New Free-Radical Precursors and Pathways

A thesis presented by Andrew J. McCarroll to the University of St. Andrews in application for the degree of Doctor of Philosophy.

March 2000

Declarations

I, Andrew James McCarroll hereby certify that this thesis has been composed by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degrees or professional qualification

Signed ___ _____ Date 15/4/2000

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st October 1996 and as a candidate for the degree of PhD. on 1st October 1997.

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Contents

	Acknowledgements	**v**
	Abbreviations and Symbols	**vi**
	Abstract	**vii**
Chapter 1	**Introduction: Methods of generating radicals in cascade reactions**	1
1.1	Radicals in Organic Synthesis	2
1.1.1	The different radical processes	2
1.2	When is a migration not a migration?	6
1.3	Other discrepancies	7
1.4	The diverse array of radical sequences	8
1.5	Reactions started by a cyclisation	9
1.5.1	Reactions that start with a double cyclisation, **CC**.	10
1.5.2	**CCC** and longer polycyclic sequences	29
1.5.3	Reactions starting with the **CF** sequence	32
1.6	Reaction sequences that start with a fragmentation	39
1.6.1	Reaction sequences that start with **FC**	39
1.6.2	Reactions that start with an **FH** sequence	44
1.6.3	Reaction sequences that start with a double fragmentation, **FF**	46
1.7	Reaction sequences that start with a hydrogen transfer	49
1.7.1	Protecting/translocating radical reactions	49
1.7.2	Other sequences that begin with an H shift.	53
1.8	Sequences containing an intermolecular addition	54

1.8.1	Radical reactions that end in an intermolecular addition	54
1.8.2	Radical annulations	55
1.9	Conclusions	64
1.10	References	65
Chapter 2	**The radical reactions of oxime derivatives**	77
2.1	Introduction	78
2.2	Results and Discussion	81
2.2.1	Investigation of the reactions of oxime esters.	81
2.2.1.1	Synthesis of oximes and oxime esters.	81
2.2.1.2	Product analysis investigations into the reactions of oxime esters	85
2.2.1.3	Investigation of radicals from oxime esters using EPR spectroscopy.	91
2.2.2	Investigation of the reactions of oxime ethers.	112
2.2.2.1	Synthesis of oxime ethers.	112
2.2.2.2	Product analysis studies of reactions of oxime ethers	114
2.2.2.3	EPR investigation of radicals from oxime ethers	117
2.2.3	Ultraviolet spectra of oxime esters and ethers	124
2.3	Conclusion	125
2.4	Experimental	127
2.5	References	155
Chapter 3	**Cyclohexadienones as radical precursors**	159
3.1	Introduction	160
3.1.1	Proaromatic compounds as radical precursors	161
3.1.2	Cyclohexadienones as potential proaromatic radical precursors	162
3.1.3	Base-mediated alkylation of phenols	163

3.1.4	Generation of the cyclohexadienyl-type ketyl radical	164
3.2	Results and Discussion	165
3.2.1	Preparation of cyclohexadienones	165
3.2.2	Observation of radicals from cyclohexadienones by EPR spectroscopy.	169
3.2.3	Investigation of radicals from cyclohexadienones by product analysis	171
3.3	Conclusion	172
3.4	Experimental	174
3.5	References	181
Chapter 4	**Novel methods of performing radical annulations**	183
4.1	Introduction	184
4.1.1	Radical Annulations	184
4.1.2	Samarium(II) iodide	184
4.1.3	Manganese(III) mediated annulations	186
4.2	Results and Discussion	187
4.2.1	Samarium(II) iodide mediated annulations	187
4.2.2	Manganese(III) picolinate mediated annulations	192
4.2.3	Tin mediated annulations	193
4.3	Conclusion	195
4.4	Experimental	196
4.5	References	204
Chapter 5	**Investigation of alkylboronic ester radicals**	206
5.1	Introduction	207
5.1.1	EPR spectroscopy and radical characterisation	207
5.1.2	Boronic esters	207

5.2	Results and Discussion	210
5.2.1	Characterisation of α-boryl radicals generated by abstraction of bromine from α-bromoalkylboronic esters	210
5.2.2.	α-Boryl radicals by addition to a double bond	222
5.2.3.	β-Boryl radicals by abstraction of bromine from β-bromoboronic esters	
5.2.4	Allylic radicals by abstraction of hydrogen or bromine	227
5.2.5	Other boronic ester containing radicals	228
5.3	Conclusion	229
5.4	Experimental	231
5.5	References	233

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Thanks are also due to the technicians in the department for all of their assistance, especially Jim Bews for his help in getting the EPR spectra in Chapter 2 in a format suitable for Word. I would also like to thank the EPSRC for funding.

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Abbreviations and Symbols

AIBN	2,2'-Azobisisobutyronitrile
BHT	Butylated hydroxytoluene
	2,6-Di-t-butyl-4-methylphenol
b.p.	Boiling point
DCC	1,3-Dicyclohexycarbodiimide
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMOP	2,4-Dimethoxyphenyl
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
	N,*N*'-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
DTBP	Di-t-butyl peroxide
EDTA	Ethylenediaminetetraacetic acid
EPR	Electron Paramagnetic Resonance
Ether	Diethyl ether
GC/MS	Gas Chromatography/Mass Spectrometry
hfs	Hyperfine splitting
HMPA	Hexamethylphosphoramide
HMDT	Hexamethylditin
m.p.	Melting point
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
P.E.	Petroleum ether
s, d, t, q	singlet, doublet, triplet, quartet
TBTH	Tri-n-butyltin hydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMOP	2,4,6-Trimethoxyphenyl
TMS	Trimethylsilyl
TPTH	Triphenyltin hydride
TTMSS	Tris(trimethylsilyl)silane

Abstract

A method of cataloguing sequential radical reactions according to the individual processes taking place has been described. The system has been used to illustrate the range and power of radical reactions in synthesis, in particular emphasising cascade reactions mediated by reagents that do not contain toxic tin. Of primary consideration were consecutive intramolecular processes, but annulation reactions, in which intermolecular additions precede cyclisations, were also discussed.

An EPR and product analysis investigation into the radical reactions of aryl aldoxime esters and ethers is described. *O*-acyl derivatives of benzaldoxime, 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime underwent direct cleavage of the N-O bond on photolysis, forming an iminyl radical and an alkyl radical via decarboxylation. Synthesis of these precursors from the corresponding carboxylic acid was high yielding, and purification was usually simple. The radicals produced by this method underwent cyclisation when appropriate unsaturation was present. Use of carbon tetrachloride as solvent enabled synthesis of chlorinated products. We have shown that *p*-methoxyacetophenone acts as a sensitiser in these reactions. The formation of iminyl radicals enabled g-factors of alkyl radicals to be calculated simply in EPR experiments, while not interfering with the main spectrum. Cleavage of the N-O bond in *O*-alkyl arylaldoximes was much less efficient, and cannot be used as a synthetic method. Radical addition to the iminyl double bond was a more efficient process.

The ability of cyclohexadienones to act as radical precursors was investigated. Preparations of suitable precursors were not efficient enough to enable the technique to be synthetically useful. 2-Allyl-2,4,6-trimethylcyclohexa-3,5-dien-1-one, **10a**, and 4-allyl-2,4,6-trimethylcyclohexa-2,5-dien-1-one, **11a**, expelled the allyl radical on reaction with the trimethylstannyl radical, as evidenced by EPR spectroscopy. 2-Benzyl-2,4,6-

trimethylcyclohexa-3,5-dien-1-one **10b** acted as a precursor to the benzyl radical, and toluene product was identified by GC/MS analysis.

Samarium(II) iodide was shown to be a suitable reagent for performing radical annulation reactions. The cyclopentenol derivatives obtained in this study readily dehydrated, and in at least one case underwent thermal rearrangement. Tin based methods were shown to be much less suitable for annulations, while manganese(III) picolinate based annulations were not investigated due to low yielding precursor preparations.

Radicals containing a boronic ester group have been characterised by EPR spectroscopy. The boronic ester group was shown to provide little stabilisation to an adjacent radical centre. The barrier to rotation around the C-B bond in unsymmetric radical **5b** was determined as 2.9 ± 0.7 kcal mol^{-1}. Hydrogen abstraction from methylboronic ester **8** by the t-butoxyl radical was shown to not be facile, and homolytic substitution was competitive. Addition to vinylboronic ester **12** by nucleophilic radicals was efficient under EPR conditions. β-Bromoboronic esters are susceptible to homolytic substitution at the boron centre under certain conditions. At lower temperatures, bromine abstraction occurs readily.

Chapter 1

Introduction: methods of generating radicals in cascade reactions

1 Introduction

1.1 Radicals in organic synthesis

The use of radicals in organic synthetic reactions has increased exponentially since the early 1980s, and numerous reviews have appeared on the subject.[1] An intriguing feature of radical reactions is the way such a wide range of different processes, contained under this large umbrella of reactions, can be carefully orchestrated to give a sequence of processes resulting in complex but predictable products. Serendipity, as usual, plays its part, and a sequence may only be discerned in retrospect, but every new sequence adds to our knowledge of the often unique behaviour of radical reactions.

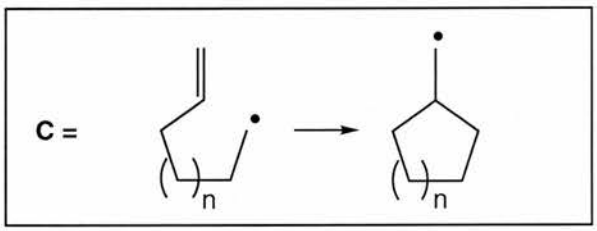
This introduction examines the different sequences encountered in radical chemistry, considering in particular the variety of ways of generating radicals that have been used in sequential reactions. Over a decade ago, Curran described the main techniques for performing radical reactions and, while advancements have been made, little of major consequence has changed.[1b] Tin is still a much used reagent in radical chemistry - by far the most prevalent in tandem syntheses - but we shall investigate other methods and see the range that non-tin methods can encompass, as well as some of the limitations. The consideration of cascade reactions should provide an indication of the scope that radical reagents can cover, and whether they may prove worthy adversaries to the 'tyrant' that is tin.[1a]

1.1.1 The different radical processes

Radical processes can be classed in many different ways, and the individual processes are described by Ingold and Beckwith.[2] Intramolecular processes are of most use in sequential radical reactions. Intermolecular processes have a big rôle to play, but are not

usually conducive to cascade reactions. Our priority will be with intramolecular processes and annulations. We shall consider only the propagation steps of a reaction as being part of a sequence, thus ignoring steps such as bromine abstraction by tin centred radicals.

The most common, and the most useful intramolecular process in its own right, is cyclisation. This class contains a large number of subtypes, all of which result in the formation of one or more ring systems. The most prevalent cyclisation in radical chemistry is the 5-*exo*[3] cyclisation resulting in a 5-membered ring. 6-*Endo* and 6-*exo* cyclisations are also not unusual. We shall introduce the notation **C** to refer to a cyclisation process, especially one that occurs in a sequential reaction (Scheme 1).

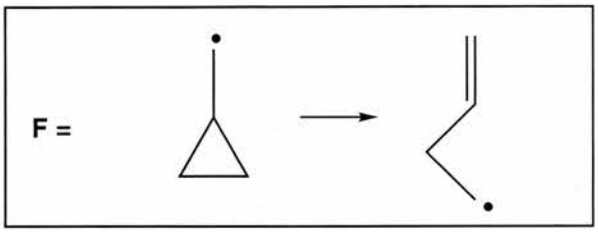


Scheme 1

Another common reaction that radicals can undergo is fragmentation. This is simply the reverse of a cyclisation, and for many processes it is thermodynamically unfavourable; for example cyclopentylmethyl radicals rarely fragment to the 6-hexenyl radical. 3-*Exo* radical cyclisations are rare because the thermodynamic equilibrium which lies too far towards the uncyclised radicals. Ring opening (i.e. fragmentation) of cyclopropylmethyl radicals is consequently an extremely rapid process. Only when a trapping process occurs sequentially, or when favourable molecular architecture is present, can processes such as the 3-*exo* cyclisation become apparent. Theoretically, a radical can often follow a number of fragmentation pathways, but again the controlling factors are well understood, so fragmentations can be useful in designed radical reactions. Fragmentation reactions will be referred to as **F**, and an example is shown in Scheme 2.

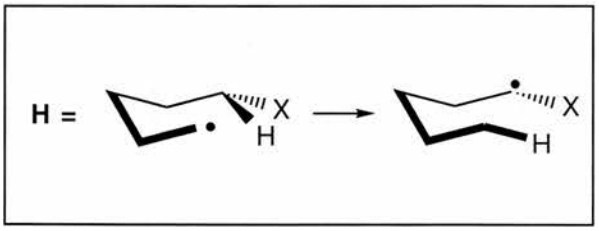
The type of fragmentation that is to be considered as most important in this review is that in which the molecule is not degraded during the process. A degradative fragmentation

process, e.g. decarboxylation, can be extremely useful in certain circumstances, and when it is referred to here, will be described by **$\underline{F_2}$**.



Scheme 2

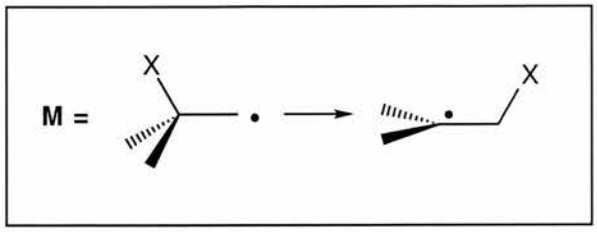
A third type of intramolecular process is hydrogen abstraction. The selectivity of hydrogen abstraction is usually dictated by the geometry of the intermediate, and so 1,5 hydrogen abstractions are the most common, but 1,6 abstractions are also very well known. Occasional 1,4 shifts can be found in the literature, but it should be noted that what may appear to be one hydrogen shift, may in reality be two sequential shifts. The overall result is the same. By the same token, it is certainly possible that a radical process ends with an unnoticed intramolecular hydrogen shift if termination involves intermolecular hydrogen abstraction from a metal hydride. A deuteride study reveals this last step, as do other methods that don't involve H abstraction in the termination step. Occasionally a final hydrogen transfer is discovered because an unexpected species is trapped, for example the product of a 3-*exo* cyclisation. Hydrogen transfers will be designated **$\underline{H}$** (Scheme 3).



Scheme 3

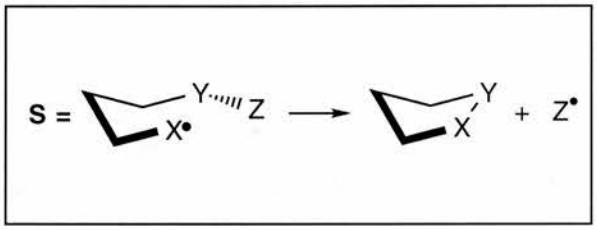
The three processes mentioned above are the main intramolecular processes, but other intramolecular processes do occur such as migration and homolytic substitution.

Migrations have been described in detail by Ingold and Beckwith, and are the most difficult to define.[2] (See Section **1.2**). The migration as we will define it rarely occurs in sequential radical synthetic processes and will be designated **M** (Scheme 4).



Scheme 4

Homolytic substitutions,[4] which occasionally occur intramolecularly as part of a sequential radical reaction will be referred to as **S** (Scheme 5).



Scheme 5

With the exception of fragmentations, the intramolecular processes described above have intermolecular analogues. Intermolecular additions have been comprehensively studied, but we are mainly concerned with intramolecular sequences. It is of interest, though, to consider intermolecular reactions (i.e. additions) that take place as part of a mainly intramolecular sequence, and we shall refer to such processes as **A**.

Other reaction types such as radical pair combination or disproportionation need not concern us here.

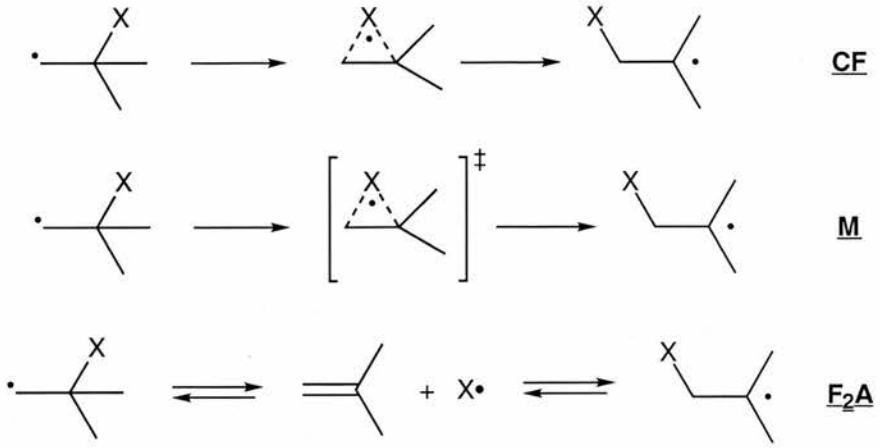
Radicals also undergo electron transfer reactions, and can be oxidised or reduced. The conversion of radicals to charged species is an important reaction, but will not be covered in this review unless the electron transfer is simply used as a terminating step, such as in manganese(III) chemistry.

1.2 When is a migration not a migration?

It is important to consider overlap between one class of reaction and another. A simple example is hydrogen abstraction, **H**, which is nothing more than an intramolecular S_H2 reaction **S** at a univalent atom. The concept of a migration becomes more difficult to define. A migration can be seen as a cyclisation, **C**, followed by an alternative fragmentation, **F**, as shown in Scheme 6 for a vinyl migration.

Scheme 6

However, not all migrations occur like this. Crich and coworkers have shown that 2-(vinyloxy)alkyl radicals rearrange to 4-ketobutyl radicals via a **CF** mechanism.[5] The β-(acyloxy)alkyl rearrangement also proceeds by this mechanism,[5] but the β-(phosphatoxy)alkyl rearrangement does not.[5b] This migration does also not involve fragmentation to a cage pair, followed by recombination. It has been shown, however, that the [2,3] allylperoxyl rearrangement does proceed by a dissociative mechanism.[6] The whole question of migration mechanisms has been addressed by Beckwith and Ingold.[2] The technique adopted will consider the nature of the mechanistic pathway. If the migration pathway proceeds via a discrete intermediate then the process is considered to be **CF** (even when the species remain in a cage), if it proceeds via a dissociative mechanism then it is an $\mathbf{F_2A}$ process, and if it proceeds via a concerted process with no discrete intermediate then this is defined as **M** (Scheme 7). It should be noted that the concerted process, **M**, is also a special type of intramolecular homolytic substitution in which the attacked centre is adjacent to the radical centre, however the distinction between **S** and **M** is appropriate because **S** requires a linear transition state.



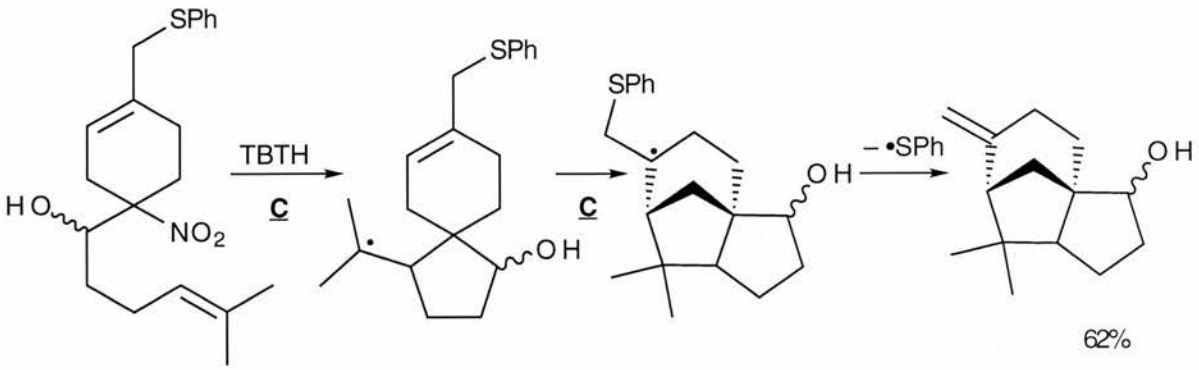
Scheme 7

Often the exact mechanism of a 'migration' will not be known, and a major factor will be the terminology used in the original paper, and it may be that informed guesswork may have to be used to describe the process. A case in point is the 1,2 phenyl migration. It is believed that this usually goes via the cyclohexadienyl radical, i.e. a **CF** process, which has not been observed by EPR spectroscopy, but has by laser flash photolysis.[2] It is not certain whether all phenyl migrations occurs by this mechanism, but we will consider them to do so.

1.3 Other discrepancies.

In our discussion of tandem reactions, we will consider mainly tandem intramolecular processes. All the tin hydride reactions can be considered to be tandem, if intermolecular abstractions are counted, but we will consider only propagation steps. This approach will also be applied to terminating fragmentations. For example, the synthesis of a norcedenone precursor shown in Scheme 8[7] will be categorised with the **CC** reactions, despite the β-scission in the final step.

The radical cyclisation onto a phenyl ring is also a process that needs clarification. Most cyclisations onto an aromatic ring are followed by a rearomatisation process, the mechanism of which is unclear. All cyclisations onto a phenyl ring will be considered as a normal cyclisation, **C**.



Scheme 8

1.4 The diverse array of radical sequences.

The purpose of this introduction is to review the wide range of different sequences of radical reactions that has been described in the literature, and to consider the various ways of generating radicals, and how these have been focussed so far. It is worth noting that the terms sequential, tandem, and cascade may be used interchangeably with regard to a reaction process.

The simplest sequence is a two step sequence, but in the last few years the control over such processes has been developed to the extent that sequences of 5, 6, or even 7 steps have been reported. We will concentrate on the sequences that have behaved as desired, but the unexpected ones are worth noting, because a sequence that is unwanted in one situation may be helpful or instructive in another. The main two step sequences may be arranged as shown in table 1.

Code for Unimolecular 2-Stage Cascades

Initial Step	2nd Step		
	C	**H**	**F**
C	**CC**	**CH**	**CF**
H	**HC**	**HH**	**HF**
F	**FC**	**FH**	**FF**

Table 1

These vary from extremely common (**CC**) to the seemingly trivial (**HH**), and this introduction will try to cover, in a fairly logical order, how the different sequences have been used in syntheses.

The table for 3-step sequences, apart from being much larger, contains many more little used sequences. There are not enough dimensions on a piece of paper to illustrate 4-step sequences in a single matrix, but there are fewer 4-step or longer sequences, and they consist mainly of ring expansions (**CF**) and cyclisations in sequence, and we shall consider these as well.

Code for Unimolecular 3-Stage Cascades

Initial Step	2nd Step C	2nd Step H	2nd Step F	Final Step
C	CCC	CHC	CFC	C
	CCH	CHH	CFH	H
	CCF	CHF	CFF	F
H	HCC	HHC	HFC	C
	HCH	HHH	HFH	H
	HCF	HHF	HFF	F
F	FCC	FHC	FFC	C
	FCH	FHH	FFH	H
	FCF	FHF	FFF	F

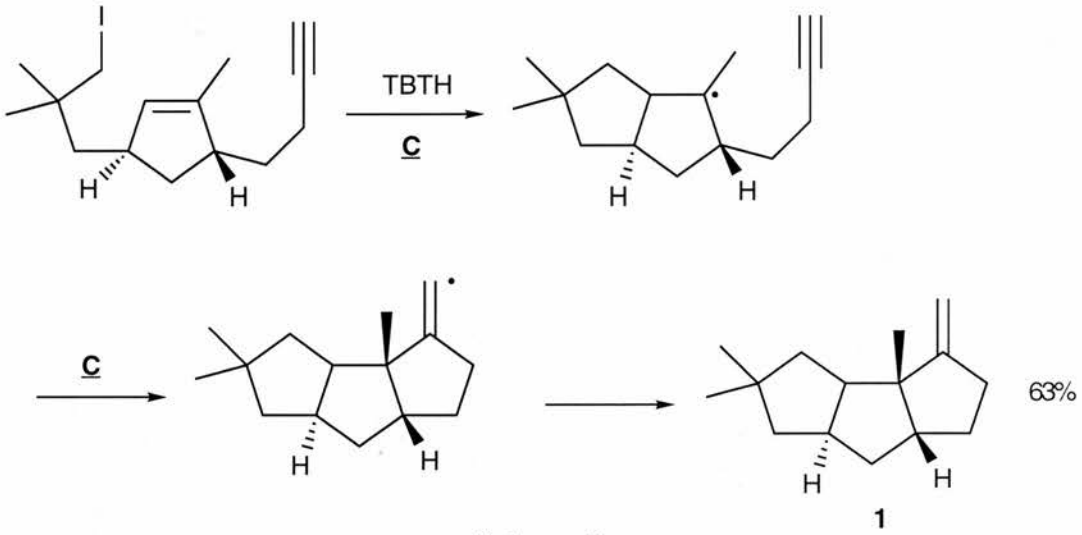
Table 2

1.5 Reactions started by a cyclisation

Tandem cyclisations are by far the most common, and are too numerous to describe comprehensively. Instead we will look at as diverse a range of reactions as possible, illustrating the different types of polycyclisation, and the methods used to achieve them.

1.5.1. Reactions that start with a double cyclisation, CC.

The simplest type is the double cyclisation. The tin hydride method is the most common way of generating an alkyl radical, and Curran used this method in his early syntheses of hirsutene **1**[8] (Scheme 9) and $\Delta^{9(12)}$capnellane.[9] These are both examples of what Malacria described as utilising a "one-ring template strategy,"[1i] in which the central ring is crucial. This is one of the categories into which we can divide cascade cyclisations.



Scheme 9

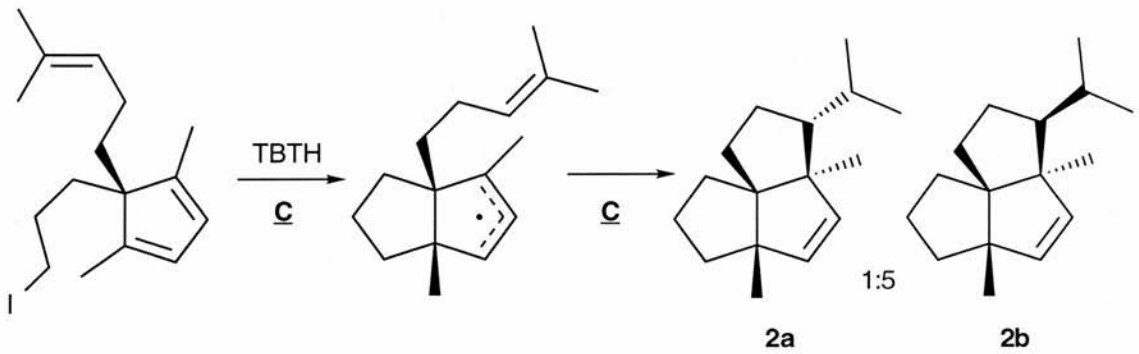
1.5.1.1 The one-template ring strategy.

These reactions utilise precursors that already contain a ring and "bias the stereochemical outcome of the cyclisation."[1i] A vast majority of these types of reaction use tin centred radicals to mediate the reaction.

1.5.1.1.1 Tin hydride based methods of generating alkyl radicals.

The syntheses described above were early examples of a boom in the syntheses of natural products using tandem radical reactions, and a review of radical based syntheses of natural products appeared in 1991.[10] The one-ring template strategy was also used by Curran in the **CC** syntheses of (±)-silphiperfol-6-ene and (±)-9-episilphiperfol-6-ene,[11](±)-modhephene and (±)-epimodhephene,[12] and the BCD ring section of crinipellin A, **2a**.[13]

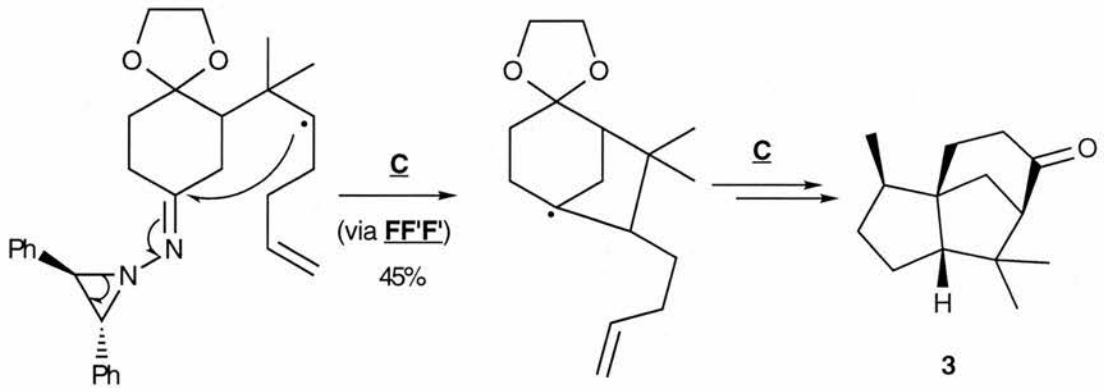
This last example demonstrated an interesting range of sequential reactions towards the same target molecule. The methods all require the cyclisation of an allylic radical, which worked well, but gave the 'wrong' isomer **2b** in a 5:1 ratio. The main point of note is the 1,3 transposition of the intermediate radical. Curran's 'Protecting Group/Radical Translocation' method (See Section **1.7.1**) was also used (**HCC**), as were selenyl esters to generate an acyl radical. Unfortunately the unnatural isomer was always the major product.



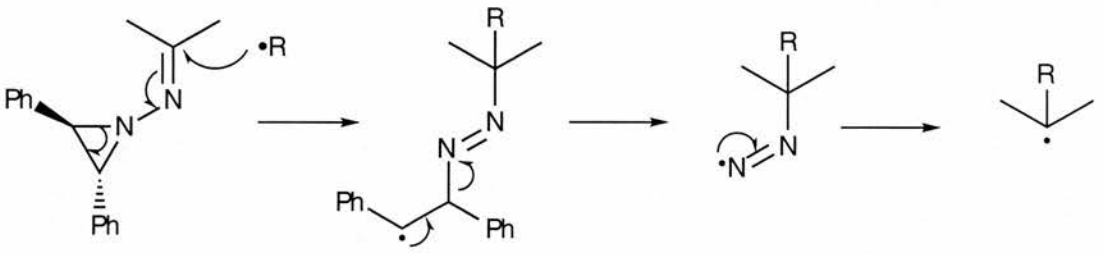
Several natural products (or frameworks) have been synthesised in the lab of Parsons since 1991 using "one-ring template strategy" tandem **CC** processes; lysergic acid derivatives,[14] a model for pseudocopsinine,[15,16] and aspidosperma (in only 6% yield).[16] Morphine,[17] (±)-α-cedrene,[7] and α- and β-biotol[18] have also been targeted using these techniques.

The above reactions are all fairly standard tandem reactions; the radicals are generated using tin hydride, intermediates are carbon centred alkyl radicals, and the cyclisations proceed in the 5-*exo* mode. This need not be the case however, and exploration of other types begins to reveal how diverse cascade radical reactions can be, even in the limits of "one-ring template" **CC** reactions. One of the many syntheses of α-cedrene **3** provides an illustration of the potential value of *N*-aziridinylimines in cascade radical reactions (Scheme 10).[19] *N*-Aziridinylimines act as geminal radical donors/acceptors,[20] a rôle also performed by isonitriles among others, which means that the carbon onto which addition has taken place is also the carbon from which the subsequent addition will occur. (The actual process that results in the radical donor being on the same carbon as the radical acceptor is a cascade $\mathbf{FF_2F_2}$ sequence as shown in Scheme 11, but we shall disregard this.)

Kim also used the same technique in the syntheses of *dl*-pentalenene,[21] *dl*-zizaene, and *dl*-khusimone,[22] and the technique has also been used in the synthesis of (+)-7-deoxypancratistatin, in which the second cyclisation was onto an aldoxime ether.[23]

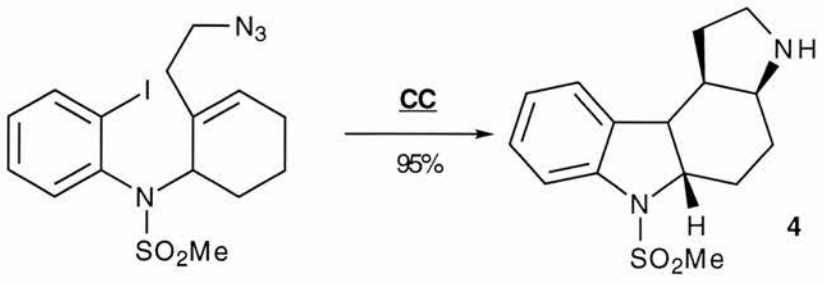


Scheme 10



Scheme 11

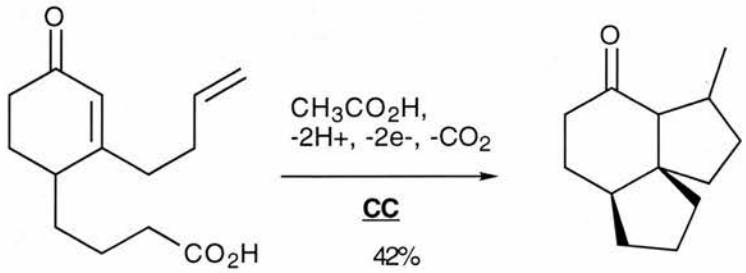
Cyclisation onto an azide moiety results, via a fragmentation, in the formation of an aminyl radical.[24] Kizil and Murphy have incorporated this into a **CC** process, resulting in the polycycle **4** in 95% yield (Scheme 12).[25]



Scheme 12

1.5.1.1.2 Double cyclisation of alkyl radicals generated electrochemically from a carboxylic acid

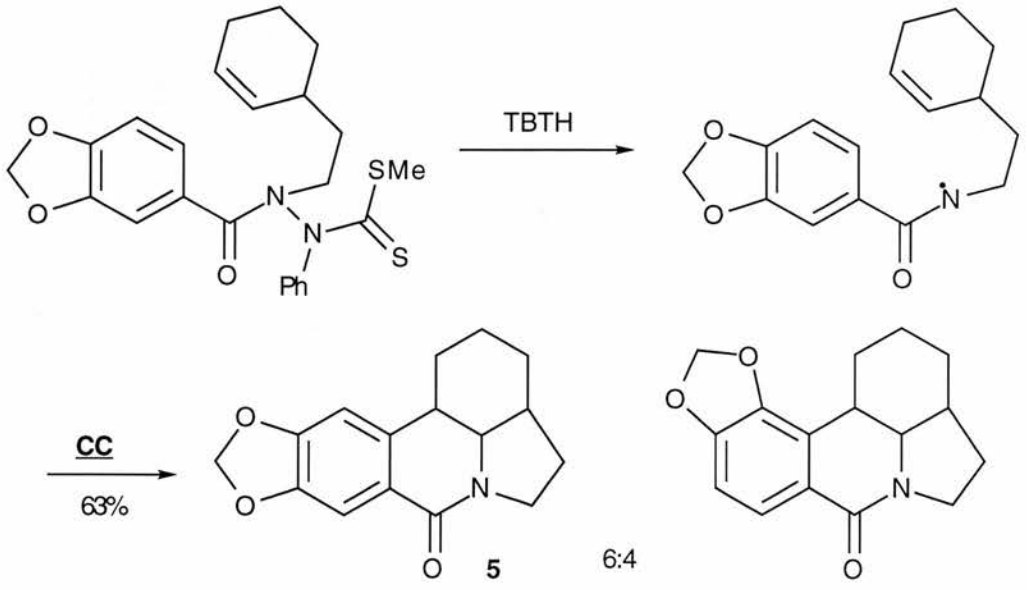
Alkyl radicals can be generated electrochemically - the Kolbe electrolysis - and a cascade **F_2CC** reaction has been described (Scheme 13).[26] Reaction conditions were crucial, with current density being the important factor.



Scheme 13

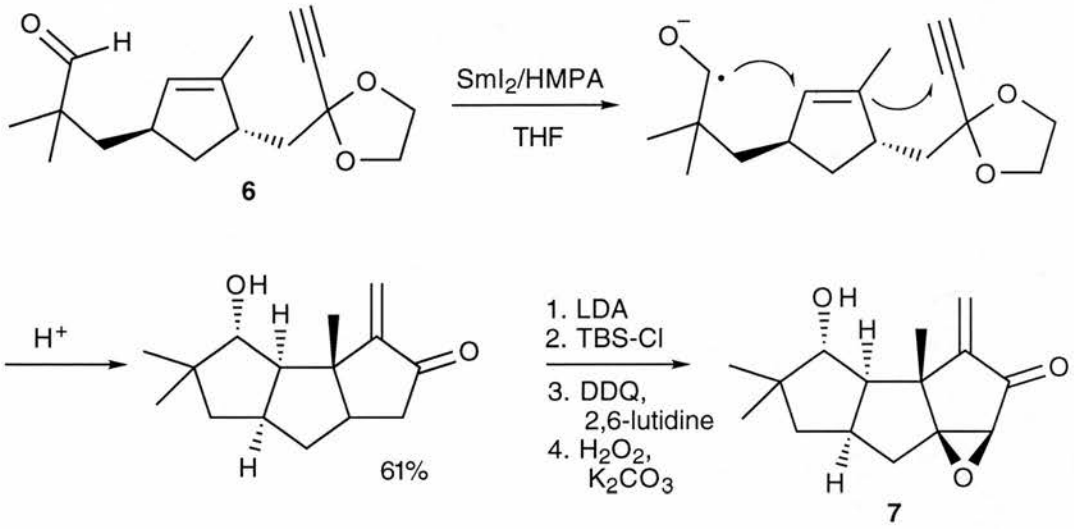
1.5.1.1.3 CC reactions of radicals other than alkyl radicals

It need not be alkyl radicals that are used in these cascade reactions. Cyclisation of an amidyl radical was used in the **CC** synthesis of (±)-γ-lycorane (Scheme 14).[27] The cyclised product was a 6:4 mixture of desired (major product) and undesired regioisomers. The major isomer **5** was reduced to (±)-γ-lycorane with lithium aluminium hydride.



Scheme 14

Curran used samarium(II) iodide, an under-used reagent in cascade radical-mediated syntheses, to generate a ketyl radical in his syntheses of (±)-hypnophilin (total) and (±)-coriolin (formal).[28] The synthesis of (±)-hypnophilin is shown in Scheme 15. Other methods of generating ketyl, or ketyl-like radicals failed; Corey's TMSCl/Zn method,[29] and a method in which aldehyde **6** was irradiated in HMPA.[30]



Scheme 15

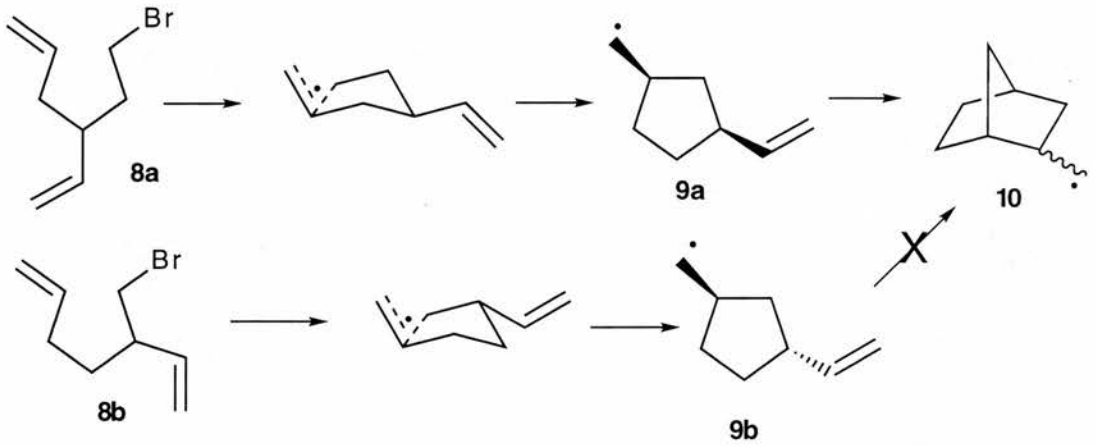
1.5.1.2 The Acyclic approach

The "acyclic approach"[1i] in **CC** reactions shows an even greater diversity than the one-ring template approach. In this approach there are no rings already present to enable easy stereoselectivity;[31] however stereoselectivity is often still extremely good.

In the early 1980s Beckwith described bicycle syntheses from acyclic precursors as part of his investigations into stereoselectivity of ring closure of substituted hex-5-enyl reactions, illustrating potential pitfalls.[32,33] The radical obtained from bromodiene **8a** cyclises to give predominantly **9a**, with a *cis* configuration, which can undergo a second cyclisation to give bridged bicycle **10**. **8b** cyclises to give the same radical, but this time

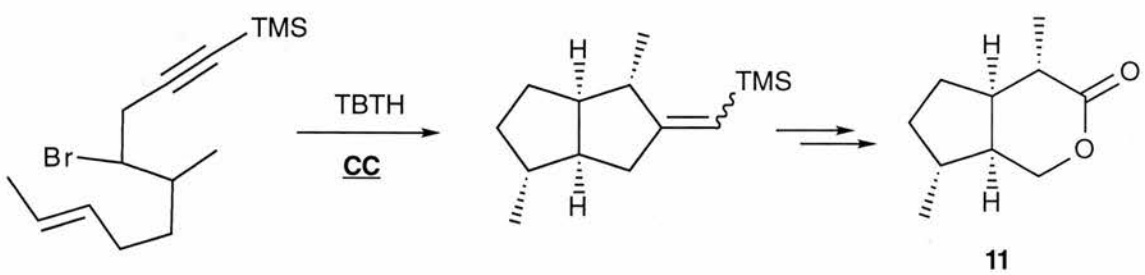
predominantly in the *trans* configuration, which cyclises very slowly. Only small amounts of bicycles were formed.

Sometimes it is the case, as we shall see later, that two different configurations of the same radical undergo completely different sequences.



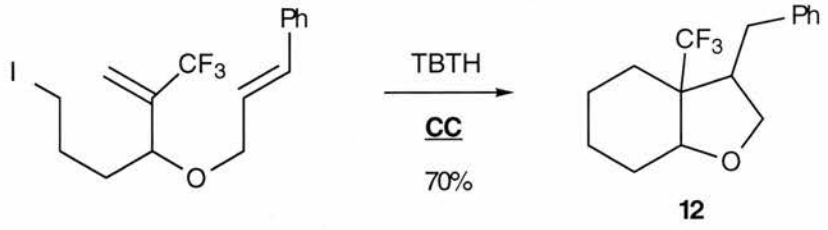
1.5.1.2.1 The tin hydride method; sequences containing 5-*exo*, 6-*endo*, and 6-*exo* cyclisations

We shall start off by considering a small selection of simple cascade **CC** reactions initiated by the metal hydride method. An early example of an acyclic system being used in the synthesis of a natural product framework was provided by Parsons, in an avermectin A_{2b} synthesis.[34] Kilburn used a simple **CC** reaction in the synthesis of isoiridomyrmecin, **11**, demonstrating the high degree of stereoselectivity that can be obtained even without a template ring (Scheme 16),[35] while Adrio *et al.* reported unusual stereoselectivities when the final cyclisation of a **CC** sequence was onto an α,β-unsaturated sulfone.[36]



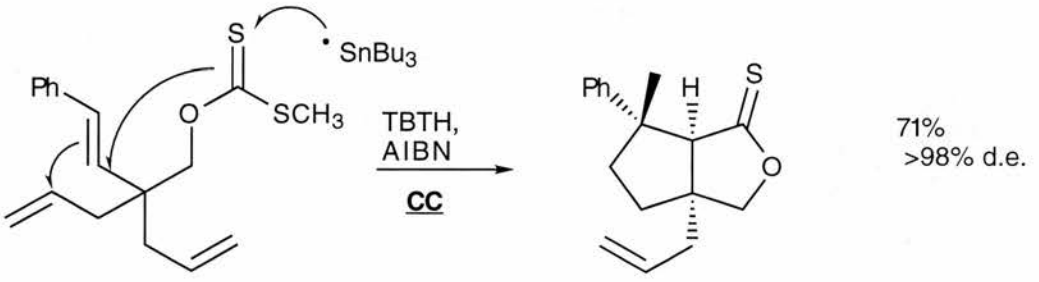
Scheme 16

Morikawa *et al.* demonstrated that awkward angular trifluoromethyl substituted bicycles such as **12** could be synthesised by a **CC** sequence that started with a 6-*endo* cyclisation.[37]



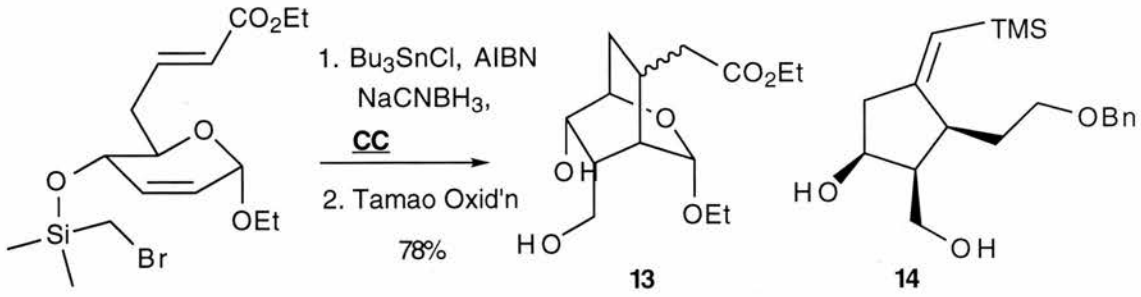
12

γ-Thionolactones have been synthesised in an unusual use of xanthates (although the method still makes use of tin hydride).[38] An example is shown in Scheme 17. The initially generated radical cyclises rather than fragmenting, resulting in sulfur containing products. At no time was an undesired **CCC** reaction observed. The product γ-thionolactones provide a route to the more useful γ-lactones.



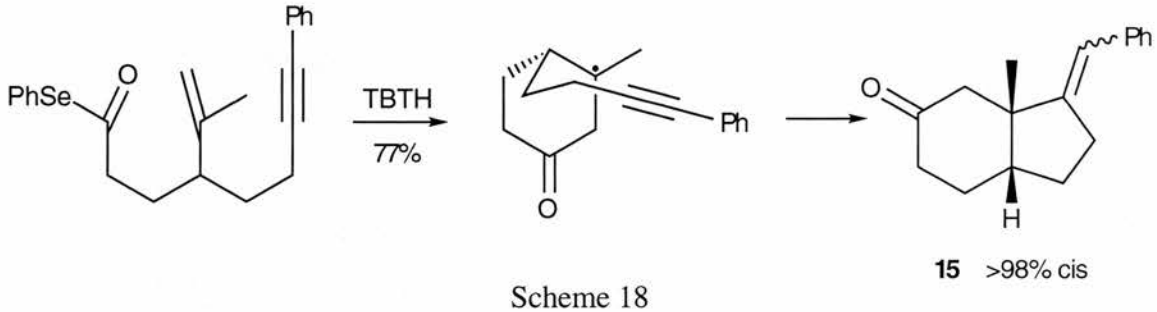
Scheme 17

(Bromomethyl)dimethylsilyl allyl ethers have been the subject of extensive studies, mainly by the group of Malacria, who have reviewed the work.[1i,39] The silicon is used as a tether, utilising the increased stereocontrol inherent in the cyclisation reactions. Tamao oxidation[40] results in the formation of a 1,3 diol in a stereoselective manner. Much of the work involves long, complex and elegant sequences, which will be covered later, but a couple of examples of simple **CC** sequences are illustrative. The technique, which originated from the work of Nishiyama,[41] was used by Fraser-Reid as a means to a Woodward reserpine **13**, in enantiomerically pure form,[42] and more recently by Belval *et al.* as a synthetic route to **14**, an isoprostanoid precursor.[43]



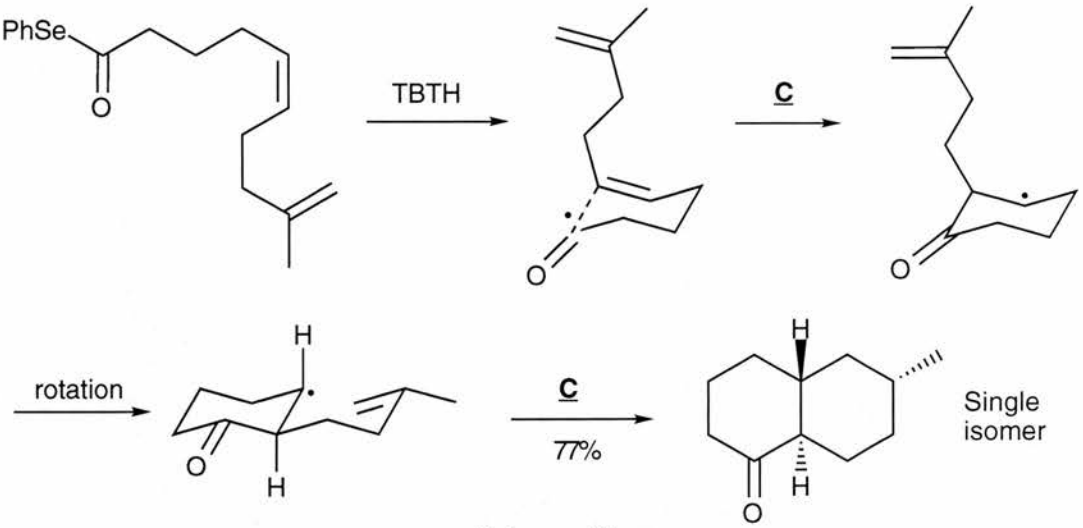
1.5.1.2.2 Acyl radical cyclisations

The tin hydride method is one way in which an acyl radical can be generated, usually from a phenylselenide, and is often the most convenient. The chemistry of acyl radicals, including cascade reactions, has recently been comprehensively reviewed[44] so only a couple of illustrative examples will be described here. Boger and Mathvink have demonstrated the cyclisations of acyl radicals in a cascade sequence that begins with a 6-*endo* cyclisation (Scheme 18).[45] Related reactions involving a 6-*exo* cyclisation displayed a much poorer stereoselectivity.



Scheme 18

Literature reports on the tandem reactions starting from acyl radicals have concentrated on consecutive 6-*endo* cyclisations. This may be due, as Chatgilialoglu *et al.* pointed out,[44] to the fact that consecutive 6-*endo* cyclisation can lead to fused polycyclic rings. It helps, though, that the initial acyl radicals are more likely to cyclise in a 6-*endo* fashion, either directly or by ring expansion. One example of a 6-*endo*/6-*endo* **CC** reaction is shown in Scheme 19.[46] Longer sequences from acyl radicals have also been reported, and these are described in Section **1.5.2**.

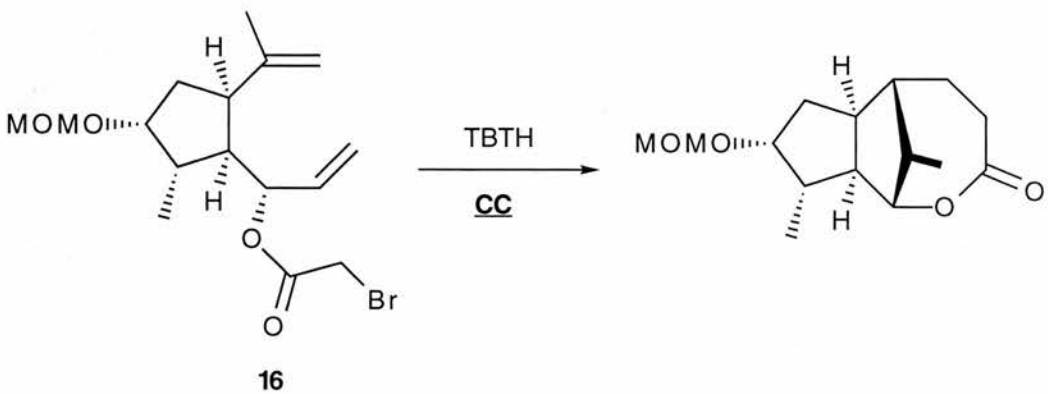


Scheme 19

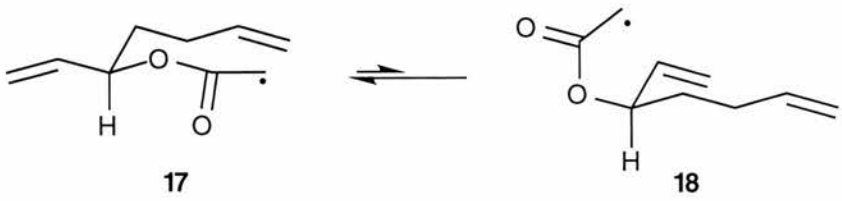
1.5.1.2.3 Unusual and disfavoured cyclisations

Again, cascade cyclisations are not limited to 5-*exo*, 6-*endo*, and 6-*exo*. Other sequences are possible, including steps disfavoured according to Baldwin's rules,[3] as we will see later.

5-*Exo* cyclisations do not always occur readily. Having made guaianolide via a 5-*exo*/7-*endo* sequence,[47] Lee *et al.* were optimistic that a tricyclic γ-lactone could be synthesised from **16** via a 5-*exo*/7-*endo* sequence.[48] Instead, the initial (alkoxycarbonyl)methyl radical preferred to cyclise in an 8-*endo* fashion, and underwent an 8-*endo*/5-*exo* **CC** sequence (Scheme 20). The simple (alkoxycarbonyl)methyl radicals favour the *Z*-conformation **17**, unsuitable for 5-*exo* cyclisation.

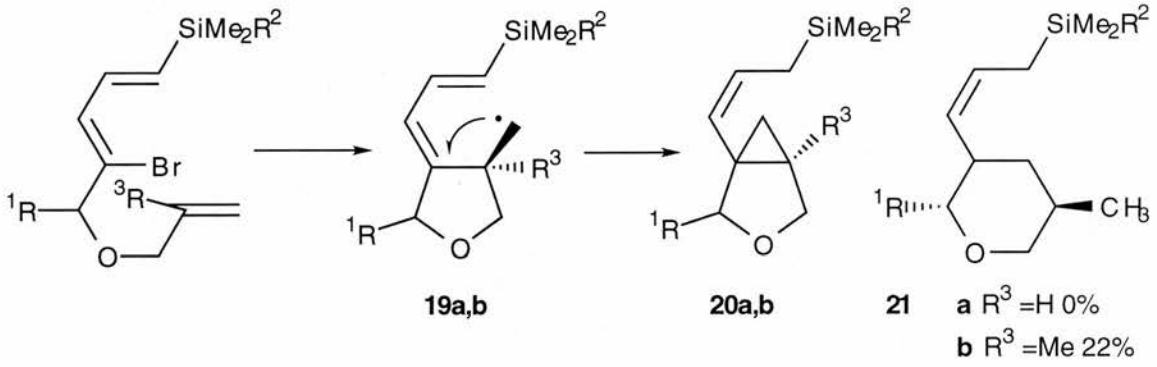


Scheme 20



17 18

Under certain conditions, 3-*exo* cyclisations can occur irreversibly, for example when the resultant radicals are stabilised as in the **CC** reaction shown in Scheme 21.[49] Radical **19b** led to the ring-opened product **21b** due, it was claimed, to the extra stability conferred by an additional methyl group (rather than simple steric effects). An extension to this technique was seen by Malacria, when a cyclopropyl ring was formed as the final step of a **CCC** reaction.[50]



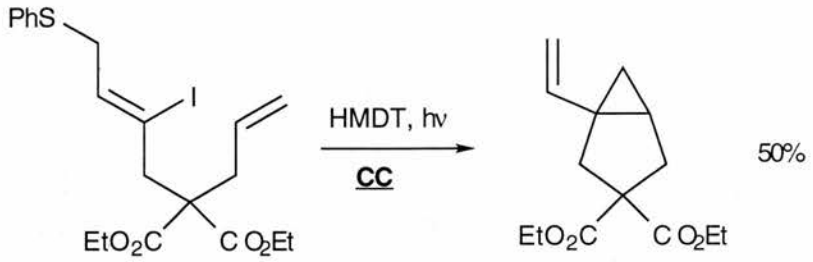
19a,b **20a,b** **21** **a** R^3 =H 0% **b** R^3 =Me 22%

Scheme 21

A similar sequence in which the radical was generated electroreductively will be seen in Section **1.5.1.2.6.**

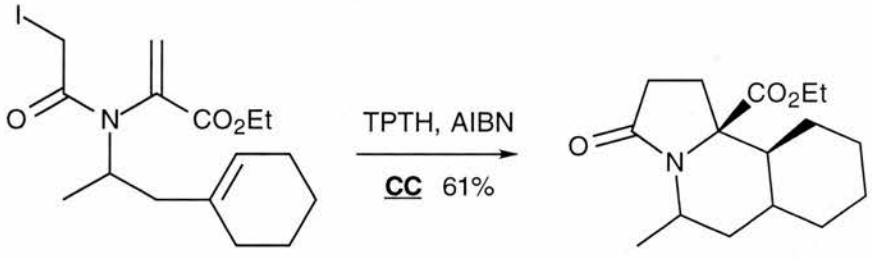
Gravel used two different methods involving cascade radical cyclisations to generate 3-membered rings, both of which involved the initial cyclisation of a vinyl radical.[51] The work of Srikrishna *et al.*[52] was verified in a **CC** reaction that showed that cyclopropane rings are readily formed if the strain present in the ring is already present in the precursor, and this is only partially overcome even when a strong radical stabilizing group (such as a phenyl group) is adjacent, to try to prevent the 3-*exo* cyclisation.[51a] His group also trapped the cyclopropyl ring by following the reversible 3-*exo* cyclisation with an effectively irreversible fragmentation (Scheme 22).[51b] The reaction worked fairly well with an initial 5-

exo cyclisation, but a [1,5]H shift was found to be preferred to 6-*exo* cyclisation, resulting in an **HC** sequence, which was followed by a terminating fragmentation.



Scheme 22

5-*Endo* reactions are 'disfavoured' and uncommon, especially in hydrocarbons (although we shall later see one in a cascade reaction), but the presence of heteroatoms can enable such ring closures to take place. α-Carbamoylmethyl radicals can cyclise in a 5-*endo* fashion, and appropriate derivatives have been used by Parsons in **CC** reactions to give indolizidinones via a 5-*endo*/6-*endo* sequence (Scheme 23).[53] Attempts at pyrrolizidine synthesis from similar compounds with appropriately placed electron withdrawing groups failed.

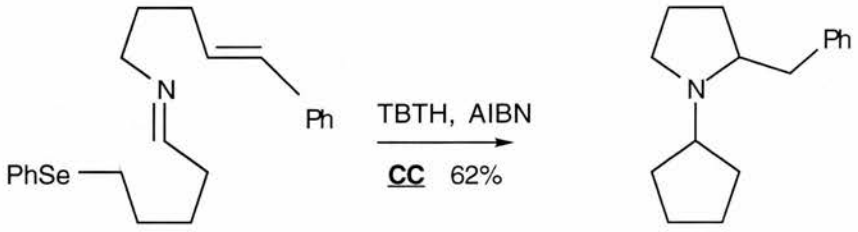


Scheme 23

The presence of the carbonyl group in the precursor was vital - enamines merely underwent decomposition, presumably because the carbonyl group crucially affects the geometry of the radical. These enamide radicals have been generated by other methods (Ni[54] and $Mn(OAc)_3$[55]), but not yet used in cascade reactions. The same radicals can also undergo 4-*exo* cyclisations under favourable conditions, to give β-lactams, but again this has not so far been used in cascade reactions.[56]

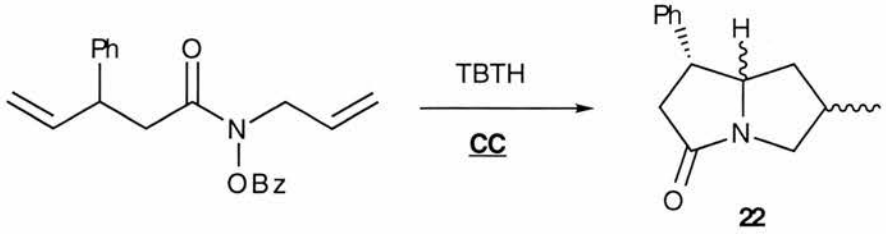
1.5.1.2.4 Sequences involving hetero-centres

Tandem cyclisations involving hetero-centred radicals are also fairly common, especially nitrogen-centred radicals. Free-radical cyclisations involving nitrogen were reviewed in 1997.[57] Nitrogen-centred radicals can not be generated by halogen abstraction, so other methods have to be used. Bowman generated aminyl radicals by cyclisation onto an imine (Scheme 24), and designed the system such that further cyclisation occurred.[58] Sometimes, a Lewis acid was required, and yields were variable.



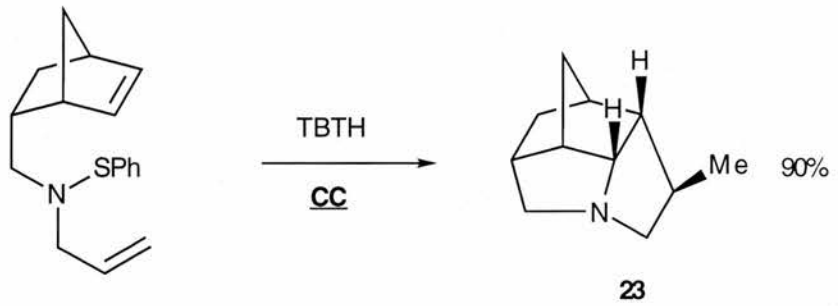
Scheme 24.

Apart from Kim's geminal donor/acceptor *N*-aziridinylimine method,[19] and the work of Bowman,[58] cyclisation onto a functionality to give a hetero-centred radical for use in cascade reactions does not seem to have been exploited. There have been a few examples of nitrogen-centred radicals being generated initially, that then undergo cascade cyclisations. Zard's method in the synthesis of (±)-γ-lycorane has already been described, in the one-ring template section, but amidyl radicals have also been generated from *N*-hydroxypyridine-2-thione imidate esters (or 'PTOC imidate esters'),[59] - a non-tin method! - and *O*-acyl hydroxamic acid derivatives,[60] and used in cascade cyclisations resulting in products such as **22**, containing a bridgehead nitrogen.



22

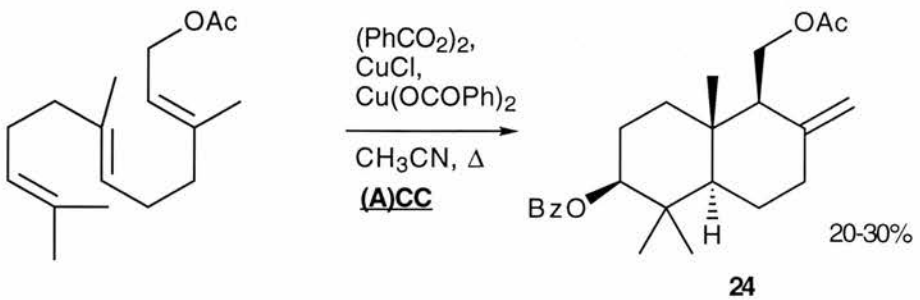
Aminyl radicals are less electrophilic than amidyl radicals, and seem to be less well behaved, but can still undergo cascade cyclisations. They too can be generated from the PTOC ester, and have been used in a tandem fashion,[61] but Bowman has described a series of reactions in which aminyl radicals generated from phenylsulfenamides have undergone **CC** reactions, including the formation of polycycle **23**, in an excellent yield (90%).[62]



23

1.5.1.2.5 Oxidative methods of generating radicals used in tandem 'acyclic method' double cyclisations.

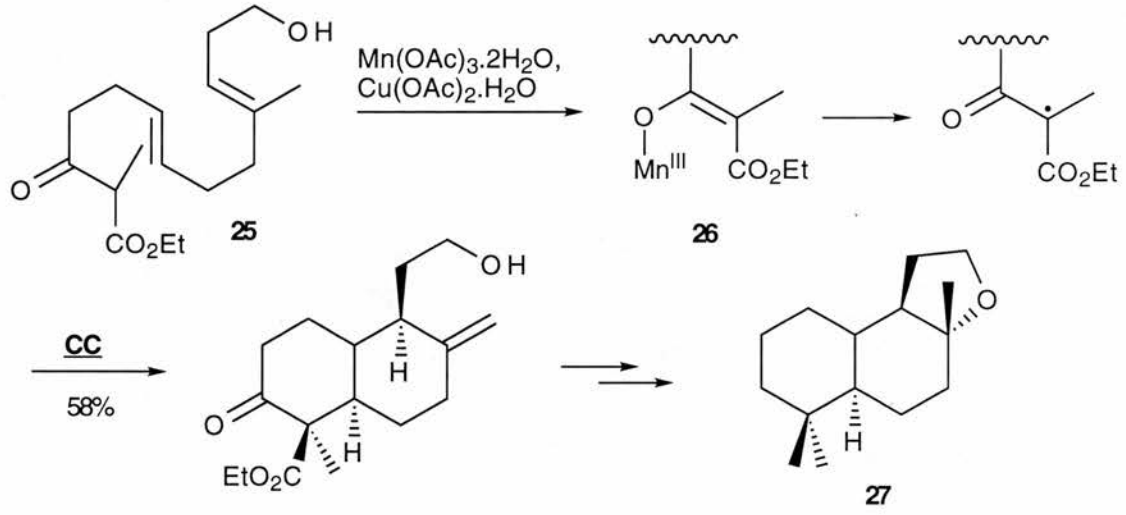
As long ago as 1968, a tandem oxidative cyclisation was reported by Breslow (Scheme 25).[63] The reaction, which was initiated by the addition of a benzoylperoxy radical to an alkene, consisted of consecutive 6-*endo* cyclisations, followed by an oxidative termination step. Although this method appears not to be generally applicable, it was followed by a great number of related oxidative cyclisations, mostly using manganese(III) acetate. The extensive use of this one-electron oxidant in tandem cyclisations and annulations was comprehensively reviewed in 1996,[64] and another review of the subject is also available.[65]



24

Scheme 25

Many of the **CC** cyclisations performed using manganese(III) acetate were models for longer sequences (see Section **1.5.2**), and a single example, which illustrates the use of the technique in synthesis, is sufficient to demonstrate the method. (-)-Norlabdane oxide, **27**, is highly valued in the fragrancy industry, and a precursor is made by the tandem cyclisation of the radical derived from **25**.[66] (Scheme 26) The radical is formed via the enolate **26** (although the exact mechanism depends on whether or not the β-keto ester is α-substituted or not[67]), and the electrophilic carbon centred radical undergoes a tandem cyclisation before oxidation takes place, in this, and most other cases, by a Cu(II) salt, to form the alkene. Natural products that have been synthesised utilising a Mn(III) **CC** method include aloesaponol III and okicenone,[68] and the gibberellic acid CD ring system.[69]



Scheme 26

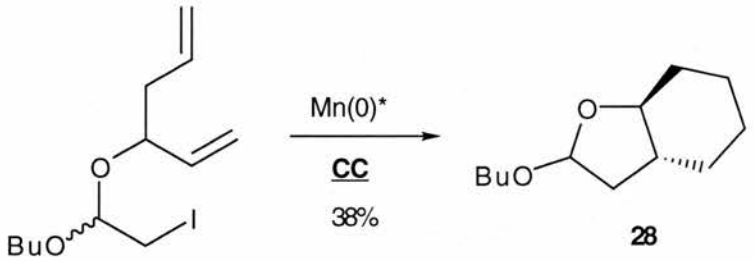
Unfortunately, the simple system is not available as a replacement for tin hydride in radical reactions, as only hydrogens on enolisable carbons are (effectively) abstracted, but it provides a neat, complementary method.

1.5.1.2.6 Other techniques in the acyclic method.

Of the vast number of ways in which a radical sequence can be initiated,[1a] some are wide-ranging in their scope, and some are limited, but many can still be used in tandem cyclisations. The triethylborane/oxygen system has been increasingly used, including

tandem cyclisations,[70,71] (and contains an interesting example of a reaction which proceeds well for one steroisomer, but not for another) but other, less well known methods provide interesting cases. Pattenden used cobalt(I) dimethylglyoxime to mediate tandem reactions on the way to lactones, but the yield was found to be higher if the cobaloxime intermediate was isolated, rather defeating the point![72]

Recently, an active manganese(0) species has been shown to induce radical cyclisation such as the tandem sequence shown in Scheme 27.[73] Significantly, the reaction precursor is an iodide, so the undesirable tin hydride could also have been used for this reaction (assuming that the unusual 6-*endo* second cyclisation is not a consequence of the method). Unfortunately, yields of the bicyclic product **28** are moderate.

