Studies of aminyl radicals

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Studies of Aminyl Radicals

by

Hitesh Shah

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

for the award of

Doctor of Philosophy

at Loughborough University

September 1999
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ABSTRACT

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Introduction.
This section contains a brief overview of alkyl radicals in synthesis and methods for their generation. The aminyl radical section gives a brief description of the nature of the radical and then proceeds with general techniques used, or now abandoned, for aminyl radical formation. It also reviews amidyl, aminium cation and Lewis acid metal complexed aminyl radicals describing their superiority over neutral aminyl radicals. Various methodologies are also described using aminyl radicals in the synthesis of heterocyclic and natural products.

Ring (3+2) Annulation.
In the early phase of the research, different types of sulfenamide precursors were synthesised for the generation of aminyl, urethanyl, amidyl and Lewis acid complexed radicals. The subsequent reactions of these radicals with various alkenes in ring annulation were investigated to assess their potential towards the synthesis of nitrogen heterocycles. The results of this investigative study show that ring annulation for the various nitrogen centered radicals is limited to urethanyl and amidyl radicals with the more reactive cyclic enol ethers.

Pyridine-2-thioneoxycarbonyl (PTO) Carbamates.
The next phase of our investigative research deals with the generation of the more reactive aminium cation radical via the use of a PTOC carbamate under acidic conditions, for studies towards ring annulation with various enol ethers. The results demonstrate that using this methodology, ring annulation is possible but reactions are difficult to control and give varying results. The use of PTOC carbamates in the generation of aminyl radicals, derived from amino esters, and their subsequent intramolecular cyclisation were also studied in an aim to improve the results of cyclised products compared with those derived from sulfenamides.

Imines as Radical Acceptors
The final stage of our work involved intramolecular cyclisation onto type 2 imines. Initially we studied aryl radical cyclisation onto alkyl imines. These imines were difficult to purify and subsequent cyclisations gave poor yields. We developed a new methodology whereby alkyl cyclisation onto aromatic imines proceeded in modest yields. The imines prepared in this fashion were of high yield and purity. Tandem cyclisation using this methodology has proved very promising. Consequently, our research led to the investigation of cyclisation of biphenyl-2-yl radicals onto imines. Again, initial results have proved very encouraging.
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Introduction
1.1 Brief History and Background

Historically, it is generally accepted that the first free radical was identified by Gomberg in 1900, \(^1\) in the form of a trivalent compound, triphenyl methyl radical. Organic syntheses with free radicals began in 1937 with Heys and Waters, \(^2\) but in general the use of free radicals in organic transformations remained difficult to control and led to a mixture of products. From 1940 onwards deeper insights into the formation, structure and reactions of free radicals showed that these reactive species could be tamed. However, it was the 1970’s, after the pioneering work by Lamb \(^3\) and Julia \(^4\), that witnessed the beginning of new synthetic methodologies involving free radicals. \(^5\)-\(^7\) Since its discovery, it has become apparent that the last two decades have witnessed an overwhelming interest in radical chemistry. Information on various kinds of radicals, their properties, chemistry and uses in organic chemistry have culminated in a wealth of literature. By far the most, and yet most useful reaction, the radical cyclisation has and continues to receive a lot of attention due to its synthetic value in the design and synthesis of many natural products containing heterocyclic rings.

The majority of this report will be involved in discussing the use of different types of aminyl radicals, \(R_2N^+\), including iminyl radicals \(R_2C=N^+\). However, it is worth mentioning the chemistry of alkyl radicals, as much of the chemistry associated with aminyl radicals is closely related.

1.2 Why Use Radicals?

From a synthetic point the use of free radicals in carrying out organic transformations have several advantages which include:-

1. They are neutral.
2. Solvation is less important.
3. Operation in polar and hindered environments is effective.
4. Mild reaction conditions.
5. High regioselectivity (5-exo favoured over 6-endo).
Compared to carbanions and carbocations, free radicals are considered to neutral species. Carbanions and carbocations suffer from solvent and aggregation phenomena, hence being more bulky intermediates in reality. In contrast, the small and more penetrating free radical is effective in carrying out transformations in highly hindered environments with a high degree of chemoselectivity. Therefore, molecules which contain many polar functional groups are tolerated by free radicals. The majority of radical reactions are performed in the absence of strong acids or bases so that competing ionic reactions such as racemisation or epimerisation do not occur.

1.3 Carbon Centered Radicals

Since numerous excellent reviews regarding the use of carbon centred radicals in chemistry, from theoretical studies\(^8\) to reactions and applications in organic synthesis,\(^9,10,11,12,13\) have been published, the aim of this section is to highlight some of the important aspects associated with them.

1.3.1 Intermolecular Additions

In order to apply successful reactions between radicals and non-radicals (olefins) in synthesis, chain reactions must be built up and the following conditions must be obeyed:-

1. Selectivity of radicals have to differ from each other.
2. Reaction between radicals and non-radicals have to be faster than radical combination reactions.

This can be best illustrated by the following scheme below (Scheme 1) showing the desirable and competing reactions. As far as radical generation is concerned, the use of alkyltin hydride, e.g. tributyltin hydride (Bu\(_3\)SnH), is currently the method of choice.\(^14\) Formation of the tributyltin radical (Bu\(_3\)Sn\(^-\)) is initiated by reaction using a sub-stoichiometric amount of 2,2'-azobisobutyronitrile (AIBN), Scheme 2. The tributyltin radical abstracts halide from the alkyl halide 1 to give the corresponding alkyl radical 4, which in turn reacts with a molecule of alkene 2 to give the radical adduct 5. Trapping of this adduct with Bu\(_3\)SnH yields the product 3 and regenerates the
Bu$_3$Sn$^-$ to set up a chain reaction. Already, in the above reaction (Scheme 1) conditions have to be met for the desired reactions to take place to yield product 3. Therefore, the radicals in the chain must meet certain selectivity and reactivity prerequisites.

**Desired reaction**

\[
RX + Y + Bu_3SnH \longrightarrow R_H + Bu_3Sn-X
\]

**Propagation sequence**

(a) \( Bu_3Sn^+ + R-X \longrightarrow R^+ + Bu_3Sn-X \)

(b) \( R^+ + Y \longrightarrow R_Y \)

(c) \( R_Y + Bu_3Sn-H \longrightarrow R_H + Bu_3Sn-H \)

**Undesirable competing reactions**

Reduction

\[
R^+ + Bu_3SnH \longrightarrow R-H + Bu_3Sn^+ \]

Polymerisation

\[
R_Y + Y \longrightarrow R_Y etc. \]

Hydrostannylation

\[
Bu_3Sn^+ + Y \longrightarrow Bu_3Sn-Y \]

Scheme 1
By examination of the above chain reaction, radical 4 must add preferentially to alkene 2 rather than being reduced to the alkane 6 by Bu₃SnH i.e. \( k_1 > k_2 \) (Scheme 3).

Furthermore, the adduct radical 5 should react preferentially with Bu₃SnH to give the product 3 rather than with another molecule of alkene 2, i.e. \( k_3 < k_4 \), to give the polymerisation product 7 (Scheme 4).
This means that the radicals have to differ in selectivity. The rate of addition depends largely on the substituents on both the alkene and the radical. Alkyl radicals are considered to be essentially nucleophilic, hence prefer to add to electron poor alkenes (cyclohexyl radicals react 8500 times faster with acrolein than with 1-hexene). Contrastingly, the trifluoromethyl radical, as an electrophile, undergoes addition reactions most efficiently with electron rich alkenes such as enamines or enol ethers.

Although each of the three propagation steps in Scheme 1 (a, b and c) are thermodynamically favourable, an optimum yield of the desired product 3 will only be obtained by slow addition of the Bu$_3$SnH to the alkyl iodide in the presence of an approximately 10-100 fold excess of alkene 2.

Alkyl chlorides cannot be used as substrates since the C-Cl bond is sufficiently stronger than C-Br and C-I bond. Hence, halogen atom abstraction by the tin radical is a slower process than its addition to the alkene 4 which would result in the hydrostannylation product 8 (see Scheme 1). In the case of alkyl bromides, halogen atom abstraction and addition to the olefin are equally attractive possibilities for Bu$_3$Sn', and occur at similar rates. Hence, the choice of alkyl iodides, with the weaker carbon–iodine bond, ensures that formation of the iodostannane dominates over addition and that the alkyl radical 3 is constantly regenerated.

The use of a high concentration of alkene 2 ensures that radical 4 reacts with a molecule of the alkene 2 and not with Bu$_3$SnH. An obvious danger in this approach is that radical adduct 5 is capable of consecutive additions to alkene 2 leading to polymerisation, e.g. 7. Hydrogen transfer to radical 5 is 10,000 times faster than addition of radical 5 to alkene 2, thus an optimum ratio is to use a 100 fold excess of alkene 4 to Bu$_3$SnH.

High stereoselectivities can be observed with cyclic radicals, where the presence of a vicinal centre of defined stereochemistry in a cyclic array is sufficient to induce stereoselectivity with a preference for the expected trans disposition of substituents (Scheme 5).
Several factors influence the degree of stereoselection obtained including ring size (5>6), degree of saturation in the accepting olefin and the nature of the neighbouring substituent R (NHCOCH3>CH3>OCH3). However, at the acyclic level, such degree of stereoselection is poor and is often lower than that of cations. The ability of cations to form bridged intermediates to give the trans product is less pronounced with radicals.

1.3.2 Intramolecular additions

Intramolecular radical reactions are sufficiently faster than competing intermolecular radical reactions thus finding greater utility in synthesis. Also, intramolecular addition to an olefin, or cyclisation, can occur by two possible modes of process, exo or endo–addition (Scheme 6). Normally, the former is a kinetic process and the latter a thermodynamic one.

Many studies on intramolecular radical reactions have been studied, in particular on the 5-hexenyl radical, 9, by Beckwith and co-workers (Scheme 7). Their results show that cyclisations occur under kinetic control to give the substantially greater 5-exo product 10, i.e. the less stable isomer, than the 6-endo product 11 which correlates with Baldwin’s rules.
Cyclisation is the fastest and most exo regioselective for the hexenyl radical with a rate constant of about $10^6 \text{s}^{-1}$ at 20 °C. This being increased by having electron withdrawing groups at the double bond. On examination, it would appear strange that the 5-exo reaction leading to a less stable primary radical takes precedence over the 6-endo cyclisation which leads too the more stable secondary radical. This high degree of stereoselectivity is explained by a "chair like" transition state shown in Fig. 1. In this transition state, there is better SOMO-HOMO overlap to give the 5-membered ring than there is to give the 6-membered ring. It has been calculated that the angle of attack for an intermolecular attack of a radical to an alkene is very close to 100 °C. Approximately the same angle of approach is operating in the 5-exo mode to give the 5-hexenyl radical 10. Thus, it would seem, both intermolecular and 5-exo attack are geometrically compatible.

As a direct result, the pseudoequatorial array of substituents leads to stereoselective preference, so that substituents at either the 1 or 3 position lead predominantly to the products having the cis configuration and trans for the other positions. Even if the transition state were to adopt the more strained boat configuration for 6-endo reaction to proceed, other factors such as 1,3 diaxial interactions can impede 6-endo attack. As mentioned previously, 5-exo cyclisation
proceeds via kinetic control but if conditions exist for thermodynamic control (reversible cyclisations) then it is possible to increase the yield of the 6-endo product with the more stable secondary radical.\textsuperscript{4,25,26,27} Further, if 5-exo cyclisation is hindered then 6-endo cyclisation becomes the preferred mode of attack. Treatment of the polyolefin selenyl ester 12 with Bu$_3$SnH and AIBN generates the acyl radical intermediate 13 which undergoes stereospecific tandem 6-endo-trig cyclisation, giving the angular-fused cyclohexane 14 (Scheme 8). The reaction offers immense scope for the construction of steroid systems.\textsuperscript{28}

The latter example further demonstrates the advantage of radical cyclisation over non-radical methods. In this protocol, rings A, B, C and D of the steroidal skeleton are put together in a one-pot radical cascade reaction, which would otherwise require laborious multi-step alternative syntheses.

1.4 Synthesis of Heterocycles by Radical Cyclisation

The use of heteroatom containing precursors to generate alkyl radicals is a good way to synthesise heterocycles, the majority of which incorporate nitrogen and or oxygen heteroatoms. Also, most radical cyclisations used for the syntheses of heterocycles proceed by 5-exo-trig regioselectivity. Stereoselective synthesis of heterocycles has become increasingly popular and a number of reviews which include the synthesis of heterocycles via radical cyclisation have been published.\textsuperscript{29,30,31} Only a few examples will be provided here using nitrogen heterocycles.

The synthesis of nitrogen heterocycles via radical cyclisation still remains at the forefront of radical chemistry which is partly due to the abundance of many nitrogen containing natural products. Treatment of the precursor 15 under standard radical conditions gives the alkyl radical
16, which can cyclise in both *endo* and *exo* fashions via 17 and 19 to give the indolizidone 18 and the pyrrolidizidone 20 respectively (Scheme 9). Reaction of the precursor 21 under standard radical conditions (Bu$_3$SnH/AIBN) gives the alkyl radical 22 which undergoes 5-*exo* cyclisation to yield the proline derivative 23 (Scheme 10). Synthesis of the indolizidone 18, pyrrolidizidone 20 and proline derivative 23, show how simple precursors can be used to build nitrogen heterocycles. With further elaboration precursors can be designed to synthesise more complex heterocycles, for example (-)-α-kainic acid 27, using a novel radical protocol involving addition of the tin radical to the thioaldehyde precursor 24 to give, via the intermediate 25, the cyclised product 26, which after further manipulation gives 27 (Scheme 11).
The above examples demonstrate that the radical can be generated in a number of positions relative to the $N$-heteroatom. Also, in Scheme 9 the intermediate 16 which can cyclise in both *exo* and *endo* fashion yields predominantly the indolidizone 18 from *endo* cyclisation. This behaviour has been attributed to the steric bulk at the 5-*exo* site and the radical stabilising property of the bromine atom. This effect is also observed with other heteroatoms such as nitrogen and oxygen as well as by a benzyl group, pushing the unfavourable equilibrium towards 6-*endo* cyclisation.

### 1.5 Reagents for Radical Cyclisation

The majority of radical cyclisations still involve using a slight excess of Bu$_3$SnH and a sub-stoichiometric amount of a radical initiator, usually AIBN. It should be noted that triorganotin hydrides are toxic and separation of the organotin residue still posses a practical problem. Several methods have been suggested which significantly reduce the level of the organotin residue. Firstly, by washing the reaction mixture with saturated potassium fluoride until no more precipitation of flocculant organotin fluoride is observed.$^{35}$ A second solution makes use of the lipophilic nature of tin residues. Simple partitioning between polar solvents such as acetonitrile and light petroleum can prove more effective for more polar substrates.$^{36}$ Another solution for removal of distannanes and organotin halides employs treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and iodine followed by a short column chromatography.$^{37}$ The purification
problem can be partially overcome by using a strategy developed by Corey using a small amount of tributyltin chloride (Bu$_3$SnCl) and sodium borohydride (NaBH$_4$). The Bu$_3$SnCl (or Bu$_3$SnX where X = radical leaving group) is reduced in situ to produce Bu$_3$SnH which is continually being used up generating more Bu$_3$SnCl in a cycle. A slightly modified procedure was used by Jones and co-workers in the cyclisation of aryl radical 29 from 28 to form the quinoline or benzazepine derivative 30 as shown in Scheme 12. In general the cyclisation of vinyl or aryl radicals has proved to be a useful method of ring construction in the synthesis of natural products.

![Scheme 12]

The introduction of tris(trimethylsilyl)silane (TTMS) as a free radical mediator is shown to rival Bu$_3$SnH and is less toxic. The Si-H bond strength of TTMS is reported to be similar to that of the Sn-H bond in Bu$_3$SnH. Giese and co-workers have carried out a comparative study of the two reagents using 6-bromo-1-hexene 31, studying the generation and subsequent cyclisation which yields methyl cyclopentane 32, cyclohexane 33 and the reduced product 1-hexene 34 (Scheme 13). TTMS is a slower, but an effective hydrogen atom donor and is slightly more efficient. It is also expensive! Pattenden and Hitchcock used TTMS for the intramolecular radical macrocyclisation of substrate 35 to afford the cyclised product 36 and further manipulation yielded optically active (-)-zeeralenone 37 (Scheme 14).
Since its first report by Barton and co-workers, the generation of alkyl radicals by chain decomposition of N-pyridine-2-thioneoxycarbonyl (PTOC) esters has become a very popular reaction with wide applications in organic synthesis. The thiones are generally bright yellow compounds and decompose by initiation with Bu₃Sn which adds to the thiocarbonyl unit to give 39 (Scheme 15). Decomposition of 39 generates the acyloxy radical 40 and the pyridine product 41. Rapid elimination of carbon dioxide from 40 gives the alkyl radical 42 which may undergo reduction or cyclisation, given the appropriate presence of a group with an affinity for radicals in the molecule. The driving force for the decomposition is the formation of the aromatic pyridine by-product 41. However, light from a tungsten filament lamp is also sufficient to cleave the weak N-O bond to initiate radical reaction.
An extension of this methodology has been elaborated by Zard and co-workers using S-
alkoxycarbonyl xanthates as radical precursors.\textsuperscript{47} Irradiation of the xanthate 38 with visible light
leads to rupture of the C-S bond to give the alkoxy carbonyl radical 44 and xanthate radical 45.
The alkoxy carbonyl radical can either decarboxylate to give the deoxygenated alkyl xanthate 46
after abstraction of a xanthate unit from 43 or undergo intramolecular addition to a suitably placed
alkene to give the intermediate lactone radical 47 (Scheme 16). Again, abstraction of the xanthate
unit from 43 gives the product 48. An application of this protocol is shown in Scheme 17 for the
synthesis of methylenolactocin 52.\textsuperscript{48} The radical precursor 49 upon irradiation yields the cyclic
xanthate 50. Protolytic elimination of the xanthate group afforded the methyl ester and subsequent
hydrolysis furnished methylenolactocin 52.
The latter examples can be deemed as group transfer reactions whereby the intermediate abstracts the xanthate group from the radical precursor. Previous work from Curran and co-workers reported that the cyclisation of 2-iodo-2-methyl-6-heptyne 53 led to the unusual formation of (iodomethylene)cyclopentane 56 via the intermediates 54 and 55 respectively. The mechanism is as outlined in Scheme 18, and this type of cyclisation was assigned as "atom transfer cyclisation".

The situation improves by employing hexabutylditin (Bu$_3$Sn)$_2$ as the radical initiator instead of the conventional procedure using Bu$_3$SnH and AIBN, which suffers from possible reduction of the radical precursor to give the reduced starting material. This protocol allows facile cyclisation, terminating the radical cyclisation with a functional group such as a halogen to give a product with a reactive centre amenable to further chemical transformation. An example from Curran and co-workers show that irradiation of the iodo ester 57 with a sub-stoichiometric amount of the
hexabutylditin afforded the lactone 58. By contrast, reaction of 57 with Bu3SnH/AIBN gave only the reduced product 59 (Scheme 19).52

![Scheme 19](image)

Tris(methylseleno)- and tris(phenylseleno)boranes are reagents for the generation of R-Se radicals. Treatment of the radical precursor 60 with tris(phenylseleno)borane provided the pyrrolidine derivatives 61 and 62 in a 4:1 ratio respectively (Scheme 20).53

![Scheme 20](image)

Many chemical redox methods are reported to induce radical cyclisation via a one electron transfer process, most notably using manganese (III) acetate30, 54, 55 and samarium (II) iodide.56 The N-crotyl methoxyacarbonylacetamide 63 was cyclised with Mn(OAc)3 by Orena and co-workers to give a mixture of pyrrolidin-2-ones 65 and 66 in a 70:30 ratio from the radical intermediate 64 (Scheme 21).57 The major isomer 65 was used for the synthesis of (R)-3-pyrrolidineacetic acid 67. Reduction of the aldehyde 68 with SmI2 starts up the process of stereospecific tandem cyclisations via the α-oxy radical 69 to yield the triquinane 70 which on hydrolysis provided the enone 71.59 Simple manipulation of 70 can lead to hypnophilin 72 or
coriolin 73 as required (Scheme 22).\textsuperscript{59,60} Using chemical redox methods also has the advantage of carrying out radical reactions at room temperature or lower.

\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{CON}_{\text{Ph}} & \quad \text{CON}_{\text{Ph}} \\
\text{MeO} & \quad \text{MeO} \\
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}

Scheme 21

\begin{align*}
63 & \quad \xrightarrow{\text{Mn(OAc)}_3} \quad 64 \\
65 & \quad \xrightarrow{\text{Sm(III)}} \quad 67 \\
68 & \quad \xrightarrow{\text{SmI}_2} \quad 69 \\
71 & \quad \xrightarrow{\text{TIOH, acetone}} \quad 72 \\
73 & \quad \xrightarrow{\text{OH}} \\
\end{align*}

Scheme 22
The above methods highlight some of the major methods employed for generation of radicals and is by no means comprehensive. The field of radical chemistry continues to grow with new methods being developed. One example being has been the use of fluoroalkyl(fluorous)tin hydride. Due to its insolubility in normal organic solvents and water, has allowed easy separation of the tin reagents from the reaction mixture. However, solubility problems have to be overcome before its general use in the synthesis of heterocyclic chemistry is substantiated.

1.6 Tandem Cyclisations

Endless versions of tandem cyclisations are possible, ranging from combinations of inter- and intramolecular cyclisations to purely intramolecular cyclisations as shown in Scheme 8. The abundant choice of radical precursors, the variety of methods available for the generation of radicals, and the ability to build molecules of extensive structural diversity by concomitant assembly of several cyclic structures in one operation show the synthetic potential for this kind of reaction. A remarkable tandem cyclisation comes from Malacria and co-workers. Multiple tandem cyclisation of the silyl ether radical 75, generated from the precursor 74, gives the bicyclic radical 76 which then adds to acrylonitrile followed by a further 5-exo cyclisation, and after oxidative cleavage of the silyl ether gives the diol 77 in a modest 51% yield (Scheme 23).

A number of radical tandem cyclisations have been in the area of triquinane synthesis most notably by Curran and co-workers. An example of these syntheses is the linear triquinane
natural product hypnophilin 72 and coriolin 73. Both linear, angular and propellane triquinane structures have been constructed using this approach.

1.7   Nitrogen Centered Radicals

It has been demonstrated that radicals can be generated in a number of positions relative to the N-heteroatom. The chemistry of nitrogen centered radicals has received less attention than their carbon relatives and their use as intermediates in organic chemistry has long been appreciated.\textsuperscript{62,63} The potential of nitrogen radicals in the area of alkaloid and heterocyclic synthesis of the pyrrolidine nucleus is high and has been reviewed.\textsuperscript{64,65,29}

1.7.1 Electronic States of Nitrogen Radicals

An aminyl radical has two characteristic electronic states (Fig. 2). The more stable is the $^2B_1$ state, where the unpaired electron is in the $p$-orbital perpendicular to the plane of the molecule ($\pi$ type radical). The other, the high energy electronic state $^2A_1$, has the two electrons in the $p$-orbital and the unpaired electron in the $sp^2$ orbital ($\sigma$ type orbital).\textsuperscript{66}

![Figure 2. Electronic states for an aminyl radical](image)

The types of nitrogen radicals discussed in this report include aminyl radicals (I), aminium cation radicals (II), metal complexed aminyl radicals (III) and amidyl radicals (IV) (see Fig. 3). Nitrogen centred compounds, \textit{e.g.} amines, are nucleophilic in nature, hence, this character is also seen in aminyl radicals and can be considered to be nucleophilic species. Aminyl radicals are easily protonated by Brønsted acids to give aminium cation radicals, and readily complex with Lewis acids to form metal complexed radicals. These types of radicals are essentially electrophilic. Amidyl radicals are formed from the corresponding amides, where the electron
withdrawing effect of the carbonyl functionality endows the amidyl radical with electrophilic properties, though not as electrophilic as either the aminium cation or metal complexed aminium radicals.

\[
\begin{align*}
\text{(I)} & \quad \text{R}_1\text{N}^+\text{R}_2^+ \\
\text{(II)} & \quad \text{R}_1\text{N}^+\text{H} \\
\text{(III)} & \quad \text{R}_1\text{N}^+\text{M} \\
\text{(IV)} & \quad \text{O}^+\text{N}^+\text{R}_2^+
\end{align*}
\]

Figure 3. Various states of nitrogen centered radical

EPR spectra and theoretical calculations on amidyl radicals indicate that the more stable electronic structure is the \( \pi \) type with little electron delocalisation onto oxygen (Fig. 4); the \( \sigma \) structure is higher in energy.66

\[
\begin{align*}
\pi_N & \quad \pi_O
\end{align*}
\]

Figure 4. Electronic states for an amidyl radical

### 1.8 Generation of Aminyl Radicals

There are many methods for the generation of aminyl radicals some of which are analogous to their carbon relatives. This part of the introduction is intended as a brief summary of the main methods that have been used by chemists.

#### 1.8.1 Tetrazenes

Early investigations of aminyl radicals were conducted using tetrazenes.67 Thus, under thermolytic conditions the aminyl radical 79 was readily formed from the tetrazene 78 to afford the pyrrolidine 80 in 41% yield and the piperidine 81 in 16% yield (Scheme 24). Indeed, Newcomb and co-workers also studied the feasibility of using tetrazenes for cyclisation and found
that thermal decomposition of tetrazene 82 gave only the 5-\textit{exo} cyclised product 84 and the uncyclised reduced product 85 in a 1:1 ratio from the aminyl radical 83 (Scheme 25).68

\[
\begin{align*}
\text{Bu} & \text{Bu} \text{Bu} \text{Bu} \\
\text{N} & \text{N} \\
\text{Pr} & \text{Pr} & \text{Pr}
\end{align*}
\]

\[
\begin{align*}
\text{78} & \xrightarrow{-\text{N}_2} \Delta \\
\begin{align*}
\text{79} & \xrightarrow{\text{Pr} \text{Pr}} \\
\text{80} & \xrightarrow{41\%} \\
\text{81} & \xrightarrow{16\%}
\end{align*}
\]

Scheme 24

\[
\begin{align*}
\text{78} & \xrightarrow{-\text{N}_2} \Delta \\
\begin{align*}
\text{82} & \xrightarrow{\text{Pr} \text{Pr} \text{Pr}} \\
\text{83} & \xrightarrow{\text{Bu} \text{Pr}} \\
\text{84} & \xrightarrow{\text{Bu} \text{Pr} \text{Pr}} \\
\text{85} & \xrightarrow{\text{Bu} \text{Pr} \text{Pr}}
\end{align*}
\]

Scheme 25

Tetrazenes are potentially explosive and difficult to prepare, but aminyl radicals are readily formed upon photolysis or thermolysis. However, radicals produced in this fashion do not undergo efficient radical chain reactions because high concentration of radicals are obtained and usually good chain propagation steps are not available. Nowadays they are not the preferred method as precursors to aminyl radicals.

1.8.2 Lithium dialkylamides

The generation of aminyl radicals from amide bases and organic oxidants occurs via an electron transfer process. Suginome and co-workers have studied the cyclisation of aminyl radicals 87 generated from lithium alkenylamide 86 by electrolysis in a mixture of THF/HMPA and lithium perchlorate at -10 °C using a platinum electrode and found it to yield exclusively \textit{cis}-1-methyl-2,5-disubstituted pyrrolidine 88 (Scheme 26).69 Lowering the reaction temperature had the unexpected result of lowering the yield. The high stereochemical outcome of the reaction,
which does not parallel the less selective 5-hexenyl radical where the trans-product is favoured, might be due to steric constraints of the reaction on the electrode surface. Further, the position of the double bond proved crucial for cyclisation. No endo products were observed, 6- and 4-exo substrates gave only the acyclic and $\beta$-scission products.

Scheme 26

1.8.3 $N$-Chloramines

$N$-Chloramines are readily synthesised by treatment of primary or secondary amines with $N$-chlorosuccimide. The use of $N$-chloramines, in principle, allows the facile generation of aminyl radicals upon UV photolysis or thermolysis in neutral media. Ogata and co-workers have shown that aminyl radicals generated from monochloramine add to cyclohexene by means of radical intermediates, to give trans-2-chlorocyclohexylamine. However, results rarely exceeded 10%, and a variety of products were formed (Scheme 27).

Scheme 27

Intramolecular cyclisations of aminyl radicals from the chloramine have been studied in alcoholic media (iso-propyl alcohol), which serve as hydrogen atom sources, by Surzur and workers. Their results achieved acceptable yields of cyclic products to acyclic amine via the radical intermediates respectively (Scheme 28). Interestingly, product is generated via an atom transfer reaction. In acidic media, however, cyclisation was predominant
owing to the formation of the more reactive aminium cation radical being generated.\textsuperscript{73,74} Even the use of Lewis acids, to give the metal complexed radical species, have been used and these reactions have been reviewed by Stella.\textsuperscript{75}

\[
\begin{align*}
\text{Pr}^+ & \text{N}^- \text{Cl} \quad \text{hv} \quad \text{Pr}^+ \text{N}^+ \text{Cl} \\
92 & \quad 93 & \quad 94 & \quad 95 \\
& \quad \text{PrOH} & \quad \text{PrOH} \\
\text{NH} & \text{Cl} & \text{Cl} \\
96 & 97 & \\
\end{align*}
\]

Scheme 28

Using the alkenyl substituted \textit{N}-chloropiperidine 98, Broker and Eng used a catalytic mixture of copper (I) chloride and copper (II) chloride to generate the copper complexed aminyl radical 99 which cyclised to give the chlorides 100 and 101. Subsequent dehalogenation gave gephyrotoxin 102 in a 4.8:1 ratio with the isomer 103 (Scheme 29).\textsuperscript{76}

\[
\begin{align*}
\text{N}^+ \text{Cl} \quad \text{CuCl/CuCl}_2 \\
98 & \quad 99 & \quad 100 & \quad 101 \\
\end{align*}
\]

Scheme 29
More recently, Senboko and co-workers have reported the stereo selective synthesis of trans-2-butyl-5-heptyl-1-methylpyrrolidine 107 by cyclisation of the neutral aminyl radical 105 generated from the N-chloramine 104 and Bu₃SnH/AIBN (Scheme 30).⁷⁷

1.8.4 N-Nitrosamines

N-Nitrosoamines are carcinogenic and hence not suitable substrates. The use of these compounds has largely been terminated as safer and cleaner methods have been developed. Photolysis of the nitrosamine 107 provides the aminyl radical 108 and nitrosyl radical 109 (Scheme 31), but poor results are observed, presumably because the aminyl and nitrosyl radicals recombine faster than other reactions of aminyl radicals.⁶⁷,⁷⁸

1.8.5 N-Hydroxypyridine-2(1H)-thione carbamates

N-Hydroxypyridine-2-thione carbamates 110 are related to Bartons N-hydroxy-pyridine-2-thione esters 38 and exhibit many of the features of their ester counterparts. For convenience, the carbamates are given the acronym PTOC (pyridine-2-thionoxygenycarbonyl). Extensive studies by Newcomb and co-workers have shown the PTOC carbamates 110 readily generate aminyl radicals upon photolysis.⁷⁹ The mode of mechanism for generation of aminyl radicals from PTOC carbamates 110, analogous to the ester 38, involves cleavage of the N–O bond effected by several methods. Photochemical decomposition via visible light is most commonly used to initiate
reaction to give the pyridine species 111 and a carbamoyloxy radical 112 which rapidly decarboxylates to generate the aminyl radical 108 (Scheme 32).

\[
\begin{align*}
\text{110} & \xrightarrow{\text{hv}} \text{111} + \text{112} & \xrightarrow{-\text{CO}_2} \text{108}
\end{align*}
\]

Scheme 32

From cyclisation studies of \(N\)-butyl-4-pentenylaminyl radical, generated from the PTOC 113 upon photolysis, Newcomb and co-workers showed that cyclisation of the aminyl radical 114 to the cyclic radical 115 might be reversible, as a mixture of acyclic 116 and cyclic products 117, in the presence of a hydrogen donor (\(t\)-BuSH), were obtained (Scheme 33).\(^8^0\) In contrast, under acidic conditions cyclisation was highly favoured and good yields of the pyrrolidine product 117 were obtained, due to the more reactive aminium cation radical being generated. In some cases the cyclised product was formed exclusively.\(^8^0,8^1\) The use of Lewis acids have also been investigated and found to give good yields of cyclised products.\(^8^2\)

\[
\begin{align*}
\text{113} & \xrightarrow{\text{hv} -\text{CO}_2} \text{114} + \text{111} \\
\text{114} & \xrightleftharpoons{\text{t-BuSH}} \text{116} \\
\text{115} & \xrightarrow{\text{t-BuSH}} \text{117}
\end{align*}
\]

Scheme 33

25
It was concluded that cyclisation of the neutral aminyl radicals might be reversible and that under acidic media the aminium cation radicals are superior intermediates for the synthesis of alkaloid skeletons.83 The addition of dialkylaminium cations to enol ethers has also been investigated by Newcomb and Kumar.84 They have shown that the aminium cation radical 119 generated from the PTOC carbamate 118 under acidic media adds readily to ethyl vinyl ether to afford the adduct radical 120. Trapping radical 120 with the hydrogen donor, \( t\)-BuSH, gave the addition product 121 (Scheme 34). When \( N\)-allyl amine 122 was used the aminium cation 123 that was generated underwent addition (124) followed by a 5-exo cyclisation (125) to yield the pyrrolidine product 126 after trapping with \( t\)-BuSH, as a mixture of isomers (Scheme 35).84

\[
\begin{align*}
R^1 & = R^2 = \text{C}_8\text{H}_8 \\
\text{Scheme 34}
\end{align*}
\]

\[
\begin{align*}
Y & = \text{PTOC} \\
\text{Scheme 35}
\end{align*}
\]

1.8.6 Se-Phenyl Benzoselenohydroximate Derivatives

An alternative approach to the generation of aminyl radicals comes from Kim and Lee.85 Treatment of the carbamate 127 with \( \text{Bu}_3\text{SnH}/\text{AIBN} \) gives the radical intermediate 128 which rapidly decarboxylates leading to the facile generation of aminyl radical 108 via a mechanism similar to that for the PTOC carbamates (Scheme 36).
Cyclisation studies were also conducted by Kim and Lee. They synthesised the carbamate 129 which was cyclised to afford the pyrrolizidine 133 in 50% yield along with the reduced uncyclised product 132 in 30% yield via the intermediate radicals 131 and 130 respectively (Scheme 37). Interestingly, the reaction was carried out in refluxing tetrahydrofuran the authors reported that the reaction was cleaner than in refluxing benzene, an observation that has been reported before. 

