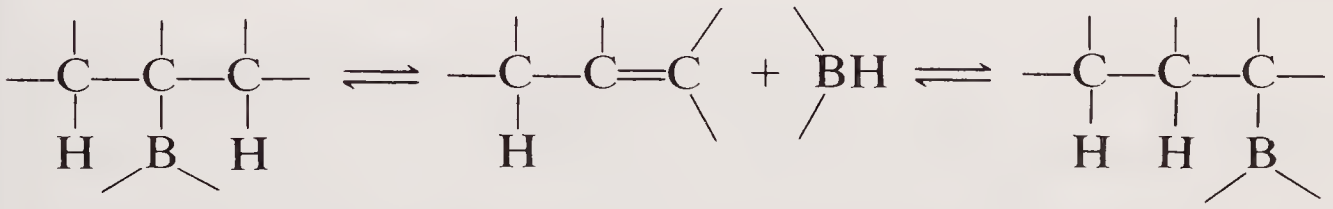


11.3.4 Reaction with organic acids

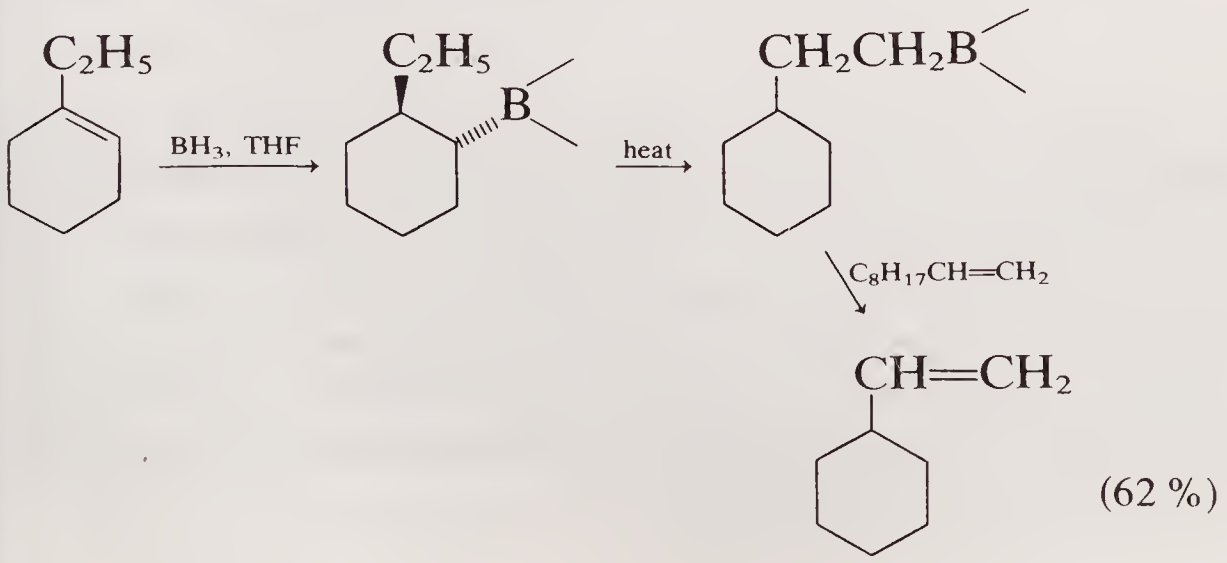
Organic acids convert alkylboranes into alkanes. Propanoic acid is often used for this purpose but the reaction has not enjoyed wide synthetic use presumably because of the availability of simpler procedures for reduction of alkenes. The method is more widely used in the decomposition of vinylboranes (cf. section 11.5). Boranes may also be used as selective reducing agents for the carboxyl group (see section 11.6).

11.3.5 Thermal reactions of alkylboranes

When heated, alkylboranes isomerise so that the boron migrates to the least hindered position of the alkyl group. It is thought that the isomerism takes place by dissociation of the alkylborane followed by hydroboration:

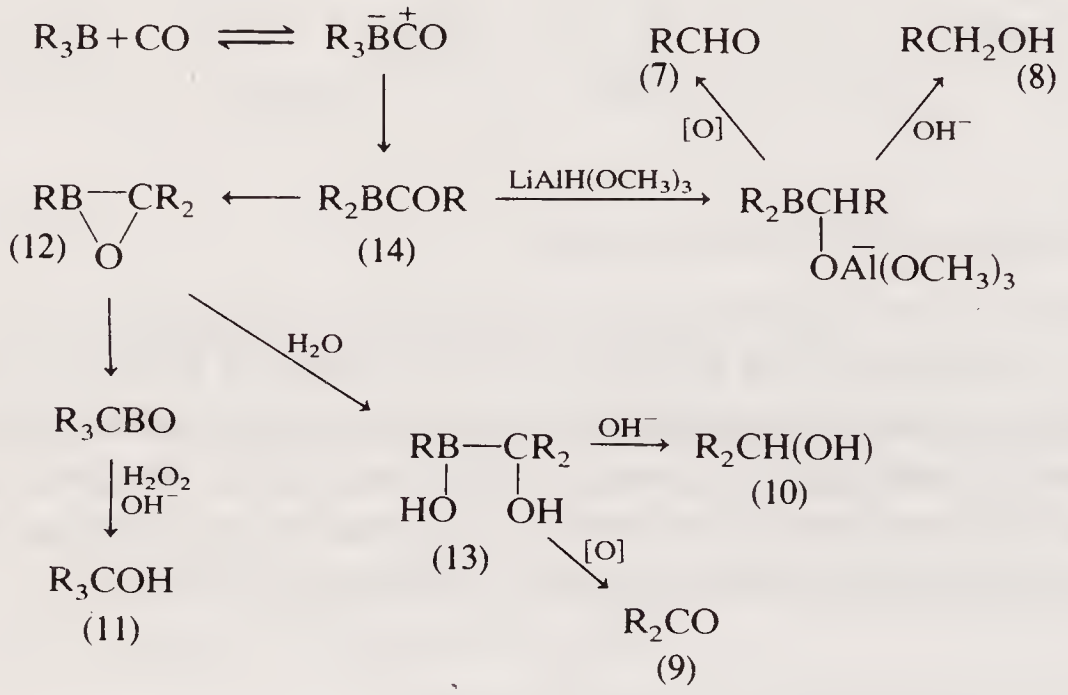


It follows from this mechanism that, if the borane is heated in presence of a reactive alkene, a less reactive alkene can be liberated. This can be used in the isomerism of alkenes, for example:



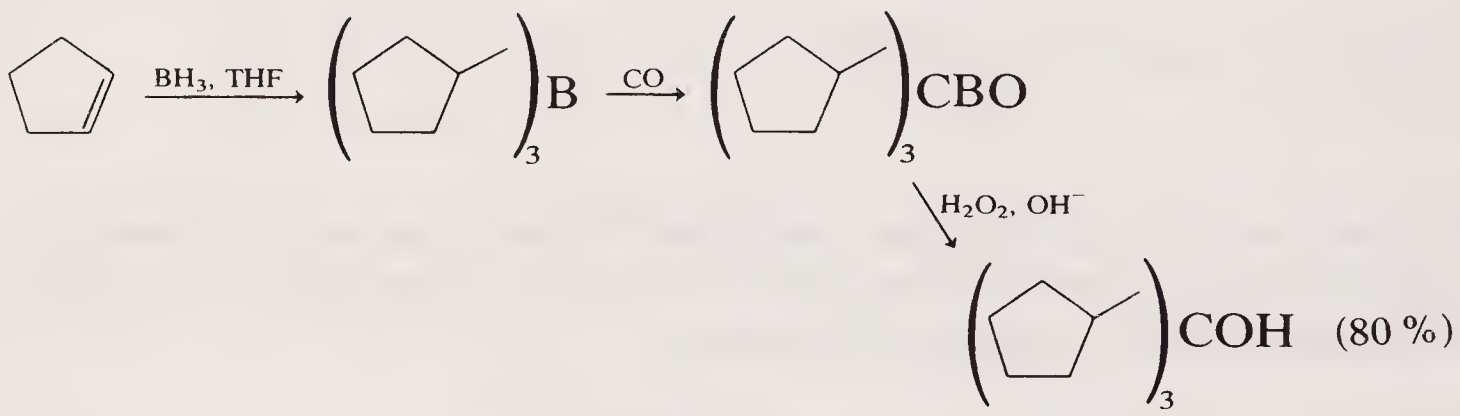
11.3.6 Reactions involving carbon monoxide

Depending on the conditions, boranes react with carbon monoxide giving intermediates which result from the migration of one, two or three alkyl groups from boron to carbon. Oxidation of these intermediates results in the formation of aldehydes (7), ketones (9) and tertiary alcohols (11), respectively. Primary (8) and secondary (10) alcohols can also be formed. The overall reaction is shown in scheme 11.2.

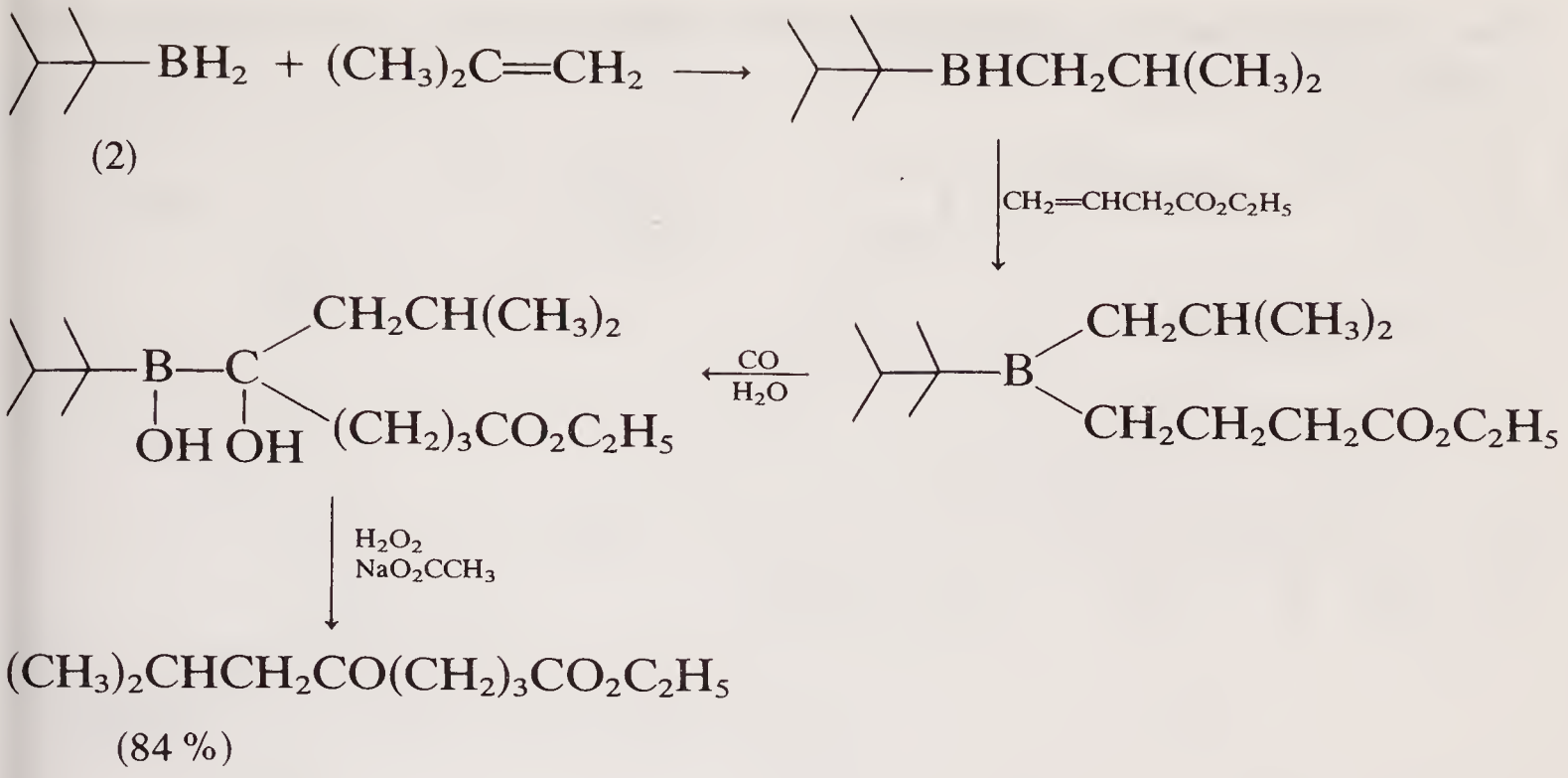


Scheme 11.2

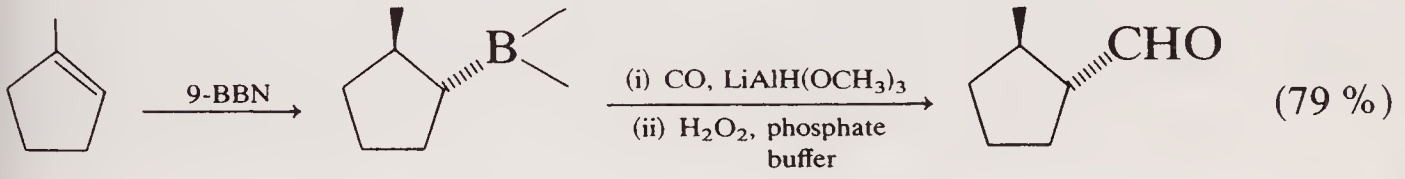
Thus, under anhydrous conditions, all three alkyl groups migrate, and on reaction of the intermediate with alkaline peroxide a tertiary alcohol is formed:



When a trace of water is present, the reaction is intercepted when only two alkyl groups have migrated and the intermediate boraepoxide (12) is hydrolysed to a boraglycol (13). The boraglycol can be hydrolysed to the secondary alcohol or oxidised to the ketone. With a trialkylborane, one alkyl group is lost but, when hydroboration is performed using thexylborane, the thexyl group usually shows least susceptibility to migration. Unsymmetrical ketones can be prepared in cases where thexylborane can be monoalkylated by hindered alkenes:

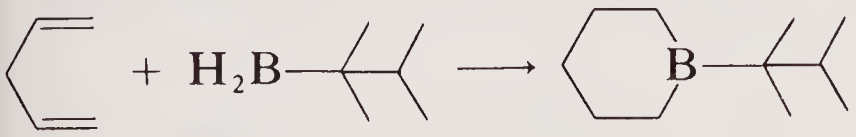


If the reaction is carried out in presence of a reactive hydride reducing agent, the boraketone (14) formed on migration of the first alkyl group is reduced. The reduction product is hydrolysed to the primary alcohol and oxidised to the aldehyde. In this case, two of the alkyl groups of the trialkylborane are lost, but use of 9-BBN as hydroboration reagent circumvents the loss of valuable alkyl groups:



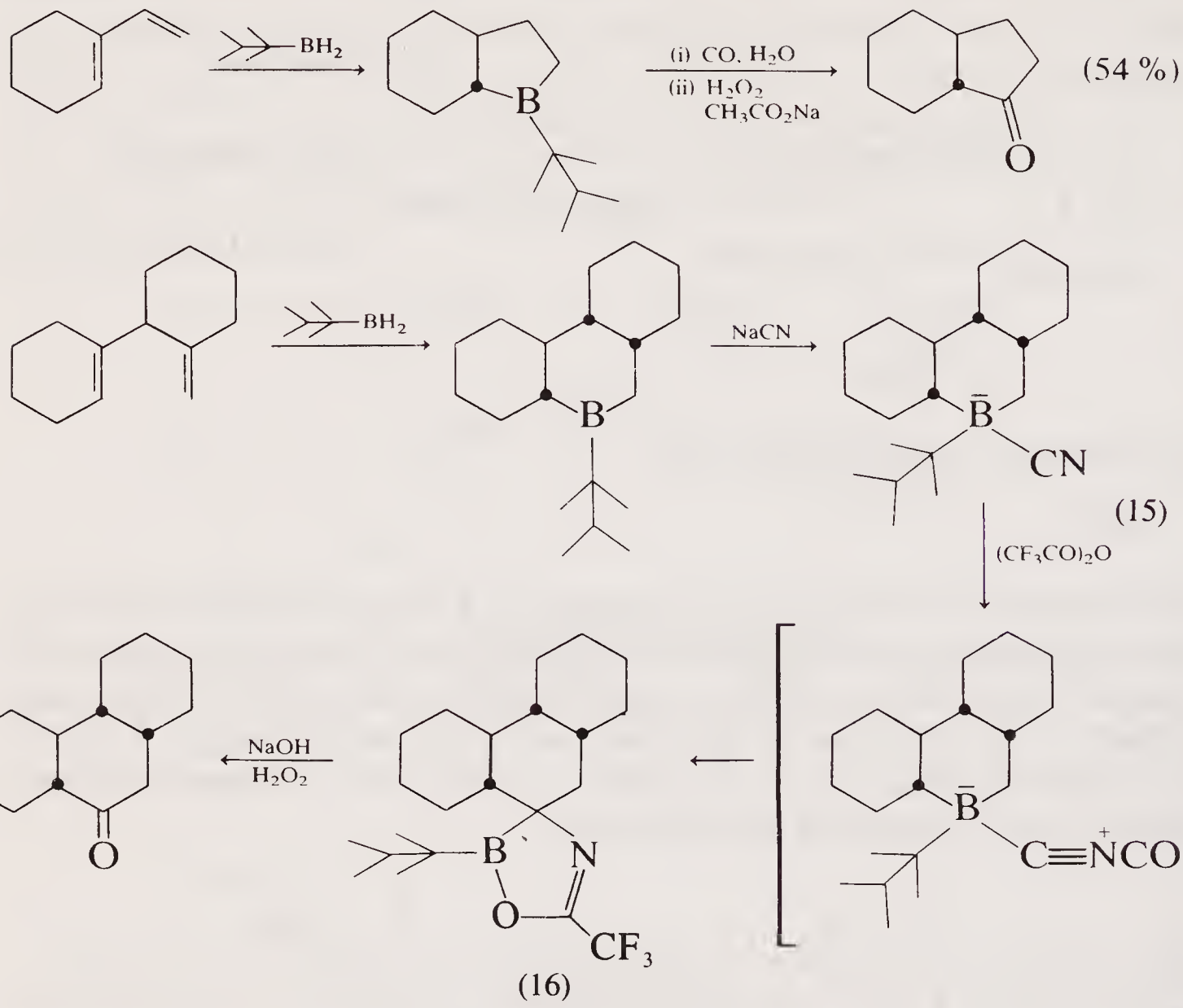
11.4 Hydroboration of dienes

Hydroboration of 1,3-, 1,4-, and 1,5-dienes leads to the formation of boracycloalkanes. Use of borane itself may lead to considerable polymerisation and, in most cases, use of thexylborane is preferred. An exception is, of course, the preparation of 9-BBN (cf. section 11.2.3).



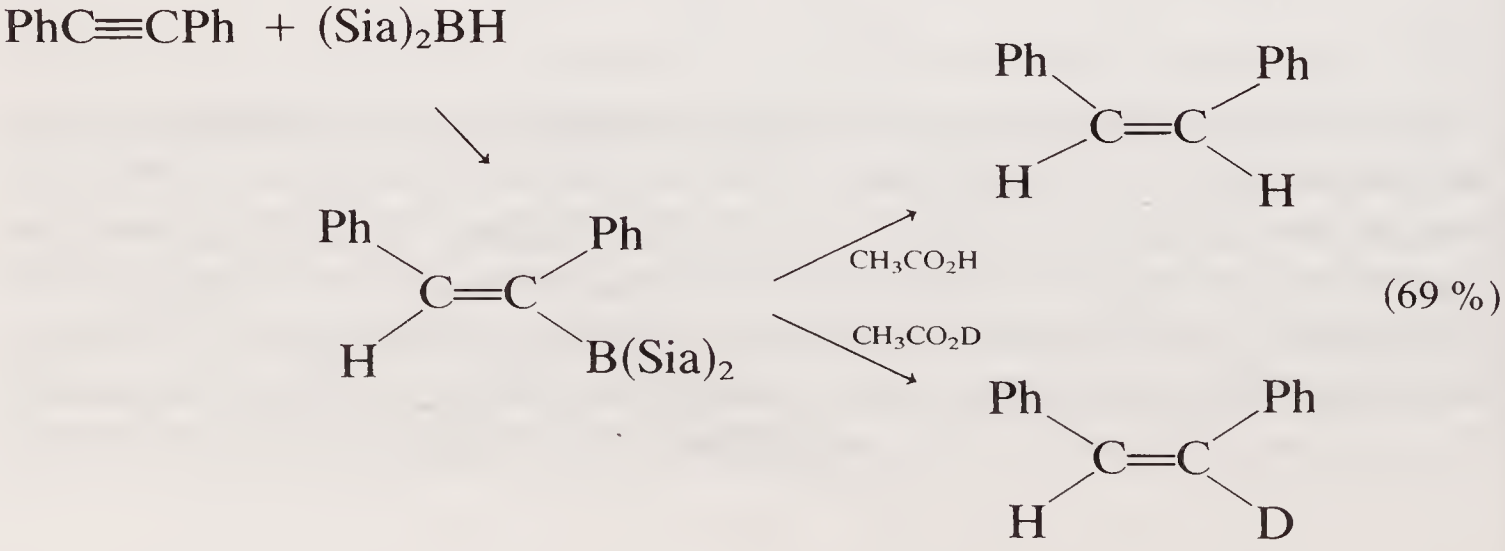
One of the principal synthetic applications of boracycloalkanes is in the preparation of cyclic ketones. This can be achieved by use of the carbonylation reaction (cf. section 11.3.5) but, because of the high pressure of carbon monoxide (70 atm) required to cause reaction with thexylboracycloalkanes, an alternative procedure involving acylation of cyanoborates [e.g. (15)] represents a more convenient synthetic method. Acylation of cyanoborates results in the migration of two alkyl groups to form the

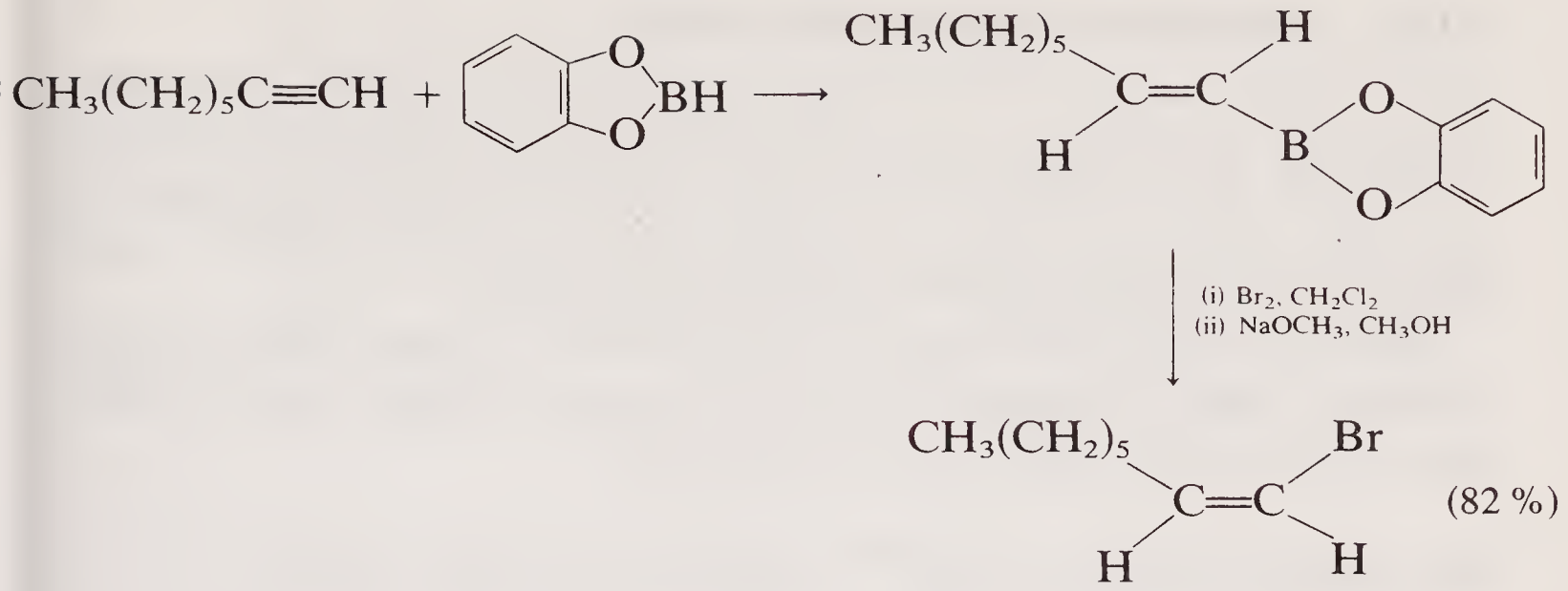
boradihydrooxazole intermediate (16) which can be decomposed in the usual way:

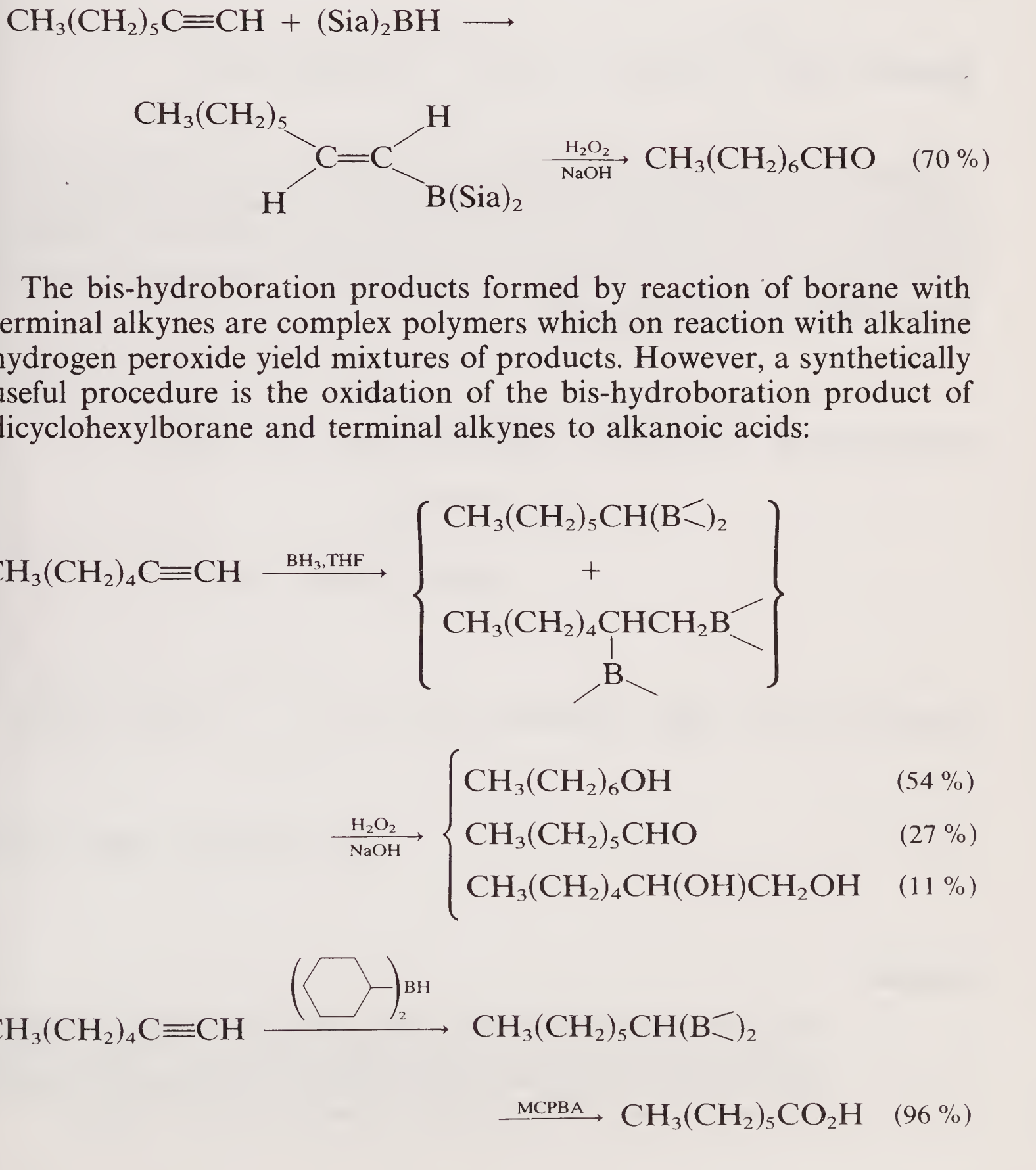


11.5 Hydroboration of alkynes

Monohydroboration of non-terminal alkynes can be achieved by use of controlled amounts of borane, but use of a hindered borane such as disiamylborane prevents further hydroboration. Disiamylborane also yields monohydroboration products on reaction with terminal alkynes which give only bis-hydroboration products with borane itself. Boranes formed by monohydroboration of alkynes undergo many of the transformations described in section 11.3. Some representative examples having synthetic utility include the following:







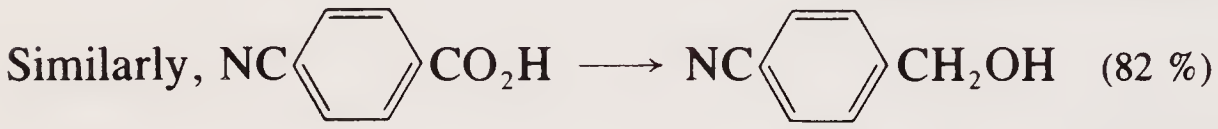
The bis-hydroboration products formed by reaction of borane with terminal alkynes are complex polymers which on reaction with alkaline hydrogen peroxide yield mixtures of products. However, a synthetically useful procedure is the oxidation of the bis-hydroboration product of dicyclohexylborane and terminal alkynes to alkanoic acids:

11.6 Reduction of carboxylic acids

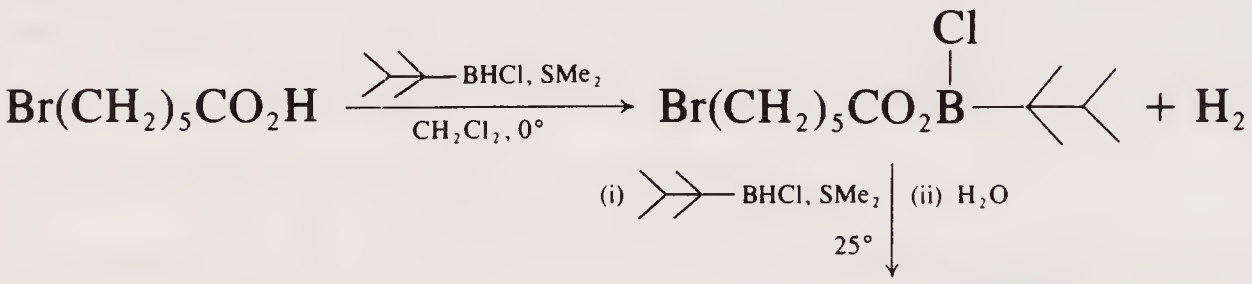
It was noted in section 8.2 that aluminium hydrides are versatile reducing agents, and the same is true of boron hydrides. Reduction of alkenes to alkanes, and of alkynes to *Z*-alkenes, have already been mentioned (sections 11.3.4 and 11.5, respectively). Boranes are also used to good effect in the selective reduction of carboxylic acids.

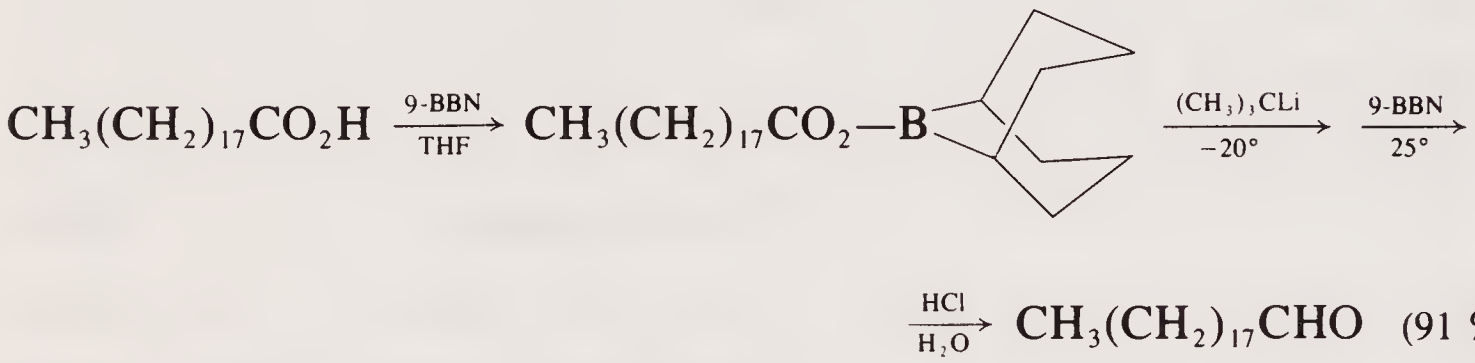
Reduction using the borane-tetrahydrofuran reagent gives primary alcohols. Other potentially reducible functional groups such as halogeno, nitro, cyano, and ester are unaffected.

$$HO_2C(CH_2)_4CO_2C_2H_5 \xrightarrow[\text{(ii) } H_2O]{\text{(i) } BH_3,\ THF} HO(CH_2)_5CO_2C_2H_5 \quad (88\ \%)$$

Similarly,  (82 %)

Hindered boranes may be used for the reduction of carboxylic acids to aldehydes. Chlorothexylborane-dimethyl sulphide (which is readily prepared from 2,3-dimethylbut-2-ene and chloroborane-dimethyl sulphide) and 9-BBN have both been used: aromatic acids are less easily reduced than aliphatic or alicyclic acids.





Notes

1. Borane dimerises in the gas phase and is then more correctly called diborane, B_2H_6. In solvents such as THF the reactive species is THF:BH_3. Hydroboration may be carried out using THF:BH_3 or by reacting the substrate with sodium borohydride and boron trifluoride in THF or diglyme.

2. The term is literally an abbreviated version of 'di-secondary-isoamylborane'. The name approved by *Chemical Abstracts* is bis-(1,2-dimethylpropyl)borane.

3. Literally, 'tertiary-hexyl-borane'; the approved name is 1,1,2-trimethylpropylborane.

4. Cf. H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37,** 3547 (1981).

12 Phosphorus reagents

In recent years, there has been an increasing interest in the application of phosphorus reagents in organic synthesis. In the space available in this book, it is possible only to describe some highlights of this field.

12.1 Introduction to organophosphorus chemistry

The versatility of phosphorus is due in large part to several aspects of its chemistry, e.g.:

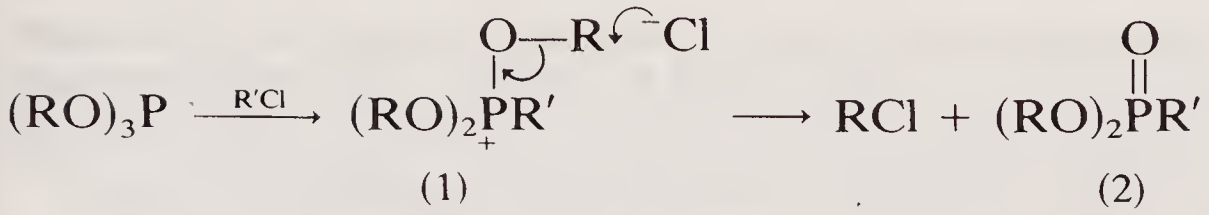
(i) phosphorus exists as di-, tri-, tetra-, penta- and hexa-co-ordinate species and many interconversions of these are known;
(ii) tervalent phosphorus compounds are weakly basic and highly nucleophilic species, and they react by nucleophilic attack at a variety of sites (e.g. nitrogen, oxygen, sulphur, halogen and electrophilic carbon);
(iii) phosphorus forms strong bonds with many other elements including carbon, nitrogen, halogen, sulphur and oxygen, with the P=O bond being of particular strength and importance;
(iv) phosphorus is capable of stabilising adjacent anions.

The highly nucleophilic character of trialkyl- or triarylphosphines is exemplified by their ready reaction with alkyl halides. The quaternary salts formed from triphenylphosphine are the precursors of the familiar Wittig reagents (cf. section 5.3.1): for example,

$$Ph_3P + CH_3I \rightarrow Ph_3\overset{+}{P}CH_3\ I^- \xrightarrow{\text{base}} Ph_3\overset{+}{P}—\bar{C}H_2$$

The stabilisation of the carbanion in these reagents is due to the adjacent phosphorus.

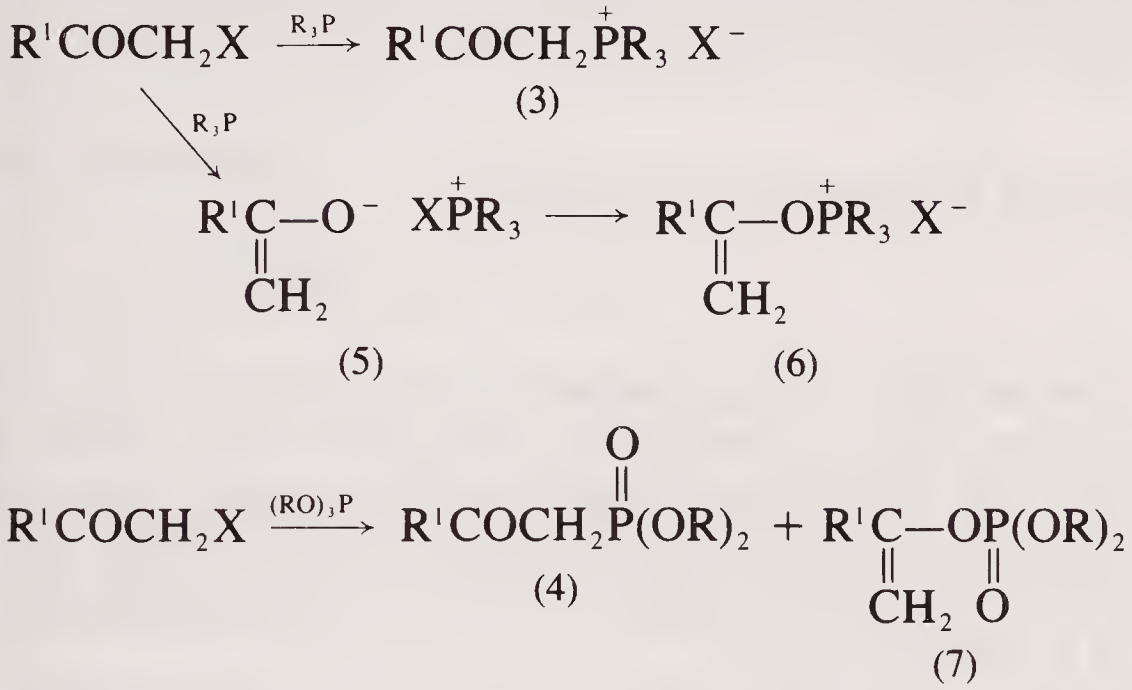
In the case of phosphites, the reaction takes a different course. In this, the **Michaelis–Arbusov reaction,** the alkoxyphosphonium salts (1) formed undergo further reaction resulting in the formation of phosphonate esters (2):



(1) (2)

A range of functional groups can be accommodated in the halide, and phosphonate esters of the type $(RO)_2P(O)CH_2R^2$ where R^2 is an electron accepting ($-M$) group, are of particular synthetic utility (cf. section 12.2).

Reactions of phosphines and phosphites with α-halogenoketones, which might have been expected to yield ketophosphonium salts (3) and ketophosphonates (4), respectively, are in fact more complex. The reaction involving phosphines may take two paths: nucleophilic displacement (S_N2) of the halogen, to give the salt (3), is indeed observed, but direct nucleophilic attack on the halogen may also give a halogenophosphonium enolate (5) and thence an enol phosphonium halide (6). A trialkyl phosphite can similarly react with an α-halogenoketone in two ways, resulting in the formation of a ketophosphonate (4) (the Michaelis–Arbusov product) or an enol phosphate (7) (the **Perkow** product).



(3) (5) (6) (4) (7)

Halogenophosphonium salts (5) have a number of synthetic applications (cf. section 12.3.1).

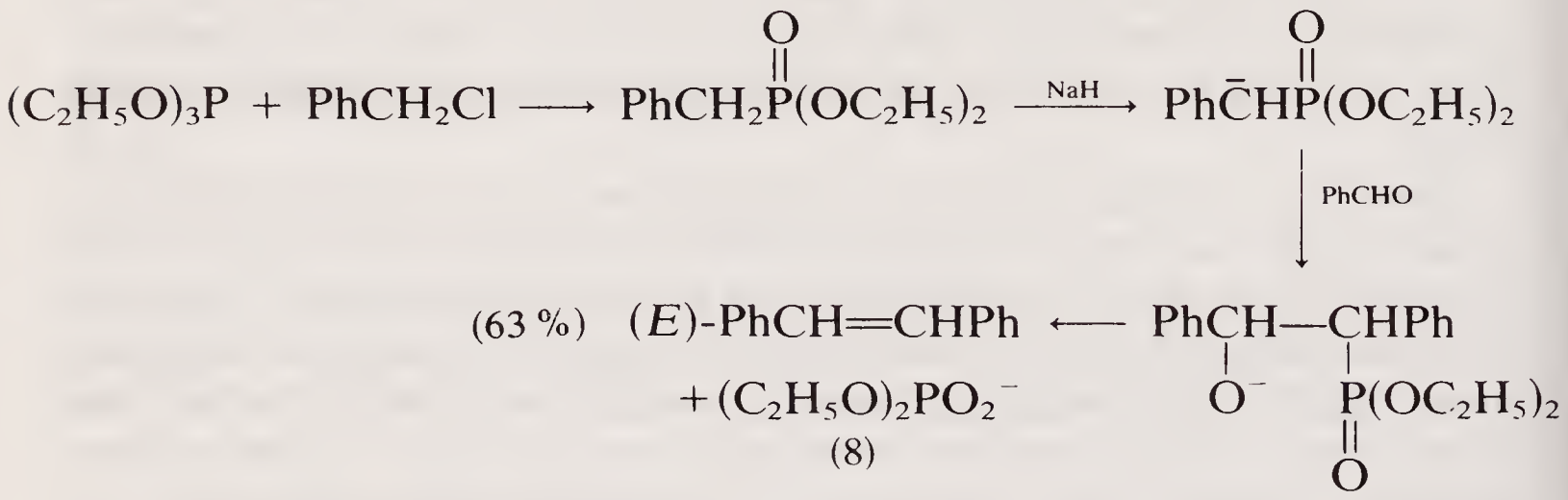
The size and polarisability of phosphorus enable it to react more easily at sulphur than at the first row elements oxygen and nitrogen. Indeed, phosphites and phosphines react with sulphur in air to give thionophosphates, $(RO)_3P{=}S$, and phosphine sulphides, $R_3P{=}S$, respectively, rather than the oxygen analogues.

12.2 Formation of carbon–carbon multiple bonds

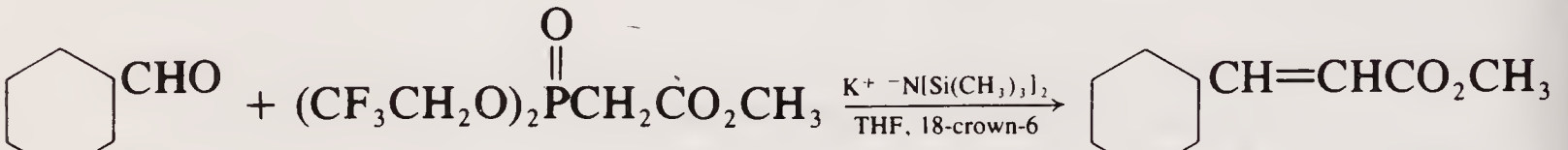
12.2.1 Formation of alkenes

The Wittig reaction has now become one of the most familiar reactions to the synthetic chemist, and it has been discussed in some detail in sec-

tion 5.3.1. An alternative procedure which may have certain advantages over the Wittig reaction was developed by Horner and by Wadsworth and Emmons among others. This involves reaction of aldehydes and ketones with stabilised carbanions derived from phosphonate esters.

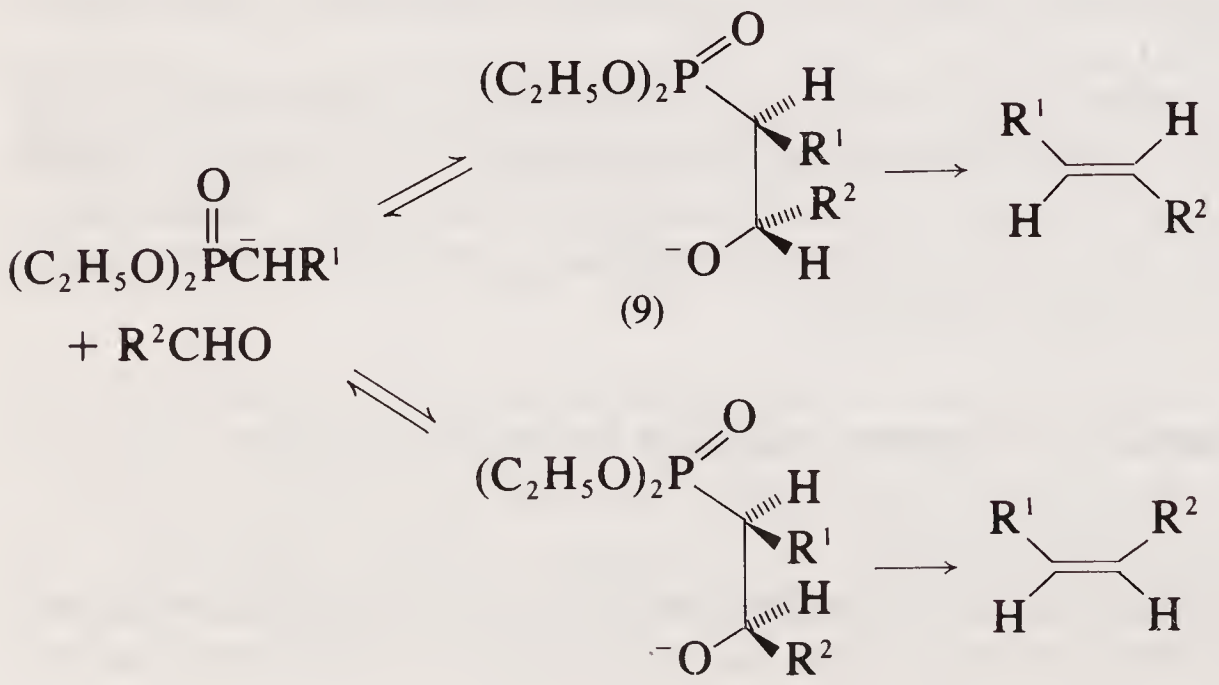


Like Wittig reactions involving stabilised ylides, the *E*-(or *trans*-)alkene usually predominates, but in some cases it has been shown that the *Z*:*E* ratio can be significantly increased by the use of a bis-(2,2,2-trifluoroethyl)phosphonate ester and a base of low complexing ability, e.g.



(80 %; $Z:E > 50:1$)

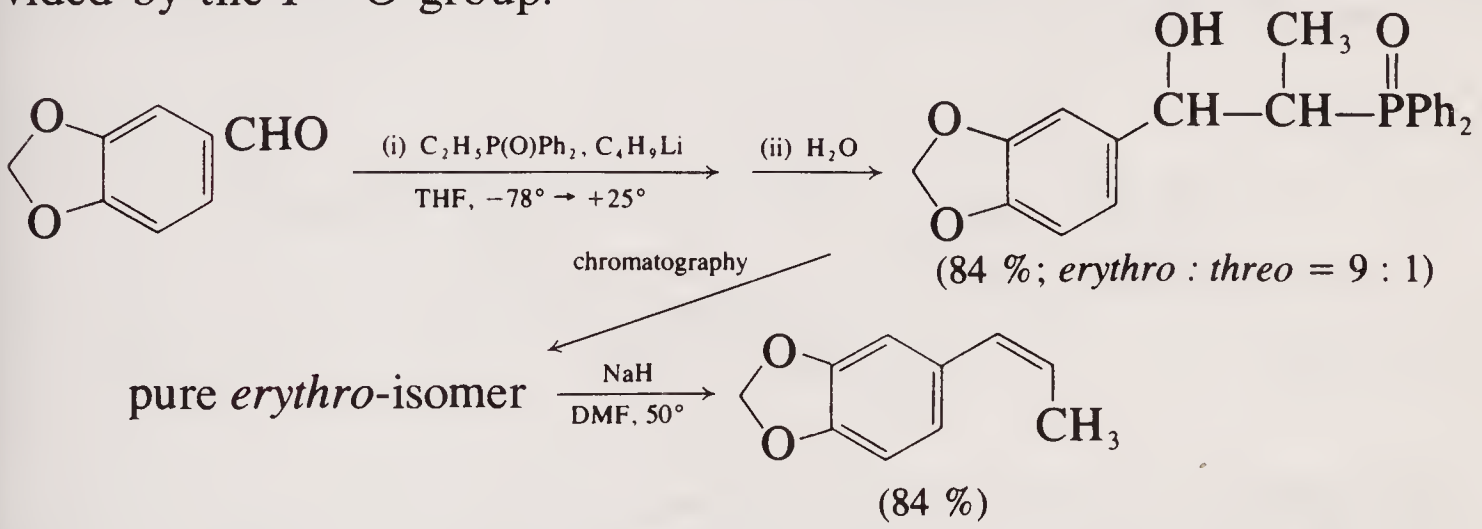
All these reactions are believed to involve the formation of anions of β-hydroxyphosphonates, and a subsequent elimination step which is highly stereospecific. The *threo*-isomer (9) of the intermediate anion is the more stable thermodynamically, and for those reactions which proceed under thermodynamic control (Sykes, p. 42) this intermediate predominates and the *E*-alkene results.



Advantages claimed for this reaction over the Wittig procedure include the following:

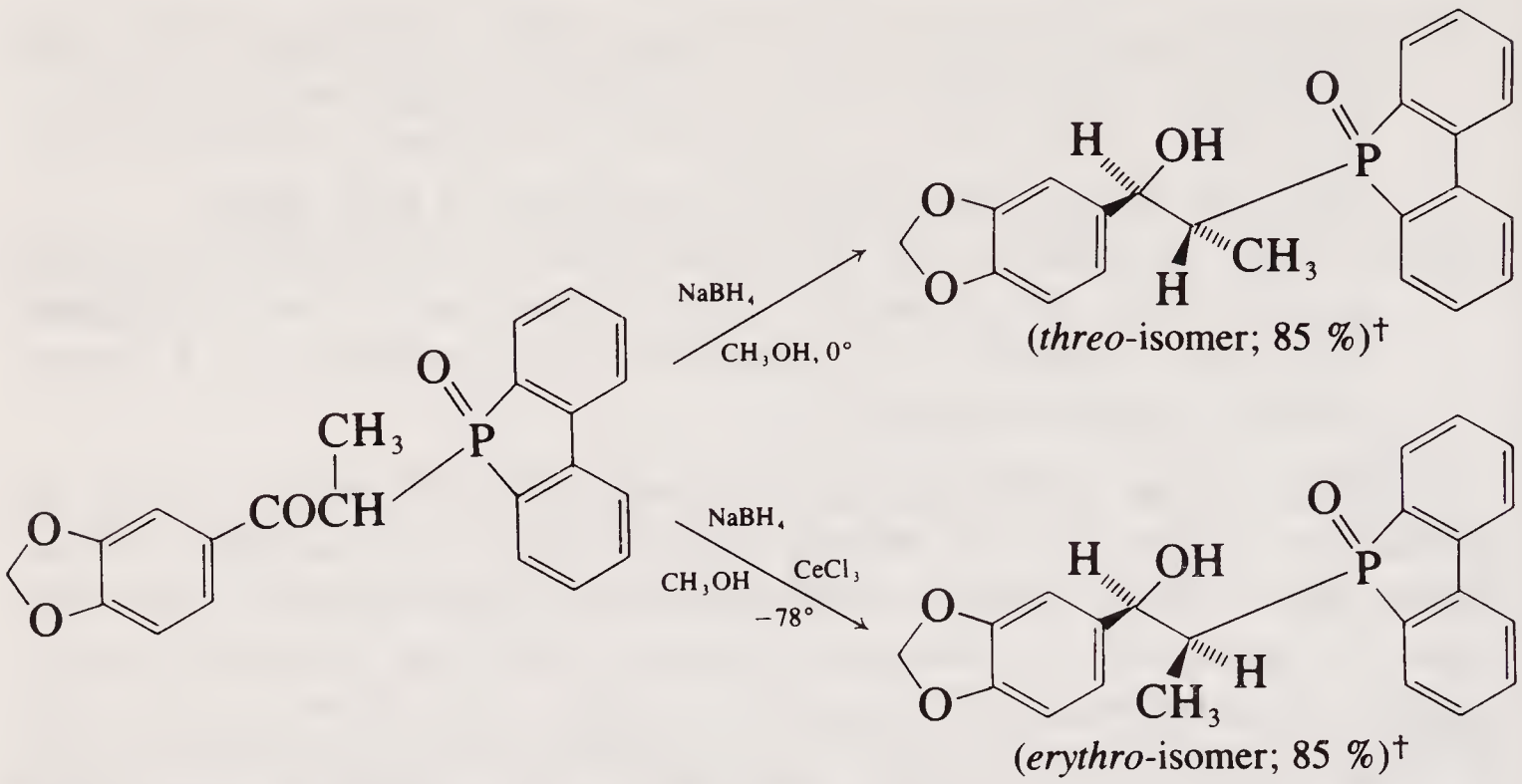
(i) Wittig reactions involving stabilised ylides are slow and, since additional stabilisation by an electron-withdrawing group is required in almost all successful P=O stabilised carbanion reactions, the latter is the preferred procedure in such cases;
(ii) a major problem in the Wittig procedure is the separation of the product from the phosphine oxide formed; with P=O stabilised carbanion reactions the phosphorus is eliminated as a water-soluble phosphate anion (8).

Another variant of this procedure, developed by Warren, provides an alternative to the classical Wittig reaction with non-stabilised ylides. *Threo*- and *erythro*- isomers of (β-hydroxyalkyl)phosphine oxides can often be separated by chromatography, and these purified isomers undergo base-induced decomposition to give, respectively, *E*- and *Z*-alkenes in a high degree of purity. The (β-hydroxyalkyl)phosphine oxides may be prepared directly by reaction of an alkyldiphenylphosphine oxide with a strong base and an aldehyde or ketone; it should be noted that no stabilisation of the carbanion is required other than that provided by the P=O group.



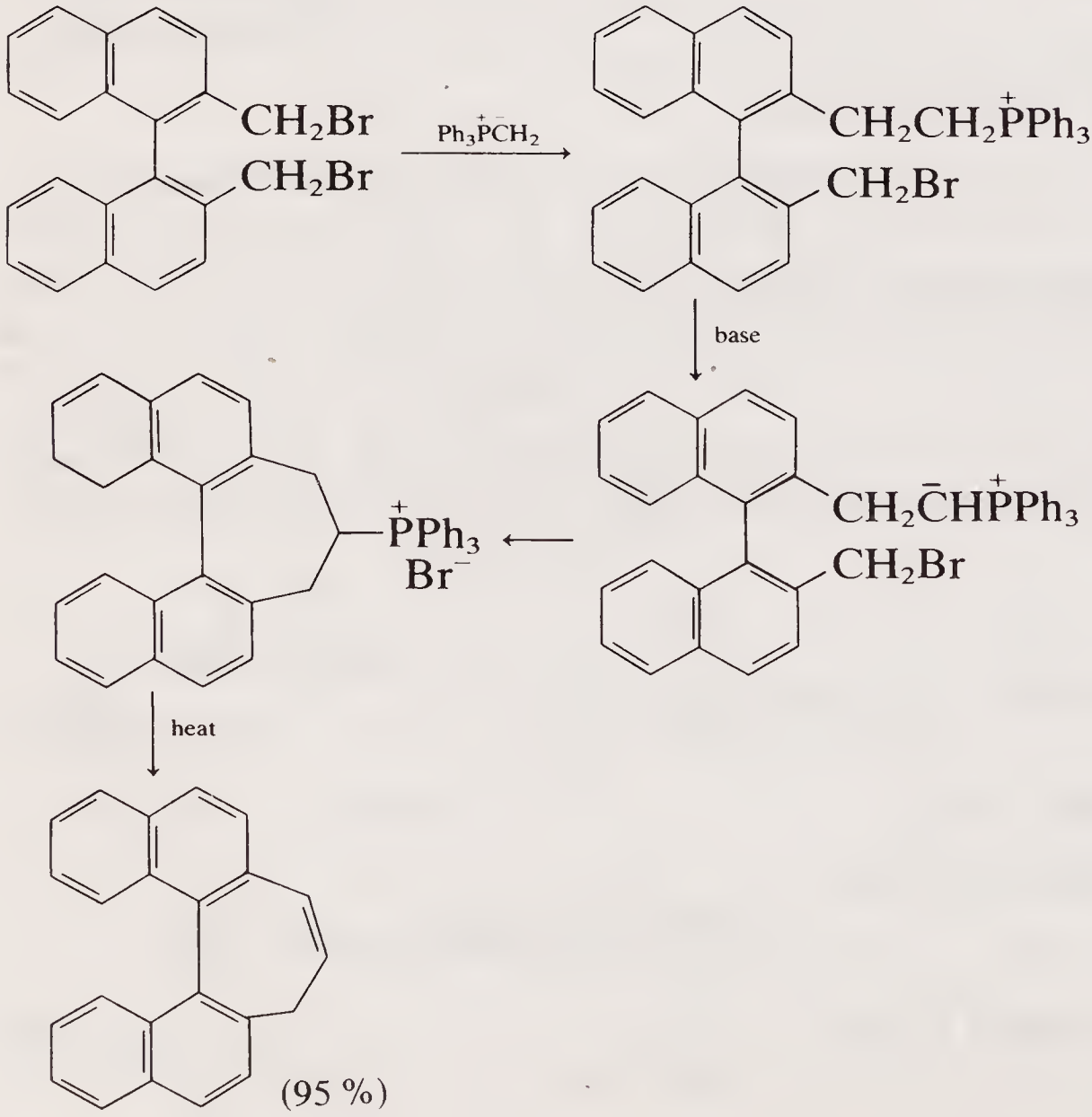
Alternatively, the (β-hydroxyalkyl)phosphine oxide may be obtained by acylation of the phosphorus-stabilised carbanion followed by reduction, e.g.

Some (β-ketoalkyl)phosphine oxides give widely differing *erythro*: *threo* ratios according to the reducing agent used, e.g.

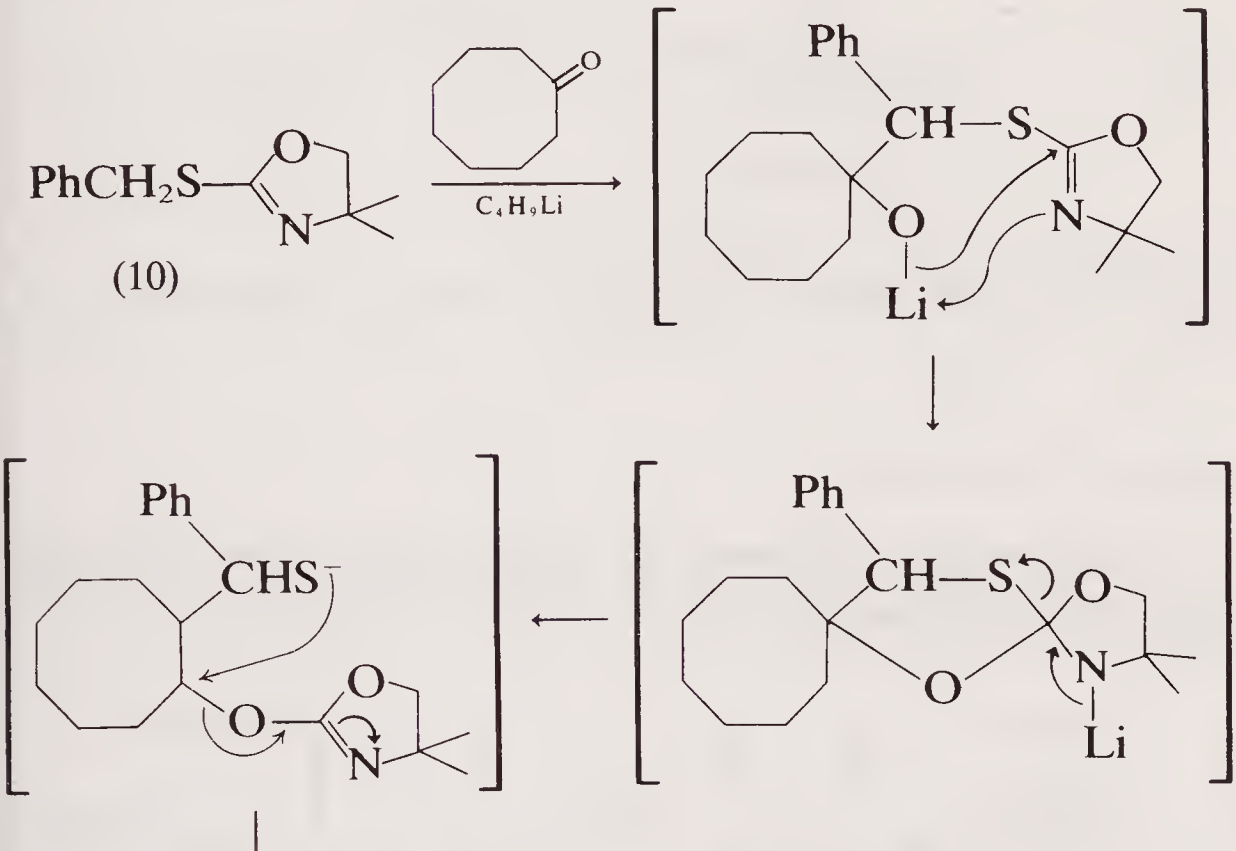


† 15% of the other diastereoisomer is formed in each reaction.

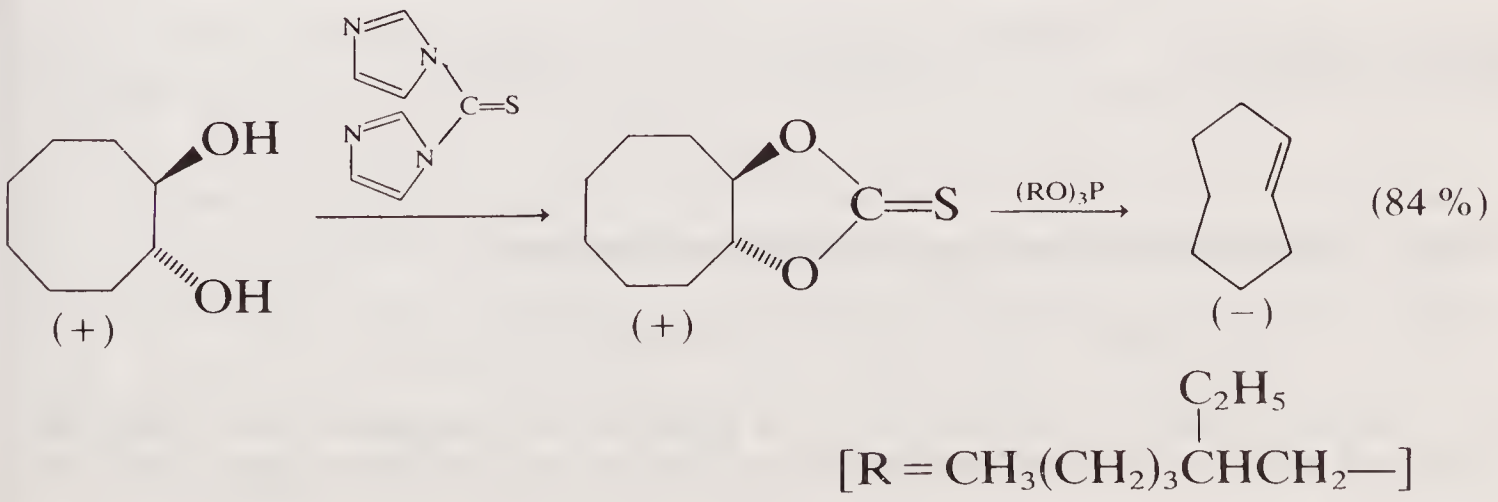
An extension of the Wittig reaction which leads to the formation of cycloalkenes should also be mentioned here. This involves intramolecular *C*-alkylation of an ylide, e.g.



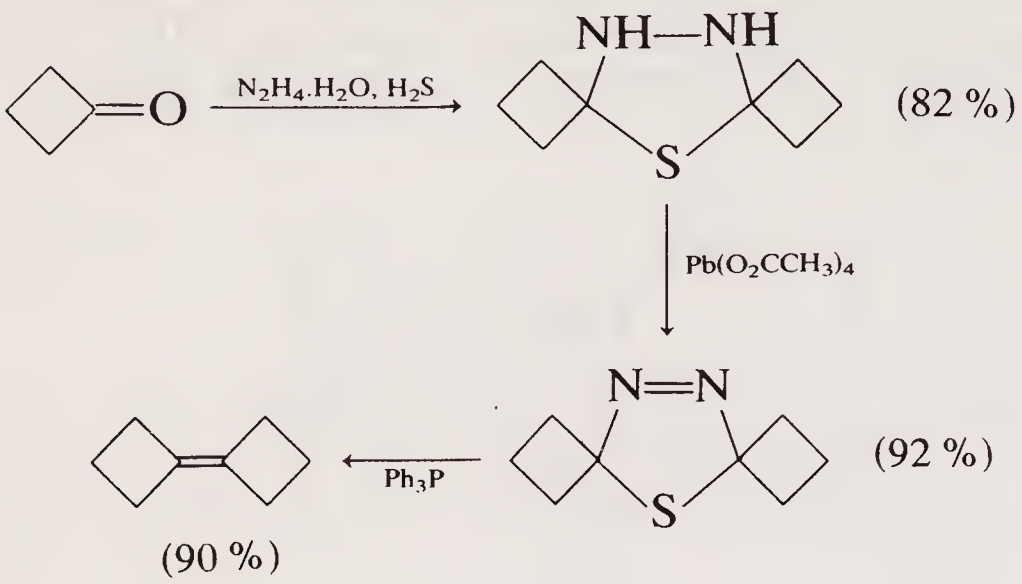
The ready reaction of tervalent phosphorus compounds with sulphur has already been noted. Thiirans undergo elimination of sulphur on reaction with phosphines and phosphites, yielding an alkene in which the stereochemistry is retained. The thiirans themselves may be obtained by the base-catalysed reaction of 2-(alkylthio)-oxazolines [e.g. (10)] with aldehydes or ketones. Where $E:Z$ isomerism is possible the E-isomer predominates:



Another extrusion reaction initiated by reaction of tervalent phosphorus at sulphur is the conversion of 1,2-diols into alkenes *via* an intermediate thionocarbonate. *Z*-Alkenes are derived from *erythro*-diols and *E*-alkenes from *threo*-diols. This has been used in many reactions including the synthesis of *trans*-cyclo-octene shown below:

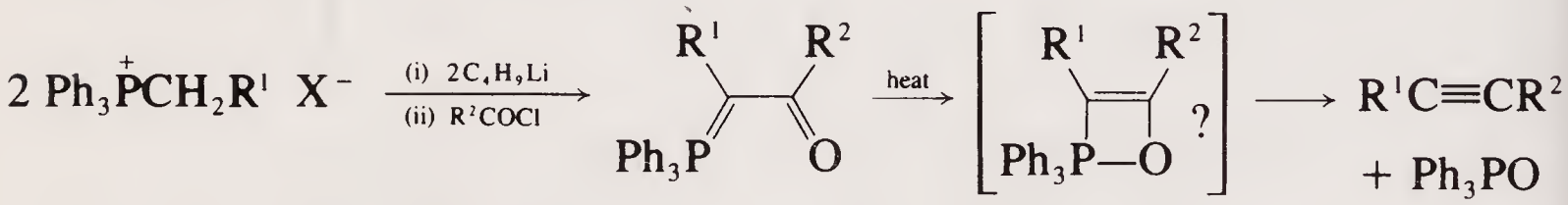


In these reactions the double bond is produced by elimination from a compound containing an already formed single bond. Double extrusion reactions have also been reported, e.g.

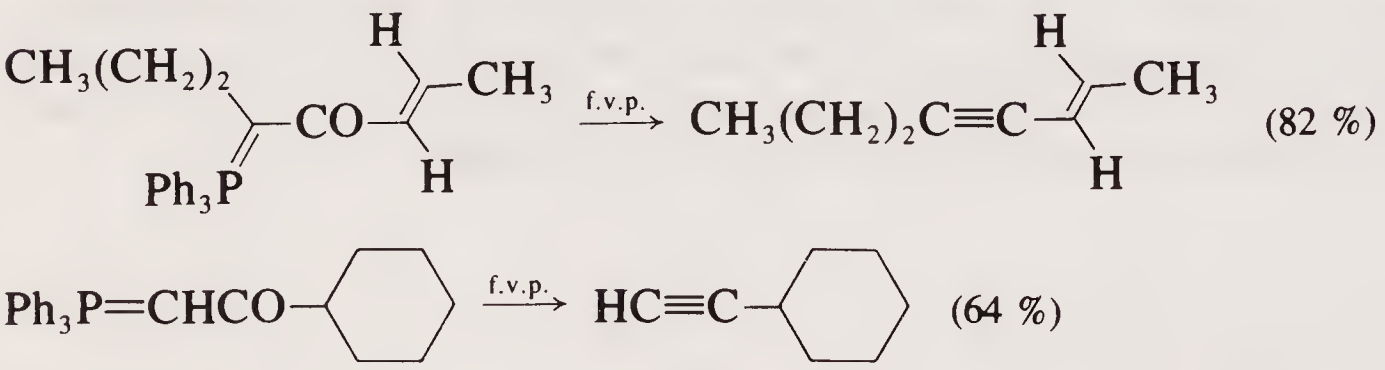


12.2.2 Formation of alkynes

Acylation of a Wittig reagent, followed by thermolysis of the resulting β-ketoalkylidene-triphenylphosphorane, provides an attractive route to alkynes:



Conventional pyrolysis techniques allow the formation of alkynes only when R^1 is electron-withdrawing. However, the use of flash vacuum pyrolysis (f.v.p.)[1] permits the extension of the method to a wide range of alkynes, including alk-1-ynes, e.g.

