The Chemistry of Cyclopropylmethyl and Related Radicals

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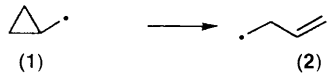
1 Introduction

Ring opening of the cyclopropylmethyl radical (1) gives the but-3-enyl radical (2) with a rate constant at 37 °C of 1.2×10^8 s^{-1}.[1]



(1) (2)

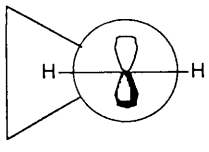
The cyclopropylmethyl carbanion also undergoes ring opening giving the but-3-enyl anion. The rate of this process is very much slower than that of the corresponding radical and has been estimated to be about 9.5×10^{-5} s^{-1} at -24 °C.[2] Unlike the corresponding cations, cyclopropylmethyl radicals do not rearrange to cyclobutane derivatives.

The rapidity of the ring opening of the cyclopropylmethyl radical has resulted in the widespread use of cyclopropane rings as a probe of reaction mechanism both in chemical and enzyme-catalysed reactions. This is only a valid probe if the ring opening of the cyclopropylmethyl radical is more rapid than any competing reactions. For this reason it is essential to have a sound appreciation of the factors which control rates of ring opening of substituted cyclopropylmethyl radicals. As will be demonstrated, hypersensitive radical probes can be used, *i.e.* substituted cyclopropylmethyl radicals which ring open much faster than the parent cyclopropylmethyl radical.

The variation in the rate of ring opening with substituents either at the radical centre or on the cyclopropane ring will be discussed in this review along with the regioselectivity of the ring opening process. Examples of the application of cyclopropylmethyl radical ring opening to the study of enzyme mechanisms and to synthetic methodology will also be discussed.

2 Characteristics of the Rearrangement

The parent cyclopropylmethyl radical contains *ca.* 115 kJ mol^{-1} of strain and hence homolytic cleavage of the C_β–C_γ bond to give a but-3-enyl radical is highly exothermic. EPR studies show that the preferred conformation of the radical is bisected, (3).[3]



(3)

Derek Nonhebel received his B.Sc. degree from King's College, University of London in 1954 and his D.Phil. from the University of Oxford where he worked under the supervision of the late Prof. W. A. Waters, F.R.S. He was elected a Fellow of the Royal Society of Edinburgh in 1982. His research interests centre on various aspects of radical chemistry. He has co-authored two books on radical chemistry.

The cyclopropyl group exerts a small but significant stabilizing effect on an adjacent radical centre. The cyclopropylmethyl C–H bond dissociation energy is 412 kJ mol^{-1}, which is slightly less than that of the C_2H_5–H bond dissociation energy (420 kJ mol^{-1}), *i.e.* there is a small but significant interaction between the SOMO and the orbitals containing the C_β–C_γ bond.

3 Rates of Ring Opening of Cyclopropylmethyl Radicals

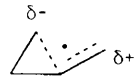
Table 1 lists a selection of kinetic data for the ring opening of a series of substituted cyclopropylmethyl radicals. A study of these data indicates that the rates of rearrangement are influenced by the following parameters:

(i) The stability of the initial radical. Substituents which stabilize the initial radical result in a decreased rate of rearrangement. Thus, the radical (6) ring opens much less rapidly than (7) because of benzylic stabilization of the radical centre. The radical (11) ring opens very much less readily than (1) due in part to stabilization of the radical centre by the ester group.

(ii) The stability of the rearranged radical. The rates of ring opening of (7) and (5) are much faster than those of (1) and (4) as ring opening leads to benzylic and tertiary radicals respectively. The ester group in (12) similarly promotes ring opening.

(iii) Relief of strain in the rearranged radical. The rate of ring opening of the strained bicyclo[2.1.0]pent-2-yl radical (13) is much faster than that of comparable monocyclic radicals.

(iv) Dipolar factors. It has been proposed that the transition state for ring opening has dipolar character, *cf.* (14).



(14)

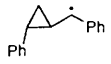
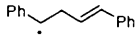
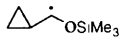
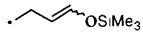
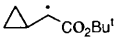
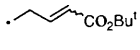
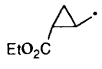
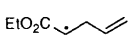
It appears that substitution at the 1-position in the cyclopropane ring has little effect on the rate of ring opening.

4 Regioselectivity of Ring Opening of Cyclopropylmethyl Radicals

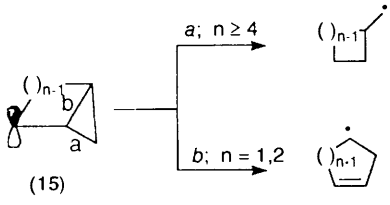
In conformationally mobile radicals, rotation of the group carrying the unpaired electron usually takes place so that the SOMO overlaps the more substituted C_β–C_γ bond, which then cleaves to give the more stabilized radical. Thus (7) ring opens to give a benzylic radical, and (5) gives a tertiary rather than a primary radical. The *cis*-2-methylcyclopropylmethyl radical (8) cleaves to give predominantly the secondary pen-4-en-2-yl radical.[1] In contrast the isomeric *trans*-radical (9) gives preferentially the primary 2-methylbut-3-en-1-yl radical. The reason for this is not clear.

Bicyclo[*n*.1.0] radicals ring open to give either the ring-enlarged cycloalk-3-enyl radical, when the internal bond in the cyclopropane ring *b* is cleaved, or the cycloalk-2-enylmethyl radical, when the outer bond *a* is broken.[8] The external bond *a* overlaps best with the SOMO (bond *b* is formally in the nodal plane of the SOMO) and hence is cleaved preferentially if the larger ring in the radical (15) is six-membered or larger ($n \geqslant 4$). If the ring containing the radical centre is three- or four-membered, relief of strain in mode *a* ring opening is much larger than for mode *b* scission and this then becomes the preferred mode. The bicyclo[3.1.0]hex-2-yl radical is intermediate in type and undergoes both types of bond scission.

Table 1 Rates of ring opening of substituted cyclopropyl methyl radicals to but-3-enyl radicals

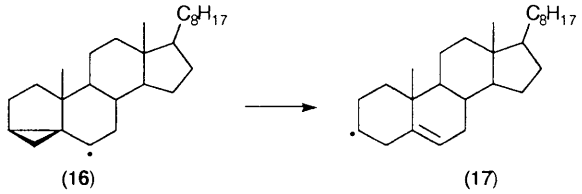
Radical	Initial radical	Rearranged radical	$10^{-8}\,k_R/s^{-1}$ (37 °C)	log[A]/s^{-1}	E/kJmol^{-1}	Ref.
(1)			1.2	13.15	29.5	1
(4)			0.8	13.15	30.9	1
(5)			20	12.85	20.9	1
(6)			3.6			4
(7)			3000[a]	13.9	14.8	5
(8)			2.3	12.85	23.4	1
			8.0	12.85	26.8	
(9)			1.6	12.85	27.2	1
			1.8	12.85	27.2	
(10)			0.2[a]			6
(11)			*ca.* 10^{-4}			6
(12)			> 500[b]			7
(13)			21	13.05	21.7	1

[a] At 25 °C. [b] At 60 °C.