1.8.7 Sulfenamides

Bowman and co-workers have shown sulfenamides 134 to be excellent precursors of aminyl radicals 108 under standard Bu3SnH/AIBN conditions (Scheme 38). However, they also realised that cyclisations of the neutral aminyl radical were poor. Cyclisation of the
sulfenamide 135 gave both cyclised 117 and uncyclised reduced 116 products (Scheme 39), similar to the results obtained by Newcomb and co-workers (see Section 1.8.5).

\[
\begin{align*}
\text{Bu}_3\text{SnH} \quad &\text{Bu}_3\text{SnH} \\
\text{R}^1\text{N}-\text{SPh} \quad &\text{AIBN} \\
\text{134} \quad &\text{108} \\
\end{align*}
\]

Scheme 38

\[
\begin{align*}
\text{Bu}_3\text{SnH} \quad &\text{Bu}_3\text{SnH} \\
\text{Bu}_3\text{SnH} \quad &\text{AIBN} \\
\text{135} \quad &\text{116} \quad + \\
\text{117} \\
\end{align*}
\]

Scheme 39

In view of this they have developed their methodology for tandem cyclisations in hope of trapping the cyclised radical.\(^{88,90}\) Thus in their studies of tandem cyclisation of the sulfenamide 136 they obtained both the cyclised 138 and reduced uncyclised 137 products (Scheme 40). Further they investigated the trapping of the radical onto an "activated alkene" i.e. an alkene with a styrene terminus. Tandem cyclisation of sulphenamide 139 resulted in the formation of the pyrrolizidines 133 as a mixture of diastereomers and the indolidizine 142. No uncyclised material was observed (Scheme 41). By incorporating a styrene terminus into the precursor cyclisation of the aminyl radical 130 gives the benzylic stabilised radical 131 thus effectively trapping the radical. Stable carbon radicals are known in certain cases to undergo reversible cyclisation/ring-opening and allow some thermodynamic control. This results in the formation of the thermodynamically more stable secondary radical 141 to be formed and not only the kinetically favoured 5-exo radical 140.
Surprisingly, Kim and Lee did not report any findings of the 6-endo product in their investigations of tandem cyclisations from the precursor 129 (see Section 1.8.6).

1.9 Reactivity of Nitrogen Centered Radicals

Neutral aminyl radicals undergo poor 5-exo cyclisation reactions, as reflected by the yields of products obtained. Modification of the electron density at the nitrogen atom by protonation, complexation with a metal or by use of an electron withdrawing substituent renders the radical electrophilic, leading to a remarkable increase in reactivity, or, as we have seen, cyclisation of the aminyl radical to give a stable radical also leads to a higher yield of the cyclised product.
1.10 Aims

Synthesis using radical cyclisation to construct the pyrrolidine nucleus requires suitably placed alkenes which can involve considerable synthetic work. The use of radical (3+2) ring annulation (addition/cyclisation) overcomes this problem. The concept has not been widely applied and there is only one example of the use of aminium radicals in (3+2) radical ring annulation.\(^40\) We intended to exploit radical ring annulation using ω-chiral aminyl radicals for the construction of nitrogen heterocycles, especially novel hydroxyprolines and aza-sugars,\(^91\) compounds with intense interest because of their biological activity, especially as inhibitors of enzymes in carbohydrate metabolism. Rendering the nitrogen radical electrophilic, by use of a suitable protecting group, the electrophilic aminyl radical 143 should react faster with the nucleophilic enol ether 144 at high concentration than with Bu₃SnH at low concentration to give the adduct radical 145 which should undergo fast 5-exo cyclisation to provide the cyclised radical intermediate 146. Finally, hydrogen abstraction from Bu₃SnH provides the proline derivative 147 (Scheme 42). Scheme 42 illustrates the synthesis of 4-hydroxyprolines 148 (R¹ = H) (also analogues of kainic acid, a glutamate receptor agonist) and 4,5-dihydroxyprolines (R¹ = OR²) (aza-3-deoxyfuranic acids 149).

![Scheme 42](attachment:image.png)
Results & Discussion
2.1 Introduction to Ring (3+2) Annulation

Radical ring (3+2) annulation has been studied by Cekovic and Saicic in their synthesis of the cyclopentane rings under standard radical conditions using homoallyl halides with an excess of electron deficient alkenes.\textsuperscript{92} Using the iodo precursor \textbf{150}, the nucleophilic homoallyl radical \textbf{151} generated adds to acrylonitrile to give the adduct radical \textbf{152} which rapidly cyclised in a 5-\textit{exo} manner to give the stabilised cyclised radical \textbf{153}. Finally, hydrogen abstraction from Bu$_3$SnH yields the cyclopentane product \textbf{154} in 52\% yield as a mixture of isomers (Scheme 43).

![Scheme 43](image)

Flyn and Żabrowski have also studied radical (3+2) annulation studies under atom transfer conditions.\textsuperscript{93} The reaction of the electrophilic malonate radical \textbf{156}, generated from the iodomalonate precursor \textbf{155} reacts with N-Boc-allylamine \textbf{157} to give the cyclised cyclopentane radical \textbf{158}. Abstraction of iodine from the starting iodomalonate \textbf{155} gives product \textbf{159} in 45\% overall yield (Scheme 44).
The idea of using two simple substrates to synthesise a functionalised cyclised product in a one pot reaction is indeed remarkable. Employing nitrogen centered radicals as precursors provides a facile route to pyrrolidine products. The main aim of our study was to investigate the use of urethanes as radical intermediates towards ring (3+2) annulation.

2.2 Aminyl Radicals in Ring (3+2) Annulation

We briefly explored the concept of radical ring (3+2) annulation using sulfenamides of secondary amines as precursors with an electrophilic radical acceptor. We were aware of the fact that neutral aminyl radicals undergo poor radical intramolecular cyclisation and this would be exacerbated when extended to intermolecular additions. However, we had hoped that by electronically matching the substrates, i.e. nucleophilic radical adding to an $\alpha,\beta$-unsaturated system, we might just be able to trap the resulting aminyl radical. To investigate this hypothesis we synthesised $N$-benzyl allylamine 161 from the corresponding allylamine 160 either by treating with benzyl bromide or by reductive amination; treatment of allylamine with benzaldehyde followed by reduction with sodium borohydride (Scheme 45). Both methods gave modest yields of the amine 161, though the reaction was cleaner via the reductive amination methodology.
2.2.1 Synthesis of an Amine Derived Sulfenamide

Preparation of the sulfenamides was initially attempted using benzenesulfonyl chloride \textbf{164}. Benzenesulfonyl chloride was freshly prepared by the reacting diphenyl sulfide \textbf{162} with sulfuryl chloride \textbf{163} using a catalytic amount of pyridine (Scheme 46). This methodology has superseded previous methods\textsuperscript{94} It has the advantage that the volume of benzenesulfonyl chloride \textbf{164} produced can be accurately calculated, no storage of the reagent is required as it is unstable, reaction times are reduced and the reagent can be freshly prepared.

\[
\text{PhSSPh} + \text{SO}_2\text{Cl}_2 \rightarrow 2 \text{PhSCI}
\]

Possible Mechanism

However, treatment of \textit{N}-benzyl allylamine \textbf{161} with benzenesulfonyl chloride \textbf{164} led to a mixture of products including the starting amine \textbf{160}, along with the sulfenamide \textbf{165}. Attempts to purify the reaction mixture were unsuccessful, leading to decomposition of the sulfenamide \textbf{165} through hydrolysis. As an alternative method, reaction of \textit{N}-benzyl allylamine \textbf{161} with \textit{N-}(phenylthio)phthalimide \textbf{166} gave the sulfenamide \textbf{165} in near quantitative yield without the need of further purification (Scheme 47). The phthalimide by-product \textbf{166} was simply filtered off.
In order to investigate the suitability of the sulfenamide 165 as a radical precursor, it was subjected to standard radical conditions (Bu$_3$SnH/AIBN). The allylamine 161 was obtained in quantitative yield. This is accounted for by a radical mechanism whereby the aminyl radical 167, generated from the sulfenamide 165, abstracts hydrogen from Bu$_3$SnH to give the reduced product, N-benzyl allylamine 161 (Scheme 48). With AIBN absent from the reaction mixture the sulfenamide 165 was recovered in 68% yield.

2.2.2 Ring (3+2) Annulation Studies of Aminyl Radicals

Radical annulation studies of the sulfenamide 165 were conducted using 2(5H)-furanone 168 in a 10 fold excess. The nucleophilic aminyl radical 167 generated should prefer to add to 2(5H)-furanone 168 to give the adduct radical 169. Fast 5-exo cyclisation followed by hydrogen abstraction from Bu$_3$SnH would yield the pyrrolidine product 170 (Scheme 49).
Further, the tributyltin radical is nucleophilic and can add to electron poor double bonds such as furanone 168 to give the hydrostannylation product 171 (see Scheme 1; section 1.3.1). The reaction conditions for the attempted ring annulation of the aminyl radical 167 with furanone 168 are shown in Table 1.

**Table 1. Results for ring annulation using 2(5H)-furanone 168.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 165&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Furanone 168&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Bu&lt;sub&gt;3&lt;/sub&gt;SnH&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Addition period&lt;sup&gt;d&lt;/sup&gt;</th>
<th>% Yield of amine 161&lt;sup&gt;e&lt;/sup&gt;</th>
<th>% Yield of product 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.0784</td>
<td>0.785</td>
<td>0.0167</td>
<td>7 h</td>
<td>63</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Molar concentration of sulfenamide. <sup>b</sup>Molar concentration of alkene. <sup>c</sup>Molar concentration of Bu<sub>3</sub>SnH. <sup>d</sup>Addition period of Bu<sub>3</sub>SnH and AIBN to reaction mixture at 80 °C. <sup>e</sup>Isolated yield. <sup>f</sup>Toluene was used as solvent.

From Table 1, it can be seen that a high percentage of the amine 161 was recovered and none of the expected product 170 could be detected by either GC-MS or <sup>1</sup>H NMR spectroscopy. In particular, from <sup>1</sup>H NMR spectroscopy, the signal attributed to the methyl group (doublet) in product 170 was not observed. This would suggest that the rate of reduction is greater than the rate of addition, *i.e.* k<sub>2</sub>>k<sub>1</sub>. No attempts were made to determine if the hydrostannylation product of 171 was produced.

The use of an enol ether such as butyl vinyl ether 172 was also explored. However, we were aware that the electronics of the reaction were not compatible, *i.e.* a nucleophilic aminyl radical
adding to an electron rich alkene but realised that if addition did occur, would generate the stable radical adduct 173. Fast 5-exo cyclisation of radical intermediate 173 followed by hydrogen abstraction from Bu₃SnH would yield the pyrrolidine product 174 (Scheme 50).

\[
\begin{array}{c}
\begin{tikzpicture}
  \node (A) {\text{Bn}};
  \node (B) [right of=A] {\text{N}};
  \node (C) [right of=B] {\text{O}};
  \node (D) [right of=C] {\text{Bu}};
  \node (E) [below of=A] {\text{K}};
  \node (F) [below of=E] {\text{Bu}};
  \node (G) [below of=F] {\text{H}};
  \node (H) [below of=G] {\text{Bn}};
  \draw (A) -- (B) -- (C) -- (D);
  \draw (E) -- (F) -- (G) -- (H);
\end{tikzpicture}
\end{array}
\]

Bu₃SnH \[ k_2 \]

\[
\begin{array}{c}
\begin{tikzpicture}
  \node (A) {\text{Bn}};
  \node (B) [below left of=A] {\text{NH}};
\end{tikzpicture}
\end{array}
\]

Scheme 50

The results displayed in Table 2 for the use of butyl vinyl ether 172, clearly show that none of the expected product was observed and the reduced amine 161 was recovered in 69% yield along with small amount of unreacted starting sulfenamide 165.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 165 a</th>
<th>Butyl vinyl ether 172 b</th>
<th>Bu₃SnH c</th>
<th>Addition period d</th>
<th>% Yield of amine 161 e</th>
<th>% Yield of product 174</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 f</td>
<td>0.0784</td>
<td>0.779</td>
<td>0.0167</td>
<td>7 h</td>
<td>69</td>
<td>0</td>
</tr>
</tbody>
</table>

\text{a}Molar concentration of sulfenamide. \text{b}Molar concentration of alkene. \text{c}Molar concentration of Bu₃SnH. \text{d}Addition period of Bu₃SnH and AIBN to reaction mixture at 80 °C. \text{e}Isolated yield. \text{f}Toluene was used as solvent.

Intramolecular cyclisations involving the neutral aminyl radical 167 were poor, and its use in ring annulation was optimistic but justifiable in that a stable carbon centered radical would be produced, hoping that this driving force would be sufficient to trap the adduct radical. In any event, the result confirms that the use of neutral aminyl radicals is limited and further attempts at ring annulation with such species would be futile.
2.3 Urethanyl Radicals in Ring (3+2) Annulation

Rather than pursue ring annulation studies with neutral aminyl radicals, we turned our attention to the use of urethanyl radicals. In essence these are similar to amidyl radicals. Urethanes are common protective groups for amines and are easily removed by hydrogenation. Amides, although easily introduced, require vigorous conditions for their removal. Urethanyl radicals are not as electrophilic as amidyl radicals, but should be sufficiently more reactive than aminyl radicals. Intramolecular cyclisation studies of urethanyl radicals have been studied by Zard and co-workers. Reaction of the radical precursor 175 under standard radical conditions provides the urethanyl radical 177, from dissociation of the radical intermediate 176, which yields the desired cyclic urethane 178 along with uncyclised material 179 (Scheme 51).

2.3.1 Synthesis of an Urethane Derived Sulfenamides

To investigate the feasibility of radical (3+2) ring annulation of urethanyl radicals, initial studies were confined to simple derivatives of allylamine 160. Treatment of amine 160 with benzyl chloroformate 180 gave the urethane N-benzyloxycarbonyl allylamine 181 in 60% yield. Subsequent reaction with freshly prepared benzenesulfonyl chloride 164 afforded N-benzenesulfonyl-N-benzyloxycarbonyl allylamine 182 in 30% yield (Scheme 52).
2.3.2 Ring (3+2) Annulation Studies of Urethanyl Radicals

As before, the urethane derived sulfenamide 182 was subjected to standard radical conditions to ensure its suitability as a radical precursor. Thus treatment with Bu₃SnH/AIBN gave the reduced urethane product 181 in 90 min., which is accounted for by a radical mechanism similar to that shown in Scheme 46. With AIBN absent from the reaction mixture no reduction was observed and the starting sulfenamide 182 was recovered in 83% yield. Having demonstrated that the sulfenamide 182 undergoes efficient radical reduction to the urethane 181, ring annulation reactions were studied employing butyl vinyl ether 172. We hoped that amidyl radical 183 would be sufficiently electrophilic to be trapped by the enol ether 172 to give the adduct radical 184 which after 5-exo cyclisation and subsequent hydrogen abstraction from Bu₃SnH would yield the desired product 185 (Scheme 53).

The results for the attempted ring annulation using butyl vinyl ether 172 are displayed in Table 3. Surprisingly, in all the attempts none of the expected 5-exo product 185 could be
detected by either GC-MS or $^1$H NMR spectroscopy. From the first entry, using cyclohexane as solvent, the reduced urethane product was isolated in 68% yield. However, subsequent attempts (entries 2, 3 and 4) used toluene as solvent and a different batch of Bu$_3$SnH. Entries 2 and 3 show that a significant proportion of the starting sulfenamide was recovered along with the reduced urethane. The result obtained in entry 4 is the outcome of using 3.5 mole equivalents of Bu$_3$SnH and 48 mole equivalents of butyl vinyl ether 172. Even so, the results obtained indicate that the rate of reduction is greater than the rate of addition i.e. $k_2 \gg k_1$.

Table 3. Results for ring annulation using butyl vinyl ether 172.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 182$^a$</th>
<th>Butyl vinyl ether 172$^b$</th>
<th>Bu$_3$SnH$^c$</th>
<th>Addition period$^d$</th>
<th>% Yield of urethane 181$^e$</th>
<th>% Yield of sulfenamide 182$^e$</th>
<th>% Yield of product 185</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^f$</td>
<td>0.95</td>
<td>0.478</td>
<td>0.0267</td>
<td>10 h</td>
<td>68</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2$^g$</td>
<td>0.22</td>
<td>0.219</td>
<td>0.0125</td>
<td>7 h</td>
<td>24</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td>3$^g$</td>
<td>0.22</td>
<td>0.219</td>
<td>0.0142</td>
<td>7 h</td>
<td>37</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0.16</td>
<td>7.695</td>
<td>0.042</td>
<td>6 h</td>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Molar concentration of sulfenamide. $^b$Molar concentration of alkene. $^c$Molar concentration of Bu$_3$SnH. $^d$Addition period of Bu$_3$SnH and AIBN to reaction mixture. $^e$Isolated yield. $^f$Cyclohexane was used as the solvent. $^g$Toluene was used as the solvent.

Several batches of Bu$_3$SnH received during the initial course of our studies were found to be impure, a problem later found to afflict other groups outside our own. The Bu$_3$SnH was cloudy in appearance (previous batches were clear liquids) and purification by distillation under reduced pressure did provide a clear liquid which on standing reverted back to a milky liquid even when stored under a nitrogen atmosphere. Analysis by GC-MS showed other impurities to be present the most likely impurity being tributyltin oxide.

The use of a cyclic enol ether, 2,3-dihydropyran 186, was next investigated. By a similar mechanism shown in Scheme 54 we hoped to synthesise the bicyclic product 188 from 5-exo cyclisation.
The results are summarised in Table 4 for the attempted ring annulation employing dihydropyran 186. Again, initial studies (entry 1) showed no indication either by \(^1\)H NMR spectroscopy or GC-MS studies of the desired product 188, with the urethane 181 being largely recovered. The experiment was repeated (entry 2) prolonging the addition of \(\text{Bu}_3\text{SnH}\) from 6 h to 12 h, in an attempt to decrease the concentration of the hydrogen atom source thus allowing trapping of the amidyl radical 183 with dihydropyran 186. As before, no sign of product was detected by \(^1\)H NMR spectroscopy or GC-MS and again the urethane 181 was recovered in high yield. From the above results, it was apparent that the reactivity of the urethanyl radical was less than envisaged with the rate of reduction to the urethane 181 being greater than the rate of addition to give the intermediate adduct radical 187 i.e. \(k_2 \gg k_1\).

**Table 4. Results for ring annulation using 3,4-dihydro-\(2H\)-pyran 186.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 182(^a)</th>
<th>Dihydropyran 186(^b)</th>
<th>(\text{Bu}_3\text{SnH})(^c)</th>
<th>Addition period(^d)</th>
<th>% Yield of urethane 181(^e)</th>
<th>% Yield of product 188</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^f)</td>
<td>0.05</td>
<td>0.24</td>
<td>0.02</td>
<td>6 h</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>2(^f)</td>
<td>0.36</td>
<td>2.06</td>
<td>0.02</td>
<td>12 h</td>
<td>76</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Molar concentration of sulfenamide. \(^b\)Molar concentration of alkene. \(^c\)Molar concentration of \(\text{Bu}_3\text{SnH}\). \(^d\)Addition period of \(\text{Bu}_3\text{SnH}\) and AIBN to reaction mixture at 90 °C. \(^e\)Isolated yield. \(^f\)Toluene was used as the solvent.
The final part to our ring annulation studies with the sulfenamide were concluded using 2,3-dihydrofuran 189 as the electron rich alkene. With the greater ring strain inherent in 2,3-dihydrofuran 189, it should therefore be more reactive and allow a facile approach to ring annulation with the electrophilic urethanyl radical 183 to give the cyclised product 191 from the adduct radical 190 (Scheme 55). Table 5 shows the conditions for ring annulation studies employing the more reactive alkene 189.

![Scheme 55](image)

**Table 5. Results for ring annulation using 2,3-dihydrofuran 189.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 182&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dihydrofuran 189&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Temp. °C</th>
<th>Bu&lt;sub&gt;3&lt;/sub&gt;SnH&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Addition period&lt;sup&gt;d&lt;/sup&gt;</th>
<th>% Yield of urethane 181&lt;sup&gt;e&lt;/sup&gt;</th>
<th>% Yield of product 191&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.156</td>
<td>1.023</td>
<td>90</td>
<td>0.03</td>
<td>6 h</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>2&lt;sup&gt;f, g&lt;/sup&gt;</td>
<td>0.068</td>
<td>0.359</td>
<td>85</td>
<td>0.02</td>
<td>12 h</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>3&lt;sup&gt;h&lt;/sup&gt;</td>
<td>0.017</td>
<td>0.164</td>
<td>80</td>
<td>0.011</td>
<td>7 h</td>
<td>92</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Molar concentration of sulfenamide. <sup>b</sup>Molar concentration of alkene. <sup>c</sup>Molar concentration of Bu<sub>3</sub>SnH. <sup>d</sup>Addition period of Bu<sub>3</sub>SnH and AlBN to reaction mixture. <sup>e</sup>Isolated yield. <sup>f</sup>Toluene was used as the solvent. <sup>g</sup>2 mole equivalents of 2,3-dihydrofuran 51 were added every 3 h. <sup>h</sup>Cyclohexane was used as the solvent.

The initial result (entry 1), obtained employing 2,3-dihydrofuran 189 as the electron rich alkene, was very encouraging. The cyclised product 191 was obtained in 20% yield and identified...
by $^1$H NMR spectroscopy and GC-MS studies. However, the $^1$H and $^{13}$C NMR spectra were very complex, but the important resonances for the methyl group, split as doublets in the region between $\delta$ 1.08–1.13 ppm, for the two major diastereomers were easily identified. From comparisons of the possible geometry's of the transition states, it was evident that the predominant isomers would be those having the cis-ring junction, the trans isomers being too stereochemically demanding (Fig. 5). By increasing the addition period of Bu$_3$SnH to 12 h and decreasing the temperature to 85 °C, we were able to increase the yield of the pyrrolidine product to 36% (entry 2). A further decrease in temperature to 80 °C, by refluxing in cyclohexane as solvent, led to a dramatic loss of product and the reduced urethane was isolated in near quantitative yield (entry 3). This result was not easily explainable, though a question of whether the alkene 189 was soluble in such a non-polar solvent does arise.

![Figure 5. Isomers of 191 having the cis-ring junction shown with their enantiomers](image)

Even with yields of the product being less than 40%, it was encouraging to show that radical ring annulation of the urethanyl radical 183 was possible, despite having to use the more reactive alkene 189. It is difficult to ascertain whether the low yield for the product 191 is a direct result of the rate of reduction still being greater than the rate of addition i.e. $k_2 > k_1$, or due to the volatility of 2,3-dihydrofuran (b.p. 54-55 °C) even though excess dihydrofuran was added to the reaction mixture every 3 h (entry 2). An attempt was made to perform the reaction under photolytic conditions where the use of AIBN under such conditions has proven to be particularly useful.97
From the result shown in Table 6 it can be seen that although the sulfenamide was not completely consumed, a high proportion of the reduced urethane was isolated and only 2% of the desired product 191 was isolated as a mixture of isomers. Again the reaction was performed in cyclohexane as the solvent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide $^{182a}$</th>
<th>Dihydrofuran $^{189b}$</th>
<th>Bu$_3$SnH$^c$</th>
<th>Addition period$^d$</th>
<th>% Yield of urethane $^{181e}$</th>
<th>% Yield of sulfenamide $^{182e}$</th>
<th>% Yield of product 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^e$</td>
<td>0.017</td>
<td>0.171</td>
<td>0.012</td>
<td>10 h</td>
<td>42</td>
<td>34</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$Molar concentration of sulfenamide. $^b$Molar concentration of alkene. $^c$Molar concentration of Bu$_3$SnH. $^d$Addition period of Bu$_3$SnH and AIBN to reaction mixture. $^e$The reaction mixture was initiated with light of 360 nm.

Unfortunately the electrophilicity of the urethanyl radical $^{183}$ proved less than anticipated presumably as the mesomeric effect from oxygen is greater than that for nitrogen. Thus it seems that ring annulation is limited to the use of 2,3-dihydrofuran $^{189}$. Reactions performed in cyclohexane gave disappointing results especially in view of the fact that radicals in general do not suffer from solvation effects.

### 2.4 Amidyl Radicals in Ring (3+2) Annulation

Despite the apparent lack of reactivity of the urethanyl radical we found it prudent to study the use of an amidyl radical in ring annulation. With its greater reactivity, greater success was anticipated in achieving the ring annulated product. Intramolecular cyclisation studies of amidyl radicals by Newcomb and Esker indicate that these species are more reactive than aminyl and urethanyl radicals. These reactions are essentially irreversible and unlike the reactive aminium cation radicals, reactions can be carried out under neutral conditions. Thus, photolysis of the PTOC imidate ester $^{192}$ generates the amidyl radical $^{193}$ which undergoes $5$-$exo$ cyclisation to give the cyclised radical $^{194}$. Hydrogen abstraction from tert-butyl thiol ($t$-BuSH) yields the lactam product $^{195}$ (Scheme 56). The electron withdrawing ability of the carbonyl group endows the nitrogen with electrophilic properties thus making it a reactive intermediate.
2.4.1 Synthesis of an Amide Derived Sulfenamide

By using pentafluorobenzoyl chloride 196, reaction with the allyl amine 160 gave the amide 197 in almost quantitative yield. Subsequent reaction with benzenesulfonyl chloride 164, freshly prepared, gave the sulfenamide 198 in 36% yield (Scheme 57). The pentafluoro derivative 198 was synthesised primarily because the electron withdrawing effect of the fluorine should render the amidyl radical 199 highly electrophilic.

![Scheme 56](image)

Scheme 57

2.4.2 Ring (3+2) Annulation Studies of Amidyl Radicals

For our ring annulation studies we were confident that the amidyl radical 199, like the urethanyl radical 183, would react with dihydrofuran 189. Thus in order to ascertain the greater reactivity of the amidyl radical 199, we decided to use dihydropyran 186 as our model. If our prediction was correct then trapping of the electrophilic amidyl radical 199 with dihydropyran
186 to give the adduct radical 200, should be faster than its reduction to the amide 197. Fast 5-exo cyclisation should provide the desired product 201 after hydrogen abstraction (Scheme 58).

The result of the ring annulation study between the amidyl radical 199 and dihydropyran 186 is shown in Table 7. From GC-MS spectroscopy we were able to detect a product (<5%) which had a mass spectrum consistent with it being the desired product 201. However, attempts to isolate this component were unsuccessful. The amide 197 was recovered in high yield, along with a trace amount of the sulfenamide 198. We had hoped for a greater degree of success but the reduction of the sulfenamide 198 to the amide 197 has proven to be a dominant reaction (as is the case for the urethanyl radical 167), despite using a highly electrophilic species.

Table 7. Results for ring annulation using dihydropyran 186

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 198</th>
<th>Dihydropyran 186</th>
<th>Bu3SnH</th>
<th>Addition period</th>
<th>% Yield of amide 197</th>
<th>% Yield of product 201</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>0.036</td>
<td>1.084</td>
<td>0.018</td>
<td>10 h</td>
<td>36</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

*aMolar concentration of sulfenamide. *bMolar concentration of alkene. *cMolar concentration of Bu3SnH. *dAddition period of Bu3SnH and AIBN to reaction mixture at 83 °C. *eIsolated yield. *fYield from GC-MS. *gToluene was used as the solvent.
2.5 The use of Lewis Acid Complexed Aminyl Radicals in Radical Ring Annulation.

Complexation of the aminyl radical with a Lewis acid gives a species that is highly electrophilic. Lewis acids offer potentially milder conditions than protic acids and are a proven alternative for activation of aminyl radicals. Newcomb and Ha have shown that using the PTOC carbamate 113 as a model, Lewis acid complexation followed by initiation with light gave the radical complex 202 which underwent efficient cyclisation to yield up to 98% of the cyclised product 204 from the cyclised radical 203 (Scheme 59). Further, for several of the Lewis acids used in their studies, they exhibited true catalytic behaviour. Lewis acid association-dissociation probably is rapid, but cyclisation must involve the complexed radical 202 because radical 114 has been shown not to give appreciable yields of cyclic product under neutral conditions (see section 1.8.5).

In our ring annulation studies, it was anticipated that Lewis acid complexation of the sulfenamide 165 would yield the highly electrophilic radical 205 via the complexed species 167 (Scheme 60).
It was hoped that facile addition of the radical 205 to butyl vinyl ether 172 followed by rapid 5-exo cyclisation, would provide the cyclised product 174 from the radical intermediate 206 after abstraction of the hydrogen from Bu3SnH (Scheme 61). The Lewis acids investigated in our studies included boron trifluoride diethyl etherate (BF3·OEt2) and magnesium bromide diethyl etherate (MgBr2·OEt2). Table 8 shows the conditions and results of our investigations.

![Scheme 61](image)

**Table 8. Results for ring annulation using Lewis acids.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide 165a</th>
<th>Butyl vinyl ether 172b</th>
<th>Lewis acid</th>
<th>Equiv. c</th>
<th>Bu3SnHd</th>
<th>Addition periode</th>
<th>% Yield of amine 161</th>
<th>% Yield of product 174</th>
</tr>
</thead>
<tbody>
<tr>
<td>1f</td>
<td>0.151</td>
<td>7.55</td>
<td>BF3·OEt2</td>
<td>1</td>
<td>0.038</td>
<td>8 h</td>
<td>Trace</td>
<td>0</td>
</tr>
<tr>
<td>2f</td>
<td>0.249</td>
<td>12.42</td>
<td>MgBr2·OEt2</td>
<td>0.5</td>
<td>0.062</td>
<td>7 h</td>
<td>Trace</td>
<td>0</td>
</tr>
</tbody>
</table>

aMolar concentration of sulfenamide. bMolar concentration of alkene. cEquivalents of Lewis acid present. dMolar concentration of Bu3SnH. eAddition period of Bu3SnH and AIBN (catalytic) to reaction mixture at 80 °C. fToluene was used as solvent.

No product was detected by 1H NMR spectroscopy, and more importantly, in both cases, only trace amounts of amine 161 were detected by 1H NMR spectroscopy. Whereas Newcomb and Ha used mild photolytic conditions to generate the Lewis acid complexed aminyl radical 202 from the PTOC carbamate 113, we attempted to prepare the complexed radical 205 from the sulfenamide 165 using high temperatures (80 °C). This protocol has proved unsatisfactory leading to decomposition. Thus, it seems that the use of low temperatures for Lewis acid complexation...
would have been desirable. It would therefore have been valuable to perform the experiments under photolytic conditions as the reactions can be carried out at room temperature or lower.

2.6 Conclusion

We had hoped to develop a methodology in using urethanyl radicals in ring annulation to synthesise novel pyrrolidine products. However, the procedure employing urethanyl radicals has proved not to be general but limited to the use with dihydrofuran. In all cases, reduction to the parent urethane has proved to be the dominant reaction. A brief study of the amidyl radical in ring annulation surprisingly showed it to be of similar reactivity to the urethanyl radical despite being more electrophilic. In contrast, intramolecular cyclisation studies have shown amidyl radicals to be superior intermediates. By suppressing reduction of the urethanyl radical 183, it should be possible to promote ring annulation. This should be possible by performing reactions under atom transfer conditions. Under these conditions, reduction should not be a problem as no hydrogen source is available and the synthesis of the pyrrolidine ring could possibly be achieved. Thus the urethanyl radical 183 generated from the sulfenamide 182 should add to the nucleophilic enol ether 144 to give the cyclised radical 207 which finally abstracts the sulfenyl group of the precursor 182 to provide the pyrrolidine product 208 (Scheme 62). Development of the ring (3+2) annulation remains a possibility but considerable further studies would be required.

\[
\begin{align*}
\text{Cbz} & \quad \text{SPh} \\
\text{182} & \quad \text{(Bu$_3$Sn)$_2$/hv} \\
\text{Cbz} & \quad \text{OR}^2 \\
\text{183} & \quad \text{R}^1 \\
\text{144} & \quad \text{OR}^1 \\
\text{207} & \quad \text{R}^2 \\
\text{208} & \quad \text{SPh} \\
\end{align*}
\]

Scheme 62
2.7 PTOC Carbamates in Ring Annulation

The use of sulfenamides derived from urethanes or amides have proved disappointing in our ring annulation studies. It is obvious that a more reactive aminium cation species is required for ring annulation as demonstrated by Newcomb and Kumar (see Section 1.8.5). The use of acids would certainly have led to hydrolysis of the sulfenamides at elevated temperatures and the use of Lewis acids led, as we have seen, to decomposition. At this stage we decided to abandon this work in favour of PTOC carbamates in ring annulation.

Using the procedure of Newcomb and Kumar, we decided to investigate this methodology for the facile generation of aminyl radicals. Thus, treatment of N-benzyl allylamine 161 with triphosgene 209 followed by subsequent reaction with 2-mercaptopuridine-N-oxide 210, afforded the PTOC carbamate [N-benzyl-N-hydroxypyridine-2(1H)-allylamine] 122 in a 42% yield as a yellow crystalline compound (Scheme 63).

![Scheme 63](image)

Initially, the reaction of PTOC carbamate 122 with butyl vinyl ether 172 was studied using the optimum conditions found by Newcomb and Kumar. Reactions were run in the presence of a weak acid and t-BuSH which served as a hydrogen donor. In radical chain reactions initiated by light, the PTOC carbamate 122, after being protonated, should dissociate to give the dialkylaminium cation radical 123. Radical 123 can react with t-BuSH to give the reduced amine 161, or, radical 123 can react with butyl vinyl ether 172 to afford the adduct radical 211. Fast 5-exo cyclisation would yield the cyclised radical 212 which, after abstraction of the hydrogen from t-BuSH, would provide the pyrrolidine product 174 (Scheme 64). The conditions employed and the results are shown in Table 9.
Table 9. Reaction conditions for attempted ring annulation using PTOC carbamate 122.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PTOC 122&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Butyl vinyl ether 172&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent</th>
<th>% Yield of product 174&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.05</td>
<td>5.2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>0</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.05</td>
<td>5.2</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Molar concentration of PTOC. <sup>b</sup>Molar concentration of alkene. <sup>c</sup>Isolated yield. <sup>d</sup>0.2 M malonic acid and 0.2 M thiophenol were used and the reaction mixture was irradiated with light of 360 nm.

Our initial attempt to affect ring annulation (entry 1) proved somewhat confusing. TLC studies indicated that the PTOC carbamate 122 had been consumed and a complex mixture of new slow running components was observed. An attempt was made to purify the crude mixture by chromatography on neutral alumina. However, only partial purification was possible with many of the fractions still containing several components. Those fractions were combined and extracted with aqueous acid to remove all amine type residues. After re-basifying, examination of the extract by <sup>1</sup>H NMR spectroscopy revealed it not to be the expected product 174 but rather a product (213) resulting from the addition between the thiopyridyl radical 111 and butyl vinyl ether 172, an addition species not previously reported (Scheme 65).
The experiment was repeated (entry 2) using a different work-up procedure whereby the reaction mixture was initially washed with 30% KOH to remove acid residues and thiophenol, followed by an acid wash to protonate the amine residues, which were isolated by treating with 15% NaOH. This work-up procedure proved effective as analysis by $^1$H NMR spectroscopy indicated, by the characteristic set of doublets for the methyl groups, the presence of the desired compound 174, as a mixture of diastereomers (1 : 1.2). However the crude still contained a complex mixture of several other components as indicated by TLC studies. Attempts of further purification by chromatography using neutral alumina provided the major diastereomer pure enough for characterisation in a 3% yield. On examination, from Figure 1, we would expect this to be the cis–isomer as this would be the preferred array of substituents if the more stable chair like transition state was adopted.