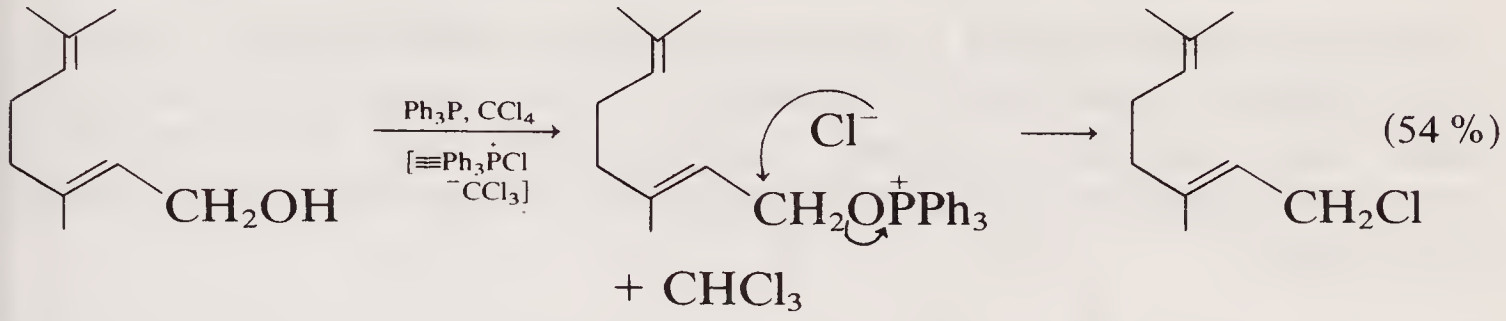


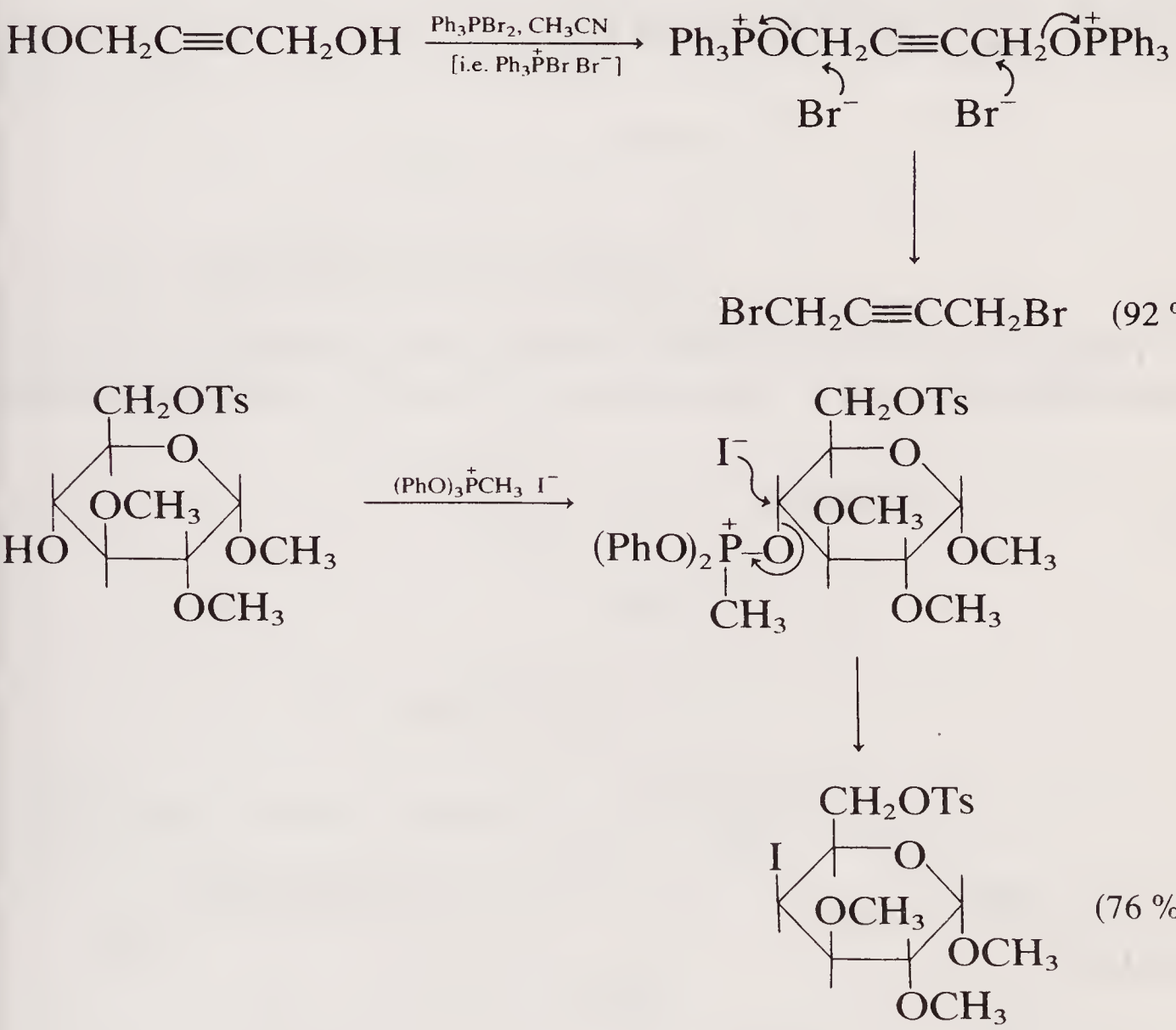
12.3 Functional group transformations

12.3.1 Conversion of hydroxyl into halogen

As was indicated in section 2.7.1, a number of reagents have been developed which convert alcohols into alkyl halides with relatively little

racemisation and rearrangement. Many systems have been investigated and although it is not possible to generalise, it appears that for chlorination, carbon tetrachloride with triphenylphosphine is best, while for bromination and iodination, Ph_3PBr_2 and $(PhO)_3\overset{+}{P}CH_3\ I^-$, respectively, have been widely used. Examples of these reactions include:





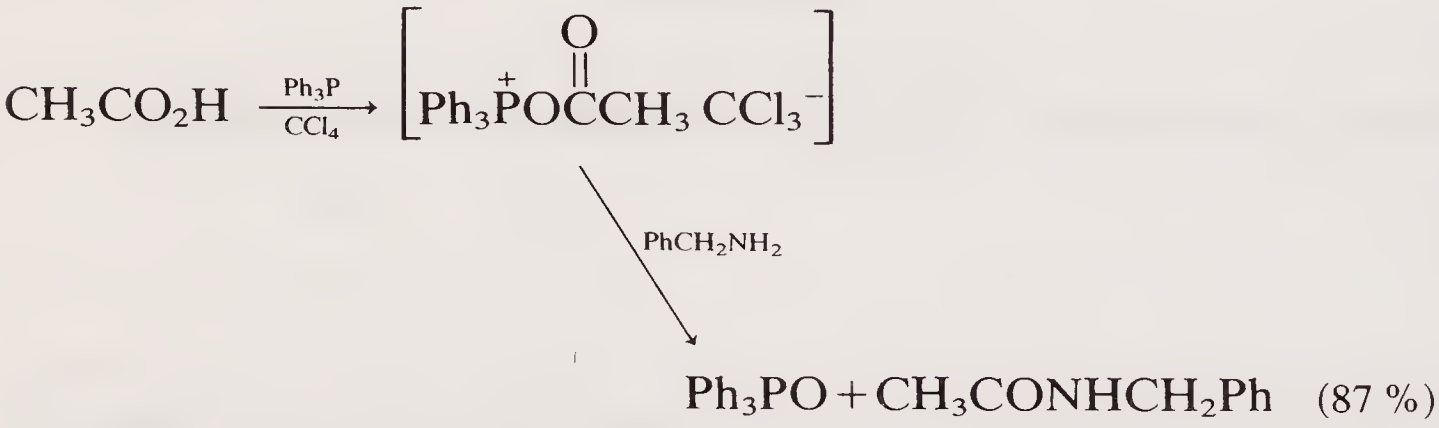
In each case, the reaction is normally of the S_N2 type with inversion at the reaction centre; the chlorination and bromination sequences involve initially the attack of a halogenophosphonium ion on the hydroxyl group. Reactions of secondary alcohols are slower than those of primary alcohols, and elimination may be a competing side-reaction in the former case when more polar solvents, e.g. dimethylformamide, are used. Many other functional groups, except those with acidic hydrogens, are unaffected.

At low temperatures, certain alkoxyphosphonium salts can be isolated

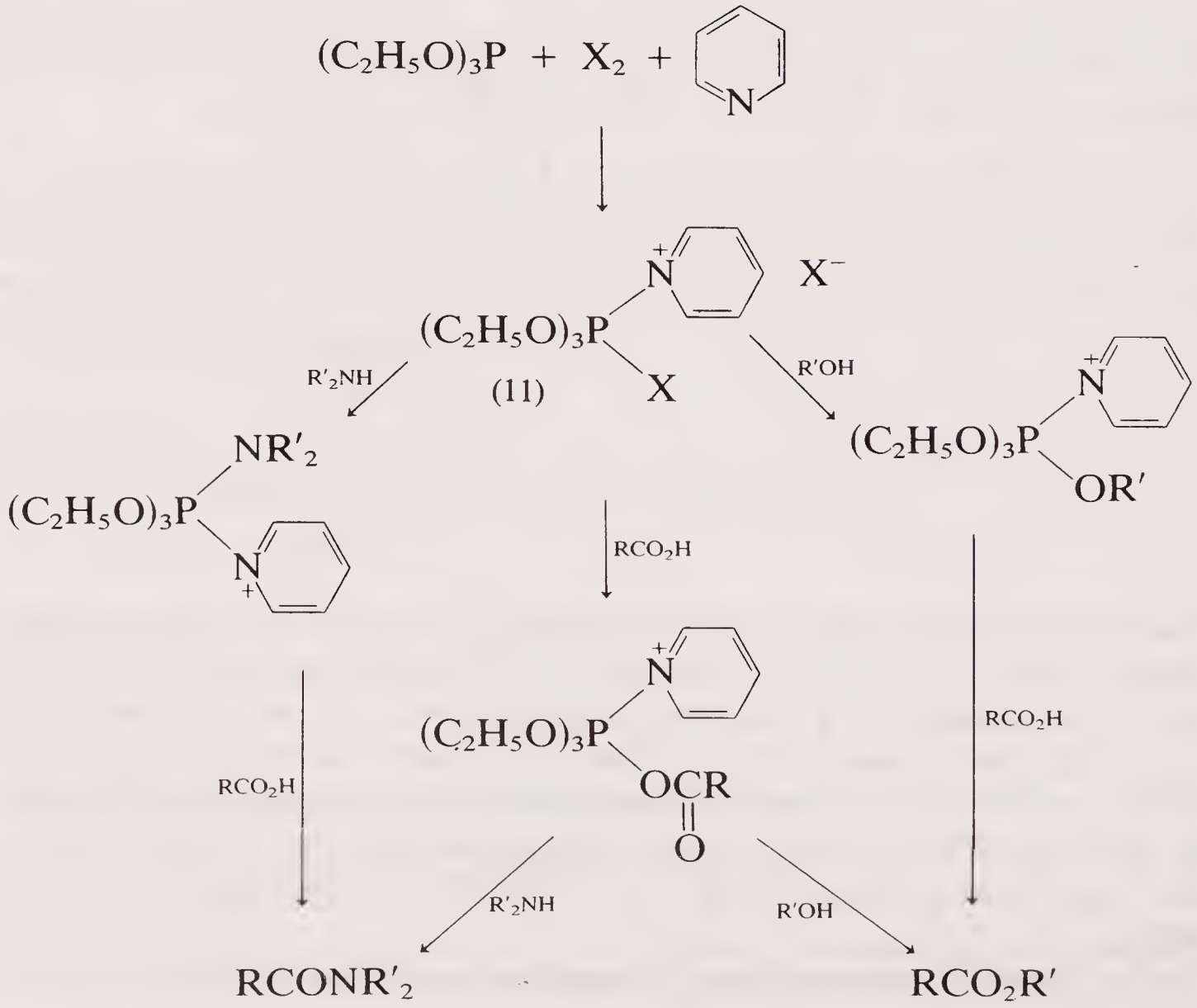
and these, on reaction with the appropriate nucleophiles, can be converted into products such as amines, thiols, nitriles, azides and thiocyanates.

12.3.2 Formation of amides and esters and related reactions

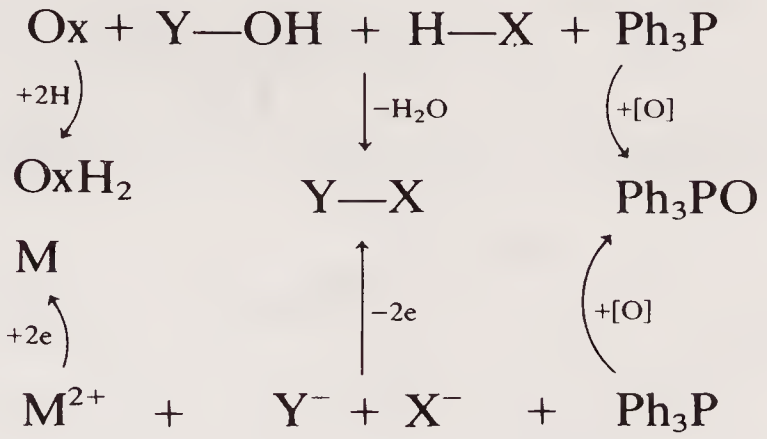
Triphenylphosphine with carbon tetrachloride, and triethyl phosphite with pyridine in presence of bromine or iodine, promote the reaction of acids with alcohols or amines. In the former case, an intermediate acyloxyphosphonium salt is the electrophilic species which reacts readily with amines.



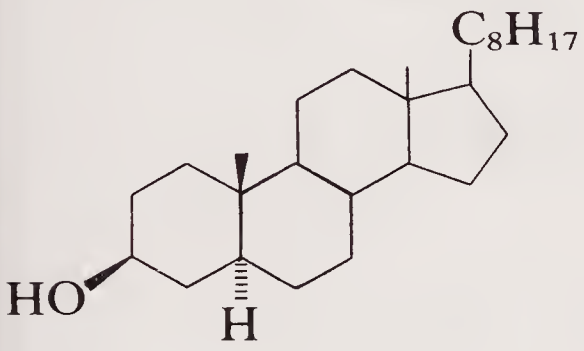
The phosphite/pyridine/halogen reaction involves a reactive penta-coordinate intermediate (11) which reacts with amines, alcohols or acids.



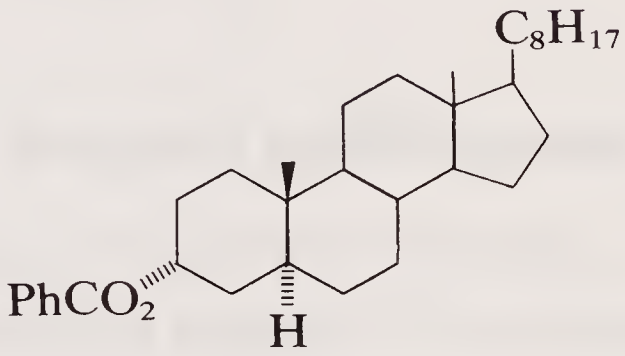
An alternative strategy for esterification and amide formation involves an oxidation–reduction process:



Oxidants which have been used in these reactions include diethyl azodicarboxylate, sulphenamides and disulphides. Examples include the following[2]:



$$\xrightarrow[PhCO_2H]{C_2H_5O_2CN{=}NCO_2C_2H_5,\ Ph_3P}$$



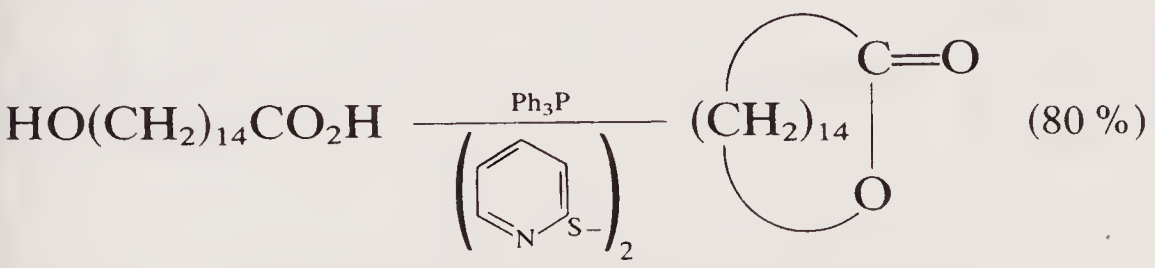
(100 %)

[N.B. inversion of configuration in product]

$$2CH_3(CH_2)_3NHSPh + 2Ph_3P + [CH_3(CH_2)_4CO_2]_2Cu \longrightarrow$$

$$2CH_3(CH_2)_3NHCO(CH_2)_4CH_3 + 2Ph_3PO + (PhS)_2Cu$$

(95 %)

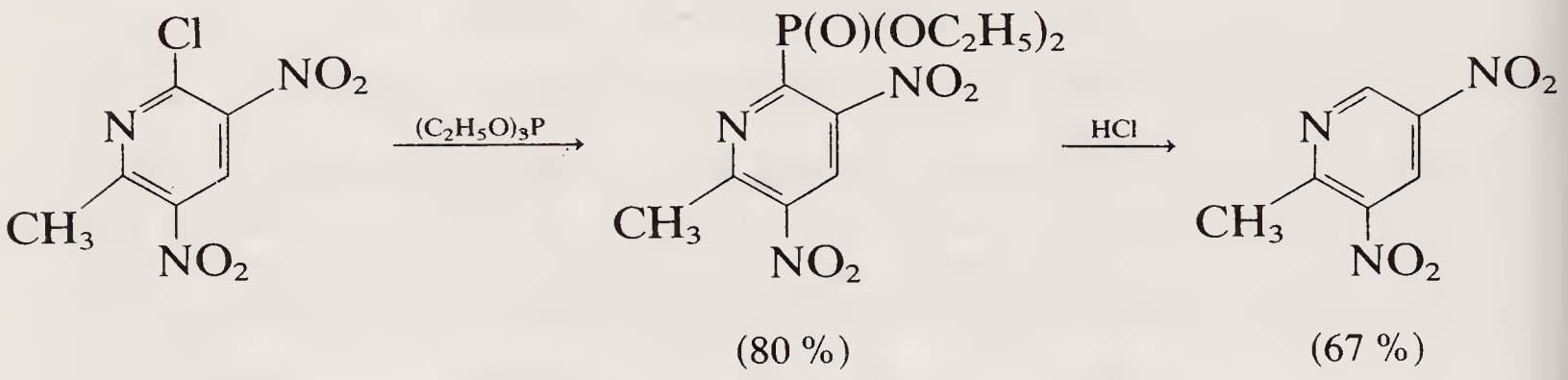


(80 %)

12.3.3 Dehalogenation of aryl halides

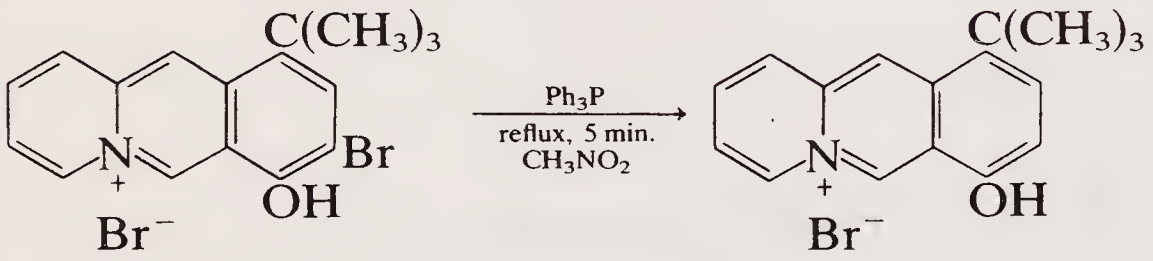
Although aryl halides are generally unreactive towards tervalent phosphorus compounds, two dehalogenation reactions are worth noting.

Halogens activated towards nucleophilic attack react with triethyl phosphite to give phosphonates which are cleaved with acids:



(80 %) (67 %)

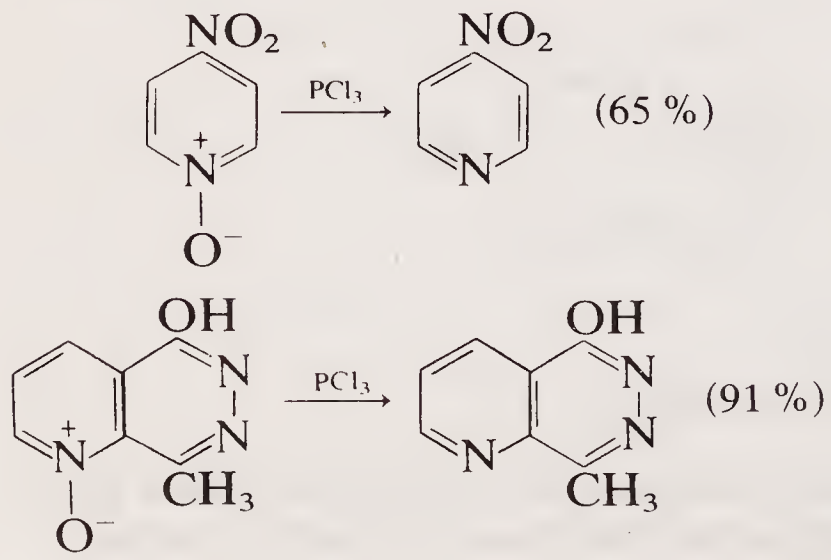
Triphenylphosphine brings about a very rapid debromination of *o*- and *p*-bromophenols, e.g.



12.4 Deoxygenation reactions

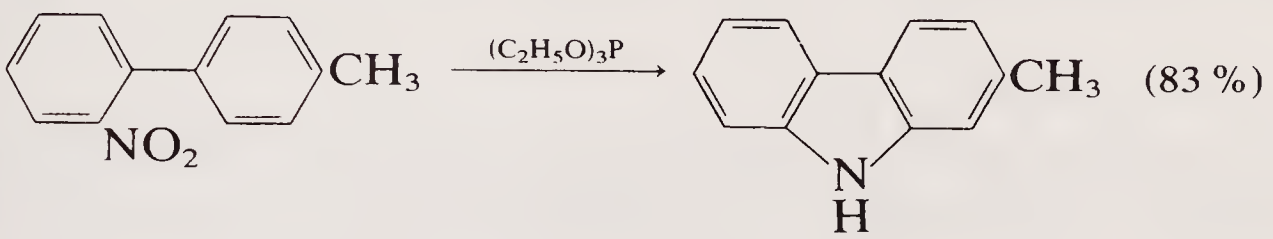
12.4.1 Reduction of amine *N*-oxides

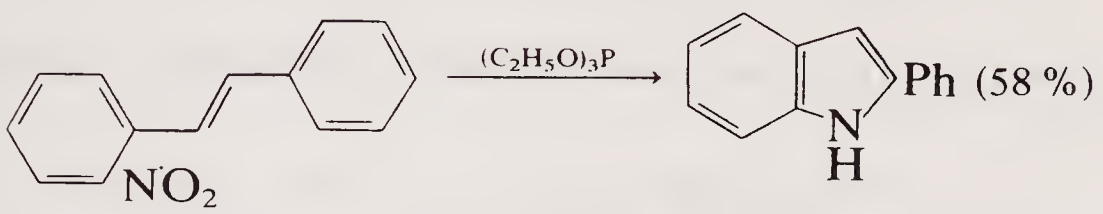
Deoxygenation of *N*-oxides is a synthetic procedure of considerable significance because, in many instances, it is necessary to carry out substitution reactions on electron-deficient heteroaromatic *N*-oxides rather than on the free bases (cf. section 2.6). Tervalent phosphorus compounds are particularly effective reagents for reduction of *N*-oxides. In general PCl_3 is the most reactive, but its use may cause side reactions involving replacement of active nitro groups or halogenation of hydroxyl groups.

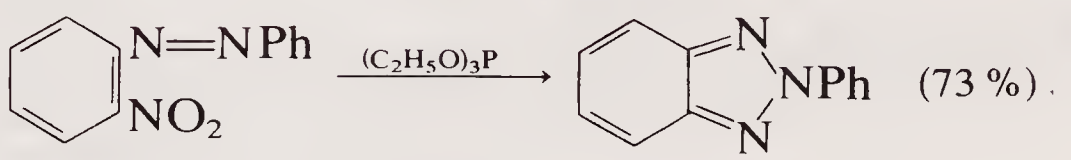


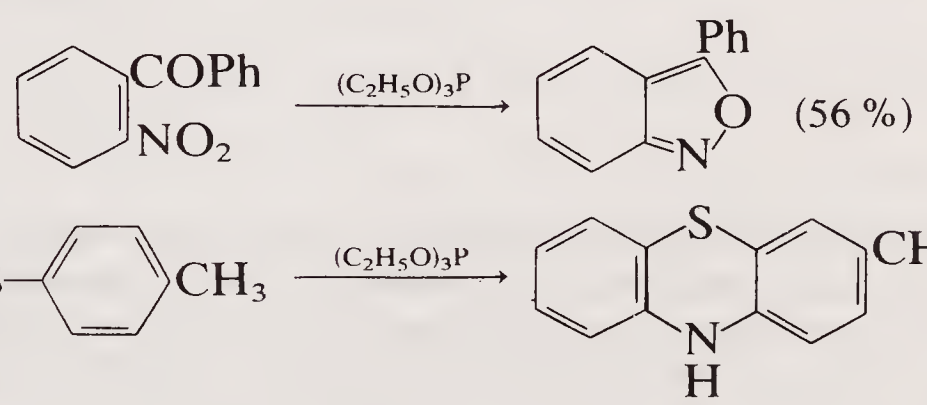
12.4.2 Cyclisation reactions involving nitro- and nitroso-groups

Aryl nitro- and nitroso-compounds react with tervalent phosphorus compounds to give products which may be ascribed to the intermediacy of a nitrene. Thus if the molecule possesses a group appropriately situated which can react with the nitrene, a nitrogen-containing heterocyclic compound is obtained. Some illustrative reactions are given:

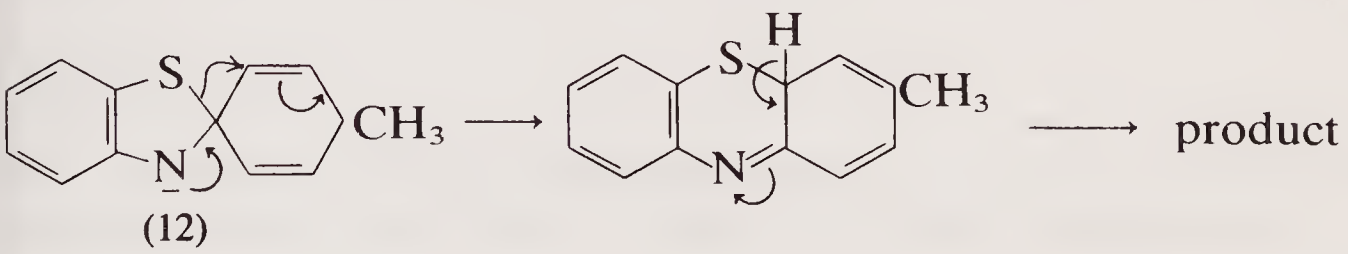






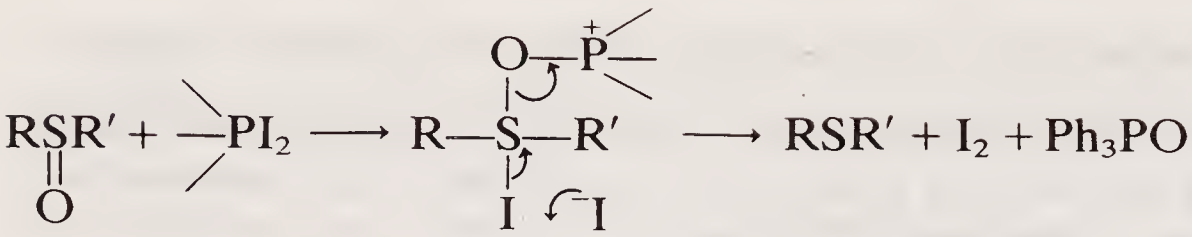


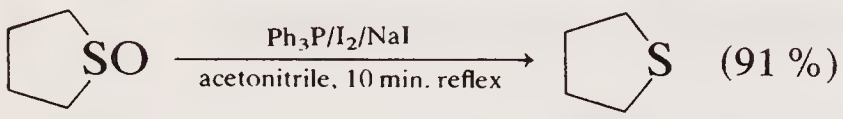
Note that this last reaction involves the initial formation of a five-membered spirodienyl intermediate (12) which undergoes rearrangement:

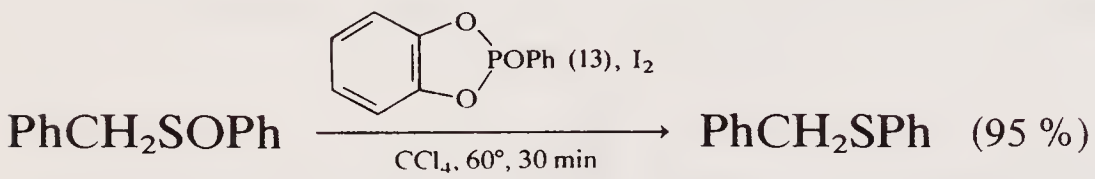


12.4.3 Deoxygenation of sulphoxides

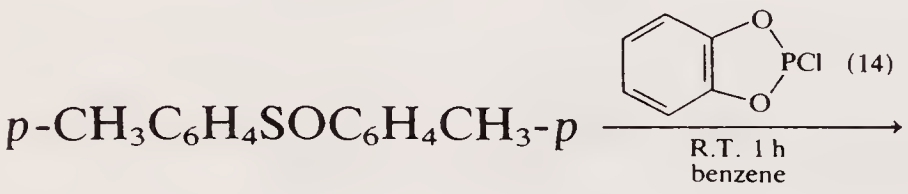
Unlike *N*-oxides, sulphoxides react only slowly with tervalent phosphorus compounds. However, sulphoxides are readily reduced by the following mixtures: $Ph_3P/I_2/NaI$ and 2-phenoxy-1,3,2-benzodioxaphosphole (13)/carbon tetrachloride/I_2. Both reactions may involve a di-iodide:







2-Chloro-1,3,2-benzodioxaphosphole (14) also effectively deoxygenates sulphoxides:



Notes

1. In flash vacuum pyrolysis, the substrate is passed, in the vapour phase under reduced pressure, through a tube heated to high temperatures (typically 400–900°). Since each molecule spends only a short time in the hot zone, and reacts in isolation (free from other molecules of substrate, product or solvent), the technique is mild and side-reactions are avoided.

   For further details, see R. F. C. Brown, *Pyrolytic Methods in Organic Chemistry*, Academic Press, 1980.

2. Cf. O. Mitsunobu, *Synthesis*, **1981**, 1.

13 Silicon reagents

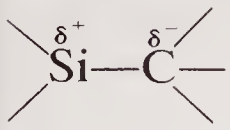
In recent years, organosilicon compounds have found widespread use as intermediates in synthetic sequences. This chapter describes some of the more important features of the chemistry of these compounds, and the synthetic applications which result.

13.1 Introduction to organosilicon chemistry

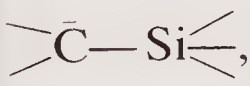
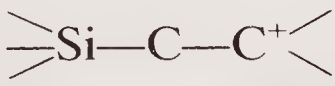
Silicon occupies a position below carbon in group 14 of the periodic table. Its electronic configuration, $3s^2$. $3p^2$, indicates quadrivalence but several aspects of its bonding to other elements differ from those of carbon. For example,

(i) Si forms stronger bonds with O and F than does C but weaker bonds with C and H;
(ii) the $3p$-electrons of Si do not overlap effectively with the $2p$-electrons of C or O. Multiple bonds C=Si and O=Si are not, therefore, commonly found in stable molecules;
(iii) unlike C, Si can form stable hexaco-ordinate systems, e.g. SiF_6^{2-};
(iv) F^- can attack a vacant $3d$ orbital of Si, giving a pentaco-ordinate anion. Intermediates of this type have been postulated in a number of fluoride-catalysed reactions.

In addition to the foregoing, one must remember that silicon is less electronegative than carbon and therefore Si–C bonds are polarised:



This results in alkylsilanes being prone to attack by nucleophilic reagents. Silicon also has the ability to stabilise α-carbanions,

 , and β-carbocations,  .

13.2 Synthesis of organosilicon compounds

Among readily available organosilicon reagents are the chlorosilanes, $SiCl_4$, $RSiCl_3$, R_2SiCl_2 and R_3SiCl. These halides undergo facile nucleo-

philic substitution reactions in which valuable synthetic intermediates are formed, as illustrated below:

$$SiCl_4 + 2C_2H_5MgBr \xrightarrow[\text{ether}]{} (C_2H_5)_2SiCl_2 \quad (75\ \%)$$

$$(CH_3)_3SiCl + BrMgC{\equiv}CCH_2OH \xrightarrow[\text{ether}]{} (CH_3)_3SiC{\equiv}CCH_2OH \quad (44\ \%)$$

$$(CH_3)_3SiCl + NaN_3 \rightarrow (CH_3)_3SiN_3 \quad (87\ \%)$$

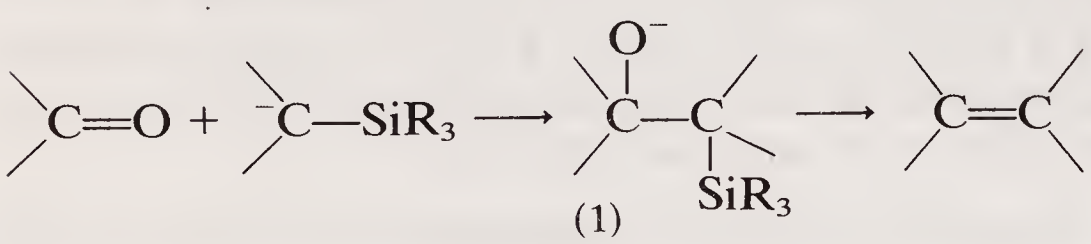
$$(CH_3)_3SiCl + CH_3CONH_2 \xrightarrow{(C_2H_5)_3N} (CH_3)_3SiNHCOCH_3 \quad (90\ \%)$$

$$\left[(CH_3)_2N\text{-}C_6H_4\right]_3SiCl \xrightarrow[\text{ether}]{LiAlH_4} \left[(CH_3)_2N\text{-}C_6H_4\right]_3SiH \quad (98\ \%)$$

13.3 Carbon–carbon bond forming reactions

13.3.1 Reactions involving silicon-stabilised carbanions

When α-silylcarbanions react with carbonyl compounds, the intermediate (1) often decomposes spontaneously to give an alkene. This process (the **Peterson synthesis**) is obviously analogous to the Wittig reaction (cf. section 5.3.1) and the Wadsworth–Emmons–Horner reaction (cf. section 12.2).



(1)

However, unlike the Wittig reaction, in most cases where *E* and *Z* isomers can be produced both isomers are formed in almost equal proportions: for example,

$$(CH_3)_3SiCH_2\overset{O}{\overset{\|}{S}}Ph \xrightarrow[THF,\ -70°]{(CH_3)_3CLi} (CH_3)_3Si\bar{C}H\overset{O}{\overset{\|}{S}}Ph \xrightarrow{PhCHO} PhCH{=}CH\overset{O}{\overset{\|}{S}}Ph \quad (87\ \%)$$

$$E:Z = 1:1$$

This lack of stereospecificity results from the formation, under kinetic control, of almost equal amounts of *threo*- and *erythro*-isomers of (1), which have been shown to decompose, with a high degree of selectivity, to the *E*- and *Z*-alkenes, respectively. An advantage over the Wittig reaction, however, is that the normal by-product in the Peterson reaction is

hexamethyldisiloxane, $(CH_3)_3SiOSi(CH_3)_3$; this is a volatile liquid (b.p.101°) which is readily removed from the reaction mixture by distillation.

α-Silylcarbanions can also be prepared by reaction of a polysilylated methane with an alkoxide. The driving force for this reaction is presumed to be the thermodynamically favoured formation of a silicon–oxygen bond. The carbanions so formed have been used in the preparation of alkenes from non-enolisable ketones, as exemplified below:

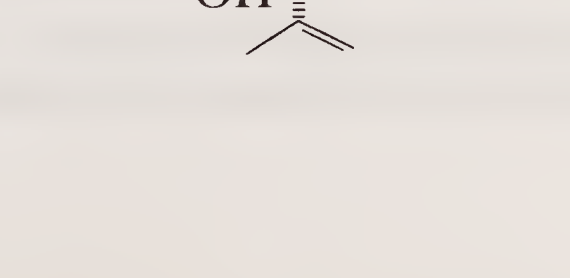
$$[(CH_3)_3Si]_2CH_2 + NaOCH_3 \longrightarrow (CH_3)_3SiCH_2^-Na^+ + (CH_3)_3SiOCH_3$$

$$\downarrow \text{PhCOPh}$$

$$Ph_2C{=}CH_2 \quad (53\ \%)$$

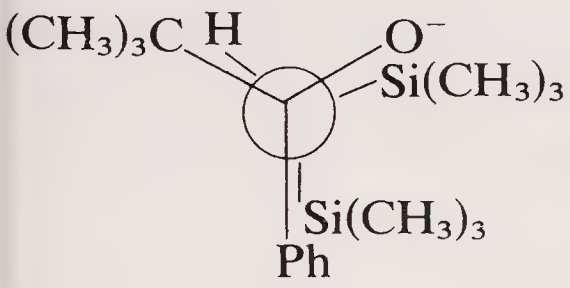
$$[(CH_3)_3Si]_3CH + LiOCH_3 \longrightarrow [(CH_3)_3Si]_2CH^-Li^+ + (CH_3)_3SiOCH_3$$

$$\downarrow \text{PhCOC}(CH_3)_3$$



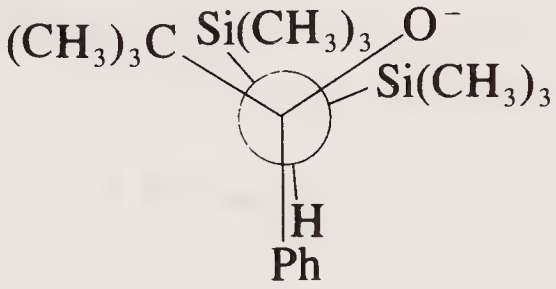
(13 %)

It should be noted that in the latter case only one geometrical isomer (*Z*) is formed. This has been explained as resulting from *cis*-elimination from the more stable eclipsed conformation (1A) of the intermediate anion.



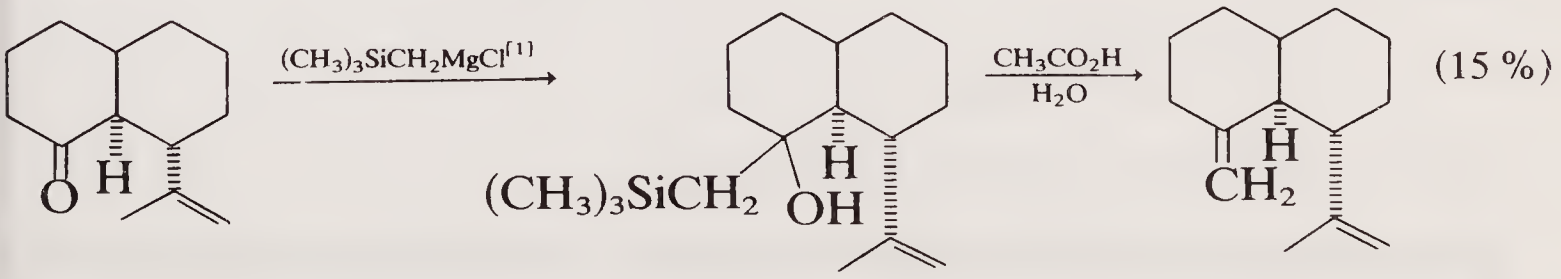
(1A)

more stable than



(1B)

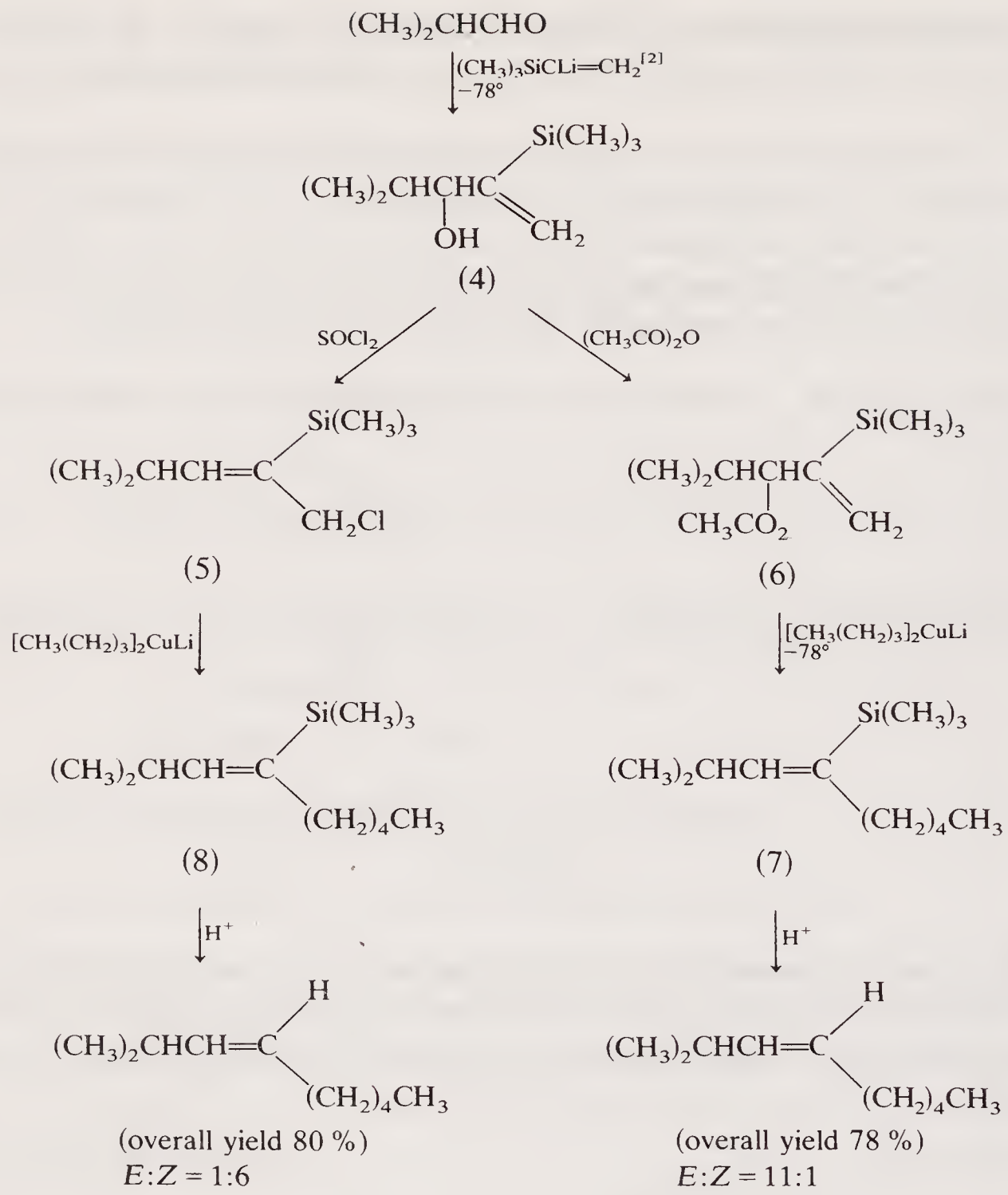
α-Silyl Grignards are useful reagents which on reaction with carbonyl groups form alcohols. Elimination results in the formation of alkenes, and the procedure appears to have, in some instances at least, advantage over the Wittig reaction for the conversion of $\diagup C{=}O$ into $\diagup C{=}CH_2$, for example (2) → (3) [(2) is unreactive towards $Ph_3P{=}CH_2$].



(15 %)

(2)

(3)



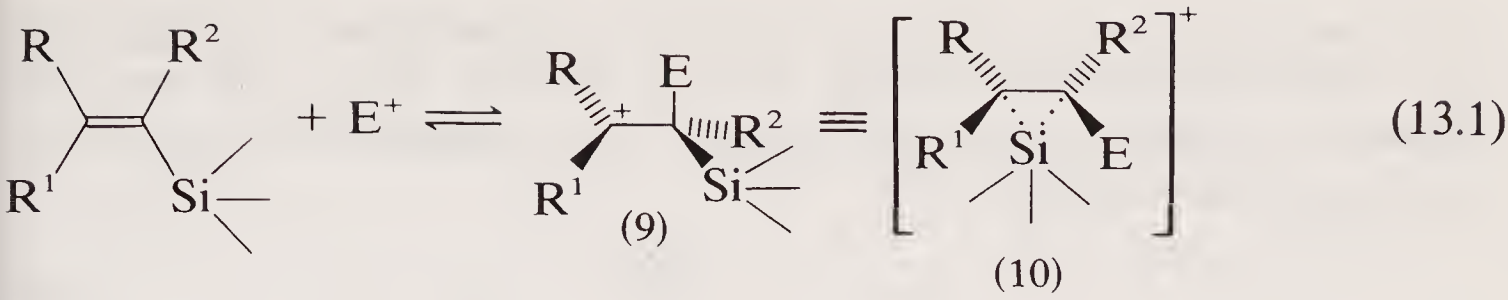
Scheme 13.1

Scheme 13.1 outlines a series of reactions whereby a preponderance of either *E*- or *Z*-disubstituted alkenes can be obtained.

Stereoselective synthesis of trisubstituted alkenes can be achieved by reaction of the isomeric vinylsilanes (7) and (8) with electrophiles (cf. section 13.3.2).

13.3.2 Reactions involving vinylsilanes

The orientation of addition of electrophiles to vinylsilanes is governed by the ability of silicon to stabilise a carbocation β to it (13.1):

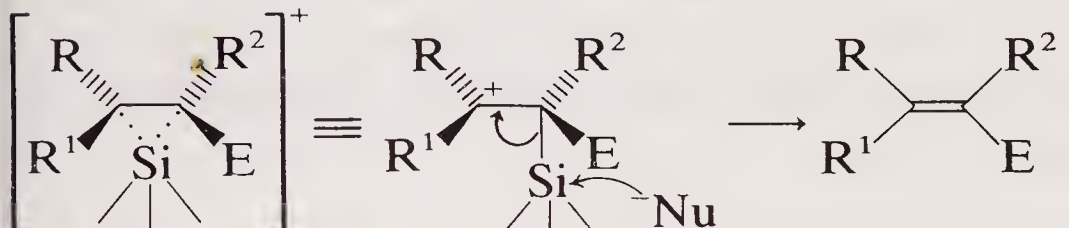


(13.1)

(9)

(10)

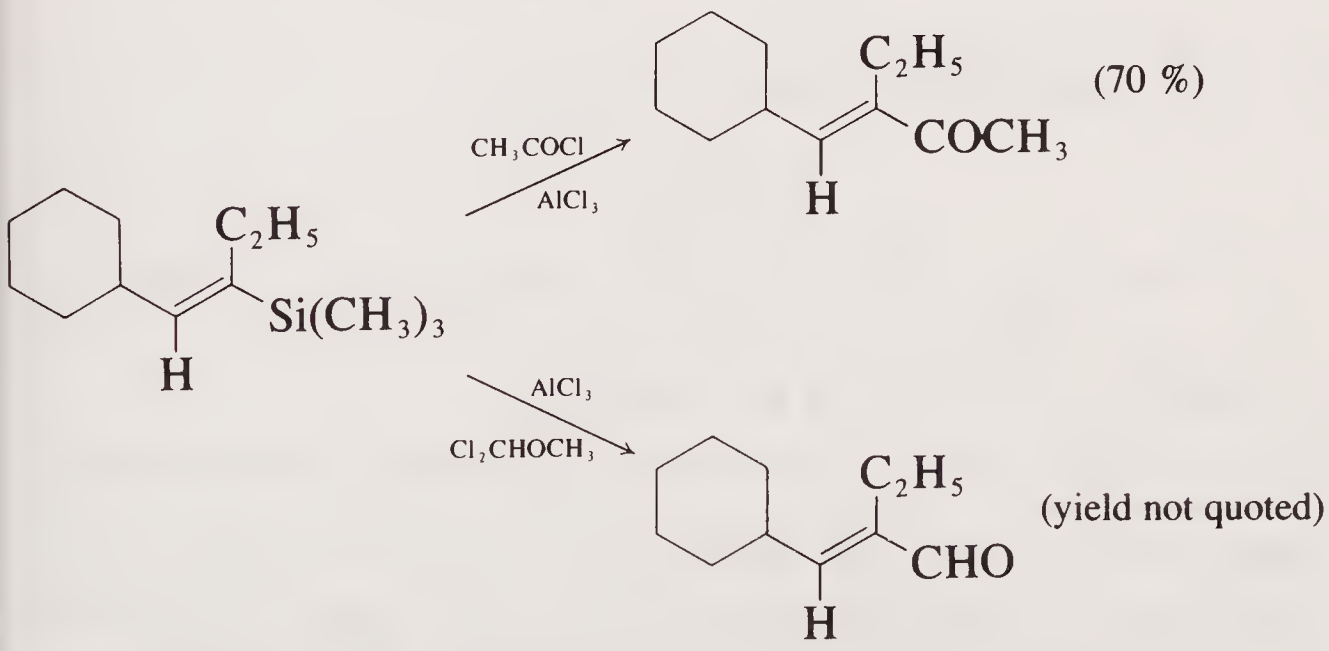
Rotation about the C–C bond of (9) takes place so that the full stabilisation of the carbocation by silicon, indicated by (10), can take place. Nucleophilic displacement at silicon can now take place, releasing as the leaving group an alkene in which the silyl group has been replaced stereospecifically by the electrophile (13.2). Vinylsilanes may thus be regarded as the synthetic equivalents of simple alkenes in electrophilic substitution reactions; in many cases they are more easily handled than the simpler alkenes.[3] [Alkynylsilanes may also serve as the synthetic equivalents of simple alkynes, with the same handling advantages.[3] Use is made of $PhC{\equiv}CSi(CH_3)_3$ as the equivalent of $PhC{\equiv}CH$ in section 13.3.6.]



(13.2)

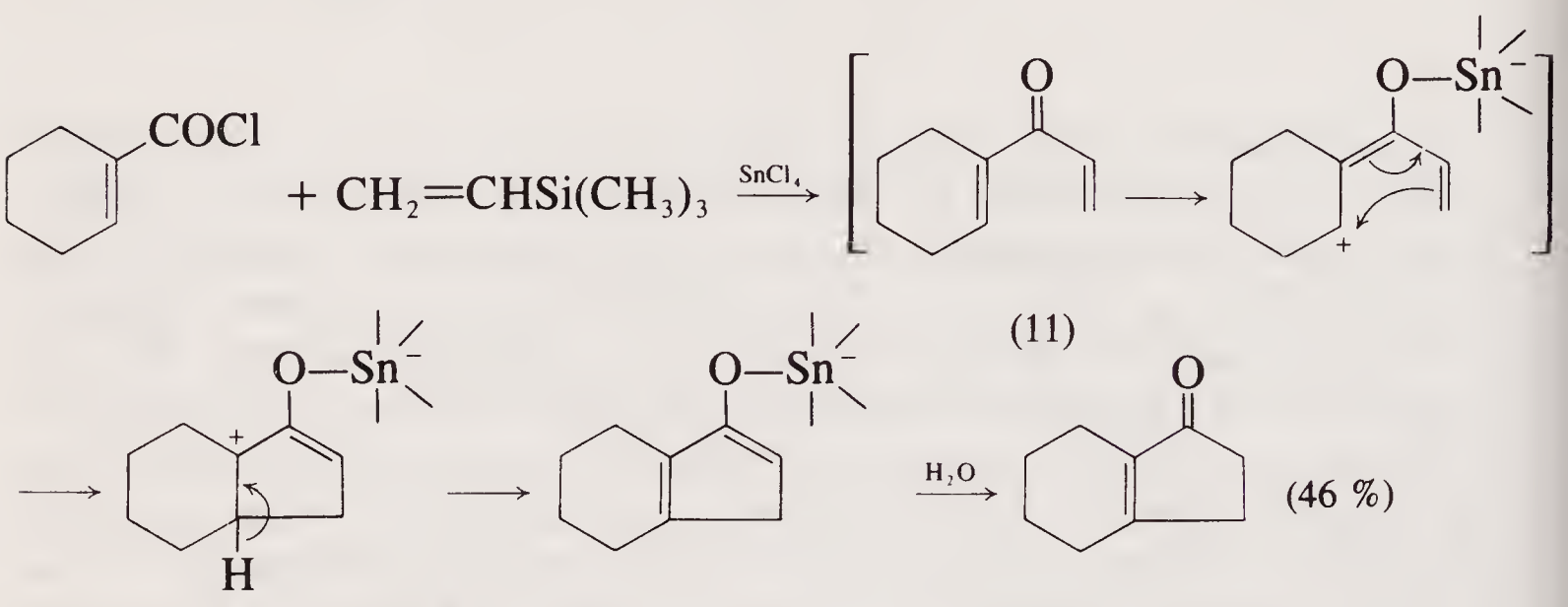
(10)

Reaction of a vinylsilane with an electrophile normally requires a Lewis acid catalyst. If the electrophile is an acyl halide, an α,β-unsaturated ketone is formed, whereas an α,β-unsaturated aldehyde is produced from α,α-dichlorodimethyl ether:[4]



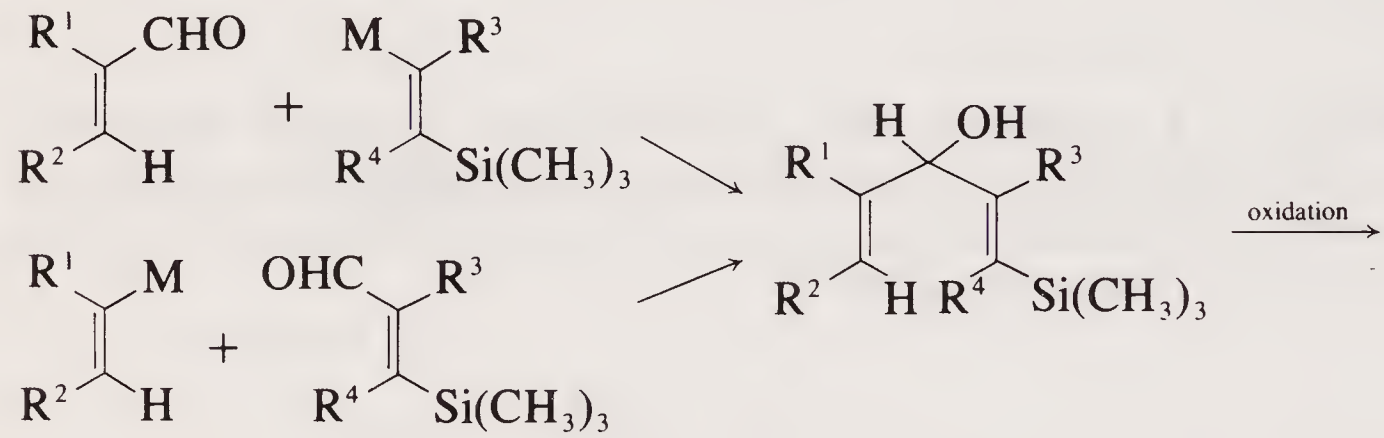
If the electrophile is a cyclic α,β-unsaturated acyl halide, the initially formed dienone (11) may undergo cyclisation under the influence of the

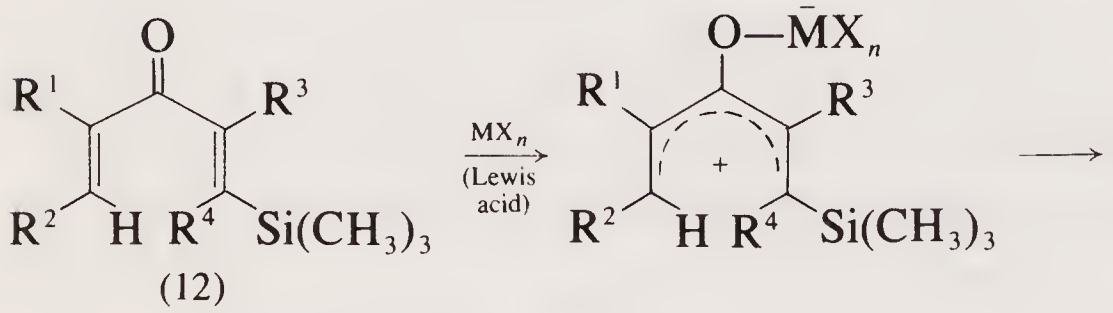
Lewis acid catalyst to give an annulated cyclopentenone in which the more highly substituted double bond is formed. This is the so-called **Nazarov** cyclisation, a reaction which is not observed with acyclic α,β-unsaturated acyl halides.



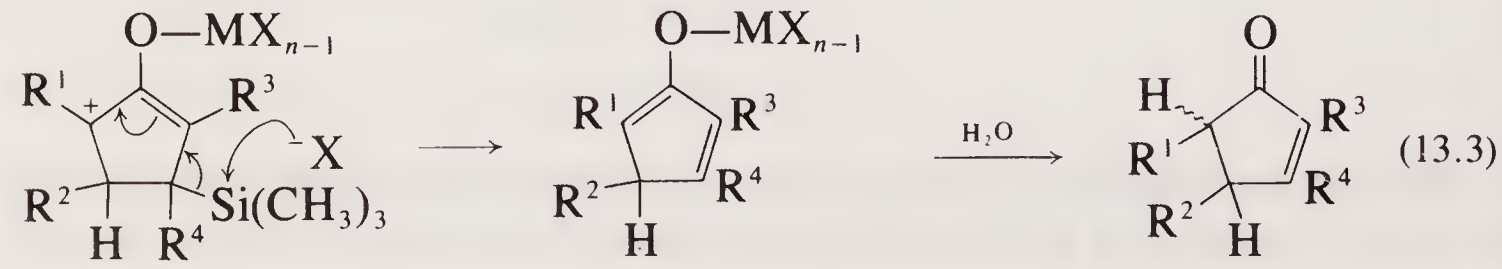
(11)

The Nazarov cyclisation leads to the more stable (i.e. more highly substituted) alkene. 4,5-Annulated cyclopent-2-enones are obtained regiospecifically, however, by Lewis acid-catalysed cyclisations of dienones (12) containing a β-silyl substituent [reaction (13.3)]. The dienones are accessible by two general routes.



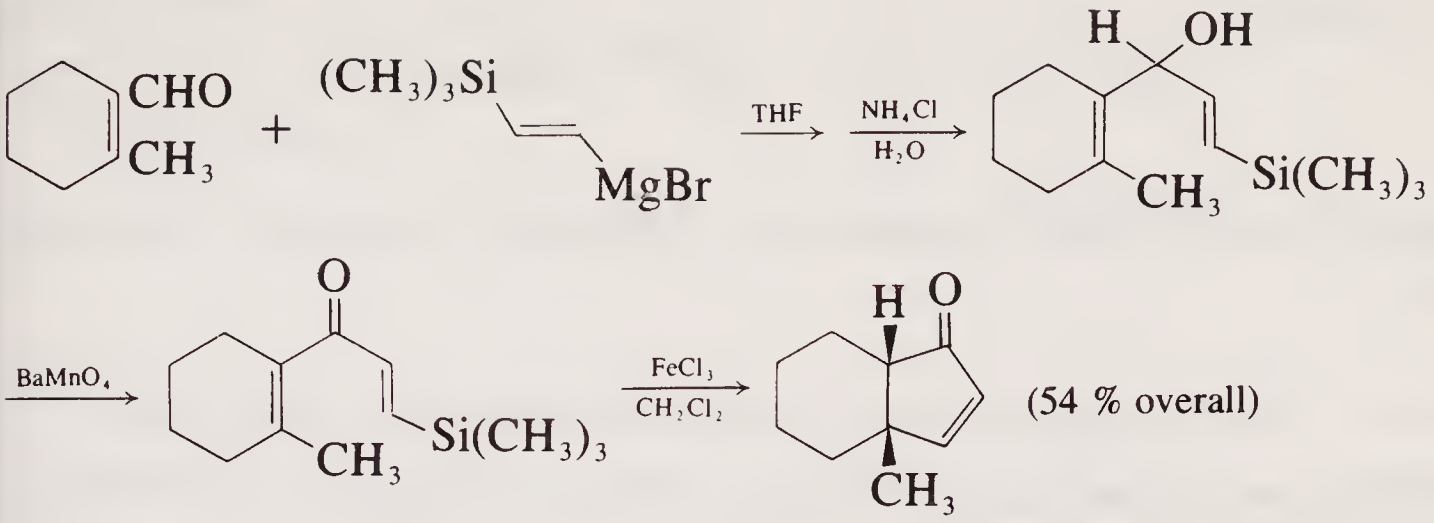


(12)



(13.3)

For example,

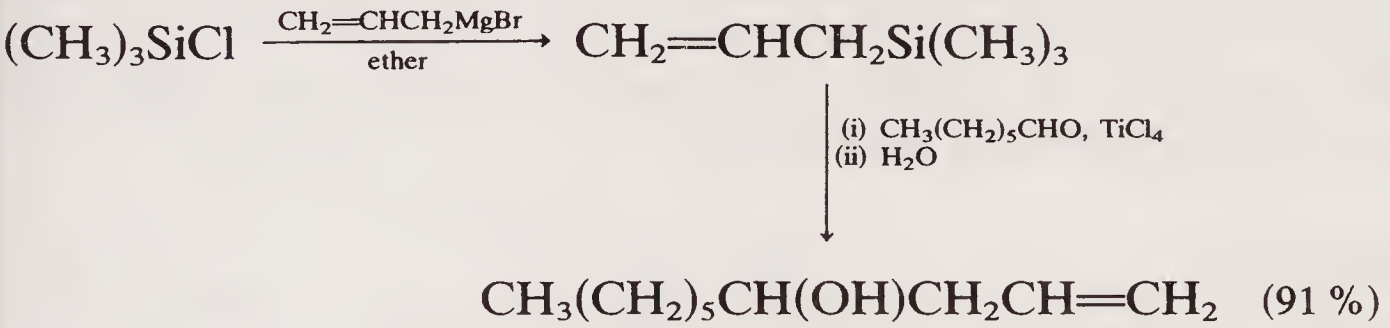


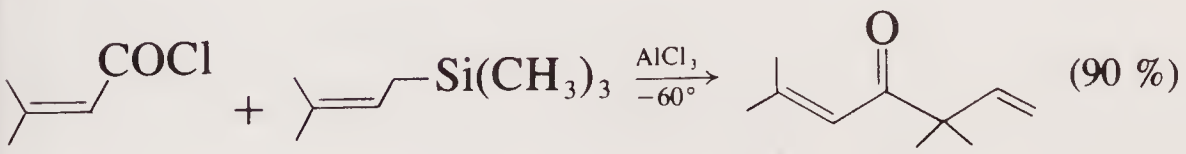
13.3.3 Reactions involving allylsilanes

Addition of electrophiles to allylsilanes results in the electrophile being attached to the carbon remote from the silyl group because of the stability of the β-silyl carbocation (13). Removal of the silyl group occurs as a result of nucleophilic substitution at silicon (13.4):

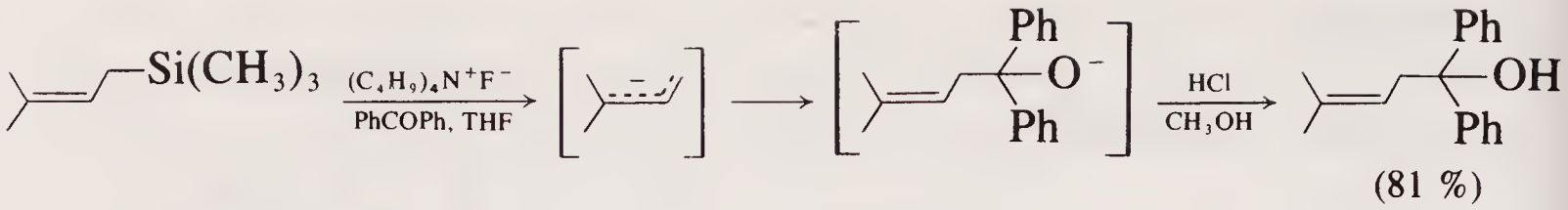
(13) (13.4)

The following reactions illustrate the reaction of allylsilanes with the electrophilic carbonyl carbon:





This procedure is much more regiospecific than reactions of allylic Grignard reagents, where products of reaction at both ends of the allylic system may be obtained. The opposite regioselectivity may sometimes be obtained by using a tetra-alkylammonium fluoride instead of the Lewis acid: the high affinity of the fluoride ion for silicon causes the formation of an allylic anion, which reacts preferentially with electrophiles at its less hindered end, e.g.

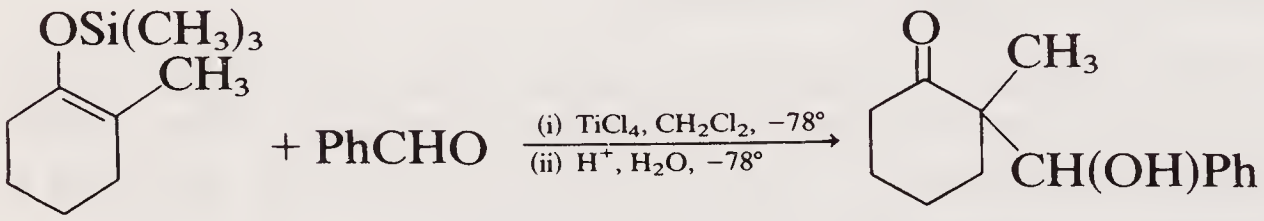


(81 %)

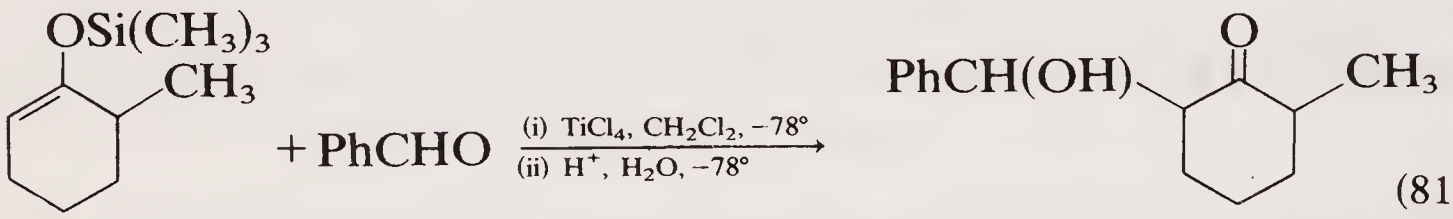
Other fluoride-induced reactions are described in sections 13.3.6 and 13.4.

13.3.4 Reactions involving silyl enol ethers (silyloxyalkenes)

Carbonyl compounds may undergo α-alkylation regiospecifically using silyl enol ether intermediates.



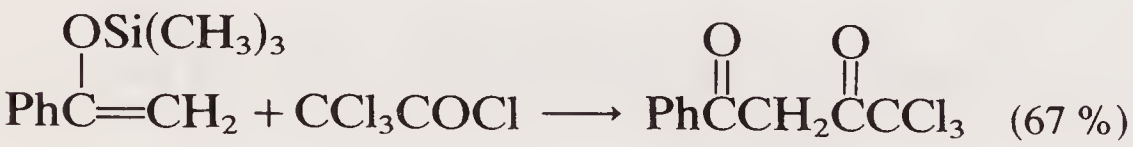
(60 %)



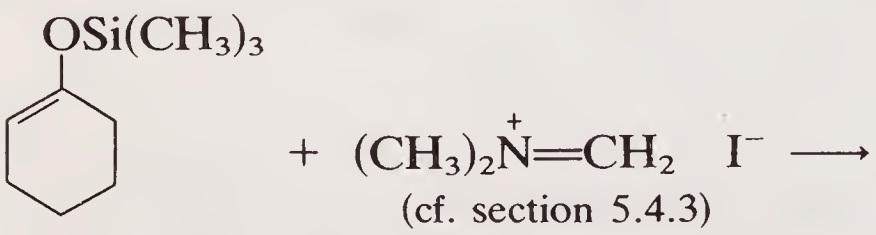
(81 %)

These reactions also illustrate the effectiveness of silyl enol ethers in the formation of 'mixed aldol' products without the problems of a mixed condensation reaction (cf. section 5.2.4).