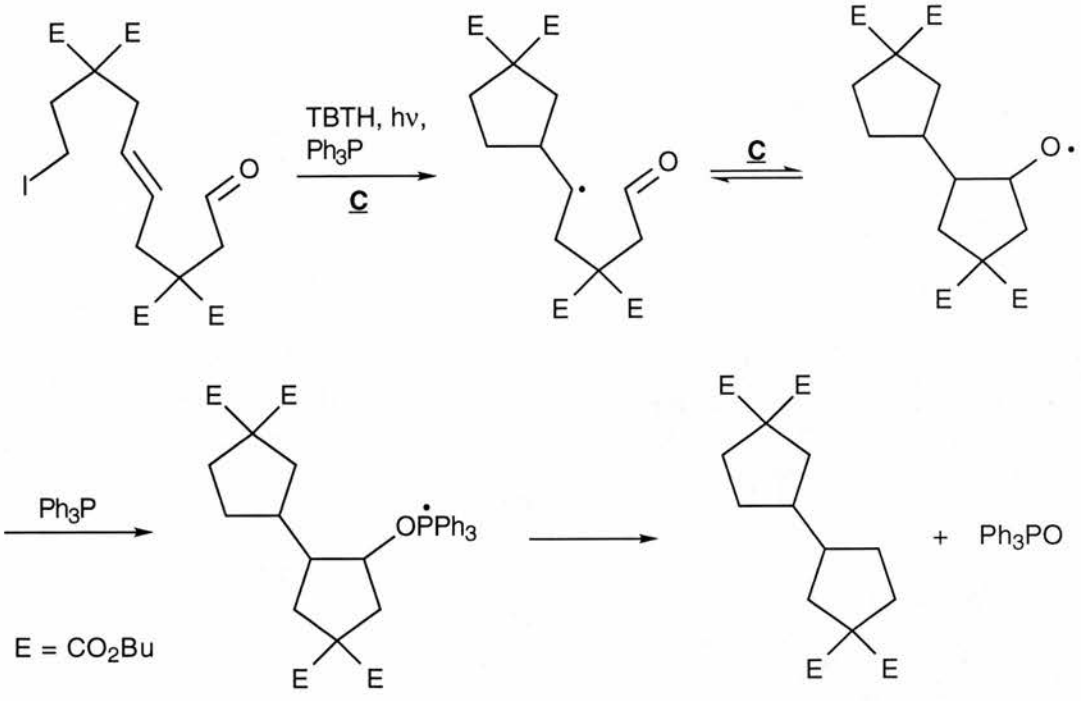


28

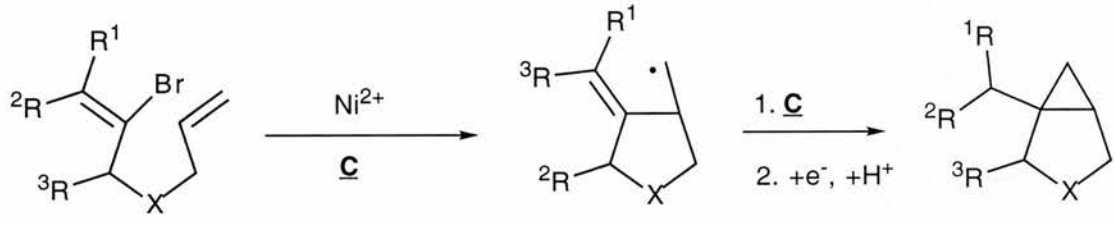
Scheme 27

Kim showed that cyclisations onto aldehydes could precede deoxygenation with organophosphorus(III) compounds, and that this method was feasible in tandem reactions as well (Scheme 28),[74] although in fact the whole process can be considered a **CCAF$_2$** process. While this method may facilitate the use of precursors where the terminal alkene is more awkward to prepare than the aldehyde, it still employs tin hydride and may not have wide application.

It was seen in Section **1.5.1.2.3** how 3-*exo* cyclisations may be rendered irreversible by stabilising the product radical. This technique was used to generate a cyclopropane ring from a radical generated electroreductively, with the reaction catalysed by a nickel complex (Scheme 29).[75] It is necessary for R^1 and R^2 to be radical stabilising groups, and best yields (66%) were obtained when $R^1 = R^2 = R^3 = Ph$, X = O.



Scheme 28

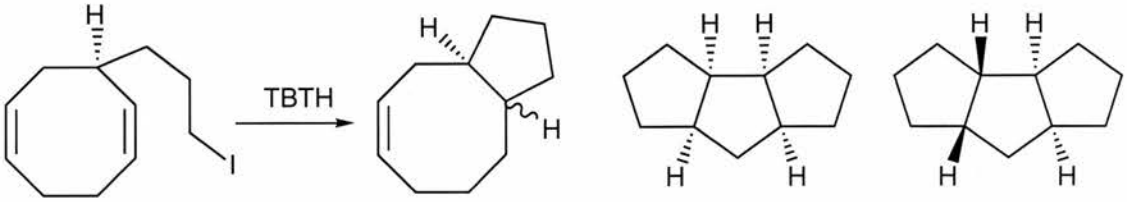


X = O, NTs, NBn, $C(CO_2Et)_2$

Scheme 29

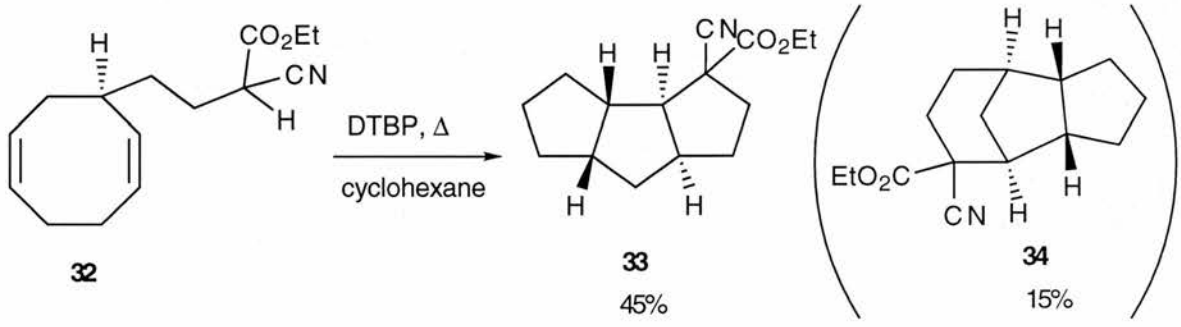
1.5.1.3 Transannular CC reactions

A different type of tandem cyclisation is the transannular cyclisation. Again, these are potentially very useful reactions which may have been passed over for some years because of perceived difficulties in the synthesis of medium and large rings, which are the precursors. A study by Winkler and Sridar on the formation of linear fused cyclopentanoids (Scheme 30) revealed that the first cyclisation occurred mainly (3:1) in a *trans* fashion, which did not allow the second cyclisation to take place.[76]



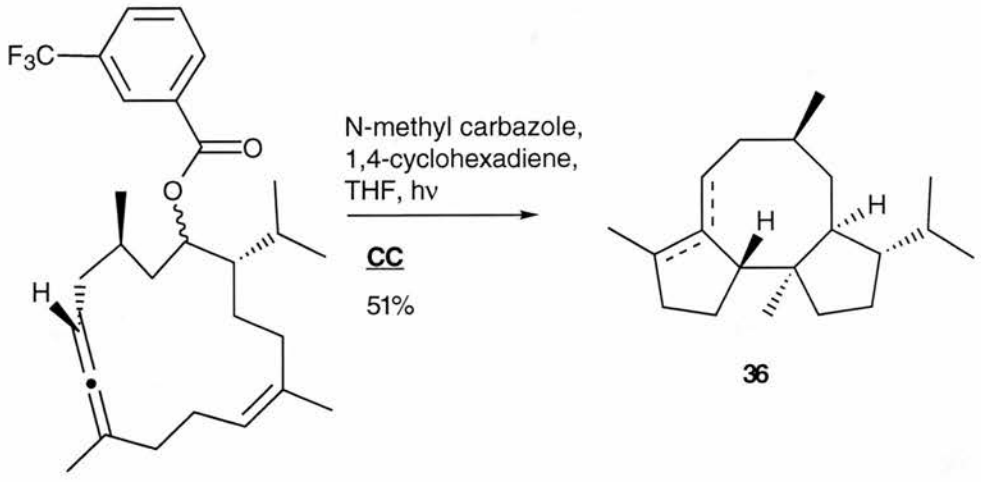
Scheme 30

However, the presence of the radical stabilising groups in cyclooctadiene **32** rendered the cyclisation reversible, and the more stable *cis* ring system was formed, resulting in **33** as the major product in 45% yield (Scheme 31).[76] Conformational studies indicated that a substituent in the 4-position *trans* to the alkyl chain should also improve the proportion of *cis*-fused product, and this was found to be the case, although the effect was only fairly small.[77]



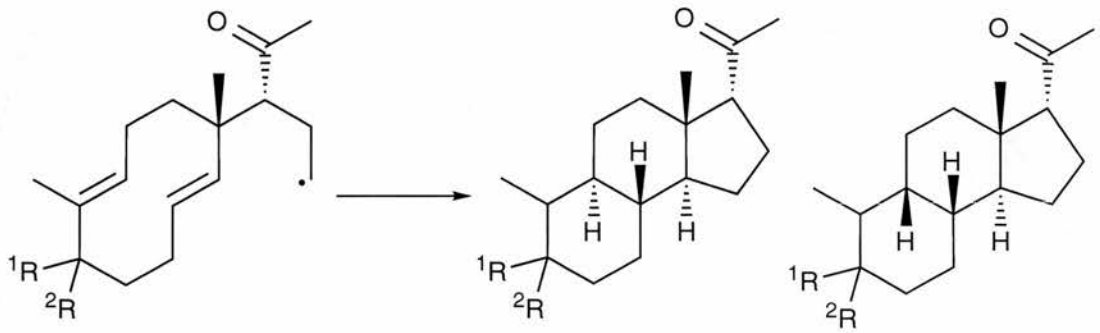
Scheme 31

Myers and Condroski performed a tandem transannular **CC** reaction as the key step in their synthesis of (±)-7,8-epoxy-4-basmen-6-one.[78] Both cyclisations were transannular. Tin based radical generation methods were unsuccessful due to the tendency of the tin-centred radical to add to the allene moiety in the radical precursor. The successful method involved illumination of the (trifluoromethyl)phenyl ester **35** with *N*-methylcarbazole and 1,4-cyclohexadiene in THF, which resulted in the target precursor **36** in 51% yield.



35 36

Recently, the progesterone BCD ring system has been synthesised using transannular methodology.[79] The authors used MM2 transition state models to predict the stereochemical outcome of reactions from two different precursors, **37a** and **b**. These showed that the ketone would favour the undesired product, whereas the acetal, **b**, would almost exclusively favour the desired isomer. The acetal was used in the reaction with the expected result.



37a R1,R2 = O
37b R1,R2 = -OCH_2CH_2O-

38a 22%
38b 87%

39a 56%
39b 1%

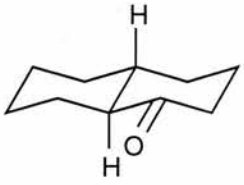
Scheme 32

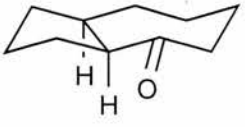
Pattenden has shown a continued interest in the use of transannular cyclisations, and taken the method a stage further by forming the macrocycle in an *endo* radical cyclisation as well, thus avoiding the difficulty of forming a medium-sized ring in a separate step. An early application was to synthesise the taxane ring system in low yield via a 12-*endo*-6-*exo*

sequence,[80] or via a 12-*endo*/8-*endo* sequence,[81] (in which alternatives to the tin method, such as TTMSS, were tried, and found to be less successful) and the method has also been used to make fused lactones and lactams.[82] More recently, his group has contributed a detailed investigation of the scope of the reaction.[83] The macrocyclisation needs to be onto an enone e.g **40** or **41**, and it was shown that **40** and **41** followed different pathways, which were ascribed to the different conformations adopted by the two macrocyclic radicals.

40

41





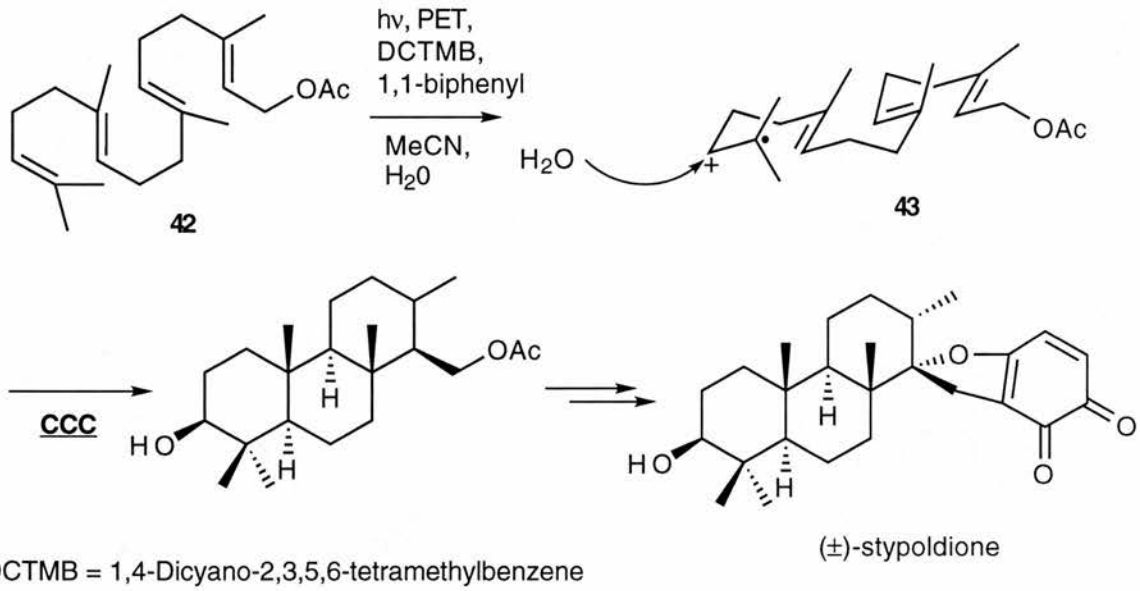
From **40**	28%	42%	0
From **41**	34%	0	34%

Scheme 33

A variety of **CC** reactions were investigated,[83a] mainly with success, although it was noted that 5-*exo* cyclisations will occur "given half a chance" in preference to macrocyclisation. Another surprising limitation was discovered when a 3-*exo* cyclisation occurred instead of macrocyclisation, and was rendered irreversible by sequential 5-*exo* cyclisation to give a stabilised α-keto radical.[84] The technique was extended to **CCC** reactions, and this is described in Section **1.5.2**.

1.5.2 CCC and longer polycyclic sequences

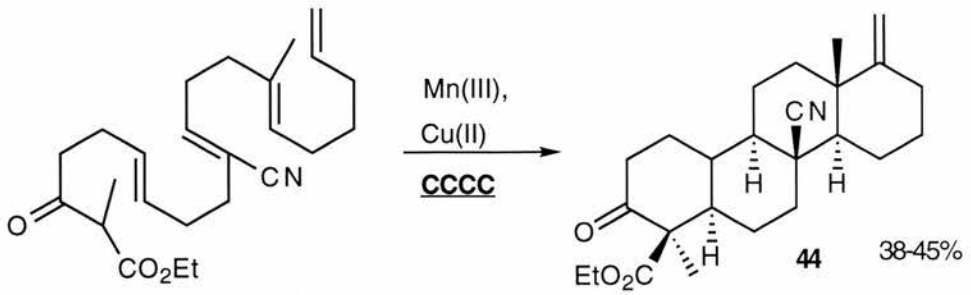
Longer cascades of cyclisations are more likely to involve precursors which contain repeating units, as exemplified by the cascade initiated by an unusual photoelectron transfer method that is shown in Scheme 34.[85] Although the mechanism involves an initial cationic process, the tandem cyclisation is purely a radical process,[86] and was applied to the synthesis of (±)-stypoldione.



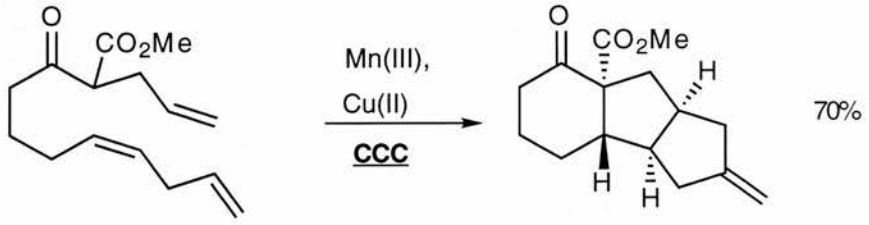
Scheme 34

A large number of **CCC** sequences have been described using manganese chemistry, many of which use systems similar to that used in the PET method seen in Scheme 34. The defining feature is the linearity; the radical acceptor units are all on the same chain, not branched or broken by the initial radical site. This is seen in the syntheses of *d,l*-isopongiadiol,[87] *d,l*-spongiatriol,[88] and in **CCCC** extensions in which the steroid skeleton is constructed (Scheme 35).[89]

Exceptions include the cyclisation of polyene **45**, in which the product **46** is formed in good yield as a single diastereoisomer,[90] but Snider's recent synthesis of a precursor of (±)-isosteviol and (±)-beyer-15-ene using this 'branched' method illustrates that it is more likely to suffer from lower yields due to alternative cyclisations taking place.[91]

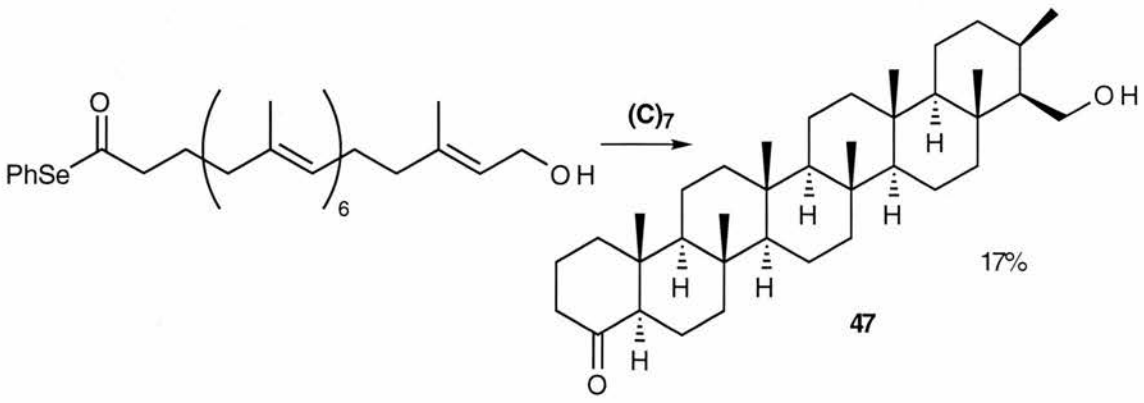


Scheme 35



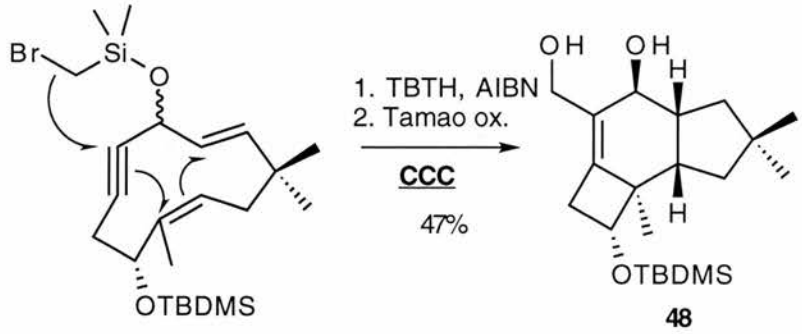
Pattenden has used the fact that acyl radicals favour the 6-*endo* mode of cyclisation, investigating the scope, regio- and chemoselectivity of the sequences starting from acyl radicals (which were generated from phenyl selenoates) in the construction of the perhydrophenanthrone and decalone ring systems,[46,92] and extended to **CCC** sequences and impressive **CCCC** sequences leading to the steroid ring systems, in which the yields were 60-80% and just two D ring epimers were formed.

More recently his group used the methodology to synthesise spongian-16-one via a **CCC** sequence,[93] and extended the range of tandem cyclisations dramatically with a remarkable **CCCCCCC** all *endo* sequence which formed the heptacycle **47** in a very acceptable 17% yield.[94]



Pattenden has also extended the macrocyclisation-transannulation sequences,[83b] and performed several **CCC** sequences, although unexpected or undesired reactions often served merely to highlight some of the drawbacks of the system. An ambitious attempt at the steroid ring system by a macrocyclisation-transannulation approach, (via a 17-*endo*/6-*exo*/6-*exo*/5-*exo* **CCCC** sequence failed completely. Jahn and Curran attempted a similar reaction, which also failed due to an unwanted H-abstraction step midway through the sequence, giving a **CCH** sequence.[95] A small amount (4%) of tetracycle was formed in this instance.

Of the few examples of triple and higher cyclisations occurring in systems which are very irregular in the arrangement of radical acceptors, most occur in the silicon tether reactions previously mentioned. One of the triple cyclisations that has been performed however, involved transannular methodology. The sequence is a remarkable 5-*exo-dig*/4-*exo-trig*/5-*exo-trig* **CCC** sequence, and was used in the synthesis of epi-illudol (Scheme 36) which is shown in protected form (**48**).[96] Most other **CCC** sequences seen using the method are unsurprising, and covered in the recent review.[39]



Scheme 36

1.5.2.1 Other sequences that start with tandem cyclisations, $(\underline{C})_n$.

We have already come across a sequence in which a polycyclisation was prevented because of a premature hydrogen transfer. A similar **CCH** problem was also encountered by Malacria in attempts to synthesise a steroid skeleton,[97] but he has reported a **CCCCHC**

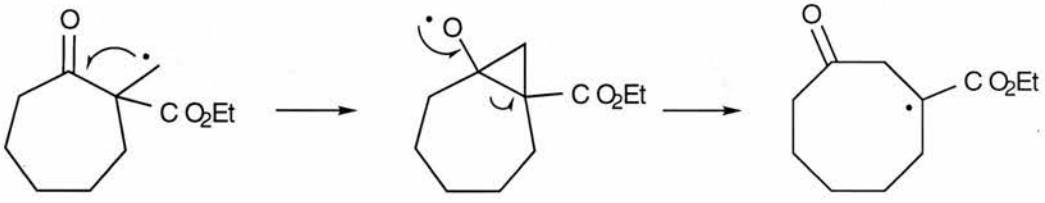
process (which was followed by elimination of a trimethylsilyl radical) as part of his investigations into the synthesis of linear triquinanes.[98]

There is a distinct lack of variety in the methods used to generate the radical for longer sequences. Apart from the oxidative methods, which are not general, tin hydride has had a monopoly on radical generation, illustrating the need for a general, efficient alternative.

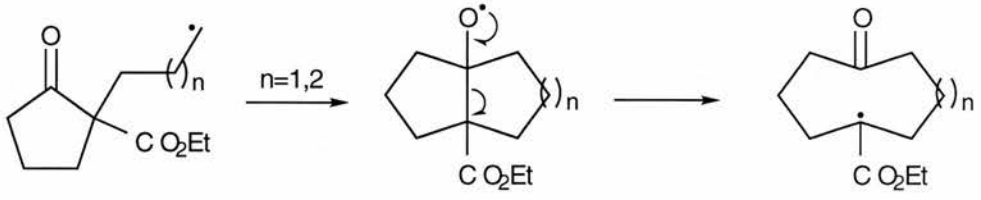
1.5.3 Reactions starting with the CF sequence

1.5.3.1 The 'Dowd-type' ring expansion

The sequence **CF** is a common sequence in radical chemistry, partly due to the regular occurrence of the 'Dowd-type' ring expansion via a **CF** mechanism, which is often the equivalent of a homolytic substitution at an sp^2 centre. Common examples are the one-,[99] three- and four-carbon expansions shown in Schemes 37 (one-carbon) and 38.



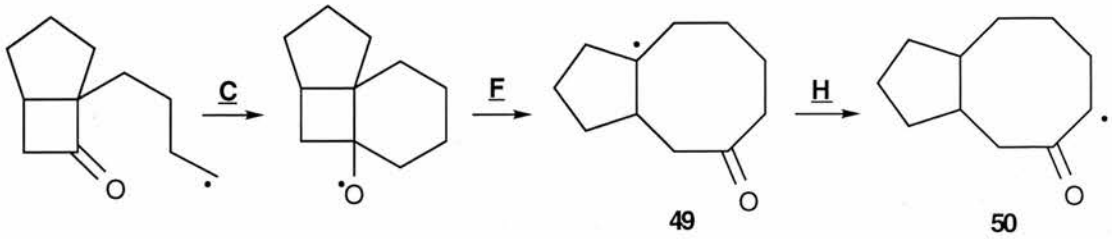
Scheme 37



Scheme 38

The whole topic of radical ring expansions was comprehensively reviewed by Dowd and Zhang in 1993,[1h] and they continued to investigate such reactions, and extensions to **CCF** and similar processes[100] (including a rare **CFH** process resulting in **50**, an α-acyl

radical, although the further radical processes from this radical were not investigated.[100e] The hydrogen transfer from **49** leads to product **50** with mainly *trans* configuration.)



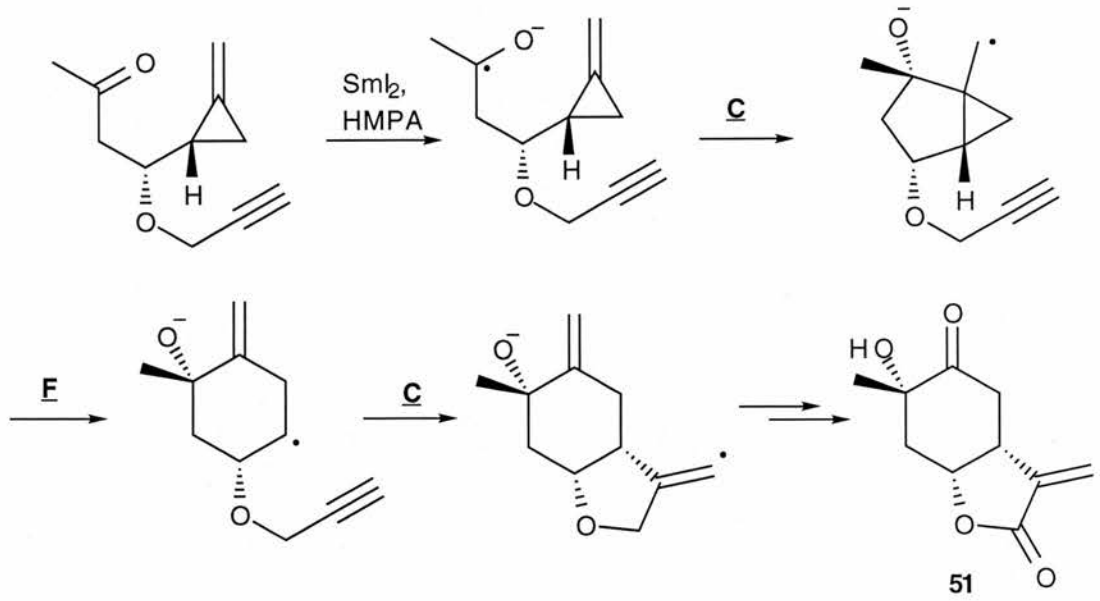
Scheme 39

The ring expansion phenomenon may explain (or partly explain) other anomalous reactions, such as acyl radicals cyclising in 6-*endo* fashion in preference to 5-*exo*, and are extremely common. We shall instead consider **CF** sequences that are not ring expansions, and a couple of important multi-step processes containing ring expansions that have been published since Dowd and Zhang's review. Use of the ring expansion method to synthesise medium sized rings has been recently reviewed by Yet.[1j]

Curran studied the scope of **CFC** reactions, investigating the effects of varying ring size on ring expansions and competing reactions such as hydrogen transfers,[101] while Nemoto *et al.* used a **CFC** process in their syntheses of *cis*-decalins.[102]

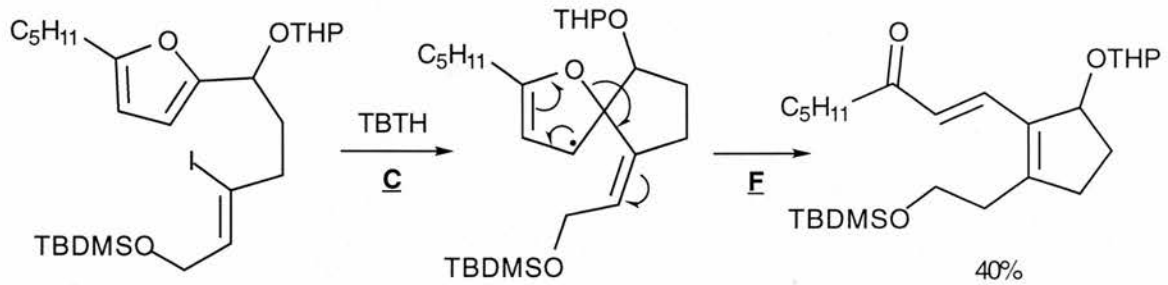
Kilburn has reported many variations on the cyclisation onto the methylenecyclopropane unit, with subsequent ring opening.[103] Tandem cyclisation using tin hydride (**CFC**) has led to bicycles,[103c] and spirocycles,[103d] and the technique has been extended to **CFCC** sequences in the synthesis of tricycles.[103e] Samarium diiodide was employed to generate ketyl radicals, which were used in similar processes,[103a,b] notably in the diastereoselective synthesis of paeonilactone B **51** (Scheme 40).[103b] Toyota *et al.* used a similar **CF** ring expansion method in the synthesis of (±)-methyl atis-16-en-19-oate.[104]

Pattenden incorporated a ring-opening of a cyclopropyl ring into his group's macrocyclisation-transannular cascade methodology, resulting in a **CFCC** process.[105] Unfortunately, two different 5-*exo* cyclisations are possible in the final step, and a mixture of products resulted.



Scheme 40

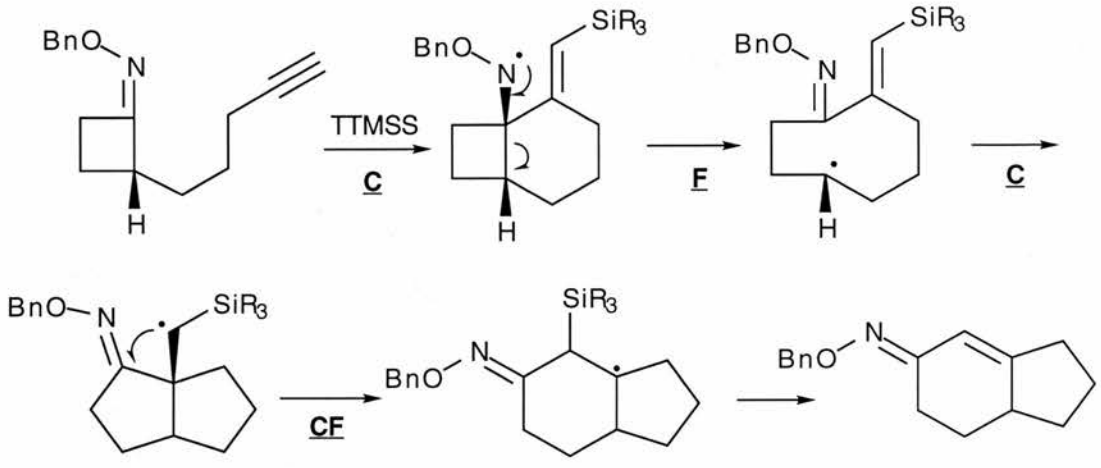
Parsons utilised a different type of **CF** reaction in the formation of enones.[106] Cyclisation of a vinyl radical onto a furan ring, as shown in Scheme 41, gives an allylic radical which fragments to the enone. This is another example of the allyl system being used to 'translocate' a radical. Replacement of the silyl protected alcohol with a phenylsulfyl group (which can be eliminated as a final step) resulted in a product suitable for a Cope-type rearrangement, which occurred *in situ*.



Scheme 41

Unusual **CFC** reactions in which cyclisation onto an oxime ether was followed by fragmantation to a medium sized ring and transannular cyclisation were investigated by Pattenden. The processes that occurred subsequently depended on subtle differences in the

systems used. **CFCC** reactions sometimes occurred, and a **CFCCF** sequence that contains two separate ring expansions is shown in Scheme 42.[107] Nishida has also described processes that involve two separate ring expansions.[108]



Scheme 42

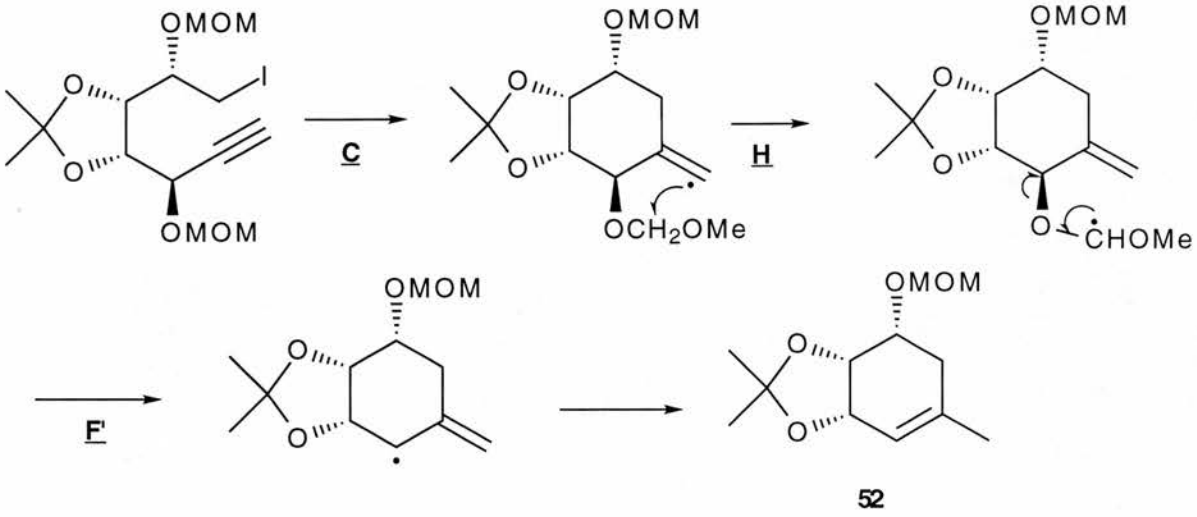
Engman also postulated unusual **CFC**s sequences to account for unexpected products in the investigation of 2,3-dihydrobenzo[b]thiophene-5-ol derivatives involving initial 6-*endo* or 4-*exo* cyclisations, and fragmentations leading to sulfur centred radicals.[109]

Reactions starting with CH sequences

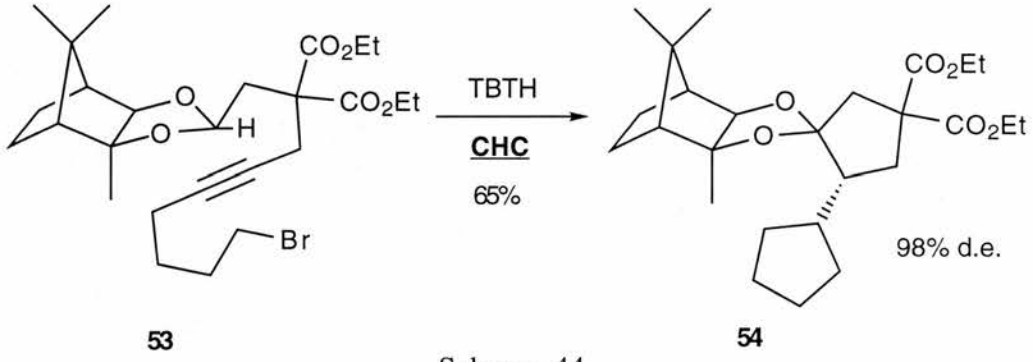
Reactions which end in a hydrogen transfer, as already mentioned, are rarely recognised as such, so **CH** reactions are rare. In a recent paper, a **CHF_2** mechanism was postulated to rationalise the formation of unwanted product **52** shown in Scheme 43.[110]

CHC sequences are more common, and have proved to be of some utility. Stien *et al.* published a report concerning a chiral acyl radical equivalent that included the interesting sequence shown in Scheme 44.[111] The same functional group is the acceptor for both cyclisations, and the product is formed in good yield, and high diastereomeric excess. The large acyl equivalent group is important for both the stereoselectivity and increasing the population of the conformer that enables a faster **H** step due to non-bonding electrons on the oxygens interacting with the C-H σ* orbital. Interestingly, use of the catalytic tin method

resulted in an increased yield, but slightly lowered diastereoselectivity (92%.) Clive used a similar technique in the formal synthesis of methyl *epi*-jasmonate.[112]

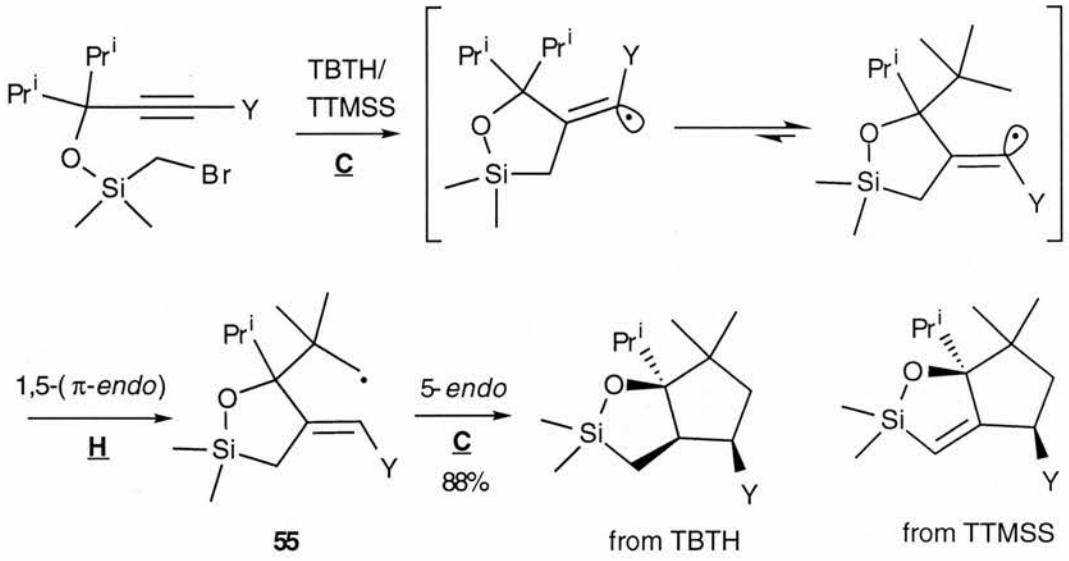


Scheme 43



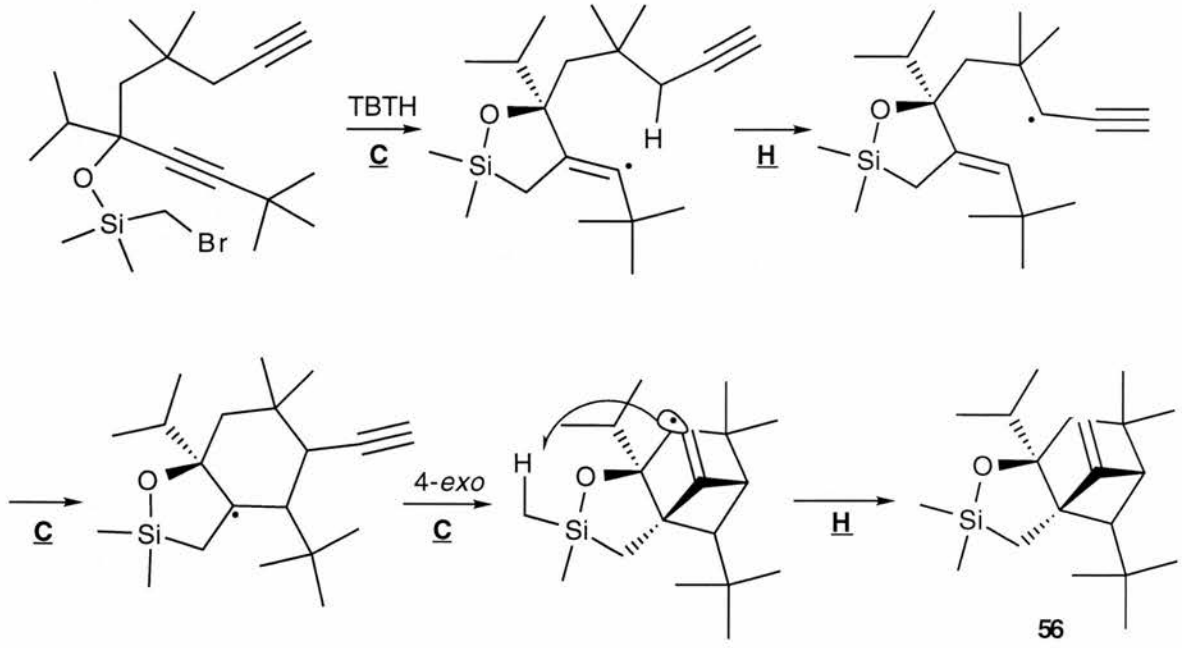
Scheme 44

Radical reactions of (bromomethyl)dimethylsilyl allyl and propargyl ethers have already proved to be a rich source of unusual sequences. Many **CHC** sequences have been reported,[113,39] and one is shown in Scheme 45. The unusual 1,5-(π-*endo*) H-shift is followed by an even rarer 5-*endo* cyclisation involving no ring heteroatoms![113b] The intermediate radical was sometimes seen to undergo a process believed to be a second sequential 1,5 H shift leading to an allyl type radical (**CHH**), a rare sequence due to the fact that tandem hydrogen abstractions are very difficult to recognise.



Scheme 45

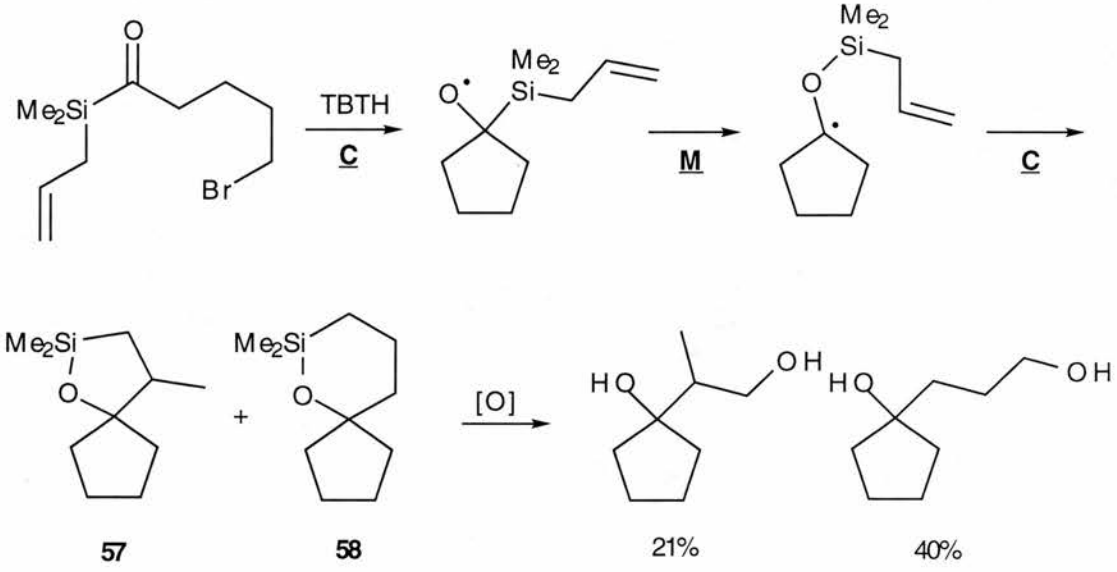
Longer sequences have occurred including various **CHCF**s[113c] but the most impressive is the **CHCCH** sequence shown in Scheme 46.[113e] The initial 5-*exo*/1,6H shift/6-*endo* sequence is not too surprising but this is followed, remarkably, by a 4-*exo* cyclisation, which is trapped by the sequential 1,6H shift. The yield of 85% is also highly remarkable, and the reaction occurs with good stereoselectivity.



Scheme 46

1.5.5 CM reactions.

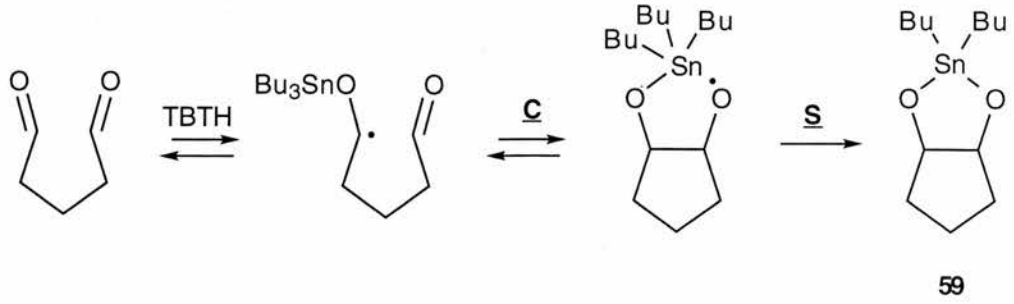
The Brook rearrangement is a migration as we defined it in Section **1.1.1**, and involves a 1,2-shift of a silicon group from a carbon atom to an oxygen centred radical. Tsai has developed this into a useful method, in which an acylsilane acts as a geminal radical acceptor/donor.[114] The basic reaction is **CM**, but the advantage occurs when further reactions take place. Tsai performed **CMC** and **CMCC** reactions, one of which is shown in Scheme 47. The reactions of acylsilanes complement those of acylgermanes which react in the same way as acid chlorides do in nucleophilic substitutions, i.e. the carbonyl reforms, eliminating $R_3Ge\bullet$.[115]



Scheme 47

1.5.6 CS sequences

A **CS** sequence has been described as part of a pinacol coupling type reaction which led to the *cis* isomer of **59** as the major product.[116]



1.6 Reaction sequences that start with a fragmentation.

Reactions that contain a fragmentation are often followed, at some point in a sequential reaction, by a cyclisation, because the fragmentation process results in the formation of a double bond. Other sequences are known, as we shall see.

One set of 'tandem sequences' that we have to discount are the reactions mediated by iron(III) salts studied by Booker-Milburn and others.[117] These have been shown to occur by an initial sequence that does not involve the fragmentation of an alkoxyl radical, as originally assumed, although the effect is the same.[117f] The method, however, is a useful one, and still has potential for incorporation in many radical and tandem radical reactions.

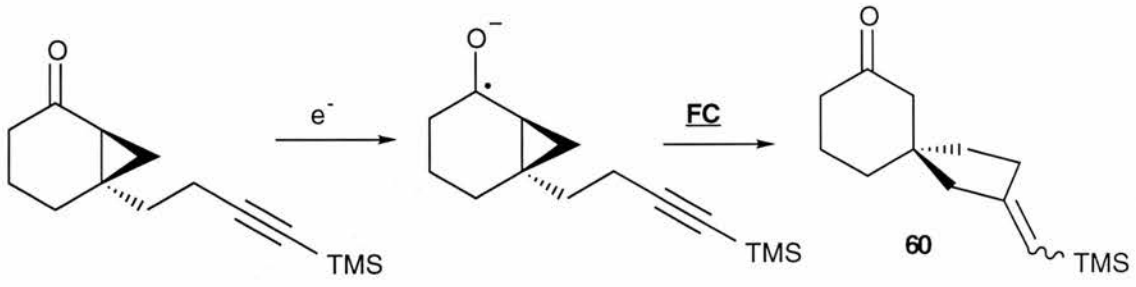
Relief of ring strain is not the only driving force in the fragmentation of alkoxyl radicals, which are known to fragment very easily, As such, 5-membered and larger rings can fragment and have been used quite frequently in tandem reactions.

1.6.1 Reaction sequences that start with FC

There has been a diversity in the way radicals have been generated prior to undergoing **FC** reactions. In this part, however, we shall arrange the sections around the size of ring opened.

1.6.1.1 Ring openings of 3-membered rings.

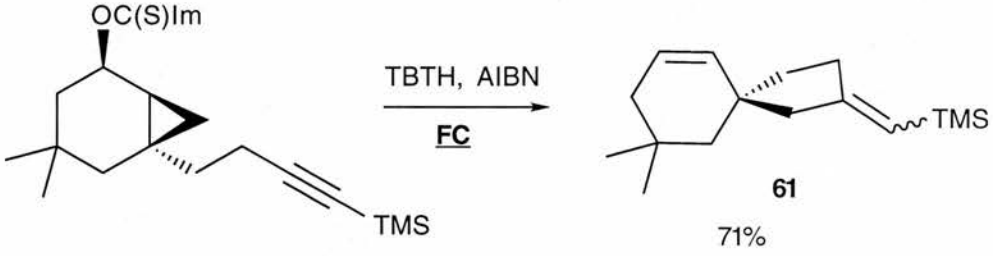
Motherwell has studied in detail the **FC** sequence of the type shown in Scheme 48.[118] The ketyl radical that starts the sequence was generated in four different ways; a method based on Corey's zinc method, and a trialkyltin method both gave moderate yields of **60** of about 50%, while use of sodium naphthalenide gave poorer results (25%). The best yield was obtained using samarium diiodide, with DMPU, which resulted in formation of the desired product in 79% yield. Perhaps soon we will start to see the use of tin eradicated at least in the formation of ketyl radicals.



Scheme 48

Fagnoni *et al.* investigated a very similar system (using a terminal rather than silylated alkyne) in which the ketyl radical was generated by illuminating the ketone in triethylamine and acetonitrile,[119] and the reaction proceeded in a yield of 23%. Kim *et al.* performed a reaction of this type in their investigations into cyclisations onto azide moieties - an **FCF$_2$** sequence.[24]

Motherwell has also investigated very similar reactions of alkyl radicals generated from the thiocarbonylimidazole (again using TBTH).[120] The reaction proceeds in a manner analogous to those above, forming bicycle **61** in a 71% yield. In both these and the ketyl radical studies, an **FCC** reaction was also investigated.

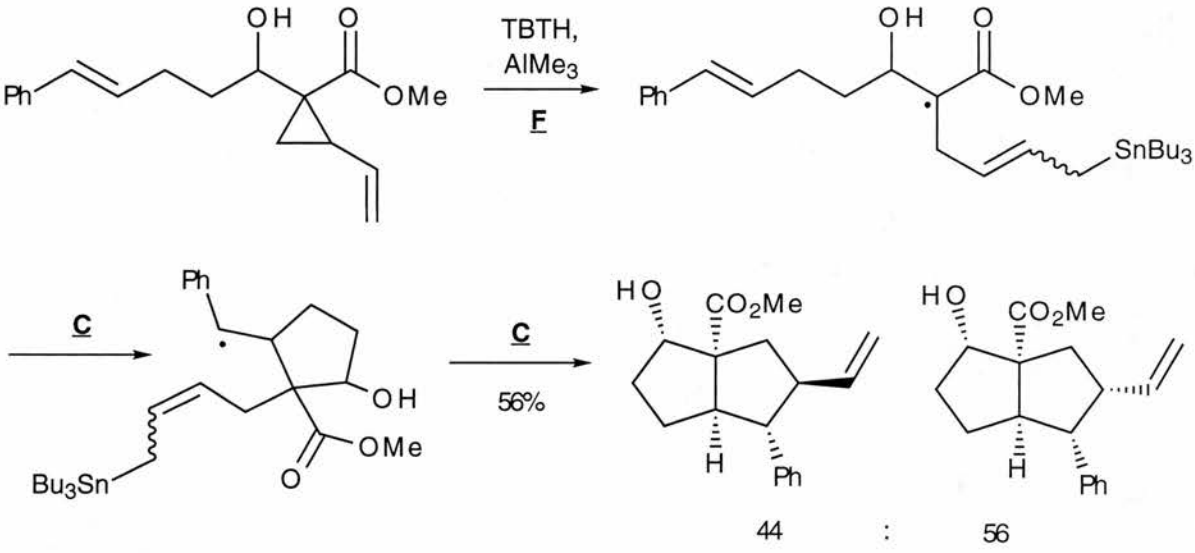


Enholm and Jia have put the 'Motherwell **FC**' technique to good use in a route to linear and angular triquinanes, which were obtained in excellent yield, but again the ketyl radical was generated using tributyltin hydride.[121] A unique and fascinating variation of this type of reaction, in which the **FC** sequence is preceded by an intermolecular addition and followed by a further cyclisation, is seen in Section **1.8.2.6**.

The cyclopropyl ring opening appears to behave in different ways in the reactions mentioned here and the 'Dowd type' discussed in Section **1.5.3.1**, in which the more

stable secondary radical was formed. The reactions are consistent, however; both occur under stereoelectronic control,[122] which here results in the formation of the primary radical.

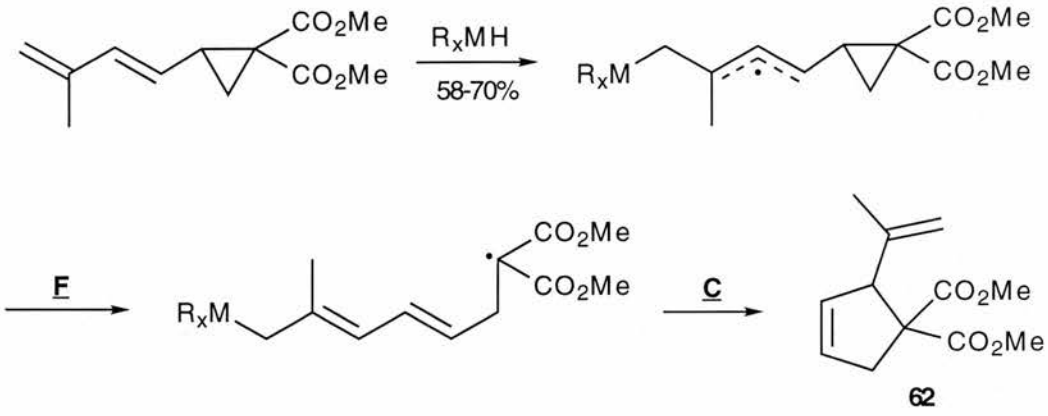
Reactions started by fragmentation of a cyclopropylcarbinyl group that are not fused to another ring have also been reported. Bertrand *et al.* described **FCC** processes as routes to bicyclic lactones, lactams and ketones.[123] Feldman adapted his group's [3+2] cycloaddition strategy (Section **1.8.2.2**) for intramolecular use in the synthesis of (±)-rocaglamide[124] and brefeldin[124b] while a recent example demonstrates the excellent stereoselectivity that a Lewis acid can induce: Renaud *et al.* used the fragmentation method to perform the **FC** reaction shown in Scheme 49.[125] In the absence of trimethyl aluminium at least 8 isomers were formed, but addition of this Lewis acid influenced the reaction to the extent that only two isomers were formed, in a combined yield of 56%.



Scheme 49

Miura *et al.* described an **FC** sequence involving allyl radical translocation. The reaction is similar in concept to Curran's synthesis of the Crinipellin A BCD ring system,[13] and an example is shown in Scheme 50. The design is such that the radical that adds intermolecularly is also the radical that is eliminated to terminate the reaction, and can theoretically be used as a catalyst. Different radical sources were used, and triphenyltin hydride generally gave the best results, but use of thiophenol resulted in only slightly

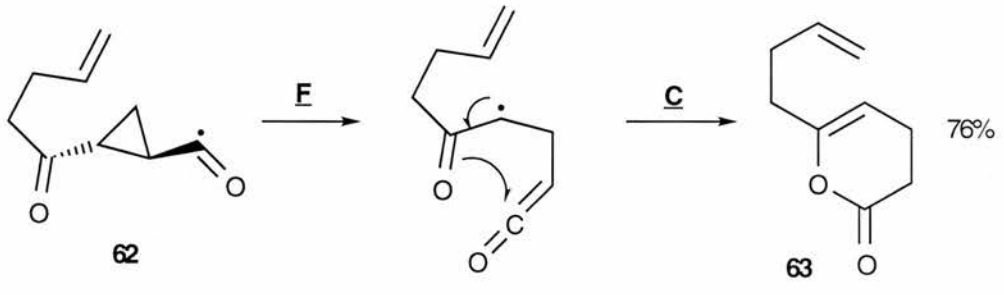
decreased yield. The authors applied the method to an aziridine ring, forming a 5-membered nitrogen heterocycle.[126]



Scheme 50

Epoxycarbinyl and aziridinylcarbinyl radicals (as we saw above) also ring open efficiently, but the products are almost always heteroatom centred radicals. Several years ago Johns and Murphy described the ring opening of an epoxide followed by cyclisation of the alkoxyl radical onto a double bond. Further cyclisation was possible (**FCC**) for one isomer formed.[127] More recently, another **FC** reaction involving a homoallylic aminyl radical from an aziridinylmethyl radical has been described.[128]

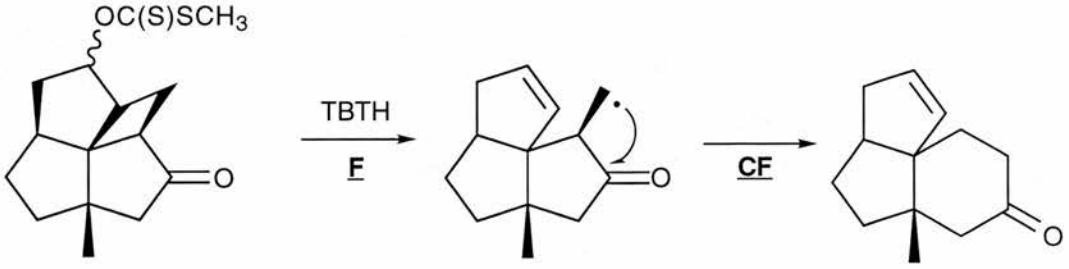
In a surprising and unusual reaction, Pattenden described the synthesis of unsaturated lactone **63** from acyl radical **62** which was generated as usual from a selenide (Scheme 51).[129] Ring opening occurred as usual, but sequential cyclisation occurred not onto the alkene, but onto the ketene functionality.



Scheme 51

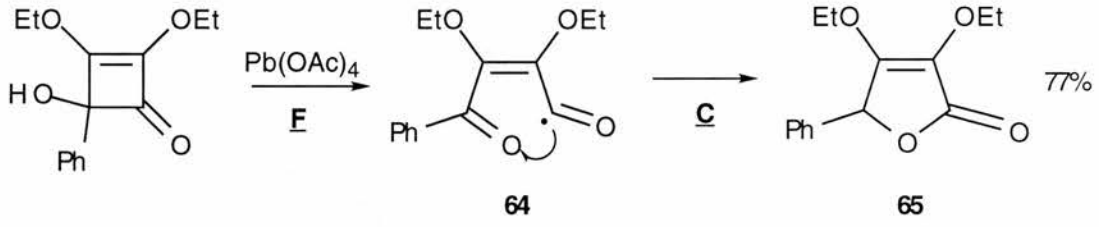
1.6.1.2 Ring openings of 4-membered rings.

Cyclobutylcarbinyl radicals also undergo rapid ring opening reactions. Crimmins described a series of reactions in which a ring opening was followed by a ring expansion - **FCF** - as epitomised by the reaction in Scheme 52.[130]



Scheme 52

An unusual series of reactions was described by Eguchi, an example of which is shown in Scheme 53.[131] Lead tetraacetate was used to generate an alkoxyl radical from an alcohol, and ring opening to give acyl radical **64** was followed by cyclisation back onto the oxygen of the newly generated carbonyl group! The overall effect of this **FC** reaction is a ring opening to give an unsaturated lactone, **65**. This unusual sequence was also reported by O'Dell *et al.* in a reaction in which an alkoxyl radical was generated using mercuric oxide/iodine.[132]



64 65

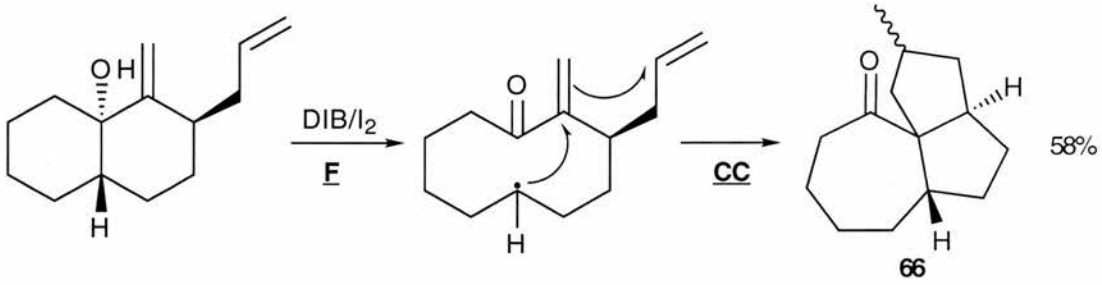
Scheme 53

1.6.1.3 Ring opening of larger rings.

Cyclopentylcarbinyl and larger radicals do not ring open because the reaction is thermodynamically unfavourable. While larger ring cycloalkoxyl radicals will open, there have been few examples of this being followed by cyclisation(s), apart from when the

alkoxyl radical is generated by cyclisation onto a carbonyl i.e. the Dowd-type ring expansion seen in Section **1.5.3.1**.

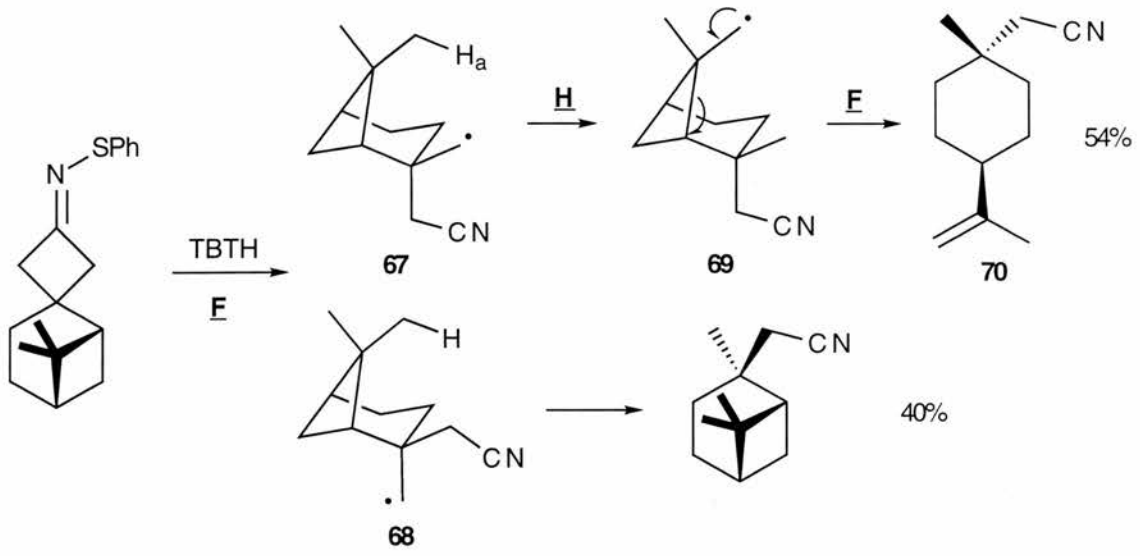
Pattenden synthesised the core structure of laurenene using the **FCC** process shown in Scheme 54.[133] The stereochemistry was critical to the success of the reaction; with the allylic side chain *cis* to the hydroxyl group abstraction of the allylic hydrogen was preferential. Axial substituents were also found to render the final cyclisation unfavourable.



Scheme 54

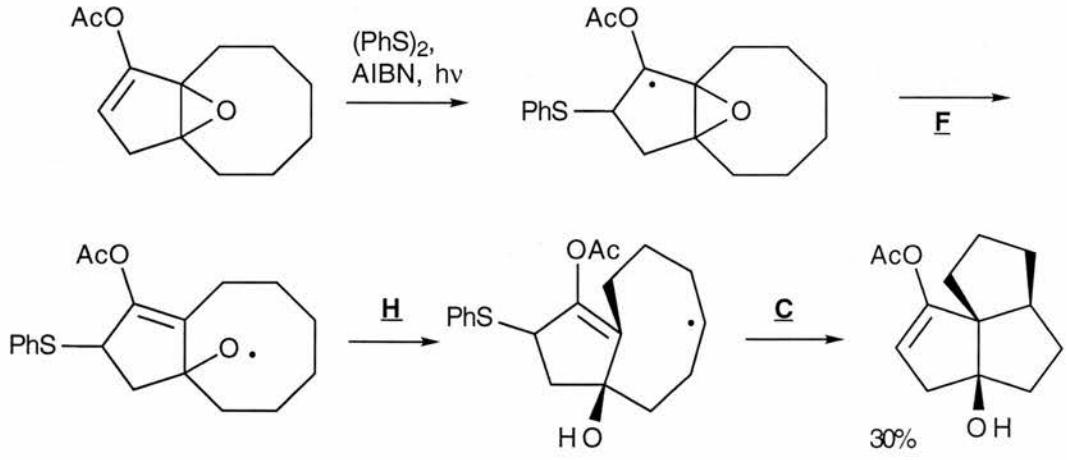
1.6.2 Reactions that start with an FH sequence

There have been a few examples of reactions starting with this unusual sequence. Zard generated iminyl radicals which fragmented to start **FHF** reactions, and provide more intriguing examples of reactions in which different isomers undergo different reactions.[134] Scheme 55 shows an example. After cyclobutylcarbinyl fragmentation, radical **67** can abstract H_a, but radical **68** can undergo no further reaction. Remarkably, abstraction of H_a appears to be facile, despite the fact that the resulting radical is primary, and it is followed by a second cyclobutylcarbinyl ring opening which leads to **70** in 54% yield. An example was even provided of an **FHF** sequence in which a secondary alkyl radical underwent a 1,5 H shift leading to a primary radical!



Scheme 55

Krishnamurthy and Rawal executed an elegant **FHC** sequence as a route to both linear and angular triquinanes.[135] The route to an angular triquinane is shown in Scheme 56. There are many notable points about this reaction, not least the use of a catalytic amount of diphenyl disulfide instead of a tin compound to mediate the reaction. Of course, the use of this technique is specific to only a few reactions, given that the final alkyl radical is suitably placed to eliminate PhS•, but is illustrative of another technique in the fight against tin. Similar reactions have been investigated by the same group, including the ring opening of cyclopropyl rings, which is followed by a rare H-abstraction by an alkyl radical.[136]

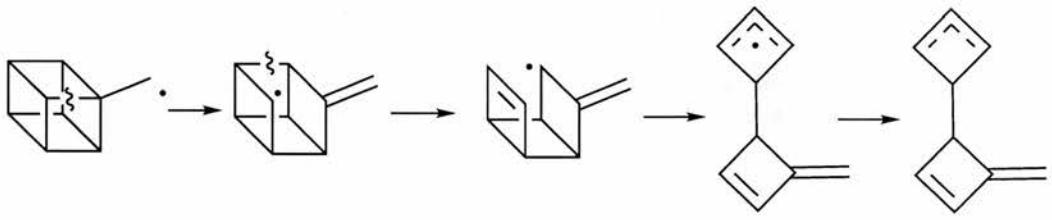


Scheme 56

Other **FH** sequences, discovered by accident, are mentioned in the next section.

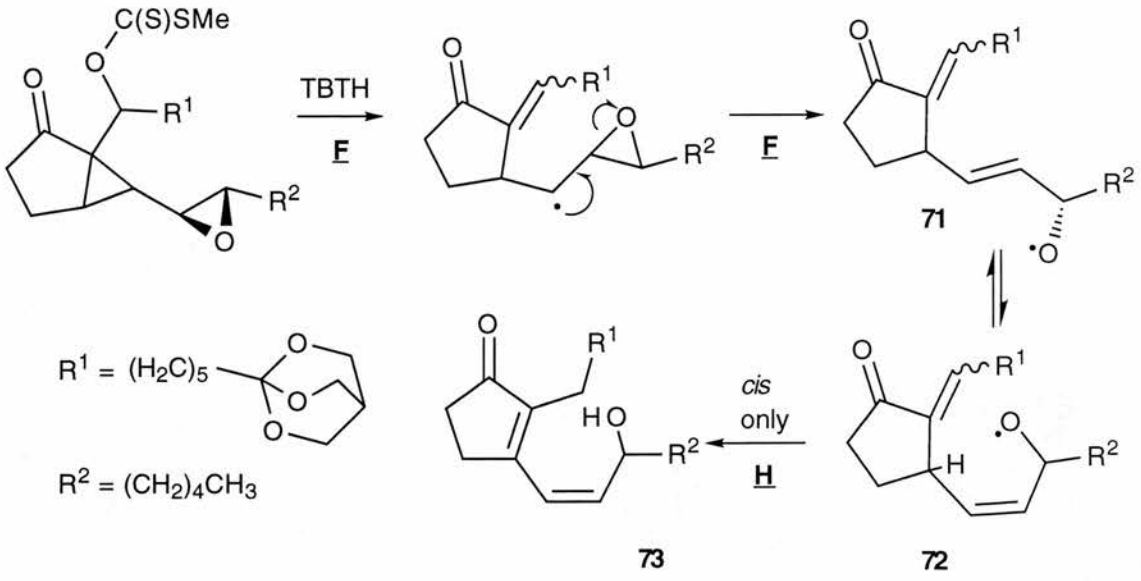
1.6.3 Reaction sequences that start with a double fragmentation, FF.