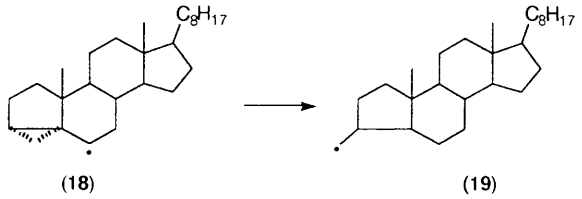


(15)

The maximum overlap rule is particularly well illustrated in the rearrangement of the isomeric radicals (16) and (18), which give stereospecifically the radicals (17) and (19) respectively: the bond that breaks is that which overlaps most efficiently with the SOMO.[9]



(16) (17)



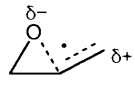
(18) (19)

5 Ring Opening of Hetero-analogues of Cyclopropylmethyl Radicals

Cyclopropyloxyl and cyclopropylaminyl radicals ring open more rapidly than cyclopropylmethyl radicals.[10] 1-Aziridinylmethyl radicals which, unlike cyclopropylmethyl radicals, exist in the perpendicular conformation, ring open less rapidly than their carbon analogues.[11]

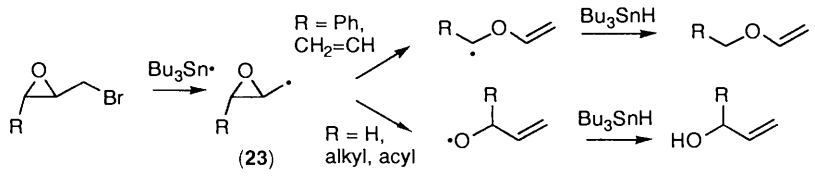
(20) (21)

Oxiranylmethyl radicals (23) could conceivably ring open either by scission of a C–O or a C–C bond. The latter would be expected on thermodynamic grounds because a C–C bond is weaker than a C–O bond. However, if the dipolar nature of the transition state (22) were important, cleavage of the C–O bond might be preferred.



(22)

Experimentally it is observed that for the unsubstituted radical, and also for alkyl and acyl substituted radicals, exclusive C–O scission takes place, though if the rearranged radical has a stabilizing group, *e.g.* phenyl or vinyl, then C–C scission



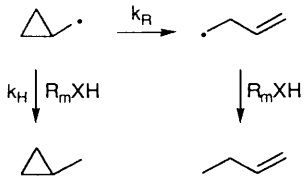
(23)

occurs.[12] Thus reaction of the corresponding bromomethyl oxiranes with tributyltin hydride leads either to an allyl alcohol or a vinyl ether depending on the nature of the bond scission. The oxiranylmethyl radical ring opens much faster than the cyclopropylmethyl radical: the dipolar character of the transition state would be expected to lower its energy relative to that for the cyclopropylmethyl radical.

While the rates of ring opening of cyclopropylmethyl radicals and anions are very different they both give the same products (after hydrogen atom and proton abstraction respectively), and this may limit the use of substrates containing the cyclopropylmethyl moiety as a probe of radical reactions. 3-Aryloxiranylmethyl radicals and carbanions, however, undergo C—C and C—O bond cleavage respectively. Epoxides are thus a discriminating probe to distinguish between radical and anionic reactions.

6 Cyclopropylmethyl Radical Rearrangements as Radical Clocks

The formation of ring-opened products from substrates containing the cyclopropylmethyl group has been widely used as an indication that a particular reaction proceeds *via* a radical intermediate.[10,13] In order to establish the credibility of a substituted cyclopropylmethyl radical for probing whether a particular reaction proceeds *via* a radical mechanism, it is essential to establish that the probe radical would ring open at a rate such that it can compete with other reactions. A probe can also be used in a quantitative sense to determine the rate of reaction of the radical intermediate with a second reactant. When the rate of ring opening of the radical has been determined, this can be used as a comparison or 'clock reaction' to compare the rate of this process with a competing bimolecular reaction. This technique involves determination of the yields of ring-opened and unrearranged products. For example, the rate of hydrogen abstraction by the cyclopropylmethyl radical from different hydrogen donors, R_xM-H, can be determined by analysis of the variation of the yields of methylcyclopropane and but-1-ene as a function of the concentration of the hydrogen donor (see Scheme 1). The rate of the competing hydrogen abstraction reaction can be calculated from the expression:



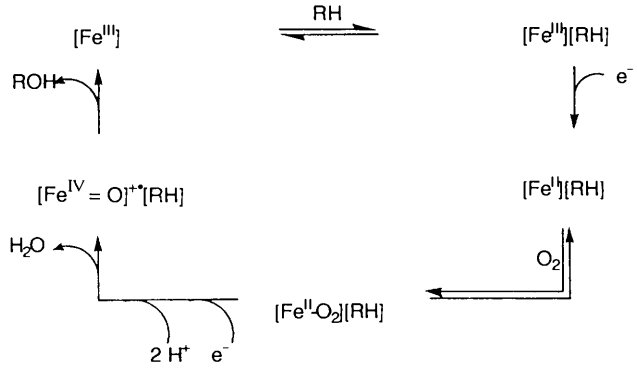
Scheme 1

7 Cyclopropylmethyl Radicals as Probes of Reaction Mechanism in Enzyme-catalysed Reactions

A range of cyclopropylmethyl radicals has been employed to provide evidence for radical intermediates in both enzymic and non-enzymic reactions.[14] The reactions discussed have been selected to give some indication of the breadth of the method.

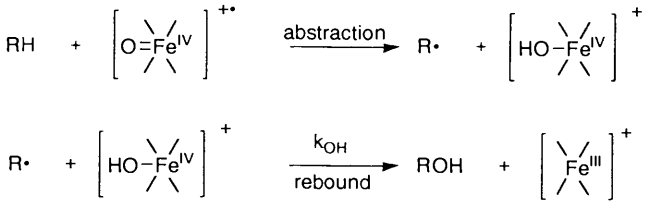
7.1 Hydroxylations of Alkanes with Cytochrome P 450

The hydroxylation of alkanes is often effected in nature by Cytochrome P 450, an enzyme containing an iron protoporphyrin as the oxygenation catalyst.[15] The catalytic cycle is depicted in Scheme 2.



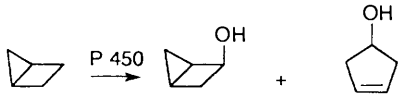
Scheme 2

The precise mechanism of oxygen insertion into the C—H bond has been proposed to involve hydrogen abstraction from the C—H bond followed by a transfer of a hydroxyl radical to the resulting alkyl radical (Scheme 3).



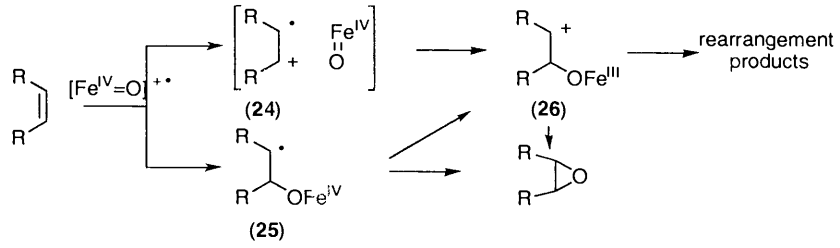
Scheme 3

The so-called *oxygen rebound* mechanism requires a very rapid capture of the intermediate radical to account for the stereochemical integrity of such reactions. Microsomal oxidations of methylcyclopropane gave cyclopropylmethanol with no detectable amount of but-3-en-1-ol, the expected product from ring opening of a cyclopropylmethyl radical. This could mean either that the reaction did not involve radical intermediates or that the oxygen rebound step was so rapid that the radical had insufficient time to ring-open. These two possibilities were distinguished by studying the hydroxylation of bicyclo[2.1.0]pentane, as the bicyclo[2.1.0]pent-2-yl radical ring opens much faster than the parent cyclopropylmethyl radical.[15] The reaction was found to give a 7:1 mixture of *endo*-bicyclo[2.1.0]pentan-2-ol and cyclopent-3-enol, *i.e.* some ring opening occurred in the mode expected for free-radical intermediates (Scheme 4). From the previously determined rate of ring opening of the bicyclo[2.1.0]pent-2-yl radical, this is consistent with a radical process in which the rate constant of oxygen rebound, k_{OH}, was $2.2 \times 10^{10}\ s^{-1}$.



