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Skeletal and polycyclic sterically hindered alkenes

B M Lerman

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Abstract. Data on the chemistry of strained tetrasubstituted alkenes with skeletal and polycyclic fragments are surveyed. A systematic account is given of information concerning the methods of their synthesis and data are presented on the deformation of their molecular geometry relative to the usual geometry. The characteristic features of the reactivity of skeletal compounds of this type are considered—the formation of unusual adducts and substitution products in reactions with electrophiles. The oxidation reactions of the alkenes are discussed and their value as starting materials for the synthesis of stable dioxetanes, which have found practical application as chemiluminescent labels and probes in immunology and molecular biology, is demonstrated. The bibliography includes 152 references.

I. Introduction

Effective routes to the synthesis of many organic substances proceed via reactions involving addition to alkenes, and this has been a permanent stimulus for the expansion of the available range of the latter. Each year there is a growth in the number of new and saturated compounds involved in practical organic synthesis; apart from the usual, unstrained alkenes, strained compounds are beginning to be used with increasing frequency in synthesis, including sterically hindered alkenes (SHA). The atoms involved in the SHA double bond have substituents comprising bulky groups or strained fragments shielding the bond. The presence of such substituents induces a steric strain in the molecule and can lead to definite structural deformations. The group of SHA includes substituted ethenes with branched alkyl substituents, polycyclanes, and skeletal compounds with an exocyclic double bond incorporated in a rigid polycyclic system as well as alkylidenepolycyclanes with bulky substituents in the side chain, and α-octamethyl-substituted cycloalkylidenecyclanes.

SHA occupy a special place in the chemistry of unsaturated compounds. They are less readily available than the usual alkenes and their synthesis therefore constitutes an independent synthetic problem. The reactivity of the shielded double bond in SHA differs significantly from that of the corresponding bond in the usual alkenes; the specificity of the reactions involving it is also different, especially in the case of skeletal SHA.

The unusual chemical properties of skeletal SHA have attracted considerable attention by investigators during the last decade. Nevertheless, the chemistry of SHA was not duly described in the review[1] devoted to strained organic molecules; its individual aspects (as regards the state in 1977) have been examined by Tidwell[2] in a review of sterically hindered molecules. Even in the familiar review of the chemistry of alkenes[3] as well as monographs[4,5] and reviews[6–8] devoted to the chemistry of skeletal compounds, very little attention has been devoted to the chemistry of SHA.

In the present review, an attempt is made to survey data on the synthesis, structure, and chemical properties of polycyclic and skeletal SHA with a tetra-substituted double bond and also the applications of the dioxetanes obtained from these compounds (in the discussion of the limits of the applicability of synthetic methods, of the degree of deformation of the molecules, and of the relative strain in SHA, data on aliphatic and aromatic compounds are quoted).

II. Methods of synthesis of sterically hindered alkenes

Only a few of the synthetic approaches known for the usual alkenes are used to obtain SHA. These are mainly methods which lead to the creation of the carbon skeleton with simultaneous introduction of the double bond; they are based on the dimerisation (coupling) of ketones or their derivatives. Numerous modifications of these methods, involving a transition to increasingly more reactive synthons, have expanded their possibilities and have made many SHA available.

Another route to strained alkenes of this type is via the Diels–Alder synthesis. Novel methods of synthesis, involving elimination, the use of sulfur-containing synthons, the participation of organometallic reagents, etc. have been proposed for individual SHA.

1. Synthesis of sterically hindered alkenes by the reductive coupling of ketones (the McMurry method)

Certain steric SHA with a symmetrical structure can be obtained in one stage by the McMurry reaction via the intermolecular reductive coupling of ketones under the influence of low-valence titanium reagents.[9–12] The latter are obtained in situ from $TiCl_3$ or $TiCl_4$ on treatment with reductants and are used in the

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Table 1. Syntheses of sterically hindered alkenes by McMurry's method.

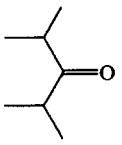
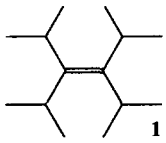
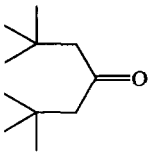
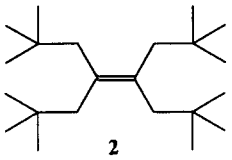
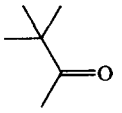
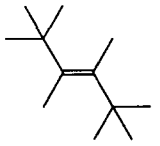
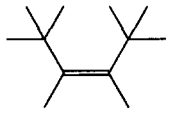
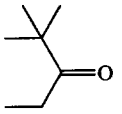
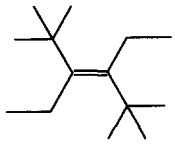
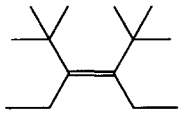
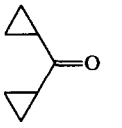
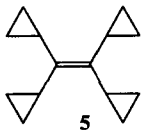
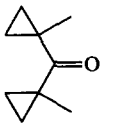
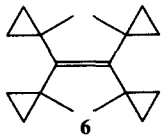
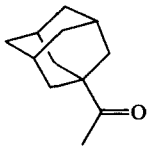
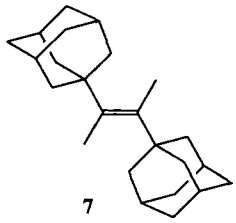
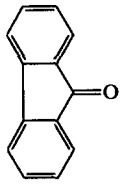
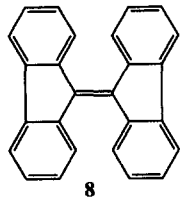
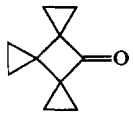
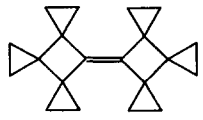
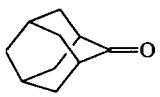
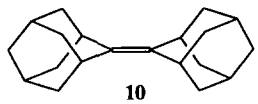
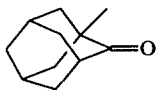
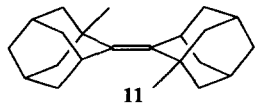
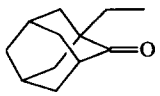
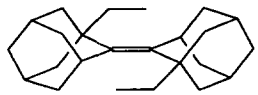
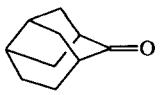
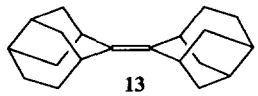
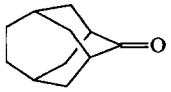
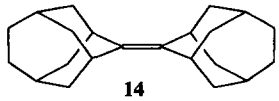
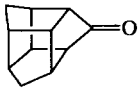
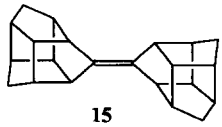
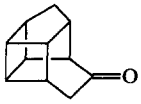
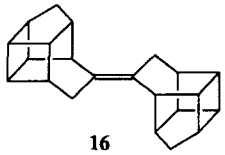
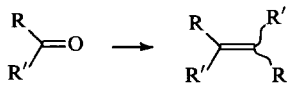
Initial ketone	Reaction product	Titanium reagent	Yield (%)	Ref.
	 **1**	$TiCl_3-K$	37	11, 14
		$TiCl_3-LiAlH_4$	12	15
		$TiCl_3-Zn-Cu$	87	12
	 **2**	$TiCl_3-LiAlH_4$	40	16
	 +  **3**	$TiCl_3-Zn$	68[a]	17
		$TiCl_4-LiAlH_4$	70[b]	18
	 +  **4**	$TiCl_3-LiAlH_4$	8[c]	19
	 **5**	$TiCl_4-Zn$	25	20
		$TiCl_3-LiAlH_4$	15	21
	 **6**	$TiCl_3-LiAlH_4$	13	22
	 **7**	$TiCl_4-Zn$	15	20
	 **8**	$TiCl_3-K$	85	11
		$TiCl_3-Mg-Hg$	-	23
	 **9**	$TiCl_3-LiAlH_4$	8	24

Table 1 (continued)

Initial ketone	Reaction product	Titanium reagent	Yield (%)	Ref.
	 **10**	$TiCl_3-LiAlH_4$	85	9
		$TiCl_3-K$	82	11
		$TiCl_3-Li$	91	11
		$TiCl_4-Zn$	98	25
	 **11**	$TiCl_3-K$	52	26
	 **12**	$TiCl_3-K$	40	27
	 **13**	$TiCl_3-K$	45	20, 28
	 **14**	$TiCl_3-K$	40	29
	 **15**	$TiCl_4-Zn$	51	30
	 **16**	$TiCl_3-LiAlH_4$	32	30

[a] The yield of the (*E*)-isomer is quoted; [b] *E* : *Z* is 1 : 1; [c] *E* : *Z* is 12 : 1.

form of $TiCl_4-Zn$, $TiCl_3-K$, $TiCl_3-Li$, $TiCl_3-LiAlH_4$, etc. systems.†

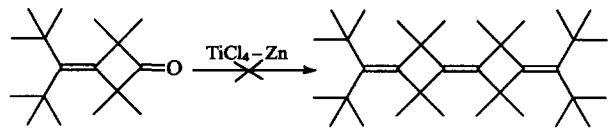


The tetraalkylethenes **1**–**7** and the polycyclic and skeletal alkenes **8**–**16** have been synthesised in this way. The reagents employed for the synthesis of the alkenes and the yield of the latter are presented in Table 1. It is seen from the table that the method is particularly effective for the synthesis of adamantylideneadamantane (2,2′-bisadamantylidene) **10**, for which an almost quantitative yield has been achieved. The yield of other SHA depends significantly on the extent to which the double bond is sterically hindered, diminishing with increasing branching of the substituents at the bond itself (tetrasubstituted ethenes) or following the introduction of alkyl substituents in the α-position relative to the bond (dialkyladamantylideneadamantanes). The choice of the system as a whole — the nature of the reductant and the solvent — has a significant influence on the yield of the SHA. This can be seen in relation to 1,1,2,2-tetraisopropylethene **1** and adamantylideneadamantane **10**. High stereoselectivity — the formation of only the *trans*-isomer — is characteristic of reactions leading to dimethyladamantylideneadamantane **11** and diethyladamantylideneadamantane **12**. The ratio of the (*E*)- and (*Z*)-isomers of 1,2,-di-*tert*-butyl-1,2 dimethylene **3** depends on the nature of the reductant.

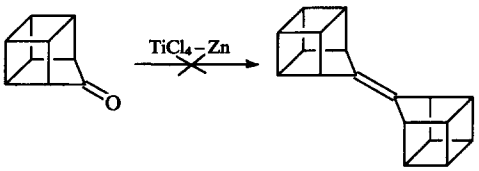
The limitations of the method are associated mainly with the difficulty of the introduction into the reductive coupling reaction of ketones with branched alkyl substituents — *tert*-butyl isopropyl ketone, di-*tert*-butyl ketone, *tert*-butyl neopentyl ketone,[16] and also 3-(di-*tert*-butylmethylene)-2,2,4,4-tetramethylcyclobutanone **17**.[31]

The attempt to achieve the single-stage synthesis of the diskeletal alkene **18** from homocubanone was unsuccessful.[32]

† Various aspects of the preparation of these reagents, the mechanisms of their action, and their applications in organic synthesis have been described in Lenoir's review.[13]

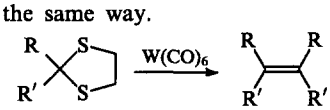


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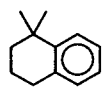
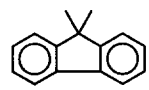


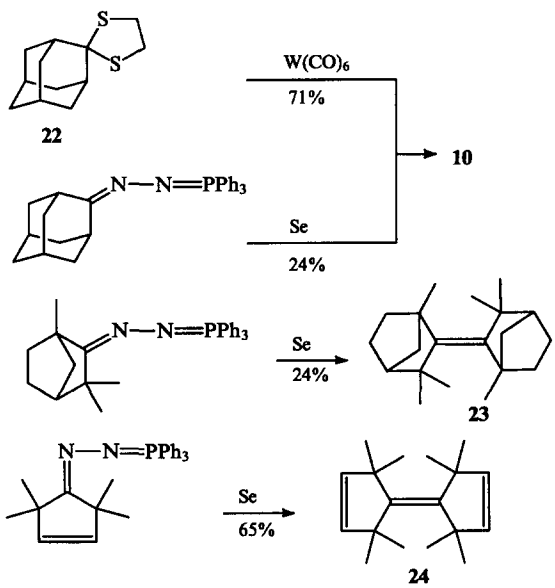
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Together with the reductive coupling of the ketones themselves, examples of similar reactions have been described for the thio- and seleno-derivatives. Thus the desulfurisation of aromatic dithioketals by $W(CO)_6$ leads to the corresponding alkenes **19–21**, while the analogous reaction of the adamantanone dithioketal **22** affords adamantylideneadamantane **10**.[33] The latter has also been obtained in the reaction of adamantanone triphenylphosphorylidenehydrazone with selenium. Fenchylidenefenchane **23** [34] and 1,1′-bis(2,2,5,5-tetramethylcyclopent-3-enylidene) **24** [35,36] have been synthesised in the same way.