A fragmentation is often a ring-expansion reaction, although if it isn't preceded by a cyclisation step then suitable functionality has to be present in the precursor. Double fragmentation sequences are not that common, but there is still an elegant variety in the literature. There have even been a few reports of triple fragmentation **FFF** sequences; cubylcarbinyl radicals have been found, under the right conditions, to yield just two major products, resulting from the **FFF** sequence shown in Scheme 57. The ring openings are strictly stereoelectronically controlled, and use of good hydrogen donors enabled the intermediates to be trapped.[137] Conversely, the 9-basketyl radical undergoes an **FFF** sequence only under the most extreme conditions, and the homocubyl radical does not fragment at all![138] The dramatic differences are put down to a mixture of kinetic and thermodynamic factors.



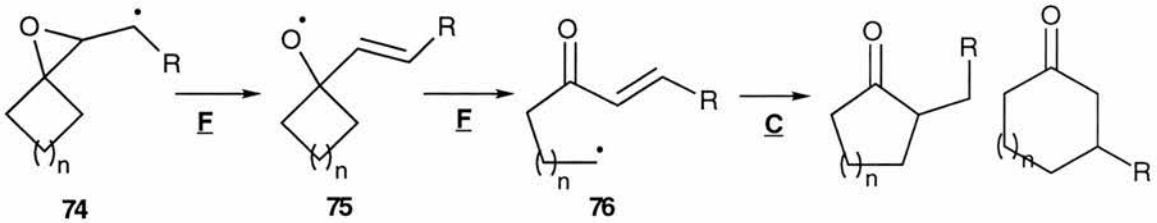
Scheme 57

Ziegler and Peterson have utilised an unusual **FFH** sequence in their elegant synthesis of prostaglandin B_1 (Scheme 58).[139] Two 3-membered ring openings result in the formation of radicals **71** and **72**, which are in rapid equilibrium, and of which only the *cis* form, **72**, can undergo the H-abstraction, which isomerises the double bond into the desired position. Synthesis of the prostaglandin B_1 from **73** is trivial.



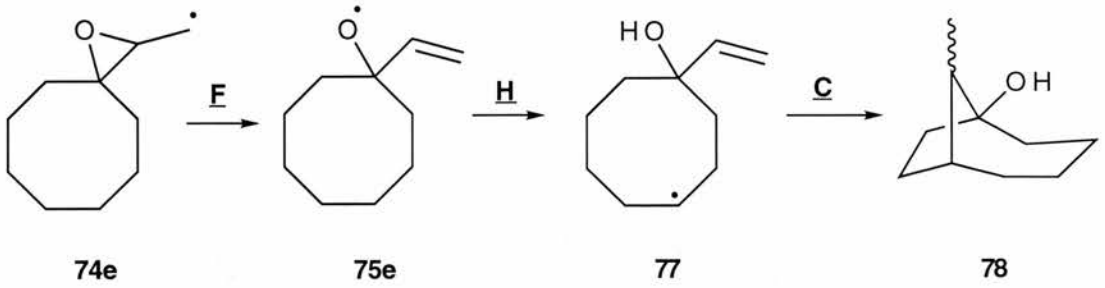
Scheme 58

The synthetic possibilities of a certain type of **FFC** reaction have been investigated by three different groups.[140] The reactions all have the same premise; initial ring opening of an epoxide gives an alkoxyl radical, **75**, which ring opens a second time to give an alkyl radical **76**. This can cyclise onto the newly generated enone moiety, forming cycloalkanones.



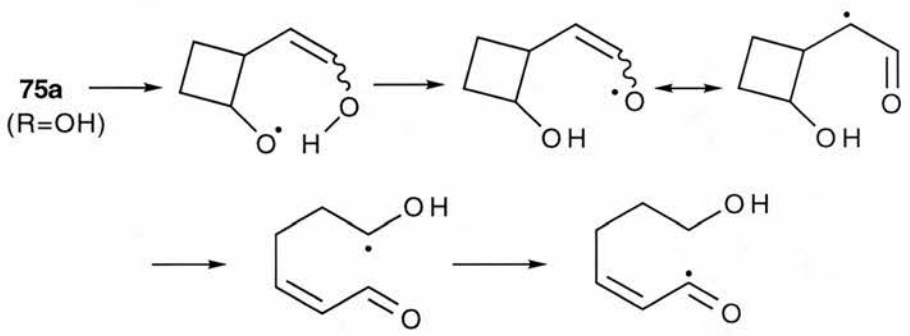
Scheme 59

The reactions were, in general, well behaved but a couple of interesting alternative pathways were also described. Galatsis found that, for the larger rings, H-transfer was competitive with ring opening.[140b] For **74e** (n=5), this resulted in a species that was able to cyclise to give the bicycle **78** in 39% yield; an **FHC** process.



74e **75e** **77** **78**

For n=8 an even more unusual process occurred; two hydrogen abstractions occurred (assumed) which were followed by a 1,2-vinyl shift (**FHHCF**). Walton discovered an **FHFH** sequence undertaken by the radical **75a** (R=OH), which was generated by hydrogen abstraction using DTBP (Scheme 60).[140a] The rest of these procedures used tin centred radicals.

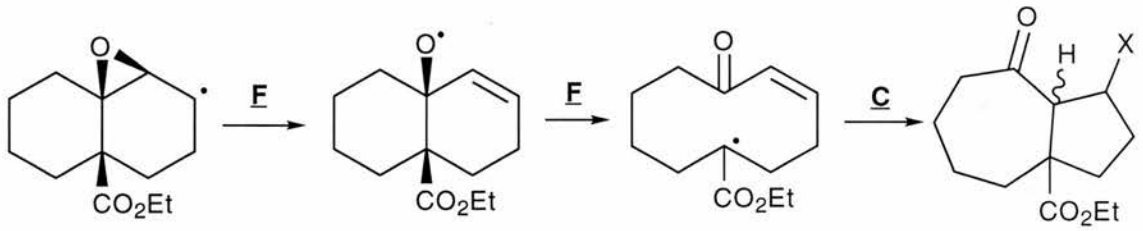


Scheme 60

Cyclohexyloxyl radicals can ring open, and Suárez has described a series of tandem reactions starting from such a fragmentation, in which the alkoxyl radical was generated from the alcohol using (diacetoxyiodo)benzene and iodine.[141] Most of these incorporated intermolecular addition of oxygen, but an **FF** process in which the second fragmentation involves the opening of a cyclopropyl ring has also been described.[141b]

A combination of the above processes was described by Rawal and Zhang, and was used in the synthesis of medium sized fused rings (Scheme 61).[142] Tin hydride mediated generation of **79** from the corresponding thiohydroxamate ester was followed by epoxide fragmentation generating an alkoxyl radical suitably disposed towards causing the fragmentation of a bridging carbon-carbon bond. The product radical was on a medium

sized ring. Cyclisation can take place on to the newly formed carbon-carbon double bond (in a 5-*exo* manner) and the overall sequence is **FF** or **FFC**, depending on conditions, which can be adjusted to favour the desired product.



79

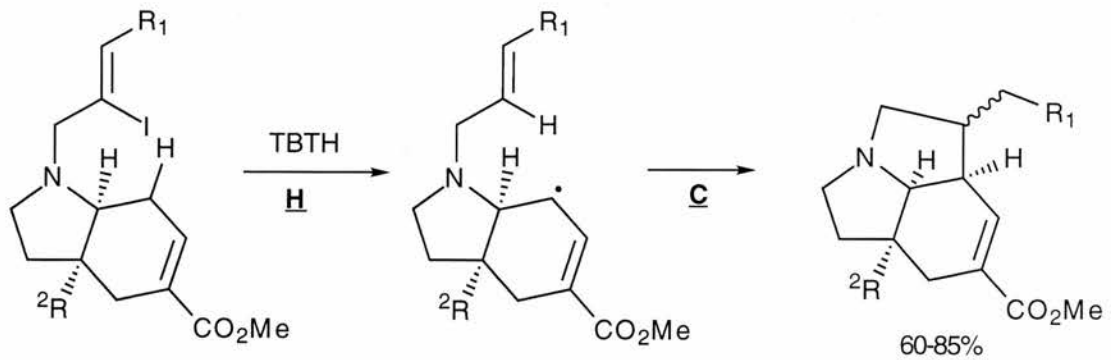
Scheme 61

Zard described a tandem cyclobutyl/cyclopropyl fragmentation process as part of the investigation of ring-openings induced by iminyl radicals, a process that occurred in high yield. He followed this up with an impressive annulation sequence, **FFAC**. (See Section **1.8.2.1**)

1.7 Reaction sequences that start with a hydrogen transfer.

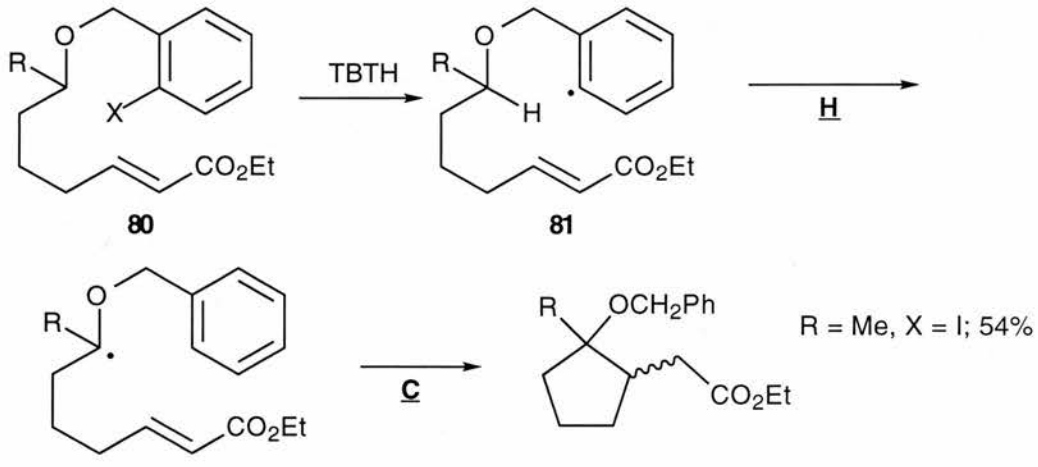
1.7.1 Protecting/translocating radical reactions

Most of the reactions in which the first step is **H** are followed by a cyclisation step **C**, and it is these we shall consider first. When the initial radical generated is a vinyl radical, 1,5H transfer automatically results in a radical set up for a 5-*exo* cyclisation (a system that was extensively studied by Curran in 1993[143]). An early example of this **HC** reaction was described by Lathbury *et al.* as a route to the pyrrolizidine ring system, and is shown in Scheme 62.[144]



Scheme 62

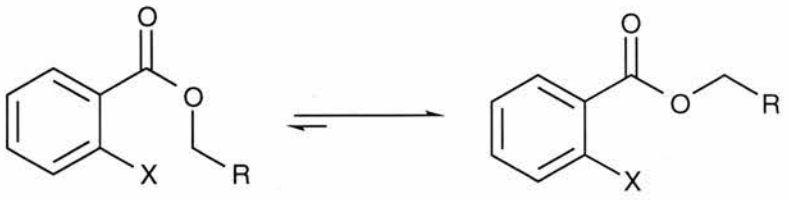
Curran reported similar reactions, and also described examples in which the initial species are aryl radicals.[145] This was the start of a considerable body of work which Curran named 'Protecting/Translocating Radical' Reactions (PRT). Scheme 63 illustrates the theory. Readily prepared halobenzyl ether **80** contains a weaker C-H bond α- to the oxygen atom. The usual methods for abstracting such hydrogens, for example using the t-butoxyl radical, are not selective enough; any weak C-H bond in the molecule is likely to be abstracted. However, on generation of the aryl radical **81** using TBTH, 1,5 hydrogen abstraction is very rapid (the reaction is extremely exothermic), selectively generating a radical α- to the oxygen atom that can undergo further cyclisations onto a moiety at some other place in the molecule. The product is a benzyl ether, i.e. a protected alcohol. Curran found that the (o-bromophenyl)dimethylsilyl group was a more efficient hydroxyl protecting group when it came to the radical reactions. The PRT method means that tin centred radicals can be used for what is effectively a hydrogen abstraction, which is normally not possible because the reaction is highly endothermic.



Scheme 63

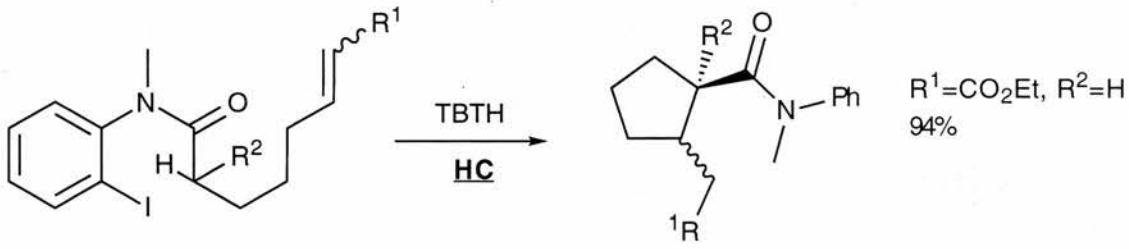
As well as being used to selectively generate radicals with protected alcohols,[145,146] the method has been used with protected amides (or amines),[146a,147] and carboxylates.[148] When an amide or carboxyl group is involved a further consideration has to be taken into account; the configuration of the molecule. Esters adopt exclusively the *syn* configuration

(Scheme 64), and 1,5H abstraction is impossible, so esters cannot be used as PRT groups for carboxylic acids.[148b]



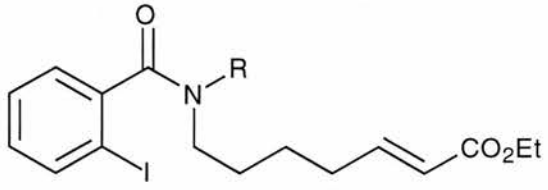
Scheme 64

Anilides are predominantly in the correct configuration, especially in benzene, the reaction medium, and o-iodoanilides can function as PRT groups for acids. An example is shown in Scheme 65.



Scheme 65

Amides such as **82** are in the correct configuration for some R (not R = Ph), and the reaction works best when R = $-(CH_2)_4CH=CHCO_2Et$, so one group has to be in the right position for a 1,5H shift due to symmetry.[146a]

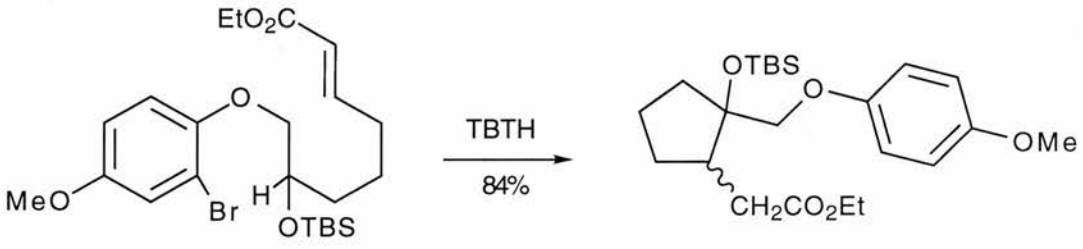


82

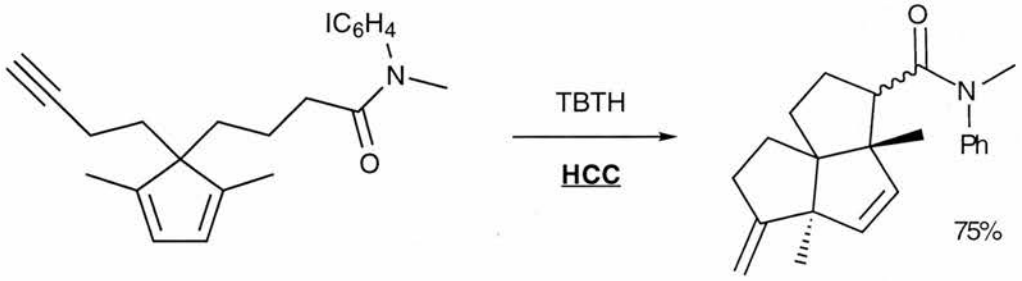
Curran deduced that the strength of the C-H bond was not as crucial as the geometry of the system where intramolecular hydrogen abstractions were concerned.[149] He developed *o*-bromo-*p*-methoxyphenyl ethers as PRT groups which would generate radicals

β to oxygens in protected alcohols (Scheme 66).[150] 1,5H transfer is most efficient (80-85%) when a tertiary alkyl radical is generated. Deprotection is performed using ceric ammonium nitrate (CAN).

The examples described involve **HC** sequences. However, an **HCC** sequence was performed to demonstrate the further utility of the reactions,[148a] and is shown in Scheme 67. The reaction was a development of the reactions we have already seen which use the allyl system to transfer the site of radical reaction. The technique has been further developed by other groups; for example Rancourt *et al.* used the method in the formation of γ-lactams.[151]



Scheme 66



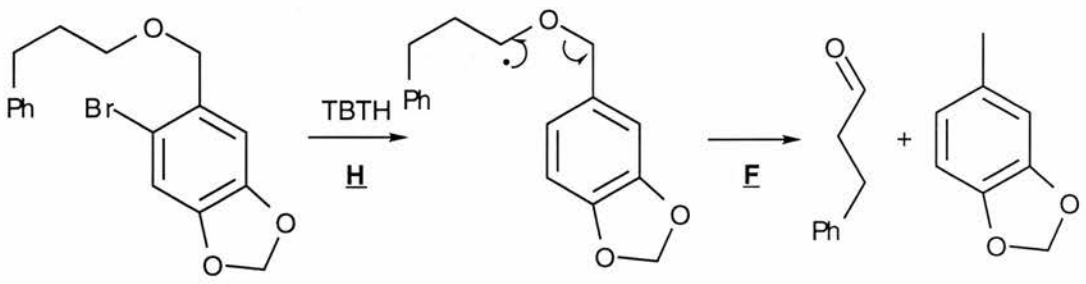
Scheme 67

The extremely rapid H-abstraction enables intermolecular reactions to be undertaken, as was shown early on by Snieckus *et al.*[146a] Williams *et al.* also performed **HA** sequences in the synthesis of unsubstituted amines,[152] and the method has recently been used in stereoselective synthesis. The group of Snieckus synthesised β-substituted β-amino acids enantioselectively using this method,[153] whilst Giraud and Renaud perfomed stereoselective allylations,[154] and Gosain *et al.* have used *N*-*o*-iodobenzyl protected 1,3-oxazolidines to stereoselectively functionalise the 2-position of β-amino alcohols.[155]

1.7.1.1 Other variations of PRT.

Curran designed a PRT group for alcohols in which deprotection and oxidation to the aldehyde occurred during the radical reaction via an **HF$_2$** process (Scheme 68).[156]

Booth *et al.* developed a samarium iodide process in which an anion was generated α- to a nitrogen using radical translocation methodology, but this is not a tandem radical process.[157]



Scheme 68

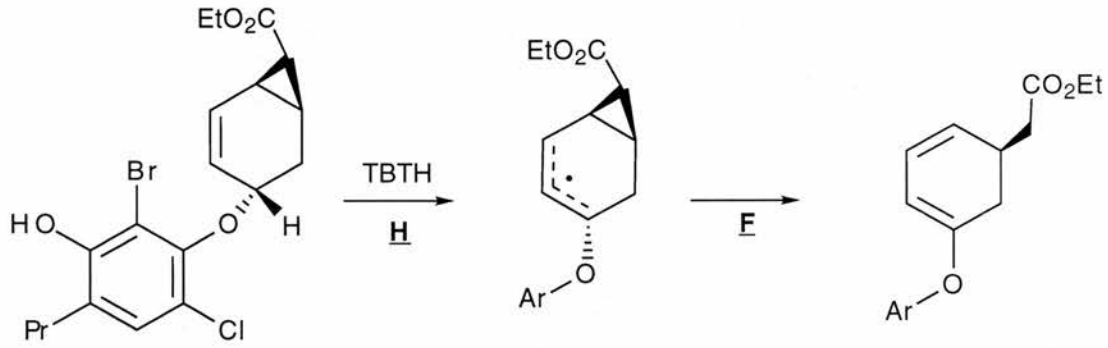
1.7.2 Other sequences that begin with an H shift.

1.7.2.1 Sequences that begin with H C

Several **HC** reactions have been described already in the discussion of PRT, but there are more which are not PRT reactions. Beckwith and Storey showed that if no alternative is available for a radical translocated from an aryl group, then cyclisation onto the aryl ring is possible.[158] Other groups have concentrated on translocations to vinyl groups. Over a decade ago, Cekovic and Ilijev used non-tin methods to generate alkoxyl radicals which underwent a simple **HC** reaction.[159] Bosch and Bachi have used an **HC** process in the synthesis of bicyclic β-lactams.[160], Robertson *et al.* investigated the method as a route to (±)-helistridane and (*6S,7S*)-dihydroxyhelistridane,[161] and Stien *et al.* have generated an acyl radical equivalent from a vinyl radical and used it in an **HC** process.[111] This technique was developed further in a **CHC** process (Section **1.5.4**).

1.7.2.2. HF processes.

As with the H-abstraction-fragmentation process already mentioned, most examples are actually **HF_2**. For example, Brown *et al.* tried to make vinyl benzyl ethers using an **HF_2** methodology with limited success.[162] Clive and Daigneault demonstrated a true **HF** sequence, but an unexpected and undesired one (Scheme 69). A **CF** sequence was expected. The hydrogen abstraction is a rare 1,4 process.[163]



Scheme 69

1.7.2.3 HCF processes

A couple of interesting examples have appeared in the literature in which a ring contraction (**HCF**) was competitive with the desired ring expansion (**CF**),[164] and these are covered in more detail in Dowd and Zhang's review.[1h] An example of an **HCF** sequence has also been seen in a rearrangement of the norbornene system.[165]

1.8 Sequences containing an intermolecular addition.

1.8.1 Radical reactions that end in an intermolecular addition.

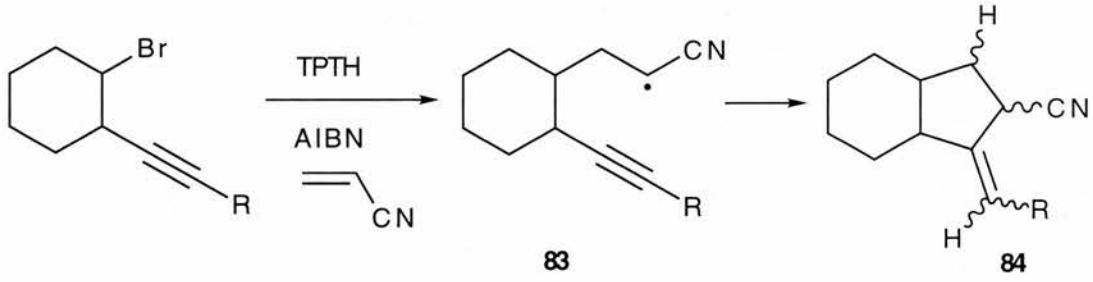
The relative rates of inter- and intramolecular radical reactions mean that it is usually possible to perform an intermolecular addition after a sequence of intramolecular reactions by using a large excess of radical acceptor, and keeping the concentration of other reagents low. The only difficulty may be in preventing further unwanted reactions, but this is not usually a problem. As the possibilities are huge, and many have been exploited to a certain

extent, they shall not be considered here. Instead we shall consider the more awkward sequences where an intramolecular process follows an intermolecular addition.

1.8.2 Radical annulations

1.8.2.1 Tin hydride - a little used reagent!

The possibility of joining two acyclic fragments in an effective [3+2] cycloaddition is appealing. In contrast to other tandem reactions, the tin hydride method has not been utilised to a great extent, indicative that such reactions are problematic. An early example from Clive and Angoh occurred in a reasonable yield (Scheme 70).[166] A yield of 56% was obtained when R=Ph but only 34% for R=n-C_6H_{11}.

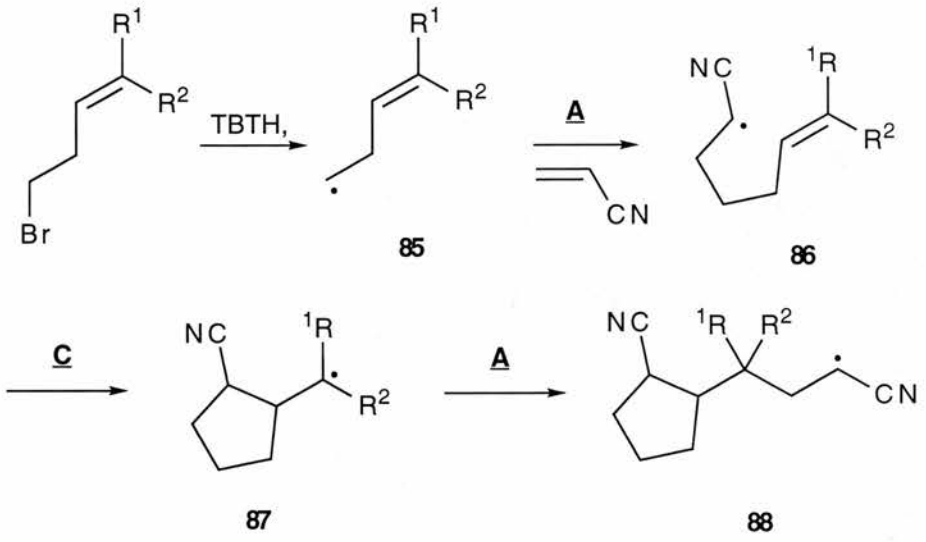


Scheme 70

A more extensive study by Saicic and Cekovic illustrated the problems associated with the method.[167] A low concentration of tin hydride is required before cyclisation (to favour radical addition), but a high concentration is required after it (to prevent unwanted further addition). The problem stems from the fact that radicals **85** and **87** (Scheme 71) are almost identical in terms of nucleophilicity, but one is required to undergo addition and the other H-abstraction from tin hydride. The higher yield from Clive and Angoh's annulation (Scheme 70) is a consequence of the phenyl group increasing the difference in character between the radicals.

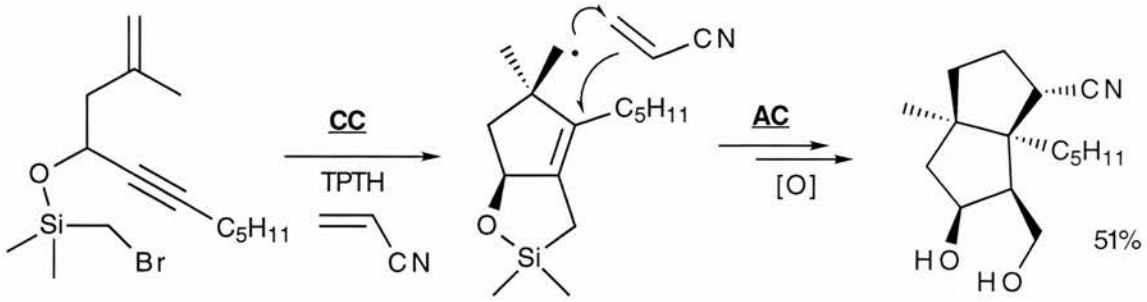
The difference in radical character is presumably also the reason why a similar tin hydride mediated annulation reported by Srikrishna and Hemamalini was successful:[168] bicyclo[3.3.1]nonanes were synthesised in a fair yield using an annulation method in which

cyclisation resulted in a tertiary α-acyl radical. The problems described above were also encountered when Barton esters were used to generate the radicals; **ACA** sequences occurred.[167d,169]



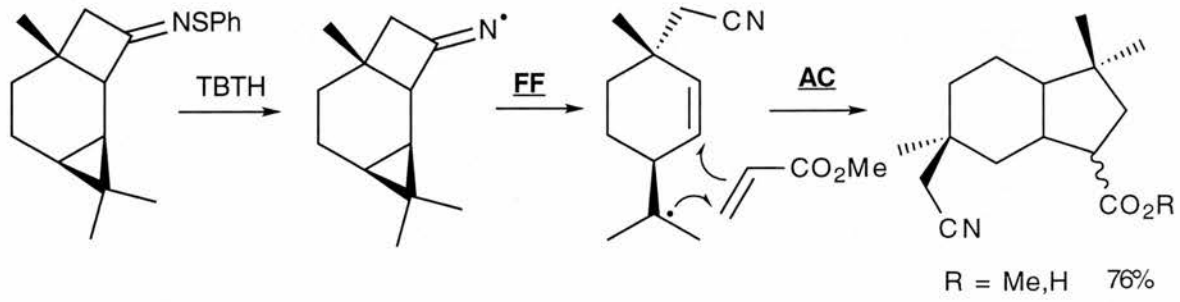
Scheme 71

Yet again, a remarkable tandem reaction has emerged from the lab of Malacria thanks to his work on silicon tethered radical reactions. Scheme 72 shows a **CCAC** reaction (followed by Tamao oxidation) performed using the tin hydride method.[170] The reaction is remarkable in that annulation is successful despite the excess of acrylonitrile. Steric hindrance prevents oligomer formation. This explanation can also be used to explain the success of an early annulation used in the synthesis of a steroidal skeleton.[171]



Scheme 72

Zard performed an annulation (preceded by two fragmentations) using the tin hydride method which succeeded for no obvious reason (Scheme 73).[134] The radical centre at which intermolecular hydrogen abstraction takes place does not appear to be especially crowded, nor to have reduced reactivity to alkenes, but an excellent 76% yield was obtained.

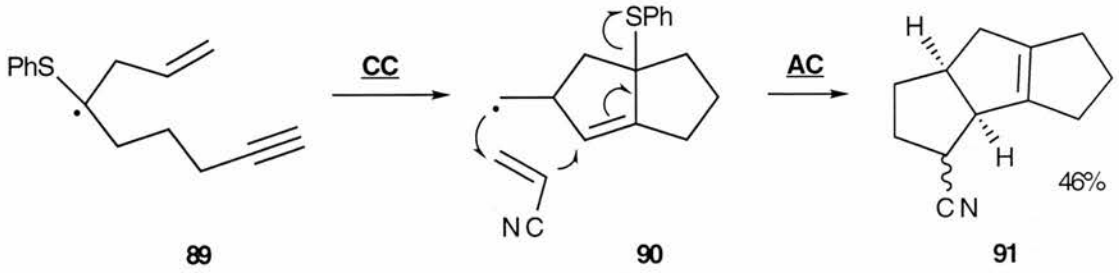


Scheme 73

An annulation involving intermolecular addition of electron poor radicals to electron rich alkenes has recently been described.[172] This succeeds because the final radical is not electronically suited to add to the alkene acceptor but addition to the xanthate precursor is facile. Xanthates were used in the annulation based synthesis of (±)-matrine - an **ACC** process.[173]

The problems seen in many of the annulation reactions can be overcome by terminating the reaction sequence with a fragmentation step that is sufficiently quick that further addition cannot take place. There exist several examples of this in the literature, and the radical leaving group of choice is often a thiyl.[167b,e] Sometimes this is built into the precursor,[167b,e,174] but elegant tandem sequences have been designed where this is not required (See Section **1.8.2.2**).

The fragmentation method has been put to use in an annulation synthesis of the linear triquinane skeleton. The annulation is preceded by a double cyclisation; overall the reaction is a **CCAC** sequence (Scheme 74).[167c] Radical **89** is generated from a Barton-type ester in the presence of 22 equivalents of acrylonitrile, ensuring addition is successful.



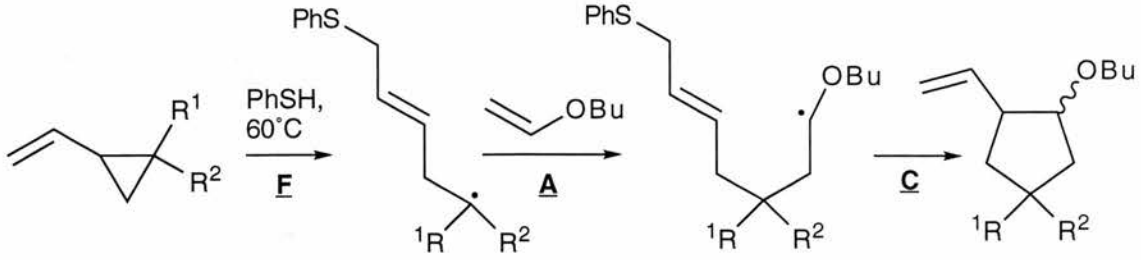
Scheme 74

Appropriate placement of a thiyl group enables the trapping of a cyclopropyl group formed from a 3-*exo* cyclisation following an annulation reaction.[174] This is a similar reaction to the trapping of cyclopropanes that was seen in Section **1.5.1.2.3**.

Curran has shown that the fragmentation of a tin radical is also a viable, if unpleasant method for terminating annulations and maintaining the chain. It was shown that both allyl and vinyl stannanes were suitable precursors in this method.[175]

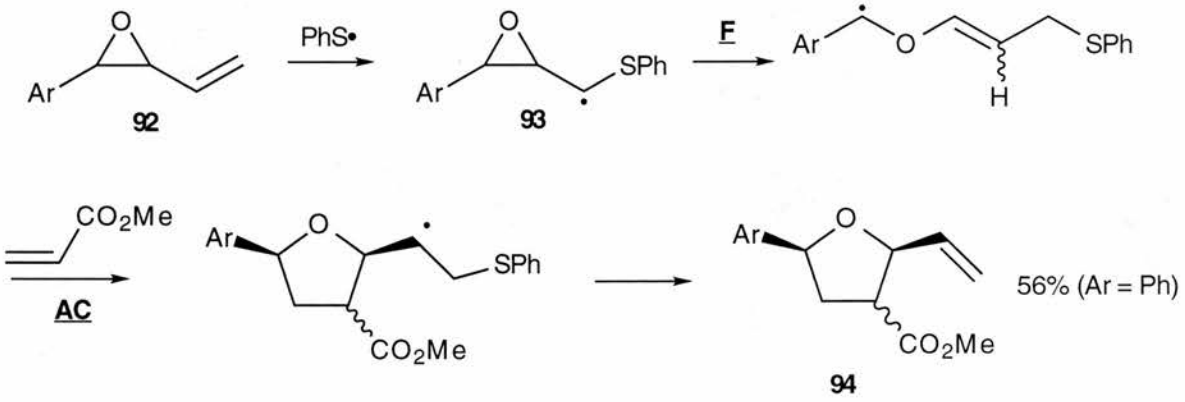
1.8.2.2 Generation of an alkenyl radical acceptor *in situ*.

An elegant method of performing annulations is to utilise an **FAC** sequence in which addition of a (thiyl) radical to a vinylcyclopropane results in fragmentation to a homoallylic radical, and annulation then follows. The design of the system is such that the thiyl radical is rapidly expelled, and so can be used catalytically, at least in principle. This method has been extensively investigated by the groups of Feldman,[176] Singleton[177] and Oshima.[178] The reactions have been performed using both electron rich and electron poor alkenes. The reaction is typified by the work of Oshima, which is shown in Scheme 75. When R^1 and R^2 are both electron withdrawing groups (CO_2Me), annulation proceeded well with electon rich alkenes such as butyl vinyl ether. When only R^1 was electron withdrawing the reaction was high yielding with both electron rich and electron poor alkenes. This provides scope for synthesis of a wider range of cyclopentanes via an annulation processes mediated by a theoretically catalytic process which does not involve tin compounds.



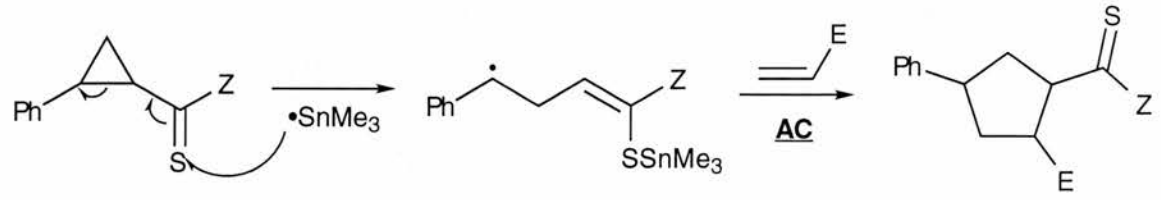
Scheme 75

Variations on this theme have also been reported. Use of dioxygen in place of the alkene gave 1,2-dioxolanes,[176e] while annulation of vinylepoxides, **92**, with electron poor alkenes gave tetrahydrofurans in reasonable yield.[179] The presence of the aryl group (usually phenyl) is essential, for otherwise C-O bond fragmentation is favoured to give the alkoxyl radical.



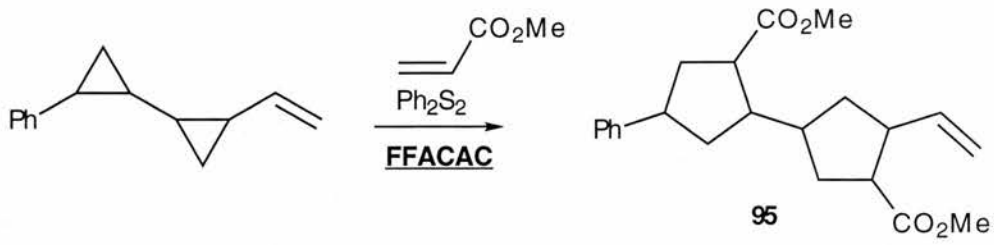
Scheme 76

Thiocarbonyl compounds were investigated as part of a similar strategy (Scheme 77).[180] The reaction worked in good yield and modest stereoselectivity, but the major disadvantage with the reaction is the reversion to tin. Stannyl radicals were generated thermally from bis(trimethylstannyl) benzopicolinate.[181]



Scheme 77

A double annulation was also reported resulting in the formation of **95**; an **FFACAC** reaction.[176d]

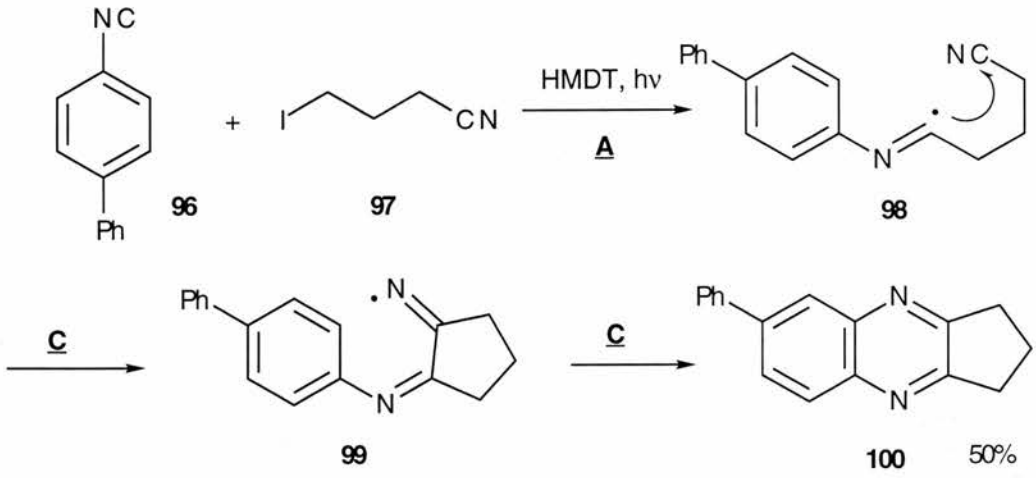


1.8.2.3 The atom transfer method.

Curran has also investigated the halogen transfer method as a way of performing annulation reactions, mainly using propargyl and allyl iodomalonitriles.[182] The reaction is based on the premise that iodides are sensitive to substituent effects, and will differentiate between the radicals involved in the reaction, so suitable design will enable annulation to take place without unwanted further addition. While this was found to be the case, the reaction is limited in its scope and suffers other disadvantages such as sensitivity of the precursors, so interest in the method has waned. The reaction also involves the use of hexamethylditin to initiate the reaction. However, the work does provide the only example, to our knowledge, of an **ACH** sequence, albeit an undesired one.[182d]

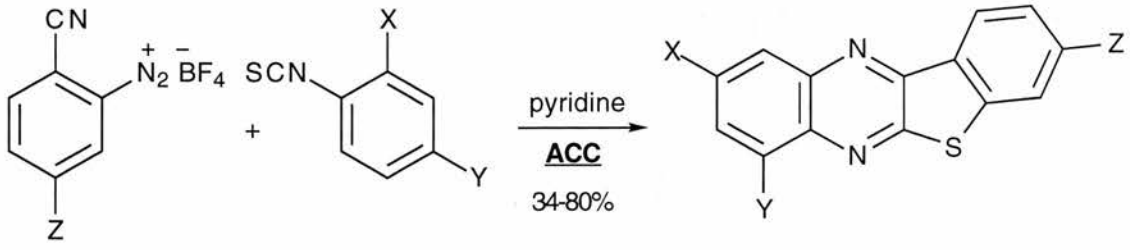
1.8.2.4 Annulations using isonitriles, and related processes.

The groups of Nanni and Zanardi have shown a long-standing interest in imidoyl radicals, generated by hydrogen abstraction from imines, or by radical addition to isonitriles or isothiocyanates.[183] Their work contains many examples of processes not often encountered: cyclisation of iminyl and imidoyl radicals, radical addition to isonitriles, a geminal radical donor/acceptor,[20] cyclisation onto a phenyl ring, and annulations. One of their simple **ACC** annulations is shown in Scheme 78.



Scheme 78

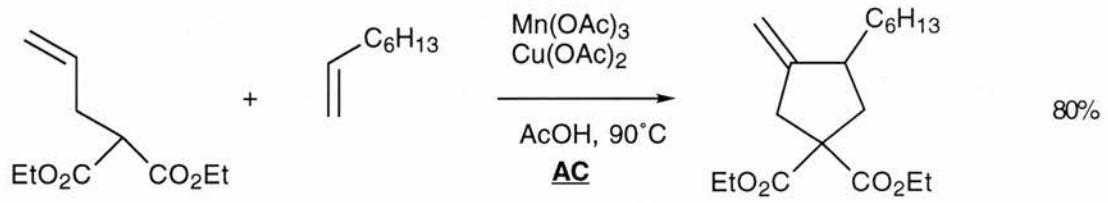
The success of the reaction is due to the difference in the character of the radicals involved, and also to the fact that the final cyclisation is onto an aromatic ring, so further reaction is unlikely. It is suggested that the cyclohexadienyl radical formed undergoes electron transfer from **96**, generating **96**$^{+\bullet}$, followed by proton transfer.[183a] It is also believed the cyclisation onto the aromatic ring proceeds via an initial 5-*exo* cyclisation, followed by rearrangement to give the thermodynamically more stable 6-membered ring, which can rearomatise. A wide variety of related annulations have been performed, including that shown in Scheme 79, which avoided the use of tin compounds, and usually occurred in yields of over 65%. Curran has used a related annulation of isonitriles in the synthesis of (±)-camptothecin.[184]



Scheme 79

1.8.2.5 Annulations using oxidative methods.

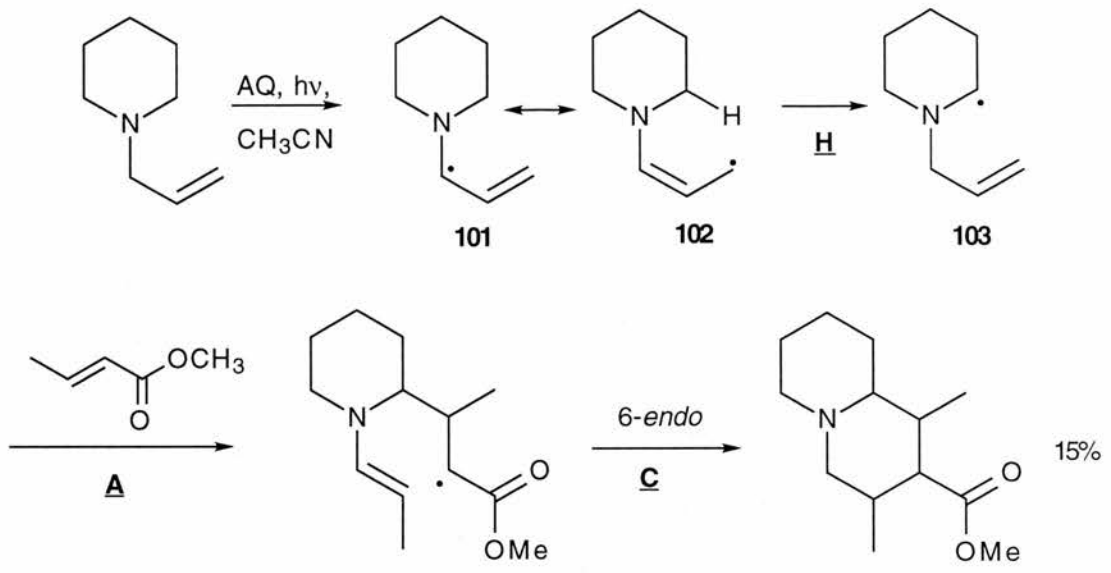
The manganese(III) method for performing radical reactions is suited for annulation reactions because the radicals involved in the reaction are different in character. These annulations, which were recently reviewed,[64] often involve cyclisation onto an aromatic ring but this need not be the case, and an example of one which doesn't is shown in Scheme 80.[185]



Scheme 80

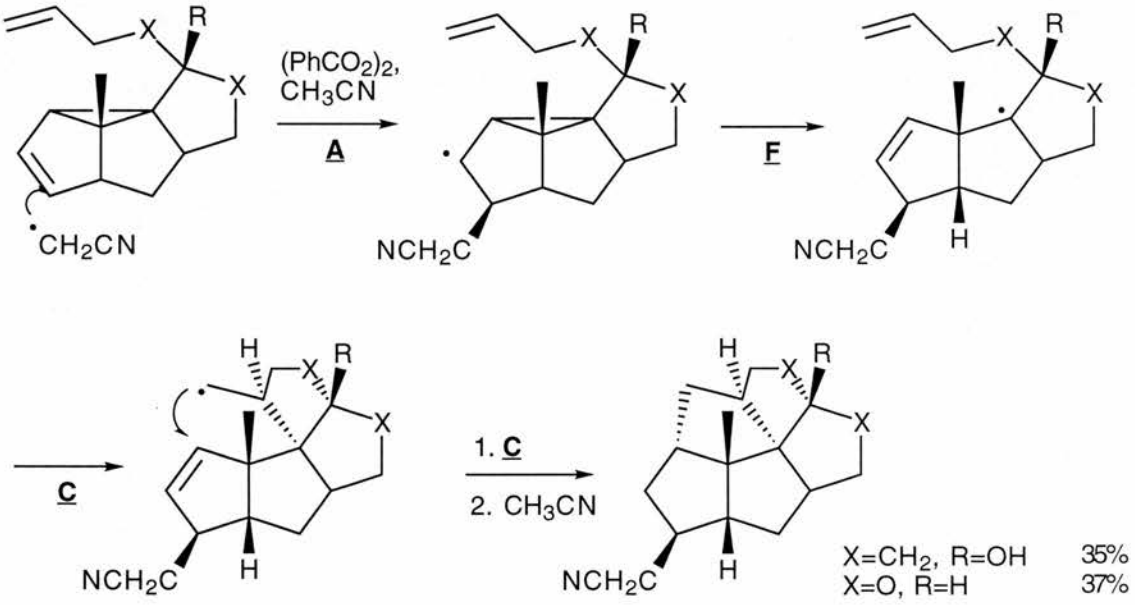
1.8.2.6 Exotica.

Finally, a couple of remarkable annulation reactions employing rarely used techniques. The first uses photoelectron tranfer, followed by proton transfer to anthraquinone, to generate allylic radical **101/102**, which undergoes a 1,5H shift to generate α-aminyl radical **103**.[186] Annulation with an unsaturated ester then occurs in good yield; an **HAC** process (including an allyl 'transposition' step) is the overall result. The mechanism should be regarded with some suspicion, even though **104** is only a minor product, considering that it involves an unlikely abstraction of a primary hydrogen by an allylic radical, and a subsequent 6-*endo* cyclisation under unfavourable conditions. Formation of the major product (not shown), was rationalised by the same hydrogen abstraction followed by ionic reaction.



Scheme 81

Wender has described a truly remarkable synthesis of *cis,cis,cis,trans*-[5.5.5.5]-fenestranes which is shown in Scheme 82.[187] The reaction does not involve tin, and the chain carrier is derived from the solvent! The product was the first example of a fenestrane with the energetically unfavourable *trans* ring fusion.



Scheme 82

1.9 Conclusions

Tandem radical reactions have a large and important rôle in organic synthesis. We have introduced a simple notation that describes the many different sequences. This notation could be expanded, for example $\underline{C_{5x}}$ could describe a 5-*exo* cyclisation, or $\underline{C_T}$ transannular cyclisation. However, it is unlikely that the system could ever be developed to such an extent that it would provide an empirical indicator of whether a postulated radical cascade would be successful. The success of the sequences that have been observed often depends on extremely subtle factors.

The tin hydride method continues to be the method of choice for performing many types of radical reactions, and the review emphasises the need for non-toxic alternatives. Many examples have been provided in which alternatives can be used, and occasionally these are greatly superior.

The most common type of cascade radical reaction is the tandem cyclisation, but other sequences have been developed to fulfil a particular purpose. The most obvious examples are the **HC** PRT method (Section **1.7.1**), the **CF** ring expansion (Section **1.5.3.1**), and the **CM** geminal radical donor/acceptor technique (Section **1.5.5**). There are few 3-step sequences that haven't been exploited, although there is room for development in many cases.

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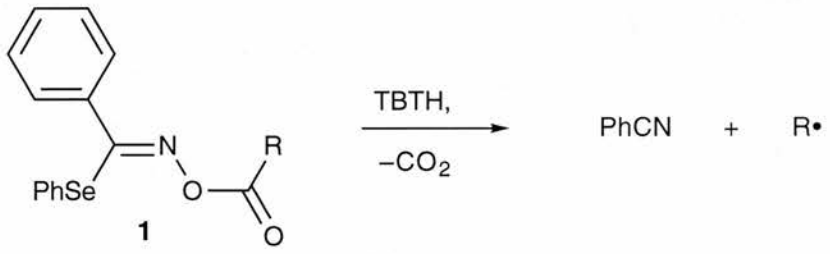
Chapter 2

The radical reactions of oxime derivatives

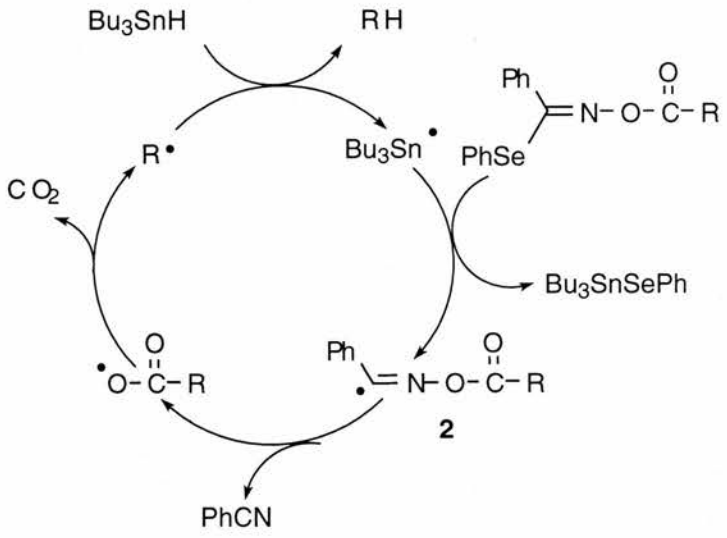
2.1 Introduction.

Recently, Kim *et al.* described the use of phenylselenohydroximate derivatives **1** as an efficient method of generating alkyl radicals (Scheme 1).[1] Closely related derivatives were used as precursors to alkoxyl or aminyl radicals.[1] The method for generating alkyl radicals actually proceeds via an $\underline{\mathbf{F}_2\mathbf{F}_2}$ mechanism (Scheme 2)! It is known that iminyl hydrogens are abstractable by t-butoxyl radicals, usually generated by the photolysis di-t-butyl peroxide (DTBP),[2] hence it was anticipated that Kim's method could be extended to using the simpler oxime ester or ether derivatives, and DTBP. This would remove the need for selenium and tin compounds, and reduce the toxicity of the reaction. The intermediate radical would be the same (**2**) as in Kim's method. It was also postulated that the technique designated by Roberts as 'Polarity Reversal Catalysis' (PRC) could aid this method.[3]



Scheme 1

It has been shown that benzophenone oxime esters will photolyse (by the breaking of the N-O bond) to give an alkyl radical, via decarboxylation, and an iminyl radical, which was found to dimerise.[4] This is an alternative pathway which we have also investigated.



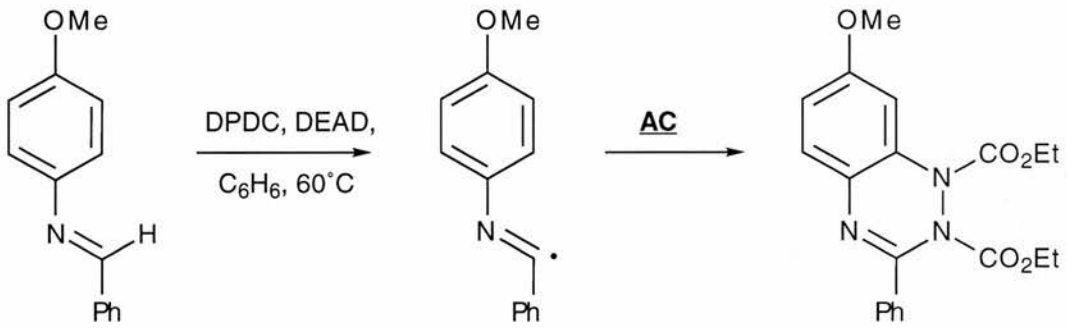
Scheme 2

A search of the literature revealed the use of oxime ethers in radical reactions to be quite extensive, but the majority of reactions involved alkyl radical addition (inter- or intramolecular) onto oxime ethers. In 1983, Corey and Pyne reported that ketyl radical cyclisation onto an aldoxime ether was efficient,[5] (but ketoxime ethers are not always good acceptors for ketyl radicals[6,7]) while oxime ethers have been shown to be good acceptors for alkyl radicals both intermolecularly,[8] and intramolecularly.[9] Use of a Lewis acid was shown to enhance yields in radical addition to oxime ethers, by lowering the LUMO energy of the oxime ether and decreasing the electron density of the iminyl carbon atom.[10] Vinyl and aryl radicals also add efficiently to oxime ethers,[11] and we saw in chapter 1 that oxime ethers have occasionally been used in tandem radical reactions.[11c,12] Recently, Clive and Subedi described a tin hydride mediated cyclisation onto a triphenylmethyl oxime ether, in which the triphenylmethyl radical was expelled, regenerating the oxime functionality.[13]

There have been no examples of the oximyl H-abstraction taking place, but this can be put down to the fact that carbon radicals are electronically unsuitable for hydrogen abstraction.

However, the use of imidoyl radicals similar to **2** has been described in synthesis. Nanni *et al.* have generated these radicals both by addition to an isonitrile, and by hydrogen

abstraction by an alkoxyl radical.[14] An example when imidoyl radicals were used in an **AC** annulation is shown in Scheme 3.



DPDC = di-isopropylperoxydicarbonate

73%

Scheme 3

We have already mentioned the use of benzophenone oxime esters as a source of radicals. Zard has developed the use of benzoates (phenyl oxime esters) as a method to generate ketiminyl radicals using a suitable reducing agent.[15] Nickel powder and stannyl radicals have both been used to generate the radicals from these precursors.

In one very surprising reaction, considering the reactions described above, a 6-*endo* cyclisation onto the *nitrogen* of an oxime ester has been described.[16] The addition is followed by elimination of $PhCO_2$•, leading to 3,6-dihydropyridines.

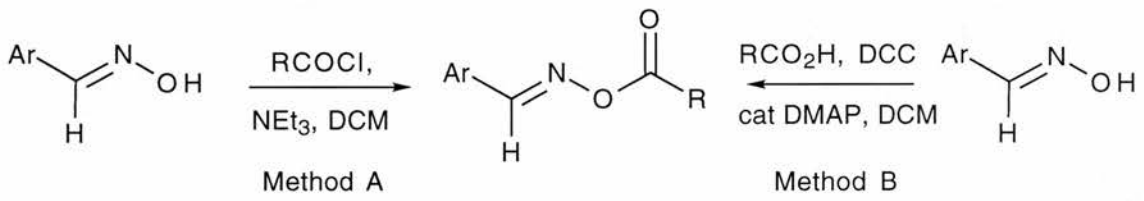
We intended to investigate the mechanisms of the reactions of oxime esters and ethers with DTBP, to see if H-abstraction was a viable reaction and examine the direct photolysis reactions of these compounds. We used EPR spectroscopy to look at intermediates in the reactions, and preparative experiments to consider the products.

2.2 Results and discussion.

2.2.1 Investigation of the reactions of oxime esters.

2.2.1.1 Synthesis of oximes and oxime esters.

A diverse selection of oxime esters was synthesised, in generally good yield from one of two methods. Early preparations were performed by adding an oxime to the acid chloride of choice mediated by triethylamine in DCM (Method A). Following preparation of 'awkward' oxime ester **8d** (see later) it was discovered that an alternative method, DCC coupling of an oxime with the corresponding carboxylic acid (catalysed by DMAP), was usually more convenient and often led directly to crystalline products without the need to resort to column chromatography (Method B). The syntheses are shown in Scheme 4, and the results summarised in Table 1.



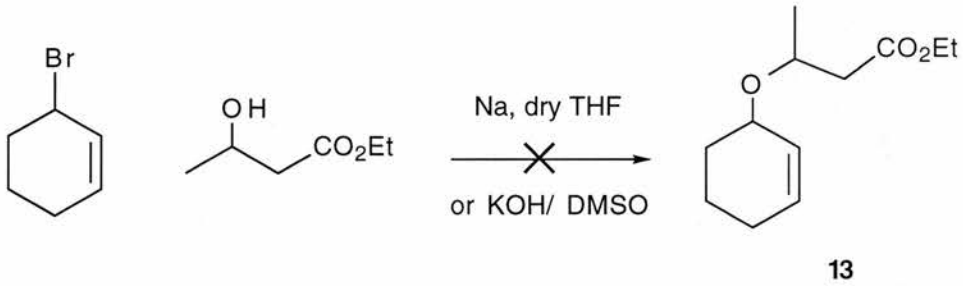
Scheme 4

A wide selection of aromatic groups was investigated to compare the electronic effects of the substituents. If the hydrogen abstraction process was taking place, then it was expected that electron withdrawing groups on the phenyl ring, such as in pentafluorobenzaldoxime esters, would aid the radical process by weakening the oximinyl C-H bond. The oximes chosen for investigation, which were prepared using standard methods from the corresponding aldehyde and hydroxylamine hydrochloride, were benzaldoxime **3**,[17] p-nitrobenzaldoxime **4**,[17] pentafluorobenzaldoxime **5**,[18] 2,4-dimethoxybenzaldoxime **6**,[19] and 2,4,6-trimethoxybenzaldoxime **7**.[20] The simple derivatives **8-12 a**, **b**, **e**, **f**, **g**, **i**, **j**, **k** and **l** were prepared (see table 1, p84) for EPR

investigations, or to investigate the possibility of intermolecular addition using this method, whilst **8-12 c**, **d**, and **h** were prepared to look at intramolecular reactions. Synthesis of *O*-trichloroacetyl *p*-nitrobenzaldoxime **9k** has previously been attempted, along with *O*-trichloroacetyl 3,4-dimethoxybenzaldoxime,[21] and the products reported to be unstable. We found this also to be true for 2,4,6-trimethoxybenzaldoxime **12k** and **12l**.

The oximes, and the derivatives, are believed to be the *syn* isomers. The synthesis of benzaldoxime **3** was specific to the *syn* isomer[17] but the other reported syntheses did not indicate which isomers were formed. Pejkovi´c-Tadi´c *et al.* reported that the oximyl hydrogen chemical shifts of various substituted benzaldoximes were dramatically different for the *syn* and *anti* isomers.[22] All the *syn* isomers had protons with $\delta>8$, while the *anti* isomers had $\delta<7.5$. This distinction enabled us to assign the configuration of **3-7** and **8-12** as *syn* with confidence.

The preparation of *O*-(cyclohexenyloxy)propionoyl benzaldoxime, **8d**, was problematic. An initial attempt at preparing a related compound, **13**, from 3-bromocyclohexene failed (Scheme 5).

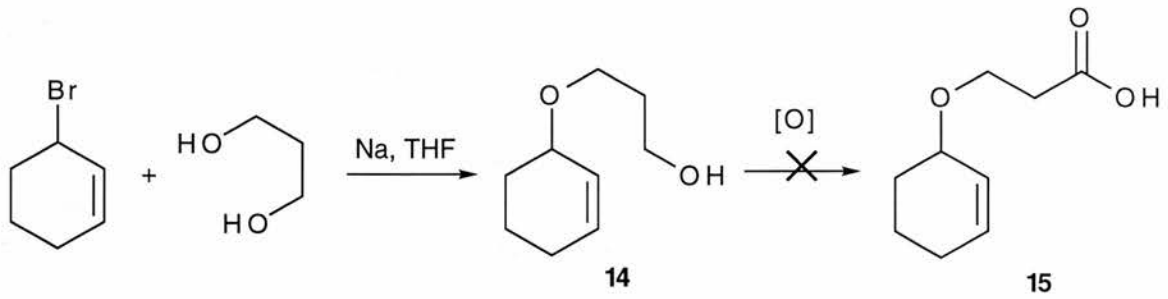


13

Scheme 5

An alternative route to the carboxylic acid precursor **15** via hydroxy ether **14**, was devised (Scheme 6). 3-(3-Cyclohexenyloxy)-propan-1-ol **14** was made successfully from 3-bromocyclohexene and propane-1,3-diol using sodium, but proved difficult to oxidise. Three methods were attemped; the standard method, using chromic acid proved to be too harsh,[16] and the molecule fell apart; a method using TEMPO (a stable radical), bleach, and sodium bromide gave no product.[23,24] An attempt to do the two stages of the oxidation

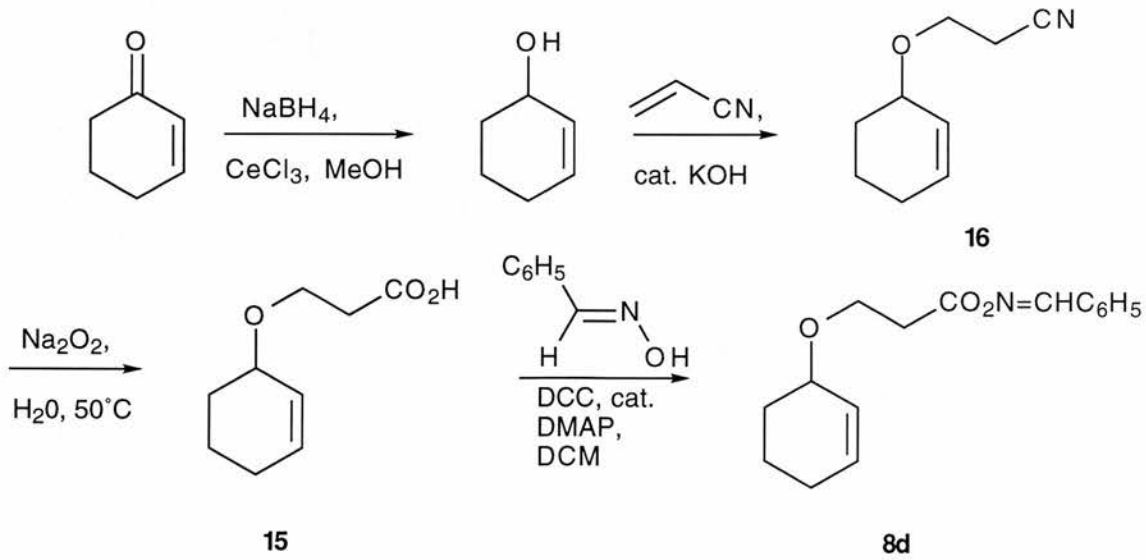
separately, i. e. first to the aldehyde, by Swern oxidation,[25] then using an Oxone system[26] to oxidise the aldehyde to the acid, failed at the second stage.



14 **15**

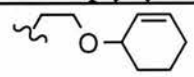
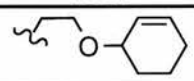
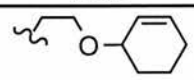
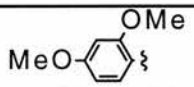
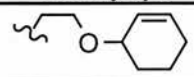
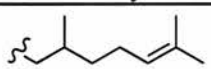
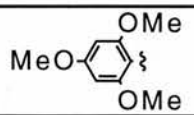
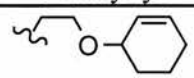
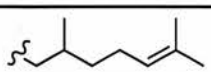
Scheme 6

Eventually a route was found to a suitable precursor (Scheme 7). 2-Cyclohexen-1-one was selectively reduced to cyclohexenol using sodium borohydride/cerium(III) chloride heptahydrate,[27] (note that an alternative method using calcium chloride instead of cerium(III) chloride[28] failed in our hands). Michael addition of cyclohexenol with acrylonitrile was performed, using a catalytic amount of potassium hydroxide[29,30]. The nitrile **16** was hydrolysed to the acid **15** using sodium peroxide in warm water[31,32] and the acid coupled to the oxime using DCC/cat. DMAP in DCM.[4] An earlier method using DCC (but no DMAP)[33] failed. Attempts to convert the carboxylic acid **15** to the acid chloride failed due to the tendency of the acid to fall apart when treated with oxalyl chloride. Reaction occurred at the allylic ether position.



Scheme 7

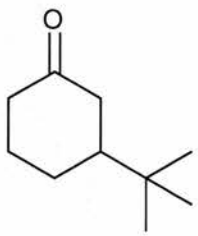
Table 1. Synthesis of oxime esters

Ester	Ar	R	Method	Yield
8a	Ph	t-bu	A	79%
8b	Ph	c-C_6H_{11}	A	48%
8c	Ph	6-heptynyl	A	50%[a]
8d	Ph		B	48%
9a	p-nitrophenyl	t-bu	A	77%
9d	p-nitrophenyl		B	80%
10a	C_6F_5	t-bu	A	73%
10d	C_6F_5		B	62%
11a		t-bu	A	62%
11b	"	c-C_6H_{11}	B	78%
11c	"	6-hexynyl	B	87%
11d	"		B	81%
11e	"	allyl	B	89%
11f	"	isopropyl	B	91%
11g	"	n-hexyl	B	55%
11h	"		B	70%
12a		t-bu	B	96%
12c	"	6-hexynyl	B	80%
12d	"		B	44%
12h	"		B	63%
12i	"	n-Bu	A	65%
12j	"	cyclopropyl	B	89%
12k	"	trichloromethyl	B	-
12l	"	trifluoromethyl	B	90%[b]

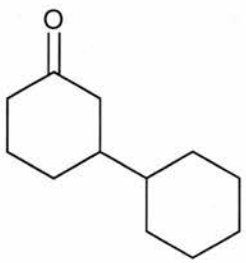
[a] Yield of two step synthesis from 6-heptynoic acid. [b] Crude

2.2.1.2 Product analysis investigations into the reactions of oxime esters

Initial intermolecular reactions were performed with simple benzaldoxime esters **8a** and **8b** using 2-cyclohexen-1-one as a radical acceptor. The oxime ester and 2-cyclohexen-1-one were irradiated for 2 hours in neat DTBP or in DTBP in cyclohexane using a medium pressure mercury lamp, and analysed by GC/MS. Analysis indicated that adducts **17** and **18** were formed from **8a** and **8b** respectively, with little by-product. Use of pinacolone as an external standard indicated that the yield was low (~6%). Use of benzoyl peroxide as a thermal initiator resulted in a yield of zero. Analysis of results by NMR spectroscopy was rendered impossible owing to the highly convoluted nature of the spectra This also led to the analysis of the reaction of *O*-(cyclohexenyloxy)propionoyl benzaldoxime **8d** being impossible. The peak from the methylenecyclopentane product could not be seen on the GC/MS plot, because it was entirely covered by the benzene solvent.

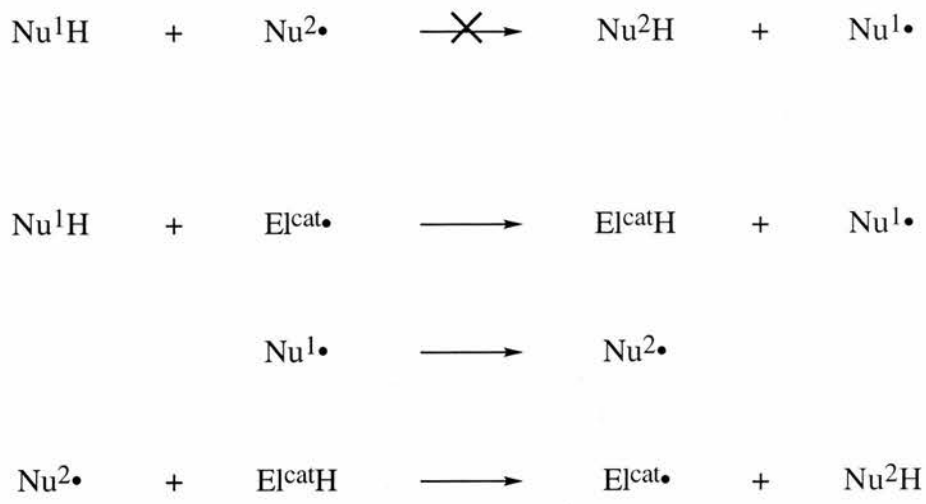


17



18

'Polarity-reversal catalysis' (PLC) is a term coined by Roberts[3] to describe the effect whereby a catalyst enables a propagation step, in which both attacking and leaving radicals are of the same philicity, to be maintained. The principle is illustrated in Scheme 8. A nucleophilic radical $Nu^{2}\bullet$ is electronically unsuitable for abstracting hydrogen from $Nu^{1}H$ (where Nu• represents a nucleophilic radical, and El• represents an electrophilic radical), but $Nu^{2}\bullet$ can abstract hydrogen from the catalyst $El^{cat}H$, and the chain is maintained. The technique also applies when electrophilic radicals are involved.