Scheme 4

The microsomal oxidation of *cis*- and *trans*-1,2-dimethylcyclopropanes give mixtures of the corresponding unrearranged



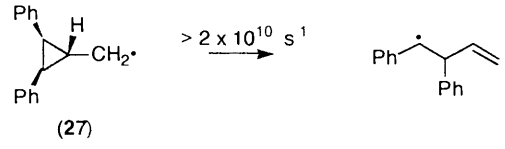
Scheme 5

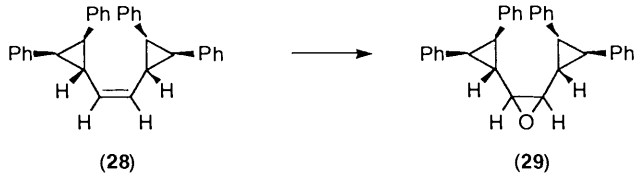
alcohols, *cis*- and *trans*-2-methylcyclopropanols and mixtures of the primary and secondary ring-opened alcohols, pent-4-en-2-ol and 2-methylbut-3-en-1-ol Significantly, the ratios of the isomeric alcohols in these oxidations was the same as the ratios of *O*-alkenyl hydroxylamines encountered in the trapping of *cis*- and *trans*-2-methylcyclopropylmethyl radicals by the stable nitroxide TEMPO This indicates that when these radicals are formed from their parent hydrocarbons in the hydrophobic pocket of cytochrome P-450 they are not detectably constrained in their subsequent reactions by their environment within the enzyme

trans-1-Methyl-2-vinylcyclopropane undergoes hydroxylation with *Pseudomonas oleovorans* monooxygenase (POM) to give 4-phenylbut-1-en-4-ol, again indicating a radical mechanism [16]

7.2 Monooxygenase-catalysed Epoxidations of Alkenes

The iron–oxygen species, believed to be the active iron-containing intermediate in the epoxidation of alkenes, is the same as that in the hydroxylation of alkenes by cytochrome P-450 [17] Radical, radical cation, and cation intermediate have been proposed for the epoxidation of alkenes by cytochrome P-450 (Scheme 5) The possible involvement of radical intermediates (25) in the epoxidation of alkenes has been studied using as a biomimetic model an iron porphyrin, and bis-1,2-(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (28) as the substrate This compound was selected as the probe because the rate of ring opening of the derived radical, the *trans*-2,*trans*-3-diphenylcyclopropylmethyl radical (27), was estimated to be about $2 \times 10^{10}\ s^{-1}$, *i e* over two orders of magnitude faster than that of the parent cyclopropylmethyl radical Ring opening would also be expected to occur if the reaction proceeded via the radical cation but not if the carbocation was formed in the initial step This alkene underwent epoxidation in 92—95% yield with no trace of ring opened products This indicates that if the reaction proceeded *via* a radical intermediate the rate of conversion of the radical into the epoxide must exceed $10^{12}\ s^{-1}$ thereby excluding (25) as a discrete intermediate Similarly (24) can only be a viable intermediate if it is trapped with a rate constant exceeding $2 \times 10^{10}\ s^{-1}$

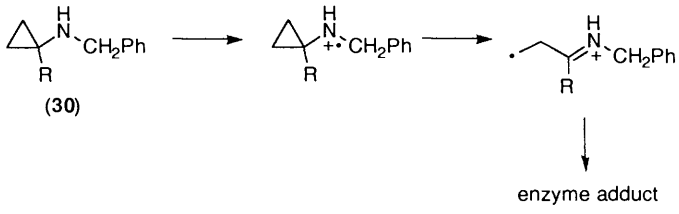




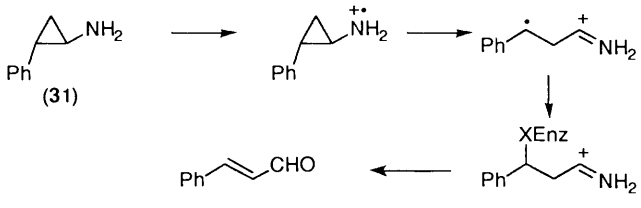
Epoxidation of *trans*-2-phenyl-1-vinylcyclopropane with manganese(III) salen complexes also proceeded with no evidence for the formation of ring-opened products, supporting a mechanism with a manganese(V)-oxo intermediate as the epoxidation species [18]

7.3 Mechanism of Inhibition of Monoamine Oxidase by Cyclopropylamines

Mitochondrial monoamine oxidase (MAO), a flavin-dependent enzyme, catalyses the deamination of physiologically active monoamines [19] This reaction is inhibited by cyclopropylamines, examples of which include *N*-benzylcyclopropylamine (30, R = H) and *N*-benzyl-1-methylcyclopropylamine (30, R = Me) It was originally thought that the former acted as a cyclopropanone equivalent, but this is clearly not possible with the latter It was then postulated that oxidation of the cyclopropylamine, as a result of electron transfer to a flavin, gives the corresponding radical cation which could then ring open (Scheme 6) the ring-opened amine radical cation then couples to the flavin radical anion *trans*-2-Phenylcyclopropylamine (31) has similarly been shown to inhibit the monoamine oxidase enzyme (Scheme 7)



Scheme 6

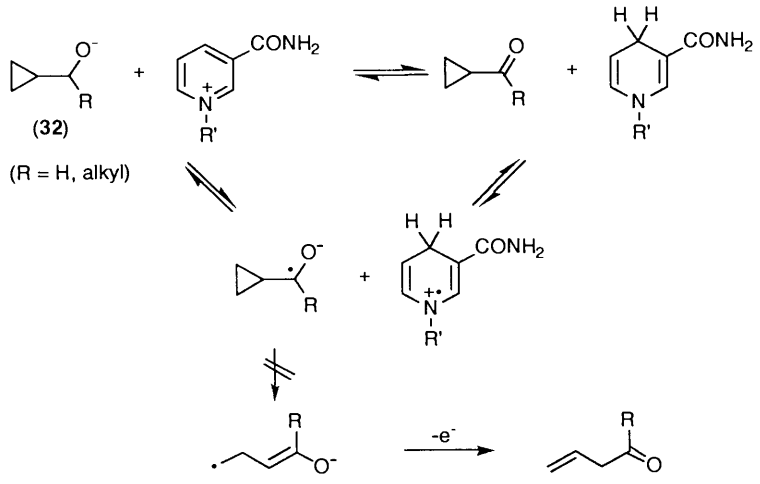


Scheme 7

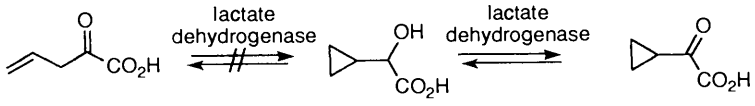
The intermediate radical cation should ring open very rapidly due to the radical-stabilizing ability of the 2-phenyl group by analogy with the rate of ring opening of the 2-phenylcyclopropylmethyl radical Subsequent hydrolysis of the flavin-radical adduct gives rise to cinnamaldehyde

7.4 Hydrogen Transfer by Nicotinamide Co-enzymes

The possibility that hydrogen transfer reactions by nicotinamide co-enzymes may involve single electron transfer processes leading to the intermediacy of radical intermediates has been proposed by several groups (*cf* Scheme 8) [20] The mechanism of this reaction can be probed by studies of the oxidations of cyclopropylmethanols (32) In no instance could any ring-opened product be detected, indicating the absence of radical intermediates As the rates of hydrogen transfer by horse liver alcohol dehydrogenase have been shown to be in the range 30—100 s^{-1}, radical intermediates would have sufficient time to open Model experiments showed that ring opening occurred in the tributyltin hydride reduction of bicyclo[4 1 0]heptane-1-carboxaldehyde



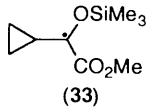
Scheme 8



Scheme 9

but not in the oxidation of bicyclo[4.1.0]heptane-1-methanol with triphenylmethyl tetrafluoroborate, thereby demonstrating that ring opening could be expected to take place if the reaction proceeded *via* a radical but not a cationic intermediate. Moreover the model radical (10) ring opens only slightly slower than the cyclopropylmethyl radical (1) (see Table 1). No ring opening occurred in analogous dehydrogenations of 2,2-dimethyl- and 2,2,3,3-tetramethyl-cyclopropanemethanols: the analogous radical intermediates in these reactions would be expected to ring open much faster than the species from cyclopropanemethanol. The absence of ring-opened products is consistent with a mechanism involving hydride transfer and not a single electron transfer process.