19–21

R, R′ = Ph, Me (**19**);  (**20**);  (**21**)



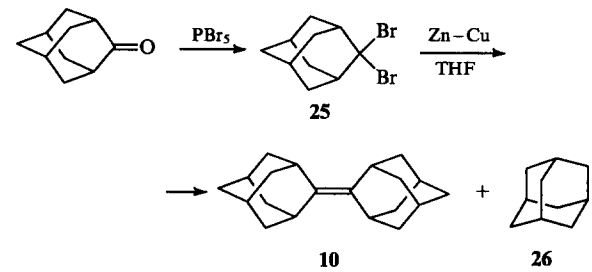
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2. The 'carbenoid' method of synthesis of sterically hindered alkenes

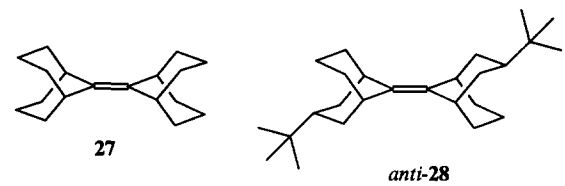
The synthesis of one of the best known SHA—the alkene **10**—from adamantanone via 2,2-dibromoadamantane **25** with subsequent debromination of the latter by the zinc–copper couple has been proposed by Geluk.[37] This method was used widely for a long time as a preparative procedure. The low yield of adamantylideneadamantane (60%–75%) owing to the side reaction **25**→**26** in the second stage and the need for the numerous repetitions of this stage must be regarded as its disadvantages. The yield of the target product depends on the quality of the zinc and the activity of the zinc–copper couple. Subsequently this method came to be called the 'carbenoid' method.



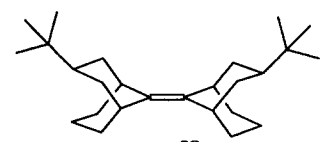
25

10 26

Bis(bicyclo[3.3.1]non-9-ylidene) **27** as well as its di-*tert*-butyl derivative **28** have been synthesised similarly in the form of a mixture of two stereoisomers.[39]

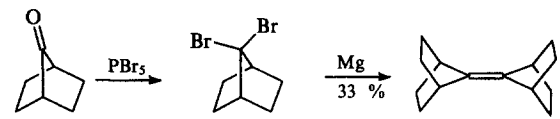


27 *anti*-**28**

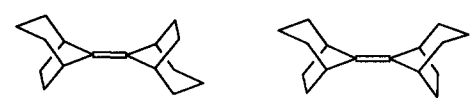


syn-**28**

The use of magnesium instead of the zinc–copper couple made it possible to increase the yield of the alkene **10** to 83%.[40] Bis(bicyclo[2.2.1]hept-7-ylidene) **30** [40] and bis(bicyclo[3.2.1]oct-8-ylidene) **31** have been synthesised in the same way in the form of a mixture of the *syn*- and *anti*-isomers.[41]

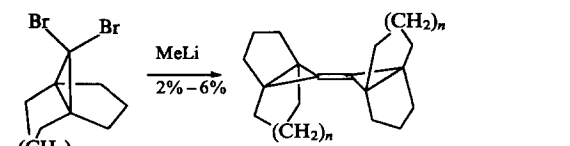


29 30

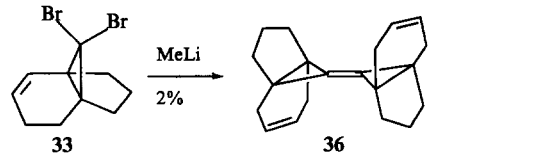


anti-**31** *syn*-**31**

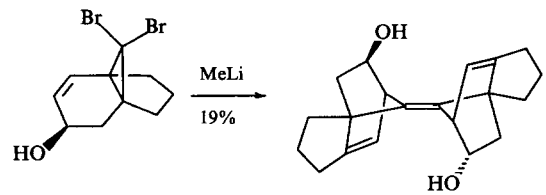
The SHA **35–37** are formed as side products (2%–19%) in the reactions of MeLi with *gem*-dibromo-substituted tricyclanes and tricyclenes with the propellane structure. The carbene dimers **35a, b** and **36** with fragments of the initial propellane structure have been obtained from the corresponding dibromo-derivatives **32a, b** and **33**, while the dimer **37** with a rearranged structure has been synthesised from the dibromo-derivative **34**. The structure of the dimer **37** has been confirmed by X-ray diffraction.[42,43]



32a, b **35a, b** *n* = 1 (**a**), 2 (**b**)



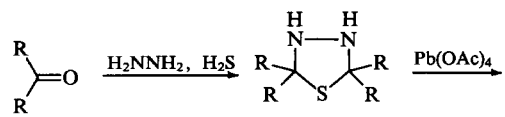
33 36



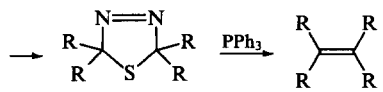
34 37

3. Double elimination (the thia- and selena-diazoline method) in the synthesis of sterically hindered alkenes

The thiadiazoline method has been used to obtain a series of asymmetric and strained symmetrical SHA. The method is based on the double elimination principle proposed by Barton and Willis[44] — the elimination of nitrogen and sulfur from synthons having the general formula **B**.[44]

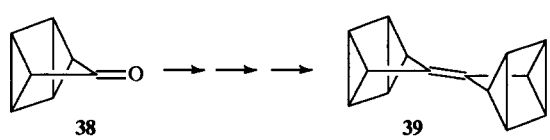


A



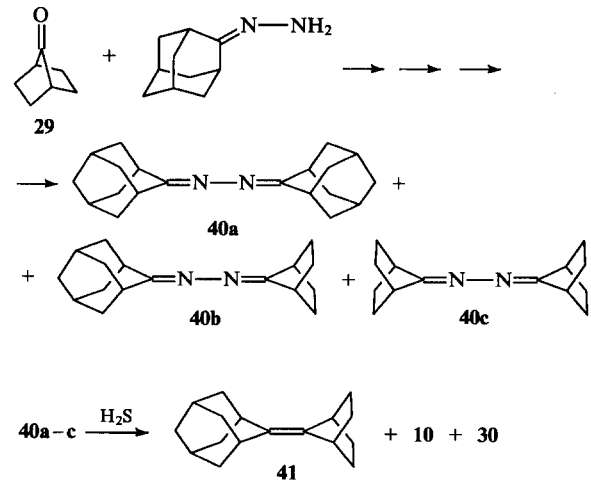
B

In the version proposed initially, the thiadiazolidine **A** was obtained from the corresponding ketone by treatment with hydrazine or H_2S (or as a result of the treatment of an azine by the latter). The oxidation of compound **A** by $Pb(OAc)_4$ led to Δ^3-1,3,4-thiadiazoline **B** and the latter was converted by treatment with PPh_3 into the alkene. Bisquadricyclene **39** has been synthesised[45] by this procedure from the ketone **38** as well as a series of symmetrical alkenes: the yield of the alkene **10**, obtained by the thiadiazoline method, is then the same as that of the products synthesised by the carbenoid method,[46] while the yield of the alkenes **27**, **28**, and **30** is significantly lower.[39]



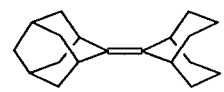
38 **39**

The use of the thiadiazoline method in order to obtain asymmetric alkenes has been demonstrated in relation to bicyclo[2.2.1]heptylideneadamantane.[41] The mixture of the azines **40a–c** formed on interaction of the ketone **29** with adamantanone hydrazone was treated with hydrogen sulfide and then oxidised and subjected to the elimination reaction. The alkene **41** was isolated by preparative gas–liquid chromatography (GLC) from its mixture with the alkenes **10** and **30**.



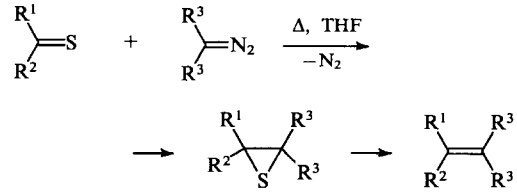
41

Bicyclo[3.3.1]nonylideneadamantane **42** has been obtained similarly.[39]

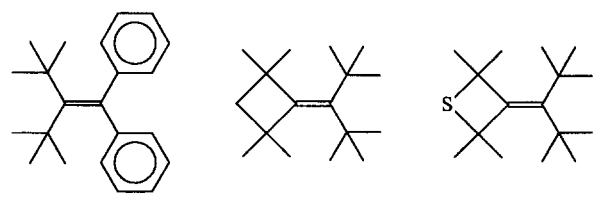


42

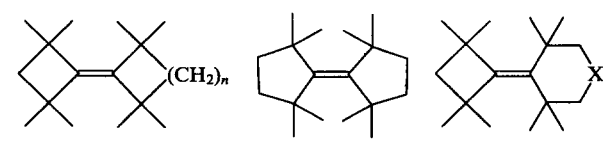
Certain more hindered asymmetric alkenes, which could not be obtained in accordance with the scheme indicated above, have been synthesised via a two-stage version in which a thione and a diazo-compound were used as synthons.[47]



The strained di-*tert*-butyldiphenylethene **43** has been obtained by this procedure from di-*tert*-butyl thioketone and diphenyldiazomethane (or from thiobenzophenone and di-*tert*-butyldiazomethane).[48] This route proved to be effective also for the synthesis of strained SHA such as 1,1,2,2-tetra(methylcyclopropyl)ethene **6**,[49] 2-(di-*tert*-butylmethylene)-1,1,3,3-tetramethylcyclobutane **44** and its thia-analogue **45**,[50] the keto-alkene **17**,[31] the octamethylbicycloalkylidenes **46–50** and their hetero-analogues **51–53**, the cycloalkylideneindans **54** and **55**, the triene **24**,[52,53] cyclobutylidene-Δ^1-pyrazoline **56**, and di(Δ^1-pyrazolylidene) **57**.[54,55]



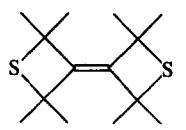
43 **44** **45**



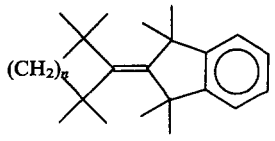
46–49 **50** **51, 52**

n = 1 (**46**), 2(**47**), 3(**48**), 4(**49**)

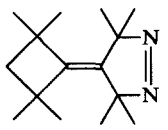
51: X = S,
52: X = O



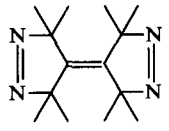
53



54, 55
54: n = 1,
55: n = 2

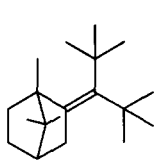


56

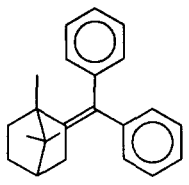


57

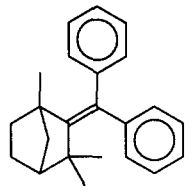
Di-*tert*-butylmethylenecamphane **58** has been obtained by means of this two-stage scheme from (±)-thiocamphor and di-*tert*-butyldiazomethane, while (±)-diphenylmethylenecamphane **59** has been obtained from the same thione and diphenyldiazomethane.[47] (±)-2-Diphenylmethylenefenchane **60**[48] and its individual (+)- and (−)-forms[47] as well as camphenylidenetetramethylcyclobutane **61**, camphenylideneadamantane **62**, adamantylidenecamphane **63**, camphenylidenecamphenylene **64**,[56] and the alkene **23**[52,53] have been synthesised similarly.



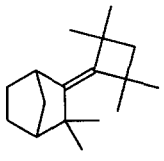
58



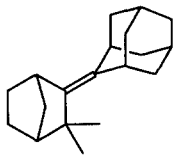
59



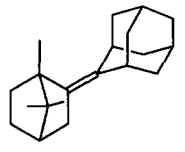
60



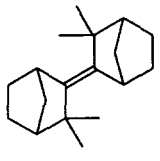
61



62



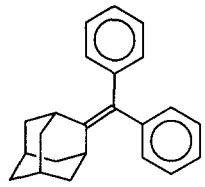
63



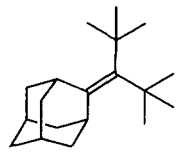
64

A series of methyleneadamantanes such as diphenylmethyleneadamantane **65**[57] and di(*tert*-butylmethylene)adamantane **66**,[58] adamantylidenefluorene **67**,[58] and adamantylidene-*N*-methylacridine **68** have been synthesised in accordance with the same scheme.[59]

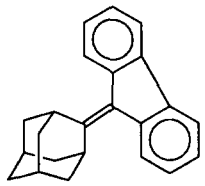
The preparation of the adamantane **66** in the thiadiazoline decomposition stage is complicated by the formation of adamantylideneadamantane **10**, the content of which in a mixture with the adamantane **66** reaches 53%.