Scheme 8

It was envisaged that if the reaction was proceeding via the 'hydrogen abstraction' mechanism then PLC would improve the reaction. The products of the reactions are carbon-centred alkyl radicals which are electronically unsuitable for abstracting oximyl hydrogens, so it would be difficult to maintain the chain without such a catalyst. The catalyst would serve no function when DTBP was used in stoichiometric amounts. Thiols have been used as the catalyst in the decarbonylation of aldehydes, and it was assumed that our oxime derivatives are electronically similar to the aldehydes, so these thiol catalysts would help our reactions as well. Methyl thioglycolate was the thiol of choice.

The addition of a catalytic amound of methyl thioglycolate to the reaction mixture resulted in no improvement in yield whether the reaction was performed using DTBP or benzoyl peroxide. This indicated that negligible hydrogen abstraction was taking place. EPR investigations (see Section **2.2.1.3.1**) verified this.

The reactions of oxime esters with different aromatic groups were now investigated under the same reaction conditions (irradiation of ester in DTBP and cyclohexane). Product analysis of the cyclisation reactions of **8d**, **9d**, **10d**, and **11d** revealed that some adduct was formed from all esters except the pentafluorobenzaldoxime derivatives. The highest yields (approximated from peak areas) were obtained from the 2,4-dimethoxy derivatives, while the *p*-nitrobenzaldoxime derivatives showed the poorest results, pentafluoro

derivatives excepted. A large peak due to (cyclohexenyloxy)propionic acid was observed from *O*-(cyclohexenyloxy)propionyl 4-nitrobenzaldoxime **9d**, indicating that the decarboxylation did not compete effectively with hydrogen abstraction of the intermediate carbonyloxyl radicals. Further work concentrated on benzaldoxime, 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime derivatives.

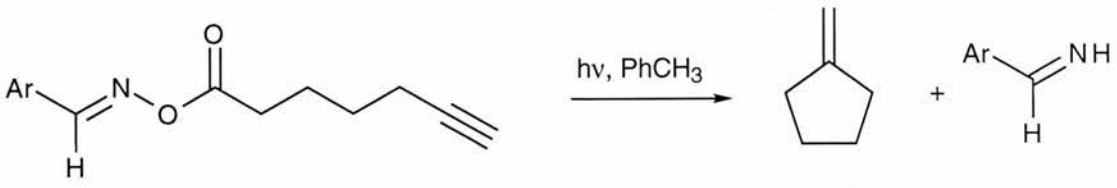
The cyclisation reactions of **8**, **11** and **12 c**,**d** and **h** were also investigated by direct photolysis in toluene in the absence of DTBP. The discovery that *p*-methoxyacetophenone (PMAP) could be used as a sensitiser (Section **2.2.1.3.3**) led to the investigation of cyclisations in which this additive was included. Samples of oxime ester, and sensitiser where appropriate, were dissolved in toluene in a quartz tube, and degassed by passing a stream of nitrogen through the mixture for 15 minutes. The solution was illuminated for 2 hours using a medium pressure 400W mercury lamp, and the yields were obtained in most cases from NMR integral traces, compared with a known amount of added standard such as 1,4-dioxane.

The reaction described in Scheme 9 was investigated under preparative conditions. Results are displayed in table 2.

Table 2. Results of reaction shown in Scheme 9

Ester	Ar[a]	Sensitiser	Yield[b]
8c	Ph	None	6%[c]
8c	Ph	PMAP[e]	28%[c]
8c	Ph	acetophenone	21%[c]
11c	DMOP	None	39%[c]
11c	DMOP	PMAP[e]	77%[c]
11c	DMOP	None	55%[d]
12c	TMOP	None	28%[c]
12c	TMOP	PMAP[e]	35%[c]

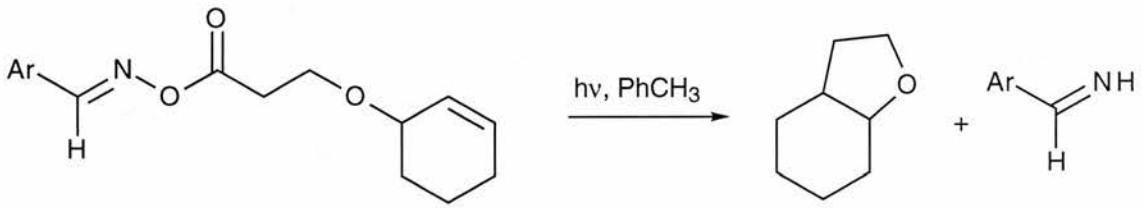
[a] DMOP = 2,4-dimethoxyphenyl. TMOP = 2,4,6-trimethoxyphenyl. [b] Yields obtained from integral trace of 300 MHz ^{1}H NMR spectrum. [c] Reactions performed in toluene. [d] Reaction performed in 1,3,4-trimethylbenzene. [e] PMAP = *p*-methoxyacetophenone



8c, 11c, 12c **19**

Scheme 9

The results clearly indicate that the presence of *p*-methoxyacetophenone enhances the yield of the reaction, especially for **8c** and **11c**. The yield from the trimethoxy derivative **12c** is disappointing, but may be due to its lower solubility in toluene. The trimethoxy derivatives were, almost without exception, the easiest to prepare as they crystallised readily, and could be recrystallised from toluene, toluene/hexane or DCM/hexane.

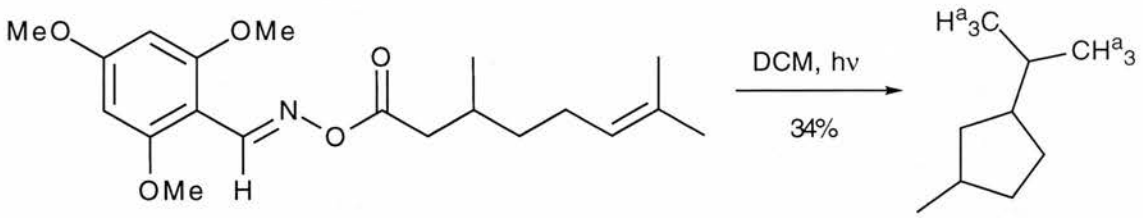


8d, 11d, 12d **20**

Scheme 10

The reaction shown in Scheme 10 was also investigated using product analysis reactions. Unfortunately, problems were encountered in determining yields. The peaks that we wished to use for analysis purposes occurred at ~3.9 ppm, and so were covered by -OCH_3 peaks from both the sensitiser and, in the case of **11d** and **12d**, any aryl containing compounds such as imine present in the product. GC/MS analysis indicated that reactions were clean, but the volatility of the products coupled with limitations of the scale of reaction meant that attempts to isolate products were largely unsuccessful. However bicyclic ether **20** was isolated from reaction of **12d** in 12% yield (yield 72% by NMR). The reaction was also performed in ether, as a volatile hydrogen donor and this afforded approximately 21% of ether **20**.

A third set of precursors that should result in a radical cyclisation reaction was also prepared (**11h** and **12h**). Again, determination of yield was difficult. In this example, all protons resonated in the same region. The reaction shown in Scheme 11 occurred in an approximate yield of 34% (estimated using the integral trace of the doublet due to $6H^a$).



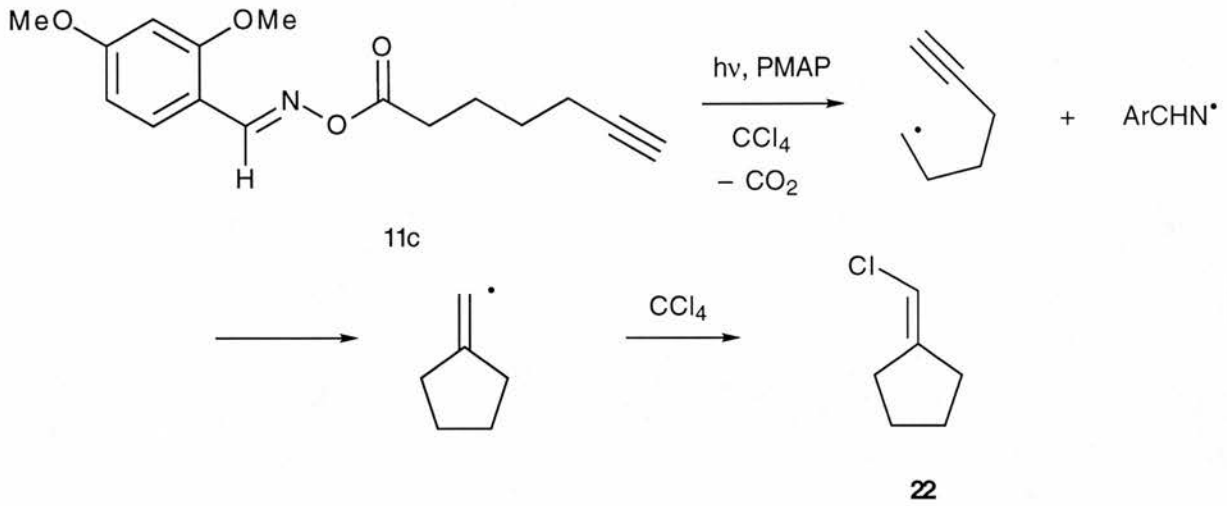
12h **21**

Scheme 11

Hasebe and Tsuchiya described the synthesis of simple alkyl chlorides by illuminating benzophenone oxime esters in carbon tetrachloride.[4a,b] This possiblility was also investigated in our system.

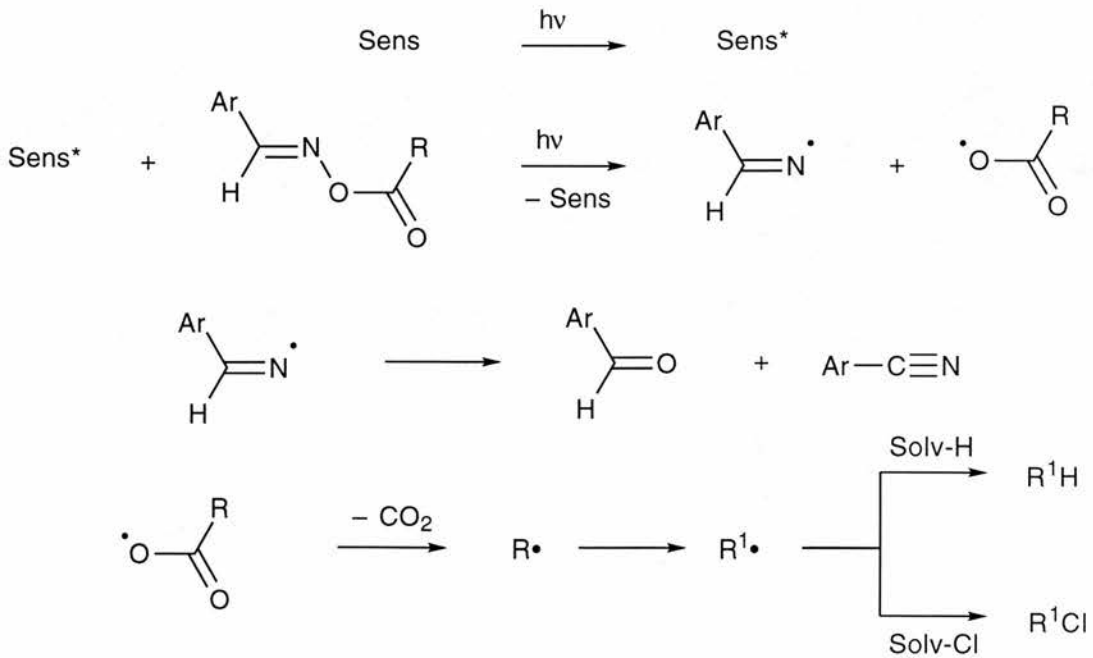
The reactions were found to be awkward to perform. Illumination of a solution of any oxime ester in carbon tetrachloride in a quartz tube resulted in the formation of a cloudy yellow mixture. Best results were obtained when extremely low concentrations were used. *O*-Heptanoyl 2,4-dimethoxybenzaldoxime **11g** was converted (in the presence of *p*-methoxyacetophenone) into 1-chlorohexane in 44% yield (77% based on reacted starting material). However no chlorocyclohexane could be detected from the reaction of *O*-cyclohexylcarbonyl 2,4-dimethoxybenzaldoxime **11b** under the same conditions.

The use of this technique to generate a chloride after a cyclisation has taken place is unprecedented. No chlorinated products (cyclised or otherwise) could be detected from the illumination of **11d** or **11h**. Photolysis of a dilute solution of *O*-heptynoyl 2,4-dimethoxybenzaldoxime **11c** in carbon tetrachloride resulted in the formation of chloromethylenecyclopentane **22** in an approximate yield of 62% (Scheme 12).



Scheme 12

In summary, the esters of benzaldoxime, 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime act as radical precursors, and can be used in preparative experiments in a variety of solvents. Chlorinated products can be prepared by performing the reaction in carbon tetrachloride. The evidence suggests that the reaction proceeds via direct cleavage of the oxime N-O bond followed by decarboxylation (Scheme 13), and not the mechanism shown in Scheme 2. The reaction is enhanced considerably by the presence of a sensitiser, *p*-methoxyacetophenone.



Scheme 13

The process describes a general method by which carboxylic acids or acid chlorides can be converted into alkyl radicals and thus alkanes, chloroalkanes, or cyclised derivatives. It is metal free and, as such, offers a 'green' alternative to radical processes currently available.

2.2.1.3 Investigation of radicals from oxime esters using EPR spectroscopy.

2.2.1.3.1 Attempted abstraction of oximinyl hydrogen using DTBP.

The *O*-acyl arylaldoxime radical precursors were also investigated by EPR spectroscopy. Initial studies were concentrated on *O*-trimethylacetyl benzaldoxime **8a**. A degassed solution of **8a** in DTBP was illuminated by a 500W super pressure mercury lamp and the resulting spectra showed that the desired t-butyl radical [a(9H) = 22.8G] was present at 240 K, but also (at least) two other radicals. One was the iminyl radical **23a**, from direct cleavage of the N-O bond, characterised by its very large hydrogen splitting.[34] The EPR spectrum obtained at 265 K is shown in Figure 1. (N. B. The figures show the spectra obtained at the temperatures given in the text, or table, unless stated otherwise.)

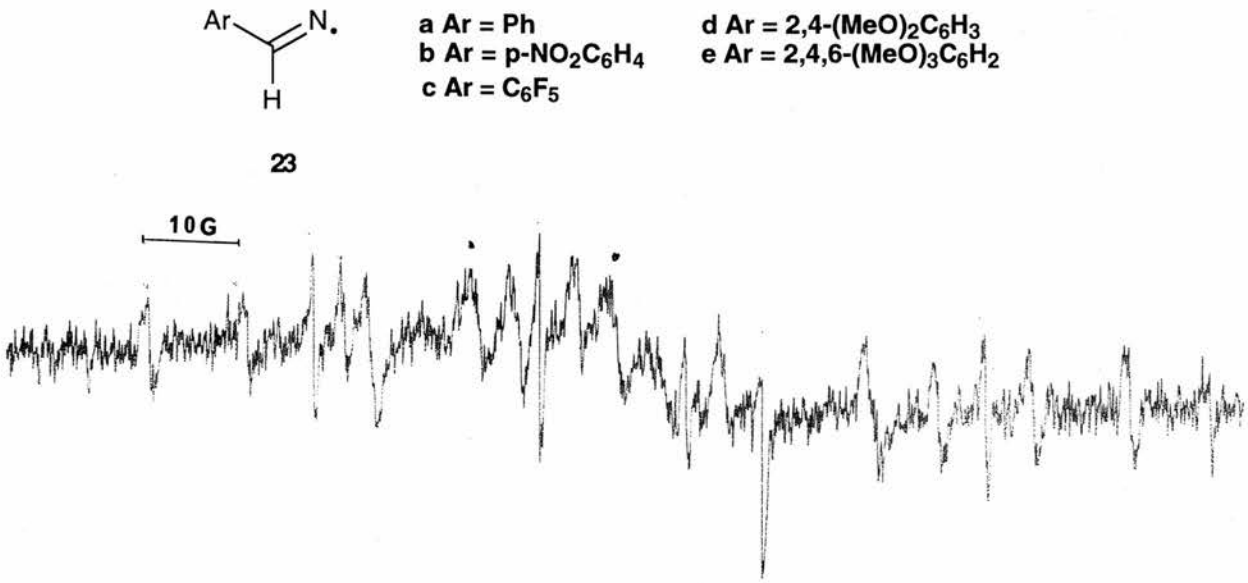
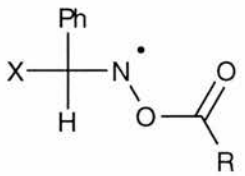


Figure 1. Spectrum of three radicals obtained from the photolysis of **8a** in DTBP, including the iminyl radical **23a**, the t-butyl radical, and aminyl radical **24a**

Another radical had hfs of a(N) = 15.0 G, and a(H) = 21.2 G. This is probably adduct **24a**, formed by the addition of radical X• to the oxime double bond. The obvious candidate for X• is the t-butoxyl radical, but this is not necessarily the case. Radicals such as **24** were also seen in the absence of t-BuO• (See Section **2.2.1.3.3**) and Forrester *et al.* also reported this type of radical generated by addition to oxime ethers, when no t-butoxyl radicals were present.[35]

The only radical seen from reaction of **8d** under the same conditions was the related adduct **24d** [a(N) = 15.0 G, a(H) = 19.0 G]. Oxime ester **8c** gave unidentified spectra.



24 a R = t-Bu
d R = (cyclohexenyloxy)ethyl

Two radicals were observed from photolysis of trimethylacetyl pentafluorobenzaldoxime **12a** in DTBP (Table 3). The radical which dominated at lower temperatures (250 - 310 K) was a triplet of doublets, with further resolution just possible, but its identity is not certain. At higher temperatures, a second radical dominated, and has been partly identified as the adduct radical **25a**. Surprisingly, in a repeat of the experiment only the radical **25a** could be observed, even under the same conditions.

We were unable to obtain spectra from reaction of *O*-(cyclohexenyloxy)propionoyl pentafluorobenzaldoxime **10d** under these conditions.

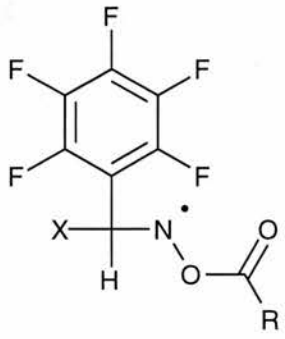
Table 3. EPR investigation of radicals from pentafluorobenzaldoxime esters.

Precursor	T/K[a]	a(N) / G	a(H) / G	a(2F) / G	Radical
12a	375	14.47	26.96	2.07	**25a**
	310	13.61	5.01	1.42	Unknown

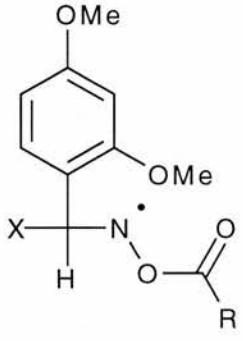
[a] Reaction performed in t-butylbenzene.

Unidentified radicals were obtained from dimethoxybenzaldoxime ester **11c** on photolysis in DTBP. Only very weak spectra were obtained from *O*-pivaloyl 2,4-dimethoxybenzaldoxime **11a**, but included the iminyl radical **23d**. In this case adduct radical **26** could not be identified. Addition to the sterically crowded **12a** was also not observed to take place. The major radical in DTBP/t-butylbenzene was a primary radical: a(2H) = 21.76 G, a(6H) = 1.07G at 245K. While this could be the radical resulting from H-abstraction from the t-butyl group of **12a**, it is more likely that H-abstraction from t-butylbenzene solvent had taken place. A weak spectrum corresponding to iminyl radical **23e** could also be identified. The preference for reaction with the solvent rather than the substrate may be partly a consequence of the low solubility of the *O*-acyl trimethoxybenzaldoximes in t-butylbenzene, which was often problematic.

The parameters of the aminyl radicals, which are summarised in Table 4, are discussed, along with the parameters of other aminyl radicals observed in this study, in Section **2.2.2.3.1**.



25a R = t-Bu



26

Table 4. Summary of parameters of aminyl radicals **24** and **25**.

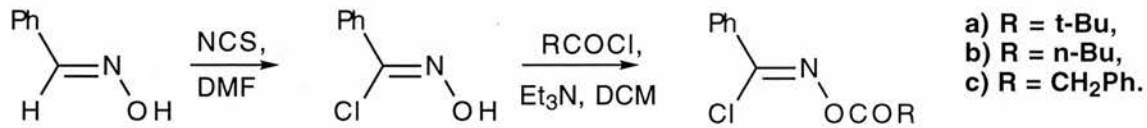
Radical	Temp/K	a(N)/G	a(H)/G	a(Other)/G
24a	250	15.0	21.2	
24d	320	15.0	19.0	
25a	375	14.47	26.96	2.07 (2F)

[a] Reaction performed in t-butylbenzene.

The radicals produced when *p*-nitrobenzaldoxime esters were illuminated were independent of the presence of DTBP, so are covered in the next section.

2.2.1.3.2 EPR investigation of radicals from *O*-acyl benzohydroximoyl chlorides.

The oximidoyl radical **2** was at no time observed by EPR spectroscopy of oxime esters. An alternative method of generation of this radical is by halogen abstraction from *O*-acyl benzohydroximoyl chlorides. (Selenium derivatives, as used by Kim, are rarely suitable for EPR investigations.) Benzohydroximoyl chloride was prepared by the action of NCS in DMF on the parent oxime,[36] and acylated in DCM with triethylamine and an acid chloride in moderate yield (37-50%) (Scheme 14)



3 **27** **28**

Scheme 14

Table 5. EPR data of radicals from *O*-acyl benzohydroximoyl chlorides **28**.

Precursor	T/K[a]	a(N) / G	a(Other) / G	Identity
28a	320	26.3	0.73 (1Cl) 0.73 (4H) 0.35 (1H)	**32a**
	270[b]	7.84[c]		**33**
	270[b]	15.15		**34**
28b	280	26.8[c]		**32b**
	260	4.30	12.05 (2H)	
28c	320	26.9[c]		**32c**
	310[b]	15.0	8.5 (2H)	
	255	11.4	4.6 (2H)	

[a] t-Butylbenzene solvent. [b] Persistent radical [c] Unresolved.

A degassed solution of **28** and hexamethylditin in t-butylbenzene was illuminated by a 500W super pressure mercury lamp under EPR conditions. The results are shown in table

5. Three radicals, all of which were persistent, were observed from *O*-trimethylacetyl benzohydroximoyl chloride **28a**. The radical shown in figure 2 had a large nitrogen splitting [a(N) = 26.3 G], which is characteristic of iminoxyl radicals and alkylalkoxyl radicals. It was considered unlikely that this radical was oximidoyl radical **2**. The t-butyl radical resulting from collapse of radical **2** as described in Scheme 2 was not observed, and the nitrogen hfs is unduly large for a radical of this type.

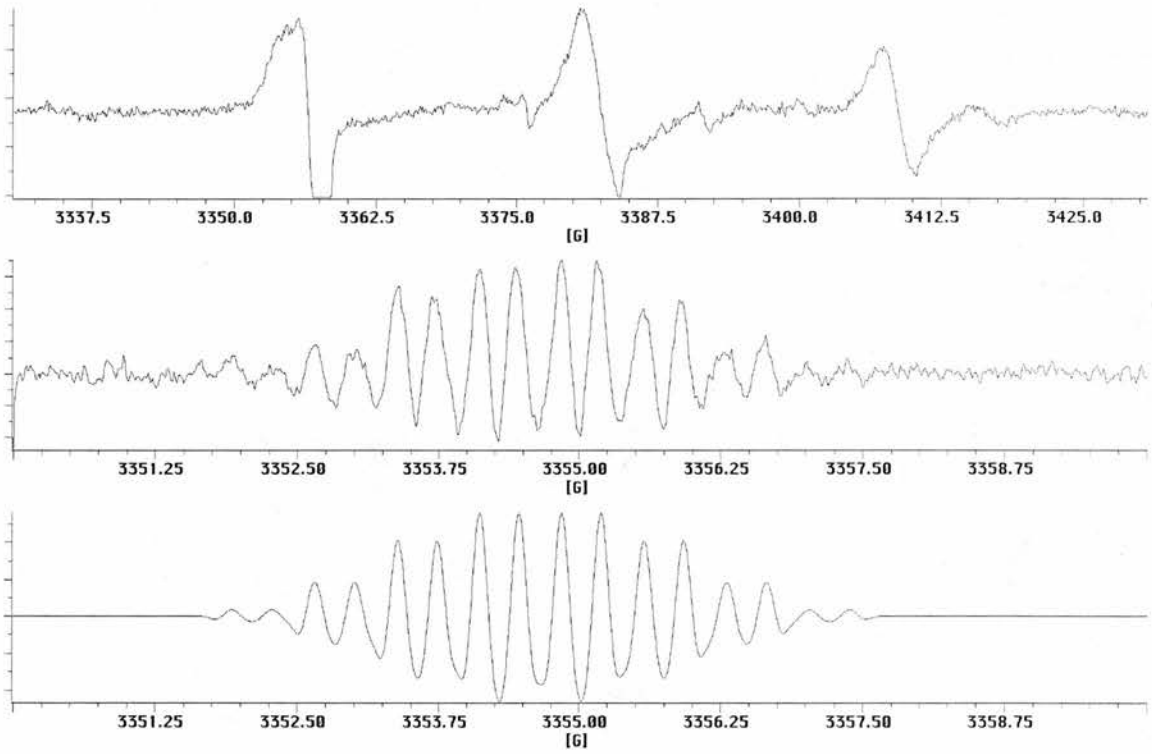
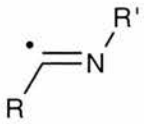


Figure 2. Spectrum (top) of radical **32a** from **28a** at 240 K. The left hand peak from this spectrum, and its simulation (bottom) is also shown under high resolution conditions at 320 K.

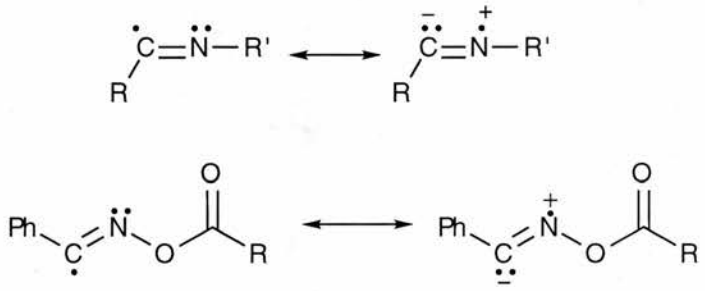
While oximidoyl radicals of type **2** are unknown in the literature (apart from Kim's work), imidoyl radicals of type **29** have been formed and investigated by EPR spectroscopy. They were generated by H abstraction from imines[2,37], or by radical addition to isonitriles.[38] The derivatives with R = Ph did not give resolvable spectra (the line widths were very large), but reported values for a(N) are in the range of 1.4 - 2.4 G for similar

radicals with R = alkyl. For R' = t-Bu, Davies[37] and Roberts[38] observed the spectrum due to t-Bu$^{\bullet}$ above 220K, due to the radical collapsing.



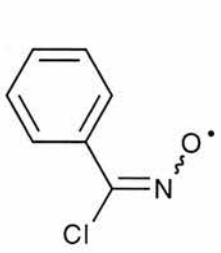
29

Danen and West suggested that the low values of a(N) were due to the positive spin density on the nitrogen caused by a resonance effect (Scheme 15) nearly balancing the negative spin density induced by a spin polarization mechanism.[2] It is conceivable that the different N-substituents present in our system would have an effect on the a(N) values, but unlikely to result in a nitrogen hfs of 26 G.

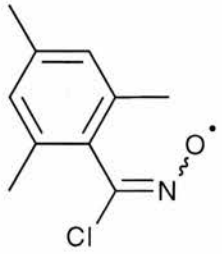


Scheme 15

Comparison with literature data indicates that the radical is unlikely to be iminoxyl radical **30**.[39] Related iminoxyl radicals, such as **31**,[39a] all had nitrogen hfs of 30-31 G in t-butylbenzene (for both *syn* and *anti* isomers), while Norman and Gilbert noted that iminoxyl radicals almost always give a mixture of isomeric radicals.[40] We found no evidence for the presence of an isomeric radical.

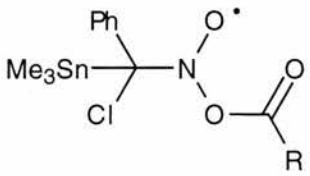


30



31

Acyloxynitroxides are also extremely persistent, and the observed radical may have been **32**, possibly formed by reaction with a trace amount of oxygen.

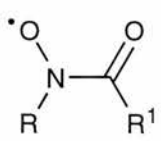


32

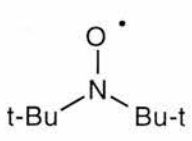
a R = t-Bu,
b R = n-Bu,
c R = CH_2Ph.

α-Chloroalkylalkoxynitroxides radicals have been previously observed in water at pH 1.8,[41] and in benzene[42] and trichlorofluoromethane.[42] Kayen *et al.* reported a(Cl) = 3.5 - 3.8 G, a(N) = 22.7 - 24.2 G in benzene or trichlorofluoromethane.[42] However, Norman commented that β-chlorine hfs are usually small or undetectable, and that nitrogen splittings are usually in the range 24-29 G.[41] The simulation shown in Figure 2 fits well with the experimental values, and suggests that **32** is the observed radical.

The two other radicals observed from the reaction of *O*-trimethylacetyl benzohydroximoyl chloride **28a** were probably also nitroxides. The nitrogen hyperfine splitting of one of the radicals [a(N) = 7.84 G (plus unresolved fine structure)] was indicative of an acyl nitroxide **33**. The obvious candidates for R and R^1 are phenyl and t-butyl. Benzoyl t-butyl nitroxide (**33**; R = t-Bu, R^1 = Ph) has been observed,[43] but showed no fine structure. Trimethylacetyl phenyl nitroxide has also been observed, and hfs due to all five aromatic hydrogens were present.[44] The mechanism to account for the formation of **33** was unclear.



33



34

The third radical had a nitrogen splitting of 15.15 G, with no fine structure. This is likely to be di-t-butyl nitroxide **34**, formed by an unknown process.[45]

O-Valeryl benzohydroximoyl chloride **28b** showed two radicals. One was closely related to the radical previously observed from **28a**, and likely to be acyloxynitroxide **32b**. The spectrum could not be fully resolved. The other radical present has not been identified. *O*-Phenylacetyl benzohydroximoyl chloride **28c** also formed the acyloxynitroxide **32c**, along with two unidentified radicals.

We have observed several radicals from *O*-acyl benzohydroximoyl chlorides **28**. However, none of these were the oximidoyl radicals **2**.

2.2.1.3.3 Illumination of oxime esters in the absence of DTBP.

It has proved impossible to verify the hydrogen abstraction mechanism postulated for the formation of alkyl radicals; indeed addition products appear to be favoured, so attention is now turned to the direct cleavage of the N-O bond mediated by UV light under EPR conditions.

A sample of *O*-heptynoyl benzaldoxime **8c** was dissolved in t-butylbenzene, and degassed using a stream of nitrogen. When illuminated with a super pressure Hg lamp under EPR conditions, iminyl radical **23a** [$\underline{a}$(N) = 9.93 G, $\underline{a}$(H) = 80.03 G] was visible, but a signal due the expected 5-hexynyl radical was not observed. A 'fairly persistent' ($t_{0.5}$ = seconds) radical was observed [$\underline{a}$(N) = 7.14G, $\underline{a}$(H) = 1.45 G] which has yet to be identified.

Better spectra were obtained from t-butyl derivative **8a**, in which the t-butyl radical can be seen. p-Methoxyacetophenone has been used as a sensitiser for DTBP, enabling better EPR spectra to be obtained.[46] Addition of a small amount of this to our sample prior to degassing had a dramatic effect on the signal - vastly improved signals were obtained. Figure 3 shows the spectrum from **8a**, with 1 equivalent of sensitiser (see table 7 for the parameters of all alkyl radicals observed in this study). To obtain an indication of the optimum quantities of sensitiser required samples of varying (known) concentrations (but

fixed concentration of **8a**) were prepared and the relative iminyl and t-butyl radical concentrations calculated by double integrating the signals. (One large, clear peak from each spectrum was chosen and the values adjusted to compensate for different peaks being due to a different proportion the radical signal.) It was found that, while best results were obtained with 0.5-1 equivalents, excellent results could be obtained with as little as 0.1 equivalents. Spectra were enhanced by a factor of ≈ 5. Figure 4 shows a graph of the relative radical concentrations versus the amount of sensitiser.

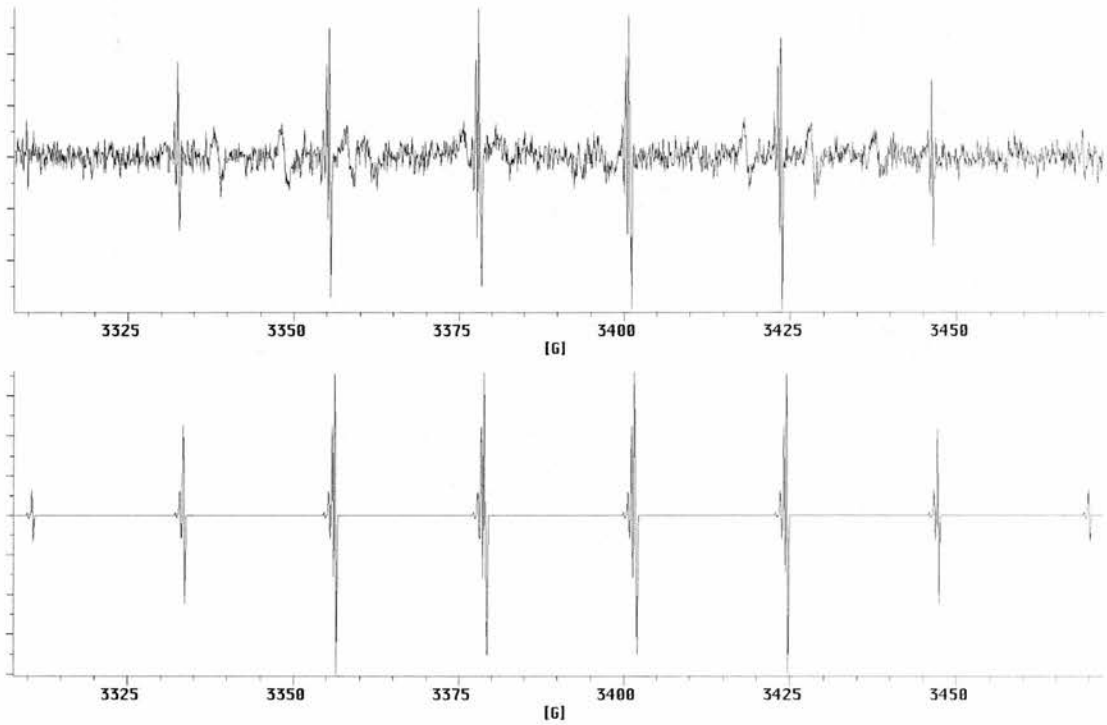


Figure 3. Spectrum (top) of iminyl radical **23a** and the t-butyl radical obtained from photolysis of **8a**. The simulation of the t-butyl radical is also shown..

The g-factor of the t-butyl radical is known (g = 2.00276)[47] and hence the g-factor of **23a** could be calculated (g = 2.00338) using equation 1, where n represents the known radical, x represents the unknown radical and B_x stands for the magnetic field centres of the spectrum of x, in Gauss. This result has important consequences for the use of oxime esters in EPR investigations. Calculation of an unknown g-factor usually requires an inconvenient setup in which samples in two different EPR tubes have to be recorded at the same time. In this case the unknown g-factor can be calculated easily. Crucially, the large

splitting of the iminyl hydrogen means that there is little likelihood of overlap of important peaks from the two spectra.

$$g_x = g_n\{1 - [\Delta B/(B_n + \Delta B)]\} \qquad \text{eq (1)}$$

$$\Delta B = B_n - B_x$$

Graph of relative concentration of t-butyl and iminyl radicals with different amounts of sensitiser

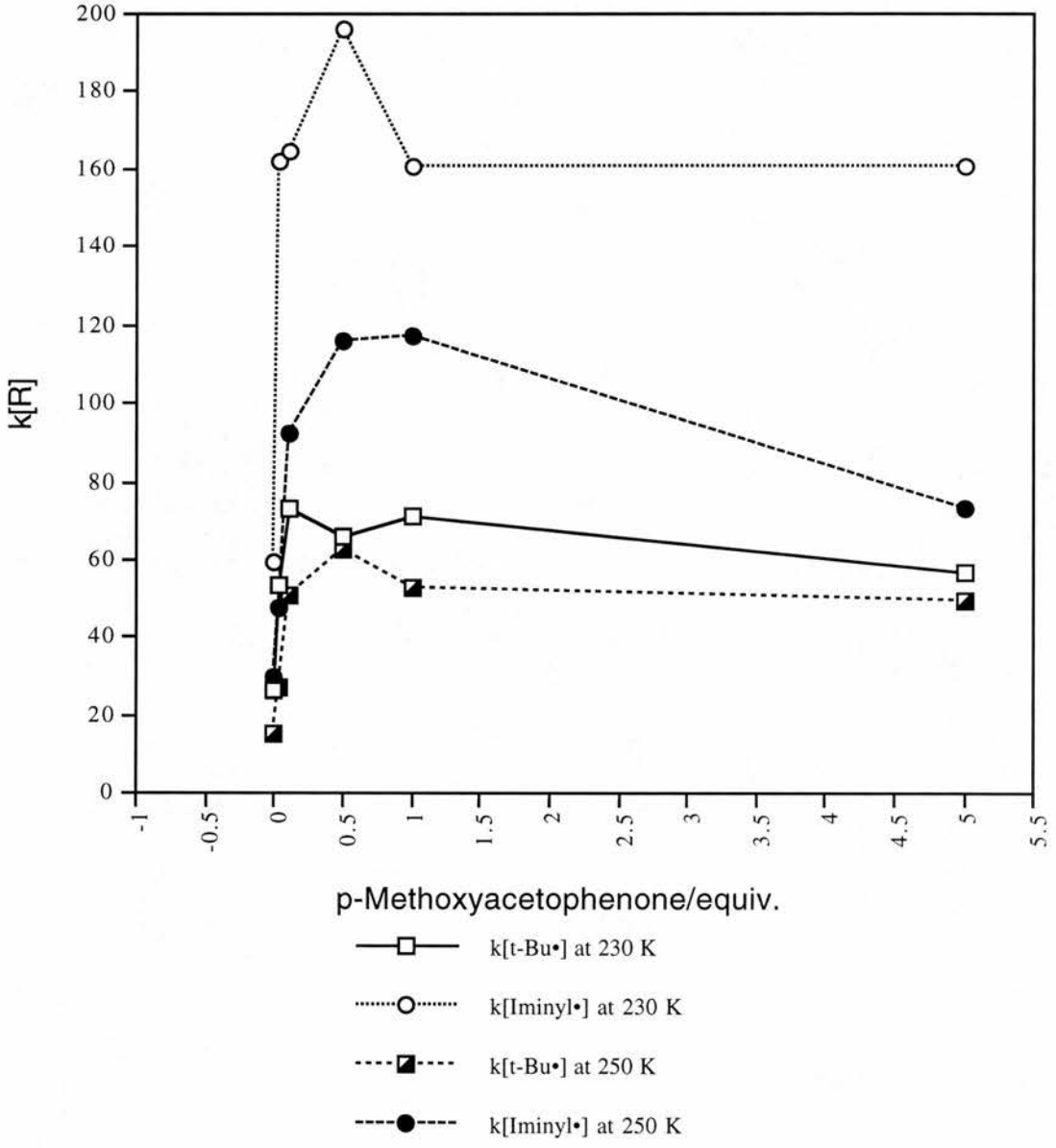
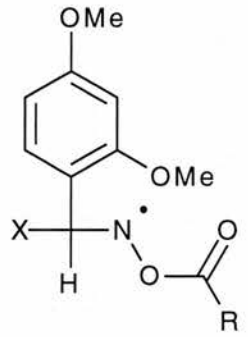


Figure 4

2,4-Dimethoxybenzaldoxime esters gave noticeably stronger signals than the unsensitised benzaldoxime derivatives. Again, addition of p-methoxyacetophenone resulted in stronger spectra. In all cases, the iminyl radical **23d** was observed: a(N) = 9.8-10.1 G, a(H) = 79-81G. The parameters of all iminyl radicals obtained are given in Table 9 on page 109.

Illumination of *O*-cyclohexylcarbonyl 2,4-dimethoxybenzaldoxime under EPR conditions indicated the presence of an aminyl radical **26b** [a(N) = 14.94 G, a(H) = 18.65 G @ 280 K] similar to those described when DTBP was present. This type of aminyl radical was also observed from *O*-(cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime **11d** [a(N) = 14.81 G, a(H) = 18.58 G @ 300 K]. This is further evidence that the radical X• that adds to oxime esters to give **24-26** is not necessarily the t-butoxyl radical when the reaction was performed in DTBP (Section **2.2.1.3.1**).



26b R = cyclohexyl
26d R = (cyclohexenyloxy)ethyl

The best spectra of the aminyl radical **26d** were obtained in the absence of sensitiser. When *p*-methoxyacetophenone was present, weak spectra were obtained which appeared to have a nitrogen triplet [a(N) = 32.0 G @ 245 K] with some fine structure. If this attribution is correct, then this radical is likely to be iminoxyl radical ArCH=N-O•. Iminoxyl radicals have a characteristic nitrogen hfs of about 32 G, and Forrester has observed the iminoxyl radical in similar experiments, caused by photolytic cleavage of the C-O bond.[48]

Illumination of *O*-i-propyl 2,4-dimethoxybenzaldoxime **11f** which, like **11b**, should give a secondary radical, showed only the desired isopropyl radical (Table 7) plus the iminyl radical **23d**.

Primary alkyl radicals could also be observed using this method. Apart from the iminyl radical **23d**, no identifiable spectra were obtained from *O*-2,6-dimethylhept-5-enecarbonyl 2,4-dimethoxybenzaldoxime **11h**, and only the aminyl radicals previously described were observed from *O*-(cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime **11d**, but the 5-hexynyl radical could be observed from *O*-heptynoyl 2,4-dimethoxybenzaldoxime **11c** (Table 7). The 1-hexanyl radical could be observed clearly enough from *O*-heptanoyl 2,4-dimethoxybenzaldoxime **11g** for resolution of γ-hydrogen splittings. (Table 7). This spectrum is shown in Figure 5.

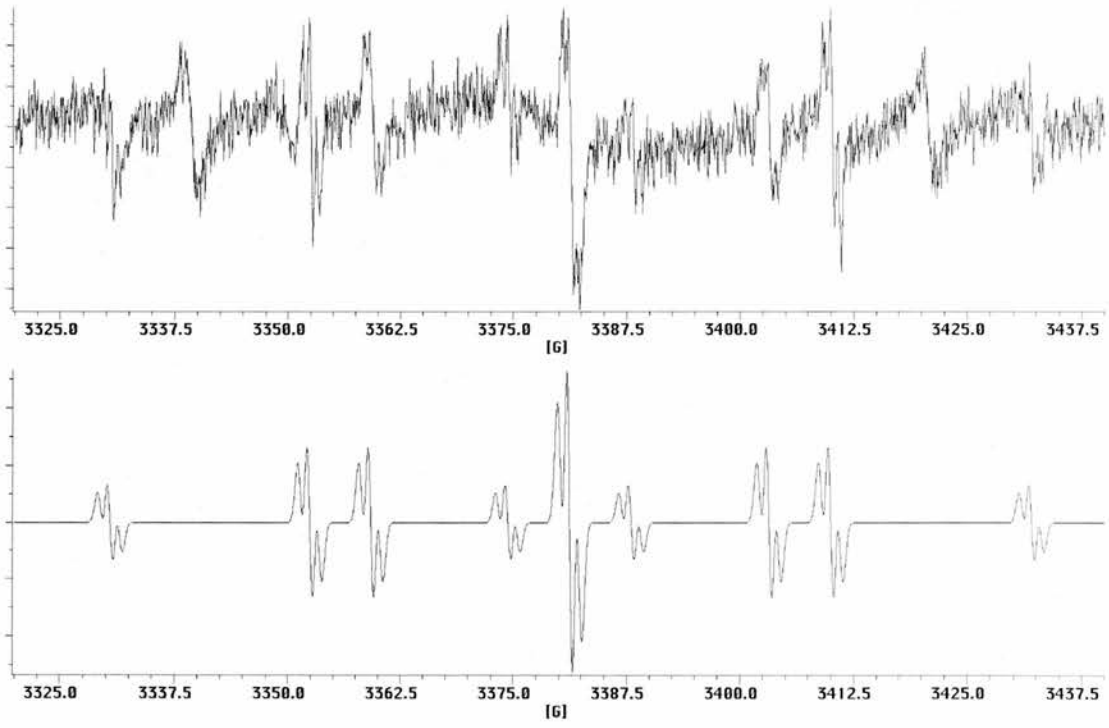


Figure 5. Partial spectrum (top) of the 1-hexanyl radical and iminyl radical **23d** obtained from photolysis of **11g**. The simulation of the 1-hexanyl radical is also displayed.

O-Vinylacetyl 2,4-dimethoxybenzaldoxime **11e** gave excellent spectra of the desired allyl radical (Table 7), one of which is shown in Figure 6. The experiment was repeated in the absence of sensitiser, resulting in a dramatic decrease in signal intensity, but no

quantitative measurements were made. The g-factor of the allyl radical is known (g = 2.0026)[49] and hence the g-factor of **23d** was determined as g = 2.0034.

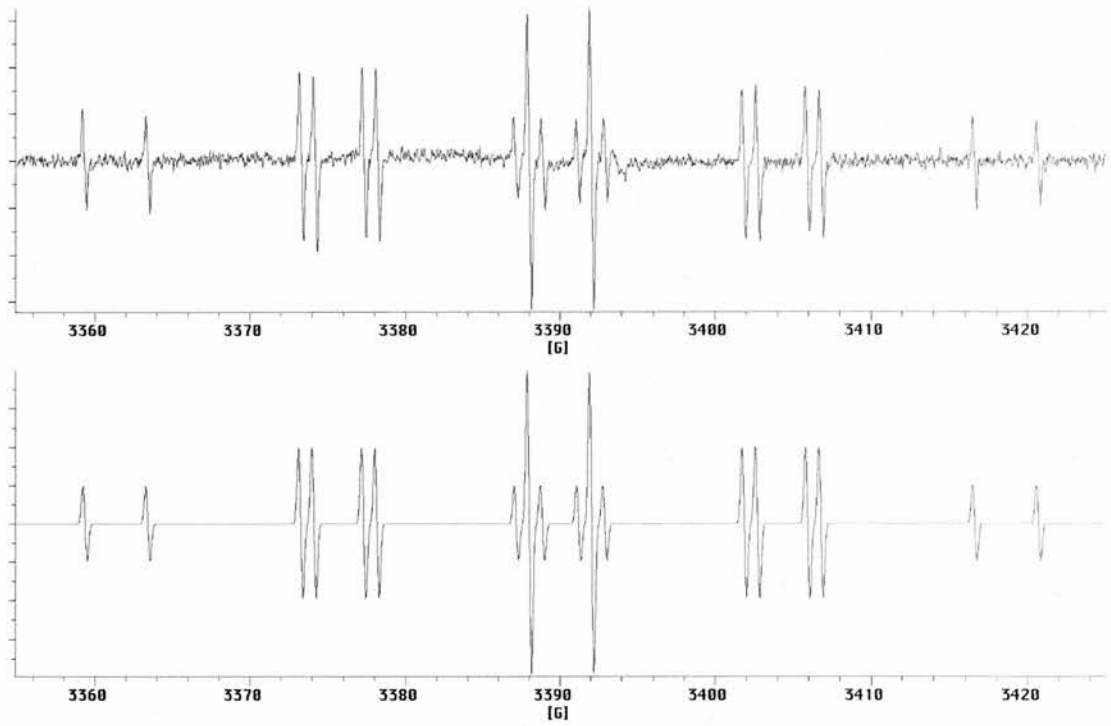


Figure 6. Spectrum (top) and simulation of the allyl radical obtained from photolysis of **11e**

Table 6. Parameters of aminyl radicals obtained from 2,4-dimethoxybenzaldoxime esters in the absence of DTBP.

Radical	Temp/K[a]	a(N)/G	a(H)/G
26b	280	14.94	18.65
26d	300	14.81	18.58

[a] Reaction performed in t-butylbenzene

2,4,6-Trimethoxybenzaldoxime esters also gave stronger spectra than derivatives of benzaldoxime **3**, but occasionally the precursors **12** were virtually insoluble at the temperatures required for EPR spectroscopy. The effect of the sensitiser was less dramatic in spectra from 2,4,6-trimethoxybenzaldoxime esters.

O-Trimethylacetyl-2,4,6-trimethoxybenzaldoxime **12a** gave excellent spectra of the t-butyl radical. The primary radical which would be expected to form from

O-(cyclohexenyloxy)propionyl 2,4,6-trimethoxybenzaldoxime **12d** (prior to cyclisation) was not observed, although strong signals from iminyl radical **23e** were observed. The n-butyl radical, also primary, was observed from **12i** and the spectra were of excellent quality (Figure 7). The g-factor of the n-butyl radical is known (g = 2.0027),[50] and hence the g-factor of **23e** was calculated as 2.0034.

Very weak spectra of the desired primary radical were obtained from *O*-2,6-dimethylhept-5-enecarbonyl 2,4,6-trimethoxybenzaldoxime **12h** (Table 7). The identity was verified by the g-factor, calculated to be 2.0027. Also present was a radical identified as acyl radical **35** [a(2H) = 1.1 G, g = 2.00056], with a characteristically small H hfs and small g-factor.[51] It is likely that **35** was formed by H-abstraction from traces of aldehyde either accompanying the oxime ester precursor, or from *in situ* hydrolysis.

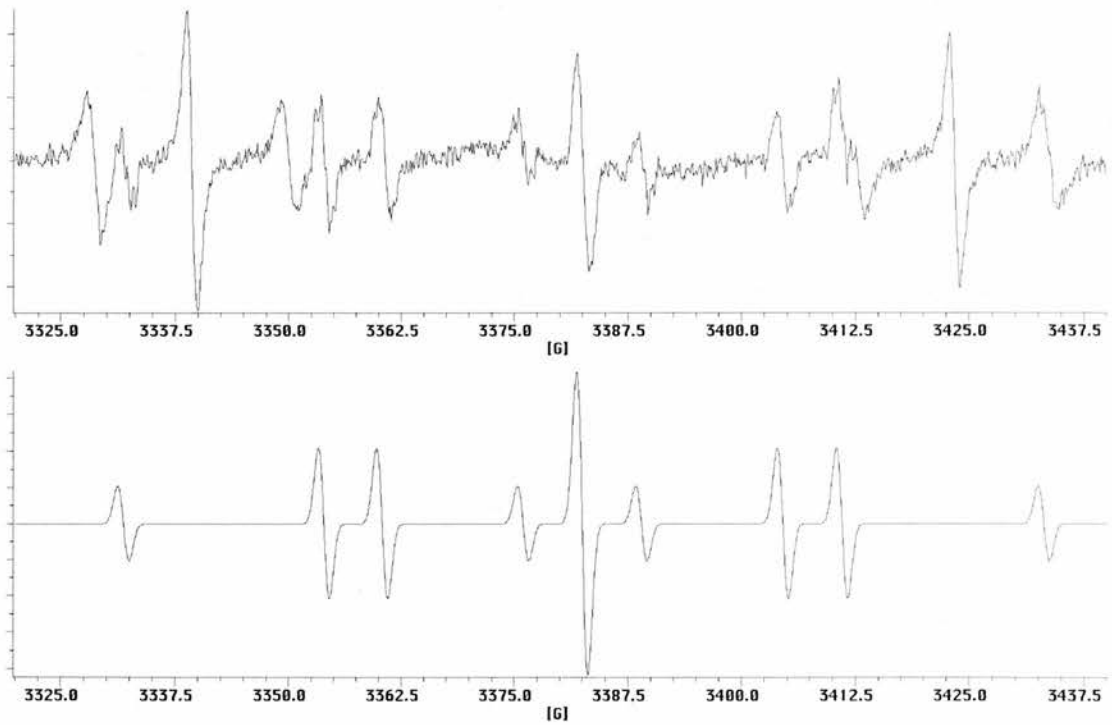
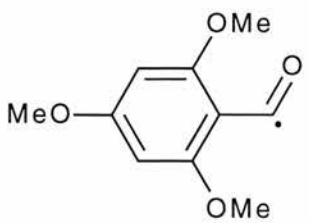
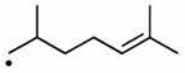


Figure 7. Partial spectrum (top) of the n-butyl radical and iminyl radical **23e** obtained from photolysis of **12i**. The simulation of the n-butyl radical is also shown.



35

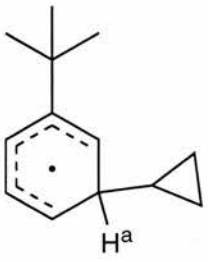
Table 7. Parameters of alkyl radicals obtained from oxime esters.

Precursor	T/K[a]	hfs/G	Identity
8a	225	a(9H) = 22.75	t-Bu•
11c	220	a(2H) = 22.09 a(2H) = 28.32	1-hex-5-ynyl
11e	200	a(1H) = 4.06 a(2H) = 13.89 a(2H) = 14.74	allyl
11g	205	a(2H) = 21.99 a(2H) = 28.78 a(2H) = 0.98	1-hexanyl
11f	205	a(1H) = 21.91 a(6H) = 24.76	i-Pr•
12h	300	a(1H) = 30.62 a(2H) = 22.54	
12i	235[b]	a(2H) = 22.07 a(2H) = 28.57	n-Bu•

[a] Reaction performed in t-butylbenzene [b] At higher temperatures, a further splitting could be resolved: a(2H) = 0.68 G

Attempts were made to observe other 'more unusual' radicals using this method. Photolysis of *O*-cyclopropylcarbonyl 2,4,6-trimethoxybenzaldoxime **12j** under EPR conditions in t-butylbenzene led to the observation not of the expected cyclopropyl radical, but of a radical containing five separate hydrogen splittings [a(H) = 35.11 G, a(H) = 13.23 G, a(H) = 9.24 G, a(H) = 8.07 G, a(H) = 2.75 G @ 200 K]. The spectrum, and simulation, are shown in Figure 8. The σ-type cyclopropyl radical adds to the t-butylbenzene solvent at the *meta* position resulting in cyclohexadienyl radical **36**. σ-Type radical addition to t-butylbenzene has been previously reported,[52] and an H^a hfs of ~36 G is characteristic. Attempts to generate the cyclopropyl radical in t-butylbenzene from

cyclopropyl bromide and hexamethylditin were unsuccessful. Only the allyl radical could be observed, and the reasons for this are unknown. No allyl bromide impurity was present in the starting material. The (oxime ester) reaction was repeated in cyclopropane, but only iminyl radicals were detected. *O*-Cyclopropylcarbonyl 2,4,6-trimethoxybenzaldoxime was not very soluble in cyclopropane.



36

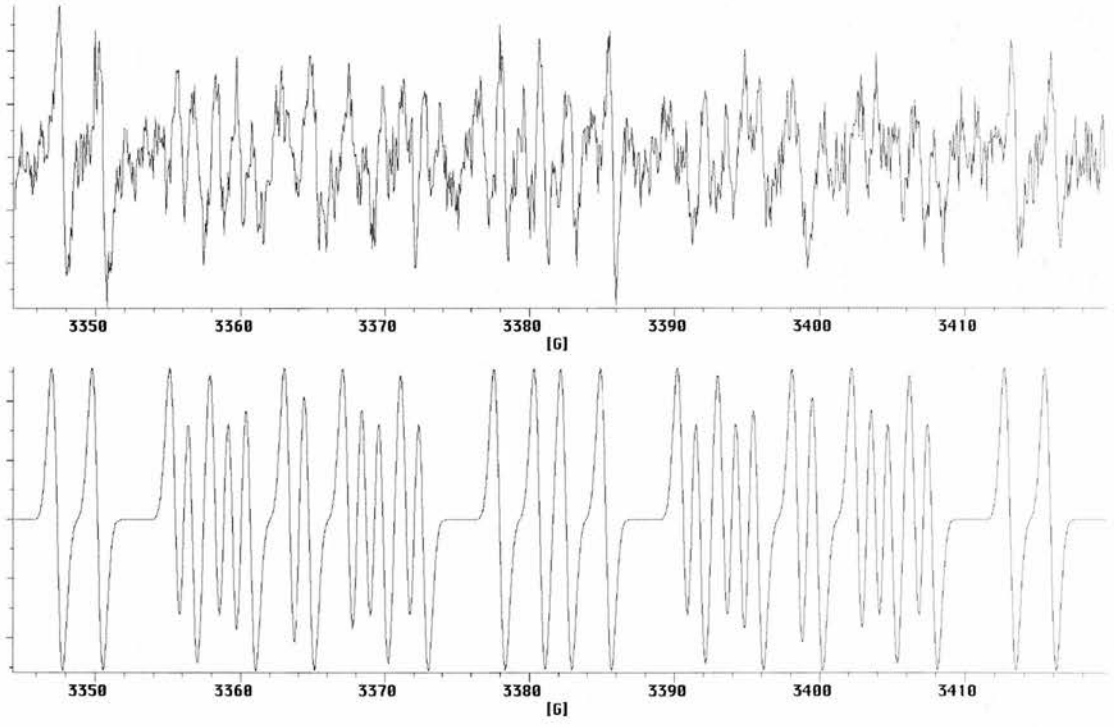
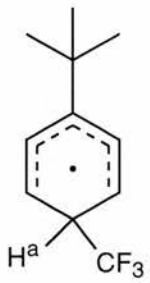


Figure 8. Spectrum (top) and simulation of radical **36** obtained from **12j** in t-butylbenzene.

As previously mentioned, *O*-trichloromethyl 2,4,6-trimethoxybenzaldoxime and *O*-trifluoromethyl 2,4,6-trimethoxybenzaldoxime were found to be unstable. Both samples had to be used in crude form. Photolysis of *O*-trichloromethyl

2,4,6-trimethoxybenzaldoxime gave only spectra of iminyl radical **23e**, but *O*-trifluoromethyl 2,4,6-trimethoxybenzaldoxime also showed radicals of a type previously unseen in this investigation, [a(2H) = 1.95 G, a(2H) = 6.87 G, a(1H) = 9.95 G @ 195 K]. One possibility for the structure is cyclohexadienyl radical **37**, albeit without the large hydrogen splitting characteristic of the *meta*- substituted cyclohexadienyl radicals. Another possibility, *ipso* addition to form **38**, seems unlikely for steric reasons. The trifluoromethyl radical was not observed.



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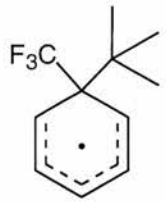
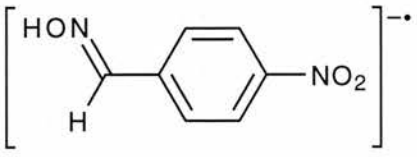


38

We have already seen (Section **2.2.1.3.1**) that two radicals were formed when *O*-trimethylacetyl pentafluorobenzaldoxime **10a** was illuminated in DTBP. Illumination of **10a** in t-butylbenzene in the presence of sensitiser resulted in the formation of a different radical being observed. Again this was possibly an aminyl radical, but the parameters are different from those previously obtained; [a(N) = 13.55 G, a(H/F) = 5.90 G, a(H/F) = 4.42 G @ 270 K.] As with many of the aminyl radicals observed, this radical was moderately persistent.

Photolysis of p-nitrobenzaldoxime ester **9d** gave only broad signals. When t-butyl ester **9a** was illuminated (in DTBP or t-BuPh) a persistent radical was observed with a hyperfine pattern suggesting two nitrogen atoms were present (Table 9). One possible explanation was that we were observing the radical anion occurring from some electron transfer process (albeit with the counterion unknown). There was literature precedent for similar species; radical anion **39** was formed by electrolytic reduction of *p*-nitrobenzaldoxime: [a(N) = 7.3 G, a(2H) = 3.0 G, a(2H) = 1.0 G, a(1H) = 1.0, a(1H) =

0.3 G, a(N) = 2.0 G @ 300 K].[53] The parameters of **39** are similar to those obtained from **9a**, with the exception of those due to the nitrogen of the nitro group, but the spectra of **39** were obtained in DMF. Repeating our experiment in DMF (in a capillary tube) showed little change in the radical parameters, indicating that the observed radical is not the radical anion **39**. The spectrum obtained from **9a** is shown in Figure 9.



39

Table 8. Hfs for radical from illumination of **9a**.

Solvent	T/K	a(N)/G	a(2H)/G	a(2H)/G	a(N)/G	a(1H)/G
t-BuPh	270	12.65	3.04	1.12	1.12	0.67
DMF[53]	270	13.01	3.04	1.12	1.12	0.67

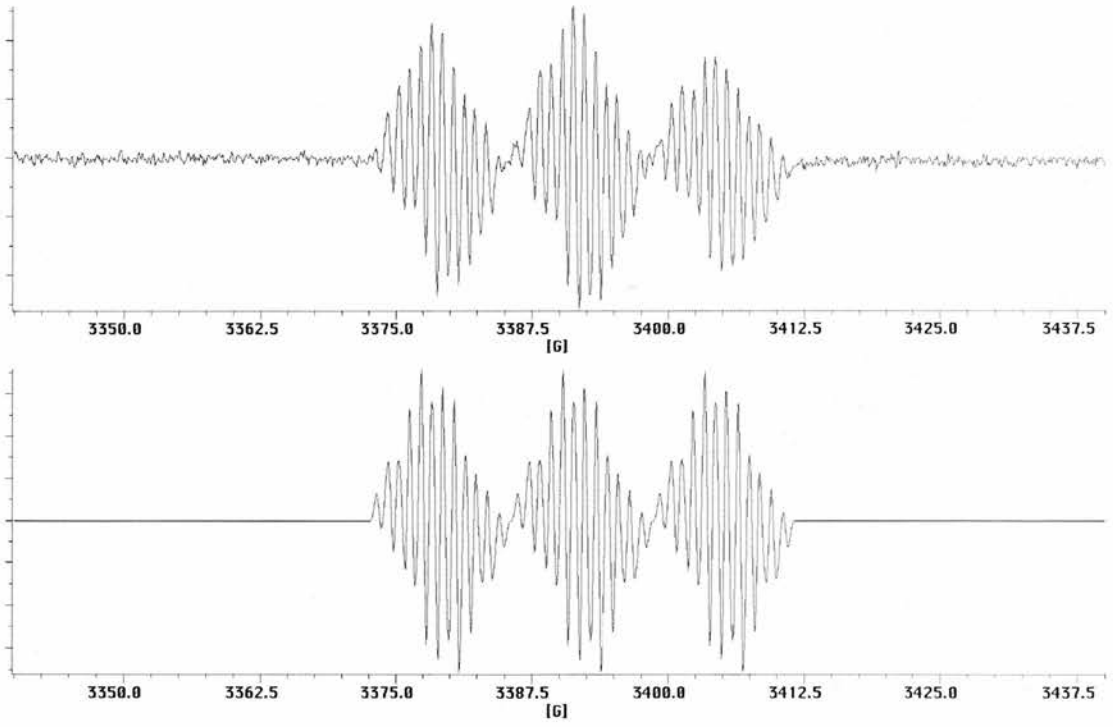


Figure 9. Spectrum (top) and simulation of radical obtained from **9a**

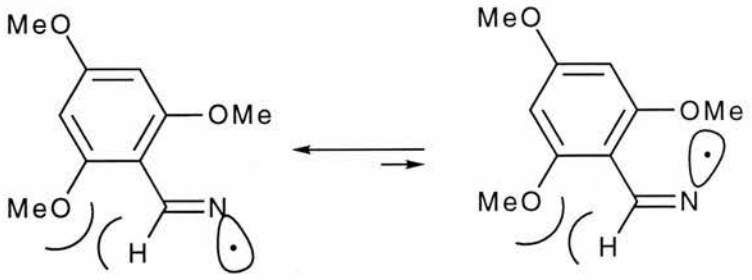
Table 9. EPR data of iminyl radicals **23**.

Precursor	Iminyl	T/K[a]	a(H)/G	a(N)/G	a(Other)/G
8a	**23a**[b]	225	79.87	9.84	0.42 (2H) 0.46 (2H)
8c	**23a**	220	80.03	9.93	
11b	**23d**	280	81.20	10.02	
11c	**23d**	250	81.20	10.03	0.42 (2H)
11d[c]	**23d**	260	79.32	9.90	
11e	**23d**[d]	250	81.23	10.02	
11f	**23d**	260	81.03	10.05	
11g	**23d**	205	81.18	10.18	
11h	**23d**	270	81.00	10.05	
12a	**23e**	230	84.08	10.65	
12c	**23e**	235	84.06	10.73	
12c	**23e**	270	83.96	10.62	
12d	**23e**	240	84.78	10.80	
12h	**23e**	275	83.96	10.62	
12i	**23e**[e]	300	83.98	10.70	
12j	**23e**	240	83.96	10.62	
12k	**23e**	240	84.06	10.70	
12l	**23e**	255	83.96	10.68	

[a] Reaction performed in t-butylbenzene [b] g = 2.00338 [c] No sensitiser present. [d] g = 2.0034 [e] g = 2.0034

The parameters of the iminyl radicals deserve some comment. It can be seen from table 9 that the hfs of the iminyl hydrogen increases as from **23a** to **23d** to **23e**, i.e. as the degee of ring methoxy substitution increases. There are two possible causes. Methoxy groups are π-donor groups, and the ring electron density will be increased by an increasing number of methoxy substituents, thus the electron density of the conjugated system will be

increased. The effect will be small, due to the unpaired electron occupying an orbital with substantial s-character. The inductive effect of the oxygen will be negligible due to the large distance from the unpaired electron.



23ei **23eii**

Alternatively, the effect may be steric in origin. The extremely large hfs is caused by the excellent overlap of the orbital containing the unpaired electron, and the C-H bond σ-orbital. Again this effect will be lessened by the delocalisation of electrons onto the phenyl ring. We can see in **23ei** that there will be steric interaction between the methoxy groups and the iminyl hydrogen. This will result in the phenyl ring twisting out of plane slightly, and thus delocalisation of electron density will be less effective, increasing the amount of electron density in the aldiminyl system.

The increase in the nitrogen hfs is also rationalised by the above argument. Both invoke the mesomeric effect, whereas a σ-type radical is involved, and thus the effects are fairly small.

The nature of the σ-radical is such that 'flipping' can occur, in which the unpaired electron would be *syn* or *anti* to the iminyl hydrogen. This would result in a dramatic temperature dependance of a(H) so we can conclude that this flipping does not occur in the accessible temperature range.

The concentration of the iminyl radicals should be the same as the the concentration of the alkyl radicals, on the assumption that the rate of termination is the same for the two species. Comparison of the iminyl radical concentration with allyl radical concentration in photolysis of **11e** revealed that the ratio was approximately 1:1 at higher temperatures

(> 270 K), but there was a greater proportion of iminyl at lower temperatures (~3:1 @ 235 K). This is presumably due to small differences in termination rates.

The spectra of iminyl radicals from **8a**, **11b**, **11c**, and **12h** were recorded under high resolution conditions. There was no resolution of the long range hfs of 2,4,6-trimethoxybenzaldiminyl radical **23e** from **12h**, and we were unable to obtain resolution of the spectra of **23d** from **11b**. The spectrum of 2,4-dimethoxybenzaldiminyl radical **23d** was resolved when obtained from **11c** (Figure 10). The best simulation was obtained with a(2H) = 0.42 G. This splitting is most probably caused by the *meta*-hydrogens on the aromatic ring.

Fine structure could also be observed in the spectrum of iminyl radical **23a** from **8a**. This contained more hyperfine structure (Figure 11), and a reasonable simulation was obtained using a(2H) = 0.42 G, a(2H) = 0.46 G. This could be accounted for by assuming the *ortho*- and *meta*- hydrogens all cause splitting.

