THE REARRANGEMENT OF SOME SUBSTITUTED CYCLOPROPYLCARBINYL RADICALS

by

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A Thesis presented in part fulfilment
of the requirements for the
Degree of Doctor of Philosophy

DEPARTMENT OF PURE AND APPLIED CHEMISTRY

THE UNIVERSITY OF STRATHCLYDE

January 1991

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. D.C. Nonhebel, for all his help and patience during this work.

Thanks are also due to Dr. J. Walton for running the e.s.r. spectra and to Dr. P. Bladon for help with n.m.r. analysis.

The invaluable help of all the technical staff and fellow students is also gratefully acknowledged.

Finally, thanks to Margaret Smith for typing this thesis from my handwritten scrawl.

SUMMARY

The ring-opening of cyclopropylcarbinyl radicals has been postulated to proceed via a dipolar transition state. In this thesis it was hoped to delineate some of the factors that influence the rate of ring-opening of some substituted cyclopropylcarbinyl radicals and hence estimate their relative importance. This would allow the involvement of the dipolar transition state in the ring-opening process to be assessed.

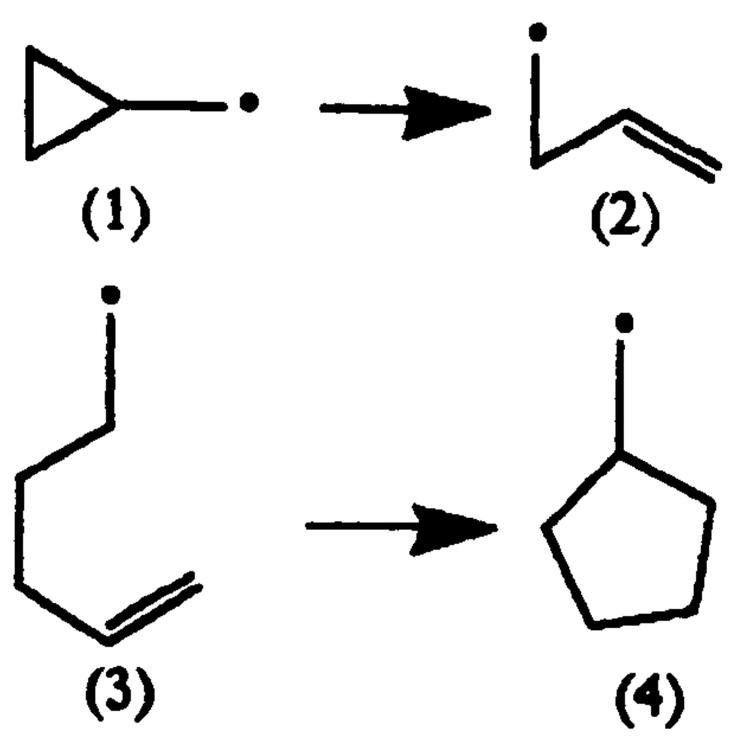
In order to achieve the above objective it was necessary to synthesise methylcyclopropanes with substituents at both the α-position and the 2-position. Such compounds should readily react with t-butoxyl radicals to give a series of cyclopropylcarbinyl radicals. The bulk of the synthetic work was in two parts, the first involved synthesis of 2,2-difluoro substituted cyclopropanes, to determine the influence of fluorine substituents in the cyclopropane ring. The second section involved cyclopropanations using carboethoxycarbene.

Radicals were generated, from successfully synthesised precursors, and their electron spin resonance spectra recorded. The data obtained provided evidence for the involvement of a dipolar transition state in some of the ring-opening rearrangements. However, in several of the radicals other factors are clearly influencing the observed ring-opening. In another section of the work the effect of phenyl and ferrocenyl substituents on the ring-opening of cyclopropylcarbinyl radicals was assessed.

CONTENTS

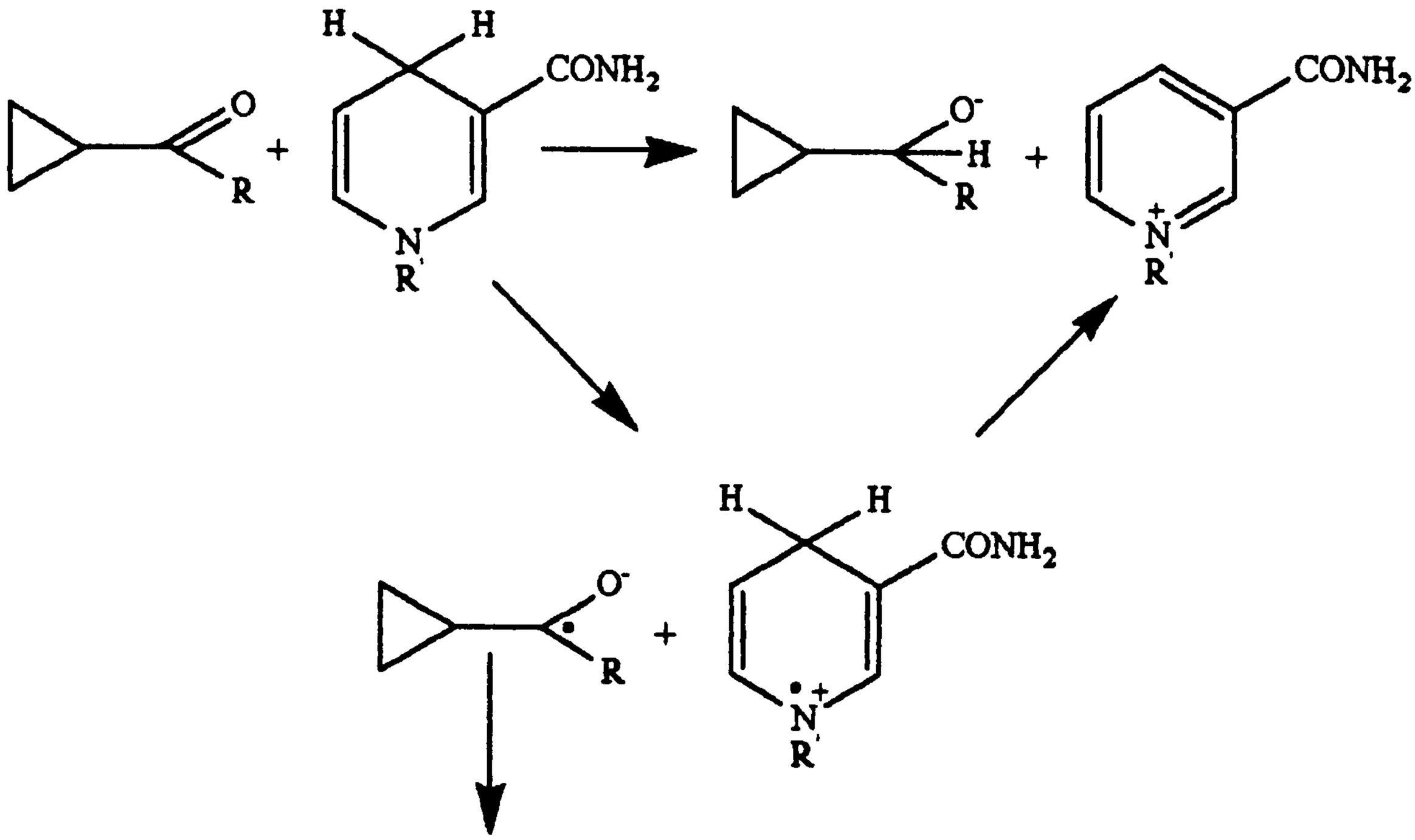
1. INTRODUCTION

Radical rearrangements are increasingly being used to probe reaction mechanisms. This is because under favourable conditions the presence, or otherwise, of radical intermediates in a reaction of unknown or uncertain mechanism can be probed by using as a potential intermediate a species which, if it is a free radical, will undergo rearrangement. Examples of this, which are widely used, are substrates possessing the cyclopropylcarbinyl and hex-5-enyl groups, which would give as intermediates the cyclopropylcarbinyl (1) and hex-5-en-1-yl (3) radicals. These radicals rearrange readily to afford but-3-en-1-yl (2) and cyclopentylmethyl (4) radicals respectively.



We need to know the rate at which these rearrangements occur as well as the typical rearrangement products. The rate of rearrangement of the suspected radical intermediate must be rapid enough to compete with other reactions of that intermediate, otherwise the absence of rearranged products has no significance.

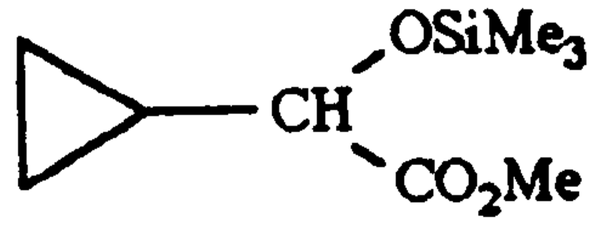
To illustrate this, consider the mechanism of hydrogen transfer by nicotinamide dependent horse liver alcohol dehydrogenase.[1-3] This has variously been considered to involve hydride transfer and single electron transfer with involvement of radical intermediates (see Scheme I).



Scheme I

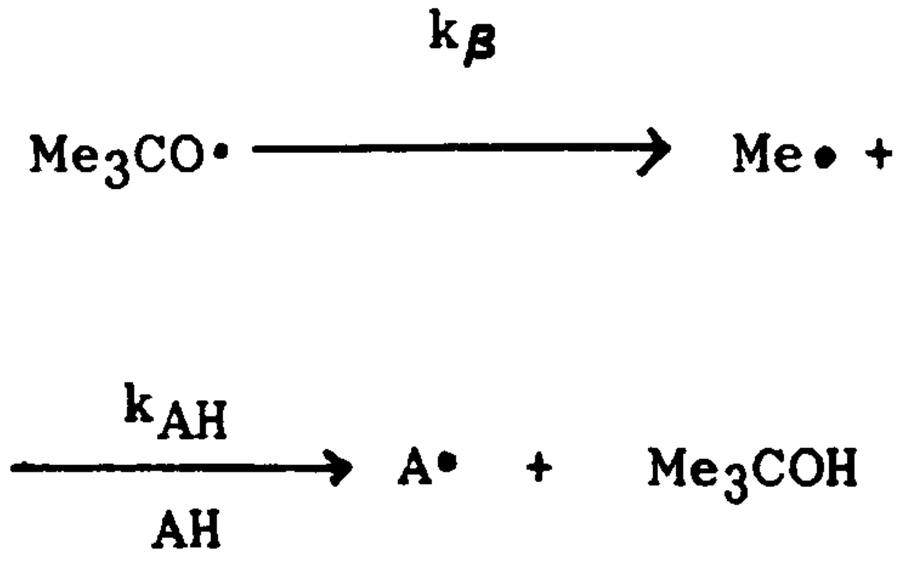
If radical intermediates are involved the rearrangement of the cyclopropylcarbinyl radical, generated from the probe species, must be fast enough to compete effectively with other reactions of the cyclopropylcarbinyl radical. In this case no rearranged products were isolated and it is proposed that hydride transfer is the mechanism occurring. However in a similar study of lactate dehydrogenase[3,4] utilizing the probe species methyl 2-cyclopropyl-2-trimethylsilyloxyacetate (5) the rate of rearrangement of the possible radical intermediate is not fast enough to exclude the possibility of radical involvement. In processes like those described above the radical rearrangement acts as a timing device, or

free-radical clock,[5] and provides a method for quantitative examination of radical-molecule reactions.



(5)

Clock reactions are not, however, confined to radical rearrangements. The β-scission of t-butoxyl radicals is perhaps the simplest example of a radical clock reaction and has been used to measure relative rates of hydrogen abstraction from organic compounds in solution[6] (see Scheme II).



Scheme II

In the presence of a hydrogen donor AH, competition between β-scission and hydrogen abstraction occurs. At low conversions, the concentration of AH remains essentially unchanged and the ratio of the rate of abstraction to the rate of β-scission can be determined by product analysis for acetone and t-butanol (Equation (1)).

$$\frac{k_{AH}}{k_{\beta}} = \frac{[Me_3COH]}{[AH][Me_2CO]} \qquad \text{(eq. 1)}$$

If a separate experiment is carried out under the same conditions with a second substrate BH, the relative ratio of hydrogen abstraction k_{AH}/k_{BH} can be calculated. If the value of k_{β}, the rate of β-scission, is known then the free-radical clock is said to be calibrated and absolute values of k_{AH} and k_{BH} can be calculated.

1.1 Calibration of Clock Reactions

To use unimolecular clock reactions to determine absolute rate constants for radical-molecule reactions, under typical experimental conditions, we need to have a series of calibrated free-radical clocks.[5] For primary alkyl radicals, probably the most extensively studied class of radicals, a reasonable series of calibrated free-radical clocks exist. If we look at the following species, the neophyl radical ($k_r^{25\,°C} = 59\ s^{-1}$), the hex-5-enyl radical ($k_r^{25\,°C} = 1 \times 10^5\ s^{-1}$), and the cyclopropylcarbinyl radical ($k_r^{25\,°C} = 1 \times 10^8\ s^{-1}$), we can see that their rates of rearrangement, k_r, cover seven orders of magnitude. For classes of radicals other than primary alkyls, there is often a distinct lack of suitable clock reactions.

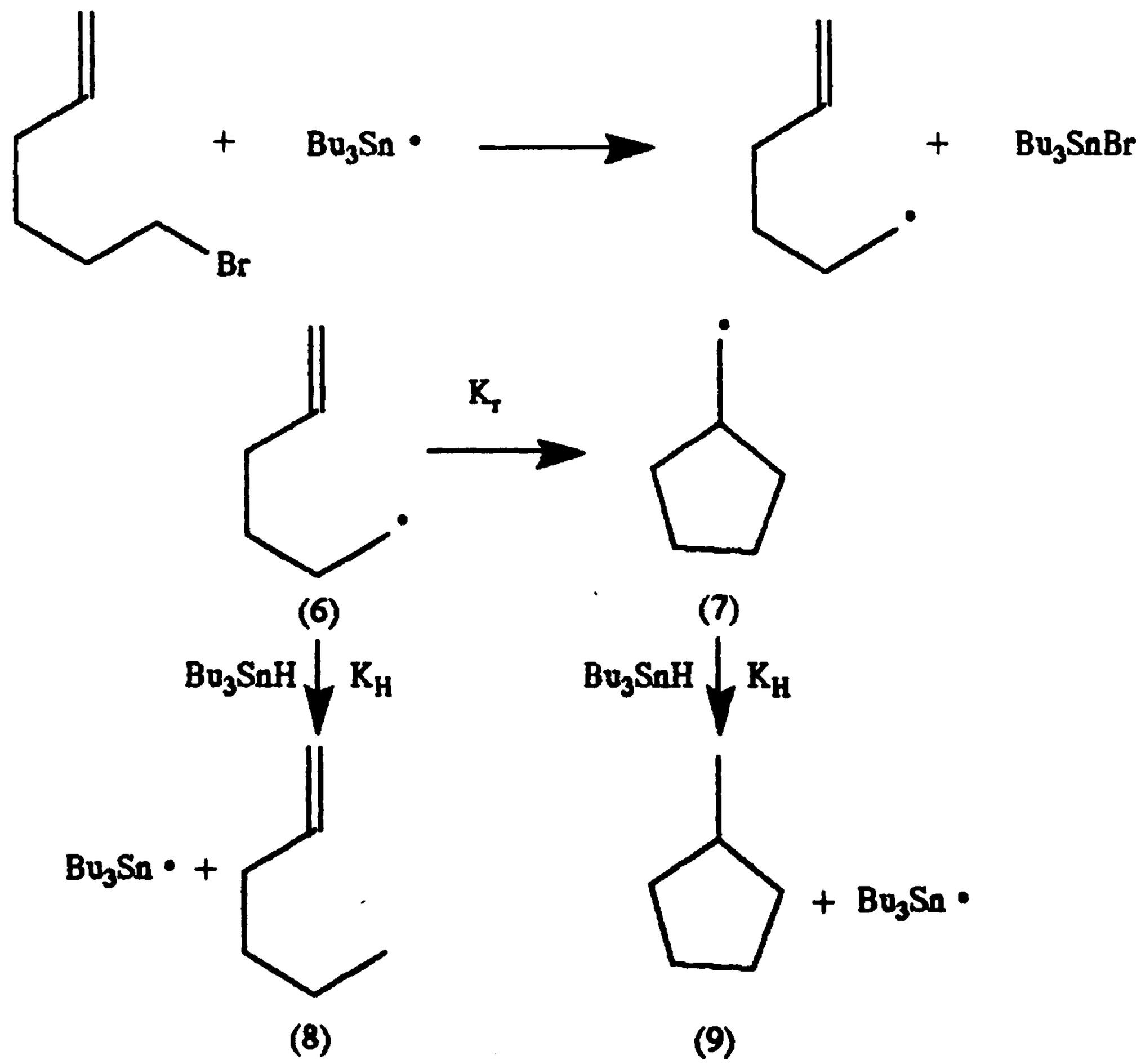
The methods available for the measurement of rates of rearrangement in free-radical reactions[7,8] can be split into two broad categories: direct and indirect methods.

1.1.1 Indirect methods

Indirect methods for determination of the rate of a unimolecular radical reaction involve a competition between this process and some other reaction of known or readily determined rate.

(a) <u>The "tin hydride method"</u>

One of the commonly used indirect methods is the so called "tin hydride method" (see Scheme III). The ratios of hex-1-ene (8) to methylcyclopentane (9) were measured at 40°C for different concentrations of tri-butyltin hydride.[9]



Scheme III

The abstraction of hydrogen from tri-butyltin hydride by various alkyl radicals has been studied using laser flash photolysis techniques.[10] This work provided values of k_H and showed the rates of abstraction to be almost independent of radical structure[11] i.e. for primary, secondary and tertiary radicals k_H is the same. From the ratio of (8):(9) and the value of k_H it is possible to evaluate the rate constant, k_r, for the rearrangement.

(b) Di-t-alkyl nitroxides

Stable di-t-alkyl nitroxides can be used to trap unstable carbon centred radicals (see Scheme IV), giving stable alkoxyamine products.[12,13]

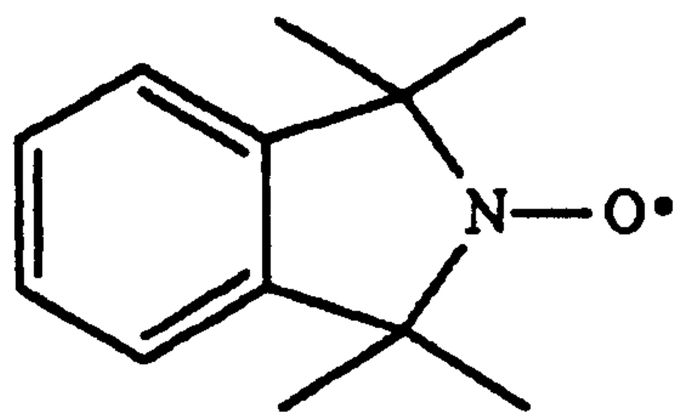
$$R_2N\text{-}O\bullet + R'\bullet \longrightarrow R_2N\text{-}O\text{-}R'$$

Scheme IV

The ratios of these products elucidates the reaction pathway involved. To obtain rate constants for competing reactions the rate constant for the trapping reaction is required.

The di-t-alkyl nitroxides have the ability to scavenge alkyl radicals at near diffusion-controlled rates[14,15] ($k = 10^7$-10^9 s^{-1}), and yet not combine with oxygen-centred radicals. The technique depends on the isolation of the alkoxyamine products and determination of their structure by conventional spectroscopic methods. The presence of a good u.v. chromophore in the nitroxide allows the products to be analysed by h.p.l.c. with u.v. detection.

The nitroxide (10) meets these conditions and has been used to study radical-polymerisation reactions[16-18] in which there are multiple pathways.



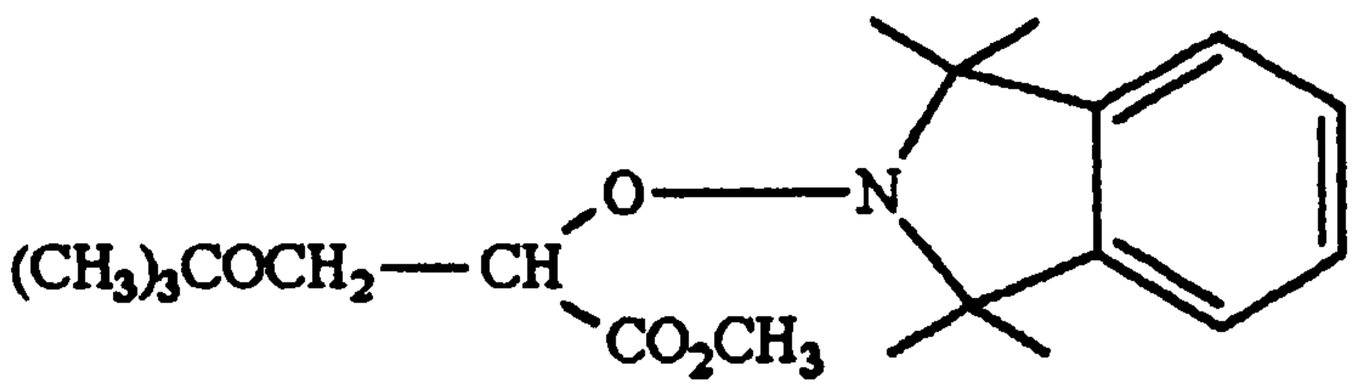
(10)

t-Butoxy radicals react with the vinyl monomer methyl acrylate via several competing pathways. The major pathway is, addition of the t-butoxy radical to the unsubstituted terminus of the double bond of the alkene ("tail" addition) (see Scheme V, path i).

			%
i)	$(CH_3)_3CO\bullet + CH_2=CH(CO_2CH_3)$	$\longrightarrow (CH_3)_3COCH_2\dot{C}H(CO_2CH_3)$	62.9
ii)	$(CH_3)_3CO\bullet + CH_2=CH(CO_2CH_3)$	$\longrightarrow (CH_3)_3COCH(CO_2CH_3)\dot{C}H_2$	0.9
iii)	$(CH_3)_3CO\bullet + CH_2=CH(CO_2CH_3)$	$\longrightarrow (CH_3)_3COH + CH_2=CHCO_2\dot{C}H_2$	8.8
iv)	$CH_2=CHCO_2\dot{C}H_2 + CH_2=CH(CO_2CH_3)$	$\longrightarrow$ dimer radical	3.4
v)	$(CH_3)_3CO\bullet$	$\longrightarrow (CH_3)_2CO + \dot{C}H_3$	12.4
vi)	$\dot{C}H_3 + CH_2=CH(CO_2CH_3)$	$\longrightarrow CH_3CH_2\dot{C}H(CO_2CH_3)$	5.1
vii)	$(CH_3)_3COCH_2\dot{C}H(CO_2CH_3) + CH_2=CH(CO_2CH_3)$	$\longrightarrow$ dimer radical	5.5
viii)	$(CH_3)_3COCH(CO_2CH_3)\dot{C}H_2 + CH_2=CH(CO_3CH_3)$	$\longrightarrow$ dimer radical	0.4

Scheme V

However smaller amounts of "head" addition (path ii), H-abstraction (path iii), and fragmentation of the t-butoxy radical to give methyl radicals and acetone (path v) are observed. Due to the high rate of trapping of (10) no polymer results from these reactions and the products from paths i-viii are trapped as the alkoxyamines, e.g. for path i the alkoxyamine product is (11).

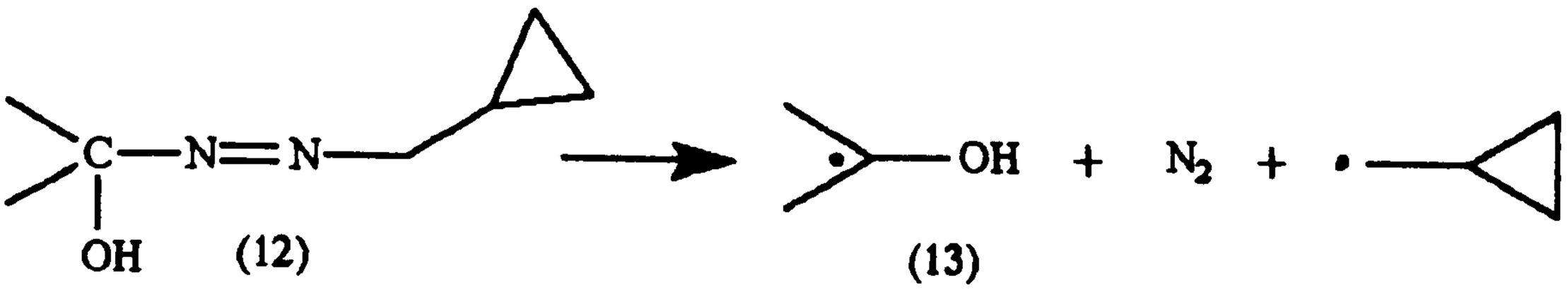


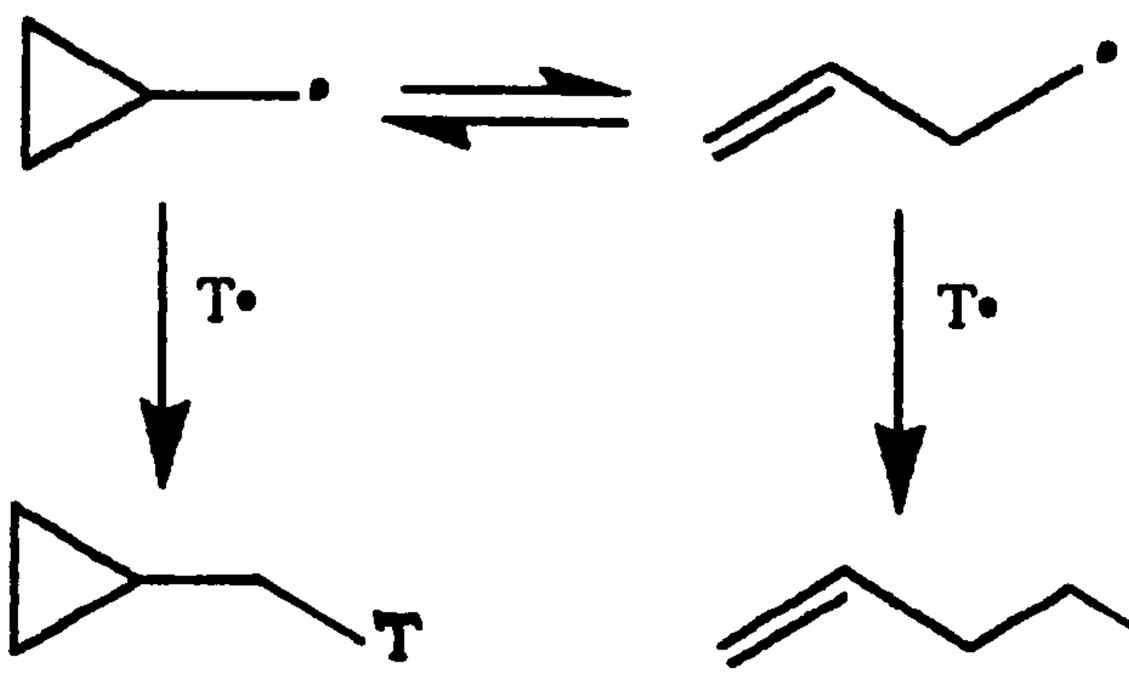
(11)

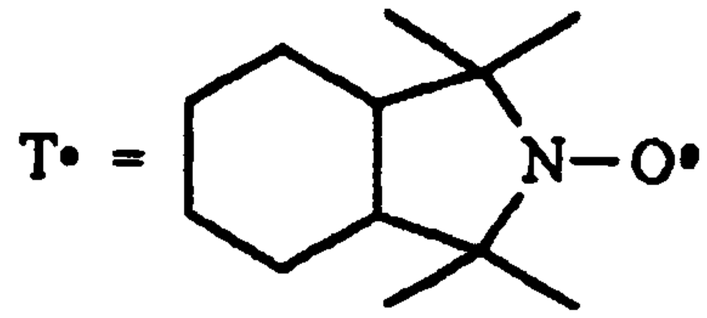
In an e.s.r. spin trapping study of the above reaction using the trap nitroso t-butane only the product formed via path i could be detected.

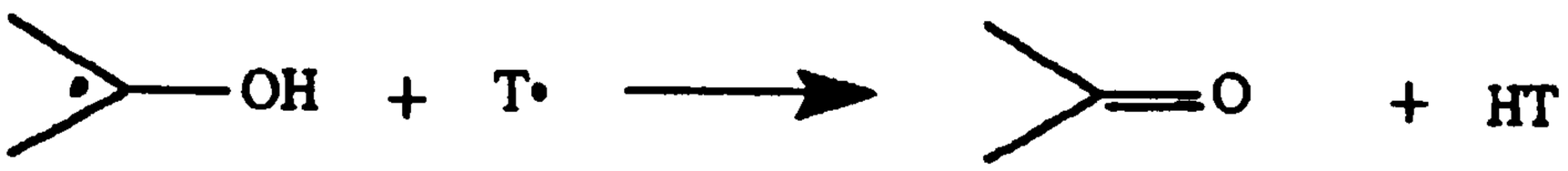
The cyclopropylcarbinyl-allylcarbinyl rearrangement has been studied by this method.[19,125] It has two advantages over e.s.r. studies namely: (i) reactions can be investigated at ambient temperatures and (ii) the possibility of reversibility of the rearrangement can be probed. If the rearrangment is irreversible the product ratios are independent of nitroxide concentration and vice versa.

In one of these studies[125] the cyclopropylcarbinyl radical was generated from the diazene (12) and the various radical products trapped with nitroxide (10) (see Scheme VI). The ratio of the trapped products (14):(15) was determined by h.p.l.c., g.c.m.s., and ^{1}H n.m.r. spectroscopy. The other radical product (13) gives the hydroxy isoindoline HT and was identified by similar means.









Scheme VI

1.1.2 Direct methods

The direct methods involve the study of free-radical rearrangements by a physical technique. The most commonly used tool in such a study is e.s.r. spectroscopy and this is considered first.

(a) E.s.r. spectroscopy

Certain rearrangement processes can be studied directly provided both the initial and rearranged radials can be observed by e.s.r. spectroscopy. For this to be a viable procedure it is necessary that the steady state concentration of the radicals is

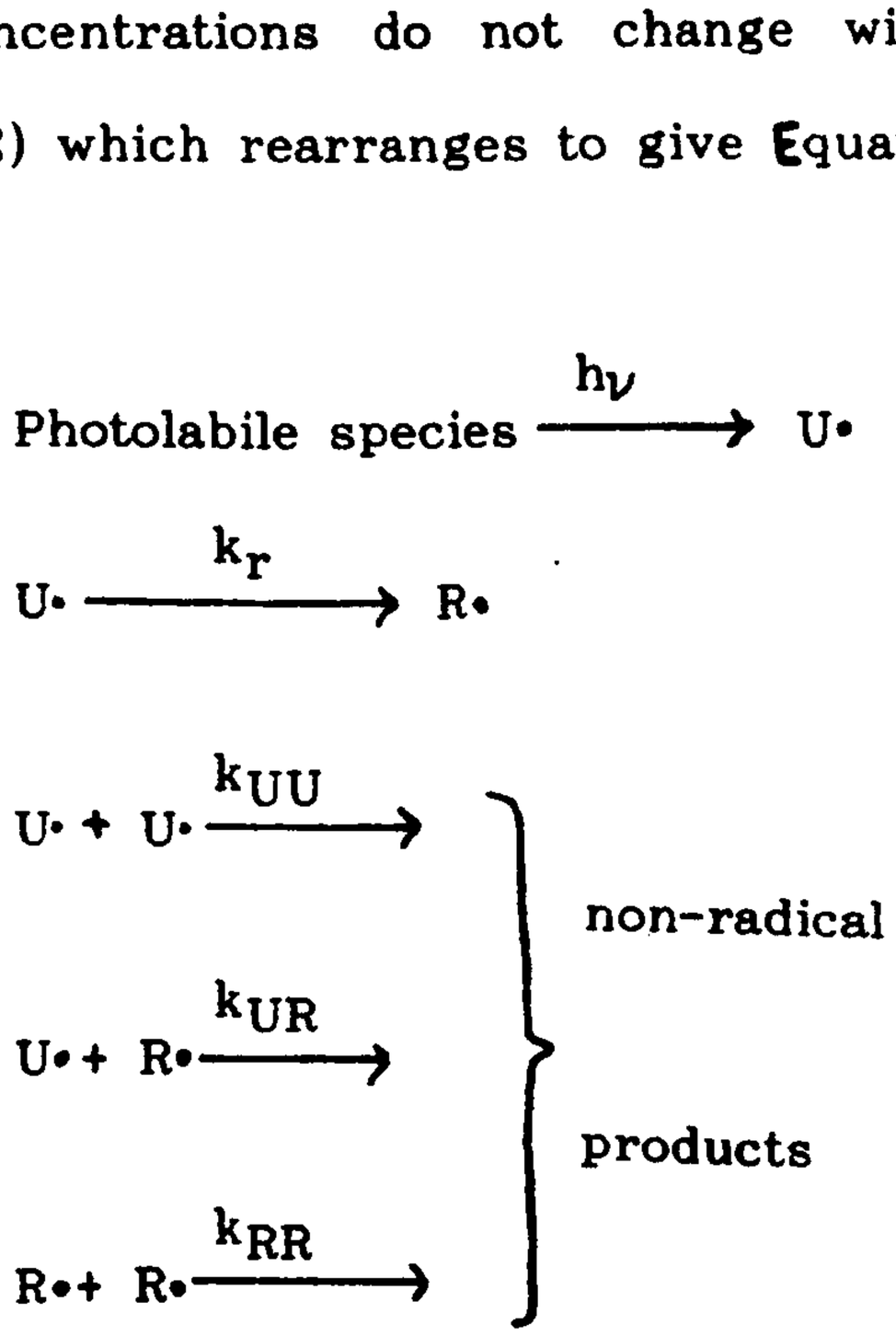
$\geqslant 10^{-6}$M.[7,20] This requirement can severely restrict the temperature range over which experiments can be conducted.

At these concentrations most radicals decay with second-order kinetics by diffusion-controlled bimolecular self-reaction.[7] If we have conditions where:

i) The unrearranged radical U• can be generated photochemically and detected in the cavity of the e.s.r. spectrometer (see Scheme VII).

ii) The temperature of the sample can be adjusted until both the unrearranged radical U• and the rearranged radical R• can be observed simultaneously.

Then under conditions of steady-state photolysis,[21,23] where the radical concentrations do not change with time, we can write Equation (2) which rearranges to give Equation (3).



Scheme VII

$$\frac{d[R\bullet]}{dt} = 0 = k_r[U\bullet]-2k_{UR}[U\bullet][R\bullet]-2k_{RR}[R\bullet]^2 \qquad \text{(eq. 2)}$$

$$\frac{1}{[R\bullet]} = \frac{2k_{UR}}{k_r} + \frac{2k_{RR}[R\bullet]}{k_r[U\bullet]} \qquad \text{(eq. 3)}$$

At each temperature the radical concentrations are varied by changing the incident light intensity. In this way a plot of $1/[R\bullet]$ vs $[R\bullet]/U\bullet]$ has a straight line of slope $2k_{RR}/k_r$.[21-25] Normally the e.s.r. signals are too weak to make measurements except at full light intensity. Usually this problem is discounted as the radicals in question generally undergo an irreversible coupling and/or β-disproportionation, during their bimolecular self-reaction. Bimolecular self-reactions occur at diffusion-controlled limits[26] giving $k_{UU} = k_{RR} = k_{UR}$, Equation (3), can now be simplified to Equation (4).

$$\frac{k_r}{2k_{RR}} = [R\bullet]\left[1 + \frac{[R\bullet]}{[U\bullet]}\right] \qquad \text{(eq. 4)}$$

Only one measurement of $[R\bullet]$ and $[U\bullet]$ at full light intensity is now needed to calculate $k_r/2k_{RR}$.

To get the absolute value for k_r we must obtain a value for $2k_{RR}$. This is done in a separate e.s.r. experiment[26] by generating R from an independent source and monitoring its decay under the same conditions as used in the previous experiment.

(b) Laser-flash photolysis

Laser-flash photolysis uses nano or pico second pulses from a laser source to generate transient radical species. These species are then observed by a variety of spectroscopic techniques. The use of such short pulses of energy to generate the transient species allows the study of processes with rate constants of up to 10^{12} s^{-1}. The monochromaticity of the laser pulses allow the photolysis of only one component in a solution, while the others are effectively transparent to the pulse.

Laser-flash photolysis has been used to study various reactions including hydrogen abstraction by t-butoxyl radicals,[27] determination of rate constants for some reactions of triethylsilyl radicals,[28] and in determination of the rate constants for the reaction of alkyl radicals with tri-butyltin hydride.[10,29] Using the last case as an example, a system had to be found where the alkyl radical was generated in a first-order process from precursors that were not reactive towards alkyl or tin radicals (see Scheme VIII). The wavelength of the excitation pulse must be such that the tri-butyltin hydride is "transparent".

i) $(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2(CH_3)_3CO\bullet$

ii) $(CH_3)_3CO\bullet + R_3As \longrightarrow R_3AsO\dot{C}(CH_3)_3$

iii) $R_3AsO\dot{C}(CH_3)_3 \longrightarrow R\bullet + R_2AsOC(CH_3)_3$

iv) $R\bullet + Bu_3SnH \longrightarrow RH + Bu_3Sn\bullet$

v) $(CH_3)_3CO\bullet + Bu_3SnH \longrightarrow (CH_2)_3CO + Bu_3Sn\bullet$

Scheme VIII

The pulse is absorbed by the peroxide which decomposes and initiates the sequence of reactions (i) → (iii) to produce the alkyl radicals. The alkyl radicals then attack tri-butyltin hydride to give the tri-butyltin radical, which is detectable. It is essential that reaction (ii) occurs faster than reaction (v) otherwise the observed tri-butyltin radical concentration is not produced solely by the alkyl radicals. This problem is alleviated by having a high $[R_3A_s]$:$[Bu_3SnH]$ ratio. When the reaction was carried out the build-up of the detectable tri-butyltin radical was seen to follow pseudo first-order kinetics and an experimental rate constant, R_{exp}, was obtained. If a series of experiments are carried out varying the concentration of tri-butyltin hydride then k_1 can be obtained from a plot of k_{exp} vs $[Bu_3SnH]$ by using Equation (5).

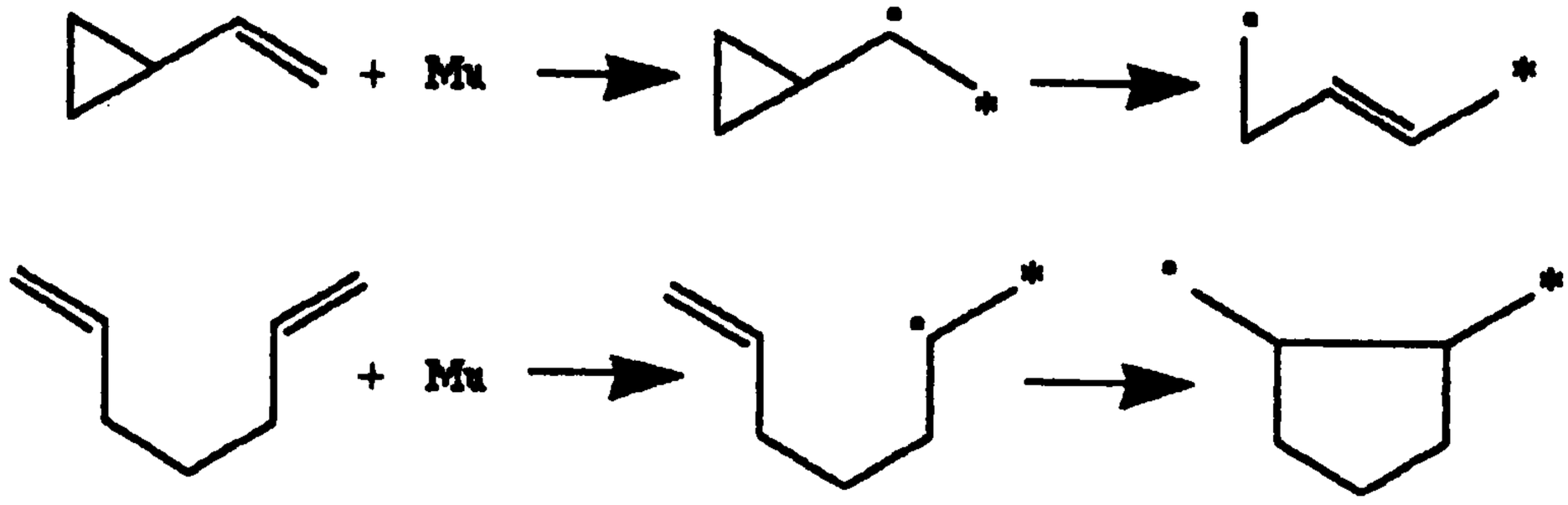
$$k_{exp} = T_r^{-1} + k_1\,[n\text{-}Bu_3SnH] \qquad \text{(eq. 5)}$$

T_r is the lifetime of the alkyl radicals in the solvent without n-Bu_3SnH and excludes any second-order processes. The values of the rate constant obtained in this work led to the revision[10] of the kinetic data for several widely used clock species <u>e.g.</u> for the hex-5-enyl system the previous value [5] of $k_r^{25\,°C} = 1.0 \times 10^5\ s^{-1}$ was raised to give $k_r^{25\,°C} = 2.3 \times 10^5\ s^{-1}$.

(c) <u>Muon spin rotation</u>

In muon spin rotation, spin polarised positive muons are stopped, in a solution of interest, in transverse magnetic fields and the subsequent time evolution of the spin polarization observed.

In unsaturated organic compounds free radicals form by addition of muonium (Mu = μ^+e^-), a light hydrogen isotope (see Scheme IX).



Scheme IX

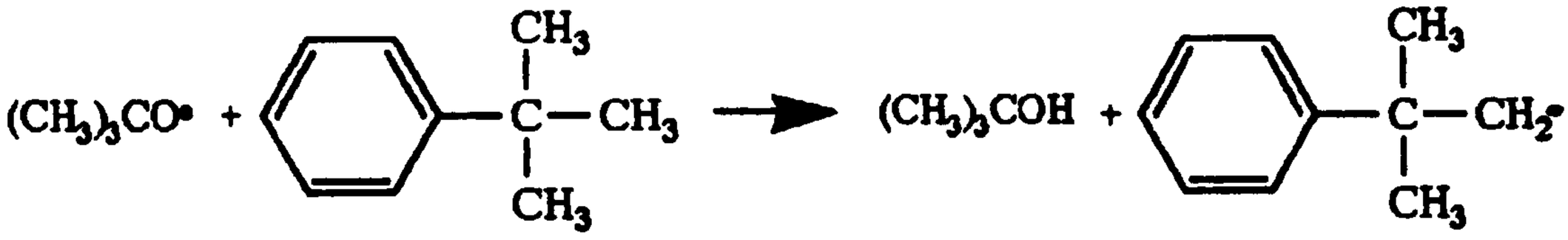
They are identified by their muon-electron hyperfine interactions. Reactions of the radicals lead to a decay of the radical signals and from the resultant line broadening of Fourier transform spectra the rate constants are extracted. This work has been carried out on a variety of substituted hex-5-enyl and cyclopropylcarbinyl radicals.[30,31] The results obtained agree well with previous studies using e.s.r. and other techniques.

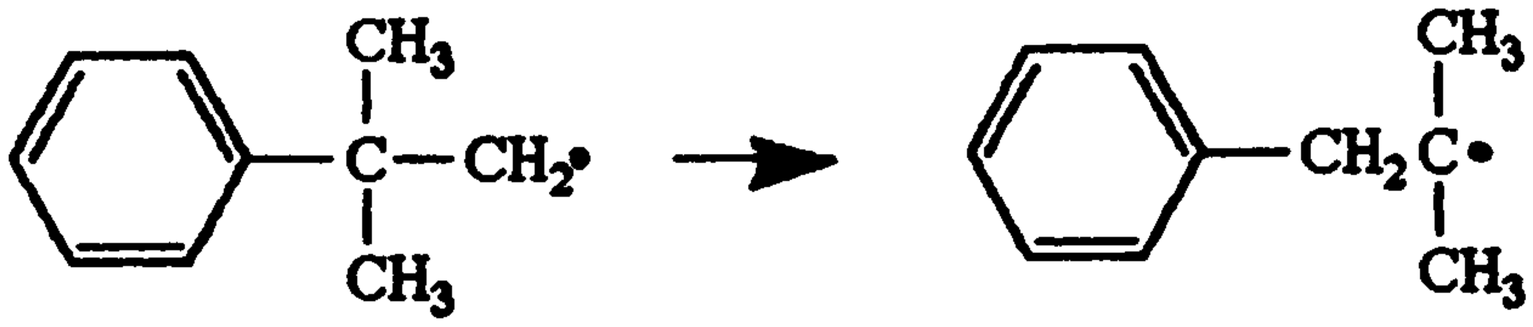
1.2 Examples of Specific Classes of Clock Reactions

Various radical rearrangements will be considered in this section. Three species, the neophyl, the hex-5-enyl and the cyclopropylcarbinyl radicals will be discussed. It has already been noted that the rate constants for the rearrangements of these radicals cover seven orders of magnitude. Each rearrangement will be discussed in turn and its use as a probe species considered. Finally, the effect of substituents on the cyclopropylcarbinyl radical will be considered in greater detail.

1.2.1 Neophyl rearrangement

The neophyl rearrangement was first discovered by Urry and Kharasch[31] in 1944 in a careful product study of the cobalt (II) chloride-catalysed reaction of phenylmagnesium bromide with neophyl chloride. The existence of the neophyl rearrangement can be easily shown nowadays by u.v. photolysis of a di-t-butyl peroxide solution of t-butylbenzene[33] in the cavity of an e.s.r. spectrometer (see Scheme X).



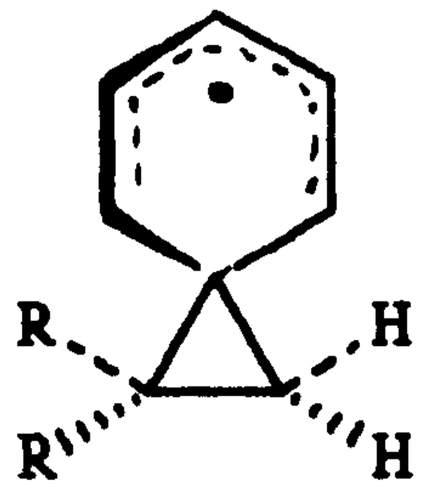


(16) (17)

Scheme X

At room temperature only the radical (16) is observed, but at higher temperatures the radical (17) is also seen. The rate constant[32-35] determined for the neophyl rearrangement is $k^{25°C}$ = 59 s^{-1}. Evidence[36] suggests that the neophyl rearrangement is

intramolecular and must proceed via a spiro[2.5]octadienyl intermediate or transition state (18).



(18)

Neophyl-like rearrangements are enhanced by various factors. The stabilization of (18) by delocalization leads to an increase in the rate of rearrangement. This is exemplified by the comparative rates of rearrangement of the phenyl (19) and β-naphthyl (20) systems (see Table 1).

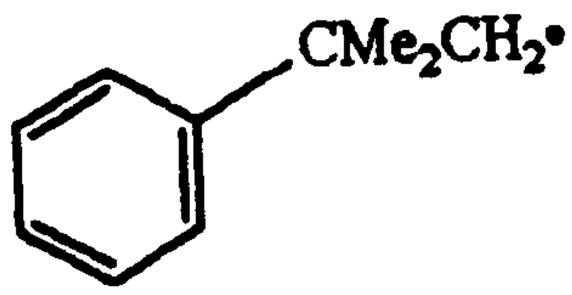
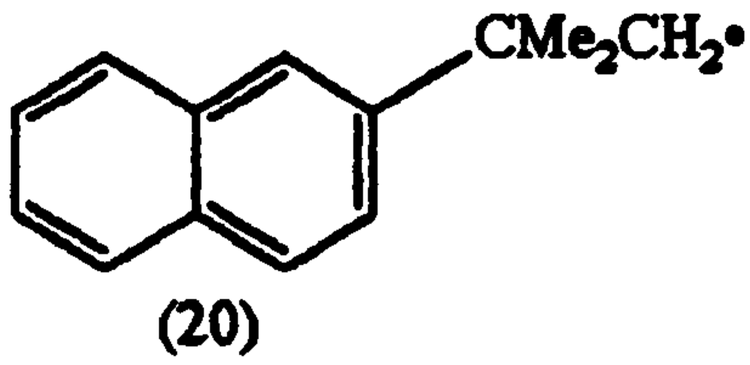
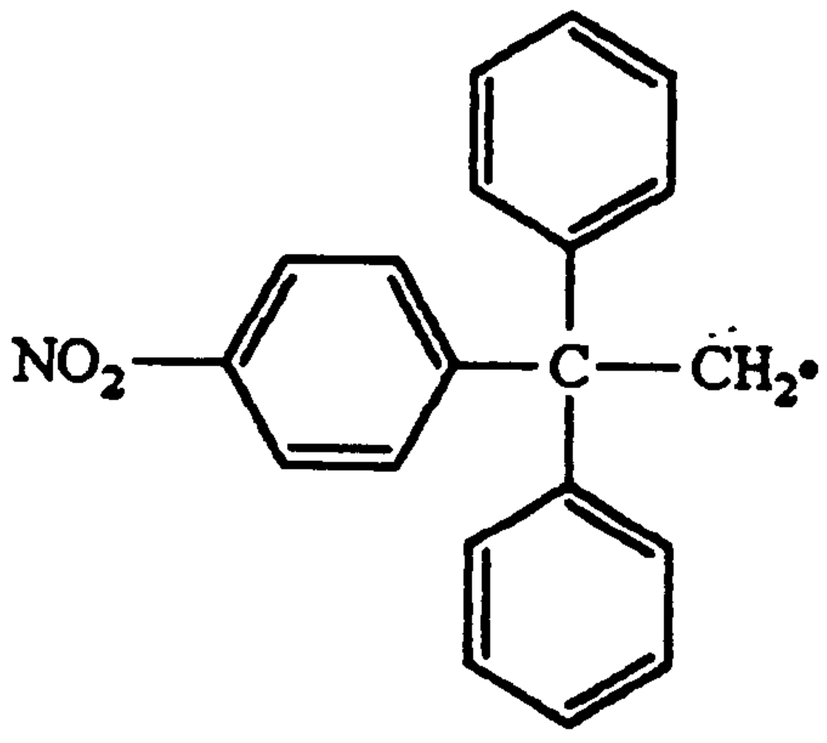
Unrearranged radical	Rate constant at 25°C
 (19)	59 s^{-1}
 (20)	2900 s^{-1}
$(C_6H_5)_3CCH_2^{\bullet}$ (21)	3.6×10^5 s^{-1}

Table 1 Rate constants for the rearrangement of some neophyl-like radicals.