A similar study of the oxidation of cyclopropaneglycolic acid with lactate dehydrogenase also showed that no ring opening occurred (Scheme 9).[20] This result does not, however, indicate conclusively that radical intermediates are not involved, as the potential radical species is a capto-dative stabilized radical and an analogous radical (33) has been shown not to rearrange at temperatures as high as 100 °C.

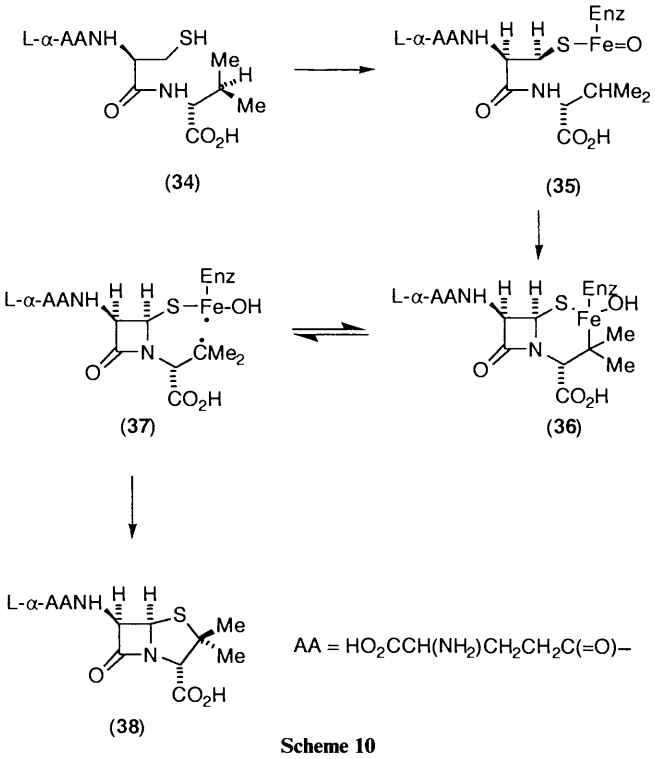


(33)

Similarly, the conclusion that radical intermediates are not involved in the decarboxylation of cyclopropylglyoxalate by pyruvate decarboxylating enzymes with thiamine pyrophosphate cofactors seems at best questionable as the intermediate radicals would be subject to capto-dative stabilization and hence would not be expected to ring open under the reaction conditions.[21]

7.5 Mechanism of Penicillin Biosynthesis

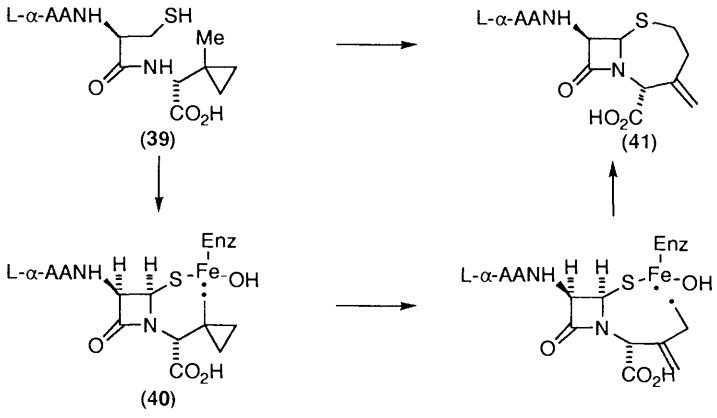
A stepwise mechanism has been proposed for the action of isopenicillin N synthase, which is responsible for the conversion of an acyclic tripeptide (34) into isopenicillin (38).[22] The first step in the mechanism is postulated to involve an enzyme-bound iron species (35). This then undergoes stereospecific insertion into a C—H bond forming a species with an iron–carbon bond (36). Reversible dissociation of this gives a biradical (37) which then couples at sulfur in an S_H2 reaction to give the penicillin. Evidence in support of a radical intermediate comes from the observation that the ring-enlarged product (41) is formed with the reaction of the substrate containing a cyclopropane ring (39): the intermediate cyclopropylcarbinyl radical (40) undergoes a cyclopropylmethyl-but-3-enyl ring opening (Scheme 11). It is significant that no product containing a cyclobutane ring could be detected, arguing against the involvement of a cyclopropylcarbinyl cation intermediate.



Scheme 10

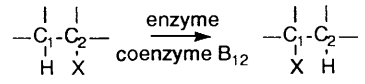
7.6 Mechanism of Coenzyme B_{12}-modified Rearrangements

In the form of its coenzyme adenosylcobalamin, vitamin B_{12} catalyses a series of rearrangements in which there is 1,2-



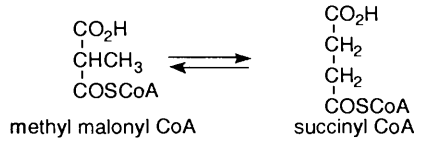
Scheme 11

migration of a hydrogen atom and the reverse migration of a group X.[23] In humans, conversion of methylmalonyl coenzyme



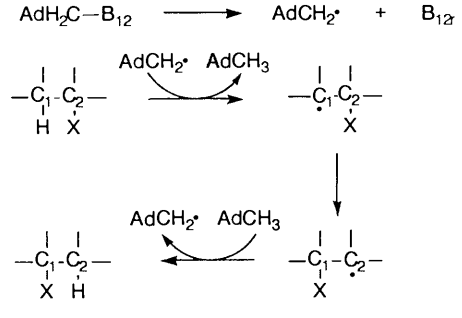
X = OH, NH_2, COSCoA, $C(=CH_2)CO_2H$

A into succinyl coenzyme A is catalysed by the enzyme methylmalonyl coenzyme A mutase. Labelling experiments show that intramolecular migration of the thioester and not the carboxyl group occurs. Coenzyme B_{12} is cobalt(III) derivative of a corrin (a tetrapyrrole-like macrocycle) to which a 5′-deoxyadenosyl residue is attached to the cobalt by an axial σ-bond. The Co–C



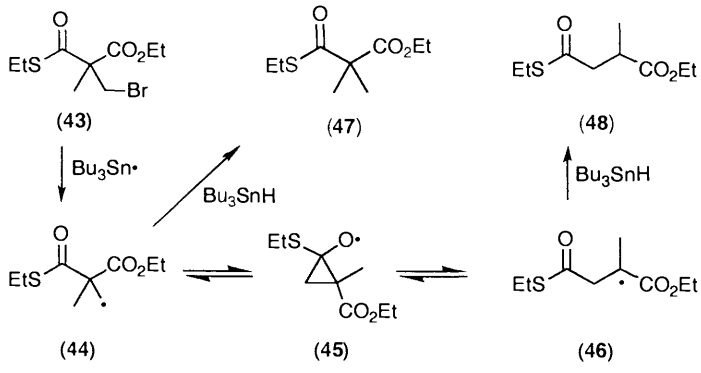
methyl malonyl CoA succinyl CoA

bond is a relatively weak bond which readily undergoes homolysis when the coenzyme is bound to its enzyme partner to give a 5′-deoxyadenosyl radical and a cobalt(II) species. The deoxyadenosyl radical is postulated to abstract a hydrogen atom from the substrate: the resultant substrate radical then rearranges and finally retrieves a hydrogen from the 5′-deoxyadenosine (Scheme 12).