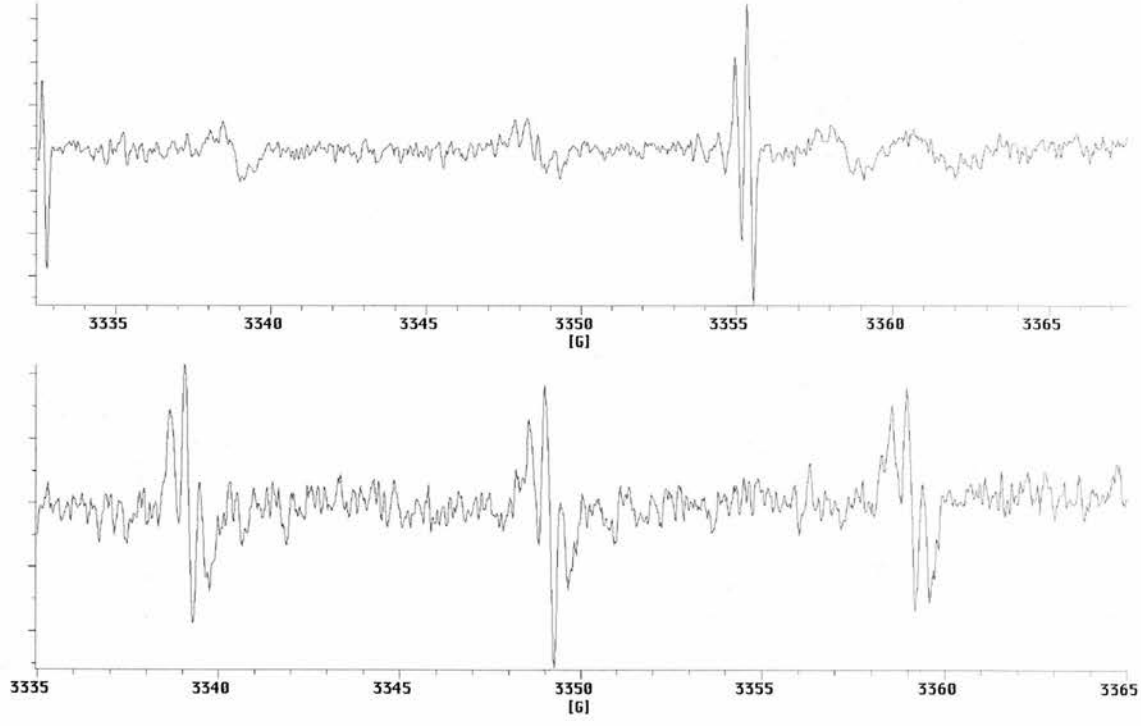


Figure 10 (top) Spectrum of LHS of iminyl radical **23a** (from **8a**) under high resolution conditions. (N.B. the larger peaks are due to the t-butyl radical.)

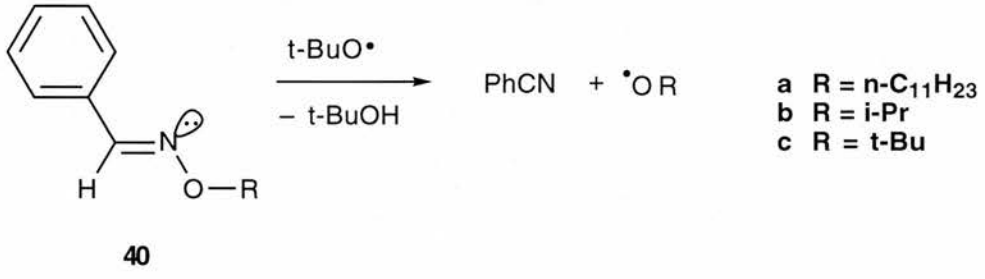
Figure 11 (bottom). Spectrum of LHS of iminyl radical **23d** (from **11b**) under high resolution conditions.

Although the splitting pattern of the 2,4-dimethoxybenzaldiminyl radical is not completely understood, the lack of fine splitting in the spectrum of the 2,4,6-trimethoxybenzaldiminyl radical can be rationalised by invoking the aforementioned argument that the *ortho*- substituents force the ring out of plane. Delocalisation of the unpaired electron onto the aromatic hydrogens becomes less important.

2.2.2 Investigation of the reactions of oxime ethers.

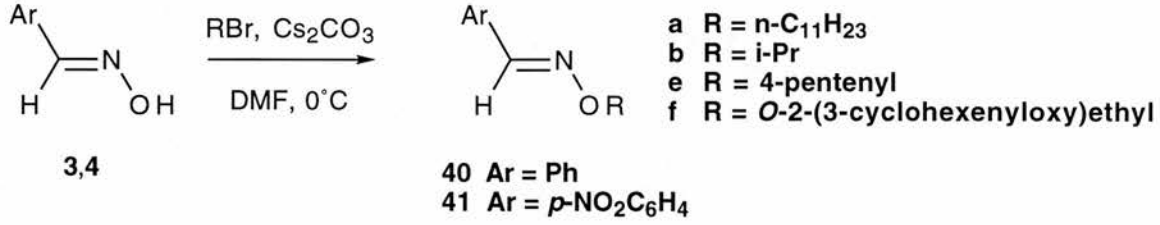
2.2.2.1 Synthesis of oxime ethers.

It was also anticipated that oxime ethers could be used as precursors to alkoxyl radicals, possibly in a way analogous to Kim's phenylselenyl route (Scheme 16).[1] A variety of oxime ethers with a variety of different aryl and alkyl groups were prepared. Most *O*-alkyl benzaldoximes and *O*-alkyl nitrobenzaldoximes were prepared via the method shown in Scheme 17, using cesium carbonate in DMF (Method A).[1]



40

Scheme 16



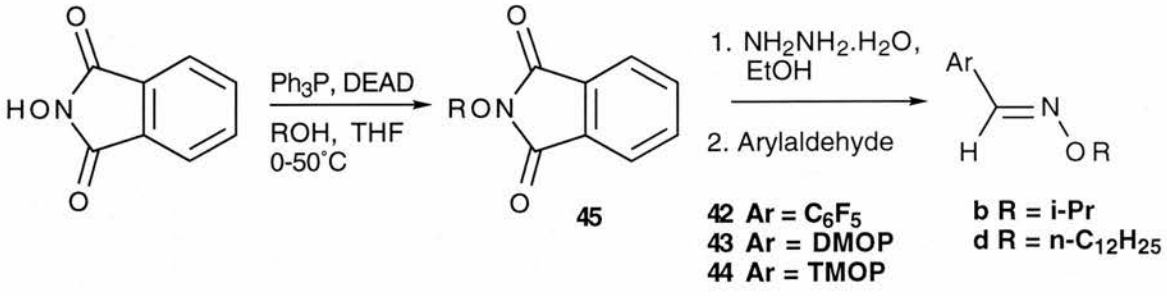
3,4

40 Ar = Ph
41 Ar = *p*-$NO_2C_6H_4$

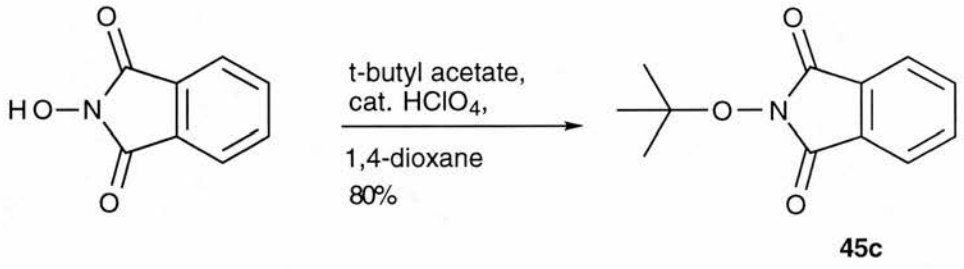
Scheme 17

Pentafluorobenzaldoxime, 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime derivatives **42-44** as well as *O*-t-butyl oximes **40c** and **41c** could not be prepared using this method, so an alternative route was employed, building on

the work of Moody *et al.*, who had shown that *N*-alkoxyphthalimides (prepared from *N*-alkoxyphthalimide and an alcohol under Mitsonobu conditions) could be converted to the corresponding oxime ethers with hydrazine hydrate and benzaldehyde (Scheme 18; method B).[54] Attempts to make t-butoxyphthalimide failed using Mitsonobu conditions.[55] An alternative synthesis using t-butyl acetate was carried out successfully (Scheme 19),[56] and conversion of **45c** to oxime ethers **42-44c** was performed as described above.



Scheme 18



Scheme 19

The syntheses of *N*-alkoxyphthalimides are summarised in Table 10, while those of oxime ethers **40-44a-d** are summarised in Table 11.

Table 10. Synthesis of *N*-alkoxyphthalimides.

Phthalimide	R	Method	Yield
45b	i-Pr	A	85%
45c	t-Bu	B	80%
45d	n-$C_{12}H_{25}$	A	69%

Table 11. Synthesis of oxime ethers.

Oxime ether	Ar	R	Method	Yield
40a	Ph	n-$C_{11}H_{23}$	A	51%
40b	Ph	i-Pr	A	78%
40c	Ph	t-Bu	B	44%
40e	Ph	pent-4-enyl	A	80%
40f	Ph	CHOE[a]	A	55%
41a	p-$NO_2C_6H_4$	n-$C_{11}H_{23}$	A	62%
41b	p-$NO_2C_6H_4$	i-Pr	A	95%
41c	p-$NO_2C_6H_4$	t-Bu	B	65%
42b	C_6F_5	i-Pr	B	62%
42c	C_6F_5	t-Bu	B	54%
42d	C_6F_5	n-$C_{12}H_{25}$	B	61%
43c	DMOP	t-Bu	B	79%
44b	TMOP	i-Pr	B	70%
44c	TMOP	t-Bu	B	27%
44d	TMOP	n-$C_{12}H_{25}$	B	61%

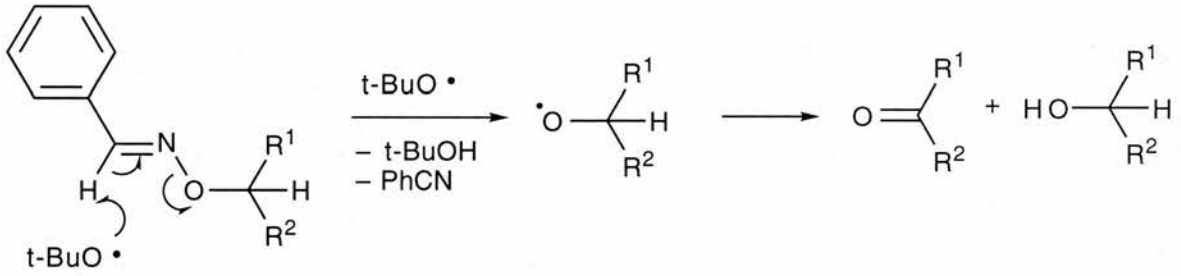
[a] CHOE = 2-(3-cyclohexenyloxy)ethyl

2.2.2.2 Product analysis studies of reactions of oxime ethers

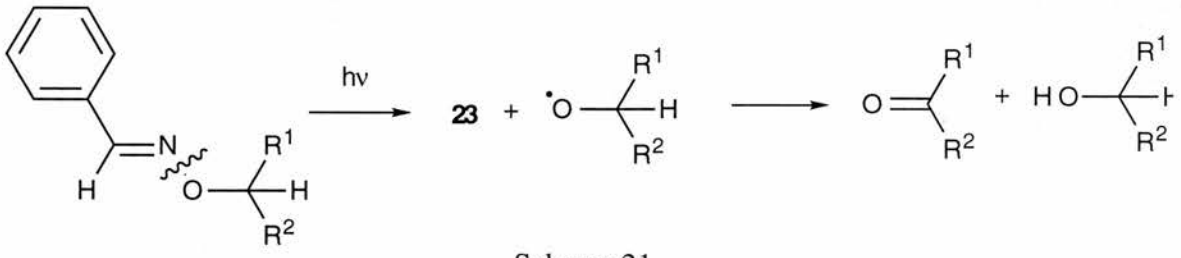
The undecyl oxime ether **40a**, was added to neat DTBP, and photolysed at 25°C for 6 hours using a medium pressure Hg lamp. GC/MS analysis showed a peak corresponding to the desired undecanol product, and a smaller peak corresponding to undecanal. Three mechanisms are postulated for the formation of undecanal and undecanol (Schemes 20-22). The presence of undecanal can be rationalised when undecyloxyl radicals are formed. Disproportionation of two undecyloxyl radicals would lead to undecanol and undecanal. Other mechanisms, such as simple oxidation can also be invoked.

Peaks corresponding to t-butanol and benzonitrile were also present, as would be expected if the oximyl hydrogen abstraction mechanism was taking place. The reaction was clean according to GC/MS analysis, but the conversion was extremely low (<5%), and was not improved by prolonged photolysis.

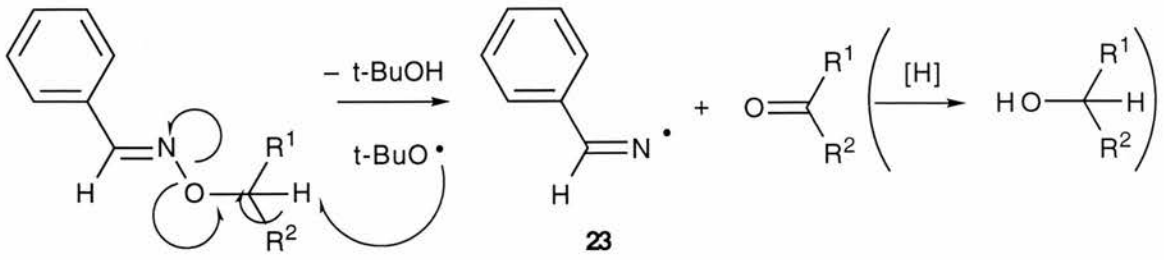
Conversion was not improved by the use of methyl thioglycolate as a 'Polarity Reversal' catalyst, but the undecanol/undecanal ratio was greatly increased, which suggested at first that hydrogen abstraction from the thiol catalyst is faster than disproportionation. This does not constitute proof that the 'Kim-type' mechanism (Scheme 20) is taking place. Direct N-O bond cleavage would also result in the formation of undecyloxyl radicals, and this mechanism could also account for the results described above (Scheme 21). The other mechanism, shown in Scheme 22, in which undecanal is formed following abstraction of a hydrogen α- to the oxime oxygen, can also provide an explanation for these results.



Scheme 20



Scheme 21

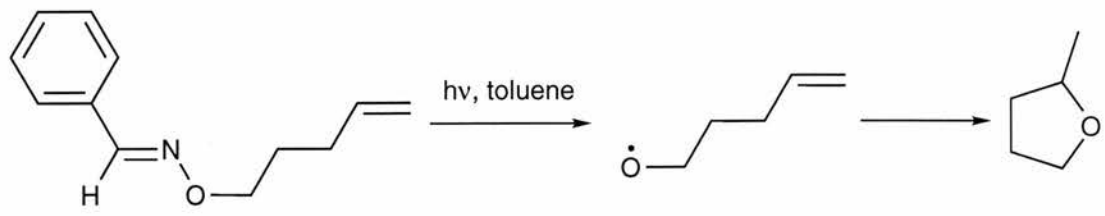


Scheme 22

Thermal radical initiators benzoyl peroxide and t-butyl peroxyoxalate[57] were also used, with results indistinguishable from those obtained under photolytic conditions. No reaction occurred in a control experiment at 60°C with no radical initator. However, illumination of the oxime ether in the absence of DTBP resulted in alcohol and aldehyde again being formed. This indicated that direct cleavage of the N-O bond was occurring, but good yields could not be obtained.

O-Alkyl arylaldoximes **41a**, **42d**, and **44d** all gave undecyl or dodecyl alcohol, along with the corresponding aldehyde under photolytic conditions in the presence of DTBP, as described for **40a**. It appeared that best conversions had been obtained using the benzaldoximes **40**, so further product analysis studies on **41-44** were not undertaken. Photolysis of *O*-dodecyl pentafluorobenzaldoxime **42d** in DTBP and benzene yielded (in addition to dodecanol and dodecanal) 1-dodecene, an observation that has not been rationalised.

To try to determine the nature of the reaction occurring, a degassed mixture of *O*-pent-4-enyl benzaldoxime **40e** was irradiated in toluene for 3 hours. GC/MS analysis revealed a trace of 2-methyltetrahydrofuran as the only product (apart from benzonitrile and starting materials) (Scheme 23). This indicates that photolysis of the oxime ether does result in direct cleavage the N-O bond, but only to a very small extent.



40e

Scheme 23

2.2.2.3 EPR investigation of radicals from oxime ethers

2.2.2.3.1 EPR investigation of radicals from oxime ethers using DTBP

The reactions of *O*-alkyl benzaldoximes with the t-butoxyl radical were investigated by EPR, although the desired alkoxyl radicals would not be detected.

An EPR investigation of *O*-undecyl benzaldoxime **40a** in neat DTBP revealed that the aminyl radical (**46a**), similar to that observed from some oxime esters, was formed. Iminyl radical **23a** [a(N) = 9.68 G, a(H) = 79.66 G @ 250 K] was also observed, and this enabled the g-factor of **46a** to be determined as 2.0049. The spectrum of radicals obtained from **40a** is shown in Figure 12.

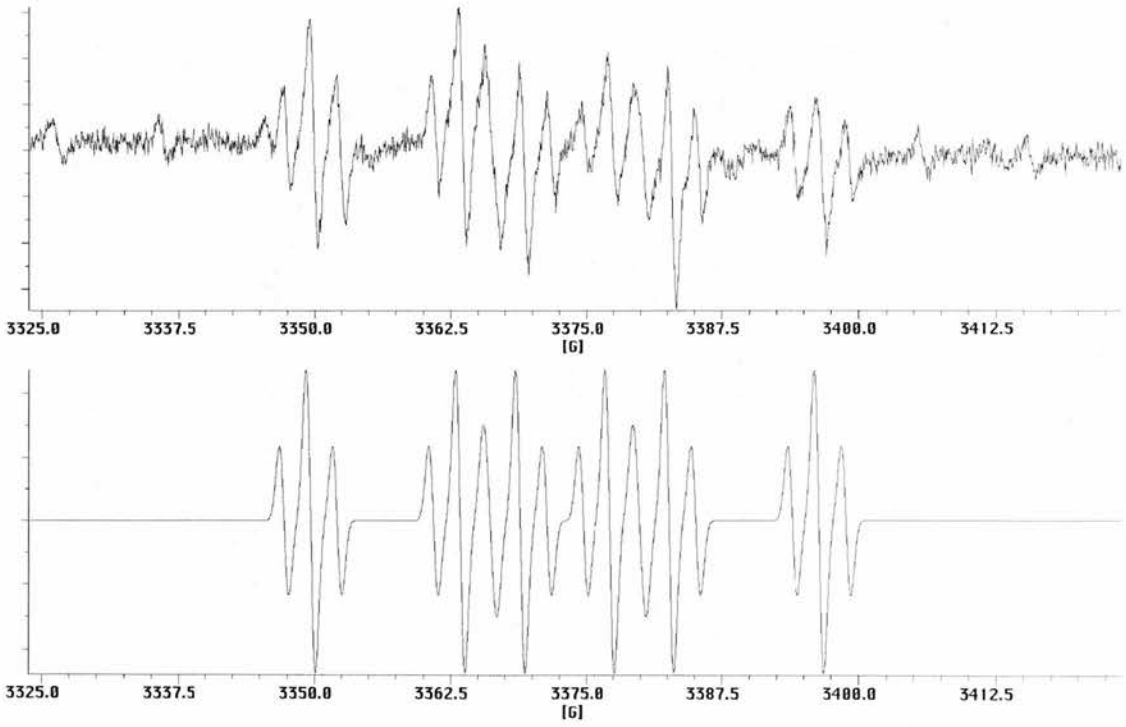


Figure 12. Spectrum (top) of aminyl radical **46a** and iminyl radical **23a** obtained from **40a** in DTBP. The simulation of **46a** is also shown.

O-i-Propyl benzaldoxime **40b** gave closely related radicals under the same conditions. Simulations of the aminyl radical **46b** (which in this instance did not persist long enough to be recorded in the absence of UV light) indicated that a splitting caused by two aromatic hydrogens was also present. The iminyl radical was also observed, and the signal was much stronger from **40b** than **40a** [$\underline{a}$(N) = 9.86 G, $\underline{a}$(H) = 79.44 G @ 280 K].

t-Butyl benzaldoxime **40c** showed 3 radicals in the EPR spectrum under the same conditions. At higher temperatures the main radical had parameters consistent with those of the aminyl radicals previously observed. This radical, like many of the aminyl radicals, is slightly persistent, but this should not be too surprising considering the bulky nature of the surrounding groups. The main radical at lower temperatures was a more persistent radical, perhaps a nitroxide, and there was a third, unidentified radical also present. The parameters for these radicals could not be determined. At no time was the iminyl radical **23a** observed.

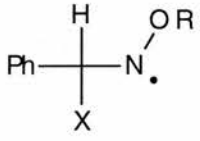
No signals were observed when *O*-2-(3-cyclohexenyloxy)ethyl benzaldoxime **40f** in DTBP was investigated under EPR conditions.

While it is possible that the formation of the iminyl radical was due to direct homolysis of the N-O bond, it is much more likely that it was caused by hydrogen abstraction from the alkyl chain (Scheme 22). This mechanism has been previously described,[48] and can also account for the presence of undecyl or dodecyl aldehyde in the product analysis reactions. The absence of the iminyl radical in the reaction of *O*-t-butyl benzaldoxime **40c** also provides evidence for this mechanism, as the t-butyl group contains no readily abstractable hydrogens. The relative strength of the iminyl radical signal from **40b** (as compared with that from **40a**) was due to the hydrogen being more readily abstracted, as a tertiary radical results.

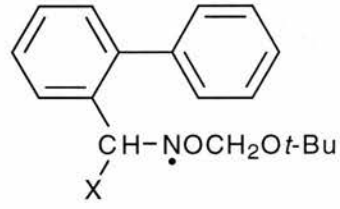
It has already been seen that addition to an oxime ester takes place under these conditions, but the attacking radical is not necessarily the t-butoxyl radical. Consequently, we cannot assume that the t-butoxyl radical has attacked the oxime ethers. Forrester has previously described the EPR parameters of aminyl radical **47** which was obtained by addition of an unknown radical to an oxime ether, in which the attacking radical was NOT t-butoxyl radical.[35] To further investigate this, the reaction was repeated using diphenyl

disulfide in t-butylbenzene in place of DTBP. The phenyl thiyl radical is less suited to alkyl radical abstraction, and this was reflected in the lack of an iminyl radical signal in the spectrum. However, an aminyl radical was observed. The hfs parameters of this radical, the radical **47** observed by Forrester *et al.* and of the aminyl radicals **41** observed in our study, are given in table 12. The parameters of **46b** and **46bi** are sufficiently different, even allowing for temperature effects, to suggest that the product radicals are not the same.

The most likely explanation to account for all the results, including those of Forrester,[35] is that t-butoxyl or phenylthiyl radicals are the attacking species when they are present, but other radicals (such as carboxyl radicals from oxime esters) add in the same way to generate closely related radicals.



46a R = n-$C_{11}H_{23}$
46b R = i-Pr
46c R = t-Bu



X is unknown

47

Table 12. EPR parameters of radicals **46** and **47**.

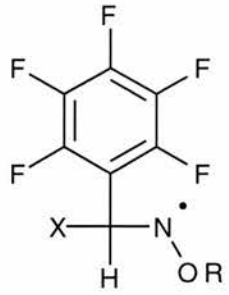
Radical	T/K[a]	a(N)/G	a(H)/G	a(Other)/G	a(Other)/G	g-factor
46a	250	13.75	19.25	2.45 (2H)		2.0049
46b	270	13.8	19.9	2.3 (1H)	1.6 (2H)	
46c	310	14.30	16.53			
46bi[b]	300	14.46	12.44	1.94 (1H)		
47[35]	348	14.35	20.0	2.62 (2H)		2.0049

[a] Reaction performed in t-butylbenzene [b] Reaction performed using diphenyl disulfide.

EPR investigations of the reactions of pentafluorobenzaldoxime ethers under the same conditions revealed that aminyl radicals **48b-d** were formed. In this instance, no iminyl radicals were detected at any time. The spectrum from **48b** is shown in Figure 13.

Table 13. EPR data for radicals obtained from *O*-alkyl pentafluorobenzaldoximes in DTBP.

Radical	Temp/K	a(N)/ G	a(2F)/ G	a(1H)/ G	a(Other)/G
48b	320	13.93	2.00	22.54	2.00 (1H)
48c	320	14.12	1.94	22.23	
48d	320	14.06	2.31	22.15	2.31 (2H)



48b R = i-Pr
48c R = t-Bu
48d R = n-$C_{12}H_{25}$

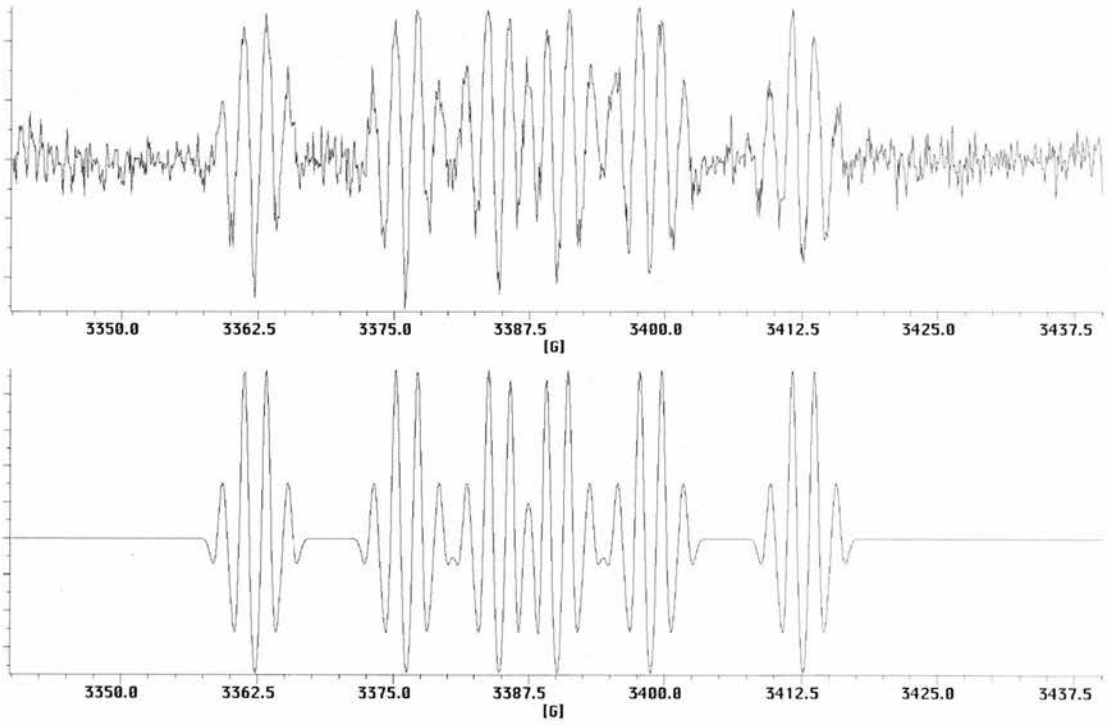


Figure 13. 2nd derivative spectrum (top) and simulation of aminyl radical **48b**, obtained from **42b**.

No spectra could be obtained from *O*-alkyl *p*-nitrobenzaldoximes in the presence (or in the absence) of DTBP.

Photolysis of *O*-t-butyl 2,4-dimethoxybenzaldoxime in the presence of DTBP yielded two radicals, either of which could be an aminyl radical. The major radical consisted of a quartet, which could have been due to either three equivalent hydrogens [a(3H) = 14.25 G @ 280 K] or due to a nitrogen and an hydrogen of coincidentally equivalent hfs [a(H) = 14.25 G, a(N) = 14.25 G @ 280 K]. The minor radical was always partially obscured, but simulation indicated that a(N) = 14.5 G, a(H) = 16.1 G @ 320 K provided a plausible description of the parameters.

The spectrum of iminyl radical **23e** was observed on photolysis of *O*-dodecyl 2,4,6-trimethoxybenzaldoxime in the presence of DTBP in the EPR cavity. The presence of this radical can be attributed to the same mechanism by which radical **23a** was formed from *O*-alkyl benzaldoximes **40a** and **40b** (Scheme 22).

The values of the parameters of the aminyl radicals merit some discussion. The nitrogen hfs do not vary very much from radical to radical; the values are between 13.7 and 15.0 G. The slightly higher values of a(N) in aminyl radicals derived from oxime esters is thus somewhat surprising. a(H) Values are more variable. As β-substituents the hfs are conformation, and thus temperature, dependent. Hydrogens on the alkyl chain could be observed in several cases, and the hfs showed little variation. In several cases, the values coincided with the splittings due to the *o*-substituent on the aromatic ring.

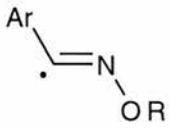
2.2.2.3.2 EPR investigation of the photolytic reactions of oxime ethers in the absence of DTBP.

In general, radicals were not observed when a sample of oxime ether in t-butylbenzene was photolysed in the EPR cavity. Benzaldoxime ethers **40b** and **40e**, 2,4-dimethoxybenzaldoxime ether **43c**, and 2,4,6-trimethoxybenzaldoxime ether **44d** all failed to produce signals. The investigation of **40b, 43c** and **44d** was repeated with *p*-methoxyacetophenone as sensitiser present, with the same result.

Prolonged photolysis of *O*-t-butyl benzaldoxime **40c** resulted in a mixture of radicals being observed, including a persistent radical [a(N) = 14.0 G, a(H) = 12.4 G @ 320 K]. Considering the length of time that was required for this radical to be observed, it is likely that this and the other unidentified radicals are formed in secondary processes and not relevant to our study.

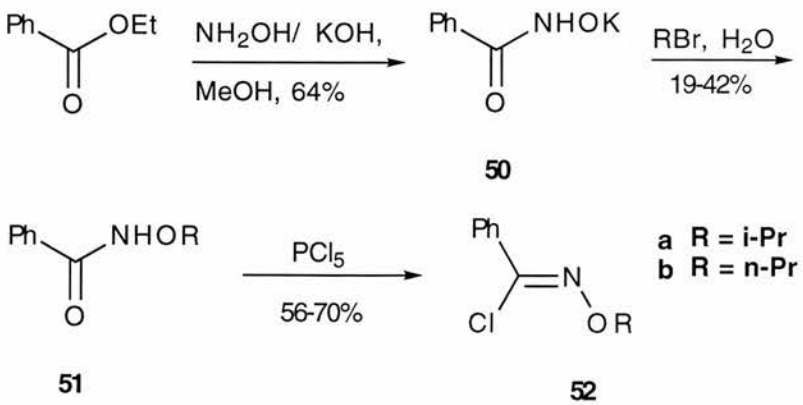
2.2.2.3.3 EPR investigation into the reactions of *O*-alkyl benzohydroximoyl chlorides

The oximidoyl radical **49** was at no time observed in the EPR investigation of oxime ethers. An alternative method of generation of this radical might be by halogen abstraction from *O*-alkyl benzohydroximoyl chlorides.



49

O-Alkyl benzohydroximoyl chlorides were prepared according to the method of Johnson (Scheme 19).[58,59] Potassium benzohydroxamate, prepared from ethyl benzoate in fair yield,[60] was alkylated in water with i-propyl or n-propyl bromide. Attempts to synthesize the *O*-benzyl derivative **51c** were unsuccessful. Treatment of *O*-alkyl benzohydroxamates **51a** and **51b** with phosphorus pentachloride gave *O*-alkyl benzohydroximoyl chlorides **52**, albeit in a poor overall yields.



Scheme 24

A degassed solution of *O*-alkyl benzohydroximoyl chloride and hexamethylditin in t-butylbenzene was illuminated by a 500W super pressure mercury lamp under EPR conditions. Good spectra were obtained in both cases, and the parameters are listed in table 14. Figure 14 shows the spectrum obtained from **52a**, together with the simulation. The parameters of the two radicals are very similar, indicating that the *O*-alkyl group exerts little influence on the spectrum. The radicals may be **49** (Ar = Ph), with *ortho*- and *para*-hydrogens having the same hfs, however the nitrogen hfs are much larger than in related iminyls.[2] We have been unable to propose any other structure that fits the data.

Table 14. EPR data of radicals from **52**

Precursor	Temp/K	a(N)/G	a(2H)/G	a(3H)/G
52a	270	14.12	1.17	3.63
52b	280	13.99	1.07	3.52

[a] Reaction performed in t-butylbenzene with hexamethylditin.

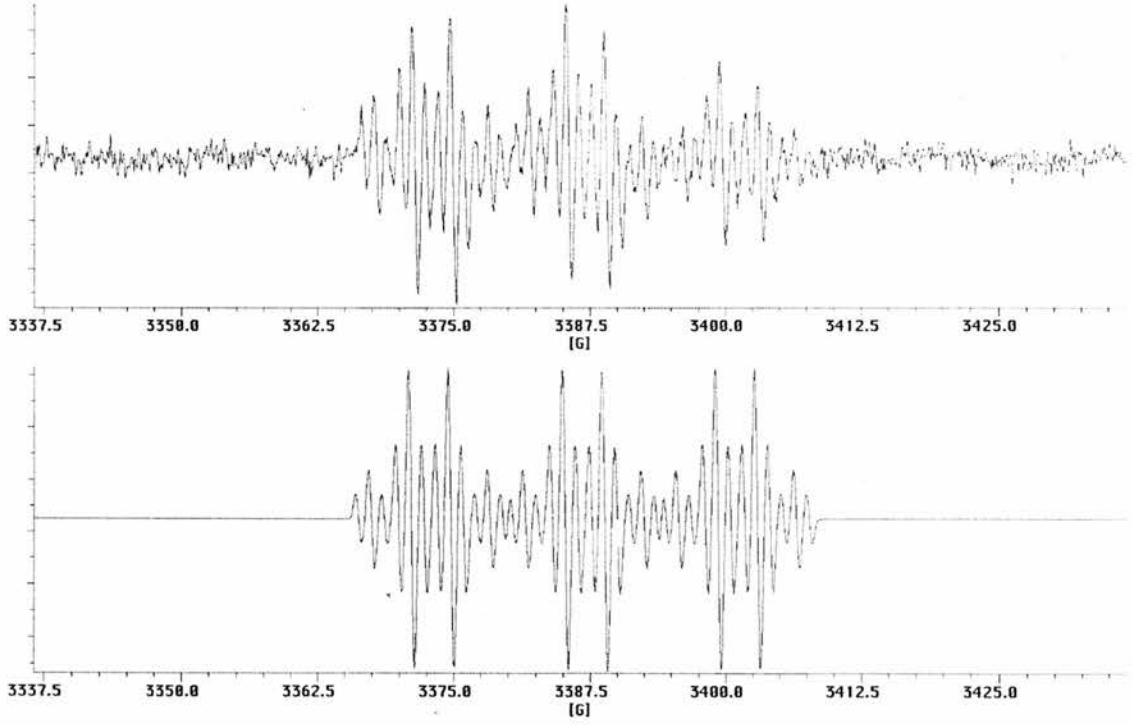


Figure 14. Spectrum (top) and simulation of radical obtained from **45a**.

2.2.3 Ultraviolet spectra of oxime esters and ethers

It was considered that the UV spectra of the oxime may provide a rationalisation of their behaviour in UV light. A variety of esters and ethers were analysed, and the results shown in Table 15.

Table 15. UV parameters of a selection of oxime esters and ethers.

	λ_1	ε_1	λ_2	ε_2	λ_3	ε_3	λ_4	ε_4
8a	208	21960	254	17340				
8c	208	17390	254	15670				
8d	204	17080	253	11390				
9a	203	13010	282	10260				
10a	202	10680	245	14620				
11a	202	18570	231	15260	273	16360	313	13270
11b	210	13420	231	12170	273	14150	313	11860
11c	211	12430	231	12550	273	14470	312	12430
11e	211	13990	231	13670	273	15310	313	13450
11f	202	12290	231	9250	273	9530	312	7800
12i	202	22330	231	17480	288	23380		
40a	206	16610	263	14310				
40b	211	14330	262	14280				
40e	207	18680	262	16740				
41a	201	20600	224	11160	306	14880		
42b	202	11420	260	14240				
42c	203	9820	259	13650				
42d	202	10400	261	13250				
44b	200	16520	226	17480	282	15970		

[a] Units : cm^{-1} [b] Units : $10^{-2}m^2mol^{-1}$ N.B.Shaded areas correspond to λ_{max} and $\varepsilon_{max.}$

The 'extra' absorbances at a higher wavelength may explain the increased photosensitivity of the 2,4-dimethoxy- and 2,4,6-trimethoxy- benzaldoxime esters.

2.3 Conclusions

It has been shown that benzaldoxime, 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime esters can all act as alkyl radical precursors. Radical production occurs by direct bond cleavage by the action of ultraviolet light. In the absence of other additives, best results were obtained from 2,4-dimethoxybenzaldoxime and 2,4,6-trimethoxybenzaldoxime esters. These compounds absorb in the ultraviolet region at longer wavelengths than other oxime esters. No evidence has been found for the abstraction of the oximyl hydrogen by t-butoxyl radical. *p*-Methoxyacetophenone acts as a photosentisiser, enhancing both the signals from EPR spectroscopy, and yields in preparative experiments (in which the first cyclisations using this method were performed). The results have particular consequence in EPR spectroscopy, as the spectrum of the iminyl radical is distinctive and has a 'window' of at least 60 G in which spectra can be obtained. This enables facile determination of g-factors of radicals obtained using this method. The iminyl radicals **23a**, **23d**, and **23e** were all found to have g-factors of 2.0034. A variety of different types of radical could be observed by this technique; primary, secondary, tertiary and allyl radicals were all detected. Unfortunately trifluoromethyl and trichloromethyl radicals could not be observed, mainly due to their high reactivity. The cyclopropyl radical was not observed; instead the cyclohexadienyl radical caused by addition of the cyclopropyl radical to the t-butylbenzene solvent was observed. In some cases radical addition to the oxime C=N double bond occurred, resulting in aminyl radicals. When DTBP was present, then it is likely that the t-butoxyl radical was adding, but aminyl radicals were also observed in the absence of DTBP. It is likely that the addition is reversible, especially at higher temperatures, as there was no sign of addition products in the product analysis experiments. EPR investigations of the reactions of *O*-acyl benzohydroximoyl chlorides failed to confirm the formation of oximidoyl radicals.

The mechanism of the reaction of oxime ethers with DTBP is less certain. In many cases abstraction of hydrogen atoms α- to the oxygen occurs, with subsequent collapse to

the familiar iminyl radical, and formation of aldehyde. Product analysis revealed the presence also of the related alcohol, indicating that more than one mechanism was occurring. The observation that 2-methyltetrahydrofuran was formed in trace amounts by the action of UV light on *O*-pent-4-enyl benzaldoxime **40e** indicated that a small amount of direct N-O bond cleavage was occurring. Again, no evidence was seen for oximinyl hydrogen abstraction. EPR investigations of the reactions of *O*-alkyl benzohydroximoyl chlorides failed to confirm the formation of oximidoyl radicals.

2.4 Experimental

^{1}H NMR spectra were obtained using a Bruker AM 300 MHz spectrometer unless otherwise stated, in which case the spectrum was obtained using a Varian Gemini 200 MHz spectrometer. ^{13}C spectra were run at 75 MHz using the Bruker mentioned above. All samples were dissolved in deuteriochloroform, with tetramethylsilane as an internal standard. GC/MS analysis was carried out using a Finnigan Incos 50 quadrupole mass spectrometer interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase. Mass spectra were obtained with electron impact ionisation on a VG Autospec spectrometer by peak matching. EPR spectra were recorded with a Bruker EMX 10/12 spectrometer operating at 9 GHz. All EPR experiments were illuminated by UV light from a 500 W super pressure mercury lamp. In all cases where spectra were obtained, they were analysed to determine the hfs and a computer simulation was run to confirm the values.

Materials were purchased from Aldrich, Avocado or Lancaster. THF and ether were distilled under nitrogen from sodium benzophenone ketyl prior to use. Where dry DCM was used, it was distilled over CaH_2. Petroleum ether (PE) refers to the fraction boiling between 40 and 60°C unless otherwise stated. Ether refers to diethyl ether. t-Butyl hydroperoxide was purified by distilling in a Dean-Stark apparatus to remove water, and then distilling at water pump pressure. Other organic compounds were used as received. Column chromatography was performed using BDH silica gel (40 - 63 mm).

syn-Benzaldoxime[17]

To a solution of sodium hydroxide (14 g; 0.33 mol) in H_2O (40 cm^3) was added benzaldehyde (21 g; 20 cm^3; 0.2 mol), then hydroxylamine hydrochloride (15 g; 0.22 mol) portionwise, with vigourous stirring. On cooling, and leaving overnight, a crystalline mass formed. Water was added until this dissolved (~150 cm^3) and CO_2 was passed through. The mixture went white, and an oil formed. The product was extracted with ether (4 × 75

cm^3), dried ($MgSO_4$), and concentrated. The product was distilled at reduced pressure (115°C @ 10mmHg), giving a colourless liquid. (20.17 g, 93%) (lit.[17] m.p. 35°C). δ_H 7.35-7.5 (3H, m, ArH), 7.55-7.65 (2H, m, ArH), 8.20 (1H, s, PhCH=N), 8.55 (1H, bs, NOH).

_p_-Nitrobenzaldoxime[17]

_p_-Nitrobenzaldehyde (10 g; 66.17 mmol), hydroxylamine hydrochloride (10 g), and pyridine (1 g) were added to ethanol (100 cm^3), and the mixture refluxed for 3 hours. The ethanol was removed at low pressure, and water (10 cm^3) was added, and mixture cooled to 0°C with stirring. The precipitate was filtered and recrystallised ($EtOH/H_2O$) to give pure _p_-nitrobenzaldoxime (10.20g; 93%) as pale yellow crystals, m.p. 127.5-129.5°C (lit.[61] 129°C).

Pentafluorobenzaldoxime[18]

To hydroxylamine hydrochloride (15 g) in H_2O (200 cm^3) was added pentafluorobenzaldehyde (12 g, 0.061 mmol) in ethanol (30 cm^3). To this vigorously stirred mixture was added sodium carbonate (23 g) portionwise. After stirring overnight, the mixture was cooled to 0°C, and the solid filtered, and recrystallised (DCM) to give pentafluorobenzaldoxime (12.68g; 98%) as white crystals, m.p. 131.0-133.0°C (lit.[18] 132-133°C). δ_H 8.24 (1H, s, CH=N), 9.09 (1H, s, NOH). δ_C 107.4 (m) 136.4 (m) 139.3 (s, CH) 143.4 (m) 146.7 (m). δ_F ($CDCl_3$ 300 MHz) –162.3 - –162.1 (m), –157.2 (tt, J_1 = 17.8 Hz, J_2 = 2.7 Hz), –141.3 - –141.1 (m).

2,4-Dimethoxybenzaldoxime[19]

2,4-Dimethoxybenzaldaldehyde (3.32 g; 0.02 mol) and hydroxylamine hydrochloride (1.38 g; 0.02 mol) were added to a mixture of 12% aqueous NaOH solution (10 cm^3) and ethanol (2.4 cm^3). The mixture was refluxed for 40 minutes, then cooled to 0°C and left to stand overnight. The solid that precipitated was filtered, and recrystallised ($EtOH/H_2O$) to give 2,4-dimethoxybenzaldoxime (3.02 g; 82%) as white crystals, m. p. 100-101.5°C (lit.[19] 104-105°C).

2,4,6-Trimethoxybenzaldoxime[20]

To methanol (~40 cm^3) was added 2,4,6-trimethoxybenzaldehyde (2 g; 10.1 mmol), and the mixture was stirred. Hydroxylamine hydrochloride (0.8 g) in the minimum water was added, and the mixture refluxed for 4 hours, then allowed to cool. Large amounts of water were added, and the mixture left to stand overnight. 2,4,6-Trimethoxybenzaldoxime precipated as white crystals, which were recrystallised from methanol, m.p. 207-210°C (lit[20] m. p. 201-203°C) (1.83 g; 86%). δ_H 3.84 (3H, s, OMe), 3.86 (6H, s, OMe), 6.14 (2H, s, ArH), 8.51 (1H, s, CH=N).

3-Bromocyclohexene[17]

Benzoyl peroxide (0.35 g) was added to a mixture of cyclohexene (35 g; 0.43 mol) and *N*-bromosuccinimide (24.9 g; 0.14 mol) in carbon tetrachloride (100 cm^3). The mixture was stirred for 2 hours, then slowly heated to reflux, and maintained at reflux for 3.5 hours. The mixture was then cooled, filtered and the filtrate was concentrated. The crude product was distilled to give 3-bromocyclohexene (b.p. 61°C @ 12 mmHg) as a colourless oil (15.71 g; 70%). δ_H (200 MHz) 1.60-2.35 (6H, m), 4.85 (1H, m, CHBr), 5.75-6.00 (2H, m, CH=CH).

Attempted synthesis of ethyl 3-(2-cyclohexenyloxy)butanoate 13 using sodium wire

Sodium wire (0.26 g; 11 mmol) was added over a period of 15 minutes to a stirred mixture of 3-bromocyclohexene (1.50 g; 9.3 mmol) and ethyl 3-hydroxybutyrate (9.85 g; 74.5 mmol) in dry THF (30 cm^3) in a nitrogen atmosphere. The mixture was refluxed for 12 hours, and stirred for a further 16 hours. The mixture was filtered, and concentrated, yielding only an intractable tar which could not be purified. A modification, in which the 3-bromocyclohexene was added after the other reagents had been refluxed for 2 hours, also formed only an intractable tar.

Attempted synthesis of ethyl 3-(2-cyclohexenyloxy)butanoate 13 using potassium hydroxide in DMSO[62]

Powdered KOH (4.5 g; 80 mmol) was stirred in DMSO for 5 mins. Ethoxy-3-hydroxybutyrate (2.6 g; 20 mmol) was added, followed by 3-bromocyclohexene (6.5 g; 40

mmol). The mixture was stirred for 3 hours, then poured into water. The mixture was extracted with ether (3×50 cm^3), dried ($MgSO_4$) and concentrated to yield an intractable tar.

3-(3-Cyclohexenyloxy)propan-1-ol 14[63]

Sodium wire (1.44 g; 0.062 mol) was added over 15 minutes to propane-1,3-diol (18.87 g; 0.248 mol) in dry THF (200 cm^3) under nitrogen. The mixture was refluxed for 5 hours, then 3-bromocyclohexene (10 g; 0.062 mol) was added. The mixture was heated under reflux for a further 48 hours, then the mixture was allowed to cool, filtered, and concentrated. Water (100 cm^3) was added, and the mixture extracted with ether (3×75 cm^3), then dried ($MgSO_4$) and concentrated. The product was distilled (b.p. 61°C @ 0.05 mmHg) to give 3-(3-cyclohexenyloxy)propan-1-ol as a colourless oil. δ_H (200 MHz)[63] 1.50-2.10 (8H, m, ring CH_2s, CH_2), 2.60 (1H, bs, -OH), 3.54-3.88 (5H, m), 5.72-5.89 (2H, m, HC=CH).

Attempted TEMPO mediated oxidation of 3-(3-cyclohexenyloxy)propan-1-ol to (cyclohexenyloxy)propionic acid[23,24]

The pH of 15% sodium perchlorate was adjusted to 9.5 by the addition of sodium hydrogen carbonate. This solution (40 cm^3) was added to a mixture of 3-(3-cyclohexenyloxy)propan-1-ol, TEMPO (0.03 g; 0.19 mmol), potassium bromide (0.18; 1.5 mmol) and Aliquat ® 336 (0.3 g; 0.74 mmol) in DCM (50 cm^3) and H_2O (2 cm^3) at 10-15 °C. The mixture was stirred for 30 minutes, then the layers were separated. The organic layer was washed with a solution of 10% HCl (10 cm^3) which contained ~125 mg potassium iodide, a 10% aqueous solution of sodium thiosulfate (10 cm^3), and water (10 cm^3). The organic layer was dried ($MgSO_4$) and concentrated, yielding only starting material. Back extraction of combined aqueous layers with ether also failed to yield product.

Swern oxidation of 3-(3-cyclohexenyloxy)propan-1-ol to 3-(3-cyclohexenyloxy)propanal[25]

To a three-necked flask, fitted with two pressure equalised dropping funnels and a drying tube, containing oxalyl chloride (1.0 cm^3; 11 mmol) in DCM (25 cm^3) was added

DMSO (1.7 cm^3; 22 mmol) in DCM (5 cm^3). The mixture was stirred for 2 minutes, then 3-(3-cyclohexenyloxy)-propan-1-ol (1.56 mmol; 10 mmol) in DCM (10 cm^3) was added, then the mixture cooled to –75°C and stirred for a further 15 minutes. Triethylamine (7.0 cm^3; 50 mmol) was added, and the mixture was stirred for a further 5 minutes, then allowed to warm to room temperature. Water (50 cm^3) was added, and the mixture extracted with DCM (2 × 50 cm^3). The combined organic layers were washed with brine (100 cm^3), 1% HCl (70 cm^3), H_2O (70 cm^3), a 5% aqueous solution of Na_2CO_3 (100 cm^3) and H_2O (100 cm^3), then dried ($MgSO_4$) and concentrated. Distillation yielded 3-(3-cyclohexenyloxy)propanal (3.00 g; 65 %), b.p. 42-44°C @ 0.5 mmHg. δ_H (200 MHz) 1.50-2.10 (6H, m, cycloalkyl CH_2s), 2.63-2.74 (2H, m, CH_2CO), 3.78-3.95 (3H, m, R_2CHO and OCH_2), 5.70-5.95 (2H, m, CH=CH), 9.81 (1H, s, CHO).

Attempted oxidation of 3-(3-cyclohexenyloxy)propanal to (cyclohexenyloxy)propionic acid using Oxone®[26]

To a vigorously stirred solution of 3-(3-cyclohexenyloxy)propanal (0.79 g; 5.11 mmol) in acetone (5 cm^3) and water (15 cm^3) was added sodium hydrogen carbonate (3.50 g; 41.7 mmol) followed by a solution of Oxone® (potassium peroxymonosulfate; $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; 5.53 g; 9.00 mmol) in aqueous EDTA (4 × 10^{-4} M; 36 cm^3). The reaction was stirred for one hour, then quenched with 50% w/w aqueous sodium bisulfite solution (18.0 cm^3) and acidified with 6M HCl (10 cm^3). The aqueous layer was extracted with ether (3 × 40 cm^3), and the organic layers extracted with 1% sodium carbonate solution (3 × 60 cm^3). The basic layers were acidified with 6M HCl, and back extracted with ether (3 × 70 cm^3). The combined organic layers were dried ($MgSO_4$) and dried to give a mixture of unidentified and inseparable products.

Cyclohexenol[27]

Cyclohexenone (24g, 0.25 mol) was dissolved in a 0.4M solution of $CeCl_3.7H_20$ (93 g; 0.25 mol) in methanol (620 cm^3). Sodium borohydride (9.5 g, 0.25 mol) was added portionwise, then water (100 cm^3) was added. The product was extracted with ether (a large amount of brine was added in order to get the layers to separate), dried ($MgSO_4$), and concentrated yielding an oil which was distilled (bp 66°C @ 12 mmHg), giving pure

cyclohexenol (14.93 g; 61 %) as a colourless liquid. δ_H 1.5-2.2 (7H, m, 3 × CH_2, and OH), 4.2 (1H, s, C(OH)H), 5.6-5.9 (2H, m, HC=CH).

(Cyclohexenyloxy)propionitrile 16[29,30]

Crushed potassium hydroxide (0.02 g) was added to cyclohexenol (4.9 g; 0.05 mol) and the mixture stirred until a solution was formed. Acrylonitrile (3.3 cm^3; 2.65 g; 0.05 mol) was added, and the mixture stirred until evolution of heat had ceased. The mixture was heated at 80°C for a further hour, and the mixture was distilled to give (cyclohexenyloxy)propionitrile (bp 76°C @ 0.04 mmHg) as a colourless oil (5.50 g; 73%). δ_H 1.57-2.05 (6H, m, ring CH_2s), 2.57-2.63 (2H, m, OCH_2), 3.68-3.76 (2H, m, CH_2CN), 3.93 (1H, bs, HCOR) 5.75-5.91 (2H, m, HC=CH). δ_C 18.9, 19.3, 25.1, 28.1, 62.8, 73.6, 115.8, 126.9, 131.9.

Attempted synthesis of (cyclohexenyloxy)propionic acid 15 by base hydrolysis of (cyclohexenyloxy)propionitrile

(Cyclohexenyloxy)propionitrile (1.81 g; 0.012 mol) was added to a solution of sodium hydroxide (0.92 g; 0.023 mol) in H_2O (2.6 cm^3). The mixture was refluxed for 15 hours, until there was only a single layer. The dark brown mixture was allowed to cool. Acidification followed by aqueous work-up revealed that 3-cyclohexenol was the only product.

(Cyclohexenyloxy)propionic acid 15[31]

To a stirred mixture of (cyclohexenyloxy)propionitrile (1.81 g; 0.012 mol) in water (40 cm^3) at 50°C was added sodium peroxide (2 g; 0.026 mol) portionwise over a period of 0.5 hours. The mixture was stirred for 2 hours, but there was still an immiscible layer, so more sodium peroxide (0.5 g) was added, and the mixture stirred overnight, and non-acidic impurities extracted with ether. The mixture was then acidified to pH 5 (cHCl) and extracted with ether, then dried and concentrated, yielding (cyclohexenyloxy)propionic acid as an oil. (1.53 g; 75%). δ_H 1.50-2.10 (6H, m, ring CH_2s), 2.57-2.63 (2H, m, OCH_2), 3.68-3.76 (2H, m, CH_2CO_2H), 3.93 (1H, bs, HCOR) 5.75-5.91 (2H, m, HC=CH).. IR spectroscopy showed no peak at 2251 cm^{-1} (C≡N). GC/MS analysis showed one product with M^+ = 170.

Typical syntheses of oxime esters.

Method A: To a stirred mixture of oxime (20 mmol) and triethylamine (20 mmol) in DCM (100 cm^3) at 0°C was added acid chloride (20 mmol) in DCM (20 cm^3) dropwise. The mixture was stirred for 20 mins, then 2N HCl was added (100 cm^3). The organic layer was washed with saturated aqueous sodium bicarbonate (3 × 100 cm^3) and brine (1 × 100 cm^3), then dried ($MgSO_4$), and concentrated. Column chromatography on silica gel yielded pure product.

Method B: Carboxylic acid (2.54 mmol), oxime (2.54 mmol) and DMAP (0.02 g) were stirred in DCM (9 cm^3) at 0°C. DCC (2.54 mmol) was added, and the mixture stirred at 0°C for twelve hours. The mixture was filtered, and the filtrate concentrated. Recrystallisation or column chromatography on silica gel yielded pure product.

***O*-Trimethylacetylbenzaldoxime 8a**[64]

Prepared from benzaldoxime and trimethylacetyl chloride according to method A, to give *O*-trimethylacetylbenzaldoxime as white crystals (3.06 g, 79%) after column chromatography, m. p. 38.5-40°C. δ_H 1.32 (9H, s, $C(CH_3)_3$), 7.44-7.50 (3H, m, ArH), 7.75 (2H, d, J = 6.2 Hz, ArH), 8.38 (H, s, PhCH=N), δ_C 27.3, 38.5, 128.6, 129.1, 130.5, 131.8, 156.5, 175.6. (Found: M^+, 231.1263. $C_{12}H_{15}NO_2$ requires *M*, 231.1259.)

***O*-Cyclohexylcarbonyl benzaldoxime 8b**

Prepared from benzaldoxime and cyclohexylcarbonyl chloride according to method A to give *O*-cyclohexylcarbonylbenzaldoxime (1.11g, 48%) as white crystals after column chromatography, m.p. 78 - 79°C. δ_H 1.25-2.02 (10H, m, alkyl Hs), 2.44-2.52 (1H, m, CHR_2) 7.39-7.47 (3H, m, ArH), 7.73-7.76 (2H, m, ArH), 8.36 (1H, s, PhCH=N). δ_C 25.5, 25.7, 29.0, 42.1, 128.6, 129.1, 130.5, 131.8, 156.3, 173.5. (Found: M^+, 205.1109. $C_{12}H_{15}NO_2$ requires *M*, 205.1103.)

***O*-6-Heptynoyl benzaldoxime 8c**

To DCM (20 cm^3) was added 6-heptynoic acid (0.25g; 2mmol) and oxalyl chloride (0.30g; 2.4 mmol). The mixture was stirred overnight, and then concentrated. The product was used directly in the synthesis of *O*-6-heptynoylbenzaldoxime **8c** (method A) which was

formed as white crystals, (0.23g from acid; 50%) after column chromatography (PE/DCM), m. p. 59.5-60.5°C. δ_H 1.6-1.7 (2H, tt, J_1 = 7.7 Hz, J_2 = 7.2 Hz, CH_2) 1.8-1.9 (2H, tt, J_1 = 7.4 Hz, J_2 = 7.8 Hz, CH_2) 1.96 (1H, t, J = 2.6 Hz, C≡CH) 2.21-2.28 (2H, td, J_1 = 2.6 Hz, J_2 = 6.6 Hz, $CH_2CH_2C{\equiv}CH$) 2.48-2.54 (2H, t, J = 7.4 Hz $COCH_2$) 7.40-7.50 (3H, m, ArH), 7.70- 7.75 (2H, m, ArH) 8.35 (1H, s, CH=N). δ_C 18.2, 23.9, 27.8, 32.3, 68.8, 84.0, 128.6, 129.1, 130.4, 131.9, 156.3, 171.2. (Found: M^+, 229.1098. $C_{14}H_{15}NO_2$ requires *M*, 229.1102.)

O-(Cyclohexenyloxy)propionoyl benzaldoxime 8d.

Prepared from benzaldoxime and (cyclohexenyloxy)propionic acid (3.76 mmol) according to method B to give *O*-(cyclohexenyloxy)propionoyl benzaldoxime (0.46 g; 48%) as a colourless oil after column chromatography (PE/DCM). δ_H 1.51-2.05 (6H, m, ring Hs), 2.76 (2H, t, J = 6.6 Hz, $CH_2C(O)$), 3.79-3.95 (3H, m, OCR_2H, OCH_2), 5.75-5.89 (2H, m, HC=CH), 7.39-7.51 (3H, m, ArH), 7.72-7.75 (2H, m, ArH), 8.37 (1H, s, CH=N). δ_C 19.1, 25.2, 28.1, 34.2, 63.3, 73.3, 127.7, 128.5, 129.0, 130.3, 131.2, 131.8, 155.3, 169.6. (Found: M^+, 273.1371. $C_{16}H_{19}NO_3$ requires *M*, 273.1365.)

O-Trimethylacetyl-*p*-nitrobenzaldoxime 9a[64]

Prepared from *p*-nitrobenzaldoxime and pivaloyl chloride according to method A to give *O*-trimethylacetyl-*p*-nitrobenzaldoxime (1.92 g; 77%) as pale yellow crystals after recrystallisation (CH_3CN), m.p. 167.5-168.0°C (lit.[64] 170-172°C) δ_H 1.34 (9H, s, $C(CH_3)_3$), 7.95 (2H, d, J = 9.1 Hz, ArH), 8.29 (2H, d, J = 8.8 Hz, ArH), 8.48 (1H, s, CH=N). δ_C 27.1, 38.4, 124.2, 129.2, 136.4, 149.7, 154.0, 175.1.

O-(Cyclohexenyloxy)propionyl 4-nitrobenzaldoxime 9d

Prepared from 4-nitrobenzaldoxime and (cyclohexenyloxy)propionic acid (5.12 mmol) according to method B to give *O*-(cyclohexenyloxy)propionyl 4-nitrobenzaldoxime (1.24 g; 80%) as yellow crystals after column chromatography (PE/DCM), m.p 66-68°C. δ_H 1.52-2.02 (6H, m, ring Hs), 2.78 (2H, t, J = 6.5 Hz, $CH_2C(O)$), 3.80-3.95 (3H, m, OCR_2H, OCH_2), 5.74-5.90 (2H, m, HC=CH), 7.93 (2H, d, J = 8.8 Hz, ArH), 8.30 (2H, d, J = 8.8 Hz, ArH), 8.46 (1H, s, CH=N). δ_C 19.2, 25.2, 28.2, 34.1, 63.2, 73.5, 124.3,

127.6, 129.4, 131.5, 136.4, 149.8, 154.0, 169.1. (Found: C, 60.7; H, 5.9; N, 8.9%. Calc. for $C_{16}H_{18}N_2O_5$: C, 60.4; H, 5.7; N, 8.8%.)

_O_-Trimethylacetyl pentafluorobenzaldoxime 10a.

Prepared from pentafluorobenzaldoxime and pivaloyl chloride according to method A to give _O_-trimethylacetyl pentafluorobenzaldoxime as white crystals (2.05 g; 73%) after column chromatography (DCM), m.p. 53-55°C. δ_H 1.35 (9H, s, $C(CH_3)_3$), 8.5 (1H, s, CH=N), δ_C 27.1, 38.4, 105.9-106.3 (m), 136.0-136.5 (m), 139.4-139.8 (m), 140.2, 141.0-141.3 (m), 143.6-143.9 (m), 144.4-144.9 (m), 145.4, 147.1-147.4 (m), 174.4.

_O_-(Cyclohexenyloxy)propionoyl pentafluorobenzaldoxime 10d.

Prepared from pentafluorobenzaldoxime and (cyclohexenyloxy)propionic acid according to method B to give _O_-(cyclohexenyloxy)propionoyl pentafluorobenzaldoxime (0.58 g; 62%) as an oil after column chromatography (DCM). δ_H 1.51-2.05 (6H, m, ring CH_2s) 2.79 (2H, t, J = 6.4 Hz, $CH_2C(O)$), 3.79-3.94 (3H, m, OCR_2H, OCH_2), 5.73-5.89 (2H, m, HC=CH), 8.49 (1H, s, CH=N). δ_C 19.2, 25.3, 28.2, 34.0, 63.2, 73.5, 127.7, 131.5, 145.5, 168.9. (Found: C, 52.9; H, 3.8; N, 3.9. Calc for $C_{16}H_{14}F_5NO_3$: C, 52.9; H, 3.9; N, 3.9%.)

_O_-Trimethylacetyl 2,4-dimethoxybenzaldoxime 11a[21]

Prepared from 2,4-dimethoxybenzaldoxime (2.5 mmol) and pivaloyl chloride according to method A, and purified by column chromatography (DCM/PE) to give a colourless oil, which slowly crystallised, and could be recrystallised from toluene/hexane to give pure _O_-trimethylacetyl 2,4-dimethoxybenzaldoxime (0.41 g; 62%) as white crystals, m.p. 66-67°C (lit.[21] 89°C) δ_H 1.32 (9H, s, $C(CH_3)_3$), 3.82 (6H, s, OMe), 6.56 (1H, s, ArH), 6.88 (2H, d, J = 2.2 Hz, ArH), 8.30 (1H, s, CH=N). (Found: C, 63.5; H, 7.3; N, 5.4. Calc for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.2; N, 5.3%.)

_O_-Cyclohexanecarbonyl 2,4-dimethoxybenzaldoxime 11b

Prepared from 2,4-dimethoxybenzaldoxime (2.5 mmol) and cyclohexylcarboxylic acid according to method B to give _O_-cyclohexanecarbonyl 2,4-dimethoxybenzaldoxime (0.58 g; 78%) as white crystals after recrystallisation (toluene), m. p. 91-93°C. δ_H 1.28-2.01 (10H, m, alkyl Hs), 2.41-2.49 (1H, m, CHR_2), 3.84 (3H, s, OMe), 3.84 (3H, s,

OMe), 6.44 (1H, d, J = 2.2 Hz, ArH), 6.52 (1H, dd, J_1 = 2.5 Hz, J_2 = 8.8 Hz, ArH), 7.94 (1H, d, J = 8.5 Hz, ArH), 8.68 (1H, s, CH=N). δ_C 25.4, 25.7, 29.0, 42.2, 55.5, 55.6, 98.2, 105.6, 111.5, 128.9, 151.9, 159.9, 163.9, 173.6. (Found: C, 66.7; H, 6.8; N, 4.9%. Calc. for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8%.)

_O_-Heptynoyl 2,4-dimethoxybenzaldoxime 11c

Prepared from 2,4-dimethoxybenzaldoxime and heptynoic acid according to method B to give *O*-heptynoyl 2,4-dimethoxybenzaldoxime (0.64 g; 87%) as white crystals after recrystallisation (toluene), mp 101-103°C. δ_H 1.65 (2H, m, CH_2) 1.81-1.90 (2H, m, CH_2), 1.96 (1H, t, J = 2.6 Hz, C≡CH), 2.21-2.28 (2H, td, J_1 = 2.6 Hz, J_2 = 7.0 Hz, CH_2CH_2CCH) 2.49 (2H, t, J = 7.4 Hz $COCH_2$) 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 6.43 (1H, d, J = 2.3 Hz, ArH) 6.52 (1H, m, ArH), 7.92 (1H, d, J = 8.7 Hz, ArH) 8.68 (1H, s, CH=N). δ_C 18.1, 23.9, 27.8, 32.4, 55.5, 55.6, 68.7, 83.9, 98.2, 105.6, 111.3, 128.6, 151.9, 160.0, 164.0, 171.2. (Found: M^+, 289.1309. $C_{16}H_{19}NO_4$ requires *M*, 289.1314.)

_O_-(Cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime 11d

Prepared from 2,4-dimethoxybenzaldoxime and (cyclohexenyloxy)propionic acid according to method B to give *O*-(cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime (0.68 g; 81%) as white crystals after column chromatography (PE/EtOAc), m.p 60.0-61.0°C. δ_H 1.53-2.04 (6H, m, ring Hs), 2.76 (2H, t, J = 6.6 Hz, $CH_2C(O)$), 3.78-3.94 (9H, m, OCR_2H, OCH_2, 2 × CH_3O), 5.74-5.88 (2H, m, HC=CH), 6.56 (1H, t, J = 2.2 Hz, ArH), 6.85 (2H, d, J = 2.2 Hz, ArH), 8.28 (1H, s, CH=N). δ_C 19.2, 25.2, 28.2, 34.3, 55.7, 63.3, 73.4, 104.6, 106.3, 127.7, 131.3, 132.1, 156.6, 161.3, 169.6. (Found: C, 64.9; H, 7.1; N, 4.4%. Calc. for $C_{18}H_{23}NO_5$: C, 64.9; H, 7.0; N, 4.2%.)

_O_-Vinylacetyl 2,4-dimethoxybenzaldoxime 11e

Prepared from vinylacetic acid (2.54 mmol) and dimethoxybenzaldoxime according to method B to give *O*-vinylacetyl 2,4-dimethoxybenzaldoxime (0.56 g; 89%) as white crystals after recrystallisation. (toluene), m. p. 64.5 - 65.5°C. δ_H 3.25 (2H, m, CH_2), 3.85 (6H, s, 2 × OCH_3), 5.21-5.28 (2H, m, $=CH_2$), 5.96-6.05 (1H, m, CH=), 6.44 (1H, d, J = 2.2 Hz, ArH), 6.52 (1H, dd, J_1 = 2.2 Hz, J_2 = 8.8 Hz, ArH), 7.92 (1H, d, J = 8.8

Hz, ArH), 8.68 (1H, s, CH=N). δ_C 38.0, 55.6, 55.7, 98.4, 105.9, 111.5, 119.2, 129.1, 130.0, 152.4, 160.3, 164.3, 169.6. (Found: M^+, 249.1008. $C_{13}H_{15}NO_4$ requires *M*, 249.1001.)

_O_-i-Butyroyl 2,4-dimethoxybenzaldoxime 11f

Prepared from i-butyric acid and 2,4-dimethoxybenzaldoxime according to method B to give *O*-i-butyroyl 2,4-dimethoxybenzaldoxime (0.58 g; 91%) as white crystals after recrystallisation (toluene), m.p. 67.5-68.5°C. δ_H 1.15-1.28 (6H, d, J = 6.8 Hz, 2 × CH_3), 2.66-2.72 (1H, m, C*H*(CH_3)$_2$), 3.85 (6H, s, 2 × OCH_3), 6.44 (1H, d, J = 2.2 Hz, ArH), 6.52 (1H, dd, J_1 = 2.2 Hz, J_2 = 8.8 Hz, ArH), 7.94 (1H, d, J = 8.8 Hz), 8.68 (1H, s, CH=N). δ_C 19.0, 32.9, 55.5, 55.6. 98.2, 105.6, 111.4, 128.9, 152.0, 159.9, 163.9, 174.7. (Found: C, 62.5; H, 7.1; N, 5.8%. Calc. for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6%.)

_O_-Heptanoyl 2,4-dimethoxybenzaldoxime 11g

Prepared from 2,4-dimethoxybenzaldoxime and heptanoic acid according to method B to give *O*-heptanoyl 2,4-dimethoxybenzaldoxime (0.41 g; 55%) as white crystals after recrystallisation (toluene), m.p. 53.0-57.0°C. δ_H 0.89 (3H, t, J = 6.6 Hz) 1.31-1.38 (4H, m, 2 × CH_2), 1.72 (2H, m, CH_2) 2.44 (2H, t, J = 7.6 Hz, CH_2), 3.85 (6H, s, 2 × OMe), 6.44 (1H, d, J = 2.2 Hz) 6.52 (1H, dd, J_1 = 2.5 Hz, J_2 = 8.8 Hz, ArH), 7.93 (1H, d, J = 8.8 Hz, ArH) 8.67 (1H, s, CH=N). δ_C 14.0, 22.5, 24.9, 28.9, 31.4, 33.0, 55.5, 55.6, 98.2, 105.6, 111.4, 128.8, 151.8, 159.9, 163.9, 171.6. (Found: M^+, 293.1635. $C_{16}H_{23}NO_4$ requires *M*, 293.1627.)