We conducted a series of ring annulation experiments using the PTOC carbamate 122 with dihydrofuran 189 and dihydropyran 186 using the conditions and procedures outlined by Newcomb and Kumar.84 Due to problems of isolation of the pyrrolidine 174, we did not attempt to isolate those products obtained from employing dihydrofuran 189 and dihydropyran 186 (Scheme 66). All yields and products were identified solely by GC-MS.
Our results did not compare favourably with those achieved by Newcomb and Kumar, as we used a \( N \)-benzyl derivative whereas the substrate used by Newcomb and Kumar was the \( N \)-heptyl derivative. Nevertheless, we had not expected a dramatic difference in our results. From dihydrofuran 189, we detected a very low yield (less than 7\%) of product 214 as a mixture of two isomers in a ratio of 1:6.3. The major component was suggested to be the addition product 216 by the mass spectrum. When dihydropyran 186 was employed, a better result was achieved as we obtained a higher yield of the expected product 215, present as a single isomer, as suggested by its mass spectrum, but the major component was still the addition product 217 (1:1.5 ratio respectively). Figure 6 shows the addition products 216 and 217.

Despite the simplicity of ring annulation using PTOC carbamates, attempts towards this attractive goal were ceased as results were capricious, poor yields were obtained and the work-up to isolate the desired compounds proved troublesome.
2.8  PTOC Carbamates in the Cyclisation of Aminyl Radicals Derived from Amino Esters

Bowman and co-workers have studied the cyclisation of aminyl radicals 219, generated from sulphenamide precursors 218. They showed that the aminyl radicals 219 undergo S-exo cyclisation reactions onto the suitably placed alkenyl chain of the amino acid to give the proline derivative 220. They reported that the α-ester group imparts moderate electrophilicity to the aminyl radical which facilitates cyclisation (Scheme 67). The electron withdrawing effects can be predicted because α-amino esters are ca. 10^3 times less basic than the corresponding amines.

\[
\begin{align*}
\text{Carbonyl} & \quad \text{PhS} \quad \text{R} \quad \text{CO}_2\text{Me} \\
& \text{Bu}_3\text{SnH} \quad \text{AIBN} \quad \left[ \text{Bonds broken} \right] \\
\text{218a,b} & \quad \text{219a,b} \quad \text{220a,b} \quad \text{221a,b}
\end{align*}
\]

a, R = H  
\(\text{b, R = Bn}\)  

Scheme 67

Under standard radical conditions, generation of the aminyl radical 219a from the sulphenamide 218a was most successful and gave the cyclised proline derivative 220a in a 92% yield with a d.e. of 57% along with a small amount of uncyclised reduced amino ester 221a. The intermediate aminyl radical 219b resulting from the N-benzyl sulphenamide 218b gave poor cyclisation results, with the cyclised product 220b in a 44% yield and the uncyclised amino ester 221b in a 30% yield. The poor cyclisation result is partly explained by the lower electrophilicity of the dialkyl aminyl radical 219b relative to the primary aminyl radical 219a.

We decided to investigate the intramolecular cyclisation of the PTOC carbamates 223b,c readily prepared from the corresponding amino esters 221b,c by treating them with the cyclic pyridinium salt 222 (Scheme 68).
The ethyl amino ester 221c had previously been prepared within our group. The methyl amino ester 221b was prepared by initially condensing glycine methyl ester 224 with benzaldehyde to give \( N-(\text{phenylmethylidene})\text{glycine methyl ester} \) 225 in a good yield (81%). Deprotonation at the \( \alpha \)-carbon with sodium hydride, followed by addition of 4-bromobut-1-ene yielded methyl 2-\([(1-\text{phenylmethylidene})\text{amino}]\)-5-hexenoate 226 in a 54% yield. Finally, reduction of the imine 226 with sodium borohydride provided the methyl amino ester 221b in a 51% yield (Scheme 69).

Using this methodology, only a racemic mixture of the desired amino acid could be obtained.

We anticipated that using the PTOC carbamates 223b,c as radical precursors, initiation of radical reaction by light would provide the respective aminyl radicals 219b,c. As no hydrogen source would be available, cyclisation should be the predominant reaction pathway to give the cyclised radical intermediate 227b,c, which after abstraction of the pyridyl unit from the precursor 223b,c, would provide the cyclised product 228b,c (Scheme 70).
Initial attempted cyclisation of the PTOC carbamate 223c failed to provide the desired product 228c. Analysis of the reaction mixture by TLC showed that the PTOC carbamate had been consumed. Surprisingly, a product isolated from the reaction mixture was characterised by $^1$H NMR spectroscopy as being the starting amino ester 221c (12% isolated). As no hydrogen source was available, it can only be concluded that the aminyl radical 219c, rather than undergo cyclisation, had abstracted a hydrogen most likely from the α-position of another molecule of the PTOC precursor 223c as shown in Scheme 71, to give the amino ester 221c and the stabilised PTOC carbamate radical 229c.

The cyclisation of the PTOC carbamate 223b was also investigated under the same conditions. As before, no product was observed and the amino ester 221b was isolated in a 45% yield. The cyclisation of the PTOC carbamate was also performed in the presence of malonic acid. Under acidic conditions, the PTOC carbamate should, after protonation, dissociate to afford the more reactive aminium cation radical 230b and cyclise rapidly and irreversibly to give the radical intermediate 231b. Abstraction of the pyridyl unit from the precursor would provide the product 228b (Scheme 72).
After analysis of the reaction mixture, we were astonished that under the acidic conditions none of the expected product $228b$ was observed and the amino ester $221b$ was isolated in 38% yield. As before, the results suggest that abstraction of hydrogen either from the $\alpha$-position or from malonic acid has resulted in the formation of the amino ester $221b$. The poor result could also be explained by low basicity of the intermediate aminyl radical $219b$, i.e. poor protonation to yield the required aminium cation radical.

We are unable to satisfactorily explain why using PTOC carbamates in attempting to perform intramolecular cyclisation, no products were detected. Yet, using sulfenamide $218b$ as the radical precursor, Bowman and co-workers were able to effect cyclisation using $\text{Bu}_3\text{SnH}/\text{AIBN}$ to give the cyclised product $220b$ in a 44% yield. From these results, we can only assume that maybe the use of $\text{Bu}_3\text{SnH}$ is facilitating the cyclisation either by activating the double bond or more likely by complexing to the aminyl radical.$^{99}$

2.9 Conclusion

Our attempts to perform ring annulation using the PTOC carbamate $122$ were very poor compared to those results obtained by Newcomb and Kumar in using the $N$-heptyl derivative. Further, our attempts in intramolecular cyclisation of the $N$-benzyl derivative of the PTOC carbamates $223b,c$ gave no cyclised product and coupled with the poor results obtained by Bowman and co-workers for their cyclisation of $218b$ suggests that the effect of an $N$-benzyl substituent is more dramatic than realised. A possible explanation could be that the benzyl group exerts more of a nucleophilic effect onto the aminyl radical thus inhibiting cyclisation.
2.10 Introduction of Radical Addition to Imines

Surprisingly, relatively little has been published regarding radical addition onto imines in general, especially in view of the fact that the polarisation in the imine bond makes them good radical acceptors. Bowman and co-workers have studied cyclisations of $sp^3$ carbon-centered radicals onto "type 1 and 2" imines as shown in Scheme 73, primarily for the purpose of generating aminyl radicals. Their results show that the intermediate radical generated from either type 1 or type 2 imines, undergoes cyclisation to give predominantly the exo product, the endo product being highly disfavoured. For type 2 imines some endo cyclisation is observed.

Bowman and co-workers have exploited this methodology in tandem cyclisations for the synthesis of a number of nitrogen bicycles found in natural products. The tandem cyclisation of the intermediate radical 233, generated from the imine 232, gave predominantly the pyrrolizidine 234 (Scheme 74).
The precursor imine 235 was used for the synthesis of the spirocyclic amine 237 via 5-exo cyclisation of the intermediate radical 236 (Scheme 75). They also showed that the use of Lewis acids dramatically improves tandem yields. The Lewis acid complexes with the nitrogen of the imines, thereby making the imines more electrophilic which enhances the rate of cyclisation of the nucleophilic alkyl radicals in 233 and 236. The rate of cyclisation of the resulting aminyl radicals is also increased by complexation with the Lewis acid which also makes the intermediate aminyl radical more electrophilic.

![Scheme 75](image)

Aryl radical cyclisation onto imines of general type 1 and 2 has largely been studied by Warkentin and co-workers.\textsuperscript{102,103,104} Reaction of the type 1 imine 238 under standard radical conditions provides the aryl radical 239 which can either cyclise by 5-exo addition onto the nitrogen to yield the indoline 240 or 6-endo onto the nitrogen to give the tetrahydroquinoline 241 (Scheme 76). Their results showed that the quinoline derivative was formed almost exclusively when \( R^1 = \text{H} \) and \( R^2 = \text{iPr} \) with an endo : exo ratio of 55:1. An aryl substituent present on the imine (\( R^1 = \text{H} \) and \( R^2 = \text{Ph} \)) changed the ratio 6-endo : 5-exo to 4:1 as cyclisation on to the nitrogen generates the stable benzylic radical.

![Scheme 76](image)
The cyclisations were found to be irreversible and the high \textit{endo} preference is attributed to cyclisation of the nucleophilic aryl radical onto the electrophilic imine carbon, resulting in the formation of a C-C bond rather than a C-N bond. The formation of a less strained cyclic product where the transition state for the \textit{endo} approach of the bulky aryl radical is less strained than for the \textit{exo} approach. In contrast, the reactions with alkyl radicals, analogous to those in Scheme 73, gives almost complete 5-\textit{exo} cyclisation. As part of the work paralleling that of Warkentin, Takano and co-workers have shown that cyclisation of the nucleophilic 3,4-dimethoxyaryl radical 243 derived from the imine 242 gave the indoline 244 as the sole product (Scheme 77).\textsuperscript{105} Cyclisation onto the nitrogen provided the highly stabilised diphenylmethyl radical.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_77.png}
\caption{Scheme 77}
\end{figure}

Warkentin and co-workers have also shown that imines of this type can be used in asymmetric induction.\textsuperscript{102} Thus aryl radical cyclisation of the imine 245 at 80 °C, where the chiral center is as close as possible to the site of attack, provided the isoquinolines 246 and 247 in a ratio of 3.7:1 respectively. That ratio translates to a \textit{d.e.} of 58% (Scheme 78). A somewhat higher ratio (4.7:1) was obtained by performing the reaction at a lower temperature of 60 °C (\textit{d.e.} 65%).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme_78.png}
\caption{Scheme 78}
\end{figure}
Their studies into the cyclisation of the type 2 imine 248, as shown in Scheme 79, yielded primarily 1-indanylamine 249 as the only cyclised product.

Scheme 79

2.11 Aryl Radical Cyclisation Studies onto Type 2 Imines

Our studies on the cyclisation into imines had the central aim of providing a new route to the generation of aminyl radicals. The protocol would allow the use of a stable bromoarene as the precursor rather than the unstable sulfinamide or chloramines. An example of the overall protocol is shown in Scheme 80.
The aldehyde 250 would provide a sacrificial auxiliary for generating aminyl radicals for cyclisation, i.e. the imine intermediate 252 would be the aminyl radical precursor. We envisaged that the reactive aryl radical would rapidly cyclise by 5-exo cyclisation, thereby generating a new aminyl radical. Once the tandem cyclisation was complete, hydrogenolysis of the benzylic bond of the indane product would remove indane and leave the cyclised amino ester derivative. We anticipated that the α-chiral amino ester would impart some degree of stereoselectivity onto the new chiral center.

Synthesis of the key intermediate 3-(2-bromophenyl)propanal 250 was readily achieved via a multi-step synthesis according to the procedure of Warkentin and co-workers.102 Treatment of 2-bromobenzyl bromide 253 with oxazoline 254 provided 2-[2-(2-bromophenyl)ethyl]-4,4-dimethyl-2-oxazoline 255 which on hydrolysis afforded 3-(2-bromophenyl)propanoic acid 256. Subsequent reduction to 3-(2-bromophenyl)propan-1-ol 257 followed by oxidation, yielded the desired aldehyde 250 in 55% overall yield (Scheme 81).

We decided to test the protocol with a simple cyclisation of imines derived from the aldehyde 250 and α-amino esters. If this proved successful, the tandem cyclisation would be fully investigated. Therefore, we initiated the study using the α-amino methyl ester of L-phenyl alanine 258. Condensation of L-phenyl alanine methyl ester 258 with the aldehyde 250, according to the procedure outlined by Warkentin, provided the imine 259 as a crude sample (Scheme 82).
Analysis of the material by $^1$H and $^{13}$C spectroscopy gave a very complex spectrum despite the simplicity of the compound. However, signals attributed to the aldehyde 258 moiety were absent from both $^1$H and $^{13}$C spectra. Attempts to purify this material proved inadequate leading to decomposition with recovery of the starting amino ester 258. Not surprisingly, Warkentin describes that the sensitive imines that they had synthesised were not purified, but used crude. Cyclisation of the crude imine 259 under standard radical conditions provided the desired cyclised product 260 in 12% yield as a 1:1.2 mixture of diastereomers (Scheme 82).

![Scheme 82](image.png)

We were disappointed by the low selectivity and attempts to separate the diastereomers were unsuccessful. The high selectivity achieved for the 6-endo cyclisation of the imine 242 is attributed to attack of the radical $\alpha$ to the chiral center. In our cyclisation the attack of the aryl radical onto the carbon atom of the imine is $\beta$ to the chiral center. Synthesis of the amino ester derivative 260 was also achieved by condensing the amino ester 258 with indanone 261 under Dean and Stark conditions followed by subsequent reduction with sodium borohydride (Scheme 83). Comparison by $^1$H NMR spectroscopy of the product obtained under these conditions with that obtained from cyclisation of the imine 259 showed that the compounds were identical.
Despite the poor selectivity obtained, we investigated this methodology for use in tandem cyclisations with an unsaturated aliphatic amine. This reaction was studied to determine whether the tandem cyclisation protocol was feasible and therefore the amine chosen was designed to strongly favour the cyclisation of the intermediate aminyl radical. Synthesis of (Z)-5-amino-1-phenylpent-1-ene 265 was readily achieved from 3-bromobutanonitrile 262 whereby formation of the Wittig salt 263 followed by subsequent treatment with benzaldehyde provided (Z)-phenylbut-3-enonitrile 264. Reduction of the nitrile afforded the amine 265 (Scheme 84).

Condensation of the aldehyde 250 with the amine 265 provided the crude imine 266 which on analysis by $^1$H and $^{13}$C spectroscopy showed it to contain more than the expected number of peaks. However, IR spectroscopy showed the absence of a N-H stretch as did $^{13}$C spectroscopy for resonance of the aldehydic carbon. Without further purification the imine was subjected to cyclisation under standard radical conditions (Scheme 85).
The cyclisation of the crude imine 266 gave a complex mixture of components which on analysis by $^1$H NMR spectroscopy showed it to contain the important resonance attributed to the benzylic methine proton ($\delta$ 4.6-4.74 ppm). Purification of the crude product mixture led to the isolation of both diastereomers of the tandem amine product 267 in a 8% overall yield.

2.12 Alkyl Radical Cyclisation Studies onto Aromatic Imines

The results obtained for cyclisation of the imines 259 and 266 gave low yields of products. We were unable to achieve the same kind of success achieved by Warkentin and co-workers for cyclisation of their imines. Possibly, synthesis of the sensitive imines has led to the formation of impurities, as seen by $^1$H and $^{13}$C spectroscopy, and subsequent cyclisation of the impure imines has resulted in poor yields of the desired products. Rather than pursue aryl radical cyclisation onto an alkyl imines, we developed a new methodology by simply reversing the situation whereby cyclisation of an alkyl radical 268 onto an aromatic imine, as shown in Scheme 86, would provide the same product 249. The advantage being that the imine precursors of aromatic imines would be stabilised by conjugation and therefore easier to purify. Although the alkyl radical is less reactive than the aryl radical, the rate of cyclisation was predicted to be fast.
The key intermediate, 2-(2-bromoethyl)benzaldehyde 271, was prepared according to the synthesis of Rieche and Schmitz (Scheme 87). Typically, bromination of isochroman 269 affords 1-bromoisochroman 270 which is hydrolysed in situ to yield the desired aldehyde 271 in a one-pot reaction in high yield (65%), which can be further purified by distillation under reduced pressure. We envisaged that preparation of imines using the aldehyde 271 would be cleaner.

Subsequent condensation of aldehyde 271 with L-valine methyl ester 272 with a catalytic amount of acid in toluene and 4 Å molecular sieves to remove water, failed to provide the desired imine 273. A complex mixture of components, as seen by 1H NMR spectroscopy was observed (Scheme 89). Presumably, nucleophilic displacement of the bromine with the imine nitrogen is complicating the situation. Curiously, when the reaction was performed in a protic solvent without any acid, we obtained the cyclic iminium salt 274 which was further characterised by reduction to the tetrahydroisoquinoline 275 (Scheme 89).
Iminium salts of a similar type having an amino alcohol residue instead have been used for asymmetric epoxidation of alkenes by other members of the organic section at Loughborough University. They have shown that treatment of the iminium salt with Oxone™ gives the oxaziridine which in the presence of an alkene can transfer the oxygen unit onto a double bond of the alkene to form the corresponding epoxide (Scheme 90).

It was envisaged that the iminium salt 274 with a chiral amino ester residue should have similar properties for asymmetric induction. This work is being currently carried out by other members of the organic section.

Reduction of diphenyl diselenide 276 with sodium borohydride to phenylselenol 277 followed by treatment with 2-(2-bromoethyl)benzaldehyde 271 gave 2-[2-(phenylselenyl)ethyl]benzaldehyde 278. Unlike the bromoaldehyde 271, the selenyl derivative 278 was expected to be
less susceptible to nucleophilic displacement because of the relatively poor leaving group ability of PhSe, thus making imine formation more amenable (Scheme 91). The phenylselenyl derivatives are also good radical precursors.

![Scheme 91](image)

Condensation of the selenyl derivative 278 with an amino ester should allow a facile approach to imine synthesis. Table 10 shows the results for imine formation of the amino esters studied and Table 11 the results from cyclisation of those imines under standard radical conditions. The imines were prepared by condensing the selenyl aldehyde 278 with the respective amino esters in toluene with a catalytic amount of PTSA and 4Å molecular sieves to remove any water. After stirring overnight, filtration to remove the sieves followed by concentrating, afforded the imines as essentially pure oils in high yields which were subjected to cyclisation without the need of further purification.

Subsequent cyclisations of the imines allowed easier isolation of the products and good yields were obtained. In the case of cyclisation of imine 284, some of the reduced uncyclised selenyl product 288 was isolated. As with the type 2 imines described in Section 2.12, cyclisation of the aryl imines also led to poor stereoselectivity.
**Table 10.** Condensation of 2-{2-(phenylselenyl)ethyl}benzaldehyde with various α-amino esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="272" alt="Image" /></td>
<td><img src="279" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td><img src="258" alt="Image" /></td>
<td><img src="280" alt="Image" /></td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td><img src="281" alt="Image" /></td>
<td><img src="282" alt="Image" /></td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td><img src="283" alt="Image" /></td>
<td><img src="284" alt="Image" /></td>
<td>66</td>
</tr>
</tbody>
</table>

The use of a Lewis acid, MgBr$_2$·OEt$_2$, was investigated in the cyclisation of imine 280. It was postulated that the Lewis acid should complex with the nitrogen of the imine 280 thereby making the imine more electrophilic which should enhance the rate of cyclisation of the nucleophilic alkyl radical. We had also hoped that the Lewis acid would also impart some stereochemical control over the cyclisation. Thus, cyclisation of imine 280 with 1.5 equivalents of the Lewis acid failed to provide the cyclised product 260. An extremely complex mixture of components was observed by TLC which could not be separated satisfactorily using column chromatography. However, by analysis of several fractions from column chromatography by $^1$H NMR spectroscopy we were able to identify three of the major components from the mixture. The high running component had a spectrum consistent with it being the 6-endo product 289. We did not expect to see any of the 6-endo product as cyclisation should have been highly favoured towards 5-exo.
Table 11. Radical cyclisation of the imine derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Product</th>
<th>Isolated yield (%)</th>
<th>Diastereomer ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Imine 279" /></td>
<td><img src="image" alt="Product 285" /></td>
<td>43</td>
<td>1:1.5</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Imine 280" /></td>
<td><img src="image" alt="Product 260" /></td>
<td>42</td>
<td>1:1.2</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Imine 282" /></td>
<td><img src="image" alt="Product 286" /></td>
<td>58</td>
<td>1:1.4</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Imine 284" /></td>
<td><img src="image" alt="Product 287" /> <img src="image" alt="Product 288" /></td>
<td>52</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>

cyclisation and thus cannot easily explain this outcome. The $^1$H NMR spectrum of the mid-running component suggested it to be the reduced uncyclised product 290. Finally, a low running component had a spectrum which was consistent with it being the reduced selenide derivative 291. This would suggest that complexation of the imine bond with the Lewis acid has rendered it highly polarised, and then the Bu$_3$SnH has acted as a hydride source towards the imine. Unlike the results achieved by Bowman and co-workers$^{101}$ in the use of Lewis acids with alkyl imines, the imine 280 did not react in a similar fashion.
The use of (Z)-5-amino-1-phenylpent-1-ene 257 was investigated for the subsequent tandem cyclisation using this new methodology. Condensation of the amine 257 with the aldehyde 278 provided the imine 292 in excellent yield and purity. Subsequent cyclisation afforded the tandem cyclised product as a mixture of diastereomers (ca. 1:5, 67% d.e.) in a 58% overall yield (Scheme 93).

Cyclisation of the imines derived from various amino esters (Table 10) and tandem cyclisation of the imine 292, gave comparable results, in terms of yields, to those obtained by Warkentin and co-workers. We next studied the tandem cyclisation of an imine derived from an amino ester with a suitably placed alkenyl group. Methyl-2-amino-5-hexenoate 293, simply prepared from hydrolysis of methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate 226, was condensed with the aldehyde 278 to provide the imine 294 in an 84% yield (Scheme 94).
Cyclisation of the imine 294 provided a complex mixture of components as seen by TLC and GC-MS. Attempts to purify the mixture using column chromatography were unsuccessful. Those fractions which showed similar TLC patterns, were combined and the several combined fractions on re-analysis by GC-MS showed six components to have molecular ions of m/z 259 expected for the product 295. The expected product 295 resulting from sequential 5-exo cyclisation contains three chiral centers from which we would expect to see four diastereomers and from the 6-endo product 296, which contains two chiral centers, we expect to see two diastereomers. From GC-MS studies, of the six components having the same molecular ion, four of them had similar fragmentation patterns consistent with them being the 5-exo product 295. The other two components which had identical fragmentation patterns, but different to the other four, were possibly related to the 6-endo product 296.

Although signs of the tandem cyclised product 295, along with possible signs of the 6-endo product 296, were detected by GC-MS, we were unable to isolate those components. Compared to the methodology by Bowman and co-workers\(^{86a}\) for the cyclisation of the sulfenamide 218b, the
use of the imine as a method for the synthesis of the proline derivative 295 was not stereoselective and gave rise to a mixture of components.

2.13 Attempted Removal of the Indane Group through Hydrogenation

The idea of using either of the imines described in Section 2.11 or 2.12 as templates allows us to generate aminyl radicals which ultimately lead to the desired product 297. All products synthesised in this manner contain the indane moiety, and being benzylic to the nitrogen should be easily removed via hydrogenation to furnish the deprotected amine product 298 along with indane 299 as shown in Scheme 96.

![Scheme 96](image_url)

The benzyl-nitrogen bond undergoes hydrogenation with more difficulty than does the benzyl-oxygen bond. Nevertheless, a wide variety of benzyl amines have been reduced successfully under mild conditions in alcoholic media (or acetic acid) at times with added mineral acids. As with benzyl-oxygen compounds, benzyl-nitrogen compounds have been reduced by a number of catalysts, however, palladium catalysts are used more than any other. Palladium catalysts are the most active for hydrogenolysis and least likely to cause concomitant ring saturation. We initially studied hydrogenation of the cyclised product 285 whereby cleavage of the benzyl-nitrogen bond would yield L-valine methyl ester 272 (Scheme 97). However, using 10% palladium on charcoal in methanol at atmospheric pressure and room temperature, failed to provide the amino ester 272 and the starting material 285 was recovered in quantitative yield.

In general, the ease of hydrogenation of benzyl amines under ambient conditions increases in the series primary < secondary < tertiary < quaternary ammonium salts. Debenzylation of
secondary amines does not occur as readily as tertiary amines. Further, some N-alkylbenzyl amines have been reported to be resistant to hydrogenolysis under mild conditions.\(^\text{109}\) Increasing the pressure, thereby making the reaction conditions more forceful, also had little effect in cleaving the benzyl-nitrogen bond with the starting material 285 being recovered. As a final attempt, the hydrogenation was performed under pressure using acidic conditions (hydrochloric acid). Possibly, reduction as the ammonium salt would have a less inhibitory effect on the catalyst. However, as before, the starting material was recovered in quantitative yield.

Rather than pursue hydrogenation using palladium on charcoal, the use of the Pearlman catalyst, 20\% palladium (II) hydroxide \([\text{Pd(OH)}_2]\) on charcoal, was investigated as an alternative catalyst for the attempted cleavage of the indane group from the cyclised product 260 to provide the amino ester 258 (Scheme 98). The Pearlman catalyst is particularly active for the hydrogenation of benzyl-nitrogen bonds and has proved to be successful even where other palladium on charcoal catalysts have failed.\(^\text{110}\)

But, as before, only the starting material was found to be present when hydrogenolysis was attempted at atmospheric, increased pressure and in the presence of hydrochloric acid. Failure to
successfully cleave the benzyl-nitrogen bond in either 260 or 285 could be attributed to steric effects or possibly due to impurities such as tin residues present in the starting materials which are poisoning the catalyst. Nevertheless, it should be possible, with further studies, to find the conditions necessary for hydrogenation such as the use of higher temperatures and/or higher catalyst loading.

Unfortunately, hydrogenation of the tandem product 267 was not investigated, but being a tertiary amine should be relatively facile compared to either of the secondary amino esters 260 or 285.

2.14 Conclusion

The use of type 2 imines as templates provided yet another means to the generation of aminyl radicals. Syntheses of the imines described in Section 2.13 were achieved readily in high yields. Although we have shown the imines in Table 10 cyclised successfully to provide the desired products, even though stereoselectivity was poor, cyclisation of imine 294 was problematic with a mixture components obtained. The desired product 295 was detected by GC-MS, however, we were unsuccessful in its isolation. The use of the imine 294 to obtain the proline derivative 295 was not as successful than the previous methodology used by Bowman and co-workers86 for the synthesis of their proline derivative 220b via the sulfenamide 218b. Considering the success achieved by Bowman and co-workers in the cyclisation of their alkyl imines under Lewis acid conditions, it should be possible to achieve cyclisation of the imine 300 to provide the proline derivative 295 with greater success. Synthesis of the imine 300 could be readily achieved by condensing the aldehyde 250 with methyl-2-amino-5-hexenoate 293 (Scheme 99).
Further, by using an imine such as 301 or 302, with a styrene terminus, subsequent 5-\textit{exo} cyclisation should be favoured as this would generate the stable benzylic radical 303, as compared with the successful cyclisation of the imine 292 in Scheme 93, which should provide the necessary driving force to give the proline derivative 304. Compared to cyclisation of the imine 294, this procedure should also proceed with fewer side reactions (Scheme 100).
2.15 Addition of Aryl Radicals Derived From Biphenyls onto Imines

Another aspect of radical addition onto carbon-nitrogen double bonds comes from Leordini and co-workers. In their studies of type 1 imines, the biphenyl-2-yl-radical 305a,b, cyclised to give predominantly the 5-exo products 306a,b and the 6-endo 307 product, depending on the substituent, with 5-exo cyclisation dominating as shown in Scheme 101.

![Scheme 101](image)

Their studies on type 2 imines showed that the biphenyl-2-yl-radical 308a cyclised exclusively to give the 5-exo product 309a whereas radical 308b afforded 309b and 2-cyanobiphenyl 310. The radical 308b can rearrange through 1,5 hydrogen abstraction to the imidoyl radical 311b which leads to 310 by β-scission (Scheme 102).

![Scheme 102](image)
In relation to our studies for the generation of aminyl radicals, the use of type 2 imines were examined. The biphenyl radical cyclisation onto imines of type 2 reported in the literature suggested that a protocol based on these reactions could be superior to those generating indane products. The products resulting from tandem reactions (such as those to indanes shown in Scheme 80) would be fluorenyl amines. The benzylic-amine bond would be considerably better than in the indane case and possibly readily cleaved by hydrogenolysis, or even $S_{N}1$ type hydrolysis. The protocol is shown in Scheme 103.

![Scheme 103]

2.15.1 Synthesis of 2'-bromobiphenyl-2-ylcarboxaldehyde

The key intermediate, 2'-bromobiphenyl-2-ylcarboxaldehyde 314, as reported by the authors, was prepared as shown in Scheme 104. Treatment of 1,2 dibromobenzene 312 with butyl lithium (BuLi) afforded the coupled product 2,2'-dibromobiphenyl 313. Preparation of the Grignard followed by addition of triethyl orthoformate and subsequent hydrolysis afforded the aldehyde 314. However, the authors reported the purification of the aldehyde 314, contaminated with 2,2'-dibromobiphenyl 313, proved troublesome and the yield was not reported.

![Scheme 104]
We realised that the aldehyde could be easily prepared via a palladium coupling. Syntheses of biaryls in a cross-coupling reaction from monoaryl precursors using catalytic methods, have been developed over the last two decades. The Stille and Suzuki reactions are probably the most versatile and can tolerate a wide variety of substituents on both coupling partners. The palladium catalysts employed are usually added as the Pd(II) complex, being reduced to Pd(0) in situ. However, the palladium (0) complex, tetrakis(triphenylphosphine)palladium(0) \([\text{Pd(PPh}_3\text{)}_4]\), is one example of a pre-formed catalyst which has found widespread use in cross-coupling reactions.112,113

### 2.15.2 Stille Coupling.

Arylstannanes \((\text{ArSnR}_3)\) are the most commonly used precursor in the Stille reaction and aryl halides or triflates as the coupling partner. A number of ortho substituted biphenyls have been successfully prepared using the Stille reaction.112 The preparation of the organostannane 317 was readily achieved using 2-bromobenzaldehyde 315 as shown in Scheme 105. Initial protection of the aldehyde 315 as the acetal 316, followed by lithium halogen exchange with BuLi and addition of \(\text{Bu}_3\text{SnCl}\) afforded, after hydrolysis the stannane 317 in quantitative yield.

![Scheme 105](image)

Coupling of the organostannane 317 with 2-bromoiodobenzene 318, to provide the aldehyde 314, was attempted initially with bis(dibenzylideneacetone)palladium (0) \([\text{Pd(dba)}_2]\) in refluxing toluene. After refluxing for 18 hours, only the starting stannane was observed by TLC studies and was recovered in 90% yield. The experiment was repeated using DMF as solvent and \(\text{Pd(PPh}_3\text{)}_4\) as the catalyst. After heating overnight at 100 °C, the starting stannane was again recovered in 92% yield (Scheme 106).
The reason for the inherent lack of coupling is probably due to the steric bulk of the \textit{ortho} substituents. Although the use of copper (I) salts have been used to facilitate the Stille reaction, this was not investigated as was not the use of other ligands. Further use of the Stille reaction was abandoned at this point in favour of the Suzuki reaction.

\subsection*{2.15.3 Suzuki reaction}

The major disadvantage of the Stille reaction is the toxicity of the organo tin reagents and by-products. The Suzuki reaction\textsuperscript{113} like the Stille reaction, has proved extremely versatile and has found extensive use in natural product synthesis. Aryl boronic acids \([\text{ArB(OH)}_2]\) are the usual precursors and aryl halides or triflates are the coupling partners. The syntheses of biphenyls containing large \textit{ortho} substituents are readily available using the Suzuki methodology, whereas the Stille coupling suffers from steric effects giving much lower yields. Interestingly, synthesis of the biaryl \textit{319} (Figure 7) could not be achieved using the Stille reaction whereas the Suzuki reaction afforded a good yield\textsuperscript{114}.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{biaryl.png}
\caption{Biaryl synthesised using the Suzuki reaction}
\end{figure}
The key intermediate for the synthesis of the aldehyde 314 using the Suzuki methodology was 2-formylbenzeneboronic acid 321. The boronic acid 321 was found to be commercially available but was expensive. We attempted to synthesise it using the procedure outlined by Wytko and co-workers as shown in Scheme 107.\textsuperscript{115} Synthesis of the acetal 320 from ethylene glycol and 2-bromobenzaldehyde 315 proceeded in a quantitative yield. However, preparation of the Grignard reagent followed by quenching with trimethyl borate and an acidic work-up provided the boronic acid 321 in a low yield (33%), (cf. 65%). Preparation of the Grignard was found to be capricious, at times with no reaction even when freshly washed magnesium turnings were used and reflux of the reaction mixture was maintained \textit{via} external heating. The synthesis of the boronic acid 321 was improved using BuLi for the metal halogen exchange instead of magnesium followed by quenching with trimethyl borate, hydrolysis afforded the boronic acid 321 in a 65% yield.\textsuperscript{116,117}

\[ \text{Scheme 107} \]

The Suzuki coupling of the boronic acid 321 with 2-bromoiodobenzene 318, using commercially available Pd(PPh\textsubscript{3})\textsubscript{4} as the catalyst provided the aldehyde 314 in a 39% yield (Scheme 108).

\[ \text{Scheme 108} \]
We attributed the low yield of the aldehyde 314 to the poor quality of the commercially available palladium catalyst. The stability of palladium (0) catalysts can be altered by air and/or light. When freshly prepared, Pd(PPh₃)₄ is bright yellow in appearance, however, the commercially available catalyst was brown indicating that some decomposition had occurred. The Pd(PPh₃)₄ was freshly prepared by reduction of palladium (II) chloride (PdCl₂) according to the procedure given by Coulson and co-workers shown in Scheme 109 and was isolated as bright yellow crystals in a 23% yield. As a consequence, the yield of the aldehyde 314 obtained by using fresh Pd(PPh₃)₄ as catalyst was greatly improved (68%).

\[
2 \text{PdCl}_2 + 8 \text{P(Ph)}_3 + 5 \text{NH}_2\text{NH}_2\text{H}_2\text{O} \rightarrow 2 \text{Pd(PPh}_3)_4
\]

Scheme 109

2.15.4 Formation of imines and subsequent cyclisations

The protocol was initially tested using using a simple α-amino ester to determine whether the cyclisation of biphenyl radicals onto imines was feasible. Condensation of L-phenylalanine methyl ester 258 with the aldehyde 314 provided the imine 322 in a 78% yield as shown in Scheme 110. Analysis by \(^1\)H and \(^{13}\)C NMR spectroscopy showed a complex spectrum despite the simplicity of the molecule. This phenomena, known as atropisomerism, is due to the bulky ortho substituents adjacent to the central bond hindering free rotation around the biaryl axis.

![Scheme 110](image)

Cyclisation of the imine 322 under standard radical conditions led to the formation of two major products (Scheme 111). The high running component was shown to be 2-cyanobiphenyl.
310 and was isolated in a 31% yield, resulting from a 1,5 hydrogen shift followed by a β-scission as described earlier. The lower running component was the desired fluorene product 323 and was isolated in a 49% yield as a crystalline solid. The X-ray structure for 323 is shown in Figure 8 (see Appendix for X-ray data).

