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# AMIDOCYCLOHEXADIENES IN SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

**A thesis presented by Antonio Franco Bella to the University of St. Andrews in application for the degree of Doctor of Philosophy.**

**December 2003**

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# Memorandum

This thesis is an account of the original research performed by the author in the School of Chemistry, University of St. Andrews, between October 2000 and October 2003. Where findings of other works have been used, due references have been given.

# Contents

# Acknowledgements

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# Abbreviations and Symbols

| | |
|---|---|
| AIBN | 2,2'-Azobisisobutyronitrile |
| CPU | Central processing unit |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DEAD | Diethyl azodicarboxylate |
| *n*-Dec | *n*-Decane |
| DIEA | Diisopropylethylamine |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone |
| DTBP | Di-*tert*-butyl peroxide |
| DTBPO | Di-*tert*-butyl peroxyoxalate |
| DMAP | Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulphoxide |
| DCC | Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| EPR | Electron Paramagnetic Resonance |
| GC-MS | Gas Chromatography/Mass Spectrometry |
| HMPA | Hexamethylphosphoramide |
| In• | Initiator |
| hfs | Hyperfine splitting |
| 40/60 Pet. Ether | Light petroleum |
| $M^+$ | Molecular ion |
| MAP | 4-Methoxyacetophenone |
| mp | Melting point |
| m/z | Mass to charge ratio |
| *neo*-Pn | 2,2-Dimethylpropyl |
| NMR | Nuclear Magnetic Resonance |
| Py | pyridine |
| PTSA | *p*-toluenesulfonic acid |
| s, d, t, q, $q^i$ | Singlet, doublet, triplet, quartet, quintet |
| TIPPS | 2,4,6-Triisopropylphenyl selenyl |
| TBDMS | *Tert*-butyldimethylsilyl |

| | |
|---|---|
| TEMPO | Tetramethylpiperidine N-oxide |
| TFAA | Trifluoro acetic acid |
| TMEDA | N,N,N',N'-Tetramethylethylene diamine |
| TTMSS | Tris(trimethylsilyl)silane |
| TLC | Thin layer chromatography |
| TPA | N,N,N-tris(2-pyridylmethyl) amine |
| Ts | *p*-Toluenesulfonyl. Tosyl |

# Abstract

A summary of tin hydride mediated reactions in generating radicals in organic synthesis is presented, together with some of the many alternative methods available for conducting radical reactions. Particular attention has been given to the development of tin-free organic radical precursors. This is followed by three chapters describing research on the use of pro-aromatic 1-carbamoyl-1-methylcyclohexa-2,5-dienes as free-radical precursors.

A variety of 1-carbamoyl-1-methylcyclohexa-2,5-dienes, *N*-benzyl protected-amide, free-radical precursors have been prepared and utilised in subsequent experiments. EPR studies confirmed the formation of the delocalised cyclohexadienyl radical at low temperatures. At higher temperatures cyclohexadienyl radicals underwent homolysis with release of the associated aminoacyl (carbamoyl) radicals. Measurement of radical concentrations in DTBP solution from the aquired EPR spectra allowed us to calculate the rates of dissociation for several of these aminoacyl radicals. We concluded that the dissociations of cyclohexadienyl radicals, and the carbamoyl radical cyclisations, were both fast enough for chain propagation to be sustained.

The formation of pyrrolidin-2-ones was tested by examining the decomposition of but-3-enyl amides induced thermally with dibenzoyl peroxide. 3-Alkyl-*N*-benzylpyrrolidin-2-ones were obtained in moderate yields, along with significant amounts of the corresponding formamides. Reactions with other initiators, including photochemical processes with di-*t*-butyl peroxide, showed no significant advantage. A cyclohexadienyl amide containing bis-methyl substitution of the butenyl chain was prepared; in the hope that ring closure of the carbamoyl radical would be more efficient because of a Thorpe-Ingold effect. In practice, the yield of the corresponding pyrrolidinone was a disappointing 20 %. Evidence from characterisation of by-products suggested that radical-radical reactions were important.

The use of cyclohexadienyl amides for the preparation of β-lactams was also investigated. The cinnamyl-substituted amide **144** (Chapter 3) was chosen because the phenyl substituent confers resonance stabilisation on the cyclised radical and hence should expedite the *4-exo*-cyclisation step. However, as an additional consequence of this resonance stabilisation the hydrogen-atom abstraction step was disfavoured.

The thermal and photochemical reactions gave the corresponding azetidin-2-one, in low yields. Addition of a good H-atom donor enabled the ring closed benzyl type radical to be trapped. Reactions initiated with di-*t*-butyl peroxyoxalate, including 1.2 mol equiv. of methyl thioglycolate (RSH) produced 1,3-dibenzylazetidinone (**148,** Chapter 3) in increased yields. When a catalytic amount of RSH was employed, the β-lactam yield increased, but radical-radical reactions again became important. Use of lauroyl peroxide as initiator, in concert with 1 equiv. of RSH, led to a greatly improved β-lactam yield. It is likely that polarity reversal catalysis played a part in enhancing the yield of β-lactam. The azetidinylbenzyl radical is resonance stabilised and nucleophilic. Hence a polar effect favoured hydrogen-abstraction from the electronegative RSH. The electrophilic thiyl radical ($RS^{\bullet}$) generated in this way, in turn, abstracted more readily from the cyclohexadienyl site thus regenerating RSH and continuing the chain. In the lauroyl peroxide initiated reactions, products derived from the initiator included undecane and docosane which significantly increased the viscosity of the reaction medium thus slowing radical-radical reactions which are normally diffusion controlled.

Overall, the induced carbamoyl-cyclohexadiene decompositions represent novel, comparatively 'clean', tin-free radical routes that are applicable for the preparation of a range of lactams from secondary amine starting materials. Inclusion of methyl thioglycolate in the reaction medium leads to increased lactam yields.

Cyclisation onto an oxime ether C=N double bond was faster and more efficient, and the product heterocycles contain N-functionality at C(3), exactly as required in many antibiotics. Amidocyclohexadiene precursors containing oxime ether functionality were therefore designed and assembled. The radical-induced decompositions were studied by EPR spectroscopy which showed the expected cyclohexadienyl radicals at low temperatures. At higher temperatures, alkoxyaminyl radicals were also observed.

Cyclisations of the corresponding carbamoyl radicals were so fast that they were not observable by EPR spectra. When reactions were carried out preparatively, amino benzopyrrolidinone derivatives were isolated in good yields. Addition of methyl thioglycolate in dilauroyl peroxide mediated radical reactions, again improved product yields.

An elegant use of *O*-trityl oxime ethers, in which the oxime functionality was ultimately regenerated had attracted our attention. We sought to adapt this tactic to our system and, accordingly, we prepared an *O*-trityl oxime ether substituted cyclohexadienecarboxamide precursor. The standard initiation followed by β-scission of the cyclohexadienyl radical, produced the corresponding carbamoyl radical which ring closed to yield the alkoxyaminyl radical. However, the reaction took a novel route because trityl alkoxyaminyl radicals containing *O*-trityl moiety, underwent a second β-scission to extrude the highly stabilised trityl radical with production of a nitroso-compound.

The use of our strategy was planned for a tin-free, radical-mediated synthesis of benzepril (ACE inhibitor). 7-*exo*-ring closure onto the oxime ether radical acceptor would be sufficiently rapid to facilitate the otherwise difficult ring closure. Carbamoyl radical released from a specifically designed 1-methylcyclohexadiene carboxamide containing *O*-trityl oxime ether moiety would undergo 7-*exo*-cyclisation to afford the desired 7-membered lactam oxime ether (tautomer of the corresponding nitroso-compound).
Due to time limitations, work in this area could not be completed but this remains a promising avenue for future work.

# Chapter 1

# Introduction

## 1.1 Radicals in Organic Synthesis

Radical reactions involve homolytic bond-breaking processes in which the two electrons in a covalent bond are divided symmetrically producing highly reactive intermediates called "free radicals" which each contain one unpaired electron. All free radicals contain an odd number of electrons and nowadays the term "radical" is often used in place of free radical.

Radical chemistry is a newer branch of organic chemistry than the more familiar field of ionic organic reactions. For many years the chemistry of radicals was very much the province of mechanistic and physical organic chemists. More recently the situation has changed with the realisation that radical methods are often compatible with a range of functional groups. The reduced need for protection and deprotection steps has led to an increased interest in the use of radicals in synthesis. The past twenty years has seen an explosion of interest in free radicals as their pivotal role in both chemistry and biology has come to light.

Today, thousands of industrial and biological processes are very much dependent on reactions involving free radicals. Extensive research into their reactivity and future uses is being carried out by both industrialists and academics. Thus, free radical reactions have evolved to join their counterparts, electrophilic, nucleophilic, and pericyclic processes in the arsenal of synthetic organic chemistry. Furthermore, structural data on radicals has become available. An understanding of the kinetic and the structural information of these reactive intermediates paved the way for the development of modern synthetic radical chemistry.[1]

The use of radical intermediates in organic synthesis offers some great advantages such as mild and neutral reaction conditions, the compatibility of these conditions with various functional groups, the amount of kinetic data that is available and the level of regio-selectivity that can now be achieved.

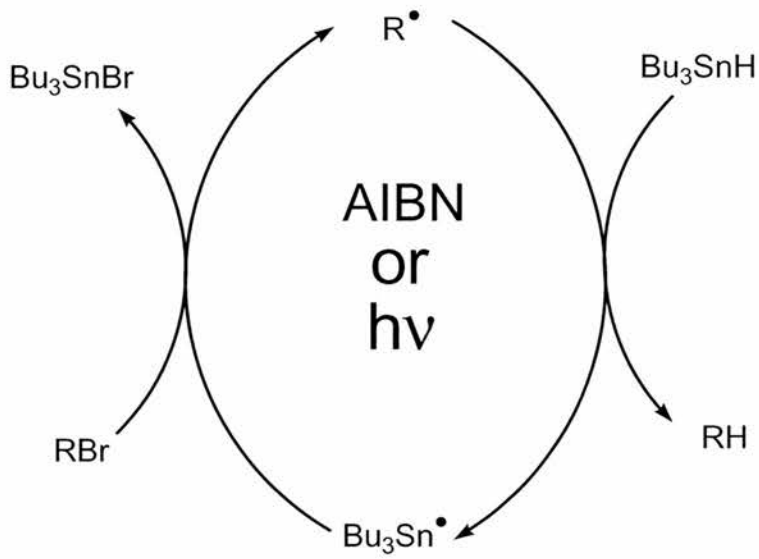
Free radical reactions have played a dominant and determining role in the development of polycyclic ring synthesis via tandem radical cyclisations,[2] particularly when they are carried out in an intramolecular and sequential ring-forming fashion. Examples of these powerful cyclisation methods abound in the contemporary literature,[3,4] several books and reviews have documented achievements, including the syntheses of diverse natural products.[5-7] Other important radical reactions include additions of radicals to centres of unsaturation and radical decarboxylations.

The most common method for generating radicals in organic synthesis involves tin hydrides ($Bu_3SnH$, $Me_3SnH$, and $Ph_3SnH$). At present, tin-reagents dominate free-radical chemistry. They have proved particularly serviceable for the substitution of hydrogen in place of halogen, hydroxyl, amino, nitro, thiol, selenide, carboxylate, and other functional groups. They also mediate alkylation and allylation of alkenes, as well as one-carbon ring expansions of alicyclic and heterocyclic ketoesters. Most importantly, tin hydrides facilitate a huge range of ring closures and cascades involving many kinds of radicals and ring types.[8-10] The downside of this success story is the serious neurotoxicity of organotin compounds, which are hazardous to handle, expensive to dispose of, and the residues are notoriously difficult to remove. One of the major problems in tin-based radical chemistry is the toxicity of the trialkyl tin hydrides.[11,12] Furthermore, it is difficult to completely remove the toxic tin by-products which are generated in stoichiometric amounts during the reaction. Complete removal of tin-containing by-products is frequently a problem, purification therefore needs laborious procedures.[13,14] These disadvantages have rendered pharmaceutical companies exceedingly reluctant to use tin-mediated methods in the preparation of anything intended for human or animal consumption. It is therefore highly desirable to have alternative;[1] non-toxic reagents, which could replace tin in some, if not all applications. There would therefore be considerable benefit in terms of synthetic efficiency, and consequent environmental gain, if better, non-toxic free-radical precursors could be developed and radical methodology applied in the pharmaceutical industries.

The aim of this introduction is to summarize recent achievements in tin-free radical chain reactions and describe the literature on modified tin hydrides, for which efficient purification protocols have been developed.

## 1.2 Tin Hydride for Free-Radical Generation

Tributyltin hydride is the reagent most commonly used to conduct free radical reactions. Simple reduction of an organic halide[15] by tin hydride involves a controlled chain reaction as illustrated in scheme 1.

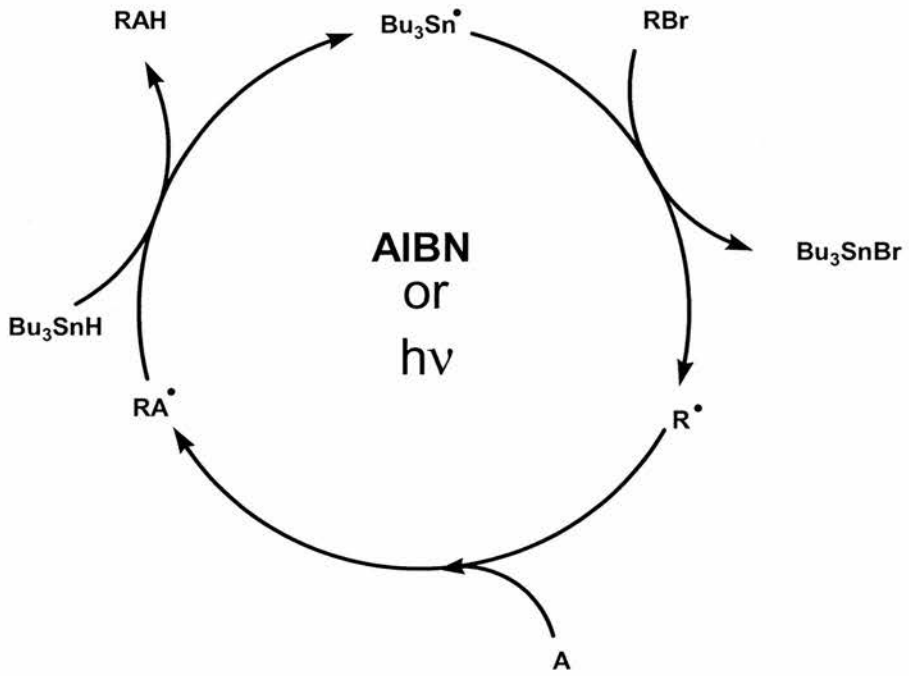



**Scheme 1**

The Sn-H bond can be broken homolytically by the presence of a catalytic amount of AIBN producing the $Bu_3Sn^{\bullet}$ radical which has a high affinity for halogens and can readily abstract chlorine, bromine or iodine atoms from alkyl halides. A site-specific radical $R^{\bullet}$ is generated from an organic substrate RX by atom or group abstraction. The radical $R^{\bullet}$ then reacts with tin hydride to generate the reduced product RH and to regenerate $Bu_3Sn$ radicals.[16,17]

The exchange of an RX bond for a strong R-H bond and the exchange of a relatively weak Sn-H bond for a very strong Sn-X bond drives the overall reaction.

A carbon-centered radical R$^{\cdot}$ can undergo reactions other than hydrogen atom abstraction (Scheme 2).



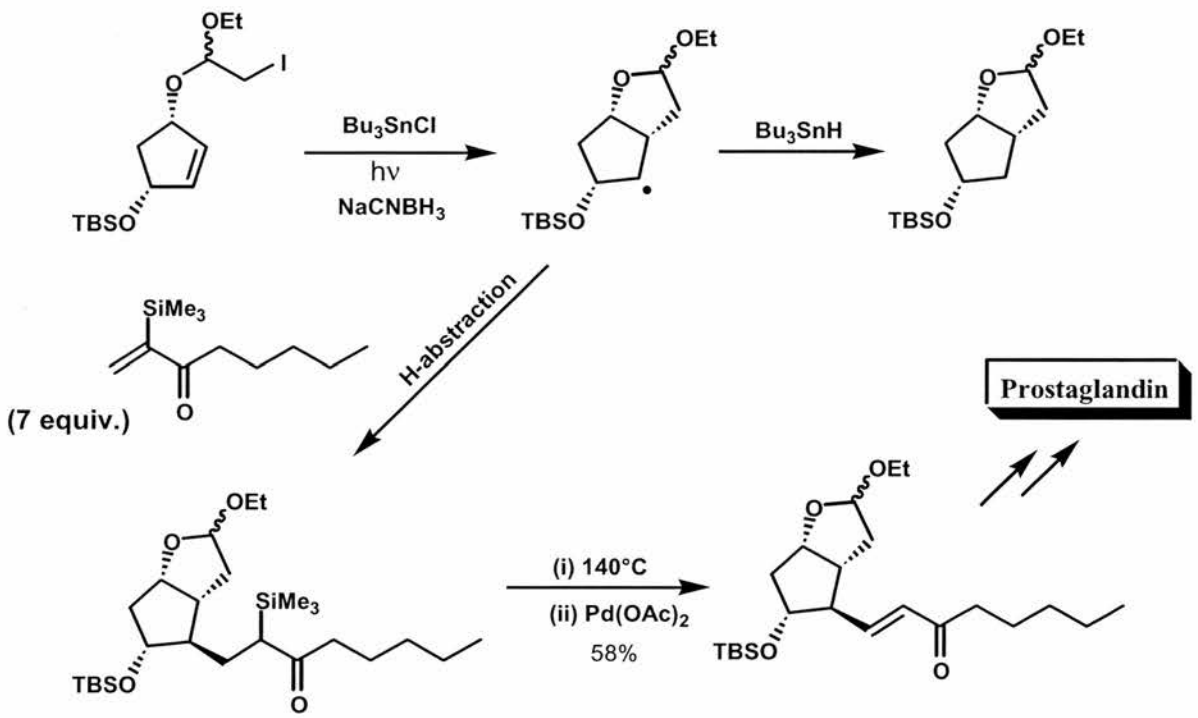

**Scheme 2**

Addition to a multiple bond generates a new radical RA$^{\cdot}$ and intramolecular addition (cyclisation) is particularly fast. The initial radical R$^{\cdot}$ is converted to RA$^{\cdot}$ to yield RAH and $Bu_3Sn^{\cdot}$. The alkyl radical R$^{\cdot}$ has therefore two available options, either hydrogen abstraction from the tin hydride to give the undesired reduction product RH, or addition to A, to give the desired product RAH after hydrogen atom abstraction. If radical addition and hydrogen atom abstraction are competitive, mixtures of RH and RAH result. Several methods favouring the radical addition to an alkene have been developed in order to control this competition.

### 1.2.1 Prostaglandin $F_{2\alpha}$

Stork proposed a synthetic route to Prostaglandin $F_{2\alpha}$[18] in which he suggested that a large excess of the alkene (7 equivalents of alkene were used) can encourage the radical addition, and the tributyltin hydride should be added portionwise to maintain a low concentration of the tin hydride in the reaction mixture.

The method shown below (Scheme 3) involves reduction to the tin-hydride of a catalytic amount of tributyltin chloride, and the tin-halogen by-products formed during the radical reaction, by a slight excess of a mild reducing agent, so that a low concentration of organotin hydride is maintained and a catalytic cycle results. The primary alkyl radical resulting from iodine atom abstraction underwent 5-*exo*-cyclisation to produce the corresponding cyclised radical, which added to activated trimethylsilyl alkene (7 equiv.) followed by H-abstraction from $Bu_3SnH$ to obtain trimethylsilyl ketone in crude form. This was thermally isomerised to the corresponding trimethylsilyl enol ether (step i) and oxdised (step ii) to give unsatured ketone, prostaglandin precursor, in 58% yield.

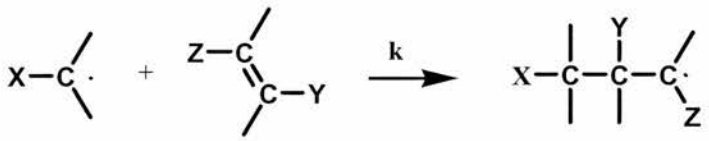



**Scheme 3**

A limitation of the method is that tin hydride is by nature a reducing agent. Under normal circumstances both a C-X functional group and a carbon-carbon $\pi$ bond are sacrificed so that desired products RAH are often contaminated by reduced starting material RH. Complete removal of tin-containing by-products from desired products is frequently a problem. A further solution is the use of organotin reagents that posses no Sn-H bond, $Me_6Sn_2$[19,20] for which a hydrogen source must be provided to avoid polymerisation. Another alternative to the tin hydride chain-transfer step[9] is the use of allyl or vinyl stannanes.[21]

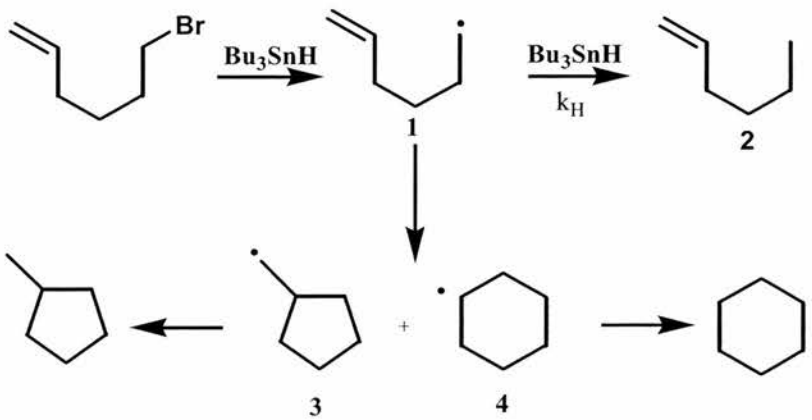
## 1.3 Addition of Free Radicals to Double Bonds

There are many reactions in which C-C bonds are formed by addition of free radicals to multiple bonds and these processes are particularly useful in organic synthesis. Additions of free radicals to alkenes are strongly exothermic, since a σ-bond is formed an a π-bond is broken.[22] The rate of radical addition to multiple bonds is controlled by steric and polar effects[23] and is determined by the substituents X at the free radical and by the substituents Y and Z at the alkene (Scheme 4).




**Scheme 4**

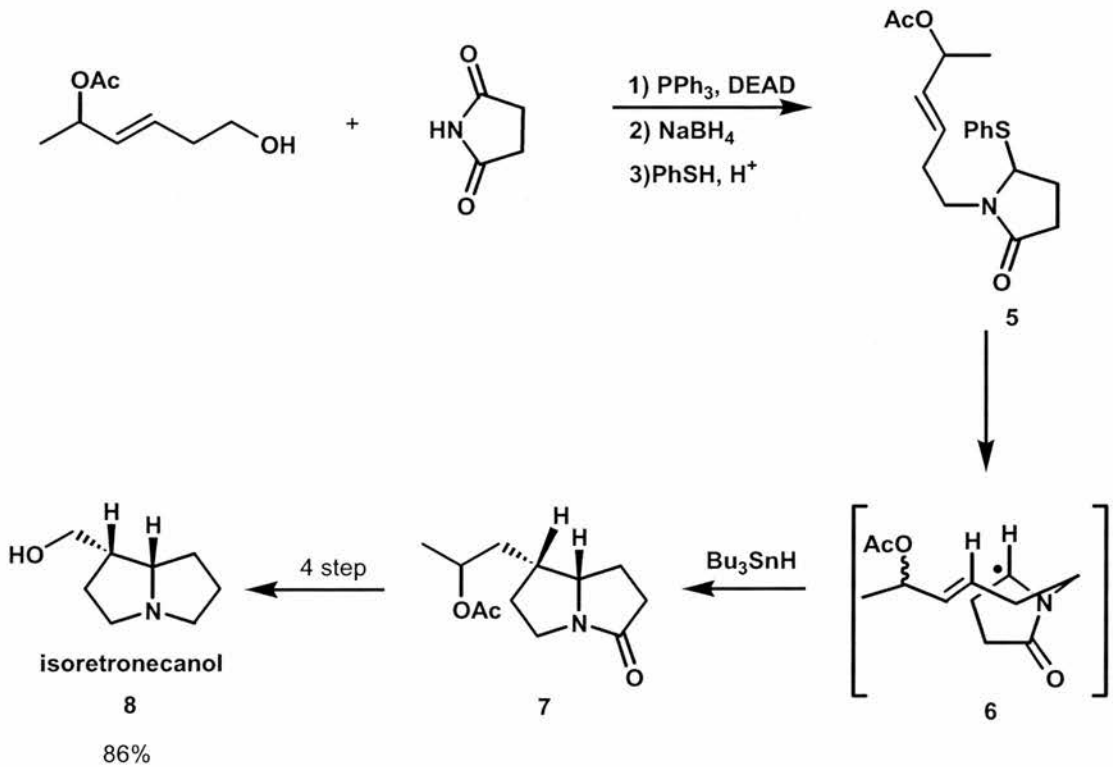
Intramolecular reactions generally occur more readily than their intermolecular counterparts because the latter involve substantial loss of translation entropy whereas the former involve only the loss of internal rotational degrees of freedom. Furthermore the entropy change associated with loss of rotational freedom becomes increasingly unfavourable with increasing size of the ring being formed. The hex-5-enyl radical (**1**) provides a nice example of a homolytic process (Scheme 5) which proceeds contrary to the thermochemical criteria. Ring closure of radical **1** affords cyclopentylcarbinyl (**3**) and relatively little of the cyclohexyl radical (**4**). The latter would be expected to be more stable, being a secondary radical and having an unstrained cyclohexane ring.




**Scheme 5**

Cyclisations are usually faster for the formation of 5-membered rings than for any other ring size and are thus least subject to competitive formation of reduced, uncyclised products (**2**).

Hart's concise syntheses of pyrrolizidine alkaloids by using α-acylamino radicals was historically the first comprehensive synthetic strategy that was founded on radical cyclisations.[24-26] The synthesis of isoretronecanol (Scheme 6) reported in 1984, is a prototype of the execution of this strategy.

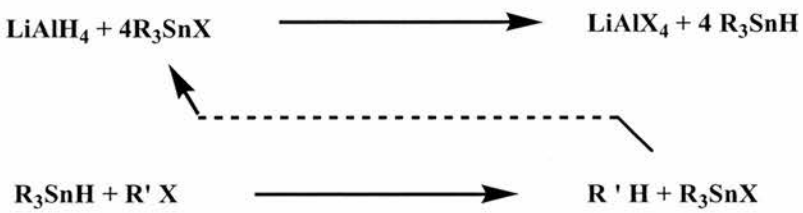



**Scheme 6**

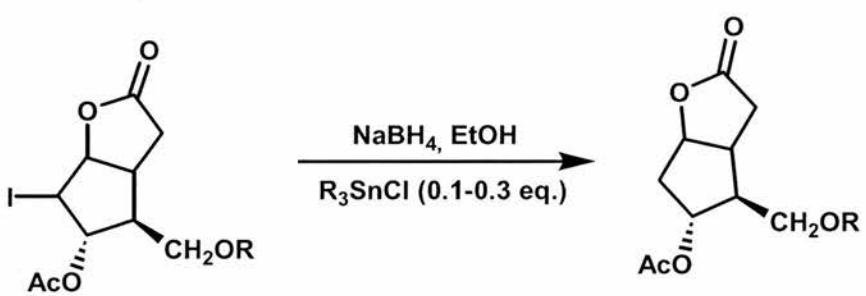
The radical precursor **5** gave a 9:1 mixture of **7** and its diastereomer in 86% yield. The stereochemistry of the cyclisation is consistent with a chair-like transition state **6**, in which the alkene orients itself on the concave face of the forming bicycle. Slow addition of tin hydride is required in order to minimize formation of the uncyclised reduced byproduct. The regioselectivity of the cyclisation, and the stereoselective formation of the thermodynamically disfavored product is a valuable example of the use of radical mechanisms in organic synthesis, however, the toxicity of tin residues makes these methods inappropriate for anything intended for human or animal consumption.

## 1.4 Catalytic Tin Hydride Reactions

Tin hydrides are usually employed in stoichiometric amounts. The product, once formed by these procedures, must be separated from a full 1 equivalent of trialkyltin halide. The observation that reduction of organotin halides by lithium aluminium hydride occurs very rapidly[27] suggested that organotin halides might be used as hydrogen carriers as shown in the following equations.




However the use of a stoichiometric amount of the reactive lithium aluminium hydride greatly limits the method. In 1975 Corey developed a catalytic process[28] for the generation of the valuable prostaglandin precursor **10** from the halolactone **9** using the milder sodium borohydride.

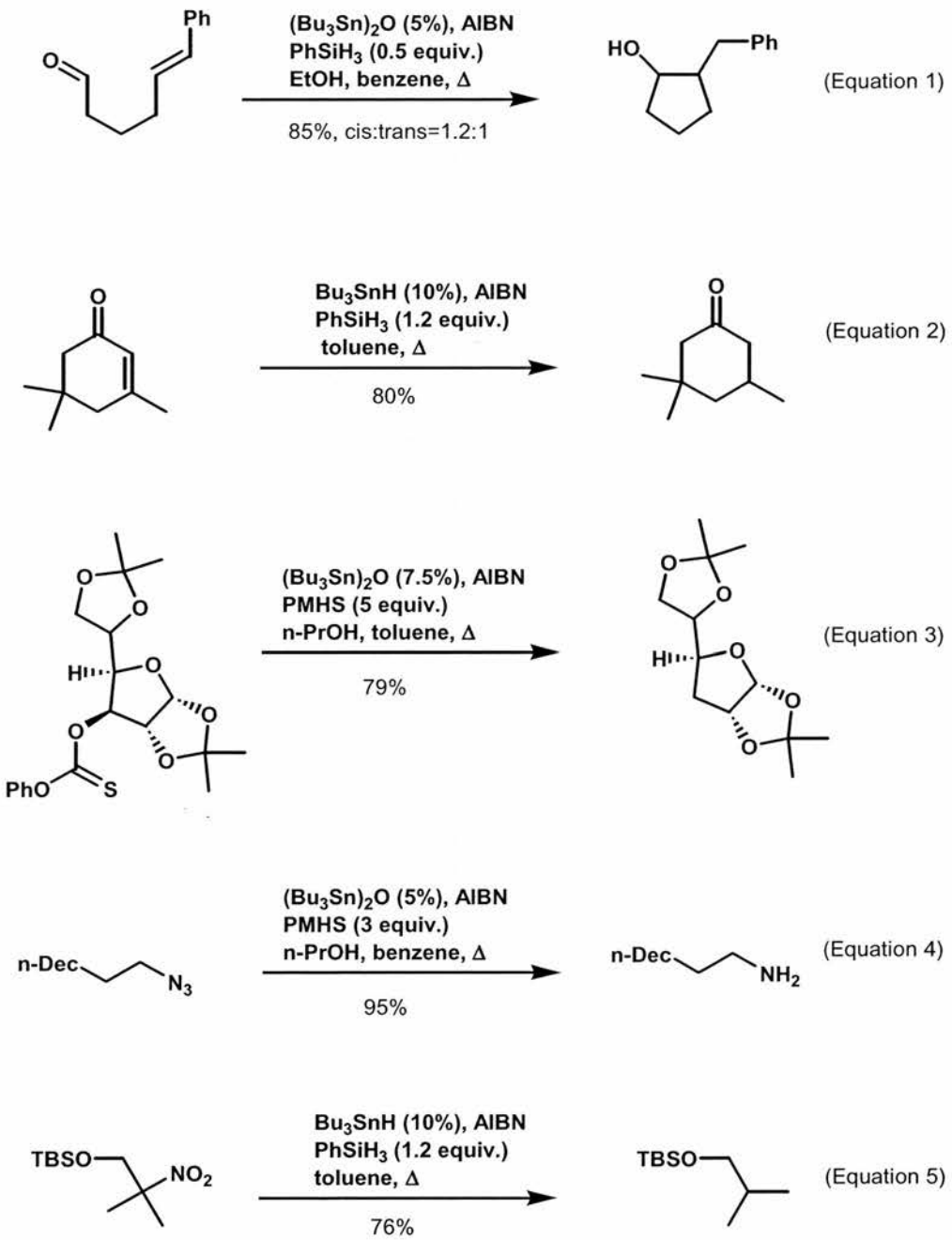



**9** **10**

A further improvement to the catalytic procedure was established by Stork, who used sodium cyanoborohydride as the stoichiometric reducing agent in *t*-butanol.[29]

More recently Fu reported the development of $Bu_3SnH$-catalyzed reactions by using the commercially available phenylsilane ($PhSiH_3$) or polymethylhydrosiloxane (PMHS) to regenerate the tin hydride. Reductive cyclizations of enals and enols were performed with catalytic $(Bu_3Sn)_2O$.[30] An example is depicted in Scheme 7 (Equation 1). In addition, conjugated reduction of α,β-unsatured ketones (Equation 2),[31] Barton-McCombie deoxygenations (Equation 3),[32] reduction of azides to amines (Equation 4),[33] and the reduction of tertiary nitroalkanes to alkanes (Equation 5)[34] were achieved

with $PhSiH_3$ or PMHS as stoichiometric reducing reagents. However, since $PhSiH_3$ and PMHS do not reduce tin halides, these methods are limited to the recycling of tin alkoxides and tin amides.




**Scheme 7**

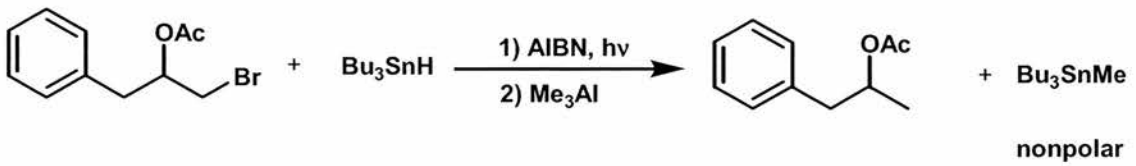
## 1.5 Special Workup Procedures

There is a need to search for new methodologies for the disposal of organotin wastes, because of the environmental problems caused by the well-known toxicity of triorganotin residues. Creation of innovative purification techniques, which improve the extraction of tin residues from the radical mixtures, has therefore been a priority.

The reduction product has generally been separated from the organotin halide byproducts by distillation, gas chromatography, selective extraction, column chromatography, sublimation or a combination of some of these techniques. A facile, general method for the isolation of reduction products from the concomitantly formed organotin halide byproducts was introduced by Jacobus in 1979.[35] In general, the reactant and products of the reduction reaction are soluble in nonpolar organic solvents, and a simple solubility-based separation of the reduction product and the organotin halide cannot be achieved. In contrast trialkyl- and triaryltin fluorides are high melting, non-volatile, insoluble polymeric materials which readily precipitate out of solution. Simple extraction of the reduction mixture, dissolved in a nonpolar solvent, with a solution of potassium fluoride in water converts the organotin halides to the insoluble (in either the organic or aqueous phase) organotin fluoride which can be readily separated by filtration. Filtration removes the majority of the tin residues, however, even after column chromatography there remains about 2% of tin contamination.[36] Furthermore, this method also gave problems when using silyl protecting groups (deprotection) and esters (transesterification). By analogy, a fused mixture of CsF:CsOH and silica gel can be used to remove trialkyltin halides from nonpolar organic coproducts.[37]

Crich[38] proposed a method for the removal of organotin residues by reduction with $NaBH_3CN$ of the halides, regenerating the tin hydrides, which are very nonpolar compounds that can be washed rapidly from silica gel with hydrocarbon eluants. In a similar procedure Renaud[39] has recently reported a method for the removal of organotin residues from reaction mixtures by $Me_3Al$ to convert the tin halides into the corresponding nonpolar methyl tin compounds. Trialkyltin halides react with $Me_3Al$ at room temperature to give a rapid and clean formation of methyltrialkyltin.[40] Tetraalkyltin derivatives are highly non-polar compounds that can be washed easily

from silica gel with hexane, it is possible therefore to transform the trialkyltin halides formed during the radical reaction by a one-pot treatment with $Me_3Al$ (Scheme 8). The methyltributylstannane is easily separated from the product by filtration over a short column of silica gel with hexane as eluent.




**Scheme 8**

Unfortunately, this procedure cannot be considered for all reactions as several functional groups (aldehydes and ketones) will interact with $Me_3Al$ and break down.

Furthermore, polymer- bound tin hydrides have successfully been used in reductive radical chain reactions. To limit the residual tin contamination, organotin hydrides have been anchored to an insoluble polymer so that the byproducts can be separated by simple filtration. The recovered polymeric tin halides can generally be recycled back to the tin hydride for further use. Neumann[41,42] has reported polymers to be of general use in synthesis. However, these reagents are not commercially available and therefore must be prepared prior the use.

### 1.5.1 Modified tin hydrides

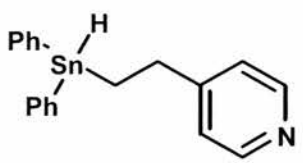
Several modified tin hydrides for which the corresponding tin halides are readily separated from the organic reaction products, have been designed. The alkyl groups in these tin compounds are replaced by special phase makers.[43]

The novel pyridylstannane **11** (Scheme 9) which contains the tin functionality[44] is readily soluble in polar organic solvents, the tin-halogen byproducts have very low $R_f$ values in ethyl acetate:hexane (1:3), which allows the desired product to be efficiently isolated by chromatography. These reagents can be used to form products in comparable yields to those obtained using the standard tin hydride method.

Curran introduced fluorous tin hydrides such as tris[2-(perfluorohexyl)ethyl]tin hydride reagent **12** as a versatile reducing agent which behaves like tri-*n*-butyltin hydride in radical reduction but offers the advantage of easy separation of the tin byproducts from the reduced compound by liquid extraction.[45] The reaction is carried out in trifluoromethylbenzene, which is evaporated off upon completion and replaced with a mixture of dichloromethane and perfluorocyclohexane. The fluorous tin-byproducts remain in the fluorocarbon layer, while the desired organic product passes into the dichloromethane where it can be isolated from any tin contamination.

Breslow [46] developed a new water soluble tri-(methoxyethoxypropyl)tin hydride **13** to perform tin radical chemistry in water. The trialkyltin species are easily recovered. Acidifying the water to pH < 2 with HCl regenerates the trialkyltin chloride, which is extracted into $CHCl_3$, distilled, and reduced with $BH_3$ in THF, regenerating the tri-(methoxyethoxypropyl)tin hydride.

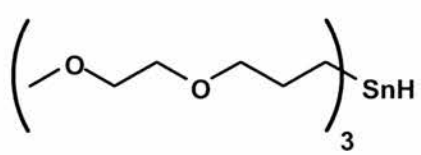
Collum[47] and co-workers have described an improved water-soluble tin reagent **14** which can be reduced in situ with $NaBH_4$ to a tin hydride that can be used in radical dehalogenation reactions. This novel compound has provided consistently high yields, comparable to those of conventional $Bu_3SnH$/AIBN method. Regretfully these compounds must be synthesised in the lab prior to use and this prevents them from becoming popular replacements.




11

$(C_6F_{13}CH_2CH_2)_3SnH$

12

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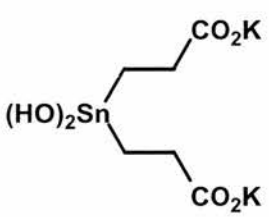



14

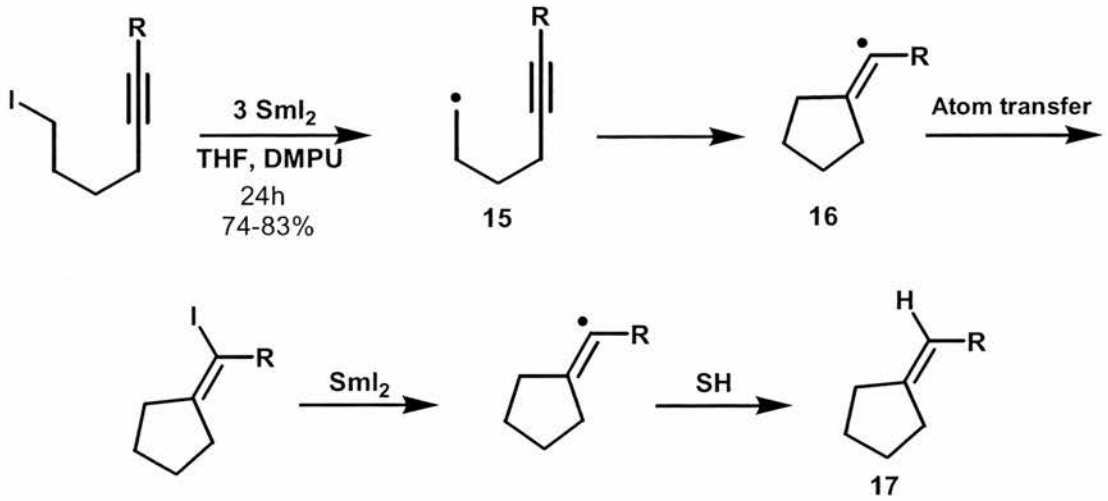
**Scheme 9**

The trouble with all these new reagents is that the problems of tin toxicity and tin waste remain a constant menace.

## 1.6 Alternative Radical Sources

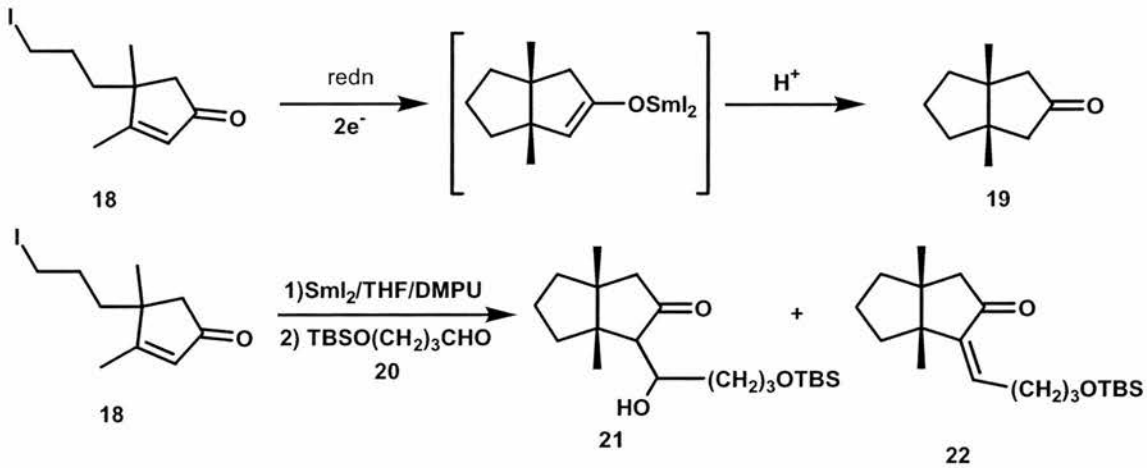
### 1.6.1 Samarium diiodide initiated radical reactions

The one-electron reducing agent samarium diiodide has shown a remarkable versatility in promoting numerous synthetic transformations for the construction of complex organic compounds.[48] Many properties of this reagent have contributed to its immense success. Because of its moderate oxidation potential and high oxophilicity, the divalent lanthanide reagent displays a general functional group selectivity in the reduction step and, when relevant, leads to the formation of products with high diastereoselectivities. In addition, the creation of C-C bonds, otherwise difficult to form by other means, may be realized with this reagent. An alkyl halide (Scheme 9), which accepts an electron from $SmI_2$, displacing the halide and forming an alkyl radical, is a typical precursor. The reductive reaction conditions required for the generation of the radical also promote reduction of radicals to the corresponding anions. Thus any desired radical reaction ($k_{rad}$) must take place significantly faster than reduction of the radical to the corresponding Grignard-type organosamarium anion ($k_{redn}$). Several classes of radical cyclizations fall in this category and, in suitably designed systems, these reactions provide a useful alternative to reactions initiated by tin hydride. Radical $SmI_2$ mediated cyclization of 6-halohex-1-ynes,[49] in presence of DMPU in THF solution, provides the alkyl radical **15** (Scheme 10) which undergoes cyclization to cyclopentylidene radical **16.** The latter then abstracts an iodine atom from the starting material, generating an alkenyl halide, which can be eventually reduced back to a cyclopentylidene radical by $SmI_2$, and the resulting alkenyl radical can abstract a hydrogen from the solvent to provide exomethylenecyclopentanes **17.**




**Scheme 10**

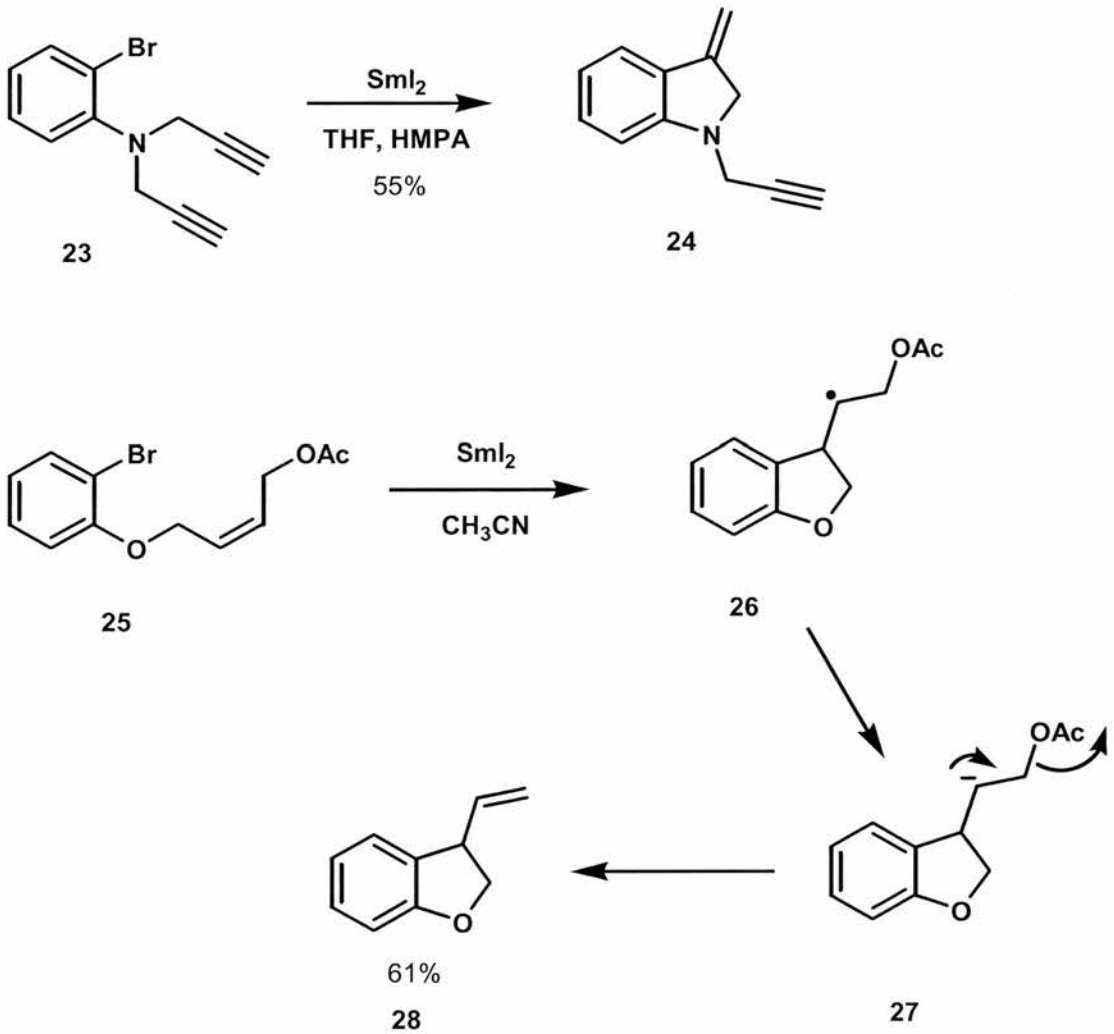
In 1991 Curran demonstrated that when enone **18** was slowly added to a THF solution of $SmI_2$ (2.5 equiv) containing DMPU (10 equiv), after standard acidic work-up and chromatography, ketone **19** was isolated in 70% yield (Scheme 11). When aldehyde **20** was added in place of a proton source, aldol **21** was isolated in 60% yield alongside variable amounts (5-20%) of the dehydrated product **22**.




**Scheme 11**

$SmI_2$ can also promote the formation of vinyl[50] and aryl[51] radicals which are not reduced to the corresponding anions at rates that are competitive with hydrogen atom abstraction from the solvent resulting in a general approach to the synthesis of benzofurans and indoles.

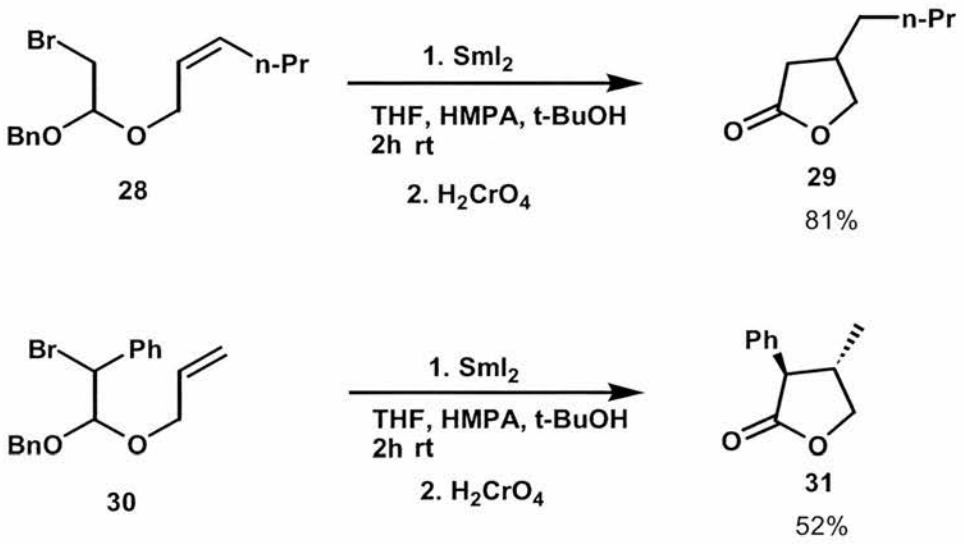
For example, when bromide **23** was treated with the reducing agent, the substituted indole **24** was obtained in 55% yield (Scheme 10). Radical addition/elimination starting from bromide **25**, using the allylic acetate as radical acceptor, can be utilized to create a new carbon-carbon bond and retain olefin functionality in the final product. Cyclization of the aryl radical coming from bromide **25** (Scheme 12) yielded the secondary radical **26.** In the absence of a hydrogen donor, this radical accepted another electron from $SmI_2$ giving carbanion **27** which underwent β-elimination to furnish substituted dihydrobenzofuran **28**.




**Scheme 12**

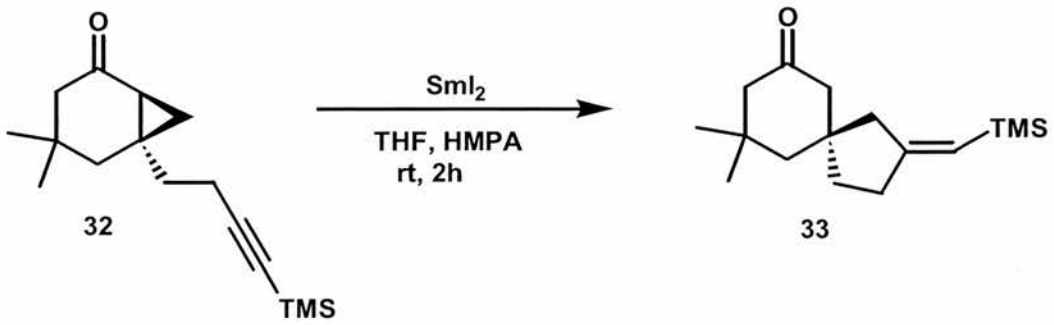
Alkyl radicals containing oxygen within the chain cyclize onto alkenes and alkynes with rates generally an order of magnitude faster than their carbon-analogues.

Straightforward cyclization of bromide **28** (Scheme 13) into lactone **29** was accomplished by a two-step process involving treatment of the bromide with $SmI_2$ for 2h at room temperature followed by Jones oxidation.[52] Analogously, alkenyl bromide **30** resulted in the formation of the corresponding cyclic product **31.** The diastereoselectivity of the reaction was quite high, and was adequately explained through the standard chair transition structure.



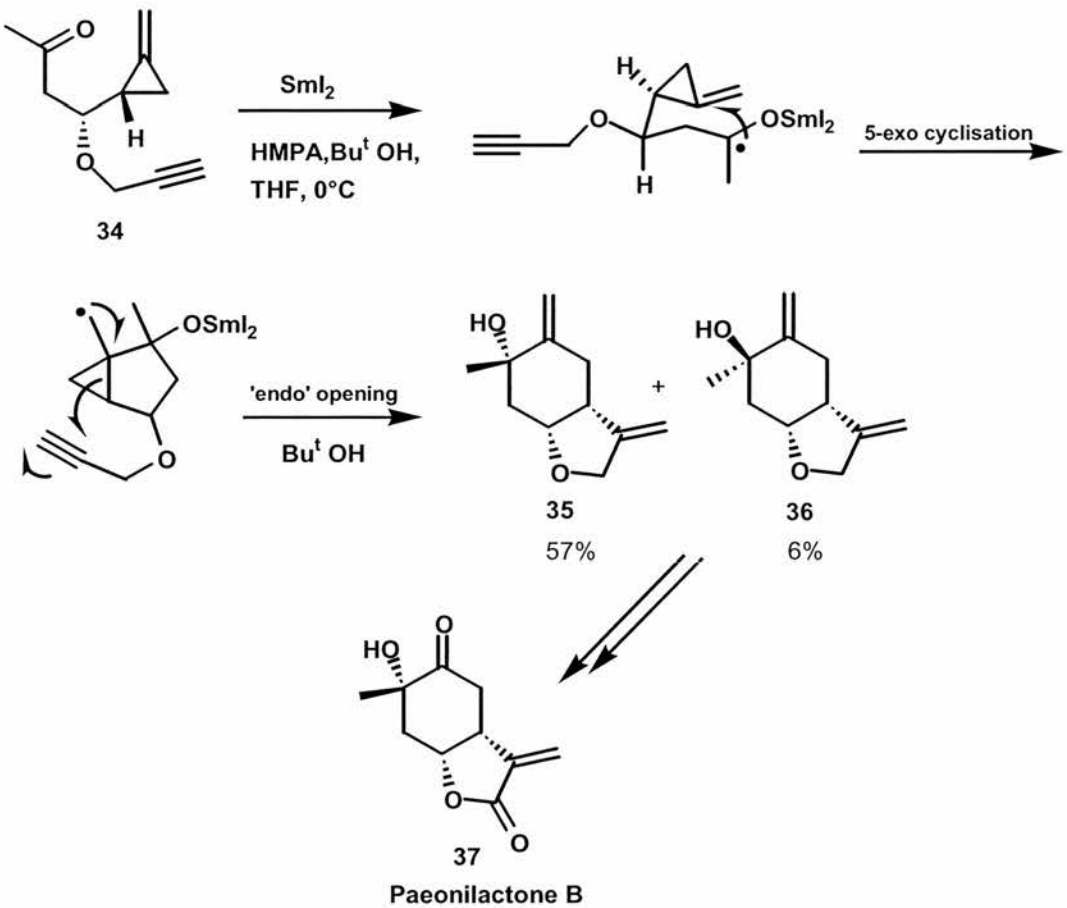

**Scheme 13**

There are other ways to generate alkyl radicals using $SmI_2$ aside from the reduction of halides. For example reductive cleavage of cyclopropyl ketone **32** (Scheme 14) to a cycloalkylmethyl radical via a cyclopropylcarbinyl/homoallylic radical rearrangement process[53] provides the spirocyclic ring **33.**




**Scheme14**

Cascade reactions, initiated by $SmI_2$ have also received attention recently. Processes, initiated by $SmI_2$ and using exclusively radical intermediates are, however, complicated and limited by the fact that each radical intermediate can undergo competitive reduction to the corresponding organosamarium species, which may then effectively terminate the intended cascade sequence. Kilburn has recently provided a novel method for the synthesis of Paeonilactone B **37** (Scheme 15).[54] Treatment of ketone **34** with $SmI_2$, under standard conditions gave the desired bicyclic products as a readily separable mixture of diastereoisomers, **35** and **36**, in 57% and 6% yields respectively. The examples illustrate the versatility of samarium(II) iodide and its potential uses in organic chemistry. Moreover when compared with the traditional tin hydride methods, $SmI_2$ exhibits easier work-up procedures and the potential of the *in situ* formation of organosamarium intermediates. However, the studies so far have involved relatively simple molecules and it remains to be seen whether $SmI_2$ can be used with success in syntheses of natural products. A further drawback to the use of $SmI_2$ is its mild radioactivity.

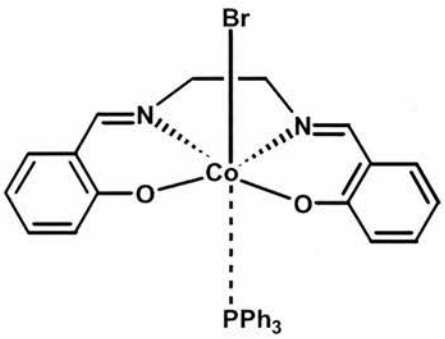



**Scheme 15**

### 1.6.2 Cobalt reagents

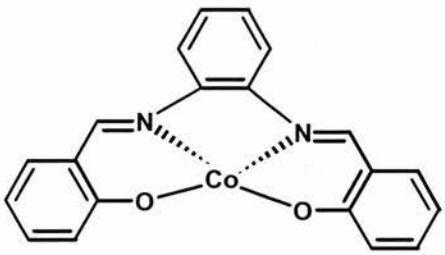
Cobalt is the transition metal present in vitamin $B_{12}$ which has been extensively studied. Investigations demonstrated that biological reactions are initiated by homolytic cleavage of the carbon cobalt bond.[55,56]

Homolysis of organocobalt molecules could therefore provide a good source of carbon radicals. Organocobalt complexes which model the vitamin $B_{12}$ structure, such as bromo (triphenylphosphine) cobalt(III) salen **38** and cobalt(II) salophen **39** can be used to generate alkyl, aryl and acyl radicals that are suitable for use in organic syntheses.




**38**

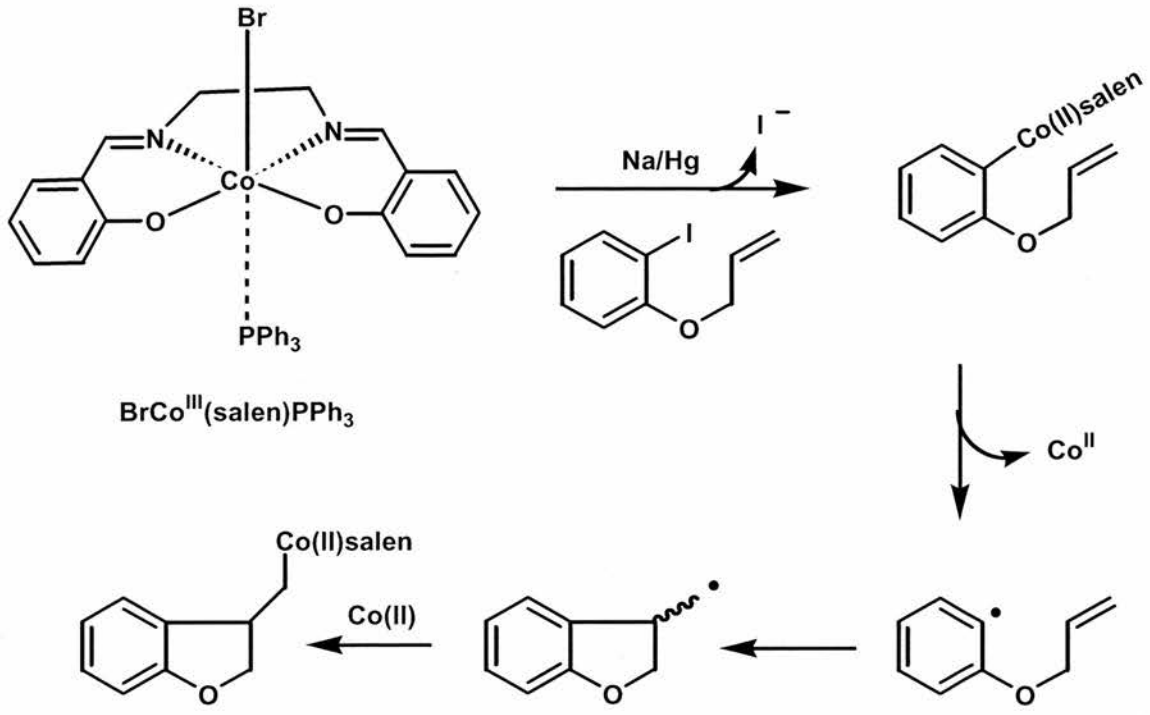
**$BrCo^{III}$ (salen)$PPh_3$**




**39**

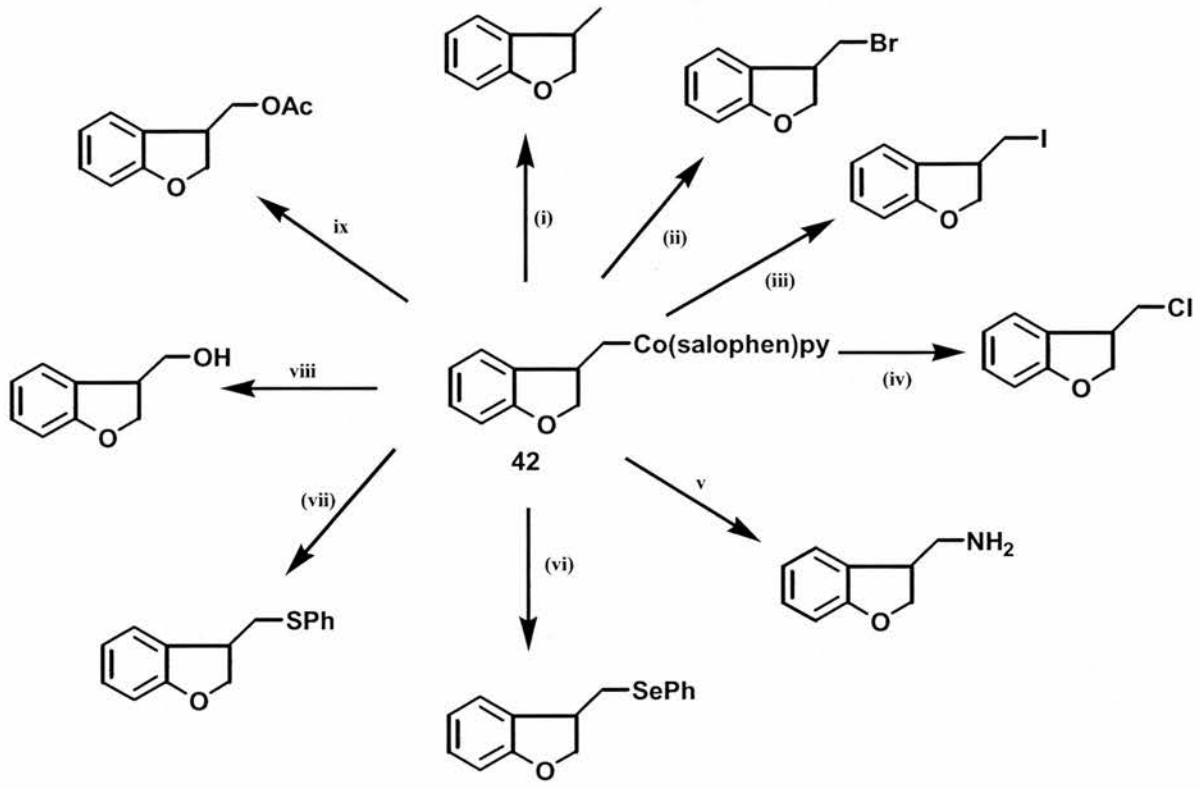
**$Co^{II}$ (salophen)**

For example when the cobalt complex **38** was treated with a small amount of sodium amalgam in THF, followed by addition of aryl iodide **40** (Scheme 16), benzofuran **41** was delivered in 65 % yield.[57]




**Scheme16**

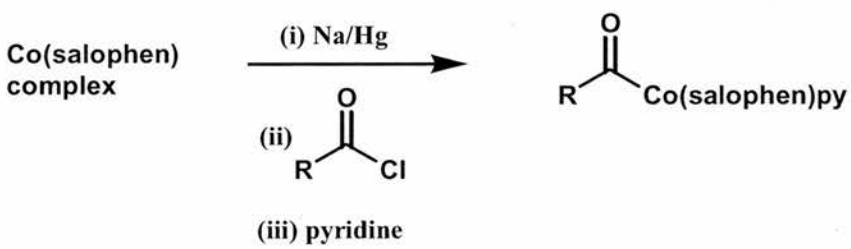
The cobalt compound **41** can undergo a series of reactions in order to introduce new functionality into the molecule. Thus, the analogous cobalt (salophen) complex **42** (Scheme 17) has been converted into phenylselenides, phenylsulphides, oximes and amines, alcohols, esters, chlorides, bromides and iodides in good yields as shown in scheme 17.[58]




(i)light, (ii) $BrCCl_3$, 79%, (iii) $I_2$, 42%, (iv) $MeSO_2Cl$, 78%, (v) NO, DMF, $Et_3N$, then Na, $^iPrOH$, (vi) $Ph_2Se_2$, 75%, (vii) $Ph_2S_2$, 85%, (viii) $O_2$, (ix) TEMPO (2,2,6,6-tetramethylpiperidinyloxyl), Zn, $CH_3CO_2H$

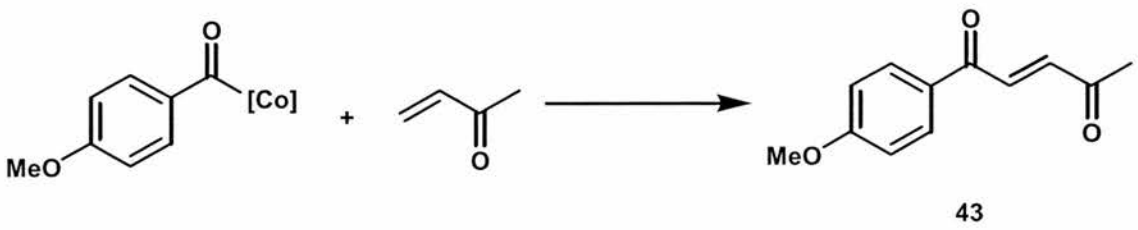
**Scheme 17**

Organocobalt reagents can also generate acyl radicals which are prepared by the reduction of the cobalt (salophen) complex using sodium amalgam in presence of the appropriate acid chloride followed by chromatographic purification (scheme 18).



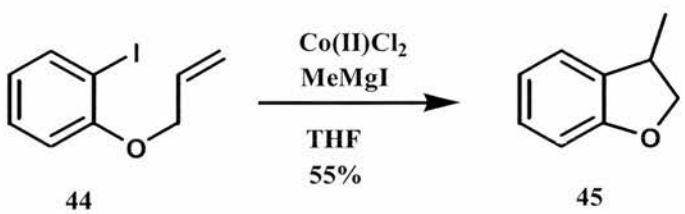

**Scheme 18**

When heated, these complexes generate acyl radicals which can add to activated alkenes before β–elimination occurs to generate the conjugated enone **43** (Scheme 19).




**Scheme 19**

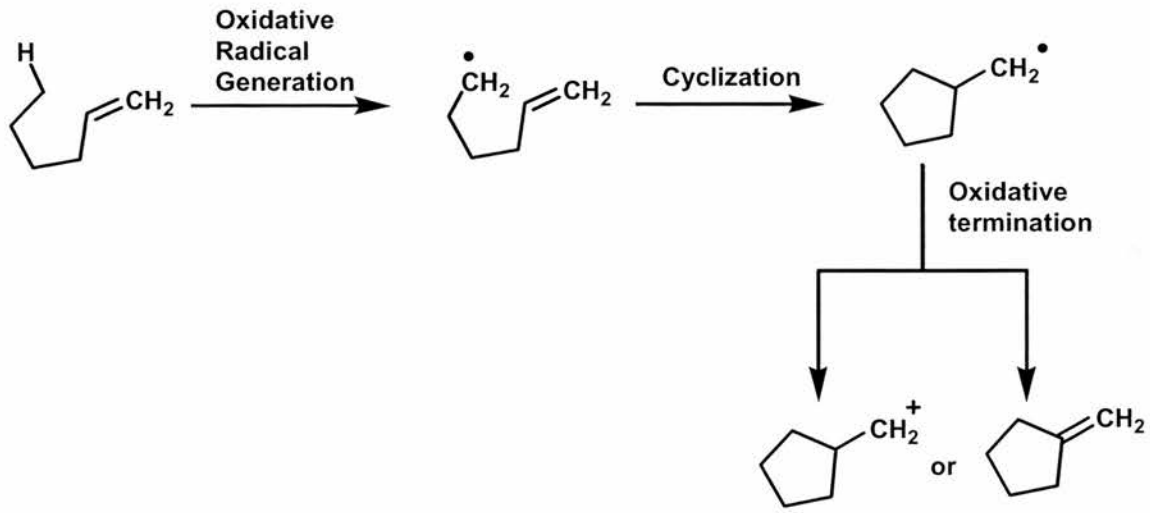
An alternative to tin-hydride mediated aryl radical cyclisation has been reported by Jones.[59] Iodide **44** has been cyclised to dihdrobenzofuran **45** in 54% yield when added to anhydrous $Co(II)Cl_2$ in THF, followed by addition of the Grignard reagent MeMgI, (or EtMgBr), under reflux (Scheme 20). Organocobalt species are formed from the reaction of the Grignard reagent and Co(II) chloride, which subsequently reacts with the aryl iodide to generate the corresponding aryl radical.




**Scheme 20**

## 1.6.3 Manganese(III)-based oxidative radical formation

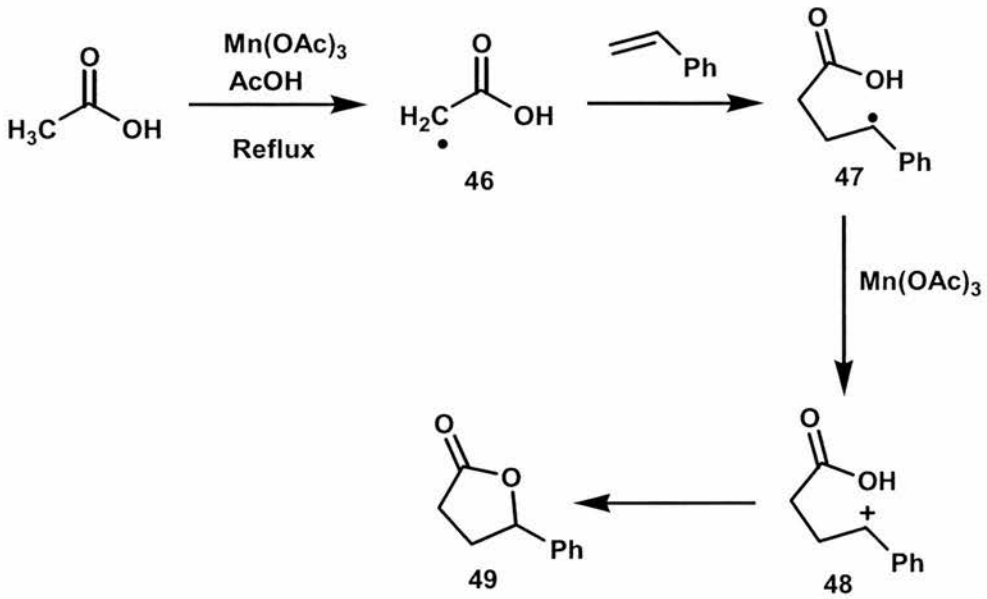
The use of metal oxidants in the generation of carbon-centred radicals, particularly manganese acetate $Mn(OAc)_3.2H_2O$, is a valuable alternative over the traditional use of tin compounds. Oxidative free-radical cyclisations in which the initial radical is generated oxidatively and the cyclic radical terminated oxidatively, can provide highly functionalized and versatile products which allow supplementary reactions to be performed and can be prepared from simple precursors (Scheme 21).




**Scheme 21**

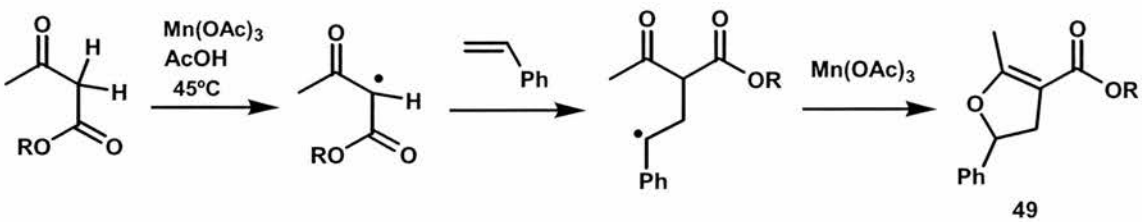
A potential disadvantage in the use of this method is that the type of molecule which can act as a substrate is limited and the majority of it's applications are restricted to 1,3 dicarbonyl compounds. The cyclisation product may also be susceptible to further deprotonation and oxidation. Nevertheless, the formation of carbon-centred radicals by metal oxidants has been used in natural product synthesis.

The oxidative addition of acetic acid to an alkene reported by Heiba[60] and Bush[61] in 1968 provides the basis for a general approach to metal-based oxidative free radical cyclization. Heating $Mn(OAc)_3$ in acetic acid at reflux (115°C) generates the carboxymethyl radical **46** (Scheme 22) which, in the presence of an electron-rich alkene, gives adduct radical **47.** This radical is more prone to oxidation than **46** and, in the presence of a second equivalent of $Mn(OAc)_3$, an electron transfer from the carbon-centred radical results in the formation of the corresponding cation **48**. The neighbouring carboxylic acid group finally attacks the ionic intermediate to give γ-lactone **49.**



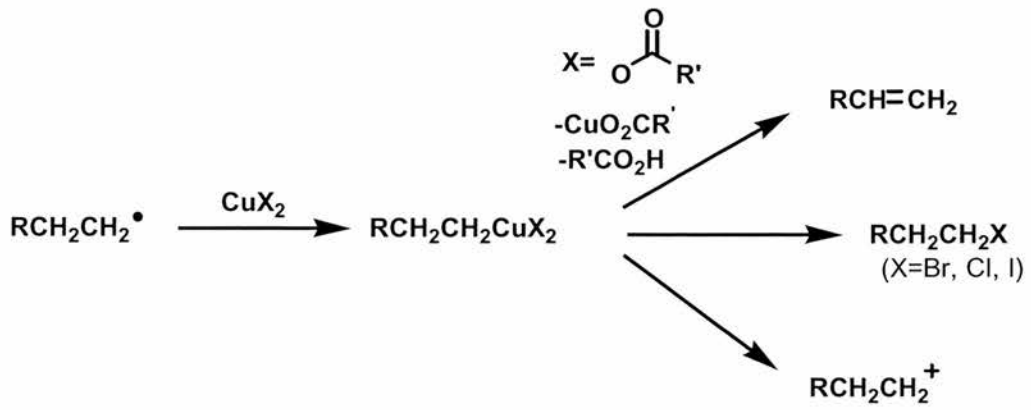

**Scheme 22**

Unfortunately Mn(III)-based oxidative cyclisations of unsatured acids are not possible since the optimal solvent for these reactions, acetic acid, will be oxidized preferentially. However Heiba and Dessau performed a series of experiments on β-ketoesters and related dicarbonyl compounds under milder conditions in order to show these novel manganese complexes could be used with no competitive oxidation of the solvent. For instance, oxidation of ethyl acetoacetate in the presence of styrene affords dihydrofuran **49** (scheme 23).




**Scheme 23**

In the 1960's Kochi demonstrated that Cu(II) reacts rapidly with radicals to give alkylcopper(III) intermediates (Scheme 24).

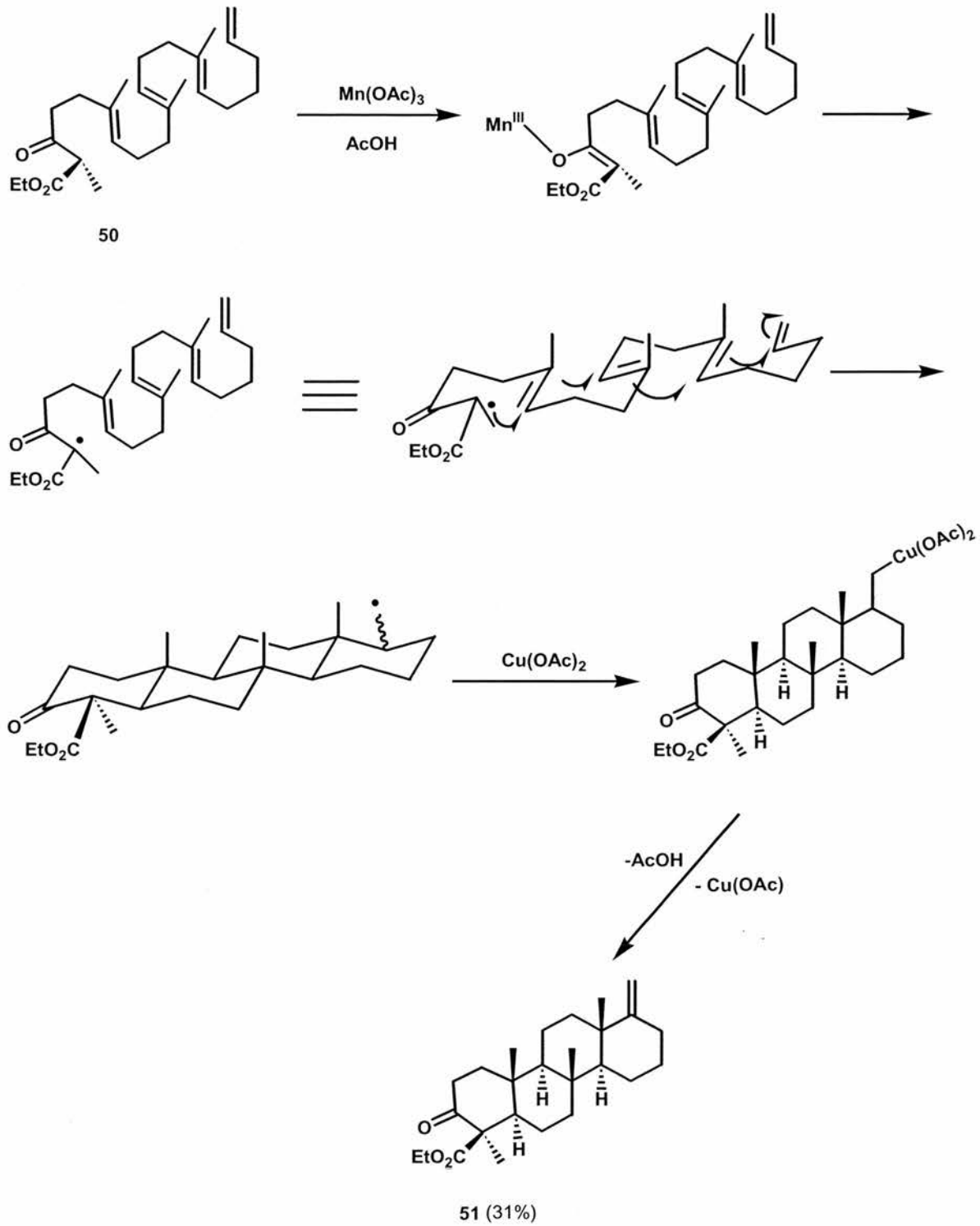



**Scheme 24**

These intermediates can react further with loss of Cu(I) to either form an alkene by oxidative elimination, transfer a ligand to give $RCH_2CH_2X$, or form a carbocation.[62]

Heiba and Dessau demonstrated that the use of $Cu(OAc)_2$ in conjunction with $Mn(OAc)_3$ oxidizes secondary radicals much faster than Mn(III).[63] The Cu(I) produced from the reaction is rapidly oxidized to Cu(II) by Mn(III) so that only a catalytic amount of $Cu(OAc)_2$ is required.

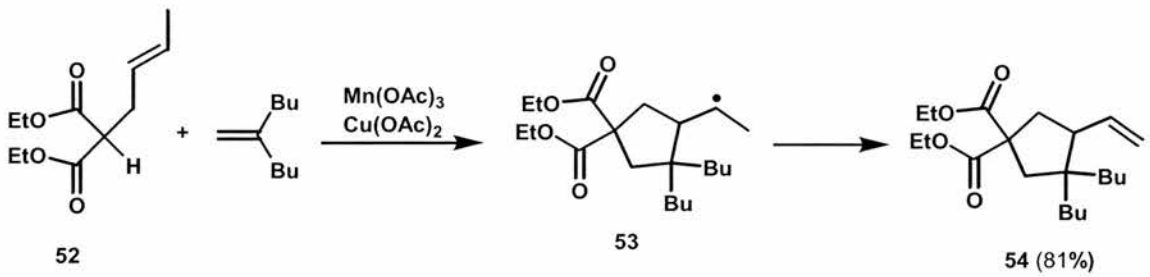
Zoretic has developed a very efficient tetracyclisation leading to *trans*-decalin ring systems (Scheme 25).[64] β–Ketoester **50** was converted into tetracyclic compound **51** in 31 % yield. The stereoselectivity of the reaction was remarkable as only one of the sixty-four possible isomers was formed. Functionality was added to the product released by β-hydride elimination to form an *exo*-positioned double bond due to the presence of $Cu(OAc)_2$ in the reaction mixture which has been shown to result in oxidative termination. The advantage of terminating this tandem radical process with the formation of an olefin is obvious. These examples illustrate that such reactions can be performed to form complex natural products. Numerous references to other applications of this methodology are cited in Snider's paper.[65]




**Scheme 25**

Manganese(III) oxidative free-radical cyclisation can also be used for annulations-tandem free-radical reactions in which a carbon carbon bond is formed by

intermolecular addition followed by cyclisation. For example the oxidation of diethyl crotyl malonate **52** in the presence of an alkene produces a radical, which undergoes 5-*exo*-cyclisation to give cyclopentylethyl radical **53** (Scheme 26) that is oxidized by $Cu(OAc)_2$ selectively to the least substituted alkene **54**, 81% yield.



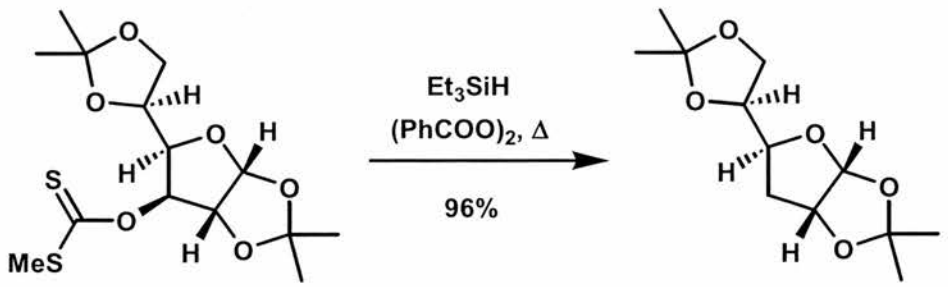

**Scheme 26**

These examples illustrated the synthetic potential of Mn(III) based oxidative radical reactions. However, further development is needed in order to assess the scope, limitations and mechanism of these reactions.

### 1.6.4 Silanes as tin hydride substitutes

Trialkylsilanes $R_3SiH$ represent a viable alternative to trialkyltin hydrides. Silicon centred radicals are extremely efficient in abstracting halogens from alkyl halides, in order to generate the corresponding alkyl radicals. However, H-abstraction from simple trialkylsilanes by C-radicals is too slow to participate in radical chain reactions at ordinary temperatures because the silicon-hydrogen bond is usually too strong for efficient H-abstraction. Moreover alkyl radicals are nucleophilic species and the hydrogen atom in triethylsilane is also electron rich. Therefore, the abstraction of hydrogen from triethylsilane by an alkyl radical to give the reduced product is unfavourable and this disrupts the chain process. For example for the reduction of a primary C-radical with $Et_3SiH$ at 50°C, there is 40% H-abstraction from the ethyl groups in $Et_3SiH$ and only about 60% at the Si-H moiety.[66] $Ph_3SiH$ is slightly more reactive in the reduction of C-radicals than $Et_3SiH$. Barton and Jaszberenyi reported the reduction of alkyl bromides and isonitriles by $Ph_3SiH$ in excellent yield.[67] However, the corresponding iodides and chlorides were reduced in poor yields while phenylselenyl derivatives were completely unreactive. There are some applications

using these less reactive silanes which have been reported to be useful alternatives to tributyltin hydride.[68,69] The Barton McCombie reaction works especially well with these unreactive silanes. For example, deoxygenation of xanthate **55** can be achieved in neat triethylsilane solutions affording tetrahydrofuran **56** in 96% yield (Scheme 27), provided that effective initiation is maintained by the portionwise addition of benzoyl peroxide.



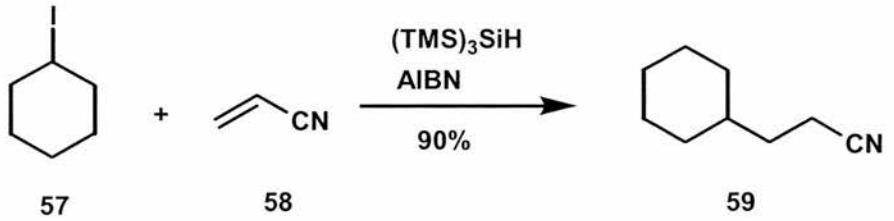

**55** **56**

**Scheme 27**

In general the high reaction temperatures (refluxing toluene, 120-140°C) and the use of large quantities of initiator to create and maintain the radical chain reaction are often undesirable and it is unlikely that either triethylsilane or triphenylsilane will be widely used in organic synthesis to mediate radical reactions.