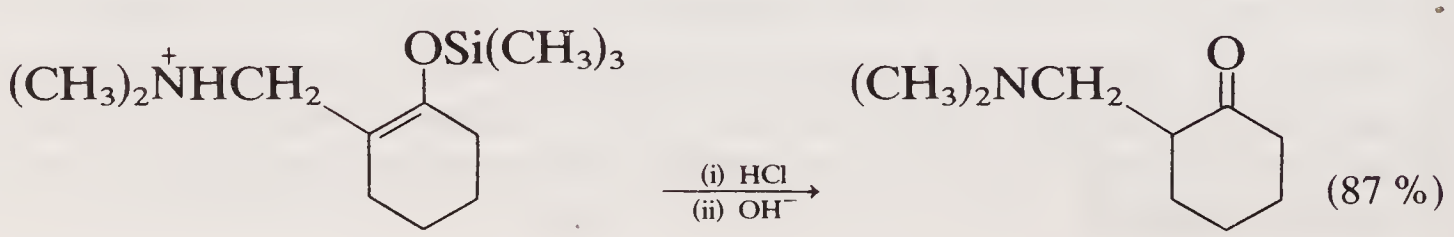
Other reactions of synthetic significance include those with acyl halides, iminium salts and nitroalkenes:



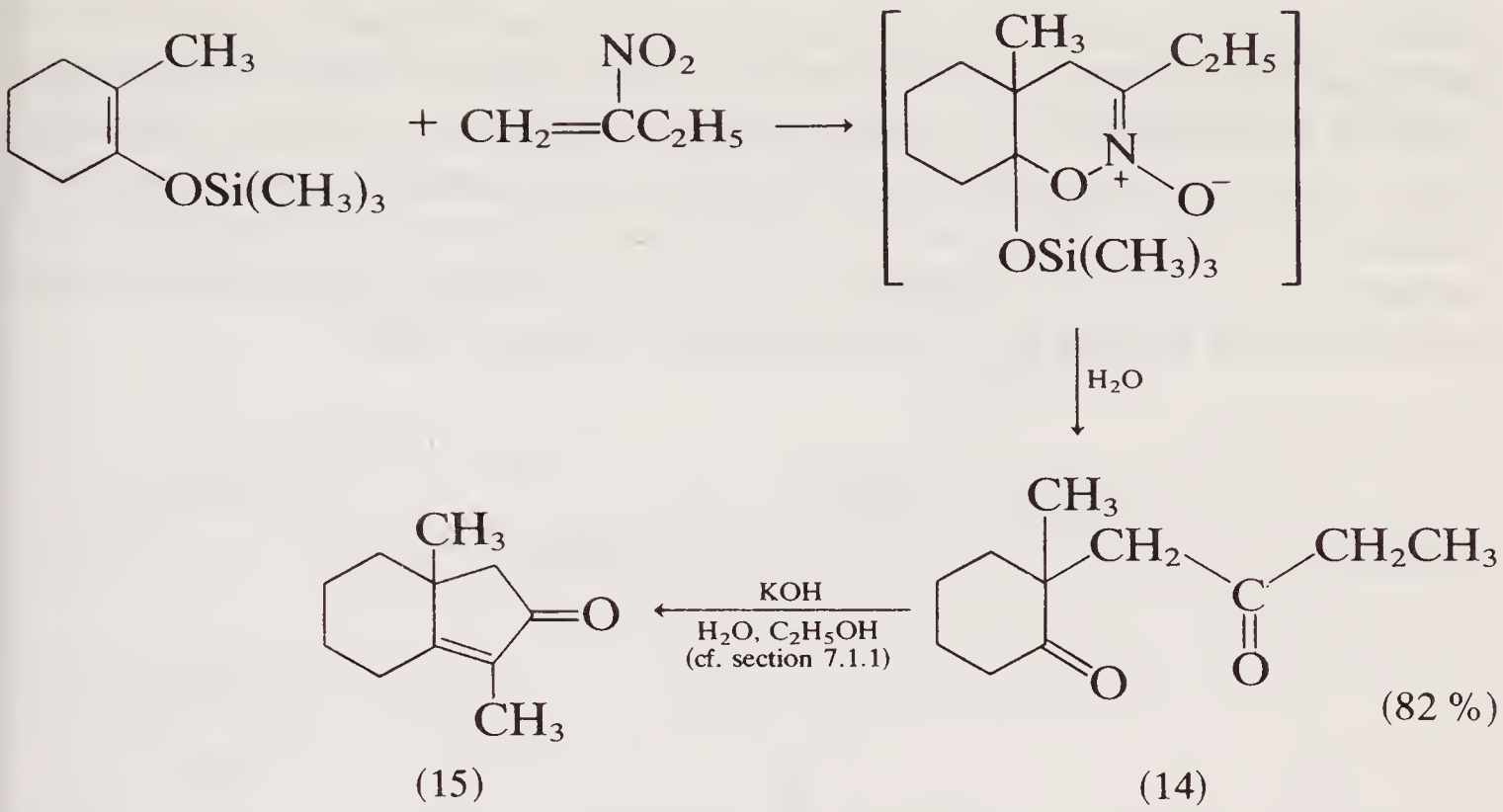
(67 %)



(cf. section 5.4.3)

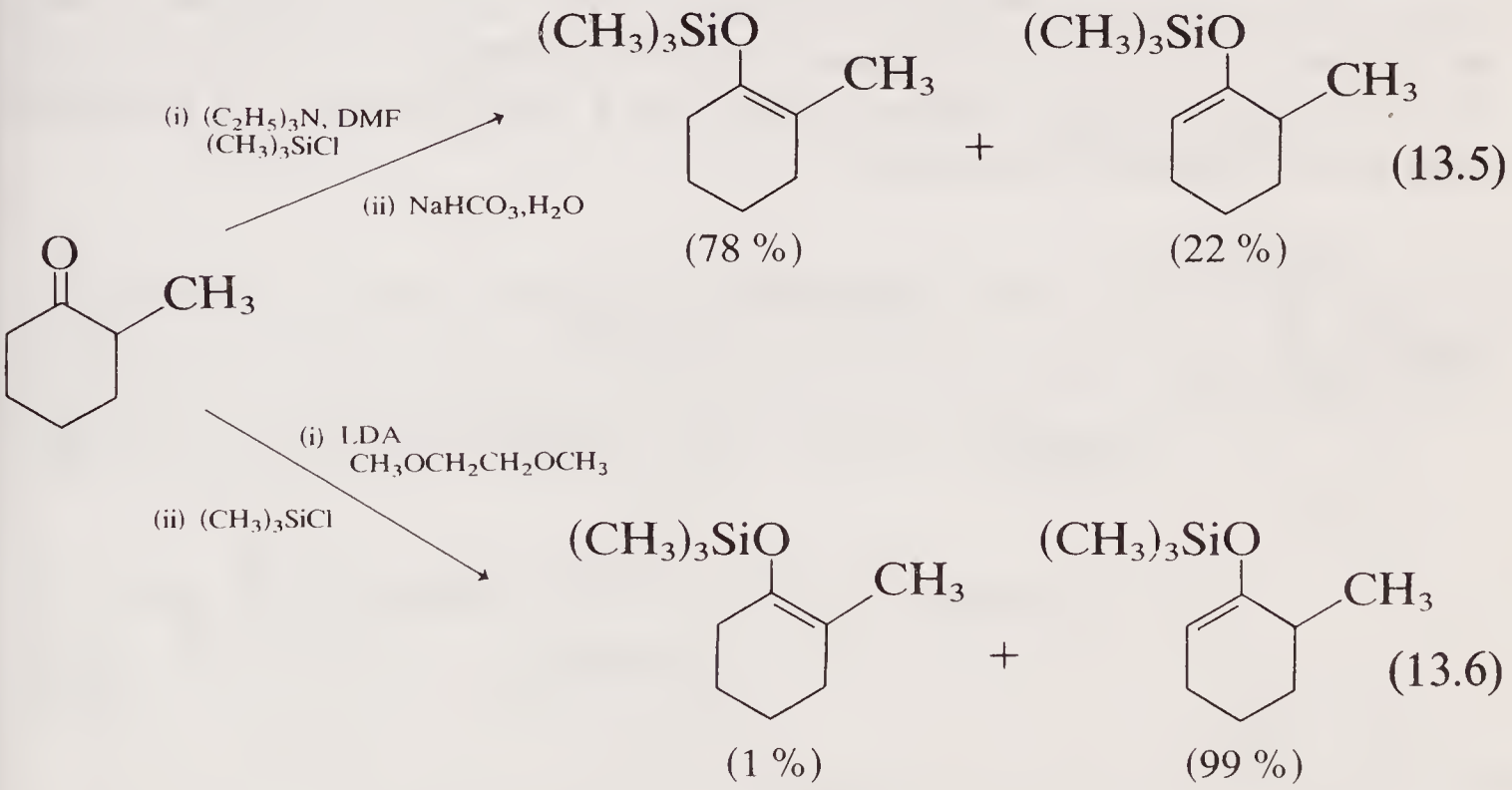


(87 %)



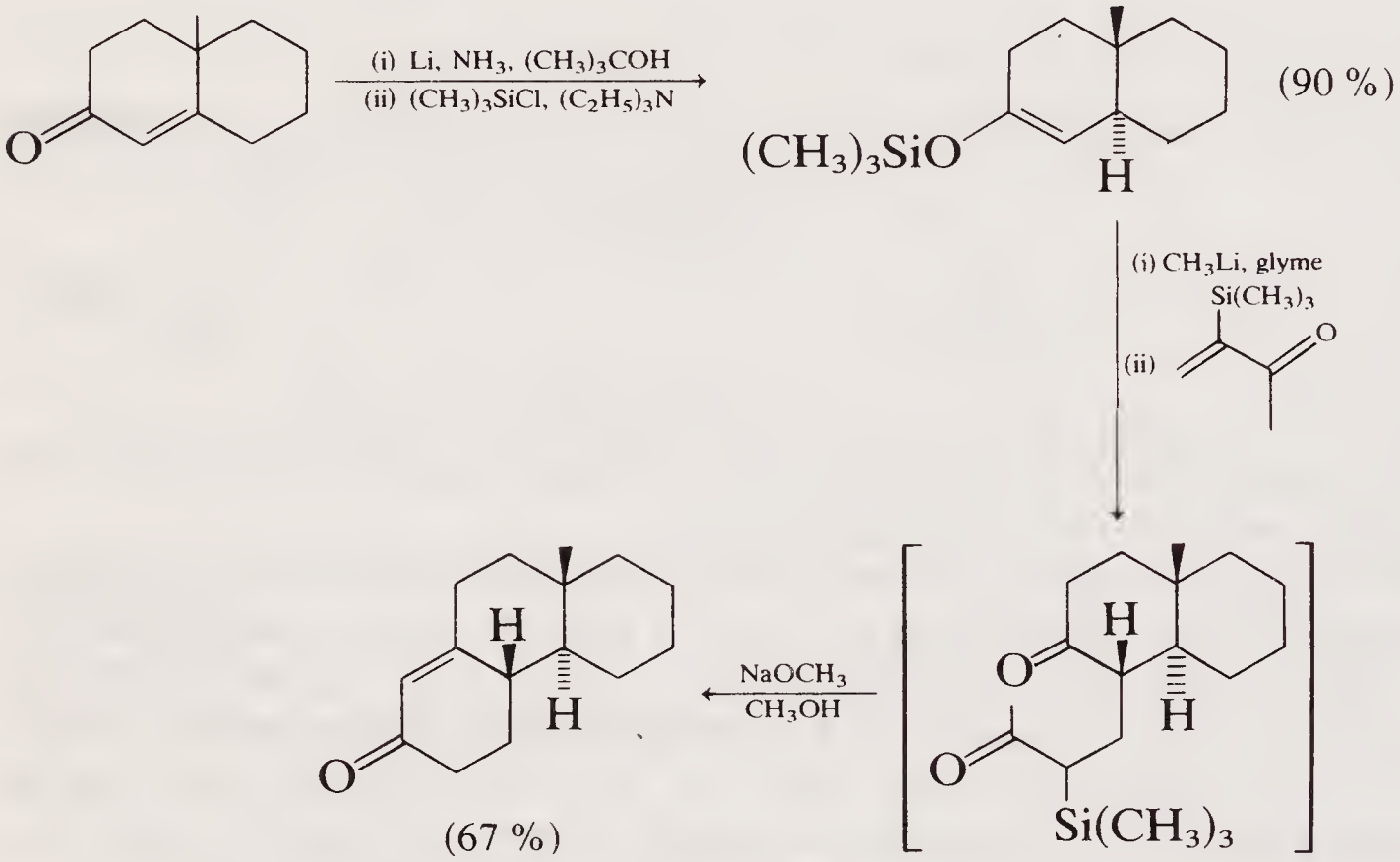
The 1,4-diketones [e.g. (14)] formed in the last reaction are precursors of partially reduced indenones [e.g. (15)].

Since silyl enol ethers can be formed either under conditions favouring thermodynamic control [e.g. the user of tertiary amine, reaction (13.5)] or under conditions favouring kinetic control [e.g. the use of lithium diisopropylamide, reaction (13.6)], products derived from either enolate of an unsymmetrical ketone such as 2-methylcyclohexanone can be obtained without the problems of equilibration encountered in reactions involving the use of an excess of strong base (cf. section 5.2.1):

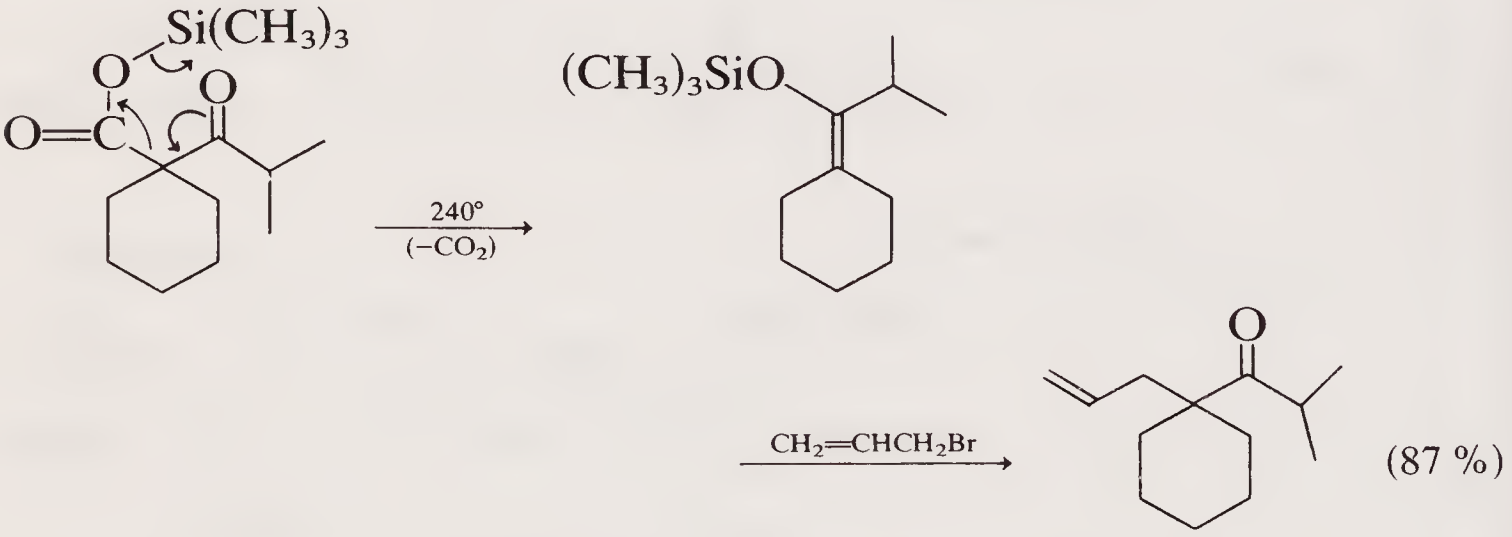


In addition to these methods, specific enolates (cf. section 5.2.3.2) can be formed by a number of procedures including dissolving metal reduction of α,β-unsaturated ketones and rearrangement of trimethylsilyl

β-keto-esters. In the former reaction, the enolate formed by reduction of the unsaturated ketone is trapped by chlorotrimethylsilane and can be purified and identified spectroscopically. The lithium enolate is regenerated in an aprotic solvent and can then, for example, participate in a Michael reaction with an α-trimethylsilylvinyl ketone. An example of this sequence as part of an annulation reaction is shown, the reaction on the enolate anion taking place from the less hindered side:



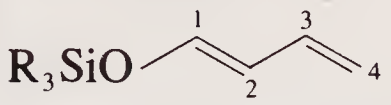
Thermal rearrangement of trimethylsilyl β-keto-esters involves migration of the silyl group with elimination of CO_2 and formation of the silyl enol ether in a process analogous to the decarboxylation of β-keto-acids. The following example demonstrates how a silyl enol ether so formed is used in an alkylation reaction:



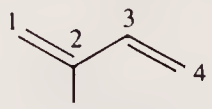
13.3.5 Reactions of silyloxybutadienes

Both 1- and 2-silyloxybutadienes, (16) and (17), have been studied. In general, these compounds react with carbon electrophiles in the same

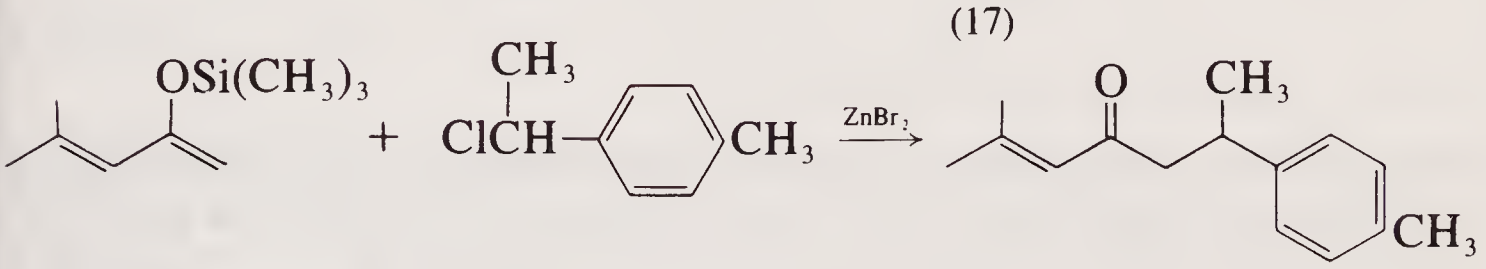
manner as silyl enol ethers. In the case of the 2-silyloxy-isomer, reaction takes place at C-1, but in the case of the 1-silyloxy-isomer, reaction may take place at C-2 or C-4. Although the latter is often preferred, the product ratio may be altered by varying the substituents on silicon.



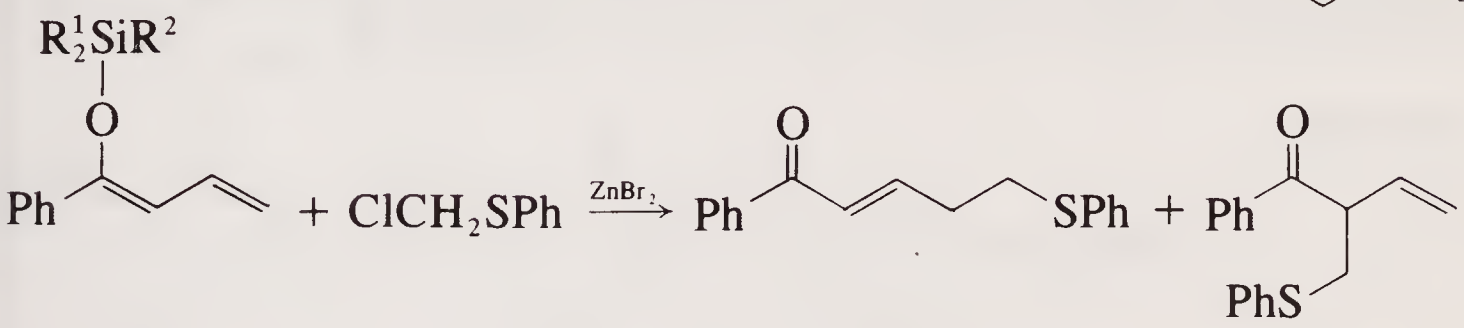
(16)



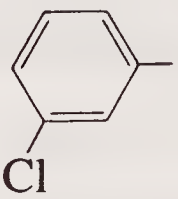
(17)



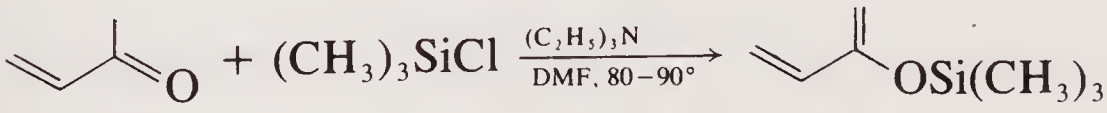
(88 %)

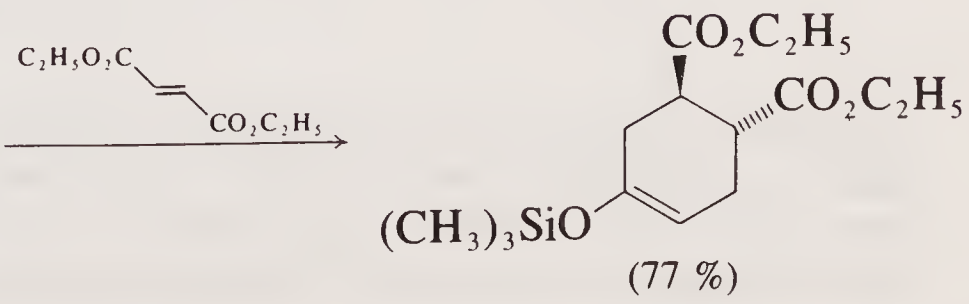


(18) (19)

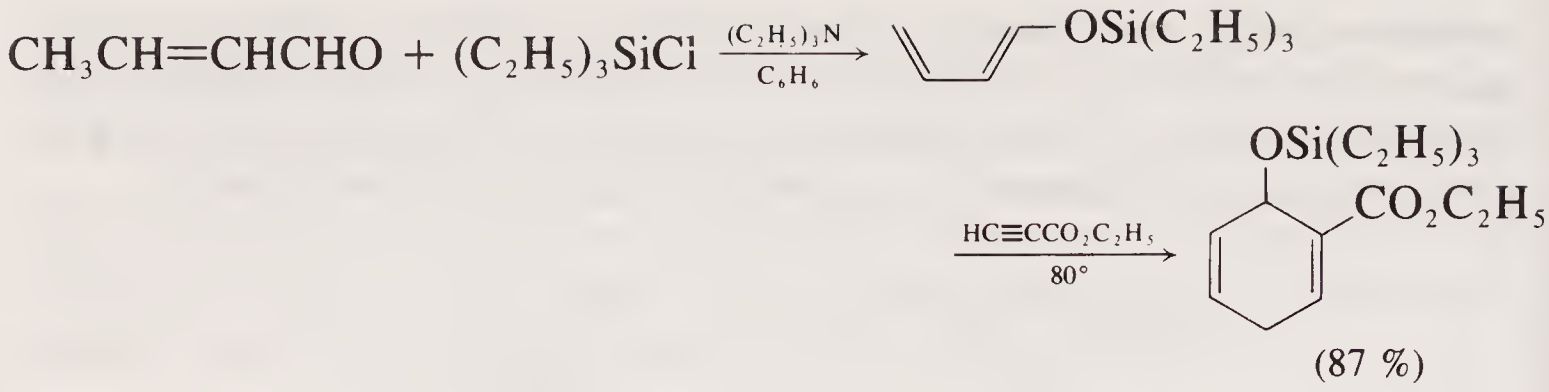
R^1	R^2	Yield	Ratio of (18) : (19)
CH_3	$(CH_3)_3C$	62 %	23 : 77
C_2H_5		68 %	100 : 0

Silyloxy-substituted butadienes undergo Diels–Alder reactions (cf. section 7.2.1). Not only are these dienes easily prepared (they are the silyl enol ethers of α,β-unsaturated aldehydes and ketones), but their cycloaddition reactions are highly regio- and stereo-selective.



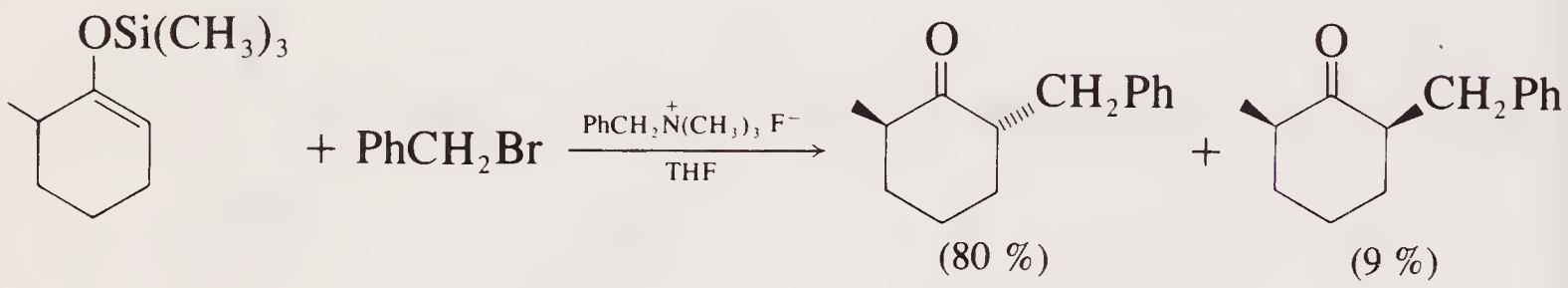


(77 %)

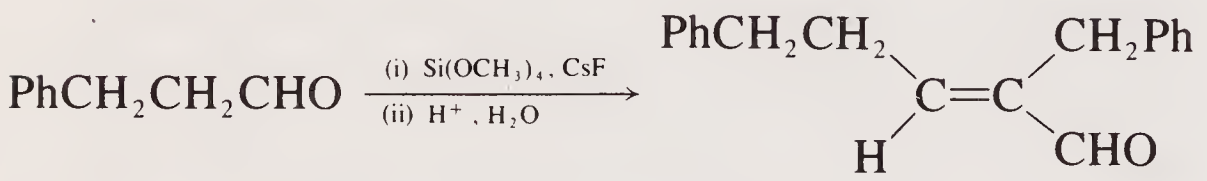


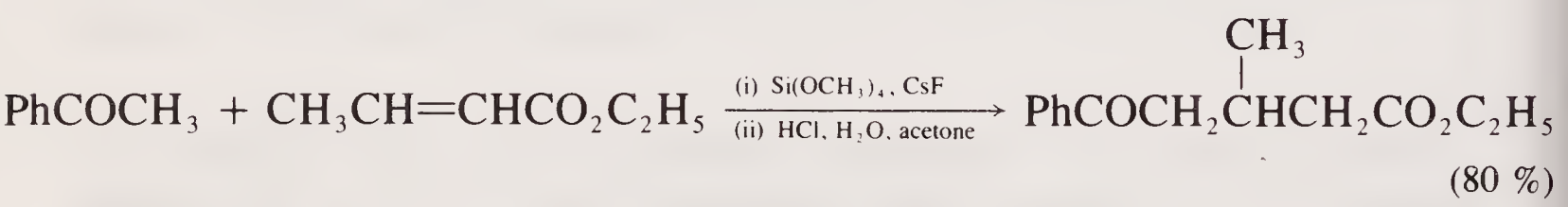
13.3.6 Fluoride-induced reactions

In section 13.3.3, mention was made of the formation of allylic anions by the reactions of allylsilanes with ionic fluorides. Fluoride ions may also be used to generate enolates from silyl enol ethers, e.g.



Tetra-alkoxysilanes, in presence of caesium fluoride, catalyse reactions such as aldol condensations and Michael additions. These reactions involve *in situ* formation of silyl enol ethers and further conversion of these into enolates by the caesium fluoride, e.g.

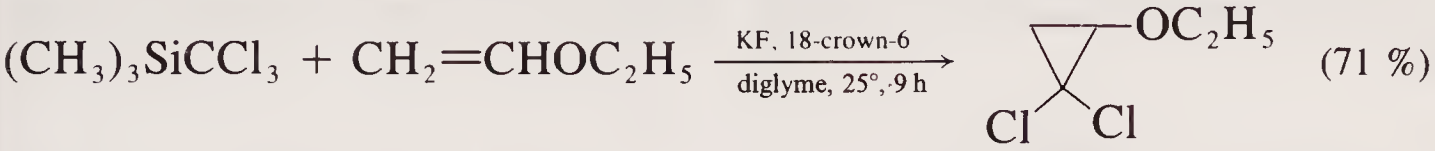


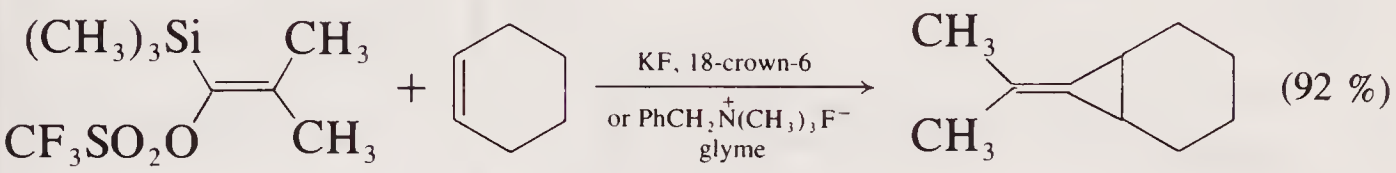


The same general approach allows acetylide ions to be produced under effectively non-basic conditions, e.g.

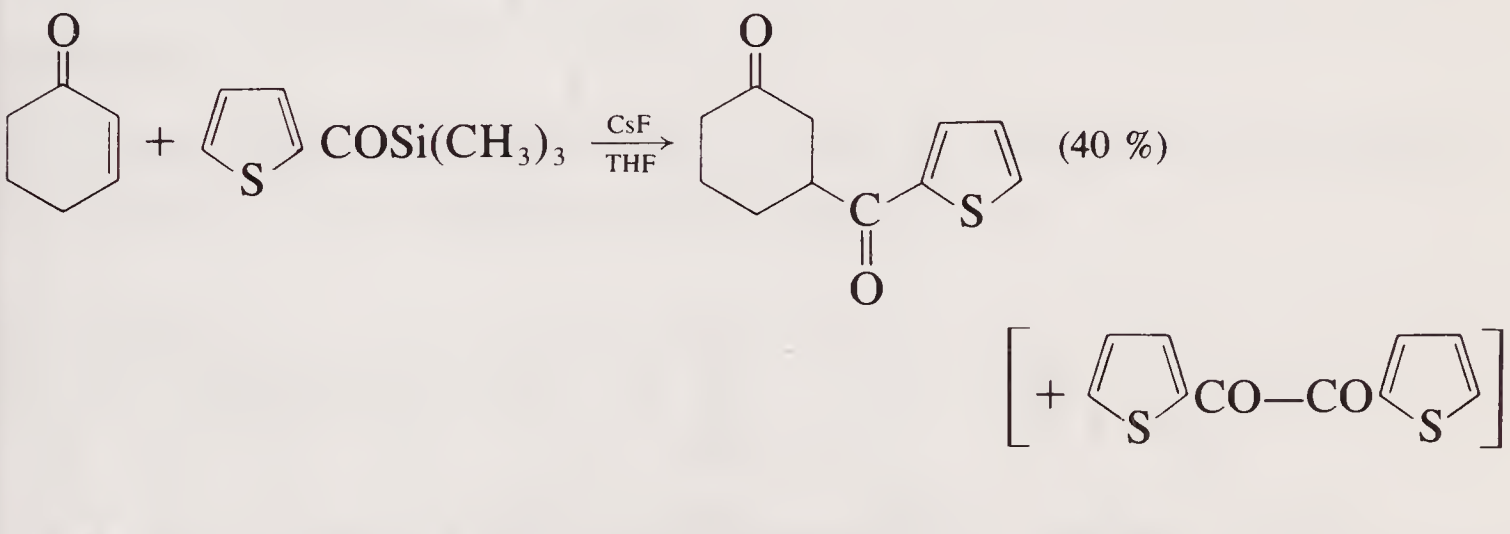
Fluoride-induced decomposition of suitably substituted silanes provides a convenient means of generating carbenes under neutral conditions.[5] For the generation of an alkylidenecarbene, trifluoromethanesulphonate is apparently the preferred leaving group;

and the use of a crown ether accelerates reactions involving potassium fluoride.





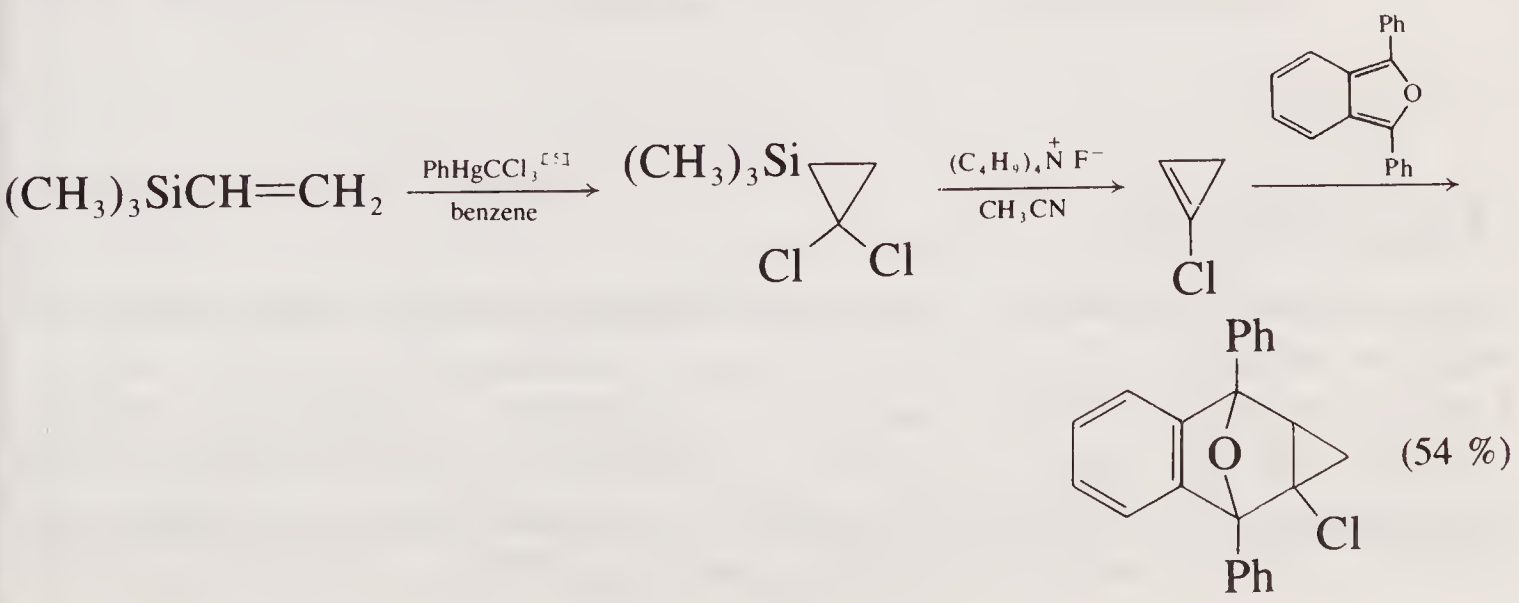
Acylsilanes and fluoride ions may be envisaged as the synthetic equivalent of the synthon RCO^-. In some cases, these reagents do serve as precursors for acyl nucleophiles, but by-product formation may reduce the yield considerably, e.g.



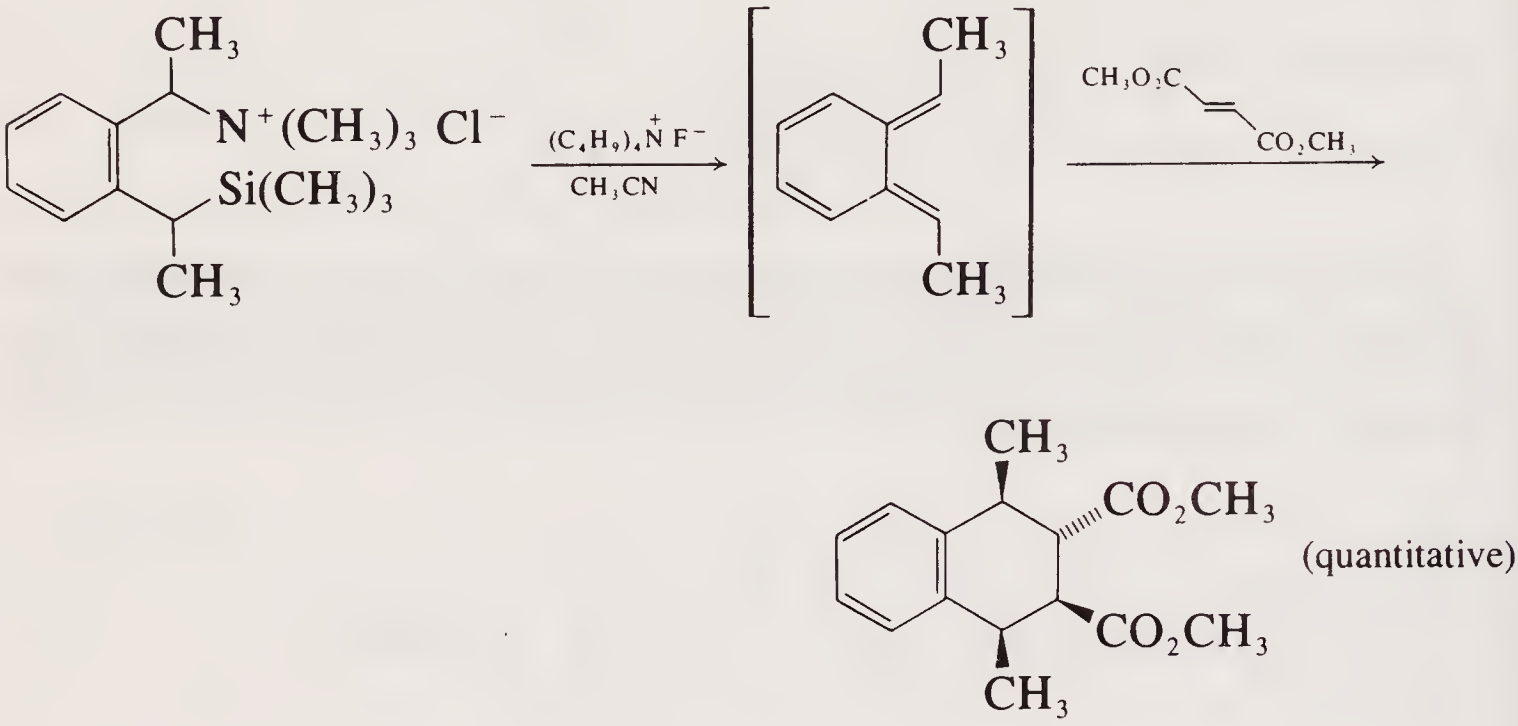
13.4 Fluoride-induced reactions not involving carbon–carbon single bond formation

13.4.1 Elimination reactions

Reaction of silanes with fluoride ions enables the synthesis, under mild and neutral conditions, of highly reactive alkenes which are otherwise not easily isolated. 1-Chlorocyclopropene, for example, may be prepared as follows, identified in solution (by ^1H n.m.r. spectroscopy), and trapped as its adduct with 1,3-diphenylisobenzofuran.



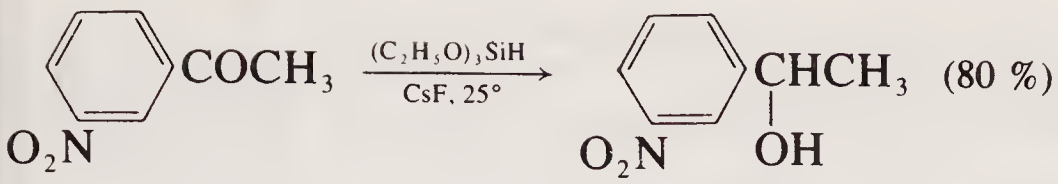
Also, *o*-quinodimethanes (*o*-xylylenes) may be formed by this method and trapped as Diels–Alder adducts. An interesting intramolecular variant has been used in steroid synthesis, as shown for oestrone methyl ether (20).

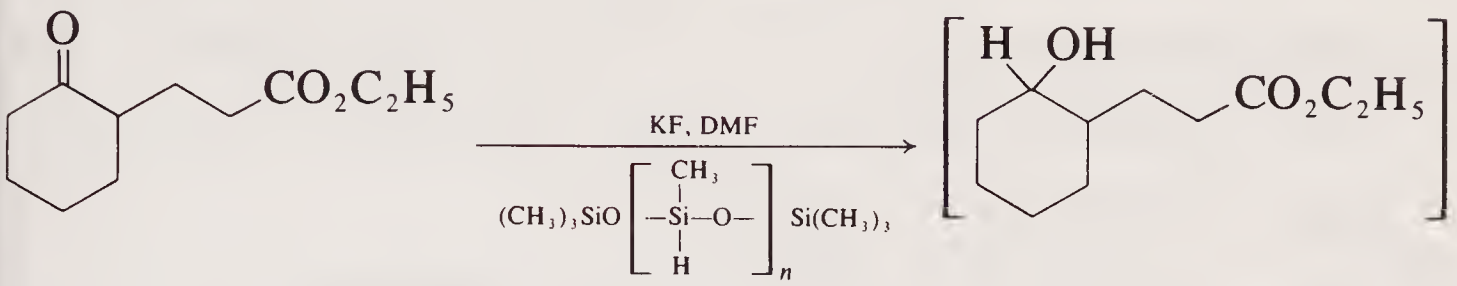


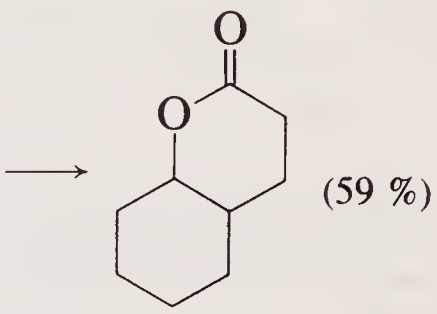
(20)

13.4.2 Reduction

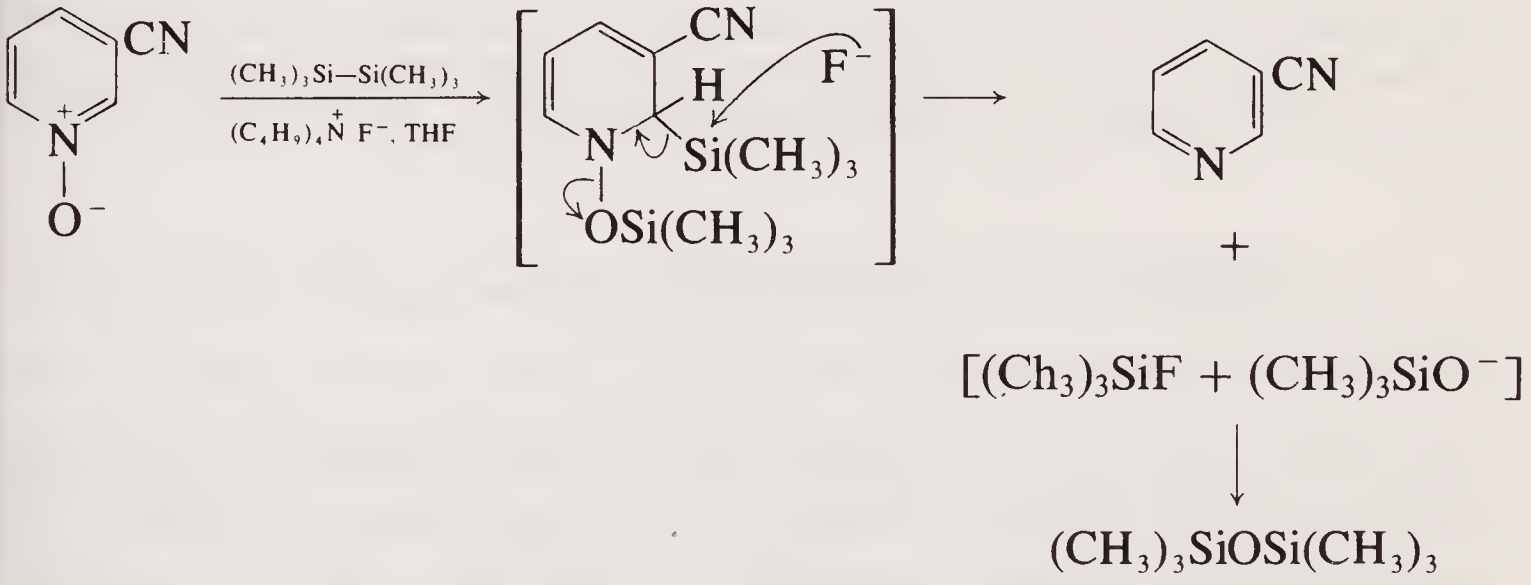
Organosilicon hydrides, in presence of fluoride ions, provide a means of selective reduction of functional groups containing electrophilic carbon. Among carbonyl groups, the ease of reduction is aldehyde > ketone > ester; and the ease of reduction depends also on the silane used [$(C_2H_5O)_3SiH > (C_2H_5O)_2(CH_3)SiH > Ph_2SiH_2$] and on the fluoride (CsF is a more powerful fluoride donor than KF).







Deoxygenation of *N*-oxides may be achieved using hexamethyldisilane in presence of tetrabutylammonium fluoride, e.g.

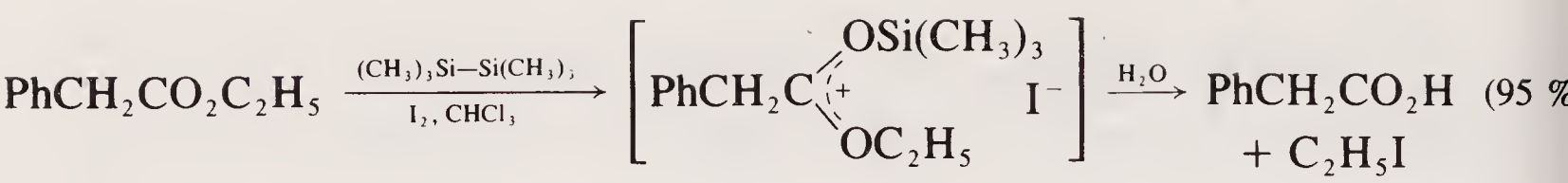


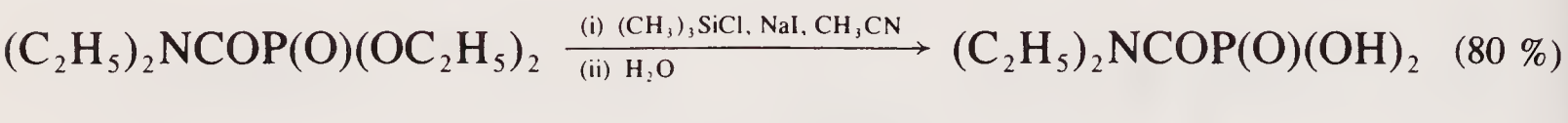
13.5 Synthetic applications of iodotrimethylsilane

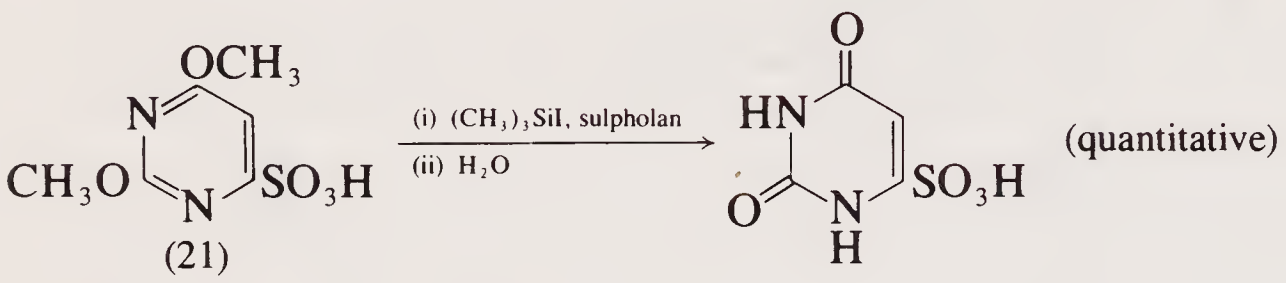
Iodotrimethylsilane is an electrophilic reagent which, on reaction with oxygen nucleophiles, forms a strong Si–O bond and liberates the strongly nucleophilic iodide ion. The reagent itself is rather unstable, and is probably best prepared *in situ* either by reaction of hexamethyldisilane with iodine, or of chlorotrimethylsilane with sodium iodide.

13.5.1 Dealkylation reactions

The dealkylation of a wide variety of esters and ethers has been reported. The following are representative examples.



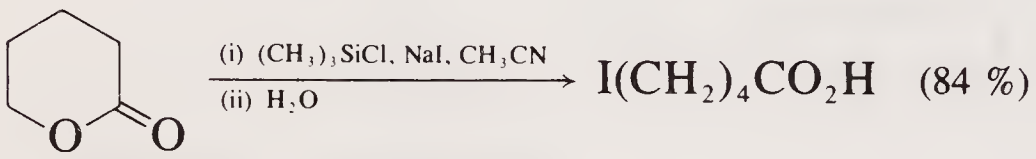




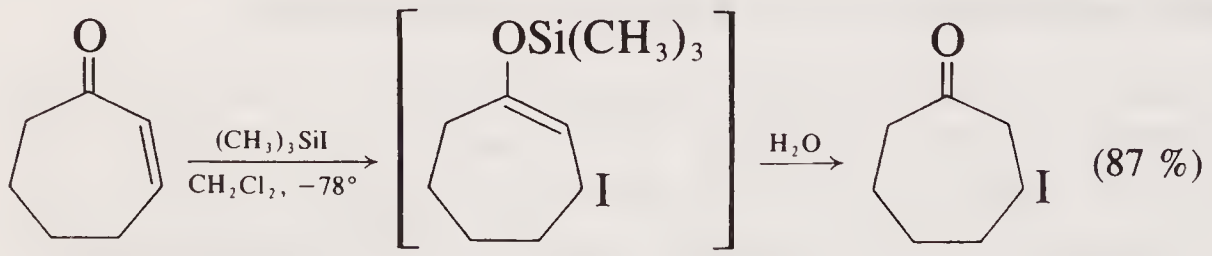
It should be noted that hydrolysis of (21) in aqueous acid also effects the replacement of the sulphonic acid group by OH, and gives barbituric acid.

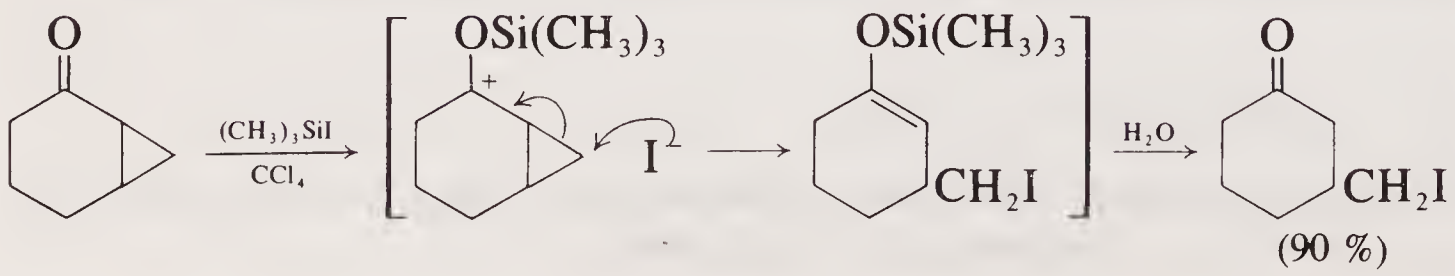
13.5.2 Formation of iodo-compounds

The dealkylation of esters, illustrated in the preceding section, involves the formation of an iodoalkane as the by-product. When the ester is cyclic (i.e. is a lactone), iodo-carboxylic acids result, e.g.



The reaction of iodotrimethylsilane with enolisable ketones can give silyl enol ethers. With α,β-unsaturated or cyclopropyl ketones, iodinated silyl enol ethers are obtained, and these on hydrolysis give β- or γ-iodoketones, e.g.

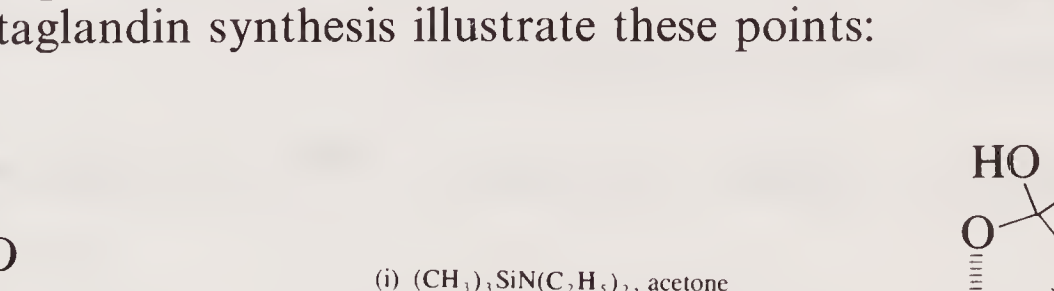




Iodotrimethylsilane can also bring about the conversion of alcohols into iodides. The reaction normally proceeds with inversion of configuration, in the manner expected for an S_N2 reaction; but bridgehead alcohols such as adamantan-1-ol, which are usually highly unreactive, also undergo this substitution in good yield.

$$S\text{-}CH_3(CH_2)_5CH(OH)CH_3 \xrightarrow[CHCl_3]{(CH_3)_3SiI} R\text{-}CH_3(CH_2)_5CHICH_3 \quad (83\ \%)$$

$$(+12\%\ S\text{-enantiomer})$$



(85 %)

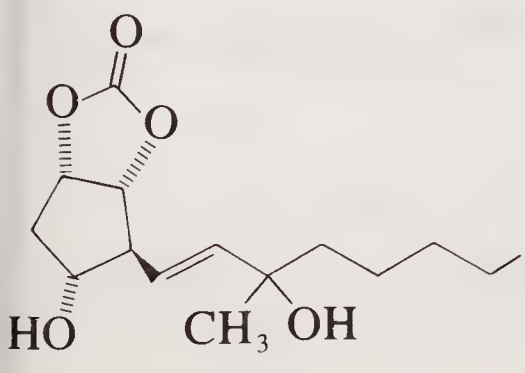
13.5.3 Reduction of sulphoxides

Deoxygenation of sulphoxides by iodotrimethylsilane has also been recorded, e.g.

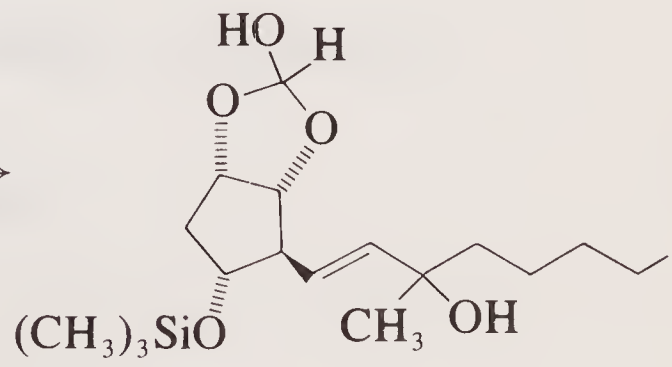
$$PhCH_2SOCH_2Ph \xrightarrow[CH_3CN,\ -15°]{(CH_3)_3SiCl,\ NaI} PhCH_2SCH_2Ph \quad (91\ \%) \quad (+I_2?)$$

13.6 Silyl groups as protective groups for alcohols

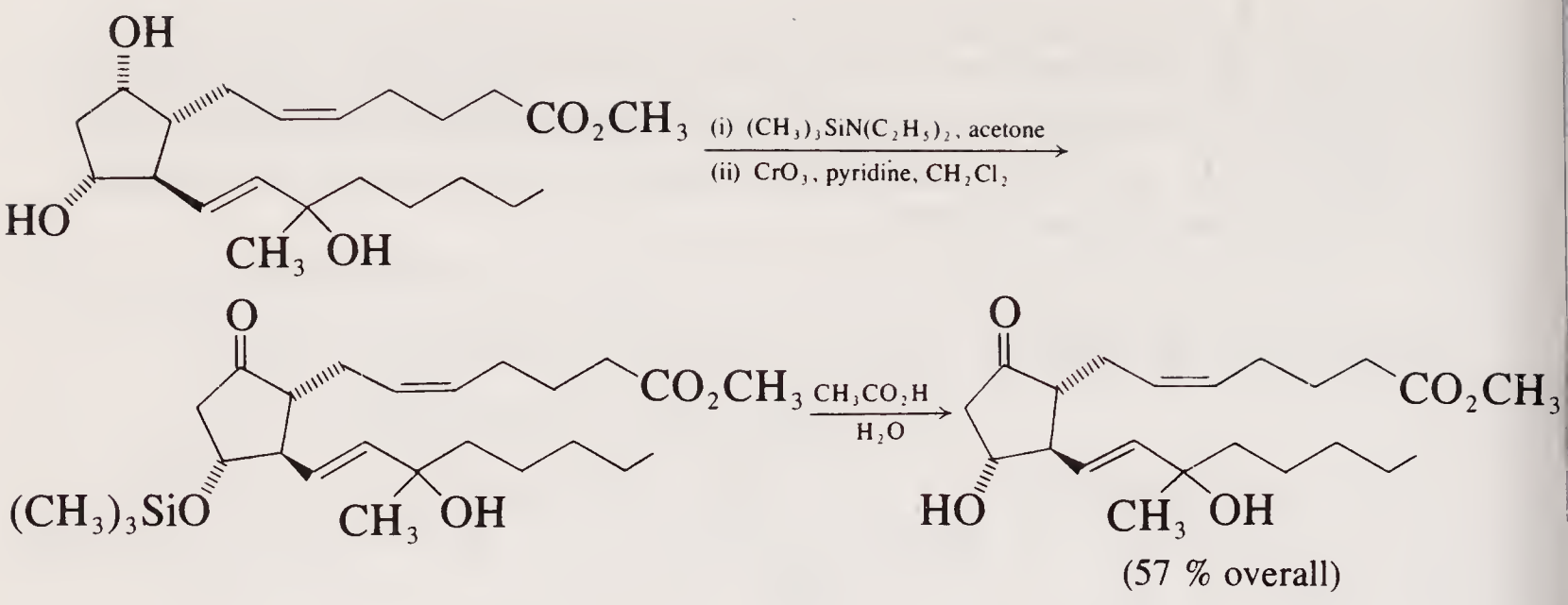
As has already been noted (cf. section 10.2.1), trimethylsilyl groups have enjoyed much success in derivatisation of hydroxyl groups for gas chromatography and for mass spectrometry. The limited stability of trimethylsilyl ethers towards hydrolysis limits their applicability in protection of hydroxyl groups; however, the use of trimethylsilyldiethylamine permits the selective trimethylsilylation of unhindered hydroxyl groups. The trimethylsilyl group has been shown to be stable towards di-isobutylaluminium hydride (DIBAL-H) reduction (section 8.2) and chromium(VI) oxide–pyridine oxidation (section 9.3.1.1). The following steps in a prostaglandin synthesis illustrate these points:



(i) $(CH_3)_3SiN(C_2H_5)_2$, acetone
(ii) DIBAL-H, toluene, −78°

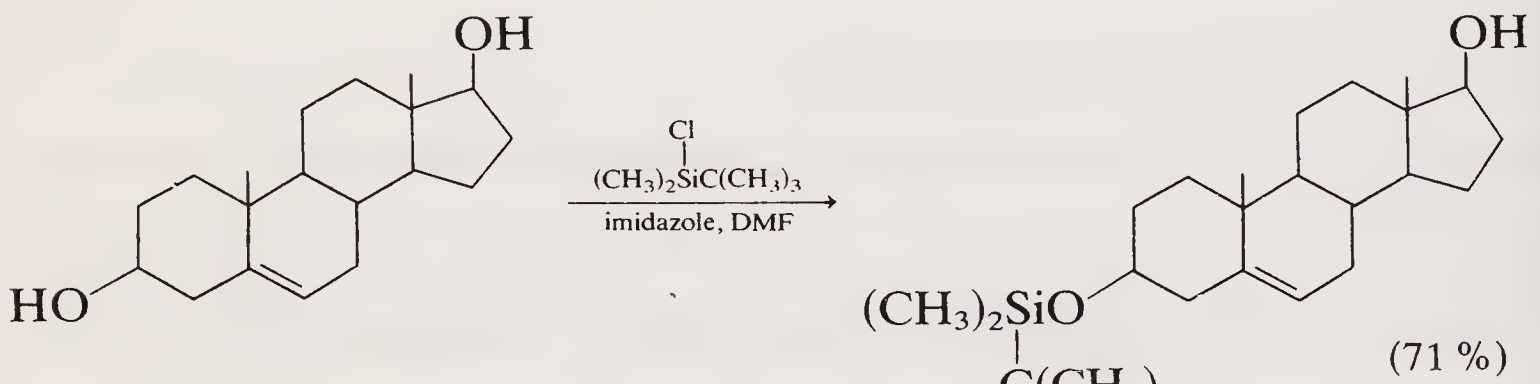


(95 %



(57 % overall)

Other alkylsilyl ethers are more stable and are formed somewhat more selectively than trimethylsilyl ethers. For example,



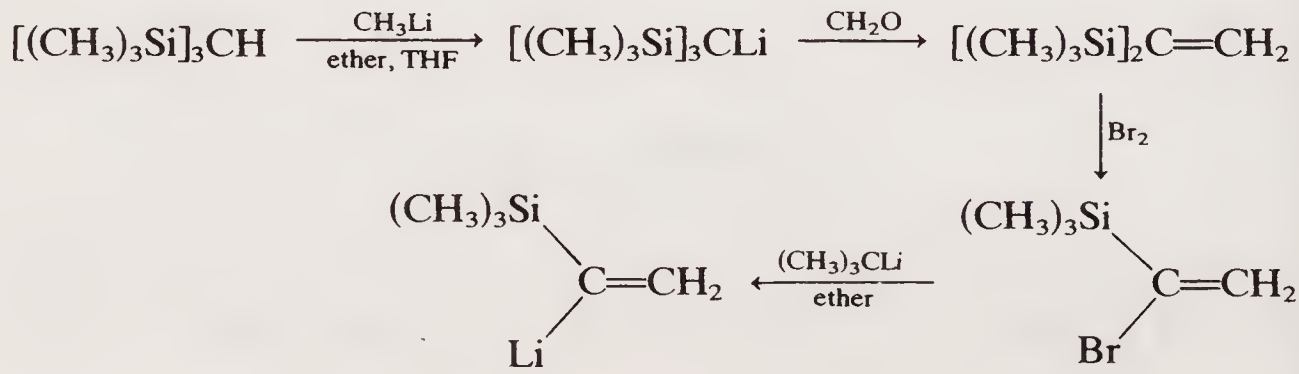
(71 %)

t-Butyldimethylsilyl ethers are more stable than tetrahydropyranyl ethers (cf. section 10.2.1). They are resistant to strong base, oxidation, metal hydride reduction, and catalytic hydrogenation. The group is readily removed, however, by mild acid treatment or by treatment with tetrabutylammonium fluoride in THF.

Notes

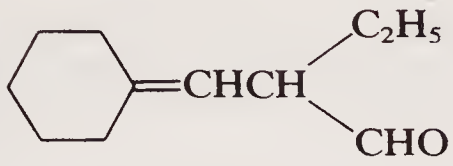
1. The halide used in formation of this reagent is produced by chlorination of tetramethylsilane.

2. The reagent is formed in the following way:



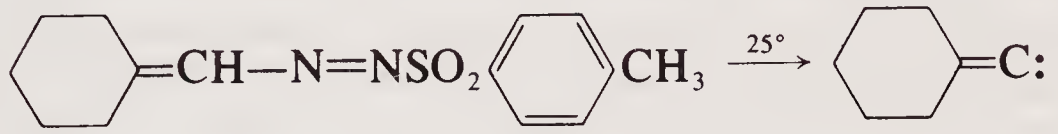
3. $CH_2{=}CHSi(CH_3)_3$, b.p. 55°; cf. $CH_2{=}CH_2$, b.p. − 104°.
$CH{\equiv}CSi(CH_3)_3$, b.p. 53°; cf. $CH{\equiv}CH$, b.p. − 75°.

4. In this case both *E*- and *Z*-vinylsilanes react to give the *E*-isomer due to equilibration *via*



5. Alternative procedures for the formation of carbenes under neutral conditions include

$$PhHgCCl_3 \xrightarrow[\text{or NaI, 30°}]{\text{heat (80°)}} PhHgCl + :CCl_2$$



14 Selenium reagents

Until the early 1970s, the only selenium-containing reagents regularly used by organic chemists were the element itself (a reagent for dehydrogenation) and selenium dioxide (an oxidising agent; cf. sections 9.2.2 and 9.5.2). Since that time, however, a wider variety of useful synthetic methods involving selenium reagents has been developed.[1]

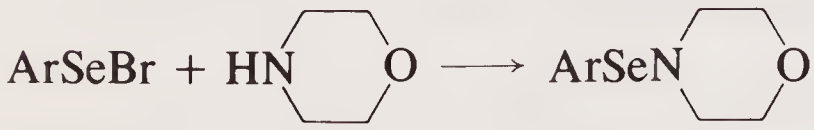
Selenium-containing functional groups of various kinds have been known for many years, and most of these have counterparts in sulphur chemistry, e.g. selenides, $RSeR^1$ (cf. sulphides), selenocyanates, RSeCN (cf. thiocyanates), or selenoketals, $R_2C(SeR^1)_2$ (cf. thioketals). As indicated below, selenoxides [$RSe(O)R^1$], which are the analogues of sulphoxides, are of particular value as synthetic intermediates (section 14.3). The reactivity of selenium-containing compounds is frequently different from that of their sulphur analogues, however, and most of the synthetic methods exploit the reactivity *difference* rather than any unique properties of the selenium-containing group.

14.1 Availability and synthesis of reagents

Commercially available reagents containing selenium(II) include potassium selenocyanate, KSeCN; areneselenols, ArSeH; diaryl diselenides, ArSeSeAr; and areneselenenyl halides, ArSeX (X = Cl, Br or I). Simple functional group transformations may also be used if necessary, e.g.

$$ArN_2^+X^- + {}^-SeCN \longrightarrow ArSeCN \quad (1)$$

$$ArSeSeAr + Br_2 \longrightarrow ArSeBr$$



$$ArSeBr + HN\bigcirc O \longrightarrow ArSeN\bigcirc O$$

$$\left.\begin{matrix} ArSeSeAr \\ \text{or } ArSeCN \end{matrix}\right\} + NaBH_4 \longrightarrow ArSe^-Na^+$$

$$ArSe^-Na^+ + RX \longrightarrow ArSeR$$

A common by-product of reactions described in this chapter is an areneselenenic acid, ArSeOH; this is readily oxidised *in situ* to an areneseleninic

acid, $ArSeO_2H$, or reduced to a diaryl diselenide, ArSeSeAr, either of which may be re-used.

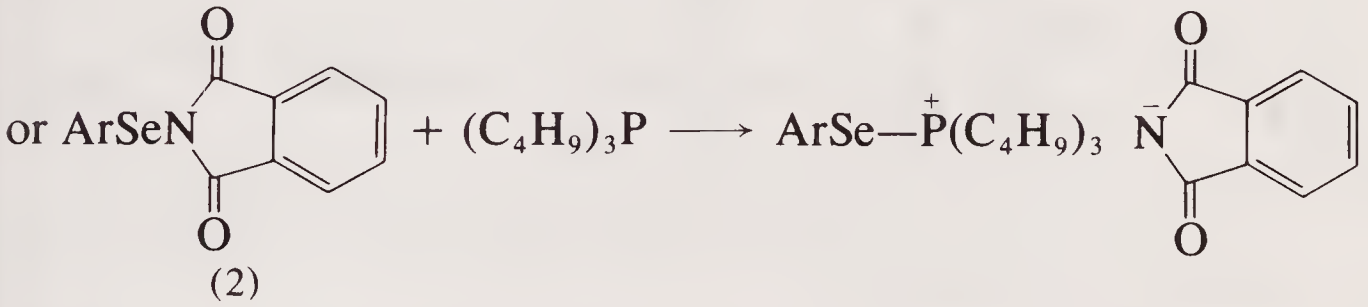
$$2\ ArSeOH \rightarrow ArSeSeAr$$

Among commercially available reagents containing selenium(IV) are benzeneseleninic acid, PhSe(O)OH, and benzeneseleninic anhydride, $(PhSeO)_2O$.

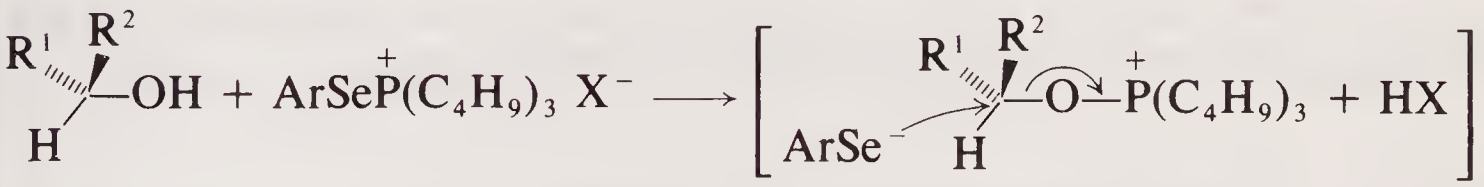
14.2 Functional group interconversion: alcohols into bromides

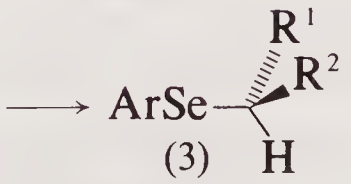
Simple alcohols are converted into alkyl aryl selenides (3) by reaction with aryl selenocyanates (1) or *N*-(arylseleno)phthalimides (2) in presence of tributylphosphine [reaction (14.1)]. The selenides (3) may be further converted into alkyl bromides by reaction with bromine in presence of a base [reaction (14.2)]: since both of these steps are S_N2 processes, involving inversion of configuration, the complete sequence permits the conversion of alcohols into alkyl bromides with *overall retention of configuration.*

$$ArSeCN + (C_4H_9)_3P \rightarrow ArSe{-}\overset{+}{P}(C_4H_9)_3\ CN^-$$

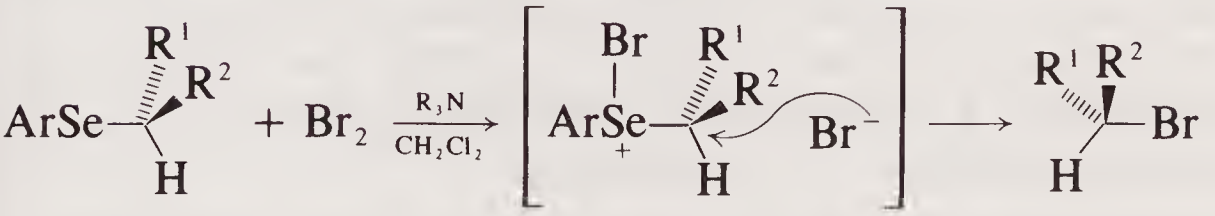


(2)





(3) (14.1)



(14.2)

For example,

$$R\text{-}(-)\text{-}CH_3(CH_2)_5CH(OH)CH_3 \rightarrow R\text{-}(-)\text{-}CH_3(CH_2)_5CHBrCH_3 \quad (67\ \%)$$

(less than 8% of the *S*-enantiomer is formed).

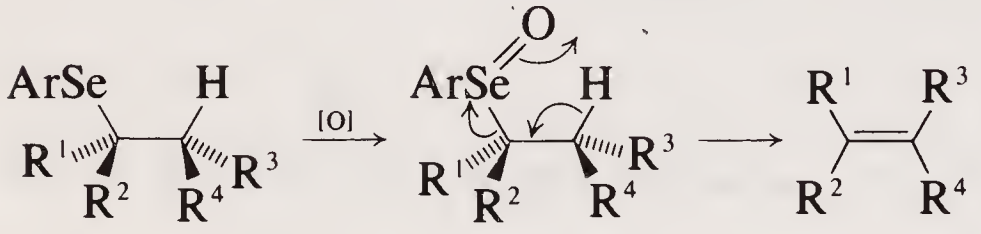
It should be noted that this method is not applicable to the synthesis of chlorides or iodides.

14.3 *syn*-Elimination from selenoxides

14.3.1 General features of the elimination reaction

Oxidation of selenides to selenoxides may be carried out by a range of oxidising agents, including hydrogen peroxide, peroxy-acids, sodium periodate, and ozone. These reactions are analogous to the oxidation of sulphides to sulphoxides (section 9.7.2), although it is worthy of note that further oxidation seldom occurs in the selenium series, whereas sulphoxides readily undergo oxidation to sulphones.

Selenoxides which contain a β-hydrogen are thermally unstable, and readily undergo thermal elimination reactions, giving alkenes and areneselenenic acids [reaction (14.3)]. These are intramolecular *syn*-eliminations, and have counterparts in the reactions of sulphoxides (see p. 297) and tertiary amine oxides. The particular advantage of the selenoxide method lies in the ease of reaction; in most cases the selenoxide is not isolated, elimination occurring spontaneously.



(14.3)

14.3.2 Synthetic applications

The principal variants of the procedure arise in the preparation of the selenide rather than in the oxidation–elimination stage.

14.3.2.1 Selenides from substitution reactions

Selenides may be obtained by three types of substitution:

(a) from an electrophilic selenium reagent (e.g. PhSeBr) and a carbon nucleophile, e.g. a stabilised carbanion (sections 5.1 and 5.2);
(b) from a nucleophilic selenium reagent (e.g. $PhSe^-Na^+$) and a carbon electrophile, e.g. an alkylating agent (section 3.3.1);
(c) from a simpler selenide, e.g. by alkylation.

The three methods are illustrated below [reactions (14.4–14.6)].

(a) $RCH_2CH_2CO_2R' \xrightarrow[\text{(ii) PhSeBr}]{\text{(i) LDA, THF, } -78^\circ} RCH_2\underset{\underset{\text{SePh}}{|}}{C}HCO_2R'$ (4) (14.4)

(b) $RCH_2CHBrCO_2R' \xrightarrow[C_2H_5OH]{PhSe^-Na^+} (4)$ (14.5)

(c) $BrCH_2CO_2R' \xrightarrow{PhSe^-Na^+} PhSeCH_2CO_2R' \xrightarrow[(ii)\ RCH_2Br]{(i)\ LDA,\ THF,\ -78^\circ} (4)$ (14.6)

The reaction sequence is completed by oxidation of (4), using either hydrogen peroxide or a peroxy-acid; thus, for example.

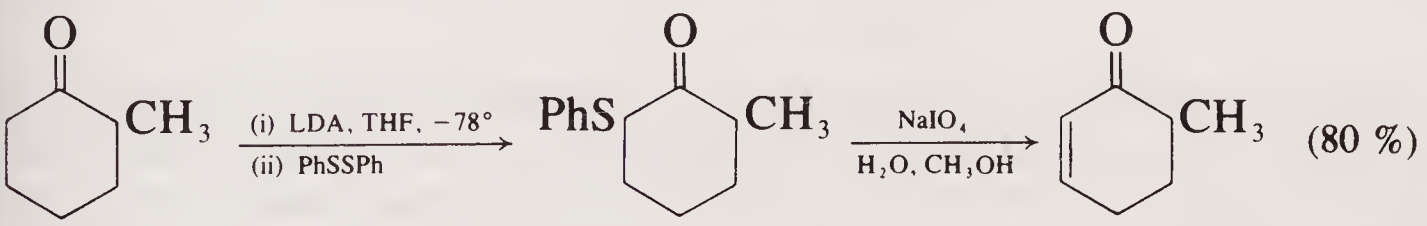
$$PhCH_2\underset{\displaystyle SePh}{\underset{|}{C}}HCO_2C_2H_5 \xrightarrow{[O]} \left[PhCH_2\underset{\displaystyle O{=}SePh}{\underset{|}{C}}HCO_2C_2H_5\right] \longrightarrow \begin{matrix} Ph & & H \\ & \diagdown\!\!=\!\!\diagup & \\ H & & CO_2C_2H_5 \end{matrix} \quad (65-85\ \%)$$

Where geometrical isomerism in the product is possible, *E*-isomers predominate; these presumably arise by *syn*-elimination from the less sterically hindered eclipsed conformer of the selenoxide.

For the introduction of a double bond in conjugation with an electron-accepting ($-M$) group, method (a) is usually the most convenient, e.g.

$$PhCOC_2H_5 \xrightarrow[(ii)\ PhSeBr]{(i)\ LDA,\ THF,\ -78^\circ} PhCO\underset{\displaystyle SePh}{\underset{|}{C}}HCH_3 \xrightarrow[H_2O,\ CH_3OH]{NaIO_4} PhCOCH{=}CH_2 \quad (77\ \%)$$

It should be noted that in these circumstances an analogous elimination involving a sulphoxide may be equally satisfactory, e.g.

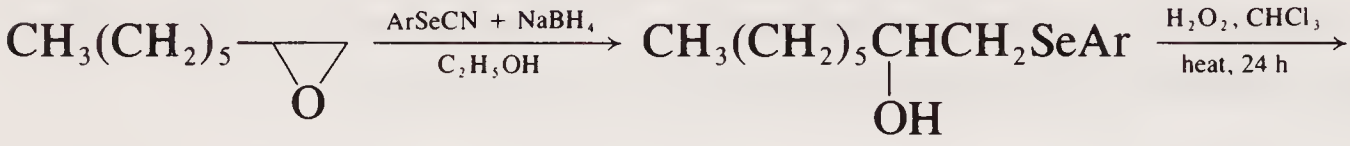


Elimination from a primary alkyl selenoxide, to give an alk-1-ene, is relatively difficult. The yield of alkene may often be improved, however, if the other substituent on the selenium is *o*-nitrophenyl, since the stability of the selenoxide is thereby reduced, e.g.