Unfortunately, in the biphenyl precursor under study the intermediate imidoyl radical 324 undergoes β-scission to yield a stable radical 325 possibly indicating a problem with this protocol.

One aspect of imine formation not mentioned previously, was the possibility of the imines to undergo a 1,3 hydrogen shift resulting in racemisation, as shown in Scheme 112. However, the imines described in section 2.12 displayed an optical rotation which did not deteriorate over a
period of time (i.e. weeks at room temperature) suggesting that such a shift does not occur for these type of imines.

![Scheme 112]

In order to determine whether our protocol would yield tandem cyclisation via the aminyl radical, a simple alkenyl amine, (Z)-5-amino-1-phenylpent-1-ene 257, was used. Using our methodology, the tandem cyclisation of the imine 326 was investigated. The imine 326 was readily prepared from condensing the aldehyde 314 with the amine 257. Cyclisation afforded a mixture of components, as seen by TLC, from which the major product 2-cyanobiphenyl 310 was
isolated in a 39% yield. The expected 5-exo product 327 was isolated in a 12% yield (Scheme 113).

\[
\begin{array}{c}
\text{Br} \quad \text{O} \\
\text{314} \\
\end{array} \quad + \quad \begin{array}{c}
\text{Ph} \\
\text{257} \\
\end{array} \quad \xrightarrow{\text{Toluene/PTSA}} \quad \begin{array}{c}
\text{Br} \quad \text{Ph} \\
\text{N} \\
\text{326} \\
\end{array} \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{327} \\
\end{array} \quad + \quad \text{310}
\]

Scheme 113

Tandem cyclisation was also investigated using the imine 328 prepared from the aldehyde 314 and the amino ester 293. However, like the imine 294, a complex mixture of components was obtained which could not be satisfactorily separated. GC-MS Studies of the mixture showed it to contain four isomers which had the molecular ion of \( m/z \) 307. One isomer had a fragmentation pattern consistent with it being the expected 5-exo product 329 and another isomer had a fragmentation pattern indicating it to be the reduced uncyclised product 330 (Scheme 114).

\[
\begin{array}{c}
\text{Br} \quad \text{O} \\
\text{314} \\
\end{array} \quad + \quad \begin{array}{c}
\text{H}_2\text{N} \quad \text{CO}_2\text{Me} \\
\text{293} \\
\end{array} \quad \xrightarrow{\text{Toluene/PTSA}} \quad \begin{array}{c}
\text{Br} \quad \text{N} \\
\text{CO}_2\text{Me} \\
\text{328} \\
\end{array} \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad \begin{array}{c}
\text{329} \\
\end{array} \quad \xrightarrow{\text{AIBN}} \quad \begin{array}{c}
\text{Ph} \quad \text{CO}_2\text{Me} \\
\text{330} \\
\end{array} \quad + \quad \text{310}
\]

Scheme 114

The use of biphenyls as precursors for the generation of aminyl radicals has also proved to be of potential use for tandem cyclisation. However, compared to the synthesis of the proline
derivative 295, the synthesis of 329 has not proved to be any better, complicated further by the presence of the β-scission product 310. Further studies to improve the protocol were precluded by lack of time. Cleavage of the fluorenyl-amine bond was not attempted. Further study is required on this protocol but the 1,5-H abstraction followed by β-scission is an obvious disadvantage.

2.16 Attempted Syntheses of Aldehydes bearing Heteroatoms

Attempted purification of the sensitive imine 259 (described in section 2.11) proved troublesome leading to degradation. Therefore, an alternative aldehyde was sought. One approach investigated, within our group, was the attempt to synthesise 2-(o-bromophenoxy)ethanal 333. It was envisaged that the α-aryloxy group would enhance the electrophilicity of the aldehyde to facilitate imine formation. However, the synthesis of the aldehyde was remarkably more difficult! The ester 331 was easily formed from 2-bromophenol and methyl bromoacetate. However, either direct reduction of the ester 331 to the aldehyde 333 using DIBAL, or complete reduction to the alcohol 332 with LiAlH₄, followed by attempted oxidation using PCC or the Swern oxidation failed to provide the aldehyde 333 in any appreciable amount (Scheme 115).

![Scheme 115](image-url)
Similarly, in an alternative approach, attempted hydrolysis of the acetal 334 failed to provide the aldehyde 333, even when concentrated hydrochloric acid was used (Scheme 116).

![Scheme 116](image)

Rather than continue with the synthesis of the aldehyde 333, we investigated the synthesis of the nitrogen equivalent. The nitrogen should exert a similar effect in enhancing the electrophilicity of the aldehyde for amenable imine formation. Starting from 2-bromoaniline 335, treatment with bromoethanol provided N-(2-bromophenyl)ethanolamine 336 in a 45% yield. Attempted mild oxidation of the alcohol 336 using PCC failed to provide the aldehyde 337, giving rise to a mixture of components from which the starting alcohol 336 was recovered in a 65% yield. In the case of the Swern oxidation, analysis by TLC and $^1$H NMR spectroscopy also showed a complex mixture of components. However, by $^1$H NMR spectroscopy a small peak with a resonance at 9.77 ppm, typical for an aldehydic proton, was observed. Further investigations in the synthesis of the aldehyde were not attempted (Scheme 117).

![Scheme 117](image)

Possibly, the oxidation of the alcohol 336 was being complicated due to the presence of the nitrogen. Through further studies, with the nitrogen protected, it should be possible to achieve oxidation of the alcohol. The use of a N-acetate 338 derivative could prove to be an interesting alternative for the synthesis of the corresponding aldehyde 339 as shown in Scheme 118.
Scheme 118
Experimental
3.1 Experimental Index

2. (1-Phenylmethylidene)allylamine 160a.
4. Benzenesulfenyl chloride 164.
6. Reaction of N-(benzenesulfenyl)-N-(benzyl)allylamine 165 with Bu₃SnH and AlBN.
8. Attempted synthesis of 3-(butyloxy)-4-methyl-1-(benzyl)tetrahydro-1H-pyrrole 174.
11. Reaction of N-(benzenesulfenyl)-N-(benzyloxycarbonyl)allylamine 182 with Bu₃SnH and AlBN.
15. N-(Pentafluorobenzoyl)allylamine 197.
18. Attempted synthesis of 3-(butyloxy)-4-methyl-1-(benzyl)tetrahydro-1H-pyrrole 174.
19. PTOC carbamate of N-(benzyl)allylamine 122.
20. 3-(Butyloxy)-4-methyl-1-(benzyl)tetrahydro-1H-pyrrole 174.
21. Reaction between the PTOC carbamate of N-(benzyl)allylamine 122 and dihydrofuran 189.
22. Reaction between the PTOC carbamate of N-(benzyl)allylamine 122 and dihydropyran 186.

23. Cyclic pyridinium salt 222.

24. PTOC carbamate of ethyl N-(benzyl)-2-amino-5-hexenoate 223c.


26. Methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate 226.

27. Methyl 2-(benzylamino)-5-hexenoate 221b.

28. PTOC carbamate of methyl N-(benzyl)-2-amino-5-hexenoate 223b.


31. 2-[2-(2-Bromophenyl)ethyl]-4,4-dimethyl-2-oxazoline 255.

32. 3-(2-Bromophenyl)propionic acid 256.

33. 3-(2-Bromophenyl)propanol 257.

34. 3-(2-Bromophenyl)propanal 250.


36. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260.

37. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 from Dean and Stark method.

38. 3-(Cyanopropyl)triphenylphosphonium bromide 263.

39. (Z)-4-Phenylbut-3-enonitrile 264.

40. (Z)-5-Amino-1-phenylpent-1-ene 265.

41. N1-[(E)-3-(2-Bromophenyl)propylidene]-N-[(Z)-5-phenylpent-4-enyl]amine 266.

42. 1-(2,2-Dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267.

43. 2-(2-Bromoethyl)benzaldehyde 271.

44. Attempted synthesis of methyl (2S)-2-((E)-1-[2-(2-bromoethyl)phenyl)methylidene]-amino)-3-methylbutanoate 273.

45. Methyl (2S)-2-(3,4-dihydroisoquinolinium-2-yl)-3-methylbutanoate 274.
46. Methyl (2S)-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)butanoate 275.

47. 2-[2-(Phenylselenyl)ethyl]benzaldehyde 278.


49. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-methylbutanoate 285.


51. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260.

52. Methyl (2S)-4-methyl-2-[(E)-1-{2-[2-(phenylseleno)ethyl]phenyl}methylidene]amino]-pentanoate 282.

53. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-methylpentanoate 286.


55. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-(methylthio)butanoate 287.

56. N1-[(E)-1-{2-[2-(phenylseleno)ethyl]phenyl}methylidene]-(Z)-5-phenylpent-4-en-1-amine 292.

57. 1-(2,3-Dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267.


59. Attempted synthesis of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 using magnesium dibromide diethyl etherate.

60. Methyl 2-amino-5-hexenoate 293.


63. Attempted hydrogenation of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-methylbutanoate 285.

64. Attempted hydrogenation of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260.

65. 1-Bromo-2-[di(methyloxy)methyl]benzene 316
66. 2-(1,1,1-Tributylstannyl)benzene-1-carbaldehyde 317.
67. Attempted synthesis of 2-(2'-bromophenyl)benzaldehyde 314.
68. 2-(o-Bromophenyl)-1,3-dioxolane 320.
69. 2-Formylphenylboronic acid 321.
70. Tetrakis(triphenylphosphine)palladium (0).
71. 2-(2'-Bromophenyl)benzaldehyde 314.
72. Methyl (2S)-2-((Z)-1-[2-(2-bromophenyl)phenyl]methylidene)amino)-3-phenylpropanoate 322.
73. Methyl (2S)-2-(9H-fluoren-9-ylamino)-3-phenylpropanoate 323.
75. 1-(9H-fluoren-9-yl)-2-(phenylmethyl)tetrahydro-1H-pyrrole 327.
76. Methyl 2-((Z)-1-[2-(bromophenyl)phenyl]methylidene)amino)-5-hexenoate 328.
77. Methyl 1-(9H-fluoren-9-yl)-5-methyltetrahydro-1H-pyrrole-2-carboxylate 329.
78. N-(2-bromophenyl)ethanolamine 336.
3.2 Experimental Procedures

All solvents were distilled before use: light petroleum (refers to the fraction boiling between 40 °C and 60 °C), diethyl ether and ethyl acetate from calcium chloride; dichloromethane and toluene from phosphorous pentoxide; ethanol and methanol from magnesium and iodide. Anhydrous solvents (toluene, diethyl ether, dichloromethane etc.) were obtained from Aldrich Chemical Co. Ltd. and Lancaster Synthesis Ltd. and were distilled or recrystallised as required.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with either potassium permanganate or ninhydrin dip, followed by heating. Flash column chromatography was carried out using Merck Kieselgel 60 H silica unless otherwise stated. Pressure, when required, was applied at the column head using hand bellows. Samples were applied as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Nicolet 205 FT-IR Spectrometer, with internal calibration. \(^1\)H and \(^13\)C NMR spectra were recorded using either a Bruker AC250 or a DPX400 Spectrometer. \(J\) values are given in Hz.

Electron Impact (E. I.) mass spectra were recorded on a Kratos MS80 instrument and on a JEOL SX 102. Chemical Ionisation (C. I.) mass spectra were recorded on a VG Analytical ZAB-E instrument (EPSRC Mass Spectroscopy Service, Swansea).

Melting points were determined on a Leica Galen III Instrument.
3.3 Experimental

1. *N*-Benzyl)allylamine 161.121

\[
\begin{align*}
\text{N} & \quad \text{CH}_2\text{N} \\
\text{160} & \quad \text{161}
\end{align*}
\]

Benzyl bromide (11.58 g, 0.07 mol) was added dropwise to a stirred solution of allylamine 160 (11.6 g, 0.2 mol) in THF (20 cm\(^3\)) at 0 °C under nitrogen atmosphere over a period of 5 h. The reaction mixture was evaporated to dryness and partitioned between diethyl ether (50 cm\(^3\)) and water (50 cm\(^3\)). The organic layer was separated, washed with water (2 x 25 cm\(^3\)), dried and evaporated to dryness to afford a yellow oil which was subjected to distillation under reduced pressure to afford *N*-(benzyl)allylamine 161 pale yellow oil (6.3 g, 63%), b.p. 102 °C at 20 mbar (lit.121 b.p. 70-79 °C at 5.5 Torr); \(v_{\text{max/cm}^{-1}}\) (neat) 3315, 3064, 3027, 1644, 1605, 1106, 994, 918, 736 and 698; \(\delta_{\text{H}}\) (400 MHz; CDCl\(_3\)) 1.29 (1 H, s, NH), 3.25 (2 H, dt, \(J\) 1.3 and 5.9, \(\text{CHCH}_2\text{N}\)), 3.77 (2 H, s, \(\text{CH}_2\text{Ar}\)), 5.1 (1 H, dd, \(J\) 1.3 and 10.2, \(\text{CH}=\text{CH}_A\text{H}_B\)), 5.20 (1 H, ddd, \(J\) 1.3, 3.1 and 17.3, \(\text{CH}=\text{CH}_A\text{H}_B\)), 5.92 (1 H, ddt, \(J\) 5.9, 10.2 and 17.3, \(\text{CH}=\text{CH}_A\text{H}_B\)) and 7.22-7.31 (5H, m, \(\text{ArCH}\)); \(\delta_{\text{C}}\) (100 MHz; CDCl\(_3\)) 52.21 (\(\text{CH}_2\text{NH}\)), 53.71 (\(\text{ArCH}_2\)), 116.35 (\(\text{CH}=\text{CH}_2\)), 127.35, 128.59, 128.81 (\(\text{ArCH}\)), 137.30 (\(\text{CH}=\text{CH}_2\)) and 140.78 (\(\text{ArC}\)).

2. (1-Phenylmethylidene)allylamine 160a.122

\[
\begin{align*}
\text{N} & \quad \text{CH}_2\text{N} \\
\text{160} & \quad \text{160a}
\end{align*}
\]

Benzaldehyde, freshly distilled (23.4 g, 0.22 mol) was added to allylamine 160 (12.6 g, 0.22 mol) at 0 °C over a period of 1 h under a nitrogen atmosphere. The reaction mixture was stirred for 3 h
at this temperature. The mixture was taken up into diethyl ether (100 cm$^3$) dried and concentrated to give the imine 160a as an oil (31.98 g, 99%); $\nu_{\text{max}}$ cm$^{-1}$ (neat) 3063, 3026, 1640, 1597, 993, 921, 755 and 694; $\delta_H$ (250 MHz; CDCl$_3$), 4.25 (2 H, dd, $J$ 5.6 and 1.5, CH$_2$N), 5.15 (1 H, dd, $J$ 1.5 and 11.3, CH=CH$_A$H$_B$), 5.23 (1 H, dd, $J$ 1.5 and 17.0, CH=CH$_A$H$_B$), 6.06 (1 H, ddt, $J$ 5.6, 11.3 and 17, CH=CH$_A$H$_B$), 7.38-7.42 (3 H, m, ArCH) 7.73-7.76 (2 H, m, ArCH), 8.28 (1 H, s, CH=N); $\delta_C$ (62.9 MHz; CDCl$_3$) 63.45 (CH$_2$N); 115.98 (CH=CH$_2$), 128.07, 128.51, 130.62 (ArCH), 135.64 (CH=CH$_2$), 136.14 (ArC) and 161.89 (CH=N).


Sodium borohydride (6.75 g, 0.178 mol) was added in portions to a solution of (1-phenylmethylidene)allylamine 160a in dry ethanol (150 cm$^3$) and the mixture was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction mixture was evaporated to dryness and partitioned between diethyl ether (100 cm$^3$) and water (50 cm$^3$). The organic layer was separated, washed with water (2 x 50 cm$^3$) before extracting with 15% aq. HCl (2 x 50 cm$^3$). The aqueous layers were combined, re-basified to pH 14 using 15% NaOH before extracting with diethyl ether (2 x 75 cm$^3$). The organic layers were combined, washed with water (2 x 30 cm$^3$), dried and evaporated to dryness to give an oil which was subjected to distillation under reduced pressure to afford *N*-benzylallylamine as a clear oil (20.85 g, 64%). The IR and NMR spectra were identical with previously prepared material.

4. Benzenesulfonyl chloride 164.

Sodium borohydride (6.75 g, 0.178 mol) was added in portions to a solution of (1-phenylmethylidene)allylamine 160a in dry ethanol (150 cm$^3$) and the mixture was stirred at room temperature under a nitrogen atmosphere for 2 h. The reaction mixture was evaporated to dryness and partitioned between diethyl ether (100 cm$^3$) and water (50 cm$^3$). The organic layer was separated, washed with water (2 x 50 cm$^3$) before extracting with 15% aq. HCl (2 x 50 cm$^3$). The aqueous layers were combined, re-basified to pH 14 using 15% NaOH before extracting with diethyl ether (2 x 75 cm$^3$). The organic layers were combined, washed with water (2 x 30 cm$^3$), dried and evaporated to dryness to give an oil which was subjected to distillation under reduced pressure to afford *N*-benzylallylamine as a clear oil (20.85 g, 64%). The IR and NMR spectra were identical with previously prepared material.
To a solution of diphenyl disulfide 162 (1.0 g, 4.58 mmol) in dry dichloromethane (10 cm³) was added sulfuryl chloride 163 (4.8 cm³ of a 1 M solution in dichloromethane) and pyridine (0.05 cm³). The reaction mixture was heated under reflux for 15 min under a nitrogen atmosphere to produce a red solution of benzenesulfenyl chloride 164; νmax/cm⁻¹ (neat) 3606, 1578, 1474 and 748. No attempt was made to purify benzenesulfenyl chloride due to its instability resulting in decomposition to diphenyl disulfide.


\[
\text{H}_2\text{C} \quad \text{N} \quad \text{H} \quad \text{S} \quad \text{N} \quad \text{H} \quad \text{C}_6\text{H}_5
\]

a) A solution of benzenesulfenyl chloride 164 (1.32 g, 9.12 mmol) in dichloromethane (10 cm³) was added to a solution of N-(benzyl)allylamine 161 (2.94 g, 0.02 mol) and triethylamine (3.04 g, 0.03 mol) in dichloromethane (20 cm³) at -20 °C under a nitrogen atmosphere over a period of 1 h. The reaction mixture was stirred for 7 h at this temperature. The white precipitate which had developed was filtered off and the filtrate concentrated to yield a dark brown residue. Analysis of this residue by ¹H NMR spectroscopy gave a complex spectra but showed resonances at 3.25 ppm (CH₂N) and 3.75 ppm (ArCH₂) which correspond to N-benzyl allylamine 161 and new resonances at 3.55 ppm (=CHCH₂N) and 4.12 ppm (ArCH₂) which presumably correspond to the title product. Attempts to purify the reaction mixture were unsuccessful.

b) A solution of N-(benzyl)allylamine 161 (1.00 g, 6.80 mmol) and N-(benzenesulfenyl)phthalimide 166 (1.91 g, 7.48 mmol) in DCM (15 cm³) was refluxed for 48 h. The white precipitate which had developed was filtered and washed with aliquots of dichloromethane (2 x 10 cm³). The filtrate was evaporated to dryness to afford a thick white residue which was triturated with light petroleum to afford a white solid. The supernatant was

97
filtered off and the filtrate evaporated to dryness to yield \(N\)-(benzenesulfenyl)-\(N\)-(benzyl)allylamine 165 as an oil (1.523 g, 83%); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3062, 3029, 1642, 1583, 1068, 991, 922, 738 and 697; \(\delta_H\) (250 MHz; CDCl\(_3\)) 3.55 (2 H, d, \(J = 6.4\), CH\(_2\)N), 4.13 (2 H, s, CH\(_2\)Ar), 5.12-5.14 (1 H, m, CH=CH\(_{AB}\)), 5.19 (1 H, br s, CH=CH\(_{AB}\)), 5.93 (1 H, ddt, \(J = 6.4, 16.2, 11.1\) and 11.07, CH=CH\(_{AB}\)) and 7.15-7.39 (10 H, m, ArCH); \(\delta_C\) (62.5 MHz; CDCl\(_3\)) 59.9 (CH\(_2\)N), 61.7 (CH\(_2\)Ar), 117.9 (CH=CH\(_2\)), 126.3, 126.9, 127.4, 128.3, 128.7, 128.8 (ArCH), 135.3 (CH=CH\(_2\)), 138.6 and 139.1 (ArC).

6. Reaction of \(N\)-(benzenesulfenyl)-\(N\)-(benzyl)allylamine 165 with Bu\(_3\)SnH and AIBN.

\[
\begin{align*}
\text{165} & \quad \text{\rightarrow} \\
\text{161}
\end{align*}
\]

a) A deoxygenated solution of Bu\(_3\)SnH (0.83 g, 2.85 mmol) and AIBN (20 mg) in dry toluene (40 cm\(^3\)) was added to a solution of sulfenamide 165 (0.27 g, 1.06 mmol) in dry toluene (15 cm\(^3\)) at 90 °C under a nitrogen atmosphere. Heating was continued for 2 h. The reaction mixture was evaporated to dryness and the residue subjected to column chromatography using light petroleum with 2% Et\(_3\)N as eluant to isolate \(N\)-(benzyl)allylamine 161 as an oil (0.11 g, 72%).

b) The above experiment was repeated in the absence of AIBN. A deoxygenated solution of Bu\(_3\)SnH (0.82 g, 2.82 mmol) in dry toluene (40 cm\(^3\)) was added to a solution of sulfenamide 165 (0.24 g, 9.41 mmol) in dry toluene (15 cm\(^3\)) at 90 °C under a nitrogen atmosphere. Heating was continued for 2 h. The reaction mixture was evaporated to dryness and the residue subjected to column chromatography using light petroleum with 2% Et\(_3\)N as eluant to isolate \(N\)-(benzenesulfenyl)-\(N\)-(benzyl)allylamine 165 as an oil (0.18 g, 75%).
7. **Attempted synthesis of 3-methyl-(benzyl)perhydrofuro[3,4-b]pyrrol-4-one 170.**

![Reaction Scheme]

A deoxygenated solution of Bu₃SnH (0.194 g, 0.67 mmol) and AIBN (0.194 g, 0.11 mmol) in dry toluene (40 cm³) was added to a deoxygenated solution of sulfenamide 165 (0.113 g, 0.44 mmol) and furanone 168 (0.35 g, 4.16 mmol) in dry toluene (5 cm³) at 90 °C under a nitrogen atmosphere over a period of 7 h. The reaction mixture was extracted with 20% aq. HCl (2 x 10 cm³). The aqueous layers were combined, washed with diethyl ether (2 x 10 cm³) before re-basifying to pH 14 with 10% NaOH. The aqueous phase was extracted with diethyl ether (2 x 15 cm³) and the combined organics were washed with water (2 x 10 cm³), dried and evaporated to dryness. Analysis by GC-MS and ¹H NMR spectroscopy failed to show indication of product. The resulting residue was subjected to column chromatography using light petroleum:ethyl acetate (4:1) with 2% triethylamine as eluant to isolate the major component as an oil, which was characterised by ¹H NMR spectroscopy to be the amine 161 (35 mg, 53%).

8. **Attempted synthesis of 3-(butyloxy)-4-methyl-1-(benzyl)tetrahydro-1H-pyrrole 174.**

![Reaction Scheme]

A deoxygenated solution of Bu₃SnH (0.19 g, 0.67 mmol) and AIBN (0.20 g, 0.12 mmol) in dry toluene (40 cm³) was added to a deoxygenated solution of sulfenamide 165 (0.10 g, 0.44 mmol) and butyl vinyl ether 172 (0.39 g, 3.90 mmol) in dry toluene (5 cm³) at 80 °C under a nitrogen atmosphere over a period of 7 h. The mixture was extracted with 20% aq. HCl (2 x 10 cm³). The
aqueous layers were combined, washed with diethyl ether (2 x 15 cm$^3$) and re-basifying to pH 14 with 10% NaOH. The aqueous phase was extracted with diethyl ether (2 x 15 cm$^3$) and the combined organic layers were washed with water (2 x 10 cm$^3$), dried and evaporated to dryness. The resulting residue was subjected to column chromatography using light petroleum with 2% Et$_3$N as eluant to afford the sulfenamide (10 mg, 9%) and the amine 161 (39.5 mg, 59%) as characterised by $^1$H NMR spectroscopy.

9. N-(Benzyloxy carbonyl)allylamine 181

\[
\begin{align*}
\text{NH}_2 & \quad \rightarrow \quad \text{O} \quad \text{C} \\
160 & \quad \rightarrow \quad 181
\end{align*}
\]

A solution of benzyl chloroformate 180 (25 g, 0.147 mol) in dichloromethane (100 cm$^3$) was added over a period of 30 min to a stirred solution of allylamine 160 (9.56 g, 0.167 mol) and triethylamine (16.94 g, 0.167 mol) in dichloromethane (75 cm$^3$). The reaction mixture was washed with 15% aq. HCl (2 x 75 cm$^3$) and water (2 x 100 cm$^3$), dried and evaporated to dryness to afford a yellow oil (26.83 g). Distillation of this oil under reduced pressure afforded N-(benzyloxy carbonyl)allylamine 181 as a yellow oil (16.69 g, 59.6%), b.p. 165 °C at 1.0 mm/Hg (lit.$^{123}$ b.p. 104-106 °C at 0.3 Torr); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3334, 3066, 1704, 1645, 1530, 1250, 991, 920, 738 and 698; $\delta_H$ (400 MHz; CDCl$_3$) 3.79 (2 H, br s, CH$_2$N), 4.97 (1 H, br s, NH), 5.10 (2 H, s, CH$_2$Ar), 5.11 (1 H, dd, J 1.5 and 10.0, C=CH$_2$H$_B$), 5.17 (1 H, dd, J 17.1 and 1.5, C=CH$_2$H$_B$), 5.82 (1 H, ddt, J 5.5, 10.0 and 17.0, CH=CH$_2$) and 7.27-7.36 (5 H, complex, ArCH); $\delta_C$ (100 MHz; CDCl$_3$) 43.47 (CH$_2$N), 66.73 (CH$_2$Ar), 116.01 (CH$_2$=CH), 128.10, 128.50 (ArCH), 134.49 (CH=CH$_2$), 136.54 (ArC) and 156.30 (C=O).

\[
\begin{align*}
\text{181} & \quad \text{182}
\end{align*}
\]

*N*-Benzyl phenyl sulfonyl-N-(benzyloxycarbonyl)allylamine 181 (2 g, 10.46 mmol) was added to a stirred suspension of sodium hydride (0.3 g, 12.55 mmol) in dry DMF (20 cm\textsuperscript{3}) at -20 °C under a nitrogen atmosphere. Stirring was continued for 1 h before a solution of benzenesulfenyl chloride 164 (1.51 g, 10.44 mmol) in dichloromethane (5.3 cm\textsuperscript{3}) was added to the reaction mixture over a period of 5 min. The reaction mixture was stirred for 7 h after which time the reaction mixture was partitioned between water (50 cm\textsuperscript{3}) and diethyl ether (70 cm\textsuperscript{3}). The aqueous layer was separated and the organic layer was further washed with water (2 x 50 cm\textsuperscript{3}), dried and evaporated to dryness to give a dark brown residue which was subjected to column chromatography [light petroleum:diethyl ether (9:1)] to isolate the product as an oil. Recrystallisation was effected from hexane to afford *N*-benzyl phenyl sulfonyl-N-(benzyloxycarbonyl)allylamine 182 as platelets (0.94 g, 30%), m.p 41.3 - 42.3 °C; \( \nu_{\text{max/ cm}} \) (neat) 1682, 1646, 1520, 1342, 1244, 990 and 928; \( \delta_{\text{H}} \) (250 MHz; CDCl\textsubscript{3}) 4.2 (2 H, ddd, \( J \) 1.3, 1.3 and 6.0, CH\textsubscript{2}N), 5.14 (2 H, s, CH\textsubscript{2}Ar), 5.17-5.21 (2 H, m, CH=CH\textsubscript{2}), 5.85 (1 H, ddt, \( J \) 6.0, 10.3 and 16.9, CH=CH\textsubscript{2}) and 7.18-7.35 (10 H, m, 2 x ArCH); \( \delta_{\text{C}} \) (100 MHz; CDCl\textsubscript{3}) 56.43 (CH\textsubscript{2}N), 68.72 (CH\textsubscript{2}Ar), 117.81 (CH=CH\textsubscript{2}), 125.44, 126.92, 127.89, 128.15, 128.48, 129.04 (2 x ArCH) 133.07 (CH=CH\textsubscript{2}), 136.00 (ArC), 138.03 (ArC) and 157.63 (C=O).
11. Reaction of N-(benzenesulfenyl)-N-(benzyloxy carbonyl)allylamine 182 with Bu₃SnH and AIBN.

a) A deoxygenated solution of Bu₃SnH (0.3 cm³, 1.2 mmol) and AIBN (0.05 g) in dry toluene (3 cm³) was added to a deoxygenated solution of the sulfenamide 182 (0.3 g, 1.0 mmol) in toluene (5 cm³) at 90 °C under a nitrogen atmosphere. Heating was continued for a further 95 min. The reaction mixture was evaporated to dryness and the residue subjected to column chromatography using light petroleum:diethyl ether (9:1) as eluant to isolate the major component as an oil (0.25 g, 97%). Analysis by ¹H and ¹³C NMR spectroscopy showed it to be consistent with N-(benzyloxy carbonyl)allylamine 181.

b) The above experiment was repeated in the absence of AIBN. A deoxygenated solution of Bu₃SnH (0.3 cm³, 1.2 mmol) in dry toluene (3 cm³) was added to a deoxygenated solution of sulfenamide 182 (0.3 g, 1.0 mmol) in toluene (5 cm³) at 90 °C under nitrogen atmosphere. Heating was continued for a further 95 min. The reaction mixture was evaporated to dryness and the residue chromatographed using light petroleum:diethyl ether (9:1) as eluant to isolate the major component as an oil (0.249 g, 83%). Analysis by ¹H and ¹³C NMR spectroscopy showed it to be consistent with the starting N-(benzenesulfenyl)-N-(benzyloxy carbonyl)allylamine 182.

\[
\text{Bn} - \text{O}\text{N} - \text{SPh} + \text{OBu} \quad \rightarrow \quad \text{O} - \text{N} - \text{Bn} \\
182 \quad 172 \quad 185
\]

a) A deoxygenated solution of \( \text{Bu}_3\text{SnH} \) (0.31 g, 1.1 mmol) and AIBN (60 mg, 0.37 mmol) in dry cyclohexane (40 cm\(^3\)) was added to a stirred deoxygenated solution of the sulfenamide 182 (0.2 g, 0.68 mmol) and butyl vinyl ether 172 (0.34 g, 3.35 mmol) in refluxing dry cyclohexane (7 cm\(^3\)) under a nitrogen atmosphere over a period of 10 h. TLC indicated the formation of a new component. The reaction mixture was evaporated to dryness and the resulting residue subjected to column chromatography using light petroleum:ethyl acetate (9: 1) as eluant to isolate the major component as an oil. The \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra of this oil were consistent with it being the urethane 181 (86 mg, 68%).

b) A deoxygenated solution of \( \text{Bu}_3\text{SnH} \) (0.146 g, 5 mmol) and AIBN (20 mg, 0.12 mmol) in dry toluene (40 cm\(^3\)) was added to a deoxygenated solution of the sulfenamide 182 (0.1 g, 0.33 mmol) and butyl vinyl ether 172 (0.33 g, 3.34 mmol) in dry toluene (15 cm\(^3\)) at 90 °C under a nitrogen atmosphere over a period of 7 h. The reaction mixture was evaporated to dryness and the resulting residue subjected to column chromatography (light petroleum) to initially remove the tin components and then light petroleum:ethyl acetate (9:1) to initially isolate the high running component as an oil which was characterised by \(^1\text{H}\) NMR spectroscopy to be the sulfenamide 182 (69 mg, 69%). The other major component was isolated as an oil which was characterised by \(^1\text{H}\) NMR spectroscopy to be the urethane 181 (15 mg, 24%).

c) The procedure in (b) was repeated using \( \text{Bu}_3\text{SnH} \) (0.165 g, 0.57 mmol). As before, TLC showed only those components with similar \( R_f \)'s to the starting sulfenamide 182 and urethane 181. Both
components were isolated by column chromatography and characterised by $^1$H NMR spectroscopy to be the sulfenamide 182 (53 mg, 53%), and urethane 181 (24 mg, 37%).

d) A deoxygenated solution of Bu$_3$SnH (0.49 g, 1.68 mmol) and AIBN (26 mg, 0.16 mmol) in dry toluene (40 cm$^3$) was added to a deoxygenated mixture of sulfenamide 182 (0.144 g, 0.48 mmol) and butyl vinyl ether 172 (2.3 g, 23.18 mmol) at 90 °C under a nitrogen atmosphere over a period of 6 h. The reaction mixture was evaporated to dryness and the resulting residue subjected to column chromatography (dichloromethane). The major component was isolated as an oil and was characterised by $^1$H NMR spectroscopy to be the urethane 181 (65 mg, 72%).


![Chemical Structure](image)

a) A deoxygenated solution of Bu$_3$SnH (0.33 g, 1.1 mmol) and AIBN (0.08 g, 0.49 mmol) in dry toluene (50 cm$^3$) was added to a deoxygenated solution of the sulfenamide 182 (0.32 g, 1.1 mmol) and dihydropyran 186 (0.52 g, 6.18 mmol) in dry toluene (3 cm$^3$) at 90 °C under a nitrogen atmosphere over a period of 6 h. TLC showed the formation of a new component. The reaction mixture was evaporated to dryness. Analysis by GC-MS and $^1$H NMR spectroscopy failed to show indication of product 188. The resulting residue was subjected to column chromatography using light petroleum:diethyl ether (4:1) as eluant to isolate the major component as an oil. Analysis by $^1$H and $^{13}$C NMR spectroscopy showed it to be consistent with the urethane 181 (0.17 g, 83%).
b) A deoxygenated solution of Bu$_3$SnH (0.33 g, 1.1 mmol) and AIBN (0.08 g, 0.49 mmol) in dry toluene (60 cm$^3$) was added to a deoxygenated solution of sulfenamide 182 (0.3 g, 1.0 mmol) and dihydropyran 186 (0.41 g, 4.9 mmol) in dry toluene (20 cm$^3$) at 90 °C under a nitrogen atmosphere over a period of 14 h. TLC showed a new component which was isolated by the procedure outlined in a) to afford the product as an oil. Analysis by $^1$H and $^{13}$C NMR spectroscopy showed it to be consistent with the urethane 181 (0.15 g, 76%).