The most successful tin hydride substitute to date was introduced by Chatgilialoglu in 1988. Tris(trimethylsiyl)silane (TTMSS)[70] is commercially available and can satisfactorily replace tin hydrides in the more common radical reactions because of its greater hydrogen donating ability compared to trialkylsilanes. This is due to stabilisation of the resulting silyl radical achieved by back-bonding into the adjacent, vacant, d-orbital on each of the silicon atoms. Moreover, since the Si-H bond strength is approximately 5 kcal/mol stronger than the Sn-H bond of tributyltin hydride, the less reactive $(TMS)_3SiH$ often allows radical reactions using a stoichiometric amount of the silane in the initial reaction mixture to be performed, preventing, in some cases premature reduction of intermediate radicals by tributyltin hydride.[71] The reactions are generally conducted, in analogy to the tin hydride mediated reactions, using azobis isobutyronitrile (AIBN) as initiator in benzene or toluene. An example of a reductive chain reaction using $(TMS)_3SiH$ is given in Scheme 28. The Giese-type reductive

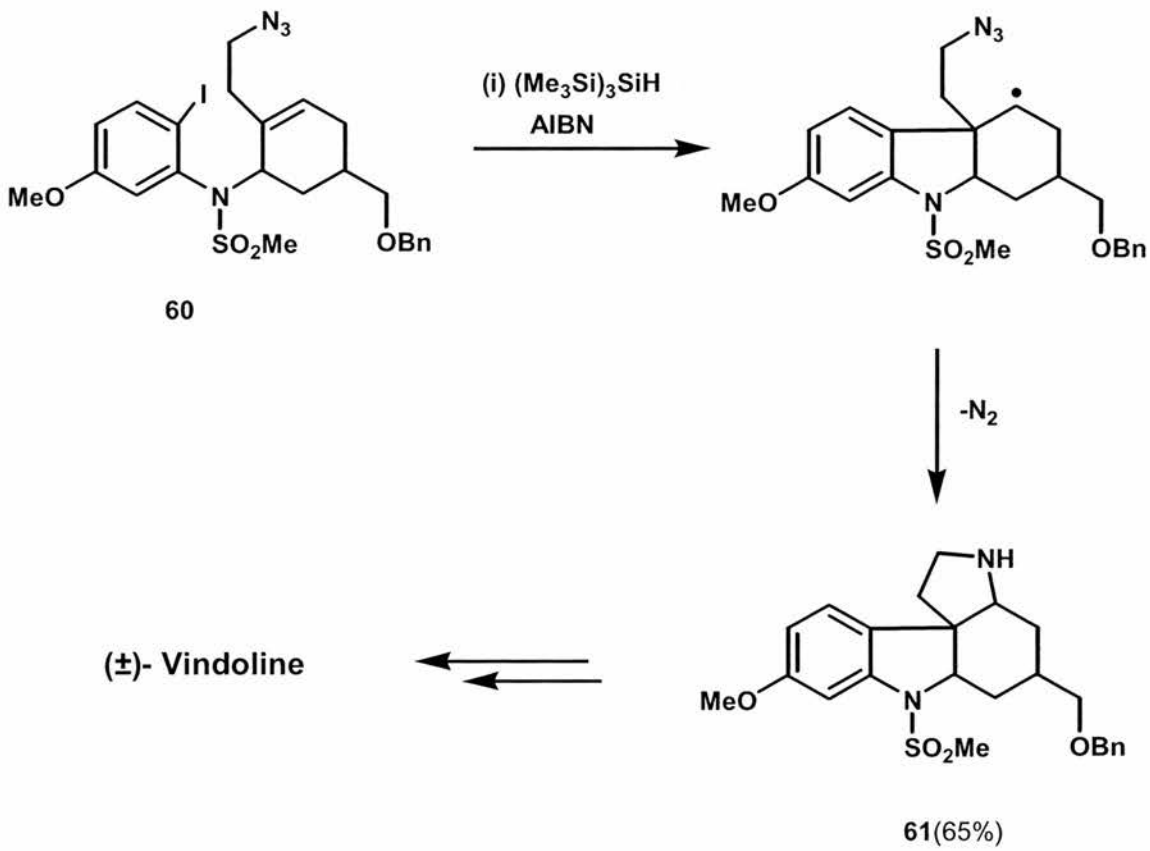
addition reaction of cyclohexyl iodide **57** onto activated olefins **58** afforded the desired product **59** in 90% yield, which was comparable to that obtained by the tin method.




57 58 59

**Scheme 28**

In a recent publication Murphy and co-workers[72] presented an intramolecular tandem radical cyclization employing iodoaryl azide **60** in the formal total synthesis of the clinically important anticancer agent (±)-vindoline (Scheme 29). When iodide **60** was treated with TTMSS in the presence of AIBN the aryl radical resulting from iodine atom abstraction, cyclised in a 5-*exo* fashion generating a new C-centred radical which attacked the azide group, assembling the tetracycle **61** in 65% yield.

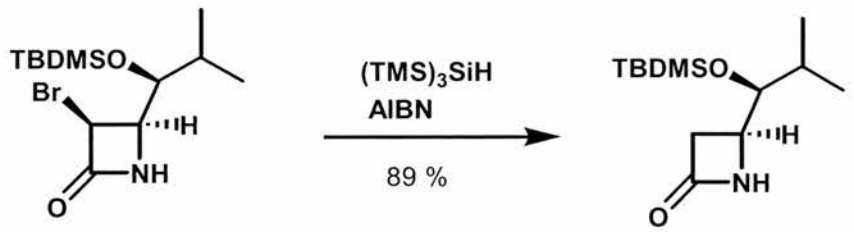



60

61(65%)

**Scheme 29**

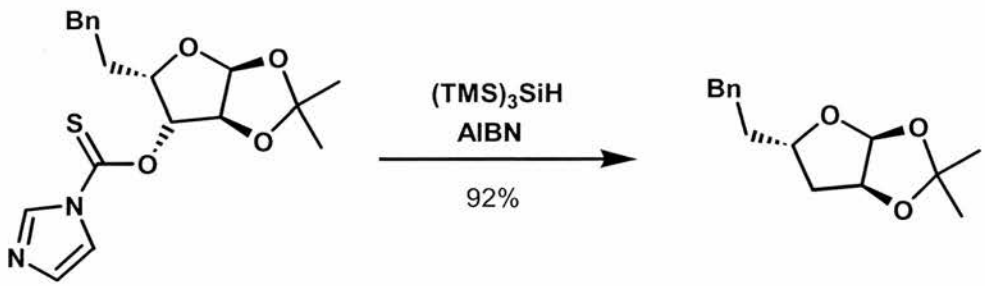
A useful modification of halolactams has been achieved with a dehalogenation procedure by using TTMSS as radical mediator.[73] Treatment of α-bromoazetidinone **62** in toluene with TTMSS in the presence of AIBN furnished the 3-unsubstituted azetidinone **63** in 89% yield (Scheme 30).




62 63

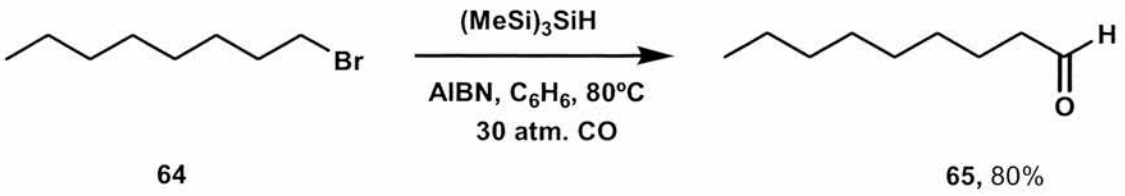
**Scheme 30**

Barton McCombie reactions can usefully be conducted with TTMSS.[74] (Scheme31)




**Scheme 31**

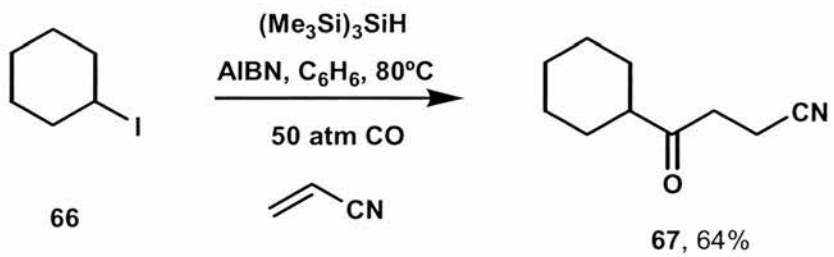
Free radical carbonylation has recently gained distinction as a promising method for the introduction of carbonyl groups into molecules. Extensive research has been carried out in this area using organotin compounds as radical mediators.[75] However, these processes must be carried out under high pressures in order to encourage the alkyl radical to react with carbon monoxide instead of abstracting hydrogen from the tin hydride. For example, octyl bromide **64** was converted into aldehyde **65** in 80% yield when refluxed in benzene in the presence ofTTMSS, AIBN and 30 atmospheres of CO (Scheme 32).




64 **65,** 80%

**Scheme 32**

Due to the stronger Si-H bond in TTMSS compared to tin hydride, direct reduction is less of a problem and this allows the pressure of CO to be reduced. When this reaction was carried out using tin hydride methods, the optimal pressure of carbon monoxide was 50 atmospheres and even then, the yield of aldehyde was only 63% with octane forming in 36% yield. Using TTMSS it was also possible to carry out reactions which involved addition of an alkyl radical to CO, followed by addition of the acyl radical to an alkene prior to hydrogen abstraction in order to obtain the corresponding ketone in good yields. Thus, iodide **66** was converted into β-cyano ketone **67** in 64% yield as shown in Scheme 33.

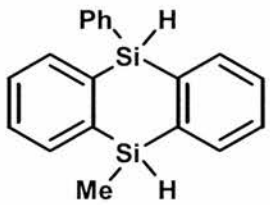



66 **67**, 64%

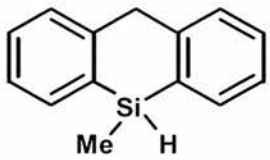
**Scheme 33**

Although tris(trimethylsilyl) silane shows great versatility and can be used to mediate a number of useful radical reactions, its use entail some disadvantages. For example, the silyl radicals generated from this reagent are very efficient at hydrosilylating double and triple bonds, leading to reduced yields by forming unwanted side products.[76] Another disadvantage is that it is expensive although it can be prepared by treating trichlorosilane and trimethylsilyl chloride with lithium. Chatgilialoglu and Griller have reported a catalytic use of TTMSS using sodium borohydride to regenerate the reagent from the silicon-halogen byproduct.[77] The method described gives yields comparable to the stoichiometric methods and reduces costs and waste.

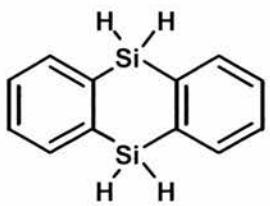
As documented, the incorporation of different groups on the central silicon has only a small effect on the strength of the Si-H bond. It has been found, however, that the siladihydroanthracenes **68-70,** (Scheme 34) where the phenyl substituents at the silicon atom are conformationally locked, show enhanced H-donor abilities in radical reactions.[78-80] Of the three silanes shown, the most effective reagent was silane **68** which can efficiently be used for the reduction of alkyl halides and deoxygenation of alcohols. Silane **69** was surprisingly unreactive for mediating such reactions.




**68**




**69**

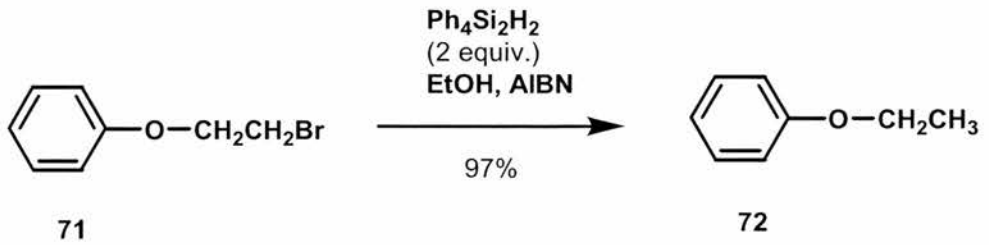



**70**

**Scheme 34**

Silane **70** was also capable of deoxygenating alcohols under mild conditions. Interestingly, Togo and Yamazaki prepared various water-soluble arylsilanes that showed enhanced reactivity, if the chain reactions are conducted in water. They used them successfully in radical dehalogenations.[81] Taking into consideration the ease of preparation of these silanes[82] it is possible that they could replace TTMSS as new reducing agents.

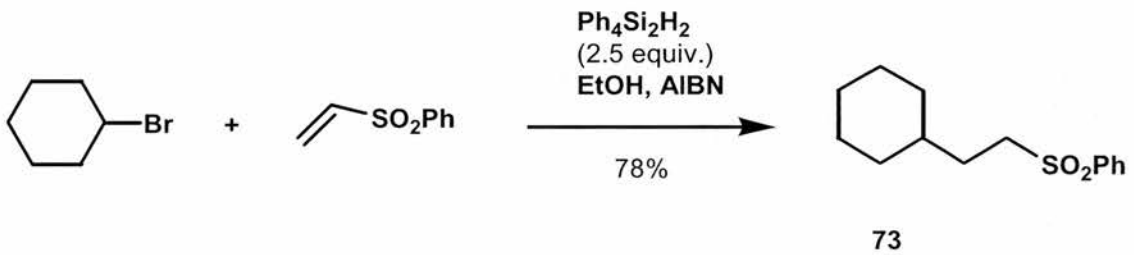
Togo has intensively studied 1,1,2,2-tetraaryldisilanes ($Ph_4Si_2H_2$) as novel tin hydride substitutes in various reductive chain reactions.[83] For example in the reduction of 2-bromoethyl phenyl ether **71** (Scheme 35), with $Ph_4Si_2H_2$ and AIBN as radical initiator under refluxing conditions, furnished the reduced ethyl phenyl ether **72** in 93% and 97% yield with 1 and 2 equivalents of $Ph_4Si_2H_2$ respectively. The use of 0.5 equivalent of $Ph_4Si_2H_2$ under the same conditions yielded just 49 % of the desired product. These results indicate that one of the two hydrogen atoms participates in the reaction and, therefore this radical reduction requires more than 1 equivalent of $Ph_4Si_2H_2$ in order to obtain the reduction product in good yield. On the other hand, the radical reduction of **71** with 1 equivalent of $Ph_2SiH_2$ gave only a 3% yield of ethyl phenyl ether showing a considerable difference in reactivity between $Ph_4Si_2H_2$ and $Ph_2SiH_2$.




71 72

**Scheme 35**

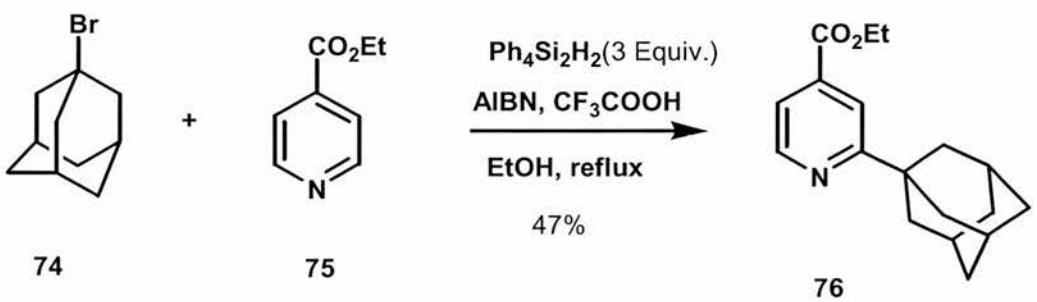
Giese-type addition of cyclohexyl bromide (Scheme 36) to a carbon-carbon double bond with phenyl vinyl sulfone was carried out in the presence of $Ph_4Si_2H_2$ and AIBN in ethanol giving the corresponding reductive addition product **73** in 78 % yield.




**73**

**Scheme 36**

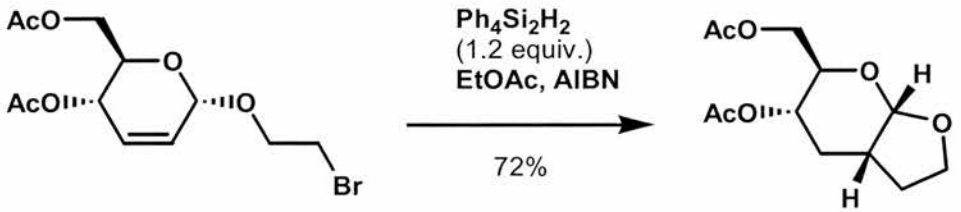
Radical alkylation onto heteroaromatic bases, activated by protonation with trifluoroacetic acid has also been investigated.[83] When adamantyl bromide **74**, $Ph_4Si_2H_2$, AIBN and ethyl isonicotinate **75,** in the presence of trifluoroacetic acid, was refluxed in ethanol it gave the corresponding alkylated heteroaromatic base **76** (Scheme 37).




74 75 76

**Scheme 37**

Many other types of heteroaromatic bases such as benzothiazole, caffeine, ethyl pyridine, and pyrimidines were also effectively alkylated with alkyl bromides in the presence of $Ph_4Si_2H_2$ in good yields. For example, 5-*exo* cyclisations (Scheme 38) can be performed with tetraaryldisilanes as the radical reducing agents.



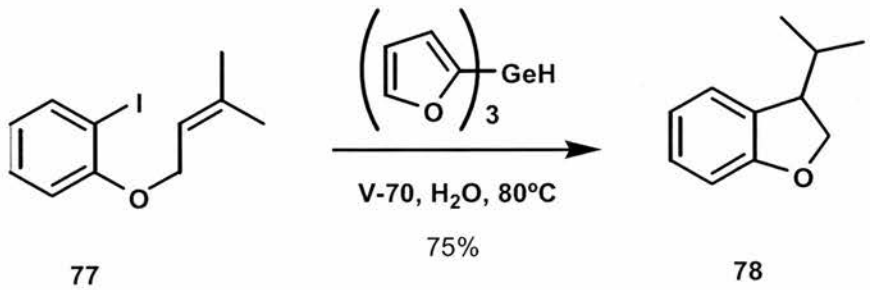

**Scheme 38**

In conclusion $Ph_4Si_2H_2$ is a useful and diversified radical reagent for the reduction of alkyl bromides, alkyl addition to activated olefin, and for alkylations onto heteroaromatic bases. Further, the present reactions proceed in ethanol instead of other toxic organic solvents such as benzene.

Germanium hydrides have been evaluated in reductive radical chain reactions. In General germanes are more reactive than silanes, but less reactive than the corresponding tin hydrides. Tributylgermanium hydride derives its principal benefit from the low reactivity of its metal-hydrogen bond. In reactions with olefins,[84,85] the intermolecular addition of the longer-lived alkyl radical can proceed with essentially equimolecular amounts of halide and olefin. However the germanium hydride method is restricted to iodides as radical precursors, due to the lower reactivity of germanium radicals with halides. Furthermore, tributylgermanium hydride is more prone to react with olefins than its tin counterpart.

The most potent H-donor towards C-radicals to date is $(TMS)_3GeH$,[86] which reduces primary C- radicals about three times faster than $Bu_3SnH$. $(TMS)_3GeH$ has been used in radical dehalogenations, in Barton-McCombie reductions, in deaminations via isonitriles, and in deselenations.[87]

Recently Oshima used tri-2-furylgermane as a potent tin hydride substitute for radical dehalogenations and deoxygenations.[88] Moreover, radical cyclization reactions can be performed with tri-2-furylgermane. The reactions are generally conducted in THF using $Et_3B/O_2$ as radical initiator. Moreover, reduction of organic halides by tri-2-furylgermane can be performed in water. V-70 [2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)] was used as a water soluble initiator in these reactions. For example, when a suspension o-iodophenol **77** and tri-2-furylgermane in water was treated with V-70, and the whole mixture was stirred at 80°C for 4.5h, the corresponding cyclic product **78** was obtained in 75% yield (Scheme 39).




**77** **78**

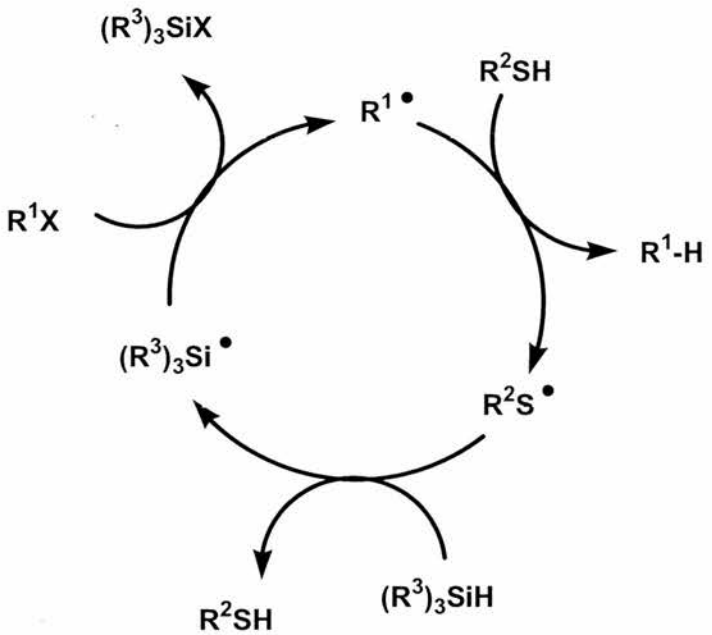
**Scheme 39**

However, although these reagents have some advantages, they are not an ideal alternative to organotin hydride, not least due to the cost and are therefore not used very often in preparative radical chemistry.

# 1.7 Sulfur Compounds as Organic Alternatives to Toxic Tin

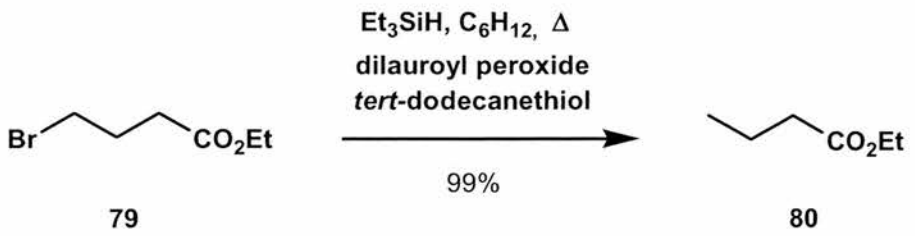
## 1.7.1 Polarity Reversal Catalysis

Polarity reversal catalysis (PRC) by thiols has successfully been applied in reductive radical chain reactions using stoichiometric amounts of trialkylsilanes.[89] Alkyl radicals are nucleophilic species, and the hydrogen atom in trialkylsilanes is also electron rich. Therefore, the abstraction of hydrogen from trialkylsilanes by an alkyl radical to give the reduced products is unfavourable. In 1991 Roberts overcame to this problem by adding a catalytic amount of an alkanethiol, such as *tert*-dodecanethiol (XSH), in union with trialkylsilane, to the reaction mixture.[90] In the chain, the C-radical $R^1$ (Scheme 40) is readily reduced by the thiol catalyst to provide the corresponding reduced product $R^1H$, in yields greater than 90%, along with the thiyl radical $R^2S^{\cdot}$. The thiyl radical is then reduced with a trialkylsilane $(R^3)_3SiH$ to regenerate the thiol catalyst $R^2SH$ along with the silyl radical $(R^3)_3Si$, which is able to propagate the chain reaction.




**Scheme 40**

For example ethyl 4-bromobutyrate **79** was quantitatively reduced to ethyl butyrate **80** using triethylsilane and dilauroyl peroxide as initiator in refluxing cyclohexane (Scheme 41). *t*-Dodecanthiol was used as the polarity reversal catalyst in the reaction.

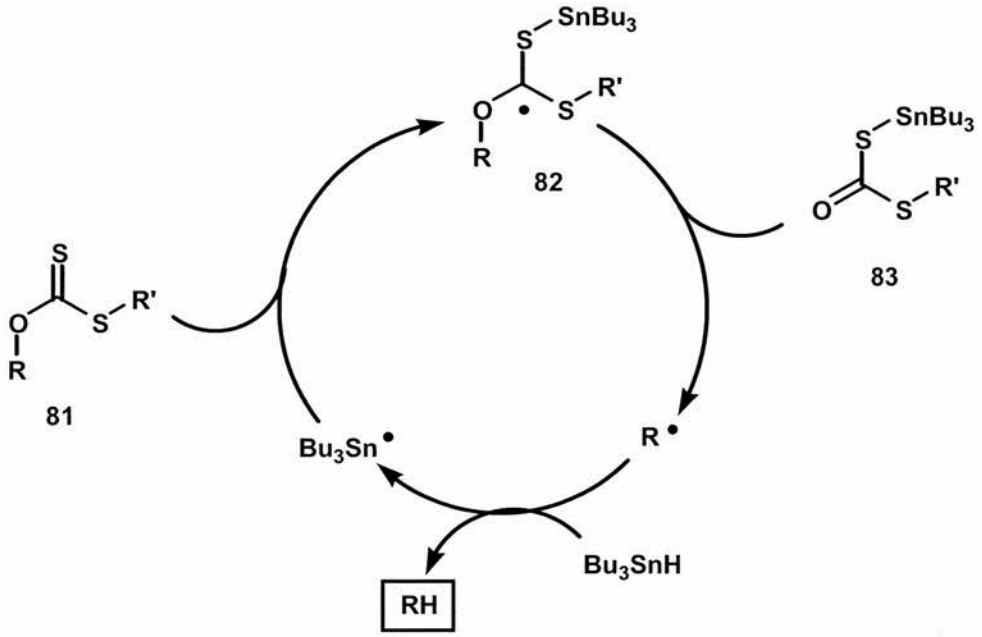



**79** **80**

**Scheme 41**

## 1.7.2 Xanthates in radical chain reactions

Barton McCombie radical deoxygenation using organotin hydrides and thiocarbonyl compounds,[91] has been widely used in organic synthesis, especially for the modification of carbohydrates, and as a convenient source of radicals from alcohols in general. The method requires the conversion of an alcohol into a xanthate **81** which is readily attacked by tributyltin hydride in the presence of a radical initiator (AIBN) to give the carbon-centred radical adduct **82** undergoing a preferential β-scission of the carbon-oxygen bond to form alkyl radical **R**· and the carbonyl co-product **83** (Scheme 42).[92]

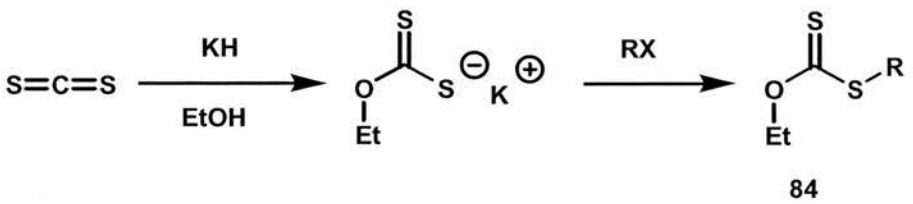



**Scheme 42**

The use of cheap reagents is the major advantage of this procedure; however, the reappearance of organotin hydrides in the reaction mechanism prevents this method being used outside laboratories.

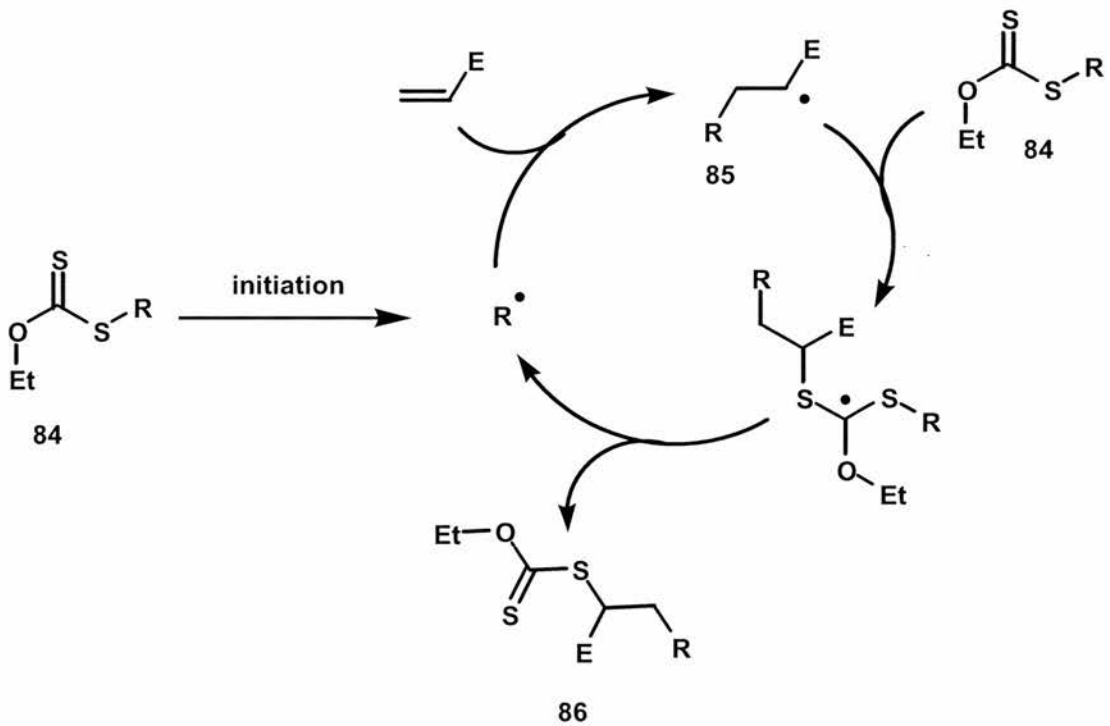
## 1.7.3 Xanthates in tin-free radical processes.

Zard and co-workers have made a very intensive study of the homolytic chemistry of a variety of xanthates.[92] O-Ethyldithiocarbonates, for example, promote tin-free radical chain additions quite efficiently.[93-95] No heavy or toxic metals are involved in such a process and the starting materials are cheap and readily available. For example *O*-ethyldithiocarbonate **84** can be made by nucleophilic displacement of an alkyl halide with potassium *O*-ethyl xanthate (Scheme 43).




**Scheme 43**

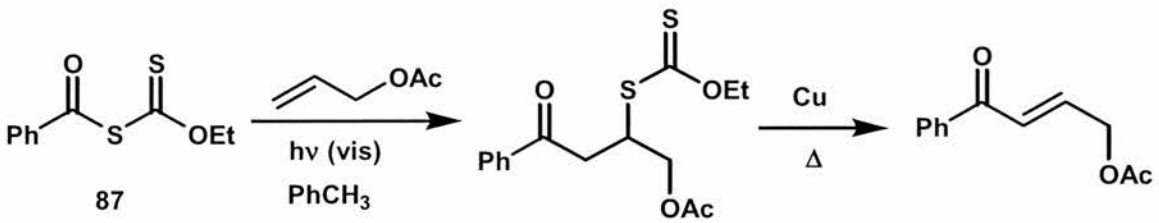
On chemical or photochemical initiaton, *O*-ethyldithiocarbonate **84** cannot undergo β-scission on the carbon-oxygen bond since it would produce an ethyl radical, which is thermodynamically unstable; a radical **R**· is thus generated. **R**· reacts with an alkene placed in the medium leading to an adduct radical **85** which in turn reacts with the starting xanthate **84** to generate, after two reversible steps, **R**· and the new xanthate **86**. The released radical can then add to the alkene or cyclise before continuing the chain by addition to more xanthate **84** (Scheme 44). The chain reaction is initiated using a catalytic amount of peroxide to give the xanthate **86** as the major product which can be employed as a starting point for another radical sequence, or modified further. The xanthate functionality can also be removed by reduction with dilauroyl peroxide in propan-2-ol or treatment with DBU in order to furnish the required addition product. The array of functionality that can be obtained by using the xanthate procedure is quite amazing and has many interesting applications.




**Scheme 44**

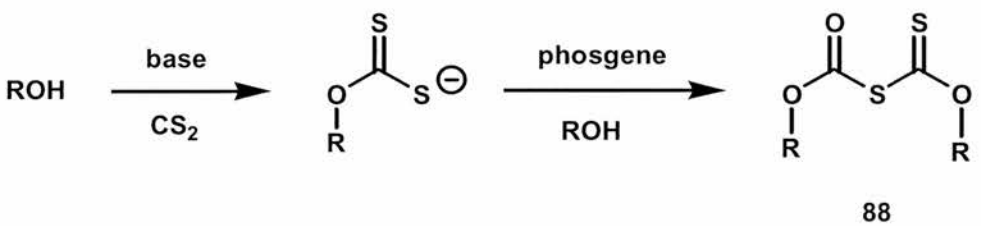
Acyl radicals can be formed from the appropriate S-acyl xanthates, preparation of which is quite simple. For example, treatment of benzoyl chloride with potassium O-ethyl xanthate furnishes S-acyl xanthate O-ethyl derivative **87**. Acyl radicals can be generated by irradiating the corresponding S-acyl xanthate with visible light and captured in an inter- or intra-molecular fashion by using the appropriate olefin (Scheme 45).

In this example the xanthate moiety can be easily removed with base or by heating with copper powder yielding the alkene function.



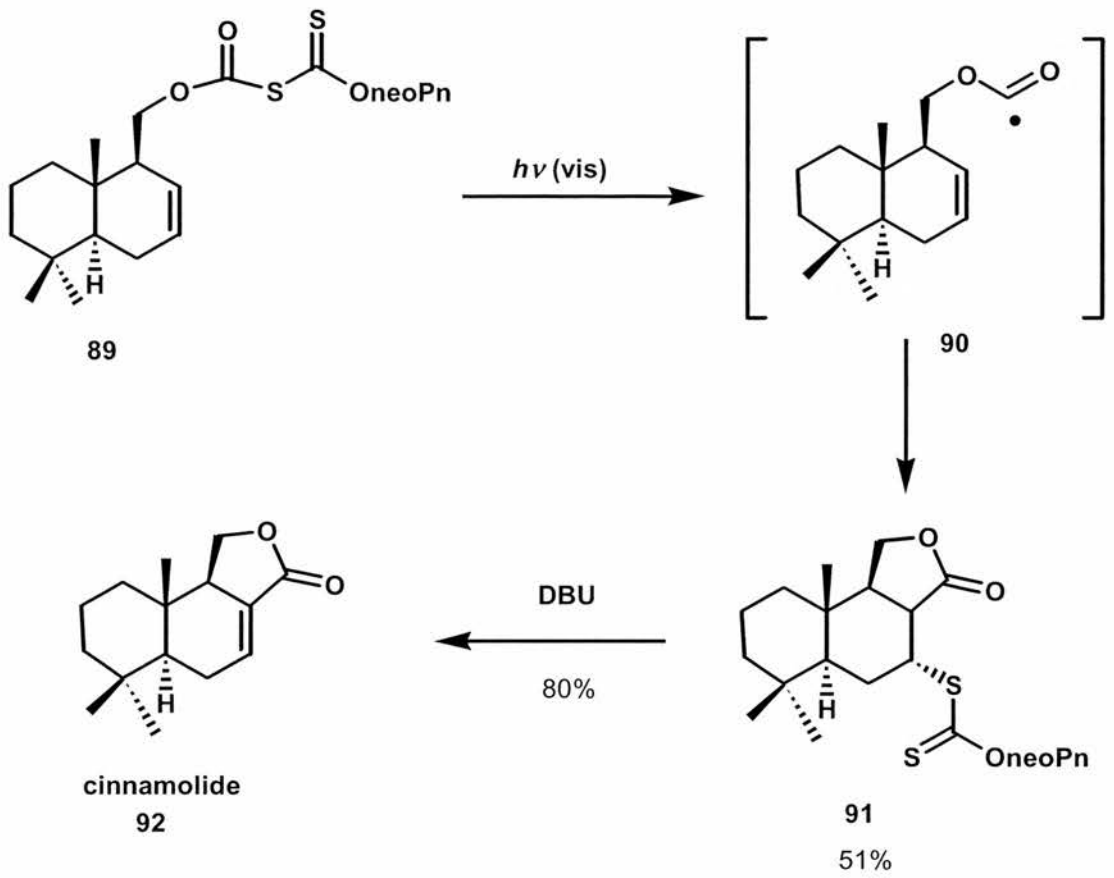

**Scheme 45**

The unsymmetrical xanthic anhydrides **88** which can easily be made from alcohols via the xanthate salt (Scheme 46) also have an interesting chemistry.




**Scheme 46**

Xanthic anhydride **88** can be employed in a process which constitutes a simple approach for generating radicals from primary or secondary alcohols. One application of this variation is the synthesis of cinnamolide **92**. Irradiating the unsymmetrical xanthic anhydride **89** with visible light generates the alkoxycarbonyl radical **90** which captures the internal double bond leading to cyclised lactone **91** in 51% yield. Base induced β-elimination of the xanthate group introduces the required unsaturation in order to generate the desired cinnamolide **92** in 80% yield (Scheme 47).

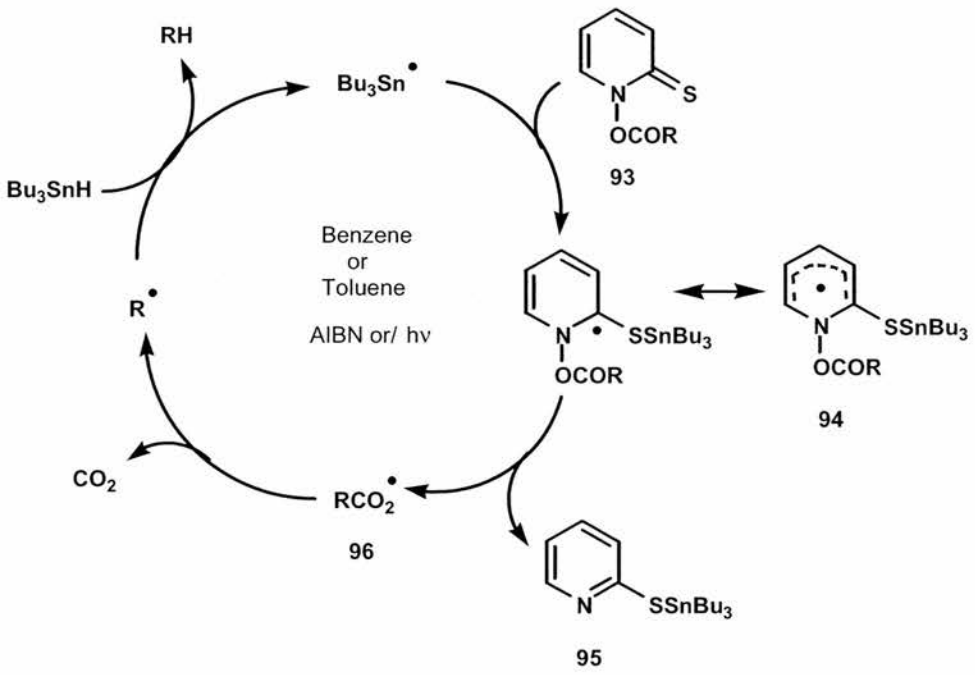



**Scheme 47**

Xanthic anhydrides derived from tertiary alcohols are generally not stable since they can undergo intramolecular Chugaev-type elimination.[96]

### 1.7.4 Barton's thiohydroxamic esters

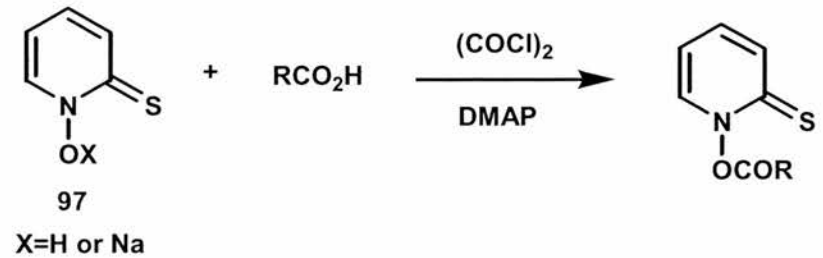
Reductive decarboxylation of carboxylic acids can efficiently be performed by use of thiohydroxamic esters **93**, which have been shown to be facile sources of carbon-centred radicals under mild conditions. Treatment of O-esters of thiohydroxamic acids with tributyltin hydride in presence of AIBN, or photochemically, results in the formation of delocalised radical **94**. Radical **94** fragments to give the pyridylthiostannane **95** as a byproduct and alkoxycarbonyl radical **96** which extrudes carbon dioxide generating carbon-centred radical **R**·. This radical abstracts hydrogen from tin hydride to give the reduction product RH and the chain-carrying tin radical (Scheme 48).[97]




**Scheme 48**

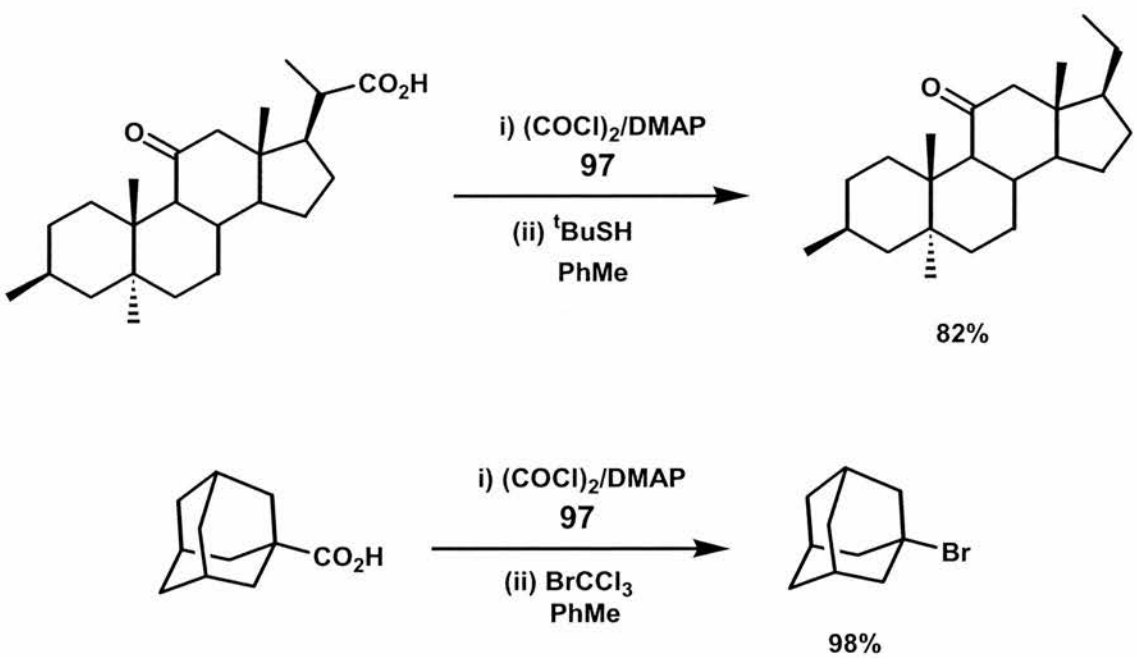
The success of this methodology is due to the well known affinity of tin for sulphur, as well as for the passage from thiocarbonyl to carbonyl, the weakness of the N-O bond, aromatisation of pyridine nucleus as a favourable thermodynamic driving force, and gain of entropy upon fragmentation in creating three products from two reactants.

Thiohydroxamic esters **93** are readily obtained from the reaction of a slight excess of commercially available N-hydroxypyridine-2-thione **97** and carboxylic acids which are activated by oxalyl chloride in the presence of a catalytic amount of DMAP (Scheme 49). The esters formed are not usually isolated but reacted in situ with tri-*n*-butylstannane in order to obtain the reduced hydrocarbons.



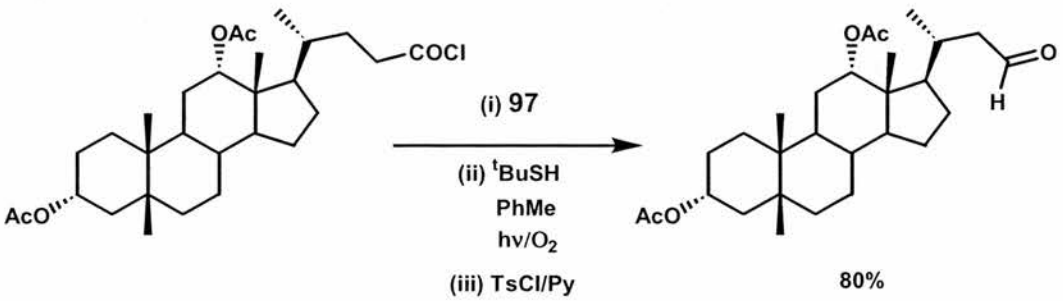

**Scheme 49**

The disadvantage of this method is the use of organotin hydrides to generate alkyl radicals, therefore alternative reagents have been used in order to initiate the chain reaction. For example the use of the poorly nucleophilic *t*-butylmercaptan was found to be a valuable alternative for the decarboxylative reduction of carboxylic acids. The success of this initiator is due to the affinity of the thione functionality for sulphur centred radicals. The decomposition of thiohydroxamic esters **93** serves as initiator for the reaction which proceeds via a radical chain mechanism. Similar overall yields were obtained for the stannane and mercaptan reductions, the latter having the distinctive advantage that simple aqueous extractions and flash chromatography gave pure products. Chain reactions have also been carried out in bromotrichloromethane as solvent and halogen atom source and in the presence of carbon tetrachloride which resulted in the formation of alkyl bromides, or alkyl chlorides ($^{\cdot}CCl_3$ as the chain carrier) respectively. This method constitutes a valid, mild method for the decarboxylative halogenation of carboxylic acids without recourse to strong electrophilic reagents. Examples of these radical reactions are given in Scheme 50.




**Scheme 50**

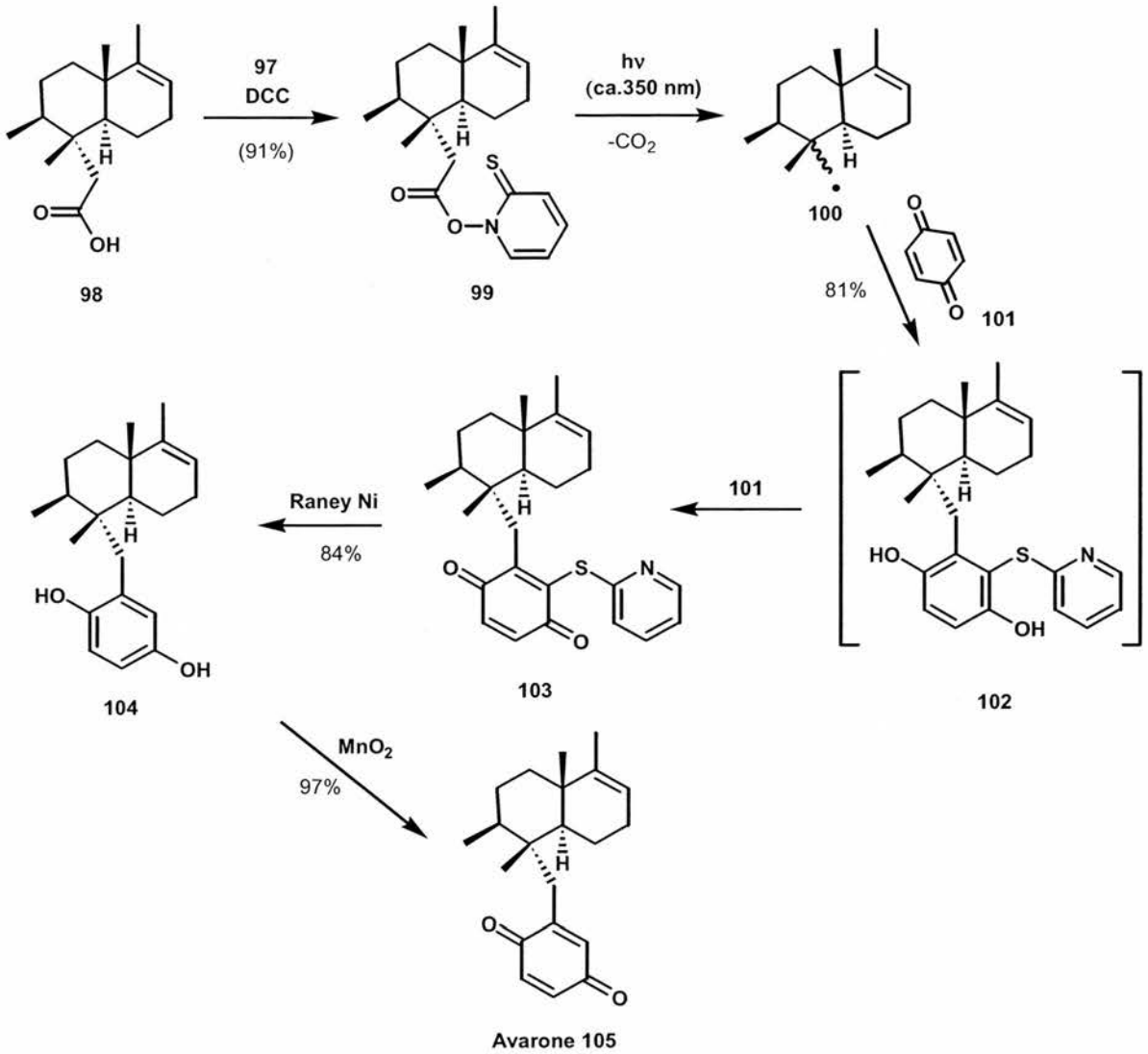
The thermal or photolytic decomposition of thiohydroxamic ester **93** in the presence of *t*-butylmercaptan in toluene saturated with oxygen led to alkylhydroperoxides, which could then be converted in situ by pyridine and sulphonyl chloride into aldehydes or ketones (Scheme 51).




**Scheme 51**

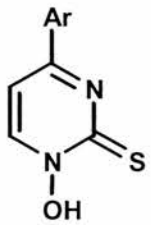
The reaction was developed and extensively reported by Barton and co-workers and tolerates a wide range of functional groups hence giving evidence of the mildness and selectivity of this methodology.

Theodorakis[98] achieved rapid construction of the marine metabolite avarone **105**, which exhibits antimitotic and antileukemic biological properties, by use of Barton's thiohydroxamate radical decarboxylation and quinone addition (Scheme 52). DCC-induced esterification of carboxylic acid **98** with commercially available N-hydroxypyridine-2-thione **97** furnished thiohydroxamic ester **99** in 91% yield. Photochemical activation of **99** induced decarboxylation, generating carbon-centered radical **100** which, in the presence of the radicophile benzoquinone **101** (3.0 equiv.), gave the initial substituted hydroquinone adduct **102**. Further oxidation of **102** in situ with excess of **101** produced quinone **103** in 81% yield. Radical reductive desulfurization by Raney nickel produced avarol **104** in high yield. Avarone **105** was then readily obtained from **104** by heterogeneous oxidation with $MnO_2$.

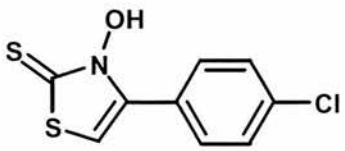



**Scheme 52**

One inconvenience in the use of thiohydroxamic esters is instability. An alternative to Barton-type esters is 1-acyloxy-2(1H)-pyrimidine-2-thiones **106,** developed and studied by Liebscher,[99] which can be stored for several days without decomposing, thus conserving the ability to act as radical precursors. *N*-Hydroxy-4-(*p*-chlorophenyl) thiazole-2(3H)-thione **107** reveals similar stability and reactivity. However these alternatives need vigorous reaction conditions to assist radical initiation or require the presence of organotin compounds.




106

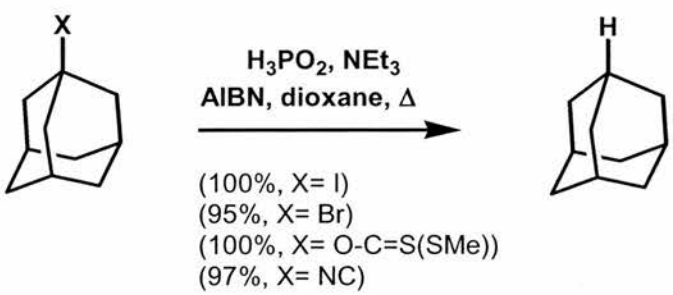



107

The chief inconvenience of this chemistry lies in the stench, which accompanies the use of many sulfur compounds. This odour can be tolerated in laboratory but would be insufferable on an industrial scale.

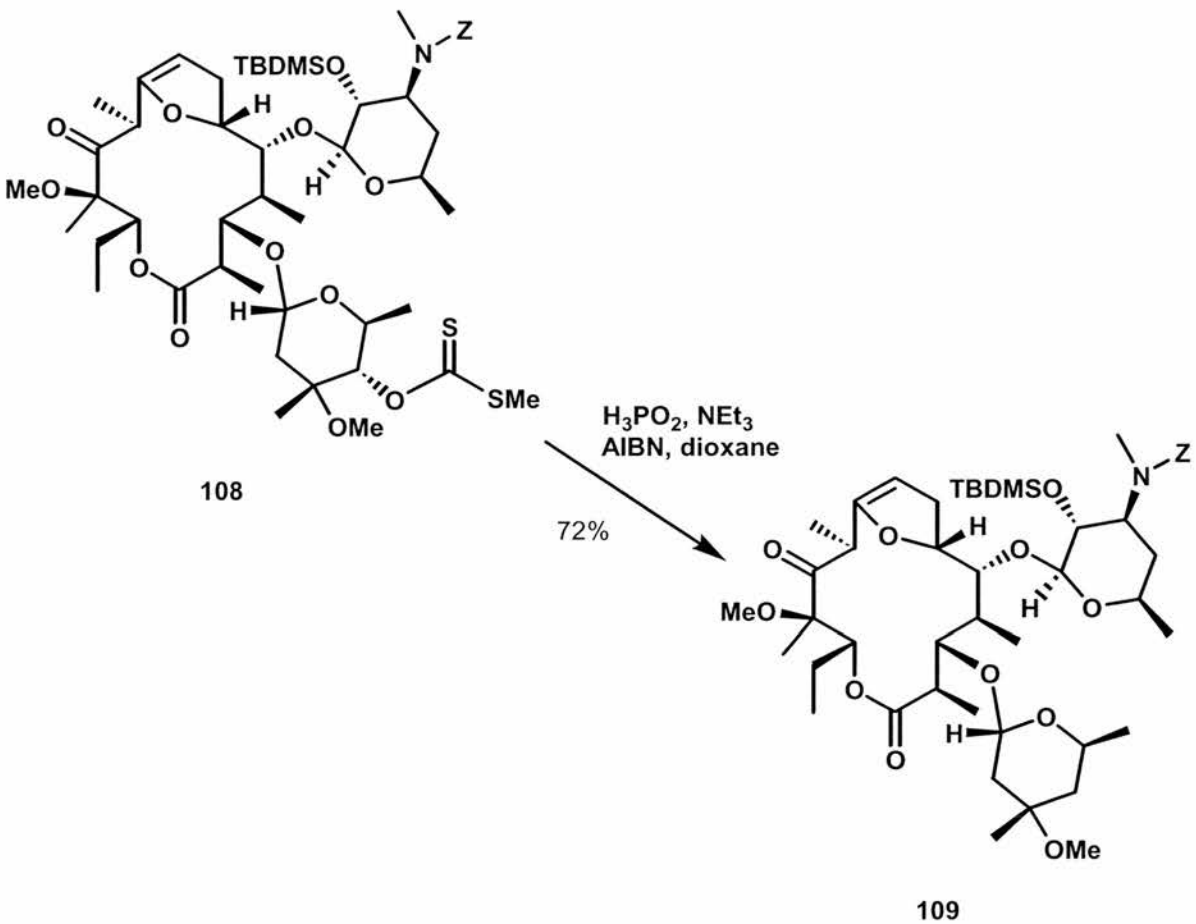
## 1.8 Hypophosphorous Acid and its Salts

The use of hypophosphorous acid and its salts in reductive radical chain reactions was first studied by Barton.[100-103] Hypophosphorous acid and its salts contain weak P-H bonds which can readily be abstracted by radical initiators to produce phosphorus centred radicals. These were initially used in reductive radical chain reactions such as deaminations via isonitriles, deoxygenations via xanthates or thiocarbonates and dehalogenations (Scheme 53). The reactions are best conducted in dioxane as solvent using conventional AIBN as radical initiator. Commercial hypophosphorous acid can be used as an aqueous solution (50%) for these radical reactions. However water sensitive substrates would give hydrolysed products, therefore it is better to remove water by azeotropic distillation prior to use.



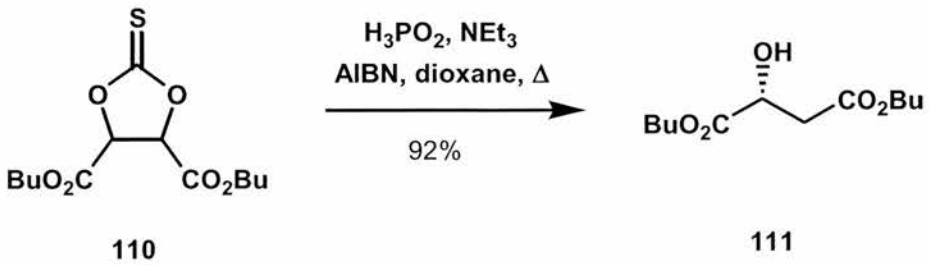

**Scheme 53**

The pure acid can be converted to the desired salt by using DABCO (1,4-diazabicyclo[2.2.2]octane), triethylamine, DBU(1,8-diazabicyclo[5.4]undec-7-en), *N*-ethyl piperidine or other bases. These methods have recently been used for the radical deoxygenation of an erythromycin precursor **108** to give the reduced compound **109** in 72% yield[104] (Scheme 54).




**Scheme 54**

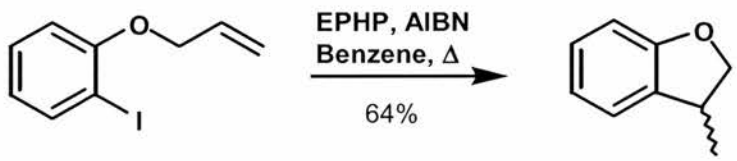
The cyclic thiocarbonate **110** derived from (R,R)-tartrate has also been readily deoxygenated by $H_3PO_2/NEt_3$ to yield enantiomerically pure alcohol **111** (Scheme 55).[105]




110 111

**Scheme 55**

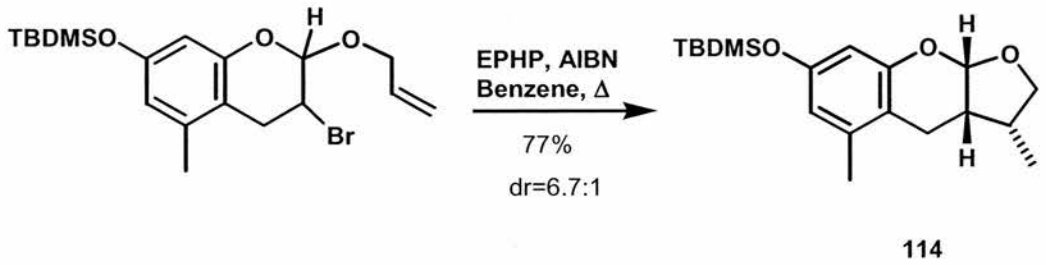
Hypophosphorous acid salts can be used in radical C-C-bond forming reactions. Murphy first looked at a number of aryl and alkyl iodides suitable for intramolecular cyclisation.[106] The reactions were carried out in refluxing benzene using AIBN as initiator together with *N*-ethylpiperidine hypophosphite (EPHP). The released phosphorus-centred radical readily abstracts iodine from iodide **112** to form the corresponding aryl radical, which undergoes a 5-*exo*-trig cyclisation to give the cyclised product **113** in good yield (Scheme 56).




112 113

**Scheme 56**

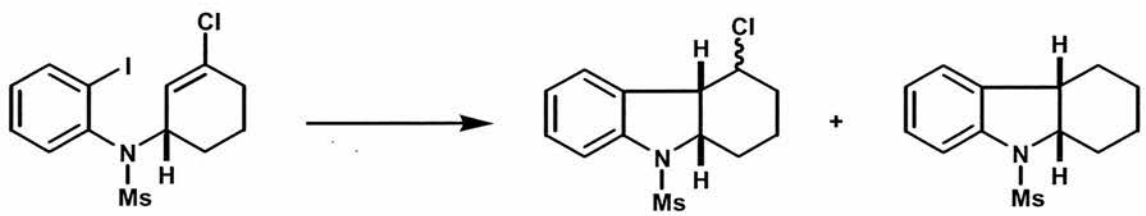
The use of *N*-ethylpiperidine hypophosphite is not restricted to cyclisation of aryl radicals as shown for the recent total synthesis of alboatrin **114**, a phytotoxic metabolite. This example illustrates how this reagent can be utilised to form specific stereoisomers in high yields (Scheme 57).




114

**Scheme 57**

The use of hypophosphorous acid and its salts has many advantages over traditional radical methods. They are inexpensive reactants and can be separated from the organic product by simple aqueous wash. Phosphorus centred radicals also have limited reactivity towards aryl chlorides, in contrast with tin compounds. This halide selectivity could have a great potential in organic synthesis. For example iodochloride **115** undergoes a selective cyclisation to **116** when using a phosphorus reagent in contrast with its counterpart tributyltin hydride which affords **116** in reduced yield because of the formation of large quantities of dehalogenated by-product **117** (Scheme 58).




115

116

EPHP= 78%
$Bu_3SnH$= 36%

117

EPHP= 0%
$Bu_3SnH$= 40%

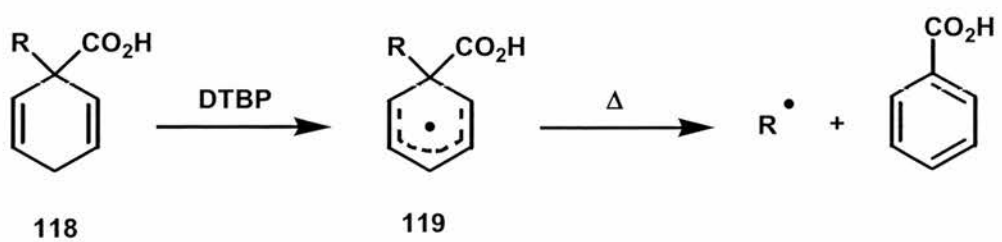
**Scheme 58**

## 1.9 Functionalized Cyclohexa-2,5-dienes in Radical Chain Reactions

The main attributes for a clean radical precursor include independence from use of toxic metals, afford single radicals under mild conditions and should not produce toxic or smelling by-products. A potential method of avoiding tin dependence consists of arranging hydrogen abstraction from a suitable reagent containing activated C-H bonds, as the first step of chain propagation, rather than halogen transfer as with tin reagents. Carbon-centered radicals are unselective in H-abstraction propagation steps. However several series of 'pro-aromatic' appropriately substituted cyclohexadienes and related compounds deliver the required selectivity by means of bisallylic activation of hydrogen, simultaneously taking advantage of re-aromatisation as the driving force for extrusion of some desired initial radicals. This new generation of initiator compounds can therefore be cleanly used in reductive radical chain reactions.[107-109]

### 1.9.1 Alkylcyclohexa-2,5-diene-1-carboxylic acids

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids **118** are efficient precursors for radical generation. Photolysis of carboxylic acids **118** with DTBP generated the delocalised radical **119** which underwent β-scission, at increased temperatures, yielding the desired alkyl radical accompanied by inoffensive benzoic acid; an easily removable by-product (Scheme 59).[108,110]



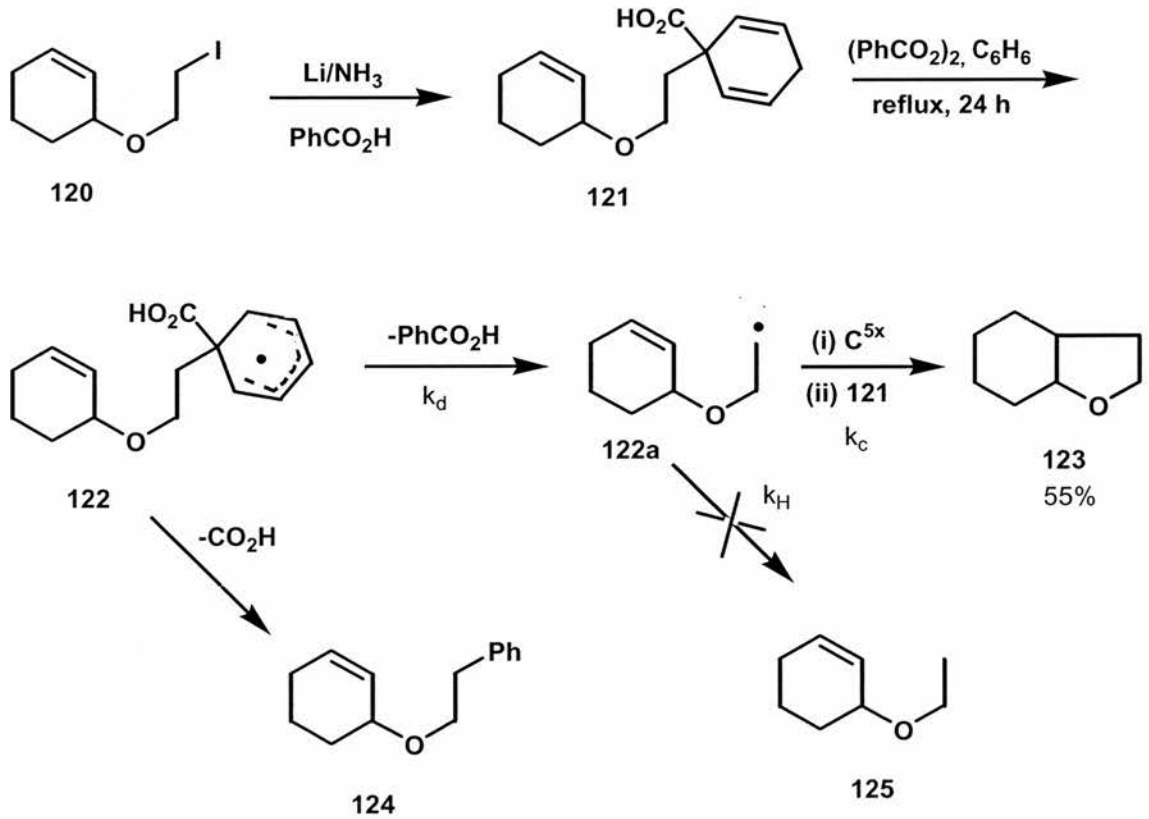

**118** **119**

**Scheme 59**

The ease of fragmentation followed the order *tert*-alkyl > *sec*-alkyl > *n*-alkyl showing that the rate of β–scission increased with the thermodynamic stability of the released alkyl radical.[108] Furthermore, the competitive β-scission was inhibited since the hydroxylformyl radical has a low thermodynamic stability.

A series of acids **118** was synthesised in good yields using the well-known Birch reduction/alkylation of benzoic acid with lithium metal in liquid ammonia and quenching the blue solution obtained with alkyl halides.

Intramolecular cyclisation of transient radicals released from suitably designed 1-alkylcyclohexa-2,5-diene-1- carboxylic acids was found to be efficient. For example the unsaturated ether **121**, made by alkylation with cyclohexenyloxyethyl iodide **120** when refluxed in benzene in the presence of dibenzoyl peroxide as initiator, generated the delocalised radical **122.** Cyclisation of the released radical **122a** afforded octahydrobenzofuran **123** in 55% yield (Scheme 60).

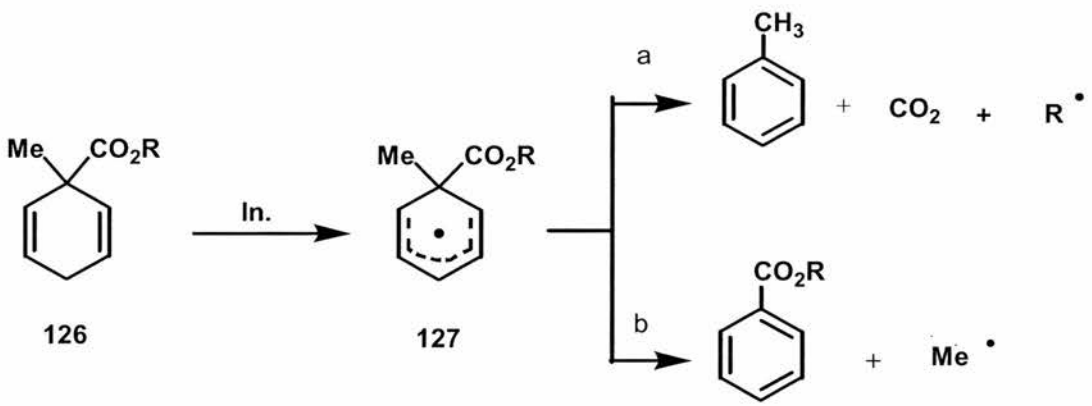



**Scheme 60**

A distinctive advantage of using acid **121** was that, because of the slow hydrogen transfer from **121,** reduced product **125** was not isolated, as compared with 12% by-product when using tributyltin hydride. A moderate amount of 2-phenylethoxy cyclohexene **124** suggested the possibility of unwanted formation of hydroxyformyl radical $^{\cdot}CO_2H$. The product **124** can also be considered to derive from the intermolecular addition reaction of alkyl radical **122a** with benzene.

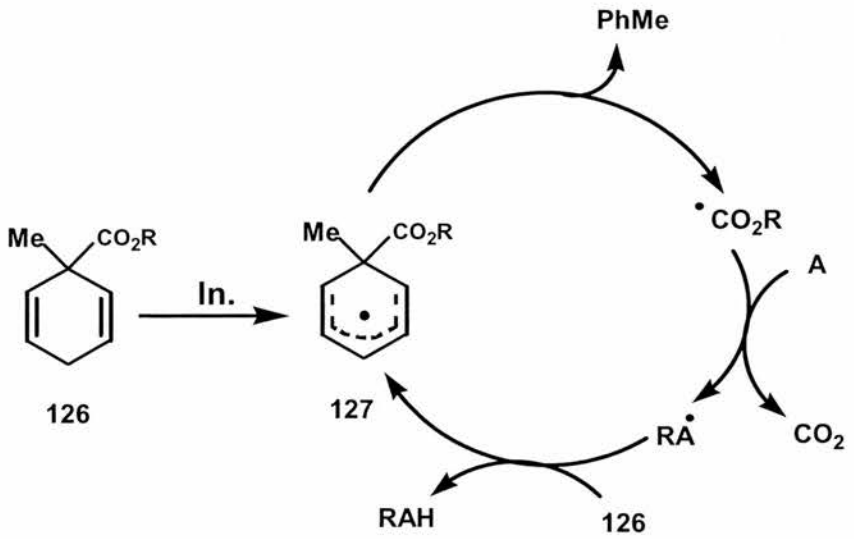
## 1.9.2 Alkylcyclohexa-2,5-diene-1-carboxylates.[110, 111]

1-Methylcyclohexa-2,5-diene-1-carboxylates, containing bisallylic activation, have been shown to undergo radical induced fragmentation to give the alkyl radical R$^{\cdot}$ and toluene, in the presence of the radical initiator dibenzoyl peroxide, (Scheme 61).




**Scheme 61**

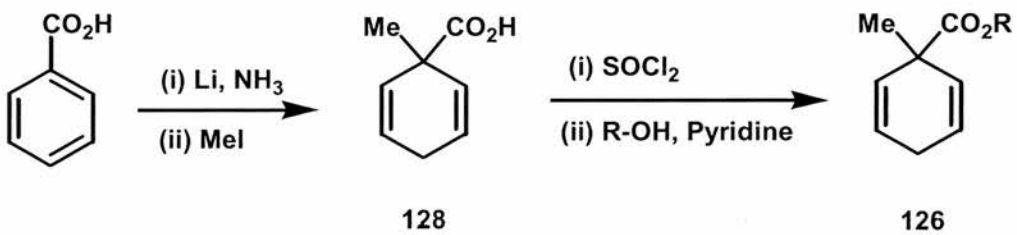
Methylcyclohexa-2,5-diene-1-carboxylates **126** afforded cyclohexadienyl radicals **127** which mainly underwent β-scission above ca. 80°C to produce toluene and alkoxycarbonyl radical, $\cdot CO_2R$ (Scheme 62). The latter underwent decarboxylation, thus generating the alkyl radical R$^{\cdot}$. This alkyl radical then reacted to give RA$^{\cdot}$, which abstracted hydrogen from more **126** to give the product RAH and delocalised radical **127**, hence continuing the chain process.




**Scheme 62**

Hence, 1-methylcyclohexa-2,5-dienecarboxylic esters could potentially mediate chain reactions by a route analogous to that of scheme 62.

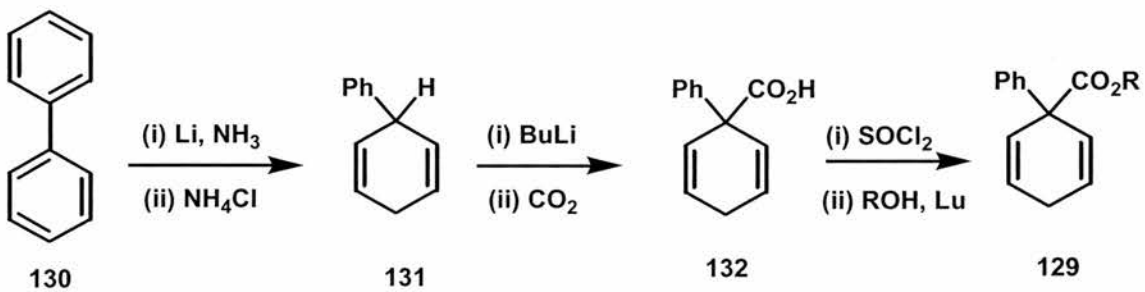
The advantages in using this scheme are the slower H-transfer step in comparison to organotin hydrides, which allows more time for intermolecular alkene addition, and the only by-product is the benign toluene, which can easily be removed. Esters **126** are easily prepared from 1-methylcyclohexe-2,5-diene-1-carboxylic acid **128,** via the corresponding acid chloride, followed by addition of the appropriate alcohol (Scheme 63).




**Scheme 63**

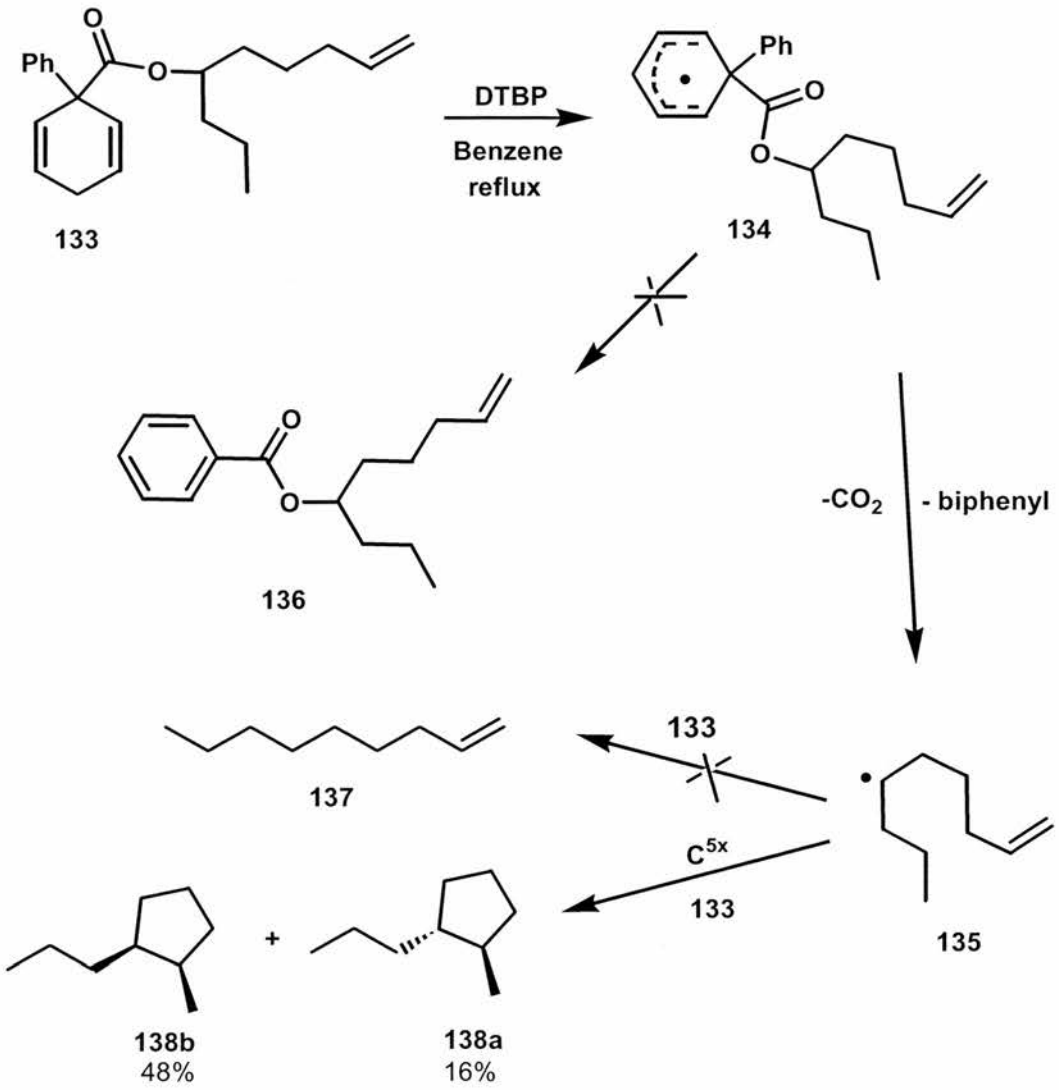
The main obstacle with this approach has been competition from the alternative scission (Scheme 61, route b) in which a methyl radical is extruded and benzoate ester by-product is produced in amounts comparable to the desired product leading to reduced yields.

1-Substitution of cyclohexadiene-1-carboxylate with a phenyl group instead of a methyl group overcomes the problem of methyl loss, because phenyl radical formation is thermodynamically disfavoured. The best way to synthesise 1-phenylcyclohexa-2,5-diene-1-carboxylate ester **129** involves Birch reduction of the commercially available biphenyl **130,** performed by a similar procedure as described previously, quenching the reaction with ammonium chloride in order to furnish 1,4-dihydrobiphenyl **131** in high yield. Treatment of 1,4-dihydrobiphenyl with BuLi followed by pouring of the resultant mixture onto crushed dry ice gave 1-phenylcyclohexa-2,5-diene-1-carboxylic acid **132** as the major product. Esters **129** were then prepared via the acid chloride with the appropriate alcohol and 2,6-dimethyl pyridine (lutidine, Lu) as the base (Scheme 64).




**Scheme 64**

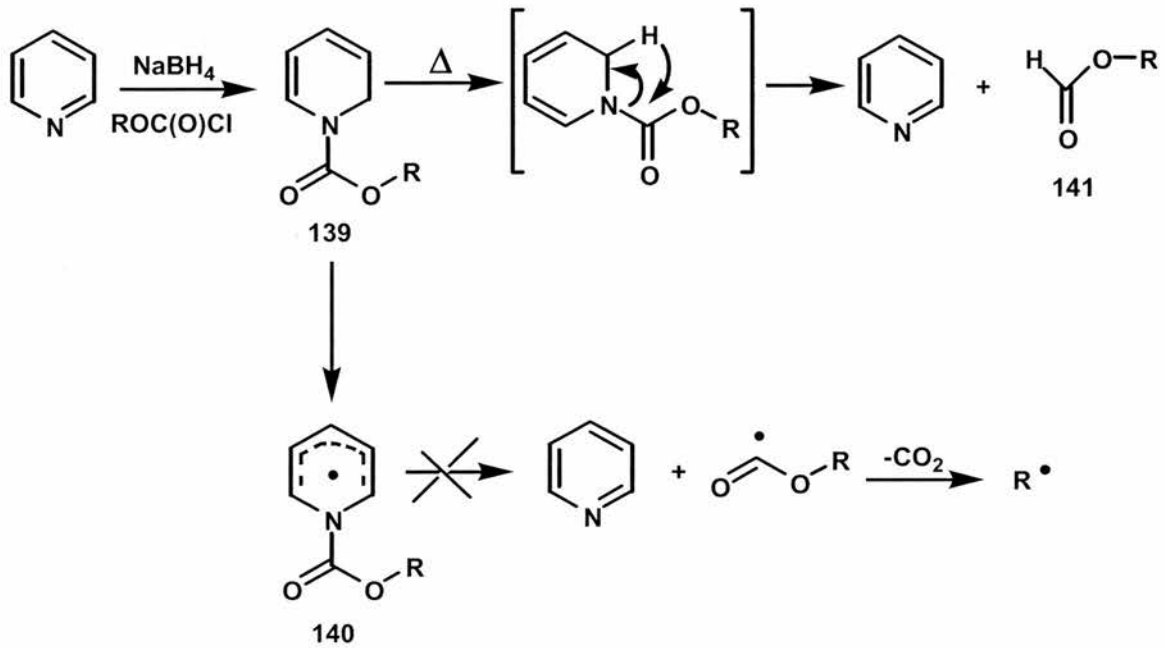
A range of 1-phenylcyclohexa-2,5-diene-1-carboxylate esters were therefore prepared and used as free radical precursors in order to diminish the undesired β-scission leading to alkylbenzoates.[111] Nonenyl ester **133** was prepared and isolated in 83% yield from the phenyl carboxylic acid **132**. Dibenzoyl peroxide induced reaction of ester **133** in refluxing benzene afforded biphenyl together with 1-methyl-2-propylcyclopentane **138** in 64% yield as a mixture of the *trans*- and *cis*-isomers (Scheme 65)




**Scheme 65**

Neither nonenyl benzoate **136** nor dec-1-ene **137** were detected from the reaction mixture showing that competing loss of a phenyl radical from the intermediate cyclohexadienyl radical **134** did not occur. The intermediate alkoxycarbonyl radical underwent decarboxylation rapidly (thermodynamically favoured formation of secondary radical **135**) allowing an intramolecular addition to take place prior to hydrogen abstraction. These examples demonstrated that 1-phenyl esters **129** could be used as mediators of free radical ring closures processes. However, this procedure required a large amount of radical initiator in order to maintain the radical chain and generally gave poor yields of the cyclised products because of difficulties in separation from initiator debris.

N-Alkoxycarbonyl-1,2-dihydropyridines **139** have also been tested as potential alternatives[112] to cyclohexadienyl esters. These compounds have been synthesised by treatment of pyridine with sodium borohydride and addition of the appropriate chloroformate (Scheme 66). Formation of azacyclohexadienyl radical **140** followed by extrusion of the corresponding alkoxycarbonyl radical and final decarboxylation would release the desired alkyl radical.

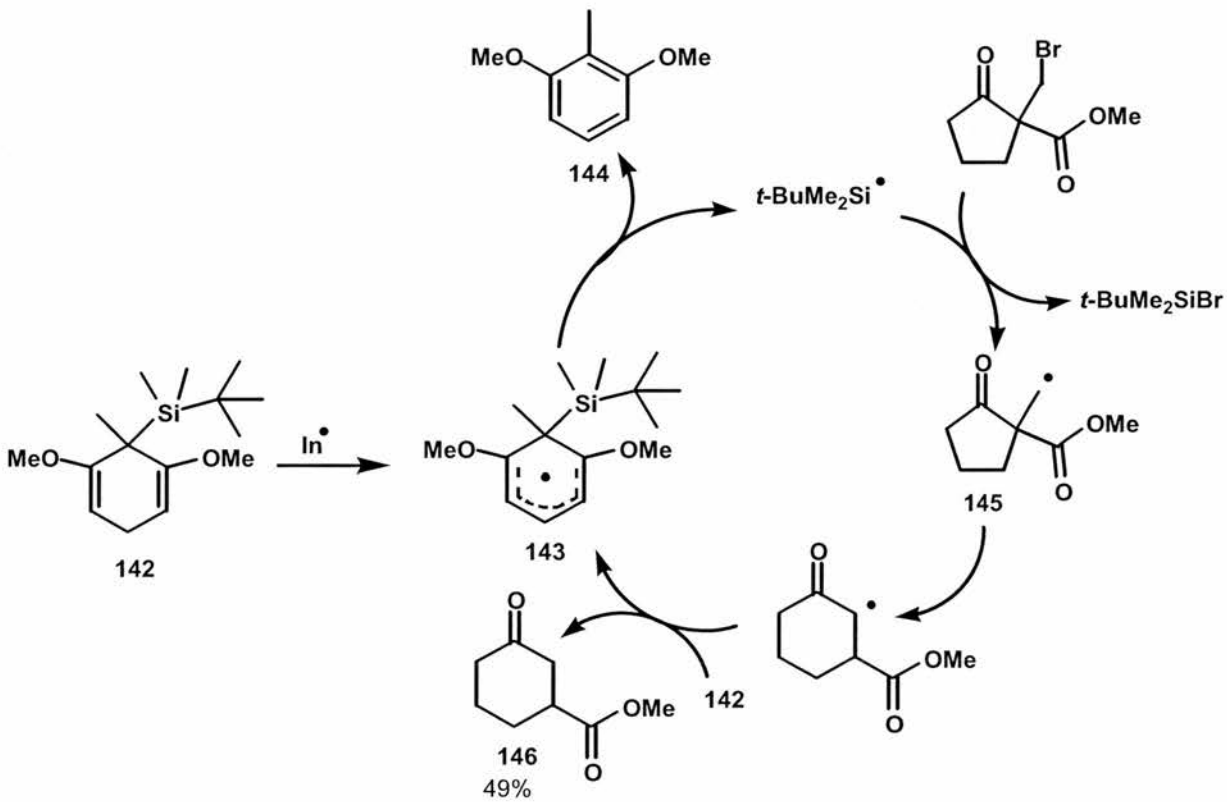



**Scheme 66**

The advantage in the use of this precursor would be the easy acidic work-up to remove the by-product pyridine, and there were no additional alkyl groups which could compete with the desired N-C bond scission. EPR analysis of 1,2-dihydropyridines in the presence of a radical initiator, confirmed the presence of aza-cyclohexadienyl radical **140** but gave no evidence for the generation of alkyl radicals. In a range of radical reactions with various alkenes there was no formation of the desired addition products, the major route seemed to be a direct thermal β-elimination of N-alkoxycarbonyl 1,2-dihydropyridines **139** with production of pyridine and the corresponding alkyl formate **141.**

### 1.9.3 Silylated cyclohexadienes as radical reducing agents

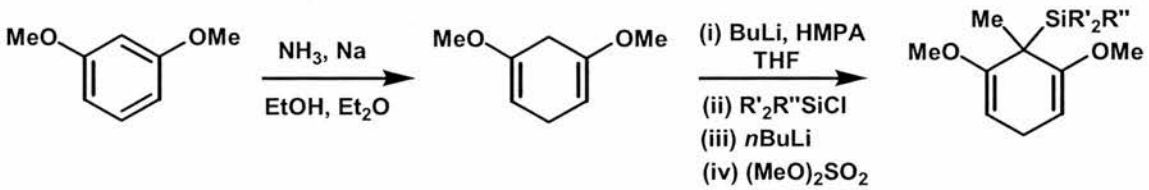
Based on the observations made by Walton on the use of cyclohexadienes as free radical mediators, Studer has recently introduced new silylated cyclohexadienes[113] which can act as efficient hydrogen donors suitable to replace tin hydrides in radical chain reductions. For example *t*-butyldimethylsilyl derivative **142** in the presence of radical initiators such as AIBN in *n*-hexane produced the corresponding cyclohexadienyl radical **143** (Scheme 67).




**Scheme 67**

Rearomatization of **143** releases *t*-butyldimethylsilyl radicals which can propagate the chain by halogen abstraction from an alkyl halide to give the desired alkyl radical **145**. Intramolecular addition to carbonyl, followed by ring expansion and subsequent bisallylic H-abstraction from more **142,** produced cyclohexanone methyl ester **146** in 49% yield. Methylated resorcinol diether **144** and halogenated silane are the only by-products formed from the overall radical process.

Silylated cyclohexadienes can be readily prepared starting from the commercially available resorcinol dimethyl ether by Birch reduction followed by one-pot silylation-methylation as described in Scheme 68.[114]

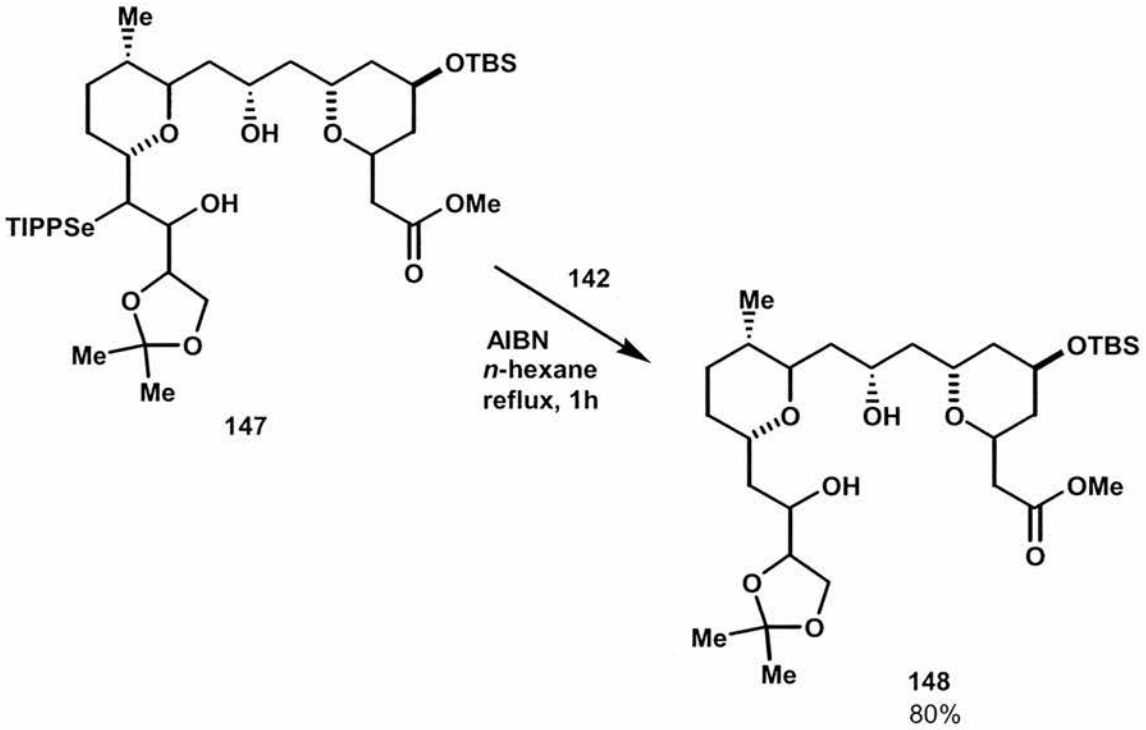



**Scheme 68**

For example, silylated cyclohexadiene **142** was obtained in 80% overall yield as a crystalline product which could easily be stored and handled.