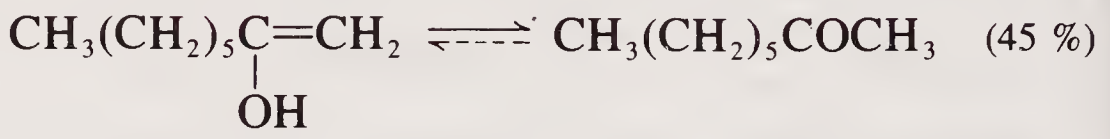
$$CH_3(CH_2)_{11}Br \xrightarrow[(ii)\ H_2O_2,\ THF]{(i)\ o\text{-}O_2NC_6H_4Se^-Na^+,\ C_2H_5OH} CH_3(CH_2)_9CH{=}CH_2 \quad (60\ \%)$$

Alkylation of arylselenide ions may be achieved, not only using alkyl halides as in the last example, but also using epoxides (cf. section 3.3.1, p. 26); the products of these reactions are β-hydroxyselenides. If the arylseleno-group is attached to the terminal carbon of a chain, oxidation gives a selenoxide which is relatively stable but which decomposes on

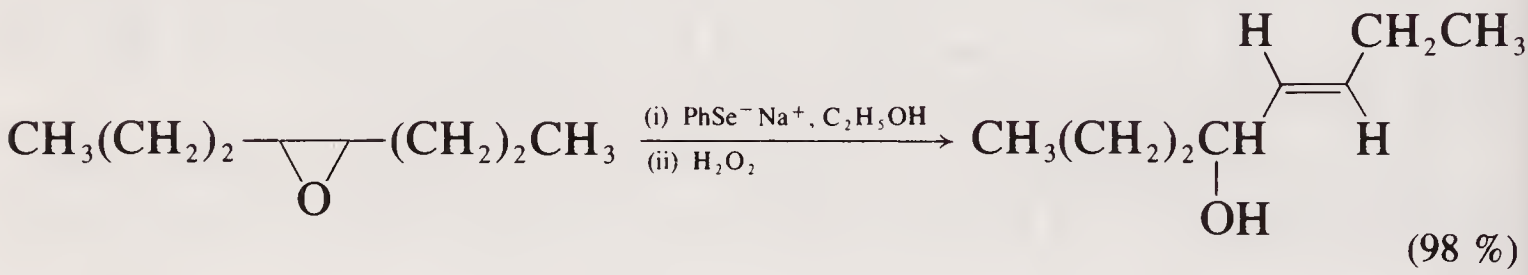
heating to give a ketone. If, however, the selenoxide may undergo an alternative elimination to give an allylic alcohol, this occurs under mild conditions at the expense of ketone formation.



(Ar=*o*-$O_2NC_6H_4$)

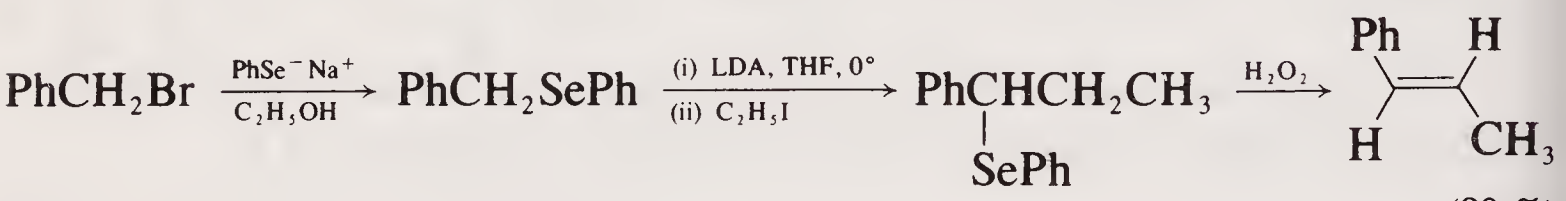


(45 %)



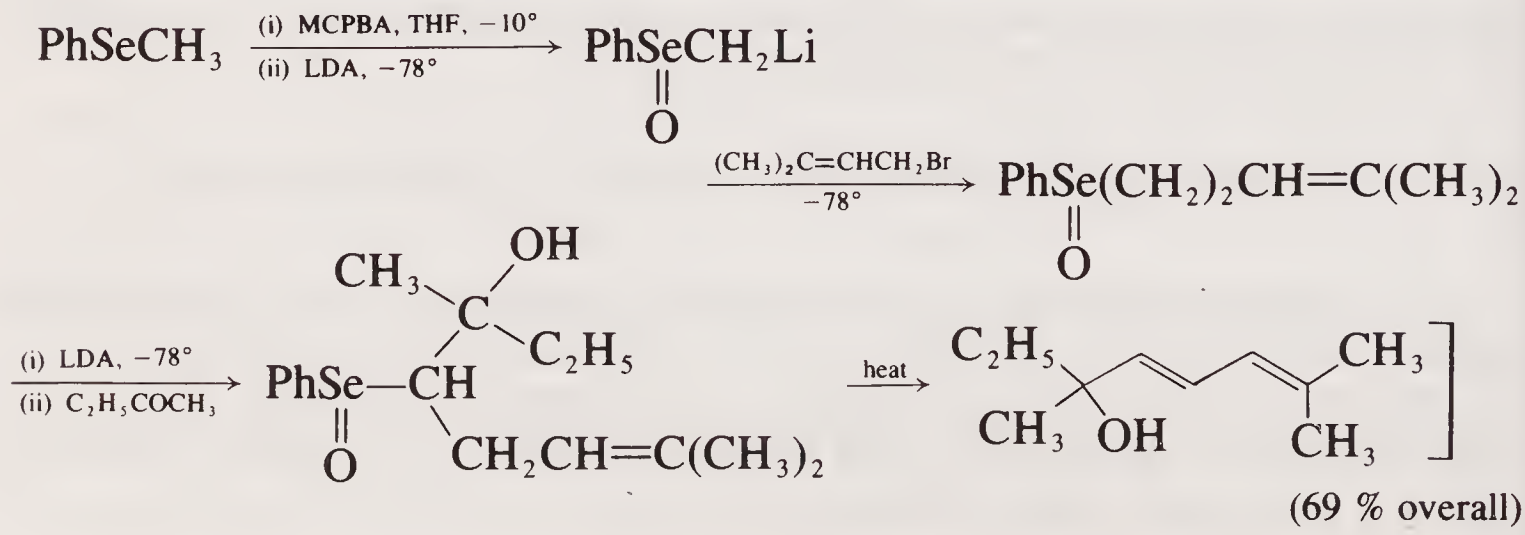
(98 %)

Preparation of selenides by alkylation of simpler selenides [method (c) on p. 296] is practicable only when deprotonation of the latter is facilitated by a $-M$ group, as in reaction (14.6); or when the intermediate carbanion is generated by reaction of a diseleno-acetal or -ketal (section 14.5.2.1, p. 304); or in the case of benzylic selenides, e.g.



(80 %)

[The selenoxide group, however, is a carbanion-stabilising group in its own right, and provided that the reaction temperature is kept below that at which elimination occurs, selenoxides may be formed and alkylated *in situ*. The sequence is demonstrated by the following 'one-pot' synthesis:

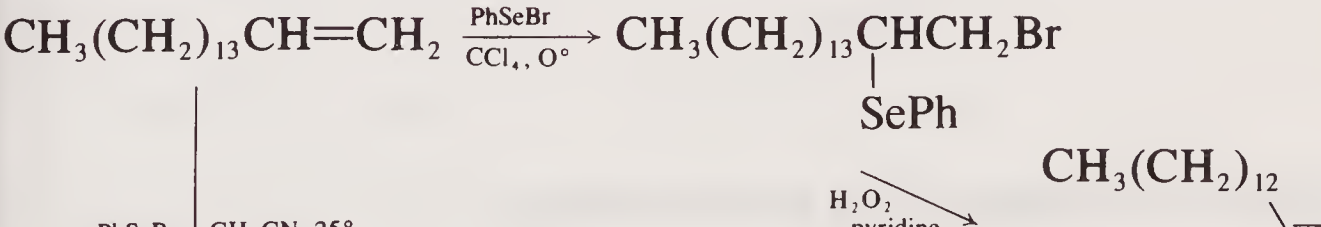


(69 % overall)

14.3.2.2 Selenides from addition reactions

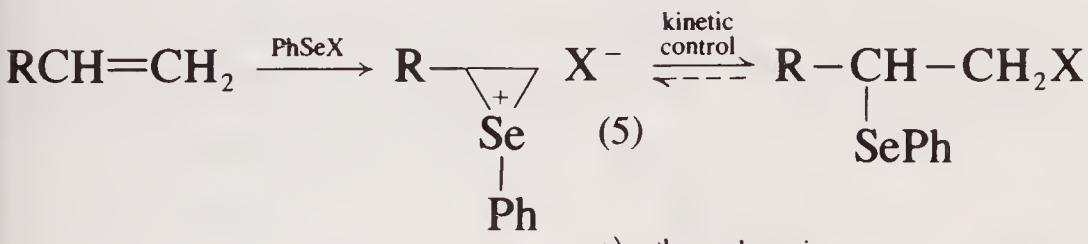
Selenides may also be obtained by the addition of electrophilic selenium reagents to alkenes. For example, benzeneselenenic acid (produced *in situ* from the seleninic acid and the diselenide) may be added to alkenes to give β-hydroxyselenides, which on oxidation followed by elimination, give allylic alcohols (cf. section 14.3.2.1).

$$[PhSeO_2H + PhSeSePh + H_2O \longrightarrow 3PhSeOH]$$



The overall reaction amounts to an allylic oxidation, with a rearrangement of the double bond; a similar result may be obtained (*via* a different intermediate) using selenium dioxide (section 9.2.2).

Addition of arylselenenyl halides to alkenes gives β-halogenoselenides, and these are convertible by oxidation–elimination into halogenoalkenes; the initial addition proceeds *via* a seleniranium ion (5). Under conditions of kinetic control[2] (low temperature, non-polar solvent) halide attack occurs at the less-substituted carbon of (5) [reaction (14.7a)]; whereas in more polar media and at higher temperatures (conditions of thermodynamic control[2]) the more stable addition product (corresponding to 'Markownikoff addition') is obtained [reaction (14.7b)].

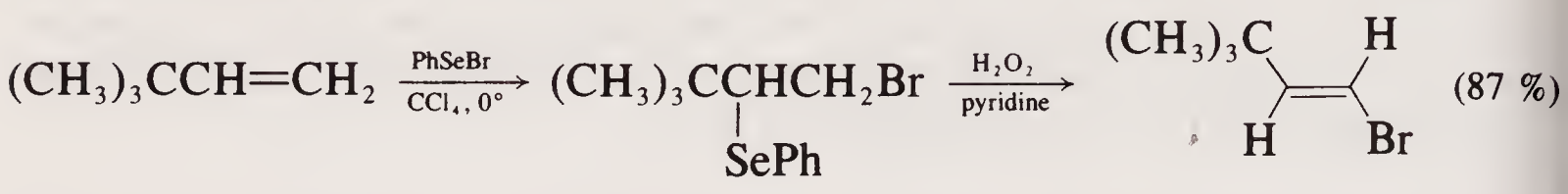


(14.7a)

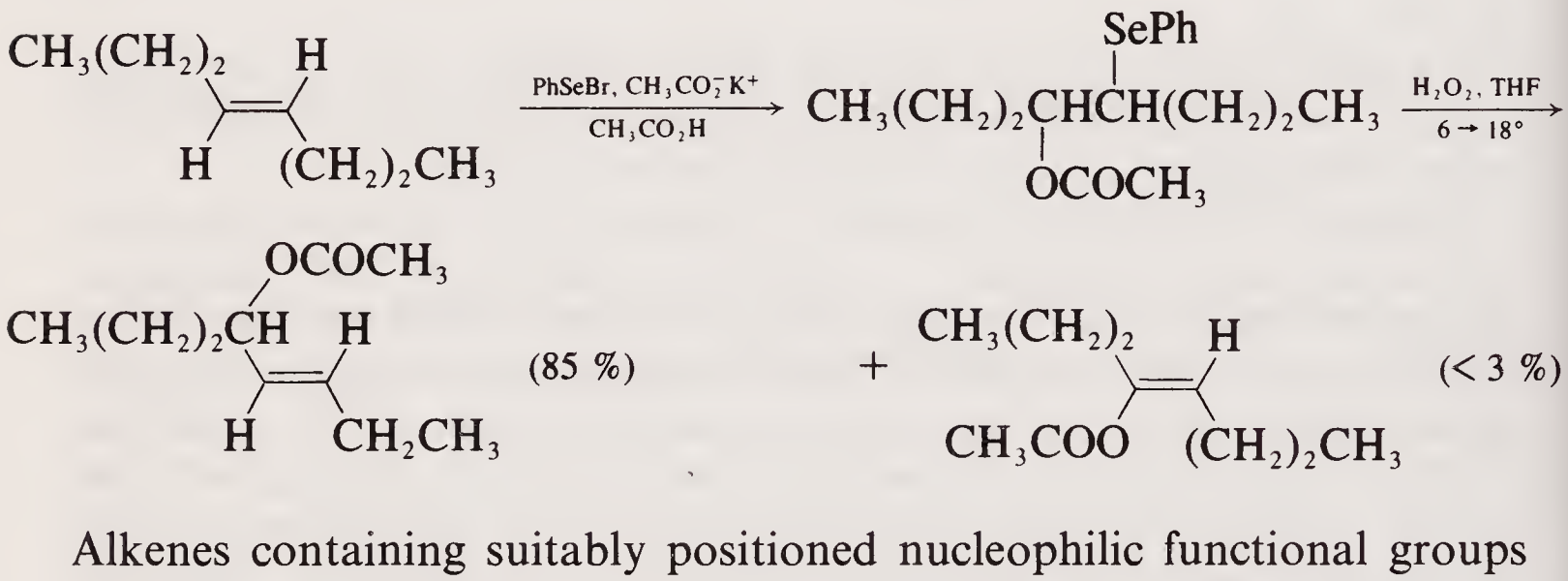
(14.7b)

For example,

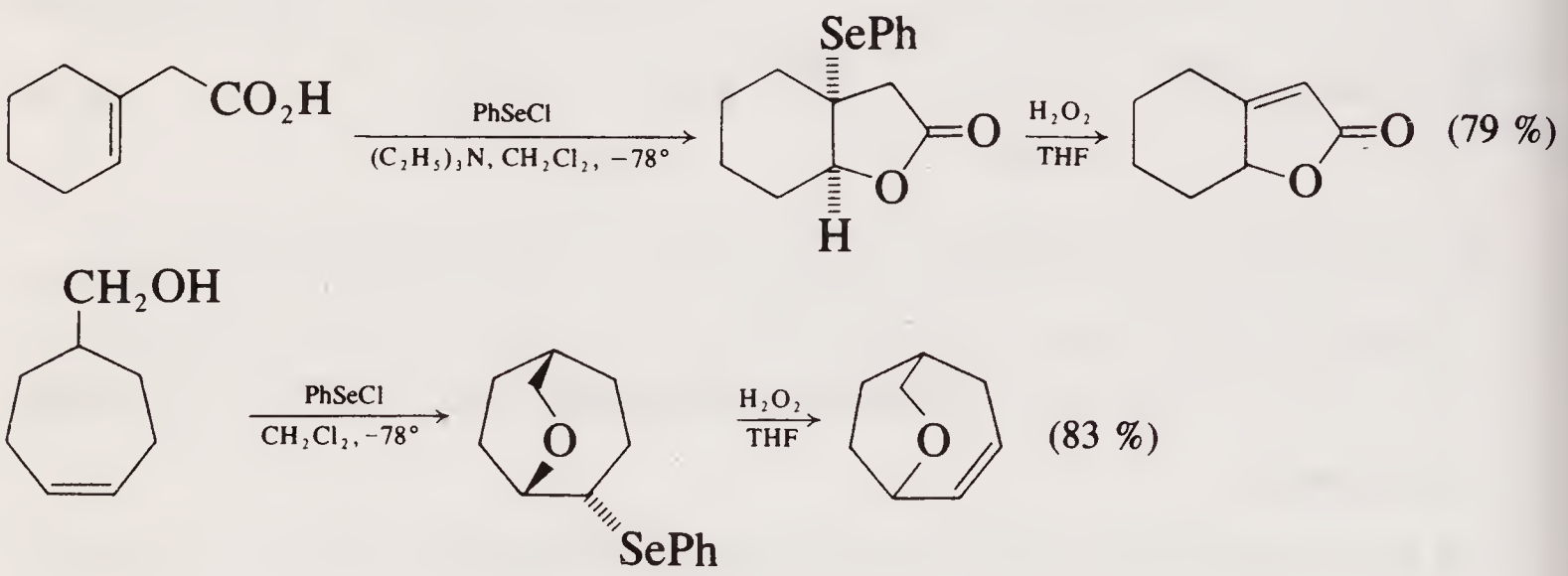
It should be noted that a 1-bromoalk-1-ene is not formed under either set of conditions. Such a product is formed only if no alternative mode of elimination is possible, e.g.



If the addition of the selenenyl halide is carried out in alcoholic solvents, or in acetic acid, β-alkoxy- or β-acetoxyselenides are formed. (The latter also result from reaction of alkenes with benzeneseleninic acid in acetic acid.)



Alkenes containing suitably positioned nucleophilic functional groups may undergo cyclisation by reaction with selenenyl halides, e.g.

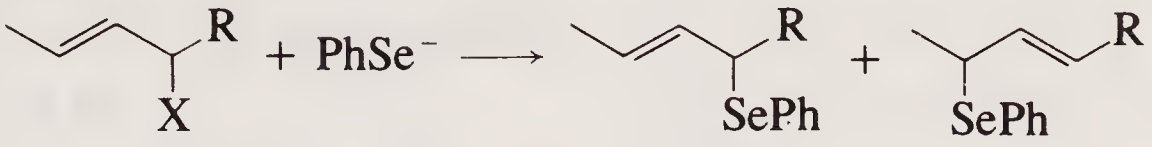


14.4 Allylic selenides and selenoxides

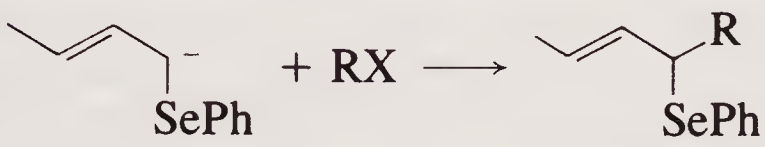
14.4.1 Preparation of allylic selenides: general features

The variety of routes available for the preparation of allylic selenides makes such compounds attractive synthetic intermediates. The familiar routes involving substitution processes may be used, e.g.

(a) reaction of an allyl halide with a selenide anion:[4]

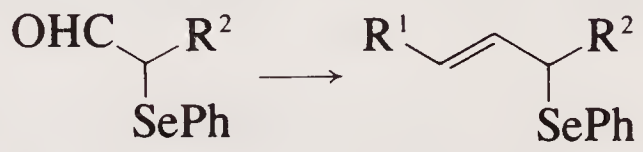


(b) alkylation of an allylselenide anion:



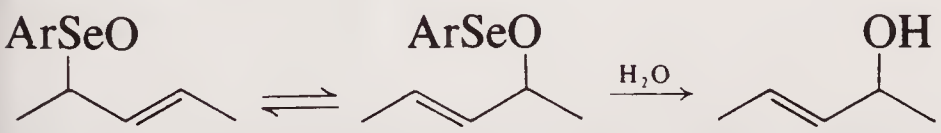
A third possibility, however, involves formation of the double bond by a Wittig or Wittig–Horner reaction (cf. sections 5.3.1 and 12.2), e.g.

(c) $Ph_3P{=}CHR^1$ +



14.4.2 The allyl selenoxide rearrangement

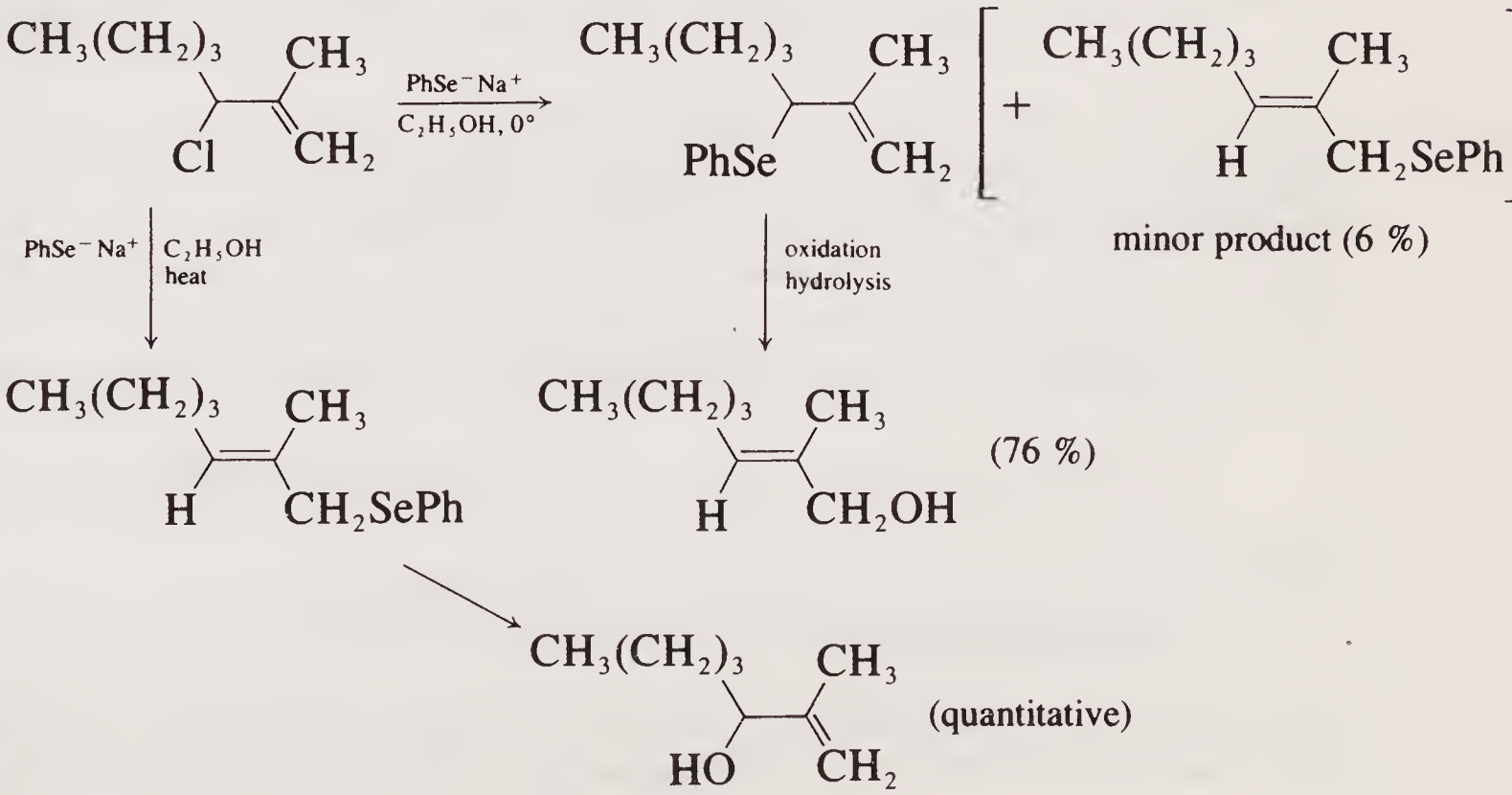
Allyl selenoxides undergo a very facile rearrangement to allyl selenenates [reaction (14.8)], and the latter may be hydrolysed to allylic alcohols. 'Normal' elimination from allyl selenoxides is therefore not generally observed.



(14.8)

The following examples illustrate the flexibility of the method for the synthesis of allylic alcohols, and they also illustrate the three routes to allyl selenides outlined above.

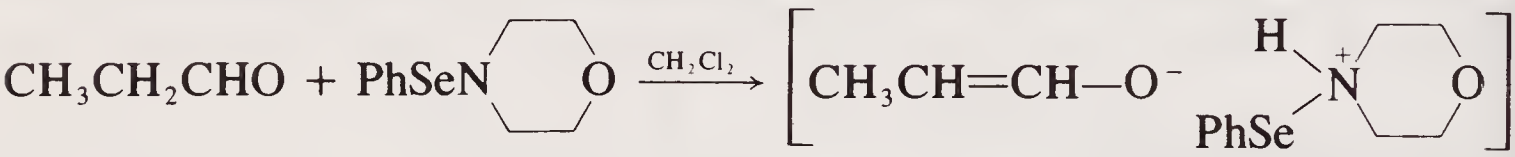
(a)

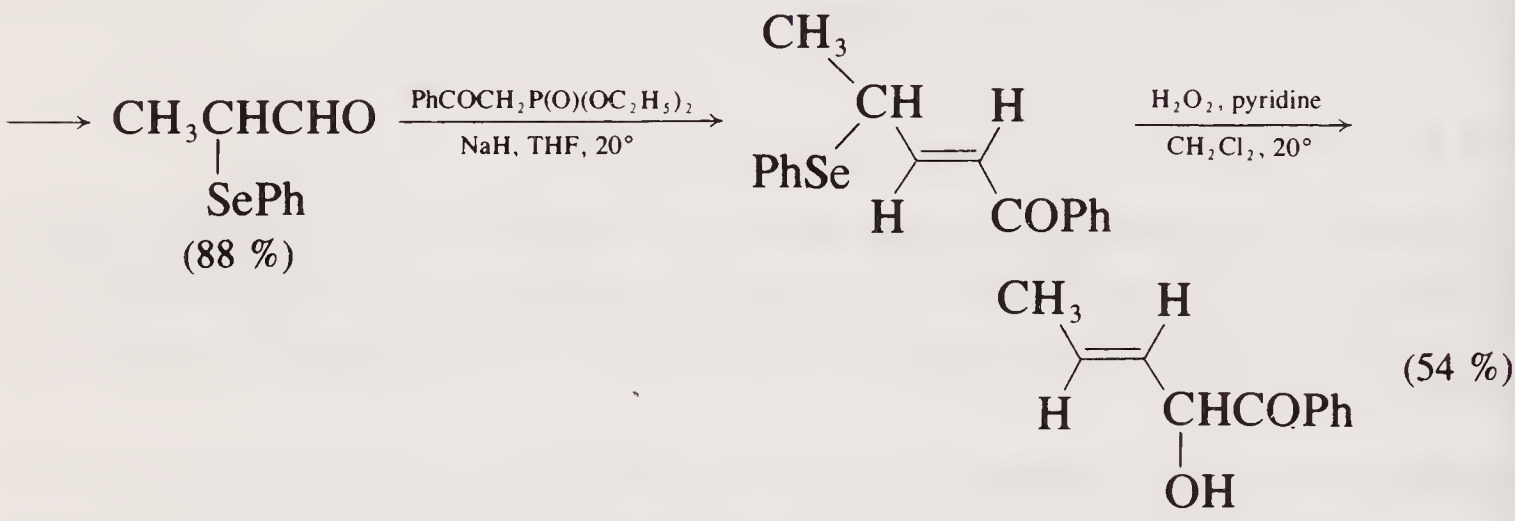


(b) $[PhSe^-Na^+ + BrCH_2CH{=}CH_2 \rightarrow]\ PhSeCH_2CH{=}CH_2 \xrightarrow[\text{(ii) } Ph(CH_2)_3Br]{\text{(i) LDA, THF, } -78^\circ}$

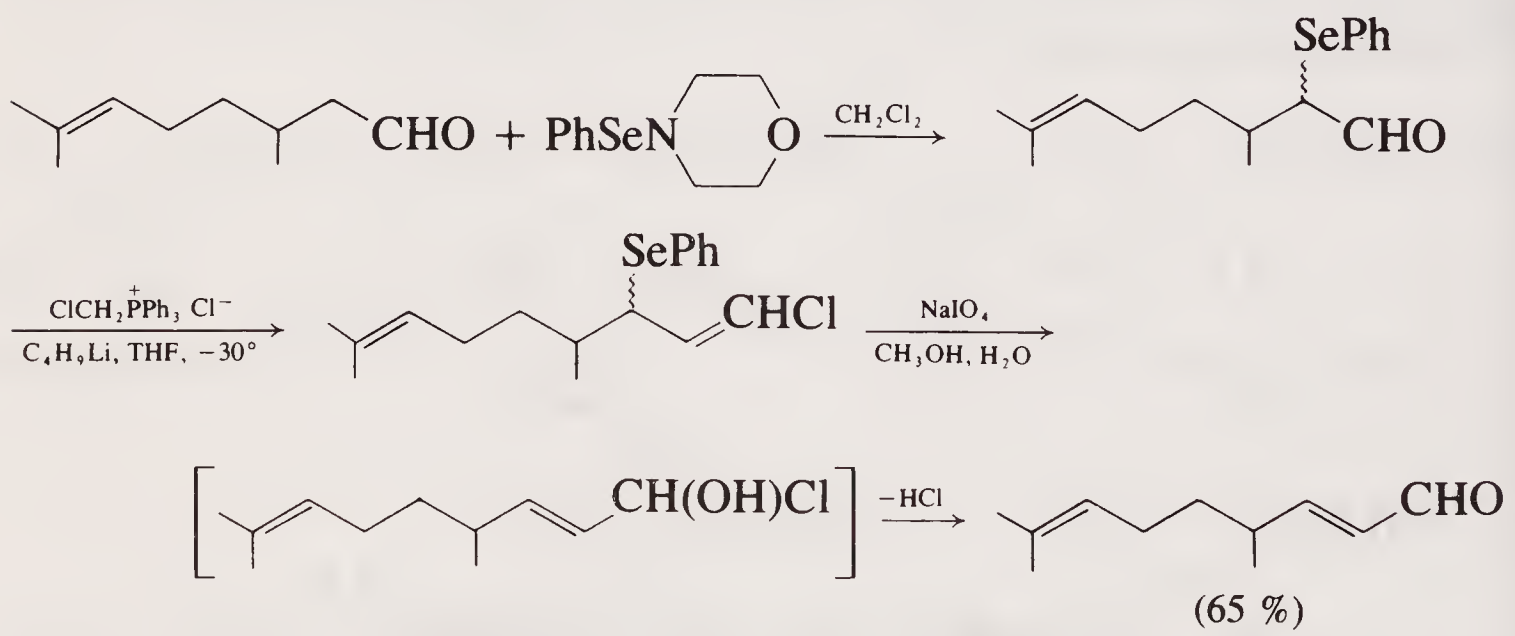
$$Ph(CH_2)_3CH(SePh)CH{=}CH_2 \xrightarrow[\text{pyridine, } 20^\circ]{H_2O_2,\ CH_2Cl_2} \underset{H}{\overset{Ph(CH_2)_3}{\diagdown}}\!\!=\!\!\underset{CH_2OH}{\overset{H}{\diagup}} \quad (68\ \%)$$

(c) α-Selenoaldehydes are formed in high yield by reaction of simple aldehydes with, for example, a morpholinoselenide. In this example, the selenoaldehyde is converted into the allyl selenide by the Wittig–Horner reaction.





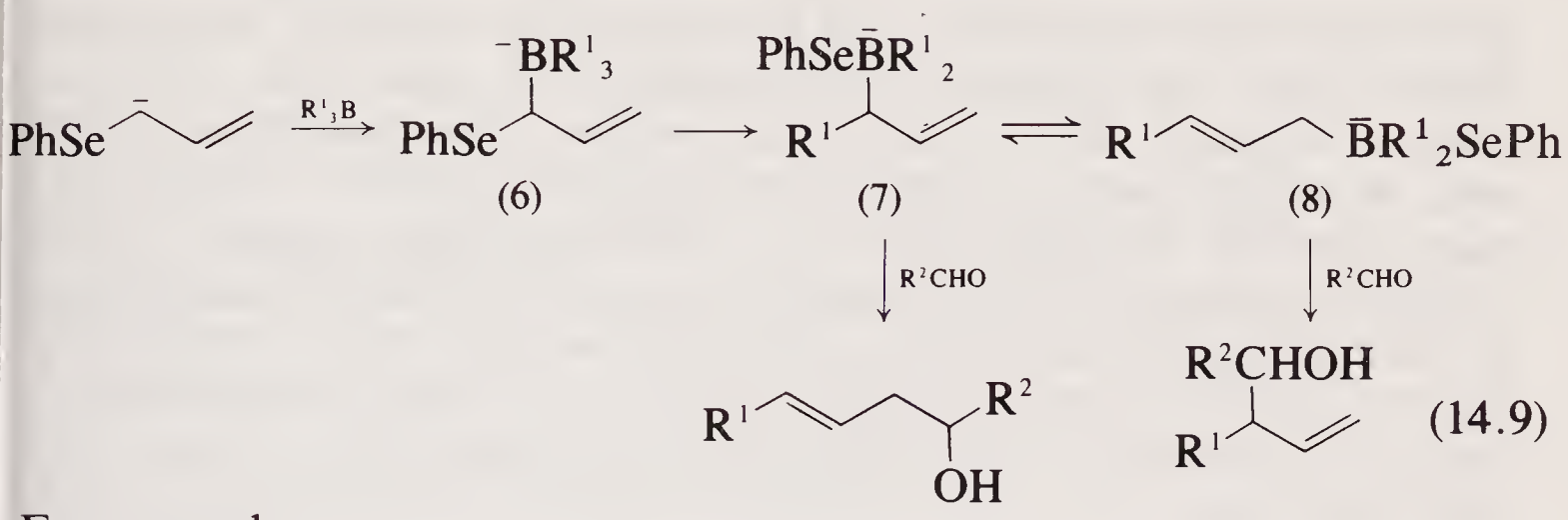
In a variant of this last method, aldehydes, RCH_2CHO, are converted into enals, $RCH{=}CHCHO$, containing *one* additional carbon atom:



14.4.3 Reaction with trialkylboranes: synthesis of β-hydroxyalkenes

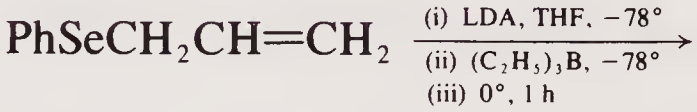
The sequence is shown below [reaction (14.9)]. The anion of an allyl phenyl selenide reacts with a trialkylborane to give an adduct (6), which

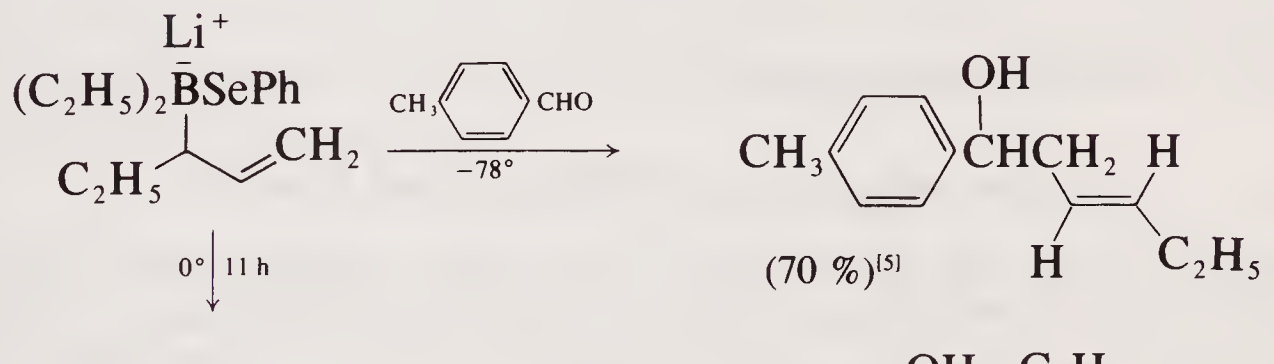
rearranges with interchange of the phenylseleno group and one of the alkyl groups. The product (7) may isomerise further giving (8); both (7) and (8) react with aldehydes to produce β-hydroxyalkenes:

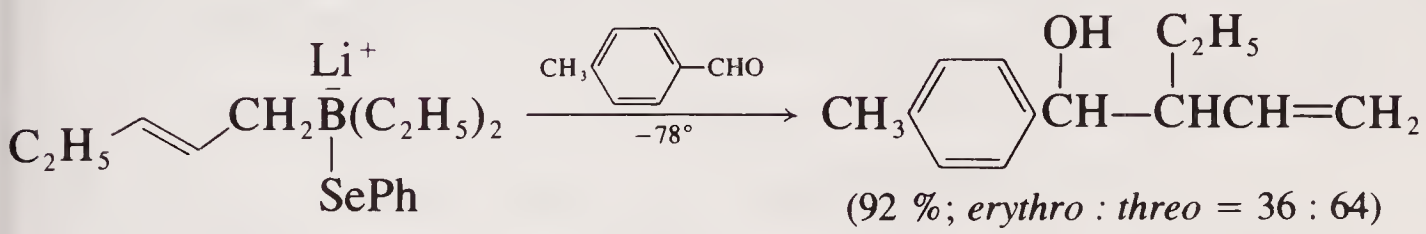


(14.9)

For example,

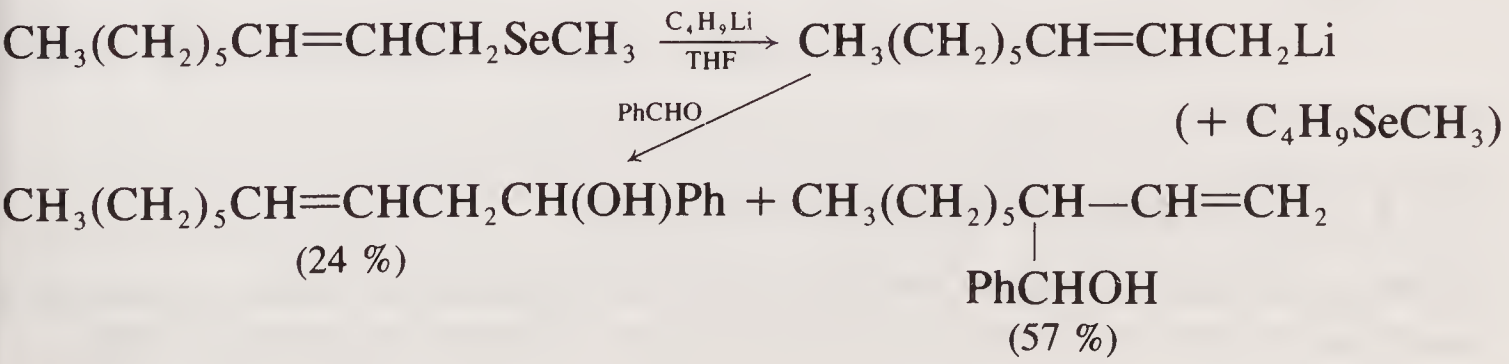






14.4.4 Reaction with alkyl-lithium reagents: selenium–lithium exchange

Allyl selenides undergo deselenation by reaction with alkyl-lithium reagents. The reaction proceeds more readily, and the selenium-containing by-product is more easily removed from the reaction mixture, with allyl methyl selenides than with allyl phenyl selenides. The variety of routes available for the preparation of allylic selenides makes this an attractive route to allyl-lithium reagents which may otherwise be difficult to obtain.



14.5 Hydrogenolysis of carbon–selenium bonds

14.5.1 Introduction

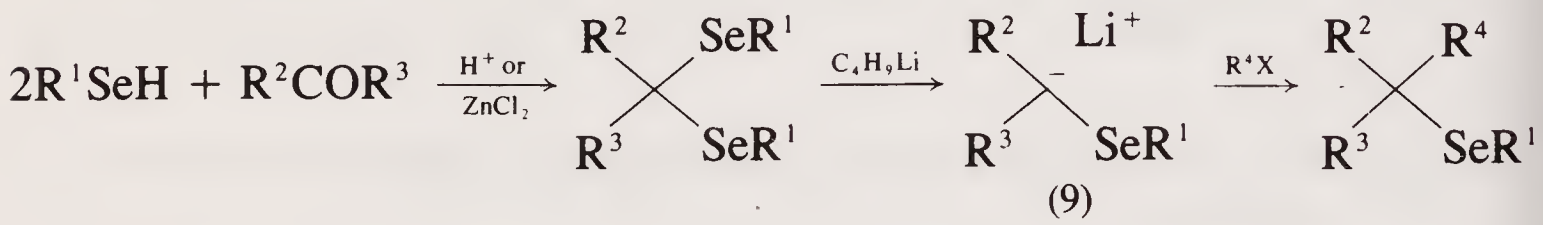
Hydrogenolysis of selenides may be effected by a number of reagents. Raney nickel and lithium in ethylamine can be used under mild conditions, although these reagents also reduce other functional groups, such as sulphide and carbonyl. Triphenyltin(IV) hydride, Ph_3SnH, is a more selective reducing agent for carbon–selenium bonds, but the reagent is expensive and air-sensitive; the reactions require heating (e.g. in boiling toluene); and reaction times may be long. 'Nickel boride', produced *in situ* by reaction of nickel chloride and sodium borohydride, is the most satisfactory: the conditions are mild and reaction times relatively short, e.g.

$$PhSe(CH_2)_{11}CO_2CH_3 \xrightarrow[THF,\ CH_3OH,\ 0°]{NiCl_2,\ NaBH_4} CH_3(CH_2)_{10}CO_2CH_3 \quad (90\ \%)$$

14.5.2 Synthetic applications

14.5.2.1 Reductive alkylation of aldehydes and ketones

Diselenoacetals and diselenoketals, like allyl selenides, are cleaved by reaction with butyl-lithium, and the resulting carbanions (9) may be alkylated in the usual way. [The alkylation occurs in higher yield if R^1 in (9) is alkyl rather than aryl.]



(9)

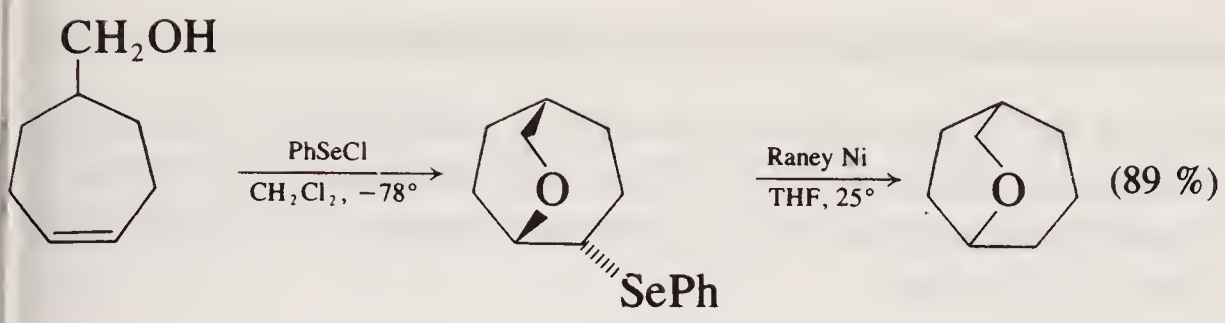
Subsequent hydrogenolysis of the final selenide completes a sequence which amounts to a reductive alkylation of the aldehyde or ketone, e.g.

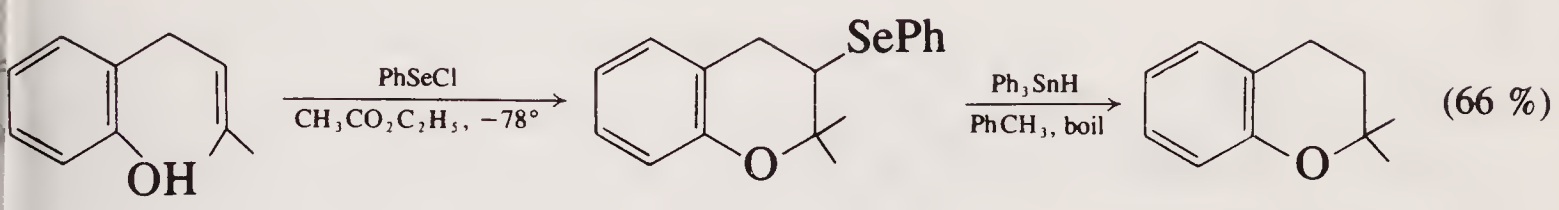
$$CH_3(CH_2)_5CHO \xrightarrow[ZnCl_2]{CH_3SeH} CH_3(CH_2)_5CH(SeCH_3)_2 \xrightarrow[(ii)\ CH_3(CH_2)_5Br,\ 25°]{(i)\ C_4H_9Li,\ THF,\ -78°}$$

$$CH_3(CH_2)_5\underset{\displaystyle SeCH_3}{\underset{|}{C}}H(CH_2)_5CH_3 \xrightarrow[C_2H_5NH_2]{Li} CH_3(CH_2)_{11}CH_3 \quad (48\ \%)$$

14.5.2.2 Formation of reduced heterocycles

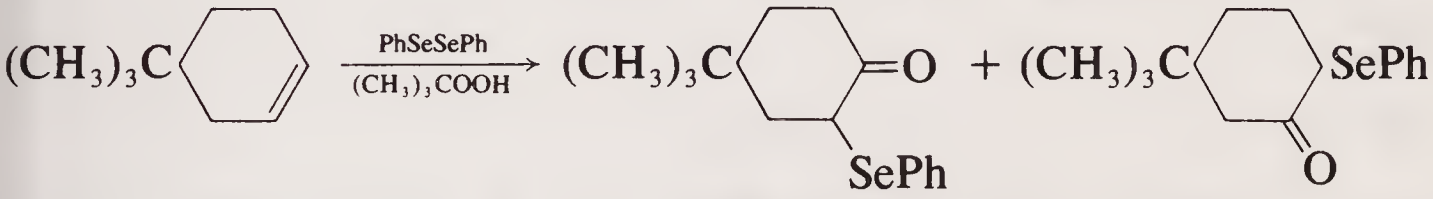
Hydrogenolysis has been widely used in conjunction with cyclisation reactions of the type already introduced in section 14.3.2.2 (p. 300).





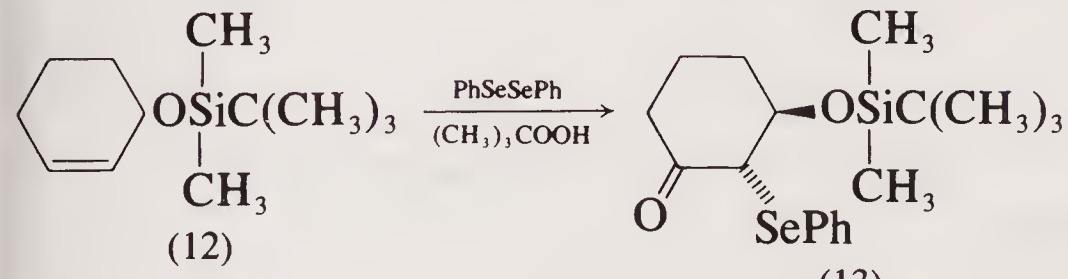
14.5.2.3 Oxidation of alkenes to ketones

α-(Phenylseleno)ketones result by the reaction of an alkene with diphenyl diselenide and t-butyl hydroperoxide. Although unsymmetrical alkenes give rise to a mixture of products, e.g. 4-t-butylcyclohexene gives a 55:45 mixture of (10) and (11), the presence of a bulky α-substituent in the alkene can lead to a reaction which is highly regioselective, as in the conversion of (12) into (13).

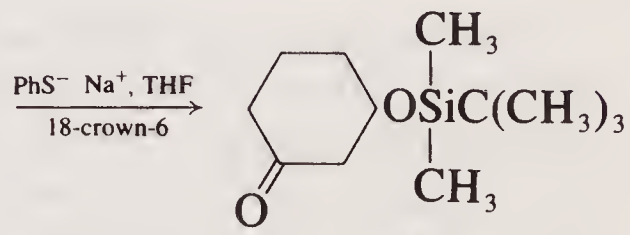


(10) (11)

(combined yield 70 %)



(12) (13)

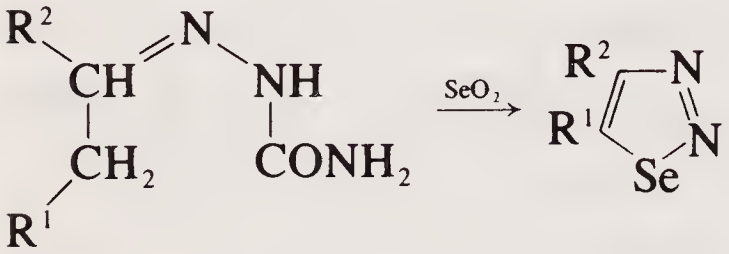


(65 %)

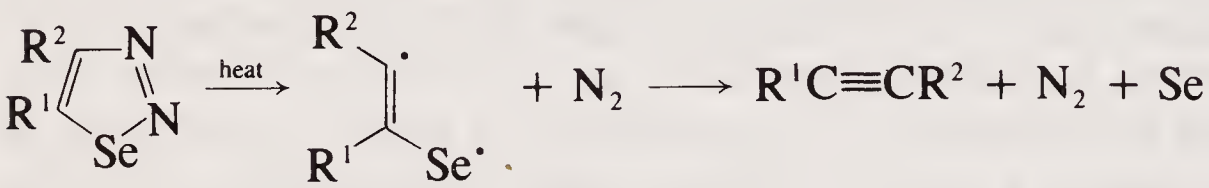
Hydrogenolysis of α-(phenylseleno)ketones may be achieved by reaction with an arenethiolate ion. If the initial addition to the alkene can be made regiospecific, the sequence constitutes a useful conversion of alkenes into ketones without the need for strong acids or bases, or powerful oxidising agents.

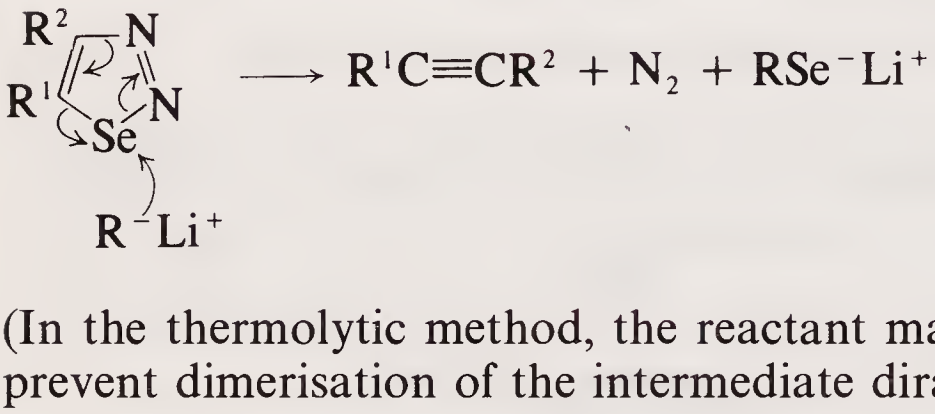
14.6 Elimination reactions of 1,2,3-selenadiazoles

Ketones containing an α-methylene group are oxidised by selenium dioxide to 1,2-diketones (section 9.5.2). The semicarbazones of ketones containing an α-methylene group, however, are oxidised by selenium dioxide to 1,2,3-selenadiazoles:



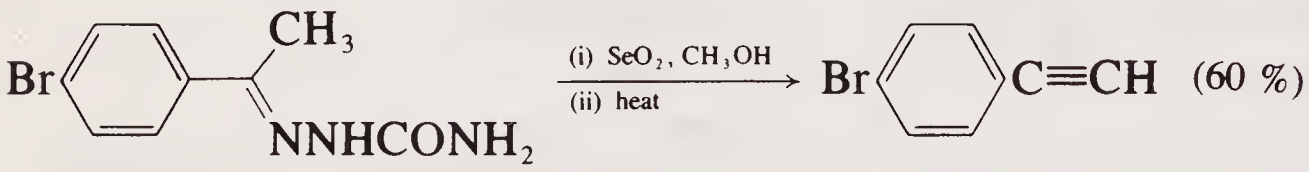
These selenadiazoles are decomposed thermally, or by reaction with butyl-lithium, to alkynes:



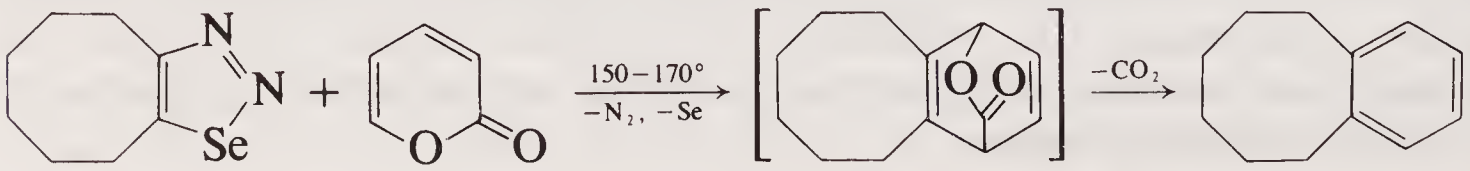


(In the thermolytic method, the reactant may be diluted with sand, to prevent dimerisation of the intermediate diradical.)

For example,



Cycloalkynes may be prepared from the appropriate fused-ring selenadiazole. Yields are low in the thermolytic process, and somewhat higher using butyl-lithium at $-70°$. In many cases, however, side-reactions of various kinds reduce the synthetic value of the method. Formation of the cycloalkyne in good yield has sometimes been indicated by trapping experiments, in which the cycloalkyne undergoes a Diels–Alder cyclo addition, e.g. with α-pyrone:



14.7 Oxidation using selenium(IV) reagents

Apart from selenium dioxide (sections 9.2.2, 9.5.2 and 14.6), two other commercially available selenium(IV) reagents are used in oxidative procedures, *viz.* benzeneseleninic acid and benzeneseleninic anhydride.

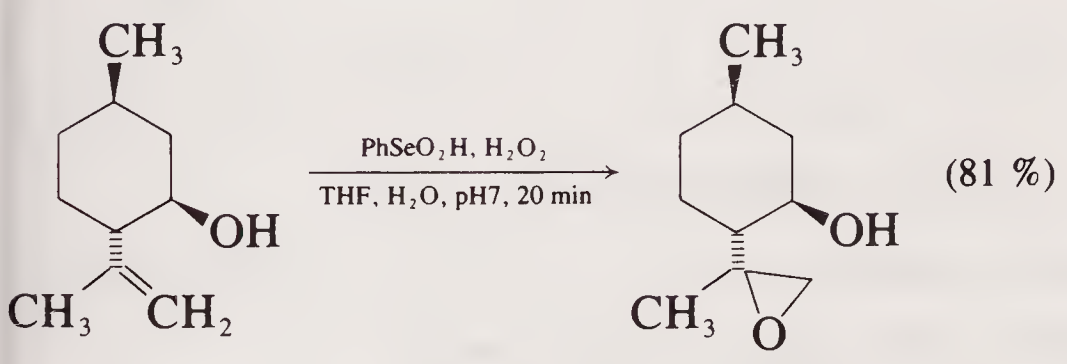
14.7.1 Oxidation using benzeneseleninic acid

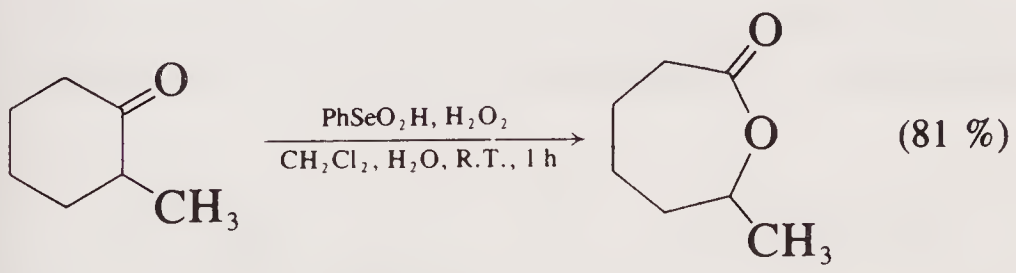
Unlike the corresponding sulphinic acid, benzeneseleninic acid is a versatile oxidant: for example, it oxidises aldehydes to carboxylic acids, thiols to disulphides (section 9.7.1), sulphinic to sulphonic acids, and hydrazine to nitrogen. Also, whereas hydrogen peroxide oxidises benzenesulphinic acid to benzenesulphonic acid, it oxidises benzeneseleninic acid to peroxybenzeneseleninic acid (14). This is a powerful oxidant in its own right, being used, for example, in the epoxidation of alkenes (cf. section 9.2.5.1) and in the Baeyer–Villiger reaction (cf. section 9.5.3).

$$\text{PhSO—OH} \xrightarrow{H_2O_2} \text{PhSO}_2\text{—OH}$$

$$\text{but PhSeO—OH} \xrightarrow{H_2O_2} \text{PhSeO—O—OH}$$

(14)

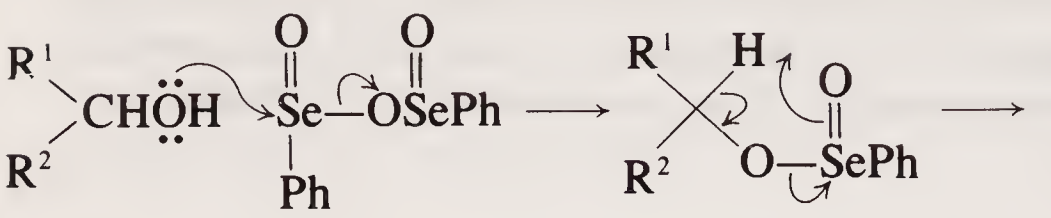




14.7.2 Oxidations using benzeneseleninic anhydride

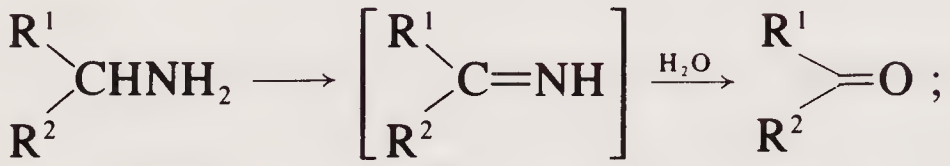
Like the anhydrides of carboxylic acids, benzeneseleninic anhydride is an electrophilic reagent, reacting with nucleophiles such as alcohols, phenols, enols or amines in what are, effectively, the selenium equivalents of acylation processes. The products, however, are either selenoxides or selenoxide-related molecules, and they readily undergo elimination reac-

tions, as shown below [reactions (14.10–14.13); cf. section 14.3].

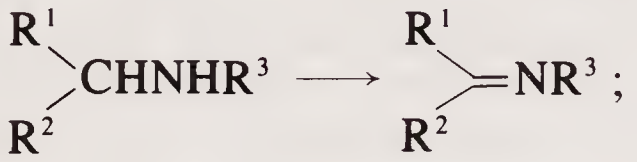


(14.10)

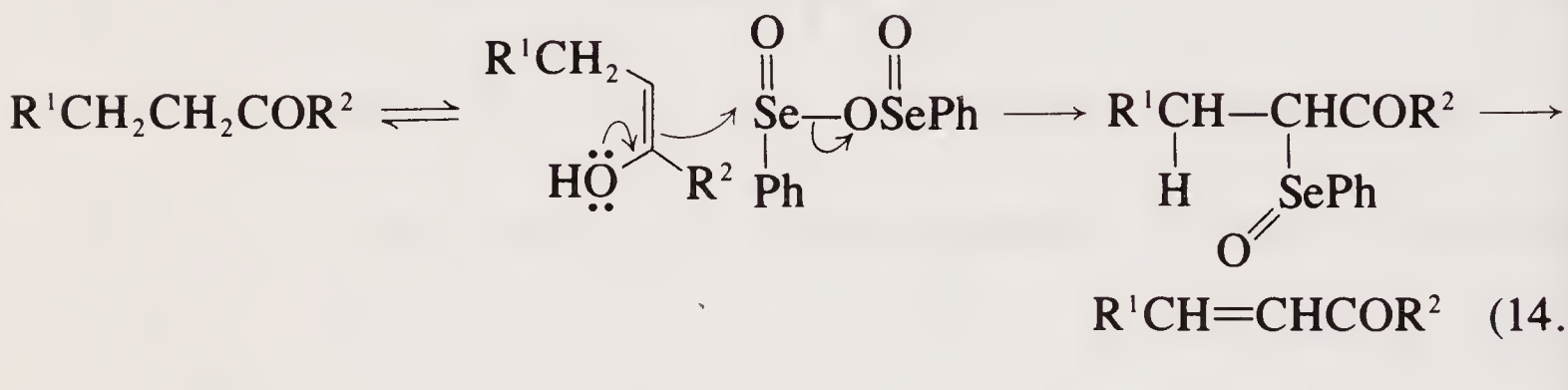
Similarly



(14.11)



(14.12)



(14.13)

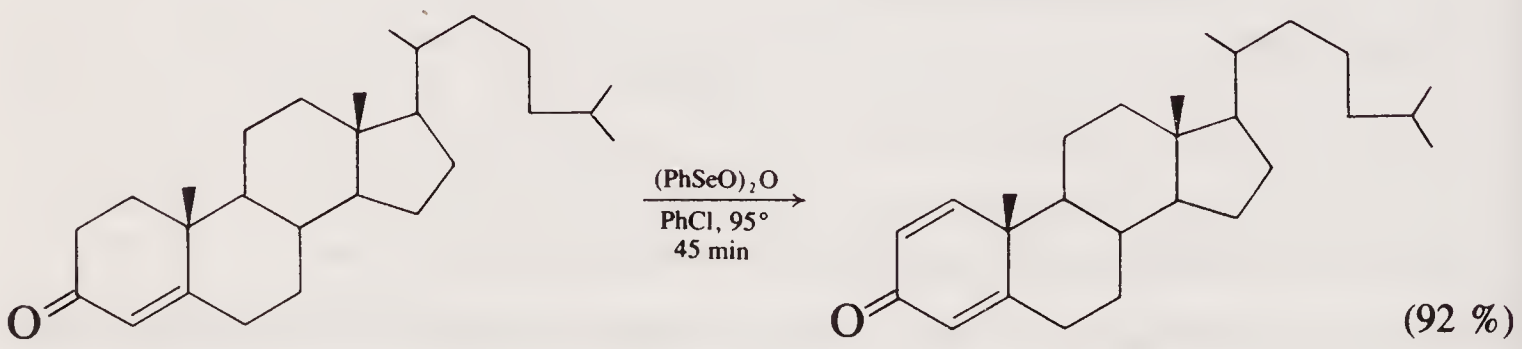
For example,

$$PhCH(OH)CO_2CH_3 \xrightarrow[C_6H_6,\ heat,\ 10\ min]{(PhSeO)_2O} PhCOCO_2CH_3 \quad (97\ \%)$$

$$Ph_2CHNH_2 \longrightarrow Ph_2CO \quad (88\ \%)$$

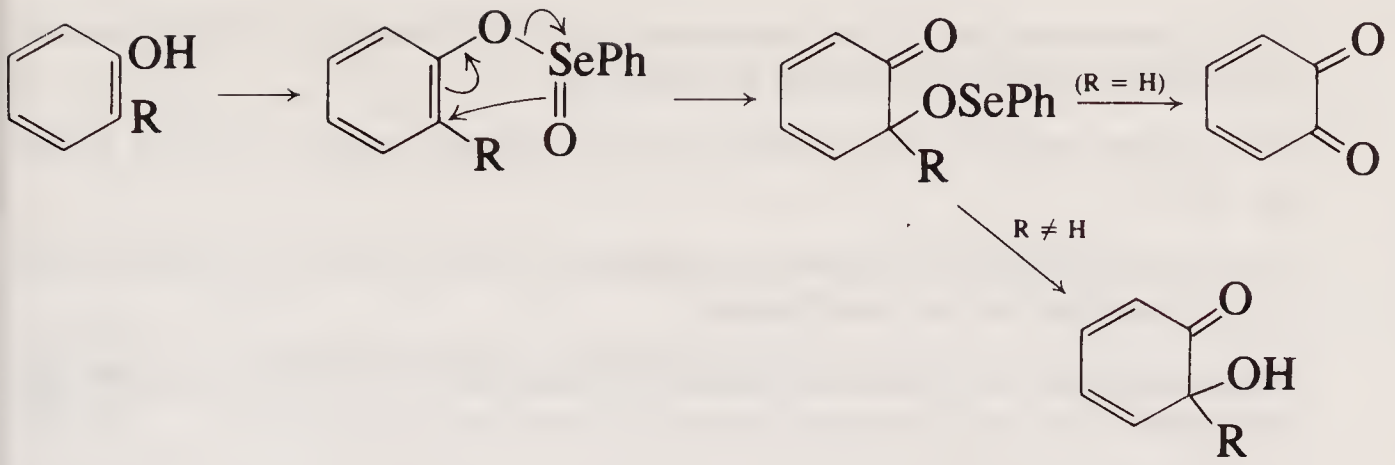
$$PhCH_2NH_2 \longrightarrow [PhCH{=}NH] \xrightarrow[(PhSeO)_2O]{excess} PhCN \quad (96\ \%)$$

$$[PhCH{=}NH] \xrightarrow{H_2O} [PhCHO] \longrightarrow PhCO_2H$$



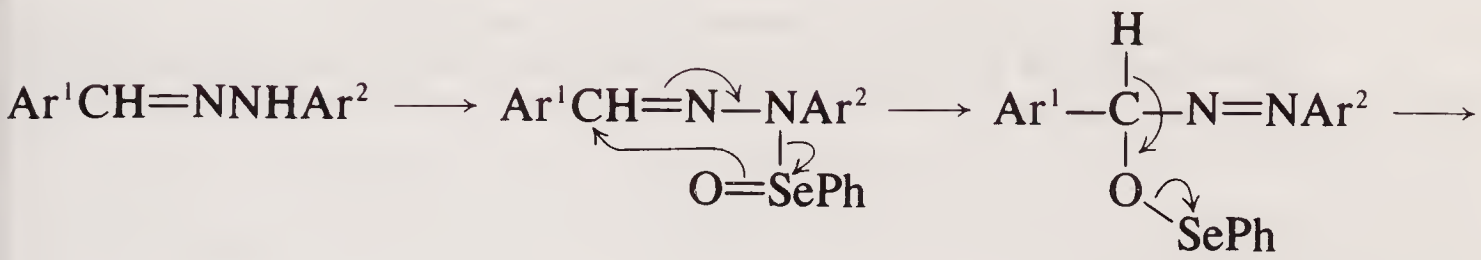
(92 %)

If the selenoxide analogue produced in the initial reaction contains a β,γ-double bond, rearrangement (cf. section 14.4.2) may then occur, as in reactions (14.14) and (14.15).



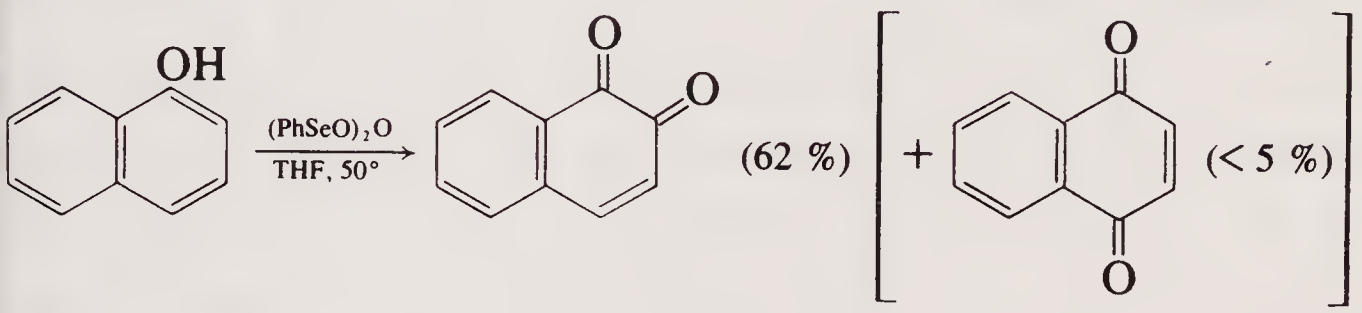
(14.14a)

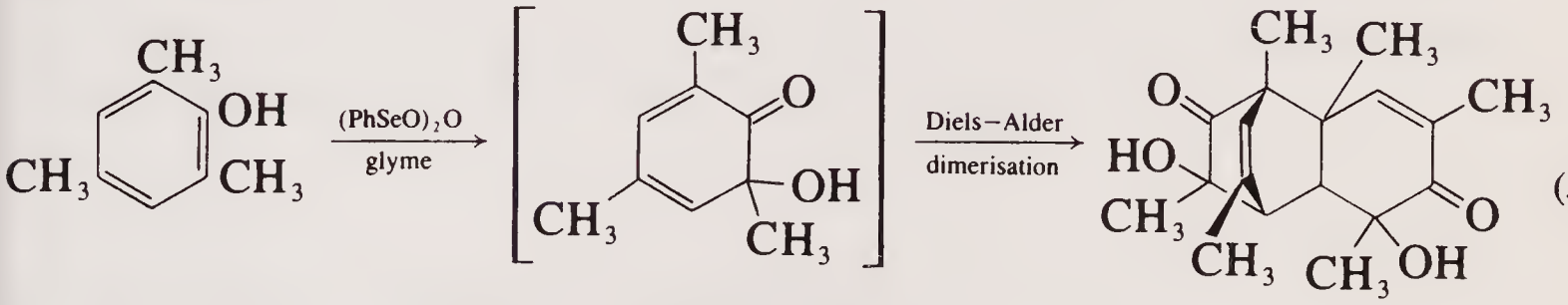
(14.14b)



$Ar^1CON{=}NAr^2$ (14.15)

For example,

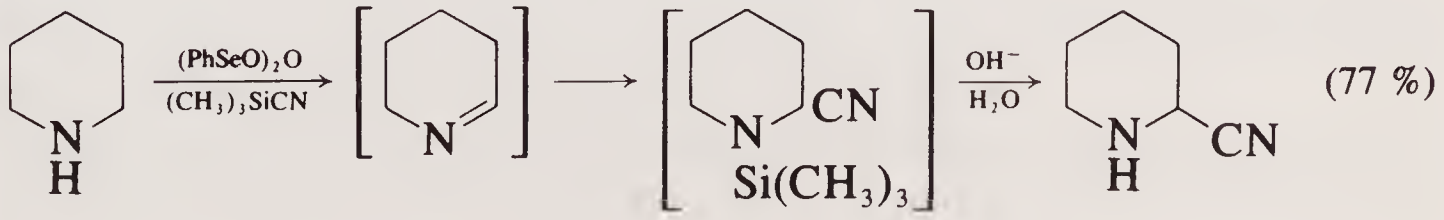




$PhCH{=}NNHPh \xrightarrow[THF,\ 40-50°,\ 1\ h]{(PhSeO)_2O} PhCON{=}NPh$ (67 %)

All of the above oxidations take place under mild and essentially neutral conditions. They may be used in combination with other reactions to produce useful 'one-pot' procedures, e.g. for the amination of phenols:

or the preparation of α-cyanoamines:



Notes

1. All selenium-containing compounds are to be regarded as highly toxic, and appropriate precautions taken for their use.

2. For a fuller explanation of kinetic and thermodynamic control, see Sykes, pp. 42–3.

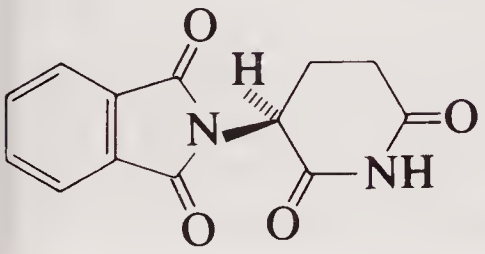
3. The di-isopropylamine is added to remove the benzeneselenenic acid formed as a by-product of the elimination.

4. Rearrangement in substitution reactions of allylic compounds is mentioned in section 3.3.4, and discussed more fully by Sykes (p. 85).

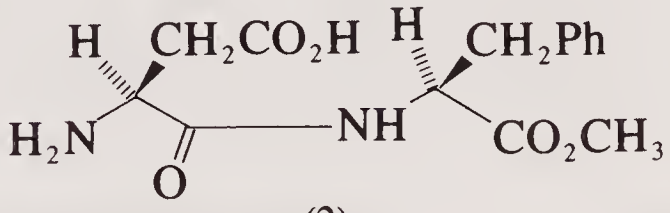
5. Although only one alkene is isolated in this particular case, other examples show significant quantities of the *Z*-isomer and the rearrangement product (the alk-1-ene).

15 Asymmetric synthesis

Asymmetric synthesis is undoubtedly the single area of organic synthesis which has undergone the greatest development during the 1980s. 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, but only the (−)-enantiomer (1) has teratogenic properties (i.e. produces foetal deformities). 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*,[1] 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-polarised light is rotated, and also *R*- and *S*- (according to the Cahn–Ingold–Prelog rules[2]), 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 enantioners (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 (g.l.c. or h.p.l.c.) on a chiral stationary phase, n.m.r. 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. by n.m.r. or h.p.l.c.).[3]

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*). A synthetic step which introduces a new stereogenic centre into a molecule which already contains one or more stereogenic centres will produce a mixture of two diastereomers.

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 enantiomerically pure. 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[4] 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

$$S{-}X^* \xrightarrow{R} P^*{-}X^* \qquad (15.1)$$

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)].

$$S \xrightarrow{A^*} S{-}A^* \xrightarrow{R} P^*{-}A^* \xrightarrow{-A^*} P^* \qquad (15.2)$$

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.