Scheme 12

In the mechanism of rearrangement of methylmalonylcoenzyme A the substrate radical is postulated to proceed *via* cyclization to a cyclopropyloxyl radical (42), which ring opens to give the rearranged radical. The overall reaction involves the rearrangement of a primary radical to a carbonyl-stabilized secondary radical. The mechanism of this rearrangement has been probed by demonstrating that the reaction of the bromide (43) with tributylin hydride yields a mixture of the reduced product (47) and the rearranged product (48). The latter arises from the radical (47) formed as a result of the rearrangement of (46) *via* the cyclopropyloxyl radical (45) (Scheme 13).[24] Another



Scheme 13

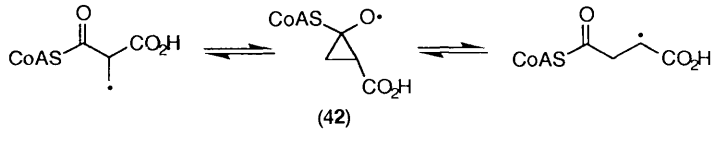
example of a vitamin B_{12}-catalysed rearrangement is the reaction of α-methyleneglutarate to 3-methylitaconate which is effected by the enzyme α-methyleneglutarate mutase. The migration of the acrylate group is postulated to proceed *via* a cyclopropylmethyl radical.[23]

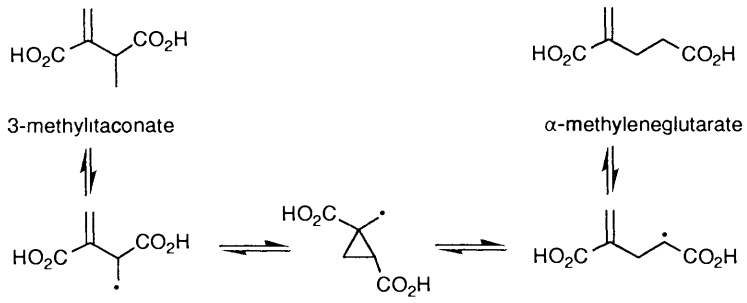
7.7 Mechanism of Biosynthesis of Ethylene from 1-Aminocyclopropanecarboxylates

The biosynthesis of ethylene in *e.g.* apple tissue has been shown to start from methionine and proceed *via* 1-aminocyclopropanecarboxylic acid. A model study was made of a series of 2,3-dimethyl-1-aminocyclopropanecarboxylates: these were converted by apple tissue into a 5:1 mixture of *cis*- and *trans*-but-2-enes.[25] An identical product mixture was obtained in a model chemical study which would involve radical intermediaries (Scheme 14).

7.8 Mechanism of Dephosphorylation of Organophosphates by *Escherichia coli*

Organophosphonates are readily cleaved by *E. coli.* cells. One mechanistic hypothesis is that this proceeds by homolysis of the





carbon–phosphorus bond in the organophosphonate (Scheme 15).[26] This was tested by studying the degradation of cyclopropylmethylphosphonic acid which gave but-1-ene thus implicating the cyclopropylmethyl radical which ring opened to the but-3-enyl radical.

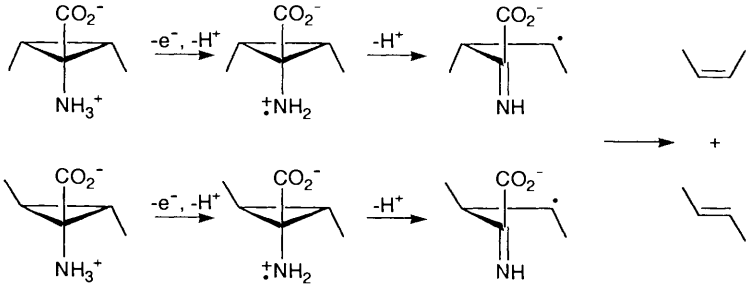
8 Cyclopropylmethyl Radicals as Probes of Reaction Mechanism in Chemical Reactions

8.1 Oxidation of Cyclopropylmethyl Radicals by Metal Salts

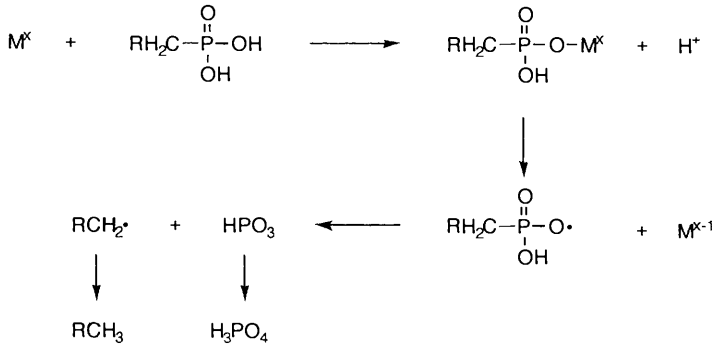
Cyclopropylmethyl radicals generated by thermolysis of bis-(cyclopropylacetyl) peroxide in presence of copper(II) chloride or bromide give mixtures of the corresponding cyclopropylmethyl halides and 4-halobut-1-enes with no trace of any cyclobutyl halide. This indicates that the reaction does not involve oxidation of the radical to the cation followed by nucleophilic capture of the cation.[27] The reaction is best represented as an atom or ligand transfer reaction from the copper(II) halide to the radical (Scheme 16). From the relative proportions of the two products and the rate constant for ring opening, k_R, it is possible to calculate that the rates of atom transfer, k_L, with copper(II) chloride and bromide are 1.1 and 4.3 × 10^9 M^{-1} s^{-1}, respectively. In contrast, oxidation of cyclopropylacetic acid with lead tetraacetate gives a mixture of cyclopropylmethyl acetate, cyclobutyl acetate, and 4-acetoxybut-1-ene indicating that the reaction proceeds *via* the cyclopropylmethyl cation.[28]

8.2 Mechanism of Reaction of Alkyl Halides with Metalate Anions

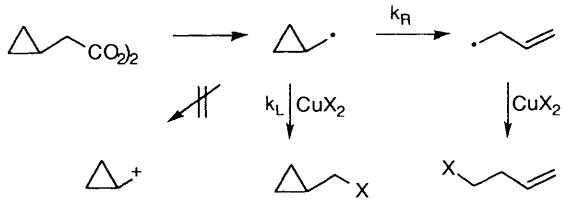
The mechanism of reaction of alkyl halides with metalate anions could involve either initial electron transfer with the generation of radicals or an S_N2 process (Scheme 17).[29] These two possibilities were distinguished by studying the reactions of cyclopropyl-



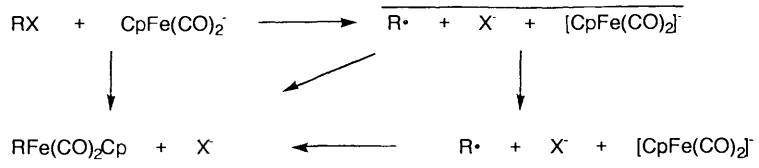
Scheme 14



Scheme 15



Scheme 16

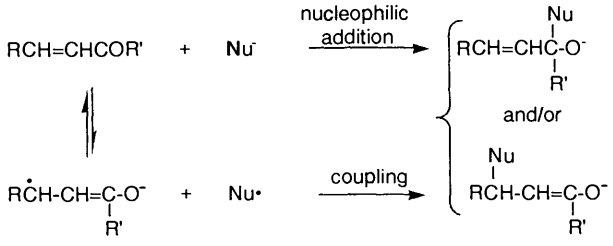


Scheme 17

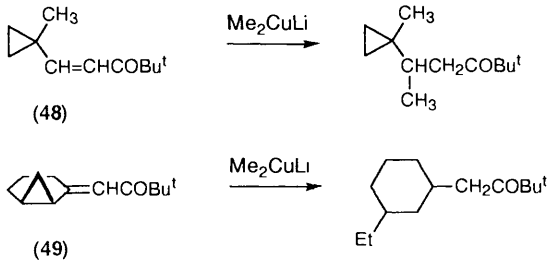
methyl halides with $CpFe(CO)_2Na$ and Me_3SnLi. Reactions of the iodides gave mixtures of the cyclopropylmethyl metalate and the ring-opened product. The amount of ring-opened product decreased as the halide was varied in the order I > Br > Cl indicating the increasing importance of the competing S_N2 process.