Silylated cyclohexadienes have successfully been used on various radical precursors that are typically employed in radical synthesis. Barton-McCombie deoxygenation of secondary alcohols using thiocarbonate esters, reduction of phenylselenides, as well as radical additions and cyclisations worked efficiently by the use of these new silylated tin hydride substitutes.

Recently Carreira demonstrated that silylated cyclohexadienes can successfully be used as tin-free reducing agents in syntheses of natural products on the way to his total synthesis of Leucascandrolide A.[115] Reductive deselenylation of intermediate **147** was achieved using silylated cyclohexadiene reagent **142** which provided the desired reduced product **148** in 80% yield (Scheme 69).

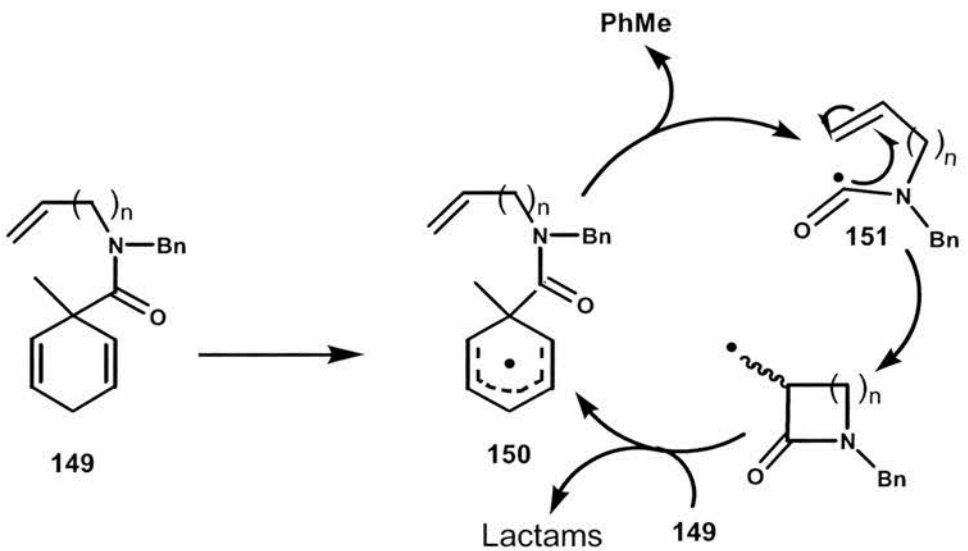



**Scheme 69**

A large number of reductive radical additions can be performed with these new Si-reagents. As reported, they work perfectly well with most of the common radical precursors used in radical chemistry. Furthermore, the by-products formed from the radical process can easily be removed in contrast with TTMSS which is the most successful tin hydride substitute to date. Another advantage consists in the fact that silyl radicals of different reactivity can be incorporated, depending on the particular synthetic needs, providing a versatile and environmentally friendly tin-free radical mediator which can be used as a powerful tool in organic synthesis.

# Aims and Objectives of the Project

Our project involves the synthesis of amidocyclohexadienes and their use in model reactions to test the scope and limitations of their applicability as free radical precursors. Subsequently, work mainly focused on their use for synthesis of β- and γ-lactams. Hydrogen atom abstraction from 1-carbamoyl-1-methylcyclohexa-2,5-dienes **149** generates the corresponding delocalised 1-carbamoyl-1-methylcyclohexa-2,5-dienyl radicals **150** at temperatures below ca. 300 K. At higher temperatures suitably substituted examples dissociate to produce toluene and aminoacyl radicals **151** (Scheme 70).

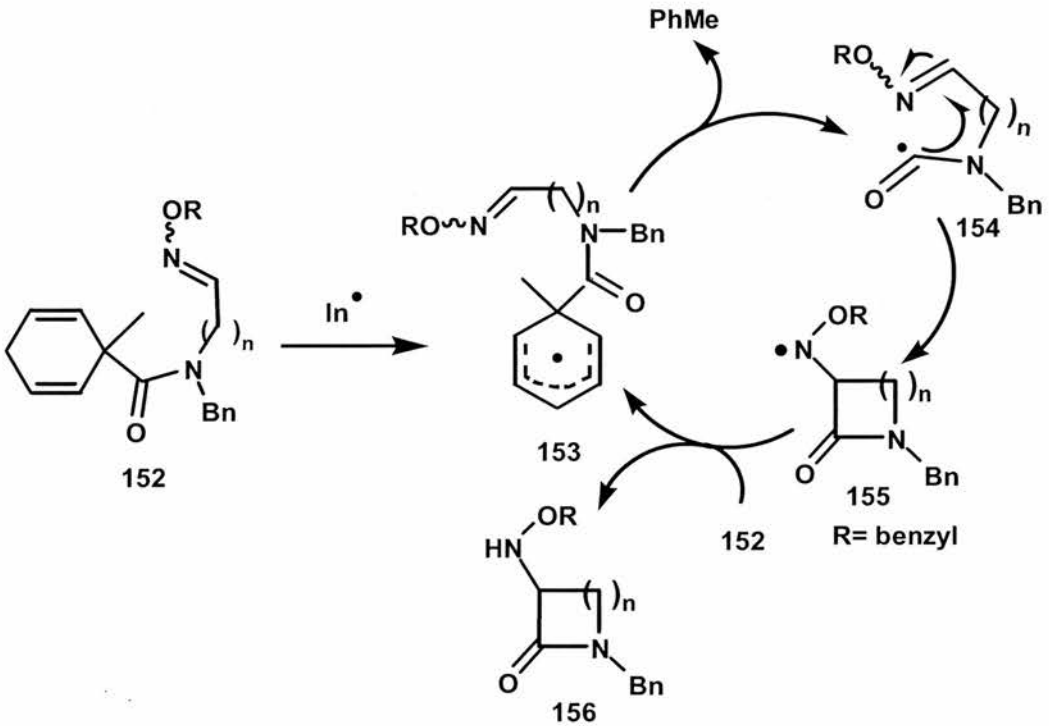



**Scheme 70**

Both types of radical intermediates were detected and characterised in solution by 9.5 GHz EPR spectroscopy. No competition from Me· radical loss was detectable; so that improved yields of cyclised products could potentially be obtained.

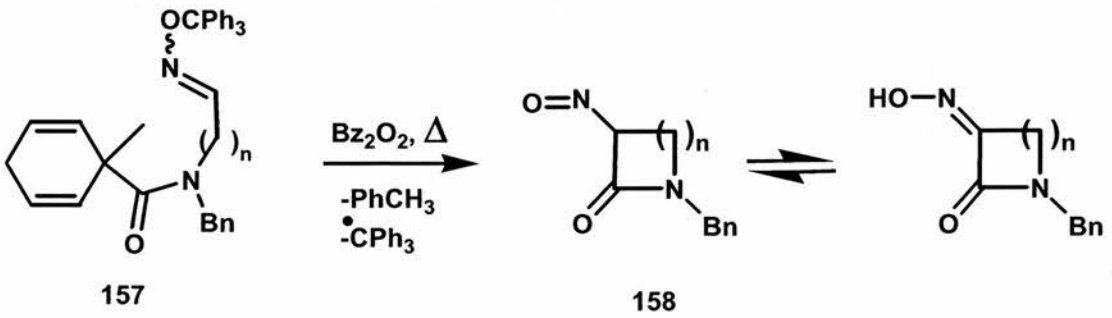
Ring closure of aminoacyl radicals of type **151** (n = 1, 2) takes place satisfactorily on alkene groups to yield β– and γ-lactams. Carbapenems and norcadicins are important monocyclic antibiotic classes containing smaller, β-lactam rings that might, therefore, be accessible starting from the appropriate amidocyclohexadienes. A novel tin free route from amines to a range of nitrogen heterocycles could thus become available.

Cyclohexadiene carboxamides containing oxime ether functionality could also be exploited. Ring closure onto oxime ethers is faster than onto alkenyl moieties[116] and hence this radical acceptor could improve the yields for the difficult 4-*exo* cyclisations. Amides **152** containing oxime ether functionality, treated with peroxide, generate delocalised radicals **153**, which dissociate to afford aminoacyl radicals **154**. Cyclisation to alkoxyaminyl radicals **155** (R=benzyl, alkyl) followed by H-abstraction from more **152** could potentially furnish lactams **156** (Scheme 71).




**Scheme 71**

Cyclohexadienyl carboxamide oxime ether **157** (R = $CPh_3$), under photolytic or thermolytic conditions, in the presence of a radical initiator such as di-*tert*-butyl peroxide or dibenzoyl peroxide, should release the corresponding aminoacyl radical to undergo 5-*exo*-cyclisation with loss of the stable trityl radical hence producing lactams **158.** The process would not constitute a radical chain due to the formation of the stable trityl radical which would not be able to propagate the chain, but could be efficiently used in syntheses of lactams bearing nitroso functionality at C(3) (Scheme 72).




**Scheme 72**

Radical chains which involve oxime ethers can be effectively used for the preparation of β- and γ-lactams in which small ring formation is efficient and the product lactams contain nitrogen functionality at C(3)-exactly as required in many antibiotics of this class.

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# Chapter 2

# EPR kinetic studies on 1-methylcyclohexa-2,5-diene-1-carboxamides

# 2.1 Electron Paramagnetic Resonance

In the early part of this century, scientists found that a molecule or atom has discrete (or separate) states, each with a corresponding energy. Spectroscopy is the measurement and interpretation of the differences in these energies[1]. With this information, it is possible to gain insight into the identity, structure, and dynamics of the samples under study.

Electron paramagnetic resonance EPR (sometimes called electron spin resonance or ESR) is a spectroscopic method employing magnetic fields and microwaves[2] in the frequency range between 1 GHz and 500 GHz to study materials and molecules with unpaired electrons (radicals, transition metal complexes, etc.). EPR is successful in obtaining details of electron density distributions, molecular and geometric structures of the radicals. The structures and properties of certain molecules can be determined, using EPR spectroscopy in solutions and solids. The dynamics of molecules can be determined, in proteins, the redox-active centers can be characterized, often selectively. Additionally, the kinetics of chemical reactions can be studied. All of these properties can be observed at room temperature, but frequently spectroscopy is carried out at low temperatures.

The "spin" of an electron refers to the intrinsic angular momentum called spin observed when the electron is in space without any outside forces acting upon it. The angular momentum also creates a magnetic field around the electron because of its charge. The spin is characterized by the quantum number $M_s = \pm 1/2$ that gives two spin states differing in $M_s$ whose functions are designated as α (↑) or ß (↓)

$$\mu_E^Z = -M_S \cdot g_E \beta_E = \begin{matrix} -(+1/2) g_E \beta_E \text{ for } M_S=+1/2 \\ -(-1/2) g_E \beta_E \text{ for } M_S=-1/2 \end{matrix} \qquad \textbf{(1)}$$

Where $\beta_E$ is the Bohr magneton ($eh/4\pi m_e$ = 9.2733E-2 erg/gauss, $e$ and $m_e$ are the charge and mass of the electron, respectively and $h$ = 6.624E-27 erg·sec is Plank's constant) and $g_E$ is a dimensionless number whose value for a free electron is 2.0023. This ideal value of $g_E$ is never found in a real molecule as the spin of an unpaired

electron "senses" other electrons and nuclei in its nearby environment and this changes the observed g-value.[3-5]

The z-axis is chosen with the specific direction of the applied magnetic field. In the absence of applied magnetic fields, the two spin states with $M_s = \pm 1/2$ are degenerate (they have the same energy). The electron acts like a compass when placed in a magnetic field, $B_0$. It will have a state of lowest energy when the moment of electron ($\mu_E$) is aligned along the magnetic field and a state with highest energy when this is aligned against the magnetic field. The spin states are no longer degenerate (Zeeman effect). The two states are labelled by the projection of electron spin, $M_s$, on the direction of the magnetic field. Because the electron has spin ½, the parallel state is designated as $M_s = -1/2$ and the antiparallel state as $M_s = + 1/2$. From quantum mechanics, we obtain the most basic equations of EPR.

$$E = -\mu_E^Z \cdot H = +\left(M_s \cdot g_E \cdot \beta_E\right) \cdot \mathrm{B}_0 \qquad \textbf{(2)}$$

The energy differences we study in EPR spectroscopy are due to the interaction of unpaired electrons in the sample with an external magnetic field and are proportional to the intensity $B_0$ of this field (Fig. 1).

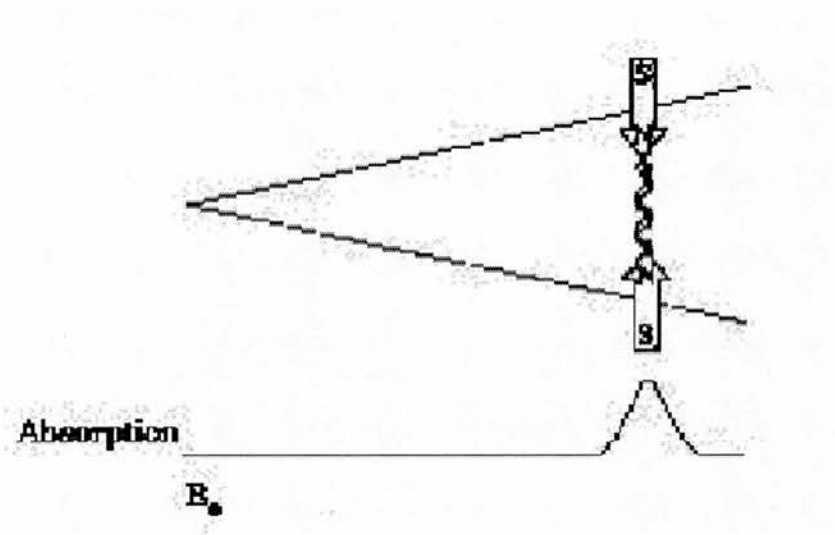
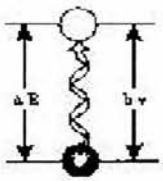



**Figure 1** The energies of spin states diverge linearly as the magnetic field increases

Transitions from one Zeeman level to the other (i.e. between $E_1$ and $E_2$), in which the electron changes its spin state, occur when the system is exposed to an electronic

radiation with a resonance frequency ν. This frequency is determined by the resonance conditions:

$$\Delta E = h\nu = g_E \cdot \beta_E \cdot \mathrm{B}_0 \qquad \textbf{(3)}$$




Because we can change the energy differences between the two spin states by varying the magnetic field strength, we have an alternative means to obtain spectra. We could apply a constant magnetic field and scan the frequency of the electromagnetic radiation as in conventional spectroscopy. Alternatively, we could keep the electromagnetic radiation frequency constant and scan the magnetic field. A peak in the absorption will occur when the magnetic field "tunes" the two spin states so that their energy difference matches the energy of the radiation. This field is called the "field for resonance". Owing to the limitations of microwave generators, the latter method offers superior performance; therefore, EPR spectrometers use this technique.

In contrast with NMR spectrometers, ESR spectrometers are arranged to record the first derivative of the absorption curve. This gives a greater sensitivity and also better resolution (Fig. 2).

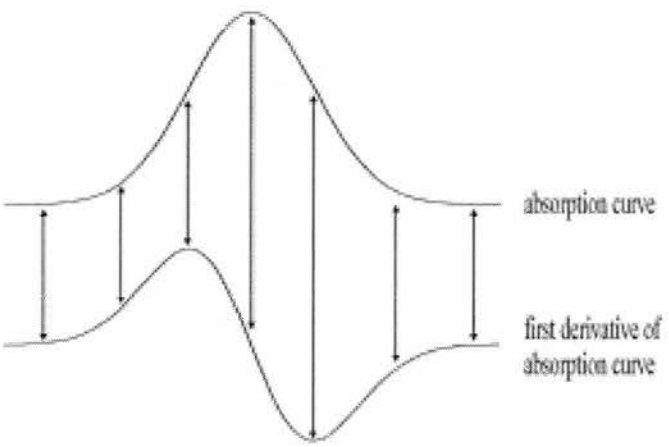



**Figure 2**

The area under the absorption curve is proportional to the number of spins in the sample. A double integration of the first derivative curve and comparison of this area

with that obtained from a solution of long-life radicals at known concentration enables radical concentrations to be determined.

### 2.1.1 g-Factor

The field for resonance is not a unique fingerprint for identification of a compound because spectra can be acquired at several different frequencies. The g-factor being independent of the microwave frequency is much better for this purpose.
The effective magnetic moment of the unpaired electron in a radical, and hence its spin states, are influenced by the local atomic environment. Given the resonance condition for the free electron:

$$\mu_E = -g_E \cdot \beta \cdot M_S \qquad \textbf{(4)}$$

For a non-free electron there is a variation of the *g*-value (*g*-factor shift) to ensure resonance at a given magnetic field

$$\mu = -g \cdot \beta \cdot M_S \qquad \textbf{(5)}$$

It thus follows that every radical possesses its own typical *g*-factor. The effective magnetic moment of a molecule arises from the coupling between the spin and orbital angular momentum called spin-orbit coupling of the electron in a radical which depends on the orientation of the radical with respect to the applied field. This results in the molecular electron having a different effective magnetic moment from that of the free electron. Hence, for a given frequency, radicals with different *g*-factors resonate at different field strengths. The differences are small, but nevertheless they can give valuable information about the structure of a radical.

### 2.1.2 Hyperfine interactions

Measurement of g-factors can give some useful information; however, it does not tell much about the molecular structure of the sample. Fortunately, the unpaired electron is very sensitive to its local surroundings. The nuclei of the atoms in a molecule or

complex often have a magnetic moment, which produces a local magnetic field at the electron.

Nuclei with a non-zero spin quantum number $I$ in a magnetic field $B_0$ involve the component of the nuclear magnetic moment $\mu_N$ in the direction $z$ of the field $\mu_N^Z$.

$$\mu_N^Z = +M_I \cdot g_N \cdot \beta_N \qquad \textbf{(6)}$$

$\mu_N^Z$ depends on the spin quantum number $M_I$. The latter can have (2I + 1) values. The values of $\mu_N^Z$ are smaller than $\mu_E^Z$. In a strong magnetic field $B_0$ the interaction between the unpaired electron and a magnetic nucleus comes into play as a small perturbation δE to the Zeeman levels $E_1$ and $E_2$ of the electron spin. This perturbation is made up of two terms:

$$\delta E = \delta E_{aniso} + \delta E_{iso} \qquad \textbf{(7)}$$

The interaction between an unpaired electron and nuclei with non-zero nuclear spin is called the "hyperfine interaction". It can give rise to features in an EPR spectrum. Any observed hyperfine coupling constant theoretically consists of two contributions; *isotropic and anisotropic*. The isotropic (or Fermi contact) contribution[6] $A_{iso}$, is a measurement of the s orbital character of the unpaired electron. Anisotropic contributions depend upon the orbital angular momentum of the electron and hence are a measure of d and/or p orbital character. The observed hyperfine interaction contains both isotropic and anisotropic contributions.

The diagram in figure 3 refers to radicals in which the unpaired electron interacts only with one nucleus having a spin quantum number $I$ of $1/2$ or 1 (i.e. $^1H$ or $^{14}N$). The levels $E_1$ and $E_2$ of the electron spin states with $M_S = -1/2$ and $M_S = +1/2$ each split into two of three sub-levels corresponding to the two quantum numbers of the proton $(M_I = -1/2, +1/2)$ or the three quantum numbers $(M_I = -1, 0, +1)$ of the nitrogen. The selection rules $\Delta M_S = \pm 1; \Delta M_I = 0$ state that only those transitions are allowed which occur between spin states with the same quantum number $M_I$. Consequently, two hyperfine lines are detected in the spectrum resulting from the interaction of the unpaired electron with a proton $(I = 1/2; 2I + 1 = 2)$, and three hyperfine lines when the electron interacts with $^{14}N$ $(I = 1; 2I + 1 = 3)$.

The separation between the adjacent lines gives the hyperfine coupling constants (hfcc or hfs) of the nuclei. These are independent of the field and characteristic of the nucleus-electron interaction in the radical

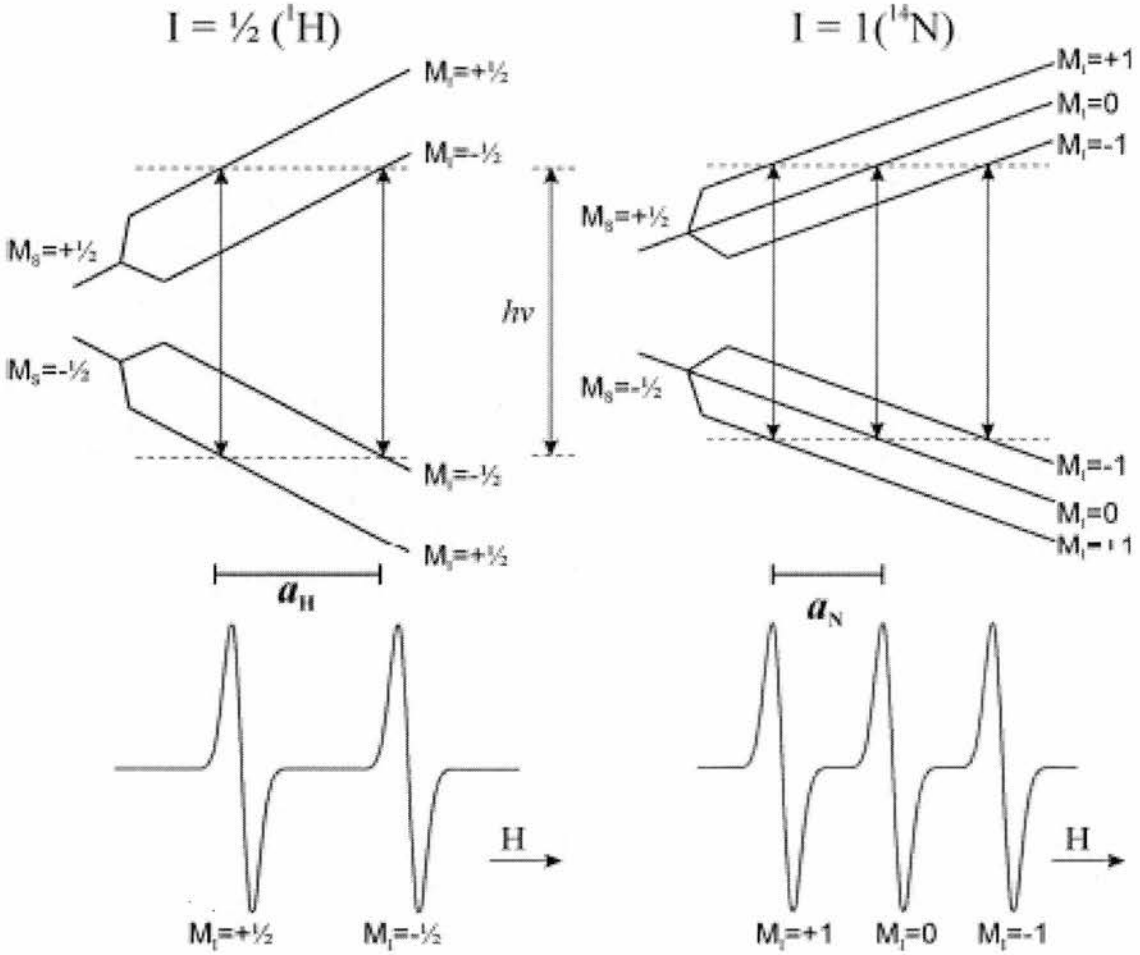



**Figure 3**

In general, $n$ equivalent nuclei with spin quantum number $I$ give rise to $(2nI+1)$ equidistant hyperfine lines.[7] Therefore for $I=1/2$ the intensity of the lines is represented by Pascal's triangle. Thus the EPR spectrum of a radical centred on nitrogen (I=1) consists of a 1:1:1 triplet, otherwise for two equivalent nuclei with $I=1/2$, the spectrum consists of three lines with an intensity distribution 1:2:1.

The hyperfine splittings or $a$-values between these lines brought about by a magnetic nucleus can be measured in millitesla (mT) using the SI system of nomenclature or in gauss (1 mT= 10 gauss). Therefore, detailed analysis of the number and position of the

spectral lines leads to the determination of the physical and electronic structure of the observed radical.

EPR spectra are in general much more complex than NMR spectra because coupling with β-protons is frequently as great as if not greater than that with α-protons.

### 2.1.3 Generation of radicals

The generation of free radicals can be achieved by three main techniques that can produce a sufficiently high steady-state concentration of radicals.

a) Generation of radicals in a matrix at very low temperature. "Freezing" the radical in a solid matrix of a diamagnetic material (e.g. freon $CFCl_3$ at 77K)[8] decreases the reactivity of the radical itself and this increases the lifetime. However, a result of freezing is that the dipole-dipole interaction between the unpaired electron and the magnetic nuclei does not average out and the EPR hyperfine lines are extensively broadened.

b) Use of a flow system[9-11]. In the "flow technique" two reactants which generate the radicals flow separately into a mixing chamber and then the mixture flows through the spectrometer cavity.

c) Ultraviolet or X-ray irradiation of a solution of a radical precursor, e.g. diacyl peroxides, peresters or azo-compounds, within the cavity of the EPR spectrometer. [11-15]

### 2.1.4 EPR spectrometer

The EPR instrument is made up of a source of radiant energy, an absorption cell, a detector, and a magnet. An external magnetic field is a prerequisite for the absorption of energy (as in NMR). The field can generally reach 10,000 Gauss between the pole pieces (10-30 cm across) which is characterised by a high grade of homogeneity (Figure 4). In the homogeneous field region is placed a resonant cavity, which accommodates the sample and is connected to all other components. Energy is supplied to the cavity through a wave-guide, the source being a valve called a Gunn diode, capable of emitting electromagnetic radiation in a narrow range of the microwave region. In principle, the resonance condition may be attained for any

frequency, but there are several considerations which limit the choice of the radiation frequency. The primary concern is sensitivity; this requirement dictates that the frequency be as high as possible $[\text{sensitivity} \propto \nu^2]$, but three factors limit the microwaves employed. First, at high frequencies, the microwave-resonant-cavity dimensions are of the order of few millimetres. Thus, although the sensitivity per unit volume is high, the sample volume is limited to about 0.02 $cm^3$. Second, high frequencies require high magnetic fields, which must be homogeneous. With conventional magnets, sufficiently homogeneous magnetic fields exceeding 25,000 Gauss are difficult to produce. Third, for aqueous samples dielectric absorption seriously impairs sensitivity as frequency increases. These factors have resulted in the choice of about 9.5 GHz as the working frequency of most commercial spectrometers (the X-band), which require a field of 0.34 T when the *g*-factor $\approx$ 2. Interposed between the Gunn diode (or klystron) and the wave-guide are an attenuator, to regulate the power input, and a ferrite insulator, to protect the source from reflected radiation. (Figure 4).

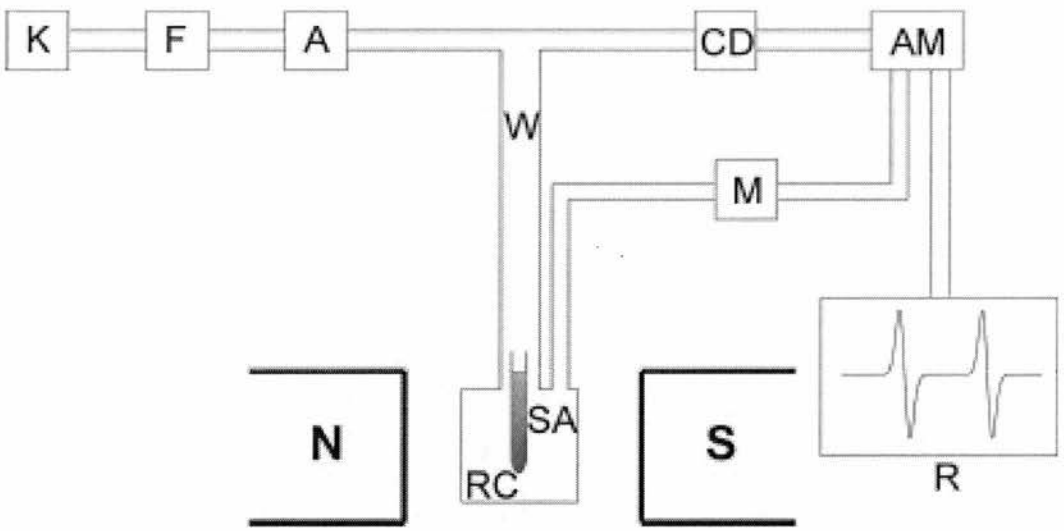



**Figure 4**

| | | | |
|---|---|---|---|
| **N** and **S** | = poles of an electromagnet | **A** | = attenuator |
| **RC** | = resonant cavity | **CD** | = crystal detector |
| **SA** | = sample | **AM** | = amplifier |
| **W** | = wave-guide | **R** | = recorder |
| **K** | = Gunn diode | **M** | = modulator |
| **F** | = ferrite insulator | | |

This radiation reaches the detector, a crystal diode, via a *T*-shaped bridge. The bridge can be so adjusted that no radiation reaches the detector if no absorption of microwaves occurs in the resonator. To raise the sensitivity of the crystal diode, however, one must supply a small amount of energy to it, even in the absence of absorption. This can be done by throwing the bridge slightly out of equilibrium. The noise which then appears is the usual background of the signal: it arises partly from intrinsic noise of the detector and partly from the frequency noise of the source.

## 2.2 Theoretical Calculations.

Theoretical calculations give valuable assistance with the assignment of hfs in EPR spectra and help to determine the chemical and steric structure of radicals. With the rapid improvement in computer technology, combined with increasingly accurate computational schemes, theoretical predictions of radical hyperfine structures are today serving an important role in the understanding of the proprieties of radicals and their reactions. Due to the high reactivity of most radical systems, relatively little experimental information can in general be obtained on such species. Theory may be of assistance through comparisons of observed and computed hyperfine coupling constants, which may lead to the assignment of plausible geometries and the identification of reaction products. Further analyses of the theoretical data also enable us to answer questions regarding reaction barriers, transition states, charge and spin distributions and various other properties.

In computational chemistry, there are mainly three branches: molecular mechanics,[16] semi-empirical SCF MO methods[17,18] such as INDO[19] or AMI[20] and *ab-initio*.MO methods.[21] Each branch has carved out a niche within which it is supreme, and from which it can recognise the eminence of the other two. Thus, the conformations of macromolecules are most affectively studied using the techniques of molecular mechanics, while the electronic properties of small molecules are most accurately calculated using *ab- initio* methods. In the middle lie the semi-empirical methods.

*Ab-initio* MO methods have proven able to generate hyperfine splittings in good agreement with experiment by using large basis sets (the hyperfine coupling constants map the electron distribution of radicals and give the distribution of the singly

occupied molecular orbital *SOMO*).[22-25] One problem with the *ab-initio* methods is that they are computationally quite expensive even for moderately sized systems.

An alternative approach for calculating the hyperfine coupling constants is represented by the advanced hybrid of density functional theory *DFT* with the non-local Becke's three-parameter function to describe the exchange and correlation energy. The good applicability of DFT is due to an improved inclusion of electron correlation compared to semi-empirical and less sophisticated *ab-initio* treatments, which need a considerably shorter CPU time.

However, exact DFT contains a function of the electron density, which is unknown. Current practical DFT theories approximate the exact exchange-correlation function either by a parameterised functional of the local electron density or by the electron-density gradient. For the calculation of organic molecules and their chemical properties, one of the most successful methods is the B3LYP[26-28] functional, which is the result of the combination of the best parameterised functional available till now. Compared with other *ab-initio* methods, *e.g.* Hartree-Fock (HF), Møller-Plesset correlation energy correction (MP), and local density approximation (LDA), this method (B3LYP) has been frequently confirmed to give the best results for molecular geometry and vibrational frequencies consistent with short computation times. It has been reported that, for the hfs of some sulfur-or-nitrogen-containing radicals, this method can provide better results than the computationally more demanding *ab-initio* calculations with the same basis sets.

## 2.3 Determination of Unimolecular Radical-Reaction Rate Constants by EPR Experiments

EPR can be used as a powerful tool, by the physical organic chemist, to give results that answer some questions which deal with reaction mechanism and kinetics, as well as the structural properties of free radicals.

The main problem is that many radicals of interest in organic chemistry are very short-lived. Solution to this problem came over a decade ago when it was shown that U.V. photolysis of samples within the spectrometer cavity was an excellent method for radical generation.[29] Di-*tert*-butyl peroxide used as photolabile reagent has the advantage that it is miscible with most organic liquids, the *tert*-butoxyl radical

produced is highly reactive in H-abstraction and can not be observed by EPR spectroscopy in solution.[30]

The accurate kinetic data for the *tert*-butyl radical self-termination obtained by Fischer and co-workers is typical.[31]

$$\text{Log } 2k_t/M^{-1}s^{-1} = 11.69-(2.4/\text{kcal mol}^{-1})/2.3RT \qquad \textbf{(8)}$$

This data can be used as a standard against which the rates of other reactions can be measured; at 25°C in *n*-heptane

$$2k_t = 2.7 \times 10^9\ M^{-1}s^{-1} \qquad \textbf{(9)}$$

If both reagent radical and product radical can simultaneously be detected by EPR spectroscopy[32] in a particular temperature range, it is possible to use new computer software to double-integrate the differential spectrum and give the associated area under the EPR peak which can be converted into a value of radical concentration by direct comparison to a standard, with a known radical concentration.

This method can be efficiently used to calculate the reaction kinetics for radical β-fragmentations of 1-carbamoyl-1-methylcyclohexa-2,5-dienyl radicals into their corresponding aminoacyl radicals and confirm the potential of these radical precursors as organotin substitutes. The general mechanism of radical fragmentation of the cyclohexadienyl carboxamide radical is represented below:

$$\text{Precursor} \xrightarrow{k_i} UR^{\bullet}$$

$$UR^{\bullet} \xrightarrow{k_d} R^{\bullet}$$

$$R^{\bullet} + \text{Precursor} \xrightarrow{k_H} UR^{\bullet} + RH$$

$$2UR^{\bullet} \xrightarrow{k_1}$$

$$UR^{\bullet} + R^{\bullet} \xrightarrow{k_2} \text{non radical product}$$

$$2R^{\bullet} \xrightarrow{k_3} \qquad k_1=k_2=k_3=2k_t$$

Since it is well-established that unimolecular radical reactions of all simple radicals proceed at the diffusion-controlled limit, and by making the steady state approximation, the following equation can be derived:

$$\frac{k_d}{2k_t} = \frac{k_H}{2k_t} \frac{[R\cdot]}{[UR\cdot]} [AH] + [R\cdot] + \frac{[R\cdot]^2}{[UR\cdot]}$$

**(Eq 10)**

$k_d$ = Rate constant of β-fragmentation

$k_H$ = Rate constant of hydrogen abstraction

$2k_t$ = Diffusion controlled termination rate constant[33]

[AH] = Initial sample concentration

[UR·] = Concentration of unrearranged radical

[R·] = Concentration of rearranged radical

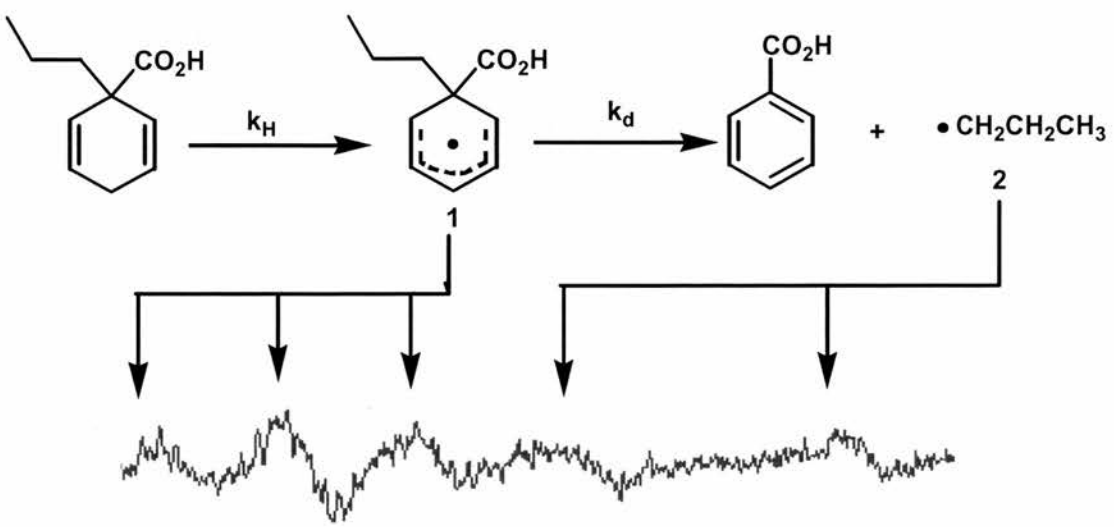
For most of the cyclohexadienyl carboxamides used in kinetic experiments the sample concentration [AH] had little influence on the concentration of the transient radicals and therefore the first term on the right of eq. (10) can be considered negligible. This leads to a further simplification of the steady state equation from which the value of $k_d$ can be directly obtained from the concentrations of unrearranged and rearranged radicals in solution, i.e. from eq. (11).

$$k_d/2k_t = [R^\bullet] + [R^\bullet]^2/[UR^\bullet] \qquad \textbf{(Eq 11)}$$

By EPR measurement it is therefore possible to determine the radical rate constant $k_d$ for a unimolecular radical fragmentation reaction. It is quite accurate to use Fisher's *tert*-butyl radical value for $2k_t$, suitably corrected for solvent viscosity. Many free radical rate constants have been calibrated in this way.[34]

### 2.3.1 Determination of free-radical concentrations by EPR spectroscopy

As previously mentioned, the absorption intensity of EPR signals generated by transient free radicals is directly proportional to the radical concentration. However, measurements of these values are relatively difficult as the reactive radicals exist in very low concentration and often are very difficult to detect. Preceding methods of calculating this area involved manual double integration procedures which often led to inaccurate results. The introduction of new computer software packages successfully aid the manipulation and elucidation of EPR data which is nowadays widely used for this purpose. For example Bruker WinEPR software provides the opportunity to manipulate isotropic EPR spectra on-screen, allowing the quick measurement of hyperfine splitting and g-values. However the major advantage in the use of new software packages is the capability to select a small portion of the EPR differential spectrum on which can easily be performed a double integration making possible the accurate determination of the area underneath the selected peaks in a similar manner to that used in NMR. For example kinetic data have successfully been calculated by an EPR spectroscopic method developed for determining the hydrogen transfer ($k_H$) and dissociation ($k_d$) steps of the chain propagation steps of 1-alkyl cyclohexa-2,5-diene-1-carboxylic acids.[35,36] The EPR spectra acquired on photolysis of 1-*n*-propylcyclohexa-2-5-diene-1-carboxylic acid at 345 K showed peaks that were generated by both the delocalised cyclohexadienyl radical **1** and the *n*-propyl radical **2** (Figure 5).




First derivative spectra

1st Integral

2nd Integral

**Figure 5**

First integral of the first derivative EPR spectra was obtained by using WinEPR software which gave a profile with a distorted baseline. Fortunately the software is provided with a baseline correction facility, which allows the baseline to be reset in such manner that the second integral can be obtained giving step diagram similar to that used in NMR. Accurate measurement of the integral heights was possible by the use of the pointer incorporated into the computer program, and hence the transient radical concentrations were obtained. In order to obtain the actual concentration of a transient radical, comparison of the double integral value with that obtained from a standard solution containing a stable radical of known concentration was necessary. A standard solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) in toluene having a known concentration of $10^{-4}$ M was prepared and 250 µl aliquot was placed in a quartz EPR tube before being thoroughly degassed with $N_2$. The sample was inserted into the resonant cavity, and the EPR spectra acquired using identical parameters of both power and modulation to those used with the cyclohexadienyl acid. A well-resolved EPR spectrum was obtained (Figure 6) from which the double integral was obtained as described above.

**Figure 6**

This approach allowed the calculation of the concentrations of transient radicals by placing the double integral values into the following derived equation:

$$[R\bullet] = [DPPH]\left(\frac{\text{double integ. R}\bullet}{\text{double integ. DPPH}}\right)\left(\frac{\text{gain DPPH}}{\text{gain R}\bullet}\right)\left(\frac{[(\text{field (R}\bullet)]^2}{(\text{field DPPH})^2}\right)\left(\frac{\text{T (R}\bullet)}{\text{T (DPPH)}}\right)F$$

**(Eq) 12**

[DPPH] = Known concentration of DPPH.

Double integ.($R^{\bullet}$)= Double integral for the transient radical $R^{\bullet}$.

Gain ($R^{\bullet}$) = EPR gain value used during spectrum acquisition.

Field ($R^{\bullet}$) = Field range of double integrated portion of the spectrum (G).

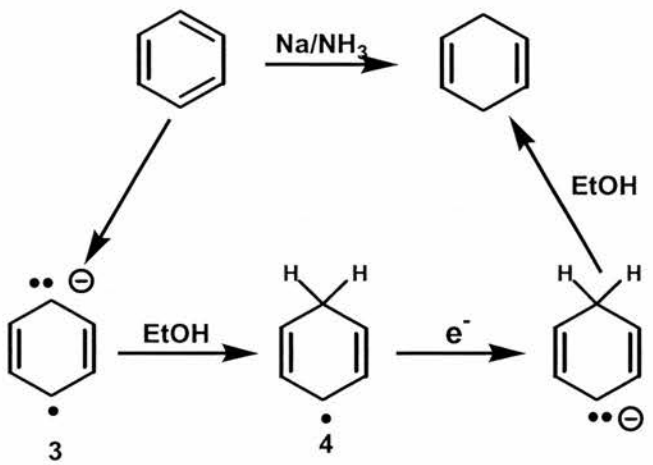
T ($R^{\bullet}$) =Absolute temperature of acquisition spectra.

F = Factor, inverse fraction for the portion of spectrum integrated.

The calculated concentration can finally be inserted into the derived steady state equation (Eq 11) from which it is possible to obtain both H-abstraction rate $k_H$ and β-fragmentation rate constant $k_d$ at a given temperature.

## 2.4 Birch Reduction

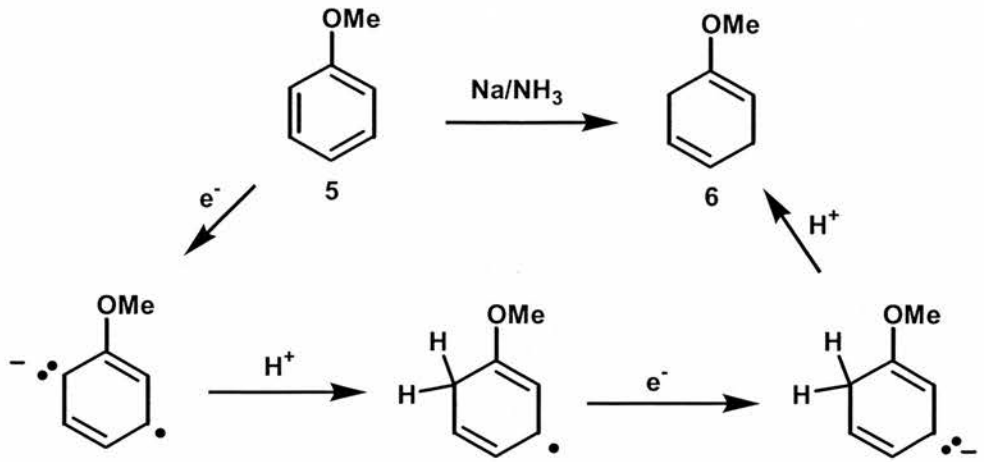
Aromatic compounds can be reduced to the corresponding non-conjugated cyclohexadienes by metal ammonia reductions, commonly referred as Birch reductions.[37,38] Thus, benzene can be reduced using Na and $NH_3$ to give cyclohexa-1-4-diene (Scheme 1). The mechanism of the reduction involves the transfer of an electron from the metal to the ammonia solution, forming a solution of solvated electrons.




**Scheme 1**

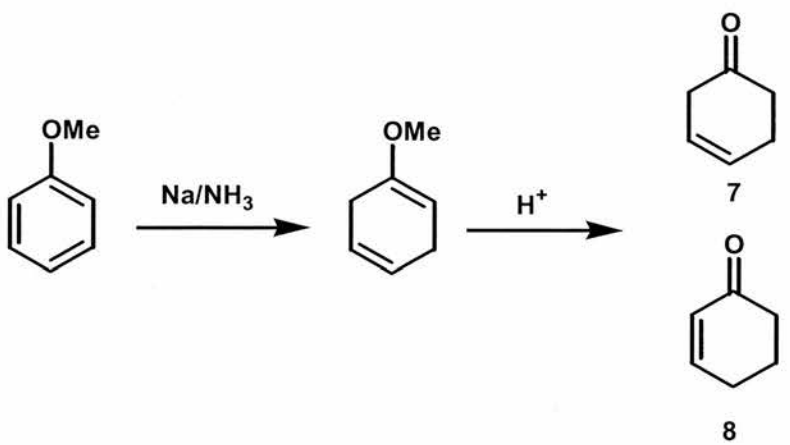
An electron is then able to add to the aromatic ring forming the radical anion **3,** which abstracts a proton (usually from a proton source such as EtOH) to give radical **4**. The latter can accept another electron followed by a proton to give the product.

When the Birch reduction is carried out with a substituted aromatic compound[39] the product obtained is controlled by the nature of the substituent. If the substituent is an electron-donating group, such as alkyl or alkoxyl, the reaction rate is decreased and the substituent is generally found on the non-reduced position of the product. For example, the Birch reduction of methoxybenzene **5** results in the formation of 1-methoxycyclohexa-1,4-diene **6** (Scheme 2).



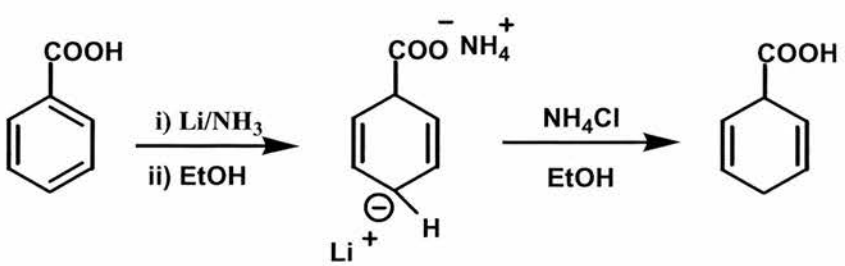

**Scheme 2**

These extremely valuable dienol ethers provide cyclohex-3-en-1-ones **7** by mild acidic hydrolysis or cyclohex-2-en-1-ones **8** when stronger acids are used (Scheme 3).



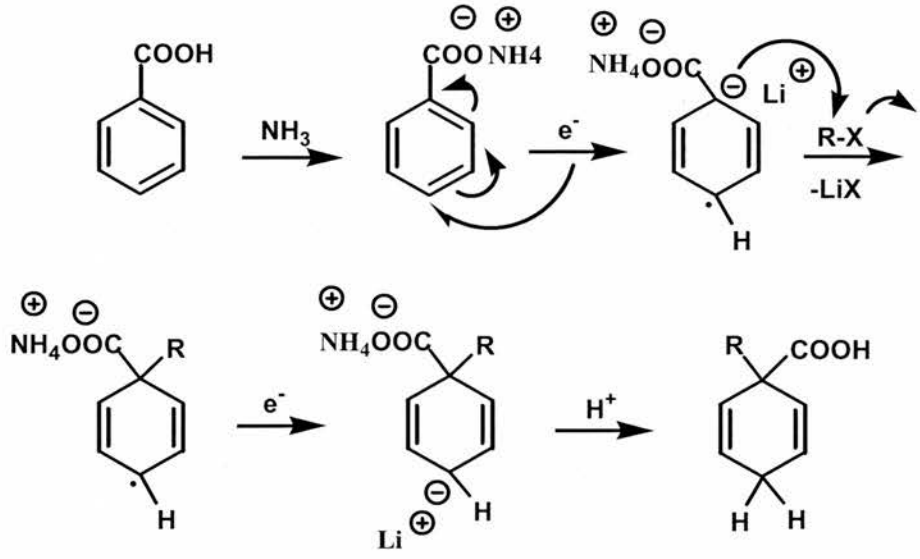

**Scheme 3**

On the other hand if the benzene ring contains electron withdrawing groups such as COOH, an increased reaction rate is produced and the substituent is found on the reduced position of the product (Scheme 4).




**Scheme 4**

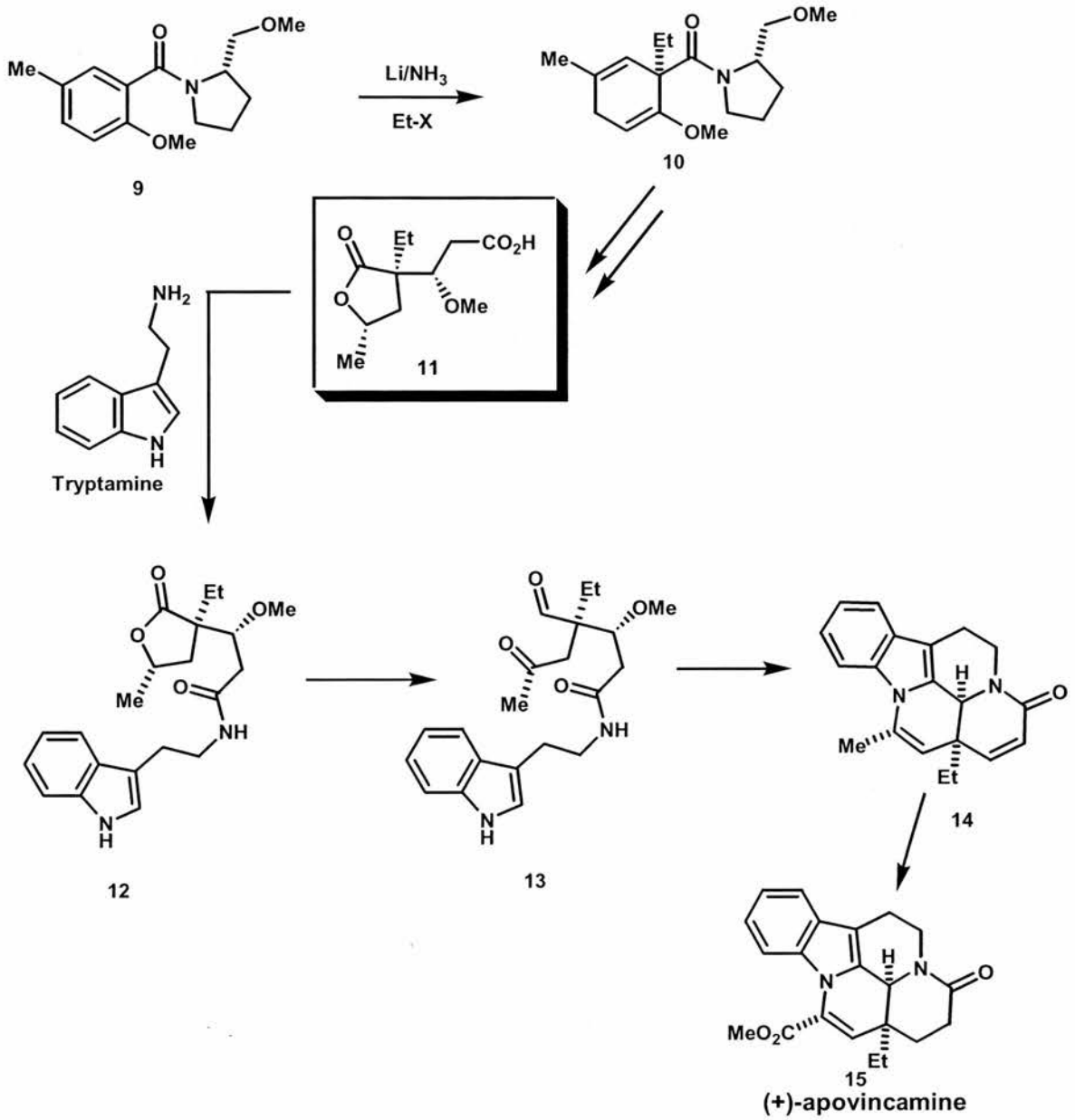
The Birch reduction/alkylation is of even greater strategic value as it allows the conversion of readily available aromatic compounds into alicyclic synthetically useful intermediates (Scheme 5).




**Scheme 5**

The high degree of diastereoselection in the chiral alkylation step, makes this approach unusually versatile for the asymmetric synthesis of many natural products.[40]

An asymmetric total synthesis of (+)-apovincamine **15,** a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (Vinca minor) for the human treatment of chronic ischemic cerebrovascular diseases, began with the Birch reduction–ethylation of the chiral 2-methoxy-5-methylbenzamide **9** to give **10** (diastereomer ratio 100:1).[41] Tryptamine was coupled to the butyrolactone carboxylic acid **11**, and the resulting amide **12** was converted to the keto aldehyde **13**. An acid-catalyzed cyclization of **13** followed by a base-induced elimination of MeOH provided the key *cis*-fused diene lactam **14**, which was converted to (+)-apovincamine **15** by a sequence of steps involving reduction of the ene lactam with $LiAlH_4$ and oxidation of the methyl substituent by an electrophilic dibromination (Scheme 6).

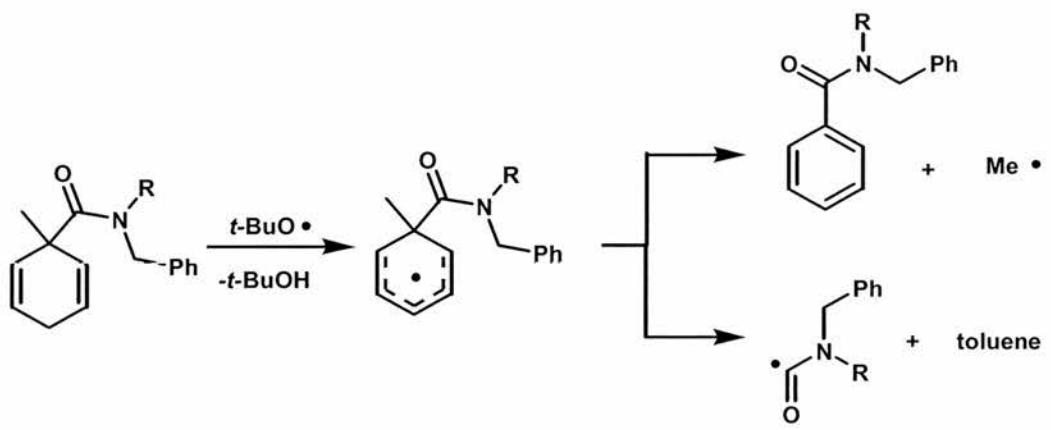

Me
OMe
OMe
9
Li/NH3
Et-X
Et
OMe
10
CO2H
11
NH2
Tryptamine
12
13
14
15
(+)-apovincamine
MeO2C

**Scheme 6**

## 2.5 Aims and Objectives

Carbamoyl-1-methylcyclohexa-2,5-dienes might be good aminoacyl radical precursors that could potentially ring close to afford lactams as the main products. The motivation of this work was to further investigate 1-carbamoyl-1-methylcyclohexa-2,5-dienes and evaluate if these alternative sources of radical generation are suitable for efficient radical sequences. Kinetic information on chain propagation steps is therefore very desirable as a tool to facilitate synthetic planning. Our aim was to detect and characterise the radical intermediates released on UV photolysis of secondary and tertiary 1-methyl-2,5-cyclohexadiene-1-carboxamides, in order to determine the rate constants of both β-fragmentation and H-abstraction steps. We envisaged that experiments, carried out within the spectrometer cavity in neat DTBP in a range of different temperatures, would therefore be appropriate for this purpose.

Secondary and tertiary 1-methyl substituted carboxyamides **18** and **19** were chosen because methyl radical is the least stabilised of the simple alkyl radicals. Unwanted β-scission of the intermediate cyclohexadienyl radicals, to produce methyl radicals and aromatic amides, should therefore be seriously disfavoured. Furthermore the produced aminoacyl radicals do not contain double bond functionality and should be formed in such a concentration to allow kinetic measurements.



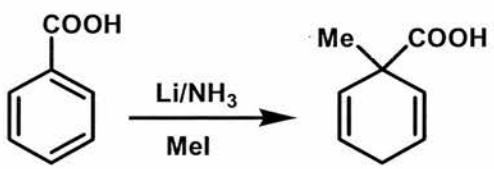

**Scheme 7**

## 2.6 Results and Discussion

Secondary and tertiary 1-carbamoyl-1-methylcyclohexa-2,5-dienes were synthesised and studied by EPR spectroscopy in order to obtain kinetic data. The hydrogen transfer ($k_H$) and dissociation ($k_d$) steps of the chain were found to be comfortably above the lowest limit for efficient synthetic sequences.

### 2.6.1 Preparation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid

The Birch reduction/alkylation of benzoic acid was carried out using liquid ammonia as solvent/co-reducing agent. The reaction was technicoloured, the solution turning yellow, orange and green during lithium metal addition. The lithium addition was stopped when a permanent deep blue colour appeared (usually 2.5-3.5 molar equivalent of lithium were needed). Following this, a large excess of methyl iodide was added to introduce the methyl group selectively and exclusively into the C-1 position (Scheme 8). The 1-methylcyclohexa-2,5-diene-1-carboxylic acid **16** was isolated using a standard aqueous workup and washed with a saturated solution of sodium thiosulfate. Kugelrohr distillation furnished the pure acid as a pale yellow partly crystalline oil in high yields.



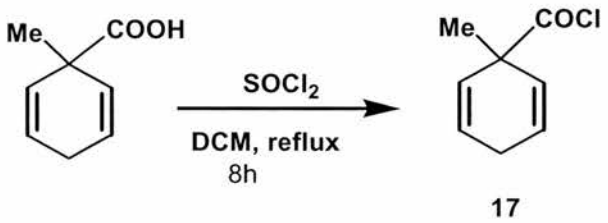

16

**Scheme 8**

### 2.6.2 Preparation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid chloride.

Treatment of 1-methylcyclohexa-2,5-diene-1-carboxylic acid with thionyl chloride in DCM solution under nitrogen, resulted in the formation of the 1-methylcyclohexa-2,5-diene-1-carboxylic acid chloride **17** (Scheme 9), in quantitative yield (estimated from $^1$H NMR spectrum of the crude reaction mixture).The reaction rate was very slow. It

was determined by TLC that the reaction started after 1h of reflux and complete conversion of the acid to the acid chloride was obtained after 8h.

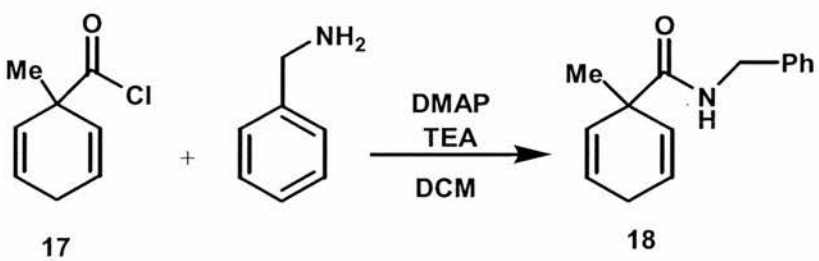



17

**Scheme 9**

### 2.6.3 Preparation of *N*-benzyl-1-methyl-2,5-cyclohexadiene-1-carboxamide (18).

When 1-methylcyclohexa-2,5-diene-1-carboxylic acid chloride **17** was refluxed for 5 h in DCM in presence of benzylamine, a catalytic amount of DMAP, and triethylamine, impure amido-cyclohexadiene **18** was obtained (Scheme 10).



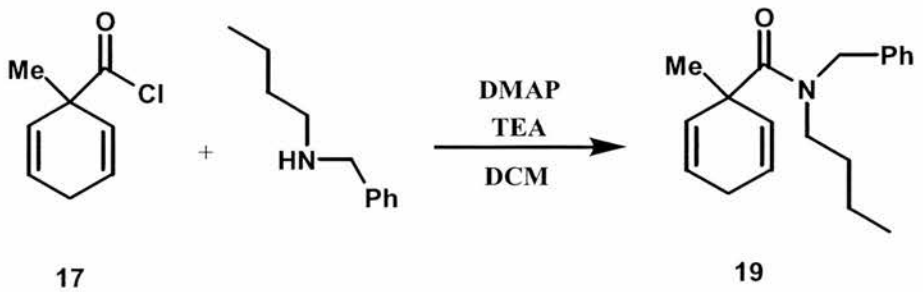

17 18

**Scheme 10**

In order to avoid decomposition of the product the reaction was carried out under gentle refluxing conditions. The crude amide **18** was purified by crystallization, using ethyl acetate-hexane as solvent.

### 2.6.4 Preparation of *N*-benzyl-*N*-*n*-butyl-1-methylcyclohexa-2,5-diene-1-carboxamide (19)

Having succeeded in preparing amide **18** the synthesis of a secondary amide (**19**) was carried out (Scheme 11).




17 19

**Scheme 11**

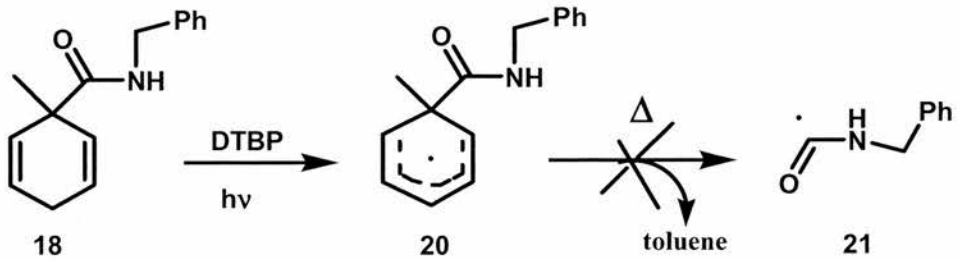
1-Methylcyclohexa-2,5-diene-1-carboxylic acid chloride was added to a solution of *N*-benzyl-*N*-butylamine, DMAP and triethylamine, the resulting solution was refluxed for 5h, a basic workup yielded the impure product as a yellow oil which was purified by column chromatography to give 1-methylcyclohexa-2,5-diene carboxylic acid benzyl-butyl-amide **(19)** as a pale yellow oil in 77% yield.The structures of **18** and **19** have been confirmed by C-H-N microanalysis and GC/MS.

### 2.6.5 EPR spectroscopic studies on amides 18 and 19.

We have used EPR spectroscopy to prove that amides **18** and **19,** can function as good sources of aminoacyl radicals. The increased stability of these radical intermediates in comparison with their counterpart alkoxyacyl alternatives would favour the dissociation of delocalised cyclohexadienyl radicals **20** and **22** to aminoacyl radicals **21** and **23** rather than the competing $Me^{\bullet}$ loss. The driving force for the reaction is the regeneration of aromaticity to release toluene as by-product which can readily be removed from the reaction mixture.

Photolysis of a solution amido-1-methylcyclohexa-2.5-diene **18** with neat di-*tert*-butyl peroxide in the resonant cavity of a Bruker 9.5 GHz EPR spectrometer generated cyclohexadienyl radical **20** (Scheme 12). The temperature was then increased at

intervals of 5 K using a fresh sample at each temperature setting and the experimental parameters were kept constant in order to maintain uniformity.




**Scheme 12**

EPR spectra were recorded in the temperature range of 240-370 K. The spectra recorded at 260 K gave good evidence of the formation of the delocalised cyclohexadienyl carboxamide radical **20** (Figure 7) but the corresponding aminoacyl radical **21** was not detectable by the EPR experiments.

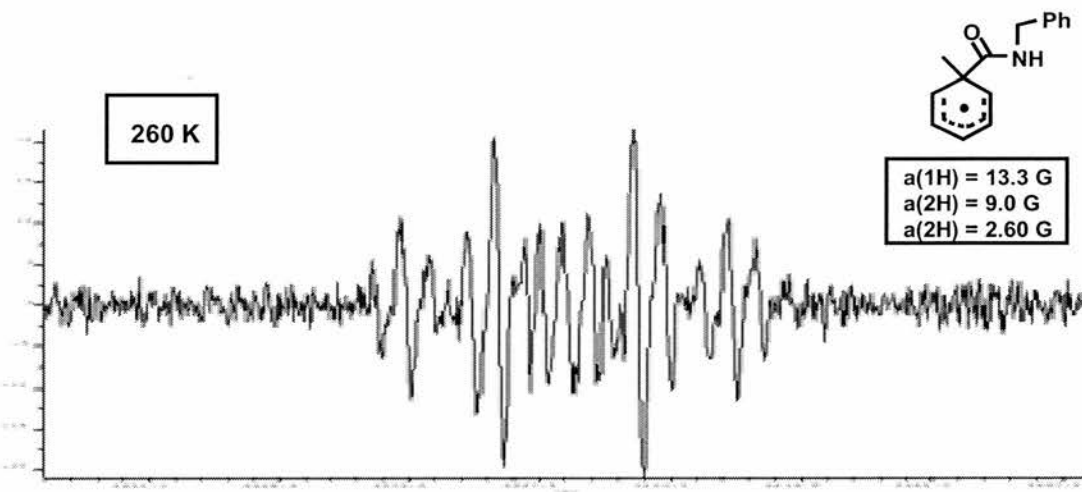
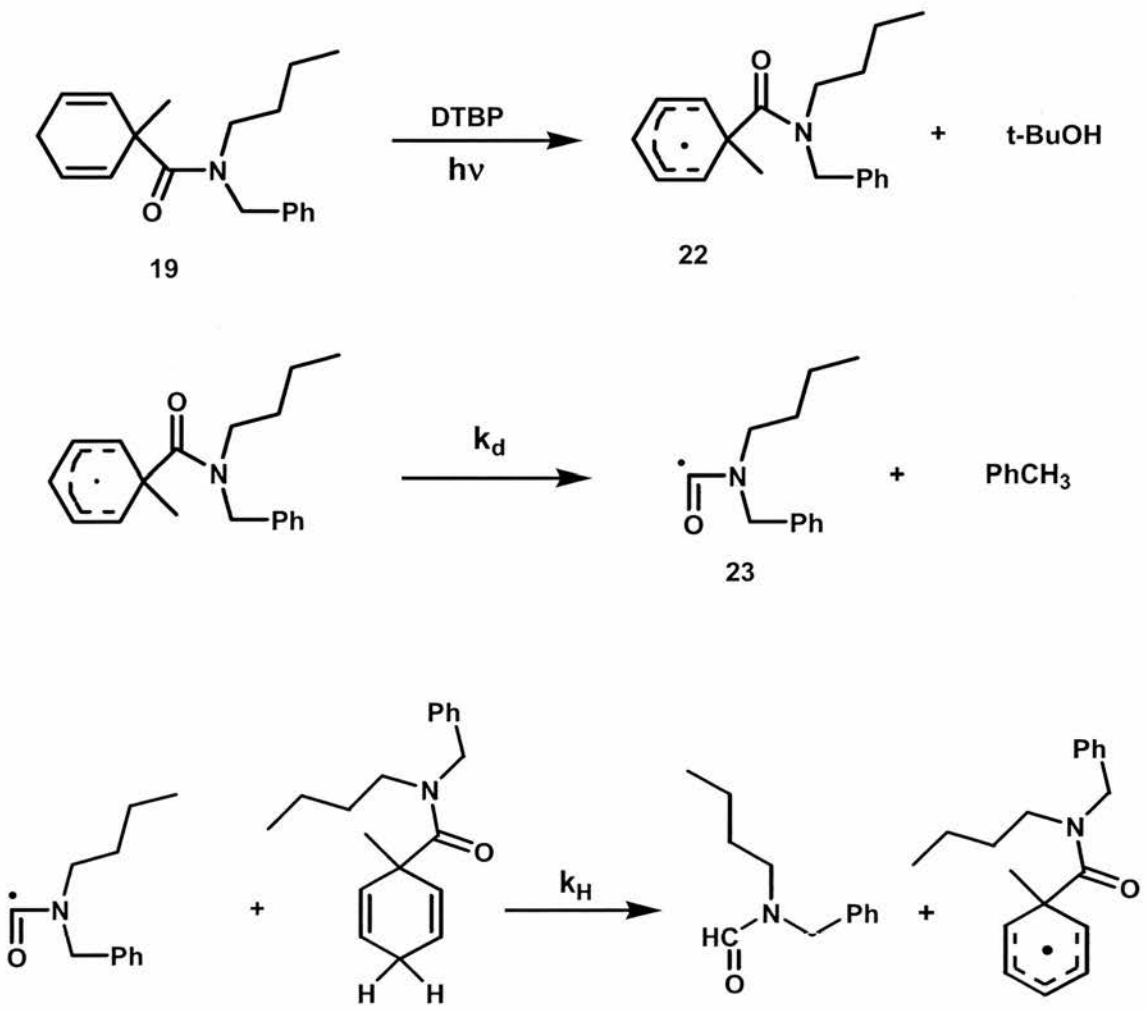


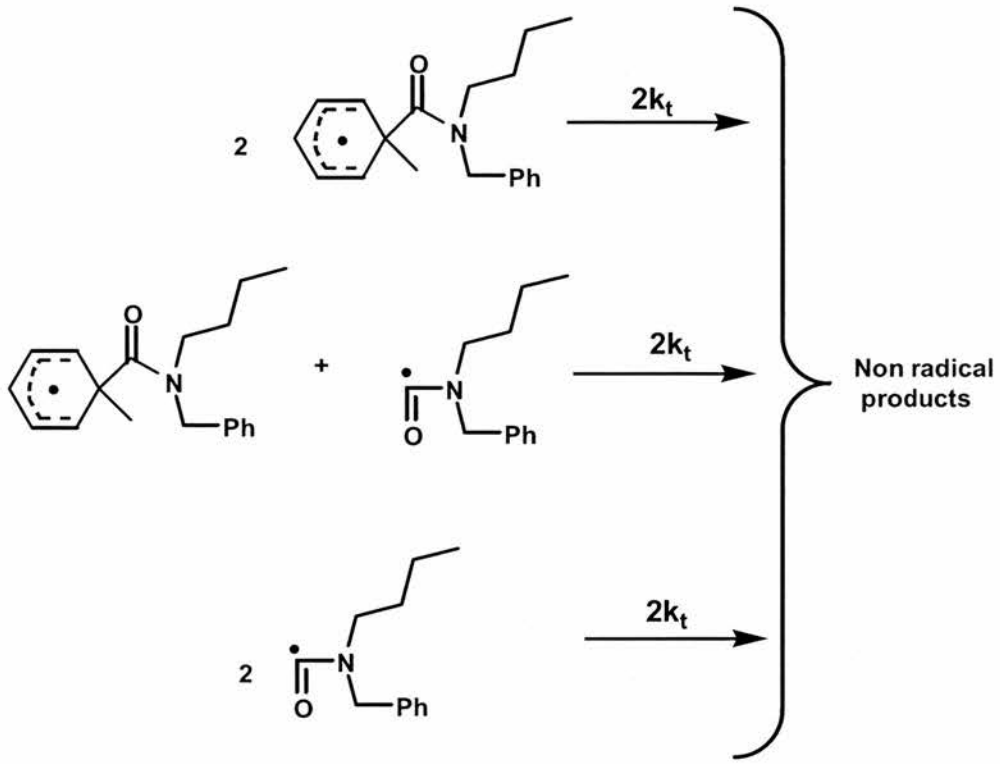

**Figure 7**

On the basis of these results it was therefore possible to conclude that H-abstraction from the carboxamide precursor occurs at 260 K. The aminoacyl radical was not observed even at 370 K showing that release of aminoacyl radicals from secondary carbamoyl cyclohexadienyl radicals is not a favoured process. This may be due to the

reduced possibility of delocalisation of the unpaired electron compared with analogous tertiary aminoacyl radicals.

Tertiary amides such as, *N*-benzyl-*N*-*n*-butyl-1-methyl-2,5-cyclohexadiene-1-carboxamide **19** produced the cyclohexadienyl radical **22** under similar photolysis conditions. The mechanism of the decomposition during the EPR experiments is represented in Scheme 13






**Scheme 13**

Cyclohexadienyl radical **22** was detected at 280 K (Figure 8). When the temperature was raised from 245 K to 345 K a new spectrum appeared and aminoacyl radical **23** was clearly detected by EPR spectroscopy (Figure 9). Spectra recorded at 245 K, showed a doublet of triplets of triplets for cyclohexadienyl radical **22**, in which the delocalised electron interacts with five hydrogen atoms, the resulting spectrum is shown in Figure 8 together with a computer simulation obtained by use of the Bruker SimFonia software.

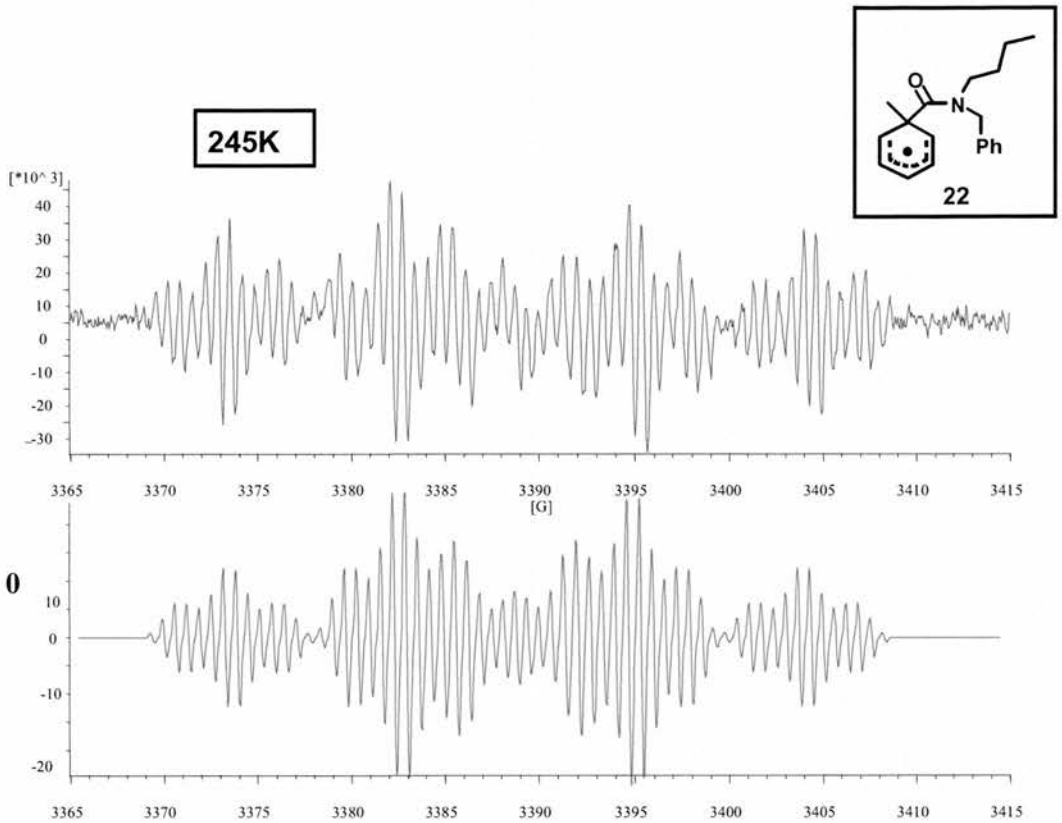



**Figure 8** 9.4 GHz EPR spectrum of cyclohexadienyl radical **22** in neat DTBP at 280 K

An accurately measured quantity of *N*-alkyl-*N*-benzyl-1-methyl-2,5-cyclohexadiene-1-carboxamide in 250 μl of DTBP was placed in a clean dry quartz tube. The resulting solution was degassed by passing a steady flow of $N_2$ through the sample for 15 minutes. The degassed solution was then placed in the resonant cavity of the EPR spectrometer, the experimental parameters were adjusted, the sample was exposed to radiation and the spectrum was recorded. The settings of the EPR spectrometer were optimized during the course of the experiment and the temperature in the EPR cavity was varied until the best spectrum was obtained for the cyclohexadienyl radical **22**. In order to observe the aminoacyl radical (Figure 9) released by β-fragmentation of the corresponding cyclohexadienyl radical, the temperature was increased at intervals of 5 K.

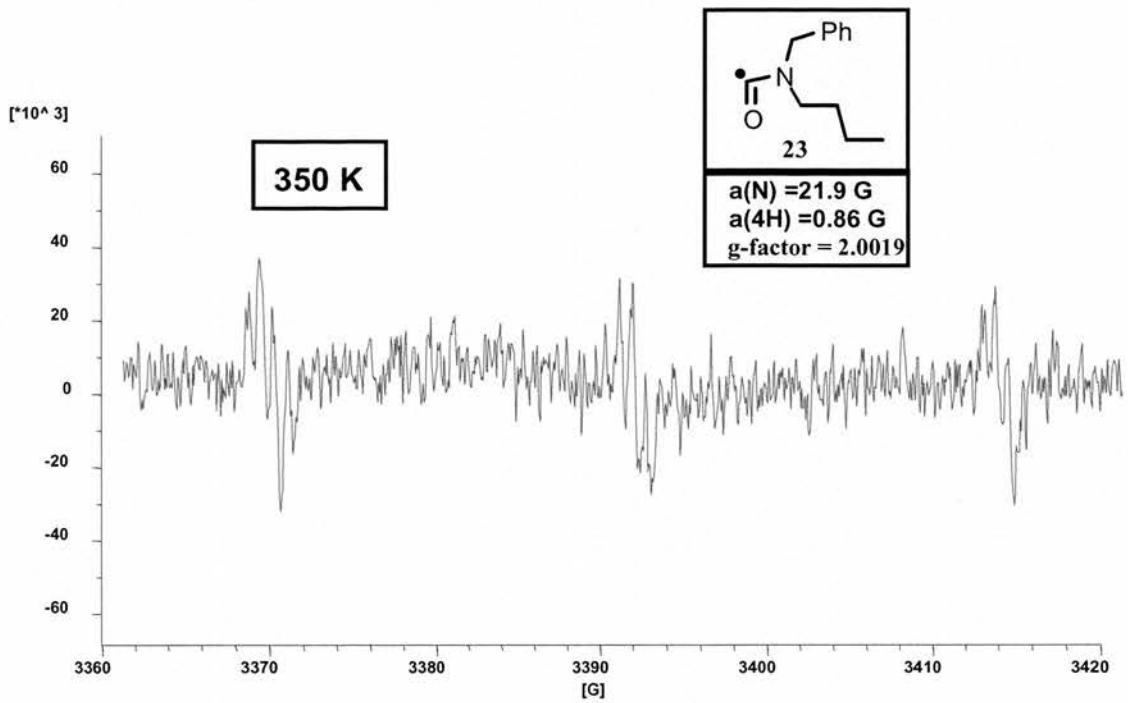



**Figure 9**

**9.4 GHz EPR Parameters of Radicals Derived from 1-Methyl-2,5-cyclohexadiene-1-carboxamides (18) and (19) in DTBP Solution[a]**

| Radical | T/K | g-factor | a(G) |
|---|---|---|---|
| 20 | 260 | [2.0027] assumed | a(2H)=2.59<br>a(2H)=9.02<br>a(1H)=13.27 |
| 22 | 245 | [2.0027] assumed | a(2H)=2.64<br>a(2H)=9.23<br>a(1H)=12.66<br>a(N)=0.66<br>a(3H)=0.66 |
| 21 | 300-350 | Not detected | Not detected |
| 23 | 350 | 2.0019 | a(4H)=0.86<br>a(N)=21.9 |

[a] All spectra in neat DTBP.

The hyperfine splittings (hfs) of radicals **20** and **22** were similar to those of other cyclohexadienyl radicals[42] and, as expected, were not very sensitive to the nature of the amide substituents. Comparison of the measured EPR parameters of the higher temperature species **23** with archetype aminoacyl radicals, previously characterised by EPR spectroscopy,[43-47] supports our identification of radical **23** as an aminoacyl. Aminoacyl radicals are capable of existing as E- and Z-isomers but it was not possible to detect separate spectra for the two forms. Individual peaks of the aminoacyl radical N-triplets were rather broad ($\Delta H_{pp} \cong 2.5$ G) and this might be the consequence of overlap of E- and Z- species with similar a(N) values.

### 2.6.6 Determination of unimolecular-radical reaction rate constants on amide 19.

A detailed examination of the spectra derived from cyclohexadienyl radical **22** and aminoacyl radical **23** showed that there were peaks within each spectrum that did not interfere with each other. Thus, portions of spectra recorded at the temperature range of 320-340 (Figure 10) were used for measurement of the growth and decline of the relative peaks.

In order to determine the rate constant for the radical fragmentation, nine EPR tubes were prepared containing 1 mg of amide **19** in 200 μl of DTBP. One tube was placed in the EPR cavity and photolysed by light from a 500 watt super pressure Hg arc at the temperature of 300 K. Radical concentrations for the fragmentation reaction from the cyclohexadienyl radical **22** to aminoacyl radical **23** were calculated by double integration of the first derivative EPR spectrum of suitable peaks from each radical (Figure 10) and comparison with the doubly integrated signal from a $1x10^{-3}$ M solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH).