Most of the recently developed methods are of this type.

(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 stoicheiometric amounts.

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

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

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.

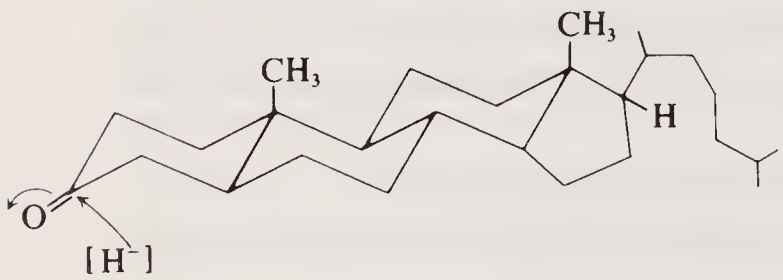
In all of the above methods, it is of course important to ensure that the configuration of a stereogenic centre is not destroyed in a subsequent step, or even in an isolation or purification procedure.

15.3 First generation methods: the use of chiral substrates

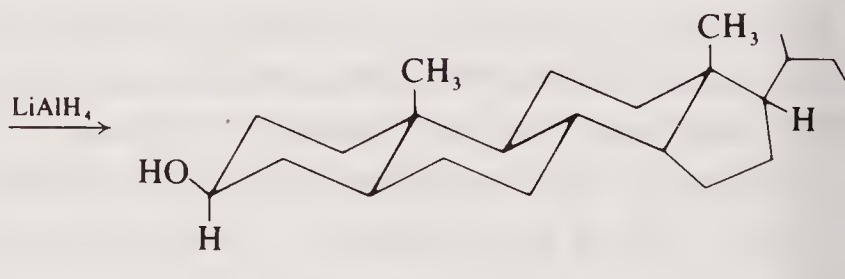
It should be obvious that a *practicable* asymmetric synthesis of this type requires that the starting material be readily available from natural sources in an enantiomerically pure form. For this reason, first-generation methods are generally confined to a limited range of substrates, such as simple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



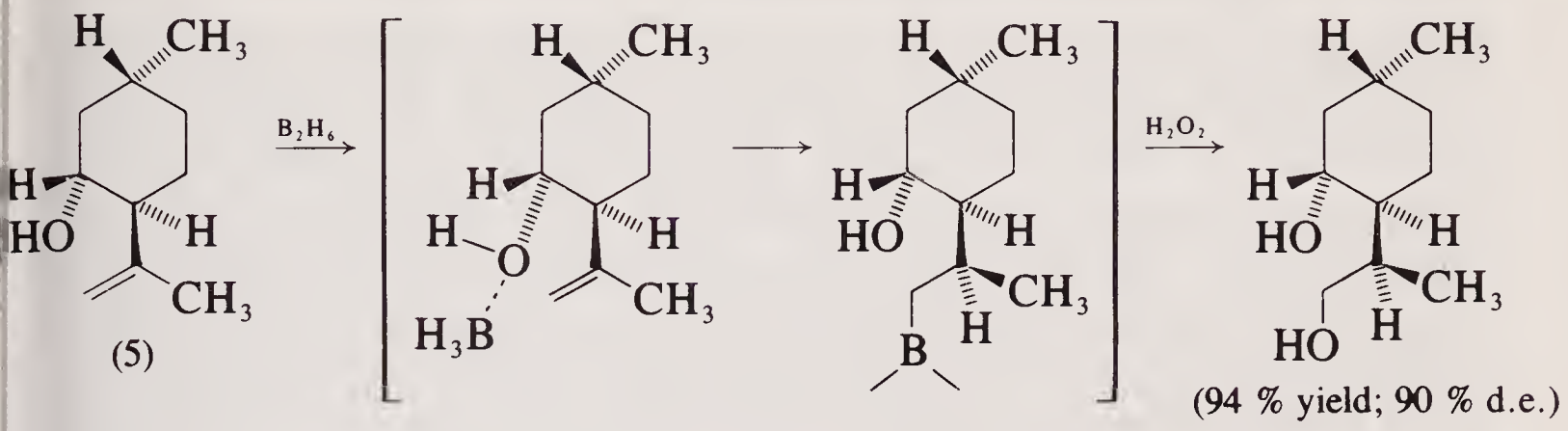
(3)



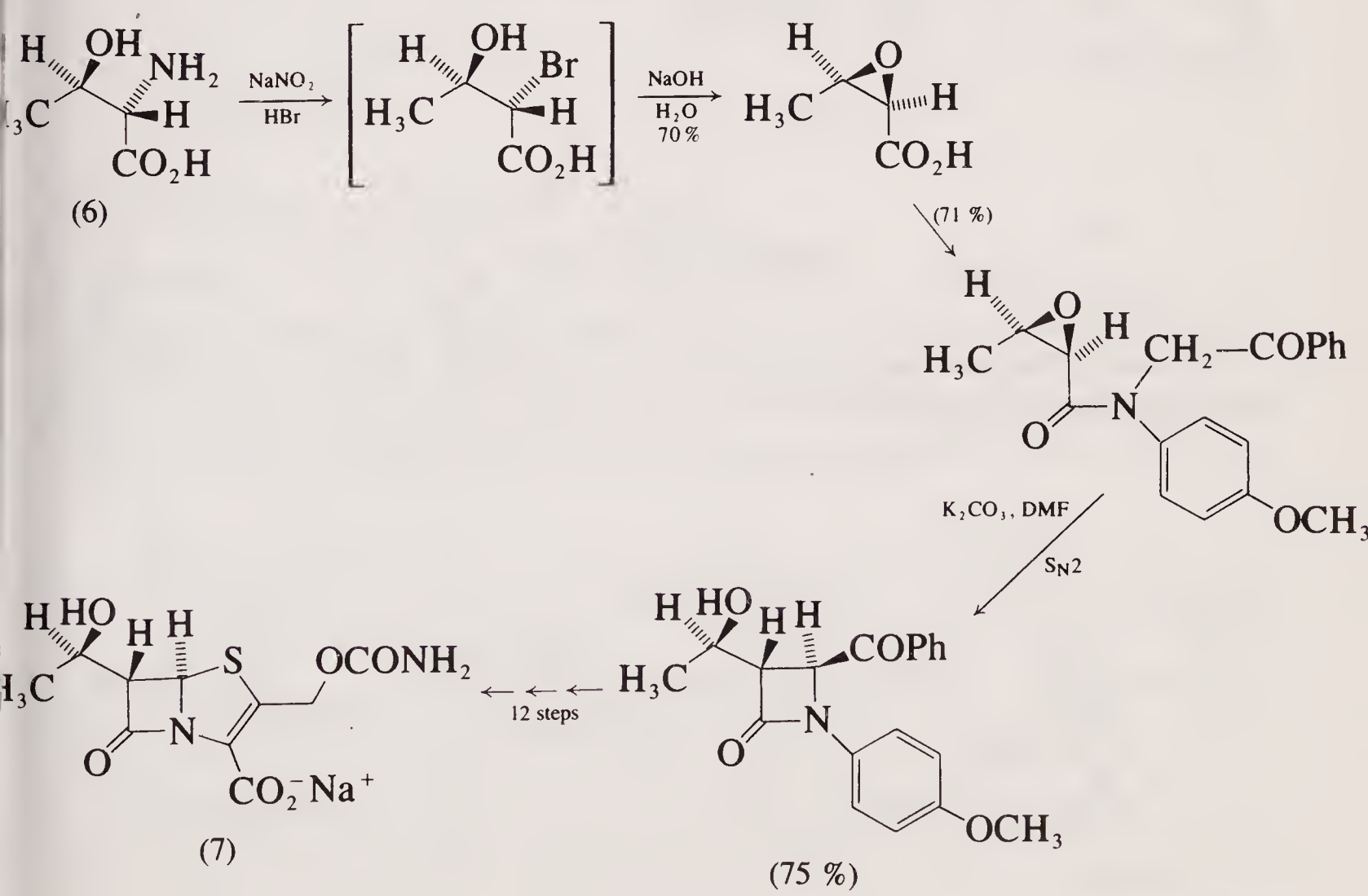
(4) (95 % yield; 83 % d.e.)

(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):



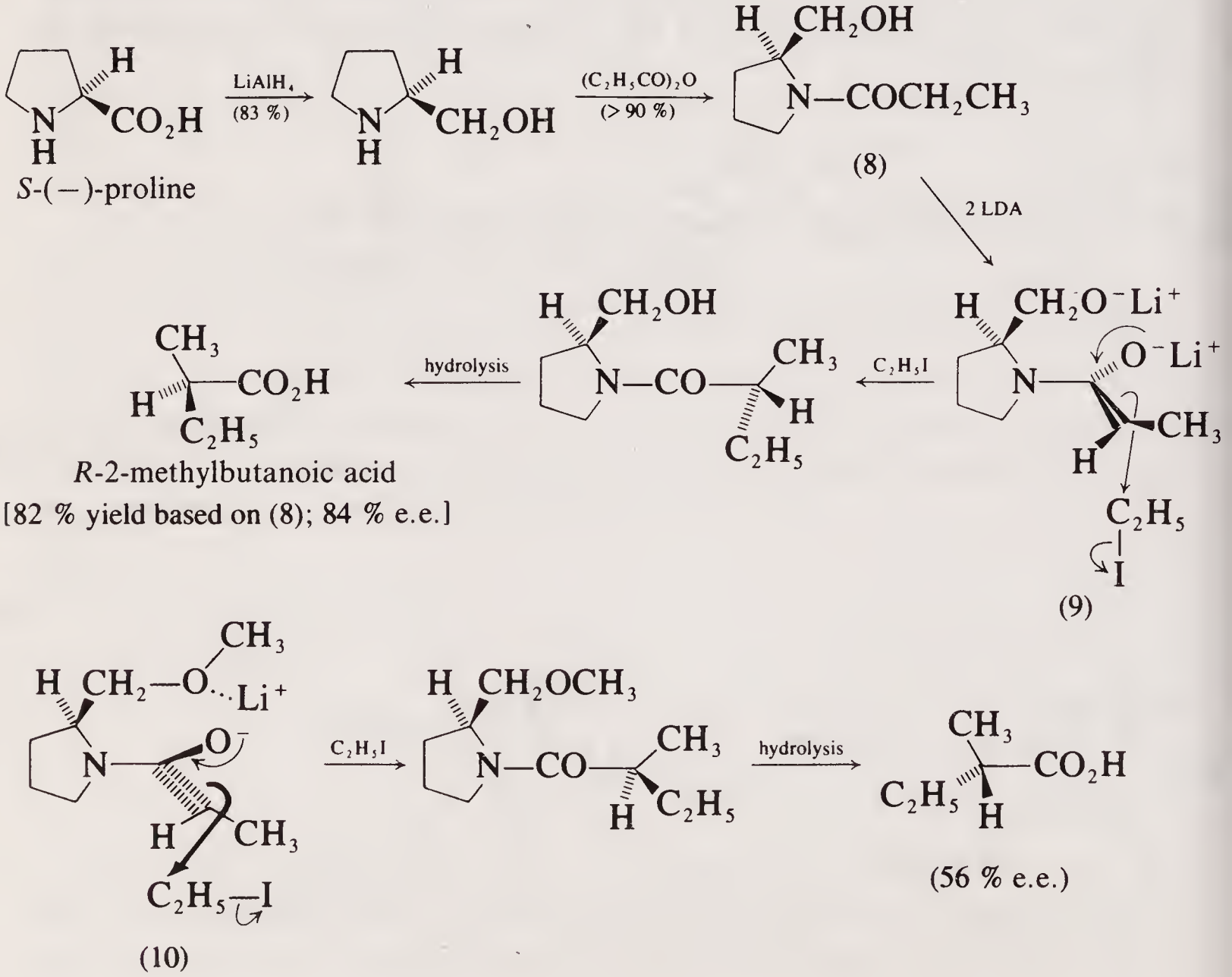
(c) Multi-stage synthetic routes to biologically active compounds may also involve first-generation processes. Two will be described in full in section 16.3, and a third is given in outline below. This involves the conversion, in fifteen steps, of (−)-threonine (6), a naturally occurring amino-acid with two adjacent stereogenic centres, into a *penem* antibiotic (7) which has three.[5] The first and third steps, shown here, are highly stereoselective, the first being controlled by neighbouring group participation of the carboxyl group (Sykes, pp. 93–6) and the third by the configuration and conformation of the enolate anion (see more detail in section 15.4.1).



15.4 Second-generation methods: the use of chiral auxiliaries

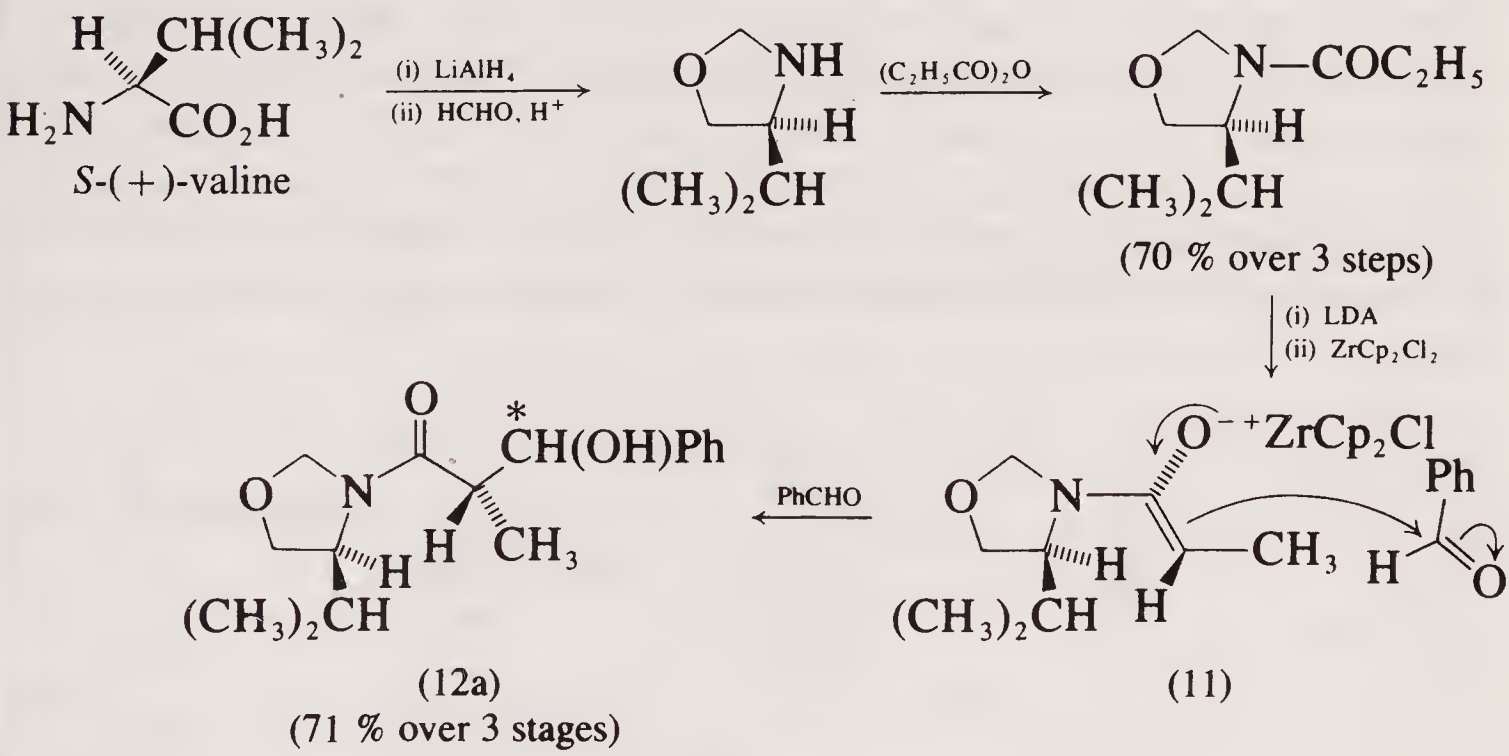
15.4.1 Alkylation of chiral enolates

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:



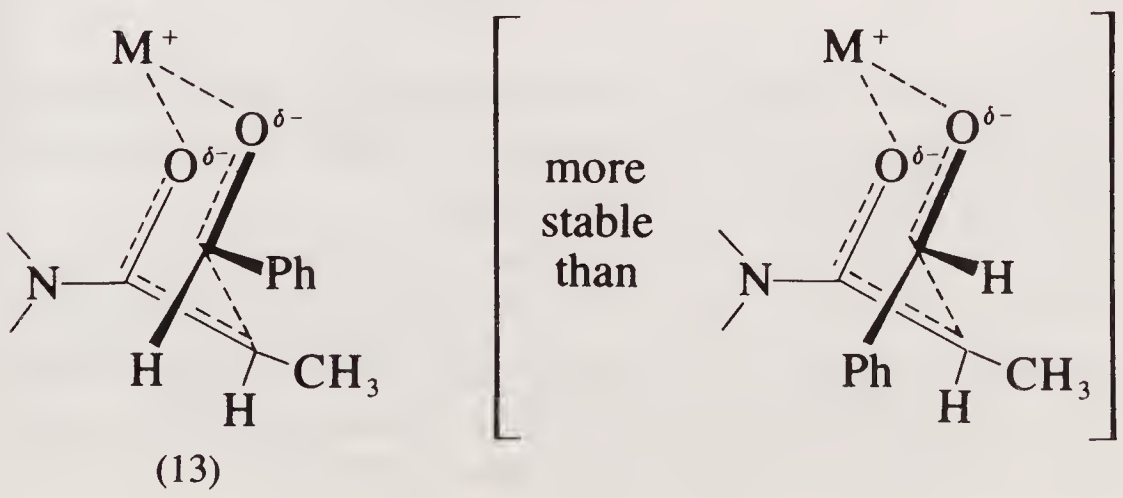
The above examples illustrate a general problem in asymmetric synthesis, *viz.*, that it is difficult to predict the configuration at the new stereogenic centre by a simple set of rules or a visual inspection of the molecule. In the present case, the configuration of the product depends critically, not only 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!)

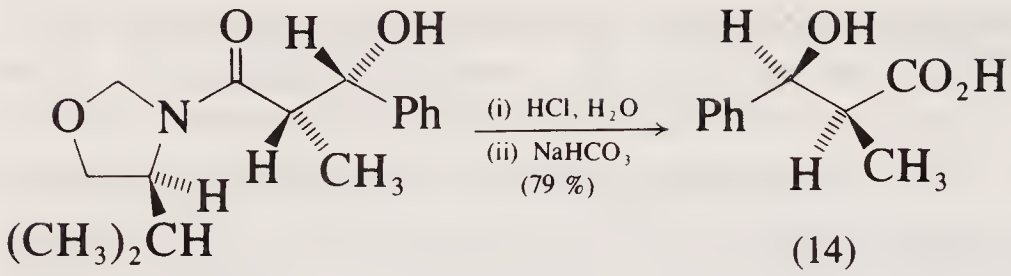
Reaction of a chiral enolate with an aldehyde (other than formaldehyde) or ketone constitutes an *asymmetric aldol reaction.* In the example below, in which a valine-derived oxazolidine serves as the chiral auxiliary, it is beneficial to exchange the lithium of the enolate for the (much bulkier) complex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



[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),[6] and the configuration of the second stereogenic centre is thus as



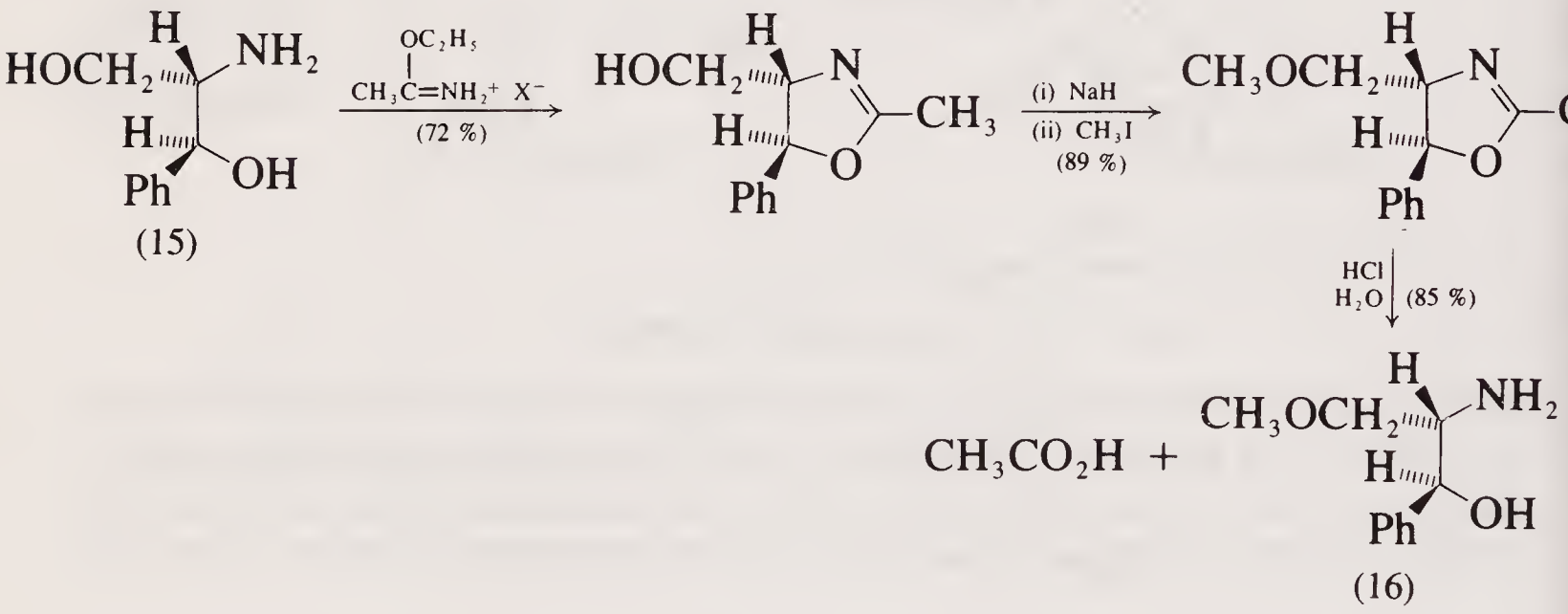


(12b) (14)

shown in (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

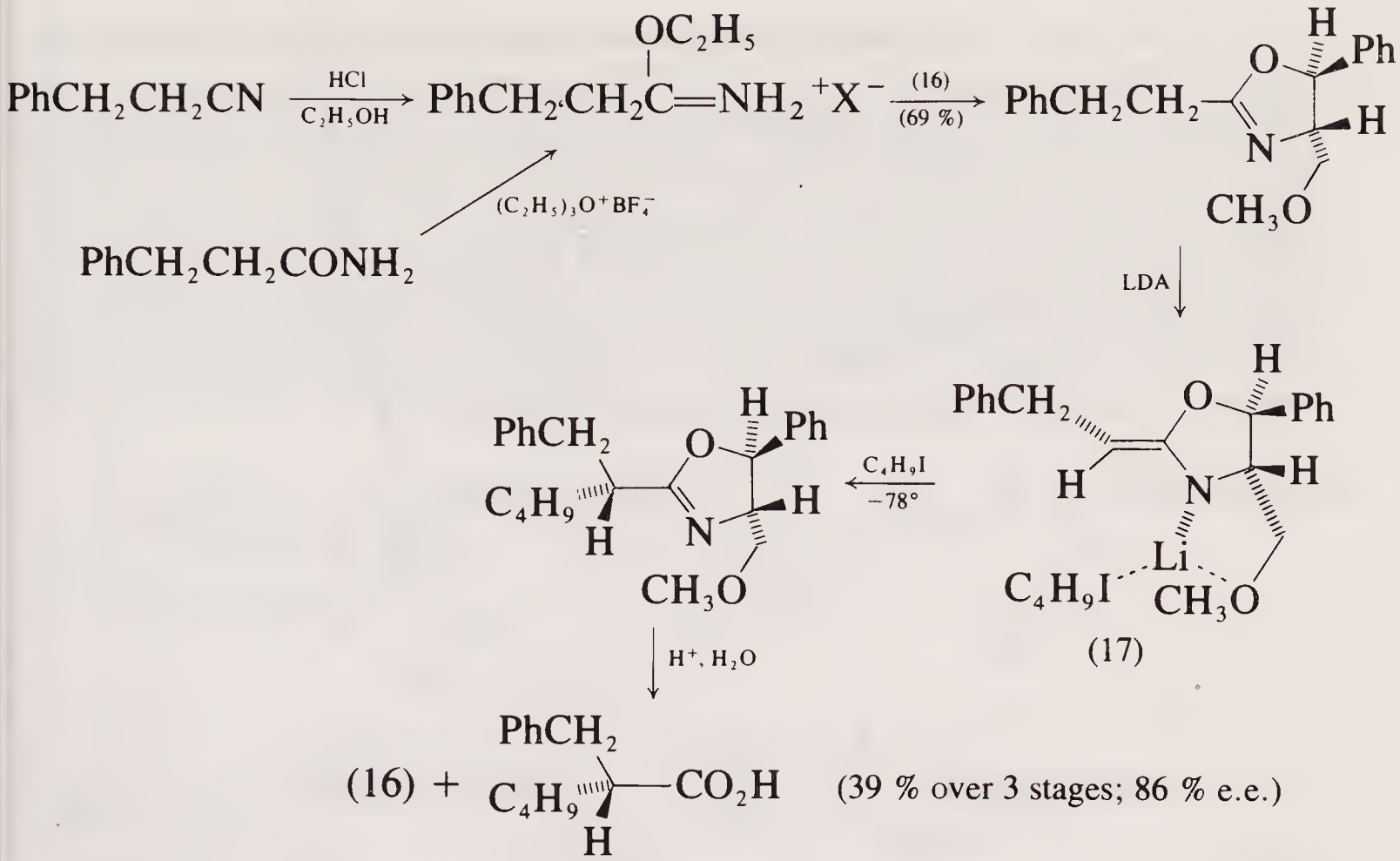
Chiral oxazolines (4,5-dihydrooxazoles) were among the first auxiliaries found to promote carbon–carbon bond formation with very high e.e. Some of these oxazolines may be derived from the natural amino-acids, but probably the most useful are derived from the *S*,*S*-(+)-aminodiol (15), which is a by-product 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).



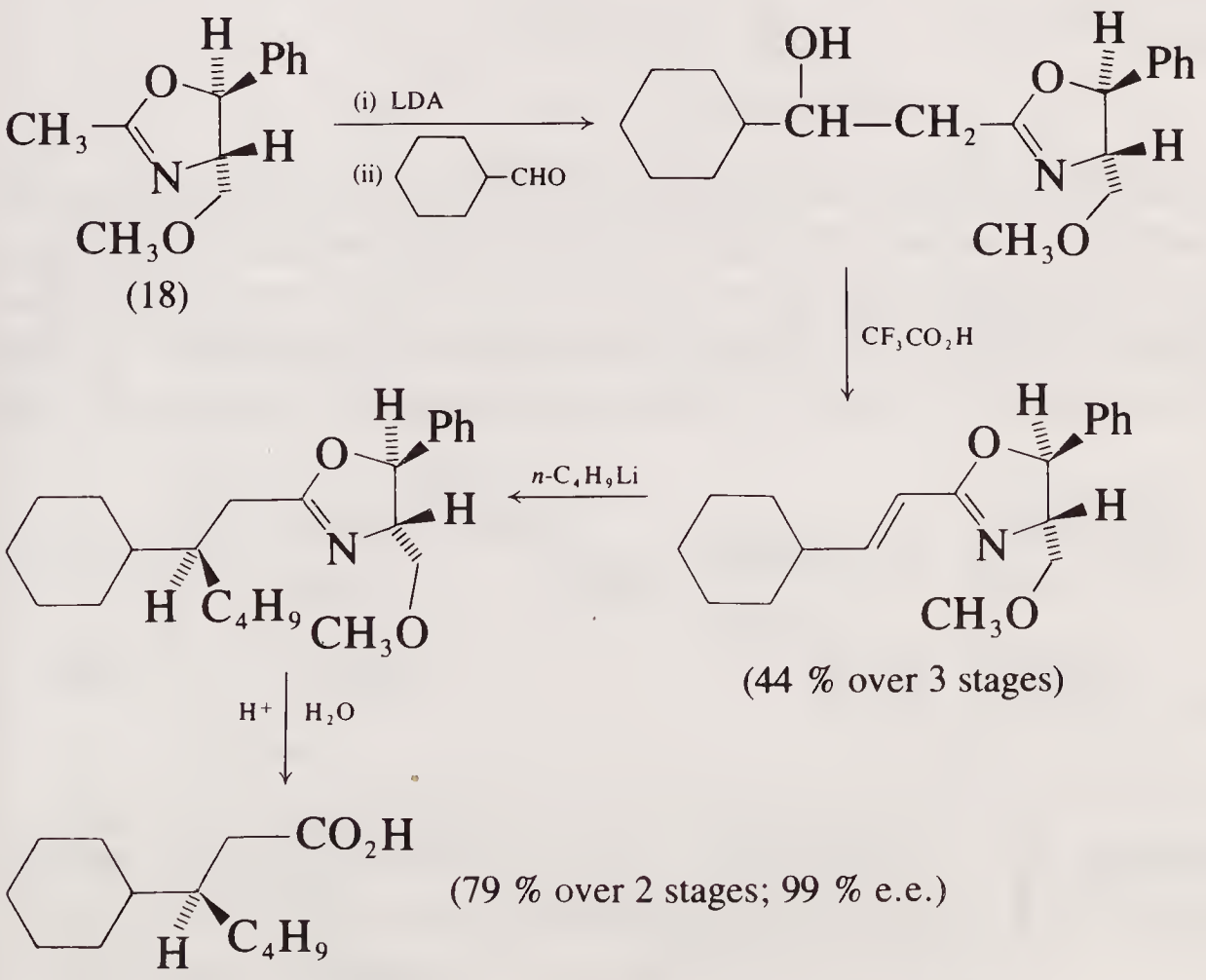
(15) (16)

C-2 of an oxazoline is, in effect, a masked carboxyl group,[7] and so asymmetric alkylation of a substituent at C-2 provides a route to asymmetrically alkylated carboxylic acids, as illustrated below.

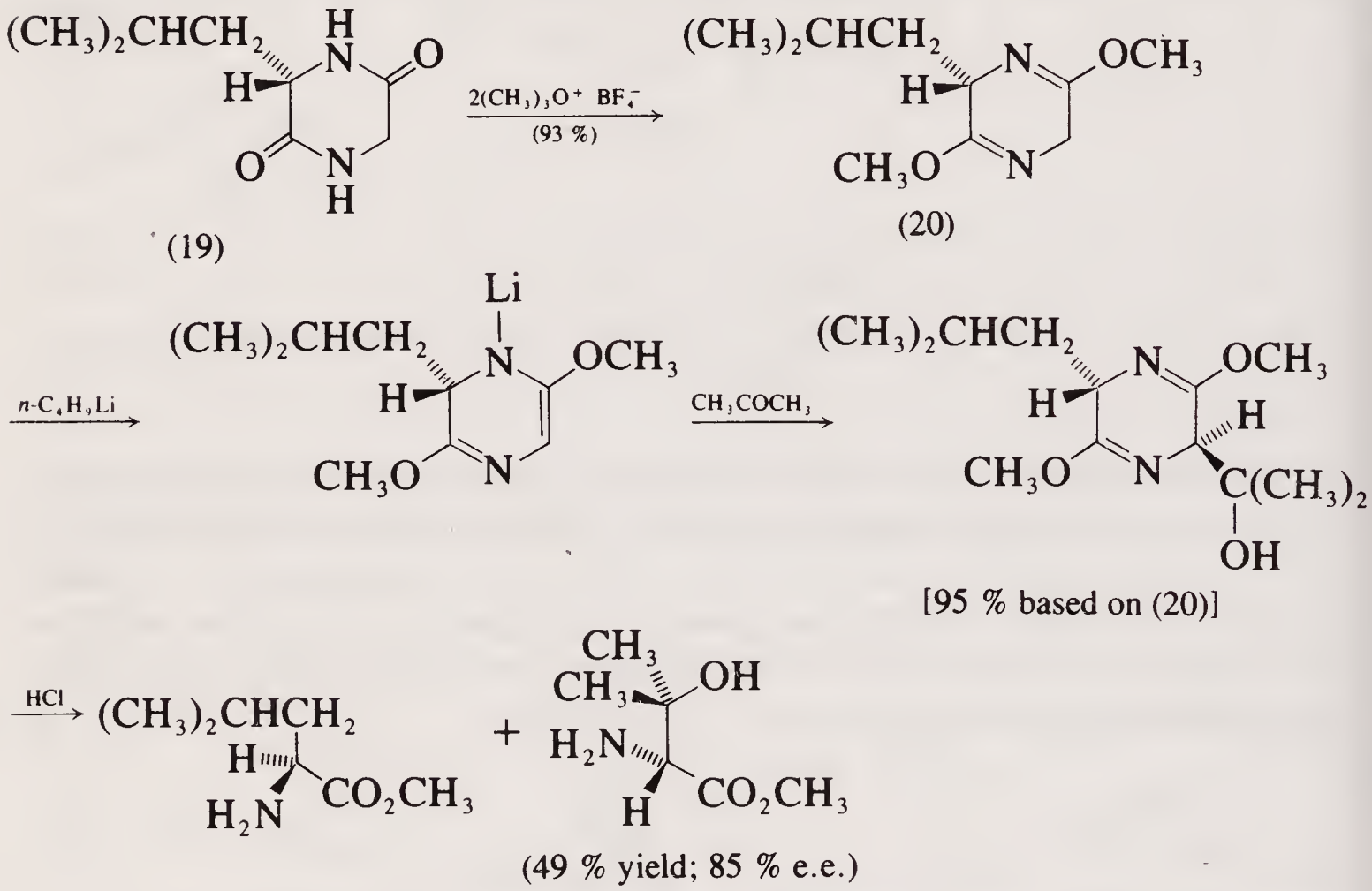
As for the enolates in the preceding section, the *Z*-configuration is preferred for the aza-enolate (17). The observed selectivity of the alkylation step in this case is consistent with the incoming electrophile being guided to the lower face of (17) by the lithium. Here again, chelation of the ether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



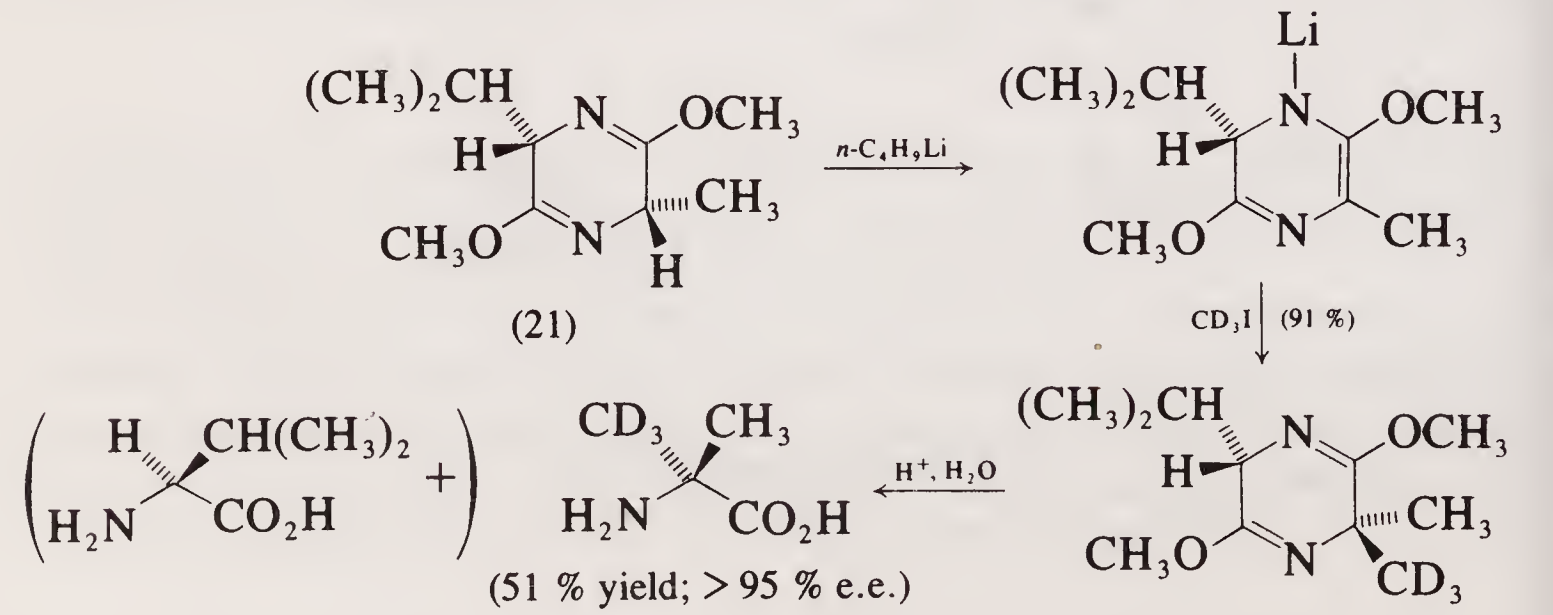
Asymmetrically β-alkylated carboxylic acids may be obtained by a similar method. The 2-methyloxazoline (18) (a chiral synthetic equivalent of acetic acid[7]) undergoes an aldol-type condensation to give a 2-alkenyloxazoline which can undergo asymmetric conjugate addition (cf. sections 3.3.4 and 4.1.4). Hydrolysis of the adduct gives the β-alkylcarboxylic acid in excellent e.e.



A second type of asymmetric synthesis using chiral aza-enolates utilises as starting materials chiral 3-alkylpiperazine-2,5-diones, e.g. (19). These are, in effect, cyclic dipeptides, and may be obtained by cyclisation of an acyclic dipeptide or two amino-acids; for example, (19) is derived from *S*-leucine and glycine. *O*-Methylation of (19) gives a chiral bis-imidate ester (20), which is deprotonated selectively at C-6. (This is not only the less hindered position, but the carbanion produced is secondary rather than tertiary.[8]) Electrophilic attack then occurs on the side of the molecule remote from the bulky isobutyl group, e.g.

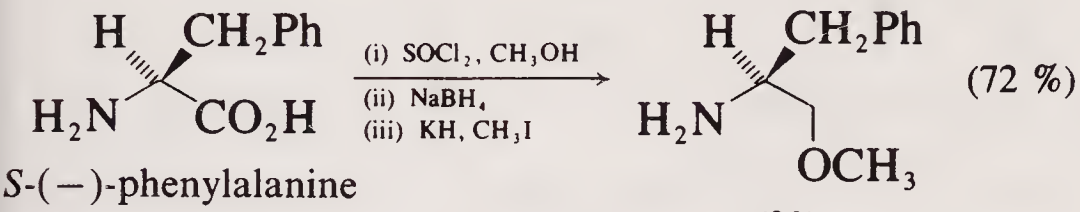


In another variant of this method, the bis-imidate (21), derived from *S*-valine and *S*-alanine, is selectively deprotonated as shown, at the less hindered position. Although this deprotonation destroys the alanine-derived stereogenic centre, it is regenerated under the influence of the valine-derived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



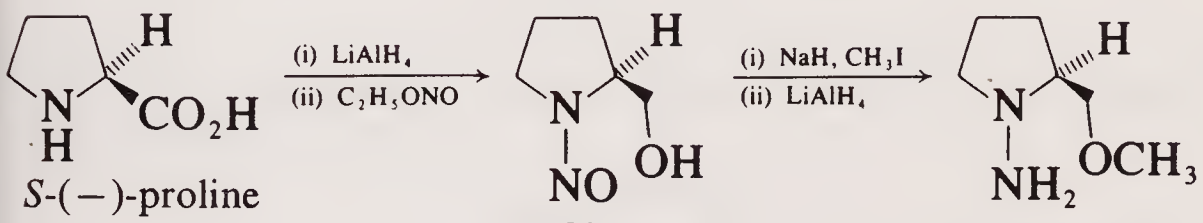
15.4.3 Alkylation of chiral imines and hydrazones

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

(22)



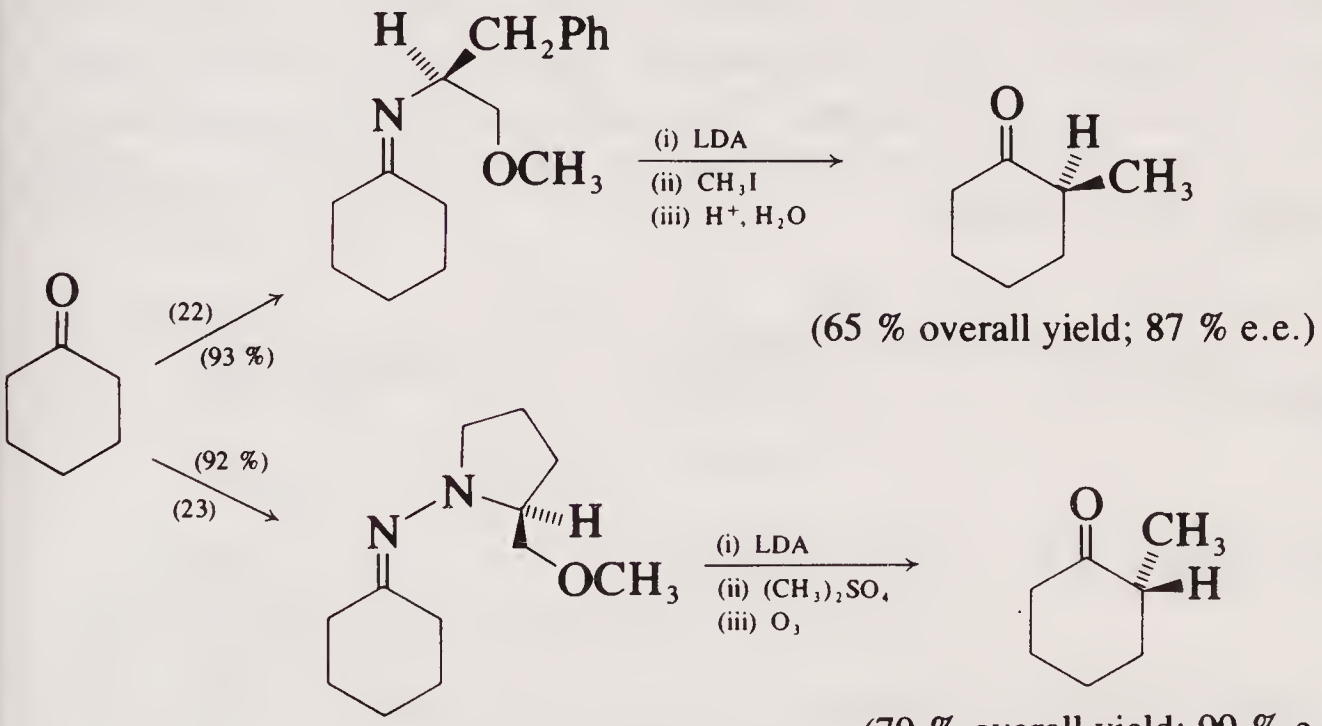
S-(−)-proline

(83 %)

(72 %)

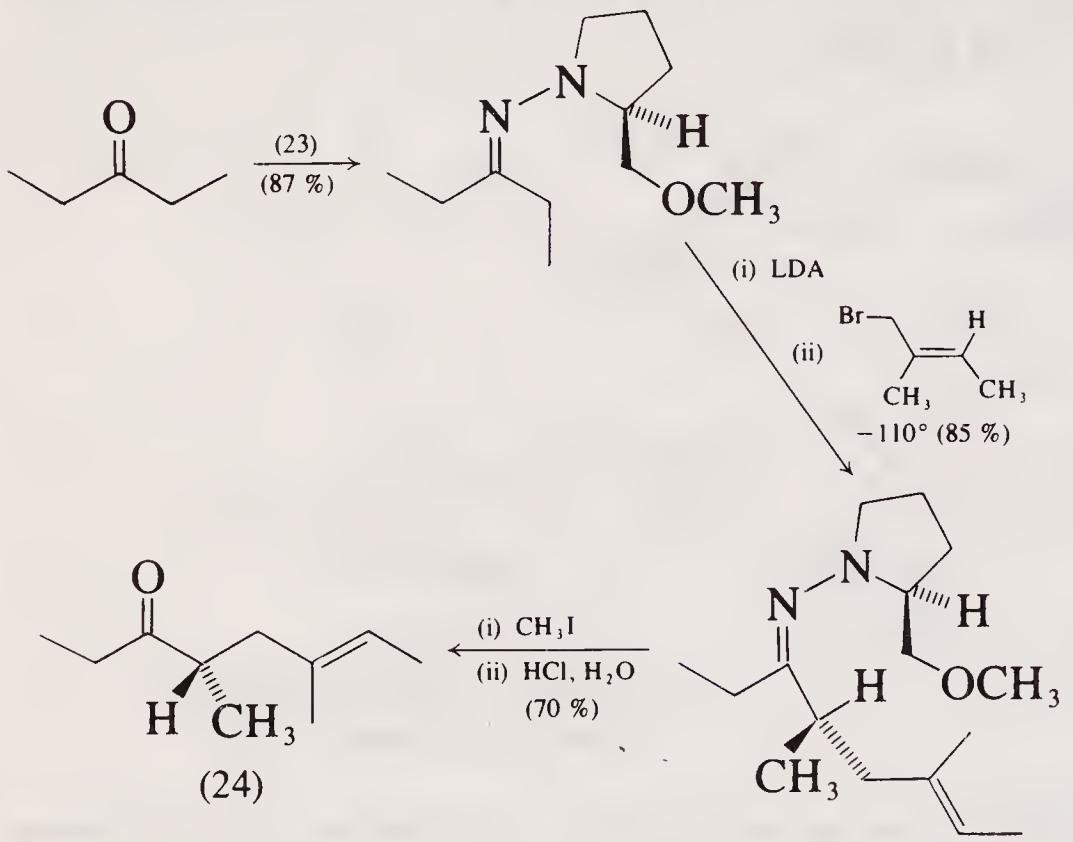
S-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) (23)

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.



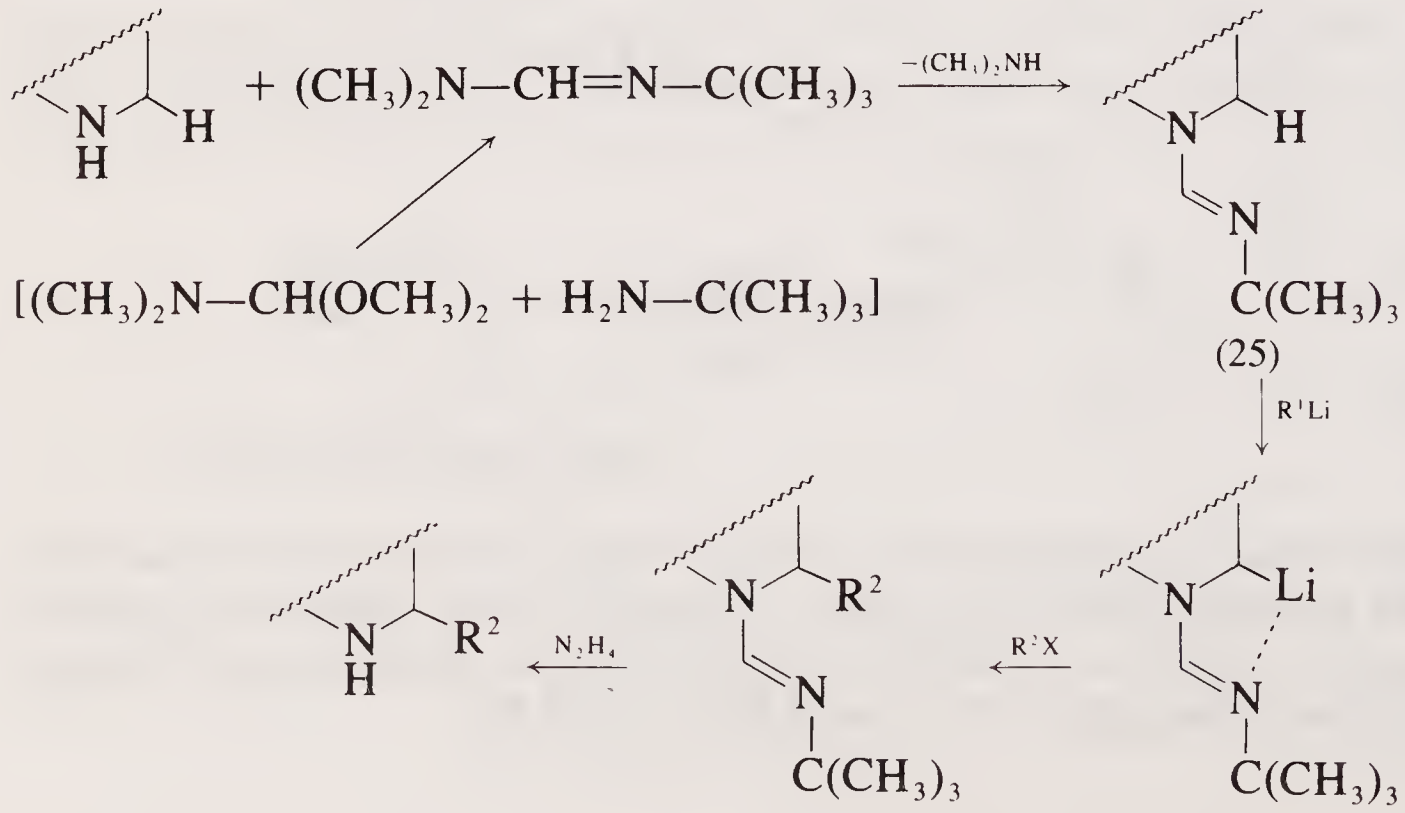
The imine or hydrazone may be removed in either case by hydrolysis, but in the latter case ozonolysis (cf. section 9.2.6) offers an attractive alternative; in this case the chiral auxiliary is recovered as the *N*-nitroso-compound which may be reduced back to SAMP.

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%.

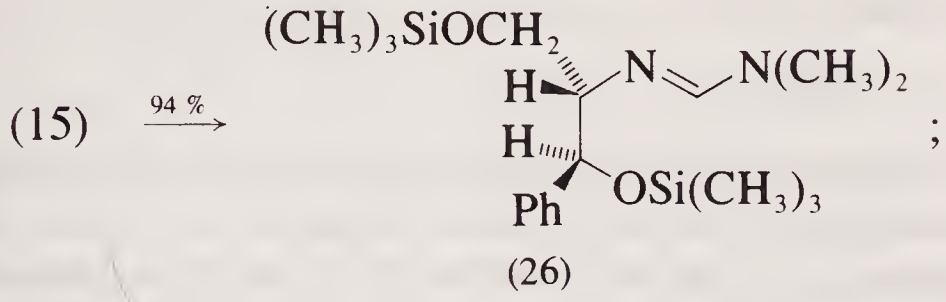


15.4.4 Alkylation α to nitrogen: chiral formamidines

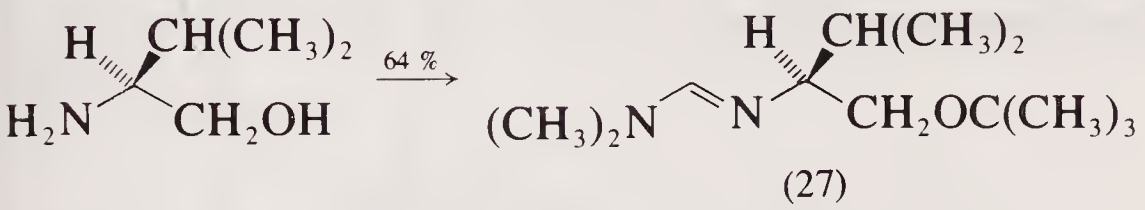
Asymmetric alkylation at the α-position of an amine is of great value, since many biologically active compounds, particularly alkaloids, have a stereogenic centre next to nitrogen. The α-alkylation of an amine may be achieved in an achiral sense by first converting the amine into a t-butylformamidine (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), which is derived from the amino-diol (15), and the t-butyl ether (27) derived from *S*-valinol.

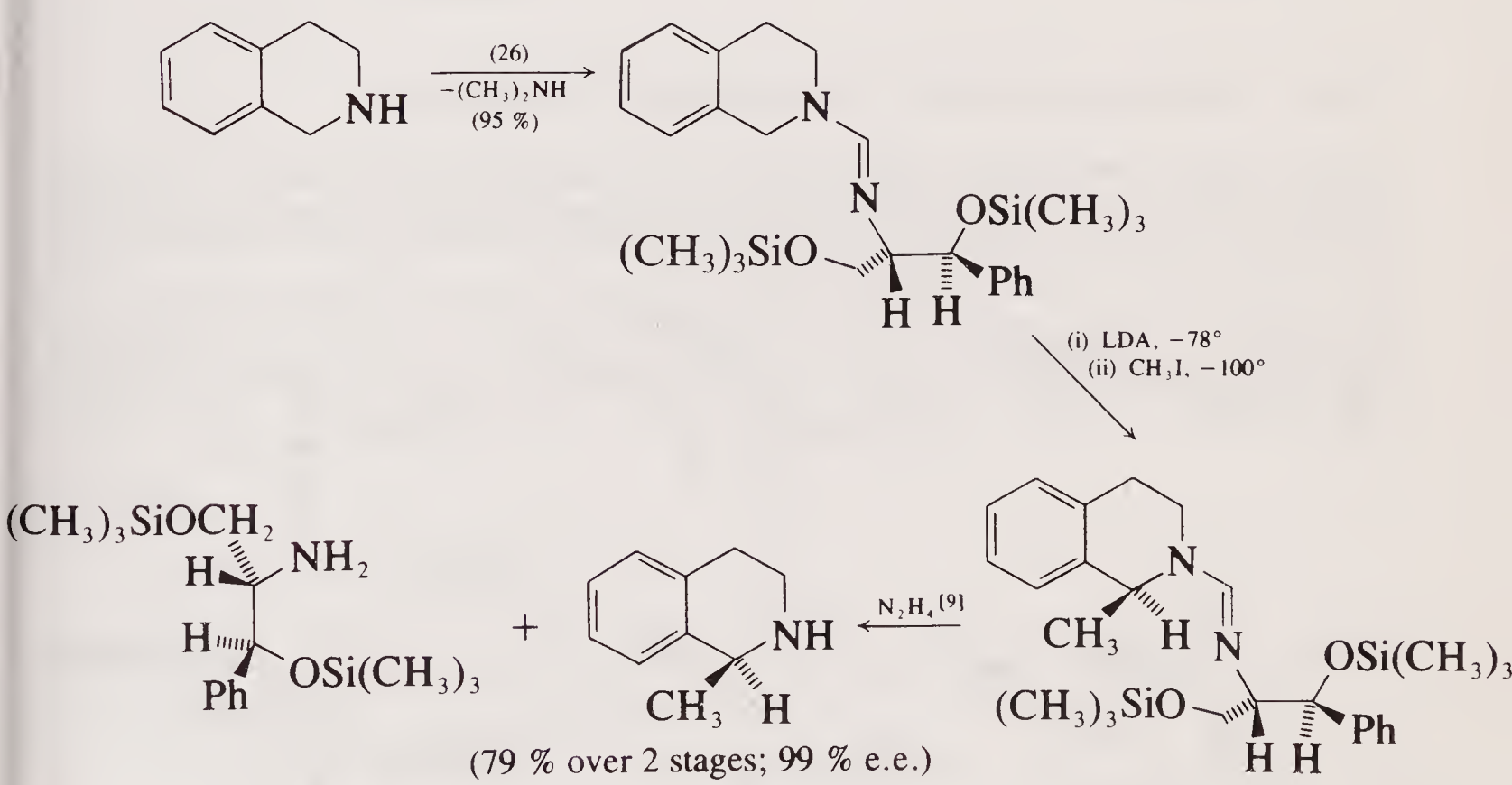


(26)



(27)

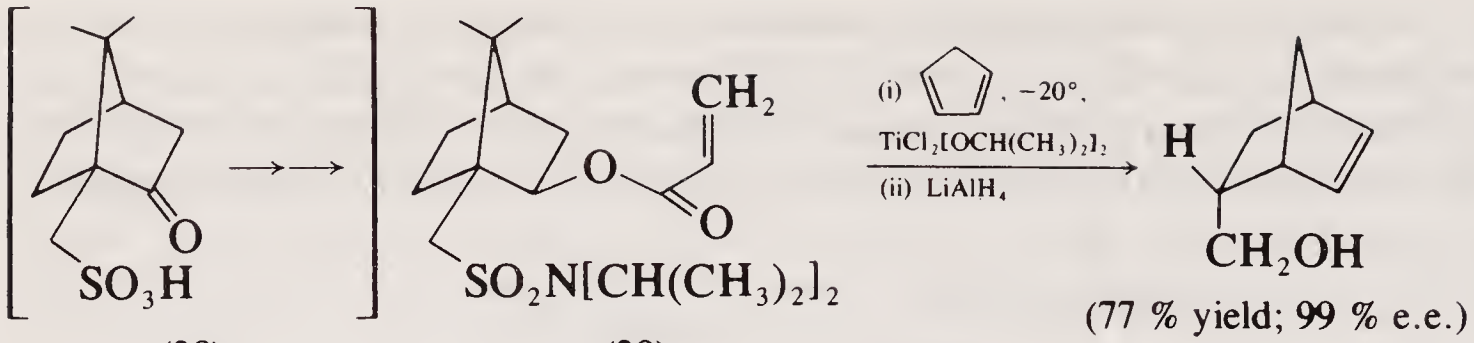
Thus, for example, 1,2,3,4-tetrahydroisoquinolines may be alkylated at C-1 with e.e. > 95%:



(79 % over 2 stages; 99 % e.e.)

15.4.5 Asymmetric Diels–Alder reactions

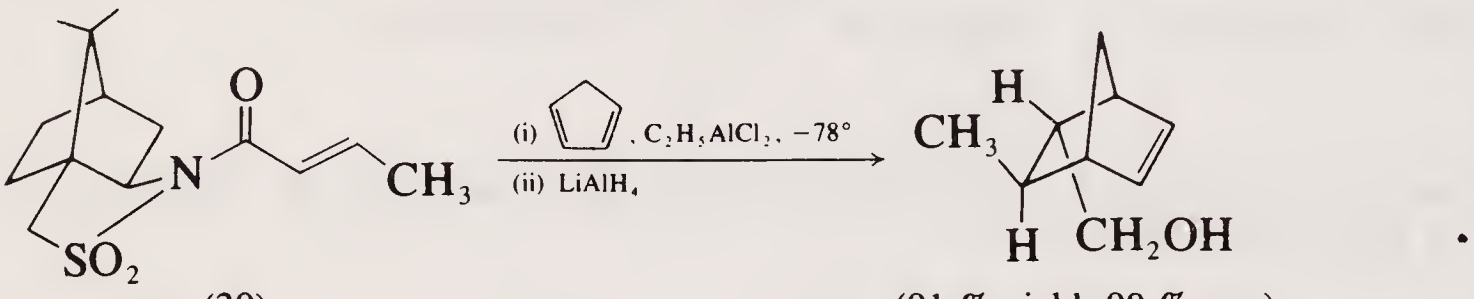
The majority of 'second-generation' asymmetric Diels–Alder reactions involve the reaction of an achiral diene with a chiral dienophile, commonly a derivative of acrylic acid. The acrylate ester (29), for example, which is derived from the ready available (+)-camphor-10-sulphonic acid (28), shows excellent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



(28) (29)

(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.

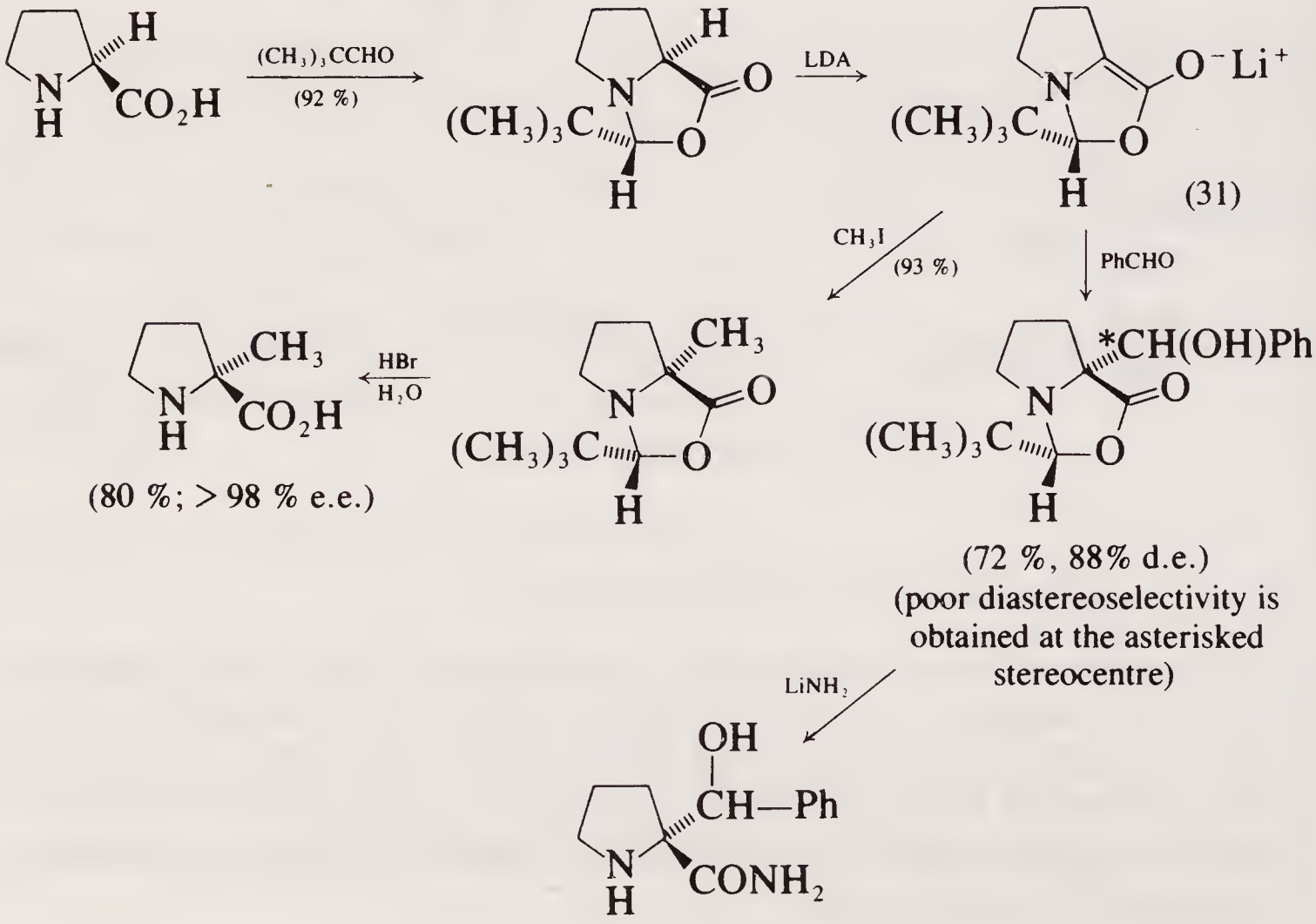


(30)

(91 % yield; 98 % e.e.)

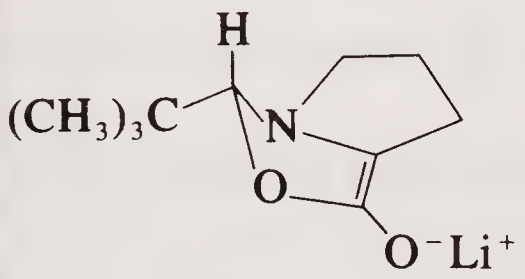
15.4.6 Self-regeneration of stereogenic centres

In this type of reaction, a chiral substrate is derivatised 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.

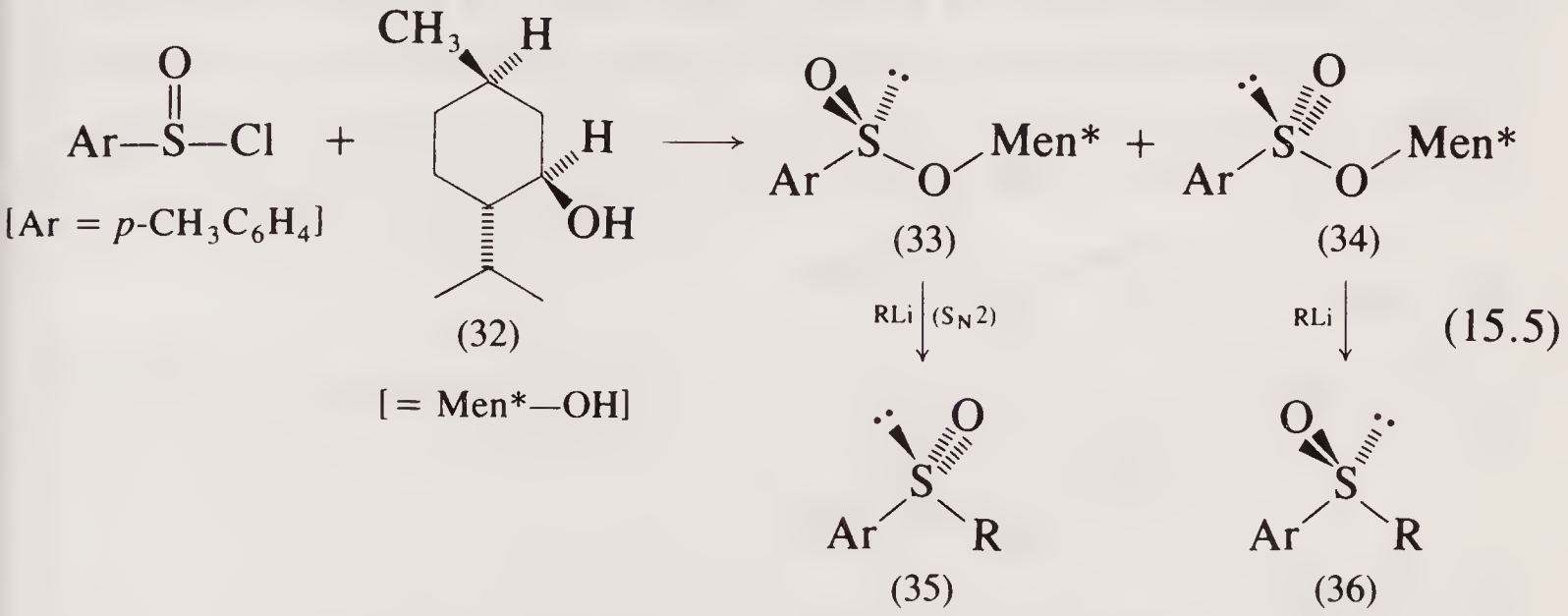
At first sight it may appear strange that the electrophile becomes attached to the lower face of the molecule, on the same side as the extremely bulky t-butyl group. In fact, however, in the enolate (31) the t-butyl group seeks to occupy a 'pseudo-equatorial' position, and the resulting conformation of the molecule, represented by (31a), below, is such that the lower face of the molecule is actually less hindered than the upper.



(31a)

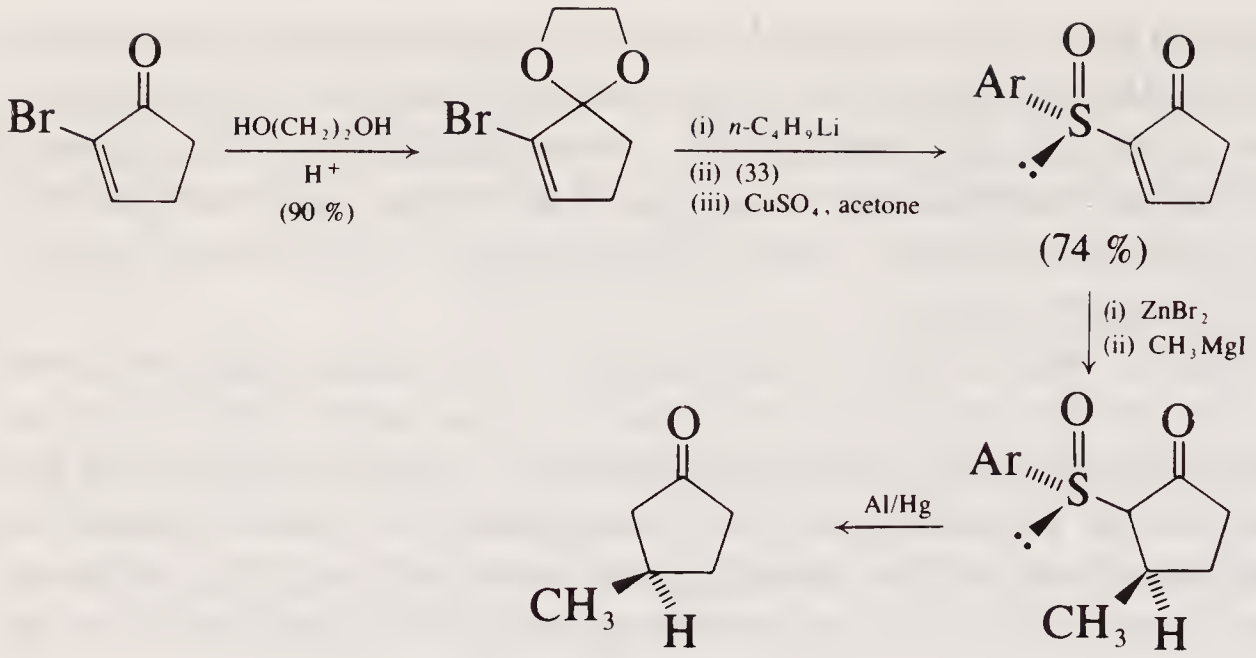
15.4.7 Chiral sulphoxides

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



(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 2 stages; 87 % e.e.)

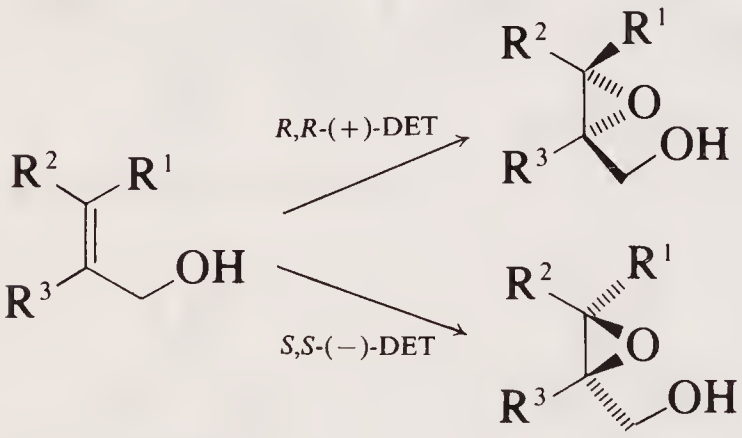
The sulphoxide substituent is readily removed by reaction with aluminium amalgam.

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

15.5 Third generation methods: the use of chiral reagents

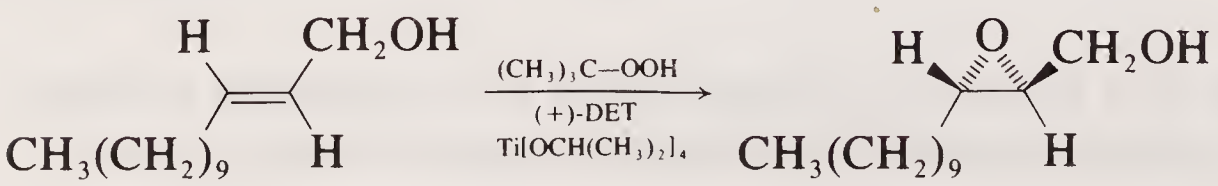
15.5.1 Asymmetric oxidations

The asymmetric epoxidation of the double bond in allylic alcohols is an important and versatile synthetic procedure. The reaction 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.