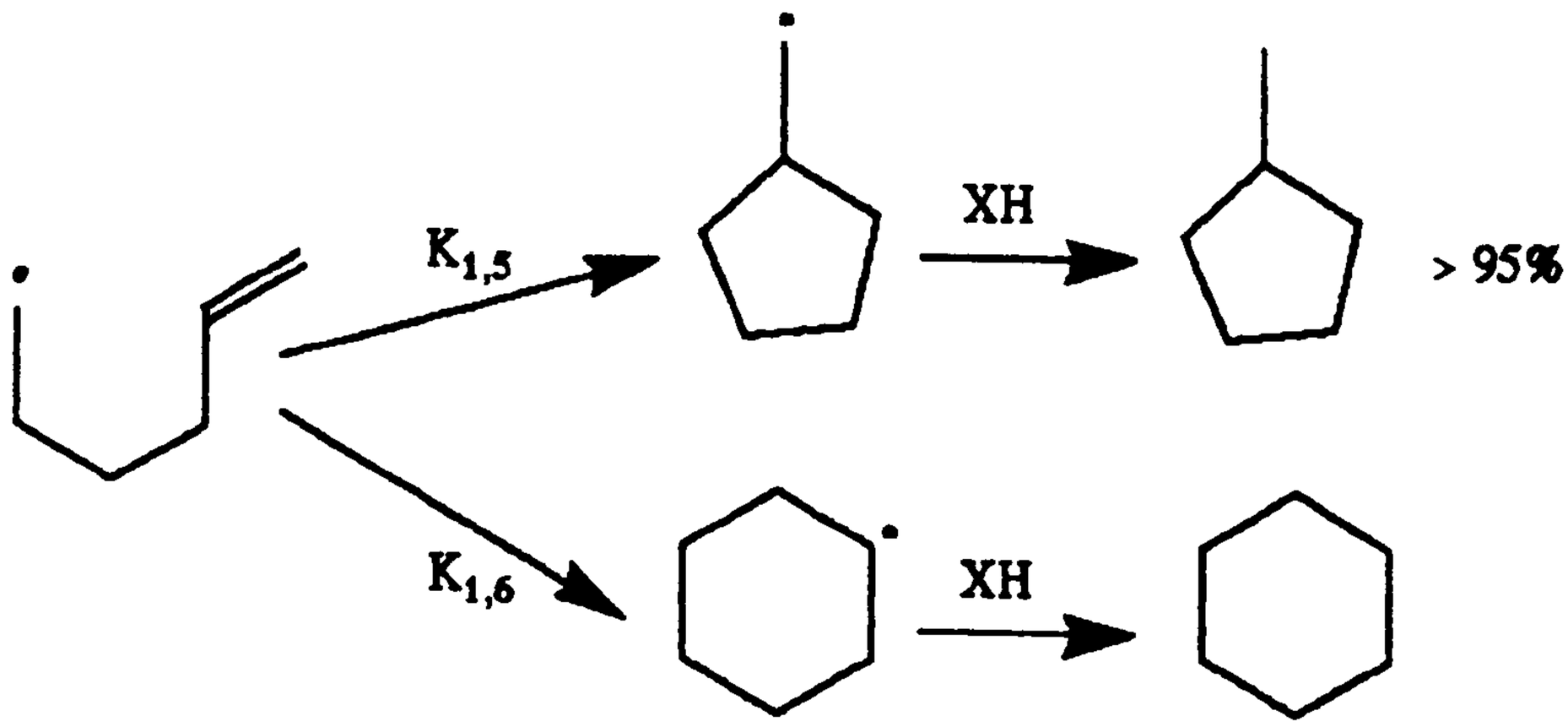
Neophyl-like rearrangements are often driven by the relief of steric strain as a hindered primary alkyl radical rearranges to a less congested tertiary alkyl radical; c.f. the rates of rearrangment of radicals (19) and (21) (see Table 1). The tertiary radical formed by rearrangement of radical (21) is also further resonance stabilized. Electron-withdrawing groups e.g. p-NO_2 also facilitate neophyl-like rearrangements. The rearrangement of radical (22) is at least 8 times faster than that of the analogous radical (21).[39] The effect of electron-withdrawing substituents is attributed to delocalization of the unpaired electron onto the substituent, with consequent stabilization.



(22)

1.2.2 Hex-5-enyl radical

The hex-5-enyl radical undergoes cyclisation in a highly regiospecific manner by intramolecular addition to give predominantly (⩾ 95%) the cyclopentylmethyl[9] radical. Many reactions[40-58] have been carried out with this species and it was often found that cyclohexyl products were not isolated. Careful analysis of the reaction of 1-bromohex-5-ene with tributyltin hydride at 65°C confirmed that cyclohexane was formed[58] in a real, although minor, pathway (see Scheme XI).

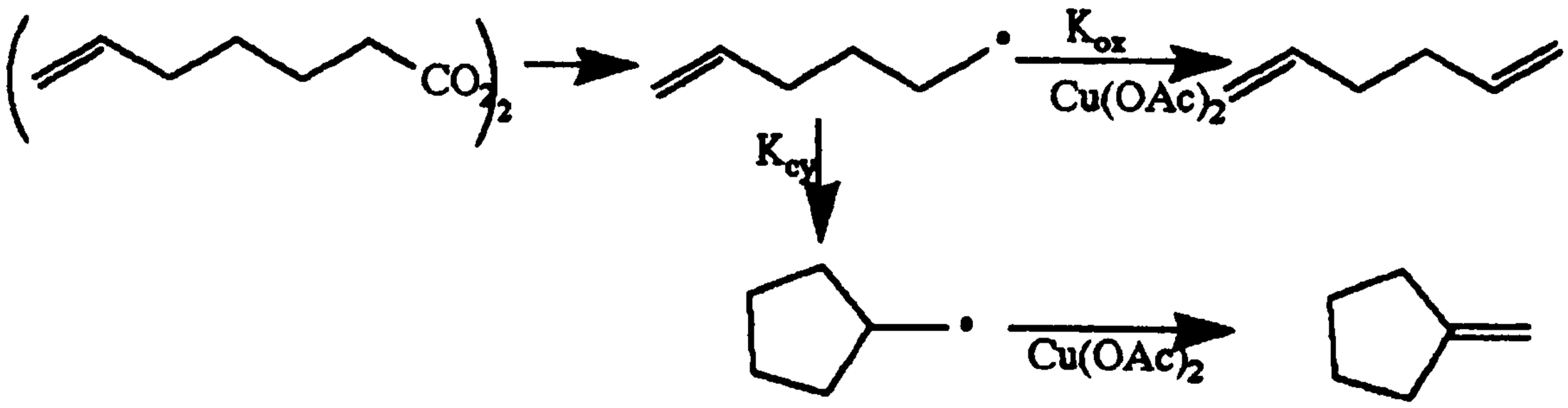


Scheme XI

Experiments in which cyclopentylmethyl and cyclohexyl radicals were generated separately demonstrated the irreversibility[43,49-51] of each mode of cyclisation and the fact that the rearrangements do not go via a common intermediate.[43,48] Since the relevant hydrogen atom transfer steps are fast and irreversible, the relative yields of cyclohexane and methylcyclopentane[9,52,53,58] reflect the relative rates of the two ring-closure processes. Thermodynamic[59,60] and kinetic[61] data show cyclohexyl to be more stabilized than cyclopentylmethyl. Cyclisation of the hex-5-enyl radical is a highly selective process that follows the thermodynamically less-favoured pathway.

The absolute values of the rate constants for cyclisation of hex-5-enyl radicals at ambient temperatures were determined as early as 1968[11,52] and in 1974[40,46] by steady state e.s.r. methods. Subsequent revision of these rate constants by a variety of methods has led to a generally accepted value of $k_r^{60\,^{\circ}C} = 7.5 \times 10^5\ s^{-1}$ for the hex-5-enyl radical.

The tendency of the hex-5-enyl radical to undergo 1,5-cyclisation makes this system a useful tool for identifying the nature of reactive intermediates. The hexenyl cation forms only six-membered rings[62] whereas the anion undergoes 1,5-ring closure but very slowly[63]. The magnitude of rate constants allows the cyclisation of hex-5-enyl radicals to be used as a free-radical clock reaction (see Scheme XII).

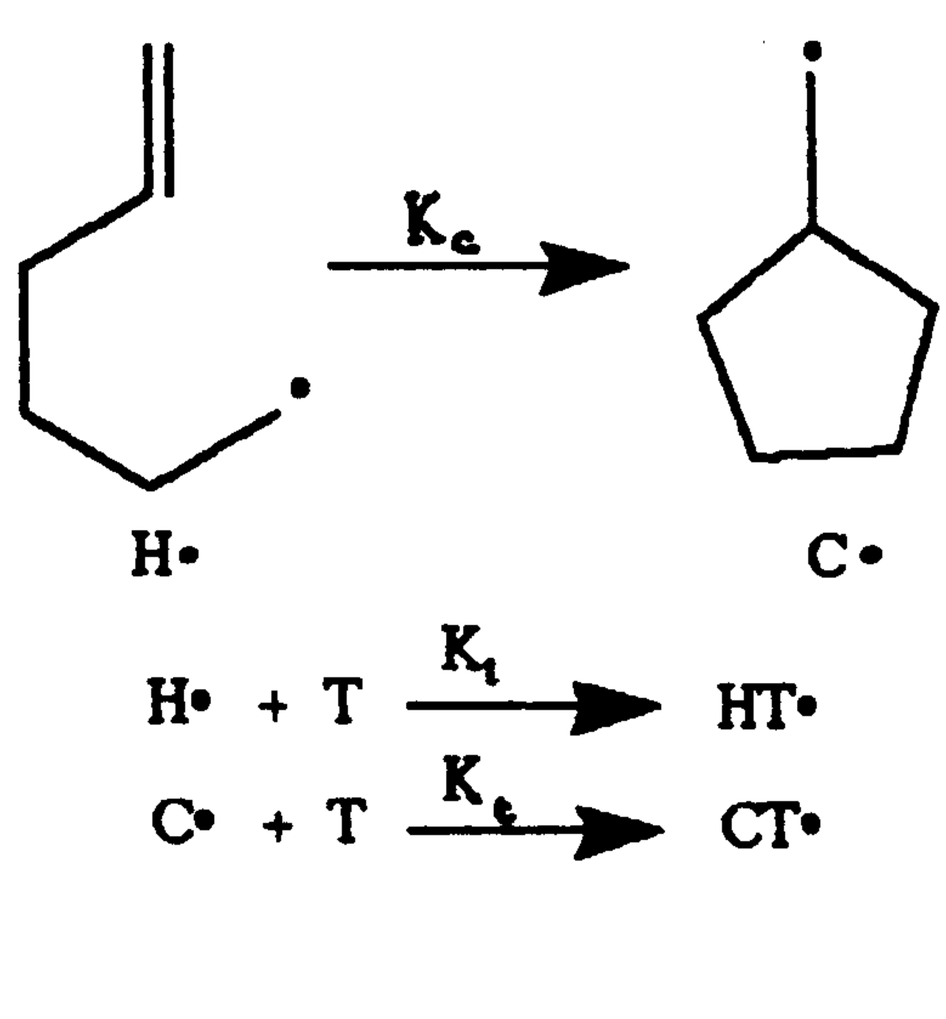


Scheme XII

The decomposition of 6-heptenoyl peroxide in the presence of copper(II) acetate[56,64] afforded hexa-1,5-diene and methylene-cyclopentane in a good combined yield. The absence of cyclohexene from the product mixture indicates that the oxidative elimination step does not involve an intermediate carbonium ion. Oxidation of the hex-5-enyl radical competes with its cyclisation, thus the ratio of the yields of cyclic to acyclic products is linearly related to the copper(II) acetate concentration and to k_{ox}/k_{cy}. The value of k_{cy} is known and k_{ox} can be calculated[45] at ambient temperatures to give $k_{ox} = 1.2 \times 10^6\ s^{-1}$.

Another use of the hex-5-enyl radical rearrangement has been in the determination of rate constants for the spin trapping of primary alkyl radicals.[14,65] The technique of spin trapping has been qualitatively used in the detection and identification of free radicals. A lack of information on the rate of reaction of radicals with the standard spin traps has posed several problems.

In the reaction of radicals H• and C• with the spin trap T (see Scheme XIII), the rate constant k_c for the rearrangement of the hex-5-enyl radical is reliably known. Both the radicals H• and C• are primary alkyls and will form spin adducts with T that have very similar properties. A distinction between HT• and CT• is obtained by labelling H• with ^{13}C at C(1). The hyperfine splitting (h.f.s.) obtained in the e.s.r. spectrum from this carbon will only be detectable in HT•.



Scheme XIII

The ratio of [HT•]/[CT•] is independent of reaction time, indicating that the spin trapping is irreversible. The rate constants for the trapping k_t can be calculated from Equation (6).

$$k_t = \frac{k_c[HT\bullet\ ]}{[T][CT\bullet\ ]} \qquad \text{(eq. 6)}$$

This work was carried out using phenyl N-t-butylnitrone and 2-methyl-2-nitrosopropane as the spin traps and the rate constants are $k_t^{40^\circ C}$ = 1.3 x 10^5 M^{-1} s^{-1} and 90.2 x 10^5 M^{-1} s^{-1} respectively.

Another use of an intramolecular 1,5-cyclisation process was made recently in a study of single-electron transfer, in the reactions of lithium dimethylcuprate with alkyl halides.[66] Various 5-substituted-1-cyclooctenes, (see Table II), were reacted with lithium dimethylcuprate. In this reaction when the 5-substituent is iodine (23) the product distribution supports a radical pathway, as more than half the products are bicyclo[3.3.0]octane derivatives. These bicyclic products are formed by an intramolecular 1,5-cyclisation of the radical generated when single-electron transfer from the cuprate to the iodide (23) occurs.

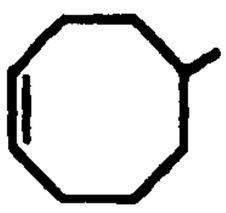
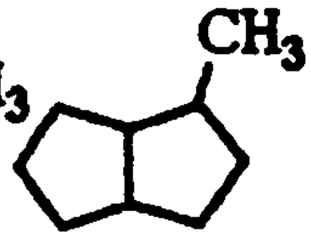
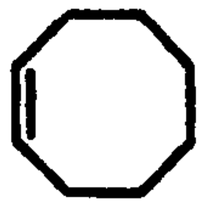
X =	% Yield					
	Recovered substrate					Other
I (23)	0	13.1	4.4	16.7	23.4	21.8
Br (24)	69.6	3.9	0	2.9	12.1	0
OTs (25)	0	56.4	0	0	0	30.4

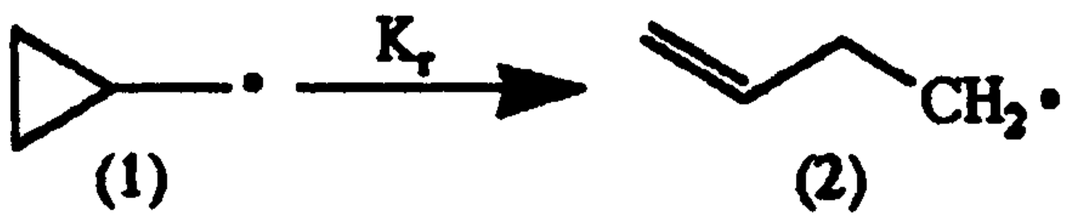
Table II Reactions of 5-substituted 1-cyclooctenes with $LiCuMe_2$.

The tosylate (25), on the other hand, gives only uncyclised substitution and elimination products. The bromide (24) only undergoes very slow reaction (30% after 20 days) and suggests that neither an electron transfer process, as for the iodide, or a direct substitution, as for the tosylate, are particularly favourable reaction pathways. However significant amounts of cyclised product are formed, suggesting radical involvement in the reaction pathway.

Other uses of the hex-5-enyl radical rearrangement as a probe have been in aromatic homolytic substitution reactions,[67-69] the reductive demercuration of alkyl mercury(II) halides,[54,55] the Wittig rearrangement,[70] the reaction of alkali benzophenone ketyl with alkyl iodides,[71] the reduction of alkyl halides by sodium napthalenide,[72,73] the reaction of enones with various organo-metallic species,[56,72-78] the formation and oxidation of Grignard reagents[69-81] etc.

1.2.3 The cyclopropylcarbinyl radical

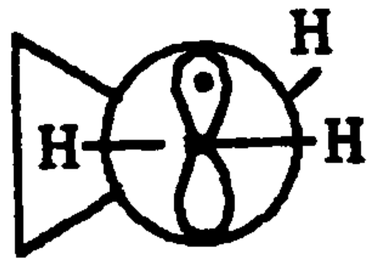
The cyclopropylcarbinyl-allylcarbinyl radical rearrangement (see Scheme XIV) has been reasonably well studied and shows some interesting features.



Scheme XIV

If cyclopropylcarbinyl radicals are generated in the cavity of the e.s.r. spectrometer[81-83] at temperatures of -140°C or lower, only the expected spectrum for the cyclopropylcarbinyl radical is observed. Between -140°C and -100°C both the cyclopropylcarbinyl and allylcarbinyl radicals are observed, and above -100°C the only observed species is the allylcarbinyl radical.

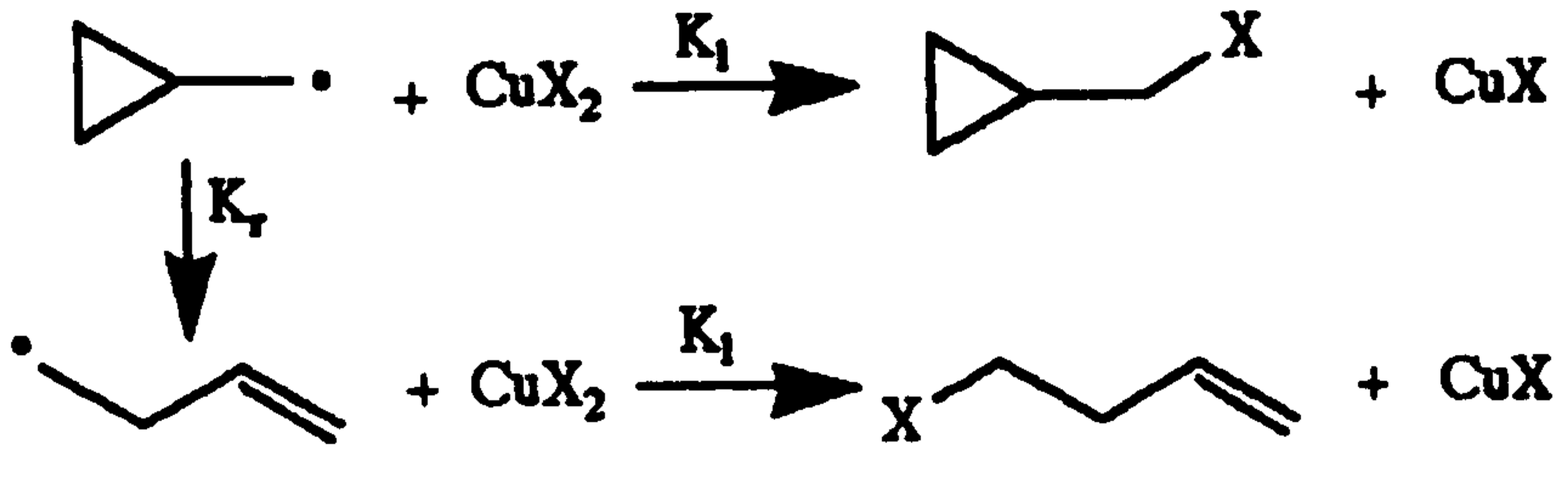
The e.s.r. spectrum of the cyclopropylcarbinyl species indicates a bisected conformation (26) is preferred.[83-86]



(26)

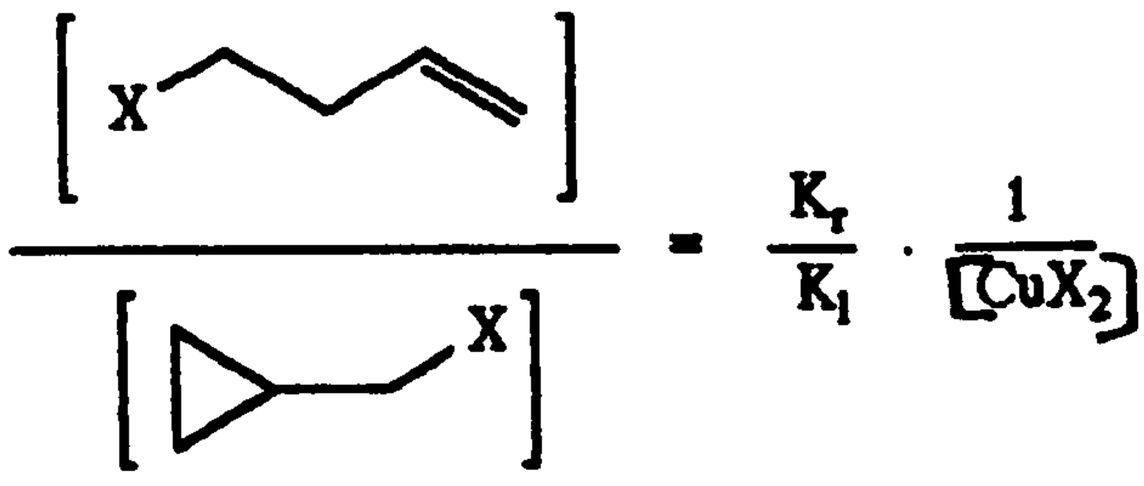
The rate constant for the cyclopropylcarbinyl-allylcarbinyl rearrangement is $k_r^{25°C} = 1.3 \times 10^8\ s^{-1}$.[82,87,88]

Like the hex-5-enyl system the cyclopropylcarbinyl-allylcarbinyl rearrangement can be used as a free-radical clock, but as the rate of rearrangement is faster it allows different reactions to be studied. The rate constants for ligand transfer of halides from copper(II) halides to alkyl radicals have been determined[87-91] in this manner (see Scheme XV). The reaction of copper(II) bromide with cyclopropylacetyl peroxide produces predominantly cyclopropylcarbinyl bromide, but some allylcarbinyl bromide was also produced due to rearrangement of the cyclopropylcarbinyl radical.



Scheme XV

An increase in the copper(II) bromide concentration overwhelms the competing rearrangement and gives a higher yield of cyclopropylcarbinyl bromide. The two competing reactions are shown (see Scheme XV). The value for the rate constant $k_r^{25^\circ C}$ = 1.3 x10^8 s^{-1} allows k_1(Br) to be calculated from Equation (7).

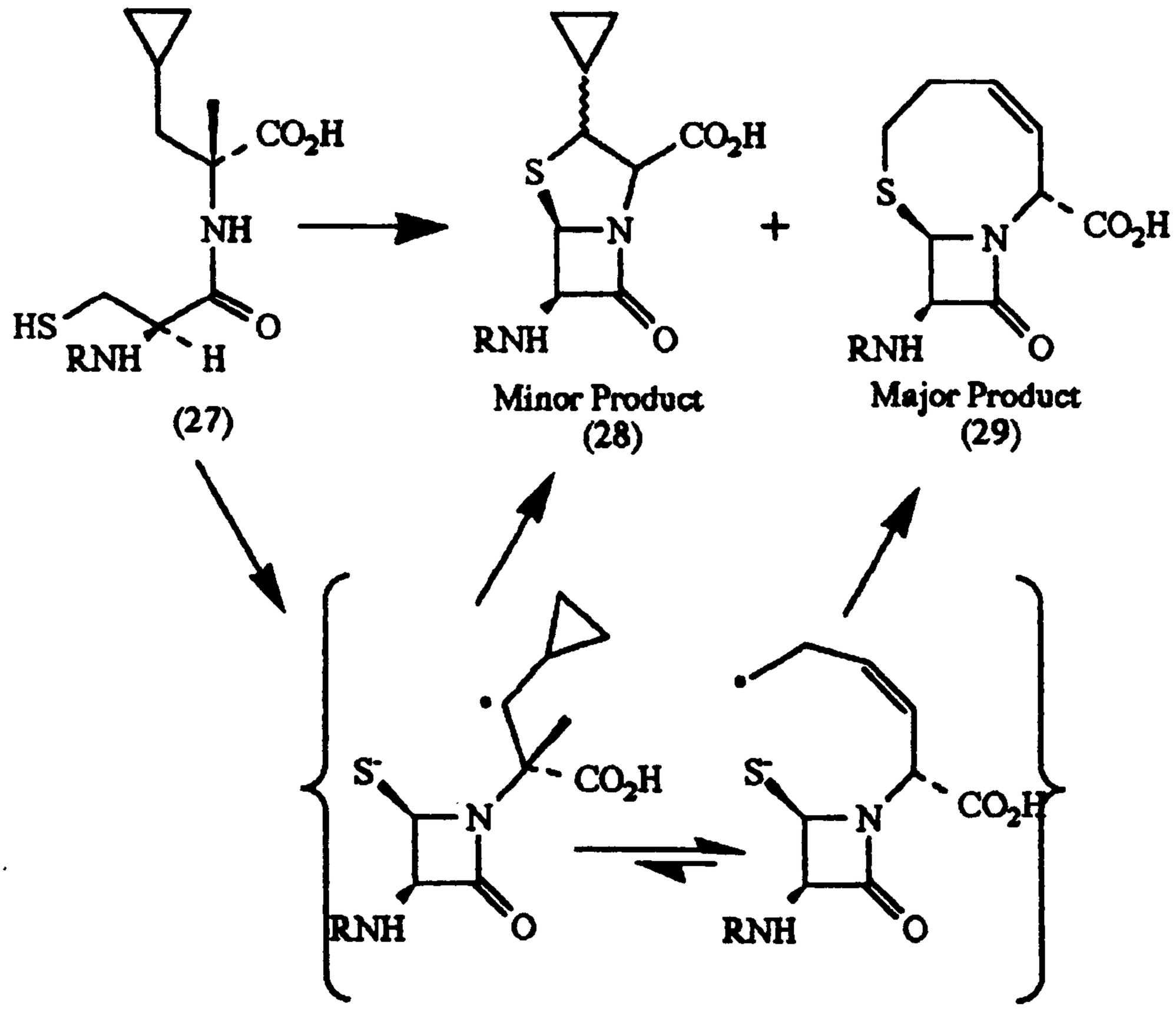


(eq. 7)

A value of k_1(Br) = 4.3 x 10^9 M^{-1} s^{-1} was obtained. The oxidation of cyclopropylacetyl peroxide by copper(II) chloride produced a mixture of isomeric chlorides. Analysis as for copper(II) bromide gave a 2nd order rate constant of k_1(Cl) = 1.1 x 10^9 M^{-1} s^{-1} for the chlorine transfer.

The cyclopropylcarbinyl-allylcarbinyl rearrangement has also been used to study various biologically based systems. One use, in

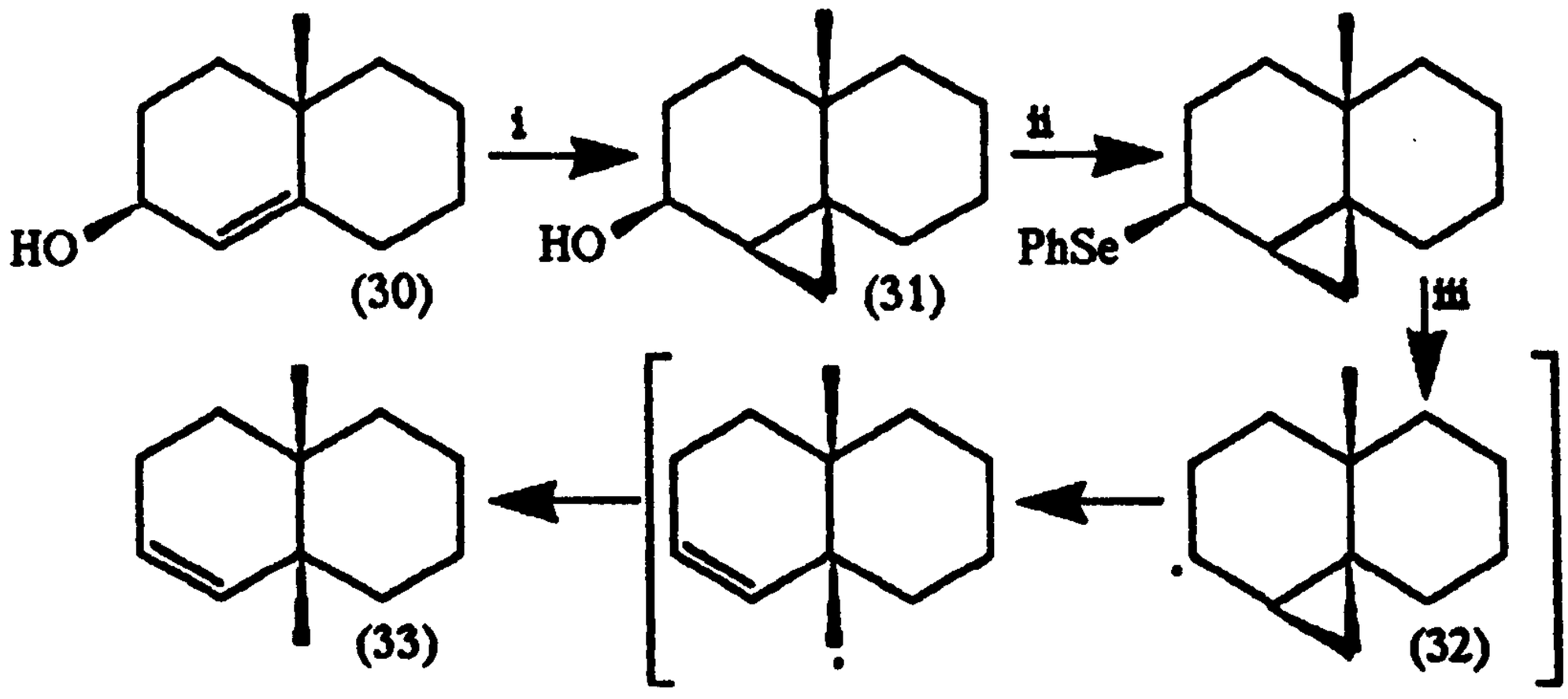
the study of hydrogen transfer to and from nicotinamide coenzymes, has been mentioned previously (section 1).[1-4] The intermediacy of free radicals in penicillin biosynthesis[92] has been probed. The cyclopropyl-containing substrate (27), (see Scheme XVI), was incubated with the enzyme isopenicillin N synthetase to give predominantly the ring-opened product (29) and the penicillin (28) as a minor component. This observation is consistent with the involvement of a free-radical intermediate in the reaction pathway, leading to ring opening of the cyclopropane ring.



Scheme XVI

Other uses of the cyclopropylcarbinyl-allylcarbinyl radical rearrangement to study the involvement of radical intermediates in biological systems include studies of cytochrome P-450 catalysed hydroxylation[93] and the cleavage of the C-P bond in degradation of organophosphate.[94] The rearrangement has been used to probe many other reactions e.g. the detection of radical intermediates in the reaction of lithium dimethylcuprate[56,57,95,96] with enones; the reactions of metalate anions with alkyl halides;[97,98] and in various photochemical[99-106] reactions.

In addition to its use as a probe species the cyclopropyl-carbinyl-allylcarbinyl radical rearrangement has also been used in synthetic applications.[126] it has been reported that preparation and opening of cyclopropylcarbinyl radicals constitutes a general synthetic method for the attachment of alkyl and substituted alkyl groups to an existing cyclic structure. The cyclic allylic alcohol (30) can be converted to the cyclopropane (31) (see Scheme XVII). The cyclopropylcarbinyl radical (32) is generated and subsequently ring opens to give the alkyl substituted system (33).



i, CH_2I_2, Zn(Cu), ether, 16 h; ii, Bu_3P, PhSeCN, THF, - 78° C to 25°C, 16h; iii, Bu_3SnH, hν hexane, 10-30°C, 2·5h.

Scheme XVII

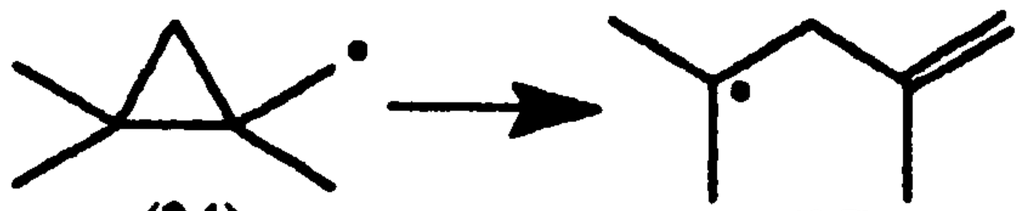
1.2.4 Substituted cyclopropylcarbinyl radicals

As noted previously the cyclopropylcarbinyl-allylcarbinyl rearrangement has several interesting features and has been used as a mechanistic probe in the detection of radical intermediates and to obtain rate data of competing processes. In its simplest form it is a reasonably well documented system but little is known about the effect of substituents[9] at the radical centre or on the ring.

Whether a radical undergoes a rearrangement, and if so, the direction and rate of that rearrangment is dependent on several factors. These factors will be considered in turn.

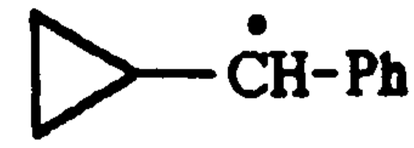
(a) Stability of the unrearranged and rearranged radicals

The relative stabilities of the unrearranged and rearranged radicals can determine which species will be observed. In the following rearrangement the initial radical (34) cannot be observed as the rearranged species (35) is a more stable tertiary radical.[107]

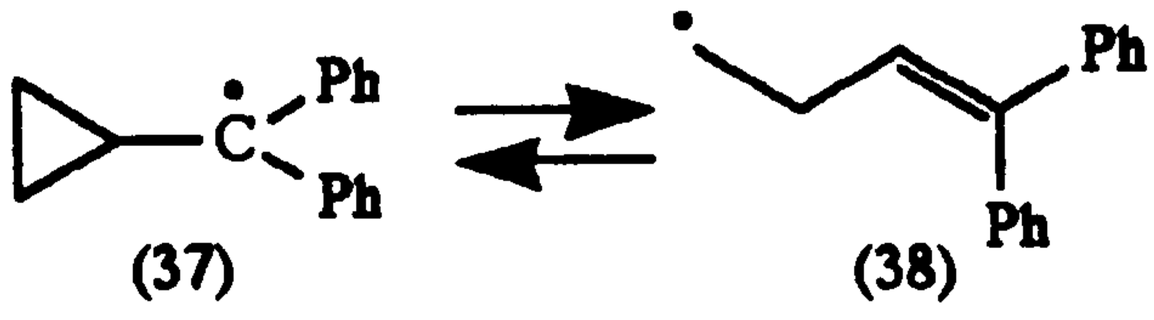


(34) (35)

The phenyl substituted radical (36) rearranges considerably less rapidly[108] than the unsubstituted cyclopropylcarbinyl radical because the radical is resonance stabilized by delocalization of the unpaired electron into the benzene ring. Even greater stabilization occurs in radical (37) which rearranges only slowly[109] and which is in equilibrium with (38).

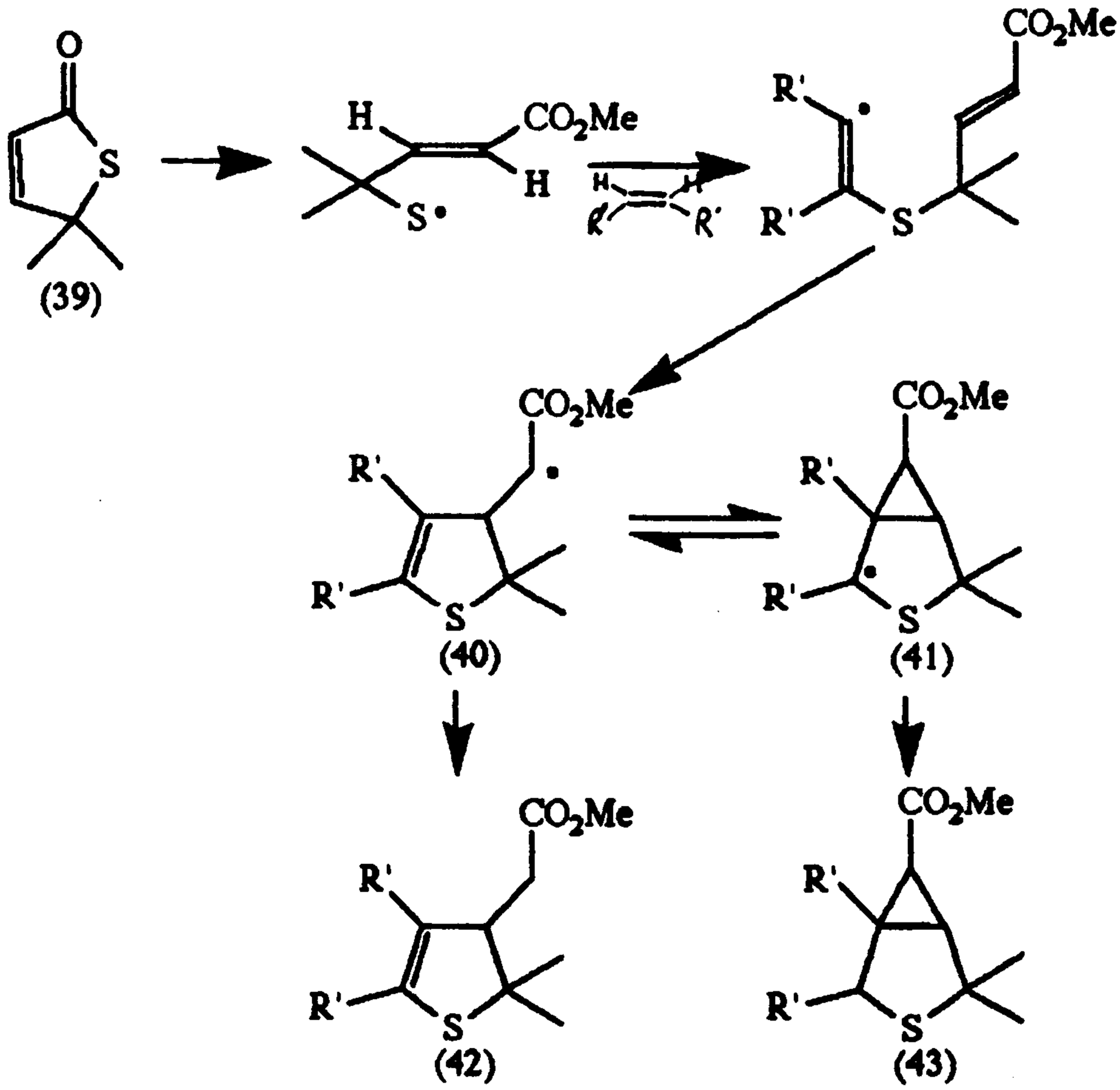


(36)



(37) (38)

It has also been shown recently[127] that a sulphur atom vicinal to the radical centre, as compared with a carbon atom, will stabilise the cyclopropylcarbinyl radical (see Scheme XVIII). Photolysis of the thiophen-2(5H)-one (39) gives, after cyclization of the initial radical, the radicals (40) and (41):



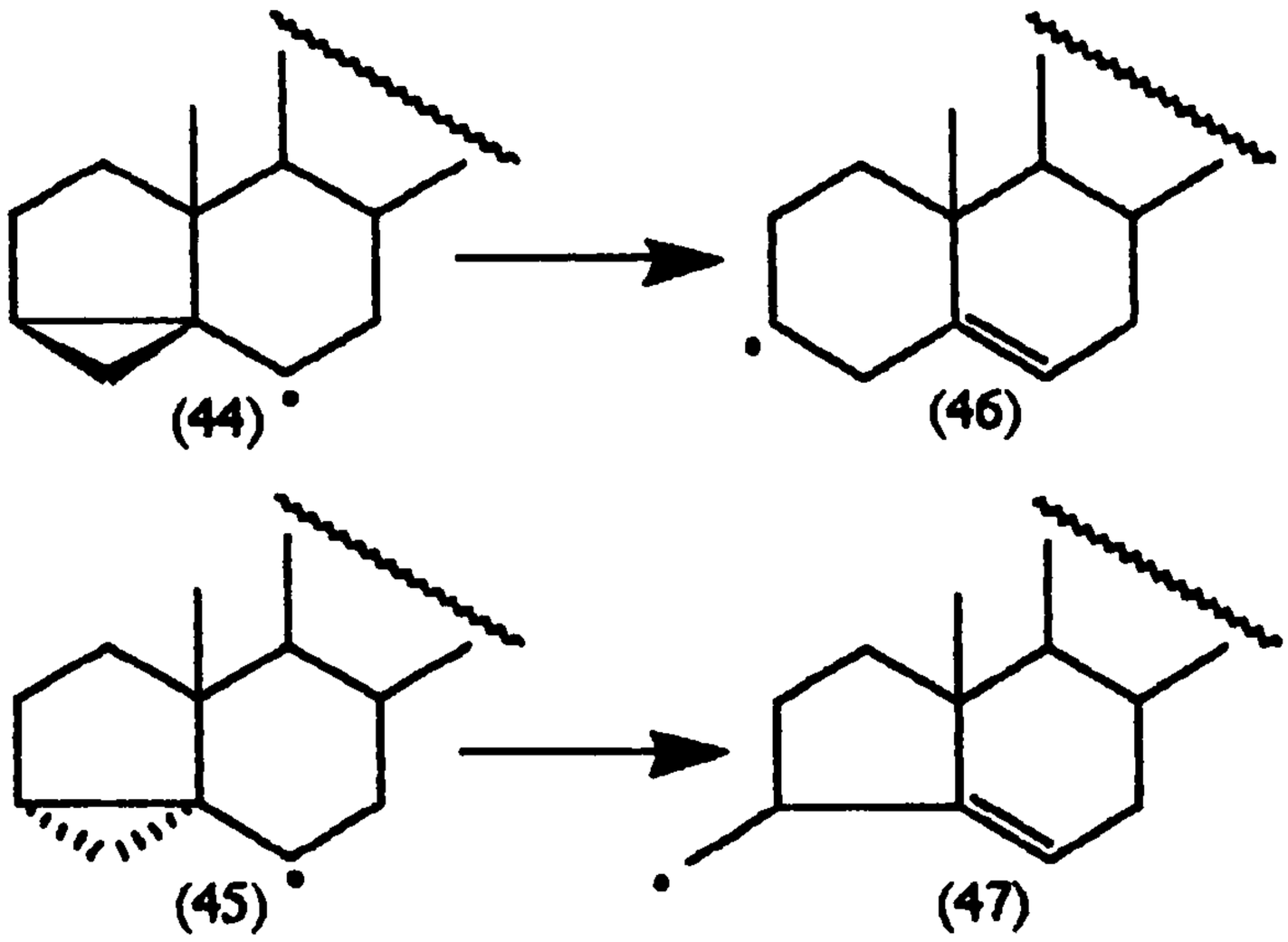
(39) (40) (41) (42) (43)

Scheme XVIII

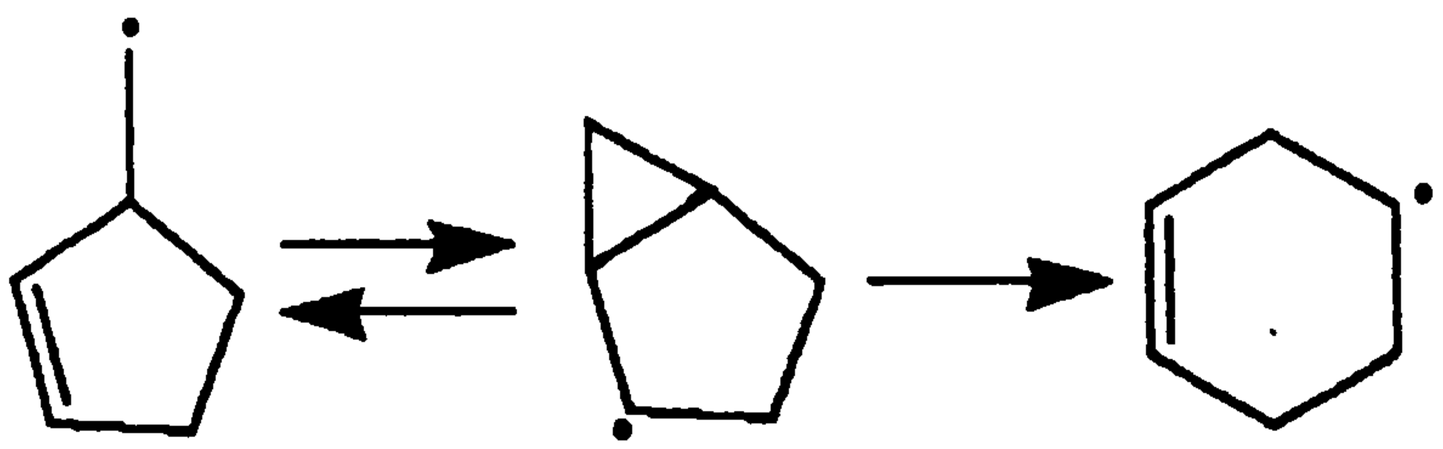
these radicals were identified as their respective products (42) and (43). It is reported that when R' = CH_3 the ratio of (42):(43) is 2:3. The presence of the sulphur atom stabilises the radical (41) and leads to the predominance of the product (43). When R' = $(CH_3)_3Si$ a further stabilisation is seen due to the presence of a silicon atom and the ratio of (42):(43) is 1:4.

(b) Stereoelectronic effects

The rate and direction of ring opening is expected to be dependent on the geometry of the orbitals involved. The two isomeric steroid radicals (44) and (45) ring open in different directions to give (46) and (47) respectively.[110]

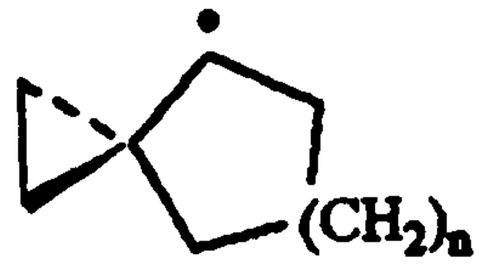


Another example of this is the bicyclic radical (49), which rearranges to give predominantly the less stable primary alkyl radical (48) together with the secondary radical (50) as a minor product.



(48) (49) (50)

The observed direction of ring opening indicates that the β–γ bond, which cleaves preferentially, is the one which is most nearly in the eclipsed conformation with respect to the semi-occupied p-orbital. This fact can be explained if the transition state for the β-scission of an alkyl radical allows maximal interaction between the semi-occupied orbital and the σ^* orbital of the bond undergoing cleavage.[99,110] A high degree of overlap however is not a prerequisite for ring opening as radicals in a fixed conformation such as radical (51) can undergo ring opening, albeit less rapidly.[8]

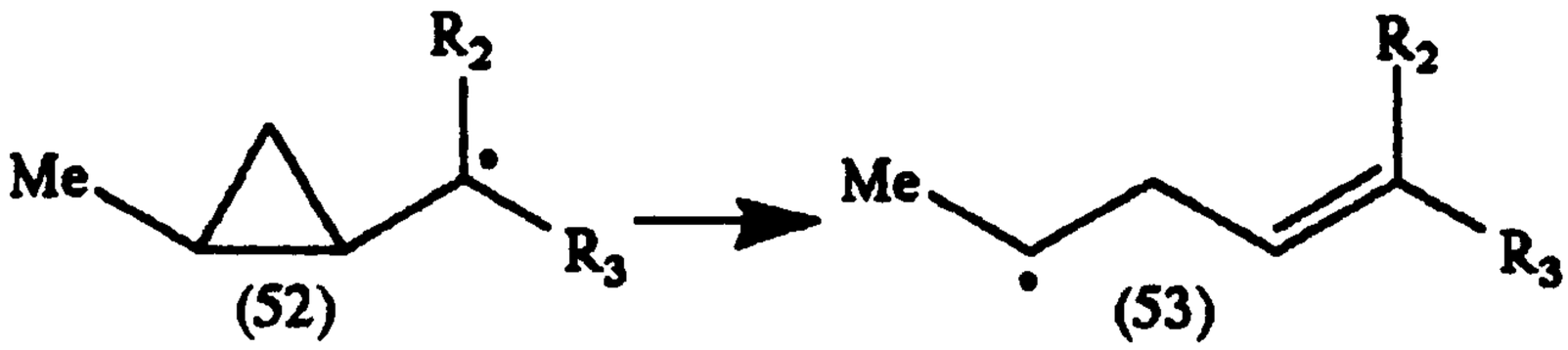


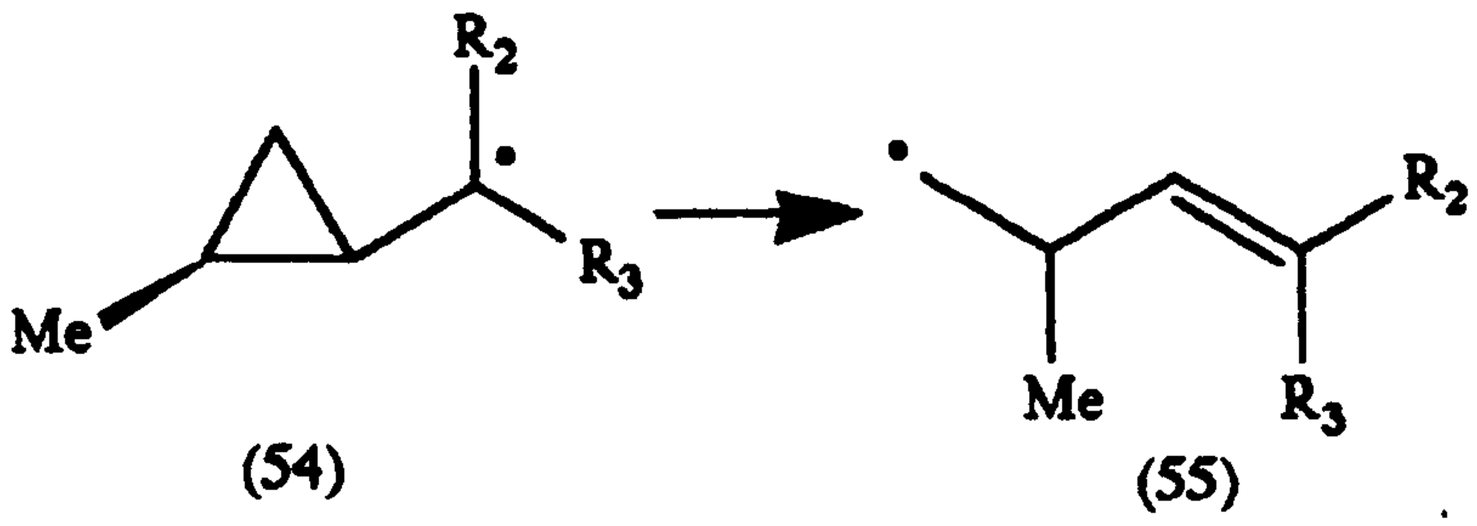
(51)

(c) Steric factors

Studies of the isomeric 2-alkyl-substituted cyclopropylcarbinyl radicals (52) and (54)[112-121] (see Scheme XIX) have shown that the radicals from the *cis*-isomers (52) rearrange to the

thermodynamically more stable secondary radicals (53).[112-119] The *trans* isomers (54) anomalously give the less stable primary radicals (55).





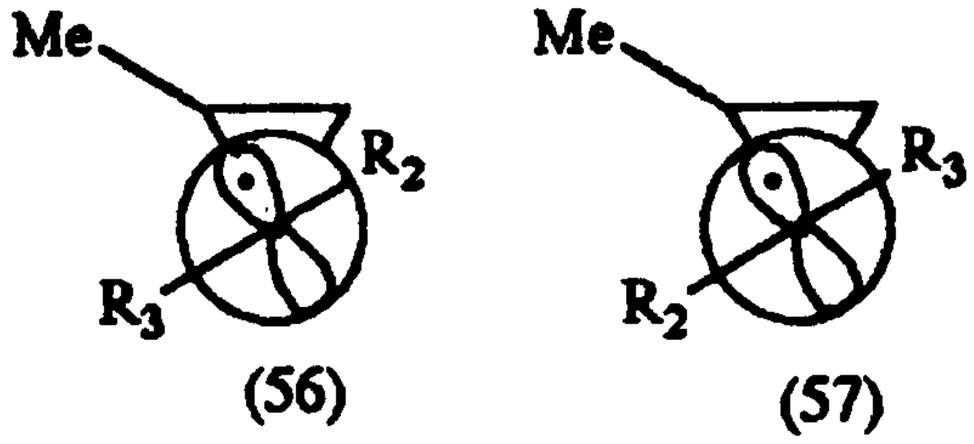
a. $R_2 = R_3 = H$

b. $R_2 = OH$, $R_3 = Me$

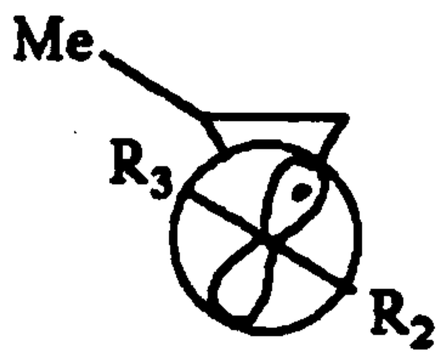
c. $R_2 = OSnBu_3$, $R_3 = Me$

Scheme XIX

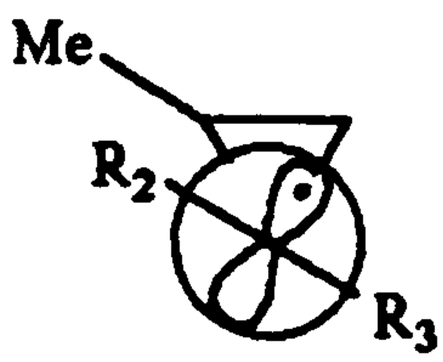
Considering the *cis*-isomers (52) first, there will be a large steric interaction between the 2-alkyl substituent and the substituents at the radical centre. The sterically favoured conformations of the *cis*-radicals (52) are shown below (56 and 57).