8.3 Reactions of Organometallic Compounds with Enones

Nucleophilic addition to β-cyclopropyl-α,β-unsaturated ketones would be expected to give the normal 1,2- and 1,4-addition products, whereas the operation of an electron-transfer mechanism would generate a cyclopropylmethyl radical intermediate, which would be anticipated to ring open rapidly leading to rearranged products (Scheme 18). Reaction of (48) with lithium dimethylcuprate gives mainly the ring-closed product whereas (49) underwent 1,2-addition with extensive rearrangement, indicating that a radical mechanism was operative.[30]



Scheme 18



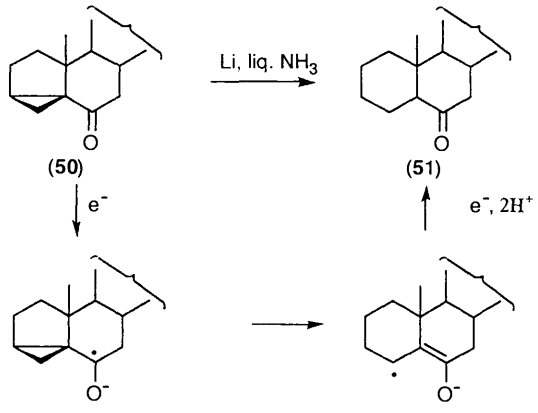
(48)

(49)

Recent work raises some questions as to the reliability of the probes used in this work. It has been shown that the generation of ketyl radical anions from aryl cyclopropyl ketones is slow and reversible, and thus the lack of ring opening cannot always be taken to imply that an electron transfer mechanism is not involved. The rapidity of ring opening of the ketyl radical anions and also the position of equilibrium is much more favourable with phenyl 2-phenylcyclopropyl ketyls (this ketyl would ring open to give a benzylic radical anion).[31]

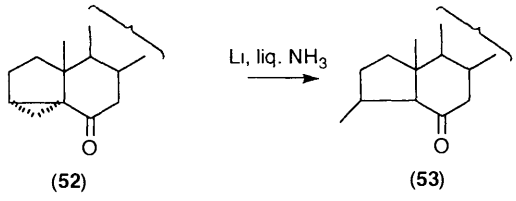
8.4 Dissolving-metal Reductions of Cyclopropyl Ketones

Reductions of the isomeric 3α,5- and 3β,5-cyclocholestan-6-ones, (50) and (52), with lithium in liquid ammonia proceed regiospecifically to cholestan-6-one (51) and 3α-methyl-A-nor-coprostan-6-one (53).[32] The results are comparable with the regioselectivity of ring opening of (16) and (18) and point strongly to a pathway involving radical anion intermediates (Scheme 19): selective scission of the bond in the cyclopropane



(50) (51)

Scheme 19

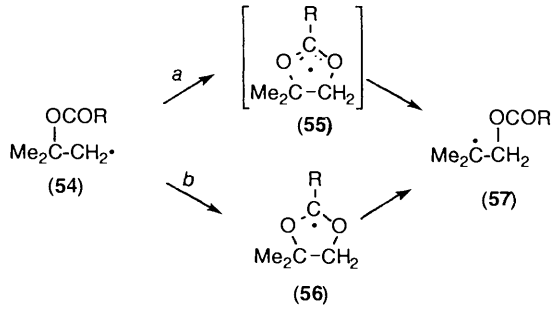


(52) (53)

which overlaps more efficiently with the SOMO of the ketyl carbon occurs.

8.5 Mechanism of 1,2-Acyloxy Migrations in Radicals

1,2-Migrations of an acyloxy group have been postulated to proceed either *via* a concerted pathway *a* or *via* an intermediate 1,3-dioxolan-2-yl radical (56) (path *b*) (Scheme 20). The 1,2-acetoxy rearrangement of (54; R = Me) proceeds slower than the ring opening of the corresponding dioxolanyl (56) and hence the intervention of the 1,3-doxolan-2-yl radical cannot be ruled out. However (54; R = cyclopropyl), rearranged without opening of the cyclopropane ring even though (56; R = cyclopropyl) underwent ring opening of the cyclopropane but not the dioxolane ring, thus indicating that the rearrangement proceeds *via* a concerted mechanism.[33]

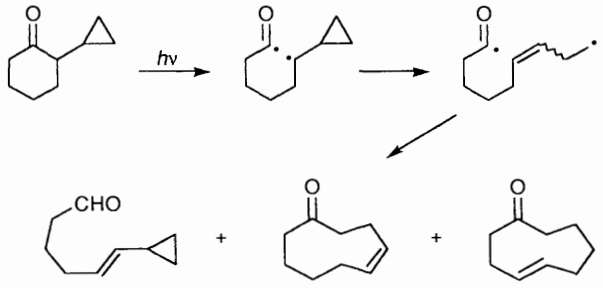


(54) (55) (56) (57)

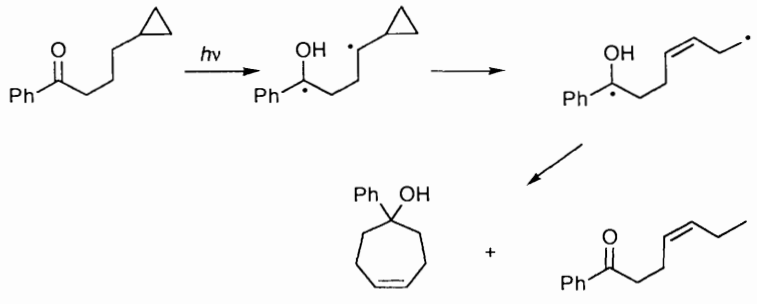
Scheme 20

8.6 Evidence for Radical Intermediates in Photochemical Reactions

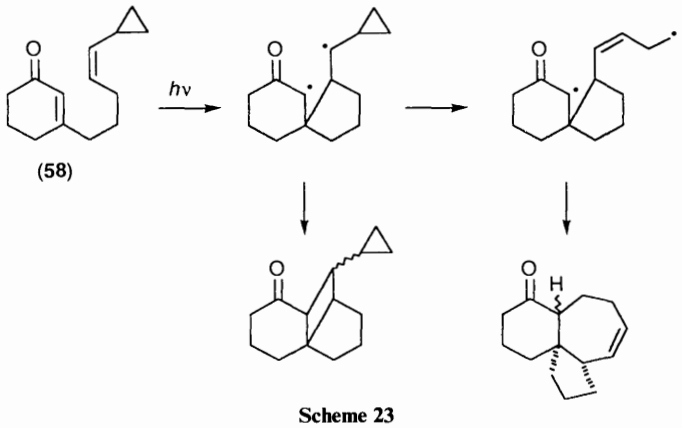
Evidence for the presence of radical intermediates in Norrish type I (Scheme 21) and type II (Scheme 22) processes has been obtained from studies of substrates containing a suitably placed cyclopropane ring.[34] Similarly ring opening of a cyclopropane



Scheme 21



Scheme 22



Scheme 23

ring has been observed in a Paterno-Büchi reaction.[35] 1,4-Biradicals have been postulated as intermediates in [2 + 2]cycloadditions of alkenes to enones. Evidence for this and that the initial bond is formed between the alkene and the β-carbon of the photoexcited enone has only recently been obtained by studying the intramolecular [2 + 2]photocycloaddition of the cyclopropyl-substituted enone (58) (Scheme 23).[36]

8.7 Determination of the Lifetime of Biradicals

Ultraviolet irradiation of a mixture of *N*-benzoylindole and cyclopropylethene gives a 2:1 mixture of (61) and (62), the latter being formed from the rearranged biradical (60) (Scheme 24).[37] The rate constant for ring opening of secondary cyclopropylcarbinyl radicals has been estimated to be $2 \times 10^7\ s^{-1}$. Using this value for the rearrangement of the initial biradical (59) and assuming that (62) is derived entirely from (60), the sum of the rate constants for closure of (59) to (61) and reversion of (59) to starting materials can be estimated to be about $1 \times 10^7\ s^{-1}$ and hence the lifetime of the biradical (59) 100 ns.