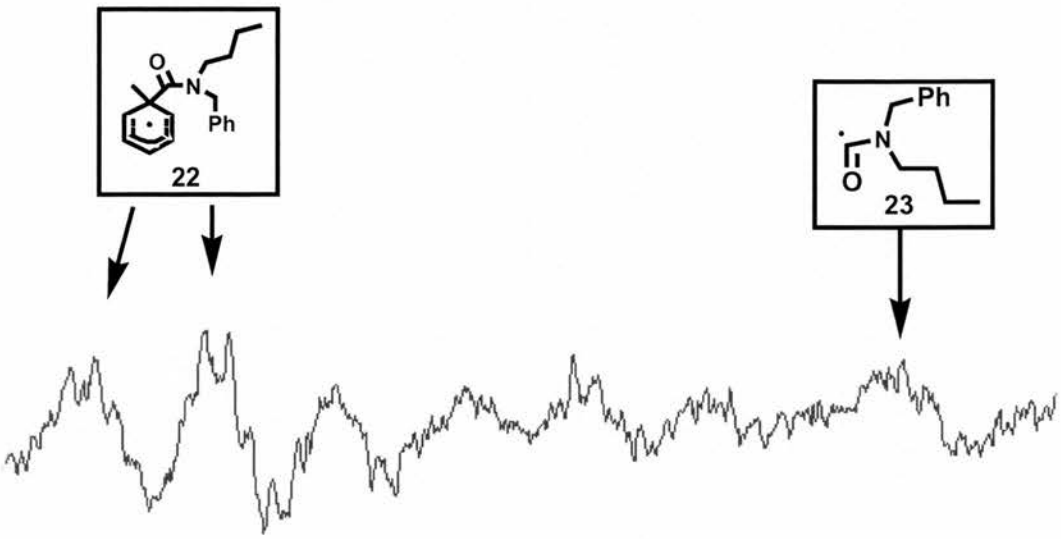



**Figure 10**

Application of the steady state approximation leads to the following rate expression:

$$k_d/2k_t + k_H/2k_t \{[\mathbf{19}][\mathbf{23}]/[\mathbf{22}]\} = [\mathbf{23}]^2/[\mathbf{22}] + [\mathbf{23}] \qquad \textbf{(Eq 13)}$$

Note that if the H-abstraction step is fast the second term in this equation comes into play and the results will depend on the initial amide concentration [**19**]. To test this possibility, two sets of data were obtained using amide concentrations of 0.018 and 0.071 mol $dm^{-3}$. The experiment was repeated at increasing temperature using a fresh sample for each temperature setting. No significant differences in the two sets of data were observed and hence H-abstraction seemed to be negligible under these conditions. $k_d/2k_t$ could therefore calculated from the simple expression:

$$k_d/2k_t = [\mathbf{23}]^2/[\mathbf{22}] + [\mathbf{23}] \qquad \textbf{(Eq 14)}$$

$2k_t$ values were taken from the literature data for termination of *t*-Bu radicals in *n*-heptane. The rate constants obtained from equation (14) were also corrected for changes in solvent viscosity.[48] Equation (15) relates the termination rate constant in *n*-heptane at the temperature of the experiment ($\theta = 2.3RT$). Correction for viscosity differences of the two solvent (*n*-heptane and DTBP respectively) at a given

temperature can be calculated by equation (16) and (17). Equation (18) allows the estimation of $2k_t$, constant for DTBP solvent and, finally by equation (19) it is possible to calculate the β-fragmentation rate constant.

$$\text{Log}\, 2k_t\,(n\text{C}_7) = 11.63 - \left(\frac{2.25}{\theta}\right) \qquad \textbf{(Eq.15)}$$

$$\text{Log}\ \eta\ (n\text{C}_7) = 10^3/\text{T}\ (0.42) - 1.82 \qquad \textbf{(Eq.16)}$$

$$\text{Log}\ \eta(\text{DTBP}) = 10^3/\text{T}\ (0.473) - 1.689 \qquad \textbf{(Eq.17)}$$

$$\text{Log}\, 2k_t\,(\text{DTBP}) = \text{Log}\, 2k_t\,(n\text{C}_7) + \text{Log}\eta\,(n\text{C}_7) + \text{Log}\eta\,(\text{DTBP}) \qquad \textbf{(Eq 18)}$$

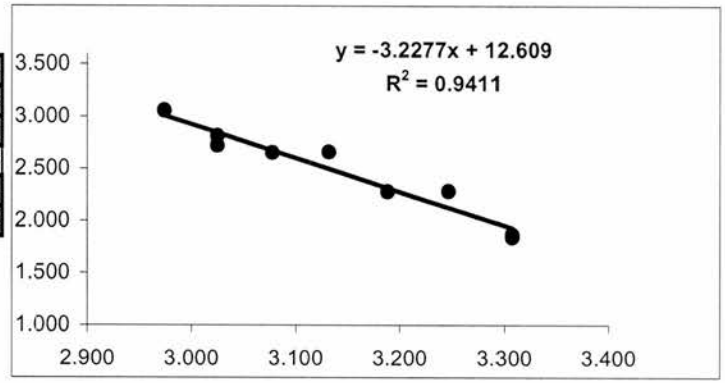
$$\text{Log}\, k_d\,(\text{DTBP}) = \text{Log}\frac{k_d}{2k_t} + \text{Log}\, 2k_t\,(\text{DTBP}) \qquad \textbf{(Eq 19)}$$

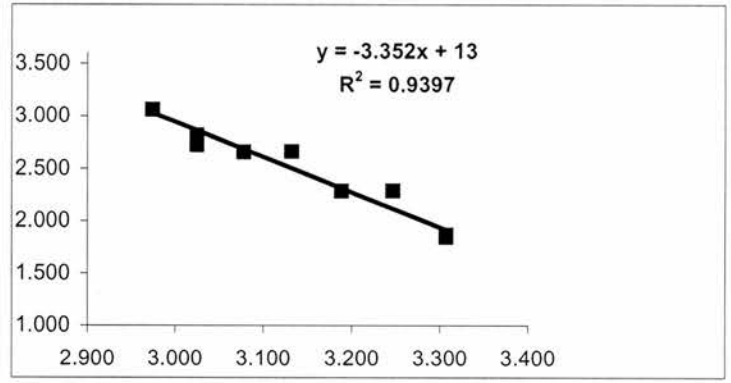
# Table 1

Kinetics of n-Bu, benzylchd amide 1 mg in 200 µl dtbp

| Dial Temp | Actual Temp K | Gain | Double Int r˙ | Double Int a˙ | [r˙] | [a˙] | kd/2kt | logkd/2kt | log2kt (nC7) | $10^3/T$ | log ηc7 | log η DTBP | log2kt DTBP | log kd DTBP | log kd c7 | kd |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 300 | 302 | 2.00E+06 | 14 | 25.3 | 1.234E-08 | 5.948E-08 | 1.490E-08 | -7.827 | 10.002 | 3.307 | -0.43 | -0.12 | 9.696 | 1.869 | 2.175 | 7.39E+01 |
| 300 | 302 | 2.00E+06 | 13.5 | 26.4 | 1.190E-08 | 6.207E-08 | 1.419E-08 | -7.848 | 10.002 | 3.307 | -0.43 | -0.12 | 9.696 | 1.847 | 2.154 | 7.04E+01 |
| 305 | 308 | 2.00E+06 | 31.4 | 40.9 | 2.820E-08 | 9.796E-08 | 3.632E-08 | -7.440 | 10.032 | 3.247 | -0.46 | -0.15 | 9.729 | 2.289 | 2.592 | 1.94E+02 |
| 310 | 314 | 2.00E+06 | 27 | 28.8 | 2.469E-08 | 7.024E-08 | 3.338E-08 | -7.477 | 10.060 | 3.188 | -0.48 | -0.18 | 9.760 | 2.284 | 2.584 | 1.92E+02 |
| 315 | 319 | 2.00E+06 | 48.5 | 28.4 | 4.516E-08 | 7.051E-08 | 7.408E-08 | -7.130 | 10.088 | 3.132 | -0.50 | -0.21 | 9.791 | 2.661 | 2.958 | 4.58E+02 |
| 320 | 325 | 2.00E+06 | 40.52 | 19.7 | 3.840E-08 | 4.978E-08 | 6.801E-08 | -7.167 | 10.115 | 3.077 | -0.53 | -0.23 | 9.821 | 2.654 | 2.948 | 4.50E+02 |
| 325 | 331 | 2.00E+06 | 31.7 | 5.9 | 3.056E-08 | 1.517E-08 | 9.213E-08 | -7.036 | 10.141 | 3.025 | -0.55 | -0.26 | 9.850 | 2.814 | 3.105 | 6.52E+02 |
| 325 | 331 | 2.00E+06 | 33.6 | 9.7 | 3.239E-08 | 2.494E-08 | 7.447E-08 | -7.128 | 10.141 | 3.025 | -0.55 | -0.26 | 9.850 | 2.722 | 3.013 | 5.27E+02 |
| 330 | 336 | 2.00E+06 | 52.9 | 10.3 | 5.187E-08 | 2.693E-08 | 1.518E-07 | -6.819 | 10.166 | 2.974 | -0.57 | -0.28 | 9.877 | 3.058 | 3.347 | 1.14E+03 |

| | |
|---|---|
| [DPPH] | 1.00E-03 |
| Gain DPPH | 2.00E+03 |
| Doub. Int DPPH | 303.6 |
| temp DPPH | 305 |
| F[r] | 3 |
| F[a] | 8 |



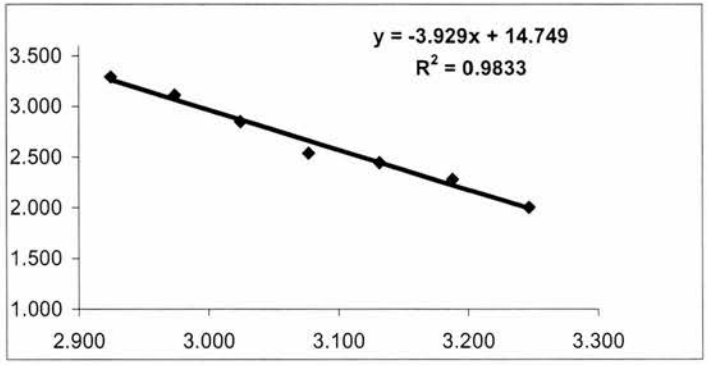



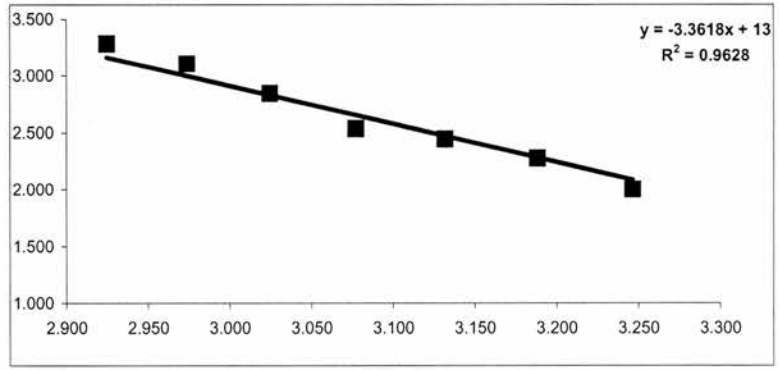
# Table 2

Kinetics of n-Bu, benzylchd amide 4 mg in 200 μl dtbp

| Dial Temp | Actual Temp K | Gain | Double Int r˙ | Double Int a˙ | [r˙] | [a˙] | kd/2kt | logkd/2kt | log2kt (nC7) | $10^3/T$ | log η c7 | log η DTBP | log2kt DTBP | log kd DTBP | log kd c7 | kd |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 305 | 308 | 2.00E+06 | 18.9 | 63.6 | 1.697E-08 | 1.523E-07 | 1.887E-08 | -7.724 | 10.032 | 3.247 | -0.46 | -0.15 | 9.729 | 2.004 | 2.307 | 1.01E+02 |
| 310 | 314 | 2.00E+06 | 30.5 | 62 | 2.790E-08 | 1.512E-07 | 3.304E-08 | -7.481 | 10.060 | 3.188 | -0.48 | -0.18 | 9.760 | 2.280 | 2.580 | 1.90E+02 |
| 315 | 319 | 2.00E+06 | 37.9 | 50.5 | 3.529E-08 | 1.254E-07 | 4.522E-08 | -7.345 | 10.088 | 3.132 | -0.50 | -0.21 | 9.791 | 2.447 | 2.744 | 2.80E+02 |
| 320 | 325 | 2.00E+06 | 39.1 | 36.1 | 3.705E-08 | 9.122E-08 | 5.210E-08 | -7.283 | 10.115 | 3.077 | -0.53 | -0.23 | 9.821 | 2.538 | 2.832 | 3.45E+02 |
| 325 | 331 | 2.00E+06 | 59.4 | 30.2 | 5.726E-08 | 7.764E-08 | 9.950E-08 | -7.002 | 10.141 | 3.025 | -0.55 | -0.26 | 9.850 | 2.847 | 3.139 | 7.04E+02 |
| 330 | 336 | 2.00E+06 | 82.9 | 28.2 | 8.128E-08 | 7.373E-08 | 1.709E-07 | -6.767 | 10.166 | 2.974 | -0.57 | -0.28 | 9.877 | 3.110 | 3.399 | 1.29E+03 |
| 335 | 342 | 2.00E+06 | 94.1 | 22.4 | 9.382E-08 | 5.955E-08 | 2.416E-07 | -6.617 | 10.190 | 2.925 | -0.59 | -0.31 | 9.904 | 3.287 | 3.573 | 1.94E+03 |

| | |
|---|---|
| [DPPH] | 1.00E-03 |
| Gain DPPH | 2.00E+03 |
| Doub. Int DPPH | 303.6 |
| temp DPPH | 305 |
| F[r] | 3 |
| F[a] | 8 |



The kinetic data are shown in table 1.and table 2 where **r** stands for aminoacyl radical **23** and **a** stands for amidocyclohexadienyl radical **22** which incorporates all the equations reported above and enables the final $k_d$ values to be calculated.

Linear interpolation of log $k_d$ *vs* $10^3/T$ gave an equation whose intercept with the y-axis is the A-factor of the Arrhenius law (Equation 20) and whose gradient allows calculation of the activation energy of the process.

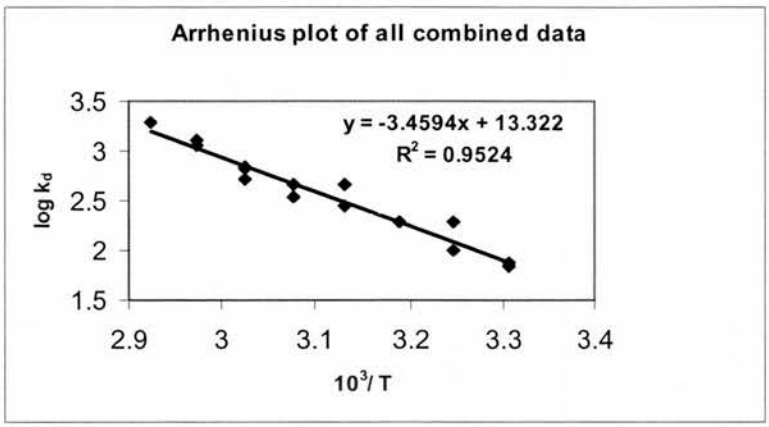
$$\ln k_d = \ln A_d - \frac{E_d}{RT} \qquad \textbf{(Equation 20)}$$

The kinetic data from the second series of photolyses using four times as much amide are shown in table 2. When the data from both sets of experiments are combined figure 11 was obtained which showed that within the experimental error there is no difference in the measured $k_d$ values. This proves that the H-abstraction step is negligible in the EPR experiments.

The Arrhenius plot of all the data combined gives:

$$\text{Log } (A_d/s^{-1}) = 13.32$$
$$E_d = 15.83 \text{ kcal mol}^{-1}$$
$$k_d/s^{-1}(300 \text{ K}) = 59$$

The measured pre-exponential factor was close to the 'normal' value of 13 for unimolecular processes. This is good evidence that the results are dependable. The rate constant for dissociation (59 $s^{-1}$ at 300 K) is close to the value of $10^2$ $s^{-1}$ which is the lowest limit for efficient synthetic sequences and shows that the chain should propagate well at higher temperatures.




$$\ln k_d = \ln A_d - \frac{E_d}{RT}$$

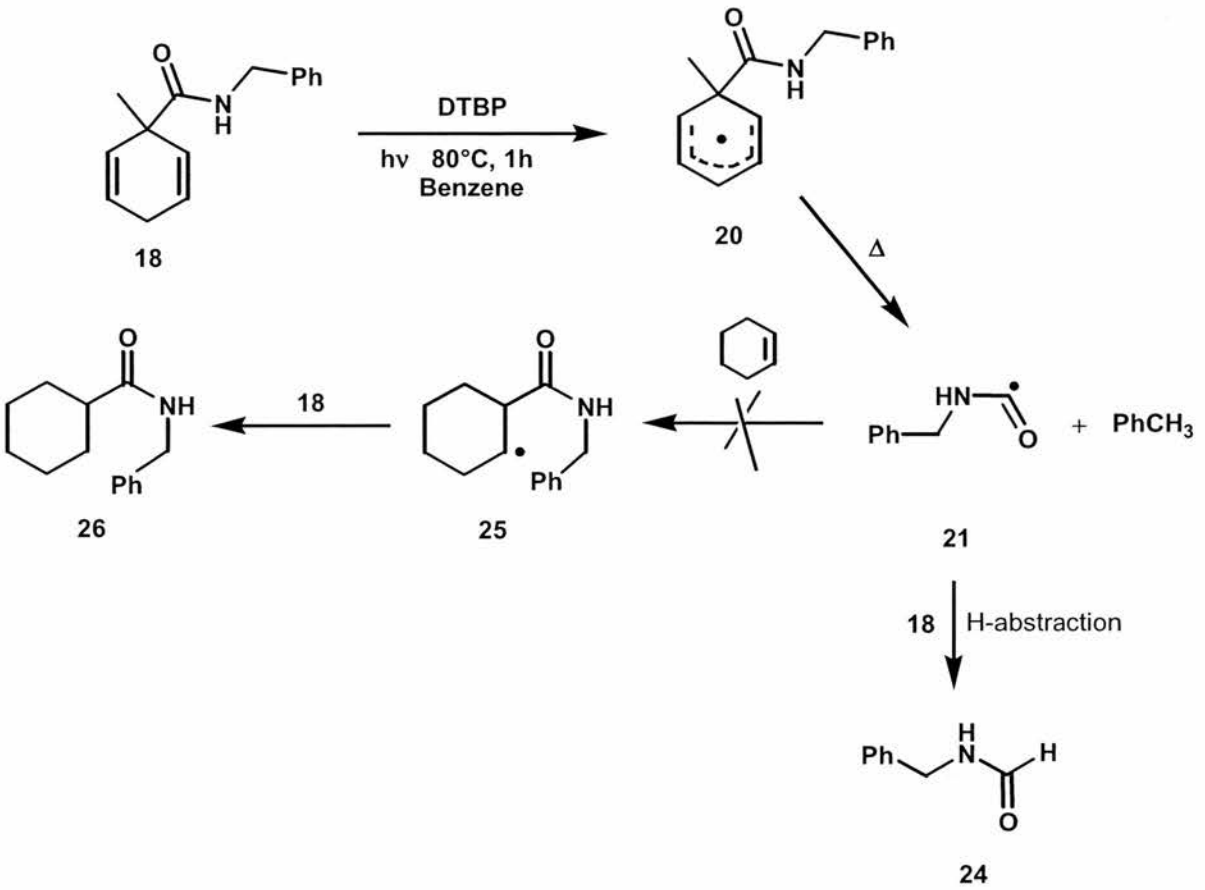
$E_d$= 15.85 kcal/mol

$k_d/s^{-1}$(300 K)= 59

**Figure 11**

### 2.6.7 Generation of aminoacyl radicals in the presence of cyclohexene.

Treatment of 1-methyl-2,5-cyclohexadiene-1-carboxamide **18** with DTBP in the presence of cyclohexene in solution in benzene, may result in the formation of the corresponding aminoacyl radical, which can subsequently undergo intermolecular addition with cyclohexene to give the corresponding addition product as illustrated in Scheme 14. The reaction mixture was analyzed by GC/MS in which no toluene formation was detected. However, the presence of benzylformamide **24** and 1,2 diphenylethane in the reaction mixture showed that amido-cyclohexadienyl radical **20** underwent β–scission to give the corresponding aminoacyl radical **21**. The complete absence of amide **26** in the reaction mixture meant that intermolecular H-abstraction from amide **18** was faster than intermolecular addition to cyclohexene.




**Scheme 14**

## 2.7 Computational Studies of Dissociation for Carbamoyl Cyclohexadienyl Radicals.

The hfs of the $Me_2NC^{\bullet}O$ and *cis*-$MeN(H)C^{\bullet}O$ radicals as models have been computed by using the DFT method, (UB3LYP with a 6-31+G(d,p) basis set variant was employed) which gave N- and H-atom parameters close to the experimentally measured data for the models[43-46] and for aminoacyl radical **23** [49](Table 3).

The AM1 semi-empirical SCF MO method[50] was used in order to determine the structures and energies of two representative amidocyclohexadienyl radicals, some related species, and their dissociation products (Table 4). The rings of the cyclohexadienyl radicals were computed to be planar with C(1)-$C(O)NR_2$ bond lengths of ca. 1.55 Å, i.e. as long as the longest computed for C(1)-alkyl in the analogous 1-alkylcyclohexa-2,5-dienyl-1-carboxylic acid radicals.[36] The computed enthalpies of reaction ($\Delta H_o$) for both modes of dissociation are listed in Table 4.

**9.5 GHz EPR parameters for aminoacyl radicals in DTBP**

| Aminoacyl radicals | T/K or method | *g*-factor | *a*(N)/G | *a*(H)/G |
|---|---|---|---|---|
| $Me_2NCO$ | 293 | 2.0019 | 22.5 | 6 H 0.7 |
| $Me_2NCO$ | DFT[b] | | 23.0 | 3 H –0.5<br>3 H –0.7 |
| MeHNCO | 208 | 2.0015 | 21.2 | 1 H 25.1 |
| MeHNCO | DFT[b] | | 25.2 | 1 H 23.7<br>3 H –0.7 |
| **23** | 350 | 2.0019 | 21.9 | 4 H 0.9 |

**Table 3.**

**AM1 computed reaction enthalpies and activation energies for cyclohexadienyl radicals[a]**

| **CHD radical [b] 1-substituents** | **Products** | **$\Delta H_o$** (-COX) | **$E^{\ddagger}$** (-COX) |
|---|---|---|---|
| (Me)$CONMe_2$ | PhMe + $CONMe_2$ | 0.19 | 18.90 |
| (Me)CONHMe | PhMe + CONHMe | 5.19 | 17.80 |
| (Me)COOMe | PhMe + COOMe | 15.50 | 25.20 |
| (Me)COOH | PhMe + COOH | 15.91 | 26.30 |
| (Pr-*n*)COOH | PhPr-*n* + COOH | 15.79 | 21.60 |
| | | **$\Delta H_o$** (-R)[b] | **$E^{\ddagger}$** (-R)[b] |
| Me($CONMe_2$) | PhCO$NMe_2$ + Me | 22.40 | 28.20 |
| Me(CONHMe) | PhCONHMe + Me | 24.80 | 27.80 |
| Me(COOMe) | PhCOOMe + Me | 31.10 | 27.85 |
| Me(COOH) | PhCOOH + Me | 20.40 | 27.40 |
| Pr-*n*(COOH) | PhCOOH + *n*-Pr | 12.0 | 20.09 |

[a] Enthalpies and energies in kcal $mol^{-1}$ [b] CHD = cyclohexa-2,5-dienyl, R = Me or *n*-Pr

**Table 4**

The transition states (TS) for dissociation were also examined using the AM1 method for loss of C(O)X radicals (X = $NR_2$, OR, or OH). Similar structures were computed for loss of a methyl radical, the C(1)-Me distances being slightly longer at 2.11 and 2.14 Å. The computed activation energies $E^{\ddagger}$ for release of the aminoacyl radicals were in quite good agreement with experimental data obtained from EPR kinetic experiments. The computed $\Delta H_o$ values indicate •C(O)$NMe_2$ loss is almost thermoneutral but •C(O)NHMe loss is more endothermic, in agreement with experiment. Experimental rate data is not available for release of •COOMe, but

previous EPR experiments[51-56] showed the activation energies must be higher than for aminoacyl release, also in agreement with the computations (Table 4). Computed $\Delta H_o$ and $E^{\ddagger}$ values for release of Me• both indicate this dissociation to be much less favourable than aminoacyl loss; in good agreement with experiment.

Enthalpies [$\Delta H_o$] for the decarbonylation reactions (Equation 21) of model aminoacyl radicals were computed by semi-empirical AM1 and ab-initio DFT methods.

$$^{\bullet}C(O)NRMe \rightarrow CO + {}^{\bullet}NRMe \qquad \textbf{equation 21}$$

Semi-empirical AM1 and ab-initio UB3LYP computations indicate the decarbonylation to be more endothermic than dissociation of the parent carbamoylcyclohexadienyl radicals (see Table 4 top 2 rows).

Computed enthalpies for decarbonylations of aminoacyl radicals.

| Decarbonylation reaction | $\Delta H_o$/kJ mol$^{-1}$ AM1 | $\Delta H_o$/kJ mol$^{-1}$ UB3LYP[a] |
|---|---|---|
| Equation 21 R = H | 154.2 | 69.5 |
| Equation 21 R = Me | 115.8 | 50.2 |

[a] 6-31+G(d,p) basis set: values include ZPVE and thermal energy correction to 298 K.

**Table 5**

Thus, decarbonylation of aminoacyl radicals is unlikely to be significant in the temperature range studied. The comparatively moderate endothermicities, computed by the DFT method, do however suggest, that decarbonylation could become important at higher temperatures.

Thus, 1-carbamoyl-1-methylcyclohexa-2,5-dienes containing secondary amide groups are good aminoacyl precursors and can potentially function in radical chain mediated preparations of β- and γ-lactams.

# Experimental

$^1$H NMR spectra were obtained using a Varian Gemini spectrometer at 200 MHz or a Bruker AM 300 spectrometer at 300 MHz unless otherwise stated. $^{13}$C NMR were obtained at 75 MHz using the Bruker previously mentioned. All samples were dissolved in deuterated chloroform unless otherwise stated, using $Me_4Si$ as an internal standard. Coupling constants are expressed in Hz. EI mass spectra were obtained with 70 eV electron impact ionisation and CI spectra with isobutane as the target gas on a VG Autospec spectrometer. GC/MS work was carried out using a Finnigan Incos 50 quadrupole mass spectrometer and/or using the VG Autospec, interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a 25 m HP 17 capillary column (50% phenyl methyl silicone). When calculating yields from GC data, the detector response was calibrated using known amounts of authentic materials (or close analogues). Commercial DTBP was passed down a column of dry neutral alumina and then distilled under reduced pressure. EPR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 kHz modulation. Samples of the substrate (0.3 to 40 mg) and DTBP (0.01 to 0.5 $cm^3$), or *tert*-butylbenzene (up to 0.5 $cm^3$), in 4 mm od quartz tubes, were de-aerated by bubbling nitrogen for 20 min, and photolysed in the resonant cavity by unfiltered light from a 500 W super pressure mercury arc lamp. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations using the Bruker SimFonia software package. For kinetic measurements, amide samples were used in 'single shot' experiments, i.e. new samples were prepared for each temperature and each amide concentration, to minimise sample depletion effects. EPR signals were double integrated using the Bruker WinEPR software and radical concentrations were calculated by reference to a known concentration of DPPH as described previously.

All NaOH and HCl solutions were approximately 2 M. THF and ether were distilled under nitrogen from sodium benzophenone ketyl prior to use. Where DCM was used, it was distilled over $CaH_2$. Petroleum ether refers to the fraction boiling between 40 and 60 °C. Other organic compounds were used as received. Ammonia was obtained from BOC and used directly from the cylinder. Chromatographic purifications were carried out using either Sorbsil C60 40/60A or BDH 40-63 μm silica gel eluting with the given solvent mixture.

**Preparation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid [51] (16)**

Benzoic acid (10g, 82 mmol) was dissolved in liquid ammonia (600 $cm^3$) in a 21 three necked, round bottom flask. Lithium (1.44g; 208mmol; 2.55 mol eq) was added in small portions until a permanent deep blue colour appeared. Following this, an excess of methyl iodide (29.65g; 208mmol) was added slowly dropwise, which returned the mixture to a colourless solution, containing an insoluble white solid. After addition the ammonia was left to evaporate. The residue was treated with a water-ice mixture, acidified with 50% $H_2SO_4$ and the organic matter extracted with ether (4 x 100 $cm^3$). The combined ether layers were washed with thiosulphate solution (100$cm^3$), then with water (100 $cm^3$) and dried ($MgSO_4$). After evaporation to dryness, the orange-yellow crude product was distilled, on a Kugelrohr apparatus (0.4 mmHg, 85 °C), to yield a yellow, oily crystalline solid (10.7g, 95%, m.p. 36°C). $^1H$ NMR $\delta_H$(200 MHz, $CDCl_3$) 1.4 (s, 3H), 2.6 (m, 2H), 5.8 (m, 4H), 12.3 (bs, 1H); $^{13}C$ NMR $\delta$ 26.6 ($CH_3$), 27.7 ($CH_2$), 44.1 (C) 125.4 (CH), 128.5 (CH), 182.6 (CO). Mass spectrum m/z (%) 138 ($M^+$, 2), 123(1), 93 (100), 91 (80), 77 (90), 65 (26), 51 (31), 45 (16), 39 (49), 27 (23).

**Preparation of 1-Methylcyclohexa-2,5-diene-1-carboxylic Acid Chloride (17).**

Thionyl chloride (3.33 g, 28mmol) was added dropwise to a stirred solution of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (1g, 7mmol) in dry DCM (30 $cm^3$).
The resultant solution was then refluxed for 8h before removing the solvent at reduced pressure to leave the desired acid chloride. $\delta_H$ (200 MHz, $CDCl_3$) 1.45 (3 H, s, $CH_3$), 2.73 (2H, br s, bisallylic H), 5.65-5.80 (2 H, m, olefinic H), 5.92-6.06 (2H, m, olefinic H).

**Preparation of *N*-benzyl-1-methylcyclohexa-2,5-diene-1-carboxamide (18).**

Benzylamine (0.77g, 7.2 mmol) was added dropwise to a rapidly stirred solution of the acid chloride (1.12g, 7.2 mmol), triethylamine (0.72g, 7.2mmol) and a catalytic amount of DMAP in dry DCM (30 $cm^3$). The resulting solution was refluxed for 5 h before removing the solvent at reduced pressure to leave the desired amide **18** as a white solid. The impure amide was taken up in ether (50 $cm^3$) and washed briefly with

dilute NaOH (50 $cm^3$) and water (50 $cm^3$). The organic fraction was dried ($MgSO_4$) before the solvent was removed under reduced pressure. Finally this crude product was purified by crystallisation with pentane-ethyl acetate yielding the pure cyclohexadiene as a white crystalline solid (1.4g, 86%); mp 79-80°C; $\delta_H$ (300 MHz, $CDCl_3$). 1.40 (3H, s, $CH_3$), 2.70 (2H, s, bisallylic H), 4.42 (2H, m, $PhCH_2N$), 5.7-6.0(4H, br m, olefinic H), 6.0-6.2 (1H, br s, NH), 7.1-7.4 (5H, m, ArH); $\delta_C$ (75 MHz, $CDCl_3$), 25.4 ($CH_3$), 25.9 (bisallylic $CH_2$), 43.6 (C), 44.9 and 45.2 (benzyl $CH_2$), 125.1 (vinyl CH), 127.3 (CH), 128.6 (CH), 130 (vinyl CH), 138.5 (C), 174.6 (-CONH-); found: C, 78.81; H, 7.49; N, 6.09. Calc. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. *m/z* (%), 227($M^+$,5), 212(5) 134 (5), 94 (5), 91 (100), 77 (50), 65 (38), 51 (18), 39 (24).

**Preparation of *N*-benzyl-*N*-*n*-butyl-1-methylcyclohexa-2.5-diene-1-carboxamide (19)**

Benzyl-*n*-butylamine (0.52g, 3.2 mmol) was added dropwise to a rapidly stirred solution of the acid chloride (0.5g, 3.2 mmol), triethylamine (0.32g) and a catalytic amount of DMAP (0.1g). The resulting solution was refluxed for 5h before removing the solvent at reduced pressure to leave the desired amide as a yellow oil (0.8g, 88%). The impure cyclohexadiene was taken up in ether (50 $cm^3$) and washed briefly with dilute NaOH (50 $cm^3$) and water (50 $cm^3$). The organic fraction was dried ($MgSO_4$) before the solvent was removed under reduced pressure. Finally, this crude product was purified by column chromatography on silica gel, using ethyl acetate- hexane as eluent to yield the pure amide (**20**) as yellow oil (0.70g, 77%). $\delta_H$ (300 MHz, $CDCl_3$) 0.87 (3H, t, $CH_3$, $^3J$=6.57 Hz) 1.05-1.35 (2H, m, $CH_3\underline{CH_2}$), 1.38 (3H, s, $CH_3$), 1.49 (2H, m, N-$CH_2\underline{CH_2}$) 2.57-2.82 (2H, m, bisallylic H, $^2J$=19 Hz), 3.15, 3.34 (2H, 2t, N-$\underline{CH_2}$, $^3J$=7 Hz), 4.58, 4.69 (2H, 2s, $Ph\underline{CH_2}N$), 5.29-5.76 (4H, m, olefinic H), 7.10-7.33 (5H, m, ArH), $\delta_C$ (75 MHz, $CDCl_3$) 13.8 ($\underline{C}H_3$), 20.2 ($\underline{CH_2}$), 25.7 ($CH_3$), 25.9 (bisallylic C), 30.5 (C), 45.7 and 46.6 (N-$\underline{C}H_2$), 48.9 and 50.8 (benzyl $CH_2$), 122.7 (CH), 126.8 (CH), 127.4 (CH), 128.4 (CH), 130.6 (CH), 137.8 (Ar-$\underline{C}$), 173.6 (C=O) found: C, 79.92; H, 8.51; N, 5.44. Calc. for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94; *m/z* (%), 283 ($M^+$,0.5), 190 (5), 91 (100), 77 (12), 65 (5).

**Photolysis of *N*-benzyl-1-methylcyclohexa-2.5-diene-1-carboxamide (18) with cyclohexene in presence of DTBP.**

The cyclohexadiene carboxamide **18,** (20 mg) in benzene (0.2 $cm^3$), was added to a solution of cyclohexene (2 mol eq.) and DTBP (0.2 $cm^3$). The solution was photolysed with light from a 400 watt medium pressure Hg arc for 1h at room temperature and the reaction mixture analyzed by GC/MS (table 6).

**Conditions: 40°C, 10°C/min, 200°C**

| Scan No | Peak ht % | Compound | MS | Fit |
|---|---|---|---|---|
| 64 | 100 | Acetone | $M^+58$, $B^+43$ | 939 |
| 97 | 70 | Benzene | $M^+78$, $B^+39$ | 940 |
| 151 | 62 | DTBP | $M^+146$, $B^+43$ | 858 |
| 594 | 2 | Benzylformamide | $M^+135$, $B^+28$ | 870 |
| 756 | 1 | 1,2 diphenyl ethane | $M^+182$, $B^+182$ | 966 |

**Table 6**

**EPR experiment on amido-1-methylcyclohexa-2,5-diene 19**

Amide **19** (5 mg) in DTBP (200 µl) was degassed by $N_2$ for 15 min. The solution was photolysed with light from a 500 W super pressure Hg arc in the resonant cavity of the EPR spectrometer. Good spectra were obtained (page 92 and 93) in the range 245 dT (**figure 8**) to 355 dT (**figure 9**). At 245 dT. a(1H)=12.66, a(2H)=9.23, a(2H)=2.64, a(3H)= 0.66, a(N)=0.66G. At higher temperature this spectrum weakened and a new spectrum appeared, a(N) = 21.9, a(4H) = 0.86, g = 2.0019. Clean GC/MS obtained with no other products apart from those displayed in Table 7.

**Conditions: 50°C, 10°C/min, 200°C**

| Scan No | Peak ht % | MS | Compound | Fit |
|---|---|---|---|---|
| 95 | 100 | $M^+$?, $B^+$ 28 | $N_2$ | 926 |
| 143 | 24 | $M^+$ 92, $B^+$ 91 | Toluene | 960 |
| 476 | 12 | $M^+$191, $B^+$ 91 | *N*-Bn *N*-butyl formamide | 949 |
| 619 | 23 | $M^+$283, $B^+$91 | Amide 19 | 934 |
| 651 | 1 | $M^+$281, $B^+$119 | N-Benzyl-N-butyl-4--methyl-benzamide | 922 |

**Table 7**

# References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# Chapter 3

# Preparation of β-and γ-lactams from unsaturated aminoacyl radicals released from 1-carbamoyl-1-methylcyclohexa-2,5-dienes

# 3.1 Introduction

One of the most important free radical reactions is cyclisation to form rings. This type of reaction has been used to prepare a variety of cyclic natural products. Many new protocols are being developed to synthesise a wide range heterocycles which are of interest to organic chemists.[1] The majority of radical cyclisations in heterocyclic chemistry are still carried out using tributyltin hydride but other radical generating procedures are becoming more common.[2]

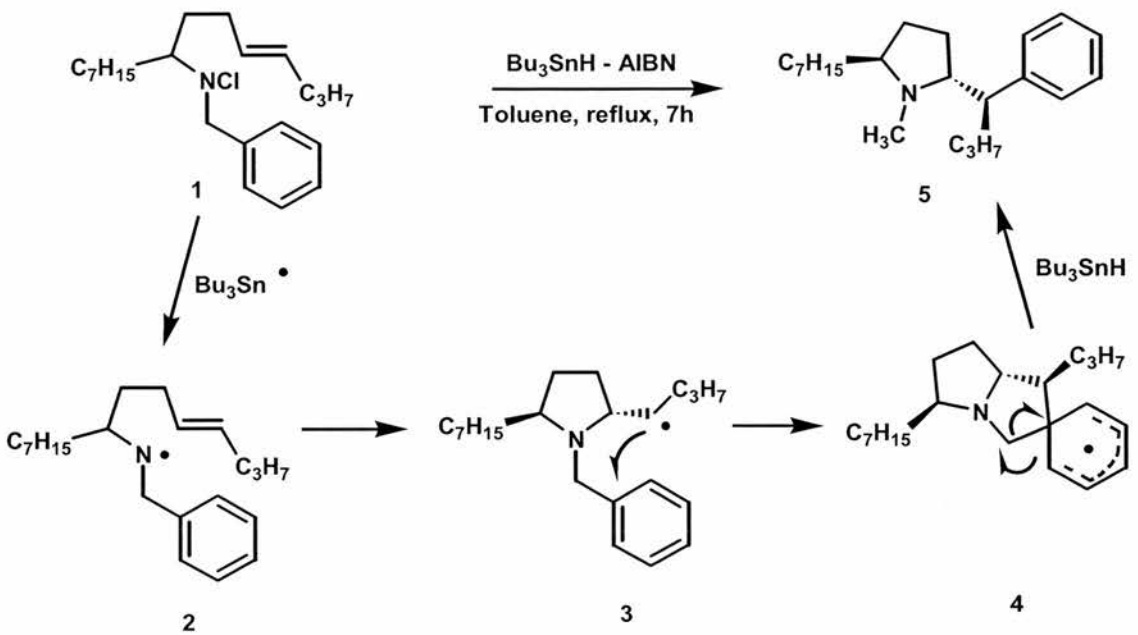
The use of radical cyclisation procedures allows complex ring systems to be put together without much functional group protection or problems of racemisation. These advantages, along with the use of one-pot cascade reactions, facilitate syntheses which avoid time consuming multi-step protocols. Radical reactions are also increasingly used to facilitate stereoselective cyclisations.

## 3.1.1 Nitrogen heterocycles by radical cyclisation.

One of the most common uses of radical cyclisation is the synthesis of nitrogen heterocycles, especially 5-*exo* cyclisation for the preparation of pyrrolidines. The radical can be generated in various positions relative to the N-heteroatom.

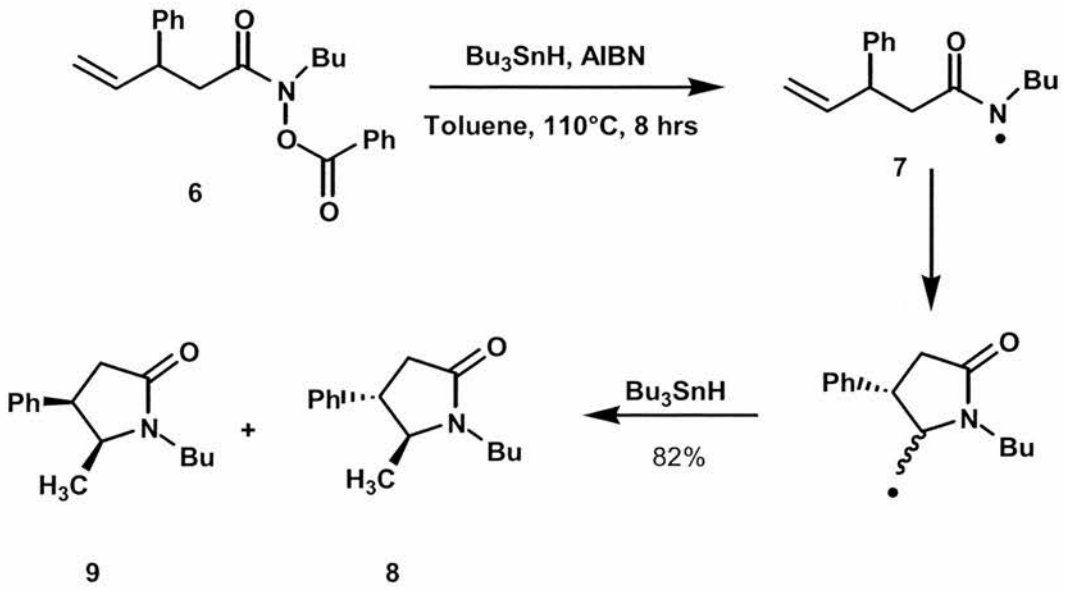
Aminyl radicals can obviously be applied in radical cyclisations to form nitrogen heterocycles. Aminyl radicals have been generated from *N*-chloramines using $Bu_3SnH$ and undergo 5-*exo* cyclisation to yield *trans*-2,5-disubstituted pyrrolidines.[3] Radical reaction of isolated *N*-chloroamine **1** gave *trans*-*N*-methyl-2-heptyl-5-(1-phenylbutyl)pyrrolidine **5** exclusively, in 60% yield (Scheme 1). These results indicate that a highly stereoselective cyclization of an aminyl radical, followed by an efficient migration of a phenyl group, occurs in this cyclization. The exclusive formation of aryl group-migrated pyrrolidines is thought to result from an aminyl radical cyclization-1,4-aryl migration sequence. Stereoselective 5-*exo* cyclization of aminyl radical **2**, generated from N-chloroamine **1**, affords the intermediate radical **3** having a *trans*-2,5-disubstituted pyrrolidine skeleton. Attack of the resulting secondary alkyl radical on an *ipso* position of the phenyl ring of an N-benzyl group gives cyclohexadienyl radical **4**. Rearomatization by a β-scission results in 1,4-aryl migration to give an N-methyl

radical, stabilized by a neighbouring nitrogen atom. Hydrogen abstraction from $Bu_3SnH$ gives product **5**.



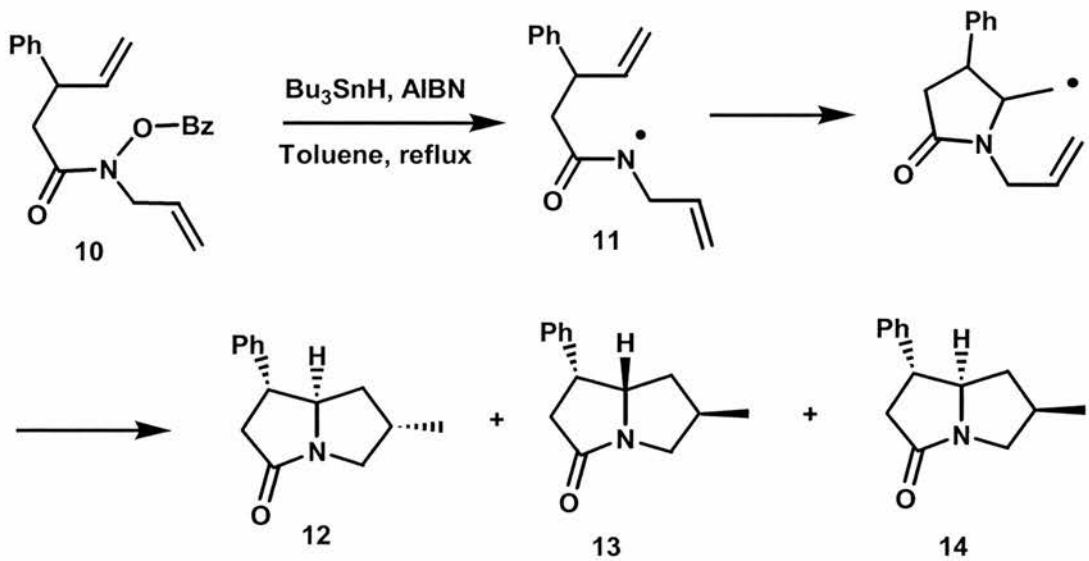

**Scheme 1**

Amidyl radicals are much more electrophilic than aminyl radical and undergo cyclisation more easily. Tributyltin mediated homolysis of O-benzoyl hydroxamic acid **6** generates amidyl radical **7** which undergoes 5-*exo-trig* cyclisation to give a mixture of *cis* and *trans* pyrrolidinones **8** and **9** together with minor quantities of reduced product (Scheme 2).[4] The major cyclised products were assigned as having the *trans* configuration as predicted by application of the Beckwith model, which predicts that cyclisation preferentially takes place *via* a chair-like transition state with the substituent (R) in a pseudo-equatorial position.[5-8] The formation of a β-lactam using amidyl radical cyclisation techniques has also been studied.[9] Laser flash photolysis techniques allowed the calculation of the associated reaction kinetics, in order to confirm that cyclisations of amidyl radicals occur much more rapidly than those involving carbon-centred radicals. However, as later study suggests that the cyclisation is reversible.[10]



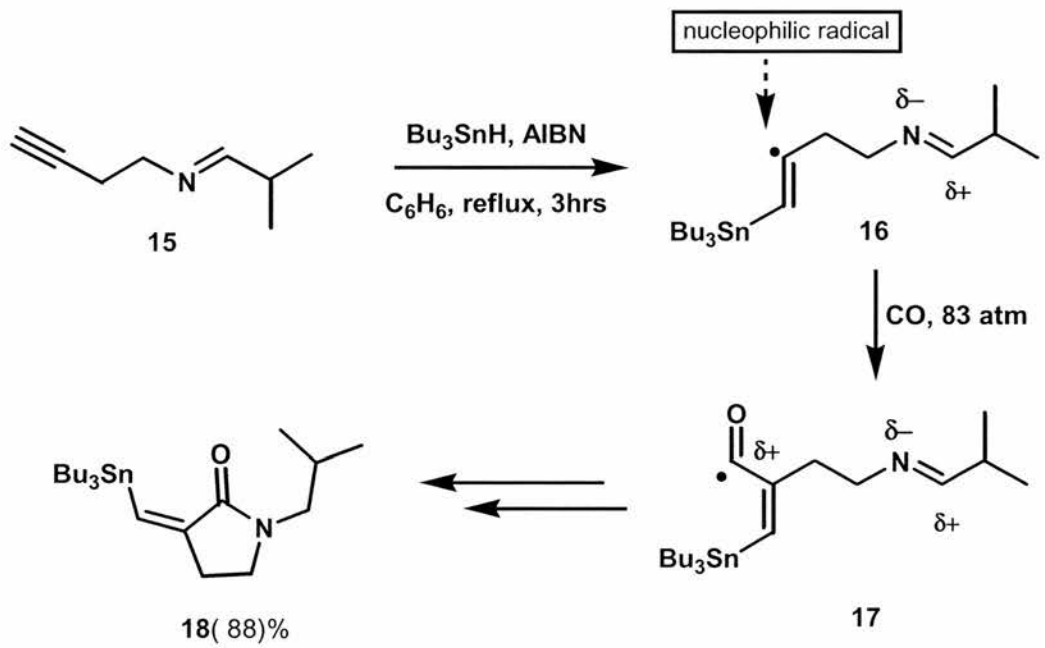

**Scheme 2**

Amidyl radicals, generated from O-benzoylhydroxamic acid derivatives in $Bu_3SnH$ mediated reactions, have also been used to synthesise pyrrolizidines and other bicyclic nitrogen heterocycles (Scheme 3).[11] The precursor **10** was synthesised by selective N-acylation followed by O-acylation of the corresponding N-alkylhydroxylamine salt and reacted with $Bu_3SnH$ to generate an intermediate amidyl radical **11** which underwent two 5-*exo* cyclisations to yield a mixture of diastereomeric pyrrolizidines **12**, **13** and **14**.(12:13:14 = 3:2:1)




**Scheme 3**

The attack of alkyl radicals onto C=N double bonds can provide an alternative for the synthesis of nitrogen heterocycles. However this procedure often presented little level of selectivity, providing a mixture of nitrogen containing heterocycles via 5-*exo* and 6-*endo* cyclisation.[12-14] Recently Ryu and co-workers adapted these systems by introducing a polar acyl radical in various positions relative to the imine nitrogen in order to promote N-philic cyclisation in a "polarity-matched" α,β-unsatured acyl radical/imine combination which resulted in an efficient cyclisation leading to α-stannylmethylene lactams, precursors for α-methylene lactams (Scheme 4).[15]



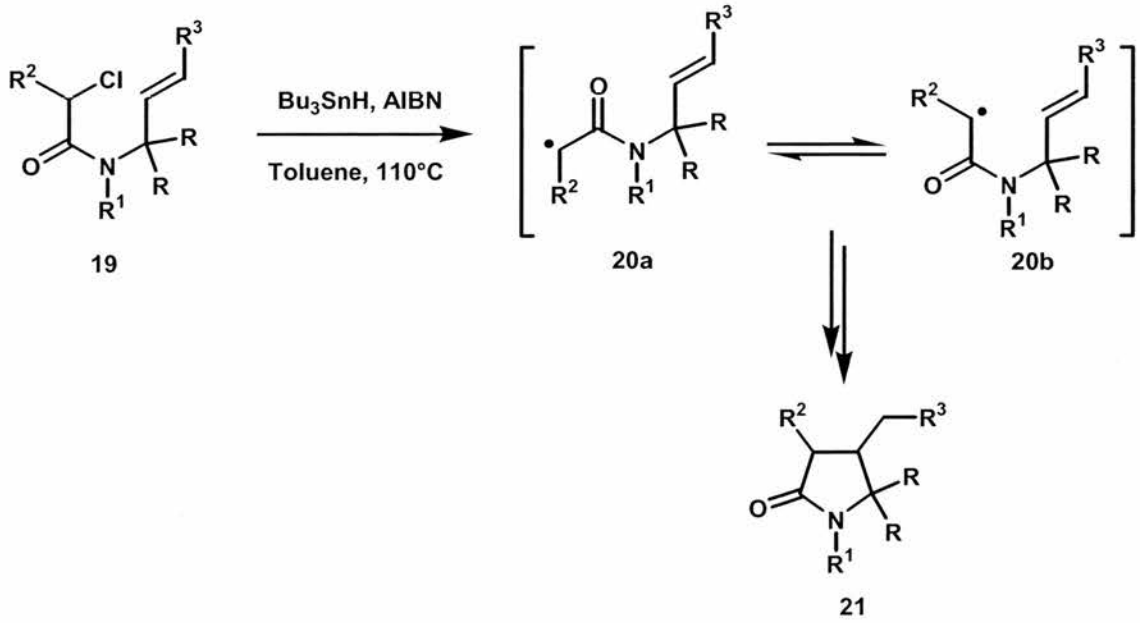

**Scheme 4**

Vinyl radical **16** was generated from azaenynes such as **15** using tributyltin hydride and AIBN. Carbon monoxide at high pressure (83 atm) was used in order to deliver the intermediate α,β-unsatured acyl radical **17**, which underwent N-philic 5-*exo* cyclisaton onto the nitrogen of the imine group, generating α-stannylmethylene γ-lactam **18** in 88% yields. Product analysis confirmed the complete absence of five-membered ring which would result from a C-philic 5-*endo* cyclisation of the nucleophilic vinyl radical **16** onto the carbon of the imine group, suggesting that the intermediate vinyl radical **16** gives 5-*endo* product at very slow rate. On the other hand vinyl radical **16** is extremely reluctant to undergo 4-*exo* cyclisation onto the nitrogen of the imine group (polarity-mismatched).[16,17] This allows time for the slow addition of carbon monoxide to

generate the desired α,β-unsatured acyl radical **17**. Vinylstannanes are versatile functional groups which can be applied to several destannylative reactions[15]. In summary, free-radical mediated stannylcarbonylation of azaenynes provides a general [n+1]-type annulation leading to α-stannylmethylene lactams Cyclisations occur with high regioselectivity favouring the N-philic mode for the synthesis of 4-, 5-, 6-, 7-, and 8-membered rings.

One important method for the synthesis of pyrrolidines and pyrrolidin-2-ones involves 5-*exo* cyclisations of radicals β to the nitrogen atom, *i.e.* α to the amide carbonyl group (α-amide radicals), onto alkenes. This method have been used for the synthesis of a wide range of γ-lactams.[18,19]

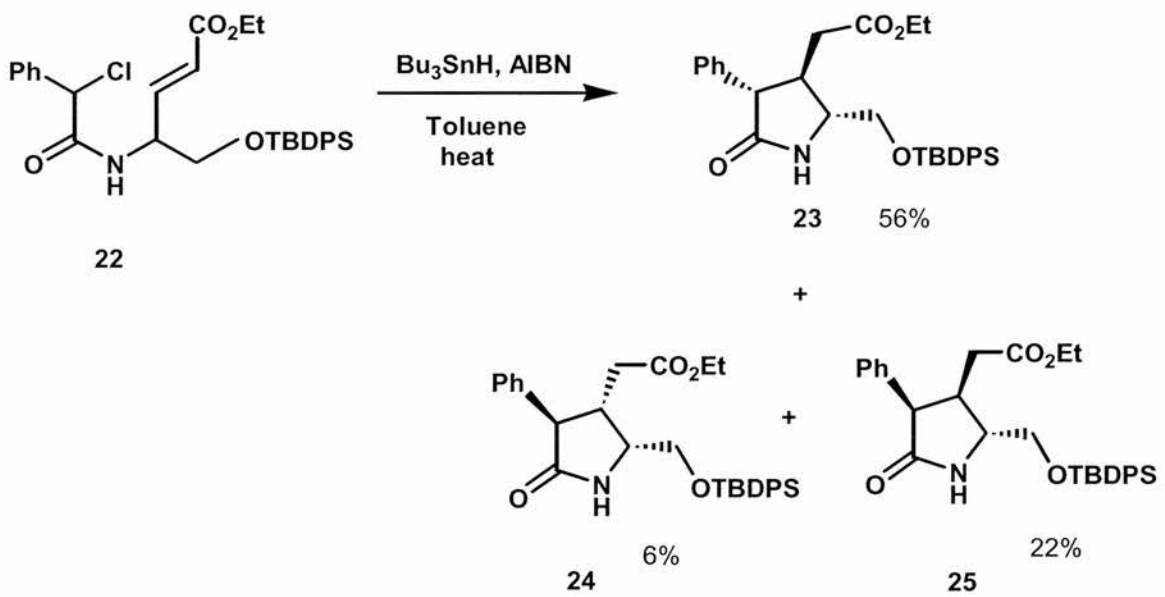
Tin hydride-mediated 5-*exo-trig* cyclisation of unsaturated haloamides of type **19** in the presence of AIBN under mild, neutral reaction conditions produces the intermediate carbamoylmethyl radical **20** which interacts with the β-alkene to form pyrrolidinones **21** in reasonable yields. A large N-protecting group ($R^1$) favours the *anti*-conformer **20b** over the *syn*-conformer **20a** which can cyclise onto the alkene double bond, leading to improved yields (Scheme 5).




**Scheme 5**

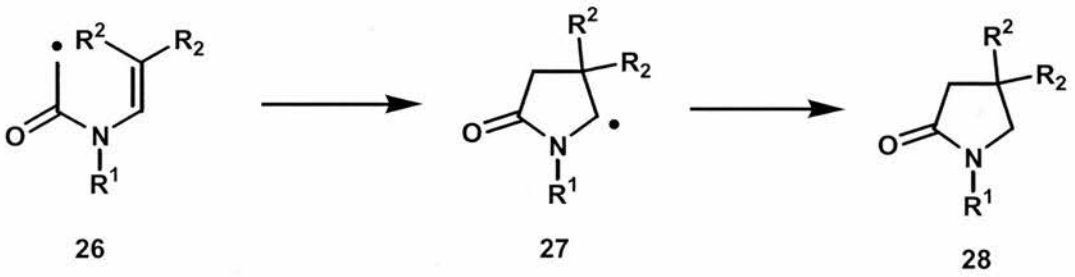
The nature of the substituents attached to the site of radical generation ($R^2$) along with the acceptor carbon-carbon double bond ($R^3$) were found to influence the yield of the cyclisation product and the stereoselectivity of the cyclisation.

The introduction of substituents alpha to nitrogen (R) can also influence the conformer population leading to improved yields and substituted pyrrolidinones could be isolated in up to 76% yield. To test the feasibility of this approach, Parsons carried out the preparation of benzylic chloride **22**, containing an α-silyl protected alcohol, starting from DL-serine (Scheme 6).[20] Reaction of the haloamide precursor **22** with tin hydride in refluxing toluene yielded three separable pyrrolidinones **23**, **24**, and **25** in a combined yield of 84%. Simple reduction of the intermediate radical was only observed in moderate yield.




**Scheme 6**

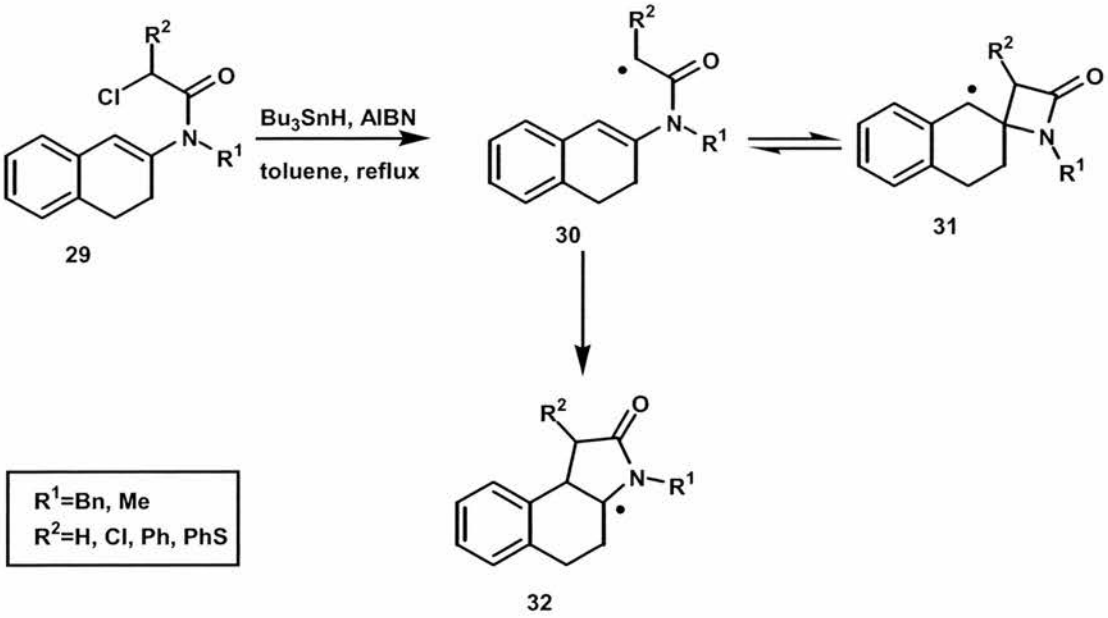
Parsons and Ikeda demonstrated that the β-radicals can undergo kinetically disfavoured 5-*endo-trig* cyclisations onto an α-alkene in order to generate γ-lactams from the N-vinyl precursors.[21-23] N-Vinylic carbamoylmethyl radicals **26**, generated from the corresponding α-halo amides, cyclise generally in a 5-*endo-trig* manner yielding γ-lactam **28** through the radical intermediate **27** (Scheme 7).




**Scheme 7**

Radicals β-to nitrogen containing N-vinyl groups can be used to synthesise highly strained β-lactams by 4-*exo-trig* cyclisations. The introduction of stabilising groups at a carbon-carbon double bond acceptor, such as phenylthio or phenyl, leads to the formation of β-lactams.[24]

Ikeda examined the regioselectivity of a range of 2-halo-N-(3,4-dihydro-2-naphthyl)acetamides **29** in $Bu_3SnH$-mediated radical cyclisations (Scheme 8)[25] and demonstrated the important role of the substituent attached to the initially formed carbamoylmethyl radical **30.**

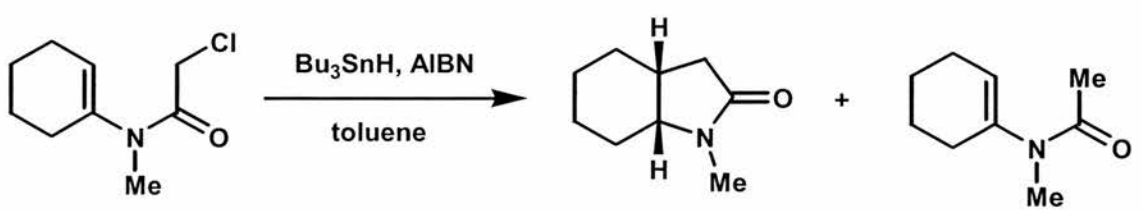



**Scheme 8**

When $R^2$ = H or Cl in the intermediate radicals **30**, the β-lactam formation is favoured, while radical stabilising substituents lead to γ-lactams predominantly or exclusively.

One possible explanation for these results is based on a consideration of the reversibility of the 4-*exo-trig* cyclisation and ring-opening between **30** and **31**. The 4-*exo-trig* cyclisation is the kinetically favoured process compared to the 5-*endo-trig* one, so that the carbamoylmethyl radical **30** would give initially the benzylic radical **31**. In the case $R^2$ = H or Cl, the subsequent reduction step is faster than the ring-opening step, and hence the β-lactam formed. When $R^2$ is a radical stabilising group, ring opening of benzyl radical **31** gives the relatively stabilised initial radical **30**. The reduction step takes place after the thermodynamically more stable radical **32** has been formed by the 5-*endo-trig* cyclisation of **30**, leading to the formation of the γ-lactam. These results indicate that the 4-*exo* cyclisation is a kinetically favoured process, whereas at higher temperature (in boiling toluene), the ring-opening of the radicals **31** occurs, and the resulting radicals **30** cyclise in a 5-*endo-trig* manner to give the thermodynamically stable radicals **32**.

5-*endo*-Cyclisation of α-amidyl radicals onto cycloalkenes has been used for generating bicyclic nitrogen-containing heterocycles. For instance, the $Bu_3SnH$-mediated 5-*endo-trig* radical cyclisation of N-(cyclohex-1-enyl)-α–haloamides **33** occurred with a high degree of efficiency to yield bicycles **34** and only a moderate amount of reduced uncyclised material **35** (Scheme 9).[26]

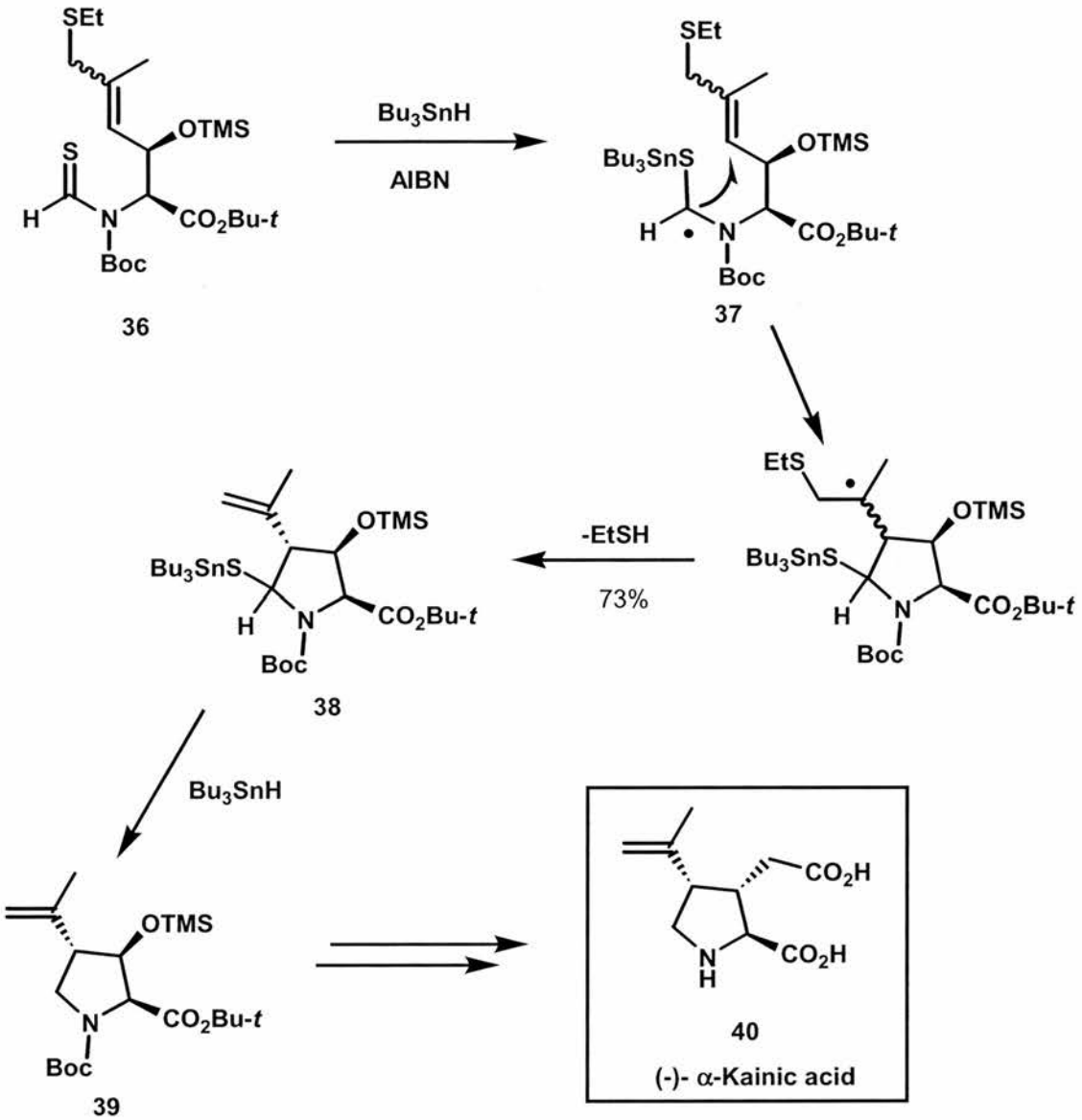



**33** **34** **35**

**Scheme 9**

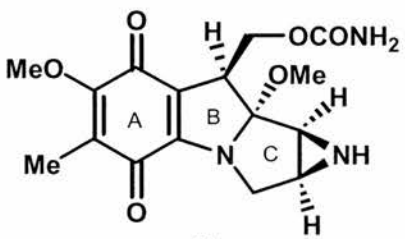
The synthesis of pyrrolidines and pyrrolidinones by cyclisation of radicals α-to the nitrogen atom onto γ-alkenes is of less common use. However Bachi and Melman have used a novel radical procedure for the total synthesis of (-)-α-Kainic acid **40** which has been shown to exhibit potent neurological activity. The synthetic pathway involves

addition of tributyltin radicals to the sulphur atom of the thioaldehyde precursor **36** (Scheme 10).[27,28] The intermediate radical **37** undergo stereoselective 5-*exo* cyclisation to yield α-thiostannyl pyrrolidine **38**. The $Bu_3SnS$ group was then reduced off during the radical reaction by using further $Bu_3SnH$ in order to yield the trisubstituted pyrrolidine **39** which was converted to (-)-α-Kainic acid **40**.



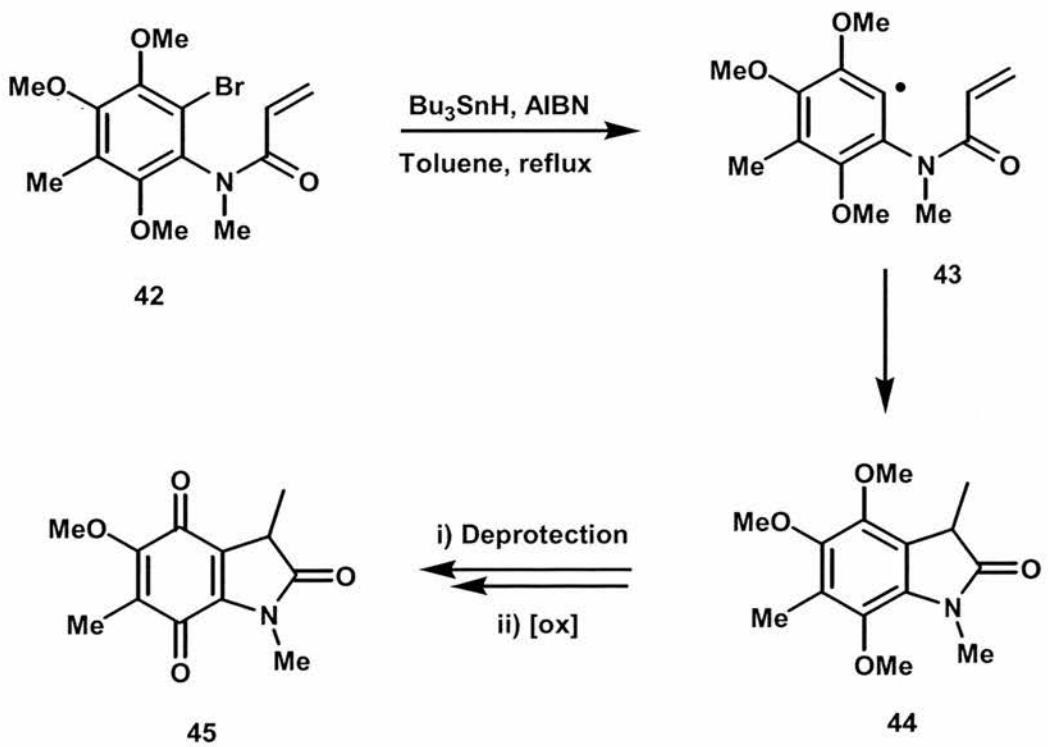

**Scheme 10**

Mitomycins **41** are a family of molecules that exhibit potent antibiotic and cytotoxic properties, with mitomycin C being used clinically in the treatment of adenocarcinomas of the stomach, pancreas and the colon.



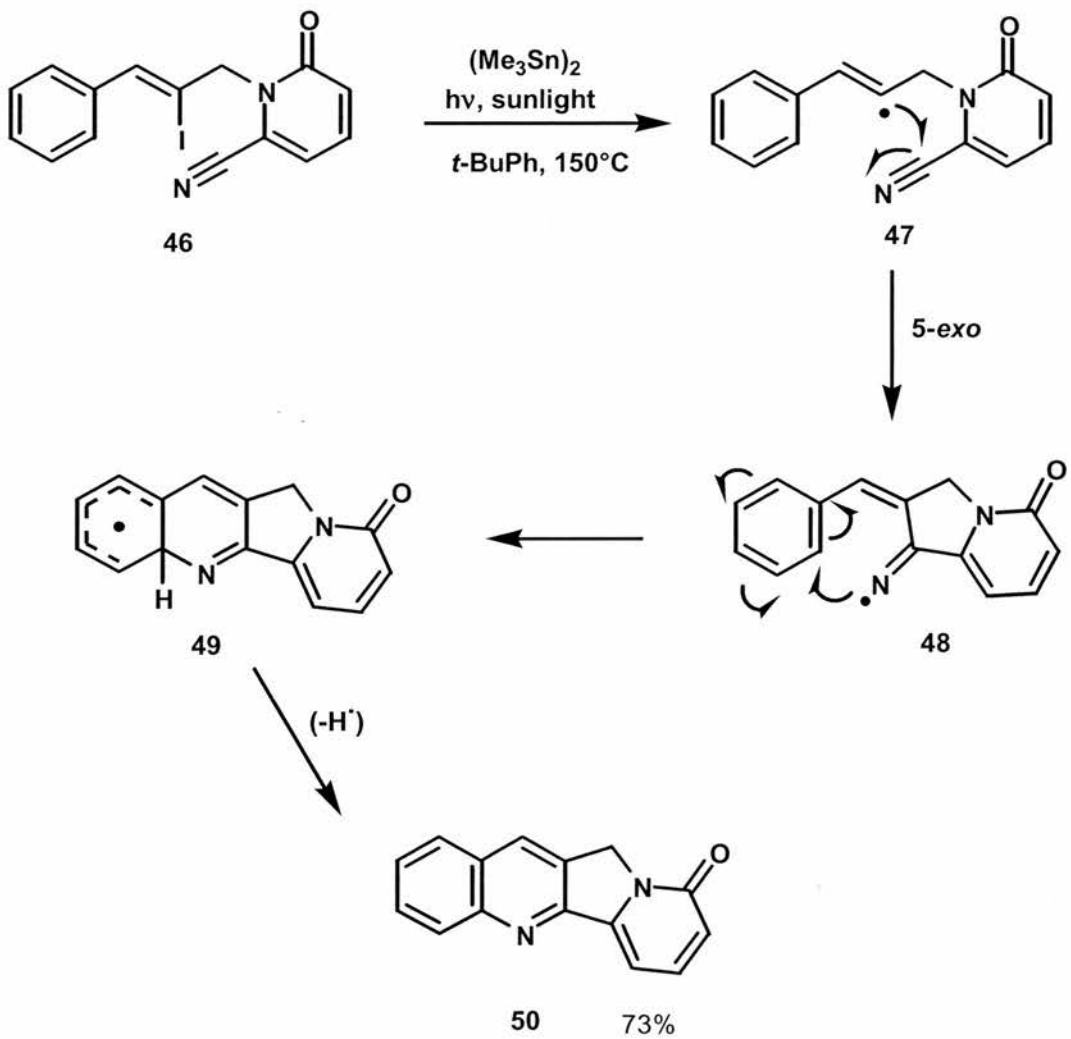

**41**
**Mitomycin A**

Aryl radical cyclisation onto vinyl amides has been used by Jones to construct oxindole **44** containing all the functionality required for ring-A of the mitomycins (Scheme 11).[29] Radical cyclisation of arylbromoamide **42** using tributyltin hydride in toluene at reflux with AIBN as initiator gave the aryl radical intermediate **43** which undewent 5-*exo*-trig cyclisation furnishing the desired oxindole **44** in 97 % yield. Removal of the methyl ether protecting group gave the desired quinone **45** as required for the A ring of the mitomycins.




**Scheme 11**

A novel cascade cyclisation uses vinyl halides as radical precursors for the generation of intermediate vinyl radicals which undergo 5-*exo*-cyclisation onto nitrile groups[30] to yield intermediate iminyl radicals followed by cyclisation onto arenes. This method has recently been proposed by Bowman to synthesise the tetracyclic rings A–D (tetracycle indolizino[1,2-b]quinolin-9(11H)-one) **50** of the anticancer alkaloids camptothecin (Scheme 12).[31] The cascade radical reaction of vinyl iodide precursor **46** was carried out using hexamethylditin which generated the intermediate trimethyltin radical under irradiation with sunlamps. Radical attack of the vinyl radical intermediate **47** generated iminyl radical **48** which underwent cyclisation to give tetracyclic π-radical **49**. H-abstraction by methyl radicals, generated from the breakdown of trimethylstannyl radicals ($Me_3Sn$ ) was proposed as a possible H-abstraction route with formation of the desired tetracyclic indolizino[1,2-b]quinolin-9(11H)-one **50** in 73% yields.




**Scheme 12**

## 3.2 Tin-free Radical Mediators in Syntheses of Heterocycles

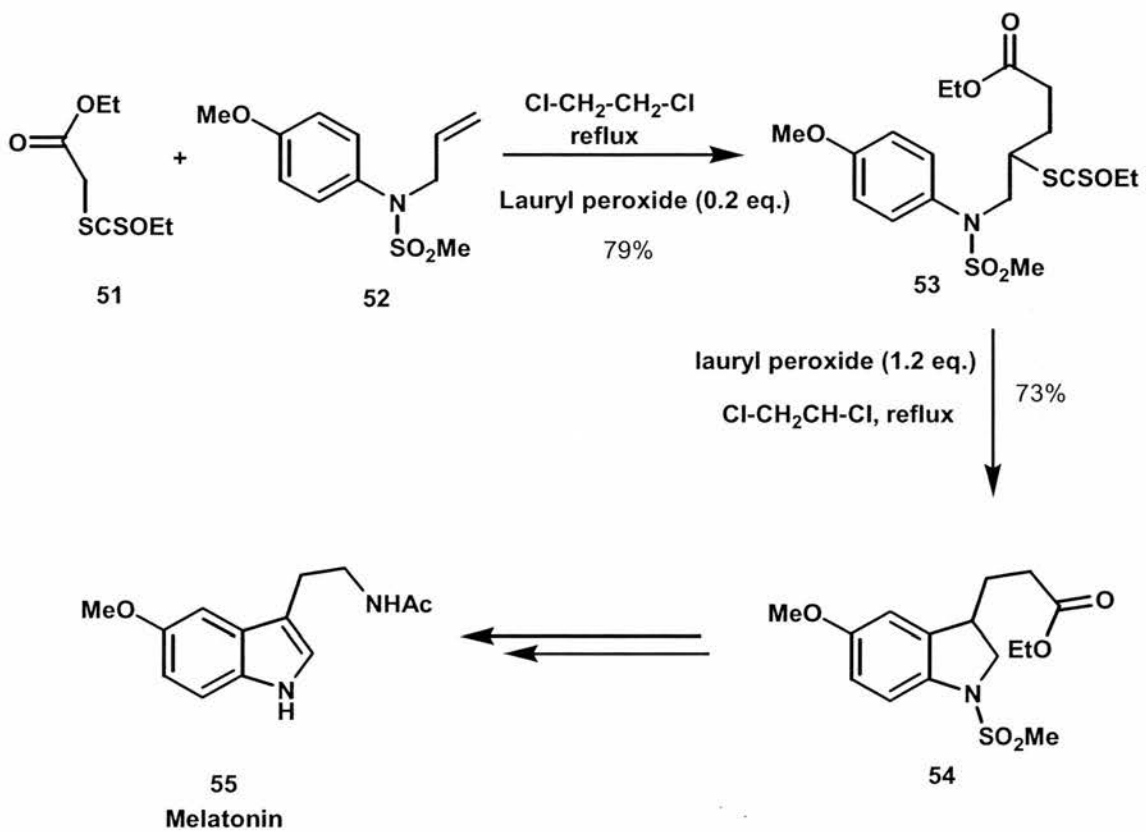
Synthesis of heterocycles using radical cyclisation depends on the same advances in radical synthetic methodology as non-heterocyclic systems. The progress made over the past 30 years in carbon–carbon bond formation mediated by free radical chemistry using organotin reagents, has been impressive. However, problems in separation of reaction products from organotin contaminants and the toxicity of the tin reagents and by-products has prevented their application to pharmaceutical manufacture. Recently many highly original alternative reagents and processes for free radical chemistry have been described and, after effective modification, employed in syntheses of heterocyclic compounds. This includes the use of xanthates, hypophosphorous acid and the corresponding 1-ethylpiperidine salt (*N*-ethylpiperidine hypophosphite, EPHP), tetrathiafulvalene, other Group 14 element hydrides, cyclohexadienyl derivatives and solid phase, polymer supported, tin hydrides.

### 3.2.1 Sulfur alternatives in radical cyclisation

Zard and co-workers have made a very intensive study of the homolytic chemistry of a variety of xanthates.[32,33] O-Ethyldithiocarbonates, for example, promote tin-free radical chain additions quite efficiently. Heavy or toxic metals are not involved in such a process and the starting materials are cheap and readily available. Radicals formed from xanthates acquire a relatively long effective lifetime, due to their continuous regeneration, which allows difficult radical cyclisations, or additions to inactivated olefins. Moreover the release of a final product that contains xanthate functionality opens up a sulfur chemistry which, if desired, can be used for another radical sequence. This strategy can therefore be applied to radical cyclisations for the synthesis of lactams.

The indole nucleus is a key structural feature in a large number of alkaloids and related compounds, many of which exhibit potent pharmacological activity. Zard has applied xanthates as radical precursors in the synthesis of melatonin **55** (Scheme 13),[34] a hormone mainly secreted by the pineal gland, and known to play a key role in the regulation of sleep and temperature rhythms in mammals. Intermolecular radical addition of xanthate **51**, prepared in 93% yield by heating ethyl bromoacetate with

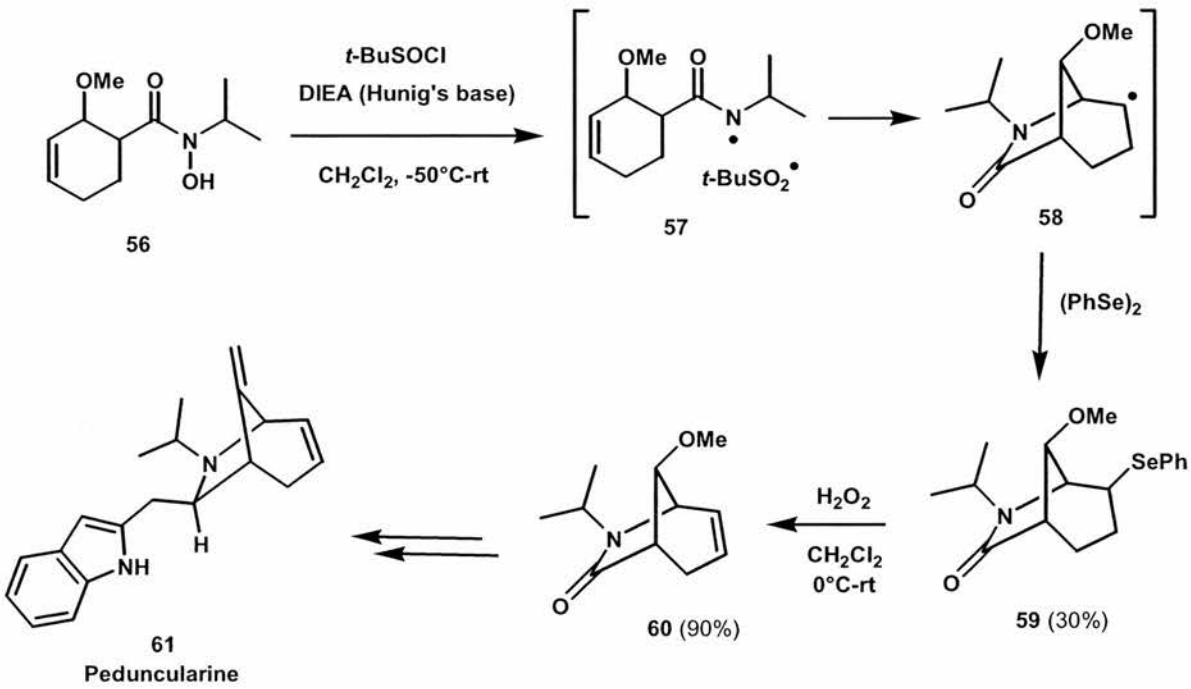
commercially available potassium O-ethylxanthate, with protected N-allylaniline **52**, in the presence of a small amount of lauroyl peroxide (radical initiator) as radical mediator, provided adduct **53** in 79 % yield. Radical ring closure to the aromatic ring, brought about by a catalytic amount of peroxide, (non-radical chain) in refluxing 1,2-dichloroethane, produced indoline **54** in 73% yield.




**Scheme 13**

A novel protocol that uses sulfinyl compounds for free-radical generation of amidyl radicals has successfully been employed in the total synthesis of the indole alkaloid peduncularine **61**. Treatment of olefinic hydroxamic acid **56** with *tert*-butylsulfinyl chloride and Hunig's base from 50°C to room temperature in the presence of a radical trap such as diphenyl diselenide, diphenyl disulfide or TEMPO afforded the desired azabicyclooctane system **59** (30%), derived from an amidyl radical cyclization, as a single diastereomer (probably the *exo* selenide). Amidyl radicals **57** were produced from N-sulfinyl amides generated in situ from hydroxamic acid **56** and *tert*-butylsulfinyl chloride. The use of the bulky sulfinyl compound slowed the

recombination of the caged radical pair **57** to the corresponding N-sulfonylamide,[35] allowing the formation of the intermediate cyclization product **58** (Scheme 1).[36] Oxidation of the selenide **59** with hydrogen peroxide then afforded the requisite alkene **60** in high yield, which could be converted into peduncularine **61** (Scheme 14).[37]



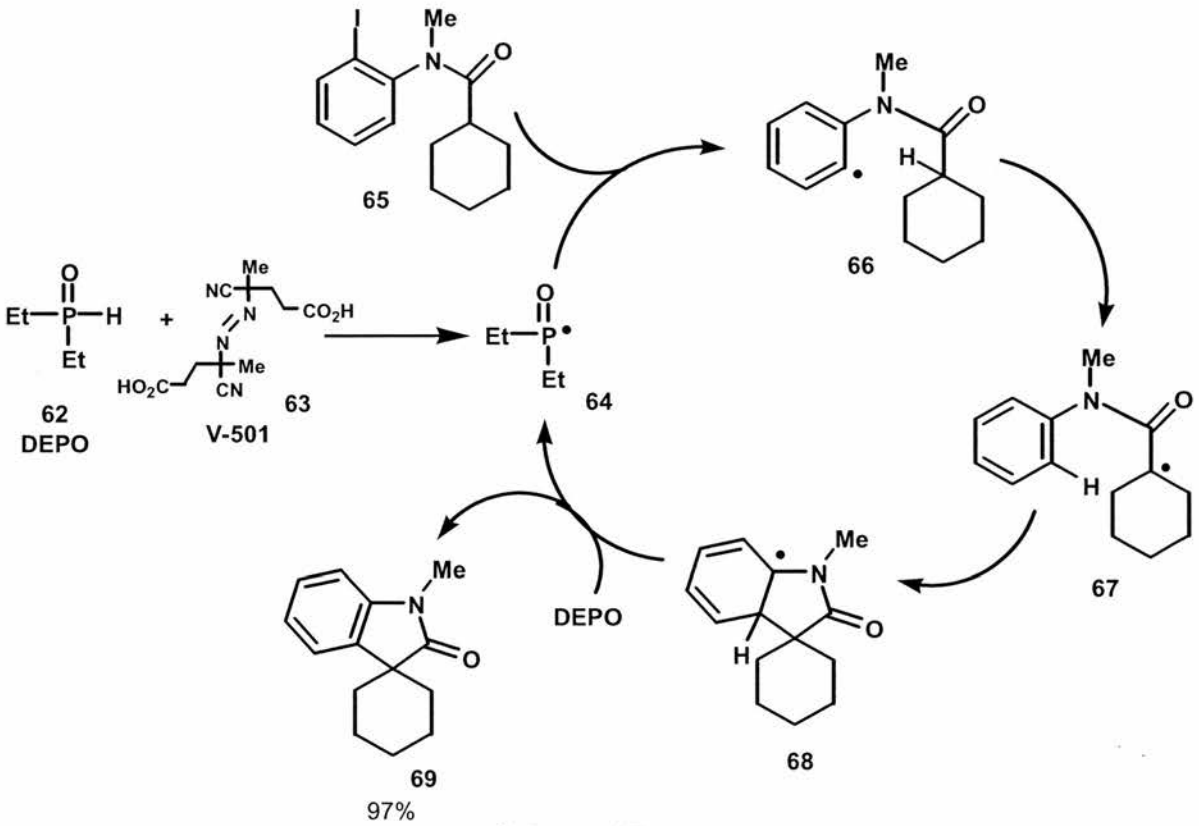

**Scheme 14**

### 3.2.2 Phosphorus in radical cyclisations

Hypophosphorous acid and its salts[38,39] are economical and can be used in water or in organic solvents (the lipophilic salt, N-ethylpiperidinium hypophosphite, EPHP) and, after workup, separation of organic reaction products is easily achieved by acid-and base-washing.

The use of water as a solvent for carrying out radical reactions is welcome because it is more environmentally safe and cheap. Water soluble phosphorus based initiators have recently been developed for carrying out radical reactions in water. For the synthesis of heterocycles, Murphy and co-workers have directed attention to simple procedures for radical reactions using phosphine oxides $R_2P(O)H$, which are more lipophilic than hypophosphorous acid, but still totally soluble in water. Diethylphosphine oxide **62**

(DEPO) reveals the best features of solubility, either in water or in organic solvents, as well as a high decomposition temperature. Diethylphosphine oxide (DEPO) at 80°C in water in the presence a catalytic amount of the water soluble initiator V-501 releases phosphinyl radical **64** which abstracts iodine from aryl iodide **65** to produce the corresponding aryl radical **66**. H-atom transfer followed by cyclisation and rearomatization gave indolone **69** in 97% yield (Scheme 15).[40]

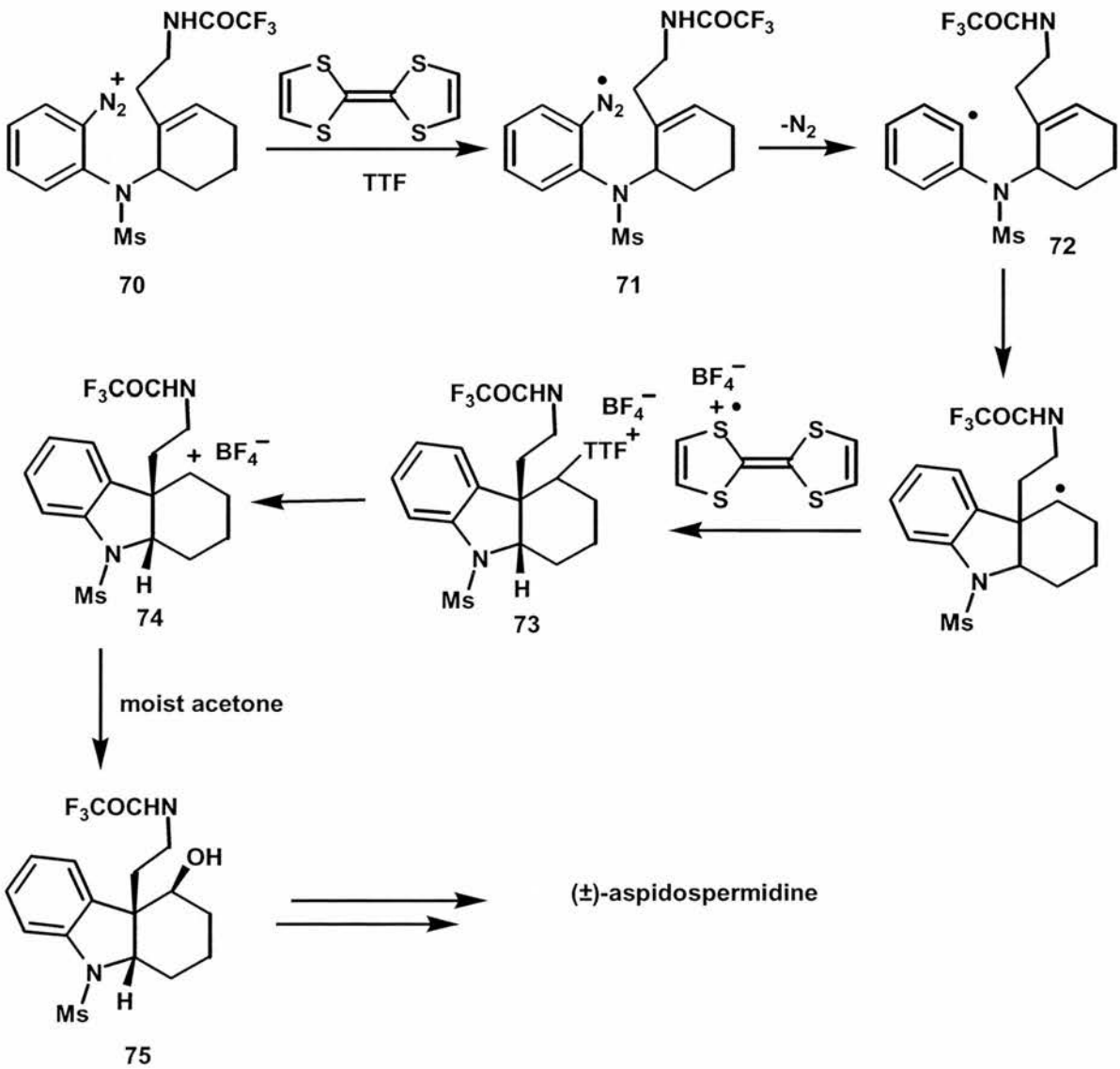



**Scheme 15**

DEPO is a new radical initiator that can work in water with no need for additives. The easy basic workup affords essentially pure products, free from phosphorus or initiator-derived by-products. The process proceeds at a much lower temperature than is required with toxic tributyltin hydride in benzene and permits significantly higher isolated yields than the corresponding reaction mediated by ethylpiperidine hypophosphite (EPHP).