These conformations minimise the interaction between the substituents at the radical centre and the alkyl group. In both of these conformations there is maximum overlap of the SOMO and the σ^* orbital of the C_1-C_2 bond. The C_1-C_2 bond undergoes cleavage to give the secondary radical (41). The sterically less-favoured conformations (58 and 59) for the *cis*-radicals (52), are shown below.



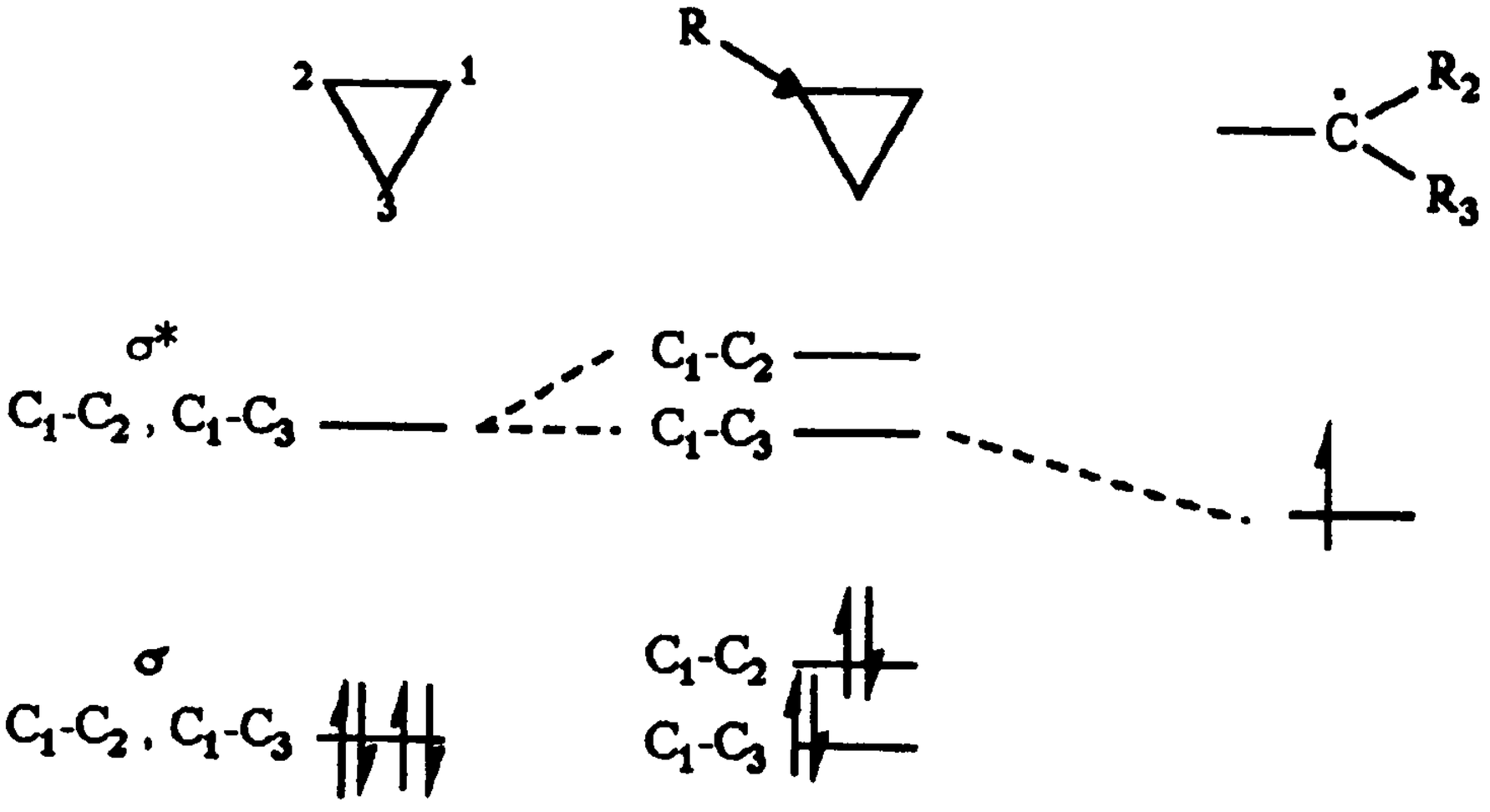
(58)



(59)

These conformations would lead to the cleavage of the C_1-C_3 bond which is not observed experimentally. It appears as if steric factors control the direction of ring-opening of *cis*-2-alkyl substituted cyclopropylcarbinyl radicals.

The ring-opening of the radicals from the *trans*-isomers (54) to give the primary radicals can be envisaged in terms of frontier molecular orbital theory.[124] In cyclopropane the orbital energies for all three C-C bonds are degenerate. The presence of a 2-alkyl group on the cyclopropane ring will raise the energies of the σ and σ^* orbitals of the C_1-C_2 bond above the energies for the C_1-C_3 bond (see Scheme XX). The interaction of the SOMO of the radical is with the σ^* rather than the σ orbital and this leads to cleavage of the C_1-C_3 bond. This cleavage would result in the primary radical being formed.



Scheme XX

For the *cis*-isomers (52) there is a large steric interaction between the two *cis* groups in the conformations that would lead to C_1-C_3 cleavage. This large steric interaction overides any effect seen by the raising of the orbital energies of the C_1-C_2 bond. The direction of ring-opening of the *cis*-radicals is controlled by steric factors and the *trans*-radicals by polar factors.

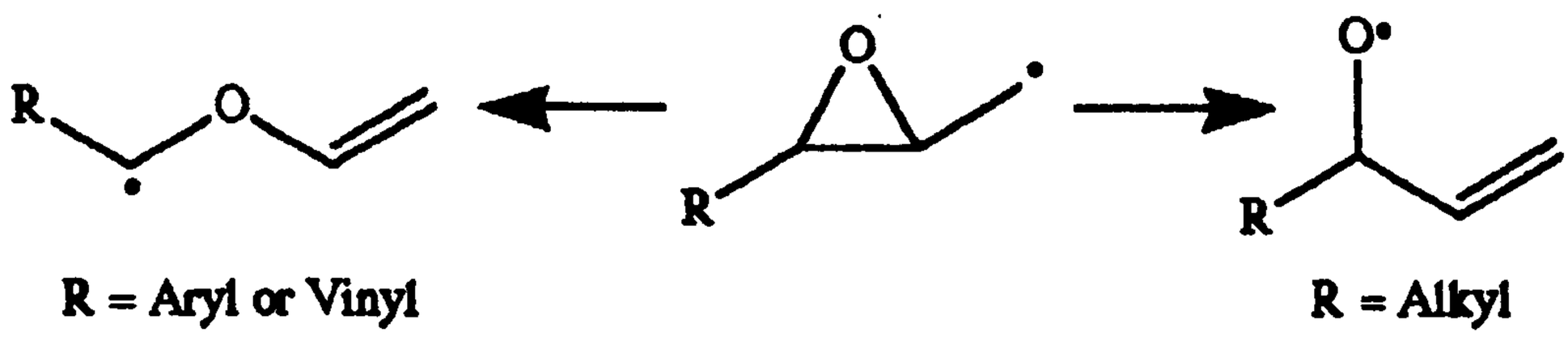
(d) Polar effects

We now look at some substituted cyclopropylcarbinyl radicals in turn. First the oxiranylmethyl radical (60)[115] undergoes rearrangement at least an order of magnitude faster than the cyclopropylcarbinyl species.

(60)

(61)

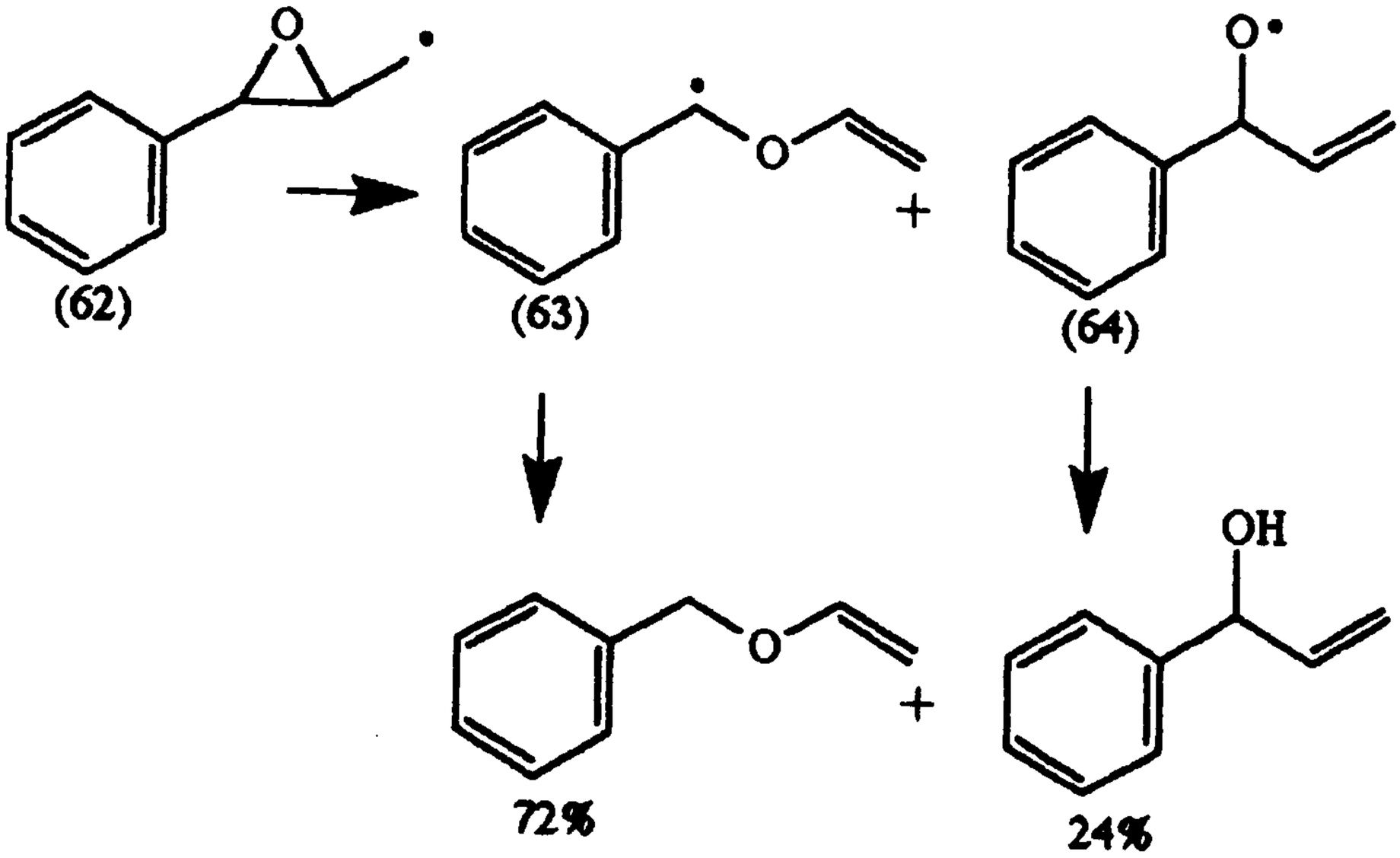
The rearrangement occurs by exclusive C-O bond cleavage even though a C-O bond is generally 4-20 kJ mol^{-1} stronger than a C-C bond. This is consistent with the involvement of the dipolar transition state (61) which is stabilised by the presence of an oxygen atom. However, if the product radical is sufficiently stabilized then C-C bond cleavage may occur rather than the C-O bond cleavage[128-132] (see Scheme XXI). This observation has been



Scheme XXI

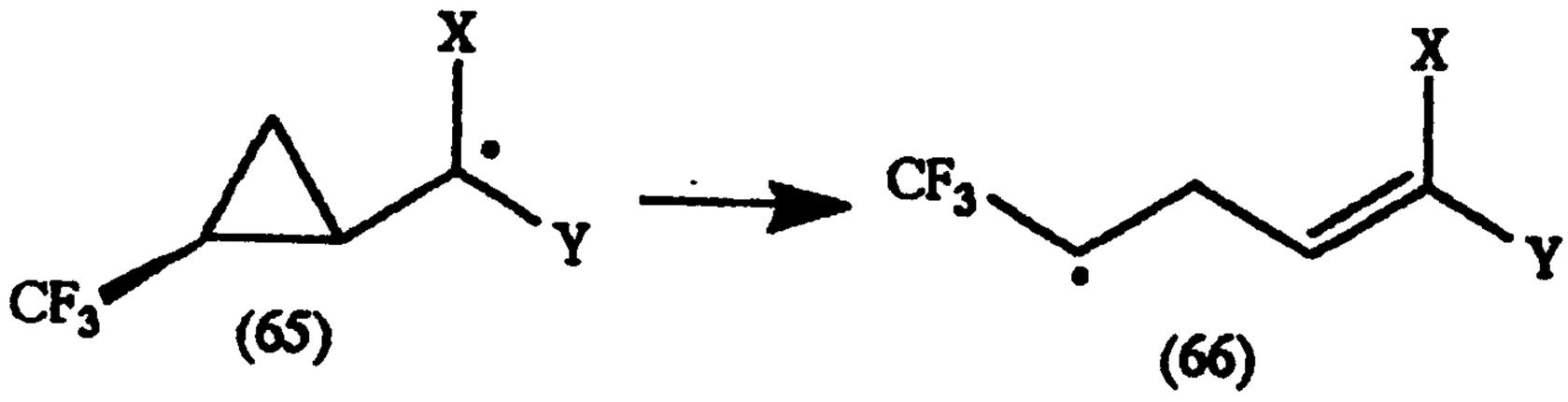
used synthetically in the production of novel vinyl ethers[123] (see Scheme XXII). The radical (62) rearranges to give predominantly

the aryl stabilised product radical (63). C-C bond cleavage is also proposed[130] as a step in the biosynthesis of the antibiotic Rifamycin S.

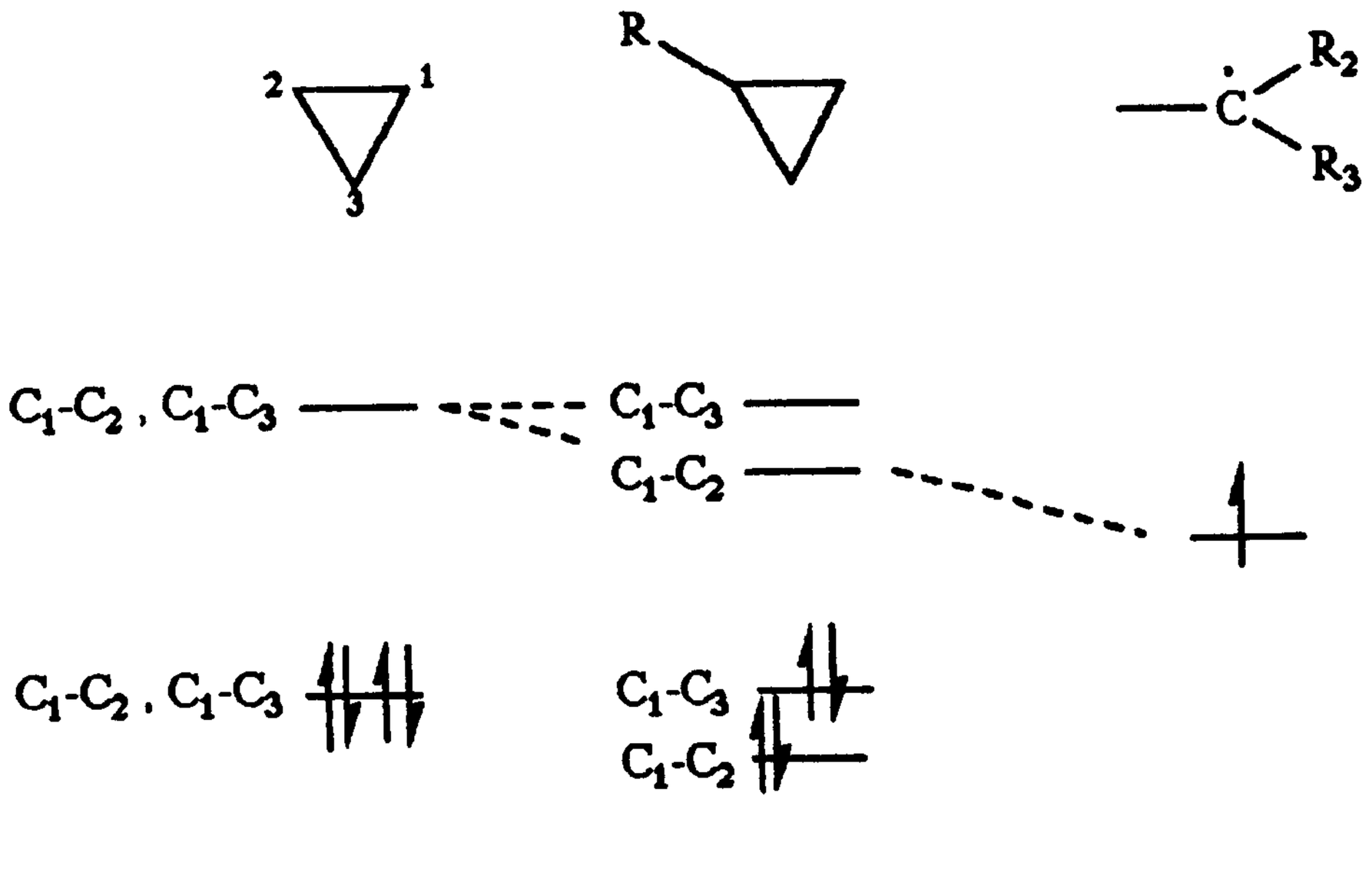


Scheme XXII

The *trans*-2-trifluoromethylcyclopropylcarbinyl radical (65) gives preferentially the secondary radical (66);[124] this is in contrast to the analogous *trans*-2-methylcyclopropylcarbinyl radical (54), which gives predominantly the primary radical, but is consistent with the proposed dipolar transition state for the rearrangement.

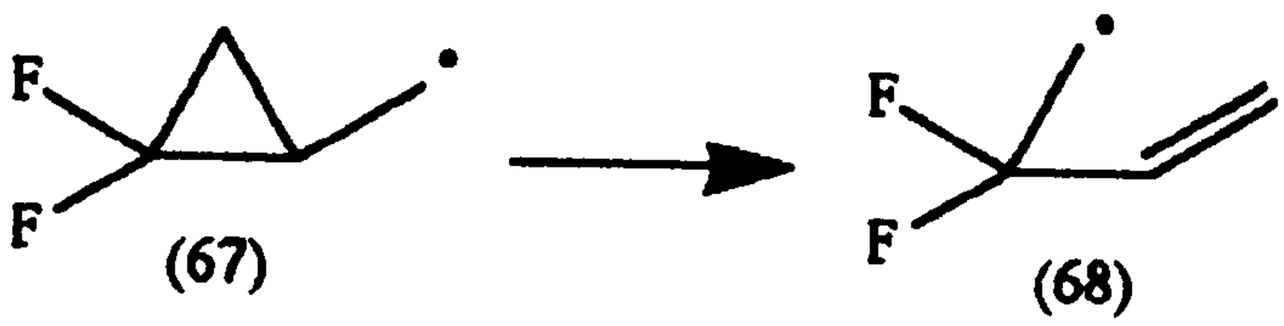


Frontier molecular orbital theory can be used to explain the differences observed between *trans*-2-trifluoromethyl and the *trans*-2-methylcyclopropylcarbinyl radicals.[124] The ring-opening of the *trans*-2-methylcyclopropylcarbinyl radical has already been discussed in this manner (see section 1.2.4. (c)). The presence of a *trans*-2-trifluoromethyl group will have the opposite effect to the *trans*-2-methyl group. A 2-trifluoromethyl group on the cyclopropane ring will lower the energies of the σ and σ^* orbitals of the C_1-C_2 bond below those of the C_1-C_3 bond (see Scheme XXIII). The interaction of the SOMO of the radical is with the σ^* orbital and will lead to cleavage of the C_1-C_2 bond. This cleavage results in the secondary radical being formed.

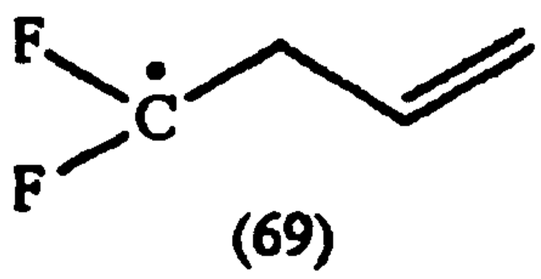


Scheme XXIII

On rearrangement the 2,2-difluorocyclopropylcarbinyl radical (67) gives only the primary product radical (68).[123]



The other possible product radical is the more stable difluoro alkyl radical (69). The formation of the primary radical product has been

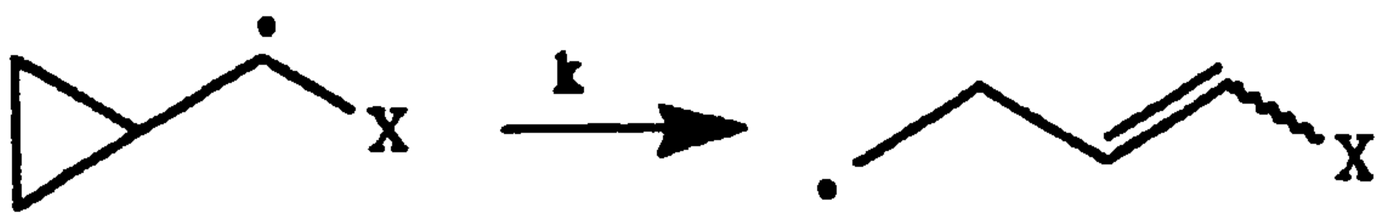


explained in two ways. The dipolar transition state for the rearrangement is less favoured in the case of the secondary radical product resulting in only the primary radical (67) being observed. It has also been suggested[123] that the effect of the fluorine substituents is to weaken the C-C bond opposite the substituents. The preferential cleavage of this bond results in formation of the primary product. Further information about the process involved could be obtained from a detailed kinetic study of the rearrangement. If the rate of the ring-opening rearrangement of the radical (67) is faster than that found for the unsubstituted cyclopropylcarbinyl radical then the bond-weakening theory holds. If the rate is slower then a dipolar transition state is implicated.

Substituents that would enhance the stability of the transition state might be expected to increase the rate of ring opening of the radical, as in the case of the oxiranylmethyl radical (48). Conversely substituents that reduce the stability of the transition state would be expected to decrease the rate of ring-opening, as for esters, nitriles and other electron-withdrawing groups.

2. DISCUSSION

The ring-opening of cyclopropylcarbinyl radicals has been postulated to proceed via a dipolar transition state.[133] It is expected that the nature of substituents on the ring and at the radical centre would affect the rate of ring-opening. It is found[134] (see Table III) that a species with an electron-withdrawing group at the radical centre will ring-open several orders of magnitude less rapidly than the parent radical.



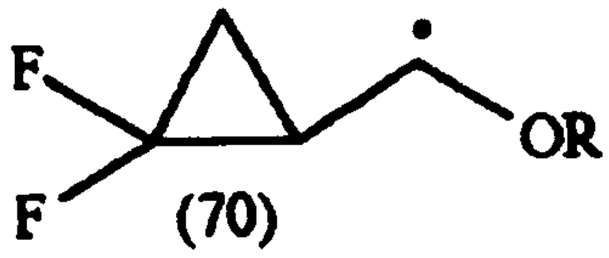
Substituent X	Highest temp at which unrearranged radical observed (K)	Max value of $k(s^{-1})$ at 298K
H		2.2×10^8
$COOBu^t$	310	4×10^2
$COOCH_3$	290	2×10^3
CN	220	4×10^5
C≡CH	290	2×10^3

Table III: Rates of rearrangement of cyclopropylmethyl radicals with an electron-withdrawing group at the radical centre

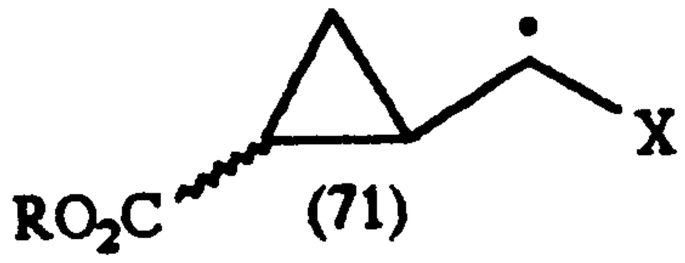
These findings are in agreement with a postulated dipolar transition state for the rearrangement. In all the radicals noted (see Table III) however, the rate of ring-opening may be

significantly lower than that of the parent radical due to delocalisation of the unpaired electron on to the α-substituent in the initial radical. It was hoped in this thesis to estimate the relative importance of factors that influence the rate of ring-opening of substituted cyclopropylcarbinyl radicals and to examine the evidence for the proposed dipolar transition state.

At the start of the project several target radicals were proposed so that the effect of the substituents could be observed without delocalisation of the unpaired electron occurring. The difluorocyclopropyl compound (70) was chosen to enable the electron-withdrawing effect of the fluorine groups on the

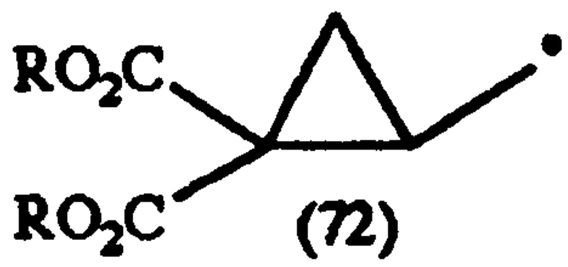


(70)

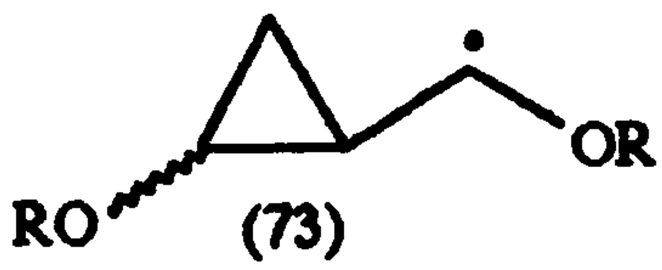


(71)

ring-opening to be studied. The target compound (71) would allow an assessment of the effect of an ester group on the radical rearrangement. It would be important to separate the stereoisomers of this compound because, as mentioned previously (see section 1.2.4 (c) and (d)), the *cis* and *trans*-isomers can ring-open in different directions. To eliminate these stereochemical considerations the diester (72) was thought of as a target radical.

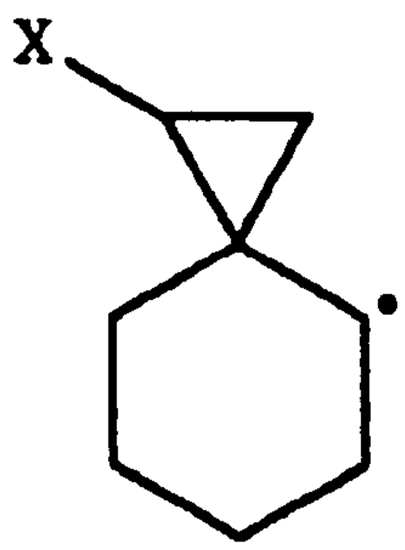


(72)

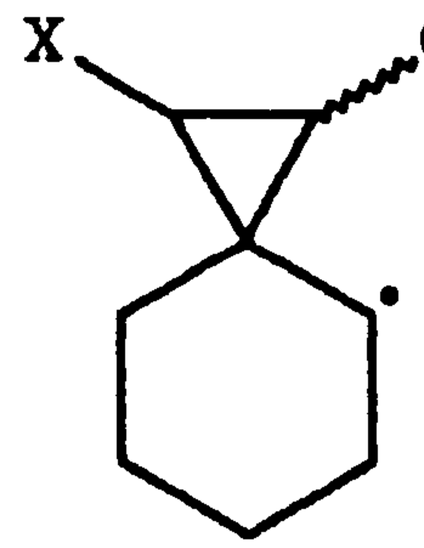


(73)

The synthesis of a precursor for the radical (73) would allow the study of the effect, on the ring-opening, of an electron-withdrawing OR group. The two spiro radicals (74) and (75) were suggested as targets for two reasons. It is known[135] that t-butoxyl radicals

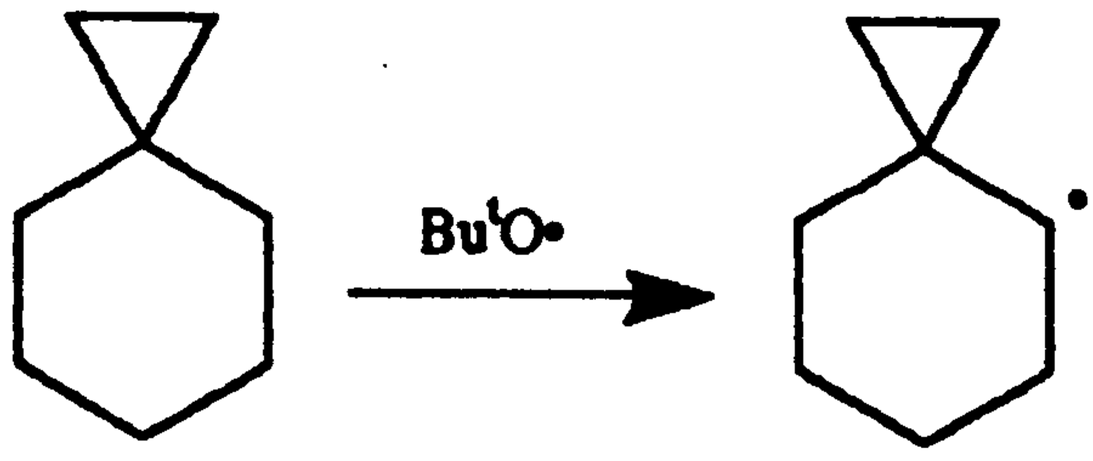


(74)



(75)

abstract hydrogen from spiro[2.5]octane (76) to give almost exclusively the spiro[2.5]oct-2-yl radical (77).



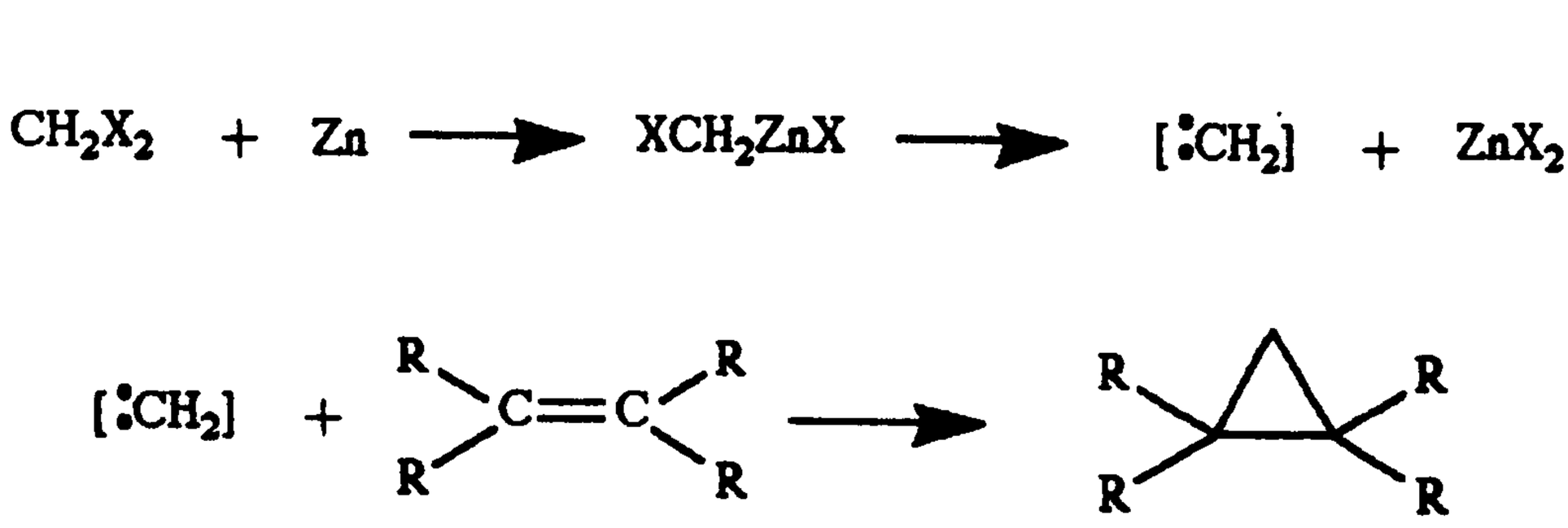
(76) (77)

This abstraction would allow us to generate these spiro radicals easily for use in e.s.r. spectroscopy. It was also anticipated, misguidedly, that the synthesis of the precursors for these radicals would be relatively straightforward.

The bulk of the synthetic work carried out was directed towards the production of precursors for the difluorocyclo-

propane compounds. Most success was achieved in obtaining precursors that would give the radical species (71), (72), and (73). Spiro compounds that would have given radicals (74) and (75) were not successfully synthesised. The bulk of the synthetic work is in two major sections, the first covering the difluorocyclopropane compounds (see section 2.1) and the second relating to the other substituted cyclopropanes (see section 2.2).

The majority of cyclopropane syntheses were undertaken by the generation of a carbene or a carbenoid species and its subsequent addition to an alkene. The reaction of a carbene with an alkene is a standard route to cyclopropanes. The well documented Simmons-Smith reaction involves the addition of methylene carbene, $:CH_2$, to an alkene to give the cyclopropane (see Scheme XXIV).



Scheme XXIV

The addition of a carbene is not limited to methylene carbene but other substituted carbenes can be generated from suitable precursors. Two substituted carbenes, difluorocarbene, $:CF_2$, and carboethoxycarbene, $:CHCO_2CH_2CH_3$ are discussed in the following work.

A carbene, under certain circumstances will undergo an insertion reaction into a C-O or C-halogen bond. This insertion reaction was observed while attempting to carry out cyclopropanation reactions using some allylic compounds; these reactions are discussed in section 2.2.3.

In section 2.3 the reduction of cyclopropyl phenyl ketone and cyclopropyl ferrocenyl ketone by tributyltin hydride is discussed and the differing extent to which a phenyl and ferrocenyl group stabilise a cyclopropylcarbinyl radical is reported. An attempt was also made to use the radical trap 1,1,3,3-tetramethylisoindolin-2-yloxyl in this study. The production of this radical trap and its use are discussed in section 2.4.

To return to one of the major sections of work, the synthesis of 1,1-difluorocyclopropanes is discussed below.

2.1 Synthesis of 1,1-Difluorocyclopropanes

The synthesis of 1,1-difluorocyclopropanes is reported in the literature. The majority of the methods reported are based on the production of difluorocarbene and its subsequent addition to an alkene to give the difluorocyclopropane. There are four methods of synthesis listed below: methods (1) to (3) are based on generation of difluorocarbene while method (4) involves the cyclopropanation of a fluorinated alkene.

(1) decomposition of methyl chlorodifluoroacetate, $ClCF_2CO_2CH_3$, by a lithium chloride/HMPA complex.[136,137]

(2) decomposition of phenyl(trifluoromethyl)mercury by sodium iodide.[138-141]

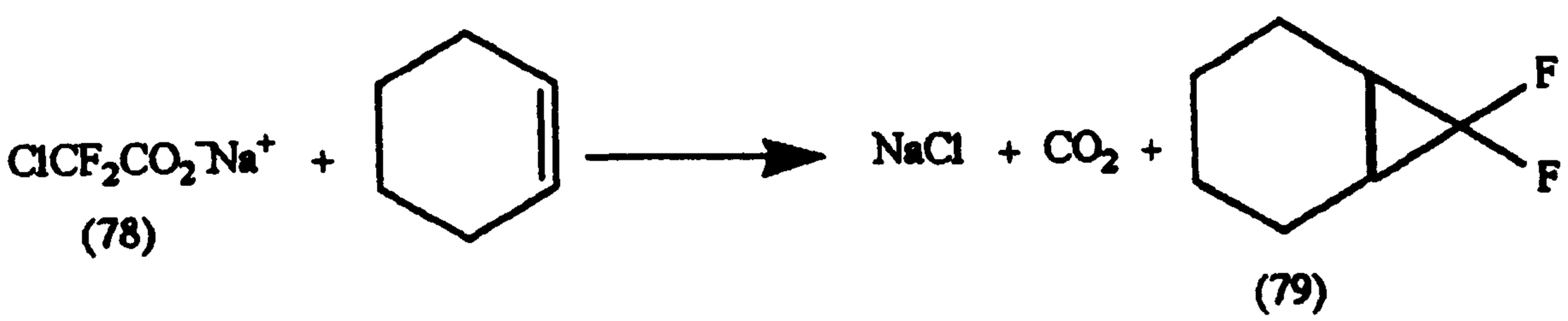
(3) decomposition of halodifluoromethylphosphonium salts by alkali metal fluorides.[142]

(4) cyclopropanation of ethyl 3,3-difluoroacrylate.[143,144]

All four methods have been attempted with varying degrees of success. Taking each method in turn the work undertaken and the problems encountered are discussed.

2.1.1 Decomposition of methyl chlorodifluoroacetate by a LiCl/HMPA complex

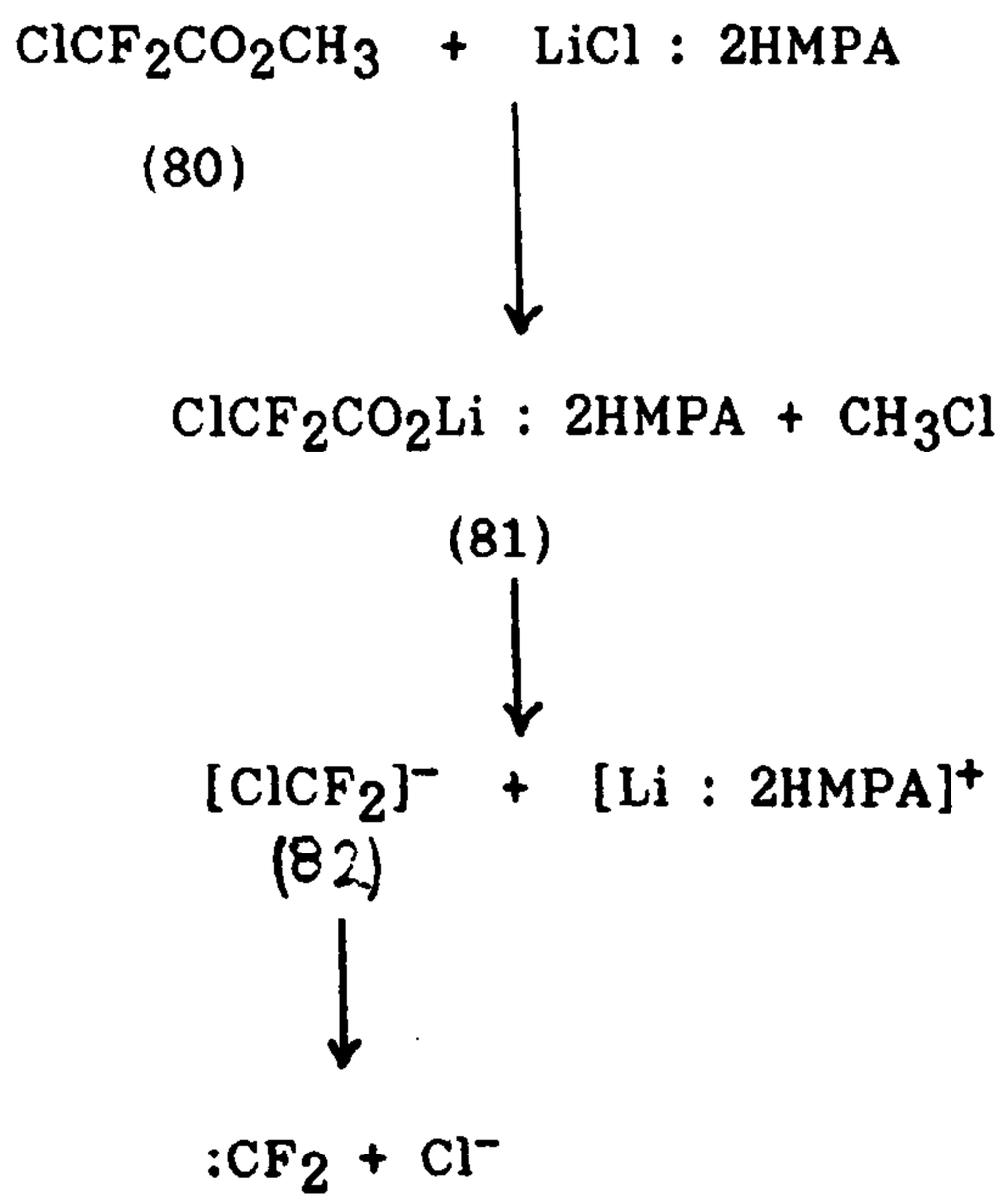
It has been reported that sodium or lithium chlorodifluoroacetate can be decarboxylated in the presence of an alkene to give the corresponding difluorocyclopropane. The decarboxylation of sodium chlorodifluoroacetate (78) in the presence of cyclohexene gave difluoronorcarane (79)[145] (see Scheme XXV). These reactions have several disadvantages, they are said to require a large excess of the acetate salt before reasonable yields of the cylcopropane are obtained. The acetate salts are extremely



Scheme XXV

hygroscopic and must be handled under rigorously anhydrous conditions, usually in a "dry box". It is also reported that difluorocarbene generated in this way is less efficiently trapped than when the carbene is generated from organometallics[138-141] (see section 2.1.2) or difluorodiazirine.[146]

The difficulties mentioned above have led to the development, by Wheaton and Burton,[136,137] of a reaction involving the addition of the readily synthesised methyl chlorodifluoroacetate (80) to a lithium chloride/hexamethylphosphoramide complex (see Scheme XXVI). In this reaction the acetate salt complex (81) is generated in-situ and on decarboxylation at 80°C gives the chlorodifluoro-



Scheme XXVI

methide ion (82). The chlorodifluoromethide ion spontaneously decomposes to give difluorocarbene and chloride. The difluoro-

carbene produced is trapped by an alkene to form the difluoro-cyclopropane. The reaction (Scheme XXVI) is carried out in the presence of excess alkene to favour the carbene-alkene addition reaction over the possible carbene-carbene coupling reaction.

This procedure of Wheaton and Burton was used in an attempt to produce the difluorocyclopropanes required as radical precursors. Two different types of reaction conditions were used:

(1) anhydrous conditions and a dry nitrogen atmosphere (see Table IV); and

(2) <u>in-vacuo</u> in sealed glass vials (see Table V).

Both of these methods proved to be unsuccessful. This failure was probably due to insufficiently anhydrous reaction conditions. The experiments carried out are listed below (see Tables IV and V). The alkene used in most of these experiments was the reportedly[136,147,148] good carbene trap 2,3-dimethylbut-2-ene. The reaction mixtures were analysed by g.l.c., however, for most of the experiments, no indication of any reaction taking place was seen. For the reactions carried out at atmospheric pressure most of the reaction mixtures showed, on analysis by g.l.c., only the presence of the starting alkene. Two of the reactions carried out showed the presence of a minor product on g.l.c. analysis. This product had a shorter retention time than the starting alkene. It was attempted, without success, to isolate this material by fractional distillation from the reaction mixture.

The sealed tube reactions were carried out in order to reduce the amount of alkene present and hopefully ease the

LiCl (mol)	HMPA (mol)	$CClF_2CO_2CH_3$ (mol)	Alkene used (mol)	Temp(^oC)	Time(h)	Solvent
0.1	0.2	0.05	2,3-dimethylbut-2-ene 0.2	80	34	Triglyme[a]
0.1	0.2	0.05	" " "	110	24	Triglyme[b]
0.025	0.05	0.025	" " "	80	18	none[c]
0.05	0.02	0.05	" " "	41	42	CH_2Cl_2[d]
0.05	0.01	0.05	" " "	41	90	CH_2Cl_2[e]

(a) Recovered unreacted alkene; (b) g.l.c. showed slight reaction had occurred; (c) g.l.c. showed slight reaction had occurred; (d) g.l.c. showed no reaction had occurred; (e) g.l.c. analysis showed no reaction had occurred.

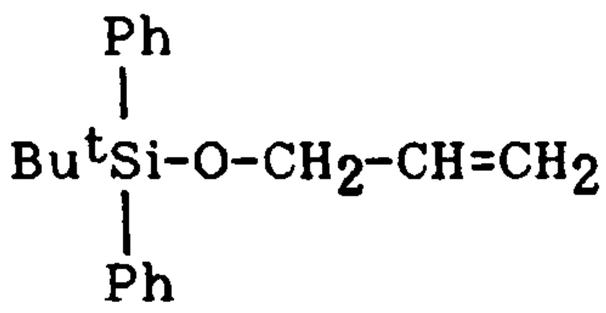
Table IV Reaction conditions for the attempted production of trapping :CF_2 from $CClF_2CO_2CH_3$ under anhydrous conditions and a dry N_2 atmosphere.

LiCl(mol)	HMPA(mol)	$CClF_2CO_2CH_3$(mol)	Alkene used (mol)	Temp(°C)	Time(h)	Solvent
$3.3x16^{-3}$	$6.6x10^{-3}$	$1.6x10^{-3}$	2,3-dimethylbut-2-ene $6.6x10^{-3}$	150	42	Triglyme 3ml
$3.3x10^{-3}$	$6.6x10^{-3}$	$1.6x10^{-3}$	cyclopentane $6.6x10^{-3}$	150	42	Triglyme 3 ml
$99x10^{-3}$	$19.9x10^{-3}$	$4.9x10^{-3}$	2,3-dimethylbut-2-ene $2.52x10^{-3}$	80	24	none
$2.5x10^{-2}$	$5x10^{-2}$	$1.25x10^{-2}$	2,3-dimethylbut-2-ene	80	20	none
$2.5x10^{-2}$	$5x10^{-2}$	$2.5x10^{-2}$	2,3-dimethylbut-2-ene	80	20	none
0.01	0.02	0.01	t-Bu $Si(Ph_2)$-O-CH_2-CH=CH_2	80	18	none
0.05	0.1	0.05	2,3-dimethylbut-2-ene	80	24	none

Table V Reaction conditions for the attempted production of trapping :CF_2 from $CClF_2CO_2CH_3$ in vacuo in sealed glass vials.

detection and isolation of any product. It was also hoped that it would be simpler to keep these reactions anhydrous. On analysis by g.l.c. the only material recovered, in these reactions, was the starting alkene.

In an attempt to make a less volatile product the alkene 3-(t-butyldiphenylsilyloxy)prop-1-ene (83) was used in the above reaction at atmospheric pressure. The 3-(t-butyldiphenylsilyloxy)-



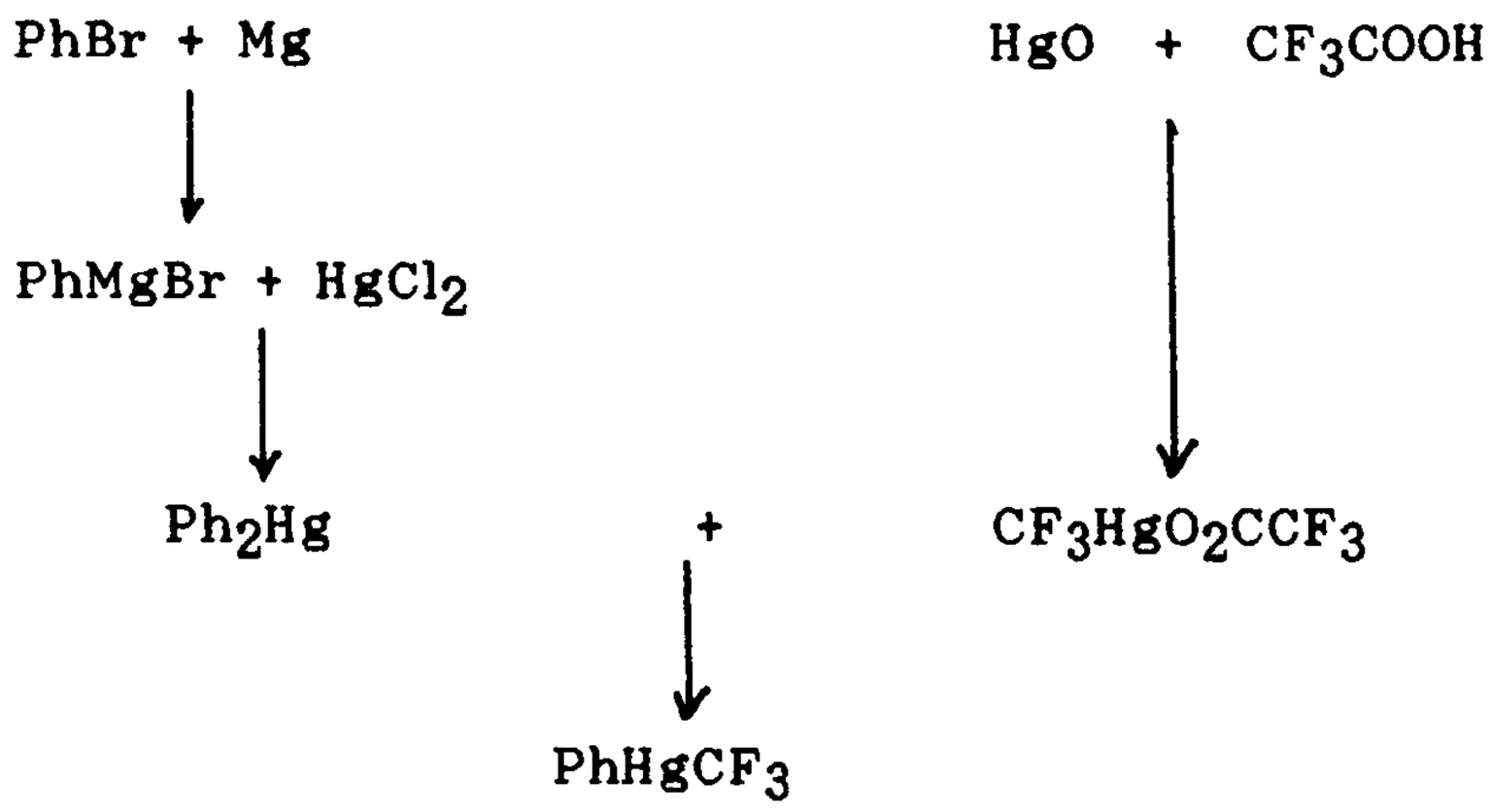
(83)

prop-1-ene was synthesised by a standard route from t-butyl-chlorodiphenylsilane and allyl alcohol. The t-butyldiphenylsilyloxy group was chosen for this reaction because of its bulk and high molecular weight. It was hoped that any cyclopropane formed, by addition of difluorocarbene, would be relatively non-volatile and easier to isolate and analyse. The t-butyldiphenylsilyloxy group is also less prone to hydrolysis and easier to handle than the trimethylsilyloxy analogue.

No product from the reaction of difluorocarbene with the alkene (83) was seen by g.l.c. analysis, the only material evident being the alkene (83).

2.1.2 Decomposition of phenyl(trifluoromethyl)mercury by sodium iodide

This method depends on the production and spontaneous decomposition of a trifluoromethide ion. This route to difluorocarbene was pioneered by Seyferth et. al.[138-141] A major disadvantage of this method is the lengthy procedure required for the production of the starting material phenyl(trifluoromethyl)-mercury (see Scheme XXVII).



(84)

Scheme XXVII

The overall yield of phenyl(trifluoromethyl)mercury (84) is low. The difluorocarbene is generated from phenyl(trifluoromethyl)mercury (84) by heating with sodium iodide. It has been postulated that the decomposition occurs via an intermediate trifluoromethide ion (85) (see Scheme XXVIII).

$$PhHgCF_3 + NaI \longrightarrow PhHgI + Na^+[CF_3]^-$$

(84) (85)

$$Na^+[CF_3]^- \longrightarrow NaF + :CF_2$$

(85)

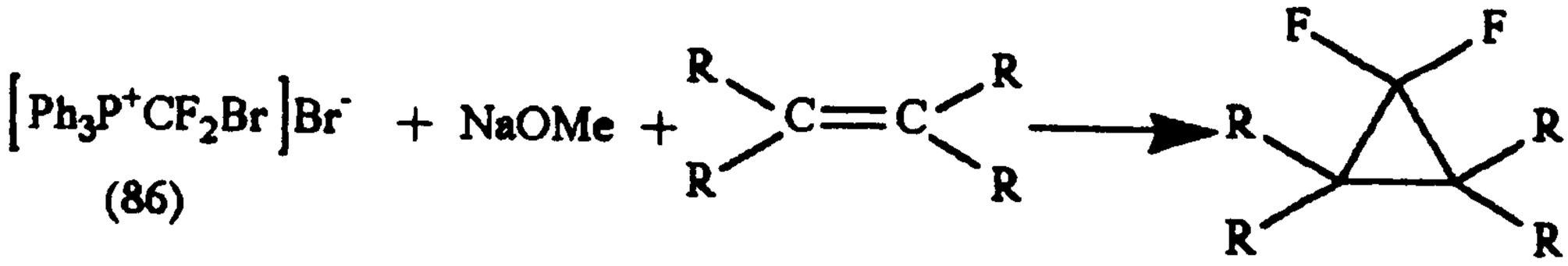
Scheme XXVIII

This reaction was carried out in the presence of an excess of the alkene 2,3-dimethylbut-2-ene but over several attempts the only compound isolated from the reaction mixture was the alkene. It is believed with hindsight that the anhydrous conditions used were not stringent enough at excluding moisture to allow a reaction to proceed. The alkene and sodium iodide must be rigorously dried for any reaction to occur; handling the sodium iodide while maintaining its anhydrous nature was difficult and probably not rigorous enough. The drying of the phenyl(trifluoromethyl) mercury is not easily achieved as aqueous based reaction steps are involved in its production.