![Chemical structure](image)

a) A deoxygenated solution of Bu$_3$SnH (0.49 g, 1.68 mmol) and AIBN (25 mg, 0.15 mmol) in dry toluene (55 cm$^3$) was added to a deoxygenated solution of sulfenamide 182 (0.28 g, 0.94 mmol) and dihydrofuran 189 (0.43 g, 6.14 mmol) in dry toluene (6 cm$^3$) at 90 °C under a nitrogen atmosphere over a period of 6.3 h. TLC indicated the formation of a new component, similar to that of urethane, and several new low running components. The reaction mixture was evaporated to dryness and the resulting residue subjected to column chromatography (light petroleum) to remove the tin components before moving to light petroleum:ethyl acetate (4:1). The high running component was isolated and characterised by $^1$H NMR spectroscopy to be the urethane 181 (92 mg, 52%). The lower running components were isolated to afford 191 as a 1:1 mixture of diastereomers (49 mg, 20%); $v_{\text{max}}$/cm$^{-1}$ (neat) 3033, 1704, 736 and 699; $\delta_H$ (250 MHz; CDCl$_3$) 1.09, 1.12 (6 H, 2xd, 2xCH$_3$), 2.19 (3 H, m, OCH$_2$CH$_2$ and CHCH$_3$), 2.91 (2 H, m, ArCH$_2$), 3.77 (3 H, m, OCH$_2$, CHN), 4.27 (H, m, OCH), 5.14 (2 H, m, ArCH$_2$) and 7.26 (5 H, m ArCH); $\delta_C$ (100 MHz; CDCl$_3$) 11.3 (2xCH$_3$), 33.9, 35.0 (OCH$_2$CH$_2$), 37.6, 38.0 (CHCH$_3$), 51.8, 52.0 (CH$_2$N), 63.0, 63.6 (CHN), 66.8, 66.9 (ArCH$_2$), 68.4, 68.5 (OCH$_2$), 84.7, 85.5 (OCH), 127.7-
128.5 (ArCH), 136.9 (ArC) and 154.2, 154.3 (C=O); m/z 261.1365 [M+ 261 (100), C_{15}H_{19}NO_{3} requires 261.1365], 216 (6), 188 (4), 170 (6), 154 (24), 126 (11), 91 (100) and 84 (15).

b) A deoxygenated solution of Bu_{3}SnH (0.146 g, 0.5 mmol) and AIBN (30 mg, 0.18 mmol) in dry toluene (25 cm^{3}) was added to a deoxygenated solution of sulfenamide 182 (0.1 g, 0.33 mmol) and dihydrofuran 189 (0.126 g, 1.8 mmol) in dry toluene (7 cm^{3}) at 85 °C under a nitrogen atmosphere over a period of 12.5 h. Dihydrofuran 189 (46 mg, 0.66 mmol) was added to the reaction mixture every 3 h. The reaction mixture was evaporated to dryness and the residue subjected to column chromatography (light petroleum) to remove the tin components before using to light petroleum:ethyl acetate (4:1) to isolate the urethane 181 as an oil (26 mg, 41%) and 191 as an oil (31 mg, 36%).

c) A deoxygenated solution of Bu_{3}SnH (0.126 g, 0.43 mmol) and AIBN (20 mg, 0.12 mmol) in dry cyclohexane (40 cm^{3}) was added to a deoxygenated solution of sulfenamide 182 (0.1 g, 0.33 mmol) and dihydrofuran 189 (0.23 g, 3.28 mmol) in refluxing dry cyclohexane (20 cm^{3}) under a nitrogen atmosphere over a period of 7 h. The reaction mixture was evaporated to dryness and the resulting residue was subjected to column chromatography (light petroleum) to remove the tin components before moving to light petroleum:ethyl acetate (4:1) to isolate the major component as an oil. The ^{1}H NMR spectrum of the oil was consistent with that of the urethane 181 (59 mg, 92%).

d) A deoxygenated solution of Bu_{3}SnH (0.136 g, 0.47 mmol) and AIBN (15 mg, 0.09 mmol) in dry cyclohexane (40 cm^{3}) was added to a deoxygenated solution of sulfenamide 182 (0.1 g, 0.33 mmol) and dihydrofuran 189 (0.24 g, 3.4 mmol) dry cyclohexane (10 cm^{3}) over a period of 10 h whilst irradiating the reaction mixture with 360 nm UV light. TLC showed a complex mixture of components present. The reaction mixture was evaporated to dryness and the resulting residue was subjected to column chromatography (light petroleum) to remove the tin components before using light petroleum:ethyl acetate (9:1) to isolate all other components. The first component isolated was characterised by ^{1}H NMR spectroscopy and shown to be the sulfenamide 182 (34
mg, 34%). The second component isolated was the urethane 181 (27 mg, 42%) as indicated by $^1$H
NMR spectroscopy. The low running components were isolated and characterised by $^1$H NMR
spectroscopy to be a diastereomeric mixture of 191 (2 mg, 2%).

15. N-(Pentafluorobenzoyl)allylamine 197.

\[
\begin{align*}
\text{NH}_2 & \quad + \quad \text{Cl} \quad \text{C} \quad \text{F} \\
160 & \quad 196 & \quad 197
\end{align*}
\]

Pentafluorobenzoyl chloride 196 (1 g, 4.33 mmol) was added to a solution of allylamine 160
(0.5 g, 8.76 mmol) in dichloromethane (10 cm$^3$) over a period of 10 min and the reaction mixture
was stirred overnight under a nitrogen atmosphere. The precipitate which had developed was
filtered off and the filtrate was evaporated to dryness to afford N-(pentafluorobenzoyl)allylamine
197 as a white solid (0.96 g, 89%), m.p 72.3 - 73.0 °C; $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3245, 3072, 1662, 1519,
1245, 989 and 905; $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 4.01 (2 H, t, $J\, 5.6$, CH$_2$N), 5.16-5.27 (2 H, m,
CH=CH$_2$), 5.78-5.93 (1 H, m, CH=CH$_2$) and 6.65 (1 H, br s, NH); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 42.56
(CH$_2$N), 111.61 (tm, $^1$J$_{\text{C-F}}$ 19.1, ipso-phenyl C), 117.08 (CH=CH$_2$), 132.76 (CH=CH$_2$), 137.63
(dm, $^1$J$_{\text{C-F}}$ 256.0, meta-phenyl C), 142.32 (dtt, $^1$J$_{\text{C-F}}$ 257.6, 14.1 and 5.0, para-phenyl C), 144.25
(ddd, $^1$J$_{\text{C-F}}$ 252.5, 16.1, 8.0 and 4.2, ortho-phenyl C) and 157.47 (C=O); m/z 251.0370 [M$^+$ 251
(9%), C$_{10}$H$_6$NOFs requires 251.0370], 236 (16), 195 (100), 167 (25), 148 (3) and 117 (12).


\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{N} & \quad \text{SPh} \\
197 & \quad 198
\end{align*}
\]

$^\dagger$ Signal too weak to observe all C-F coupling.

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Sodium hydride (0.08 g, 3.33 mmol) was added to a solution of amide 197 (0.5 g, 2.0 mmol) in dry DMF (10 cm³) at -20 °C and the mixture was stirred for 1 h. A solution of benzenesulfenyl chloride 164 (0.288 g, 2.00 mmol) in dichloromethane (10 cm³) was added to the mixture over a period of 20 min and the reaction mixture stirred overnight. The mixture was partitioned between water (100 cm³) and diethyl ether (50 cm³). The organic phase was separated, washed with water (2 x 10 cm³), dried and evaporated to dryness to give a residue which was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to isolate N-(benzenesulfenyl)-N-(pentafluorobenzoyl)allylamine 198 as an oil (0.25 g, 36%); ν_max/cm⁻¹ (neat) 2924, 2854, 1681, 1502, 1354, 1241 and 989; δ_H (400 MHz; CDCl₃) 4.4 (2 H, d, J 5.9, CH₂N), 5.25-5.30 (2 H, m, CH=CH₂), 5.90 (1 H, ddt, J 5.9, 10.0 and 17.2, CH=CH₂), 7.11-7.13 (2 H, m, ArCH), 7.25-7.29 (1 H, m, ArCH) and 7.33-7.37 (2 H, m, ArCH); δ_C (100 MHz; CDCl₃) 53.46 (CH₂N), 118.90 (CH=CH₂), 111.88 (td, † J_C-F 21.0 and 4.0, ipso-phenyl C), 125.32, 128.04, 129.40 (ArCH), 131.32 (CH=CH₂), 135.45 (ArC), 137.54 (dm, † J_C-F 253.0, meta-phenyl C), 142.00 (dtt, † J_C-F 255.0, 14.0 and 5.0, para-phenyl C), 143.05 (dddt, † J_C-F 249.0, 17.0, 9.0 and 4.0, ortho-phenyl C) and 164.29 (C=O); m/z 359.0403 (C₁₆H₁₀NOF₅S requires 359.0403).


![Chemical structure](image)

A deoxygenated solution of Bu₃SnH (79 mg, 0.27 mmol) and AIBN (15 mg) in dry toluene (15 cm³) was added to a deoxygenated solution of the sulfenamide 198 (65 mg, 0.18 mmol) and dihydropyran 186 (0.456 g, 5.43 mmol) at 83 °C under a nitrogen atmosphere over a period of 10 h. A GC-MS study on the reaction mixture showed it to contain many new components. A minor

† Signal too weak to observe all C-F coupling.

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product with a MS predicted for the expected product was observed; m/z 335 (13%), 293 (13), 207 (13), 195 (100), 167 (15), 140 (10), 109 (34) and 83 (80). Attempts to isolate this component by column chromatography using light petroleum:ethyl acetate (10:1) as eluant were unsuccessful. The sulfenamide 198 was isolated (5.85 mg, 9%) along with the amide 197 (16 mg, 36%).

18. Attempted synthesis of 3-(butyloxy)-4-methyl-1-(benzyl)tetrahydro-1H-pyrrole 174.

\[
\begin{align*}
165 & \quad + \quad \begin{array}{c}
\text{OBu} \\
\text{Bn}
\end{array} \\
& \quad \rightarrow \\
174
\end{align*}
\]

a) A solution of BF$_3$OEt$_2$ (0.107 g, 0.75 mmol) was added to a solution of sulfenamide 165 (0.193 g, 0.76 mmol) in toluene (5 cm$^3$) at -78 °C. The mixture was warmed to room temperature before adding butyl vinyl ether 172 (3.78 g, 37.7 mmol) and the reaction mixture was heated to 80 °C before adding a solution of Bu$_3$SnH (0.44 g, 1.51 mmol) and AIBN (30 mg, 0.18 mmol) in toluene (40 cm$^3$) over a period of 8 h. The resulting dark brown solution was extracted with 15% aq. HCl (2 x 30 cm$^3$) and the aqueous layers were combined and washed with light petroleum (2 x 50 cm$^3$). The pH of the aqueous layer was adjusted to pH 14 with 15% NaOH before extracting with diethyl ether (2 x 30 cm$^3$). The organic layers were combined, dried and evaporated to dryness to give an oil (50 mg). Analysis of the oil by $^1$H NMR spectroscopy gave a complex spectrum with no indication of product but resonances that were consistent with the amine 161.

b) MgBr$_2$.OEt$_2$ (0.16 g, 0.62 mmol) was added to a solution of sulfenamide 165 (0.317 g, 1.24 mmol) in dry toluene (5 cm$^3$) at 0 °C. The mixture was stirred at this temperature before introducing butyl vinyl ether 172 (6.22 g, 62.13 mmol). The reaction mixture was heated to 80 °C and a solution of Bu$_3$SnH (0.72 g, 2.47 mmol) and AIBN (52 mg, 0.32 mmol) in toluene (40 cm$^3$) was added over a period of 6 h. The resulting dark brown solution was extracted with 15% aq.
HCl (2 x 30 cm\(^3\)) and the aqueous layers were combined, washed with diethyl ether (2 x 50 cm\(^3\)) before re-basifying to pH 14 with 15% NaOH. The aqueous was extracted with diethyl ether (2 x 50 cm\(^3\)), washed, dried and evaporated to dryness to afford an oil (110 mg). Analysis of the oil by \(^1\)H NMR spectroscopy showed no indication of required product and showed resonances that were consistent with the amine 161.

19. PTOC carbamate of N-(benzyl)allylamine 122.

\[ \text{161} \quad \rightarrow \quad \text{122} \]

A solution of triphosgene 209 (2.02 g, 6.8 mmol) in toluene (10 cm\(^3\)) was added to a solution of N-(benzyl)allylamine 161 (2 g, 0.013 mol) and triethylamine (1.36 g, 0.013 mol) in toluene (15 cm\(^3\)) at 0 °C under a nitrogen atmosphere. The mixture was warmed to room temperature and stirred overnight. The white precipitate which had developed was filtered off and to the filtrate was added 2-mercaptopryridine N-oxide 210 (1.73 g, 0.014 mol) and triethylamine (1.36 g, 0.013 mol). The reaction vessel was wrapped in aluminum foil and the reaction mixture stirred overnight under nitrogen atmosphere. The reaction mixture was filtered and the filtrate evaporated to dryness to afford a yellow residue which was chromatographed using light petroleum:ethyl acetate (1:4) as eluant to isolate the product as a yellow oil. Crystallisation was effected from ethyl acetate/light petroleum to afford the PTOC carbamate 122 as yellow needles (1.71 g, 42%). mp 99-100 °C (decomposition); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3065, 1758, 1642 and 1606; the \(^1\)H and \(^13\)C NMR spectra recorded at room temperature were very complex. Simplification of the spectra was achieved by recording at 52 °C; \(\delta_{\text{H}}\) (250 MHz; CDCl\(_3\)) 4.04 (2 H, br s, CH\(_2\)N), 4.67 (2 H, br s, ArCH\(_2\)), 5.22 (1 H, dd, J 0.8 and 10.2, CH=CH\(_A\)HB), 5.26 (1 H, br s, CH=CH\(_A\)HB), 5.88 (1 H, m, CH=CH\(_A\)HB) and 6.61-7.70 (9 H, m, ArCH); \(\delta_{\text{C}}\) (62.5 MHz; CDCl\(_3\)) 49.8 (CH\(_2\)N), 50.9 (CH\(_2\)Ar), 111.9 (ArCH), 118.2 (CH=CH\(_2\)), 128.2, 128.5, 129.2 (ArCH), 132.8 (CH=CH\(_2\)), 136.3 (ArC), 137.4, 139.1 (ArCH), 152.1 (C=O) and 176.5 (C=S).
20. 3-(Butyloxy)-4-methyl-1-(benzyyl)tetrahydro-1H-pyrrole 174.

\[
\text{122} + \text{172} \rightarrow \text{174} + \text{213}
\]

a) A stirred deoxygenated solution of PTOC carbamate 122 (0.267 g 0.89 mmol), malonic acid (0.278 g, 2.67 mmol), thiophenol (0.39 g 3.56 mmol), and butyl vinyl ether 172 (9.27 g, 0.093 mmol) in acetonitrile (17.8 cm³) was irradiated with a sun lamp for 6 h. The reaction mixture was evaporated to dryness and the residue was subjected to column chromatography on neutral alumina using hexane:ethyl acetate (4:1) as eluant. Separation was inadequate, so the combined fractions were extracted with 10% aq. HCl (2 x 20 ml). The aqueous layers were combined, washed with diethyl ether (2 x 15 cm³) and re-basified to pH 14 with 15% aq. NaOH before extracting with diethyl ether (2 x 15 cm³). The organic layers were combined, dried and concentrated to give an oil (22 mg) which on analysis by ¹H NMR spectroscopy showed it not to be the desired product 174, due to the lack of the characteristic doublet representative of the methyl group. The ¹H NMR indicated that the product (213) obtained was the result of addition between the pyridinethiyl radical and butyl vinyl ether 172. δH (250 MHz, CDCl₃) 0.91 (3 H, t, CH₂CH₃), 1.35 (2 H, sextet, CH₂CH₃), 1.56 (2 H, quintet, CH₂CH₂CH₃), 3.39 (2 H, t, OCH₂CH₂S), 3.48 (2 H, t, OCH₂CH₂CH₂CH₃), 3.69 (2 H, t, OCH₂CH₂S), 6.97- 7.6 (3 H, m, ArCH), 8.4-8.42 (2 H, m, ArCH).

b) The experiment above was repeated using a different work-up procedure: the reaction mixture was evaporated to dryness and the residue taken up into diethyl ether (50 cm³), washed with 30% aq. KOH (2 x 20 cm³) and brine (2 x 20 cm³) before extracting with 15% aq. HCl (2 x 20 cm³). The aqueous layers were combined, re-basified to pH 14 with 15% aq. NaOH and extracted with diethyl ether (2 x 30 cm³). The organic layers were combined, dried and concentrated to yield an oil which was characterised by ¹H NMR spectroscopy to be a diastereomeric mixture 1:1 of the
pyrrolidine 174. The oil was subjected to column chromatography using light petroleum:ethyl acetate (4:1) with 3% triethylamine as eluant to isolate the pyrrolidine 174 as an oily mixture of diastereomers (12 mg, 8%). The product was subjected to a further column chromatography using light petroleum:ethyl acetate (6:1) with 3% triethylamine as eluant to isolate a single diastereomer of the pyrrolidine product (5 mg, 3%).

\[ \text{H} (400 \text{ MHz}, \text{CDCl}_3) 0.91 (3 \text{ H}, t, J 7.2, \text{CH}_2\text{CH}_2\text{CH}_3), 0.99 (3 \text{ H}, d, J 7, \text{CHCH}_3), 1.36 (2 \text{ H}, m, \text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 1.53 (2 \text{ H}, m, \text{CH}_2\text{CH}_2\text{CH}_3), 2.17 (1 \text{ H}, m, \text{NCH}_A\text{H}_A'), 2.29 (1 \text{ H}, m, \text{CHCH}_3), 2.36 (1 \text{ H}, m, \text{NCH}_B\text{H}_B'), 2.91 (1 \text{ H}, m, \text{NCH}_A\text{H}_A), 3.13 (1 \text{ H}, m, \text{NCH}_B\text{H}_B'), 3.36 (2 \text{ H}, m, \text{OCH}_2), 3.62 (1 \text{ H}, d, J 13.1, \text{ArCHCH}_3\text{C}'), 3.64 (1 \text{ H}, d, J 13.1, \text{ArCHCH}_3\text{C}'), 3.83 (1 \text{ H}, m, \text{OCH}), 7.23-7.33 (5 \text{ H}, m, \text{ArCH}); \delta_c (100 \text{ MHz}, \text{CDCl}_3) 12.12 (\text{CHCH}_3), 13.96 (\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 19.46 (\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 32.01 (\text{NCH}_A\text{H}_A'), 36.82 (\text{CHCH}_3), 59.87, 60.12 (\text{NCH}_2), 69.95 (\text{ArCH}_2), 69.83 (\text{OCH}_2), 79.84 (\text{OCH}), 127.32, 128.21, 128.36, 129.11, 129.67 (\text{ArCH}).

21. Reaction between the PTOC carbamate of N-(benzyl)allylamine 122 and dihydrofuran 189.

\[
\begin{align*}
\text{N} \quad \text{O} \quad \text{S} \quad \text{O} \quad \text{N} & \quad \text{N} \\
\text{Bn} & \quad \text{122} & \quad \text{189} & \quad \text{214} & \quad \text{216}
\end{align*}
\]

A deoxygenated solution of the PTOC carbamate 122 (0.03 g, 0.1 mmol), malonic acid (0.42 mg, 4.0 mmol), dihydrofuran 189 (7.28 g, 0.1 mol) and thiophenol (0.44 g, 4.0 mmol) in dry MeCN (20 cm\(^3\)) was irradiated with a sun lamp for 20 h. The reaction mixture was evaporated to dryness and treated with 30% aq. KOH. The aqueous layer was separated and the organic extract washed with water (10 cm\(^3\)) before extracting with 15% aq. HCl (3 x 5 cm\(^3\)). The combined aqueous layers were washed with ethyl acetate and re-basified to pH 14 with 30% aq. KOH. The aqueous layer was extracted with diethyl ether (3 x 5 cm\(^3\)), combined, dried and evaporated to dryness. Analysis by \(^1\text{H NMR spectroscopy indicated resonances for alkenyl and tetrahydrofuran}\)
derivatives. Analysis by GC-MS of the residue showed that three of the components had a molecular ion corresponding to the expected product in a ratio of 1:6.3:354. The lesser components (< 7%) had fragmentation patterns consistent with that of the expected product 214; m/z 217 (10%), 188 (12), 174 (5), 120 (20) and 91 (100). The mass spectrum for the major component had a fragmentation pattern suggesting it not to be the desired product but rather the product 216 arising from addition of the aminyl radical to tetrahydrofuran; m/z 217 (26%), 186 (22), 174 (25), 158 (35), 146 (60), 134 (35), 106 (30), 91 (100) and 71 (60).

22. Reaction between the PTOC carbamate of N-(benzyl)allylamine 122 and dihydropyran 186.

\[
\begin{array}{c}
\includegraphics[width=0.5\textwidth]{reaction}
\end{array}
\]

A deoxygenated solution of the PTOC carbamate 122 (0.03 g, 0.1 mmol), malonic acid (0.42 mg, 4.0 mmol), dihydropyran 186 (7.74 g, 0.1 mol) and thiophenol (0.44 g, 4.0 mmol) in dry MeCN (20 cm³) was irradiated with a sun lamp for 48 h. The reaction mixture was evaporated to dryness and treated with 30% aq. KOH. The aqueous layer was separated and the organic extract washed with water (10 cm³) before extracting with 15% aq. HCl (3 x 5 cm³). The combined aqueous layers were washed with ethyl acetate and re-basified to pH 14 with 30% aq. KOH. The aqueous layer was extracted with diethyl ether (3 x 5 cm³), combined, dried and evaporated to dryness. Analysis by \(^1\)H NMR spectroscopy of the residue indicated that the desired product 215 of radical cyclisation was formed, by the presence of the characteristic doublet attributed to the methyl group (\(\delta 0.96\) ppm). The spectrum also showed more than the expected number of peaks presumably attributed to the product of addition of the aminyl radical to tetrahydropyran. Analysis by GC-MS showed that three of the components had a molecular ion corresponding to the expected product in a ratio of 1:55:87. The lesser components had a fragmentation pattern consistent to that of the
expected product 215; m/z 231 (25%), 188 (45), 174 (18), 120 (47) and 91 (100). The mass spectrum for the major component had a fragmentation pattern suggesting it not to be the desired product but rather the product 217 arising from addition of the aminyl radical to tetrahydropyran; m/z 231 (6%), 173 (8), 160 (90), 134 (22), 91 (100).

23. Cyclic pyridinium salt 222.36

2-Mercaptopyridine N-oxide 210 (1 g, 7.86 mmol) was added to a stirred solution of triphosgene 209 (2.33 g, 7.86 mmol) in dry toluene (20 cm³) and the reaction mixture was stirred overnight. The reaction mixture was filtered under reduced pressure and the precipitate was washed with aliquots of diethyl ether (3 x 10 cm³). The organic phases were combined, dried and evaporated to dryness to afford the cyclic pyridinium salt 222 as a white solid (1.29 g, 87%), mp 107-110 °C (decomposition), (lit.36 mp 108-110 °C); νmax/cm⁻¹ (nujol) 1786, 1603, 1571, 1277, 982 and 796.

24. PTOC carbamate of ethyl N-(benzyl)-2-amino-5-hexenoate 223c.

The cyclic pyridinium salt 222 (90 mg, 0.47 mmol) was added to a stirred solution of ethyl 2-amino-5-hexenoate 221c (115 mg, 0.47 mmol) in dry MeCN (20 cm³) and the reaction mixture was stirred for 2 h. The reaction mixture was evaporated to dryness and the residue was subjected to column chromatography using light petroleum:ethyl acetate (4:1) as eluant to isolate the
PTOC carbamate of ethyl N-(benzyl)-2-amino-5-hexenoate, 223c, as a yellow oil (60 mg, 35%);

\(v_{\text{max}}/\text{cm}^{-1}\) (neat) 2978, 1765, 1737, 1640, 1608, 1527, 1448, 1220 and 738; \(\delta_H\) (400 MHz; CDCl\(_3\)) 1.23-1.32 (3 H, m, CH\(_3\)), 2.06-2.21 (2 H, m, NCHCH\(_2\)), 4.07-4.14 (2 H, m, OCH\(_2\)), 4.15-4.26 (1 H, m, NCH), 4.82-4.86 (2 H, m, CH\(_2\)CH=CH\(_2\)), 4.94-5.04 (4 H, m, PhCH\(_2\) and CH=CH\(_2\)), 6.60-6.63 (1 H, m, ArCH) and 7.20-7.69 (8 H, m, ArCH);

\(\delta_C\) (100 MHz; CDCl\(_3\)) 14.03 (CH\(_3\)), 28.42 (NCHCH\(_2\)), 30.19 (CH\(_2\)CH=CH\(_2\)), 51.81 (PhCH\(_2\)), 60.65 (NCH), 61.47 (OCH\(_2\)), 112.71 (CH=CH\(_2\)), 115.80, 127.72, 128.18, 128.49, 133.40 (ArCH), 136.22 (ArC), 137.00, 137.55 (ArCH), 138.58 (CH=CH\(_2\)), 151.99 (C=S), 169.83 (NC=O) and 176.28 (C=O).

25. N-(Phenylmethylidene)glycine methyl ester 225\(^{86a,b}\)

\[
\text{HCl.H}_{2}\text{N} \xrightarrow{\text{CO}_{2}\text{Me}} \text{N} \xrightarrow{\text{CO}_{2}\text{Me}} \]

224 225

Triethylamine (8.0 g, 79.06 mmol) was added to a suspension of glycine methyl ester hydrochloride (10.0 g, 79.64 mmol) in dry dichloromethane (100 cm\(^3\)) and the mixture was stirred for 10 min after which time benzaldehyde (8.0 g, 75.39 mmol) and 4Å molecular sieves were added. The reaction mixture was stirred overnight under a nitrogen atmosphere. The mixture was filtered and the filtrate was washed with water (2 x 50 cm\(^3\)) and brine (50 cm\(^3\)), dried and evaporated to dryness to afford N-(phenylmethylidene)glycine methyl ester 225 as an orange oil (10.87 g, 81%); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 2953, 2880 and 1748; \(\delta_H\) (250 MHz; CDCl\(_3\)) 3.77 (3 H, s, OMe), 4.42 (2 H, d, J 1.27, CH\(_2\)), 7.37-7.46 (3 H, m, ArCH), 7.76-7.80 (2 H, m, ArCH) and 8.29 (1 H, t, J 1.27, CH=N); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 52.0 (CH\(_3\)), 61.9 (CH\(_2\)), 128.4, 128.5, 131.2 (ArCH), 135 (ArC), 165.3 (CH=CH\(_2\)) and 170.4 (CO\(_2\)Me).
26. Methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate 226.86a,c

\[
\begin{align*}
&\text{N-(Phenylmethylidene)glycine methyl ester } 225 \text{ (9.5 g, 53.61 mmol) in dry tetrahydrofuran (10 cm}^3) \text{ was added to a stirred suspension of 60% sodium hydride (2.14 g, 53.61 mmol) in dry}\n\text{tetrahydrofuran (60 cm}^3) \text{ at -78 °C. The mixture was warmed to 0 °C and stirring continued for a further 30 min after which time a deep red solution was produced. The reaction mixture was}\n\text{cooled to -20 °C and 4-bromobut-1-ene (7.24 g, 56.43 mmol) was added over a period of 20 min.}\n\text{The reaction mixture was warmed to room temperature and stirred overnight under a nitrogen}\n\text{atmosphere. The orange suspension was filtered through a pad of celite and the filtrate was}\n\text{evaporated to dryness. The residue was extracted into diethyl ether (75 cm}^3) \text{, washed with water}\n(2 x 30 cm}^3) \text{ and brine (2 x 30 cm}^3), \text{dried and evaporated to dryness to afford a dark orange oil}\n\text{which was subjected to Kugelrohr distillation to yield methyl 2-[(1-phenylmethylidene)amino]-5-}\nhexenoate 226 as a yellow oil (6.8 g, 54%); b.p. 165 °C at 0.5 mbar (lit.86c b.p. 132-134 °C at 0.1}\n\text{Torr); } \nu_{\text{max}}/\text{cm}^{-1} (\text{neat}) 3064, 2951, 2850, 1739, 1643, 1581, 1451, 915, 755 \text{ and } 694; \delta_H (250}\n\text{MHz; CDCl}_3 1.80-1.88 (2 H, m, CH}_2\text{CH=CH}_2), 2.06-2.16 (2 H, m, CH}_2\text{CHN}), 3.76 (3 H, s,}\n\text{OCH}_3), 4.06 (1 H, t, J 5.2, CHN), 4.98-5.10 (2 H, m, CH=CH}_2), 5.71-5.89 (1 H, m, CH=CH}_2),}\n7.38-7.47 (3 H, m, ArCH), 7.77-7.81 (2 H, m, ArCH) and 8.28 (1 H, s, CH=N), δ_C (100 MHz; CDCl}_3) 29.89 (CH}_2\text{CHN}), 32.17 (CH}_2\text{CH=CH}_2), 52.17 (OCH}_3), 72.56 (NCHCO}_2\text{CH}_3), 115.52 (CH=CH}_2), 128.56, 128.62, 131.18 (ArCH), 135.62 (ArC), 137.35 (CH=CH}_2), 163.72 (C=N) \text{ and } 172.55 (C=O).
27. Methyl 2-(benzylamino)-5-hexenoate 221b.  

Sodium borohydride (0.18 g, 4.8 mmol) was added to a solution of methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate 226 (1.10 g, 4.8 mmol) in methanol (40 cm³). The reaction mixture was stirred at room temperature until evolution of gas had ceased. The reaction mixture was evaporated to dryness and the residue partitioned between water (15 cm³) and diethyl ether (25 cm³). The aqueous layer was separated, extracted with diethyl ether (15 cm³) and the combined organic layers washed with water (2 x 10 cm³), dried and evaporated to dryness. The resulting residue was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to isolate methyl 2-(benzylamino)-5-hexenoate 221b as a pale yellow oil (0.66 g, 59%); \( \nu_{\text{max}} /\text{cm}^{-1} \) (neat) 3331, 2949, 1737, 1641, 1453, 1197, 1173, 914, 736 and 699; \( \delta_{\text{H}} \) (250 MHz; CDCl₃) 1.63-1.78 (2 H, m, NCHCH₂), 1.8 (1 H, s, NH), 2.09-2.19 (2 H, m, CH₂CH=CH₂), 3.26 (1 H, dd, \( J = 6.0 \) and 7.4, NCH), 3.59 (1 H, d, \( J = 13.0 \), PhCH₂H₂), 3.68 (3 H, m, OCH₃), 3.79 (1 H, d, \( J = 13.0 \), PhCH₂H₂), 4.94-5.02 (2 H, m, CH₂CH=CH₂), 5.75 (1 H, ddt, \( J = 10.3 \), 17.0 and 6.6, CH=CH₂), 7.18-7.33 (5 H, m, ArCH); \( \delta_{\text{C}} \) (100 MHz; CDCl₃) 29.9, 32.6, 51.6 (OCH₃), 52.1 (PhCH₂), 60.0 (NCH), 115.1 (CH=CH₂), 127.0, 128.2, 128.3 (ArCH), 137.6 (CH=CH₂), 139.8 (ArC), 175.8 (C=O).

28. PTOC carbamate of methyl N-(benzyl)-2-amino-5-hexenoate 223b.
A solution of methyl 2-amino-5-hexenoate 221b (1.0 g, 4.29 mmol) and triethylamine (0.44 g, 3.35 mmol) in dry toluene (10 cm³) was added to a solution of cyclic pyridinium salt 222 (0.82 g, 4.32 mmol) in dry toluene (20 cm³) at 0 °C over a period of 15 min. The reaction mixture was warmed to room temperature and stirring continued overnight. The reaction mixture was washed with water (2 x 30 cm³) and brine (30 cm³), dried and evaporated to dryness. The residue was subjected to column chromatography using light petroleum:ethyl acetate (4:1) as eluant to isolate methyl N-(benzyl)-N-(hydroxypyridine-2-thione)-2-amino-5-hexenoate 223b as a yellow oil (0.62 g, 37%); νmax/cm⁻¹ (neat) 2951, 1765, 1743, 1641, 1528, 1449, 912 and 732; δH (400 MHz; CDCl₃) 2.04-2.16 (2 H, m, NCHCH₂), 3.61 (3 H, s, OCH₃), 4.50-4.52 (1 H, m, NCH), 4.89-5.01 (2 H, m, CH=CH₂), 5.60-5.70 (1 H, m, CH=CH₂), 4.55-4.84 (2 H, m, CH₂CH=CH₂), 6.60-6.62 (1 H, m, ArCH) and 7.18-7.68 (8 H, m, ArCH); δC (100 MHz; CDCl₃) 28.31 (NCHCH₂), 30.13 (CH₂CH=CH₂), 51.47 (ArCH₂), 52.31 (OCH₃), 60.40 (NCH), 112.21 (ArCH), 115.96 (CH=CH₂), 127.80, 128.18, 128.57, 133.57 (ArCH), 136.12 (ArC), 136.96, 137.18 (ArCH), 138.65 (CH=CH₂), 151.86 (C=S), 170.42 (NC=O) and 176.22 (C=O).


![Chemical structures](image)

A deoxygenated solution of PTOC carbamate of ethyl N-(benzyl)-2 amino-5-hexenoate 223c (40 mg, 0.11 mmol) in dry MeCN (2 cm³) under a nitrogen atmosphere was irradiated with a sun lamp overnight. The reaction mixture was concentrated and subjected to column chromatography using ethyl acetate:light petroleum (1:9) as eluant to isolate the major component as an oil, which was identified by ¹H NMR spectroscopy as the amino ethyl ester 221c (10 mg, 40%). A lower
running component was isolated and characterised by $^1$H NMR spectroscopy to be 2,2'-dipyridyl disulfide (2 mg). None of the expected product 228c was observed.


\[
\begin{align*}
223b & \quad \Rightarrow \quad 228b
\end{align*}
\]

a) A deoxygenated solution of PTOC carbamate of methyl N-(benzyl)-2 amino-5-hexenoate (0.51 g, 1.32 mmol) 223b in dry MeCN (200 cm$^3$) was irradiated with a sun lamp overnight under a nitrogen atmosphere. The reaction mixture was concentrated and subjected to column chromatography using ethyl acetate:light petroleum (1:9) as eluant to isolate the major component as an oil, which was identified by $^1$H NMR spectroscopy as the amino methyl ester 221b (0.14 g, 45%). A lower running component was isolated and characterised by $^1$H NMR spectroscopy to be 2,2'-dipyridyl disulfide (35 mg). None of the expected product 228b was observed.

b) The experiment was repeated as above in the presence of malonic acid (0.25 g, 0.25 mmol). As before, no indication of the product 228b was observed by $^1$H NMR spectroscopy and the methyl ester 221b was isolated in 38% yield along with the 2,2'-dipyridyl disulfide (27 mg).