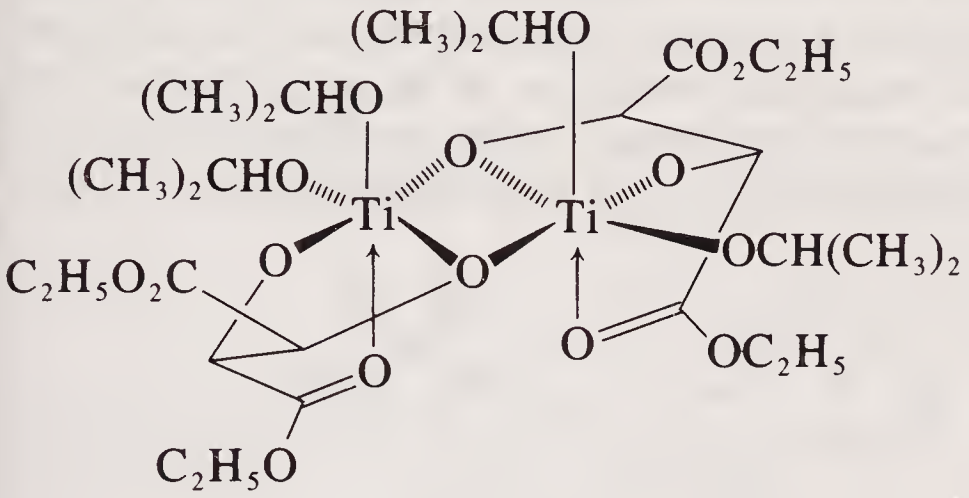
(15.6)

For example,



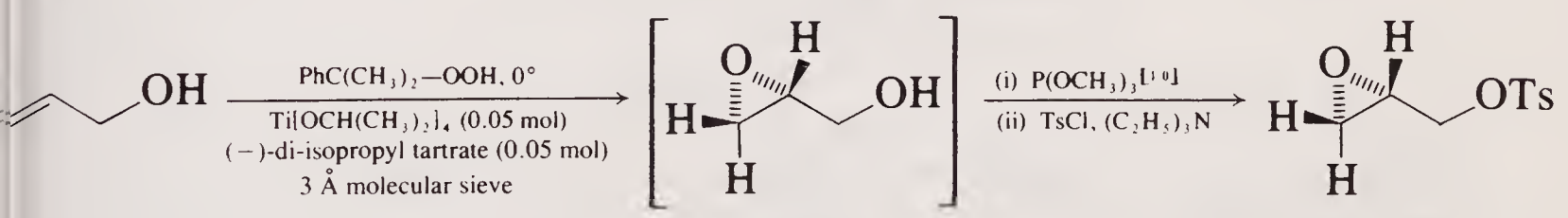
(79 % yield; > 95 % e.e.)

The major catalytic species in this reaction is the binuclear titanium complex (37), 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.



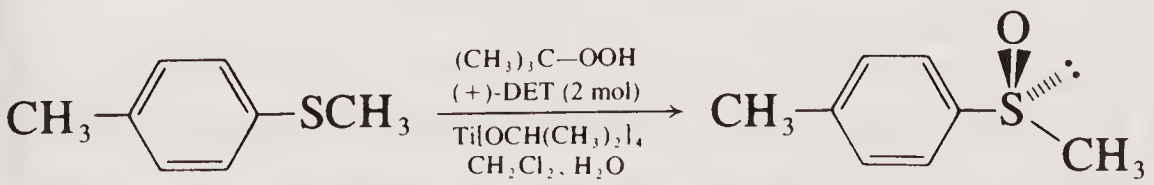
(37)

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 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 (38), and their conversion into isolable derivatives, e.g. toluene-*p*-sulphonates:



(38) (40 % overall; 94 % e.e.)

The same reagent system may also be used for the asymmetric oxidation of sulphides to sulphoxides. In this case, water is actually required in order to achieve good selectivity.



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

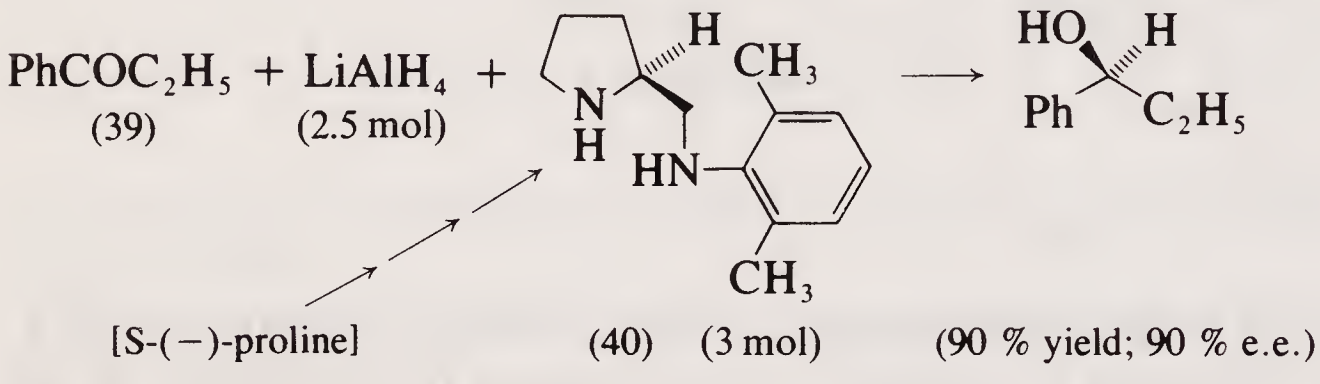
15.5.2 Asymmetric reduction using lithium aluminium hydride

Lithium aluminium hydride can supply all four of its hydrogens as hydride ions for reduction, and several more selective reducing agents may

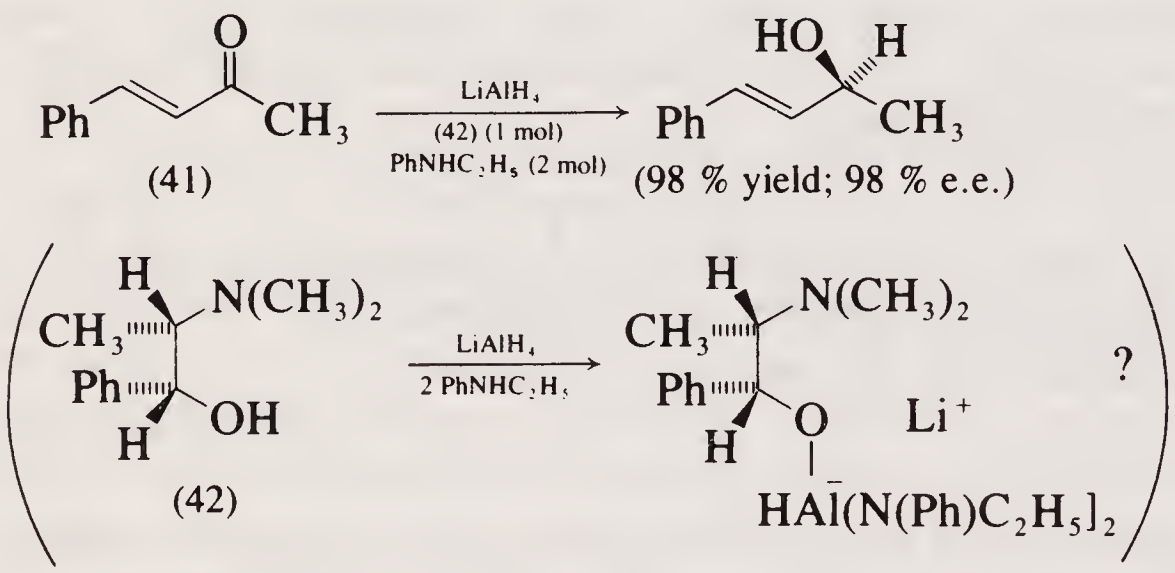
be obtained by reaction of lithium aluminium hydride with a stoicheiometric amount of a proton donor, e.g.

$$LiAlH_4 + 3(CH_3)_3COH \longrightarrow LiAlH[OC(CH_3)_3]_3 \quad \text{(cf. section 8.2)}$$

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 (39) with lithium aluminium hydride in presence of the proline-derived diamine (40) gives *S*-1-phenylpropan-1-ol with high selectivity.

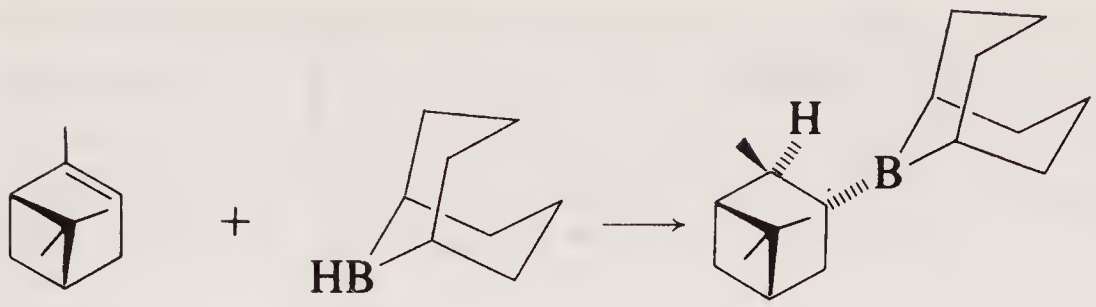


The reduction of the conjugated enone (41) in presence of (−)-*N*-methyl ephedrine (42) and *N*-ethylaniline is even more efficient.

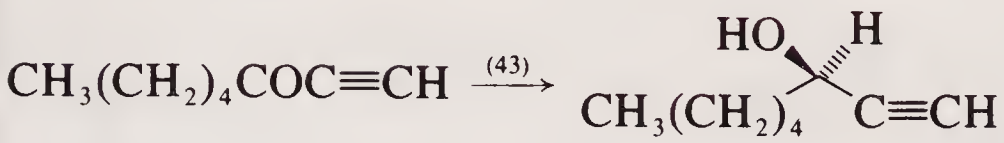


15.5.3 Asymmetric reduction using boron reagents

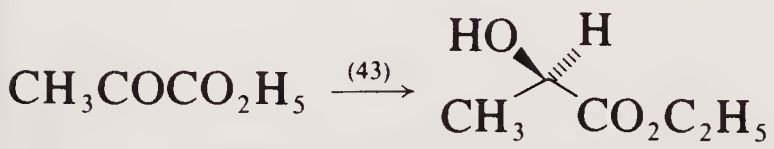
Reference has already been made (section 11.2.4) to the formation of chiral boranes by the hydroboration of terpenes such as α-pinene. The products are useful asymmetric reducing agents: for example, the reagent (43), formed by reaction of (+)-α-pinene with 9-borabicyclo[3.3.1]-nonane (9-BBN) is commercially 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 (43)

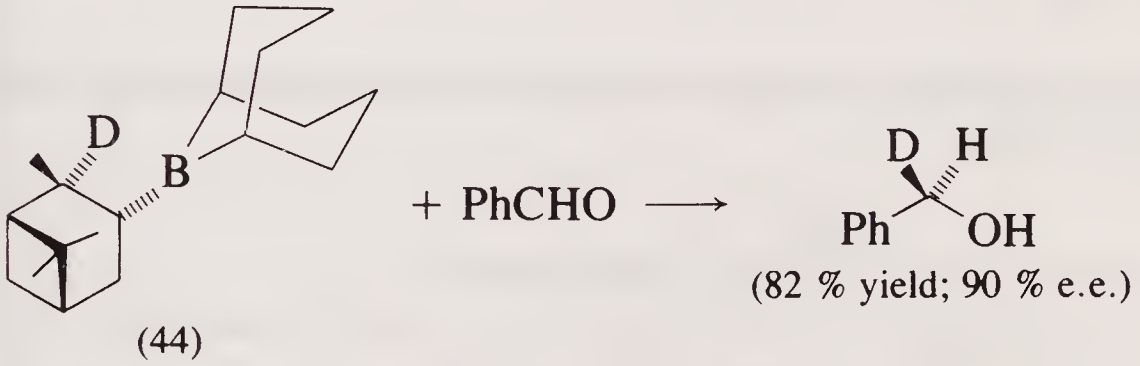


(90 % e.e.; no yield given)



(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 (43), *viz.* (44):



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

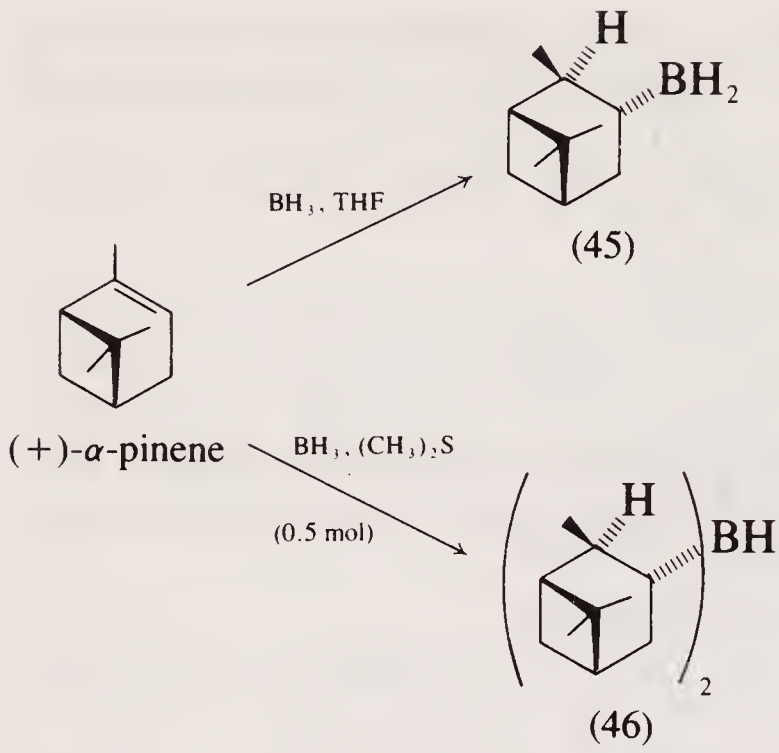
(44)

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.

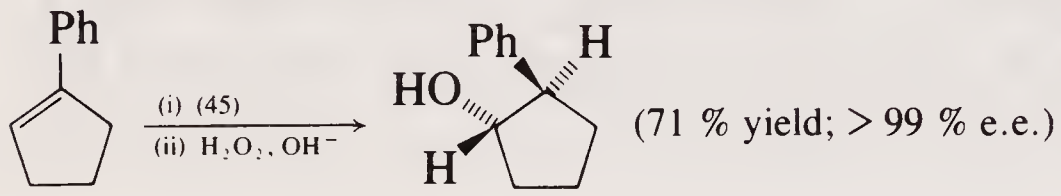
The corresponding *borohydrides* ('Alpine hydrides'®) are also commercially available, and usable for the asymmetric reduction of carbonyl compounds. With simple ketones, however, these reactions generally proceed with relatively low e.e. (ca. 30%).

15.5.4 Asymmetric hydroboration

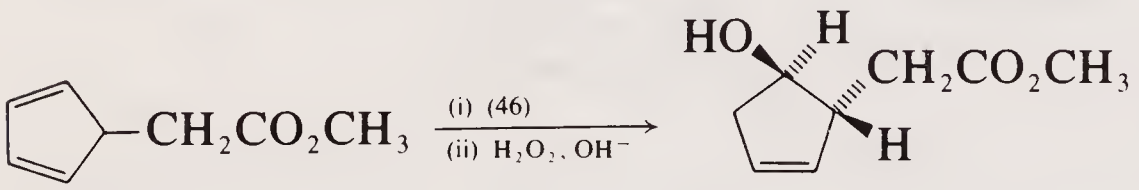
Hydroboration is one of the most useful methods for functionalisation of a double bond (cf. sections 11.1–11.3), and the reagents formed from borane and one or two equivalents of α-pinene, *viz.* (45) and (46), can be used to achieve this process asymmetrically.



The former is the more reactive (and the less hindered), and it is the reagent of choice for hydroboration of trisubstituted alkenes, e.g.

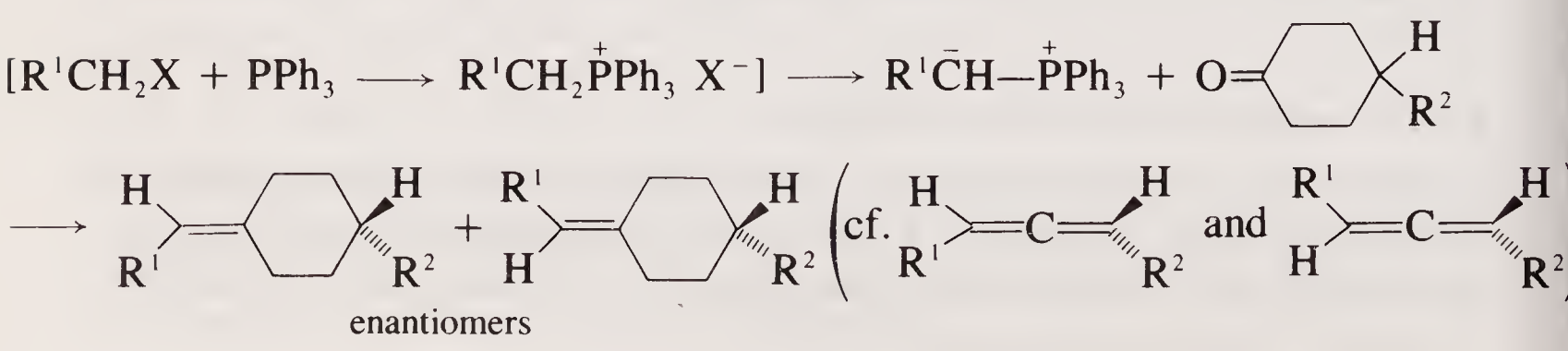


Z-Disubstituted alkenes, on the other hand, react smoothly with the disubstituted borane (46).

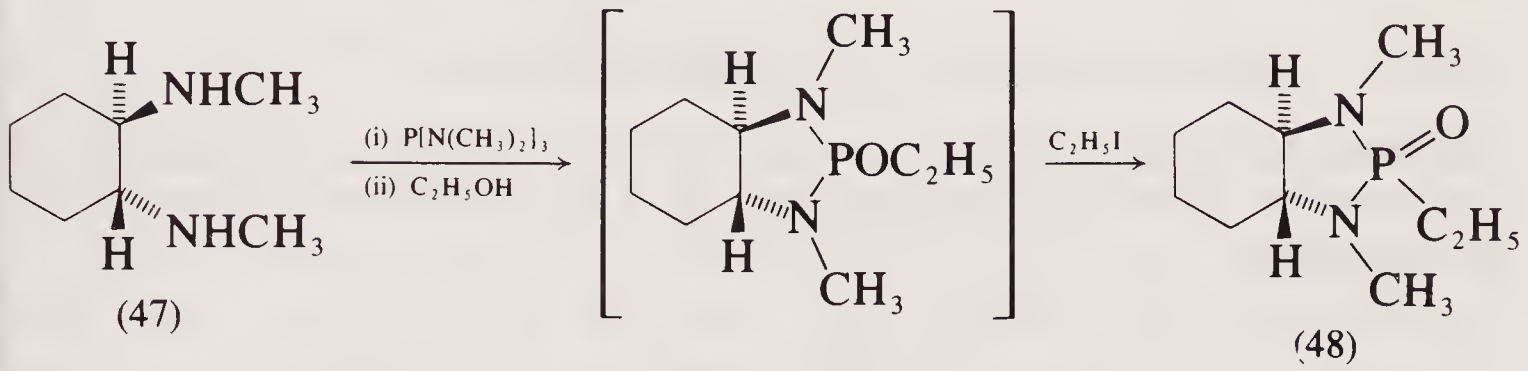


15.5.5 Asymmetric Wittig-type reactions

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):



If the Wittig reagent itself is chiral, the reaction may become acceptably enantioselective. For example, the chiral Wittig-type reagent (48) [preparable from tris(dimethylamino)phosphine and the chiral diamine (47) in a sequence involving a Michaelis–Arbusov reaction (section 12.2)] brings about the asymmetric Wittig reaction (50) → (51).



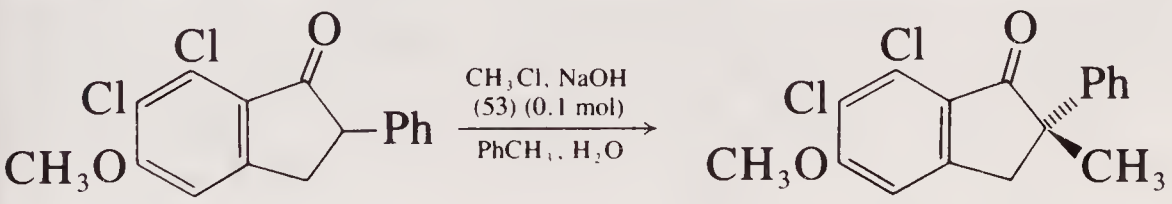
(47)

(48)

15.6 Fourth-generation processes: asymmetric catalysis

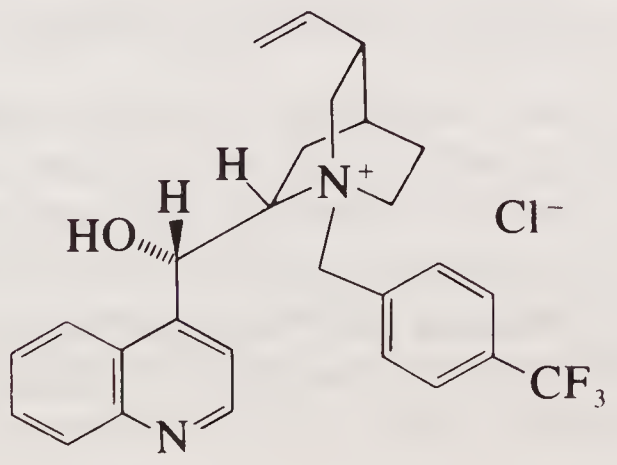
15.6.1 Catalytic asymmetric alkylation

This type of reaction has been carried out successfully in some cases, although extensive optimisation of the reaction conditions may be required in order to obtain a high e.e. In the following example, α-methylation of the 2-phenylindan-1-one derivative (52) gives, almost exclusively, the *S*-enantiomer. The reaction is carried out in a two-phase system



(52)

(98 % yield; 94 % e.e.)

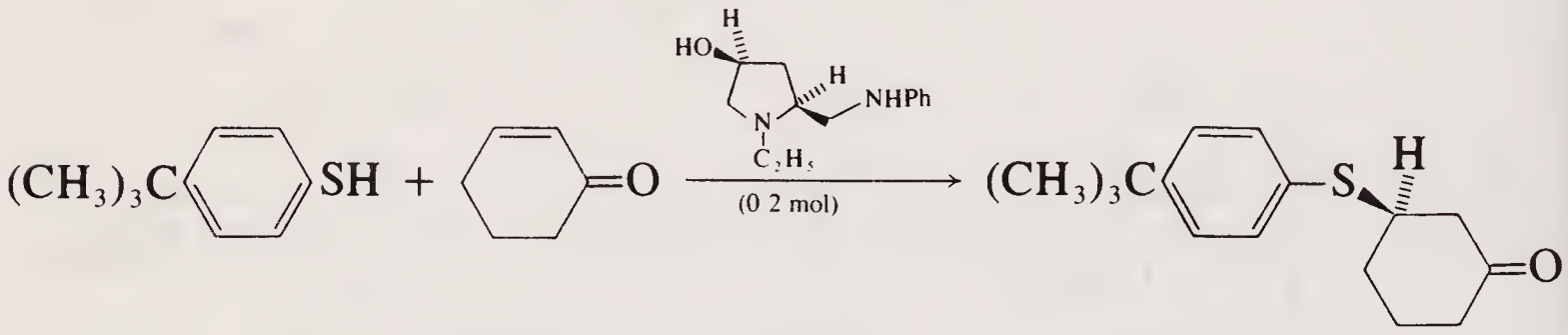


(53)

(toluene–water) in presence of a quaternary ammonium salt ('phase-transfer' conditions[12]); the salt in this case is the chiral quaternary ammonium salt, (53), derived from the alkaloid cinchonine.[13] The high e.e. is believed to be the result of the initial formation of a highly specific complex between the enolate of (52) and the catalyst.

15.6.2 Catalytic asymmetric conjugate addition

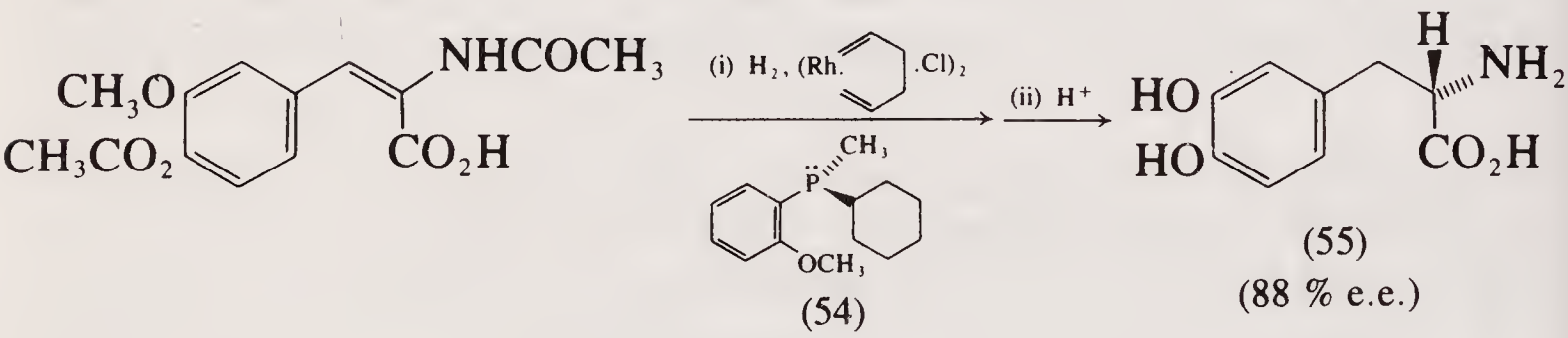
Alkaloids and other chiral amines give good selectivity in the addition of nucleophiles, particularly thiophenols, to α,β-unsaturated ketones; thus, for example,



(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 (54), prepared by resolution, is used to produce the important pharmaceutical, L-DOPA [*S*-3-(3,4-dihydroxyphenyl)alanine, (55)].



(54)

(55)
(88 % e.e.)

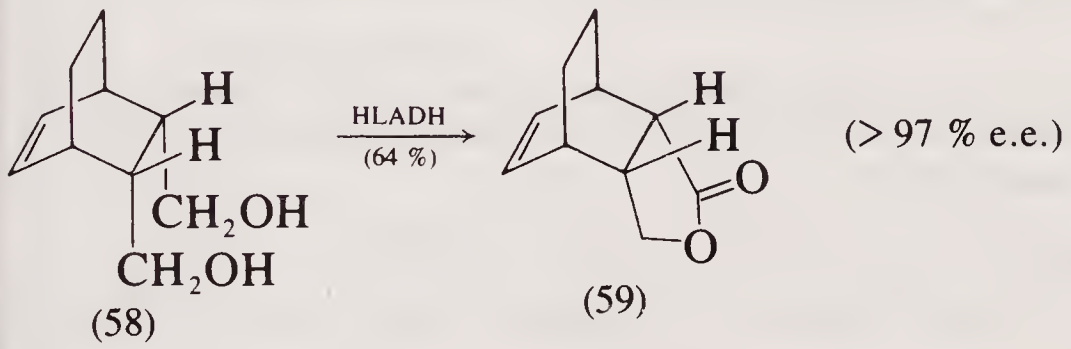
15.6.4 Reactions catalysed by enzymes and other proteins

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 acetoacetate (56) can be reduced to the

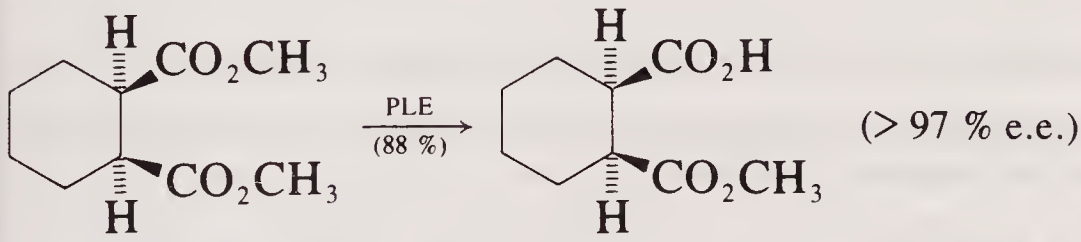
S-hydroxy-ester using baker's yeast (60% yield, 97% e.e.), whereas the homologue (57) gives very poor selectivity under the same conditions. The bacterium, *Thermoanaerobium brockii*, however, effects the reduction of compound (57) to the *S*-hydroxy-ester (93% e.e.) in 40% yield.

(56): R = CH_3
(57): R = C_2H_5

Enantioselective reactions of meso-compounds have, until recently, only been possible using enzymes. For example, horse liver alcohol dehydrogenase (HLADH) selectively oxidises the diol (58) to the lactone (59), and pig liver esterase (PLE) brings about selective hydrolysis of the diester (60).

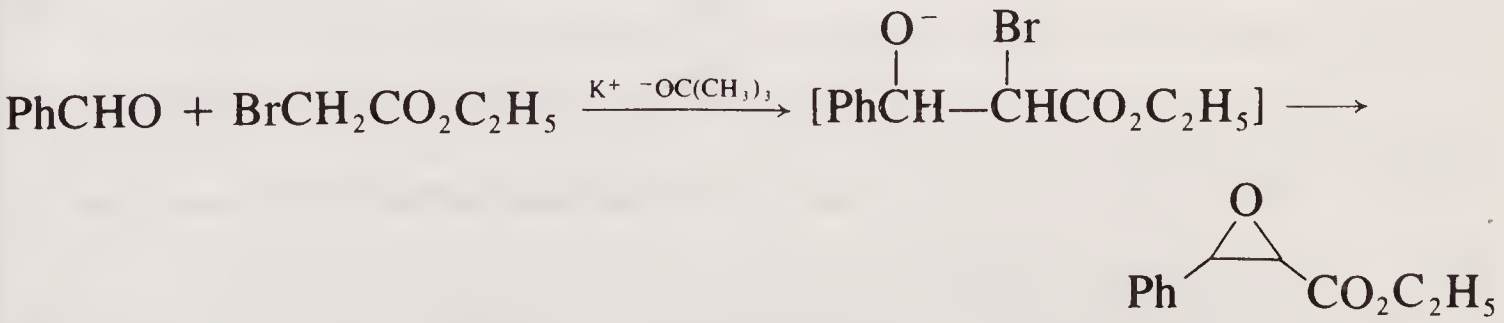


(58) (59) (> 97 % e.e.)

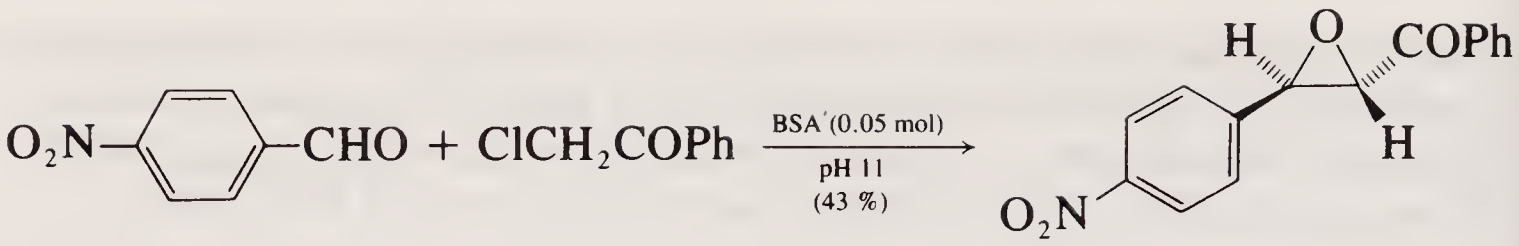


(60) (> 97 % e.e.)

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 presence of the readily available protein, bovine serum albumin, an asymmetric Darzens reaction becomes possible, e.g.



(100 % d.s.; 62 % e.e.)

Notes

1. Chirality is a property of the whole molecule, and cannot be localised in a particular centre. For this reason, the widely used term 'chiral centre' is, strictly, incorrect and should be replaced by 'stereogenic centre', i.e. a centre giving rise to stereoisomers.

2. See F. D. Gunstone, *Guidebook to Stereochemistry*, Longman, 1975, Chapter 3; R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem. Internat. Edit.*, **5**, 385 (1966).

3. These methods are described in detail in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Vol. 1, 1983.

4. For an extensive list of readily available chiral compounds, together with an indication of their cost, see J. W. Scott, in *Asymmetric Synthesis* (cf. Note 3, above), Vol. 4, Chapter 1.

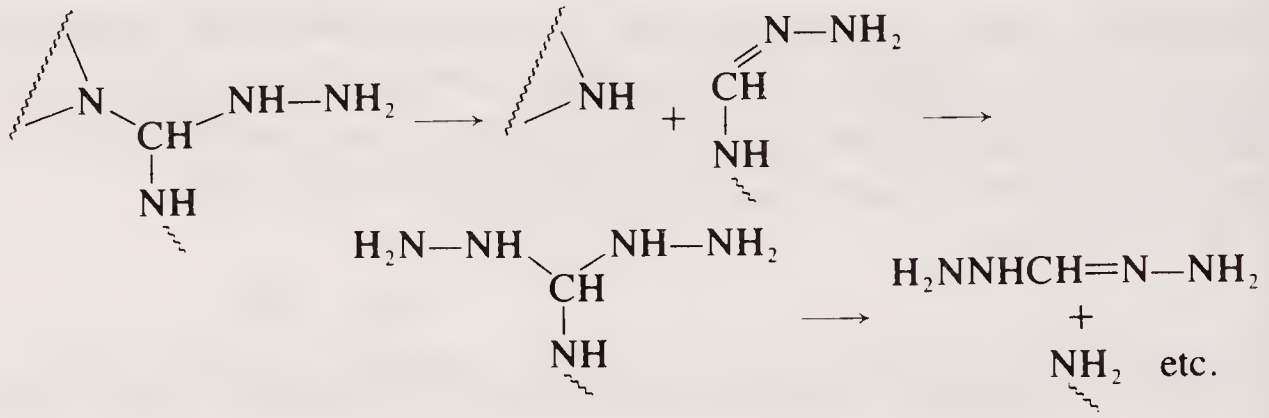
5. For full details, see *J. Am. Chem. Soc.*, **107**, 1439 (1985).

6. These 'directed aldol' reactions are reviewed in *Org. Reactions*, **28**, 203 (1982).

7. This is an example of *latent functionality* (cf. Chapter 10, Note 1).

8. See the comment on p. 67, paragraph (b), on the relative acidities of pentane-2,4-dione and its 3-methyl derivative.

9. The hydrazine presumably reacts by nucleophilic addition to the C=N bond, thereby giving



10. The trimethyl phosphite serves to reduce any unreacted hydroperoxide.

11. KDA is the potassium analogue of LDA, *viz*, $[(CH_3)_2CH]_2N^-K^+$.

12. See, for example, E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, Verlag Chemie, 1980.

13. Note that this molecule contains one stereogenic centre at nitrogen, as well as four at carbon.

16 Selected syntheses

This final chapter contains a number of syntheses which, it is hoped, will help to illustrate some of the ideas contained in the earlier parts of the book. At the beginning of each section, some indication is given of the importance of the compound or class of compound under discussion.

16.1 Introduction

The organic chemist, when faced with the synthesis of any given molecule, must plan the synthesis so that (i) readily available starting materials are used, (ii) the smallest number of efficient stages is involved, (iii) reactions involving separation of complex mixtures are avoided, and (iv) the synthesis is unambiguous. To do this may involve a small number of very obvious reactions in simple situations or, in a somewhat more complex case, application of the synthon–disconnection approach described in Chapter 3. However even the latter approach may be too cumbersome, and the chemist may be forced to plan a synthesis by, for example, intuitively recognising a key intermediate from which, perhaps by analogy with published syntheses, the target molecule may be obtained.

Two extreme strategies for a multi-stage synthesis can be identified. In one, known as **linear synthesis,** reactions are carried out step by step, each one adding a new part of the target molecule. This approach suffers from two principal drawbacks:

(i) even if each step proceeds in excellent yield, the overall yield in a multi-stage synthesis can be very low;
(ii) reactive functional groups may have to be carried unchanged through a large number of steps.

The alternative strategy is **convergent synthesis,** in which major parts of the target molecule are synthesised separately and these parts are linked together towards the end of the synthesis. The overall yield may be higher than that obtained in a linear synthesis (cf. section 16.9.1) and the labile features of the target molecule are contained within smaller units.

16.2 *Z*-Heneicos-6-en-11-one

In section 3.1, various ways in which *Z*-heneicos-6-en-11-one could be synthesised from smaller fragments were suggested. We shall now consider further how this pheromone might be synthesised and then look in detail at three published syntheses.

When we consider possible synthetic routes to the target molecule, we should note several points. Firstly, *Z*-alkenes are often prepared by partial hydrogenation of alkynes (cf. section 8.4.2) or by the salt-free Wittig reaction (cf. section 5.3.1.3). Secondly, the functional groups are sufficiently remote from each other to suggest that they can be treated independently. Thirdly, in the case of a synthesis involving alkynes, the alkyne is more stable than the carbonyl group, particularly towards nucleophilic reagents, and so it is preferable to introduce it first.

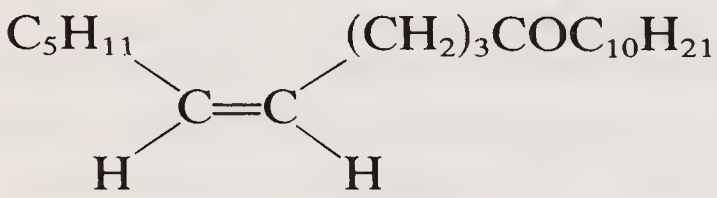
Looking at possible syntheses involving alkynes we note disconnections for alkynes in table 4.1 and those for ketones in tables 4.1 and 5.1. Synthetic equivalents are found in tables 4.2 and 5.2.

$RC{\equiv}CR' \Rightarrow RC{\equiv}C^- + R'^+$

$RCOR' \Rightarrow R^- + {}^+COR'$

$RCH_2COR' \Rightarrow R^+ + {}^-CH_2COR'$

Let us now look at our target molecule and consider the possibilities:



$\Longrightarrow C_5H_{11}C{\equiv}C(CH_2)_3COC_{10}H_{21}$

(a) $C_5H_{11}C{\equiv}C(CH_2)_3^-\ {}^+COC_{10}H_{21}$

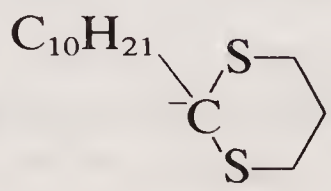
i.e. $C_5H_{11}C{\equiv}C(CH_2)_3MgX + C_{10}H_{21}CONR_2$

or $[C_5H_{11}C{\equiv}C(CH_2)_3]_2CuLi + C_{10}H_{21}COCl$

(b) $C_5H_{11}C{\equiv}C(CH_2)_2^+\ {}^-CH_2COC_{10}H_{21}$

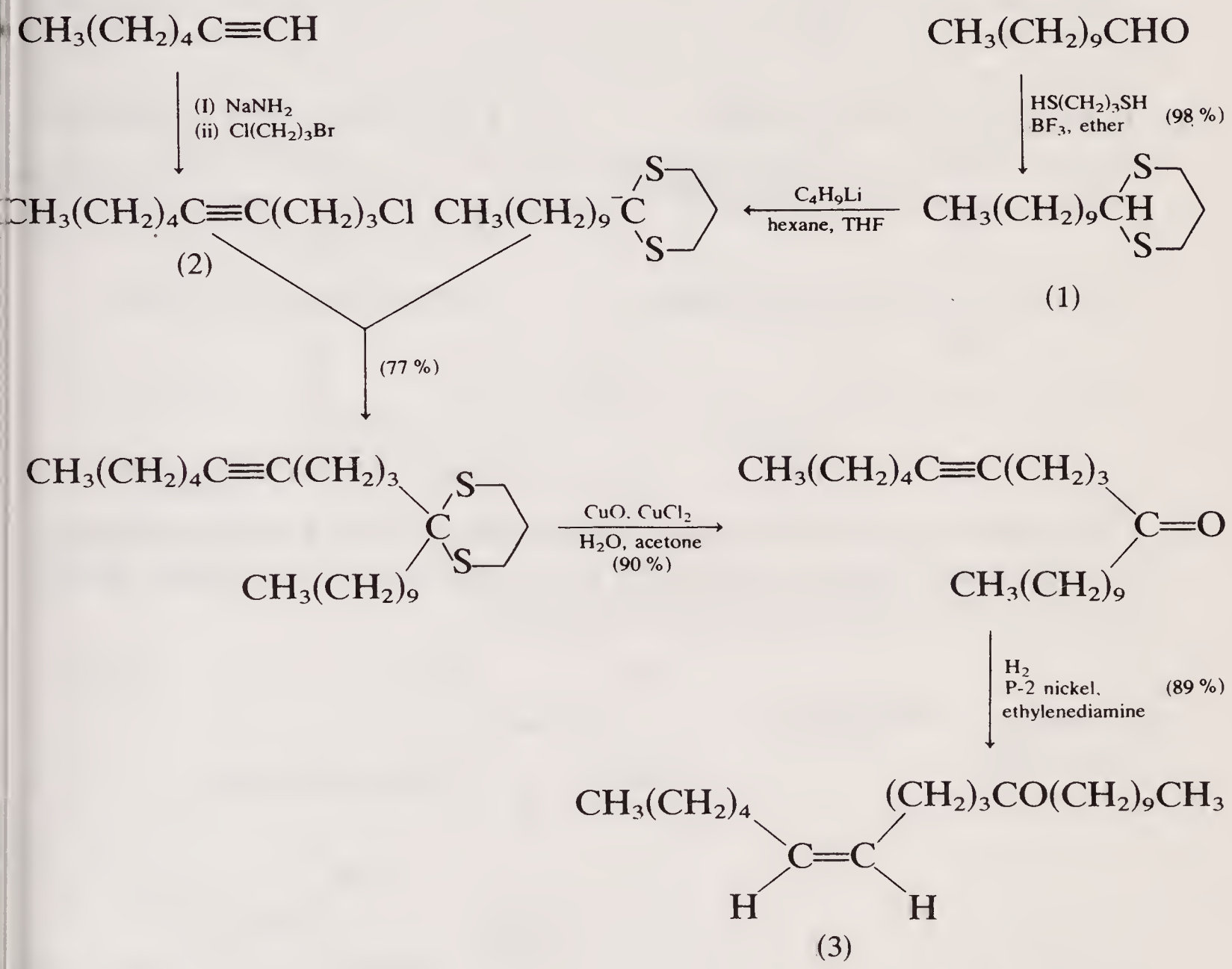
i.e. $C_5H_{11}C{\equiv}C(CH_2)_2X + C_{10}H_{21}CO\bar{C}HCO_2R$

(c) $C_5H_{11}C{\equiv}C(CH_2)_3^+\ {}^-COC_{10}H_{21}$

i.e. $C_5H_{11}C{\equiv}C(CH_2)_3X +$ 

Of the synthetic equivalents for the decyl-containing synthons, that from disconnection (c) is readily prepared from commercially available undecanal (syntheses of this compound are given on pp. 46 and 97) and so this disconnection probably offers the best possibility. The electrophilic synthetic equivalent required in (c) is a 1-halogenodec-4-yne. 1-Chlorodec-4-yne could be prepared from the anion of hept-1-yne and 1-chloro-3-bromo- (or iodo-)propane when the more reactive halogen (Br or I) will undergo nucleophilic substitution.

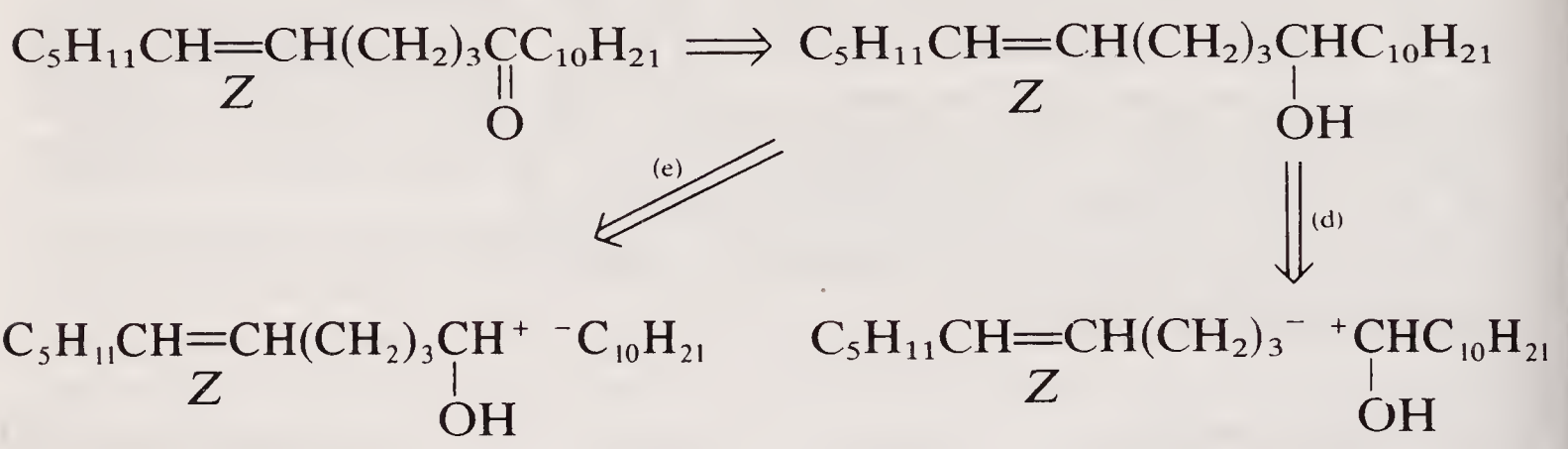
The first synthesis of the pheromone, reported in 1975,[1] followed the sequence shown below:



The alkyl chain is formed by nucleophilic substitution by the anion of the dithian (1) derived from undecanal on the chloroalkyne (2) formed by reaction of the anion of hept-1-yne with 1-bromo-3-chloropropane. The dithian is cleaved using copper(II) oxide and copper(II) chloride in aqueous acetone, and the pheromone, *Z*-heneicos-6-en-11-one (3), is formed by partial hydrogenation using a P-2 nickel catalyst in presence of ethylenediamine.[2]

As suggested in the preamble, *Z*-alkenes can be prepared by the salt-free Wittig procedure. A second synthesis[3] of the pheromone utilises

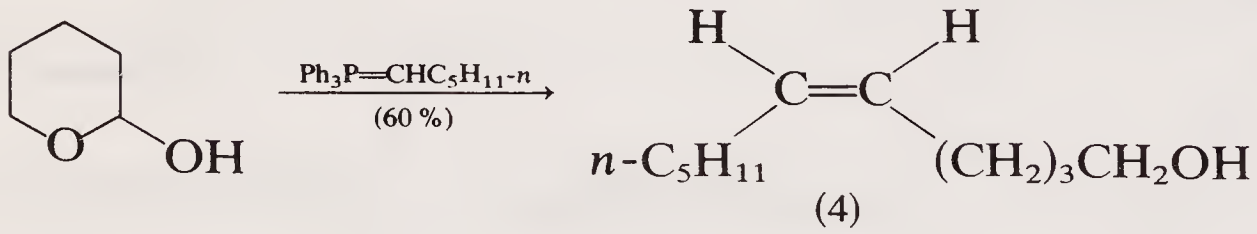
this method and the *Z*-alkene function is introduced initially. The carbonyl group is prepared *via* the secondary alcohol. The disconnections involved in this route are thus:

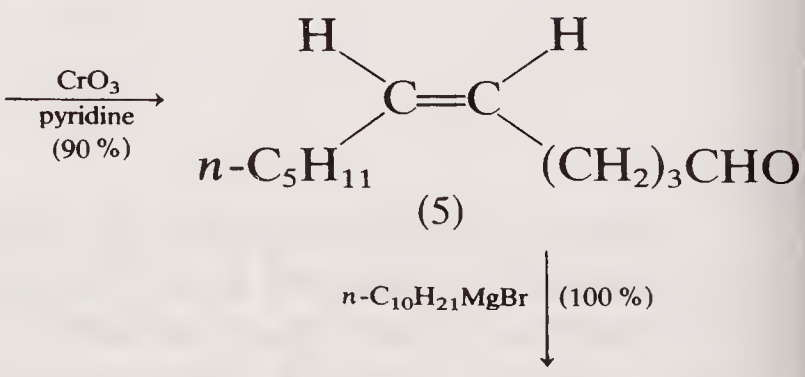


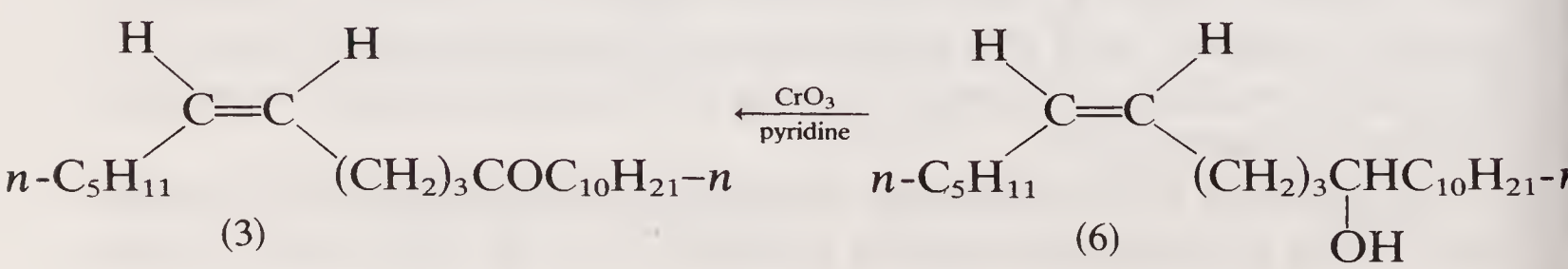
i.e. $C_5H_{11}CH{=}CH(CH_2)_3CHO$ (*Z*) + $C_{10}H_{21}MgBr$ ⇓ $C_5H_{11}CH{=}CH(CH_2)_3CH_2OH$ (*Z*) (4)

i.e. $C_5H_{11}CH{=}CH(CH_2)_3MgBr$ (*Z*) + $C_{10}H_{21}CHO$ ⇓ $C_5H_{11}CH{=}CH(CH_2)_3Br$ (*Z*) ⇓ $C_5H_{11}CH{=}CH(CH_2)_3OH$

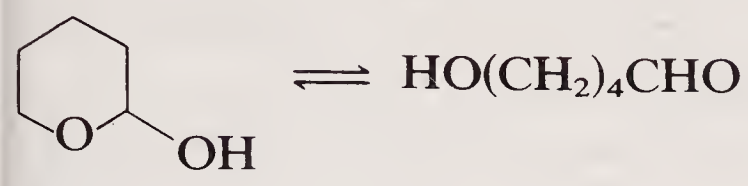
Both (d) and (e) lead to unsaturated alcohols as the key intermediates. As will be seen below, compound (4) is prepared in a salt-free Wittig reaction from 2-hydroxytetrahydropyran.[4]





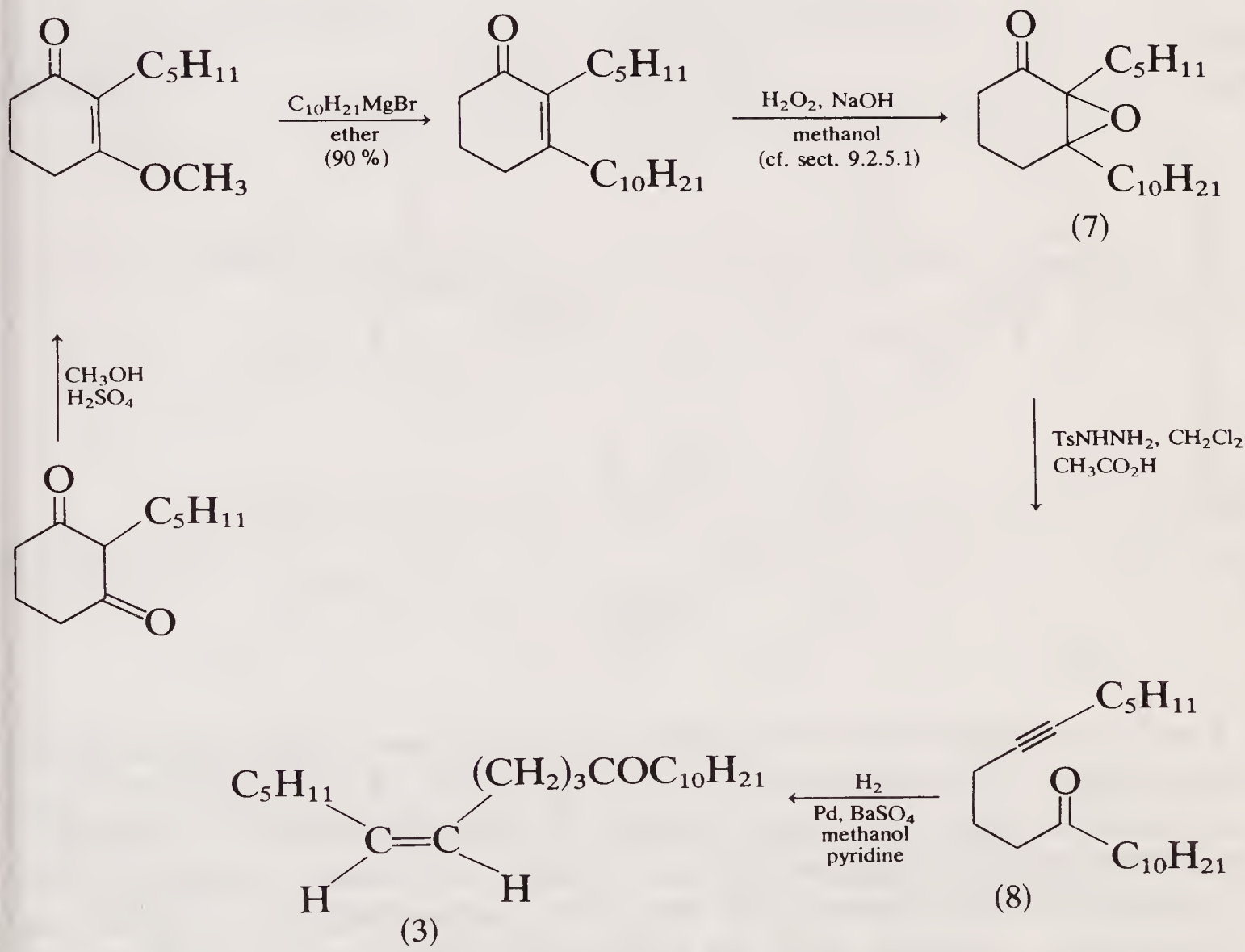


2-Hydroxytetrahydropyran is the hemiacetal tautomer of 5-hydroxypentanal and its reaction with the Wittig reagent leads to *Z*-undec-5-en-1-ol (4).

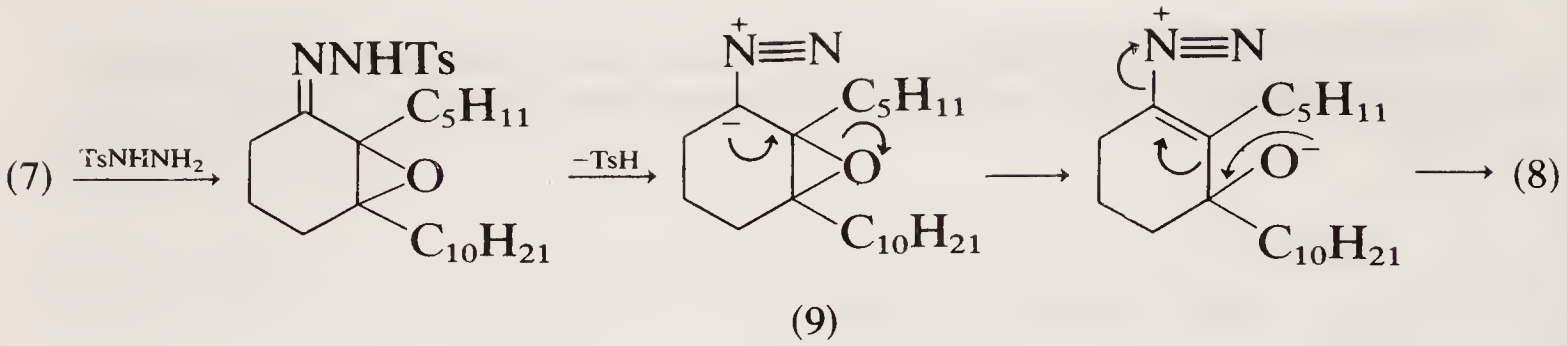


The remainder of the synthesis follows the route suggested by disconnection (e). It should be noted that the oxidations (4) → (5) and (6) → (3) are carried out in a basic medium to avoid *Z*–*E* isomerisation. *Z*–*E* isomerisation may also occur on the route indicated by disconnection (d), during the conversion of the unsaturated alcohol into the bromide.

In a third synthesis of *Z*-heneicos-6-en-11-one the acetylene and carbonyl groups are formed together in an efficient ring opening reaction developed by Eschenmoser.[5]



The mechanism of the ring opening (7) → (8) involves the unstable epoxy-diazoalkane intermediate (9):

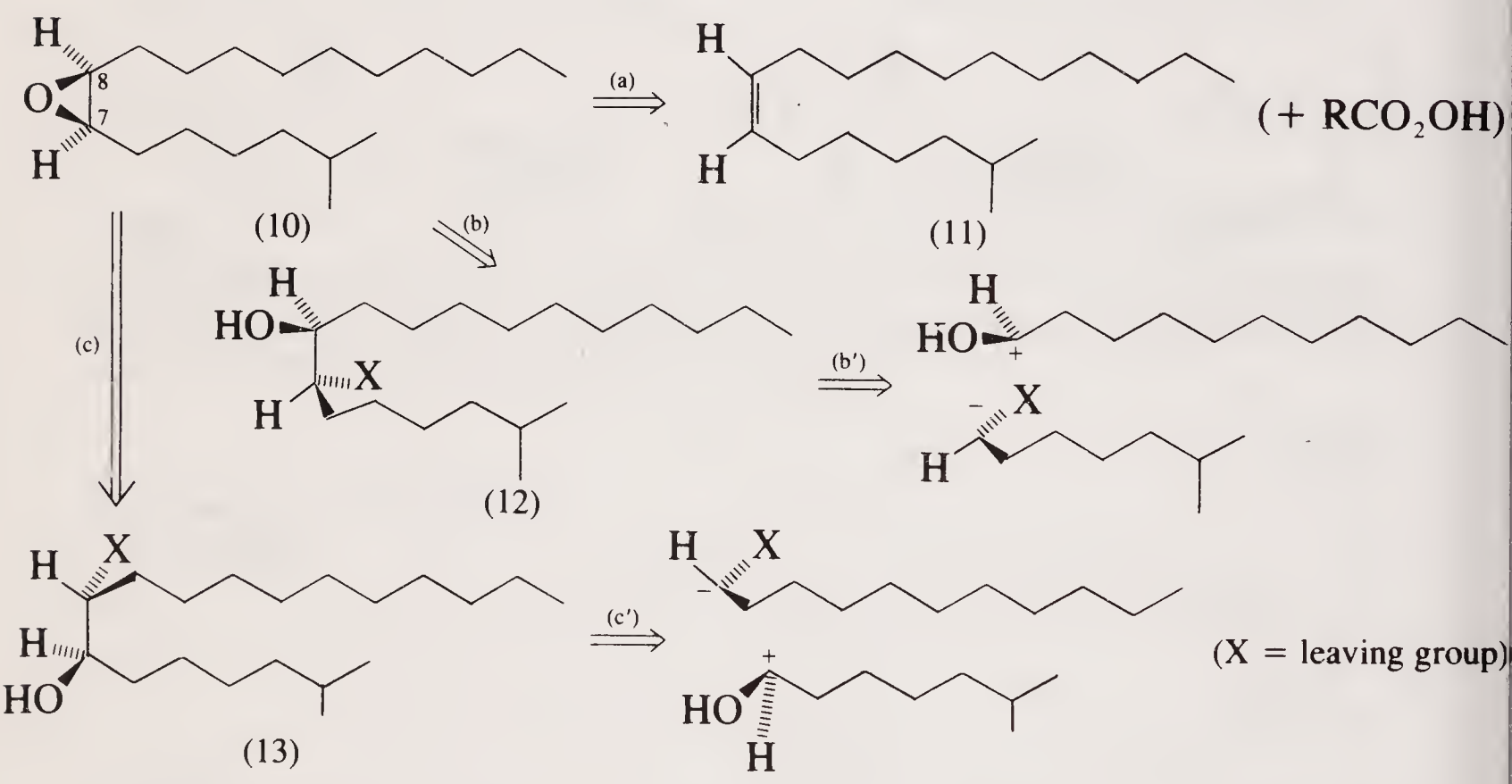


(9)

16.3 (+)-Disparlure

This is another relatively simple insect pheromone: it is the sex attractant of the female gypsy moth. Unlike the previous example, however, it is a chiral molecule, only the (+)-enantiomer (10) possessing biological activity.

The most obvious synthetic route to an epoxide is the reaction of an alkene with a peroxy-acid [section 9.2.4.1; disconnection (a)]. The required *Z*-alkene (11) ought to be available by a 'salt-free' Wittig reaction (section 5.3.1.3). However, epoxidation of (11) will occur *on either face of the molecule* to give both (+)- and (−)-disparlure.

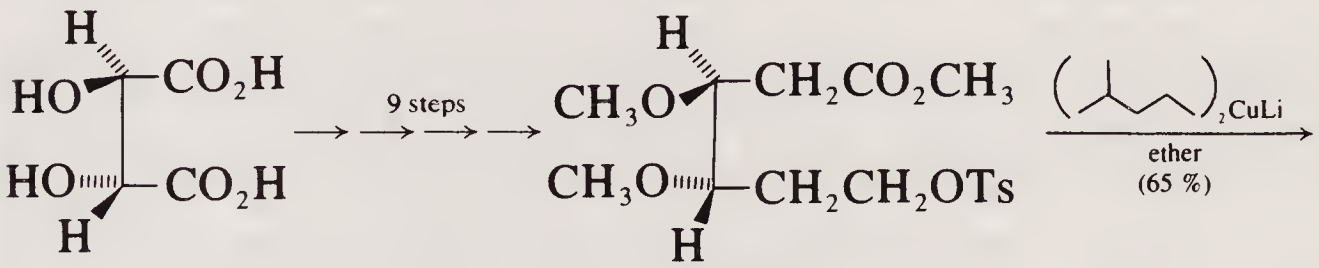


The other simple route to epoxides involves intramolecular nucleophilic substitution [disconnection (b) or (c)], which, if it follows the S_N2 mechanism, ought to be stereospecific. All three syntheses of (+)-disparlure described below utilise this nucleophilic substitution method for the production of the heterocyclic ring. The first method is not strictly an asymmetric synthesis since the stereogenic centres of the product are present in the starting material, while the second is a 'first-generation' method (section 15.3). Both reveal several of the disadvantages of such routes; the third, however, makes use of a chiral auxiliary (section 15.4)

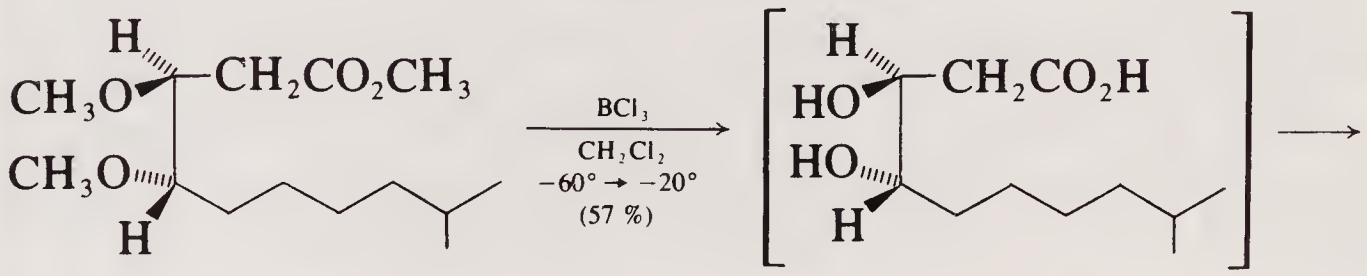
which is subsequently converted into the leaving group X, and this is undoubtedly the most elegant of the three.

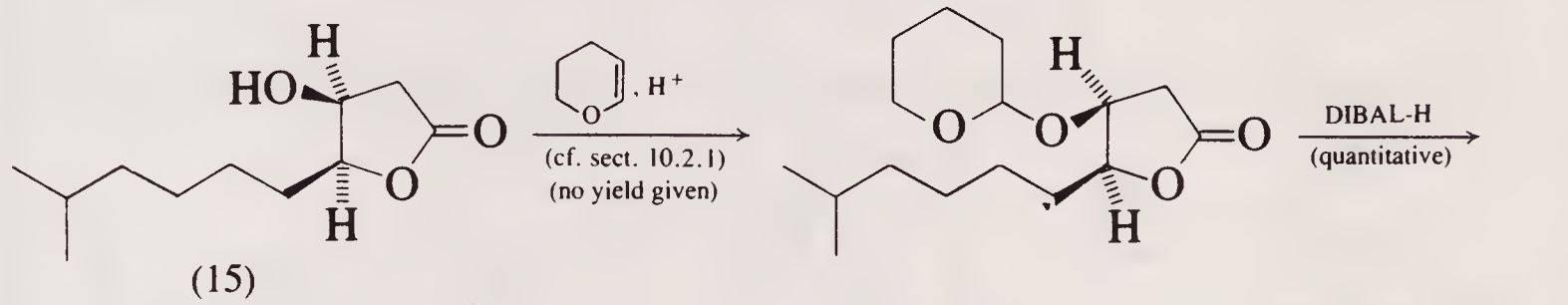
Since the configuration of the epoxide substituents in disparlure is *cis*-[7*R*,8*S* in the (+)-enantiomer], and since the S_N2-type ring closure involves inversion of configuration at one centre, the acyclic precursor (12) or (13) must have a *threo*-configuration. In the first synthesis of (+)-disparlure,[6] the starting material is (2*R*,3*R*)-(+)-tartaric acid, in which the *threo*-relationship between the two stereogenic centres is already 'built in'.

The reaction sequence is shown below. Essentially it consists of building up the two alkyl side-chains of precursor (12) without altering the

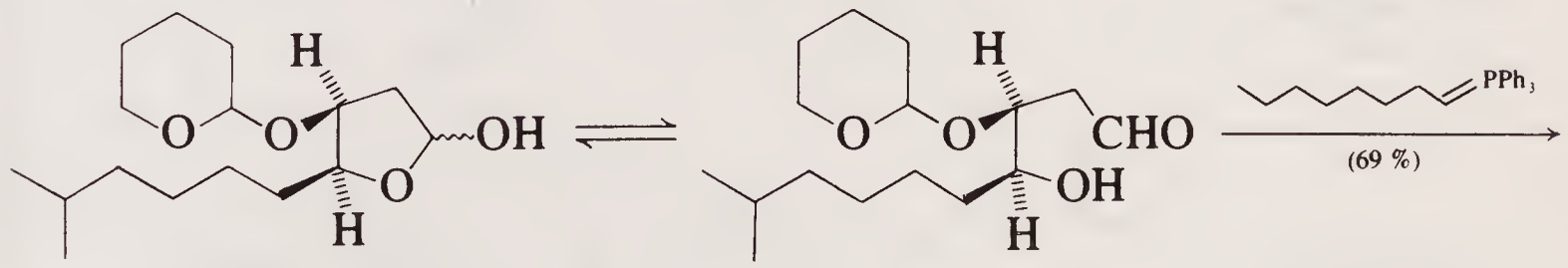


(14) (~9 % overall)

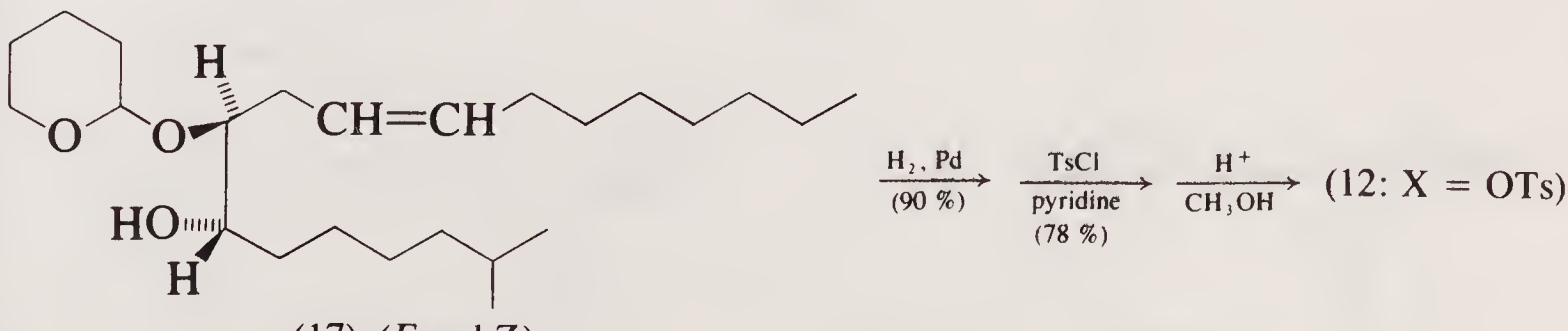




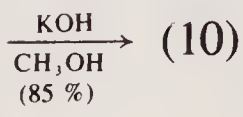
(15)



(16) (16a)



(17) (*E* and *Z*)

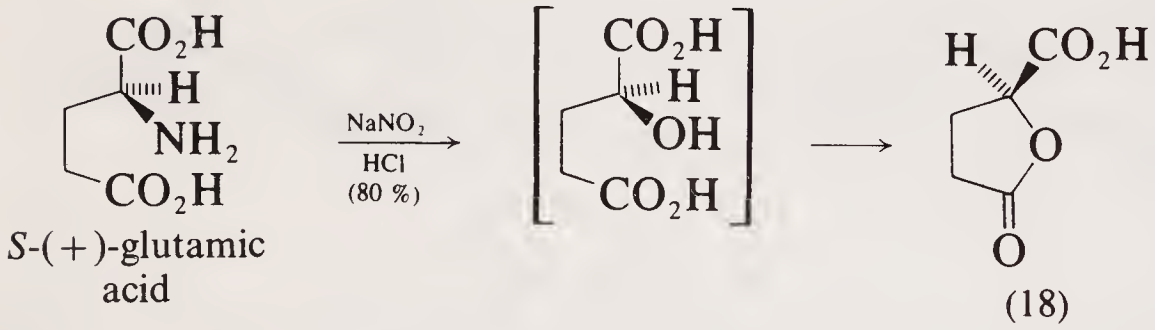


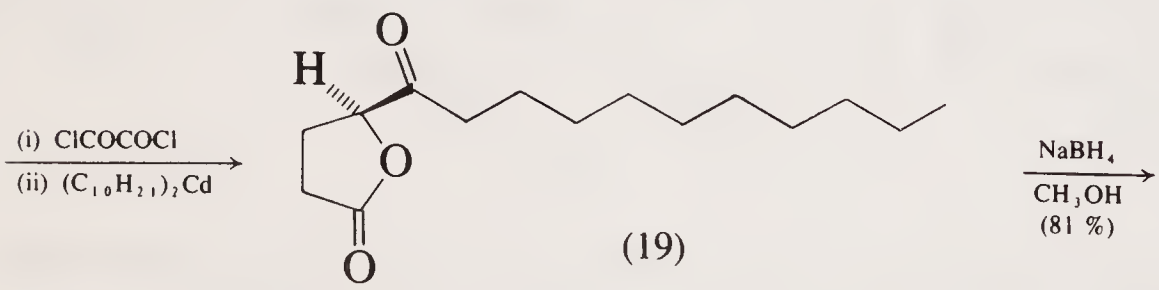
(10)

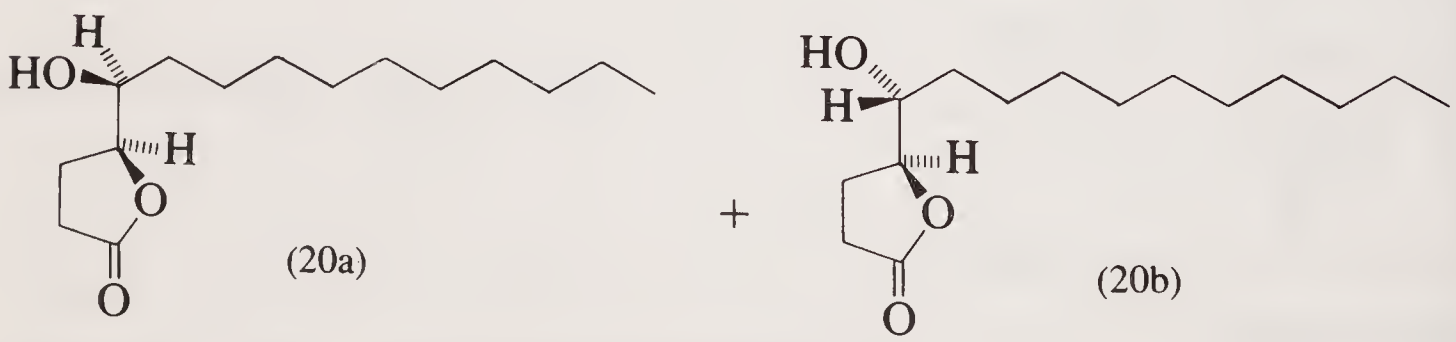
configuration at either stereogenic centre. The tartaric acid is converted, in nine steps, into the tosyloxy-ester (14); the tosyloxy group is then displaced using a cuprate (section 4.2.3), and demethylation using boron trichloride (section 10.2.1) gives a β,γ-dihydroxy-acid which spontaneously forms the γ-lactone (15). Protection of the remaining hydroxyl group, and reduction of the lactone with DIBAL-H (section 8.2) leads to a hemiacetal (16) which, as its acyclic tautomer (16a), undergoes a Wittig reaction to give (17). The remainder of the synthesis is simple functional group transformation, giving (12: X = OTs) and thus (10) with >95% e.e.