2.1.3 Decomposition of halodifluoromethylphosphonium salts by alkali metal fluorides

In the previous two methods for difluorocarbene production, sections 2.1.1 and 2.1.2, the precursors were toxic, difficult to synthesise, handle or obtain in large quantities. This method, developed by Burton and Naae,[142] is based on the discovery that

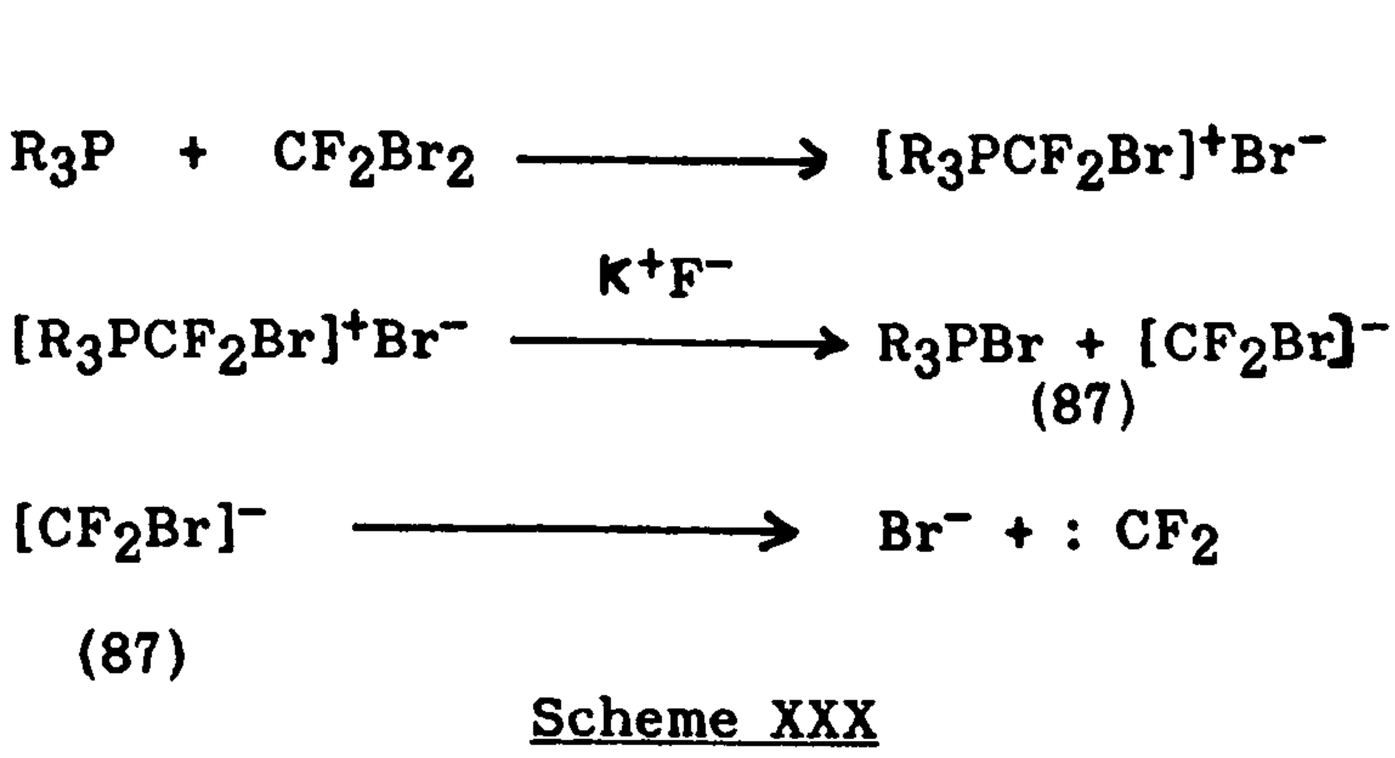
when bromodifluoromethylphosphonium bromide (86) was treated with sodium methoxide in the presence of an alkene the difluoro-cyclopropane adduct was obtained, albeit in low yield (see Scheme XXIX).



Scheme XXIX

The methoxide is believed to attack the phosphonium salt to generate the bromodifluoromethide ion (87) which decomposes to give the diflurocarbene and bromide. The low yield of the cyclopropane adduct is possibly due to competition between the methoxide and the alkene for the carbene. The use of potassium fluoride as a base alleviated this problem as the potassium fluoride did not compete with the alkene for the carbene produced.

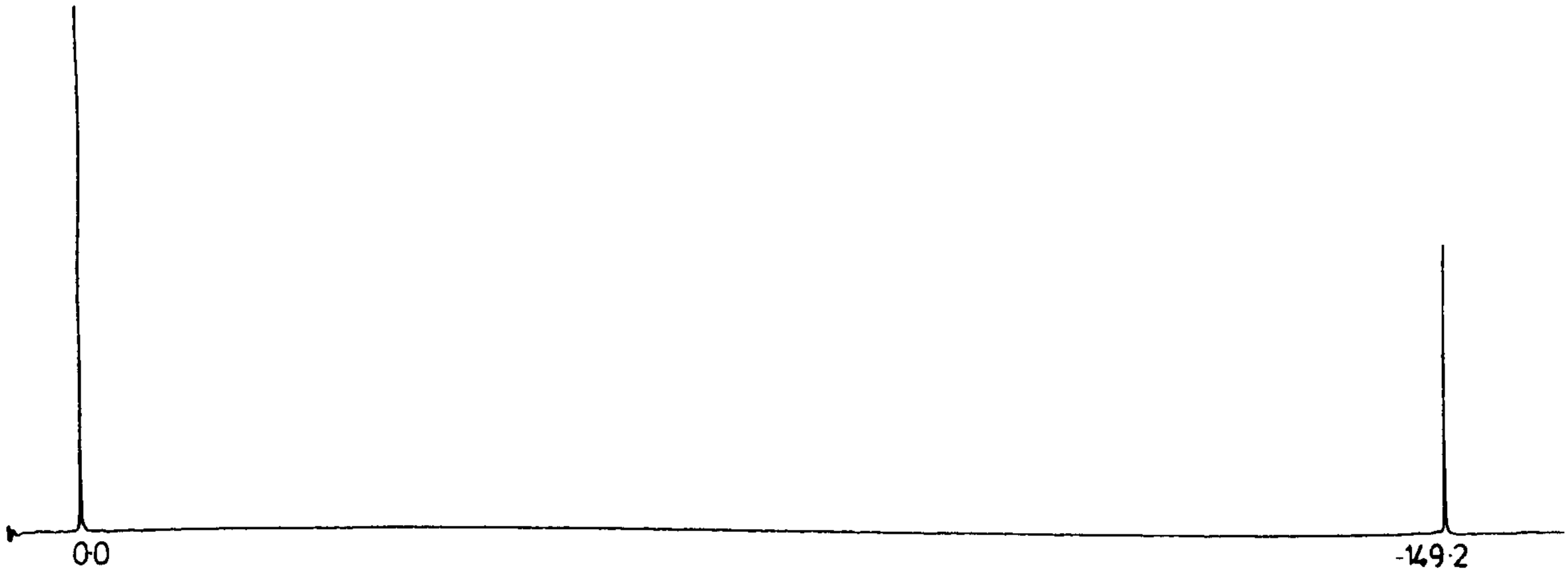
It was also discovered that the phosphonium salt could be generated <u>in situ</u> and so give a "one-pot" synthetic method (see Scheme XXX).



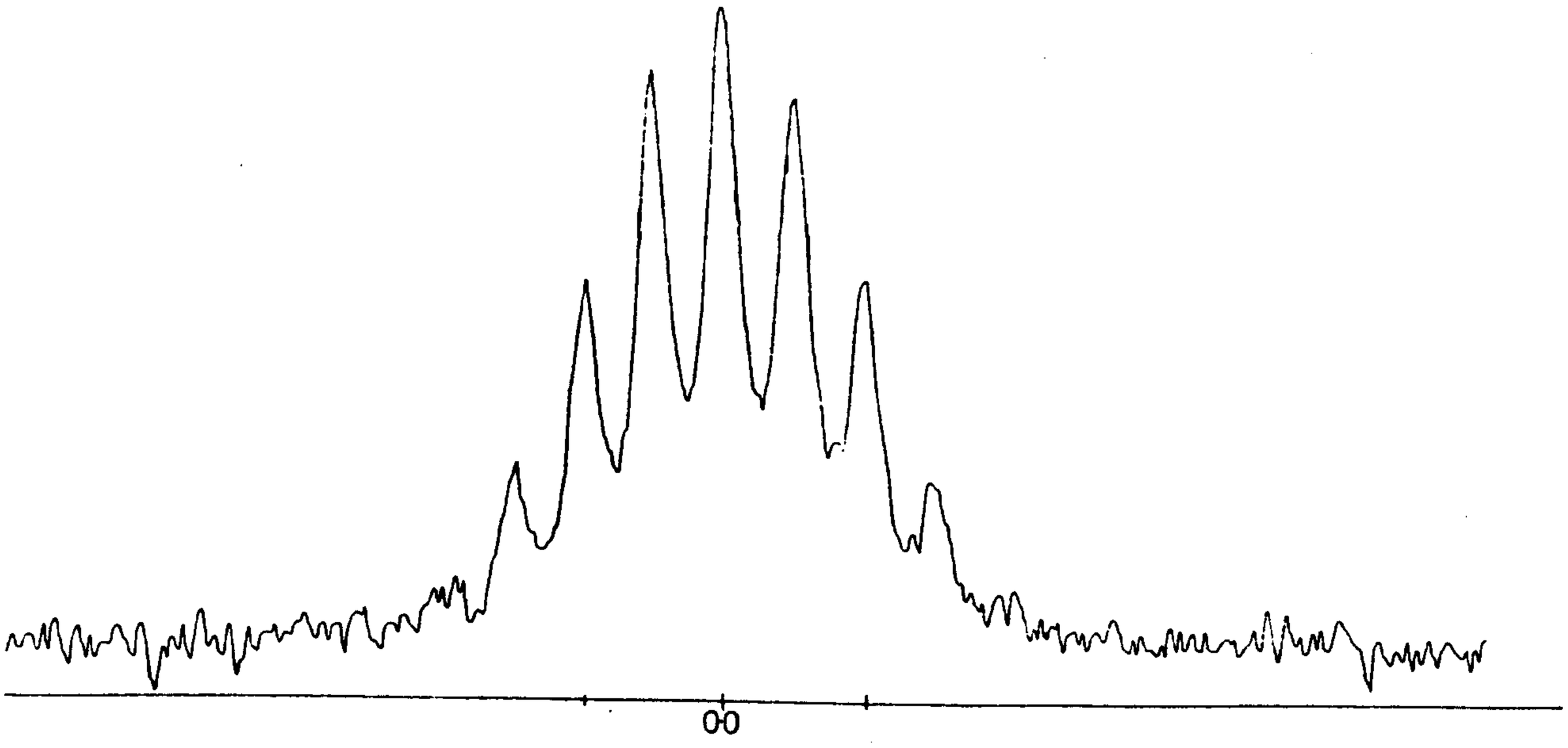
Scheme XXX

The phosphonium salt was formed spontaneously on stirring triphenylphosphine with dibromodifluoromethane in the reaction solvent. This procedure for difluorocarbene production was attempted using the alkene, 2,3-dimethylbut-2-ene to trap any difluorocarbene produced. The phosphonium salt was formed easily but no product from any subsequent reaction could be isolated. Further investigation indicated that the use of rigorously anhydrous conditions was needed and, in particular, the solvent triglyme had to be carefully dried. The use of sodium as a drying agent for the triglyme was not effective; refluxing with $LiAlH_4$ for several hours was necessary before it was sufficiently dry. The use of this well dried solvent and the alkene, 2,3-dimethylbut-2-ene gave some success in the form of a very low yield of 1,1-difluoro-2,2,3,3-tetramethylcyclopropane. This product was not very pure but from ^{1}H and ^{19}F n.m.r. spectroscopy the desired product was evident. The proton n.m.r. spectrum showed a strong singlet δ_H = 1.1 from the four methyl groups. The proton decoupled ^{19}F spectrum showed one signal at 149.2 Hz. The proton coupled ^{19}F spectrum apparently gave a septet but on closer inspection the relative intensities of the lines seem to suggest a 13 line signal. This pattern arises from the 12 protons of the methyl groups which couple with each fluorine and give the value J_{H-F} = 2.05 Hz, (see Scheme XXXI).

One of the major problems with this method is the extraction of the volatile cyclopropane, once it is formed, from the solvent triglyme. The extraction is carried out by flash distillation, under high vacuum, of the volatile material into a trap cooled in liquid



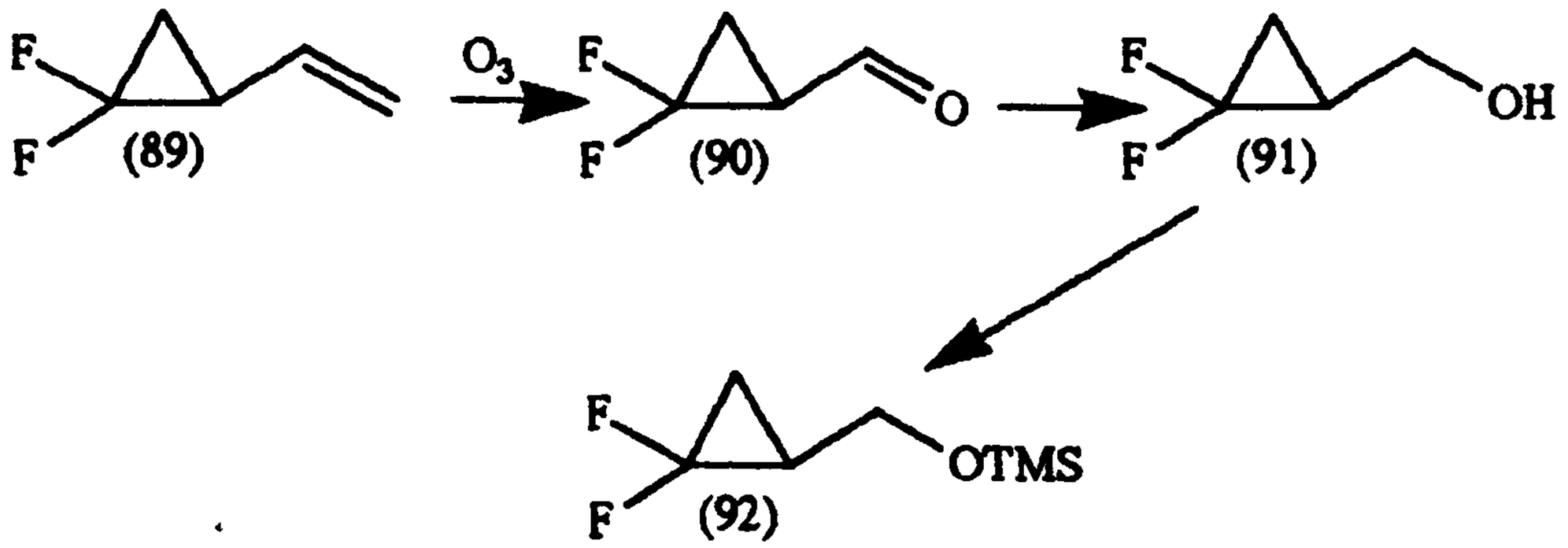
^{19}F Proton decoupled spectra



^{19}F Proton coupled spectra J_{H-F} = 2 Hz (coupled with 6 equivalent proton environments)

Scheme XXXI ^{19}F n.m.r. spectra of 2,2,3,3-tetramethyl-1,1-difluorocyclopropane.

nitrogen. A very small quantity of volatile material was extracted and subsequently purified with difficulty by fractional distillation at atmospheric pressure. After producing this small quantity of the difluorocyclopropane (88) the above reaction was carried out using the highly reactive alkene buta-1,3-diene in the hope that the yield of isolated product could be increased. It was hoped that 2,2-difluoro-1-vinylcyclopropane (89) would be formed in this reaction. The vinyl group would enable subsequent modification (see Scheme XXXII) to give 1-(α-trimethylsilyloxymethyl)-2,2-difluorocyclopropane (92), which is a precursor for one of the target radicals discussed previously (see section 2). The vinyl



Scheme XXXII

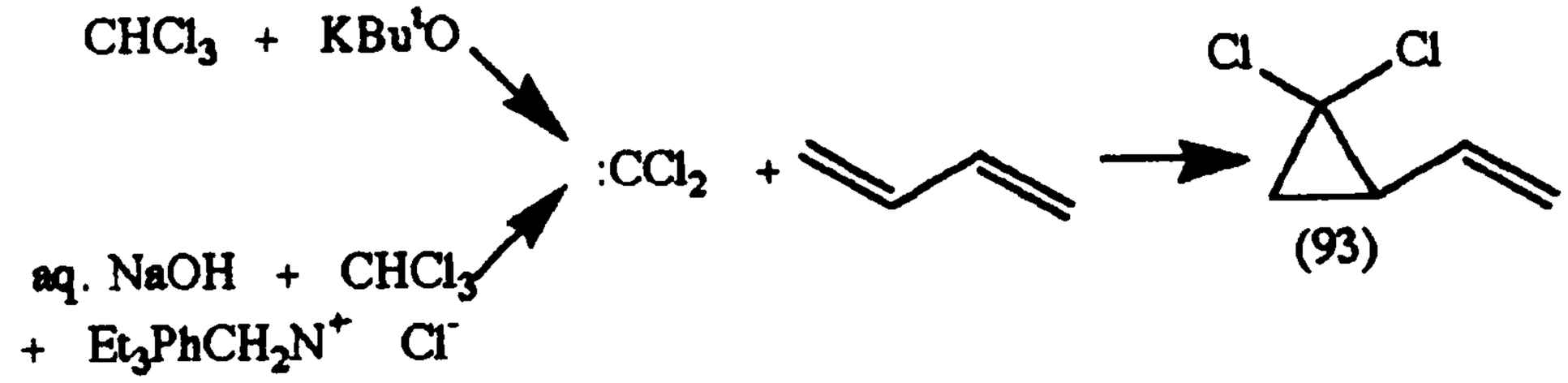
group was to be converted to the aldehyde (90) via the ozonide, then the aldehyde was to be reduced to the alcohol (91). The alcohol would then be easily convertible to the trimethylsilyl ether

(92). When the cyclopropanation reaction was carried out with buta-1,3-diene as the carbene trap the yield of cyclopropane was no better than for the previous alkene, 2,3-dimethylbut-2-ene. The yield reported by Dolbier and Sellers[149] for 2,2-difluoro-1-vinyl-cyclopropane production could not be matched. Due to the low yield the proposed conversion to the (α-trimethylsilyloxymethyl) derivative could not be carried out. It is believed that the problems encountered with this experiment lie in the extraction of the volatile product from the reaction mixture.

The compound 2,2-dichloro-1-vinylcyclopropane (93) was synthesised. This compound was to be used to test the proposed conversion of the vinyl group to the trimethylsilyloxy group (see Scheme XXXII) before attempting the conversion with the difluorocyclopropane (89). The 2,2-dichloro-1-vinylcyclopropane was synthesised by reaction of dichlorocarbene with buta-1,3-diene. The dichlorocarbene was generated by two different routes (see Scheme XXXIII):

1) by action of potassium-t-butoxide on chloroform,[150,151] and

2) using aqueous sodium hydroxide and chloroform in the presence of a phase-transfer catalyst.[152-155]

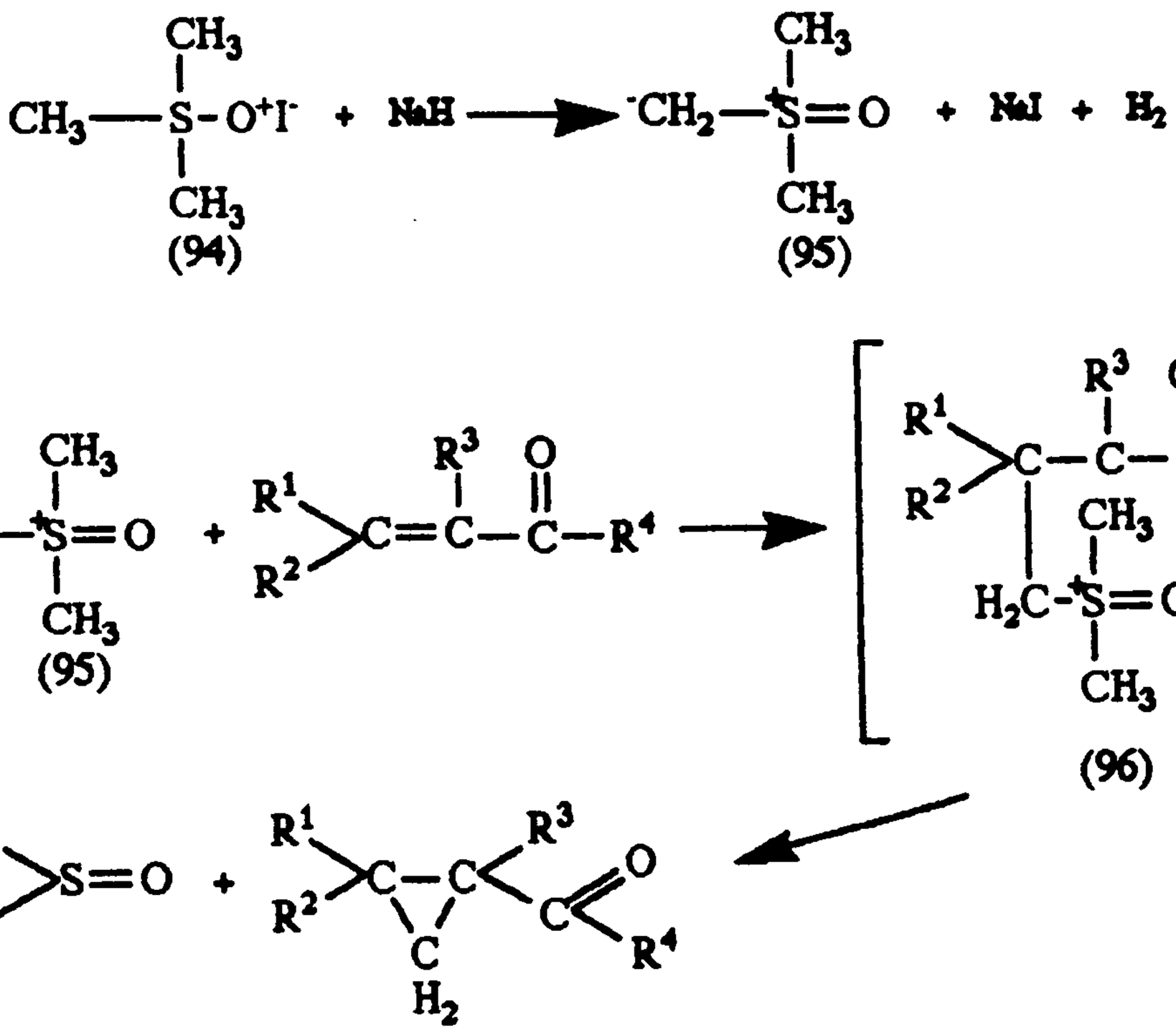


Scheme XXXIII

Both of these reactions were carried out in the presence of buta-1,3-diene and 2,2-dichloro-1-vinylcyclopropane was isolated, from both, in good yield. The conversion of the vinyl group (see Scheme XXXII) was not proceeded with due to the lack of success in producing enough of the 2,2-difluoro-1-vinylcyclopropane.

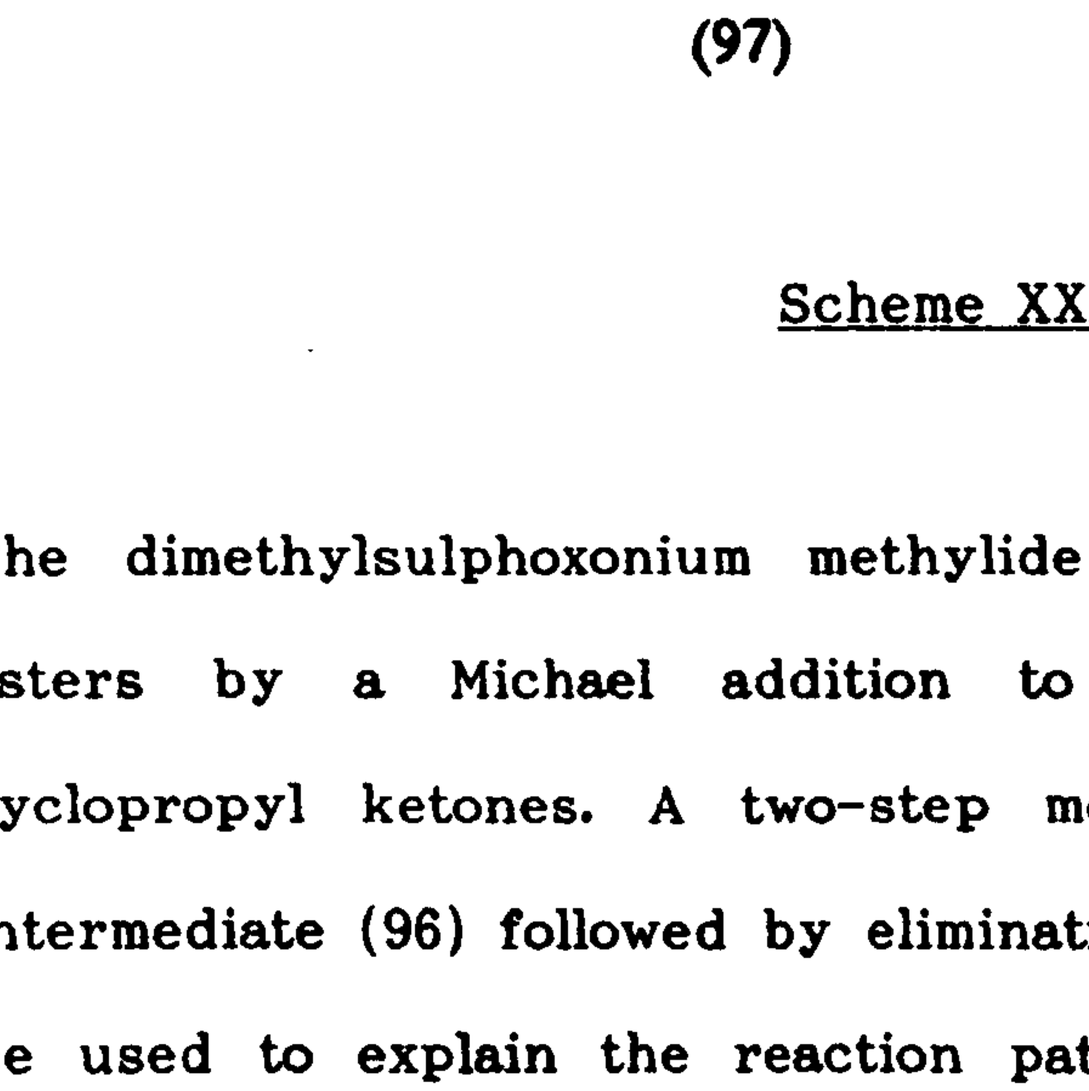
2.1.4 Synthesis and attempted reaction of ethyl 3,3-difluoro-acrylate

Due to the problems experienced with the use of difluorocarbene in the production of difluorocyclopropanes an alternative synthesis was sought. Cyclopropanes can be generated from α,β-unsaturated esters by reaction with dimethylsulphoxonium methylide (95) (see Scheme XXXIV). This reaction was developed by Landor and Punja[144] from earlier work by Corey and Chaykovsky.[156-158] The dimethylsulphoxonium methylide is formed spontaneously by reaction of trimethylsulphoxonium iodide (94) with sodium hydride in dimethylformamide.



(94) (95)

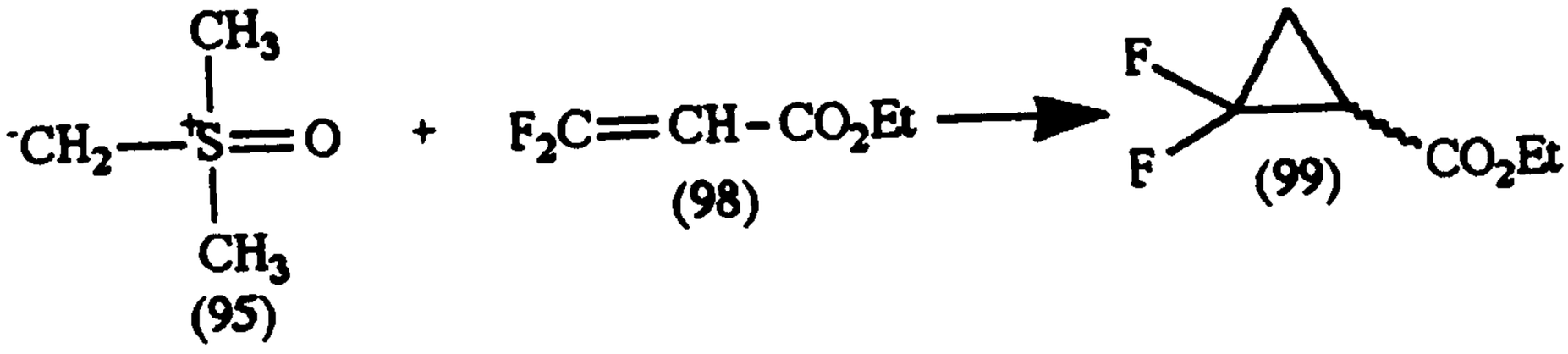
(95) (96)



(97)

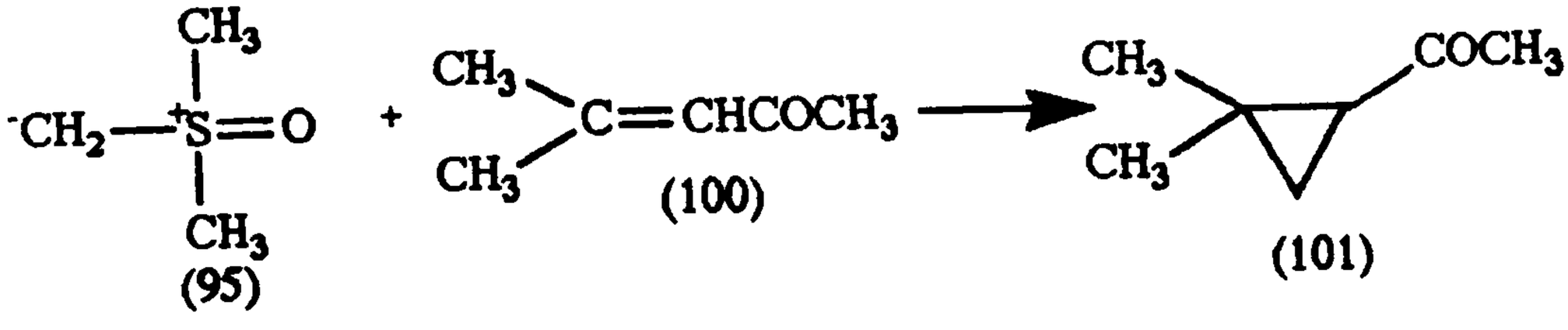
Scheme XXXIV

The dimethylsulphoxonium methylide reacts with α,β-unsaturated esters by a Michael addition to the double bond to give cyclopropyl ketones. A two-step mechanism involving a dipolar intermediate (96) followed by elimination of dimethyl sulphoxide can be used to explain the reaction pathway (see Scheme XXXIV). It was planned to synthesise ethyl 1,1-difluorocyclopropanecarboxylate (99) using this procedure (see Scheme XXXV). The α,β-unsaturated compound used in this reaction is ethyl 3,3-difluoroacrylate (98). Before producing any ethyl 3,3-difluoroacrylate the cyclo-



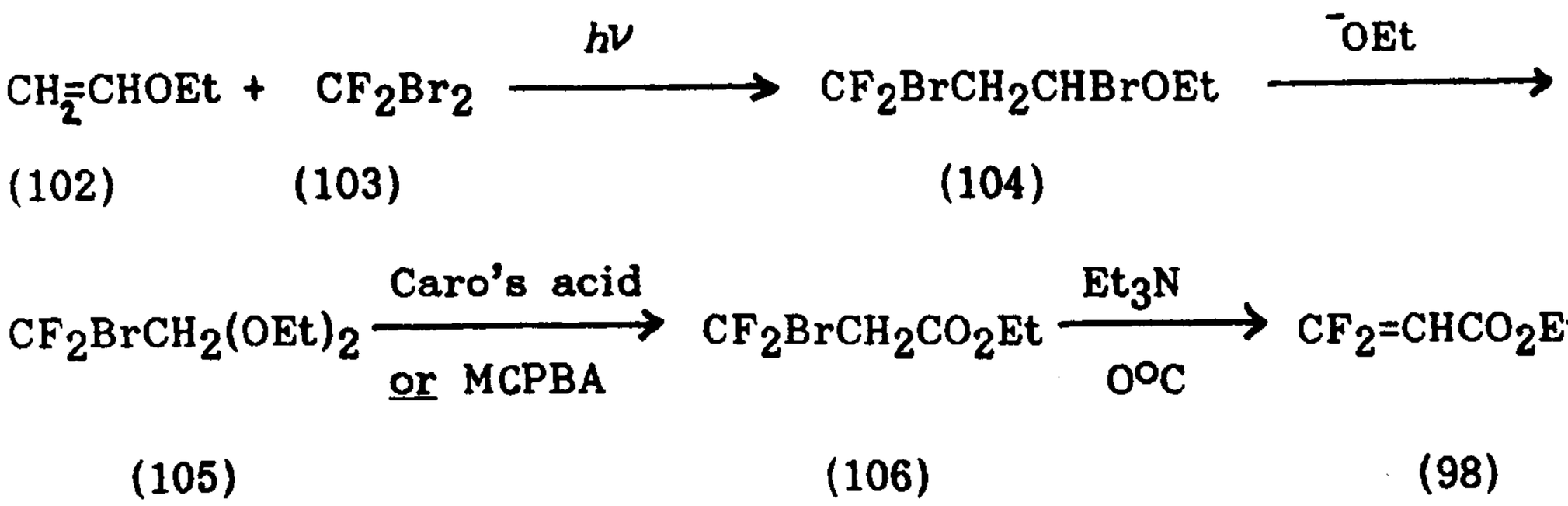
Scheme XXXV

propanation reaction was attempted with the α,β-unsaturated mesityl oxide (100) (see Scheme XXXVI). The 2,2-dimethylcyclopropyl ketone (101) produced from mesityl oxide was obtained in a similar yield to that reported in the literature.[44] Due to the success of



Scheme XXXVI

this reaction the ethyl 3,3-difluoroacrylate was synthesised. The synthesis of ethyl 3,3-difluoroacrylate was achieved using a method developed by Wakselman et.al.[143] (see Scheme XXXVII). The readily available materials ethyl vinyl ether (102) and dibromodifluoro-



Scheme XXXVII

methane (103) were reacted under u.v. irradiation to produce an α-bromo ether (104) which on treatment with ethanol gave the bromodifluoroacetal (105). The next step involved oxidation of the acetal to the ethyl ester (106) with either 3-chloroperoxybenzoic acid (MCPBA) or Caro's acid : Caro's acid is a mixture of conc. sulphuric acid and ammonium persulphate. The rapid dehydrobromination of the ester (106) with triethylamine at 0°C gives ethyl 3,3-difluoroacrylate (98). This last step required careful monitoring of the reaction temperature and rapid quenching of the reaction as soon as it was complete.

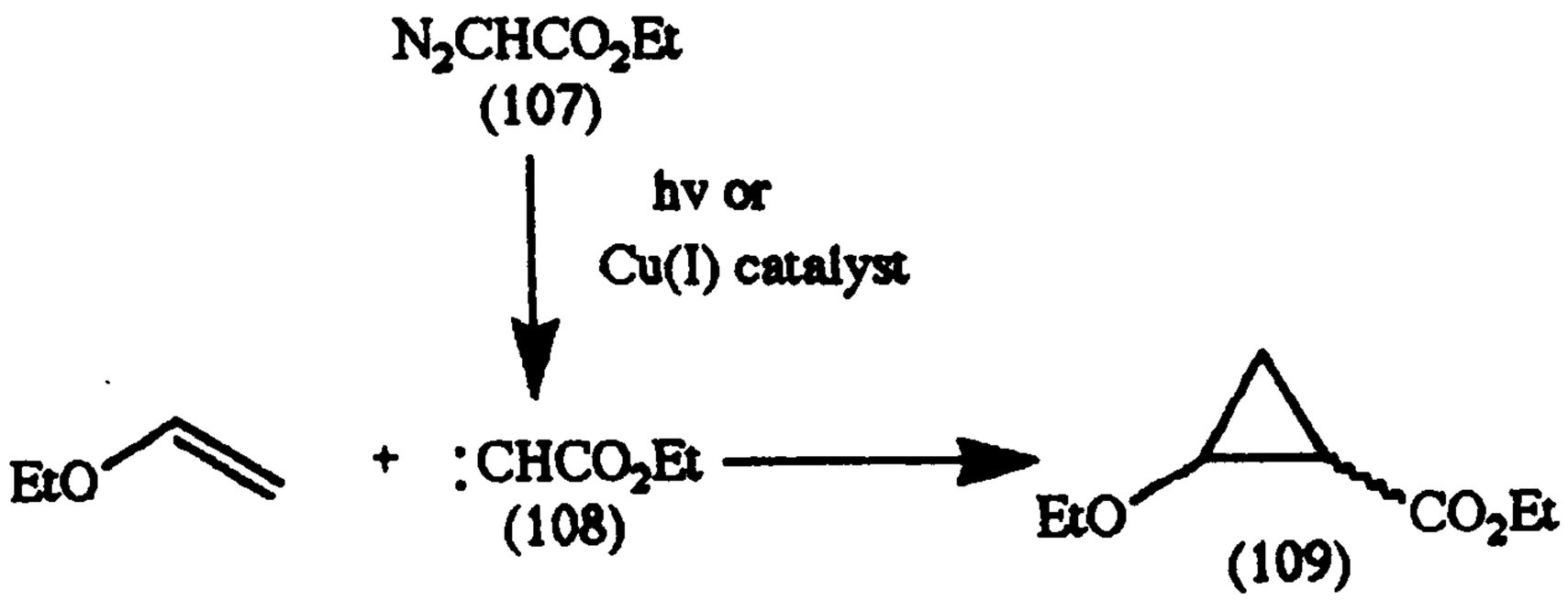
Once the ethyl 3,3-difluoroacrylate was produced in sufficient quantity it was treated with dimethylsulphoxonium methylide. This reaction did not give the desired cyclopropane and after several attempts was abandoned. The lack of success with this reaction is not fully understood. It was thought that the electron-withdrawing fluorine groups would enhance the reaction by making the Michael receptor site more susceptible to attack from the dimethylsulphoxonium methylide. No reasonable explanation for the total absence of cyclopropyl product could be envisaged.

2.2 Synthesis of Other Substituted Cyclopropane Compounds

This section deals with the generation, or attempted generation, of precursors for the substituted cyclopropyl radicals (71), (72) and (73) mentioned in section 2. The synthesis of precursors for the spiro target radicals (74) and (75) is also covered. The bulk of the work in this section is concerned with the production and reactions of carboethoxycarbene (108), generated from ethyl diazoacetate (107).

2.2.1 Generation and reaction of carboethoxycarbene

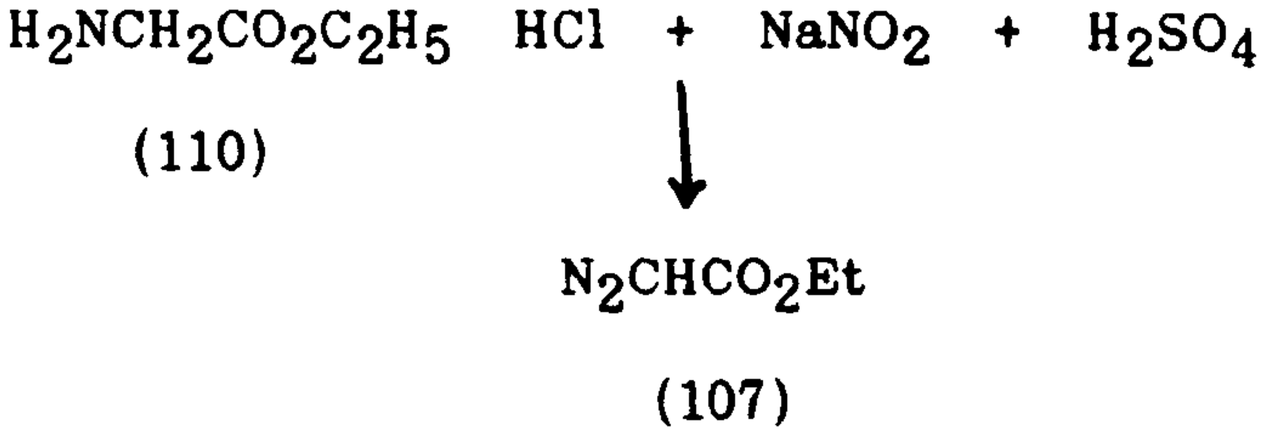
As mentioned previously (see section 2) the generation of a carbene and its addition to an alkene is a potential route to cyclopropyl compounds. The generation of carboethoxycarbene and its reaction with the alkene, ethyl vinyl ether (see Scheme XXXVIII) would result in the production of the useful cyclopropane compound ethyl 2-ethoxycyclopropanecarboxylate (109).



Scheme XXXVIII

This cyclopropane (109) could easily be converted into a precursor for one of the target radicals (see section 2.2.2).

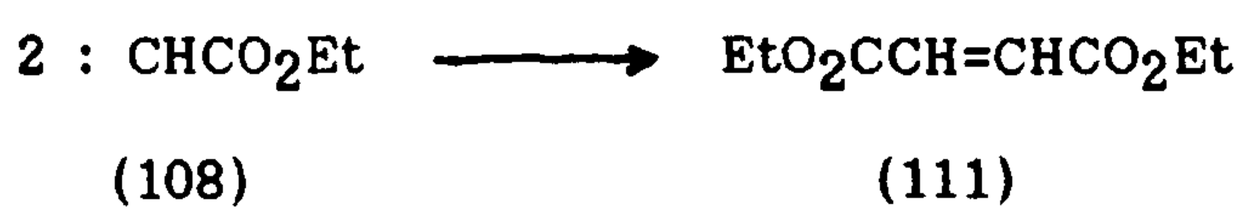
Various reactions of carboethoxycarbene were carried out and are discussed in sections 2.2.2 and 2.2.3. The source of carboethoxycarbene, ethyl diazoacetate,[159,160] was readily made by treating glycine ethyl ester hydrochloride (110) with sodium nitrite and sulphuric acid (see Scheme XXXIX).



Scheme XXXIX

a) Synthetic method for carbene generation and reaction

The generation of carboethoxycarbene from ethyl diazoacetate was carried out, by photolysis or thermally, in the presence of copper or a copper salt as a catalyst. The generation of the carbene was carried out in the presence of a large excess of the alkene. This maximised the carbene-alkene addition reaction and reduced the quantity of carbene-carbene combination product, diethyl maleate (111) (see Scheme XL). However, in all the reactions



Scheme XL

carried out traces of the carbene-carbene combination product were detected. Two methods of initiating the reactions were used: heating at various temperatures or photolysis with a 100 watt bulb (this photolysis also generated heat, so the two processes were not

entirely exclusive). Both of these methods were carried out in the presence of a copper based catalyst. It was also found that there was an initiation period before the reaction started. To prevent a violent reaction care was needed to allow for this initiation period. The majority of the carbene source was added slowly to the reaction after it was seen to start. The favoured and quickest method of completing these reactions was to warm the reaction vessel, containing half of the alkene, the copper catalyst, and a small portion of the ethyl diazoacetate, in a water bath at 70-80°C. A reaction, noted by vigorous nitrogen evolution, generally began after 10-15 minutes. The heated bath was removed and a solution of the remaining alkene and the ethyl diazoacetate was added slowly, maintaining a steady nitrogen evolution. The reaction is exothermic and provides enough heat to sustain carbene generation. If the ethyl diazoacetate was added too fast greater amounts of carbene-carbene combination were formed. The light-initiated reactions gave the same products but the yields were lower, and the amount of non-characterisable residue and carbene-carbene product greater.

b) <u>Catalysts for carbene production</u>

Various copper catalysts were used in these experiments, the two most successful being copper acetoacetonate or a 1:1 w:w mixture of copper bronze:anhydrous copper sulphate; copper(I) trimethylphosphite[161,162] was also synthesised and used. No discernable difference could be found between the first two catalysts, the copper(I) trimethylphosphite however was not so successful as reaction mixtures were more complex and contained

large amounts of tarry residue. There are literature reports of different catalysts giving different products from the same alkene substrate. These are discussed more fully later (see section 2.2.3).

2.2.2 Cyclopropanation reactions of carboethoxycarbene

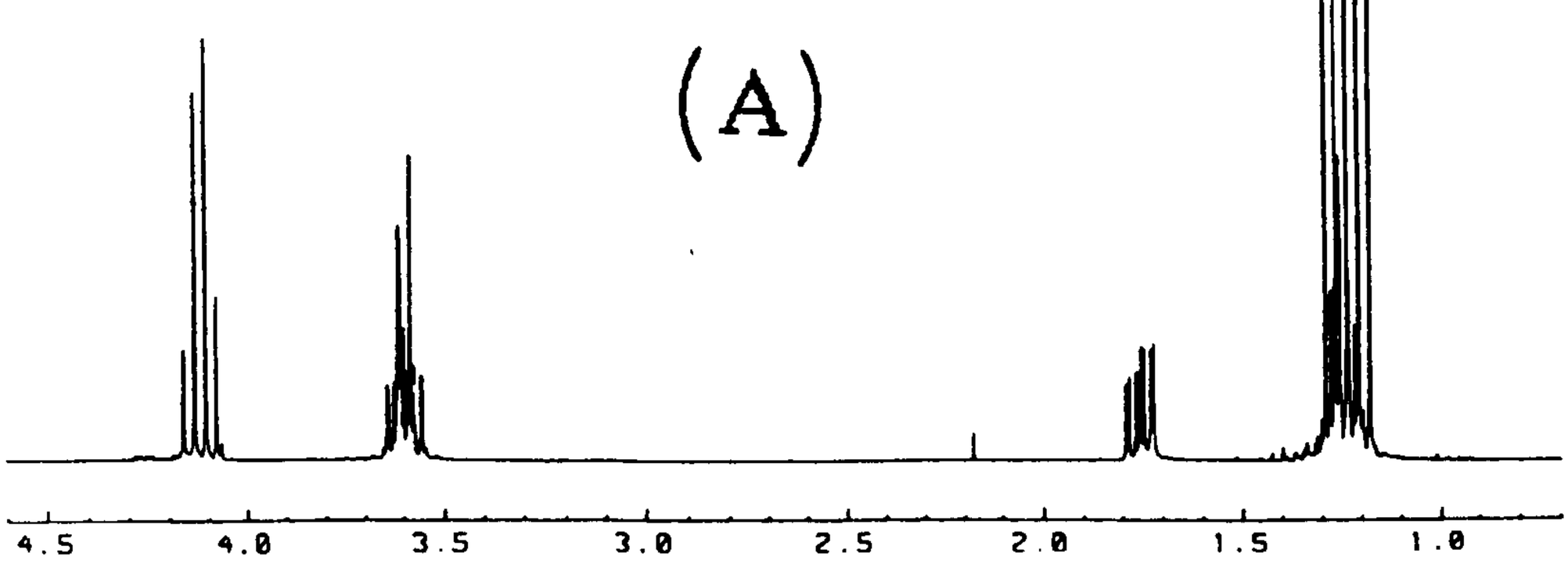
(a) Carboethoxycarbene and ethyl vinyl ether

As shown previously (see Scheme XXXVIII) carboethoxycarbene and ethyl vinyl ether react to give ethyl 2-ethoxycyclopropanecarboxylate. This cyclopropane can easily be converted to a precursor for one of the desired target radicals (see Scheme XXXIV). The carbene addition to the alkene resulted in both *cis* and *trans* ethyl 2-ethoxycyclopropanecarboxylate being formed. The two isomers were found in the ratio 60% *cis*, 40% *trans* and are easily distinguished by g.l.c. The separation of the isomers was necessary because, as previously noted (see section 1.2.4 (c)), *cis*- and *trans*-substituted cyclopropylmethyl radicals can ring-open in different directions. It was found that the *cis* and *trans*-isomers of ethyl 2-ethoxycyclopropanecarboxylate could be separated by careful fractional distillation on a 1 metre spinning band column. The separation was very time consuming as a slow take-off rate from the column was required to achieve a clean separation. The hold up volume of the column and the requirement to carry out further synthetic steps on each isomer necessitated the production of a large quantity of the cyclopropane. The boiling points of the isomers are, *trans* - 69–71°C at 22 mm Hg and *cis* - 78°C at 25 mm Hg.

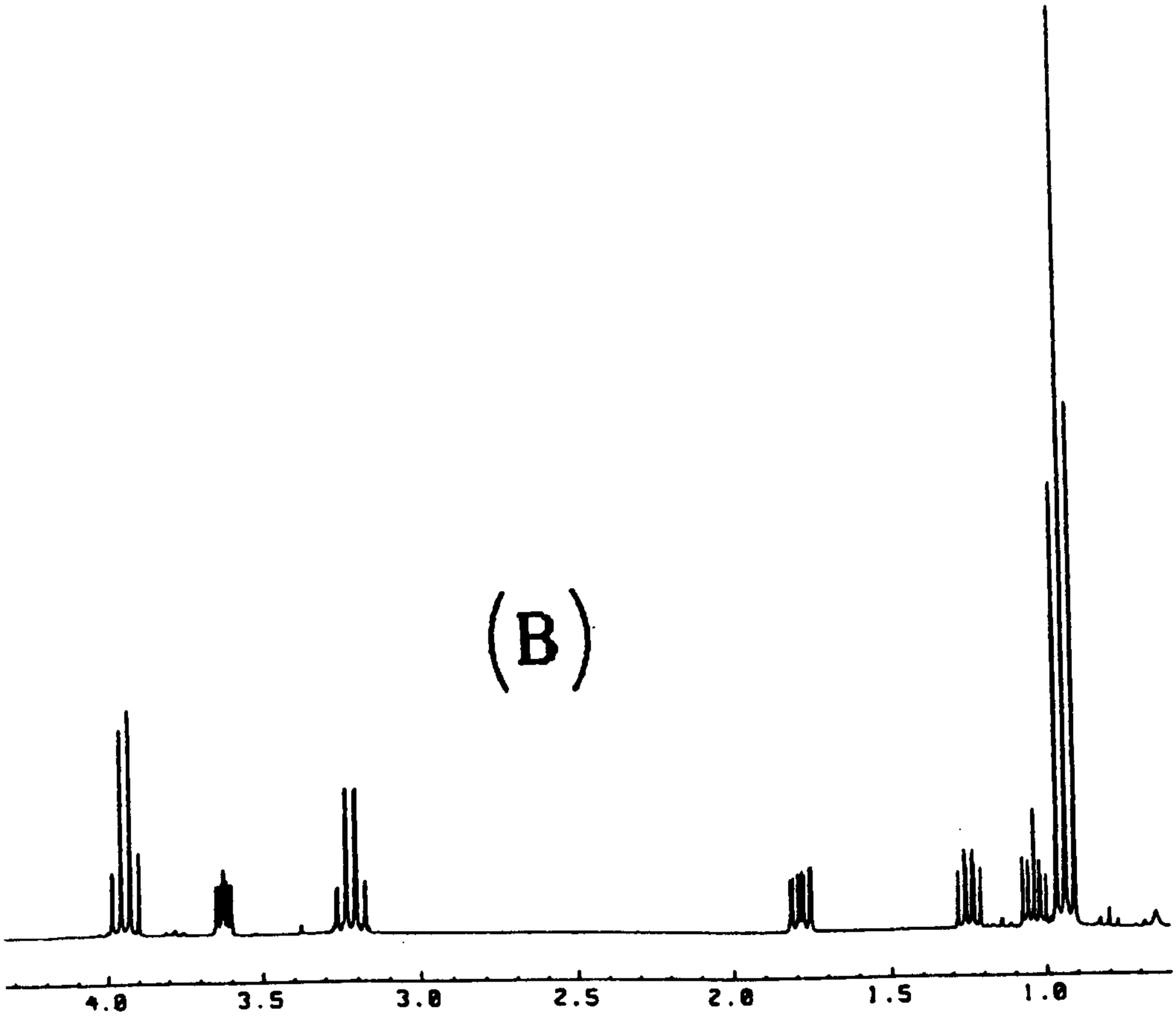
The *cis* and *trans*-isomers were characterised by ^{1}H and ^{13}C n.m.r. spectroscopy. The 250 MHz ^{1}H n.m.r. spectra of the two

isomers, were recorded using $CDCl_3$ as a solvent, were complicated, with many overlapping signals. A complete assignment of the signals observed could not be made from these spectra. The use of d_6-benzene as a solvent gave much clearer spectra with most of the signals separated from each other (see Scheme XLI). Even with these clearer spectra it was still not possible to determine which isomer was the *cis* and which the *trans*. The elucidation of which isomer was which was achieved using theoretically derived spectra. These spectra were generated using computer software called PANIC. This programme uses as a starting point experimentally determined chemical shifts and any splitting values that can be determined manually. The chemical shift of H_1 can be unequivocally assigned in both the *cis* and *trans* spectra. H_1 has the most downfield signal of the cyclopropyl protons as it is attached to a carbon atom with an oxygen substituent. The experimental values available are subject to an iterative process that generates a detailed theoretical spectrum with the splitting pattern clearly defined. This programme was used to generate the theoretical spectra of the cyclopropyl protons in both the *cis* and *trans*-isomers. Comparison of the theoretical spectra for each isomer with the two experimental spectra (see Scheme XLII) enabled the *cis* and *trans*-isomers to be identified. The theoretical and experimental details for the ring protons are tabulated for both isomers (see Table VI).