_O_-2,6-Dimethylhept-5-enecarbonyl 2,4-dimethoxybenzaldoxime 11h

Prepared from citronellic acid and 2,4-dimethoxybenzaldoxime on a 5.12 mmol scale according to method B to give *O*-2,6-dimethylhept-5-enecarbonyl-2,4-dimethoxybenzaldoxime (1.19 g; 70 %) as a colourless oil. δ_H 1.02 (3H, d, J = 6.6 Hz, CH(C*H*$_3$)), 1.22-1.61 (4H, m, 2 × CH_2) 1.61 (3H, s, =C(CH_3)), 1.68 (3H, s, =C(CH_3)), 1.95-2.11 (1H, m, C*H*(CH_3)), 2.21-2.49 (2H, m, C(O)CH_2), 3.85 (6H, s, 2 × OMe), 5.11 (1H, t, J = 7.1 Hz, CH=), 6.44 (1H, d, J = 2.2 Hz, ArH), 6.52 (1H, dd, J_1 = 2.2 Hz, J_2 = 8.8 Hz, ArH), 7.94 (1H, d, J = 8.8 Hz, ArH), 8.67 (1H, s, CH=N). δ_C 17.7,

19.7, 25.5, 25.8, 30.2, 36.9, 40.4, 55.6, 55.7, 98.4, 105.8, 111.7, 124.5, 129.1, 131.8, 152.1, 160.3, 164.2, 171.2. (Found: M^+, 333.1953. $C_{19}H_{27}NO_4$ requires *M*, 333.1940.)

_O_-Trimethylacetyl-2,4,6-trimethoxybenzaldoxime 12a

Prepared from 2,4,6-trimethoxybenzaldoxime and trimethylacetic acid according to method B to give *O*-trimethylacetyl-2,4,6-trimethoxybenzaldoxime (0.72g; 96%) as white crystals after recrystallisation (toluene/hexane), m.p. 87.5-89°C. δ_H 1.30 (9H, s, $C(CH_3)_3$), 3.86 (3H, s, *p*-OMe), 3.89 (6H, s, *o*-OMe), 6.12 (2H, s, ArH), 8.75 (1H, s, CH=N). δ_C 27.3, 38.3, 55.8, 90.5, 90.6, 100.7, 151.8, 152.0, 161.4, 164.2, 175.8. (Found: M^+, 295.1414. $C_{19}H_{27}NO_4$ requires *M*, 295.1420.)

_O_-Heptynoyl 2,4,6-trimethoxybenzaldoxime 12c

Prepared from 2,4,6-trimethoxybenzaldoxime and heptynoic acid according to method B to give heptynoyl 2,4,6-trimethoxybenzaldoxime (0.65g; 80%) as white crystals after recrystallisation (DCM/hexane), m.p. 94.0-95.0°C. δ_H 1.61-1.66 (2H, m, CH_2), 1.82-1.88 (2H, m, CH_2), 1.95 (1H, t, J = 2.6 Hz, C≡CH), 2.24 (2H, dt, J_1 = 2.6 Hz, J_2 = 6.8 Hz, CH_2C≡CH), 2.48 (2H, t, J = 7.4 Hz,) 3.85 (3H, s, OMe), 3.88 (6H, s, 2 × OMe), 6.12 (2H, s, ArH), 8.74 (1H, s, CH=N). δ_C 18.2, 24.0, 27.9, 32.5, 55.5, 56.2, 68.7, 84.1, 90.7, 100.7, 152.0, 161.5, 164.4, 171.6. (Found: C, 63.6; H, 6.7; N, 4.5. Calc. for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4%.)

_O_-(Cyclohexenyloxy)propionoyl 2,4,6-trimethoxybenzaldoxime 12d

Prepared from 2,4,6-trimethoxybenzaldoxime and (cyclohexenyloxy)propionic acid (3.78 mmol) according to method B to give *O*-(cyclohexenyloxy)propionoyl 2,4,6-trimethoxybenzaldoxime (0.61g 44%) as white crystals after chromatography (PE/DCM) and two recrystallisations (DCM, THF), m. p. 83.0-85.5°C. δ_H 1.53-2.01 (6H, m, ring Hs), 2.76 (2H, t, J = 6.9 Hz, $CH_2C(O)$), 3.78-3.91 (12H, m, OCR_2H, OCH_2, 3 × CH_3O), 5.75-5.87 (2H, m, HC=CH), 6.12 (2H, s, ArH), 8.74 (1H, s, CH=N). δ_C 19.2, 25.2, 28.2, 34.3, 55.4, 56.0, 63.4, 73.2, 90.5, 100.4, 127.7, 130.9, 151.9, 161.2, 164.1, 169.6. (Found: C, 62.9; H, 6.9; N, 3.9. Calc. for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.9; N, 4.1%.)

_O_-2,6-Dimethylhept-5-enecarbonyl 2,4,6-trimethoxybenzaldoxime 12h

Prepared from citronellic acid and 2,4,6-trimethoxybenzaldoxime according to method B to give _O_-2,6-dimethylhept-5-enecarbonyl 2,4,6-trimethoxybenzaldoxime as white crystals (0.54 g; 63%) after recrystallisation (DCM/hexane), m.p. 47.0-48.0°C. δ_H 1.02 (3H, d, J = 6.6 Hz, CH(CH_3)), 1.22-1.61 (4H, m, $2CH_2$) 1.61 (3H, s, =C(CH_3)), 1.68 (3H, s, =C(CH_3)), 1.97-2.14 (1H, m, C*H*(CH_3)-), 2.21-2.49 (2H, m, C(O)CH_2), 3.85 (3H, s, _p_-OMe), 3.88 (6H, s, _o_-OMe), 5.11 (1H, m, CH=), 6.44 (1H, d, J = 2.2 Hz, ArH), 6.12 (2H, ArH), 8.74 (1H, s, CH=N). δ_C 17.7, 19.7, 25.5, 25.8, 30.1, 36.9, 40.5, 55.5, 56.2, 90.7, 100.8, 124.6, 131.7, 151.9, 161.1, 164.3, 171.3. (Found: C, 66.3; H, 8.2; N, 4.0. Calc. for $C_{20}H_{29}NO_5$: C, 66.1; H, 8.0; N, 3.9%.)

_O_-Valeryl-2,4,6-trimethoxybenzaldoxime 12i

Prepared from 2,4,6-trimethoxybenzaldoxime (2 mmol) and valeryl chloride according to method A to give _O_-valeryl-2,4,6-trimethoxybenzaldoxime (0.38 g; 65%), as white crystals after column chromatography (PE/EtOAc), and recrystallisation (toluene/hexane), m.p. 75-76.5°C. δ_H 0.93 (3H, t, J = 7.1 Hz, CH_3), 1.40 (2H, m, CH_2CH_3), 1.73 (2H, m, CH_2), 2.40-2.65 (2H, m, CH_2), 3.85 (3H, s, _p_-OMe), 3.88 (6H, s, _o_-OMe), 6.12 (2H, s, ArH), 8.74 (1H, s, CH=N). δ_C 13.74, 22.38, 27.02, 32.82, 55.51, 56.16, 90.68, 100.78, 151.83, 161.47, 164.31, 172.03. (Found: C, 61.1; H, 7.7; N, 4.7. Calc. for $C_{15}H_{21}NO_5$: C, 61.0; H, 7.2; N, 4.7%.)

_O_-Cyclopropylcarbonyl 2,4,6-trimethoxybenzaldoxime 12j

Prepared from cyclopropanecarboxylic acid and 2,4,6-trimethoxybenzaldoxime according to method B to give _O_-cyclopropylcarbonyl 2,4,6-trimethoxybenzaldoxime (0.63 g; 89%) as white crystals after recrystallisation (toluene) m.p. 113.5-115°C. δ_H 0.89-0.95 (2H, m, cyclopropyl Hs), 1.11-1.16 (2H, m, cyclopropyl Hs), 1.70-1.81 (1H, m, C*H*(CH_2)$_2$), 3.84 (3H, s, _p_-OCH_3), 3.88 (6H, s, _o_-OCH_3), 6.12 (2H, s, ArH), 8.77 (1H, s, CH=N). δ_C 8.6, 11.5, 55.4, 56.1, 90.5, 100.6, 151.1, 161.2, 164.0, 172.9. (Found: C, 60.5; H, 6.2; N, 5.2. Calc. for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0%.)

Trichloromethyl 2,4,6-trimethoxybenzaldoxime 12k

Prepared from trichloroacetic acid and 2,4,6-trimethoxybenzaldoxime according to method B. Product decomposed very rapidly. δ_H (200 MHz) 3.87 (3H, s, *p*-OCH_3), 3.91 (6H, s, *o*-OCH_3), 6.13 (2H, s, ArH), 8.93 (1H, s, CH=N).

Trifluoromethyl 2,4,6-trimethoxybenzaldoxime 12l

Prepared from trifluoroacetic acid and 2,4,6-trimethoxybenzaldoxime according to method B to give trifluoromethyl 2,4,6-trimethoxybenzaldoxime (90% crude yield). δ_H 3.87 (3H, s, *p*-OCH_3), 3.91 (6H, s, *o*-OCH_3), 6.13 (2H, s, ArH), 8.91 (1H, s, CH=N). (Found: C, 46.4; H, 4.4; N, 5.2. Calc. for $C_{12}H_{12}F_3NO_5$: C, 46.9; H, 3.9; N, 4.6%.)

Benzohydroximoyl chloride 9[36]

To benzaldoxime (3.63 g; 0.03mol) in DMF (25 cm^3) at 28°C was added N-chlorosuccinimide (0.8 g), resulting in a slight temperature decrease. The reaction was initiated by bubbling gas from the headspace of an HCl bottle through the DMF. Once a rise in temperature indicated that reaction had started, the remainder of the N-chlorosuccinimide (3.2 g; total 0.03 mol) was added, and the mxture stirred at 20°C for 3 hours. Water (100 cm^3) was added, and the mixture extracted with ether (2 × 75 cm^3), and the organic extracts washed with water (2 × 75 cm^3), then dried ($MgSO_4$) and concentrated, to give the product as a yellow oil. δ_H 7.4-7.5 (3H, m, ArH), 7.9 (2H, m, ArH), 9.0 (1H, bs, NOH).

***O*-Trimethylacetylbenzohydroximoyl chloride 28a**

To a stirred mixture of benzohydroximoyl chloride (10 mmol) and triethylamine (10 mmol) in DCM (50 cm^3) at 0°C was added acid chloride (10 mmol) in DCM (10 cm^3) dropwise. The mixture was stirred for 20 mins, then 2N HCl was added (50 cm^3). The organic layer was washed with saturated aqueous sodium bicarbonate (3 × 50 cm^3) and brine (50 cm^3), then dried ($MgSO_4$), and concentrated to give a yellow oil which was purified by bulb to bulb distillation (95-100°C @ 0.2 mmHg) to give *O*-trimethylacetylbenzohydroximoyl chloride as a colourless liquid (0.88 g; 37%) δ_H 1.38 (9H, s, t-Bu), 7.40-7.52(3H, m, ArH), 7.97-8.00 (2H, d, J = 7.7 Hz, ArH). δ_C 27.2, 38.9, 112.6, 128.5, 128.8, 132.2, 174.5. No peak corresponding to the quaternary carbon. (Found: M^+, 239.0706. $C_{12}H_{14}{}^{35}ClNO_2$ requires *M*, 239.0708.)

_O_-Valerylbenzohydroximoyl chloride 28b

Treatment of benzohydroximoyl chloride (5 mmol) with valeryl chloride as described for _O_-trimethylacetylbenzohydroximoyl chloride gave an oil which was purified by bulb to bulb distillation (100 dt @ 0.04 mmHg) to give O-valerylbenzohydroximoyl chloride as an oil (0.50 g; 42%) which solidified at approximately 10°C. δ_H 0.97 (3H, t, J = 7.3 Hz, CH_3) 1.42 (2H, m, CH_2CH_3) 1.74 (2H, m, $CH_2CH_2CH_3$) 2.56 (2H, t, J = 7.4 Hz, $COCH_2$) 7.4-7.5 (3H, m, ArH) 7.9-8.05 (2H, m, ArH). δ_C 13.6, 22.7, 26.8, 32.3, 128.4, 128.7, 132.2, 131.6, 147.1, 170.1. (Found: M^+, 239.0709. $C_{12}H_{14}{}^{35}ClNO_2$ requires _M_, 239.0708.)

_O_-Phenylacetyl benzohydroximoyl chloride 28c

Treatment of benzohydroximoyl chloride with phenylacetyl chloride as described for _O_-trimethylacetylbenzohydroximoyl chloride (5 mmol scale) gave an oil which purified by bulb to bulb distillation (140 dt @ 0.04 mmHg) to give _O_-phenylacetyl benzohydroximoyl chloride as an oil (0.68 g; 50%). δ_H 3.87 (2H, s, CH_2) 7.30-7.51 (8H, m, ArH), 7.9-8.0 (2H, m, ArH). δ_C 39.8, 127.7, 128.5, 128.8, 129.0, 129.6, 131.5, 132.3, 132.9, 147.9, 167.8. (Found: M^+, 273.0548. $C_{15}H_{12}{}^{35}ClNO_2$ requires _M_, 273.0552.)

_N_-t-Butoxyphthalimide 45c[56]

To 1,4-dioxane (300 cm^3) was added t-butyl acetate (75 cm^3). _N_-hydroxyphthalimide (8.15 g; 0.05 moles) and 72% perchloric acid (0.5 cm^3). The mixture was stirred in a stoppered flask for 24 hours at room temperature. A saturated aqueous solution of sodium bicarbonate was added slowly until the effervescence subsided (~200 cm^3). The dioxane layer was separated, and DCM added, but separation didn't occur, so the solvents were removed at reduced pressure, yielding crystals which were dissolved in ether, dried ($MgSO_4$), and concentrated, then recrystallised (PE) to give _N_-t-butoxyphthalimide as white crystals (8.81 g; 80%), m. p. 110.5-113°C (lit.[56] 110-111°C). δ_H 1.43 (9H, s, t-Bu) 7.65-7.85 (4H, m, ArH).

_N_-i-Propoxyphthalimide 45b[65]

To i-propanol (0.56 g; 9.25 mmol) in dry THF (100 cm^3) at 0°C was added _N_-hydroxyphthalimide (3.00 g, 18.5 mmol), triphenylphosphine, (4.82 g; 18.5 mmol) and diethyl azodicarboxylate (3.2 cm^3; 20.2 mmol). The mixture was warmed to 50°C and stirred at this temperature for 3 days, then allowed to cool. The THF was removed under reduced pressure, and ether (100 cm^3) and a saturated aqueous solution of sodium carbonate (100 cm^3) added. The ether layer was separated, and washed with further portions of saturated aqueous sodium carbonate solution (4×50 cm^3), and the aqueous layers combined and back extracted with ether (3×50 cm^3). The combined ether layers were dried ($MgSO_4$) and concentrated, and the product purified by column chromatography (ether/PE) to give white crystals (1.61 g; 85%), m.p. 52.0-54.0°C (lit[65] 53-54°C). δ_H 1.38 (6H, d, J = 6.0 Hz, $CH(CH_3)_2$), 4.51-4.59 (1H, septet, J = 6.3 Hz, $CH(CH_3)_2$), 7.73-7.87 (4H, m, ArH). δ_C 20.8, 80.7, 123.6, 129.1, 134.5, 164.6.

_N_-Dodecoxyphthalimide 45d

Prepared from dodecanol (9.25 mmol) and _N_-hydroxyphthalimide and purified in same way as _N_-i-propoxyphthalimide, to give _N_-dodecoxyphthalimide (2.11 g; 69%) as white crystals, m.p. 64-65°C . δ_H 0.88 (3H, t, J = 6.6 Hz, CH_3), 1.26-1.31 (16H, m, $8 \times CH_2$), 1.45-1.50 (2H, m, $OCH_2CH_2CH_2$), 1.77-1.82 (2H, m, OCH_2CH_2), 4.22 (2H, J = 6.7 Hz, OCH_2), 7.73-7.76 (2H, m, ArH), 7.83-7.87 (2H, m, ArH). δ_C 14.1, 22.7, 25.6, 28.2, 29.4, 29.5, 29.6, 29.7, 32.0, 78.8, 123.7, 129.2, 134.6, 163.9. (Found: C, 72.5; H, 8.8; N, 4.3. Calc. for $C_{20}H_{29}NO_3$: C, 72.5; H, 8.8; N, 4.2%.)

3-(Bromoethoxy)cyclohexene[66]

Sodium wire (0.92g; 40 mmol) was added to a stirred mixture of 3-bromocyclohexene (2.6 g; 16 mmol) and 2-bromoethanol (25 g; 0.2 mol) in dry THF (40 cm^3). The mixture was refluxed for 24 hours, after which it was filtered and concentrated. Water (100 cm^3), and cyclohexane (50 cm^3) were added, and the aqueous layer was separated and extracted twice more with cyclohexane (2×50 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated and the resulting brown liquid was distilled (40-42°C @ 0.04 mmHg) to give 3-(bromoethoxy)cyclohexene (2.11g; 64%) as a

colourless oil. δ_H 1.44-2.12 (6H, m, ring CH_2s) 3.42-3.47 (2H,t, CH_2), 3.75-3.86 (2H, m, CH_2), 3.87-3.95 (1H, m, $OCHR_2$), 5.72-5.93 (2H, m, HC=CH).

Typical syntheses of *O*-alkyl benzaldoximes

Method A: To a stirred mixture of oxime (12 mmol) and alkyl bromide (10 mmol) in DMF (33 cm^3) at 0°C was added caesium carbonate (3.98 g; 12 mmol). The mixture was stirred overnight. Water (25 cm^3) was added, and the product extracted with ether (3 × 25 cm^3), then washed extensively with water, and the organic layer dried ($MgSO_4$) and concentrated. Recrystallisation or column chromatography yielded pure product.

Method B A suspension of *N*-alkoxyphthalimide (3.31 mmol) in ethanol (5 cm^3) was heated until the solid dissolved. Hydrazine hydrate (180 µl; 3.64 mmol) was added, and the mixture stirred at the elevated temperature for a few minutes, then allowed to cool to room temperature. Arylaldehyde (3.50 mmol) was added, and the mixture stirred overnight. The mixture was filtered, then concentrated. DCM was added (~10 cm^3) and the mixture filtered again. Column chromatography yielded pure product.

***O*-Undecyl benzaldoxime 40a**

Prepared from benzaldoxime and undecyl bromide according to method A to give *O*-undecyl benzaldoxime as a colourless oil (1.41g; 51%) after column chromatography (PE/EtOAc). δ_H 0.85-0.90 (3H, t, J = 7.1 Hz, CH_3), 1.26-1.38 (16H, m, alkyl H), 1.68-1.73 (2H, m, OCH_2CH_2), 4.17 (2H, t, J = 6.8 Hz, OCH_2) 7.35-7.37 (3H, m, ArH), 7.56-7.59 (2H, m, ArH), 8.07 (1H, s, CH=N). δ_C 14.1, 22.7, 25.9, 29.1, 29.3, 29.5, 29.6, 31.9, 74.4, 126.9, 128.6, 129.6, 132.8, 148.2. (Found: M^+, 275.2258. $C_{18}H_{29}NO$ requires *M*, 275.2249)

***O*-*i*-Propyl benzaldoxime 40b**[67]

Prepared from benzaldoxime and i-propyl bromide according to method A to give *O*-i-propyl benzaldoxime as a colourless oil (1.27g; 78%) after column chromatography (PE/EtOAc). δ_H (200 MHz) 1.27 (6H, d, J = 6.2 Hz, 2 × CH_3), 4.17 (1H, septet, J = 6.7 Hz, $CH(CH_3)_2$), 7.35-7.40 (3H, m, ArH), 7.56-7.61 (2H, m, ArH), 8.08 (1H, s, CH=N).

_O_-t-Butyl benzaldoxime 40c

Prepared from benzaldehyde and *N*-t-butoxyphthalimide according to method B to give *O*-t-butyl benzaldoxime (0.26 g; 44%) as a colourless oil after column chromatography (PE/DCM). δ_H 1.36 (9H, s, t-Bu), 7.36 (3H, m, ArH), 7.60 (2H, m, ArH), 8.05 (1H, s, CH=N). δ_C 27.7, 79.3, 127.0, 128.8, 129.5, 133.5, 147.4. (Found: M^+, 177.1148. $C_{11}H_{15}NO$ requires *M*, 177.1153)

_O_-Pent-4-enyl benzaldoxime 40e

Prepared from benzaldoxime and 5-bromopent-1-ene according to method A to give *O*-pent-4-enyl benzaldoxime as a colourless oil (1.52g; 80%) after column chromatography (PE/DCM). δ_H 1.77-1.87 (2H, m, CH_2), 2.14-2.21 (2H, m, CH_2CH=), 4.18 (2H, t, J = 6.6 Hz, OCH_2), 4.97-5.10 (2H, m, CH_2=CH), 5.78-5.92 (1H, m, CH_2=C*H*), 7.34-7.38 (3H, m, ArH), 7.55-7.60 (2H, m, ArH), 8.07 (1H, s, CH=N). δ_C 28.4, 30.0, 73.7, 115.0, 127.1, 128.8, 129.8, 132.6, 148.5. (Found: M^+, 189.1154. $C_{12}H_{15}NO$ requires *M*, 189.1149.)

_O_-2-(3-Cyclohexenyloxy)ethyl benzaldoxime 40f

Prepared from benzaldoxime and 3-(bromoethoxy)cyclohexene according to method A to give *O*-2-(3-cyclohexenyloxy)ethyl benzaldoxime as a colourless oil (0.65g; 55%). δ_H 1.66-2.04 (6H, m, alkyl Hs), 3.75-3.87 (2H, m, OCH_2), 3.93 (1H, m, $OCHR_2$), 4.32 (2H, t, J = 5.1 Hz, OCH_2) 5.77-5.87 (2H, m, HC=CH), 7.37 (3H, t, J = 3.1 Hz, ArH), 8.13 (1H, s, CH=N). δ_C 19.3, 25.3, 28.3, 66.5, 73.5, 74.0, 127.3, 128.0, 128.9, 130.0, 131.1, 149.1. (Found: M^+, 245.1423. $C_{15}H_{19}NO_2$ requires 245.1416.)

_O_-Undecyl _p_-nitrobenzaldoxime 41a

Prepared from *p*-nitrobenzaldoxime and undecyl bromide according to method A to give *O*-undecyl *p*-nitrobenzaldoxime (1.00 g; 62%) as white crystals after column chromatography (PE/EtOAc), m.p. 41-43°C. δ_H 0.87 (3H, t, J = 6.7 Hz, CH_3), 1.26 (16H, m, 8 × CH_2), 1.73 (2H, m, J = 7.1 Hz, OCH_2CH_2), 4.21 (2H, t, J = 6.7 Hz, OCH_2) 7.73 (2H, d, J = 8.8 Hz, ArH), 8.12 (1H, s, CH=N), 8.22 (2H, d, J = 8.8 Hz, ArH) δ_C 14.1, 22.7, 25.9, 29.2, 29.4, 29.5, 29.7, 32.0, 75.4, 124.2, 127.6, 139.0, 146.1, 148.5. (Found: M^+, 320.2106. $C_{18}H_{28}N_2O_3$ requires *M*, 320.2100.)

_O_-i-Propyl-_p_-nitrobenzaldoxime 41b

Prepared from _p_-nitrobenzaldoxime and _i_-propyl bromide according to method A to give _O_-i-propyl _p_-nitrobenzaldoxime (0.99 g; 95%) as pale yellow crystals, m.p. 51.5-53°C after column chromatography (PE/EtOAc). δ_H 1.32 (6H, d, J = 6.2 Hz, $CH(CH_3)_2$), 4.46-4.54 (1H, septet, J = 6.2 Hz, $CH(CH_3)_2$), 7.76 (2H, d, J = 8.6 Hz, ArH), 8.09 (1H, s, CH=N), 8.22 (2H, d, J = 8.6 Hz, ArH). δ_C 21.1, 123.3, 123.7, 127.1, 131.1, 138.7, 142.4. (Found: C, 57.85; H, 5.48; N, 13.45. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45%.)

_O_-t-Butyl 4-nitrobenzaldoxime 41c

Prepared from _p_-nitrobenzaldehyde and _N_-t-butoxyphthalimide according to method B to give _O_-t-butyl _p_-nitrobenzaldoxime (0.41 g; 65%) as pale yellow crystals, m. p. 59-60.5°C after column chromatography (PE/DCM). δ_H 1.37 (9H, s, $C(CH_3)_3$), 7.74 (2H, d, J = 8.8 Hz, ArH), 8.09 (1H, s, CH=N), 8.22 (2H, d, J = 8.8 Hz, ArH). δ_C 27.5, 80.5, 124.2, 127.5, 131.5, 139.6, 145.3. (Found: C, 59.6; H, 6.4; N, 12.7. Calc. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.4; N, 12.6%.)

_O_-i-Propyl pentafluorobenzaldoxime 42b.

Prepared from pentafluorobenzaldehyde and _N_-i-propoxyphthalimide according to method B to give _O_-i-propyl pentafluorobenzaldoxime (0.52 g, 62%) as a colourless oil after column chromatography (DCM). δ_H 1.26 (6H, d, J = 6.0 Hz, $CH(CH_3)_2$) 4.49-4.61 (1H, septet, J = 6.3 Hz, $CH(CH_3)_2$) 8.11 (1H, s, CH=N). δ_C 21.5, 108.0-108.4 (m), 131.3, 135.9-136.2 (m), 136.4, 139.3-139.7 (m), 142.8-143.3 (m), 146.5-146.8 (m). (Found: M^+, 267.0526. $C_{11}H_{10}F_5NO$ requires _M_, 267.0532.)

_O_-t-Butyl pentafluorobenzaldoxime 42c

Prepared from pentafluorobenzaldehyde and _N_-t-butoxyphthalimide according to method B to give _O_-t-butyl pentafluorobenzaldoxime (0.48 g; 54%) as a colourless oil after column chromatography (PE/DCM). δ_H 1.36 (9H, s, $C(CH_3)_3$) 8.10 (1H, s, CH). δ_C 27.4, 80.8, 108.3-108.7 (m), 130.7, 135.8, 136.1-136.3 (m), 139.3-139.6 (m), 142.6-143.4 (m, possibly two overlapping multiplets), 146.4-146.7. (Found: M^+, 237.1357. $C_{11}H_{10}F_5NO$ requires _M_, 237.1365.)

***O*-Dodecyl pentafluorobenzaldoxime 42d.**

Prepared from pentafluorobenzaldehyde and *N*-dodecoxyphthalimide according to method B (on a 1.65 mmol scale) to give *O*-dodecyl pentafluorobenzaldoxime (0.38 g, 61%) as a colourless oil after column chromatography (DCM). δ_H 0.88 (3H, t, J = 6.7 Hz, CH_3), 1.26-1.54 (18H, m, alkyl Hs), 1.67-1.74 (2H, m, OCH_2CH_2), 4.20-4.25 (2H, t, J = 6.7 Hz, OCH_2), 8.13 (1H, s, CH=N). δ_C 14.1, 22.7, 25.8, 29.0, 29.4, 29.4, 29.6, 29.6, 29.7, 31.9, 53.4, 75.5, 131.7, 136.1 (m), 136.8, 139.5-139.6 (m), 143.0-143.2 (m), 146.6 (m).

***O*-t-Butyl-2,4-dimethoxybenzaldoxime 43c**

Prepared from t-butoxyphthalimide and 2,4-dimethoxybenzaldoxime according to method B to give *O*-t-butyl-2,4-dimethoxybenzaldoxime as a colourless oil (0.31g; 79%). δ_H 1.36 (9H, s, $C(CH_3)_3$), 3.81 (6H, s, 2 × OMe), 6.45 (1H, t, J = 2.2 Hz, ArH), 6.75 (2H, m, ArH), 7.96 (1H, s, CH=N) δ_C 27.5, 55.3, 79.2, 101.6, 104.8, 147.2, 161.0. (Found: M^+, 237.1358. $C_{13}H_{19}NO_3$ requires *M*, 237.1365.)

***O*-i-Propyl 2,4,6-trimethoxybenzaldoxime 43b**

Prepared from i-propoxyphthalimide and trimethoxybenzaldehyde according to method B to give *O*-i-propyl-2,4,6-trimethoxybenzaldoxime as a colourless oil (0.59 g; 70%) after column chromatography (DCM). *Z* isomer: δ_H 1.30 (6H, d, J = 6.1 Hz, $CH(CH_3)_2$), 3.82 (9H, s, $(OCH_3)_3$), 4.42-4.50 (1H, m, $CH(CH_3)_2$), 6.12 (2H, s, ArH), 8.35 (1H, s, CH=N). *E* isomer 1.23 (6H, d, J = 6.3 Hz, $CH(CH_3)_2$), 3.82 (9H, s, $(OCH_3)_3$), 4.42-4.50 (1H, m, $CH(CH_3)_2$), 6.11 (2H, s, ArH), 7.34 (1H, s, CH=N). δ_C (*Z* only) 21.7, 55.3, 56.0, 74.9, 91.0, 103.3, 143.5, 160.2, 162.3. (Found: M^+, 253.1319. $C_{13}H_{19}NO_4$ requires *M*, 253.1314)

***O*-t-Butyl 2,4,6-trimethoxybenzaldoxime 43c**

Prepared from t-butoxyphthalimide and trimethoxybenzaldehyde according to method B to give *O*-t-butyl-2,4,6-trimethoxybenzaldoxime as white needles, that contained t-butoxyphthalimide impurity that could not be removed by column chromatography or recrystallisation. δ_H 1.36 (9H, s, $C(CH_3)_3$), 3.82 (9H, s, 3OMe), 6.13 (2H, s, ArH), 8.32 (1H, s, CH=N). δ_C 27.4, 55.4, 56.2, 78.2, 91.4, 104.2, 142.7, 160.2, 162.1.

_O_-Dodecyl 2,4,6-trimethoxybenzaldoxime 43d

Prepared from dodecoxyphthalimide (1.65 mmol) and 2,4,6-trimethoxybenzaldoxime according to method B to give _O_-dodecyl-2,4,6-trimethoxybenzaldoxime (0.38 g; 61%) as a colourless oil after column chromatography (DCM), which crystallised slowly, m.p. 32.0-32.5°C . δ_H 0.87 (3H, t, J = 7.1 Hz, CH_3), 1.25-1.38 (18H, m, 9 × CH_2), 1.69 (2H, m, CH_2), 3.82 (6H, s, _p_-OCH_3), 3.83 (6H, s, _o_-OCH_3), 4.14 (2H, t, J = 6.9 Hz, CH_2), 6.12 (2H, s, ArH), 8.38 (1H, s, CH=N). δ_C 14.1, 22.6, 26.0, 29.1, 29.3, 29.5, (includes CH_2s) 29.6, 31.9, 55.9, 56.2, 74.0, 90.9, 102.9, 117.8, 144.0, 144.2, 160.3, 162.5. (Found: M^+, 379.2729. $C_{22}H_{37}NO_4$ requires _M_, 379.2722)

Potassium benzohydroximate 50[60]

Solutions of potassium hydroxide (56.1g; 1 mole) in methanol (140 cm^3) and hydroxylamine hydrochloride (46.7 g; 0.67 mol) in methanol (240 cm^3) were prepared at the solvent's boiling point. Both solutions were cooled slowly to 40°C and the potassium hydroxide solution was added slowly with shaking to the hydroxylamine solution, keeping the temperature low with an ice bath. The mixture was then allowed to stand for 5 minutes in an ice bath, then ethyl benzoate (50 g; 0.33 mol) was added with thorough shaking, the mixture was promptly filtered, and the residue washed with methanol. The filtrate was allowed to stand for 48 hours, and the solid which precipitated was filtered, washed (EtOH), and dried in air to give pale brown crystals (36.90 g; 64%), m.p. >285°C.

_O_-i-Propyl benzohydroxamate 51a[58]

To a solution of potassium hydroxide (10.6 g; 0.19 mol) and potassium benzohydroxamate (11.21 g; 0.064 mol) in water (200 cm^3) was added i-propyl bromide (8.86 g; 0.072 mol). The mixture was stirred for 5 days at 75°C, then cooled in an ice bath and acidified with glacial acetic acid. The solid was filtered, dried, and recrystallised (ether-hexane) to give _O_-i-propyl benzohydroxamate as white crystals (2.01 g; 19%), m.p. 87.0-89.0°C (lit[58]; 89-90°C).

_O_-n-Propyl benzohydroxamate 51b[59]

To a solution of potassium hydroxamate (9.11 g; 0.162 mol) and potassium benzohydroxamate (9.63 g; 0.055 mol) in water (175 cm^3) was added n-propyl bromide (7.63 g; 0.062 mol). The mixture was stirred for 7 days at 75°C, then cooled in an ice bath and acidified with glacial acetic acid. A red sludge was formed, which proved impossible to crystallize, so was purified by chromatography to give an oil, which went crystalline after 5 days on bubbling air through with a pipette (3.80 g; 42%). δ_H 0.95 (3H, t, J = 7.5 Hz, CH_3), 1.65-1.76 (2H, m, CH_2CH_3), 3.93-3.99 (2H, t, J = 6.8 Hz, OCH_2), 7.35-7.50 (3H, m, ArH), 7.73-7.77 (2H, d, J = 7.0 Hz, ArH) 9.4 (1H, bs, NH).

_O_-i-Propyl benzohydroximoyl chloride 52a[58]

To isopropyl benzohydroxamate (0.82 g, 5 mmol) was added phosphorus pentachloride (5.25 mmol), and the mixture stirred at 0°C initially, and the mixture allowed to warm to room temperature. The mixture was heated at 98°C for 4 hours, then allowed to cool, and extracted with DCM. The mixture was concentrated to give a colourless oil (0.69 g; 70%) δ_H 1.35 (6H, d, J = 6 Hz, 2 × CH_3), 4.56 (1H, septet, J = 6.5 Hz, $CHMe_2$), 7.4 (3H, m, ArH), 7.9 (2H, m, ArH).

_O_-n-Propyl benzohydroximoyl chloride 52b[59]

To n-propyl benzohydroxamate (2.51 g, 15 mmol) was added phosphorus pentachloride (2.90 g; 1.75 mmol), and the mixture stirred at 0°C initially, and the mixture allowed to warm to room temperature. The mixture was heated at 50°C for 4 hours, then allowed to cool, and extracted with DCM. The mixture was purified by column chromatography, then twice purified by bulb to bulb distillation (b.p. 52°C @ 0.04 mmHg) to give *O-n*-propyl benzohydroximoyl chloride as a colourless oil (1.54 g; 56%). δ_H 1.35 (6H, d, J = 6 Hz, 2 × CH_3), 4.56 (1H, septet, J = 6.5 Hz, $CHMe_2$), 7.40 (3H, m, ArH), 7.90 (2H, m, ArH).

Di-t-butyl peroxyoxalate[57]

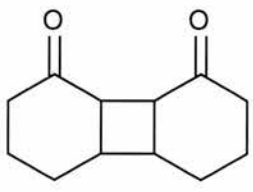
Oxalyl chloride (0.64 g; 5 mmol) in pentane (5 cm^3) was added over 5 minutes to a stirred solution of pyridine (0.80 g) and t-butyl hydroperoxide (0.90 g; 10 mmol) in pentane (5 cm^3) at ~ -5°C. The solution was allowed to warm slowly to near room temperature, and

the pyridinium chloride was filtered, and washed with pentane. The combined filtrates were stood in dry ice/acetone until the perester precipitated. The mixture was filtered (0.70 g; 69%), and the product stored in the freezer.

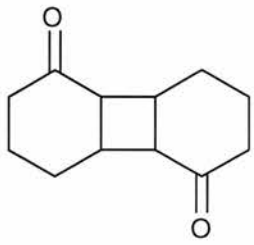
Product analysis reactions of oxime esters in the presence of DTBP

Photochemical reaction of *O*-trimethylacetylbenzaldoxime 8a with 3-cyclohexenone

A degassed solution of *O*-trimethylacetyl benzaldoxime **8a** (124 mg; 0.61 mmol), 3-cyclohexenone (124 mg; 1.29 mmol) in DTBP (400 µl) was photolysed for 3 hours using a 125 W medium pressure Hg lamp, and the product mixture analysed by GC/MS. peak no. 101, t-butanol, *m/z* (relative intensity) 59 (100), 57 (14), 43 (22), 41 (30), 32 (18), 31 (45), 28 (72); peak no. 193, cyclohexenone; peak no. 200, trimethylacetic acid; peak no. 214, benzonitrile, 103 (M^+) (100), 77 (9), 76 (40), 75 (15), 52 (10), 51 (18), 50 (29), 39 (11), peak no. 308, 3-t-butylcyclohexanone **17**, 154 (M^+) (8), 98 (40), 97 (28), 83 (18), 69 (31), 57 (100), 55 (44), 41 (92), 29 (34), 27 (26); peak no. 500, adduct **53** or **54**, 192 (M^+) (9), 150 (15), 96 (17), 79 (21), 68 (100), 55 (30), 41 (29), 39 (48), 27 (32); peak no. 535, cycloadduct **53** or **54**, 192 (M^+) (14), 136 (20), 97 (39), 96 (54), 79 (53), 68 (100), 55 (41), 41 (48), 39 (73), 27 (54). There was no sign of unreacted starting material. The yield of 3-t-butylcyclohexanone was estimated to be 6% using pinacolone as an external standard.



53



54

Photochemical reaction of *O*-cyclohexanecarbonylbenzaldoxime 8b with 3-cyclohexenone

A degassed solution of *O*-cyclohexylcarbonyl benzaldoxime **8b** (131 mg; 0.57 mmol), 3-cyclohexenone (230 mg; 2.40 mmol) and DTBP (20 μl) in cyclohexane (500 μl) was photolysed for 6 hours using a 125 W medium pressure Hg lamp, and the product mixture analysed by GC/MS. peak no. 101, t-butanol; peak no.193, cyclohexenone; peak no. 211, benzaldehyde 106 (M^+) (62), 105 (65), 78 (29), 77 (100), 52 (21), 51 (76), 50 (49), 32 (22), 28 (95); peak no. 214, benzonitrile; peak no. 334, cyclohexanecarboxylic acid, *m/z* (relative intensity) 128 (M^+) (12), 83 (30), 73 (48), 68 (29), 56 (33), 55 (100), 41 (72), 39 (59), 29 (31), 27 (56); peak no. 445, 3-cyclohexylcyclohexanone, 180 (M^+) (2), 97 (100), 83 (20), 69 (22), 67 (21), 55 (78), 41 (83), 39 (31); peak no. 504, adduct **53** or **54**; peak no. 517, adduct **53** or **54**. There was no sign of unreacted starting material.

Photochemical reactions of *O*-(cyclohexenyloxy)propionoyl arylaldoximes 8d-11d in DTBP

A degassed solution of *O*-(cyclohexenyloxy)propionoyl arylaldoxime (~0.065 mmol) in DTBP (150 μl) [or in DTBP (150 μl) and benzene (100 μl) for **9d** and **11d** due to lack of solubility in DTBP] was photolysed for 24 hours using a medium pressure 125 W Hg lamp. The mixtures were analysed using GC/MS.

O-(Cyclohexenyloxy)propionoyl pentafluorobenzaldoxime illuminated in DTBP; peak no. 96, t-butanol; peak no. 145, pentafluorobenzonitrile, *m/z* (relative intensity) 193 (M^+) (100), 162 (12), 124 (37), 93 (21), 78 (20), 57 (19), 32 (30), 31 (55); peak no. 294, pentafluorobenzoic acid. Unidentified peak at 407.

O-(Cyclohexenyloxy)propionoyl 2,4-dimethoxybenzaldoxime illuminated in DTBP and benzene; peak no. 95, t-butanol; peak no. 184; $C_8H_{14}O$; *m/z* (relative intensity) 126 (M^+) (29), 98 (100) 71 (63), 70 (82), 44 (50), 42 (88), 40 (64), 27 (85); peak no. 209, $C_8H_{14}O$; 126 (M^+) (3), 97 (38), 82 (41), 78 (29), 68 (42), 57 (40), 54 (39), 41 (100), 28 (75), 27 (50); peak no. 216, $C_8H_{14}O$, 126 (M^+) (17), 84 (40), 83 (100), 55 (38), 42 (38), 39 (45), 27 (46), 29 (33); peak no. 390, 2,4-dimethoxybenzaldehyde; 166 (M^+) (100), 165

(45), 135 (40), 122 (27), 107 (29), 77 (45), 63 (46), 51 (42), 41 (32); peak no. 395, 2,4-dimethoxybenzonitrile, 163 (M^+) (100), 134 (47), 133 (42), 103 (90), 90 (39), 77 (50), 65 (60), 62 (39), 51 (40), 38 (40).

O-(Cyclohexenyloxy)propionoyl *p*-nitrobenzaldoxime illuminated in DTBP and benzene; peak no. 197; $C_8H_{14}O$; peak no. 223, $C_8H_{14}O$; peak no. 359, *p*-nitrobenzonitrile; *m/z* (relative intensity) 148 (M^+) (38), 102 (86), 90 (27), 75 (62), 51 (38), 50 (44), 30 (100), peak no.408, *O*-(cyclohexenyloxy)propionic acid.

O-(Cyclohexenyloxy)propionoyl benzaldoxime illuminated in DTBP; peak no. 197; $C_8H_{14}O$; peak no. 205, benzaldehyde; peak no. 211, benzonitrile, peak no. 219, $C_8H_{14}O$; peak no. 565, *O*-(cyclohexenyloxy)propionoyl benzaldoxime.

Radical reactions of *O*-(cyclohexenyloxy)propionoyl arylaldoximes 8d-11d using di-t-butyl peroxyoxalate as a radical initiator

A degassed solution of *O*-(cyclohexenyloxy)propionoyl arylaldoxime (~0.080 mmol) and di-t-butyl peroxyoxalate in cyclohexane (500 µl) [or in cyclohexane (300 µl) and benzene (300 µl) for **9d** and **11d** due to lack of solubility in cyclohexane] was heated at 65°C in an NMR tube for 72 hours. The mixtures were analysed using GC/MS.

O-(Cyclohexenyloxy)propionoyl pentafluorobenzaldoxime and t-butyl peroxyoxalate heated in cyclohexane; peak no. 90, t-butanol; peak no. 120, DTBP, peak no. 160, cyclohexanone; peak no. 329, bicyclohexyl, *m/z* (relative intensity) 166 (M^+) (18), 83 (75), 82 (100), 68 (40), 67 (45), 56 (58), 54 (72), 41 (60), 28 (50). There were several other unidentified peaks.

O-(Cyclohexenyloxy)propionoyl *p*-nitrobenzaldoxime and t-butyl peroxyoxalate heated in cyclohexane and benzene; peak no. 90, t-butanol; peak no. 120, DTBP, peak no. 160, cyclohexanone, *m/z* (relative intensity) 98 (M^+) (18), 69 (18), 55 (72), 42 (100), 41 (40), 39 (45), 28 (28), 27 (57); peak no. 329, phenylcyclohexane, 156 (M^+) (3), 100 (18), 59 (42), 57 (100), 56 (17), 41 (35), 39 (18), 29 (24); peak no. 336, bicyclohexyl. Unidentified peak at 404.

O-(Cyclohexenyloxy)propionoyl benzaldoxime and t-butyl peroxyoxalate heated in cyclohexane; peak no. 88, t-butanol; peak no. 115, DTBP, peak no. 160, cyclohexanone;

peak no. 324, bicyclohexyl; peak no. 396, cyclohexenylpropionic acid, *m/z* (relative intensity) 170 (M^+) (4), 98 (50), 97 (65), 70 (55), 55 (57), 41 (70), 28 (100), 27 (55); peak no. 565, *O*-(cyclohexenyloxy)propionoyl benzaldoxime. There were several other unidentified peaks.

O-(Cyclohexenyloxy)propionoyl 2,4-dimethoxybenzaldoxime and t-butyl peroxyoxalate heated in cyclohexane and benzene; peak no. 90, t-butanol; peak no. 120, DTBP, peak no. 170, cyclohexanone, peak no. 339, phenylcyclohexane; peak no. 396, bicyclohexyl. There were several other unidentified peaks.

Product analysis reactions of oxime esters in the absence of DTBP.

General procedure for photochemical reactions of oxime esters.

A degassed solution of oxime ester (and ~1 equivalent of sensitiser if desired) in the selected solvent (~0.13 M) was photolysed for 3 hours in an EPR tube (or larger quartz tube) using a medium pressure 450 W Hg lamp. A known amount of DCM, 1,4-dioxane or toluene was added, and the reaction yield determined by comparison of the integral trace of a known peak in the product. Reaction was sometimes also analysed by GC/MS. NMR yields obtained from this technique are given in the text.

Reaction of *O*-(cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime in 1,2,4-trimethylbenzene

A degassed solution of *O*-(cyclohexenyloxy)propionyl 2,4-dimethoxybenzaldoxime (0.0076 g; 0.028 mmol) in 1,2,4-trimethylbenzene (300 µl) was photolysed for 3 hours at ~50°C using a medium pressure 450 W Hg lamp. The product mixture was analysed using GC/MS. peak no. 94, methylenecyclopentane, *m/z* (relative intensity) 82 (M^+) (28), 81 (13), 67 (100), 54 (29), 41 (28), 39 (39), 28 (17), 27 (20).

Isolation of 2-oxabicyclo[4.3.0]nonane.

A degassed solution of *O*-(cyclohexenyloxy)propionoyl 2,4,6-trimethoxybenzaldoxime **12d** (0.25 g; 0.69 mmol) and *p*-methoxyacetophenone (0.12 g; 0.80 mmol) in DCM (6 cm^3) was illuminated for 3 hours at ~50°C using a medium pressure 400 W Hg lamp. The mixture was concentrated at room temperature, and the residue repeatedly washed with ether. The solution was again concentrated at room temperature and

purified using microdistillation apparatus to give 2-oxabicyclo[4.3.0]nonane (0.01 g; 12%) as a colourless oil. δ_H[66] 1.15-1.27 (2H, m, CH_2), 1.39-1.68 (6H, m, 3 × CH_2), 1.83-2.04 (3H, m, CH_2, CH), 3.75-3.87 (2H, m, OCH_2), 3.97 (1H, q, J = 7.9 Hz).

Reaction of undecyl or dodecyl oxime ethers in DTBP

A solution of oxime ether and DTBP in benzene or cyclohexane, plus any additive (e.g. methyl thioglycolate) was degassed with nitrogen, and illuminated in an EPR tube using either a medium pressure 125 W Hg lamp (20 hours) or a medium pressure 400 W Hg lamp. The product mixture was analysed by GC/MS.

O-Undecyl benzaldoxime and DTBP illuminated in cyclohexane; peak no. 98, t-butanol; peak no. 207, benzonitrile; ,peak no. 336, undecanal, *m/z* (relative intensity) 126 (4), 82 (23), 57 (53), 56 (48), 55 (50), 44 (41), 43 (90), 41 (100), 29 (70), 27 (45); peak no. 364, undecanol, 154 (M^+–H_2O) (1), 126 (4), 83 (28), 69 (51), 56 (62), 55 (84), 43 (89), 41 (100), 29 (52); peak no. 596*O*-undecyl benzaldoxime; 274 (M^+-1) (1), 244 (3), 146 (10), 132 (12), 104 (29), 77 (34), 57 (48), 55 (44), 43 (100), 41 (83).

The above reaction was performed using benzoyl peroxide as initiator in refluxing benzene; peak no. 98, t-butanol, peak no. 199, benzaldehyde; peak no. 213, benzonitrile; peak no. 336, undecanal; peak no. 346, benzoic acid; peak no. 368, undecanol; peak no. 596, *O*-undecyl benzaldoxime.

The above reactions were repeated using methyl thioglycolate as a polarity reversal catalyst. The same products were obtained.

The above reactions were repeated using di-t-butyl peroxyoxalate as a radical initiator in refluxing cyclohexane. The same products were obtained.

O-Dodecyl 2,4,6-trimethoxybenzaldoxime and DTBP were illuminated in benzene; peak no. 98, t-butanol; peak no. 378, dodecanal; *m/z* (relative intensity) 166 (2), 82 (57), 67 (47), 57 (71), 55 (55), 43 (68), 41 (100), 29 (56); peak no. 401, dodecanol; 168 (M^+–H_2O) (1), 140 (4), 97 (11), 83 (26), 69 (36), 56 (48), 55 (90), 43 (79), 41 (100), 29 (62), peak no. 401, 2,4,6-trimethoxybenzonitrile; 193 (M^+) (100), 164 (35), 150 (28), 104 (29), 77 (40), 76 (31), 69 (80), 55 (43), 41 (48), 29 (34), peak no. 556, *O*-dodecyl 2,4,6-trimethoxybenzaldoxime. Mixture also contained unidentified impurities.

O-Dodecyl pentafluorobenzaldoxime and DTBP were illuminated in benzene; peak no. 98, t-butanol; peak no. 149, pentafluorobenzonitrile; peak no. 297, 1-dodecene, 168 (M^+) (5), 84 (24), 70 (63), 69 (43), 57 (38) 56 (58), 55 (100), 43 (80), 41 (89), 27 (70); peak no. 377, dodecanal; peak no. 403, dodecanol; peak no. 502, *O*-dodecyl pentafluorobenzaldoxime.

O-Undecyl *p*-nitrobenzaldoxime and DTBP were illuminated in benzene; peak no. 98, t-butanol; peak no. 340, undecanal; peak no. 367, undecanol, peak no. 585, *O*-undecyl *p*-nitrobenzaldoxime.

Degassed solutions of oxime ethers (~0.025 mmol) **40-43c**, and **44c** in toluene (100 μl) were photolysed for 24 hours, and the products analysed by GC/MS. In all cases the alcohols and aldehydes described above were formed.

A solution of *O*-undecyl benzaldoxime in toluene was heated for 6 hours at 60°C. GC/MS analysis showed only starting materials.

2-Methyltetrahydrofuran from illumination of *O*-pent-4-enyl benzaldoxime

A degassed solution of *O*-pent-4-enyl benzaldoxime (~20 mg) in toluene (~300 μl) in an EPR tube, was illuminated for 3 hours using a 400 W Hg lamp. The product mixture was analysed by GC/MS; peak no.100, 2-methyltetrahydrofuran, *m/z* (relative intensity) 86 (M^+) (12), 71 (100), 45 (24), 43 (95), 42 (70), 41 (98), 39 (28), 27 (35); peak no. 204, benzonitrile; peak no. 382, *O*-pent-4-enyl benzaldoxime.

Preparation of oxime esters and ethers for use in EPR spectroscopy

A sample of oxime ester or ether (~0.03 g), and sensitiser where required, was added to t-butylbenzene (~300 μl) and the mixture degassed by passing a stream of nitrogen through it.

For reactions performed in cyclopropane, the solution was degassed on a vacuum line using the freeze-pump-thaw technique, and the tube flame sealed.

Preparation of *O*-alkyl and *O*-acyl benzohydroximoyl chlorides for use in EPR spectroscopy

O-alkyl or *O*-acyl benzohydroximoyl chloride (~0.03 g) and hexamethylditin (~0.03 g) were dissolved dissolved in t-butylbenzene (~300 μl), and the mixture degassed by passing a stream of nitrogen through it.

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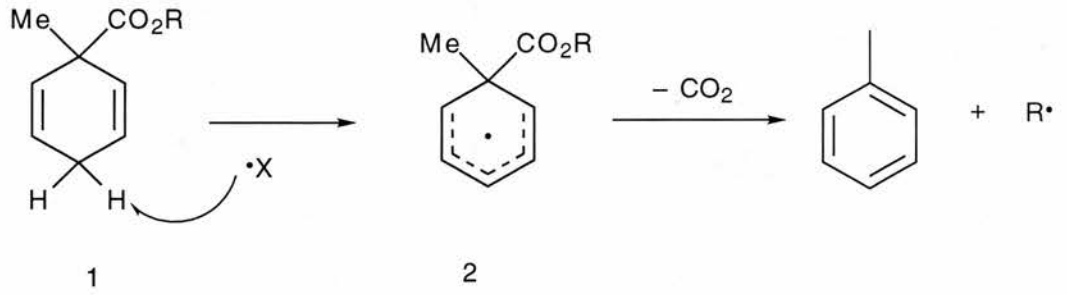
Chapter 3

Cyclohexadienones as radical precursors

3.1 Introduction

3.1.1 Proaromatic compounds as radical precursors.

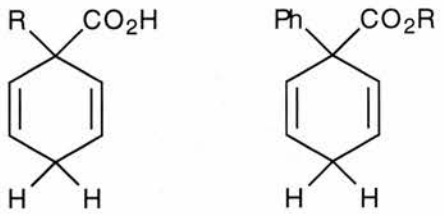
The use of "proaromatic" compounds as precursors to alkyl radicals has been investigated by the Walton group.[1] A large proportion of those investigated have been cyclohexa-2,5-diene derivatives, as the bisallylic hydrogens can be selectively abstracted by carbon centred radicals, yielding cyclohexadienyl radicals. Aromatisation is the driving force behind the generation of the radical R• (Scheme 1).[2] 1-Methylcyclohexa-2,5-diene-1-carboxylic esters **1** were partially successful, but had limitations. Methyl radical production was often competitive with formation of the desired radical.



Scheme 1

Cyclohexa-2,5-diene-1-carboxylic acid derivatives **3** were also successful but radical production was problematic. Loss of the hydroxyformyl radical •CO_2H was competitive,[3] especially when the intended product radical R• was a primary. 1-Phenylcyclohexa-2,5-diene-1-carboxylic esters **4** are the most efficient proaromatic radical precursors of this type so far unearthed. There is only one viable pathway available to the intermediate cyclohexadienyl radical; expulsion of a phenyl radical does not occur. A remaining problem

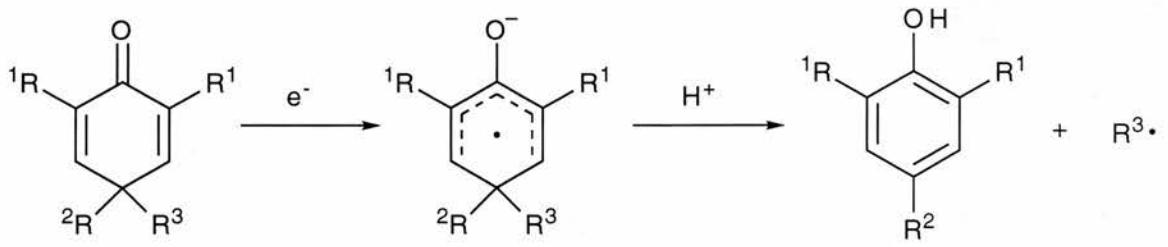
of this approach to radical production is the synthesis of the precursors; the Birch reduction is often prohibitively inefficient, so superior methods are still being sought.



3 **4**

3.1.2 Cyclohexadienones as potential proaromatic radical precursors.

We considered that cyclohexadienones could act as proaromatic radical precursors. Delocalised ketyl radicals derived from cyclohexadienones are very similar to the cyclohexadienyl radicals generated from cyclohexa-2,5-diene derivatives, and should aromatise analogously, expelling an alkyl radical (Scheme 2). Removal of the phenolic by-products should be non-problematic.

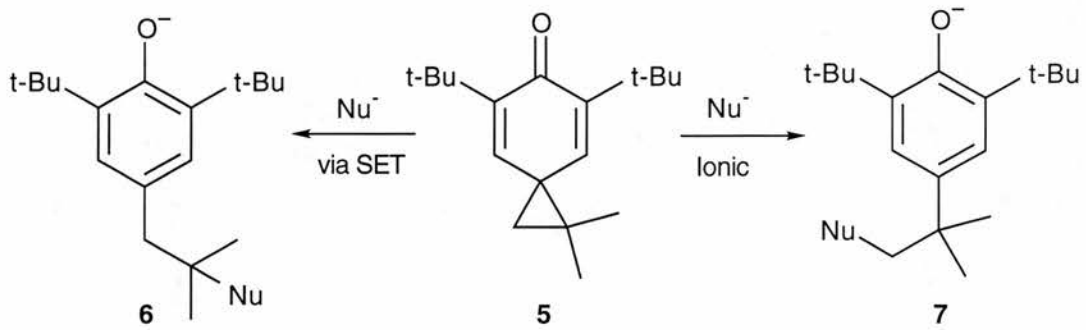


Scheme 2

Tanko described a similar technique,[4] in which 1,1-dimethyl-5,7-di-t-butylspiro[2.5]octa-4,7-dien-6-one **5** acts as a radical probe. Reactions that occur via a single electron transfer mechanism will be intercepted by **5**, forming a cyclohexadienyl ketyl radical. Subsequent cyclopropyl ring opening yields the more stable radical, leading to **6**. In a purely ionic mechanism, direct nucleophilic attack at the cyclopropyl ring leads to **7.**

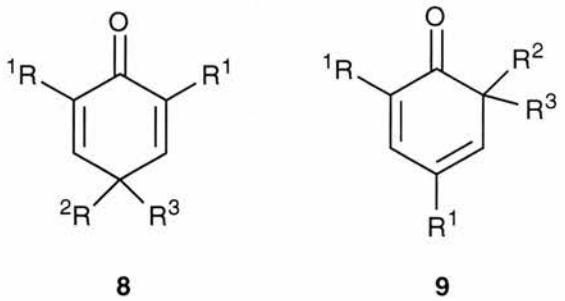
There are two driving forces behind the reaction that leads to **6**; the aromatisation and cyclopropyl ring opening. The proposed mechanism by which cyclohexadienones

would generate alkyl radicals is driven mainly by aromatisation. However, aromatisation of cyclohexa-2,5-diene radicals similar to **2** provides sufficient driving force for the expulsion of an alkyl radical, so it is conceivable that the same would be true of the mechanism shown in Scheme 2.



Scheme 3

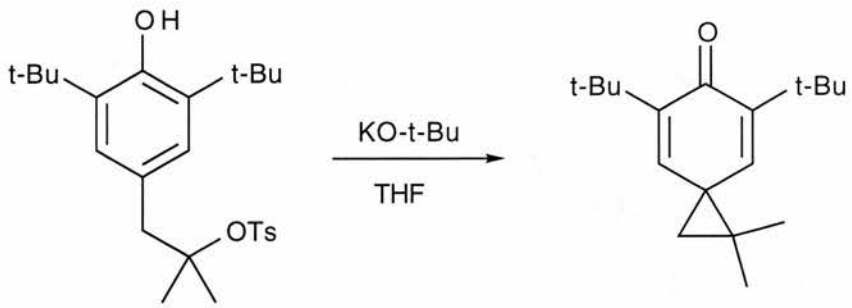
There are a couple of notable differences between the proposed method and the cyclohexadiene method. The proposed reaction is not a chain reaction, but this should not be detrimental, because good H-donors can be added or used as solvents. Also, the regiochemistry of the dienone should not matter; both **8** and **9** should be equally effective.



3.1.3 Base-mediated alkylation of phenols.

While 4-methylenecyclohexa-2,5-dien-1-ones are fairly common in the literature, 4,4-dialkylcyclohexa-2,5-dien-1-ones are comparatively rare. Tanko's synthesis of 1,1-dimethyl-5,7-di-t-butylspiro[2.5]octa-4,7-dien-6-one, was a modification of a method described by Schwartz *et al.* and utilised an intramolecular cyclisation from a phenol

(Scheme 4).[5] Syntheses of 4,4-dialkylcyclohexa-2,5-dien-1-ones reported in the literature involve a variant of this.



Scheme 4

The main problem to be overcome is usually *O*-alkylation. A method for making 4-alkyl-2,4,6-trimethylcyclohexa-2,5-dien-1-ones (**8**; R^1,R^2 = Me) using sodium hydroxide as the base in an aqueous solution was described by the group of Schmid.[6] We considered that it would be advantageous to use 2,6-di-t-butylphenols as starting materials, so that a single product would result. A stronger base would be required to form the phenoxide; potassium hydride has been shown to form the phenoxide salt from such hindered phenols in a few minutes.[7]

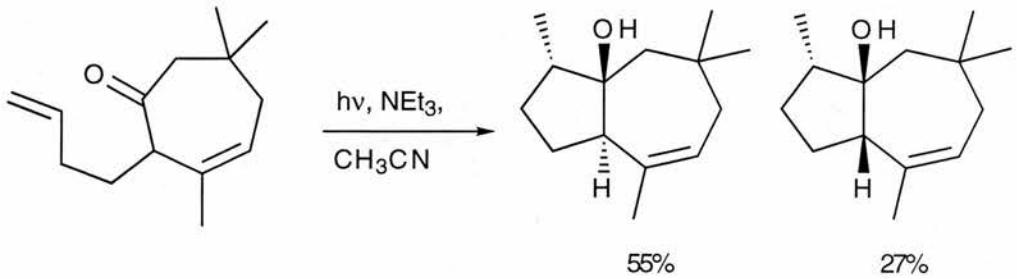
Finally, a report by Miller and Margulies described the effects of both solvent and alkylating agent on alkylation of the 2,6-di-t-butyl-4-methylphenoxide ion;[8] potassium t-butoxide in t-butanol gave a higher yield of *C*-alkylated product than sodium hydride in DMSO, which tended to favour formation of the *O*-alkylated product.

3.1.4 Generation of the cyclohexadienyl-type ketyl radical.

There are a number of methods of generating ketyl radicals from carbonyl compounds. A simple method was exemplified by Cossy in her synthesis of (+/-)-isoafricanol in which illumination of the precursor and triethylamine at 254 nm in acetonitrile generated a ketyl radical which underwent cyclisation (Scheme 5).[9]

Addition of trialkyltin radicals to ketones generates ketyl radicals, but use of tin compounds is the very thing we are trying to eliminate from our methods. Other single

electron donors can also be used but have drawbacks: samarium iodide[10] is expensive and air sensitive, pentamethyldisilyl radicals are generated from a precursor, pentamethyldisilane, the synthesis of which is not trivial,[11] and alkali metals. It is not considered important at the present time whether, the initially generated ketyl is a neutral radical, or a radical anion.



55% 27%

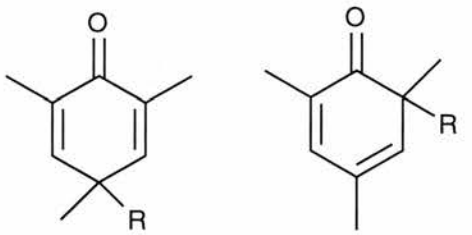
Scheme 5

For the method to be synthetically useful it must be efficient, and the synthesis of the precursors should also be efficient as well as fairly cheap. In addition, awkward experimental procedures such as ultraviolet irradiation should be avoided if possible. Preliminary experimental results, including the use of EPR spectroscopy to detect radicals from such precursors, are described in this chapter.

3.2 Results and Discussion

3.2.1 Preparation of cyclohexadienones

The initial experiments concentrated on the adaptation of the methods of Schmid[6] to 2,6-di-t-butylphenol and 2,6-di-t-butyl-4-methylphenol (BHT). Unfortunately these compounds, unlike mesitol, are insoluble in sodium hydroxide solution under all the attempted reaction conditions. Reaction of the heterogeneous mixture gave the expected negative result. 4-Allyl-2,4,6-trimethylcyclohexa-2,5-dien-1-one, **10a**, and 2-allyl-2,4,6-trimethylcyclohexa-3,5-dien-1-one, **11a**, were synthesised from mesitol by the literature method.[6]

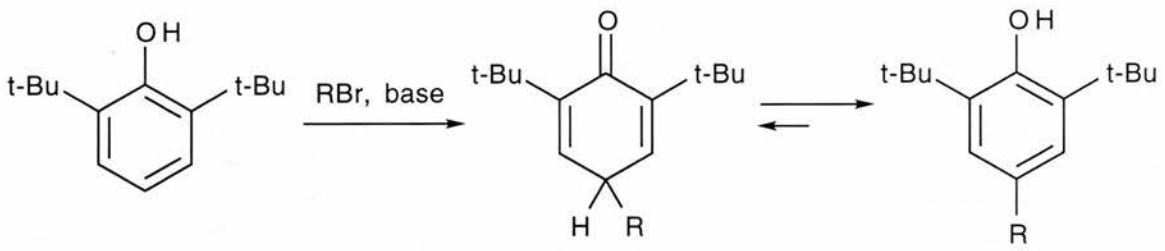


10 **11**

a R = allyl
b R = benzyl
c R = (2-naphthyl)methyl

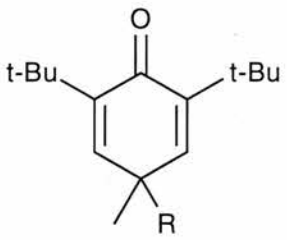
The allyl radical, formed from precursors **10a** and **11a** could be analysed by EPR spectroscopy, but not used in preparative experiments; the product would be too volatile to analyse satisfactorily. Synthesis of precursors that would lead to less volatile products was undertaken. 2-Benzyl-2,4,6-trimethylcyclohexa-3,5-dien-1-one, **11b**, and 4-(2-methylnaphthyl)-2,4,6-trimethylcyclohexa-2,5-dien-1-one, **10c** were also prepared (in low yield) by the method described for **10a** and **11a**. It was conceived that 4-t-butylphenol could act as a precursor to suitable cyclohexadienones; however there are no steric effects preventing *O*-alkylation, which was found to occur when the reaction was performed in THF, using sodium hydride as base.

Attempts to *C*-alkylate 2,6-di-t-butylphenol with sodium hydride and iodohexadecane failed. *C*-Alkylated product was not observed as it tautomerised to the alkylated phenol (Scheme 6). This is not a surprising result, considering the aromaticity of the undesired tautomer.



Scheme 6

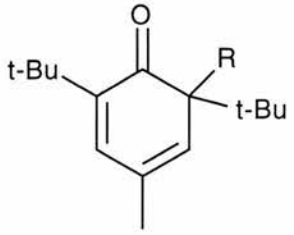
All further attempts at *C*-alkylation took place using compounds such as BHT or 2,4,6-trimethylphenol in which the desired products cannot tautomerise. The sodium hydride mediated alkylation failed to give any product, and use of potassium t-butoxide in THF[5] gave desired product **12a**, but in only minute yield (<1%).



12

a R = $(CH_2)_{15}CH_3$
b R = $(CH_2)_7CH_3$

Reactions in which bromides or tosylates[5] were used as the leaving group failed. Miller and Margulies[8] reported that reasonable yields of *C*-alkylated products (including straight chain alkanes, unlike the previous methods considered) could be obtained when the BHT was treated with potassium t-butoxide in t-butanol, and allowed to react with the appropriate iodide or bromide. Use of sodium hydride in DMSO gave predominantly *O*-alkylated product. Interestingly, when 'activated' bromides such as allyl bromide were used, there was a much larger proportion of product alkylated in the 2-position (**13**).[8] These would be unsuitable as radical precursors, as a t-butyl radical would be eliminated in preference to the desired radical on rearomatisation.

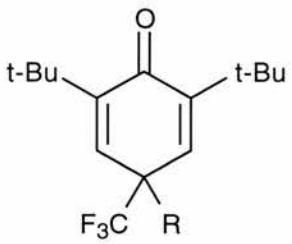


13

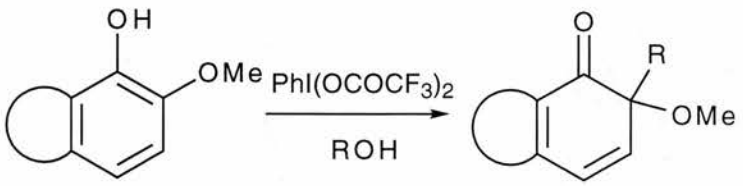
An attempted synthesis of 2,6-di-t-butyl-4-methyl-4-octylcyclohexa-2,5-dienone **12b**, by the method of Miller and Margulies,[8] yielded only starting material and an unidentified product [isolated in a very small yield (<1%)]. NMR spectra suggested this contained the desired carbonyl group (δ_C 186.0), and cyclohexadienyl protons (δ_H 6.55), but the aliphatic region contained only a peak due to the 18 protons from the t-butyl group.

This experiment was attempted using a longer alkyl chain than described in the literature,[8] which may explain the failure of the reaction.

Improved methods need to be found to synthesise the cyclohexadienones before they can be considered as viable precursors for the generation of radicals. The necessity of using 4-disubstituted products may lead to a second problem. While our method should be successful for the generation of allylic, benzylic, tertiary and secondary radicals, previous work with the cyclohexadienes indicates that for R = (primary alkyl) the alternative fragmentation, resulting in a methyl radical, could become competitive.