The second synthesis[7] is different in principle, because the starting material, *S*-(+)-glutamic acid, contains only one of the required stereogenic centres; reduction of a ketonic carbonyl group generates the other.

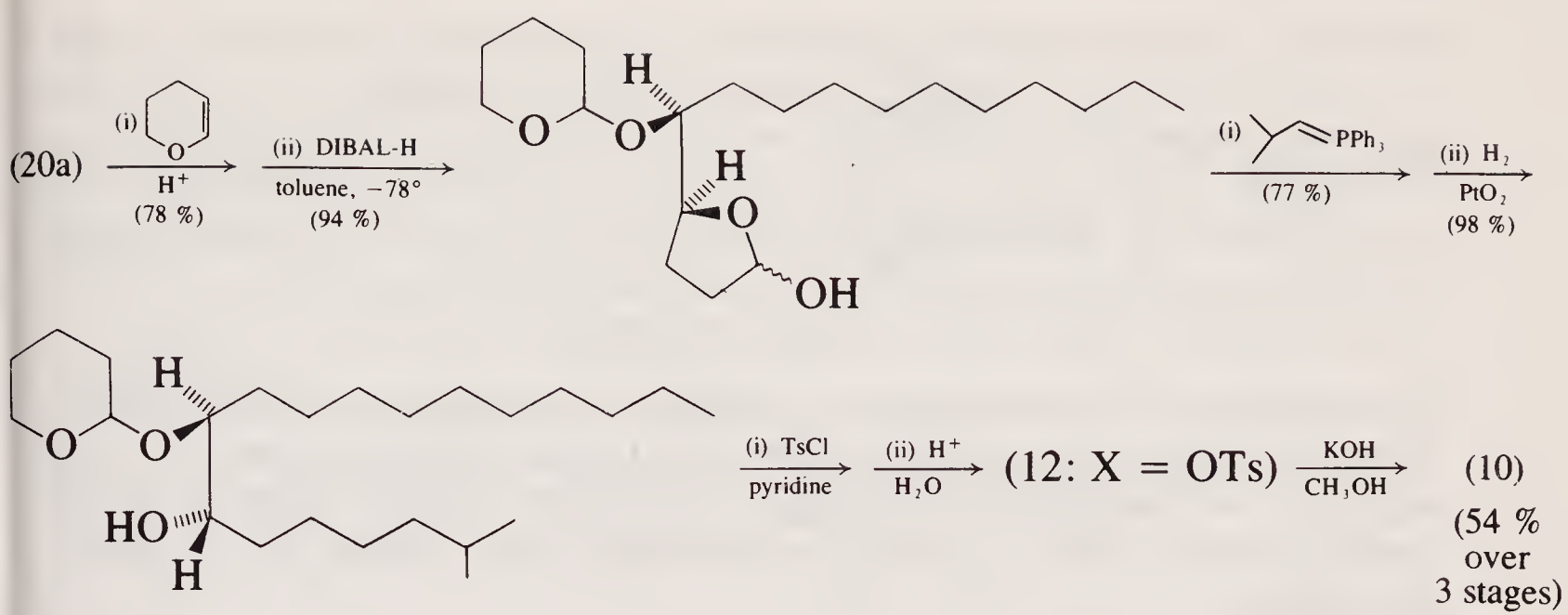
The glutamic acid is converted, by reaction with 'nitrous acid', into the corresponding hydroxy-acid, which spontaneously forms the γ-lactone (18). This sequence occurs with retention of configuration at the stereogenic centre because of *neighbouring group participation* (Sykes, pp. 93–6) by the adjacent carboxyl group. The remaining free carboxyl group in (18) is then converted into the ketone (19), and the latter is reduced to a diastereomeric mixture of hydroxy-lactones, (20a) and (20b), which are separated by chromatography and recrystallisation. The remainder of the synthesis follows a similar pattern to the previous method, giving eventually (12:X = OTs) and thence (10). The claimed e.e. is 88.4%.





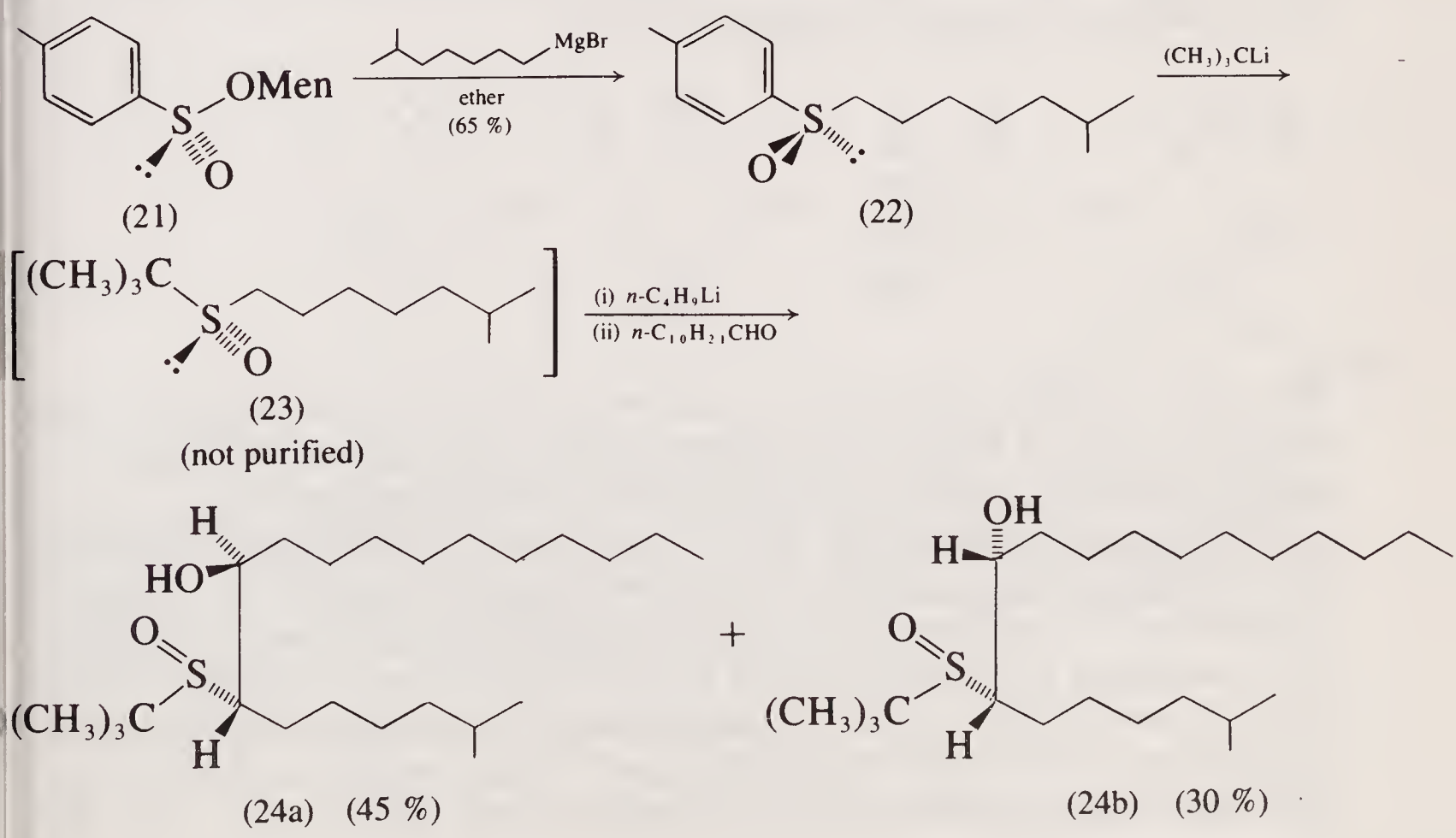


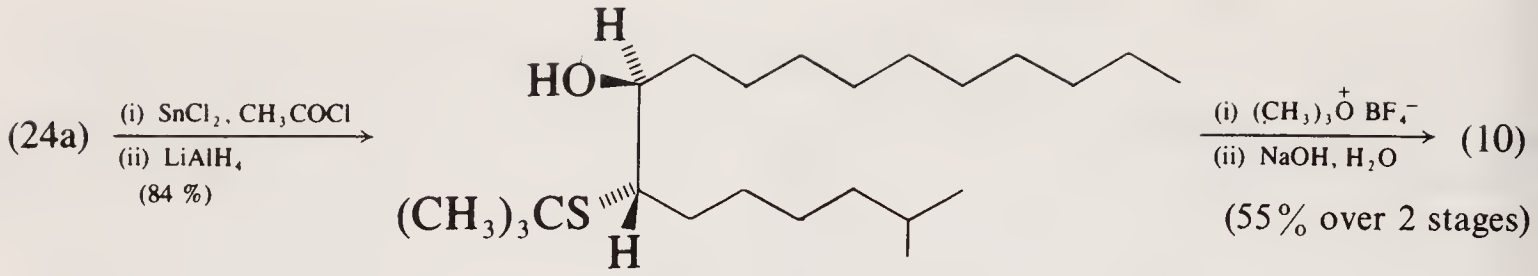
(separated by chromatography)



The third, and most recent, synthesis[8] uses a chiral sulphoxide as auxiliary (cf. section 15.4.7) for the asymmetric addition to the carbonyl group of an aldehyde [This corresponds to the subsidiary disconnection (b′) on p. 340].

The chiral menthyl toluene-*p*-sulphinate (21), which is obtainable, diastereomerically pure, from (−)-menthol and toluene-*p*-sulphinyl chloride, is converted into the chiral sulphoxide (22) by reaction with 6-methylheptylmagnesium bromide, and the *p*-tolyl substituent is then replaced by t-butyl. (Both of these steps, being S_N2 processes, cause an inversion of configuration at sulphur.) Deprotonation of the t-butyl sulphoxide (23), and addition to undecanal, give a mixture of diastereomeric sulphinyl-alcohols (24a) and (24b), which are separable by chromatography. The major isomer, (24a), is converted into disparlure



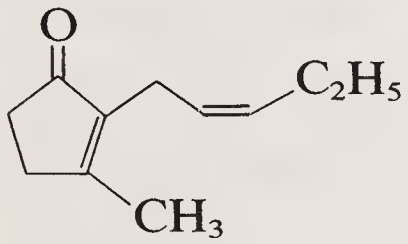


(12: X = $SC(CH_3)_3$)

by reduction of the sulphoxide to sulphide, *S*-methylation using trimethyloxonium fluoroborate (cf. section 3.3.1), and a final cyclisation using aqueous sodium hydroxide as base and t-butyl methyl sulphide as the leaving group. The e.e. of the final product is not stated, but is clearly very high.

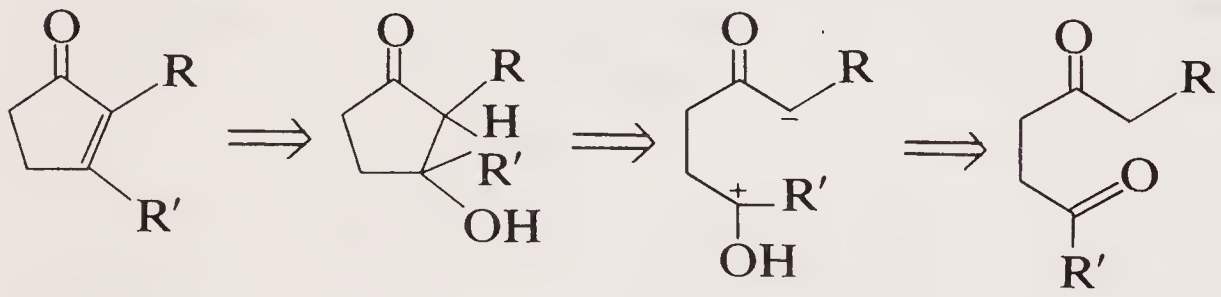
16.4 *Z*-Jasmone

Z-Jasmone (25) is a constituent of jasmine flowers and is widely used in perfumery to reproduce the jasmine fragrance.



(25)

Synthetic routes might involve a pre-formed five-membered ring precursor such as cyclopentadiene or involve cyclisation of a 1,4-diketone to the cyclopent-2-enone (cf. section 7.5.3):

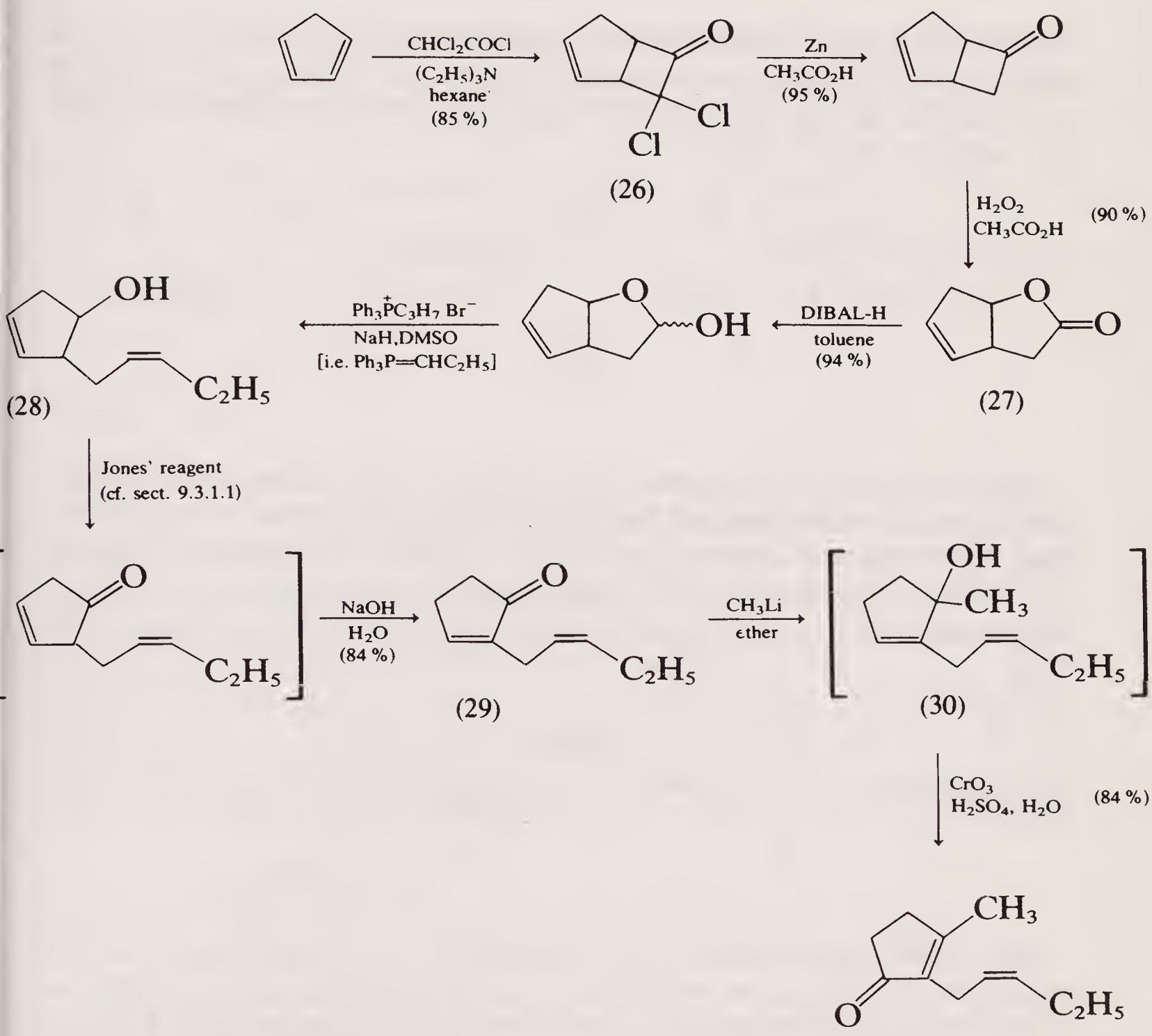


We shall consider three of the syntheses of *Z*-jasmone described in the literature. Two of these adopt variants of the latter approach[9] and one, which we shall describe first, starts from cyclopentadiene.[10]

Dichloroketen (formed in *situ* by reaction of dichloroacetyl chloride with triethylamine) is known to react with cycloalkenes by (2 + 2) cycloaddition.[11] Cyclopentadiene and dichloroketen give the cycloadduct (26); reductive dehalogenation of the latter and Baeyer–Villiger oxidation (cf. section 9.5.3) of the product give the lactone (27). Reduction of the lactone to the lactol (hemiacetal), and Wittig reaction of the latter to give the γ-hydroxyalkene (28), are familiar steps from section 16.3; the

use of 'salt-free' conditions for the Wittig reaction ensures Z-stereochemistry in the product. (No E-isomer is detectable in this case.)

Oxidation of the alcohol (28) gives an unsaturated ketone, which is converted in base, without isolation, into the more stable conjugated isomer (29). Reaction of (29) with methyl-lithium gives the tertiary alcohol (30), which on oxidation under acidic conditions undergoes allylic rearrangement and leads directly to jasmone (25). The overall yield is around 40%.

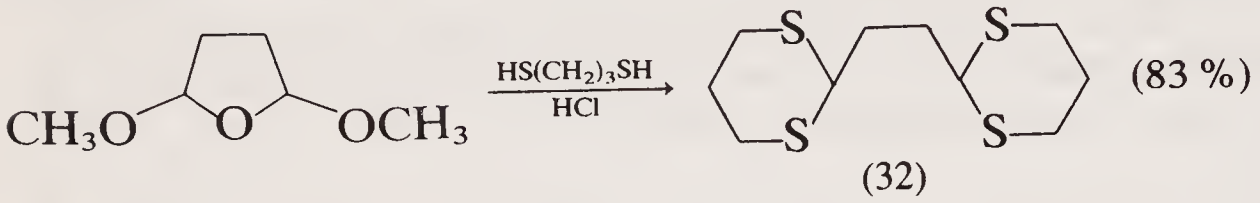


The other two methods involve cyclisation of the 1,4-diketone (31). It is, of course, undesirable to carry the carbonyl groups through the other steps in the sequence and the two methods differ in their solution of this problem. In the first, the carbonyl groups are present in the form of 1,3-dithians which can be alkylated (cf. section 5.3.2).

$CH_3CO(CH_2)_2CO(CH_2)_2CH{=}CHC_2H_5$

(31)

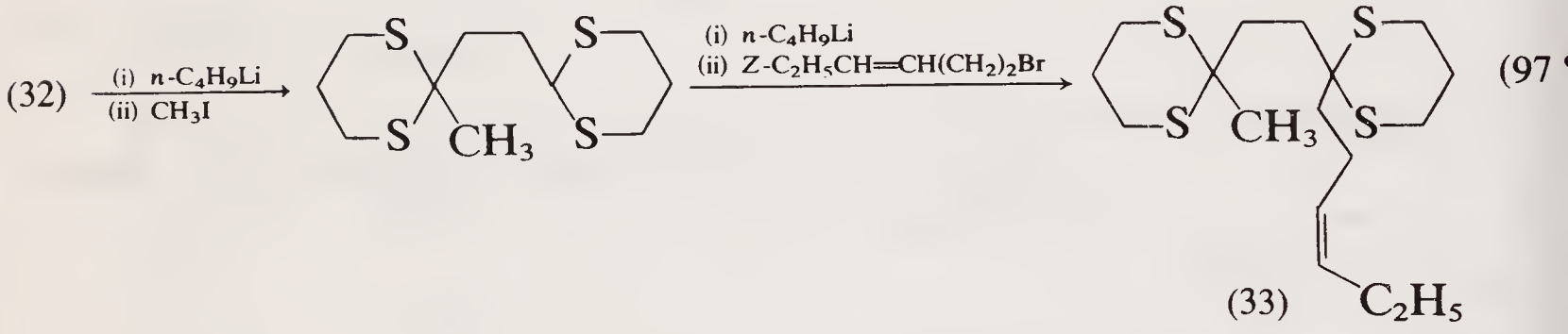
The starting material for this synthesis is 2,5-dimethoxytetrahydrofuran. This is a bis-acetal and on treatment with acid in presence of propane-1,3-dithiol it is converted to the bis-1,3-dithian of butanedial (32):



(83 %)

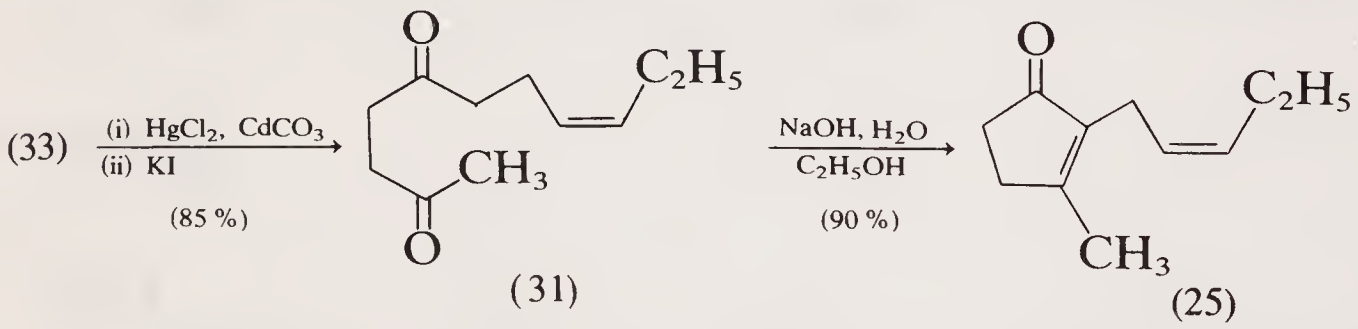
(32)

The next stage is the successive alkylation at C-1 and C-4 by the methyl and *Z*-hexenyl groups present in jasmone. These steps are carried out in the usual way (metallation using butyl-lithium followed by reaction with the alkyl halide):



(97 %

Hydrolysis of (33) by mercuric chloride and cadmium carbonate results in oxymercuration of the double bond. The product must, therefore, be treated with potassium iodide to isolate the required enedione (31) which yields jasmone by intramolecular base-catalysed condensation (cf. section 7.1). The overall yield of jasmone prior to purification is 61 %.



(31)

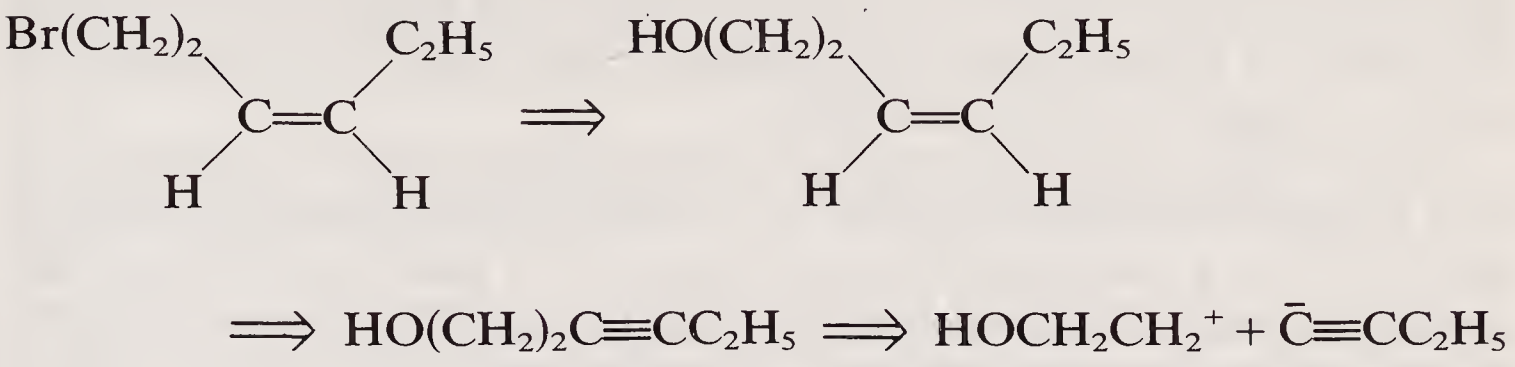
(25)

The remaining problem is the synthesis of *Z*-1-bromohex-3-ene. We recall that *Z*-alkenes are produced by partial hydrogenation of alkynes (cf. section 8.4.2). The problem is now that of synthesising either 1-bromo hex-3-yne or a compound which could be converted to the bromo compound by functional group interconversion. Table 4.1 gives the appropriate disconnection for alkynes and for RCH_2CH_2OH (R—OH → R—Br being a possible functional group interconversion[12]):

$$RC{\equiv}CR' \Longrightarrow RC{\equiv}C^- + {}^+R' \qquad \text{(electrophile R'–Y)}$$

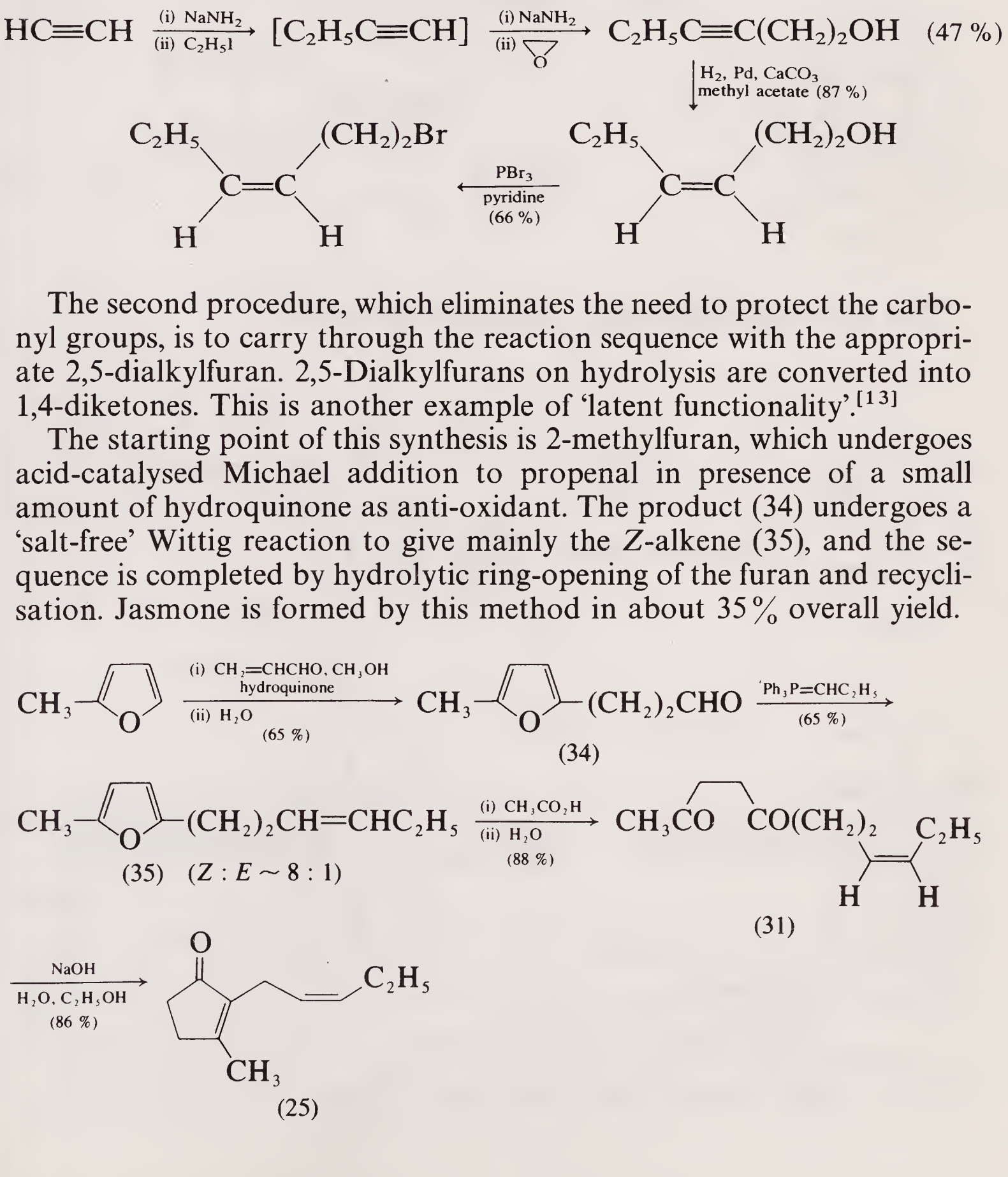
$$RCH_2CH_2OH \Longrightarrow R^- + {}^+CH_2CH_2OH \quad \left(\text{electrophile } \triangledown_{O}\right)$$

The appropriate set of disconnections for *Z*-1-bromohex-3-ene is the following:



$$\Longrightarrow HO(CH_2)_2C{\equiv}CC_2H_5 \Longrightarrow HOCH_2CH_2^+ + \bar{C}{\equiv}CC_2H_5$$

The synthesis, in fact, starts from acetylene and is shown below:



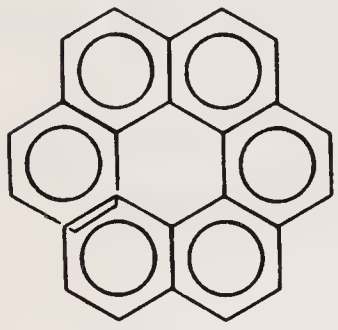
The second procedure, which eliminates the need to protect the carbonyl groups, is to carry through the reaction sequence with the appropriate 2,5-dialkylfuran. 2,5-Dialkylfurans on hydrolysis are converted into 1,4-diketones. This is another example of 'latent functionality'.[13]

The starting point of this synthesis is 2-methylfuran, which undergoes acid-catalysed Michael addition to propenal in presence of a small amount of hydroquinone as anti-oxidant. The product (34) undergoes a 'salt-free' Wittig reaction to give mainly the *Z*-alkene (35), and the sequence is completed by hydrolytic ring-opening of the furan and recyclisation. Jasmone is formed by this method in about 35% overall yield.

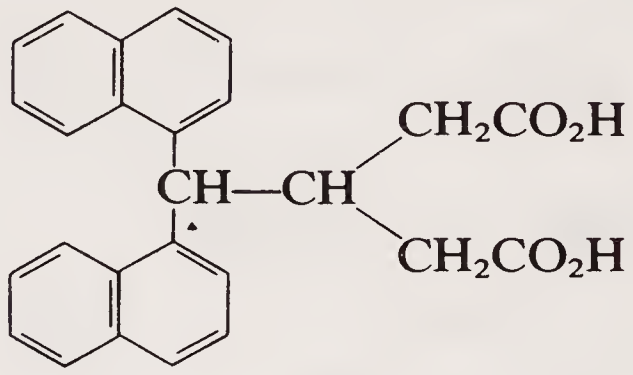
16.5 Helicenes

Interest in chiral molecules in which benzene rings are fused together in an angular manner so that they eventually form a helix (36) (which can, of course, be right-handed or left-handed) has resulted in various synthetic strategies for such molecules.

In the 1950s a 'classical' synthesis of hexahelicene (36) was devised.[14] The strategy involved synthesis of a 3-(di-α-naphthylmethyl)-glutaric acid (37) (i.e. a compound having rings 1, 2, 5, and 6 pre-formed) the acidic groups of which might cyclise on to the naphthyl groups in a Friedel–Crafts type reaction giving a six-ring system.

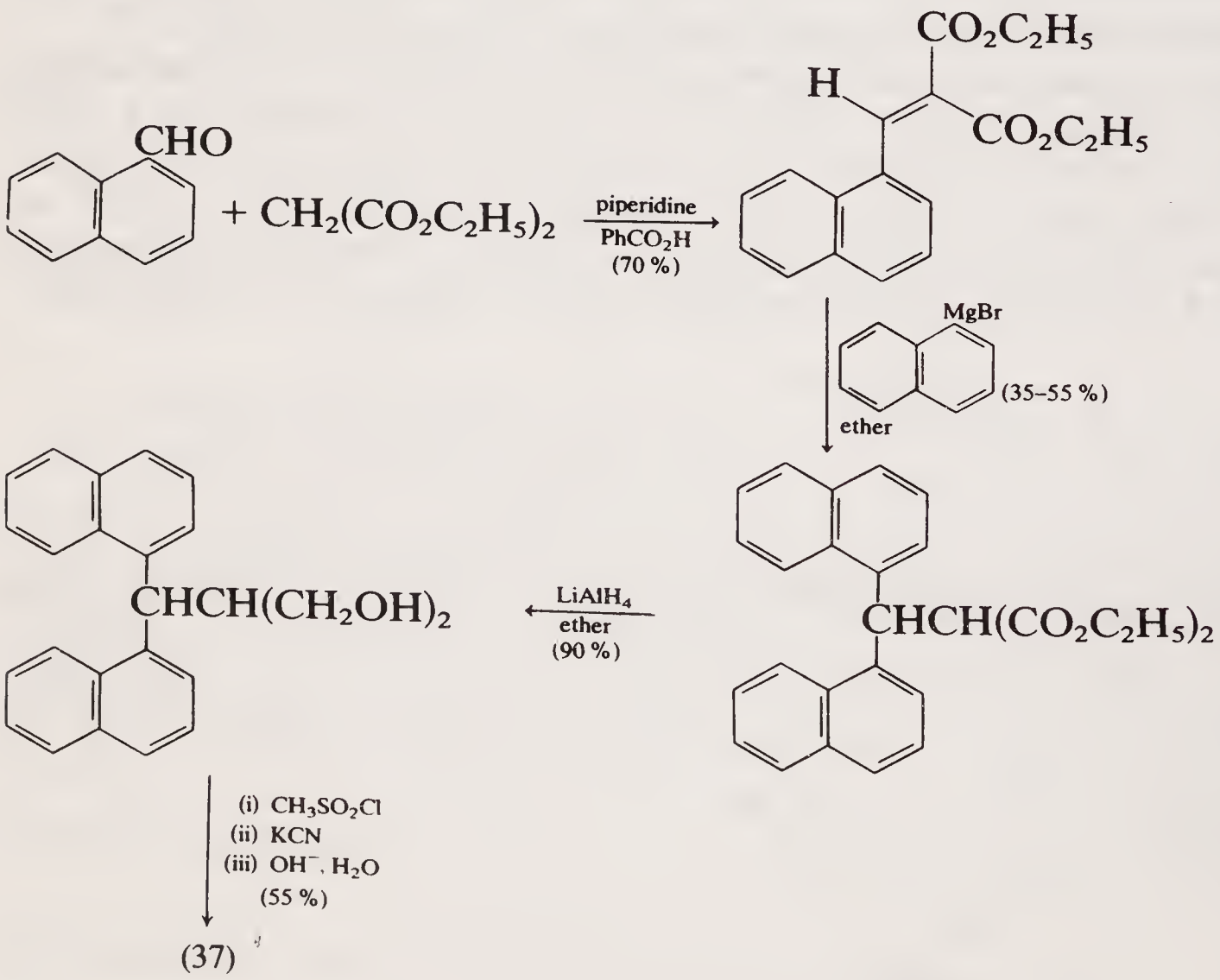


(36)



(37)

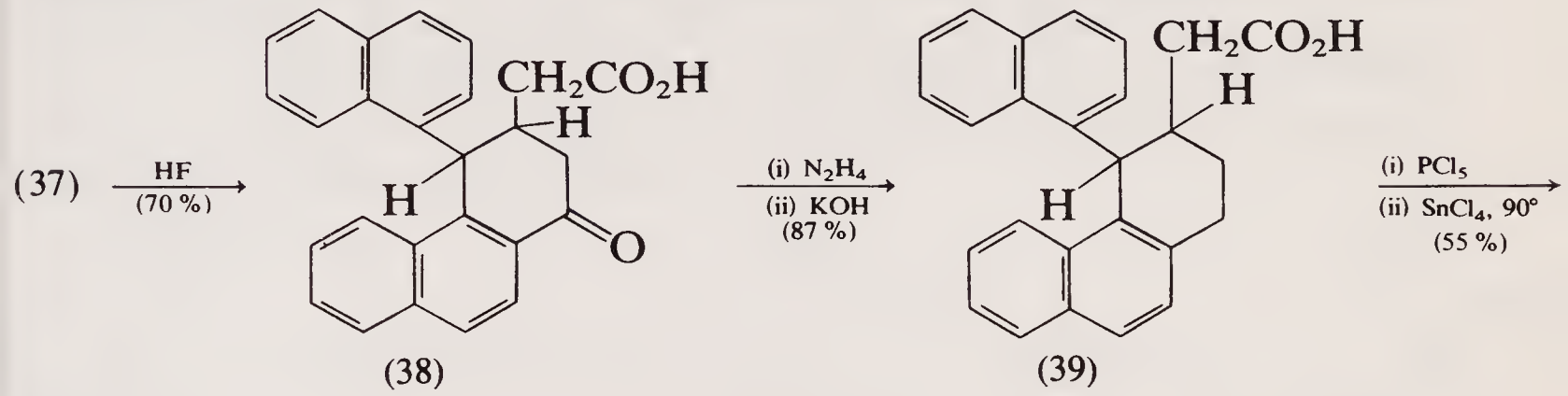
This key intermediate was synthesised as shown:

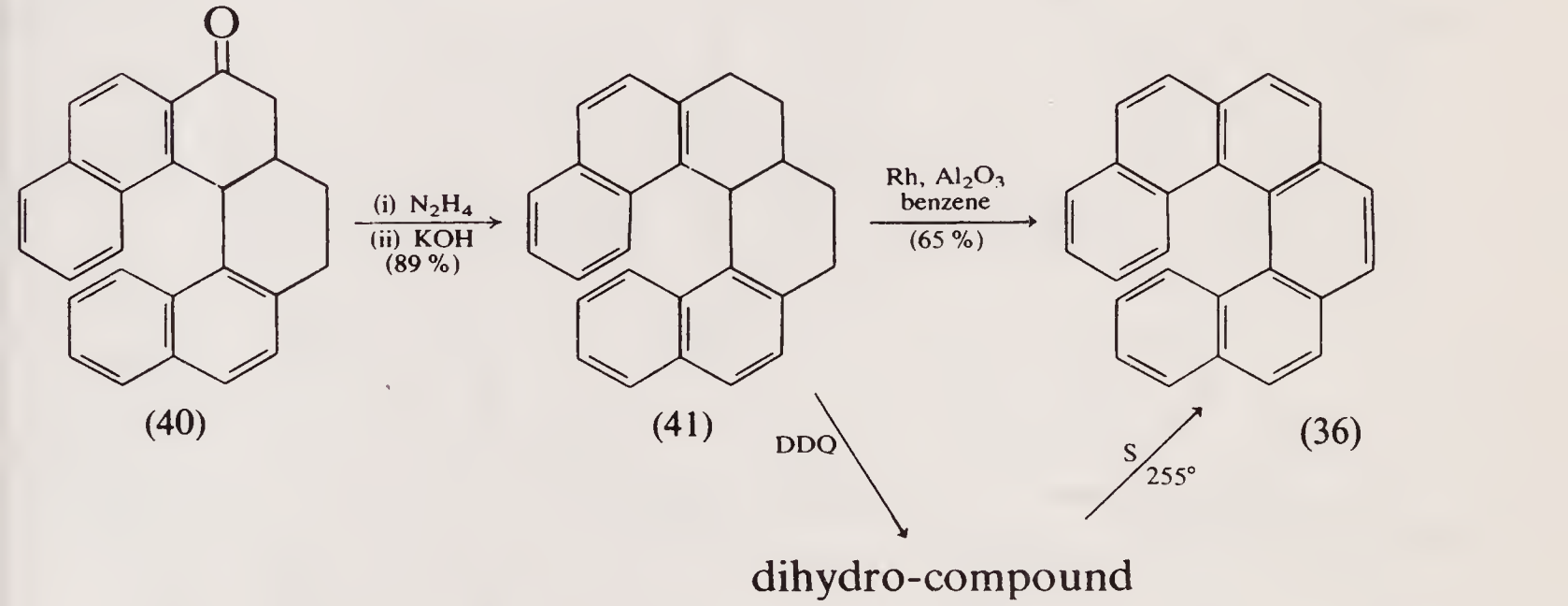


1-Naphthaldehyde and diethyl malonate undergo a Knoevenagel condensation (cf. section 5.1.4) to give the naphthylidenemalonic ester. Conjugate addition of α-naphthylmagnesium bromide, reduction of the ester groups with lithium aluminium hydride, and chain extension by the following sequence gives the required glutaric acid (37):

$$ROH + CH_3SO_2Cl \rightarrow ROSO_2CH_3 \xrightarrow{KCN} RCN \xrightarrow[H_2O]{OH^-} RCO_2H$$

Treatment of compound (37) with anhydrous HF (Friedel–Crafts acylation) results in only one cyclisation on to a naphthyl group. The fact that the second ring closure does not take place is due to the increased strain. So the two rings must be formed separately:





It should be noted that both ketones, (38) and (40), are reduced by the Wolff–Kishner method (cf. section 8.4.3.3) and that the conditions required for the second ring closure (39) → (40) are more severe than usual.

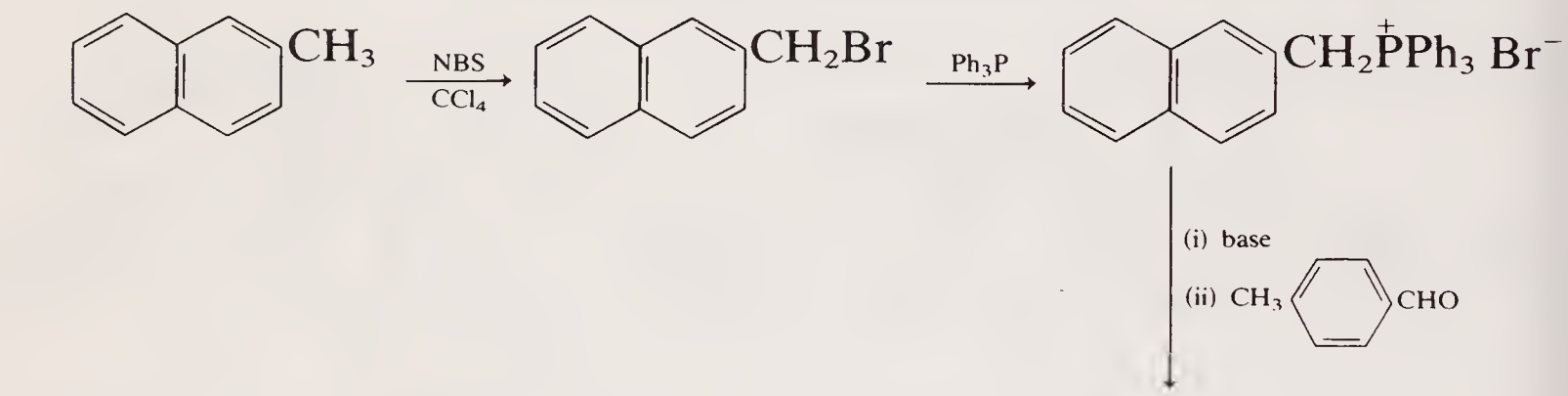
The remaining problem is the dehydrogenation of the two central rings in (41). Again this proved to be more difficult than might have been expected (cf. section 9.2.4) and the only direct method which was successful was a catalytic method using a rhodium catalyst.

One of the standard methods for dehydrogenation, use of DDQ (cf. section 9.2.4), gave a dihydro-compound which proved to be very resist-

ant to further dehydrogenation. It was suggested that the increase in delocalisation energy in this final dehydrogenation is small due to the lack of coplanarity of the rings in hexahelicene and that any increase in delocalisation energy would be offset by an increase in strain.

A shorter and much more practicable route to helicenes has been devised by Martin.[15] This is illustrated below for hexahelicene (36): the key steps are Wittig syntheses of diarylethylenes, e.g. (42) and (44), and iodine-catalysed photocyclisations of these (cf. section 7.3) to produce angularly fused aromatic systems, as in (43) and (36) itself.

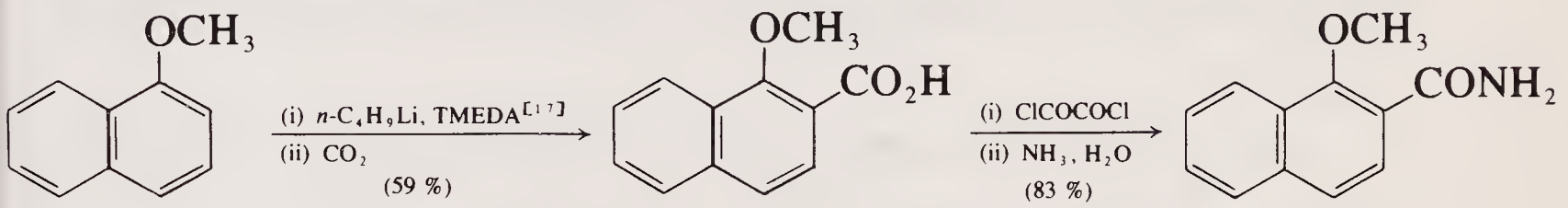
Higher helicenes have also been prepared by modifications of this route.



16.6 Asymmetric synthesis of chiral biaryls

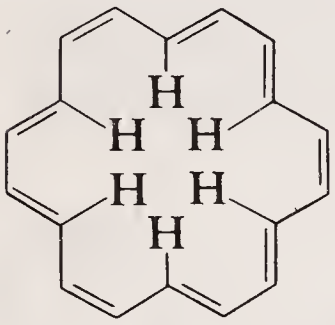
Although much of the interest in helicenes (section 16.5) derives from their chirality, individual helicene enantiomers have been obtained to date (1989) only by resolution of racemic mixtures, and not independently by asymmetric synthesis. Enantioselective syntheses are known, however, for simpler chiral aromatic compounds such as biaryls,[16] which owe their chirality not to a stereogenic centre or centres, but to restricted rotation about the central C–C single bond. The general principles are illustrated for the synthesis of the 1,1′-binaphthyl derivative (45); the method uses an oxazoline (cf. section 15.4.2) as chiral auxiliary.

1-Methoxy-2-naphthoic acid is converted, as described in section 15.4.2, into the chiral oxazoline (46). Reaction of this oxazoline with the Grignard reagent derived from 1-bromo-2-methoxynaphthalene results in nucleophilic displacement of the 1-methoxy-group of (46), and formation of the chiral binaphthyl (47) with high diastereoselectivity. Removal of the auxiliary is best achieved by hydrolysis followed by reduction, giving the primary alcohol (45).

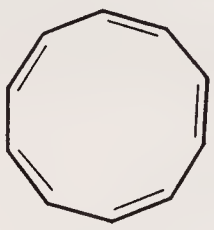


16.7 Annulenes

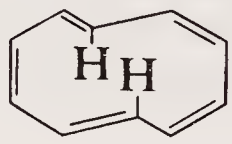
The name *annulene* is used to describe monocyclic hydrocarbons constructed from alternating double and single bonds. Interest in such compounds arises from Hückel's rule which states that such compounds, provided that the carbon framework can be virtually planar, are aromatic if they contain $(4n + 2)$ π-electrons (i.e. those with ten, fourteen and eighteen carbons in the ring will be aromatic). In the case of the eighteen-membered ring, the structure (48) is stable; however, in the case of ten-membered rings, structure (49) incorporates too much angle strain to exist as a stable molecule, and in (50) the interactions between the two internal hydrogens prevent the ring carbons achieving coplanarity. Stable aromatic molecules have been made containing a 1,6-bridge [structure (51): Z = CH_2, O, S, etc.].



(48)



(49)

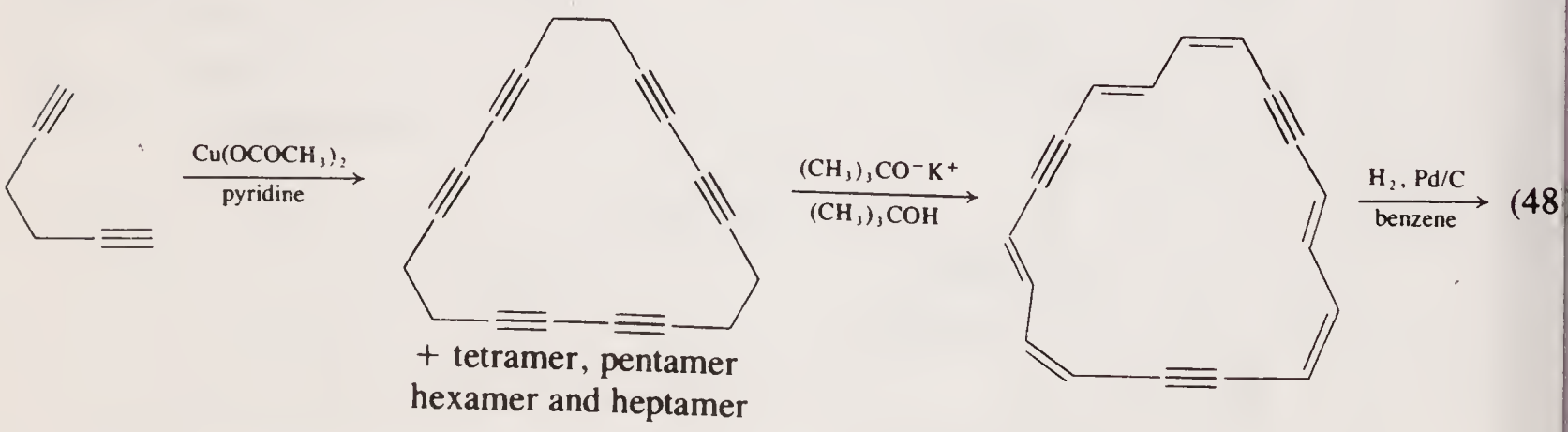


(50)

(51)

16.7.1 [18]Annulene[18]

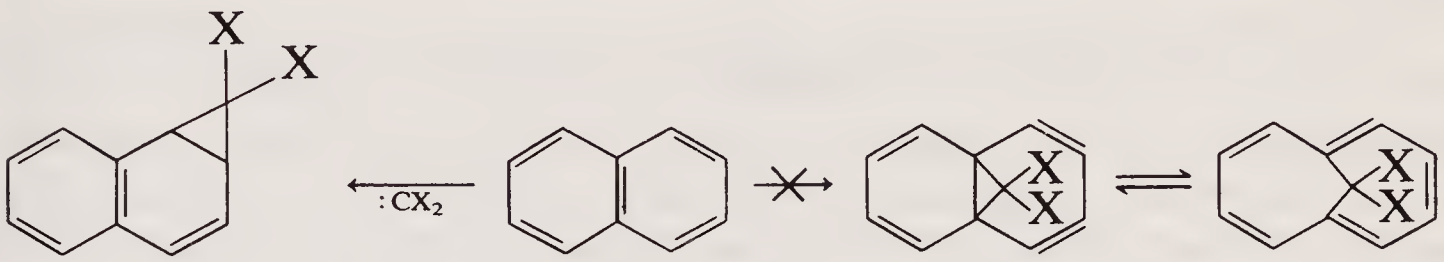
Oxidative coupling of hexa-1,5-diyne under Glaser conditions (section 4.3.2), using a copper(I) salt and oxygen, gives long-chain oligomers. Coupling using copper(II) acetate in pyridine, however, gives cyclic rather than acyclic oligomers; the eighteen-membered ring trimer (52) is present in the mixture to the extent of about 6%. This trimer is convertible into [18]annulene in two simple steps: base-catalysed rearrangement to the fully conjugated trisdehydro[18]annulene,[19] then catalytic hydrogenation. It should be noted that, in this case, an *E*-double bond is produced, and that because of the stability of the 18π-system, there is no need for a reduced-activity catalyst.



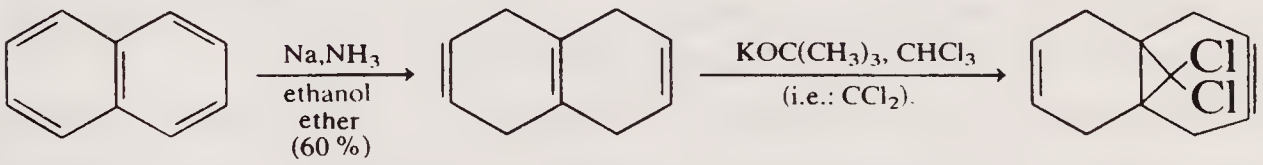
The overall yield from hexa-1,5-diyne is only about 0.7%.

16.7.2 1,6-Methanocyclodecapentaene[20]

This compound, (51:Z = CH_2), is a bridged [10]annulene, and the synthesis of such molecules does not depend on cyclisation to give a ten-membered ring. The target molecule is, formally, derived from naphthalene by addition of :CH_2; however, carbenes add preferentially to the *1,2-bond* of naphthalene to give products in which benzenoid stabilisation of one ring is maintained.

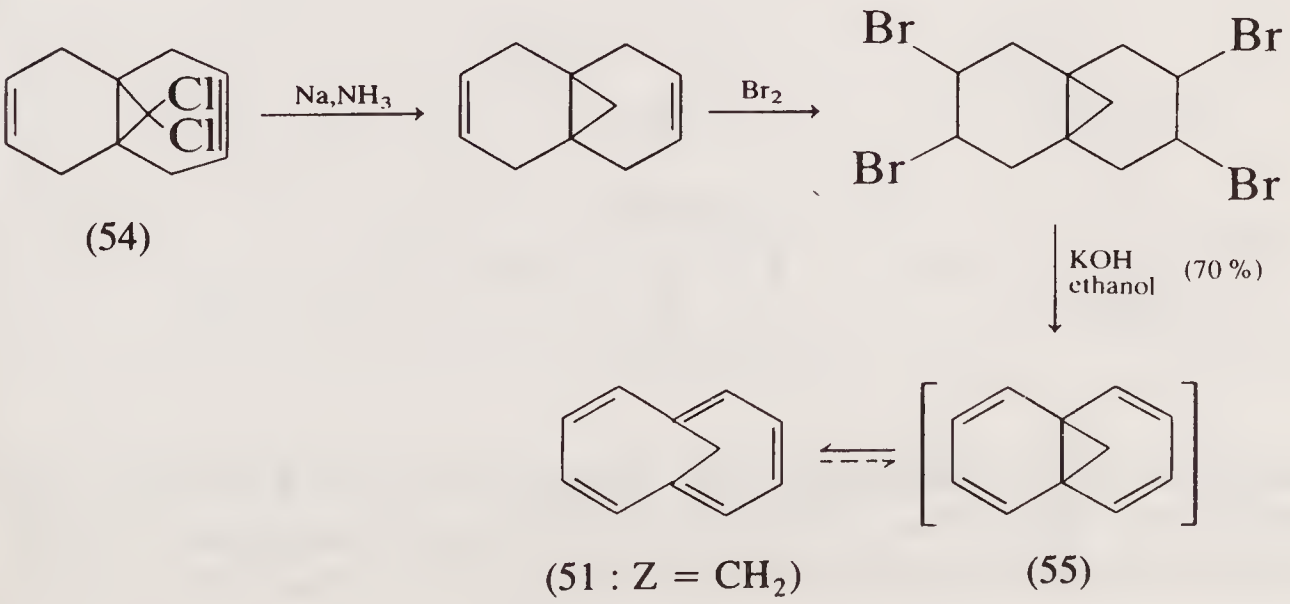


The synthesis therefore begins with Birch reduction (cf. section 8.9) of naphthalene, and addition of dichlorocarbene to the tetrahydro-product (53). It should be noted that addition takes place exclusively at the more reactive tetrasubstituted double bond to form the cyclopropane (54):



(53) (54)

The carbon–halogen bonds in (54) are reductively cleaved by a dissolving metal method. The next step is to introduce two additional double bonds [giving (55)] by a bromination–dehydrobromination procedure (cf. section 9.2.4.2). Compound (55) can undergo pericyclic ring opening (cf. section 7.3) to the desired compound (51:Z = CH_2). Spectroscopic and chemical properties of the product indicate that it is aromatic and therefore has structure (51):



(54)

(51 : Z = CH_2) (55)

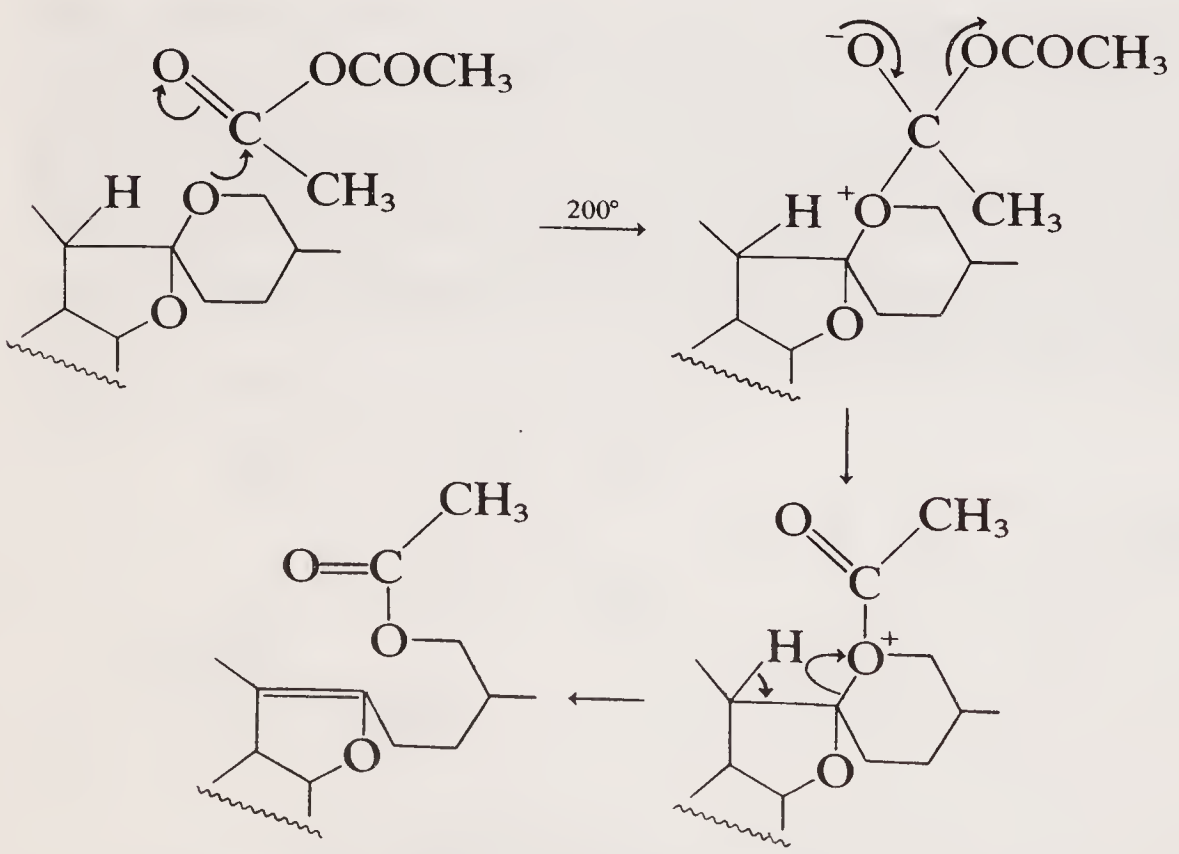
16.8 Steroids: progesterone and cortisone

Steroids have presented a challenge to the synthetic chemist since the early 1930s, when the correct structure of cholesterol was first proposed. Initially these steroid syntheses were attempted in order to verify the structures elucidated (mainly) by degradation of the natural products. Once the importance of some steroids as pharmaceuticals was recognised, however, the need for synthetic sources of these materials became obvious.

The synthesis of steroids from simple compounds (*total synthesis*) was important in the early days to establish the precise structures, including stereochemistry, of the steroid molecules. Such total syntheses, however, do not normally represent practicable commercial syntheses; for example, a total synthesis of cortisone (56) may involve more than thirty stages,[21] and the overall yield is therefore very small (ca. 0.01 %).

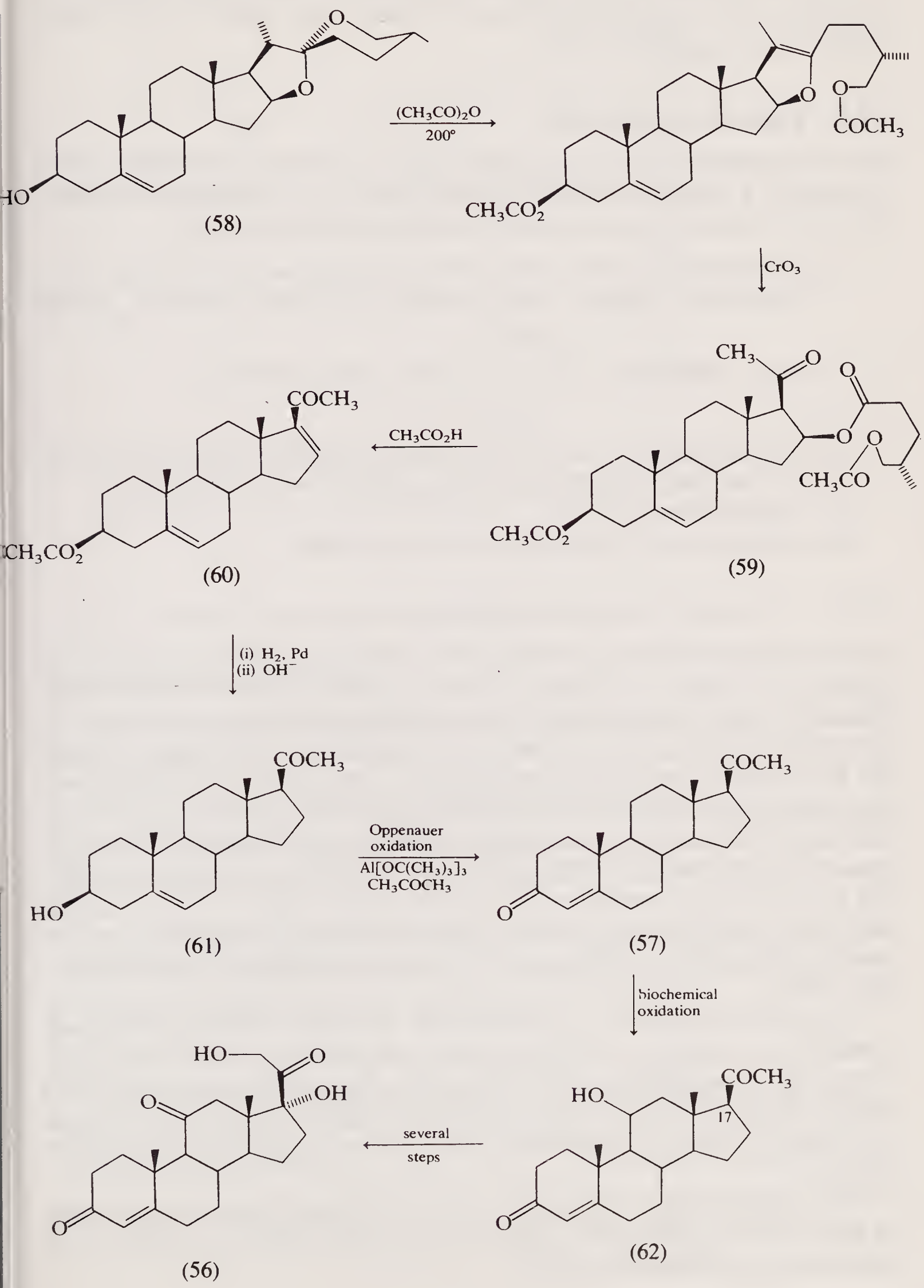
The best solution to this problem, in most cases, is to use as starting material an abundant natural steroid, such as a *sapogenin* (derived from plant glycosides).[22] Such a raw material contains many of the structural features (e.g. stereogenic centres of the correct configuration), and some of the desired functionality, of the final synthetic target molecule. The sequence opposite [23] shows the conversion of diosgenin (58)[22] into the hormone progesterone (57) in an overall yield of ca. 50 %.

In the first step, the hydroxyl group in diosgenin is acetylated, and the six-membered ring of the spiroketal opened, by reaction with acetic anhydride. The product undergoes oxidative ring opening to an ester of a



β-hydroxyketone (59). Acid-catalysed elimination then gives the α,β-unsaturated ketone (60). The α,β-unsaturated ketone is selectively hydrogenated and the acetate hydrolysed to give pregn-5-en-3β-ol-20-one (61).

This can be converted by a number of oxidative procedures including Oppenauer oxidation, into progesterone (57).



Biochemical oxidation of progesterone, using micro-organisms of the *Rhizopus* species, results in the formation of 11α-hydroxyprogesterone (62) in yields as high as 95%. Further oxidation of this hydroxyl group to carbonyl, and elaboration of the 17-substituent, lead in a few more simple steps to cortisone (56).

16.9 Peptide synthesis

This section deals with the principles used in synthesis of peptides rather than giving a detailed account of the synthesis of a particular compound. There are several features common to all peptide syntheses:

(i) protection of amino and carboxyl groups not involved in bond formation, together with protection of other functional groups (e.g. —OH and —C(=NH)NH$_2$) which might interfere;

(ii) minimisation of racemisation of the component amino-acids (this is a problem particularly during peptide bond formation);

(iii) optimisation of yield;

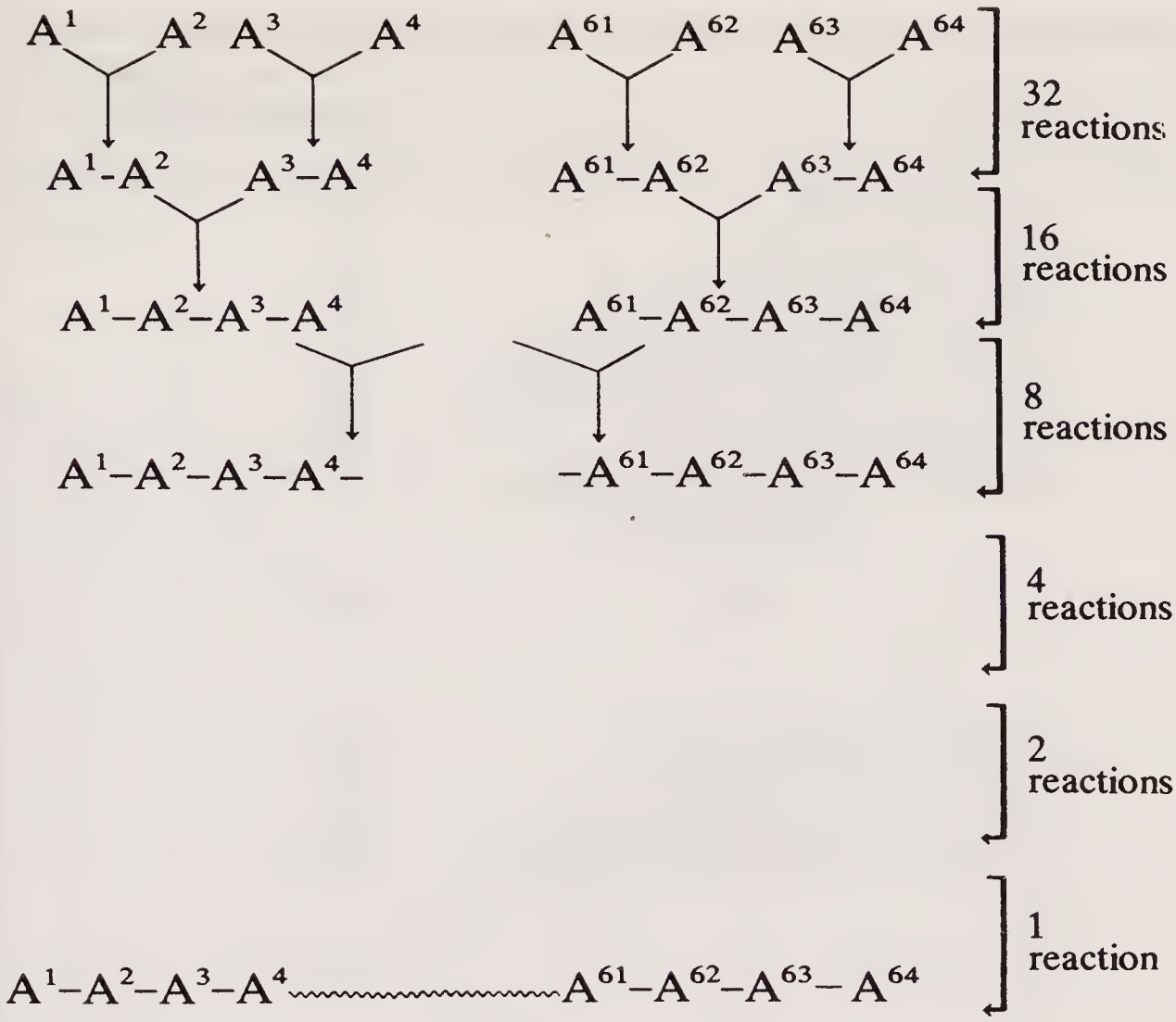
(iv) optimisation of the activity of the product.

16.9.1 Strategy of peptide synthesis

As has been pointed out previously, two extreme possibilities exist for the linking of n amino-acid units to form a peptide. In one, the **linear synthesis,** the chain is extended by one amino-acid unit in each step. The complete synthesis thus involves n—1 peptide bond-forming steps and the final yield is predictably low (e.g. if $n = 64$ and each peptide bond-forming step proceeds in 90% yield, the overall yield is $0.9^{63} \times 100\%$, i.e. 0.13%). In the other, the **convergent synthesis,** amino-acid units are connected in pairs and the resultant dipeptides linked to form tetrapeptides, the process being repeated until all amino-acid units are linked. In this case, if $n = 64$, six sets of reactions depicted below are required, and the overall yield is $0.9^6 \times 100\%$, i.e. 53%, if each individual step proceeds in 90% yield.

In practice, however, a combination of these methods, the **block synthesis,** is normally used. The product is divided into small blocks containing up to, say, fifteen amino-acid units. These blocks are synthesised independently, often by a linear synthesis using the solid phase technique (cf. section 16.9.2.3). The blocks are then connected to form the required peptide.

The original blocks are chosen so that the final connections are made at sites where racemisation either cannot take place or is liable to be unimportant (cf. section 16.9.3).



16.9.2 Techniques of peptide synthesis

16.9.2.1 Protective groups

In order that amino-acids can be linked together in the correct order, it is necessary to protect the amino group in one component and the carboxyl group in the other. The most common protective groups for the amino groups are benzyloxycarbonyl or t-butyloxycarbonyl, because in most cases the use of these groups appears to minimise racemisation at adjacent centres. Acids are usually protected as esters, often as benzyl esters.

Other functional groups (see table 16.1) may also require protection. In particular the guanidinyl group of arginine is nitrated and hydroxyl groups, e.g. in serine, are converted into benzyl ethers.