31. 2-[2-(2-Bromophenyl)ethyl]-4,4-dimethyl-2-oxazoline 255,102a

\[
\begin{align*}
253 & \quad + \quad 254 & \quad \Rightarrow \quad 255
\end{align*}
\]
Butyllithium (10.5 cm$^3$ of a 2.5 M solution in hexane, 26.25 mmol) was added to a solution of oxazoline 254 (2.78 g, 24.57 mmol) in dry THF (100 cm$^3$) at -78 °C under a nitrogen atmosphere. After stirring at this temperature for 40 min, a solution of 2-bromobenzylbromide 253 (6.14 g, 24.57 mmol) in dry THF (20 cm$^3$) was added over a period of 15 min. The solution was stirred at this temperature for a further 15 min before allowing it to warm to room temperature and stirring was continued for a further 2 h. The reaction mixture was quenched with water (5 cm$^3$), added cautiously, before evaporating to dryness. The residue was taken up into diethyl ether (100 cm$^3$) and the solution was extracted with 10% aq. HCl (5 x 20 cm$^3$). The aqueous layers were combined, re-basified to pH 14 with 10% aq. NaOH and extracted with diethyl ether (5 x 20 cm$^3$). The organic layers were combined, washed with brine (2 x 30 cm$^3$), dried and evaporated to dryness to afford 2-[2-(2-bromophenyl)ethyl]-4,4-dimethyl-2-oxazoline 255 as a colorless oil (6.47 g, 93%); $\nu_{\text{max}}$ /cm$^{-1}$ (nujol) 2852, 1701, 1437, 785 and 751; $\delta_{\text{H}}$ (250 MHz, CDCl$_3$) 1.25 (6 H, s, 2 x CH$_3$), 2.57 (2 H, t, $J$ 7.8, ArCH$_2$), 3.07 (2 H, t, $J$ 7.8, ArCH$_2$CH$_2$), 3.90 (2 H, s, OCH$_2$), 7.02-7.09 (1 H, m, ArCH), 7.18-7.28 (2 H, m, ArCH) and 7.50-7.53 (1 H, m, ArCH); $\delta_{\text{C}}$ (62.9 MHz, CDCl$_3$) 28.22 (ArCH$_2$CH$_2$), 28.44 (2 x CH$_3$), 32.67 (ArCH$_2$), 79.00 (OCH$_2$), 127.43, 128.02 (ArCH), 130.39 (ArC), 130.48, 132.86 (ArCH), 139.89 (ArC) and 165.77 (C=N).

32. 3-(2-Bromophenyl)propionic acid 256\textsuperscript{102a}

\[
\begin{align*}
\text{255} \quad &\rightarrow \quad \text{256}
\end{align*}
\]

A solution of oxazoline 255 (6 g, 21.26 mmol) in 10% aq. HCl (80 cm$^3$) was refluxed for 1 h. The mixture was cooled and extracted with diethyl ether (5 x 20 cm$^3$). The combined organic extracts were washed with brine (30 cm$^3$) and extracted with 10% NaOH (5 x 20 cm$^3$). The aqueous layers were combined, washed with diethyl ether (30 cm$^3$) before adjusting the pH to 1 with 20% HCl and extracted with diethyl ether (5 x 20 cm$^3$). The organic extracts were combined, washed
with brine (30 cm$^3$), dried and evaporated to dryness to afford 3-(2-bromophenyl)propionic acid 256 as a white solid which was recrystallised from DCM (4.14 g, 85%), mp 92 °C (lit.$^{102b}$ 95-97 °C); $\nu_{\text{max}}$ /cm$^{-1}$ (nujol) 2852, 1701, 1437, 785 and 751; $\delta_H$ (250 MHz, CDCl$_3$) 2.72 (2 H, t, J 8.2, ArCH$_2$), 3.07 (2 H, t, J 8.2, ArCH$_2$CH$_2$), 7.05-7.12 (1 H, m, ArCH), 7.21-7.28 (2 H, m, ArCH) and 7.52-7.56 (1 H, m, ArCH); $\delta_C$ (62.9 MHz, CDCl$_3$) 31.12 (ArCH$_2$CH$_2$), 33.69 (ArCH$_2$), 124.39, 127.68, 128.25 (ArCH), 130.48 (ArC), 132.98 (ArCH), 139.38 (ArC) and 179.04 (C=O).

33. 3-(2-Bromophenyl)propanol 257.$^{102a}$

A solution of AlCl$_3$ (5.34 g, 40.06 mmol) in dry diethyl ether (100 cm$^3$) was added to a solution of LAH (1.52 g, 40.06 mmol) in dry diethyl ether (40 cm$^3$) under a nitrogen atmosphere. The mixture was stirred vigourously for 15 min before introducing a solution of 3-(2-bromophenyl)propanoic acid 256 (6.9 g, 30.12 mmol) in dry diethyl ether (100 cm$^3$) over a period of 20 min. The reaction mixture was stirred for 4 h, after which time water (50 cm$^3$) was added dropwise cautiously. The reaction mixture was washed with 20% aq. H$_2$SO$_4$ (2 x 50 cm$^3$), water (50 cm$^3$) and brine (2 x 50 cm$^3$), dried and evaporated to dryness to afford the 3-(2-bromophenyl)propanol 257 as an oil (5.95 g, 92%); $\nu_{\text{max}}$ /cm$^{-1}$ (nujol) 3350, 2820, 2720, 1435 and 1015; $\delta_H$ (400 MHz, CDCl$_3$) 1.60 (1 H, br s, OH), 1.86-1.92 (2 H, m, CH$_2$CH$_2$OH), 2.81-2.85 (2 H, m, ArCH$_2$CH$_2$), 3.70 (2 H, t, J 6.4, CH$_2$OH), 7.04-7.08 (1 H, m, ArCH), 7.21-7.26 (2 H, m, ArCH) and 7.51-7.54 (1 H, m, ArCH); $\delta_C$ (100 MHz, CDCl$_3$) 32.37 (CH$_2$), 32.72 (CH$_2$), 62.13 (CH$_2$OH), 124.43 (ArC), 127.47, 127.65, 130.41, 132.82 (ArCH) and 141.08 (ArC).
34. 3-(2-Bromophenyl)propanal 250.\textsuperscript{102a,b}

A solution of 3-(2-bromophenyl)propanol 257 (2.5 g, 11.62 mmol) in DCM (2.5 cm\textsuperscript{3}) was added to a stirred suspension of PCC (3.76 g, 17.43 mmol) in dry DCM (25 cm\textsuperscript{3}) under a nitrogen atmosphere and the mixture was stirred vigourously for 2 h. The mixture was filtered and the residue was washed with aliquots of diethyl ether (3 x 25 cm\textsuperscript{3}) and the combined organic extracts were passed through a pad of silica. The filtrate was evaporated to dryness and subjected to Kugelrohr distillation to afford 3-(2-bromophenyl)propanal 250 as a clear oil (1.75 g, 71%), b.p. 150 °C at 0.5 mbar (lit.\textsuperscript{102b} 95-100 °C at 0.1-0.2 Torr); \(\nu_{\text{max}}\) cm\textsuperscript{-1} (nujol) 2820, 2720, 1725, 1435 and 1015; \(\delta_H\) (400 MHz, CDCl\textsubscript{3}) 2.80 (2 H, t, J 17.6, ArCH\textsubscript{2}), 3.70 (2 H, t, J 17.6, ArCH\textsubscript{2}CH\textsubscript{2}), 7.04-7.10 (1 H, m, ArCH), 7.23-7.26 (2 H, m, ArCH), 7.52-7.55 (1 H, m, ArCH) and 9.83 (1 H, s, CHO); \(\delta_C\) (100 MHz, CDCl\textsubscript{3}) 28.68 (ArCH\textsubscript{2}CH\textsubscript{2}), 43.67 (ArCH\textsubscript{2}), 124.27 (ArC), 127.67, 128.13, 130.52, 132.95 (ArCH), 139.67 (ArC) and 201.06 (CHO).

35. Methyl (2S)-2-\{(E)-3-(2-bromophenyl)propylidene|amino\}-3-phenylpropanoate 259.

Method A:

\(L\)-Phenylalanine methyl ester hydrochloride (1.01 g, 4.69 mmol) and triethylamine (0.475 g, 4.69 mmol) were added to a solution of 3-(2-bromophenyl)propanal 250 (1.0 g, 4.69 mmol) in dry...
DCM (5 cm³) containing 4Å molecular sieves and the reaction mixture was stirred under a nitrogen atmosphere overnight. The reaction mixture was filtered, washed with water (2 x 10 cm³) and brine (10 cm³), dried and evaporated to dryness to give an oil. Analysis by ¹H and ¹³C NMR spectroscopy gave complex spectra, with more than the expected number of peaks. Attempts to purify the oil by Kugelhor distillation (150 °C, 0 mbar) provided a clear oil which was characterised by ¹H NMR spectroscopy to be the L-phenylalanine methyl ester 258.

Method B:
A catalytic amount of PTSA was added to a solution of 3-(2-bromophenyl)propanal 250 (1.64 g, 7.7 mmol) and L-phenylalanine methyl ester 258 in dry toluene (20 cm³) containing 4Å molecular sieves. The reaction mixture was stirred overnight under a nitrogen atmosphere. The reaction mixture was washed with sat. NaHCO₃ (2 x 10 cm³) and brine (15 cm³), dried and evaporated to dryness to provide a clear oil (1.32 g). ¹H and ¹³C NMR again gave complex spectra but showed the absence of the aldehyde 250. Further purification was not attempted and the product imine 259 was used crude.

36. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260.

A deoxygenated solution of Bu₃SnH (2.0 g, 6.87 mmol) in dry toluene (50 cm³) and a deoxygenated solution of AIBN (140 mg) in dry toluene (10 cm³) were added to a solution of compound 255 (1.0 g, 2.67 mmol) at 90 °C over a period of 7 h. The reaction mixture was evaporated to dryness and the residue taken up into MeOH (100 cm³) to which NaBH₄ (0.6 cm³) was added. After stirring for 2 h, the mixture was evaporated to dryness and the residue
partitioned between water (50 cm$^3$) and diethyl ether (50 cm$^3$). The organic layer was separated and washed with brine (2 x 30 cm$^3$), dried and evaporated to dryness to afford a yellow oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to provide as a 1:1.2 mixture of diastereomers methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 (92 mg, 12%); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2924, 1734, 1456, 1436, 1200, 1169, 744, 700 and 668; $\delta_H$ (250 MHz, CDCl$_3$) major diastereomer, 1.58-1.78 (1 H, m, ArCH$_2$CH$_AH_B$), 1.87 (1 H, br s, NH), 2.16-2.37 (1 H, m, ArCH$_2$CH$_AH_B$), 2.67-2.80 (1 H, m, ArCH$_A$H$_B$), 2.87-3.03 (3 H, m, ArCH$_A$H$_B$ and CH$_2$CHCO$_2$Me), 3.67 (3 H, s, OCH$_3$), 4.07-4.17 (1 H, m, ArCH) and 7.13-7.32 (9 H, m, ArCH); $\delta_C$ (100 MHz, CDCl$_3$) 30.33 (ArCH$_2$CH$_2$), 33.04 (ArCH$_2$CH), 40.27 (ArCH$_2$CH$_2$), 51.73 (OCH$_3$), 61.11 (NHCHCO$_2$CH$_3$), 61.75 (ArCHNH), 123.83, 124.65, 126.36, 126.65, 127.52, 128.38, 129.24 (ArCH), 137.51, 143.64, 144.68 (ArC) and 175.60 (C=O); minor diastereomer, 1.58-1.78 (1 H, m, ArCH$_2$CH$_AH_B$), 1.87 (1 H, br s, NH), 2.16-2.37 (1 H, m, ArCH$_2$CH$_AH_B$), 2.67-2.80 (1 H, m, ArCH$_A$H$_B$), 2.87-3.03 (3 H, m, ArCH$_A$H$_B$ and CH$_2$CHCO$_2$Me), 3.64 (3 H, s, OCH$_3$), 4.07-4.17 (1 H, m, ArCH) and 7.13-7.32 (9 H, m, ArCH); $\delta_C$ (100 MHz, CDCl$_3$); m/z (EI) 295.1575 [M$^+$ (15%), C$_{19}$H$_{21}$N$_2$O$_2$ requires 295.1572], 236 (20), 117 (100), 91 (30).

37. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 from Dean and Stark method.

A solution of indanone 161 (1.0 g, 7.56 mmol), L-phenylalanine methyl ester 258 (1.36 g, 7.58 mmol) and a catalytic amount of PTSA in dry toluene (25 cm$^3$) were refluxed under Dean and Stark conditions for 24 h. The reaction mixture was evaporated to dryness and the residue taken up into methanol (30 cm$^3$) to which sodium borohydride (1.14 g, 0.03 mol) was added. The
reaction mixture was stirred for 3 h before evaporating to dryness. The residue was taken up into
diethyl ether (50 cm$^3$) washed with water (2 x 20 cm$^3$), dried and evaporated to dryness to afford
a brown oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate
(4:1) as eluant to provide, as a mixture of diastereomers, methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 (0.55 g, 25%). The IR and NMR were identical with previously
prepared material.

38. 3-(Cyanopropyl)triphenylphosphonium bromide 263$^{,89}$

$$\text{NC} \quad \text{Br} \quad \text{PPh}_3 \quad \text{Br}$$

A solution of 3-bromobutanonitrile 262 (25.0 g, 0.17 mol) and triphenyphosphine (44.4 g, 0.17
mol) in dry toluene (500 cm$^3$) was refluxed under a nitrogen atmosphere for 48 h. On cooling,
colourless crystals precipitated out which were filtered off, washed with cold toluene followed by
a light petroleum wash and dried to yield 3-(cyanopropyl)triphenylphosphonium bromide 263
(46.29 g, 78%), mp 214-216 °C (lit. $^{,89}$ 215-217 °C); $\delta_H$ (250 MHz; CDCl$$_3$$) 1.96-2.11 (2 H, m,
CH$_2$CH$_2$CH$_2$), 3.11 (2 H, t, $J$ 6.9, CH$_2$CN), 4.08-4.18 (2 H, m, CH$_2$PPh$_3$) and 7.68-7.91 (15 H,
m, ArH); $\delta_C$ (62.9 MHz; CDCl$$_3$$) 17.82 (CH$_2$CH$_2$CH$_2$), 19.68 (CH$_2$CN), 21.74 (CH$_2$PPh$_3$),
117.45 (CN), 119.10 (ArC) and 135.25, 133.60, 130.57 (ArCH).

39. (Z)-4-Phenylbut-3-enanonitrile 264$^{,89}$

$$\text{NC} \quad \text{PPh}_3 \quad \text{Br} \quad \text{Ph} \quad \text{CN}$$

To a stirred suspension of sodium hydride (1.75 g, 0.073 mol) in dry tetrahydrofuran (200 cm$^3$),
at 0 °C under a nitrogen atmosphere, 3-cyanopropylphosphonium bromide 264 (27.0 g,
0.066 mol) was added over a period of 10 min. The reaction mixture was stirred at this
temperature for 2 h before benzaldehyde (8.37 g, 0.079 mol) was introduced to the reaction
mixture over a period of 1 h. The mixture was allowed to warm to room temperature and stirring continued overnight. The reaction mixture was evaporated to dryness and ice/water (150 cm$^3$) added to the residue. The pH of the mixture was adjusted to pH 1-2 with 20% aq. HCl before extracting with diethyl ether (3 x 50 cm$^3$). The organic extracts were combined, washed with water (2 x 50 cm$^3$) and brine (2 x 50 cm$^3$), dried and evaporated to dryness to afford a dark brown oil which was subjected to Kugelrohr distillation to afford (Z)-4-phenylbut-3-enonitrile 264 as a clear oil (6.91 g, 67%); b.p. 110 °C at 0.5 mbar; $\nu_{\text{max}}$ /cm$^{-1}$ (neat) 3019, 2246, 1657, 1598, 1493, 1446, 767 and 700; $\delta_H$ (250 MHz; CDCl$_3$) 2.43 (2 H, t, $J$ 7.2, CH$_2$CN), 5.65 (1 H, dt, $J$ 7.1 and 11.45, PhCH=CH), 6.61 (1 H, br d, PhCH=CH) and 7.22-7.39 (5 H, m, ArH); $\delta_C$ (62.9 MHz; CDCl$_3$) 17.5 (CH$_2$CN), 24.35 (CH$_2$C=C), 119.13 (CN), 126.5 (ArCH), 127.2 (PhCH=CH), 128.4, 128.5 (ArCH), 132.1 (PhCH=CH) and 136.46 (ArC); m/z 157.0894 [M$^+$ (24%), C$_{11}$H$_{11}$N requires 157.0891], 126 (16), 117 (100), 91 (22), 51 (14) and 39 (15).

40. (Z)-5-Amino-1-phenylpent-1-ene 265,89

\[ \text{Ph} \quad \text{CN} \quad \rightarrow \quad \text{Ph} \quad \text{NH}_2 \]

264 265

A solution of (Z)-4-phenylbut-3-enonitrile 264 (2.0 g, 0.013 mol) in dry diethyl ether (30 cm$^3$) was added dropwise to a stirred suspension of lithium aluminium hydride (1.20 g, 0.032 mol) in dry diethyl ether (50 cm$^3$) at 0 °C under a nitrogen atmosphere over a period of 30 min. The reaction mixture was stirred for 2 h at this temperature after which time 20% aq. NaOH was added cautiously until effervescence ceased. The white precipitate which had developed was filtered off, washed with diethyl ether (2 x 50 cm$^3$) and the organic extracts combined before extracting with 20% aq. HCl (3 x 20 cm$^3$). The aqueous layers were combined, washed with diethyl ether (3 x 20 cm$^3$), re-basified to pH 14 with 20% aq. NaOH and extracted with diethyl ether (3 x 30 cm$^3$). The combined organic extracts were washed with water (50 cm$^3$) and brine.
(50 cm³), dried and evaporated to dryness to afford (Z)-5-amino-1-phenylpent-1-ene 265 as a clear oil (1.86 g, 91%); v_max /cm⁻¹ (neat) 3367, 3301, 2925, 756 and 700; δ_H (250 MHz; CDCl₃) 1.43 (2 H, br s, NH₂), 1.60 (2 H, quintet, J 7.4, CH₂CH₂CH₂), 2.37 (2 H, dq, J 1.8 and 7.4, CH=CHCH₂), 2.72 (2 H, t, J 7.4, CH₂NH₂), 5.66 (1 H, dt, J 11.6 and 7.3, PhCH=CHCH₂), 6.44 (1 H, dt, J 1.8 and 11.7, PhCH=CH) and 7.18-7.37 (5 H, m, ArCH); δ_C (62.9 MHz; CDCl₃) 25.88 (CH₂CH₂CH₂), 33.87 (CH=CHCH₂), 41.75 (CH₂NH₂), 126.51 (PhCH=CH), 128.12, 128.69, 129.2 (ArCH), 132.28 (PhCH=CH) and 137.57 (ArC).

41. N1-[(E)-3-(2-Bromophenyl)propylidene]-N-[(Z)-5-phenylpent-4-enyl]amine 266.

\[
\begin{align*}
&\text{Br} \quad + \quad \text{H}_2\text{N} \quad \text{Ph} \\
\text{250} & \quad \text{265} \\
\rightarrow & \quad \text{Ph} \\
\text{266}
\end{align*}
\]

A solution of 3-(2-bromophenyl)propanal 250 (0.6 g, 2.82 mmol) and 5-amino-1-phenylpent-1-ene 265 (0.46 g, 2.85 mmol) in dry DCM (5 cm³) with 4Å molecular sieves was stirred under a nitrogen atmosphere for 3 h. The reaction mixture was filtered and evaporated to dryness to give an oil which on analysis by ¹H NMR spectroscopy was shown to be very complex. The ¹³C NMR spectrum showed more than the expected number of peaks. The IR spectrum showed the absence of an NH stretch and a new peak at 1668 representative of an imine stretch; v_max /cm⁻¹ (nujol) 2927, 1668, 1470, 1446, 1025, 751 and 699. The crude imine was reacted directly and not further purified.

42. N1-(2,3-Dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267.

\[
\begin{align*}
&\text{Br} \\
\text{266} \\
\rightarrow & \quad \text{Ph} \\
\text{267}
\end{align*}
\]
A deoxygenated solution of Bu$_3$SnH (1.1 g, 3.78 mmol) and AIBN (0.1 g, 0.63 mmol) in dry toluene (20 cm$^3$) was added to a deoxygenated solution of N-[(E)-3-(2-bromophenyl)propylidene]-N-[(Z)-5-phenylpent-4-enyl]amine 266 (0.9 g, 2.53 mmol) in dry toluene (80 cm$^3$) at 85 °C under a nitrogen atmosphere over a period of 13 h. The reaction mixture was extracted with 40% aq. HCl, the aqueous layers were combined and washed with diethyl ether (30 cm$^3$), re-basified to pH 14 using 10% aq. NaOH and extracted with diethyl ether (3 x 30 cm$^3$). The organic layers were combined, washed with brine (2 x 30 cm$^3$), dried and evaporated to dryness to afford an oil (0.36 g). Analysis of this oil by $^1$H NMR spectroscopy gave a complex spectrum but showed resonances between 4.18 and 4.26 ppm which are consistent with a benzylic methine hydrogen. Column chromatography using light petroleum: ethyl acetate (9:1) afforded N1-(2,3-dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267 as an oil (56.00 mg, 8%). See experiment number 57 for characterisation.

43. 2-(2-Bromoethyl)benzaldehyde 271$^{106}$

![Chemical Structure](image)

Bromine (60.00 g, 0.37 mmol) was added to a solution of isochroman 269 (50.00 g, 0.37 mmol) in carbon tetrachloride (200 cm$^3$) at 0 °C over a period of 5 min. After the vigorous reaction subsided the cooling bath was removed and the mixture was refluxed until the mixture became pale yellow and the evolution of HBr gas ceased (ca. 1 h). The solvent was removed under reduced pressure, 48% aq. HBr (75 cm$^3$) was added and the mixture refluxed again for 30 min. After cooling, the mixture was extracted with diethyl ether (3 x 100 cm$^3$) and the combined organic fractions washed with saturated NaHCO$_3$, dried and evaporated to dryness to give a dark orange brown oil. Kugelrohr distillation under reduced pressure afforded 2-(2-bromoethyl)benzaldehyde 271 as a pale yellow oil (39.95 g, 50%), b.p. 150 °C at 0.5 mbar (lit.$^{106}$ 82-83 °C at 0.1 Torr); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 1697, 1600, 1575 and 755; $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 3.58-3.62 (4 H, m,
CH₂CH₂), 7.32-7.36 (1 H, m, ArCH), 7.45-7.60 (2 H, m, ArCH), 7.81-7.85 (1 H, m, ArCH) and 10.15 (1 H, s, HC=O); δC (62.9 MHz; CDCl₃) 32.67 (ArCH₂), 36.23 (CH₂Br), 127.61, 132.05, 133.66 (ArCH), 133.86 (ArC), 134.43 (ArCH), 140.48 (ArC) and 192.86 (HC=O); m/z (El) 211.9833 [M⁺ (8), C₉H₈OBr requires 211.9837], 199 (9), 148 (7), 133 (100), 117 (15), 105 (15), 91 (13) and 77 (21).

44. Attempted synthesis of methyl (2S)-2-((E)-1-[2-(2-bromoethyl)phenyl]methylidene)-amino)-3-methylbutanoate 273.

2-(2-Bromoethyl)benzaldehyde 271 (1.51 g, 7.09 mmol), PTSA (catalytic) and 4Å molecular sieves were added to a solution of L-valine methyl ester 272 (0.93 g, 7.09 mmol) in dry toluene (35 cm³). The mixture was stirred for 24 h under a nitrogen atmosphere. Analysis of this reaction mixture by TLC showed a mixture of components. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (50 cm³). The organic layer was washed with water (2 x 30 cm³) and brine (30 cm³) dried and evaporated to dryness to afford a yellow oil (2.05 g). A ¹H NMR spectroscopic study (250 MHz; CDCl₃) of this oil showed a complex spectrum with no resonance in the region of δ 8.00–8.50, indicating the absence of the imine (CH) proton.

45. Methyl (2S)-2-(3,4-dihydroisoquinolinium-2-yl)-3-methylbutanoate 274.
2-(2-Bromoethyl)benzaldehyde 271 (1.51 g, 7.09 mmol) was added to a solution of L-valine methyl ester 272 (0.93 g, 7.09 mmol) in 100% ethanol (20 cm³) and the reaction mixture stirred for 48 h under a nitrogen atmosphere. The solution was evaporated to dryness and the residue extracted into diethyl ether (50 cm³). The organic solution was washed with water (30 cm³) and brine (30 cm³), dried and evaporated to dryness to afford methyl (2S)-2-(3,4-dihydroisoquinolinium-2-yl)-3-methylbutanoate 274 as a dark orange oil (1.41 g, 92%); [α]_D = -5.1 (c = 0.632, CHCl₃); ν_{max}/cm⁻¹ (neat) 2967, 2189, 1744, 1642, 1604, 1573 and 730; δ_H (250 MHz; CDCl₃) 1.19 (3 H, d, J 5.8, CH₃), 1.22 (3 H, d, J 5.7, CH₃), 2.61-2.75 (1 H, m, CH₃CHCH₃), 3.37-3.43 (2 H, m, ArCH₂), 3.86 (3 H, s, OCH₃), 4.01-4.15 (1 H, m, CH₃H₂BN), 4.39-4.47 (1 H, m, CH₃H₂BN), 5.59 (1 H, d, J 9.2, NCH₂CO₂CH₃), 7.48-7.54 (2 H, m, ArCH), 7.77-7.84 (1 H, m, ArCH) and 8.27-8.30 (1 H, m, ArCH); δ_C (62.9 MHz; CDCl₃) 18.94 (CH₃), 19.53 (CH₃), 25.39 (ArCH₂), 29.11 (CH₃CHCH₃), 47.33 (CH₂N), 53.29 (NCH₂CO₂CH₃), 75.76 (OCH₃), 124.36 (ArC), 128.24, 128.61, 135.67 (ArCH), 136.80 (ArC), 139.06 (ArCH) 167.49 (C=O) and 170.04 (HC=NC). Further characterisation was achieved by reduction to the tetrahydroisoquinoline 275.

46. Methyl (2S)-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)butanoate 275.

Sodium borohydride (0.35 g, 9.25 mmol) was added to a solution of methyl 2-(3,4-dihydroisoquinolinium-2-yl)-3-methylbutanoate 274 (1.0 g, 3.07 mmol) in dry methanol (50 cm³) in portions and the mixture stirred overnight under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (50 cm³). The organic layer was then washed with water (3 x 50 cm³) and brine (2 x 50 cm³), dried and evaporated to dryness to afford an oil. This oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to isolate methyl (2S)-3-(1,2,3,4-tetrahydroisoquinolin-2-yl)butanoate 275
as a clear oil (0.475 g, 63%); \([\alpha]_D = -11.0 \text{ (c = 1.055, CHCl}_3\); \(\nu_{\text{max/cm}^{-1}}\) (neat) 2960, 1731, 1497, 1464, 1192, 1151 and 744; \(\delta_H (250 \text{ MHz; CDCl}_3) 0.92 \text{ (3 H, d, } J 6.6, \text{ CH}_3)\), 1.00 (3 H, d, \(J 6.6, \text{ CH}_3\)), 2.11-2.26 (1 H, m, \text{CH}_3\text{CHCH}_3), 2.60-2.70 (1 H, m, \text{CH}_2\text{CH}_2\text{H}_2\text{N}), 2.84-2.88 (2 H, m, \text{ArCH}_2\text{CH}_2\text{)}, 2.96 (1 H, d, \(J 10.5, \text{NCH}_2\text{CO}_2\text{CH}_3\)), 2.94-3.03 (1 H, m, \text{CH}_2\text{CH}_2\text{H}_2\text{N}), 3.70 (3 H, s, OCH)_3\), 3.75 (2 H, br s, \text{ArCH}_2\text{N}) and 6.99-7.13 (4 H, m, \text{ArCH}); \(\delta_C (62.9 \text{ MHz; CDCl}_3\) 19.30 (CH_3), 19.77 (CH_3), 26.95 (CH_3\text{CHCH}_3), 29.95 (CH_2\text{CH}_2\text{N}), 46.47 (\text{ArCH}_2\text{CH}_2\text{)}, 50.57 (OCH)_3, 52.57 (\text{ArCH}_2\text{N}), 74.09 (\text{NCH}_2\text{CO}_2\text{CH}_3), 125.38, 125.84, 126.36, 128.67 (\text{ArCH}), 134.61, 135.26 (\text{ArC}) and 172.05 (C=O); \(m/z\) (EI) 248.1652 [MH\(^+\) (90%), C_{15}H_{22}NO_2 requires 248.1650], 203 (90), 187 (100), 171 (20), 157 (15), 131 (50), 116 (30) and 90 (10).

47. 2-[2-(Phenylselenyl)ethyl]benzaldehyde 278.

\[
\begin{align*}
\text{Br} & \quad \rightarrow \\
271 & \quad 278
\end{align*}
\]

Sodium borohydride (0.85 g, 22.47 mmol) was added to a stirred solution of diphenyl diselenide (2.33 g, 7.47 mmol) in dry ethanol (200 cm\(^3\)) in portions. The reaction mixture was stirred for 2 h under a nitrogen atmosphere before the addition of a solution of 2-(2-bromoethyl)benzaldehyde 271 (3.20 g, 15.02 mmol) in dry ethanol (10 cm\(^3\)) and the mixture was left to stir for 48 h. After this time aq. 20% HCl (20 cm\(^3\)) was added and the mixture was evaporated to dryness. The residue was extracted into diethyl ether (100 cm\(^3\)) and washed with water (2 x 50 cm\(^3\)) and brine (2 x 50 cm\(^3\)), dried and evaporated to dryness to afford an orange oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to afford 2-[2-(phenylselenyl)ethyl]benzaldehyde 278 as a pale yellow oil (1.77 g, 41%); \(\nu_{\text{max/cm}^{-1}}\) (neat) 1697, 1599, 1575, 737 and 691; \(\delta_H (250 \text{ MHz; CDCl}_3) 3.12-3.19 \text{ (2 H, m, CH}_2\text{SePh)}, 3.37-3.44 \text{ (2 H, m, ArCH}_2\text{)}, 7.24-7.28 \text{ (4 H, m, ArCH), 7.38-7.44 \text{ (1 H, m, ArCH)}, 7.48-7.55 \text{ (3 H, m, ArCH), 7.79-7.82 \text{ (1 H, m, ArCH) and 10.13 \text{ (1 H, s, HC=O)}; \delta_C (62.9 \text{ MHz; CDCl}_3) 28.42 \text{ (CH}_2\text{SePh), 33.57 \text{ (CH}_2\text{Ar), 126.93, 127.15, 129.07 \text{ (ArCH), 129.99 \text{ (ArC), 131.41, 132.68, 133.02, 133.79}}}}\]

131
(ArCH), 143.01 (ArC) and 192.40 (HC=O); m/z (EI) 290.0211 [M+ (70%), C_{15}H_{14}OSe requires 290.0209], 157 (20), 133 (100), 115 (35), 105 (70), 91 (70) and 77 (70).


![Chemical structure diagram](image)

To a solution of L-valine methyl ester 272 (0.44 g, 3.32 mmol) in dry toluene (10 cm$^3$) was added a solution of 2-[2-(phenylselenyl)ethyl]benzaldehyde 278 (0.96 g, 3.33 mmol) in dry toluene (10 cm$^3$), PTSA (catalytic) and 4Å molecular sieves. The reaction mixture was stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was washed with water (2 x 20 cm$^3$) and brine (30 cm$^3$), dried and concentrated to afford methyl-(2S)-3-methyl-2-[(E)-1-{2-[2-(phenylseleno)ethyl]phenyl}methylidene]amino]butanoate 279 as a yellow oil (1.18 g, 89%); [α]$_D$ = -82.8 (c = 0.99, CHCl$_3$); $\nu_{max}$/cm$^{-1}$ (neat) 1741, 1638, 1600, 1578, 734 and 691; $\delta_H$ (250 MHz; CDCl$_3$) 0.92 (3 H, d, J 6.8, CH$_3$), 0.95 (3 H, d, J 6.7, CH$_3$), 2.30-2.44 (1 H, m, CH$_3$CHCH$_3$), 3.07-3.15 (2 H, m, CH$_2$SePh), 3.21-3.29 (2 H, m, ArCH$_2$), 3.57 (1 H, d, J 6.8, NCHCD$_2$CH$_3$), 3.74 (3 H, s, OCH$_3$), 7.16-7.38 (6 H, m, ArCH), 7.50-7.55 (2 H, m, ArCH), 7.83-7.87 (1 H, m, ArCH) and 8.32 (1 H, s, HC=N); $\delta_C$ (62.9 MHz; CDCl$_3$) 18.55 (CH$_3$), 19.47 (CH$_3$), 28.66 (CH$_2$SePh), 31.62 (CH$_3$CHCH$_3$), 33.97 (Ar-CH$_2$), 51.86 (OCH$_3$), 80.55 (NCHCO$_2$CH$_3$), 126.91, 127.02, 129.12, 129.41, 130.40, 130.71, 132.95, 133.33, (ArCH), 133.25, 140.95 (ArC), 161.72 (CH=N) and 174.05 (C=O); m/z (EI) 402.1092 [M$^+$ (25%), C$_{21}$H$_{25}$NO$_2$Se requires 402.1092], 343 (10), 272 (15), 245 (100), 185 (20), 129 (20), 114 (55), 91 (30) and 77 (10).
49. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-methylbutanoate 285.

\[
\begin{align*}
\text{SePh} \quad \text{CO}_2\text{Me} \\
279 & \quad \rightarrow \\
\text{HN} \quad \text{CO}_2\text{Me} \\
285
\end{align*}
\]

A deoxygenated solution of Bu$_3$SnH (1.25 g, 4.29 mmol) in dry toluene (45 cm$^3$) and a deoxygenated solution of AIBN (0.3 g) in toluene (30 cm$^3$) were added to a deoxygenated solution of methyl (2S)-3-methyl-2-[(E)-1-2-[2-(phenylseleno)ethyl]phenyl]-methylidene)amino]butanoate 279 (1.15 g, 2.86 mmol) in dry toluene (250 cm$^3$) at 90 °C under a nitrogen atmosphere over a period of 10 h. The reaction mixture was heated for a further 2 h, cooled and evaporated to dryness. The residue was dissolved in dry methanol (100 cm$^3$) to which sodium borohydride (0.30 g, 7.93 mmol) was added in portions and the mixture was stirred for 45 min. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (100 cm$^3$). The organic layer was washed with water (3 x 50 cm$^3$), dried and evaporated to dryness to afford a yellow oil. The oil was subjected to column chromatography with light petroleum to initially remove the tin components before moving to a slightly polar system [light petroleum:ethyl acetate (9:1)] to isolate methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-methylbutanoate 285 as a mixture of diastereomers (1:1.5) as a yellow oil (305 mg, 43%);

$\nu_{\text{max}}$/cm$^{-1}$ (neat) 3440, 2959, 1732, 1463, 1197, 1152 and 747; $\delta_H$ (250 MHz; CDCl$_3$) major diastereomer, 0.90-0.98 (6 H, m, 2 x CH$_3$), 1.61-1.98 (3 H, m, CH$_3$CHCH$_3$, NH and ArCH$_2$CH$_2$ArH$_B$), 2.13-2.38 (1 H, m, ArCH$_2$CH$_2$ArH$_B$), 2.65-2.82 (1 H, m, ArCH$_2$ArH$_B$), 2.89-3.08 (1 H, m, ArCH$_2$ArH$_B$), 3.13 (1 H, d, $J$ 6.35, NHCHCO$_2$CH$_3$), 3.69 (3 H, s, OCH$_3$), 4.10 (1 H, t, $J$ 6.8, ArCHCH$_2$), 7.14-7.21 (3 H, m, ArH) and 7.31-7.39 (1 H, m, ArH); minor diastereomer, 0.90-0.98 (6 H, m, 2 x CH$_3$), 1.61-1.98 (3 H, m, CH$_3$CHCH$_3$, NH and ArCH$_2$CH$_2$ArH$_B$), 2.13-2.38 (1 H, m, ArCH$_2$CH$_2$ArH$_B$), 2.65-2.82 (1 H, m, ArCH$_2$ArH$_B$), 2.89-3.08 (1 H, m, ArCH$_2$ArH$_B$), 3.14 (1 H, d, $J$ 5.9, NHCHCO$_2$CH$_3$), 3.73 (3 H, s, OCH$_3$), 4.07 (1 H, t, $J$ 5.9, ArCHCH$_2$), 7.14-7.21 (3 H, m,
ArH) and 7.31-7.39 (1 H, m, ArH); δC (62.9 MHz; CDCl3) major diastereomer, 19.22 (CH3), 19.41 (CH3), 30.37 (ArCH2CH2), 32.24 (CH3CHCH3), 34.88 (ArCH2), 51.44 (OCH3), 63.46 (NHCHCO2CH3), 66.08 (ArCH2CH2), 124.48, 124.55, 126.01, 127.27 (ArCH), 143.32, 145.48 (ArC) and 176.67 (C=O); minor diastereomer, 18.50 (CH3), 18.66 (CH3), 30.42 (ArCH2CH2), 31.81 (CH3CHCH3), 32.96 (ArCH2), 51.44 (OCH3), 61.95 (NHCHCO2CH3), 65.45 (ArCH2CH2), 123.72, 124.68, 126.32, 127.51 (ArCH), 143.84, 144.93 (ArC) and 176.22 (C=O); m/z (EI) 248.1649 [MH+ (40%), CI5H21N02 requires 248.1650], 204 (15), 188 (50), 132 (35), 117 (100), 91 (20) and 72 (70).