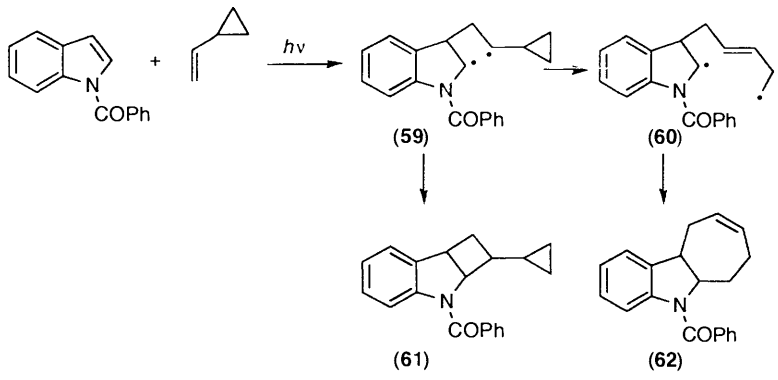
9 Syntheses Based on the Ring Opening of Cyclopropylcarbinyl and Related Radicals

9.1 1,5-Addition Reactions of Vinylcyclopropanes

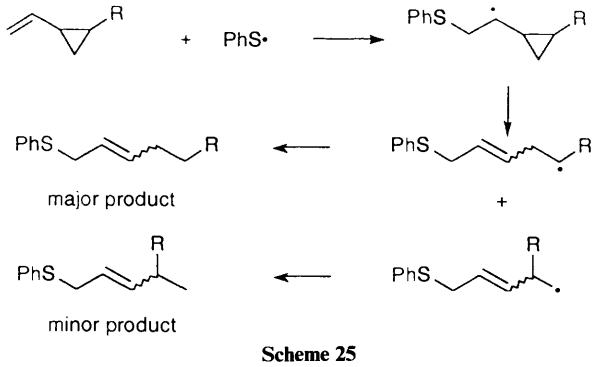
Thiophenol and tin hydrides add to vinylcyclopropanes to give mixtures of (*E*) and (*Z*)-alkenyl phenyl sulfides (Scheme 25) and alkenyl trialkyl stannanes.[38] The cyclopropane ring opens to give predominantly the more stable (more substituted) radical. Similarly *p*-toluenesulfonyl iodide adds to vinylcyclopropanes to give 1-iodo-5-*p*-toluenesulfonylpent-3-enes.[39] Vinylcyclopropanes have also been shown to undergo ring-opening polymerization.[40]

9.2 Syntheses of Dioxolanes, Cyclopentanes, and Cyclopentenes from Vinylcyclopropanes by [3 + 2] Additions

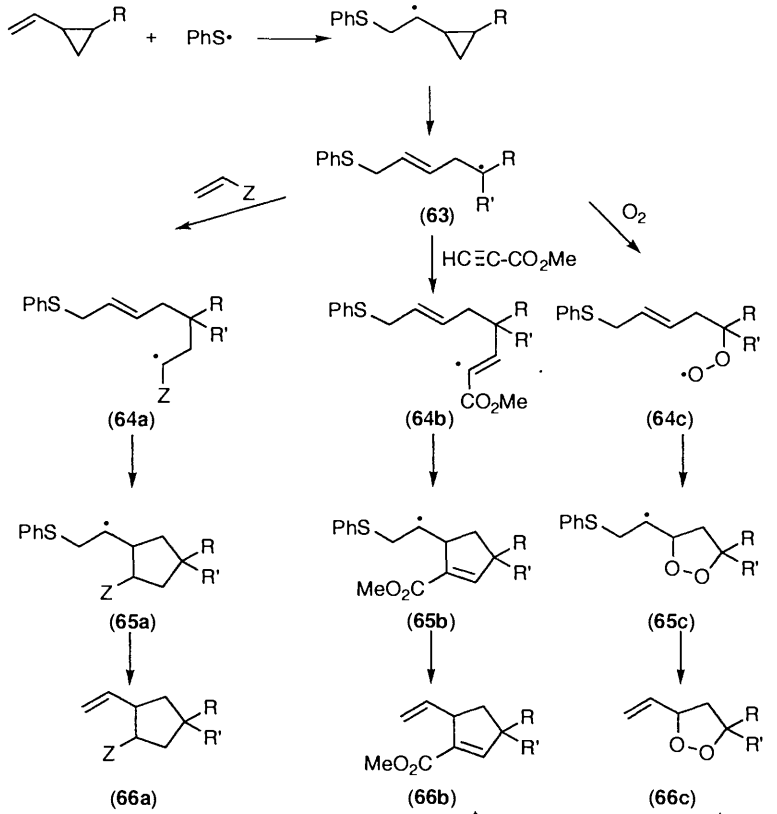
Addition of diphenyl disulfide to vinylcyclopropanes has been investigated. In the absence of thiol, the rearranged radical (63) can couple with a suitable substrate, *e.g.* an alkene, an alkyne or oxygen.[41] The addend radicals (64), which are hex-5-enyl radicals, then cyclize to give five-membered cyclic radicals (65), which finally undergo loss of the phenylthio radical to give respectively a cyclopentane (66a), a cyclopentene (66b), or a dioxolane (66c) (Scheme 26). The reactions work best when the alkene has an electron-withdrawing substituent and the cyclopropane ring an electron-donating group or *vice versa*. Under these circumstances the addition reaction involves an electrophilic radical and an electron-rich alkene, or a nucleophilic radical and an electron-deficient alkene. The products are obtained as a mixture of stereoisomers. This class of reaction is classified as a [3 + 2] radical addition. Using a similar sequence of reactions, [3 + 2] additions of alkenes to vinyloxiranes leads to tetrahydrofurans (Scheme 27).[41] It is necessary to use 2-aryl-3-vinyloxir-



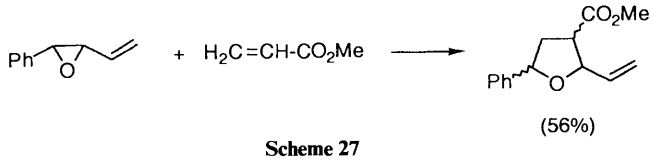
Scheme 24



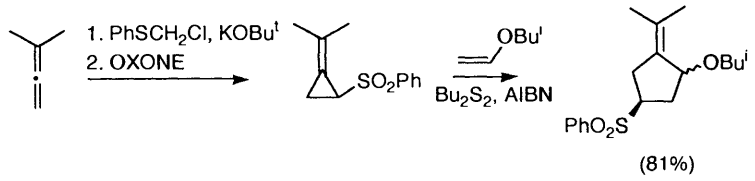
Scheme 25



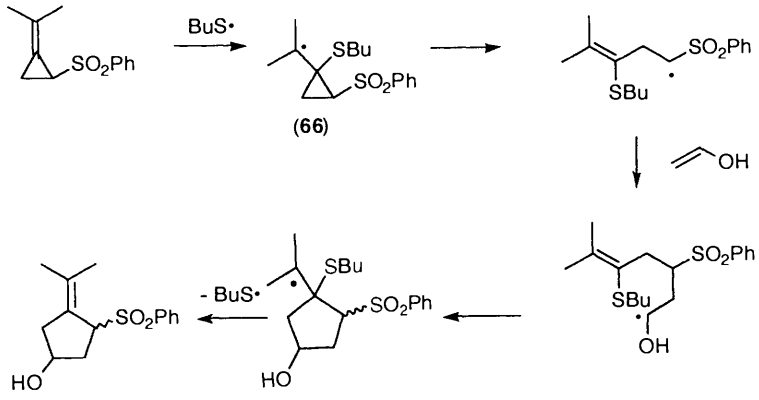
Scheme 26



Scheme 27



Scheme 28



Scheme 29

anes, which on radical addition undergo C—C and not C—O ring opening.