### 3.2.3 TTF-induced radical-polar crossover

Tetrathiafulvalene has been applied by Murphy and co-workers to promote aryl radical cyclisations by their (TTF)-induced radical-polar crossover protocol.[41-49] The advantages in using TTF mediated radical reactions include the ability to carry out radical sequences under mild conditions, use in catalytic amounts, and the opportunity for the incorporation of new functionality. The precursor for radical formation is a diazonium salt which accepts an electron from TTF generating a TTF radical cation giving an aryl radical with loss of nitrogen.[50]

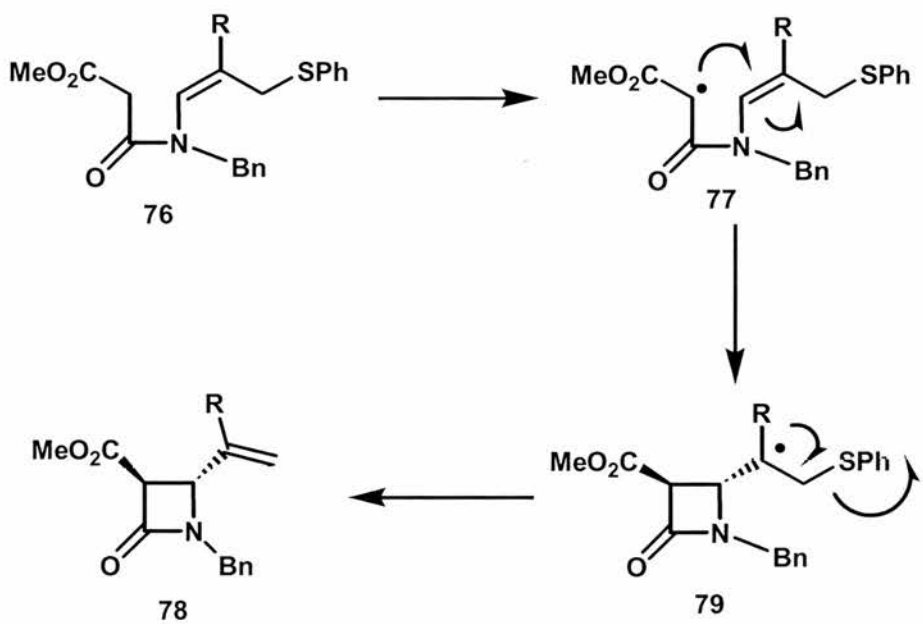



**Scheme 16**

The alkaloids aspidospermidine, vinblastine, vincristine and the clinically valuable vinorelbine® all contain the tetracyclic substructure of aspidospermidine. Thus, treatment of diazonium salt **70** with TTF gives diazonium radical **71** which releases nitrogen gas to form aryl radical **72.** Cyclisation of **72** onto the double bond and addition of the cyclised radical on TTF radical cation gives **73**. The radical-polar crossover comes into play leading to $S_N1$ substitution by water *via* a cation **74** to yield **75**, an intermediate used for further elaboration for the synthesis of (±)-aspidospermidine (Scheme 16). [50]

### 3.2.4 β-Lactams by Mn(III)-promoted cyclization

The β-lactam nucleus is the key feature in penicillin and cephalosporin antibiotics. The construction of β-lactams has largely relied on ionic chemistry and radical reactions have only recently been found to allow the formation of such strained ring systems. Syntheses of β-lactams can be achieved by radical cyclisation starting from enamides of type **76** (Scheme 17).[51,52]

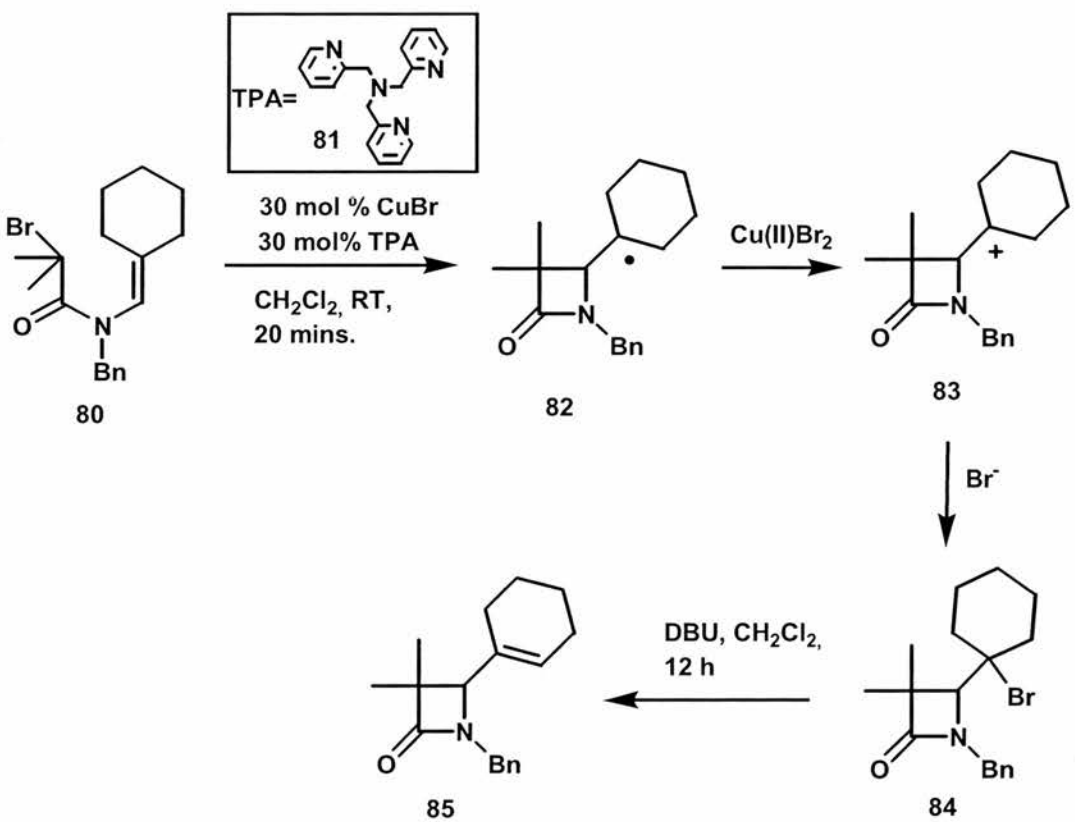



**Scheme 17**

β-Dicarbonyl compound **76** is readily oxidised by Mn(III) to carbinyl radical **77,** centred on the carbon atom between the two carbonyl groups, which readily cyclises affording azeditin-2-one **78** in 58% yield.. The cyclisation is driven by elimination of phenyl sulfanyl radicals from the cyclised radical **79** which in this case undergoes 4-*exo trig* cyclisation with high stereoselectivity, leading to *trans* azeditinone **78**.

### 3.2.5 β-Lactams by Cu(I) complex catalysis

Catalytic amounts of copper halide complexes of multidentate amines, multidentate pyridines, alkylpyridylamines and TMEDA mediate the atom transfer radical cyclisation of bromo-enamides to give β-lactams exclusively. The nature of the ligand in copper(I) mediated atom transfer cyclisations has a dramatic effect upon the rate and regioselectivity of atom transfer cyclisation reactions.[53-55] Reaction of enamides containing β-substitution **80** with 30 mol% CuBr and 30 mol% of N,N,N-tris (2-pyridylmethyl) amine (TPA) **81** in $CH_2Cl_2$ at room temperature for 20 minutes followed by work-up by passing through a silica plug furnished the bromo 4-*exo* atom transfer product **84** in 96% yield (Scheme 18).



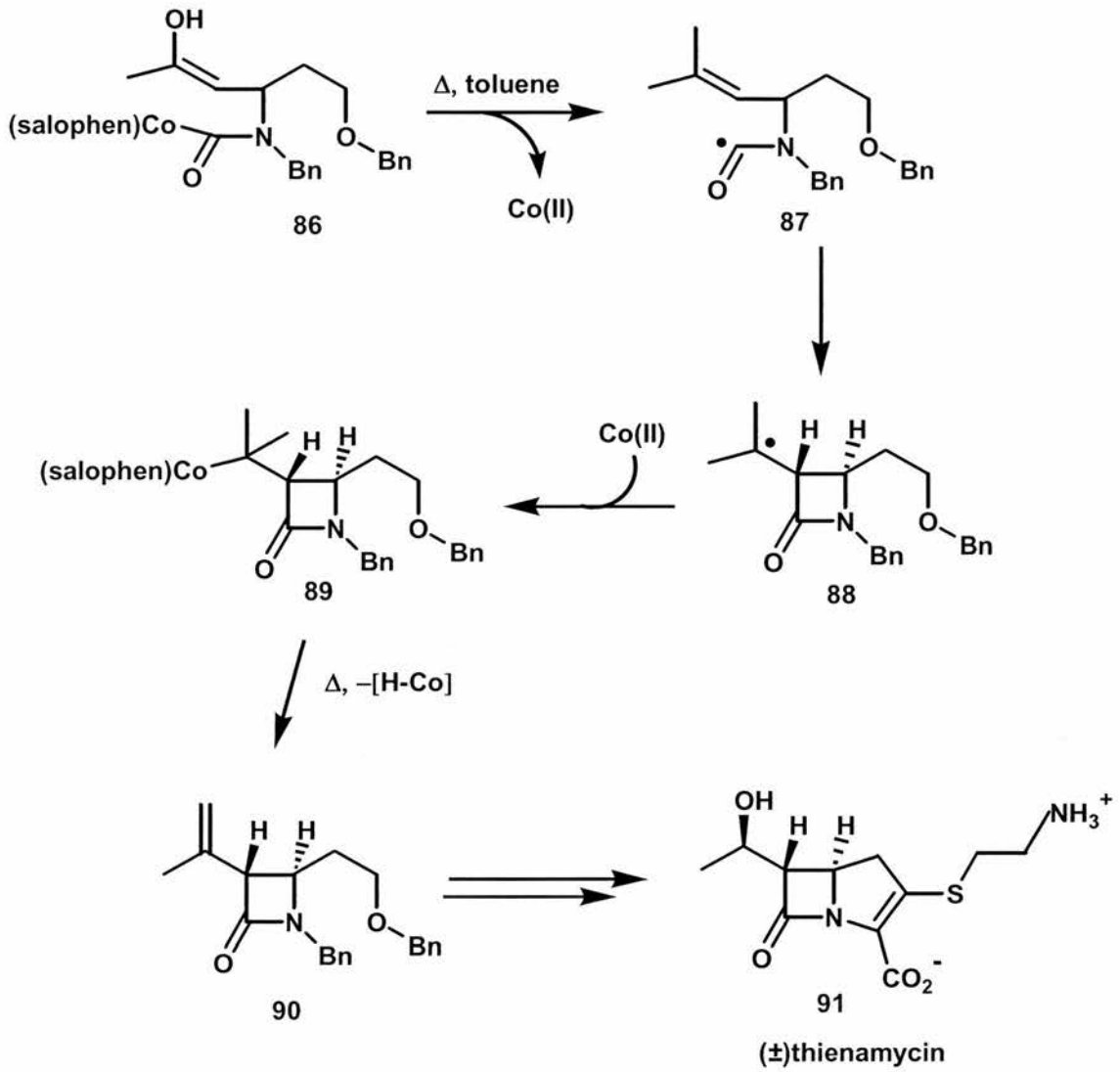

**Scheme 18**

Stirring the *tertiary* bromide **84** with one equivalent of DBU in $CH_2Cl_2$ at room temperature for 12 h furnished the elimination product **85** in excellent yield (94%).
Active atom transfer catalysts allows rapid trapping of the intermediate radicals at ambient temperature favouring the production of the kinetic β-lactam products. Interestingly, even at 110°C in toluene, the 4-*exo* product is formed exclusively, highlighting the efficient nature of the atom transfer catalyst used in trapping out the intermediate cyclised radical.

### 3.2.6 Carbamoylcobalt salophens

Organocobalt reagents can efficiently be used in the generation of carbon-centred radical intermediates. Pattenden described the synthesis of several carbamoylcobalt salophen reagents as precursors of carbamoyl radical intermediates, which allowed the synthesis of a variety of cyclic compounds, including both γ- and β-lactams.[56] The important antibiotic agent thienamycin has been synthesised starting from the appropriate *N*-alkenyl-*N*-alkylcarbamoylcobalt(III) salophen **86**, a suitable precursor for the generation of the corresponding intermediate carbamoyl radical **87**, which cyclised in 4-*exo* mode to give the desired β-lactam ring.

When a deoxygenated solution of carbamoylcobalt (III) salophen compound **86** was heated in dry refluxing toluene the corresponding carbamoyl radical **87** was generated. This highly reactive intermediate was rapidly trapped by the β-alkene moiety furnishing β-lactamcobalt(III) salophen derivative **89.** Dehydrocobaltation of **89** produced exclusively the *trans*-disubstituted β-lactam **90** in an overall yield of 40%. Subsequent conversion of the β-lactam allowed the complete synthesis of the biologically important thienamycin **91** (Scheme 19).[57]



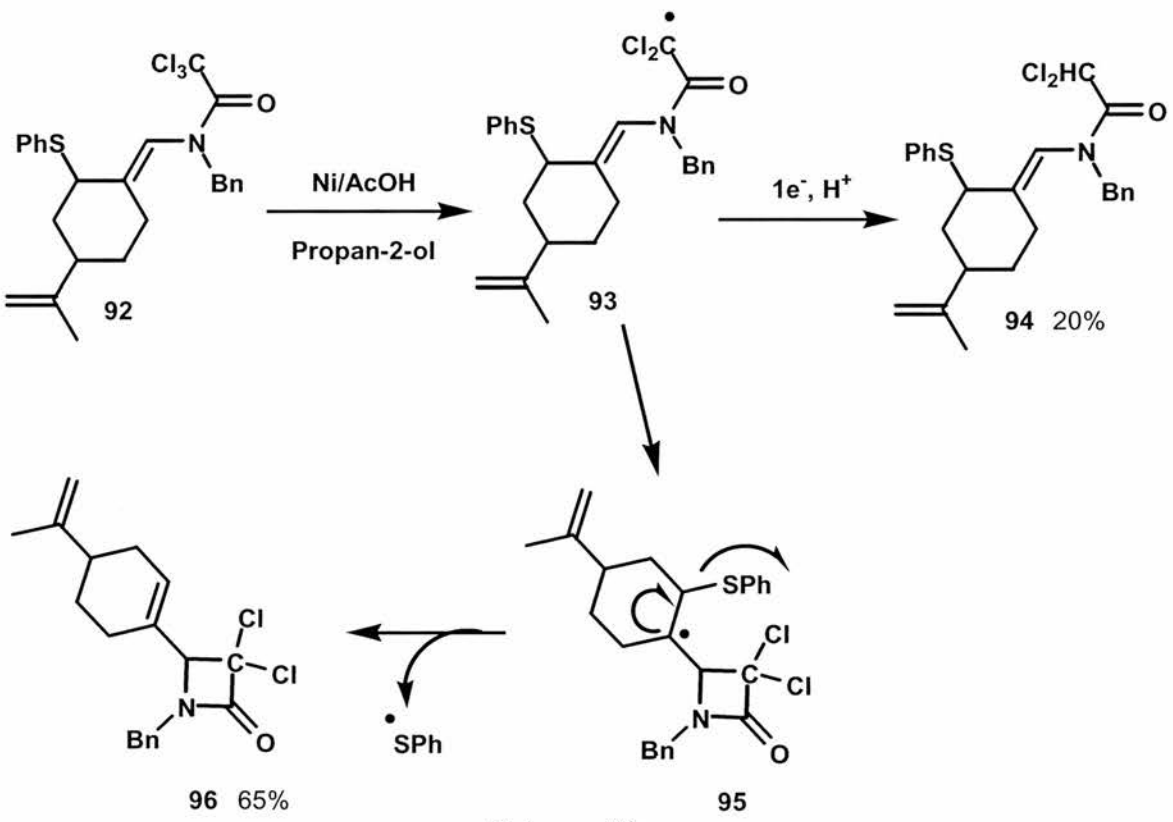

**Scheme 19**

### 3.2.7 Reductive method: Ni powder, AcOH

Metal-induced radical reactions[58-60] have successfully been introduced as an alternative to the usual tributyltin hydride method. Redox-based radical sequences have the advantage of introducing functionality into the molecule after the radical sequence. For reductive processes, the difficulty lies in finding a system able to transfer one electron to the radical precursor while the second one electron reduction remains sufficiently slow to allow the radical intermediate to undergo cyclisation. Formation of small rings such as β-1actams involves a slow and reversible cyclisation step; a strategy to force this equilibrium can be achieved by involving an irreversible step following the 4-*exo*

cyclisation which would drive the equilibrium towards the formation of β-lactams.[61] Zard and co-workers have introduced a method based on the use of nickel powder and acetic acid and illustrated their use in the construction of β-and γ-lactams.[62]

Radical precursors such as **92** were prepared by condensation of aldehydes or ketones with a primary amine followed by acylation of the resulting imine with trichloroacetyl chloride. When subjected to nickel powder and acetic acid in refluxing 2-propanol, these compounds gave radicals **93** via an intermediate radical anion. As the second one-electron reduction leading to reduced products **94** is relatively slow, 4-*exo* cyclisation occurs to give radical **95** which undergoes rapid β-fragmentation to release the stabilised sulfanyl radical, affording β-lactam **96** in 65% yield (Scheme 20).




**Scheme 20**

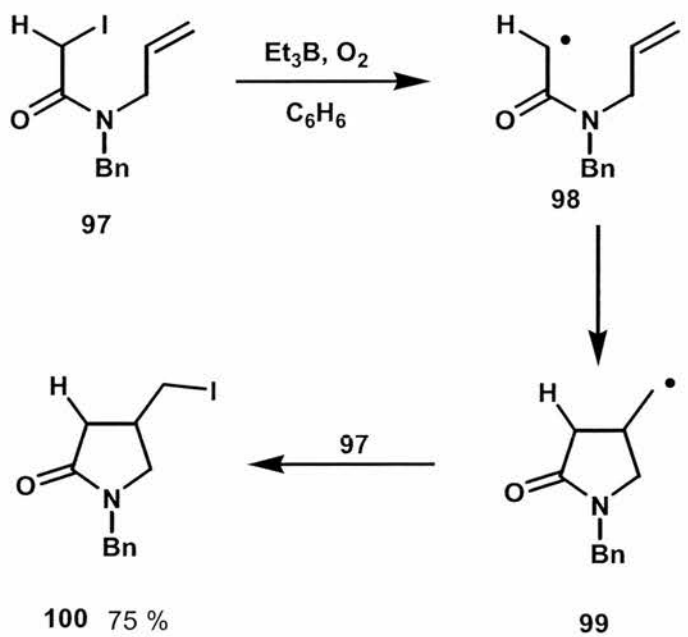
The rapid loss of the stabilised sulphide radical prevented ring opening and therefore none of the competing 5-*endo-trig* cyclisation product was observed. Attempts to trap the β-lactam radical, using alkenes, gave a mixture of β-and γ-lactams due to the slower intermolecular reaction that favoured the re-opening of radical **95** allowing the irreversible 5-*endo-trig* cyclisation to occur.

### 3.2.8 Triethylborane: iodine atom transfer radical cyclisations

Triethylborane in the presence of oxygen produces ethyl radicals (Scheme 21) which can abstract an iodine atom from iodoalkanes, and this property has been used for the inter- and intra-molecular atom-transfer radical additions of iodoalkanes to alkynes or alkenes.[63]


**Scheme 21**

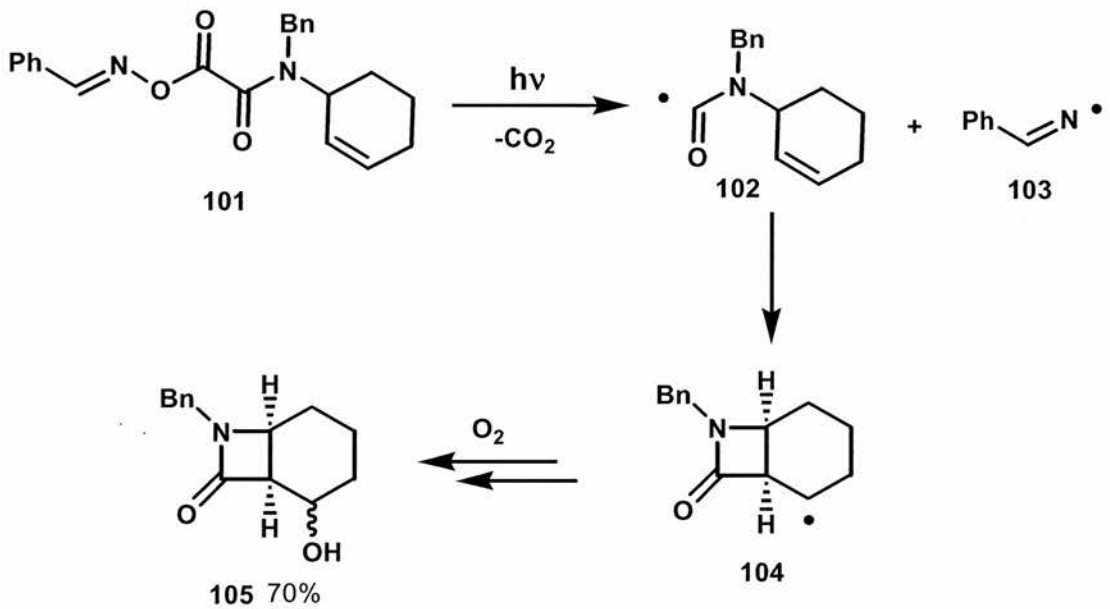
In contrast to the tin hydride-mediated radical cyclisations in which the last step is a simple reduction, atom-transfer radical cyclisations can introduce a versatile halogen atom into the cyclised products. For example, atom-transfer cyclisation of amide **97,** initiated by an ethyl radical generated from triethylborane and oxygen, gave the carbamoylmethyl radical **98.** Radical **98** then underwent cyclisation to yield new radical **99**, which abstracted an iodine atom from the starting α-iodo-amide **97** to afford the cyclised product **100**, in 75% yield, and regenerate the radical **98** (Scheme 22).




**Scheme 22**

### 3.2.9 Oxime oxalate amides in syntheses of lactams

Recently Walton and Scanlan have introduced a new, mild, free-radical precursor for generation C-centred radicals which can be obtained by photolyses of oxime oxalate amides. These novel radical precursors function as clean sources of aminoacyl radicals. Suitably unsaturated aminoacyl radicals then ring close, so that the final outcome would be the establishment of a new synthetic route from secondary amines to lactams. Photolysis of dilute solutions of oxime oxalate amide **101** in toluene (prepared by reacting mono-oximes of oxalyl chloride with one equivalent of primary or secondary alkenylamines) in presence of photosensitiser, MAP, released aminoacyl radical **102,** accompanied by rapid $CO_2$ loss. Radical **102** underwent 4-*exo-trig* cyclisation onto the alkene moiety, affording the bicyclic β-lactam **105** (Scheme 23).[64]



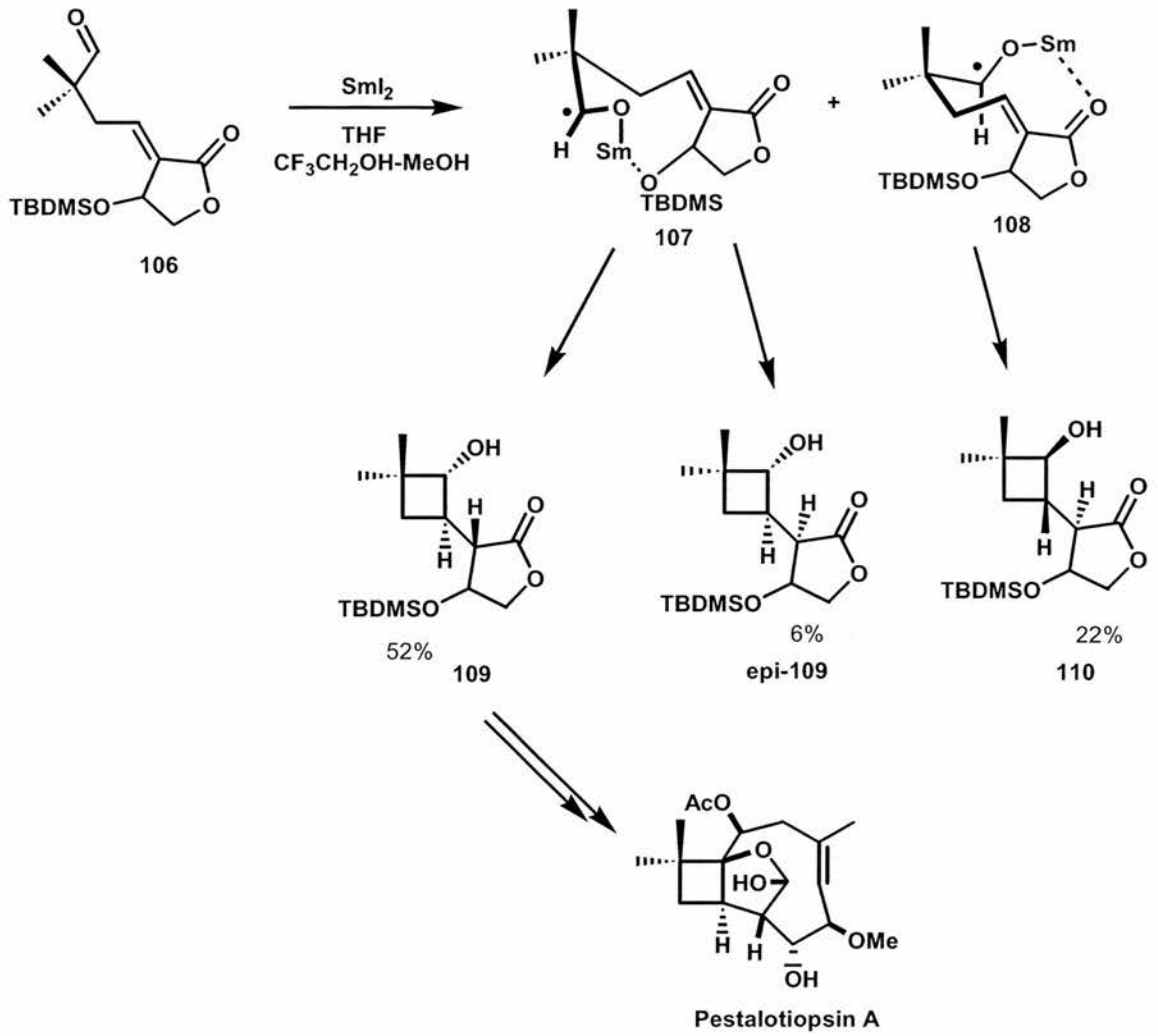

**Scheme 23**

Iminyl radicals **103** formed as co-intermediates abstract hydrogen from the solvent to give an imine that is hydrolysed on work-up and the only significant by-product derived from **103** was benzaldehyde. Negligible amounts of reduced aminoacyl radicals were produced in practice; therefore, interference from undesired by-products was unproblematic.

Product derived from competitive 5-*endo* cyclisation was not detected due to the formation of stabilised secondary radical **104** which favoured 4-*exo* cyclisation instead. Interestingly, hydrogen abstraction from the toluene was slower for the secondary precursor radical **104**, so that addition of dissolved dioxygen occurred. The peroxyl radicals formed in this way would be converted to more reactive oxyl radicals (by self-coupling and $O_2$ loss)[65] that abstracted hydrogen, affording the hydroxyl derivatives **105** which could be further manipulated to other functional groups.

### 3.2.10 Remote stereocontrol in Sm(II)-mediated radical cyclisations.

Procter has recently developed a stereoselective samarium(II)-mediated 4-*exo-trig* cyclisation of γ,δ-unsatured aldehydes, leading to functionalised cyclobutanols which are the core of the natural product pestalotiopsin A. This cyclisation proceeds under mild conditions and allows generation of up to three stereocenters with excellent stereocontrol, leading to enantiomerically pure cyclobutanol products. TBDMS-protected γ,δ-unsatured aldehyde **106** on treatment with $SmI_2$ in THF using 2,2,2 trifluoroethanol as co-solvent, produced a radical which was thought to generate nine-membered chelate intermediate **107,** formed by coordinating a TBDMS group on the lactone ring, which directed radical attack to the front face of the alkene generating cyclobutanol diastereoisomers **109** and *epi*-**109** in 52% and 6% yield respectively. When the bulky TBDMS group acts as a non-coordinating group, the formation of 9-membered intermediate **108** led to a steric front face blocking effect, and the radical attack was forced on the opposite face of the alkene, producing the stereochemistry of cyclobutanol **110** (22%) (Scheme 24).[66]




**Scheme 24**

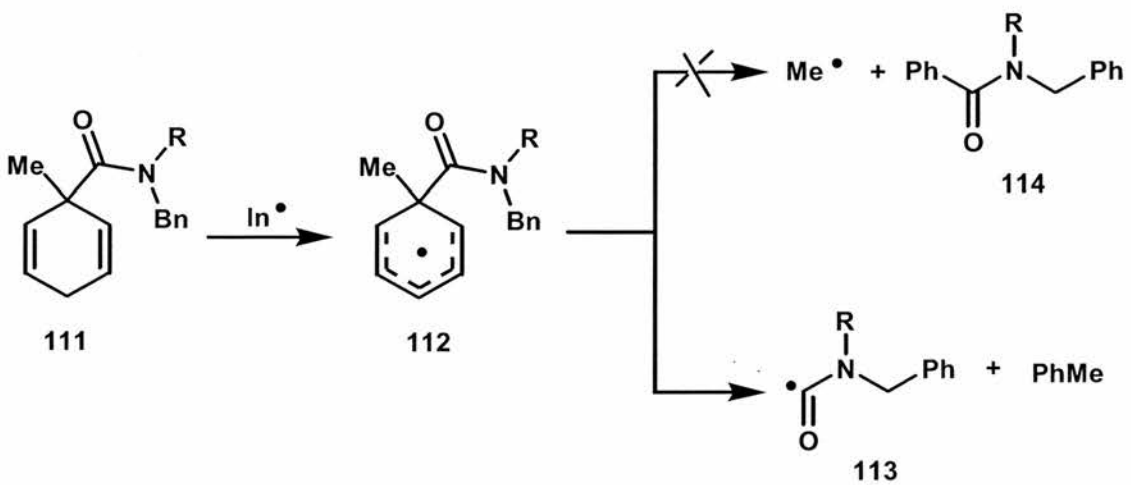
Importantly, **109** and **110** are potential precursors to either enantiomer of the pestalotiopsin core. This is desirable as the absolute stereochemistry of the natural product is not known. This approach allows synthetic studies to be carried out in either enantiomeric series starting from a single enantiomer of starting material.

### 3.2.11 Aminoacyl radicals from "proaromatic" cyclohexadiene carboxamides

Proaromatic cyclohexadienes such as 1-alkyl-cyclohexa-2,5-diene-1-carboxylic acid, esters of 1-methylcyclohexa-2,5-diene-1-carboxylic acid, and 1-phenylcyclohexa-2,5-carboxylic acid, as well as silylated cyclohexadienes are capable of releasing alkyl or silyl radicals upon induced homolysis.[67] The main disadvantage of their use was the unwanted, competitive, dissociation of the intermediate 1-methyl-1-

carboxalatocyclohexadienyl radicals to generate methyl radicals and benzoate esters as by-products.

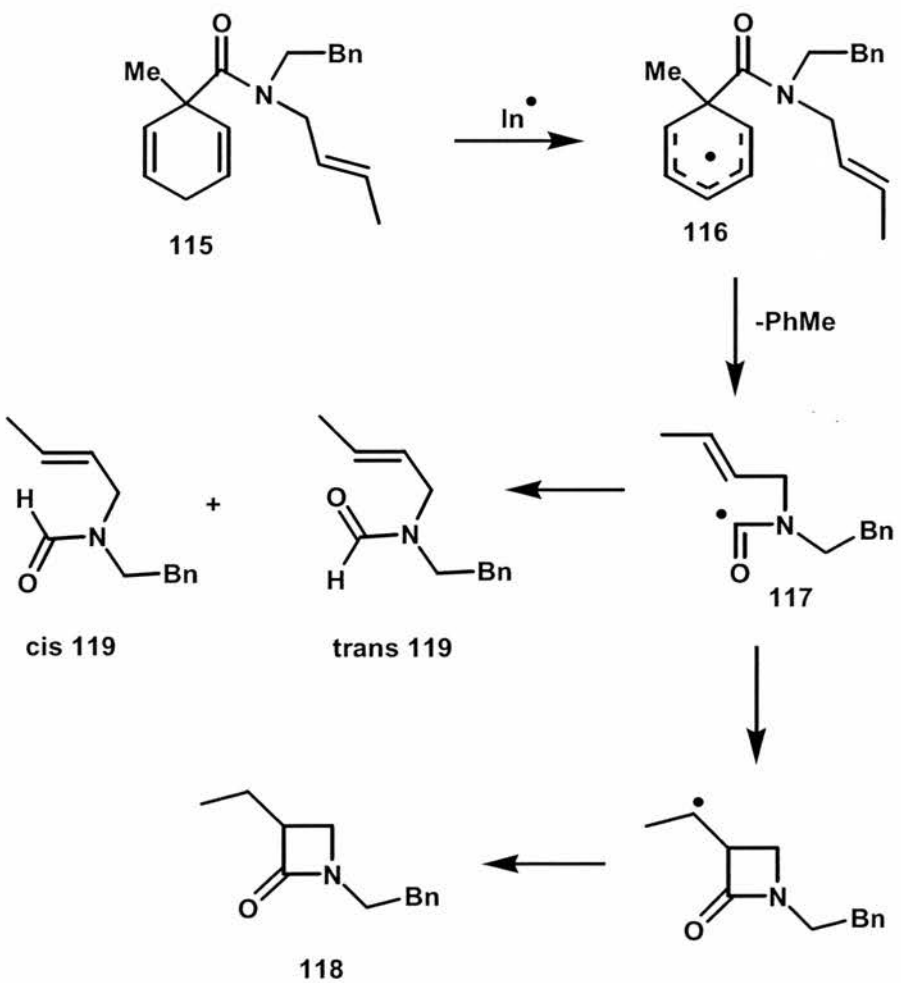
It was envisaged that the analogous amides **111** might function as precursors of aminoacyl radicals (carbamoyl radicals) **113**, due to the increased stability of these radical intermediates in comparison to their alkoxyacyl alternatives. Cyclohexadiene carboxamides **111** in presence of hydrogen atom abstractor such as di-*t*-butyl peroxide or dibenzoyl peroxide under photolytic or thermolytic conditions release the corresponding, delocalised, cyclohexadienyl radicals **112,** that undergo the favoured β-scission in order to generate the desired aminoacyl radical **113** and toluene, rather than the alternative dissociation of the unstable methyl radical with production of amide **114** (Scheme 25).[68] The driving force for the reaction is the restoration of aromaticity in toluene; which can easily be removed from the reaction mixture.




**Scheme 25**

Suitably functionalised examples can undergo radical cyclisation to afford lactams as the main products. A number of unsatured carboxamides has been prepared starting from Birch reduction/alkylation of benzoic acid, which produced methylcyclohexa-2,5-diene carboxylic acid, that was converted into the corresponding acid chloride and condensed with appropriate unsaturated secondary amines to give the corresponding cyclohexadienyl carboxamides.

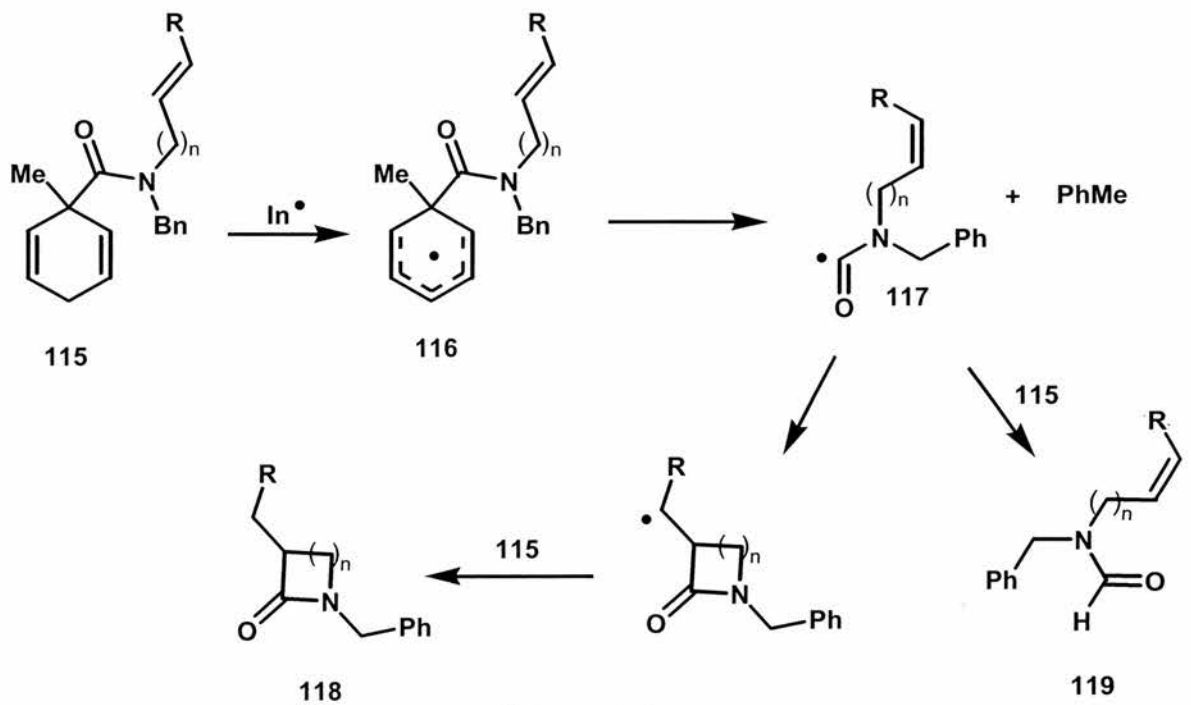
EPR spectroscopic techniques have shown that 1-carbamoyl-1-methylcyclohexa-2,5-diene **115** on treatment with DTBP as initiator under photolytic conditions produced the delocalised cyclohexadienyl radical **116** at ca. 300 K. At increased temperatures β-scission of **116** released toluene and aminoacyl radical **117**. The induced decomposition of amide **115** was also carried out under thermolytic conditions with dibenzoyl peroxide as initiator in refluxing benzene. 4-*exo-trig* Cyclisation of the unsatured aminoacyl radical **117** followed by H-abstraction from more amide **115** produced 1-benzyl-3-ethylazetidin-2-one **118** (34%), and a significant amount of *N*-benzyl–*N*-but-2-enylformamide **119** as a mixture of *trans*- and *cis*-isomers (31%) (Scheme 26). In conclusion, the amide decomposition represents a novel tin-free radical route that can be employed for the preparation of a range of β- and γ-lactams from secondary amine starting materials.




**Scheme 26**

# Aims and Objectives of the Project

The results obtained from EPR experiments on amides **18** and **19** (Chapter 2) established both the greater stability of the aminoacyl radical, and the favoured dissociation of the delocalised cyclohexadienyl radical to aminoacyl radical, over the alternative dissociation to methyl radical. Unsaturated cyclohexadiene carboxamides **115** in presence of di-*t*-butyl peroxide or dibenzoyl peroxide under photolytic or thermolytic conditions could potentially release the corresponding, delocalised, cyclohexadienyl radicals **116,** which could undergo β-scission to generate the desired unsaturated aminoacyl radical **117**. Aminoacyl radical **117** either can abstract hydrogen from more **115** to cyclise to the corresponding lactam **118** or produce formamide **119**, (Scheme 27).




**Scheme 27**

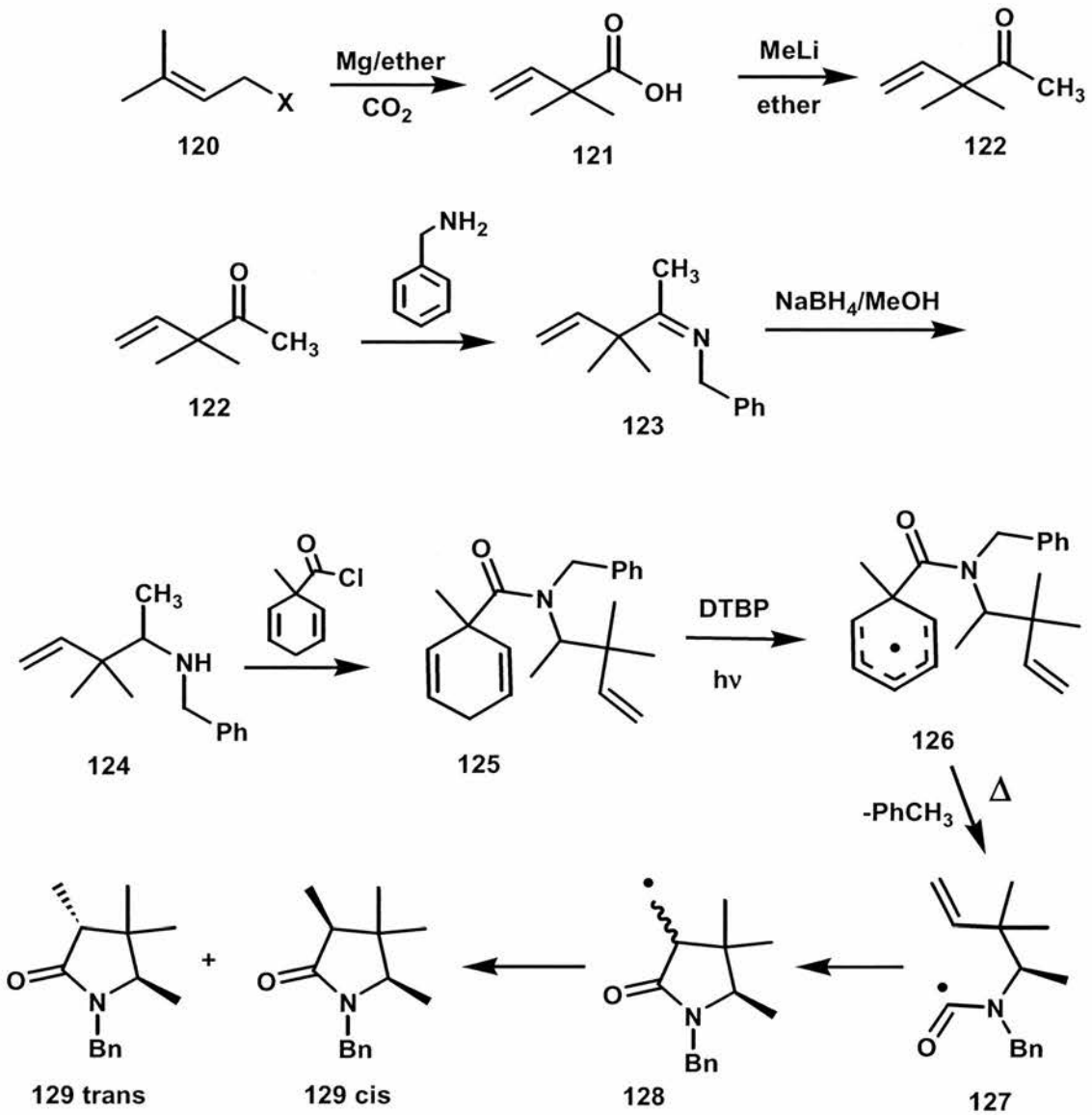
Unsaturated carbamoyl-1-methylcyclohexa-2,5-dienes might therefore be good aminoacyl radical precursors and could potentially ring close to afford lactams as the main products. The motivation of this work was to further investigate 1-carbamoyl-1-methylcyclohexa-2,5-dienes and test if these alternative radical sources are suitable for efficient synthesis of β- and γ-lactams starting from simple functionalised cyclohexadienyl amides.

## 3.3 Results and Discussion

A number of unsaturated carboxamides was prepared starting from Birch reduction/alkylation of benzoic acid,[69-72] which produced methylcyclohexa-2,5-diene carboxylic acid, that was converted into the corresponding acid chloride and condensed with appropriate unsaturated secondary amines to give the corresponding cyclohexadienyl carboxamides.

### 3.3.1 1-Methyl-2,5-cyclohexadiene-1-carboxamides in syntheses of γ–lactams.

Aminoacyl radicals did not decarbonylate at moderate temperatures and hence could be used in free radical chain cyclisations. For example synthesis of pyrrolidinones could be achieved starting from appropriate amides, under photolytic or thermolytic conditions. Treatment of unsaturated halide **120** under Grignard conditions, followed by carbonylation, produced the rearranged unsaturated acid **121** which was methylated by MeLi in ether to give ketone **122**. Reductive amination of ketone **122** with benzylamine furnished the desired γ,δ-unsaturated amine **124,** which was reacted with 1-methylcyclohexa-2,5-diene-1-carbonyl chloride producing tertiary amide **125**. Aminoacyl radical **127** released by heating a benzene solution of **125** in the presence of dibenzoyl peroxide, underwent 5-*exo* cyclisation in order to furnish N-benzyl pyrrolidinone **129** as a mixture of *cis*- and *trans*-diastereoisomers (Scheme 28).



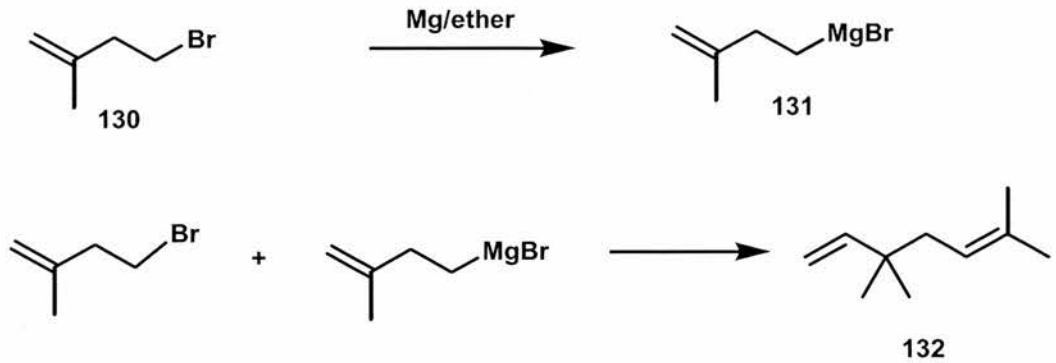

**Scheme 28**

Important lactam rings may, therefore be synthesized starting from appropriate 1-methyl-2,5-cyclohexadiene-1-carboxamide and subsequent ring closures of alkenylaminoacyl radicals.

### 3.3.2 Synthesis of 2,2-dimethyl-3-butenoic acid (121)

In the preparation of all Grignard reagents there are side reactions and chief among these is the coupling reaction to give R-R compounds.[73] Like other β-substituted allyl halides 1-bromo-3-methyl-2-butene **130** required special conditions in order to obtain

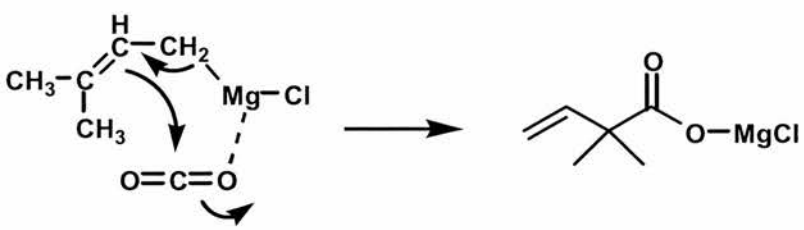
good yields of the Grignard reagent. It was evident from the experiments that when 1-bromo-3-methyl-2-butene was added to a nitrogen-filled dry flask containing enough ether to cover magnesium turnings, a great tendency to couple was exhibited. The Grignard reaction gave a small percentage yield of **131** and the major product of the reaction was 3,3,6-trimethyl-1,5-heptadiene **132** (Scheme 29).



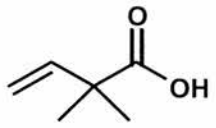

**Scheme 29**

However, the yield of **131** was improved by increasing the time of addition of the bromide and the ratio of solvent to bromide, as well as using 20-30 mesh magnesium turnings which were prepared just before use.

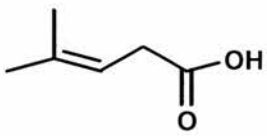
When 1-chloro-3-methyl-2-butene (designated as the prenyl[74] Grignard) was used instead of bromide **130** the subsequent addition reaction of carbon dioxide gave further improved yields of 2,2-dimethyl-3-butenoic acid. It has been demonstrated[75,76] that unsaturated Grignard reagents in addition reactions with carbon dioxide behave without exception as though rearrangement had occurred prior to reaction. These observations have been reconciled[76,77] with a cyclic mechanism of coupling or addition.



prenyl magnesium chloride reacted with carbon dioxide with the formation of 2,2-dimethyl-3-butenoic acid **121** in good yield. Neither the alternative product, 4-methyl-3-pentenoic acid **133**, nor any other product was isolated.



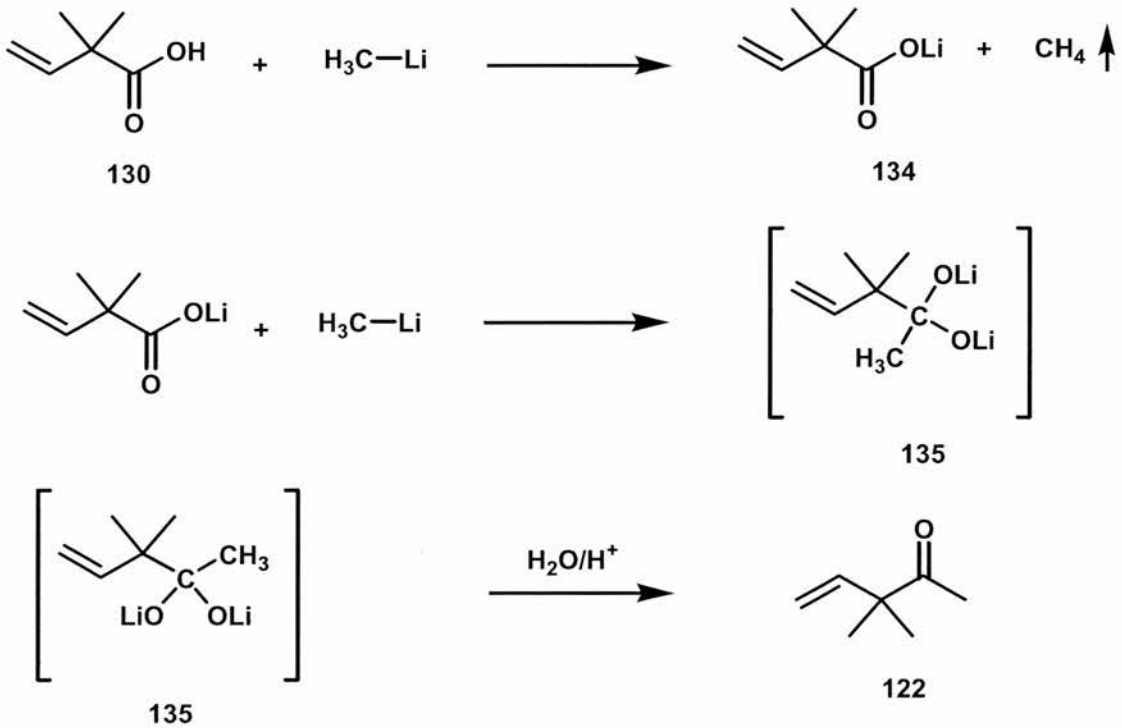

**121**




**133**

### 3.3.3 Preparation of 3,3-dimethyl-4-penten-2-one (122)

The 2,2 dimethylcarboxylic acid **121** was converted into 3,3-dimethyl-4-penten-2-one **122** by action of methyllithium. To a cold solution of acid **121** (-40°C) in ether, an equivalent of methyl lithium was slowly added forming lithium salt **134** (Scheme 30).

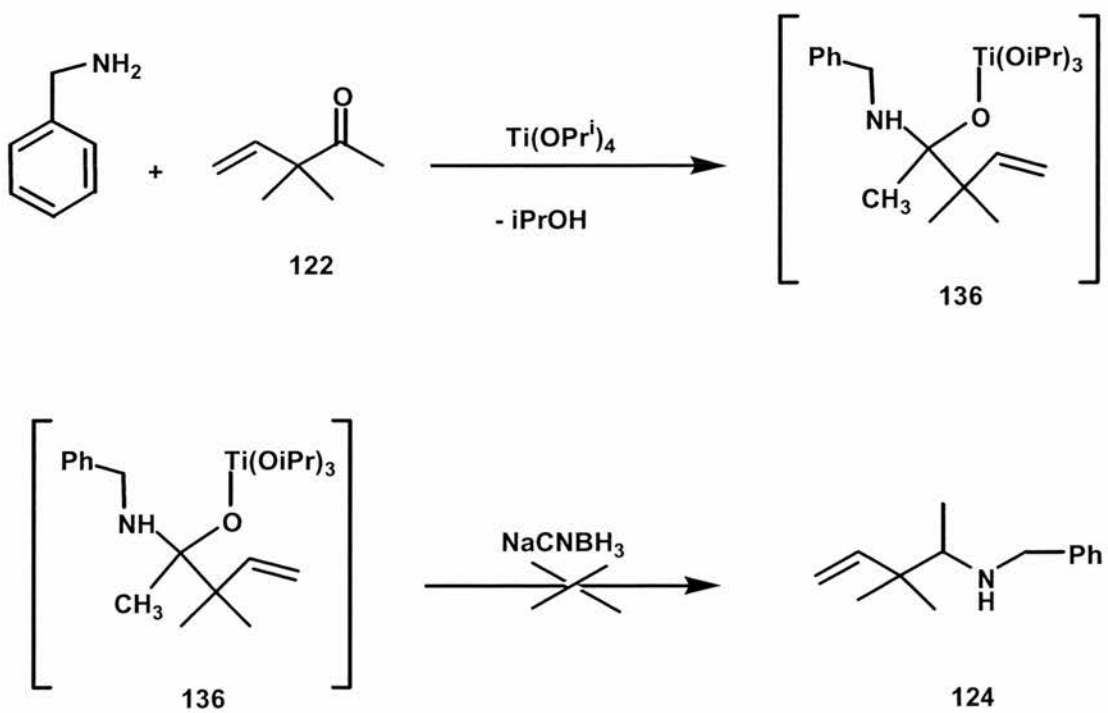



**Scheme 30**

To the lithium salt was added one more mol/equivalent of methyllithium, and the dilithium salt **135** was obtained as a white suspension, which on acid hydrolysis yielded 3,3-dimethyl-4-penten-2-one **122** in accordance with the above reaction. It was noted that no addition to the double bond occurred in this reaction.

### 3.3.4 Attempted titanium(IV) catalysed reductive amination of 3,3-dimethyl-4-penten-2-one (122).[78,79]

Titanium(IV) isopropoxide can potentially be used as a catalyst in the reductive amination of ketone **122** because it is a mild and effective Lewis acid for the reductive amination of ketones. One possible mechanism for this one-pot procedure, is that the stable titanium complex **136** is formed, which is then reduced directly by sodium borocyanohydride to give amine **124** (Scheme 31). An equimolar ratio of benzylamine and 3,3-dimethyl-4-penten-2-one **122** was reacted with an excess of titanium(IV) isopropoxide and sodium cyanoborohydride via the general procedure. The solvent and reducing agent had to be added only after the intermediate titanium/ketone/amine adduct **136** had been allowed to form (1hr). After 20 hr under reflux TLC indicated no disappearance of the starting material. We attempted to continue with the procedure but the NMR spectrum confirmed these results.



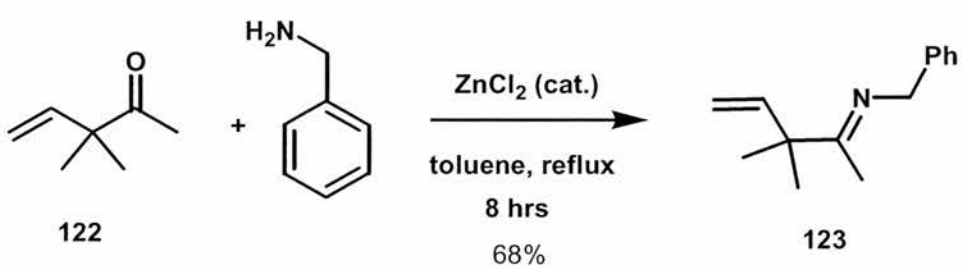

**Scheme 31**

### 3.3.5 Attempted cyanohydridoborate reductive amination of ketone 122[80]

Preparation of unsatured amine **124** was attempted by reaction of ketone **122** with benzylamine at pH~6-7 in the presence of sodium cyanoborohydride ($NaBH_3CN$) *via* reductive amination of the carbonyl group. The reaction was carried out at room temperature for 20 hr and, because the reduction consumes acid, it was necessary to monitor the reaction by pH paper; methanolic HCl was then added to regenerate and maintain the appropriate pH. Both TLC and NMR spectra of the crude reaction mixture showed that starting material was not converted under these conditions.

### 3.3.6 Preparation of *N*-phenylmethyl-*N*-(1,2,2-trimethyl-3-butenylidene) amine (123)

An efficient method for the preparation of imine **123** was condensation of carbonyl compound **122** with benzyl amine. Among solvents tested for the reaction, were ethanol, methanol and tetrahydrofuran. In tetrahydrofuran the reaction failed to proceed, it was slow and gelatinous, while in ethanol, yields were rather low. Inexpensive benzylamine was used in equimolecular proportion with respect to ketone **122**. When the reaction was carried out in the presence of a catalytic amount of zinc chloride[81] in refluxing toluene with azeotropic removal of water *via* a Dean and Stark trap, pure unsaturated imine **123** was produced in good yields (68%) (Scheme 32). The Lewis acid zinc chloride was used as catalyst which is milder than aluminium chloride and is particularly effective in catalyzing reactions that eliminate molecules of water, ammonia or mercaptan.

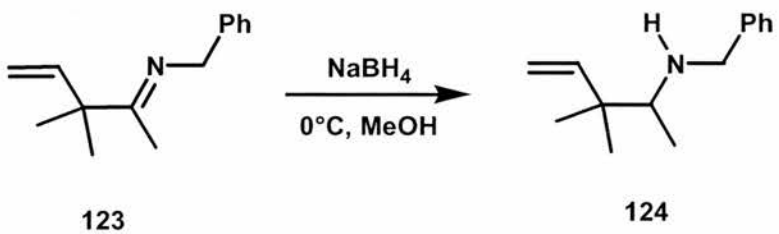



**Scheme 32**

The method is inexpensive, relatively rapid, operationally simple and suitable for large-scale preparation.

### 3.3.7 Preparation of *N*-benzyl-3,3-dimethyl-4-penten-2-amine (24).[57]

Sodium borohydride reduction of imine **123** was performed in order to selectively protonate the imine function and generate the corresponding amine **124** (Scheme 33). The reaction followed a procedure, previously described by Pattenden, where the imine was reduced by slow addition of $NaBH_4$ to a stirred solution of imine **123** at 0°C in dry methanol.




**123** **124**

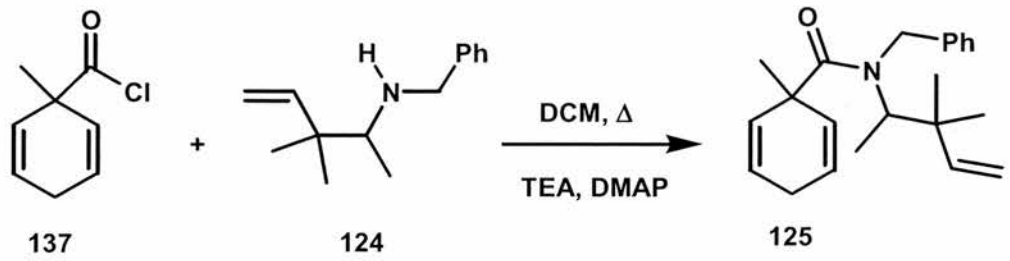
**Scheme 33**

The mixture was allowed to warm to room temperature and stirred for 18h. The crude reaction mixture was treated with concentrated HCl followed by extraction with ether. The organic layer was then washed with a KOH solution in order to liberate the desired amine. Kugelrohr distillation generated pure amine **124** as a colourless oil in 63% yield.

### 3.3.8 Synthesis of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide.

Amidocyclohexadiene **125** was prepared by slow addition of crude methyl acid chloride **137** (prepared following the procedure described in Chapter 2 p. 89) to a mixture of purified amine **124**, triethylamine and a catalytic amount of DMAP in DCM as solvent (Scheme 34). The resultant solution was refluxed for 8 h before a basic workup yielded the impure product, which was purified by flash chromatography to

furnish 1-methylcyclohexa-2,5-diene carboxamide **125** as a pale yellow oil in 74 % yield.

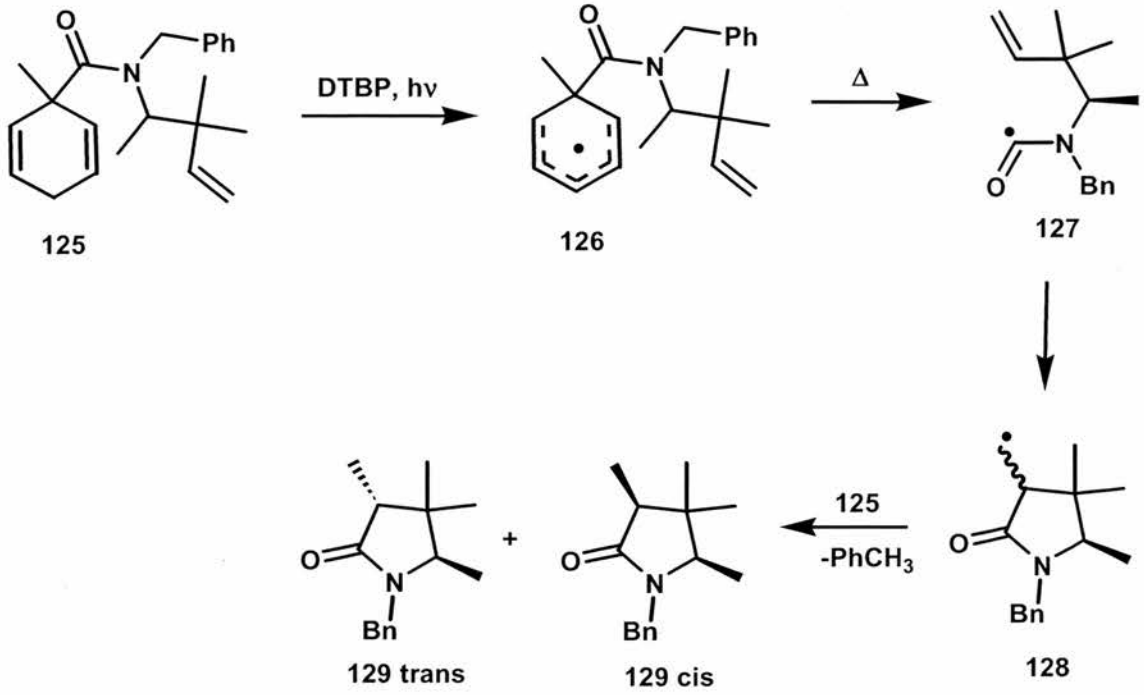



137 124 125

**Scheme 34**

### 3.3.9 EPR experiment on photolysis of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide (125).

Previous studies on 1-methyl-2,5-cyclohexadiene carboxamides **18** and **19** (Chapter 2) outlined the ability of this substrate to produce delocalised 1-carbamoyl-1-methylcyclohexa-2,5-dienenyl radicals (below 300 K) and to release aminoacyl radicals at higher temperature. We were interested in determining the rate of allylic hydrogen abstraction from analogous cyclohexadienyl amides which would result in the release of aminoacyl radicals containing N-alkenyl functionality and might therefore undergo radical cyclisation to give the corresponding lactams (Scheme 35).




**Scheme 35**

An accurately measured quantity of cyclohexadienyl carboxamide **125** (5 mg) was placed in a clean dry quartz tube, before a total of 0.4 $cm^3$ of DTBP was added, and degassed for approximately 20 min. The sample was placed in the EPR resonant cavity which was held at 230 K and a preliminary EPR spectrum was acquired on irradiation with the UV light in order to initiate the radical chain. The temperature was increased at intervals of 5 K and at 245 K cyclohexadienyl carboxamide **125** started to release the delocalised cyclohexadienyl radical **126** which was observed by an EPR spectrum that was straightforward to characterise (Figure 1 and table 1).

**9.5 GHz EPR spectra obtained on photolysis of *N*-benzyl-*N*-1,2,2-trimethylbut-3-enyl-1-methyl-cyclohexa-2,5-diene-1-carboxamide (125)**

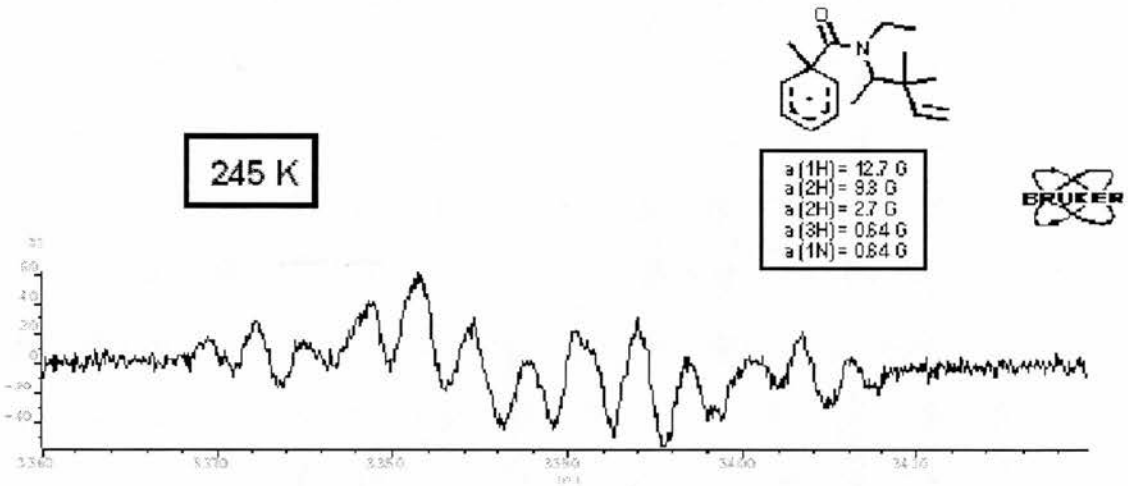
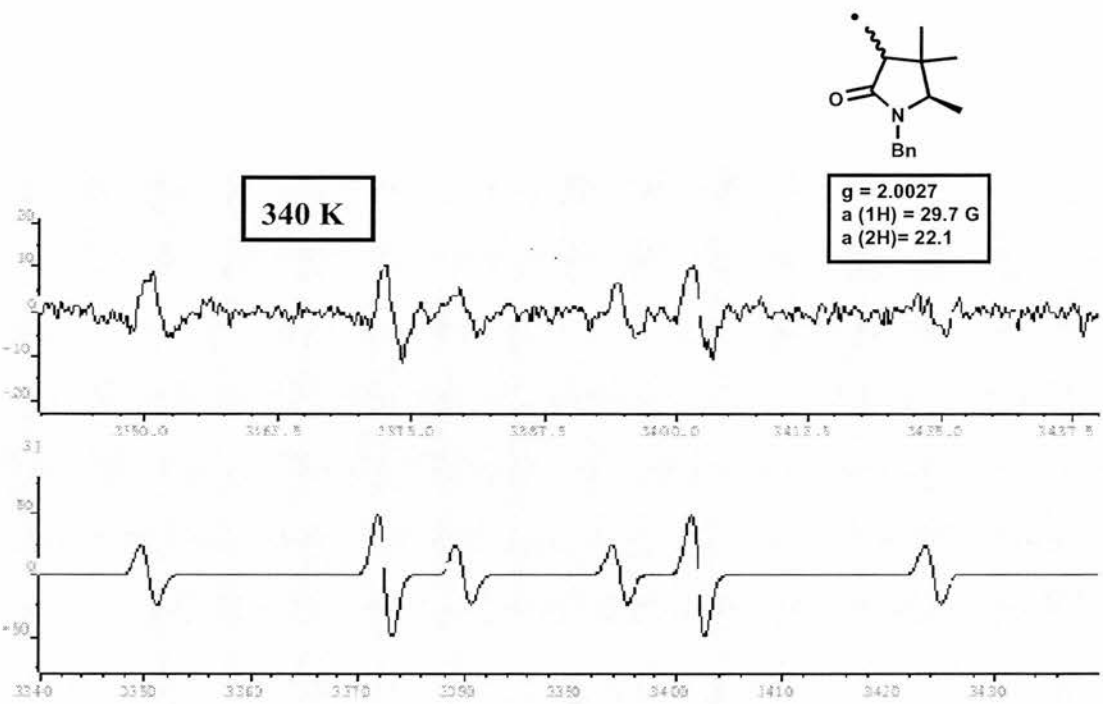



**Figure 1**

When the temperature of the EPR cavity was increased at 330 K the spectrum of the cyclohexadienyl radical **126** weakened and at 340 K it was replaced by a spectrum consisting of a doublet of triplets (Figure 2 and table 1).




Top: Spectrum of ring closed trimethyl-2-oxopyrrolidinylmethyl radical **128** at 340 K.
Bottom: Simulation with $a$(2H) = 22.1 G, $a$(1H) = 29.7 G, $\Delta H_{pp}$ = 1.35 G.

**Figure 2**

**9.4 GHz EPR Parameters of Radicals Derived from *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide(125) in solution.[a]**

| radical | T/K | g-factor | a(G) |
|---|---|---|---|
| **126** | **245** | **2.0027 Assumed** | **a(1H) = 12.7<br>a(2H) = 9.3<br>a(2H) = 2.7<br>a(3H) = 0.64<br>a(1N) = 0.64** |
| **128** | **340** | **2.0027** | **a(1H) = 29.7<br>a(2H) = 22.1** |

[a] All spetra in neat DTBP

**Table 1**

This spectrum can be attributed to the *N*-benzyl-4,4,5-trimethyl-2-oxopyrrolidinylmethyl radical **128**. The observed hfs for the β-hydrogen is greater than that of the cyclopentylmethyl radical.[82] However, the magnitudes of $H_\beta$ hfs depends on the preferred conformation about the $C_\alpha$–$C_\beta$ bond and this is strongly influenced by adjacent substituents.[83] In this case, aminoacyl radical **127** was not detected, therefore, the ring closure step is comparatively fast. Radical **127** is so quickly transformed to cyclised radical **128** that the latter was the only species detected. Rate constants were calculated as previously described (Chapter 2) from measurements of the concentrations of cyclohexadienyl radical **125** and cyclised radical **128**. Further analysis performed on a stock solution of amide **125** in DTBP (9 equivalent EPR samples) of known amide concentration allowed us to calculate the free radical rate constant, $k_d$ for the β-fragmentation by locating a temperature range where the recorded spectra progressively changed from the delocalised radical **126** to the cyclised radical **128**. It was also possible to focus on a small portion of the acquired spectra where peaks from both transient radical species could be detected. Radical concentrations were calculated by double integration of suitable peaks from the first derivative EPR spectra from each radical, using the WinEPR software, followed by comparison with a doubly integrated EPR signal from a 1 x $10^{-3}$ M solution of DPPH. These concentration data were placed into the equation derived from the steady state treatment (see above). The values of $k_d$ for the β-fragmentation of amide **125** at each temperature were calculated by assuming that each aminoacyl radical **127** was completely transformed into a cyclised radical **128** (Table 2).

| Actual T /K | [128] M | [126] M | kd/2kt | logkd/2kt | log2kt (nC7) | $10^3$K/T | log2kt DTBP | log kd DTBP | kd/$s^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| 302 | 6.058E-09 | 3.234E-08 | 7.193E-09 | -8.143 | 10.002 | 3.307 | 9.696 | 1.552 | 3.57E+01 |
| 308 | 1.935E-08 | 3.294E-08 | 3.071E-08 | -7.513 | 10.032 | 3.247 | 9.729 | 2.216 | 1.64E+02 |
| 314 | 1.936E-08 | 1.427E-08 | 4.564E-08 | -7.341 | 10.060 | 3.188 | 9.760 | 2.420 | 2.63E+02 |
| 319 | 1.435E-08 | 9.684E-09 | 3.562E-08 | -7.448 | 10.088 | 3.132 | 9.791 | 2.343 | 2.20E+02 |
| 308 | 1.179E-08 | 4.069E-08 | 1.521E-08 | -7.818 | 10.032 | 3.247 | 9.729 | 1.911 | 8.14E+01 |
| 314 | 1.201E-08 | 2.402E-08 | 1.802E-08 | -7.744 | 10.060 | 3.188 | 9.760 | 2.016 | 1.04E+02 |
| 319 | 1.663E-08 | 2.103E-08 | 2.978E-08 | -7.526 | 10.088 | 3.132 | 9.791 | 2.265 | 1.84E+02 |
| 325 | 1.493E-08 | 1.145E-08 | 3.441E-08 | -7.463 | 10.115 | 3.077 | 9.821 | 2.358 | 2.28E+02 |
| 336 | 2.833E-08 | 1.185E-08 | 9.607E-08 | -7.017 | 10.166 | 2.974 | 9.877 | 2.860 | 7.24E+02 |

**Table 2**

An Arrhenius plot of the $k_d$ values is shown in Figure 3.

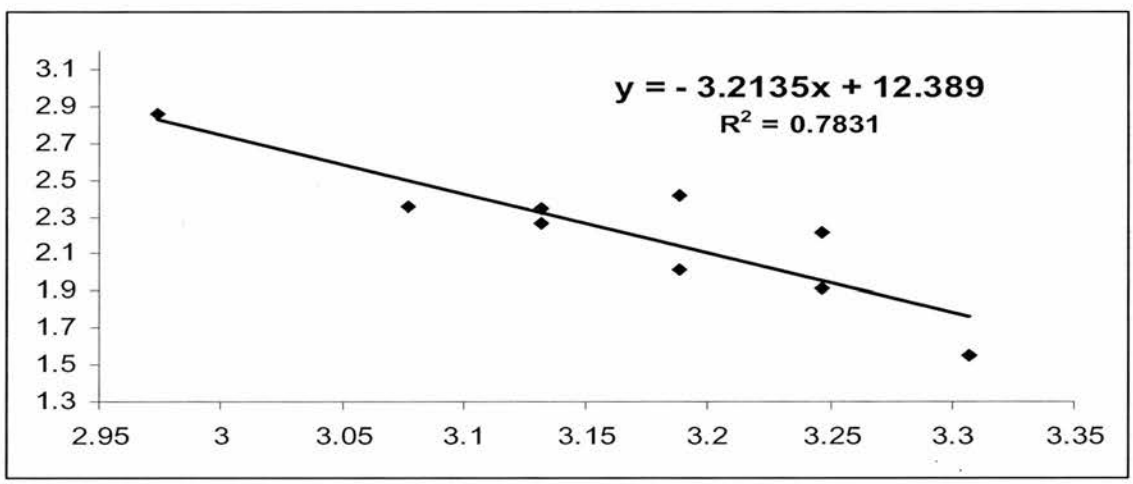



**Figure 3**

The points show some scatter, as might be expected from the moderate signal/noise ratio of the spectra. However, the energy of dissociation ($E_d$), and pre-exponential factor $A_d$ and the rate of dissociation at 300 K ($k_d$) were obtained by linear regression analysis:

$$\text{Log } k_d = \text{Log } A_d - E_d/2.3\ RT$$

$$E_d = 14.7 \text{ kcal mol}^{-1},$$

$$k_d/s^{-1} \text{ (300 K)} = 49$$

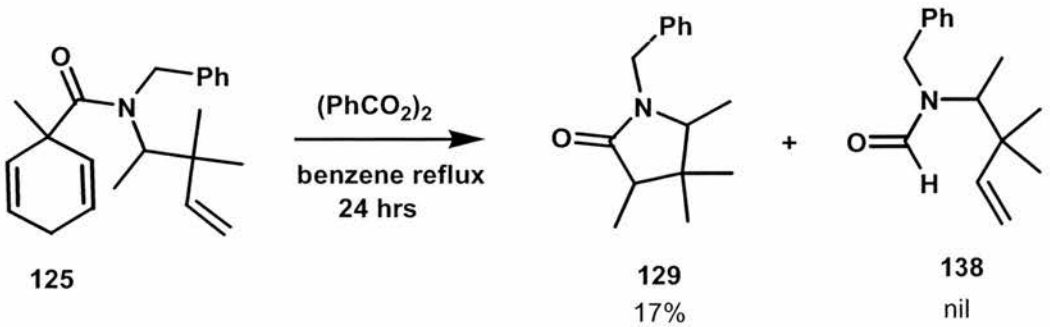
$$k_d/s^{-1} \text{ (350 K)} = 1.7\ 10^3$$

$$\text{Log}(A_d/s^{-1}) = 12.4$$

The measured pre-exponential factor is close to the 'normal' value of $10^{13}$ $s^{-1}$ for unimolecular dissociations and this gives confidence that the kinetic data are trustworthy. Even at the lowest temperature of 302 K cyclisation was faster than dissociation. It follows that $k_C$ (**127**, Scheme 27) $\geq k_d \geq 49$ $s^{-1}$ at 300 K and $\geq 1.7 \times 10^3$ $s^{-1}$ at 350 K. Therefore the rate constants all relate to the dissociation $k_d$. The considerably faster cyclisation of radical **127** is due to the bis-methyl substitution which increases the rate of the cyclisation step *via* a Thorpe Ingold type effect. For comparison the rate constants of hex-5-enyl[84] and 2,2-dimethylhex-5-enyl cyclisation are[85] $2 \times 10^5$ and $4 \times 10^6$ $s^{-1}$ at 300 K respectively. It is not surprising, therefore, that the aminoacyl radical is completely transformed to the ring closed species. The rate constant values for the radical cyclisation of simple acyl radicals[86,87] at 300 K indicated that aminoacyl radical cyclisation may be slower than simple acyl cyclisation, probably due to the increased thermodynamic stability of the amide bonds in the former.

### 3.3.10 DBP mediated thermolysis of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide (125).

On the basis of the data obtained by EPR kinetic studies we envisaged that pure amide **125** in the presence of dibenzoyl peroxide (DBP) as radical initiator under thermolytic conditions in refluxing benzene would undergo radical fragmentation. The appropriate proximity of the double bond encouraged 5-*exo* cyclisation in order to furnish cylised γ-lactam **129** (Scheme 36) which was isolated from the crude reaction mixture by column chromatography in 17% yield



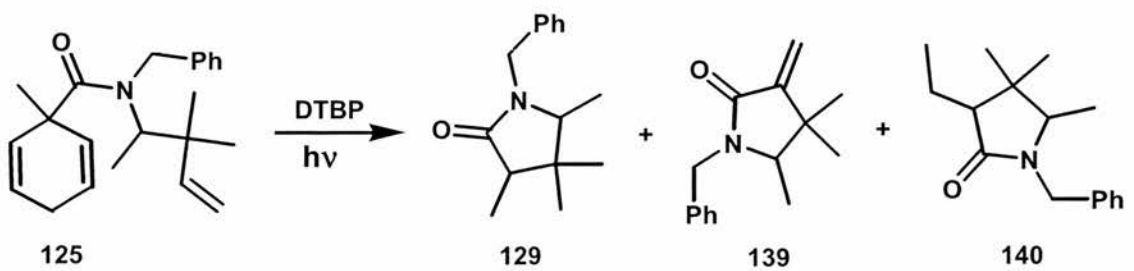

**125** **129** 17% **138** nil

**Scheme 36**

GC-MS and NMR analysis of the crude reaction mixture revealed the presence of both by-products derived from the radical initiator and cyclised γ-lactam **129** as a mixture of *cis*- and *trans*-diastereoisomers. A slow addition of radical initiator by using a syringe pump, served to avoid formation of uncyclised formamide **138**. In fact there was no evidence of either uncyclised formamide **138** or aromatic amide type **114** (Scheme 25). The poor isolated yield of **129** was due to difficulties in separating the two isomers from initiator debris and from each other. Therefore amides of type **125** might have a high potential as clean aminoacyl radical sources, with promise of considerable generality for syntheses of important biologically active lactams.

### 3.3.11 DTBP mediated photolysis of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide (125).

The alternative photolytically induced radical fragmentation of amide **125** was also studied in order to determine any change in product yields. Irradiation of amide **125** in neat DTBP at 60°C gave a crude reaction mixture which was analysed by GC-MS. A mixture of *cis*-and *trans*- cyclised γ-lactams (diastereoisomers) **129** was detected as the major products together with 1-benzyl-4,4,5-trimethyl-3-methylene-pyrrolidin-2-one **139**, arising by H-atom loss from cyclised radical **128** (probably formed by disproportionation), and 1-benzyl-3-ethyl-4,4,5-trimethyl-pyrrolidin-2-one **140,** which was formed by radical chain termination reaction between trimethyl-2-oxopyrrolidinylmethyl **128** and a $CH_3$ radical derived from the *t*-butoxyl radicals (Scheme 37).



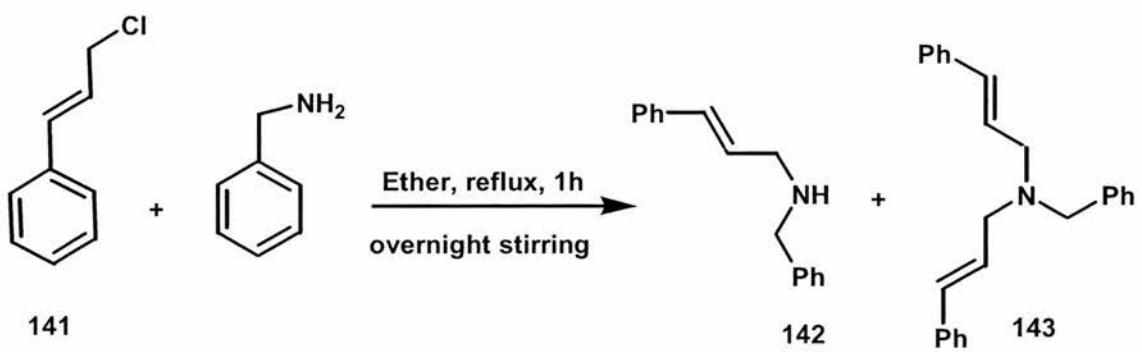

125 129 139 140

**Scheme 37**

Yields were measured by GC, comparing the peak areas to that of a known quantity of an amide standard. Amide **125** was formed in a similar amount to that observed for the thermally initiated reaction (21%). Careful analysis of the GC-MS spectra gave no evidence of benzamide formation *via* the competitive dissociation of cyclohexadienyl radical **126**.

### 3.3.12 Preparation of *N*-benzyl-3-phenyl-2-propen-1-amine (142)

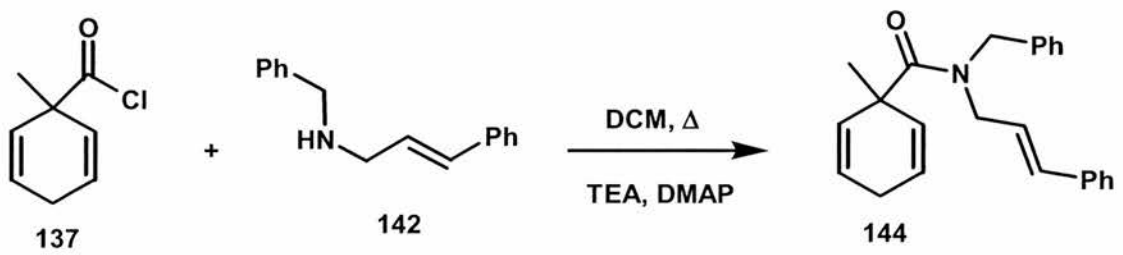
In order to generate unsaturated amine **142**, benzylamine was slowly added to a stirred ether solution of 3-chloro-1-propenylbenzene (cinnamyl chloride) **141**, left at reflux for 1 h, and stirred overnight at room temperature. The reaction mixture was dissolved in HCl solution (2 M) and washed with ether before sodium carbonate forced the desired product to separate out of solution. Finally, the amine was extracted with ether and the organic layers were concentrated at reduced pressure to give a yellow crude product containing the desired amine **142** as the main product. Purification by column chromatography gave the pure amine **142** as a colourless oil in 64% yield together with a white solid by-product that was isolated and identified as *N*-benzyl-3-phenyl-*N*-(3-phenyl-2-propenyl)-2-propen-1-amine **143** which was possibly formed from the competitive reaction of more secondary amine **142** with cinnamyl chloride **141** (Scheme 38).




**Scheme 38**

### 3.3.13 Preparation of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide (144)

The carbamoylcyclohexadienyl carboxamide **144** was obtained in satisfactory yield on addition of 1-methyl-2,5-cyclohexadiene-1-carboxylic acid chloride **137**, which was prepared as previously described (chapter 2 p. 89), to DCM solutions of pure amine containing $Et_3N$ and a catalytic amount of DMAP (Scheme 2). The resultant solution was refluxed for 8 hours before a basic work-up yielded product which was purified by column chromatography to give the pure benzyl-1-methyl-*N*-3-phenyl-2-propenyl-2,5-cyclohexadiene-1-carboxamide **144** as a pale yellow oil in 95% yield (Scheme 39).




**Scheme 39**

### 3.3.14 EPR experiments on photolysis of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide (144)

The preceding amides delivered intense and well resolved EPR spectra for the delocalised cyclohexadienyl radicals, when initiated photochemically. An EPR sample was prepared (10 mg of amide **144** in 250 µl of DTBP), before being placed in the EPR cavity, which was held at the temperature of 230 K. The EPR spectra recorded at 250 K in the presence of UV light, had similar hfs to all the previous cyclohexadienyl radicals (Figure 4) and therefore confirmed the presence of radical **145** (Scheme 40 and Figure 4).

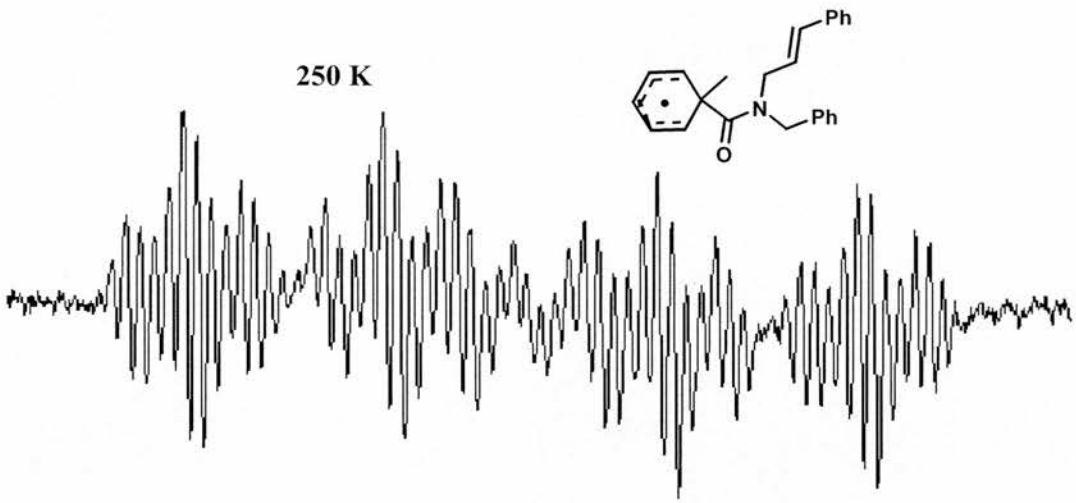


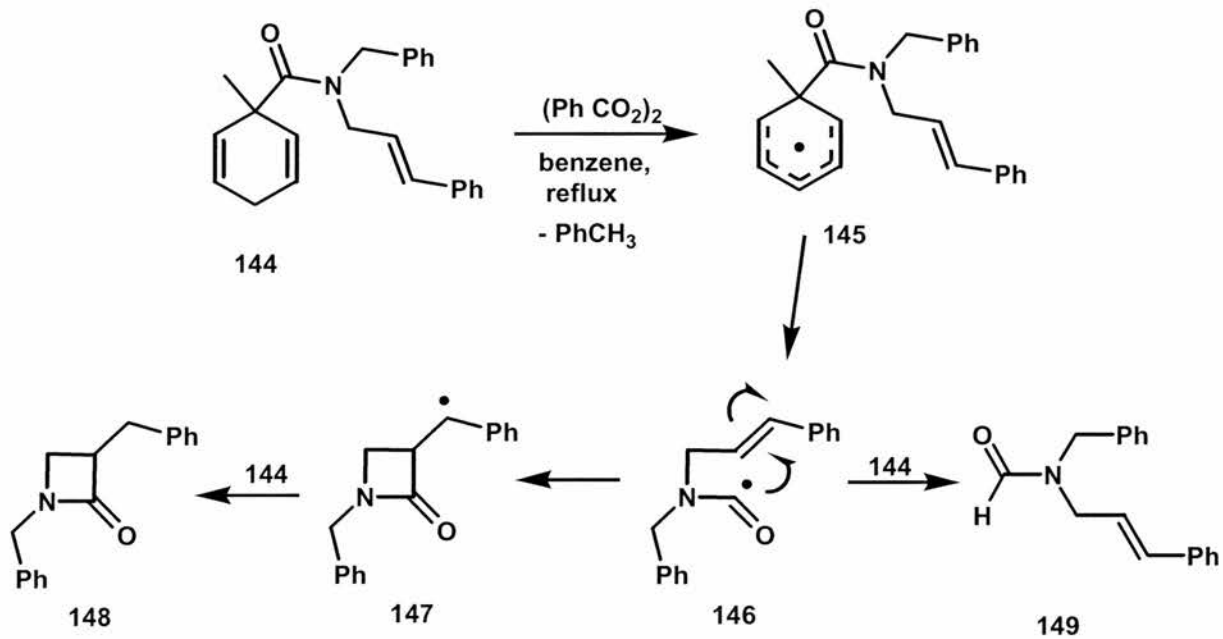

**Figure 4**

As the temperature of the EPR cavity was systematically increased to a maximum of 365 K, the spectrum attributed to cyclohexadienyl radical **145** diminished in size and was replaced by an undefined spectrum consting of several narrow lines, which it was not possible to assign either to the released aminoacyl radical **146** or to the formation of the stabilised benzyl radical **147**. However EPR spectra of benzyl radicals are typically characterised by small hfs and narrow lines, giving rise to complex EPR spectra which are difficult to observe and interpret. Our inability to detect radical **147** did not, therefore, rule out the occurrence of the cyclisation step.