It was found that the *trans*-isomer had the lower b.p. (67-71°C at 25 mm Hg) and the shorter retention time on g.l.c. analysis (see Scheme XLIII). The *cis*-isomer had the longer g.l.c. retention time and the higher boiling point (78°C at 25 mm Hg). It

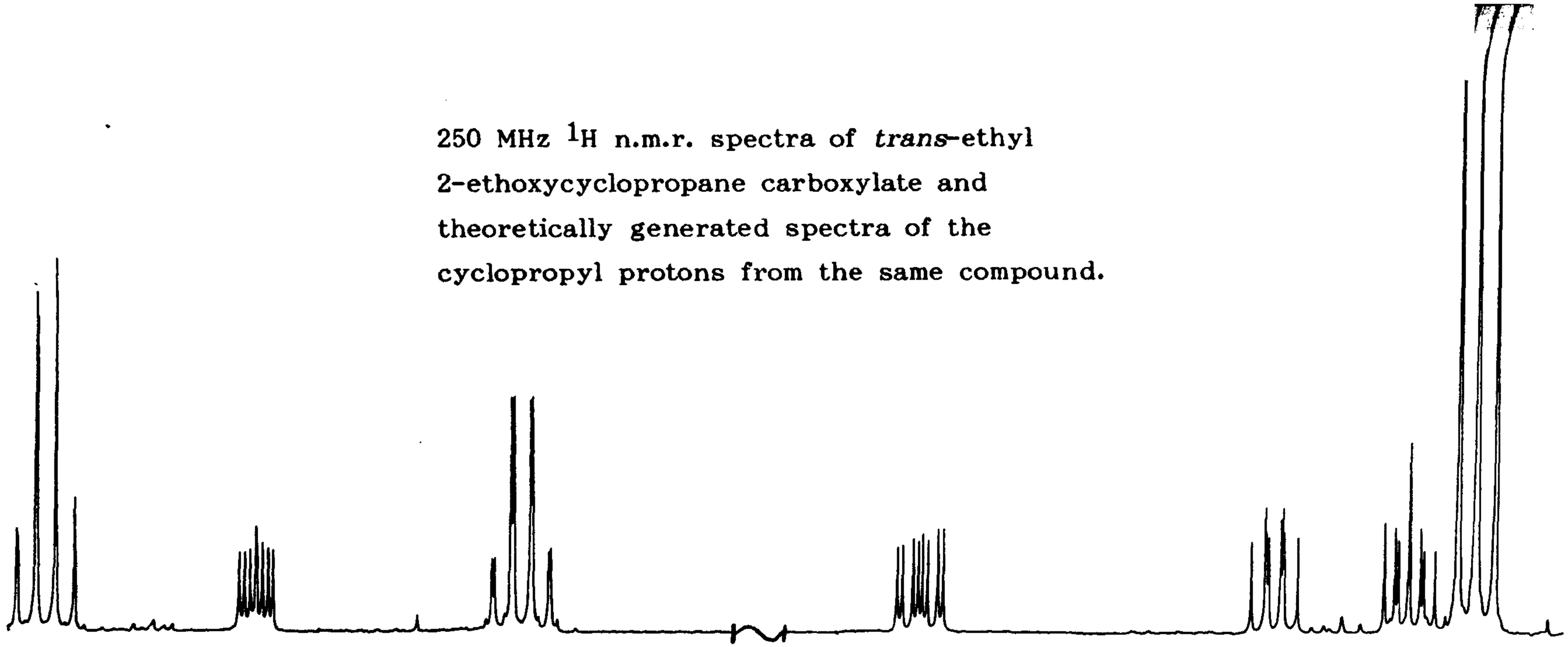


250 MHz ^{1}H n.m.r. spectra of *trans*-ethyl 2-ethoxycyclopropane carboxylate in $CDCl_3$ (A) and C_6D_6 (B).

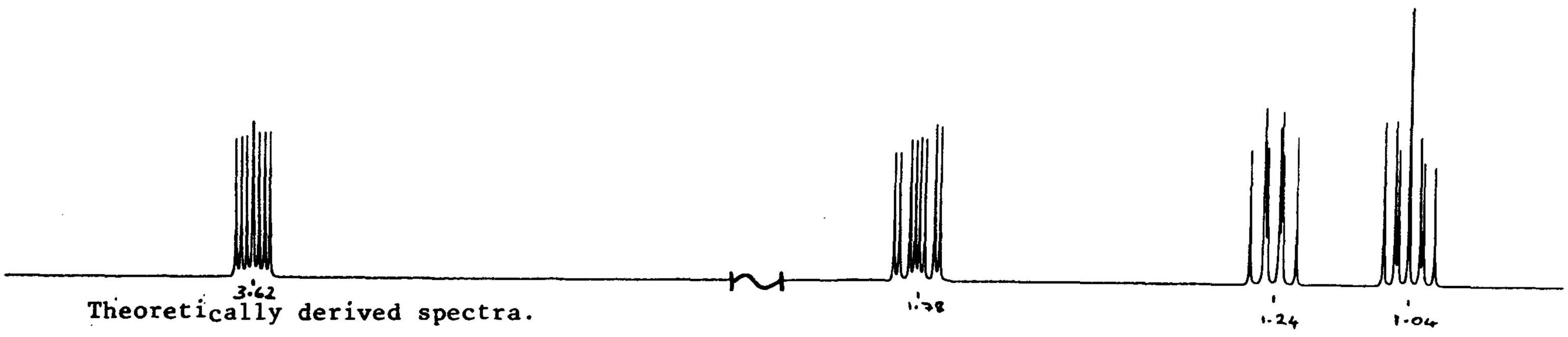


Scheme XLI

250 MHz ^{1}H n.m.r. spectra of *trans*-ethyl 2-ethoxycyclopropane carboxylate and theoretically generated spectra of the cyclopropyl protons from the same compound.



·250 MHz ^{1}H n.m.r.



Theoretically derived spectra.

Scheme XLII

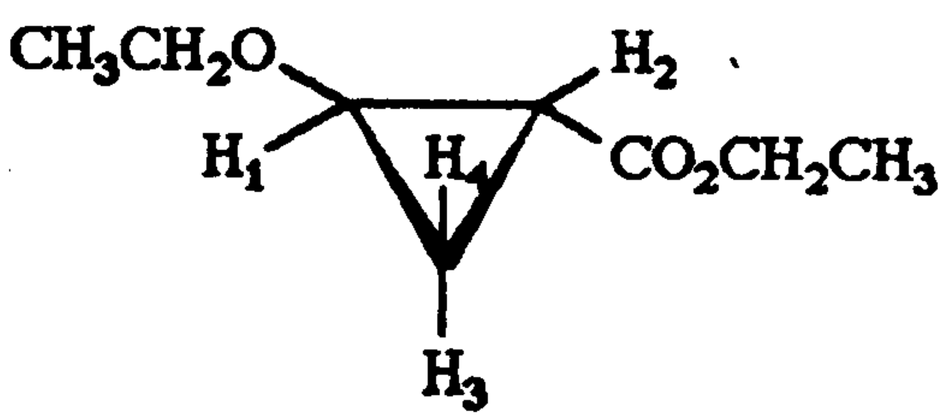
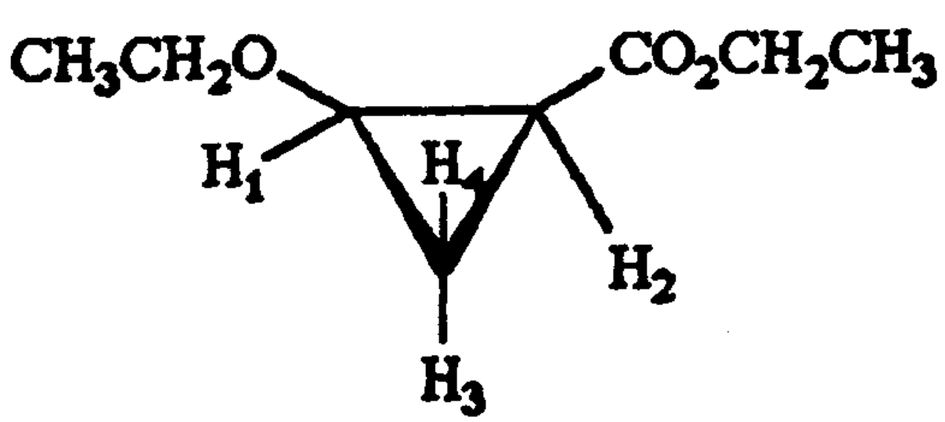
		Chemical Shift		Experimental Splitting	Theoretical Splitting
 *trans*-isomer	H_1	3.62	J_{12}	2.2	2.01
	H_2	1.78	J_{13}	6.64	6.609
	H_3	1.24	J_{14}	4.18	4.16
	H_4	1.04	J_{23}	5.88	5.858
			J_{24}	9.52	9.512
			J_{34}	-5.37	-5.36
 *cis*-isomer	H_1	3.04	J_{12}	4.72	4.73
	H_2	1.64	J_{13}	6.76	6.69
	H_3	1.42	J_{14}	6.60	6.63
	H_4	0.52	J_{23}	6.75	6.69
			J_{24}	5.77	5.75
			J_{34}	-8.48	-8.51

Table VI Experimental 250 MHz ^1H n.m.r. data[(a),(b)] and theoretical splitting values for *trans*-ethyl 2-ethoxycyclopropanecarboxylates.

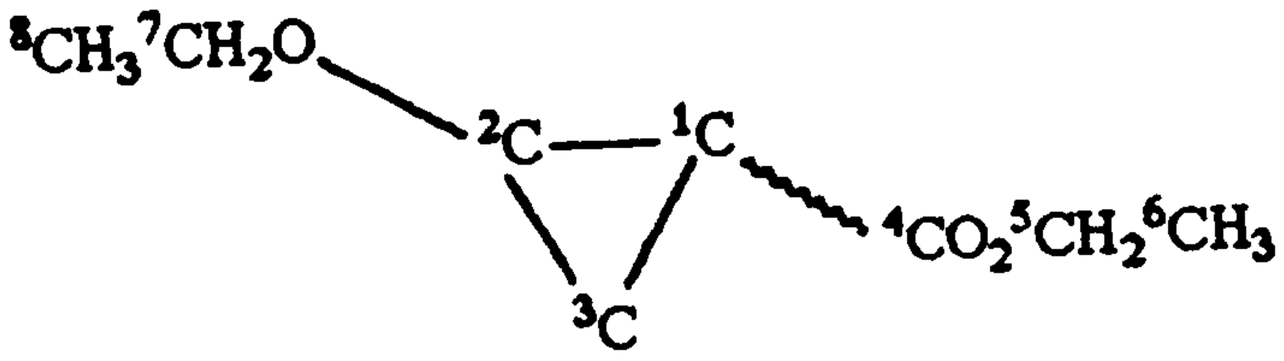
(a) δ_H in ppm relative to TMS
(b) Spectra run in C_6D_6

could also be seen from the spectra that the *trans*-isomer was reasonably pure, while the "*cis*"-isomer, isolated, contained about 20% of the *trans*-isomer.

The ^{13}C n.m.r. spectra of the two isomers were also obtained. Analysis of these spectra, below, supports the *cis/trans* assignment made from the ^{1}H spectra as detailed previously. The ^{13}C n.m.r. spectra of a series of ethyl 2-substituted cyclopropanecarboxylates have been reported by Kusuyama and co-workers.[150,163,164] They found that the resonances for the ring carbons and the carbonyl group of the *cis*-isomer were further upfield than the *trans*-isomer. The ^{13}C n.m.r spectra of *cis* and *trans* ethyl 2-ethoxycyclopropanecarboxylate were reported in these communications. In our ^{13}C n.m.r. spectra of the two isomers obtained the same behaviour was observed. The assignment of the two isomers supported the results obtained from the ^{1}H spectra. The ^{13}C n.m.r. data obtained for the two isomers is recorded (see Table VII). It is also evident from the spectra obtained that the *cis* isomer isolated is not as pure as hoped but contains approximately 20% of the *trans*-isomer. This agrees with the findings from the ^{1}H n.m.r. spectra.

Theoretically derived ^{1}H n.m.r. spectra have also been used to characterise another 1,2-disubstituted-cyclopropane. 1-Bromo-2-phenylcyclopropane was produced by a colleague and the *cis* and *trans*-isomers were distinguished using theoretically generated spectra. It was noted that the *trans*-isomer of this compound had the shorter retention time on g.l.c. analysis and was eluted first during purification by silica gel column chromatography. The *cis*-isomer had the longer g.l.c. retention time

and was eluted second on column chromatography. The observation that the *trans*-isomers have the lower b.p.'s and the shorter



	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
cis-isomer	20.2	58.5	12.5	170.0	60.0	14.4	66.4	13.8
trans-isomer	20.7	60.0	15.1	172.6	60.0	14.5	66.4	13.8

Table VII ^{13}C n.m.r. chemical shift assignments[a] for *cis* and *trans* ethyl 2-ethoxycyclopropane carboxylates

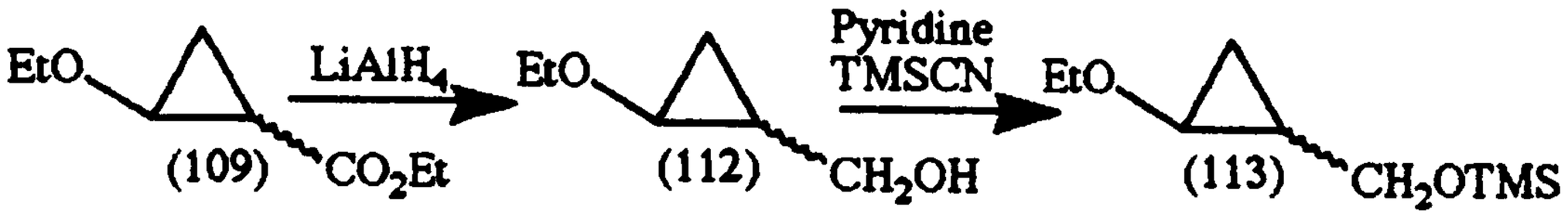
[a] chiral shifts are in ppm downfield from TMS.

retention times is slightly surprising. It was thought that with substituents on each side of the ring the *trans*-species was bulkier and more likely to be sterically hindered than the *cis*-isomer. It appears that for 1,2-substituted cyclopropanes the *trans*-isomers are more volatile.

It was also found that the predominant (60%) *cis*-isomer could be converted into the *trans*-isomer by treating with potassium t-butoxide in t-butanol. Starting with pure *cis*-isomer the pure *trans*-isomer was easily recovered from the reaction

mixture. This procedure did not obviate the need for the fractional distillation but made it easier to obtain in larger quantities a pure sample of the *trans*-isomer.

Once the two were obtained they were individually converted to the corresponding trimethylsilyl ethers (113) (see Scheme XLIV). The ester group was easily reduced to the alcohol (112), using lithium aluminium hydride, with no isomerisation occurring. The trimethylsilyl ethers (113) were made by treating the alcohols with chlorotrimethylsilane in the presence of pyridine. Purification

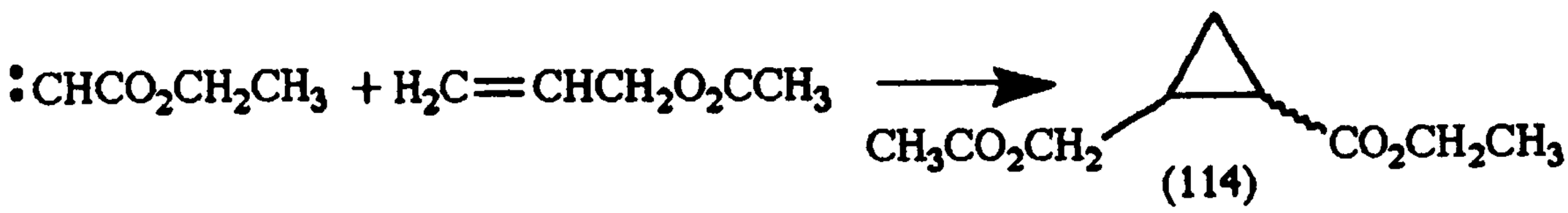


Scheme XLIV

and storage of the trimethylsilyl ethers was difficult as they are readily hydrolysed back to the alcohol. Purification was achieved by preparative g.l.c. The desired compounds were collected, as clear, colourless liquids, off the g.l.c. column in a liquid nitrogen trap and stored in sealed ampoules. The purified silyl ethers were used directly to generate the desired radical in the cavity of an electron spin resonance spectrometer.

(b) Carboethoxycarbene and allyl acetate

When carboethoxycarbene was generated in the presence of allyl acetate the cyclopropane ethyl 2-acetoxymethylcyclopropane-carboxylate (114) was formed (see Scheme XLV). ^{13}C and ^{1}H n.m.r. spectral analysis showed that both the *cis* and *trans*-isomer were formed. Evidence of both isomers was present on g.l.c. analysis. Two distinct peaks could not be obtained but a peak with a large shoulder was seen. All attempts to obtain the individual



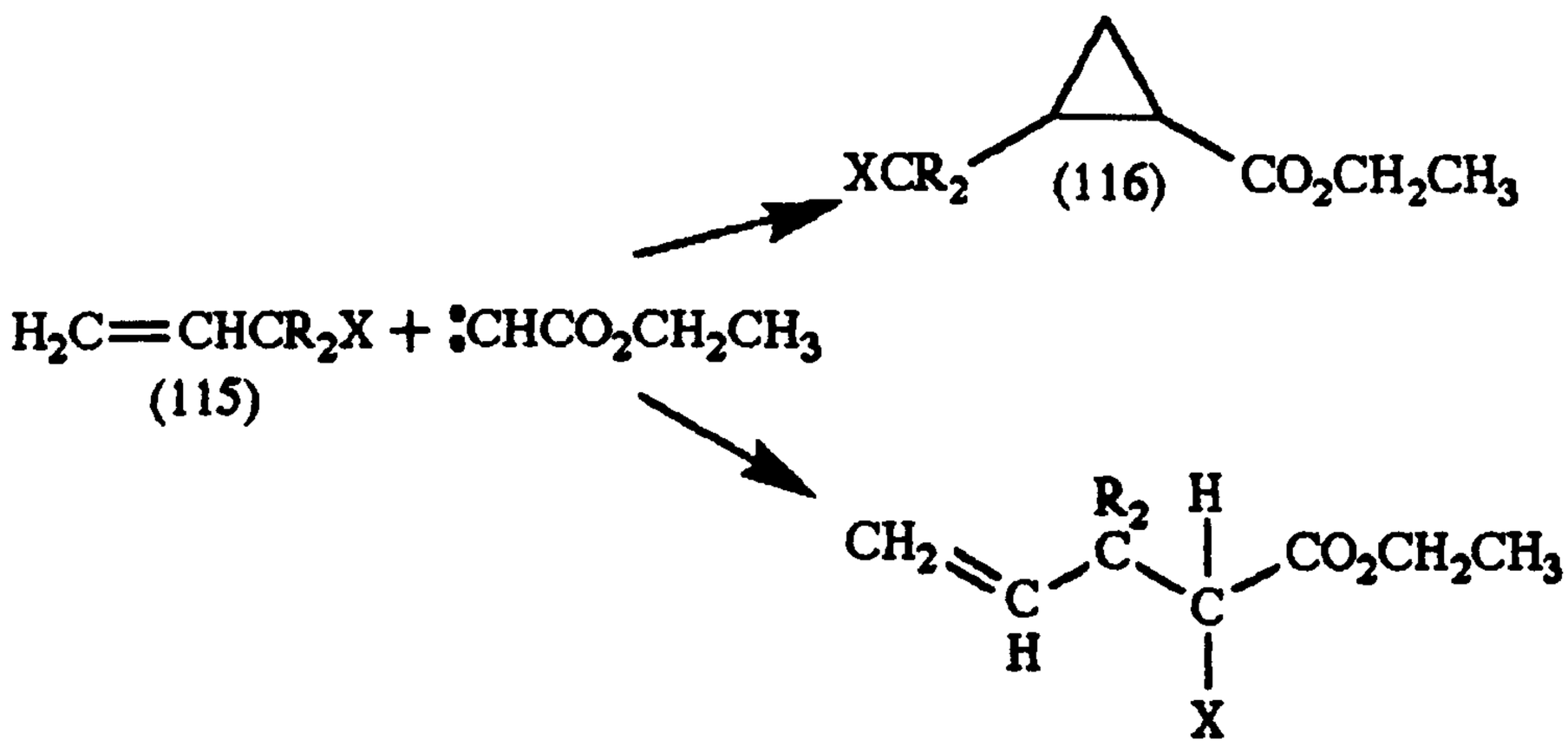
Scheme XLV

isomers by fractional distillation proved unsuccessful. The *cis/trans* mixture was purified as the mixture by preparative g.l.c. and was used as such to generate radicals in the cavity of the e.s.r. spectrometer (see section 3).

To provide a comparison with (114) the non-substituted cyclopropanemethyl acetate (115) was synthesised from cyclo-propanemethanol and acetic anhydride. This compound was purified and on abstraction of a hydrogen atom the e.s.r. spectrum was recorded.

2.2.3 Insertion reactions of carboethoxycarbene

Some alkenes gave no cyclopropane product when carboethoxycarbene was generated and reacted with them in the standard manner. The products from these reactions were found to result from carbene insertion into a C-O or C-halogen bond (see Scheme XLVI). The insertion reactions were first observed



a. R = H , X = Br

b. R = H , X = Cl

c. R = H , X = OH

d. R = CH_3 , X = OH

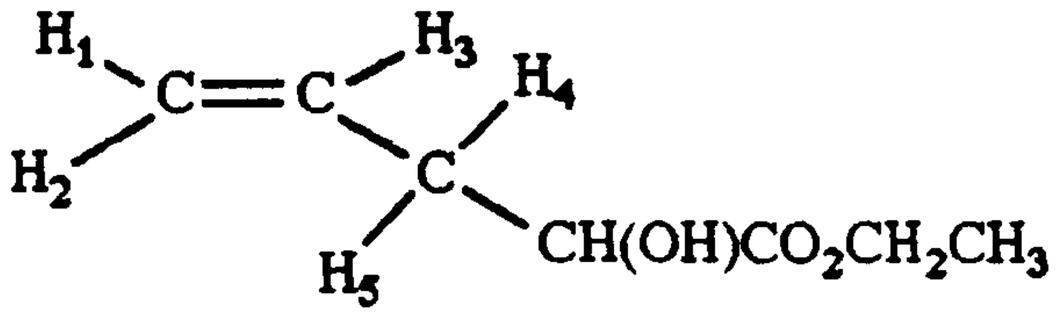
Scheme XLVI

during the attempted production of ethyl 2-bromomethylcyclopropanecarboxylate (116a) from allyl bromide and carboethoxycarbene. The major product isolated was ethyl 2-bromopent-4-enoate (117a), formed by insertion of the carbene into the C-Br bond. This insertion reaction was also observed with allyl chloride (115b),

allyl alcohol (115c) and 2-methylbut-3-en-2-ol (115d). The insertion products were produced using the same procedure for generation and reaction of the carbene as used in the cyclopropanation reactions. The products were isolated by fractional distillation from the reaction mixture and characterised by standard analytical methods. The 250 MHz ^{1}H n.m.r. spectrum of the reaction product from carboethoxycarbene and allyl alcohol, after distillation, is shown overleaf (see Scheme XLVII). This spectrum shows a very distinctive pattern of signals in the region δ 5-6. This distinct pattern is also found in the spectrum of allyl alcohol, the starting material (see Scheme XLVIII), and is due to the 3 protons on the double bond. The retention of this splitting pattern in the reaction product shows clearly that the double bond of the starting material has been untouched in the reaction <u>i.e.</u> no cyclopropanation occurred.

The insertion products were the major species obtained from these reactions but they were generally not as clean as the cyclopropanations (see section 2.2.2) and also gave a variety of minor products. These minor products included the carbene-carbene addition product, diethyl maleate and a considerable amount of a tar-like residue. The occurrence of insertion reactions rather than cyclopropanations when using carboethoxycarbene is mentioned in the literature.[165-170]

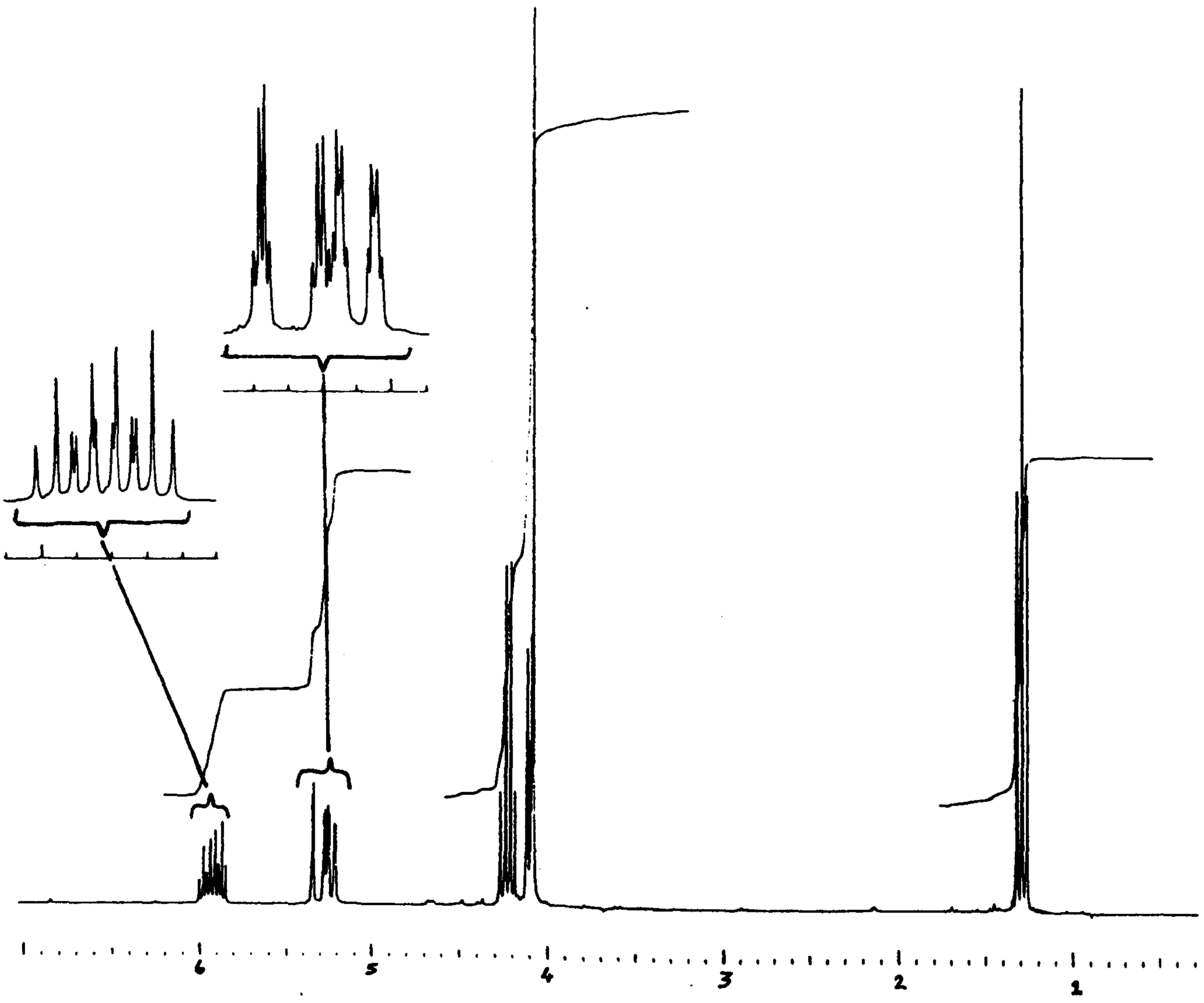
Studies have been carried out to assess the effect of the catalyst used on the ratio of cyclopropane to insertion product obtained. There appears to be a consensus of opinion that rhodium and ruthenium based catalysts favour the cyclopropanation reaction. For the reaction of carboethoxycarbene with allyl bromide,



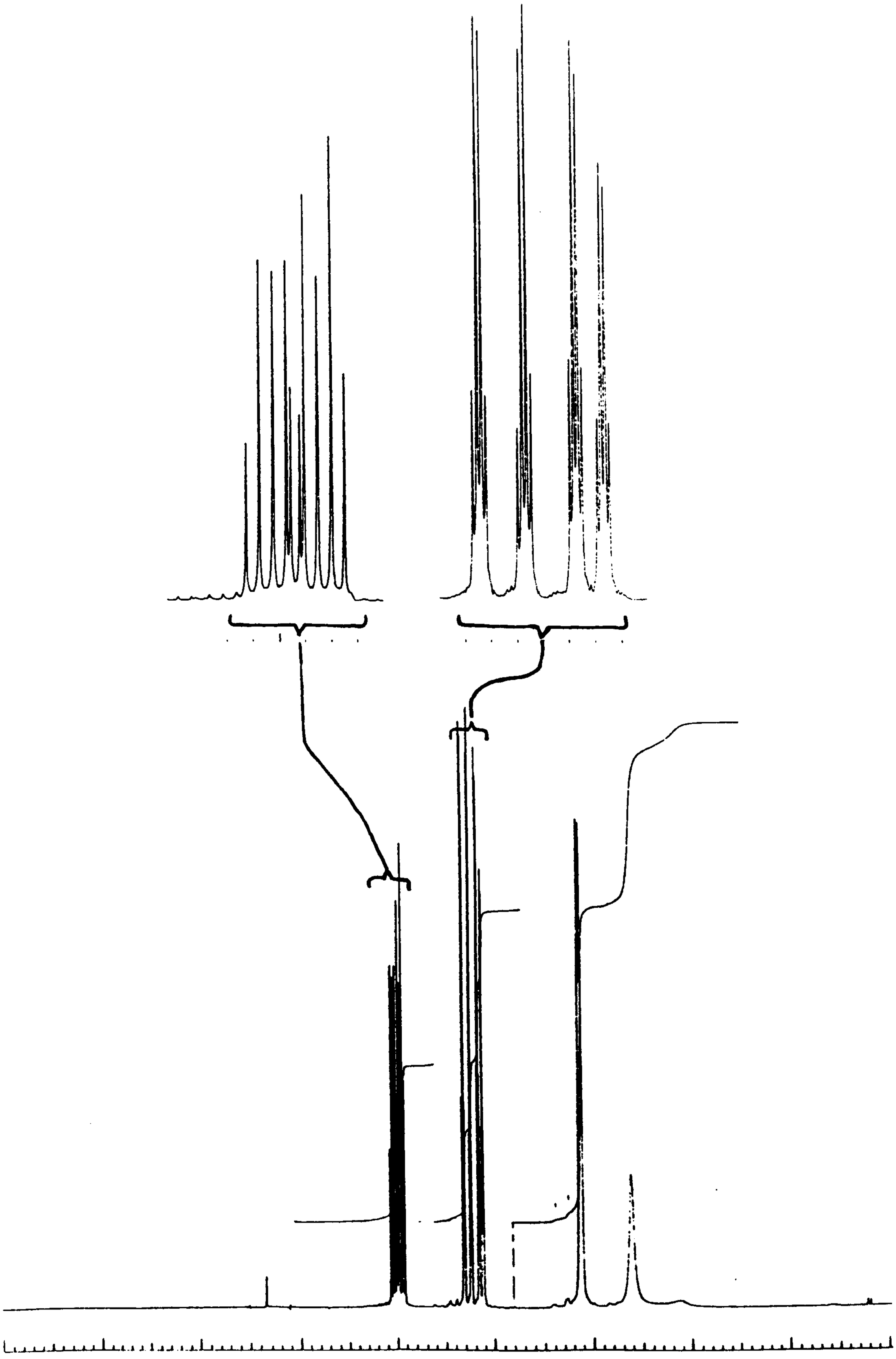
Signal centred on $\delta = 5.93$ due to H_3 dddd couples with H_1, H_2, H_4 and H_5.

Signal centred on $\delta = 5.30$ due to H_2 ddt couples with H_3, H_1 and (H_4+H_5).

Signal centred on $\delta = 5.23$ due to H_1 ddt couples with H_3, H_2 and (H_4+H_5).



Scheme XLVII

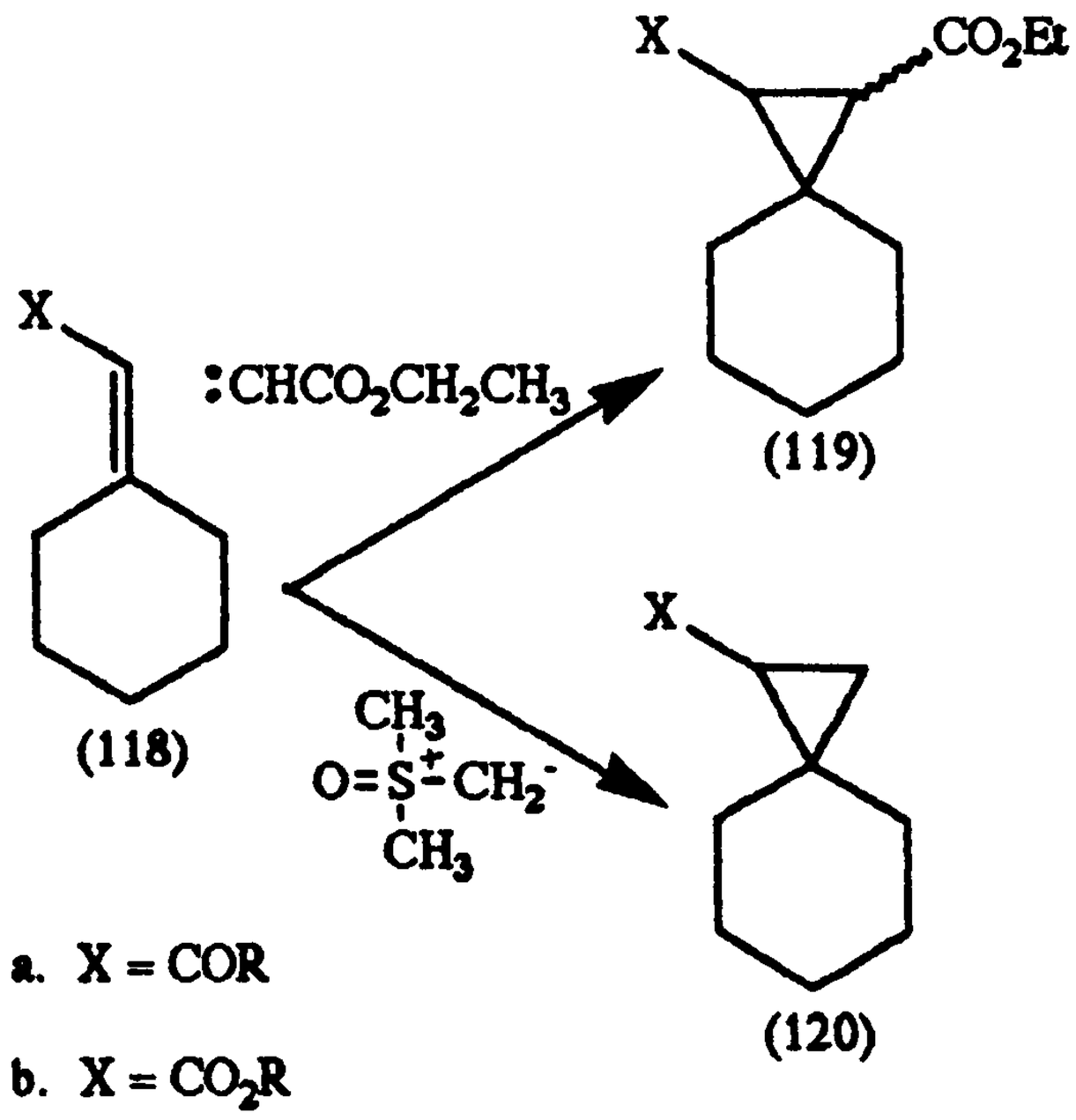


Scheme XLVIII

it has been reported[165] that on changing from copper to rhodium based catalysis the ratio insertion:cyclopropantion changes from 13 to 0.23. Reports[167] of copper catalysis providing the cyclopropane species from allyl chloride and carboethoxycarbene disagree with our findings, where no cyclopropane was observed.

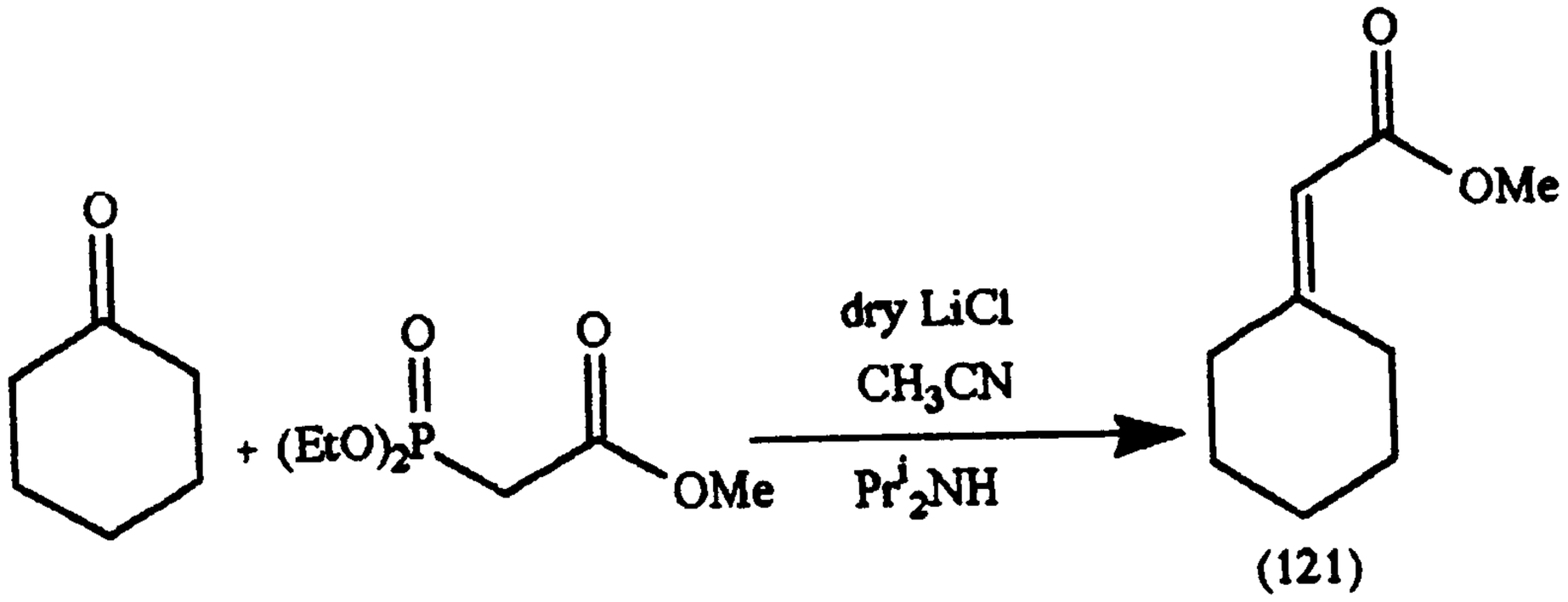
2.2.4 Synthesis/attempted synthesis of spiro compounds and other miscellaneous cyclopropyl compounds

As mentioned previously (see section 2), it is known[135] that t-butoxyl radicals will abstract a hydrogen atom from spiro[2.5]-octane (76) to give, almost exclusively, the spiro[2.5]oct-2-yl radical (77). This would allow us to generate, easily, radicals based on this structure, in the e.s.r. specrometer. It was proposed to synthesise precursors for the target radicals (74) and (75) by reaction of a methylene cyclohexane derivative (118) with either carboethoxycarbene or trimethylsulphoxonium methylide[144] (see Scheme XLIX).



Scheme XLIX

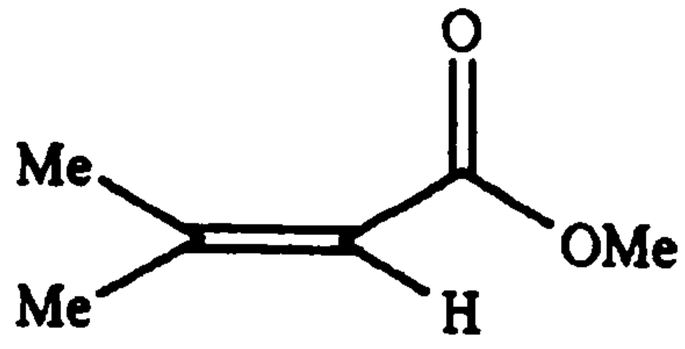
The synthesis of the methylene cyclohexane derivatives needed for these reactions did not prove as simple as anticipated. The compound methyl cyclohexylideneacetate (121) was successfully made from cyclohexanone using a modified Horner-Wadsworth-Emmons reaction[171] (see Scheme L). The methyl cyclohexylidene-



(121)

Scheme L

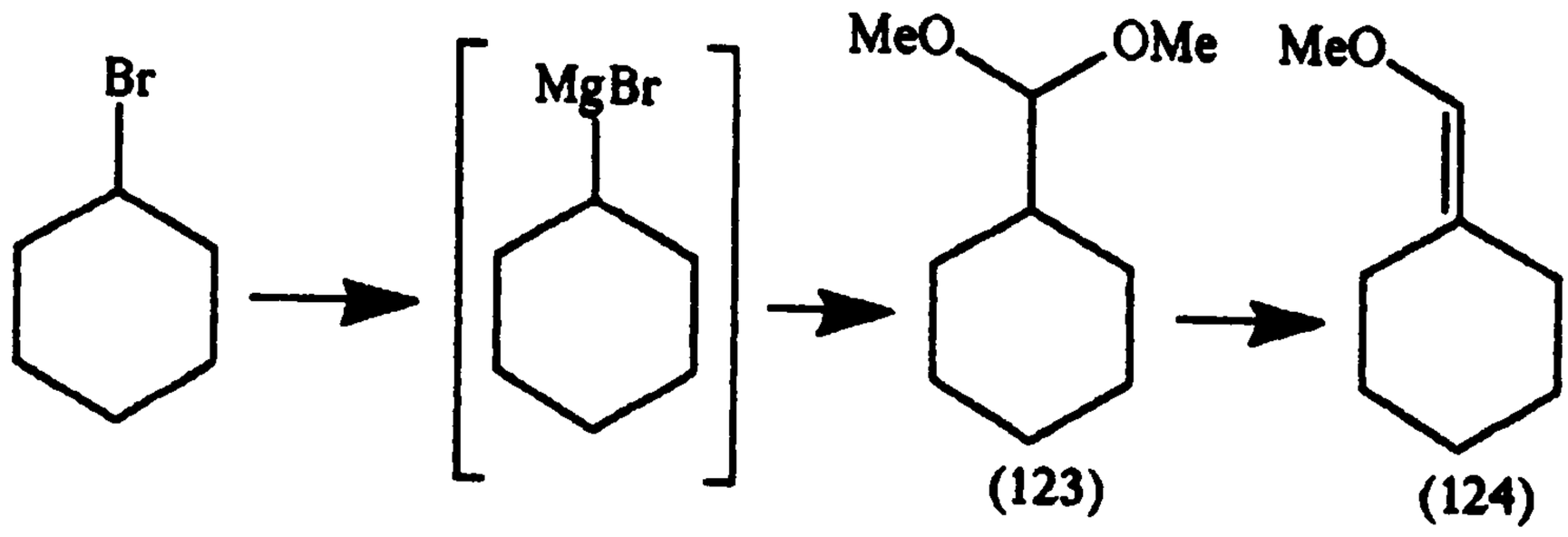
acetate (121) was reacted, as proposed, with both carboethoxy-carbene and trimethylsulphoxonium methylide. In the reaction with carboethoxycarbene the only product isolated from a black intractable mixture was diethyl maleate, the carbene-carbene addition product. When methyl cyclohexylideneacetate (121) was reacted with trimethylsulphoxonium methylide, according to the method of Landor and Punja[144] (see section 2.1.4), fractional distillation of the tar-like reaction mixture failed to give any identifiable product. The reasons for the failure of this reaction are not fully understood. The analogous compound (122) undergoes reaction with trimethylsulphoxonium methylide to give the cyclopropane albeit in a low yield (9%).[144]



(122)

This reported reaction is not a maximized yield. Perhaps with careful manipulation of the reaction conditions the desired cyclopropanation could have been carried out.

In an attempt to make the spiro compounds (119a) and (120a), the synthesis of methoxymethylenecyclohexane (124) was tried. This synthesis followed a procedure described by Wenkert et.al.[172] (see Scheme LI). The dimethoxy methylcyclohexane (123) was easily

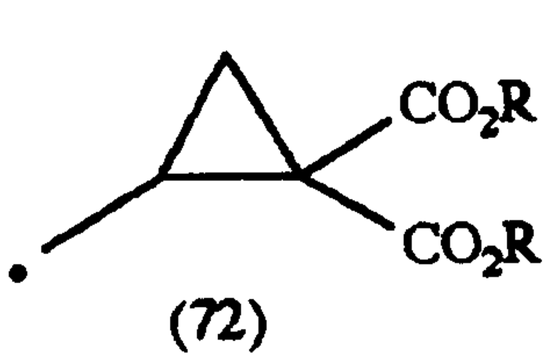


(123) (124)

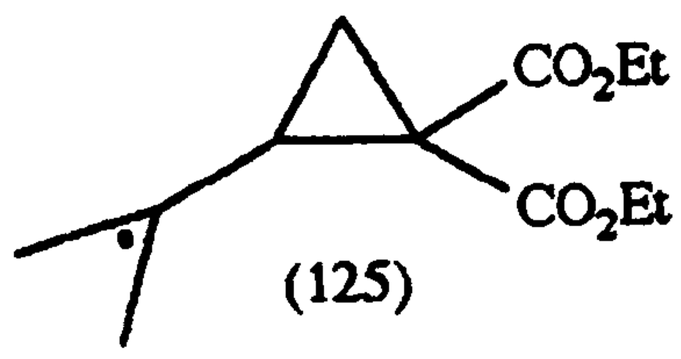
Scheme LI

produced from the Grignard reagent cyclohexylmagnesium bromide and methyl orthoformate. The conversion of the dimethoxy compound (123) to the methoxymethylenecyclohexane (124) by removal of methanol in the presence of c.H_2SO_4 could not be repeated. None of the methoxymethylenecyclohexane (124) was produced and further reaction with carboethoxycarbene or trimethylsulphoxonium methylide could not be attempted.

Leaving the attempted production of spiro compounds and turning to proposed target radicals of the type (72), an impure sample of diethyl 2-isopropylcyclopropane-1,1-dicarboxylate (126)

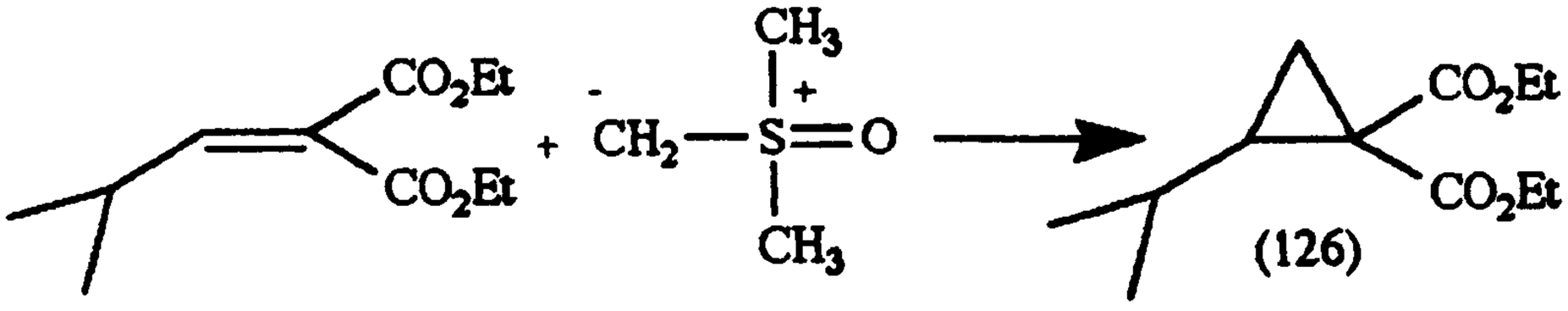


(72)



(125)

was obtained from a colleague. This compound had been synthesised from ethyl isobutylidenemalonate and trimethyl-sulphoxonium methylide (see Scheme LII), by the method described by Landor and Punja[144] (see section 2.1.4). It was envisaged that the radical (125) could be generated from this precursor. The



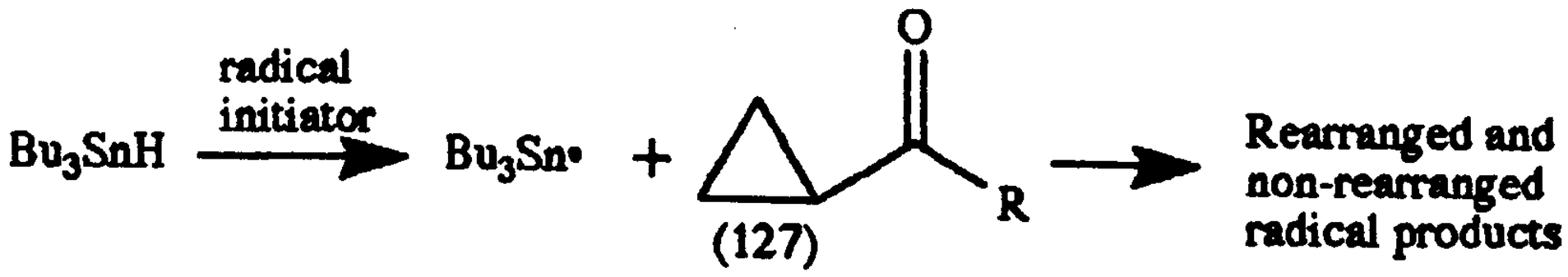
(126)

Scheme LII

cyclopropane (126) was purified by preparative g.l.c. in sufficient quantity to attempt to generate the desired radical (125) in the e.s.r. spectrometer.

