Synthesis of nitrogen containing heterocycles *via* radical cyclisation.

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Declaration

The work described in this thesis is the original work of the author, except where acknowledgement has been made to results and ideas previously reported. The work was carried out in the Department of Chemistry, University of Warwick between October 1st 1996 and October 1st 1999 and has not been previously submitted for a degree at any other institution.

Abstract

O-benzoyl hydroxamic acids were found to be suitable precursors for the generation of amidyl radicals. A stereoselectivity study was performed to investigate the 5-*exo* cyclisations of the amidyl radicals formed. Hence a range of methyl and phenyl 2-substituted *N*-alkyl-*N*-benzoyloxy-pent-4-enamides were synthesised and cyclised using tributyltin hydride and AIBN. A small preference for the *trans* isomer was observed in all cases (10-36%) with the phenyl pendant series giving the highest selectivities. The observed *trans* isomer was not that expected by current theories (Beckwith and Houk model). The effect of the *N*-substituent was found to exert little or no influence on the stereoselectivity of any of the reactions. Due to the difficulties in removing toxic tin residues from the reaction mixture alternative methods for the generation and 5-*exo* cyclisation of amidyl radicals utilising *N*-acyl hydroxamic acids were investigated using $Cu(OTf)_2$ and SmI_2. The effect of concentration, solvent and nature of the *O*-acyl group was found to be significant for the $Cu(OTf)_2$ mediated reactions. Then using copper again this time in the form of CuCl(*N*-pentyl-2-pyridylmethanimine) under atom transfer conditions the cyclisation of prochiral *N*-benzyl/*N*-tosyl-dichloroacetamides in the 5-*exo* mode was investigated. The dichloro-acetamide precursors were readily cyclised with yields and diastereoselectivities generally higher than those previously reported. The methodology was extended to include mono-halogenated precursors with results indicating that tertiary monohalogented precursors cyclised efficiently while primary monohalogented precursors did not, even under forcing conditions. The success of the CuCl(*N*-pentyl-2-pyridylmethanimine) then led to the development of a solid supported version. The ligand was immobilised on aminopropylated silica and used to study the 5-*exo* and 5-*endo* cyclisation of haloacetamides. The sense

and degree of selectivity observed was comparable to that observed for the homogenous catalyst although elevated temperatures were required. A screening program was devised to furnish new more active atom transfer catalysts. The program established that aliphatic amine derived ligands proved to be more efficient atom transfer catalyst than the aromatic pyridine/imine derived ligands. $TrenMe_6$ proved to be the best and was used to investigate the cyclisation of prochiral monohaloacetamides in the 5-*exo* mode with good selectivities observed (9:1-25:1) in favour of the *trans* isomer. Another useful alternative to tributyltin hydride proved to be 1-ethylpiperidine hypophosphite-AIBN and it was used to cyclise various haloacetamides with good diastereoselectivities being observed. However, when using secondary monohaloacetamides significant amounts of reduction and cleaved products were observed in the reaction mixture.

Abbreviations

abs.	Absolute
AIBN	Azobisisobutyronitrile
ap	Apparent
Ar	Aryl
ARTC	Atom transfer radical cyclisation
ATRP	Atom transfer radical polymerisation
Bipy	Bipyridine
Bn	Benzyl
br	Broad
Bu	Butyl
t-Bu	Tertiary butyl
Bz	Benzoyl
CI	Chemical ionisation
d	Doublet
DBN	Diazabicyclononene
DBU	Diazabicycloundecene
dd	Doublet of doublets
d.e.	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
dt	Doublet of triplets
EI	Electron impact
EPHP	1-ethylpiperidine hypophosphite
eq.	Equivalents
Et	Ethyl

g	Grams
HOMO	highest occupied molecular orbital
Hz	Hertz
i	*ipso*
ICP	
i-Pr	isopropyl
IR	Infra-red
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	*meta*
m	Multiplet
M	Molar
Me	Methyl
mg	Milligrams
mmol	Millimole
mol	Mole
m.p.	Melting point
MS	Mass spectrum
Ms	Mesyl
N.M.R.	Nuclear magnetic resonance
n.O.e	Nuclear Overhauser effect
o	*ortho*
p	*para*
Ph	Phenyl
p.p.m.	Parts per million
PTOC	Pyridine-2-thioneoxycarbonyl

q	Quartet
RT	Room Temperature
s	Singlet
SOMO	Singly occupied molecular orbital
sp	Septet
sx	Sextet
t	Triplet
Tf	Trifluoromethane sulphonate
tlc	Thin layer chromatography
TMEDA	Tetramethyl-ethylenediamine
TMS	Trimethylsilyl
Ts	4-Toluenesulfonyl

Chapter 1

Introduction

1.1 General introduction.

Radicals are species that contain at least one unpaired electron which, in contrast to ionic species (anions/cations), react easily with themselves. In the liquid phase most radical-radical reactions occur with diffusion controlled rates.[1] The rates of such reactions can be slowed sterically and such species are normally termed persistent radicals. Electronic stabilisation has little effect on the rates of recombination/disproportionation as the reactions are normally highly exothermic. The high absolute rate constants for radical/radical combination, coupled with the high amounts of initiator often required and significant radical solvent side-reactions, limit the synthetic utility of radical-radical reactions. However, reactions between radicals and non-radicals have a greater scope for synthetic development. They have three distinct advantages over radical-radical reactions in that a non-stoichiometric amount of initiator can be employed, reactions are not diffusion controlled and the concentration of non-radicals can easily be controlled.

Radicals are now considered as valued synthetic intermediates because they can be used for transformations that are often difficult to achieve by other means, in addition radical reactions often show high selectivity and tolerance to functional groups.[2] The kinds of protection schemes that are often essential for ionic reactions are rarely required for radical reactions. Generally, carbon centred radicals only attack functional groups when the bimolecular rate constant k exceeds 10^2 $mol^{-1}s^{-1}$ therefore, carbonyl substituents and heteroatom hydrogen bonds (OH, NH) do not usually pose problems in

radical reactions.[1] However, protecting groups may still be required for other steps in a synthetic sequence, and nearly all popular classes of protecting groups are tolerated.[3]

1.2 Carbon radicals.

The last decade has witnessed an impressive growth in the development and use of radicals in organic synthesis. Much of the effort in this area has centred on the creation of carbon-carbon bonds using carbon centred radicals.[1,4-5] Carbon-carbon bond formation is the most important synthetic step in the construction of more complex organic molecules. This is being increasingly achieved by the addition of carbon centred radicals to carbon-carbon multiple bonds.[1,4-5] The effects that substituents, located on both the carbon radical and the multiple bond have upon the rate and regioselectivity of the addition process have been established.[6-8] The increase in the synthetic applications of radical reactions has been in part due to the large number of mechanistic studies and kinetic information that have been reported.[9]

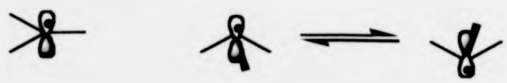
1.2.1 Stability and structure.

The relative stability of substituted carbon-centred radicals can be estimated by applying a simple rule, the lower the bond dissociation of the carbon-hydrogen bond the more stable the radical.[10] Table 1 shows the relative stability and bond dissociation energies of several carbon centred radicals.[11]

Table 1. C-H bond dissociation energies (KJ mol^{-1}).

Allyl	Benzyl	Tertiary	Secondary	Primary	Me	Vinyl	Aryl
360	368	401	402	418	438	439	464

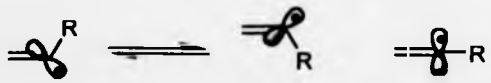
Carbon centred radicals can adopt either a planar or pyramidal structure. Conjugating substituents favour the planar structure while alkyl, electron withdrawing (e.g. F) and heteroatom substituents can cause pyrimidalisation (fig. 1).[12]



Planar Pyrimidal and inverting

Figure 1. Structure of alkyl radicals.

The barrier to inversion in the pyramidal structure is very low and as a consequence stereochemical information at the prochiral centre is lost.[13] Vinyl radicals are usually thought to be bent and also have a low barrier to inversion.[14] However, inversion can be slowed with the introduction of electronegative substituents.[15-16] Vinyl radicals can either exist in the bent form or the linear form (fig. 2). The latter is preferred with conjugating substituents.[3]



Bent and inverting Linear

Figure 2. Structure of vinyl radicals.

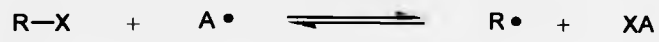
1.2.2 Radical reactions.

Aside from oxidation (to give cations) and reduction (to give anions), most radical molecule reactions can be grouped into two classes. The first of these are atom/group transfer reactions sometimes called abstractions, homolytic substitutions or S_H2

reactions and the second is the addition to π bonds (or the reverse β fragmentation/elimination). The diversity that is available from the reactions of radicals comes from the broad range of reactants that participate in these two fundamental classes.

1.2.3 Atom transfer reactions.

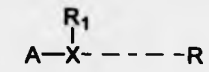
This is a very broad class of reactions in which a univalent atom such as hydrogen or halogen (e.g. I, Br, Cl) or a group (e.g. SR) is transferred from a neutral molecule to a radical to form a new bond and a new radical (eq. 1).



Equation 1. Atom transfer reaction.

The site of the new radical is determined by the location of the abstracted group X. The position of the equilibrium is affected by the relative strengths of the forming and breaking bonds, and hence the rates of such reactions are often paralleled by their exothermicity. Endothermic atom/group transfer is rarely rapid enough to proceed with a useful rate and most exothermic transfers are irreversible under normal reaction conditions.[4]

Radical atom transfer reactions probably proceed through a transition state where the forming and breaking bonds are roughly linear (scheme 1).[17a-b] The reactions are usually thought of as concerted, but the possibility exists that the indicated transition state is actually an intermediate in a shallow energy well, especially for atoms like bromine and iodine.

Atom transfer	Group transfer
	
when X=H or halogen roughly linear, long forming bond	when X=chalcogen roughly T-shaped, long forming bond

Scheme 1. Proposed transition state for atom transfer/group transfer reactions.

Group transfer reactions of chalcogenides are thought to proceed *via* the T-shaped structure (scheme 1), although there is still debate about whether these structures are transition states or intermediates. Most synthetically useful reactions in this class are rapid and have early transition states.[3,18a-b]

Polar factors are important in atom transfer reactions and often play a significant part in the regioselectivity of abstraction.[19] A frequently cited example is the hydrogen abstraction from propionic acid (1) by either the methyl or chlorine radical (scheme 2). In this case the electrophilic chlorine radical (3) abstracts the more electron rich carbon-hydrogen bond to avoid unfavourable polar interactions, whereas the nucleophilic methyl radical (2) preferentially abstracts the more electron poor C-H bond.[4] The electronic characteristics of radicals will be discussed in section 1.2.4.1.1.

Scheme 2. Regioselectivity of hydrogen atom abstraction.

The scope of such reactions both inter/intramolecularly have received a great deal of attention in recent years.[20,21]

1.2.4 Addition reactions.

The most important class of radical reaction is considered to be the addition reaction, as this represents one of the mildest and most efficient ways for the creation of carbon-carbon bonds. Both inter- and intra-molecular addition reactions are important and shall be dealt with in two separate sections. However, the content of each shall be unequally balanced with a bias towards intramolecular addition as this has direct relevance to the research contained within this thesis.

1.2.4.1 Intermolecular addition.

Carbon centred radicals can undergo intermolecular addition to both carbon-carbon double and triple bonds. The formation of a new σ C-C bond (368 kJ mol^{-1}) is at the expense of a π C=C bond (226 kJ mol^{-1}) and is a highly energetically favourable exothermic process.[13] The rate of addition of the radical, and the rate of trapping of the final radical must be greater than that of termination caused by unwanted side reactions for intermolecular addition processes to be successful. Theoretical studies have shown that carbon radical addition to alkenes is along a preferred tetrahedral trajectory with a long forming bond (fig. 3).[22-23]

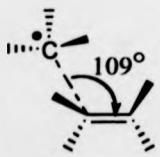


Figure 3. Radical attack on an alkene.

1.2.4.1.1 Electronic nature of carbon radicals.

All carbon-centered radicals can be classified as nucleophilic, electrophilic or ambiphilic depending upon the substituents attached to the carbon atom. The electronic character of the radical will be the main controlling factor in determining their reactivity. Due to the high exothermicity of most additions an early transition state can be postulated for radical addition to alkenes. This allows such reactions to be rationalized using frontier molecular orbital (FMO) theory.[24]

1.2.4.1.1 a) Nucleophilic radicals.

Many radicals are nucleophilic (despite being electron deficient) because they have relatively high lying singly occupied molecular orbitals (SOMO) (e.g. heteroatom-substituted, vinyl, aryl and acyl and most importantly alkyl radicals). The SOMO of the radical can theoretically react with either the lowest unoccupied molecular orbital (LUMO) or the highest occupied molecular orbital (HOMO) of the carbon-carbon multiple bond (fig. 4).[9] Nucleophilic radicals, such as alkyl radicals, react preferentially with electron deficient alkenes which have a relatively low lying LUMO.

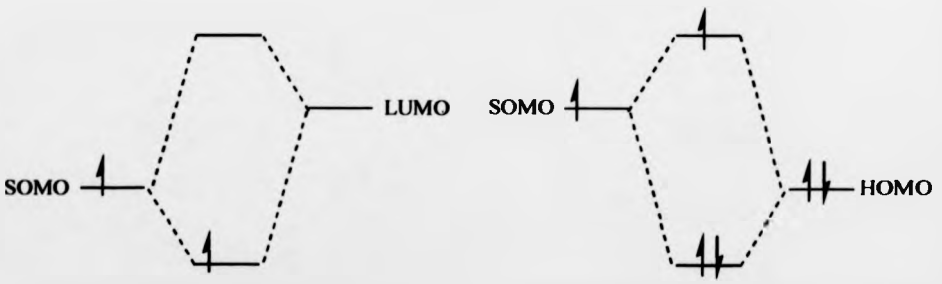
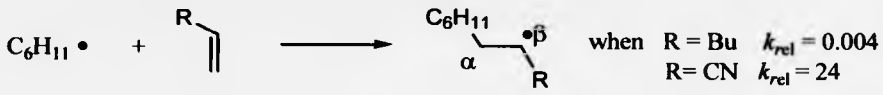


Figure 4. Orbital interactions between electrophilic and nucleophilic radicals and alkenes.

Generally, intermolecular additions of nucleophilic radicals to unactivated alkenes are too slow as to render them synthetically useful. However, the rates of these reactions can be made more efficient by electronic modifications to the alkene partner or the radical itself. The addition of electron donating substituents on the radical centre serves to raise the energy of the SOMO and often gives rise to a small increase in rate, hence the order of reactivity is tertiary>secondary>primary.[25] Conversely, intermolecular additions can be accelerated by as much as a factor of 10^4 by the introduction of an electron withdrawing substituent on the β position of the alkene (eq. 2).[4] Electron withdrawing substituents introduced in the α position also serve to lower the LUMO but the rate of acceleration is not so marked.

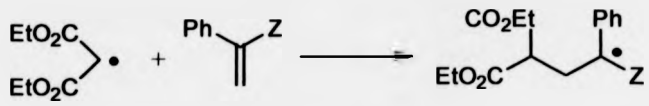


Equation 2. Rate of addition of nucleophilic carbon radicals to β substituted alkenes.

1.2.4.1.1 b) Electrophilic and ambiphilic radicals.

Until recently radicals that contained one conjugated electron withdrawing substituent were considered as electrophilic. The notion that ambiphilic radicals exist as intermediate between both electrophilic and nucleophilic radicals is relatively new. The distinction between electrophilic and ambiphilic radicals is not at all clear. Generally radicals with two electron withdrawing substituents are normally classed as electrophilic, while those with one electron withdrawing substituents will be classed as ambiphilic.

Electrophilic radicals possess relatively low lying SOMO and react preferentially with electron rich alkenes that contain high energy HOMO's. FMO theory predicts that the introduction of electron withdrawing substituents to the radical centre and electron donating substituents on the alkene will have the effect of lowering the SOMO and raising the HOMO respectively, which will increase the rate of such an addition. The introduction of electron donating groups on the alkene only gives rise to modest increases in the rate of addition (eq. 3).[26]



when $Z = CO_2Et$ $k_{rel} = 0.27$
$Z = OMe$ $k_{rel} = 2.1$

Equation 3. Rate of addition of electrophilic carbon radicals to substituted alkenes.

Ambiphilic radicals have SOMO energies that are intermediate between that of nucleophilic and electrophilic radicals. The addition reactions of ambiphilic radicals would be accelerated by introduction of either electron withdrawing or electron donating alkene substituents. This has been confirmed by kinetic studies on such radicals.[26] Both electrophilic and nucleophilic radicals react faster with alkenes than alkynes.[9] This is in direct contrast to nucleophilic anions, as they attack triple bonds faster than double bonds.

1.2.5 Intramolecular addition (cyclisation).

Reactions that form cyclic systems are central to the synthesis of complex natural products. However, it has only been recently recognized that intramolecular radical

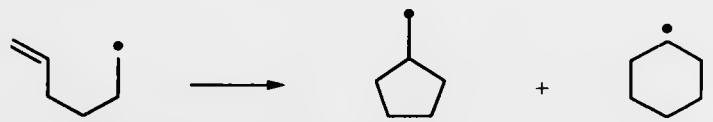
addition reactions are among the most powerful tools available to the synthetic chemist. This section endeavours to outline the scope and limitations of such methodologies. The emphasis will be placed on the regio- and stereo-selective outcome of such reactions.

1.2.5.1 Hexenyl and related radical cyclisations.

Hexenyl radical cyclisations are the most popular class of cyclisation, and have been probed in depth kinetically and mechanistically.[5, 27-28] Cyclisation of these radicals are typically irreversible at normal operating temperatures. 5-*Exo* cyclisations are generally favoured over their 6-*endo* counterparts primarily for stereoelectronic reasons, this is in accordance with Baldwin's rules.[29] Substituent effects on 5-*exo*/6-*endo* selectively are well understood and have been studied in some detail.[30-31]

1.2.5.2 Regioselectivity.

Cyclisation of the simple 5-hexenyl radical (4) at 25°C gives both the 5-*exo* product (5) and the 6-*endo* product (6) in a ratio of 98:2 (scheme 3). The rate of cyclisation has been measured and found to be of the order of 2×10^6 s^{-1} for the 5-*exo* and 4×10^5 s^{-1} for the 6-*endo* cyclisation.[32]



(4) (5) (6)

98% : 2%

Scheme 3. Regioselective outcome of a simple 5-hexenyl radical cyclisation.

The reaction itself is under kinetic control and is highly exothermic and irreversible. High level theory (STO-3G, MM2) seem to indicate that the less strained transition state is that which leads to the smaller ring (5), and that the main product of cyclisation occurs *via* the strain free chair-like transition state (fig. 5).

Figure 5. The chair-like 1,5 transition state.

1.2.5.3 Stereochemistry.

The importance of understanding stereochemistry is a key factor in all areas of chemistry. The significance of stereoselectivity in 5-*exo* cyclisations forms a significant part of the work outlined within this thesis, as such the topic will be discussed at length. The Beckwith-Houk transition state model currently serves as the basis for prediction of stereoselectivity in 5-*exo* hexenyl radical cyclisations. The model is simple to use as it makes unambiguous predictions for most classes of radicals. To work with the Beckwith-Houk transition state model, requires an understanding of the transition states of the hexenyl radical itself. The key details of the transition structures were first deduced by Beckwith, [33] and an in-depth understanding of the details was advanced by the calculations of Beckwith & Schiesser[34] and Spellmeyer & Houk.[31] The Spellmeyer & Houk paper discusses the features of the transition states of the 5-hexenyl radical cyclisation and shows these features are affected by the introduction of substituents.[31]

The hexenyl radical can accommodate the preferred tetrahedral-like approach of the radical to the alkene by folding into either of two conformations. The first conformation was termed the chair (fig. 6) by Beckwith and this formed the basis of the first stereochemical model (Beckwith model) for hexenyl radical cyclisation.[34] The importance of the second conformation was recognised by Spellmeyer and Houk as important to the understanding of many cyclisations, and this was termed the boat (fig. 6).[31]

chair transition state boat transition state

Figure 6. The chair- and boat-like 1,5 transition states.

The stereochemical outcome of the cyclisation of 1-, 2-, 3- and 4-substituted 5-hexenyl radicals have been studied and have been rationalized by the Beckwith-Houk model.[33, 31] The model states that the main products of cyclisation occur *via* a chair-like transition state with substituents preferentially occupying pseudoequatorial positions.

1.2.5.3 a) 1-Substituents.

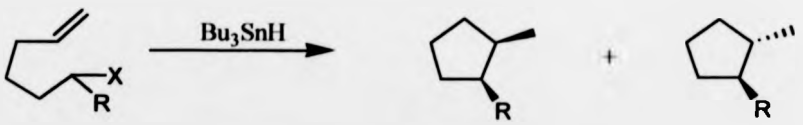
Many types of 1-substituents have been studied, and the *cis/trans* ratios vary over a wide range. The behaviour of the parent 1-methyl hexenyl radical is typical of many of the members of the class. In accordance with the Beckwith-Houk model this provides *cis*-1,2-dimethylcyclopentane as the major stereoisomer (scheme 4), but with modest selectivity (66/34 at 65°C).[31] The *cis* product was presumably formed *via* the chair

equatorial transition state, and the *trans* product presumably arises from both the boat equatorial and the chair axial transition states (fig. 7).[31]

chair equatorial (gives *cis* products) | boat equatorial (gives *trans* products) | chair axial (gives *trans* products)

Figure 7. The lowest energy transition states for the 1-methyl hexenyl radical.

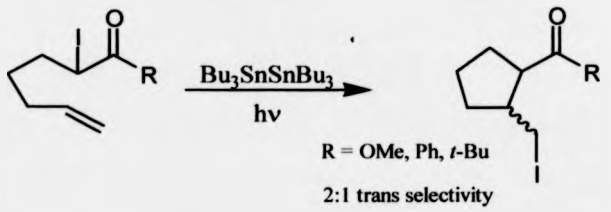
The underlying reasons for the commonly observed selectivity with 1-substituted hexenyl radicals have been the subject of some discussion. The methyl and methylene group are nearly eclipsed in the chair equatorial transition state causing an increase in energy (fig. 7).[31] However, calculations by Spellmeyer and Houk suggest that because the forming bond is very long in the transition state, the energetic penalty for eclipsing the two groups is very small. The cyclisation of substrates containing more bulky substituents in the C-1 position can lead to *trans* selectivities, which contravenes the Beckwith-Houk model. A point in case is the 1-*t*-butyl hexenyl radical (scheme 4), cyclisation of this radical exhibits *trans* selectivity.[35] The increased interaction between the *t*-butyl and methylene group in the chair equatorial transition state is likely to be the causing factor.



when R = Me 66/34
R = *t*-Bu 25/75

Scheme 4. Cyclisation of 1-substituted hexenyl radicals.

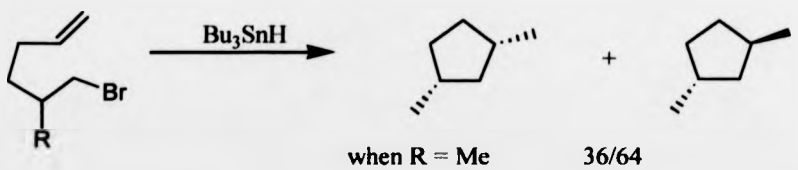
There are also a few other cases where modest *trans* selectivity has been observed. Reactions of carbonyl substituted radicals have been studied by a number of groups, often conducted under atom transfer conditions.[36] Low selectivities are typically observed and the *trans* isomer is frequently favoured over the *cis* (scheme 5).[37]



Scheme 5. Atom transfer cyclisation of carbonyl substituted 1-hexenyl radicals.

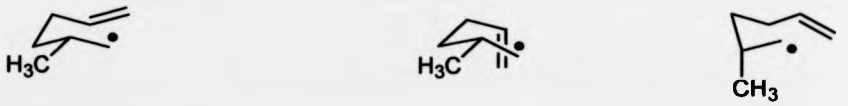
1.2.5.3 b) 2-Substituents.

The Beckwith-Houk model predicts that 2-substituted hexenyl radicals should cyclise to give *trans* 1,3-di-substituted cyclopentanes. A literature survey would seem to suggest that the model is an excellent generalization for carbon radicals. The 2-methyl hexenyl radical provides a 36/64 ratio of *cis/trans* 1,3-dimethyl cyclopentanes (scheme 6). Spellmeyer and Houk indicate the major product again comes from the chair equatorial transition state (fig. 8).[31]



Scheme 6. Cyclisation of 2-methyl hexenyl radical.

The minor *trans* product arises presumably from the boat equatorial and the chair axial transition states (fig. 8). Other 2-substituted radicals tend to give variable *trans* selectivities depending on the nature of the substituent.[3] Smaller ether substituents exhibit no selectivity[38] but large alkyl or aryl substituents give increased selectivity.[39]

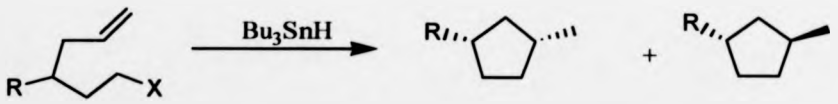


chair equatorial (gives *trans* products) | boat equatorial (gives *cis* products) | chair axial (gives *cis* products)

Figure 8. The lowest energy transition states for the 2-methyl hexenyl radical.

1.2.5.3 c) 3-Substituents.

The predicted 1,3-*cis* di-substituted cyclopentanes are typically observed with modest *cis* selectivities. The 3-methyl hexenyl radical (7) closes to give 1,3-dimethyl cyclopentane in a 71/29 ratio at 80°C (scheme 7).



when R = Me (7) — 71/29
R = *t*-Bu (8) — 85/15

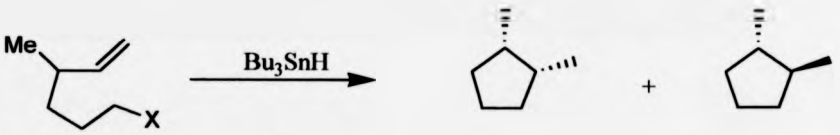
Scheme 7. Cyclisation of 3-substituted hexenyl radicals.

The increased selectivity in the *t*-Bu case (8) (scheme 7) can be attributed to the fact that the large *t*-butyl group resists occupying an axial position.[40] For reasons that are

not known, electronegative substituents can erode this selectivity and certain fluorinated esters even provide good levels of *trans* selectivity.[41]

1.2.5.3 d) 4-Substituents.

The 4-substituted hexenyl radical typically exhibits the highest selectivities of any of the simple hexenyl radicals. Closure of the 4-methyl hexenyl radical provides predominantly the *trans* isomer (scheme 8). Cyclisation of haloacetals,[42] haloesters[43] and haloamides[44] provide efficient routes to lactones and lactams, and the use of sulfonyl or carbonyl nitrogen substituents promotes the formation of *cis* products.[45]



ratio *cis*/*trans* = 17/83

Scheme 8. Cyclisation of 4-methyl hexenyl radical.

1.2.6 Methods to perform carbon radical reactions.

There are many different types of transformations that can be conducted *via* the use of radicals, however there are relatively few methods to conduct radical reactions. Any suitable method must be able to generate radicals from non-radicals site selectively, allowing the radicals sufficient time to react and to trap out the product radical formed prior to radical/radical or radical/solvent termination. The type of method utilised will determine the fate of the intermediate radical.[3] Identical radicals generated by different methods may have different life-times and hence, provide different products.

The rate constants for many of the most popular types of reactions are now available, and so an appropriate method can generally be selected in advance.[3]

1.2.7 Chain reactions.

Radical reactions are most commonly conducted in chains because the chain transfer step conveniently links the generation of an initial radical from a suitable precursor with the trapping of the final radical to form a stable product. Chain reactions comprise of initiation, propagation and termination steps. The initiation step generates radicals from non-radicals, while the termination steps act in the opposite manner forming non-radicals. All desired transformations occur in the propagation steps, which can involve inter-/intra-molecular reactions of radicals with non-radicals.[5]

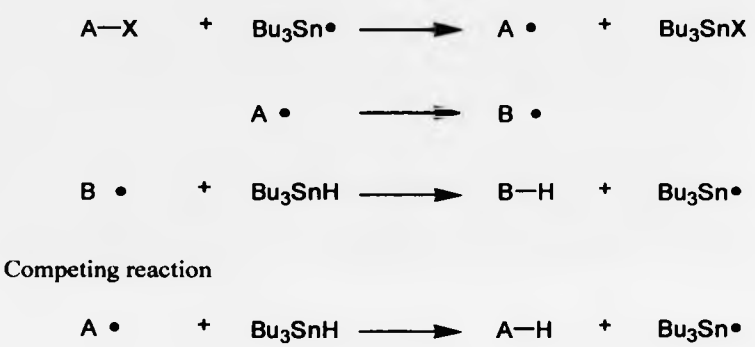
Initiation can be accomplished by photochemical or redox action on a initiator (e.g. AIBN, BPO) but is most often achieved by homolytic bond cleavage of an initiator by the action of heat. The amount of initiator used depends on the efficiency of the chain (chain length) and temperature. The concentration of radicals generated are controlled by the rate of the initiation which is typically slow thus, keeping the concentration of radicals low and so reducing undesired radical/radical terminations.[3]

1.2.8 Metal hydrides.

1.2.8.1 Tributyltin hydride & *tris*(trimethylsilyl) silane $(TMS)_3SiH$ methods.

These two compounds are the most popular among an increasing collection of reagents for conducting metal hydride radical reactions. The chain for Bu_3SnH[46] mediated

reactions is shown in scheme 9 and an analogous chain can be written for $(TMS)_3SiH$.[47] Abstraction of an atom or group X from a precursor by the $Bu_3Sn^{\cdot}$ radical generates the initial radical $A^{\cdot}$ which then undergoes a transformation (inter- or intra-molecularly) to provide a new radical $B^{\cdot}$. Hydrogen atom transfer then forms the final product B-H and regenerates the tributyltin radical to continue the chain.



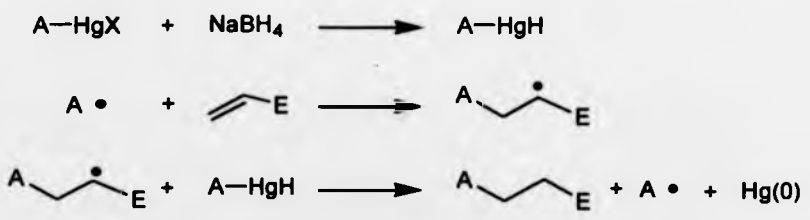
Scheme 9. Chain reaction using tributyltin hydride.

The standard problem in both tin and silicon hydride reactions is the premature reduction of $A^{\cdot}$ by the reagent itself. If the rate of conversion of $A^{\cdot}$ to $B^{\cdot}$ is slow, then it is common to use low concentrations of the hydride reagent to reduce the rate of the competing reaction (scheme 9). Syringe pump techniques are often used to maintain a steady, low concentration of this reagent. Other techniques used include polymer bound tin hydrides, [48-50] and the generation of trialkyltin hydrides *in situ* by reaction of a catalytic amount of tin halide with a standard reducing agent ($NaBH_4$ or $NaCNBH_4$).[51-53] The use of $(TMS)_3SiH$ instead of Bu_3SnH is advantageous as $(TMS)_3SiH$ is a poorer hydrogen donor, therefore lower rates of hydrogen transfer are achieved often leading to less premature reduction of $A^{\cdot}$.[47]

Many radical precursors can be used in both the $(TMS)_3SiH$ and the tin hydride method. Beckwith and Pigou devised a scale of reactivity of various substrates towards reduction by trialkyltin hydride.[54] They found that the order of reactivity towards S_H2 attack by the tributyltin radical is I>Br>PhSe>secondary and tertiary xanthate esters>tertiary nitro>Cl>*p*-CNC_6H_4S>PhS>*p*-MeC_6H_4S>MeS. For the least reactive alkyl chlorides and alkyl phenyl sulfides the rate of abstraction may not be sufficient to propagate a chain even with a rapid intermediate cyclisation. The degree of stabilisation of the initial radical is also an important factor, hence $XCH_2CO_2Et>RCH_2OCH_2X>RCO_2CH_2X>RCH_2X$.[54]

1.2.8.2 Mercuric hydrides.

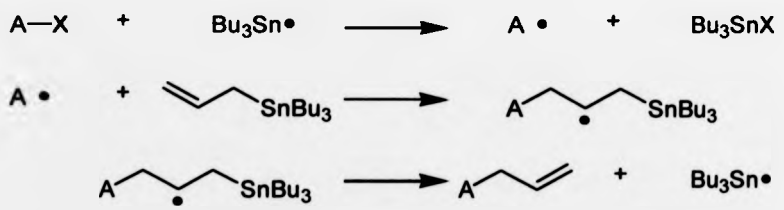
Related reactions of *in situ* generated mercuric hydride have also been frequently used.[3] These reactions have several advantages over their tin counterparts as they are easy to conduct at ambient temperatures, are rapid, clean and easy to purify. However the reduction is fast due to the superior hydrogen transfer from mercuric reagents. This methodology is typically used for the rapid addition of nucleophilic radicals to electron poor alkenes as summarised in scheme 10.[55-56]



Scheme 10. Chain reaction for mercuric chloride.

1.2.8.3 Fragmentation method.

The fragmentation method involves the generation of the chain transfer agent by a fragmentation rather than by hydrogen atom abstraction. Instead of obtaining reduced products, substitution products are formed as an alkene is regenerated in the fragmentation step. The process makes use of the fact that relatively weak bonds such as C-Br, C-SnR and C-SR can fragment if they are located β to a radical. Allyl stannanes have become the most popular reagents for this method. The accepted chain mechanism for allylation with allyltributylstannane is shown in scheme 11. Abstraction of X (normally a halogen) by the tributyltin radical is followed by the addition of the generated radical A˙ to allyltributylstannane. Rapid β–fragmentation then provides the allylated product and the regenerated tributyl tin radical.[3] Vinylations can also be accomplished by this approach.[57]



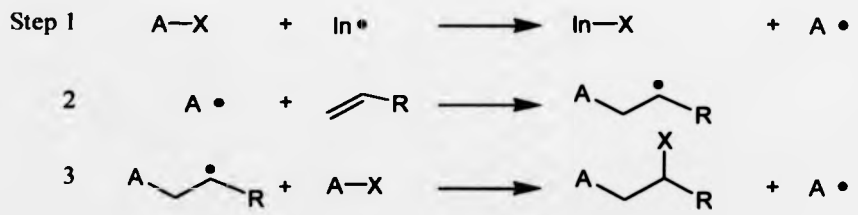
Scheme 11. Chain reaction for allyltributylstanne mediated allylation.

This approach has many of the advantages of the tin hydride method without the associated liability of premature trapping of A˙ by the metal hydride. Since the addition of most radicals to allyltributylstannane is not a particularly fast reaction, it is often possible to conduct one or more reactions in between radical generation and allylation.[58] The power of the method lies in the fact that the β–fragmentation process

is rapid and unimolecular. Reactions with allylstannanes are easy to conduct,[59] and a number of related reagents have also been used.[60-61]

1.2.8.4 Atom transfer.

As a significant amount of the work reported in this thesis utilises the generation of radicals *via* metal-mediated atom transfer reactions this section will be discussed at length. Transformations in which the chain transfer step involves a homolytic substitution of a product radical with that of a precursor, belong to the atom or group transfer methods. Primarily developed by Kharasch, the addition of a reagent X-Y across a carbon-carbon multiple bond has by this approach become an important reaction in free radical chemistry.[62] A generalized mechanism for this class of reaction is shown in scheme 12. The atom or group X in A-X acts as both the radical precursor and the radical trap.[3]



Scheme 12. Atom transfer reaction scheme.

The limiting factor is the rate of atom transfer in step 3. If this is too slow then polymerization can occur. Generally, the more exothermic the atom transfer step the less chance of any telomerisation. This is usually achieved by using reactive iodides as radical precursors.[3] Julia has studied hydrogen atom transfer cyclisations, but while

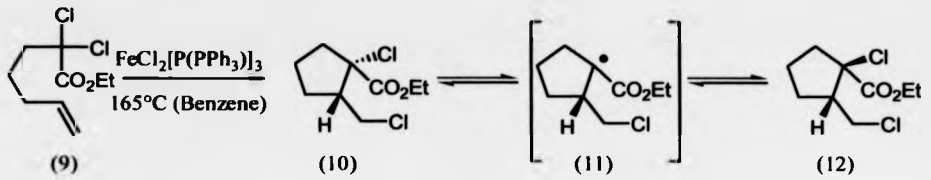
hydrogen atom transfer reactions are well known they have limited synthetic usefulness.[21] Halogen atom transfer reactions however have much more scope for synthetic development.

1.2.8.4.1 Transition metal mediated halogen atom transfer reactions.

The last decade has seen the emergence of transition metal promoted atom transfer radical reactions as a useful alternative to the stannane based radical chemistry, mainly due to the excellent work of Kharasch[62] and others.[63-64] The advantages of transition metal mediated atom transfer are that it is not a reductive process and reactions usually terminate with the inclusion of functionality. Another distinct advantage is the reaction work up does not involve the problems associated with the removal of the toxic tin side products formed in the stannane case. Seemingly the most popular types of transition metal systems tend to be based on iron, ruthenium, and copper although other metals have been utilised.[20]

1.2.8.4.1 a) Iron complexes.

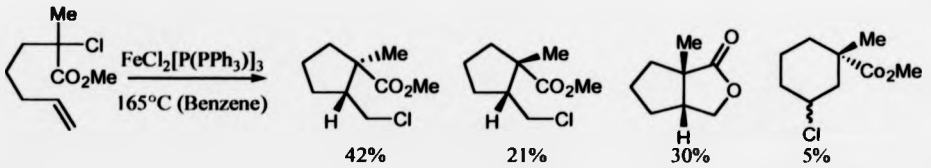
Iron (II) complexes act as good catalysts in promoting the Kharasch reaction with various halocarbons and alkenes.[65-68] Iron (II) complexes generate radicals *via* reductive processes which are terminated by halogen atom transfer. Weinreb has utilized iron (II) in the form of $FeCl_2[P(PPh_3)]_3$ in the intramolecular addition of unsaturated α,α-dichloroesters (9) (scheme 13).[69]



(9) (10) (11) (12)

Scheme 13. Iron mediated intramolecular addition of α,α-dichloroesters.

The ratio of diastereoisomers (10/12) was found to be dependent upon catalyst concentration and the reaction time. These variances were attributed to isomerisation *via* reversible α-chlorine abstraction and recombination *via* the planar radical (11). The scope of this methodology was extended to encompass less activated α-chloroesters (13) with a high degree of success.[70] Generally, these reactions were high yielding, however they produced a complex mixture not only of the *exo*-products (14), (15) and *endo*-closure products (17) but also the lactone (16) (30%) as shown in scheme 14.



42% 21% 30% 5%

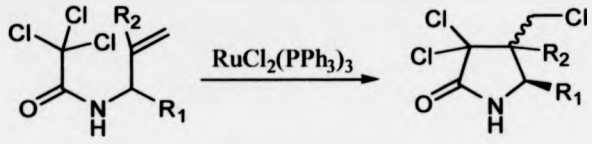
(13) (14) (15) (16) (17)

Scheme 14. Iron mediated intramolecular addition of α-chloroesters.

The reaction rate for the α-chloroester (13) was considerably slower than for the dichloro analogue (9) due to slower formation of the initial α-carboxylate stabilised radical. Fe-$FeCl_3$ has been shown to promote the cyclisation of *N*-allyl-*N*-benzyl-2,2-dichloroacetamides although in poor yields.[71] Very recently Fe (II) *tris*-pyridine-2-ylmethyl-amine has been utilized in the synthesis of various lactones.[72]

1.2.8.4.1 b) Ruthenium complexes.

Matsumoto reported that $RuCl_2(PPh_3)_3$ catalysed the addition of α-chloroesters to alkenes.[73] Itoh then developed this complex in the preparation of γ-lactams as an alternative to the conventional method of cyclisation *via* acyl-nitrogen bond formation. Itoh showed that secondary amides (18) underwent 5-*exo* cyclisation in modest yields (scheme 15).[74]

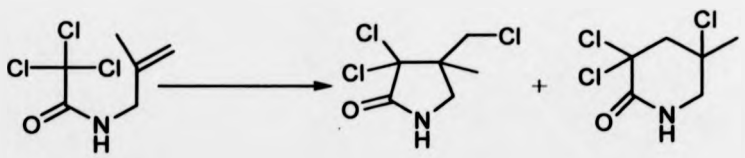


(18) (19)

where R_1 and R_2 = H, Me

Scheme 15.

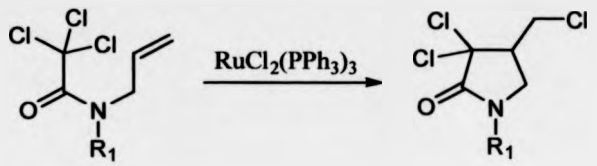
No δ-lactams were detected in any reactions with the exception of (20). This was rationalized by the increased steric hindrance around the *exo*-carbon (scheme 16).



(20)

Scheme 16.

The introduction of a third nitrogen substituent R_1 (21) caused significant improvements in the yield (scheme 17).

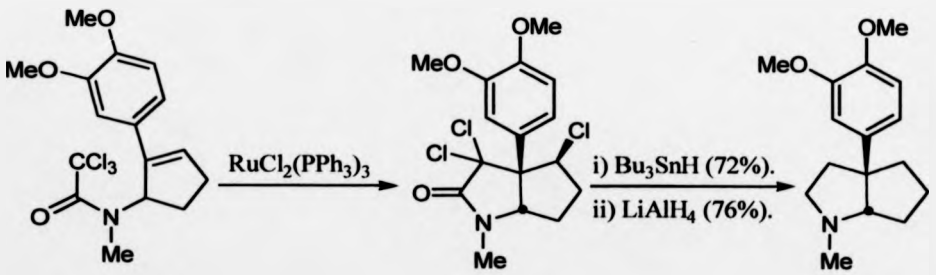


(21) (22)

where R_1 = H (68%)
$CH_2CH{=}CH_2$ (84%)

Scheme 17.

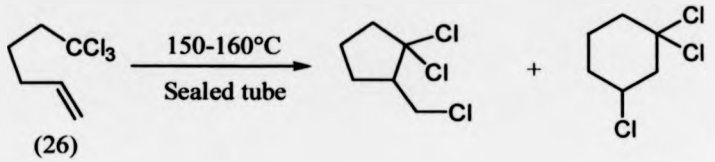
$RuCl_2(PPh_3)_3$ was used to cyclise *N*-allyl-trichloroacetamides with cyclohexenyl or cyclopentenyl (23) groups that were appropriately substituted to form the corresponding *cis* fused trichlorinated γ-lactams (scheme 18).[75] Furthermore, reductive dechlorination by Bu_3SnH followed by reduction with $LiAlH_4$ gave pyrrolidine alkaloid mesembrine (25) in a yield of over 70% in both steps.[75]



(23) (24) (25)

Scheme 18.

Bergbreiter developed an excellent bi-phasic polymer-bound ruthenium (II) catalyst and showed its application to intramolecular addition of trichloroalkenes (26).[76] Comparison with the unsupported catalyst proved favourable, as shown in the scheme below (scheme 19).



(26)

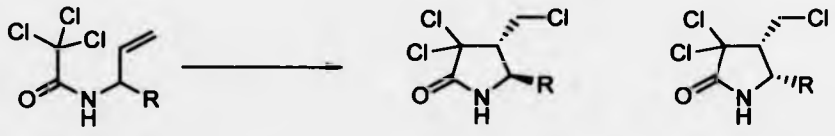
$RuCl_2(PPh_3)_3$	5 mol%	79%	10%
$RuCl_2(PEPPh_2)_3$	0.4 mol%	72%	8%

Scheme 19. Comparison between Ru bound catalyst and the conventional Ru catalyst.

Weinreb *et al* utilized $RuCl_2(PPh_3)_3$ in the cyclisation of trichloroalkenes (27) and (28) and found that the regioselectivity was dependent on their structures.[77] Trichloroalkene (27) gave the expected *exo* closure products, however trichloro-substituted ketone (28) gave predominantly *endo* closure.[77]

(27) (28)

Itoh followed up his initial work on secondary *N*-allyl-trichloroacetamides to investigate the stereochemical outcome of substituted trichloroacetamides (29) (scheme 20), observing good diastereoselectivity in favour of the *trans* isomer (30).[78]

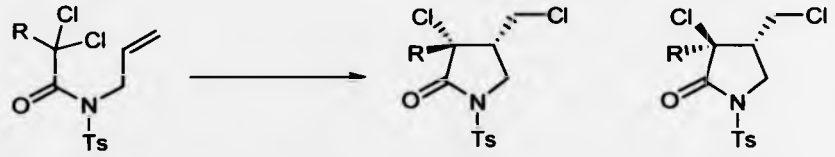


(29) (30)

R = Me	84	16
R = Ph	100	0
R = *n*-Pr	89	11

Scheme 20. Diastereoselectivity in the cyclisation of substituted trichloroacetamides.

Slough studied the cyclisation of prochiral *N*-tosyl acetamides (31) under $RuCl_2(PPh_3)_3$ catalysis.[79] Slough showed that a smooth transition from predominantly *trans* (33) to *cis* (32) selectivity occurred as R increased in size from methyl (scheme 21).



(31) (32) (33)

R = Me	27	73
R = *i*-Pr	77	23
R = CH_2Ph	95	5

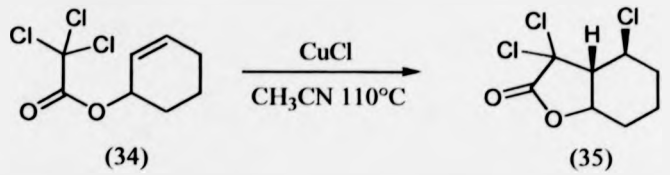
Scheme 21. The effect of substituent R on the stereochemical outcome of cyclisation for *N*-tosyl acetamides.

With very large alkyl substituents (*t*-amyl) no *trans* isomer was observed. However, yields proved to be moderate and in the range of 54-70%. Slough then investigated the ruthenium isomerisation of the α-chloro-*N*-tosyl-2-pyrrolidinones and concluded that the rate of isomerisation was too slow to alter the steroeselectivity to any significant extent in the reaction time scale of 4 hours.[80] The second main conclusion was in agreement with Weinreb that α-chlorine abstraction was the most reasonable mechanism for the isomerisation process (section 1.2.8.4.1 a).

1.2.8.4.1 c) Copper complexes.

Itoh has shown that cuprous salt catalyses the intramolecular addition of *N*-alkyl trichloroacetals to form the corresponding trichlorinated γ-lactones.[74, 81-82] The stereochemical outcome was found to be dependent on the structure of the starting trichloroacetates. Cyclisation of 2-cyclohexyl trichloroacetate (34) gave the *cis* fused

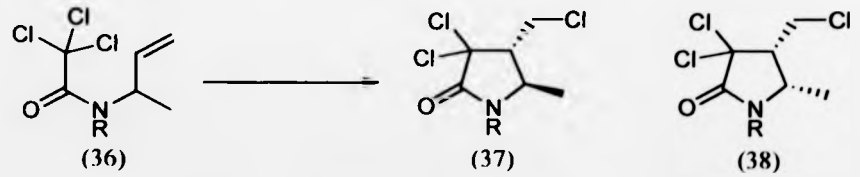
lactone (35) (scheme 22), whereas the corresponding alicyclic precursors gave *trans* substituted lactones.



(34) (35)

Scheme 22. Copper mediated cyclisation of 2-cyclohexyl trichloroacetate (34).

The stereoselectivities in the Cu(I)-catalysed cyclisation of *N*-substituted trichloroacetamides (36) were dependent on the protecting group (scheme 23). Cyclisation of either the *N*-benzyl- (36a) or *N*-methyl-*N*-allyl-trichloroacetamide afforded the corresponding *trans* isomer predominantly. On the other hand, cyclisation of *N*-tosyl (36b), *N*-mesyl, *N*-Cbz, or *N*-*t*-Boc analogues provided the corresponding *cis* isomer with good stereoselectivity.[83]



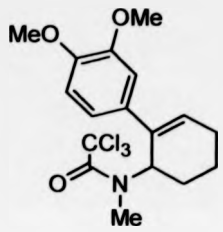
(36) (37) (38)

a) R = CH_2Ph 93% (95:5)
b) R = Ts 90% (15:85)

Scheme 23. Effect of the *N*-protecting group on the cyclisation of *N*-substituted trichloroacetamides.

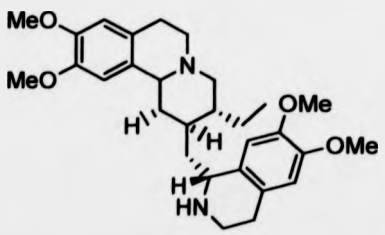
A similar effect has also been reported for the $RuCl_2(PPh_3)_3$ catalysed reaction of trichloroacetamides. Itoh's research also showed that Cu(Bipy)Cl catalysed the cyclisations much more rapidly than CuCl alone, or $RuCl_2(PPh_3)_3$. Other bidentate

ligands such as tetramethylethylenediamine (TMEDA) and sparteine were also effective as ligands. The rate of reaction was also shown to be solvent dependent. Use of THF or dichloroethane as the solvent gave rates comparable to dichloromethane, whereas reaction in acetonitrile was slower. Cyclisation of certain *N*-allyl-trichloroacetamides have been utilized in the stereoselective synthesis of several bicyclic lactams, which possess the pyrrolidine alkaloid skeletons. Mesembrane has been synthesised in good yields by the Cu(I)-catalyzed cyclisation of the *N*-allyl-trichloroacetamide (39).[75]



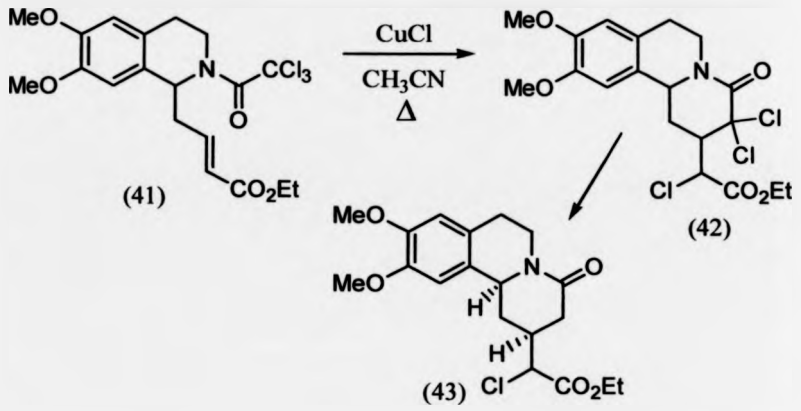
(39)

Cu(Bipy)Cl methodology has also been extended to the sequencing of both intramolecular and intermolecular reactions of α,α,α-trichloroacetamides.[84] Yamazaki and co workers have achieved the formation of six-membered rings by halogen atom transfer cyclisation as a model reaction towards the synthesis of the alkaloid emitine (40) (scheme 24).[85] Thus the treatment of the trichloroacetamide (41) with CuCl in CH_3CN in a sealed tube at 140°C formed the intermediate by 6-*exo* radical cyclisation (42).



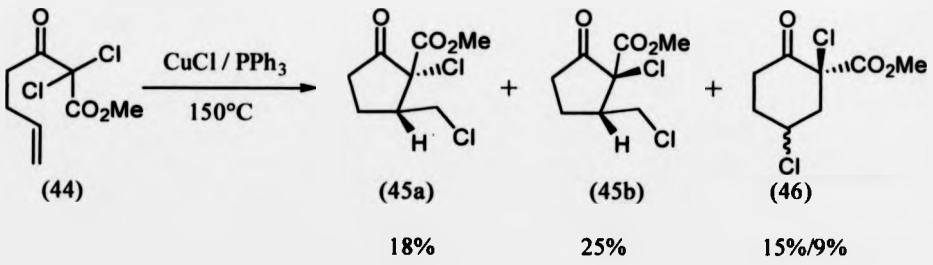
(40)

Reductive removal of the chlorine atoms α to the carbonyl group afforded the key precursor (43) in 93% yield.



Scheme 24. Halogen atom transfer cyclisation as a model reaction towards the total synthesis of emitine.

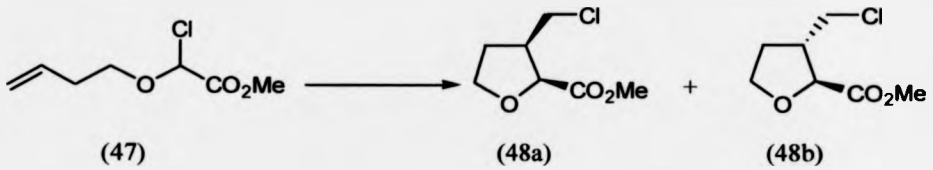
Cyclisation of the α,α-dichloro-β-keto ester (44) with CuCl-PPh_3, has been shown (scheme 25) to proceed to give a mixture of *exo* products (45a-b) and two *endo* cyclisation products (46)[20].



Scheme 25. Cyclisation of α,α-dichloro-β-keto ester (44).