![Chemical structure](image)

To a solution of L-phenylalanine methyl ester 258 (0.50 g, 2.79 mmol) and 2-[2-(phenylseleno)ethyl]benzaldehyde 278 (0.80 g, 2.77 mmol) in dry toluene (15 cm³) was added PTSA (catalytic), 4Å molecular sieves and the reaction mixture stirred overnight under a nitrogen atmosphere. The mixture was filtered and the filtrate was washed with water (2 x 20 cm³) and brine (30 cm³), dried and evaporated to dryness to afford methyl (2S)-2-[(E)-1-{2-[2-(phenylseleno)ethyl]phenyl}methylidene]amino]-3-phenylpropanoate 280 as a yellow oil (0.95 g, 76%); [α]D = -112.5 (c = 1.01, CHCl3); νmax/cm⁻¹ (neat) 1741, 1637, 1600, 1578, 1436, 1201, 1167, 739 and 700; δH (250 MHz; CDCl3) 2.74-3.11 (4 H, m, ArCH2CH2), 3.13 (1 H, dd, J13.6 and 9.5, PhCHAHB), 3.37 (1 H, dd J13.6 and 4.4, PhCHAHB), 3.76 (3 H, s, OCH3), 4.07 (1 H, dd, J9.5 and 4.4, NCHCO2CH3), 7.08-7.34 (11 H, m, ArCH), 7.42-7.48 (2 H, m, ArCH), 7.81-7.85 (1 H, m, ArCH) and 7.97 (1 H, s, HC=N); δC (62.9 MHz; CDCl3) 28.36 (CH2SePh), 33.63 (ArCH2), 39.58 (PhCH2), 52.25 (OCH3), 75.42 (NCHCO2CH3), 126.61, 126.86, 126.95, 128.36 (ArCH), 134.
128.57 (ArC), 128.73, 129.07 (ArCH), 129.25 (ArC), 129.69, 130.18, 130.76, 132.77 (ArCH), 137.35, 140.94 (ArC), 161.97 (CH=N) and 172.03 (C=O); m/z (El) 452.1079 (M+ C25H25NO2Se requires 452.1083), 451 (60%), 359 (20), 293 (100), 272(75), 115 (80) and 91 (70).

51. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260.

A deoxygenated solution of Bu3SnH (1.00 g, 3.44 mmol) and AIBN (0.10 g) in dry toluene (50 cm3) was added to a solution of methyl (2S)-2-[((E)-1-[2-[2-(phenylseleno)ethyl]-phenyl)methylidene]amino]-3-phenylpropanoate 280 (0.92 g, 2.04 mmol) in dry toluene (300 cm3) at 85 °C under a nitrogen atmosphere over a period of 10 h. The reaction mixture was heated for a further 2 h, cooled and evaporated to dryness. The residue was dissolved in dry methanol (200 cm3) to which sodium borohydride (0.5 g) was added in portions and the mixture was stirred for 1 h. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (150 cm3). The organic layer was washed with water (2 x 50 cm3) and brine (50 cm3), dried and evaporated to dryness to afford a yellow oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate (9.5:0.5) as eluant to isolate methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 as a mixture of diastereomers as a clear oil (0.25 g, 42%) in a 1:1.2 ratio. The IR and NMR spectra were identical to a previously prepared sample.

\[
\text{SePh} \quad \text{H}_2\text{N} \quad \text{CO}_2\text{Me} \quad \text{SePh} \\
\text{278} \quad \rightarrow \quad \text{281} \quad \rightarrow \quad \text{282}
\]

To a solution of L-leucine methyl ester 281 (0.50 g, 3.45 mmol) and 2-[2-(phenylseleno)ethyl]benzaldehyde 278 (1.00 g, 3.46 mmol) in dry toluene (30 cm\(^3\)) was added PTSA (catalytic), 4Å molecular sieves and the reaction mixture stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was washed with water (50 cm\(^3\)) and brine (50 cm\(^3\)), dried and evaporated to dryness to give methyl (2S)-4-methyl-2-[['(E)-1-{2-[2-(phenylseleno)-ethyl]phenyl}methylidene]amino]-pentanoate 282 as a yellow oil (1.27 g, 88%); \([\alpha]_D = -17.4 \text{ (c = 1.09, CHCl}_3\text{)}; \nu_{\text{max/cm}^{-1}} \) (neat) 2954, 1741, 1639, 1600, 1579, 1197, 736 and 692; \(\delta_H \) (250 MHz; CDCl\(_3\)) 0.86 (3 H, d, \(J 6.5, \text{CH}_3\)), 0.93 (3 H, d, \(J 6.6, \text{CH}_3\)). 1.46-1.63 (1 H, m, \text{CH}_3\text{CHCH}_3\)), 1.74-1.94 (2 H, m, NCHCH\(_2\)), 3.06-3.16 (2 H, m, CH\(_2\)SePh), 3.20-3.28 (2 H, m, ArCH\(_2\)), 3.72 (3 H, s, OCH\(_3\)), 3.98 (1 H, dd, \(J 5.6 \text{ and 8.8, NCHCO}_2\text{CH}_3\)), 7.16-7.37 (6 H, m, ArCH), 7.49-7.54 (2 H, m, ArCH), 7.85 (1 H, dd, \(J 1.6 \text{ and 7.5, ArCH}\)) and 8.40 (1 H, s, HC=N); \(\delta_C \) (62.9 MHz; CDCl\(_3\)), 21.30 (CH\(_3\)), 23.13 (CH\(_3\)), 24.39 (CH\(_3\)CH\(_3\)), 28.61 (CH\(_2\)Se), 33.87 (Ar-CH\(_2\)), 41.92 (NCHCH\(_2\)), 52.04 (OCH\(_3\)), 71.91 (NCHCO\(_2\)CH\(_3\)), 126.90, 126.97, 129.04, 130.30, 130.71, 132.84 (ArCH), 133.30, 140.87 (ArC), 161.45 (C=N) and 172.73 (C=O); \(m/\epsilon \) (El) 417.1214 [M\(^+\) (50%), \(\text{C}_{22}\text{H}_{27}\text{NO}_2\text{Se}\) requires 417.1207], 259 (100), 114 (45) and 90 (23).
53. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-methylpentanoate 286.

To a deoxygenated solution of methyl (2S)-4-methyl-2-[((E)-1-{2-[2-(phenylseleno)ethyl]-phenyl}methylidene)amino]pentanoate 282 (1.23 g, 2.95 mmol) in dry toluene (250 cm³) was added a deoxygenated solution of Bu₃SnH (1.37 g, 4.71 mmol) in dry toluene (45 cm³), and a solution of AIBN (0.30 g) in dry toluene (30 cm³), over a period of 10 h. The reaction mixture was heated for a further 5 h, cooled and evaporated to dryness. The residue was dissolved in dry methanol (100 cm³) to which sodium borohydride (0.45 g, 11.82 mmol) was added in portions and the reaction mixture was stirred for 3 h. 20% aq. HCl (35 cm³) was added and the reaction mixture was evaporated to dryness. The residue was partitioned between diethyl ether (100 cm³) and water (75 cm³). The organic layer was removed and the aqueous layer was washed with diethyl ether (2 x 50 cm³), separated, neutralised with sodium hydrogen carbonate and extracted with diethyl ether (3 x 30 cm³). The combined organic fractions were washed with water (50 cm³) and brine (50 cm³), dried and evaporated to dryness to afford methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-methylpentanoate 286 as a mixture of diastereomers (1:1.4) as a yellow oil (0.45 g, 58%); v_max /cm⁻¹ (neat) 3445, 2960, 1731, 1542, 1220 and 730; δ_H (250 MHz; CDCl₃) major diastereomer, 0.85-0.93 (6 H, m, 2 x CH₃), 1.42-1.50 (2 H, m, CHCH₂CH), 1.64-1.88 (3 H, m, NH, NHCHCO₂CH₃ and ArCH₂CH₄H₄A), 2.17-2.37 (1 H, m, ArCH₂CH₄H₄A), 2.66-2.83 (1 H, m, ArCH₃H₃B), 2.91-3.08 (1 H, m, ArCH₃H₃B), 3.70 (3 H, s, OCH₃), 4.07-4.15 (1 H, m, ArCH₂CH₂), 7.14-7.25 (3 H, m, ArCH) and 7.30-7.36 (1 H, m, ArCH); minor diastereomer, 0.85-0.93 (6 H, m, 2 x CH₃), 1.42-1.50 (2 H, m, CHCH₂CH), 1.64-1.88 (3 H, m, NH, NHCHCO₂CH₃ and Ar-CH₂CH₄H₄A), 2.17-2.37 (1 H, m, ArCH₂CH₄H₄A), 2.66-2.83 (1 H, m, ArCH₃H₃B), 2.91-3.08 (1 H, m, ArCH₃H₃B), 3.72 (3 H, s, OCH₃), 4.07-4.15 (1 H, m, ArCH₂CH₂), 7.14-7.25 (3 H, m, ArCH) and 7.30-7.36 (1 H, m, ArCH); δ_C (62.9 MHz; CDCl₃) major diastereomer, 22.72
(CH₃), 22.87 (CH₃), 24.82 (CH₂CH₃), 30.44 (CHCH₂CH), 34.95 (ArCH₂CH₂), 43.31 (ArCH₂), 51.62 (OCH₃), 58.58 (NHCHCO₂CH₃), 62.65 (ArCHCH₂), 123.64, 124.62, 126.01, 127.33 (ArCH), 143.42, 145.19 (ArC) and 177.25 (C=O); minor diastereomer, 22.00 (CH₃), 22.23 (CH₃), 24.76 (CH₂CH₃), 30.44 (CH₂CH₂CH), 33.02 (ArCH₂CH₂), 43.15 (ArCH₂), 51.62 (OCH₃), 58.02 (NHCHCO₂CH₃), 61.57 (ArCHCH₂), 124.45, 124.65, 126.34, 127.52 (ArCH), 143.65, 144.87 (ArC) and 176.94 (C=O); m/z (El) 261.1728 [M⁺ (10%), C₁₆H₂₃NO₂ requires 261.1729], 202 (20), 132 (20), 117 (100) and 86 (37).


To a solution of \(L\)-methionine methyl ester 283 (0.56 g, 3.43 mmol) and 2-[2-(phenylseleno)ethyl]benzaldehyde 278 (1.00 g, 3.46 mmol) in dry toluene (30 cm³) was added PTSA (catalytic), 4Å molecular sieves and the reaction mixture stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was washed with water (50 cm³) and brine (50 cm³), dried and evaporated to dryness to give methyl \((2S)-4-(methylthio)-2-[(\(E\))-1-{2-[2-(phenylseleno)ethyl]phenyl}methylidene]amino]butanoate 284 as a yellow oil (0.98 g, 66%); \([\alpha]_D = -24.3\) (c = 1.05, CHCl₃) \(\nu_{max}/\text{cm}^{-1}\) (neat) 2916, 1740, 1638, 1600, 1578, 1478, 1436, 1200, 736 and 692; \(\delta_H\) (250 MHz; CDCℓ₃) 2.08 (3 H, s, SCH₃), 2.19-2.29 (2 H, m, CH₂S), 2.36-2.62 (2 H, m, CH₂S), 3.07-3.29 (4 H, m, ArCH₂CH₂SePh), 3.74 (3 H, s, OCH₃), 4.10 (1 H, dd, \(J = 5.5\) and 7.7, NCHCO₂CH₃), 7.15-7.38 (6 H, m, ArCH), 7.49-7.56 (2 H, m, ArCH), 7.83-7.87 (1 H, m, ArCH) and 8.44 (1 H, s, HC=N); \(\delta_C\) (62.9 MHz; CDCℓ₃) 15.13 (SCH₃), 28.62 (ArCH₂), 30.23 (CH₂CH₂SCH₃), 31.76 (CH₂SCH₃), 33.91 (CH₂Se), 52.19 (OCH₃), 71.50 (NCHCO₂CH₃), 126.91, 126.95, 129.05, 129.08, 130.38, 130.87, 132.84 (ArCH), 133.14, 133.72,
141.05 (ArC), 162.85 (C=N) and 172.05 (C=O); m/z (El) 436.0846 [MH\(^+\) 436 (10%), C\(_{21}\)H\(_{26}\)NO\(_2\)SeS requires 436.0848], 280 (55), 164 (30), 132 (60), 117 (35) and 78 (100).

55. Methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-(methylthio)butanoate 287.

A deoxygenated solution of Bu\(_3\)SnH (0.96 g, 3.30 mmol) in dry toluene (45 cm\(^3\)) and a deoxygenated solution of AIBN (0.20 g) in dry toluene (30 cm\(^3\)) was added to a deoxygenated solution of methyl (2S)-4-(methylthio)-2-[\((E)-1-[2-(phenylseleno)ethyl]phenyl]methylidene)amino]butanoate 284 (0.96 g, 2.21 mmol) in dry toluene (250 cm\(^3\)) at 85 °C under a nitrogen atmosphere over a period of 10 h. The reaction mixture was evaporated to dryness and the residue was dissolved in dry methanol (75 cm\(^3\)) to which sodium borohydride (0.25 g, 6.61 mmol) was added in portions and the reaction mixture was stirred for 1 h. The reaction mixture was evaporated to dryness and the residue was extracted into diethyl ether (50 cm\(^3\)). The organic layer was washed with water (2 x 50 cm\(^3\)) and brine (2 x 50 cm\(^3\)), dried and evaporated to dryness to afford an orange oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to isolate the major component as a yellow oil (0.83 g). However, further column chromatography with dichloromethane:methanol (19:1) as eluant was necessary to isolate methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-4-(methylthio)butanoate 287 as a pure mixture of diastereoisomers (1:1.4) which was a clear oil (0.32 g, 52 %); \(\nu_{\text{max}} /\text{cm}^{-1}\) (neat) 3060, 2978, 1740, 1599, 1460, 1186, 760 and 700; \(\delta\) (400 MHz; CDCl\(_3\)) major diastereomer, 1.68-2.0 (4 H, m, NH, ArCH\(_2\)H\(_A\) and SCH\(_2\)CH\(_2\)), 2.08 (3 H, s, SCH\(_3\)), 2.19-2.39 (1 H, m, ArCH\(_2\)CH\(_A\)H\(_A\)), 2.61-2.67 (2 H, m, SCH\(_2\)), 2.72-2.83 (1 H, m, ArCH\(_B\)H\(_B\)), 2.94-3.09 (1 H, m, ArCH\(_B\)H\(_B\)), 3.54-3.59 (1 H, m, NHCH\(_2\)CO\(_2\)Me), 3.74 (3 H, s, OCH\(_3\)), 4.12-4.18 (1 H, m, ArCHCH\(_2\)), 7.18-7.22 (3 H, m, ArCH) and 7.31-7.37 (1 H, m, ArCH); minor diastereomer, 1.68-2.0 (4 H, m, NH,
ArCH₂CH₄H₄ and SCH₂CH₂), 2.09 (3 H, s, SCH₃), 2.19-2.39 (1 H, m, ArCH₂CH₄H₄), 2.61-2.67 (2 H, m, SCH₂), 2.72-2.83 (1 H, m, ArCH₂H₂B̅), 2.94-3.09 (1 H, m, ArCH₂H₂B̅), 3.54-3.59 (1 H, m, NHCHCO₂Me), 3.76 (3 H, s, OCH₃), 4.12-4.18 (1 H, m, ArCH₂CH₂), 7.18-7.22 (3 H, m, ArCH) and 7.31-7.37 (1 H, m, ArCH); δC (62.9 MHz; CDCl₃) major diastereomer, 15.43 (SCH₃), 30.37 (CH₂S), 30.52 (ArCH₂CH₂), 33.18 (CH₂CH₂S), 51.94 (OCH₃), 58.74 (NHCHCO₂CH₃), 62.73 (ArCH₂CH₂), 124.45, 124.65, 126.13, 127.43, (ArCH), 143.83, 145.08 (ArC) and 176.21 (C=O); minor diastereomer, 15.27 (SCH₃), 30.45 (CH₂S), 30.64 (ArCH₂CH₂), 32.99 (CH₂CH₂S), 34.77 (ArCH₂), 51.94 (OCH₃), 58.26 (NHCHCO₂CH₃), 61.71 (ArCHCH₂), 123.58, 124.77, 126.39, 127.64 (ArCH), 143.44, 144.75 (ArC) and 176.41 (C=O); m/z (El) 279.1293 [M+ 279 (7%), C₁₅H₂₁N₀₂S requires 279.1293], 220 (34), 162 (54), 132 (97), 117 (100), 104 (70), 88 (30) and 61 (18). A lower running component was also isolated on performing the latter column chromatography which was identified as being the uncyclised, reduced product 288 (0.09 g, 14%); δH (250 MHz; CDCl₃) 1.51 (1 H, s, NH), 1.69-1.99 (2 H, m, CH₂CH₂SCH₃), 2.06 (3 H, s, SCH₃), 2.46-2.64 (2 H, m, CH₂SCH₃), 3.02-3.19 (2 H, m, ArCH₂CH₂), 3.35 (1 H, dd, J 5.2 and 8.2, CHN), 3.56 (1 H, d, J 12.3, ArCH₄H₄NH), 3.73 (1 H, d, ArCH₄H₄NH), 3.74 (3 H, s, OCH₃), 7.14-7.30 (7 H, m, ArCH) and 7.50-7.55 (2 H, m, ArCH); δC (62.9 MHz; CDCl₃) 15.43 (SCH₃), 28.35 (CH₂SCH₃), 30.56 (CH₂SePh), 32.86 (CH₂CH₂SCH₃), 33.28 (ArCH₂CH₂SePh), 49.73 (ArCH₂NH), 51.81 (OCH₃), 59.75 (NCHCO₂CH₃), 126.55, 126.80, 127.53, 129.00, 129.47, 129.64, 132.61 (ArCH), 137.19, 139.82 (ArC) and 175.39 (C=O).

To a solution of (Z)-5-amino-1-phenylpent-1-ene 257 (0.45 g, 2.79 mmol) and 2-[2-(phenylselenyl)ethyl]benzaldehyde 278 (0.81 g, 2.80 mmol) in dry toluene (20 cm$^3$) was added PTSA (catalytic), 4Å molecular sieves and the reaction mixture stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was washed with water (30 cm$^3$) and brine (30 cm$^3$), dried and evaporated to dryness to give N1-((E)-1-[2-[2-(phenylseleno)ethyl]phenyl]methylidene)-(Z)-5-phenylpent-4-en-1-amine 292, as yellow oil (1.05 g, 87%); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2927, 1639, 1599, 1578, 1477, 1437, 757, 735, 692 and 668; $\delta_H$ (250 MHz; CDCl$_3$) 1.82 (2 H, quintet, $J$ 7.2, CH$_2$CH$_2$CH$_2$), 2.41 (2 H, dq, $J$ 1.7 and $J$ 7.2, CH=CHCH$_2$), 3.01-3.09 (2 H, m, CH$_2$Se), 3.14-3.22 (2 H, m, ArCH$_2$), 3.54 (2 H, dt, $J$ 1.3 and 6.9, CH$_2$N), 5.69 (1 H, dt, $J$ 7.4 and 11.7, CH=CHCH$_2$), 6.45 (1 H, dt, $J$ 1.7 and 11.7, PhCH=CH), 7.13-7.34 (12 H, m, ArCH), 7.50-7.54 (2 H, m, ArCH), 7.74-7.78 (1 H, m, ArCH) and 8.32 (1 H, br s, CH=N); $\delta_C$ (62.9 MHz; CDCl$_3$) 26.33 (CH$_2$CH$_2$CH$_2$), 28.77 (CH$_2$Ar), 31.13 (CH$_2$N), 33.81 (CH$_2$Se), 125.2 (CH=CHCH$_2$), 126.46, 126.84, 126.98, 128.08, 128.16, 128.35, 128.65, 128.67, 128.98, 129.06, 129.26, 130.16 (ArCH and ArC), 132.20 (PhCH=CH), 132.91 (ArC), 137.5 (ArC), 140.41 (ArC) and 159.16 (CH=N); $m/z$ 433.1317 [M$^+$ (67%), C$_{26}$H$_{27}$NSe requires 433.1309], 275 (100), 247 (61), 159 (54), 146 (56), 130 (61), 117 (93) and 91 (78).

57. 1-(2,3-Dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267.

A deoxygenated solution of Bu$_3$SnH (1.00 g, 3.44 mmol) in dry toluene (45 cm$^3$) and a deoxygenated solution of AIBN (0.30 g) in dry toluene (30 cm$^3$) were added to a deoxygenated solution of N1-((E)-1-[2-[2-(phenylseleno)ethyl]phenyl]methylidene)-(Z)-5-phenylpent-4-en-1-amine 292 (1.00 g, 2.31 mmol) in dry toluene (200 cm$^3$) at 85 °C under a nitrogen atmosphere.
over a period of 10 h. The reaction mixture was heated for a further 1 h, cooled and evaporated to dryness. The residue was dissolved in dry methanol (100 cm\(^3\)) to which sodium borohydride (0.2 g) was added in portions and the mixture was stirred for 2 h. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (30 cm\(^3\)). The organic layer was washed with water (2 x 20 cm\(^3\)) and extracted with 20% aq. HCl (3 x 15 cm\(^3\)). The aqueous layers were combined, washed with diethyl ether (2 x 10 cm\(^3\)), re-basified to pH 14 with 40% aq. NaOH and extracted with diethyl ether (3 x 15 cm\(^3\)). The organic layers were combined, washed with water (20 cm\(^3\)) and brine (20 cm\(^3\)), dried and evaporated to dryness to afford a yellow oil. The oil was subjected to column chromatography on neutral alumina using light petroleum:ethyl acetate (9:1) as eluant to isolate 1-(2,3-dihydro-1H-inden-1-yl)-2-(benzyl)tetrahydro-1H-pyrrole 267 as two diastereomers (0.19 g, 29% and 0.11 g, 17%) as clear oils; diastereomer 1; \(\nu_{\text{max}} \text{cm}^{-1}\) (neat) 2941, 1602, 1494, 1479, 1453, 1365, 1119, 740 and 699; \(\delta_H\) (250 MHz; CDCl\(_3\)) 1.48-1.75 (4 H, m, CH\(_{\text{fHfCHgHg}}\)), 2.01-2.10 (2 H, m, CH\(_{bHb'}\)), 2.32-2.42 (1 H, m, CH\(_{fHf}\)), 2.54-2.71 (2 H, m, CH\(_{dHd'}\) and CH\(_{iHj}\)), 2.76-3.09 (4 H, m, CH\(_{cHc'}\), CH\(_{e}\) and CH\(_{d}d\)), 4.69 (1 H, m, CH\(_{a}\)), 7.15-7.28 (8 H, m, ArCH) and 7.39-7.43 (1 H, m, ArCH); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 22.58 (CH\(_2\)CH\(_2\)N), 23.71 (NCH\(_2\)CH\(_2\)CH\(_2\)), 30.77 (ArCH\(_2\)CH\(_2\)), 30.85 (PhCH\(_2\)CH\(_2\)), 40.98 (ArCH\(_2\)CH\(_2\)), 46.72 (CH\(_2\)N), 62.52 (PhCH\(_2\)CH\(_2\)), 63.74 (ArCH\(_2\)CH\(_2\)), 124.45, 125.18, 125.86, 126.18, 127.12, 128.14 (ArCH), 128.99 (ArC), 129.39 (ArCH), 140.85 and 143.08 (ArCH); \(m/z\) 277.1829 [M\(^+\) (55%), C\(_{20}\)H\(_{23}\)N requires 277.1830], 186 (77), 117 (100), 91 (27) and 70 (97); diastereomer 2; \(\nu_{\text{max}} \text{cm}^{-1}\) (neat) 2941, 1602, 1494, 1479, 1453, 1365, 1119, 740 and 699; \(\delta_H\) (250 MHz; CDCl\(_3\)) 1.51-1.82 (4 H, m, CH\(_{fHfCHgHg}\)), 2.10 (1 H, ddt, \(J_{a,b}\) 8.2, \(J_{b,b'}\) 13.4, \(J_{b,c}\) and \(J_{b,c'}\) 5.0, CH\(_{b}H_{b'}\)), 2.26-2.41 (2 H, m, CH\(_{b}H_{b'}\) and CH\(_{iHj}\)), 2.47 (1 H, dd, \(J_{d,e}\) 9.7 and \(J_{d,d'}\) 13.1, CH\(_{d}H_{d'}\)), 2.85 (1 H, dd, \(J_{c,c'}\) 9.0 and \(J_{c,b}\) 8.9, CH\(_{c}H_{c'}\)), 2.95-3.02 (2 H, m, CH\(_{c}H_{c'}\) and CH\(_{iHj}\)), 3.07 (1 H, dd, \(J_{d,e}\) 4.1 and \(J_{d,d'}\) 13.1, CH\(_{d}H_{d'}\)), 3.15-3.24 (1 H, m, CH\(_{e}\)), 4.68 (1 H, dd, \(J_{a,b}\) 4.8 and \(J_{a,b'}\) 8.2, CH\(_{a}\)), 7.12-7.26 (8 H, m, ArCH) and 7.37-7.41 (1 H, m, ArCH); \(\delta_C\) (62.9 MHz; CDCl\(_3\)) 22.51 (CH\(_2\)CH\(_2\)N), 30.26 (NCH\(_2\)CH\(_2\)CH\(_2\)), 30.52 (ArCH\(_2\)CH\(_2\)), 30.87 (PhCH\(_2\)CH\(_2\)), 41.95 (ArCH\(_2\)CH\(_2\)), 48.19 (CH\(_2\)N), 62.12 (PhCH\(_2\)CH\(_2\)), 63.87 (ArCH\(_2\)CH\(_2\)), 124.87, 125.72, 125.79, 125.84, 127.46, 128.19 (ArCH),
129.14 (ArC), 129.31 (ArCH), 140.16 and 144.87 (ArC); m/z 277.1831 [M+ (84%), C20H23N requires 277.1830], 185 (100), 117 (94), 91 (36) and 70 (88).


![Chemical structure](image)

To a stirred solution of methyl (2S)-2-[(E)-1-[2-[2-(phenylseleno)ethyl]phenyl]methylidene]amino]-3-phenylpropanoate 280 (0.5 g, 1.11 mmol) in dry methanol (100 cm³), sodium borohydride (0.12 g, 3.17 mmol) was added in portions over a period of 30 min and the reaction mixture was stirred for 4 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness, the residue taken up into dichloromethane (50 cm³), washed with water (2 x 35 cm³) and brine (30 cm³), dried and evaporated to dryness to afford an oil. The oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to give N-[2-[2-(phenylselenyl)ethyl]benzyl]-L-phenylalanine methyl ester 291 as a clear oil (0.25 g, 50%); [α]D = -3.2 (c = 1.01, CHCl₃) νmax /cm⁻¹ (neat) 3027, 2948, 1734, 1578, 1494, 1477, 1454, 1436, 1197, 1171, 740 and 700; δH (250 MHz; CDCl₃) 1.76 (1 H, br s, NH), 2.83-3.11 (6 H, m, ArCH₂CH₂Se and PhCH₂), 3.44-3.51 (1 H, m, NHCH), 3.54 (1 H, d, J 12.5, ArCH₁H₂NH), 3.66 (3 H, s, OCH₃), 3.71 (1 H, d, J 12.5, ArCH₂H₂NH), 7.09-7.31 (12 H, m, ArCH) and 7.47-7.51 (ArCH); δC (62.9 MHz; CDCl₃) 28.28 (CH₂SePh), 33.26 (CH₂Ar), 39.73 (CH₂Ph), 49.63 (ArCH₂NH), 51.67 (OCH₃), 62.27 (NHCH), 126.53, 126.66, 126.80, 127.49, 128.36, 129.03, 129.14, 129.49, 129.53, 132.59 (ArCH), 137.09, 137.24, 139.87 (ArC) and 174.99 (C=O).
59. Attempted synthesis of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3-phenylpropanoate 260 using magnesium dibromide diethyl etherate.

![Chemical Structures](image)

a) A deoxygenated solution of Bu₃SnH (1.13 g, 3.88 mmol) in dry toluene (45 cm³) and AIBN (0.30 g) in dry toluene (30 cm³) was added to a solution of methyl (2S)-2-[(E)-1-{2-[(phenylseleno)ethyl]phenyl}-methylidene]amino]-3-phenylpropanoate 280 (1.17 g, 2.60 mmol) and magnesium bromide diethyl etherate (1.0 g, 3.87 mmol) in dry toluene (250 cm³) at 95 °C under a nitrogen atmosphere over a period of 10 h. The reaction mixture was evaporated to dryness and the residue was dissolved in dry methanol (100 cm³) to which sodium borohydride (0.60 g) was added in portions and the mixture was stirred for 1 h. The reaction mixture was evaporated to dryness and the residue extracted into diethyl ether (100 cm³). The organic layer was washed with water (3 x 60 cm³) and brine (60 cm³), dried and evaporated to dryness to afford an oil. The oil was subjected to column chromatography with light petroleum:ethyl acetate (9:1) as eluant to remove initially the high running tin components. The lower running components were collected together to afford, after evaporating to dryness, a yellow oil (0.30 g). TLC studies of this oil showed it to consist of a mixture of close running components. Further column chromatography using light petroleum:ethyl acetate (9:1) as eluant was performed in an attempt to separate these components. A partial separation of the components was achieved. The fractions containing the major components were combined and analysed by ¹H NMR spectroscopy and was consistent with it being N-[2-(2-phenylselenyl)ethyl phenyl methylidene]-L-phenylalanine methyl ester 36. A higher running minor component analysed by ¹H NMR spectroscopy had a spectrum consistent with it being the 6-endo product; δH (250 MHz; CDCl₃) 2.80-3.24 (6 H, m, ArCH₂CH₂N and PhCH₂), 3.61 (3 H, s, OCH₃), 3.67 (1 H, dd, J 5.9 and 9.3, NCHCO₂CH₃), 3.83...
(1 H, d, J 14.7, ArCH\textsubscript{A}H\textsubscript{B}N), 3.91 (1 H, d, J 14.7, ArCH\textsubscript{A}H\textsubscript{B}N) and 7.00-7.30 (9 H, m, ArCH).

The expected product was not seen, by \textsuperscript{1}H NMR spectroscopy, in any of the fractions collected.

b) The above experiment was repeated with the addition period of Bu\textsubscript{3}SnH and AIBN reduced to 4 h. A higher concentration of N-[2-(2-phenylselenyl)ethyl phenyl methylidene]-L-phenylalanine methyl ester 36 was observed along with the 6-\textit{endo} product. None of the expected product was seen by \textsuperscript{1}H NMR spectroscopy.

60. Methyl 2-amino-5-hexenoate 293.86a

![Chemical structure](image)

A suspension of methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate 226 (6.8 g, 29.44 mmol) in 30% aq HCl (150 ml) was stirred overnight under a nitrogen atmosphere. The resulting mixture was washed with diethyl ether (3 x 30 cm\textsuperscript{3}), neutralised with sodium bicarbonate to pH 9 and extracted with diethyl ether (3 x 50 cm\textsuperscript{3}). The organic extracts were combined, washed with water (2 x 30 cm\textsuperscript{3}) and brine (2 x 30 cm\textsuperscript{3}), dried and evaporated to dryness to afford an orange oil containing methyl 2-amino-5-hexenoate 293. No further purification was necessary; \(\nu_{\text{max}} / \text{cm}^{-1}\) (neat) 3381, 2952, 1737, 1641, 1437, 1200, 998 and 914; \(\delta\)\textsubscript{H} (250 MHz; CDCl\textsubscript{3}) 1.57-1.71 (3 H, m, NH\textsubscript{2} and CH\textsubscript{A}CHN), 1.78-1.92 (1 H, m, CH\textsubscript{A}CHN), 2.12-2.22 (2 H, m, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.47 (1 H, dd, \(J\) 5.3 and 7.8, CHN), 3.73 (3 H, s, OCH\textsubscript{3}), 4.93-5.11 (2 H, m, CH=CH\textsubscript{2}) and 5.80 (1 H, ddt, \(J\) 6.7, 10.3 and 17.0, CH=CH\textsubscript{2}); \(\delta\)\textsubscript{C} (62.9 MHz; CDCl\textsubscript{3}) 29.81 (CH\textsubscript{2}CHN), 33.95 (CH\textsubscript{2}C=CH\textsubscript{2}), 51.97 (OCH\textsubscript{3}), 53.78 (CHN), 115.37 (CH=CH\textsubscript{2}), 137.46 (CH=CH\textsubscript{2}) and 176.51 (CO\textsubscript{2}).