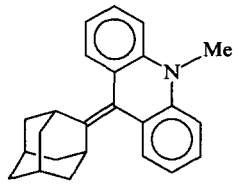
65



66

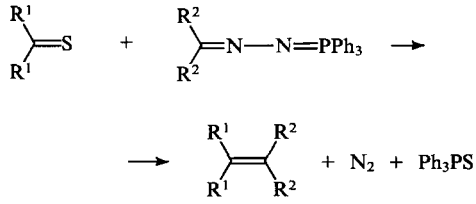


67

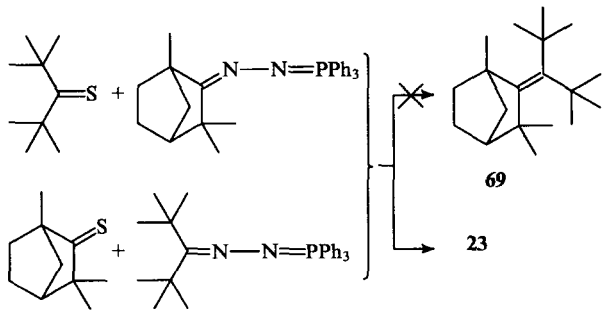


68

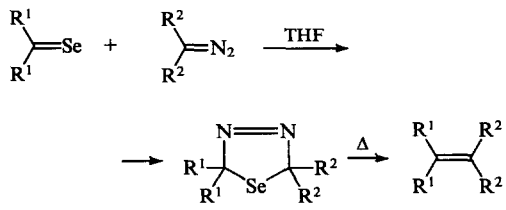
The possibility of using phosphorylidenehydrazones instead of diazo-compounds in the reactions considered has been demonstrated in the synthesis of the alkenes **58**–**60**. This version makes it possible to obtain the alkenes **58**–**60** in one stage but the yield of the product is then lower than in the two stage synthesis via diazo-compounds.[47]



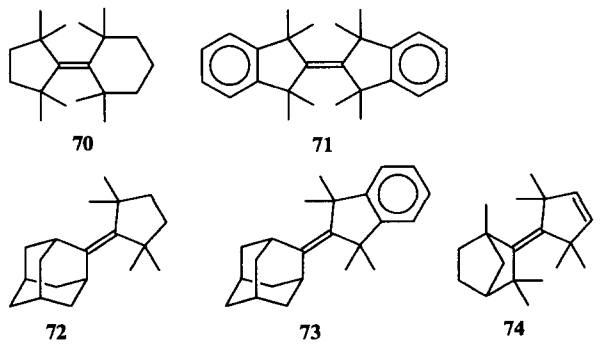
The attempts to obtain the strained di-*tert*-butylmethylenefenchane **69** in this way were unsuccessful and only the alkene **23** was isolated.[47]



The selenadiazoline method proved to be effective for the synthesis of a series of SHA which could not be obtained by the thiadiazoline procedure. The corresponding thia- and selenadiazolines are formed under the same conditions. More severe conditions are necessary for the synthesis of the alkene **42** from the thiadiazoline than for its synthesis from the selena-analogue.[60]

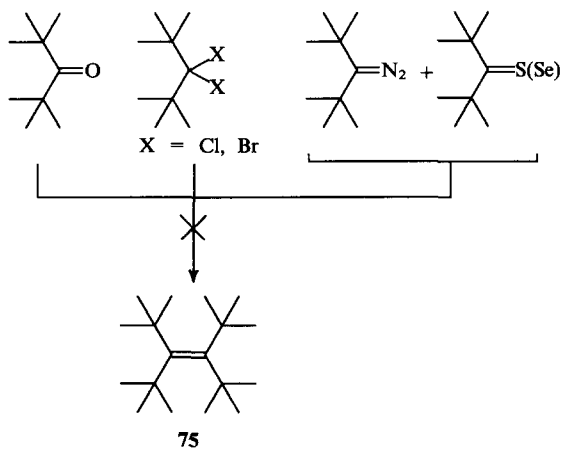


The alkene **24**,[36] the octamethylbicycloalkylidenes **70** and **71**,[51] and the adamantane-containing alkenes **72** and **73**[39] have been synthesised by means of the selenadiazoline method. The preparation of 1,1'-bis(2,2,5,5-tetramethylcyclopent-3-enylidene)fenchane **74** by the procedure indicated is complicated by the formation of side products (60%) — the alkene **23** and the triene **24**.[36]



70 **71** **72** **73** **74**

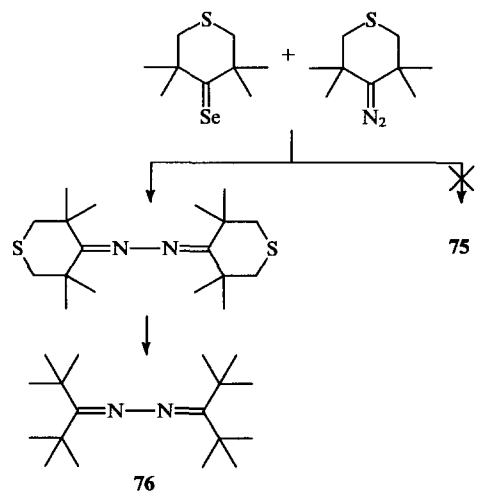
However, the attempt to obtain strained tetra-*tert*-butylethene **75** by the methods indicated above proved unsuccessful.[36,47,48,51,52] The alkene **75** could not be synthesised by the photolytic decomposition of di-*tert*-butyldiazomethane either.[61]



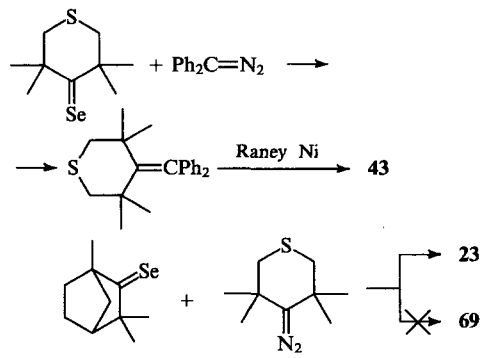
75

The unusual strategy combining the selenadiazoline method and the use of sulfur-containing synthons (synthons bound 'from the rear') also failed to afford the alkene **75**: instead of alkene **75**, the di-*tert*-butyl ketone azine **76** was isolated. This approach had been used successfully in a previous synthesis of the alkene **43**.

The sterically hindered alkene **69** could not be synthesised by this procedure either and the alkene **23** was obtained instead.[62]



76

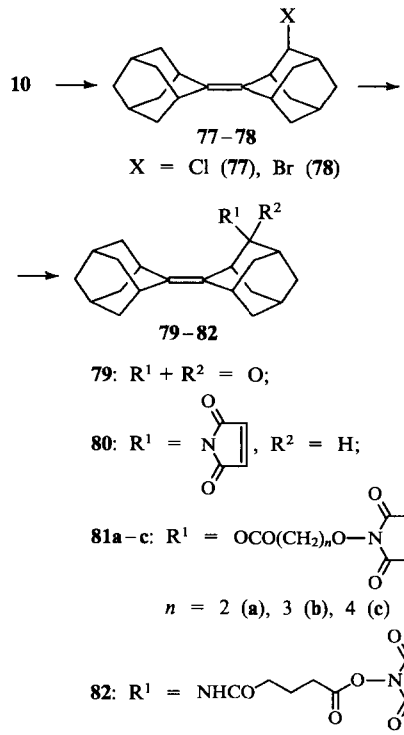


Thus the synthesis of compound **75** still remains an attractive and hitherto unattained aim.

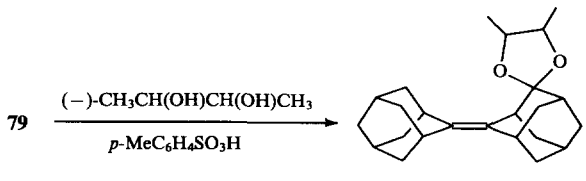
4. Syntheses as a result of the modification of sterically hindered alkenes

Certain alkenes, which can be obtained by the methods examined above, served in their turn as precursors in the synthesis of more strained SHA. Thus a series of 4-substituted adamantylideneadamantanes have been obtained from adamantylideneadamantane **10** in accordance with schemes involving the halogenation of the alkene **10** with formation of 4*e*-haloketenes **77** and **78**[63,64–67] and further synthetic transformations in the side chains. The ketoalkene **79**[63] and the maleimido-derivatives **80**, **81a–c**, and **82** have been obtained in this way (see Scheme 1).[68]

Scheme 1

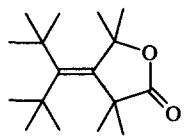


A mixture of the diastereoisomeric ketals (+)-**83** and (−)-**83** has been synthesised from the ketalkene **79** and the optically active pure (−)-butane-2,3-diol. The ketal (−)-**83** was isolated from this mixture with 95% purity.[69]

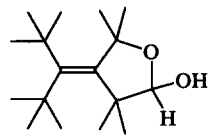


(+)-**83**, (−)-**83**

Highly strained di-*tert*-butylalkenes with lactone (compound **84**) and lactol (compound **85**) fragments have been obtained from the ketoalkene **17** via ring expansion reactions.[31]



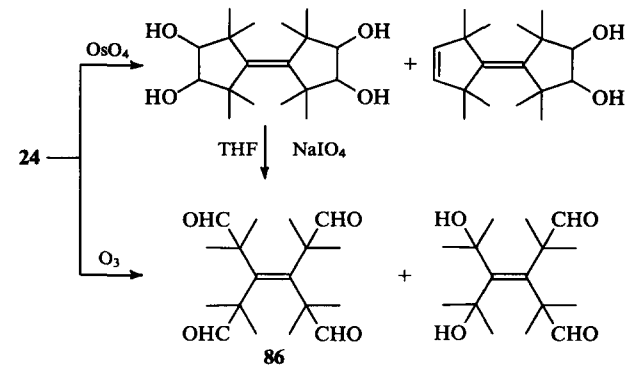
84



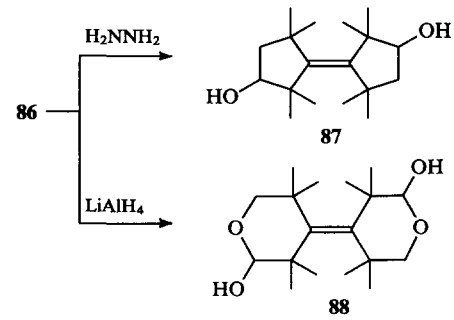
85

In the search for approaches to the hypothetical alkene **75**, the triene **24** has been used as the synthon. The triene was converted into the tetraaldehyde **86** by ozonolysis or hydroxylation with subsequent oxidative ring opening. The attempts to convert the tetraaldehyde **86** into the alkene **75** were unsuccessful and only the dilactol **87** and the diol **88** were obtained.[52,53]

A series of SHA without quadricyclane fragments have been obtained from bisquadricyclylidene **39**. The transformation of one or both quadricyclane fragments into methylenenorbornene fragments was achieved via the diene synthesis reaction employing dienophiles such as dimethyl ethynedicarboxylate [acetylenedicarboxylate (DEAC)], dicyanoethyne, maleic anhydride, vinylidene carbonate, and dimethyl azodicarboxylate (see Scheme 2). The 1:1 adducts **89–92** and the 2:1 adducts **93–98** obtained constitute two new structural types of SHA. In addition, SHA of a third structural type (compound **99**) can be obtained from the 1 : 1 adducts as a result of the isomerisation of the quadricyclane fragment to the norbornadiene fragment.[70]



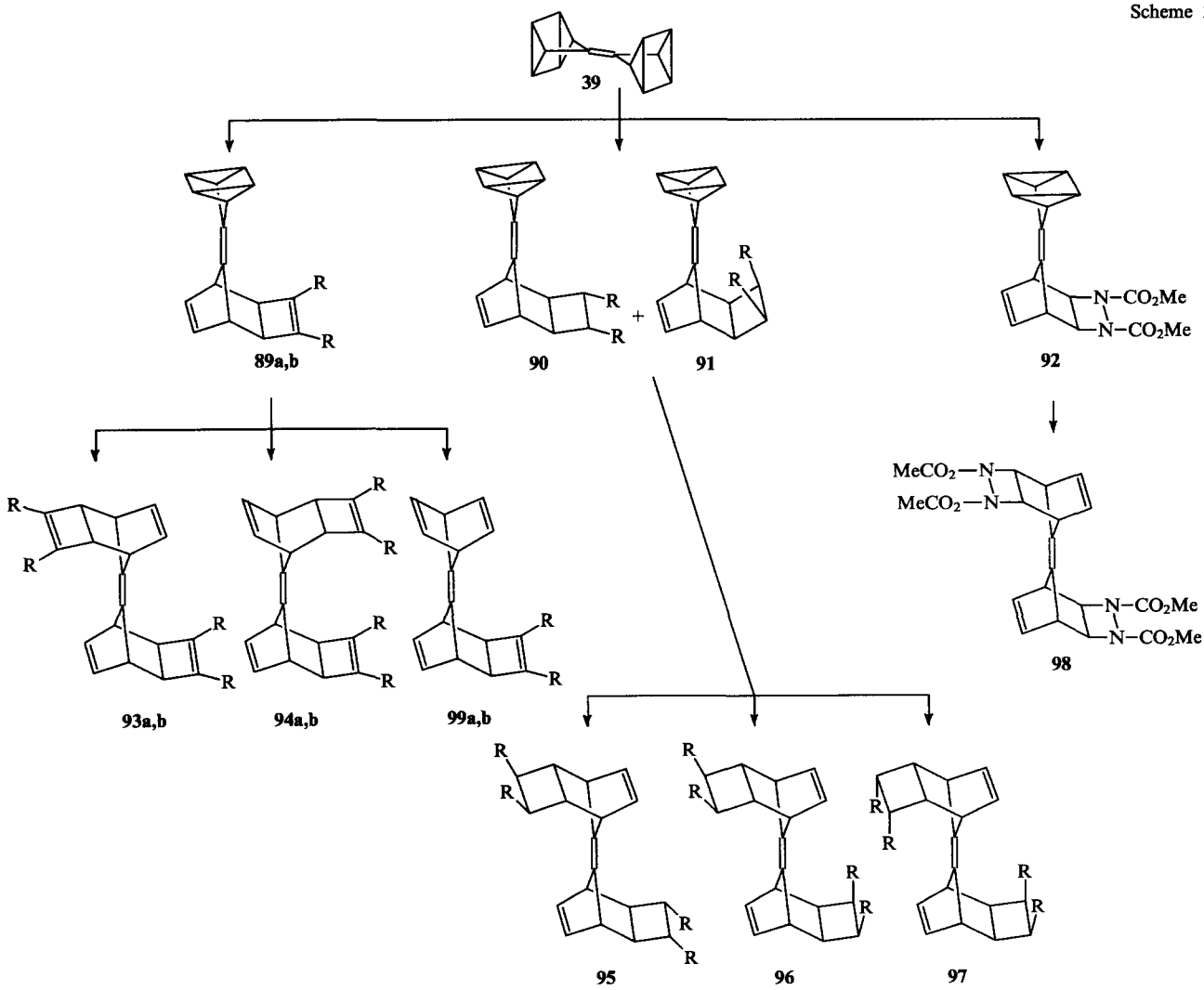
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87