Speckamp *et al* developed the use of a catalytic Cu(Bipy)Cl system in the treatment of 2-(3-alken-1-oxy)-2-chloroacetate (47) to give good yields of 3-(1-chloroalkyl)-2-

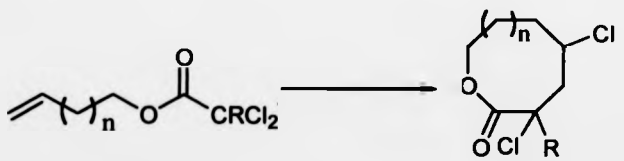
tetrahydrofuran carboxylic esters (48).[86] The stereochemical course of the radical cyclisation showed a preference for the formation of 2,3-*cis* substituted tetrahydrofurans (48a) in all cases (scheme 26).



(47) (48a) (48b)

Scheme 26.

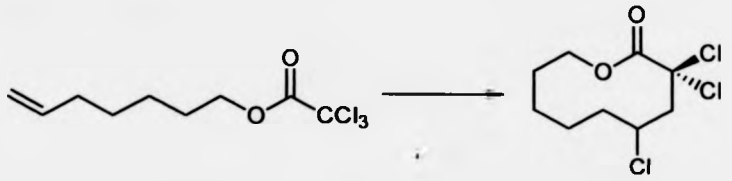
Speckamp also showed that medium sized lactones (49) (eight to eleven membered rings) are effectively formed by Cu(Bipy)Cl catalyzed cyclisation of various alkenyl di- and tri-chloroacetals (50) at temperatures ranging from 80 to 190°C (scheme 27).[87] One notable exception was the cyclisation in either the 6-*exo* or the 7-*endo* mode which failed. Only telomerisation products could be detected. This was thought to be due to the unwillingness of the ester group to adopt a *trans* conformation during the cyclisation.



n= 1 - 4 (49) (50)

Scheme 27.

Verlhac recently reported the use of copper *tris*-pyridin-2-ylmethyl-amine in the cyclisation of hept-6-enyl trichloroacetate (51) which was successful in direct contrast to Cu(Bipy)Cl (scheme 28)[72].



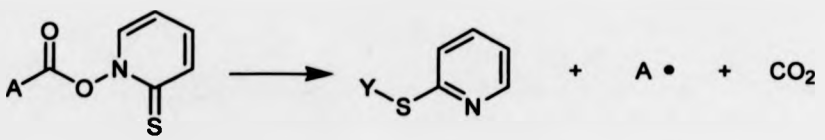
(51) 70%

Scheme 28. Copper *tris*-pyridin-2-ylmethyl-amine mediated cyclisation of hept-6-enyl trichloroacetate.

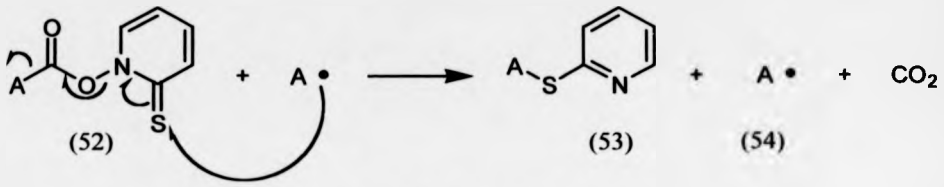
Ghelfi reported the use of $CuCl(TMEDA)_2$ in the cyclisation of *N*-allyl-*N*-benzyl-2,2-dichloro-2-alkylacetamides at RT and claimed it to be superior to both Cu(Bipy)Cl and $RuCl_2(PPh_3)_3$.[71] While it was possible to mediate cyclisations using $CuCl(TMEDA)_2$ at RT conversions were often low with poor diastereoselectivities.

1.2.8.5 Group transfer (thiohydroxamate method).

The thiohydroxamate method was developed by Barton and involves the use of thiohydroxamate esters (eq. 4).[88-89] The method involves a thiopyridyl group transfer reaction, but differs from the reactions previously described in that the group is transferred by an addition/elimination mechanism rather than a homolytic substitution as shown in scheme 29.[3]



Equation 4. The basic reaction.



Scheme 29. Propagation.

Precursors (52) are usually derived from carboxylic acids, and decarboxylation occurs during the course of the reaction. The precursor (52) serves as the trap for the product radical (54). Other reactions of radical A˙ (54) (addition, cyclisation etc.) are possible provided that they are faster than the group transfer reaction with the precursor (52). Furthermore, addition of better radical traps (X-Y) than the precursor (52) can provide an assortment of other products (eq. 5). Trapping with a heteroatom can enable a functional handle to be attached and exploited later in a synthetic sequence.

Equation 5.

In all of these more sophisticated reactions, the competing reaction of initial radical A˙ (54) with (52) can be minimised by keeping a low concentration of (52). This is usually achieved by the use of slow addition techniques such as the use of a syringe pump or addition using large dilutions.

1.2.9 Other methods.

Non-chain methods can involve radical/radical coupling, oxidation and reduction. Radical/radical coupling can only be selective if the rates of all possible couplings are not the same. Reactions of organocobalt complexes are good examples of this method.[20] Oxidative methods are often based on $Mn(OAc)_3$. In this approach radicals are trapped by oxidation to a cation or by (oxidative ligand transfer).[90] Reductive generation of radicals is usually followed by reductive trapping to form anions. Many one-electron reducing agents have been used with samarium (II) iodide being the most popular.[91]

1.3 Nitrogen centred radicals.

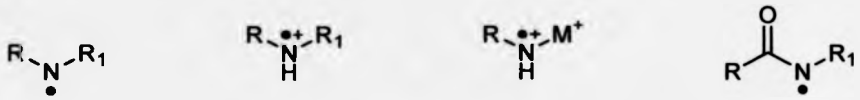
1.3.1 Introduction.

The use of nitrogen centred radicals in organic transformations is becoming increasingly popular in synthetic organic chemistry.[92] However, nitrogen centred radical reactions are less well developed than those of their carbon counterparts, even though the potential in the areas of alkaloid and heterocyclic chemistry is considerable.[93] The electronic nature of the nitrogen-centred radical is crucial to its mode of reaction and is controlled by the reaction conditions and the radical precursor employed.[92]

The main types of nitrogen centred radical are:-

- Neutral aminyl radicals (amino radicals) (55) - nucleophilic
- Aminium cation radicals (protonated aminyl radicals) (56)- electrophilic

- Metal complexed aminyl radicals (57) - electrophilic
- Amidyl radicals (58)– electrophilic



(55) (56) (57) (58)

Figure 9. Types of nitrogen centred radicals.

While there are other examples of nitrogen radicals (e.g. sulfonamidyls, iminyl and urethanyl radicals) these are beyond the scope of this thesis. Amidyl radicals will now be examined in more detail as these have a direct relevance to the work contained within this thesis.

1.3.2 Amidyl radicals.

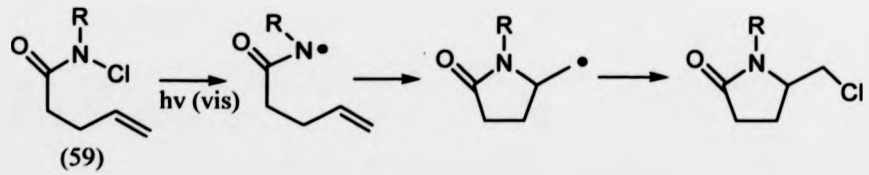
Amidyl radicals are thought to be intermediate in reactivity between the nucleophilic neutral aminyl radicals and electrophilic aminium cation radicals, due to the electron-withdrawing ability of the carbonyl group. They have the advantage therefore of increased electrophilicity without the need to generate them in acidic media. The ability to work in neutral conditions is important when there are other acid-sensitive groups in the compound. E.S.R. studies have shown that the amide radical is best described with location of the radical centred on N in a 2p orbital.[94] This has been used to explain the observation for intramolecular H-abstraction with preferential transfer of H to N rather than O.[95]

Amidyl radicals have been prepared from a variety of different precursors such as *N*-chloro and *N*-nitroamides and more recently from *N*-acyl-alkyl PTOC carbamates and *O*-benzoyl hydroxamic acids. Although the above list is not exhaustive they will be the methods discussed in more detail.

1.4 Precursors for amidyl radicals.

1.4.1 *N*-halo (59) and *N*-nitrosoamides (60).

Originally amidyl radicals were generated by UV photolysis of *N*-chloroamides (59) and *N*-nitrosoamides (60). In molecules with a suitably situated double bond the radicals were found to undergo efficient 5-*exo* cyclisation in neutral media, to form substituted 2-pyrrolidinones and substituted pyrrolidine amides *via* an atom transfer mechanism (Scheme 30). These cyclisation reactions are often complicated by competing 1,5-H-atom abstraction, a sequence that is promoted by the presence of the halogen radicals that are formed on initiation, especially Br. This side reaction can be suppressed by the presence of cuprous ions which scavenge the halogen radicals and thus yields of the cyclisation products improve.[93]

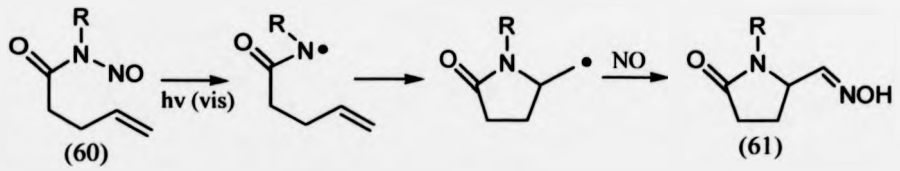


Scheme 30. Photolysis of *N*-chloroamides.

N-chloroamides (59) can be prepared by chlorination of deprotonated lithium amide derivatives with *N*-chlorosuccinimide or simply by treatment of the corresponding

amides with commercial bleach. *N*-haloamides are relatively strong oxidising agents that are not always easily prepared and handled, especially in the context of complex or fragile molecules. Their high reactivity makes it difficult sometimes to dissociate their ionic from their radical chemistry.[96]

N-nitrosoamides (60) are characterised by their orange-yellow colour and are thermally stable only at or below RT. Their thermal stability is very much dependent upon the structure of the parent amine and on the acyl group. In general, the nitrosoamides derived from primary, secondary and tertiary *N*-alkylamines show increasing instability, whereas those derived from aromatic amines show a wide range of stability depending on the substituent group. They are prepared by nitrosation of *N*-alkylamides with excess sodium nitrite in a mixture of acetic acid and acetic anhydride.

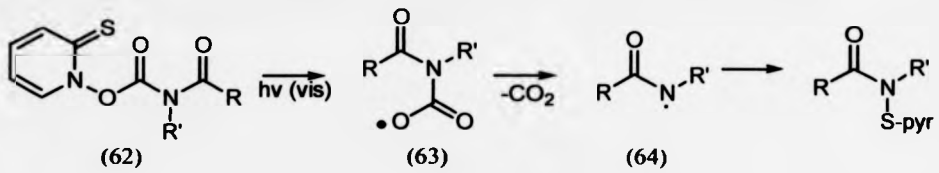


Scheme 31. Photolysis of *N*-nitrosoamides.

Scheme 31 shows the photolysis of *N*-nitroso amide (60) to produce both the 2-substituted pyrrolidinones and (61). In these particular reactions trapping is facilitated by the free NO present, which then tautomerises to give the more stable oxime (61). A further limitation in the reaction of *N*-halo and *N*-nitrosoamides are that only products of halogen atom transfer or nitroso group transfer are usually obtained after the radical addition step.

1.4.2 *N*-acyl-*N*-alkyl PTOC carbamates.

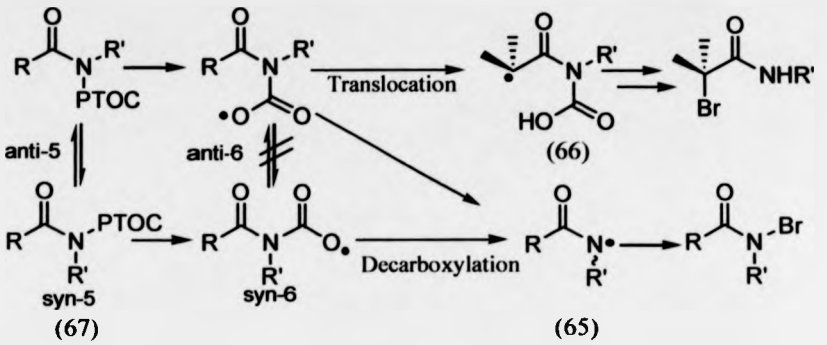
It has been shown that PTOC imidates ester react in chain reactions to give amidyl radicals.[97] More recently however, research has shown that amidyl radicals can also be generated from (62) (Scheme 32).[98] These particular precursors are more stable than the PTOC imidate esters and are as such more synthetically useful. Visible light irradiation of precursor (62) or radical addition to the thione functionality initially generates an *N*-acylcarbamoyloxyradical (63) which decarboxylates rapidly to generate an amidyl radical (64) (the carbamoyloxy radical's lifetime is, in fact too short for its detection).



(62) (63) (64)

Scheme 32. Photolysis of *N*-acyl-*N*-alkyl PTOC carbamates.

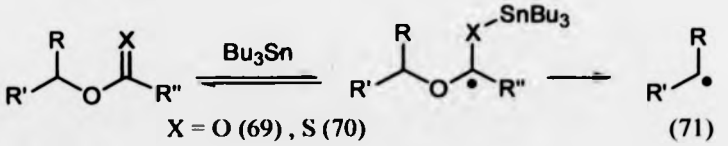
The decarboxylation of *N*-acylcarbamoyloxy radicals is, however, slower than 1,5 hydrogen atom abstraction of a suitably reactive α-hydrogen atom (scheme 33).[98] Hence amidyl (65) or α-amide radicals (66) are formed depending on whether decarboxylation or translocation occurs. Decarboxylation to generate amidyl radicals was found to be the dominant pathway when a bidentate Lewis acid, (e.g. $MgBr_2$) was present. It appears that the Lewis acid complexes the carbonyl groups of the carbamoyloxy radical thus giving the *syn-5* (67) conformation from which translocation was not possible.



Scheme 33. Mechanistic pathways of *N,N*-diakyl PTOC carbamates upon radical addition/photolysis.

1.4.3 *O*-benzoyl hydroxamic acid derivatives.

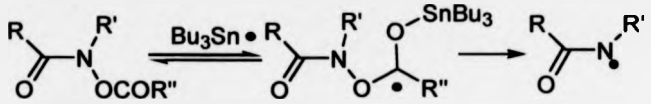
Zard has recently shown that amidyl radicals can be formed by the cleavage of *O*-benzoyl hydroxamic derivatives (68).[96] Earlier work had shown that the cleavage of oxime benzoates with stannyl radicals gave iminyl radicals.[95] The cleavage of ordinary esters (C=X = C=O) (69) with tributylstannane was described some time ago by Khoo and Lee but it has limited applicability as a method of radical deoxygenation.[99] The Barton-McCombie reaction, where the carbonyl oxygen is replaced by a sulphur atom (C=X = C=S) (70) works much better (Scheme 34).[100]



Scheme 34. Barton-McCombie reaction.

The driving force of the reaction is the energy gained by the transition from a C=S to a

C=O double bond. Trialkyltin radicals are particularly suitable for this reaction because the Sn-S bond is very stable and trialkyltin hydrides are exceptionally good H-donors. Ordinary esters do not react as readily due to the much lower reactivity of a carbonyl group towards tin radicals as compared with a thiocarbonyl group. This causes the equilibrium to shift to the left, resulting in a lower concentration of the intermediate adduct radical and a slower fragmentation rate and hence shorter chain length. For the reaction to be practical the initial radical must be stabilised (e.g. by resonance/delocalisation) (Scheme 35).



(68)

Scheme 35.

With esters of hydroxamic acids however, the weakness of the N-O bond strongly favours the fragmentation step that compensates for an inefficient initial addition of stannyl radicals onto the carbonyl group.

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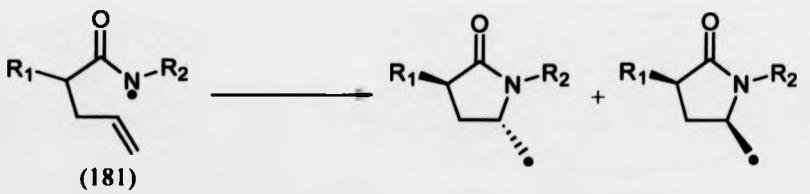
100. D. H. R. Barton and S. W. M^{c}Combie, *J. Chem. Soc., Perkin Trans.* 1, **1975**, 1574.

Chapter 2

Investigation into the stereochemistry of 5-*exo* cyclisations of amidyl radical cyclisations.

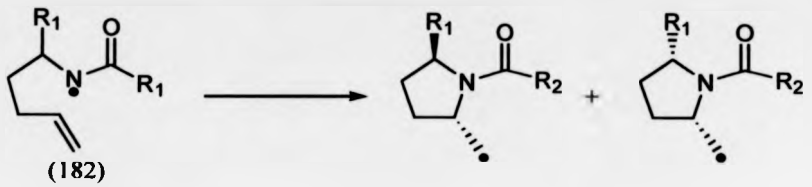
2.1 Introduction.

In order for amidyl radical cyclisations to be synthetically useful for the formation of complex cyclic arrays, it is important to understand the stereochemical outcome of such reactions. While the stereoselectivities of intramolecular carbon radical addition reactions to alkenes in the 5-*exo* mode is well understood and have been described earlier (section 1.2.5),[1a-b] the analogous nitrogen-centred radical cyclisations have received much less attention. In particular, there is little or no published information on the stereochemistry of amidyl radical cyclisations. Two possible cyclisation modes exist for amidyl radicals, cyclisation onto the acyl side chain (181) (scheme 36) and onto the alkyl side chain (182) (scheme 37). Newcomb has shown that the rate of cyclisation depends upon whether cyclisation occurs *via* the acyl side chain (5-*exo* 1 x 10^7 s^{-1} at 27°C)[2] or alkyl side chain (5-*exo* 2 x 10^6 s^{-1}).[3] In both cases cyclisation is quicker than reduction of the initial amidyl radical by Bu_3SnH (acyl; 4 x 10^4 $s^{-1}M^{-1}$, alkyl 1 x 10^5 $s^{-1}M^{-1}$).[2] In theory this enables both types of cyclisation to be carried out efficiently if concentrations of Bu_3SnH are in the region of 0.4 M.



(181)

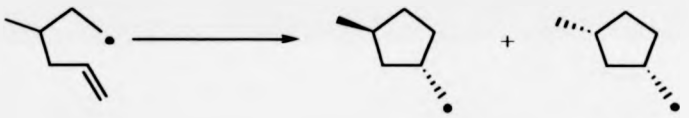
Scheme 36. Cyclisation onto the acyl side chain.



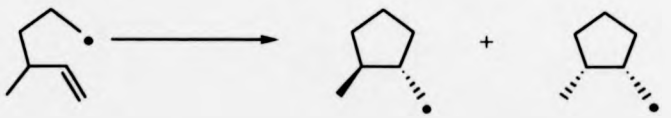
(182)

Scheme 37. Cyclisation onto the alkyl side chain.

The factors which effect the stereochemical outcome of simple substituted 5-hexenyl carbon radical cyclisations are well established (see section 1.2.5). For example 1- or 3-substituted radicals preferentially give *cis* di-substituted products, while 2- or 4-substituted radicals give *trans* di-substituted products (scheme 38).[1a-b]



trans:cis 29:71



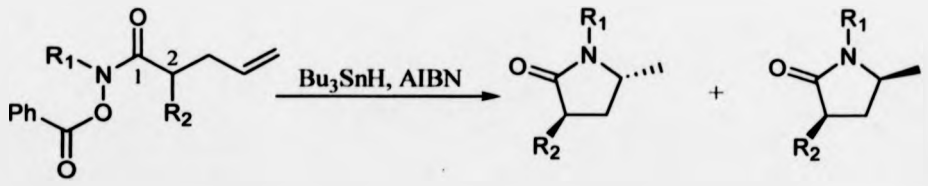
trans:cis 83:17

Scheme 38. Stereochemical outcome of simple substituted 5-hexenyl radical cyclisations.

This has been rationalised by Beckwith by invoking a chair-like transition state for radical additions that contain clearly distinguishable C-2, C-3, and C-4 pseudo axial and equatorial positions. In order to gain a better understanding of what factors may influence diastereoselectivity in amidyl radical mediated cyclisations, we commenced a detailed investigation into the effect of substituents upon these types of reactions.

2.2 Precursor Selection.

At the start of the research two procedures for the generation of amidyl radicals had recently been published. The use of *N*-acyl sulfenamides as radical precursors had been reported by Newcomb[3], while the use of *O*-benzoyl hydroxamic acid derivatives had been explored by Zard.[4] Both groups had demonstrated that amidyl radicals can undergo efficient cyclisation reactions under neutral conditions. However, previous work within the group had shown the use of *N*-acyl sulfenamides had associated problems. Therefore the use of Zard's methodology in the acyl mode was chosen to investigate the stereochemistry of 5-*exo* amidyl radical cyclisations. A considerable amount of research had been carried out within the group on the 5-*exo* cyclisation of amidyl radical generated from *N*-benzoyl protected hydroxamic acid derivatives. The acyl mode was selected with the substituent in the 2-position (scheme 39) by virtue of the fact that work had been previously been published by other members of the group on the 5-*exo* amidyl radical cyclisation in the alkyl mode[5] and in the acyl mode when the substituent was located in the 3-position.[6]



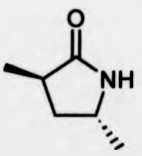
R_1= Me, *i*-Pr, CH_2Ph, *n*-butyl.

R_2= Me, Ph.

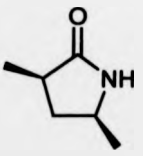
Scheme 39. Cyclisation of 2-substituted *N*-alkyl-*N*-benzoyloxypent-4-enamides .

2.2.1 Choice of precursors.

The 2-methyl and 2-phenyl substituents were selected to provide both a contrast in steric bulk and variation in the degree of hybridisation of the carbon attached to the chain. The corresponding 3-methyl and phenyl substituted compounds have been prepared and cyclised by another member of the group and these results will be compared later.[5] A number of *N*-alkyl groups were chosen to investigate the influence of the nitrogen substituent upon the stereochemical outcome of the cyclisation. The substituents were chosen to provide a degree of steric variance. Ideally, the use of primary, secondary and tertiary groups would provide good steric variety. Work previously carried out within the group indicated that a tertiary group could not be tolerated, as attempted cyclisation of *t*-butyl precursors failed.[6] The selections were made based on availability of the corresponding starting materials. The groups finally decided upon were methyl, *n*-butyl, *i*-propyl and benzyl. This would provide comparison between a small and medium sized primary group, a secondary group and an easily removable *N*-protecting group. The use of an easily removable protecting group would be useful in assigning the stereochemistry of the products, as both *cis* and *trans* isomers of the debenzylated analogues (183) and (184) have been previously reported in a diastereomerically pure form.[7]



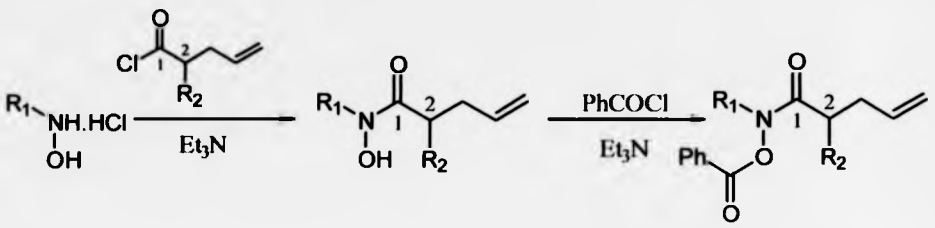
(183)



(184)

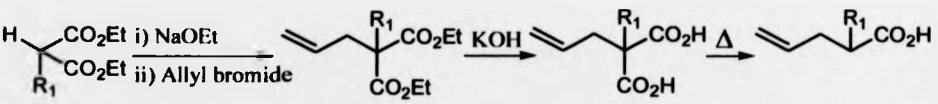
2.2.2 Preparation of precursors (78)-(82), method 1.

The precursors were prepared by one of two routes. The first method[8] utilised a two step approach (scheme 40). Step one involved the initial *N*-acylation of commercially available hydroxylamine hydrochloride salts with the suitably substituted acid chloride, and step two involved the *O*-acylation with benzoyl chloride.



Scheme 40. Method 1.

The substituted carboxylic acids (74) and (76) were prepared via standard literature methods from the corresponding commercially available diethyl malonates (scheme 41).[9]

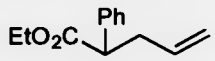


R_1 = Me (72), Ph (75) R_1 = Me (73) R_1 = Me (74), Ph (76)

Scheme 41.

The first step involved the allylation of diethyl methyl or phenyl malonate to form the corresponding 2-allyl-malonic acid diethyl diester (72) (73%) and (75) (78%). The base catalysed hydrolysis of (72) then furnished the corresponding 2-allyl-2-methyl malonic

acid (73). The decarboxylation of 2-allyl-2-methylmalonic acid (73) then furnished 2-methyl-pent-4-enoic acid (74) in a yield of 89%. However, the hydrolysis of (75) furnished the corresponding 2-phenyl-pent-4-enoic acid ethyl ester (77) (68%) which then required further hydrolysis to yield (76) directly in a yield of 93%. This was thought to arise from the partial hydrolysis of (75) followed by decarboxylation during distillation.



(77)

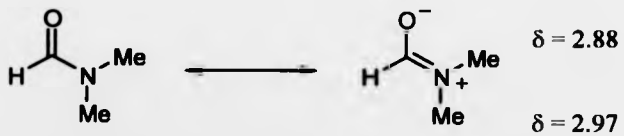
The substituted carboxylic acid chlorides were then produced in quantitative yields from their corresponding acids by refluxing with oxalyl chloride and used immediately without further purification. With both acid chlorides in hand we then prepared a range of precursors (83-88) *via* their intermediate hydroxamic acids (78-82).

Step1 involved the *N*-acylation of their commercially available hydroxylamine hydrochloride salts. Hence to a mixture of the corresponding hydroxylamine hydrochloride salts (1 eq.) was added triethylamine (3 eq.) followed by the slow addition of the acid chlorides (0.8 eq.) (74) or (76), the yields of which are shown in table 3. The yields expressed in table 3 were all good (59-78%) with the exception of entry 3. The lower yield in this case was due to its loss during aqueous acid work-up presumably because of its increased solubility in the aqueous phase.

Table 3. Yields of the intermediate hydroxamic acids (78)-(82)

Entry	No.	R_1	R_2	Yield %	E:Z ratio
1	(78)	$PhCH_2$	Me	59	4:1
2	(79)	*i*-Pr	Me	78	3:1
3	-	Me	Me	trace	-
4	(80)	$PhCH_2$	Ph	72	1.5:1
5	(81)	Me	Ph	75	1:1
6	(82)	*i*-Pr	Ph	69	1:2.3

The intermediate hydroxamic acids (78-82), isolated during the first step all gave N.M.R. spectra that were split, presumably due to restricted rotation around the amide bond. There exists two possible conformations for simple amides to adopt either (E) or (Z). Conjugation between the nitrogen lone pair and the carbonyl, leads to increased double bond character in the C-N bond and hence some degree of restricted rotation about this bond at RT. This effect can be observed in the N.M.R. spectrum of *N,N*-dimethylformamide which shows two signals for the methyl groups at RT (scheme 42).[10]



Scheme 42. Resonance forms of dimethylformamide.

At high temperatures (130°C) only one signal is observed in the N.M.R. timescale due to rapid equilibration. Secondary amides however, generally produce sharp resonances in their N.M.R. spectra, which is attributable to the more sterically favoured (E) conformation (scheme 43). The (Z) conformation is much higher in energy and therefore not populated to any significant extent.

Scheme 43. Conformation of secondary amides.

Hydroxamic acids however, have the ability through hydrogen bonding to significantly populate the less sterically favoured (Z) conformer (scheme 44). The hydrogen bonding reduces the difference in energy between the two conformations significantly.

Scheme 44. Conformation of secondary hydroxamic acids.

This can be observed in the N.M.R. spectra of (78) which shows the splitting of the affected resonance (fig. 11). The rate of interconversion between the two conformations (E) and (Z) can be altered by running the N.M.R. spectra at either low or high temperatures. The assignment of the signals for compounds (78-82) to either (Z)

or (E), is based on the fact that the signals for the Z conformation are much further down field (table 4).[11]

Table 4. E:Z ratios and H-C=O chemical shifts for both conformers

Entry	No.	R_1	R_2	H-C=O	
				Z	E
1	(78)	$PhCH_2$	Me	3.21	2.63
2	(79)	*i*-Pr	Me	3.16	2.66
3		*t*-Bu	Me		2.51
4	(80)	$PhCH_2$	Ph	4.25	3.68
5	(81)	Me	Ph	4.30	3.60
6	(82)	*i*-Pr	Ph	4.72	3.60
7		*t*-Bu	Ph		3.60

* All N.M.R. samples run in $CDCl_3$ and chemical shifts quoted in p.p.m..

The percentage of (Z) conformer in the (Z)/(E) equilibrium decreased with the increase in the size of the substituent at nitrogen (fig. 10). When R_1 is small and primary the (Z) conformer is favoured over the more sterically favoured (E) conformer in both the phenyl and methyl pendant series (fig. 10).

This graph shows the percentage of E conformer vs R_1.

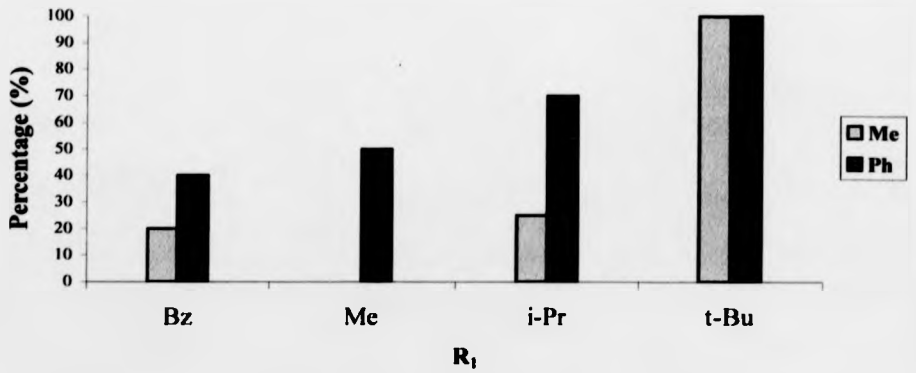


Figure 10.

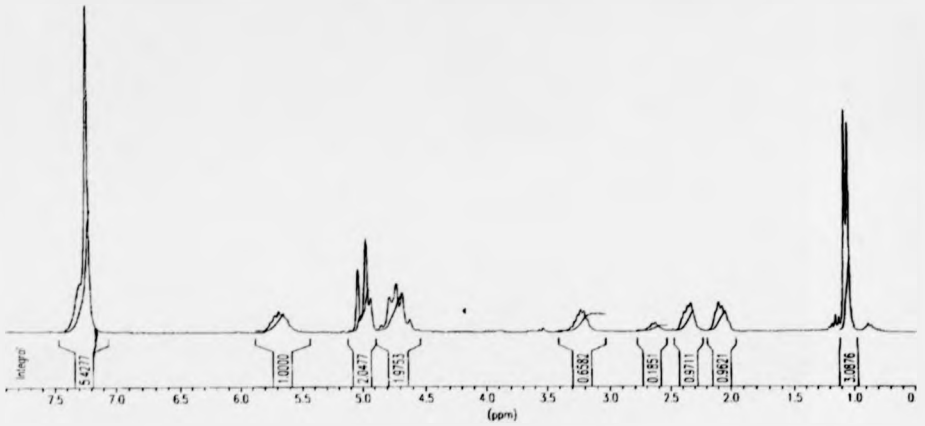


Figure 11. N.M.R. spectra of *N*-benzyl-*N*-hydroxyl-2-methyl pent-4-enamide (78).

The results showed that the energetic penalty for the increased steric interaction between R_1 and R_2 is outweighed by the formation of the hydrogen bond when R_1 is primary. This can be clearly seen in the results shown in figure 10. There exists a generally smooth transition from the (Z) conformation present in the smaller primary *N*-substituent to an excess of the (E) conformer for the secondary nitrogen substituent, with the tertiary substituent exhibiting sharp spectral lines indicating only the presence of the (E) conformer (fig. 12).

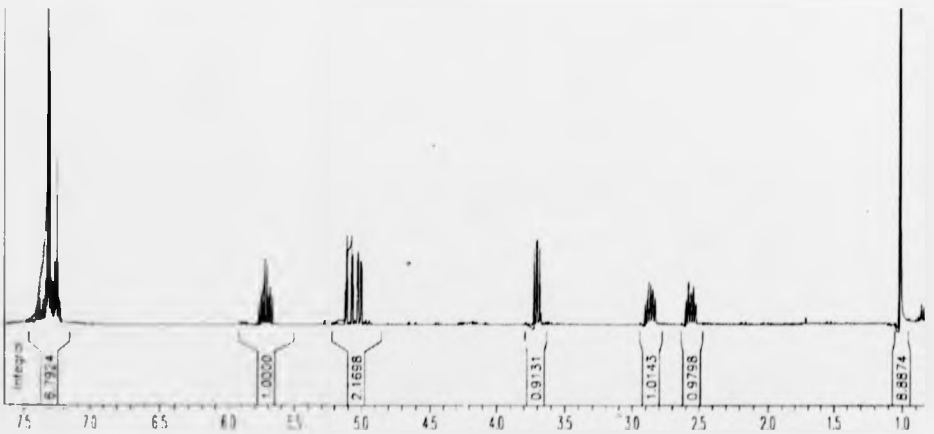


Figure 12. N.M.R. spectra of *N*-*t*-butyl-*N*-hydroxyl-2-phenyl pent-4-enamide.

2.2.3 Manipulation of hydroxamic acids (78-82) to the *O*-benzoyl protected versions (83-88).

With the desired hydroxamic acids (78-82) in hand we then proceeded to benzoylate the free OH group to furnish the desired precursors (83-88). Hence to (78-82) in dichloromethane was added triethylamine (1 eq.) to which was added benzoyl chloride (1 eq.) dropwise. As shown in table 5 yields were generally good to excellent with the exception of entry number 2.

Table 5. Yields of the *O*-benzoyl protected hydroxamic acids (83)-(88)

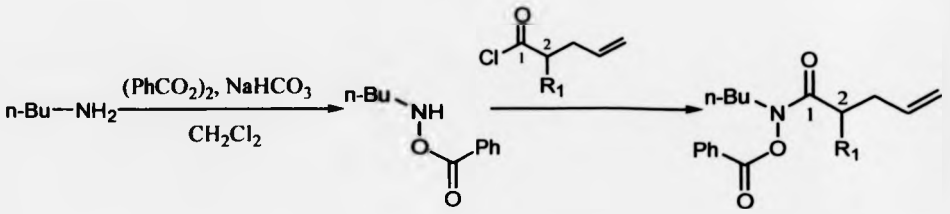
Entry	No.	R_1	R_2	Yield %	Total yield %
1	(83)	$PhCH_2$	Me	74	44
2	(84)	*i*-Pr	Me	58	45
3	(85)	Me	Me	90	90
4	(86)	$PhCH_2$	Ph	90	65
5	(87)	Me	Ph	86	65
6	(88)	*i*-Pr	Ph	80	55

However, the methodology was expanded upon during the course of the research to facilitate both steps in one pot. This was due to the intermediate hydroxamic acid for precursor (85) being water soluble, and therefore an aqueous acid work up was prohibited.

2.2.4 Preparation of precursors (89) and (90), method 2.

We also prepared the related *n*-butyl precursors (89) and (90) (table 6). However, due to the unavailability of the *n*-butyl hydroxylamine hydrochloride salt commercially we

utilised an alternative method. The second method was based on the procedures of Zinner[12] and Milewska[13] and involved a two-step, one pot reaction starting from *n*-butylamine. Hence a slurry of $(PhCO_2)_2$ (1 eq.) in dichloromethane was added to a solution of $NaHCO_3$ (5 eq.) and *n*-butylamine (1 eq.) in dichloromethane at RT.



R_1 = Me (89)
Ph (90)

Scheme 45. Method 2.

Table 6. Yields of (89)-(90)

Entry	No.	R_1	Yield %
1	(89)	Me	63
2	(90)	Ph	63

2.2.5 Summary.

Method 1 gave comparable yields in the main, and required only trivial purification and therefore the method most frequently employed. However, the *N*-Me, methyl substituted precursor was not amenable to this methodology in its current form, as the intermediate hydroxamic acid formed proved to be water soluble and was subsequently washed from the reaction mixture during work-up. Therefore this precursor was synthesised without any work-up and the second step was performed *in-situ*. The

modification of the first method to facilitate both steps in one pot served to increase the overall yield dramatically. With hindsight this could have been a better method to use to synthesise all the precursors shown in table 5.

2.2.6 ^{13}C Spectra.

It should be noted that the ^{13}C spectra of all the precursors showed broad signals for their carbonyl resonances, due to long relaxation times. Relaxation usually occurs *via* energy transfer to protons. Carbonyl carbons generally relax by dissipating energy to the protons α to the carbonyl group. However, for the OCOPh carbonyl, which has no α protons, the energy is subsequently dissipated *via* another route causing the relaxation time to be extended. The NCO carbonyl signal is also broad presumably due to restricted rotation around the amide bond. To overcome this the ^{13}C N.M.R. spectra of the precursors were collected with a larger number of scans to increase the relative intensity to a visible level.

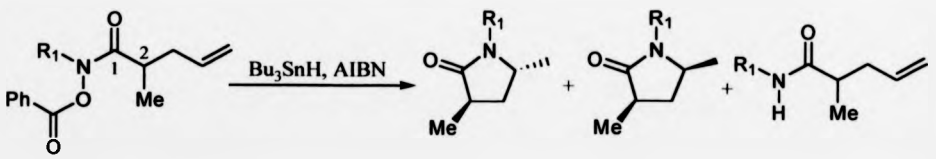
2.3 Cyclisation reactions.

The cyclisations were conducted by slow addition over 8 hours *via* a syringe pump of a solution of tributyltin hydride (1.1 eq.) and AIBN (0.1 eq.) in toluene to a refluxing solution of the precursor in toluene/cyclohexane (1:1). After refluxing for a further 12 hours, analysis by TLC showed the reactions not to be fully complete and in each case with the exception of *N*-benzyl-3,5-dimethyl pyrrolidine-2-one (91), an additional amount of tributyltin hydride (0.65eq.) AIBN (0.1 eq.) was added over 8 hours. After work up, the majority of tin residues were removed by partitioning the crude product between acetonitrile and hexane. Flash column chromatography was used to purify the

mixtures further. Generally, the diastereoisomers formed could not be separated fully but in some cases [e.g. (95) and (97)] a pure sample of both diastereoisomers could be obtained after chromatography.

2.3.1 Cyclisations of methyl pendant precursors.

Table 7 shows the results of the cyclisations of the 2-methyl substituted precursors. A combined yield for both diastereoisomers is reported in every case. The ratio of cyclised to reduced products was determined from the ^{1}H N.M.R. of the crude product after partitioning between hexanes and acetonitrile to remove the excess tin residues. ^{1}H N.M.R. spectra of the corresponding hexane partitions were checked to ensure that no cyclised or reduced products had been taken up in the solvent. In all cases the hexane was found to be free of any such products.



R_1= Me, *i*-Pr, CH_2Ph, *n*-butyl.

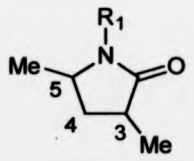
Table 7. Results of the cyclisation of the 2-methyl substituted precursors

Entry	No.	R_1	d.e.[c]	Cyclised/ Reduced[b]	Yield[a]
1	(91)	$PhCH_2$	10%	100:0	90%
2	(92)	*i*-Pr	10%[d]	70:30	47%
3	(93)	Me	8%	90:10	64%
4	(94)	*n*-Bu	12%[d]	70:30	40%

[a]Combined yields are quoted in each case. [b]Cyclised/reduced ratios determined by ^{1}H NMR. [c]d.e. determined by crude ^{1}H NMR unless otherwise stated. [d]d.e determined by gas chromatography.

Results indicated that the nature of the nitrogen substituent had little or no effect on the diastereoselectivity of the cyclisation reactions (table 6). The *n*-butyl group compound (94) gave the best diastereoselectivity, but the values for all the cyclised products are within experimental error of each other. It should be noted that the diastereoselectivity is much poorer than for the simple hex-5-enyl radical cyclisations (*cis*:*trans* 71:29) and is not great enough to be synthetically useful. This is probably due to the fact that the transition state for cyclisation of the amidyl radicals is much flatter due to the sp^2 hybridised carbon of the carbonyl than for simple alkyl radicals. This should lead to poorer stereoselectivity due to lower energy differences between the alternative transition states.

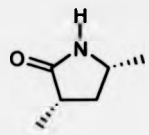
Comparison of the ^1H N.M.R. spectra of each of the cyclised products showed that the signal for the major isomer at 5-H position was always upfield of the minor isomer in each of the four cases studied, coupled with this was the fact that the signal for the major isomer at 4-H position was significantly split with one proton in the 1.1-1.2 ppm region and the other in the 2.2-2.5 ppm region. One can therefore conclude with a high degree of certainty that the major isomer in each case was of the same sense.



Determination as to which diastereoisomer was in excess proved to be more challenging. A survey of the literature provided no previously prepared authentic samples of either the *cis* or *trans* *N*-alkyl-pyrrolidinones (91-94) formed for direct comparison by N.M.R.. An attempt to furnish the debenzylated version *via* hydrogenation on Pd/C (in methanol) of *N*-benzyl-3,5-dimethyl pyrrolidin-2-one (91)

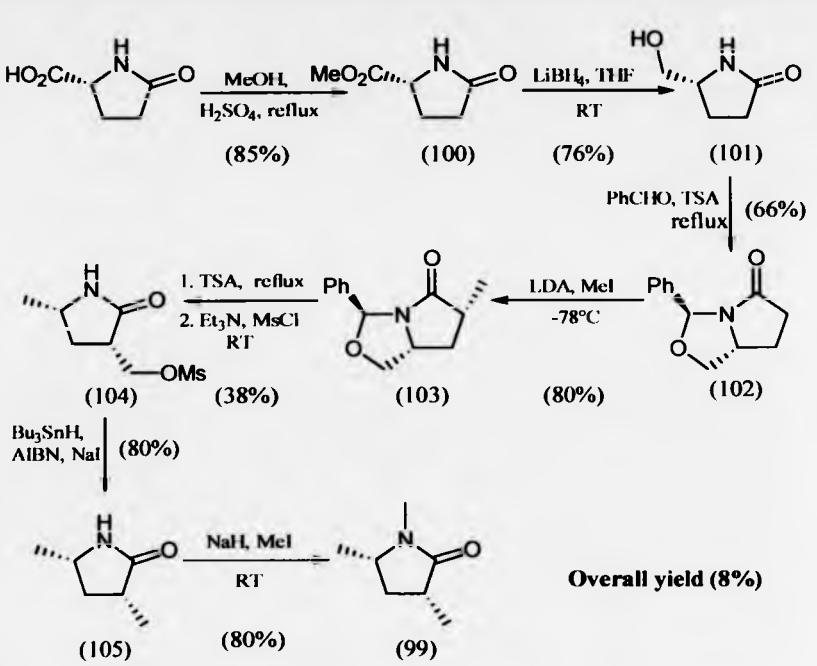
proved unsuccessful yielding only starting material. The reason for this failure was unclear.

The major isomer was eventually assigned as *trans* in all cases on the basis of both nuclear Overhauser effect (n.O.e) and by chemical correlation. The chemical correlation was carried out by following an elegant stereoselective route to the corresponding unprotected pyrrolidinone (99) that had been developed by Armstrong,[14] the synthesis for which is outlined in scheme 46.



(99)

Hence *S*-2-pyrrolidinone-5-carboxylic acid was esterified using methanol and gave the ester (100) in 85% yield. Reduction of the ester to the alcohol followed by simultaneous protection of the NH and OH groups furnished the bicyclic lactam (102) in 66% yield. Deprotonation and methylation furnished compound (103) (ratio 82:18 *cis*:*trans*). Deprotection and mesylation followed by flash column chromatography furnished pure samples of both the *cis* and *trans* mesylate (104). Subsequent produced both the known *cis* and *trans* 3,5-dimethyl pyrrolidinone (105); with an authentic sample of both *cis* and *trans* 3,5-dimethyl pyrrolidinone (105) in hand, both were *N*-methylated. Simple *N*-methylation with methyl iodide then furnished the desired products (99) for direct chemical correlation with compound (93) which was produced *via* 5-*exo* cyclisation.



Scheme 46. Stereoselective synthesis of *N*-methyl-S-*cis*-2,5-dimethylpyrrolidin-2-one (99).

Both the ^{1}H N.M.R. spectra of the authentically prepared *trans* and *cis* 3,5-dimethyl-*N*-methyl-pyrrolidin-2-one (99) were compared with the spectral results obtained for compound (93) (table 8). Analysis of the data showed that the major isomer present in the mixture was the *trans* isomer.

Table 8. Comparison of the ^{1}H N.M.R. spectra of (93) and (99)

Authentic sample of *trans* isomer (99) (400 MHz).	**Major isomer of product (93) (400 MHz).**	**Minor isomer of product (93) (400 MHz).**	**Authentic sample of *cis* isomer (99) (400 MHz).**
1.15 (3H, d, J=7.3Hz)	1.15 (3H, d, J=7.3Hz)	1.18 (3H, d, J=7.0Hz)	1.16 (3H, d, J=7.0Hz)
1.18 (3H, d, J=6.3Hz)	1.17 (3H, d, J=6.3Hz)	1.20 (3H, d, J=6.3Hz)	1.19 (3H, d, J=6.3Hz)
1.75 (2H, m)	1.75 (2H, m)	1.18-1.20 (1H, m)	1.17-1.20 (1H, m)
2.50 (1H, m)	2.49 (1H, m)	2.32-2.43 (2H, m)	2.30-2.43 (2H, m)

2.78 (3H, s)	2.78 (3H, s)	2.77 (3H, s)	2.77 (3H, s)
3.60 (1H, m)	3.48 (1H, m)	3.39 (1H, m)	3.46 (1H, m)

* All δ are quoted in p.p.m

The n.O.e effect was used as an aid to determining the stereochemistry. The n.O.e effect is useful in determining which protons in a molecule are in close proximity to each other. If two protons are within 3.5 Angstroms of each other then irradiation of one will result in the enhancement of the signal of the other. The increase in the intensity of the signal can be as much as 50% but it is typically less than 5%. The effect is normally viewed by obtaining a n.O.e difference spectrum. A conventional ^1H spectrum is recorded, followed by the spectrum in which a specific signal is irradiated. Subtraction of the conventional ^1H spectra from the irradiated spectra gives the n.O.e difference spectrum, which only exhibits the enhanced portions of the spectra, i.e. the protons that are close in space.

This type of experiment could only be used on *trans* *N*-benzyl-3,5-dimethyl pyrrolidin-2-one (91) (as a small amount of pure sample of the major isomer was obtained (figure 13). The other compounds could not be investigated by n.O.e difference as the ^1H signals were generally too close in proximity for them to be effectively irradiated in isolation. Irradiation would have caused the enhancement of both isomers rendering the results ambiguous.

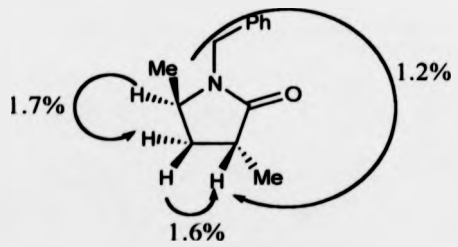


Figure 13. n.O.e evidence for the major isomer of (91)

The percentage enhancements shown in figure 13 in isolation are possibly too low to confer confidence in assigning the major isomer to either *cis* or *trans*. However, coupled with the information gleaned by comparison of ^1H spectra of the authentically prepared samples with compound *N*-benzyl-3,5-dimethyl pyrrolidin-2-one (91) it turned out to be an additional piece of evidence. Therefore, one can conclude with a high degree of certainty that the major isomer present in the mixtures for compounds (91)-(94) was indeed *trans*.

The *trans* selectivity directly contravenes that predicted by the Beckwith and Houk model[1a-b]. The Beckwith and Houk model predicts that there are eight major transition states of consequence as shown in figure 14. The most significant of which arise from the chair like transition states a,b and e,f with the boat like transitions c,d and g,h states thought to be significantly less populated due to the fact that they are higher in energy. Both the chair and boat-like transition states shall be discussed in isolation.

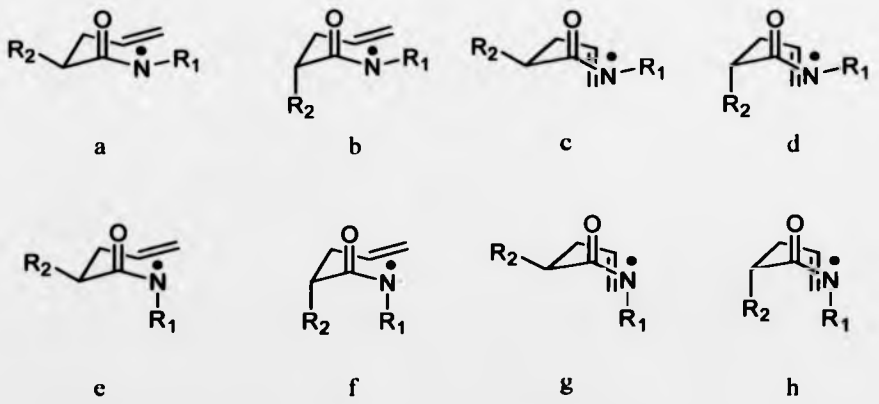


Figure 14. Possible chair and boat transition states.

The chair-like transition states e and f can be discounted from any argument, as they would be significantly less well populated, due to the amide group being in the higher

energy (Z) conformation. Out of the two remaining transition states (a) and (b), (a) would be favoured if the Beckwith Houk model be applied and this would give rise to the *cis* isomer being formed preferentially. However, the *trans* product was preferentially formed during the course of the study. However, due to the incorporation of an sp^2 centre in the chain the transition state cannot be truly chair like in nature but will be relatively flattened. If one were to examine the O=C-CR_2 bond one would arrive at the Newman projections (fig. 15) (1) and (2) for the transition states (a) and (b) respectively.

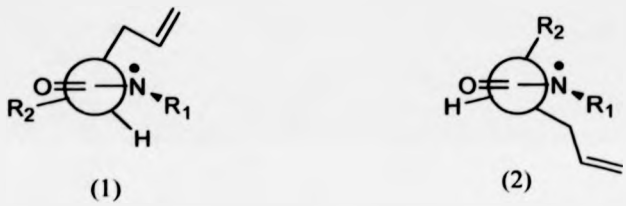


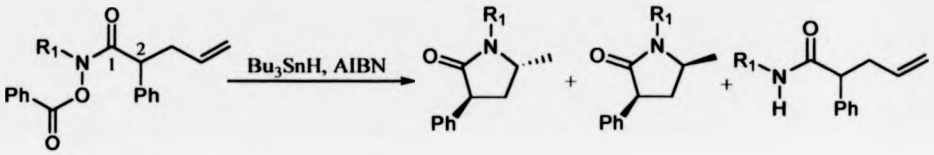
Figure 15. Newman projections of the O=C-CR_2 bond for transition states a and b.

It can be clearly seen from these projections that there exists a significant eclipsed interaction between R_2 and the carbonyl group (1) that is absent in the transition state where R_2 adopts an axial position. It is likely that this interaction will be intensified in this case due to flattening of the conventional Beckwith chair-like transition state. One may argue that transition state (b) would be lower in energy and therefore populated to a higher degree than transition state (a), this would then account for the observed *trans* selectivity. For the boat like transition states the same arguments as above may be applied, with the transition state (d) being the most favoured. If this were the case then again this transition state would give rise to the observed *trans* selectivity. However, attempts to model these transition states using PC model failed to predict that the lowest energy conformation was that which led to the *trans* product. This was probably due to

the uncertainty of how to accurately model an amidyl radical combined with the very low selectivities observed.

2.3.2 Cyclisations of phenyl substituted precursors.

Using the same cyclisation protocol as before we turned our attention to the cyclisation of the phenyl substituted precursors. Table 9 shows the results of the cyclisation of the 2-phenyl substituted precursors.



R_1= Me, *i*-Pr, CH_2Ph, *n*-butyl.

Table 9. Results of the cyclisation of the 2-phenyl substituted precursors

Entry	No.	R_1	d.e.[c]	Cyclised/ Reduced[b]	Yield[a]
1	(95)	$PhCH_2$	26%[d]	94:6	73%
2	(96)	*i*-Pr	36%	90:10	52%
3	(97)	Me	26%[d]	90:10	86%
4	(98)	*n*-Bu	36%	88:12	68%

[a]Combined yields are quoted in each case. [b]Cyclised to reduced ratios determined by NMR.
[c]d.e. determined by crude NMR unless otherwise stated. [d]Both diasteroisomer isolated.

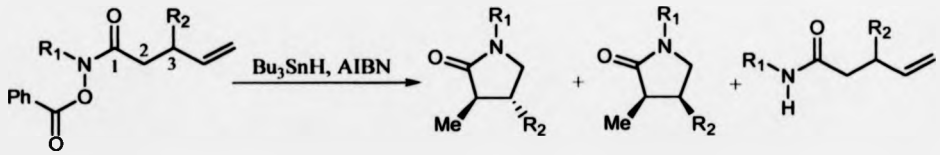
The major isomer was thought to be of the same sense for each cyclisation with the major diastereoisomer adopting the *trans* configuration. The diastereoselectivity observed was greater than that observed for the methyl series, which is in accord with the larger R group having a greater preference to be in the pseudo-axial position due to

a greater eclipsing interaction with the C=O group (fig. 15). The selectivities conferred by the results of both the 2-methyl and 2-phenyl precursors were too low to be exploited synthetically.