### 3.3.15 DBP mediated thermolysis of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide (144)

We proceeded to investigate the thermally initiated radical fragmentation of amide **144** in order to examine the products formed on release of the γ,δ-unsaturatedaminoacyl radicals. We envisaged that β-lactam formation would be preferred over the competitive 5-*endo*-cyclisation for both kinetic and thermodynamic reasons. It was expected that the high regioselectivity of aminoacyl radical cyclisation and the resonance stabilisation of the cyclised benzyl type radical **147** would predominantly shift the equilibrium towards the formation of the 4-membered ring.

Slow addition of a benzene solution of dibenzoyl peroxide to a refluxing benzene solution of amide **144** furnished a complex mixture of products. GC-MS analysis revealed the presence of both cyclised product **148** and uncyclised formamide **149** (Scheme 40) in a 2:1 ratio together with by-products derived from the breakdown of the radical initiator. However GC-MS analysis revealed a reduced conversion of amide **144** which was detected as major component of the crude reaction mixture. The yield of cyclised product was modest (12 %), as determined by addition of a known amount of *N,N* dimethylbenzamide as standard to the crude reaction mixture and comparison with the measured integral value of suitable GC peaks.




**Scheme 40**

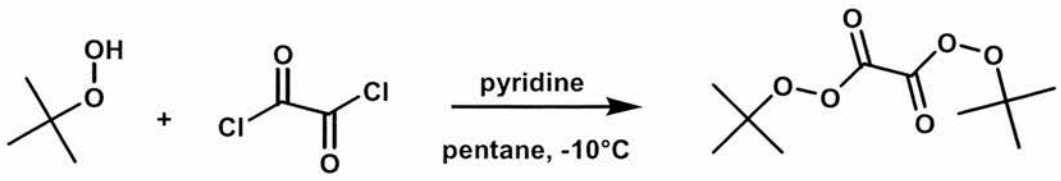
Although a series of different solvents and temperature conditions were tested in order to improve release of aminoacyl radical **146** and subsequent intramolecular radical cyclisation, no significant enhancements in product yields were observed. Therefore, it was impossible to drive the reaction to completion under these conditions.

### 3.3.16 DTBP mediated photolysis of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide (144)

In an attempt to improve β-lactam yields we also tested the photolytic radical fragmentation of cyclohexadienyl amide **144** using a benzene solution containing di-*tert* butyl peroxide as radical initiator which was irradiated with UV light, at 70 °C for 5h. Analysis by GC-MS of the crude reaction mixture revealed the presence of cyclised β-lactam **148**, uncyclised formamide **149** and starting amide **144** in a similar ratio and yields to that previously observed for the thermally DBP initiated reaction. The only detectable impurities were those derived from the photolytic breakdown of DTBP. One explanation for the low yield could be the slow H-atom donation by the cyclohexadienyl amide **144** due to the high thermodynamic stability of the benzyl radical intermediate **147** which will be a poor hydrogen abstractor. Chain propagation was consequently not very efficient and a large quantity of radical initiator was required in order to maintain the chain.

### 3.3.17 Preparation of di-*t*-butyl peroxyoxalate (DTBPO)

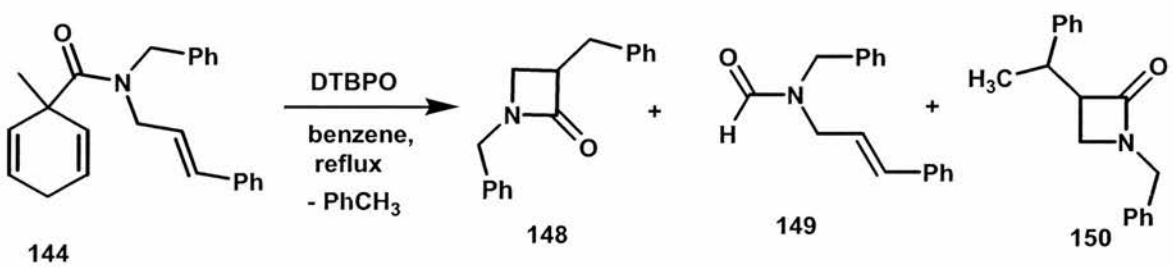
Di-*t*-butyl peroxyoxalate under thermolytic conditions undergoes concerted decomposition yielding carbon dioxide and *t*-butoxyl free radicals as primary decomposition products. This decomposition mechanism, in contrast to that of benzoyl peroxide, shows a greatly facilitated decomposition and lowered energy and entropy of activation. The advantage in the use of *t*-butyl peroxyoxalate as radical initiator is the increased propensity of the *t*-BuO$^{\cdot}$ radicals for hydrogen abstraction and its clean decomposition in benzene which affords just carbon dioxide, and *t*-butoxy radicals. The latter radical gives *t*-butyl alcohol and acetone as products from thermal breakdown, which can be easily removed from the reaction mixture. Therefore, this system might be particularly suitable to initiate thermally induced radical reactions, cleanly and under mild conditions. Di-*t*-butyl peroxyoxalate was readily prepared by dropwise addition of an anhydrous pentane solution of oxalyl chloride to a stirred solution of an equivalent quantity of commercially available *t*-butyl hydroperoxide and anhydrous pyridine in decane solution (Scheme 41).




**Scheme 41**

### 3.3.18 DTBPO mediated thermolysis of *N*-benzyl-1-methyl-*N*-3-phenyl-2-propenyl-2,5-cyclohexadiene-1-carboxamide (144)

*t*-Butoxyl radicals are electrophilic species. On the other hand, the hydrogen atoms in cyclohexadienyl carboxamides are nucleophilic. Therefore, the abstraction of hydrogen from cyclohexadienyl carboxamides by an alkoxyl radical could potentially lead to improved yields of cyclised product. In order to test this possibility, a thermally DTBPO mediated radical fragmentation of amide **144** was performed. A benzene solution containing DTBPO was added, over 8 hours, to a refluxing solution of pure amide **144** in benzene and the resulting mixture was left to reflux for a further 16 hours. GC-MS analysis of the crude reaction mixture revealed the presence of amide starting material, biphenyl, unknown polymerisation products, which probably derive from radical termination reactions, 1,3-dibenzyl-2-azetidinone **148** and formamide **149** in a 1.2:1 ratio respectively together with a small amount of 1-benzyl-3-(1-phenylethyl)-2-azetidinone **150** (Scheme 42).




**Scheme 42**

Treatment of the impure mixture of products with ether separated biphenyl which was filtered out of solution and the solvent evaporated at reduced pressure. The impure reaction mixture was purified by column chromatography which allowed us to

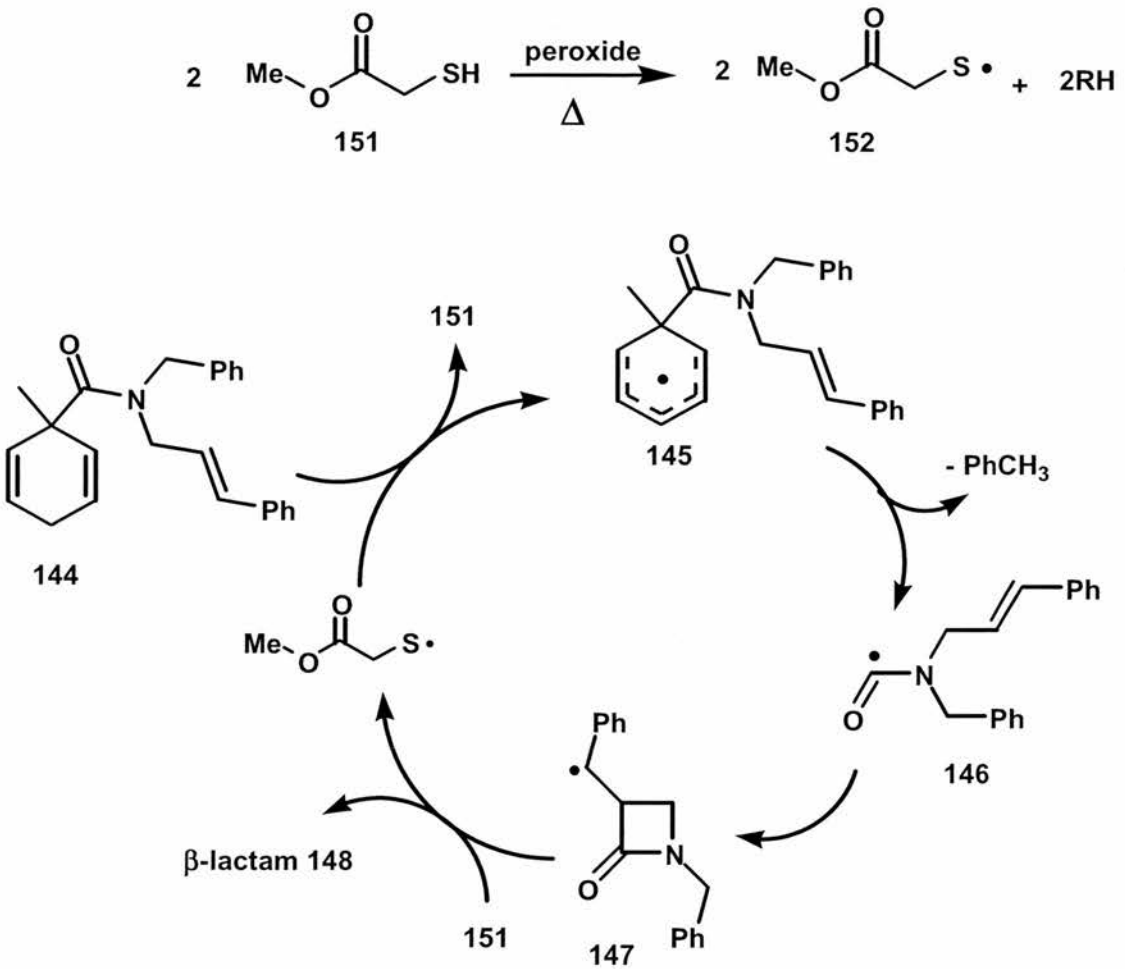
characterise the products. Yields were measured by GC- which indicated that cyclised β-lactam **148** was formed in 15% yield and uncyclised formamide **149**, (mixture of the two possible isomers) in a yield of 10 % together with azeditin-2-one **150** and unreacted starting amide **144** in 5% and 16 % yield respectively.

Although a cleaner system was found in these thermally induced reactions initiated with di-*t*-butyl peroxyoxalate (DTBPO) and photochemically initiated reactions with di-*t*-butyl peroxide (DTBP), the reactions were difficult to drive to completion under these conditions.

### 3.3.19 Polarity reversal catalysis (PRC) by thiols in thermolysis of *N*-benzyl-1-methyl-*N*-3-phenyl-2-propenyl-2,5-cyclohexadiene-1-carboxamide (144)

As mentioned previously, one of the reasons for the low β-lactam yields can be attributed to the formation of thermodynamically stabilised intermediate **147**, which leads to inefficient hydrogen abstraction from amide **144** allowing, therefore, radical termination reactions to compete. On the basis of these considerations we envisaged that addition of an H-donor could facilitate radical chain propagation. We chose methyl thioglycolate **151** which can also function as a polarity reversal catalyst. Carbamoylcyclohexadienyl radicals are nucleophilic. On the other hand, peroxide initiators usually release alkoxyl radicals that readily rearrange to alkyl radicals that are also electron rich. Therefore, the abstraction of hydrogen from carboxamide **144** by an alkyl radical to give the carbamoylcyclohexadienyl radical is unfavourable. We postulated that it would be possible overcome this problem by adding a catalytic amount of an alkanethiol, such as methyl thioglycolate **151**, in union with peroxides, to the reaction mixture.

In the chain, the carbon centred radical R• released from the initiator (Scheme 43) is readily reduced by the thiol catalyst to provide the corresponding reduced product RH, along with the thiyl radical **152**˙, then the thiyl radical should abstract hydrogen from carbamoyl amide **144** to generate the delocalised radical **145** which will release toluene to produce aminoacyl radical **146**. Intramolecular radical cyclisation of **146** gives cyclised benzyl radical **147** which can easily abstract hydrogen from thiol **151** to reproduce thiyl radical **152** and propagate the chain reaction.

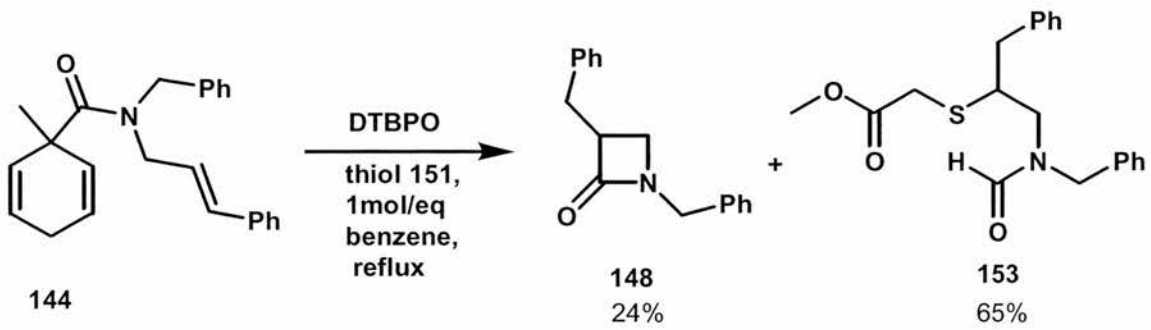



**Scheme 43**

A benzene solution containing DTBPO and 1.2 mol/equivalent of methyl thioglycolate was divided in four portions and added to a refluxing benzene solution of amide **144** over 12 h and then left to reflux for 24 h. GC-MS analysis of the crude reaction mixture confirmed the presence of the cyclised β-lactam **148** together with methyl ({1-benzyl-2-[benzyl(formyl)amino]ethyl}sulfanyl)acetate **153** (Scheme 44). The GC-MS spectra also detected the presence of only small amounts of unreacted starting material which meant that the reaction could go to completion under these conditions.

GC-MS and NMR spectra yield measurements showed that β-lactam **148** was formed in 24 % yield whereas formamide **153** was formed in 65% yield. Evidently the high concentration of thiyl radicals in solution, under these conditions, lead to the prevalent

formation of formamide **153** which was presumably produced by addition of thiyl radical **152** to the double bond of the formamide produced from uncyclised radical **146**.

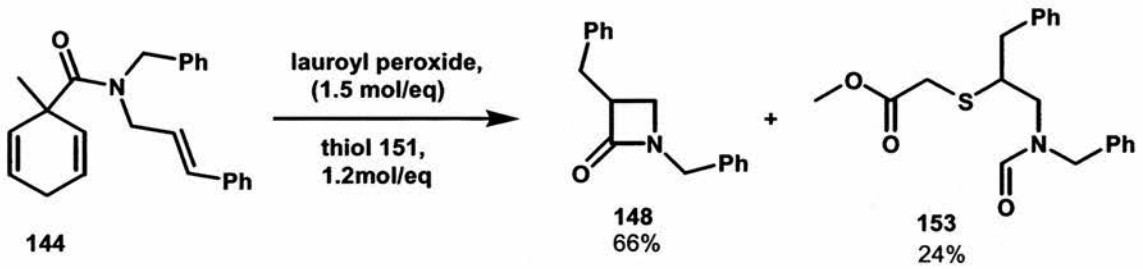



**Scheme 44**

The radical fragmentation of amide **144** was also carried out using a catalytic amount of thiol **151** in the same conditions as described above. GC-MS spectra of the crude product obtained from basic work-up of the reaction mixture revealed that starting amide **144** was totally converted under these conditions and, as predicted, formamide **153** was not formed when only a catalytic amount of thiol was added . The yields were calculated by measurement of the GC peak areas and confirmed from NMR spectral integration. Cyclised lactam **148** was formed in 38 % yield, together with 1-benzyl-3-(1-phenylethyl)-2-azetidinone **150** (28%) and a small amount of uncyclised formamide **149** (11%).

β-Lactam yields could probably be improved by reducing the equivalents of DTBPO or by employing a different radical initiator which does not release $CH_3$• in order to promote hydrogen abstraction by cyclised radical **147** over the undesired termination reaction leading to azetidin-2-ones such as **150**. On the basis of this consideration we performed a thermal fragmentation of amide **144** using dilauroyl peroxide as radical initiator which releases bulky alkyl radicals, by loss of carbon dioxide. Coupling of benzyl radical **147** with alkyl radical derived from dilauroyl peroxide was therefore unfavourable and desired H-abstraction occurred preferentially, to form β-lactam **148** (Scheme 45). GC-MS analysis of the crude product obtained from basic work-up of the reaction mixture showed the presence of products derived from thermal breakdown of dilauroyl peroxide and by-products derived from coupling of thiyl radicals **152**, and formamide **153** together with β-lactam **148** which were formed as major products in

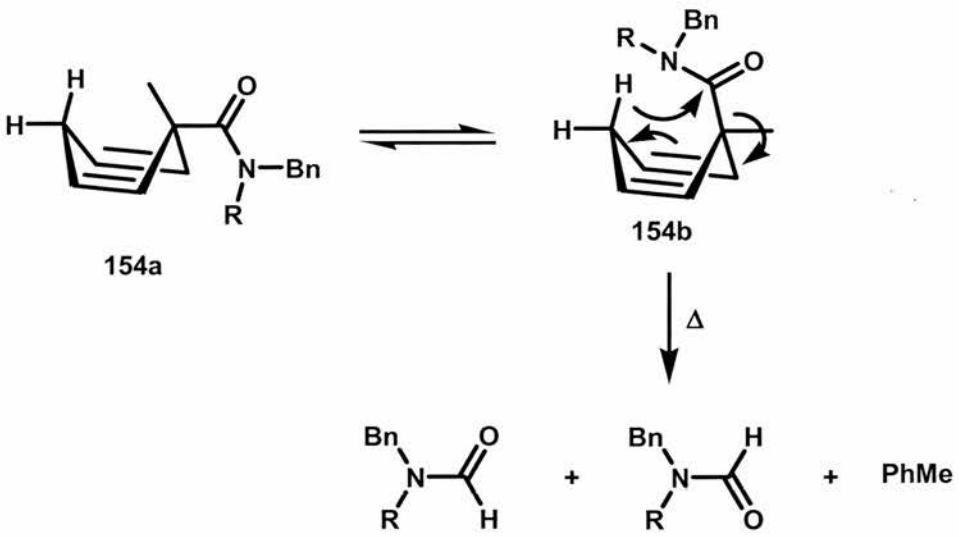
24% and 66% yields respectively. Formamide **149** was not observed under these conditions and only a small amount of unreacted amide **144** was detected (10%).




**Scheme 45**

# Summary and Conclusions

Thermolytic and photolytic fragmentation of unsatured amidocyclohedienes confirmed their ability to be good aminoacyl radical precursors from which ring closure afforded lactams in modest yields. Therefore, 4-*exo-trig*- and 5-*exo-trig*-cyclisation were allowed to proceed in order to generate the corresponding β- and γ-lactams. These physiologically important compounds were isolated and characterised. There was no evidence for the formation of products derived from the competing, unfavourable, 5-*endo* or 6-*endo* cyclisations. Kinetic EPR studies confirmed the dissociation rate constant for these compounds to be in the order of $10^2$ within the accessible temperature range. Significant yields of formamides accompanied all the cyclisations which appeared be formed from non-radical electrocyclic elimination. The lowest energy conformation of cyclohexadiene carboxamides is probably **154a** with the methyl group in pseudoaxial position. However there will be a minor component of conformer **154b** with the amide group in pseudoaxial position which could lead to electrocyclic elimination of formamide as shown in Scheme 46.




**Scheme 46**

A solution of cyclohexadiene carboxamide **125** in $CDCl_3$, in absence of radical initiator, was heated at 82°C and photolysed with UV light in a sealed tube. Monitoring by $^1H$ NMR showed no reaction after 23 h. Production of formamide by electrocyclic process was therefore ruled out. In conclusion the induced cyclohexadienyl amide decompositions represent 'clean' tin-free radical routes applicable for the preparation of a range of lactams from secondary amine starting materials.

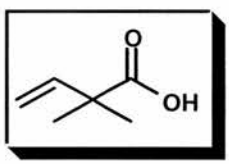
Polarity reversal catalysis in thermolysis of amide **144** using DTBPO and lauroyl peroxide as radical initiators facilitate hydrogen abstraction from carboxamide **144** leading to improved yields of cyclised β-lactam **144**. In conclusion, DTBPO mediated thermolysis of amide **144** with a catalytic amount of thiol **151**, seems to provide a system which is easy to purify. The high yield of β-lactam obtained from lauroyl peroxide mediated thermolysis of **144** in presence of thiol **151** looks very promising. However the number of by-products formed from thermolytic breakdown of lauroyl peroxide and coupling of thiyl radical make the purification difficult but the high yield of the strained β-lactam **148** would make further research into this area worthwhile. Consequently, cyclohexadienyl carboxamides provide a tin-free route to the synthesis of small and possibly medium size lactams, which are suitable for the conversion into useful, biologically active compounds. Strict time restraints prevented the optimisation of polarity reversal catalysis in thermolysis of cyclohexadiene carboxamides containing C-C double bond in β-position to the nitrogen atom; however, continuation of this work could provide and enhance the significance of these systems in the synthesis of natural products.

# Experimental

Chemicals and solvents were purchased from commercial sources and were used as received unless otherwise stated. Air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen) using oven dried glassware (145 °C). Analytical thin-layer chromatography (TLC) was performed on glass plates coated with silica gel (0.25 mm). Developed plates were air dried and analysed under a UV lamp (366 nm) and stained with ceric ammonium molybdate solution. Melting points were measured using an Electrothermal 9100 capillary melting point apparatus. $^{1}H$ Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300.1MHz) or a Varian Gemini 2000 (300 MHz) spectrometer. All chemical shifts δ are recorded in ppm using $CDCl_3$ ($\delta_H$ 7.27 ppm or $\delta_C$ 77.0 ppm), to dissolve the samples and as internal standard using the deuterated solvent as the lock and the residual solvent as the internal reference in all cases. $^{13}C$ NMR spectra using the PENDANT sequence were recorded on a Bruker Avance 300 (75.5 MHz) spectrometer. All other $^{13}C$ spectra were recorded on a Varian Gemini 2000 (75.5 MHz) spectrometer using composite pulse. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet, q, , multiplet and br, broad. The reporting of chemical shifts is in ppm and coupling constants (J) are calculated in Hz. Fourier Transform Infrared (FT IR) spectra were recorded as Nujol mulls for solids or neat for liquids on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer. Only selected absorptions are reported. Absorptions are reported in wavenumbers ($cm^{-1}$) Low resolution mass spectral analysis, (EI and CI) was recorded on a VG AUTOSPEC mass spectrometer or on an Agilent 5890 plus gas chromatograph equipped with a 5973N mass selective detector (EI mode) and 7683 series injector/ autosampler. Chromatographic separations were performed using a HP-5MS (5% Phenyl Methyl Siloxane) capillary column (30 m x 250 μm with a film thickness of 0.25 μm). Helium was used as a carrier gas. For the analysis 1 μl of solution was injected, the temperature of the injection port was 280°C, split 40:1, velocity 40 $cm.s^{-1}$ (1.2 $ml.min^{-1}$). The temperature program used was 50°C-hold 5 min then at 20°C.$min^{-1}$ to 290°C-hold 20 min. The solvent delay was 2.0 min. and the *m/z* ratio considered was

10-800. Electrospray mass spectrometry (ESMS) was recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only major peaks are reported and intensities are quoted as percentages of the base peak.

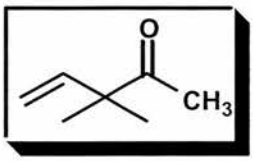
**Synthesis of 2,2-dimethyl-3-butenoic acid (121).[88]**




Dried magnesium turnings (30g) and sodium dried ether (300 $cm^3$) were placed in a 500 $cm^3$ round-bottom flask together with a catalytic amount of iodine. 1-chloro-3-methyl-2-butene (20g) was dissolved in dry diethyl ether (50 $cm^3$) and slowly added (0.33 $cm^3$/min) to the previous solution. A small amount of methylmagnesium iodide was used to initiate the reaction. After addition was complete, the gray suspension was stirred for 3 h.

A good yield of prenyl magnesium chloride was obtained when ether was used as solvent and the usual precautions against coupling[89] were observed. The above Grignard reagent was added to an excess of crushed dry ice, as recommended by Lane, Roberts and Young.[90] After the excess dry ice had evaporated, the mixture was hydrolyzed by stirring in concentrated hydrochloric acid (50 $cm^3$). The product was extracted from the ether layer with 2M NaOH and then the aqueous phase was acidified and extracted repeatedly with ether. The combined organic solutions were washed with saturated NaCl solution and dried over $MgSO_4$. The residue from the ether was distilled to afford 14 g (64% yield) of a clear liquid b.p.184-187°C (760 mm). $\delta_H$ (300 MHz, $CDCl_3$) 1.3 (6H, s, 2 x $CH_3$) 5.08-5.18 and 6.0 (3H, ABC system, -$CH{=}CH_2$), 11.6 (1H, broad OH); $\delta_c$ 24.3 (2 x $CH_3$), 44.7 (quaternary-C), 113.3 (olefinic-$CH_2$); 141.8 (olefinic-CH), 183.2 (C=O), IR (/$cm^{-1}$) 3000 (broad, carboxyl OH), 1695 (C=O), 1637 (C=C), and 925(CH=$CH_2$), *m/z* (rel. intensity) 114 ($M^+$, 3), 99 (14), 69 (72), 41 (100), and 39 (20), HRMS (EI) found 114.0695 ($M^+$) (calcd for $C_6H_{10}O_2$: 114.0681). Anal. calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.81, H, 8.53.

**Preparation of 3,3-dimethyl-4-penten-2-one (122)**

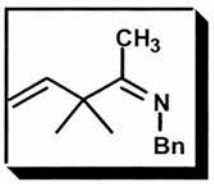



To a cold solution (-40 to -60°C) of 2,2-dimethyl-3-butenoic acid (3 g, 26.3 mmol) and ether (50 $cm^3$) was added, dropwise and with stirring and cooling, 40 $cm^3$ of an ether solution containing methyllithium (52.6 mmol). After approximately 1 equivalent of the methyllithium solution had been added and the vigorous evolution of methane subsided, the mixture was warmed and maintained at -10°C while the second equivalent of methyllithium was added. After the resulting viscous white suspension had been stirred at room temperature for 5 h, it was added, with vigorous stirring to a dilute aqueous solution of HCl and then extracted with ether. The ethereal extract was washed with NaOH, dried, and distilled yielding the title compound (2.1g, 71%) a colorless oil bp 115-117°C (760 mm). $\delta_H$(300MHz, $CDCl_3$) 1.2 (6H, s, 2 x $CH_3$), 2.1 (3H, s, $CH_3$), 5.1 and 5.9 (3H, ABC system, -CH=$CH_2$); $\delta_C$(300 MHz, $CDCl_3$) 23.4 (2 x $CH_3$), 25.3 ($CH_3$), 50.9 (quaternary-C), 114.1 (olefinic-$CH_2$), 142.4 (olefinic-CH), 209.9 (C=O), Ir($cm^{-1}$), 1710(C=O), 1635(C=C), and 935(CH=$CH_2$), MS, *m/z* 112($M^+$, 25), 97(27), 70(21), 69(72), 59,(13), 43(100), 41(77).

**Attempted sodium cyanoborohydride reductive amination of ketone 122**[91]

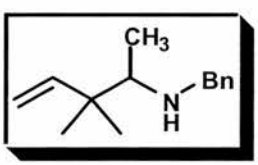
To a stirred solution of benzylamine (0.30g, 2.80mmol) in MeOH (10 $cm^3$) was added methanolic HCl (6M) so as to adjust the pH to 6-7. Ketone **134** (0.3g, 2.67 mmol) was then added followed by $NaBH_3CN$ (0.17g, 2.65 mmol), and the mixture stoppered, and stirred at room temperature for 20 h. The MeOH was then removed at reduced pressure, before addition of water (20ml) and $KOH_{(s)}$ so as to adjust the pH to > 10. The aqueous layer was saturated with NaCl and then extracted with ether (3 x 25ml). The combined organic extracts were washed with 20% $FeSO_4$ 2 x 40 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was analysed by NMR which revealed only a low amount of amine **138** and unreacted starting material.

**Preparation of *N*-phenylmethyl-*N*-(1,2,2-trimethyl-3-butenylidene) amine (123)**




Benzylamine (2g, 18.7 mmol) 3,3 dimethyl-4 penten-2-one (2.1g, 18.7 mmol) together with a catalytic amount of zinc chloride (~ 50 mg) were refluxed in toluene (40 $cm^3$) with azeotropic removal of water via a Dean and Stark trap. The mixture was then cooled, the catalyst was filtered off, and the solution evaporated under reduced pressure to yield (2.56g, 68% yield) a viscous yellow oil. The crude product was purified by distillation in vacuo. $\delta_H$ (300 MHz, $CDCl_3$) 1.2 (6H, s, 2 x $CH_3$), 1.8 (3H, s, $CH_3$), 4.5 (2H, s, benzylic-$CH_2$) 5.0 (2H, m, olefinic-$CH_2$), 5.9 (1H, m, olefinic-CH), 7.1-7.3 (5H, m, phenyl); $\delta_c$($CDCl_3$) 14.4 ($CH_3$), 24.8 (2 x $CH_3$), 47.3 (quaternary-C), 54. (benzylic- $CH_2$), 112.2 (olefinic-$CH_2$), 126.2 (CH), 127.2 (CH), 128.1 (CH), 140.7 (quaternary-C), 145.5 (olefinic-CH), 174.0 (C=N).

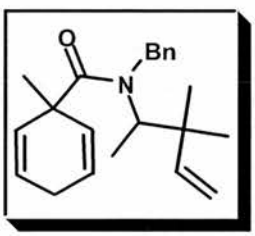
**Preparation of *N*-benzyl-3,3-dimethyl-4-penten-2-amine (124)**




Sodium borohydride (0.2g, 5.3 mmol) was added portion wise over a period of 10 min to a stirred and cooled (0 °C) solution of the imine (2.56g, 12.7 mmol) in dry methanol (40 $cm^3$) under an atmosphere of nitrogen. The solution allowed to warm to room temperature and then stirred for 20h, during which time the yellow colour of the solution faded. The solution was cooled (0 °C) before concentrated HCl was added dropwise until the mixture attained pH 1. The resulting suspension was evaporated under reduced pressure to leave a white solid residue. The residue was dissolved in water (50 $cm^3$) and the resulting aqueous solution was washed with ether (2 x 100 $cm^3$). The remaining aqueous solution was brought to pH 10 by careful addition of potassium hydroxide pellets, and the liberated amine was extracted into ether (3 x 100 $cm^3$). The combined organic phases were dried ($MgSO_4$) and then evaporated to dryness under reduced pressure to leave a pale yellow oil. The impure product was

purified by distillation to yield the title amine (1.63g, 63%) as a colorless liquid; $\delta_H$(300 MHz, $CDCl_3$) 0.9-1.0 (9H, 3 x $CH_3$), 2.3 (1H, q, CH, $^3J$=6.27 Hz), 3.7 (2H, AB system, benzylic-$CH_2$, $^2J$=13.5), 5.0 (2H, m, olefinic-$CH_2$), 5.7 (1H, m, olefinic- CH), 7.2-7.3 (5H, m, ArH). $\delta_C$($CDCl_3$) 14.5 ($CH_3$), 21.9 ($CH_3$), 24.4 ($CH_3$), 40.9 (quaternary-C), 52.2 (benzylic-$CH_2$), 59.8(CH), 112.0 (olefinic-$CH_2$), 126.66, 128.09, 128.20 (5 x ArH), 140.9 (quaternary-C), 146.8 (olefinic-CH). IR (neat): 3083, 3026, 2967, 1637, 1628, 1453, 1413, 1372, 1128, 912, 735, 697. Mass spectrum (CI) m/e (%) 204($M^+$+1, 100), 167(10), 134(17), 57(24). HRMS m/*z* (Found $M^+$+ 1 204.1745, $C_{14}H_{22}N$ requires $M^+$+ 1 204.1752).

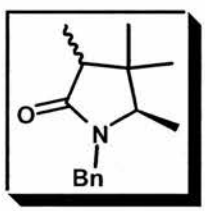
**Preparation of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide (125).**




To a rapidly stirred solution containing *N*-benzyl-3,3-dimethyl-4-penten-2-amine (1.63g, 8.0 mol), TEA (1.2g, 12 mmol), and a catalytic amount of DMAP in dry DCM (30 $cm^3$), was added, dropwise, a DCM solution (5 $cm^3$) containing 1-methyl-2,5-cyclohexadiene-1-carbonyl chloride (1.30g, 8.3 mmol). The resulting solution was refluxed for 8h before removing the solvent at reduced pressure to leave the desired amide as viscous yellow oil. The impure product was taken up into ether (50 $cm^3$) and washed with dilute NaOH (50 $cm^3$). The organic fraction was dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Finally this crude product was purified by column chromatography on silica gel using ethyl acetate-hexane 1:9 as eluent yielding the pure amide (1.91g, 74%) as a pale yellow oil. $\delta_H$(300 MHz, $CDCl_3$) 1.00 (3H, s, $CH_3$), 1.10 (3H, s, $CH_3$), 1.13 (3H, d, $CH_3$), 1.30 (3H, s, $CH_3$), 2.43-2.87 (2H, br m, allylic-$CH_2$), 4.14 and 4.73 (2H, AB system, benzylic-$CH_2$), 4.46 (1H, q, J=6.75, CH), 4.99-5.05 and 5.80-6.05 (7H, m, olefinic-CH), 7.05-7.37 (5H, m, ArH); $\delta_C$($CDCl_3$) 15.05 ($CH_3$), 23.46 ($CH_3$), 25.78 ($CH_3$), 27.96 ($CH_3$), 29.67 (bisallylic-$CH_2$), 41.45 (quaternary-C), 45.67 (quaternary-C), 47.12 (benzylic-$CH_2$), 59.25 (CH), 112.69 (olefinic-$CH_2$), 122.26 (olefinic-CH), 122.35 (olefinic-CH), 126.11, 126.35, 129.09 (5xCH), 130.80 (olefinic-CH), 132.42 (olefinic-

CH), 139.70 (quaternary-C), 145.32 (olefinic-CH), 174.41 (C=O). IR (neat) $cm^{-1}$: 1724 (stretch CH), 1168, 921, 701; MS (CI) m/z (%) 324($M^+$+1, 100), 254(9), 230(11), 58(7), and 43(29). HRMS m/*z*, (Found $M^+$+1 324.2339, $C_{22}H_{30}NO$ requires $M^+$+1 324.2327).

**Thermally initiated reaction of *N*-benzyl-1-methyl-*N*-(1,2,2-trimethyl-3-butenyl)-2,5-cyclohexadiene-1-carboxamide (125)**



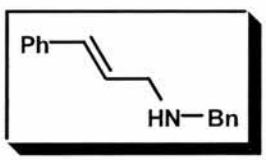

Amide **125** (0.15g, 0.46 mmol) was dissolved in benzene (5 $cm^3$) and heated to reflux before dibenzoyl peroxide (0.12g, 0.50mmol) was added portionwise over a period of 24h. After complete addition, the solvent was evaporated before dissolving the impure product in ether (30$cm^3$), washing with NaOH (30 $cm^3$), HCl (30 $cm^3$) and water (2 x 50 $cm^3$) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil 0.28g (26%), which was analysed by GC/MS; peak no.403, benzoic acid (from initiator); peak no. 423, biphenyl (from initiator); peak no.528, phenyl benzoate (from initiator; peak nos. 583 and 590 (identical MS), *cis*- and *trans*-1-benzyl-3,4,4,5-tetramethyl-2-pyrrolidinone), **129** *m/z* (relative intensity) 231 ($M^+$, 59), 216 (42), 161 (6), 140 (9), 134 (17), 106 (10), 91 (100), 83 (11), 70 (10), 65 (9), 55 (14); peak no. 717, unreacted amide. The product was purified by column chromatography, eluting with 10% ethyl acetate in hexane to give γ-lactam **129** a mixture of the two diastereoisomers (4:1) (0.018 g, 17%), major isomer (60% de) $\delta_H$ (300 MHz, $CDCl_3$) 0.80 (3H, s, $CH_3$), 0.98 (3H, s, $CH_3$), 1.02 (3H, d, $CH_3$, $^3J$=6.75), 1.07 (3H, d, CH, $^3J$=7.72), 2.29 (1H, q, CH, $^3J$=7.23), 2.98 (1H, q, CH, $^3J$=6.75), 3.87 (1H, d, benzylic-$CH_2$, $^2J$=14.95), 5.02 (1H, d, benzylic-$CH_2$, $^2J$=14.95), 7.22-7.31 (5H, m, ArH); major isomer $\delta_c$ ($CDCl_3$) 9.07 ($CH_3$), 13.10 ($CH_3$), 22.77 (2 x $CH_3$), 38.91 (quaternary- C), 44.23 (CH), 45.38 (benzylic-$CH_2$), 60.77 (CH), 127.38, 128.26, 128.51 (5 x ArH), 136.93 (quaternary-C), 176.14 (C=O); IR (nujol) ($cm^{-1}$), 1682, (C=O), 1268 and 701; minor isomer $\delta_H$ (300 MHz, $CDCl_3$) 0.74 (3H, s, $CH_3$), 0.95 (3H, s, $CH_3$), 1.03 (3H, d, $CH_3$, $^3J$=6.75), 1.11 (3H, d, CH, $^3J$=7.23), 2.17 (1H, q, CH, $^3J$=7.23), 3.14 (1H, q, CH, $^3J$=6.75), 4.00 (1H, d, benzylic-$CH_2$, $^2J$=14.95), 4.94 (1H, d,

benzylic-$CH_2$, $^2J$=14.95), 7.22-7.31 (5H, m, ArH); minor isomer $\delta_c$ ($CDCl_3$) 12.65 ($CH_3$), 16.34 ($CH_3$), 22.47 (2 x $CH_3$), 39.01 (quaternary- C), 43.92 (CH), 48.22 (benzylic-$CH_2$), 60.89 (CH), 127.19, 128.11, 128.17 (5 x ArH), 137.26 (quaternary-C), 169.06 (C=O). Mass spectrum (CI) *m/z* (%) 204 ($M^+$+1, 100), 167(10), 134(17), 57(24). Mass spectrum (EI) *m/z* (%) 231($M^+$, 58), 216(49), 134(26), 91(100). HRMS *m/z* (Found $M^+$ 231.1625, $C_{15}H_{21}NO$ requires $M^+$ 231.1623).

**Photochemically initiated reaction of amide 125**

Amide **125** (0.03 g) was dissolved in DTBP (200 µl) and placed in a quartz tube. The tube was capped and irradiated 60°C with light from a 400 W high pressure Hg lamp for 7 h before DTBP was removed from the reaction mixture by warming the mixture under high vacuum to leave a yellow crude oil. Analysis of the reaction mixture by GC/MS confirmed the presence of *cis*- and *trans*-N-benzyl-3,4,4,5-tetramethyl-2-pyrrolidinone isomers **129** (ratio 1:5.4 de = 69%) together with unreacted **125** and impurities derived from the photolytic breakdown of DTBP. Benzyl(1,2,2-trimethyl-3-butenyl) formamide **138** was formed only in traces, but 1-benzyl-4,4,5-trimethyl-3-methylene-pyrrolidin-2-one **139**, *m/z* (%) 229 ($M^+$, 54), 228 (54), 214 (13), 196 (31), 131 (37), 119 (54), 105 (35), 91 (100), 77 (22) and 1-benzyl-3-ethyl-4,4,5-trimethyl-pyrrolidin-2-one **140** *m/z* (%) 245 ($M^+$, 19), 231 (16), 178 (15), 162 (29), 134 (26), 105 (30), 91 (100), 57 (15) were observed as minor components. NMR yield measurements, using *N*,*N*-dimethylbenzamide as standard, confirmed that the pyrrolidinone **129** was formed in 21% yield.

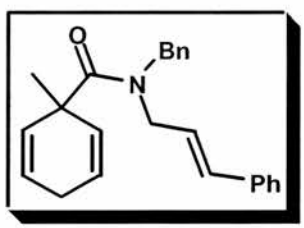
**Preparation of *N*-benzyl-3-phenyl-2-propen-1-amine (142)**[92]




3-Chloro-1-propenylbenzene (5g, 32.8mmol) in diethyl ether (60ml) was added dropwise to a stirred solution of the benzyl amine (19g, 177mmol) in diethyl ether (30 ml). The reaction mixture was refluxed for 1h, stirred overnight at room temperature and then the solvent was removed at reduced pressure. The mixture was diluted with water (200 ml), acidified with dilute hydrochloric acid and stirred for 1h maintaining

the pH acid. The aqueous solution was filtered before dissolving the precipitate in aqueous NaOH (100ml, 2M) and extracted with ether to yield a pale yellow oil, which was purified by column chromatography, eluting with 5% ethylacetate in hexane in order to furnish *N*-benzyl-3-phenyl-*N*-(3-phenyl-2-propenyl)-2-propen-1-amine **143** $\delta_H$ (300 MHz, $CDCl_3$) 1.50 (1H, s, NH exchangeable), 3.29 (4H, d, $CH_2$, $^3J$=6.34), 3.68 (2H, s, benzylic-$CH_2$), 6.22-6.59 (4H, m, AB system, olefinic-CH), 7.18-7.41 (15H, m, ArH) and the desired amine (4.7g, 64%) as a colourless oil. $\delta_H$ (300 MHz, $CDCl_3$) 1.50 (1H, s, NH exchangeable), 3.42 (2H, d, $CH_2$, $^3J$=6.27), 3.81 (2H, s, benzylic-$CH_2$), 6.23-6.56 (2H, m, AB system, olefinic-CH), 7.18-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$) 51.68 (allylic-$CH_2$), 53.80 (benzylic $CH_2$), 126.75 (2 x ArH), 127.46 (olefinic-CH), 127.82, 128.68, 128.91, 129.02 (8 x ArH), 131.83 (olefinic-CH), 137.60 (quaternary-C), 140.70 (quaternary- C). IR ($cm^{-1}$) 3020 (NH), 1670 (C=C), 1515 (C=C), and 1340 (CH=CH). Mass spectrum (EI) *m/z* (%) 223($M^+$, 37), 132(100), 117(26), 105(26), 91(94), 65(12); HRMS m/*z* [Found: $(M)^+$ 223.1356, $C_{16}H_{17}N$ requires $(M)^+$ 223.1361].

**Preparation of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide (144)**




Methyl-2,5-cyclohexadiene-1-carbonyl chloride (1.6g, 10 mmol) was dissolved in dry dichloromethane (10 $cm^3$) and added dropwise to a mixture of *N*-benzyl-3-phenyl-2-propen-1-amine (1.g, 4.5mmol), triethylamine (1g, 10 mmol), and a catalytic amount of DMAP in dry dichloromethane (20 $cm^3$). The resultant mixture was refluxed for 8 h before stirring with water (100 $cm^3$) and drying (Mg $SO_4$). The solvent was evaporated at reduced pressure to give the crude product as brown oil, which was purified by column chromatography; $R_f$ = 0.52 (silica, EtOAc: hexane 3:7) yielding the desired amide (1.46 g, 95%) as a colorless oil; $\delta_H$ (300MHz, $CDCl_3$) 1.40 (3H, s, $CH_3$), 2.43-2.86 (2H, m, bisallylic-$CH_2$), 4.00-4.17 (2H, m, N-$\underline{CH_2}$), 4.60-4.72 (2H, m, benzylic-$CH_2$), 5.66-6.32 (6H, m, olefinic-CH), 7.18-7.34 (10H,m, ArH); $\delta_c$ ($CDCl_3$) 25.80 (bisallylic-$CH_2$), 28.78 ($CH_3$), 45.07 (quaternary-C), 48.07, 48.40 (N-$\underline{CH_2}$), 48.80, 52.83 (benzylic, $CH_2$), 123.07 (2 x olefinic-CH), 126.27, 126.98, 127.16, 128.44,

128.50 (10 x ArH ), 127.62 (olefinic-CH), 130.43 (2 x olefinic-CH), 132.65 (olefinic-CH), 136.55 (quaternary-C), 137.77 (quaternary-C), 173.66 (C=O); IR (nujol) $cm^{-1}$: 1712 (C=O, stretch), 1586 (C=C), 1270 (C=C), 711; MS (CI) *m/z* (%) 344($M^+$+1, 100), 252(12), 117(7), 58(7). HRMS m/*z* (Found: $M^+$+1 344.2022, $C_{30}H_{26}NO$ requires $M^+$+1 344.2014).

**DBP mediated thermolysis of *N*-benzyl-1-methyl-N-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide(144)**

Dibenzoyl peroxide (0.3 g, 1.2 mmol) was dissolved in benzene (2 $cm^3$) and added dropwise over a period of 24 h, by using a syringe pump, to a refluxing benzene solution (7 $cm^3$) containing amide **144** (0.3 g, 0.9 mmol). After complete addition, the mixture was left to reflux for 24 h. The solvent was evaporated before dissolving the impure product in ether (50 $cm^3$), washing with NaOH (2 × 50 $cm^3$), HCl (2 × 50 $cm^3$) and water (2 × 50 $cm^3$) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil (0.25 g), GC/MS peak no. 330, biphenyl (from initiator); peak no 438 phenyl benzoate; (from initiator); peak no.512 and 591, triphenyl, (from initiator); peak no 569, *N*-benzylbenzamide, peak no.618, 1,3-dibenzyl azetidin-2-one **148** (12%), *m/z* (relative intensity) 251 ($M^+$, 7) 160 (9), 118 (100), 117 (82), 105 (5), 91 (55), 77 (7) 65 (15), peak no.648 *N*-benzyl-(3-phenyl-2-propenyl)formamide **149** (5%), *m/z* (relative intensity) 251 ($M^+$, 20), 160 (55), 134 (8), 115 (100), 105 (10), 91 (65), 77 (9), 65 (12); peak no. 772, unreacted amide **144** (64%)

**DTBP mediated photolysis of *N*-benzyl-1-methyl-*N*-3-phenyl-2-propenyl-2,5-cyclohexadiene-1-carboxamide(144)**

Amide **144** (0.2 g, 0.6 mmol) was dissolved benzene (2 $cm^3$), which contained DTBP (0.5g, 3.42 mmol). The resultant solution was placed in a quartz tube, heated to 70 °C using a quartz paraffin oil bath and the sample was irradiated with light from a 400 W medium pressure Hg lamp over an 8 h period. Analysis of the reaction mixture by GC/MS indicated that photolytic radical fragmentation of cyclohexadienyl amide **144** lead to identical peaks in the GC/MS to those observed with the thermally initiated radical reaction. GC-MS measurement using *N*,*N*-dimethylbenzamide as a standard,

demonstrated that the β-lactam **148** and formamide **149** were formed in a similar percentage to that obtained from thermal decomposition.

**Preparation of di-*t*-butyl peroxyoxalate**[93]

Oxalyl chloride (3.2 g, 25 mmol) in pentane (20 $cm^3$) was added over 20 minutes to a stirred cold solution (- 10°C) of pyridine (4g, 50 mmol) and *t*-butyl hydroperoxide (4.5 $cm^3$) of a 5.5 M decane solution, 25 mmol) in pentane (50 $cm^3$). During the addition the temperature was held between -10 and 0°C. The solution was allowed to warm slowly to near room temperature and the pyridinium chloride was filtered off and washed with cold pentane. The combined filtrate was cooled in a dry ice-acetone mixture and allowed to stand about 30 min. to precipitate the perester as fine white crystals. The perester was collected quickly in a sintered glass filter, dissolved in a minimal amount of pure pentane at room temperature and the solution dried with magnesium sulphate. When this solution was cooled down (-50 to -70°C) long clear crystals of perester were formed. The crystals were filtered off and stored at -25°C. The yield was 3.5 g, (60%). With melting point 50.5-51 °C. It was necessary to take precautions when transferring the crystals, especially when they are completely free of solvent. Anal. calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.20, H, 7.57.

**DTBPO mediated thermolysis of *N*-benzyl-1-methyl-*N*-(3-phenyl-2-propenyl)-2,5-cyclohexadiene-1-carboxamide(144)**

Amide **144** (0.2 g, 0.6 mmol) was dissolved in benzene (10 $cm^3$) and heated to reflux before DTBPO (0.25 g, 1 mmol) was added, by syringe pump, over a period of 8 h. After complete addition, the solvent was evaporated before dissolving the mixture in ether (30 $cm^3$); a residue separated from the organic layer which was filtered off the solution. The solvent was evaporated under reduced pressure to yield a yellow oil (0.25 g). GC/MS, peak min. 14.77, biphenyl (from initiator); peak min. 23.95, 1,3-dibenzyl azetidin-2-one **148**, (15.4%), *m/z* (relative intensity) 251 ($M^+$, 7) 160 (9), 118 (100), 117(82), 105 (5), 91 (55), 77 (7) 65 (15); peak min. 24.74, N-benzyl-(3-phenyl-2-propenyl)formamide ) **149**, (10.1%), *m/z* (relative intensity) 251 ($M^+$, 20), 160 (55),

134 (8), 115 (100), 105 (10), 91 (65), 77 (9), 65 (12) (unresolved isomers); peak min. 25.54, 1-benzyl-3-(1-phenylethyl)-2-azetidinone **150** (4.5%), *m/z* (relative intensity), 265 ($M^+$, 5), 237 (8), 207 (15), 174 (58), 105 (63), 91 (100), 77 (43), 65 (10), 28 (100), 18(32), peak min. 29.10, unreacted amide (15.74%). The product was purified by column chromatography, eluting with 20% ethyl acetate in hexane to give the β-lactam, **148**; $\delta_H$ (300MHz, $CDCl_3$) 2.87-2.90 and 3.17 (2H, m, $^3J$= 2.41, $J_{gem}$ = 5.31 Hz, CH2), 2.91-3.13 (2H, ddd, $^2J$= 14.47, $^3$J= 4.82 and 8.2Hz, AB system, benzylic-$CH_2$), 3.51 (1H, m CH), 4.17-4.47 (2H, dd, $J$=15.44 Hz, AB system, benzylic-N$CH_2$), 7.18-7.40 (10H, m, ArH), $\delta_C$ (75 MHz, $CDCl_3$) 34.2 (benzylic ($CH_2$), 43.9 (CH), 45.7 (benzylic $CH_2$), 50.7 ($CH_2$), 126.6, 127.6, 127.9, 128.6 128.7, 129.1 (10 × CH), 135.5 (C), 138.0 (C) 169.7 (C=O); IR ($\nu_{max}$ $cm^{-1}$) 1740; HRMS (FAB) *m/z* (found: ($M^+$+1) 252.1390.$C_{17}H_{18}NO$: requires ($M^+$+1) 252.1388). The mixture of *cis*- and *trans*-N-benzyl-(3-phenyl-2-propenyl)formamides **149** (major:minor = 1.4:1) $\delta_H$ (300MHz) (major isomer shifts first), 3.89, 4.01 (2x2 H, d, $J$=6.75 $CH_2$), 4.41, 4.57 (2x2 H, s, $CH_2$) 5.98-6.50 (2x2 H, br m, CH), 7.12-7.45 (2x10 H, m, Ar H), 8.30, 8.36 (2x 1 H, s, HC=O).

**Polarity reversal catalysis (PRC) by thiols in thermolysis of *N*-benzyl-1-methyl-*N*-3-phenyl-2-propenyl-2,5-cyclohexadiene-1-carboxamide(144)**

**1. Initiated by DTBPO**

DTBPO (0.1g, 0.43 mmol) was dissolved in benzene (1.5 $cm^3$) and added portionwise, over 12 h, to a refluxing benzene solution containing amide **144** (0.1g, 0.3 mmol) and methyl thioglycolate **151** (0.032 g, 0.3 mmol). After complete addition the solution was refluxed for 24 h, the solvent evaporated at reduced pressure leaving a crude product which was dissolved into DCM (20 $cm^3$) and treated with a warm 6M solution of KOH (50 $cm^3$). The aqueous phase was extracted 3 times with DCM (3x25 $cm^3$) and the combined organic layer evaporated at reduced pressure to leave a yellow crude product. GC-MS, peak min. 23.95 1,3-dibenzylazetidin-2-one **148**, (24%), $\delta_H$ (300MHz, $CDCl_3$) 2.87-2.90 and 3.17 (2H, m, $^3J$= 2.41, $J_{gem}$ = 5.31 Hz, CH2), 2.91-3.13 (2H, ddd, $^2J$= 14.47, $^3$J= 4.82 and 8.2Hz), AB system, benzylic-$CH_2$), 3.51 (1H, m

CH), 4.17-4.47 (2H, dd, *J*=15.44 Hz, AB system, benzylic-N$\underline{CH_2}$), 7.18-7.40 (5H, m, ArH), *m/z* (relative intensity) 251 ($M^+$, 7) 160 (9), 118 (100), 117(82), 105 (5), 91 (55), 77 (7) 65 (15); peak min. 28.56 *cis* and *trans*-methyl({1-benzyl-2-[benzyl(formyl) amino]ethyl}sulfanyl)acetate **153** (65%), *m/z* (relative intensity) 357 ($M^+$, 2) 284 (22), 252 (40), 222(25), 177 (10), 160 (8), 149 (28), 116 (20), 91 (100), 77 (5) 65 (12), peak min. 29.10, unreacted amide. **144**. When only a catalytic amount of thiol **151** was used the yield of β-lactam **148** increased to 38%, sulfanyl formamide **153** was not detected, only 11% of formamide **149** together with 28% of azetidin-2-one **150** was formed under these conditions.

## 2. Initiated by lauroyl peroxide

Amide **144** (0.1 g, 0.3 mmol) was dissolved in benzene (7 $cm^3$) and heated to reflux before lauroyl peroxide (total 0.18 g, 0.45 mmol) in benzene (3 $cm^3$) was added in portions (0.35 $cm^3$ of soln.) over a period of 8 h. Following the first addition, the solution was refluxed for 5 min and then methyl thioglycolate **151** (0.032 g, 0.3 mmol) was added. After complete addition, the solvent was evaporated to yield a yellow crude product. GC-MS, peak min. 3.61, methyl thioglycolate **151**, peak min. 10.28, undecane (from initiator), peak min. 16.13, disulphide (dimer of thiol **151**), peak min. 17.10, lauric acid (from initiator) peak min. 23.45, docosane (from initiator), peak min. 23.95, 1,3-dibenzylazetidin-2-one **148**, (66%), $\delta_H$ (300MHz, $CDCl_3$) 2.87-2.90 and 3.17 (2H, m, $^3J$= 2.41, $J_{gem}$ = 5.31 Hz, CH2), 2.91-3.13 (2H, ddd, $^2J$= 14.47, $^3$J= 4.82 and 8.2Hz), AB system, benzylic-$CH_2$), 3.51 (1H, m CH), 4.17-4.47 (2H, dd, *J*=15.44 Hz, AB system, benzylic-N$\underline{CH_2}$), 7.18-7.40 (5H, m, ArH), MS (EI) m/z (%), 251 ($M^+$, 7) 160 (9), 118 (100), 117(82), 105 (5), 91 (55), 77 (7) 65 (15); peak min. 25.70, undecyl laurate (from initiator), peak min. 28.56 *cis* and *trans*-methyl({1-benzyl-2-[benzyl(formyl) amino]ethyl}sulfanyl)acetate **153** (24%), *m/z* (relative intensity) 357 ($M^+$, 2) 284 (22), 252 (40), 222(25), 177 (10), 160 (8), 149 (28), 116 (20), 91 (100), 77 (5) 65 (12), peak min. 29.10 (10%), unreacted amide **144**.

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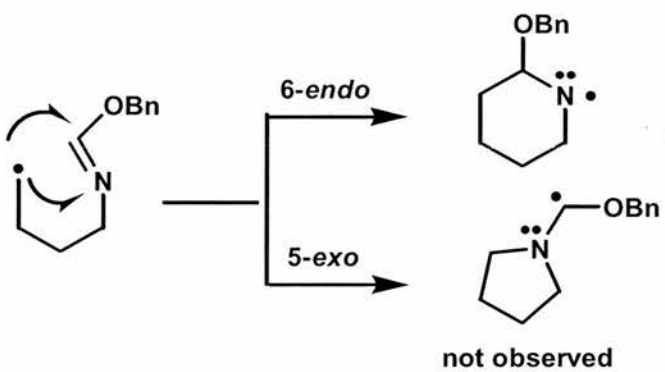
# Chapter 4

# Preparation of benzopyrrolidinones *via* cyclisation of aminoacyl radicals onto oxime ether functionality

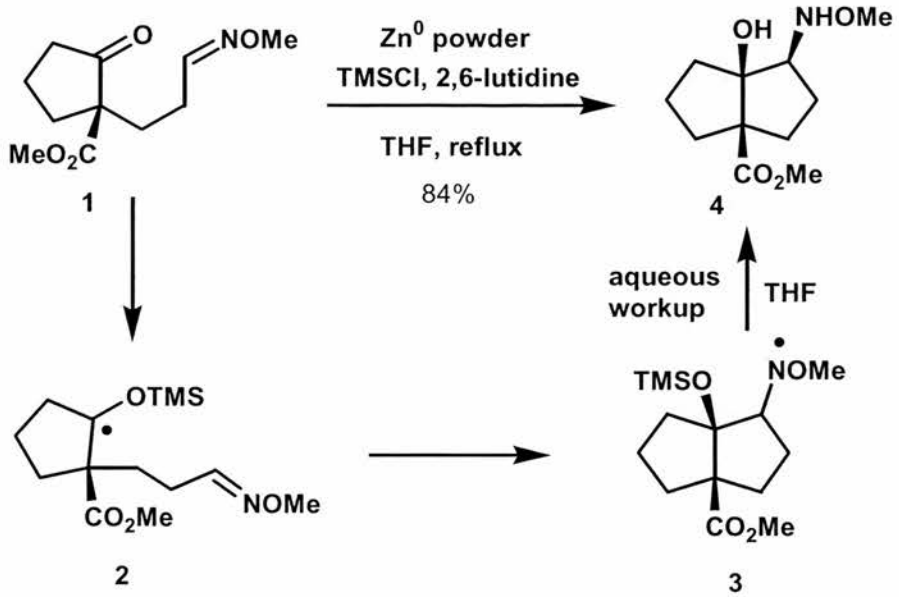
# 4.1 Introduction

The demand for efficient, mild and general synthetic methodology makes radical addition to oxime ethers an increasingly important alternative. This particular functional group can exhibit up to three orders of magnitude higher radical addition rates than the analogues alkene acceptors.[1] Moreover a useful functional group remains available for further synthetic elaboration, either by fragmentation or by traditional functional group transformation of closed-shell products. Currently, radical addition onto oxime ether derivatives is rapidly developing and is becoming a reliable synthetic strategy which can efficiently be applied in syntheses of complex natural products.[2-5] Oximes are by far the most commonly used radical receptors among the various C=N containing functional groups[6-14] because of their extraordinary stability to hydrolysis and tautomerization with respect to the analogous imines, moreover attack at the carbon of the C=N bond is almost exclusively observed. This high regioselectivity has been demonstrated by Warkentin's competition studies between 5-*exo* and 6-*endo* cyclisation[15] with alkyl radical ring closures, wherein 6-*endo* attack at the carbon centre was preferred over 5-*exo* cyclisation at the nitrogen (Scheme 1).




**Scheme 1**

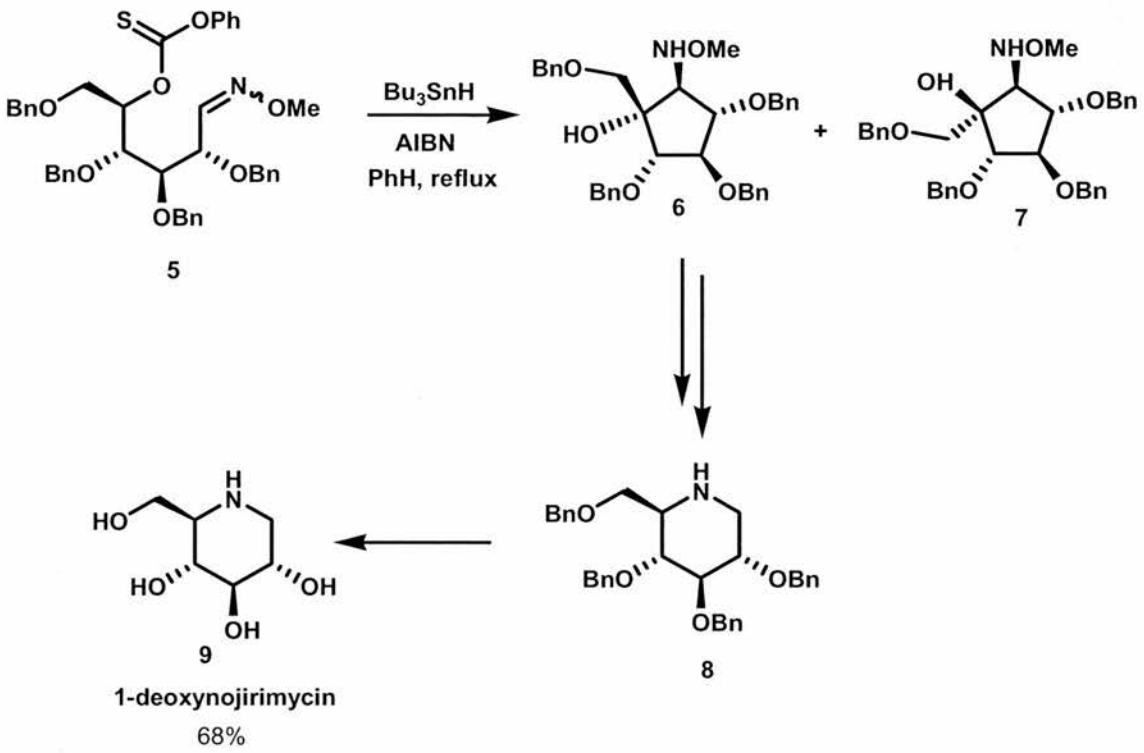
In 1983 Corey reported the first radical cyclisation involving an oxime ether acceptor.[16] Reduction of cyclic ketone **1** with zinc powder in the presence of trimethylsilyl chloride and 2,6-lutidine generated ketyl radical **2** which underwent intramolecular addition to the pendant O-methyl oxime ether to afford alkoxyaminyl radical **3**. Hydrogen abstraction from THF, then generated bicyclo[3.3.0]octane hydroxylamine **4** (Scheme 2).




**Scheme 2**

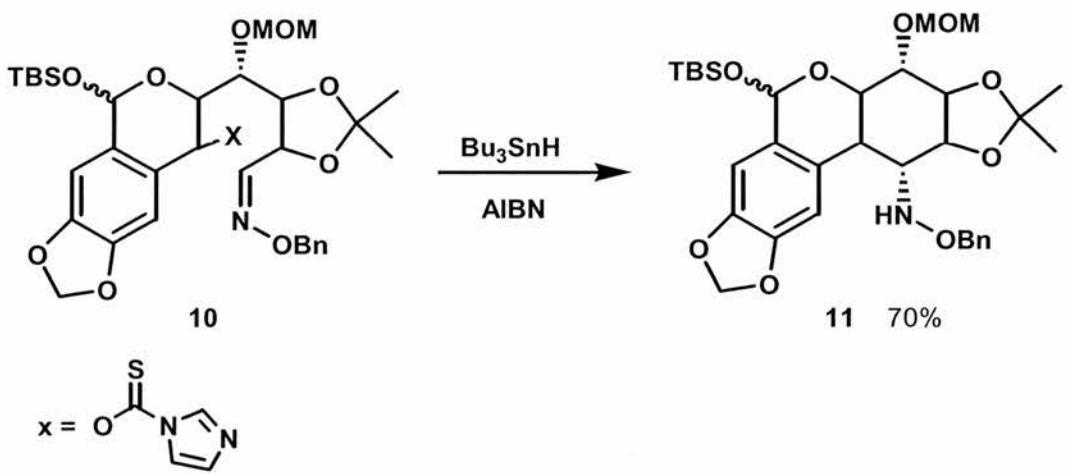
The action of zinc-TMSCl on the unsatured ketone **1** generates an α-trimethylsilyloxy radical, by electron transfer and silylation, which adds to the δ,ε–multiple bond to form the 5-membered ring in bicycle **4**. The function of 2,6-lutidine is to prevent proton or zinc chloride-catalysed elimination of the tertiary trimethylsilyloxy group. The alkoxyaminyl radical which results from this type of cyclisation seems to have special stability which may be due to a possible 3-electron π bonding interaction by the adjacent oxygen lone pair which stabilise the nitrogen radical centre.

A number of glycosidase and chitinase inhibitors have received particular attention due to their potential to treat various metabolic disorders. Naito and coworkers[17] investigated the synthesis of 1-deoxynojirimycin **9**. Phenyl thionocarbonate **5** with tributyltin hydride in the presence of AIBN as radical initiator, cyclised to the *cis* and *trans* mixture of **6** and **7** in 68% yield. Further manipulation of **6** afforded tetrabenzyl ether **8**, which is an intermediate for the synthesis of 1-deoxynojirimycin **9** (Scheme 3).



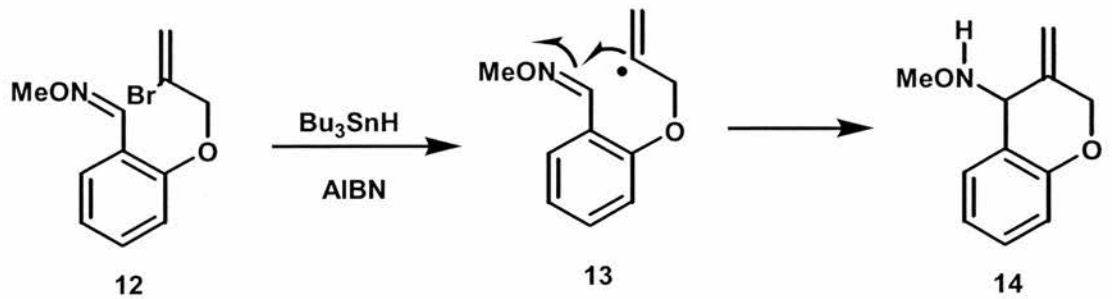

**Scheme 3**

In the total synthesis of (+)-7-deoxypancratistatin, which exhibits therapeutic antineoplastic and antiviral activity, Keck and coworkers[18] employed a 6-*exo* cyclisation of a benzyl radical, generated by deoxygenation of radical precursor **10** with tributyltin hydride and AIBN, onto an oxime ether to construct the highly functionalised cyclohexane nucleus in the desired material **11** which was isolated in 70 % yield as single stereoisomer (Scheme 4).



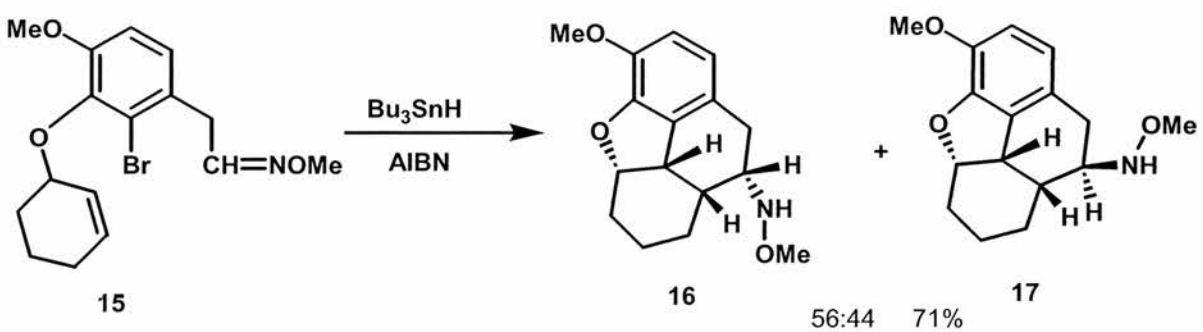

**Scheme 4**

Jenkins and coworkers[19] have prepared six and seven membered ring cyclic ethers by cyclisation of vinyl radicals onto oxime ethers. Vinyl bromide **12** with tributyltin hydride in the presence of AIBN generated the corresponding vinyl radical **13** which underwent 6-*exo* cyclisation to afford the heterocyclic olefin **14** in 76 % yield (Scheme 5).




**Scheme 5**

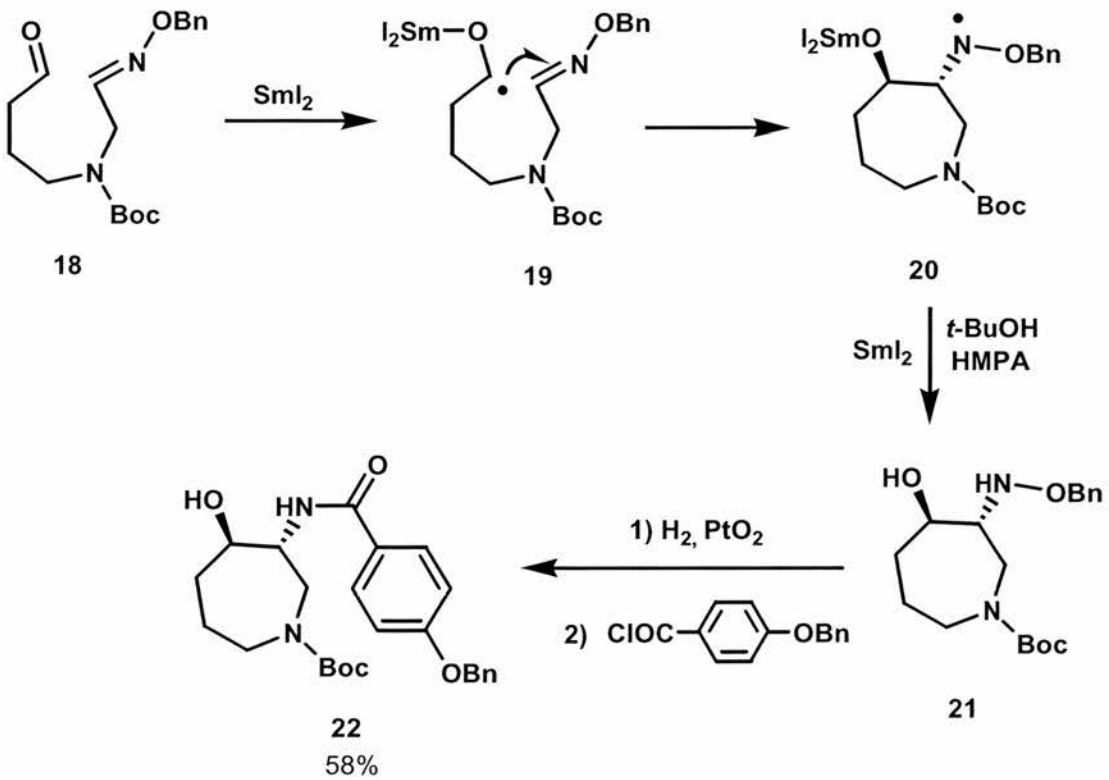
Aryl radical cyclisations onto oxime ethers have been investigated by Parker and co-workers in the radical based approach to the morphine skeleton.[20] Oxime ether **15** was employed as the final acceptor in an intramolecular tandem aryl radical cyclisation onto cyclohexene. A 6-*exo* cyclisation furnished an epimeric mixture at the amino ether centre in a total yield of 71% (Scheme 6).




**Scheme 6**

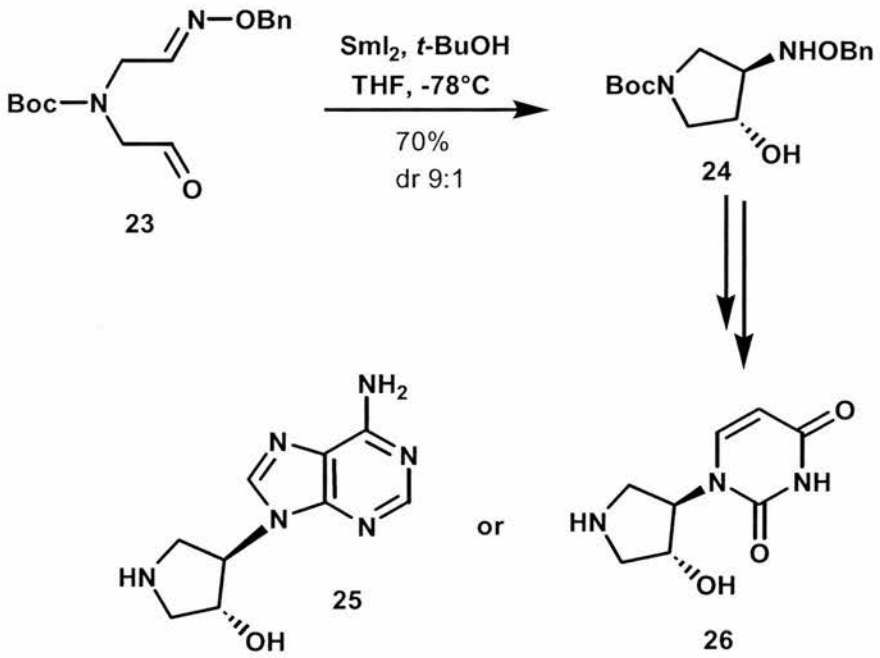
Cyclisation onto oxime ethers is particularly successful for the synthesis of not only five- and six-membered compounds but also for the seven-membered ring.[21-25] For example, Naito and co-workers succeeded in the preparation of a racemic hexahydroazepine **22** which represents a fragment of (-)Balanol, the selective inhibitor against protein kinase C (PKC) that mediates a range of signal transduction processes

in cells[26] and has been implicated in a number of diseases such as cancer, cardiovascular disorders and HIV infection.[27] The intramolecular reductive coupling of *O*-benzyl oxime **18** was performed by the use of the unique single-electron reducing agent $SmI_2$. Cyclisation was achieved in the presence of *t*-BuOH as proton donor, a 0.1 M solution of $SmI_2$ in THF and HMPA which was found to be essential for successful cyclisation of **18** to afford the desired *trans* seven-membered ring **20** as the major reaction product.[28] Single electron transfer by $SmI_2$ to the formyl group of **18** generated ketyl radical **19** which then attacked the oxime ether moiety to give alkoxyaminyl radical **20**. Hydrogen abstraction from *t*-BuOH furnished the desired seven membered ring amino alcohol **21**. Subsequent hydrogenolysis of the alkoxyamino group of *trans* product **21** in the presence of platinum dioxide in MeOH followed by *N*-acylation of the resulting amine with *p*-(benzyloxy)benzoyl chloride afforded the desired racemic hydroazepine **22** in 58% yield (Scheme 7).



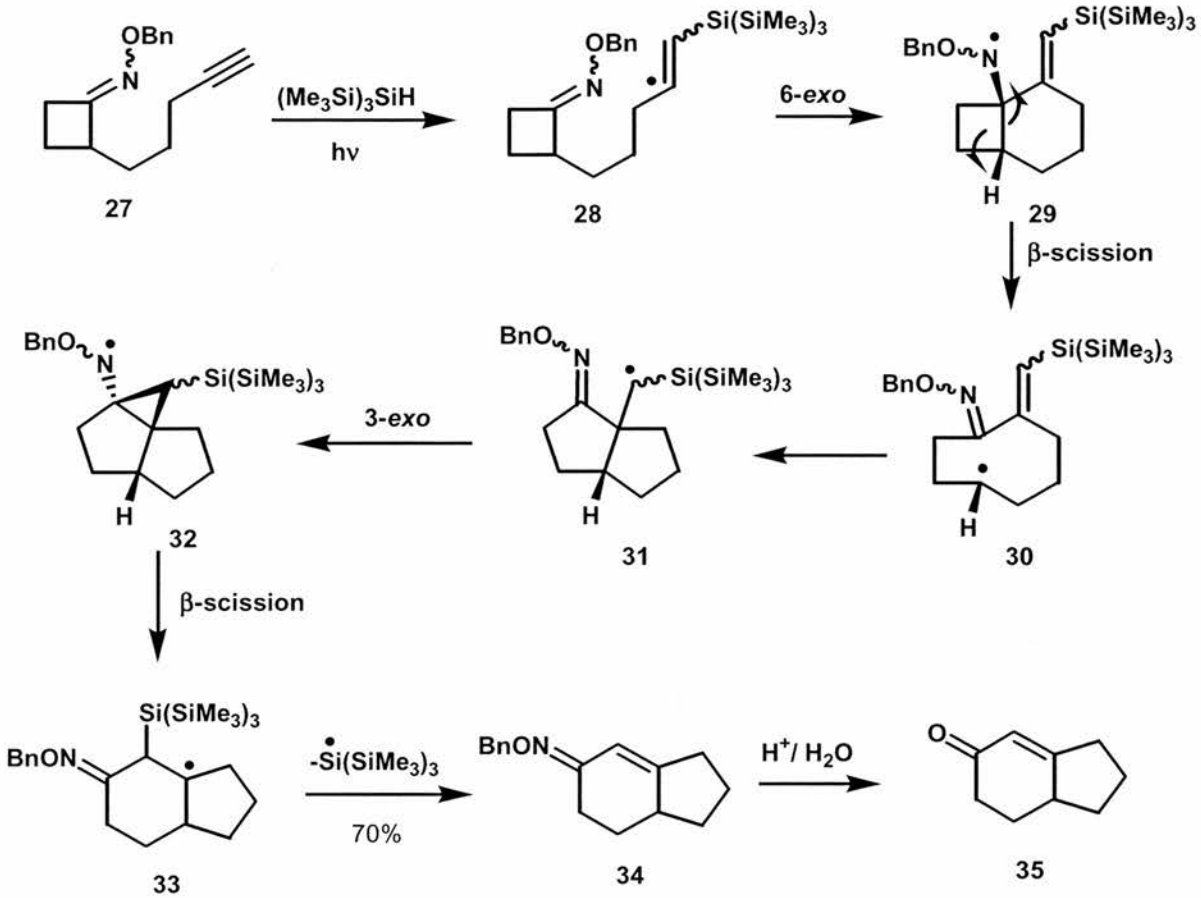

**Scheme 7**

Similar chemistry has been used for the preparation of pyrrolidine nucleoside analogues.[29] 5-*Exo* cyclisation of aldehydo-oxime ether **23** upon treatment with $SmI_2$ in the presence of *t*-BuOH provided *trans* amino alcohol **24** in 70% yield. Hydrogenolysis of the N-O bond and construction of pyrimidine and purine rings led to nucleoside **25** or **26** (Scheme 8).



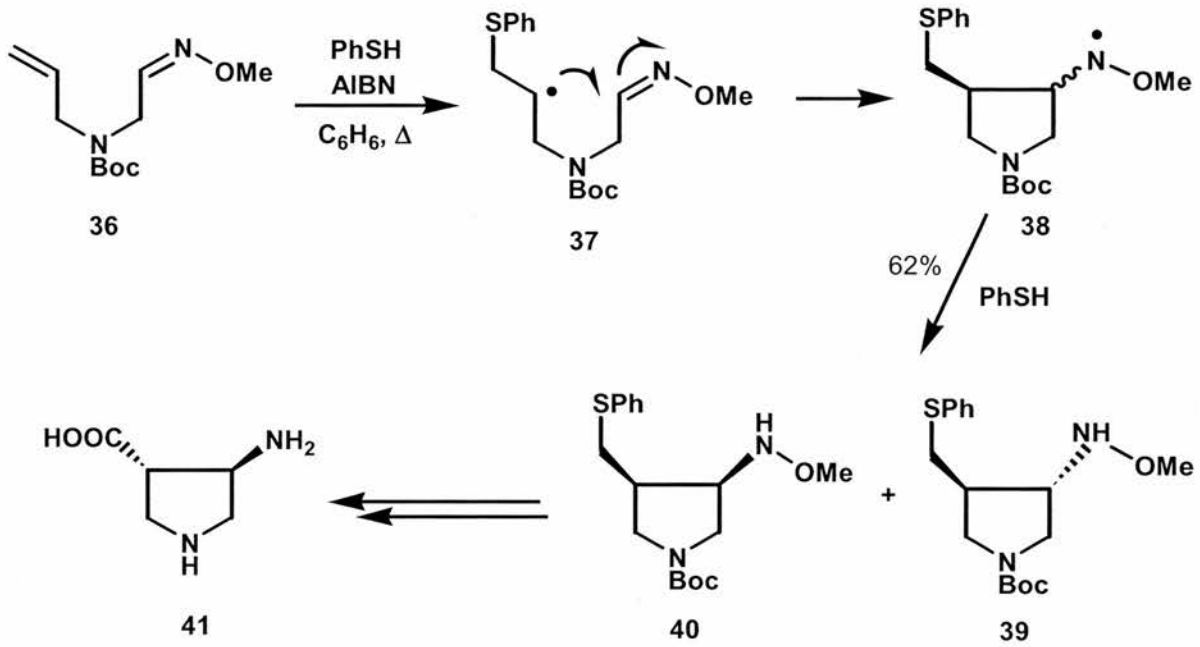

**Scheme 8**

Radical cascade sequences in which oxime ethers play a key role have been examined by Pattenden in the synthesis of bicycle **34**.[30] When cyclobutanone oxime **27** was reacted with TTMSS and irradiated with UV light it formed vinyl tris(trimethylsilyl)silyl radical **28**. 6-*Exo* cyclisation afforded radical **29** followed by β-scission to lead, in sequence, to **30** and **31**. A third ring closure gave the α-cyclopropylaminyl radical **32**. A second β-scission regenerated the oxime functionality to give radical **33** followed by a final elimination of the tris(trimethylsilyl)silyl species to produce the bicyclic product **34** in 70% yield which was subsequently hydrolysed to the corresponding desired enone **35** (Scheme 9).



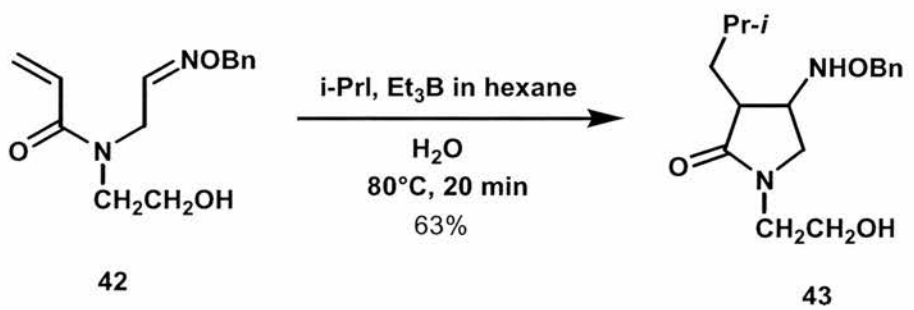

**Scheme 9**

Recently Naito and co-workers explored a new efficient carbon-carbon bond forming reaction based on sulfanyl radical addition-cyclisation,[31,32] which proceeded by a carbon centered radical species generated by the addition of a sulfanyl radical to a multiple bond followed by intramolecular addition of the resulting carbon-centered radical to the carbon-nitrogen multiple bond of an oxime ether acceptor. When unsatured oxime ether **36** was treated with thiophenol and AIBN as radical initiator in refluxing benzene it gave a mixture of the *cis*- and *trans*-cyclopentylamines **39** and **40** in 88 % yield. The mechanism involves the initial addition of the sulfanyl radical to the terminal alkenyl goup in the substrate **36** to provide alkyl radical **37** which undergoes 5-*exo* cyclisation onto the oxime ether moiety to produce the cyclised alkoxyaminyl radical **38**. H-abstraction from more thiophenol gave the expected cyclic *cis* and *trans* amines **39** and **40**. Subsequent conversion of the phenylsulfanylmethyl group into the carboxyl group furnished *trans*-4-amino-3-pyrrolidinecarboxylic acid **41** (Scheme 10), which represents a crucial component of β-17 a β-peptide, which is active against four species of bacteria, including vancomycin-resistant and methicillin-resistant strains.[33]




**Scheme 10**

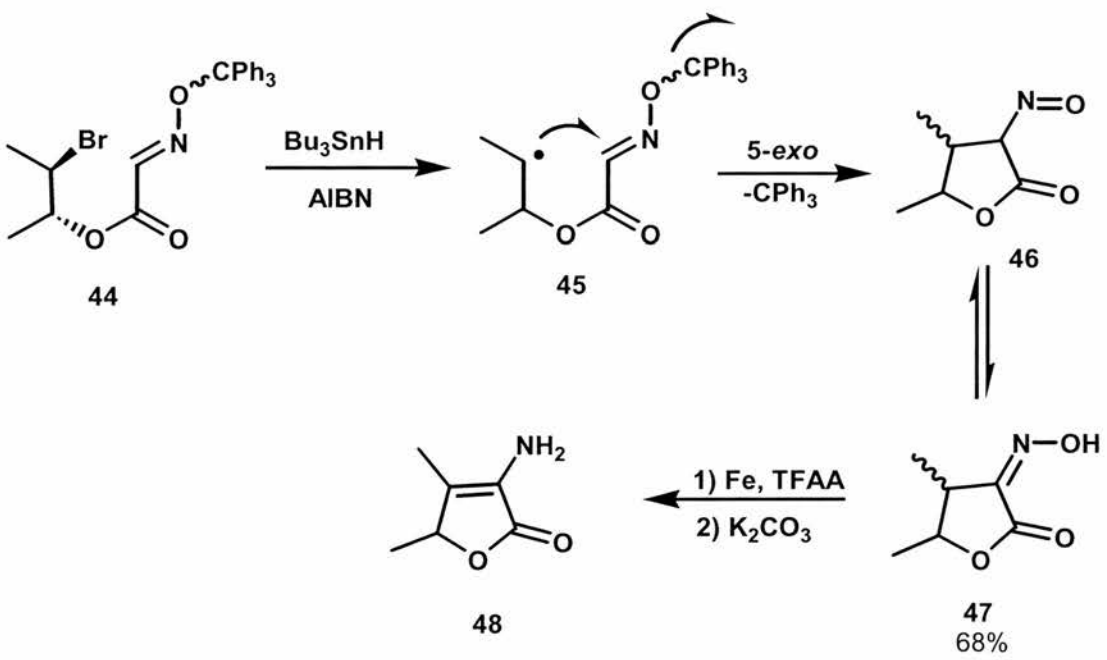
Intramolecular radical cyclisations of alkyl radicals onto oxime ethers have also been performed in water as solvent.[34] Treatment of oxime ether **42** with triethylborane (hexane solution) and isopropyl iodide in water at 80°C gave cyclised product **43** in 62% yield via two carbon-carbon bond-forming steps[35] (Scheme 11).




**Scheme 11**

Triethylborane worked well as radical initiator and terminator to trap the intermediate alkoxyaminyl radical even in the biphasic reaction to give the chain-propagating ethyl radical.