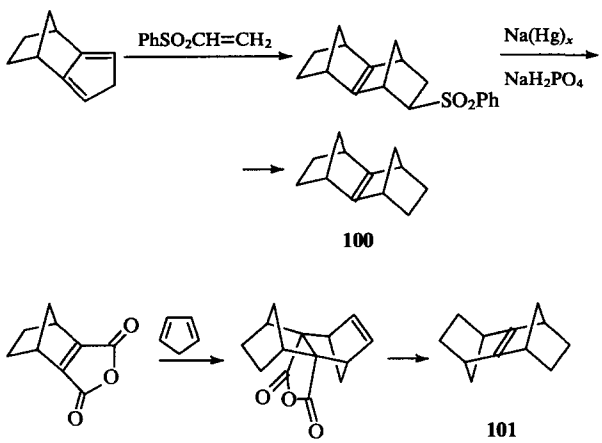
88

Scheme 2



5. Sterically hindered alkenes obtained by diene synthesis with participation of 1,3-dienes and fulvenes

The syntheses of SHA based on the diene synthesis reactions of cyclo-1,3-dienes and skeletal fulvenes with various dienophiles are considered in this subsection. *syn*-Sesquinorbornene **100** and *anti*-sesquinorbornene **101** have been obtained in this way. The scheme for the synthesis of the norbornene **100** includes the stereospecific cycloaddition of phenyl vinyl sulfone to isobicyclopentadiene and the subsequent reductive desulfonation of the adduct.[71,72] The alkene **101** was synthesised by the cycloaddition of cyclopentadiene to the anhydride of norbornenedicarboxylic acid and the subsequent hydrogenation and decarboxylation of the adduct.[73]



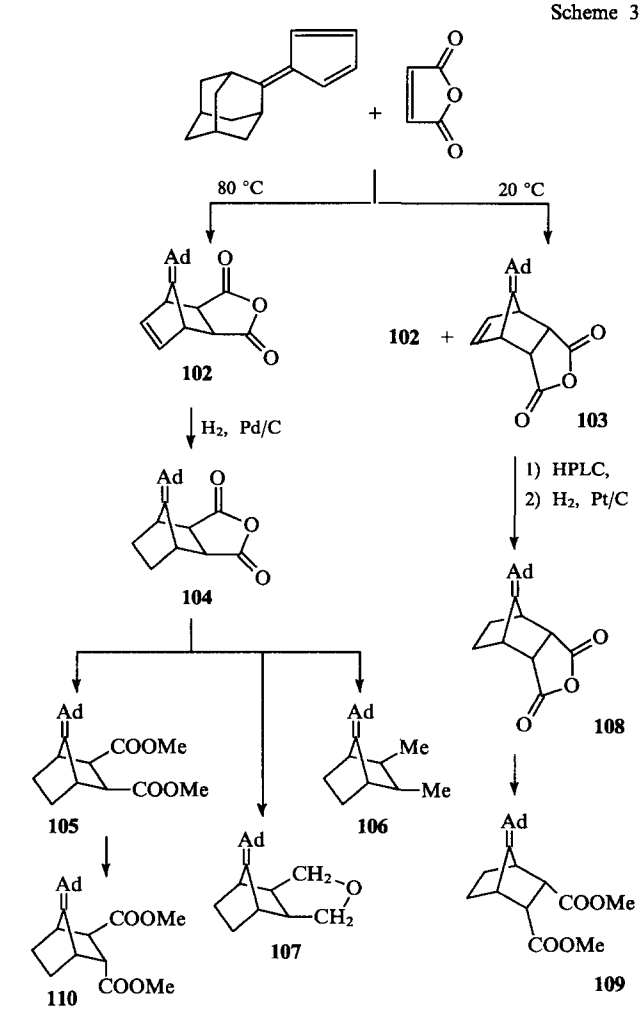
The second group of SHA which can be obtained by diene synthesis comprises asymmetric alkenes with functional-group substituents and an exocyclic double bond incorporated in the polycyclic and skeletal fragments. These compounds are obtained from skeletal fulvenes. When maleic anhydride is used as the dienophile, the monocyclic fragment in the above fulvenes is built up to the norbornene fragment and when the dienophile is DEAC or hexafluorodimethylethyne, it is built up to the norbornadiene fragment. Further synthetic transformations of the adducts (hydrogenation, photocyclisation) make it possible to achieve a transition to SHA with norbornane and quadricyclane fragments respectively.

A series of isomeric 2,3-disubstituted 7-adamantylidenenorbornanes have been obtained in accordance with the scheme involving the diene synthesis reaction of cyclopentadienylideneadamantane with maleic anhydride (Scheme 3). The *exo, exo*-adduct **102** is formed at 80 °C, while a mixture of the *exo, exo*- and *endo, endo*-isomers **102** and **103** in proportions of 1 : 1 is produced at 20 °C. Subsequently, the *endo, endo*-isomer is isolated from the mixture. The alkenes **104**–**107** can be obtained from the *exo, exo*-adducts as a result of appropriate synthetic transformations, while the alkenes **108** and **109** can be formed from the *endo, endo*-adducts. The isomerisation of the *exo, exo*-diester **105** leads to the formation of the *exo, endo*-diester **110**.[74]

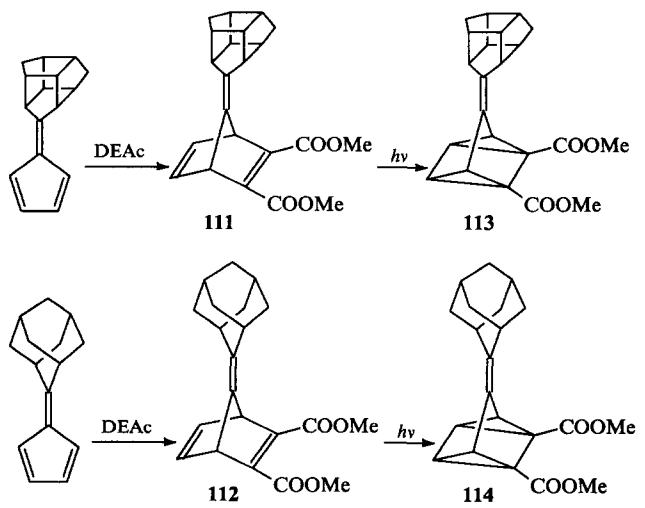
The biskeletal trienes **111** and **112** have been obtained by the diene synthesis reaction of DEAC with the corresponding skeletal fulvenes. The subsequent photocyclisation of the trienes **111** and **112** leads to the SHA **113** and **114** with a quadricyclane fragment.[75]

The reactions of tetrasubstituted cyclopentadienylidenequadricyclanes **115a, b** with DEAC or hexafluorodimethylethyne are accompanied by the isomerisation of the quadricyclane fragment and lead to mixtures of the corresponding isomeric SHA (**116a, b** + **117a, b**) with the bisnorbornadiene structure. The subsequent photocyclisation in one or both norbornadiene fragments leads to polysubstituted derivatives of quadricyclylidenenorbornadiene (**118a, b**) and bisquadricyclylidene

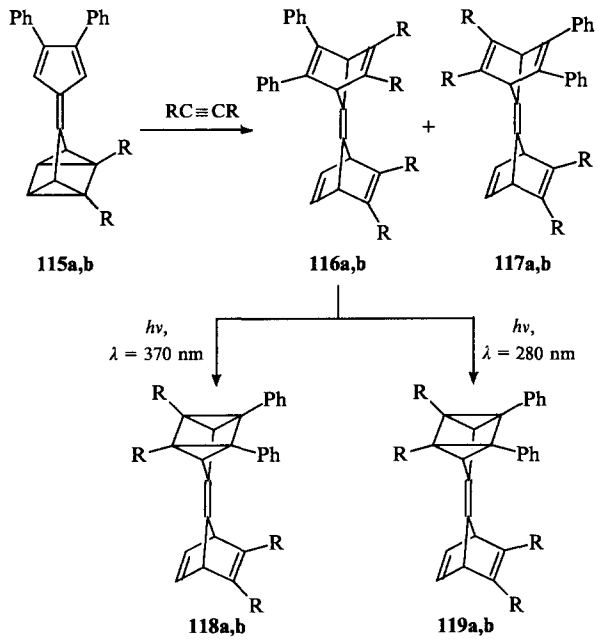
Scheme 3



Here and henceforth the designation Ad has been retained for adamantylidene

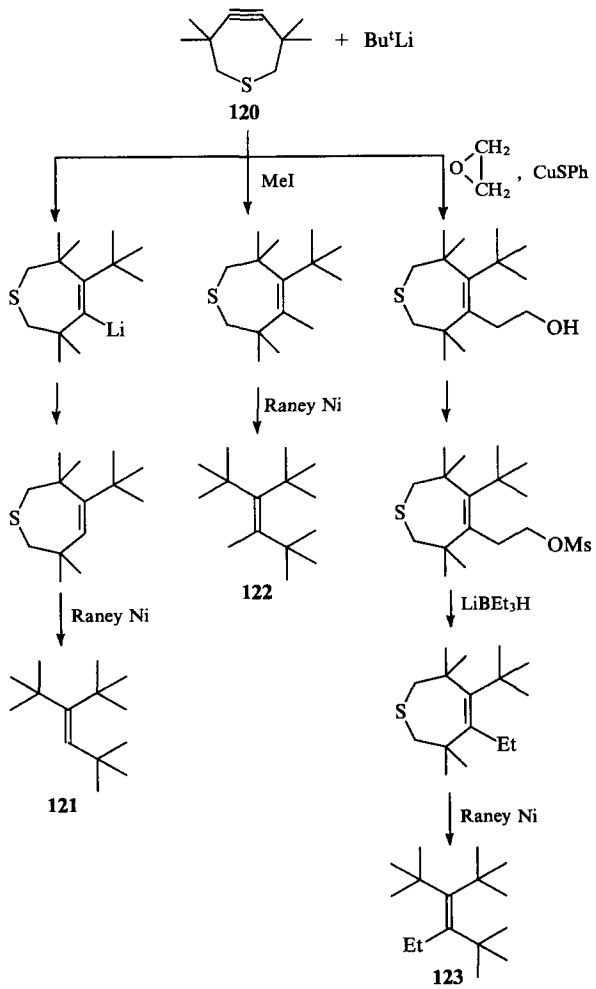


(**119a, b**) respectively.[46] We have already spoken above about the involvement of similar adducts in diene synthesis with formation of new SHA.

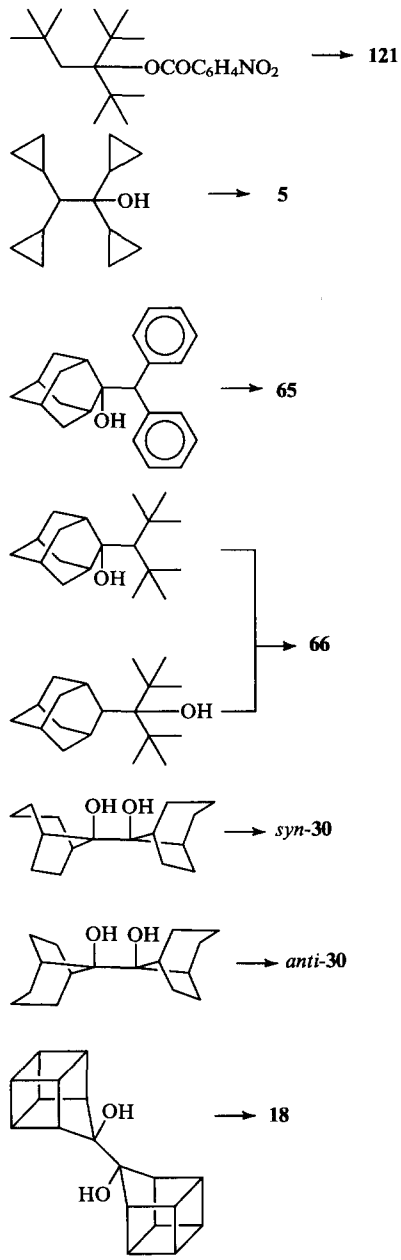


6. Other syntheses

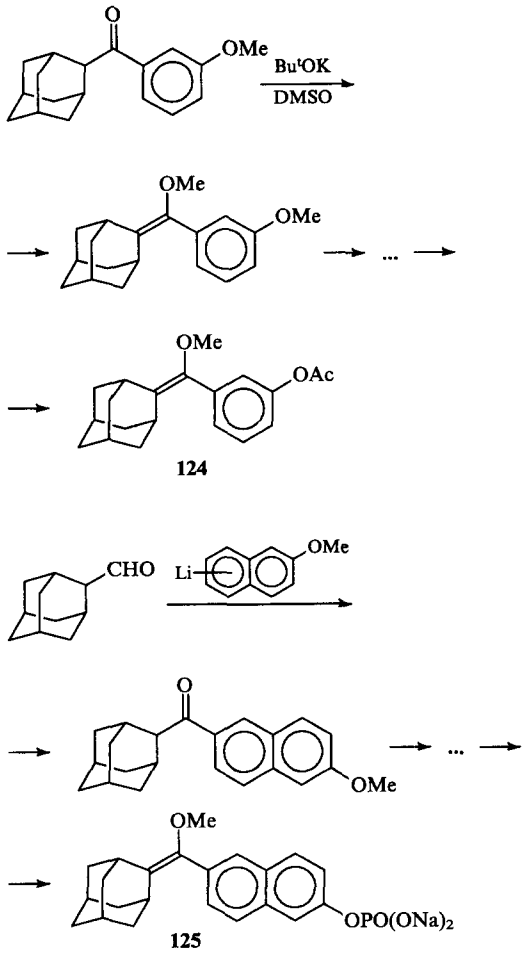
Other synthetic approaches, different from those examined above, have been proposed for certain types of SHA or their individual representatives. Thus tri-*tert*-butylethene **121** and its homologues **122** and **123** have been synthesised from the sulfur-containing synthon **120** in accordance with the schemes below:[52,53]



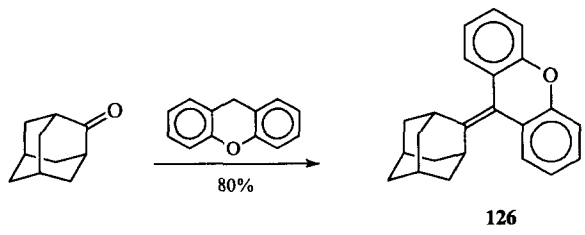
The syntheses of a series of SHA, including reactions involving the elimination of hydroxylated intermediates or their derivatives, have been described. Thus the alkene **121** has been obtained by the pyrolysis of the branched tetradecyl *p*-nitrobenzoate,[76,77] the alkenes **5**, **65**, and **66** have been synthesised by the dehydration of the corresponding carbinols,[78,79] and the *syn*- and *anti*-alkenes **30** and the biskeletal alkene **18** have been prepared by the dehydroxylation of diols.[32,41]