2.4 Discussions and conclusions.

A preference for a *trans* stereochemistry was established in all cyclisations although the diastereoselectivity was low with the nature of the *N*-alkyl group having little or no controlling effect. The increased diastereoselectivity for the phenyl substituents over the methyl was presumably a consequence of a greater energy difference between competing transition states due to increased steric interactions.

A comparison of the results presented here with those obtained by another member of the group for the corresponding 3-substituted precursors are shown in figure 16.



R_1 = Me, *i*-Pr, CH_2Ph, *n*-butyl.
R_2 = Me, Ph

A direct comparison cannot be made as different transition states are being dealt with, but as before the best stereoselectivities were observed for the phenyl series.

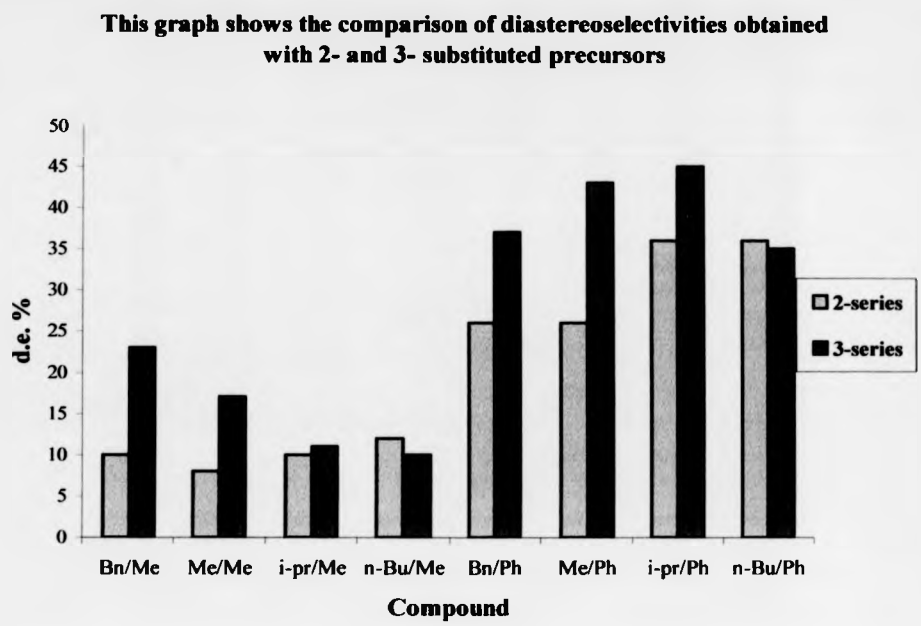
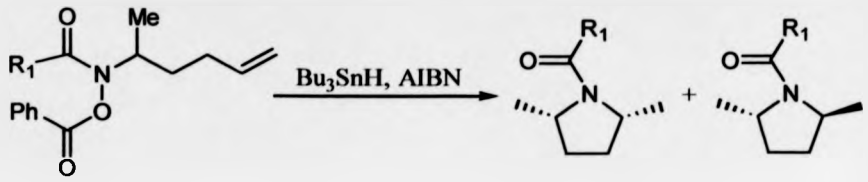


Figure 16.

Interestingly the diastereoselectivities observed were considerably lower than those of the corresponding carbon radical cases.[1b] Presumably the flattening of the chair like transition state led to less energy difference between competing transition states.

Research carried out by another member of the group when the carbonyl group is *exo* to the forming ring also showed a preference for *trans* selectivity with a significant increase in diastereoselectivity as compared to the corresponding carbon radical case (R_1=Me, Bu; *trans:cis* 5:1).[6]



These results indicated that the electronic nature of the nitrogen substituent played an important role in the degree of diastereoselection (R_1 = OMe, 15:1).

2.5 Future work.

The reactions are currently performed in refluxing cyclohexane/toluene; lower temperatures should have the desired effect of increasing the stereoselectivity of the reaction. In order to carry out a tin hydride mediated cyclisation at lower temperatures, triethylborane/oxygen mixture can be used[15] to initiate the reaction and therefore reactions could be performed at much lower temperatures. Molecular modelling could also help to explain why the *trans* selectivities were observed and also which substituents would give rise to the largest stereoselectivity.

Replacement of the alkyl chain substituents with a hydroxyl group could be used to cyclise the precursors in the presence of a Lewis acid. This would form a five membered bidentate chelate between the hydroxyl group and the amide carbonyl. Locking the conformation in this way may lead to greater diastereoselectivities (fig.17). A range of different Lewis acids could be analysed in this way.

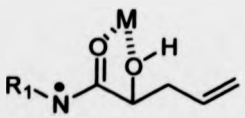


Figure 17. Lewis acid bound amidyl radical

Chapter 3

New alternative methods for generating amidyl radicals.

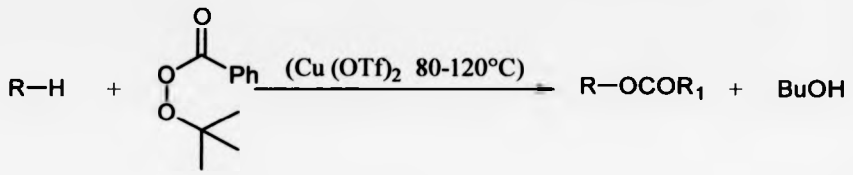
3.1 Introduction.

As mentioned earlier in the introduction (1.4) a number of methods have been developed to conduct amidyl radical cyclisation reactions. However, both *N*-haloamides and *N*-nitrosoamides are difficult to prepare and handle, while PTOC imidate esters are relatively unstable and the use of PTOC carbamates leads to competition between the required decarboxylation and radical translocation pathways.

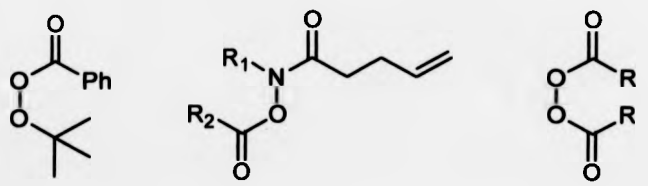
At the start of the research two new methods for the generation of amidyl radicals had been recently been published; Newcomb's *N*-acyl sulfenamides[3] and Zard's *O*-benzoyl hydroxamic acid derivatives.[4] Both of the above methods relied upon the use of tributyltin hydride to facilitate radical formation. We chose to try and develop non-tin hydride methodologies as a means of furnishing amidyl radicals. This was in the main due to the inherent difficulties in purifying the products obtained in chapter 2 from tin residues formed during their reaction. Due to the easy of preparation of the hydroxamic acid precursors (83-90) we decide to investigate alternative methods to homolytically cleave the N-O bond.

3.2 $Cu(OTf)_2$ mediated amidyl radical formation.

With the experience of using Zard type precursors in chapter two, the work published by Singh proved to be of significant interest.[16] The research showed that $Cu(OTf)_2$ and DBU/DBN in the presence of peroxides act as an efficient catalyst for the allylic oxidation of olefins (as shown below), the mechanism of which presumably involved the homolytic cleavage of the O-O bond to furnish an oxygen radical. If this was the case then the methodology may be adapted to the formation of nitrogen centred amidyl radicals.



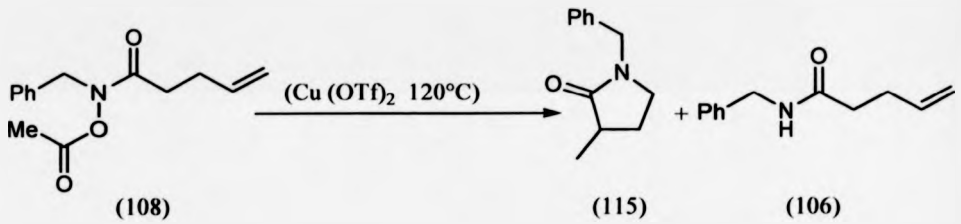
On closer inspection of the paper it was apparent that the *t*-butyl perbenzoate (a) was very similar in structure to the protected hydroxamic acids (b) produced in the previous chapter and it was interesting to speculate whether the N-O bond could be cleaved homolytically under similar conditions. In addition copper salts have also been used in the decomposition of weak O-O bonds in diacyl peroxides to give acyloxy radicals; again similarities in the structures of (b) and (c) were immediately apparent.



(a) (b) (c)

3.2.1 Precursor selection.

The initial precursor selected to test whether copper salts could effect the homolytic cleavage of the N-O bond in (b) was the *N*-acetoxy-*N*-benzyl pent-4-enamide (108). It was anticipated that any amidyl radical produced would cyclise to give (115), competing reduction of the initially formed radical to give (106) may also take place (scheme 47). In addition by varying the *O*-acyl group it may be possible to fine-tune the ease of cleavage of the N-O bond by changing the N-O bond's strength by influencing its electron distribution.



(108) (115) (106)

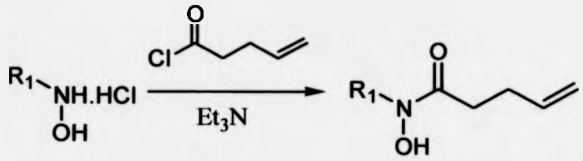
Scheme 47. $Cu(OTf)_2$ mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide.

The variation of the *N*-benzyl group was thought to be important to extend the methodology further so as to encompass a range of *N*-substituents. The selection of an unsubstituted acyl chain in the precursors was thought to be important, as the introduction of any stereochemical features would only serve to complicate matters.

3.2.2 Precursor synthesis.

The precursors were prepared by the method outlined in section (2.2.1)[8] utilising a two step approach. Step one involved the initial *N*-acylation of commercially available hydroxylamine hydrochloride salts with the pent-4-enoyl chloride (scheme 48)

(produced from the commercially available pent-4-enoic acid by the action of oxalyl chloride), and step two involved the *O*-acylation with a suitable acid chloride (scheme 48).



Scheme 48. Step 1.

Table 10. Yields of (107) and (112)

Entry	No.	R_1	Yield %
1	(107)	$PhCH_2$	87
2	(112)	Me	19

The yields of the two hydroxamic acids (107) and (112) differed significantly due to compound (112) being highly water-soluble. During the work-up procedure a significant amount of the hydroxamic acid (112) was washed from the organic layer. Both the intermediate hydroxamic acids (107) and (112) exhibited a broadened ^1H N.M.R. spectrum (fig. 18) but, with no distinct splitting of any resonance in direct contrast to the intermediate hydroxamic acids produced in section (2.2.1).

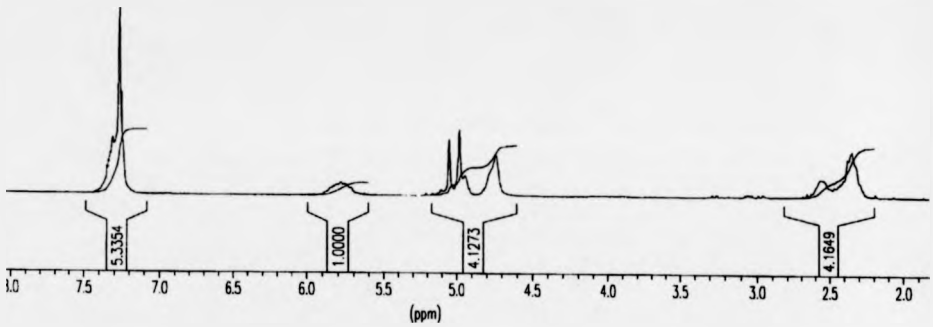
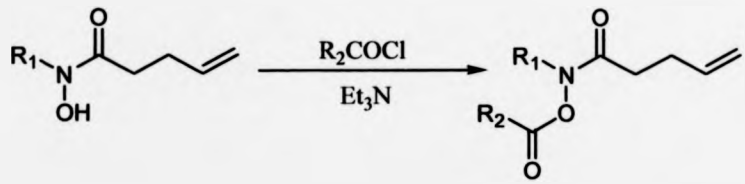


Figure 18. N.M.R. spectra of *N*-benzyl-*N*-hydroxyl pent-4-enamide (107).

Step two involved the *O*-acylation with benzoyl chloride and proceeded in good to excellent yields (table 11).



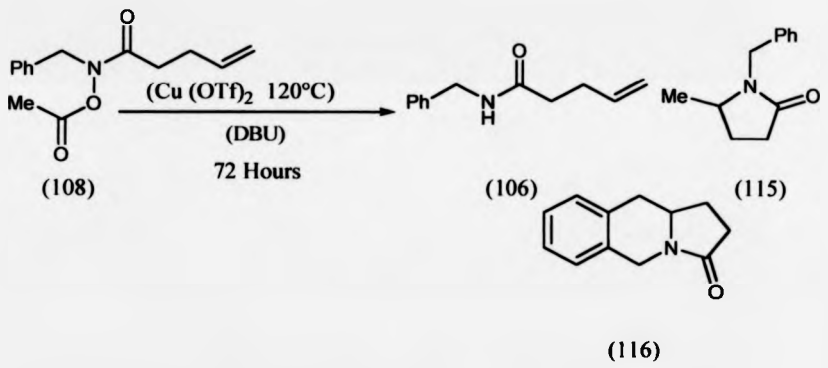
Scheme 49. Step 2.

Table 11. Yields of the *O*-protected hydroxamic acids (108)-(113)

Entry	No.	R_1	R_2	Yield %	Total yield %
1	(108)	$PhCH_2$	Me	90	78
2	(109)	$PhCH_2$	Ph	93	81
3	(110)	$PhCH_2$	p-NO_2Ar	84	73
4	(111)	$PhCH_2$	OMe	72	55
5	(113)	Me	Me	92	17

3.2.3 Preliminary cyclisation reaction.

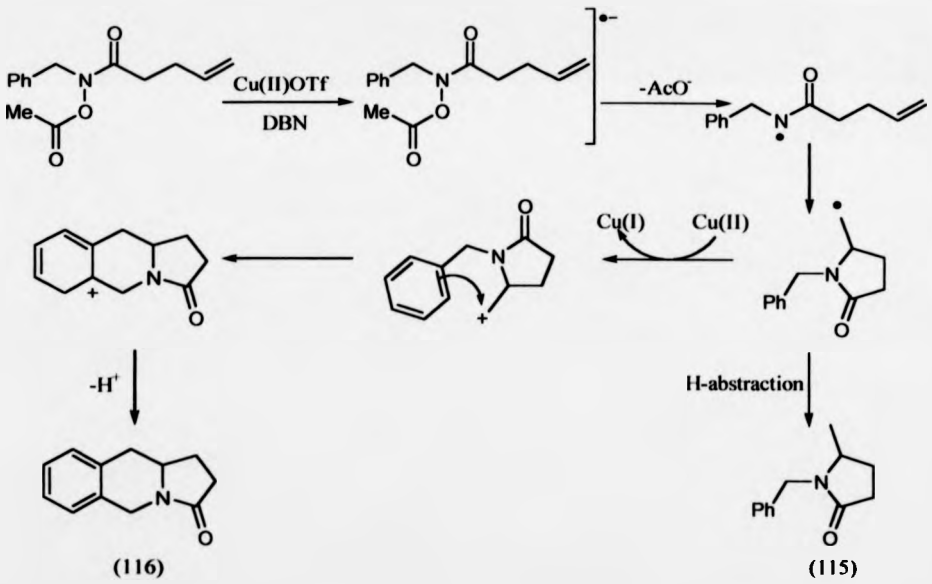
A solution of DBU (1.1 eq.) and copper (II) triflate (1 eq.) in dry acetone was stirred at RT. To this dark brown solution was added dropwise *N*-acetoxy-*N*-benzyl pent-4-enamide (108). The reaction mixture was placed in a sealed tube and heated at 120°C for a period of 72 hours. Initially we chose to use the same solvent (acetone) and concentration (0.19 M) as outlined in the publication by Singh for the homolytic cleavage of O-O bonds.[16] The result proved to be encouraging facilitating the cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (scheme 50). The reaction



Scheme 50. $Cu(OTf)_2$ mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108).

yielded the expected mono-cyclised product (115) along with significant amounts of the reduced compound (106) and a third component which was assigned as the tandem product (116). The major constituent of the three component mixture isolated was that of the tandem product (116) in a 25% yield which proved very encouraging. However, the methodology required significant development to reduce the amount of the other two components present, as the reduced (106) and the mono-cyclised (115) product gave isolated yields of 20 and 15% respectively.

The proposed mechanism for the formation of compound (116) is shown in scheme 51. The first step of which is the formation of a radical anion that presumably collapses to form the amidyl radical and the acetate anion. The intermediate amidyl radical formed, then cyclises in a 5-*exo* fashion to yield the intermediate pyrrolidinone radical. The intermediate pyrrolidinone radical can then follow two distinctly separate routes, the first of which being hydrogen abstraction by the intermediate from the solvent to form the mono-cyclised product (115). The second pathway involves Cu(II) mediated oxidation of the primary radical to furnish a primary cation which is then trapped followed by elimination of a proton to yield the tandem product (116).



Scheme 51. Proposed mechanism for the $Cu(OTf)_2$ mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108).

Interestingly, it is not known what oxidation state of copper is responsible for facilitating the reaction. There is a precedent in the literature to suggest that Cu(I) may be the active agent.[17] Other literature sources suggest that the active species is

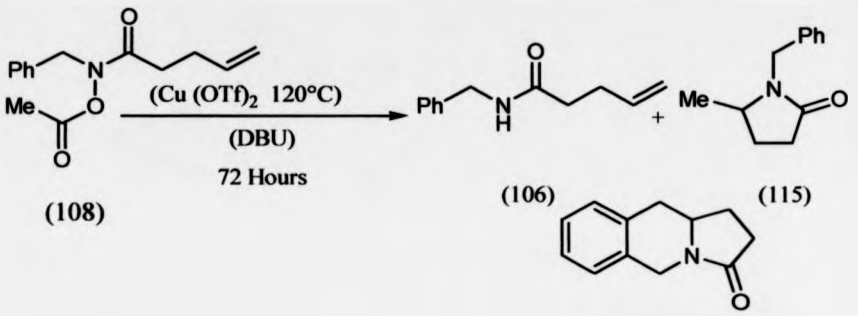
Cu(II).[18] However, there is a third possibility namely that there exists a dynamic equilibrium between both Cu(I) and Cu(II) which is essential for the reaction to proceed smoothly.

3.2.4 Optimisation and development.

As stated earlier the development of this methodology would be crucial for it to be exploited for the synthesis of other cyclic systems. The goals set during the optimisation are two-fold, to reduce the number of the components present in the mixture and to increase the amount of cyclisation product observed relative to the reduction product. Three separate areas for development were investigated, a) the solvent type, b) the nature of the *O*-acyl group and c) the concentration of the reaction.

3.2.4.1 Solvent type.

While the preliminary reaction was carried out in dry acetone, it was thought that replacement of this solvent with another might affect the ratio of the three products formed. This assumption was based on the fact that it was thought that reduction to give (106) was caused *via* a hydrogen abstraction process from the solvent. Three different dry solvents were selected each with appreciably different rate constants for H-abstraction (acetone, tetrahydrofuran and acetonitrile). The cyclisation was then carried out using the same precursor as before (108) in accordance with the method outlined in section (3.2.3), at 0.19M.



(108)

(106)

(115)

(116)

Table 12. Effect of the solvent on the cyclisation of (108)

Entry	Solvent	Conc.	Yield[a]	Ratio[b] (106:115:116)
1	Acetone	0.19M	85%	58:15:27
2	THF	0.19M	85%	44:18:38
3	MeCN	0.19M	84%	76:4:20

[a] Combined yields of all three components.

[b] Ratio determined by 400 MHz N.M.R..

Although using both acetone and THF as solvent gave more cyclised product (115) and less reduced product (106) than for CH_3CN. The fact that the latter reaction (entry 3) only gave a trace amount of (115) simplified analysis and thus CH_3CN was subsequently used in all further development work.

3.2.4.2 *O*-Acyl group.

The selection of the acetate group was initially not thought to be of any consequence. The precursor was selected due to the ease of synthesis and large stock available. On closer inspection it was thought that the *O*-acyl group may play an important role in the

electronic distribution of the N-O bond and therefore may have an effect on the course of the reaction. Four different *O*-acyl groups were selected with the aim of providing electronic variation in the N-O bond. The groups chosen were the electron withdrawing *p*-nitrobenzoyl group, the aromatic benzoyl group, the acetoxy group and the electron rich CO_2Me group. The results indicated that the nature of the *O*-acyl substituent was crucial for successful cyclisation with the acetate group being optimal. The use of electron donating (entry 4) and withdrawing (entry 3) substituents led to reduction only. The reasons for this were unclear.

Table 13. Effect of the *O*-acyl group on the cyclisation of (108)

Entry	No.	Solvent	Conc.	R_2	Yield[a]	Ratio[b] (106:115:116)
1	40	MeCN	0.19M	OAc	85%	58:15:27
2	41	MeCN	0.19M	OBz	91%	86:6:8
3	42	MeCN	0.19M	O-*p*-NO_2Bz	77%	100:0:0
4	43	MeCN	0.19M	CO_2Me	84%	100:0:0

[a] Combined yields of all three components.

[b] Ratio determined by 400 MHz N.M.R..

3.2.4.3 Concentration.

Generally, concentration plays the most significant part in the outcome of free radical reactions. Using acetonitrile as the solvent and the *N*-acetoxy-*N*-benzyl pent-4-enamide (108) as substrate, the effect of concentration was investigated. It was decided to use the concentration of the preliminary cyclisations (0.19M) as a convenient starting point; this concentration was then halved and the process repeated a further 3 times. The results of which are shown in table 14.

Table 14. Effect of concentration on the cyclisation of (108)

Entry	Solvent	Conc.	Yield[a]	Ratio[b] (106:115:116)
1	MeCN	0.19M	85%	58:15:27
2	MeCN	0.09M	96%	72:3:25
3	MeCN	0.05M	81%	62:3:35
4	MeCN	0.02M	93%	56:3:41
5	MeCN	0.01M	72%	43:0:57

[a] Combined yields of all three components.

[b] Ratio determined by 400 MHz N.M.R..

As can be seen from the results the lower the concentration the lower the amount of mono-cyclised product (106) formed with its complete exclusion when the concentration is 0.01M. The concentration of 0.01M proved to be the best providing the finest result, in fact the only result where the amount of tandem product (116) reached a synthetically useful yield of 46% (determined by N.M.R.).

Concentration effects on the Cu(II)(OTf)$_2$ mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108).

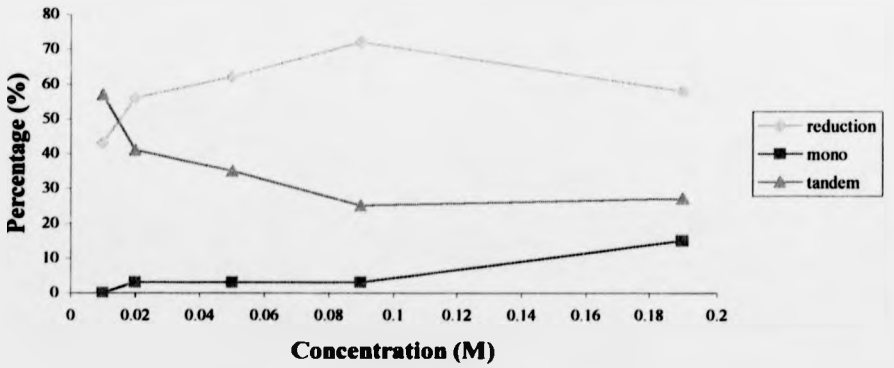
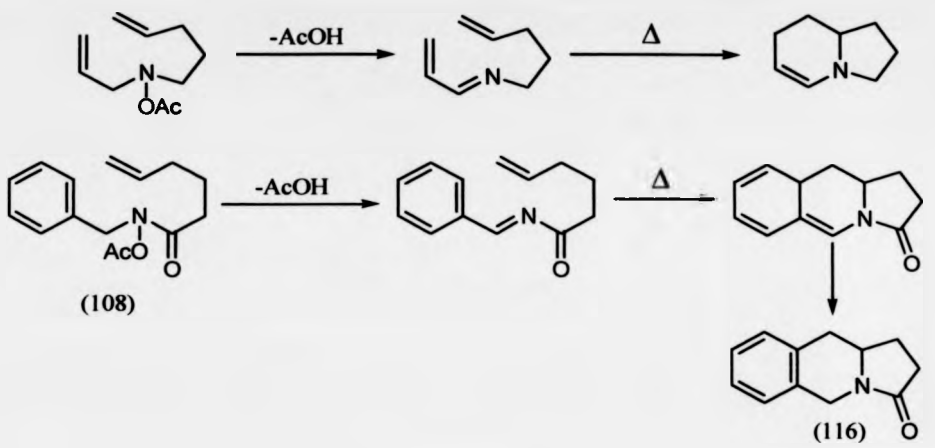


Figure 19. Effect of concentration on the Cu(II)(OTf)$_2$ mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108).

The effect of concentration may well give an insight into the mechanism involved in forming each of the observed products. If the mechanism described in scheme 51 was correct then one might expect that as the concentration was reduced the amount of tandem product (116) observed would also decrease, due to the lower concentration of the copper (II) species. This may indicate that the proposed mechanism is wrong and that the process does not involve the copper (II) oxidation to the corresponding cation but is a radical type process. The amount of monocyclised product (115) observed remained constant with a slight decrease when the concentration was reduced. This would be consistent with the hydrogen abstraction mechanism proposed, as the variation in solvent concentration would have little effect as it was present in such a large excess. The amount of reduction product was reduced when the concentration was decreased, implicating the concentration of the Cu(II) salt in its mechanism of formation.

However, very recently my attention was drawn to a paper published on the Diels Alder reaction shown in scheme 52.[19a-b] The precursor employed to investigate this type of Diels Alder reaction was strikingly similar to that used to investigate the $Cu(OTf)_2$ mediated cyclisation as shown in scheme 52. This indicates that two separate mechanisms may be in operation.

- Cu(II) causing cleavage of the N-O bond to give a radical which can undergo mono-cyclisation and reduction (section 3.2.3).
- Aza Diels Alder reaction to give the tricyclic compound (116).

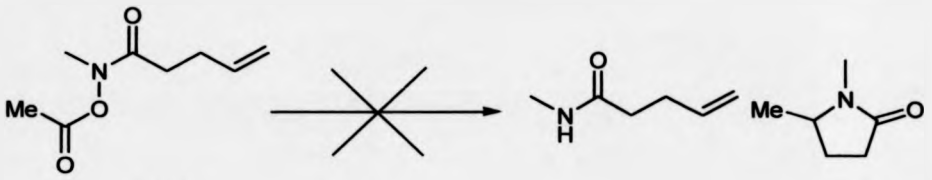


Scheme 52

The two mechanisms are probably in direct competition. At low concentrations there is very little initiation by copper to give the radical and thus little reduction and monocyclisation are observed. Therefore, when the copper is in low concentration a high proportion of the tricyclic compound is observed *via* the Diels Alder mechanism. At higher concentrations of copper the alternative mechanism is more prevalent and proceeds *via* the Cu(II) mechanism to give more reduction and mono-cyclised products.

The amount of monocyclisation is always small relative to reduction due to the competing hydrogen abstraction reaction with the vast excess of solvent present. The aza-Diels-Alder mechanism also provides an explanation why different ratios of products are observed with different *O*-acyl protecting groups. Each of the different *O*-acyl groups would have different abilities to undergo elimination from the precursor. The corollary of this is that had the mechanism come to light before the end of the research, significantly better yields of the tri-cyclic compound (116) could have been isolated.

In an attempt to broaden the scope of the reaction we investigated the cyclisation of the related *N*-acetoxy-*N*-methyl pent-4-enamide (113). Several different attempts however using the reaction conditions discovered for the reaction of (113) led to failure, with starting material being isolated.



(113)

This may indicate that the inclusion of a *N*-benzyl group protecting the nitrogen may be essential for the reaction to be successful indicating the mechanism may be more complicated than first thought. Indeed, it may mean that the redox potential of the copper salt system may have to be refined for each different precursor. This would render the reaction almost synthetically useless. In order to try to generate radicals from this second precursor we screened a wide variety of other copper reagents as the redox potential of the copper salt may be the important factor. However when the $Cu(OTf).C_6H_6$, $Cu(OTf)_2$.DBN or $Cu(OTf)_2$.DBU were utilised the reactions gave only starting material. When the Cu(I) reagent $Cu(CH_3CN)_4PF_6$ was utilised the starting material underwent quantitative reduction, with no cyclised material detected.

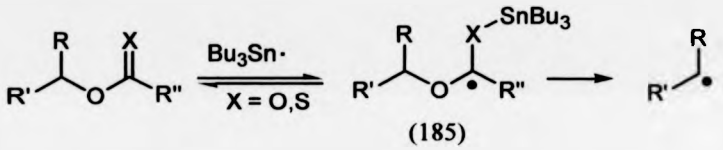
3.2.4.4 Future work.

Future work could be carried out to determine if the Diels Alder mechanism is in fact operative in the reaction. This would only require repeating the reaction with no copper salt present at the temperature stated. Also if the mechanism is operative then future

work could include looking at various different precursors with suitably substituted double bonds. The stereochemistry of such reactions may also be probed.

3.3 Tin mediated radical cyclisation of *N*-acetoxy-*N*-benzyl-pent-4-enamide (108).

The cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) with tin will test Zard's hypothesis that the initial radical formed (185) must be further stabilised by delocalisation (i.e. into a phenyl ring of a benzoyl-protecting group) (scheme 53).



Scheme 53. Barton-McCombie reaction.

Research carried out showed that the substitution of the benzoyl group with an acetyl group did not cause the reaction efficiency to decrease. Comparison between the cyclisation of the benzoyl and acetyl precursor proved favourable with comparable amount of cyclised and reduction product being formed in each case.

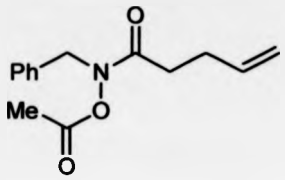
The reaction would also allow us to compare the product ratios obtained from the cyclisation of (108) with $Cu(OTf)_2$ with that of tin. Also, to determine whether this benzoyl stabilisation was truly necessary for the tin mediated generation of amidyl radicals we reacted (108) with tributyltin hydride. Cyclisation of (108) with Bu_3SnH added over 8 hours using AIBN *via* syringe pump was successful giving 28% (115) and 30% (106). The best result obtained with $Cu(OTf)_2$ gave 51% cyclisation [combination

of mono (115) (6%) and tandem (116) (45%) cyclised products] and 17% reduced (106). In the tributyltin hydride case no tandem product was observed presumably due to the absence of any oxidising agent.

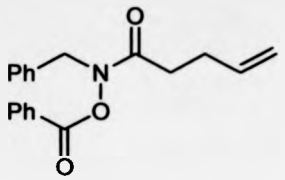
3.4 Attempted formation of amidyl radicals by the action of SmI_2.

3.4.1 Introduction.

In the last decade, the samarium Barbier reaction has been developed into a valuable synthetic method. Discovered by Kagan in 1980, its mechanism is not fully understood as yet. Nevertheless, one thing is certain, radicals are implicated in many of the key steps. Samarium diiodide has been shown to be successful at promoting the reactions of organic halides to perform radical cyclisations as studied by Molander.[20] However, it has been shown that primary and secondary alkyl radicals can be further reduced to anions by samarium diiodide. Various groups have postulated as to the reason why this is the case and to what the intermediates are.[21-22] Precedent has been set in the literature for the use of samarium diiodide in the reductive cleavage of N-O bonds in hydroxamic acids however, none of the substrates used had suitably positioned double bonds with which to undergo cyclisation.[23] The use of the precursors (108 and 109) would allow us to investigate if the amidyl radicals formed are long lived enough to undergo cyclisation or whether they are rapidly reduced to amide anions with a second equivalent of SmI_2.



(108)



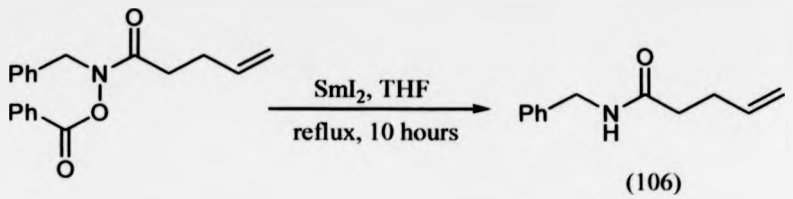
(109)

3.4.2 Attempted cyclisations.

N-benzoyloxy-*N*-benzyl pent-4-enamide (109) was initially used to investigate two key areas:

- The number of equivalents of SmI_2 to facilitate the cleavage of the N-O bond.
- The optimum temperature.

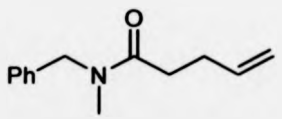
The first reaction was carried out using strictly one equivalent of SmI_2 added via a syringe pump over a period of 6 hours at RT and left to react for a further 10 hours in accordance with the previously reported methodology. After which time the reaction mixture only indicated the presence of starting material. Therefore to the reaction mixture was added another equivalent of SmI_2 as before. Again only starting material could be detected and the reaction mixture was worked up and the starting material reclaimed. In the next reaction it was decided to add two equivalents directly over a period of 6 hours at RT and again only un-reacted starting material was observed. Rather than simply reclaiming the starting material the mixture was put on to reflux and monitored *via* tlc. After a period of 10 hours the reaction had gone to completion with the formation of the reduction product (scheme 54) pent-4-enamide (106) in a yield of 89%, the structure of which was determined by chemical correlation to an authentically prepared sample (9.2.1).



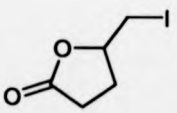
(106)

Scheme 54. Action of SmI_2 on *N*-acetoxy-*N*-benzyl pent-4-enamide (108).

As the type of acyl group attached to the nitrogen of the amide had a considerable effect in the $Cu(OTf)_2$/DBN system, it was decided to try the *N*-acetoxy-*N*-benzyl pent-4-enamide (108) precursor. The replacement of benzoyloxy with the acetoxy-protecting group had no effect leading again to an almost quantitative yield of the reduced form (106). It appears that the process may involve the initial formation of a radical that was then subsequently reduced to the anion, indicating the redox potential of SmI_2 was not conducive to radical formation. In order to verify the intermediacy of the amide anion it was decided to trap the anion *in situ* with MeI. However when the reaction was carried out the expected *N*-methyl amide (186) was not produced but the cyclic lactone (114) was isolated in 43% yield.

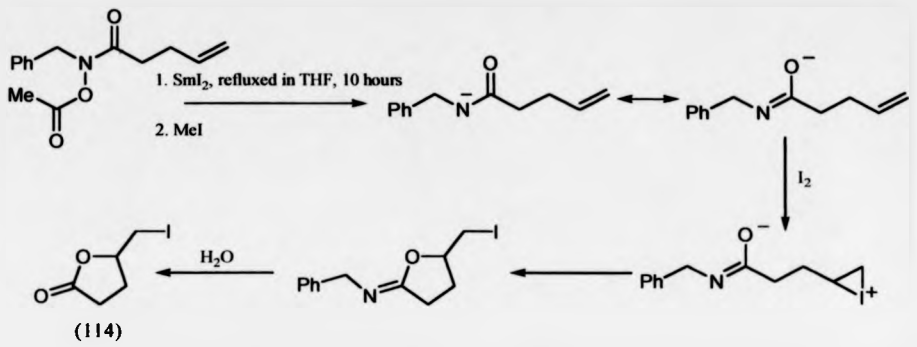


(186)



(114)

The structure was elucidated by comparison of spectroscopic data previously published. The possible mechanism for the reaction is shown in the scheme 55.



(114)

Scheme 55. Mechanism for the formation of 5-iodomethyl-dihydro-furan-2-one (114).

The free iodine was thought to arise from the reaction of SmI_2 with MeI as shown in equation 6. This possibility was suggested by the presence of a strong violet colour that appeared on the addition of MeI to the reaction mixture. This colour slowly faded during the reaction presumably due to formation of the iodonium cation.

$$SmI_2 \quad + \quad MeI \longrightarrow MeSmI \quad + \quad I_2$$

Equation 7.

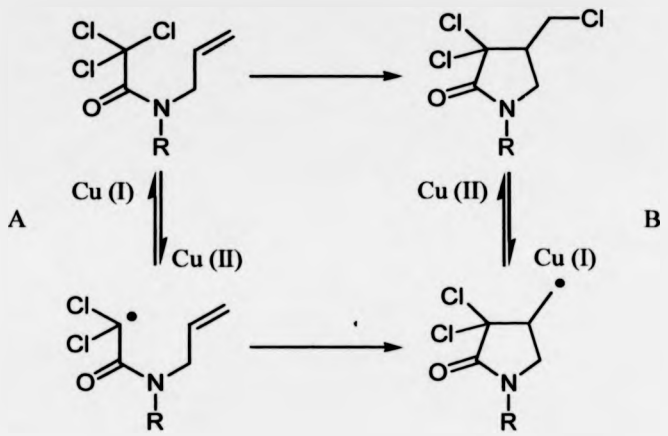
One can therefore conclude that the transfer of a second electron to the initial amidyl radical to give an anion was faster than the rate of cyclisation so further development of that methodology was abandoned.

Chapter 4

Copper (I) mediated atom transfer cyclisation of *N*-allylhaloacetamides.

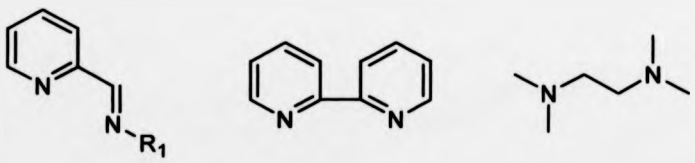
4.1 Introduction.

In recent years transition metal mediated free radical processes have gained in importance. In particular atom transfer radical cyclisation (ATRC) reactions of α,α,α-trichlorinated carbonyl compounds with a range of transition metal catalysts have been reported including ($RuCl_2(PPh_3)_3$,[24] $FeCl_2(P(OEt)_3)_3$, [25] CuCl(Bipy),[26] $CuCl(TMEDA)_2$[27] and CuCl (*N*,*N*,*N'*,*N'*,*N''*-pentamethyldiethylenetriamine).[28] However, even with these catalysts generally high temperatures (60-160°C) and activated carbon-halogen bonds (e.g. α,α,α-trihaloacetyl groups) as initiators were required. The most widely used catalysts in ATRC are CuCl(Bipy) and $CuCl(TMEDA)_2$. In order to improve the efficiency of catalysis and to allow reaction to occur at RT with less activated precursors (e.g. monohaloacetamides), it would be necessary to effect the equilibrium A and B [i.e. the redox potential of the Cu complexes (scheme 56)]. This can be achieved by the alteration of the copper ligands. In copper-mediated ATRC of activated trichloroacetamides the mechanism of the reaction was thought to be that shown below.



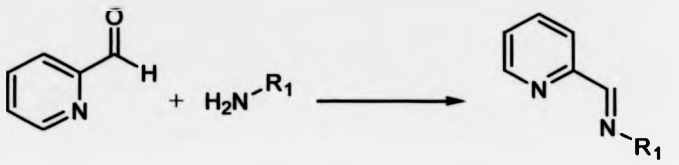
Scheme 56.

While a range of different catalyst systems have been reported, no study on the modification of existing ligands e.g. Bipy (188) or TMEDA (189) to elucidate structure-activity relationships has been undertaken. This is possibly due to the inherent synthetic difficulties in chemical modification of ligands such as bipyridine. The preparation of modified bipyridine ligands was not a trivial task so therefore the related class of ligands (187) was selected for investigation.



(187) (188) (189)

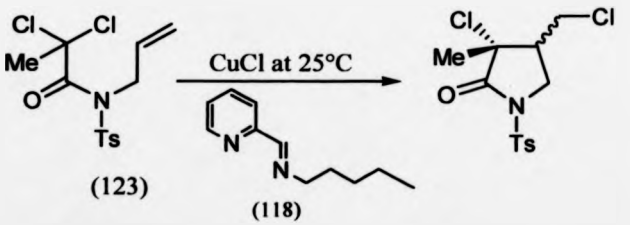
These ligands were relatively easy to prepare in one step from the corresponding amine and pyridine carboxaldehyde as shown in scheme 57. As a wide range of amines and pyridines were commercially available a great number of structurally related ligands can be prepared and studied.



Scheme 57. Preparation of *N*-alkyl-2-pyridylmethanimines.

4.2 Initial work already undertaken within the group.

Other results carried out within the group indicated that the most suitable R_1 group was derived from primary amines and that the optimum ratio of bidentate ligand to Cu was found to be 2:1 for the reaction of the dichloro derivative (123) (scheme 58).



Scheme 58. Reaction for determining the relative rate of cyclisation versus number of ligand equivalents.

A plot of $\ln[X]_t/[X]_0$ against time for each run (0.5, 1.0, 2.0 and 3.0 equivalents of ligand to CuCl) produced the result shown in figure 20[29].

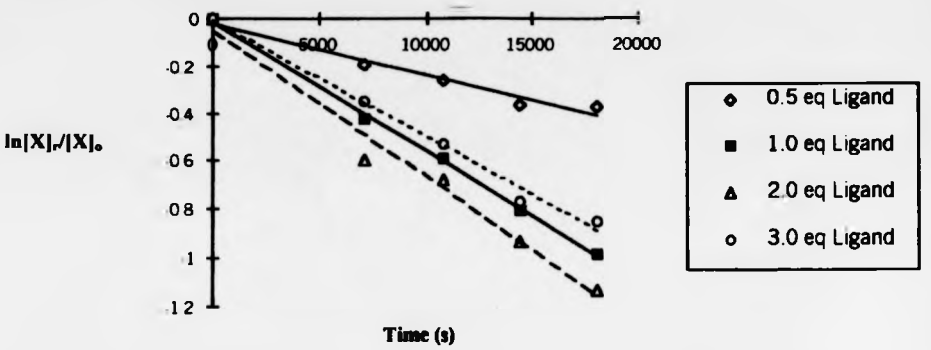
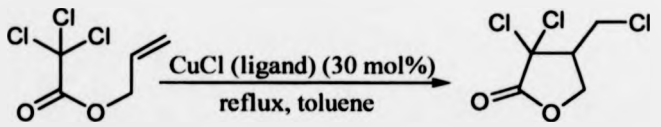


Figure 20. Relative rate of cyclisation of (123) with different equivalents of ligand (118).

The difference between the rate of reaction using 1:1 and 2:1 ligand to copper was not thought to be considerable enough to warrant the use of the larger amount of ligand in further studies. Therefore all studies carried out here were based upon using a 1:1 ratio of ligand (118) to copper.

Initial work to determine the efficiency of the CuCl complex of this ligand (118) as an atom transfer catalyst, involved investigating the known cyclisation of α,α,α-trichloroacetate (190).



(190) (191)

Scheme 59. Comparison of efficiency between TMEDA, bipyridine and *N*-pentyl-2-pyridylmethanimines (118).

Reaction of this ester (190) under atom transfer conditions using CuCl(Bipy) had been previously reported[30] and hence comparison could be made. Reaction of (190) with 30 mol% CuCl and 30 mol % of either (118), TMEDA or bipyridine as ligand in refluxing toluene was then attempted. After 4 hours the reactions were quenched and the ratio of product (191) to starting material (190) was determined (table 15). Ligand (118) showed a moderate rate enhancement over the other two ligands, indicating that this ligand would be a good starting point for investigation of ATRC reactions in general.

Table 15. Comparison of effeciency between TMEDA, Bipy and (118)

Ligand	Ratio of (190):(191)[a]
TMEDA	4:1
Bipyridine	5:1
(118)	1:1

Other groups have also reported the cyclisation of α,α-dichloro-α-alkyl-acetamides however they generally required elevated temperatures 60-130°C. Ghelfi recently reported the cyclisation of *N*-benzyl-α,α-dichloro-α-alkyl-allylacetamides with $CuCl(TMEDA)_2$ at 60°C while Slough reported the cyclisations of the related *N*-tosyl

e.g R_2 = Ts, cat = $RuCl(PPh_3)_3$
R_2 = Bn, cat = $CuCl(TMEDA)_2$

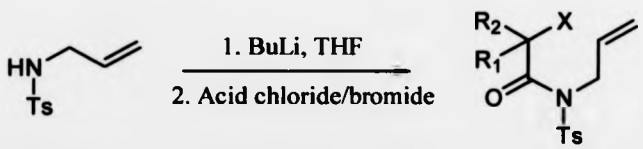
Scheme 60.

analogues with $RuCl_2(PPh_3)_3$ at 100-130°C (scheme 60).[24b] The enhanced activity of our catalyst system to that of CuCl(bipy) in the cyclisation of (190) prompted us to re-examine the substrates used in these studies with our catalyst system. The aim was to extend the scope of the reactions, use less activated substrates and to reduce the operating temperature to RT or below.

4.3 Precursor synthesis.

4.3.1 Synthesis of *N*-tosyl-α,α-dichloro-α-alkyl-allylacetamides.

Consequently we prepared a range of substrates to compare the efficiency of the pyridylmethanimines system (118) to Bipy. The general procedure for the preparation of the cyclisation of initially chosen precursors (121-126) was carried out using standard literature procedures. A solution of BuLi was added dropwise over 5 minutes to a stirred solution of *N*-allyl-toluene-4-sulfonamide (119) (previously prepared by the standard literature procedure) in dry THF at –78°C under nitrogen and the mixture stirred for 30 minutes at this temperature (scheme 61).



(119) (121-126)

Scheme 61. Synthesis of *N*-tosyl-α,α-dichloro-α-alkyl-allylacetamides.

The appropriate acid halide for (121-126) was added and the mixture stirred for 2 hours. The reaction was quenched with ammonium chloride and allowed to warm to

RT. The crude compounds generally needed purification by column chromatography, but overall the yields were generally moderate to excellent (64-90%) (table 16).

Table 16. Yields of N-tosyl di-/mono-haloacetamides

Entry	No.	R_1	R_2	X	Yield %
1	(121)	Cl	Cl	Cl	70
2	(122)	H	Cl	Cl	72
3	(123)	Me	Cl	Cl	75
4	(124)	$PhCH_2$	Cl	Cl	90
5	(125)	Me	Me	Br	72
6	(126)	H	H	Br	64

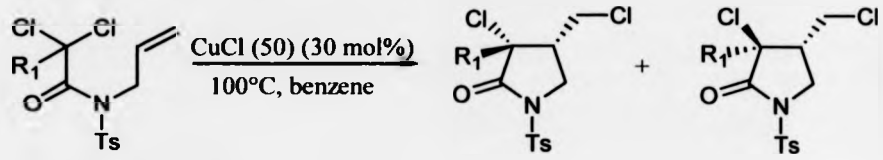
The acid halides used, when not commercially available, were generally prepared from their corresponding acids by the action of refluxing oxalyl chloride. Table 16 shows the different precursors prepared by this methodology.

4.4 Cyclisation reactions.

4.4.1 Comparison of efficiency with the previously reported $RuCl_2(PPh_3)_3$ atom transfer cyclisation catalysts.

We initially chose to evaluate the cyclisation reactions of the prochiral precursors (122-124), upon cyclisation two diastereoisomers were produced and it was interesting to determine how the new catalyst system affected the diastereoselectivity as well as rate and yield (scheme 62). Comparisons were initially made with the previously reported reactions of *N*-tosyl-α,α-dichloro-α-alkyl-allylacetamides, using the $RuCl_2(PPh_3)_3$ catalyst system under the same conditions as outlined in the report.[30] To a 0.12M

solution of *N*-tosyl acetamide in dry benzene under nitrogen was added either CuCl or CuBr (30 mol%) and *N*-pentyl-2-pyridylmethanimine (118) (30 mol%). The mixture was then placed in a sealed tube and heated to 100°C for a period of 4 hours. The resulting mixture was eluted through a short silica plug with dichloromethane and the solvent removed in *vacuo* to give the crude products. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.



(122) R_1 = H
(123) R_1 = Me
(124) R_1 = Bn

Scheme 62. Cyclisation of *N*-tosyl-α,α-dichloro-α-alkylacetamides in benzene.

Table 17. Comparison between CuCl(118) and $RuCl_2(PPh_3)_3$

Entry	No.	R_1	CuCl(118) *cis:trans*	Yield %	$RuCl_2(PPh_3)_3$ *cis:trans*	Yield %
1	(122)	H	3:1	88	1:3.5	65
2	(123)	Me	1:5.3	90	1:2.7	69
3	(124)	Bn	99:1	98	19:1	57

The results of the cyclisation of precursors (122-124) with CuCl(118) and $RuCl_2(PPh_3)_3$ are shown in table 17. The results clearly show that the Cu system gave far superior yields and greater diastereoselectivities in the main. The one notable exception being that of entry 1, the diastereoselectivity being slightly better with the $RuCl_2(PPh_3)_3$

system and the major diastereoisomer being of the opposite sense. The reason for this major difference was however unclear.

We next attempted to reduce the operating temperature of the reactions to see if this would affect the selectivities. However the use of benzene as a solvent was not appropriate. This was thought to be due to the insolubility of the CuCl(118) system in benzene at low temperatures, a fact that was consistent with those observed when conducting atom transfer radical polymerisation (ATRP) reactions. However by switching to CH_2Cl_2 the reactions could be carried out at RT. Hence, repeating the reactions at the same concentration of 0.12M provided similar results to those described in table 18 for the benzene cyclisation, but with a slight decrease in diastereoselectivity (table 17).

Table 18. Comparison between CuCl(118) in CH_2Cl_2 at RT and in benzene at 100°C

Entry	No.	R_1	CuCl(118) in CH_2Cl_2 *cis:trans*	Yield %	CuCl(118) in C_6H_6 *cis:trans*	Yield %
1	(123)	Me	1:2.7	95	1:5.3	90
2	(124)	Bn	99:1	88	99:1	98

Cyclisation of precursor (122) failed to proceed at RT but proceeded smoothly at reflux over 24 hours (4:1 *cis:trans*, 86%). The difference in rate between (122) and (123) was briefly investigated by comparison of their relative rates at 28°C, using the same methodology as outlined in section 4.1. A plot of $\ln[X]_t/[X]_0$ against time for each precursor (122) and (123) produced the results shown in the figure 21, indicating cyclisation of the secondary precursor (122) was approximately 30 times slower than

that of the tertiary precursor (123). This was likely to be due to the increased bond strength of the C-X bond.

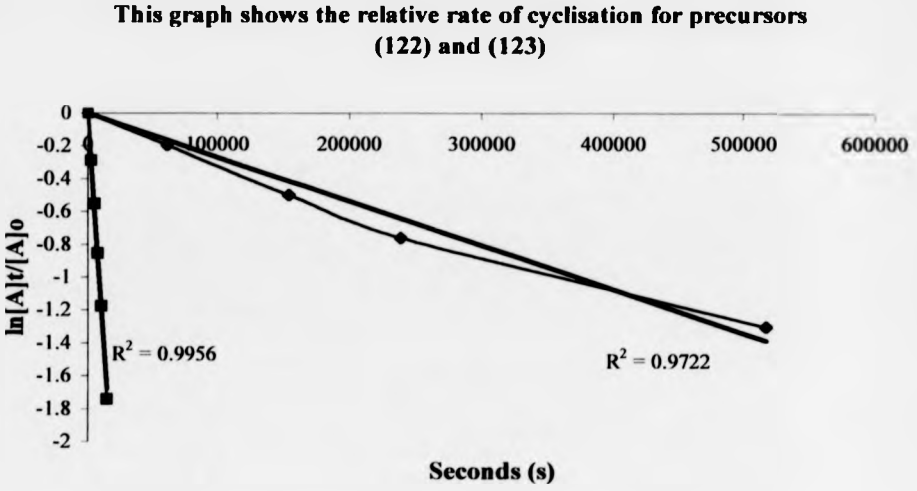


Figure 21. The difference in rates between (122) and (123) at 28°C.

4.4.2 Effect of concentration and time on the diastereoselectivity of (123).

Lowering the concentration in our reactions was found to have an effect on the rate of the reaction (0.009M, 1:1 mixture of starting material:product, after 3 days) however, there proved to be little benefit in running the reaction at higher concentrations than that of 0.12M. In the work using $RuCl_2(PPh_3)_3$ reported by Slough he discussed that the diastereoselectivities of the cyclisation of *N*-tosyl-*N*-allyl-acetamides were dependent upon the time of the reaction. Hence, we investigated how time affected the cyclisation of (123) using CuCl(118) (figure 22).

This graph shows diastereoselectivity versus time for the cyclisation of (123)

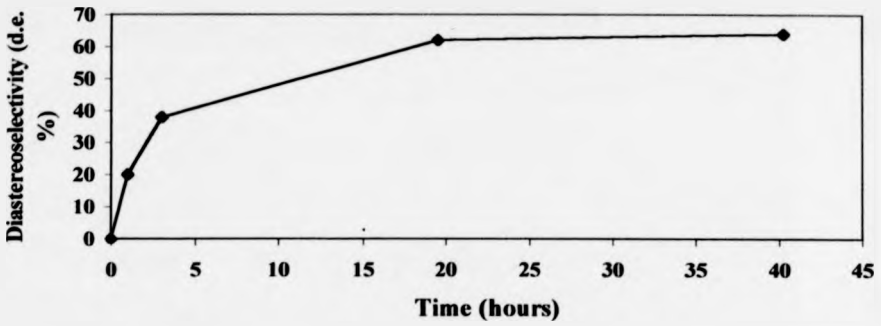
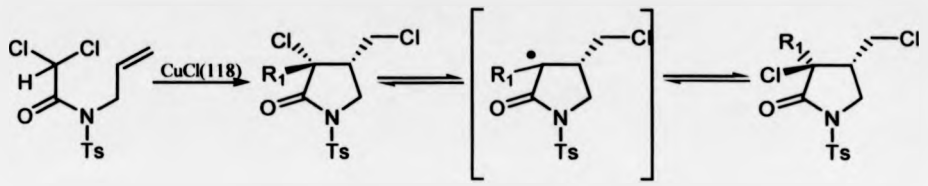


Figure 22.