9.3 Syntheses of Alkylidencyclopentanes from Alkylidenecyclopropanes by [3 + 2] Additions

A variant on the [3 + 2] radical cycloaddition reaction involves the addition of alkylidenecyclopropanes to electron-rich alkenes (Schemes 28 and 29).[42] Radical addition to methylenecylopropane occurs at the cyclopropane end of the double bond, possibly reflecting the greater stability of the addend radical (66) due to the stabilizing influence of the cyclopropane ring. Trimethylsilyloxyl radicals add to the non-terminal carbon of methylenecyclopropane to give a primary cyclopropylmethyl radical, which immediately rearranges to the but-3-enyl radical, rather than the alternative tertiary cyclopropyl radical.

9.4 Synthesis of Cycloalkenes from Bicyclo[*n*.1.0]alkan-2-ols

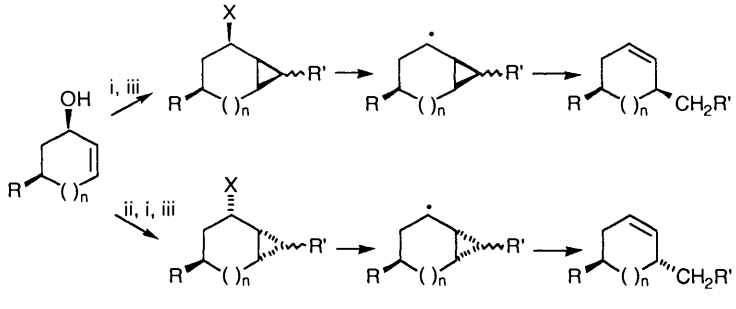
Cyclopropylcarbinols, which are readily accessible by a number of routes, can be converted, by radical deoxygenation and subsequent opening of the cyclopropane ring system, into alkyl-substituted cycloalkenes.[43] The procedure (Scheme 30) involves regioselective ring opening of cyclopropylcarbinyl radicals and allows placement of the substituent on either face of the starting material. Substrates containing the bicyclo[4.1.0]heptane unit open cleanly to give substituted cyclohexenes, whereas rearrangements of the corresponding bicyclo[3.1.0]hexan-2-ols were less selective, in keeping with the propensity of the intermediate bicyclo[3.1.0]hexan-2-yl radicals to undergo β-scission to give both five- and six-membered products. The reactions are more selective when there is an electron-withdrawing substituent at the non-bridgehead carbon of the cyclopropane ring (this facilitates the ring opening due to the enhanced stability of the ring-opened radical): in the absence of such a substituent it is necessary to carry out the reaction at low temperatures. This methodology was extended to the synthesis of benzofurans using an intramolecular addition of a remote radical centre to generate the cyclopropylcarbinyl radical (67) which then underwent ring opening (Scheme 31).[44]

9.5 Intramolecular Reactions of Allyloxyl and Allylaminyl Radicals

Allyloxyl and allylaminyl radicals, generated from oxiranylmethyl and 1-aziridinylmethyl radicals respectively (*cf.* Section 5), in the presence of a pendant alkenyl group undergo intramolecular cyclization to give tetrahydrofurans and pyrrolidines. Scheme 32 gives examples of these reactions based on geraniol.[45]

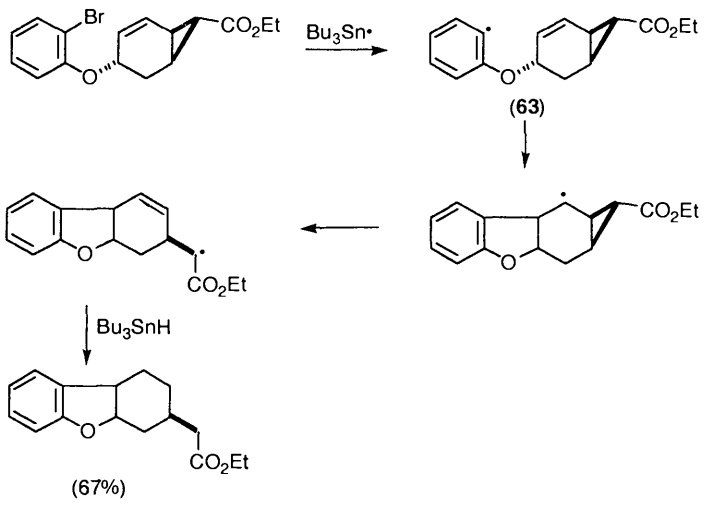
9.6 Radical Rearrangements *via* Intermediate Cyclopropyloxyl Radicals

An important method for one-carbon ring expansion is based on the formation of intermediate cyclopropyloxyl radicals (Scheme 33).[46] A (2-oxocycloalkyl)methyl radical (69), generated by reaction of a 2-(halogenomethyl)- or 2-(phenylselenomethyl)-

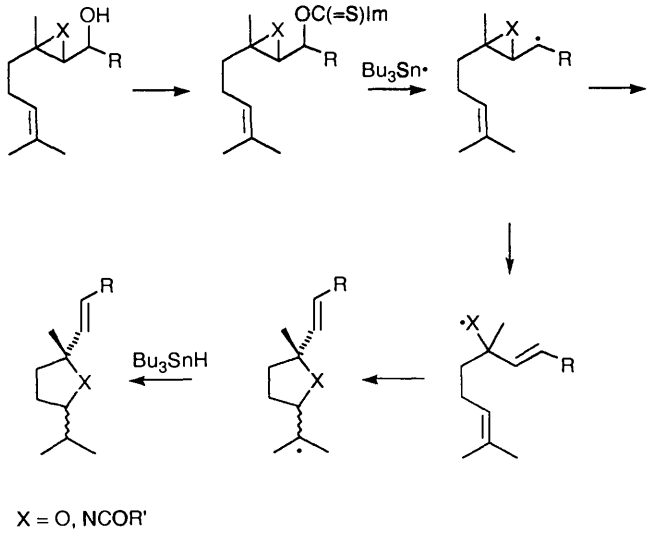


(i) Cyclopropanation, (ii) Mitsunobo inversion, (iii) X = OH → SePh, (iv) Ph_3SnH

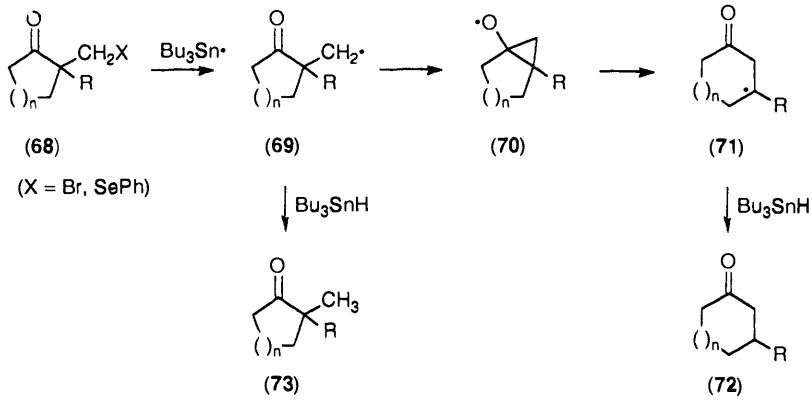
Scheme 30



Scheme 31



Scheme 32



Scheme 33

cycloalkanone (68) with a tin radical, cyclizes to give the bicyclic cyclopropyloxyl radical (70) which ring open to give the ring-enlarged radical (71). This, after hydrogen transfer, affords the ring-enlarged cycloalkanone (72). The overall reaction is effectively a 1,2-carbonyl migration. An essential requirement of the reaction is that the substituent R must be an electron-withdrawing group capable of stabilizing the rearranged radical (71). A competing reaction is the reduction of the initial radical to give the 2-methylcycloalkanone (73). This is the sole product in the absence of an electron-withdrawing substituent (R).

10 Conclusion

The topics covered in this review have been chosen to illustrate the breadth of the chemistry of cyclopropylmethyl radicals and their hetero analogues. It is not designed to be comprehensive.

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