2.3 Reduction of Cyclopropyl Phenyl Ketone and Cyclopropyl Ferrocenyl Ketone

This work was proposed to study the differing extent to which a phenyl and a ferrocenyl group will stabilise a cyclopropyl radical. The products of a series of reactions involving either cyclopropyl phenyl ketone (127a) or cyclopropyl ferrocenyl ketone (127b) with tri-butyltin radicals were studied (see Scheme LIII). The products formed in these reactions were analysed by g.l.c.



a. R = Ph

b. R = Fc

Scheme LIII

This analysis required the synthesis of the possible reaction products (see Table VIII) as reference compounds. These compounds were produced by standard synthetic routes. The tri-butyltin hydride reductions were carried out (see Table IX) by placing the reactants in sealed tubes in-vacuo and heating in a thermostatic oil bath. The tubes were then opened and the contents analysed by g.l.c. From the results of reactions a. and g. (see Table IX) it was found that a radical initiator was necessary

for any reaction to occur, this suggests a radical mechanism is involved. The initiator used was azoisobutyronitrile (AIBN).

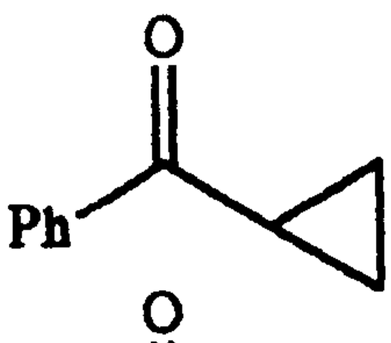
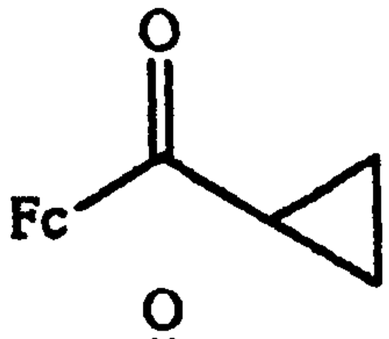
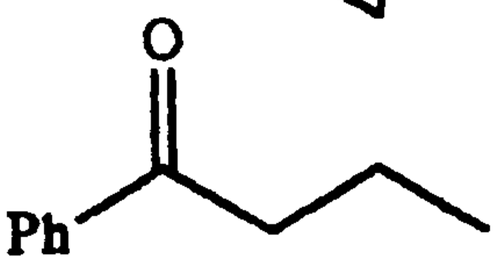
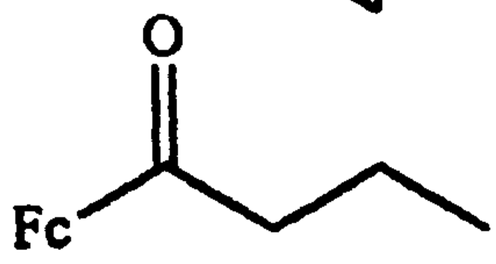
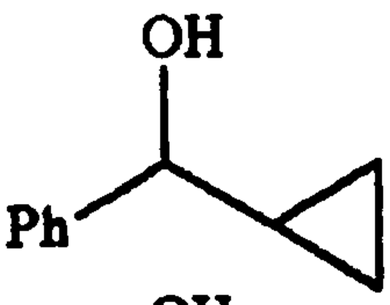
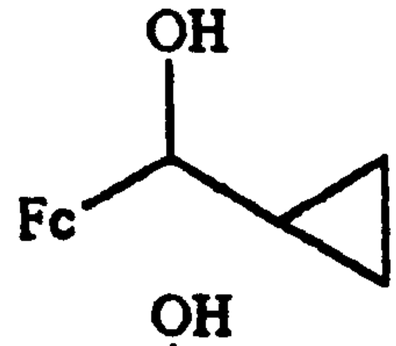
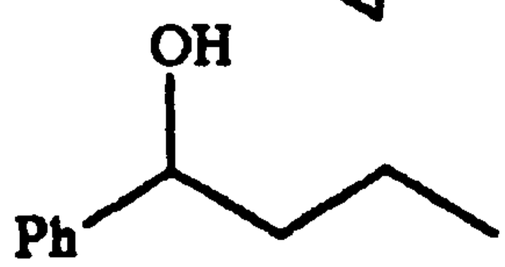
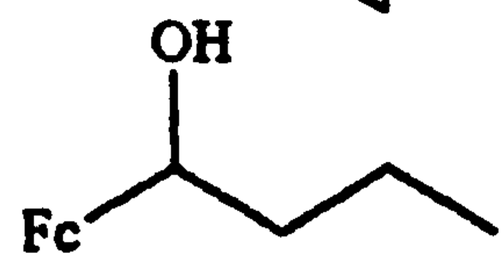
Reference compound	Comments	Reference compounds
 (127a)	starting material	 (127b)
 (128)	ring-opened ketone (rearranged)	 (129)
 (130)	ring-closed alcohol (unrearranged)	 (131)
 (132)	ring-opened alcohol (rearranged)	 (133)

Table VIII Reference compound for g.l.c. analysis

As well as the study mentioned above it was also proposed to investigate this reaction using the nitroxide 1,1,3,3-tetramethyl-isoindolin-2-yloxyl as a trap for any radical species formed during the reaction (see section 2.4. (b)).

In all the reactions carried out the predominant compound found on analysis of the reaction mixture, by a variety of g.l.c.

Inhibitor	Temp (O°C)	Time (h)	[Bu_3SnH] (mol)	Unreacted ketone	Closed chain alcohol	Closed chain ketone	Open chain alcohol
a none	68-70	20	0.1	100%	---	---	---
b AIBN (0.05 mol)	68-70	20	0.1	major	---	minor	---
c "	104	5	0.1	major (80%)	trace	minor (70%)	---
d "	104	20	0.1	major (80%)	trace	minor (60%)	---
e "	104	20	0.25	minor (20%)	trace	major (80%)	---
f "	104	20	0.5	minor (20%)	trace	major (80%)	---
g none	68-70	20	0.1	100%	---	---	---
h AIBN (0.05 mol)	68-70	20	0.1	major	---	minor	---
i "	104	5	0.1	major (80%)	---	minor (70%)	---
j "	104	20	0.1	major (80%)	---	minor (60%)	---
k "	104	20	0.25	major (60%)	---	minor (40%)	---
l "	104	20	0.5	minor (40%)	---	major (60%)	---

Table IX Reduction of Cyclopropyl Phenyl Ketone (a-f) and Cyclopropyl Ferrocenyl Ketone (g-l) by tri-butyltin hydride

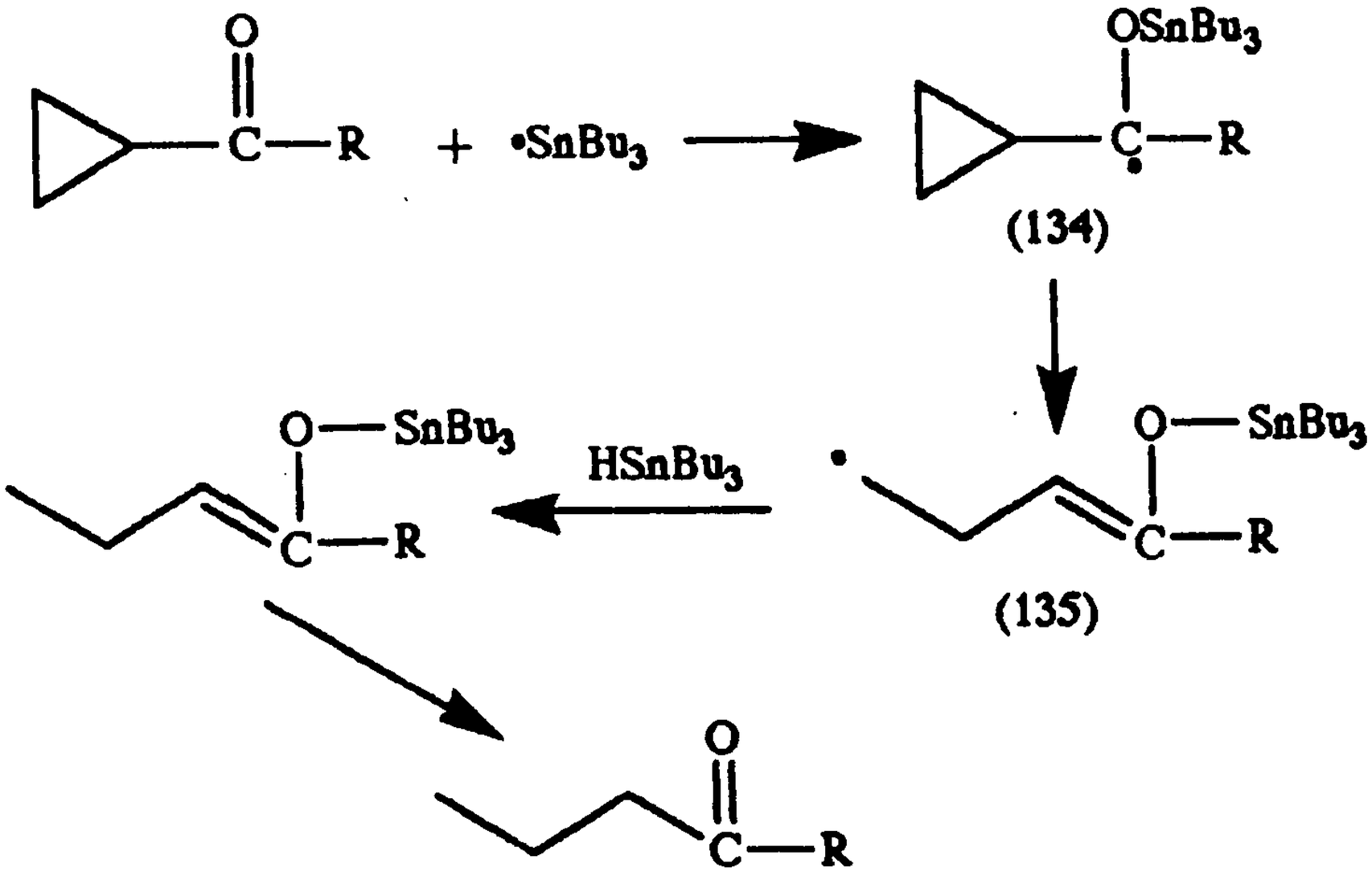
columns, was the unreacted ketone (127). It was found that increasing any one of, the concentration of tri-butyltin hydride, the reaction temperature and the reaction time, all increased the amount of reaction occurring and reduced the amount of unreacted ketone recovered. Discounting the recovered starting material, the major reaction products for the phenyl and ferrocenyl compounds (see Table X) were the corresponding open-chain ketones (128) or (129). In the phenyl case trace amounts of the product 1-phenyl-cyclopropanemethanol (130), the ring-closed alcohol, were found.

Products found	Starting Material	Ring Opened Ketone	Ring Closed Alcohol	Ring Opened Alcohol
Phenyl	Always present	Main product	Trace	Not found
Ferrocenyl	Always present	Main product	Not found	Not found

Table X Summary of products found in reaction of cyclopropyl phenyl and cyclopropyl ferrocenyl ketone with tri-butyltin hydride.

In none of the ferrocenyl reactions were any of the alcohols (131) or (133) formed. A small quantity of the ring-opened alcohol (132) may have been found from the further reduction of ketone (128) as the ring-opened alcohol (132) was not completely separable from the starting material (127a) on any of the g.l.c. columns available. In a similar reaction Tanner et.al[173] observed none of the ring-opened alcohol (132) and only a trace of the ring-closed alcohol (130), in agreement with our findings.

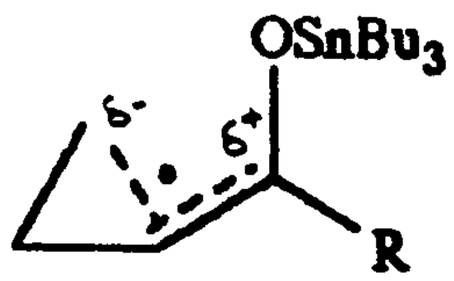
The major products formed, the open-chain ketones (128) and (129), probably result from rearrangement of a radical intermediate with the unpaired electron on the carbonyl carbon (see Scheme LIV). This mechanism is similar to that proposed by Tanner et.al.[173] It is proposed that the radical intermediate (134),



Scheme LIV

formed by addition of a tributyltin radical to the ketone (127), undergoes rearrangement to give the radical (135), which subsequently gives the open-chain ketone. Further reduction of the open-chain ketone, not observed in these reactions, would lead to the open-chain alcohol. The trace of 1-phenylcyclopropane-methanol that was found must be generated by a pathway competing with the ring-opening reaction. The fact that only a small quantity of 1-phenylcyclopropanemethanol is found suggests that under these conditions the ring-opening rearrangement is

favoured. The ring-closed alcohol is not seen in the ferrocenyl case; this implies that the intermediate ferrocenylmethyl radical (134, R = Fc) rearranges faster than the corresponding benzyl radical (134, R = Ph). This observation indicates that the phenyl group stabilises the intermediate radical to a greater extent than the ferrocenyl group. The differences in the rate of the ring-opening rearrangement are controlled by two main factors. The first is the relative stability of the intermediate radicals formed and the second, differences in the stabilities of the possible dipolar transition states (136). It is reported that ferrocenylmethyl carbocations possess exceptional stability.[174-176]



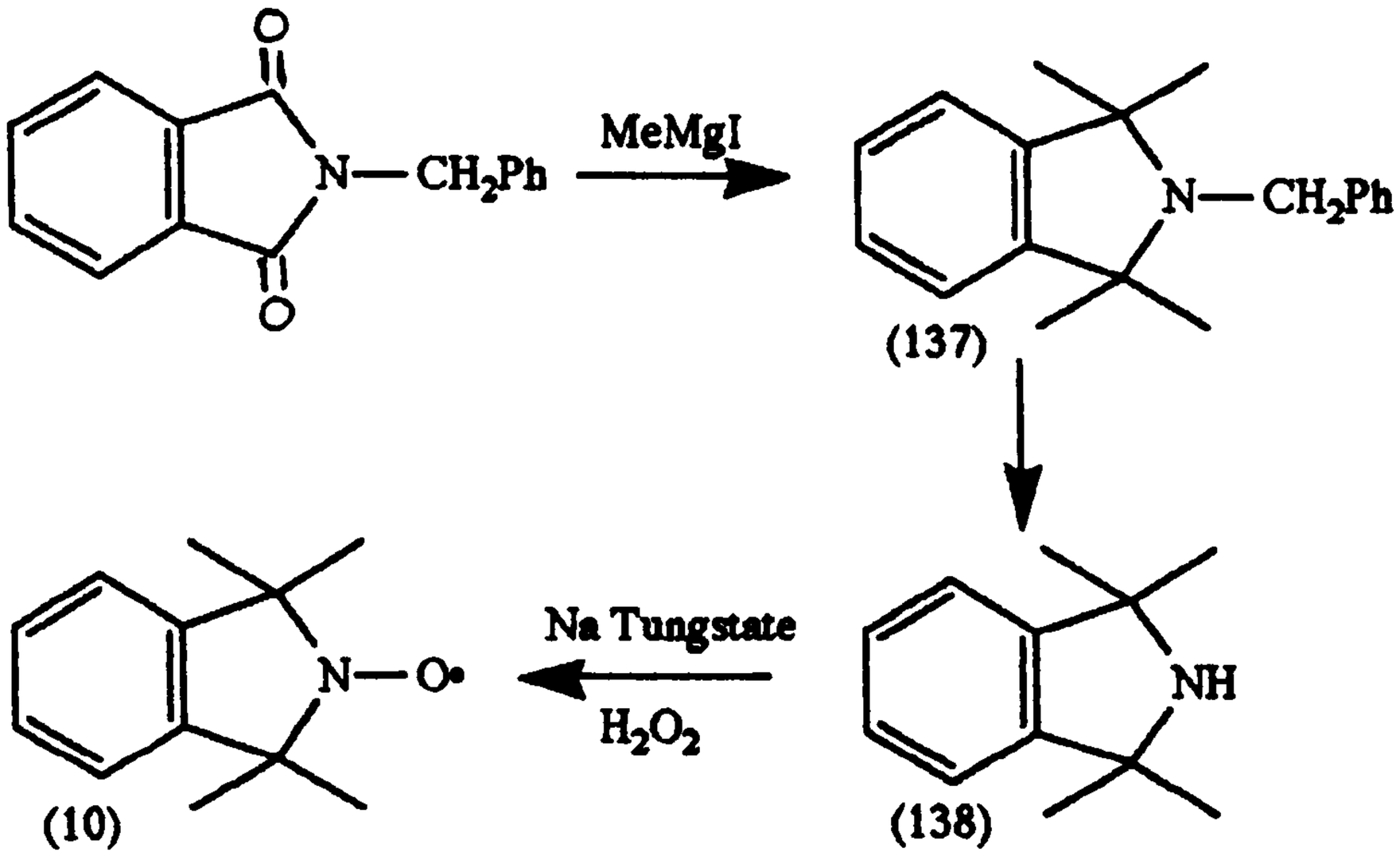
(136)

Thus the ferrocenyl group would stabilise the dipolar transition state and this should accelerate the rate of ring-opening. Our results show that while the phenyl group stabilises the intermediate radical which slows the ring-opening, it appears as though the ferrocenyl group accelerates the ring-opening as mentioned above. This result is in disagreement with recent work of Creary et.al[177] They found that the ferrocenyl group had a radical stabilising ability just greater than that of a phenyl group.

2.4 Synthesis and use of 1,1,3,3-Tetramethylisoindolin-2-yloxyl

a) Preparation of 1,1,3,3-tetramethylisoindolin-2-yloxyl

As mentioned in the introduction (see section 1.1.1.(b)), the nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxyl (10) can be used in the measurement of rates of rearrangement reactions.[178] The synthesis of this compound was first reported by Solomon et.al.[179] However an attempt to repeat this work had very limited success until modifications were made to the reaction conditions. The nitroxide was synthesised (see Scheme LV) by heating previously prepared N-benzylphthalimide with the Grignard reagent methylmagnesium iodide to give 2-benzyl-1,1,3,3-tetramethylisoindoline (137). The gelatinous nature of the reaction mixture made the product difficult to extract but the reported yields could be achieved with care. The hydrogenation of the isoindoline (137) was carried out and the residue, after evaporation, was treated with alkali to a pH of 11. The product 1,1,3,3-tetramethylisoindoline (138) was obtained at this pH whereas the reported pH of 8.5 did not give the free product from the acid salt. The oxidation of the isoindoline (138) to the nitroxide using hydrogen peroxide proceeded easily to give the final product 1,1,3,3-tetramethylisoindol-2-yloxyl (10).



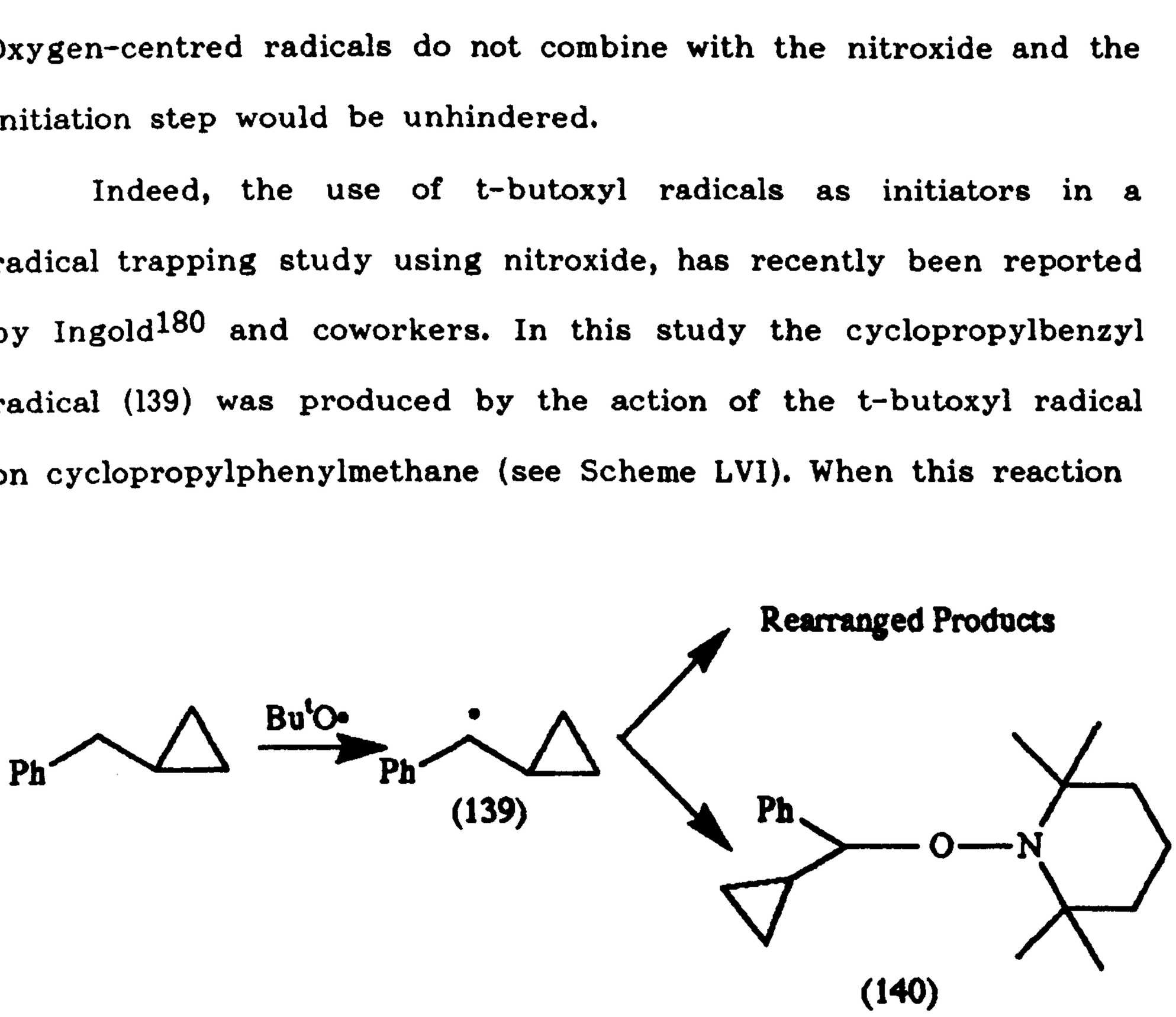
Scheme LV

b) Use of 1,1,3,3-tetramethylisoindolin-2-yloxyl

It was intended to use the nitroxide in an investigation of the reduction of phenyl and ferrocenyl cyclopropyl ketones with tri-butyltin hydride (see section 2.3). The nitroxide was to be used to trap any radical intermediates formed in these reactions. The initial intermediates formed on reaction of tributyltin radicals with the cyclopropyl ketones would be the cyclopropyl radicals; the corresponding ring-opened radicals may also be generated by rearrangement of the initial cyclopropyl radical. An analysis of the products formed, or trapping of the radical intermediates by the nitroxide, would provide information about the rate of the radical rearrangement. In retrospect however the proposed trapping experiment was seriously flawed. In the proposed scheme

tributyltin radicals were to be generated from tributyltin hydride using the radical initiator azoisobutylronitrile (AIBN) and heat. The tributyltin radicals would then react with the phenyl or ferrocenyl cyclopropyl ketones. However the radicals produced on decomposition of AIBN, and any tin radicals formed, were trapped by the nitroxide, stopping the production of any radicals from the cyclopropyl ketones. For the nitroxide to be of any use in these studies the cyclopropyl radicals must be generated via a route that does not produce any intermediate radical species that can be trapped by the nitroxide. It may be possible to use oxy radicals, produced from a peroxide, to give the cyclopropyl radicals. Oxygen-centred radicals do not combine with the nitroxide and the initiation step would be unhindered.

Indeed, the use of t-butoxyl radicals as initiators in a radical trapping study using nitroxide, has recently been reported by Ingold[180] and coworkers. In this study the cyclopropylbenzyl radical (139) was produced by the action of the t-butoxyl radical on cyclopropylphenylmethane (see Scheme LVI). When this reaction



Scheme LVI

was carried out in the presence of the nitroxide (69) only one trialkylhydroxylamine (140) was observed, resulting from the combination of the nitroxide with the cyclopropylbenzyl radical.

3. ELECTRON SPIN RESONANCE STUDIES

Once the precursors for the desired target radicals were synthesised and purified the radical species were generated and their e.s.r. spectra recorded.

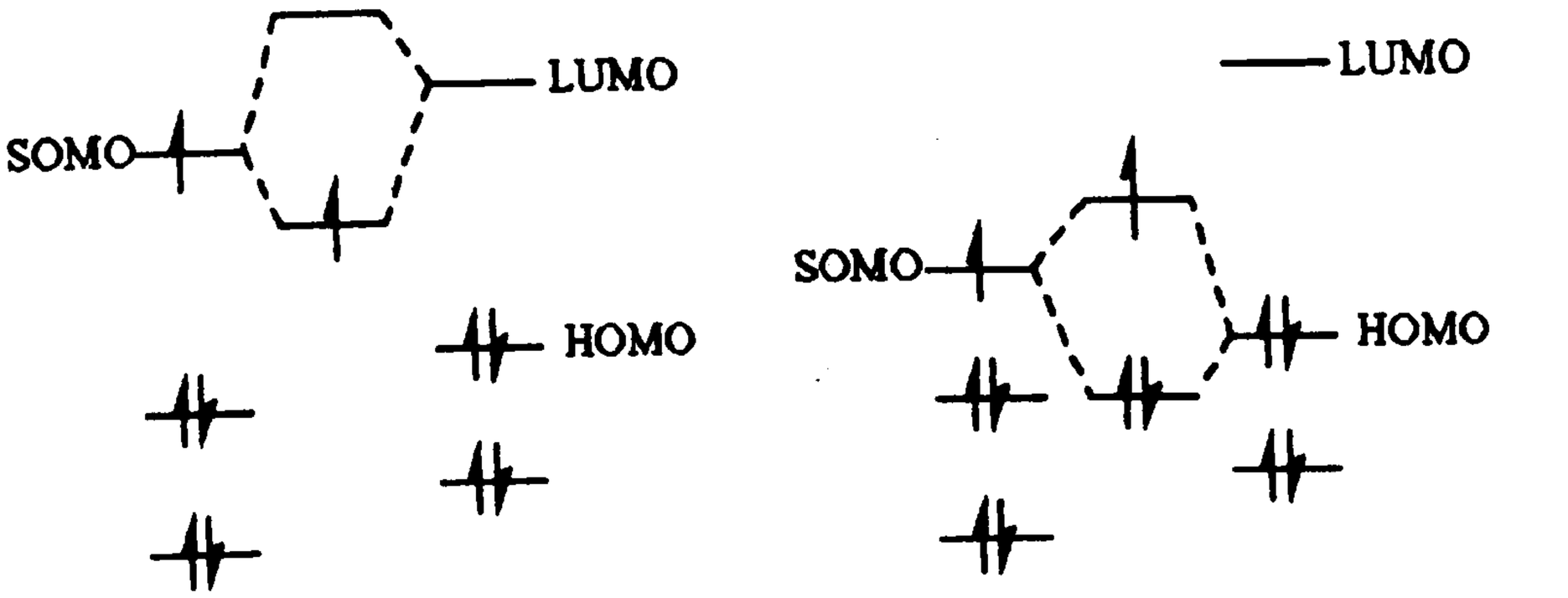
3.1 Generation of Radical Species

The radicals were generated, from the precursor compounds, directly in the cavity of the e.s.r spectrometer. A solution of the radical precursor and tert-butyl peroxide, in an inert solvent, was subjected to u.v. irradiation. The tert-butyl peroxide decomposes to give a tert-butoxyl radical, which then abstracts a hydrogen atom from the precursor compound to give a radical species.

The site of abstraction depends on the relative ease of abstraction of the various hydrogen atoms present in the precursor and can be explained in terms of frontier orbital theory. The frontier orbital of the radical is the SOMO (singly occupied molecular orbital), which will interact with either the HOMO (highest occupied molecular orbital) or the LUMO (lowest unoccupied molecular orbital) of the precursor (see Scheme LVII).

Radicals with high energy SOMOs typically interact with the LUMO of another species and generally show nucleophilic properties. With a low energy SOMO a radical interacts with the HOMO and shows electrophilic properties.

Alkoxyl radicals are electrophilic and hence attack bonds with high HOMO energies e.g. α-C-H bonds of ethers and amines and C-H bonds of alkyl groups in esters. Nucleophilic alkyl

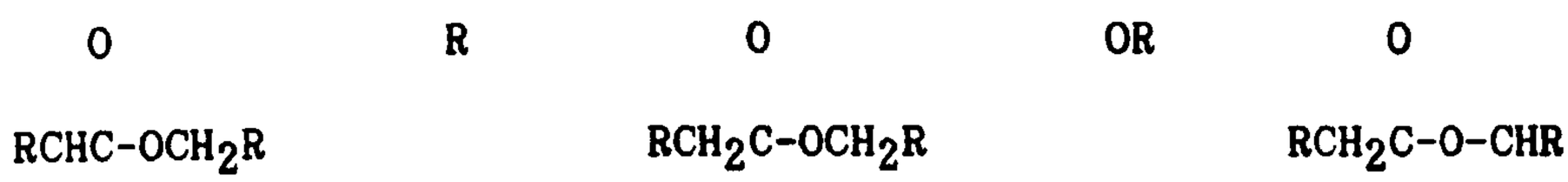


Radical with a high energy SOMO (nucleophilic)

Radical with a low energy SOMO (electrophilic)

Scheme LVII

radicals abstract hydrogen from the acyl group of esters as this bond has a lower LUMO energy.



The t-butoxyl radical has a low energy SOMO, shows electrophilic properties, and will normally interact with the HOMO of another species. Experimentally it is known that radicals abstract hydrogen in the following order of preference: allylic > tertiary > secondary > primary. This preference follows the same order as the energies of the HOMOs of the substrates. A radical with a high energy SOMO will react in preference with a substrate with a low energy HOMO. Consideration of the SOMO energy of the radical and the HOMO

energy of a possible abstraction site allows us to make tentative predictions as to the preferred site(s) of hydrogen abstraction.

In the next section each radical precursor is taken in turn and the e.s.r. spectrum observed is discussed.

3.1.1 The radicals from *trans*-1-trimethylsilyloxymethyl)-2-ethoxycyclopropane

When *trans*-1-(α-trimethylsilyloxymethyl)-2-ethoxycyclopropane (113) and t-butyl peroxide were photolysed in the cavity of the e.s.r. spectrometer two radical species were observed; spectral details are listed below (see Table XI).

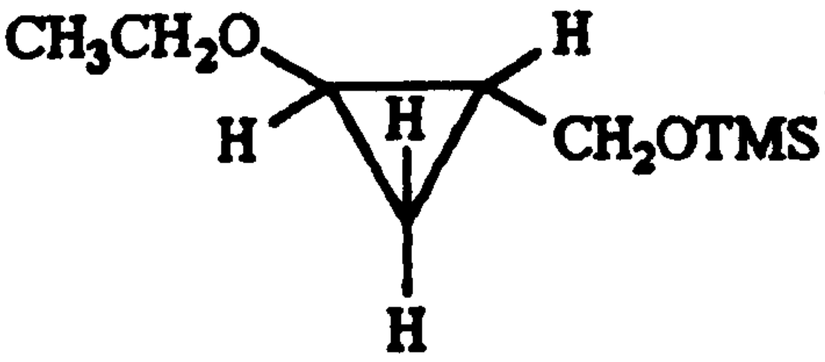
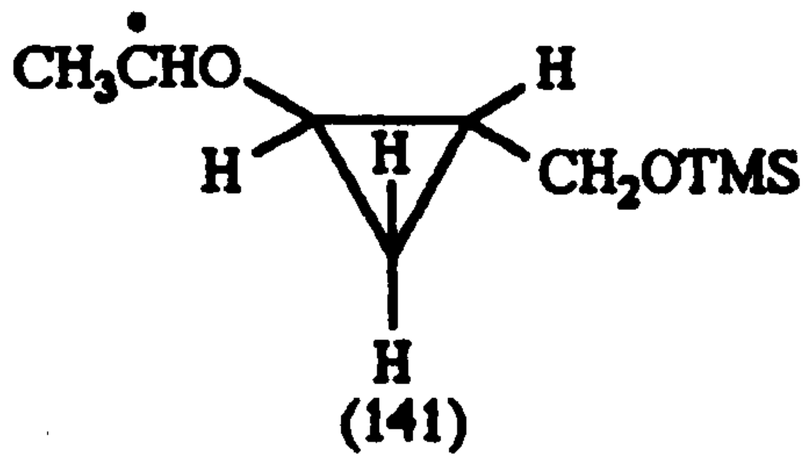
Precursor	Radicals observed	h.f.s.
 (113)	 (141)	α(1H) 15.0 β(3H) 22.8 γ(1H) 1.9
	$CH_3CH_2O\dot{C}HCH_2CH{=}CHOTMS$ (142)	α(1H) 14.2 β(2H) 21.3 γ(2H) 1.7 γ(1H) 0.8

Table XII Radicals from *trans*-1-(trimethylsilyloxymethyl)-2-ethoxycyclopropane.

The α and β splittings for the radical (141) are consistent with abstraction of a hydrogen atom from the CH_2 of an ethoxy group; the further γ splitting is from the hydrogen on the carbon α to the oxygen. Comparison of the spectrum for the radical (141) with that reported for the radical (143) from diethyl ether shows that they have similar splittings (see Table XII).

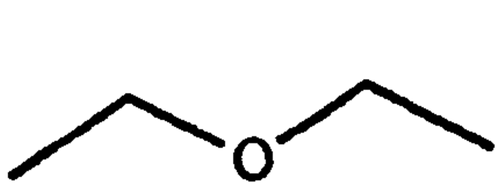
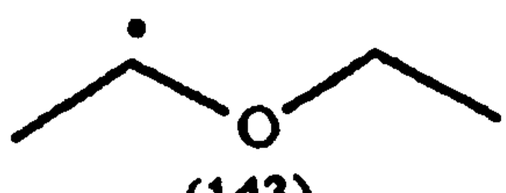
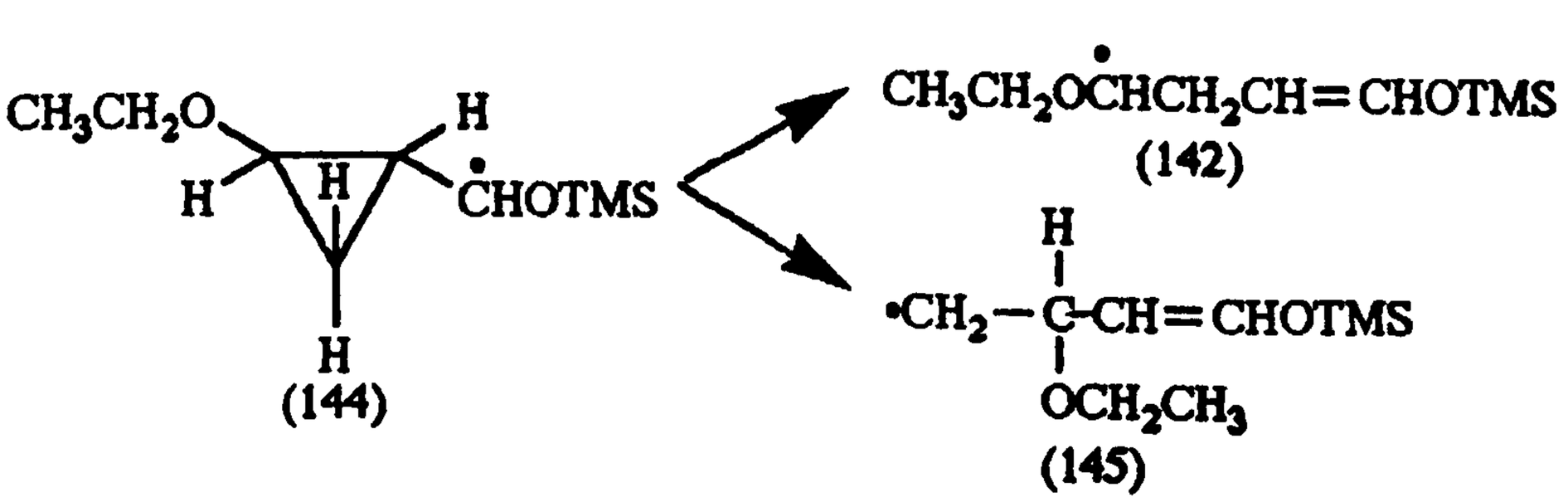
Precursor	Radical	h.f.s.	Ref.
	 (143)	α (1H) 13.93 β (3H) 21.62 γ (2H) 1.5	181-183

Table XII Radicals from diethyl ether

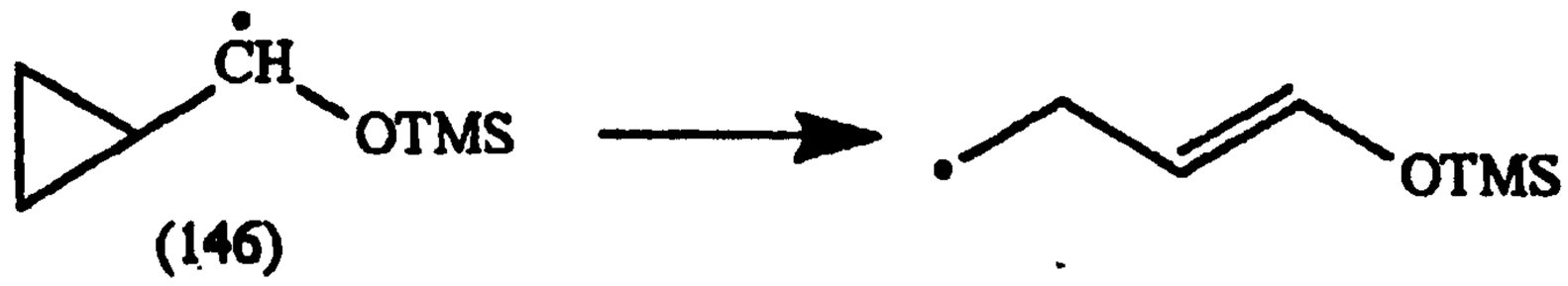
The other radical observed (142) (see Table XI) has a splitting pattern that would suggest a CH radical with an adjacent CH_2 group i.e. α(1H), β(2H). It is suggested that this radical has the structure shown and is formed by rearrangement of the substituted cyclopropylcarbinyl radical (144) (see Scheme LVIII).



Scheme LVIII

The cyclopropylmethyl radical (144) is generated by abstraction of a hydrogen atom from the CH_2 site of the trimethylsilyloxymethyl substituent. The radical observed is not the cyclopropylcarbinyl radical as it would have an α(1H), β(1H) splitting pattern with further splitting by γ C-H protons; this pattern is not observed. Ring-opening rearrangement of the cyclopropylcarbinyl radical (144) can give two possible product radicals (142) and (145). The primary radical (145) does not fit the observed spectrum as it would give a α(2H) β(1H) splitting pattern. The other possible radical from the rearrangement (142) fits the observed spectrum with an α(1H), β(2H) splitting pattern. There is also further splitting by γ C-H protons. Comparison of the spectrum recorded with that for the radical (143) (see Table XII), shows similar γ splitting values.

Comparison of the data obtained for the ring-opening rearrangement of radical (144) (see Scheme LVIII) with that reported[184] for the non-substituted parent radical (146) (see Scheme LIX) shows that the rearrangment occurs faster for the substituted radical. The parent radical (146) does not rearrange at



(146)

137K whereas the 2-ethoxy derivative is completely rearranged by 133K. This increase in the rate of rearrangement is probably due to

the stabilisation of the product radical (142) by the 2-ethoxy group; such a stabilisation is known to occur with OR groups in general.[185]

Another point to consider with the ring-opening rearrangement of radical (144) (see Scheme LVIII) is the direction in which ring-opening occurs. The rearranged radical observed in the e.s.r. spectrum is the secondary radical (142). The secondary radical is the expected product radical as secondary radicals are generally more stable than primary radicals. It is noted however that rearrangement of the *trans*-2-methylcyclopropylcarbinyl radical (42) results in formation of the less stable primary radical. This anomalous finding can be explained in terms of frontier molecular orbital theory (see section 1.2.4(c)).

The fact that abstraction occurs from two sites on the precursor molecule (113) is not totally unexpected as both sites are CH_2 groups with an adjacent oxygen atom. The HOMO energies of the two sites wil be very similar and can both interact with the SOMO of the t-butoxyl radical. A cleaner spectrum, with abstraction occurring only from the desired site, could be obtained by use of a 2-methoxy or 2-t-butoxy group rather than the 2-ethoxy group.

3.1.2 The radicals from ethyl 2-acetoxymethylcyclopropane-carboxylate

The radical precursor ethyl 2-acetoxymethylcyclopropanecarboxylate could not be separated into the pure *cis* and *trans*-isomers and was used as an isomeric mixture with approximately a 2:3 *cis:trans* ratio. The radicals were generated by u.v. photolysis

of a solution of t-butyl peroxide and the radical precursor (114). Two radicals were observed in the e.s.r. spectrum (see Table XIII).

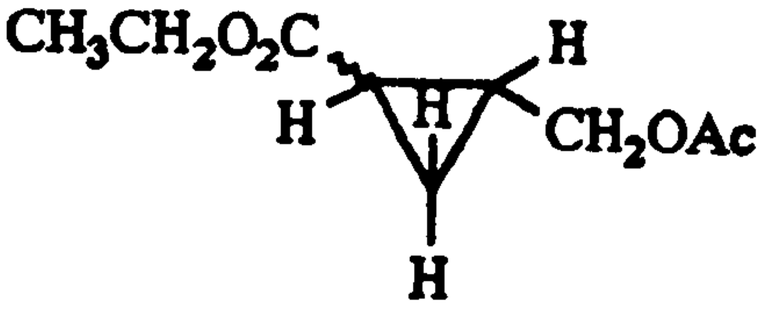
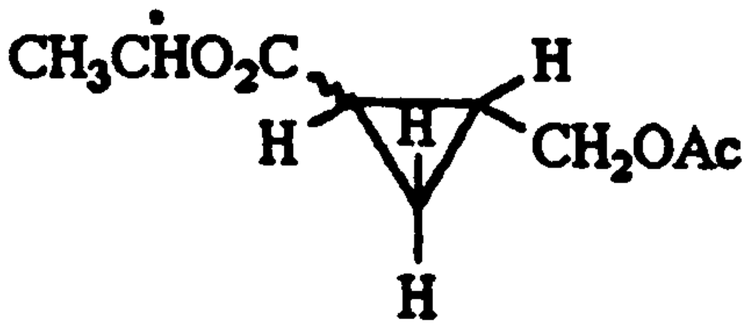
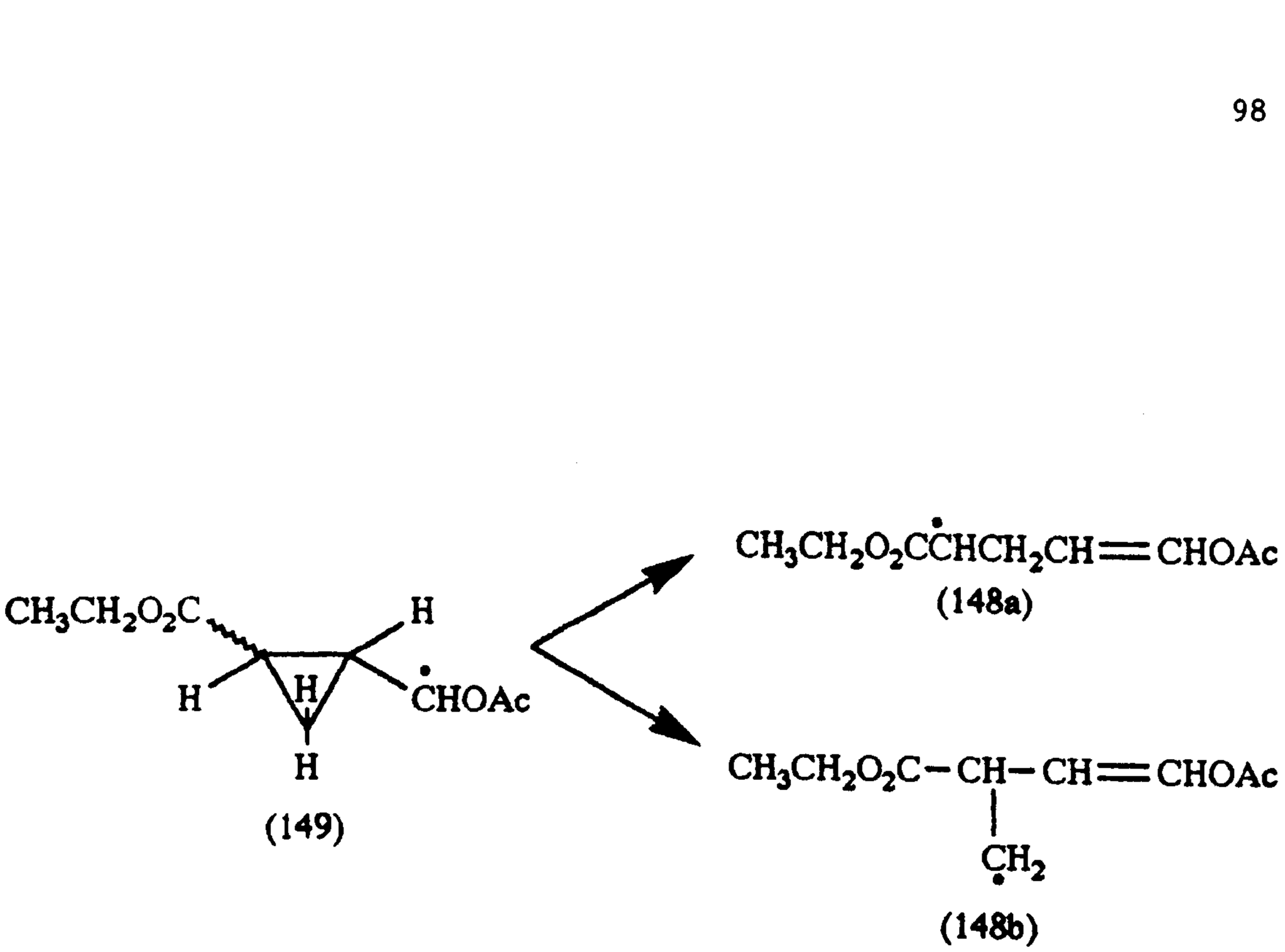
Precursor	Radcials observed	h.f.s
 (114)	 (147)	α(1H) 20.3 β(3H) 24.3
	$CH_3CH_2O_2CC\dot{H}CH_2CH{=}CHOAc$ (148a)	α(1H) 20.8 β(2H) 24.3

Table XIII Radicals from ethyl 2-acetoxymethylcyclopropanecarboxylate

The major radical (147) observed showed the following splitting α(1H), β(3H). This is similar to that for radical (141) and arises from abstraction of a hydrogen atom from the CH_2 of an ethyl group. There is also a much weaker spectrum evident which it is suggested arises from the rearrangement of radical (149). A ring-opening rearrangement of the substituted cyclopropylcarbinyl radical (149) could give two possible radicals (148a) and (148b). (see Scheme LX).



Scheme LX

The cyclopropylcarbinyl radical (149) is formed by abstraction of a hydrogen atom from the CH_2 of the acetoxy methyl group in (114). Abstraction from this site is as feasible as that observed for radical (147); in both cases the CH_2 groups will have similar HOMO energies. If the substituted cyclopropylcarbinyl radical (149) was observed we would expect an α(1H), β(1H) splitting pattern, this is not seen. The spectrum observed has an α(1H), β(2H) or an α(2H), β(1H) splitting pattern that could be accounted for by the ring-opened radical (148a) or (148b) respectively. Comparison of the spectrum obtained with radicals of a similar structure to the possible product radical (148a) showed a close correlation (see Table XIVc). The other possible product radical (148b) was compared with similar radicals (see Table XIVb). This comparison did not hold up as in all the similar radicals the α splitting was always less than the β splitting. From our experimental data the

Radical	h.f.s.	Ref.
$CH_3CH_2O_2C\dot{C}HCH_2CH{=}CHOAc$ (148a)	α(1H) 20.8 β(2H) 24.3	this work
$CH_3CH_2\dot{C}HCOOH$ (150)	α(1H) 20.17 β(2H) 23.78	186
$CH_3\dot{C}HCOOCH_3$ (151)	α(1H) 20.3 β(3H) 24.9 γ(3H) 0.13	187-188

Table XIVa Comparison of radical (148a) with similar radicals.

Radical	h.f.s.	Ref.
$CH_3CH_2O_2C-CH(\dot{C}H_2)-CH{=}CHOAc$ (148b)	α(2H) 24.3 β(1H) 20.8	this work
$HO_2C-CH(\dot{C}H_2)-CH_3$ (165)	α(2H) 22.0 β(1H) 25.3	187,188,210
$CH_3O_2C-CH(\dot{C}H_2)-CH_3$ (166)	α(2H) 21.9 β(1H) 25.4	187
$HO_2C-CH(\dot{C}H_2)-OH$ (167)	α(2H) 22.1 β(1H) 26.6	188,211,212

Table XIVb Comparison of radical (148b) with similar radicals.

radical (148b) would require an α splitting larger than the β splitting. On this evidence it is suggested that the radical observed has the structure shown (148a). The spectrum for this ring-opened radical (148a) first appears very weakly at 160K. The rearrangement would appear to be complete at 180K. At temperatures below 160K any signal due to the unrearranged radical (149) is swamped by the much larger signal from radical (147). The rearrangement of the radical (149) from ethyl 2-acetoxymethylcyclopropanecarboxylate is compared with the rearrangement of the radical from cyclopropanemethyl acetate (see section 3.1.3).

The e.s.r. spectrum obtained from ethyl 2-acetoxymethylcyclopropanecarboxylate could be simplified by using the methyl 2-acetoxymethylcyclopropanecarboxylate. This would eliminate one of the sites of hydrogen abstraction and any radicals seen would result from the generation of the methyl ester analogue of radical (149) and its rearranged products.

3.1.3 The radicals from cyclopropanemethyl acetate

This work was undertaken to provide a comparison with the radicals generated from the 2-(ethoxycarbonyl) derivative described previously (see section 3.1.2). The radicals were generated as described for the 2-(ethoxycarbonyl) derivative and the e.s.r. spectrum recorded over a range of temperatures. Two different radicals were observed and the spectral details are recorded below (see Table XV). At 150K a signal for one radical species (152) is observed which on warming to 190K disappears and a different signal due to another radical (153) is seen. On lowering the temperature back to 150K the signal for the first radical reappears. The signal from the first radical has an α(1H), β(1H) splitting pattern with further smaller γ splittings. The radical (152) fulfils these observed properties and is obtained by abstraction

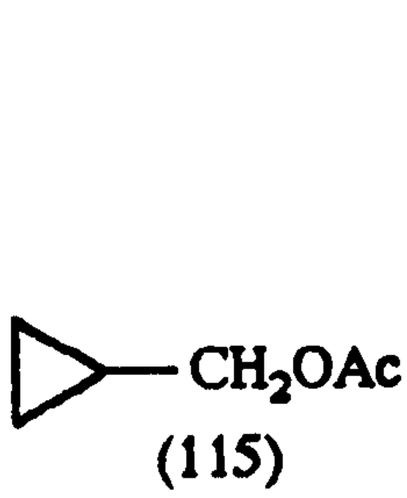
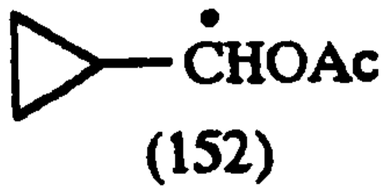
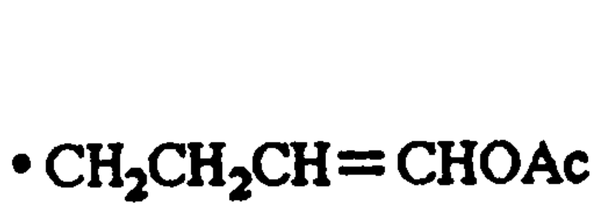
Precursor	Radicals observed	h.f.s.	Temp
	 (152)	α(1H) 20.4 β(1H) 4.8 γ(4H) 1.6	150k
	 (153)	α(2H) 22.6 β(1H) 30.8 γ(1H) 0.75	190k

Table XV Radicals from cyclopropanemethyl acetate

of a hydrogen atom from the CH_2 α to the cyclopropane ring. Comparison of the spectrum obtained for the radical (152) with the similar radical (154) shows a close correlation (see Table XVI) for the α splitting. The differences in the β splitting values are due to the ring system of the radical (154).