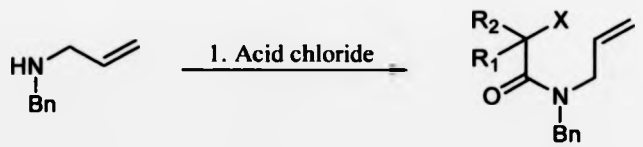
The reaction was carried out using *N*-allyl-*N*-toluenesulphonyl-2,2-dichloropropionamide (123) in refluxing dichloromethane and the diastereoselectivities determined by N.M.R. after varying times. The results can be seen in figure 22, these clearly show that the diastereoselectivity changes with time presumably reaching the thermodynamic ratio after a period of one day. Slough concluded that the rate of isomerisation was not great enough to alter the diastereoselectivity significantly over the course of his reactions. However, over an extended reaction time the rate of isomerisation may play a significant part in the degree of diastereoselectivity. Therefore, care must be taken when comparing the diastereoselectivity for reactions with significantly different reaction times and at different temperatures. The most probable mechanism for isomerisation was that proposed by Weinreb *via* α-chlorine abstraction of the product (scheme 63).[31]



Scheme 63. The proposed mechanism for the isomerisation of *N*-tosyl-α,α-dichloro-α-alkyl-allylacetamides.

4.4.3 Synthesis of *N*-benzyl-α,α-dichloro-α-alkyl-allylacetamides precursors.

We also investigated the effect of the *N*-protecting group upon cyclisation. The general procedure for the preparation of these *N*-benzyl cyclisation precursors was carried out again using standard literature procedures. Acid chloride (1eq) was added dropwise over a period of 5 minutes to a stirred solution of *N*-allyl-*N*-benzylamine (120) (2 eq.) in dichloromethane under nitrogen and the mixture allowed to stir for 2 hours at RT (scheme 64).



(120) (127-129)

Scheme 64. Synthesis of *N*-benzyl-α,α-dichloro-α-alkyl-allylacetamides.

Table 19. Yields of *N*-benzyl haloacetamides (127)-(129)

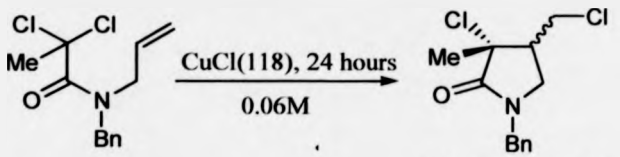
Entry	No.	R_1	R_2	X	E:Z	Yield %
1	(127)	Cl	Cl	Cl	1.8:1	80
2	(128)	H	Cl	Cl	2:1	82
3	(129)	Me	Cl	Cl	1.5:1	74

The *N*-benzyl protected precursors (127-129) all gave N.M.R. spectra which were broad with individual signals and split, presumably due to restricted rotation around the amide bond. Conjugation between the nitrogen lone pair and the carbonyl leads to increased double bond character in the C-N bond and there was some degree of restricted rotation about this bond at RT. The major rotamer in each case presumably arose from the corresponding (E) conformation due to the (Z) conformation being higher in energy. The ratio of (E) to (Z) proved to be dependent on the relative size of the substituents R_1. The smaller the substituent R_1 the larger the amount of the (Z) conformation observed in the N.M.R. (table 19). The broadening of the spectra was in agreement with those previously prepared and published.[27b] The yields of the precursors were generally good and in line with literature values.

4.4.4 Comparison with the previously published $CuCl(TMEDA)_2$ atom transfer cyclisation catalysts.

Following the successful comparison with the *N*-Tosyl systems using $RuCl_2(PPh_3)_3$ we next examined the related *N*-benzyl systems and compared the results to those published using $CuCl(TMEDA)_2$. To follow up the comparisons made with the $RuCl_2(PPh_3)_3$ the CuCl(118) system was screened against the precursors employed by Ghelfi.[27b] Ghelfi reported the cyclisation of *N*-benzyl-α,α-dichloro-α-alkyl-acetamides (127-129) at 60°C using $CuCl(TMEDA)_2$ catalyst. We thus conducted cyclisations of (127-129) using the same conditions outlined in his report. Hence to a 0.12M solution of *N*-benzyl-α,α-dichloro-α-alkyl-acetamide (127-129) in CH_2Cl_2 under nitrogen was added CuCl (30 mol%) and *N*-pentyl-2-pyridylmethanimine (118) (30 mol%). The mixture was then refluxed for between 12 and 24 hours. The change in solvent from acetonitrile (Ghelfi) to dichloromethane was not thought to be significant due to the results shown

in scheme 65. Ghelfi used MeCN as a solvent, to confirm that a change to CH_2Cl_2 would not have any effect on the d.e. the reaction shown in scheme 65 was carried out.



CH_2Cl_2 = d.e. 24%

CH_3CN = d.e. 20%

Scheme 65. Effect of solvent on the cyclisation of *N*-allyl-*N*-toluene-sulphonyl-2,2-dichloropropionamide (128).

Table 20. Comparison between CuCl(118) and $CuCl(TMEDA)_2$

Entry	No.	R_1	CuCl(118) *cis:trans*	Yield %	$CuCl(TMEDA)_2$ *cis:trans*	Yield %
1	(127)	Cl	-	98	-	99
2	(128)	H	2:1	75[a]	2.5:1	99
3	(129)	Me	2.6:1	95	1.7:1	99

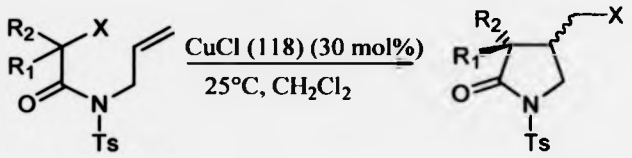
[a] percentage conversion

Results indicated that both catalyst systems were comparable (table 20) however, the elevated temperature used for the $CuCl(TMEDA)_2$ reaction was the cause of the differences expressed in entry 2.

4.4.5 Cyclisation of monohaloacetamides.

Along with the elevated reaction temperatures, almost all of the published atom transfer cyclisation procedures utilise activated α,α,α-tri and α,α-dichloroacetamides. Although the use of the highly functionalised cyclic systems can be of benefit, this

methodology has limits in the generation of natural products. The inclusion of too many halogen atoms usually necessitates a dehalogenation reaction later in the synthesis. Therefore, it was thought to be of synthetic value if the CuCl(118) system could be used to cyclise mono-halogenated precursors (scheme 66). Initially the selection of the precursor used was made on the availability of the corresponding bromo-acid.



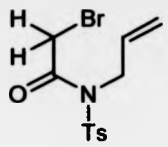
(125-126)

Scheme 66.

Table 21. Cyclisation of mono haloacetamides (125)-(126) using CuCl(118)

Entry	No.	R_1	R_2	X	Yield %
1	(125)	Me	Me	Br	97
2	(126)	H	H	Br	-

While the result for cyclisation of the tertiary bromide (125) (table 21 entry 1) proved to be very encouraging, attempts to cyclise the precursor (126) at RT failed completely only producing starting material. This was thought to be due to the deactivation by introduction of H in place of the methyl groups, a similar observation was made in section 1.2.1.



(126)

Selection of a higher reaction temperature was thought to provide the necessary remedy based on the results expressed in section 1.2.1. However, carrying out the reaction of (126) in refluxing dichloromethane only yielded starting material. Increasing the reaction temperature to 100°C only managed to yield a trace of the corresponding 4-bromomethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one. Thus indicating that the rate of the cyclisation was slowed to a level beyond the capabilities of this catalyst system.

4.5 Conclusions.

In conclusion the research has shown that CuCl(118) was an effective system for facilitating the atom transfer of both activated and unactivated α-haloacetamides. The comparisons made with previously reported systems $CuCl(TMEDA)_2$ and $(RuCl(PPh_3)_3$ have shown that the system was better, with higher diastereoselectvities and greater yields than those published using $RuCl_2(PPh_3)_3$ and comparable with the $CuCl(TMEDA)_2$ system reported by Ghelfi.

4.6 Future work.

Work is currently underway in the group to investigate how electronic effects in the ligands modify the reactivity. In addition the relative ease of the synthesis of this class of ligands, should allow for the development of solid-supported atom-transfer radical

cyclisation catalysts attached to solid supports *via* tethering to the imine nitrogen substituent and is the subject discussed in chapter 7.

Chapter 5.

Ligand geometry effects in copper mediated atom transfer radical cyclisation.

5.1 Introduction.

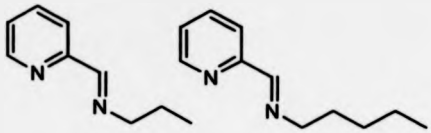
Having shown in the last chapter that the CuCl(118) system was capable of cyclising tertiary mono-halo substrates but not primary substrates we decide to investigate if another type of ligand class would be more reactive. While a range of different ligand systems has been investigated by a number of groups, no direct comparative study on how the changes in the ligand structure affect the rate of cyclisation has appeared in the literature. We endeavoured to synthesise and obtain a variety of different ligands and set up a screening program to investigate any structure-activity relationships. The most successful catalyst systems previously published CuCl(Bipy)[26], $CuCl(TMEDA)_2$[27] and CuCl (*N,N,N',N',N''*-pentamethyldiethylenetriamine) (PMDETA)[28] were included as a means of comparison.

5.2 Ligand synthesis.

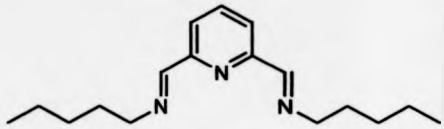
A series of different ligands were synthesised in accordance with standard literature procedures. The group of ligands can be roughly divided into two separate classes

- Aromatic pyridine/imine derived ligands (contains sp^2 nitrogen).
- Aliphatic amine derived ligands (contains sp^3 nitrogen).

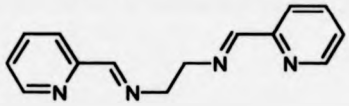
The aromatic pyridine/imine derived ligands (138)-(139) and (118) were prepared *via* standard literature procedure in good to excellent yields (77, 79 and 98% respectively). Ligands (192) and (193) were obtained from stock samples prepared by other members of the group. The range of ligands was chosen to contain different numbers of bonding nitrogen atoms. Ligands (138) and (118) are bidentate while (139) are tridentate and (192) and (192) tetradentate; while (118), (138) and (139) are likely to bond one metal atom, (192) and (193) in theory could bond either one (tetrahedral) or two (bidentate).



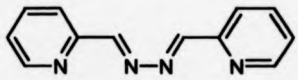
(138) (118)



(139)

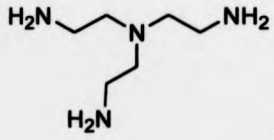


(192)



(193)

Aliphatic derived ligand (141) was also synthesised using standard literature procedures in a good yield (89%). The unprotected version of (141) *tris*(2-aminoethyl) amine (194) was also utilised in the screening program and was obtained from Aldrich at the highest available grade. The pyridyl imine derivative of (194) was also prepared (71%) for the commercially available *tris*(2-aminoethyl) amine.



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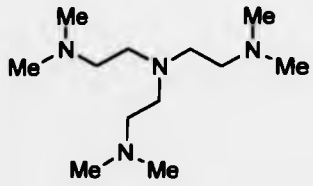
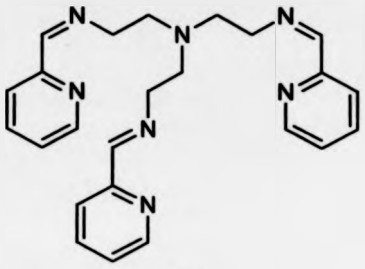
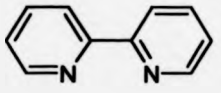


(141)

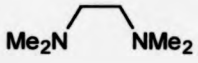


(140)

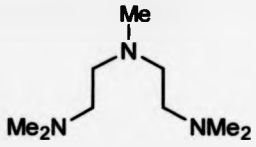
In addition to these ligands we also screened the previously reported ligands (195-197). The ligands (195-197) were obtained from the Aldrich catalogue at the highest grade possible.



(195)



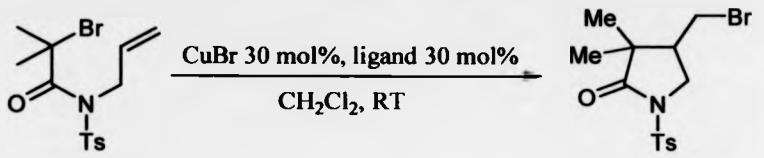
(196)



(197)

5.3 Screening.

The forementioned ligands were screened *via* the cyclisation of *N*-allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (125) (scheme 66). Hence, to a 0.12 M solution of *N*-allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (125) in CH_2Cl_2 at RT was added 30 mol% of ligand and CuBr. The solution was stirred at RT for 30 minutes and the sample was then quickly eluted through a small silica plug by suction to remove CuCl(ligand) complex. The ratio of starting material:product was determined by 250MHz ^1H N.M.R.. In all cases the mass balances for the reactions were excellent (90-98%) and the reactions were clean with only starting material and product peaks observable in the N.M.R..



(125) (136)

Scheme 67.

Table 22. Results of the screening program

Ligand	Conversion[a]	Mass balance
138	6%	94%
118	11%	98%
139	20%	98%
192	<2%	98%
193	0%	96%
141	100%	92%
140	100%	96%
195	75%	92%
196	5%	98%
197	100%	90%
141	20%[b]	94%
197	<2%[b]	90%

[a] 30 mol% CuBr, 30 mol% ligand, 0.12M

[b] 10 mol% CuBr, 10 mol% ligand, 0.03M

As can be seen from table 22 the catalysts derived from Bipy (195), PMDETA (197), and Tren(Me)$_6$ (141) were particularly active with 75%, 100% and 100% conversion to products respectively after 30 minutes. Particularly notable was that the *N*-pentyl-2-pyridylmethanimine ligand (118) was much slower than Bipy (195) in the cyclisation of (125). This result was in direct contrast to that previously mentioned (2.2.1) for the cyclisation of the trichloroacetate-*O*-allyl ester for which bipy was found to give poorer

product:starting material ratios. The conditions for this latter reaction however, were very different (toluene, 110°C) indicating that the solvent may have a crucial role to play in controlling the reactions presumably by effecting the solubility of the complex. Repeating the reactions with PMDETA (197) and Tren(Me)$_6$ (141) at lower catalyst loadings and lower concentrations for 2 hours allowed us to determine that the tetradentate ligand (141) was at least ten times faster at mediating the cyclisation of (125) than tridentate ligand (197). Interestingly the tetra/tri-dentate and tri-amine ligands were found to be more active than the tetra- and tri-dentate pyridine-imine hybride ligands (192) and (139). The tri-dentate pyridine-imine hybrid (139) proved to be significantly faster than the tetra-dentate version (192).

In parallel to our results Matjaszewski has recently indicated that the rate of ATRP of methacrylates increases in the order TMEDA<PMTEDA<trenMe$_6$ and that multi-dentate amine ligands generally catalyse polymerisation reactions faster than Bipy. This was explained by the lower redox potential of copper amine complexes compared to copper pyridine derived complexes.

5.4 Conclusions.

In conclusion we have shown that the rate of copper mediated atom transfer radical cyclisation reactions were heavily dependent upon ligand. It is highly likely that both effects alter the redox potential and solubility of the catalyst system and this in turn will affect the efficiency of the cyclisation. Simple copper amine complexes have been reported to have lower redox potentials than related pyridine derived ligands although more information may be needed before firm conclusions can be drawn. The major differences between the efficiency of TMEDA (196) and trenMe$_6$ (141) suggest that the

geometry of the ligand may also be a controlling factor. Assuming that the rate limiting step in the cyclisation reactions was the removal of a halogen atom from the starting material by a copper (I) chloride ligand complex to furnish a radical and a copper (II) complex, then ligands which stabilise the preferred geometry of copper (II) complexes (e.g. square pyramidal, trigonal bi-pyramidal and distorted octahedral) relative to copper (I) complexes (tetrahedral) should also facilitate cyclisation. $TrenMe_6$ (141) is known to co-ordinate to copper in a trigonal bi-pyramidal arrangement which may explain why it is so reactive a ligand in ATRC as it biases the equilibrium towards the copper (II) side of the equilibrium.

$$CuCl + R{-}X \underset{rds}{\rightleftharpoons} R\bullet + CuCl_2$$

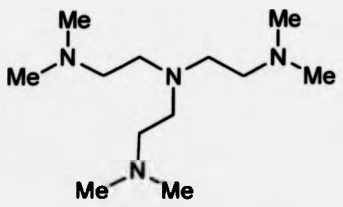
In addition bipyridine (195) and related complexes have low lying π^* orbitals that can accept electron density from the metal. This has the effect of stabilising low metal oxidation states. Hence bipyridine related ligands are better at stabilising Cu(I) complexes than the related amine ligands which do not have this back donating ability.

Chapter 6

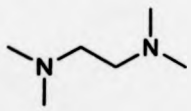
Copper trenMe$_6$ mediated atom transfer cyclisations of *N*-allylhaloacetamides.

6.1 Introduction

In the last chapter we reported that the CuCl(trenMe$_6$) derivative (141) was more efficient at ATRC of (125) than the pyridine imine ligands that we discussed in chapter 2. While the pyridine imine ligands were obvious analogues of the previously reported Bipy, the tren ligand (141) is a derivative of TMEDA and thus it was interesting to compare its catalyst activity to that of TMEDA reported by Ghelfi.[27b]



(141)

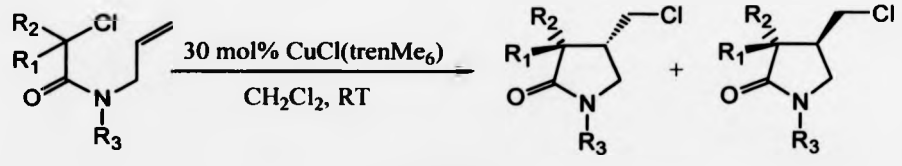


(196)

6.2 Cyclisation of dihaloacetamide substrates.

We initially chose to evaluate the efficiency and stereoselectivity of the one to one complex of CuCl and trenMe$_6$ (141) in atom transfer radical cyclisations of the previously prepared acetamides shown in table 23. Initial experiments involved comparison of the efficiency of this catalyst, with that of the previously reported

catalysts for the cyclisation of these acetamides (121-123) and (127-129), those being CuCl(PMDETA) (197), CuCl(Bipy) (195), CuCl(TMEDA)$_2$ (196) and $RuCl_2(PPh_3)_3$ (see chapter 4). The preparation of the substrates mentioned and trenMe6 have previously been described (chapter 4 and 5 respectively). The active catalyst was prepared *in situ* by the reaction of a 1:1 ratio of CuCl with the trenMe$_6$ in CH_2Cl_2. The substrate was then added to the catalyst (scheme 68). It was not necessary to use rigorously dried solvents or glassware or to use an inert atmosphere in order to carry out these reactions efficiently although for means of accurate comparison we did take these precautions. After the reactions were complete the crude reaction mixtures were passed through a short silica plug (eluted with CH_2Cl_2) and the solvent evaporated to furnish the atom transfer products in high yield (88-98%). In all cases the reactions proceeded cleanly with only products arising from cyclisation being detected.



Scheme 68.

Table 23. The results of the cyclisation of precursors (121)-(123) and (127)-(129)

Entry	No.	R_1	R_2	R_3	Time/Min	Yield (%)	Diastereoselectivity (%)[a]
1	(121)	Cl	Cl	Ts	<0.5	92	-
2	(122)	Cl	H	Ts	<120	96	66 (56)[b]
3	(123)	Cl	Me	Ts	<30	98	76 (46)[b]
4	(127)	Cl	Cl	Bn	<5	94	-
5	(128)	Cl	H	Bn	240	90	62 (44)[c]
6	(129)	Cl	Me	Bn	120	88	80 (2)[d]

[a] Ratio determined by 250 MHz N.M.R. [b] Ratio in brackets from $RuCl_2(PPh_3)_3$ cyclisation a 100-130°C.
[c] Ratio in brackets from CuCl(TMEDA)$_2$ cyclisation at 80°C. [d] Ratio in brackets from CuCl(TMEDA)$_2$ cyclisation at RT.

While cyclisations of both (121) and (127) using CuCl(Bipy) at RT have been reported to take 15 minutes and 1 hour respectively, with our catalyst system the reactions were over in less than 30 seconds and 5 minutes respectively. No advantage was found in running the reactions at lower concentrations, and all reactions were consequently run at 0.12M in substrate (identical to that reported for the $RuCl_2(PPh_3)_3$ mediated cyclisation of (121). While the reactions of 2,2,2-trichloracetamide derivatives (121) and (127) were over rapidly at RT, the less activated dichloroacetamide substrates (122) and (123) took approximately 120 and 30 minutes respectively. Both reactions furnished mixtures of diastereoisomers with (122) giving the *cis* isomer as the major product (ratio=17:83) while 123 gave the *trans* isomer as the major product (ratio=85:15).

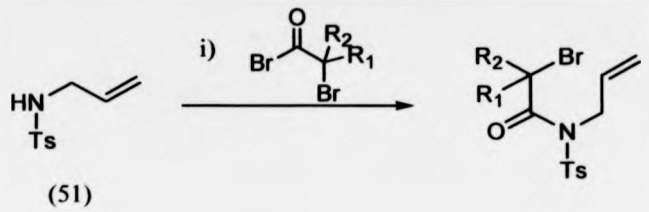
The effect of catalyst loading on the efficiency of the cyclisation of (123) was briefly investigated. Hence (123) was reacted with either 10, 5, 1 or 0.5 mol% of catalyst at RT over a 24 hour period. While the reactions with 10 and 5 mol% of catalyst proceeded to completion (by N.M.R.) within the 24 hour period, the reactions with loadings of 1 or 0.5 mol% of catalyst proceeded to give 57 and 33% conversions respectively. While the results indicate that it was possible to mediate the cyclisations at RT with lower catalyst loadings for the rest of the work, we continued to utilise 30 mol% of catalyst in order to keep the reaction times conveniently low.

Having shown that the CuCl(trenMe$_6$) catalyst was superior to $RuCl_2(PPh_3)_3$ for the cyclisation of *N*-tosylacetamides, we next compared its efficiency to that of CuCl(TMEDA)$_2$ in the cyclisation of the *N*-benzyl compound (127-129). While Ghelfi reported that the cyclisation of (128) with CuCl(TMEDA)$_2$ required 20 hours at RT and proceeded to give a 51:49 mixture of *cis*:*trans* isomers, we were delighted to find that using CuCl(trenMe$_6$) the reaction was over in 2 hours giving a superior 9:1 ratio of

products. For (128), selectivity was marginally greater using the CuCl(trenMe$_6$) catalyst system. The sense of the diastereoselectivity in both examples was identical to that reported by Ghelfi and co-workers. Having shown that activated trichloroacetamides and dihaloacetamides underwent atom transfer cyclisation reactions at RT in a more efficient manner than CuCl(TMEDA)$_2$, we next investigated the reactions of the less activated monohaloacetamides. Cyclisation of these unactivated systems have not previously been investigated with CuX(bipy), CuX(TMEDA)$_2$ or $RuCl_2(PPh_3)_3$. We thus chose to prepare a range of tertiary, secondary and primary mono-haloacetamides substrates (125-126, 143-144). We also investigated the effect of alkene substitution (146, 198) and whether 5-*exo* cyclisation onto an alkene was possible. In addition we prepared the mono-halo substrate (147) to investigate whether efficient 6-*exo* cyclisation was possible.

6.3 Synthesis of monohaloacetamide precursors.

The general procedure for the preparation of the mono-halo toluene-4-sulfonamide cyclisation precursors was carried out as follows. A solution of BuLi was added dropwise over 5 minutes to a stirred solution of *N*-allyl-toluene-4-sulfonamide in dry THF at –78°C under nitrogen and the mixture was stirred for 30 minutes at this temperature (scheme 69). To this solution the appropriate acid halide was added and the mixture stirred for a further 2 hours. The crude compounds generally needed purification by column chromatography.



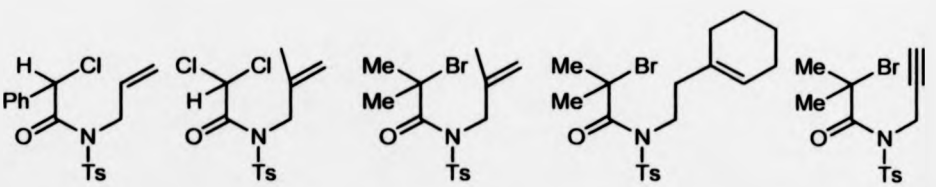
(51)

Scheme 69. Synthesis of *N*-tosyl-α-bromo-α-alkyl-allylacetamides.

Table 24. Yields of (125)-126) and (143)-(144)

Entry	No.	R_1	R_2	Yield
1	(125)	Me	Me	72%
2	(143)	Me	H	70%
3	(144)	*i*-Pr	H	64%
4	(126)	H	H	64%

The remaining cyclisation precursors (145)-(148) were prepared from their corresponding lithium amides using the same methodology as applied above (table 24). The precursor (198) was prepared by another member of the group.



(145) (198) (146) (147) (148)

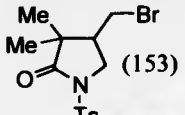
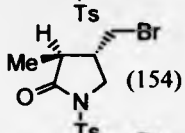
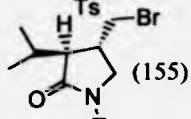
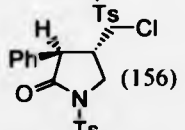
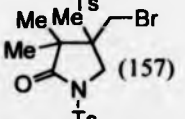
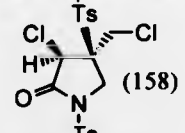
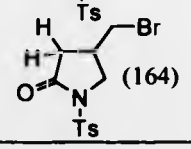
65% 75% 76% 69%

Yields throughout were generally moderate to good (64-76%).

6.3.1 Cyclisation of monohaloacetamide substrates (125)-(126), (143)-(146).

The five bromo precursors (125-126), (143-144) and (146) underwent cyclisation with 30 mol% of CuBr(trenMe$_6$) to furnish the expected cyclisation products (153-158) and (164) respectively. It was discovered that as the degree of substitution at the α-carbon decreased, the rate of cyclisation reactions slowed markedly.

Table 25. Yields and d.e. for precursors (125)-(126), (143)-(146) and (199)

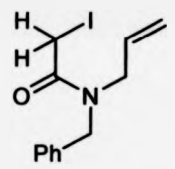
Entry	Substrate	Product	Yield % (*cis*:*trans*)[a,b]
1	(125)	 (153)	92%
2	(143)	 (154)	92% (1:9)
3	(144)	 (155)	95% (1:8.7)
4	(145)	 (156)	86% (1:>25)
5	(146)	 (157)	96%
6	(199)	 (158)	89% (1:5.5)
7	(126)	 (164)	18[c]

[a] 30 mol% CuBr, 30 mol% trenMe$_6$, in CH_2Cl_2 at RT (0.12M).

[b] Determined by 300 MHz ^{1}H N.M.R. of the crude mixture.

[c] Reaction carried out in $ClCH_2CH_2Cl$ in a sealed tube for 24 hours.

Hence, cyclisation of the tertiary precursors (125) or (146) proceeded with the fastest rate and were over after a few hours at RT, while cyclisation of the primary halide (126) required heating (100°C, sealed tube) over an extended period of time. Under these conditions (126) furnished a mixture of products with the cyclised product (164) being obtained in low yield (18%). A significant amount of deacetylated product *N*-allyl-*N*-toluene-4-sulfonamide (119) was also detected. In this case cleavage of the amide bond was the major reaction pathway, indicating that the use of high temperatures was not applicable to this methodology. While the reaction of (126) was not very efficient the result was significant in that Nagashima *et al.* reported that CuCl(Bipy) failed to cyclise the related *N*-allyl-*N*-benzyl-iodoacetamide (200).[26d]



(200)

Atom transfer cyclisation of the secondary bromoacetamides (143), (144) and (145) furnished the expected 5-exo products (154), (155) and (156) as a mixture of diastereoisomers. The major products in all cases were determined to be *trans* diastereoisomers. The major isomer of (154) was isolated, crystallised and the structure confirmed by X-ray analysis as shown in figure 23.

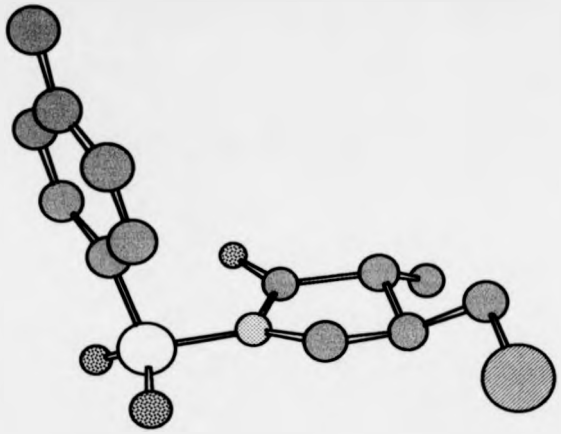


Figure 23. X-ray structure of compound (154).

The structure of the major isomer of (155) was elucidated using n.O.e. evidence, figure 24 shows the percentage enhancements. The percentage enhancements shown are large enough to infer a reasonable degree of accuracy in assignment of the structure as *trans*.

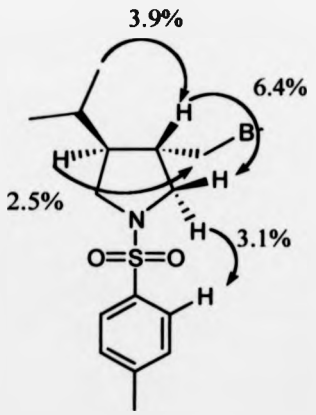
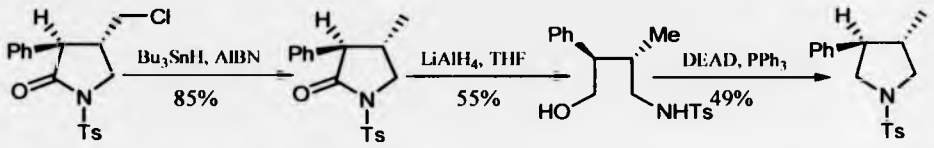


Figure 24. n.O.e. evidence for the major isomer of (155).

The major isomer of (156) was identified by chemical correlation with the known (165) (scheme 70).[32] Hence reductive removal of the halogen groups furnished (166) in a

good yield. Attempts to directly reduce the lactam (166) with $LiAlH_4$ failed as $LiAlH_4$ caused the cyclic structure to ring open *via* the cleavage of the N-C=O bond. Reports in the literature have shown that N-C=O cleavage can be a facile process when the nitrogen bears a strongly electron withdrawing group such as (166). Instead of investigating alternative reducing agents e.g. BH_3.THF we facilitated ring closure utilising Mitsunobu conditions. Hence reaction of the amine alcohol derivative (167) with DEAD and PPh_3 in the THF solvent produced the desired (165) in 49% yield.



(156) (166) (167) (165)

Scheme 70.

The product (165) showed identical spectral details to that published for an authentic sample,[32] the spectrum of which is shown below (fig.25)

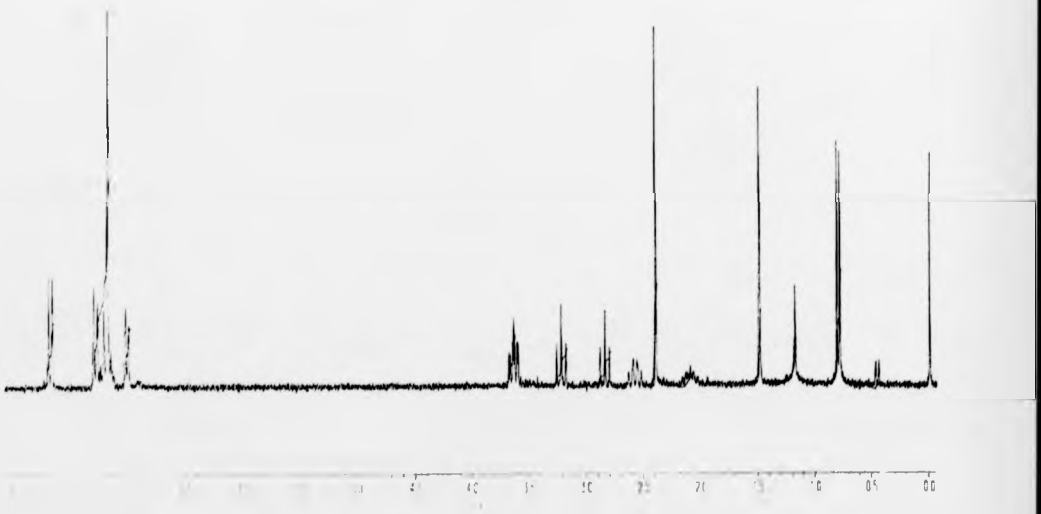


Figure 25 ^{1}H spectrum for (165).

The high *trans* selectivity can be rationalised by examining the potential transition states of cyclisation. Transition states for pathways leading to both *cis* and *trans* products were computed using MOPAC.[33] The calculations indicated that cyclisation *via* the *trans* pathway TS was lower in energy than that for the *cis* pathway (DE=4.0 kJ mol^{-1}).

6.3.2 Cyclisation of substrates (146, 199).

Having shown that it was possible to efficiently mediate the cyclisation of both tertiary and secondary mono-halo precursors in the 5-*exo* mode on to unsubstituted alkenes, we next investigated the reactions of substituted compounds (146, 199). Cyclisation of the *N*-(2-methyl-allyl)-*N*-(4-tolylsulfonyl)amide derived precursor (146) furnished the 5-*exo* cyclisation product (157) exclusively, with no 6-*endo* product being detected in the crude N.M.R. spectra. The cyclisation to furnish (158) also showed no detectable amount of 6-*endo* products in the crude N.M.R. The stereochemistry of (158) was confirmed as *trans* by n.O.e. difference data, the percentage reinforcements are shown in figure 26.

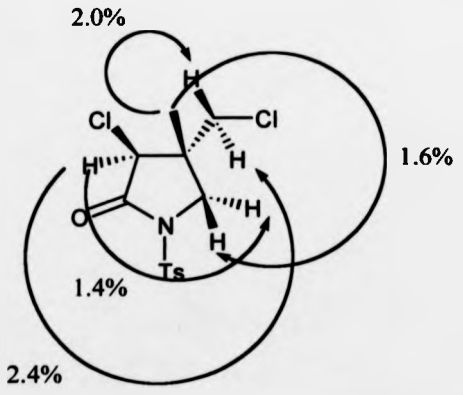
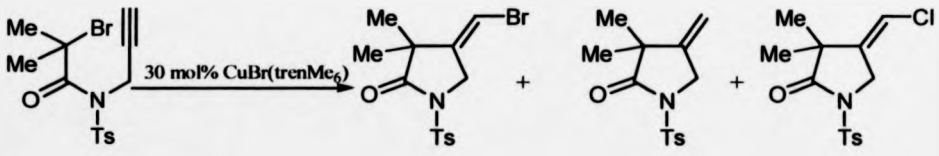


Figure 26. n.O.e evidence for the major isomer of (158)

The *trans* stereochemistry of (158) was opposite to the corresponding precursor analogue (122) that does not have a methyl substituted double bond. The reason for this could be that the methyl group caused the transition state to adopt the opposite conformation giving rise to the *trans* not *cis* isomer. This effect would have to be more fully investigated to apply that logic to other such systems.

6.4 Cyclisation onto alkynes.

The report that CuCl(TMEDA)$_2$ failed to mediate the cyclisation of radicals onto alkynes[27b] prompted us to investigate the cyclisation of the prop-2-ynyl acetamide (148). Reactions with 30 mol% CuBr(trenMe$_6$) in CH_2Cl_2 at RT gave a mixture of products (scheme 71). Analysis of the crude reaction mixture indicated that the expected bromoalkene derivative (159) (3:1) mixture of (E)- and (Z)- isomers) had been formed along with a significant amount of the reduced alkene (160) (ratio (159):(160)=1:1).



(148) (159) (160) (161)

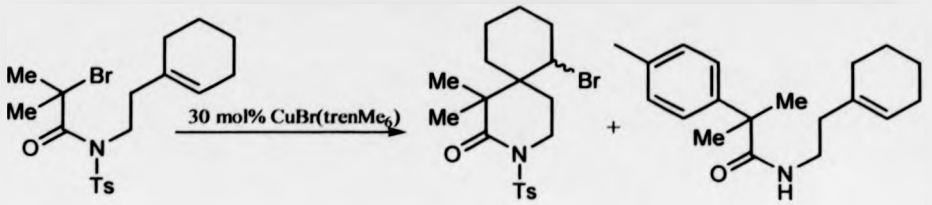
Scheme 71.

The expected bromoalkene derivative (159) ((3:1) mixture of (E)- and (Z)- isomers) had been formed along with a significant amount of the reduced alkene (160) (ratio (159):(160)=1:1). In addition, a trace amount (<2%) of a mixture of compounds, tentatively assigned as the chloroalkene derivatives (161), was also detected. The

products (160) and (161) presumably arose from the chlorine atom and hydrogen atom abstraction from the solvent (CH_2Cl_2) respectively. Repeating the reaction using tetrahydrofuran as solvent (which is a better hydrogen atom donor than CH_2Cl_2), furnished the reduced product (160) almost exclusively in high yield (90%) even though a catalytic amount of CuBr(trenMe$_6$) was used. In this case it was unclear whether the tetrahydrofuranyl radical formed by the reduction of the intermediate vinyl radical could facilitate cleavage of the carbon-bromine bond in the precursor (148) thus completing the chain reaction. These competing reactions were not observed for any of the other cyclisations reported here. This can be rationalised in terms of the greater reactivity of the intermediate vinyl radical arising from the reaction of (148) with respect to the primary radicals arising from the cyclisation of the substrates mentioned previously.

6.5 Attempt at 6-*exo* cyclisation.

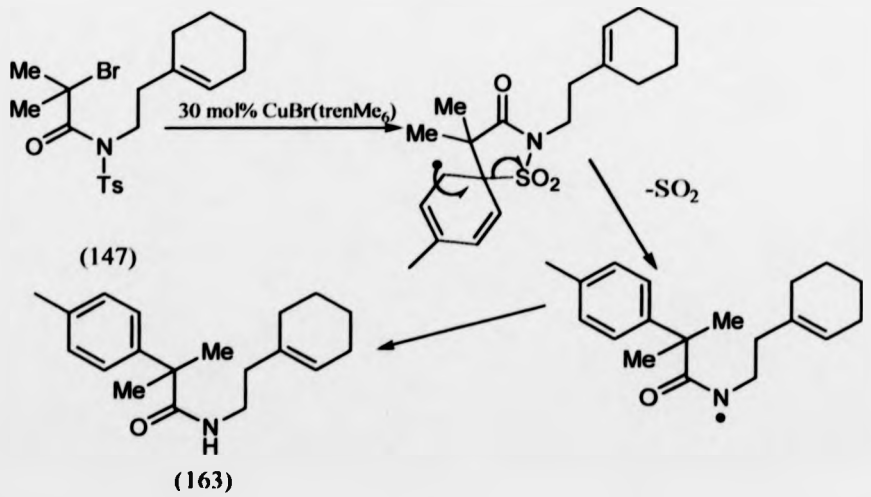
Cyclisation of (147) furnished three products. Chomatography produced two samples the first of which contained two products while the second contained a small amount of a single product. Careful N.M.R. and LC-MS analysis indicated that two inseparable products were in fact one diastereoisomer (162) (stereochemistry undetermined) of the 6-*exo* cyclisation product (162) together with the amide (163) (scheme 72). The third product could not be obtained absolutely pure and was not fully characterised but was tentatively assigned as the second diastereoisomer of (162) on the basis of N.M.R and mass spectra analysis.



(147) (162) (163)

Scheme 72.

The unexpected formation of the amide (163) can be explained by a competing 5-*exo* *ipso* aromatic radical substitution as shown in scheme (73). This new radical can then undergo rearomatisation followed by C-S bond cleavage and ultimately loss of SO_2 to furnish the observed product (163). The competitive migration of arylsulphonyl groups in relatively slow radical cyclisations mediated by tributyltin hydride, has been observed before and Motherwell has exploited this method in the formation of substituted biphenyls.[34] In this case the relatively slower rate of the 6-*exo* cyclisation relative to the previous 5-*exo* cyclisations allows for competitive migration to be observed.



(147) (163)

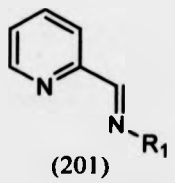
Scheme 73.

Chapter 7

Solid supported catalysts for atom transfer radical cyclisation of haloacetamides.

7.1 Introduction

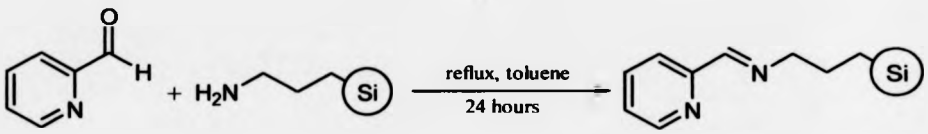
With the renaissance in solid supported chemistry, the design and use of novel solid supported reagents has become an area of great interest.[35] In the area of free radical chemistry, the vast majority of radical cyclisation reactions are initiated by organotin hydride reduction of carbon-halogen bonds. As a consequence the use of solid supported organotin hydride reagents has been reported by Neumann and others.[36] These have been shown to mediate efficient radical cyclisation reactions, however, the reductive nature of these cyclisations is a major disadvantage. Consequently we investigated the applicability of transition metal mediated solid supported catalysts to facilitate atom-transfer radical cyclisation reactions. We have already shown that *N*-alkyl 2-pyridyl-methanimines (201) can act as good ligands for copper-mediated atom-transfer cyclisation and Haddleton recently reported[37] that these ligands can be readily immobilised onto polystyrene and used in atom-transfer polymerisation reactions. As a consequence our initial aim was to produce a solid-supported catalyst that could be used in ATRC. The cheapest commercially available solid-supported amine (aminopropylated silica £17.80/10g) was chosen as the starting material to prepare the desired catalyst.



(201)

7.2 Preparation of the solid support.

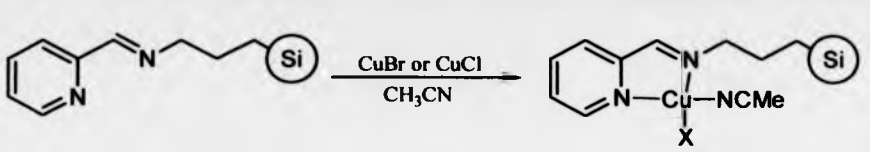
The solid supported catalysts were prepared by reacting 9% functionalised aminopropyl silica gel with an excess of pyridine-2-carboxaldehyde in toluene at reflux for 24 hours (with a soxhlet containing crushed 4 A molecular sieves to remove water) (scheme 74).



(168)

Scheme 74. Formation of solid support.

We had already determined that for efficient catalysis the best *N*-alkyl group was one that was derived from a primary amine, hence the use of the primary tethered amine was expected to give rise to the activated catalyst. After careful isolation of the light orange solid supported ligand and repeated washing with solvent to remove unattached absorbed ligands it was characterised by infrared spectroscopy, elemental analysis and solid state ^{13}C CP/MAS N.M.R.. The active catalysts (169a) and (169b) were then prepared by the reaction of the solid-supported ligands with either CuCl or CuBr dissolved in acetonitrile (scheme 75). After the solution was stirred for 1 hour, and washed with a large excess of acetonitrile, the dark brown solid catalysts were isolated.



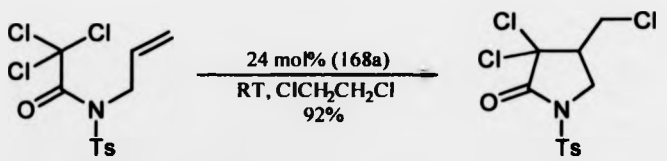
X= Cl (169a), Br (169b).

Scheme 75. Formation of solid supported catalyst.

ICP analysis indicated that they contained 4.3 and 4.7% copper, respectively. While the copper was likely to be bound directly to the attached ligand, the possibility that it was absorbed onto the surface of the silica cannot be completed discounted.

7.3 Reuseablility of the solid supported catalyst.

With the solid supported catalyst in hand our attention was turned to see if a) it was active in ATRC, and b) if it could be reused. Hence, reaction of solid supported catalyst (169a) (24 mol% based upon 4.3% copper content) with *N*-tosyl-*N*-allyl-2,2,2-trichloroacetamide in dichloromethane at RT for 3 hours furnished the expected atom transfer radical cyclisation product (202) in 92% yield after purification (scheme 76). The catalyst was reclaimed by filtration from the reaction mixture and was then reused with a new batch of (121) under identical conditions (second run; 90% in 18-24 hours).



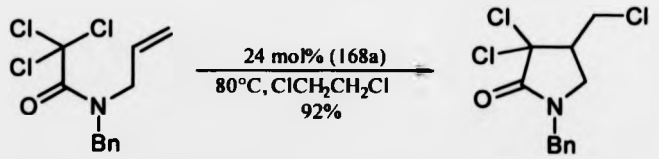
(121) (202)

Scheme 76. Cyclisation of *N*-tosyl-*N*-allyl-2,2,2-trichloroacetamide (121).

After filtration the catalyst was recycled a third time to give (202) in 86% in 24-36 hours. The dramatic increase in time required for completion was not found to be due to any leeching of the copper from the solid support as ICP analysis indicated that even after the third recycling the catalyst still contained 4.3% copper. During the course of these successive runs, the colour of the solid support gradually changed from dark brown to green, and the deactivation of the catalyst was therefore likely to be due to the formation of an inactive $CuCl_2$ complex. Whether this deactivated copper complex remained bound to the ligand or was extracted from the ligand by the surface silanol groups remains unclear. Encouraged by the successful application of the methodology to the ATRC of (121) we next examined a range of other substrates.

7.4 Cyclisation reactions.

Cyclisation of the less activated *N*-allyl-*N*-benzyl-2,2,2-trichloro precursor (127) required elevated temperatures but proceeded smoothly to give (133) in high yield after only 1 hour at 80°C (scheme 77). However, the rates of these cyclisations were much slower than those obtained using 30 mol% CuCl and (118) under homogeneous catalysis conditions as (121) furnished (202) in less than 1 minute at RT, while using heterogenous conditions the reaction required 2 hours at RT.

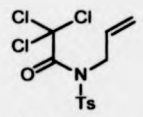
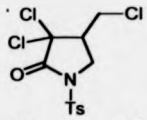
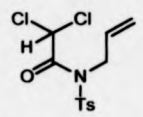
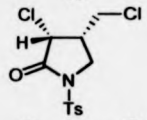
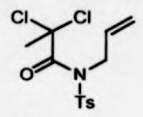
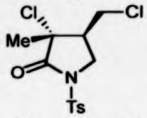
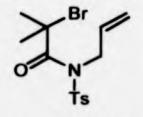
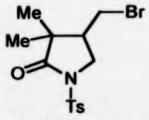
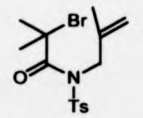
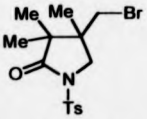
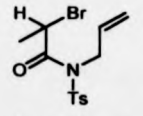
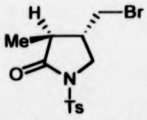
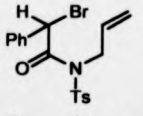
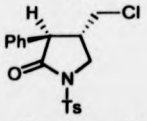
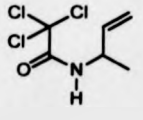
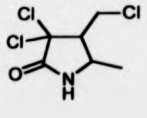


(127) (133)

Scheme 77. Cyclisation of *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide (127).

To determine the scope of the new solid supported methodology, we screened both catalysts (169a) and (169b) with a number of substrates (table 26), using 24 mol% catalyst in refluxing 1,2-dichloroethane at 80°C.

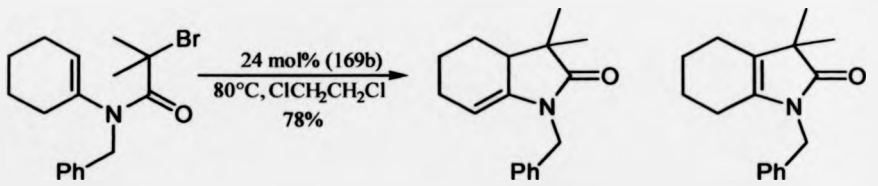
Table 26. Yields and d.e. using (169a) and (169b)

Entry	Substrate	Product[a]	Time (hr)	Yield[b] (%)
1			3[c]	96
2			20	96[d]
3			18	90[e]
4			24	92
5			36	90
6			24	92[f]
7			22	94[g]
8			48	75[h]

[a] All reactions were carried out in $ClCH_2CH_2Cl$ at reflux with 25 mol% catalyst.
[b] Combined yields of both diastereoisomers, major diastereoisomers shown.
[c] Reaction carried out at room temperature in $ClCH_2CH_2Cl$. [d] 55%. [e] 64%. [f] 64%. [g] 66%. [h] 72%.

While cyclisation of the *N*-allyl-*N*-benzyl-2,2,2-trichloroprecursor (127) proceeded smoothly at 80°C, the more deactivated 2,2-dichloroacetamide derivatives entries 2 and 3 required 18 hours (90%, de=64%) and 24 hours (96%, de=55%), respectively. The major product produced from the cyclisation of entry 3 was identical to that reported for the related Ru-mediated atom transfer cyclisation, while that from entry 2 was found to be of the sense opposite to that previously reported.[24] The selectivities were slightly poorer than those obtained using homogeneous catalysis mediated by CuCl and (118). Cyclisation of the unsubstituted amide entry 8 under the same reaction conditions also proved unproblematic, although an extended reaction time of 2 days was now required. The diastereoselectivity of the reaction was again similar to that reported for the related CuCl(Bipy) cyclisation. Having established that the solid-supported catalyst was active in mediating the cyclisation of the known trichloro- and dichloroacetamides, we next turned our attention to mediating the reaction of monohaloacetamides entries 4,5,6 and 7. Pleasingly it was possible to mediate the cyclisation of these relatively deactivated monohaloacetamides (table 26). Cyclisation of mono-halo derivatives entries 6 and 7 gave rise to the *trans* isomers as the major products (table 26). The stereochemistry of the major isomer shown in entry 7 was determined by chemical correlation to a known pyrrolidine (see section 6.3.1), while that of entry 6 was determined by x-ray analysis (see section 6.3.1). Cyclisation of the dimethyl-substituted precursors entries 4 and 5, were unproblematic and gave the expected 5-*exo* products in 92 and 90% yields, respectively. The success of the latter cyclisations indicated that steric hindrance at both the radical and the radical acceptor site were tolerated by the solid-supported reagent. Once again these reactions were much slower than those conducted under homogeneous catalysis using CuBr and (118). Under these conditions the precursors in entries 4 and 5 underwent complete conversion at RT and did not require heating.

It was also possible to mediate the 5-*endo* cyclisation of enamide (203) in a highly efficient manner. Cyclisation proceeded *via* a 5-*endo* reaction pathway to give the two alkene derivatives (170a) and (170b) in 78% yield as a 1:1 mixture of double bond regioisomer (scheme 78).



(203) (170a) (170b)

Scheme 78. Cycilsation of *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide (203).

While these isomers could be separated by column chromatography, they underwent rapid equilbration back to a 1:1 mixture in $CDCl_3$. Presumably 5-*endo* cyclisation followed by oxidation of the heterostabilised tertiary radical to the cation and elimination of H^+ led to the observed product.

7.5 Summary.

In conclusion we have shown that efficient 5-*exo* and 5-*endo* atom transfer radical cyclisations can be mediated by the solid supported Schiff base copper complexes (169a) and (169b) and that these catalysts can be reused, albeit with a substantial drop in activity. It was possible to mediate the cyclisation of trichloro-and dichloro-acetamides as well as the relatively unactivated mono-haloacetamides. However, the rates of reactions were significantly slower than for the homogenous counterparts using CuX(118).