14



15

Scheme 7

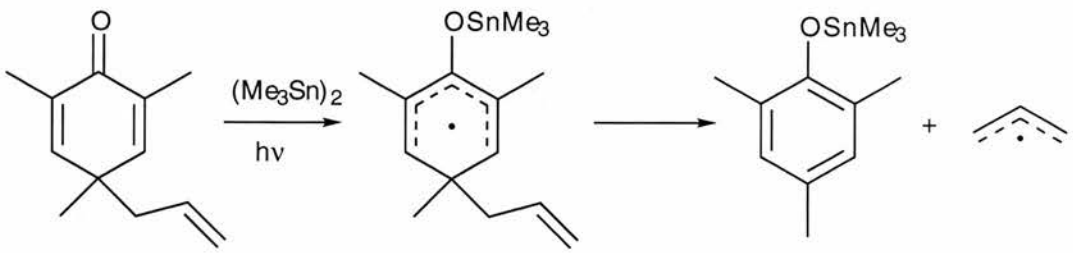
A method to circumvent this problem would be to use a precursor such as **14**. Loss of the trifluoromethyl radical would not be competitive. An alternative is to use the product of the reaction shown in Scheme 7. 2-Methoxyphenol (or 2-methoxynaphth-1-ol) can be selectively alkylated at the 2-position using phenyl iodonium triflate[12] and an enol ether,

which gives a product **15** that should be capable of yielding even primary radicals, as expulsion of MeO• will not be competitive.

3.2.2 Observation of radicals from cyclohexadienones by EPR spectroscopy.

The allyl and benzyl derivatives of mesitol, **10a,b** and **11a**, were used in EPR experiments to evaluate them as radical precursors by observing the corresponding radicals. Cossy generated ketyl radicals from ketones by irradiating them in triethylamine and acetonitrile, but this technique cannot be used in EPR experiments as acetonitrile is not a suitable solvent; a tuning signal can't be obtained due to the high dielectric constant.

No identifiable signals were observed from 4-allyl-2,4,6-trimethylcyclohexa-2,5-dien-1-one when the reaction was performed with triethylamine in t-butylbenzene, suggesting that acetonitrile plays a crucial role in the reaction. A second way of generating ketyl radicals was needed. Hexamethylditin was the reagent of choice, in t-butylbenzene solvent. Gratifyingly, the allyl radical [a(1H) = 4.20G, a(2H) = 13.87G, a(2H) = 14.81G @ 270K] could be observed from both 2-allyl-2,4,6-trimethylcyclohexa-3,5-dien-1-one and 4-allyl-2,4,6-trimethylcyclohexa-2,5-dien-1-one (Scheme 8), although the spectra weren't very strong (Figure).



Scheme 8

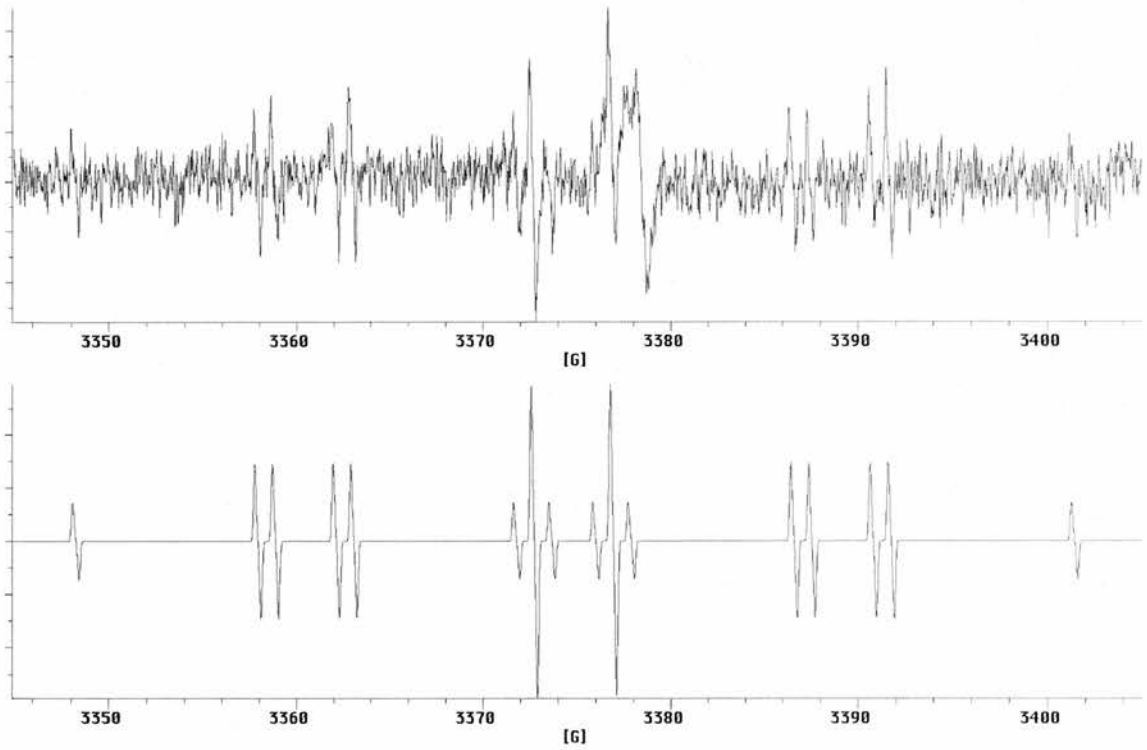
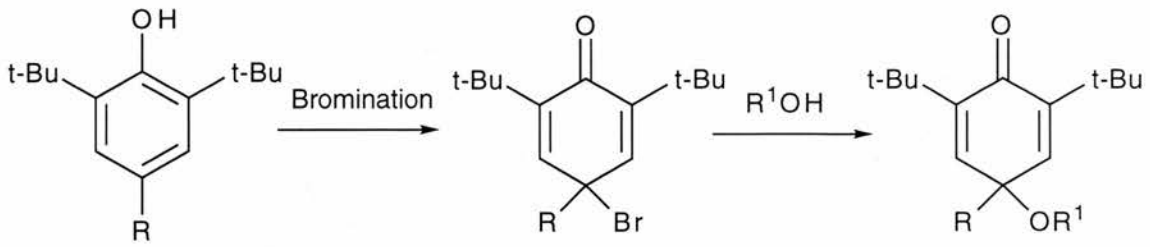


Figure. Spectrum (top) and simulation of allyl radical obtained from **10a** at 270 K.

The cyclohexadienyl radicals could not be observed. Ershov and co-workers managed to observe these cyclohexadienyl radicals when cyclohexadienones were treated with sodium metal.[13] It should be noted that their method of synthesising these compounds was very inefficient, and not worth pursuing as part of a synthetic plan.[14] However, their work referred, in passing, to a synthesis of 4-alkoxycyclohexadienones, via the 4-bromocyclohexadienone (Scheme 9).[14,15] The starting phenol, unfortunately, has to contain the radical leaving group R• from the outset.[16] We have already found a route to these compounds! Alkylation of a 2,6-dialkylphenol in the 4-position using methods previously devised gives products which will tautomerise to the alkylated phenols. It is likely, however, that quinones are more suitable precursors.[16] Other workers have also observed ketyl radicals or radical anions by EPR spectroscopy.[17]

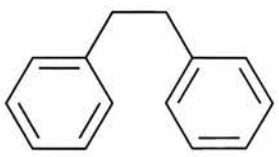


Scheme 9

Disappointingly, no radicals could be observed by EPR spectroscopy from **11b** or **10c**, but this may be due to the fact that we were unable to get these compounds absolutely pure, which is often necessary for EPR investigations.

3.2.3 Investigation of radicals from cyclohexadienones by product analysis

While **10a** and **11a** could not be used in product analysis reactions (the product - propene - is too volatile, and the allyl radical too thermodynamically stabilised to undergo intermolecular additions efficiently), benzyl and naphthyl derivatives **11b** and **10c** can be used. **11b** was mixed with triethylamine (10 eq) in acetonitrile and THF, degassed, and illuminated with 400 W UV light for 4 hours. Product analysis by GC/MS clearly showed the presence of toluene, as well as trimethylphenol and unreacted starting material. In the absence of THF in the mixture, dibenzyl (**16**), formed from the dimerisation of two benzyl radicals, was the major product owing to the lack of abstractable hydrogens in the reaction mixture. Reaction of **10c** failed to form identifiable products.



16

3.3 Conclusions and Future Work.

This chapter has presented our preliminary investigation of cyclohexadienone derivatives as radical precursors.

For the method to become an attractive general method for the generation of radicals, it has to be efficient and use readily available precursors. This means that the cyclohexadienone derivatives must be preparable in high yield. Unfortunately, in our hands, this has not been the case (with yields often <10%, sometimes <1%). The compounds that should be the easiest to prepare in terms of lack of steric hindrance, 2,6-dialkyl-4-monoalkylcyclohexa-2,5-dienones, tautomerised to the alkylated phenol, and other compounds often showed a reluctance to alkylate at all. However, Miller and Margulies reported acceptably high yields in their preparation of a limited range of suitable compounds.[8] If this method is applicable to a wide range of alkyl bromides, then the potential for these products to act as radical precursors increases dramatically. The method of Schmid *et al.* in which the products were derived from 2,4,6-trimethylphenol may be limited to 'activated' bromides, and would furnish products substituted at both the 2- and the 4- positions. This second problem would not be restrictive, though, as both isomers provide the desired radicals (at least in the allyl example that we studied). On the plus side, we have observed the desired allyl radicals using EPR spectroscopy in the only compounds we have managed to obtain in high purity so the compounds are indeed suitable for the production of allyl radicals. The EPR investigations used a tin compound to generate the ketyl radical, but product analysis studies showed that benzyl radicals were produced when the precursors were illuminated in triethylamine and acetonitrile, as hoped. The other product, trimethylphenol, was also observed.

The future work has already been alluded to, and involves a) improving yields or finding alternative successful methods for the synthesis of 2,4,6-trialkylcyclohexadienones, b) investigating the synthesis and use of alternatives to 2,4,6-trialkylcyclohexadienones, such as **15**, which has the added advantage that loss of a radical other than that which is desired is not competitive, c) investigating the different methods of generating ketyls in our system, and d) using the method in synthetic studies, once the previous aims have been completed.

3.4 Experimental

^{1}H NMR spectra were obtained using a Bruker AM 300 MHz spectrometer unless otherwise stated, in which case the spectrum was obtained using a Varian Gemini 200 MHz spectrometer. ^{13}C spectra were run at 75 MHz using the Bruker mentioned above. All samples were dissolved in deuteriochloroform unless otherwise stated, using tetramethylsilane as an internal standard. GC/MS work was carried out using a Finnegan Incos 50 quadrupole mass spectrometer coupled to a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase. Mass spectra were obtained with electron impact ionisation on a VG Autospec spectrometer by peak matching. EPR spectra were recorded with a Bruker EMX 10/12 spectrometer operating at 9.1 GHz. All EPR experiments were illuminated by UV light from a 500 W super pressure mercury lamp. In all cases where spectra were obtained, they were analysed to work out the hfs and a computer simulation was run to confirm the values.

Attemped preparation of 2,6-di-t-butyl-4-methyl-4-allylcyclohexa-2,5-dienone

To a solution of NaOH (1.6 g; 0.04 mol) in water (20 cm^3) was added 2,6-di-t-butyl-4-methylphenol (8.81 g; 0.044 mol). The mixture was stirred overnight, then warmed, but failed to dissolve. Allyl bromide (3.85 cm^3; 0.040 mol) was added and the mixture stirred overnight. Hexane (50 cm^3) was added, and the organic layer washed with 10% NaOH solution (7 × 50 cm^3). The organic layer was dried ($MgSO_4$), and concentrated, but yielded only starting material.

Attemped preparation of 2,6-di-t-butyl-4-allylcyclohexa-2,5-dienone

The above method was also attempted with 2,6-di-t-butylphenol, but this too failed to dissolve.

Attemped preparation of 2,6-di-t-butyl-4-hexadecylcyclohexa-2,5-dienone

Sodium hydride (0.46 g of a 60% dispersion in mineral oil; 11.5 mmol) was stirred in dry THF (30 cm^3) under nitrogen for 40 minutes, then cooled to 0°C. 2,6-Di-t-butylphenol (1.90 g; 9.22 mmol) in THF (5 cm^3) was added dropwise, the mixture refluxed for 10 hours, and then cooled. Water (20 cm^3) was added carefully, followed by ether (30 cm^3). The organic layer was washed with water, 10% sodium thiosulfate solution, and then again water, then dried ($MgSO_4$) and concentrated. The mixture was partially purified by column chromatography (PE/DCM) to give a mixture of iodohexadecane and a material which is probably 2,6-di-t-butyl-4-hexadecylphenol. There was no peak in the region δ5.5-6.5 on the NMR spectrum, which is where other cyclohexadienyl protons have appeared.

Attemped preparation of 4-benzyl-2,6-di-t-butylcyclohexa-2,5-dienone

A suspension of potassium hydride in oil (1.2 g; 6.0 mmol) was washed under nitrogen with pentane (3 × 15 cm^3). Dry THF (25 cm^3) was added, and the mixture stirred. A solution of 2,6-di-t-butylphenol (1.03 g; 5 mmol) in THF was added slowly over 30 minutes, and allowed to stir for a further hour. Benzyl bromide (0.86 g; 5 mmol) in THF was added, and the mixture was stirred for 4 hours under reflux. The mixture was cooled, and water was added, with extreme care, until reaction ceased. Ether (50 cm^3) was added, and the organic layer was separated and washed with water (3 × 50 cm^3), dried ($MgSO_4$), and concentrated, to give an oil which NMR indicated was mainly 4-benzyl-2,6-di-t-butylphenol. δ_H 1.42 (18H, s, $C(CH_3)_3$), 3.90 (2H, s, CH_2Ph), 5.08 (1H, s, OH), 6.98 (2H, s, ArH), 7.12-7.30 (5H, m, ArH).

Dodecyl *p*-toluenesulfonate

Dodecan-1-ol (1.86 g; 10 mmol) was stirred in dry DCM (10 cm^3) at 0°C. Pyridine (1.62 cm^3; 20 mmol) was added, followed by *p*-toluenesulfonyl chloride (2.85 g; 15 mmol), in small portions. After 3 hours ether (30 cm^3) and water (7 cm^3) were added, and the organic layer was washed with 2M HCl, 5% $NaHCO_3$ solution, and water, then dried ($MgSO_4$), and concentrated. Product was purified by column chromatography (PE/ether), to give product as white crystals (1.7 g; 47%) which were purified further by recrystallisation (PE/ethyl acetate). δ_H[18] (200 MHz) 0.85-0.91 (3H, m, CH_2CH_3)

1.15-1.40 (18H, m, 9 × CH_2), 1.55-1.70 (2H, m, OCH_2CH_2), 2.45 (3H, s, $ArCH_3$), 4.02 (2H, t, J = 6.6 Hz, OCH_2), 7.36 (2H, d, J = 8.2 Hz, ArH), 7.80 (2H, d, J = 8.4 Hz, ArH).

Attemped preparation of 2,6-di-t-butyl-4-dodecyl-4-methylcyclohexa-2,5-dienone, 2,6-di-t-butyl-4-benzyl-4-methylcyclohexa-2,5-dienone, and 2,6-di-t-butyl-4-cyclohexenyl-4-methylcyclohexa-2,5-dienone

A suspension of potassium hydride in oil (1.2 g; 6.0 mmol) was washed under nitrogen with pentane (3 × 15 cm^3). Dry THF (25 cm^3) was added, and the mixture stirred. A solution of 2,6-di-t-butyl-4-methylphenol (1.1 g; 5 mmol) in THF was added slowly over 30 minutes, and allowed to stir for a further hour. Dodecyl p-toluenesulfonate (1.70 g; 5 mmol) was added as a solution in THF, and the mixture refluxed for 4 hours. The mixture was cooled, and water was added, with extreme care, until reaction ceased. Ether (50 cm^3) was added, and the organic layer was washed with water (3 × 50 cm^3), dried ($MgSO_4$), and concentrated, yielding only starting material.

Reactions with benzyl bromide and 3-bromocyclohexene, instead of the tosylate, also yielded only starting materials.

4-Allyl-2,4,6-trimethylcyclohexa-2,5-dienone 10a, and 2-allyl-2,4,6-trimethylcyclohexa-3,5-dienone 11a.[6]

To a solution of NaOH (1.6 g; 0.04 mol) in water (20 cm^3) was added mesitol (5.45 g; 0.04 mol), and the mixture was stirred overnight. A further 0.2 g NaOH and 10 cm^3 H_2O was added to obtain complete solution. Allyl bromide (3.85 g; 0.044 mol) was added dropwise, and the mixture was stirred for 24 hours at room temperature. The mixture was extracted with pentane (3 × 50 cm^3), and washed with 10% sodium hydroxide solution (2 × 50 cm^3) and water (3 × 50 cm^3), then dried ($MgSO_4$), and concentrated. Purification by column chromatography (pentane/diethyl ether 9/1) yielded 4-allyl-2,4,6-trimethyl-cyclohexa-2,5-dienone (0.41 g; 11%) and 2-allyl-2,4,6-trimethyl-cyclohexa-3,5-dienone (0.24 g; 7%), both as colourless oils.

4-Allyl-2,4,6-trimethylcyclohexa-2,5-dienone: ν_{max}/cm^{-1} 1670 (C=O) 994 and 916 (-CH=CH_2). δ_H 1.19 (3H, s, CH_3 on C-4), 1.89 (6H, s, CH_3 on C-2,6), 2.27 (2H, d, J

= 7.4 Hz, allyl Hs), 4.98-5.03 (2H, m, $=CH_2$), 5.51-5.62 (1H, m, vinyl H), 6.66 (2H, s, vinyl Hs).

2-Allyl-2,4,6-trimethyl-cyclohexa-3,5-dienone: δ_H 1.12 (3H, s, CH_3), 1.84 (3H, s, CH_3), 1.90 (3H, s, CH_3), 2.11-2.59 (2H, m, allyl Hs), (4.85-5.02 (2H, m, $CH=CH_2$), 5.41-5.63 (1H, m, $CH=CH_2$), 5.85 (1H, s, =C*H*), 6.69 (1H, s, =C*H*).

2-Benzyl-2,4,6-trimethyl-cyclohexa-3,5-dienone 11b.

To a solution of NaOH (1.2 g; 0.03 mol) in water (20 cm^3) was added mesitol (4.08 g; 0.04 mol), and the mixture was stirred until a solution formed. Benzyl bromide (5.12 g; 0.03 mol) was added dropwise, and the mixture was heated to 60°C and stirred for 1 hour, then at 20-40°C for a further hour. The mixture was extracted with pentane (2×25 cm^3), and washed with 10% sodium hydroxide solution (2×20 cm^3) and water (4×20 cm^3), then dried ($MgSO_4$) and concentrated. Purification by column chromatography (pentane/diethyl ether 9/1 then a second column with petrol/DCM 9/1) yielded 2-benzyl-2,4,6-trimethylcyclohexa-3,5-dienone (0.30 g; 6%) as a pale yellow oil. δ_H 1.21 (3H, s, CH_3 at C-4), 1.76 (3H, s, CH_3), 1.82 (3H, s, CH_3), 2.70 (1H, d, J = 12.8 Hz, benzyl H), 3.08 (1H, d, J = 12.8 Hz, benzyl H), 5.87 (1H, s, =CH), 6.46 (1H, s, =CH), 6.99-7.01 (2H, m, ArH), 7.13-7.20 (3H, m, ArH). δ_C 15.3, 21.1, 24.8, 47.1, 126.3, 127.5, 129.7, 138.7, 142.4, 205.5. 4-Benzyl-2,4,6-trimethyl-cyclohexa-2,5-dienone was not isolated.

4-(2-Naphthylmethyl)-2,4,6-trimethylcyclohexa-2,5-dienone 10c.

Prepared from 2-(bromomethyl)naphthalene and mesitol as described above yielding, after column chromatography 4-(2-methylnaphthalene)-2,4,6-trimethyl-cyclohexa-2,5-dienone (0.10 g; 7%), and a lot of unreacted starting material. The product contained some 2-(bromomethyl)naphthalene as an impurity which was not removed by recrystallisation. δ_H ($CDCl_3$, 300 MHz) 2.15 (3H, s, CH_3), 2.19 (3H, s, CH_3), 2.24 (3H, s, CH_3), 4.18 (2H, s, CH_2), 6.90 (2H, s, =CH), 7.2-7.8 (7H, m, ArH). δ_C 12.2, 15.9, 19.7, 35.5, 127.8, 128.8, 129.7, 131.9, 133.6, 135.3, 137.5, 150.3. (Found M^+ 276.1512. $C_{20}H_{20}O$ requires *M* 276.1514)

Attemped preparation of 2-hexadecyl-4-t-butylcyclohexa-3,5-dienone

To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.0 g; 25 mmol) in dry THF (150 cm^3) under nitrogen, was added 4-t-butylphenol (3.00 g; 20 mmol). The mixture was stirred for 60 mins, then iodohexadecane (7.05 g; 20 mmol) in dry THF was added, and the mixture refluxed gently for 4 hours, then stirred overnight. Water was added, very carefully, followed by ether (100 cm^3). The organic layer was washed with water, 10% sodium thiosulfate solution, and water, then dried ($MgSO_4$), and concentrated. Product purified by column chromatography (PE/DCM) to give hexadecyl 2,4,6-trimethylphenyl ether as white crystals, which were further purified by recrystallisation (EtOAc/MeCN). The product was found to still contain iodohexadecane as an impurity. Hexadecyl 4-t-butylphenyl ether: δ_H 1.23-1.50 (38H, m), 1.71-1.82 (2H, m, OCH_2CH_2), 3.93 (2H, t, J = 6.6 Hz, OCH_2), 6.80-6.85 (2H, m, ArH), 7.25-7.31 (2H, m, ArH). δ_C 14.2, 22.8, 26.2, 29.4, 29.7, 29.8, 31.6, 32.0, 34.1, 68.1, 114.2, 126.4, 143.3, 157.2. (Found M^+ 374.3559. $C_{26}H_{46}O$ requires *M* 374.3549.)

Attemped preparation of 2,6-di-t-butyl-4-methyl-4-octylcyclohexa-2,5-dienone 12b.

To potassium t-butoxide (2.20 g; 20 mmol) in t-butanol (40 cm^3) was added 2,6-di-t-butyl-4-methylphenol (4.40 g; 20 mmol) and the mixture stirred for 30 minutes. 1-Iodooctane was added (7.92g; 33 mmol) and the mixture stirred in the dark for 6 days. Further potassium t-butoxide (1.1 g; 10 mmol) was added, followed 10 minutes later by 1-iodooctane (3.96 g; 16.5 mmol) and the mixture stirred for three days. This extra addition was repeated twice more, then the mixture was extracted with DCM (3×50 cm^3). The DCM layer was washed extensively with water, then dried ($MgSO_4$) and concentrated. Column chromatography on basic alumina (PE) gave a small amount of product, (~0.4 g) as well as large amounts of starting materials. The product, formed as a dark oil, was left open, and after several weeks started to crystallise, but failed to completely crystallise. The mixture was washed with hexane, to give pale yellow crystals which have not been

identified. δ_H 1.23 (18H, s, t-Bu), 1.44 (3H, s, CH_3), 1.82 (1H, s, Impurity), 6.58 (2H, s, =CH). δ_C 28.0, 29.4, 34.5, 67.4, 143.2, 145.4, 186.0.

2,6-Di-t-butyl-4-hexadecyl-4-methylcyclohexa-2,5-dienone

To 2,6-di-t-butyl-4-methylphenol (4.41g; 0.02 moles) in dry THF (30 cm^3) in a nitrogen atmosphere was added potassium t-butoxide, followed by further THF (20 cm^3). The mixture was stirred for 1 hour, (in which time the mixture went a peach colour), the iodohexadecane (7.05 g; 0.02 moles), and the mixture stirred for 24 hours, refluxed for 6 hours, then stirred for 5 days. Water (40 cm^3) and ether (40 cm^3) were added, and the organic layer separated, then washed with water, brine, and water again. The organic layer was dried ($MgSO_4$), then purified by column chromatography (PE/EtOAc). The fastest running spot was isolated (impure) and again purified by column chromatography (Pentane/Ether 9/1). A very small amount (0.07 g; 0.8 %) of 2,6-di-t-butyl-4-hexadecyl-4-methylcyclohexa-2,5-dienone was isolated as a yellow oil. δ_H 0.88 (3H, t, J = 6.6 Hz, CH_3). 1.12-1.28 (39H, m), 6.40 (2H, s, =CH) δ_C 14.1, 22.7, 24.7, 27.1, 29.1, 29.2, 29.4-29.7, 29.9, 30.3, 30.4, 31.9, 34.6, 40.0, 41.4, 146.3, 147.0, 186.7. (Found M^+ 444.4337. $C_{31}H_{56}O$ requires *M*, 444.4331.)

3.4.2 Preparation of samples for EPR spectroscopy.

Attempt to observe the allyl radical from 10a using triethylamine in t-butylbenzene.

4-Allyl-2,4,6-trimethylcyclohexa-2,5-dienone **10a** (~20 mg) and triethylamine (~100 mg) were added to t-butylbenzene in a quartz tube (diameter ~ 2 mm), and nitrogen bubbled through for 20 minutes.

Attempt to observe the radicals from 10a,c and 11a,b using hexamethylditin in t-butylbenzene.

In a typical example, **10a** (~20 mg) and hexamethylditin (~30 mg) were added to t-butylbenzene in a quartz tube (diameter ~ 2 mm), and nitrogen bubbled through for 20 minutes.

Investigation of radical reactions by product analysis.

2-Benzyl-2,4,6-trimethyl-cyclohexa-3,5-dienone, **11b**, (0.09 g), and triethylamine (0.1 g; 5 equiv) were dissolved in acetonitrile (1 cm^3). The mixture was degassed with nitrogen, and the mixture illuminated using a 400W mercury lamp for 4 hours. The reaction was analysed using GC/MS; peak no.125, toluene (trace); peak no. 294, 2,4,6-trimethylphenol, *m/z* (relative intensity) 136 (74), 135 (29), 121 (100), 91 (35), 77 (21), 41 (22), 39 (24), 28 (30); peak no. 410, dibenzyl, 182 (M^+) (10), 91 (100), 65 (18), 51 (6), 41 (8), 39 (9), 28 (6), 18 (24); peak nos. 449, 479, 498, 226 (M^+) (3), 136 (3), 92 (6), 91 (100), 79 (4), 77 (5), 65 (15), 51 (4), 41 (8), 39 (11), 18 (4). Spectrum also contained high-boiling unidentified components.

The above procedure was repeated, with mixture containing THF (0.5 cm^3);. peak no.121, toluene, 92 (M^+) (47), 91 (100), 86 (12), 84 (10), 65 (17), 51 (14), 49 (30), 41 (12), 39 (22); peak no. 361, 2,4,6-trimethylphenol; peak no 554, 226 (M^+) (3), 136 (4), 92 (8), 91 (100), 79 (3), 77 (5), 65 (11), 41 (6), 39 (8), 18 (8).

3.5 References

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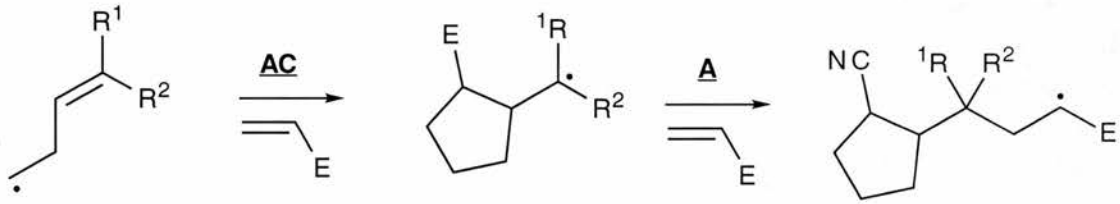
Chapter 4

Novel methods of performing radical annulations

4.1 Introduction

4.1.1 Radical Annulations

It was seen in chapter 1 that the radical annulation (**AC**) can be a powerful process, but that tin hydride is often unsuitable for performing such reactions. The lack of suitability of tin compounds in such reactions is due to butenyl radical **1** being very similar in character to alkyl radical **2**. A radical acceptor is unable to distinguish between the two, so oligomerisation to **3** occurs.



1 **2** **3**

Scheme 1

Radical annulation techniques were considered based on tin hydride, samarium(II) iodide, and manganese(III) chemistry.

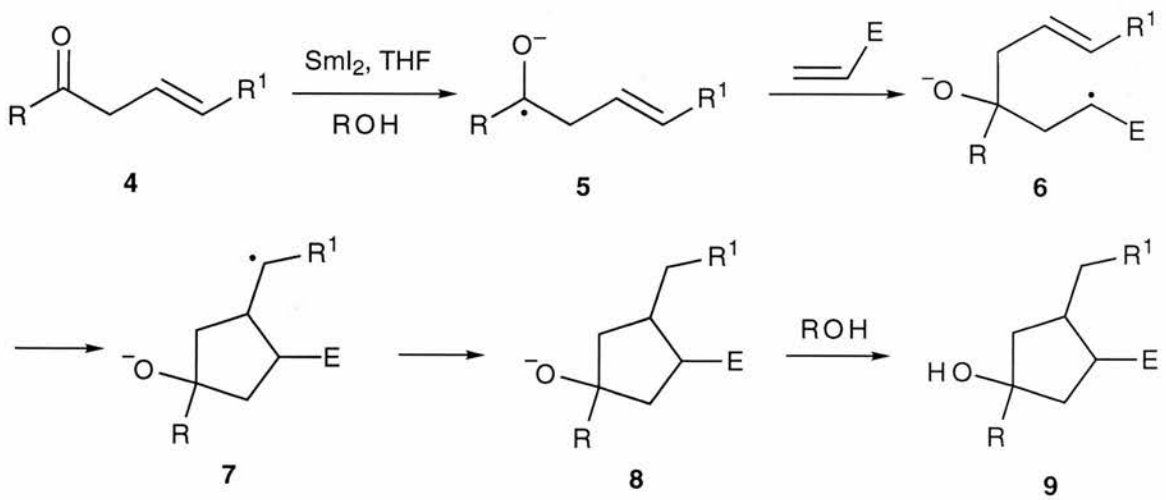
4.1.2 Samarium(II) iodide

Samarium(II) iodide has been shown to be a versatile reagent of remarkable power.[1,2] Molander noted that it 'stands alone in terms of its selectivity, efficiency, and ease of use.'[1] One of the main reasons that it shows such versatility as a reagent is that it can promote both one- and two- electron reduction processes. Under carefully controlled conditions these processes can be achieved in any order, and thus samarium(II) iodide shows even greater potency as a mediator of sequential reactions.[1,2]

A feature of samarium(II) iodide is its ability to generate both ketyl radical anions from a ketone or aldehyde and alkyl radicals from an alkyl halide. In the latter case, the ability of samarium(II) iodide to act as a two electron reductant can be unfavourable because radical reaction has to be rapid in order that reduction to an anion does not take place. One consequence of this is that intermolecular additions of alkyl radicals mediated by samarium(II) iodide are very rare.[3]

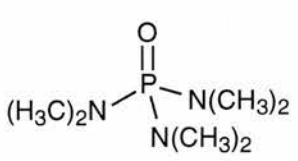
There are surprisingly few examples of tandem radical processes that use samarium(II) iodide to mediate the reaction. These were described in Chapter 1. In all these cases samarium(II) iodide is used to generate a ketyl radical. This low number of tandem processes can be explained in part by the ease of use of tin hydride in performing tandem reactions involving alkyl radicals, but why more sequential processes haven't been performed starting from ketyl radicals is a mystery.

Samarium(II) iodide appears to be an ideal reagent to mediate radical annulations. Ketyl radicals such as **5** are nucleophilic, and add readily to alkene acceptors containing electron-withdrawing groups. A large excess of acceptor is not required.[4] Alkenyl radical **6** should cyclise rapidly to cyclopentylmethyl radical **7** which, crucially, would be much less nucleophilic than the ketyl radical **5**. The reaction should result in the formation of **9**, but the mechanism shown in Scheme 2 may be simplified. Samarium(II) iodide can further reduce radical **7** forming a dianionic species, however the overall result is unchanged.



Scheme 2

Donor cosolvents such as HMPA (hexamethylphosphoramide), **11**, enhance the reducing power of samarium(II) iodide,[5] and are often necessary for successful reaction. DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone or *N*,*N*'-dimethylpropyleneurea), **12**, is another frequently used co-solvent, having been identified as a good, non-toxic alternative to HMPA.[6] Unfortunately, DMPU is not always as effective as HMPA.[7] A higher concentration (30 equivalents with respect to SmI_2) is required for DMPU to be fully effective, whereas with HMPA only 4 equivalents are required.[8]



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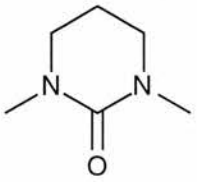

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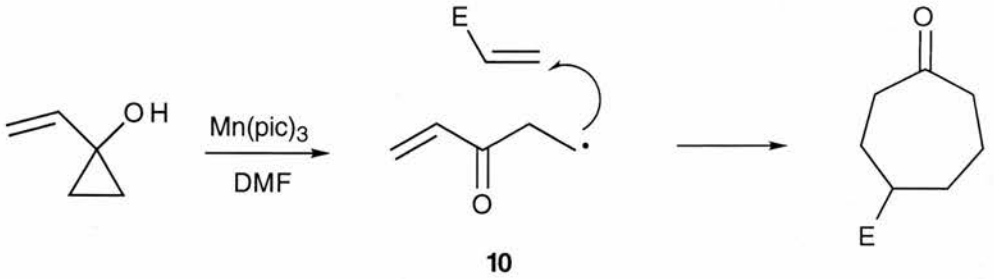
4.1.3 Manganese(III) mediated annulations

A number of manganese(III) acetate mediated annulations have been reported, and they are described in Chapter 1 and in more detail in Snider's review.[9] One approach to annulations that has not been previously described utilises the manganese(III) picolinate method of generating alkyl radicals from a cyclopropanol.[10] The theoretical annulation is shown in Scheme 2.



10

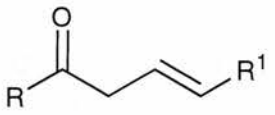
Scheme 3

This is likely to suffer from the same problem as the tin hydride mediated annulations, because radical **10** is an alkyl radical; oligomerisation is likely to take place.

4.2 Results and discussion

4.2.1 Samarium(II) iodide mediated annulations

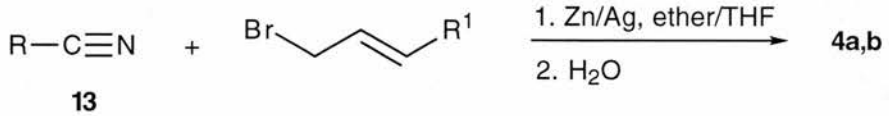
For the cyclisation step of a radical annulation to be as facile as possible, i. e. a 5-*exo* cyclisation, the radical precursor has to be an β,γ-unsaturated alkenone such as **4**.



4

a R = CH_3, R^1 = H
b R = n-Pr, R^1 = H
c R = CH_3, R^1 = Ph

The simplest suitable ketone is pent-4-en-2-one **4a**. The synthesis, described by Rousseau and Conia, proceeded via an organozinc intermediate which underwent addition to nitrile **13** (Scheme 4).[11] Hydrolysis yielded pent-4-en-2-one **4a**. Work-up proved to be problematic due to the volatility of product, the similar boiling points of starting materials and product and, most seriously, the instability of the product with respect to the α,β-unsaturated product 3-penten-2-one **14**. Repeated careful distillation gave **4a** in 39% yield. Unfortunately, isomerisation to **14** occurred readily, so **4a** had to be prepared immediately prior to performing annulation reactions.



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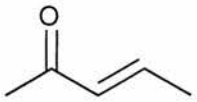
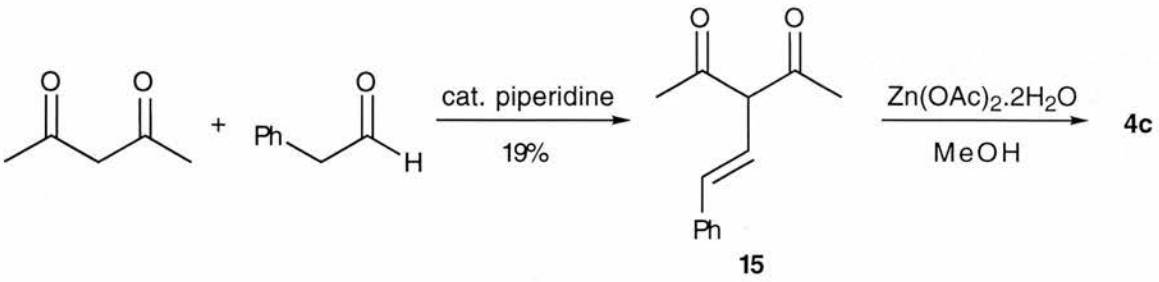
Scheme 4



14

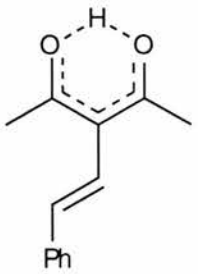
The closely related analogue **4b** was synthesised by the same technique, in the hope that purification would be easier. Distillation was again very difficult, but the higher boiling point of **4b** compared to **4a** meant that column chromatography could be performed. (With **4a** this was impossible because evaporation of the eluents would have led to loss of product.) Chromatography on silica had also previously been avoided because it was suspected that isomerisation on the column would take place. This was not the case, (helped by the fact that the product was the fast running in PE/DCM) and **4b** was isolated in 40% yield. It was disappointing to note that isomerisation to hept-2-en-4-one occurred on standing for 24 hours, again necessitating immediate use of **4b** upon preparation.

It was considered isomerisation may be prevented if R^1 was aromatic. There are a variety of high yielding syntheses of 5-phenylpent-4-en-2-one **4c** described in the literature, but a low yielding method was chosen on the grounds of simplicity, cost, and safety. The synthesis is shown in Scheme 5. A simple Knoevenagel condensation yielded 3-styryl-pentane-2,4-dione, **15**.[12] NMR data indicated that this existed as **16**; the ^{13}C NMR spectrum showed only that 9 equivalent carbon atoms were present and ^1H NMR revealed the presence of one set of alkyl protons.



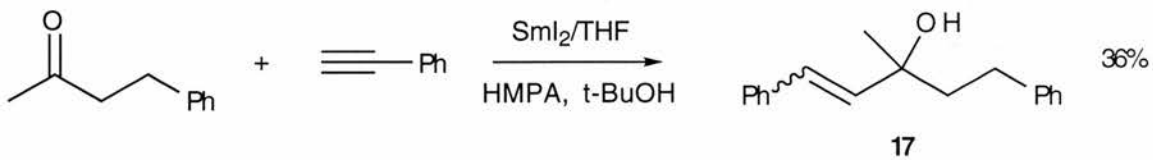
Scheme 5

Methanolysis of **15** in the presence of zinc acetate dihydrate gave the desired 5-phenylpent-4-en-2-one **4c** in 65% yield.[13] Gratifyingly, this proved to be stable, and could be kept on the bench indefinitely.



16

Samarium(II) iodide was used to promote an intermolecular coupling reaction prior to annulations being attempted (Scheme 6).[4] To a solution of samarium(II) iodide in THF (0.1M), phenylacetylene (3.mmol), t-butanol (5 mmol) and HMPA (5 cm^3) in a nitrogen atmosphere was added benzylacetone (2 mmol). The deep purple colour disappeared in a few seconds, and work up followed by column chromatography produced 1,5-diphenyl-3-methylpent-1-en-3-ol **17** in a disappointing 36% yield. Only the *E*-isomer was isolated in pure form, but the *Z*-isomer was obtained in impure form: *E/Z* ~ 80/20. Inanaga *et al.* obtained a yield of 91% for this reaction (*E/Z* = 80/20), but did not report the work-up.[4]



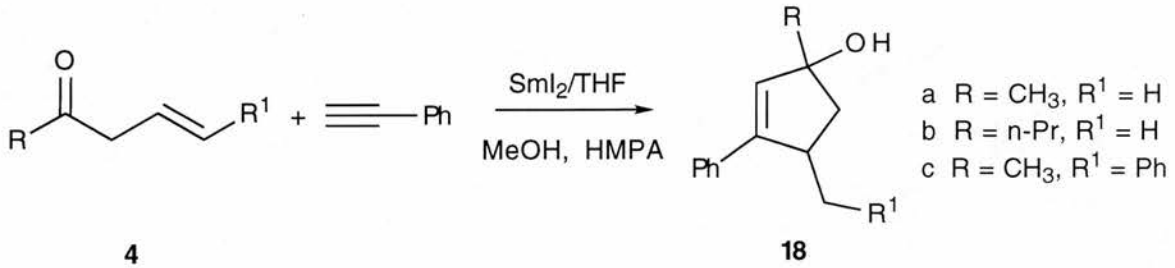
17

Scheme 6

The experiment was repeated using pent-4-en-2-one in a radical annulation reaction (Scheme 2). Isolation and purification of the product, and of all of the other annulation products synthesised in this study, was problematic. The small scale of the reaction was one factor, but a major difficulty was the almost identical R_F values of the product and starting material in whichever solvent system was used.

The annulation was believed to have been successful, although pure product could not be isolated. NMR spectroscopy indicated that the annulated product had been formed; there was a characteristic singlet at 5.95, corresponding to an uncoupled alkenyl proton. GC/MS

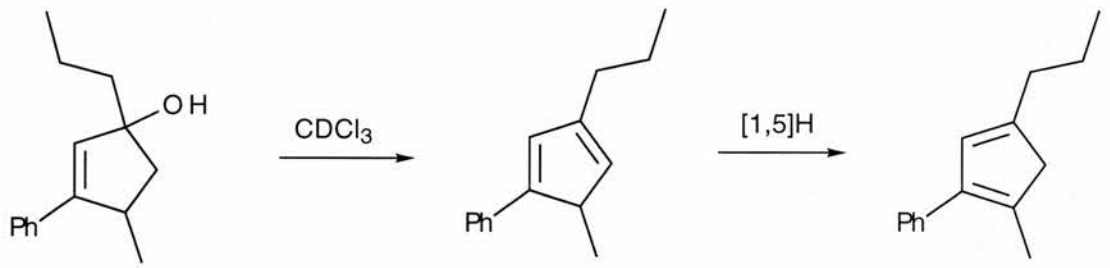
analysis also indicated that the product **18a** (or dehydrated product) had been formed. Unfortunately it proved impossible to isolate absolutely pure material, and assign the structure with certainty.



4 **18**

Scheme 7

The annulation shown in Scheme 7 was repeated using hept-1-en-4-one **4b**. Column chromatography yielded what was believed to be **18b**. Addition of this material to deuteriochloroform resulted in the formation of a cloudy emulsion due to the expulsion of water. NMR analysis of the (dried) material indicated that **18b** dehydrated with concomitant thermal rearrangement to give the thermodynamically more stable cyclopentadiene **20** (Scheme 8). Mass spectroscopy of the initial product (i.e. product that had not been added to deuteriochloroform) verified this, but indicated that some enol **18b** was present, even under the operating conditions of the mass spectrometer. The overall yield was a disappointing 27%. It is considered likely that an analogous process occurred from **18a**.

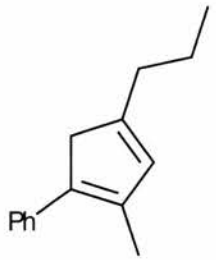


18b **19** **20**

Scheme 8

An alternative structure of the cyclopentadiene product, **21**, is also plausible based on the evidence available. Formation of this compound would require two consecutive [1,5]H

shifts, and there would appear to be no driving force for this reaction to take place. However, it is conceivable that the rearrangement reaction is reversible, so the possibility that **21** has been isolated cannot be ruled out.

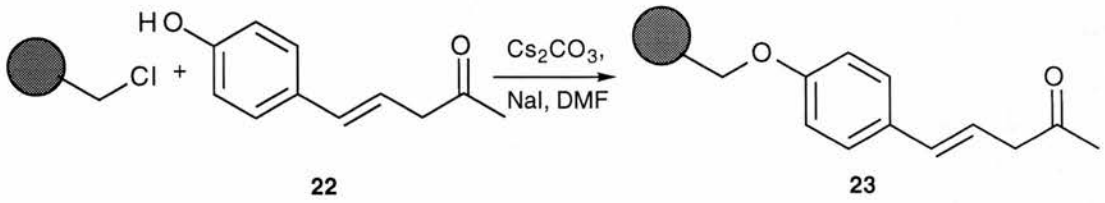


21

Use of the more stable precursor enone **4c** again led to annulated product which was not isolated successfully. Use of DMPU as a co-solvent in place of the highly toxic HMPA[6,7] greatly slowed the reaction. After 3 days of stirring, the reaction mixture was still deep blue. NMR analysis revealed that there was a substantial amount of starting material left in the mixture.

Use of HMPA as the co-solvent resulted in complete reaction in under a minute. Unfortunately, purification by repeated column chromatography was not successful, but GC/MS analysis indicated that the annulated product had been formed. Also present were starting materials (but no 1-phenylpent-1-en-4-one), and some unidentified products. It was suspected that loss of product was occurring during column chromatography. Cyclopentadienes can undergo Diels-Alder reactions with themselves, and it is possible that this was causing reduction of yield.

The technique is a completely novel way of performing radical annulations. It requires development before it can be considered to be a useful approach towards the synthesis of 5-membered rings. It is likely that the problems occur mainly in the purification step. One way of overcoming this problem would be to attach the enone to a solid support such as in Scheme 9. Removal of impurities could be effected by washing, and cleavage of the solid support would ensure isolation of product.



22 23

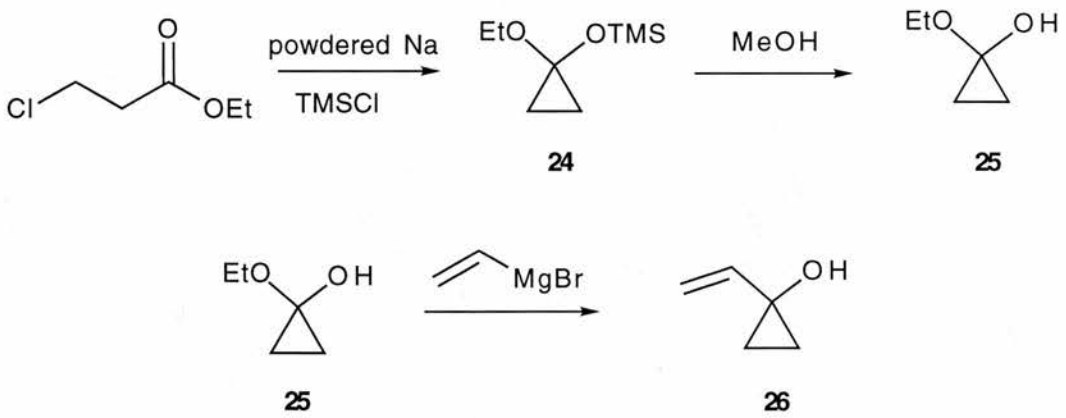
Scheme 9

4.2.2 Manganese(III) picolinate mediated annulations

The proposed annulation was shown in Scheme 3. Manganese(III) picolinate was prepared in good yield according to the method of Ray *et al.*[14] from manganese(III) acetylacetonate (Scheme 10).[15]

Scheme 10

The synthesis of 1-vinylcyclopropanol was problematic, and the product was only obtained in impure form according to the method described in Scheme 11.



Scheme 11

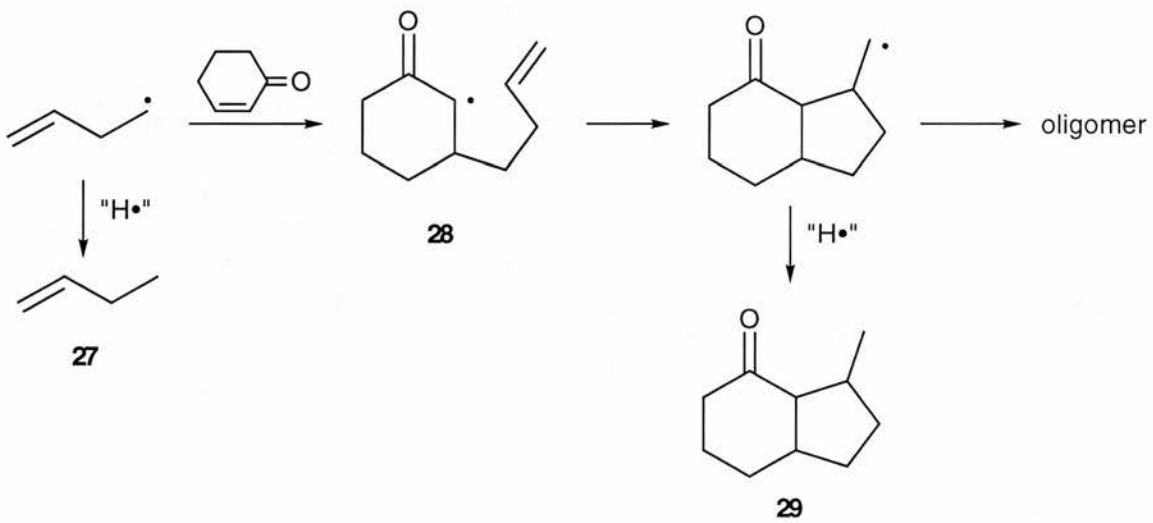
1-Ethoxy-1-trimethylsiloxycyclopropane **24** was prepared in good yield from 3-ethyl chloropropionate according to the method of Rühlmann, using powdered sodium.[16]

Methanolysis yielded 1-ethoxycyclopropanol,[17] but the final step of the reaction (conversion to 1-vinylcyclopropanol using vinylmagnesium bromide[18]) proceeded poorly in our hands, and only a tiny amount of impure 1-vinylcyclopropanol was isolated.

Owing to the poor yields, and the suspected inefficiency of the annulation reaction, this approach was discontinued.

4.2.3 Tin mediated annulations.

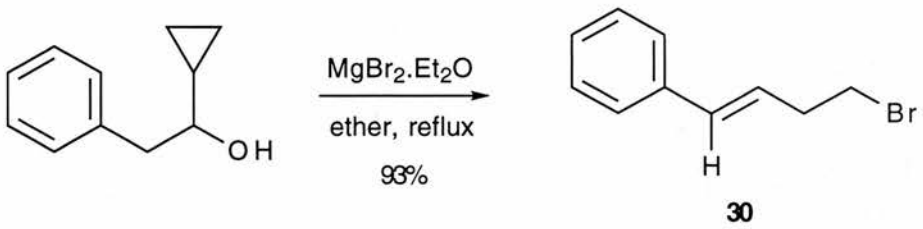
The difficulties associated with tin mediated annulations have already been described. A series of experiments was undertaken in which the 4-butenyl radical was generated from 4-bromobut-1-ene in the presence of only one equivalent of radical acceptor (Scheme 12) using tributyltin hydride or hexamethylditin.



Scheme 12

Not surprisingly, in the presence of tributyltin hydride (in benzene), the main product was but-1-ene, even when the tin hydride was added extremely slowly. When hexamethylditin was used in place of tributyltin hydride (with toluene as solvent) similar results were achieved, even though toluene is a much poorer hydrogen donor than tributyltin hydride. Trace quantities of annulated bicycle **29** were observed by GC/MS analysis. No oligomer was detected.

Use of 4-bromo-1-phenylbut-1-ene, **30**, which was prepared from α-cyclopropylbenzyl alcohol (Scheme 13),[19] failed to improve the conversion or yield.



30

Scheme 13

4.3 Conclusion

Tin compounds are not suitable mediators of simple annulations when only one equivalent of radical acceptor is used, due to the slow rate of intermolecular addition.

An investigation into annulations from β-carbonyl radicals generated from 1-vinylcyclopropanol using $Mn(pic)_3$ was abandoned due to perceived difficulties related to the above, and experimental difficulties in preparing the precursor.

Samarium(II) iodide is a suitable mediator of radical annulations, and three novel radical annulations were performed. The success is due to the difference in reactivity of the radicals involved in the reaction. The ketyl radicals generated are highly reactive, and intermolecular addition does not require a large excess of radical acceptor. Oligomerisation does not occur because the final alkyl radical is much less reactive.

When the product is a cyclopentenol, dehydration is likely and, in at least one example, a concomitant [1,5]H shift occurs, forming a more stable cyclopentadiene. The less than excellent yield is probably a consequence of difficulties encountered in purification, and may be overcome by attaching the enone to a resin.

HMPA was found to be a superior cosolvent to DMPU in the annulation reaction of 5-phenylpent-4-en-2-one with phenylacetylene.

4.4 Experimental

^{1}H NMR spectra were obtained using a Bruker AM 300 MHz spectrometer unless otherwise stated, in which case the spectrum was obtained using a Varian Gemini 200 MHz spectrometer. ^{13}C spectra were run at 75 MHz using the Bruker mentioned above. All samples were dissolved in deuteriochloroform, with tetramethylsilane as an internal standard. GC/MS analysis was carried out using a Finnigan Incos 50 quadrupole mass spectrometer interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase. Mass spectra were obtained with electron impact ionisation on a VG Autospec spectrometer by peak matching.

Materials were purchased from Aldrich, Avocado or Lancaster. THF and ether were distilled under nitrogen from sodium benzophenone ketyl prior to use. Petroleum ether (PE) refers to the fraction boiling between 40 and 60°C unless otherwise stated. Ether refers to diethyl ether. Samarium(II) iodide was purchased from Aldrich as a 0.1 M solution in THF. Acetylacetone (2,4-pentanedione) was distilled prior to use. Other organic compounds were used as received. Column chromatography was performed using BDH silica gel (40 - 63 mm).

Zinc-silver couple[13]

Zinc filings (83 g) were added to a refluxing solution of silver acetate (0.1 g) in glacial acetic acid (200 cm^3). The mixture was refluxed for a further 30 seconds, then cooled in an ice bath. The mixture was decanted, and the zinc-silver couple washed repeatedly with ether, until there was no acetic acid present.

A zinc-silver couple was also prepared from zinc dust, using an identical method.

Pent-4-en-2-one 4a[11]

Allyl bromide (32.4 g; 23.2 cm^3; 0.27 mol) was added, over a period of 2.5 hours, to a mixture of acetonitrile (8.2 g; 10.4 cm^3, 0.2 mol) and zinc-silver couple (filings: 18 g; ~0.27 mol) in THF (5 cm^3) and ether (45 cm^3). The mixture was stirred overnight, then poured into a mixture of ether (100 cm^3), saturated aqueous ammonium chloride solution (200 cm^3) and ice water (100 g). The mixture was stirred for 10 minutes, then the aqueous layer was separated and extracted with ether. The combined organic layers were dried ($MgSO_4$), then the solvents were removed by distillation at room temperature. Careful bulb to bulb distillation (105°C @ 760 mmHg) yielded pure pent-4-en-2-one as a colourless oil (6.59 g; 39%). δ_H (200 MHz) 2.17 (3H, s, CH_3), 3.29 (2H, d, J = 6.6 Hz, $C(O)CH_2$), 5.07-5.23 (2H, m, $=CH_2$), 5.80-6.08 (1H, m, CH=).

Hept-1-en-4-one 4b[11]

Allyl bromide (17.51 g; 12.25 cm^3; 0.146 mol) was added, over a period of 2.5 hours, to a mixture of butyronitrile (7.46 g; 0.108 mol) and zinc-silver couple (powder: 9.46 g) in ether (27 cm^3). The mixture was stirred overnight, then poured into a mixture of ether (100 cm^3), saturated aqueous ammonium chloride solution (200 cm^3) and ice water (100 g). The mixture was stirred for 10 minutes, then the aqueous layer was separated and extracted with ether (3 × 75 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated at room temperature. Column chromatography (PE→DCM, with contact time of product on silica kept as short as possible) yielded hept-1-en-4-one as a colourless oil (4.82 g; 40%). δ_H 0.92 (3H, t, J = 7.4 Hz, CH_3), 1.60 (2H, m, CH_2CH_3), 2.42 (2H, t, J = 7.4 Hz, CH_2CH_2CO), 3.16 (2H, d, J = 6.9 Hz, $COCH_2CH=$), 5.11-5.20 (2H, m, $=CH_2$), 5.86-5.98 (1H, m, $CH=CH_2$).

3-Styryl-pentane-2,4-dione 15[12,13]

Pentane-2,4-dione (10.01g; 0.1 mol), phenylacetaldehyde (1.20 g; 0.1 mol) and piperidine (0.1 g) were stirred for 24 hours. DCM (100 cm^3) was added, and the mixture washed with 5% HCl (50 cm^3) and water (50 cm^3), then dried ($MgSO_4$), and concentrated. Column chromatograpy (PE/EtOAc) yielded title compound (3.80 g; 19%). δ_H 1.73 (6H, s,

CH_3), 6.42 (1H, d, J = 16.2 Hz, CH=), 6.75 (1H, d, J = 16.2 Hz, CH=), 7.26-7.45 (5H, m, ArH). δ_C 24.3, 111.6, 123.0, 126.3, 127.9, 128.9, 134.5, 137.3, 191.5.

1-Phenylpent-1-en-4-one 4c[13]

3-Styryl-pentane-2,4-dione (0.80 g; 3.96 mmol) and zinc acetate dihydrate (0.02 g) were refluxed in methanol for 24 hours. Bulb to bulb distillation yielded 1-phenylpent-1-en-4-one **4c** (60°C @ 0.04 mmHg) as a pale yellow oil (0.41 g; 65%). δ_H 2.24 (3H, s, CH_3), 3.35 (2H, d, CH_2), 6.25-6.55 (2H, m, CH=CH), 7.18-7.45 (5H, m, ArH).

1,5-Diphenyl-3-methylpent-1-en-3-ol 17[4]

To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 41 cm^3; 4.1 mmol) followed by phenylacetylene (330 µl; 3 mmol), HMPA (5 cm^3), t-butanol (480 µl; 5 mmol), and benzylacetone (300 µl; 2 mmol). The mixture was decoloured, so more samarium(II) iodide solution was added (15 cm^3; 1.5 mmol), then the mixture was stirred for 20 minutes. 3% HCl was added (50 drops), followed by hexane (30 cm^3) and silica gel (10g). The mixture was filtered, and the filtrate allowed to stand. An inorganic solid precipitated, and the mixture was filtered again. HMPA was removed by bulb to bulb distillation under vacuum pressure, and the remaining material was purified by column chromatography (hexane/ether 1/1) to give *trans*-1,5-diphenyl-3-methylpent-1-en-3-ol (0.155 g; 28%) as pure material, and *cis*-1,5-diphenyl-3-methylpent-1-en-3-ol (0.035 g; 8 %) which contained a small amount of benzylacetone impurity. *trans*-1,5-Diphenyl-3-methylpent-1-en-3-ol: δ_H (200 MHz) 1.5 (3H, s, CH_3), 1.60 (1H, s, OH), 1.95 (2H, m, CH_2CH_2Ph), 2.7 (2H, m, $PhCH_2$), 6.33 (1H, d, J = 16.1 Hz, HC=), 6.65 (1H, d, J = 16.1 Hz, HC=) 7.2-7.5 (10H, m, ArH). δ_C 29.1, 31.1, 45.5, 73.8, 126.4, 127.1, 128.1, 128.9 (× 2), 129.0, 136.9, 137.5, 142.9. (Found M^+ 252.1505. $C_{18}H_{20}O$ requires *M*, 252.1514.) *cis*-1,5-Diphenyl-3-methylpent-1-en-3-ol: δ_H 1.42 (3H, s, CH_3), 1.63 (1H, bs, OH), 1.84-1.96 (2H, m, CH_2CH_2Ph), 2.80-2.95 (2H, m, CH_2Ph), 5.75 (1H, d, J = 12.7 Hz, HC=), 6.60 (1H, d, J = 12.8 Hz, HC=), 7.15-7.37 (10H, m, ArH). δ_C 30.2, 31.1, 46.0, 75.1, 126.2, 126.7, 127.6, 128.7, 128.8, 128.9, 129.0, 129.3, 137.9, 138.8, 143.0.

SmI_2 mediated annulation of 4-penten-2-one and phenylacetylene

To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 41 cm^3; 4.1 mmol) followed by phenylacetylene (330 µl; 3 mmol), HMPA (5 cm^3), t-butanol (480 µl; 5 mmol), and benzylacetone (300 µl; 2 mmol). The mixture was decoloured, so more samarium(II) iodide solution was added (15 cm^3; 1.5 mmol), then the mixture was stirred for 20 minutes. 3% HCl was added (50 drops), followed by hexane (30 cm^3) and silica gel (10g). The mixture was filtered, and the filtrate allowed to stand. An inorganic solid precipitated, and the mixture was filtered again. The mixture was partially purified by repeated column chromatography. δ_H 1.2 (3H, d, CH_3), 1.5 (3H, s, CH_3), 1.65 (bs, OH or H_2O), 2.45 (2H, m), 3.45 (1H, m), 5.97 (1H, s), 7.20-7.50 (5H, m, ArH) δ_C 21.1, 28.3, 37.1, 48.7, 127.2, 128.2, 129.3, 129.4, 149.7. The mixture was also analysed by GC/MS; peak no. 405, *m/z* (relative intensity) 170 (68), 155 (100), 128 (50), 115 (46), 91 (68), 77 (61), 51 (53), 39 (63).

SmI_2 mediated annulation of 1-hepten-4-one and phenylacetylene: synthesis of 1-methyl-2-phenyl-4-propylcyclopentadiene 20

To a flame dried 3-necked flask, purged with nitrogen, was added HMPA (5 cm^3), t-butanol (0.56 g; 7.5 mmol), phenylacetylene (0.51 g; 5 mmol), and 1-hepten-4-one (0.34 g; 3 mmol) followed by a solution of samarium(II) iodide in THF (0.1M; 60 cm^3; 6 mmol). The mixture was kept at –20°C overnight, then a saturated aqueous solution of ammonium chloride was added (50 cm^3). The mixture was separated, and the aqueous layer extracted with ether (5 × 30 cm^3). The combined organic extracts were washed with water (50 cm^3) and brine (50 cm^3), then dried ($MgSO_4$) and concentrated. The mixture was purified by column chromatography (Hexane/Ether 3/1). Addition of isolated product to deuteriochloroform resulted in the formation of water droplets. The solution was dried over molecular sieves to give 1-methyl-2-phenyl-4-propylcyclopentadiene (0.22 g; 27%) as an oil. δ_H 0.95 (3H, t, J = 7.3 Hz, CH_2CH_3), 1.59 (2H, m, CH_3CH_2), 2.11 (3H, s, CH_3), 2.35 (2H, t, J = 7.6 Hz, $CH_3CH_2CH_2$), 3.00 (2H, s, ring CH_2), 6.26 (1H, s, CH=), 7.21-7.39 (5H, m, ArH). δ_C 14.1 (CH_3), 14.7 (CH_3), 22.8 (CH_2), 32.9 (CH_2), 49.0 (CH_2), 126.2 (CH), 127.8 (CH), 128.2 (CH), 129.1 (CH), 135.4, 137.3, 139.2, 146.4 (all quaternary

carbons). The product that had not been added to deuteriochloroform was analysed by mass spectroscopy: *m/z* (relative intensity) 198 (M^+) (39), 183 (22), 173 (100), 169 (39), 155 (10), 141 (10), 129 (9), 128 (10) 115 (10), 91 (16). There was a very small peak (1%) present at *m/z* 216. (Found: M^+ 198.1401. $C_{15}H_{18}$ requires *M*, 198.1409.)

SmI_2 mediated annulation of 1-phenylpent-1-en-4-one and phenylacetylene

To a flame dried 3-necked flask, purged with nitrogen, was added a solution of samarium(II) iodide in THF (0.1M; 50 cm^3; 5.0 mmol) followed by phenylacetylene (330 µl; 3 mmol), DMPU (5 cm^3), t-butanol (480 µl; 5 mmol), and 1-phenylpent-1-en-4-one (0.32 g; 2 mmol). The mixture was stirred for 3 days under nitrogen, after which the mixture was still deep blue, then a saturated aqueous solution of sodium hydrogen carbonate was added (50 cm^3), and the mixture extracted with ether (3×30 cm^3), dried ($MgSO_4$) and concentrated. NMR and GC/MS analysis indicated that there was still a substantial amount of 1-phenylpent-1-en-4-one present. Repeated column chromatography (hexane/ether and hexane/ethyl acetate) failed to isolate pure annulated product, but GC/MS indicated that a product of the correct mass had been formed. *m/z* (Relative intensity) 246 (100), 160 (45), 155 (95), 145 (56), 117 (93), 115 (59), 91 (64), 43 (44). (Found: M^+ 246.1402. $C_{19}H_{18}$ requires *M*, 246.1409.)

The reaction was repeated as above using HMPA instead of DMPU as co-solvent. The reaction was complete in under a minute, and no 1-phenylpent-1-en-4-one was present in the reaction mixture. Again, pure product could not be isolated.

Manganese(III) acetylacetonate[15]

Powdered potassium permanganate (5.0 g; 31.7 mmol) was dissolved in the minimum amount of water, with gentle warming, and the solution was filtered. Acetylacetone (22.0 g; 220 mmol) was added to the solution with vigorous stirring. The mixture was stirred at 80°C for 5 minutes, then allowed to cool. Dark brown crystals of $Mn(acac)_3$ (9.4 g; 82%) were filtered off, and washed several times with acetylacetone-water (1:1), then dried *in vacuo,* m.p. 155 °C (decomp.) [lit.[15] 155°C (decomp.)].

Manganese(III) pyridinecarboxylate[14]

A solution of 2-picolinic acid (1.24 g; 10 mmol) in dry ethanol (50 cm^3) was added to manganese(III) acetylacetonate (3.6 g; 10 mmol) in ethanol (120 cm^3). A very fine bronze powder precipitated. This was filtered, washed with dry ethanol, and kept under vacuum over $CaCl_2$. A further solution of picolinic acid (3.7 g; 30 mmol) in ethanol (50 cm^3) was added to the mother liquor. Manganese(III) pyridinecarboxylate precipitated as a red solid, (3.38 g; 80 %) which was filtered, washed with ethanol, and stored in a vacuum over $CaCl_2$.

1-Ethoxy-1-trimethylsiloxycyclopropane 24[16]

Powdered sodium was prepared by carefully heating sodium (7.5 g; 0.33 mol) in xylene until it melted, then shaking vigorously. The powdered sodium was decanted, and washed with ether.

3-Ethyl chloropropionate (20.4 cm^3; 0.15 mol) was added dropwise to a stirred mixture of powdered sodium (7.5 g; 0.33 mol) and trimethylsilyl chloride (22.5 cm^3; 0.18 mol) in ether (60 cm^3) under nitrogen at such a rate that gentle reflux was maintained. The mixture was stirred overnight, then the mixture was filtered and concentrated to yield pure 1-ethoxy-1-trimethylsiloxycyclopropane as an oil (17.9 g; 69%). δ_H (200 MHz) 0.18 (9H, s, $Si(CH_3)_3$), 0.85 (4H, m, cyclopropyl Hs), 1.2 (3H, t, J = 7.4 Hz), 3.67 (2H, t, J = 7.0 Hz, CH_3).

1-Ethoxycyclopropanol 25[17]

1-Ethoxy-1-trimethylsiloxycyclopropane (17.9 g; 0.11 moles) was stirred in methanol (225 cm^3) for 10 hours, and the product purified by bulb to bulb distillation to give 1-ethoxypropanol, b.p. 37°C @ 3 mmHg (lit.[17] b.p. 59°C @ 17 mmHg), as a colourless oil (2.20 g; 20%). δ_H^{20} 0.94 (4H, m, cyclopropyl Hs), 1.22 (3H, J = 7.2 Hz, CH_3), 3.76 (2H, t, J = 7.2 Hz, CH_2CH_3).

1-Vinylcyclopropanol 26[20]

1-Ethoxycyclopropanol (0.80 g; 7.8 mmol) in THF (5 cm^3) was added dropwise over 40 minutes to a refluxing solution of 1M vinylmagnesium bromide in THF (25 cm^3; 25 mmol) under nitrogen. The mixture was stirred under reflux for a further 30 minutes, then poured into a saturated aqueous ammonium chloride solution (25 cm^3). The aqueous layer

was separated and extracted with ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated to give a very small quantity of impure material. This material was not further purified.

4-Bromo-1-phenylbut-1-ene 30[19]

A solution of α-cyclopropylbenzyl alcohol (3.6 g; 0.24 moles) in ether (10 cm^3) was added to a stirred solution of magnesium bromide etherate (8.5 g; 0.33 mol) in ether (240 cm^3) under an atmosphere of nitrogen. The mixture was refluxed for 2.5 hours, then stirred overnight. The mixture was washed with water (2 × 100 cm^3) and brine (1 × 100 cm^3), then dried ($MgSO_4$) and concentrated. Bulb to bulb distillation yielded 4-bromo-1-phenylbut-1-ene (4.71 g; 93%) as a colourless oil, b.p. 155°C @ 12 mmHg. δ_H (200 MHz) 2.80 (2H, q, J = 7.0 Hz, CHCH_2), 3.48 (2H, t, J = 7.0 Hz, CH_2Br), 6.1-6.3 (1H, m, CHCH_2), 6.50 (1H, d, J = 15.8 Hz, PhCH), 7.2-7.45 (5H, m, ArH)

Typical tin mediated annulation of 3-cyclohexenone and 4-bromobut-1-ene

To 3-cyclohexenone (0.07 g; 0.74 mmol) and 4-bromobut-1-ene (0.10 g; 0.74 mmol) in benzene (0.5 – 20 cm^3) was added tributyltin hydride (1.1 – 1.2 equiv) (and AIBN where necessary) in benzene (0.5 cm^3) over a period of 8 hours. In some reactions the mixture was irradiated using a 125 W medium pressure mercury lamp. The reaction was cooled and analysed by GC/MS.