Recently Clive and Subedi reported stannane induced radical ring closures onto *O*-trityl oximes.[36] The special feature of such reactions was that the $sp^2$ state of the acceptor carbon is preserved, a different result from the one seen in the classic cyclisation onto *O*-alkyl oxime ethers.[37,38] Slow addition of a toluene solution containing tributyltin hydride and AIBN to a refluxing toluene solution of *O*-trityl oximino ester bromide **44** produced alkyl radical **45** which underwent 5-*exo* cyclisation onto the *O*-trityl oxime ether functionality with concerted release of trityl radical to generate nitroso lactone **46** (Scheme 12). Regeneration of the oxime function involves[39,40] tautomerization of nitroso compound **46** to give oxime lactone **47**. Treatment of **47** with iron powder in TFAA followed by hydrolysis with aqueous $K_2CO_3$ gave enamine **48** which is a naturally-occurring substance used in the treatment of disorders of a psychological nature.

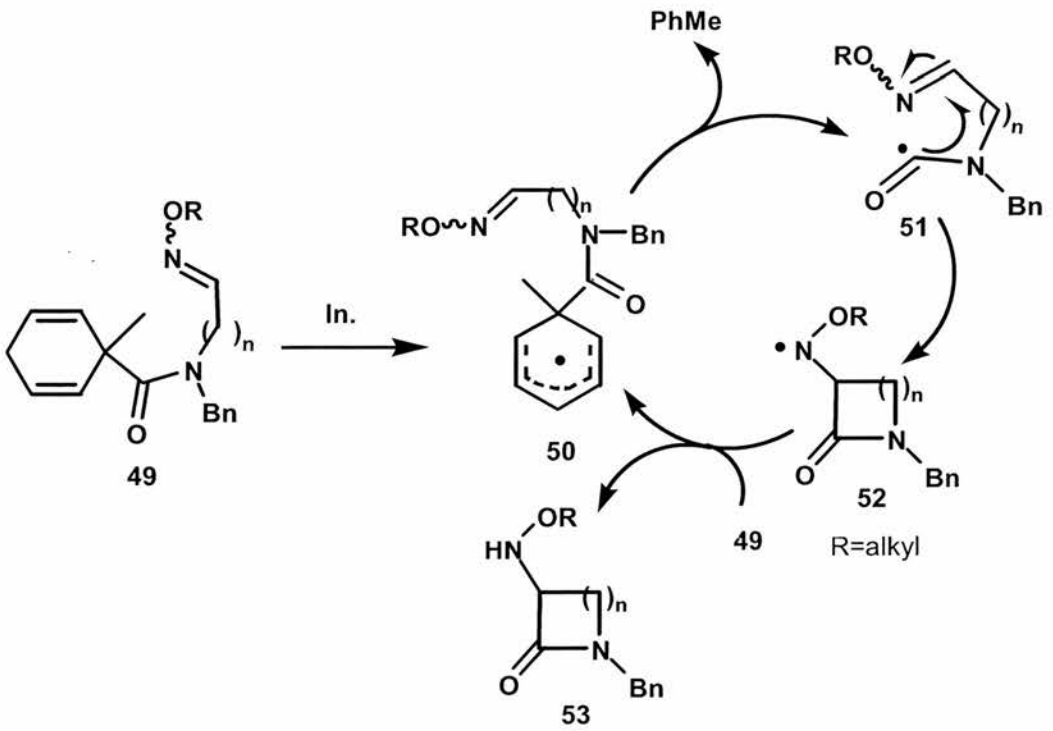



**Scheme 12**

# Aims and Objectives of the Project

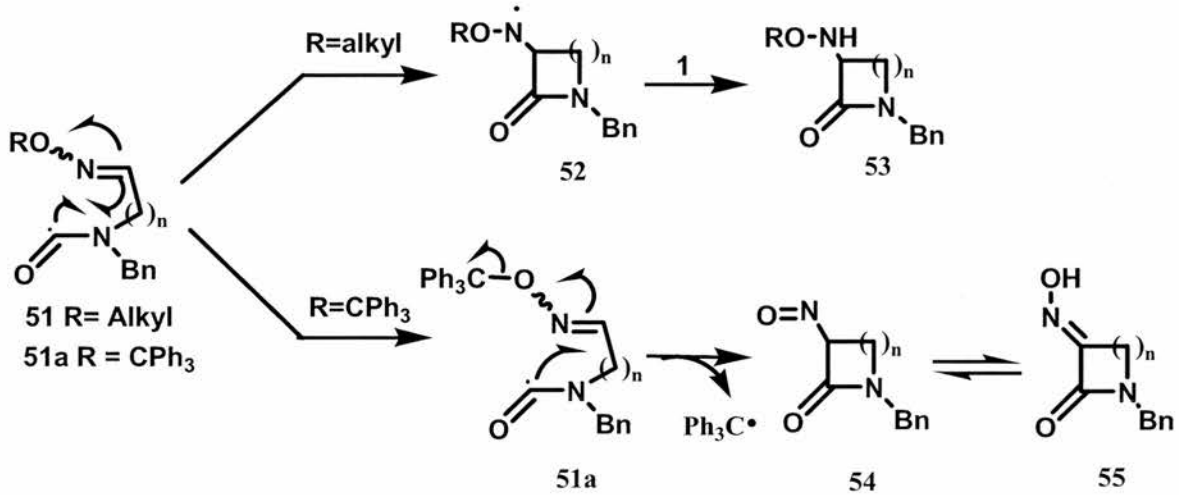
The aim of the project was to develop a synthetic route, starting from especially designed 1-carbamoyl-1-methylcyclohexa-2,5-dienes containing oxime ether double bonds, for the synthesis of the biologically interesting core of benzopyrrolidinones, via aminoacyl radical cyclisation onto oxime ether functionality.

Ring closure onto oxime ethers is known to be about three orders of magnitude faster than hex-5-enyl cyclisation.[1] Therefore the use of this functionality in place of C-C double bonds could potentially lead to improved lactam yields. Appropriate amides of type **49**, containing oxime ether functionality, treated with peroxides may generate delocalised radicals **50** which dissociate with loss of toluene to afford aminoacyl radicals **51**. Intramolecular cyclisation to alkoxyaminyl radical **52** (R=benzyl, alkyl) followed by H-abstraction from more **49** should produce lactams **53** plus a new delocalised radical which could continue the radical chain (Scheme 13).




**Scheme 13**

Dissociation of **51a** (R=$CPh_3$) would follow a diverse pathway which does not constitute a radical chain but could efficiently be used in synthetic sequences. Aminoacyl radical **51a** containing O-trityl functionality, may undergo ring closure with loss of the stable trityl radical to yield nitroso-lactam **54** which could tautomerise to regenerate the oxime functionality in lactam **55** (Scheme 14).




**Scheme 14**

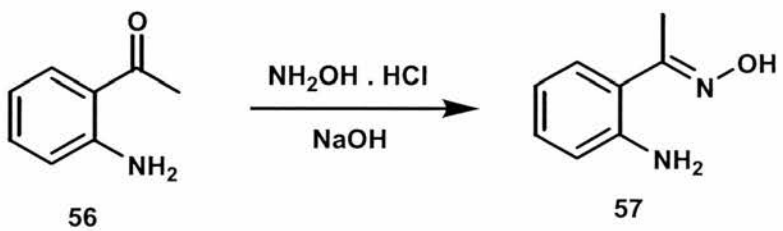
Oxime ether precursors **51** and **51a** might therefore be used in syntheses of lactam rings for which conventional homolytic cyclisations onto alkene moieties are slow. This tactic could also be particularly relevant for 6- and 7-membered lactam rings for which cyclisation onto the oxime ether double bond will be significantly more efficient than onto the analogous alkenes.

# 4.2 Results and Discussion

### 4.2.1 Attempted preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime (61)

**Route 1**

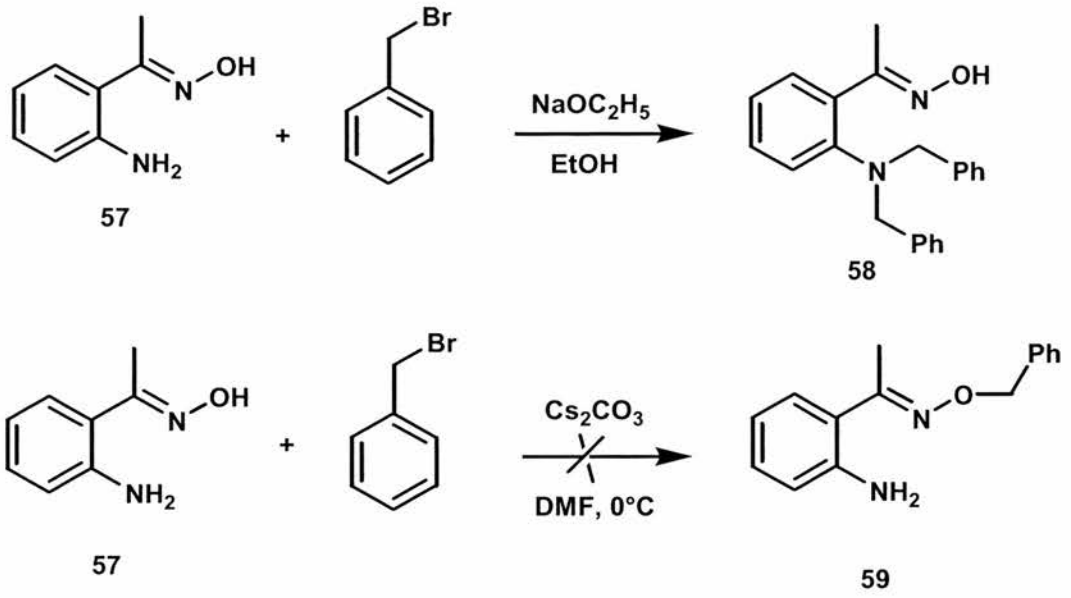
1-(2-Aminophenyl)ethanone oxime **57** was prepared according to a typical procedure used in preparation of benzophenone oxime with hydroxylamine hydrochloride in the presence of alkali.[41] To a mixture of 1-(2-aminophenyl)ethanone **56** and hydroxylamine hydrochloride was added sodium hydroxide in portions with shaking. When all the sodium hydroxide was added the temperature was raised to 60° and maintained for 30 minutes. Acidic work up, extraction with DCM and evaporation of the organic solvent furnished 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime **57** (Scheme 15) as a white solid.




56 57

**Scheme 15**

We attempted the preparation of 1-(2-aminophenyl)ethanone *O*-benzyloxime **59** using a method[42] in which the oxime functionality of **57** is first deprotonated by a strong base such as sodium ethoxide followed by nuclephilic attack on benzyl bromide (Scheme 16). When a ethanolic solution containing sodium ethoxide was slowly added to a refluxing solution of 1-(2-aminophenyl)ethanone oxime **57** and benzyl bromide in ethanol and the mixture refluxed for two hours a flocculent product was formed. Addition of water before refluxing one additional hour allowed the separation of a white crystalline solid from the reaction mixture which was filtered and washed with ethanol and water. The product obtained was characterised as 1-[2-(dibenzylamino)phenyl]ethanone oxime **58** which was formed from the double nucleophilic attack of amine group in compound **57** on benzyl bromide (Scheme 16).

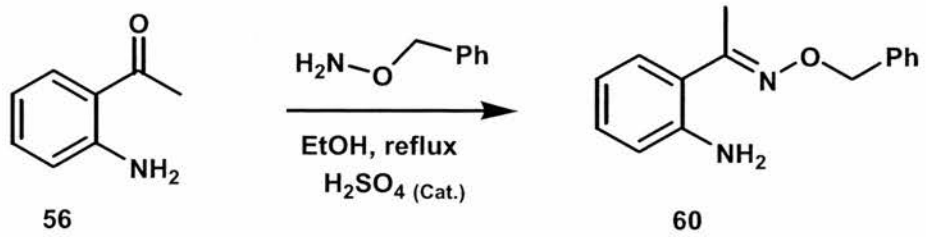



**Scheme 16**

An alternative attempted method to prepare 1-(2-aminophenyl)ethanone *O*-benzyloxime **59** was treatment of **57** with 1 molar equivalent of benzyl bromide at 0°C in DMF in the presence of caesium carbonate (Scheme 16). The mixture was stirred overnight at room temperature. TLC and $^{1}H$ NMR analysis of the reaction mixture revealed only the presence of unchanged starting material. It was therefore not possible to generate the *O*-benzyl functionality by the nucleophilic attack of oxime **57** on benzyl bromide.

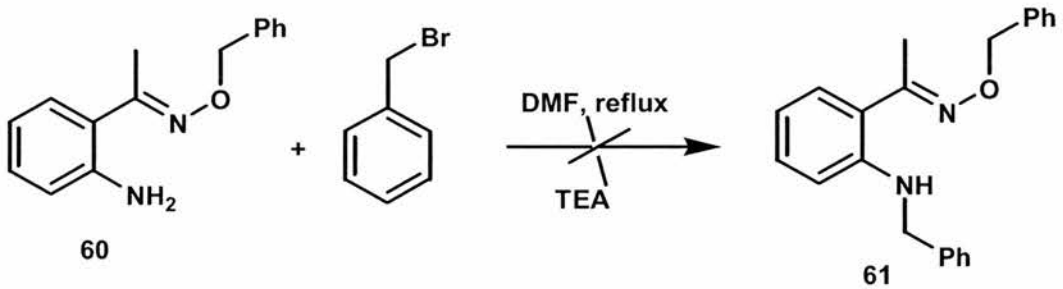
**Route 2**

Acid catalysed condensation of 1-(2-aminophenyl)ethanone **56** with *O*-benzylhydroxylamine in refluxing ethanol for ten hours followed by a basic workup resulted in the formation of a brown oil. Impurities were distilled under high vacuum at 75 °C. The residue was dissolved in aqueous hydrochloridric acid and subsequently washed with NaOH. Extraction with DCM afforded a pale yellow oil which was analysed by $^{1}H$ and $^{13}C$ NMR and determined to be the desired 1-(2-aminophenyl)ethanone *O*-benzyloxime **60** (Scheme 17).




**Scheme 17**

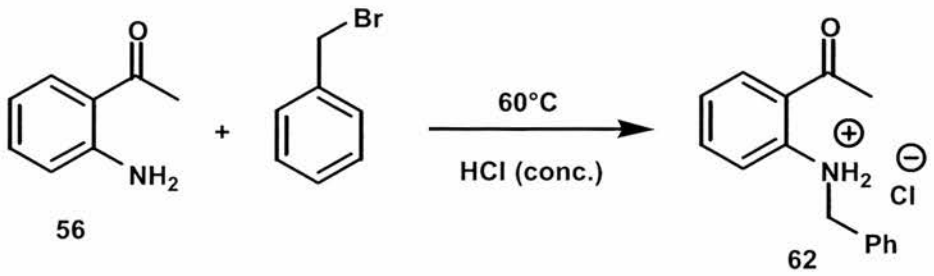
Transformation of benzyl oxime ether **60** into the *N*-benzyl derivative **61** was attempted by $S_N2$ reaction of **60** with 1 molar equivalent of benzyl bromide in the presence triethylamine in refluxing DMF (Scheme 18). TLC and NMR analysis of the crude reaction mixture showed only unchanged starting material.




**Scheme 18**

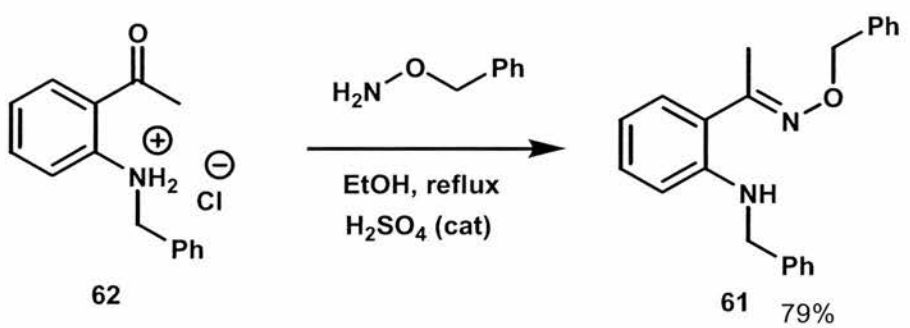
**Preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime (61)**

Reaction of 2 molar equivalents of aminobenzophenone **56** with benzyl bromide at 60°C in absence of solvent produced a yellow dark solid mass (Scheme 19) which was dissolved in concentrated hydrochloric acid (36%). The acidic solution was then poured into water, filtered, washed with plenty of water and dried under high vacuum. Crystallisation from a mixture of petroleum ether/ethanol gave the desired (2-acetyl-phenyl)-benzyl-ammonium chloride **62** as yellow crystalline solid in good yield.



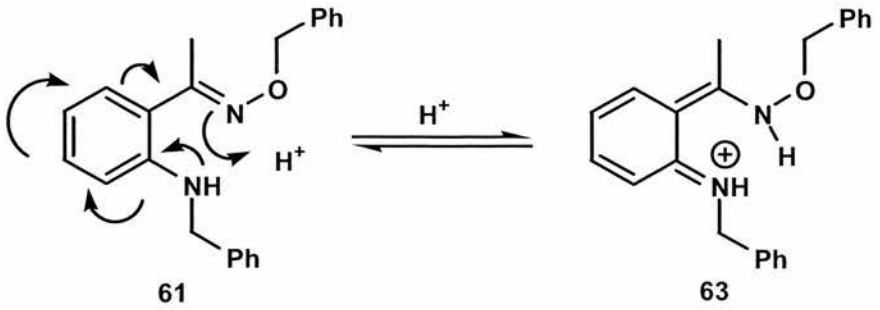

**Scheme 19**

Acetophenone ammonium salt **62** was then dissolved in ethanol and heated to reflux, before *O*-benzylhydroxylamine was added portionwise. The solution obtained was refluxed for 30 minutes before adding a drop of concentrated sulphuric acid (98%). The reaction mixture was refluxed overnight and the solvent eliminated under reduced pressure to leave a slurry residue. Basic workup allowed free amine formation which separated out from solution. The resultant oil was extracted with DCM, dried with magnesium sulphate and the solvent evaporated under reduced pressure to furnish a yellow oil, which was further purified by column chromatography (alumina) to give a colourless oil. Crystallisation from cold hexane furnished 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime **61** as a white crystalline solid in 79 % yield (Scheme 20).




**Scheme 20**

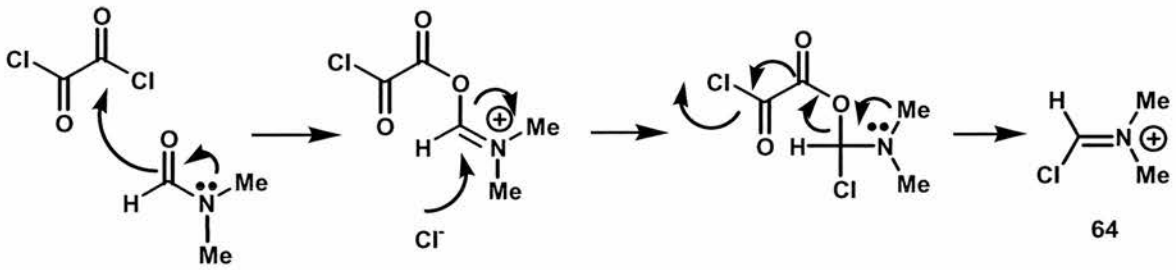
Product **61** when treated with acid such as dilute hydrochloric acid or left in contact with silica gel was transformed into an unidentified green compound which turned back to product **61** in basic conditions. One explanation of such behaviour might be the generation of delocalised compound **63** formation of which would be favoured in acidic conditions (Scheme 21).




**Scheme 21**

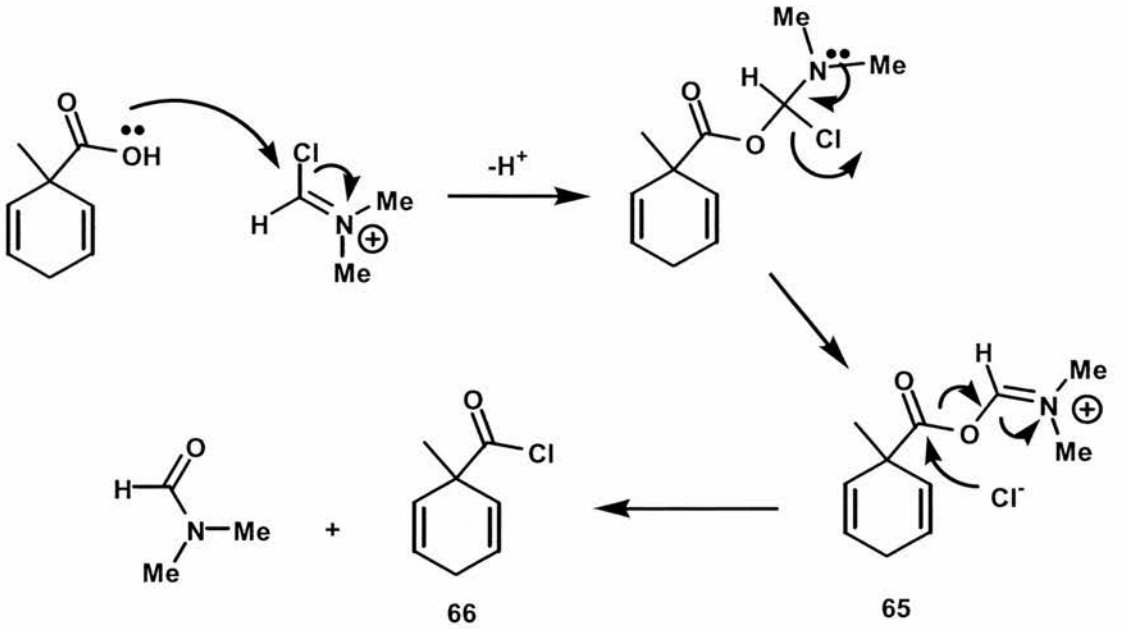
### 4.2.2 Preparation of 1-methyl-2,5-cyclohexadiene-1-carbonyl chloride.

A modification of the thionyl chloride method for making acyl chlorides uses oxalyl chloride plus a catalytic amount of DMF. The oxalyl chloride reacts with DMF to produce the highly electrophilic intermediate **64** plus CO and $CO_2$ (Scheme 22)




**Scheme 22**

The highly electrophilic intermediate **64** reacts rapidly with 1-methyl-2,5-cyclohexadiene-1-carboxylic acid producing intermediate **65** which intercepts $Cl^-$ to give 1-methyl-2,5-cyclohexadiene-1-carbonyl chloride and regenerate DMF (Scheme 23). The advantage in the use of oxalyl chloride plus DMF over thionyl chloride as chlorinating agent was the higher yields obtained and the shorter reaction time required for going to completion.

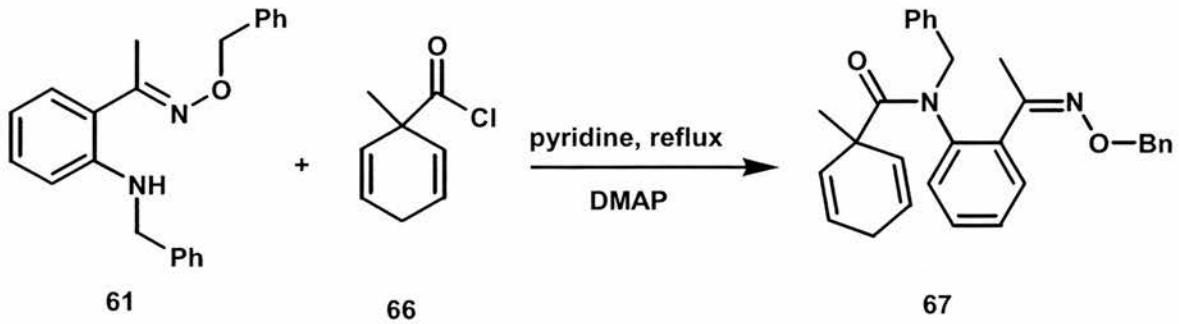



**Scheme 23**

### 4.2.3 Preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)

We first attempted the preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide **67** following the typical procedure in which slow addition of methyl acid chloride **66** to a mixture of purified amine **61**, triethylamine and a catalytic amount of DMAP in dry DCM was refluxed for 8h. TLC and $^1$H NMR analysis of the crude reaction mixture showed no conversion of starting material. The reaction was therefore carried out in pyridine as solvent and hydrochloric acid trap. To a solution of dry pyridine containing amine **61** and a catalytic amount of DMAP, was added dropwise a DCM solution containing 1.5 molar equivalent of methyl acid chloride **66**. The resulting solution was refluxed overnight, cooled down to room temperature, poured into 50 cm$^3$ of a 6M HCl solution and stirred for 10 minutes. The aqueous layer was then extracted with DCM, dried, and the solvent evaporated at reduced pressure to leave a brown crude oil which was purified by column chromatography to yield a pale yellow oil. Crystallisation from a mixture of ethyl acetate in hexane yielded a colourless crystalline solid in 86% yield.

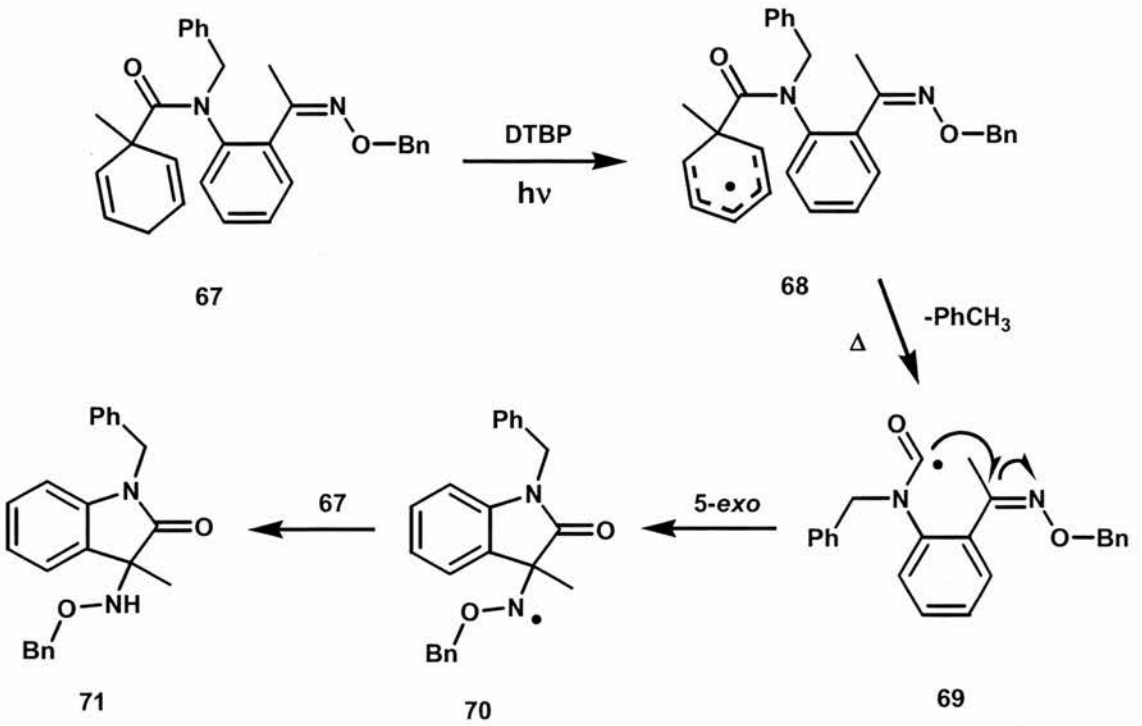
which was characterised as *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide **67** (Scheme 24).




**Scheme 24**

### 4.2.4 EPR experiment on the photolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)

We were interested in determining the radical chain pathway from cyclohexadienyl carboxamide **67,** which could result in the release of the corresponding aminoacyl radical containing oxime ether functionality **69**, and might therefore undergo radical cyclisation to give the corresponding benzopyrrolidinone **71** (Scheme 25). The *O*-benzyl carboxamide radical precursor **67** was therefore investigated by EPR spectroscopy. An accurately measured quantity of cyclohexadienyl carboxamide **67** (5 mg) was placed in a clean dry quartz tube, before of DTBP was added and degassed for approximately 20 min. The sample was placed into the EPR cavity which was held at 230 K and illuminated by a 500 W super pressure lamp. A preliminary EPR spectrum was acquired on irradiation with the UV light in order to initiate the radical chain. The temperature was increased at intervals of 5K and at 260 K, cyclohexadienyl carboxamide **67** started to release the delocalised cyclohexadienyl radical **68** (Scheme 25) which was observed by an EPR spectrum (Figure 1).




**Scheme 25**

**9.5 GHz EPR spectra obtained on photolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)**

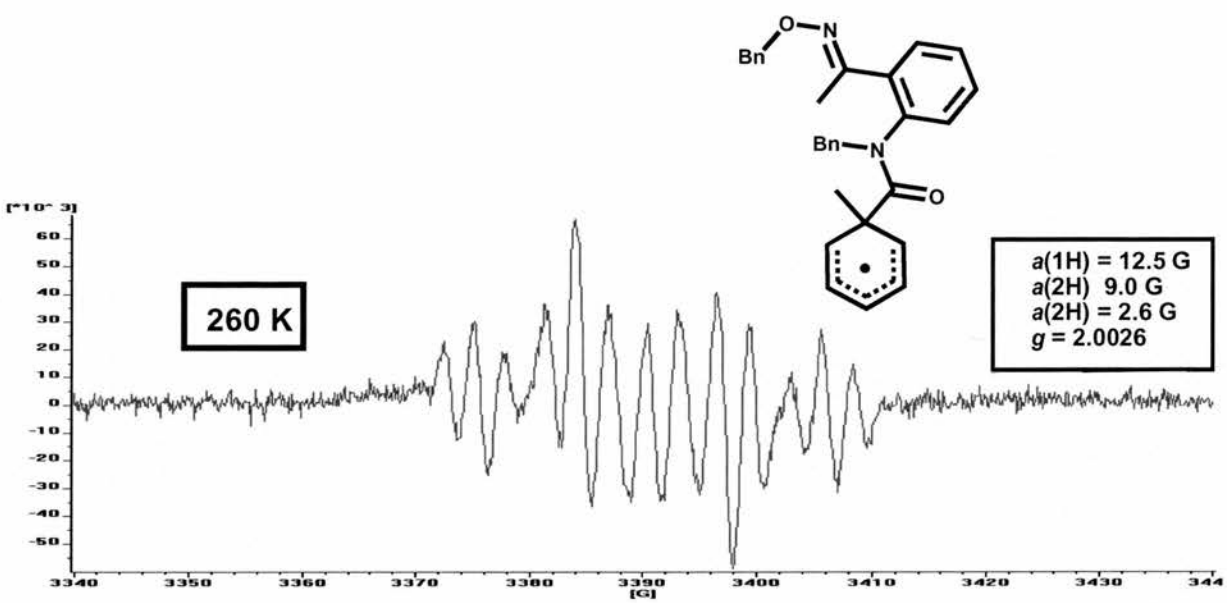



**Figure 1**

When the temperature of the EPR cavity was increased, the spectrum of the cyclohexadienyl radical **68** weakened and at 310K it was replaced by a triplet of triplets having an *a*(N) value of 13.6 G (table 1 and figure 2). This spectrum can be attributed to alkoxyaminyl radical **70**. The hyperfine splitting (hfs) and *g*-factor were similar to those of other alkoxyaminyl radicals previously reported in the literature.[43] The intermediate aminoacyl radical **69** was not detected by EPR spectroscopy.

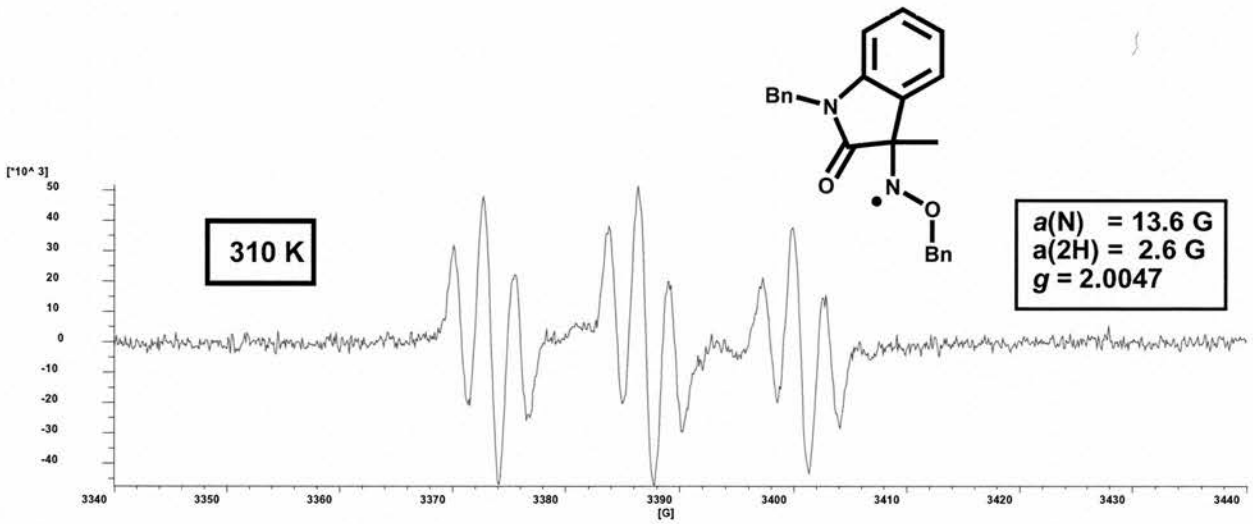



**Figure 2**

**9.4 GHz EPR parameters of radicals derived from *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67) in solution[a]**

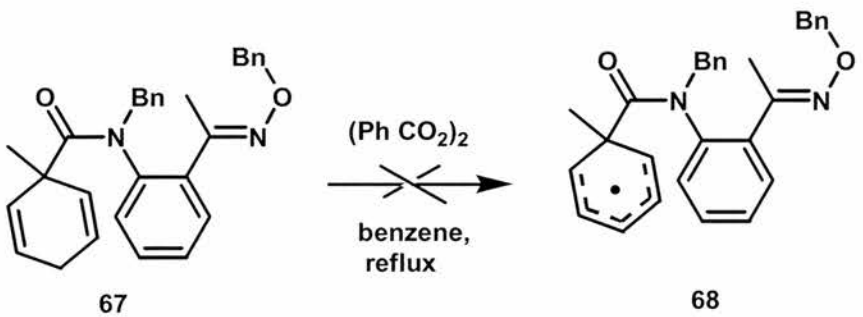
| Radical | T / K | *g*-factor | *a* (G) |
|---|---|---|---|
| 68 | 260 | [2.00026] | *a* (1H) = 12.5<br>*a* (2H) = 9.0<br>*a* (2H) = 2.6 |
| 70 | 310 | 2.0047 | *a* (N) = 13.6<br>*a* (2H) = 2.6 |

[a] All spetra in neat DTBP

**Table 1**

### 4.2.5 DBP mediated thermolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)

We wanted to investigate the DBP thermally initiated radical fragmentation of amide **67** in order to examine the products formed on release of the aminoacyl radical **69**. We envisaged that 5–*exo* cyclisation would be fast, leading to good yield of benzopyrrolidinone **71**. Addition of a benzene solution of dibenzoyl peroxide to a refluxing benzene solution of amide **67** furnished a mixture of products. GC-MS analysis revealed only the presence unchanged amide starting material together with byproducts deriving from photolytic breakdown of DBP. Although the reaction was performed under different conditions of temperature by varying the solvent, it was not possible to initiate the radical chain by the use of DBP (Scheme 26).



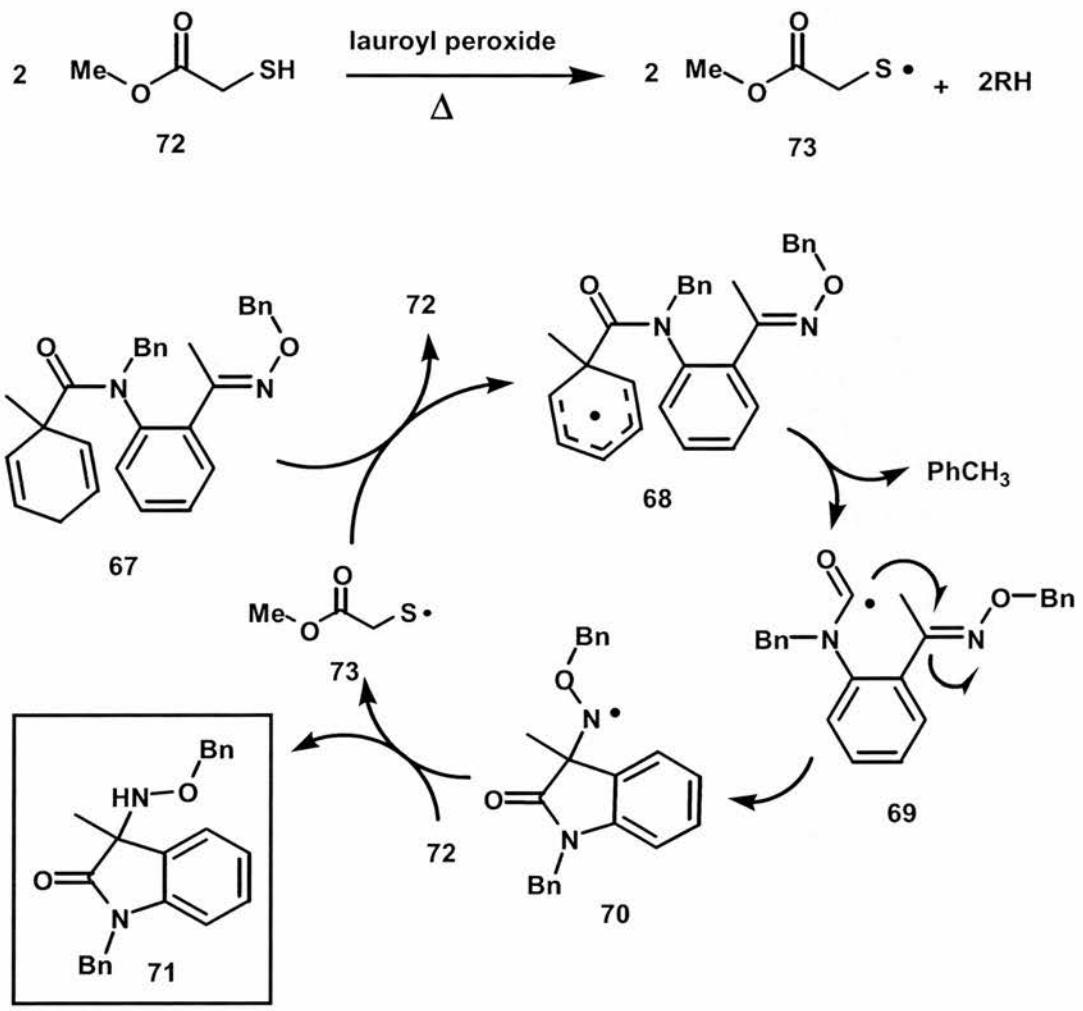

67 68

**Scheme 26**

### 4.2.6 Polarity reversal catalysis (PRC) by thiols in thermolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67).

Addition of an alkanethiol to generate the electrophilic thiyl radical could favour chain propagation. We predicted it was possible to efficiently initiate the wanted radical chain reaction by the use of a catalytic amount of methyl thioglycolate **72**, (0.05 $cm^3$) which can also function as hydrogen donor, in union with dilauroyl peroxide, as initiator. The carbon centred radical R• released from the lauroyl peroxide is readily reduced by the thiol catalyst to provide the corresponding reduced product RH, along with the thiyl radical **73**, then the thiyl radical abstracts hydrogen from carbamoyl amide **67** to generate the delocalised cyclohexadienyl radical **68** which releases toluene

to produce aminoacyl radical **69**. Intramolecular radical cyclisation of **69** gives cyclised alkoxyaminyl **70** which can easily abstract hydrogen from thiol **72** to regenerate thiyl radical **73** and propagate the chain reaction.




**Scheme 27**

A benzene solution containing dilauroyl peroxide was divided in four portions and added to a refluxing benzene solution of amide **67** over 9 h and left to reflux for 30 h. GC-MS analysis of the crude reaction mixture indicated the presence of the cyclised benzopyrrolidinone **71** as a major reaction product, together with by-products derived from thermolytic breakdown of lauroyl peroxide and from radical termination reactions of the thiyl radical. The GC-MS chromatogram also revealed the presence of small amounts of unreacted starting amide which meant that the reaction can be driven

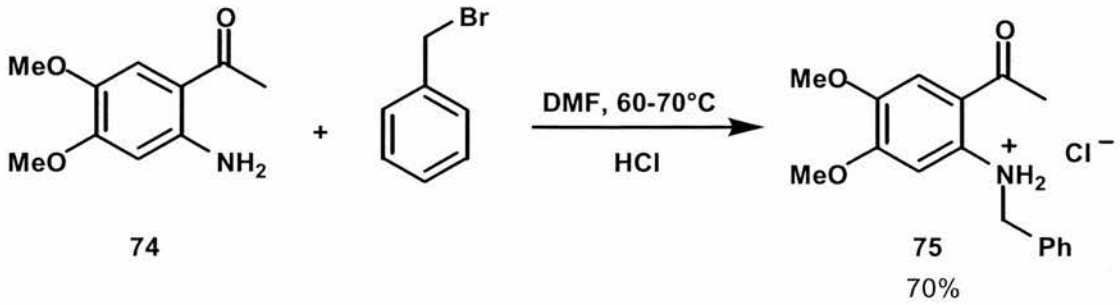
to completion under these conditions. The crude reaction product was then treated with a warm aqueous solution of KOH (6M), in order to hydrolyse the disulphide by-product into the corresponding carboxylic acid potassium salt. Extraction with DCM yielded a yellow product. Column chromatography furnished a pale yellow oil which was crystallised from a mixture of ethyl acetate in hexane to furnish a white crystalline solid, identified as the desired 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71** in 68% yield.

### 4.2.7 DTBP mediated photolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy) ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)

The alternative photolytic radical fragmentation of amide **67** was also studied. Irradiation of amide **67** in neat DTBP at room temperature for 3 hours, gave a crude reaction mixture which was analysed by GC-MS. 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71** was detected as a major product, together with a small amount of unreacted starting material. When photolysis of amide **67** was performed at 100°C in neat DTBP for a period of three hours, GC-MS analysis of the obtained reaction mixture revealed only the cyclised benzopyrrolidinone **71**, and by-products derived from photolytic breakdown of DTBP.

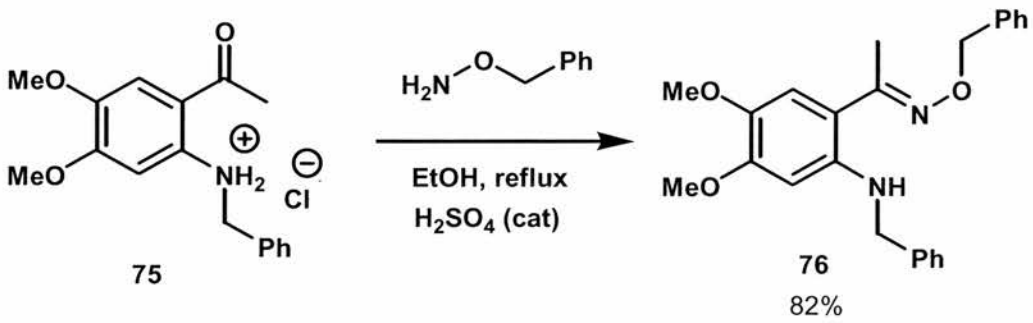
### 4.2.8 Preparation of 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone *O*-benzyloxime (76)

To a stirred solution of 1.5 molar equivalent of 1-(2-amino-4,5-dimethoxyphenyl)ethanone **74**, in DMF, was added benzyl bromide and heated at 60-70°C for 3 hours. The reaction mixture was then poured in 300 $cm^3$ of water containing 10 $cm^3$ of HCl (36%) and stirred overnight to furnish a wine red solid, which was filtered out, dried and crystallised from a mixture of ethanol in petroleum ether to give (2-acetyl-4,5-dimethoxyphenyl)benzyl ammonium chloride **75** as yellow crystalline solid in good yield (Scheme 28).




**Scheme 28**

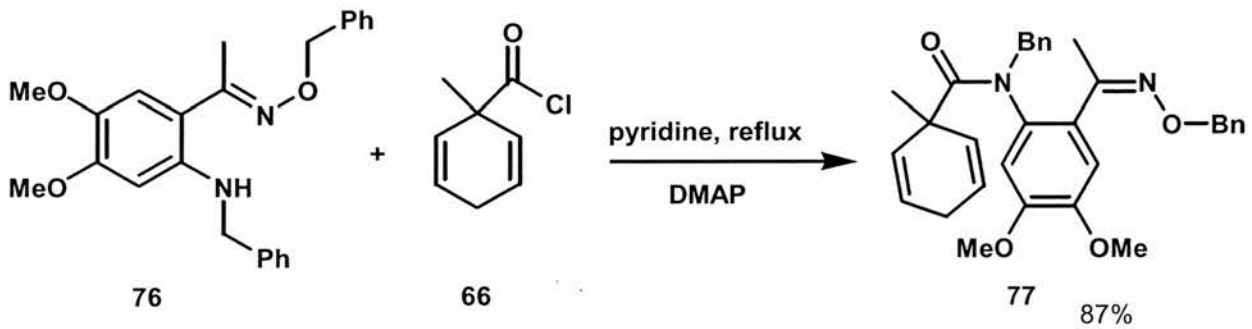
Product **75** was then reacted with *O*-benzylhydroxylamine in the presence of a catalytic amount of sulphuric acid, following the same procedure used for the preparation of compound **61**. The reaction mixture was refluxed overnight and the solvent eliminated under reduced pressure before basic workup. The free amine separated from the aqueous solution was extracted with DCM, dried with magnesium sulphate and the solvent evaporated under reduced pressure to furnish a yellow crude oil. Column chromatography (alumina) and crystallisation from a mixture of ethyl acetate in pentane furnished 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone *O*-benzyloxime **76** as a yellow pale crystalline solid in 82 % yield (Scheme 29).




**Scheme 29**

### 4.2.9 Preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (77)

The preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide **77** was carried out in pyridine in the presence of a catalytic amount of DMAP in a similar fashion as previously described for the preparation of amide **67**. To a solution of dry pyridine containing amine **76** and DMAP, was added dropwise a DCM solution containing 1.5 molar equivalents of methyl acid chloride **66**. The resulting solution was refluxed overnight, cooled down to room temperature, poured into 50 $cm^3$ of a 6M HCl solution and stirred for 10 minutes. The aqueous layer was then extracted with DCM, dried, and the solvent evaporated at reduced pressure to yield a yellow crude oil which was purified by column chromatography to give *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide **77** as a yellow pale oil in 87 % yield (Scheme 30).




**Scheme 30**

### 4.2.10 EPR experiment on photolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (77)

To confirm the radical chain mechanism, previously discussed for the EPR experiment of amide **67,** we analysed the analogous amide **77**. Both the corresponding cyclohexadienyl radical and alkoxyaminyl radical were detected and characterised by EPR spectroscopy (Table 2).

**9.4 GHz EPR parameters of radicals derived from *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (77)**

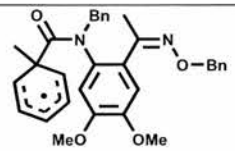
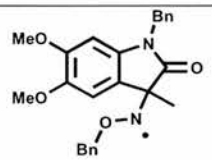
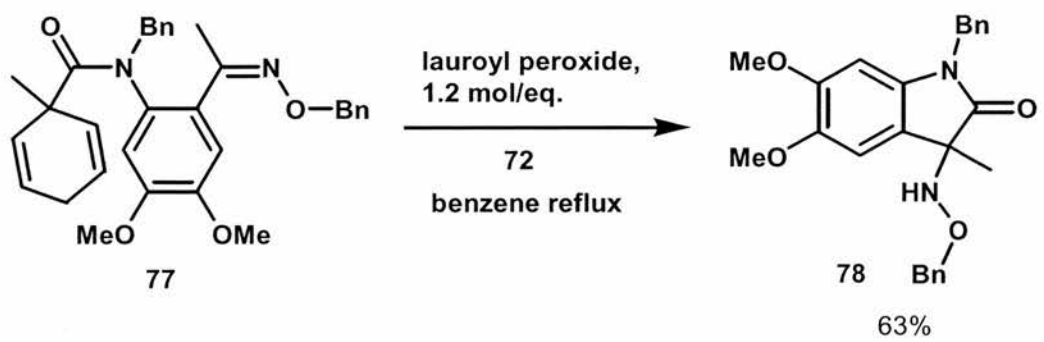
| Radical | T / K | *g*-factor | *a* (G) |
|---|---|---|---|
|  | 255 | [2.0026] | *a* (1H) = 12.4<br>*a* (2H) = 9.0<br>*a* (2H) = 2.6 |
|  | 310 | 2.0044 | *a* (N) = 13.7<br>*a* (2H) = 2.5 |

**Table 2**

### 4.2.11 Preparation of 1-benzyl-3-[(benzyloxy)amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2*H*-indol-2-one (78).

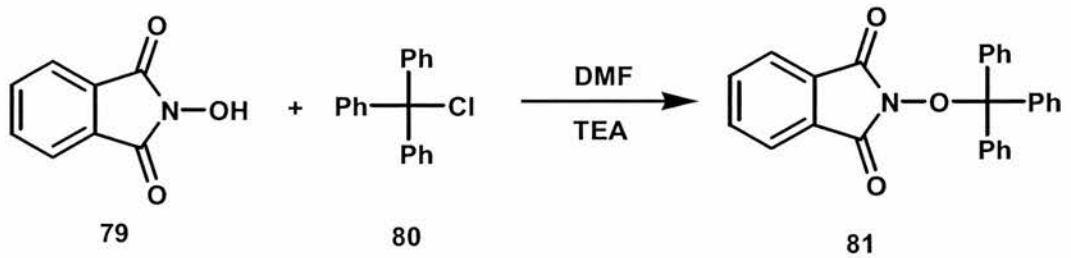
Lauroyl peroxide mediated thermolysis of amide **77** in the presence of 0.05 $cm^3$ of methyl thioglycolate **72** in refluxing benzene for 30 hours furnished a crude oil which was analysed by GC-MS. GC-MS analysis revealed the presence of benzopyrrolidinone **78** as the major product deriving from radical precursor **77**. The by-products were those derived from thermolytic breakdown of dilauroyl peroxide and from radical termination reactions of thiol **72**. Basic workup of the crude product followed by extraction with DCM furnished a crude brown solid which was purified by column chromatography to give 1-benzyl-3-[(benzyloxy)amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2*H*-indol-2-one **78** as a yellow pale oil in reasonable yields (Scheme 31).




**Scheme 31**

### 4.2.12 Preparation of trityloxyamine.

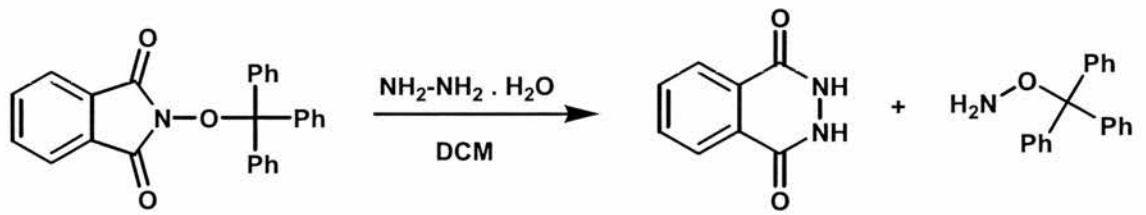
O-Trityloxyphthalimide **81** was prepared by reaction of *N*-hydroxyphthalimide **79** with powdered trityl chloride **80** in the presence of triethylamine in enough DMF to make a dense slurry solution. The mixture obtained was then left to stand for 36 hours, redispersed in 2-propanol, poured into water and filtered, in order to obtain *N*-trityloxyphthalimide **81** as white powder (Scheme 32).




79 80 81

**Scheme 32**

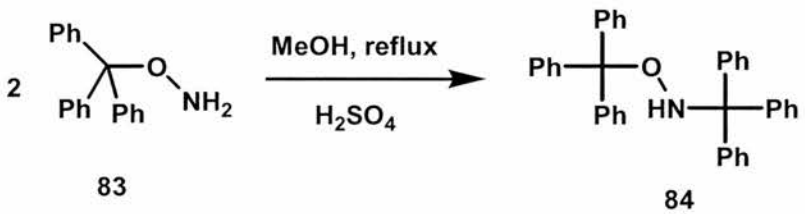
Preparation of trityloxyamine was performed by hydrazinolysis of compound **81**. When a solution of *N*-trityloxyphthalimide **81** was reacted with hydrazine hydrate in DCM solution for about 30 minutes, phthalazine-1,4-dione **82** separated as a white solid, which was redissolved by treating the solution with ammonium hydroxide. The aqueous solution was then extracted with DCM and dried with magnesium sulphate, before the solvent was evaporated at reduced pressure to leave a residue which was crystallised from methanol to give trityloxyamine **83** as white crystals in very good yield (Scheme 33).




81 82 83 92%

**Scheme 33**

It was noticed that on heating to reflux a concentrated methanolic or ethanolic solution of trityloxyamine **83** in the presence of sulphuric acid, a white insoluble solid separated. The solid was analysed by $^{1}H$ and $^{13}C$ NMR and identified to be *O,N*-bis-trityl-hydroxylamine **84**, formation of which may be due to the release of stable trityl carbocations probably formed, in hot methanol or ethanol, which, might react with trityloxyamine **83** to give product **84** (Scheme 34).

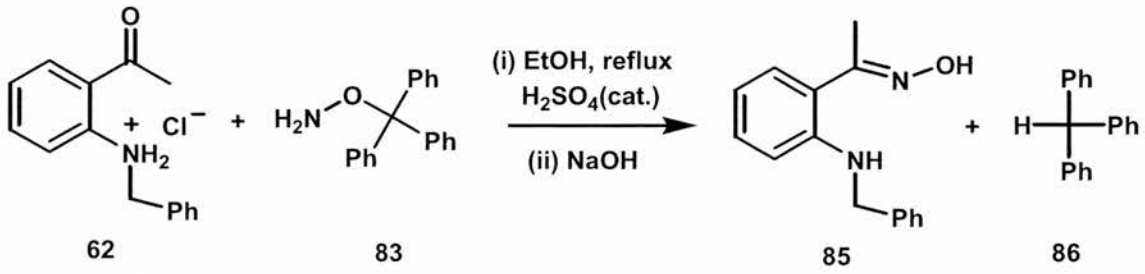



**83** **84**

**Scheme 34**

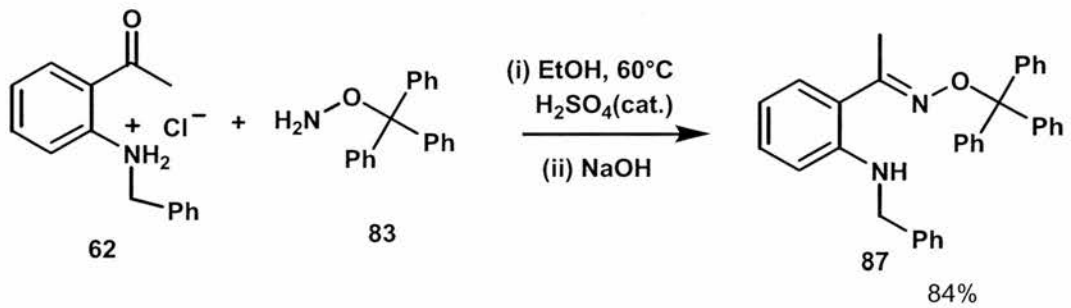
### 4.2.13 Preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime.

We first attempted the condensation of trityloxyamine **83** with (2-acetylphenyl)benzylammonium chloride **62** in refluxing benzene in the presence of a catalytic amount of sulphuric acid. The reaction mixture was refluxed overnight to give a yellow ethanolic solution. The ethanol was evaporated at reduced pressure to leave a slurry residue which was treated with aqueous NaOH, extracted with DCM before the solvent was eliminated at reduced pressure leaving a viscous yellow oil. Column chromatography of the crude product gave triphenylmethane **86** as the first fraction. A yellow pale solid which eluted as second fraction was determined to be *trans*-1-[2-(benzylamino) phenyl] ethanone oxime **85**, which was isolated as the major product and a small quantity of *cis*-1-[2-(benzylamino)phenyl] ethanone oxime was also obtained. On the basis of these observations we envisaged that the high reaction temperature, in conjugation with visible light might cause the radical cleavage of the preliminary formed, 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime to generate the stable trityl radical. The products formed from radical cleavage of amine **87** are shown in Scheme 35.




**Scheme 35**

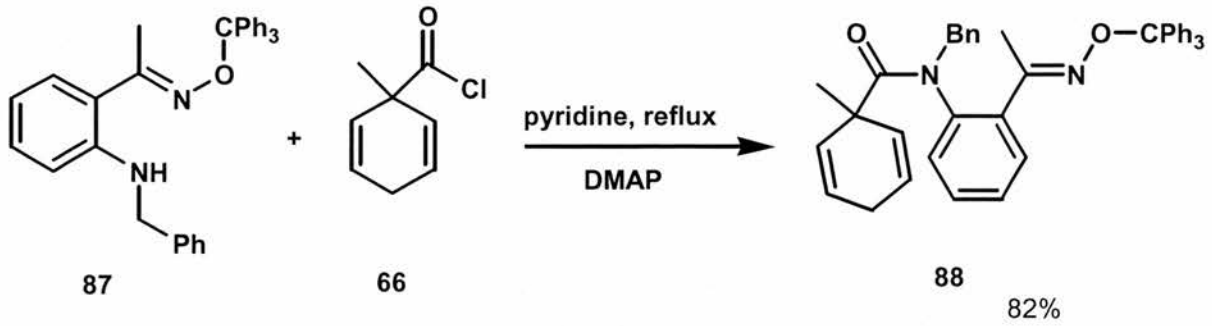
When the reaction was performed at 60°C, a white crystalline solid separated from the ethanolic solution. The product obtained was extensively washed with cold ethanol and dried under vacuum. The product obtained was characterised as the desired 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime (Scheme 36).




**Scheme 36**

### 4.2.14 Preparation of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]-phenyl}-2,5-cyclohexadiene-1-carboxamide (88).

A DCM solution containing 1.5 molar equivalents of methyl acid chloride **66** was added dropwise to a stirred solution of amine **87** and DMAP, in dry pyridine and the resulting mixture refluxed overnight and treated with a 6M HCl. The aqueous layer was then extracted with DCM, washed with a little $NaHCO_3$, dried, and the solvent evaporated at reduced pressure to yield a reddish crude oil which was purified by column chromatography to give a white solid which was crystallised from a mixture ethyl acetate/hexane/DCM to yield the desired *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide **88** (Scheme 37).




**Scheme 37**

Interestingly, X-ray analysis of amide **88** showed the preferred formation of the *trans* isomer over the *cis* with respect to the C=N double bond (Figure 3), in contrast with the general observation of the formation of *cis/trans* mixture, when oxime ether double bond generation is involved.

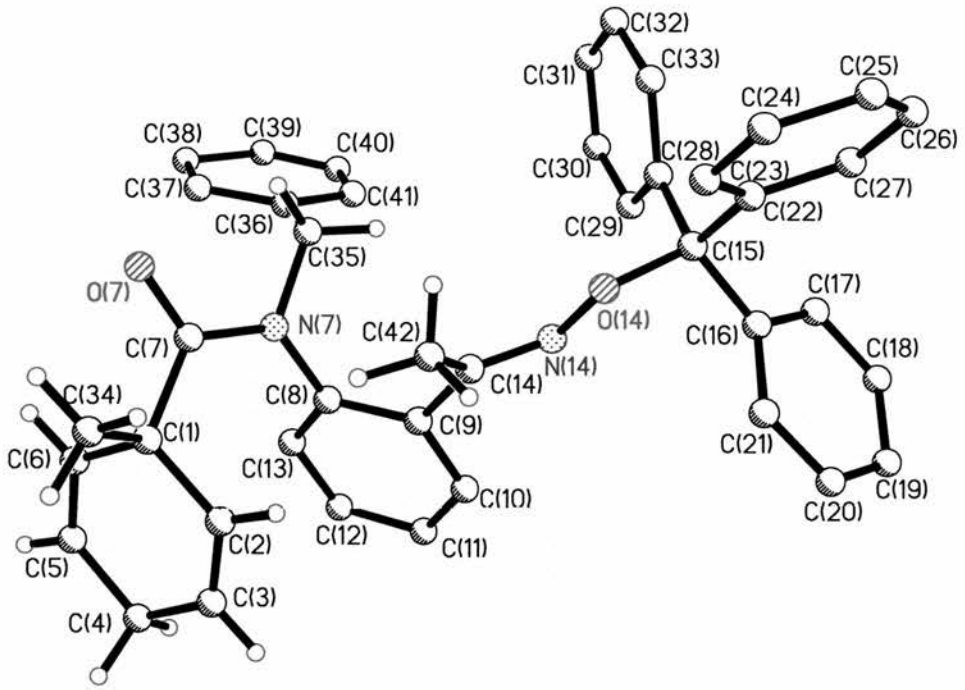



**Figure 3**

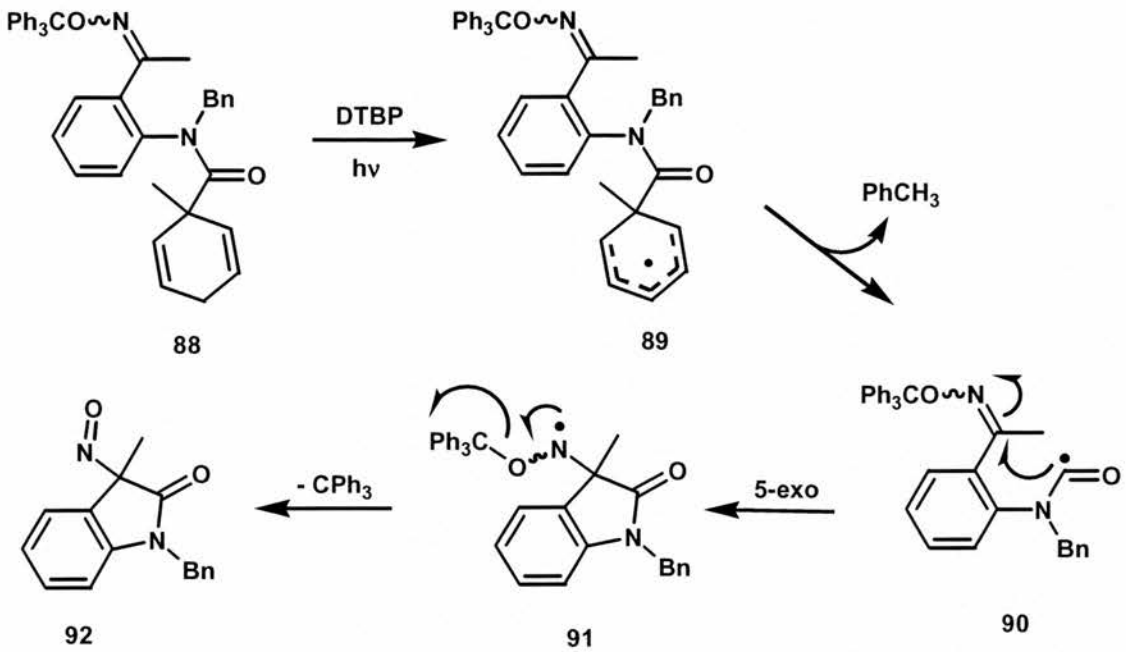
X-Ray data revealed that the C(1)-(C7) bond, which is involved in the radical β-scission to release the corresponding aminoacyl radical, was slightly longer than a normal C-C bond (Table 3). As expected the amidic C-N bond was shorter than a simple C-N bond showing some double bond character. In addition the O(14)-C(15) bond of the oxime ether was also comparatively long, as might be expected.

| atom-atom | Bond length [Å] | atom-atom-atom | Angle [°] |
|---|---|---|---|
| C(1)-C(7) | 1.555(4) | C(2)-C(1)-C(7) | 117.9(2) |
| C(7)-O(7) | 1.220(3) | N(7)-C(7)-C(1) | 121.1(2) |
| C(7)-N(7) | 1.367(3) | N(14)-C(14)-C(42) | 124.23(19) |
| C(14)-N(14) | 1.281(3) | N(14)-C(14)-C(9) | 112.93(18) |
| N(14)-O(14) | 1.418(2) | C(42)-C(14)-C(9) | 122.79(18) |
| O(14)-C(15) | 1.458(3) | C(14)-N(14)-O(14) | 110.51(17) |

**Table 3**

### 4.2.15 EPR investigation of radicals from *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).

Dissociation of amide **88** followed a diverse pathway in which cyclisation onto trityloxime ether was followed by a second β-scission with extrusion of the highly stabilised trityl radical and production of nitroso-compound **92**. The process does not constitute a radical chain but can efficiently be used in synthetic sequences. We have used EPR spectroscopy to determine how the mechanism differed from that seen for the photolysis of amides **67** and **77**. An accurately measured quantity of cyclohexadienyl carboxamide **88** (5 mg) was placed in a clean dry quartz tube, before DTBP was added and degassed for approximately 20 min. The sample was placed into the EPR cavity which was held at 230 K and illuminated by a 500 W super pressure Hg lamp. The EPR spectrum recorded at 230 K in the presence of UV light, had similar hfs to the previous cyclohexadienyl radicals (Figure 3 and table 4) and therefore confirmed the presence of cyclohexadienyl radical **89** (Scheme 38 and Figure 4).




**Scheme 38**

**9.5 GHz EPR spectrum obtained on photolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).**

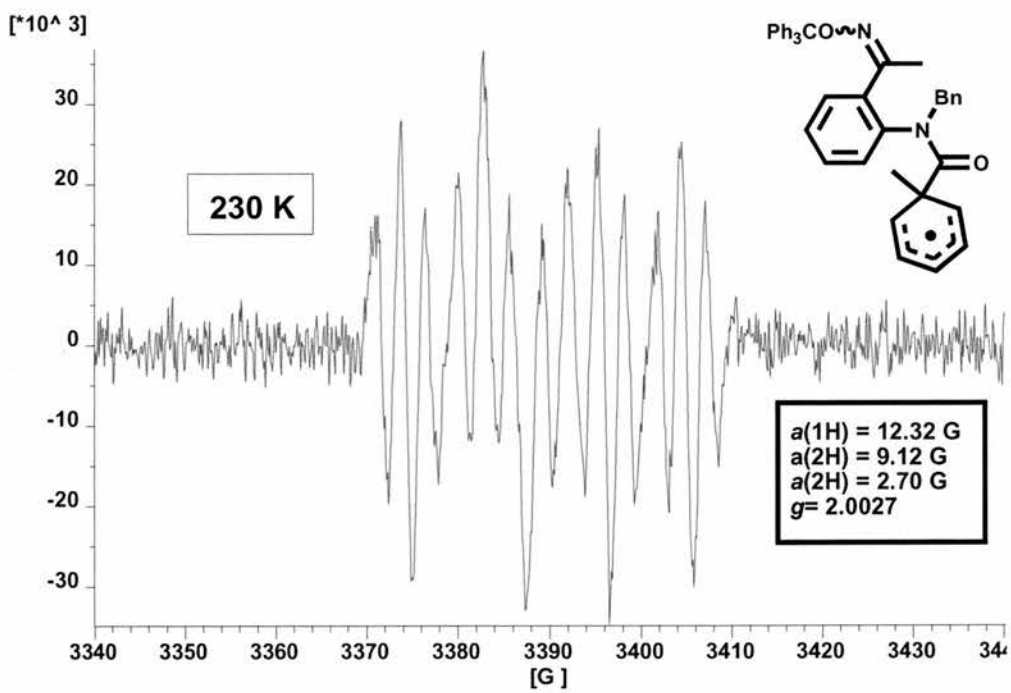



**Figure 4**

As the temperature of the EPR cavity was systematically increased at intervals of 5 K, the spectrum attributed to cyclohexadienyl radical **89** diminished in size. The spectra recorded at 320 K showed three pronounced lines, which gave a good evidence of the formation of cyclised alkoxyaminyl radical **91** (Figure 5).

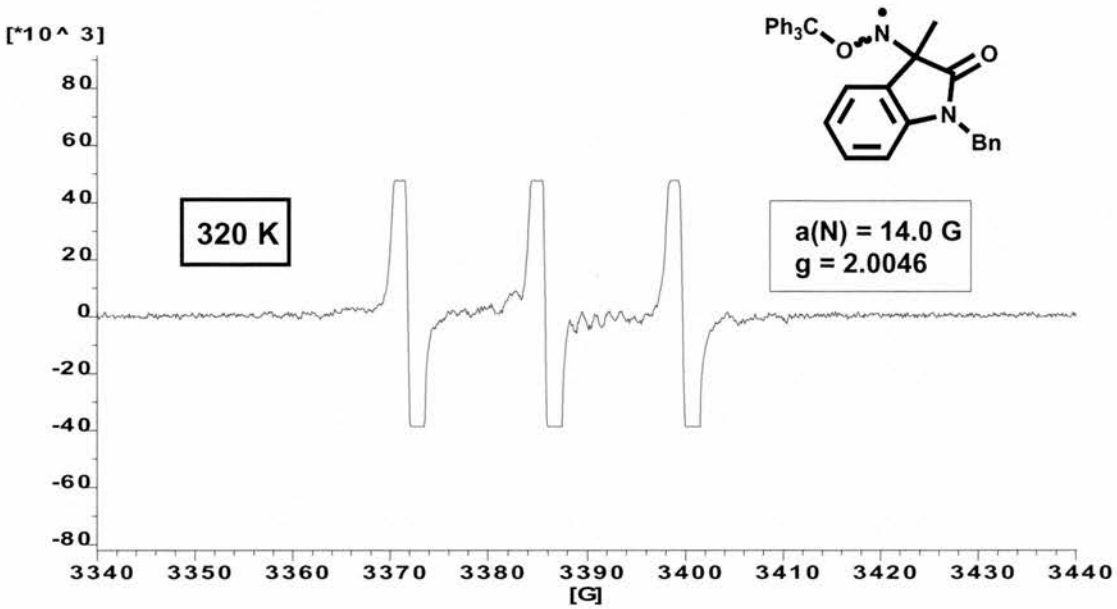



**Figure 5**

At 330 K the alkoxyaminyl radical started to release the stable trityl radical which was dected by EPR spectra (Figure 6).

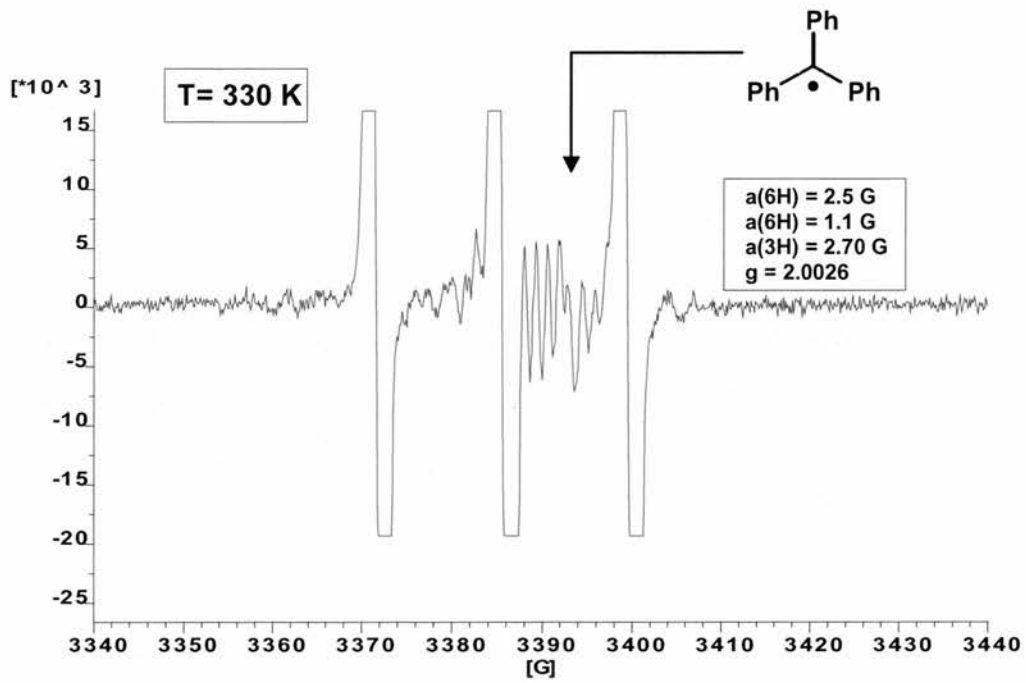



**Figure 6**

At higher temperatures, we observed the formation of an additional radical having a narrow nitrogen splitting [$a$(N) = 7.4 G] and $g$ = 2.0064, which are characteristic of acyl nitroxide radicals (Figure 7 and Table 4). The detected acyl nitroxide radical was probably formed from the free radical coupling reaction of the released nitroso benzopyrrolidinone **92** with aminoacyl radical **90**.

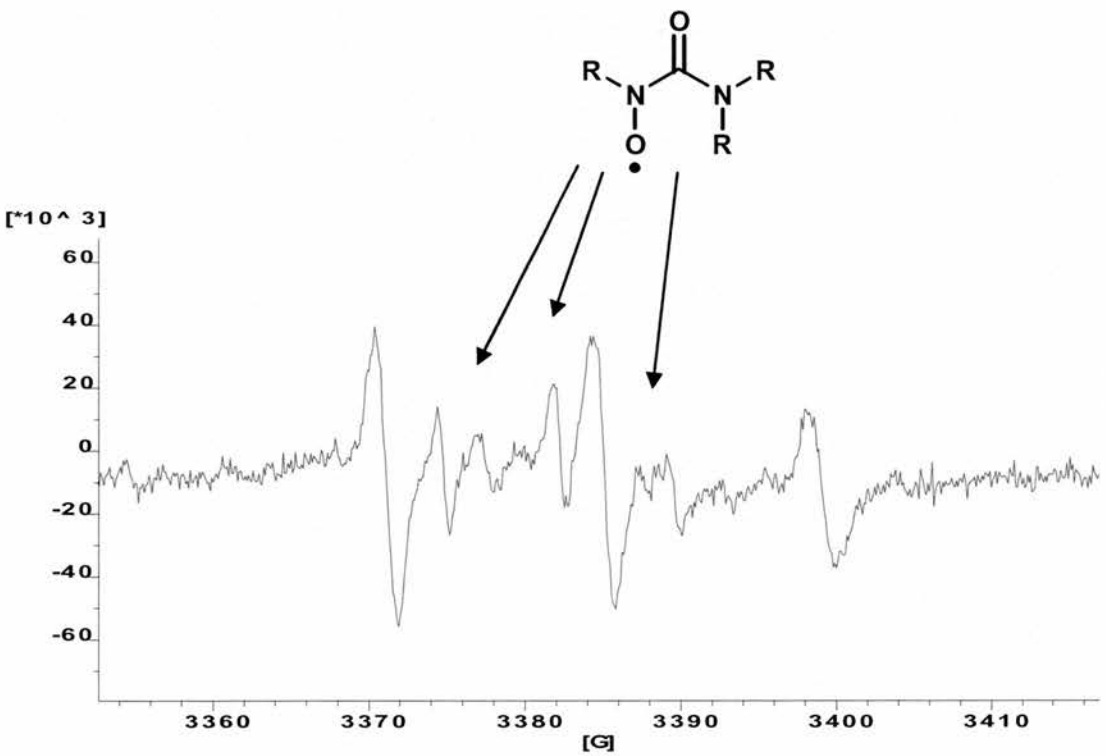



**Figure 7**

Further increments of temperature generated a complex EPR spectrum in which the peaks from radical **91** and trityl radical was replaced by the spectra of several nitroxides. An explanation is that the nitroso compound formed from release of trityl radicals can act as a radical trap for the aminoacyl radical **90** and other radicals in the system, leading to the formation of a mixture of nitroxide radicals in solution.

**9.4 GHz EPR parameters of radicals derived from *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).**

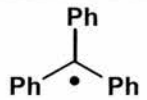
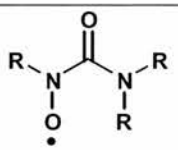
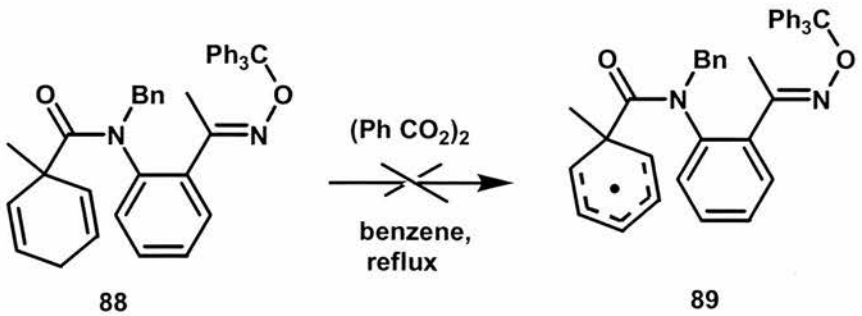
| Radical | T / K | *g*-factor | *a* (G) |
|---|---|---|---|
| **89** | 230 | 2.0027 | *a* (1 H) = 12.3<br>*a* (2 H) = 9.1<br>*a* (2 H) = 2.7 |
| **91** | 320 | 2.0046 | *a* (N) = 14.0 |
|  | 330 | 2.0026 | *a* (6 H) = 2.5<br>*a* (6 H) = 1.1<br>*a* (3 H) = 2.7 |
|  | 340-350 | 2.0064 | *a* (N) = 7.4 |

**Table 4**

### 4.2.16 DBP mediated thermolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).

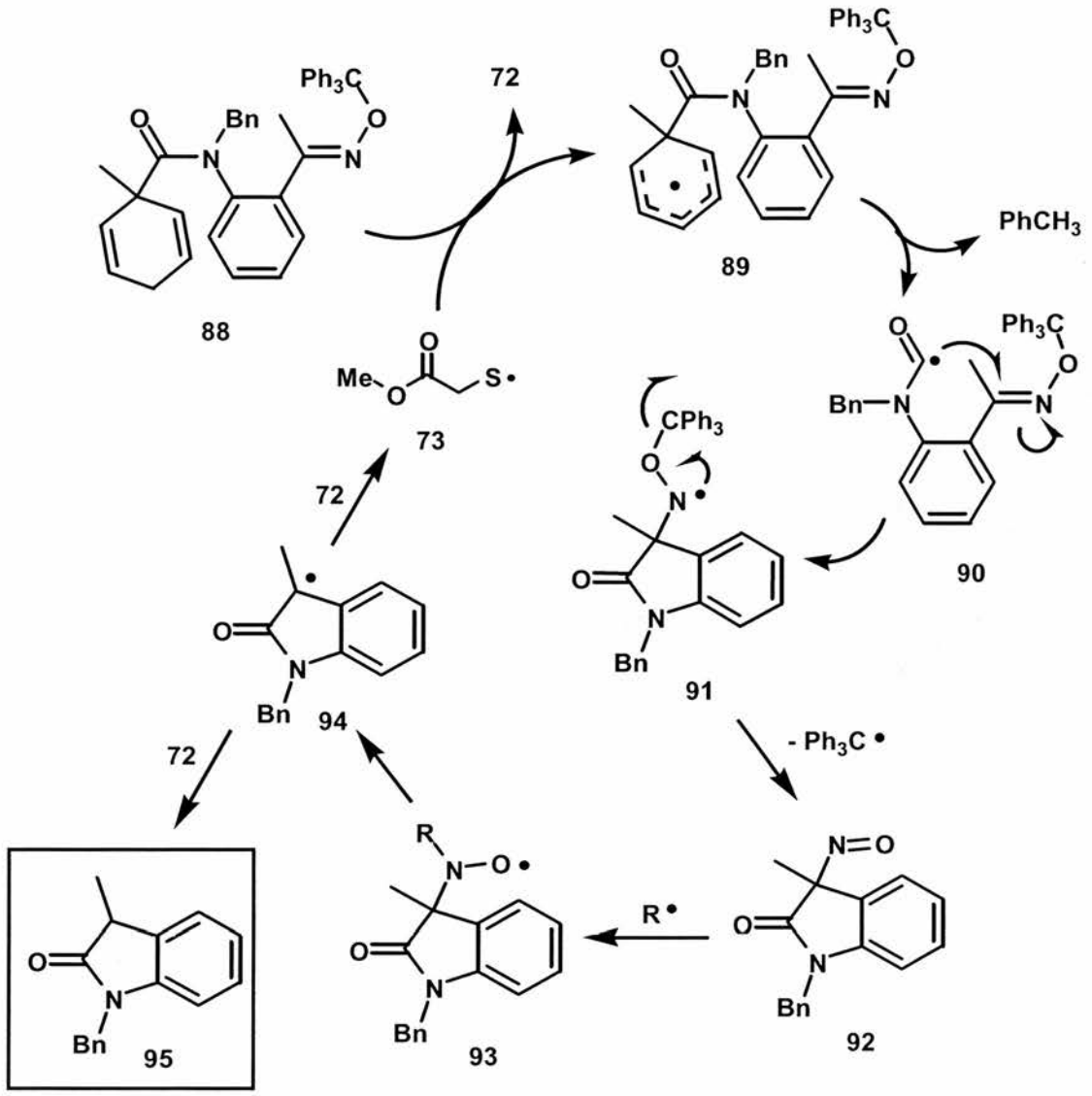
Induced radical fragmentation of amide **88** was carried out thermally with DBP in benzene and in toluene. DBP was added portionwise to a refluxing benzene or toluene solution of amide **88**. GC-MS analysis of the crude reaction mixtures revealed only the presence of unchanged amide starting material together with byproducts deriving from photolytic breakdown of DBP. Although the reaction was performed under different settings of temperature by varying the solvent, it was not possible to initiate the radical chain under these conditions (Scheme 39).




**Scheme 39**

### 4.2.17 Polarity reversal catalysis (PRC) by thiols in thermolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).

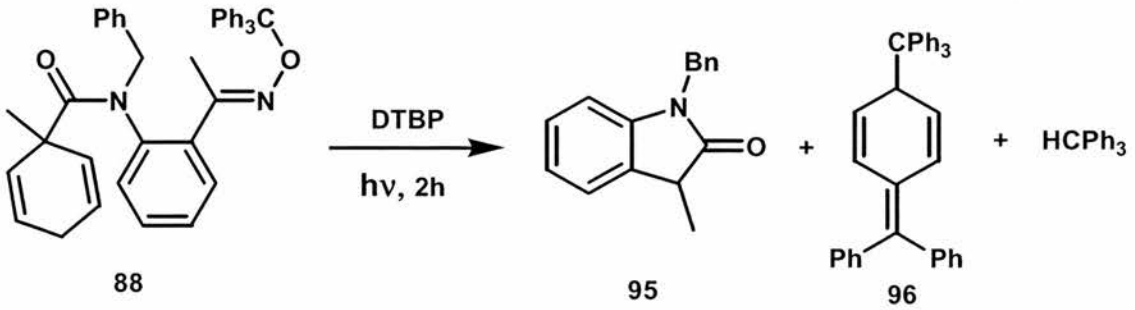
A benzene solution containing 2 molar equivalent of dilauroyl peroxide was added over 8 hours to a refluxing benzene solution containing cyclohexadiene carboxamide **88** and methyl thioglycolate **72**, (0.05 $cm^3$) and then refluxed for 24 hours. GC-MS analysis of the crude reaction mixture confirmed the presence of the cyclised 1-benzyl-3-methyl-1,3-dihydro-2*H*-indol-2-one **95** as the major reaction product, together with triphenylmethane and [[4-(diphenylmethylene)-2,5-cyclohexadien-1-yl](diphenyl)methyl]benzene **96** (dimer of triphenylmethane) derived from thermolytic β-scission of radical **91**. Other by-product were those derived from thermolytic breakdown of lauroyl peroxide and radical termination reactions of thiyl radicals. The reaction species detected by GC-MS suggested a mechanism in which thiyl radical **73** abstracted hydrogen from carbamoyl amide **88** to generate the delocalised cyclohexadienyl radical **89** followed by release of toluene to produce aminoacyl radical **90**. Intramolecular cyclisation of **90** gives indolylaminyl radical **91** which undergoes a second β-scission to generate the nitroso-indole **92**. It appeared that nitroso-indole **92** acted as a spin trap for other radicals in the system to give acyl nitroxides or alkyl nitroxides **93** which can easily undergo β-scission to release the extensively resonance stabilised radical **94**. Radical **94** can therefore abstract hydrogen from methyl thioglycolate to produce 1-benzyl-3-methyl-1,3-dihydro-2*H*-indol-2-one **95** as the major product, with regeneration of thiyl radical **73** which can propagate the chain reaction (Scheme 40).




**Scheme 40**

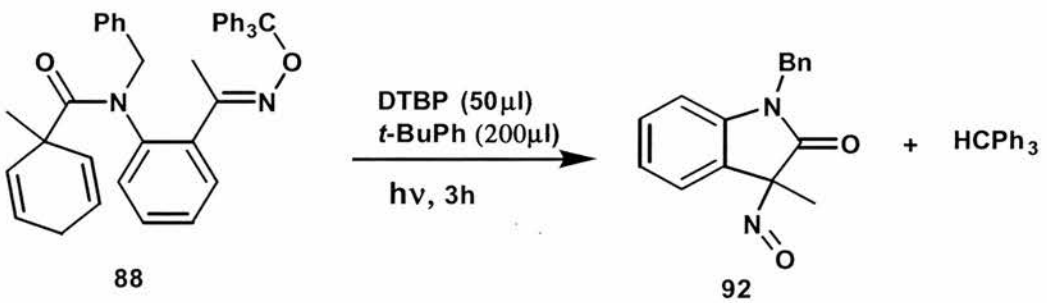
### 4.2.18 DTBP mediated photolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy) ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).

The photolytic radical fragmentation of amide **88** was also studied in order to determine the products formed under these conditions. Irradiation of amide **88** in neat DTBP at room temperature for two hours gave a crude reaction mixture. GC-MS analysis showed the presence of 1-benzyl-3-methyl-1,3-dihydro-2*H*-indol-2-one **95** together with triphenylmethane and [[4-(diphenylmethylene)-2,5-cyclohexadien-1-yl](diphenyl)methyl]benzene **96** (Scheme 41).




**Scheme 41**

DTBP mediated photolysis of amide **88** was also performed, in *t*-butylbenzene as co-solvent. The reaction mixture was photolysed at room temperature for three hours before the solvent was eliminated under high vacuum to give a yellow crude reaction mixture. GC-MS analysis showed the presence of 1-benzyl-3-methyl-3-nitroso-1,3-dihydro-2*H*-indol-2-one **92** as major product together with triphenylmethane (Scheme 42).

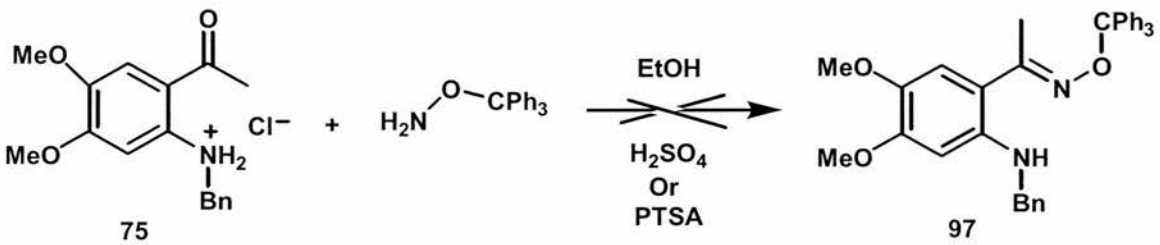



**Scheme 42**

### 4.2.19 Attempted preparation of 1-(2-benzylamino-4,5-dimethoxy-phenyl)-ethanone *O*-trityl-oxime

A solution containing *O*-tritylhydroxylamine and 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone hydrochloride) **75** in ethanol (10 $cm^3$) was heated at 60 °C and stirred for 10 minutes before a drop of sulphuric acid was added. The solution obtained was refluxed for 3 hours before the solvent was evaporated under reduced

pressure and the slurry residue made basic by a 6N NaOH and extracted with DCM (3 x 20 $cm^3$). The combined organic layer was dried with $MgSO_4$, filtered and the solvent eliminated at reduced pressure to give yellow crude oil. Both TLC and NMR analysis showed the presence of product deriving from thermolytic breakdown of 1-(2-benzylamino-4,5-dimethoxy-phenyl)-ethanone *O*-trityl-oxime. Below 60°C there was no conversion of the starting materials. The reaction was also carried out using PTSA as acid catalyst. A solution containing 1.5 molar equivalent of *O*-tritylhydroxylamine and 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone hydrochloride in dry DCM was heated at reflux and stirred for 10 minutes before a catalytic amount of PTSA was added. The reaction was monitored by TLC and $^1$HNMR during 24 hours reflux which showed only the presence of unchanged starting material (Scheme 43).