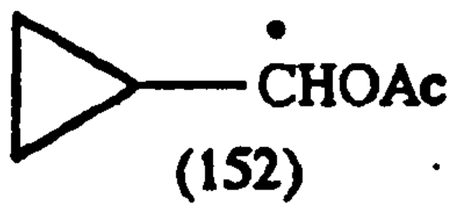
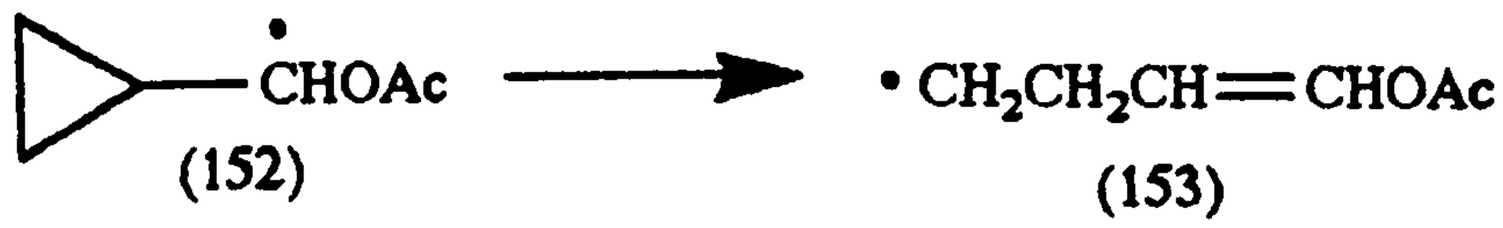
Radical	h.f.s.	Ref
 (152)	α(1H) 20.4 β(1H) 4.8 γ(4H) 1.6	this work
$(CH_3)_2\dot{C}HCHO_2COCH_2CH(CH_3)_2$ (154)	α(1H) 18.3 β(1H) 24.5	22

Table XVI Comparison of radical (152) with radical (154).

The second radical (153), which appears at higher temperatures, has a spectrum which could arise from a ring-opening rearrangement of the cyclopropylcarbinyl radical (152) (see Scheme LXI). The signal observed in the spectrum has an α(2H), β(2H)



Scheme LXI

splitting pattern with a further small γ splitting. Comparison of the spectrum observed with the reported values for similar radicals (155-157) (see Table XVII) provides a further check on the

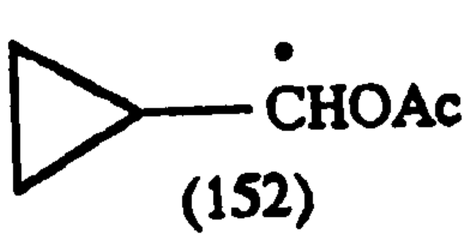
Radicals	h.f.s.	Ref
• $CH_2CH_2CH=CHOAc$ (153)	α(2H) 22.6 β(2H) 30.8 γ(1H) 0.7	this work
• $CH_2CH_2CH=CH_2$ (155)	α(2H) 22.17 β(2H) 28.7 γ(1H) 0.061	41,86
• $CH_2CH_2CH=CHCH_3$ (156)	α(2H) 22.3 β(2H) 29.3 *trans* 30.9 *cis* γ(1H) 0.07	86
• $CH_2CH_2CH=CHOH$ (157)	α(2H) 21.96 β(2H) 28.26 *trans* 29.64 *cis* γ(1H) 0.06	86

Table XVII Comparison of radical (153) with similar radicals.

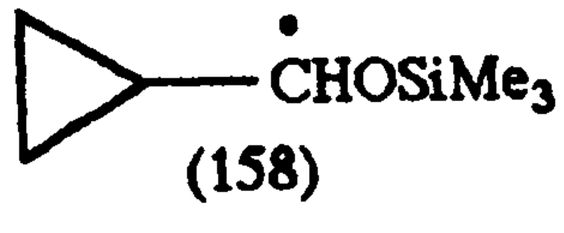
structure suggested for the radical (153). A close correlation is found with these similar radicals, in support of the suggested structure (153).

It is seen from the results for the rearrangement of radical (152) and its 2-(ethoxycarbonyl) substituted analogue (149) that the effect of the 2-ethoxycarbonyl group is small. The 2-(ethoxycarbonyl) derivative (149) probably rearranges slightly faster than the parent radical (152). This result can be explained by the fact that the 2-(ethoxycarbonyl) group helps to stabilise the rearranged radical (149).[185] There will be no such stabilisation for the rearranged radical (153) from cyclopropanemethyl acetate.

The rearrangement observed for the radical from cyclopropanemethyl acetate was compared with the reported rearrangement of the radical from α-trimethylsilyloxymethylcyclopropane (158). The radical (158) was fully rearranged at 137K while the

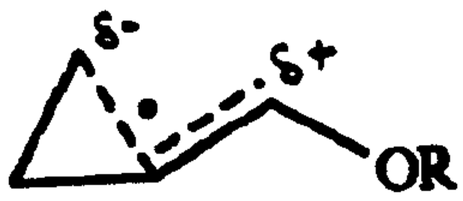


(152)



(158)

radical (152) did not rearrange until 180K. These differences in the rate of rearrangement can be explained by a dipolar transition state (159) for the rearrangement. A group which stabilises the



(159)

transition state will lead to a faster rearrangement (see section 1.2.4 (d)). The electron donating effect of the $OSiMe_3$ group is greater than that of the OAc group and thus provides a greater stabilisation of the transition state. This stabilisation leads to the observed increase in the rate of rearrangement.

3.1.4 The radical from diethyl 2-isopropylcyclopropane-1,1-dicarboxylate

A solution of diethyl 2-isopropylcyclopropane-1,1-dicarboxylate and t-butyl peroxide was placed in the e.s.r. spectrometer and treated as previously described. Only one radical species (160) was observed over the temperature range 150-270K. This radical has an α(1H), β(3H) splitting pattern (see Table XVIII). The

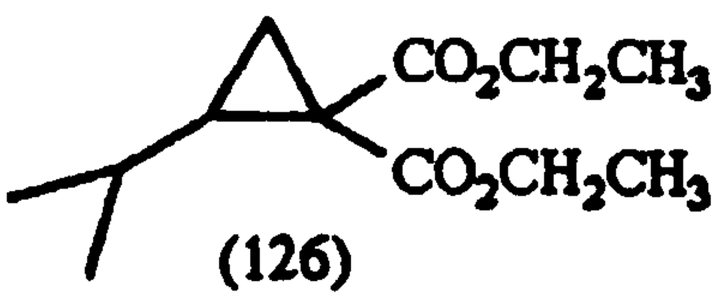
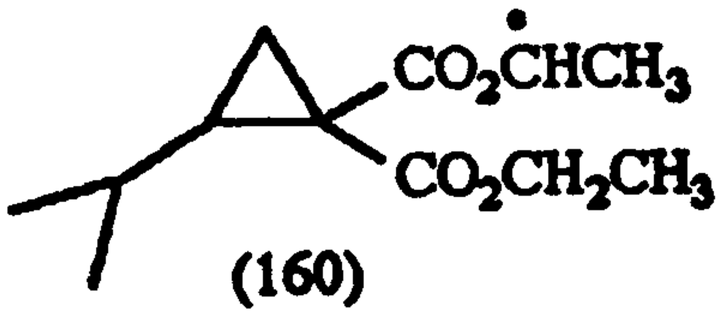
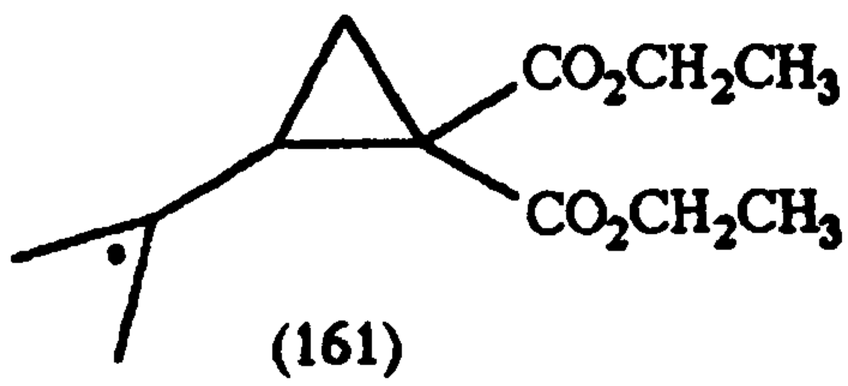
Precursor	Radical	h.f.s.
 (126)	 (160)	α(1H) 20.5 β(3H) 24.3

Table XVIII Radical from diethyl 2-isopropylcyclopropane-1,1-dicarboxylate

spectral details obtained are consistent with the abstraction of a hydrogen atom from the CH_2 of an ethyl group. It is believed that radical (160) results from the abstraction of a hydrogen atom from the CH_2 of one of the ethoxycarbonyl substituents in the precursor. The spectrum obtained for this radical (160) is almost

identical to that observed for the radical (147) (see section 3.1.2, Table XIII) which was formed by a similar abstraction.

It was hoped that hydrogen atom abstraction would occur from the CH site of the isopropyl group. Why the observed radical (160) is formed rather than the desired radical (161) can be rationalised in terms of frontier molecular orbital theory.

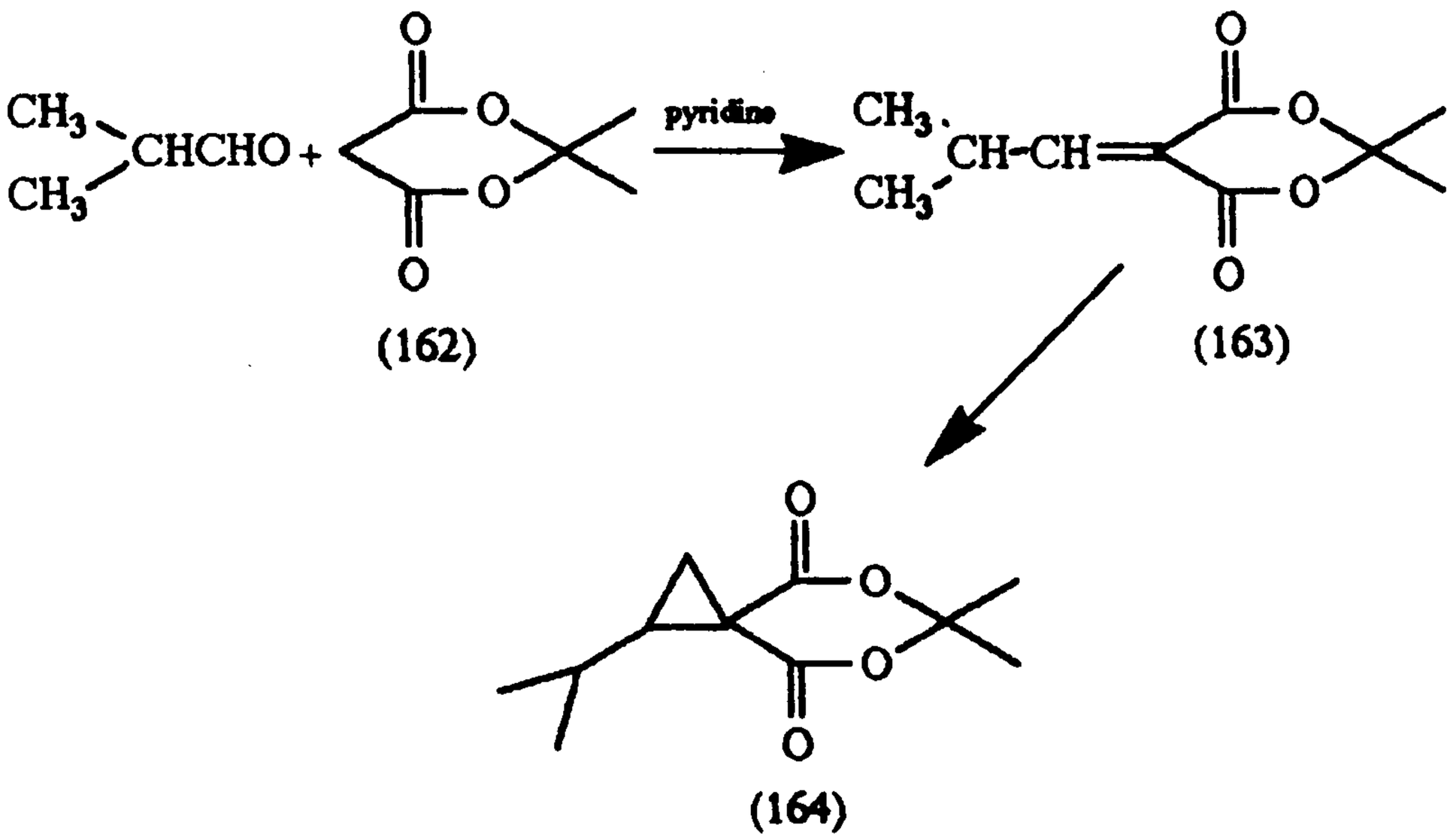


(161)

The SOMO of the electrophilic t-butoxyl radical will interact preferentially with the highest energy HOMO. In general a tertiary site would have a higher energy HOMO than a secondary site due to the effects of hyperconjugation. For the compound (126) the electron donating effect of the oxygen adjacent to the CH_2 site raises the HOMO energy for this site above that of the CH of the isopropyl group. The CH_2 site thus has the highest energy HOMO and this interacts with the SOMO of the abstracting t-butoxyl radical.

Modifications to the precursor compound (126) that would favour production of the desired radical could be made. The use of the methyl esters instead of the ethyl esters would eliminate the CH_2 of the ethyl group as a possible site of abstraction and leave the CH site of the isopropyl group with the highest energy HOMO. Another possibility is to produce the compound (164); this could be synthesised using Meldrums acid (162). Meldrums acid, isopropyl-

idene malonate, reacts with aldehydes in the presence of pyridine to give the alkene species (163) (see Scheme LXII). The cyclo-



(162) (163)

(164)

Scheme LXII

propane species (164) could be generated from the alkene by reaction with trimethylsulphoxonium methylide. The abstraction of a hydrogen atom from this species would almost certainly occur at the CH of the isopropyl group.

4. EXPERIMENTAL

General Remarks

Infra-red spectra were recorded on a Perkin-Elmer 397 spectrometer. Liquid film spectra were run using NaCl plates. Potassium chloride or potassium bromide discs were used to run solid samples.

Unless otherwise stated n.m.r. spectra were run, in deuterochloroform with tetramethylsilane as an internal standard, on a Perkin-Elmer R32 90 MHz spectrometer. 250 MHz spectra were recorded on a Bruker WM250 MHz spectrometer.

Melting points were recorded on a Gallenkamp apparatus and are uncorrected.

G.l.c. analysis was carried out on a Perkin-Elmer 3B machine with a flame ionization detector. The carrier gas used in all cases was nitrogen. Columns were 2m long and packed with 5% Carbowax, 5% F.F.A.P. or 5% Apiezon on a Chromosorb G support.

E.s.r. spectra

The e.s.r. spectra were recorded by Dr. J. Walton at the University of St. Andrews, using a Bruker ER 200D spectrometer. The samples were degassed and sealed in spectrosil tubes with cyclopropane as a solvent and di-t-butyl peroxide as a radical initiator. The samples were then photolysed with light from a 500W high pressure Hg arc and the spectra recorded.

4.1 Experimental for the Synthesis of 1,1-Difluorocyclopropanes

4.1.1 Experimental for decomposition of methyl chlorodifluoroacetate by a LiCl/HMPA complex

a) Methyl chlorodifluoroacetate[136]

A solution of chlorodifluoroacetic acid (100 g, 0.76 mmol), absolute methanol (38.7 g, 1.15 mol) and concentrated sulphuric acid (30.64 ml) was refluxed for 18 h. The reaction mixture was cooled to room temperature and added to ice/water (500 ml). The organic phase was separated, washed with 5% aqueous sodium bicarbonate solution (2 x 200 ml) and water (2 x 200 ml). After drying over anhydrous sodium sulphate, the organic phase was stored over activated 4 A molecular sieves for 12 h then fractionally distilled to give methyl chlorodifluoroacetate (100.1 g, 70%), b.p. 79-80°C (lit.[136] 79-81°C); ε_H 3.98 (3H, s, CH_3); ν_{max} (liquid film) 1785 cm^{-1} (C=O).

b) General procedures for attempted difluorocyclopropane production using LiCl/HMPA decomposition of methyl chlorodifluoroacetate[137,137]

Method (1) Under nitrogen at atmospheric pressure.

A mixture of lithium chloride (0.1 mol) and hexamethylphosphoramide (0.2 mol) in dry triglyme (200 ml) (redistilled from sodium wire) was placed under nitrogen in an oven-dried flask. The mixture was stirred until the lithium chloride dissolved, then the alkene (0.2 mol) and methyl chlorodifluoroacetate (0.05 mol) were added. The solution was heated to 80°C for 24 h then flash distilled, the volatile components were collected in a trap cooled in liquid nitrogen. The distillate was fractionally distilled and the various components analysed by g.l.c.

Method (2) In sealed vials.

The method is described for the attempted production of difluorocarbene and its subsequent reaction with 2,3-dimethylbut-2-ene. The same method was used with the other alkenes reported. Methyl chlorodifluoroacetate (0.53 ml, 5 x 10^{-3} mol) lithium chloride (0.425 g, 1 x 10^{-2} mol) hexamethylphosphoramide (3.5 ml, 2 x 10^{-2} mol), and the alkene (3 ml) were placed in a 15 ml thick-walled glass tube and degassed by a minimum of four freeze-evacuate-thaw cycles at liquid nitrogen temperature and 0.2 mm Hg. The tubes were then frozen in liquid nitrogen and evacuated to 0.2 mm Hg before sealing. The sealed tubes were heated in an oil bath at varying temperatures and reaction times. After cooling to room temperature the tubes were frozen down in liquid nitrogen, opened and the contents analysed by g.l.c.

In both methods (1) and (2) the reactions were carried out under anhydrous conditions using dried reagents. The lithium chloride was vacuum dried, (100°C at 0.2 mm Hg for 24 hours). The hexamethylphosphoramide and the alkene were redistilled from sodium and stored over activated 4 A molecular sieves. The methyl chlorodifluoroacetate was also redistilled and stored over activated 4 A molecular sieves.

c) 2,3-Dimethylbut-2-ene[194,195]

The Grignard reagent, methylmagnesium iodide, was prepared from magnesium turnings (50 g, 2.06 mol) and iodomethane (283.88 g, 2.0 mol) in dry ether (1 l). This solution of the Grignard reagent was cooled in an ice-bath and a solution of ethyl isobutyrate (116.16 g, 1.0 mol) in dry ether (250 ml) was added

dropwise over 2-3 h, while stirring. The mixture was stirred for a further 3 h before decanting the liquid from any residual magnesium. Maintaining the temperature at < 3°C this liquid was added to a saturated ammonium chloride solution (750 ml). The organic phase was separated and the aqueous phase extracted with ether (200 ml). The combined organic phases were dried over anhydrous sodium sulphate and the solvent removed on a rotary evaporator to give a clear yellow liquid. 50% w/w sulphuric acid (10 ml) was added dropwise to this liquid keeping the temperature at < 5°C. The resulting mixture was extracted with ether and the combined organic phases were washed with saturated aqueous sodium bicarbonate solution, before drying over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the residue fractionally distilled to give 2,3-dimethylbut-2-ene (33.24 g, 39%); b.p. 73°C (lit.[194,195] 73°C); δ_H 1.78 (12H, s, 4 x CH_3).

d) *tert*-Butylchlorodiphenylsilane[196]

To dry pentane (100 ml), under nitrogen, in well dried glassware, was added t-butyllithium (10 g, 100 ml of 1.8M solution in pentane) and dichlorodiphenylsilane (39.5 g, 0.15 mol). The contents of the flask were refluxed overnight then cooled to room temperature before adding dropwise water (250 ml). The organic layer was separated and the aqueous layer extracted with 40-60°C petroleum ether (100 ml). The combined organic extracts were washed with water (2 x 100 ml) then dried over anhydrous sodium sulphate and the solvent removed by evaporation. The residue was fractionally distilled to give *tert*-butylchlorodiphenylsilane as a clear colourless liquid (41.2 g, 93%) b.p. 144°C/2 mm Hg (lit.[196]

90°C/0.015 mm Hg); δ_H 0.95 (9H, s, 3 x CH_3), 7.28 (6H, m, Ar), 7.64 (4H, m, Ar); ν_{max} (liquid film) 1425 and 1105 (Si-Ph), 815 (Si-C), 700 and 740 cm^{-1} (mono-sub Ar).

e) 3-(*tert*-Butyldiphenylsilyloxy)prop-1-ene[196]

To a stirred solution of allyl alcohol (5.8 g, 0.1 mol) and pyridine (8.4 g, 0.1 mol) in dry pentane (100 ml) was added t-butylchlorodiphenylsilane (27.4 g, 0.1 mol). The mixture was stirred for 5 h then filtered and the solids washed with dry pentane (75 ml). The filtrate was concentrated on a rotary evaporator and the remaining liquid fractionally distilled to give 3-(*tert*-butyldiphenylsilyloxy)prop-1-ene (18.9 g, 64%), b.p. 132°C/20 mm Hg; δ_H 1.05 (9H, s, 3 x CH_3), 4.2 (2H, m, $=CH_2$), 5.2 (2H, m, $O-CH_2-$), 5.85 (1H, m, -C=), 7.35 (6H, m, Ar), 7.68 (4H, m, Ar); ν_{max} (liquid film) 1425 and 1110 (Si-Ph), 920 cm^{-1} (Si-O).

4.1.2 Experimental for the decomposition of phenyl(trifluoromethyl)mercury by sodium iodide

a) Diphenyl mercury[189,190]

Phenylmagnesium bromide was formed from bromobenzene (94.2 g, 0.6 mol) and magnesium turnings (15 g, 0.6 mol) in dry ether (400 ml). A soxhlet extractor was filled with mercury(II) chloride (81.3 g, 0.3 mol) and continuously extracted with the ether into the phenylmagnesium bromide solution. This gave a precipitate of the sparingly soluble phenylmercury(II) chloride. Dry benzene (300 ml) (from sodium/benzophenone) was distilled directly into the reaction vessel to enhance the solubility of the phenylmercury(II) chloride. The extraction was continued for 48 h, the contents of the reaction flask were cooled to room temperature and then filtered. The solids were washed with benzene and retained as they were, mainly phenylmercury(II) chloride that could be recycled. The filtrate was concentrated on a rotary evaporator to give diphenylmercury as a light brown solid which was recrystallised from benzene (95.7 g, 89%), m.p. 123-124°C, (lit.[189,190]); δ_H 7.4 (10H, s, Ar).

b) Trifluoromethylmercuric trifluoroacetate[191]

To a stirred slurry of yellow mercury(II) oxide (43.5 g, 0.2 mol) and distilled water (200 ml) in a glass basin, was added trifluoroacetic acid (50 g, 0.45 mol). The mixture became homogeneous with complete solution of the mercury(II) oxide. The basin was placed on a steam bath and most of the water evaporated off leaving an opaque gel. This gel was placed in a 100 ml flask equipped with a distillation head and take-off tube. The

take-off tube led to a 3-necked receiving flask equipped with a condenser and immersed in ice. The distillation pot was heated with a bunsen burner. The gel melted and the pot was heated cautiously while the decarboxylation began and the residual water passed over. When the vapour temperature reached 220°C the receiver was changed to eliminate water from the final product. It was now important to contain the path to the receiver at >100°C to prevent clogging of the take-off tube occurring; the product passed over with a vapour temperature of 270-280°C. The distillation was continued until the distillation pot contained a solid yellow/green mass. The product solidified in the receiver to give a white solid. The solid was removed with difficulty and stored *in vacuo* over phosphorus pentoxide, this gave trifluoromethylmercuric trifluoroacetate (40.7 g, 53%), m.p. 107-110°C. The product was used in this crude form without further purification. A small sample was recrystallised from chloroform to give white needles m.p. 115-117°C; (lit.[191] 116-117°C); ν_{max} (KBr disc) 1675 cm^{-1} (C=O), no OH band present.

c) Phenyl(trifluoromethyl)mercury[141]

A mixture of trifluoromethylmercury(II) trifluoroacetate (21.1 g, 0.055 mol) and diphenylmercury (19.4 g, 0.054 mol) in dry benzene (100 ml) was stirred and refluxed under nitrogen for 1 h. The mixture was left to cool to room temperature and saturated aqueous ammonium chloride solution (50 ml) was added. An exothermic reaction occurred and large amounts of white precipitate (mostly phenylmercury(II) chloride) was formed. The mixture was cooled in ice and then filtered. The filtrate was

separated and the organic phase dried over anhydrous sodium sulphate. Concentration gave a white solid which on recrystallisation from hexane gave phenyl(trifluoromethyl)mercury (14.27 g, 76%), m.p. 140-141°C, (lit.[141] 141-143°C).

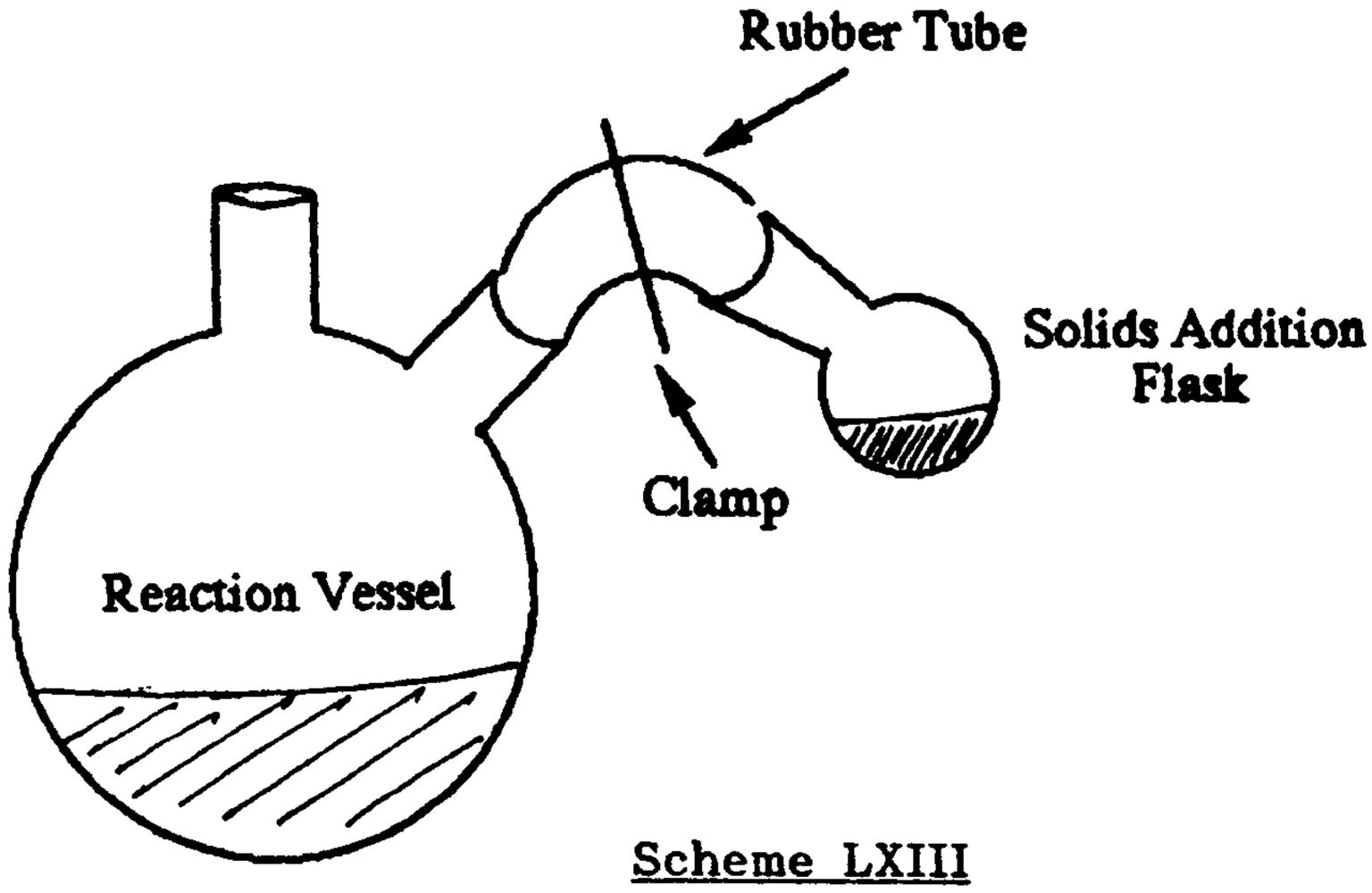
d) Attempted generation of difluorocarbene from $PhHgCF_3$ and NaI[141]

A round-bottomed flask equipped with magnetic stirrer, condenser, nitrogen inlet and bubbler, was charged under dry nitrogen with 2,3-dimethylbut-2-ene (redistilled from CaH_2) (10.4 g, 0.12 mol), sodium iodide (vacuum dried, 120°C at 0.2 mm Hg for 48 h) (18.5 g, 0.12 mol), and phenyl(trifluoromethyl)mercury (14.3 g, 0.04 mol). Dry benzene (80 ml) was distilled directly into the flask from sodium/benzophenone. The reaction mixture was refluxed for 18 h then cooled to room temperature and the solid residue removed by filtration. The filtrate was trap to trap distilled at reduced pressure into a receiver at -78°C to give a few mls of a clear colourless liquid. It was attempted to fractionally distill this liquid at atmospheric pressure however this was not successful. On analysis by g.l.c. most of the liquid appeared to be the alkene 2,3-dimethylbut-2-ene.

4.1.3 Experimental for decomposition of halodifluoromethyl phosphonium salts by alkal i metal fluorides

The procedure used is that developed by Burton and Naae.[142] It was attempted numerous times before any of the desired difluorocyclopropane was obtained. The successful procedure is noted below for the synthesis of 2,2-difluoro-1-vinylcyclopropane. The major factor hindering the first attempts was the presence of traces of water. The solvent triglyme must be dried from lithium aluminium hydride rather than sodium, the potassium fluoride must be well dried and transferred under anhydrous conditions. The potassium fluoride was placed in a wide-necked flask and dried under vacuum (120°C at 0.2 mm Hg for 48 h). This flask was connected to the reaction vessel, under a dry nitrogen atmosphere, by a short length of wide bore rubber tubing (see Scheme LXIII). The potassium fluoride was introduced to the reaction vessel by removing the metal clamp and tilting the small flask until the contents fell into the reaction flask.

The reaction was attempted using various alkenes but was successful only with 2,3-dimethylbut-2-ene and buta-1,3-diene.



Scheme LXIII

a) <u>1,1-Difluoro-2,2,3,3-tetramethylcyclopropane</u>[142]

A 3-necked flask was equipped with a septum seal, dry-ice condenser, mechanical stirrer, and a solids addition flask. All the glassware was well dried, assembled and maintained under dry oxygen-free nitrogen. The solid addition flask was charged with potassium fluoride (19.3 g, 0.33 mol) (vacuum dried, 0.2 mm Hg at 120°C for 48 h). Triphenylphosphine (21.8 g, 0.08 mol) and triglyme (150 ml) (redistilled from $LiAlH_4$) were placed in the reaction flask. Dibromodifluoromethane (17.5 g, 0.08 mol) was then added via a syringe. A white precipitate formed and the mixture was stirred for 30 min. To the stirred suspension was added, by injection, 2,3-dimethylbut-2-ene (6.79 g, 0.08 mol), followed by the potassium fluoride from the solids addition flask. The reaction mixture was then stirred for 50 h at room temperature. The reaction mixture was filtered and the filtrate flash distilled into a liquid nitrogen cooled trap to obtain the volatile fractions from the mixture. Only a small quantity of this volatile material (1 ml) was obtained. On g.l.c. analysis it was seen to be the major peak plus several impurities. 90 MHz ^1H n.m.r. was run off the product. δ_H (90 MHz, $CDCl_3$, TMS), 1.1 (12H, s, 4 x CH_3). This product is not the alkene, 2,3-dimethylbut-2-ene, as under identical spectral conditions it gave the following signal 1.65 (12H, s, 4 x CH_3). A 94 MHz ^{19}F n.m.r. was run on the liquid obtained, the proton decoupled spectra shows 1 signal for the CF_2 group δ = 149.288. The proton coupled spectra shows this signal to be a septet J_{H-F} = 2 Hz; this arises from the six equivalent proton environments of the methyl groups.

b) 2,2-Difluoro-1-vinylcyclopropane[149]

The following glassware was well dried, assembled and maintained under dry oxygen-free nitrogen. A 3-necked flask was equipped with a septrum, dry-ice condenser, and a solids addition flask containing potassium fluoride (19.3 g, 0.332 mol) (vacuum dried 0.2 mm Hg, at 120°C for 48 h). Into the reaction flask was added triphenylphosphine (21.8 g, 0.083 mol) and dry triglyme (150 ml) (redistilled from $LiAlH_4$). Dibromodifluoromethane (17.5 g, 0.083 mol) was added to the flask via a double-ended needle, a white precipitate formed gradually, and the mixture was stirred for 30 min. Buta-1,3-diene (9 g, 0.166 mol) was condensed into a flask containing activated 4 A molecular sieves and then introduced to the flask via a double-ended needle. The potassium fluoride was now added from the solids addition flask, and the mixture stirred at room temperature for 24 h. All the volatile materials were flash distilled into a trap cooled in liquid nitrogen and the excess buta-1,3-diene was allowed to evaporate. The remaining liquid was fractionally distilled with difficulty and a few drops, b.p. 20-50°C were collected. A n.m.r. spectra was obtained on this material, although impure, the following signals could be seen. δ_H 0.9-2.0 (2H, m, ring C$\underline{H}_2$), 2.0-2.6 (1H, m, ring C$\underline{H}$), 5.0-5.8 (3H, m, vinylic H).

c) 2,2-Dichloro-1-vinylcyclopropane

Method (1)[150-153]

A three-necked flask equipped with magnetic stirrer and dry-ice condenser was charged with potassium t-butoxide (25 g, 0.2 mol) and buta-1,3-diene (34 ml, 0.45 mol). To this mixture was added

dropwise dry chloroform (18 g, 0.15 mol). The mixture was stirred for 4 h then quenched with water (50 ml). The organic phase was separated, dried over anhydrous magnesium sulphate, then fractionally distilled to give 2,2-dichloro-1-vinylcyclopropane (16 g, 78%), b.p. 123-125°C (lit.[150-151] 122.5°C). τ_H 1.2-1.9 (2H, m, ring H), 2.3 (1H, m, ring H), 5.1-5.8 (3H, m, vinylic H); ν_{max} (liquid film) 3090 (ring C-H), 1825 (C=C), 1635 cm^{-1} (C=C).

Method (2)[154-155]

A flask equipped with mechanical stirrer and dry-ice condenser was charged with 50% aqueous sodium hydroxide solution (20 ml), triethylbenzylammonium chloride (0.4 g), chloroform (12 g, 0.1 mol) and buta-1,3-diene (7.5 ml, 0.1 mol). The mixture was stirred vigorously for 24 h, then diluted with water (30 ml). The reaction mixture was extracted with ether (3 x 20 ml) and the ether extracts dried over anhydrous sodium sulphate. The ether was removed by fractional distillation to give 2,2-dichloro-1-vinyl cyclopropane (7.9 g, 58%), b.p. 123-125°C. I.r. and n.m.r. data as for Method (1).

4.1.4 Experimental for the synthesis and attempted reaction of ethyl 3,3-difluoroacrylate

a) 3-Bromo-3,3-difluoropropanal diethyl acetal[143,192]

A solution of dibromodifluoromethane (227 g, 1 mol) and ethyl vinyl ether (72 g, 1 mol) was stirred at 0°C and irradiated with an ultra-violet lamp (Hanovia Medium Pressure Mecury Arc) for 10 h. Any unchanged material was removed at reduced pressure and the remainder fractionally distilled to give 1,3-dibromo-3,3-difluoro-1-ethoxypropane (242.5 g, 0.86 mol), b.p. 65°C/15 mm Hg, (lit.[143,192] 53.5°C/5 mm Hg). δ_H (1.3 (3H, t, CH_3), 3.1-4.1 (4H, 2 x CH_2), 6.15 (1H, dd, CH). The product decomposes on contact with the air giving white fumes and was utilized immediately in the following step.

Absolute ethanol (200 ml) was placed in a 1 ℓ 3-necked flask with stirrer, condenser, and dropping funnel. To the stirred ethanol was added dropwise all the previously prepared 1,3-dibromo-3,3-difluoro-1-ethoxypropane; the addition took about 45 min and was exothermic. The solution was stirred for 1.5 h at room temperature, then washed well with water. The crude product was separated and dried over drierite, then fractionated on a Vigreux column to give 3-bromo-3,3-difluoropropanal diethylacetal (172.9 g, 70% overall yield), b.p. 63-67°C/15 mm Hg (lit.[143] b.p. 61-67°C/14 mm Hg); δ_H 1.21 (6H, t, 2 x C$\underline{H}_3$), 2.75 (2H, dt, J_F 14 Hz, J_H 6Hz, C$\underline{H}_2$), 3.61 (4H, q, 2 x C$\underline{H}_2$), 4.88 (1H, t, C$\underline{H}$); ν_{max} 1105 and 1050 (C-O cm^{-1}.

b) Ethyl 3-bromo-3,3-difluoropropanoate[143]

To a vigorously stirred solution of 3-bromo-3,3-difluoropropanal diethylacetal (24.7 g, 0.1 mol) in absolute ethanol (200 ml) at 5-10°C, was added Caro's acid [prepared from 85% sulphuric acid (144 g) and ammonium persulphate (114 g)].[193] After being stirred for 16 h at room temperature, the mixture was diluted with cold water (600 ml) and extracted with ether (3 x 250 ml). The combined organic phases were washed with brine (2 x 200 ml) and dried over anhydrous sodium sulphate. Concentration under vacuum and distillation gave ethyl 3-bromo-3,3-difluoropropanoate (17.16 g, 79%) b.p. 59°C/15 mm Hg (lit.[143] 60-61°C/20 mm Hg); δ_H 1.3 (3H, t, J_H 8 Hz, $-CH_3$), 3.45 (2H, t, J_F 16 Hz $F_2CBr-C\underline{H}_2$), 4.25 (2H, q, J_H 8 Hz, $-O-C\underline{H}_2$); ν_{max} 2990, 2940, 2910 and 2880 (CH), 1740 (C=O), 1225 (CO), 1020 (CO) cm^{-1}.

c) Ethyl 3,3-difluoroacrylate[143]

To a well stirred solution of ethyl 3-bromo-3,3-difluoropropanoate (7.4 g, 0.034 mol) in dichloromethane (30 ml) was added dropwise triethylamine (5 ml, 0.035 mol) at 0°C. When the addition was complete the mixture was filtered and the solid rinsed with ice-cold dichloromethane (2 x 30 ml). The filtrate was washed successively with 15% hydrochloric acid (10 ml) and brine (2 x 30 ml), then dried over anhydrous sodium sulphate. The solvent was removed by distillation and the residue fractionally distilled to give ethyl 3,3-difluoroacrylate (3.3 g, 71%) b.p. 97-99°C (lit.[143] 97-98°C); δ_H 1.32 (3H, t, J 8 Hz, $C\underline{H}_3$), 4.24 (2H, q, J 8 Hz, $-O-C\underline{H}_2$), 5.0 (1H, dd, $J_{F\,trans}$ 2.8 Hz, $J_{F\,cis}$ 22 Hz, $= C\underline{H}CO_2Et$); ν_{max} 1700 br. (C=O), 1280 (C-O), 1040 (C-O) cm^{-1}.

d) Ethyl 2,2-difluorocyclopropanecarboxylate[141]

To a stirred suspension of sodium hydride (1.58 g, 2.65 g, of 60% dispersion in mineral oil, 0.066 mol) in dry DMF (50 ml), under nitrogen, was added solid trimethylsulphoxonium iodide (14.5 g, 0.066 mol) in one portion. An exothermic reaction occurred with the evolution of hydrogen, after the evolution of gas ceased the mixture was stirred for a further 20 min. Ethyl 3,3-difluoroacrylate (9.72 g, 0.066 mol) in dry DMF (20 ml) was added dropwise and the mixture stirred for 1 h. The mixture was worked-up by treatment with ice-cold 3% aqueous HCl solution (100 ml), and then extracted with ether (4 x 50 ml). The combined organic phases were washed with water (4 x 50 ml) then dried over anhydrous magnesium sulphate. The solvent was removed by distillation leaving a dark coloured residue, which could not be further purified and was not successfully characterised.

e) 2,2-Dimethylcyclopropyl methyl ketone[144]

The previous reaction was carried out using mesityl oxide (9.8 g, 0.1 mol) as the α,β-unsaturated ketone. This gave the expected cyclopropane, 2,2-dimethylcyclopropyl methyl ketone (9.4 g, 84%), b.p. 48°C/40 mm Hg (lit.[144] 40-42°C/30 mm Hg); δ_H 0.7 (1H, m, ring H), 0.99 (3H, s, CH_3), 0.9-1.1 (1H, m, ring H), 1.1 (3H, s, CH_3), 1.72 (1H, m, ring H), 2.2 (3H, s, CH_3); ν_{max} 1710 cm^{-1} (C=O).

4.2 Experimental for the Synthesis of Other Substituted Cyclopropane Compounds

4.2.1 Experimental for the synthesis of carboethoxycarbene

(a) Ethyl diazoacetate

Method (1)[159]

To glycine ethyl ester hydrochloride (140 g, 1 mol) in water (250 ml) and dichloromethane (600 ml), was added a solution of sodium nitrite (83 g, 1.2 mol) in ice-cold water (250 ml). The mixture was stirred and the temperature lowered to -10°C by using an acetone/dry ice bath. 5% w/w Sulphuric acid (95 g) was added slowly maintaining the temperature at <2°C. The reaction mixture was stirred for 15 min after completion of the addition, and the vessel allowed to come to room temperature. The organic phase was separated and the aqueous phase washed with dichloromethane (200 ml). The combined organic phases were washed successively with water (100 ml), saturated aqueous sodium bicarbonate solution (2 x 100 ml), and water (100 ml), then dried over anhydrous sodium sulphate. The solvent was removed at 0°C on a rotary evaporator to give ethyl diazoacetate (97.5 g, 85%); δ_H 1.29 (3H, t, J 8 Hz, CH_3), 4.22 (2H, q, J 8 Hz, CH_2), 4.72 (1H, s, CH); ν_{max} 2100 s (C=N=N), 1685 s, cm^{-1} (C=O). The i.r. and n.m.r. data agree with the literature values.[198]

Method (2)[160]

A solution of glycine ethyl ester hydrochloride (279 g, 2.0 mol) and sodium acetate (1.4 g, 0.017 mol) in water (550 ml) was stirred vigorously with pentane (800 ml) while cooling in an ice/salt bath. 2N Sulphuric acid (70 ml) was added to a solution of sodium nitrite

(220 g, 3.2 mol) in water (300 ml) and cooled to 0°C. This solution was added slowly to the stirred glycine ethyl ester hydrochloride solution maintaining the temperature below 5°C. On completion of the addition the mixture was stirred for a further 15 min then the aqueous layer was separated and extracted with pentane (2 x 200 ml). The combined organic phases were washed successively with water (400 ml), saturated aqueous sodium bicarbonate solution (300 ml), and water (400 ml), then dried over anhydrous sodium sulphate. The solvent was removed at 0°C on a rotary evaporator to give ethyl diazoacetate, (194 g, 85%). This method gave identical spectral data to Method (1).

b) <u>General method for reaction of carboethoxy carbene with an alkene</u>

A flask was charged with 50% of the alkene (0.125 mol) and the copper catalyst (≈ 0.2 g). Into an addition funnel was placed the remaining 50% of the alkene (0.125 mol) and ethyl diazoacetate (0.16 mol). A few mls of the solution from the addition funnel was added to the flask and the mixture warmed to ≈ 60°C in a water bath. When nitrogen evolution became apparent the water bath was removed and the contents of the dropping funnel added at a rate which maintained a steady nitrogen evolution. When nitrogen production ceased the mixture was stirred for a further 15 min, then filtered to remove the catalyst. The reaction mixture was normally fractionally distilled to give the various reaction products.

c) Trimethyl phosphite copper(I) iodide[161,162]

To a solution of trimethyl phosphite (2.48 g, 0.02 mol) in dry benzene (50 ml), was added copper(I) iodide (3.8 g, 0.02 mol). This mixture was refluxed for 16 h and the hot suspension filtered to remove any residual copper(I) iodide. The filtrate was concentrated to give a white solid. Recrystallisation gave white needles of trimethyl phosphite copper(I) iodide (3.51 g, 55%); m.p. 187-191°C (from ether/chloroform, 50/50), (lit.[161,162] 192-193°C).

4.2.2 Experimental for cyclopropanation reactions of carboethoxy-carbene

Carboethoxycarbene was generated and reacted in the manner previously described, with ethyl vinyl ether and allyl acetate. Both of these reactions resulted in the formation of a cyclopropane species. In the ethyl vinyl ether reaction the separation of isomers and subsequent conversion of substituent groups was necessary to give the target molecule, 1-trimethyl-silyloxymethyl-2-ethoxycyclopropane.

a) Reaction of ethyl vinyl ether with carboethoxycarbene

When ethyl vinyl ether (18.0 g, 0.25 mol) was reacted with ethyl diazoacetate (18.2 g, 0.16 mol) using copper acetoacetonate as a catalyst, in the standard manner described previously, the product was ethyl 2-ethoxycyclopropanecarboxylate (18.6 g, 72%).

G.l.c. analysis showed the product to contain two isomers in the ratio 60:40. These isomers were later separated 250 MHz ^{1}H n.m.r. data provided for the separate isomers.

b) Separation of *cis* and *trans* ethyl 2-ethoxycyclopropane-carboxylate

A 60:40 mixture of *cis:trans* ethyl 2-ethoxycyclopropane-carboxylate was distilled on a 1 m spinning band fractionation column. The take-off rate from the column must be ≈ 2 ml/h for a satisfactory separation to be obtained. Two major fractions were obtained from the distillation. The first fraction was the *trans* isomer b.p. 69-71°C/25 mm Hg. The *cis* isomer, the second fraction, had a b.p. 78°C/25 mm Hg. The two isomers were distinguished by

250 MHz ^{1}H and ^{13}C n.m.r. spectra (see section 2.2.2 (a)). *trans*-Isomer δ_H (250 MHz, C_6D_6), 0.933 and 0.934 (6H, t, J_H 7 Hz, 2 x CH_3), 1.04 (1H, ddd, ring H_4), 1.24 (1H, ddd, ring H_3), 1.78 (1H, ddd, ring H_2), 3.21 (2H, q, J_H 7 Hz, CH_2-O), 3.62 (1H, ddd, ring H), 3.94 (2H, q, J 7 Hz, CH_2-O-C(O). *cis*-Isomer δ_H (250 MHz, C_6D_6), 0.52 (1H, ddd, ring H_4), 0.97 and 1.03 (6H, t, H_H 7 Hz, 2 x CH_3), 1.42 (1H, ddd, ring H_3), 1.64 (1H, ddd, ring H_2), 3.04 (1H, ddd, ring H), 3.29 (2H, q, J_H 7 Hz, CH_2-O), 4.01 (2H, q, J_H 7Hz, CH_2-O-C(O)). For ^{13}C n.m.r data see Table VII section 2.2.2. (a). ν_{max} (liquid film) 2980 (s) (C-H), 1720 (s) cm^{-1} (C=O).

c) Conversion of 100% *cis* to 100% *trans* ethyl 2-ethoxycyclopropanecarboxylate[197]

To potassium t-butoxide (2 g, 0.018 mol) in t-butanol (25 ml) was added *cis* ethyl 2-ethoxycyclopropanecarboxylate (5 g, 0.032 mol). This mixture was refluxed for 48 h. After cooling to room temperature the reaction mixture was poured into water (100 ml) and extracted with ether (3 x 50 ml). The ether extracts were washed with water (2 x 50 ml), then dried over anhydrous sodium sulphate and the solvent removed on a rotary evaporator. This gave 100% *trans* ethyl 2-ethoxycyclopropanecarboxylate (4.35 g, 87%).

d) 2-Ethoxycyclopropanemethanol

Ethyl 2-ethoxycyclopropanecarboxylate (5 g, 0.03 mol) was added dropwise to an ice-cold solution of lithium aluminium hydride (0.38 g, 0.01 mol) in dry ether (150 ml). This mixture was stirred at 0°C for 15 min then refluxed for 3 h. After cooling to 0°C the

reaction mixture was treated by successive dropwise addition of water (5 ml), 15% aqueous sodium hydroxide solution (5 ml) and finally water (15 ml). A white precipitate formed and the mixture was filtered. The filtrate was dried over anhydrous sodium sulphate and the ether removed on a rotary evaporator to give 2-ethoxycyclopropanemethanol (2.7 g, 76%), b.p. 85-90°C/25 mm Hg; δ_H 0.27 (1H, m, ring H), 0.62 (1H, m, ring H), 0.77 (3H, t, J 8 Hz, CH_3) + obscured signal (1H, m, ring H), 2.66 (1H, s, OH), 2.96 (1H, m, ring H), 3.27 (2H, m, $C\underline{H}_2$-OH), 3.37 (2H, m, $C\underline{H}_2$-O).

e) <u>*trans*-1-trimethylsilyloxy-2-ethoxycyclopropane</u>

To a stirred solution of 2-ethoxycyclopropanemethanol (3.94 g, 0.034 mol) and pyridine (3.11 g, 0.037 mol) in dry pentane (50 ml), was added dropwise trimethylchlorosilane (4.03 g, 0.037 mol). A white precipitate formed and the mixture was left stirring overnight. The mixture was filtered under dry nitrogen and the solids washed with dry pentane (25 ml). The combined organic phases were concentrated on a rotary evaporator to give *trans* α-trimethylsilyloxy-2-ethoxycyclopropanemethane (4.3 g, 67%). δ_H (90 MHz, $CDCl_3$). There is a large signal centred at δ_H = 0 due to the TMS group. All the other signals are quoted relative to this signal; 0.4 (1H, m, ring H), 0.65 (1H, m, ring H), 1.19 (3H, t, CH_3), 1.58 (1H, m, ring H), 3.123 (1H, m, ring H), 3.51 (4H, m, 2 x CH_2). The product was purified by preparative g.l.c. (140°C on an E301 column) and used to generate radicals in the cavity of the e.s.r. spectrometer.

f) Reaction of allyl acetate with carboethoxycarbene

When allyl acetate (25.03 g, 0.25 mol) was reacted with ethyl diazoacetate (18.24 g, 0.16 mol) in the standard manner described previously, the product was ethyl 2-acetoxymethylcyclopropane-carboxylate (14.6 g, 49%), b.p. 110°C/20 mm Hg. G.l.c. analysis showed no separation of the possible *cis* and *trans* isomers however, two isomers are clearly visible in the 250 MHz ^1H n.m.r spectrum; δ_H (250 MHz, $CDCl_3$), 0.9 (1H, m, ring H), 1.12 (1H, m, ring H), 1.27 (3H, t, $CH_2C\underline{H}_3$), 1.62 (1H, m, ring H), 1.78 (1H, m, ring H), 2.03 and 2.07 (3H, 2 x s, *cis* and *trans* $C\underline{H}_3C$), 3.97 (2H, m, O-$C\underline{H}_2$-CH), 4.14 (2H, q, O-$C\underline{H}_2$-CH_3). On expansion the triplet at δ_H 1.27 also shows two signals, one from each of the isomers present. The *cis/trans* mixture was purified by preparative g.l.c. This reaction proceeded with both copper acetoacetonate and copper bronze/copper sulphate catalysis.

g) Reaction of ethyl acrylate with carboethoxycarbene

When ethyl acrylate (25 g, 0.25 mol) was reacted with ethyl diazoacetate (18.24 g, 0.16 mol) in the standard manner with cooper catalysis the product was diethyl cyclopropane-1,2-dicarboxylate (3.88 g, 13%). Note The reaction which occurred was very vigorous. The mixture of ethyl diazoacetate and ethyl acrylate in the dropping funnel reacted violently and spontaneously on standing, the recovered yield was low due to this violent reaction.

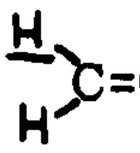
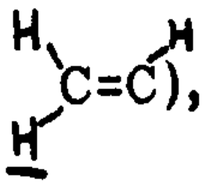
The residue was fractionally distilled to give one major fraction b.p. 110°C/20 mm Hg. On g.l.c. analysis this was seen as two peaks in the ratio 3:1. A 90 MHz ^1H n.m.r. was obtained and showed no large impurity, it is believed we are seeing the *cis* and

trans isomers on g.l.c. analysis; δ_H 1.28 (6H, t, 2 x CH_3), 1.18-1.50 (2H, m, ring CH_2), 2.10 (2H, m, 2 x ring CH), 4.18 (4H, q, 2 x CH_2).