7.6 Future work.

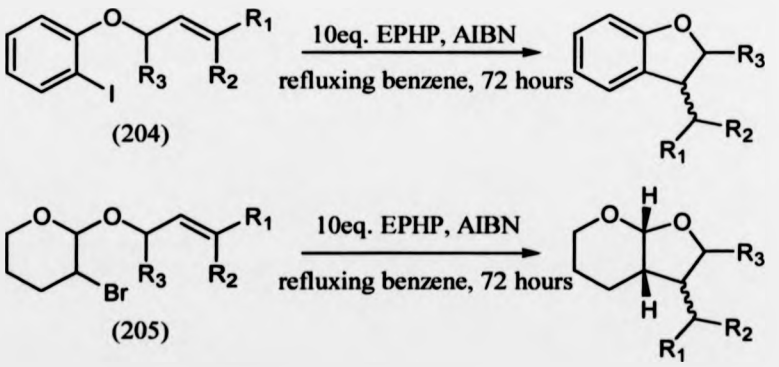
The effects of the type of support as well as tether length used in immobilising the ligands to the support could be examined in order to optimise the rates of reactions. The use of end-capped silica derivatives could be utilised to remove any potential copper SiOH interaction which may cause deactivation of the catalyst. Work carried out by Matjaszewski has shown that copper powder may be used to increase the activity of copper (I) atom transfer catalysts. This could be used to increase the reusability of the solid supported catalyst after the copper salt has been converted to the inactive copper (II) derivatives. In addition having determined in chapter 5 that the tertradentate trenMe$_6$ was a significantly better catalyst in ATRC reactions than imine(118) a range of solid supported ligands derived from trenMe$_6$ could be examined for activity.

Chapter 8

Cyclisation of haloacetamides using 1-ethylpiperidine hypophosphite.

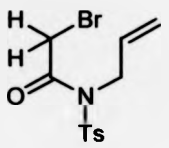
8.1 Introduction.

With an interest in furnishing radicals using novel non-tin hydride methodologies and after several attempts being made in chapter 3 we were interested to read the recently published paper of Murphy.[38] Expanding on the earlier functionalisation reactions described by Barton[39] and of Jang[40], Murphy utilised phosphorus radicals in the generation of new carbon-carbon bonds. The paper described the use of hypophosphorous acid and its *N*-ethylpiperidine salt as a "green alternative" to the problamatic tin based radical chemistry. He reported the use of both H_2PO_2 and 1-ethylpiperidine hypophosphite (EPHP) in the radical cyclisations onto various alkene side-chain units of both aryl iodide (204) and alkyl bromides (205) (scheme 79).[38]



Scheme 79.

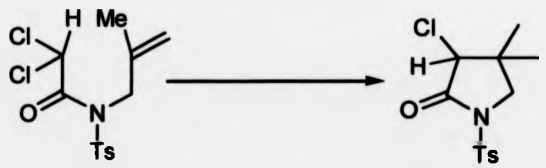
Having previously had problems with the Cu(trenMe$_6$) system described in chapter 6 in the formation and 5-*exo* cyclisation of primary alkyl radicals formed from halogenated *N*-tosyl acetamide precursor (126) we began to probe the scope of such reactions using 1-ethylpiperidine hypophosphite (EPHP). With several different *N*-tosyl acetamide precursors already in hand we conducted a study into their cyclisation using the reductive conditions of Murphy and compared it to the results (particularly stereochemistry) of the Cu(trenMe$_6$) system described in chapter 6.



(126)

8.2 Cyclisation reactions.

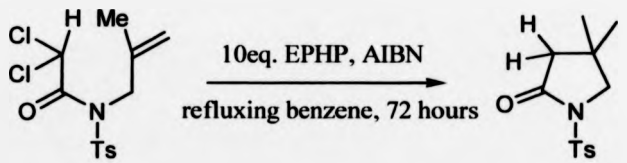
We initially chose to evaluate the cyclisation reactions of the prochiral *N*-(2,2-dichloro-acetyl)-4-methyl-*N*-(2-methyl-allyl)-benzenesulfonamide (199) (scheme 80). Comparison was made with precursor (199), using the Cu(trenMe$_6$) catalyst system under the conditions outlined in section (9.5.3.10).



(199) (206)

Scheme 80.

The cyclisation reaction was carried out by addition of 0.2 eq. of AIBN in two portions to a refluxing 0.12M solution of *N*-tosyl acetamide in dry benzene and 10 eq. of the commerically available 1-ethylpiperidine hypophosphite (EPHP). The mixture was then refluxed for a period of 72 hours. The product required no further purification as the N.M.R. was clean only yielding cyclisation product. The Cu(trenMe$_6$) catalyst system produced the expected two diastereoisomers in a ratio of 5.5:1 (*trans*:*cis*) in a yield of 89%. However, using EPHP the reaction yielded the fully dehalogenated product (171) in a yield of 79% (scheme 81). A fact consistent with both the Cu(trenMe$_6$) catalyst and the EPHP system was that a degree of steric crowding on the radical acceptor site was tolerated and that no *endo* product was observed in the ^{1}H N.M.R. spectra. The yields of both the EPHP system (79%) and the Cu(trenMe$_6$) catalyst (89%) were comparable with the Cu(trenMe$_6$) catalyst being slightly higher by 10%. The 10% difference was possibly due to differences in the work-up procedures.



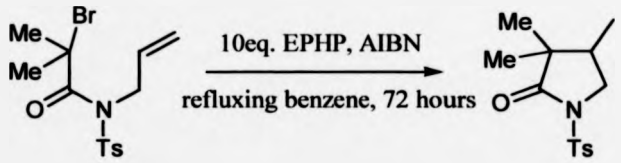
(199) (171)

Scheme 81.

With hindsight the formation of the observed product (171) should have been predicted as each molecule of EPHP contains two hydrogens that can be used in reduction, and since 10 eq. were used the reaction was conducted with a 20 fold excess of H-atom source. The consequence of that meant that a lesser amount of EPHP may be utilised. In a very recent publication by Murphy this fact was briefly investigated with his results showing that for aryl radical formation reduction in the amount of EPHP used resulted

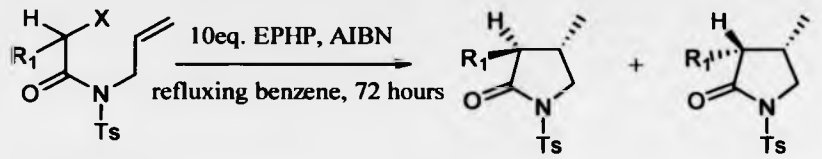
in extended reaction times.[40] This fact may not be consistent with the *N*-tosyl acetamide precursors used in this study as they were appreciably more activated so fewer eq. may not reduce the reaction times by a significant amount. However as several other reactions were already underway the 10 eq. of EPHP was thus kept constant for the rest of the reactions conducted in this study.

The next precursor selected was the mono-halogenated *N*-allyl-*N*-toluenesulphonyl-2-bromo-methylpropionamide (125). This reaction proceeded smoothly yielding the expected 4-bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (172) in a good yield of 83%, which required no further purification after work-up. Comparison of the yields with both the Cu(trenMe$_6$) (section 9.5.3) and the Cu(118) (9.3.4) system again proved comparable as they gave yields of >90%.



(125) (172)

We next chose to evaluate the cyclisation reactions of the prochiral *N*-tosyl acetamides (143-145), as before upon cyclisation two diastereoisomers (scheme 82) can be formed. The same substrates where cyclised using Cu(trenMe$_6$), that provided the opportunity of comparison for both diastereoselectivity and yield. The results of the cyclisation of precursors (143-145) with EPHP and Cu(trenMe$_6$) are shown in table 28.



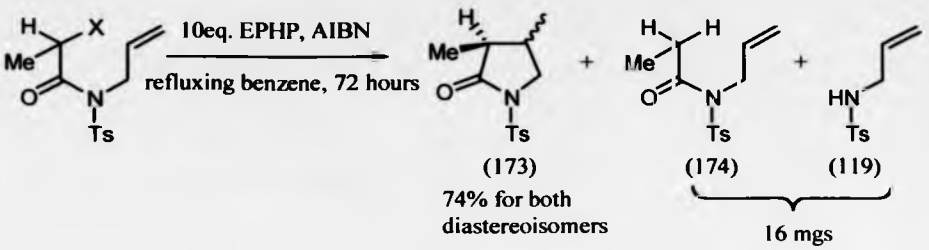
(143-145)

Scheme 82.

Table 28. Comparison of effeciency between EPHP and Cu(trenMe$_6$)

Entry	No.	R_1	EPHP *trans:cis*	Yield %	Cu(trenMe$_6$) *trans:cis*	Yield %
1	(143)	Me	8.7:1	74	9:1	92
2	(144)	*i*-Pr	18.6:1	77	8.7:1	95
3	(145)	Ph	11:1	65	>25:1	86

Entry one shows that when R_1 = Me the diastereoselectivities were comparable however, the yield was significantly reduced in the EPHP case by almost 20%. The 20% reduction was due to the formation of two side products namely the reduction compound (174) and the amide cleaved product (119) as shown in scheme 83. Both the impurities were inseparable with the major component (174) being present in large excess with only a trace of (119) being observed in the N.M.R.. The rate of cyclisation for the mono-haloacetamides could be described as being relatively slow and as such with a large excess of H- atoms present some of the formed radicals were reduced before having the chance to undergo cyclisation. If this was the path for the formation of the reduced species (174) then reduction in the amount of EPHP used should reduce the amount of reduction observed.



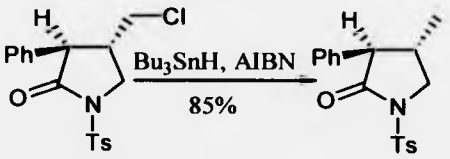
Scheme 83.

Entry 2 when R_1 = *i*-Pr the diastereoselectivity for the EPHP case was far superior (*trans*:*cis*, 18.6:1) being over double the corresponding Cu(trenMe$_6$) case (*trans*:*cis*, 8.7:1). The reason for this was unclear as the temperature in the EPHP case was approximately 100°C higher which usually gives rise to lower selectivities. The formation of the observed side product may be a factor complicating the diastereoselection. The yield was almost 20% lower than for Cu(trenMe$_6$) again due to the formation of the corresponding reduction and cleaved side products. The two side products were again inseparable however the ratio this time was 1:1. The decrease in the amount of reduction compound observed could be due to the increased steric hindrance around the radical centre which may prohibit to a degree any further reduction by the EPHP. Interestingly with R_1 = Ph the diastereoselectivities for the EPHP (*trans*:*cis*, 11:1) was less than that observed for the corresponding Cu(trenMe$_6$) case (*trans*:*cis*, >25:1)and shows the opposite trend to that above.

8.2.1 Stereochemical assignment.

The major diastereoisomer of all three pyrrolidinones (143-145) were assigned as *trans* in all cases *via* chemical correlation with the previously prepared pyrrolidinone (166) (see section 9.5.4.2). The synthesis of (156) was described in section 9.5.2.6 by the action of Cu(trenMe$_6$) at RT. This was then dehalogenated *via* tributyltin hydride

reduction to produce (166) in a yield of 85% (scheme 84). The ^{1}H NMRs for both the *trans* 4-chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (177) prepared by the action of EPHP and (166) formed by tributyltin hydride reduction are compared in table 29.



(156) (166)

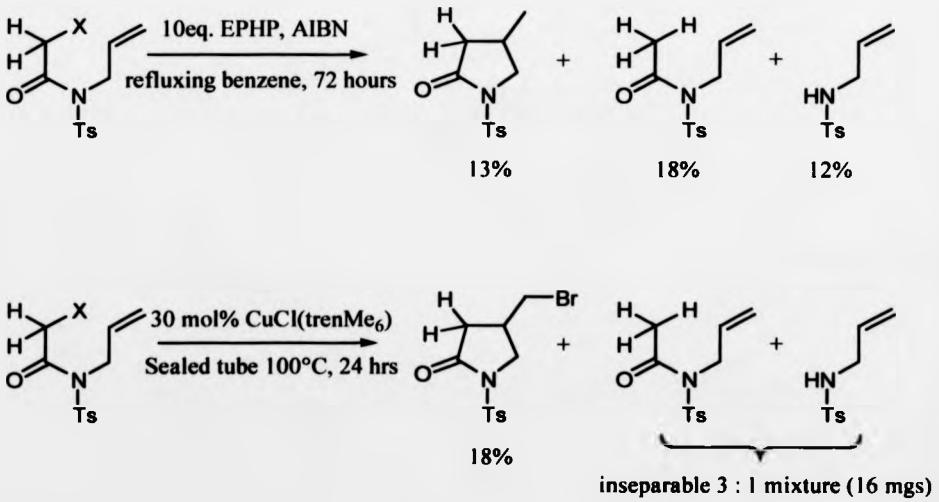
Scheme 84.

Table 29. Comparison of the ^{1}H N.M.R. spectra of (166) and (177)

^{1}H δ_H(400MHz; $CDCl_3$) for *trans* (166).	^{1}H δ_H(300MHz; $CDCl_3$) for *trans* (177).
1.04 (3H, d, J=6.4 Hz, CH_3)	1.04 (3H, d, J=6.4 Hz, CH_3)
2.31 (1H, m, $CHCH_3$)	2.32 (1H, m, $CHCH_3$)
2.38 (3H, s, CH_3)	2.40 (3H, s, CH_3)
3.08 (1H, d, J=11.1 Hz, CHPh)	3.06 (1H, d, J=11.1 Hz, CHPh)
3.27 (1H, t, J=10.4 Hz, HCHN)	3.26 (1H, t, J=9.8 Hz, HCHN)
4.09 (1H, dd, J=10.4, 2.25 Hz, HCHN)	4.07 (1H, dd, J=9.8, 2.25 Hz, HCHN)
6.99 (2H, d, J=8.1 Hz, Ar)	6.99 (2H, d, J=8.1 Hz, Ar)
7.19 (5H, m, Ph)	7.19 (5H, m, Ph)
7.94 (2H, d, J=8.1 Hz, Ar)	7.94 (2H, d, J=8.1 Hz, Ar)

8.3 Cyclisation of *N*-allyl-4-toluenesulfonyl-2-bromoacetamide (126).

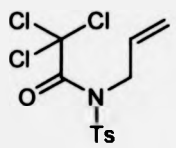
The rate of cyclisation for primary mono-haloacetamide (126) can be described as significantly slower than that observed for the other acetamides (143-145). This was confirmed when attempts to cyclise (126) using CuX(118) failed to yield any cyclised product even when elevated temperatures and extended reaction times were employed. This reaction was repeated with the superior Cu(trenMe$_6$) catalyst system and although cyclisation product was observed the yield was low (18%) with the formation of considerable amounts of side products (scheme 85). It was therefore thought to be worthwhile in attempting the cyclisation of (126) using the methodology developed by Murphy. It was hoped that employment of this methodology would give rise to increased yields of the desired pyrrolidinone (179) and less of the undesirable side products.



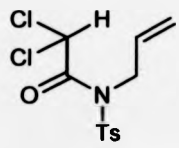
Scheme 85.

As with the other mono-haloacetamides (143-145) the reaction furnished three products. These included the desired pyrrolidinone (179) however, the yield was disappointing (13%) and was comparable with that observed for Cu(trenMe$_6$). The other two isolated side products were namely the reduction compound (180) and the cleaved compound (119) also observed for the Cu(trenMe$_6$) system (scheme 85).

While it was observed that primary radicals underwent relatively slow cyclisation using both methodologies secondary or tertiary radical cyclisations were very successful. In fact the desired product (179) would be best obtained using either the di- or tri-halogenated analogues (121) or (122). Therefore one may conclude that this method may be described as complementary to that of the transition metal mediated ATRC described in chapters 4 and 6.



(121)



(122)

8.4 Conclusions.

The research has shown that EPHP cyclises various haloacetamides in the 5-*exo* mode efficiently. The yields and diastereoselectivities are generally comparable to those encountered in the transition metal mediated ATRC of chapters 4 and 6. However, the cyclisations of the secondary monohaloacetamides (143-145) did not proceed as cleanly as those conducted with CuCl(trenMe$_6$) (chapter 6). There was seemingly no benefit in

reducing the number of halogens in the precursors as the EPHP removes them all mainly due to its large excess.

8.5 Future work.

The reactions are currently performed using 10 equivalents of EPHP, lower amounts of EPHP should decrease the amount of reduction seen in the di- or even tri-haloacetamide products. This would leave a useful functional handle that could be exploited to do further chemistry. The use of 10 equivalents of EPHP may also be advantage when utilising di- or tri-haloacetamides as this may enable both intra- and inter-molecular additions to be carried out in a one-pot procedure. The effect of the nitrogen substituent could also be looked at as this may be the cause of the observed side products in the cyclisation of the monohaloacetamides (143-145). The substitution of the *N*-Ts with less electron withdrawing substitutents such as *N*-Me of *N*-Bn may reduce the amount of side products observed.

Discussion. References

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CHAPTER 9

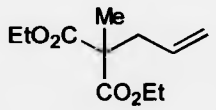
Experimental Notes.

Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Accurate Mass determinations were performed either on a Kratos MS80 at the University of Warwick or on a LC-MS SSS at Knoll Pharmaceuticals. Only molecular ions (M+ or MH+) and major peaks are reported and the intensities of these peaks are quoted as a percentage of the base peak. G.C. analysis was recorded on a Shimadzu G.C. using a polar type capillary column dimensions 25m/0.22 mm id. Microanalysis was recorded on a Leeman Labs Inc. CE440 Elemental Analyser. Infra-red spectra were recorded in a solution cell, as nujol mulls or neat, as stated in the text on a Perkin-Elmer 1720X Fourier transform spectrometer, with only selected absorbances (ν_{max}) being reported. ^{1}H N.M.R. spectra were recorded at either 250 MHz, 300MHz, or 400MHz on a Bruker ACF250, Bruker DPX300 or Bruker ACP400 instrument respectively. ^{13}C N.M.R. spectra were recorded at 62.9 Mhz, 75 MHz, and 100.6 Mhz. Chemical shifts (δ) are quoted in parts per million (ppm) with residual solvent as an internal standard. Chemicals used in the experimental were obtained from either Lancaster or Sigma-Aldrich at the highest grade available. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when needed by literature methods. Flash Chromatography was carried out on silica gel (Merck Kieselgel $60F_{254}$, 230-400 mesh). TLC was carried out using aluminium backed plates pre-coated with silica (0.2mm, $60F_{254}$). The tlc plates were developed using one or more of the following agents: U.V. fluorescence (254nm), or potassium permanganate.

9.1 Experimental for Chapter 2.

9.1.1Acid synthesis.

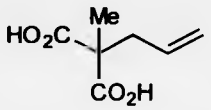
9.1.1.1 2-Allyl-2-methylmalonic acid diethyl ester (72).



To a stirred solution of anhydrous ether and absolute ethanol (50 cm^3), sodium metal (2.9 g, 0.126 mol) was added until completely dissolved. The solution was cooled to RT and diethyl methylmalonate (21.8 g, 0.125 mol) was added dropwise over a period of 30 minutes. After an additional period of 30 minutes allyl bromide (15.12 g, 0.125 mol) was added and the mixture refluxed for 1 hour. On addition of allyl bromide a white precipitate was formed. The mixture was then allowed to cool to RT and filtered through a bed of celite. The filtrate was concentrated and then distilled under reduced pressure (110°C at 10mm Hg) to yield 2-allyl-2-methylmalonic acid diethyl ester (72) (19.1 g, 73%) as a clear oil. Spectral details matched those previously reported.[1]

ν_{max} (neat)/cm^{-1} 2981, 1726, 1464; δ_H(250MHz; $CDCl_3$) 1.18 (6H, t, J=7.0 Hz, $CH_2\underline{Me}$), 1.35 (3H, s, Me), 2.55 (2H, dt, J=7.3, 1.2 Hz, CH_2), 4.10 (4H, q, J=7.0 Hz, $\underline{CH_2}Me$), 5.03 (2H, m, $CH=\underline{CH_2}$). 5.58 (1H, m, $\underline{CH}=CH_2$); δ_C(63MHz; $CDCl_3$) (2x) 13.79 (q), 19.44 (q), 39.80 (t), 53.17 (s), (2x) 60.95 (t), 118.79 (t), 132.45 (d), (2x) 171.64 (s).

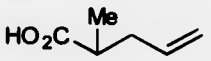
9.1.1.2 2-Allyl-2-methylmalonic acid (73).



To a stirred solution of 2-allyl-2-methylmalonic acid diethyl ester (72) (15 g, 0.07 mol) was added KOH (30 cm^3, 12M) dropwise. The mixture was then refluxed for 1 hour allowed to cool to RT and then acidified with 6M HCl in abs.ethanol. The mixture was then concentrated and extracted with dichloromethane (150 cm^3). The organic extract was then washed with water (2x 50 cm^3) and dried over anhydrous $MgSO_4$. Purification by recrystallisation (hexane/ethyl acetate) yielded 2-allyl-2-methylmalonic acid (73) (7.3 g, 66%) as a white crystalline solid; m.p. 87-89°C (lit m.p. 88-91°C).[1] Spectral details matched those previously reported.[1]

ν_{max} (neat)/cm^{-1} 3050, 1725, 1460; δ_H(250MHz; $CDCl_3$) 1.46 (3H, s, Me), 2.65 (2H, d, J=7.3 Hz, CH_2), 5.13 (2H, m, CH=$\underline{CH_2}$), 5.70 (1H, m, $\underline{CH}$=CH_2), 10.79 (2H, br s, 2x CO_2H); δ_C(63MHz; $CDCl_3$) 19.98 (q), 40.26 (t) 61.10 (s), 120.21 (t), 132.26 (d), (2x) 177.73 (s).

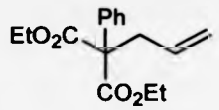
9.1.1.3 2-Methyl-pent-4-enoic acid (74).



2-Allyl-2-methylmalonic acid (73) (5.88 g, 37.2 mmol) was distilled at 150°C at 10mm Hg to yield 2-methyl-pent-4-enoic acid (74) (3.8 g, 89%) as a colourless liquid. Spectral details matched those previously reported.[1]

ν_{max} (neat)/cm^{-1} 3078, 1706, 1462; δ_H(250MHz; $CDCl_3$) 1.18 (3H, d, J=6.7 Hz, Me), 2.18 (1H, m, CH), 2.45 (2H, m, CH_2), 5.04 (2H, m, CH=$\underline{CH_2}$), 5.72 (1H, m, $\underline{CH}$=CH_2), 11.60 (1H, br s, CO_2H); δ_C(63MHz; $CDCl_3$) 16.64 (q), 37.79 (t), 39.50 (d), 117.55 (t), 135.44 (d), 183.25 (s).

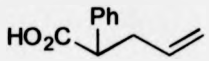
9.1.1.4 2-Allyl-2-phenylmalonic acid diethyl ester (75).



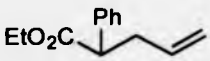
To a stirred solution of anhydrous ether and abs.ethanol (50 cm^3), sodium metal (2.9 g, 0.126 mol) was added until completely dissolved. The solution was cooled to RT and diethyl phenylmalonate (29.5 g, 0.125 mol) was added dropwise over a period of 30 minutes. After an additional period of 30 minutes allyl bromide (15.12 g, 0.125 mol) was added and the mixture refluxed for 1 hour. On addition of allyl bromide a white precipitate was formed. The mixture was then allowed to cool to RT and filtered through a bed of celite. The filtrate was concentrated and then distilled under reduced pressure (180°C at 10mm Hg) to yield 2-allyl-2-phenylmalonic acid diethyl ester (75) (26.5 g, 78%) as a clear oil. Spectral details matched those previously reported.[2]

ν_{max} (neat)/cm^{-1} 2980, 1728, 1446; δ_H(250MHz; $CDCl_3$) 1.17 (6H, t, J=7.0 Hz, $CH_2\underline{Me}$), 2.55 (2H, dt, J=7.0, 1.2 Hz, CH_2), 4.17 (4H, q, J=7.0 Hz, $\underline{CH_2}Me$), 5.00 (2H, m, $CH=\underline{CH_2}$), 5.72 (1H, m, $\underline{CH}=CH_2$), 7.25 (5H, m, Ph); δ_C(63MHz; $CDCl_3$) (2x) 14.32 (q), 40.71 (t), (2x) 61.82 (t), 63.04 (s), 119.07 (t), 127.87 (d), (4x) 128.90 (d), 133.47 (d), 137.21 (s), (2x) 170.54 (s).

9.1.1.5 2-Phenyl-pent-4-enoic acid (76).



To a stirred solution of 2-allyl-2-phenylmalonic acid diethyl ester (75) (20 g, 0.074 mol) was added KOH (30 cm^3, 12M) dropwise. The mixture was then refluxed for 1 hour allowed to cool to RT and then acidified with 6M HCl in abs.ethanol. The mixture was then concentrated and extracted with dichloromethane (150 cm^3). The organic extract was then washed with water (2x 50 cm^3) and dried over anhydrous magnesium sulphate. Distillation of the crude mixture (120-130°C at 10mm Hg) yielded 2-phenyl-pent-4-enoic acid ethyl ester (77) (10.2 g, 68%). Spectral details matched those previously reported.[3]



(77)

ν_{max} (neat)/cm^{-1} 2978, 1728, 1453; δ_H(250MHz; $CDCl_3$) 1.20 (3H, t, J=7.0 Hz, $CH_2\underline{Me}$), 2.51 (1H, m, CH_2), 2.83 (1H, m, CH_2), 3.62 (1H, t, J=7.0 Hz, CH), 4.12 (2H, q, J=7.0 Hz, $\underline{CH_2}Me$) 5.01 (2H, m, $CH=\underline{CH_2}$), 5.71 (1H, m, $\underline{CH}=CH_2$), 7.25 (5H, m, Ph); δ_C(63MHz;

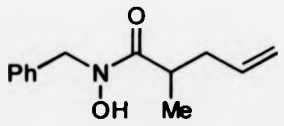
$CDCl_3$) 14.53 (q), 38.06 (t), 51.91 (d), 61.14 (t), 117.32 (t), 127.67 (d), (2x) 128.31 (d), (2x) 128.99 (d), 135.72 (d), 139.11 (s), 173.79 (s).

Repeat of the above conditions using 2-phenyl-pent-4-enoic acid ethyl ester (77) (10 g, 0.05 mol) yielded 2-phenyl-pent-4-enoic acid (76) (8.2 g, 93%) as a colourless liquid. (Found M^+ 176.0833 $C_{11}H_{12}O_2$ requires 176.0837).

ν_{max} (neat)/cm^{-1} 3053, 1713, 1414; δ_H(250MHz; $CDCl_3$) 2.50 (1H, m, CH_2), 2.86 (1H, m, CH_2), 3.61 (1H, t, J=7.0 Hz, CH), 5.04 (2H, m, $CH=\underline{CH_2}$), 5.67 (1H, m, $\underline{CH}=CH_2$), 7.25 (5H, m, Ph), 10.38 (1H, br s, CO_2H); δ_C(63MHz; $CDCl_3$) 37.46 (t), 51.81 (d), 117.66 (t), 127.99 (d), (2x) 128.46 (d), (2x) 129.11 (d), 135.30 (d) 138.27 (s), 180.22 (s); *m/z* (EI) 176 (M^+, 1%), 131 (72), 91 (100).

9.1.2 *N*-Alkyl-*N*-benzoyloxy-2-methyl pent-4-enamides (Method 1).

9.1.2.1 *N*-Benzyl-*N*-hydroxyl-2-methyl pent-4-enamide (78).

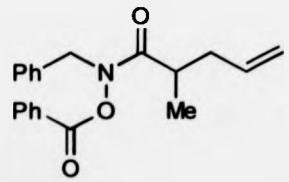


To a mixture of *N*-benzylhydroxylamine hydrochloride (0.42 g, 2.64 mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (25 cm^3) at 0°C was added a cold solution of 2-methyl pent-4-enoyl chloride (0.35 g, 2.64 mmol) (prepared by the reaction of 2-methyl pent-4-enoic acid (74) with excess oxalyl chloride) in dichloromethane (25 cm^3) over a period of 1 hour. The mixture was then allowed to warm to RT and allowed to

stir for an additional 2 hours. The reaction mixture was quenched with water (50 cm^3), and the organic layer was treated with 10% HCl (50 cm^3) and brine, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator. Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-benzyl-*N*-hydroxyl-2-methyl pent-4-enamide (78) (0.34 g, 59%) as a 4:1 mixture of rotamers in the form of a clear yellow oil. (Found MH^+ 220.1334 $C_{13}H_{18}NO_2$ requires 220.1338)

ν_{max} (neat)/cm^{-1} 3183, 1607, 1454; δ_H(250MHz; $CDCl_3$) 1.04 (3H, d, J=6.7 Hz, Me), 2.03 (1H, m, CH_2), 2.32 (1H, m, CH_2), 2.63 (1H, m, CH *minor rotamer*), 3.21 (1H, m, CH *major rotamer*), 4.62 (2H, m, $\underline{CH_2}Ph$), 4.93 (2H, m, $CH=\underline{CH_2}$), 5.65 (1H, m, $\underline{CH}=CH_2$), 7.24 (5H, m, Ph); δ_C(63MHz; $CDCl_3$) *major rotamer* 16.45 (q), 34.71 (d), 37.50 (t), 52.07 (t), 116.49 (t), 127.51 (d), (2x) 128.48 (d), (2x) 128.82 (d), 136.13 (d), 136.38 (s), 177.16 (s); *m/z* (CI; NH_3) 220 (MH^+, 5%), 204 (100), 91 (48%).

9.1.2.2 *N*-Benzoyloxy-*N*-benzyl-2-methyl pent-4-enamide (83).

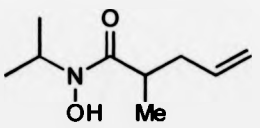


To a solution of *N*-benzyl-*N*-hydroxyl-2-methyl pent-4-enamide (78) (0.30 g, 1.37 mmol) in dichloromethane (5 cm^3) at 0°C was added triethylamine (0.19 cm^3, 1.37 mmol). The mixture was stirred for 15 minutes after which time benzoyl chloride (0.16 cm^3, 1.37 mmol) was added dropwise. The solution was stirred at 0°C for a period of 2 hours, allowed to warm to RT, and stirred for an additional 2 hours. The reaction mixture was

washed with water, 10% HCl, brine and then dried over anhydrous magnesium sulphate. Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-benzoyloxy-*N*-benzyl-2-methyl pent-4-enamide, (83) (0.33 g, 74 %) as a clear yellow oil. (Found M^+ 323.1519. $C_{20}H_{21}NO_3$ requires 323.1521).

ν_{max} (neat)/cm^{-1} 2929, 1765, 1673, 1452; δ_H(250MHz; $CDCl_3$) 1.14 (3H, d, J=6.7 Hz, Me), 2.08 (1H, m, CH_2), 2.42 (1H, m, CH_2), 2.59 (1H, sx, J=6.7 Hz, CH), 4.91 (2H, s, $\underline{CH_2}$Ph), 4.91 (2H, m, CH=$\underline{CH_2}$), 5.63 (1H, m, $\underline{CH}$=CH_2), 7.25 (5H, m, Ph), 7.42 (2H, t, J=7.6 Hz, *m*-Ph), 7.59 (1H, t, J=7.6 Hz, *p*-Ph), 7.95 (2H, d, J=7.3 Hz, *o*-Ph); δ_C(63MHz; $CDCl_3$) 16.64 (q), 35.75 (d), 37.60 (t), 51.51 (t), 116.80 (t), 126.64 (d), (2x) 127.80 (d), (2x) 128.49 (d), (2x) 128.82 (d), (2x) 129.82 (d), 130.45 (d), 134.39 (d), 134.50 (s), 135.39 (s), 164.28 (s), 176.05 (s); *m/z* (EI) 332 (M^+, 4%), 105 (100), 77 (77), 91 (53).

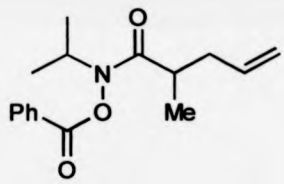
9.1.2.3 *N*-Hydroxyl-*N*-*i*-propyl-2-methyl pent-4-enamide (79).



To a 0°C mixture of *N*-*i*-propylhydroxylamine hydrochloride (0.295 g, 2.64 mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (25 cm^3) was added a cold solution of 2-methyl pent-4-enoyl chloride (0.35 g, 2.64 mmol) the same procedure was followed as outlined in section (9.1.2.1). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-hydroxyl-*N*-*i*-propyl-2-methyl pent-4-enamide, (79) (0.35 g, 78%) as a 3:1 mixture of rotamers in the form of a clear yellow oil. (Found M^+ 171.1255. $C_9H_{17}NO_2$ requires 171.1259).

ν_{max} (neat)/cm^{-1} 3173, 1605 1464; δ_H(250MHz; $CDCl_3$) 1.07 (2H, d, J=6.7 Hz, Me *minor rotamer*), 1.15 (5H, d, J=6.7 Hz, Me *major rotamer*), 1.32 (2H, d, J=6.7 Hz, Me), 2.04 (1H, m, CH_2), 2.34 (1H, m, CH_2), 2.66 (1H, sx, J=6.7 Hz, CH *minor rotamer*), 3.16 (1H, sx, J=6.7 Hz, CH *major rotamer*), 4.24 (1H, sp, J=6.7 Hz, MeCHMe *minor rotamer*), 4.62 (1H, sp, J=6.7 Hz, MeCHMe *major rotamer*), 4.96 (2H, m, CH=CH_2), 5.67 (1H, m, CH=CH_2), 8.87 (1H, bs, OH); δ_C(63MHz; $CDCl_3$) *major rotamer* 16.63 (q), (2x) 19.16 (q), 35.25 (d), 37.83 (t), 47.59 (d), 116.55 (t), 136.61 (d), 177.12 (s); *m/z* (EI) 171 (M^+, 20%), 155 (72), 97 (100).

9.1.2.4 *N*-Benzoyloxy-*N*-*i*-propyl-2-methyl pent-4-enamide (84).

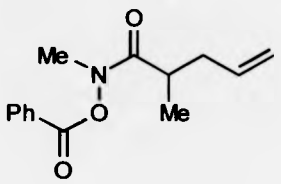


Following the procedure outlined in section (9.1.2.2), a solution of *N*-hydroxyl-*N*-*i*-propyl-2-methyl pent-4-enamide (79) (0.33 g, 1.93 mmol) in dichloromethane (5 cm^3) was reacted with triethylamine (0.27 cm^3, 1.93 mmol) and benzoyl chloride (0.22 cm^3, 1.93 mmol). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-benzoyloxy-*N*-*i*-propyl-2-methyl pent-4-enamide, (84) (0.31 g, 58%) as a clear yellow oil. (Found M^+ 275.1526. $C_{16}H_{21}NO_3$ requires 275.1521)

ν_{max} (neat)/cm^{-1} 2977, 1765, 1671, 1451; δ_H(250MHz; $CDCl_3$) 1.13 (9H, m, 3x Me), 2.07 (1H, m, CH_2), 2.45 (1H, m, CH_2), 2.59 (1H, m, CH), 4.89 (1H, sp, MeCHMe), 5.00 (2H, m, CH=CH_2), 5.66 (1H, m, CH=CH_2), 7.51 (2H, t, J=7.6 Hz, *m*-Ph), 7.66 (1H, t,

J=7.6 Hz, *p*-Ph), 8.10 (2H, d, J=7.6 Hz, *o*-Ph); δ_C(63MHz; $CDCl_3$) 16.61 (q), (2x) 19.19 (q), 36.06 (d), 37.57 (t), 49.82 (d), 116.56 (t), 128.83 (d), (2x) 129.83 (d), (2x) 130.45 (d), 134.25 (d), 135.55 (s), 165.22 (s), 186.70 (s); *m/z* (EI) 275 (M^+, 3%), 105 (100), 77 (74).

9.1.2.5 *N*-Benzoyloxy-*N*-methyl-2-methyl pent-4-enamide (85).



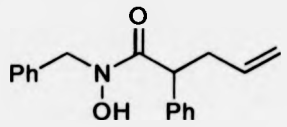
To a 0°C mixture of *N*-methylhydroxylamine hydrochloride (0.267 g, 3.20 mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (25 cm^3) was added a cold solution of 2-methyl pent-4-enoyl chloride (0.35 g, 2.64 mmol) the same procedure was followed as outlined in section (9.1.2.1). The intermediate *N*-hydroxyl-*N*-methyl-2-methyl pent-4-enamide was used without aqueous workup or purification. Following the procedure outlined in section (9.1.2.2), a solution of *N*-hydroxyl-*N*-methyl-2-methyl pent-4-enamide (0.68 g, 4.80 mmol) in dichloromethane (5 cm^3) was reacted with triethylamine (0.67 cm^3, 4.8 mmol) and benzoyl chloride (0.55 cm^3, 4.8 mmol). Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-benzoyloxy-*N*-methyl-2-methyl pent-4-enamide, (85) (1.08 g, 90%) as a clear yellow oil. (Found M^+ 247.1205. $C_{14}H_{17}NO_3$ requires 247.1208)

ν_{max} (neat)/cm^{-1} 2986, 1762, 1670, 1451; δ_H(250MHz; $CDCl_3$) 1.11 (3H, d, J=6.7 Hz, Me), 2.05 (1H, m, CH_2), 2.38 (1H, m, CH_2), 2.59 (1H, app sx, J=6.7 Hz, MeCH), 3.40 (3H, s, NMe), 4.96 (2H, m, CH=CH_2), 5.63 (1H, m, CH=CH_2), 7.47 (2H, t, J=7.6 Hz, *m*-Ph),

7.63 (1H, t, J=7.6 Hz, *p*-Ph), 8.06 (2H, d, J=7.6 Hz, *o*-Ph); δ_C(63MHz; $CDCl_3$) 17.04 (q), 36.09 (d), 38.03 (t), 53.84 (q), 117.11 (t), 127.20 (d), (2x) 129.27 (d), (2x) 130.29 (d), 134.82 (d), 135.95 (s), 164.67 (s), 172.25 (s); *m/z* (EI) 247 (M^+, 2%), 105 (100), 77 (67).

9.1.3 *N*-Alkyl-*N*-benzoyloxy-2-phenyl pent-4-enamides (Method 1).

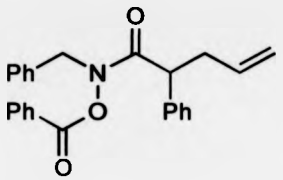
9.1.3.1 *N*-Benzyl-*N*-hydroxyl-2-phenyl pent-4-enamide (80).



To a mixture of *N*-benzylhydroxylamine hydrochloride (0.492 g, 3.08 mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (50 cm^3) at 0°C was added 2-phenyl pent-4-enoyl chloride (0.50 g, 2.60 mmol) the same procedure was followed as outlined in section (9.1.2.1). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-hydroxyl-*N*-benzyl-2-phenyl pent-4-enamide, (80) (0.53 g, 72%) as a 1.5:1 mixture of rotamers in the form of a clear yellow oil. (Found (M^+-16) 265.1465 $C_{18}H_{19}NO$ requires 265.1467).

ν_{max} (neat)/cm^{-1} 3206, 1618 1453; δ_H(250MHz; $CDCl_3$) 2.40 (1H, m, CH_2), 2.78 (1H, m, CH_2), 3.68 (1H, m, CH *minor rotamer*), 4.25 (1H, m, CH *major rotamer*), 4.71 (2H, s, Ph), 4.94 (2H, m, CH=CH_2), 5.69 (1H, m, CH=CH_2) 7.12 (10H, m, 2x Ph); δ_C(100MHz; $CDCl_3$) *major rotamer* 37.52 (t), 47.59 (d), 51.87 (t), 116.44 (t), (2x) 126.90 (d), (2x) 127.58 (d), (2x) 128.14 (d), (2x) 128.48 (d), (2x) 128.84 (d), 135.90 (d), 138.15 (s), 139.32 (s), 173.71 (s); *m/z* (EI) 265 (M^+-16), 265 (17%), 131 (77), 91 (100).

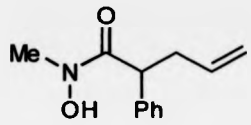
9.1.3.2 *N*-Benzyloxy-*N*-benzyl-2-phenyl pent-4-enamide (86).



Following the procedure outlined in section (9.1.2.2), a solution of *N*-benzyl-*N*-hydroxyl-2-phenyl pent-4-enamide (80) (0.43 g, 1.53 mmol) in dichloromethane (5 cm^3) was reacted with triethylamine (0.21 cm^3, 1.53 mmol) and benzoyl chloride (0.2 cm^3, 1.7 mmol). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-benzoyloxy-*N*-benzyl-2-phenyl pent-4-enamide, (86) (0.55 g, 90%) as a clear yellow oil. (Found M^+ 385.1670 $C_{25}H_{23}NO_3$ requires 385.1678)

ν_{max} (neat)/cm^{-1} 2924, 1765, 1675, 1451; δ_H(400MHz; $CDCl_3$) 2.45 (1H, m, CH_2), 2.88 (1H, m, CH_2), 3.73 (1H, t, J=7.4 Hz, PhCH), 4.97 (2H, s, CH_2Ph), 4.97 (2H, m, CH=CH_2), 5.68 (1H, m, CH=CH_2), 7.25 (10H, m, Ph), 7.41 (2H, t, J=7.6 Hz, *m*-Ph), 7.60 (1H, t, J=7.6 Hz, *p*-Ph), 7.81 (2H, d, J=7.6 Hz, *o*-Ph); δ_C(100MHz; $CDCl_3$) 38.04 (t), 48.74 (d), 51.58 (t), 116.70 (t), 127.71 (d), 127.97 (d), (2x) 128.40 (d), (2x) 128.48 (d), (2x) 128.67 (d), (2x) 128.81 (d), (2x) 128.91 (d), (2x) 129.63 (d), (2x) 130.46 (d), 134.50 (s), 135.52 (s), 138.17 (s), 163.76 (s), 173.10 (s); *m/z* (EI) 385 (M^+, 5%), 105 (100), 77 (48), 91 (45).

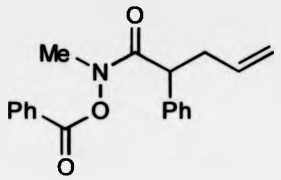
9.1.3.3 *N*-Hydroxyl-*N*-methyl-2-phenyl pent-4-enoic acid (81).



To a mixture of *N*-methylhydroxylamine hydrochloride (0.500g, 2.60mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (50 cm^3) at 0°C was added a cold solution of 2-phenyl pent-4-enoyl chloride (0.26 g, 3.08 mmol) the same procedure was followed as outlined in section (9.1.2.1). Purification by flash column chromatography eluting with 1:1 light petroleum ether:ethyl acetate gave *N*-hydroxyl-*N*-methyl-2-phenyl pent-4-enamide, (81) (0.40 g, 75%) as a 1:1 mixture of rotamers in the form of a clear yellow oil. (Found MH^+ 206.1179 $C_{12}H_{16}NO_2$ requires 206.1181).

ν_{max} (neat)/cm^{-1} 3174, 1614 1434; δ_H(250MHz; $CDCl_3$) 2.40 (1H, m, CH_2), 2.74 (1H, m, CH_2), 3.12 (1.5H, s, NMe), 3.25 (1.5H, s, NMe), 3.60 (1H, m, CH *minor rotamer*), 4.30 (1H, m, CH *major rotamer*), 4.92 (2H, m, CH=CH_2), 5.62 (1H, m, CH=CH_2) 7.26 (5H, m, Ph); δ_C(63MHz; $CDCl_3$) *major rotamer* 35.94 (t), 38.28 (q), 47.46 (d), 117.08 (t), 127.40 (d), (2x) 128.13 (d), (2x) 128.81 (d), 135.23 (d), 139.49 (s), 167.05 9s); *m/z* (EI) 205 (M^+), 205 (1%), 189 (22), 131 (97), 91 (100).

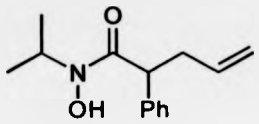
9.1.3.4 *N*-Benzyloxy-*N*-methyl-2-phenyl pent-4-enamide (87).



Following the procedure outlined in section (9.1.2.2), a solution of *N*-hydroxyl-*N*-methyl-2-phenyl pent-4-enamide (81) (0.28 g, 1.37 mmol) in dichloromethane (5 cm^3) was reacted with triethylamine (0.19 cm^3, 1.37 mmol) and benzoyl chloride (0.16 cm^3, 1.37 mmol). Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate gave *N*-benzoyloxy-*N*-methyl-2-phenyl pent-4-enamide, (87) (0.36 g, 86%) as a clear yellow oil. (Found M^+ 309.1360 $C_{19}H_{19}NO_3$ requires 309.1365)

ν_{max} (neat)/cm^{-1} 2976, 1768, 1680, 1453; δ_H(250MHz; $CDCl_3$) 2.47 (1H, m, CH_2), 2.89 (1H, m, CH_2), 3.43 (3H, s, NMe), 3.77 (1H, t, J=7.5 Hz, PhCH), 5.01 (2H, m, CH=CH_2), 5.70 (1H, m, CH=CH_2), 7.24 (5H, m, Ph), 7.52 (2H, t, J=7.6 Hz, *m*-Ph), 7.70 (1H, t, J=7.6 Hz, *p*-Ph), 8.01 (2H, d, J=7.6 Hz, *o*-Ph); δ_C(63MHz; $CDCl_3$) 36.28 (t), 38.57 (q), 49.12 (d), 117.09 (t), (2x) 127.56 (d), (2x) 128.40 (d), (2x) 129.00 (d), (2x) 129.28 (d), (2x) 130.37 (d), 134.76 (t), 136.07 (s), 138.83 (s), 164.19 (s), 173.63 (s); *m/z* (EI) 309 (M^+, 6%), 105 (100), 77 (58), 131 (37).

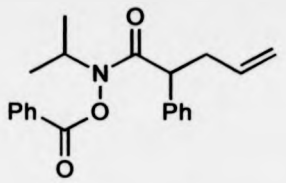
9.1.3.5 *N*-Hydroxyl-*N*-*i*-propyl-2-phenyl pent-4-enamide (82).



To a mixture of *N*-*i*-propylhydroxylamine hydrochloride (0.34 g, 3.08 mmol) and triethylamine (1.2 cm^3, 8.71 mmol) in dichloromethane (50 cm^3) at 0°C was added a cold solution of 2-phenyl pent-4-enoyl chloride (0.50 g, 2.6 mmol) the same procedure was followed as outlined in section (9.1.2.1). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-hydroxyl-*N*-*i*-propyl-2-phenyl pent-4-enamide, (82) (0.42 g, 69%) as a 2.3:1 mixture of rotamers in the form of a viscous brown/yellow oil. (Found MH^+ 233.1419 $C_{14}H_{19}NO_2$ requires 233.1416).

ν_{max} (CH_2Cl_2)/cm^{-1} 3113, 1602 1421; δ_H(400MHz; $CDCl_3$) 0.86 (2H, d, J=6.3 Hz, MeCHMe *major rotamer*), 0.98 (1H, d, J=6.3 Hz, MeCHMe *minor rotamer*), 1.16 (1H, d, J=6.3 Hz, MeCHMe *minor rotamer*), 1.31 (2H, d, J=6.3 Hz, MeCHMe *major rotamer*), 2.47 (1H, m, CH_2), 2.85 (1H, m, CH_2), 3.60 (1H, t, J=7.4 Hz, CH *major rotamer*), 4.20 (1H, sp, J=6.3 Hz, MeCHMe), 4.72 (1H, t, J=7.4 Hz, CH *minor rotamer*), 4.92 (2H, m, CH=CH_2), 5.67 (1H, m, CH=CH_2), 7.26 (5H, m, Ph) 8.38 (1H, s, OH); δ_C(100MHz; $CDCl_3$) *major rotamer* 19.02 (q), 19.96 (q), 38.42 (t), 47.46 (d), 50.27 (d), 116.89 (t), 127.23 (d), (2x) 127.51 (d), (2x) 128.75 (d), 135.49 (d), 138.70 (s), 165.85 (s); *m/z* (EI) 233 (M^+), 233 (4%), 217 (7%), 131 (100).

9.1.3.6 *N*-Benzoyloxy-*N*-*i*-propyl-2-phenyl pent-4-enamide (88).

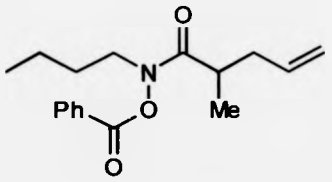


Following the procedure outlined in section (9.1.2.2), a solution of *N*-hydroxyl-*N*-*i*-propyl-2-phenyl pent-4-enamide (82) (0.30 g, 1.29 mmol) in dichloromethane (5 cm^3) was reacted with triethylamine (0.18 cm^3, 1.29 mmol) and benzoyl chloride (0.15 cm^3, 1.29 mmol). Purification by flash column chromatography eluting with 5:1 light petroleum ether:ethyl acetate gave *N*-benzoyloxy-*N*-*i*-propyl-2-phenyl pent-4-enamide, (88) (0.35 g, 80%) as a clear yellow oil. (Found M^+ 337.1681 $C_{21}H_{23}NO_3$ requires 337.1678)

ν_{max} ($CDCl_3$)/cm^{-1} 2978, 1769, 1664, 1452; δ_H(250MHz; $CDCl_3$) 1.20 (6H, brs, MeCHMe), 2.41 (1H, m, CH_2), 2.92 (1H, m, CH_2), 3.68 (1H, brs, CH), 4.95 (1H, brs, MeCHMe), 5.06 (2H, m, CH=CH_2). 5.81 (1H, m, CH=CH_2), 7.21 (5H, m, Ph), 7.57 (2H, t, J=7.6 Hz, *m*-Ph), 7.70 (1H, t, J=7.6 Hz, *p*-Ph), 8.01 (2H, brs, *o*-Ph); δ_C(100MHz; $CDCl_3$) 18.62 (q), 18.95 (q), 38.57 (t), 49.15 (d), 60.25 (d), 116.47 (t), (4x) 127.90 (d), (2x) 128.37 (d), (2x) 128.64 (d), (2x) 129.98 (d), 134.21 (d), 135.57 (s), 138.23 (s), 164.82 (s), 174.25 (s); *m/z* (EI) 337 (M^+, 15%), 105 (100), 77 (65), 131 (70).

9.1.4 *N*-*n*-Butyl-*N*-benzoyloxy-2-methyl pent-4-enamide (Method 2).

9.1.4.1 *N*-*n*-Butyl-*N*-benzoyloxy-2-methyl pent-4-enamide (89).

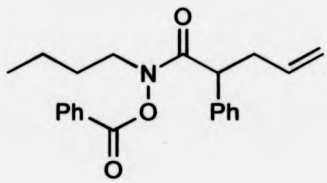


A slurry of $(PhCO_2)_2$ (1.2 g, 2.4 mmol) in dichloromethane (5 cm^3) was added to a solution of $NaHCO_3$ (1.145 g, 10.2 mmol) and n-butylamine (0.175 g, 2.4 mmol) in dichloromethane (5 cm^3) at RT. The reaction was stirred for 2 hours, after which time 2-methyl pent-4-enoyl chloride (0.35 g, 2.65 mmol) (prepared by the reaction of 2-methyl pent-4-enoic acid with oxalyl chloride) was then added dropwise and the reaction left stirring for a further 2 hours. The reaction was quenched with water and the organic layer extracted with dichloromethane (2x 100 cm^3). The organic phases were dried over anhydrous magnesium sulphate and evaporated under reduced pressure. Purification by flash column chromatography eluting with 6:1 light petroleum ether:ethyl acetate furnished *N*-*n*-butyl-*N*-benzoyloxy-2-methyl pent-4-enamide (89) (0.44 g, 63%) as a yellow oil. (Found M^+ 289.1676 $C_{17}H_{23}NO_3$ requires 289.1678)

ν_{max} (neat)/cm^{-1} 2962, 1761, 1669, 1451; δ_H(250MHz; $CDCl_3$) 0.89 (3H, t, J=7.3 Hz $\underline{Me}CH_2$), 1.12 (3H, d, J=7.0 Hz, Me), 1.39 (2H, sx, J=7.3 Hz, $\underline{CH_2}Me$), 1.56 (2H, qn, J=7.3 Hz, $\underline{CH_2}CH_2$), 2.06 (1H, m, CH_2), 2.41 (1H, m, CH_2), 2.58 (1H, sx, J=7.0 Hz, CH), 3.70 (2H, m, $\underline{CH_2}N$), 4.98 (2H, m, $CH=\underline{CH_2}$), 5.65 (1H, m, $\underline{CH_2}CH=CH_2$), 7.46 (2H, t, J=7.6 Hz, *m*-Ph), 7.52 (1H, t, J=7.6 Hz, *p*-Ph), 8.04 (2H, d, 7.6 Hz, *o*-Ph); δ_C(100MHz; $CDCl_3$)

13.60 (q), 16.68 (q), 19.76 (t), 29.02 (t), 35.75 (d), 37.63 (t), 47.22 (t), 116.59 (t), 125.49 (d), (2x) 128.75 (d), (2x) 129.66 (d), 134.18 (d), 135.54 (s), 162.92 (s), 173.25 (s); *m/z* (EI) 289 (M^+, 8%), 105 (100), 77 (65), 122 (40).

9.1.4.2 *N*-Benzoyloxy-*N*- *n*-butyl -2-phenyl pent-4-enamide (90).

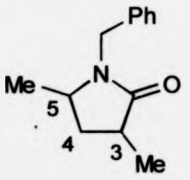


Prepared using the above procedure (9.1.4) with *n*-butylamine (0.14 g, 1.91 mmol). Purification by flash column chromatography 5:1 light petroleum ether:ethyl acetate yielded *N*-*n*-butyl-*N*-benzoyloxy-2-phenyl pent-4-enamide (90) (0.43 g, 63%) as a yellow oil. (Found M^+ 351.1829 $C_{22}H_{25}NO_3$ requires 351.1834).