To 3-cyclohexenone (0.07 g; 0.74 mmol) and 4-bromobut-1-ene (0.10 g; 0.74 mmol) in toluene was added hexamethylditin (0.6 – 1.2 equiv) over a period of time, (8 hours – 72 hours) during which the mixture was photolysed using a 125 W medium pressure mercury lamp. The reaction was cooled and analysed by GC/MS.

GC/MS of all reactions performed as described above gave; peak no. 99, but-1-ene *m/z* (relative intensity) 56 (M^+) (23), 41 (100), 39 (64), 37 (8), 29 (15), 28 (32), 27 (48), 26 (22); peak no. 326 $C_{10}H_{16}O$, 152 (M^+) (18), 137 (36), 110 (43), 97 (49), 81 (100), 67 (40), 41 (78), 39 (80), 27 (63); peak no. 336 $C_{10}H_{16}O$, 152 (M^+) (16), 97 (100), 81 (68), 67 (70), 55 (48), 41 (69), 39 (75) 27 (64). Unreacted starting materials, and tin containing compounds were also present.

Tin mediated annulation of 3-cyclohexenone and 4-bromo-1-phenylbut-1-ene

The annulation reaction was performed as described above, and analysed using GC/MS. peak no. 281, 1-phenylbut-1-ene *m/z* (relative intensity) 132 (M^+) (33), 117 (100), 115 (59), 91 (52), 77 (20), 65 (22), 51 (30), 39 (41); peak no. 553 $C_{10}H_{16}O$, 228 (M^+) (9), 131 (36), 123 (54), 110 (100), 97 (55), 91 (84), 55 (39), 41 (64), peak no. 565 $C_{10}H_{16}O$, 228 (M^+) (9), 123 (59), 110 (100), 97 (83), 91 (79), 65 (38), 55 (39), 41 (64), 39 (38). Unreacted starting materials, and tin containing compounds were also present.

4.5 References

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Chapter 5

Investigation of alkylboronic ester radicals

5

5.1 Introduction

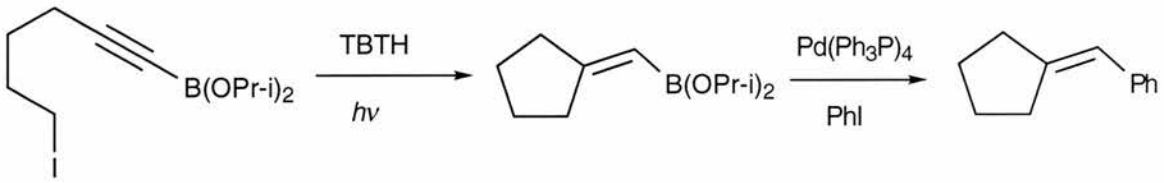
5.1.1 EPR spectroscopy and radical characterisation.

EPR spectroscopy is a well established technique for investigating species containing one or more unpaired electrons.[1] One of the major uses is in the observation of organic radicals, and a review of the use of EPR spectroscopy of organic species has appeared, covering all the main aspects.[2] EPR spectroscopy can provide information about both the nature and structure of the radical. It detects unpaired electrons in a sample by their absorption of energy from microwave irradiation when the sample is placed in a strong magnetic field. The spin of the electron can interact with the spin of nearby nuclei, giving a characteristic hyperfine structure. The important parameters are the g-factor, which is a measure of the local field experienced by the electron, hyperfine structure, which arises from the interaction of electron spins with nearby nuclear spins, and intensity, because the number of unpaired spins is proportional to the area under the signal, although it is the first derivative of the signal that is usually obtained.

5.1.2 Boronic esters

Boronic esters have been developed into highly useful synthetic intermediates in organic reactions. They can be converted to a variety of functional groups and have found much use in aromatic coupling processes.[3] A review discussing the range of functional groups compatible with boronic ester chemistry has recently been published,[4] but prior to our work

commencing there had only been a few reports of radical reactions of compounds containing the boronic ester moiety. Carboni,[5] Batey,[6,7] and Takai[8] have demonstrated the synthetic utility of alkenylboranes in inter- and intramolecular radical reactions. A simple example of Carboni's work illustrates the potential of the system (Scheme 1).



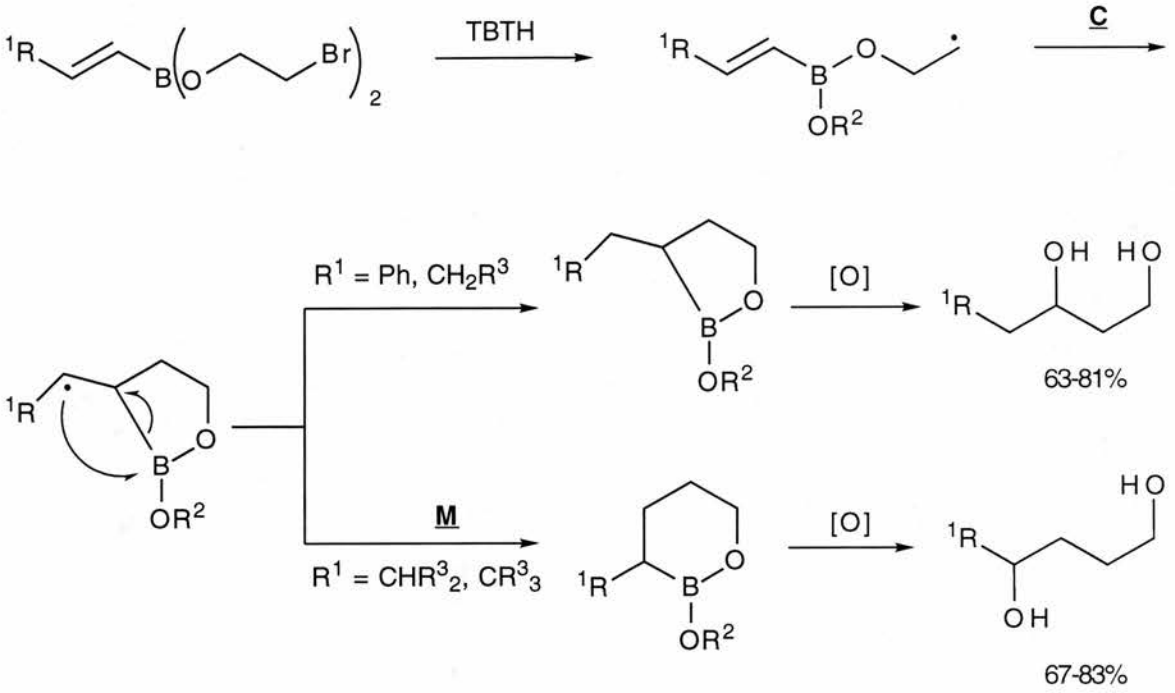
Scheme 1

α-Haloboronic esters have found extensive use in organic synthesis, facilitated by the ease of synthesis of stereochemically pure material. A large proportion of the work has investigated S_N2 reactions of these reagents, i.e. in anionic rather than radical reactions.[9] The literature that does exist on boronic ester radicals is mostly concerned with α-boronic ester radicals. Batey generated these radicals, which were found to be ambiphilic, from α-haloboronic esters[6] whereas Carboni generated them mainly by addition to a double bond.[5] Takai employed chromium(II) chloride to form α-boronic ester radicals from the corresponding α-chloroborate.

The radical and ionic methods could prove to be extremely compatible with each other, as a chloromethylene group can be 'inserted' stereoselectively between the alkyl functionality and the boronic ester after a radical reaction has been performed.[9]

Carboni described reactions involving β-boryl radicals,[5] and Batey has recently performed cyclistions using the C-B-O linkage of a boronic ester group as a tether in which β-boryl radicals were generated by cyclisation onto an alkene (Scheme 2). In some cases, unexpected products due to a radical rearrangement (**CM**) were formed.

Overall, there are fewer examples of β-boronic ester radicals than α-boronic ester radicals in the literature.



Scheme 2

We have undertaken an extensive EPR study of radical intermediates which contain the boronic ester functionality. These radicals have been characterised, kinetic and thermodynamic data have been ascertained, and the efficacy of different boronic ester radicals as synthetic intermediates has been considered.

The investigation has encompassed bromoalkylboronic esters, alkylboronic esters and vinylboronic esters as radical precursors, enabling analysis of a wide range of boronic ester radicals.

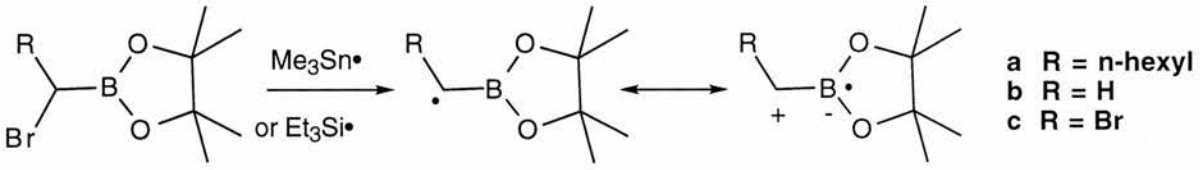
5.2 Results and discussion

5.2.1 Characterisation of α-boryl radicals generated by abstraction of bromine from α-bromoalkylboronic esters.

Radicals **2a**,**b** were generated by bromine abstraction from **1** with trimethylstannyl radicals in t-butylbenzene solution (Scheme 3) and their EPR parameters are shown in Table 1. Spectra obtained in this study were generally of sufficient quality for ^{10}B hfs to be resolved. In the absence of an isotope effect, the ^{10}B hfs should equal $\underline{a}(^{11}B)$ multiplied by the ratio of the magnetic moments (μ) and corrected to allow for their different spin multiplicities (**S**) (eq. 1), and our results verified this relationship. Figure 1 shows the spectrum and simulation[10] for the radical **2a**, in which a splitting due to γ-hydrogens was visible. The peaks from the radical containing ^{10}B can clearly be seen, and are indicated on the left hand side of the spectrum by arrows. No spectra were obtained for radical **2c**.

$$\underline{a}(^{10}B) = \underline{a}(^{11}B) \times [\mu(^{10}B) \times \mathbf{S}(^{10}B)/\mu(^{11}B) \times \mathbf{S}(^{11}B)] \qquad \text{eq. 1}$$

$$= \underline{a}(^{11}B) \times [(1.80 \times 1.5)/(2.69 \times 3)]$$



1 **2** **3**

Scheme 3

Table 1. Hfs of symmetric α-boryl radicals derived by bromine abstraction from α-bromoboronic esters.

Radical	T/K	$\underline{a}(^{11}B)$/G	$\underline{a}(H_\alpha)$/G	$\underline{a}(H_\beta)$/G	$\underline{a}(H_\gamma)$/G	$\underline{a}(^{10}B)$/G
2a	220[a]	12.0	20.0	23.5	0.5	4.0
2b	220[a]	12.3	20.9	N/A	N/A	4.1

[a] t-BuPh solvent

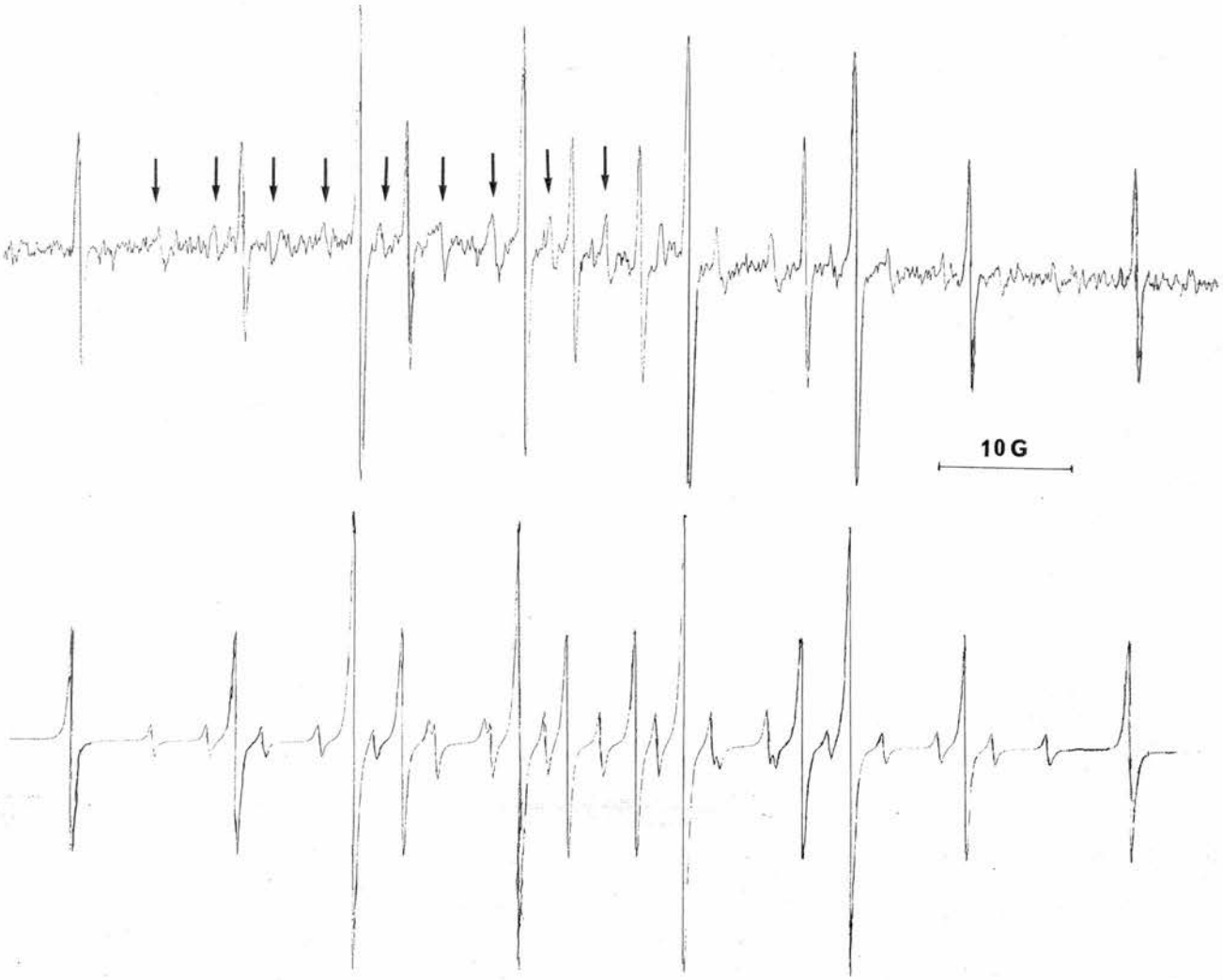


Figure 1. Spectrum (top) and simulation of radical **2a** (from **1a**) at 220 K

Unknown g-factors can be ascertained by comparison of the spectrum centre point with that of a radical of known g-factor as described previously (Chapter 2; Eq. 1). The g-factor of radical **2b** was determined, using TEMPONE (g=2.0060) as standard, as 2.0028 (normal for carbon centred radicals).

By altering the intensity of the light using calibrated gauzes these radicals were found to decay by a mixture of first and second order processes, in a similar way to normal substituted methyl radicals. (Using the steady state equations we can deduce that [Radical] = $(\Phi I_a/2k_t)^{0.5}$ for bimolecular decay, where Φ = quantum yield, I_a is the intensity of the absorbed light and $2k_t$ is the rate constant for the bimolecular termination step.[11] Thus log [Radical] = 0.5 log I_a - 0.5 log k_t + c. If termination is purely a bimolecular process, the gradient of the graph from Table 2 should have gradient = 0.5, and deviation from this value indicates the extent to which other processes are occurring.) The results were

collected at two different gains, and are shown in table 2. In each experiment results were recorded using both increasing and decreasing intensity - the average of which is listed - to compensate for sample depletion.

Delocalisation of the unpaired electron into the vacant p-orbital on the adjacent B atom may occur in α-boryl radicals. The hyperfine splitting (hfs) a, is directly proportional to the unpaired spin density at the nucleus, $\Psi^2(0)$,[2] and the observed α-H hfs (Table 3) are smaller than in 'normal' alkyl radicals (usually ~22G) suggesting that some delocalisation does occur.

Table 2. Decay of radical **2b**.

Fraction of light transmitted	Mean peak ht/mm Gain = 2 x 10^5	Mean peak ht./mm Gain = 3.2 x 10^5
1	53.5	74.5
0.65	43	55
0.45	31	39
0.32	26	34.5

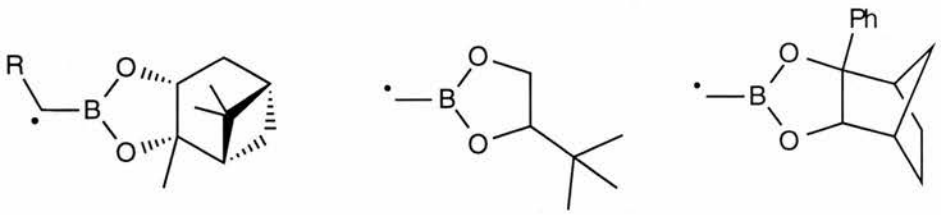
The graph of log (Intensity) vs. log (average peak height) gave straight lines. The gradients were 0.657 (gain = 2 x 10^5) and 0.704 (gain = 3.2 x 10^5) leading to the above conclusion.

The addition, via a radical process, of CCl_4 to CH_2=CH-B$(OBu)_2$ has been shown to occur with small chain transfer constants, leading to the conclusion that delocalisation and hence stabilisation of the intermediate radical by the boronic ester group was substantial.[12] However, in an apparent contradiction of these results, the H-abstraction by Cl• atoms from the CH_3B group of $CH_3B(OBu\text{-}t)_2$ was favoured only by a factor of 1.1-1.5 over attack on the C-methyl groups.[13,14]

The stabilisation energy of the H_2BCH_2• radical was computed to be 11 kcal mol^{-1} by Pasto *et al.*[15] and 9.7 kcal mol^{-1} by Coolidge *et al.*[16] These figures indicate a very large stabilising effect of an adjacent boron in boranes, but introduction of oxygen on the boron (i.e. in the boronic ester system) is expected to decrease the stabilisation by both mesomeric

and inductive effects. The relative reactivities towards free radical bromination were found to decrease in the order: boranes > borinates > boronates.[15] If **3** does make a substantial contribution to the structure of the boronic ester radical, then there should be an appreciable barrier to rotation about the B-C bond. The symmetry of radical **2b** means that the α-Hs will always be equivalent, but in radicals **5b**, **6** and **7** this is not the case, and it is possible to investigate the barrier to rotation.

When the rotation is slowed, the two α-hydrogens will be non-equivalent on the EPR timescale. Unsymmetric radicals **5**,**6** and **7**, generated from the corresponding bromides, were all investigated at low temperatures using EPR spectroscopy (Table 3).



5 a R = n-hexyl
b R = H

6

7

Table 3. Hfs of unsymmetric α-boryl radicals derived by bromine abstraction from α-bromoboronic esters.

Radical	T/K	a(^{11}B)/G	a(H_α)/G	a(H_β)/G	a(H_δ)/G	a(^{10}B)/G
5a	220[a]	12.2	19.0	23.6	*	4.1
5b	145[b]	12.4	21.1		1.1	4.2
6	165[c]	12.3	21.1		1.04	
7	170[c]	12.2	20.9		1.1	4.0

[a]t-BuPh solvent. [b]Cyclopropane solvent. [c]n-Propane solvent. *Not observed.

The spectrum of **5b** showed selective line broadening due to restricted rotation about the C-B bond at temperatures lower than 150K. The C_α-B torsion barrier is thus greater than the analogous C_α-C_β barrier in alkyl radicals like $^\bullet CH_2CH_3$ which show no exchange broadening.[17,18]

Even at the lowest attainable temperatures (~90 K), values for the hfs of the non equivalent Hs could not be obtained, partly due to indiscriminate line broadening below

115K, but computer simulations of the exchange broadened regions enabled good estimates for the rate of exchange k_e to be obtained. Computer simulation also indicated that $\delta\underline{a} = 0.6$ G, where $\delta\underline{a}$ is the difference in the hfs of the non-equivalent hydrogens. The coalescence temperature was 100±10K. The spectra at various different temperatures, and the simulations, are shown in Figure 2.

An Arrhenius plot (Figure 3) of k_e at various temperatures gave log $(A_e/s^{-1}) = 11.9$, $E_e = 2.9 \pm 0.7$ kcal mol^{-1}. (E_e was corrected from value for gradient shown in Figure 3). Radicals **6** and **7** gave similar values, and again the splittings of the non equivalent hydrogens could not be determined in temperature range employed. The spectra obtained from radicals **6** and **7** are shown in Figure 4. The results give lie to the suggestion that a radical is stabilised to a significant level by an α-boronic ester. The barrier to rotation is only about the same as the barrier to rotation in an ethane molecule (2.9 kcal mol^{-1}),[19] and substantially less then the value calculated for the H_2BCH_2• radical.[15,16]

Arrhenius plot for rotation of C-B bond in 5b

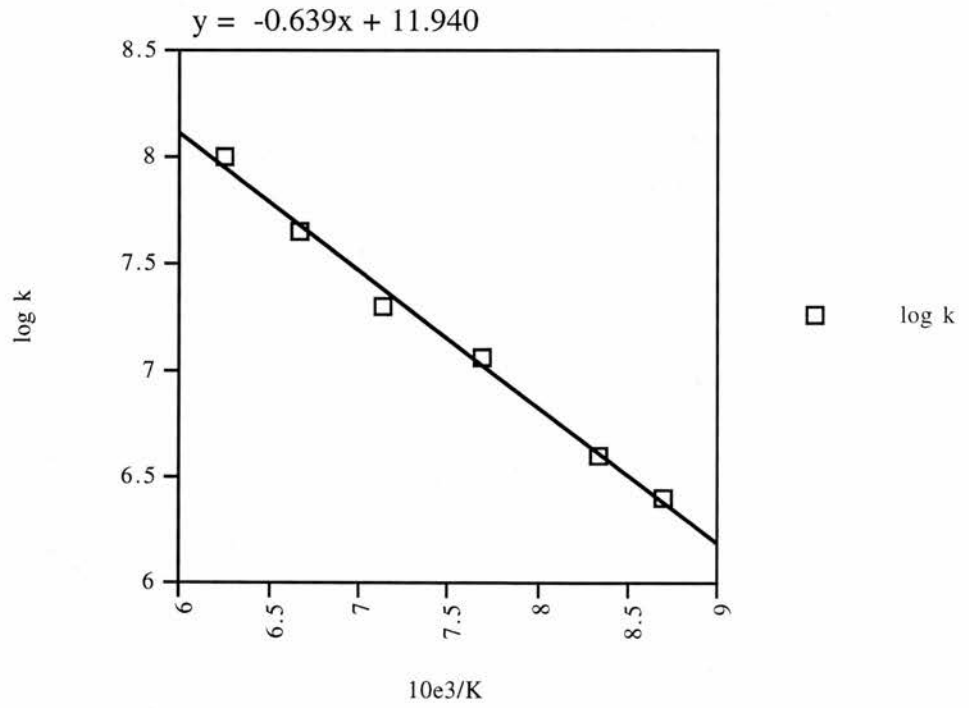
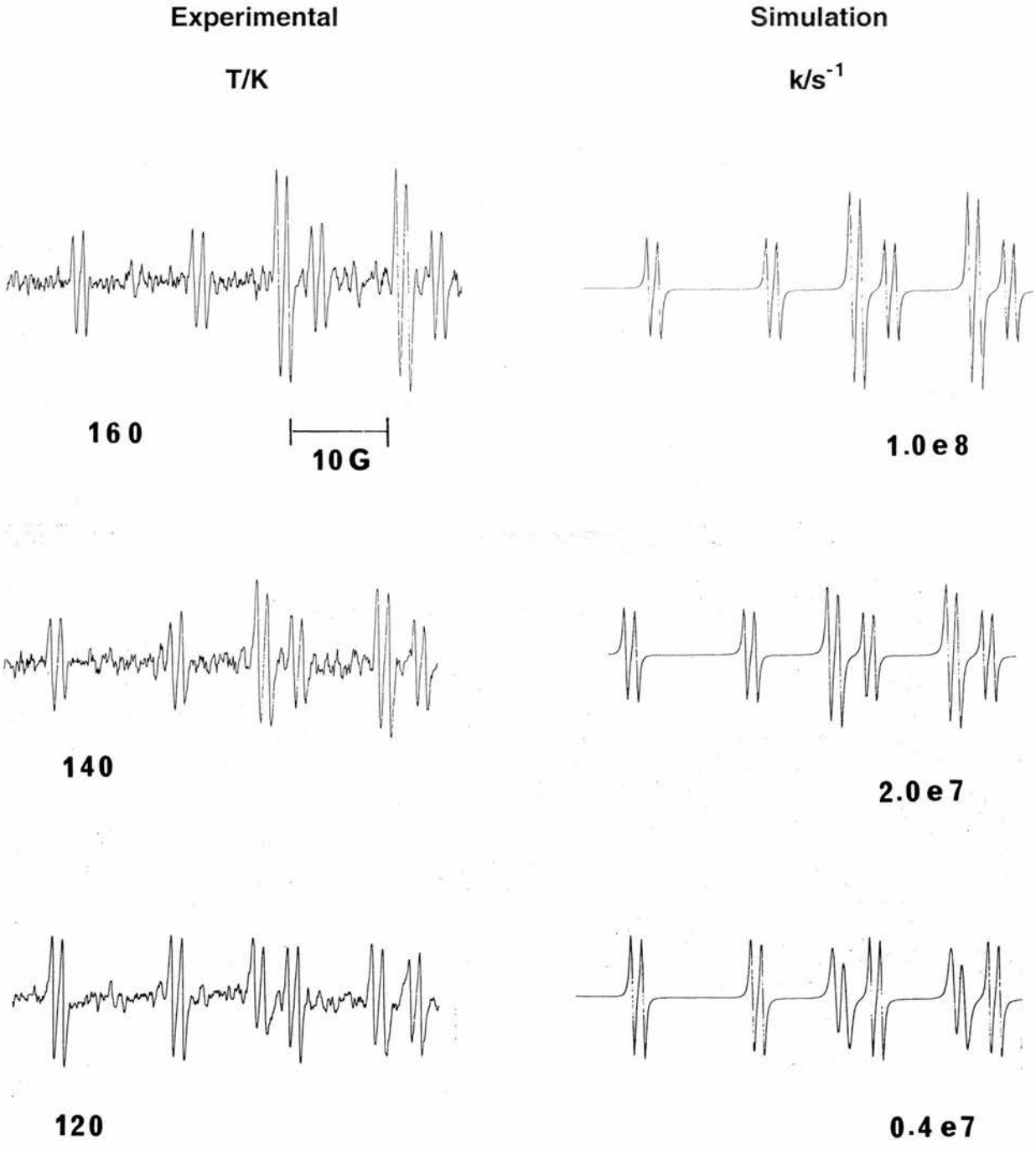


Figure 3



Low field halves of EPR spectra in n-propane of radical **5b**

Figure 2

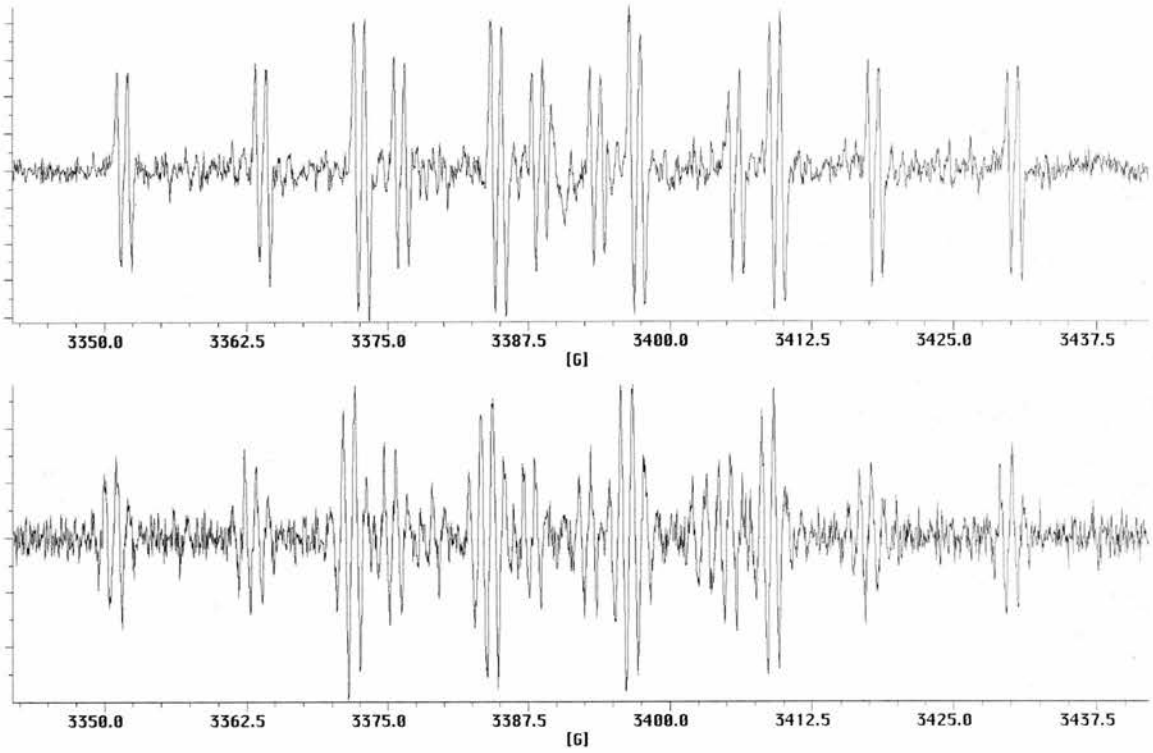


Figure 4a (top). EPR spectra obtained from radical **7** derived from a solution of the corresponding bromide and triethylsilane/DTBP in n-propane at 160 K.

Figure 4b (bottom). EPR spectra obtained from radical **6** derived from a solution of the corresponding bromide and hexamethylditin in n-propane at 165 K.

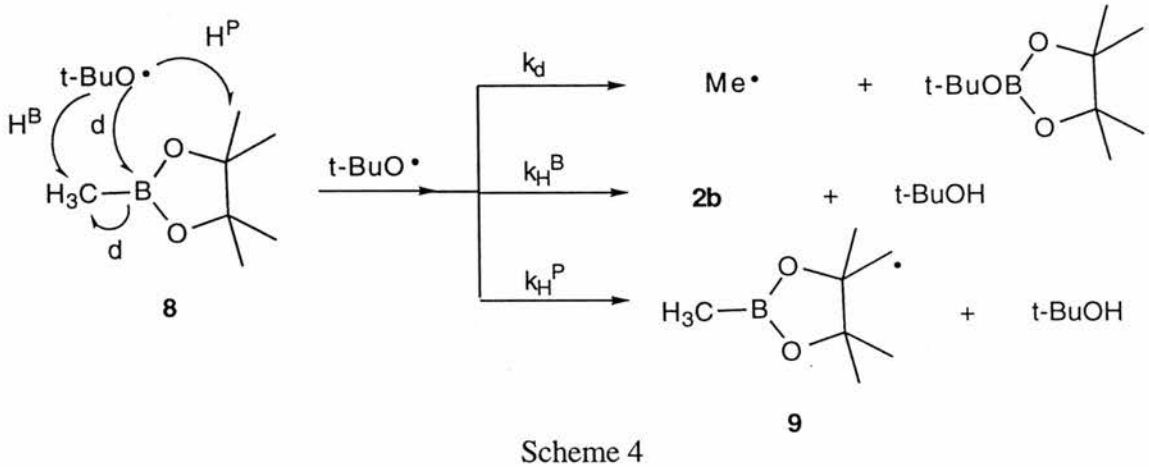
Table 4. Rates of exchange of α-hydrogens in radical **5b**.

T/K	160	150	140	130	120	115
k_t/s^{-1} [a]	1×10^8	4.5×10^7	2×10^7	1×10^7	4×10^6	2.5×10^6

[a]Values obtained from computer simulation.

Radical **2b** can also be generated by the abstraction of an H atom from **8** by the t-butoxyl radical. The t-butoxyl radical can also displace a methyl radical from the boronic ester in a homolytic substitution reaction, or it can abstract a hydrogen from the 'rear end' of the boronic ester, yielding radical **9**. When the reaction is carried out in cyclopropane, abstraction of a hydrogen from the solvent is possible, leading to the cyclopropyl radical.

When the reaction was performed in cyclopropane, peaks from 3 radicals were visible; the methyl radical, cyclopropyl radical and **2b**, with the proportions depending on the temperature. Computer simulations enabled approximate values for their mole fractions to be obtained. With the (known) amounts of starting materials remaining effectively constant throughout, relative rate constants for the three processes (H abstraction from **8**, displacement of Me• from **8**, and H abstraction from cyclopropane) could be obtained.



Scheme 4

Application of the steady state approximation to the mechanism shown in Scheme 4 gave equations for relative rates:

$$k_H^B/k_H(\Delta) = ([\mathbf{2b}] \times [c\text{-}C_3H_6])/([\Delta\bullet] \times [\mathbf{8}]) \qquad \text{(eq 3)}$$

$$k_d/k_H(\Delta) = ([Me\bullet] \times [c\text{-}C_3H_6]/([\Delta\bullet] \times [\mathbf{8}]) \qquad \text{(eq 4)}$$

where $k_H(\Delta)$ is the rate constant for hydrogen abstraction by t-BuO• from cyclopropane, and the other rate constants refer to the reactions shown in Scheme 4.

The concentrations of the starting materials are known, and the relative concentrations of the relevant radicals (methyl, cyclopropyl, and **2b**) can be determined by performing double integration calculations of the EPR spectra. The relative rates $k_H^B/k_H(\Delta)$ and $k_d/k_H(\Delta)$ can thus be deduced from equations 3 and 4.

The absolute rate constant for H abstraction from cyclopropane was obtained in a similar way. A competition reaction was set up in order to determine the relative rates of hydrogen abstraction by t-BuO• from cyclopropane and methanol. The absolute rate

constant for hydrogen abstraction from methanol is known [log $(A_H^M/s^{-1}) = 9.1$, E_H = 5.31 kcal mol^{-1}].[20] The values of $k_H(\Delta)$ that were calculated at various temperatures are shown in Table 5.

Table 5. Values of the rate constant for hydrogen abstraction from cyclopropane.

T/K	150	160	170	180	195	210
$k_H(\Delta)/M^{-1}s^{-1}$	0.068	0.195	0.431	0.900	2.974	7.832

From these data, the values of k_H^B and k_d could be determined. The experiment was performed in duplicate, and the rate constants obtained are given in Table 6 [along with calculated and extrapolated values for $k_H(\Delta)$]. An Arrhenius plot (figure 5; note that values for 2 + log $k_H(\Delta)$ were used for clarity) was satisfactorily linear and gave the following activation data:

E_H^B = 6.3 kcal mol^{-1} $\quad$ E_d = 7.3 kcal mol^{-1}

$\log(A/s^{-1})_H^B = 8.2$ $\quad$ $\log(A/s^{-1})_d = 8.3$

Comparison of the parameters for H-abstraction by the t-butoxyl radical from **8** with those of an illustrative selection of molecules (Table 7) reveals that the activation barrier is considerably higher than for H-abstraction from cyclopentane, and the rate constant at 300K is about two orders of magnitude lower than with cyclopentane,[21] methanol,[20] and toluene,[22] and only about five times the value for abstraction from the deactivated cyclopropane. These kinetic data concur with the previously described thermodynamic data which indicate that a radical is not stabilised by an α-boronic ester group.

Radical **9** was observed only at higher temperatures (≥240 K), when the reaction was performed in neat DTBP; $\underline{a}(2H_\alpha) = 22.4$ G, g = 2.0028 at 240 K.

Table 6. Rate constants for reactions H^B and d in Scheme 4

T/K	$k_H(\Delta)/M^{-1}s^{-1}$	$k_a/M^{-1}s^{-1}$	$k_b/M^{-1}s^{-1}$	$k_a/M^{-1}s^{-1}$	$k_b/M^{-1}s^{-1}$
150	0.068	0	0.226	0	0.095
170	0.488	0	1.63	0	0.683
190	2.24	1.0	10.0	0.7	5.10
210	7.79	3.9	43.7	3.7	22.4
230	21.84	22	195.2	13	135.5
250	51.91	97	744.9	59	445.9
265	91.2	240	1868	160	1032

k_H (Δ) = rate of H-abstraction from Δ.

Table 7. Comparison of kinetic data of hydrogen abstraction from different materials.

Substrate	T/K	$k/M^{-1}s^{-1}$	$\log(A/s^{-1})$	E/kcal mol^{-1}	Ref.
c-C_5H_{10}	302	9.6×10^5	8.5	3.5	21
CH_3OH	293	1.3×10^5	9.1	5.3	20
$PhCH_3$	295	2.3×10^5			22
c-C_3H_6	300	2.7×10^2	6.0	4.9	b
8	300	4.2×10^3	8.2	6.3	b
8[a]	300	8.7×10^2	8.3	7.3	b

[a] Data for displacement of methyl radical by t-BuO•. [b] This work

For primary radicals of type $H_2C^{\bullet}$–X it has been demonstrated that there exists a linear relationship between the internal rotation barriers (E_e) and the standard gas phase bond dissociation energies of the corresponding H-CH_2X bonds.[23,24] Updating the thermodynamic data to acknowledge improved experimental methods and rationalisations between differing techniques,[25,26] yields the empirical relationship:[27]

$$BDE(RCH_2\text{-}H)/kcal\ mol^{-1} = 101.1 - 0.86E_e \qquad \text{eq. 5}$$

Inserting the value of E_e obtained for radical **5b** into equation 5 gives a value for the bond dissociation energy of radicals of type **8** of 98.6 kcal mol^{-1}. This is only 2 kcal mol^{-1} less than the value from Et-H, and concurs with the results that suggest that the boronate group does not activate adjacent methylene groups to a significant extent.

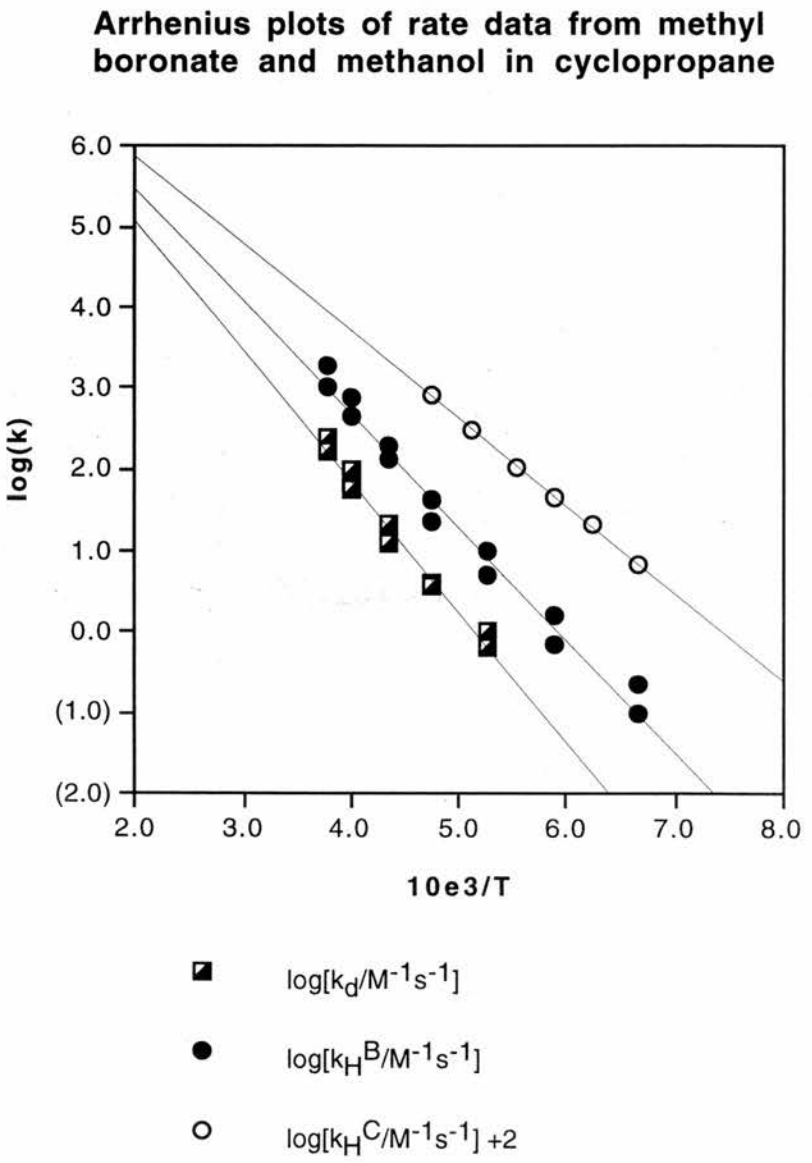


Figure 5

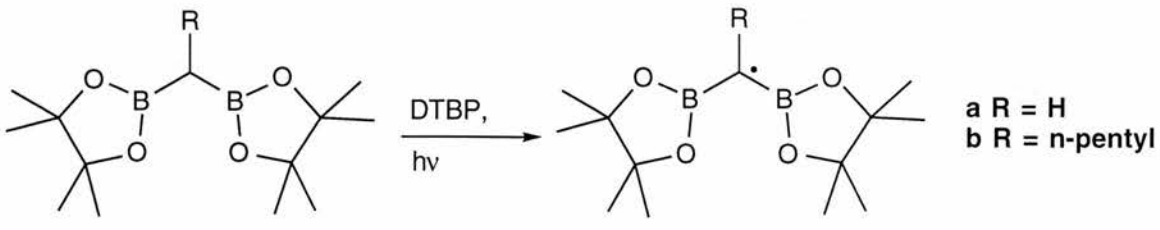
Brocks *et al.* have re-evaluated the linear relationships between H_α and H_β hfs and BDE(C-H) values.[28] Two expressions were found to provide reliable estimates for bond dissociation energies in planar radicals:

$$BDE(C\text{-}H) = 1.61\underline{a}(H_\alpha) + 62.4 \qquad \text{eq. 6}$$

$$BDE(C\text{-}H) = 1.93\underline{a}(H_\alpha) + 57.8 \qquad \text{eq. 7}$$

Most of the values for $\underline{a}(H_\alpha)$ in α-boryl boronic esters were 21.0 ± 0.1 G (Tables 1,3). These radicals are expected to be planar, so equations 6 and 7 should be valid. Substitutions of this value into equations 6 and 7 yields 96.2 and 98.3 kcal mol^{-1} respectively for $BDE[(RO)_2BCH_2\text{-}H]$.[27] These values are in good agreement with the value for BDE obtained from the rotation barriers.

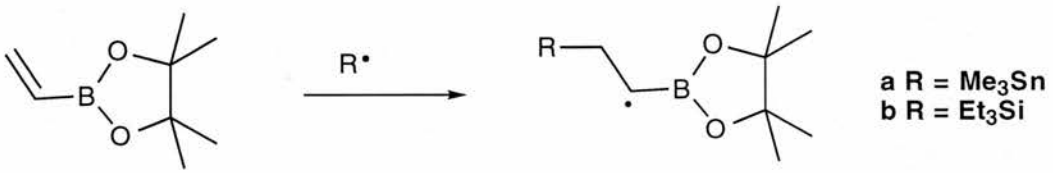
Attempts were also made to generate the bis(boronic ester) radicals **11a,b** by hydrogen abstraction from bis(boronic ester)s **10a,b**. If a radical is stabilised by an adjacent boronic ester group, then a bis(boronic ester) should show extra stabilisation. Unfortunately no spectra corresponding to **11** could be observed, although a weak triplet was observed ($\underline{a}(2H_\alpha)$ = 21.6 G), which may be due to hydrogen abstraction from one of the eight equivalent methyl groups present. Use of a polarity reversal catalyst, Et_3BH_3,[29] also failed to produce the desired spectrum. The stabilising effect of the boronic ester group is not sufficient to counteract the weakening of the spectrum caused by a more complicated hfs pattern.



10 **11**

5.2.2. α-Boryl radicals by addition to a double bond.

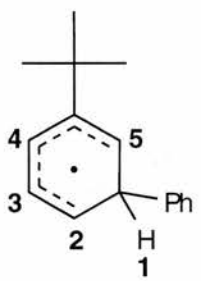
Radical addition to vinylboronic esters has been relatively common, and was used in the first synthesis of α-haloboronic esters.[30] Addition of various radicals to vinyl boronic ester **12** was investigated by EPR spectroscopy (Scheme 5).



12 **13**

Scheme 5

The only radical observed with CCl_3Br as the radical source was $\bullet CCl_3$ which apparently did not add to the double bond. A spectrum was observed from a solution of **12** in t-butylbenzene saturated with benzoyl peroxide: $\underline{a}(H^3)$ = 2.8 G, $\underline{a}(H^{2/5})$ = 8.1 G, $\underline{a}(H^{5/2})$ = 9.2 G, $\underline{a}(H^4)$ = 13.1 G, $\underline{a}(H^1)$ = 36.0 G @ 210 K. This was assigned to radical **14** formed by addition of the phenyl radical to the solvent. The hfs for the 5 hydrogens were confirmed by computer simulation: The radical is very similar to previously observed 1-alkyl-3-t-butylcyclohexadienyl[31] and 1-phenylcyclohexadienyl[32] radicals.



14

The trimethyltin radical, generated from hexamethylditin, added readily to vinylboronic ester **12**, resulting in good spectra which were assigned to radical **13a** (Figure 6) Similarly, generation of the triethylsilyl radical in the presence of **12** gave good

spectra of adduct radical **13b**. However, during prolonged photolysis an unidentified radical was also formed. The hfs of radicals **13a** and **13b** are given in table 8.

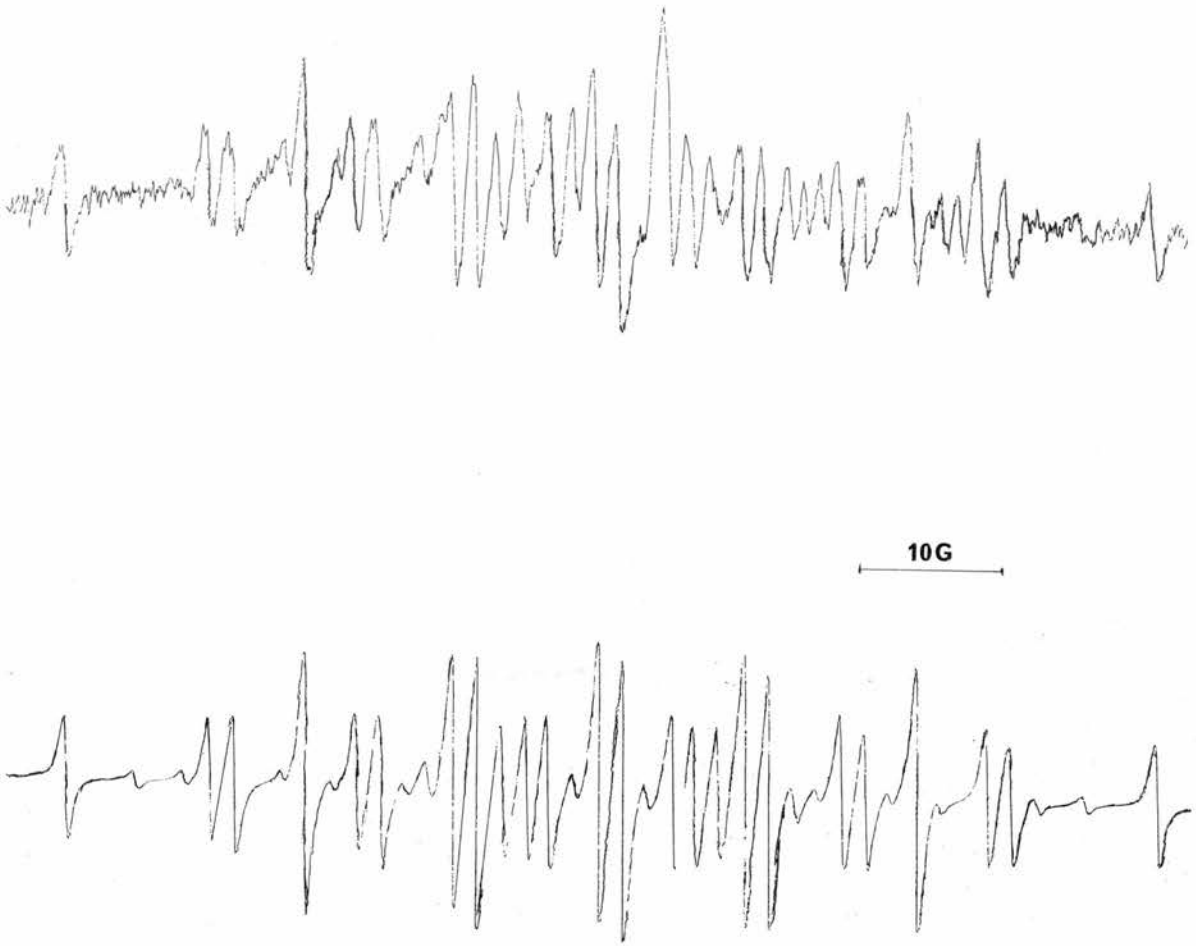


Figure 6. Spectrum (top) and simulation of radical **13a**, formed by addition of a trimethyl tin radical to **12**, at 235 K.

Table 8: Hfs of radicals generated by addition to vinyl boronic ester.

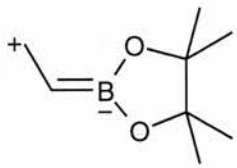
Radical	T/K	$\underline{a}(^{11}B)$/G	$\underline{a}(H_\beta)$/G	$\underline{a}(H_\alpha)$/G	$\underline{a}(H_\beta)$/G	$\underline{a}(^{10}B)$/G
13a	235[a]	10.1	11.8	16.7	16.7	3.4
13b	195[a]	10.8	9.1	18.3	23.8	3.6

[a] t-BuPh solvent

Adducts from addition of the phenylthiyl radical (derived from diphenyl disulfide) and diphenylaminyl radical $Ph_2N^\bullet$ (from tetraphenylhydrazine) were not observed.

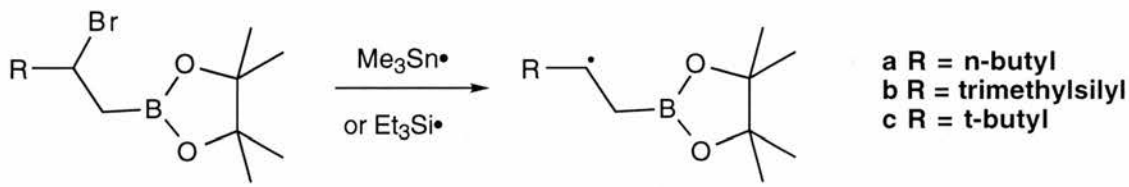
The results show that the nucleophilic radicals $Me_3Sn^\bullet$ and $Et_3Si^\bullet$ add efficiently to the vinyl boronic ester under EPR conditions (Carboni showed that alkyl radicals add efficiently to these compounds[5]), but electrophilic radicals do not. This is in agreement

with the suggestion that structure **15** makes an appreciable contribution to the ground state of **12**,[14] but does not necessarily contradict the previously shown addition of electrophilic radicals such as $\bullet CCl_3$ to vinylboronic esters, as the reactions were conducted at different temperatures.[33]



15

5.2.3. β-Boryl radicals by abstraction of bromine from β-bromoboronic esters.



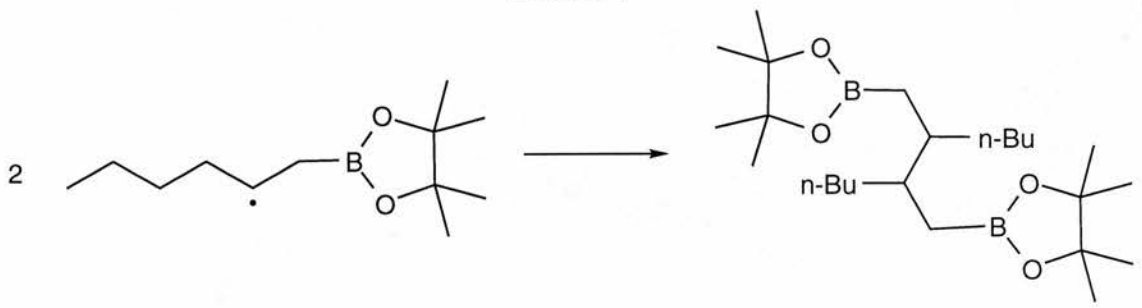
16 **17**

Scheme 6

A degassed solution of β-boronic ester **16a** and hexamethylditin in t-butylbenzene was photolysed under EPR conditions. No peaks due to radical **17a** were visible. GC/MS analysis of the product showed a large peak due to hex-1-ene and this was initially assumed to indicate that the radical had decomposed in the manner shown in Scheme 7. (This type of mechanism has been previously mentioned by Pasto *et al.*).[34] A dimerised product (**19**) was also detected (Scheme 8). The reaction was twice repeated in cyclopropane at lower temperatures, (once using triethylsilane/DTBP as radical initiator) and good spectra of **17a** were obtained in both cases. Product analysis showed much more dimer relative to the amount of hex-1-ene. A spectrum of **17a** at 180 K can be seen in Figure 7.

17a **18**

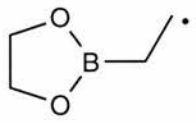
Scheme 7



17a **19**

Scheme 8

This result supports the elimination mechanism for the formation of hex-1-ene, but there were no signals from the boron centred radical, and attempts at spin trapping (with 2-methyl-2-nitrosopropane and t-butyl hyponitrite) were unsuccessful. Addition of pyridine to ligate the boron centred radical failed to make it EPR visible.

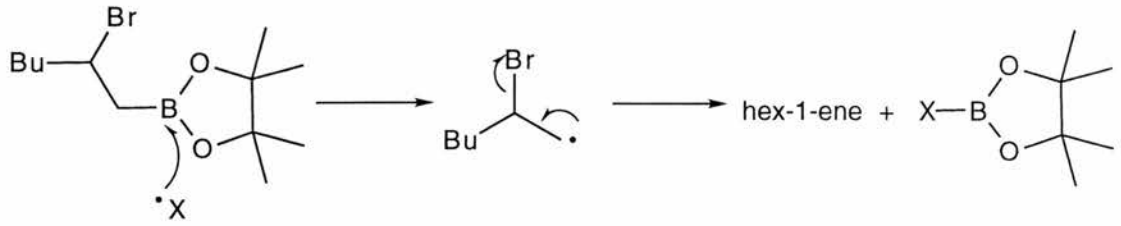


20

Ab initio calculations on a closely related species, **20**, showed that the proposed mechanism would be endothermic by 30.8 kJ mol^{-1}, and so is clearly not feasible.[35] An alternative mechanism is possible, (Scheme 9) in which homolytic substitution occurs at the boron atom, displacing the 2-bromohexyl radical, which can easily undergo elimination of bromine. While this sort of reaction is well known for attack by electrophilic oxygen centred radicals (which were present when triethylsilane was used as a radical initiator), the hex-1-ene product was also observed when only the nucleophilic trimethyltin radicals were

present as a radical initiator, so the result is surprising. It is possible that bromine atoms (eliminated from the 2-bromohexyl radicals) are the chain carriers.

Batey and Smil observed a similar process in their cyclisation reactions and deduced that an intramolecular S_Hi mechanism was taking place, where a (nucleophilic) carbon centred radical attacked the boron centre resulting in a ring expansion (**CM**; Scheme 2).[7] Their calculations showed that the activation barrier for the 'S_Hi' reaction was much lower than for the β-scission reaction of the type that we had originally postulated.



16a **21**

Scheme 9

Spectra were also obtained for radical **17b**, but not for **17c**. The hfs of the β-boryl radicals generated by abstraction of bromine are given in Table 9.

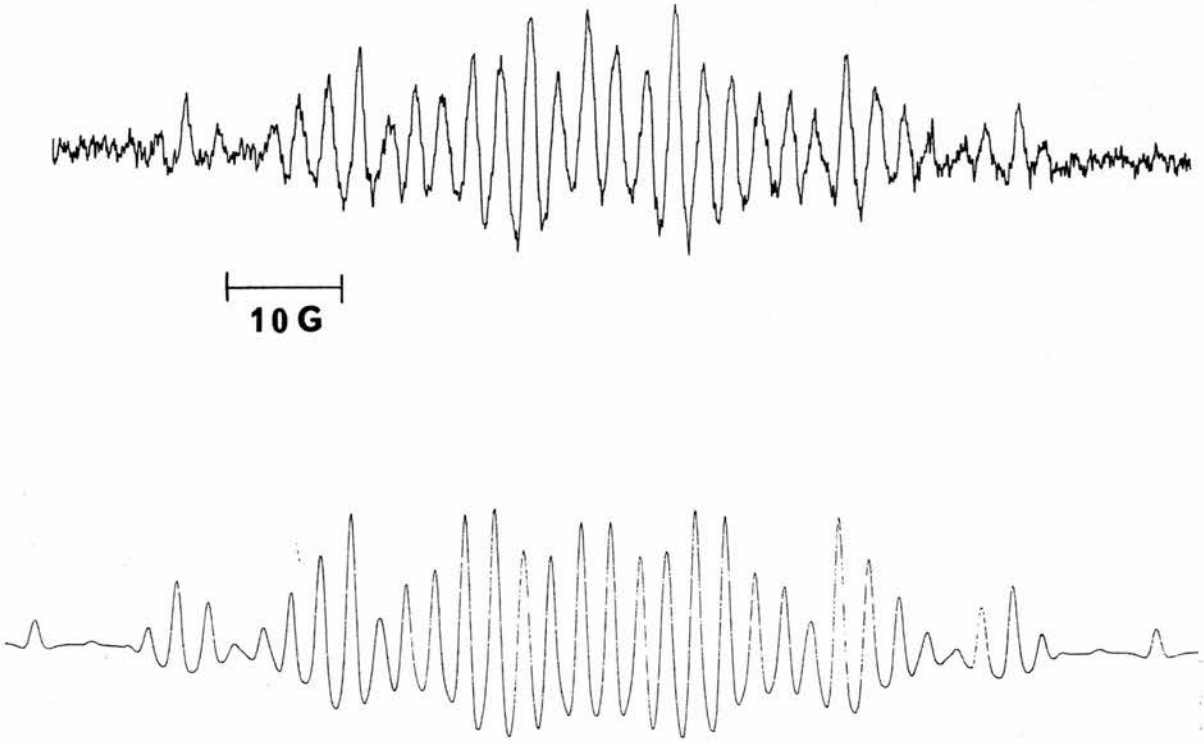


Figure 7. 2nd derivative spectrum (top) and simulation of radical **17a** at 180 K.

Table 9. Hfs of the β-boryl radicals generated by abstraction of bromine.

Radical	T/K	$\underline{a}(^{11}B)$/G	$\underline{a}(H_\beta)$/G	$\underline{a}(2H_\alpha)$/G	$\underline{a}(2H_\beta)$/G	$\underline{a}(^{10}B)$/G
17a	180[a]	17.7	22.1	22.1	27.0	5.9
17b	180[a]	23.3	20.0	18.0	N/A	7.8

[a] Cyclopropane solvent

5.2.4 Allylic radicals by abstraction of hydrogen or bromine.

The only radical formed from reaction of allylic boronic ester **22** was the allylic radical **23a** generated by abstraction of a hydrogen atom. This was apparently much more favourable than addition to the double bond, presumably because of allyl stabilisation. There was no evidence for attack of the t-butoxy radical at the boron, which would lead to the allyl radical being displaced. A similar species (**23b**) was generated by bromine abstraction from **23**. The hfs for **23a** were determined by computer simulation: $\underline{a}(^{11}B)$ = 8.0G; $\underline{a}$(2H) = 13.1G; $\underline{a}$(1H) = 3.45G; $\underline{a}$(1H) = 13.9G; $\underline{a}(^{10}B)$ = 2.7G at 205K in t-BuPh, while the related **23b** gave spectra with $\underline{a}(^{11}B)$ = 7.9G; $\underline{a}$(2H) = 13.1G; $\underline{a}$(1H) = 3.4G under the same conditions. A spectrum of **23b** is shown in figure 8.

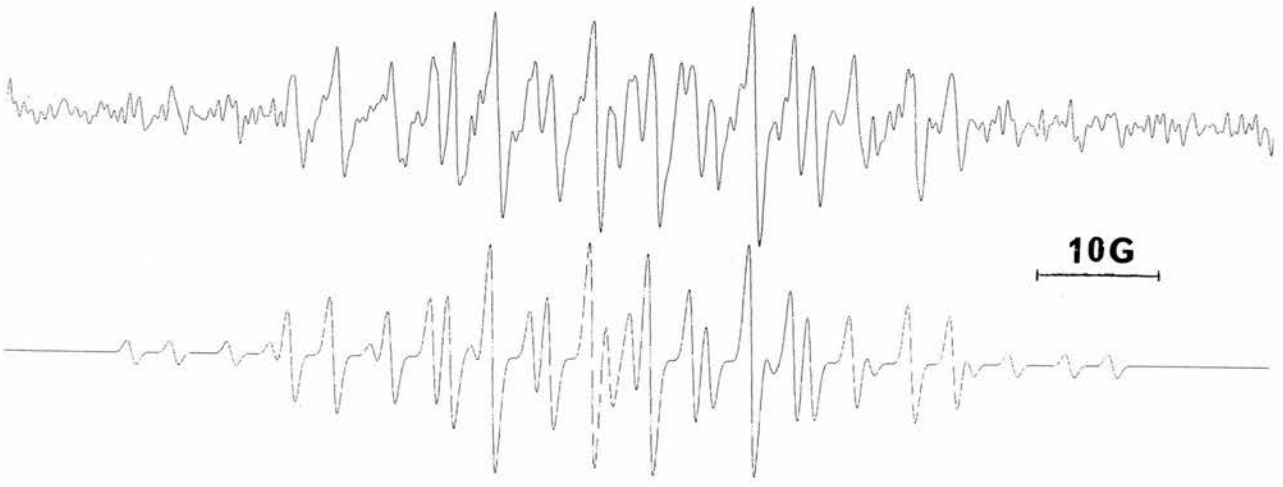
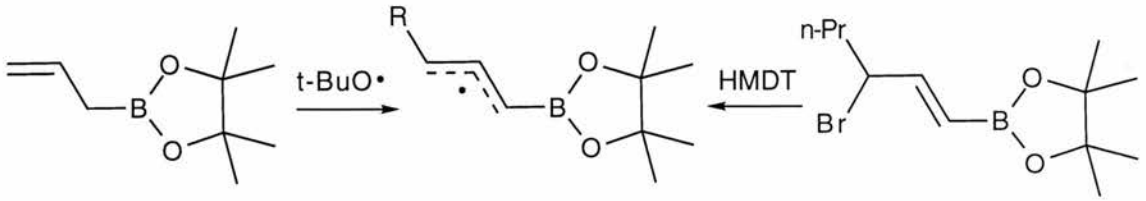


Figure 8. Spectrum (top) and simulation of radical **23b**, formed from **24**, at 205 K.

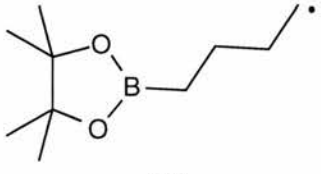


22 **23** **a** R = H **b** R = n-Pr **24**

Scheme 10

5.2.5 Other boronic ester containing radicals

Radical **25** was generated from the corresponding bromide under EPR conditions. There were no long-distance effects of the boronic ester and the splittings were consistent with those of a terminal alkyl radical; $\underline{a}(H_\alpha)$ = 22.1 G, $\underline{a}(H_\beta)$ = 28.2 G, $\underline{a}$(2H) = 0.9 G at 215 K in t-BuPh. Product analysis showed the presence of the direct reduction product. There was no evidence to suggest that displacement of an alkoxy radical had taken place; there is a strong thermodynamic bias favouring boronic esters over borinic esters.[37]



25

5.3 Conclusions.

We have used EPR spectroscopy to characterise various different types of radicals containing a boronic ester functionality. There was very little kinetic or thermodynamic stabilisation conferred by the boronic ester group in α-boryl radicals. The barrier to rotation around the C-B bond was determined for asymmetric boronic esters to be 2.9 ± 0.7 kcal mol^{-1}.

Competition reactions enabled the activation parameters to be determined for the two main processes when the t-butoxyl radical attacks the methyl boronic ester **8**. For homolytic substitution at the boron centre, E = 6.3 kcal mol^{-1}, while for H-abstraction E = 7.3 kcal mol^{-1}.

Observable radicals could not be generated by hydrogen abstraction from bis(boronic esters) using DTBP. This concurs with the result that α-boryl group provides little kinetic stabilisation.

Nucleophilic radicals added efficiently to the vinyl boronate **12**, but under the EPR conditions no evidence was found for addition of electrophilic radicals.

α-Boronic ester radicals are useful synthetic species which are easily generated by bromine abstraction or addition to a double bond. They are well behaved, and have a lot of potential in organic synthesis. The stabilisation by delocalisation of the unpaired electron into the vacant p-orbital is very small - the oxygen atoms in the boronic ester are also electron donating and this is competitive - resulting in only a slight increase in the barrier to rotation of the C-B bond, and also showing no significant enhancement of the rates of hydrogen abstraction from methylboronic ester **8.**

β-Boronic ester radicals can also be generated by bromine abstraction, but homolytic displacement reactions can be competitive. Generation of β-boronic ester radicals by radical addition to a double bond in an allylic boronic ester is unlikely to be a feasible process. Electrophilic radicals such as the t-butoxyl radical will abstract hydrogen preferentially.

Allylic boronic ester radicals readily generated by either hydrogen or bromine abstraction.

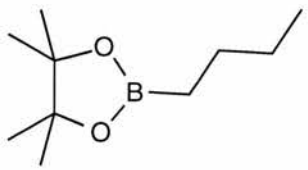
Radicals from a δ-bromoboronic ester showed no long range effect due to the boron centre.

5.4 Experimental

The boronic esters were prepared by Dr. B. Carboni and were used as received. EPR spectra were obtained with Bruker ER 200D and EMX 10/12 spectrometers operating at 9.5 GHz with 100 kHz modulation. Samples of the substrate (~ 30 mgs) and either hexamethyldin (~ 30 mgs), triethylsilane (~30 mgs) and DTBP (~ 30 mgs), or DTBP (~30 mgs) in t-butylbenzene (~ 400 μl) were degassed by bubbling nitrogen for 20 minutes, and photolysed in the resonant cavity by light from a 500 W super pressure mercury arc lamp. EPR spectra were simulated with programs employing a two jump model.[10,38] Samples in cyclopropane were degassed using a freeze-pump-thaw method, and photolysed as above. GC/MS analyses were run on a Finnigan Incos 50 quadrupole instrument interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase.

Product analysis of photolytic reactions of 16a with hexamethylditin in t-butylbenzene at 250 K.

Peak no. 110, hex-1-ene (30), 84 (M^+) (9), 69 (13), 56 (46), 55 (48), 43 (29), 42 (48), 41 (100), 39 (55), 29 (22), 27 (64); Peak no. 333, 2-n-butyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **26**, (50), 210 ($M\text{-}2^+$) (3), 153 (11), 109 (11), 84 (100), 83 (55), 69 (48), 55 (65), 43 (46), 41 (90), 39 (31); Peak no. 629, dimer **19**, 365 (1), 153, (18), 101 (32), 85 (50), 84 (100), 83 (75), 69 (40), 55 (45), 43 (40), 41 (48). The chromatogram also indicated the presence of solvent and tin-containing components.



26

Product analysis of photolytic reactions of 16a with hexamethylditin and DTBP in cyclopropane at 180 K.

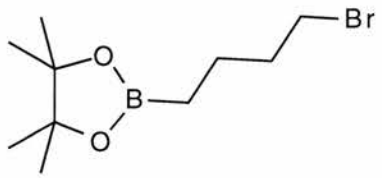
Peak no. 107, hex-1-ene (20); Peak no. 335, 2-n-butyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **26**, (60); Peak no. 629, dimer **19**, (40). The chromatogram also showed solvent and tin-containing components.

Product analysis of photolytic reactions of 16a with triethylsilane and DTBP in cyclopropane at 180 K.

Peak no. 335, 2-n-butyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **26**, (40); Peak no. 629, dimer **19**, (15).

Reduction of δ-bromoboronic ester 27 with triphenyltin hydride.

δ-Bromoboronic ester **27** (0.0173g; 0.152 mmol) and triphenyltin hydride (0.064 g; 0.182 mmol) in benzene (5 cm^3) were illuminated with light from a 400 W medium pressure mercury lamp at 60°C for 2.5 hours. The solvent was removed under removed pressure, to give 2-n-butyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **26** in 81% yield.[37] δ_H 0.78 (2H, t, J = 7.5 Hz, BCH_2), 0.88 (3H, t, J = 7.1 Hz, CH_3CH_2), 1.17-1.45 (4H, m, 2 × CH_2), 1.24 (12H, s, 4 × CH_3).



27

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