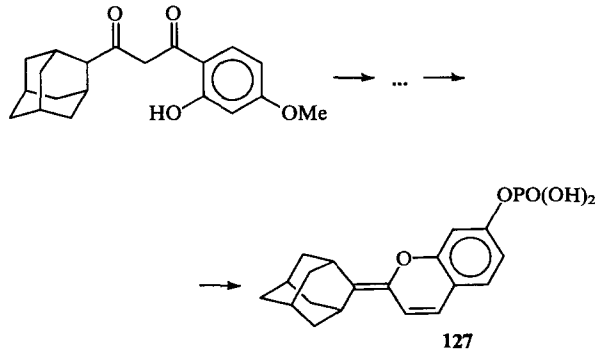
The synthesis of methoxyarylmethylideneadamantanes (enol ethers), based on the *O*-alkylation reaction of adamantyl allyl ketone, is presented below in relation to 2-[methoxy-(3′-acetoxyphenyl)methylidene]adamantane **124**[80] and the disodium salt of 2-[methoxy-(6′-phosphoryloxy)-2-naphthylmethylidene]adamantane **125**.[81]



9-Xanthylideneadamantane **126** has been obtained in one stage from adamantanone and xanthene by the Peterson reaction involving conversion into an alkene.[82]



The scheme for the synthesis of adamantylidenechromene phosphate **127** includes intramolecular cyclisation in the corresponding diketone as the key stage.[83]



III. Geometrical and thermodynamic parameters of sterically hindered alkenes

The presence in SHA of bulky substituents at the double bond or the incorporation of the latter in a rigid polycyclic system lead to appreciable intramolecular repulsive interactions and hence to a significant steric strain. The study of the influence of this factor on the structural parameters and thermodynamic characteristics of SHA is of considerable theoretical interest.

X-Ray diffraction data for strained SHA are presented in Table 2 (see next page). These compounds have a distorted (compared with the usual alkenes) molecular geometry primarily in the geometry of the double bond, the bond itself being extended up to 1.358 Å (in ethene, the bond length is 1.313 Å). Furthermore, the C–C bonds adjoining the double bond are lengthened and the angles are distorted. In the most strained SHA the double bond is twisted and the largest values of the torsional angle (24.0° – 37.5°) are characteristic of alkenes with *tert*-butyl substituents and of compound **86** — a structural analogue of the hypothetical tetra-*tert*-butylethene (for the latter, this value can be 44° according to calculated data). According to the same data, the structural analogues of the alkene **75** — the polysubstituted cycloalkylidenecycloalkanes **46** – **57** — are significantly less strained (Table 3, see p. 14). Evidently, the degree of structural deformations in this series depends on the structure of the cyclic fragments in which the double bond has been included.

There are considerable synthetic difficulties which must be overcome on the way to individual representatives of SHA. The failure of the attempts to synthesise the alkane **75** aroused considerable interest in the thermodynamic parameters of SHA. Calculations have been made of the strain energies and enthalpies of formation of a series of polyalkyl-substituted ethenes, adamantanes, and adamantylideneadamantanes (Table 4, see page 15). As can be seen, in the series of skeletal alkenes it is possible to trace clearly an increase in the energy of the double bond due to the increase in the degree of substitution in the admantane ring.

IV. Reactions of sterically hindered alkenes

The structural characteristics of SHA are responsible for the significant differences in the chemical behaviour of these compounds compared with the usual alkenes. Thus the successful hydrogenation of the double bond in SHA has been described only in relation to the alkene **121**.[95] Many alkenes of this type are inert to electrophiles; skeletal SHA are an exception, but their reactions lead as a rule to products other than those of the analogous reactions of the usual alkenes. Thus SHA with a highly shielded double bond are inert to oxidising agents; the ozonisation of skeletal SHA leads to epoxides instead of ozonides.

1. Reactions of skeletal sterically hindered alkenes with electrophiles

In most of the studies of the reactions of SHA with electrophiles, the synthetically available adamantylideneadamantane **10** was used as the model compound. Only individual examples of the involvement of other skeletal SHA in the reaction under discussion have been described.

Table 2. Torsional angles and bond lengths in sterically hindered alkenes (X-ray diffraction data).

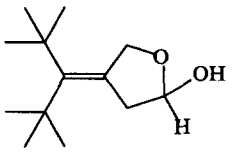
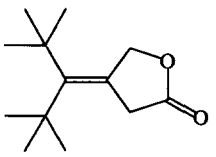
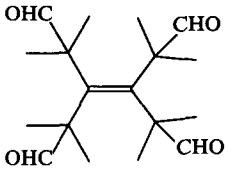
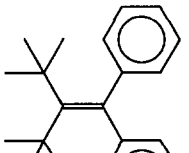
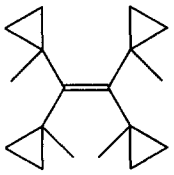
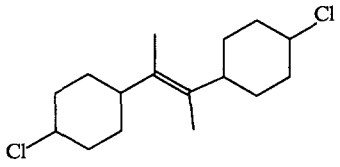
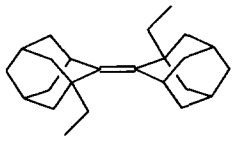
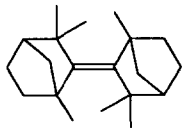
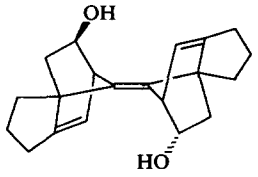
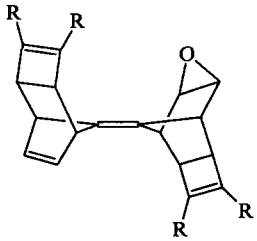
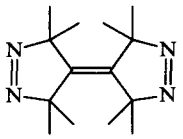
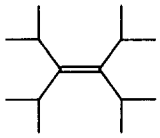
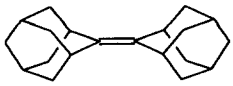
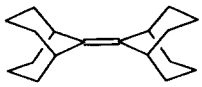
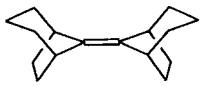
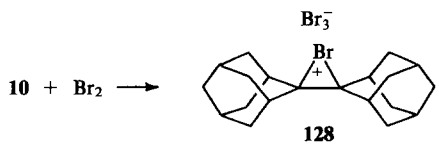
Compound	C=C torsional angle/deg	C=C bond length/A	Ref.
	37.5	1.367	31
	33.8	1.357	31
	28.6	1.357	53, 84
	24.0	1.357	85
	19.7	1.353	86
	16.0	1.353	87
	12.3	1.358	27
 **23**	11.8	1.349	88
	8.3	1.302	42

Table 2 (continued)

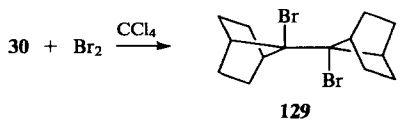
Compound	C=C torsional angle/deg	C=C bond length/A	Ref.
	5.4	1.314	70
	0.0	1.356	54
	0.0	1.347	89
	0.0	1.336	90
	0.0	1.324	91
	0.0	1.307	43

The reaction of the alkene **10** with bromine leads to the formation of an unusual adduct — the stable bromonium salt **128**.[96] The structure of the latter has been confirmed by X-ray diffraction data.[97] The structure found became a true scientific sensation because it had been postulated for many years that the reactions of the usual alkenes with bromine proceed precisely via intermediates of this kind.[98,99] The complex behaviour of the **10** + Br_2 system in solution has been investigated.[100]



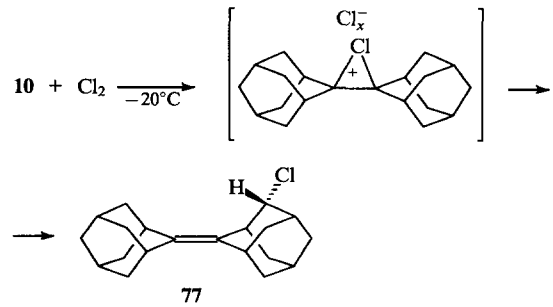
128

A bromonium salt — the adduct $C_{22}H_{33}Br_4$ insoluble in ether and hexane[26] — was also obtained in the reaction of *trans*-1,1′-dimethyladamantylideneadamantane **11** with bromine. In contrast to the alkenes **10** and **11**, the alkene **30** reacts with bromine to form the usual 1,2-adduct — the dibromo-derivative **129**.[40]



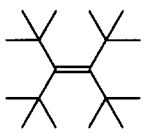
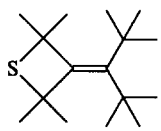
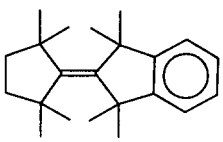
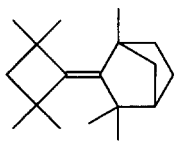
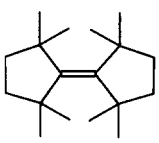
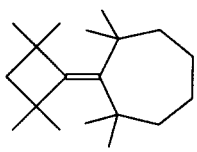
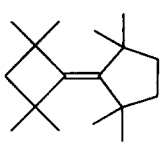
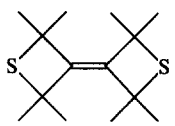
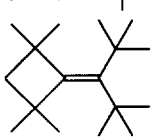
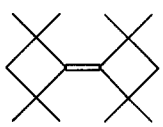
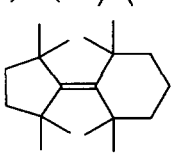
129

A substitution product — the chloroalkene **77** — has been obtained in a quantitative yield in the interaction of the alkene **10** with chlorine. In the initial stage of the chlorination reaction, the precipitation of the chloronium salt was observed visually. It was not possible to isolate it from the reaction mixture in view of its instability.[63]

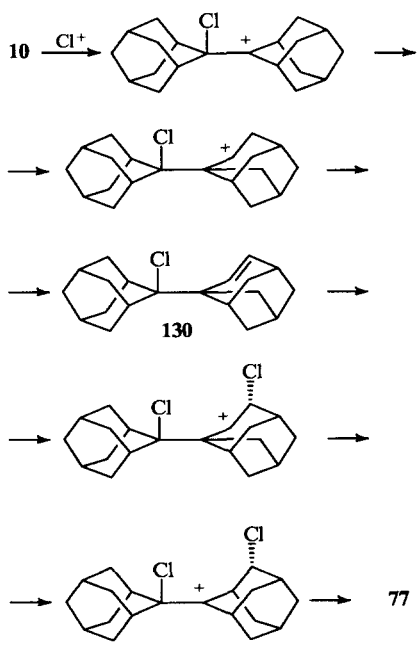


77

Table 3. Torsional angles and bond lengths in sterically hindered alkenes (calculated data[92]).

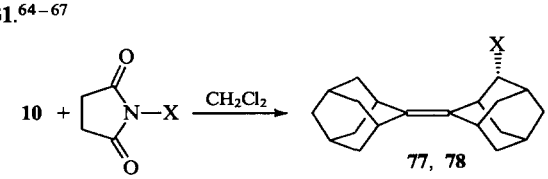
Compound	C=C torsional angle/deg	C=C bond length/A	Compound	C=C torsional angle/deg	C=C bond length/A
	44.0	1.379		4.2	1.373
	12.1	1.369		3.5	1.347
	5.5	1.371		1.0	1.370
	5.1	1.351		0.1	1.344
	5.0	1.366		0.05	1.330
	4.9	1.379			

A mechanism, the key stage of which is the formation of the protoadamantene-like intermediate **130**, has been proposed for this reaction.

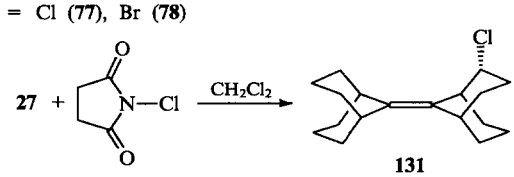


The formation of an iodonium salt in the reaction of the alkene **10** with the ICN–SbF_5 (1:1) system in SO_2 has been detected spectroscopically.[101]

The radical-chain type of halogenation of the alkenes **10** and **27** has been described. The reaction of the alkene **10** with *N*-chlorosuccinimide leads quantitatively to the halo-derivatives **77** and **78**; this reaction constitutes the simplest and preparatively the most convenient method of synthesis of the chloroalkene **77**. Similar haloalkenes are formed on chlorination with *tert*-butyl hypochlorite or the NaOCl–MeCOOH system. The reaction of the alkene **27** with *N*-chlorosuccinimide leads to the chloroalkene **131**.[64–67]

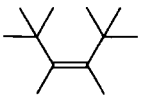
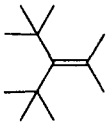
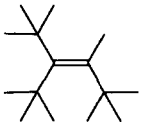
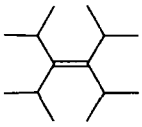
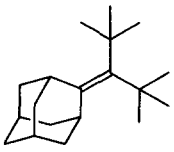
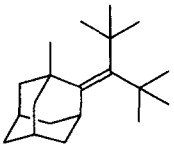
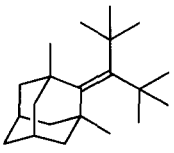
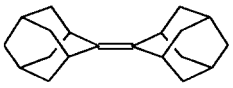
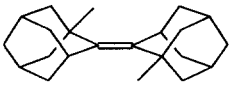
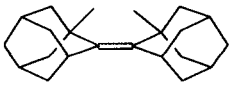
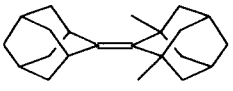
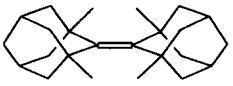


X = Cl (**77**), Br (**78**)

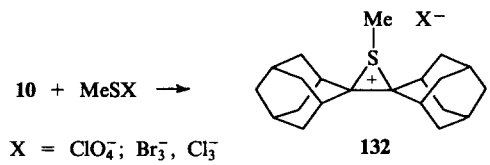


The reactions considered take place as selective homoallyl halogenation, whereas the usual alkenes afford the products of allyl halogenation on treatment with the same reagents.