ν_{max} (neat)/cm^{-1} 2927, 1765, 1670, 1452; δ_H(250MHz; $CDCl_3$) 0.83 (3H, t, J=7.3 Hz $\underline{Me}CH_2$), 1.18 (2H, m, $\underline{CH_2}Me$), 1.49 (2H, m, $\underline{CH_2}CH_2$), 2.39 (1H, m, CH_2), 2.82 (1H, m, CH_2), 3.66 (1H, t, J=7.3 Hz, CH), 3.77 (2H, m, $\underline{CH_2}N$), 5.06 (2H, m, $CH=\underline{CH_2}$), 5.64 (1H, m, $\underline{CH}=CH_2$), 7.14 (5H, m, Ph), 7.46 (2H, t, J=7.6 Hz, *m*-Ph), 7.62 (1H, t, J=7.6 Hz, *p*-Ph), 8.05 (2H, d, 7.6 Hz, *o*-Ph); δ_C(100MHz; $CDCl_3$) 14.04 (q), 20.14 (t), 29.11 (t), 38.62 (t), 48.22 (d), 49.25 (t), 117.03 (t), 127.53 (d), (2x) 128.40 (d), (2x) 129.21 (d), (2x) 129.27 (d), 130.15 (d), (2x) 130.37 (d), 134.70 (d), 136.14 (s), 139.02 (s), 164.38 (s), 172.75 (s); *m/z* (EI) 351 (M^+, 7%), 105 (100), 77 (71), 131 (68).

9.1.5 3,5-Di-substituted pyrolidinones.

9.1.5.1 *N*-Benzyl-3,5-dimethyl pyrrolidin-2-one (91).

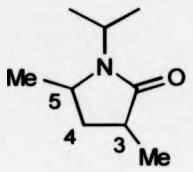


A solution of tributyltin hydride (0.11 cm^3, 0.39 mmol) and AIBN (0.01 g, 0.1 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (5 cm^3) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-benzoyloxy-*N*-benzyl-2-methylpent-4-enamide (83) (0.125 g, 0.39 mmol) in degassed toluene (5 cm^3). The reaction was then refluxed for a further 12 hours. The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. The acetonitrile portion was evaporated and the residue was further purified by flash column chromatography 2:1 hexane:ethyl acetate furnishing *N*-benzyl-3,5-dimethyl pyrrolidin-2-one (91) (0.07 g, 90%) as a inseparable mixture of diastereoisomers (ratio 55:45, *trans*:*cis*). (Found M^+ 203.1312 $C_{13}H_{17}NO$ requires 203.1310)

ν_{max} ($CDCl_3$)/cm^{-1}(*mixture*) 2967, 1669, 1452; δ_H(400MHz; $CDCl_3$) *trans* 1.11 (3H, d, J=6.3 Hz 5-Me), 1.20 (3H, d, J=7.0 Hz, 3-Me), 1.72 (1H, m, 4-H) 1.81 (1H, m, 4-H), 2.58 (1H, m, 3-H), 3.43 (1H, m, 5-H), 3.91 (1H, d, J=15.25 Hz, CH_2Ph), 4.95 (1H, d, J=15.25 Hz, CH_2Ph), 7.21 (5H, m, Ph); *cis* 1.15 (3H, d, J=6.3 Hz, 5-Me), 1.15-1.24 (1H, m, 4-H), 1.24 (3H, d, J=7.0 Hz, 3-Me), 2.32-2.47 (1H, m, 4-H), 2.58 (1H, m, 3-H), 3.40 (1H, m, 5-H), 3.99 (1H, d, J=14.8 Hz, CH_2Ph), 4.94 (1H, d, J=14.8 Hz, CH_2Ph), 7.21 (5H, m, Ph);

δ_C(100MHz; $CDCl_3$) *trans* 16.41 (q), 18.89 (q), 29.58 (t), 35.27 (d), 43.87 (d), 50.48 (t), 127.27 (d), (2x) 127.79 (d), (2x) 128.48 (d), 137.15 (s), 200.83 (s); *m/z* (EI) 203 (M^+, 41%), 84 (100), 91 (82), 188 (30).

9.1.5.2 *N-i*-Propyl-3,5-dimethyl pyrrolidin-2-one (92).

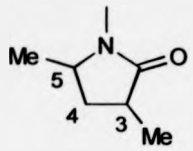


Following the procedure outlined in section (9.1.5.1), a solution of tributyltin hydride (0.15 cm^3, 0.55 mmol) and AIBN (0.01 g, 0.1 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (6 cm^3) was added to a solution of *N*-benzoyloxy-*N*-*i*-propyl-2-methyl pent-4-enamide (84) (0.150 g, 0.55 mmol) in degassed toluene (6 cm^3). Analysis by TLC indicated the reaction had not proceeded to completion therefore another half an equivalent of tributyltin hydride (0.075 cm^3, 0.28 mmol) and AIBN (0.01 g, 0.1 mmol) was added as before. The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. The acetonitrile portion was evaporated and the residue was further purified by flash column chromatography eluting with 2:1 hexane:ethyl acetate furnishing *N*-*i*-propyl-3,5-dimethyl pyrrolidin-2-one (92) (0.04 g, 47%) as a inseparable mixture of diastereoisomers (ratio 55:45 *trans*:*cis* determined using gas chromatography). (Found M^+ 155.1313 $C_9H_{17}NO$ requires 155.1310)

ν_{max} ($CDCl_3$)/cm^{-1}(*mixture*) 2964, 1661, 1456; δ_H(400MHz; $CDCl_3$) *trans* 1.10 (12H, m, 4x Me), 1.59 (1H, m, MeCHMe), 1.72 (2H, m, 4-H), 2.57 (1H, m, 3-H), 3.65 (1H, m, 5-H);

cis 1.10 (12H, m, 4x Me), 1.10 (1H, m, 4-H), 1.59 (1H, m, MeCHMe), 1.72 (1H, m, 4-H), 2.57 (1H, m, 3-H), 3.65 (1H, m, 5-H); δ_C(100MHz; $CDCl_3$) *mixture* 16.13 (q), 17.17 (q), 19.37 (q), 19.63 (q), 21.69 (q), 21.75 (q), 21.90 (q), 23.29 (q), 29.40 (t), 29.73 (t), 44.16 (d), 44.25 (d), 50.40 (d), 51.55 (d), (2x) 105.22 (d), 176.03 (s), 177.58 (s); *m/z* (EI) 155 (M^+, 15%), 57 (100), 91 (82), 71 (65).

9.1.5.3 *N*-Methyl-3,5-dimethyl pyrrolidin-2-one (93).

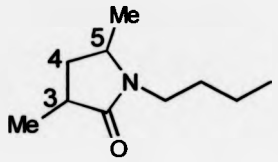


Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.33 cm^3, 1.20 mmol) and AIBN (0.02 g, 0.1 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (9 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N*-methyl-2-methyl pent-4-enamide (85) (0.300 g, 1.20 mmol) in degassed toluene (10 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. The acetonitrile portion was evaporated and the residue was further purified by flash column chromatography eluting 4:1, 2:1, light petroleum ether:ethyl acetate furnishing *N*-methyl-3,5-dimethyl pyrrolidin-2-one (93) (0.088 g, 64%) as a inseparable mixture of diastereoisomers (ratio 54:46 *trans:cis*). (Found MH^+ 128.1063 $C_7H_{14}NO$ requires 128.1075).

ν_{max} ($CDCl_3$)/cm^{-1} 2966, 1674, 1456; δ_H(400MHz; $CDCl_3$) *trans* 1.15 (3H, d, J=7.3 Hz 5-Me), 1.17 (3H, d, J=6.3 Hz, 3-Me), 1.75 (2H, m, 4-H), 2.49 (1H, m, 3-H), 2.78 (3H, s, NMe), 3.48 (1H, m, 5-H); *cis* 1.18 (3H, d, J=7.0 Hz 5-Me), 1.18-1.20 (1H, m, 4-H), 1.20

(3H, d, J=6.3 Hz, 3-Me), 2.32-2.43 (2H, m, 4-H + 3-H), 2.77 (3H, s, NMe), 3.39 (1H, m, 5-H); δ_C(100MHz; $CDCl_3$) *mixture* 16.35 (q), 16.56 (q), 18.89 (q), 20.16 (q), 27.16 (t), 27.38 (t), 35.04 (d), 35.09 (d), 36.35 (q), 36.50 (q), 53.37 (d), 53.56 (d), 177.11 (s), 177.54 (s); *m/z* (EI) 127 (M^+, 43%), 112 (100), 105 (87).

9.1.5.4 *N-n*-Butyl-3,5-dimethyl pyrrolidin-2-one (94).

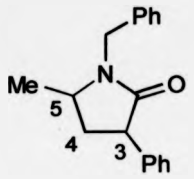


Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.20 cm^3, 0.70 mmol) and AIBN (0.011 g, 0.07 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (5 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N*-*n*-butyl-2-methyl pent-4-enamide (89) (0.200 g, 0.70 mmol) in degassed toluene (50 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography eluting with 4:1, 2:1, light petroleum ether:ethyl acetate furnishing *N*-*n*-butyl-3,5-dimethyl pyrrolidin-2-one (94) (0.047 g, 40%) as a mixture diastereoisomers (ratio 56:44 *trans:cis* determined using gas chromatography). (Found M^+ 169.1469 $C_{10}H_{19}NO$ requires 169.1467)

ν_{max} ($CDCl_3$)/cm^{-1} 2959, 1666, 1459; δ_H(400MHz; $CDCl_3$) *trans* 0.89 (3H, t, J=7.4 Hz, $\underline{Me}CH_2$), 1.10-1.37 (10H, m, 3+5-Me+$\underline{CH_2CH_2}$Me), 2.41 (2H, m, 4-H), 2.84 (1H, m, 3-H), 3.54 (3H, m, 5-H + $\underline{CH_2}$N); *cis* 0.89 (3H, t, J=7.4 Hz, $\underline{Me}CH_2$), 1.10-1.37 (10H, m, 3+5-

Me+$\underline{CH_2CH_2}$Me), 1-10-1.37 (1H, m, 4-H), 2.34 (1H, m, 4-H), 2.84 (1H, m, 3-H), 3.54 (3H, m, 5-H + $\underline{CH_2}$N); δ_C(100MHz; $CDCl_3$) *mixture* 13.48 (q), 13.68 (q), 16.44 (q), 17.40 (q), 19.13 (q), 20.00 (q), 26.71 (t), 27.72 (t), 35.28 (d), 35.39 (d), (2x) 36.53 (t), (2x) 36.59 (t), 39.62 (t), 39.72 (t), 50.99 (d), 51.12 (d), 177.06 (s), 177.25 (s); *m/z* (CI) 170 (MH^+, 100%), 126 (55), 98 (42).

9.1.5.5 *N*-Benzyl-5-methyl-3-phenyl pyrrolidin-2-one (95).

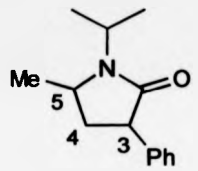


Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.20 cm^3, 0.78 mmol) and AIBN (0.013 g, 0.78 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (5 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N*-benzyl-2-phenyl pent-4-enamide (86) (0.300 g, 0.78 mmol) in degassed toluene (5 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate furnishing *N*-benzyl-5-methyl-3-phenyl pyrrolidin-2-one (95) (0.15 g, 73%) as a separable mixture of diastereoisomers (ratio 63:37 *trans:cis*). (Found M^+ 265.1469 $C_{18}H_{19}NO$ requires 265.1467)

ν_{max} ($CDCl_3$)/cm^{-1} 2968, 1673, 1451; δ_H(250MHz; $CDCl_3$) *trans* 1.22 (3H, d, J=6.1 Hz 5-Me), 2.07 (1H, m, 4-H), 2.07 (1H, m, 4-H), 3.55 (1H, m, 5-H), 3.77 (1H, t, J=8.2 Hz, 3-H), 3.95 (1H, d, J=15.0 Hz, CH_2Ph), 5.06 (1H, d, J=15.0 Hz, CH_2Ph), 7.21 (5H, m, Ph); *cis*

1.23 (3H, d, J=6.4 Hz, 5-Me), 1.58 (1H, m, 4-H), 2.57 (1H, m, 4-H), 3.49 (1H, m, 5-H), 3.65 (1H, m, 3-H), 4.10 (1H, d, J=15.2 Hz, CH_2Ph), 4.98 (1H, d, J=15.2 Hz, CH_2Ph), 7.21 (5H, m, Ph); δ_C(100MHz; $CDCl_3$) *trans* 19.24 (q), 36.22 (t), 44.29 (t), 47.01 (d), 51.12 (d), 127.02 (d), (2x) 127.60 (d), (2x) 128.32 (d), (2x) 128.76 (d), (2x)130.01 (d), 136.72 (s), 140.06 (s), 174.82 (s); *cis* 20.22 (q), 37.34 (t), 44.46 (t), 48.40 (d), 50.99 (d), (2x) 127.00 (d), (2x) 127.49 (d), (2x) 128.13 (d), (2x) 128.22 (d), (2x) 128.69 (d), 136.91 (s), 139.65 (s) 175.20 (s); *m/z* (EI) 265 (M^+, 51%), 91 (100), 118 (45).

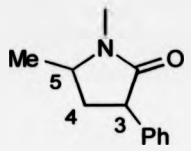
9.1.5.6 *N-i*-Propyl-5-methyl-3-phenyl pyrrolidin-2-one (96).



Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.2 cm^3, 0.74 mmol) and AIBN (0.012 g, 0.07 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (8 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N-i*-propyl-2-phenyl pent-4-enamide (88) (0.25 g, 0.74 mmol) in degassed toluene (8 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate furnishing *N-i*-propyl-5-methyl-3-phenyl pyrrolidin-2-one (96) (0.075 g, 52%) as a inseperable mixture of diastereoisomers (ratio 63:37 *trans:cis* determined using gas chromatography). (Found M^+ 217.1465 $C_{14}H_{19}NO$ requires 217.1467)

ν_{max} ($CDCl_3$)/cm^{-1} 2968, 1663, 1457; δ_H(400MHz; $CDCl_3$) *trans* 1.24 (9H, m, 5-Me + MeCHMe), 2.04 (1H, m, 4-H), 2.13 (1H, m, 4-H), 3.72 (1H, t, J=9.2 Hz, 3-H), 3.83 (1H, m, 5-H), 4.06 (1H, m, MeCHMe), 7.21 (5H, m, Ph); *cis* 1.24 (9H, m, 5-Me + MeCHMe), 1.56 (1H, m, 4-H), 2.58 (1H, m, 4-H), 3.56 (1H, t, J=9.8 Hz, 3-H), 3.83 (1H, m, 5-H), 4.07 (1H, m, MeCHMe), 7.21 (5H, m, Ph); δ_C(75MHz; $CDCl_3$) *trans* 20.20 (q), 21.29 (q), 22.40 (q), 37.92 (t), 44.70 (d), 45.01 (d), 51.18 (d), 126.20 (d), (2x) 128.43 (d), (2x) 128.61 (d), 139.42 (s) 175.10 (s); *m/z* (EI) 217 (M^+, 78%), 202 (100), 117 (50).

9.1.5.7 *N*-Methyl-5-methyl-3-phenyl pyrrolidin-2-one (97).

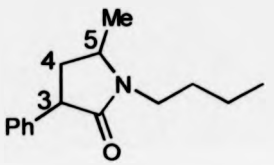


Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.22 cm^3, 0.81 mmol) and AIBN (0.013 g, 0.08 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (8 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N*-methyl-2-phenyl pent-4-enamide (87) (0.25 g, 0.81 mmol) in degassed toluene (8 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate furnishing *N*-methyl-5-methyl-3-phenyl pyrrolidin-2-one (97) (0.131 g, 86%) as a separable mixture diastereoisomers (ratio 63:37 trans:cis). (Found M^+ 189.1150 $C_{12}H_{15}NO$ requires 189.1154)

ν_{max} ($CDCl_3$)/cm^{-1} 2967, 1686, 1451; δ_H(250MHz; $CDCl_3$) *trans* 1.26 (3H, d, J=6.1 Hz 5-Me), 2.03 (1H, m, 4-H), 2.28 (1H, m, 4-H), 2.88 (3H, s, NMe), 3.65 (2H, m, 3+5-H) 7.19

(5H, m, Ph); *cis* 1.30 (3H, t, J=6.1 Hz 5-Me), 1.58 (1H, m, 4-H), 2.61 (1H, m, 4-H), 3.53 (1H, m, 5-H), 3.60 (1H, t, J=10.1 Hz, 3-H), 7.20 (5H, m, Ph); δ_C(90MHz; $CDCl_3$) *trans* 19.18 (q), 27.74 (q), 36.24 (t), 46.99 (d), 54.00 (d), 126.93 (d), (2x) 127.96 (d), (2x) 128.70 (d), 140.02 (s), 174.70 (s); *cis* 20.26 (q), 27.72 (q), 37.47 (t), 48.35 (d), 53.48 (d), 126.92 (d), (2x) 128.41 (d), (2x) 128.77 (d), 139.83 (s), 175.13 (s); *m/z* (EI) 189 (M^+, 91%), 117 (100), 174 (93).

9.1.5.8 *N-n*-Butyl-5-methyl-3-phenyl pyrrolidin-2-one (98).

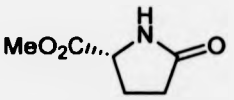


Following the procedure outlined in section (9.1.5.2), a solution of tributyltin hydride (0.22 cm^3, 0.81 mmol) and AIBN (0.013 g, 0.08 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (8 cm^3) was added to a refluxing solution of *N*-benzoyloxy-*N-n*-butyl-2-phenyl pent-4-enamide (90) (0.29 g, 0.83 mmol) in degassed toluene (8 cm^3). The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate furnishing *N-n*-butyl-5-methyl-3-phenyl pyrrolidin-2-one (98) (0.130 g, 68%) as a inseparable mixture of diastereoisomers (ratio 68:32 *trans:cis*). (Found M^+ 231.1620 $C_{15}H_{21}NO$ requires 231.1623)

ν_{max} ($CDCl_3$)/cm^{-1} 2958, 1686, 1452; δ_H(400MHz; $CDCl_3$) *trans* 0.92 (3H, t, J=7.4 Hz, $CH_2CH_2CH_2Me$), 1.25 (3H, d, J=6.3 Hz, 5-Me), 1.49 (4H, m, $CH_2CH_2CH_2Me$), 2.09 (1H, m, 4-H), 2.28 (1H, dt, J=13.0, 7.4 Hz, 4-H), 2.92 (1H, m, 5-H), 3.60 (1H, m, 3-H), 3.60 (2H, m, $CH_2CH_2CH_2Me$), 7.19 (5H, m, Ph); *cis* 0.89 (3H, t, J=7.4 Hz, $CH_2CH_2CH_2Me$), 1.29 (3H, t, J=6.0 Hz, 5-Me), 1.49 (4H, m, $CH_2CH_2CH_2Me$), 2.62 (1H, m, 4-H), 3.05 (1H, m, 4-H), 3.60 (1H, m, 5-H), 3.60 (1H, m, 3-H), 3.60 (2H, m, $CH_2CH_2CH_2Me$), 7.20 (5H, m, Ph); δ_C(100MHz; $CDCl_3$) *mixture* 13.51 (q), 13.68 (q), 20.05(q), 20.20(q), (2x) 27.73 (q), 29.38 (t), 29.47 (t), 36.40 (t), 37.42 (t), 39.98 (d), 40.15 (d), (2x) 47.05 (t), 51.33 (d), 51.49 (d), 126.68 (d), 127.74 (d), (2x) 128.06 (d), (2x) 128.16 (d), (2x) 128.56 (d), (2x) 129.95 (d), 139.83 (s), 140.05 (s), 174.54 (s), 175.10 (s); *m/z* (EI) 231 (M^+, 8%), 105 (100), 122 (70).

9.1.6 *N*-Methyl-*S*-*cis*-3,5-dimethyl-pyrrolidin-2-one (99).

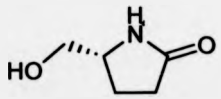
9.1.6.1 *S*-5-*Oxo*-pyrrolidine-2-carboxylic acid methyl ester (100).



To a solution of *S*-2-pyrrolidinone-5-carboxylic acid (10 g, 77.4 mmol) in methanol (90 cm^3) was added a catalytic amount of (98%) sulphuric acid and the mixture was refluxed for 24 hours. The mixture was then concentrated and extracted with dichloromethane (100 cm^3). The organic extract was then washed with water (2x 100 cm^3), dried over anhydrous magnesium sulphate and evaporated to furnish *S*-5-*oxo*-pyrrolidine-2-carboxylic acid methyl ester (100) (9.4 g, 85%) as a clear liquid. Spectral details matched those previously reported.[4]

δ_H(250MHz; $CDCl_3$) 1.99-2.40 (4H, m, CH_2 + CH_2) 3.62 (3H, s, $\underline{Me}CO_2$), 4.12 (1H, dd, J=8.5, 7.9 Hz, CH), 7.48 (1H, brs, NH).

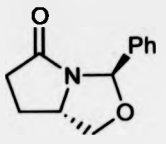
9.1.6.2 *S*-5-Hydroxymethyl-pyrrolidin-2-one (101).



A mixture of sodium borohydride (3.2 g, 85.2 mmol), dry digylme (36 cm^3) and lithium chloride (3.6 g, 85.2 mmol) was stirred vigorously under argon for 20 minutes. To the mixture was added tetrahydrofuran (25 cm^3) and stirring continued for an additional 10 minutes. The solid was then allowed to settle and a positive pressure of argon was used to filter the supernatant containing the $LiBH_4$ directly to a stirred solution of *S*-5-*oxo*-pyrrolidine-2-carboxylic acid methyl ester (100) (10 g, 77.4 mmol) in THF (25 cm^3). The reaction mixture was stirred overnight at RT, cooled in a ice bath and quenched by the slow addition of 20% acetic acid. Purification by flash column chromatography eluting with 9:1 dichloromethane:methanol furnished *S*-5-hydroxymethyl-pyrrolidin-2-one (101) as a viscous oil (3.1 g, 76%). Spectral details matched those previously published.[4]

δ_H(250MHz; $CDCl_3$) 1.59 (1H, m, CH_2) 1.95 (1H, m, CH_2), 2.17 (2H, m, $\underline{CH_2}CO$), 3.27 (1H, dd, J=11.4, 6.7 Hz, $\underline{CH_2}OH$), 3.47 (1H, dd, J=11.4, 3.4 Hz, $\underline{CH_2}OH$), 3.60 (1H, m, CH), 4.61 (1H, brs, OH), 7.52 (1H, brs, NH); δ_H(250MHz; $CDCl_3$) 22.90 (t), 30.58 (t), 56.84 (d), 65.61 (t), 180.09 (s).

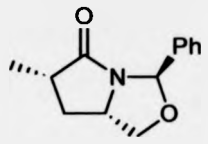
9.1.6.3 Tetrahydro-3-phenyl-(3*R-cis*)-pyrrolo[1,2-c]oxazol-5-one (102).



A mixture of *S*-5-hydroxymethyl-pyrrolidin-2-one (101) (1.55 g, 13.5 mmol), benzaldehyde (1.86 g, 17.52 mmol) and toluenesulfonic acid (0.031 g, 0.162 mmol) in dry toluene (10 cm^3) was refluxed under Dean-Stark conditions with vigorous stirring. The cooled reaction mixture was washed with 5% sodium hydrogen carbonate (2x 50 cm^3), saturated sodium bisulfite solution (2x 50 cm^3) and water (2x 50 cm^3). The organic layer was dried over anhydrous magnesium sulphate and concentrated to furnish tetrahydro-3-phenyl-(3*R*-cis)-pyrrolo[1,2-c]oxazol-5-one (102) (1.8 g, 66%) as a clear oil. Spectral details matched those previously published.[5]

δ_H(250MHz; $CDCl_3$) 1.79 (1H, m, CH_2), 2.22 (1H, m, CH_2), 2.42 (1H, m, $CH_2C{=}O$), 2.67 (1H, m, $CH_2C{=}O$), 3.38 (1H, t, J=7.6 Hz, CH_2O), 4.02 (2H, m, CH + CH_2O), 6.29 (1H, s, PhCH), 7.28 (3H, m, Ph), 7.40 (2H, m, Ph); δ_C(63MHz; $CDCl_3$) 22.73 (t), 33.09 (t), 58.50 (d), 71.34 (t), 86.82 (d), 125.66 (d), (2x) 128.10 (d), (2x) 128.20 (d), 138.69 (s), 177.80 (s).

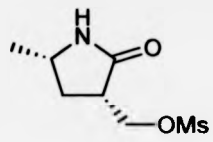
9.1.6.4 [3*R*-(3a,6a,7aa)]-Tetrahydro-6-methyl-3-phenyl-(3*S*-*cis*)-3H,5H-pyrrolo[1,2-c]oxazol-5-one (103).



A solution of *N*,*N*-diisopropylethylamine (0.760 g, 7.5 mmol) in dry THF (20 cm^3) under argon was cooled to -10°C, to which was added *n*-butyllithium (4.7 cm^3, 1.6M in hexanes) dropwise, and the resulting mixture stirred for 10 minutes. The yellow liquid was then cooled to -78°C and a pre-cooled solution of tetrahydro-3-phenyl-(3*R*-cis)-pyrrolo[1,2-c]oxazol-5-one (102) (1.3 g, 6.84 mmol) in THF (2 cm^3) was added dropwise. After 20 minutes, iodomethane (1.9 cm^3, 30.8 mmol) was added, and the reaction mixture left to stir for a period of 1 hour. The reaction mixture was then quenched with brine and extracted with dichloromethane (2x 100 cm^3). The combined organic extracts were then dried over anhydrous magnesium sulphate, filtered and concentrated. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate furnished [3*R*-(3a,6a,7aa)]-tetrahydro-6-methyl-3-phenyl-(3*S*-*cis*)-3H,5H-pyrrolo[1,2-c]oxazol-5-one (103) (1.36 g, 80%) as a inseparable mixture of diastereoisomers (ratio 82:18 *cis*:*trans*). Spectral details matched those previously published.[5]

δ_H(250MHz; $CDCl_3$) *major* 1.14 (3H, d, J=7.0 Hz, MeCH), 1.39 (1H, m, CH_2), 2.47 (1H, m, CH_2), 2.80 (1H, m, CH_2), 3.38 (1H, t, J=7.0 Hz, CH_2O), 3.94-4.17 (2H, m, CH + CH_2O), 6.33 (1H, s, PhCH), 7.28 (3H, m, Ph), 7.40 (2H, m, Ph).

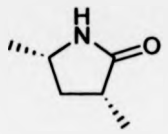
9.1.6.5 (5*R*,3*R*)-5-[(Methanesulfonyl)oxy)methyl]-2-methylpyrrolidin-2-one (104).



To a solution of [3*R*-(3a,6a,7aa)]-Tetrahydro-6-methyl-3-phenyl-(3*S*-*cis*)-3H,5H-pyrrolo[1,2-c]oxazol-5-one (103) (1.36 g, 6.67 mmol) in (9:1) methanol/water (30 cm^3) was added *p*-toluenesulfonic acid (30 mg, 0.16 mmol) which was refluxed for 12 hours. The mixture was cooled to RT concentrated to yield a crude off-white solid that was dissolved in dichloromethane (35 cm^3). To this mixture was added triethylamine (1.01 g, 10.0 mmol) and methanesufonyl chloride (0.92 g, 8 mmol). The resulting mixture was then stirred at RT for a period of 1 hour. After which time the reaction mixture was then quenched with water (20 cm^3). The organic layer was subsequently dried over anhydrous magnesium sulphate and reduced to dryness to furnish (5*R*,3*R*)-5-[(methanesulfonyl)oxy)methyl]-2-methylpyrrolidin-2-one (104) (0.52 g, 38%) as a white solid. Spectral details matched those previously published.[5]

δ_H(400MHz; $CDCl_3$) *major* 1.24 (3H, d, J=7.0 Hz, MeCH), 1.39 (1H, t, J=7.4 Hz, CH_2), 2.38 (1H, m, CH_2), 2.38 (1H, m, CH), 3.03 (3H, s, SO_2Me), 3.84 (1H, m, CH), 3.97 (1H, dd, J=10.5, 7.4 Hz, CH_2O), 4.21 (1H, dd, J= 10.2, 3.5 Hz, CH_2O), 6.93 (1H, brs, NH).

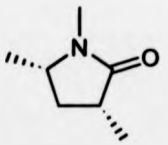
9.1.6.6 *S-cis*-2,5-Dimethylpyrrolidin-2-one (105).



A solution of (5*R*,3*R*)-5-[(methanesulfonyl)oxy)methyl]-2-methylpyrrolidin-2-one (104) (0.1 g, 0.57 mmol) in dimethoxyethane (6 cm^3) was degassed *via* a stream of argon. To this solution were added sodium iodide (0.17 g, 1.14 mmol), tributyltin hydride (0.25 g, 0.86 mmol) and AIBN (10 mg, 0.057 mmol). The cloudy white reaction mixture was then heated to reflux for 6 hours. The reaction mixture was cooled to RT, filtered and concentrated. Purification by flash column chromatography eluting with 2:1 light petroleum ether:ethyl acetate furnished *S-cis*-2,5-dimethylpyrrolidin-2-one (105) (52 mg, 80%). Spectral details matched those previously reported.[5]

δ_H(400MHz; $CDCl_3$) *major* 1.17 (3H, d, J=6.7 Hz, MeCH), 1.21 (3H, d, J=6.3 Hz, MeCH), 1.21 (1H, m, CH_2), 2.40 (2H, m, CH_2 + CH), 3.64 (1H, m, CH), 6.04 (1H, brs, NH).

9.1.6.7 *N*-Methyl-*S-cis*-2,5-dimethylpyrrolidin-2-one (99).



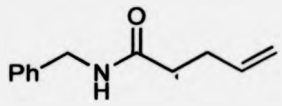
A solution of *S-cis*-2,5-dimethylpyrrolidin-2-one (105) (35 mg, 0.31 mmol) in THF (2.5 cm^3) was added to a solution of NaH (8.2 mg, 0.34 mmol) in THF (2.5 cm^3) under

nitrogen. The reaction was stirred at RT for 10 minutes and then methyl iodide (176 mg, 1.24 mmol) was added dropwise. After a period of 1 hour the reaction mixture was quenched with water, extracted into dichloromethane and dried over anhydrous magnesium sulphate. The solvent was removed in *vacuo* and further purification by flash column chromatography eluting with 7:1 CH_2Cl_2:MeOH furnished *N*-methyl-*S*-*cis*-2,5-dimethylpyrrolidin-2-one (99) (31 mg, 80%). Spectral details matched those previously reported see section (9.1.5.3).

δ_H(400MHz; $CDCl_3$) *cis* 1.18 (3H, d, J=7.0 Hz 5-Me), 1.18-1.20 (1H, m, 4-H), 1.20 (3H, d, J=6.3 Hz, 3-Me), 2.32-2.43 (2H, m, 4-H + 3-H), 2.77 (3H, s, NMe), 3.39 (1H, m, 5-H) *trans* 1.15 (3H, d, J=7.0 Hz 5-Me), 1.20 (3H, d, J=6.3 Hz, 3-Me), 1.75 (2H, m, 4-H), 2.50 (1H, m, 4-H), 2.78 (3H, s, NMe), 3.60 (1H, m, 5-H).

9.2 Experimental for Chapter 3

9.2.1 *N*-Benzylpent-4-enamide (106).



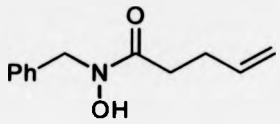
Pent-4-enoyl chloride was prepared by addition of oxalyl chloride (2.5 cm^3, 25 mmol) dropwise to pent-4-enoic acid (3.4 cm^3, 38.8 mmol) and refluxing the solution for 2 hours. The excess oxalyl chloride was removed under reduced pressure on a rotary evaporator to give pent-4-enoyl chloride in quantitative yield, which was used immediately in the next stage of the synthesis without further purification. The pent-4-enoyl chloride (1 cm^3, 8.44 mmol) was added dropwise to a stirred solution of benzylamine (2 cm^3, 18.57 mmol) in diethyl ether (150 cm^3). On addition of the pent-4-enoyl chloride a white precipitate was formed immediately and the reaction was left to stir for an additional 3 hours at RT. The reaction mixture was washed with water, 10% HCl and $NaHCO_3$. The ether layer was then dried over anhydrous magnesium sulphate and reduced to dryness. Purification by recrystallisation (hexanes) yielded *N*-benzylpent-4-enamide (106) (1.03 g, 65 %) as a white crystalline solid; m.p. 38-40°C (lit. m.p. 39-40°C).[6] (Found C 75.93, H 7.93, N 7.25. $C_{12}H_{15}NO$ requires C 76.16, H 7.99, N 7.40).

ν_{max} ($CDCl_3$neat)/cm^{-1} 3281, 1651 1454; δ_H(400MHz; $CDCl_3$) 2.70 (4H, m, $\underline{CH_2}\underline{CH_2}$), 4.42 (2H, t, J=9.3 Hz $\underline{CH_2}$Ph), 4.98 (2H, m, CH=$\underline{CH_2}$), 5.77 (1H, m, $\underline{CH}$=CH_2), 5.77 (1H br s, NH), 7.26 (5H, m, Ph); δ_C(100Hz; $CDCl_3$) 29.52 (t), 35.75 (t), 43.50 (t), 115.58 (t),

127.42 (d), (2x) 127.74 (d), (2x) 128.60 (d), 136.91 (d), 138.18 (s), 172.02 (s); *m/z* (CI; NH_3) 189 (MH^+, 18%), 91 (100), 106 (29%).

9.2.2 Precursor synthesis

9.2.2.1 *N*-Benzyl-*N*-hydroxyl pent-4-enamide (107).

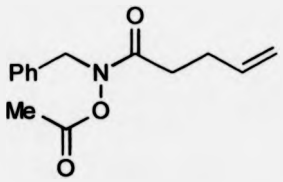


To a 0°C mixture of *N*-benzylhydroxylamine hydrochloride (1.65 g, 10.34 mmol) and triethylamine (4.3 cm^3, 31 mmol) in dichloromethane (100 cm^3) at 0°C was added a cold solution of pent-4-enoyl chloride (1.1 cm^3, 9.40 mmol) (prepared by the reaction of pent-4-enoic acid with excess oxalyl chloride) in dichloromethane (80 cm^3) over a period of 1 hour. The mixture was then allowed to warm to RT and stirred for an additional period of 2 hours. The reaction was quenched with water, and the organic layer treated with 10% HCl and brine, dried over anhydrous magnesium sulphate. The organic phase was then evaporated under reduced pressure to yield *N*-benzyl-*N*-hydroxyl pent-4-enamide (107) in the form of a yellow oil (1.68 g, 87%), which needed no further purification. (Found (MH^+) 206.1189. $C_{12}H_{16}NO_2$ requires 206.1181)

ν_{max} (neat)/cm^{-1} 3194, 1614 1454; δ_H(250MHz; $CDCl_3$) 2.02 (4H, m, $\underline{CH_2CH_2}$), 4.60 (2H, s, $\underline{CH_2}Ph$), 4.95 (2H, m, $CH=\underline{CH_2}$), 5.74 (1H, m, $\underline{CH}=CH_2$), 7.26 (5H, m, Ph), 8.41 (1H, br s, OH); δ_C(63MHz; $CDCl_3$) 28.55 (t), 31.49 (t), 51.92 (t), 115.07 (t), 127.49 (d),

(2x) 128.30 (d), (2x) 128.38 (d), 129.33 (d), 137.22 (s), 173.91 (s); *m/z* (CI; NH_3) 206 (MH^+, 4%), 190 (100), 91 (33%).

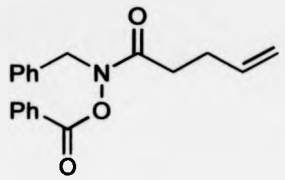
9.2.2.2 *N*-Acetoxy-*N*-benzyl pent-4-enamide (108).



To a solution of *N*-benzyl-*N*-hydroxyl pent-4-enamide (107) (0.50 g, 2.44mmol) in dichloromethane (10 cm^3) at 0°C was added triethylamine (0.34 cm^3, 2.44mmol). The mixture was stirred for 10 to 15 minutes after which time was added acetyl chloride (0.19 cm^3, 2.68 mmol) dropwise. The solution was stirred at 0°C for a period of 2 hours, allowed to warm to RT, and stirred for an additional 2 hours. The reaction mixture was washed with water, 10% HCl, brine and then dried over anhydrous magnesium sulphate. Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-acetoxy-*N*-benzyl pent-4-enamide (108), as a clear yellow oil (0.54 g, 90%). (Found M^+ 247.1212. $C_{14}H_{17}NO_3$ requires 247.1208)

ν_{max} (neat)/cm^{-1} 2924, 1793, 1670, 1436; δ_H(250MHz; $CDCl_3$) 2.08 (3H, s, OAc), 2.36 (4H, br s, $\underline{CH_2}CH_2$), 4.85 (2H, s, $\underline{CH_2}Ph$), 4.95 (2H, m, CH=$\underline{CH_2}$), 5.73 (1H, m, $\underline{CH}$=CH_2), 7.26 (5H, m, Ph); δ_C(63MHz; $CDCl_3$) 18.22 (q), 28.13 (t), 31.42 (t), 51.58 (t), 115.40 (t), 127.94 (d), (2x) 128.49 (d), (2x) 128.74 (d), 135.00 (d), 136.82 (s), 168.20 (s), 172.07 (s); *m/z* (EI) 247 (M^+, 5%), 188 (100), 91 (53).

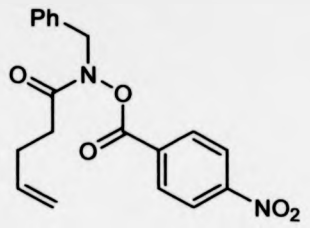
9.2.2.3 *N*-Benzoyloxy-*N*-benzyl pent-4-enamide (109).



Following the procedure outlined in section (9.2.2.2), a solution of *N*-benzyl-*N*-hydroxyl pent-4-enamide (107) (0.25 g, 1.22mmol) in dichloromethane (5 cm^3) at 0°C was added triethylamine (0.17 cm^3, 1.22mmol) and benzoyl chloride (0.16 cm^3, 1.34 mmol). Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-benzoyloxy-*N*-benzyl pent-4-enamide (109) as a yellow oil (0.35 g, 93 %). Spectral details matched those previously reported.[7]

δ_H(250MHz; $CDCl_3$) 2.42 (4H, br s, $\underline{CH_2CH_2}$), 4.93 (2H, s, $\underline{CH_2}Ph$), 4.93 (2H, m, $CH=\underline{CH_2}$), 5.73 (1H, m, $\underline{CH}=CH_2$), 7.26 (5H, m, Ph), 7.42 (2H, m, *m*-Ph) 7.60 (1H, m, *p*-Ph), 7.95 (2H, m, *o*-Ph); δ_C(63MHz; $CDCl_3$) 28.67 (t), 32.04 (t), 52.29 (t), 115.87 (t), (2x) 127.05 (d), (2x) 128.31 (d), (2x) 128.99 (d), (2x) 129.29 (d), (2x) 130.30 (d), 134.89 (d), 135.76 (s), 137.32 (s), 164.74 (s), 173.06 (s).

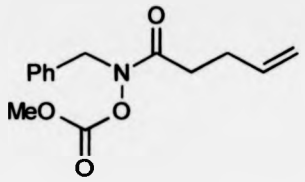
9.2.2.4 *N-p*-Nitrobenzoyloxy-*N*-benzyl pent-4-enamide (110).



Following the procedure outlined in section (9.2.2.2), a solution of *N*-benzyl-*N*-hydroxyl pent-4-enamide (107) (0.24 g, 1.17mmol) in dichloromethane (5 cm^3) at 0°C was added triethylamine (0.16 cm^3, 1.17mmol) and *p*-nitrobenzoyl chloride (0.22 g, 1.17 mmol). Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-*p*-nitrobenzoyloxy-*N*-benzyl pent-4-enamide (110) as a bright yellow viscous oil (0.35 g, 84 %). (Found M^+ 354.1239. $C_{19}H_{18}N_2O_5$ requires 354.1216)

ν_{max} (neat)/cm^{-1} 2928, 1771, 1680, 1531; δ_H(400MHz; $CDCl_3$) 2.42 (4H, m, $\underline{CH_2CH_2}$), 4.97 (2H, m, $\underline{CH_2}Ph$), 4.97 (2H, m, $CH=\underline{CH_2}$), 5.77 (1H, m, $\underline{CH}=CH_2$), 7.26 (5H, m, Ph), 8.10 (2H, d, J=8.8 Hz, *m*-$PhNO_2$), 8.28 (2H, d, J=8.8 Hz, *o*-$PhNO_2$) ; δ_C(63MHz; $CDCl_3$) 28.10 (t), 31.66 (t), 52.17 (t), 115.58 (t), (2x) 123.80 (d), (2x) 124.04 (d), 127.38 (d), (2x) 128.08 (d), (2x) 128.32 (d), 131.59 (d), 136.54 (s), 137.32 (s), 151.10 (s), 162.53 (s), 174.33 (s); *m/z* (EI;) 354 (M^+, 4%), 150 (100), 91 (55%).

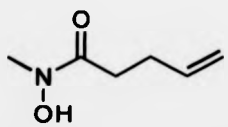
9.2.2.5 *N*-Methylformate-*N*-benzyl pent-4-enamide (111).



Following the procedure outlined in section (9.2.2.2), a solution of *N*-benzyl-*N*-hydroxyl pent-4-enamide (107) (0.54 g, 2.63 mmol) in dichloromethane (10 cm^3) at 0°C was added triethylamine (0.37 cm^3, 2.63 mmol) and methyl chloroformate (0.22 cm^3, 2.90 mmol). Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-methylformate-*N*-benzyl pent-4-enamide (111) as a clear oil (0.50 g, 72 %). (Found (MH^+) 264.1238. $C_{14}H_{18}NO_4$ requires 264.1236)

ν_{max} (neat)/cm^{-1} 2956, 1790, 1682, 1439; δ_H(250MHz; $CDCl_3$) 2.40 (4H, m, $\underline{CH_2CH_2}$), 3.84 (3H, s, O<u>Me</u>), 4.89 (2H, s, $\underline{CH_2}Ph$), 4.96 (2H, m, CH=$\underline{CH_2}$), 5.74 (1H, m, $\underline{CH}$=CH_2), 7.25 (5H, m, Ph); δ_C(100MHz; $CDCl_3$) 27.99 (t), 31.43 (t), 51.54 (t), 56.31 (q), 115.42 (t), 127.86 (d), (2x) 128.32 (d), (2x) 128.46 (d), 134.67 (s), 136.68 (d), 154.45 (s), 172.81 (s); *m/z* (EI;) 264 (M^+, 90%), 188 (100), 91 (90%).

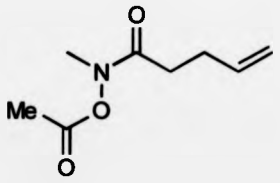
9.2.2.6 *N*-Hydroxyl-*N*-methyl pent-4-enamide (112).



Following the procedure outlined in section (9.2.2.2), a mixture of *N*-methylhydroxylamine hydrochloride (1.5 g, 17.96 mmol) and triethylamine (7.5 cm^3, 53.88 mmol) in dichloromethane (100 cm^3) at 0°C to which was added a cold solution of pent-4-enoyl chloride (2.1 cm^3, 17.96 mmol) (prepared by the reaction of pent-4-enoic acid with excess oxalyl chloride) in dichloromethane (80 cm^3). Purification by flash column chromatography eluting with 2:1 hexane:ethyl acetate gave *N*-hydroxyl-*N*-methyl pent-4-enamide (112) as a yellow oil (0.44 g, 19%). (Found MH^+ 130.0864. $C_6H_{12}NO_2$ requires 130.0868).

ν_{max} (neat)/cm^{-1} 3422, 1672 1420; δ_H(400MHz; $CDCl_3$) 2.34 (4H, br m, $\underline{CH_2}\underline{CH_2}$), 3.27 (3H, br s, NMe), 4.97 (2H, m, CH=$\underline{CH_2}$), 5.75 (1H, m, $\underline{CH}$=CH_2); δ_C(100MHz; $CDCl_3$) 28.33 (t), 30.96 (t), 35.56 (q), 115.25 (t), 136.85 (d), 170.44 (s); *m/z* (EI ; M^{+1}) 130 (MH^+, 7%), 55 (100), 83 (95%).

9.2.2.7 *N*-Acetoxy-*N*-methyl pent-4-enamide (113).

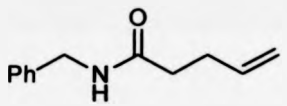


Following the procedure outlined in section (9.2.2.2), a solution of *N*-hydroxyl-*N*-methyl pent-4-enamide (112) (0.50 g, 3.88 mmol) in dichloromethane (20 cm^3) at 0°C was added triethylamine (0.54 cm^3, 3.88 mmol) and acetyl chloride (0.30 cm^3, 4.26 mmol). Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave *N*-

acetoxy-*N*-methyl pent-4-enamide (113) as a clear oil (0.61 g, 92 %). (Found (MH^+) 172.0965 $C_8H_{14}NO_3$ requires 172.0974)

ν_{max} (neat)/cm^{-1} 2924, 1713, 1620; δ_H(250MHz; $CDCl_3$) 2.21 (3H, s, OAc), 2.36 (4H, br s, CH_2CH_2). 3.29 (3H, br s, NMe), 4.97 (2H, m, CH=CH_2). 5.76 (1H, m, CH=CH_2); δ_C(63MHz; $CDCl_3$) 18.45 (q), (2x) 28.27 (t), 31.36 (t), 115.42 (t), 137.02 (d), 168.30 (s), 201.27 (s); *m/z* (CI) 172 (M^{+1}, 5%), 55 (100), 83 (53).

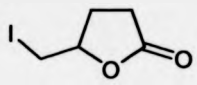
9.2.3 Reaction of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) with Samarium(II) Iodide.



A solution of SmI_2 (20 cm^3, 0.10M in THF) was added to a refluxing solution of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (250 mg, 1.0 mmol) in dry tetrahydrofuran (3 cm^3) via a syringe pump over 6 hours. The reaction was then refluxed for a further 10 hours. The reaction was diluted with dichloromethane (100 cm^3), then quenched with 10% aqueous sodium thiosulphate (50 cm^3). The organic layer was then washed with water several times, dried over anhydrous magnesium sulphate and reduced to dryness under reduced pressure to furnish *N*-benzylpent-4-enamide (106) (0.18 g, 94 %) as a white solid which required no further purification. Spectral details matched that of the authentically prepared sample in section (9.2.1).

δ_H(400MHz; $CDCl_3$) 2.70 (4H, m, $\underline{CH_2CH_2}$), 4.42 (2H, t, J=9.3 Hz $\underline{CH_2}$Ph), 4.98 (2H, m, CH=$\underline{CH_2}$), 5.77 (1H, m, $\underline{CH}$=CH_2), 5.77 (1H br s, NH), 7.26 (5H, m, Ph); δ_C(100Hz; $CDCl_3$) 29.52 (t), 35.75 (t), 43.50 (t), 115.58 (t), 127.42 (d), (2x) 127.74 (d), (2x) 128.60 (d), 136.91 (d), 138.18 (s), 172.02 (s);

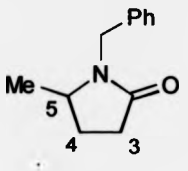
9.2.4 The attempted *in-situ* *N*-methylation of the *N*-benzyl pent-4-enamide anion formed by the action of Samarium(II) Iodide.



A solution of SmI_2 (7.1 cm^3, 0.10M in THF) was added to a refluxing solution of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (88 mg, 0.35 mmol) in dry tetrahydrofuran (1 cm^3) via a syringe pump over 6 hours. After the addition of SmI_2 was completed, iodomethane (0.1 g, 0.71 mmol) was added to the reaction mixture. After a period of 10 hours the mixture was diluted with CH_2Cl_2 (100 cm^3), then quenched with 10% aqueous sodium thiosulphate. The organic layer was then washed with water several times, dried (anhydrous $MgSO_4$) and reduced to dryness under reduced pressure. Purification by flash column chromatography eluting with 4:1 hexane:ethyl acetate gave 5-iodomethyl-dihydro-furan-2-one (114) (34 mg 43%) as a clear oil. (Found M^+ 225.9493 $C_5H_7O_2I^{127}$ requires 225.9491)

ν_{max} (neat)/cm^{-1} 2924, 1775; δ_H(250MHz; $CDCl_3$) 1.93 (1H, m, CH_2), 2.47-2.67 (3H, m, $\underline{CH_2}$C=O + CH_2), 3.27 (2H, m, $\underline{CH_2}$I), 4.53 (1H, m, CH); δ_C(63MHz; $CDCl_3$) 7.68 (t), 28.53 (t), 29.22 (t), 78.81 (d), 176.53 (s); *m/z* (EI) 226 (M^+, 25%), 99 (100), 127 (30).

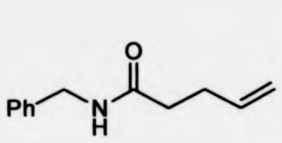
9.2.5 Tributyltin hydride mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108).



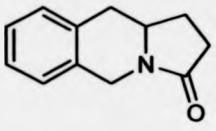
A solution of tributyltin hydride (0.27 cm^3, 1.01 mmol) and AIBN (0.016 g, 0.1 mmol) in a 1:1 mixture of degassed toluene/cyclohexane (5 cm^3) was added *via* a syringe pump over 8 hours to a refluxing solution of *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (0.165 g, 0.67 mmol) in degassed toluene (5 cm^3). The reaction was then refluxed for a further 12 hours. The solvent was removed under reduced pressure and the crude product mixture was partitioned between hexane and acetonitrile. Further purification by flash column chromatography (4:1, hexane:ethyl acetate) furnished *N*-methyl-5-methyl pyrrolidin-2-one (115) (0.035 g, 28%). (Found M^+ 189.1152 $C_{12}H_{15}NO$ requires 189.1154). Spectral details matched those previously reported.[8a-b]

ν_{max} ($CDCl_3$)/cm^{-1} 2966, 1666, 1456; δ_H(400MHz; $CDCl_3$) 1.15 (3H, d, J=6.3 Hz, 5-Me), 1.60 (1H, m, 4-CH_2), 2.16 (1H, m, 4-CH_2), 2.38 (2H, m, 3-CH_2), 3.52 (1H, m, 5-CH), 3.97 (1H, d, J=15.1 Hz, CH_2Ph) 4.94 (1H, d, J=15.1 Hz, CH_2Ph), 7.22 (5H, m, Ph); δ_C(100MHz; $CDCl_3$) 19.62 (q), 26.67 (t), 29.73 (t), 43.93 (d), 52.90 (d), 127.46 (d), (2x) 127.99 (d), (2x) 128.65 (d), 136.78 (s), 175.14 (s); *m/z* (EI) 189 (M^+, 37%), 91 (100), 146 (22).

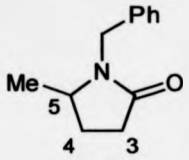
9.2.6 Copper (II) triflate mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108)



(106)



(116)



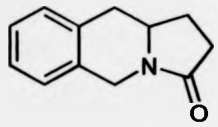
(115)

A solution of DBU (0.10 cm^3, 0.68 mmol) and copper (II) triflate (0.206 g, 0.57 mmol) in dry acetone (5 cm^3) was stirred at RT for 15 minutes. To this dark brown solution was added dropwise *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (0.140 g, 0.57 mmol) in dry acetone (1 cm^3). The reaction mixture in a sealed tube was placed in a oil bath (120°C) for a period of 72 hours. The reaction mixture was washed with water, 10% HCl, brine and then dried over anhydrous magnesium sulphate. Purification by flash column chromatography using 4:1, 2:1, 1:1 light petroleum ether:ethyl acetate furnished a mixture containing *N*-methyl-5-methyl pyrrolidin-2-one (115) (15 mg, 14%) experimental details matched those of the authentically prepared sample in section (9.2.6), *N*-benzylpent-4-enamide (106) (20 mg, 19%) experimental details matched those of the authentically prepared sample in section (9.2.1) and 1,5,10,10a-tetrahydro-2H-pyrrolo[1,2-*b*]*iso*quinolin-3-one (116), as a clear colourless oil (27 mg, 25%). (Found M^+ 187.0904 $C_{12}H_{13}NO$ requires 187.0997).

(116) ν_{max} ($CDCl_3$)/cm^{-1} 2927, 1674, 1457; δ_H(250MHz; $CDCl_3$) 1.71 (1H, m, 4-CH_2), 2.32 (3H, m, 3+4-CH_2), 2.65 (1H, dd, J=15.5, 4.25 Hz, 6-CH_2), 2.92 (1H, dd, J=15.5, 3.8 Hz, 6-CH_2), 3.73 (1H, m, 5-CH), 4.23 (1H, d, J=17.7 Hz, CH_2Ph), 4.90 (1H, d, J=17.7 Hz, CH_2Ph), 7.10 (4H, m, Ph); δ_C(100MHz; $CDCl_3$) 25.20 (t), 30.03, (t) 36.78 (t), 42.40 (t),

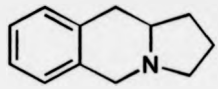
53.85 (d), (2x) 126.48 (d), (2x) 128.96 (d), 131.66 (s), 133.08 (s), 174.15 (s); *m/z* (EI) 187 (M^+, 38%), 104 (100), 130 (18).