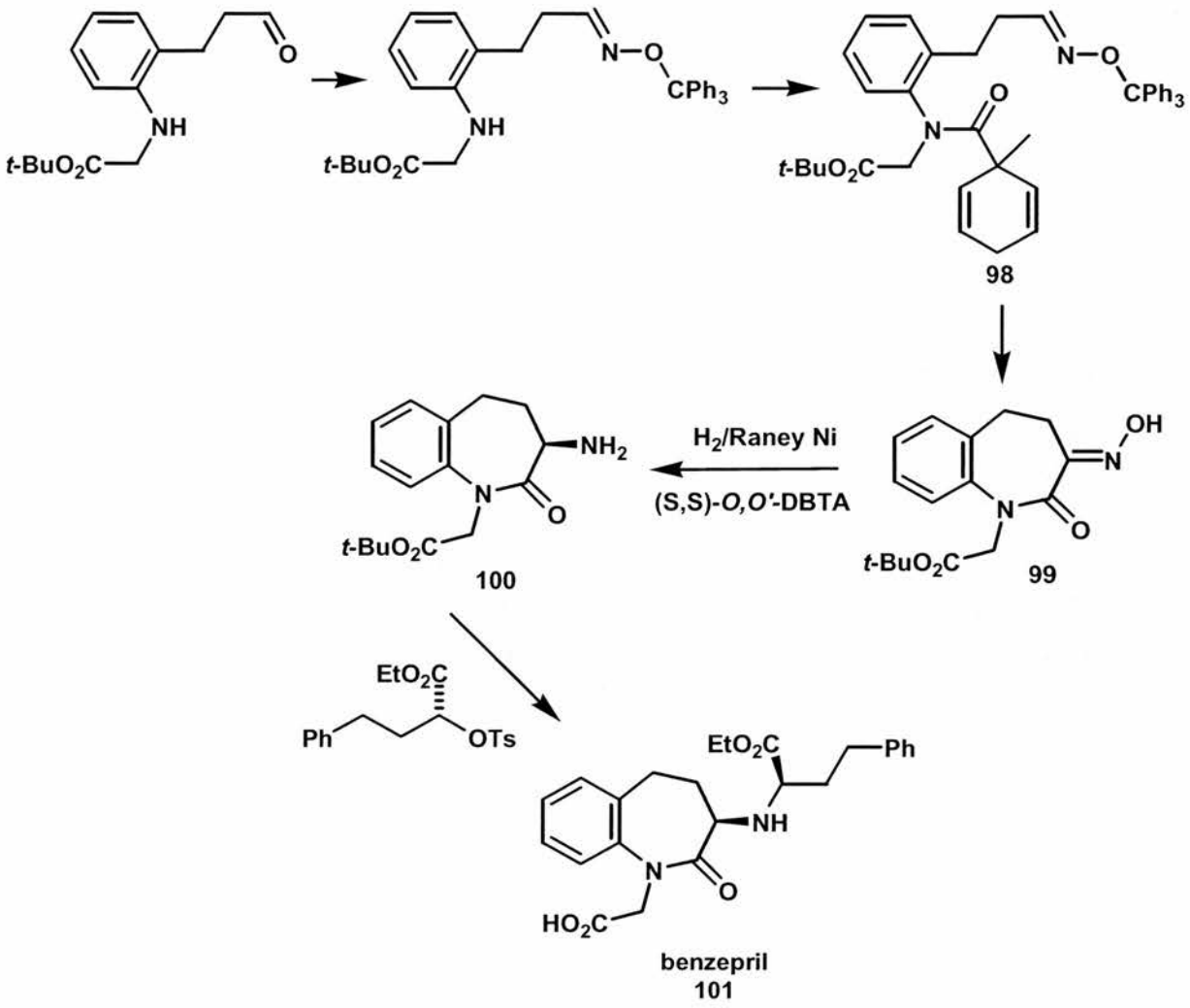

**Scheme 43**

# Summary and Conclusions

Amidocyclohexadiene precursors containing oxime ether functionality were designed and studied by EPR spectroscopy. Radical-induced decomposition gave the expected cyclohexadienyl radicals which were clearly detected at low temperatures. At increased temperatures, alkoxyaminyl radicals were also observed. Cyclisations of the corresponding carbamoyl radicals were too fast to be observable by EPR spectra. When reactions were carried out on a preparative scale, benzopyrrolidinone derivatives were isolated in good yields. The product heterocycles contain N-functionality at C(3), exactly as required in many antibiotics. Addition of methyl thioglycolate in dilauroyl peroxide mediated radical reaction, led to improved product yields.

An elegant use of *O*-trityl oxime ethers, in which the oxime functionality was regenerated, had attracted our attention. We prepared an *O*-trityl oxime ether substituted cyclohexadienecarboxamide precursor. Standard radical-induced initiation was followed by EPR spectroscopy which showed that the released cyclohexadienyl radical undergoes β-scission to produce the corresponding carbamoyl radical which ring closed to generate the alkoxyaminyl radical. The reaction took a novel route because the trityl alkoxyaminyl radicals underwent a second β-scission to extrude the highly stabilised trityl radical with production of a nitroso-compound.

We suggested the use of our developed strategy for a tin-free, radical-mediated synthesis of benzepril (ACE inhibitor). We envisaged that 7-*exo*-ring closure onto the oxime ether radical acceptor would be sufficiently rapid to facilitate the otherwise difficult ring closure. Precedent research suggested a strategy in which precursor **98** would release the desired carbamoyl radical followed by 7-*exo*-cyclisation. Extrusion of the $Ph_3C^{\bullet}$ radical should produce lactam oxime **99** (tautomer of the corresponding nitroso-compound) which could be enantioselectively be reduced to amine **100.** Known *N*-alkylation and deprotection steps could then afford benzepril **101** (Scheme 44).

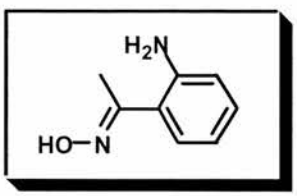



**Scheme 44**

Diversity can be introduced by using alternative aryl aldehydes and/or by alternative alkylations of amine **100**. We prepared some intermediates on the way to **98**, but time ran out on the project before the process could be tested.

# Experimental

**Preparation of 1-(2-aminophenyl)ethanone oxime (57)**




A solution containing 1-(2-aminophenyl)ethanone (2.84g, 21 mmol), hydroxylamine hydrochloride (4.38 g, 63 mmol) and sodium hydroxide (6.72 g, 168 mmol) was dissolved in 30 $cm^3$ of a mixture 15% $H_2O$/EtOH and was heated at 60°C for 30 min. The bulk of the ethanol was then concentrated by evaporation under reduced pressure, the residue was treated with dilute hydrochloridric acid (50 $cm^3$, 2M), and extracted with ether (3 x 20 $cm^3$). The organic layer was washed with water, dried with magnesium sulphate and the solvent evaporated under reduced pressure to leave a crude white solid, mp: 102-104°C (2.3 g, 73%). $\delta_H$ (300MHz, $CDCl_3$) 2.31 (3H, s, $CH_3$), 5.39 (2H, broad s, NH), 6.71-7.37 (4H, m, ArH); $\delta_c$ (75 MHz, $CDCl_3$) 12.5 ($CH_3$), 116.6, 117.1 (2 x ArH ), 118.8, (quaternary-C), 128.8, 129.5 (2 x ArH ), 145.5 (quaternary-C), 158.3 (C=N); IR (nujol): 3392 (OH stretch), 1614 (C=N, stretch), 1463, 1290, 998, 755; MS (EI), *m/z* (%) 150 ($M^+$, 100), 133(100), 118(430), 106(27), 92(32), 77(10), 65(20). HRMS, (Found: ($M^+$) 150.1805, $C_8H_{10}N_2O$ requires ($M^+$) 150.1809).

**Attempted preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime.**

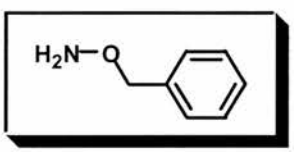
Sodium (0.35 g, 15.2 mmol was dissolved in 5 $cm^3$ of ethanol and the solution obtained was slowly added, over a period of 2 hrs, to a refluxing solution of 1-(2-aminophenyl)ethanone oxime **57** (1 g, 6.66 mmol), benzyl bromide (2.28g, 13.33 mmol) in ethanol (30 $cm^3$). The mixture was then refluxed for two additional hrs and a white flocky product separated from solution. Water 10 $cm^3$ was added and reflux was continued for 1 additional hr. The white crystalline solid separated from the reaction mixture was filtered and washed with ethanol and then with water to give pure 1-[2-

(dibenzylamino)phenyl]ethanone oxime **58** as a white solid, mp: 170-172°C, (1.48 g, 67%). $\delta_H$ (300MHz, $CDCl_3$) 2.37 (3H, s, $CH_3$), 4.11 (4H, s , benzylic-$CH_2$), 6.88-7.29 (14H, m, ArH), 7.90 (1H, br s; OH); $\delta_c$ (75 MHz, $CDCl_3$) 15.2 ($CH_3$), 55.9 (benzylic-$CH_2$), 121.7 (CH), 122.5 (CH), 127.1 (CH), 128.1 (CH), 129.1 (CH), 130.1 (CH), 132.4, (quaternary-C), 137.3, (2 x quaternary-C), 149.2 (quaternary-C), 128.44, 159.6 (C=N); IR (nujol): 1592 (C=N, stretch); MS (EI) *m/z* (%) 330($M^+$, 4), 313(5), 312(10), 297(20), 296(87), 221(23), 206(25), 91(100), 77(12), 65(8).

**Attempted preparation of 1-(2-aminophenyl)ethanone *O*-benzyloxime[44]**

To a stirred mixture of 1-(2-aminophenyl)ethanone oxime **57** (1g, 6.66 mmol) and benzyl bromide (0.95, 5.55 mmol) in DMF (20 $cm^3$) at 0 °C, was added caesium carbonate 2.16g, 6.66 mmol). The mixture was stirred overnight. Water (25 $cm^3$) was added, and the product was extracted with ether (3 x 25 $cm^3$), then washed extensively with water and the organic layer dried with magnesium sulphate and concentrated. TLC and $^1H$ NMR of the crude product confirmed the only presence of unchanged starting material.

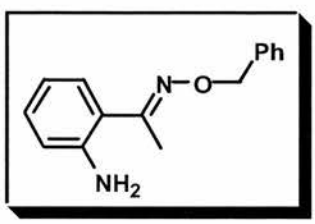
**Preparation of *O*-benzyl-hydroxylamine[45]**




A solution containing *N*-hydroxyurethane (3g, 28.6 mmol) and benzyl bromide in 20 $cm^3$ of super dry ethanol was heated to reflux. Alcoholic KOH (15 $cm^3$, 2M) was then added dropwise over a period of 2hr. Heating was continued for for another 2 hr after which 22 $cm^3$ of 20% aqueous KOH was added. The mixture was refluxed for 3 additional hr and the bulk of ethanol was removed by distillation. The residue was diluted with water and extracted with ether. This solution was washed with an excess of dilute HCl and the acid extracts was made alkaline with NaOH. The oil which separated was extracted with ether. Distillation of the dried extract yielded 1.7 g (49%) of *O*-benzyl-hydroxylamine. as a colorless oil; $\delta_H$ (300MHz, $CDCl_3$) 4.68 (2H, s, $CH_2$),

5.38 (2H, broad s , NH), 7.33-7.36 (5H, m, ArH); $\delta_c$ (300 MHz, $CDCl_3$), 77.8 (benzylic, O-$CH_2$), 127.8, 128.2, 128.3, (5 x ArH ), 137.2 (quaternary-C); IR (neat): 3050 (NH stretch), 700; Anal. Calcd for $C_7H_{10}ClNO$: C, 52.67; H, 6.32, N, 8.78. Found: C, 53.13, H, 6.51, N, 8.60.

**Preparation of 1-(2-aminophenyl)ethanone *O*-benzyloxime (60)[46]**



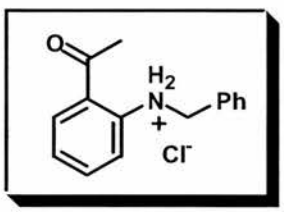

A solution of *O*-benzylhydroxylamine (0.4g, 3.2 mmol), 1-(2-aminophenyl)ethanone **56** (0.3 g 2.22 mmol) and a drop of sulphuric acid in ethanol (10 $cm^3$) was refluxed for 10 hrs. The ethanol was evaporated under reduced pressure and the slurry residue made basic by 6M NaOH and extracted with DCM (3 x 20 $cm^3$). The combined organic layer was dried with $MgSO_4$, filtered and the solvent eliminated at reduced pressure to give a brown crude oil which was distilled on a Kugelrohr under high vacuum at 75°C/0.1 Torr by using Kugelrohr distillation apparatus. The residue from distillation was dissolved in hydrochloric acid (6 M), filtered and washed with a basic NaOH (6 M), extracted with DCM (3 x 20), dried with magnesium sulphate and the solvent eliminated at reduced pressure to yielded a yellow pale, oil 0.3 g (56%). $\delta_H$ (300MHz, $CDCl_3$) 2.29 (3H, s, $CH_3$), 5.17 (2H, s benzylic-$CH_2$), 5.35 (2H, br s, $NH_2$), 6.57-7.40 (9H, m, ArH); $\delta_c$ (75 MHz, $CDCl_3$) 13.3 ($CH_3$), 75.9 (benzylic-$CH_2$), 116.3(CH), 116.6 (CH), 118.1 (quaternary-C), 127.7-129.3, (7 x ArH ), 138.0 (quaternary-C)), 145.8 (quaternary-C), 157.3 (C=N).

**Attempted preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime (61)**

Benzyl bromide (0.1g, 0.6 mmol) was added dropwise to a stirred solution of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime **60** (0.2 g, 0.6 mmol) and triethylamine (0.1g, 10 mmol) in N,-N-dimethylformamide (10$cm^3$) and then heated at reflux for 6h. The solvent was evaporated at reduced pressure to give a residue which was washed

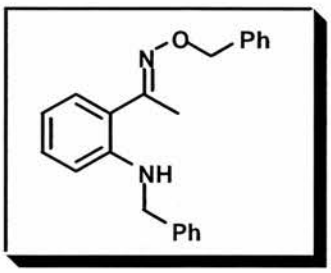
with water (100 $cm^3$) containing a little sodium carbonate and extracted with DCM (3 x 30 $cm^3$). The solvent was evaporated at reduced pressure to leave a yellow crude product. TLC and $^1H$ NMR of the crude product confirmed that starting material was not converted under these conditions.

**Preparation of (2-Acetylphenyl)benzylammonium chloride (62)**




A mixture of two parts of 1-(2-aminophenyl)ethanone **56** (5g, 37 mmol) and 1 part of benzyl bromide (3.16, 18.5 mmol) was heated at 60°C for 3h on a water bath to afford a dark yellow crystalline mass. The solid cake was dissolved in hydrochloric acid (36% water solution) re-precipitated into water 300 ($cm^3$), and filtered. The yellow solid was washed with water and further purified by crystallisation using a mixture ethanol-petroleum ether to yield (2-Acetylacetylphenyl)benzylammonium chloride **62** as a yellow pale crystalline product, mp: 72-74°C, (3g, 73%). $\delta_H$ (300MHz, $CDCl_3$) 2.61 (3H, s, $CH_3$), 4.46 (2H, s, benzylic-$CH_2$), 6.58-6.66 (2H, m, ArH), 7.25-7.34 (6H, m, ArH) 7.76-7.78 (1H, m, ArH), 9.32 (1H, br s; NH); $\delta_c$ (75 MHz, $CDCl_3$) 28.0 ($CH_3$), 46.7 (benzylic-$CH_2$), 112.2, 114.4 (2 x CH), 117.8 (quaternary-C), 126.9, 127.1, 128.6, 132.6, 135.0 (7 x CH), 138.6 (quaternary-C), 150.8 (quaternary-C) 201.0 (C=O); IR (nujol): 3321 (NH stretch), 1641 (C=O), 1568, 1515, 1227, 1164; MS (CI), *m/z* (%) 226 $(M + H)^+$, (100), 225(24), 57(27). HRMS, [Found: $M^+$+1 226.1221, $C_{15}H_{16}NO$ requires $(M + H)^+$ 226.1231]; Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71, N, 6.22. Found: C, 79.41, H, 6.68.N, 6.16.

**Preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime (61)**



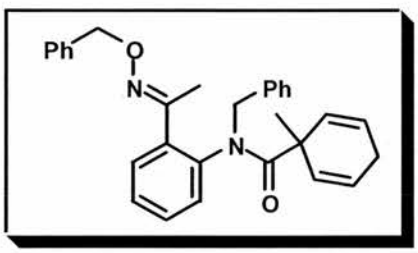

A solution of *O*-benzylhydroxylamine (0.9g, 7.3 mmol), and (2-Acetylphenyl)benzylammonium chloride **62** (1.5g, 5.7 mmol) in ethanol (10 $cm^3$) was heated to reflux for 30 minutes before a drop of sulphuric acid was added. The solution obtained was refluxed overnight before the solvent was evaporated under reduced pressure and the slurry residue made basic by 6M NaOH and extracted with DCM (3 x 20 $cm^3$). The combined organic layer was dried with $MgSO_4$, filtered and the solvent eliminated at reduced pressure to give yellow pale crude oil. Purification was performed by column chromatography (rf = 0.74), (alumina, eluiting with 10% ethyl acetate in hexane) to give 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime **61**, as a colourless oil. Crystallisation in hexane afforded a white crystalline solid, mp: 52-54 °C, 1.5 g (79 %). $\delta_H$ (300MHz, $CDCl_3$) 2.33 (3H, s, $CH_3$), 4.27 and 4.29 (2H, 2 x s, benzylic-$CH_2$), 5.01 (2H, s benzylic-$CH_2$), 6.56-6.64 (2H, m, ArH) 7.20-7.38 (12H, m, ArH)), 7.95 (1H, br s; NH); $\delta_c$ (75 MHz, $CDCl_3$) 13.2 ($CH_3$), 47.4 (benzylic-$CH_2$), 75.9 (benzylic-$CH_2$) 111.1 (CH), 115.1 (CH), 117.5 (quaternary-C), 126.9-129.8, (12 x CH ), 138.0 (quaternary-C), 139.4 (quaternary-C), 146.8 (quaternary-C), 157.8 (C=N); IR (nujol): 3305 (NH stretch), 1603 (C=N, stretch), 1515, 1335, 1319, 1272, 1011, 889, 751, and 697, MS (CI), *m/z* (%) 331 [$(M+H)^+$, (100)], 223(37), 91(16), HRMS, [Found: $(M+H)^+$ 331.1802, $C_{22}H_{23}N_2O$ requires: $(M+1)^+$ 331.1810]. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71, N, 8.48. Found: C, 79.59, H, 7.11, N, 8.50.

**Preparation of 1-methyl-2,5-cyclohexadiene-1-carbonyl chloride (66)**

To a stirred solution of oxalyl chloride (2g, 15.7 mmol), in dry DCM (20 $cm^3$) was added a catalytic amount of N,N-dimethylformamide (10 µl). When the evolution of gas finished, 1-methyl-2,5-cyclohexadiene-1-carboxylic acid (1g, 7.2 mmol), was added dropwise and the resulting solution was refluxed for 1h under nitrogen, before

removing the solvent and the excess of oxalyl chloride at reduced pressure (water bath at 35°C), to leave the crude acid chloride. The impure product was taken-up with diethyl ether filtered and the solvent evaporated under reduced pressure to yield a colourless oil identified as 1-methyl-2,5-cyclohexadiene-1-carbonyl chloride (1g, 89 %). $\delta_H$ (300 MHz, $CDCl_3$) 1.45 (3 H, s, $CH_3$), 2.73 (2H, br s, bisallylic H), 5.65-5.80 (2 H, m, olefinic H), 5.92-6.06 (2H, m, olefinic H).

**Preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67).**




1-Methylcyclohexa-2,5-diene-1-carbonyl chloride **66** (0.85g, 5.4 mmol) was dissolved in dry dichloromethane (5 $cm^3$) and added dropwise to a mixture of 1-[2-(benzylamino)phenyl]ethanone *O*-benzyloxime **61** (1.2 g, 3.6 mmol) and a catalytic amount of DMAP in dry distilled pyridine (20 $cm^3$). The resultant mixture was refluxed overnight before adding HCl (6M, 50 $cm^3$). The aqueous layer was extracted twice with $CH_2Cl_2$ (2 × 100 $cm^3$), the combined organic layer washed with water containing a little $NaHCO_3$ (20 $cm^3$), water (20 $cm^3$) and dried over $MgSO_4$. The solvent was evaporated at reduced pressure to give a brown crude oil, which was purified by column chromatography, eluting with 5 % ethyl acetate in hexane, in order to furnish the desired amide **67** as a yellow pale oil which was crystallised from a mixture ethyl acetate/ hexane affording *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide **67** as colourless crystals, mp: 62-64 °C, (1.4 g, 86 %); $\delta_H$ (300MHz, $CDCl_3$) 1.33 (3H, s, $CH_3$), 1.92-2.30 (2H, AB system, bisallylic-$CH_2$), 2.19 (3H, s, $CH_3$), 3.73 and 5.43 (2H, AX system, $J_{gem}$ = 14.34 Hz, benzylic, N-$\underline{CH_2}$), 4.80-5.67 (4H, m, vinylic, $CH_2$), 5.24 (2H, s, benzylic-O-$\underline{CH_2}$), 6.77-7.40 (14H, m, ArH)); $\delta_c$ (75 MHz, $CDCl_3$) 15.0 ($CH_3$) 25.7 (bisallylic-$CH_2$), 29.5 ($CH_3$), 45.9 (quaternary-C), 55.0 (benzylic, N-$\underline{CH_2}$), 76.2

(benzylic, O-$CH_2$), 119.8 (CH), 123.1, 126.8, 127.4, 127.6, 127.9, 127.9, 128.2, 128.7, 128.9, (12 x ArH ), 129.4, 131.65 131.8 (3 x CH), 134.8 (quaternary-C), 136.6 (quaternary-C), 137.8 (quaternary-C), 139.7 (quaternary-C), 153.4 (C=N), 174.1 (C=O); IR (nujol): 1630 (C=O, stretch), 1250, 1075, 1021, 913, and 698; MS(CI), *m/z* (%) 451($M^+$+1, 25), 253(11), 236(7), 147(10), 107 (75), 91(17), 71(14), 57 (91); HRMS, [Found: $(M + H)^+$ 451.2401, $C_{30}H_{31}N_2O_2$ requires $(M + H)^+$ 451.2385]; Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.71, N, 6.22. Found: C, 78.89, H, 6.86, N, 6.04.

**Photochemically initiated reaction of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl] phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (67)**

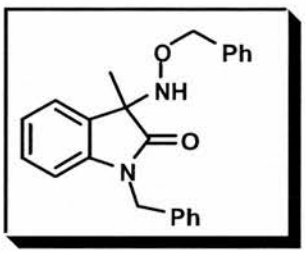
Amide **67** (0.05 g) was dissolved in neat DTBP (0.5 $cm^3$), the resultant solution was placed in a quartz tube, and the sample irradiated, at room temperature, with light from a 400 W medium pressure Hg lamp over a 3 h period. Analysis of the reaction mixture by GC/MS showed that starting material was completely converted and confirmed the presence of 5-*exo* product 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71**, Peak mins 34.33, *m/z(%)* 358 ($M^+$, 5), 357 (40), 327 (5), 281 (20), 236 (16), 207 (43), 159 (10), 91 (100), 28 (35), together with unreacted amide **67**. The only detectable impurities were those derived from the photolytic breakdown of DTBP. When a sample containing 0.05 g of amide **67** in 0.5 $cm^3$ of DTBP (0.05 $cm^3$) was heated at 100 °C and irradiated for 3 hrs with UV light. GC-MS analysis of the reaction mixture showed the only presence of, 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71**, together with by-products derived from photolytic breakdown of DTBP.

**Attempted DBP mediated thermolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl] phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide.**

Dibenzoyl peroxide (0.1 g, 0.6 mmol) was dissolved in benzene (2 $cm^3$) and added dropwise over a period of 6 h, by using a syringe pump, to a refluxing benzene solution (7 $cm^3$) containing amide **67** (0.1 g, 0.22 mmol), After complete addition, the mixture was left to reflux for 24 hrs. The solvent was evaporated before dissolving the

impure product in ether (50 $cm^3$), washing with NaOH (2 × 50 $cm^3$), HCl (2 × 50 $cm^3$) and water (2 × 50 $cm^3$) and drying ($MgSO_4$). The solvent was evaporated under reduced pressure to give a yellow oil. NMR and GC-MS analysis of the crude product showed the only presence of unchanged starting material together with by-products coming from thermolytic breakdown of DBP.

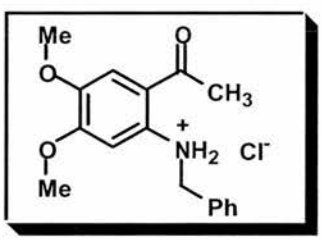
**Polarity reversal catalysis (PRC) by thiols in thermolysis of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl] phenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide.**




Lauroyl peroxide (0.13g, 0.33 mmol) was dissolved in 3 $cm^3$ of benzene. The solution was divided in 4 portions `(0.75 $cm^3$) and a first portion was added and refluxed for ten minutes before adding methyl thioglycolate **72** (0.05 $cm^3$) the remaining portions were added, over 9 hours (1 portion / 3 hrs), to a refluxing benzene solution containing amide **67** (0.1g, 0.22 mmol). After complete addition the solution was refluxed for 30 h, the solvent evaporated at reduced pressure leaving a crude product. GC-MS, peak mins. 3.61, methyl thioglycolate **72**, peak mins. 10.28, undecane (from initiator), peak mins. 16.13, disulphide (dimer of thiol), peak mins. 17.10, lauric acid (from initiator) peak mins. 23.45, docosane (from initiator), peak mins. 28.32 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71**. The crude reaction product was dissolved into DCM (20 $cm^3$) and treated with a warm 6M solution of KOH (50 $cm^3$). The aqueous phase was extracted with DCM (3 x 25 $cm^3$) and the combined organic layer dried with magnesium sulphate and evaporated at reduced pressure to leave a yellow crude oil. The crude oil was purified by column chromatography eluting with a mixture 30 % ethyl acetate in hexane ($R_f$ = 0.33) to give a colourless oil which was crystallised from ethyl acetate/ hexane to afford 1-benzyl-3-[(benzyloxy)amino]-3-methyl-1,3-dihydro-2*H*-indol-2-one **71** as a white crystalline product, mp: 99-100°C, (0.07 g, 68 %); $\delta_H$ (300MHz, $CDCl_3$) 1.40 (3H, s,

$CH_3$), 4.36 and 4.48 (2H, AB system, $J$= 10.8 Hz, benzylic-$CH_2$), 4.70 and 5.16 (2H, AB system, $J$=16.0 Hz, benzylic-$CH_2$), 6.26 (1H, br s, NH), 6.55-6.89 (2H, m, ArH), 7.03-7.24 (11H, m, ArH)), 7.44-7.46 (1H, m, ArH)); $\delta_c$ (75 MHz, $CDCl_3$) 20.2 ($CH_3$) 41.5 (benzylic N-$\underline{CH_2}$), 66.0 (quaternary-C), 77.7 (benzylic O-$\underline{CH_2}$), 109.8 (1 x ArH), 123.0 (1 x ArH), 124.0 (1 x ArH), 127.2, 127.6, 128.0, 128.5, 128.9, 129.0, 129.2, 129.4, (11 x ArH ), 130.8 (quaternary-C), 135.6 (quaternary-C), 137.2 (quaternary-C), 143.5 (quaternary-C), 179.1 (C=O); IR (nujol): 3229 and 3214 (NH stretch), 1718 (C=O, stretch); MS(EI), *m/z* (%) 358 ($M^+$, 15), 327(20), 236(53), 91(100), 65(7); HRMS, [Found: $[(M)^+$ 358.1674, $C_{23}H_{22}N_2O_2$ requires $(M)^+$ 358.1681]; Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19, N, 7.82. Found: C, 77.02, H, 6.02, N, 7.49.

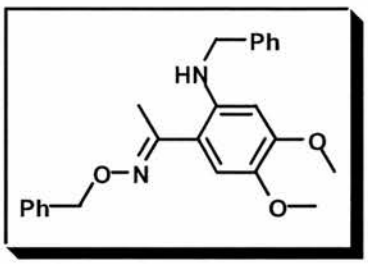
**Preparation of (2-acetyl-4,5-dimethoxyphenyl)benzyl ammonium chloride (75)**




To a stirred solution of 1-(2-amino-4,5-dimethoxyphenyl)ethanone **74** (5g, 26 mmol) and benzyl bromide (2.88 g, 16.8 mmol) in DMF was heated at 60-70°C for 3h. The reaction mixture was poured into water 300 ($cm^3$), acidified with HCl (36 %, 10 $cm^3$) and stirred overnight. The yellow solid separated from the aqueous phase and was filtered to give a red wine solid which was crystallised from a mixture of ethanol in petroleum ether to yield 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone hydrochloride **75** as a yellow pale crystalline product, mp: 118-120 °C, 3.8g (70%). $\delta_H$ (300 MHz, $CDCl_3$) 2.54 (3H, s, $CH_3$), 3.74 (3H, s, O-$CH_3$)), 3.82 (3H, s, O-$CH_3$), 4.46 (2H, s, benzylic-$CH_2$), 6.08 (1H, s, ArH) 7.17 (1H, s, ArH) 7.26-7.34 (5H, m, ArH), 9.51 (1H, br, s, NH); $\delta_c$ (75 MHz, $CDCl_3$) 28.2 ($CH_3$), 47.5 (benzylic-$CH_2$), 55.9 (O-$\underline{CH_3}$), 57.3 (O-$\underline{CH_3}$), 95.2 (1 x ArH), 110.4 (quaternary-C), 115.7(1 x ArH), 127.4, 127.6, 129.1 (5 x ArH), 139.1 (quaternary-C), 139.3 (quaternary-C), 149.1 (quaternary-C), 156.3 (quaternary-C), 198.6 (C=O); IR (nujol): 3293 (NH stretch), 1622 (C=O, stretch), 1572, 1527, 1512, 1267, 1232, 1203, 1170, 1044, 845, 815, 722, and 702; MS (EI) *m/z* (%) 285 ($M^+$, 46), 270(24), 192(12), 166(15), 91(100). HRMS,

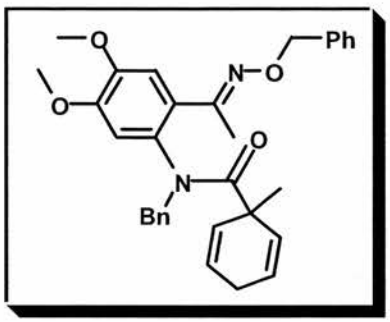
(Found: $(M)^+$ 285.1369, $C_{17}H_{19}NO_3$, requires $(M)^+$ 285.1365. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71, N, 4.91. Found: C, 71.45, H, 6.83.N, 4.89.

**Preparation of 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone *O*-benzyloxime**




A solution of *O*-benzylhydroxylamine (0.7g, 5.7 mmol), 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone hydrochloride **75** (1 .g, 3.1 mmol) in ethanol (10 $cm^3$) was heated to gentle reflux for ten minutes before a drop of sulphuric acid was added. The solution obtained was refluxed overnight before the solvent was evaporated under reduced pressure and the slurry residue made basic by 6M NaOH and extracted with DCM (3 x 20 $cm^3$). The combined organic layer was dried with $MgSO_4$, filtered and the solvent eliminated at reduced pressure to give yellow crude oil. Purification by column chromatography ($R_f$ = 0.42), (alumina, eluiting with 20 % ethyl acetate in hexane) afforded 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone *O*-benzyloxime **76** as a yellow pale crystalline solid. Crystallisation from a mixture of pentane ethyl acetate afforded a yellow pale crystalline solid, mp: 82-84°C, 1.0g (82 %). $\delta_H$ (300MHz, $CDCl_3$) 2.31 (3H, s, $CH_3$), 3.72 (3H, s , O-$CH_3$)), 3.79 (3H, s, O-$CH_3$), 4.26 (2H, s, benzylic-$CH_2$), 5.06 (2H, s, benzylic O-$\underline{CH_2}$), 6.13 (1H, s, ArH), 6.93 (1H, s, ArH), 7.22-7.28 (10H, m, ArH), 7.91 (1H, br, s, NH); $\delta_c$ (75 MHz, $CDCl_3$) 13.7 ($CH_3$), 48.4 (benzylic, N-$\underline{CH_2}$), 55.9 (O-$\underline{CH_3}$), 57.8 (O-$\underline{CH_3}$), 76.2 (benzylic O-$\underline{CH_2}$), 96.2 (1 x ArH), 109.6 (quaternary-C), 114.6 (1 x ArH), 127.4, 127.7, 128.2, 128.6, 128.8, 128.9 (10 x ArH), 138.6 (quaternary-C), 139.7 (quaternary-C), 140.0 (quaternary-C), 143.6 (quaternary-C), 151.5 (quaternary-C), 157.7 (C=N); IR (nujol): 3284 (NH stretch), 1624 (C=N, stretch), 1591, 1533, 1274, 1204, 1169, and 698 $cm^{-1}$; MS( (EI), *m/z* (%), 390 ($M^+$, 100)], 300 (55), 283 (87), 268 (14), 205 (7), 193 (12), 178 (15), 91 (60), 77 (6). HRMS, [Found: ($M^+$) 390.1930, $C_{24}H_{26}N_2O_3$ requires: ($M^+$) 390.1943]. Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71, N, 7.17. Found: C, 73.75, H, 6.74,.N, 7.14.

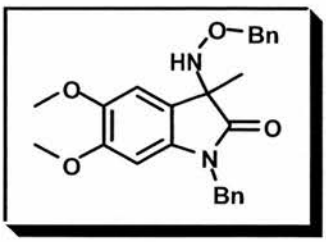
**Preparation of *N*-benzyl-*N*-{2-[*N*-(benzyloxy)ethanimidoyl]-4,5-dimethoxyphenyl}-1-methyl-2,5-cyclohexadiene-1-carboxamide (77)**




1-Methylcyclohexa-2,5-diene-1-carbonyl chloride **66** (0.5g, 3.2 mmol) was dissolved in dry dichloromethane (5 $cm^3$) and added dropwise to a mixture of 1-[2-(benzylamino)-4,5-dimethoxyphenyl]ethanone *O*-benzyloxime **76** (0.8 g, 2.0 mmol) and a catalytic amount of DMAP in dry distilled pyridine (20 $cm^3$). The resultant mixture was refluxed overnight before adding HCl (6N6M, 50 $cm^3$). The aqueous layer was extracted twice with $CH_2Cl_2$ (2 × 100 $cm^3$), the combined organic layer was washed with water containing a little $NaHCO_3$ (20 $cm^3$), water (20 $cm^3$) and dried over $MgSO_4$. The solvent was evaporated at reduced pressure to give a yellow crude oil, which was purified by column chromatography, eluting with ethyl acetate in hexane (1:9→3:7) in order to furnish the desired amide **77** as a yellow pale oil (0.7 g, 87 %); $\delta_H$ (300 MHz, $CDCl_3$) 1.25 (3H, s, $CH_3$), 1.95-2.35 (2H, m, bisallylic-$CH_2$), 2.19 (3H, s, $CH_3$), 3.47 (3H, s, $CH_3$), 3.69 and 5.51 (2H, AX system, $J_{gem}$ = 13.99 Hz, benzylic, N-CH2), 3.87 (3H, s, O-$CH_3$), 4.84-5.71 (4H, m, vinylic, CH), 5.23 (2H, s, benzylic-O-$CH_2$), 6.10 (1H, s, ArH), 6.75 (1H, s ArH) 7.09-7.41 (10H, m, ArH)); $\delta_c$ (75 MHz, $CDCl_3$) 15.6 ($CH_3$) 26.1 (bisallylic-$CH_2$), 30.0 ($CH_3$), 46.4 (quaternary-C), 55.2 (benzylic, N-$CH_2$), 55.8 (O-$CH_3$), 56.5 (O-$CH_3$), 76.6 (benzylic, O-$CH_2$), 111.4 (1 x ArH), 115.4 (1 x ArH), 119.3 (1 x ArH), 123.7 (2 x vinylic CH), 127.0 (quaternary-C), 127.4-129.8, (9 x ArH ), 132.58 (2 x vinylic-CH), 133.2 (quaternary-C), 137.8 (quaternary-C), 137.9 (quaternary-C), 147.6 (quaternary-C), 148.0 (quaternary-C), 153.8 (C=N), 174.5 (C=O); IR (nujol): 1638 (C=O, stretch), 1518 (C=C), 1260 (C=C), 1212, 1028, 864, 731, and 700 $cm^{-1}$ MS(CI), *m/z* (%) 511 [$(M+H)^+$, 100), 417(13), 311(10), 296(15), 283 (6), 107(7), 57 (82); HRMS, [Found: $(M + H)^+$ 511.2607,

$C_{32}H_{35}N_2O_4$ requires $(M + H)^+$ 511.2597; Anal. Calcd for $C_{32}H_{34}N_2O_4$: C, 75.27; H, 6.71, N, 5.49. Found: C, 74.75, H, 6.73, N, 6.35.

**Polarity reversal catalysis (PRC) by thiols. Preparation of 1-benzyl-3-[(benzyloxy)amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2H-indol-2-one (78)**




To a stirred refluxing solution of amide **77** (0.1 g, 0.25 mmol) in benzene (5 $cm^3$) was added 0.5 ml of a solution prepared dissolving 0.12 g,(0.3 mmol) of lauroyl peroxide in 2.5 $cm^3$ of benzene and left to reflux for 5 minutes before adding methyl thioglycolate **72** (0.05 $cm^3$). The remaining lauroyl peroxide solution was then added over 8 hrs. After complete addition the solution was refluxed for 30 hrs, the solvent was evaporated at reduced pressure to gave give a crude product which was analysed by GC-MS. GC-MS, peak mins. 3.61, methyl thioglycolate **72**, peak mins. 10.28, undecane (from initiator), peak mins. 16.13, disulphide (dimer of thiol), peak mins. 17.10, lauric acid (from initiator) peak mins. 23.45, docosane (from initiator), peak mins. 28.2 1-benzyl-3-[(benzyloxy)amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2*H*-indol-2-one **78**. The crude reaction product was dissolved into DCM (20 $cm^3$) and treated with a warm 6M solution of KOH (50 $cm^3$). The aqueous phase was extracted with DCM (3 x 25 $cm^3$) and the combined organic layer dried with magnesium sulphate and evaporated at reduced pressure to leave a crude brown solid. The crude product was purified by column chromatography eluting with a mixture 40 % ethyl acetate in hexane ($R_f = 0.28$) to give 1-benzyl-3-[(benzyloxy)amino]-5,6-dimethoxy-3-methyl-1,3-dihydro-2*H*-indol-2-one **78** as a yellow pale oil (0.05 g, 63 %); $\delta_H$ (300 MHz, $CDCl_3$) 1.37 (3H, s, $CH_3$), 3.74 (3H, s, O-$CH_3$), 3.84 (3H, s, O-$CH_3$), 4.40 and 4.50 (2H, AB system, *J*= 11.0 Hz, benzylic-$CH_2$), 4.70 and 5.13 (2H, AB system, *J*=15.9 Hz, benzylic-$CH_2$), 6.26 (1H, s, NH), 6.93-6.99 (1H, m, ArH), 7.10-7.26 (11H, m, ArH)), $\delta_c$ (75 MHz, $CDCl_3$) 19.9 ($CH_3$) 43.6 (benzylic N-$\underline{CH_2}$), 56.0 (O-$CH_3$), 56.5 (O-$CH_3$) 65.6 (quaternary-C), 76.4 (benzylic O-$\underline{CH_2}$), 95.3 (1 x ArH), 108.1 (1 x ArH), 120.8 (quaternary-C), 126.6, 127.1, 127.4, 127.9, 128.2, 128.4, (10 x ArH ), 135.2 (quaternary-C), 136.5 (quaternary-C), 136.8 (quaternary-C), 144.9 (quaternary-C),

149.6 (quaternary-C) 178.7 (C=O); IR (neat): 3235 (NH stretch), 1718 (C=O, stretch); MS (EI), *m/z* (%), 418 ($M^+$, 4), 312(28), 297(100), 282(35), 269(12), 178(28), 91(95);`HRMS, Found: [$(M)^+$ 418.1885, $C_{25}H_{26}N_2O_4$ requires $(M)^+$ 418.1893].

**Preparation of N-trityloxyphthalimide (81)[47]**

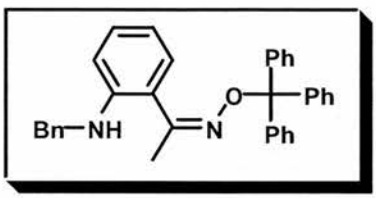
Powdered tritylchloride (9.5 g, 34 mmol) was added to a vigorously stirred solution of N-hydroxyphthalimide (5.6 g, 34 mmol) and 5 $cm^3$ of triethylamine in 15 $cm^3$ of N, N-dimethylformamide. The mixture was stirred for 20 min. and allowed to stand for 36 hrs. The solid mass was broken up, made pourable by the addition of 2-propanol and added to 500 $cm^3$ of water. The solid was filtered, redispersed in water containing a little sodium carbonate solution, and filtered; the filter cake was washed with water and dried to give 13.6 g (99 %) of white powder, mp 180-183 °C. $\delta_H$ (300 MHz, $CDCl_3$) , 7.22-7.33 (15H, m, ArH), 7.51-7.64 (4H, m, ArH)); $\delta_c$ (75 MHz, $CDCl_3$); 97.8 (quaternary-C), 122.9 (2 x CH), 127.3 (6 x CH), 126.1 (3 x CH), 127.8 (quaternary CH), 128.6 (quaternary CH) 130.1 (6 x CH), 134.0 (2 x CH), 141.6 (3 x quaternary-C), 163.9 (2 x C=O); IR (nujol): 1770, 1720; Anal. Calcd for $C_{27}H_{19}NO_3$: C, 79.98; H, 4.72, N, 3.46. Found: C, 79.97, H, 4.74, N, 3.70.

**Preparation of trityloxyamine (83)[47]**

To a stirred solution of N-trityloxyphthalimide **81** (5 g, 12.3 mmol) in 30 ml of DCM, was added 2.40 $cm^3$ (50 mmol) of hydrazine hydrate in 10 $cm^3$ of methanol. After 30 minutes the solid phthalazine-1,4-dione was dissolved by the addition of 50 $cm^3$ of 5 M ammonium hydroxide. The aqueous layer was removed and extracted with DCM (3 x 20 $cm^3$), and the combined extracts was washed with brine, dried with magnesium sulphate, stirred with decolorizing charcoal and filtered. The solvent was then evaporated at reduced pressure and the residue was crystallised from a small volume of methanol to give 3g (92 %) of white crystals, mp 83-88 °C; $\delta_H$ (300 MHz, $CDCl_3$) 4.6 (2H, br s, $NH_2$), 7.21-7.43 (15H, m, ArH)); $\delta_c$ (75 MHz, $CDCl_3$) 90.7 (quaternary-C), 127.1, 127.8, 128.8 (15 x ArH ), 143.2 (3 x quaternary-C); IR ($CCl_4$): 1580, 1490,

1450, 1035, 970, 705 $cm^{-1}$; Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22, N, 5.09. Found: C, 83.08, H, 6.22, N, 5.08.

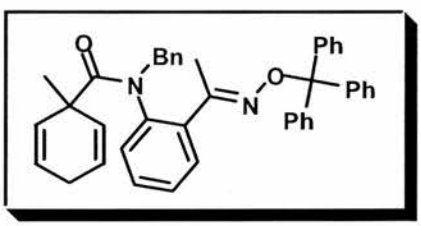
**Preparation of 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime (87).**




To a stirred solution containing (2-Acetylacetylphenyl)benzylammonium chloride **62** (1.0 g, 4.4 mmol) in warm ethanol (10 $cm^3$), was added portionwise *O*-tritylhydroxylamine **83** (1.8g, 6.5 mmol). After complete addition the mixture was heated at 60 °C and stirred for 10 minutes before adding a drop of sulphuric acid. When a white solid separated from solution, the temperature was lowered to room temperature and stirred for 20 minutes. The reaction mixture was filtered and the solid cake, extensively washed with ethanol and dried under vacuum, to give a pure, white, crystalline product **87**, mp: 160-162°C, 1.8 g (84 %). $\delta_H$ (300 MHz, $CDCl_3$) 2.54 (3H, s, $CH_3$), 3.92 and 3.94 (2H, 2 x s, benzylic N-$CH_2$), 6.35 (1H, d, ArH), 6.57 (1H, t, ArH), 6.96-7.01 (1H, m, ArH), 7.17-7.42 (21H, m, ArH)), 7.49 (1H, br s; NH); $\delta_c$ (75 MHz, $CDCl_3$) 13.8 ($CH_3$), 46.5 (benzylic-$CH_2$), 91.2 (3 x quaternary-C), 111.1 (CH), 114.7 (CH), 117.8 (quaternary-C), 126.4, 126.6, 127.1, 127.4, 127.7, 128.2, 128.9, 129.3, 129.7, (21 x CH ), 139.7 (quaternary-C), 143.0 (quaternary-C), 144.7 (quaternary-C), 146.7 (quaternary-C), 157.1 (C=N); IR (nujol): 3305 (NH stretch), 1603 (C=N), 966, 907, 749, and 703 $cm^{-1}$; MS (ES), *m/z* (%) 483 [$(M + H)^+$, (16)], 244 (26), 243 (100), HRMS, [Found: $(M+H)^+$ 483.2444, $C_{34}H_{31}N_2O$ requires: $(M+1)^+$ 483.2436]; Anal. Calcd for $C_{34}H_{30}N_2O$: C, 84.61; H, 6.27, N, 5.80. Found: C, 85.45, H, 5.80,.N, 5.39. The reaction was previously carried out in refluxing ethanol for 10 hrs, the solvent was evaporated under reduced pressure and the slurry residue made basic by 6M NaOH and extracted with DCM (3 x 20 $cm^3$). The combined organic layer dried with $MgSO_4$, filtered and the solvent eliminated at reduced pressure to give yellow pale crude oil. Separation of the products was performed by column chromatography (alumina), eluiting with 10 % ethyl acetate in hexane to give products deriving from

radical cleavage of 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime **87**; *trans*-1-[2-(benzylamino) phenyl] ethanone oxime **85** (major isomer) as a yellow pale crystalline solid, mp: 52-54°C, $\delta_H$ (300 MHz, $CDCl_3$) 2.33 (3H, s, $CH_3$), 4.40 (2H, benzylic N-$CH_2$), 6.62-6.70 (2H, m, ArH), 7.12-7.41 (7 x ArH), 7.79 (1H, br s, NH); $\delta_c$ (75 MHz, $CDCl_3$) 12.5 ($CH_3$), 47.5 (benzylic N-$CH_2$), 111.3 (1 x ArH), 115.4 (1 x ArH), 117.9 (quaternary-C), 126.9, 127.1, 128.5, 129.0, 129.9 (7 x ArH), 139.4 (quaternary-C), 146.8 (quaternary-C), 158.9 (C=N); IR (nujol) $cm^{-1}$: 3337 (NH stretch), 1604 (C=N, stretch), 1568, 1519, 897 and 733; MS (EI) *m/z* (%) 240 [$(M)^+$, 45), 223(100), 206(55), 118(22), 91 (92), 65(15); HRMS, [Found: $(M)^+$ 240.1269, $C_{15}H_{16}N_2O$ requires $(M)^+$ 240.1262], *cis*-1-[2-(benzylamino) phenyl] ethanone oxime as a white crystalline solid; $\delta_H$ (300 MHz, $CDCl_3$) 2.41 (3H, s, $CH_3$), 4.21(2H, s, benzylic N-$CH_2$), 7.05-7.64 (9H, m, ArH), 8.26 (1H, br s, NH); $\delta_c$ (75 MHz, $CDCl_3$) 13.9 ($CH_3$), 47.0 (benzylic N-$CH_2$), 109.3 (1 x ArH), 119.0, 121.9, 122.2, 126.1, 127.8, 128.9 (8 x ArH), 135.5 (quaternary-C), 135.7 (quaternary-C), 142.5 (quaternary-C), 151.8 (C=N) and triphenyl methane. $\delta_c$ (75 MHz, $CDCl_3$) 56.8 (CH), 126.2, 128.2, 129.4 (15 x ArH), 143.8 (3 x quaternary-C).

**Preparation of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).**




To a stirred mixture containing 1-[2-(benzylamino)phenyl]ethanone *O*-trityloxime **87** (1.4 g, 2.9 mmol) and a catalytic amount of DMAP in dry distilled pyridine (20 $cm^3$) was slowly added a solution prepared by dissolving 1-Methylcyclohexa-2,5-diene-1-carbonyl chloride (0.67 g, 4.4 mmol) in dry dichloromethane (5 $cm^3$). The resultant mixture was refluxed overnight before pouring in aqueous HCl (6M, 50 $cm^3$). The aqueous layer was extracted twice with $CH_2Cl_2$ (2 × 100 $cm^3$), the combined organic layer was washed with water containing a little $NaHCO_3$ (20 $cm^3$), water (20 $cm^3$) and dried over $MgSO_4$. The solvent was evaporated at reduced pressure to leave a reddish

crude oil, which was purified by column chromatography, eluting with ethyl acetate in hexane 5 % ($R_f$=0.27) in order to furnish the desired *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]-phenyl}-2,5-cyclohexadiene-1-carboxamide **88** as a white solid which was crystallised from a mixture ethyl acetate/ hexane/DCM affording colourless crystals, mp: 164-166 °C, (1.43 g, 82 %); $\delta_H$ (300 MHz, $CDCl_3$) 1.19(3H, s, $CH_3$), 1.85-2.23 (2H, AB system, bisallylic-$CH_2$), 2.42 (3H, s, $CH_3$), 3.40 and 5.51 (2H, AX system, $J_{gem}$ = 14.34 Hz, benzylic, N-CH2), 4.72-5.64 (4H, m, vinylic, $CH_2$), 6.53 (1H, d, ArH), 6.78-7.37 (23 x H, m, ArH)). $\delta_c$ (75 MHz, $CDCl_3$) 16.4 ($CH_3$) 25.6 (bisallylic-$CH_2$), 29.8 ($CH_3$), 45.8 (quaternary-C), 54.4 (benzylic, N-$CH_2$), 91.0 (quaternary-C), 120.1 (1 x ArH), 123.1 (2 x vinylic CH), 126.8, 127.0, 127.2, 127.6, 127.8, 129.2, 129.6 129.0, (23 x ArH ), 131.8 (2 x vinylic-CH), 135.1 (quaternary-C), 137.5 (quaternary-C), 138.9 (quaternary-C), 144.7 (3 x quaternary-C), 154.4 (C=N), 173.9 (C=O); IR (nujol): 1632 (C=O, stretch), 963, 754 and 699 $cm^{-1}$; MS(ES), *m/z* (%) 625 [$(M + Na)^+$, 100), 243 (8); HRMS, [Found: $(M + Na)^+$ 625.2823, $C_{42}H_{38}N_2O_2Na$ requires $(M + Na)^+$ 625.2831; Anal. Calcd for $C_{42}H_{38}N_2O_2$: C, 83.69; H, 6.35, N, 4.65. Found: C, 83.75, H, 6.49, N, 4.45. Crystal data for **88**: $C_{42}H_{38}N_2O_2$, M = 602.74, colourless platelets, crystal size 24 x 12 x 1 mm3, triclinic, space group P-1, a = 8.4178(15), b = 12.781(2), c = 16.416(3) Å, β = 83.997(3)°, V = 1674.9 (5) Å3, Dc = 1.195 Mg/m3, T = 125(2) K, R = 0.0341, Rw 0.0831 for 10017 reflections with $I>2\sigma(I)$ and 137 variables. Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (α = 0.71073 Å). The structure was solved by direct methods and refined using full-matrix least squares methods. Atomic coordinates and bond lengths and coordinates are listed in appendix 1 (table 3) and the structure is shown in Figure 3.

**DTBP mediated photolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).**

To a solution of amide **88** (0.03 g) in *tert*-butyl benzene (200µl) was added DTBP (50 µl) and placed in a quartz tube. The tube was capped and irradiated, at room temperature, with light from a 400 W high pressure Hg lamp for 3 h before DTBP was removed from the reaction mixture by warming itthe mixture under high vacuum to leave a yiellow crude oil which was analysed by GC-MS. Peak mins. 21.04, 1-benzyl-3-methyl-3-nitroso-1,3-dihydro-2*H*-indol-2-one **92**; *m/z* (%), 266 ($M^+$, 11), 119 (100), 91 (35), 57 (25), 28 (25) peak mins. 21.99, triphenyl methane, *m/z* (relative intensity) 244 ($M^+$, 100) 165 (94), 152 (25), 91(12). The only impurities detected were from photolytic breakdown of DTBP.

**Polarity reversal catalysis (PRC) by thiols. Dilauroyl peroxide mediated thermolysis of *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (88).**

To a refluxing benzene solution (5 $cm^3$) containing amide **88** (0.1 g, 0.16 mmol) was added over 8 hrs by syringe pump, a solution prepared by dissolving dilauroyl peroxide (0.12 g, 0.3 mmol) and methyl thioglycolate (0.05 $cm^3$) in benzene (2 $cm^3$). After complete addition the solution was refluxed for 24 hrs, the solvent was evaporated at reduced pressure gave a crude product which was analysed by GC-MS; peak mins. 3.61, methyl thioglycolate, peak mins. 10.28, undecane (from initiator), peak mins. 16.13, disulphide (dimer of thiol), peak mins. 17.10, lauric acid (from initiator) peak mins. 23.45, docosane (from initiator), peak mins. 21.7, triphenyl methane, peak mins. 22.14, 1-benzyl-3-methyl-1,3-dihydro-2*H*-indol-2-one **95,** *m/z* (relative intensity), 237 ($M^+$, 100), 208(35), 146(35), 128 (30), 117(10), 91(100), 77 (12), 65 (10). peak mins.23.18, triphenylmethanol, *m/z* (relative intensity), 260 ($M^+$, 43), 244(12), 235(12), 183 (100), 165(30), 154 (38), 91 (40), 77 (54). peak mins.27.4 [[4-(diphenylmethylene)-2,5-cyclohexadien-1-yl](diphenyl)methyl]benzene **96**.

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# Appendices

# Appendix 1

Table 1. Crystal data and structure refinement for *N*-benzyl-1-methyl-*N*-{2-[*N*-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (**88**).

| | | |
|---|---|---|
| Identification code | Carboxamide **88** | |
| Empirical formula | C42 H38 N2 O2 | |
| Formula weight | 602.74 | |
| Temperature | 125(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 8.4178(15) Å | α= 84.841(3)°. |
| | b = 12.781(2) Å | β= 83.997(3)°. |
| | c = 16.416(3) Å | γ = 72.819(3)°. |
| Volume | 1674.9(5) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.195 $Mg/m^3$ | |
| Absorption coefficient | 0.073 $mm^{-1}$ | |
| F(000) | 640 | |
| Crystal size | .24 x .12 x .1 $mm^3$ | |
| Theta range for data collection | 2.02 to 25.42°. | |
| Index ranges | -10<=h<=10, -14<=k<=15, -19<=l<=19 | |
| Reflections collected | 10017 | |
| Independent reflections | 5973 [R(int) = 0.0307] | |
| Completeness to theta = 25.42° | 96.7 % | |
| Absorption correction | MULTISCAN | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5973 / 0 / 418 | |
| Goodness-of-fit on $F^2$ | 1.039 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0647, wR2 = 0.1710 | |
| R indices (all data) | R1 = 0.0839, wR2 = 0.1853 | |
| Extinction coefficient | 0.017(3) | |
| Largest diff. peak and hole | 0.593 and -0.479 e.$Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$)for carboxamide **88** U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 1083(3) | 402(2) | 7898(2) | 39(1) |
| C(2) | -529(3) | 977(2) | 7522(1) | 33(1) |
| C(3) | -1990(3) | 837(2) | 7797(2) | 38(1) |
| C(4) | -2266(4) | 185(3) | 8563(2) | 54(1) |
| C(5) | -721(4) | -327(2) | 8975(2) | 53(1) |
| C(6) | 754(4) | -230(2) | 8700(2) | 52(1) |
| C(7) | 2202(3) | 1110(2) | 8085(2) | 47(1) |
| O(7) | 3697(3) | 677(2) | 8116(2) | 90(1) |
| N(7) | 1537(2) | 2201(2) | 8215(1) | 31(1) |
| C(8) | -211(3) | 2775(2) | 8315(1) | 26(1) |
| C(9) | -921(3) | 3623(2) | 7748(1) | 26(1) |
| C(10) | -2619(3) | 4171(2) | 7872(1) | 30(1) |
| C(11) | -3587(3) | 3896(2) | 8545(1) | 33(1) |
| C(12) | -2855(3) | 3084(2) | 9116(1) | 33(1) |
| C(13) | -1173(3) | 2536(2) | 9011(1) | 30(1) |
| C(14) | 80(3) | 3986(2) | 7029(1) | 27(1) |
| N(14) | -133(2) | 5023(2) | 6972(1) | 30(1) |
| O(14) | 813(2) | 5323(1) | 6272(1) | 31(1) |
| C(15) | 706(3) | 6482(2) | 6273(1) | 28(1) |
| C(16) | -1105(3) | 7176(2) | 6222(1) | 29(1) |
| C(17) | -1748(3) | 8200(2) | 6543(2) | 39(1) |
| C(18) | -3349(3) | 8854(2) | 6393(2) | 49(1) |
| C(19) | -4311(3) | 8489(3) | 5908(2) | 52(1) |
| C(20) | -3690(3) | 7470(3) | 5594(2) | 45(1) |
| C(21) | -2116(3) | 6818(2) | 5753(1) | 35(1) |

| | | | | |
|---|---|---|---|---|
| C(22) | 1689(3) | 6697(2) | 5462(1) | 27(1) |
| C(23) | 2684(3) | 5847(2) | 5004(1) | 31(1) |
| C(24) | 3549(3) | 6066(2) | 4270(1) | 37(1) |
| C(25) | 3440(3) | 7131(2) | 3989(1) | 39(1) |
| C(26) | 2470(3) | 7990(2) | 4448(2) | 37(1) |
| C(27) | 1596(3) | 7770(2) | 5175(1) | 33(1) |
| C(28) | 1539(3) | 6639(2) | 7020(1) | 27(1) |
| C(29) | 673(3) | 6731(2) | 7798(1) | 36(1) |
| C(30) | 1462(4) | 6791(2) | 8482(2) | 40(1) |
| C(31) | 3118(4) | 6766(2) | 8410(2) | 41(1) |
| C(32) | 3994(3) | 6685(2) | 7644(2) | 39(1) |
| C(33) | 3203(3) | 6624(2) | 6956(1) | 31(1) |
| C(34) | 2160(4) | -417(2) | 7278(2) | 56(1) |
| C(35) | 2695(3) | 2824(2) | 8371(2) | 35(1) |
| C(36) | 2766(3) | 2954(2) | 9265(2) | 35(1) |
| C(37) | 3479(4) | 2072(3) | 9783(2) | 59(1) |
| C(38) | 3565(6) | 2274(5) | 10630(3) | 101(2) |
| C(39) | 2891(7) | 3394(7) | 10853(3) | 109(2) |
| C(40) | 2209(6) | 4177(6) | 10347(4) | 111(2) |
| C(41) | 2138(4) | 3986(3) | 9567(2) | 65(1) |
| C(42) | 1148(3) | 3211(2) | 6424(1) | 35(1) |

Table 3. Bond lengths [Å] and angles [°] for N-benzyl-1-methyl-N-{2-[N-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (**88**).

| | |
|---|---|
| C(1)-C(2) | 1.505(3) |
| C(1)-C(6) | 1.525(4) |
| C(1)-C(34) | 1.545(4) |
| C(1)-C(7) | 1.555(4) |
| C(2)-C(3) | 1.322(4) |
| C(2)-H(2A) | 0.9500 |
| C(3)-C(4) | 1.482(4) |
| C(3)-H(3A) | 0.9500 |
| C(4)-C(5) | 1.476(4) |
| C(4)-H(4A) | 0.9900 |
| C(4)-H(4B) | 0.9900 |
| C(5)-C(6) | 1.313(4) |
| C(5)-H(5A) | 0.9500 |
| C(6)-H(6A) | 0.9500 |
| C(7)-O(7) | 1.220(3) |
| C(7)-N(7) | 1.367(3) |
| N(7)-C(8) | 1.437(3) |
| N(7)-C(35) | 1.483(3) |
| C(8)-C(13) | 1.394(3) |
| C(8)-C(9) | 1.398(3) |
| C(9)-C(10) | 1.396(3) |
| C(9)-C(14) | 1.497(3) |
| C(10)-C(11) | 1.386(3) |
| C(10)-H(10A) | 0.9500 |
| C(11)-C(12) | 1.380(3) |
| C(11)-H(11A) | 0.9500 |
| C(12) C(13) | 1.382(3) |
| C(12)-H(12A) | 0.9500 |
| C(13)-H(13A) | 0.9500 |
| C(14)-N(14) | 1.281(3) |
| C(14)-C(42) | 1.495(3) |
| N(14)-O(14) | 1.418(2) |
| O(14)-C(15) | 1.458(3) |
| C(15)-C(16) | 1.527(3) |
| C(15)-C(28) | 1.530(3) |
| C(15)-C(22) | 1.538(3) |
| C(16)-C(17) | 1.389(3) |
| C(16)-C(21) | 1.399(3) |
| C(17)-C(18) | 1.393(4) |
| C(17)-H(17A) | 0.9500 |
| C(18)-C(19) | 1.389(4) |
| C(18)-H(18A) | 0.9500 |
| C(19)-C(20) | 1.378(4) |
| C(19)-H(19A) | 0.9500 |

| | |
|---|---|
| C(20)-C(21) | 1.378(4) |
| C(20)-H(20A) | 0.9500 |
| C(21)-H(21A) | 0.9500 |
| C(22)-C(23) | 1.388(3) |
| C(22)-C(27) | 1.392(3) |
| C(23)-C(24) | 1.392(3) |
| C(23)-H(23A) | 0.9500 |
| C(24)-C(25) | 1.377(4) |
| C(24)-H(24A) | 0.9500 |
| C(25)-C(26) | 1.389(4) |
| C(25)-H(25A) | 0.9500 |
| C(26)-C(27) | 1.387(3) |
| C(26)-H(26A) | 0.9500 |
| C(27)-H(27A) | 0.9500 |
| C(28)-C(33) | 1.388(3) |
| C(28)-C(29) | 1.399(3) |
| C(29)-C(30) | 1.382(4) |
| C(29)-H(29A) | 0.9500 |
| C(30)-C(31) | 1.378(4) |
| C(30)-H(30A) | 0.9500 |
| C(31)-C(32) | 1.385(4) |
| C(31)-H(31A) | 0.9500 |
| C(32)-C(33) | 1.388(3) |
| C(32)-H(32A) | 0.9500 |
| C(33)-H(33A) | 0.9500 |
| C(34)-H(34A) | 0.9800 |
| C(34)-H(34B) | 0.9800 |
| C(34)-H(34C) | 0.9800 |
| C(35)-C(36) | 1.500(3) |
| C(35)-H(35A) | 0.9900 |
| C(35)-H(35B) | 0.9900 |
| C(36)-C(37) | 1.374(4) |
| C(36)-C(41) | 1.385(4) |
| C(37)-C(38) | 1.451(6) |
| C(37)-H(37A) | 0.9500 |
| C(38)-C(39) | 1.440(8) |
| C(38)-H(38A) | 0.9500 |
| C(39)-C(40) | 1.277(8) |
| C(39)-H(39A) | 0.9500 |
| C(40)-C(41) | 1.335(6) |
| C(40)-H(40A) | 0.9500 |
| C(41)-H(41A) | 0.9500 |
| C(42)-H(42A) | 0.9800 |
| C(42)-H(42B) | 0.9800 |
| C(42)-H(42C) | 0.9800 |

| | |
|---|---|
| C(2)-C(1)-C(6) | 110.5(2) |
| C(2)-C(1)-C(34) | 107.0(2) |
| C(6)-C(1)-C(34) | 109.1(2) |
| C(2)-C(1)-C(7) | 117.9(2) |
| C(6)-C(1)-C(7) | 106.6(2) |
| C(34)-C(1)-C(7) | 105.4(2) |
| C(3)-C(2)-C(1) | 124.2(2) |
| C(3)-C(2)-H(2A) | 117.9 |
| C(1)-C(2)-H(2A) | 117.9 |
| C(2)-C(3)-C(4) | 123.8(2) |
| C(2)-C(3)-H(3A) | 118.1 |
| C(4)-C(3)-H(3A) | 118.1 |
| C(5)-C(4)-C(3) | 112.9(2) |
| C(5)-C(4)-H(4A) | 109.0 |
| C(3)-C(4)-H(4A) | 109.0 |
| C(5)-C(4)-H(4B) | 109.0 |
| C(3)-C(4)-H(4B) | 109.0 |
| H(4A)-C(4)-H(4B) | 107.8 |
| C(6)-C(5)-C(4) | 124.4(3) |
| C(6)-C(5)-H(5A) | 117.8 |
| C(4)-C(5)-H(5A) | 117.8 |
| C(5)-C(6)-C(1) | 123.8(3) |
| C(5)-C(6)-H(6A) | 118.1 |
| C(1)-C(6)-H(6A) | 118.1 |
| O(7)-C(7)-N(7) | 120.1(2) |
| O(7)-C(7)-C(1) | 118.8(2) |
| N(7)-C(7)-C(1) | 121.1(2) |
| C(7)-N(7)-C(8) | 125.69(19) |
| C(7)-N(7)-C(35) | 117.8(2) |

| | |
|---|---|
| C(8)-N(7)-C(35) | 116.06(18) |
| C(13)-C(8)-C(9) | 119.9(2) |
| C(13)-C(8)-N(7) | 119.77(19) |
| C(9)-C(8)-N(7) | 120.15(19) |
| C(10)-C(9)-C(8) | 118.44(19) |
| C(10)-C(9)-C(14) | 119.05(19) |
| C(8)-C(9)-C(14) | 122.5(2) |
| C(11)-C(10)-C(9) | 121.3(2) |
| C(11)-C(10)-H(10A) | 119.3 |
| C(9)-C(10)-H(10A) | 119.3 |
| C(12)-C(11)-C(10) | 119.5(2) |
| C(12)-C(11)-H(11A) | 120.2 |
| C(10)-C(11)-H(11A) | 120.2 |
| C(11)-C(12)-C(13) | 120.3(2) |
| C(11)-C(12)-H(12A) | 119.9 |
| C(13)-C(12)-H(12A) | 119.9 |
| C(12)-C(13)-C(8) | 120.4(2) |
| C(12)-C(13)-H(13A) | 119.8 |
| C(8)-C(13)-H(13A) | 119.8 |
| N(14)-C(14)-C(42) | 124.23(19) |
| N(14)-C(14)-C(9) | 112.93(18) |
| C(42)-C(14)-C(9) | 122.79(18) |
| C(14)-N(14)-O(14) | 110.51(17) |
| N(14)-O(14)-C(15) | 109.52(15) |
| O(14)-C(15)-C(16) | 109.64(17) |
| O(14)-C(15)-C(28) | 107.99(17) |
| C(16)-C(15)-C(28) | 115.46(18) |
| O(14)-C(15)-C(22) | 103.45(16) |
| C(16)-C(15)-C(22) | 107.78(17) |
| C(28)-C(15)-C(22) | 111.84(18) |
| C(17)-C(16)-C(21) | 118.1(2) |
| C(17)-C(16)-C(15) | 123.3(2) |
| C(21)-C(16)-C(15) | 118.3(2) |
| C(16)-C(17)-C(18) | 120.7(2) |
| C(16)-C(17)-H(17A) | 119.6 |
| C(18)-C(17)-H(17A) | 119.6 |
| C(19)-C(18)-C(17) | 120.0(3) |
| C(19)-C(18)-H(18A) | 120.0 |
| C(17)-C(18)-H(18A) | 120.0 |
| C(20)-C(19)-C(18) | 119.7(3) |
| C(20)-C(19)-H(19A) | 120.2 |
| C(18)-C(19)-H(19A) | 120.2 |
| C(21)-C(20)-C(19) | 120.2(2) |
| C(21)-C(20)-H(20A) | 119.9 |
| C(19)-C(20)-H(20A) | 119.9 |
| C(20)-C(21)-C(16) | 121.2(2) |
| C(20)-C(21)-H(21A) | 119.4 |
| C(16)-C(21)-H(21A) | 119.4 |
| C(23)-C(22)-C(27) | 118.3(2) |
| C(23)-C(22)-C(15) | 121.91(19) |
| C(27)-C(22)-C(15) | 119.74(19) |
| C(22)-C(23)-C(24) | 120.7(2) |
| C(22)-C(23)-H(23A) | 119.7 |
| C(24)-C(23)-H(23A) | 119.7 |
| C(25)-C(24)-C(23) | 120.4(2) |
| C(25)-C(24)-H(24A) | 119.8 |
| C(23)-C(24)-H(24A) | 119.8 |
| C(24)-C(25)-C(26) | 119.6(2) |
| C(24)-C(25)-H(25A) | 120.2 |
| C(26)-C(25)-H(25A) | 120.2 |
| C(27)-C(26)-C(25) | 119.9(2) |
| C(27)-C(26)-H(26A) | 120.1 |
| C(25)-C(26)-H(26A) | 120.1 |
| C(26)-C(27)-C(22) | 121.1(2) |
| C(26)-C(27)-H(27A) | 119.5 |
| C(22)-C(27)-H(27A) | 119.5 |
| C(33)-C(28)-C(29) | 118.0(2) |
| C(33)-C(28)-C(15) | 121.09(19) |
| C(29)-C(28)-C(15) | 120.8(2) |
| C(30)-C(29)-C(28) | 120.8(2) |
| C(30)-C(29)-H(29A) | 119.6 |
| C(28)-C(29)-H(29A) | 119.6 |
| C(31)-C(30)-C(29) | 120.5(2) |
| C(31)-C(30)-H(30A) | 119.7 |
| C(29)-C(30)-H(30A) | 119.7 |

| | |
|---|---|
| C(30)-C(31)-C(32) | 119.6(2) |
| C(30)-C(31)-H(31A) | 120.2 |
| C(32)-C(31)-H(31A) | 120.2 |
| C(31)-C(32)-C(33) | 119.9(2) |
| C(31)-C(32)-H(32A) | 120.0 |
| C(33)-C(32)-H(32A) | 120.0 |
| C(28)-C(33)-C(32) | 121.2(2) |
| C(28)-C(33)-H(33A) | 119.4 |
| C(32)-C(33)-H(33A) | 119.4 |
| C(1)-C(34)-H(34A) | 109.5 |
| C(1)-C(34)-H(34B) | 109.5 |
| H(34A)-C(34)-H(34B) | 109.5 |
| C(1)-C(34)-H(34C) | 109.5 |
| H(34A)-C(34)-H(34C) | 109.5 |
| H(34B)-C(34)-H(34C) | 109.5 |
| N(7)-C(35)-C(36) | 113.56(19) |
| N(7)-C(35)-H(35A) | 108.9 |
| C(36)-C(35)-H(35A) | 108.9 |
| N(7)-C(35)-H(35B) | 108.9 |
| C(36)-C(35)-H(35B) | 108.9 |
| H(35A)-C(35)-H(35B) | 107.7 |
| C(37)-C(36)-C(41) | 119.5(3) |
| C(37)-C(36)-C(35) | 121.2(3) |
| C(41)-C(36)-C(35) | 119.3(3) |
| C(36)-C(37)-C(38) | 117.8(4) |
| C(36)-C(37)-H(37A) | 121.1 |
| C(38)-C(37)-H(37A) | 121.1 |
| C(39)-C(38)-C(37) | 116.5(4) |
| C(39)-C(38)-H(38A) | 121.7 |
| C(37)-C(38)-H(38A) | 121.8 |
| C(40)-C(39)-C(38) | 122.8(4) |
| C(40)-C(39)-H(39A) | 118.6 |
| C(38)-C(39)-H(39A) | 118.6 |
| C(39)-C(40)-C(41) | 120.4(6) |
| C(39)-C(40)-H(40A) | 119.8 |
| C(41)-C(40)-H(40A) | 119.8 |
| C(40)-C(41)-C(36) | 123.0(5) |
| C(40)-C(41)-H(41A) | 118.5 |
| C(36)-C(41)-H(41A) | 118.5 |
| C(14)-C(42)-H(42A) | 109.5 |
| C(14)-C(42)-H(42B) | 109.5 |
| H(42A)-C(42)-H(42B) | 109.5 |
| C(14)-C(42)-H(42C) | 109.5 |
| H(42A)-C(42)-H(42C) | 109.5 |
| H(42B)-C(42)-H(42C) | 109.5 |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for N-benzyl-1-methyl-N-{2-[N-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (**88**). The anisotropic displacement factor exponent takes the form: $2\pi^2[\ h^2\ a^{*2}U^{11} + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 33(1) | 34(1) | 51(2) | -14(1) | -7(1) | -5(1) |
| C(2) | 39(1) | 28(1) | 34(1) | -5(1) | -8(1) | -11(1) |
| C(3) | 38(1) | 29(1) | 50(2) | -1(1) | -15(1) | -10(1) |
| C(4) | 52(2) | 51(2) | 60(2) | 11(1) | -7(1) | -23(1) |
| C(5) | 63(2) | 45(2) | 48(2) | 11(1) | -11(1) | -12(1) |
| C(6) | 54(2) | 39(2) | 56(2) | -1(1) | -24(1) | 2(1) |
| C(7) | 30(2) | 48(2) | 63(2) | -24(1) | -8(1) | -4(1) |
| O(7) | 29(1) | 73(2) | 168(3) | -68(2) | -23(1) | 5(1) |
| N(7) | 27(1) | 34(1) | 32(1) | -5(1) | -3(1) | -11(1) |
| C(8) | 28(1) | 27(1) | 27(1) | -6(1) | -2(1) | -12(1) |
| C(9) | 33(1) | 23(1) | 25(1) | -7(1) | 1(1) | -14(1) |
| C(10) | 35(1) | 25(1) | 31(1) | -4(1) | -4(1) | -10(1) |
| C(11) | 29(1) | 35(1) | 38(1) | -10(1) | 3(1) | -12(1) |
| C(12) | 36(1) | 37(1) | 30(1) | -7(1) | 6(1) | -18(1) |
| C(13) | 37(1) | 30(1) | 25(1) | -2(1) | -4(1) | -14(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C(14) | 33(1) | 29(1) | 23(1) | -3(1) | -1(1) | -13(1) |
| N(14) | 39(1) | 30(1) | 23(1) | -1(1) | 3(1) | -16(1) |
| O(14) | 43(1) | 27(1) | 26(1) | -4(1) | 6(1) | -17(1) |
| C(15) | 35(1) | 25(1) | 27(1) | -3(1) | 1(1) | -13(1) |
| C(16) | 32(1) | 34(1) | 24(1) | -1(1) | 2(1) | -15(1) |
| C(17) | 31(1) | 40(1) | 47(2) | -11(1) | 0(1) | -12(1) |
| C(18) | 34(2) | 50(2) | 60(2) | -13(1) | 2(1) | -6(1) |
| C(19) | 26(1) | 73(2) | 52(2) | -10(1) | -3(1) | -6(1) |
| C(20) | 32(1) | 71(2) | 36(1) | -13(1) | 3(1) | -20(1) |
| C(21) | 36(1) | 48(1) | 27(1) | -8(1) | 3(1) | -20(1) |
| C(22) | 26(1) | 31(1) | 27(1) | -2(1) | -4(1) | -12(1) |
| C(23) | 32(1) | 34(1) | 27(1) | -2(1) | -3(1) | -11(1) |
| C(24) | 33(1) | 47(1) | 29(1) | -5(1) | -2(1) | -8(1) |
| C(25) | 31(1) | 57(2) | 26(1) | 7(1) | -1(1) | -14(1) |
| C(26) | 38(1) | 37(1) | 37(1) | 13(1) | -4(1) | -15(1) |
| C(27) | 30(1) | 32(1) | 35(1) | 1(1) | -1(1) | -8(1) |
| C(28) | 34(1) | 20(1) | 27(1) | -1(1) | -2(1) | -8(1) |
| C(29) | 42(1) | 38(1) | 31(1) | -5(1) | 1(1) | -19(1) |
| C(30) | 57(2) | 39(1) | 28(1) | -5(1) | 0(1) | -19(1) |
| C(31) | 54(2) | 37(1) | 33(1) | -4(1) | -12(1) | -9(1) |
| C(32) | 35(1) | 36(1) | 43(1) | -6(1) | -12(1) | -2(1) |
| C(33) | 32(1) | 27(1) | 31(1) | -4(1) | -3(1) | -3(1) |
| C(34) | 46(2) | 44(2) | 80(2) | -30(2) | 2(2) | -10(1) |
| C(35) | 29(1) | 42(1) | 39(1) | -2(1) | -4(1) | -17(1) |
| C(36) | 28(1) | 48(1) | 37(1) | -9(1) | 2(1) | -22(1) |
| C(37) | 55(2) | 81(2) | 56(2) | 22(2) | -20(1) | -47(2) |
| C(38) | 82(3) | 186(5) | 72(3) | 67(3) | -37(2) | -107(4) |
| C(39) | 81(3) | 232(8) | 65(3) | -64(4) | 21(2) | -114(5) |
| C(40) | 64(3) | 193(6) | 107(4) | -105(4) | 21(3) | -64(3) |
| C(41) | 39(2) | 79(2) | 89(2) | -48(2) | 10(2) | -29(2) |
| C(42) | 43(1) | 32(1) | 30(1) | -6(1) | 6(1) | -15(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for N-benzyl-1-methyl-N-{2-[N-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (**88**).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | -493 | 1472 | 7057 | 39 |
| H(3A) | -2917 | 1175 | 7485 | 46 |
| H(4A) | -3091 | 668 | 8944 | 64 |
| H(4B) | -2740 | -397 | 8432 | 64 |
| H(5A) | -799 | -756 | 9473 | 63 |
| H(6A) | 1669 | -572 | 9018 | 62 |
| H(10A) | -3121 | 4743 | 7487 | 36 |
| H(11A) | -4747 | 4265 | 8614 | 40 |
| H(12A) | -3510 | 2900 | 9583 | 39 |
| H(13A) | -669 | 1994 | 9415 | 36 |
| H(17A) | -1090 | 8458 | 6869 | 46 |
| H(18A) | -3782 | 9548 | 6622 | 59 |
| H(19A) | -5392 | 8941 | 5794 | 62 |
| H(20A) | -4349 | 7217 | 5266 | 54 |
| H(21A) | -1710 | 6112 | 5539 | 42 |
| H(23A) | 2775 | 5109 | 5193 | 37 |
| H(24A) | 4220 | 5476 | 3960 | 44 |
| H(25A) | 4024 | 7278 | 3485 | 46 |
| H(26A) | 2405 | 8727 | 4264 | 45 |
| H(27A) | 924 | 8362 | 5482 | 40 |
| H(29A) | -470 | 6752 | 7856 | 43 |
| H(30A) | 858 | 6850 | 9006 | 48 |
| H(31A) | 3656 | 6804 | 8882 | 49 |
| H(32A) | 5134 | 6671 | 7589 | 47 |
| H(33A) | 3811 | 6570 | 6433 | 37 |
| H(34A) | 1572 | -946 | 7182 | 84 |
| H(34B) | 3228 | -807 | 7500 | 84 |
| H(34C) | 2363 | -16 | 6759 | 84 |
| H(35A) | 2342 | 3561 | 8085 | 42 |
| H(35B) | 3829 | 2444 | 8135 | 42 |
| H(37A) | 3901 | 1354 | 9592 | 70 |

| | | | | |
|---|---|---|---|---|
| H(38A) | 4042 | 1699 | 11018 | 121 |
| H(39A) | 2956 | 3558 | 11399 | 131 |
| H(40A) | 1749 | 4899 | 10527 | 134 |
| H(41A) | 1633 | 4586 | 9204 | 78 |
| H(42A) | 640 | 3352 | 5899 | 52 |
| H(42B) | 1243 | 2454 | 6633 | 52 |
| H(42C) | 2260 | 3320 | 6343 | 52 |

Table 6. Torsion angles [°] for N-benzyl-1-methyl-N-{2-[N-(trityloxy)ethanimidoyl]phenyl}-2,5-cyclohexadiene-1-carboxamide (**88**).

| | |
|---|---|
| C(6)-C(1)-C(2)-C(3) | -7.9(3) |
| C(34)-C(1)-C(2)-C(3) | 110.8(3) |
| C(7)-C(1)-C(2)-C(3) | -130.8(3) |
| C(1)-C(2)-C(3)-C(4) | 6.6(4) |
| C(2)-C(3)-C(4)-C(5) | -1.9(4) |
| C(3)-C(4)-C(5)-C(6) | -0.4(4) |
| C(4)-C(5)-C(6)-C(1) | -1.9(5) |
| C(2)-C(1)-C(6)-C(5) | 5.6(4) |
| C(34)-C(1)-C(6)-C(5) | -111.8(3) |
| C(7)-C(1)-C(6)-C(5) | 134.8(3) |
| C(2)-C(1)-C(7)-O(7) | -155.1(3) |
| C(6)-C(1)-C(7)-O(7) | 80.1(4) |
| C(34)-C(1)-C(7)-O(7) | -35.9(4) |
| C(2)-C(1)-C(7)-N(7) | 24.9(4) |
| C(6)-C(1)-C(7)-N(7) | -99.9(3) |
| C(34)-C(1)-C(7)-N(7) | 144.1(3) |
| O(7)-C(7)-N(7)-C(8) | -170.4(3) |
| C(1)-C(7)-N(7)-C(8) | 9.6(4) |
| O(7)-C(7)-N(7)-C(35) | 1.4(4) |
| C(1)-C(7)-N(7)-C(35) | -178.6(2) |
| C(7)-N(7)-C(8)-C(13) | 67.6(3) |
| C(35)-N(7)-C(8)-C(13) | -104.3(2) |
| C(7)-N(7)-C(8)-C(9) | -116.9(3) |
| C(35)-N(7)-C(8)-C(9) | 71.2(3) |
| C(13)-C(8)-C(9)-C(10) | -3.7(3) |
| N(7)-C(8)-C(9)-C(10) | -179.19(18) |
| C(13)-C(8)-C(9)-C(14) | 174.47(19) |
| N(7)-C(8)-C(9)-C(14) | -1.0(3) |
| C(8)-C(9)-C(10)-C(11) | 0.8(3) |
| C(14)-C(9)-C(10)-C(11) | -177.46(19) |
| C(9)-C(10)-C(11)-C(12) | 1.5(3) |
| C(10)-C(11)-C(12)-C(13) | -0.9(3) |
| C(11)-C(12)-C(13)-C(8) | -2.0(3) |
| C(9)-C(8)-C(13)-C(12) | 4.4(3) |
| N(7)-C(8)-C(13)-C(12) | 179.86(19) |
| C(10)-C(9)-C(14)-N(14) | 49.5(3) |
| C(8)-C(9)-C(14)-N(14) | -128.7(2) |
| C(10)-C(9)-C(14)-C(42) | -127.8(2) |
| C(8)-C(9)-C(14)-C(42) | 54.0(3) |

| | |
|---|---|
| C(42)-C(14)-N(14)-O(14) | -1.4(3) |
| C(9)-C(14)-N(14)-O(14) | -178.70(17) |
| C(14)-N(14)-O(14)-C(15) | -173.42(19) |
| N(14)-O(14)-C(15)-C(16) | -61.9(2) |
| N(14)-O(14)-C(15)-C(28) | 64.7(2) |
| N(14)-O(14)-C(15)-C(22) | -176.67(16) |
| O(14)-C(15)-C(16)-C(17) | 152.1(2) |
| C(28)-C(15)-C(16)-C(17) | 29.8(3) |
| C(22)-C(15)-C(16)-C(17) | -96.0(2) |
| O(14)-C(15)-C(16)-C(21) | -35.2(3) |
| C(28)-C(15)-C(16)-C(21) | -157.43(19) |
| C(22)-C(15)-C(16)-C(21) | 76.7(2) |
| C(21)-C(16)-C(17)-C(18) | -0.6(4) |
| C(15)-C(16)-C(17)-C(18) | 172.1(2) |
| C(16)-C(17)-C(18)-C(19) | -0.9(4) |
| C(17)-C(18)-C(19)-C(20) | 1.5(4) |
| C(18)-C(19)-C(20)-C(21) | -0.6(4) |
| C(19)-C(20)-C(21)-C(16) | -1.0(4) |
| C(17)-C(16)-C(21)-C(20) | 1.6(3) |
| C(15)-C(16)-C(21)-C(20) | -171.5(2) |
| O(14)-C(15)-C(22)-C(23) | -12.4(3) |
| C(16)-C(15)-C(22)-C(23) | -128.5(2) |
| C(28)-C(15)-C(22)-C(23) | 103.6(2) |
| O(14)-C(15)-C(22)-C(27) | 168.0(2) |
| C(16)-C(15)-C(22)-C(27) | 51.9(3) |
| C(28)-C(15)-C(22)-C(27) | -76.1(3) |
| C(27)-C(22)-C(23)-C(24) | -0.8(3) |
| C(15)-C(22)-C(23)-C(24) | 179.5(2) |
| C(22)-C(23)-C(24)-C(25) | 0.4(4) |
| C(23)-C(24)-C(25)-C(26) | 0.6(4) |
| C(24)-C(25)-C(26)-C(27) | -1.2(4) |
| C(25)-C(26)-C(27)-C(22) | 0.8(4) |
| C(23)-C(22)-C(27)-C(26) | 0.2(3) |
| C(15)-C(22)-C(27)-C(26) | 179.9(2) |
| O(14)-C(15)-C(28)-C(33) | 94.3(2) |
| C(16)-C(15)-C(28)-C(33) | -142.6(2) |
| C(22)-C(15)-C(28)-C(33) | -18.9(3) |
| O(14)-C(15)-C(28)-C(29) | -81.5(2) |
| C(16)-C(15)-C(28)-C(29) | 41.6(3) |
| C(22)-C(15)-C(28)-C(29) | 165.3(2) |
| C(33)-C(28)-C(29)-C(30) | -0.7(3) |
| C(15)-C(28)-C(29)-C(30) | 175.2(2) |
| C(28)-C(29)-C(30)-C(31) | 0.3(4) |
| C(29)-C(30)-C(31)-C(32) | 0.3(4) |
| C(30)-C(31)-C(32)-C(33) | -0.3(4) |
| C(29)-C(28)-C(33)-C(32) | 0.7(3) |
| C(15)-C(28)-C(33)-C(32) | -175.2(2) |
| C(31)-C(32)-C(33)-C(28) | -0.2(4) |
| C(7)-N(7)-C(35)-C(36) | -97.9(3) |
| C(8)-N(7)-C(35)-C(36) | 74.7(3) |

| | |
|---|---|
| N(7)-C(35)-C(36)-C(37) | 69.4(3) |
| N(7)-C(35)-C(36)-C(41) | -112.2(3) |
| C(41)-C(36)-C(37)-C(38) | -1.1(4) |
| C(35)-C(36)-C(37)-C(38) | 177.3(2) |
| C(36)-C(37)-C(38)-C(39) | -0.1(4) |
| C(37)-C(38)-C(39)-C(40) | 1.7(6) |
| C(38)-C(39)-C(40)-C(41) | -2.0(7) |
| C(39)-C(40)-C(41)-C(36) | 0.7(6) |
| C(37)-C(36)-C(41)-C(40) | 1.0(4) |
| C(35)-C(36)-C(41)-C(40) | -177.5(3) |