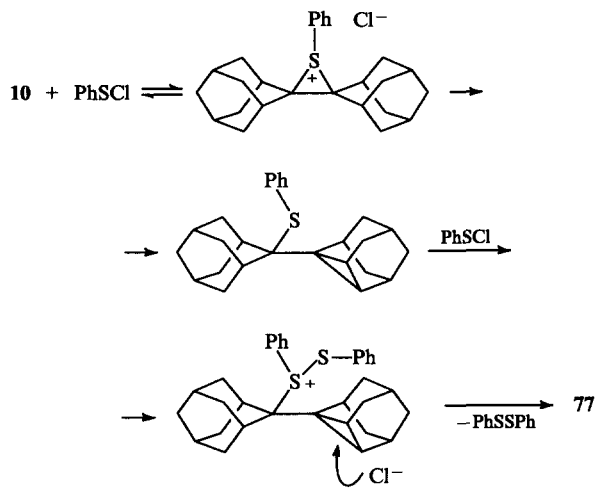
Table 4. Thermodynamic parameters of sterically hindered alkenes (calculated data).

Compound	Standard enthalpy of formation/kcal mol^{-1}	Strain energy/kcal mol^{-1}	Ref.
	—	11.1	93, 94
	—	12.0	93, 94
	—	32	93, 94
	—	18	93, 94
	−28.92	46.14	58
	−17.73	66.20	58
	−6.16	86.64	58
	−30.36	13.54	26, 37, 58
	−26.10 (26.49)	35.54	27
	−18.20	43.44	26, 27
	−24.34	37.30	26, 27
	−61.07	75.31	26, 27

The reactions of adamantylideneadamantane **10** with electrophiles containing both a halogen and sulfur or both a halogen and selenium take place in an unusual manner. Thus the reactions of the above alkene with methanesulfenyl halides lead to the formation of the stable episulfonium salt **132**.[102] The formation of such compounds as intermediates was postulated previously in reactions involving the addition of alkanesulfenyl halides to the usual alkenes.

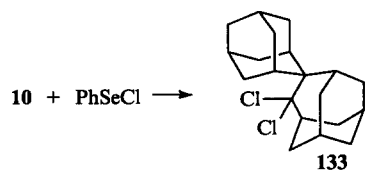


The reaction of the alkene **10** with 2 equiv. of PhSCl leads to the chloroalkene **77**.[103]

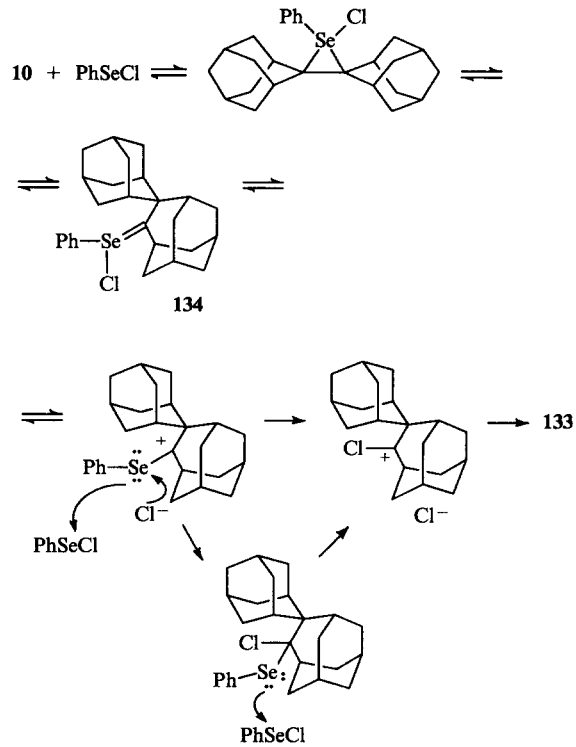


As in the interaction with chlorine, a substitution product is formed in this reaction instead of the 1,2-adduct.

The reaction of the alkene **10** with PhSeCl leads to an unexpected product — 3,3′-dichlorospiro(adamantane-2,2-homoadamantane) **133**.[104]

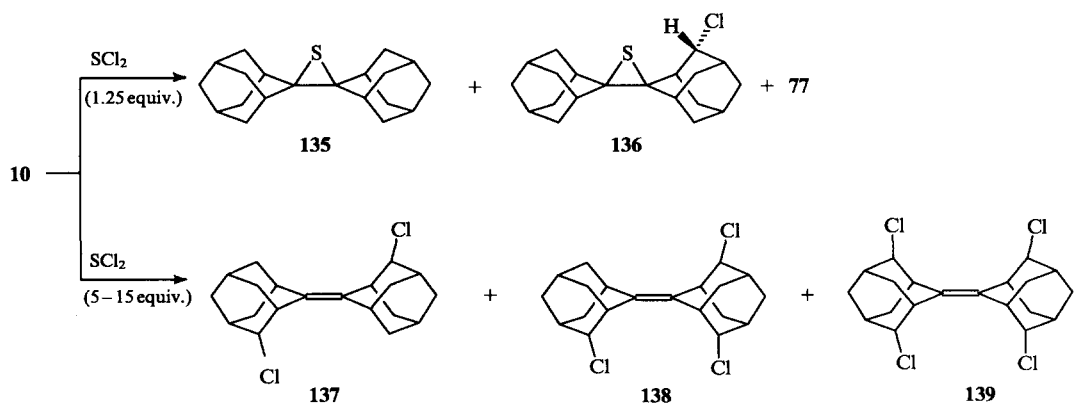


The proposed mechanism for this reaction includes a skeletal rearrangement in the intermediate **134**, the interaction of the rearranged derivative with a second molecule of the reagent, and cleavage of the salt formed.

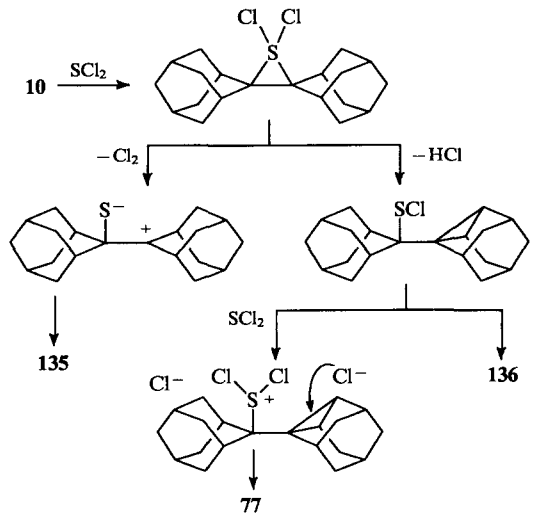


The reaction of the alkene **10** with SCl_2 leads to the epithio-compounds **135** and **136** and the (poly)chloroalkenes **77** and **137**–**139** (Scheme 4). Compounds **77**, **135**, and **136** are formed for an alkene : reagent ratio of 1 : 1, when the thiirane **135** is obtained predominantly in $CHCl_3$, the chlorothiirane **136** in CH_2Cl_2, and the chloro-derivative **77** in hexane. The specific synthesis of (poly)chloroalkenes **137**–**139** has been achieved in CH_2Cl_2 in the presence of a fivefold, sevenfold, and 15-fold excess of the reagent respectively.[105–106] The reaction of the alkene **10** with S_2Cl_2, in which the same epithio-compounds and chloroalkenes are obtained, is distinguished by a lower selectivity relative to the epi-compounds and by the formation of less chlorinated products than the reaction with SCl_2 occurring under the same conditions.[107] The structure of the chlorothiirane **136** has been confirmed by X-ray diffraction data.

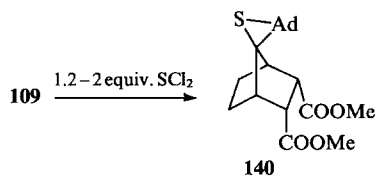
Scheme 4

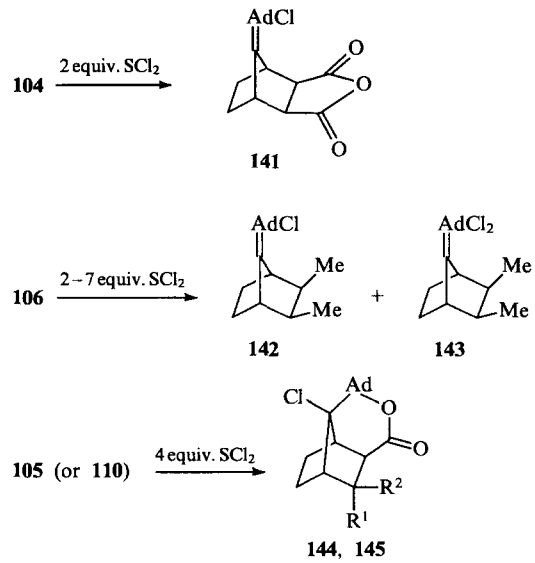


The diversity of the products formed in the reactions of the alkene **10** with SCl_2 and S_2Cl_2 may be explained by the existence of several versions of the stabilisation of the key intermediates — the primary sulfurane and sulfenyl chloride — and also by the successive chlorination of the unsaturated reaction products.

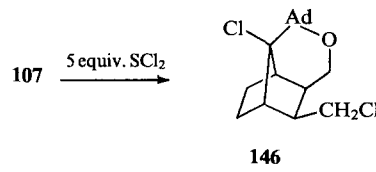


In the reactions of a series of disubstituted adamantylidenenorbornanes with SCl_2, the nature of the products depends significantly on the nature and the steric disposition of the substituents. Thus the reaction of SCl_2 with the *endo,endo*-diester **109** in $CHCl_3$ leads only to the thiirane **140**, while the reaction in CH_2Cl_2 leads to a complex mixture of products containing 17% of the latter. The chloroalkenes **141** and **142** have been obtained by the reactions of the *exo, exo*-adducts **104** and **106** respectively with 1.2–2 equiv. of SCl_2 in solution in CH_2Cl_2, while a mixture of five isomeric dichloroalkenes **143a–e** has been synthesised by the reaction of the alkene **106** with 7 equiv. of SCl_2.[74] The reactions of the *exo, exo*-diester **105** and the *exo, endo*-diester **110** with four equivalents of SCl_2 are accompanied by lactonisation, as a result of which the chlorolactones **144** and **145** respectively have been isolated in high yields. The dichloroether **146** has been obtained from the cyclic ether **107** as the product of the cleavage of the tetrahydrofuran fragment in the latter and subsequent etherification.[74]

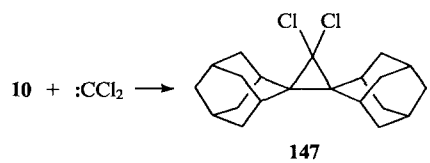




105, **144**: R^1 = H, R^2 = COOMe;
110, **145**: R^1 = COOMe, R^2 = H

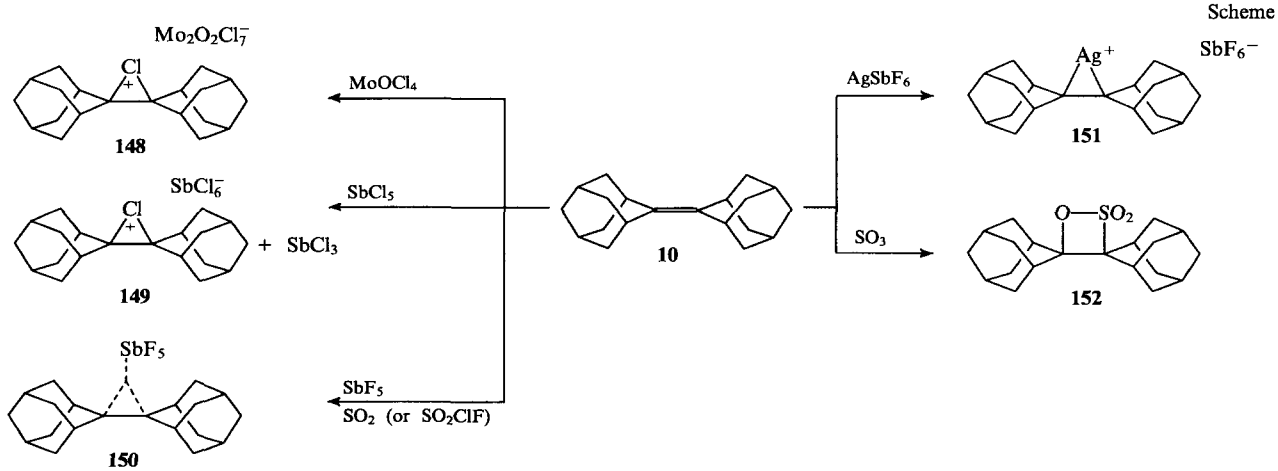


The normal cycloaddition product, the adduct **147**, is formed in the reaction of the alkene **10** with dichlorocarbene; this addition reaction takes place more slowly than with the usual alkenes, such as 2-methyladamantane (by a factor of 20) and 2-isopropylideneadamantane (by a factor of 200).[108]



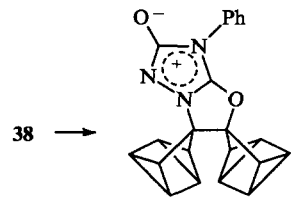
The reactions of the alkene **10** with $MoOCl_4$ and $SbCl_5$ in the presence of Lewis acids (Scheme 5) lead to the stable adamantylideneadamantanechloronium salts **148** and **149** respectively.[109]

Scheme 5



The adducts of the alkene **10** with SbF_5 and $AgSbF_6$—compounds **150** and **151** respectively[101]—as well as the β-sultone **152**[110] were detected in the reaction mixtures by ^1H and ^{13}C NMR.