9.2.7 Copper (II) triflate mediated cyclisation of *N*-acetoxy-*N*-benzyl pent-4-enamide (108)



A solution of DBU (0.052 cm^3, 0.34 mmol) and copper (II) triflate (0.103 g, 0.285 mmol) in dry acetonitrile (6 cm^3) was stirred at RT for 15 minutes. To this dark brown solution was added dropwise *N*-acetoxy-*N*-benzyl pent-4-enamide (108) (0.070 g, 0.285 mmol) in dry acetonitrile (6 cm^3). The reaction mixture in a sealed tube was placed in a oil bath (120°C) for a period of 72 hours. The reaction mixture was washed with water, 10% HCl, brine and then dried over anhydrous magnesium sulphate. Purification by flash column chromatography (4:1, 2:1, 1:1 light petroleum ether: ethyl acetate) furnished a mixture containing *N*-methyl-5-methyl pyrrolidin-2-one (115) (3 mg, 6%) experimental details matched those of the authentically prepared sample in section (9.2.6), *N*-benzylpent-4-enamide (106) (9 mg, 17%) experimental details matched those of the authentically prepared sample in section (9.2.1) and 1,5,10,10a-tetrahydro-2H-pyrrolo[1,2-*b*]*iso*quinolin-3-one (116), as a clear colourless oil (24 mg, 45%). (Found M^+ 187.0904 $C_{12}H_{13}NO$ requires 187.0997). Spectral details matched those in section (9.2.6).

9.2.8 Reduction of 1,5,10,10a-tetrahydro-2H-pyrrolo[1,2-*b*]*iso*quinolin-3-one (116).

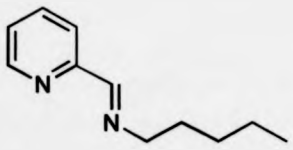


To a suspension of lithium aluminium hydride (0.030g, 0.795 mmol) in diethyl ether (2 cm^3) was added a solution of 1,5,10,10a-tetrahydro-2H-pyrrolo[1,2-*b*]*iso*quinolin-3-one (116) (0.10 g, 0.53 mmol) in diethyl ether (2 cm^3) under nitrogen at RT. After a period of 30 minutes the reaction was quenched with water, acidified with 10% HCl and the ether layer discarded. The aqueous layer was then basified with 15% NaOH, the product extracted into dichloromethane, dried over anhydrous magnesium sulphate and reduced in *vacuo* to furnish 1,2,3,10,10a-hexahydropyrrolo[1,2-b]*iso*quinoline (117) as a clear oil (65 mg, 71%). Spectral details matched those previously published.[9]

δ_H(400MHz; $CDCl_3$) 1.55 (1H, m), 1.90 (2H, m), 2.09 (1H, m), 2.27 (2H, m), 2.71 (1H, dd, J=16.2, 1.6 Hz), 2.98 (1H, dd, J=15.5, 5.4 Hz), 3.26 (1H, t, 9.2 Hz), 3.44 (1H, d J=15.5 Hz), 4.13 (1H, d, J=14.8 Hz), 7.10 (4H, m, Ph).

9.3 Experimental for Chapter 4.

9.3.1 *N*-Pentyl-2-pyridylmethanimine (118).



N-pentylamine (3.56 g, 40.8 mmol) was added to a stirred solution of 2-pyridine carboxaldehyde (4.37 g, 40.8 mmol) in diethyl ether (60 cm^3). The solution was stirred at RT for 5 minutes and anhydrous magnesium sulphate (40 g) was added. The reaction was left for a period of 3 hours after which time the reaction had proceeded smoothly to completion. The diethyl ether was removed in *vacuo* to give a dark yellow oil which was purified by vacuum distillation to give *N*-pentyl-2-pyridylmethanimine (118) (5.6 g, 79%) as a light yellow oil. Spectral details matched those previously published.[10]

δ_H(250MHz; $CDCl_3$) 0.72 (3H, t, J=6.8 Hz $CH_2\underline{Me}$), 1.16 (4H, m, $CH_2\underline{CH_2CH_2}$), 1.54 (2H, m, $\underline{CH_2}CH_2CH_2$), 3.47 (2H, m, $\underline{CH_2}N$), 7.10 (1H, br s, Ar), 7.51 (1H, t, J=7.9 Hz, Ar) 7.81 (1H, d, J=7.9 Hz, Ar), 8.21 (1H, s, $\underline{CH}N$), 8.46 (1H, br s, Ar); δ_C(63MHz; $CDCl_3$) 14.27 (q), 22.72 (t), 29.75 (t), 30.64 (t), 61.77 (t), 121.37 (d), 124.74 (d), 136.64 (d), 149.60 (d), 154.98 (s), 161.84 (d).

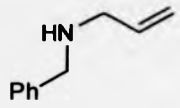
9.3.2 *N*-Allyl *N*-toluenesulphonamides and *N*-allyl *N*-benzyl amine.

9.3.2.1 *N*-Allyl-*N*-toluenesulfonamide (119).

To a stirred solution of tosyl chloride (10.0 g, 52.5 mmol) in THF (40 cm^3) was added allylamine (8.7 cm^3, 115.5 mmol). Upon the addition of allylamine the solution turned red/brown and after 2 hours the reaction was reduced in *vacuo* to remove excess allyl amine. The mixture was then extracted with dichloromethane (2x 50 cm^3) and washed with water (2x 50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure further purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate furnished *N*-allyl-toluenesulfonamide (119) (10.2 g, 92%) as a white solid, 100-102°C. Spectral details matched those previously reported.[11a-b]

δ_H(250MHz; $CDCl_3$) 2.40 (3H, s, Me), 3.53 (2H, t, J=4.6 Hz, $\underline{CH_2}CH=CH_2$), 4.92 (1H, br s, NH), 5.03 (2H, m, $CH=\underline{CH_2}$), 5.61 (1H, m, $\underline{CH}=CH_2$), 7.27 (2H, d, J=8.25 Hz, Ar), 7.72 (2H, d, J=8.25 Hz, Ar); δ_C(63MHz; $CDCl_3$) 21.32 (q), 45.54 (t), 117.41 (t),126.97 (s), (2x) 129.54 (d), (2x) 132.81 (d), 136.64 (d), 143.30 (s).

9.3.2.2 *N*-Allyl-*N*-benzyl amine (120).



Benzyl chloride (5.3 cm^3, 42 mmol) was added dropwise to a stirred solution of allyl amine (12.0 cm^3, 210 mmol) in dichloromethane over a period of 5 minutes and the mixture allowed to stir overnight at RT. The excess allyl amine was removed under reduced pressure and the mixture was extracted with dichloromethane (2x50 cm^3) and washed water (2x50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure, to furnish *N*-allyl-*N*-benzyl amine (120) (4.5 g, 73%) in the form of a yellow oil, which required no further purification. Spectral details matched those previously reported.[12a-b]

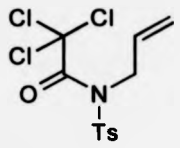
δ_H(250MHz; $CDCl_3$) 3.28 (2H, dt, J=5.8, 1.5 Hz, $\underline{CH_2}CH=CH_2$), 3.81 (2H, s, CH_2Ph), 5.11 (1H, br s, NH), 5.11 (2H, m, $CH=\underline{CH_2}$), 5.88 (1H, m, $\underline{CH}=CH_2$), 7.25 (5H, m, Ph); δ_C(63MHz; $CDCl_3$) 52.20 (t), 53.69 (t), 116.34 (t), 127.34 (d), (2x) 128.59 (d), (2x) 128.80 (d), 129.17 (d), 137.30 (s).

9.3.3 General procedure for the preparation of *N*-allyl-*N*-tosyl-*N*-tri-,di- or monohaloamides.

A solution of *n*-BuLi (2.5M in hexanes, 1 eq.) was added dropwise over a period of 5 minutes to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (1 eq.) in dry THF at -78°C under nitrogen and the mixture allowed to stir for 30 minutes. The acid chloride or

bromide (1.1 eq.) was added and the mixture stirred for 2 hours at -78°C. The reaction was quenched with saturated ammonium chloride solution and allowed to warm to RT. The mixture was extracted with dichloromethane (2x50 cm^3) and washed with saturated sodium bicarbonate (2x50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure.

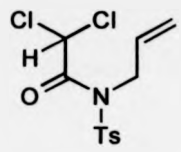
9.3.3.1 *N*-Allyl-*N*-toluenesulphonyl-2,2,2-trichloroacetamide (121).



n-BuLi (2.24 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (1.18 g, 5.6 mmol) in THF (30 cm^3) then trichloroacetyl chloride (0.7 cm^3, 6.2 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded the *N*-allyl-*N*-toluenesulphonyl-2,2,2-trichloroacetamide (121) (1.4 g, 70%) as a white crystalline solid; m.p. 75-76°C (lit. m.p. 76-78°C)[13] (Found C, 40.40; H, 3.39; N, 3.69. Calc. For $C_{12}H_{13}Cl_3NO_3S$: C, 40.41; H, 3.39; N, 3.93%). Spectral details matched those previously reported.[13]

ν_{max} (film)/cm^{-1} 2925, 1711; δ_H(250MHz; $CDCl_3$) 2.41 (3H, s, Me), 4.87 (2H, dt, J=5.5, 1.5 Hz, $\underline{CH_2}CH=CH_2$), 5.6 (2H, m, $CH=\underline{CH_2}$), 5.86 (1H, m, $\underline{CH}=CH_2$), 7.29 (2H, d, J=8.3 Hz, Ar), 7.88 (2H, d, J=8.3 Hz, Ar); δ_C(100MHz; $CDCl_3$) 21.60 (q), 50.97 (t), 91.97 (s), 119.33 (t), 129.33 (s), (2x) 129.36 (d), (2x) 132.18 (d), 134.61 (d), 145.53 (s), 158.81 (s).

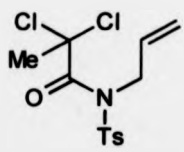
9.3.3.2 *N*-Allyl-*N*-toluenesulphonyl-2,2-dichloroacetamide (122).



n-BuLi (2.24 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (1.18 g, 5.6 mmol) in THF (30 cm^3) then 2,2-dichloroacetyl chloride (0.6 cm^3, 6.2 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded the *N*-allyl-*N*-toluenesulphonyl-2,2-dichloroacetamide (122) (1.3 g, 72%) as a white crystalline solid; m.p. 79-81 °C. (Found C, 44.67; H, 4.07; N, 4.21. Calc. For $C_{12}H_{13}Cl_2NO_3S$: C, 44.73; H, 4.07; N, 4.35%).

ν_{max} (film)/cm^{-1} 3070, 1714; δ_H(400MHz; $CDCl_3$) 2.42 (3H, s, Me), 4.39 (2H, dt, J=5.3, 1.4 Hz, $\underline{CH_2}CH=CH_2$), 5.18 (2H, m, $CH=\underline{CH_2}$), 5.72 (1H, m, $\underline{CH}=CH_2$), 6.84 (1H, s, $\underline{CH}Cl_2$), 7.29 (2H, d, J=8.4 Hz, Ar), 7.87 (2H, d, J=8.4 Hz, Ar); δ_C(100MHz; $CDCl_3$) 21.60 (q), 49.03 (t), 64.64 (d), 119.03 (t), 128.13 (s), (2x) 129.96 (d), (2x) 131.08 (d), 134.61 (d), 145.91 (s), 163,54 (s); *m/z* (EI) 321 (M^+, 3%), 155 (95), 91 (100).

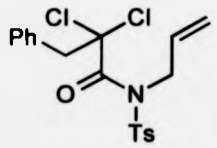
9.3.3.3 *N*-Allyl-*N*-toluenesulphonyl-2,2-dichloropropionamide (123).



n-BuLi (2.24 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (1.18 g, 5.6 mmol) in THF (30 cm^3) then 2,2-dichloropropionyl chloride (prepared by the reaction of 2,2-dichloropropionic acid with excess oxalyl chloride) (0.7 cm^3, 6.2 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded *N*-Allyl-*N*-toluenesulphonyl-2,2-dichloropropionamide (123) (1.35 g, 75%) as a white crystalline solid; m.p. 75-76°C. (Found C, 46.58; H, 4.47; N, 3.86. Calc. For $C_{13}H_{15}Cl_2NO_3S$: C, 46.44; H, 4.50; N, 4.17%).

ν_{max} (film)/cm^{-1} 2961, 1695; δ_H(400MHz; $CDCl_3$) 2.17 (3H, s, Me), 2.41 (3H, s, Me), 4.98 (2H, dt, J=3.3, 1.0 Hz, $\underline{CH_2}CH=CH_2$), 5.32 (2H, m, $CH=\underline{CH_2}$), 5.95 (1H, m, $\underline{CH}=CH_2$), 7.28 (2H, d, J=8.4 Hz, Ar), 7.86 (2H, d, J=8.4 Hz, Ar); δ_C(100MHz; $CDCl_3$) 21.59 (q), 35.62 (q), 50.61 (t), 79.68 (q), 119.01 (t), 129.05 (s), (2x) 129.17 (d), (2x) 132.82 (d), 135.39 (d), 144.97 (s), 163.98 (s); *m/z* (EI) 336 (M^+, 3%), 155 (80), 91 (100).

9.3.3.4 *N*-Allyl-*N*-toluenesulphonyl-2-benzyl-2,2-dichloroacetamide (124).

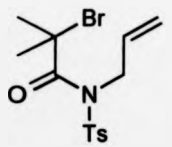


n-BuLi (0.58 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (0.36 g, 1.45 mmol) in THF (6 cm^3) then 2-benzyl-2,2-dichloroacetyl chloride (prepared by the reaction of 2-benzyl-2,2-dichloroacetic acid with excess oxalyl chloride) (0.38 g, 1.60 mmol) was added. Purification by flash column

chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded *N*-allyl-*N*-toluenesulphonyl-2-benzyl-2,2-dichloroacetamide (124) (0.57 g, 90%) as a white crystalline solid; m.p. 77-79°C . (Found C, 55.08; H, 4.77; N, 3.46. Calc. For $C_{19}H_{19}Cl_2NO_3S$: C, 55.34; H, 4.64; N, 3.40%).

ν_{max} (nujol)/cm^{-1} 2924, 1681; δ_H(250MHz; $CDCl_3$) 2.45 (3H, s, Me), 3.58 (2H, s, $\underline{CH_2}Ph$), 5.00 (2H, d, J=5.5 Hz, $\underline{CH_2}CH=CH_2$), 5.32 (2H, m, $CH=\underline{CH_2}$). 5.95 (1H, m, $\underline{CH}=CH_2$), 7.25 (5H, m, Ph), 7.30 (2H, d, J=8.4 Hz, Ar), 7.90 (2H, d, J=8.4 Hz, Ar); δ_C(100MHz; $CDCl_3$) 22.12 (q), 50.27 (t), 51.08 (t), 83.38 (s), 119.52 (t), 128.13 (d), 128.26 (s), (2x) 129.62 (d), (2x) 129.68 (d), (2x) 132.53 (d), (2x) 133.32 (d), 133.51 (d), 135.98 (s), 145.47 (s), 164.81 (s); *m/z* (EI) 412 (M^+, 1%), 83 (100), 155 (15).

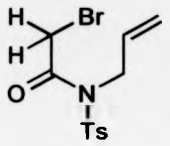
9.3.3.5 *N*-Allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (125).



n-BuLi (1.04 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (0.50 g, 2.4 mmol) in THF (15 cm^3) then 2-bromo-2-methylpropionyl bromide (0.30 cm^3, 2.60 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded *N*-allyl-*N*-4-toluenesulfonyl-2-bromo-2-methylpropionamide (125) (0.60 g, 72%) as a white crystalline solid; m.p. 83-84°C. (Found C, 46.36; H, 5.08; N, 3.55. Calc. For $C_{14}H_{18}BrNO_3S$: C, 46.67; H, 5.04; N, 3.89%).

ν_{max} (film)/cm^{-1} 2925, 1682; δ_H(250MHz; $CDCl_3$) 1.83 (6H, s, MeCBrMe), 2.38 (3H, s, Me), 4.90 (2H, dt, J=2.75, 1.8 Hz, $CH_2CH=CH_2$), 5.27 (2H, m, $CH=CH_2$), 5.87 (1H, m, $CH=CH_2$), 7.24 (2H, d, J=8.3 Hz, Ar), 7.81 (2H, d, J=8.3 Hz, Ar); δ_C(68MHz; $CDCl_3$) 2.08 (q), (2x) 32.41 (q), 51.00 (t), 57.42 (q), 118.57 (t), 129.26 (s), (2x) 129.61 (d), (2x) 133.94 (d), 136.50 (d), 145.05 (s), 170.78 (s); *m/z* (EI) 360 (M^+, 5%), 91 (100), 155 (73).

9.3.3.6 *N*-Allyl-4-toluenesulfonyl-2-bromoacetamide (126).



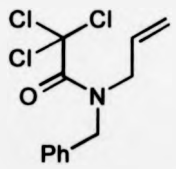
n-BuLi (2.24 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (1.15 g, 5.6 mmol) in THF (30 cm^3) then 2-bromoacetyl bromide (0.54 cm^3, 6.2 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate, afforded *N*-allyl-4-toluenesulfonyl-2-bromoacetamide (126) (1.2 g, 64%) as a white crystalline solid; m.p. 89-90°C. (Found C, 42.67; H, 4.12; N, 3.87. Calc. For $C_{12}H_{14}BrNO_3S$: C, 43.38; H, 4.25; N, 4.22%).

ν_{max} (nujol)/cm^{-1} 2923, 1694; δ_H(250MHz; $CDCl_3$) 2.41 (3H, s, Me), 4.19 (2H, s, CH_2Br), 4.41 (2H, dt, J=3.95, 1.5 Hz, $CH_2CH=CH_2$), 5.17 (2H, m, $CH=CH_2$), 5.74 (1H, m, $CH=CH_2$), 7.30 (2H, d, J=8.4 Hz, Ar), 7.78 (2H, d, J=8.4 Hz, Ar); δ_C(68MHz; $CDCl_3$) 22.07 (q), 29.40 (t), 49.60 (t), 119.07 (t), 128.52 (s), (2x) 130.31 (d), (2x) 132.44 (d), 135.92 (d), 145.84 (s), 168.14 (s); m/z (EI) 332 (M^+, 3%), 162 (83), 91 (100).

9.3.4 General procedure for the preparation of *N*-allyl-*N*-benzyl-*N*-tri- or di-haloamides.

Acid chloride (1 eq.) was added dropwise over a period of 5 minutes to a stirred solution of *N*-allyl-*N*-benzylamine (120) (2 eq.) in dichloromethane under nitrogen and the mixture allowed to stir for 2 hours at RT. The mixture was extracted with dichloromethane (2x 50 cm^3) and washed 10% HCl (2x 50 cm^3) and saturated sodium bicarbonate (2x 50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure.

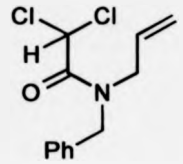
9.3.4.1 *N*-Allyl-*N*-benzyl-2,2,2-trichloroacetamide (127).



2,2,2-Trichloroacetyl chloride (0.62 cm^3, 3.4 mmol) was added dropwise to a stirred solution of *N*-allyl-*N*-benzylamine (120) (1.0 g, 6.8 mmol) in CH_2Cl_2 (10 cm^3). Purification by flash column chromatography eluting with 10:1 light petroleum ether:ethyl acetate afforded *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide (127) (0.80 g, 80%) as a 1.8:1 mixture of rotamers in the form of a white crystalline solid; m.p. 41-42°C (lit m.p. 41-42°C).[13, 14] (Found C, 49.28; H, 4.12; N, 4.46. Calc. For $C_{12}H_{12}Cl_3NO$: C, 49.26; H, 4.13; N, 4.79%). Spectral details matched those previously reported.[13, 14]

ν_{max} (nujol)/cm^{-1} 2926, 1685; δ_H(250MHz; $CDCl_3$) 3.94 (2H, br s, $\underline{CH_2}CH=CH_2$, *minor rotamer*), 4.28 (2H, br s, $\underline{CH_2}CH=CH_2$, *major rotamer*), 4.67 (2H, br s, $\underline{CH_2}Ph$, *major rotamer*), 4.97 (2H, br s, $\underline{CH_2}Ph$, *minor rotamer*), 5.09 (2H, m, $CH=\underline{CH_2}$), 5.80 (1H, m, $\underline{CH}=CH_2$), 7.23 (5H, m, Ph); δ_C(75MHz; $CDCl_3$) *major rotamer* 50.39 (t), 51.66 (t), 93.54 (s), 120.20 (t), 127.53 (d), 128.22 (d), 128.30 (d), (2x) 129.25 (d), 132.37 (d), 136.23 (s), 161.24 (s).

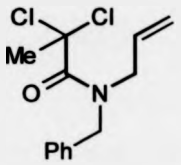
9.3.4.2 *N*-Allyl-*N*-benzyl-2,2-dichloroacetamide (128).



2,2-Dichloroacetyl chloride (0.51 cm^3, 3.4 mmol) was added dropwise to a stirred solution of *N*-allyl-*N*-benzylamine (120) (1.0 g, 6.8 mmol) in CH_2Cl_2 (10 cm^3). Purification by flash column chromatography eluting with 10:1 light petroleum ether:ethyl acetate afforded *N*-allyl-*N*-benzyl-2,2-dichloroacetamide (128) (0.72 g, 82%) as a 2:1 mixture of rotamers in the form of a clear oil. (Found C, 55.36; H, 5.00; N, 5.23. Calc. For $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43%). Spectral details matched those previously reported.[13, 14]

ν_{max} (neat)/cm^{-1} 2985, 1681; δ_H(250MHz; $CDCl_3$) *major* 3.95 (2H, brs, $\underline{CH_2}CH=CH_2$), 4.59 (2H, brs, $\underline{CH_2}CH=CH_2$), 5.08 (2H, m, $CH=\underline{CH_2}$), 5.66 (1H, m, $CH=CH_2$), 6.25 (1H, brs, $\underline{CH}Cl_2$), 7.16 (5H, m, Ph); δ_C(75MHz; $CDCl_3$) *major* 49.75 (t), 49.79 (t), 65.40 (d), 118.58 (t), 126.98 (s), (2x) 128.54 (d), (2x) 129.22 (d), 132.39 (d), 136.42 (s), 164.74 (s).

9.4.4.3 *N*-Allyl-*N*-benzyl-2,2-dichloropropionamide (129).



2,2-dichloropropionyl chloride (prepared by the reaction of 2,2-dichlropropionic acid with excess oxalyl chloride) (0.56 cm^3, 3.5 mmol) was added dropwise to a stirred solution of *N*-allyl-*N*-benzylamine (120) (1.03 g, 7.0 mmol) in CH_2Cl_2 (10 cm^3). Purification by flash column chromatography eluting with 10:1 light petroleum ether:ethyl acetate afforded *N*-allyl-*N*-benzyl-2,2-dichloropropionamide (129) (0.70 g, 74%) as a 1.5:1 mixture of rotamers in the form of a clear oil. (Found C, 57.15; H, 5.51; N, 4.98. Calc. For $C_{13}H_{15}Cl_2NO$: C, 57.37; H, 5.56; N, 5.15%). Spectral details matched those previously reported.[15]

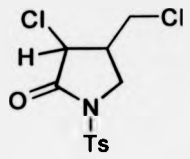
ν_{max} (neat)/cm^{-1} 3029, 1659; δ_H(250MHz; $CDCl_3$) *major* 2.38 (3H, s, $MeCCl_2$), 4.39 (2H, d, J=5.8 Hz, $CH_2CH=CH_2$), 4.62 (2H, s, CH_2Ph), 5.13 (2H, m, $CH=CH_2$), 5.68 (1H, m, $CH=CH_2$), 7.20 (5H, m, Ph); δ_C(75MHz; $CDCl_3$) *major* 36.95 (q), 48.88 (t), 51.41 (t), 81.05 (s), 119.69 (t), 127.81 (s), (2x) 128.02 (d), (2x) 129.09 (d), 131.79 (d), 133.24 (s), 165.79 (s); *m/z* (EI) 272 (M^+, 10%), 149 (85), 91 (100).

9.3.5 General procedure for atom transfer cyclisations in benzene.

To a 0.12M solution of *N*-tosyl acetamide in dry benzene under nitrogen was added either CuCl of CuBr (30 mol%) and *N*-pentyl-2-pyridylmethanimine (118) (30 mol%). The mixture was then placed in a sealed tube and heated to 100°C for a period of 4 hours. The

resulting mixture was eluted through a short silica plug with dichloromethane and the solvent removed in *vacuo* to give the crude products. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.

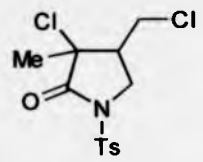
9.3.5.1 *N*-Toluenesulfonyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (130).



N-allyl-*N*-toluenesulphonyl-2,2-dichloroacetamide (122) (50 mg, 0.16 mmol) in dry benzene (1.3 cm^3) was reacted as described above at 135°C (9.3.5) to furnish *N*-toluenesulfonyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (130) (44 mg, 88%) as a inseparable mixture of diastereoisomers (ratio 3:1, *cis:trans*) in the form of a white crystalline solid; m.p. 156-157°C. (Found M^+ 322.0073 $C_{12}H_{14}Cl_2NO_3S$ requires 322.0071). Spectral details match those previously reported.[16]

ν_{max} (film)/cm^{-1} 2924, 1749; δ_H(250MHz; C_6D_6) *cis* 1.72 (1H, m, CHCH$_2$Cl), 1.83 (3H, s, Me), 2.62 (1H, m, HCHCl), 2.74 (1H, dd, J=11.6, 4.2 Hz, HCHCl), 3.16 (1H, dd, J=9.8, 8.4 Hz, HCHN), 3.40 (1H, d, J=9.5 Hz, CHCl), 3.60 (1H, m, HCHN), 6.76 (2H, d, J=8.7 Hz, Ar), 8.01 (2H, d, J=8.7 Hz, Ar); *trans* 1.55 (1H, m, CHCH$_2$Cl), 1.82 (3H, s, Me), 2.62 (1H, m, HCHCl), 2.87 (1H, dd, J=9.8, 8.4 Hz, HCHCl), 3.11 (1H, dd, J=9.8, 8.4 Hz, HCHN), 3.53 (1H, dd, J=10.2, 7.0 Hz, HCHN), 6.76 (2H, d, J=8.7 Hz, Ar), 8.01 (2H, d, J=8.7 Hz, Ar).

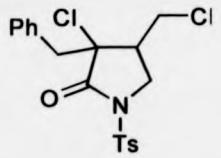
9.3.5.2 *N*-Toluenesulfonyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (131).



N-allyl-*N*-toluenesulphonyl-2,2-dichloropropionamide (123) (50 mg, 0.15 mmol) in dry benzene (1.25 cm^3) was reacted as described above (9.3.5) to furnish *N*-toluenesulfonyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (131) (45 mg, 90%) as a inseparable mixture of diastereoisomers (ratio 5.3:1, *trans:cis*) in the form of a white crystalline solid; m.p. 161-162°C. (Found C, 46.49; H, 4.47; N, 3.93. Calc. For $C_{13}H_{15}Cl_2NO_3S$: C, 46.44; H, 4.50; N, 4.17%).

ν_{max} (film)/cm^{-1} 2924, 1735; δ_H(250MHz; $CDCl_3$) *trans* 1.58 (3H, s, MeCCl), 2.43 (3H, s, Me), 2.83 (1H, m, HCCH$_2$Cl), 3.37 (1H, dd, J=11.6, 8.5 Hz, HCHCl), 3.65 (1H, dd, J=11.6, 4.3 Hz, HCHCl), 3.84 (1H, dd, J=10.7, 3.7 Hz, HCHN), 4.13 (1H, dd, J=10.7, 8.5 Hz, HCHN), 7.34 (2H, d, J=8.5 Hz, Ar), 7.88 (2H, d, J=8.5 Hz, Ar); *cis* 1.70 (3H, s, MeCCl), 2.43 (3H, s, Me), 2.53 (1H, m, HCCH$_2$Cl), 3.41 (1H, dd, J=10.1, 10.1 Hz, HCHN), 3.61 (1H, dd, J=11.3, 8.5 Hz, HCHCl), 3.77 (1H, dd, J=11.3, 5.8 Hz, HCHN), 4.19 (1H, dd, J=10.1, 7.0 Hz, HCHN), 7.34 (2H, d, J=8.5 Hz, Ar), 7.89 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) *mixture* (2x) 22.17 (q), (2x) 24.24 (q), 41.38 (t), 42.28 (t), 47.19 (d), 47.44 (d), 47.73 (t), 47.63 (t), 69.38 (d), 71.37 (d), (2x) 128.49 (s), (2x) 128.56 (d), (2x) 130.24 (d), (2x) 130.28 (d), 134.15 (d), 134.37 (d), (2x) 146.29 (s), 169.12 (s), 169.29 (s); *m/z* (EI) 336 (M^+, 4%), 155 (52), 91 (100).

9.3.5.3 *N*-Toluenesulfonyl-4-chloromethyl-3-benzyl-3-chloro-pyrrolidin-2-one (132).



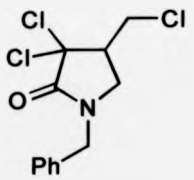
N-allyl-*N*-toluenesulphonyl-2-benzyl-2,2-dichloroacetamide (124) (100 mg, 0.25 mmol) in dry benzene (2.1 cm^3) was reacted as described above (9.3.5) to furnish *N*-toluenesulfonyl-4-chloromethyl-3-benzyl-3-chloro-pyrrolidin-2-one (132) (98 mg, 98%) as a inseparable mixture of diastereoisomers (ratio >99:1, *cis*:*trans*) in the form of a white crystalline solid; m.p. 146-147°C. (Found C, 55.46; H, 4.62; N, 3.03. Calc. For $C_{19}H_{19}Cl_2NO_3S$: C, 55.34; H, 4.64; N, 3.40%).

ν_{max} (film)/cm^{-1} 2921, 1736; δ_H(360MHz; $CDCl_3$) *trans* 2.47 (3H, s, Me), 2.62 (1H, m, HCCH$_2$Cl), 3.19 (1H d, J=14.1 Hz, CH$_2$Ph). 3.35 (1H, t, J=10.0 Hz, HCHN), 3.49 (2H, d, J=7.2 Hz, HCHCl), 3.50 (1H, d, J=14.1 CH$_2$Ph), 4.13 (1H, dd, J=10.0, 7.2 Hz, HCHN), 7.15 (5H, m, Ph), 7.35 (2H, d, J=8.5 Hz, Ar), 7.88 (2H, d, J=8.5 Hz, Ar); δ_C(90.5MHz; $CDCl_3$) *trans* 21.77 (q), 41.28 (t), 41.82 (d), 42.29 (t), 47.80 (t), 72.21 (d), (2x) 127.96 (s+d), (2x) 128.12 (d), (2x) 129.02 (d), (2x) 129.82 (d), (2x) 130.25 (d), 133.67 (s), 145.81 (s), 168.29 (s); *m/z* (EI) 412 (M^+, 5%), 149 (100), 91 (75).

9.3.6 General procedure for atom transfer cyclisations using dichloromethane.

To a 0.12M solution of *N*-benzyl acetamide in dichloromethane under nitrogen was added either CuCl of CuBr (30 mol%) and *N*-pentyl-2-pyridylmethanimine (118) (30 mol%). The mixture was then stirred at RT for 24 hours. The resulting mixture was eluted through a short silica plug with dichloromethane and the solvent removed in *vacuo* to give the crude products. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.

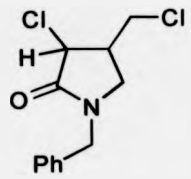
9.3.6.1 *N*-Benzyl-4-chloromethyl-3,3-dichloro-pyrrolidin-2-one (133).



N-allyl-*N*-benzyl-2,2,2-trichloroacetamide (127) (100 mg, 0.34 mmol) in dichloromethane (2.8 cm^3) was reacted as described above (9.3.6) to furnish *N*-benzyl-4-chloromethyl-3,3-dichloro-pyrrolidin-2-one (133) (90 mg, 90%) in the form of a white crystalline solid; m.p. 87-88°C (lit m.p. 89-89°C).[13] (Found C, 49.59; H, 4.13; N, 4.55. Calc. For $C_{12}H_{12}Cl_3NO$: C, 49.26; H, 4.13; N, 4.79%). Spectral details matched those previously reported.[17]

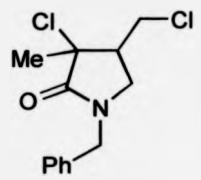
ν_{max} (film)/cm^{-1} 2927, 1728; δ_H(250MHz; $CDCl_3$) 3.00 (2H, m, HCHN and $CHCH_2Cl$), 3.45 (1H, m, CHHN), 3.66 (1H, m, CHHCl), 3.96 (1H, dd, J=11.3, 4.0 Hz, CHHCl), 4.43 (1H, d, J=14.6 Hz, CH_2Ph), 4.63 (1H, d, J=14.6 Hz, CH_2Ph). 7.20 (5H, m, Ph).

9.3.6.2 *N*-Benzyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (134).



N-allyl-*N*-benzyl-2,2-dichloroacetamide (128) (100 mg, 0.34 mmol) in dichloromethane (2.8 cm^3) was reacted at reflux as described above (9.3.6) to furnish *N*-benzyl-4-chloromethyl-3,3-dichloro-pyrrolidin-2-one (134) and starting material in the ratio (2:1) purification by chromatography eluting with 6:1 light petroleum ether:ethyl acetate furnished the pure product (134) (50 mg, 50%) as a inseparable mixture of diastereoisomers (ratio 2:1, *cis*:*trans*) in the form of a clear oil. (Found C, 55.91; H, 5.17; N, 5.19. Calc. For $C_{12}H_{13}Cl_2NO$: C, 55.83; H, 5.08; N, 5.43). Spectral details matched those previously reported.[13, 17]

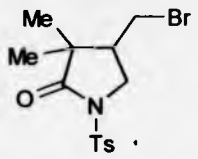
9.3.6.3 *N*-Benzyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (135).



N-allyl-*N*-benzyl-2,2-dichloropropionamide (129) (100 mg, 0.34 mmol) in dichloromethane (2.8 cm^3) was reacted at reflux as described above (9.3.6) to furnish *N*-benzyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (135) (95 mg, 95%) as a inseparable mixture of diasteroeisomers (ratio 2.6:1, *cis:trans*) in the form of a white crystalline solid; m.p. 56-57°C. (Found C, 57.51; H, 5.65; N, 5.04. Calc. For $C_{13}H_{15}Cl_2NO$: C, 57.37; H, 5.56; N, 5.15).

ν_{max} (film)/cm^{-1} 2927, 1730; δ_H(250MHz; $CDCl_3$) *cis* 1.82 (1H, s, MeCCl), 2.48 (1H, m, HCH_2Cl), 2.99 (1H, m, HCHN), 3.63 (1H, dd, J=11.3, 9.1 Hz, HCHN), 3.84 (1H, dd, J=11.0, 5.2 Hz, HCHCl), 4.36 (1H, d, J=14.6 Hz, CH_2Ph), 4.63 (1H, d, J=14.6 Hz, CH_2Ph), 7.20 (5H, m, Ph); *trans* 1.69 (1H, s, MeCCl), 2.87 (1H, m, HCH_2Cl), 2.99 (1H, m, HCHN), 3.54 (1H, dd, J=10.4, 7.0 Hz, HCHN), 3.72 (1H, m, HCHCl), 4.48 (2H, m, CH_2Ph), 7.20 (5H, m, Ph); δ_C(75MHz; $CDCl_3$) *cis* 25.45 (q), 42.58 (t), 47.49 (t), 48.03 (d), 48.07 (t), 69.38 (s), (2x) 128.36 (d), 128.46 (d), (2x) 129.30 (d), 135.77 (s), 171.57 (s); *m/z* (EI) 272 (M^+, 30%), 236 (85), 91 (100).

9.3.6.4 4-Bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (136).



N-allyl-*N*-toluenesulphonyl-2-bromo-methylpropionamide (125) (150 mg, 0.42 mmol) in dichloromethane (3.5 cm^3) was reacted as described above (9.3.6) to furnish 4-bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (136) (146 mg, 97%) in the form of a white crystalline solid; m.p. 132-133°C. (Found C, 46.65; H, 5.03; N, 3.79. Calc. For $C_{14}H_{18}BrNO_3S$: C, 46.67; H, 5.04; N, 3.89%).

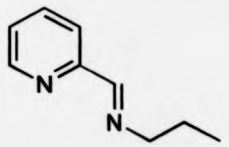
ν_{max} (nujol)/cm^{-1} 2968, 1736; δ_H(250MHz; $CDCl_3$) 0.88 (3H, s, MeCMe), 0.88 (3H, s, MeCMe), 2.42 (3H, s, Me), 2.42 (1H, m, $CHCH_2Cl$), 3.19 (1H, t, J=10.4 Hz, HCHN), 3.49 (2H, m, HCHBr), 4.14 (1H, dd, J=10.4, 7.3 Hz, HCHN), 7.32 (2H, d, J=8.2 Hz, Ar), 7.89 (2H, d, J=8.2 Hz, Ar); δ_C(75MHz; $CDCl_3$) 16.82 (q), 20.71 (q), 22.42 (q), 28.76 (t), 44.02 (d), 44.39 (s), 47.78 (t), (2x) 126.96 (s+d), (2x) 128.72 (d), 133.79 (d), 144.32 (s), 175.86 (s); *m/z* (EI) 360 (M^+, 2%), 295 (42), 149 (100).

9.3.6.5 Attempted cyclisation of *N*-allyl-4-toluenesulfonyl-2-bromoacetamide (126).

N-allyl-4-toluenesulfonyl-2-bromoacetamide (126) (100 mg, 0.30 mmol) in dichloromethane (2.5 cm^3) was reacted as described above (9.3.6) at 100°C in a sealed tube to furnish only starting material *N*-allyl-4-toluenesulfonyl-2-bromoacetamide (126) (90 mg).

9.4 Experimental for chapter 5.

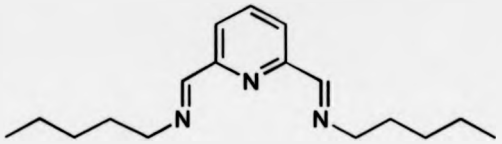
9.4.1 *N*-Propyl-2-pyridylmethanimine (138).



N-propylamine (0.36 g, 6.07 mmol) was added to a stirred solution of 2-pyridine carboxaldehyde (0.65 g, 6.07 mmol) in diethyl ether (10 cm^3). The solution was stirred at room temperature for 5 minutes and anhydrous magnesium sulphate (6 g) was added. The reaction was left for a period of 3 hours after which time the reaction had proceeded smoothly to completion. The diethyl ether was removed in *vacuo* to give a light yellow oil which was purified by vacuum distillation to give *N*-propyl-2-pyridylmethanimine (138) (0.69 g, 77%) as a light yellow oil. (Found MH^+ 149.1078. $C_9H_{13}N_2$ requires 149.1079).

ν_{max} (neat)/cm^{-1} 2931, 1649; δ_H(250MHz; $CDCl_3$) 0.80 (3H, t, J=7.3 Hz $CH_2CH_2\underline{Me}$), 1.56 (2H, sx, J=7.0 Hz, $CH_2\underline{CH_2}Me$), 3.49 (2H, t, J=7.0 Hz, $\underline{CH_2}N$), 7.13 (1H, m, Ar), 7.55 (1H, t, J=7.9 Hz, Ar) 7.84 (1H, d, J=7.9 Hz, Ar), 8.25 (1H, s, $\underline{CH}N$), 8.46 (1H, m, Ar); δ_C(75MHz; $CDCl_3$) 12.12 (q), 24.70 (t), 63.54 (t), 121.49 (d), (2x) 124.92 (d), 136.85 (d), 150.01 (s), 162.02 (d); *m/z* (CI; NH_3) 149 (MH^+, 18%), 35 (100), 165 (90%).

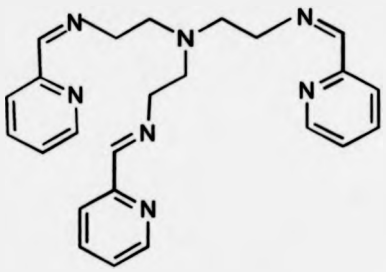
9.4.2 *N,N*-Dipentyl-2-6-pyridyl-di-methanimine (139).



N-pentylamine (0.64 g, 7.4 mmol) was added to a stirred solution of 2,6-pyridine dicarboxaldehyde (0.50 g, 3.7 mmol) in diethyl ether (30 cm^3). The solution was stirred at room temperature for 5 minutes and anhydrous magnesium sulphate (12 g) was added. The reaction was left for a period of 3 hours after which time the reaction had proceeded smoothly to completion. The diethyl ether was removed in *vacuo* to give a light yellow oil which was purified by vacuum distillation to give *N,N*-dipentyl-2-6-pyridyl-di-methanimine (139) (0.89 g, 98%) as a light yellow oil. (Found M^+ 273.2205. $C_{17}H_{27}N_3$ requires 272.2205).

ν_{max} (neat)/cm^{-1} 2932, 1651; δ_H(250MHz; $CDCl_3$) 0.79 (6H, t, J=7.0 Hz $CH_2\underline{Me}$), 1.25 (8H, m, $CH_2\underline{CH_2CH_2}$), 1.59 (4H, m, $\underline{CH_2}CH_2CH_2$), 3.47 (4H, t, J=7.0 Hz, $\underline{CH_2}N$), 7.66 (2H t, J=7.9 Hz, Ar), 7.91 (4H, d, J=7.9 Hz, Ar), 8.33 (2H, s, $\underline{CH}N$); δ_C(75MHz; $CDCl_3$) (2x) 14.42 (q), (2x) 22.86 (t), (2x) 29.90 (t), (2x) 30.75 (t), (2x) 62.00 (t), (2x) 122.52 (d), 137.48 (d), (2x) 154.74 (s), (2x) 161.82 (d); *m/z* (EI) 273 (M^+, 28%), 216 (100), 190 (35%).

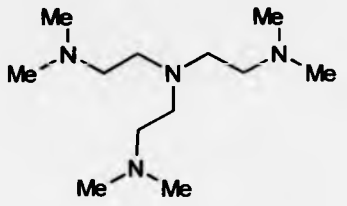
9.4.3 *N,N,N-Tris*(2-aminoethyl)amine-2,2',2''-*tris*pyridinemethanimine (140).



Tris(2-aminoethyl) amine (1.0 g, 6.8mmol) was added to a stirred solution of 2-pyridine carboxaldehyde (2.2 g, 20.5 mmol) in diethyl ether (30 cm^3). The solution was stirred at RT for 5 minutes and anhydrous magnesium sulphate (20 g) was added to remove the water formed from the condensation. The reaction was left for a period of 3 hours after which time the reaction had proceeded smoothly to completion. The diethyl ether was removed in *vacuo* to give a light yellow oil which was purified by vacuum distillation to give *N,N,N-tris*(2-aminoethyl)amine-2,2',2''-*tris*pyridine methanimine (140) (2.0 g, 71%) as a brown oil. (Found M^+ 413.2325. $C_{24}H_{27}N_7$ requires 413.2328).

ν_{max} (neat)/cm^{-1} 2912, 1649; δ_H(250MHz; $CDCl_3$) 2.75 (6H, t, J=6.4 Hz, $\underline{CH_2}CH_2N$), 3.35 (6H, t, J=6.4 Hz, $CH_2\underline{CH_2}N$), 6.97 (3H, m, Ar), 7.39 (3H, m, Ar), 7.65 (3H m, Ar), 8.11 (3H, s, $\underline{CH}N$), 8.34 (3H, m, Ar); δ_C(75MHz; $CDCl_3$) (3x) 55.61 (t), (3x) 60.16 (t), (3x) 120.90 (d), (3x) 121.60 (d), (3x) 125.04 (d), (3x) 149.72 (d), (3x) 154.74 (s), (3x) 163.13 (d); *m/z* (EI) 413 (M^+, 12%), 92 (100), 133 (72%).

9.4.4 *N,N,N*-Hexamethyl-*tris*(2-amino ethyl) amine (141).



Tris(2-aminoethyl) amine (5.0 g, 34.2 mmol) was dissolved in water (5 cm^3) to the mixture was added formic acid (98%) (16 cm^3) dropwise. The mixture was allowed to stir at RT for a period of 10 minutes. To the mixture was then added formaldehyde (13 cm^3, 37%) over a period of 10 minutes and the mixture refluxed for 12 hours. The solvent was removed in *vacuo* to yield a yellow/white semi-solid which was basified with 6M NaOH (30 cm^3) and left overnight at RT. The aqueous layer was then ran off to furnish a yellow oil which was purified by distillation under reduced pressure (150°C at 5mm Hg) (lit. 70-71°C at 0.5mm Hg)[18] to yield *N,N,N*-hexamethyl-*tris*(2-amino ethyl) amine (141) (7.0 g, 89%) as a clear yellow oil. (Found MH^+ 231.2552 $C_{12}H_{31}N_4$ requires 231.2549)

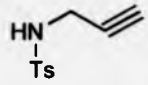
ν_{max} (neat)/cm^{-1} 2941, 1678; δ_H(250MHz; $CDCl_3$) 2.20 (18H, s, 6x Me), 2.31 (6H, br t, J=7.0Hz, 3x NCH_2), 2.55 (6H, br t, J=7.0Hz, 3x NCH_2); δ_C(63MHz; $CDCl_3$) (6x) 46.24 (q), (3x) 53.43 (t), (3x) 57.82 (t); *m/z* (CI; NH_3) 231 (MH^+, 10%), 35 (100), 172 (35%).

9.4.5 General method for screening ligand effeciency.

To *N*-allyl-*N*-toluenesulphonyl-2-bromo-methylpropionamide (125) (50 mg, 0.139 mmol) in dry dichloromethane (1.2 cm^3) under a nitrogen atomsphere at RT was added CuBr (30 mol%) and ligand (30 mol%). After 30 minutes the reaction was quickly eluted through a short silica plug with dichloromethane to remove the CuBr(ligand) complex. The ratio of starting material to product was then determined by 250 MHz ^1H N.M.R.. In all cases the mass balances for the reaction were excellent (90-98%) and the reactions were clean with only starting material and product peaks observable in the N.M.R..

9.5 Experimental for chapter 6.

9.5.1 *N*-Propargyl-*N*-toluenesulfonamide (142).



To a stirred solution of propargylamine hydrochloride (0.77 g, 8.4 mmol) in THF (20 cm^3) was added triethylamine (2.27 cm^3, 16.4 mmol). After a period of 15 minutes a solution of tosyl chloride (1.6 g, 8.4 mmol) in THF (20 cm^3) was added dropwise. After 2 hours the reaction was reduced in *vacuo*. The mixture was extracted with dichloromethane (2x50 cm^3) and washed water (2x50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure further purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate furnished *N*-propargyl-*N*-toluenesulfonamide (142) (1.4 g, 82%) as a clear viscous oil. Spectral details matched those previously reported.[19a-b]

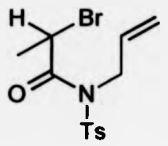
δ_H(250MHz; $CDCl_3$) 2.05 (1H, t, J=2.45 Hz, CH), 2.37 (3H, s, Me), 3.75 (2H, d, J=2.45 Hz, CH_2), 5.36 (1H, br s, NH), 7.24 (2H, d, J=8.2 Hz, Ar), 7.72 (2H, d, J=8.2 Hz, Ar).

9.5.2 General procedure for the preparation of *N*-allyl/propargyl-*N*-tosyl-*N*-monohaloacetamides.

A solution of *n*-BuLi (2.5M in hexanes, 1 eq.) was added dropwise over a period of 5 minutes to a stirred solution of *N*-allyl/propargyl-*N*-toluenesulfonamide (1 eq.) in dry THF at -78°C under nitrogen and the mixture allowed to stir for 30 minutes. The acid chloride

or bromide (1.1 eq.) was added and the mixture stirred for 2 hours at -78°C. The reaction was quenched with saturated ammonium chloride solution and allowed to warm to RT. The mixture was extracted with dichloromethane (2x 50 cm^3) and washed with saturated sodium bicarbonate (2x 50 cm^3). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure.

9.5.2.1 *N*-2-Propenyl-*N*-toluenesulphonyl-2-bromopropionamide (143).

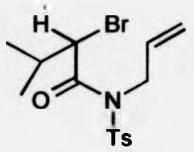


n-BuLi (1.0 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (0.50 g, 2.4 mmol) in THF (15 cm^3) then 2-bromopropionyl bromide (0.27 cm^3, 2.6 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded the *N*-2-propenyl-*N*-toluenesulphonyl-2-bromopropionamide (143) (0.58 g, 70%) as a white crystalline solid; m.p. 39-40°C. (Found C, 45.26; H, 4.69; N, 3.74. Calc. For $C_{13}H_{16}BrNO_3S$: C, 45.10; H, 4.66; N, 4.05%).

ν_{max} ($CDCl_3$)/cm^{-1} 2925, 1703, 1645; δ_H(250MHz; $CDCl_3$) 1.70 (3H, d, J=6.6 Hz, MeCHBr), 2.42 (3H, s, Me), 4.38 (1H, ddt, J=17.4, 5.5, 1.8 Hz, $CH_2CH=CH_2$). 4.67 (1H, ddt, J=17.4, 5.5, 1.8 Hz, $CH_2CH=CH_2$). 4.79 (1H, q, J=6.6 Hz, MeCHBr), 5.20 (2H, m, $CH=CH_2$). 5.81 (1H, m, $CH=CH_2$), 7.30 (2H, d, J=8.5 Hz, Ar), 7.82 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 21.54 (q), 22.09 (q), 40.00 (d), 49.08 (t), 118.34 (t), (2x) 128.64 (s+d),

(2x) 130.11 (d), 133.11 (d), 135.97 (d), 145.63 (s), 169.81 (s); *m/z* (EI) 345 (M^+, 5%), 155 (70), 91 (100).

9.5.2.2 *N*-Allyl-*N*-toluenesulphonyl-2-bromo-3-methylbutanamide (144).

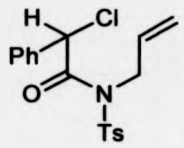


n-BuLi (0.80 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (0.40 g, 1.90 mmol) in THF (10 cm^3) then 2-bromo-3-methyl butyroyl chloride (0.42 g, 2.09 mmol) (prepared by the reaction of 2-bromo-methyl butyric acid with excess oxalyl chloride) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded the *N*-allyl-*N*-toluenesulphonyl-2-bromo-3-methylbutanamide (144) (0.45 g, 64%) as a viscous oil. (Found C, 48.55; H, 5.52; N, 3.74. Calc. For $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74%).

ν_{max} (neat)/cm^{-1} 2922, 1706, 1597; δ_H(250MHz; $CDCl_3$) 0.79 (3H, d, J=6.7 Hz, MeCHMe), 1.00 (3H, d, J=6.7 Hz, MeCHMe), 2.14 (1H, m, MeCHMe), 2.36 (3H, s, Me), 4.26 (1H, ddt, J=17.1, 5.2, 1.5 Hz, $CH_2CH=CH_2$), 4.40 (1H, d, J=9.4 Hz, CHBr), 4.55 (1H, ddt, J=17.1, 5.2, 1.5 Hz, $CH_2CH=CH_2$), 5.18 (2H, m, $CH=CH_2$), 5.82 (1H, m, $CH=CH_2$), 7.32 (2H, d, J=8.5 Hz, Ar), 7.82 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 20.16 (q), 20.87 (q), 22.06 (q), 32.60 (d), 49.14 (t), 53.17 (d), 118.60 (t), (3x) 128.54 (s+2xd), 130.12

(d), 132.99 (d), 136.17 (d), 145.58 (s), 171.49 (s); *m/z* (EI) 373 (M^+, 10%), 155 (80), 91 (100).

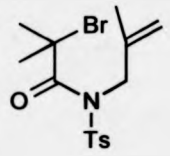
9.5.2.3 *N*-2-Propenyl-*N*-toluenesulphonyl-2-chloro-2-phenylacetamide (145).



n-BuLi (0.95 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-allyl-*N*-toluenesulfonamide (119) (0.50 g, 2.37 mmol) in THF (30 cm^3) then 2-chloro-2-phenylacetyl chloride (0.32 cm^3, 2.60 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded the *N*-2-propenyl-*N*-toluenesulphonyl-2-chloro-2-phenylacetamide (145) (0.560 g, 65%) as a white crystalline solid; m.p. 39-40°C. (Found C, 59.22; H, 4.96; N, 3.75. Calc. For $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.99; N, 3.85%).

ν_{max} (neat)/cm^{-1} 2926, 1702, 1593; δ_H(250MHz; $CDCl_3$) 2.43 (3H, s, Me), 4.27 (2H, m, $\underline{CH_2}CH=CH_2$), 5.16 (2H, m, $CH=\underline{CH_2}$), 5.72 (1H, m, $\underline{CH}=CH_2$), 6.13 (1H, s, $\underline{CH}$Ph), 7.25 (2H, m, Ar), 7.69 (2H, d, J=8.2 Hz, Ar); δ_C(75MHz; $CDCl_3$) 22.09 (q), 49.17 (t), 58.88 (d), 119.05 (t), (2x) 128.61 (s+d), (3x) 128.90 (d), (2x) 129.38 (d), (2x) 129.87 (d), (2x) 130.18 (d), 132.36 (s), 145.60 (s), 162.68 (s); *m/z* (EI) 363 (M^+, 3%), 155 (80), 91 (100).