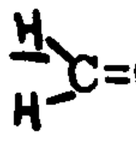
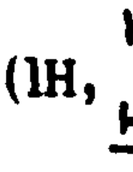
4.2.3. Experimental for insertion reactions of carboethoxycarbene

These reactions were carried out using the same method as the cyclopropanation reactions of carboethoxycarbene. The same catalysts were also employed.

a) Reaction of allyl alcohol with carboethoxycarbene

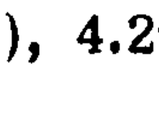
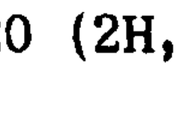
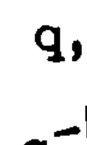
Allyl alcohol (14.5 g, 0.25 mol) was reacted in the standard manner with ethyl diazoacetate (18.24 g, 0.16 mol) and copper catalyst (0.125 g) to give ethyl 2-hydroxypent-4-enoate (13.37 g, 56%), b.p. 82-84°C/25 mm Hg; δ_H (250 MHz, $CDCl_3$, $CHCl_3$), 1.29 (3H, t, $-C\underline{H}_3$), 4.08 (1H, s, OH), 4.08-4.12 (3H, m, $C-CH_2-C$ and $C-C(OH)\underline{H}-$), 4.22 (2H, q, $C\underline{H}_2-CH_3$), 5.23 (1H, ddt, ), 5.3 (1H, ddt, ), 5.93 (1H, dddd, $H_2C=C\underline{H}$).

b) Reaction of allyl bromide with carboethoxycarbene

Allyl bromide (30.25 g, 0.25 mol) was reacted in the standard manner with ethyl diazoacetate (18.24g, 0.16 mol) and copper catalyst (0.125 g) to give ethyl 2-bromopent-4-enoate (19.17 g, 57%), b.p. 91-93°C/25 mm Hg; δ_H (250 MHz, $CDCl_3$, $CHCl_3$), 1.29 (3H, t, CH_3), 2.79 (2H, dddd, $C-CH_2-C$), 4.22 (1H, t, CH(Br)), 4.22 (2H, q, $C\underline{H}_2-CH_3$), 5.13 (1H, m, ), 5.19 (1H, ), 5.76 (1H, dddd, $CH_2=C\underline{H}$).

c) Reaction of allyl chloride with carboethoxycarbene

Allyl chloride (19.13 g, 0.25 mol) was reacted in the standard manner with ethyl diazoacetate (18.2 g, 0.16 mol) and copper catalyst (0.125 g) to give ethyl 2-chloropent-4-enoate (8.33 g, 32%), b.p. 66-68°C/25 mm Hg. δ_H (250 MHz, $CDCl_3$, $CHCl_3$), 1.27 (3H,

t, CH_3), 2.72 (2H, dddd, C-CH_2-C), 4.24 (2H, q, C$\underline{H}_2CH_3$), 4.29 (1H, t, CH(Cl)), 5.14 (1H, m, ), 5.20 (1H, m, ), 5.77 (1H, dddd, 

d) Reaction of 2-methyl-3-buten-2-ol with carboethoxycarbene

2-Methyl-3-buten-2-ol (21.5 g, 0.25 mol) was reacted in the standard manner with ethyl diazoacetate (18.2 g, 0.16 mol) and copper catalyst (0.125 g) to give ethyl 2-hydroxy-3,3-dimethylpent-4-enoate (8.56 g, 31%), b.p. 82-84°C/25 mm Hg; δ_H (90 MHz, $CDCl_3$ TMS), 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.32 (6H, s, 2 x CH_3), 3.95 (1H, s, OH), 4.20 (2H, q, C$\underline{H}_2CH_3$), 5.10 (1H, m, CH(OH)), 5.25 (2H, m, ), 5.85 (1H, dd,).

4.2.4 Experimental for the synthesis/attempted synthesis of spiro compounds and other miscellaneous cyclopropyl compounds

(a) Methyl cyclohexylideneacetate

Method (1)[171]

To a stirred suspension of lithium chloride (5.08 g, 0.12 mol) (vacuum dried, 0.5 mm Hg at 100°C for 24 h) in dry acetonitrile (150 ml), under nitrogen, was added diethyl methoxycarbonylmethyl-phosphonate (22.1 g, 0.12 mol), n-ethyldiisopropylamine (12.9 g, 0.1 mol) and finally cyclohexanone (9.8 g, 0.1 mol). This mixture was stirred for 24 h then water (300 ml) was added and the stirring continued for 5 min. The mixture was extracted with ether (2 x 250 ml). The combined ethereal layers were washed with saturated aqueous sodium bicarbonate solution (200 ml) and water (200 ml) then dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the residue fractionally distilled to give methyl cyclohexylidenacetate (11.2 g, 73%) b.p. 90°C/20 mm Hg; δ_H 1.65 (6H, s, ring CH_2), 2.22 (2H, m, ring CH_2), 2.85 (2H, m, ring CH_2), 3.7 (3H, s, CH_3), 5.62 (1H, s, =C**H**-C(O); ν_{max} (liquid film) 1715 (C=O), 1645 (C=C, 1155 (C-O), 1020 (C-O) cm^{-1}.

Method (2)[209]

The reaction was also carried out using magnesium chloride instead of lithium chloride and using triethylamine as the base.

The following reactants were placed in a round-bottomed flask and stirred under nitrogen for 48 h. Cyclohexanone (9.8 g, 0.1 mol), diethyl methoxycarbonylmethylphosphonate (18.4 g, 0.1 mol), magnesium chloride (vacuum dried 100°C/0.1 mm Hg) (9.5 g, 0.1 mol), triethylamine (redistilled) (10.1 g, 0.1 mol) and finally dry

tetrahydrofuran (100 ml). The reaction mixture was quenched with dilute hydrochloric acid (50 ml) and extracted with di-ethyl ether (3 x 50 ml). The combined organic extracts were washed with water (50 ml) then dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the residue purified by Kughelrohr distillation to give a clear colourless liquid (10.6 g, 69%), b.p. 100°C/25 mm Hg. The spectral data obtained was identical to that found in Method (1).

b) Attempted preparation of methyl spiro[2.5]octane-1-carboxylate[144]

To a stirred suspension of sodium hydride (1.36 g, 0.034 mol, 60% dispersion in mineral oil) in dry DMF (70 ml), under nitrogen, was added solid trimethylsulphoxonium iodide (7.5 g, 0.034 mol) in one portion. This caused an exothermic reaction with the evolution of hydrogen to occur. The mixture was stirred for 15 min after hydrogen evolution ceased. Methyl cyclohexylideneacetate (5.3 g, 0.034 mol) in dry DMF (10 ml) was added and stirring continued for 1 h. The mixture was poured into ice-cold 3% aqueous hydrogen chloride solution then extracted with ether (4 x 75 ml). The ether extracts were combined and washed with water (6 x 75 ml) then dried over anhydrous sodium sulphate. The solvent was removed by distillation at atmospheric pressure to give a tar-like residue. The fractional distillation of this tar-like residue was not successful and none of the desired spiro compound was isolated.

c) Reaction of methyl cyclohexylideneacetate with carboethoxy-carbene

Methyl cyclohexylideneacetate (19.2 g, 0.125 mol) was reacted in the standard manner with ethyl diazoacetate (9.1 g, 0.08 mol) and copper acetoacetonate (0.1 g). This reaction resulted in the production of a large quantity of black tar. On fractional distillation the only product recovered was diethyl maleate formed by carbene-carbene combination.

d) Attempted preparation of methoxymethylenecyclohexane[172]

The Grignard reagent cyclohexylmagnesium bromide was formed from cyclohexyl bromide (81.5 g, 0.5 mol) and magnesium turnings (12.5 g, 0.5 mol) in dry ether (200 ml). To a solution of the Grignard reagent was added dropwise trimethyl orthoformate (53.0 g, 0.5 mol) and the mixture was refluxed overnight. The reaction mixture was cooled to room temperature and 5% aqueous sodium bicarbonate solution (150 ml) was added. The organic layer was separated and the aqueous layer extracted with ether (3 x 75 ml). The combined organic phases were washed with 5% aqueous sodium bicarbonate solution (3 x 75 ml) then dried over anhydrous sodium sulphate. The ether was removed on a rotary evaporator to give dimethoxymethylcyclohexane (57.7 g, 73%), b.p. 101-105°C/20 mm Hg (lit.[172] 90-93°C/10 mm Hg). This material was used immediately in the following reaction. To the dimethoxymethylcyclohexane was added 5 drops of concentrated sulphuric acid. It was attempted to remove the methanol produced, as it was formed, by distilling it from the reaction mixture. The residue left after distillation was

black and viscous. All attempts at further purification were not successful.

e) Cyclopropanemethanol

To a stirred solution of lithium aluminium hydride (11.0 g, 0.29 mol) in dry di-ethyl ether (250 ml) at 0°C was added dropwise cyclopropanecarboxylic acid (20 g, 0.23 mol). The mixture was refluxed for 8 h then cooled to room temperature. To this mixture was added, dropwise, water (11 ml), followed by 15% aqueous sodium hydroxide solution (11 ml) and finally water (33 ml). The resulting mixture was filtered and the filtrate dried over anhydrous sodium sulphate. The di-ethyl ether was removed by distillation at atmospheric pressure and the residue was fractionally distilled to give cyclopropanemethanol (14.3 g, 86%), b.p. 22°C/760 mm Hg (lit.[198] 123-124°C/738 mm Hg); 0.28 (2H, m, ring H), 0.59 (2H, m, ring H), 1.12 (1H, m, ring H), 3.18 (1H, s, OH), 3.46 (2H, d, C$\underline{H}_2$); ν_{max} 3330 cm^{-1} (OH), (no C=O stretch visible). I.r. and n.m.r. data agrees with literature values.[198]

f) Cyclopropylmethyl acetate

A mixture of dry benzene (30 ml), cyclopropanemethanol (4.45 g, 0.062 mol), acetic anhydride (redistilled) (6.3 g, 0.062) and sodium acetate (2.6 g, 0.031 mol) were heated at reflux with stirring for 8 h. The mixture was cooled to room temperature, poured into water (100 ml), and the organic phase extracted. The organic phase was stirred vigorously with 5% aqueous sodium carbonate solution (50 ml) for 2 h. The organic phase was separated, washed with water (3 x 100 ml), and then dried over anhydrous sodium

sulphate. The benzene was removed by distillation at atmospheric pressure to give crude cyclopropylmethyl acetate (5.24 g, 74%). This crude product was purified by preparative g.l.c. δ_H (250 MHz, $CDCl_3$), 0.23 (2H, m, ring H), 0.53 (2H, m, ring H), 1.08 (1H, m, ring H), 2.03 (3H, s, $C\underline{H}_3$), 3.85 (2H, d, $C\underline{H}_2$); δ_C 2.73 (2C, t, 2 x ring CH_2), 9.34 (C, d, ring CH), 20.5 (C, q, CH_3), 68.9 (C, t, $-CH_2-O$), 171.1 (C, s, C); ν_{max} (liquid film) 1725 (C=O), 1240 and 1025 cm^{-1} (C-O).

g) Purification of diethyl 2-isopropylcyclopropane-1-1-dicarboxylate

A sample of diethyl 2-isopropylcyclopropane-1,1-dicarboxylate was obtained from a colleague. It was prepared according to the method of Landor and Punja, from the reaction of trimethylsulphoxonium methylide with ethyl isobutylidene malonate. The b.p. and spectral data obtained are in agreement with the reported[144] values. The sample was purified by preparative g.l.c. on a 20% F.F.A.P. column at 140°C; δ_H (250 MHz, $CDCl_3$), 0.96 (6H, d, 2 x $C\underline{H}_3$-CH), 1.05 (1H, m, ring H), 1.20 (3H, t, $CH_2-C\underline{H}_3$), 1.23 (3H, t, $CH_2-C\underline{H}_3$), 1.33 (1H, m, ring H), 1.66 (1H, m, ring H), 4.06 (1H, m, C<u>H</u>-), 4.18 (4H, m, 2 x CH_2).

4.3 Experimental for the Reduction of Phenyl- and Ferrocenyl-Cyclopropyl Ketone

a) 1-Phenylbutan-1-ol

To n-butyrophenone (10 g, 0.067 mol) in dry ether (50 ml), under nitrogen, was added dropwise a solution of lithium aluminium hydride (0.912 g, 0.024 mol) in dry ether (100 ml). The resulting mixture was refluxed for 2 h then cooled to 0°C, excess lithium aluminium hydride was destroyed by adding ethyl acetate (50 ml). The resulting solution was treated with saturated aqueous ammonium chloride solution (100 ml) then filtered. The organic layer of the filtrate was separated and washed with water (2 x 50 ml) then dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the crude product analysed and shown to be 1-phenylbutan-1-ol (6.8 g, 68%); δ_H 0.85 (3H, m, CH_3), 1.0-1.8 (4H, m, $-CH_2CH_2-$), 3.09 (1H, s, OH), 4.5 (1H, t, -CH-), 7.20 (5H, s, Ar); ν_{max} 3600-3100 br. s. cm^{-1} (OH), (no C=O band evident).

b) 1-Phenylcyclopropanemethanol

To a stirred solution of lithium aluminium hydride (0.91 g, 0.024 mol) in dry ether (100 ml) at 0°C was added dropwise cyclopropyl phenyl ketone (10 g, 0.068 mol). The flask was stirred at 0°C for a further 15 min then refluxed for 6 h. The reaction mixture was cooled to 0°C and water (100 ml) was added slowly. The reaction mixture was filtered, the organic layer of the filtrate was separated and washed with water (2 x 50 ml). The organic layer was dried over anhydrous sodium sulphate and the solvent removed. This gave 1-phenylcyclopropanemethanol as a clear

colourless liquid (7.8 g, 77%) 125°C/22 mm Hg (lit.[173] 129-132°C/18 mm Hg); ς_H 0.0-0.4 (4H, m, 2 x ring CH_2), 0.7-1.1 (1H, m, ring CH), 2.81 (1H, s, OH), 3.72 (1H, d, J 9 Hz, CH), 7.2 (5H, m, Ar); ν_{max} (liquid film) 3350 br cm^{-1} (OH); shows one peak on g.l.c. analysis.

c) Butanoyl chloride

To n-butyric acid (5 g, 0.057 mol) was added thionyl chloride (13.5 g, 0.114 mol). The reactants were refluxed for 2 h until hydrogen chloride production ceased. The mixture was then fractionally distilled to give unreacted thionyl chloride and butanoyl chloride (2.25 g, 37%), b.p. 102°C (lit.[200] 102°C); ν_{max} 1800 cm^{-1} (C=O), no OH band present.

d) Butanoyl ferrocene[199-201]

Butanoyl choride (2 g, 0.019 mol) in dry ether (50 ml) was added to a mixture of ferrocene (5.34 g, 0.029 mol) and aluminium chloride (5.1 g, 0.038 mol) in dry ether (100 ml) over 1 h. The mixture was maintained under nitrogen and refluxed for 3 h. The contents of the flask were poured on to a mixture of ice and ammonium chloride and then extracted with ether (2 x 50 ml). The ether extracts were washed successively with water (100 ml), saturated aqueous sodium bicarbonate solution (100 ml) and water (100 ml), then dried over anhydrous sodium sulphate. The ether was removed on a rotary evaporator and the residue chromatographed on alumina. Unreacted ferrocene was eluted using 30-40°C petroleum ether, then a second band was eluted with dichloromethane. Removal of the dichloromethane gave a deep red oil. This oil crystallised on standing to give butanoyl ferrocene (0.8 g,

43.4%); m.p. 32-33°C (lit.[201] 34-35°C); δ_H 1.0 (3H, t, J 8.1 Hz, CH_3), 1.75 (1H, t, q, J 8.1 Hz, 8 Hz, $COCH_2C\underline{H}_2CH_3$), 2.7 (2H, q, J 8 Hz, $COC\underline{H}_2$), 4.18 (5H, s, C_5H_5), 4.46 (2H, t, Cp), 4.76 (2H, t, Cp); ν_{max} (KBr disc) 1165 cm^{-1} (C=O).

e) 1-Ferrocenylbutan-1-ol[202]

To butanoyl ferrocene (0.5 g, 1.95 x 10^{-3} mol) in dry ether (50 ml), under nitrogen, was added dropwise a solution of lithium aluminium hydride (0.037 g, 9.75 x 10^{-4} mol) in dry ether (50 ml). The mixture was refluxed for 2 h then cooled to 0°C and excess lithium aluminium hydride destroyed by careful addition of ethyl acetate (50 ml). The resulting mixture was treated with an aqueous solution of ammonium chloride (0.61 g), after stirring for 30 min the mixture was filtered and the organic layer separated. The organic extract was washed with water (2 x 25 ml), dried over anhydrous sodium sulphate and then concentrated. The residual oily mass was purified on an alumina column to give 1-ferrocenylbutan-1-ol as a red/yellow oil (0.3 g, 59.8%); δ_H 0.9-1.7 (7H, m, $CH_2CH_2CH_3$), 2.07 (1H, s, OH), 3.45 (1H, m, -C(OH)H-), 4.1-4.2 (9H, m, C_5H_4 and C_5H_5); ν_{max} (liquid film) 3500-3200 br, s, cm^{-1} (OH), (no C=O band evident).

f) Cyclopropanecarbonyl chloride

To cyclopropanecarboxylic acid (20 g, 0.23 mol) was added slowly thionyl chloride (48 g, 0.46 mol), an exothermic reaction took place and the mixture was refluxed for 2 h. Hydrogen chloride production was seen to cease and the reaction was stirred for a further 2 h. Unreacted thionyl chloride was removed by distillation to give the cyclopropanecarbonyl chloride (10 g, 43%), b.p. 119-120°C

(lit.[198] 119°C); δ_H (1.22 (4H, m, ring CH_2), 2.15 (1H, m, ring CH); ν_{max} 1875 cm^{-1} (C=O), (no OH band present). I.r. and n.m.r. data agree with reported values.[198]

g) Ferrocenyl cyclopropyl ketone[203]

Cyclopropanecarbonyl chloride (10.45 g, 0.1 mol) in dry ether (200 ml) was added to a mixture of ferrocene (27.9 g, 0.15 mol) and aluminium chloride (26.6 g, 0.2 mol) in dry ether (200 ml) over 1 h. The reaction mixture was maintained under nitrogen and refluxed for 3 h, then poured on to ice and ammonium chloride. This mixture was extracted with ether (2 x 200 ml). The ether extracts were washed successively with water (150 ml), saturated aqueous sodium bicarbonate solution (150 ml) and finally water (150 ml). The ether extracts were dried over anhydrous sodium sulphate and concentrated on a rotary evaporator to give a dark red/orange solid which was chromatographed on alumina. Unreacted ferrocene was eluted with 40-60°C petroleum ether and the product band removed with dichloromethane. The dichloromethane was evaporated to give a dark red/orange oil. This oil crystallised slowly to give ferrocenyl cyclopropyl ketone, (17.3 g, 68.4%), m.p. 60-62°C (lit.[203] 65-66°C); δ_H 1.0 (2H, m, cyclopropyl CH_2), 1.2 (2H, m, cyclopropyl CH_2), 2.3 (1H, m, cyclopropyl CH), 4.25 (5H, s, C_5H_5), 4.52 (2H, t, Cp), 4.85 (2H, t, Cp); ν_{max} 1650 cm^{-1} (C=O), (lit. 1650 cm^{-1}).

h) 1-Ferrocenylcyclopropanemethanol[204,205]

To a stirred solution of lithium aluminium hydride (0.05 g, 0.0013 mol) in dry ether (50 ml), under nitrogen, was added dropwise a solution of ferrocenyl cyclopropyl ketone (1 g, 0.0039

mol) in dry ether (50 ml). This mixture was refluxed for 2 h then cooled to 0°C. Excess lithium aluminium hydride was destroyed by the addition of ethyl acetate (30 ml) and the resulting mixture was treated with an aqueous solution of ammonium chloride (1.2 g). After stirring for 30 min, at 0°C, the reaction mixture was filtered and the organic layer separated. The organic extract was washed with water (2 x 30 ml) then dried over anhydrous sodium sulphate before concentrating on a rotary evaporator. The solid residue was chromatographed on alumina, elution with petroleum ether 40-60°C, then dichloromethane removed several by-products. The desired product was eluted with a 10:1 mixture of ethyl acetate : methanol. Removal of the solvent under reduced pressure gave 1-ferrocenyl-cyclopropanemethanol as a yellow oil; δ_H 0-0.5 (4H, m, 2 x cyclopropyl CH_2), 0.7-1.1 (1H, m, cyclopropyl CH), 2.1 (1H, s, OH), 3.55 (1H, m, CH), 3.9-4.1 (4H, m, Cp), 4.0 (5H, s, C_5H_5); ν_{max} 3600-3200 (br, s) cm^{-1} (OH).

i) Tri-n-butyltin hydride[206]

Tri-n-butyltin chloride (32.5 g, 0.1 mol) was added dropwise under nitrogen to an ice-cold solution of lithium aluminium hydride (1.56 g, 0.04 mol) in dry ether (150 ml). The mixture was stirred at 0°C for 15 min, then at room temperature for 3 h. The reaction mixture was then placed in an ice-bath and cold water (100 ml) was added dropwise. The solution mixture was separated and the ether layer dried over anhydrous sodium sulphate. The ether was removed on a rotary evaporator and the residue distilled quickly through a Vigreux column using an oil bath pre-heated to 100°C.

This gave tri-n-butyltin hydride (212 g, 73%), b.p. 68-72°C/0.3 mm Hg, (lit.[206] b.p. 68-74°C/0.3 mm Hg).

j) Reaction between cyclopropyl ferrocenyl ketone and tri-n-butyltin hydride - General procedure

A stock solution which was 0.10 molar in cyclopropyl ferrocenyl ketone and 0.050 molar in internal standard was made up. The internal standard and solvent used were 9,10-dihydroanthracene and toluene respectively. Similarly, a stock solution which was 0.10 molar in tri-n-butyltin hydride was prepared. Equal aliquots of each stock solution were added to a reaction ampoule, the mixture was degassed by four freeze-thaw cycles, and then the ampoule was sealed under vacuum (0.2 mm Hg). The reaction mixture was thermostatted in an oil bath initially at 70°C for a period of 16 h. The ampoule was opened and the mixture was analysed by g.l.c. Product peaks were identified by a comparison of their retention times with those of authentic samples. The experiment was repeated under different conditions (see Table IX) using azobisisobutyronitrile as initiator.

k) Reaction between cyclopropyl phenyl ketone and tri-n-butyltin hydride - General Procedure

As described in j) above except that n-hexadecane was used as internal standard.

4.4 Experimental for the Synthesis of the Nitroxide, 1,1,3,3-Tetramethylisoindolin-2-yloxyl

a) N-Benzylphthalimide[207,208]

To a solution of phthalic anhydride (74.6 g, 0.5 mol) in glacial acetic acid (300 ml) was added benzylamine (54.3 g, 0.5 mol). The mixture was refluxed for 1.5 h, then water (400 ml) was added and the reflux continued for a further 20 min. The mixture was cooled to room temperature then filtered. The white solid obtained was recrystallised from ethanol to give N-benzylphthalimide, (97 g, 82%), m.p. 115°C (lit.[207] 115°C); δ_H 4.81 (2H, s, $-CH_2-$), 7.29 (5H, m, Ar), 7.68 (4H, m, Ar).

b) 2-Benzyl-1,1,3,3-tetramethylisoindoline[179]

A solution of the Grignard reagent, methylmagnesium iodide was prepared from iodomethane (170 g, 1.2 mol) and magnesium turnings (30.4 g, 1.25 mol) in dry ether (700 ml) under nitrogen. The solvent was removed from the Grignard reagent by distillation until the internal temperature reached 80°C. The residue was cooled to 60°C and a solution of N-benzylphthalimide (47.5 g, 0.2 mol) in toluene (600 ml) was added, with stirring, at a rate sufficient to maintain this temperature. When the addition was complete, the solvent was distilled slowly from the reaction mixture until the internal temperature reached 108-110°C. The mixture was refluxed at this temperature for 4 h, then concentrated by further distillation of the solvent until only 200 ml remained. The residue was cooled and then diluted with 30-40°C petroleum ether (500 ml). The resultant thick purple slurry was filtered, with difficulty and the solids washed extensively with 30-40°C petroleum ether. (Note:

The thick slurry clogged most filtering agents. Careful suction filtration with frequent changes of filter paper proved most successful in filtering this mass. The remaining purple solids were washed with portions of 30-40°C petroleum ether, by stirring them manually in a large conical flask with a glass rod. The solids were allowed to settle and the solvent decanted off). The combined filtrates turned purple on exposure to the atmosphere and were left standing overnight. The filtrate was passed through a short column of basic alumina and eluted with 30-40°C petroleum ether until the eluant was amine free. Removal of the solvent on a rotary evaporator left a yellow oil that solidified on standing. Recrystallisation of this solid from methanol gave 2-benzyl-1,1,3,3-tetramethylisoindoline as colourless needles (19 g, 35%), m.p. 63-64°C (lit.[179] 63-64°C); δ_H 1.29 (12H, s, 4 x CH_3), 3.98 (2H, s, $-CH_2-$), 7.75 (9H, m. Ar).

c) <u>1,1,3,3-Tetramethylisoindoline</u>[179]

A solution of 2-benzyl-1,1,3,3-tetramethylisoindoline (5.5 g, 0.02 mol) in glacial acetic acid (200 ml) was hydrogenated at 50 lb/in^2 over 5% palladium on charcoal (1 g) for 12 h at room temperature. The suspension was filtered through Kieslghur and the solvent removed on a rotary evaporator. The residue was dissolved in water (20 ml) and the solution made alkaline (pH 11) with 20% aqueous sodium hydroxide. The solution was then extracted with ether (3 x 75 ml). The combined ether extracts were dried over anhydrous sodium sulphate and evaporated to give white crystals of 1,1,3,3-tetramethylisoindoline (3.2 g, 88%), m.p. 34-37°C (crude material). A small sample was recrystallised from

methanol/water to give colourless crystals m.p. 36-37°C (lit.[179] 36-38°C); δ_H 1.45 (12H, s, 4 x CH_3), 1.95 (1H, s, NH), 7.16 (4H, m, Ar).

d) <u>1,1,3,3-Tetramethylisoindolin-2-yloxyl</u>[179]

To a solution of 1,1,3,3-tetramethylisoindoline (3.1 g, 0.017 mol) in methanol (35 ml) and acetonitrile (2.5 ml) was added successively, sodium hydrogen carbonate (1.26 g, 0.015 mol), sodium tungstate dihydrate (0.18 g, 5.5 x 10^{-4} mol) and finally 30% aqueous hydrogen peroxide (7 ml, 0.062 mol). This suspension turned bright yellow and was stirred at room temperature for 48 h. The mixture was diluted with distilled water (100 ml) and then extracted with ether (2 x 100 ml). The combined ether extracts were washed with 2N sulphuric acid (2 x 50 ml) and brine (2 x 50 ml), then dried over anhydrous sodium sulphate. Removal of the solvent on a rotary evaporator gave 1,1,3,3-tetramethylisoindolin-2-yloxyl as a bright yellow solid which was recrystallised from 30-40°C petroleum ether (2.9 g, 90%), m.p. 128-129°C (lit.[179] 128-129°C).

5. REFERENCES

1. I. MacInnes, D.C. Nonhebel, S.T. Orszulik, and C.J. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 121.
2. I. MacInnes, D.C. Nonhebel, S.T. Orszulik, and C.J. Suckling, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2777.
3. D. Laurie, E. Lucas, D.C. Nonhebel, and C.J. Suckling, *Tetrahedron*, 1986, 42, 1035.
4. D.C. Nonhebel, S.T. Orszulik, and C.J. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 1146.
5. D. Griller and K.U. Ingold, *Acc. Chem. Res.*, 1980, 13, 317.
6. J.H. Raley, F.F. Rust, and W.E. Vaughn, *J. Am. Chem. Soc.*, 1948, 70, 1336.
7. K.U. Ingold in "Free Radicals", (J.K. Kochi ed.), Vol. 1, Chapter 2, Wiley, New York, 1973.
8. A.L. Beckwith and K.U. Ingold in "Rearrangements in ground and excited states", (de Mayo ed.), Vol. 1, Chapter 4, Academic Press 1980.
9. C. Walling, J.H. Cooley, A.A. Ponaras, and E.J. Racah, *J. Am. Chem. Soc.*, 1966, 88, 5361.
10. C. Chatgilialoglu, K.U. Ingold, and J.C. Scaiano, *J. Am. Chem. Soc.*, 1981, 103, 7739.
11. D.J. Carlsson and K.U. Ingold, *J. Am. Chem. Soc.*, 1978, 90, 7047.
12. J.A. Howard and J.C. Tait, *J. Org. Chem.*, 1978, 43, 4279.
13. D.W. Gratton, O.J. Carlsson, J.A. Howard, and D.M. Wiles, *Can. J. Chem.*, 1979, 57, 2834.
14. P. Schmid and K.U. Ingold, *J. Am. Chem. Soc.*, 1978, 100, 2493.

15. R.L. Wilson, *Trans. Faraday Soc.*, 1971, 67, 3008.

16. G. Moad, E. Rizzardo, and D.H. Solomon, *Macromolecules*, 1982, 15, 909.

17. E. Rizzardo, A.K. Serelis, D.H. Solomon, *Aust. J. Chem.*, 1982, 35, 2013.

18. P. Griffiths, E. Rizzardo, and D.H. Solomon, *Tetrahedron Lett.*, 1982, 1309.

19. A.L.J. Beckwith, V.W. Bowry, M. O'Leary, G. Moad, E. Rizzardo, and D.H. Solomon, *J. Chem. Soc., Chem. Commun.*, 1986, 1003.

20. K. Adamic, D.F. Bowman, T. Gillan, and K.U. Ingold, *J. Am. Chem. Soc.*, 1971, 93, 902.

21. G.B. Watts, D. Griller, and K.U. Ingold, *J. Am. Chem. Soc.*, 1972, 94, 8784.

22. D. Griller and B.P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1972, 747.

23. A.G. Davies, D. Griller, and B.P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1972, 993.

24. A.G. Davies, D. Griller, and B.P. Roberts, *Angew. Chem. Int. Ed. Engl.*, 1971, 10, 738.

25. D. Griller and B.P. Roberts, *J. Chem. Soc., Chem. Commun.*, 1971, 1035.

26. D. Griller and K.U. Ingold, *Acc. Chem. Res.*, 1980, 13, 193.

27. H. Paul, R.D. Small Jr., and J.C. Scaiano, *J. Am. Chem. Soc.*, 1978, 100, 4520.

28. C. Chatgilialoglu, K.U. Ingold, J.C. Scaiano, and H. Wagner, *J. Am. Chem. Soc.*, 1981, 103, 3231.

29. J.C. Scaiano, *J. Am. Chem. Soc.*, 1980, 102 5400.

30. P. Burkhard, E. Roduner, J. Hochmann, and H. Fischer, *J. Phys. Chem.*, 1984, 88, 773.

31. P. Burkhard, E. Roduner, H. Fischer, *Int. J. Chem. Kinet.*, 1985, 17, 83.

32. W.H. Urry and M.S. Kharasch, *J. Am. Chem. Soc.*, 1944, 66, 1438.

33. E.J. Hamilton and H. Fischer, *Helv. Chim. Acta.*, 1973, 56, 795.

34. Y. Maeda and K.U. Ingold, *J. Am. Chem. Soc.*, 1979, 101, 4975.

35. K.U. Ingold and J. Warkentin, *Can. J. Chem.*, 1980, 58, 348.

36. J.W. Wilt in "Free Radicals", (J.K. Kochi ed.), Vol. 1, Chapter 8, Wiley, New York, 1973.

37. B. Maillard and K.U. Ingold, *J. Am. Chem. Soc.*, 1976, 98, 1224.

38. M.L. Poutsma and P.A. Iberbia, *Tetrahedron Lett.*, 1972, 3309.

39. D.Y. Curtin and J.C. Kauer, *J. Org. Chem.*, 1960, 25, 880.

40. D. Lal, D. Griller, S. Husband, and K.U. Ingold, *J. Am. Chem. Soc.*, 1974, 96, 6355.

41. J.K. Kochi and P.S. Krusic, *J. Am. Chem. Soc.*, 1969, 91, 3940.

42. D.J. Edge and J.K. Kochi, *J. Am. Chem. Soc.*, 1972, 94, 7695.

43. R.C. Lamb, P.W. Ayres, and M.K. Toney, *J. Am. Chem. Soc.*, 1963, 85, 3483.

44. R.A. Sheldon and J.K. Kochi, *J. Am. Chem. Soc.*, 1970, 92, 4395.

45. C.L. Jenkins and J.K. Kochi, *J. Am. Chem Soc.*, 1972, 94, 843.

46. P. Schmid, D. Griller, and K.U. Ingold, *Int. J. Chem. Kinet.*, 1979, 11, 333.

47. J.F. Garst, P.W. Ayres, and R.C. Lamb, *J. Am. Chem. Soc.*, 1960, 82, 4260.

48. C. Walling and M.S. Pearson, *J. Am. Chem. Soc.*, 1964, 86, 2262.

49. R.F. Garwood, C.J. Scott, and B.C.L. Weedon, *J. Chem. Soc., Chem. Commun.*, 1965, 14.

50. J.K. Kochi and T.W. Bethea, *J. Org. Chem.*, 1968, 33, 75.

51. R.C. Lamb, P.W. Ayres, M.K. Toney, and J.F. Garst, *J. Am. Chem. Soc.*, 1966, 88, 4261.

52. M. Julia, C. Descoins, M. Baillarge, B. Jacquet, D. Ugen, and F.A. Groeger, *Tetrahedron*, 1975, 31, 1737.

53. C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, 1972, 94, 6059.

54. R.P. Quirk and R.E. Lea, *Tetrahedron Lett.*, 1974, 1925.

55. R.P. Quirk and R.E. Lea, *J. Am. Chem Soc.*, 1976, 98, 5973.

56. H.O. House and P.O. Weeks, *J. Am. Chem Soc.*, 1975, 97, 2778.

57. A.L.J. Beckwith, I.A. Blair, and G. Phillipou, *Tetrahedron Lett.*, 1974, 2251.

58. A.L.J. Beckwith and G. Moad, *J. Chem. Soc., Chem. Commun.*, 1974, 472.

59. S.W. Benson, "Thermochemical kinetics", 2nd ed., Wiley, New York, 1976.

60. H.E. O'Neil and S.W. Benson in "Free Radicals", (J.K. Kochi ed.), Vol. 2, Chapter 17, Wiley, New York, 1973.

61. H. Hart and D.P. Wyman, *J. Am. Chem. Soc.*, 1959, 81, 4891.

62. P.D. Bartlett, W.D. Closson, and T.J. Cogdell, *J. Am. Chem. Soc.*, 1965, 87, 1308.

63. W.C. Kossa, T.C. Rees, and H.G. Richey, *Tetrahedron Lett.*, 1971, 3455.

64. J.K. Kochi, in "Free Radicals", (J.K. Kochi ed.), Vol. 1, Chapter 11, Wiley, New York, 1973.

65. P. Schmid and K.U. Ingold, *J. Am. Chem. Soc.*, 1977, 99, 6434.

66. E.C. Ashby and D. Coleman, *J. Org. Chem.*, 1987, 52, 4554.

67. A. Citterio, F. Minisci, O. Porta, and G. Sesana, *J. Am. Chem. Soc.*, 1977, 99, 7960.

68. A. Citterio, A. Arnoldi, and F. Minisci, *J. Org. Chem.*, 1979, 44, 2675.

69. A. Citterio, *Tetrahedron Lett.*, 1978, 2701.

70. J.F. Garst and C.D. Smith, *J. Am. Chem. Soc.*, 1976, 98, 1526.

71. J.F. Garst and C.D. Smith, *J. Am. Chem. Soc.*, 1976, 98, 1520.

72. J.F. Garst, in "Free Radicals", (J.K. Kochi ed.), Vol. 1, Chapter 9, Wiley, New York, 1973.

73. J.F. Garst and F.E. Barton, *Tetrahedron Lett.*, 1969, 587.

74. H.O. House, *Acc. Chem. Res.*, 1976, 9, 59.

75. J.F. Garst and F.E. Barton, *J. Am. Chem. Soc.*, 1974, 96, 523.

76. J.F. Garst, R.D. Roberts, and J.A. Pacifici, *J. Am. Chem. Soc.*, 1977, 99, 3528.

77. J.F. Garst, J.A. Pacifici, C.C. Felix, and A. Nigam, *J. Am. Chem. Soc.*, 1978, 100, 5974.

78. D.E. Bergbreiter and J.M. Killough, *J. Am. Chem. Soc.*, 1978, 100, 2126.

79. H.W.H.J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, 1975, 31, 1053.

80. C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, 1970, 92, 6609.

81. F.A. Davis, P.A. Macinelli, K. Balasbramanian, and U.K. Nadir, *J. Am. Chem. Soc.*, 1979, 101, 1044.

82. B. Maillard, D. Forrest, and K.U. Ingold, *J. Am. Chem. Soc.*, 1976, 98, 7024.

83. J.K. Kochi, P.J. Krusic, and D.R. Eaton, *J. Am. Chem. Soc.*, 1969, 91, 1877.

84. J.K. Kochi, *Adv. Free Radical Chem.*, 1975, 5, 189.

86. J.K. Kochi, P.J. Krusic, and D.R. Eaton, *J. Am. Chem. Soc.*, 1969, 91, 1879.

87. W.J. Hehre, *J. Am. Chem. Soc.*, 1973, 95, 2643.

88. A. Effio, D. Griller, K.U. Ingold, A.L.J. Beckwith, and A.K. Serelis, *J. Am. Chem. Soc.*, 1980, 102, 1734.

89. C.L. Jenkins and J.K. Kochi, *J. Org. Chem.*, 1971, 36, 3095.

90. C.L. Jenkins and J.K. Kochi, *J. Org. Chem.*, 1971, 36, 3103.

91. C.L. Jenkins and J.K. Kochi, *J. Am. Chem. Soc.*, 1972, 94, 856.

92. J.E. Baldwin, R.M. Adlington, B.P. Domayne-Hayman, G. Knight, and H.-H. Ting, *J. Chem. Soc., Chem. Commun.*, 1987, 1661.

93. P.R. Ortiz de Montellano and R.A. Stearns, *J. Am. Chem. Soc.*, 1987, 109, 3415.

94. M.L. Cordeiro, D.L. Pompliano, and J.W. Frost, *J. Am. Chem. Soc.*, 1986, 108, 332.

95. H.O. House and K.A.J. Snoble, *J. Org. Chem.*, 1986, 41, 3076.

96. H.O. House, W.C. McDaniel, R.E. Sieloff, and D. Vanderveer, *J. Org. Chem.*, 1978, 43, 4316.

97. P.J. Krusic, P.J. Fagan, and J. San Filippo, *J. Am. Chem. Soc.*, 1977, 99, 250.

98. J. San Filippo, J. Silbermann, and P.J. Fagan, *J. Am. Chem. Soc.*, 1978, 100, 4834.

99. W.G. Dauben, L. Schutte, R.E. Wolf, and E.J. Deving, *J. Org. Chem.*, 1969, 34, 2512.

100. H.E. Zimmerman and T.W. Fletchner, *J. Am. Chem. Soc.*, 1970, 92, 6931.

101. J.K. Crandell, P.J. Arrington, and C.F. Mayer, *J. Org. Chem.*, 1971, 36, 1428.

102. S. Moon and H. Bohn, *J. Org. Chem.*, 1971, 36, 1434.

103. N. Shimizu, M. Ishikawa, K. Ishikura, and S. Nishida, *J. Am. Chem. Soc.*, 1974, 96, 6456.

104. A.B. Smith, L. Brodsky, S. Wolff, and W.C. Agosta, *J. Chem. Soc., Chem. Commun.*, 1975, 509.

105. I.M. Takakis and W.C. Agosta, *J. Org. Chem.*, 1979, 44, 1294.

106. I.M. Takakis and W.C. Agosta, *J. Am. Chem. Soc.*, 1979, 101, 2383.

107. K.S. Chen, D.J. Edge, and J.K. Kochi, *J. Am. Chem. Soc.*, 1973, 95, 7036.

108. A.L.J. Beckwith and V. Bowry, private communication.

109. T.A. Halgren, M.E.H. Howden, M.E. Medof, and J.D. Roberts, *J. Am. Chem. Soc.*, 1967, 89, 3051.

110. A.L.J. Beckwith and G. Phillipou, *Aust. J. Chem.*, 1976, 29, 123.

111. E.C. Friedrich and R.L. Holmstead, *J. Org. Chem.*, 1972, 37, 2550.

112. A.G. Davies, B. Muggleton, J.Y. Godet, and M. Pereyre, *J. Chem. Soc., Chem. Commun.*, 1976, 813.

113. A.G. Davies, B. Muggleton, J.Y. Godet, M. Pereyre, and J.C. Pommier, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1719.

114. M. Casting, M. Pereyre, M. Raiter, P.M. Blum, and A.G. Davies, *J. Chem. Soc., Perkin Trans. 2*, 1979, 589.

115. A.G. Davies and B. Muggleton, *J. Chem. Soc., Perkin Trans. 2*, 1976, 502.

116. H. Itzel and H. Fischer, *Tetrahedron Lett.*, 1975, 563.

117. J.Y. Godet and M. Pereyre, *J. Organomet. Chem.*, 1972, 40, C23.

118. J.Y. Godet, M. Pereyre, J.C. Pommier, and D. Chevolleau, *J. Organomet. Chem.*, 1973, 55, C15.

119. J.Y. Godet and M. Pereyre, *Bull. Soc. Chim. Fr.*, 1976, 1105.

120. A.J. Bellamy, E.A. Campbell, and I.R. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1374.

121. W.G. Dauben and R.E. Wolf, *J. Org. Chem.*, 1970, 35, 2361.

122. M. Cook, O. Hares, A. Johns, J. Murphy, and C.W. Patterson, *J. Chem. Soc., Chem. Commun.*, 1986, 1419.

123. W.R. Dolbier, B.H. Alsader, S.F. Sellers, and M. Koroniak, *J. Am. Chem. Soc.*, 1981, 103, 2138.

124. M.Ratier, M. Pereyre, A.G. Davies, and R. Sutcliffe, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1907.

125. L. Mathew and J. Warkentin, *J. Amer. Chem. Soc.*, 1986, 108, 7981.

126. D.L.J. Clive and S. Daigneault, *J. Chem. Soc., Chem. Commun.*, 1989, 332.

127. R. Kiesewetter and P. Margaretha, *Helv. Chim. Acta.*, 1989, 72, 83.

128. A. Johns and J.A. Murphy, *Tetrahedron Lett.*, 1988, 29, 837.

129. J.A. Murphy, C.W. Patterson, and N.F. Wooster, *Tetrahedron Lett.*, 1988, 29, 955.

130. J.A. Murphy, C.W. Patterson, and N.F. Wooster, *J. Chem. Soc., Chem. Commun.*, 1988, 294.

131. A. Johns, J.A. Murphy, C.W. Patterson, and N.F. Wooster, *J. Chem. Soc., Chem. Commun.*, 1987, 1239.

132. R.C. Gosh, F. MacCorquodale, and J.C. Walton, *Tetrahedron*, 1989, 45, 5531.

133. A.L.J. Beckwith and G. Moad, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1473.

134. Unpublished results, D. Laurie, University of Strathclyde.

135. C. Roberts and J.C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1985, 841.

136. G.A. Wheaton and D.J. Burton, *J. Fluorine Chem.*, 1976, **8**, 97.

137. G.A. Wheaton and D.J. Burton, *J. Fluorine Chem.*, 1977, **9**, 25.

138. D. Seyferth, J. Yick-Pui Mui, M.E. Gordon, and J.M. Burlitch, *J. Am. Chem. Soc.*, 1965, 87, 681.

139. D. Seyferth, H. Dertouzos, R. Suzuki, and J. Yick-Pui Mui, *J. Org. Chem.*, 1967, 32, 2980.

140. D. Seyferth, S.P. Hopper, and K.V. Darragh, *J. Am. Chem. Soc.*, 1969, 91, 6536.

141. D. Seyferth and S.P. Hopper, *J. Org. Chem.*, 1972, 37, 4070.

142. D.J. Burton and D.G. Naae, *J. Am. Chem. Soc.*, 1973, 95, 8467.

143. J. Leroy, H. Molines, and C. Wakselman, *J. Org. Chem.*, 1987, 52, 290.

144. S.R. Landor and N. Punja, *J. Chem. Soc. (C)*, 1967, 2495.

145. J.M. Birchall, G.W. Cross, and R.N. Haszeldine, *Proc. Chem. Soc.*, 1960, 81.

146. R.A. Mitsch, *J. Heterocycl. Chem.*, 1964, 1, 59.

147. M. Braun and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, 1974, 13, 277.

148. J.M. Birchall, G.N. Gilmore, and R.N. Haszeldine, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2530.

149. W.R. Dolbier Jr., and J.F. Sellers, *J. Am. Chem. Soc.*, 1982, 104, 2494.

150. Y. Kusuyama, *Bull. Chem. Soc. Japan*, 1979, **52**, 1944.

151. Y. Kusuyama, *Bull. Chem. Soc. Japan*, 1973, **46**, 204.

152. R.G. Woodworth and P.S. Skell, *J. Am. Chem. Soc.*, 1957, **79**, 2542.

153. W. von E. Doering and A.K. Hoffmann, *J. Am. Chem. Soc.*, 1954, 76, 6163.

154. M. Makosza and M. Wawrzyniewicz, *Tetrahedron*, 1969, 53, 4659.

155. M. Makosza and M. Fedorynski, *Rocz. Chem.*, 1976, 2223.

156. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, 84, 867.

157. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, 84, 3782.

158. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, 87, 1353.

159. N.E. Searle, *Organic Synthesis Coll.*, Vol. 4, 424.

160. W.R. Moser, *J. Am. Chem. Soc.*, 1969, 81, 1135.

161. V. Dave and E.W. Warnhoff, *Org. Reactions*, 18, 258.

162. A.E. Arbuzov, *Chem. Ber.*, 1905, 38, 1171.

163. Y. Kusuyama and Y. Ikeda, *Bull. Chem. Soc. Japan*, 1977, 50, 1784.

164. Y. Kusuyama, S. Inoshita, G. Okada, M. Yanagi, K. Tokami, H. Fuchu, Y. Tsuno, and M. Mishima, *Org. Mag. Res.*, 1982, 20, 159.

165. M.P. Doyle, W.H. Tamblyn, and V. Bagheri, *J. Org. Chem.*, 1981, 46, 5094.

166. W.H. Tamblyn, S.R. Hoffmann, and M.P. Doyle, *J. Organomet. Chem.*, 1981, 216, C64-C68.

167. B.T. Golding and S. Mwesigye-Kibende, *J. Chem. Soc., Chem. Commun.*, 1983, 1103.

168. A.J. Hubert, A.F. Noels, A.J. Anciaux, and P. Teyssie, *Synthesis*, 1976, 600.

169. I.A. Dyakonov and N.B. Vinogradova, *J. Gen. Chem. U.S.S.R.*, 1952, 22, 1349.

170. I.A. Dyaknovov and N.D. Pirogova, *J. Gen. Chem. U.S.S.R.*, 1951, 21, 1979.

171. M.A. Blanchette, W. Choy, J.T. Davies, A.P. Essenfeld, S. Masamune, W.R. Roush, and T. Sakai, *Tetrahedron Lett.*, 1984, 25 (21), 2183.

172. E. Wenkert, R.A. Mueller, E.J. Reardon Jr., S.S. Sathe, D.J. Scharf, and G. Tosi, *J. Am. Chem. Soc.*, 1970, 92, 7428.

173. D.D. Tanner, G.E. Diaz, and A. Potter, *J. Org. Chem.*, 1985, 50, 2149.

174. E.A. Hill and R. Wiesner, *J. Am. Chem. Soc.*, 1969, 91, 509.

175. E.A. Hill, *J. Organomet. Chem.*, 1970, 24, 457.

176. G. Gerichelli, B. Floris, and G. Ortaggi, *J. Organomet. Chem.*, 1974, 78, 241.

177. X. Creary, M.E. Mehrsheikh-Mohammadi, and S. Macdonald, *J. Org. Chem.*, 1989, 54, 2904.

178. A.L.J. Beckwith, V.W. Bowry, M. O'Leary, G. Moad, E. Rizzardo, and D.H. Solomon, *J. Chem. Soc., Chem. Commun.*, 1986, 1003.

179. P.G. Griffiths, G. Moad, E. Rizzardo, and D.H. Solomon, *Aust. J. Chem.*, 1983, 36, 397.

180. V.W. Bowry, J. Lusztyk, and K.U. Ingold, *J. Chem. Soc., Chem. Commun.*, 1990, 923.

181. I. Biddles, A. Hudson, and P.J.T. Wiffen, *Tetrahedron*, 1972, 28, 867.

182. H.J.Hefter, T.A. Hecht, and G.S. Hammond, *J. Am. Chem. Soc.*, 1972, 94, 2793.

183. A. Hudson and K.D.J. Root, *Tetrahedron*, 1969, 25, 5311.

184. D.C. Nonhebel, C.J. Suckling, and J.C. Walton, *Tetrahedron Lett.*, 1982, 23, 4477.

185. C. Ruchardt and H. Bock, *Chem. Ber.*, 1971, 104, 577.

186. H. Fischer and G. Giacometti, *J. Polymer Sci.*, 1967, C16, 2763.

187. P. Smith, J.T. Pearson, P.B. Wood, and J.T. Smith, *J. Chem. Phys.*, 1965, 43, 1535.

188. B.C. Gilbert, R.O.C. Norman, and R.C. Sealy, *J. Chem. Soc., Perkin Trans 2*, 1975, 885.

189. H. Gilman and R.E. Brown, *J. Am. Chem, Soc.*, 1930, 52, 3314.

190. J. D'Ans, H. Zimmer, and H. Bergman, *Chem. Ber.*, 1952, 85, 583.

191. D. Seyferth, S. Hopper, and G. Murphy, *J. Organomet Chem.*, 1972, 46, 201.

192. P. Tarrant and E.C. Stamp, Jr., *J. Org. Chem.*, 1964, 29, 1198.

193. A. Nishihara and I. Kubota, *J. Org. Chem.*, 1968, 33, 2525.

194. F.L. Howard, T.W. Mears, A. Fookson, P. Pomerante, and D.B. Brooks, *J. Research Natl. Bur. Standards*, 1947, 38, 365.

195. C.K. Ingold and E.H. Ingold, *J. Chem. Soc.*, 1931, 2367.

196. S. Hanessian and P. Lavallee, *Can. J. Chem.*, 1975, 53, 2975.

197. J.E. Baldwin and C.G. Carter, *J. Org. Chem.*, 1983, 48, 3912.

198. Aldrich Chemical Co. catalogue and Library of N.M.R. and I.R. Data.

199. E.L. De-Young, *J. Org. Chem.*, 1961, 26, 1312.

200. R.L. Moffat, *J. Org. Chem.*, 1964, 29, 3726.

201. J.J. Macdonnel and D.J. Pockopien, *J. Org. Chem.*, 1971, 36, 2092.

202. F.S. Arimoto and A.C. Haven, Jr., *J. Amer. Chem. Soc.*, 1955, 77, 6295.

203. W.M. Horspool, R.G. Sutherland, and B.J. Thomson, *J. Chem. Soc. (C).*, 1971, 1558.

204. A.W. Baker and D.E. Bublitz, *Spectochim. Acta.*, 1966, **22**, 1787.

205. W.E. Watts, *J. Chem. Soc., Perkin Trans. 2*, 1976, 804.

206. H.G. Kuivila, *Synthesis*, 1970, **10**, 499.

207. *Chem. Abs.*, 19460, 39, 1922.

208. G. Vanges, *Latv. Univ. Raksti. Kim. Fak. Ser.*, 1939, 4, 405.

209. M.W. Rathke and M. Nowak, *J. Org. Chem.*, 1985, 50, 2624.

210. H. Taniguchi, K. Fukui, S. Ohnishi, H. Hatano, H. Hasegawa, T. Maruyama, *J. Chem Phys.*, 1965, 43, 1535.

211. A.J. Dobbs, B.C. Gilbert, R.O.C. Norman, *J. Chem. Soc. Perkin Trans. 2*, 1972, 2053.

212. A.L.J. Beckwith, *Aust. J. Chem.*, 1972, **25**, 1887.