The 1 : 1 adduct **153** has been obtained from the alkene **38** and *N*-phenyl-1,2,4-triazolinedione.[70]

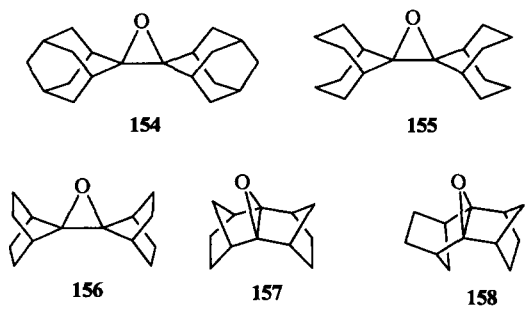


153

2. Oxidation reactions of sterically hindered alkenes

The behaviour of SHA in oxidation processes has been investigated on model reactions such as epoxidation, ozonisation, and 1,2-cycloaddition with participation of singlet or triplet oxygen.

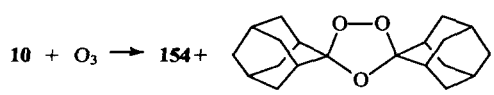
The formation of epoxides from SHA on treatment with *m*-chloroperbenzoic acid has been described for the alkenes **9**,[24] **23**,[48] **42**,[48] and **50**.[90] The epoxides **154**,[111] **155**,[38] **156**,[40] **157**,[72] and **158**[73] have been obtained in the same way from the corresponding alkenes in satisfactory yields.



154 **155**

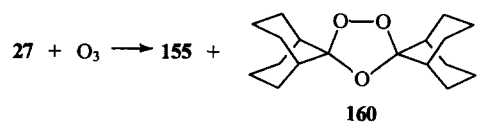
156 **157** **158**

The ozonisation of SHA in most cases does not lead to ozonides—the normal products of the usual alkenes with ozone. The alkene **121** is an exception. Its ozonisation proceeds normally and affords (after the appropriate treatment of the reaction products) di-*tert*-butyl ketone and pivalic aldehyde.[95] The reactions of other SHA with ozone proceed differently. Thus the reaction of the alkene **10** with ozone in nonpolar solvents leads to a mixture of the epoxide **154** and the ozonide **159** in proportions which depend on the nature of the solvent: the epoxide is formed exclusively in polar solvents. The reaction of O_3 with the alkene **27** proceeds similarly, leading to a mixture of the epoxide **155** and the ozonide **160** or only the former.[38,72] The thermal decomposition of the ozonide **159** results in the formation of a 1 : 1 mixture of adamantanone and a lactone.[38]



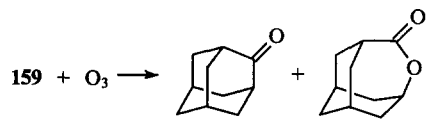
159

Solvent	Yield (%)	
	154	159
C_5H_{12}	60	33
C_5H_{12}–MeCOOEt	66	28
MeCOOEt	92	0

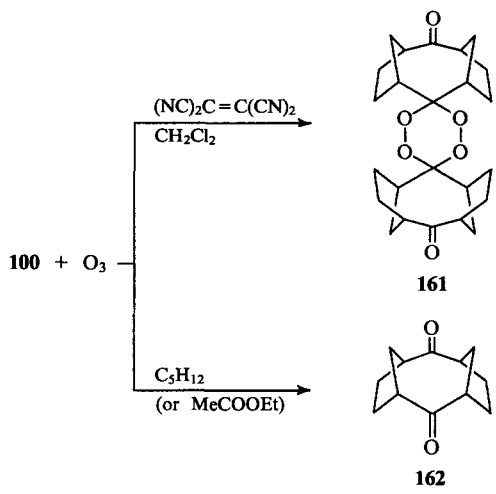


160

Solvent	Yield (%)	
	155	160
C_5H_{12}	77	18
MeCOOEt	100	0



Only the epoxide **156** has been obtained in the reaction of O_3 with the alkene **30**.[40] The ozonisation of the alkenes **23** and **100** is accompanied by the dissociation of the double bond; fenchone is formed from the first alkene,[48] while the peroxydiketone **161** or the diketone **162** is formed from the second (depending on the conditions).[72] The inertness of the alkenes **65** and **66** to O_3 has been noted.[112]



161

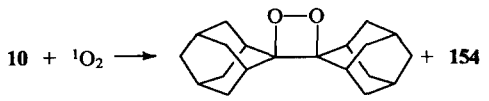
162

The oxidation of SHA of the 1,2-addition type leads to normal products—dioxetanes. The latter are more stable than the dioxetanes obtained from the usual alkenes. Thus the dioxetane **163**, synthesised from the alkene **10**, can be stored under the usual conditions. This feature of the dioxetanes obtained from SHA attracted considerable attention to them in connection with the problem of the strong chemiluminescence arising on thermal decomposition of compounds of this class.

Many SHA, especially adamantane-containing compounds, have been subjected to oxidation of the type of 1,2-addition. These alkenes have been involved in several types of reactions leading to dioxetanes: photosensitised oxidation by singlet oxygen and the radical-cation and electrochemical oxidation by oxygen. Mainly the synthetic possibilities and stereochemical characteristics of the above reactions are considered in the present review because the mechanisms of the latter and various aspects of the chemiluminescence of the dioxetanes on their decomposition have been described in detail in a monograph.[113] The synthesis and properties of various dioxetanes have been briefly considered in a review.[114]

Photochemical oxidation by singlet oxygen sensitised by dyes has been usually employed to obtain dioxetanes from SHA. The dioxetane **163** has been synthesised by precisely this method from the alkene **10**. Methylene Blue (MB) was used in this reaction as the sensitiser.[115] The structure of the above dioxetane was

confirmed by X-ray diffraction[116] (a method for the preparative synthesis of the dioxetane **163** has been described[117]).



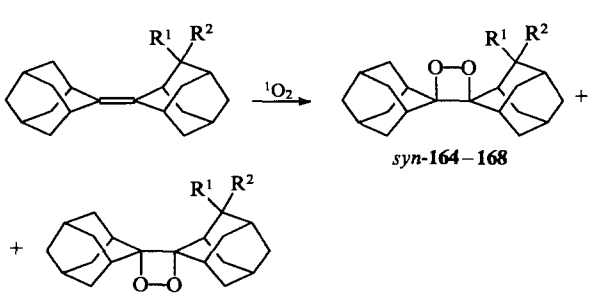
163

The above photochemical oxidation of the alkene **10** affords, together with the dioxetane **163**, also the epoxide **154**; the ratio of these products depends on the nature of the dye and the solvent (Table 5). Evidently, the dioxetane is formed selectively in the presence of MB or tetraphenylporphin (TPP).[118,119]

Table 5. Photochemical oxidation of adamantylideneadamantane **10** in acetone.[118,119]

Sensitiser	Yield of reaction products (%)	
	163	**154**
m-Tetraphenylporphin	95	traces
Methylene Blue	95	traces
Rhodamine B	95	5
Eosin	95	5
Fluorescein	90	10
Erythrosin	30	70
Rose Bengal	traces	95

The photochemical oxidation of 4-substituted adamantylideneadamantanes by singlet oxygen under the conditions of the selective synthesis of dioxetanes proceeds nonstereospecifically, affording a mixture of two isomeric dioxetanes. Thus a mixture of the *syn*- and *anti*-dioxetanes **164** in proportions of 3.1:1 has been obtained from the chloroalkene **77**.[120] Oxidation of the alkenes **80**–**82** with functional group substituents leads to the corresponding dioxetanes **165**–**167** in the form of mixtures of two isomers.[68] The analogous oxidation of the ketoalkene **79** gives rise to a 1:2 mixture of the *syn*- and *anti*-dioxetanes **168**,[121,122] while the optically active 1,2-dioxetane **169** has been obtained from the ketal (−)-**83** as the sole isomer.[69]



syn-**164**–**168**

anti-**164**–**168**

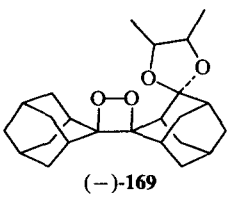
164: R^1 = Cl, R^2 = H;

165: R^1 = $NHCOCH_2CH_2COO-N$ (succinimide), R^2 = H;

166: R^1 = $O(CH_2)_nCOO-N$ (succinimide), R^2 = H;

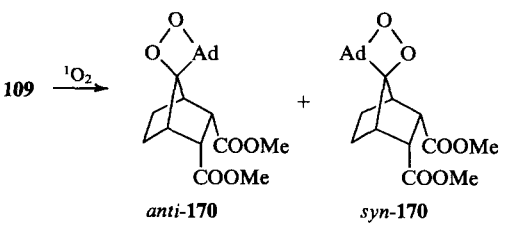
167: R^1 = $-N$ (succinimide), R^2 = H;

168: $R^1 + R^2$ = O

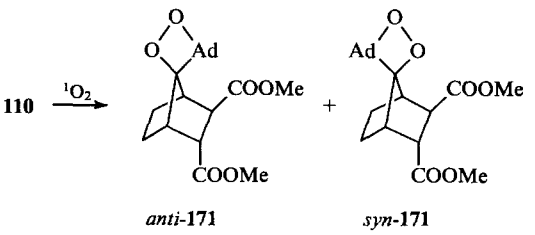


(−)-**169**

The photochemical oxidation of a series of isomeric 2,3-disubstituted 7-adamantylidenenorbornanes on treatment with $^1O_2$ was carried out in CH_2Cl_2 in the presence of MB. A 2:1 mixture of the dioxetanes *anti*-**170** and *syn*-**170** was obtained from the *endo,endo*-diester **109** in 90% yield, while the *exo,endo*-diester **110** afforded a 92% yield of 1.4:1 mixture of the dioxetanes *anti*-**171** and *syn*-**171**. The individual dioxetanes were isolated from the corresponding mixtures with the aid of high performance liquid chromatography (HPLC). The compounds of the *exo,exo*-series (**104**–**106**) are inert to singlet oxygen.[121–124]

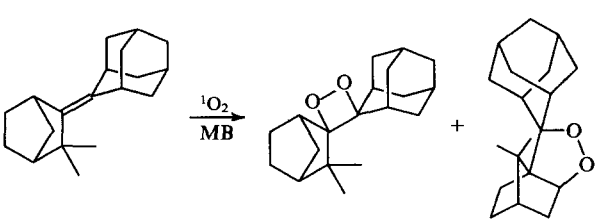


109 → *anti*-**170** + *syn*-**170**



110 → *anti*-**171** + *syn*-**171**

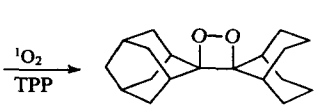
The photochemical oxidation of the alkene **62** in the presence of MB leads to the formation of the dioxetane **172** and the dioxolane **173** in proportions which depend on the nature of the solvent.[56,125]



172 **173**

Solvent	172 : 173 ratio
CH_2Cl_2	7 : 3
MeCN	3 : 7
Me_2CO	1 : 9

The photochemical oxidation of the alkene **42** in CH_2Cl_2 in the presence of TPP affords a high yield of the dioxetane **174**.[126]



174

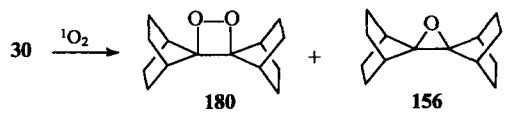
The adamantane series dioxetanes **175**–**179**, containing the phenyl (compounds **175a**–**d**), naphthyl (compounds **175e**–**k**),[81] fluorene (compound **176**),[127,128] methylacridine (compound

177),[129-131] and xanthene (compound **178**)[82] fragments as well as the methoxy-group have been synthesised similarly from the corresponding alkenes. The phosphate derivative of the dioxetane **178** (compound **179**)[132] as well as the dioxetanes **175b**, **c**, **g**–**j**[80,133,134] have been obtained in the presence of Rose Bengal (RB) bound to a polymer.

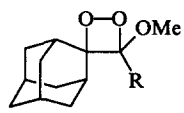
Table 6. Photosensitised oxidation of alkene **30** (see Ref. 40).

Sensitiser	Solvent	Yield of reaction products (%)	
		180	**156**
m-Tetraphenylporphin	CH_2Cl_2	60.3	39.7
	$t\text{-}C_4H_9COCH_3$	25.9	74.1
	1,4-dioxetane	24.8	75.2
	C_6H_6	18.2	81.8
	CH_3COCH_3	16.4	83.6
Methylene Blue	CH_3CN	54.0	46.0
	CH_2Cl_2	46.4	53.6
Rose Bengal	CH_3OH	44.4	55.6

The photochemical oxidation of the alkene **30** by singlet oxygen in various solvents and with the aid of different dyes leads in all cases to a mixture of the dioxetane **180** and the epoxide **156** [the content of the dioxetane **180** varies from 16% to 60% (Table 6)].[40] The dioxetane **181** has been obtained from the alkene **27** in the presence of TPP in CH_2Cl_2 (in the presence of MB, the yield of the dioxetane was 83%,[135] while according to other data[38] it was 51%).

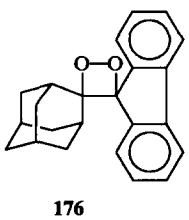


180 **156**

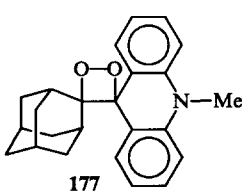


175a–l

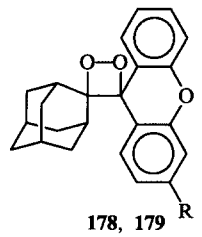
R = (175a), (175b), (175c), (175d), (175e), (175f), (175g), (175h), (175i), (175j), (175k), (175l).