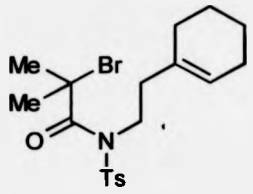
9.5.2.4 *N*-2-Methyl-2-propenyl-*N*-toluenesulphonyl-2-bromo-2-methyl propionamide (146).



n-BuLi (1.78 cm^3 2.5M) in hexanes was added to a stirred solution of *N*-2-methallyl-*N*-toluenesulfonamide (1.00 g, 4.44 mmol) in THF (60 cm^3) then 2-bromo-2-methylpropionyl bromide (0.60 cm^3, 4.88 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded *N*-2-methyl-2-propenyl-*N*-toluenesulphonyl-2-bromo-2-methyl propionamide (146) (1.25 g, 75%) as a white crystalline solid; m.p. 112-113°C. (Found C, 48.19; H, 5.38; N, 3.40. Calc. For $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74%).

ν_{max} ($CDCl_3$)/cm^{-1} 2936, 1680, 1593; δ_H(250MHz; $CDCl_3$) 1.83 (6H, s, MeCHBrMe), 1.86 (3H, s (Me)C=CH_2), 2.37 (3H, s, Me), 4.74 (2H, s, CH_2(Me)C=CH_2), 4.93 (2H, s, MeC=CH_2), 7.21 (2H, d, J=8.5 Hz, Ar), 7.78 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 20.70 (q), 22.05 (q), (2x) 32.67 (q), 55.46 (t), 58.02 (s), 112.38 (t), (2x) 129.17 (s+d), (2x) 129.55 (d), 136.24 (d), 141.27 (s), 145.07 (s), 170.80 (s); *m/z* (EI) 374 (M^+, 1%), 155 (82), 91 (100).

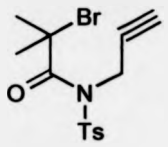
9.5.2.5 *N*-(2-Bromo-2-methylpropionyl)-*N*-toluenesulphonyl-2-(1-cyclohexene)-ethanamide (147).



n-BuLi (0.74 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-ethane-1-cyclohexene-*N*-toluenesulfonamide (0.50 g, 1.84 mmol) in THF (35 cm^3) then 2-bromo-2-methylpropionyl bromide (0.25 cm^3, 2.02 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate afforded *N*-(2-bromo-2-methylpropionyl)-*N*-toluenesulphonyl-2-(1-cyclohexene)-ethanamide (147) (0.54 g, 69%) as a white crystalline solid; m.p. 76-78°C. (Found C, 52.94; H, 6.07; N, 2.97. Calc. For $C_{19}H_{26}BrNO_3S$: C, 53.27; H, 6.12; N, 3.27%).

ν_{max} (nujol)/cm^{-1} 2923, 1695, δ_H(250MHz; $CDCl_3$) 1.44 (4H, m, $\underline{CH_2CH_2}$), 1.81 (6H, s, $\underline{Me}CHBr\underline{Me}$), 1.90 (4H, m, 2x $\underline{CH_2}C{=}CH$), 2.34 (3H, s, Me), 2.45 (2H, m, $NCH_2\underline{CH_2}$), 4.20 (2H, m, $N\underline{CH_2}CH_2$), 5.45 (1H, br s, C=$\underline{CH}$), 7.22 (2H, d, J=8.5 Hz, Ar), 7.78 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 22.06 (q), 23.17 (t), (2x) 25.60 (t), (2x) 32.19 (q), (2x) 39.15 (t), 48.37 (t), 57.07 (s), (3x) 124.15 (s+2xd), 128.95 (d), 129.65 (d), 134.25 (s), 136.73 (s), 144.91 (s), 170.82 (s); *m/z* (CI) 428 (M^+, 62%), 350 (66), 286 (100).

9.5.2.6 *N*-2-Propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (148).



n-BuLi (0.96 cm^3, 2.5M) in hexanes was added to a stirred solution of *N*-propargyl-toluenesulfonamide (142) (0.5 g, 2.4 mmol) in THF (15 cm^3) then 2-bromo-2-methylpropionyl bromide (0.32 cm^3, 2.6 mmol) was added. Purification by flash column chromatography eluting with 4:1 light petroleum ether:ethyl acetate, afforded *N*-2-propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (148) (0.65 g, 76%) as a white crystalline solid; m.p. 92-93°C. (Found C, 47.33; H, 4.55; N, 3.87. Calc. For $C_{14}H_{16}BrNO_3S$: C, 46.94; H, 4.50; N, 3.91%).

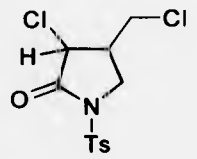
ν_{max} (nujol)/cm^{-1} 2925, 1692, 1593; δ_H(300MHz; $CDCl_3$) 1.87 (6H, s, MeCBrMe), 2.35 (3H, s, Me), 2.40 (1H, t, CH), 5.05 (2H, d, J=2.5 Hz, CH_2CCH), 7.24 (2H, d, J=8.5 Hz, Ar), 7.81 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 22.11 (q), (2x) 32.15 (q), 38.18 (t), 57.15 (s), 74.32 (d), 79.17 (s), (2x) 129.47 (s+d), (2x) 129.65 (d), 136.03 (d), 145.34 (s), 170.05 (s); *m/z* (EI) 358 (M^+, 20%), 91 (100), 186 (85).

9.5.3 General procedure for atom transfer cyclisations.

To a 0.12M solution of cyclisation precursor in dichloromethane under nitrogen was added either CuCl or CuBr (30 mol%) and *N,N,N*-hexamethyl-*tris*(2-amino ethyl) amine (141) (30 mol%). The mixture was then stirred at RT for 24 hours. The resulting mixture was

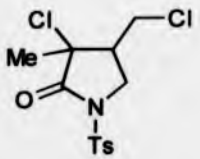
eluted through a short silica plug with dichloromethane and the solvent removed in *vacuo* to give the crude products. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.

9.5.3.1 *N*-Toluenesulfonyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (149).



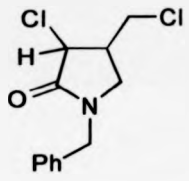
N-allyl-*N*-toluenesulphonyl-2,2-dichloroacetamide (122) (50 mg, 0.16 mmol) in dichloromethane (1.3 cm^3) was reacted as described above (9.5.3) for a period of 2 hours, to furnish *N*-toluenesulfonyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (149) (48 mg, 96%) as a inseparable mixture of diastereoisomers (ratio 4.9:1, *cis*:*trans*) in the form of a white crystalline solid; m.p. 156-157°C. (Found M^+ 322.0073 $C_{12}H_{14}Cl_2NO_3S$ requires 322.0071). Spectral details matched those previously cited in section (9.3.5.1).

9.5.3.2 *N*-Toluenesulfonyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (150).



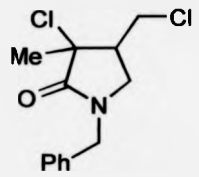
N-allyl-*N*-toluenesulphonyl-2,2-dichloropropionamide (123) (50 mg, 0.15 mmol) in dichloromethane (1.25 cm^3) was reacted as described above (9.5.3) for a period of 30 minutes, to furnish *N*-toluenesulfonyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (150) (49 mg, 98%) as a inseparable mixture of diastereoisomers (ratio 5.6:1, *trans*:*cis*) in the form of a white crystalline solid; m.p. 161-162°C. (Found C, 46.49; H, 4.47; N, 3.93. Calc. For $C_{13}H_{15}Cl_2NO_3S$: C, 46.44; H, 4.50; N, 4.17). Spectral details matched those previously cited in section (9.3.5.2).

9.5.3.3 *N*-Benzyl-4-chloromethyl-3-chloro-pyrrolidin-2-one (151).



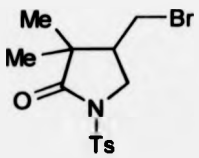
N-allyl-*N*-benzyl-2,2-dichloroacetamide (128) (100 mg, 0.34 mmol) in dichloromethane (2.8 cm^3) was reacted as described above (9.5.3) for a period of 4 hours, to furnish *N*-benzyl-4-chloromethyl-3,3-dichloro-pyrrolidin-2-one (151) (90 mg, 90%) as a inseparable mixture of diastereoisomers (ratio 4.3:1, *trans*:*cis*) in the form of a clear oil. (Found C, 55.91; H, 5.17; N, 5.19. Calc. For $C_{12}H_{13}Cl_2NO_3S$: C, 55.83; H, 5.08; N, 5.43). Spectral details matched those previously cited in section (9.3.6.2).

9.5.3.4 *N*-Benzyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (152).



N-allyl-*N*-benzyl-2,2-dichloropropionamide (129) (100 mg, 0.34 mmol) in dichloromethane (2.8 cm^3) was reacted at reflux as described above (9.5.3) for a period of 2 hours, to furnish *N*-benzyl-4-chloromethyl-3-chloro-3-methyl-pyrrolidin-2-one (152) (88 mg, 88%) as a inseparable mixture of diastereoisomers (ratio 9:1, *cis:trans*) in the form of a white crystalline solid; m.p. 56-57°C. (Found C, 57.51; H, 5.65; N, 5.04. Calc. For $C_{13}H_{15}Cl_2NO_3S$: C, 57.37; H, 5.56; N, 5.15). Spectral details matched those previously cited in section (9.3.6.3).

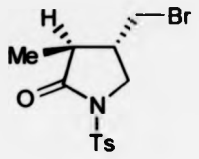
9.5.3.5 4-Bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (153).



N-allyl-*N*-toluenesulphonyl-2-bromo-methylpropionamide (125) (50 mg, 0.14 mmol) in dichloromethane (1.2 cm^3) was reacted as described above (9.5.3) for a period of 1 minute, to furnish 4-bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (153) (46

mg, 92%) in the form of a white crystalline solid; m.p. 132-133°C. (Found C, 46.65; H, 5.03; N, 3.79. Calc. For $C_{14}H_{18}BrNO_3S$: C, 46.65; H, 5.04; N, 3.89). Spectral details matched those previously cited in section (9.3.6.4)

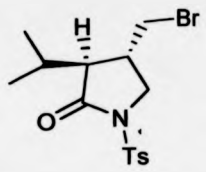
9.5.3.6 *trans*-4-Bromomethyl-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (154).



N-2-propenyl-*N*-toluenesulphonyl-2-bromopropionamide (143) (50 mg, 0.15 mmol) in dichloromethane (1.25 cm^3) was reacted as described above (9.5.3) to furnish *trans*-4-bromomethyl-3-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (154) (46 mg, 92%) as a partially separable mixture of diastereoisomers (ratio 9:1, *trans:cis*) in the form of a white crystalline solid; m.p. 126-127°C. (Found C, 45.44; H, 4.68; N, 3.65. Calc. For $C_{13}H_{16}BrNO_3S$: C, 45.10; H, 4.66; N, 4.05). X-ray crystal data has been previously reported [20-21].

ν_{max} ($CDCl_3$)/cm^{-1} 2933, 1739, 1597; δ_H(250MHz; $CDCl_3$) 1.14 (3H, d, J=6.8 Hz, MeCHBr), 2.27 (2H, m, MeCH + CHCH$_2$Br), 2.37 (3H, s, Me), 3.31 (1H, m, HCHBr), 3.51 (2H, m, HCHN + HCHBr), 4.04 (1H, m, HCHN), 7.27 (2H, d, J=8.3 Hz, Ar), 7.85 (2H, d, J=8.3 Hz, Ar); δ_C(75MHz; $CDCl_3$) 13.91 (q), 22.12 (q), 33.14 (t), 42.20 (d), 43.17 (d), 49.94 (t), (2x) 128.50 (s+d), (2x) 130.16 (d), 135.34 (s), 145.77 (s), 174.44 (s).

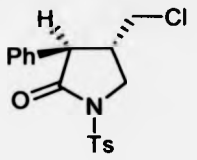
9.5.3.7 *trans*-4-Bromomethyl-3-*i*-propyl-1-toluene-4-sulfonylpyrrolidin-2-one (155).



N-allyl-*N*-toluenesulphonyl-2-bromo-3-methylbutanamide (144) (100 mg, 0.26mmol) in dichloromethane (2.2 cm^3) was reacted as described above (9.5.3) to furnish *trans* 4-bromomethyl-3-*i*-propyl-1-toluene-4-sulfonylpyrrolidin-2-one (155) (95 mg, 95%) as a inseparable mixture of diastereoisomers (ratio 8.7:1, *trans*:*cis*) in the form of a clear oil. (Found C, 48.29; H, 5.39; N, 3.75. Calc. For $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74).

ν_{max} ($CDCl_3$)/cm^{-1} 2964, 1734; δ_H(300MHz; $CDCl_3$) 0.81 (3H, d, J=5.2 Hz, MeCHMe), 0.92 (3H, d, J=5.2 Hz, MeCHMe), 2.10 (1H, m, MeCHMe), 2.25 (1H, dd, J=6.0, 4.1 Hz, CH), 2.42 (3H, s, Me), 2.54 (1H, m, $CHCH_2Br$), 3.31 (1H, dd, J=10.2, 7.4 Hz, HCHBr), 3.44 (1H, dd, J=10.2, 4.9 Hz, HCHBr), 3.62 (1H, dd, J=10.5, 5.6 Hz, HCHN), 3.98 (1H, dd, J=10.5, 8.5 Hz, HCHN), 7.31 (2H, d, J=8.3 Hz, Ar), 7.88 (2H, d, J=8.3 Hz, Ar); δ_C(75MHz; $CDCl_3$) 18.98 (q), 20.04 (q), 22.12 (q), 29.42 (d), 35.46 (d), 36.18 (t), 50.44 (t), 54.11 (d), (2x) 128.50 (s+d), (2x) 130.08 (d), 135.8 (d), 145.74 (s), 173.88 (s); *m/z* (EI) 374 (M^+, 11%), 155 (80), 91 (100).

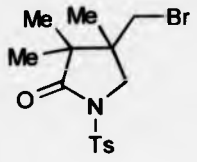
9.5.3.8 *trans*-4-Chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (156).



N-2-propenyl-*N*-toluenesulphonyl-2-chloro-2-phenylacetamide (145) (100 mg, 0.26 mmol) in dichloromethane (2.2 cm^3) was reacted as described above (9.5.3) to furnish *trans* 4-chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (156) (86 mg, 86%) as a inseparable mixture of diastereoisomers (ratio >25:1, *trans*:*cis*) in the form of a clear oil. (Found C, 59.32; H, 4.93; N, 3.58. Calc. For $C_{18}H_{18}ClNO_3S$: C, 59.42; H, 4.99; N, 3.85).

ν_{max} ($CDCl_3$)/cm^{-1} 2923, 1737, 1596; δ_H(400MHz; $CDCl_3$) 2.44 (3H, s, Me), 2.75 (1H, m, C<u>H</u>CH_2Cl), 3.50 (1H, dd, J=11.6, 6.6 Hz, <u>HC</u>HCl), 3.58 (1H, d, J=10.5 Hz, <u>HC</u>Ph), 3.64 (1H, dd, J=11.6, 3.5 Hz, HC<u>H</u>Cl), 3.71 (1H, dd, J=10.0, 8.7 Hz, <u>HC</u>HN), 4.20 (1H, dd, J=10.0, 7.7 Hz, HC<u>H</u>N), 7.06 (2H, d, J=8.5 Hz, Ar), 7.24(5H, m, Ph), 7.96 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) 22.14 (q), 43.24 (d), 44.26 (t), 48.40 (t), 53.04 (d), (2x) 128.80 (s+d), (2x) 128.88 (d), (2x) 129.01 (d), 129.86 (d), (2x) 130.20 (d), 133.13 (d), 135.29 (s), 145.91 (s), 172.33 (s); *m/z* (EI) 363 (M^+, 5%), 155 (80), 91 (100).

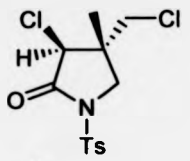
9.5.3.9 Bromomethyl-3,3-dimethyl-4-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (157).



N-2-methyl-2-propenyl-*N*-toluenesulphonyl-2-bromo-2-methyl propionamide (146) (200 mg, 0.51 mmol) in dichloromethane (4.25 cm^3) was reacted as described above (9.5.3) to furnish bromomethyl-3,3-dimethyl-4-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (157) (192 mg, 96%) in the form of a white crystalline solid; m.p. 175-176°C. (Found C, 48.43; H, 5.54; N, 3.58. Calc. For $C_{15}H_{20}BrNO_3S$: C, 48.13; H, 5.39; N, 3.74).

ν_{max} ($CDCl_3$)/cm^{-1} 2937, 1738, 1597; δ_H(300MHz; $CDCl_3$) 0.94 (3H, s, Me), 1.02 (3H, s, Me), 1.06 (3H, s, Me), 2.41 (3H, s, Me), 3.27 (2H, m, CH_2Br), 3.54 (1H, d, J=10.7 Hz, HCHN), 3.49 (1H, d, J=10.7 Hz, HCHN), 7.31 (2H, d, J=8.3 Hz, Ar), 7.88 (2H, d, J=8.3 Hz, Ar); δ_C(75MHz; $CDCl_3$) 18.98 (q), 20.17 (q), 48.11 (t), 53.21 (t), 57.82 (s), 61.43 (d), 127.25 (s), (2x) 128.53 (d), (2x) 130.34 (d), 135.26 (d), 146.69 (s), 173.79 (s); *m/z* (EI) 335 (M^+, 5%), 155 (80), 91 (100).

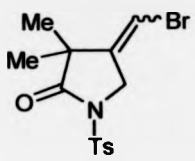
9.5.3.10 *trans*-3-Chloro-4-chloromethyl-4-methyl-1-toluene-4-sulfonyl-pyrrolidin-2-one (158).



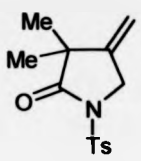
N-(2,2-dichloro-acetyl)-4-methyl-N-(2-methyl-allyl)-benzenesulfonamide (0.10 g, 0.29 mmol) in dichloromethane (2.4 cm^3) was reacted as described above (9.5.3) to furnish 3-chloro-4-chloromethyl-4-methyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (158) (89 mg, 89%) as a mixture of inseparable mixture of diastereoisomers (ratio 5.5:1, *trans*:*cis*) in the form of a clear oil. (Found C, 46.23; H, 4.50; N,4.02. Calc. For $C_{13}H_{15}Cl_2NO_3S$: C, 46.44; H, 4.50; N, 4.17).

ν_{max} (film)/cm^{-1} 2944, 1718; δ_H(300MHz; $CDCl_3$) *cis* 1.01 (3H, s, Me), 2.44 (3H, s, Me), 2.83 (2H, d, J=6.3 Hz, $\underline{CH_2}Cl$), 3.85 (1H, d, J=10.2 Hz, H$\underline{CH}$N), 3.85 (1H, d, J=10.2 Hz, H$\underline{CH}$N), 4.51 (1H, s, $\underline{CH}Cl$), 7.34 (2H, d, J=8.5 Hz, Ar), 7.91 (2H, d, J=8.5 Hz, Ar); *trans* 1.29 (3H, s, Me), 2.41 (3H, s, Me), 2.83 (2H, d, J=11.6 Hz, $\underline{CH_2}Cl$), 3.61 (1H, d, J=10.5 Hz, H$\underline{CH}$N), 3.96 (1H, d, J=10.5 Hz, H$\underline{CH}$N), 4.19 (1H, s, $\underline{CH}Cl$), 7.28 (2H, d, J=8.5 Hz, Ar), 7.83 (2H, d, J=8.5 Hz, Ar); δ_C(75MHz; $CDCl_3$) *mixture* (2x) 22.17 (q), (2x) 24.24 (q), 41.38 (t), 42.28 (t), 47.19 (d), 47.44 (d), 47.73 (t), 47.63 (t), 69.38 (d), 71.37 (d), (2x) 128.49 (s), (2x) 128.56 (d), (2x) 130.24 (d), (2x) 130.28 (d), 134.15 (d), 134.37 (d), (2x) 146.29 (s), 169.12 (s), 169.29 (s); *m/z* (EI) 335 (M^+, 5%), 155 (52), 91 (100).

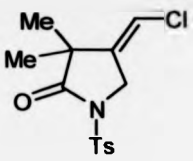
9.5.3.11 Cyclisation of *N*-2-propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (148).



(159)



(160)



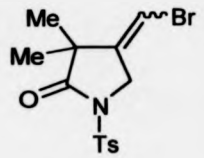
(161)

N-2-propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (148) (100 mg, 0.27 mmol) in dichloromethane (2.25 cm^3) was reacted as described above (9.5.3) to furnish a inseperable (4:5:trace) mixture of 4-bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (159, 3,3-dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (160and 4-chloromethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (161) (86 mg) in the form of a clear oil. Spectral details matched those previously reported.[19b]

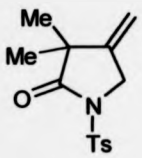
ν_{max} (nujol)/cm^{-1} *mixture* 1740, 1670, 1365, 1170; Discernible data for 3,3-dimethyl-4-methylene-1-toluene-4-sulfonylpyrrolidin-2-one (160), δ_H(400MHz; $CDCl_3$) 1.14, (6H, s, 2x Me), 2.43 (3H, s, Me), 4.37 (2H, m, CH_2), 5.04 (1H, m, C=$\underline{CH_2}$), 5.08 (1H, m, C=$\underline{CH_2}$), 7.33 (2H, m, Ar), 7.92 (2H, m, Ar); Discernible data for (E)-4-bromomethylene-3,3-dimethyl-1-toluene-4-sulfonamide (E)-(159) and (Z)-4-bromomethylene-3,3-dimethyl-1-toluene-4-sulfonamide (Z)- (159) (ratio 3 : 1), 1.20 (3H (Z), s, Me), 1.38 (3 H (E), s, Me), 2.37 (3 H (E) and (Z), s, Me), 4.44-4.37 (2H (E) and (Z), m, CH_2), 6.14 (1 H (Z), t, J=2.6 Hz, C=$\underline{CH}$Br), 6.17 (1 H (E), t, J=2.1 Hz, C=$\underline{CH}$Br), 7.30 (2 H, m, Ar), 7.94 (2 H, m, Ar); m/z LC-MS (AP^+) 4.70 minutes 280 (MH^+) 280.1022 (MH^+ $C_{14}H_{18}NO_3S$ requires

280.1001), 5.20 minutes 358 (M^+), 358.0098 (M^+, $C_{14}H_{17}Br^{79}NO_3S$ requires 358.0112), 215 (60%), 149 (46), 91 (100) and 81 (75).

9.5.3.12 Cyclisation of *N*-2-propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (149).



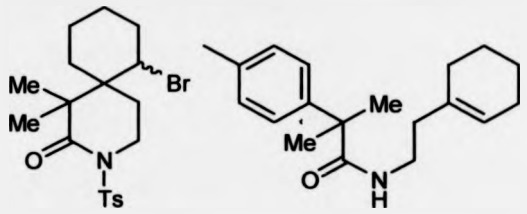
(159)



(160)

N-2-propenyl-*N*-toluenesulphonyl-bromo-2-methylpropionamide (148) (33 mg, 0.089 mmol) in THF (0.75 cm^3) was reacted as described above (9.5.3) to furnish a inseperable (1:20) mixture of 4-bromomethylene-3,3-dimethyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (159), 3,3-dimethyl-4-methylene-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (160) (26 mg) in the form of a clear oil. Spectral details matched those previously cited in section (9.5.3.11)

9.5.3.13 Cyclisation of *N*-(2-bromo-2-methylpropionyl)-*N*-toluenesulphonyl-2-(1-cyclohexene)-ethanamide (147).



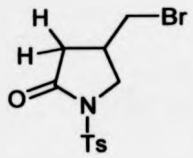
(162) (163)

N-(2-bromo-2-methylpropionyl)-*N*-toluenesulphonyl-2-(1-cyclohexene)-ethanamide (147) (100 mg, 0.25 mmol) in dichloromethane (2 cm^3) was reacted as described above (9.5.3) to furnish a inseperable (1:1) mixture of 7-bromo-1,1-dimethyl-3-(toluene-4-sulfonyl)-3-aza-spiro[5.5]undecan-2-one (162) and *N*-(2-cyclohex-1-enyl-ethyl)-2-p-tolyl-isobutyramide (163) (0.078 g) in the form of a clear oil.

ν_{max} (nujol)/cm^{-1} ***mixture*** 1740, 1670, 1365, 1170; 7-bromo-1,1-dimethyl-3-(toluene-4-sulfonyl)-3-aza-spiro[5.5]undecan-2-one (162), δ_H(300MHz; $CDCl_3$) 1.49 (6H, s, 2x Me), 1.60-2.15 (10H, m, $\underline{CH_2}CH_2N$, 4x CH_2), 2.27 (3H, s, Me), 2.87 (2H, m, CH_2N), 4.65 (1H, brs, $\underline{CH}$Br), 7.09 (4H, m, Ar); *N*-(2-cyclohex-1-enyl-ethyl)-2-p-tolyl-isobutyramide (163), 1.47 (6H, s, 2x Me), 1.60-2.15 (10H, m, $\underline{CH_2}CH_2N$, 4x CH_2), 2.28 (3H, s, Me), 3.14 (2H, q, J=6.2Hz, $\underline{CH_2}NH$), 5.08 (2H, brs, C=$\underline{CH}$, NH), 7.09 (4H, m, Ar); δ_C(75MHz; $CDCl_3$) ***mixture*** 20.07 (t), 21.05 (t), 21.31 (q), 21.41 (q), 22.59 (t), 23.08 (t), 25.09 (s), 25.47 (t), 27.08 (q), 27.19 (q), 27.29 (t), (2x) 27.40 (q), 27.74 (t), 32.37 (t), 35017 (t), 37.20 (t), 37.68 (t), (2x) 41.49 (t), 48.97 (s), 54.31 (d), 64.21 (s), 124.31 (d), (2x) 125.63 (d), (2x) 126.85 (d), (2x), 129.66 (d), (2x) 130.20 (d), 134.69 (s), 136.90 (s), 137.47 (s), 140.31 (s),

142.40 (s), 175.41 (s), 177.67 (s); m/z LC-MS (AP^+) 5.85 minutes 286 (MH^+, $C_{19}H_{28}NO$), 6.00 minutes 430 (MH^+, $C_{19}H_{28}Br^{81}NSO_3$).

9.5.3.14 4-Bromomethyl-1-toluene-4-sulfonyl pyrrolidin-2-one (164).

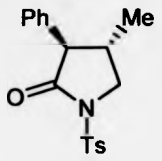


N-allyl-4-toluenesulfonyl-2-bromoacetamide (126) (0.050 g, 0.15 mmol) in dichloromethane (1.25 cm^3) was reacted at 100°C in a sealed tube as described in section (9.5.3) to furnish an inseparable mixture (1:3) of *N*-allyl-*N*-toluene-4-sulfonamide, spectral details matched those previously reported[22] and 4-bromomethyl-1-toluene-4-sulfonyl pyrrolidin-2-one (164) (18% by N.M.R.), spectral details matched those previously reported.[22]

δ_H(400MHz; $CDCl_3$) 2.35 (1H, dd, J=17.4, 6.8 Hz, HCHCO), 2.43 (3H, s, Me), 2.62 (1H, dd, J=17.4, 8.5 Hz, HCHCO), 2.78 (1H, m, CHCH$_2$Br), 3.45 (2H, m, CH$_2$Br), 3.66 (1H, dd, J=10.2, 7.6 Hz, HCHN), 4.06 (1H, dd, J=10.2, 7.6 Hz, HCHN), 7.34 (2H, d, J=8.5 Hz, Ar), 7.92 (2H, d, J= 8.5 Hz, Ar).

9.5.4 Chemical correlation of *trans*-4-Chloromethyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2one (156) to *trans*-4-methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidine (165).

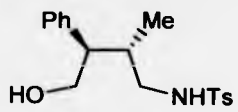
9.5.4.1 *trans*-4-Methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2one (166).



A solution of *trans*-4-chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (156) (118 mg, 0.325 mmol), Bu_3SnH, (95 mg, 0.325 mmol) and AIBN (5.3 mg) in dry toluene (5 cm^3) was heated at reflux for 1hr. The solvent was removed in *vacuo* and the residue partioned between hexane and acetonitrile. The acetonitrile layer was evaporated to give *trans*-4-methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2one (166) (79 mg, 85%) in the form of a clear oil, which was used without further purification. (Found MH^+ 330.1159 $C_{18}H_{20}NO_3S$ requires 330.1164).

ν_{max} ($CDCl_3$)/cm^{-1} 2963, 1737; δ_H(400MHz; $CDCl_3$) *trans* 1.04 (3H, d, J=6.4 Hz, Me) 2.31 (1H, m, CHMe), 2.38 (3H, s, Me), 3.08 (1H, d, J=11.1 Hz, CHPh), 3.27 (1H, t, J=10.4 Hz, HCHN), 4.09 (1H, dd, J=10.4, 2.25 Hz, HCHN), 6.99 (2H, d, J=8.1 Hz, Ar), 7.19 (5H, m, Ph), 7.94 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) *trans* 16.87 (Me), 22.11 (Me), 36.92 (CH), 52.64 (CH_2), 58.03 (CH), (2x) 128.11 (d), 128.57 (s), (2x) 128.90 (d), (2x) 129.19 (d), (3x) 133.40 (d), 135.96 (s), 145.65 (s), 173.60 (s); *m/z* (CI/NH_3) 330 (MH^+, 25%), 154 (100), 197 (55).

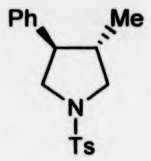
9.5.4.2 $LiAlH_4$ reduction of *trans*-4-methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2one (166).



To a solution of *trans*-4-methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidin-2-one (166) (50 mg, 0.175 mmol) in dry THF (2 cm^3) was added $LiAlH_4$ (2 eq.) at RT under nitrogen. After reaction for 12 hours the reaction was quenched with water and the mixture extracted with dichloromethane to give the crude product. Purification by column chromatography (4:1 pet ether:ethyl acetate) furnished the ring opened *N*-(4-hydroxy-2-methyl-3-phenyl-butyl)-1-toluene-4-sulfonamide (167) (55 mg, 55%) in the form of a clear oil. (Found MH^+ 334.1472 $C_{18}H_{24}NO_3S$ requires 334.1477).

ν_{max} ($CDCl_3$)/cm^{-1} 3500-3000, 2963, 1599, 1453; δ_H(400MHz; $CDCl_3$) 0.70 (3H, d, J=6.4 Hz, Me), 2.01 (1H, m, CHMe), 2.41 (3H, s, Me), 2.71 (1H, m, CHPh), 2.92 (2H, m, CH_2N), 3.79 (2H, d, J=6.3 Hz, HCHOH), 5.14 (1H, brt, J=6.3 Hz, NH), 7.07 (2H, d, J=8.4 Hz, Ar), 7.19 (5H, m, Ph), 7.73 (2H, d, J=8.4 Hz, Ar); δ_C(100MHz; $CDCl_3$) 15.79 (q), 21.41 (q), 35.11 (t), 47.19 (d), 50.59 (d), 64.80 (t), (2x) 126.99 (d), 128.01 (d), (3x) 128.44 (d), 128.70 (d), (2x) 129.63 (d), 136.74 (s), 140.21 (s), 143.26 (s); *m/z* (CI/NH_3) 330 (MH^+, 25%), 154 (100), 197 (55).

9.5.4.3 *trans*-4-Methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidine (165).

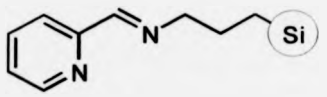


To a solution of *N*-(4-hydroxy-2-methyl-3-phenyl-butyl)-1-toluene-4-sulfonamide (167) (22 mg) in dry THF (0.4 cm^3) was added PPh_3 (20 mg, 0.079 mmol), and DEAD (11.5 mg, 0.066 mmol) and the mixture stirred at RT overnight. Water was added and the mixture extracted with dichloromethane (2 x 10 cm^3). Evaporation of the solvent followed by purification by chromatography (4:1 petroleum ether : ethyl acetate) furnished 7 mg of un-reacted starting material (167) and *trans*-4-methyl-3-phenyl-1-toluene-4-sulfonylpyrrolidine (165) (7 mg, 49%). The product showed identical spectral details to that published for an authentic sample.[23]

δ_H(400MHz; $CDCl_3$) 0.78 (3H, d, J=6.4 Hz, Me), 2.07 (1H, m, CHMe), 2.40 (3H, s, Me), 2.52 (1H, q, J=10.0 Hz, CHPh), 2.81 (1H, t, J=10.0 Hz, HCHN), 3.18 (1H, t, J=10.0 Hz, HCHN), 3.60 (2H, m, HCHN), 6.99 (2H, d, J=8.4 Hz, Ar), 7.15 (5H, m, Ph), 7.67 (2H, d, J=8.4 Hz, Ar).

9.6 Experimental for Chapter 7.

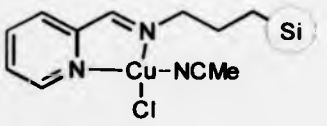
9.6.1 Solid supported catalyst (168).



A mixture of aminopropylated silica (2.00 g, 9% functionalised) and pyridine carboxaldehyde (2.4 g, 22.5 mmol) in dry toluene (50 cm^3) was heated at reflux for 24 hours with a soxhlet containing crushed 4A molecular sieves (5.0 g). The crude orange supported ligand was then washed with toluene (3 x 25 cm^3), dichloromehane (3 x 10 cm^3) and ethanol (5 cm^3), and then dried to a constant weight in an oven at 100°C to give an orange powder (168) (2.2699g).

ν_{max} cm^{-1} 1650, 1600, 1570, 1450, 1430; δ_C(126MHz; MAS) 9.6 (CH_2), 24.4 (CH_2), 60.7 (CH_2), 91.6 (HC=N), 122.5 136.0, 148.7, 154.8 (5x Ar).

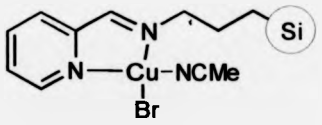
9.6.2 The preparation of the CuCl complexed solid support (169a).



To the solid supported ligand (168) (1.00 g) was added CuCl (0.17 g, 1.7 mmol) in dry acetonitrile (10 cm^3) and the mixture stirred for 30 minutes. On addition of CuCl the solid support changed in colour from bright orange to dark brown. The support was filtered

under argon and washed repeatedly with dry MeCN (10 x 15 cm^3) to give (169a) (1.0812 g). (ICP indicated 4.3% Cu).

9.6.3 The preparation of the CuCl complexed solid support (169b).

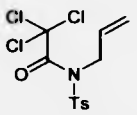
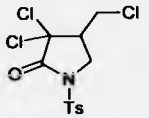
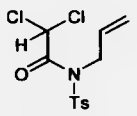
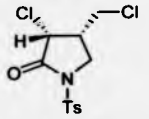
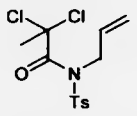
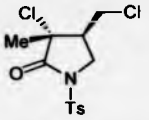
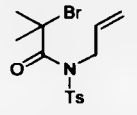
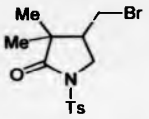
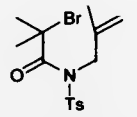
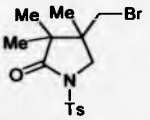
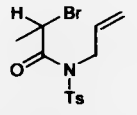
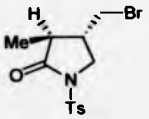
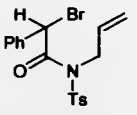
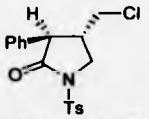
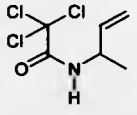
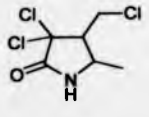


To the solid supported ligand (168) (1.00 g) was added CuBr (0.17 g, 1.2 mmol) in dry acetonitrile (10 cm^3) and the mixture stirred for 30 minutes. On the addition of CuBr the solid support changed in colour from bright orange to dark brown. The support was filtered under argon and washed repeatedly with dry MeCN (10 x 15 cm^3) to give (169b) (1.1300 g). (ICP indicated 4.7% Cu).

9.6.4 General procedure for atom transfer cyclisations.

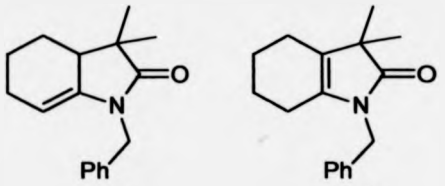
To a 0.12M solution of cyclisation precursor in dichloroethane under nitrogen was added either CuCl (169a) or CuBr (169b) solid support (25 mol%). The mixture was then refluxed for 24 hours. The resulting mixture was filtered and the solvent removed in *vacuo* to give the crude products. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.

Table 2. Results of the cyclisation of haloacetamides in the 5-*exo* mode using the solid supported catalysts (169a) and (169b)

Entry	Substrate	Product[a]	Time (hr)	Yield[b] (%)
1			3[c]	96
2			20	96[d]
3			18	90[e]
4			24	92
5			36	90
6			24	92[f]
7			22	94[g]
8			48	75[h]

[a] All reaction were carried out in $ClCH_2CH_2Cl$ at reflux with 25 mol% catalyst. [b] Combined yields of both diastereoisomers, major diastereoisomers shown. [d] 55%. [e] 64%. [f] 64%. [g] 66%. [h] 72%. [c] Reaction carried out at room temperature in $ClCH_2CH_2Cl$.

9.6.5 The cyclisation of *N*-benzyl-2,2-dimethyl-2-bromo-*N*-cyclohex-1-enylacetamide.



170a 170b

N-benzyl-2,2-dimethyl-2-bromo-*N*-cyclohex-1-enylacetamide (66 mg, 0.14mmol) in dichloroethane (1.2 cm^3) was reacted as described above (9.6.4) for a period of 24 hours to furnish 1-benzyl-3,3-dimethyl-1,3,3a,4,5,6-hexahydro-indol-2-one (170a) (19 mg, 38%) and 1-benzyl-3,3-dimethyl-1,3,4,5,6,7-hexahydro-indol-2-one (170b) (19 mg, 38%) as a 1:1 mixture of double bond regioisomers in the form of a clear oil. (Found M^+ *mixture* 255.1625 $C_{17}H_{21}NO$ requires 255.1623)

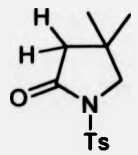
ν_{max} *mixture* (neat)/cm^{-1} 2931, 1702, 1654, 1621; δ_H(300MHz; C_6D_6) ***170a*** 0.99 (3H, s, Me), 1.14 (2H, m, CH_2), 1.26 (3H, s, Me), 1.37 (1H, m, CH_2), 1.61 (1H, m, CH_2), 1.90 (2H, m, CH_2), 2.18 (1H, m, CH), 4.55 (1H, d, J=15.2 Hz, CH_2Ph), 4.65 (1H, d, J=15.2 Hz, CH_2Ph), 4.67 (1H, s, CH=C), 7.28 (5H, m, Ph); δ_C(75MHz; C_6D_6) 20.95 (q), 22.14 (t), 22.60 (t), 23.41 (q), 23.77 (t), 42.91 (s), 43.83 (t), 46.09 (d), 97.57 (d), 127.55 (d), 127.83 (d), 128.15 (d), 128.47 (d), 128.89 (d), 138.00 (s), 140.28 (s), 179.79 (s); δ_H(300MHz; C_6D_6) ***170b*** 1.28 (6H, s, (2x) Me), 1.35 (4H, m, (2x) CH_2), 1.79 (2H, m, (2x) CH_2), 4.55 (2H, s, CH_2Ph), 7.07 (5H, m, Ph); δ_C(75MHz; C_6D_6) 19.81 (t), 21.50 (t), (2x) 22.83 (q), (2x) 22.87 (t), 43.10 (t), 46.20 (s), 120.44 (d), (2x) 127.44 (d), (2x) 128.15 (d), 128.98 (s), 134.22 (s),139.46 (s), 183.01 (s); *m/z* (EI) *mixture* 255 (M^+, 37%), 240 (29), 91 (100).

9.7 Experimental for Chapter 8.

9.7.1 General procedure for cyclisation of haloacetamides using 1-ethylpiperidine hypophosphite.

A stirred solution of 1-ethylpiperidine hypophosphite 0.11M (10 eq.)and *N*-tosyl acetamide (1 eq.) in dry toluene, under nitrogen, was heated at reflux for a period of 1 hour. To which AIBN (0.4 eq.) was added in two portions within a 30 minute time interval. After the addition the reaction was refluxed for a further 72 hours. The resulting mixture was allowed to cool, diluted with dichloromethane and washed successively with sodium bicarbonate (50 cm^3), 10% HCl (2x50 cm^3), sodium bicarbonate (50 cm^3) and brine (50 cm^3). The organic layer was then dried over anhydrous magnesium sulphate, filtered and concentrated in *vacuo*. Chromatography with light petroleum ether and ethyl acetate furnished the pure products.

9.7.1.1 *N*-Toluenesulfonyl-4-dimethyl-pyrrolidin-2-one (171).

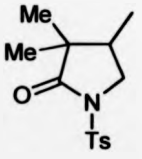


N-(2,2-dichloro-acetyl)-4-methyl-*N*-(2-methyl-allyl)-benzenesulfonamide (200 mg, 0.59 mmol) in toluene (7.0 cm^3) was reacted as described above (9.7.1) for a period of 72 hours, to furnish *N*-toluenesulfonyl-4-dimethyl-pyrrolidin-2-one (171) (134 mg, 79%) in the form

of a white crystalline solid; m.p. 89-91°C. (Found MH^+ 268.1003 $C_{13}H_{17}NO_3S$ requires 268.1007).

ν_{max} (CH_2Cl_2)/cm^{-1} 2963, 1742; δ_H(300MHz; $CDCl_3$) 1.03 (3H, s, MeCMe), 1.47 (3H, s, MeCMe), 2.18 (2H, s, CH_2), 2.36 (3H, s, Me), 3.52 (2H, s, $CH_2C{=}O$), 7.25 (2H, d, J=8.1 Hz, Ar), 7.82 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) 20.67 (q), (2x) 25.63 (q), 32.18 (s), 45.96 (t), 58.54 (t), (2x) 126.95 (d), (2x) 128.64 (d), 134.15 (s), 144.10 (s), 171.70 (s); *m/z* (CI/NH_3) 268 (MH^+, 30%), 35 (100), 114 (82).

9.7.1.2 4-Bromomethyl-3,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (172).

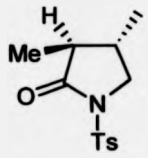


N-Allyl-*N*-4-toluenesulfonyl-2-bromo-2-methyl propionamide (125) (200 mg, 0.56 mmol) in toluene (6.0 cm^3) was reacted as described above (9.7.1) for a period of 72 hours, to furnish 3,3-dimethyl-4-methyl-1-toluene-4-sulfonylpyrrolidin-2-one (172) (130 mg, 83%) in the form of a white crystalline solid; m.p. 93-94°C. (Found M^+ 281.1082 $C_{14}H_{19}NO_3S$ requires 281.1086).

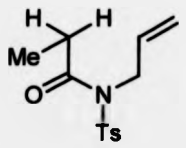
ν_{max} (CH_2Cl_2)/cm^{-1} 2970, 1732; δ_H(300MHz; $CDCl_3$) 0.73 (3H, s, MeCMe), 0.88 (3H, d, J=7.0 Hz, MeCH), 1.47 (3H, s, MeCMe), 1.95 (1H, m, MeCH), 2.36 (3H, s, Me), 3.16 (1H, t, J=9.6 Hz, HCH), 3.86 (1H, dd, J=9.6, 7.3 Hz, HCH), 7.24 (2H, d, J=8.1 Hz, Ar),

7.81 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) 10.90 (q), 16.45 (q), 20.68 (q), 21.46 (q), 36.56 (d), 43.85 (s), 49.55 (t), (2x) 126.84 (d), (2x) 128.62 (d), 134.06 (s), 144.01 (s), 177.40 (s); *m/z* (EI) 281 (M^+, 25%), 207 (100).

9.7.1.3 *trans*-4,3-Dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (173).



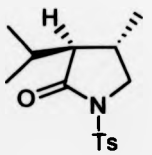
N-2-propenyl-*N*-toluenesulphonyl-2-bromopropionamide (143) (200 mg, 0.58 mmol) in toluene (6.0 cm^3) was reacted as described above (9.7.1). Purification of the two component mixture using flash column chromatography eluting with light petroleum ether:ethyl acetate (6:1) furnished *trans*-4,3-dimethyl-1-toluene-4-sulfonylpyrrolidin-2-one (173) (114 mg, 74%) as a inseparable mixture of diastereoisomers (ratio 7.7:1, *trans:cis*) in the form of a white crystalline solid; m.p. 97-98°C (Found MH^+ 281.1010 $C_{13}H_{18}NO_3S$ requires 268.1007), and an inseparable mixture of *N*-allyl-4-methyl-*N*-propionyl-benzenesulfonamide (174) and a trace amount of *N*-allyl-*N*-toluenesulfonamide (119) (16 mg) the spectral details of which matched that of the authentic prepared sample (9.3.2.1).



(174)

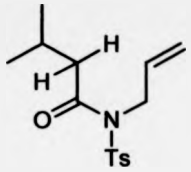
ν_{max} (CH_2Cl_2)/cm^{-1} *mixture* 2966, 1734; δ_H(300MHz; $CDCl_3$) *trans* 0.83 (3H, d, J=7.0 Hz, MeCH), 0.92 (3H, d, J=7.3 Hz, MeCH), 1.44 (1H, d, J=7.3 Hz, MeCH), 2.36 (3H, s, Me), 2.47 (1H, p, J=7.35 Hz, MeCH), 3.45 (1H, dd, J=10.0, 3.4 Hz, CH_2), 3.77 (1H, dd, J=10.0, 3.75 Hz, CH_2), 7.25 (2H, d, J=8.1 Hz, Ar), 7.82 (2H, d, J=8.1 Hz, Ar); *cis* 1.03 (6H, d, J=6.4 Hz, 2x MeCH), 1.87 (2H, m, 2x MeCH), 2.36 (3H, s, Me), 3.12 (1H, t, J=9.8 Hz, CH_2), 3.94 (1H, dd, J=9.8, 7.2 Hz, CH_2), 7.20 (2H, d, J=8.1 Hz, Ar), 7.83 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) *trans* 9.44 (q), 13.57 (q), 21.46 (q), 30.47 (d), 42.01 (d), 52.29 (t), (2x) 127.71 (d), (2x) 129.41 (d), 134.99 (s), 144.80 (s), 175.28 (s); *cis* 13.28 (q), 16.84 (q), 22.08 (q), 36.02 (d), 46.13 (d), 52.51 (t), (2x) 128.40 (d), (2x) 130.64 (d), 135.63 (s), 145.48 (s), 175.28 (s); *m/z* (CI/NH_3) 267 (MH^+, 10%), 35 (100), 114 (45).

9.7.1.4 *trans*-4-Methyl-3-*i*-propyl-1-toluene-4-sulfonylpyrrolidin-2-one (175).



N-allyl-*N*-toluenesulphonyl-2-bromo-3-methylbutanamide (144) (150 mg, 0.40mmol) in toluene (4.0 cm^3) was reacted as described above (9.7.1). Purification of the two component mixture using flash column chromatography eluting with light petroleum ether:ethyl acetate (6:1) furnished *trans*-4-methyl-3-*i*-propyl-1-toluene-4-sulfonylpyrrolidin-2-one (175) (91 mg, 77%) as a inseparable mixture of diastereoisomers (ratio 17.1:1, *trans:cis*) in the form of a white crystalline solid; m.p. 75-77°C. (Found MH^+ 296.1325 $C_{15}H_{22}NO_3S$ requires 296.1320) and *N*-allyl-4-methyl-*N*-(3-methyl-

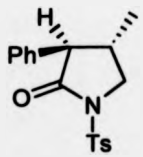
butyryl)-benzenesulfonamide (176) and *N*-allyl-*N*-toluenesulfonamide (119) as an inseperable 1:1 mixture (20 mg).



(176)

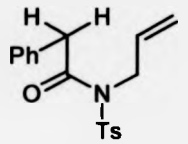
ν_{max} ($CDCl_3$)/cm^{-1} 2964, 1731; δ_H(300MHz; $CDCl_3$) *trans* 0.76 (3H, d, J=6.9 Hz, MeCHMe), 0.85 (3H, d, J=6.9 Hz, MeCHMe), 1.03 (3H, d, J=7.0 Hz, Me), 1.88 (1H, dd, J=7.7, 4.1 Hz, MeCHMeCH), 1.95 (1H, m, MeCHMe), 2.15 (1H, sp, J=7.0, CH), 2.37 (3H, s, Me), 3.18 (1H, dd, J=9.7, 7.0 Hz, HCHN), 3.88 (1H, dd, J=9.7, 1.7 Hz, HCHN), 7.25 (2H, d, J=8.1 Hz, Ar), 7.83 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) *trans* 19.30 (q), 20.05 (q), 20.12 (q), 22.08 (q), 28.70 (d), 28.98 (d), 52.84 (t), 56.94 (d), (2x) 128.42 (d), (2x) 130.01 (d), 135.58 (s), 145.43 (s), 175.14 (s); *m/z* (CI/NH_3) 296 (MH^+, 40%), 142 (100).

9.7.1.5 *trans*-4-Chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (177).



N-2-propenyl-*N*-toluenesulphonyl-2-chloro-2-phenylacetamide (145) (200 mg, 0.55 mmol) in toluene (5.0 cm^3) was reacted as described above (9.7.1). Purification of the two

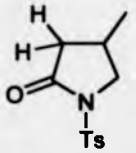
component mixture using flash column chromatography eluting with light petroleum ether:ethyl acetate (4:1) furnished *trans* 4-chloromethyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (177) (118 mg, 65%) as a inseparable mixture of diastereoisomers (ratio >10:1, *trans:cis*) in the form of a clear oil. (Found MH^+ 330.1159 $C_{18}H_{20}NO_3S$ requires 330.1164) and a 1:1 mixture of *N*-allyl-4-methyl-*N*-phenylacetyl-benzenesulfonamide (178) and *N*-allyl-*N*-toluenesulfonamide (119) as an inseperable mixture (22 mg).



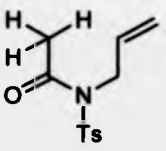
(178)

ν_{max} ($CDCl_3$)/cm^{-1} 2963, 1737; δ_H(400MHz; $CDCl_3$) *trans* 1.04 (3H, d, J=6.4 Hz, Me) 2.31 (1H, m, CHMe), 2.38 (3H, s, Me), 3.08 (1H, d, J=11.1 Hz, CHPh), 3.27 (1H, t, J=10.4 Hz, HCHN), 4.09 (1H, dd, J=10.4, 2.25 Hz, HCHN), 6.99 (2H, d, J=8.1 Hz, Ar), 7.19 (5H, m, Ph), 7.94 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) *trans* 16.87 (Me), 22.11 (Me), 36.92 (CH), 52.64 (CH_2), 58.03 (CH), (2x) 128.11 (d), 128.57 (s), (2x) 128.90 (d), (2x) 129.19 (d), (3x) 133.40 (d), 135.96 (s), 145.65 (s), 173.60 (s); *m/z* (CI/NH_3) 330 (MH^+, 25%), 154 (100), 197 (55).

9.7.1.6 4-Methyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (179).



(179)



(180)

(119)

N-allyl-4-toluenesulfonyl-2-bromoacetamide (126) (200 mg, 0.60 mmol) in toluene (6.0 cm^3) was reacted as described above (9.7.1). Purification using flash column chromatography eluting with light petroleum ether:ethyl acetate (6:1) furnished a separable 3 component mixture of 4-methyl-3-phenyl-1-toluene-4-sulphonylpyrrolidin-2-one (179) (20 mg, 13%) in the form of a clear oil (Found MH^+ 254.0857 $C_{12}H_{16}NO_3S$ requires 254.0851), *N*-acetyl-*N*-allyl-toluenesulfonamide (180) (28mg, 18%) (Found MH^+ 254.0852 $C_{12}H_{16}NO_3S$ requires 254.0851) and *N*-allyl-*N*-toluenesulfonamide (119) (15mg, 12%). Spectral details matched those previously cited in section (9.3.2.1).

(179) ν_{max} $(CH_2Cl_2)/cm^{-1}$ 2968, 1731; δ_H(300MHz; $CDCl_3$) 1.02 (3H, d, J=6.6 Hz, MeCH), 1.95 (1H, dd, J=16.8, 7.4 Hz, CH_2C=O), 2.37 (3H, s, Me), 2.41 (2H, m, CH_2C=O + MeCH), (1H, dd, J=9.9, 6.6 Hz, HCHN), 3.86 (1H, dd, J=9.9, 2.4 Hz, HCHN), 7.26 (2H, d, J=8.1 Hz, Ar), 7.84 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) 13.12 (q), 20.63 (q), 25.78 (d), 39.36 (t), 53.00 (t), (2x) 127.15 (d), (2x) 128.65 (d), 134.14 (s), 144.11 (s), 171.93 (s); *m/z* (EI) 254 (MH^+, 37%), 98 (100).

(180) ν_{max} $(CH_2Cl_2)/cm^{-1}$ 2956, 1701; δ_H(300MHz; $CDCl_3$) 2.22 (3H, s, Me), 2.38 (3H, s, Me), 4.38 (2H, dt, J=5.5, 1.5 Hz, CH_2N), 5.16 (2H, m, CH=CH_2), 5.75 (1H, m, CH=CH_2), 7.25 (2H, d, J=8.1 Hz, Ar), 7.73 (2H, d, J=8.1 Hz, Ar); δ_C(75MHz; $CDCl_3$) 20.63 (q), 23.67 (q), 47.77 (t), 117.24 (t), (2x) 126.91 (d), (2x) 128.73 (d), 131.65 (d), 135.51 (s), 143.92 (s), 168.99 (s); *m/z* (EI) 254 (MH^+, 55%), 35 (100).

Chapter 9. References

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