![Chemical Structure]

To a solution of methyl 2-amino-5-hexanoate 293 (0.50 g, 3.49 mmol) and 2-[2-(phenylseleno)ethyl]benzaldehyde 278 (1.01 g, 3.49 mmol) in dry toluene (30 cm³), PTSA (catalytic) and 4Å molecular sieves were added. The reaction mixture was stirred overnight under a nitrogen atmosphere. The mixture was filtered and the filtrate was washed with water (50 cm³) and brine (50 cm³), dried and evaporated to dryness to give methyl 2-[(E)-1-[(2-[2-(phenylseleno)ethyl]phenyl)methylidene]amino]hex-5-enoate 294 as a yellow oil (1.21 g, 83%); νmax /cm⁻¹ (neat) 2950, 1739, 1698, 1640, 1600, 1578, 1478, 1437, 1196, 737 and 692; δH (250 MHz; CDCl₃) 1.96-2.15 (4 H, m, CH₂CH₂CH=CH₂), 3.05-3.27 (4 H, m, CH₂CH₂SePh), 3.73 (3 H, s, OCH₃), 3.85-3.92 (1 H, m, NCHC=CH₃), 4.97-5.05 (2 H, m, CH=CH₂), 5.69-5.86 (CH=CH₂), 7.15-7.38 (6 H, m, ArCH), 7.47-7.54 (2 H, m, ArCH) and 7.84-7.88 (1 H, m, ArCH) and 8.36 (1 H, s, CH=N); δC (100 MHz; CDCl₃) 28.70 (CH₂Se), 29.92 (CH₂CH₂N), 32.20 (CH₂CH=CH₂), 52.17 (OCH₃), 72.90 (NCHCO₂CH₃), 115.51 (CH=CH₂), 126.98, 127.06, 129.11, 129.14, 130.41, 130.86, 132.95 (ArCH), 133.31 (ArC), 137.36 (CH=CH₂), 141.02 (ArC), 162.13 (CH=N) and 172.45 (C=O); m/z 415.1050 [M⁺ (2%), C₂₀H₂₃NSe requires 415.1050], 356 (11), 272 (38), 258 (100), 198 (13), 130 (17), 115 (100) and 91 (30).

A deoxygenated solution of Bu₃SnH (1.23 g, 4.22 mmol) in dry toluene (30 cm³) and a deoxygenated solution of AIBN (0.30 g) in dry toluene (30 cm³) were added to a deoxygenated solution of methyl 2-\(((E)-1-{2-[2-(phenylseleno)ethyl]phenyl}-methylidene)amino\)hex-5-enoate 294 (1.17 g, 2.82 mmol) in dry toluene (250 cm³) at 85 °C under a nitrogen atmosphere over a period of 10 h. The reaction mixture was extracted with 20% aq. HCl (3 x 20 cm³), washed with diethyl ether (2 x 30 cm³) neutralised with sodium hydrogen carbonate. The pH was adjusted to 14 with 20% aq. NaOH before extracting with dichloromethane (3 x 30 cm³). The organic layers were combined, washed with water (40 cm³) and brine (2 x 30 cm³), dried and concentrated to afford a yellow oil (0.35 g). TLC studies of the residue showed it to contain many new components which could not be satisfactorily separated. This was confirmed by a GC-MS study of the residue that it consisted of several major components, of which four had a fragmentation pattern consistent with that of the four expected diasteriomerics 5-exo products 295 \textit{m/z} 259 (2%, M⁺), 200 (20, M⁺-CO₂Me), 117 (100, M⁺-C₅H₉N), 84 (65, C₅H₉N). A further two components which also had a molecular ion of 259 were attributed the 6-endo product 296; \textit{m/z} 259 (2%), 200 (90), 154 (20%) and 117 (25%). Attempts to isolate these products by column chromatography using light petroleum:ethyl acetate (9:1) as eluant proved futile, leading to decomposition with only a partial purification of the mixture. A \textit{1H NMR} (250 MHz; CDCl₃) spectroscopic analysis of this partially purified sample showed resonances of singlets in the region 3.7-3.8 ppm to be consistent with -CO₂CH₃ and a multiplet in the region 4.1-4.2 ppm to be consistent with ArCHCH₂ of the expected 5-exo product. No further purification was attempted.
63. Attempted hydrogenation of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3 methylbutanoate 285.

\[
\text{HN} \quad \text{CO}_2\text{Me} \\
\text{285} 
\]

\[
\text{HN} \quad \text{CO}_2\text{Me} \\
\text{272} 
\]

\[
\text{HN} \quad \text{CO}_2\text{Me} \\
\text{299} 
\]

a) 10% Palladium on charcoal (10 mg) was added to a solution of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3 methylbutanoate 285 (0.1 g, 0.40 mmol) in methanol (2 cm\(^3\)). The flask was put under vacuum and hydrogen introduced into the flask. The reaction was stirred overnight after which time the reaction mixture was filtered and the filtrate was evaporated to dryness to afford the starting amino ester 285 (0.085 g, 85%) as indicated by \(^1\)H NMR spectroscopy.

b) The above experiment was repeated under pressure (3 bar). The starting amino ester 285 was recovered in 87% yield.

c) The above experiment was repeated under pressure (3 bar) with 20% aq. HCl (1 cm\(^3\)) added to the reaction mixture. The starting amino ester 285 was recovered in 79% yield.

64. Attempted hydrogenation of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3 phenylpropanoate 260.

\[
\text{HN} \quad \text{Ph} \quad \text{CO}_2\text{Me} \\
\text{260} 
\]

\[
\text{HN} \quad \text{Ph} \quad \text{CO}_2\text{Me} \\
\text{258} 
\]

\[
\text{HN} \quad \text{CO}_2\text{Me} \\
\text{299} 
\]
a) 20% Palladium hydroxide (15 mg) was added to a solution of methyl (2S)-2-(2,3-dihydro-1H-inden-1-ylamino)-3 phenylpropanoate 260 (0.13 g, 0.44 mmol) in methanol (3 cm³). The reaction vessel was put under vacuum and hydrogen introduced. The reaction mixture was stirred overnight after which time the mixture was filtered and the filtrate evaporated to dryness to afford an oil. Analysis of the oil by 1H NMR spectroscopy showed it to be th starting amino ester 260 (11.9 mg, 79%).

b) The above experiment was repeated under pressure (3 bar). The starting amino ester 260 was recovered in 82% yield.

c) The above experiment was repeated under pressure (3 bar) with 20% aq. HCl (1 cm³). The starting amino ester 260 was again recovered in 77% yield.

65. 1-Bromo-2-[di(methyloxy)methyl]benzene 316.124

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{315} & \quad \text{Ar} \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{OCH}_3 \\
\text{316} & \quad \text{Ar} \\
\end{align*}
\]

A mixture of 2-bromobenzaldehyde 315 (10 g, 0.05 mol), trimethyl orthoformate (8.65 g, 0.08 mol) and cerium chloride (0.5 g, 2.97 mmol) in dry methanol (30 cm³) were stirred overnight under a nitrogen atmosphere. The mixture was evaporated to dryness and the residue was taken up into diethyl ether (100 cm³), washed with water (3 x 50 cm³), dried and concentrated to afford 1-bromo-2-[di(methyloxy)methyl]benzene 316 as a clear oil (10.86 g, 87%); νmax /cm⁻¹ (neat) 3067, 1698, 1592, 1570, 1468, 1435, 1362, 1204, δH (250 MHz; CDCl₃) 3.39 (6 H, s, 2 x OCH₃), 5.57 (1 H, s, CH), 7.15-7.22 (1 H, m, ArCH), 7.30-7.36 (1 H, m, ArCH), 7.54-7.63 (2 H, m, ArCH); δC (62.9 MHz; CDCl₃) 53.81 (2 x OCH₃), 102.86 (CH), 122.86 (ArC), 127.05, 128.23, 129.95, 132.78 (ArCH) and 136.73 (ArC); m/z 229.9939 [M+ (2%), C₉H₁₁O₂⁷⁹Br requires 229.99428], 199 (100), 185 (7), 155 (4), 105 (15), 91 (12) and 75 (16).
66. 2-(1,1,1-Tributylstannyl)benzene-1-carbaldehyde 317.

\[
\begin{align*}
\text{Br} & \quad \text{OCH}_3 \\
\overset{\text{SnBu}_3}{\text{O}} & \\
\end{align*}
\]

A solution of butyllithium in hexane (7.8 cm\(^3\), 1.6 M) was added to a solution of 1-bromo-2-[di(methyloxy)methyl]benzene 316 (2.8 g, 12.12 mmol) in dry tetrahydrofuran (25 cm\(^3\)) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at this temperature before introducing tributyItin chloride dropwise over a period of 10 min. After stirring overnight, 30% aq. HCl (40 cm\(^3\)) was added dropwise cautiously and the reaction mixture was stirred for 3 h. The reaction mixture was evaporated to dryness and the resulting residue was taken up into diethyl ether (50 cm\(^3\)), washed with 10% aq. NaOH (2 x 30 cm\(^3\)) and brine (2 x 50 cm\(^3\)), dried and concentrated to afford an orange oil which was subjected to column chromatography using light petroleum:ethyl acetate (9.5:0.5) as eluant to isolate 2-(1,1,1-tributylstannyl)benzene-1-carbaldehyde 317 as a clear oil (0.83 g, 17%); \(\nu_{\text{max}} /\text{cm}^{-1}\) (neat) 2954, 1701, 1560, 1462, 1199, 753 and 665; \(\delta_H\) (400 MHz; CDCl\(_3\)) 0.86 (9 H, t, \(J\) 7.2, CH\(_3\)), 1.05-1.09 (6 H, m, CH\(_2\)CH\(_3\)), 1.26-1.33 (6 H, m, CH\(_2\)Sn), 1.45-1.53 (6 H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 7.48-7.58 (2 H, m, ArCH), 7.69-7.72 (1 H, m, ArCH), 7.78-7.84 (1 H, m, ArCH), and 9.98 (1 H, dt, \(J\) 0.8, CHO); \(\delta_C\) (100 MHz; CDCl\(_3\)) 11.01 (CH\(_2\)Sn), 14.08 (CH\(_3\)), 27.78 (SnCH\(_2\)CH\(_2\)), 29.56 (CH\(_2\)CH\(_3\)), 128.82, 133.69, 134.99, 137.98 (ArCH), 141.84, 145.72 (ArC) and 194.47 (CHO); \(m/z\) 339.0772 [M+ - Bu (100%)], C\(_{19}\)H\(_{32}\)SnO requires 339.0771, 283 (5), 225 (50) and 91 (10).

67. Attempted synthesis of 2-(2'-bromophenyl)-benzaldehyde 314,\(^{125}\)

\[
\begin{align*}
\text{O} & \quad \text{SnBu}_3 \\
\overset{\text{Br}}{\text{O}} & \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Br} \\
\overset{\text{Br}}{\text{O}} & \\
\end{align*}
\]
a) Bis(dibenzylideneacetone)palladium (0) (0.07 g, 0.122 mmol) was added to a deoxygenated solution of 2-(1,1,1-tributylstannyl)benzene-1-carbaldehyde 317 (0.5 g, 1.26 mmol) and 2-bromoiodobenzene 318 (0.39 g, 1.38 mmol) in dry toluene (35 cm³) and the reaction mixture was refluxed for 18 h. TLC studies of the mixture showed a major high running component with a similar Rf to that of the starting stannane. The reaction mixture was evaporated to dryness and the residue was subjected to column chromatography using light petroleum:ethyl acetate (9.5:0.5) as eluant to isolate the major component as a clear oil (0.45 g). 1H NMR spectroscopic studies showed this oil to be the starting stannane 317 (90%).

b) The above experiment was repeated using tetrakis(triphenylphosphine)palladium (0) and dimethylformamide as solvent. Again, the starting stannane 317 was recovered in 92% yield.

68. 2-(o-Bromophenyl)-1,3-dioxolane 320

A mixture of 2-bromobenzaldehyde 315 (25.0 g, 0.135 mol), ethylene glycol (10.0 g, 0.161 mol) and PTSA (1.0 g) in toluene were refluxed under Dean and Stark conditions for 6 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and the residue was taken up into diethyl ether (100 cm³). The organic layer was washed with 10% aq. NaOH (50 cm³) and brine (2 x 50 cm³), dried and evaporated to dryness to afford 2-(o-bromophenyl)-1,3-dioxolane 320 as a yellow oil (30.82 g, 99%); νmax/cm⁻¹ (neat) 3066, 2887, 1592, 1571, 1472, 1443, 1388, 1093 and 757; δH (250 MHz; CDCl₃) 4.02-4.21 (4 H, m, OCH₂CH₂O), 6.10 (1 H, s, ~CH~), 7.18-7.26 (1 H, m, ArCH), 7.30-7.37 (1 H, m, ArCH) and 7.54-7.62 (2 H, m, ArCH); δC (62.9 MHz; CDCl₃) 65.42 (OCH₂CH₂O), 102.55 (OCHO), 122.88 (ArC), 127.37, 127.75, 130.56,
132.92 (ArCH) and 136.54 (ArC); m/z 227.9791 [M^+ (100%), C_{9}H_{7}^{79}Br requires 227.9786). 185 (38), 182 (36), 158 (15), 156 (17), 149 (53), 119 (17), 105 (18), 89 (46) and 73 (97).

69. 2-Formylphenylboronic acid 321.115,116,117

![Chemical Structure](image)

a) A solution of 2-(o-bromophenyl)-1,3-dioxolane 320 (20.0 g, 87.3 mmol) in dry tetrahydrofuran (100 cm³) was added (via a pressure equalising dropping funnel) dropwise to a three necked flame dried flask (250 cm³) fitted with a condensor, charged with magnesium turnings (2.33 g, 95.8 mmol) under a nitrogen atmosphere. Although the mixture was self refluxing, reflux was maintained for an additional period of 45 min. The reaction mixture was cooled to -78 °C and a deoxygenated solution of trimethyl borate (17.84 g, 1.72 mol) in dry tetrahydrofuran (100 cm³) was added over a period of 15 min. The reaction mixture was warmed to room temperature and stirring continued for 2 h. The mixture was poured onto ice cold 40% aq. HCl (200 cm³) and the tetrahydrofuran removed under reduced pressure. The organic extracts were taken up into diethyl ether (150 cm³), separated, washed with water (2 x 100 cm³) before extracting with 30% aq. NaOH (2 x 100 cm³). The aqueous layers were combined washed with diethyl ether (2 x 50 cm³), re-acidified to pH 1 with concentrated hydrochloric acid and re-extracted with diethyl ether (2 x 100 cm³). The organic extracts were combined, washed with water (100 cm³) and brine (2 x 50 cm³), dried and evaporated to dryness. The resulting solid was recrystallised from dichloromethane to provide 2-formylphenylboronic acid 321 as white needles (2.92 g, 22%) mp 109-110 °C (lit.115 108-110°C); δ_{H} (250 MHz; CDCl₃) 7.59-7.70 (2 H, m, ArCH), 7.87-7.99 (2 H, m, ArCH) and 10.21 (1 H, s, CHO); m/z 150.0489 [M^+-H (74%), C_{20}H_{23}N requires 150.0488], 132 (10), 121 (5), 104 (60), 77 (56), 69 (100), 51 (23), 45 (10) and 18 (74).
b) A solution of n-butyllithium in hexane (53 cm³ of 1.6 M solution, 84.8 mmol) was added to a solution of 2-(o-bromophenyl)-1,3-dioxolane 320 (19.5 g, 85.1 mmol) in dry tetrahydrofuran (100 cm³) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min before adding trimethyl borate (16.47 g, 158.5 mmol) dropwise over a period of 30 min. The reaction mixture was warmed to room temperature and stirring continued for 1 h. The work-up, as before, gave (2-formylphenyl)boronic acid 321 (6.52 g, 65%).

70. Tetrakis(triphenylphosphine)palladium (0).\textsuperscript{118}

\[
2\text{PdCl}_2 + 8\text{P(Ph)}_3 + 5\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \rightarrow 2\text{Pd(PPH}_3)_4
\]

A deoxygenated solution of palladium chloride (1.38 g, 7.78 mmol) and triphenylphosphine (8.16 g, 0.03 mol) in dry acetonitrile (100 cm³) was refluxed for 3 h after which time dry dimethylsulphoxide (60 cm³) was added. Heating was continued at 80 °C until complete dissolution was achieved. The reaction mixture was cooled to room temperature during which time hydrazine hydrate (1.5 g, 0.03 mol) was added and the reaction mixture stirred overnight under a nitrogen atmosphere. The precipitate which had developed was filtered under a nitrogen atmosphere, washed with aliquots of ethanol (2 x 10 cm³) and ether (2 x 10 cm³) before drying under a stream of nitrogen to yield tetrakis(triphenylphosphine)palladium (0) as yellow crystals (2.10 g, 23%); mp 112 °C (lit.\textsuperscript{118} 116 °C).

71. 2-(2′-Bromophenyl)benzaldehyde 314.\textsuperscript{125}

\[
\begin{align*}
\text{321} &+ \text{318} \rightarrow \text{314}
\end{align*}
\]
a) A deoxygenated solution of (2-formylphenyl)boronic acid 321 (0.5 g, 3.33 mmol) in methanol (5 cm³) and a deoxygenated solution of 2 M sodium carbonate (10 cm³) were added to a deoxygenated solution of 2-bromoiodobenzene 318 (0.94 g, 3.32 mmol) and palladium tetrakistriphenylphosphine (0) (0.08 g, 0.069 mmol) in toluene (20 cm³). The reaction mixture was refluxed for 15 h under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and the yellow residue produced was subjected to column chromatography using light petroleum:ethyl acetate (4:1) as eluant to yield 2-(2'-bromophenyl)benzaldehyde 314 as a yellow oil (0.34 g, 39%); ν max /cm⁻¹ (neat) 3059, 2843, 2750, 1695, 1651, 1597; δ H (250 MHz; CDCl₃) 7.26-7.34 (3 H, m, ArCH), 7.38-7.45 (1 H, m, ArCH), 7.51-7.58 (1 H, m, ArCH), 7.63-7.71 (2 H, m, ArCH), 8.02-8.06 (1 H, m, ArCH) and 9.79 (1 H, d, J 0.7, CHO); δ C (62.9 MHz; CDCl₃) 123.81 (ArC), 127.33, 127.36, 128.53, 129.78, 130.79, 131.55, 132.73, 133.65 (ArCH), 138.85, 144.44 (ArC) and 191.45 (CHO).

b) The above experiment was repeated using freshly prepared palladium tetrakistriphenylphosphine (0) and dry dimethylformamide as solvent to yield 2-(2'-bromophenyl)benzaldehyde 314 (1.57 g, 60%).


\[
\begin{array}{c}
\text{Br} \quad \text{O} \\
\text{314} \\
\end{array} + \begin{array}{c}
\text{H}_2\text{N} \quad \text{Ph} \\
\text{CO}_2\text{Me} \\
\end{array} \rightarrow \begin{array}{c}
\text{Br} \quad \text{N} \quad \text{Ph} \\
\text{322} \\
\end{array}
\]

L-Phenylalanine methyl ester 258 (0.508 g, 2.83 mmol) and PTSA (0.05 g), were added to a solution of 2-(2'-bromophenyl)benzaldehyde 314 in dry toluene (15 cm³) containing 4Å molecular sieves and the reaction mixture was stirred overnight. The mixture was filtered and the
filtrate washed with water (2 x 25 cm³) and brine (2 x 30 cm³), dried and concentrated to afford methyl 2-\{(Z)-1-[2-(2-bromophenyl)phenyl]methylidene\}amino)-3-phenylpropanoate 322 as an oil (0.93 g, 78%); v_max/cm⁻¹ (neat) 3027, 1742, 1697, 1598, 755 and 700; δ_H (250 MHz; CDCl₃) 3.06-3.16 (1 H, m, CH₄HB), 3.26-3.34 (1 H, m, CH₄HB), 3.68 and 3.73 (3 H, 2 x s, OCH₃), 3.94-4.05 (1 H, m, NCHCO₂CH₃), 7.05-7.73 (13 H, m, ArCH) and 8.19-8.22 (1 H, m, CH=N); δ_C (62.9 MHz; CDCl₃) 39.58, 39.79 (CH₂), 52.13, 52.19 (OCH₃), 74.96, 75.07 (NCHCO₂CH₃), 126.36-132.49 (ArCH), 137.21, 137.37, 142.13 (ArC), 162.02, 162.14 (CH=N) and 172.02 (C=O); m/z (EI) 422.07699 [M+ 422 (20%), C₂₃H₂₀N₂79Br requires 422.0770], 344 (15), 197 (47), 180 (100), 165 (23), 120 (38), 104 (25) and 91 (31).

73. Methyl (2S)-2-(9H-fluoren-9-ylamino)-3-phenylpropanoate 323.

A deoxygenated solution of Bu₃SnH (0.91 g, 3.12 mmol) in dry toluene (42 cm³) and AIBN (0.2 g) in dry toluene (30 cm³), were added to a deoxygenated solution of methyl (2S)-2-\{(Z)-1-[2-(2-bromophenyl)phenyl]methylidene\}amino)-3-phenylpropanoate 322 (0.88 g, 2.08 mmol) in dry toluene (250 cm³) at 85 °C under a nitrogen atmosphere over a period of 10 hours. The reaction mixture was evaporated to dryness and the residue taken up into MeOH (85 cm³) to which NaBH₄ (0.35 g, 9.25 mmol) was added and the mixture stirred for 1 h. The reaction mixture was evaporated to dryness and the residue taken up into ethyl acetate (100 cm³), washed with water (50 cm³) and brine (50 cm³), dried and evaporated to dryness to afford an orange oil. This oil was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to afford initially 2-cyanobiphenyl 310 as an oil (0.12 g, 30%); v_max/cm⁻¹ (neat) 3026, 2957, 2224, 1595, 1476, 1451, 1433, 759, 735 and 700; δ_H (400 MHz; CDCl₃) 7.20-7.57 (9H); δ_C (100 MHz;
CDCI3) 111.73, 119.11 (ArC), 126.8, 129.13, 130.49, 133.20, 134.16 (ArCH), 138.56 and 145.92 (ArC); m/z (EI) 179.0735 [M+ 179 (100%), C13H9N requires 179.035], 152 (13) and 76 (7). The lower running component, methyl (2S)-2-(9H-fluoren-9-ylamino)-3-phenylpropanoate 323, was isolated and recrystallised from diethyl ether (0.39 g, 55%), mp 126.0-129.1 °C, [α]D = -32.0 (c = 1.076, CHCl3); vmax / cm⁻¹ (KBr) 3060, 2359, 1724, 1650, 1442, 1205, 1164 and 740; δH (400 MHz; CDCI3) 3.00 (1 H, br s, NCHC02CH3), 3.31 (3 H, s, OCH3), 4.85 (1 H, s, Ar-CH-Ar), 7.03-7.64 (13 H, m, ArCH); δC (100 MHz; CDCI3) 40.77 (CH2Ph), 51.45 (OCH3), 58.15 (NCHCO2CH3), 62.74 (ArCHAr), 119.58, 119.80, 124.97, 125.76, 126.58, 126.74, 127.28, 127.85, 128.07, 128.10, 129.48 (ArCH), 137.32, 140.75, 140.93, 144.35, 144.43 (ArC) and 176.21 (C=O); m/z (EI) 342.1492 [M+ 343 (1%), C23H21N02 requires 342.1494], 280 (17), 252 (100), 179 (23), 165 (100) and 91 (23).


\[ \text{314} + \text{257} \rightarrow \text{326} \]

To a solution of (Z)-5-amino-1-phenylpent-1-ene 257 (0.292 g, 1.81 mmol) and 2-(2'-bromophenyl)benzaldehyde 314 (0.45 g, 0.17 mmol) in dry toluene (30 cm³) was added PTSA (catalytic), 4Å molecular sieves and the reaction mixture stirred overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was washed with sat. sodium bicarbonate (20 cm³) and brine (20 cm³), dried and evaporated to dryness to yield N-{(E)-1-[2-(2'-bromophenyl)-phenyl]methylidene}-N-[(Z)-5-phenylpent-4-enyl]amine 326 as a clear oil (0.48 g, 69%); vmax / cm⁻¹ (neat) 1648, 1600, 1575; δH (250 MHz; CDCl3) 1.80 (2 H, quintet, J 7.3, CH2CH2CH2), 2.36 (2 H, dq, J 1.7 and 7.3, CH2CH=CH), 3.48 (1 H, dt, J 1.1 and 7.3, NCH2),
5.66 (1 H, dt, J 7.3 and 11.7, PhCH=CHCH₂), 6.40 (1 H, dt, J 1.7 and 11.7, PhCH=CHCH₂),
7.15-7.47 (11 H, m, ArCH), 7.64-7.68 (1 H, m, ArCH), 7.95 (1 H, s, ArCH) and 8.09-8.12 (1 H,
m, CH=N); δC (62.9 MHz; CDCl₃) 26.36 (CH₂CH₂CH₂), 31.06 (CH₂CH=CH), 61.14 (NCH₂),
123.85 (ArC), 126.29, 126.44, 127.15, 128.07, 128.24, 128.71, 129.09, 129.21, 129.89, 129.98,
131.59, 132.31, 132.56 (ArCH and CH=CH), 133.93, 137.56, 140.41, 141.72 (ArC) and 159.36
(C=N); m/z (EI) 403.0932 [M⁺ 403 (20%), C₂₄H₂₂N₇Br requires 403.0936], 324 (75), 194 (100),
180 (18), 165 (58), 117 (16) and 91 (14).

75. 1-(9H-Fluoren-9-yl)-2-(benzyl)tetrahydro-1H-pyrrole 327.

A deoxygenated solution of Bu₃SnH (0.45 g, 1.53 mmol) in dry toluene (30 cm³) and AIBN
(0.1 g) in dry toluene (30 cm³), were added to a deoxygenated solution of methyl N-{(E)-1-[2-(2-
bromophenyl)-phenyl]methylidene}-N-[(Z)-5-phenylpent-4-enyl]amine 326 (0.48 g, 1.18 mmol)
in dry toluene (150 cm³) at 90 °C under a nitrogen atmosphere over a period of 10 hours. The
reaction mixture was evaporated to dryness and the residue taken up into MeOH (50 cm³) to
which NaBH₄ (0.27 g, 7.14 mmol) was added and the mixture stirred for 1 h. The reaction
mixture was evaporated to dryness and the residue taken up into dichloromethane (100 cm³),
washed with water (2 x 50 cm³) and brine (50 cm³), dried and evaporated to dryness to afford an
yellow oil. This oil was subjected to column chromatography using light petroleum:ethyl acetate
(9:1) as eluant to afford initially 2-cyanobiphenyl 310 as a yellow oil (78.2 mg, 39%) and 1-(9H-
Fluoren-9-yl)-2-(benzyl)tetrahydro-1H-pyrrole 327 as an oil (46.00 mg, 12%); νmax /cm⁻¹ (neat)
3042, 2321, 1597, 1468, 1200, 738 and 705; δH (400 MHz; CDCl₃) 1.46-1.80 (4 H, m,
CH₂CH₂CH₂N), 2.17-2.27 (1 H, dd, J 7.8 and 16.5, CH₂CH₂CH₂AH₂B₂N), 2.55-2.63 (1 H, m,
CH₂CH₂CH₂NH₂, 2.59-2.68 (1 H, dd, J 9.0 and 13.1, CH₃H₂BPh), 3.08-3.15 (1 H, dd, J 4.6 and 13.1, CH₃H₂BPh), 3.52-3.64 (1 H, m, CH₂CH₃N), 5.12 (1 H, s, CH₃), 7.18-7.37 (9 H, m, ArCH); m/z (EI) 325.1828 [M⁺ 325 (2%), C₂₄H₂₃N requires 325.1830], 234 (65), 165 (100) and 91 (38).

76. Methyl 2-({(Z)-1-[2-(2-bromophenyl)phenyl]methylidene}amino)-5-hexenoate 328.

Methyl 2-amino-5-hexanoate 293 (0.28 g, 1.96 mmol) and PTSA (0.05 g), were added to a solution of 2-(2'-bromophenyl)benzaldehyde 314 (0.51 g, 1.95 mmol) in dry toluene (20 cm³) containing 4Å molecular sieves and the reaction mixture was stirred overnight. The mixture was filtered and the filtrate washed with water (2 x 25 cm³) and brine (2 x 30 cm³), dried and concentrated to afford methyl 2-({(Z)-1-[2-(2-bromophenyl)phenyl]methylidene}amino)-5-hexenoate 328 as an oil (0.93 g, 78%); νmax /cm⁻¹ (neat) 2950, 1741, 1698, 1640, 1598, 756 and 731; δH (400 MHz; CDCl₃) 1.9-2.13 (4 H, m, CH₂CH₂), 3.69 and 3.70 (3 H, 2 x s, OCH₃), 3.79-3.83 (1 H, m, NCHCO₂CH₃), 4.85-4.98 (2 H, m, CH=CH₂), 5.64-5.78 (1 H, m, CH=CH₂), 7.19-7.48 (6 H, m, ArCH), 7.64-7.70 (1 H, m, ArCH), 7.95-7.96 (1 H, m, ArCH) and 8.17-8.23 (1 H, m, CH=N); δC (62.9 MHz; CDCl₃) 29.65 (CH₂CH₂CH=CH₂), 32.01 and 32.19 (CH₂CH=CH₂), 51.99 (OCH₃), 72.18 and 72.35 (NCHCO₂CH₃), 115.39 and 115.41 (CH=CH₂), 123.76 and 123.79 (ArC), 126.72-132.68 (ArCH and ArC), 137.20-137.30 (CH=CH₂), 140.13, 142.06 and 142.17 (ArC), 161.89 and 162.00 (CH=N), 172.35 and 172.49 (C=O); m/z (EI) 385.0671 [M⁺ 385 (25%), C₂₀H₂₀NO₂Br requires 385.0677], 326 (17), 306 (100), 245 (22), 230 (15), 206 (13), 180 (35), 165 (46) and 152 (9).
78. *N*-(2-bromophenyl)ethanolamine 336.

\[ \text{ArNH}_2 \quad \text{335} \quad \rightarrow \quad \text{ArCH} - \text{OH} \quad \text{336} \]

A mixture of 2-bromoaniline 335 (5.0 g, 0.03 mol), 2-bromoethanol (5.44 g, 0.04 mol), CaCO\(_3\) (5.07 g, 0.04 mol) and water (160 cm\(^3\)) was refluxed for 30 h. The mixture was filtered and the filtrate was saturated with NaCl before extracting with diethyl ether (2 x 50 cm\(^3\)). The organic extracts were combined, dried and evaporated to dryness. The resulting residue was subjected to column chromatography using light petroleum:ethyl acetate (9:1) as eluant to isolate *N*-(2-bromophenyl)ethanolamine 336 as an orange oil (2.82 g, 45%); \(v_{\text{max}}/\text{cm}^{-1}\) (nujol) 3396, 2941, 1596, 1509, 1320, 1019 and 742; \(\delta_H\) (250 MHz, CDCl\(_3\)) 2.32 (1 H, br s, NH\text{-OH}), 3.27-3.34 (2 H, m, CH\text{\textsubscript{2}}N), 3.76-3.87 (2 H, m, CH\text{\textsubscript{2}}O), 4.59 (1 H, br s, NH/\text{OH}), 6.45-6.67 (2 H, m, ArCH), 7.13-7.24 (1 H, m, ArCH) and 7.40-7.44 (1 H, m, ArCH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 45.87 (CH\text{\textsubscript{2}}NH), 60.95 (CH\text{\textsubscript{2}}OH), 110.14 (ArC), 111.57, 118.21, 128.49, 132.51 (ArCH) and 144.86 (ArC); \(m/z\) (EI) 214.9951 [M\(^+\) (36%), C\(_8\)H\(_{10}\)NOBr requires 214.9946], 184 (100), 105 (49), 91 (10), 84 (19) and 77 (44).


\[ \text{ArCH} - \text{OH} \quad \text{336} \quad \rightarrow \quad \text{ArCH} - \text{N=O} \quad \text{337} \]

a) A mixture of the *N*-(2-bromophenyl)ethanolamine 336 (0.26, 1.23 mmol), PCC (0.39 g,) and 4Å molecular sieves in dry dichloromethane (5 cm\(^3\)) was stirred for 2 h under a nitrogen atmosphere. Dry diethyl ether (20 cm\(^3\)) was added and the mixture stirred vigorously. The mixture was filtered and the filtrate passed through a pad of silica. The filtrate was evaporated to
dryness and analysis of the residue by $^1$H NMR and IR spectroscopy failed to show characteristic signals attributed to the aldehyde. Column chromatography using light petroleum:ethyl acetate (4:1) as eluant provided the starting alcohol 336 (0.16 g, 61%).

b) TFAA (0.44 g, 2.08 mol) was added to a solution of DMSO (0.24 g, 3.05 mmol) in dry dichloromethane (10 cm$^3$) at -78 °C. The mixture was stirred for 30 min at this temperature before introducing a solution of $N$-(2-bromophenyl)ethanolamine 336 (0.3 g, 1.39 mmol) in dry dichloromethane (8 cm$^3$) over a period of 10 min. The reaction mixture was stirred for 1 h at this temperature before adding triethylamine (0.42 g, 4.17 mol) and the reaction mixture was warmed to room temperature and stirring continued overnight. The reaction mixture was washed with 15% aq. HCl (2 x 50 cm$^3$), water (50 cm$^3$) and brine (50 cm$^3$), dried and evaporated to dryness to afford an orange oil (0.23 g). The $^1$H NMR spectrum of the oil was very complex but did show a resonance at 9.77 ppm, characteristic of an aldehydic proton.
References

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Appendix
Table 1. Crystal data and structure refinement for methyl (2S)-2-(9H-fluorene-9-ylamino)-3-phenylpropanoate.

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| Unit cell dimensions| \(a = 6.1012(5)\) Å \(\alpha = 90^\circ\) \\
|                     | \(b = 37.723(3)\) Å \(\beta = 90.267(2)^\circ\) \\
|                     | \(c = 8.1374(7)\) Å \(\gamma = 90^\circ\) |
| Volume, \(Z\)       | 1872.9(3) Å\(^3\), 4 |
| Density (calculated)| 1.218 Mg/m\(^3\) |
| Absorption coefficient | 0.077 mm\(^{-1}\) |
| \(F(000)\)          | 728 |
| Crystal size        | \(0.1 \times 0.1 \times 0.3\) mm |
| \(\theta\) range for data collection | 1.08 to 23.30° |
| Limiting indices    | \(-6 \leq h \leq 6, \ -36 \leq k \leq 41, \ -7 \leq l \leq 9\) |
| Reflections collected | 8132 |
| Independent reflections | 4473 (\(R_{\text{int}} = 0.0916\)) |
| Absorption correction | None |
| Refinement method   | Full-matrix least-squares on \(F^2\) |
| Data / restraints / parameters | 4424 / 3 / 478 |
| Goodness-of-fit on \(F^2\) | 1.182 |
| Final R indices [\(I > 2\sigma(I)\)] | \(R1 = 0.0855, \ WR2 = 0.1878\) |
| R indices (all data) | \(R1 = 0.1249, \ WR2 = 0.2527\) |
| Absolute structure parameter | -1(4) |
| Extinction coefficient | 0.019(3) |
| Largest diff. peak and hole | 0.219 and -0.219 eÅ\(^{-3}\) |
Table 2. Atomic coordinate \([ x \times 10^4 \] and equivalent isotropic displacement parameters \([\AA^2 \times 10^3 \]) for methyl \((2S)-2-(9H-fluorene-9-ylamino)-3-phenylpropanoate\). \(U(eq)\) is defined as one third of the trace of the orthogonalised \(U_{ij}\) tensor.

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Table 4. Anisotropic displacement parameters [Å x 10^3] for methyl (2S)-2-(9H-fluorene-9-ylamino)-3-phenylpropanoate. The anisotropic displacement factor exponent takes the form:

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Table 5. Hydrogen coordinates (Å x 10^4) and isotropic displacement parameters (x 10^3) for methyl (2S)-2-(9H-fluorene-9-ylamino)-3-phenylpropanoate.

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