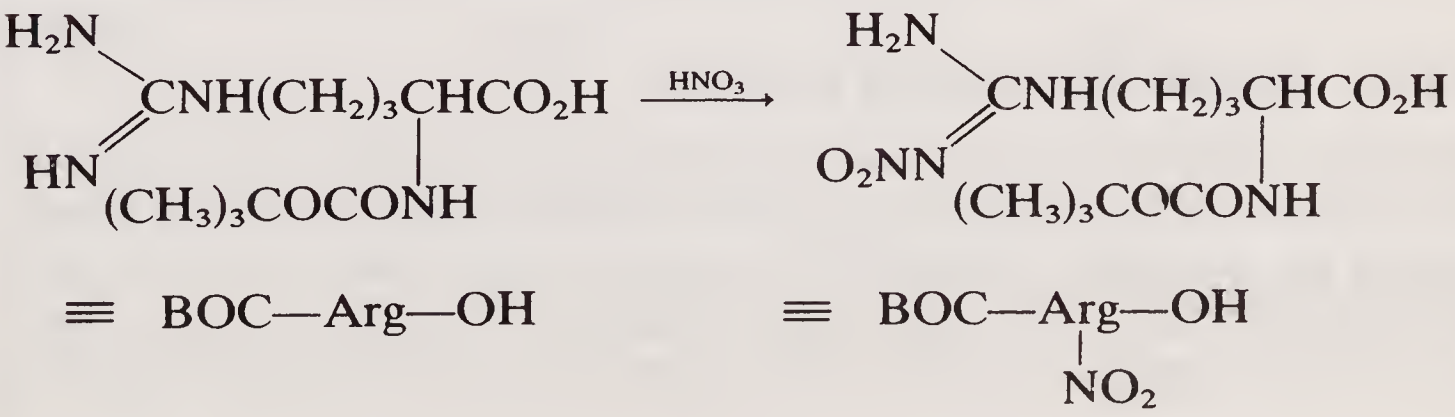
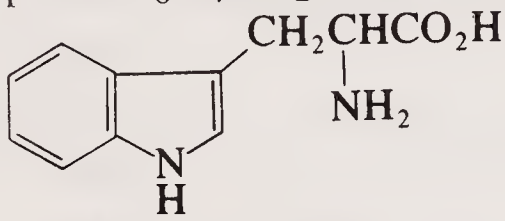
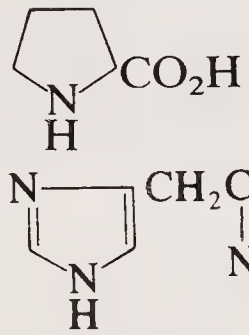
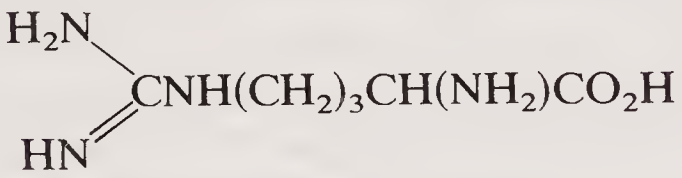


Table 16.1 Structures and abbreviations of common amino acids

Name	Formula	Abbreviation
Glycine	$H_2NCH_2CO_2H$	Gly
Alanine	$CH_3CH(NH_2)CO_2H$	Ala
Valine	$(CH_3)_2CHCH(NH_2)CO_2H$	Val
Leucine	$(CH_3)_2CHCH_2CH(NH_2)CO_2H$	Leu
Isoleucine	$CH_3CH_2CH(CH_3)CH(NH_2)CO_2H$	Ile
Phenylalanine	$PhCH_2CH(NH_2)CO_2H$	Phe
Tyrosine	p-$HOC_6H_4CH_2CH(NH_2)CO_2H$	Tyr
Tryptophan		Trp
Cysteine	$HSCH_2CH(NH_2)CO_2H$	Cys
Serine	$HOCH_2CH(NH_2)CO_2H$	Ser
Threonine	$CH_3CH(OH)CH(NH_2)CO_2H$	Thr
Methionine	$CH_3SCH_2CH_2CH(NH_2)CO_2H$	Met
Proline		Pro
Histidine		His
Aspartic acid	$HO_2CCH_2CH(NH_2)CO_2H$	Asp
Asparagine	$H_2NCOCH_2CH(NH_2)CO_2H$	Asn
Glutamic acid	$HO_2CCH_2CH_2CH(NH_2)CO_2H$	Glu
Glutamine	$H_2NCOCH_2CH_2CH(NH_2)CO_2H$	Gln
Arginine		Arg
Lysine	$H_2N(CH_2)_4CH(NH_2)CO_2H$	Lys

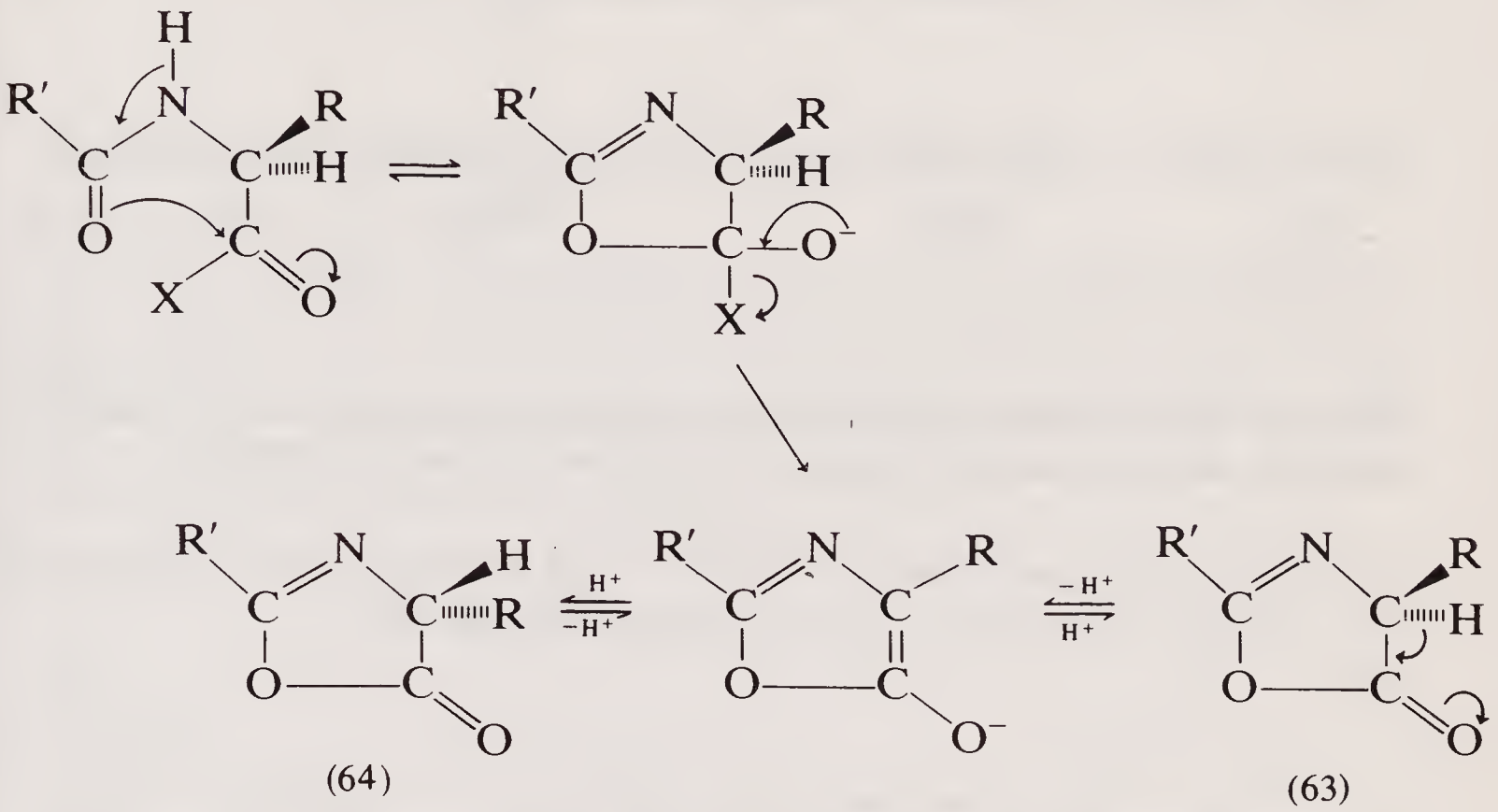
Benzyl groups are removed from the product by treatment with HBr in trifluoroacetic acid and nitro groups by catalytic hydrogenation.

16.9.2.2 Peptide bond-forming reactions

The basic reaction involved here is the linking of an amino group in one unit with the carboxyl group of another forming an amide (or peptide). Amides are normally prepared by reaction of an amine with an acid chloride, an ester, or an anhydride. Analogues of the last two are commonly used in peptide synthesis, but the use of an acid chloride leads to

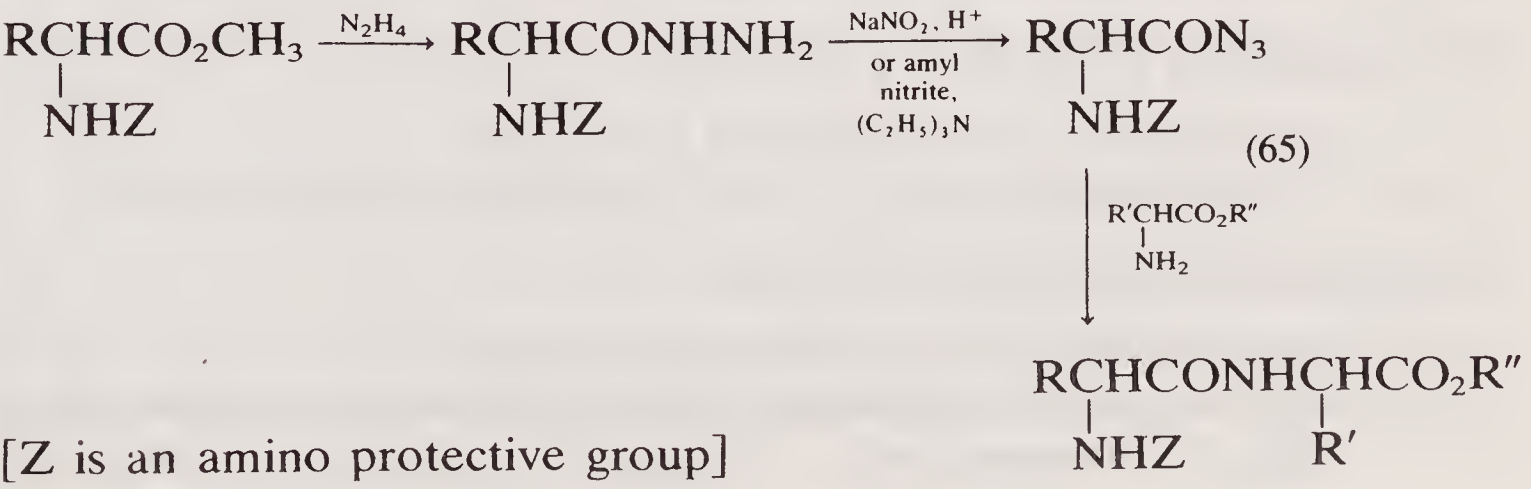
extensive racemisation of the amino-acid and this method is not therefore used here.

Racemisation during peptide bond formation results from the formation of an oxazolone (63) which readily racemises [(63) ⇌ (64)] as shown:



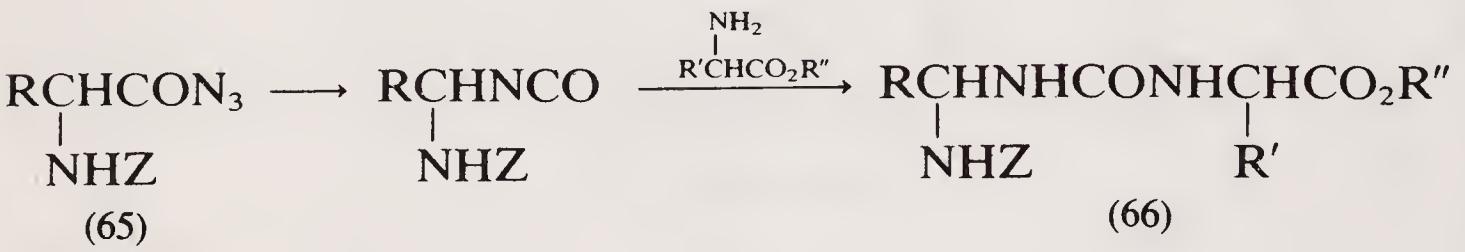
The rate of racemisation is dependent on the groups R, R′, and X. R′CO may either be the protective group for the free amino group (in which case racemisation may be minimised when R′CO is $PhCH_2OCO$ or $(CH_3)_3COCO$) or the remainder of the peptide chain (in which case little can be done to affect the degree of racemisation induced). R is determined by the amino-acid to be linked to the chain and cannot therefore be modified.[24] X is the group used to activate the acid, and a few of the more commonly used methods for carboxyl group activation are described below.

(a) *Azide method.* The reaction sequence involved in this method is outlined below:



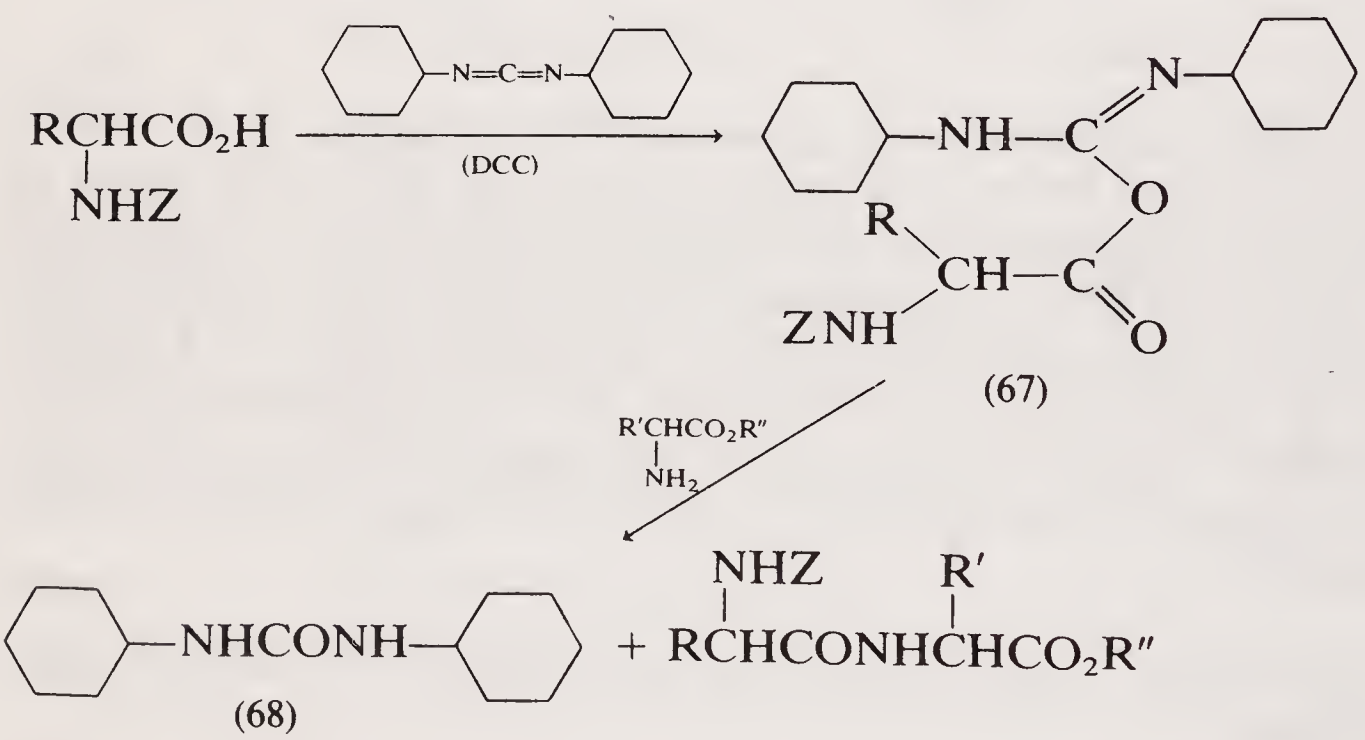
[Z is an amino protective group]

The main advantage of the method is that it results in a very small amount of racemisation but there are two major disadvantages: (i) the number of steps which are involved in $—CO_2H \rightarrow —CO_2CH_3 \rightarrow CONHNH_2 \rightarrow CON_3 \rightarrow CONHR$; and (ii) Curtius rearrangement of the azide (65) is a side-reaction; this leads to a urea derivative (66) which is difficult to separate from the peptide:



This method is often used in block synthesis where it is not feasible to connect blocks at either glycine or proline (cf. section 16.9.3).

(b) *Dicyclohexylcarbodiimide* (DCC). This involves the conversion of the carboxyl group into a type of activated ester (67):



The advantages of the DCC method are:

(i) good yields in a short reaction time; and
(ii) low racemisation when $Z = (CH_3)_3COCO$ or $PhCH_2OCO$.

Disadvantages include the following:

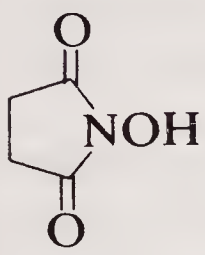
(i) racemisation if Z is an amino-acid residue;
(ii) contamination of the product with dicyclohexylurea (68) which is difficult to remove; and

(iii) reaction of activated ester (67) with the *N*-protected amino-acid to give an anhydride (69) which may be difficult to separate from the peptide:

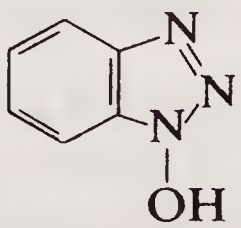
$$(67) \xrightarrow{\text{ZNHCHRCO,H}} \underset{(69)}{(\text{ZNHCHRCO})_2\text{O}} + (68)$$

DCC is the condensing agent most commonly used in the solid phase method (cf. section 16.9.2.3).

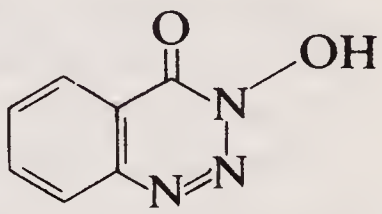
The use of additives minimises any racemisation encountered in the DCC method. The additives [*N*-hydroxysuccinimide (70), *N*-hydroxybenzotriazole (71) and 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one (72) have been quite widely used] react rapidly with the activated ester (67) to form very reactive intermediates, e.g. (73), which react with the protected amino-acid before significant racemisation can take place.



(70)



(71)

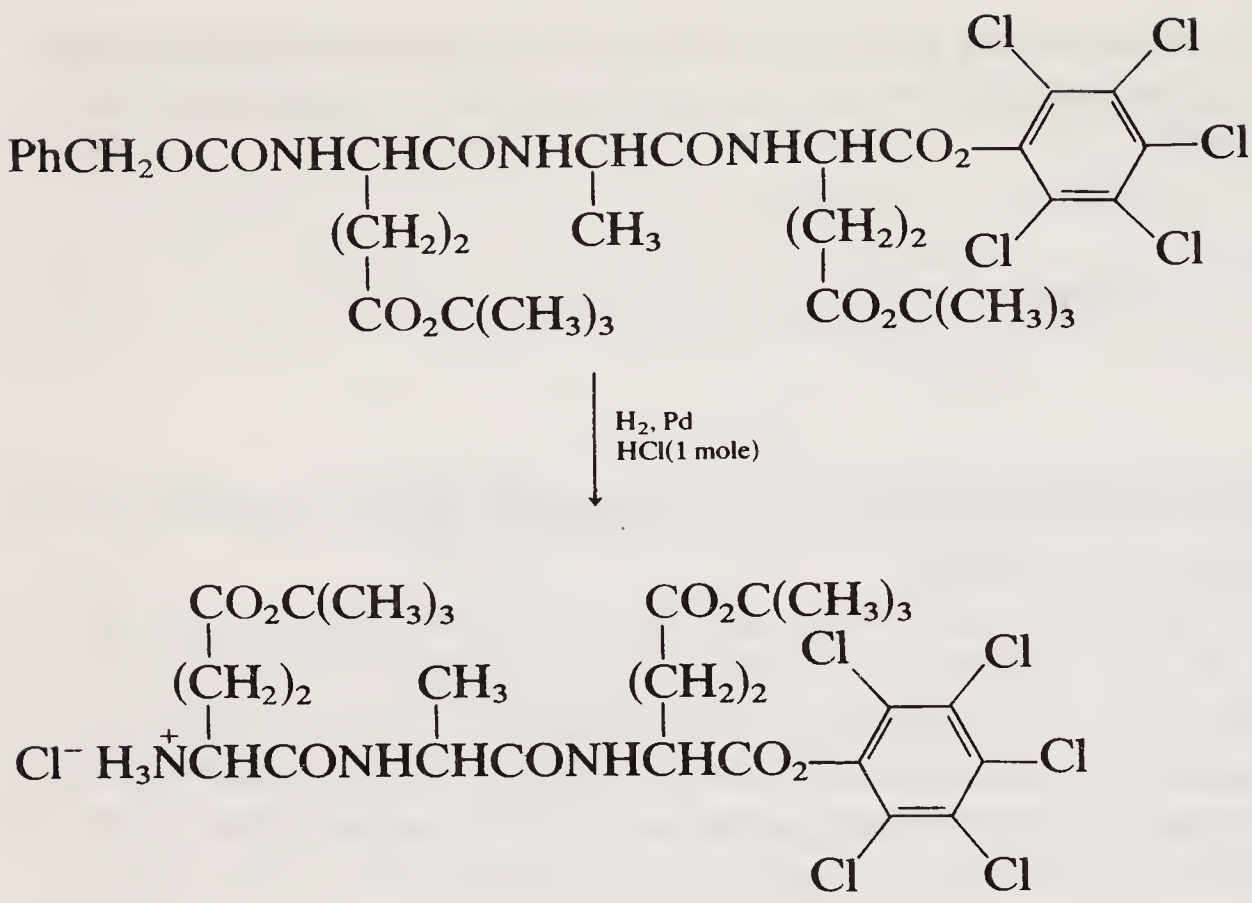


(72)

$$(70) + (67) \longrightarrow \underset{(73)}{\text{ZNHCHRC(=O)ON(C(=O)CC2)C2=O}} + (68)$$

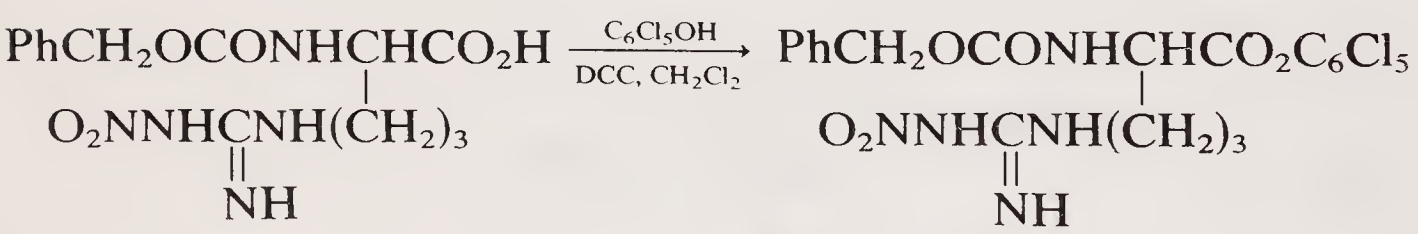
(c) *Active ester method.* If the carboxyl group can be readily converted to an ester which reacts rapidly with the free amino group, peptide bond formation takes place in high yield under mild conditions. Many esters have been investigated, including *p*-nitrophenyl and thiophenyl, but one of the most successful is the pentachlorophenyl ester.

Pentachlorophenyl esters are among the most reactive of all esters, and those of amino-acids usually have higher melting points than those of other active esters. In addition, unlike *p*-nitrophenyl and thiophenyl esters, they are stable to catalytic hydrogenation and thus are suitable when selective removal of, for example, benzyloxycarbonyl groups by catalytic hydrogenation is required:



Racemisation is particularly low and it is considered that this is due to the steric requirement of the 2- and 6-chlorine atoms which hinder oxazolone formation.

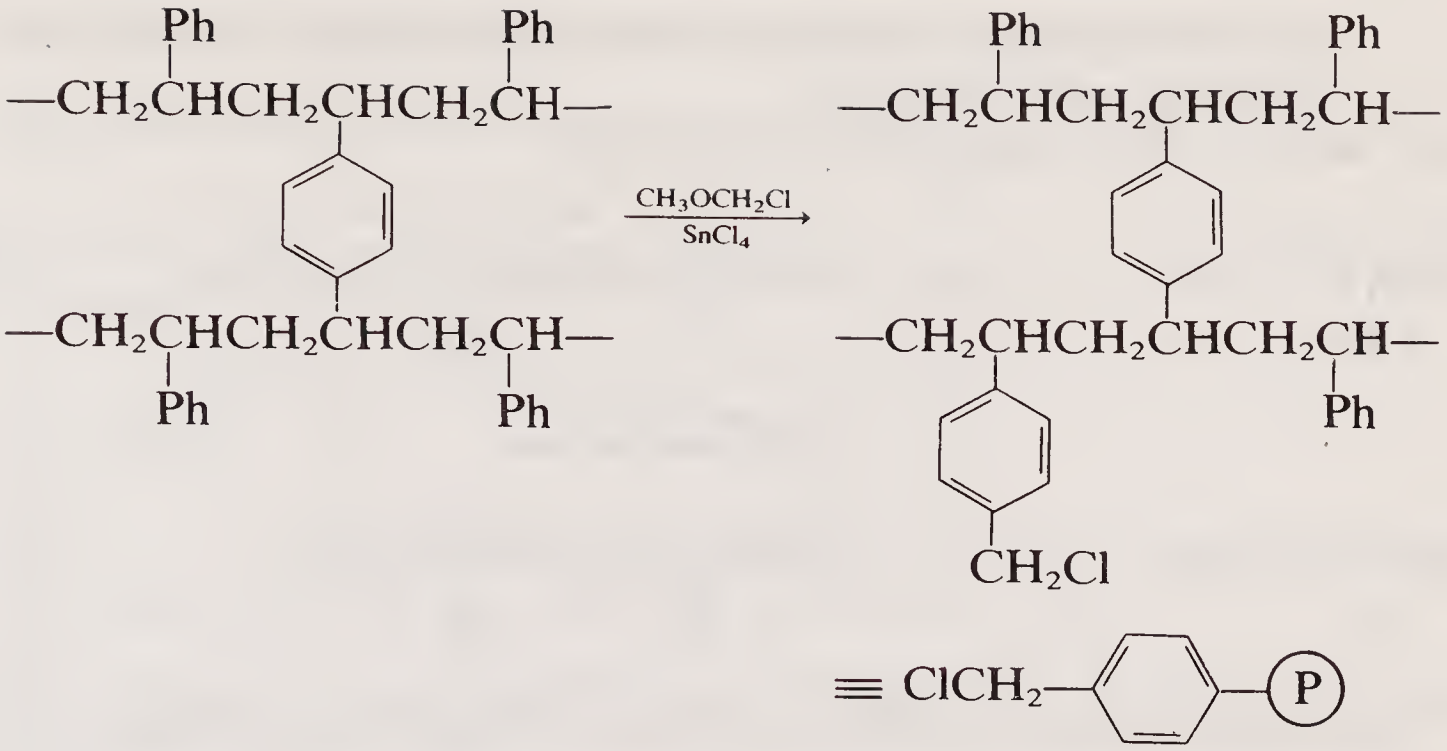
Pentachlorophenyl esters can be prepared from the amino-acid either by reaction with pentachlorophenol in presence of dicyclohexylcarbodiimide or by reaction with pentachlorophenyl trichloroacetate in presence of triethylamine:



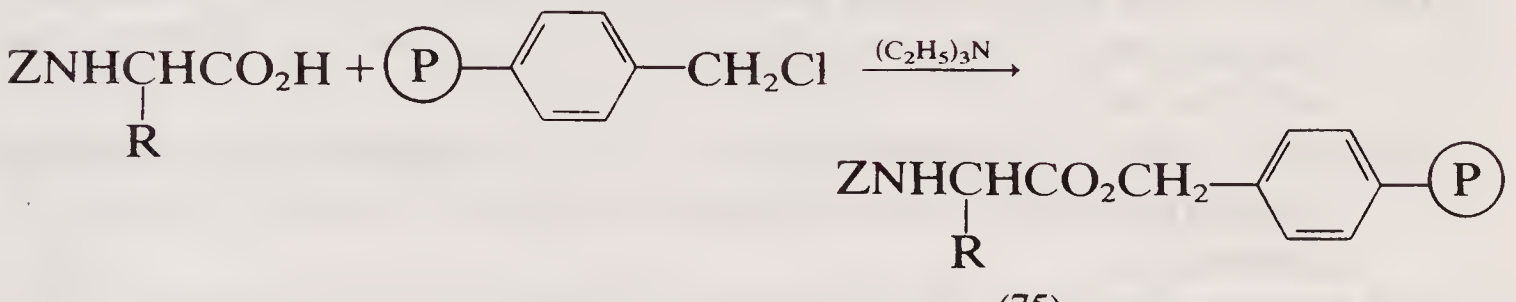
16.9.2.3 Solid-phase peptide synthesis

One of the major advances in peptide synthesis came in 1962, when Merrifield first described a synthesis of a tetrapeptide, Leu–Ala–Gly–Ala, by a solid-phase technique which is now often associated with his name. The method involves the following steps:

(i) attachment of an *N*-protected amino-acid to a styrene–divinylbenzene co-polymer which has had 5 % of its phenyl groups chloromethylated (74):



(74)

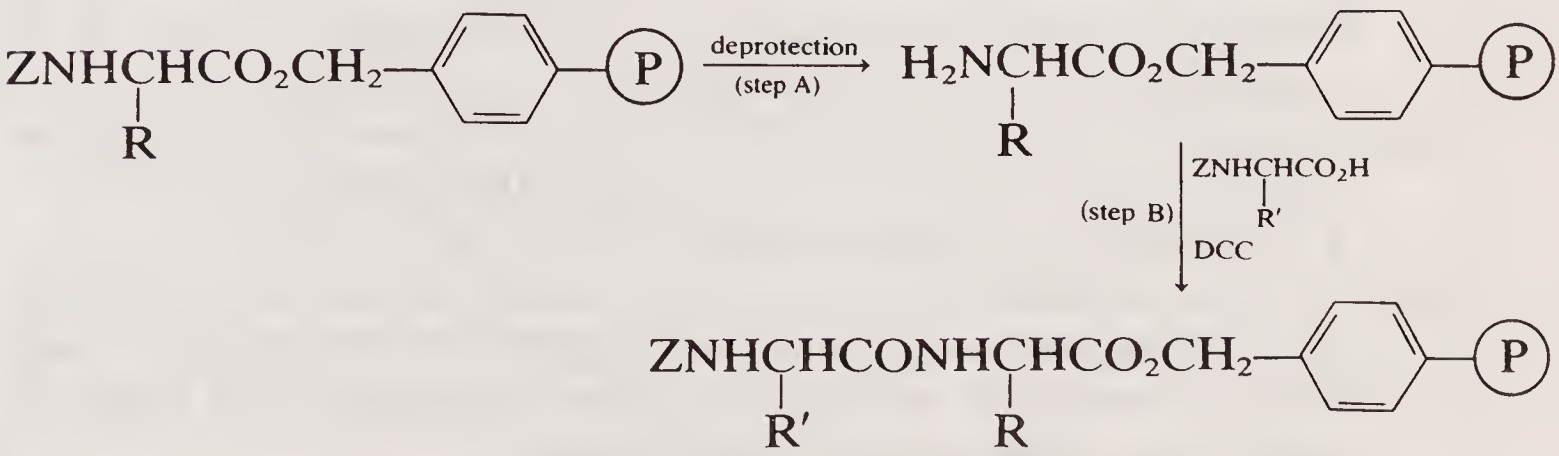


(75)

[It should be noted that (75) is a substituted benzyl ester, and hence this step not only attaches the amino-acid to the polymer support but also protects the carboxyl group.]

(ii) removal of the *N*-protective group (step A);

(iii) reaction of the free amino group with an *N*-protected amino-acid[25] often using DCC (with or without additives) as condensing agent (step B):

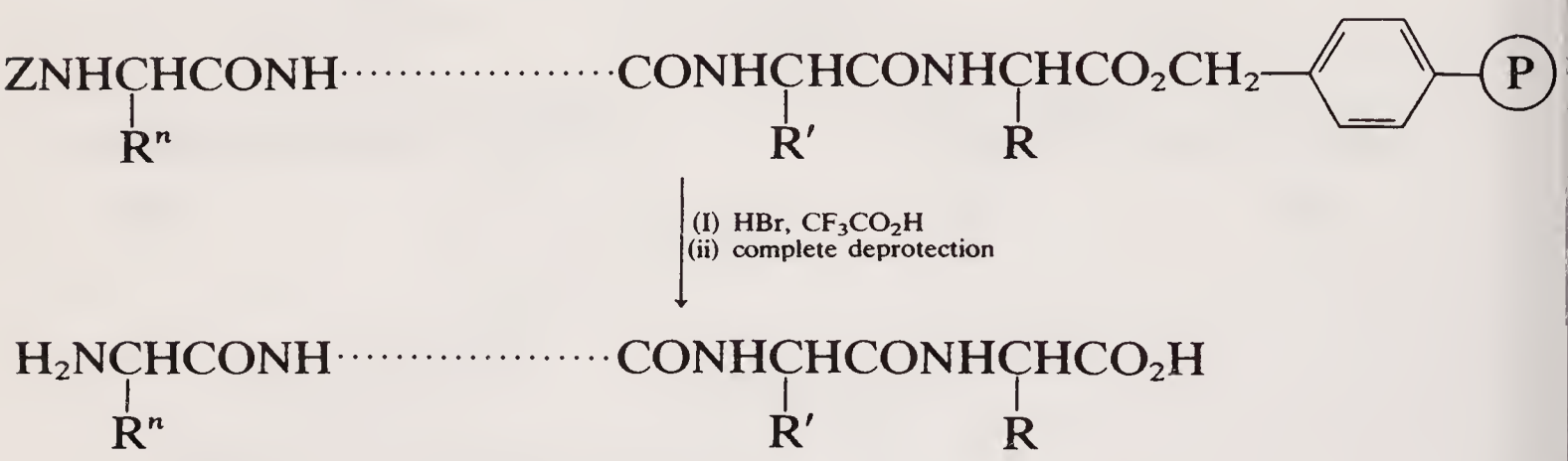


(iv) repetition of steps A and B using the required *N*-protected amino-acid until all the desired amino-acid units have been connected;

(v) removal of the protected peptide from the polymer, often using HBr in trifluoroacetic acid. This reagent will also remove many

protective groups including *N*-benzyloxy carbonyl, *N*-t-butyloxy-carbonyl, and *O*-benzyl;

(vi) removal of all other protective groups.



Advantages of the Merrifield technique include the following:

(i) reactions are rapid and high yields are obtained;
(ii) little or no racemisation takes place if Z is t-butyloxy- or benzyloxy-carbonyl, since reaction takes place at the *N*-protected amino-acid;
(iii) purification of intermediates involves nothing more than washing the polymer free of non-polymeric reagents if reaction has gone to completion;
(iv) the procedure can be automated. Efficient automatic peptide synthesisers are commercially available.

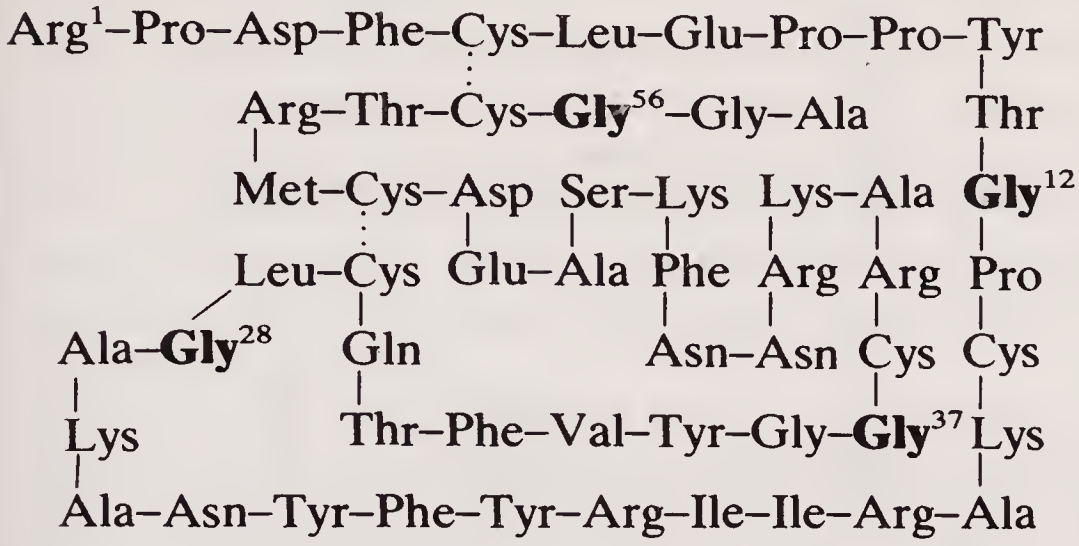
Limitations include the following:

(i) incomplete attachment of the *C*-terminal amino-acid A^1 to the benzyl groups of the polymer may lead to impurities; e.g. in the synthesis of a pentapeptide A^1-A^2-A^3-A^4-A^5 if all the chloromethyl groups on the polymer do not react with A^1, the second amino-acid A^2 may react with the remaining chloromethyl groups as well as (or instead of) with Ⓟ–A^1. The result is the formation of the tetrapeptides A^2-A^3-A^4-A^5 and A^1-A^3-A^4-A^5 as contaminants of the pentapeptide.
(ii) incomplete coupling of the *N*-protected amino-acid with the free amino group (step B) can lead to truncated peptides (e.g. A^1-A^2-A^3) and failure sequences (e.g. A^1-A^2-A^4-A^5);
(iii) lack of analytical techniques for the detection of impurities which do not necessitate removal of the peptide from the polymer. Such removal would be wasteful and time-consuming and might in itself lead to degradation of the product.

16.9.3 Synthesis of a higher molecular weight peptide, Basic Trypsin Inhibitor (BTI) from bovine pancreas

This peptide containing fifty-eight amino acid units (MW ca. 6500) has

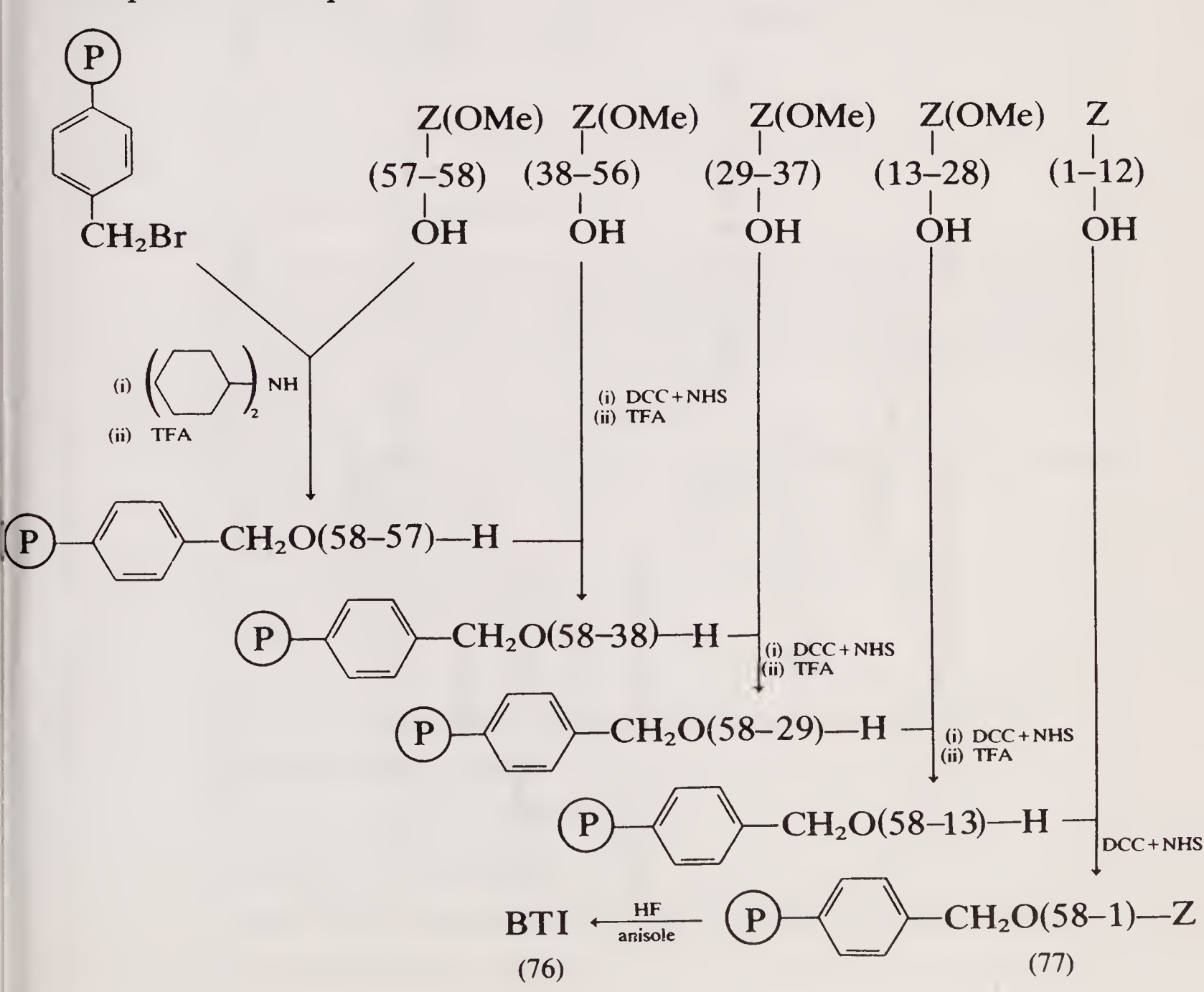
been shown to have the following sequence of amino-acid units:



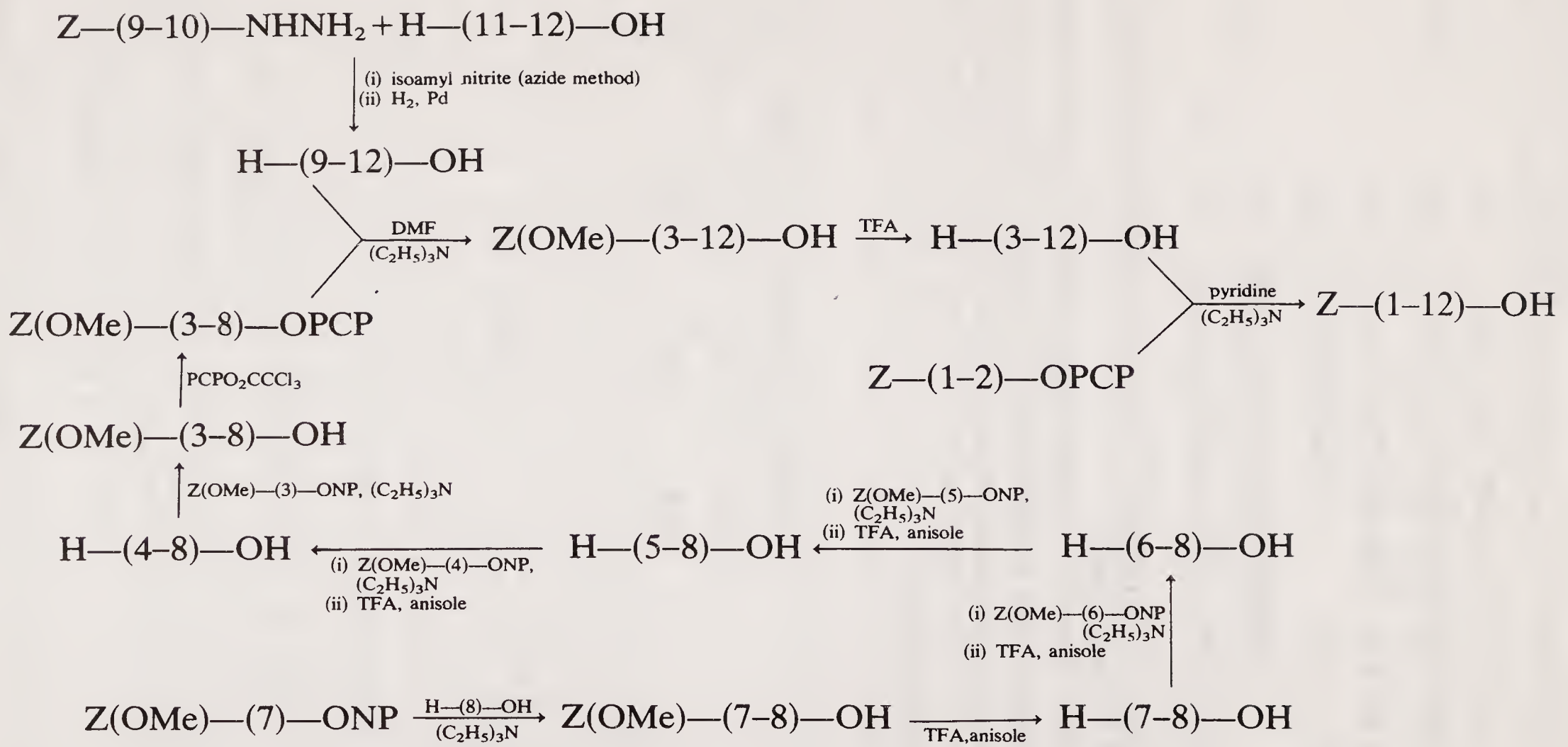
(76)

The synthesis of this peptide[26] serves to illustrate a strategy which can be adopted in such cases.

The method involves synthesising blocks[27] which eventually are linked at glycine units [indicated in bold type in (76)] in order to eliminate problems of racemisation in the final stages. Thus peptides (1–12), (13–28), (29–37), (38–56), and (57–58) are synthesised and linked by a solid-phase technique.



(76) (77)


Z—(9–10)—NHNH2 + H—(11–12)—OH
(i) isoamyl nitrite (azide method)
(ii) H2, Pd
H—(9–12)—OH
DMF
(C2H5)3N
Z(OMe)—(3–12)—OH
TFA
H—(3–12)—OH
pyridine
(C2H5)3N
Z—(1–12)—OH
Z(OMe)—(3–8)—OPCP
PCPO2CCCl3
Z—(1–2)—OPCP
Z(OMe)—(3–8)—OH
Z(OMe)—(3)—ONP, (C2H5)3N
H—(4–8)—OH
(i) Z(OMe)—(4)—ONP,
(C2H5)3N
(ii) TFA, anisole
H—(5–8)—OH
(i) Z(OMe)—(5)—ONP,
(C2H5)3N
(ii) TFA, anisole
H—(6–8)—OH
(i) Z(OMe)—(6)—ONP
(C2H5)3N
(ii) TFA, anisole
Z(OMe)—(7)—ONP
H—(8)—OH
(C2H5)3N
Z(OMe)—(7–8)—OH
TFA,anisole
H—(7–8)—OH

Gly–Ala, *N*-protected with a *p*-methoxybenzyloxycarbonyl group [Z(OMe)–Gly–Ala] is linked to a bromomethylated styrene–divinylbenzene co-polymer. Each peptide block [(38–56), (29–37), (13–28), and (1–12)] is then successively linked to the extending peptide chain using DCC with additive [*N*-hydroxysuccinimide (NHS)] as condensing agent. The active peptide is finally removed from the polymer and deprotected by treatment with HF. This is summarised in the scheme on p. 365. The overall yield of (77) is ca. 40% from which only 10% of purified active (76) can be obtained.

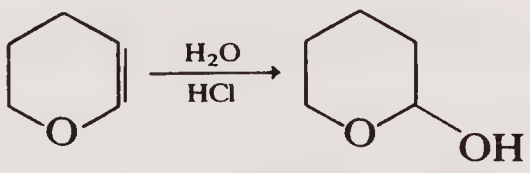
The blocks are synthesised by linking sub-blocks prepared by either linear or convergent synthesis. In the case of the block consisting of units 1–12, the linkage of sub-blocks was performed at proline units where racemisation is minimal. In most cases, linking was performed by the active ester method using either pentachlorophenyl (PCP) or *p*-nitrophenyl (NP) esters. The synthesis of the *N*-benzyloxycarbonyl protected block 1–12 [Z—(1–12)—OH] is outlined on p. 366.

In the other cases, proline units are not available as sites at which to link sub-blocks, and the final linkages of the sub-blocks are made by the azide method which is less liable to induce racemisation.

The overall activity of the product (80%) is superior to that obtained (30%) in a linear Merrifield synthesis.

Notes

1. *J. Org. Chem.*, **40,** 1593 (1975).
2. P-2 nickel is prepared by reduction of nickel(II) acetate by sodium borohydride. When poisoned with ethylenediamine, it can be used as a catalyst for hydrogenation of alkynes to alkenes with $Z:E > 97:1$. Yields are high and it is, therefore, an alternative to the Lindlar catalyst for this transformation.
3. *J. Chem. Soc. Perkin Trans. 1*, **1978**, 842.
4. 2-Hydroxytetrahydropyran is prepared by acid-catalysed addition of water to 2,3-dihydropyran.



5. *J. Org. Chem.*, **41,** 2927 (1976); cf. *Helv. Chim. Acta*, **53,** 1479 (1970).
6. *Tetrahedron Letters*, **1976**, 3953.
7. *J. Am. Chem. Soc.*, **96**, 7842 (1974).
8. *Tetrahedron Letters*, **1977,** 4009.
9. *J. Chem. Soc.* (*C*), **1969**, 1024; *J. Chem. Soc., Chem. Commun.*, **1972**, 529.
10. *J. Org. Chem.*, **37**, 2363 (1972).

11. cf. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, 1976, p. 143; W. T. Brady, *Tetrahedron*, **37,** 2949 (1981).

12. An alternative technique, applicable to the synthesis of 1-chloroalkynes, is described in section 16.2.

13. cf. Chapter 10, note 1 (p. 245).

14. *J. Am. Chem. Soc.*, **78**, 4765 (1956).

15. *Tetrahedron*, **28**, 1749 (1972); *Tetrahedron Letters*, **1968**, 3507.

16. *J. Am. Chem. Soc.*, **104**, 879 (1982); **107**, 682 (1985); **109**, 5446 (1987).

17. TMEDA = **tetra**methyl**ethylene**-**dia**mine [1,2-bis(dimethylamino)ethane].

18. *Pure Appl. Chem.*, **7,** 363 (1963).

19. Hexa-1,5-diyne itself undergoes base-catalysed rearrangement to hexa-1,3-dien-5-yne:

$$HC{\equiv}CCH_2CH_2C{\equiv}CH \xrightarrow[(CH_3)_3COH]{(CH_3)_3CO^-K^+} CH_2{=}CH{-}CH{=}CH{-}C{\equiv}CH \quad (33\%\ \text{isolated}).$$

20. Chem. Soc. Special Publication No. 21 (1967), p. 113; *Angew. Chem., Internat. Edit.*, **3,** 228 (1964).

21. *J. Am. Chem. Soc.*, **74,** 1393, 1405, 4974 (1952); **75,** 422, 1707, 2112 (1953); **76,** 1715, 5026, 6031 (1954).

22. Diosgenin is a member of the class of compounds known as *sapogenins*. *Saponins* are widely distributed plant glycosides in which the sapogenin is combined with one or more sugar residues. Hydrolysis with acid or enzyme converts the saponin into the sapogenin and the sugar(s).

23. C. W. Shoppee, *Chemistry of the Steroids*, Second Edition, Wiley, 1964, Chapter 6.

24. It should be noted that glycine is achiral and so cannot be racemised, and that proline has a low tendency to racemisation. Block synthesis is commonly carried out so that blocks are linked at glycine or at proline units (cf. section 16.9.3).

25. Other functional groups on the amino acid may also have to be protected (cf. section 16.9.2.1).

26. *Chem. Pharm. Bull.* (*Tokyo*), **22,** 1061, 1067, 1075, 1079, 1087 (1974).

27. Other functional groups on the constituent amino acids are suitably protected.

Further reading

This list of books and review articles is intended to help readers to locate some more advanced or more detailed accounts of topics referred to in this book. A number of the reviews (especially those from *Organic Reactions*) include experimental instructions.

General

R. O. C. Norman, *Principles of Organic Synthesis*, Second Edition, Chapman and Hall, 1978.

W. Carruthers, *Some Modern Methods of Organic Synthesis*, Third Edition, Cambridge University Press, 1987.

H. O. House, *Modern Synthetic Reactions*, Second Edition, Benjamin, 1972.

F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, Second Edition, Plenum Press, 1983.

Chapter 2

Free radical additions to alkenes

J. M. Tedder and J. C. Walton, *Tedrahedron*, **36,** 701 (1980).

J. M. Tedder, *Angew. Chem., Internat. Edit.*, **21,** 401 (1982).

Transformations of aliphatic amines via pyridinium salts

A. R. Katritzky, *Tetrahedron*, **36**, 679 (1980).

A. R. Katritzky and C. M. Marson, *Angew. Chem., Internat. Edit.*, **23**, 420 (1984).

Chapter 3

S. Warren, *Organic Synthesis: the Disconnection Approach*, Wiley, 1982.

S. Warren, *Designing Organic Syntheses: A Programmed Introduction to the Synthon Approach*, Wiley, 1978.

E. J. Corey, *Pure and Applied Chemistry*, **14,** 19 (1967).

Chapter 4

General

Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Vols. 13/1 (1970) and 13/2a (1973) (both in German).
E. Negishi, *Organometallics in Organic Synthesis*, Wiley, Vol. 1 (1979).

Grignard reagents

M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, 1954.
B. Blagoev and D. Ivanov, *Synthesis*, **1970,** 615.
B. J. Wakefield, *Chem. and Ind.*, **1972**, 450.

Organolithium reagents

J. M. Brown, *Chem. and Ind.*, **1972,** 454.
D. Ivanov, G. Vassilev and I. Panayotov, *Synthesis*, **1975,** 83.
B. J. Wakefield, *Organolithium Methods*, Academic Press, 1988.

Copper-catalysed reactions of Grignard and organolithium reagents

E. Erdik, *Tetrahedron* **40,** 641 (1984).

Reformatsky reaction

R. L. Shriner, *Org. Reactions*, **1,** 1 (1942).
M. W. Rathke, *Org. Reactions*, **22,** 423 (1975).

Organocadmium reagents

P. R. Jones and P. J. Desio, *Chem. Rev.*, **78**, 491 (1978).

Organocopper reagents

G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, Wiley, 1980.
J. F. Normant, *Synthesis*, **1972,** 63.
G. H. Posner, *Org. Reactions*, **19,** 1 (1972); **22,** 253 (1975).
B. H. Lipshutz, R. S. Wilhelm and J. A. Kozlowski, *Tetrahedon*, **40,** 5005 (1984) ('higher-order' cuprates).
J. Lindley, *Tetrahedron*, **40,** 1433 (1984) (nucleophilic substitution of aryl halides).
R. J. K. Taylor, *Synthesis*, **1985**, 364 (conjugate addition).

Oxidative coupling

(General) T. Kauffman, *Angew. Chem., Internat. Edit.*, **13,** 291 (1974).
(Alk-1-ynes) G. Eglinton and W. McCrae, *Adv. Org. Chem.*, **4,** 225 (1963).

Chapter 5

Dianions of β-dicarbonyl compounds

T. M. Harris and C. M. Harris, *Org. Reactions*, **17,** 155 (1969).

Knoevenagel condensation

G. Jones, *Org. Reactions*, **15,** 204 (1967).

Michael addition

E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. Reactions*, **10,** 179 (1959).

Alkylation of aldehydes and ketones *via* metal enolates

D. Caine, in *Carbon–Carbon Bond Formation*, ed. R. L. Augustine, Marcel Dekker, Vol. 1, 1979, Chapter 2.

Claisen acylation ('ester condensation')

C. R. Hauser and B. E. Hudson, *Org. Reactions*, **1,** 266 (1942).

Dihydro-1,3-oxazines

A. I. Meyers, *Heterocycles in Organic Synthesis*, Wiley, 1974, pp. 201–205.
R. R. Schmidt, *Synthesis*, **1972,** 333.

Aldol condensation

A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, **16,** 1 (1968).
Z. G. Hajos, in *Carbon–Carbon Bond Formation*, ed. R. L. Augustine, Marcel Dekker, Vol. 1, 1979, Chapter 1.

Wittig reaction

S. Trippett, *Quart. Rev.*, **17,** 406 (1963).
A. Maercker, *Org. Reactions*, **14**, 270 (1965).
I. Gosney and A. G. Rowley, in *Organophosphorus Reagents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic Press, 1979, Chapter 2.
E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **110**, 3948 (1988).

1,3-Dithians (and 1,3,5-trithians)

D. Seebach, *Synthesis*, **1969,** 17 (in German).
B.-T. Gröbel and D. Seebach, *Synthesis*, **1977,** 357 (in English, but a more advanced review).

Enamines

S. F. Dyke, *The Chemistry of Enamines*, Cambridge University Press, 1973.
P. W. Hickmott and H. Suschitzky, *Chem and Ind.*, **1970,** 1188.
M. A. Kuehne, *Synthesis*, **1970,** 510.
P. W. Hickmott, *Tetrahedron*, **38,** 1975 and 3363 (1982).
P. W. Hickmott, *Tetrahedron*, **40**, 2989 (1984) (conjugated enamines).
J. K. Whitesell and M. A. Whitesell, *Synthesis*, **1983**, 517.

Gattermann reaction

W. E. Truce, *Org. Reactions*, **9,** 37 (1957).

Gatterman–Koch reaction

N. N. Crounse, *Org. Reactions*, **5,** 290 (1949).

Hoesch reaction

P. E. Spoerri and A. S. DuBois, *Org. Reactions*, **5,** 387 (1949).

Vilsmeier–Haack–Arnold reaction

C. Jutz, *Adv. Org. Chem.*, **9/1,** 225 (1976).

Reimer–Tiemann reaction

H. Wynberg, *Chem. Rev.*, **60,** 169 (1960).
H. Wynberg and E. W. Meijer, *Org. Reactions*, **28,** 1 (1982).

Kolbe–Schmitt reaction

A. S. Lindley and H. Jeskey, *Chem. Rev.*, **57,** 583 (1957).

Mannich reaction

F. F. Blicke, *Org. Reactions*, **1,** 303 (1942).
M. Tramontini, *Synthesis*, **1973**, 703.

Thermal Michael reaction

G. L. Buchanan *et al.*, *Tetrahedron*, **25,** 5517 (1969), and references therein.

Umpolung (general)

D. Seebach, *Angew. Chem., Internat. Edit.*, **18,** 239 (1979).
H. Stetter, *Angew. Chem., Internat. Edit.*, **15,** 639 (1976).

Chapter 7

Dieckmann and Thorpe–Ziegler reactions

J. P. Schaefer and J. J. Bloomfield, *Org. Reactions*, **15,** 1 (1967).

Acyloin reaction

K. T. Finley, *Chem. Rev.*, **64,** 573 (1964).

Robinson annulation

R. E. Gawley, *Synthesis*, **1976,** 777.

Pericyclic reactions (general)

I. Fleming, *Frontier Orbitals and Organic Reactions*, Wiley, 1976.
T. L. Gilchrist and R. C. Storr, *Organic Reactions and Orbital Symmetry*, Second Edition, Cambridge University Press, 1979.
W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, 1988.

Diels–Alder reaction

J. A. Norton, *Chem. Rev.* **31,** 319 (1942).
J. G. Martin and R. K. Hill, *Chem. Rev.*, **61,** 537 (1961).
M. Petrzilka and J. I. Grayson, *Synthesis*, **1981,** 753 (hetero-substituted dienes).
O. De. Lucchi and G. Modena, *Tetrahedron*, **40**, 2585 (1984) (acetylene equivalents).
A. G. Fallis, *Can. J. Chem.*, **62**, 183 (1984) (intramolecular).
D. L. Boger, *Chem. Rev.*, **86**, 781 (1986) (heterocyclic dienes).

Photocyclisation to phenanthrenes

F. B. Mallory and C. W. Mallory, *Org. Reactions*, **30**, 1 (1984).

1,3-Dipolar cycloaddition

R. Huisgen, *Angew. Chem., Internat. Edit.*, **2,** 565, 633 (1963).

Simmons–Smith reaction

H. E. Simmons, T. L. Cairns, S. A. Vladuchick and C. M. Hoiness, *Org. Reactions*, **20,** 1 (1973).

Cope rearrangement

S. J. Rhoads and N. R. Raulins, *Org. Reactions*, **22,** 1 (1975).

Chapter 8

General

R. L. Augustine (ed.), *Reduction*, Edward Arnold/Marcel Dekker, 1968.
M. M. Baizer, *Organic Electrochemistry*, Marcel Dekker, 1973.

Catalytic hydrogenation

R. L. Augustine, *Catalytic Hydrogenation*, Edward Arnold/Marcel Dekker, 1965.
P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, 1967.
P. N. Rylander, *Hydrogenation Methods*, Academic Press, 1985.

Homogeneous catalysis in hydrogenation

F. J. McQuillin, *Prog. Org. Chem.*, **8,** 314 (1973).
A. J. Birch and D. H. Williamson, *Org. Reactions*, **24,** 1 (1976).

Transfer hydrogenation

R. A. W. Johnstone, A. H. Wilby and I. D. Entwistle, *Chem. Rev.*, **85**, 129 (1985).

Clemmensen reduction

E. L. Martin, *Org. Reactions*, **1,** 155 (1942).
E. Vedejs, *Org. Reactions*, **22,** 401 (1975).

Wolff–Kishner reduction

D. Todd, *Org. Reactions*, **4,** 378 (1948).

Dissolving metal reduction

A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8,** 1 (1972).

Meerwein–Ponndorf–Verley reduction

A. L. Wilds, *Org. Reaction*, **2,** 178 (1944).
G. H. Posner, *Angew. Chem., Internat. Edit.*, **17,** 487 (1978).

Complex metal hydride reduction

E. R. H. Walker, *Chem. Soc. Rev.*, **5,** 23 (1976).
A. Hajós, *Complex Hydrides*, Elsevier, 1979.
J. Málek, *Org. Reactions*, **34**, 1 (1985); **36**, 249 (1987).

Hydrogenolysis

G. R. Pettit and E. E. Van Tamelen, *Org. Reactions*, **12,** 356 (1962) (desulphurisation).
A. R. Pinder, *Synthesis*, **1980,** 425 (halides).

Rosenmund reduction

E. Mosettig and R. Mozingo, *Org. Reactions*, **4,** 362 (1948).

Reduction of sulphoxides

M. Madesclaire, *Tetrahedron*, **44**, 6537 (1988).

Chapter 9

General

R. L. Augustine and D. J. Trecker (eds.), *Oxidation*, Marcel Dekker, Vols. 1, 1969, and 2, 1971.
K. B. Wiberg and W. S. Trahanovsky (eds.), *Oxidation in Organic Chemistry*, Academic Press, Parts A, 1965, B, 1973 and C, 1978.

Barton reaction

R. H. Hesse, *Adv. Free-Rad. Chem.*, **3,** 83 (1969).

Selenium dioxide

M. Rabjohn, *Org. Reactions*, **24,** 261 (1976).

Étard reaction

W. H. Hartford and M. Darrin, *Chem. Rev.*, **58,** 1 (1958).

Dehydrogenation

P. P. Fu and R. G. Harvey, *Chem. Rev.*, **78,** 317 (1978) (general).
D. Walker and J. D. Hiebert, *Chem. Rev.*, **67,** 153 (1967) (DDQ).

Hydroxylation of alkenes (general)

F. D. Gunstone, *Adv. Org. Chem.*, **1,** 103 (1960).

Prévost reaction

C. V. Wilson, *Org. Reactions*, **9,** 332 (1957).

Potassium permanganate

A. J. Fatiadi, *Synthesis*, **1987,** 85.

Osmium(VIII) oxide

M. Schröder, *Chem. Rev.*, **80,** 187 (1980).

Chromium(VI) reagents

G. Piancatelli, A. Scettri and M. D'Auria, *Synthesis*, **1982**, 245 (PCC).
E. J. Corey and G. Schmidt, *Tetrahedron Letters*, **1979,** 399 (PDC).
F. S. Guziec and F. A. Luzzio, *Synthesis*, **1980,** 691 (bipyridinium chlorochromate).
G. J. S. Doad, *J. Chem. Research* (*S*), **1988**, 270 (pyrazinium chlorochromate).

Dimethyl sulphoxide

W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67,** 247 (1967).
A. J. Mancuso and D. Swern, *Synthesis*, **1981,** 165.

Oppenauer oxidation

C. Djerassi, *Org. Reactions*, **6,** 207 (1951).

Sommelet reaction

N. Blažević *et al.*, *Synthesis*, **1979,** 161 and references therein.

Elbs oxidation

E. J Behrman, *Org. Reactions*, **35**, 421 (1987).

Oxidative coupling of phenols

A. I. Scott, *Quart. Rev.* **19,** 1 (1965).
D. C. Nonhebel, P. L. Pauson, *et al.*, *J. Chem. Research* (*S*), **1977,** 12–16.

Baeyer–Villiger reaction

C. H. Hassall, *Org. Reactions*, **9,** 73 (1957).

Oxidation of sulphides to sulphoxides

M. Madesclaire, *Tetrahedron*, **42,** 5459 (1986).

Chapter 10

J. F. W. McOmie (ed.), *Protective Groups in Organic Chemistry*, Plenum Press, 1973.
J. F. W. McOmie, *Adv. Org. Chem.*, **3,** 191 (1963).

T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley–Interscience, 1981.
M. Lalonde and T. H. Chan, *Synthesis*, **1985**, 817 (silicon-containing groups).
M. Reuman and A. I. Meyers, *Tetrahedron*, **41**, 837 (1985) (oxazolines).

Chapter 11

H. C. Brown, *Hydroboration*, Benjamin, 1962.
H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, 1972.
H. C. Brown, *Organic Synthesis via Boranes*, Wiley, 1975.
G. M. L. Cragg, *Organoboranes in Organic Synthesis*, Marcel Dekker, 1973.
A. Pelter, K. Smith and H. C. Brown, *Borane Reagents*, Academic Press, 1988.
G. M. L. Cragg and K. R. Koch, *Chem. Soc. Rev.*, **6,** 393 (1977).

Chapter 12

General

A. J. Kirby and S. Warren, *The Organic Chemistry of Phosphorus*, Elsevier, 1967.
B. J. Walker, *Organophosphorus Chemistry*, Penguin Books, 1972.
J. I. G. Cadogan (ed.), *Organophosphorus Reagents in Organic Synthesis*, Academic Press, 1979.

Michaelis–Arbusov reaction

A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, **81,** 415 (1981).

Horner/Wadsworth–Emmons reaction

J. Boutagy and R. Thomas, *Chem. Rev.*, **74,** 87 (1974).

Conversion of alcohols into halides *via* oxyphosphonium intermediates

B. R. Castro, *Org. Reactions*, **29**, 1 (1983).

Tervalent phosphorus reagents

J. I. G. Cadogan, *Quart. Rev.*, **16,** 208 (1962) (reducing agents).
J. I. G. Cadogan, *Quart. Rev.*, **22,** 222 (1968) (reduction of —NO and —NO_2).
J. I. G. Cadogan and R. K. Mackie, *Chem. Soc. Rev.*, **3,** 87 (1974).

Chapter 13

General

E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, 1981.
E. W. Colvin (ed.), *Silicon Reagents in Organic Synthesis*, Academic Press, 1988.
E. W. Colvin, *Chem. Soc. Rev.*, **7,** 15 (1978).
T. H. Chan and I. Fleming, *Synthesis*, **1979,** 761.
I. Fleming, *Chem. Soc. Rev.*, **10,** 83 (1981).

Peterson reaction

D. J. Ager, *Synthesis*, **1984,** 384.

Allylsilanes

A. Hosami, *Acc. Chem. Res.*, **21,** 200 (1988).

Silyl enol ethers

J. K. Rasmussen, *Synthesis*, **1977,** 91.
P. Brownbridge, *Synthesis*, **1983,** 1 and 85.
I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, **18,** 181 (1985).

Choromethyl-trimethylsilane

R. Anderson, *Synthesis*, **1985,** 717.

Iodotrimethylsilane

G. A. Olah and S. C. Narang, *Tetrahedron*, **38,** 2225 (1982).

Silicon-containing carbonyl equivalents (Umpolung reagents)

D. J. Ager, *Chem. Soc. Rev.*, **11,** 493 (1982).

Organosilicon compounds under conditions of nucleophilic catalysis

G. G. Furin *et al.*, *Tetrahedron*, **44,** 2675 (1988).

Chapter 14

C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, 1986.
D. Liotta, *Acc. Chem. Res.*, **17,** 28 (1984).
D. Liotta (ed.), *Recent Aspects of Organoselenium Chemistry* (Tetrahedron Symposia-in-Print, No. 23), *Tetrahedron*, **41,** 4727–5060 (1985).

Chapter 15

General

J. D. Morrison (ed.), *Asymmetric Synthesis*, 5 volumes, Academic Press, 1983–5.
(This is a collection of reviews; those of specific relevance to Chapter 15 are detailed below, the book title being abbreviated to *A.S.*)

Alkylation of chiral enolates

D. A. Evans, *A.S.*, **3,** Chapter 1.

Asymmetric aldol reactions

C. H. Heathcock, *A.S.*, **3,** Chapter 2.
T. Mukaiyama, *Org. Reactions*, **28,** 203 (1982) (stereochemistry of addition).

Chiral oxazolines

K. A. Lutomski and A. I. Meyers, *A.S.*, **3**, Chapter 3.

Chiral hydrazones

D. Enders, *A.S.*, **3,** Chapter 4.

Chiral imines

D. E. Bergbreiter and M. Newcomb, *A.S.*, **2,** Chapter 9.

Chiral formamidines

A. I. Meyers, *Aldrichim. Acta*, **18,** 59 (1985).

Asymmetric cycloaddition reactions

L. A. Paquette, *A.S.*, **3,** Chapter 7.
W. Oppolzer, *Angew. Chem. Internat. Edit.*, **23,** 876 (1984).

Asymmetric epoxidation (Sharpless oxidation)

A. Pfenninger, *Synthesis*, **1986**, 89.
B. E. Rossiter, *A.S.*, **5**, Chapter 7 (synthetic aspects and applications).
M. G. Finn and K. B. Sharpless, *A.S.*, **5,** Chapter 8 (mechanism).

Reduction with chiral modifications of lithium aluminium hydride

E. R. Grandbois, S. I. Howard and J. D. Morrison, *A.S.*, **2,** Chapter 3.

Chiral boron reagents

H. C. Brown, P. K. Jadhav and A. K. Mandal, *Tetrahedron*, **37,** 3547 (1981).
D. S. Matteson, *Synthesis*, **1986,** 973.
H. C. Brown and P. K. Jadhav, *A.S.*, **2,** Chapter 1.
M. M. Midland, *A.S.*, **2,** Chapter 2.

Catalytic asymmetric hydrogenation

J. Halpern, *A.S.*, **5,** Chapter 2 (mechanism).
K. E. Koenig, *A.S.*, **5,** Chapter 3 (applications).

Enzymes as chiral catalysts

G. M. Whitesides and Chi-Huey Wong, *Aldrichim. Acta*, **16,** 27 (1983).
J. B. Jones, *A.S.*, **5,** Chapter 9.

Chapter 16

Insect pheromones

R. Rossi, *Synthesis*, **1977,** 817; **1978,** 413.

Polymer-supported syntheses

A. Akelah, *Synthesis*, **1981,** 413.
J. M. J. Frecher, *Tetrahedron*, **37,** 663 (1981).
A. Akelah and D. C. Sherrington, *Chem. Rev.*, **81,** 557 (1981).
R. B. Merrifield, *Angew. Chem., Internat. Edit.*, **24,** 799 (1985) (Nobel lecture).
P. Hodge and D. C. Sherrington (ed.), *Polymer-supported Reactions in Organic Synthesis*, Wiley, 1980.

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Guidebook to Organic Synthesis

Synthesis has always occupied a central position in the practice of organic chemistry, and is, therefore, a core constituent of undergraduate chemistry courses. Continued growth in the variety of useful synthetic methods in the literature has, however, provided both students and teachers with an ongoing problem – the need to keep abreast of developments within an ever-changing subject.

This second edition, extensively revised and enlarged to take account of recent developments, emphasises the basic principles of the subject which remain essentially unchanged. Accordingly, the first ten chapters, in which the ground work is laid (carbon-carbon bond formation, functional group transformations, etc.) have survived from the first edition with detailed additions reflecting new work, and amendments to improve clarity.

Of the remaining chapters, four (on boron, phosphorus, and silicon reagents, and selected syntheses) have undergone extensive alteration and expansion. The other two (selenium reagents and asymmetric synthesis) are completely new, the latter being unique in an introductory textbook, reflecting the current importance of this topic at the research level.

The **Guidebook** is for undergraduates in the second and subsequent years of Honours Chemistry courses, and it will also be of value to graduate students engaged in synthetic work.

R.K. Mackie and D.M. Smith are Senior Lecturers in Chemistry at the University of St. Andrews, and R.A. Aitken is Lecturer in the same department.

From reviews of the first edition:

" . . . an excellent guide both to reactions which are of importance in synthesis and to the principles underlying the formation of various types of bonds."

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