176

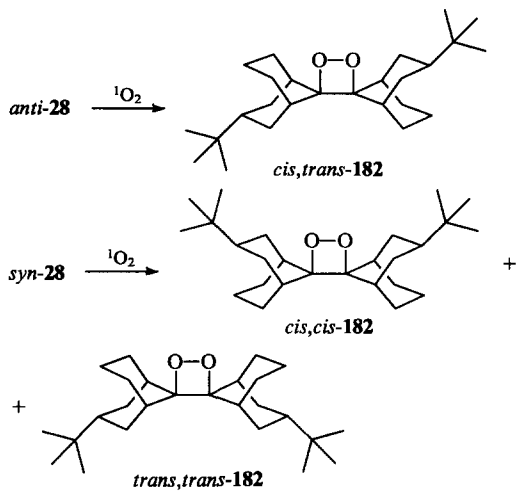


177



178, 179 R = H (**178**), $OPO_3^-H \cdot Py^+H$ (**179**)

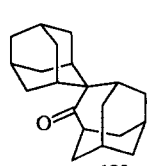
The oxidation of the *anti*-alkene **28** by singlet oxygen (with TPP as the sensitiser) afforded only the *cis,trans*-dioxetane **182**, whilst the oxidation of the alkene *syn*-**28** gave rise to a 2:1 mixture of the dioxetanes *trans,trans*-**182** and *cis,cis*-**182**.[39,126] The structure of the latter was established by X-ray diffraction.[51]



The alkenes inert to $^1O_2$ include the alkenes **23**, **64**, and **104**–**106**.[56] The attempts to obtain dioxetanes by the photochemical oxidation of the alkenes **100** and **101** were also unsuccessful. Only the epoxide **157** is formed from the alkene **100** in benzene in the presence of RB, while in acetonitrile in the presence of MB and in 1,2-dichloroethane in the presence of TPP the product is the diketone **162**.[77] Only the epoxide **158** has been obtained from the alkene **101** in benzene (with diacetyl as the sensitiser).[73]

The oxidation of SHA by oxygen under the conditions of a radical-cation chain process initiated by one-electron oxidants also leads to the formation of dioxetanes together with photochemical oxidation by singlet oxygen. Such oxidants are hexahaloantimonates of stable radical-cations: $(4\text{-}BrC_6H_4)_3N^{\cdot+}.SbCl_6^-$, $(2,4\text{-}Br_2C_6H_3)_3N^{\cdot+}.SbCl_6^-$, $(2,4\text{-}Br_2.C_6H_3)_3N^{\cdot+}.SbF_6^-$, and $NO^+PF_6^-$, $NO_2^+PF_6^-$, as well as sensitisers capable of generating radical-cations from the alkene on photoirradiation, such as, for example, 9,10-dicyanoanthracene (DCA) The radical-cations are also generated on electrochemical oxidation by oxygen.

The oxidation of the alkene **10** by oxygen in the presence of $(2,4\text{-}Br_2C_6H_3)_3N^{\cdot+}.SbCl_6^-$ results in the selective formation of the dioxetane **163**,[135] while in the presence of other oxidants the product is a mixture of the dioxetane **163** with the epoxide **154** and the spiroketone **183** in proportions which depend on the nature of the oxidant and the conditions (Table 7).[136]



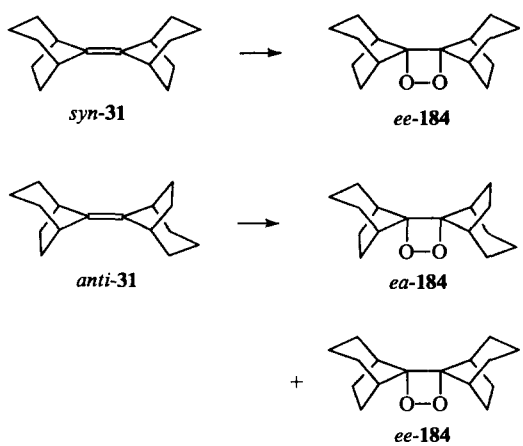
183

Table 7. Oxidation of adamantylideneadamantane **10** by oxygen in CH_2Cl_2 in the presence of oxidants.[136]

Oxidant	Content of oxidant (mol.%)	Time/min	Yield of reaction products (%)			
			163	**154**	**183**	**26**
MBPA.$SbCl_6$[a]	11.1	260	42	—	—	57
$NO^+PF_6^-$	103	2.5	6	86	—	—
$NO^+PF_6^-$	12.5	30	21	55	—	—
$NO_2^+PF_6^-$	3.5	180	40	7	—	40
$NO^+PF_6^-$	1.6	80	15	—	—	84
$NO_2^+PF_6^-$	95	2	—	—	73	—
$NO_2^+PF_6^-$	2.7	30	24	33	—	38

[a] MBPA = tris(*p*-bromophenyl)amine.

The oxidation of a series of enol ethers by the above procedure [in the presence of $(4\text{-}BrC_6H_4)_3N^{\cdot+}.SbCl_6^-$] leads to quantitative yields of the corresponding dioxetanes **175a** and **175g**.[137] A 25:1 mixture of the *syn*- and *anti*-dioxetanes **164** has been obtained similarly from the chloroalkene **77** in the presence of $(2,4\text{-}Br_2C_6H_3)_3N^{\cdot+}.SbF_6^-$.[118] A higher selectivity is attained in this reaction than in the photochemical oxidation of the above alkene by singlet oxygen. The oxidation of the isomers of the alkene **31** by oxygen in the presence of $(2,4\text{-}Br_2C_6H_3)_3N^{\cdot+}.SbCl_6^-$ resulted in the formation of only the *ee*-dioxetane **184** from the *syn*-isomer and a 4:1 mixture of the *ea*- and *ee*-dioxetanes from the *anti*-isomer.[138]

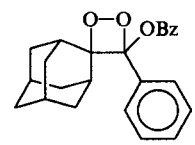


syn-**31** → *ee*-**184**

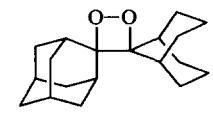
anti-**31** → *ea*-**184** + *ee*-**184**

The synthesis of dioxetanes from SHA via the DCA-sensitised photochemical oxidation by oxygen has been described in relation to the alkenes **10**, **27**, **28**, and **42**. The oxidation of the alkene **28** stereoisomers by this procedure afforded the same products as their oxidation by $^1O_2$, but the ratio of the *cis,cis*- and *trans,trans*-dioxetanes is in this case 27:22. A dioxetane is not formed from the alkene **30** under these conditions.[39,126] The sensitised photochemical oxidation of a series of enol ethers afforded high yields of the corresponding dioxetanes **175a**, **e**, **g**, **l** and **185**.[139]

The electrochemical oxidation by oxygen is also used together with the oxidation method described above for the synthesis of dioxetanes from the alkenes **10**, **27**, **28**, and **42**; the ratios of the relative reactivities of the alkenes **10**, **27**, and **42** are then 1:0.74:0.06. The formation of mixtures of *cis,trans*-, *cis,cis*-, and *trans,trans*-dioxetanes **182** in proportions of 34:24:21 (from the *anti*-isomer) and 23:51:11 (from the *syn*-isomer) from the *syn*- and *anti*-stereoisomers of the alkene **28** is evidence in support of a different reaction mechanism than in other types of oxidation. The dioxetane **186** has been obtained in the same way from the alkene **41**, while the alkene **30** is inert to oxygen under the conditions indicated.[39,126,140]



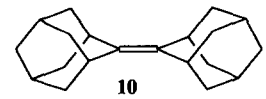
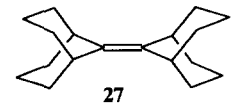
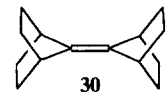
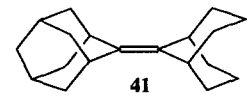
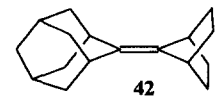
185



186

Comparison of three oxidation methods (singlet, DCA-sensitised, and electrochemical) in relation to the alkenes **10**, **27**, **30**, **41**, and **47** showed that oxidation by singlet oxygen is most effective for the preparation of dioxetanes from the above alkenes (Table 8). Among all the alkenes examined, the alkene **30**, is the most reactive.[126]

Table 8. Singlet, DCA-sensitised, and electrochemical oxidation of a series of alkenes.[39,126]

Alkene	Yield of dioxetane (%)		
	$^1O_2$	DCA	$^3O_2$
 **10**	98	66	87
 **27**	100	21	80
 **30**	15	does not react	does not react
 **41**	—	—	69
 **42**	92	59	72

The higher relative thermal stability of the dioxetanes based on SHA compared with those based on the usual alkenes is illustrated by the data in Table 9, which lists the activation energies E_a for the thermolysis of a series of dioxetanes (this is one of the characteristics of the stability of compounds of this type). The table shows that the adamantane and bridging bicyclic fragments increase the stability of dioxetanes and that, of the two stereoisomers, the *anti*-isomers are more stable than the *syn*-isomers.

Table 9. Activation energies for thermal decomposition in the chemiluminescent thermolysis of dioxetanes.

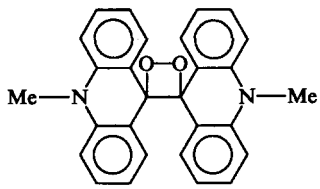
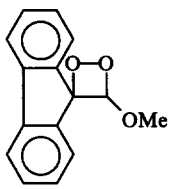
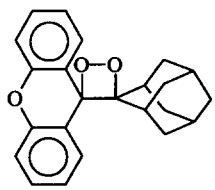
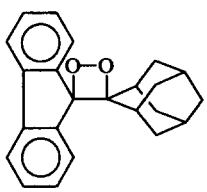
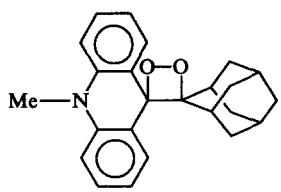
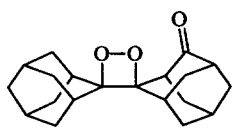
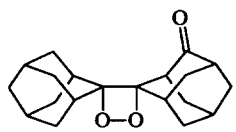
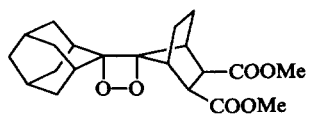
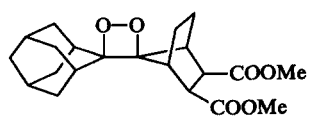
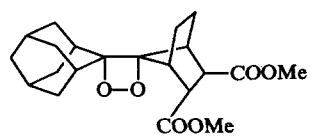
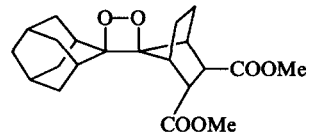
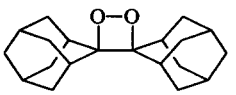
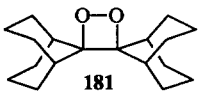
Dioxetane	E_a/kcal mol^{-1}	Ref.
	18.7	141, 142
	21.0	143
	23.8	82
	25.8	127
	26.3	131
	33.2	122
	33.5	122
	29.5	122
	33.0	122
	33.5	122

Table 9 (continued)

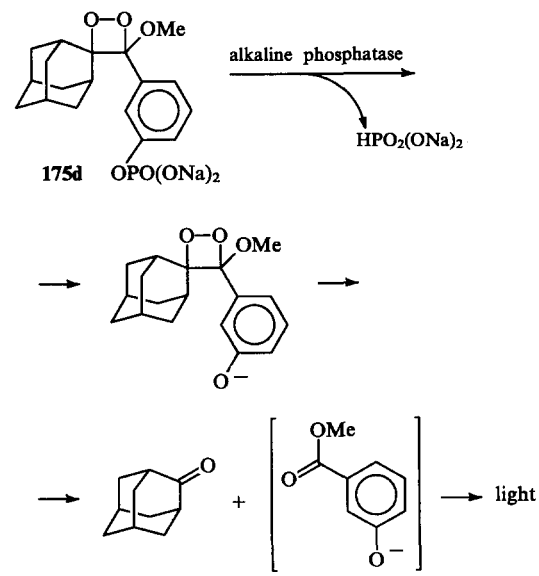
Dioxetane	E_a/kcal mol^{-1}	Ref.
	36.3	122
	34.6	144
 **181**	35.6	145

V. Applications of dioxetanes based on sterically hindered alkenes

It has been discovered in the last decade that adamantane-containing dioxetanes with functional group substituents are likely to find applications as chemiluminescent labels and probes in labelling systems and in the determination of DNA, hormones, and other biological substances. Different aspects of the use of dioxetanes in molecular biology, immunology, and biotechnology have been described in detail in reviews[146,147] and patents.[80,83,148–152]

The glow in the systems under discussion is generated under the influence of enzymes — alkaline phosphatase (in the presence of disodium phosphates), aryl esterase (in the presence of acetates) — and of the fluoride ion (in the presence of trialkylsilyl ethers). The glow is excited as a result of the splitting off of the corresponding functional group, which leads to an unstable intermediate. The latter undergoes in its turn spontaneous decomposition in the dioxetane ring accompanied by chemiluminescence.[132,134] These transformations are illustrated below in relation to the dioxetane **175d** — 3-(2′-spiroadamantane)-4-methoxy-4-(3″-phosphoryloxy)phenyl-1,2-dioxetane (AMPD) (Scheme 6).

Scheme 6



It has been suggested that dioxetanes based on 4-substituted adamantylideneadamantanes **165** and **166**,[68] adamantylidene-(hetero)tricyclanes **176–179**,[82,127–132] compounds of the methoxyarylmethylideneadamantane series **175d–i**,[80,81,83,148] and others be employed as chemiluminescent labels. A system incorporating AMPD and alkaline phosphatase has found nowadays a real practical application. This system is manufactured by the Tropix Company. An advantage of systems of this kind is the combination of a high rate of assay with a high sensitivity (an order of magnitude higher than in the case where the usual luminescent reagents are employed), safety (compared with radioactive labelling), and diversity of applications.

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